COMPLEXITY-BUILDING DERACEMIZATION AND DESYMMETRIZATION METHODOLOGIES

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ABSTRACT

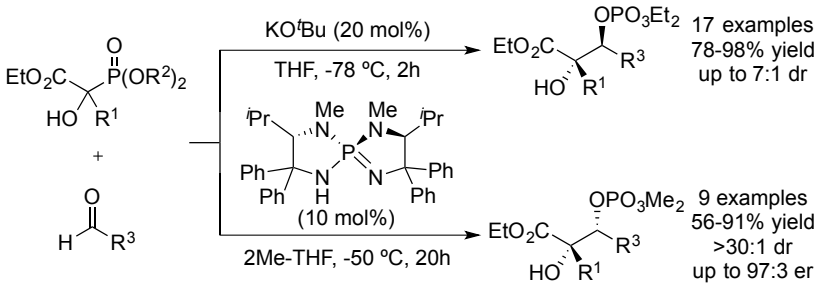
Michael Thomas Corbett: Complexity-Building Deracemization and Desymmetrization Methodologies
(Under the direction of Jeffrey S. Johnson)

I. Deracemization and Desymmetrization: A Primer

An overview of the principles of deracemization and desymmetrization techniques applied in modern asymmetric catalysis.

II. Base-Catalyzed Direct Aldolization of α-Hydroxy Trialkyl Phosphonoacetates

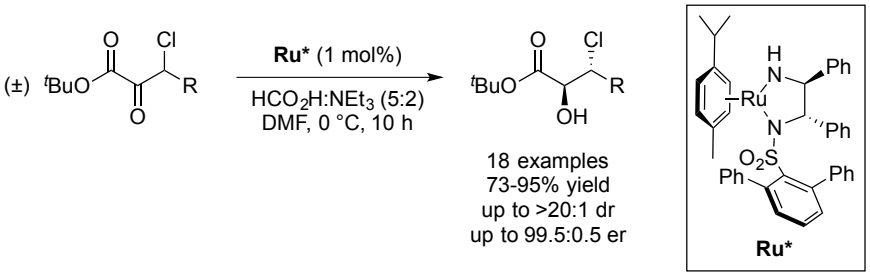
A catalytic direct aldolization of racemic α-hydroxy trialkyl phosphonoacetates to access α-hydroxy-β-phosphonyloxy esters is described. The fully-substituted glycolate enolate was generated *in situ* via [1,2]-phosphonate-phosphate rearrangement under mild proton-transfer conditions. An asymmetric variant was realized upon application of a *P*-spirocyclic chiral iminophosphorane providing excellent levels of diastereo- and enantiocontrol in the aldolization.



III. Asymmetric Synthesis of Chlorohydrins via Dynamic Kinetic Reduction

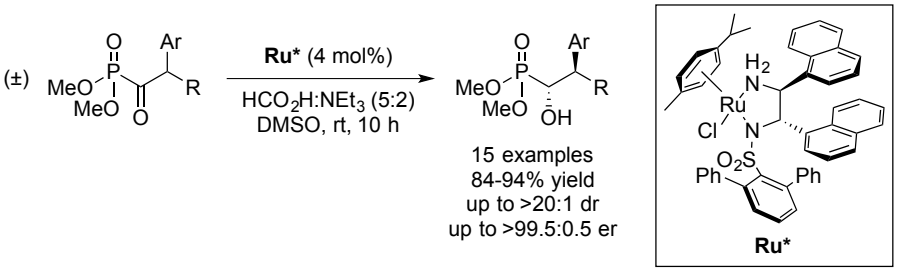
A dynamic kinetic resolution via asymmetric transfer hydrogenation (DKR-ATH) of racemic β-chloro-α-keto esters to provide access to optically active halohydrins is presented. The requisite β-chloro-α-keto esters were prepared via Ni-catalyzed direct chlorination of α-keto

esters. A Ru(II)-amido complex bearing a bulky *m*-terphenylsulfonamide ligand provided a remarkable ligand-controlled switch in diastereoselectivity in the reduction affording *anti*-chlorohydrins with high levels of diastereo- and enantiocontrol.



IV. Dynamic Kinetic Reduction of Racemic Acyl Phosphonates

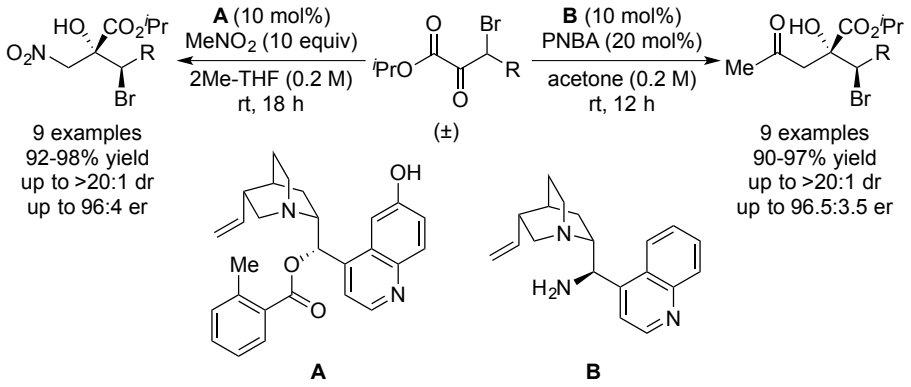
A strategy for the preparation of β-stereogenic-α-hydroxy phosphonic acid derivatives via DKR-ATH of racemic α-aryl acyl phosphonates is discussed. A (arene)RuCl(monosulfonamide) complex featuring a bulky *m*-terphenylsulfonamide ligand provided excellent levels of diastereo- and enantiocontrol in the reduction. Interestingly, this reduction was determined to be proceeding from the opposite face of the ketone providing pseudo-diastereomeric products from those obtained in the reduction of α-keto esters.



V. Dynamic Kinetic Aldolization of Configurationally Labile Electrophiles

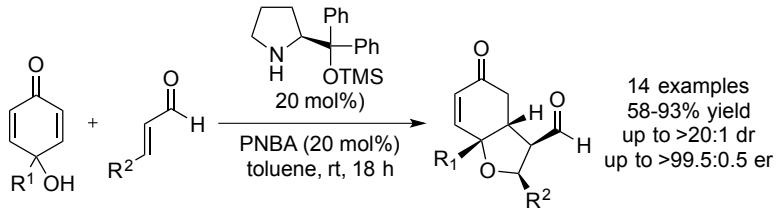
Dynamic kinetic asymmetric transformations (DyKAT) of racemic β-bromo-α-keto esters through direct aldolization of nitromethane and acetone are described. Cinchona alkaloid-derived catalysts effectively catalyzed the aldolizations providing access to fully substituted α-glycolic

acid derivatives bearing a β-stereocenter. Mechanistic studies revealed that the reactions proceed via facile catalyst-mediated racemization of the β-bromo-α-keto esters under a DyKAT Type I manifold.



VI. Enantioselective Synthesis of Hindered Cyclic Dialkyl Ethers via Organocatalytic Oxa-Michael/Michael Desymmetrization

An oxa-Michael/Michael desymmetrization strategy for the rapid construction of cyclic dialkyl ethers where both α-stereocenters of the ether linkage are set in a single step is presented. Employing a Jørgensen-Hayashi catalyst, the annulation of alkyl substituted *p*-quinols and α,β-unsaturated aldehydes provided access to densely functionalized bicyclic frameworks bearing four contiguous stereocenters.



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materials science, he never gave up on me and eventually "led me to the light." I would also like to thank Fr. Joseph Wagner, S.J. for his academic and spiritual guidance both at Xavier University and beyond. Although my time in Ithaca was brief, I have the upmost respect for the collegiality, hospitality, and professionalism shown by Cornell University's Department of Materials Science and Engineering (MSE) and Department of Chemistry. Finally, I want to thank Dr. Joseph Cordaro who not only mentored me for two summers at Sandia National Laboratories, but also told me to go work for someone by the name of Jeff Johnson.

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To my family
and
in honor of my mother
Cindy Corbett
on the celebration of her
60th birthday

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LIST OF ABBREVIATIONS AND SYMBOLS

2D-NMR	two-dimensional nuclear magnetic resonance
2Me-THF	2-methyl tetrahydrofuran
Å	ångström
Ac	acetate
AH	asymmetric hydrogenation
Ar	aryl
aq	aqueous
ATH	asymmetric transfer hydrogenation
atm	atmospheres
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	2,2´-bis(diphenylphosphino)-1,1´-binaphthyl
BIPHEP	biphenylphosphine
Bn	benzyl
Boc	benzyloxycarbonyl
br	broad
br s	broad singlet
BTSP	bis(trimethylsilyl) peroxide
^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
^{t}Bu-P4	1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ^5,4λ^5-catenadi(phosphazene)
Bz	benzoyl

^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
cat	catalytic amount or catalyst
CBS	Corey–Bakshi–Shibata
COD	1,5-cyclooctadiene
conv	conversion
COSY	correlated spectroscopy
m-CPBA	*meta*-chloroperoxybenzoic acid
CPME	cyclopentyl methyl ether
CSA	camphorsulfonic acid
Cy	cyclohexyl
C–C	carbon-carbon bond
d	doublet or days
D	dextrorotation
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
dd	doublet of doublet
ddt	doublet of doublet of triplets
DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride
DIPEA	ethyldiisopropylamine
DIPT	diisopropyl tartrate

DKR	dynamic kinetic resolution
DMA	*N,N*-dimethylacetamide
DMAP	4-*N,N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin Periodinane
DMSO	dimethyl sulfoxide
DPEN	1,2-diphenyl-1,2-ethylenediamine
dq	doublet of quartet
dr	diastereomeric ratio
dt	doublet of triplet
DyKAT	dynamic kinetic asymmetric transformation
E	*entgegen*
E^+ or El	electrophile
ent	enantiomeric
eq	equation
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
Et_3N	triethylamine
Et_2O	diethyl ether

EtOAc	ethyl acetate
EWG	electron withdrawing group
^{19}F NMR	fluorine nuclear magnetic resonance spectroscopy
FID	flame ionization detector
FMO	frontier molecular orbital
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HCO_2H	formic acid
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HheC	halohydrin dehalogenase
HOAc	acetic acid
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
I	intermediate
IR	infrared spectroscopy
J	coupling constant
k	reaction rate
kcal	kilocalorie
L	levorotation
L	liter or ligand
L-Selectride®	lithium tri-*sec*-butylborohydride

LA	Lewis acid
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
LUMO	lowest unoccupied molecular orbital
M	metal or molarity
m	multiplet
m	*meta*
M	left-handed helix (minus)
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mp	melting point
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
n	number of atoms or counterions
NCS	*N*-chlorosuccinimide
N/D	not determined
NFSI	*N*-fluorobenzenesulfonimide

NMP	*N*-methylpyrrolidone
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
Np	naphthyl
NR	no reaction
Nu	nucleophile
o	*ortho*
Oxone®	potassium peroxomonosulfate
p	*para*
P	product
P	right-handed helix (plus)
^{31}P NMR	phosphorus nuclear magnetic resonance spectroscopy
PG	protecting group
Ph	phenyl
Phth	phthalimidyl
PIDA	phenyliodine diacetate
PIFA	phenyliodine bis(trifluoroacetate)
Piv	pivaloyl
PMP	*para*-methoxyphenyl
PNBA	4-nitrobenzoic acid
ppm	parts per million
Proton-sponge®	1,8-bis(dimethylamino)naphthalene
^{i}Pr	*iso*-propyl

q	quartet
Q	quaternary ammonium salt
R	substituent or gas constant
R	*Re*
R_f	retention factor
rac	racemic
RCHO	aldehyde
Red	reduction
rt	room temperature
s	singlet
s	selectivity factor
S	starting material
S	*Si*
SEGPHOS	4,4´-bi-1,3-benzodioxole-5,5´-diylbis(diphenylphosphane)
SFC	supercritical fluid chromatography
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
T	temperature
t	triplet
t_r	retention time
TBABr	tetrabutylammonium bromide
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride

TBAI	tetrabutylammonium iodide
TBD	triazabicyclodecene
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
Tr	trityl or triphenylmethyl
triflate	trifluoromethanesulfonate
TRIP	3,3´-bis(2,4,6-triisopropylphenyl)-1,1´-bi-2-naphthol cyclic monophosphate
Troc	trichloroethyl chloroformate
Ts	*para*-toluenesulfonyl
TS	transition state
UV	ultraviolet
Val	valine
X	anionic ligand, halide, substituent, or number

Z	*zusammen*
[α]	optical rotation
δ	chemical shift or partial charge
ΔG	change in free energy
λ	wavelength
μL	microliter
Σ	sum

CHAPTER ONE: DERACEMIZATION AND DESYMMETRIZATION: A PRIMER

1.1 Introduction

Methods for the conversion of simple starting materials into functionally rich products are of great importance in organic chemistry. In particular, transformations that directly convert simple achiral, *meso*, and racemic compounds into complex chiral building blocks possessing multiple stereocenters are highly valuable. Two important approaches to realize these types of transformations are deracemization and desymmetrization. Deracemization allows for the direct conversion of a racemate into an enantiopure product with a 100% theoretical yield. Similarly, desymmetrization uses enantiofacial discrimination for the conversion of achiral or *meso* compounds into enantiopure products. This chapter will outline the principles of these two methods, serving as foundational knowledge for subsequent chapters. An introduction to each process will be presented along with relevant examples from the literature that demonstrate their utility.

1.2 Deracemization of Racemates

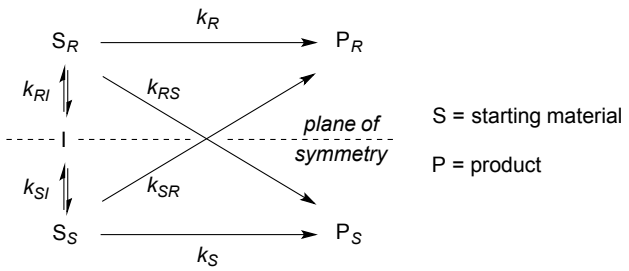
1.2.1 Fundamentals of Deracemization

As defined by Faber, "de-racemization constitutes any process during which a racemate is converted into a non-racemic product in 100% theoretical yield without intermediate separation of materials."[1] Based on this definition, dynamic kinetic resolution (DKR), dynamic kinetic asymmetric transformation (DyKAT), dynamic thermodynamic resolution, cyclic deracemization, and enantioconvergent transformation of a racemate can all be classified as methods for deracemization.[2]

To date, enzymatic processes are the most commonly employed methods for deracemization of small molecules in an industrial setting.[3] Enzymes exhibit phenomenal levels of selectivity in deracemization reactions due to their ability to undergo specific substrate recognition. As an unfortunate byproduct of this heightened substrate specificity, enzymes are often only selective for a single substrate and cannot be broadly applied across a scope of structurally similar substrates. Many modern synthetic methods are aimed at developing small molecule chiral catalysts that can achieve comparable levels of selectivity across broader substrate scopes. In the context of subsequent chapters, only the topics of nonenzymatic dynamic kinetic resolution (DKR) and dynamic kinetic asymmetric transformation (DyKAT) will be discussed henceforth.

Since the advent of asymmetric catalysis, a wide breadth of chemical transformations has been developed for the conversion of a racemate into a single enantiomer product. Faber proposed that these processes all share a common mechanistic pathway (**Figure 1-1**).[1] This general model highlights the key challenges to the development of an efficient deracemization; namely, the existence of an inherent "plane of symmetry." Therefore, conditions and catalysts must be realized that can effectively convert both enantiomers of a racemic starting material (S_R *and* S_S) into the same enantiomeric product (P_R *or* P_S). This can be achieved by either: A) identification of a method that will interconvert S_S and S_R through an achiral intermediate (I), which can operate orthogonal to the enantioselective transformation (S_R to P_R or S_S to P_S); or B) identification of a transformation that provides an enantiospecific route to a single enantiopure product from each enantiomer of starting material (i.e., S_R to P_R (via k_R) and S_S to P_R (via k_{SR})).

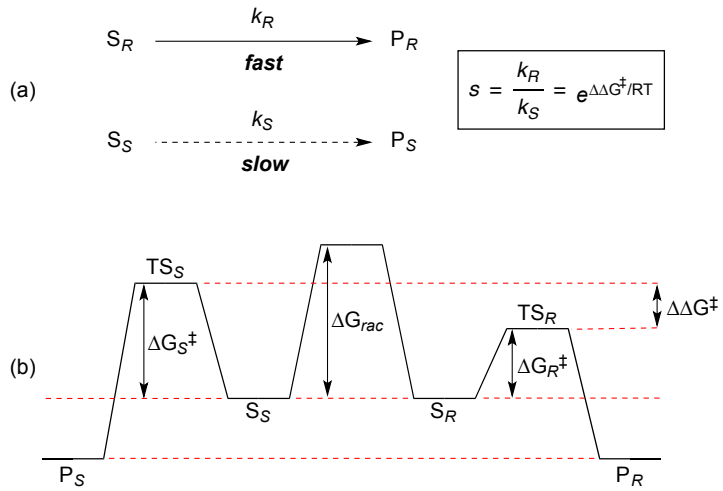
Figure 1-1. General Pathways for Deracemization



1.2.2 Dynamic Kinetic Resolution (DKR): An Overview

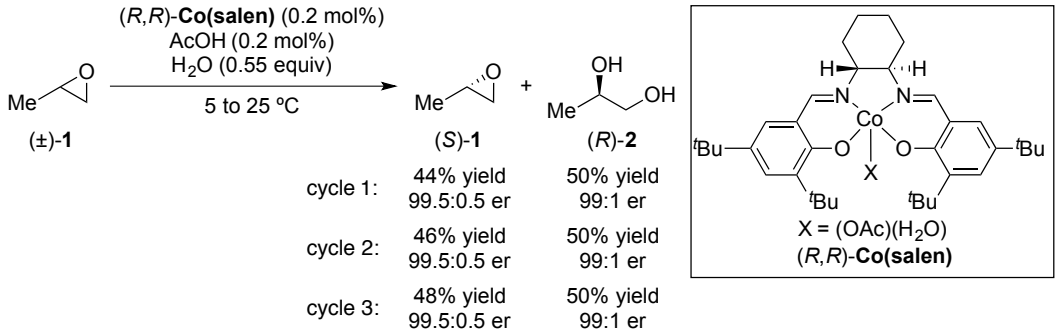
Classical kinetic resolutions remain one of the most commonly employed methods in industry for the preparation of chiral material from a racemate.[4] In a kinetic resolution, product enrichment relies solely on different reaction rates of two enantiomers in a chemical reaction promoted by a chiral catalyst or reagent via diastereomeric transition states (**Figure 1-2**). In order for an efficient kinetic resolution to be realized, the reaction rate of one enantiomer must be significantly faster than the rate of its enantiomer ($k_R >> k_S$). During the reaction, the relative concentrations of S_R/S_S and P_R/P_S are constantly changing since both enantiomers of starting material are simultaneously reacting at different rates. Therefore, the enantiomeric composition of S and P can be modeled as a function of conversion.[5] The efficiency of a kinetic resolution is measured by its selectivity factor (s), which compares the relative rates of reaction for each enantiomer. A key mechanistic feature of kinetic resolutions is that there is no pathway for interconversion of starting material enantiomers (S_R and S_S). Therefore, these processes are limited to a 50% theoretical yield of the enriched product (P_R), although recovery of the enriched unreacted starting material (S_S) is possible. Given this distinction, kinetic resolution is only a method for the separation of enantiomers based on different rates of reaction and is not a deracemization technique.

Figure 1-2. Kinetic Resolution of a Racemate



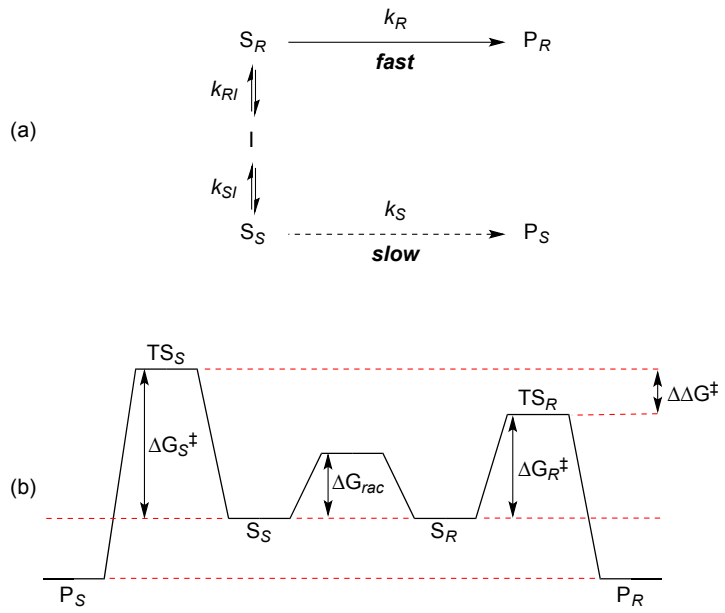
An iconic example of an efficient kinetic resolution is the hydrolytic kinetic resolution of racemic terminal epoxides developed by Jacobsen (**Scheme 1-1**).[6] Employing a Co(salen) catalyst, a near ideal kinetic resolution of racemic propylene oxide (**1**) was achieved providing 1,2-diol (*R*)-**2** in 50% yield and 99:1 er. The unreacted propylene oxide (*S*)-**1** was recovered in 44% yield and 99.5:0.5 er. Furthermore, the recovered Co(salen) catalyst could be recycled for use in subsequent kinetic resolutions providing no loss in catalytic activity or efficiency after three cycles.

Scheme 1-1. Hydrolytic Kinetic Resolution of Terminal Epoxides



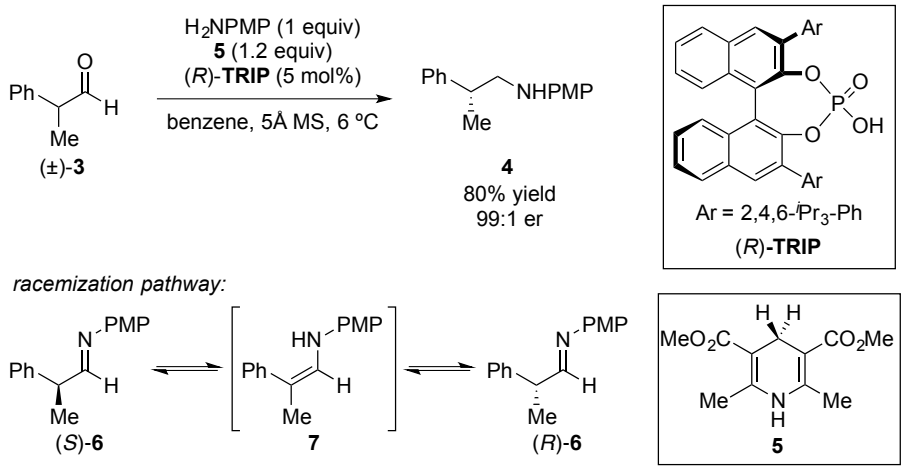
Despite a wealth of exquisitely developed highly efficient and selective kinetic resolutions in the literature, more practical processes would allow for a 100% theoretical yield where complete deracemization of a racemate is observed. In order for a process of this type to be successful, a pathway for interconversion of starting material enantiomers (S_R and S_S) must be available. The incorporation of a racemization pathway between S_R and S_S through an achiral intermediate (I) would allow for a potential dynamic kinetic resolution to be achieved (**Figure 1-3**). In an ideal DKR, interconversion of S_R and S_S should occur *at least* as fast as the asymmetric catalytic reaction being performed. Generally, product racemization is mediated by an external achiral reagent/catalyst and not the chiral catalyst that mediates the productive reaction. Dynamic kinetic resolutions are fundamentally related to kinetic resolutions because enantioselection is governed by the relative rates of reaction of the two enantiomers through diastereomeric transition states with a chiral catalyst. In a DKR, however, the relative concentrations of S_R/S_S remain constant if a highly facile racemization mechanism is identified allowing for the fast reacting enantiomer (S_R) to be continually replenished. The selectivity of the product (P_R) is a function of the relative rates of reaction of each enantiomer (k_R/k_S), which has been carefully studied and quantified by Noyori.[7] If racemization is slow ($k_R >> k_{RI}$ and k_{SI}), then the process becomes less selective and static at higher conversions and can be classified as a kinetic resolution.

Figure 1-3. Dynamic Kinetic Resolution of a Racemate



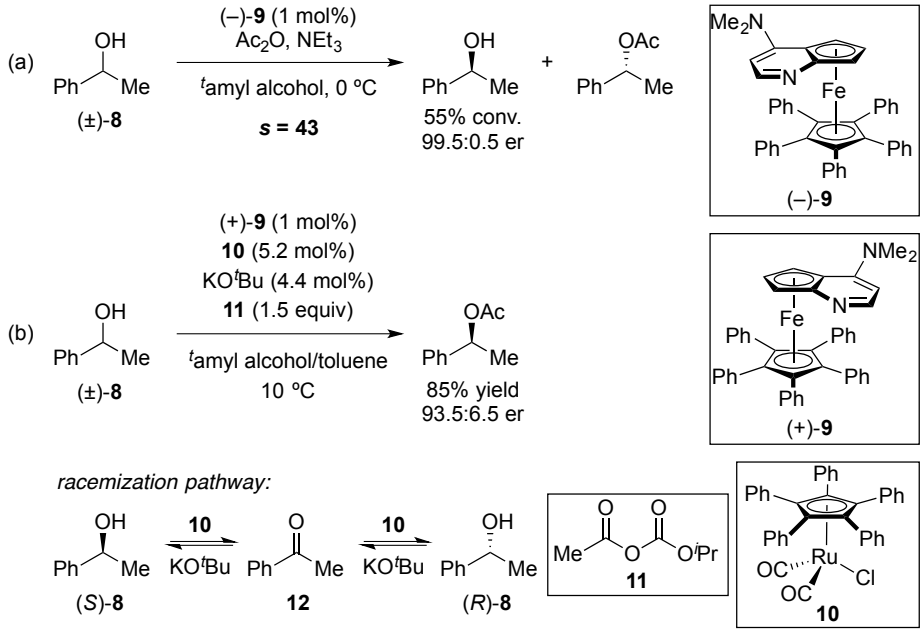
Racemization is an entropically favorable process that can be achieved through various mechanistic pathways: protonation/deprotonation, addition/elimination, oxidation/reduction, and nucleophilic substitution. The most commonly employed strategy is *in situ* racemization of carbonyls through acid/base mediated enol(ate) formation. Due to the heightened acidity of ketones and aldehydes, mild acidic or basic conditions can render the α-position configurationally labile under the reaction conditions. List applied this racemization mode in the development of a catalytic asymmetric reductive amination of racemic α-aryl aldehydes (**Scheme 1-2**).[8] Under the acidic conditions utilized for transfer hydrogenation, racemization is proposed to occur via enamine-imine tautomerization of imine **6** and achiral enamine **7**. The diastereomeric complex of matched imine (*R*)-**6** and (*R*)-TRIP was selectively reduced by Hantzsch ester **5** to afford β-branched amine **4** in excellent enantioselectivity.

Scheme 1-2. Dynamic Kinetic Resolution Approach to β-Branched Chiral Amines



Another frequently employed approach to starting material racemization utilizes reversible oxidation/reduction, which has allowed for the conversion of static kinetic resolutions into dynamic processes. This strategy has been employed mainly within the context of *sec*-alcohols and *sec*-amines, which can be subjected to reversible oxidation-reduction sequences to promote starting material racemization. In 1997, Fu reported a nonenzymatic kinetic resolution of secondary alcohols via asymmetric acylation employing planar chiral-DMAP (–)-**9** as catalyst (**Scheme 1-3a**).[9] The resolution of racemic 1-phenylethanol (**8**) was found to be highly efficient (s = 43) at 55% conversion; however, a more attractive process would arise from a dynamic reaction. Bäckvall's development of effective Ru-catalysts, such as **10**, for the reversible transfer dehydrogenation/hydrogenation of *sec*-alcohols and ketones under mild reaction conditions provided a potential racemization pathway for **8** via oxidation to acetophenone (**12**) and subsequent reduction.[10] Fu employed this racemization strategy in the dynamic kinetic resolution of *sec*-alcohols employing planar chiral-DMAP (+)-**9** as catalyst (**Scheme 1-3b**).[11] Using acyl carbonate **11**, the dynamic kinetic resolution of (±)-**8** was achieved via enantioselective acylation with high levels of selectivity in 85% yield.

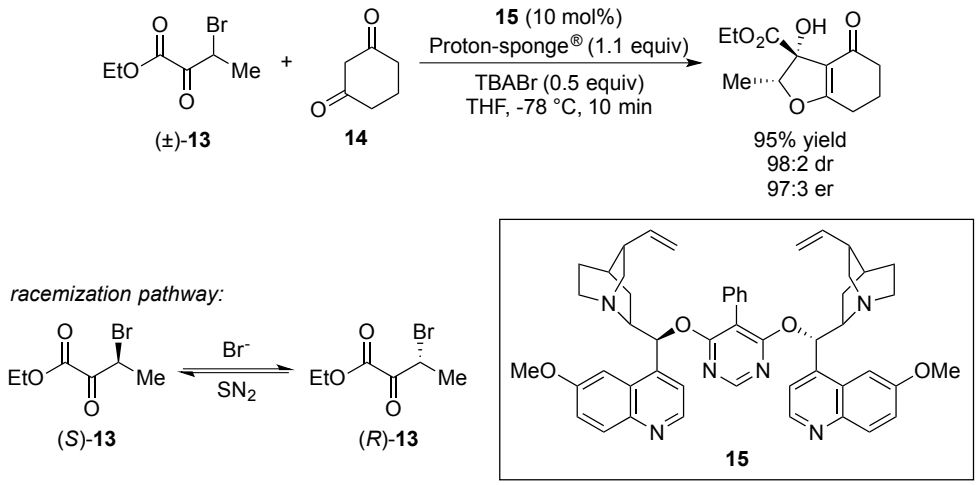
Scheme 1-3. Kinetic Resolution and Dynamic Kinetic Resolution of Secondary Alcohols via Asymmetric Acylation



Racemization through addition/elimination and nucleophilic substitution pathways is less commonly employed; however, a brief discussion of nucleophilic substitution strategies is pertinent due to its relevance to Chapter Five. Racemization pathways involving nucleophilic substitution rely on the presence of a stereogenic functional group that is susceptible to facile nucleophilic displacement (S_N2) by itself (i.e., can serve as both a nucleophile and electrophile). This requirement limits the utility of this approach and examples to date have utilized halides to promote this self-induced configurational lability. This strategy relies on the presence of a *sec*-alkyl halide that is sufficiently activated for nucleophilic substitution by an exogenous halide, such as α-halo carbonyl compounds. A pertinent example is the "interrupted" Feist−Bénary reaction of α-bromo ketone **13** and 1,3-cyclohexanedione (**14**) developed by Calter (**Scheme 1-4**).[12] Bromide generated during the reaction was presumed to induce racemization of (±)-**13** via S_N2 displacement of the α-bromo ketone. Running the reaction in polar, aprotic solvents and

introducing exogenous halide, via addition of tetrabutylammonium bromide (TBABr), was found to provide a significant increase in enantioselectivity providing strong evidence for a nucleophilic substitution racemization pathway.

Scheme 1-4. Asymmetric "Interrupted" Feist−Bénary Reaction via Dynamic Kinetic Resolution

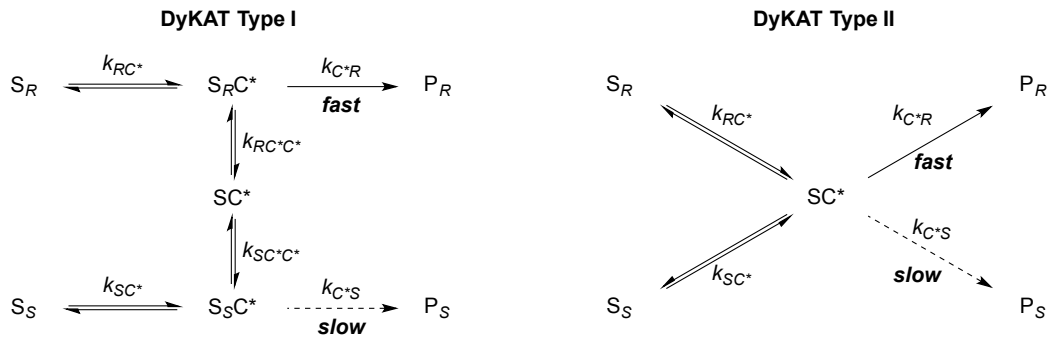


1.2.3 Dynamic Kinetic Asymmetric Transformation (DyKAT): An Overview

Dynamic kinetic asymmetric transformations share a common kinetic profile with the previously discussed dynamic kinetic resolutions, but proceed through more complex catalyst-controlled racemization pathways. Faber stated that "the de-symmetrization of racemic or diastereomeric mixtures involving interconverting diastereomeric intermediates – implying different equilibration rate of the stereoisomers – is termed dynamic kinetic asymmetric transformation."[2] This is in contrast to the interconversion of enantiomeric substrates in a DKR. DyKATs have been categorized into four types based on the nature of the transformation being conducted. DyKATs of the Types I and II achieve de-racemization of enantiomers through the formation of diastereomeric complexes with a chiral catalyst (**Figure 1-4**). Alternatively, DyKATs of the Types III and IV achieve de-epimerization of diastereomers through the

formation of diastereomeric complexes with a chiral catalyst (not shown). Within the context of this thesis, only DyKATs of the Types I and II will be discussed further since they comprise deracemization of racemates.

Figure 1-4. Deracemization of Enantiomers via Dynamic Kinetic Asymmetric Transformation

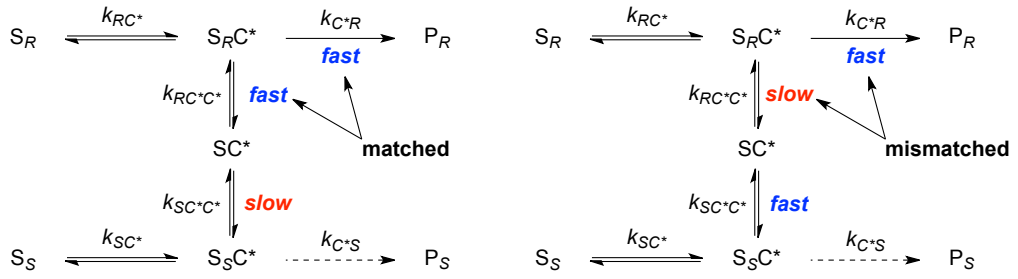


In a DyKAT Type I, each enantiomer of starting material (S_R and S_S) interacts with the chiral catalyst (C*) to generate their respective diastereomeric complexes (S_RC* and S_SC*) (**Figure 1-4**). This interaction between catalyst and substrate can be achieved through formation of a covalent bond in the case of transition metal catalysis or though contact-ion pairing in the case of Lewis acid catalysis or organocatalysis. If no pathway for interconversion of diastereomeric complexes S_RC* and S_SC* exists, then this process would constitute a simple kinetic resolution. However, if a mechanism for the interconversion of diastereomeric complexes S_RC* and S_SC* through a diastereotopic complex SC* can be realized, then the process can be rendered dynamic and a 100% theoretical yield of a single enantiomer (P_R) can be achieved.

As in DKR, the enantioselectivity of DyKAT Type I depends on both the ratio of k_{C*R}/k_{C*S} and the relative concentrations of the diastereomeric intermediates S_RC* and S_SC*. Since the relative populations of S_RC* and S_SC* are important in the overall efficiency/selectivity of the DyKAT, careful consideration of both the rates of formation of each

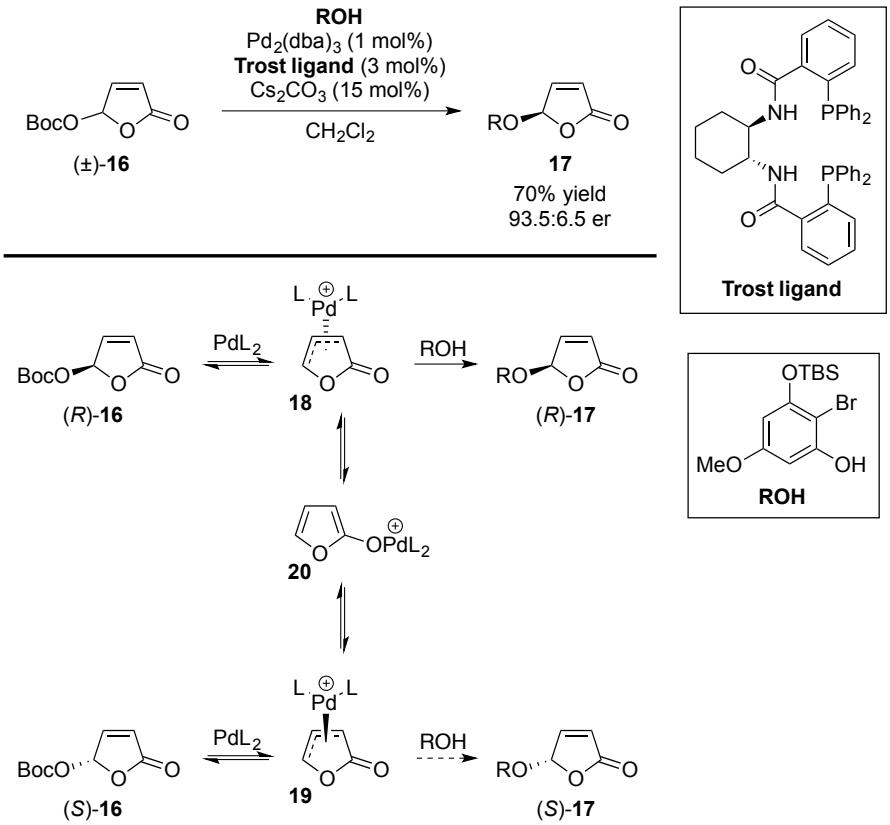
complex (k_{RC*} and k_{SC*}) and the rates of interconversion (k_{RC*C*} and k_{SC*C*}) is required. The rates of both formation and interconversion must be sufficiently fast relative to the time scale of productive reactivity. Interconversion in a DyKAT occurs through a chiral intermediate SC* and is mediated by the chiral catalyst (C*), which differs from DKR where racemization proceeds through an achiral intermediate (I), where racemization is generally mediated by a second achiral catalyst/reagent (**Figure 1-3**). A stark difference from DKR is that in DyKAT the intermediates S_RC^* and S_SC^* are diastereomers and not enantiomers. Since S_RC^* and S_SC^* are diastereomers, the rates of interconversion (k_{RC*C*} and k_{SC*C*}) are not equal suggesting that substrate "racemization" is best classified as an epimerization process. This also means that the concentrations of S_RC^* and S_SC^* are not necessarily equal during the course of the reaction, which can lead to one of two observations during a DyKAT (**Figure 1-5**). In the "matched" case, the rate of conversion of SC* to S_RC^* is *faster* then the rate of conversion of SC* to S_SC^* ($k_{RC*C*} > k_{SC*C*}$), which is matched with the faster product forming pathway (k_{C*R}). This "matched" reactivity results in higher selectivity than what would be observed in a simple DKR. Conversely, if the the rate of conversion of SC* to S_RC^* is *slower* then the rate of conversion of SC* to S_SC^* ($k_{RC*C*} < k_{SC*C*}$), then the selectivity observed in the DyKAT will be lower than a simple DKR since it is "mismatched" with the faster product forming pathway (k_{C*R}).

Figure 1-5. Matched/Mismatched Cases in DyKAT Type I



An early embodiment of DyKAT Type I was disclosed by Trost in the development of a Pd-catalyzed asymmetric allylic alkylation of phenols with racemic γ-acyloxybutenolide **16** (**Scheme 1-5**).[13] Upon ionization of (±)-**16**, two diastereomeric π-allylpalladium complexes **18** and **19** are generated. These diastereomeric η^3-complexes were driven to interconvert through σ-palladium complex **20** by aromatization of furan intermediate **20**. The equilibration of **18** and **19** was found to be faster than nucleophilic attack by the phenolate to afford **17**, rendering the reaction dynamic. Addition of exogenous chloride, ^{n}Bu$_4$NCl (30 mol%), was found to accelerate the interconversion in cases where nucleophilic addition outcompeted the epimerization pathway between **18** and **19**.

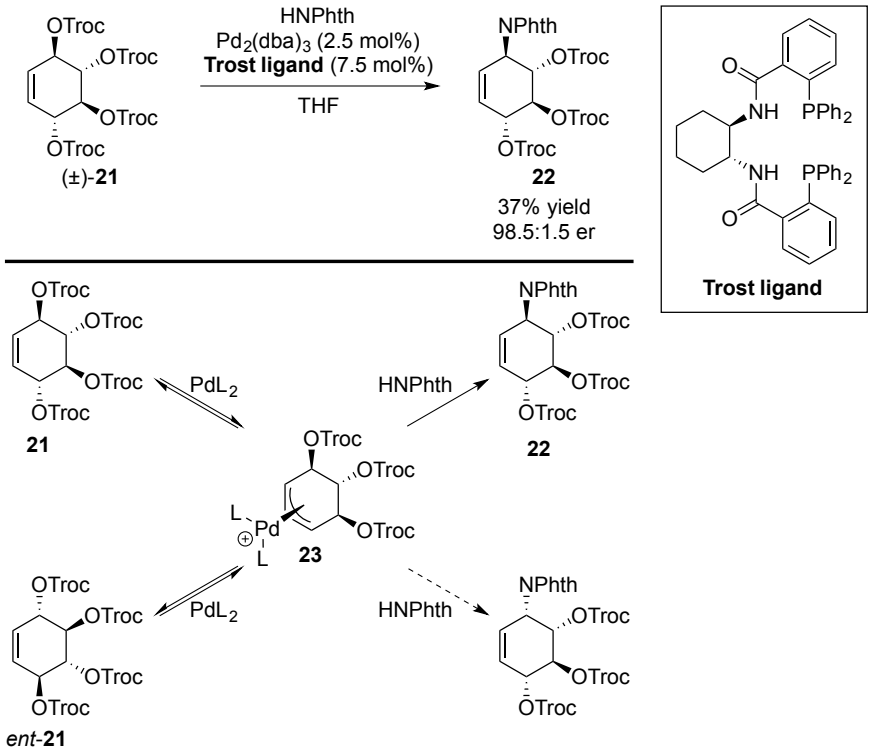
Scheme 1-5. Palladium-Catalyzed Dynamic Kinetic Asymmetric Transformations of γ-Acyloxybutenolides



In a DyKAT Type II, each enantiomer of starting material (S_R and S_S) interacts with the chiral catalyst (C*) to generate a common enantiomeric intermediate SC* (**Figure 1-4**). Interaction of the chiral catalyst results in the loss of stereochemical information held in the starting material through the convergent generation of an achiral fragment associated with a chiral catalyst, thus enabling a racemization pathway if the interaction with the chiral catalyst is reversible. This generated intermediate SC* then directly undergoes subsequent addition to generate the final products (P_R and P_S). Since DyKAT Type II operates through a locally achiral intermediate (SC*), the enantioselectivity observed in the transformation is only dependent on the ratio of the rates of product formation (k_{C*R}/k_{C*S}). The rates at which SC* is formed (k_{RC*} and k_{SC*}) only serve to determine the overall rate of the reaction and have no direct bearing on the enantioselectivity of the transformation. However, if one of the rates of formation for SC* is significantly slower than the other ($k_{RC*} >> k_{SC*}$ or $k_{RC*} << k_{SC*}$), then the reaction will appear to behave as a simple kinetic resolution since once enantiomer is formally unreactive with the chiral catalyst.

Significantly fewer examples of DyKAT Type II exist in the literature relative to Type I. Trost has provided an example utilizing the C_2-symmetry of cyclohexane tetraol conduritol B derivatives in the Pd-catalyzed allylic alkylation of phthalimide (**Scheme 1-6**).[14] Upon ionization of the racemic tetracarbonate **21** with Pd(0), a *meso* π-allylpalladium complex **23** is generated. The chiral Pd-ligand complex employed was found to efficiently ionize both enantiomers of starting material, rendering the reaction dynamic. The symmetric η^3-complex **23** underwent nucleophilic attack by phthalimide with excellent levels of enantioselectivity since addition occurs on the face opposite of the Pd-center and adjacent acetoxy groups.

Scheme 1-6. Palladium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Conduritol B Tetracarboxylates



1.3 Asymmetric Desymmetrization

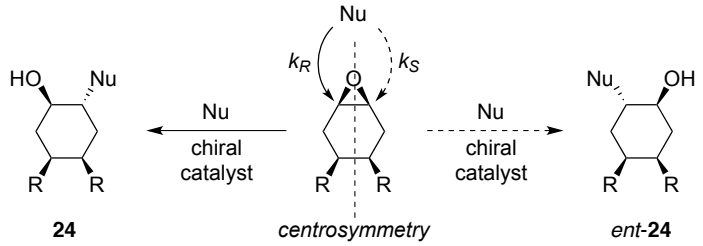
1.3.1 Fundamentals of Desymmetrization

An alternative approach to the preparation of chiral building blocks lies in the ability to convert *meso* or centrosymmetric compounds into enantiopure molecules via a process termed desymmetrization.[15] This paradigm relies on the unique ability of a chiral nucleophile to undergo a symmetry-breaking operation on enantiotopic functional groups under the action of a chiral catalyst or reagent. Since enantioselective desymmetrization relies on the differential rates of reaction of two enantiotopic groups in a chiral environment, it is similar to kinetic resolution. This similarity has allowed for crossover of catalysts developed for kinetic resolutions to desymmetrization processes.[16] While enzymatic enantioselective desymmetrization[17] is a highly

efficient method for the generation of chiral small molecules, subsequent discussion in this section will focus only on catalytic, enantioselective desymmetrization mediated by small molecule chiral catalysts.

In order for an efficient desymmetrization to be realized, highly selective discrimination of enantiotopic functional groups must be achieved (**Scheme 1-7**). Due to their ease of synthesis and centrosymmetry, *meso*-epoxides are commonly employed in desymmetrization reactions. In this example, catalyst-controlled addition of the nucleophile to one of the two enantiotopic carbon atoms of the epoxide results in the selective formation of **24**. This symmetry-breaking operation not only establishes both stereocenters of the former-epoxide, but also demonstrates that remote stereochemistry can be established (R groups) during desymmetrization processes. This reaction, however, is a simplified version of desymmetrization since there is only one reactive functional group; once the epoxide has reacted, the product is inert to further reaction (*vide infra*). Similar to a dynamic kinetic resolution, the selectivity of a desymmetrization process is directly related to the relative rates of addition (k_R/k_S) since the enantiomeric composition of the product remains unchanged during the course of the reaction.

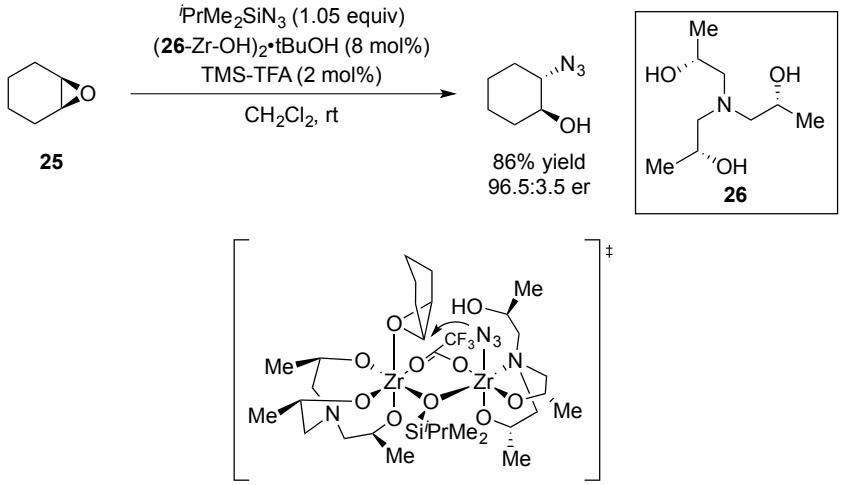
Scheme 1-7. Desymmetrization of *meso*-Epoxides



This first highly selective example of this type of reactivity was provided by Nugent in the development of a Zr(IV)-catalyzed azide opening of *meso*-epoxides (**Scheme 1-8**).[18] A mechanistic investigation into the origin of selectivity in the opening of cyclopropene oxide (**25**)

determined that cooperative interaction of two zirconium-centers was required. Cooridination of the epoxide to one zirconium allows for an intramolecular delivery of the metal-bound azide with high enantiofacial preference. This activation mode has been extensively applied to a variety of epoxide- and aziridine-opening reactions of cyclic and acyclic centrosymmetric compounds with high selectivity.[19]

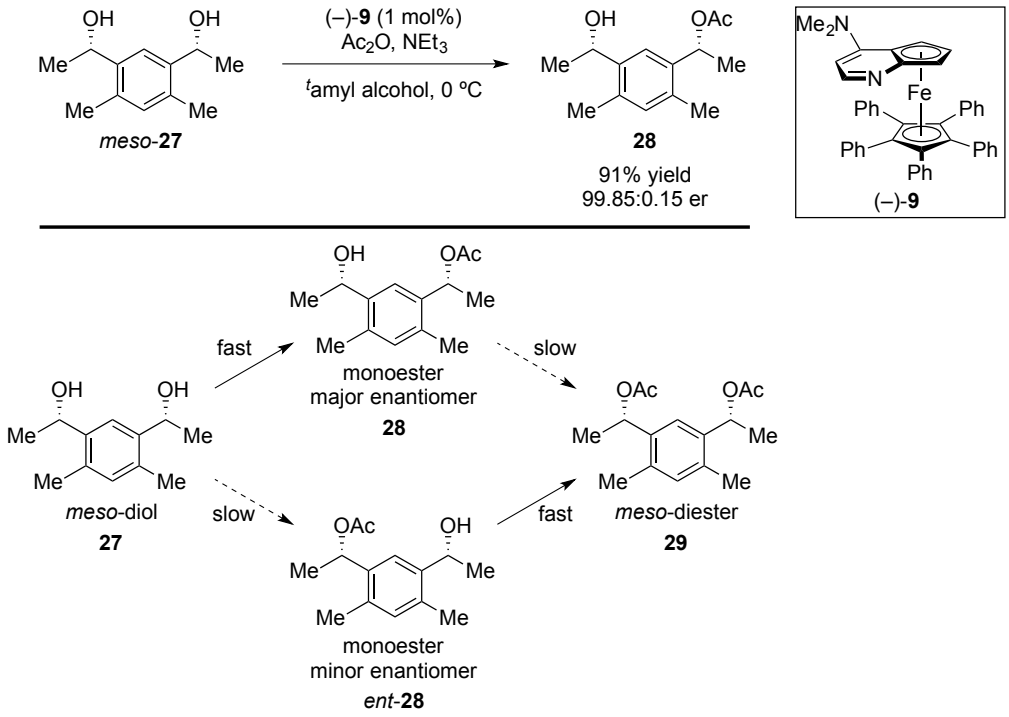
Scheme 1-8. Zirconium-Catalyzed Enantioselective Addition of Azide to *meso*-Epoxides



More complicated desymmetrizations are encountered in systems bearing two reactive enantiotopic functional groups. In these systems, the product contains functional groups that can undergo subsequent transformations under the reaction conditions. As previously described, Fu has developed enantioselective acylation conditions for both kinetic resolution and dynamic kinetic resolution of *sec*-alcohols (**Scheme 1-3**).[9,11] This methodology was then extended to desymmetrization of *meso*-diol **27** to afford the monoester **28** in excellent yield and enantioselectivity employing planar chiral-DMAP (–)-**9** (**Scheme 1-9**).[9b] Diol **27** has two reactive alcohol groups that can undergo acylation under the reaction conditions providing an enantiomeric mixture of monoester **28**. The selectivity of this process is based on the relative rate

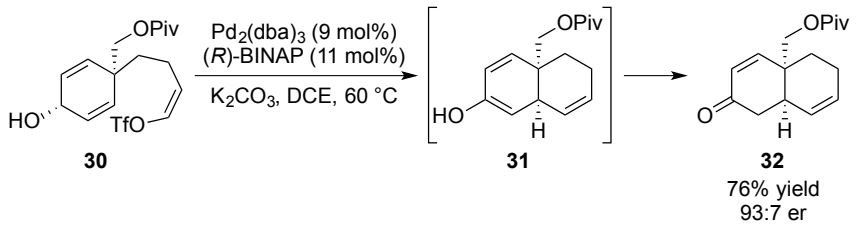
of reaction of the two alcohols. Since the monoacylation product is also reactive under the reaction conditions, the enantiomeric mixture of monoester **28** initially obtained can undergo subsequent kinetic resolution in the presence of (–)-**9**. This kinetic resolution converts the minor enantiomer of the desired product *ent*-**28** into the achiral *meso*-diester **29**. Given the enantiofacial selectivity of the chiral catalyst observed in the initial acylation step, the rate of reaction of *ent*-**28** to the *meso*-diester **29** is faster than the conversion of **28** to the *meso*-diester. By siphoning the minor enantiomer *ent*-**28** from the reaction mixture, the enantioselectivity of the desired product **28** is significantly enhanced. This strategy, governed by the Horeau Principle, is often invoked in the desymmetrization of centrosymmetric compounds bearing two reactive functional groups to amplify stereoselectivity.[20]

Scheme 1-9. Desymmetrization/Kinetic Resolution of *meso*-Diols via Enantioselective Acylation



However, the desymmetrization of achiral compounds bearing two enantiotopic functional groups cannot always be parlayed to a subsequent kinetic resolution. In the majority of examples, the nucleophile is tethered to the electrophile allowing for intramolecular reaction. Due to the inherent rate enhancement of intramolecular reactivity, the second reactive functional group will not undergo subsequent reaction. This reactivity profile was utilized by Shibasaki in the development of a Pd-catalyzed intramolecular Heck-reaction of cyclohexadiene **30** (**Scheme 1-10**).[21] Asymmetric Heck-addition of the vinyl triflate to the allylic alcohol generates enol **31**, which undergoes subsequent tautomerization to the isolated enone **32**. Although enone **32** contains unsaturation that can participate in Heck chemistry itself, productive addition of **30** to **32** would require an intermolecular reaction, which is slower than the observed intramolecular pathway.

Scheme 1-10. Asymmetric Heck Reaction of Cyclohexadienes



1.4 Conclusion

Deracemization and desymmetrization serve as complexity-building methods to directly access functionally rich chiral building blocks from simple achiral, *meso*, and racemic compounds. Although deracemization of a racemate can be achieved through a number of pathways, dynamic kinetic resolution and dynamic kinetic asymmetric transformation are the most utilized methods. DKR and DyKAT both provide direct access to enantiopure products in 100% theoretical yield providing a viable alternative to classical kinetic resolutions. Similarly,

desymmetrization allows for the generation of multiple stereocenters through functionalization of achiral or centrosymmetric compounds. Selective functionalization of enantio- or diastereotopic functional groups rapidly generates molecular complexity with a 100% theoretical yield of chiral material. The principles introduced in this chapter are designed to serve as the conceptual cornerstone of subsequent chapters.

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CHAPTER TWO: BASE-CATALYZED DIRECT ALDOLIZATION OF α-HYDROXY TRIAKLYL PHOSPHONOACETATES*

2.1 Introduction

Catalytic direct aldol reactions offer a convenient method for the rapid construction of β-hydroxy carbonyl compounds through the coupling of carbonyl donors and aldehyde acceptors.[1] The generation of the reactive enolate by a basic or nucleophilic catalyst obviates the need to preform an enolate equivalent. Due to their weak α-acidity, achieving efficient direct aldolization of carbonyl donors in the carboxylic acid oxidation state under mild reaction conditions remains a challenge to the synthetic community. In this chapter, we describe a catalytic direct aldolization of racemic α-hydroxy trialkyl phosphonoacetates to access α-hydroxy-β-phosphonyloxy esters (**Scheme 2-1**). The requisite fully-substituted glycolate enolate was generated *in situ* via [1,2]-phosphonate-phosphate rearrangement under mild proton-transfer conditions. An asymmetric variant was realized upon application of a *P*-spirocyclic chiral iminophosphorane providing excellent levels of diastereo- and enantiocontrol in the aldolization under a DyKAT Type II pathway.

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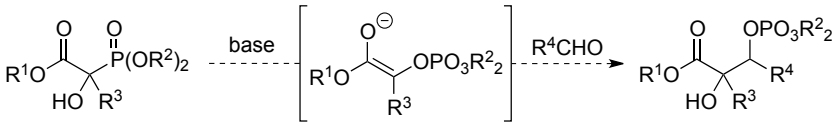
Scheme 2-1. [1,2]-Phosphonate-Phosphate Rearrangement Initiated Direct Aldolization of Glycolate Enolates



2.2 Background

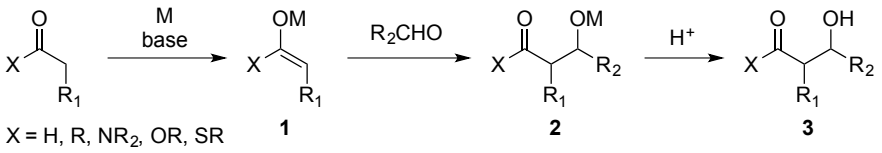
2.2.1 Catalytic Direct Aldolization

The aldol reaction is a simple, yet powerful method for the construction of C–C bonds through the coupling of two carbonyl containing compounds. Generally, the reaction takes place between a pronucleophilic carbonyl and an aldehyde generating β-hydroxy carbonyl compounds. Although aldol reactivity was first observed in the acid-catalyzed dimerization of acetaldehyde,[2] the aldol reaction has matured into a powerful method for the coupling of carbonyl fragments with excellent chemo-, regio-, and stereoselectivity. The related Mannich reaction, the coupling of carbonyl compounds and aldimines, has also been concurrently developed; however, it will not be further discussed in the present context.[3]

In its most general sense, the cross-aldol reaction between a pronucleophilic carbonyl compound (aldehyde, ketone, ester, thioester, amide, etc.) and an aldehyde can be depicted as occurring in three distinct steps (**Scheme 2-2**). Deprotonation of the carbonyl donor generates a metal enolate **1**, which can undergo nucleophilic addition into the aldehyde to generate metal alkoxide **2**. Upon aqueous workup, the metal alkoxide **2** is protonated to afford the desired β-hydroxy carbonyl compound **3**. A requirement for this type of aldolization is the use of a stoichiometric amount of base to selectively generate the metal enolate **1**. An alternative approach would allow for the catalytic generation of the enolate equivalent so that these three steps can occur concurrently in a single process. This approach, however, is hindered by the

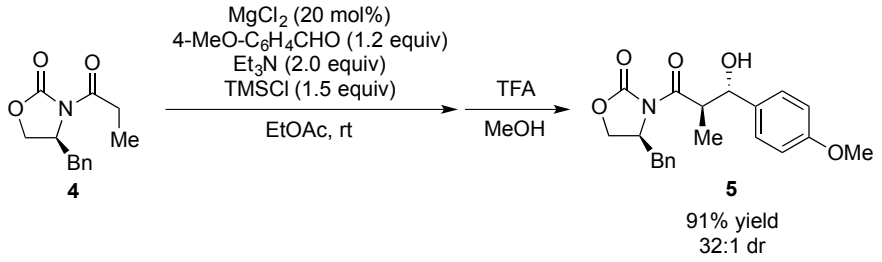
generation of an alkoxide in the product that is more basic than the starting material. Since the product alkoxide **2** is not basic enough to deprotonate the starting material, product inhibition of the catalyst is observed.

Scheme 2-2. General Mechanism for Aldol Reaction



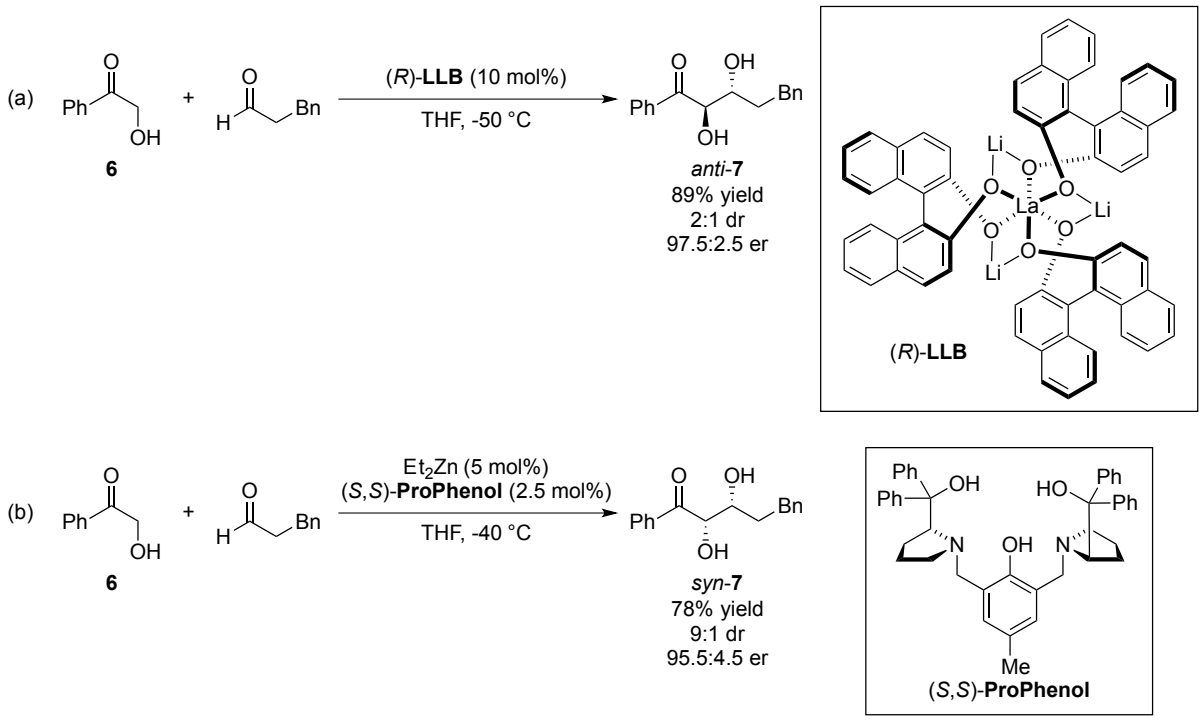
The catalytic direct aldol reaction is a more attractive embodiment of the aldol reaction since it allows for the reaction of two carbonyls in their native form.[1] The key challenge in developing a catalytic direct aldol reaction is identifying a catalytic system that can overcome the product inhibition of metal catalysts (*vide supra*). Evans reported an interesting strategy to overcome this challenge during the development of a highly diastereoselective *anti*-aldol reaction of chiral *N*-acyloxazolidinones (**Scheme 2-3**).[4] Employing soft enolization conditions, the Mg-enolate of **4** was generated and underwent nucleophilic addition into *p*-anisaldehyde. The resulting Mg-alkoxide underwent *in situ* silylation in the presence of TMSCl, which liberated $MgCl_2$ for subsequent enolization of **4**. The obtained silyl ether product could be deprotected in a second step to reveal the desired aldol adduct **5** in excellent yield and diastereoselectivity.

Scheme 2-3. Catalytic Direct Aldolization of Chiral *N*-Acyloxazolidinones



In 2001, Shibasaki and Trost concurrently reported the first two examples of the catalytic direct asymmetric aldol reaction of ketones and aldehydes under chiral base catalysis.[5] Employing heterobimetallic asymmetric catalyst (*R*)-**LLB**, Shibasaki found that 2-hydroxyacetophenone (**6**) was a competent reactant in the direct aldol addition to hydrocinnamaldehyde providing α,β-dihydroxy ketone *anti*-**7** in excellent yield and enantioselectivity, but low diastereocontrol favoring the *anti*-adduct (**Scheme 2-4a**). Similarly, Trost employed a dinuclear zinc catalyst derived from ProPhenol to affect the addition of **6** to hydrocinnamaldehyde providing α,β-dihydroxy ketone *syn*-**7** in good diastereo- and enantioselectivity favoring the opposite *syn*-adduct (**Scheme 2-4b**). Both of these multinuclear catalysts overcome the aforementioned challenges associated with catalytic direct aldolizations by utilizing a dioxygenated aldol donor **6** that is susceptible to tight chelation with metal centers. Furthermore, the propensity of **6** to chelate increases its α-acidity favoring proton-transfer from its enolate to the product **7** eliminating product inhibition of the catalyst and allowing catalyst turnover.

Scheme 2-4. Catalytic Direct Asymmetric Aldolization of α-Hydroxy Ketones

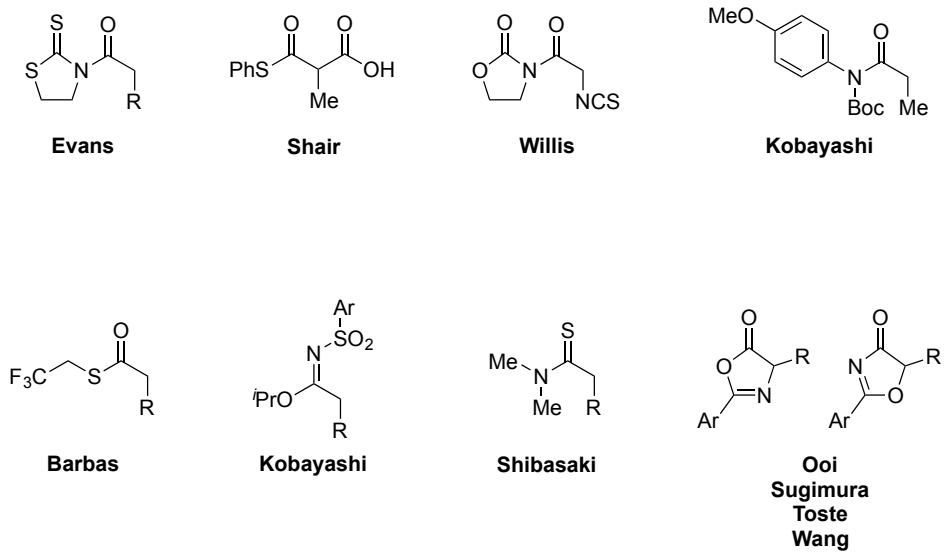


2.2.2 Catalytic Direct Aldolization of Donors in the Carboxylic Acid Oxidation State

Despite the number of successful examples of catalytic direct asymmetric aldolizations in the literature, these methods largely rely on the use of aldol donors in the aldehyde and ketone oxidation state. Ketones and aldehydes can be readily employed as aldol donors due to their relatively high α-acidity (by Brønsted base catalysis) or their ability to form an enamine (by Lewis base catalysis).[5,6] Catalytic direct aldol reactions involving donors in the carboxylic acid oxidation state are considerably more elusive.[7] Mechanistic nuances of these reactions are more diverse and reactions that give products that are fully-substituted at the α-carbon atom are difficult to achieve due to steric and electronic factors. In order to achieve catalytic direct aldolization of donors in the carboxylic acid oxidation state, a number of groups have developed and employed exotic ester surrogates (**Scheme 2-5**). These surrogates have found ample success

in aldol and Mannich-type reactions by effectively increasing the α-acidity of the donor group to enable Brønsted base catalysis. Although they address the fundamental challenge associated with this class of substrates, they often require numerous steps to convert the masked ester functionality into a tractable handle for further manipulation.

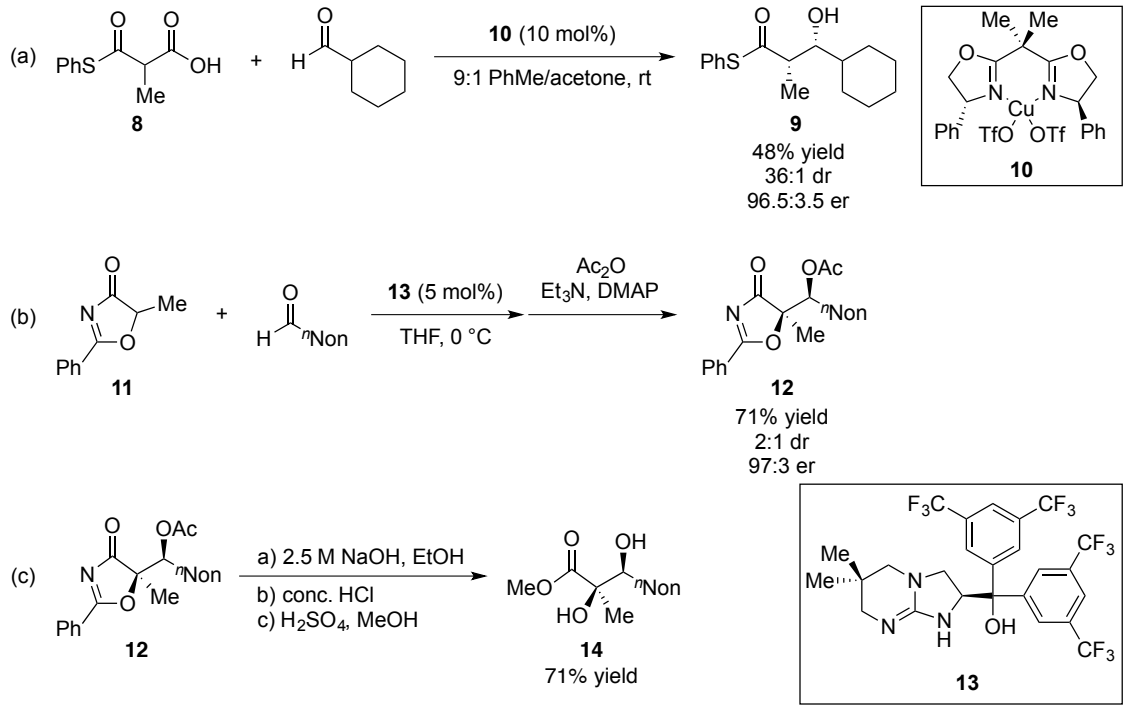
Scheme 2-5. Ester Surrogates Commonly Employed in Catalytic Direct Aldolizations



In 2005, Shair reported a novel approach to address these challenges through the use of a Cu(II)-catalyzed decarboxylative thioester aldol reaction (**Scheme 2-6a**).[7b] Employing malonic acid half thioester **8** as an ester enolate equivalent in the presence of a (*R*,*R*)-Cu(II)-catalyst **10**, the aldolization/decarboxylation sequence was found to be facile with cyclohexanecarboxaldehyde providing the aldol adduct **9** with excellent stereocontrol. This reaction is remarkable in that it proceeds under mild reaction conditions, is tolerant of base and acid sensitive functional groups, and utilizes traceless activation of the ester moiety (the carboxylic acid moiety is lost as CO_2 during the reaction). More recently, Misaki and Sugimura disclosed a method for the preparation of α,β-dihydroxy carboxylic acid derivatives featuring a

fully-substituted α-carbon atom (**Scheme 2-6b**).[7g] In order to achieve this challenging C–C bond construction, 5*H*-oxazol-4-one **11** was employed as the aldol donor in the catalytic direct asymmetric addition into decanal catalyzed by chiral guanidine **13**. Following acylation of the product to avoid retro-aldol, the protected diol **12** was isolated in high yield albeit poor diastereoselectivity. However, a 3-step sequence is required to unveil the α,β-dihydroxy ester functionality of **12**, highlighting the importance of methodologies that deliver products in their native form (**Scheme 2-6c**).

Scheme 2-6. Catalytic Direct Asymmetric Aldolizations



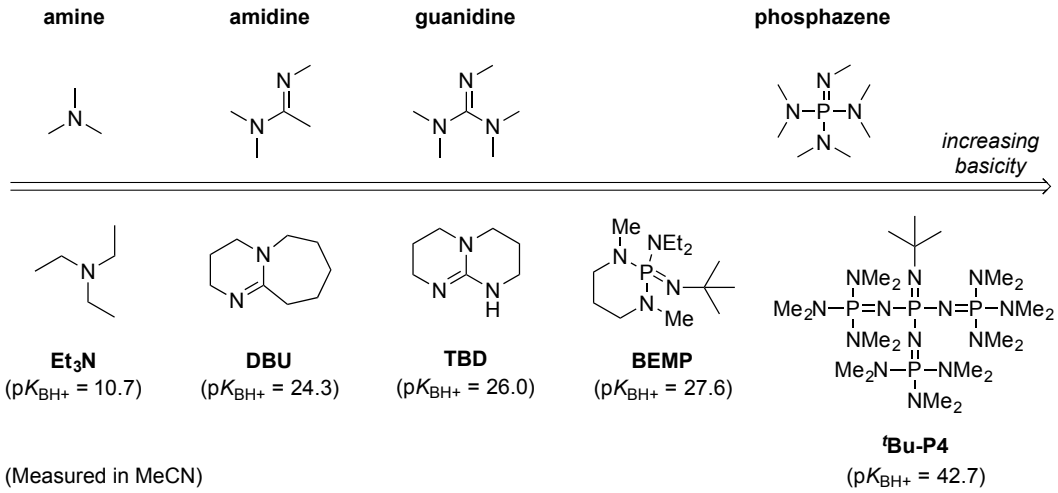
2.2.3 Chiral Organic Superbases

In the context of organic chemistry, a Brønsted base is fundamentally defined as any reagent that is capable of abstracting a proton (H^+) to generate an anionic species where the *strength* of a base is measured by its pK_{BH+}. Given this widely accepted basic understanding of acid-base theory, a superbase can be inferred as being any compound that has a very high basicity. This undescriptive classification of superbases relies solely on an arbitrary quantification of a base's properties relative to other bases. Caubère, however, has proposed a qualitative perspective to the classification of superbases: "The term "super bases" should only be applied to bases resulting from a mixing of two (or more) bases leading to new basic species possessing inherent new properties. The term super base does not mean a base is thermodynamically and/or kinetically stronger than another. Instead it means that a basic reagent is created by combining the characteristics of several different bases."[8] Given this generalized definition, super bases can be organic, organometallic, or inorganic in nature. Within the context of this chapter, only organic superbases will be further discussed.

Organic superbases are generally classified based on the number of substituted nitrogen functional groups bound to a central atom (carbon or phosphorous) due to their direct impact on the Brønsted basicity of the species.[9] Given this relationship, the general organic base classifications (in increasing Brønsted basicity) are amine, amidine, guanidine, and phosphazene (**Scheme 2-7**). In addition to their strong basicity, organic superbases possess numerous physical properties that render them more attractive than their organometallic and inorganic contemporaries. Generally, they are non-metallic, non-ionic neutral species that can be employed under mild proton-transfer reaction conditions. Relative to charged bases, they exhibit heightened reactivity, low nucleophilicity, and are highly soluble in a range of solvents. Given

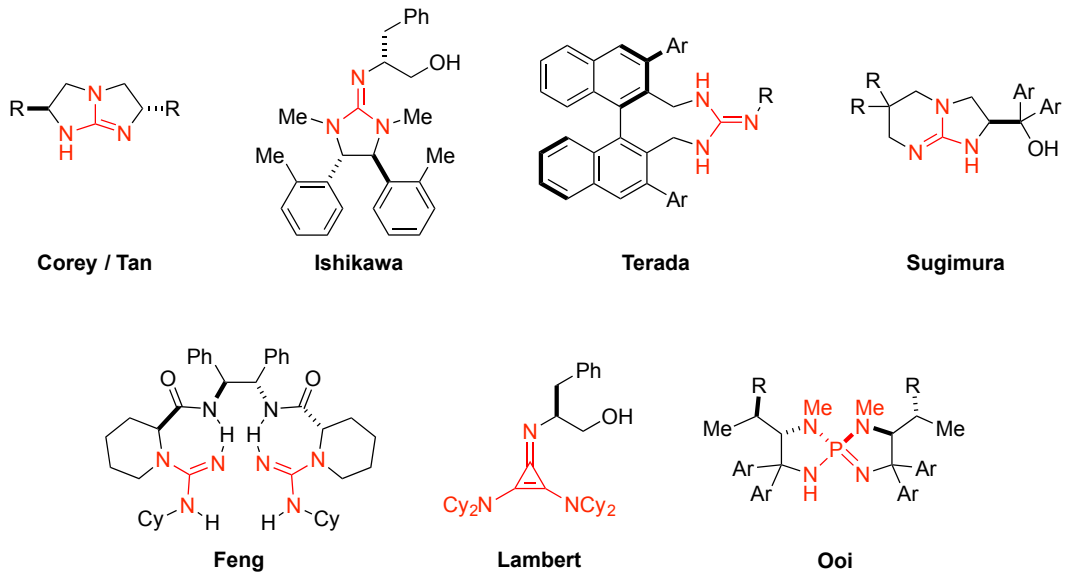
their air and moisture stability, they are highly robust and polymer-supported superbases have even found application in flow processes.[10]

Scheme 2-7. Relative Basicity of Organic Superbases



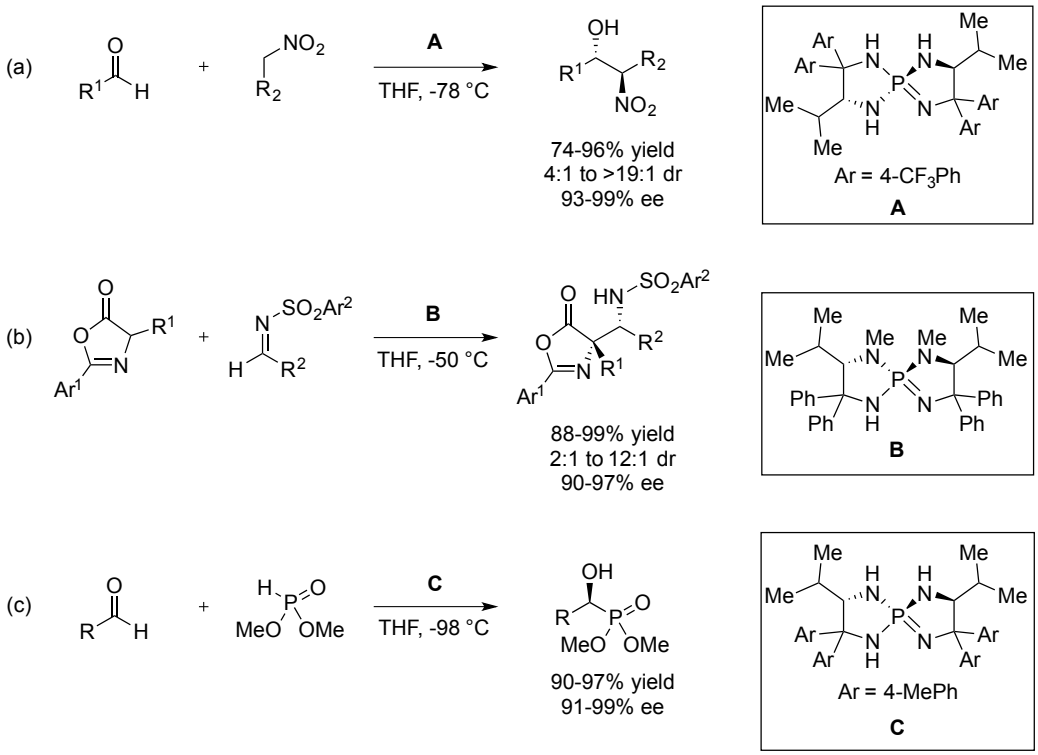
Their unique physical and chemical properties have not been ignored by the synthetic community, leading to the development of a range of uniquely structured chiral variants. A number of groups have elegantly developed catalysts for the generation of carbon, nitrogen, oxygen, phosphorus, and sulfur centered nucleophiles under proton-transfer conditions.[11] The most prevalent class of chiral organic superbases found in the literature are derived from guanidine or phosphazene frameworks since their conjugate acids are capable of participating in dual hydrogen-bonding (**Scheme 2-8**).[12]

Scheme 2-8. Organic Superbases



Phosphazenes (or iminophosphoranes) were first prepared and characterized in the mid-1970s;[13] however, their physical properties were not fully-explored until work by Schwesinger.[14] Related proazaphosphatrane systems have been developed by Verkade; however, realization of a chiral system would prove difficult due to their structural nuances.[15] Compared to guanidines, chiral phosphazene bases are much less studied despite their potential ability to serve as stonger bases, which could allow for the realization of previously unattainable reaction profiles. Although only one chiral iminophosphorane architecture has been reported in the literature to date by Ooi, there has been a renewed interest in the application of quaternary phosphonium salts in asymmetric synthesis.[16] Since their seminal report in 2007, Ooi and coworkers have disclosed several amino acid-derived spirocyclic catalysts that have found broad application in a range of activation modes (**Scheme 2-9**).[17]

Scheme 2-9. Representative Applications of Chiral Iminophosphoranes in Asymmetric Catalysis

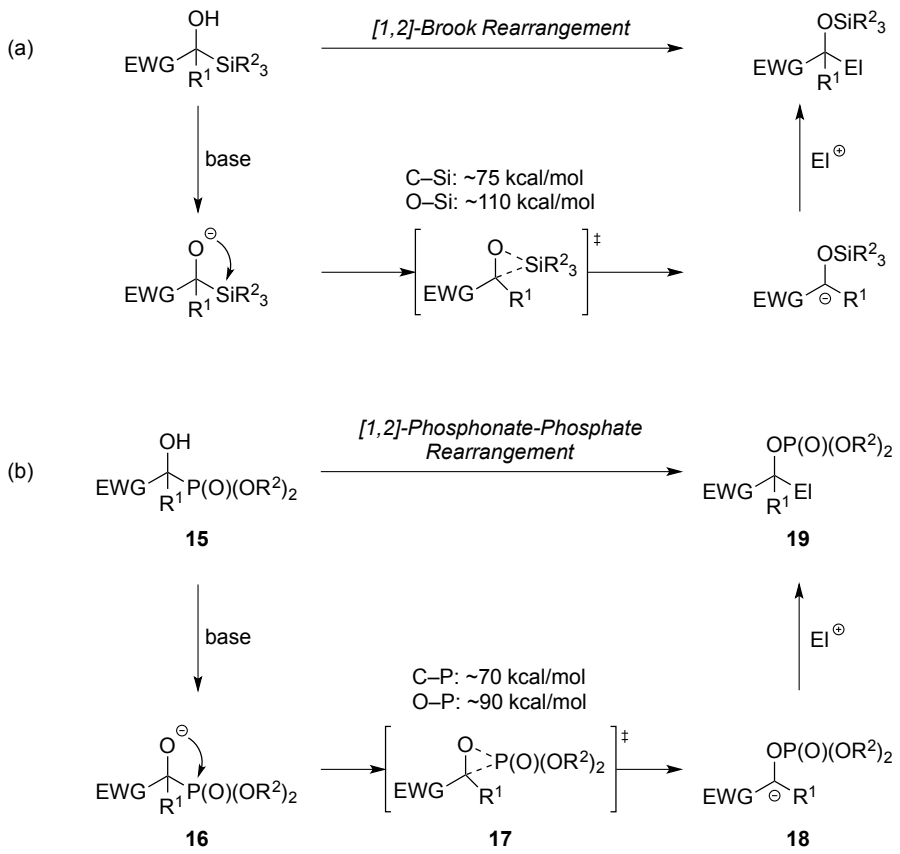


2.2.4 [1,2]-Phosphonate-Phosphate Rearrangement

Although analogous to the well-studied isoelectronic [1,2]-Brook rearrangement (**Scheme 2-10a**), the [1,2]-phosphonate-phosphate rearrangement, colloquially referred to as the Phospha-Brook rearrangement, of α-hydroxy phosphonates **15** is comparatively underutilized (**Scheme 2-10b**).[18] Similarly to the [1,2]-Brook rearrangement, the [1,2]-phosphonate-phosphate rearrangement is initiated by the generation of an alkoxide intermediate **16**. This alkoxide can initiate the [1,2]-phosphinyl migration that is proposed to proceed through a three-center four-electron bond as depicted in intermediate **17**. This transition state intermediate is rapidly converted to the carbanion **18** when an electron-withdrawing group is present to stabilize the developing charge on carbon. This migration is favored by the strength of the P–O bond being

formed relative to the P–C bond being broken (favored by ~20 kcal/mol). The carbanion **18** can then be trapped by an appropriate electrophile to provide the expected phosphate **19**.

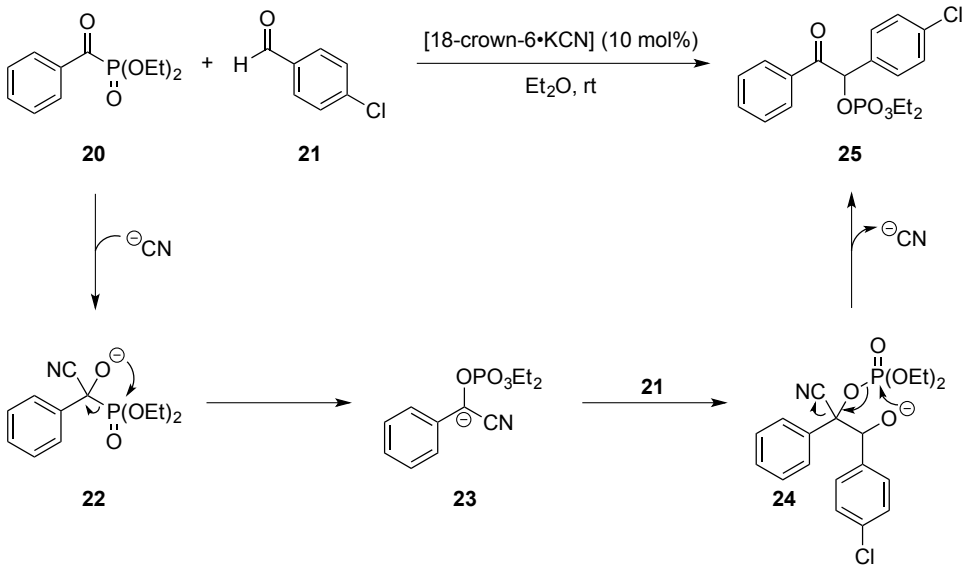
Scheme 2-10. Applications of Chiral Iminophosphoranes in Asymmetric Catalysis



Since Fitch and Moedritzer first observed the [1,2]-phosphonate-phosphate rearrangement in 1962,[19] it has been employed in the formal racemic and enantioselective reduction of α-keto esters (El = H, **Scheme 2-10b**);[20] however, it has only found sparing utility in C–C bond forming reactions.[21] The [1,2]-phosphonate-phosphate rearrangement was utilized in our laboratory by Cory Bausch during the development of a cyanide-catalyzed cross-benzoin reaction (**Scheme 2-11**).[21b] In this instance, the cyanide catalyst serves a dual purpose in that it not only promotes umpolung reactivity, but also serves as a transient electron-withdrawing group

to promote the [1,2]-phosphonate-phosphate rearrangement. Treatment of acyl phosphonate **20** with cyanide generated the tetrahedral intermediate **22**, which underwent [1,2]-phosphinyl migration to generate the carbanion **23**. Quenching the carbanion **23** with 4-chlorobenzaldehyde (**21**) generated a secondary alkoxide **24** that could undergo subsequent [1,4]-phosphinyl migration from the hindered tertiary alcohol to the secondary alcohol. Subsequent expulsion of the cyanide catalyst results in the formation of α-keto phosphate **25** in 80% yield.

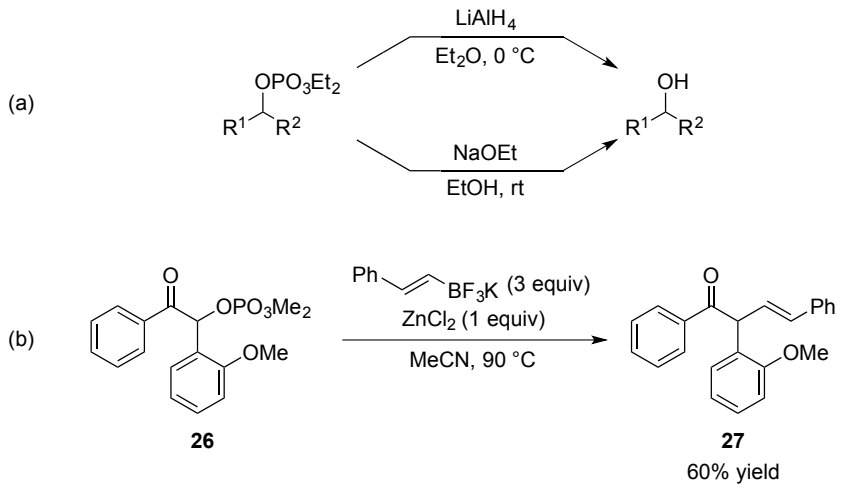
Scheme 2-11. Cyanide-Catalyzed Phospha-Benzoin Reaction



A mechanistic nuance of the [1,2]-phosphonate-phosphate rearrangement is the generation of a versatile phosphonyloxy moiety that can be either cleaved to reveal the alcohol or directly employed as an electrophile in subsequent transformations. The cleavage of phosphates has been achieved under reduction[22] or transesterification[21b,21f] conditions providing access to the alcohol moiety (**Scheme 2-12a**). Alternatively, the electrophilic nature of the phosphonyloxy moiety can be utilized in alkylation reactions through Friedel–Crafts (S_N1) or S_N2 pathways.[23] The former was developed in our laboratory by Austin Smith employing α-keto phosphates

obtained via the aforementioned cross-benzoin reaction (**Scheme 2-12b**).[23d] Lewis acid promoted ionization of the phosphonyloxy moiety in **26** generated a benzylic carbenium ion that was trapped with a potassium trifluoroborate styrenyl salt to provide adduct **27** in good yield. This methodology was applicable for a range of carbon-, nitrogen-, and sulfur-centered nucleophiles and mechanistic studies showed that the reaction proceeded through a S_N1 pathway.

Scheme 2-12. Synthetic Manipulations of Alkyl Phosphates

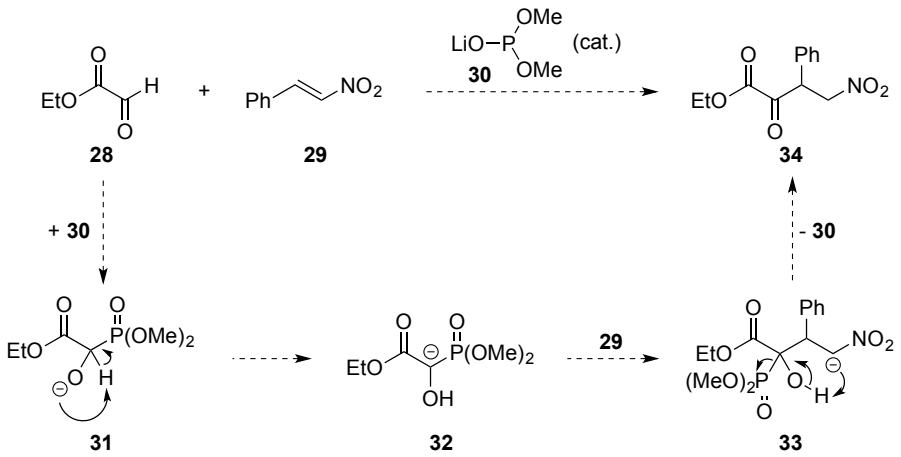


2.2.5 Proposed Application of α-Hydroxy Phosphonoacetates as Glyoxylate Anion Equivalents

The genesis of the present work stemmed from our interest in the development of new glyoxylate anion equivalents for the preparation of β-stereogenic-α-keto esters.[24] Our strategy would rely on the use of ethyl glyoxylate (**28**) as our acyl donor in the presence of a phosphite catalyst **30** to achieve Stetter reactivity (**Scheme 2-13**). We envisaged phosphite addition into ethyl glyoxylate via Pudovik reaction would generate an alkoxide **31** that could deprotonate the strong carbon acid to provide the doubly stabilized carbanion **32**. Subsequent addition of enolate **32** to β-nitrostyrene (**29**) would provide nitronate **33**. Proton-transfer and concomitant expulsion of phosphite would afford β-aryl-α-keto ester **34** and turn over the catalyst. Given our group's

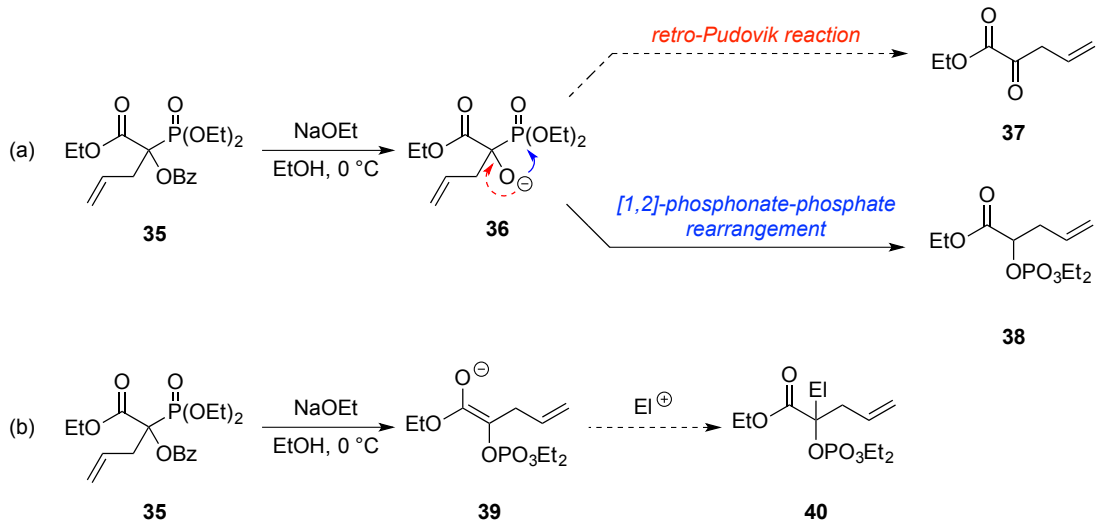
previous success in the application of nucleophilic chiral phosphite catalysts, we envisaged the potential development of an asymmetric variant.[25]

Scheme 2-13. Proposed Phosphite-Catalyzed Stetter Reaction of Glyoxylates



We reasoned that although [1,2]-phosphonate-phosphate rearrangement was possible from intermediate **36**, its steric requirements would favor expulsion of phosphite via retro-Pudovik reaction versus [1,2]-phosphinyl migration (**Scheme 2-14**). In order to test this hypothesis, we prepared fully-substituted α-benzoyloxy phosphonacetate **35** and subjected it to basic conditions, which would provide access to the key intermediate alkoxide **36** (**Scheme 2-14a**). Instead of undergoing retro-Pudovik reaction to provide the desired α-keto ester **37**, clean conversion to α-phosphonyloxy ester **38** via [1,2]-phosphonate-phosphate rearrangement was observed. Although desired reactivity was not observed, we were intrigued by the facile generation of a fully-substituted glycolate enolate **39** from α-hydroxy phosphonoacetate derivative **35** and wondered if we could intercept this intermediate with an electrophile to access fully-substituted α-glycolic acid derivative **40** (**Scheme 2-14b**).

Scheme 2-14. Mechanistic Divergence from Proposed Reactivity



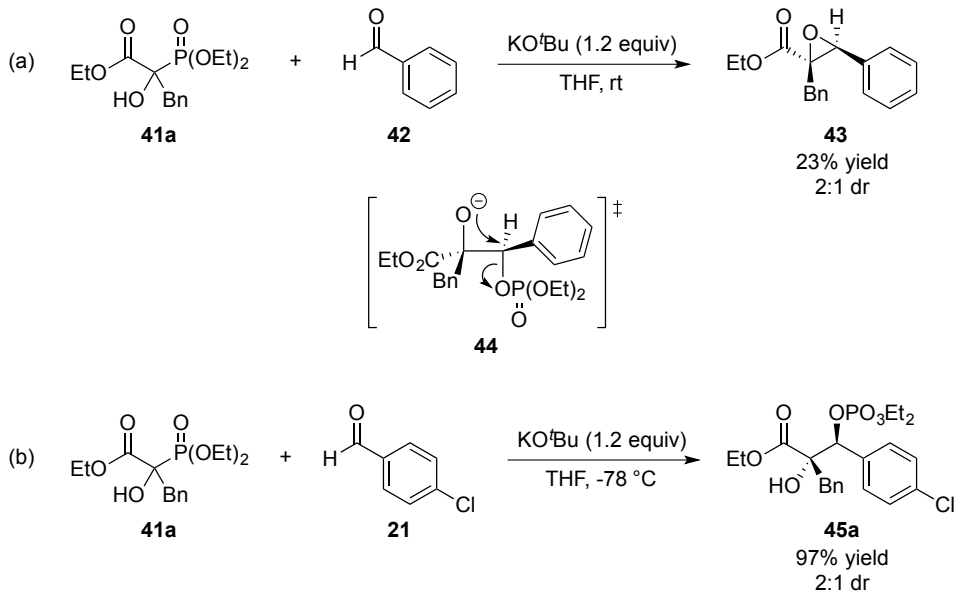
2.3 Results and Discussion

2.3.1 Discovery of Title Reaction

We commenced our studies by examining the reactivity profile of α-hydroxy phosphonoacetate **41a**, which was prepared in two steps from commercially available ethyl glyoxylate on multigram scale. Treating a solution of α-hydroxy phosphonoacetate **41a** and benzaldehyde (**42**) with KO^{t}Bu (1.2 equiv) at room temperature resulted in the exclusive formation of glycidic ester **43** in 2:1 dr (**Scheme 2-15a**). After careful consideration of mechanistic pathways that would lead to **43**, we proposed that it arised via a Darzens-type pathway.[26] Following base-mediated [1,2]-phosphonate-phosphate rearrangement, the glycolate enolate underwent aldolization with benzaldehyde and subsequent [1,4]-phosphinyl migration to provide the expected tertiary alkoxide **44**. However, this species is labile under alkaline conditions at room temperature rapidly undergoing intramolecular S_N2 displacement of the vicinal phosphate forming glycidic ester **43**. Although the Darzens-type pathway was operational at room temperature, cooling the reaction to -78 °C resulted in exclusive formation of the desired

aldol adduct **45a** from **41a** and 4-chlorobenzaldehyde (**21**) in 97% yield with 2:1 dr under otherwise identical conditions (**Scheme 2-15b**).

Scheme 2-15. Thermodynamically-Controlled Mechanistic Divergence in Aldolization

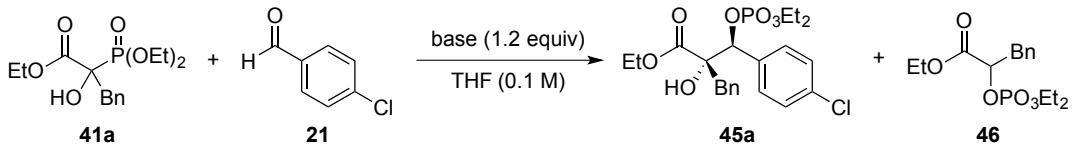


2.3.2 Optimization of Donor Structure and Reaction Conditions

Although the chemical efficiency of the reaction was excellent, the lack of diastereocontrol employing KO^{t}Bu was a topic of interest. Chelation-control is a commonly employed strategy in carbonyl addition reactions and a number of groups have studied the effects of the metal counterion in controlling diastereoselectivity.[27] A screen of inorganic bases was conducted to probe the role of the counterion's identity due to its potential effects on diastereocontrol in the aldolization (**Table 2-1**). The identity of the counterion of the base, however, was found to have little effect on the selectivity, with LiO^{t}Bu providing comparable results and NaO^{t}Bu giving the lowest diastereoselection (entries 2 and 3). A higher reaction temperature was required for MgBrO^{t}Bu and Cs_2CO_3 to initiate the [1,2]-phosphonate-phosphate rearrangement and competitive enolate quenching was observed, resulting in the formation of **46**

(entries 4 and 5). Although MgBrO^{t}Bu did not perform as well as KO^{t}Bu in the reaction, it provided an unexpected switch in diastereoselection now favoring a *syn*-relationship between the alcohols in a 2:1 dr. Other bases such as LiOEt or KHMDS were compatible with the reaction providing **45a** in comparable diastereoselectivity albeit reduced yields (entries 6 and 7).

Table 2-1. Counterion Effect on Aldol Diastereoselectivity[a]



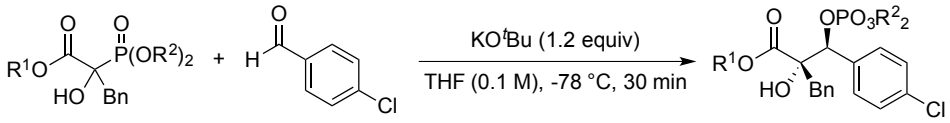
entry	base	T (°C)	t (min)	yield (%)[b] 45a	46	dr[b] (*anti*:*syn*)
1	KO^{t}Bu	-78	30	97	–	2.0:1.0
2	NaO^{t}Bu	-78	30	88	–	1.2:1.0
3	LiO^{t}Bu	-78	30	81	–	1.9:1.0
4	MgBrO^{t}Bu	-78 to rt	360	35	11	1.0:2.0
5	Cs_2CO_3	-78 to rt	360	41	58	2.0:1.0
6	LiOEt	-78	30	67	–	2.0:1.0
7	KHMDS	-78	60	74	19	2.2:1.0

[a]Reactions were performed on 0.10 mmol scale employing 1.5 equiv. of aldehyde in THF (1.0 mL). [b]Yields and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard.

Since the identity of the base provided little effect on the selectivity of the aldolization, we turned our attention to an examination of the structural properties of the α-hydroxy phosphonoacetate (**Table 2-2**). Due to their modularity and ease of synthesis, the ester and phopshonate groups of the α-hydroxy phosphonoacetate can be easily tuned. Ethyl and methyl groups were found to be highly interchangeable providing comparable levels of selectivity and reactivity (entries 1-3). Increasing the bulk of the phosphonate moiety through the use of diisopropyl groups provided a slight increase in diastereoselectivity (entry 4). Remarkably, the diisopropyl phosphonate provided the aldol adduct in 94% NMR yield despite the substantial

increase in the steric demand of the nucleophilic enolate. Employing a bulkier ^{t}Bu ester resulted in deterioration of diastereocontrol with a slight preference for the opposite *syn*-diastereomer as the major isomer (entry 5). Although the diisopropyl phosphonate provided the highest levels of diastereoselectivity in the aldolization, we continued our studies with the diethyl phosphonate due to the cost/commercial availability of the starting dialkyl phosphites.

Table 2-2. Stereochemical Effects of Carboxy and Phosphonate Ester Identity[a]

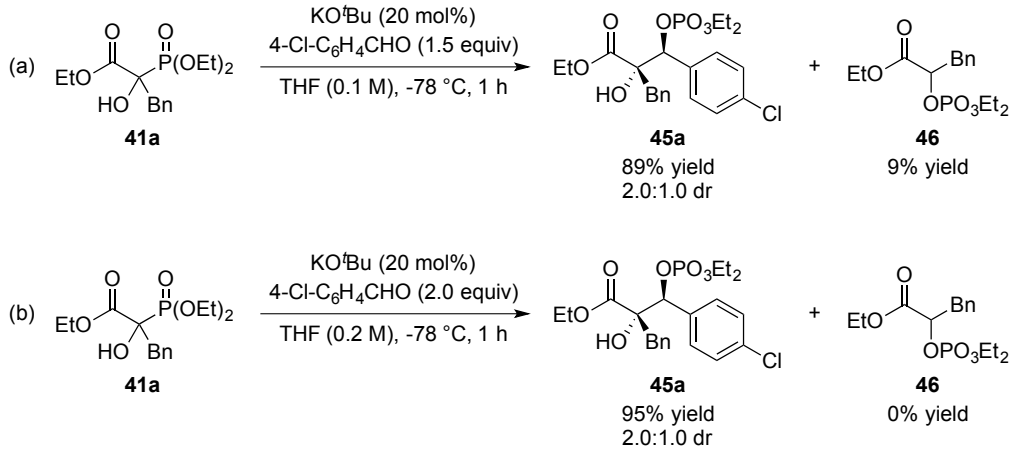


entry	R^1	R^2	yield (%)[b]	dr[b] (*anti*:*syn*)
1	Et	Et	97	2.1:1.0
2	Et	Me	95	2.1:1.0
3	Me	Me	94	1.7:1.0
4	Me	^{i}Pr	94	2.6:1.0
5	^{t}Bu	Me	89	1.0:1.3

[a]Reactions were performed on 0.10 mmol scale employing 1.5 equiv. of aldehyde in THF (1.0 mL). [b]Yields and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard.

Having identified an optimal α-hydroxy phosphonoacetate and base, we became interested in rendering the reaction catalytic in base. Gratifyingly, reducing the loading of KO^{t}Bu from 120 mol% to 20 mol% resulted in nearly identical reactivity with only a small amount of the quenched enolate **46** observed (**Scheme 2-16a**). The formation of **46** was completely suppressed by increasing both the equivalents of aldehyde and reaction concentration resulting in the isolation of **45a** in 95% yield with 2:1 dr (**Scheme 2-16b**).

Scheme 2-16. Exploration of Catalytic Conditions in the Aldolization

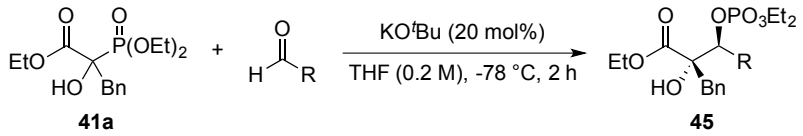


2.3.3 Examination of Substrate Scope in Catalytic Direct Aldolization

With high-yielding reaction conditions established (**Scheme 2-16b**), we examined the scope of the reaction by varying the aldehyde used in the aldolization of **41a** (**Table 2-3**). The use of electron-poor and electron-neutral aromatic aldehydes afforded the products in excellent yield, albeit with marginal diastereoselectivity (entries 1-10). The use of electron-rich aromatic, alkenyl, and alkyl aldehydes afforded product with a notable enhancement in *anti*-diastereoselectivity and the use of an excess amount (5.0 equivalents) was optimal in these cases (entries 11, 13, and 14). Heteroaromatic aldehydes, such as 2-thiophenecarboxaldehyde, provided product in good yield and 7:1 diastereoselection (entry 12). However, column chromatography purification of **45l** resulted in the cleavage of the phosphate moiety and the *anti*-diol was isolated in 81% yield in 19:1 dr. We propose that this unusual result is attributed to the strong donating ability of the 2-thienyl moiety resulting in ionization of the phosphate group on acidic SiO_2 with diastereoselective trapping of the carbenium ion with exogenous H_2O, which is mechanistically consistent with subsequent Friedel–Crafts experiments (*vide infra*). Product isolation typically only consisted of separation of the product from excess aldehyde. The major

byproduct formed during the reaction is the quenched glycolate enolate **46**. Bulkier aldehydes such as isobutyraldehyde and pivaldehyde were not tolerated under the reaction conditions.

Table 2-3. Scope of Aldehyde Partners[a]

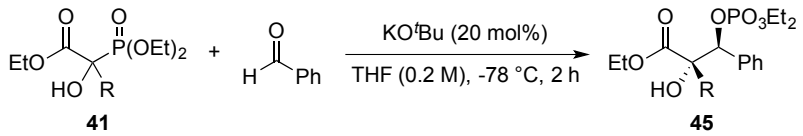


entry	R	45	yield (%)[b]	dr[c] (*anti*:*syn*)
1	4-Cl-C_6H_4	**45a**	95	2.0:1.0
2	2-F-C_6H_4	**45b**	91	2.3:1.0
3	2-NO_2-C_6H_4	**45c**	87	1.5:1.0
4	3-NO_2-C_6H_4	**45d**	92	2.4:1.0
5	4-NO_2-C_6H_4	**45e**	95	2.8:1.0
6	4-CF_3-C_6H_4	**45f**	91	2.1:1.0
7	4-CN-C_6H_4	**45g**	93	2.4:1.0
8	C_6H_5	**45h**	97	2.1:1.0
9	4-F-C_6H_4	**45i**	98	2.1:1.0
10	4-Me-C_6H_4	**45j**	97	2.0:1.0
11[d]	4-MeO-C_6H_4	**45k**	89	4.9:1.0
12	2-thienyl	**45l**	81[e]	6.7:1.0
13[d]	(*E*)-CH=CHPh	**45m**	89	4.4:1.0
14[d]	CH_2CH_2Ph	**45n**	78	5.8:1.0

[a]Unless otherwise noted, reactions were performed on 0.20 mmol scale employing 2.0 equiv. of aldehyde in THF (1.0 mL) at -78 °C for 2 h. [b]Yield of isolated product. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]With 5.0 equiv. of aldehyde. [e]Product isolated as the *anti*-diol in 19:1 dr following column chromatography.

The scope of the α-hydroxy phosphonate coupling partner was investigated, with benzaldehyde as the other partner, by varying the α-substituent (**Table 2-4**). The presence of an α-substituent was found to be critical: reactions where R = H suffered from poor reactivity (<5% conversion; entry 1). In addition to the benzyl group, other alkyl substituents were well-tolerated under the reaction conditions, thus allowing for the incorporation of functional handles such as terminal alkenes and alkynes (entries 3 and 4).

Table 2-4. Scope of α-Hydroxy Phosphonoacetate Partners[a]



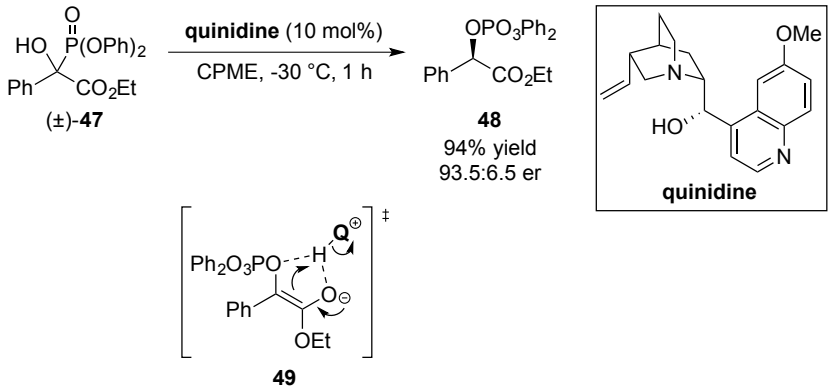
entry	R	45	yield (%)[b]	dr[c] (*anti*:*syn*)
1	H (**41f**)	**45o**	trace	–
2	CH_3 (**41b**)	**45p**	81	1.9:1.0
3	$CH_2CH{=}CH_2$ (**41c**)	**45q**	89	1.2:1.0
4	$CH_2{\equiv}CH$ (**41d**)	**45r**	93	2.9:1.0
5	CH_2Ph (**41a**)	**45h**	97	2.1:1.0

[a]Reactions were performed on 0.20 mmol scale employing 2.0 equiv. of aldehyde in THF (1.0 mL) at -78 °C for 2 h. [b]Yield of isolated product. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture.

2.3.4 Re-examination of Catalysts for the Direct Aldolization

Having established a baseline protocol for achieving a new catalytic direct ester aldol addition, efforts were directed at improving the modest reaction diastereoselectivity and developing an enantioselective variant of the title reaction. Given the poor stereochemical control provided by inorganic bases, we turned our attention to an examination of organic bases that could achieve the desired reactivity profile. During the development of our aldolization reaction, Nakamura reported a [1,2]-phosphonate-phosphate rearrangement of α-hydroxy phosphonoacetates featuring an enantioselective protonation mediated by quinidine (**Scheme 2-17**).[20d] Quinidine is proposed to deprotonate the alcohol **47** triggering [1,2]-phosphinyl migration to provide chiral ion-paired enolate **49**. Enantioselective protonation of **49** by the intimate ion-paired chiral ammonium salt results in the formation of **48** in excellent yield and enantioselection.

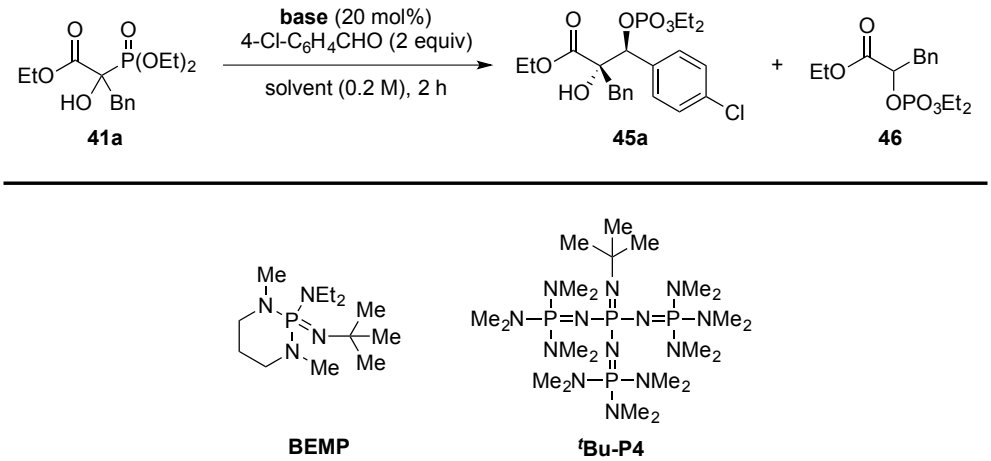
Scheme 2-17. Asymmetric [1,2]-Phosphonate-Phosphate Rearrangement via Enantioselective Protonation



Nakamura's work indicated that chiral organic bases could promote the [1,2]-phosphonate-phosphate rearrangement of α-hydroxy phosphonoacetates; however, we would need to carefully tune reaction conditions to promote aldolization instead of undesired protonation of the transient enolate. With this in mind, we screened a series of strong organic bases under our previously optimized reaction parameters (**Table 2-5**). Schwesinger's base (^{t}Bu-P4) provided similar results to KO^{t}Bu, but provided aldol adduct **45a** in 3:1 dr favoring the opposite *syn*-diastereomer (entry 2). Considering the relative basicities of known chiral guanidine and iminophosphorane catalysts in the literature (**Scheme 2-8**), we next explored BEMP, which has a comparable pK_{BH+} to these chiral catalysts. BEMP unfortunately did not promote the [1,2]-phosphonate-phosphate rearrangement of **41a** at -78 °C requiring elevated temperature to initiate the migration. In THF, the reaction at 0 °C proceeded cleanly to full conversion providing 34% NMR yield of *syn*-**45a** in 2:1 dr, but the major product was **46** suggesting that enolate quenching was a competing process (entry 3). In order to better understand the origin of this observation, the reaction with BEMP was rerun in various solvents: toluene, CH_2Cl_2, MeCN, and DMF (entries 4-7). Although no improvement in the ratio of **45a**:**46**

was observed, reactions in more polar solvents such as MeCN and DMF resulted in a noticeable increase in diastereoselection up to 6:1 and 8:1, respectively, favoring *syn*-**45a**.

Table 2-5. Organic Bases in Direct Aldolization Reaction[a]



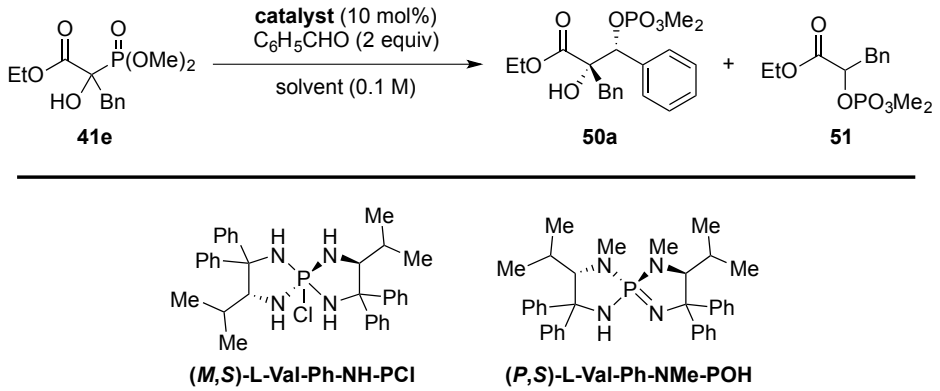
entry	base	solvent	T (°C)	yield (%)[b] 45a	yield (%)[b] 46	dr[b] (*anti*:*syn*)
1	KO^{t}Bu	THF	-78	98	–	1.9:1.0
2	^{t}Bu-P4	THF	-78	97	–	1.0:3.3
3	BEMP	THF	0	34	61	1.0:2.3
4	BEMP	toluene	0	9	88	1.0:1.3
5	BEMP	CH_2Cl_2	0	16	82	1.0:2.7
6	BEMP	MeCN	0	18	77	1.0:5.6
7	BEMP	DMF	0	36	60	1.0:7.6

[a]Reactions were performed on 0.10 mmol scale employing 2.0 equiv. of aldehyde. [b]Yields and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard.

Although results with BEMP were discouraging with respect to product distribution, it provided the *opposite* major diastereomer relative to alkali bases, hinting at a possibility that both relative and absolute stereocontrol issues could conceivably be addressed through the use of a chiral iminophosphorane base that has appropriate structural features and sufficient basicity. Exploratory experiments testing this hypothesis were undertaken in collaboration with Professor Takashi Ooi at Nagoya University who has developed a series of spirocyclic chiral

iminophosphorane catalysts derived from chiral diamines (**Table 2-6**).[17] Initial reactions were unsuccessful at -78 °C, however, (*M*,*S*)-L-Val-Ph-NH-PCl/KO^{t}Bu was able to slowly promote [1,2]-phosphonate-phosphate rearrangement of **41e** at -40 °C in both THF and DMF (entries 2 and 3). Reaction in THF predominately gave byproduct **51** and a small amount of desired product **50a** in 1:1 dr; however, reaction in DMF provided **50a** as the major product in moderate diastereoselectivity. Similarly, employing (*P*,*S*)-L-Val-Ph-NH-POH in DMF resulted in a very good ratio of **50a**:**51**, but only moderate diastereoselection (entry 4). Running the reaction in THF, however, resulted in the formation of **50a** in low yield, but >30:1 dr and 92.5:7.5 er (entry 5).

Table 2-6. Application of Chiral Iminophosphorane Catalysts[a]



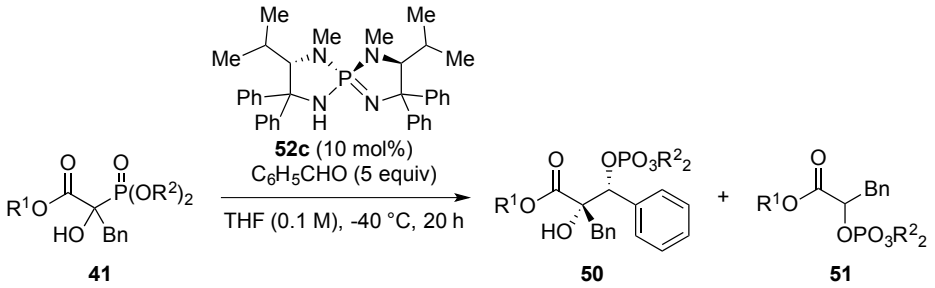
entry	catalyst	solvent	T (°C)	50a:51[b]	dr[b] (*syn*:*anti*)	er[c]
1[d]	BEMP	THF	0	1:2	3:1	–
2	(*M*,*S*)-L-Val-Ph-NH-PCl[e]	THF	-40	1:6	1:1	N/D
3	(*M*,*S*)-L-Val-Ph-NH-PCl[e]	DMF	-40	3:2	4:1	N/D
4	(*P*,*S*)-L-Val-Ph-NMe-POH	DMF	-40	6:1	5:1	N/D
5	(*P*,*S*)-L-Val-Ph-NMe-POH	THF	-40	1:2	>30:1	92.5:7.5

[a]Reactions were performed on 0.10 mmol scale employing 2.0 equiv. of aldehyde at the indicated temperature for 20 h. [b]Product distributions and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by chiral HPLC analysis. [d]Reaction performed with **41a**. [e]Active iminophosphorane catalyst prepared *in situ* via addition of KO^{t}Bu (10 mol%) at -40 °C.

2.3.5 Preparation of Chiral Iminophosphoranes and Optimization of Catalytic Direct Asymmetric Aldolization of α-Hydroxy Phosphonoacetates

We commenced our studies by examining the effects of structural perturbations to α-hydroxy phosphonoacetate **41** on the efficiency of the direct aldolization to benzaldehyde (**Table 2-7**). Unfortunately, modifications to the identity of the ester or phosphonate groups were largely unsuccessful. Decreasing the size of the ester (ethyl to methyl) resulted in a significant increase in the formation of byproduct **51**, whereas increasing its size (ethyl to *tert*-butyl) completely shut down the reaction (entries 2 and 5). Similarly, increasing the size of the phosphonate to ethyl or isopropyl resulted in decreases in conversion and enantioselectivity (entries 3 and 4). Remarkably, all α-hydroxy phosphonoacetates **41** that underwent reaction provided the desired adduct **50** with essentially complete diastereocontrol (>30:1 dr), revealing this strategy as a powerful method for stereoselective glycolate aldolization with a fully substituted α-center.

Table 2-7. Stereochemical Effects of Carboxy and Phosphonate Ester Identity[a]

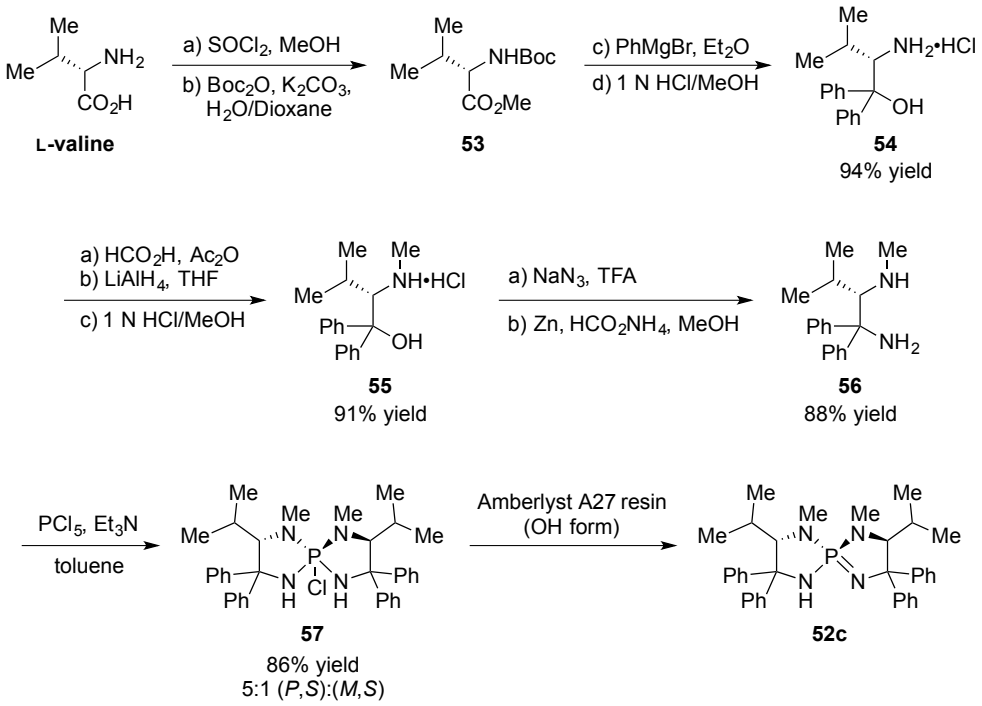


entry	R^1	R^2	conv (%)[b]	50:51[b]	dr[b] (*syn*:*anti*)	er[c]
1	Et	Me	70	1.0:1.2	>30:1	93:7
2	Me	Me	23	1.0:1.9	>30:1	90.5:9.5
3	Et	Et	45	1.0:0.9	>30:1	85.5:14.5
4	Et	^{i}Pr	<5	–	–	–
5	^{t}Bu	Me	<5	–	–	–

[a]Reactions were performed on 0.10 mmol scale employing 5.0 equiv. of aldehyde in THF (1.0 mL) at -40 °C for 20 h. [b]Conversions, product distributions, and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. [c]Determined by chiral HPLC analysis.

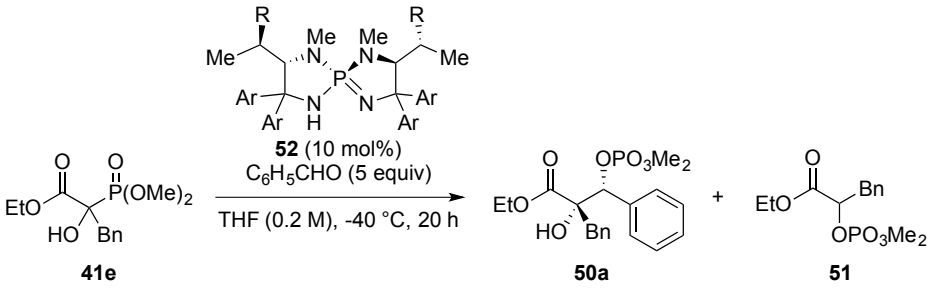
A distinct advantage of catalysts derived from (*P*,*S*)-L-Val-Ph-NMe-POH (**52c**) is the ability to tune the basicity of the iminophosphorane by varying the geminal diaryl groups. To this end, catalyst **52c** and its structural derivatives were prepared according to literature procedures with help from Yusuke Ueki and Ken Yoshioka (**Scheme 2-18**).[17b,17c] Beginning from L-valine, amino alcohol **54**•HCl bearing geminal diphenyl groups was prepared in 4 steps in 94% overall yield. Formylation of the amine and subsequent reduction provided *N*-Me amino alcohol **55**•HCl in 91% yield. Diamine **56** was prepared utilizing a TFA-mediated S_N1 displacement of the benzylic alcohol with NaN_3 followed by reduction of the azide moiety. Spirocyclization of diamine **56** with PCl_5 proceeded cleanly to afford **57** in a 5:1 dr. Separation of the diastereomers via column chromatography and ion-exchange afforded iminophosphorane **52c**.

Scheme 2-18. Synthesis of Chiral Iminophosphorane Catalysts



With a library of catalysts in hand, we screened an electronically distinct series of catalysts in the direct aldolization (**Table 2-8**). Catalysts bearing electron-rich aromatic groups (**52a** and **52b**) provided higher levels of conversion after 20 h than the parent Ph-catalyst **52c**, but provided **50a** with lower levels of enantioselectivity (entries 1 and 2). Catalysts with electron-withdrawing aromatic groups (**52d-f**) are less basic than the parent catalyst **52c** resulting in decreased reactivity; however, **52d** provided **50a** with higher levels of enantioselectivity (entries 4-6). Iminophosphorane catalyst **52g** derived from L-isoleucine was found to be inferior to L-valine derived catalyst **52c** (entry 7). Although catalyst **52d** provides slightly higher levels of enantioselectivity than **52c**, we decided to move forward with **52c** due to its higher reactivity.

Table 2-8. Screening Chiral Iminophosphorane Catalysts[a]



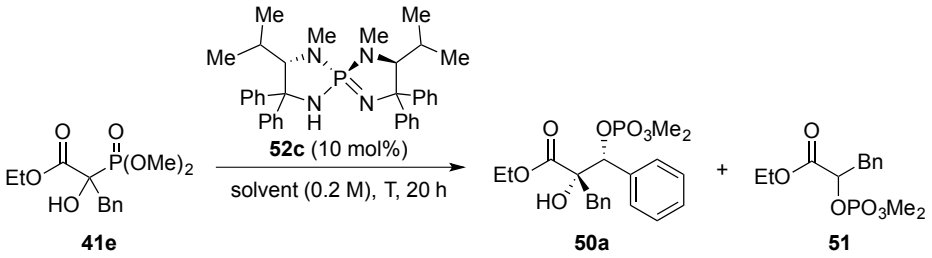
entry	R	Ar	conv (%)[b]	50a:51[b]	dr[b] (*syn*:*anti*)	er[c]
1	Me	4-OMePh (**52a**)	>95	1.0:1.1	>30:1	89.5:10.5
2	Me	4-MePh (**52b**)	80	1.0:0.7	>30:1	88:12
3	Me	Ph (**52c**)	76	1.0:0.8	>30:1	92:8
4	Me	4-FPh (**52d**)	52	1.0:0.6	>30:1	95:5
5	Me	4-ClPh (**52e**)	20	1.0:0.6	>30:1	N/D
6	Me	4-CF_3Ph (**52f**)	<5	–	–	–
7	Et	Ph (**52g**)	53	1.0:2.6	>30:1	90.5:9.5

[a]Reactions were performed on 0.10 mmol scale employing 5.0 equiv. of aldehyde in THF (0.5 mL) at -40 °C for 20 h. [b]Conversions, product distributions, and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. [c]Determined by chiral HPLC analysis.

Having identified optimized structures for the α-hydroxy phosphonoacetate and iminophosphorane catalyst, we began to optimize reaction conditions to increase the selectivity, conversion, and product distribution of the direct aldolization (**Table 2-9**). Polar solvents such as DMF effectively promoted desired reactivity giving excellent product distribution; however, **50a** was obtained in only 6:1 dr and 53.5:46.5 er (entry 2). EtOAc provided similar reactivity and enantioselectivity to THF, but with a substantial drop in diastereoselection to 9:1 (entry 3). The use of CH_2Cl_2 resulted in rapid consumption of **41e** leading to the selective generation of byproduct **51** (entry 4). Considering these results, we conducted a screen of ethereal solvents since THF provided the highest levels of selectivity in the reaction (entries 5-8). Both MTBE and 2-MeTHF provided slight increases in enantioselection, but suffered from moderate ratios of

50a:**51** at -40 °C. Although decreasing the temperature to -50 °C resulted in incomplete conversion after 20 h, an improved ratio of **50a**:**51** was obtained and **50a** was isolated in 71% yield with 20:1 dr and 95:5 er (entry 9). Examination of other reaction parameters such as catalyst loading, concentration, equivalence of aldehyde, and reaction time unfortunately provided no improvement to these optimized reaction conditions.

Table 2-9. Optimization of Solvent and Temperature[a]



entry	solvent	T (°C)	conv (%)[b]	50a:51[b]	dr[b] (*syn*:*anti*)	er[c]
1	THF	-40	76	1.0:0.8	>30:1	92:8
2	DMF	-40	>95	1.0:0.3	6:1	53.5:46.5
3	EtOAc	-40	85	1.0:1.0	9:1	89:11
4	CH_2Cl_2	-40	>95	1.0:6.9	>30:1	N/D
5	Et_2O	-40	>95	1.0:0.6	>30:1	91:9
6	CPME	-40	>95	1.0:0.9	>30:1	91:9
7	MTBE	-40	>95	1.0:0.6	>30:1	93:7
8	2-MeTHF	-40	>95	1.0:0.8	>30:1	92.5:7.5
9	2-MeTHF	-50	>90 (71)	1.0:0.4	>30:1	95:5

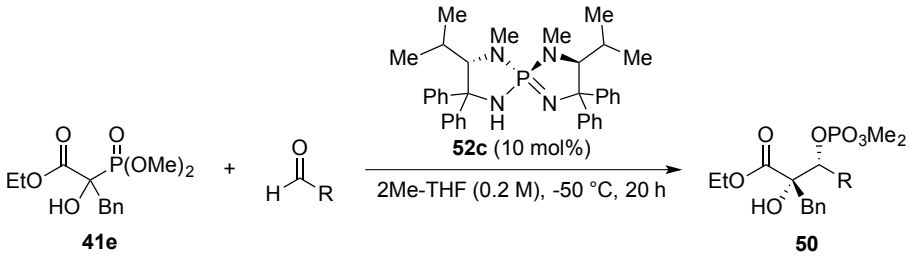
[a]Reactions were performed on 0.10 mmol scale employing 5.0 equiv. of aldehyde in solvent (0.5 mL) for 20 h. [b]Conversions, product distributions, and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard; isolated yield reported in parentheses. [c]Determined by chiral HPLC analysis.

2.3.6 Scope with Chiral Bases

Preliminary experiments suggest that application of the optimized reaction conditions to other aldehyde electrophiles provides access to enantiomerically enriched aldol adducts (**Table 2-10**). While the product yields were slightly reduced with *ortho*-substituted aldehydes, complete

diastereoselectivity is regularly observed and good enantiocontrol is maintained (entries 2-4). A variety of 3-substituted and 4-substituted aromatic aldehydes bearing electron-withdrawing groups were also competent reaction partners providing products in high yield and excellent diastereo- and enantioselectivity (entries 5-9). The structure and absolute stereochemistry of aldol adduct **50e** was determined by X-ray crystallography,[28] and other products were assigned by analogy.

Table 2-10. Scope of Aldehyde Partners[a]



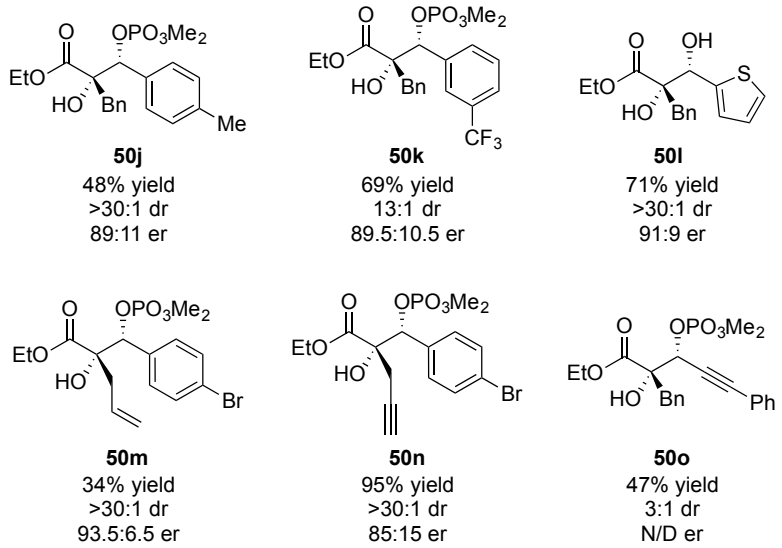
entry	R	50	yield (%)	dr[b] (*syn*:*anti*)	er[c]
1	C_6H_5	**50a**	71	>30:1	95:5
2	2-naphthyl	**50b**	68	>30:1	94.5:5.5
3	2-F-C_6H_4	**50c**	56	>30:1	94:6
4	2-Cl-C_6H_4	**50d**	64	>30:1	95:5
5	3-CN-C_6H_4	**50e**	89	>30:1	94:6
6	3-Br-C_6H_4	**50f**	87	>30:1	95:5
7	4-Cl-C_6H_4	**50g**	82	>30:1	95:5
8	4-Br-C_6H_4	**50h**	91	>30:1	95.5:4.5
9	4-CO_2Me-C_6H_4	**50i**	89	>30:1	97:3

[a]Unless otherwise noted, reactions were performed on 0.10 mmol scale employing 5.0 equiv. of aldehyde in 2Me-THF (0.5 mL) at -50 °C for 20 h. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by chiral HPLC analysis.

Although the aldolization was found to be highly effective with electron-neutral and electron-withdrawing aldehyde coupling partners, at the current level of optimization a variety of substrates were plagued by the formation of byproduct **51** resulting in reduced yields and

selectivities (**Scheme 2-19**). Electron-releasing *p*-tolualdehyde provided **50j** in only 48% yield and 89:11 er despite retaining excellent relative stereocontrol. Aldehydes possessing CF_3-groups afforded products such as **50k** in diminished diastereoselectivity, regardless of its position on the aromatic ring. Although 2-thiophenecarboxaldehyde worked well in the aldolization providing **50l** in good yield, column chromatography resulted in the cleavage of the phosphate group (*vide supra*) and provided the diol in reduced enantioselectivity. Reactions with aliphatic aldehydes generally exhibited poor chemoselectivity providing only trace amounts of the desired aldol adduct; however, aliphatic surrogates, such as ynals, were found to be compatible with the title reaction providing **50o** in moderate yield, but with poor diastereocontrol. This result may suggest that the high levels of diastereoselectivity observed in the aldolization could arise from favorable π–π interactions between the aldehyde and the iminophosphorane catalyst. Other α-hydroxy phosphonoacetate donors were examined in the reaction providing **50m** and **50n** in either reduced yield or enantioselection under the optimized reaction conditions.

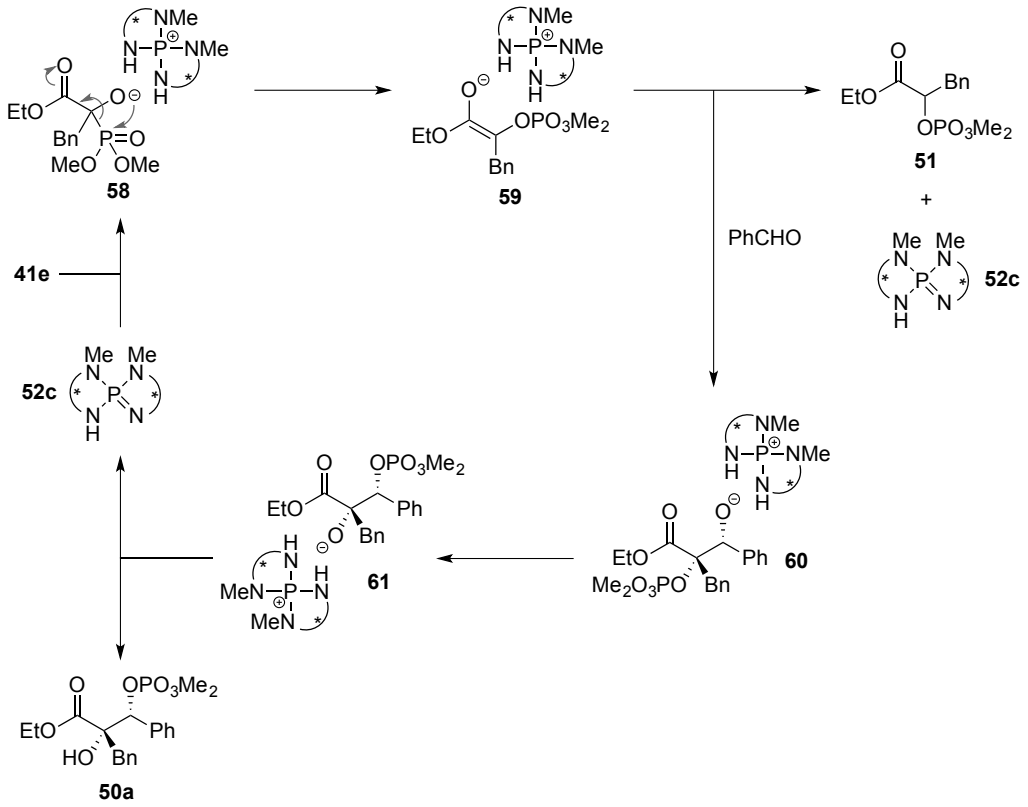
Scheme 2-19. Ineffective Aldolization Substrates



2.3.7 Proposed Mechanism

In order to account for the observed reactivity of α-hydroxy phosphonate **41e** in the aldol addition, a catalytic cycle was proposed (**Scheme 2-20**). Following deprotonation of the alcohol **41e** by **52c**, [1,2]-phosphonate-phosphate rearrangement proceeds to generate the reactive glycolate enolate **59** from **58**. FMO considerations[29] lead us to favor the illustrated (*Z*)-enolate as the kinetically preferred product of C→O phosphinyl migration. The precise structures of the enolate **59** and the aldol transition state remain open questions. Enolate addition to benzaldehyde would lead to the aldolate **60**; however, enolate **59** can be quenched by the ion-paired catalyst to afford undesired byproduct **51** in a competitive irreversible pathway. The relative rate of the irreversible asymmetric protonation pathway leading to **51** was faster than C–C bond formation to **60** for electron-rich and sterically hindered aldehydes, which is consistent with Nakamura's work (**Scheme 2-17**). Approximately thermoneutral O→O phosphinyl migration occurs from the 3° alcohol to the vicinal 2° alkoxide, presumably to reduce steric strain at the fully substituted center, affording aldolate **61**. The reaction is rendered catalytic via proton transfer between the aldolate **61** and the α-hydroxy phosphonate starting material (**41e**), either directly or via the free base **52c**.

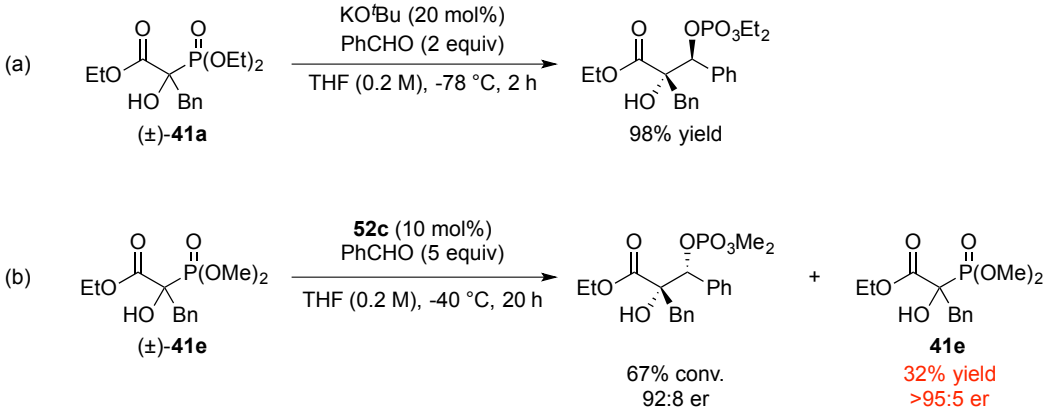
Scheme 2-20. Mechanistic Proposal



2.3.8 Evidence for DyKAT Type II Paradigm

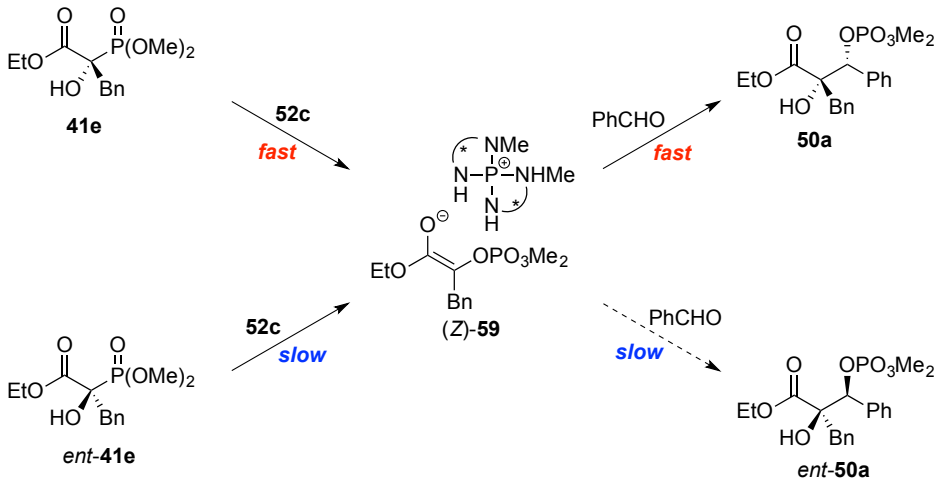
During the optimization of the iminophosphorane-catalyzed direct aldolization of α-hydroxy phosphonate **41e**, an interesting mechanistic observation was made. Namely, that the reaction employing chiral iminophosphorane **52c** was significantly slower than the racemic reaction employing KO^{t}Bu even though it was being run at higher temperature (**Scheme 2-21**). Although this was initially attributed solely to the steric demnd of the catalyst, careful consideration of the aforementioned mechanism led us to consider that the chiral nature of the base (**52c**) was responsible for this divergence in starting material consumption. Although a clean assay of **41e** could not be achieved by chiral HPLC, analysis of the recovered starting material **41e** revealed that significant enrichment (>95:5 er) occurred at 67% conversion.

Scheme 2-21. Relative Rates of Conversion



These data strongly suggest that there is a matched/mismatched deprotonation event involved in the generation of the ion-paired achiral enolate **59** and that this direct aldolization is proceeding as a dynamic kinetic asymmetric transformation (DyKAT) Type II (**Scheme 2-22**). Deprotonation of one enantiomer of **41e** (arbitrarily denoted as *R*) was more accessible to the catalyst than its enantiomer *ent*-**41e** leading to unequal rates of reaction to form intermediate **59** causing a gradual enrichment of the slower reacting enantiomer of starting material. Furthermore, **50a** is formed in uniform enantioselectivity at various conversions providing further evidence for this mechanistic pathway since the selectivity of the reaction is only dependent on the aldolization step.

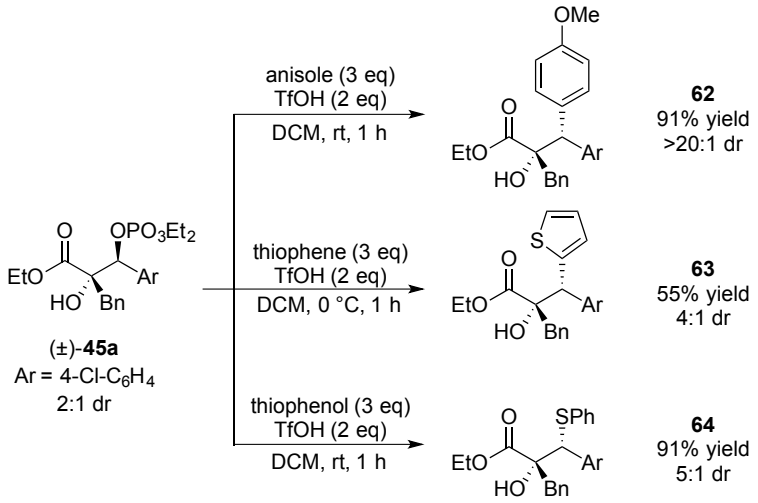
Scheme 2-22. Proposed DyKAT Type II Mechanism



2.3.9 Diastereoselective Friedel–Crafts Optimization and Scope

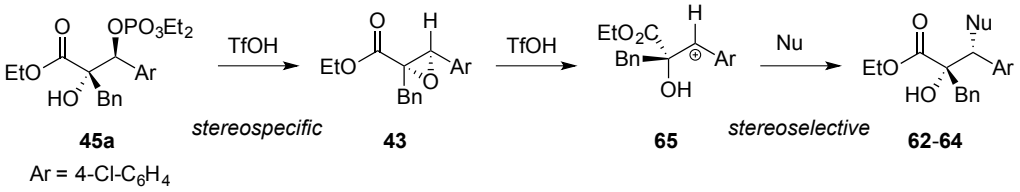
The title reaction is especially attractive since the aldolization directly installs a leaving group that can be immediately deployed in nucleophilic displacement chemistry. The $–OPO_3R_2$ groups in benzylic phosphates are viable nucleofuges in acid-promoted Friedel–Crafts alkylations.[23] In order to exploit this potential reactivity, a variety of Lewis and *Brønsted* acids were screened in the reaction of (±)-**45a** (2:1 dr) and anisole. A majority of the acids screened were found to promote ionization, but led to undesired Meinwald rearrangement;[30] however, TfOH provided the desired Friedel–Crafts alkylation adduct **62** in 91% yield as a single diastereomer. Heteroaromatic and heteroatom nucleophiles were also employed in this alkylation reaction to provide **63** and **64** in good to excellent yields (**Scheme 2-23**). The Friedel–Crafts alkylation provides β-diaryl stereogenicity in a single step with pronounced stereoconvergency.

Scheme 2-23. Stereoconvergent Friedel–Crafts Alkylations



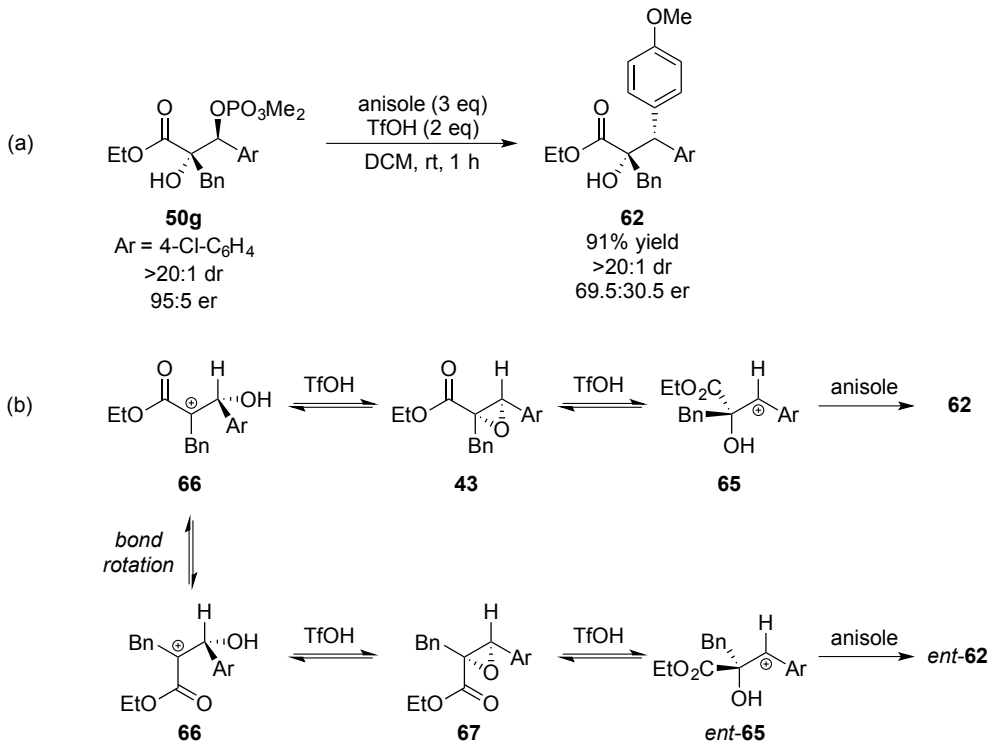
Formation of a discrete carbenium ion explains the stereoconvergence and finds precedent in the diastereoselective Friedel–Crafts alkylations pioneered by Bach and coworkers.[31] The mechanistic pathway that leads to the generation of benzylic carbenium ion **65**, however, remains a topic of discussion. We proposed acid-catalyzed conversion of α-hydroxy phosphate **45a** to epoxide **43** as the first step (**Scheme 2-24**). The intermediacy of the epoxide and the stereospecificity of the ring closure were supported by a reaction with a weaker acid, $ZnCl_2$, at 45 °C that resulted in formation of oxirane **43** with conservation of diastereomeric ratio. The epoxide **43** is then susceptible to Brønsted acid-mediated opening affording benzylic carbenium ion **65**, which undergoes stereoselective nucleophilic attack to afford the desired substitution products **62-64**.

Scheme 2-24. Proposed Mechanism for Friedel–Crafts Alkylation



Given this proposed mechanism, treatment of enantioenriched **50g** (95:5 er) and anisole with TfOH was expected to proceed with a high level of stereospecificity providing **62** with enantioretention (**Scheme 2-25a**). However, Friedel–Crafts adduct **62** was isolated in 89% yield as a single diastereomer, but in only 69.5:30.5 er. This significant erosion in enantiopurity is inconsistent with our originally proposed mechanism that relies on stereospecific epoxide formation and selective opening to benzylic carbenium **65** (**Scheme 2-24**). If epoxide opening is reversible and both tertiary carbocation **66** and benzylic carbocation **65** are thermodynamically accessible under the reaction conditions, however, then the enantiomeric integrity of the starting material can be lost during the alkylation (**Scheme 2-25b**). Free bond rotation would allow interconversion of **66** under the reaction conditions, providing access to glycidic esters **43** and **67**. Subsequent acid-catalyzed epoxide opening to generate enantiomeric benzylic carbeniums **65** and *ent*-**65** is followed by stereoselective Friedel–Crafts alkylation to provide products **62** and *ent*-**62**. This alternative mechanistic pathway is more consistent with the observed erosion in enantiopurity of the starting material observed during the acid-catalyzed alkylation of anisole.

Scheme 2-25. Proposed Racemization Pathway in Friedel–Crafts Alkylation



2.4 Conclusion

In conclusion, a catalytic direct aldol addition of α-hydroxy phosphonacetates to aldehydes to afford α-hydroxy-β-phosphonyloxy esters has been developed. A [1,2]-phosphonate-phosphate rearrangement was utilized to generate the reactive glycolate enolate *in situ* under mild basic conditions. The reaction works well for a variety of alkyl, alkenyl, aryl, and heteroaryl aldehydes affording the desired products in good to excellent yields in low to moderate diastereoselectivities. Iminophosphorane catalysts enabled positive outcomes in asymmetric versions of the title process providing excellent levels of stereocontrol under a DyKAT Type II paradigm. This methodology obviates the need to mask ester and alcohol functionality in the direct aldolization providing direct access to fully-substituted α-hydroxy

esters. Stereoconvergent second stage transformations have also been developed to enhance the synthetic utility of the methodology.

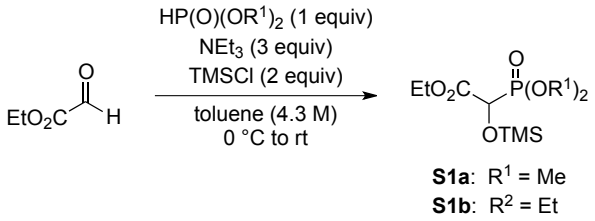
2.5 Experimental Details

Methods: Infrared spectra were obtained using a Shimadzu IRAffinity-1 or Jasco 460 Plus Fourier transform infrared spectrometer. Magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, and ^{31}P NMR) were recorded on a Bruker model DRX 400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz, and ^{31}P NMR at 162 MHz), Bruker model DRX 600 (^{1}H NMR at 600 MHz, ^{13}C NMR at 151 MHz, and ^{31}P NMR at 243 MHz), or JEOL JNM-ECS400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz, and ^{31}P NMR at 162 MHz) spectrometer. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in ppm from the solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm). Chemical shifts for ^{31}P NMR are reported in ppm from H_3PO_4 resonance (0.00 ppm) as the external standard. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, ddq = doublet of doublet of quartets, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were obtained using a Thermo Fisher Scientific Exactive or Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization (**Note:** All samples prepared in methanol). Melting points were obtained using a Stanford Research Systems OptiMelt MPA100 or Thomas Hoover UniMelt Capillary Melting Point Apparatus. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates or Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Visualization was accomplished with UV light, aqueous ceric ammonium molybdate solution, or phosphomolybdic acid in EtOH followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle or PSQ60AB (spherical, av. 55 μm; Fuji Silysia Chemical Ltd.). Enantiomeric excesses were

determined by HPLC analysis using chiral column (ϕ 4.6 mm x 250 mm, DAICEL CHIRALPAK AD3 (AD3)) with hexane (H), 2-propanol (IPA), and ethanol (EtOH) as eluent. All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring unless otherwise noted. Yield refers to isolated yield of analytically pure material unless otherwise noted.

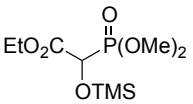
Materials: Toluene, tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were supplied from Kanto Chemical Co., Inc. as "Dehydrated solvent system". 2-Methyltetrahydrofuran (2-MeTHF) was freshly distilled from lithium aluminum hydride ($LiAlH_4$) prior to use. All aldehydes were purified by distillation or recrystallization from EtOH prior to use. Tetraaminophosphonium salts **52**[17b,c] and ethyl 2-(diethoxyphosphoryl)-2-hydroxyacetate (**41b**)[32] were prepared according to literature procedures. All other reagents were purchased and used as such without further purification.

General Procedure A for the Preparation of Protected Alcohols S1a and S1b

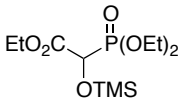


The procedure was adapted from a previously reported method by Hiersemann and coworkers.[33] A dried round-bottomed flask was charged with dialkyl phosphite (1.0 equiv) in toluene (0.23 mL/mmol) under an atmosphere of nitrogen. The solution was cooled to 0 °C in an ice water bath. Triethylamine (3.0 equiv) and ethyl glyoxalate solution (~50% in toluene, 1.0 equiv) were sequentially added dropwise. The resulting solution was stirred for one hour at room temperature. The reaction was diluted with toluene (0.1 M) and cooled to 0 °C in an ice bath.

TMSCl (2.0 equiv) was added dropwise at 0 °C and the resulting suspension was allowed to stir at room temperature for 3 h. The reaction was filtered to remove the salts and the filtercake was rinsed with DCM (3x). The resulting solution was washed with sat. aq. NH_4Cl (1x), H_2O (2x) and brine (1x). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The obtained residue was purified by column chromatography on silica gel eluting with 20% acetone:hexanes afforded the protected alcohol **S1**.



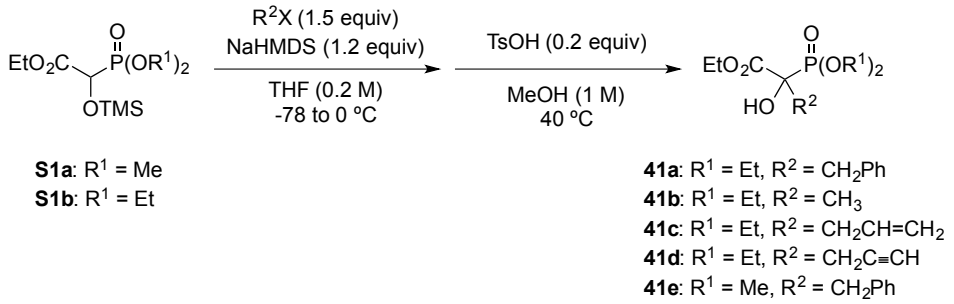
Ethyl 2-(dimethoxyphosphoryl)-2-((trimethylsilyl)oxy)acetate (S1a): The title compound was prepared according to General Procedure A using dimethyl phosphite (1.83 mL, 20.0 mmol, 1.0 equiv) and ethyl glyoxalate solution (3.96 mL, 20.0 mmol, 1.0 equiv) affording the protected alcohol **S1a** (5.21 g, 18.3 mmol, 92% yield) as a pale yellow oil. Analytical data for **S1a**: **IR** (thin film): 2959, 1748, 1254, 1132, 1059, 1034, 883, 847 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.58 (d, J = 18.3 Hz, 1H), 4.26 (ddq, J = 7.3, 3.7, 3.6 Hz, 2H), 3.83 (d, J = 0.9 Hz, 3H), 3.80 (d, J = 0.9 Hz, 3H), 1.29 (t, J = 7.3 Hz, 3H), 0.16 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.4 (d, $J_{P–C}$ = 2.9 Hz), 70.1 (d, $J_{P–C}$ = 165.5 Hz), 62.0, 54.3 (d, $J_{P–C}$ = 7.7 Hz), 54.2 (d, $J_{P–C}$ = 7.8 Hz), 14.2, -0.3; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 18.7; **TLC** (30% acetone:hexane): R_f 0.53; **HRMS** (FAB): Calcd. for $C_9H_{21}O_6NaPSi$ ($[M+Na]^+$): 307.0737, Found: 307.0738.



Ethyl 2-(diethoxyphosphoryl)-2-((trimethylsilyl)oxy)acetate (S1b): The title compound was prepared according to General Procedure A using diethyl phosphite (2.58 mL, 20.0 mmol, 1.0 equiv) and ethyl glyoxalate solution (3.96 mL, 20.0 mmol, 1.0 equiv) affording the protected alcohol **S1b** (6.19 g, 19.8 mmol, 99% yield) as a pale yellow oil. Analytical data for **S1b**: **IR** (thin film): 2983, 1754, 1254, 1138, 1026, 975, 846, 755 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.53 (d, J = 18.0 Hz, 1H), 4.24-4.13 (m, 6H), 1.32-1.24 (m, 9H),

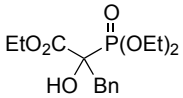
0.13 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.4 (d, $J_{P–C}$ = 2.5 Hz), 70.1 (d, $J_{P–C}$ = 163.3 Hz), 63.5 (d, $J_{P–C}$ = 6.9 Hz), 63.4 (d, $J_{P–C}$ = 7.0 Hz), 16.34 (d, $J_{P–C}$ = 1.6 Hz), 16.28 (d, $J_{P–C}$ = 1.5 Hz), 14.0, -0.5; **^{31}P NMR** (243 MHz, $CDCl_3$): δ 16.4; **TLC** (20% acetone:hexanes): R_f 0.28; **HRMS** (ESI): Calcd. for $C_{11}H_{25}CsO_6PSi$ ($[M+Cs]^+$): 445.0212, Found: 445.0189.

General Procedure B for the Preparation of α-Hydroxy Phosphonoacetates 41a-e

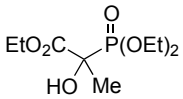


A dried round-bottomed flask was charged with the protected alcohol **S1** (1.0 equiv) in THF (0.2 M) under an atmosphere of nitrogen. After cooling the solution to -78 °C, NaHMDS (1.0 M in THF, 1.2 equiv) was added dropwise and the resulting solution stirred for 30 min at -78 °C. The alkyl halide (1.5 equiv) was added dropwise at -78 °C. Following addition of the alkyl halide, the reaction was allowed to warm slowly to 0 °C where the temperature was maintained until the reaction was adjudged complete by TLC. The reaction was quenched by the slow dropwise addition of sat. aq. NH_4Cl at 0 °C. The layers were separated and the aqueous layer was extracted with Et_2O (2x). The combined organic extracts were washed with brine (1x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved in MeOH (1.0 M) and transferred to a round-bottomed flask fitted with a reflux condenser. TsOH (0.2 equiv) was added and the reaction was warmed to 40 °C and stirred overnight. After completion of the reaction as adjudged by TLC, the reaction was concentrated *in vacuo*. The

obtained residue was purified by column chromatography on silica gel eluting with 40% acetone:hexanes afforded the α-hydroxy phosphonoacetate **41**.

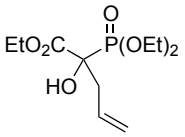


Ethyl 2-(diethoxyphosphoryl)-2-hydroxy-3-phenylpropanoate (41a): The title compound was prepared according to General Procedure B using **S1b** (1.56 g, 5.00 mmol, 1.0 equiv) and benzyl bromide (0.89 mL, 7.50 mmol, 1.5 equiv) affording the α-hydroxy phosphonoacetate **41a** (1.47 g, 4.47 mmol, 89% yield) as a white solid (mp 42-44 °C). Analytical data for **41a**: **IR** (thin film): 3446, 2983, 1733, 1647, 1235, 1098, 1019, 973, 700, 591 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.24-7.21 (m, 5H), 4.29-4.19 (m, 6H), 3.55 (ddd, J = 6.8, 1.5, 0.9 Hz, 1H), 3.39 (dd, J = 14.0, 5.1 Hz, 1H), 3.23 (dd, J = 14.0, 7.7 Hz, 1H), 1.37 (t, J = 7.4 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 171.1, 134.3 (d, $J_{P–C}$ = 14.8 Hz), 130.3, 128.0, 127.1, 77.9 (d, $J_{P–C}$ = 161.4 Hz), 64.0 (d, $J_{P–C}$ = 7.1 Hz), 63.8 (d, $J_{P–C}$ = 7.4 Hz), 63.0, 39.5, 16.5 (d, $J_{P–C}$ = 5.6 Hz), 16.4 (d, $J_{P–C}$ = 5.9 Hz), 14.0; **^{31}P NMR** (243 MHz, $CDCl_3$): δ 17.8; **TLC** (30% acetone:hexanes): R_f 0.10; **HRMS** (ESI): Calcd. for $C_{15}H_{23}O_6NaP$ ($[M+Na]^+$): 353.1130, Found: 353.1101.

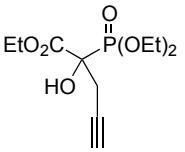


Ethyl 2-(diethoxyphosphoryl)-2-hydroxypropanoate (41b): The title compound was prepared according to General Procedure B using **S1b** (1.56 g, 5.00 mmol, 1.0 equiv) and iodomethane (0.47 mL, 7.50 mmol, 1.5 equiv) affording the α-hydroxy phosphonoacetate **41b** (0.79 g, 3.11 mmol, 62% yield) as a pale yellow oil. Analytical data for **41b**: **IR** (thin film): 3446, 2985, 1734, 1254, 1151, 1022, 975, 602 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.31-4.24 (m, 2H), 4.20-4.13 (m, 4H), 3.79 (br s, 1H), 1.60 (dd, J = 15.9, 1.3 Hz, 3H), 1.31-1.27 (m, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.4, 74.2 (d, $J_{P–C}$ = 160.5 Hz), 63.8 (d, $J_{P–C}$ = 6.8 Hz), 63.5 (d, $J_{P–C}$ = 7.4 Hz), 62.8, 21.0, 16.4 (d, $J_{P–C}$ = 4.7 Hz), 16.3 (d, $J_{P–C}$ = 4.5

Hz), 13.9; **^{31}P NMR** (243 MHz, $CDCl_3$): δ 18.9; **TLC** (30% acetone:hexanes): R_f 0.12; **HRMS** (ESI): Calcd. for $C_9H_{19}CsO_6P$ ($[M+Cs]^+$): 386.9973, Found: 386.9968.

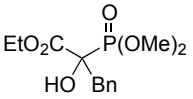


Ethyl 2-(diethoxyphosphoryl)-2-hydroxypent-4-enoate (41c): The title compound was prepared according to General Procedure B using **S1b** (1.56 g, 5.00 mmol, 1.0 equiv) and allyl bromide (0.65 mL, 7.50 mmol, 1.5 equiv) affording the α-hydroxy phosphonoacetate **41c** (1.10 g, 3.94 mmol, 79% yield) as a pale yellow oil. Analytical data for **41c**: **IR** (thin film): 3470, 2983, 2934, 1734, 1236, 1147, 1022, 974, 794, 669 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.75-5.68 (m, 1H), 5.14 (d, J = 18.7 Hz, 1H), 5.11 (d, J = 12.2 Hz, 1H), 4.30-4.27 (m, 2H), 4.23-4.15 (m, 4H), 3.63 (br s, 1H), 2.81-2.78 (m, 1H), 2.71-2.66 (m, 1H), 1.34-1.28 (m, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 171.5, 130.5 (d, $J_{P–C}$ = 13.3 Hz), 119.7, 77.2 (d, $J_{P–C}$ = 161.4 Hz), 63.9 (d, $J_{P–C}$ = 7.1 Hz), 63.7 (d, $J_{P–C}$ = 7.4 Hz), 63.0, 38.3, 16.42 (d, $J_{P–C}$ = 5.7 Hz), 16.39 (d, $J_{P–C}$ = 5.7 Hz), 14.1; **^{31}P NMR** (243 MHz, $CDCl_3$): δ 17.8; **TLC** (30% acetone:hexanes): R_f 0.18; **HRMS** (ESI): Calcd. for $C_{11}H_{21}O_6PCs$ ($[M+Cs]^+$): 413.0130, Found: 413.0144.



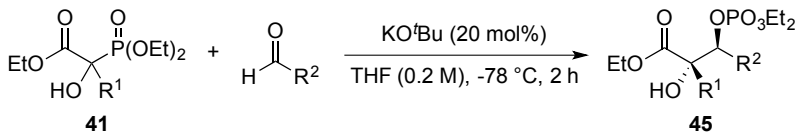
Ethyl 2-(diethoxyphosphoryl)-2-hydroxypent-4-ynoate (41d): The title compound was prepared according to General Procedure B using **S1b** (1.56 g, 5.00 mmol, 1.0 equiv) and propargyl bromide (80% in toluene, 0.84 mL, 7.50 mmol, 1.5 equiv) affording the α-hydroxy phosphonoacetate **41d** (1.17 g, 4.21 mmol, 84% yield) as a white solid (mp 53-56 °C). Analytical data for **41d**: **IR** (thin film): 3479, 3287, 2983, 2934, 2121, 1739, 1637, 1241, 1107, 1052, 1021, 976, 779, 734 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.42-4.33 (m, 2H), 4.26-4.18 (m, 4H), 3.86 (d, J = 8.0 Hz, 1H), 3.05 (ddd, J = 16.9, 2.2, 2.0 Hz, 1H), 2.83 (dddd, J = 13.3, 7.3, 2.4, 2.3 1H), 2.03 (dd, J = 4.0, 2.6 Hz, 1H), 1.36 (m, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 170.6, 76.1 (d, $J_{P–C}$ = 163.1 Hz), 71.5 (d, $J_{P–C}$ = 3.0 Hz), 64.4 (d, $J_{P–}$

$_C$ = 7.6 Hz), 63.9 (d, $J_{P–C}$ = 7.6 Hz), 63.5, 25.6 (d, $J_{P–C}$ = 6.0 Hz), 16.44 (d, $J_{P–C}$ = 3.0 Hz), 16.43 (d, $J_{P–C}$ = 4.5 Hz), 14.1; **^{31}P NMR** (243 MHz, $CDCl_3$): δ 16.3; **TLC** (30% acetone:hexanes): R_f 0.14; **HRMS** (ESI): Calcd. for $C_{11}H_{19}CsO_6P$ ([M+Cs]$^+$): 410.9973, Found: 410.9944.



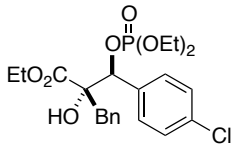
Ethyl 2-(dimethoxyphosphoryl)-2-hydroxy-3-phenylpropanoate (41e): The title compound was prepared according to General Procedure B using **S1a** (1.42 g, 5.00 mmol, 1.0 equiv) and benzyl bromide (0.89 mL, 7.50 mmol, 1.5 equiv) affording the α-hydroxy phosphonoacetate **41e** (1.22 g, 4.04 mmol, 81% yield) as a white solid (mp 75-78 °C). Analytical data for **41e**: **IR** (thin film): 3287, 2959, 2359, 2342, 1732, 1456, 1238, 1207, 1098, 1028, 853, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.24 (m, 5H), 4.26 (ddq, J = 6.9, 3.7, 3.6 Hz, 2H), 3.91 (d, J = 2.3 Hz, 3H), 3.88 (d, J = 2.3 Hz, 3H), 3.58 (d, J = 7.8 Hz, 1H), 3.37 (dd, J = 14.2, 5.5 Hz, 1H), 3.22 (dd, J = 14.0, 7.6 Hz, 1H), 1.28 (t, J = 6.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.4, 134.2 (d, $J_{P–C}$ = 14.5 Hz), 130.5, 128.3, 127.4, 78.3 (d, $J_{P–C}$ = 163.5 Hz), 63.4, 54.8 (d, $J_{P–C}$ = 6.8 Hz), 54.6 (d, $J_{P–C}$ = 6.8 Hz), 39.8, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 20.1; **TLC** (40% acetone:hexane): R_f 0.40; **HRMS** (FAB): Calcd. for $C_{13}H_{19}O_6NaP$ ([M+Na]$^+$): 325.0811, Found: 325.0811.

General Procedure C for the KO^{t}Bu-Catalyzed Aldolization of α-Alkyl-α-Hydroxy Phosphonoacetates to Afford α-Hydroxy-β-Phosphonyloxy Esters 45a-r



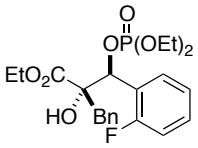
A flame-dried shell vial was charged with the α-hydroxy phosphonoacetate **41** (0.20 mmol, 1.0 equiv) and aldehyde (0.40 mmol, 2.0 equiv) and dissolved in THF (0.8 mL) under an atmosphere of nitrogen. The solution was cooled to -78 °C. A freshly prepared solution of KO^{t}Bu in THF (0.2 mL, 1.0 M, 0.20 equiv) was added dropwise to the reaction mixture. After

stirring for 2 h at -78 °C, the reaction was quenched with 1 *N* HCl (2.0 mL) and allowed to warm to 0 °C. The layers were separated and the aqueous layer was extracted with Et_2O (2x). The combined organic extracts were washed with brine (1x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The residue was purified by column chromatography on silica gel eluting with 30% acetone:hexanes to afford a diastereomeric mixture of **45**.



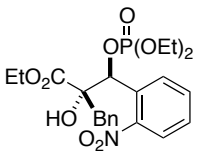
Ethyl 2-benzyl-3-(4-chlorophenyl)-3-((diethoxyphosphoryl)oxy)-2-hydroxypropanoate (45a): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 4-chlorobenzaldehyde (56.2 mg, 0.40 mmol) affording aldol adduct **45a** (89.5 mg, 0.19 mmol, 95% yield, 2.0:1.0 *anti*:*syn*) as a white solid (mp 72-79 °C). Analytical data for **45a**: **IR** (thin film): 3503, 2983, 2934, 1736, 1599, 1493, 1455, 1369, 1263, 1212, 1122, 1030, 1010, 892, 807, 701 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.38 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.25-7.18 (m, 5H), 5.63 (d, *J* = 9.4 Hz, 1H), 4.22-3.69 (m, 6H), 3.39 (d, *J* = 13.7 Hz, 1H), 3.18 (d, *J* = 13.6 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); *minor diastereomer* δ 7.54 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.25-7.18 (m, 3H), 7.11-7.10 (m, 2H), 5.58 (d, *J* = 8.2 Hz, 1H), 4.22-3.69 (m, 6H), 3.49 (br s, 1H), 2.91 (d, *J* = 13.6 Hz, 1H), 2.40 (d, *J* = 13.5 Hz, 1H), 1.31 (t, *J* = 6.8 Hz, 3H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.8, 171.9, 135.2, 135.0, 134.8, 134.6, 134.2, 133.9, 130.4, 130.1, 130.0, 129.5, 128.3, 128.2, 128.1, 128.0, 127.00, 126.96, 81.8 (d, $J_{P–C}$ = 5.4 Hz), 81.6 (d, $J_{P–C}$ = 5.4 Hz), 80.8 (d, $J_{P–C}$ = 7.7 Hz), 80.3 (d, $J_{P–C}$ = 8.5 Hz), 64.1 (d, $J_{P–C}$ = 5.7 Hz), 63.9 (d, $J_{P–C}$ = 6.0 Hz), 63.8 (d, $J_{P–C}$ = 5.9 Hz), 63.7 (d, $J_{P–C}$ = 5.9 Hz), 62.6, 62.4, 42.1, 41.2, 16.0 (d, $J_{P–C}$ = 7.1 Hz), 15.9 (d, $J_{P–C}$ = 7.4 Hz), 15.8 (d, $J_{P–C}$ = 7.1 Hz),

15.7 (d, J_{P-C} = 6.0 Hz), 14.05, 14.02; **^{31}P NMR** (162 MHz, $CDCl_3$): *major diastereomer* δ -0.4; *minor diastereomer* δ -1.3; **TLC** (30% acetone:hexanes): R_f 0.27; **HRMS** (ESI): Calcd. for $C_{22}H_{28}ClCsO_7P$ ($[M+Cs]^+$): 603.0315, Found: 603.0338.



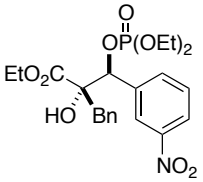
Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-3-(2-fluorophenyl)-2-hydroxypropanoate (45b): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 2-fluorobenzaldehyde (42 μL, 0.40 mmol) affording aldol adduct **45b** (82.7 mg, 0.18 mmol, 91% yield, 2.3:1.0 *anti*:*syn*) as a pale yellow oil. Analytical data for **45b**: **IR** (thin film): 3509, 2984, 2938, 1734, 1491, 1457, 1264, 1209, 1122, 1019, 761, 701 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.72 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.32-7.28 (m, 1H), 7.25-7.12 (m, 6H), 7.00 (dt, *J* = 9.5, 0.8 Hz, 1H), 6.02 (d, *J* = 9.5 Hz, 1H), 4.25-3.79 (m, 6H), 3.43 (d, *J* = 13.7 Hz, 1H), 3.20 (d, *J* = 13.7 Hz, 1H), 1.27 (dt, *J* = 7.1, 1.0 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.12 (dt, *J* = 7.1, 1.0 Hz, 3H); *minor diastereomer* δ 7.77 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.38-7.35 (m, 1H), 7.25-7.12 (m, 6H), 7.09 (dt, *J* = 9.3, 0.7 Hz, 1H), 6.05 (d, *J* = 8.4 Hz, 1H), 4.25-3.79 (m, 6H), 3.05 (dd, *J* = 13.6, 1.0 Hz, 1H), 2.44 (d, *J* = 13.7 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.20 (dt, J = 7.1, 1.0 Hz, 3H), 1.10 (dt, *J* = 7.1, 0.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.8, 172.0, 160.5 (d, J_{F-C} = 247.5 Hz), 158.9 (d, J_{F-C} = 248.5 Hz), 135.3, 134.7, 130.9 (d, J_{F-C} = 2.9 Hz), 130.6 (d, J_{F-C} = 3.5 Hz), 130.52, 130.47, 130.4, 130.3, 130.1, 128.0, 127.9, 126.9, 124.1 (d, J_{F-C} = 2.9 Hz), 123.9 (d, J_{F-C} = 3.5 Hz), 123.1 (d, J_{F-C} = 12.5 Hz), 122.9 (d, J_{F-C} = 12.1 Hz), 115.0 (d, J_{F-C} = 22.2 Hz), 114.8 (d, J_{F-C} = 22.2 Hz), 80.64 (d, J_{P-C} = 8.2 Hz), 80.57 (d, J_{P-C} = 7.4 Hz), 75.1 (d, J_{P-C} = 4.7 Hz), 74.8 (d, J_{P-C} = 5.0 Hz), 64.1 (d, J_{P-C} = 5.9 Hz), 63.91 (d, J_{P-C} = 4.7 Hz), 63.87 (d, J_{P-C} = 5.7 Hz), 63.8 (d, J_{P-C} = 5.9 Hz), 62.6, 62.5, 41.5, 40.0, 16.0 (d, J_{P-C} = 6.8 Hz), 15.9 (d, J_{P-C} = 7.7 Hz), 15.81 (d, J_{P-C} = 5.3 Hz), 15.79 (d, J_{P-C} = 7.1 Hz), 14.1, 13.8; **^{31}P**

NMR (243 MHz, $CDCl_3$): *major diastereomer* δ -0.7; *minor diastereomer* δ -1.5; **TLC** (30% acetone:hexanes): R_f 0.21; **HRMS** (ESI): Calcd. for $C_{22}H_{28}FNaO_7P$ ($[M+Na]^+$): 477.1455, Found: 477.1437.



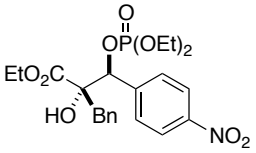
Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-3-(2-nitrophenyl)propanoate (45c): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 2-nitrobenzaldehyde (60.4 mg, 0.40 mmol) affording aldol adduct **45c** (83.8 mg, 0.17 mmol, 87% yield, 1.5:1.0 *anti*:*syn*) as a pale orange oil. Analytical data for **45c**: **IR** (thin film): 3627, 3495, 2985, 1734, 1531, 1456, 1352, 1254, 1211, 1121, 1028, 701 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.63 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.48 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.23-7.16 (m, 3H), 7.13-7.11 (m, 2H), 6.53 (d, *J* = 9.5 Hz, 1H), 4.24-3.81 (m, 6H), 3.32 (d, *J* = 13.7 Hz, 1H), 3.19 (d, *J* = 13.7 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); *minor diastereomer* δ 8.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.95 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.70 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.54 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.23-7.16 (m, 5H), 6.52 (d, *J* = 8.3 Hz, 1H), 4.24-3.81 (m, 6H), 3.25 (d, *J* = 13.6 Hz, 1H), 2.43 (d, *J* = 13.6 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.5, 172.1, 149.4, 148.4, 135.0, 134.5, 132.8, 132.3, 131.7, 131.3, 130.7, 130.3, 130.2, 130.1, 129.6, 129.5, 128.0, 127.9, 127.0, 124.2, 124.0, 80.6 (d, $J_{P–C}$ = 8.6 Hz), 80.2 (d, $J_{P–C}$ = 7.6 Hz), 75.0 (d, $J_{P–C}$ = 6.0 Hz), 74.7 (d, $J_{P–C}$ = 5.6 Hz), 64.3 (d, $J_{P–C}$ = 5.4 Hz), 64.2 (d, $J_{P–C}$ = 5.4 Hz), 64.1 (d, $J_{P–C}$ = 6.0 Hz), 64.0 (d, $J_{P–C}$ = 5.6 Hz), 63.2, 62.8, 41.2, 40.2, 16.0 (d, $J_{P–C}$ = 7.2 Hz), 15.94 (d, $J_{P–C}$ = 7.1 Hz), 15.85 (d, $J_{P–C}$ = 6.3 Hz), 15.8 (d, $J_{P–C}$ = 6.3 Hz), 14.0, 13.7; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ

-1.2; *minor diastereomer* δ -1.6; **TLC** (30% acetone:hexanes): R_f 0.15; **HRMS** (ESI): Calcd. for $C_{22}H_{28}CsNO_9P$ ($[M+Cs]^+$): 614.0556, Found: 614.0570.

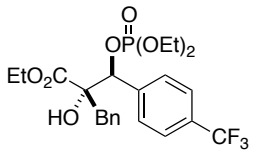


Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-3-(3-nitrophenyl)propanoate (45d): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 3-nitrobenzaldehyde (60.4 mg, 0.40 mmol) affording aldol adduct **45d** (88.6 mg, 0.18 mmol, 92% yield, 2.4:1.0 *anti*:*syn*) as an off-white solid (mp 67-72 °C). Analytical data for **45d**: **IR** (thin film): 3503, 3345, 2984, 2935, 1737, 1532, 1352, 1264, 1214, 1121, 1025, 888, 807, 702 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 8.29 (t, *J* = 1.8 Hz, 1H), 8.26 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.26-7.19 (m, 5H), 5.76 (d, *J* = 9.2 Hz, 1H), 4.24-3.77 (m, 6H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.23 (br s, 1H), 3.19 (d, *J* = 13.6 Hz, 1H), 1.33 (dt, *J* = 7.1, 1.0 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.11 (dt, *J* = 7.1, 0.9 Hz, 3H); *minor diastereomer* δ 8.46 (t, *J* = 1.8 Hz, 1H), 8.18 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.26-7.19 (m, 3H), 7.11-7.10 (m, 2H), 5.69 (d, *J* = 8.2 Hz, 1H), 4.24-3.77 (m, 6H), 3.57 (br s, 1H), 2.99 (d, *J* = 13.6 Hz, 1H), 2.40 (d, *J* = 13.6 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.26 (dt, *J* = 7.1, 1.0 Hz, 3H), 1.06 (dt, *J* = 7.1, 0.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.4, 171.8, 147.9, 147.7, 137.9, 137.6, 135.0, 134.8, 134.3, 134.1, 130.1, 130.0, 129.0, 128.2, 128.0, 127.2, 127.1, 123.91, 123.87, 123.8, 123.1, 81.3 (d, J_{P-C} = 5.4 Hz), 81.2 (d, J_{P-C} = 5.3 Hz), 80.6 (d, J_{P-C} = 7.4 Hz), 80.1 (d, J_{P-C} = 8.0 Hz), 64.3 (d, J_{P-C} = 5.9 Hz), 64.1 (d, J_{P-C} = 5.6 Hz), 64.0 (d, J_{P-C} = 5.7 Hz), 63.9 (d, J_{P-C} = 5.7 Hz), 62.8, 42.1, 41.2, 16.1 (d, J_{P-C} = 6.8 Hz), 15.9 (d, J_{P-C} = 6.8 Hz), 15.80 (d, J_{P-C} = 7.1 Hz), 15.75 (d, J_{P-C} = 8.2 Hz), 14.04, 14.00; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.5; *minor diastereomer* δ -

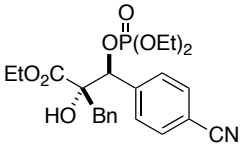
1.4; **TLC** (30% acetone:hexanes): R_f 0.16; **HRMS** (ESI): Calcd. for $C_{22}H_{28}CsNO_9P$ ($[M+Cs]^+$): 614.0556, Found: 614.0542.



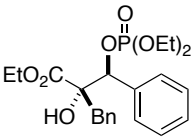
Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-3-(4-nitrophenyl)propanoate (45e): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 4-nitrobenzaldehyde (60.4 mg, 0.40 mmol) affording aldol adduct **45e** (91.4 mg, 0.19 mmol, 95% yield, 2.8:1.0 *anti*:*syn*) as an off-white solid (mp 117-124 °C). Analytical data for **45e**: **IR** (thin film): 3391, 2984, 2934, 1734, 1523, 1348, 1263, 1212, 1121, 1026, 702 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.27-7.20 (m, 5H), 5.75 (d, *J* = 9.2 Hz, 1H), 4.23-3.76 (m, 6H), 3.55 (br s, 1H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.20 (d, *J* = 13.6 Hz, 1H), 1.31 (dt, *J* = 7.2, 0.6 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.10 (dt, *J* = 7.2, 0.6 Hz, 3H); *minor diastereomer* δ 8.28 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.27-7.20 (m, 3H), 7.10-7.09 (m, 2H), 5.69 (d, *J* = 8.2 Hz, 1H), 4.23-3.76 (m, 6H), 3.20 (br s, 1H), 2.98 (d, *J* = 13.4 Hz, 1H), 2.38 (d, *J* = 13.4 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.23 (dt, *J* = 7.2, 0.6 Hz, 3H), 1.05 (dt, *J* = 7.2, 0.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.3, 171.6, 148.1, 148.0, 142.7, 142.4, 134.7, 134.1, 130.0, 129.9, 129.9, 129.1, 128.1, 127.9, 127.0, 127.0, 123.0, 122.9, 81.2 (d, J_{P-C} = 5.3 Hz), 81.1 (d, J_{P-C} = 5.4 Hz), 80.5 (d, J_{P-C} = 7.1 Hz), 80.0 (d, J_{P-C} = 8.5 Hz), 64.3 (d, J_{P-C} = 5.9 Hz), 64.0 (d, J_{P-C} = 6.0 Hz), 63.9 (d, J_{P-C} = 6.0 Hz), 63.8 (d, J_{P-C} = 5.9 Hz), 62.7, 62.6, 42.0, 41.1, 15.9 (d, J_{P-C} = 6.9 Hz), 15.8 (d, J_{P-C} = 7.1 Hz), 15.73 (d, J_{P-C} = 7.2 Hz), 15.68 (d, J_{P-C} = 7.4 Hz), 13.93, 13.91; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.3; *minor diastereomer* δ -1.2; **TLC** (30% acetone:hexanes): R_f 0.19; **HRMS** (ESI): Calcd. for $C_{22}H_{28}CsNO_9P$ ($[M+Cs]^+$): 614.0556, Found: 614.0525.



Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-3-(4-(trifluoromethyl)phenyl)propanoate (45f): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 4-(trifluoromethyl)benzaldehyde (55 µL, 0.40 mmol) affording aldol adduct **45f** (91.8 mg, 0.18 mmol, 91% yield, 2.1:1.0 *anti*:*syn*) as a white solid (mp 84-91 °C). Analytical data for **45f**: **IR** (thin film): 3624, 2985, 1735, 1326, 1263, 1167, 1124, 1068, 1029, 701, 668 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.58 (d, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.25-7.17 (m, 5H), 5.71 (d, *J* = 9.6 Hz, 1H), 4.23-3.72 (m, 6H), 3.41 (d, *J* = 13.8 Hz, 1H), 3.23 (s, 1H), 3.20 (d, *J* = 13.8 Hz, 1H), 1.31 (dt, *J* = 7.2, 0.6 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.07 (dt, *J* = 7.2, 0.6 Hz, 3H); *minor diastereomer* δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.25-7.17 (m, 3H), 7.11-7.10 (m, 2H), 5.66 (d, *J* = 9.6 Hz, 1H), 4.23-3.72 (m, 6H), 3.55 (s, 1H), 2.95 (d, *J* = 13.8 Hz, 1H), 2.39 (d, *J* = 13.8 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.23 (dt, *J* = 7.2, 0.6 Hz, 3H), 1.03 (dt, *J* = 7.2, 0.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.6, 171.8, 139.6, 139.3, 135.0, 134.4, 131.1 (d, $J_{F–C}$ = 18.1 Hz), 130.0 (d, $J_{F–C}$ = 16.2 Hz), 130.1, 130.0, 129.4, 128.6, 128.1, 128.0, 127.03, 126.99, 124.9 (q, $J_{F–C}$ = 3.3 Hz), 124.8 (q, $J_{F–C}$ = 3.3 Hz), 124.7, 122.9, 81.7 (d, $J_{P–C}$ = 6.0 Hz), 81.6 (d, $J_{P–C}$ = 6.0 Hz), 80.7 (d, $J_{P–C}$ = 7.6 Hz), 80.2 (d, $J_{P–C}$ = 9.1 Hz), 64.2 (d, $J_{P–C}$ = 6.0 Hz), 63.9 (d, $J_{P–C}$ = 6.0 Hz), 63.8 (d, $J_{P–C}$ = 6.0 Hz), 63.7 (d, $J_{P–C}$ = 6.0 Hz), 62.7, 62.5, 42.1, 41.1, 16.0 (d, $J_{P–C}$ = 7.6 Hz), 15.8 (d, $J_{P–C}$ = 7.6 Hz), 15.7 (d, $J_{P–C}$ = 7.6 Hz), 15.6 (d, $J_{P–C}$ = 7.6 Hz), 14.00, 13.95; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.5; *minor diastereomer* δ -1.3; **TLC** (30% acetone:hexanes): R_f 0.27; **HRMS** (ESI): Calcd. for $C_{23}H_{28}CsF_3O_7P$ ($[M+Cs]^+$): 637.0579, Found: 637.0562.

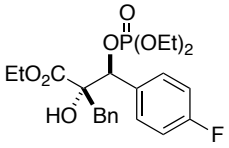


Ethyl 2-benzyl-3-(4-cyanophenyl)-3-((diethoxyphosphoryl)oxy)-2-hydroxypropanoate (45g): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 4-formylbenzonitrile (52.5 mg, 0.40 mmol) affording aldol adduct **45g** (85.8 mg, 0.19 mmol, 93% yield, 2.4:1.0 *anti*:*syn*) as a white solid (mp 94-98 °C). Analytical data for **45g**: **IR** (thin film): 3494, 2984, 2934, 2229, 1735, 1263, 1212, 1122, 1029, 891, 702 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.60 (d, *J* = 7.8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.24-7.17 (m, 5H), 5.67 (d, *J* = 9.6 Hz, 1H), 4.21-3.72 (m, 6H), 3.38 (d, *J* = 13.8 Hz, 1H), 3.20 (br s, 1H), 3.17 (d, *J* = 13.8 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); *minor diastereomer* δ 7.69 (br s, 4H), 7.24-7.17 (m, 3H), 7.09-7.08 (m, 2H), 5.62 (d, *J* = 8.4 Hz, 1H), 4.21-3.72 (m, 6H), 3.53 (br s, 1H), 2.94 (d, *J* = 13.8 Hz, 1H), 2.35 (d, *J* = 13.8 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.3, 171.6, 140.8, 140.5, 134.7, 134.1, 131.7, 131.6, 130.0, 129.9, 129.6, 128.9, 128.1, 127.9, 127.0, 127.0, 118.3, 118.2, 112.7, 112.7, 81.5 (d, $J_{P–C}$ = 6.0 Hz), 81.4 (d, $J_{P–C}$ = 6.0 Hz), 80.5 (d, $J_{P–C}$ = 7.6 Hz), 80.0 (d, $J_{P–C}$ = 9.1 Hz), 64.2 (d, $J_{P–C}$ = 6.0 Hz), 64.0 (d, $J_{P–C}$ = 6.0 Hz), 63.9 (d, $J_{P–C}$ = 6.0 Hz), 63.7 (d, $J_{P–C}$ = 6.0 Hz), 62.7, 62.5, 42.0, 41.0, 16.0 (d, $J_{P–C}$ = 7.6 Hz), 15.8 (d, $J_{P–C}$ = 7.6 Hz), 15.72 (d, $J_{P–C}$ = 7.6 Hz), 15.67 (d, $J_{P–C}$ = 7.6 Hz), 13.94, 13.91; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.4; *minor diastereomer* δ -1.2; **TLC** (30% acetone:hexanes): R_f 0.17; **HRMS** (ESI): Calcd. for $C_{23}H_{28}CsNO_7P$ ($[M+Cs]^+$): 594.0657, Found: 594.0677.



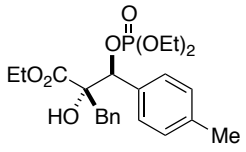
Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-3-phenylpropanoate (45h): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and benzaldehyde (41

μL, 0.40 mmol) affording aldol adduct **45h** (84.7 mg, 0.19 mmol, 97% yield, 2.1:1.0 *anti*:*syn*) as a white solid (mp 55-62 °C). Analytical data for **45h**: **IR** (thin film): 3503, 2983, 2934, 1734, 1456, 1262, 1213, 1121, 1033, 702 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.44-7.42 (m, 2H), 7.32-7.29 (m, 3H), 7.23 (m, 4H), 7.22-7.19 (m, 1H), 5.65 (d, *J* = 9.3 Hz, 1H), 4.21-3.65 (m, 6H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.21 (d, *J* = 13.7 Hz, 1H), 1.30 (dt, *J* = 7.2, 1.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.04 (dt, *J* = 7.2, 1.2 Hz, 3H); *minor diastereomer* δ 7.60-7.58 (m, 2H), 7.41-7.36 (m, 3H), 7.22-7.16 (m, 3H), 7.13-7.11 (m, 2H), 5.60 (d, *J* = 8.3 Hz, 1H), 4.21-3.65 (m, 6H), 2.94 (d, *J* = 13.6 Hz, 1H), 2.43 (d, *J* = 13.6 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.22 (dt, *J* = 7.2, 0.6 Hz, 3H), 1.01 (dt, *J* = 7.2, 0.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 173.0, 172.0, 135.6, 135.4, 135.2, 134.8, 130.1, 130.0, 129.0, 128.9, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 82.6 (d, $J_{P–C}$ = 6.0 Hz), 82.5 (d, $J_{P–C}$ = 6.0 Hz), 80.9 (d, $J_{P–C}$ = 7.6 Hz), 80.4 (d, $J_{P–C}$ = 6.0 Hz), 64.0 (d, $J_{P–C}$ = 4.5 Hz), 63.74 (d, $J_{P–C}$ = 6.0 Hz), 63.68 (d, $J_{P–C}$ = 6.0 Hz), 63.6 (d, $J_{P–C}$ = 7.6 Hz), 62.5, 62.2, 42.0, 41.1, 16.0 (d, $J_{P–C}$ = 7.6 Hz), 15.8 (d, $J_{P–C}$ = 7.6 Hz), 15.7 (d, $J_{P–C}$ = 7.6 Hz), 15.6 (d, $J_{P–C}$ = 6.0 Hz), 14.0, 13.9; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.3; *minor diastereomer* δ -1.2; **TLC** (30% acetone:hexanes): R_f 0.25; **HRMS** (ESI): Calcd. for $C_{22}H_{29}NaO_7P$ ($[M+Na]^+$): 459.1549, Found: 459.1571.



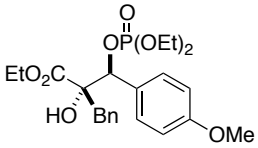
Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-3-(4-fluorophenyl)-2-hydroxypropanoate (45i): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 4-fluorobenzaldehyde (43 μL, 0.40 mmol) affording aldol adduct **45i** (89.1 mg, 0.20 mmol, 98% yield, 2.1:1.0 *anti*:*syn*) as a white solid (mp 74-78 °C). Analytical data for **45i**: **IR** (thin film): 3509, 2984, 1735, 1605, 1510, 1263, 1224, 1122, 1027, 702 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.44 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.25-7.17 (m, 5H), 7.00 (t, *J* = 8.4 Hz, 2H),

5.64 (d, J = 9.0 Hz, 1H), 4.22-3.69 (m, 6H), 3.20 (br s, 1H), 3.40 (d, J = 13.8 Hz, 1H), 3.19 (d, J = 13.8 Hz, 1H), 1.31 (dt, J = 7.2, 1.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 1.07 (dt, J = 7.2, 1.2 Hz, 3H); *minor diastereomer* δ 7.59 (dd, J = 9.0, 5.4 Hz, 2H), 7.25-7.17 (m, 3H), 7.12-7.11 (m, 2H), 7.11-7.08 (t, J = 9.0 Hz, 2H), 5.59 (d, J = 8.2 Hz, 1H), 4.22-3.69 (m, 6H), 3.51 (br s, 1H), 2.91 (d, J = 13.8 Hz, 1H), 2.40 (d, J = 13.8 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.23 (dt, J = 7.2, 0.6 Hz, 3H), 1.04 (dt, J = 7.2, 0.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 173.0, 172.0, 163.8 (d, $J_{F–C}$ = 27.2 Hz), 162.2 (d, $J_{F–C}$ = 27.2 Hz), 135.2, 134.7, 131.6, 131.2, 130.94, 130.88, 130.1 (d, $J_{F–C}$ = 10.1 Hz), 130.0 (d, $J_{F–C}$ = 8.2 Hz), 128.1, 128.0, 127.0, 126.9, 115.1 (d, $J_{F–C}$ = 13.6 Hz), 114.9 (d, $J_{F–C}$ = 12.1 Hz), 81.8 (d, $J_{P–C}$ = 6.0 Hz), 81.6 (d, $J_{P–C}$ = 4.5 Hz), 80.8 (d, $J_{P–C}$ = 7.6 Hz), 80.4 (d, $J_{P–C}$ = 7.6 Hz), 64.0 (d, $J_{P–C}$ = 4.5 Hz), 63.8 (d, $J_{P–C}$ = 6.0 Hz), 63.6 (d, $J_{P–C}$ = 6.0 Hz), 62.6, 62.3, 42.1, 41.2, 16.0 (d, $J_{P–C}$ = 7.6 Hz), 15.9 (d, $J_{P–C}$ = 6.0 Hz), 15.8 (d, $J_{P–C}$ = 7.6 Hz), 15.7 (d, $J_{P–C}$ = 6.0 Hz), 14.1, 14.0; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.4; *minor diastereomer* δ -1.3; **TLC** (30% acetone:hexanes): R_f 0.22; **HRMS** (ESI): Calcd. for $C_{22}H_{28}CsFO_7P$ ($[M+Cs]^+$): 587.0611, Found: 587.0596.



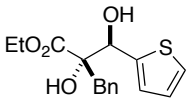
Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-3-(*p*-tolyl)propanoate (45j): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and *p*-tolualdehyde (47 μL, 0.40 mmol) affording aldol adduct **45j** (87.4 mg, 0.19 mmol, 97% yield, 2.0:1.0 *anti*:*syn*) as a white solid (mp 75-81 °C). Analytical data for **45j**: **IR** (thin film): 3508, 2982, 1735, 1455, 1264, 1209, 1122, 1029, 891, 808, 701 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.31 (d, J = 8.1 Hz, 2H), 7.25-7.16 (m, 5H), 7.10 (d, J = 8.0 Hz, 2H), 5.62 (d, J = 9.2 Hz, 1H), 4.22-3.66 (m, 6H), 3.40 (d, J = 13.7 Hz, 1H), 3.20 (d, J = 13.7 Hz, 1H), 2.30 (s, 3H), 1.30 (dt, J = 7.1, 2.4 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H); *minor diastereomer* δ 7.47

(d, J = 8.0 Hz, 2H), 7.25-7.16 (m, 5H), 7.12 (dd, J = 7.9, 1.8 Hz, 2H), 5.56 (d, J = 8.2 Hz, 1H), 4.22-3.66 (m, 6H), 2.91 (d, J = 13.7 Hz, 1H), 2.41 (d, J = 13.6 Hz, 1H), 2.36 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 173.0, 172.0, 135.6, 135.4, 135.2, 134.8, 130.1, 130.0, 129.0, 128.9, 128.1, 128.0, 127.90, 127.86, 126.83, 126.80, 82.6 (d, $J_{P–C}$ = 5.6 Hz), 82.5 (d, $J_{P–C}$ = 5.6 Hz), 82.4, 80.9 (d, $J_{P–C}$ = 7.4 Hz), 80.4 (d, $J_{P–C}$ = 8.5 Hz), 64.0 (d, $J_{P–C}$ = 5.6 Hz), 63.74 (d, $J_{P–C}$ = 6.0 Hz), 63.68 (d, $J_{P–C}$ = 6.3 Hz), 63.6 (d, $J_{P–C}$ = 6.2 Hz), 62.5, 62.2, 42.0, 41.1, 16.0 (d, $J_{P–C}$ = 7.1 Hz), 15.8 (d, $J_{P–C}$ = 6.9 Hz), 15.7 (d, $J_{P–C}$ = 7.2 Hz), 15.6 (d, $J_{P–C}$ = 5.7 Hz), 14.0, 13.9, one pair of carbons was not found due to overlap; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.5; *minor diastereomer* δ -1.4; **TLC** (30% acetone:hexanes): R_f 0.23; **HRMS** (ESI): Calcd. for $C_{23}H_{31}CsO_7P$ ($[M+Cs]^+$): 583.0962, Found: 583.0985.

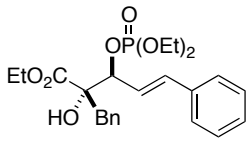


Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-3-(4-methoxyphenyl)propanoate (45k): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and *p*-anisaldehyde (122 μL, 1.00 mmol) affording aldol adduct **45k** (64.4 mg, 0.14 mmol, 69% yield, 5.0:1.0 *anti*:*syn*) as a white solid (mp 79-86 °C). Analytical data for **45k**: **IR** (thin film): 3509, 3649, 2360, 2337, 1734, 1613, 1515, 1457, 1251, 1121, 1030, 702 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.37 (d, J = 8.8 Hz, 2H), 7.25-7.14 (m, 5H), 6.82 (d, J = 8.8 Hz, 2H), 5.61 (d, J = 9.2 Hz, 1H), 4.21-3.69 (m, 6H), 3.77 (s, 3H), 3.40 (d, J = 13.7 Hz, 1H), 3.20 (d, J = 13.7 Hz, 1H), 1.30 (dt, J = 7.1, 1.0 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 1.06 (dt, J = 7.1, 1.0 Hz, 3H); *minor diastereomer* δ 7.54 (d, J = 8.8 Hz, 2H), 7.25-7.14 (m, 3H), 7.12 (dd, J = 7.9, 1.6 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.57 (d, J = 8.1 Hz, 1H), 4.21-3.69 (m, 6H), 3.82 (s, 3H), 2.91 (d, J = 13.7 Hz, 1H), 2.44 (d, J = 13.7 Hz, 1H), 1.31 (dt, J = 7.1, 1.0 Hz, 3H), 1.22 (dt, J = 7.1, 1.0 Hz,

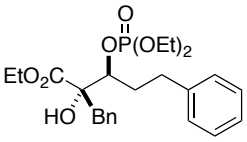
3H), 1.03 (dt, J = 7.1, 1.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 173.2, 172.1, 160.1, 159.9, 135.5, 135.0, 132.1, 130.4, 130.2, 130.14, 130.07, 129.5, 128.0, 127.9, 127.8, 126.9, 113.4, 113.3, 82.4 (d, $J_{P–C}$ = 5.4 Hz), 82.2 (d, $J_{P–C}$ = 5.4 Hz), 81.0 (d, $J_{P–C}$ = 7.7 Hz), 80.6 (d, $J_{P–C}$ = 8.5 Hz), 64.0 (d, $J_{P–C}$ = 5.6 Hz), 63.74 (d, $J_{P–C}$ = 7.1 Hz), 63.69 (d, $J_{P–C}$ = 6.2 Hz), 63.57 (d, $J_{P–C}$ = 5.7 Hz), 62.5, 62.2, 55.2, 55.1, 42.1, 41.2, 16.0 (d, $J_{P–C}$ = 7.4 Hz), 15.94 (d, $J_{P–C}$ = 6.6 Hz), 15.90 (d, $J_{P–C}$ = 6.8 Hz), 15.8 (d, $J_{P–C}$ = 7.6 Hz), 14.1, 14.0; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.5; *minor diastereomer* δ -1.4; **TLC** (30% acetone:hexanes): R_f 0.20; **HRMS** (ESI): Calcd. for $C_{23}H_{31}CsO_8P$ ([M+Cs]$^+$): 599.0811, Found: 599.0786.



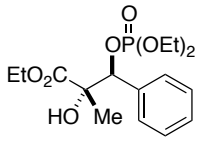
Ethyl 2-benzyl-2,3-dihydroxy-3-(thiophen-2-yl)propanoate (45l): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and 2-thiophenecarboxaldehyde (37 µL, 0.40 mmol) affording aldol adduct **45l** (49.6 mg, 0.16 mmol, 81% yield, 6.7:1.0 *anti*:*syn*) as a white solid (mp 69-72 °C). Analytical data for **45l**: **IR** (thin film): 3501, 3031, 2981, 2930, 1732, 1496, 1455, 1436, 1370, 1216, 1114, 1034, 859, 701 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.40 (d, J = 5.0 Hz, 1H), 7.33-7.21 (m, 6H), 7.08 (dd, J = 5.0, 3.5 Hz, 1H), 5.27 (d, J = 7.7 Hz, 1H), 4.28-4.19 (m, 2H), 3.64 (s, 1H), 3.01 (d, J = 13.7 Hz, 1H), 2.90 (d, J = 8.4 Hz, 1H), 2.76 (d, J = 13.7 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); *minor diastereomer* δ 7.33-7.21 (m, 7H), 6.99 (dd, J = 5.0, 3.5 Hz, 1H), 5.22 (d, J = 8.2 Hz, 1H), 4.08-4.02 (m, 2H), 3.49 (d, J = 13.7 Hz, 1H), 3.47 (s, 1H), 3.24 (d, J = 13.7 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *major diastereomer* δ 173.7, 141.5, 135.1, 130.0, 128.1, 128.1, 127.2, 126.9, 126.5, 126.3, 80.8, 74.1, 62.4, 41.6, 14.1; **TLC** (30% ethyl acetate:hexanes): R_f 0.24; **HRMS** (ESI): Calcd. for $C_{16}H_{18}O_4NaS$ ([M+Cs]$^+$): 329.0824, Found: 329.0811.



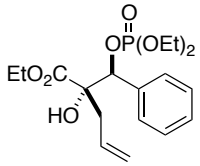
(*E*)-Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-5-phenylpent-4-enoate (45m): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and *trans*-cinnamaldehyde (126 µL, 1.00 mmol) affording aldol adduct **45m** (65.7 mg, 0.14 mmol, 71% yield, 4.2:1.0 *anti*:*syn*) as a pale yellow oil. Analytical data for **45m**: **IR** (thin film): 3395, 2982, 2934, 1734, 1684, 1653, 1541, 1456, 1263, 1203, 1119, 1031, 751, 700 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.39 (d, *J* = 7.3 Hz, 2H), 7.34 (d, *J* = 7.3 Hz, 2H), 7.27-7.19 (m, 4H), 7.22 (d, *J* = 7.3 Hz, 2H), 6.74 (d, *J* = 17.8 Hz, 1H), 6.39 (dd, *J* = 16.0, 8.9 Hz, 1H), 5.19 (t, *J* = 8.5 Hz, 1H), 4.29-3.57 (m, 6H), 3.55 (br s, 1H), 3.19 (d, *J* = 13.7 Hz, 1H), 3.12 (d, *J* = 13.7 Hz, 1H), 1.34 (dt, *J* = 7.1, 0.7 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.23 (dt, *J* = 7.1, 0.7 Hz, 3H); *minor diastereomer* δ 7.49 (d, *J* = 7.3 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.27-7.19 (m, 6H), 6.90 (d, *J* = 16.1 Hz, 1H), 6.46 (dd, *J* = 16.0, 9.2 Hz, 1H), 5.24 (t, *J* = 7.3 Hz, 1H), 4.29-3.57 (m, 6H), 3.49 (br s, 1H), 2.91 (d, *J* = 13.8 Hz, 1H), 2.86 (d, *J* = 13.7 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.28 (dt, *J* = 7.1, 0.7 Hz, 3H), 1.19 (dt, *J* = 7.1, 0.7 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.9, 172.2, 137.5, 136.2, 135.7, 135.1, 134.9, 130.2, 130.1, 128.64, 128.57, 128.5, 128.1, 128.0, 127.0, 126.8, 122.9, 122.2, 83.5 (d, $J_{P–C}$ = 5.4 Hz), 83.3 (d, $J_{P–C}$ = 5.4 Hz), 80.6 (d, $J_{P–C}$ = 6.8 Hz), 80.3 (d, $J_{P–C}$ = 7.9 Hz), 64.0 (d, $J_{P–C}$ = 6.1 Hz), 63.8 (d, $J_{P–C}$ = 6.1 Hz), 63.74 (d, $J_{P–C}$ = 5.1 Hz), 63.71 (d, $J_{P–C}$ = 4.8 Hz), 62.4, 62.3, 41.7, 41.1, 16.1 (d, $J_{P–C}$ = 6.8 Hz), 16.00 (d, $J_{P–C}$ = 6.8 Hz), 15.96 (d, $J_{P–C}$ = 7.1 Hz), 15.9 (d, $J_{P–C}$ = 6.6 Hz), 14.2, 14.1, one pair of carbons was not found due to overlap; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ 1.0; *minor diastereomer* δ 0.3; **TLC** (30% acetone:hexanes): R_f 0.40; **HRMS** (ESI): Calcd. for $C_{24}H_{31}CsO_7P$ ($[M+Cs]^+$): 595.0861, Found: 595.0844.



Ethyl 2-benzyl-3-((diethoxyphosphoryl)oxy)-2-hydroxy-5-phenylpentanoate (45n): The title compound was prepared according to General Procedure C using **41a** (66.1 mg, 0.20 mmol) and hydrocinnamaldehyde (132 μL, 1.00 mmol) affording aldol adduct **45n** (52.0 mg, 0.11 mmol, 56% yield, 5.9:1.0 *anti*:*syn*) as a pale yellow oil. Analytical data for **45n**: **IR** (thin film): 3399, 2982, 2934, 2360, 2342, 1733, 1684, 1653, 1558, 1507, 1456, 1262, 1207, 1024, 749, 701 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.32-7.18 (m, 10H), 4.73 (dt, *J* = 9.6, 2.3 Hz, 1H), 4.22-4.05 (m, 6H), 3.14 (d, *J* = 13.6 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 2.93 (ddd, *J* = 14.5, 10.1, 5.0 Hz, 1H), 2.70 (ddd, *J* = 13.9, 9.9, 6.8 Hz, 1H), 2.23 (dddd, *J* = 19.6, 14.7, 9.8, 5.0 Hz, 1H), 1.79 (dddd, *J* = 14.5, 10.4, 7.5, 4.7 Hz, 1H), 1.37 (dt, *J* = 7.1, 0.7 Hz, 3H), 1.36 (dt, *J* = 7.1, 0.7 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); *minor diastereomer* δ 7.32-7.18 (m, 10H), 4.83 (dt, *J* = 9.0, 2.9 Hz, 1H), 4.22-4.05 (m, 6H), 3.05 (ddd, *J* = 13.9, 11.4, 5.3 Hz, 1H), 2.94 (d, *J* = 13.6 Hz, 1H), 2.92 (d, *J* = 13.6 Hz, 1H), 2.79 (ddd, *J* = 13.7, 11.2, 5.8 Hz, 1H), 2.26-2.13 (m, 2H), 1.35 (dt, *J* = 7.1, 0.7 Hz, 3H), 1.32 (dt, *J* = 7.1, 0.7 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 173.0, 172.7, 141.6, 141.3, 135.2, 135.0, 130.2, 128.44, 128.39, 128.1, 128.0, 127.0, 126.9, 126.0, 82.8 (d, $J_{P–C}$ = 6.2 Hz), 82.4 (d, $J_{P–C}$ = 6.2 Hz), 80.52 (d, $J_{P–C}$ = 3.5 Hz), 80.50 (d, $J_{P–C}$ = 3.0 Hz), 64.13 (d, $J_{P–C}$ = 5.7 Hz), 64.06 (d, $J_{P–C}$ = 6.0 Hz), 64.0 (d, $J_{P–C}$ = 6.2 Hz), 63.9 (d, $J_{P–C}$ = 6.2 Hz), 62.3, 62.2, 41.8, 40.9, 33.5 (d, $J_{P–C}$ = 3.8 Hz), 32.3 (d, $J_{P–C}$ = 2.0 Hz), 31.9, 31.8, 16.4 (d, $J_{P–C}$ = 7.1 Hz), 16.0 (d, $J_{P–C}$ = 7.6 Hz), 14.0, 13.9; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ 0.1; *minor diastereomer* δ -1.1; **TLC** (30% acetone:hexanes): R_f 0.24; **HRMS** (ESI): Calcd. for $C_{24}H_{33}CsO_7P$ ($[M+Cs]^+$): 597.1018, Found: 597.1021.

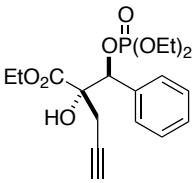


Ethyl 3-((diethoxyphosphoryl)oxy)-2-hydroxy-2-methyl-3-phenylpropanoate (45p): The title compound was prepared according to General Procedure C using **41b** (50.8 mg, 0.20 mmol) and benzaldehyde (41 μL, 0.40 mmol) affording aldol adduct **45p** (58.4 mg, 0.16 mmol, 81% yield, 1.9:1.0 *anti*:*syn*) as a pale yellow oil. Analytical data for **45p**: **IR** (thin film): 3395, 2985, 2942, 1734, 1636, 1558, 1457, 1396, 1260, 1211, 1168, 1118, 1021, 893, 708 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.46 (dd, J = 7.5, 3.2 Hz, 2H), 7.36-7.29 (m, 3H), 5.43 (d, J = 9.3 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H), 1.21 (dt, J = 7.1, 0.7 Hz, 3H), 1.15 (s, 3H), 0.98 (dt, J = 7.1, 0.7 Hz, 3H); *minor diastereomer* δ 7.36-7.29 (m, 5H), 5.42 (d, J = 8.2 Hz, 1H), 1.56 (s, 3H), 1.25 (dt, J = 7.1, 0.7 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.04 (dt, J = 7.1, 0.7 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 174.7, 173.6; 135.6, 135.0, 128.9, 128.81, 128.77, 127.90, 127.88, 127.8, 82.7 (d, $J_{P–C}$ = 5.4 Hz), 82.6 (d, $J_{P–C}$ = 5.6 Hz), 77.2 (d, $J_{P–C}$ = 7.9 Hz), 76.7 (d, $J_{P–C}$ = 8.3 Hz), 63.9 (d, $J_{P–C}$ = 5.7 Hz), 63.8 (d, $J_{P–C}$ = 5.6 Hz), 63.7 (d, $J_{P–C}$ = 5.7 Hz), 63.6 (d, $J_{P–C}$ = 5.7 Hz), 62.5, 62.2, 22.6, 21.8, 15.92 (d, $J_{P–C}$ = 9.5 Hz), 15.87 (d, $J_{P–C}$ = 7.1 Hz), 15.7 (d, $J_{P–C}$ = 8.9 Hz), 15.6 (d, $J_{P–C}$ = 7.2 Hz), 14.04, 13.95; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -1.3; *minor diastereomer* δ -0.6; **TLC** (30% acetone:hexanes): R_f 0.21; **HRMS** (ESI): Calcd. for $C_{16}H_{25}CsO_7P$ ($[M+Cs]^+$): 493.0392, Found: 493.0359.



Ethyl 2-(((diethoxyphosphoryl)oxy)(phenyl)methyl)-2-hydroxypent-4-enoate (45q): The title compound was prepared according to General Procedure C using **41c** (56.1 mg, 0.20 mmol) and benzaldehyde (41 μL, 0.40 mmol) affording aldol adduct **45q** (68.8 mg, 0.18 mmol, 89% yield, 1.2:1.0 *anti*:*syn*) as a pale yellow oil. Analytical data for **45q**: **IR** (thin film): 3503, 3074, 2983, 2933, 1735, 1642, 1456, 1395, 1370, 1264, 1227, 1161, 1034, 710 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major*

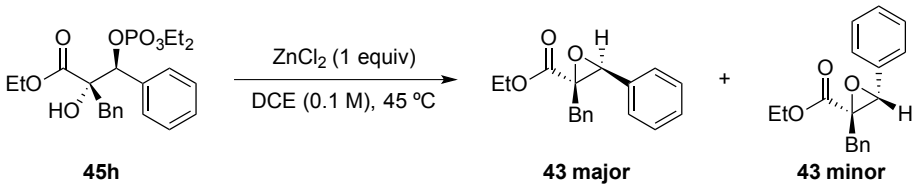
diastereomer δ 7.48 (dd, J = 7.5, 3.0 Hz, 2H), 7.35-7.33 (m, 3H), 5.67-5.60 (m, 1H), 5.45 (d, J = 8.3 Hz, 1H), 5.02 (d, J = 9.2 Hz, 1H), 5.01 (d, J = 18.8 Hz, 1H), 4.39-3.62 (m, 6H), 3.42 (br s, 1H), 2.37 (dd, J = 13.9, 8.6 Hz, 1H), 1.90 (dd, J = 13.9, 5.8 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H), 1.21 (dt, J = 7.1, 0.7 Hz, 3H), 0.97 (dt, J = 7.1, 0.8 Hz, 3H); *minor diastereomer* δ 7.37 (dd, J = 7.1, 3.0 Hz, 2H), 7.30-7.28 (m, 3H), 5.79-5.72 (m, 1H), 5.48 (d, J = 9.2 Hz, 1H), 5.11 (d, J = 24.1 Hz, 1H), 5.09 (d, J = 17.0 Hz, 1H), 4.39-3.62 (m, 6H), 3.42 (br s, 1H), 2.83 (dd, J = 13.9, 6.1 Hz, 1H), 2.63 (dd, J = 13.9, 8.6 Hz, 1H), 1.26 (dt, J = 7.1, 0.8 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.01 (dt, J = 7.1, 0.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 173.5, 172.5, 135.5, 135.1, 131.8, 131.2, 128.93, 128.85, 127.94, 127.91, 119.2, 119.1, 82.3 (d, $J_{P–C}$ = 5.6 Hz), 82.1 (d, $J_{P–C}$ = 5.3 Hz), 80.2 (d, $J_{P–C}$ = 7.7 Hz), 79.7 (d, $J_{P–C}$ = 8.0 Hz), 63.9 (d, $J_{P–C}$ = 5.7 Hz), 63.8 (d, $J_{P–C}$ = 5.7 Hz), 63.7 (d, $J_{P–C}$ = 6.3 Hz), 63.6 (d, $J_{P–C}$ = 5.9 Hz), 62.5, 62.2, 40.4, 39.6, 15.94 (d, $J_{P–C}$ = 7.4 Hz), 15.86 (d, $J_{P–C}$ = 7.6 Hz), 15.7 (d, $J_{P–C}$ = 6.5 Hz), 15.6 (d, $J_{P–C}$ = 6.8 Hz), 14.1, 14.0; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -1.3; *minor diastereomer* δ -0.5; **TLC** (30% acetone:hexanes): R_f 0.29; **HRMS** (ESI): Calcd. for $C_{18}H_{27}CsO_7P$ ($[M+Cs]^+$): 519.0548, Found: 519.0572.



Ethyl 2-(((diethoxyphosphoryl)oxy)(phenyl)methyl)-2-hydroxypent-4-ynoate (45r): The title compound was prepared according to General Procedure C using **41d** (55.6 mg, 0.20 mmol) and benzaldehyde (41 μL, 0.40 mmol) affording aldol adduct **45r** (71.5 mg, 0.19 mmol, 93% yield, 2.9:1.0 *anti*:*syn*) as a pale yellow oil. Analytical data for **45r**: **IR** (thin film): 3479, 3287, 2983, 2934, 2121, 1739, 1445, 1393, 1369, 1288, 1242, 1167, 1107, 1021, 976, 779, 734 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.38-7.36 (m, 2H), 7.33-7.29 (m, 3H), 5.46 (d, J = 9.2 Hz, 1H), 4.44-3.62 (m, 6H), 2.91 (dd, J = 16.7, 2.6 Hz, 1H), 2.83 (dd, J = 16.7, 2.6 Hz, 1H), 2.01 (t, J = 2.6 Hz, 1H),

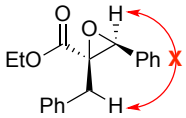
1.25 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.1 Hz, 3H); *minor diastereomer* δ 7.48-7.46 (m, 2H), 7.33-7.29 (m, 3H), 5.45 (d, J = 10.9 Hz, 1H), 4.44-3.62 (m, 6H), 2.54 (dd, J = 16.7, 2.6 Hz, 1H), 2.10 (dd, J = 16.7, 2.6 Hz, 1H), 1.96 (t, J = 2.6 Hz, 1H), 1.37 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 172.5, 171.5, 135.1, 134.4, 129.2, 129.0, 128.7, 128.1, 128.0, 127.9, 81.3 (d, $J_{P–C}$ = 5.4 Hz), 79.2 (d, $J_{P–C}$ = 7.6 Hz), 78.7 (d, $J_{P–C}$ = 8.9 Hz), 78.4, 77.7, 71.4, 71.2, 64.0 (d, $J_{P–C}$ = 5.7 Hz), 63.83 (d, $J_{P–C}$ = 7.7 Hz), 63.78 (d, $J_{P–C}$ = 6.5 Hz), 63.6 (d, $J_{P–C}$ = 5.9 Hz), 63.0, 62.7, 27.0, 26.4, 15.9 (d, $J_{P–C}$ = 7.4 Hz), 15.8 (d, $J_{P–C}$ = 6.9 Hz), 15.64 (d, $J_{P–C}$ = 6.9 Hz), 15.59 (d, $J_{P–C}$ = 7.1 Hz), 14.02, 13.95, one carbon was not found due to overlap; **^{31}P NMR** (243 MHz, $CDCl_3$): *major diastereomer* δ -0.6; *minor diastereomer* δ -1.3; **TLC** (30% acetone:hexanes): R_f 0.29; **HRMS** (ESI): Calcd. for $C_{18}H_{25}CsO_7P$ ([M+Cs]$^+$): 517.0392, Found: 517.0387.

Conversion of Aldol Adduct 45h to Epoxide 43

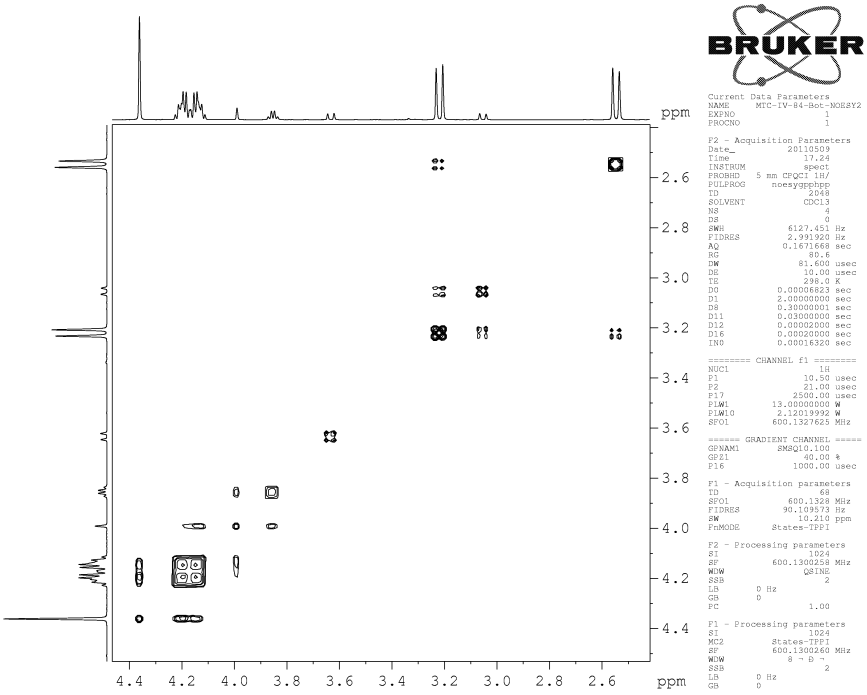


A dried shell vial was charged with phosphate **45h** (87.3 mg, 0.20 mmol, 1.0 equiv, 2:1 d.r.) in 1,2-dichloroethane (DCE) (2 mL). $ZnCl_2$ (32.7 mg, 0.20 mmol, 1.0 equiv) was added to the vial, which was then capped with a Teflon cap. The vial was heated at 45 °C until the reaction was adjudged complete by TLC. The reaction was diluted with DCM and extracted with H_2O (1x). The aqueous layer was extracted with DCM (2x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 10% ethyl acetate:hexanes to afford a diastereomeric mixture of **43** (45.7 mg, 0.16 mmol, 81% yield, 2:1 d.r.) as a pale yellow

oil. The diastereomers were separated by preparative HPLC to afford diastereomerically pure samples for nOe analysis. Analytical data for **43**: **IR** (thin film): 3063, 3031, 2980, 2932, 1750, 1727, 1454, 1372, 1242, 1191, 1121, 1018, 745, 698 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.40-7.19 (m, 10H), 4.36 (s, 1H), 4.23-4.11 (m, 2H), 3.22 (d, *J* = 15.1 Hz, 1H), 2.55 (d, *J* = 15.1 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); *minor diastereomer* δ 7.35-7.26 (m, 10H), 4.01 (s, 1H), 3.87 (q, *J* = 7.1 Hz, 2H), 3.65 (d, *J* = 14.6 Hz, 1H), 3.07 (d, *J* = 14.6 Hz, 1H), 0.87 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 169.8, 167.6, 136.4, 135.1, 133.7, 133.4, 129.6, 129.3, 128.43, 128.36, 128.24, 128.17, 128.0, 127.9, 127.0, 126.63, 126.56, 126.3, 66.4, 63.6, 62.3, 61.9, 61.7, 61.0, 39.0, 32.4, 14.0, 13.7; **TLC** (10% ethyl acetate:hexanes): R_f 0.22; **HRMS** (ESI): Calcd. for $C_{18}H_{18}CsO_3$ ($[M+Cs]^+$): 415.0310, Found: 415.0309.



43 major



BRUKER

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Current Data Parameters
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EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
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PULPROG     noesygpphpp
TD                    2048
SOLVENT              CDCl3
NS                       4
DS                       0
SWH               6127.451 Hz
FIDRES            2.991920 Hz
AQ                0.1671668 sec
RG                     80.6
DW                   81.600 usec
DE                   10.00 usec
TE                   298.0 K
D0              0.00006823 sec
D1              2.00000000 sec
D8              0.30000001 sec
D11             0.03000000 sec
D12             0.00002000 sec
D16             0.00020000 sec
IN0             0.00016320 sec

======== CHANNEL f1 ========
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P1                    10.50 usec
P2                    21.00 usec
PL7                 2500.00 usec
PLW1           13.00000000 W
PLW10           2.12019992 W
SFO1           600.1327625 MHz

====== GRADIENT CHANNEL =====
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GPZ1                  40.00 %
P16                 1000.00 usec

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FIDRES            90.109573 Hz
SW                    10.210 ppm
FnMODE         States-TPPI

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SSB                          2
LB          0 Hz
GB          0
PC                       1.00

F1 - Processing parameters
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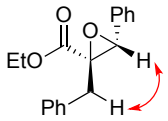
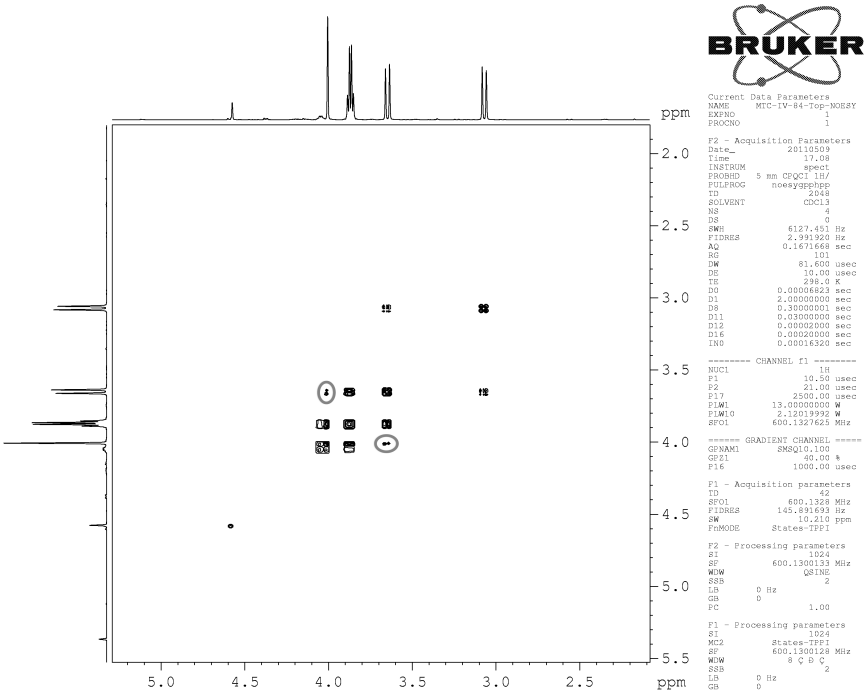
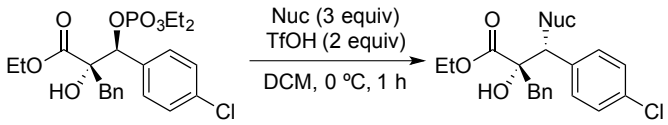


43 minor



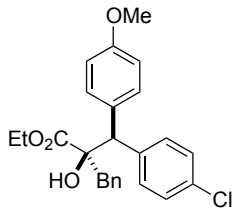
General Procedure D for the Friedel–Crafts Alkylation of Phosphate Aldol Adduct 45a



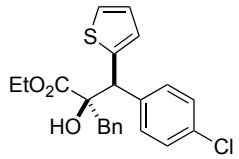
45h

A dried screw-cap vial was charged with phosphate (±)-**45a** (94.2 mg, 0.20 mmol, 1.0 equiv), nucleophile (0.60 mmol, 3.0 equiv), and DCM (2 mL). TfOH (35 µL, 0.40 mmol, 2.0 equiv) was added dropwise and the reaction stirred at room temperature for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ and the layers were separated. The aqueous layer was washed with DCM (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4,

filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The residue was purified by column chromatography on silica gel eluting with 10% ethyl acetate:hexanes to afford a diastereomeric mixture of the product.

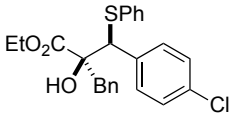


Ethyl 2-benzyl-3-(4-chlorophenyl)-2-hydroxy-3-(4-methoxyphenyl)propanoate (7): The title compound was prepared according to General Procedure D using (±)-**45a** (94.2 mg, 0.20 mmol, 2:1 d.r.) and anisole (65 µL, 0.60 mmol) affording Friedel–Crafts adduct **62** (77.3 mg, 0.18 mmol, 91% yield, >20:1 d.r.) as a pale yellow oil. Analytical data for **62**: **IR** (thin film): 3502, 3029, 2932, 1731, 1608, 1510, 1490, 1249, 1200, 1100, 1033, 827, 701 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 2H), 7.23-7.17 (m, 3H), 7.11 (d, *J* = 7.4 Hz, 2H), 6.76 (d, *J* = 7.3 Hz, 2H), 4.36 (s, 1H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.73 (s, 3H), 3.40 (s, 1H), 2.99 (d, *J* = 13.5 Hz, 1H), 2.91 (d, *J* = 13.5 Hz, 1H), 1.14 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.4, 158.5, 139.1, 135.8, 132.7, 132.2, 131.4, 130.1, 130.0, 128.5, 128.1, 126.9, 113.7, 81.2, 62.0, 57.3, 55.1, 44.7, 14.1; **TLC** (30% acetone:hexanes): R_f 0.44; **HRMS** (ESI): Calcd. for $C_{25}H_{25}ClCsO_4$ ([M+Cs]$^{+}$): 557.0495, Found: 557.0471.



Ethyl 2-benzyl-3-(4-chlorophenyl)-2-hydroxy-3-(thiophen-2-yl)propanoate (63): The title compound was prepared according to General Procedure D using (±)-**45a** (94.2 mg, 0.20 mmol, 2:1 d.r.) and thiophene (48 µL, 0.60 mmol) affording Friedel–Crafts adduct **63** (44.1 mg, 0.11 mmol, 55% yield, 4:1 d.r.) as a pale yellow oil. Analytical data for **63**: **IR** (thin film): 3497, 2980, 2929, 2853, 1731, 1492, 1243, 1200, 1100, 1015, 910, 825, 733, 700 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.22-7.17 (m, 2H), 7.14 (d, *J* =

5.0 Hz, 1H), 7.10-7.08 (m, 3H), 6.99 (d, J = 2.9 Hz, 1H), 6.87 (t, J = 4.2 Hz, 1H), 4.75 (s, 1H), 4.08-3.95 (m, 2H), 3.58 (s, 1H), 2.95 (d, J = 13.1 Hz, 1H), 2.73 (d, J = 13.4 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H); *minor diastereomer* δ 7.59 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.22-7.17 (m, 8H), 4.57 (s, 1H), 4.08-3.95 (m, 2H), 3.40 (s, 1H), 2.97 (d, J = 11.3 Hz, 1H), 2.78 (d, J = 13.4 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 174.4, 174.0, 141.8, 140.3, 138.1, 138.0, 135.55, 135.51, 133.1, 132.9, 131.5, 131.3, 129.9, 128.54, 128.47, 128.1, 128.0, 126.9, 126.15, 126.05, 125.1, 125.0, 122.4, 80.8, 80.7, 62.2, 62.0, 53.9, 53.7, 44.6, 44.3, 14.0, 14.0; **TLC** (30% acetone:hexanes): R_f 0.48; **HRMS** (ESI): Calcd. for $C_{22}H_{21}ClCsO_3S$ ([M+Cs]$^+$): 532.9954, Found: 532.9932.



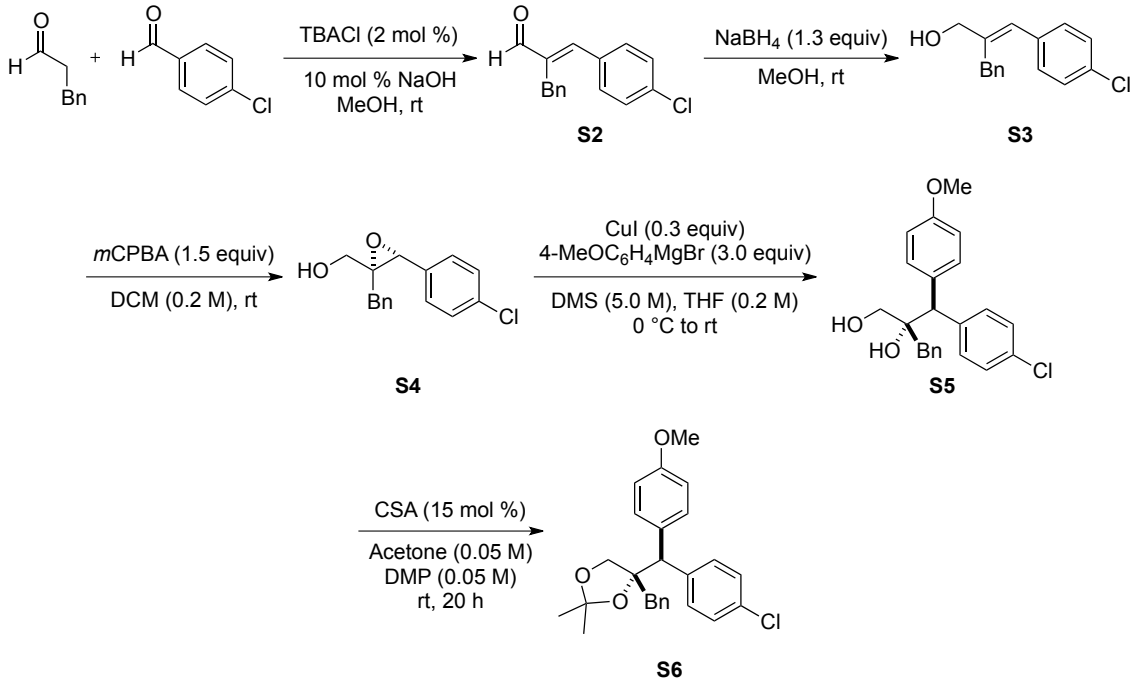
Ethyl 2-benzyl-3-(4-chlorophenyl)-2-hydroxy-3-(phenylthio)propanoate (64): The title compound was prepared according to General Procedure D using (±)-**45a** (94.2 mg, 0.20 mmol, 2:1 d.r.) and thiophenol (62 μL, 0.60 mmol) affording Friedel–Crafts adduct **64** (77.7 mg, 0.18 mmol, 91% yield, 5:1 d.r.) as a pale yellow oil. Analytical data for **64**: **IR** (thin film): 3500, 3061, 3031, 2981, 2930, 1732, 1584, 1491, 1408, 1244, 1215, 1104, 1015, 910, 734, 701 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 7.49 (d, J = 7.7 Hz, 2H), 7.34-7.19 (m, 10H), 7.08 (d, J = 6.8 Hz, 2H), 4.49 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.65 (s, 1H), 2.84 (d, J = 13.5 Hz, 1H), 2.53 (d, J = 13.5 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); *minor diastereomer* δ 7.34-7.19 (m, 14H), 4.45 (s, 1H), 3.94-3.83 (m, 2H), 3.89 (d, J = 13.5 Hz, 1H), 3.38 (s, 1H), 3.21 (d, J = 13.5 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): *mix of diastereomers* δ 173.5, 172.7, 137.8, 137.5, 135.4, 135.1, 134.8, 134.6, 133.5, 133.4, 132.4, 131.2, 130.5, 130.2, 129.9, 128.9, 128.8, 128.3, 128.15, 128.07, 127.54, 127.45, 127.03, 127.00, 81.1, 81.0, 62.4, 62.2, 61.5, 61.3, 44.6, 44.4, 14.1, 13.9; **TLC**

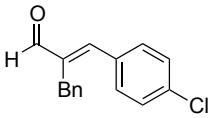
(30% acetone:hexanes): R_f 0.48; **HRMS** (ESI): Calcd. for $C_{24}H_{23}ClCsO_3S$ ([M+Cs]$^+$): 559.0110, Found: 559.0126.

Stereochemical Determination of Friedel–Crafts Adduct 62

The relative stereochemistry of Friedel–Crafts adduct **7** was determined by comparison of acetonide **S6** (obtained via stereospecific synthesis) to acetonide **S8** (obtained via derivatization of **62**).

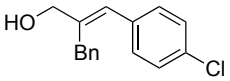
Preparation of Acetonide S6



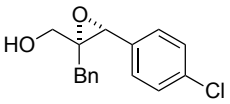


(*E*)-2-benzyl-3-(4-chlorophenyl)acrylaldehyde (S2): A 20-mL round-bottomed flask was charged with hydrocinnamaldehyde (1.0 mL, 7.1 mmol, 1.00 equiv), 4-chlorobenzaldehyde (1.0 g, 7.1 mmol, 1.00 equiv) and tetrabutylammonium chloride (40 mg, 0.14 mmol, 0.02 equiv) in MeOH (5 mL). The solution was cooled to 0 °C in an ice bath. To the vigorously stirring solution was added 10% aq. NaOH (5 mL) dropwise. The resulting solution was allowed to stir for 15 min at 0 °C before being

allowed to warm to room temperature. After 4 h, the reaction was acidified by addition of 2 M HCl until acidic by litmus paper. The layers were separated and the aqueous layer was extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude aldehyde **S2** as a pale orange oil.

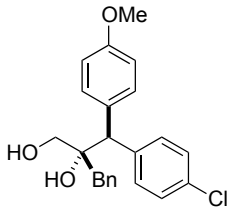


(*E*)-2-benzyl-3-(4-chlorophenyl)prop-2-en-1-ol (S3): A 250-mL round-bottomed flask was charged with the crude aldehyde **S2** in MeOH (50 mL). $NaBH_4$ (0.35 g, 9.2 mmol, 1.3 equiv) was carefully added portionwise at room temperature. The reaction stirred at room temperature until complete by TLC. The reaction was quenched with sat. aq. NH_4Cl and allowed to stir for a further 4 h. The layers were separated and the aqueous layer was extracted with DCM (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 20% ethyl acetate:hexanes to afford allyl alcohol **S3** (1.27 g, 4.9 mmol, 69% yield, >20:1 *E*:*Z*) as a white solid (mp 63-64 °C). Analytical data for **S3**: **IR** (thin film): 3391, 3026, 2919, 1652, 1601, 1491, 1452, 1092, 1013, 732, 699 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31-7.28 (m, 4H), 7.24-7.21 (m, 3H), 7.18 (d, J = 7.1 Hz, 2H), 6.75 (s, 1H), 4.14 (d, J = 1.1 Hz, 2H), 3.67 (s, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 140.3, 138.7, 135.5, 132.6, 129.8, 128.7, 128.5, 128.4, 126.4, 125.9, 66.3, 34.3; **TLC** (30% ethyl acetate:hexanes): R_f 0.29; **HRMS** (ESI): Calcd. for $C_{16}H_{15}ClNaO$ ($[M+Na]^+$): 281.0709, Found: 281.0681.

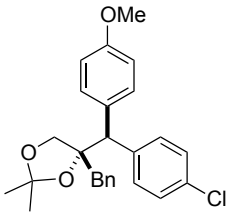


(2-Benzyl-3-(4-chlorophenyl)oxiran-2-yl)methanol (S4): A 50-mL round-bottomed flask was flame-dried and charged with the alkene **S3** (0.52g, 2.0 mmol, 1.0 equiv) in DCM (10 mL) under an atmosphere of N_2. *m*CPBA (0.52g, 3.0 mmol, 1.5 equiv) was added portionwise at room temperature. The reaction stirred at room temperature until complete by TLC. The reaction was quenched with sat. aq. $NaHCO_3$. The layers were

separated and the aqueous layer was extracted with DCM (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 20% ethyl acetate:hexanes to afford epoxide **S4** (0.53 g, 1.92 mmol, 96% yield, >20:1 d.r.) as a pale yellow oil. Analytical data for **S4**: **IR** (thin film): 3421, 3029, 2925, 1602, 1494, 1455, 1089, 1032, 1014, 799, 700 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.24-7.18 (m, 3H), 6.99 (d, *J* = 6.7 Hz, 2H), 4.28 (s, 1H), 3.79 (d, *J* = 12.6 Hz, 1H), 3.67 (d, *J* = 12.7 Hz, 1H), 2.81 (d, *J* = 14.6 Hz, 1H), 2.65 (d, *J* = 14.6 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 136.1, 134.0, 133.7, 129.2, 128.53, 128.49, 127.9, 126.8, 66.6, 62.5, 59.7, 33.7; **TLC** (30% ethyl acetate:hexanes): R_f 0.22; **HRMS** (ESI): Calcd. for $C_{16}H_{15}ClNaO_2$ ($[M+Na]^+$): 297.0659, Found: 297.0679.

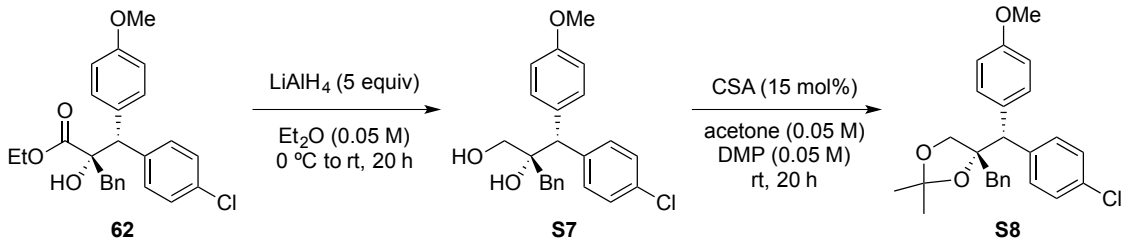


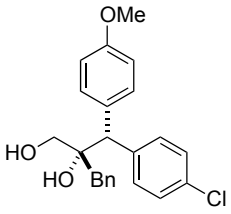
2-Benzyl-3-(4-chlorophenyl)-3-(4-methoxyphenyl)propane-1,2-diol (S5): A dried 20-mL round-bottomed flask was charged with CuI (29 mg, 0.15 mmol, 0.3 equiv) in THF (2.5 mL) and DMS (0.1 mL) under an atmosphere of N_2. The solution was cooled to 0 °C in an ice bath. 4-Methoxyphenylmagnesium bromide solution (0.5 M, 3.0 mL, 1.5 mmol, 3.0 equiv) was added dropwise and the resulting pink-purple cloudy solution stirred for 15 min at 0 °C. A solution of the epoxide **S4** (137 mg, 0.5 mmol, 1.0 equiv) in THF (2.5 mL) was added dropwise and the reaction was allowed to stir overnight as it warmed to room temperature. The reaction was quenched with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude diol **S5** as a pale yellow oil.



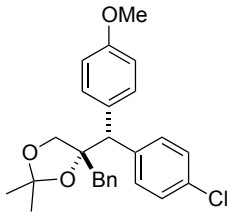
4-Benzyl-4-((4-chlorophenyl)(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxolane (S6): A 20-mL round-bottom flask was charged with the crude diol **S5** in acetone (3 mL) and 2,2-dimethoxypropane (3 mL). CSA (20 mg, 0.08 mmol, 0.15 equiv) was added and the reaction was allowed to stir overnight at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with DCM (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 5% ethyl acetate:hexanes to afford the acetonide **S6** (81.3 mg, 0.19 mmol, 38% yield, >20:1 d.r.) as a yellow oil. Analytical data for **S6**: **IR** (thin film): 2988, 2934, 2835, 1608, 1511, 1491, 1455, 1370, 1250, 1179, 1091, 1060, 1034, 828, 733, 703 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.33 (d, J = 8.7 Hz, 2H), 7.25-7.21 (m, 5H), 7.14 (d, J = 8.5 Hz, 2H), 7.02-7.00 (m, 2H), 6.86 (d, J = 8.9 Hz, 2H), 4.14 (d, J = 8.6 Hz, 1H), 3.95 (s, 1H), 3.82 (d, J = 8.6 Hz, 1H), 3.80 (s, 3H), 3.16 (d, J = 13.6 Hz, 1H), 2.98 (d, J = 13.6 Hz, 1H), 1.46 (s, 3H), 0.90 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 158.1, 139.6, 137.1, 133.1, 132.2, 131.7, 131.6, 130.7, 128.1, 127.9, 126.5, 113.6, 109.8, 85.8, 69.2, 55.2, 54.4, 43.0, 27.8, 26.3; **TLC** (5% ethyl acetate:hexanes): R_f 0.18; **HRMS** (ESI): Calcd. for $C_{26}H_{27}ClNaO_3$ ($[M+Na]^+$): 445.1547, Found: 445.1527.

Conversion of Friedel–Crafts Adduct 62 to Acetonide S8





2-Benzyl-3-(4-chlorophenyl)-3-(4-methoxyphenyl)propane-1,2-diol (S7): A dried round-bottomed flask was charged with Friedel–Crafts adduct **7** (63.7 mg, 0.15 mmol, 1.0 equiv) in Et_2O (2.5 mL) under an atmosphere of N_2. The solution was cooled to 0 °C in an ice bath. $LiAlH_4$ (28.5 mg, 0.75 mmol, 5.0 equiv) was added portionwise 0 °C. The reaction was then allowed to warm to room temperature where it stirred overnight. After diluting the reaction with Et_2O (5 mL), 0.1 mL H_2O, 0.1 mL 15% NaOH, and 0.3 mL H_2O were sequentially added dropwise affording a white precipitate. The mixture was filtered through a pad of Celite and concentrated *in vacuo* to afford the crude diol **S7** as a pale yellow oil.

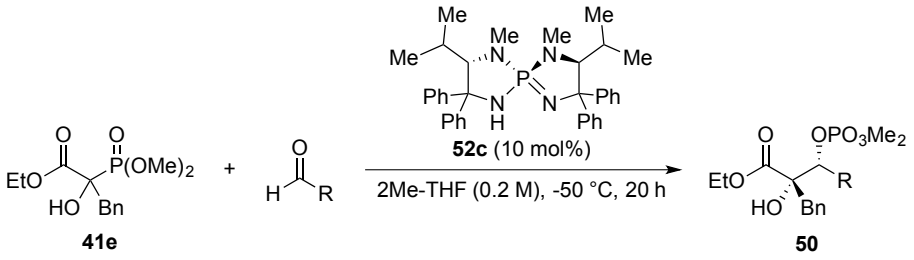


4-Benzyl-4-((4-chlorophenyl)(4-methoxyphenyl)methyl)-2,2-dimethyl-1,3-dioxolane (S8): A 20-mL round-bottomed flask was charged with the crude diol **S7** in acetone (3 mL) and 2,2-dimethoxypropane (3 mL). CSA (5 mg, 0.02 mmol, 0.15 equiv) was added and the reaction was allowed to stir overnight at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with DCM (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 5% ethyl acetate:hexanes to afford the acetonide **S8** (52.1 mg, 0.12 mmol, 82% yield, >20:1 d.r.) as a

yellow oil. Analytical data for **S8**: **IR** (thin film): 2988, 2933, 2832, 1609, 1512, 1490, 1455, 1370, 1252, 1179, 1091, 1060, 1036, 827, 734, 702 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.28-7.25 (m, 5H), 7.08 (d, *J* = 8.7 Hz, 2H), 7.02-7.01 (m, 2H), 6.82 (d, *J* = 9.4 Hz, 2H), 4.17 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 1H), 3.89 (d, *J* = 8.5 Hz, 1H), 3.80 (s, 3H), 3.14 (d, *J* = 13.7 Hz, 1H), 2.99 (d, *J* = 13.7 Hz, 1H), 1.51 (s, 3H), 0.86 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 158.2, 140.2, 137.2, 132.14, 132.10, 132.0, 131.3, 130.7, 128.1, 127.9, 126.5, 113.5, 109.7, 85.8, 69.4, 55.2, 54.2, 43.3, 28.0, 26.2; **TLC** (5% ethyl acetate:hexanes): R_f 0.18; **HRMS** (ESI): Calcd. for $C_{26}H_{27}ClNaO_3$ ($[M+Na]^+$): 445.1547, Found: 445.1527.

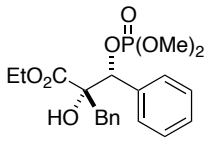
The stereochemical assignment for **S8** arises from the fact that the spectroscopic data for acetonide **S8** do not match that acquired for acetonide **S6**, which was prepared by unambiguous synthesis.

General Procedure E for the Asymmetric Aldolization of α-Alkyl-α-Hydroxy Phosphonoacetates Catalyzed by Chiral Iminophosphorane 52c

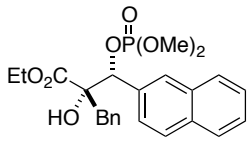


A dried test tube was charged with the α-hydroxy phosphonoacetate **41e** (0.10 mmol, 1.0 equiv) and aldehyde (0.50 mmol, 5.0 equiv) and dissolved in 2-MeTHF (500 μL, 0.2 M) under an atmosphere of argon. The solution was cooled to -50 °C. Iminophosphorane **52c** (5.81 mg, 0.01 mmol, 0.1 equiv) was added and the reaction stirred at -50 °C for 20 h. The reaction was quenched at -50 °C with 0.5 M TFA in toluene (40 μL, 0.2 equiv). The resulting solution was diluted with 1 *N* HCl at 0 °C. The aqueous layer was extracted with $CHCl_3$ (3x). The combined

organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The residue was purified by column chromatography on silica gel eluting with 30% acetone:hexane to afford a diastereomeric mixture of **50**.

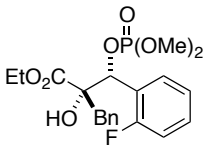


(2*S*,3*R*)-Ethyl 2-benzyl-3-((dimethoxyphosphoryl)oxy)-2-hydroxy-3-phenylpropanoate (50a): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and benzaldehyde (51 μL, 0.50 mmol) affording the aldol adduct **50a** (29.0 mg, 0.07 mmol, 71% yield, >30:1 *syn*:*anti*) as a white solid (mp 119-127 °C). Analytical data for **50a**: **HPLC**: Chiralpak AD3 column, H/IPA = 4:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.9 min (minor diastereomer), 8.7 min (minor isomer of major diastereomer), 10.4 min (major isomer of major diastereomer), 20.4 min (minor diastereomer), 95:5 e.r.; **IR** (thin film): 3391, 2359, 2342, 1736, 1495, 1456, 1261, 1212, 1126, 1034, 1016, 907, 854, 741, 712, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62-7.60 (m, 2H), 7.44-7.41 (m, 3H), 7.21-7.19 (m, 3H), 7.13-7.11 (m, 2H), 5.61 (d, J = 8.2 Hz, 1H), 4.21 (ddq, J = 7.3, 3.7, 3.1 Hz, 2H), 3.61 (d, J = 11.0 Hz, 3H), 3.52 (s, 1H), 3.39 (d, J = 11.4 Hz, 3H), 2.94 (d, J = 13.3 Hz, 1H), 2.43 (d, J = 13.7 Hz, 1H), 1.33 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.3, 135.3, 134.9, 130.3, 129.3, 129.2, 128.3, 128.1, 127.1, 83.0 (d, $J_{P–C}$ = 5.8 Hz), 80.6 (d, $J_{P–C}$ = 8.7 Hz), 62.8, 54.4 (d, $J_{P–C}$ = 5.8 Hz), 54.2 (d, $J_{P–C}$ = 5.8 Hz), 41.4, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 1.0; **TLC** (40% acetone:hexane): R_f 0.42; **HRMS** (FAB): Calcd. for $C_{20}H_{25}O_7NaP$ ([M+Na]$^+$): 431.1230, Found: 431.1231.



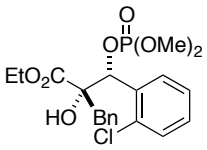
(2*S*,3*R*)-Ethyl 2-benzyl-3-((dimethoxyphosphoryl)oxy)-2-hydroxy-3-(naphthalen-2-yl)propanoate (50b): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and 2-

naphthaldehyde (78.1 mg, 0.50 mmol) affording the aldol adduct **50b** (31.2 mg, 0.07 mmol, 68% yield, >30:1 *syn*:*anti*) as a white solid (mp 145-150 °C). Analytical data for **50b**: **HPLC**: Chiralpak AD3 column, H/IPA/EtOH = 16:3:1, flow rate = 1.0 mL/min, λ = 210 nm, 15.8 min (minor diastereomer), 20.5 min (minor isomer of major diastereomer), 22.4 min (minor diastereomer), 25.3 min (major isomer of major diastereomer), 94.5:5.5 e.r.; **IR** (thin film): 3397, 2982, 2955, 2859, 2361, 2342, 1734, 1468, 1456, 1368, 1258, 1200, 1132, 1045, 1015, 957, 924, 851, 762, 696 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.92-7.86 (m, 3H), 7.82 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.54-7.52 (m, 2H), 7.20-7.17 (m, 3H), 7.12-7.10 (m, 2H), 5.80 (d, *J* = 8.2 Hz), 4.24 (q, *J* = 7.3 Hz, 2H), 3.63 (d, *J* = 11.0 Hz, 3H), 3.59 (s, 1H), 3.34 (d, *J* = 11.4 Hz, 3H), 3.01 (d, *J* = 13.7 Hz, 1H), 2.45 (d, *J* = 13.8 Hz, 1H), 1.36 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.3, 134.9, 133.7, 132.9, 132.8, 130.2, 128.9, 128.5, 128.1, 127.8, 127.1, 126.8, 126.4, 126.3, 83.2 (d, $J_{P–C}$ = 5.8 Hz), 80.8 (d, $J_{P–C}$ = 7.7 Hz), 62.8, 54.5 (d, $J_{P–C}$ = 6.8 Hz), 54.2 (d, $J_{P–C}$ = 6.8 Hz), 41.5, 14.3, one carbon was not found due to overlap; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 1.1; **TLC** (40% acetone:hexane): R_f 0.44; **HRMS** (FAB): Calcd. for $C_{24}H_{27}O_7NaP$ ($[M+Na]^+$): 481.1387, Found: 481.1388.



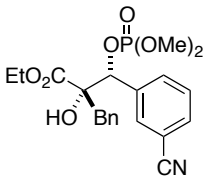
(2*S*,3*R*)-Ethyl 2-benzyl-3-((dimethoxyphosphoryl)oxy)-3-(2-fluorophenyl)-2-hydroxypropanoate (50c): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and 2-fluorobenzaldehyde (53 μL, 0.50 mmol) affording the aldol adduct **50c** (24.0 mg, 0.06 mmol, 56% yield, >30:1 *syn*:*anti*) as a white solid (mp 85-93 °C). Analytical data for **50c**: **HPLC**: Chiralpak AD3 column, H/IPA = 4:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.5 min (minor diastereomer), 9.5 min (minor isomer of major diastereomer), 10.7 min (major isomer of major diastereomer), 29.3 min (minor diastereomer), 94:6 e.r.; **IR** (thin film): 3505, 2959, 2855, 2361,

1734, 1616, 1587, 1491, 1456, 1279, 1204, 1126, 1040, 1011, 912, 851, 754, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (dt, *J* = 7.3, 1.8 Hz, 1H), 7.41-7.35 (m, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.21-7.18 (m, 3H), 7.14-7.09 (m, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 6.07 (d, *J* = 8.7 Hz, 1H), 4.21 (ddq, *J* = 7.3, 3.7, 3.2 Hz, 2H), 3.60 (d, *J* = 11.0 Hz, 3H), 3.55 (s, 1H), 3.50 (d, *J* = 11.4 Hz, 3H), 3.05 (d, *J* = 13.7 Hz, 1H), 2.44 (d, *J* = 13.8 Hz, 1H), 1.32 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.0, 159.7 (d, $J_{F–C}$ = 149.6 Hz), 134.8, 130.9 (d, $J_{F–C}$ = 2.9 Hz), 130.8 (d, $J_{F–C}$ = 8.7 Hz), 130.3, 127.1, 124.4 (d, $J_{F–C}$ = 2.9 Hz), 122.9 (d, $J_{F–C}$ = 13.6 Hz), 115.2 (d, $J_{F–C}$ = 22.3 Hz), 80.8 (d, $J_{P–C}$ = 7.7 Hz), 75.2 (d, $J_{P–C}$ = 5.8 Hz), 62.9, 54.5 (d, $J_{P–C}$ = 5.8 Hz), 54.4 (d, $J_{P–C}$ = 5.8 Hz), 40.3, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 0.9; **TLC** (40% acetone:hexane): R_f 0.38; **HRMS** (FAB): Calcd. for $C_{20}H_{24}O_7FNaP$ ([M+Na]$^+$): 449.1136, Found: 449.1138.

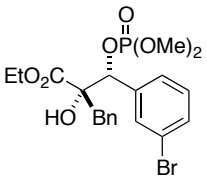


(2*S*,3*R*)-Ethyl 2-benzyl-3-(2-chlorophenyl)-3-((dimethoxyphosphoryl)oxy)-2-hydroxypropanoate (50d): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and 2-chlorobenzaldehyde (56.3 mg, 0.50 mmol) affording the aldol adduct **50d** (27.4 mg, 0.06 mmol, 64% yield, >30:1 *syn*:*anti*) as a pale yellow oil. Analytical data for **50d**: **HPLC**: Chiralpak AD3 column, H/EtOH = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 15.6 min (minor diastereomer), 16.9 min (major isomer of major diastereomer), 24.3 min (minor isomer of major diastereomer), 48.0 min (minor diastereomer), 95:5 e.r.; **IR** (thin film): 3503, 2957, 2855, 2359, 2342, 1734, 1474, 1445, 1277, 1207, 1121, 1040, 1009, 912, 851, 748, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.43 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.39 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.33 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.20-7.18 (m, 3H), 7.13-7.11 (m, 2H), 6.28 (d, *J* = 8.7 Hz, 1H), 4.24 (ddq, *J* = 7.3, 3.7, 3.3 Hz, 2H), 3.58 (d, *J* = 11.0 Hz, 3H), 3.56 (s, 1H), 3.50 (d, *J* = 11.5 Hz, 3H), 3.17 (d, *J* = 13.7 Hz, 1H), 2.40 (d, *J* = 13.8 Hz, 1H), 1.34 (t, *J* = 7.3 Hz, 3H); **^{13}C**

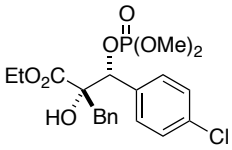
NMR (101 MHz, $CDCl_3$): δ 173.0, 134.8, 133.8, 133.6, 131.6, 130.3, 129.3, 128.1, 127.11, 127.06, 81.1 (d, $J_{P–C}$ = 8.7 Hz), 77.7 (d, $J_{P–C}$ = 5.8 Hz), 62.9, 54.5 (d, $J_{P–C}$ = 5.8 Hz), 54.4 (d, $J_{P–C}$ = 5.8 Hz), 40.2, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 1.1; **TLC** (40% acetone:hexane): R_f 0.47; **HRMS** (FAB): Calcd. for $C_{20}H_{24}O_7ClNaP$ ($[M+Na]^+$): 465.0840, Found: 465.0841.



(2*S*,3*R*)-Ethyl 2-benzyl-3-(3-cyanophenyl)-3-((dimethoxyphosphoryl)oxy)-2-hydroxypropanoate (50e): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and 3-formylbenzonitrile (65.6 mg, 0.50 mmol) affording the aldol adduct **50e** (35.4 mg, 0.09 mmol, 89% yield, >30:1 *syn*:*anti*) as a white solid (mp 108-116 °C). Analytical data for **50e**: **HPLC**: Chiralpak AD3 column, H/IPA = 4:1, flow rate = 1.0 mL/min, λ = 210 nm, 11.2 min (minor diastereomer), 12.2 min (minor isomer of major diastereomer), 14.2 min (major isomer of major diastereomer), 22.8 min (minor diastereomer), 94:6 e.r.; **IR** (thin film): 3503, 2959, 2359, 2232, 1738, 1456, 1369, 1269, 1202, 1125, 1038, 1016, 851, 746, 702 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.70 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.24-7.20 (m, 3H), 7.11-7.09 (m, 2H), 5.63 (d, *J* = 8.2 Hz, 1H), 4.21 (ddq, *J* = 7.3, 3.6, 3.2 Hz, 2H), 3.66 (d, *J* = 11.0 Hz, 3H), 3.55 (s, 1H), 3.46 (d, *J* = 11.5 Hz, 3H), 2.94 (d, *J* = 13.8 Hz, 1H), 2.36 (d, *J* = 13.8 Hz, 1H), 1.33 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.6, 137.1, 134.3, 133.5, 132.9, 132.8, 130.2, 129.2, 128.3, 127.4, 118.6, 112.7, 81.7 (d, $J_{P–C}$ = 5.8 Hz), 80.2 (d, $J_{P–C}$ = 7.7 Hz), 63.1, 54.7 (d, $J_{P–C}$ = 5.8 Hz), 54.4 (d, $J_{P–C}$ = 5.8 Hz), 41.4, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 1.0; **TLC** (40% acetone:hexane): R_f 0.35; **HRMS** (FAB): Calcd. for $C_{21}H_{24}O_7NNaP$ ($[M+Na]^+$): 456.1183, Found: 456.1182.

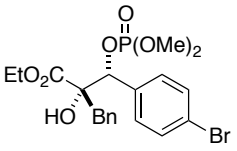


(2*S*,3*R*)-Ethyl 2-benzyl-3-(3-bromophenyl)-3-((dimethoxyphosphoryl)oxy)-2-hydroxypropanoate (50f): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and 3-bromobenzaldehyde (58 μL, 0.50 mmol) affording the aldol adduct **50f** (42.2 mg, 0.09 mmol, 87% yield, >30:1 *syn*:*anti*) as a white solid (mp 132-136 °C). Analytical data for **50f**: **HPLC**: Chiralpak AD3 column, H/IPA = 4:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.4 min (minor diastereomer), 10.5 min (major isomer of major diastereomer), 11.4 min (minor isomer of major diastereomer), 17.4 min (minor diastereomer), 95:5 e.r.; **IR** (thin film): 3503, 2957, 2359, 2342, 1734, 1570, 1456, 1431, 1271, 1209, 1125, 1038, 914, 851, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.23-7.19 (m, 3H), 7.13-7.11 (m, 2H), 5.56 (d, *J* = 8.2 Hz, 1H), 4.20 (ddq, *J* = 7.3, 6.9, 2.3 Hz, 2H), 3.64 (d, *J* = 11.4 Hz, 3H), 3.51 (s, 1H), 3.45 (d, *J* = 11.4 Hz, 3H), 2.93 (d, *J* = 13.3 Hz, 1H), 2.44 (d, *J* = 13.7 Hz, 1H), 1.32 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.0, 137.6, 134.7, 132.4, 132.1, 130.2, 129.9, 128.2, 127.8, 127.2, 122.4, 82.1 (d, $J_{P–C}$ = 5.8 Hz), 80.4 (d, $J_{P–C}$ = 7.7 Hz), 62.9, 54.5 (d, $J_{P–C}$ = 5.8 Hz), 54.3 (d, $J_{P–C}$ = 5.8 Hz), 41.4, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 0.9; **TLC** (40% acetone:hexane): R_f 0.47; **HRMS** (FAB): Calcd. for $C_{20}H_{24}O_7BrNaP$ ($[M+Na]^+$): 509.0335, Found: 509.0338.



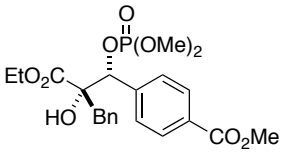
(2*S*,3*R*)-Ethyl 2-benzyl-3-(4-chlorophenyl)-3-((dimethoxyphosphoryl)oxy)-2-hydroxypropanoate (50g): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and 4-chlorobenzaldehyde (70.2 mg, 0.50 mmol) affording the aldol adduct **50g** (37.2 mg, 0.08 mmol, 82% yield, >30:1 *syn*:*anti*) as a white solid (mp 123-125 °C). Analytical data for **50g**: **HPLC**: Chiralpak AD3 column, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm,

19.6 min (minor isomer of major diastereomer), 21.0 min (minor diastereomer), 25.9 min (minor diastereomer), 33.7 min (major isomer of major diastereomer), 95:5 e.r.; **IR** (thin film): 3354, 2959, 2361, 2342, 1742, 1597, 1491, 1454, 1368, 1256, 1209, 1144, 1022, 1005, 910, 853, 748, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.21-7.19 (m, 3H), 7.12-7.09 (m, 2H), 5.59 (d, *J* = 8.7 Hz, 1H), 4.20 (ddq, *J* = 7.2, 6.9, 2.8 Hz, 2H), 3.63 (d, *J* = 11.4 Hz, 3H), 3.51 (s, 1H), 3.43 (d, *J* = 11.9 Hz, 3H), 2.91 (d, *J* = 13.3 Hz, 1H), 2.40 (d, *J* = 13.7 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.0, 135.3, 134.7, 133.9, 130.6, 130.2, 128.6, 128.2, 127.2, 82.2 (d, J_{P-C} = 5.8 Hz), 80.5 (d, J_{P-C} = 8.7 Hz), 62.9, 54.5 (d, J_{P-C} = 5.8 Hz), 54.3 (d, J_{P-C} = 5.8 Hz), 41.4, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 1.0; **TLC** (40% acetone:hexane): R_f 0.47; **HRMS** (FAB): Calcd. for $C_{20}H_{24}O_7ClNaP$ ($[M+Na]^+$): 465.0840, Found: 465.0841.



(2*S*,3*R*)-Ethyl 2-benzyl-3-(4-bromophenyl)-3-((dimethoxyphosphoryl)oxy)-2-hydroxypropanoate (50h): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and 4-bromobenzaldehyde (92.5 mg, 0.50 mmol) affording the aldol adduct **50h** (44.2 mg, 0.09 mmol, 91% yield, >30:1 *syn*:*anti*) as a white solid (mp 125-129 °C). Analytical data for **50h**: **HPLC**: Chiralpak AD3 column, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 20.3 min (minor isomer of major diastereomer), 23.3 min (minor diastereomer), 25.9 min (minor diastereomer), 40.5 min (major isomer of major diastereomer), 95.5:4.5 e.r.; **IR** (thin film): 3397, 2959, 2361, 1742, 1489, 1454, 1414, 1368, 1256, 1209, 1144, 1020, 1005, 910, 853, 747, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 9.1 Hz, 2H), 7.21-7.19 (m, 3H), 7.12-7.09 (m, 2H), 5.68 (d, *J* = 9.4 Hz, 1H), 4.20 (ddq, *J* = 7.8, 7.3, 2.7 Hz, 2H), 3.63 (d, *J* = 11.5 Hz, 3H), 3.50 (s, 1H), 3.43 (d, *J* = 11.4 Hz, 3H), 2.91 (d, *J* = 13.8 Hz, 1H),

2.40 (d, J = 13.3 Hz, 1H), 1.32 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.0, 134.6, 134.4, 131.5, 130.8, 130.2, 128.2, 127.2, 123.6, 82.2 (d, $J_{P–C}$ = 5.8 Hz), 80.4 (d, $J_{P–C}$ = 8.7 Hz), 62.9, 54.5 (d, $J_{P–C}$ = 5.8 Hz), 54.3 (d, $J_{P–C}$ = 5.8 Hz), 41.4, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 1.0; **TLC** (40% acetone:hexane): R_f 0.51; **HRMS** (FAB): Calcd. for $C_{20}H_{24}O_7BrNaP$ ([M+Na]$^+$): 509.0335, Found: 509.0337.



Methyl 4-((1*R*,2*S*)-2-benzyl-1-((dimethoxyphosphoryl)oxy)-3-ethoxy-2-hydroxy-3-oxopropyl)benzoate (50i): The title compound was prepared according to General Procedure E using **41e** (30.2 mg, 0.10 mmol) and methyl 4-formylbenzoate (82.1 mg, 0.50 mmol) affording the aldol adduct **50i** (41.6 mg, 0.09 mmol, 89% yield, >30:1 *syn*:*anti*) as a white solid (mp 155-156 °C). Analytical data for **50i**: **HPLC**: Chiralpak AD3 column, H/EtOH = 7:3, flow rate = 1.0 mL/min, λ = 210 nm, 17.5 min (minor diastereomer), 19.9 min (minor isomer of major diastereomer), 22.5 min (minor diastereomer), 28.2 min (major isomer of major diastereomer), 97:3 e.r.; **IR** (thin film): 3495, 2957, 2359, 2342, 1722, 1614, 1437, 1277, 1211, 1111, 1036, 1009, 910, 851, 723, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.23-7.19 (m, 3H), 7.11-7.09 (m, 2H), 5.67 (d, J = 8.2 Hz, 1H), 4.21 (ddq, J = 7.8, 7.3, 1.8 Hz, 2H), 3.93 (s, 3H), 3.63 (d, J = 11.0 Hz, 3H), 3.52 (s, 1H), 3.42 (d, J = 11.4 Hz, 3H), 2.95 (d, J = 13.3 Hz, 1H), 2.40 (d, J = 13.3 Hz, 1H), 1.33 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.9, 166.8, 140.2, 134.6, 131.0, 130.2, 129.5, 129.2, 128.2, 127.2, 82.3 (d, $J_{P–C}$ = 5.8 Hz), 80.4 (d, $J_{P–C}$ = 8.7 Hz), 62.9, 54.6 (d, $J_{P–C}$ = 5.8 Hz), 54.3 (d, $J_{P–C}$ = 5.8 Hz), 52.4, 41.3, 14.2; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 1.0; **TLC** (40% acetone:hexane): R_f 0.40; **HRMS** (FAB): Calcd. for $C_{22}H_{27}O_9NaP$ ([M+Na]$^+$): 489.1285, Found: 489.1285.

2.6 References

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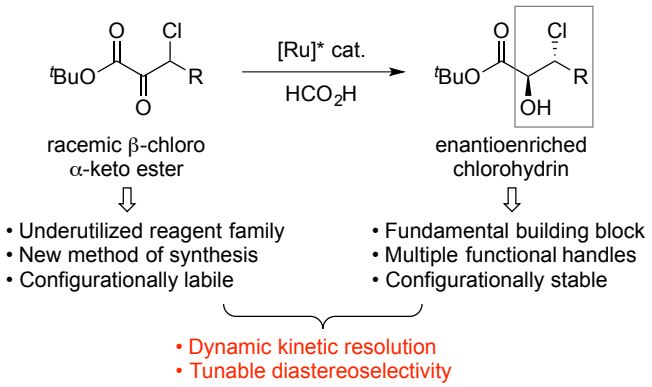
CHAPTER THREE: ASYMMETRIC SYNTHESIS OF CHLOROHYDRINS VIA DYNAMIC KINETIC REDUCTION*

3.1 Introduction

A highly stereoselective synthesis of β-chloro-α-hydroxy esters was realized through the application of a dynamic kinetic resolution via asymmetric transfer hydrogenation (DKR-ATH) of racemic β-chloro-α-keto esters (**Scheme 3-1**). The requisite β-chloro-α-keto esters were prepared via Ni(II)-catalyzed direct β-chlorination of α-keto esters under mild reaction conditions with good levels of mono:di selectivity. A Ru(II)-amido complex bearing a bulky *m*-terphenylsulfonamide ligand provided a remarkable ligand-controlled switch in diastereoselectivity in the reduction affording *anti*-chlorohydrins. Excellent levels of selectivity were observed across a wide spectrum of aliphatic and aryl β-chloro-α-keto esters providing chlorohydrins that serve as viable substrates for various secondary transformations.

Scheme 3-1. Preparation of Optically Active Halohydrins



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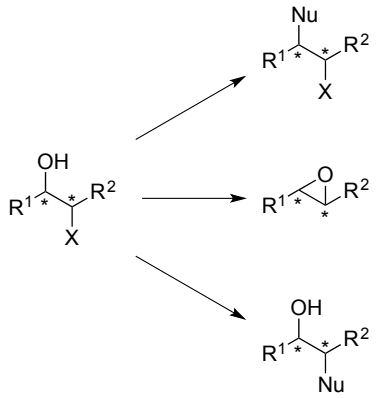
3.2 Background

3.2.1 Extant Methods for the Preparation of Optically Active Halohydrins

Optically active halohydrins are fundamental building blocks in organic chemistry. These versatile functional arrays can be converted to their derived enantioenriched epoxides or can engage in nucleophilic substitution to provide a variety of functionalized product classes (**Scheme 3-2**). The emergence of halohydrin dehalogenase (HheC), an enzyme produced by *Agrobacterium radiobacter* AD_1, as a biocatalyst for the kinetic resolution of racemic haloalcohols highlights the importance of methods for the preparation of optically pure halohydrins.[1] The catalytic asymmetric preparation of halohydrins, however, has been limited principally to desymmetrization reactions of epoxides[2] and alkenes[3] or kinetic resolution of terminal epoxides.[4]

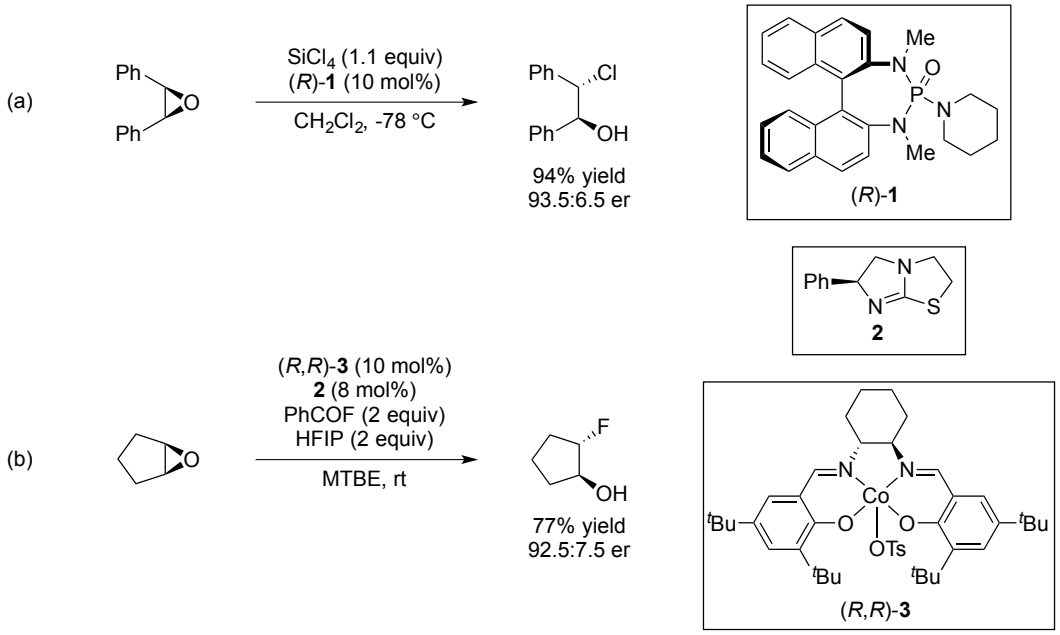
Scheme 3-2. Transformations of Optically Active Halohydrins



Given the broad utility of halohydrins, significant effort has been made towards the development of catalytic asymmetric methodologies to access this chemical motif in a highly efficient manner from simple starting materials. Early efforts utilized desymmetrization of *meso*-epoxides to access optically active internal haloalcohols, which has been achieved employing a wide-range of chiral Lewis acids and bases. Denmark and Doyle have independently applied this

strategy to the synthesis of chlorohydrins and fluorohydrins, respectively (**Scheme 3-3**). In 1998, Denmark reported a method utilizing a chiral phosphoramide (*R*)-**1** that served as a Lewis base to coordinate to tetrachlorosilane generating the nucleophilic chloride ion and silicate Lewis acid that activated the epoxide for nucleophilic attack (**Scheme 3-3a**).[2b] This methodology, however, was limited to the desymmetrization of simple acyclic *meso*-epoxides. More recently, Doyle reported a method for the preparation of fluoroalcohols through the use of a Co(salen) complex (*R*,*R*)-**3** (**Scheme 3-3b**).[21] Reaction of **2** and benzoyl fluoride provided *in situ* generation of fluoride, which underwent nucleophilic addition into cyclic *meso*-epoxides activated by the Co(salen) complex.

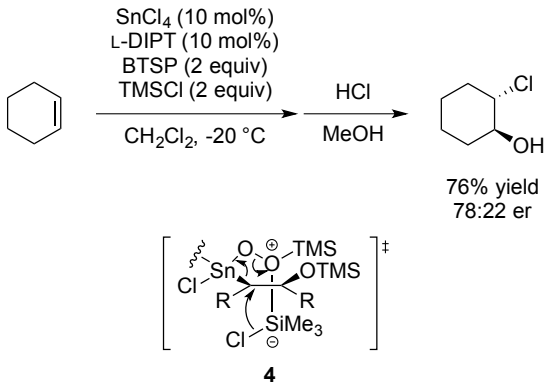
Scheme 3-3. Halohydrins via Desymmetrization of *meso*-Epoxides



In 2000, Shibasaki reported a more direct method for the preparation of internal halohydrins from their respective symmetric alkenes (**Scheme 3-4**).[3a] Insertion of the alkene into the Sn–O bond of a chiral oxotin complex, obtained via treatment of $SnCl_4$ with

bis(trimethylsilyl) peroxide (BTSP), was followed by subsequent nucleophilic displacement of the alkyl tin intermediate **4** by chloride. Acid hydrolysis of the TMS-protected chlorohydrin provides the desired product in good yield and enantioselectivity. Although this methodology does not provide comparable selectivities to extant strategies, it obviates the need to preform the epoxide through the direct functionalization of the parent alkene.

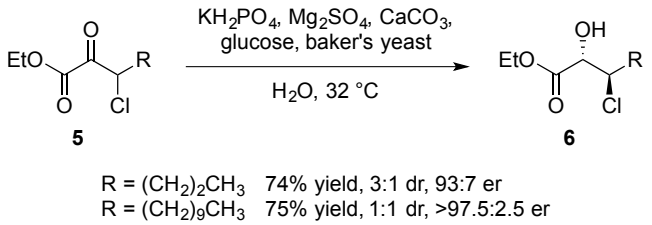
Scheme 3-4. Halohydrins via Desymmetrization of Symmetric Alkenes



Despite advances in the desymmetrization of alkenes and epoxides, methodologies designed to directly access internal chlorohydrins from unsymmetrical precursors are largely underdeveloped. In particular, strategies that provide access to chiral β-chloro-α-hydroxy carboxylic acid derivatives are typically limited to enzymatic processes or stereospecific opening of glycidic esters with strong acids. Chloride addition to optically pure glycidic esters often necessitates harsh reaction conditions, suffers from non-ideal regio- and stereoselectivity, and lacks significant precedence for aliphatic substrates.[5] While enzymatic reductions[6] and kinetic resolutions[7] have been shown to impart good levels of diastereo- and enantioselectivity, these processes are substrate limited and lack generality. Particularly relevant in the present context, Takeda developed an enzymatic reduction of β-chloro-α-keto esters **5** employing

superstoichiometric baker's yeast to access *anti*-chlorohydrins **6** in excellent enantioselectivity, but with poor diastereocontrol (**Scheme 3-5**).[6a]

Scheme 3-5. Enzymatic Reduction of β-Chloro-α-Keto Esters



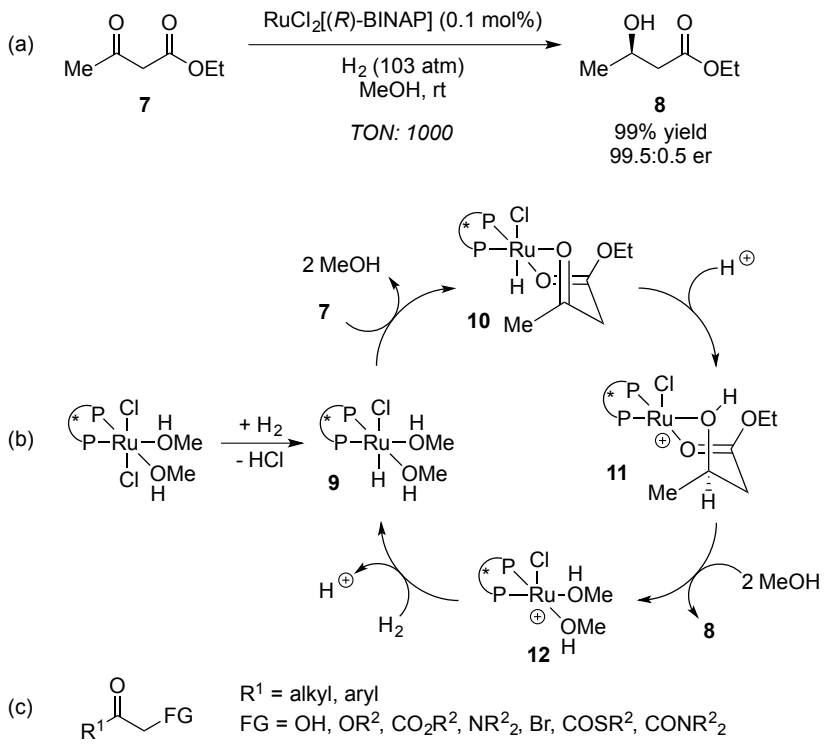
3.2.2 Asymmetric Hydrogenation and Transfer Hydrogenation of Carbonyls

Since the advent of homogenous asymmetric catalysis, significant advances in the development of well-defined homogeneous catalysts for the reduction of carbonyls have been realized. The conversion of ketones to enantiopure *sec*-alcohols has been principally achieved either through the use of metal-mediated hydrogenations or oxazaborolidine-mediated borane reductions.[8] Although both methods have demonstrated excellent enantiofacial selectivity in the reduction of ketones, the former is more attractive from an industrial perspective since asymmetric hydrogenations employ a cheap, readily available reductant (H_2) and typically exhibit high turnover numbers (TON, defined as moles of the product per mole of the catalyst) and turnover frequencies (TOF, defined as the TON per hour).

In 1987, Noyori reported the first highly enantioselective hydrogenation of ketones employing a $RuCl_2$(BINAP) catalyst (**Scheme 3-6a**).[9] The reduction of simple β-keto esters, such as ethyl acetoacetate (**7**), was found to be highly enantioselective under the hydrogenation conditions providing enantiopure β-hydroxy ester **8** in quantitative yield although high pressures were required to achieve acceptable efficiency. Previously reported hydrogenations of alkenes were performed with a $Ru(OAc)_2$(BINAP) catalyst; however, this catalyst was completely

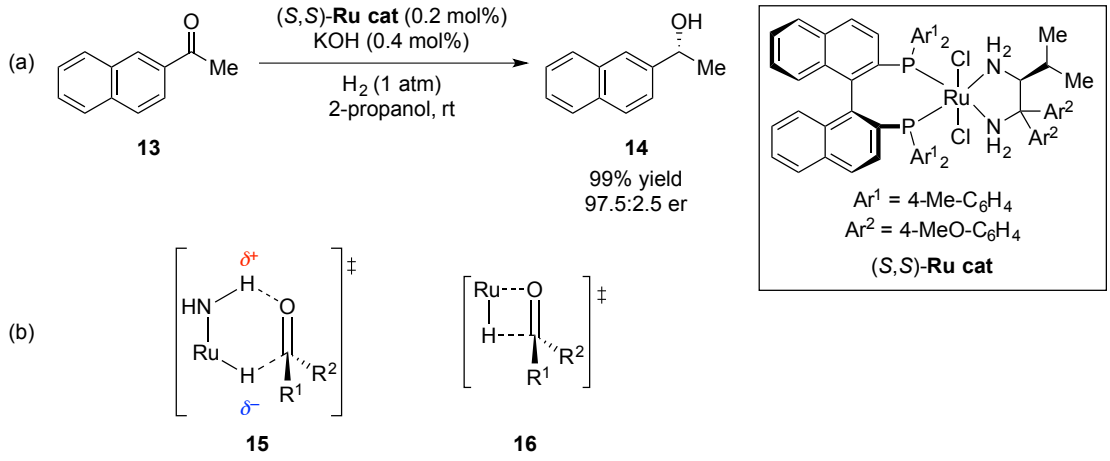
nonselective in the reduction of carbonyls (**8**: 52:48 er). The active Ru–H species **9** is generated via exposure of the $RuCl_2$(BINAP) precatalyst with H_2 generating HCl, which was found to accelerate the reaction (**Scheme 3-6b**). Coordination of β-keto ester **7** generates a complex **10**, the stereochemistry of which is controlled by the chirality of the BINAP backbone. Protonation of the ketone and subsequent diastereoselective hydride transfer results in the formation of cationic ruthenium complex **11**. Ligand exchange liberates β-hydroxy ester **8** providing cationic complex **12**, which can react with a further equivalent of H_2 to regenerate the active catalyst species **9**. This mechanism relies on the presence of a coordinating functional group geminal to the carbonyl to achieve effective discrimination of diastereotopic transition states. This methodology was quickly generalized to exhibit excellent levels of enantiofacial selectivity in the reduction of a wide-range of α-functionalized ketones (**Scheme 3-6c**).[10]

Scheme 3-6. Ruthenium-Catalyzed Asymmetric Hydrogenation of Functionalized Ketones



Despite the success of the $RuCl_2$(BINAP) system in the reduction of functionalized carbonyls, it was ineffective for the reduction of simple ketones. During optimization of reaction conditions for the asymmetric hydrogenation of methyl 2-naphthyl ketone (**13**) in 2-propanol, Noyori and coworkers observed a 1000-fold rate enhancement through the incorporation of a 1,2-diamine and KOH (**Scheme 3-7a**).[11] Employing a chiral diamine ligand derived from L-valine, the hydrogenation provided *sec*-alcohol **14** in 98% yield with 97.5:2.5 er under a balloon of H_2 at room temperature. A key structural requirement of the 1,2-diamine was the presence of at least one primary amine, suggesting that the protonated ammonium moiety was involved in the activation of the carbonyl. Given this observation, Noyori proposed that the hydrogenation was proceeding through a six-membered pericyclic transition state **15** that was later confirmed by Morris, which is mechanistically divergent from the four-membered transition state **16** observed for the hydrogenation of β-keto esters (**Scheme 3-7b**).[12]

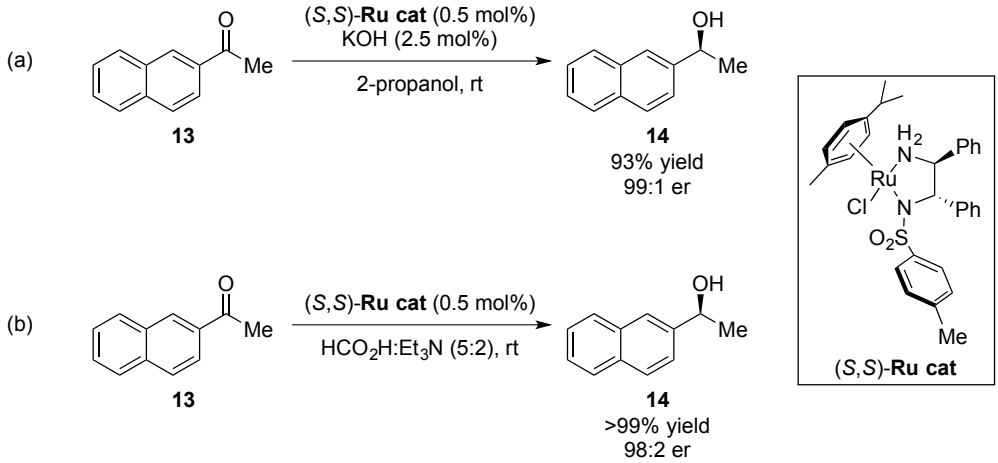
Scheme 3-7. Ruthenium-Catalyzed Asymmetric Hydrogenation of Simple Ketones



Given the success of chiral 1,2-diamine ligands on ruthenium hydrogenation catalysts for the reduction of simple ketones, Noyori began to study the potential application of ruthenium catalysts in the asymmetric transfer hydrogenation of ketones. Transfer hydrogenation is

attractive from an industrial perspective since it obviates the use of H_2 as the stoichiometric reductant (often used under high pressure).[13] Inspired by the Meerwein–Ponndorf–Verley reduction, Noyori identified a new class of (arene)RuCl(monosulfonamide) catalysts that effectively promoted the transfer hydrogenation of **13** using 2-propanol as the stoichiometric organic reductant (**Scheme 3-8a**).[14] The following year, Noyori reported a complementary asymmetric transfer hydrogenation of **13** employing the same (*S*,*S*)-TsDPEN-derived catalyst using an azeotrope of formic acid:triethylamine (5:2) as the organic reductant (**Scheme 3-8b**).[15] In addition to enabling the application of more tractable organic reductants, (arene)RuCl(monosulfonamide) complexes are highly air and moisture stable and have even found application in asymmetric transfer hydrogenation reactions in aqueous media.[16]

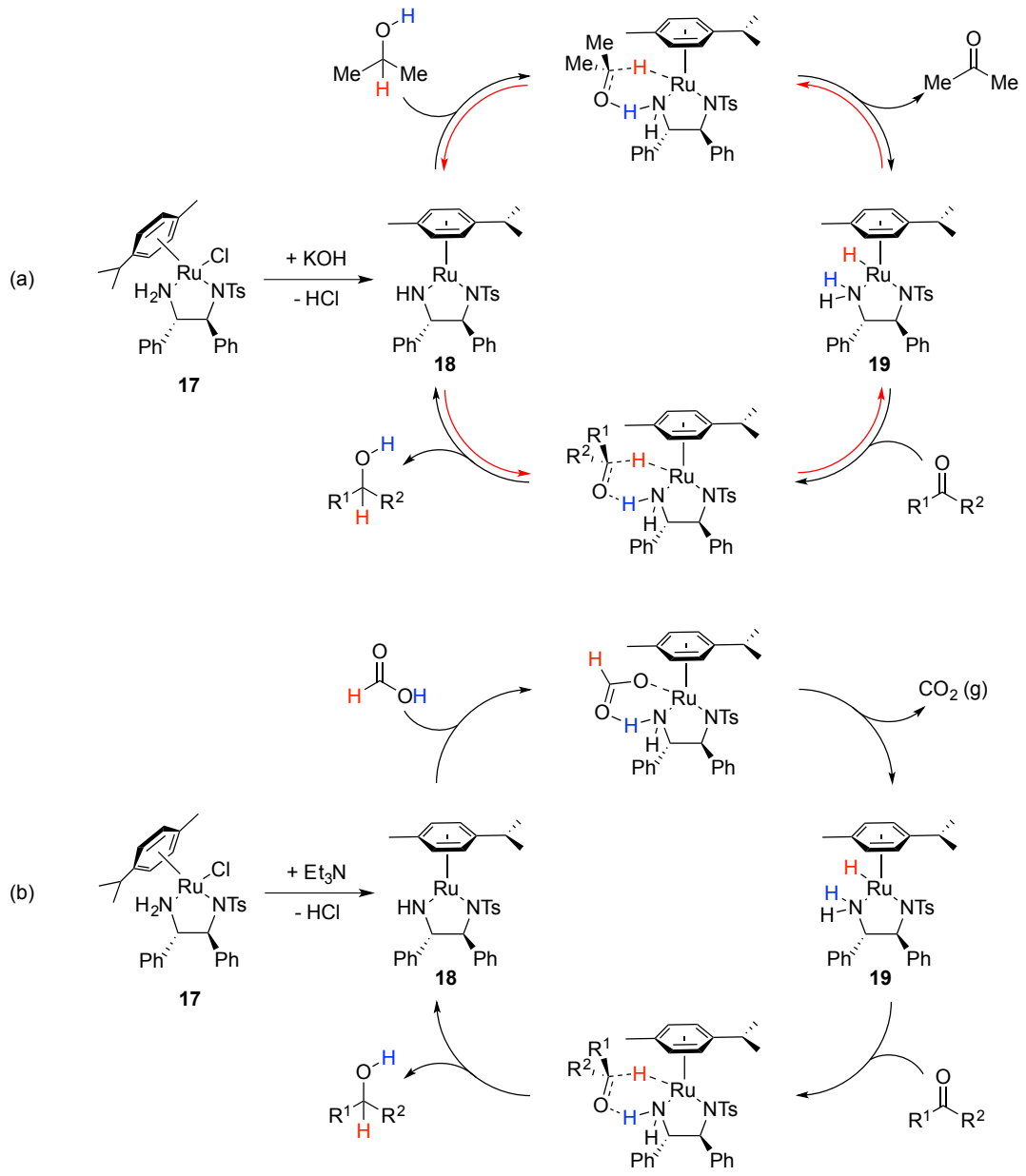
Scheme 3-8. Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Simple Ketones



Detailed mechanistic studies have revealed that the active catalyst species is the 16-electron amide complex **18**, which is generated by base-mediated dehydrohalogenation of **17** (**Scheme 3-9a**). Amide complex **18** is readily converted to ruthenium hydride complex **19** via reversible dehydrogenation of 2-propanol to acetone.[17] The carbonyl associates to hydride complex **19** through a six-membered transition state allowing for outer sphere delivery of a

hydride and a proton in a concerted mechanism to reduce the ketone to the alcohol regenerating 16-electron amide complex **18**. Despite the efficacy of this process, at higher conversions and longer reactions times this process becomes reversible since the product alcohol can undergo transfer hydrogenation with acetone providing a racemization pathway. Strategies employing formic acid:triethylamine circumvent this problem by utilizing a reductant (HCO_2H) whose byproduct is irreversibly removed from the reaction system (CO_2) eliminating product racemization pathways. Mechanistically analogous to the latter, 16-electron amide complex **18** cooridinates with formic acid to generate an intermediate formate complex that undergoes decarboxylation to generate ruthenium hydride species **19** (**Scheme 3-9b**).[18] Identical outersphere delivery of the hydride to the carbonyl substrate through a six-membered transition state with concomitant delivery of a proton from the amine delivers the desired *sec*-alcohol and regenerates the active amide complex **18**.

Scheme 3-9. Mechanism of Ruthenium-Catalyzed Asymmetric Transfer Hydrogenations

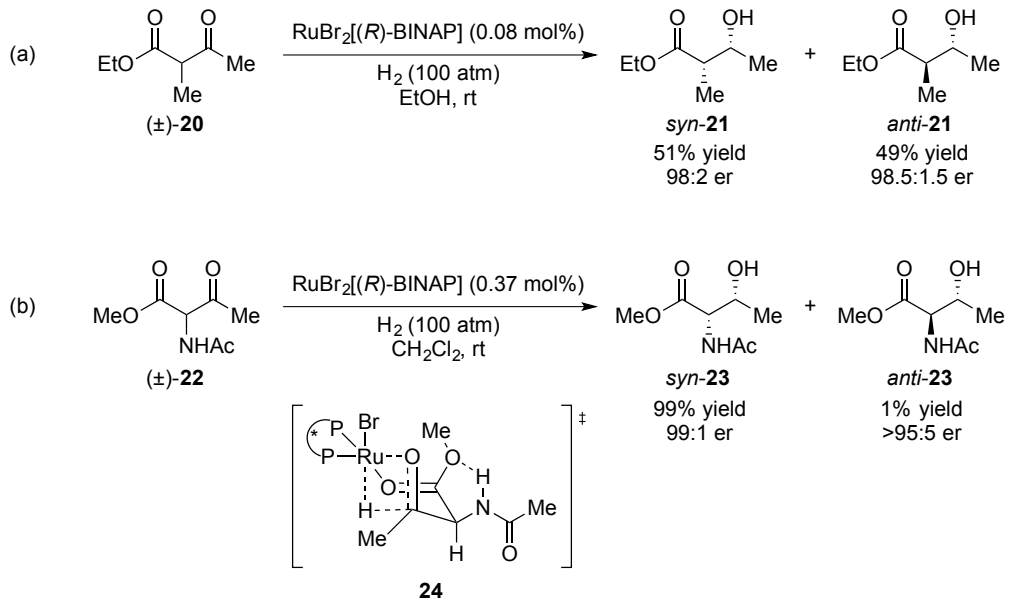


3.2.3 Dynamic Kinetic Resolution of β-Keto Esters via Asymmetric (Transfer) Hydrogenation

Having developed a series of highly efficient and selective chiral ruthenium catalysts for hydrogenation and transfer hydrogenation reactions of carbonyl compounds, Noyori became interested in exploring their utility in the synthesis of functionally rich small molecules building

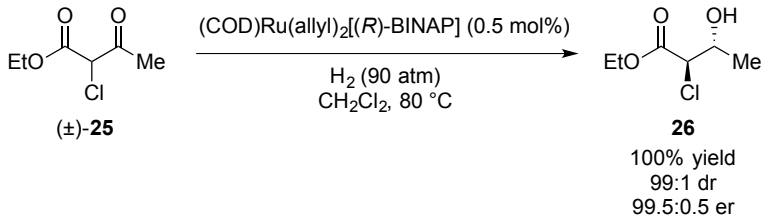
blocks. Application of $RuBr_2$[(*R*)-BINAP], a complex that provided high efficiency and selectivity in the reduction of unsubstituted β-keto esters, to the reduction of α-methyl-β-keto ester (±)-**20** resulted in the isolation of a 1:1 diastereomeric mixture of **21** (**Scheme 3-10a**).[9] Despite the poor diastereoselectivity observed in the reduction of (±)-**20**, structurally similar α-amino-β-keto ester (±)-**22** underwent facile reduction with $RuBr_2$[(*R*)-BINAP] to afford methyl acetyl-L-threoninate (*syn*-**23**) in 99% yield with 99:1 dr and 99:1 er (**Scheme 3-10b**).[19] The exceptional levels of selectivity observed in the hydrogenation are attributed to the highly diastereoselective two-point coordination of the β-keto ester to the ruthenium complex allowing for high enantiofacial selectivity in the intersphere delivery of the hydride (**24**). Notably, the hydrogenation of racemic α-amino-β-keto ester (±)-**22** proceeded via dynamic kinetic resolution resulting in the isolation of a single enantiopure product from a racemate.

Scheme 3-10. Dynamic Kinetic Resolution of β-Keto Esters via Asymmetric Hydrogenation



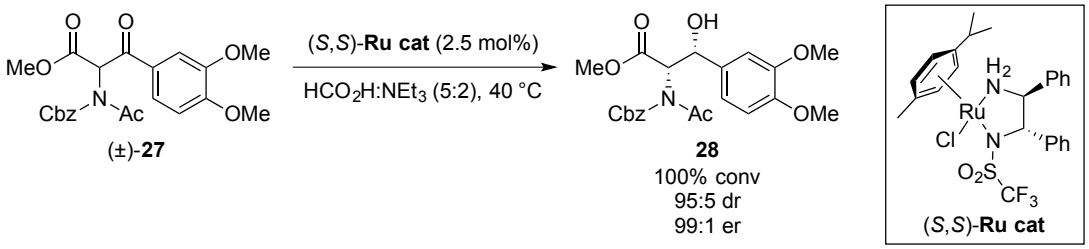
Genêt extended the scope of Noyori's dynamic kinetic resolution via asymmetric resolution (DKR-AH) of α-stereogenic-β-keto esters methodology to provide access to α-chloro-β-hydroxy carboxylic acid derivatives (**Scheme 3-11**),[20] which are particularly relevant in the context of this chapter. Although Noyori's parent $RuBr_2$[(*R*)-BINAP] complex provided **26** in poor diastereo- and enantioselectivity, a modified (COD)Ru(allyl)$_2$ precatalyst provided a marked improvement in the dynamic reduction of (±)-**25** providing **26** as a single diastereomer in quantitative yield with 99.5:0.5 er. This methodology was designed to provide efficient access to chlorohydrins that could undergo subsequent intramolecular *O*-alkylation to afford enantiopure glycidic esters through a stepwise Darzens pathway.

Scheme 3-11. DKR-AH of α-Chloro-β-Keto Esters



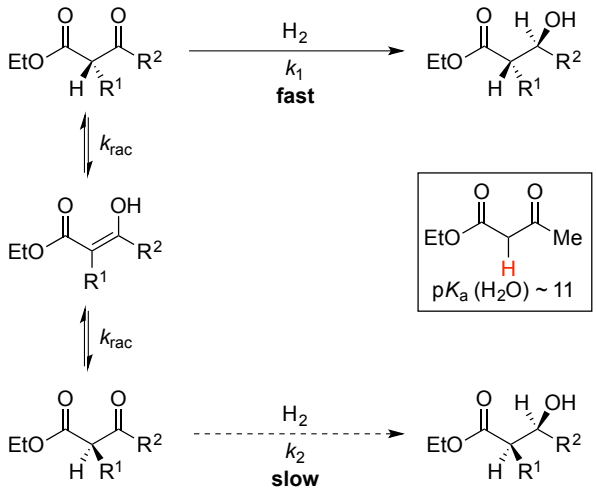
Noyori's early studies verified the viability of racemic α-stereogenic-β-keto esters to participate in dynamic kinetic resolution via asymmetric hydrogenation (DKR-AH). However, AH reactions rely on the use of high pressures of H_2 and catalysts that are difficult to prepare and handle due to their air and moisture sensitivity. Given its inherent advantages over analogous asymmetric hydrogenation processes, Wagner and Mioskowski developed conditions for the dynamic reduction of racemic α-amino-β-keto ester (±)-**27** employing a robust, easily prepared ATH catalyst (**Scheme 3-12**).[21] Departure from Noyori's (*S*,*S*)-TsDPEN ligand was found to be beneficial, as (*S*,*S*)-TfDPEN provided higher activity and selectivity in the reduction due to subtle changes in the pK_a of the ligand.

Scheme 3-12. Dynamic Kinetic Resolution of β-Keto Esters via Asymmetric Transfer Hydrogenation



The success of these dynamic kinetic resolutions relies not only on the exquisite levels of efficiency and selectivity exhibited by AH and ATH ruthenium catalysts, but also on the facile ability of the α-stereogenic-β-keto esters to racemize under the reaction conditions (**Scheme 3-13**). Highly acidic acetoacetates readily undergo keto–enol(ate) tautomerization under acidic or basic conditions providing a facile racemization pathway between the enantiomers of starting material. As described in Chapter One, the success of a dynamic kinetic resolution relies on starting material racemization occurring much faster than the enantiodetermining step. This dynamic interconversion of starting material enantiomers (k_{rac}) allows for their concentration to remain static during the course of the reduction. Diastereo- and enantioselective hydrogenation of one enantiomer of starting material ($k_1 >> k_2$) is possible via the aforementioned mechanisms providing access to a single enantiopure product from a racemate.

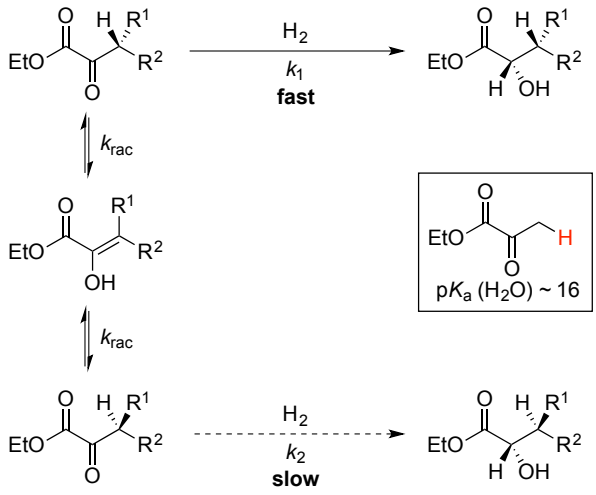
Scheme 3-13. Dynamic Kinetic Resolution of α-Stereogenic-β-Keto Esters



3.2.4 Dynamic Kinetic Resolution of α-Keto Esters via Asymmetric Transfer Hydrogenation

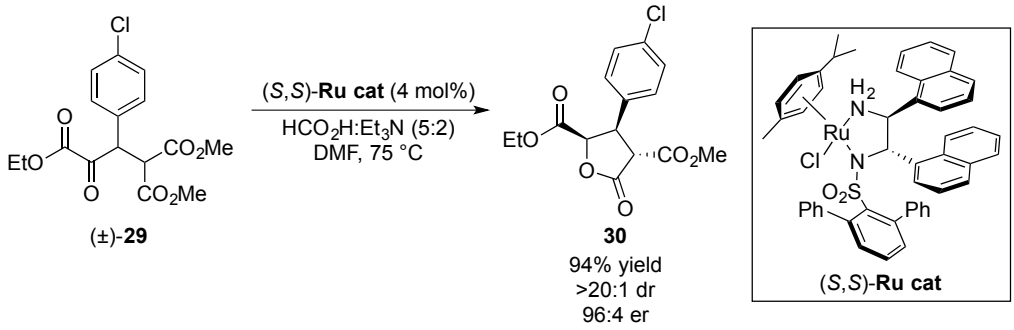
The Ru-catalyzed asymmetric (transfer) hydrogenation of β-keto esters has served as the archetypal dynamic kinetic resolution due to its generality and efficiency.[22] Although this concept had been extended to the dynamic reduction of other α-labile carbonyls,[23] it had not been applied to the reduction of β-stereogenic-α-keto esters to access isomeric product classes (**Scheme 3-14**). Despite the structural similarities of α-keto esters to the aforementioned β-keto esters (**Scheme 3-13**), a distinct difference is the acidity of the carbon stereogenic center in the starting material. Although ethyl acetoacetate (pK_a ~ 11) is easily tautomerized under asymmetric transfer hydrogenation conditions, ethyl pyruvate (pK_a ~ 16) is considerably less acidic. Therefore, the configurational lability (k_{rac}) of β-stereogenic-α-keto esters may not sufficient under the reduction conditions to achieve an efficient dynamic process.

Scheme 3-14. Dynamic Kinetic Resolution of β-Stereogenic-α-Keto Esters



With these challenges in mind, Kimberly Steward in our group investigated the dynamic kinetic resolution of racemic β-aryl-α-keto ester (±)-**29** under asymmetric transfer hydrogenation conditions (**Scheme 3-15**).[24] It was hypothesized that the incorporation of a β-aryl group would heighten the acidity of α-keto ester (±)-**29** relative to the parent pyruvate enabling facile racemization under the reaction conditions. Initial trials employing Noyori's parent (arene)RuCl(monosulfonamide) complex derived from (*S*,*S*)-TsDPEN provided **30** in 90% yield albeit 57:43 er. Interestingly, the reaction proceeded to provide the cyclized γ-butyrolactone **30** as a single diastereomer where diastereoselective reduction of the carbonyl was followed by diastereoselective lactonization onto one of the proximal methyl esters to establish a third stereocenter. Extensive ligand screening led to the development of a modified (arene)RuCl(monosulfonamide) complex that provided **30** as a single diastereomer in 96:4 er. The success of this catalyst structure relied on a synergistic effect between the chiral α-naphthyl diamine backbone and the *m*-terphenylsulfonamide to affect high enantiofacial selectivity in the reduction.

Scheme 3-15. Dynamic Kinetic Resolution of β-Aryl-α-Keto Esters via Asymmetric Transfer Hydrogenation



3.2.5 Proposed Dynamic Kinetic Resolution of β-Halo-α-Keto Esters via Asymmetric Transfer Hydrogenation

Given the success of β-aryl-α-keto esters in the DKR-ATH reaction, we became interested in exploring the generality of this methodology to provide access to a diverse range of β-stereogenic-α-glycolic acid derivatives. In considering new substrates that might be useful for DKR-ATH reactions, the potential integration of β-halo substituents was appealing on several levels (**Scheme 3-16**). As previously discussed, optically active halohydrins are fundamental building blocks in organic chemistry, and these functional arrays can be converted to enantioenriched epoxides or engage in nucleophilic substitution to provide a variety of functionalized product classes. Also, we reasoned that the electronegativity of a haloalkane might similarly engender the α-keto ester with a sufficient level of C–H acidity required to favor a dynamic process under transfer hydrogenation conditions (formic acid:triethylamine). This methodology would provide isomeric products to those reported by Genêt in the DKR-AH of α-chloro-β-keto esters employing a chiral Ru(BINAP) complex (**Scheme 3-11**).

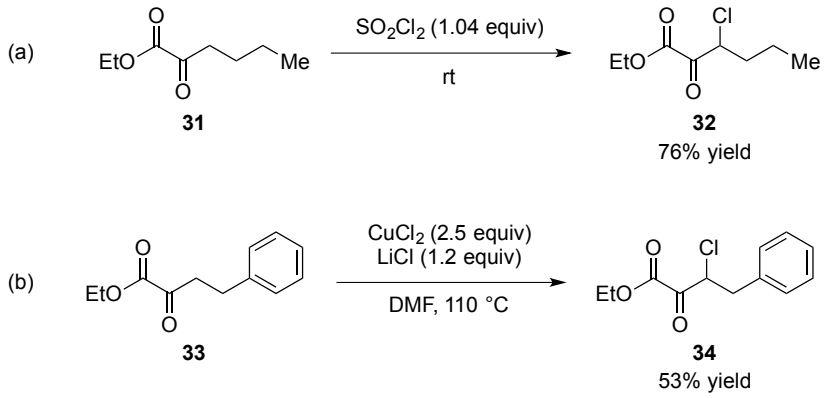
Scheme 3-16. Proposed DKR-ATH of β-Halo-α-Keto Esters

3.3 Results and Discussion

3.3.1 Identification of a Direct β-Chlorination of α-Keto Esters

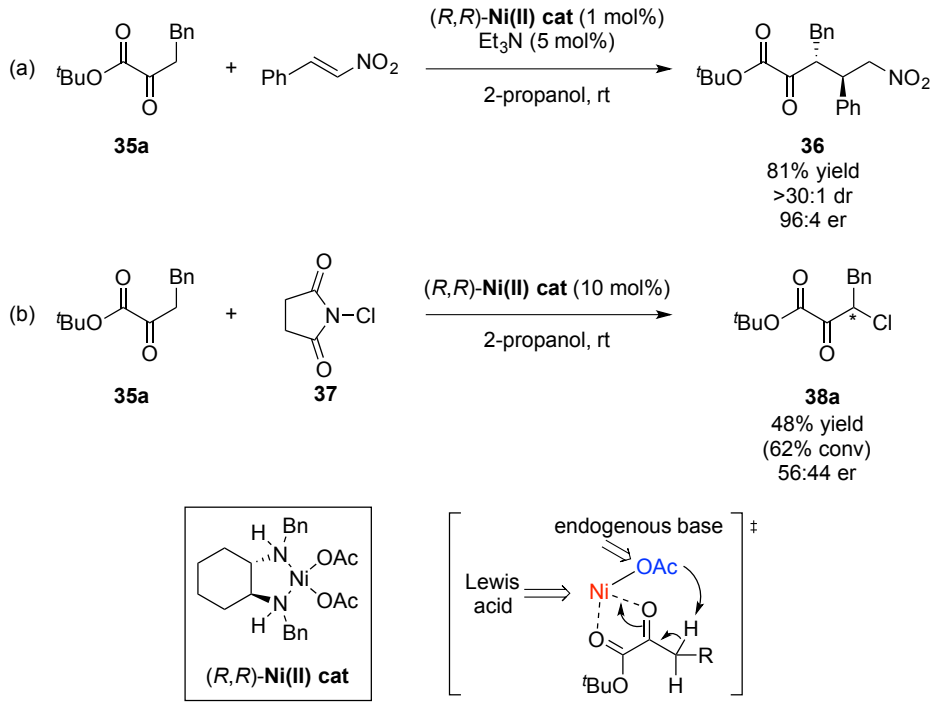
Given Genêt's success in the application of chloroalkanes in the DKR-AH, we chose to initially explore the reactivity of β-chloro-α-keto esters in our proposed DKR-ATH reaction. However, the relative dearth of catalytic direct β-functionalizations of α-keto esters presented an obstacle to the implementation of this synthetic plan; in particular, methods for the direct β-halogenation of α-keto esters are scarce.[6b,6c,25] Prior to our study, only two examples of the direct β-chlorination of singly activated α-keto esters had been reported in the literature. In 1971, Takeda reported that treatment of α-keto ester **31** with sulfuryl chloride provided slow conversion to the desired β-chloro-α-keto ester **32** in good yield after 60 h (**Scheme 3-17a**).[25a] More recently, Tsuboi demonstrated that $CuCl_2$ and LiCl effected the direct chlorination of α-keto ester **33** under driving reaction conditions to afford **34** in 53% yield (**Scheme 3-17b**).[6b] Although both of these methodologies provide access to the requisite β-chloro substrates, they require either long reaction times or harsh reaction conditions.

Scheme 3-17. Extant Methods for the Direct β-Chlorination of α-Keto Esters



We sought to develop a mild chlorination reaction of α-keto esters that could proceed under Lewis acid catalysis. A survey of the literature led us to a recent report by Sodeoka that utilized a chiral $Ni(OAc)_2$-diamine complex to achieve the direct Michael addition of α-keto esters to nitroolefins (**Scheme 3-18a**).[26] The Michael addition proceeded under mild reaction conditions to afford **36** as a single diastereomer in 96:4 er. Although exogenous base was utilized to promote catalyst turnover, Sodeoka proposed that $Ni(OAc)_2$ served both as a Lewis acid to activate the 1,2-dicarbonyl moiety through chelation as well as provided an endogenous base to enable intramolecular deprotonation of the α-keto ester to generate the reactive enolate species. We proposed that an analogous activation mode could be applied towards the preparation of β-chloro-α-keto ester **38a** by treating α-keto ester **35a** with *N*-chlorosuccinimide (NCS, **37**) under otherwise identical reaction conditions (**Scheme 3-18b**). The reaction proceeded to moderate conversion in 2-propanol providing **38a** in 48% yield. It should be noted that the chlorination proceeded with poor enantioselectivity (56:44 er); however, this is partially attributed to product racemization during column chromatography. We were encouraged to observe desired reactivity in the asymmetric β-chlorination of α-keto esters and began to develop a racemic variant of this reaction.

Scheme 3-18. Ni(II)-Catalzyed Direct Functionalization of α-Keto Esters

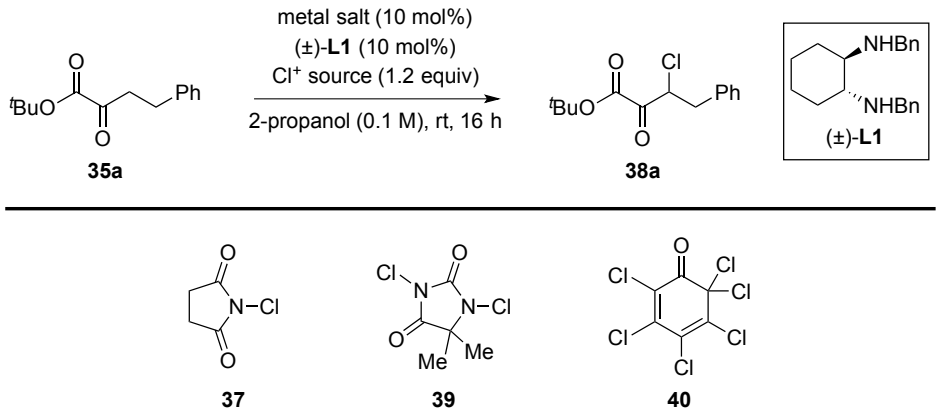


3.3.2 Optimization of Ni(II)-Catalyzed β-Chlorination of α-Keto Esters

We began our optimization studies by exploring the effects of the metal precatalyst and chlorine source in the catalytic direct β-chlorination of α-keto ester **35a** utilizing (±)-**L1** as a standard ligand for screening (**Table 3-1**). A variety of metal precatalysts bearing acetate counterions were screened in the chlorination reaction utilizing NCS (**37**), $Ni(OAc)_2$ and $Cu(OAc)_2$ performed comparably providing **38a** in the highest yields (entries 1 and 2). Interestingly, application of other Cu(II) and Ni(II) salts, such as $CuBr_2$ or $NiBr_2$, provided only trace conversion in the chlorination reaction after 18 h, highlighting the importance of an endogenous base in the enolization step (entries 3 and 4). Utilizing $Ni(OAc)_2$-**L1** as the catalyst complex, the electrophilic source of chlorine was subsequently investigated. Although **39** did not afford any desired product, **40** worked well in the reaction providing **38a** in 51% yield (entries 5

and 6). Since **40** only provided marginal improvement on the yield of the chlorination reaction, we moved forward with NCS (**37**) since it is inexpensive and easier to handle.

Table 3-1. Initial Optimization of Catalytic Direct β-Chlorination of α-Keto Esters[a]



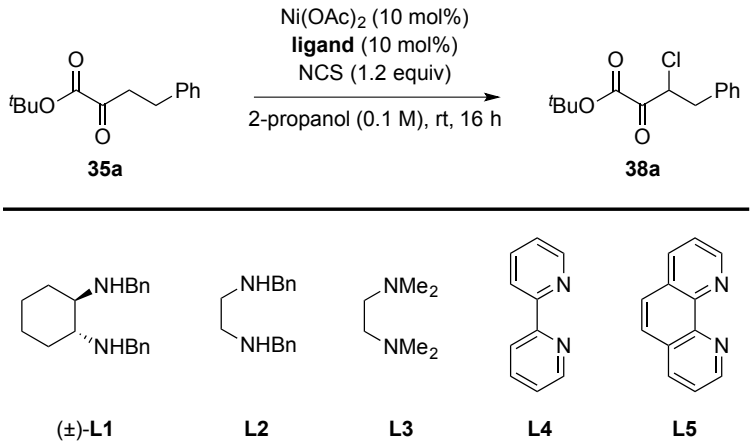
entry	metal salt	Cl^+ source	yield (%)[b]
1	$Ni(OAc)_2$	**37**	48
2	$Cu(OAc)_2$	**37**	46
3	$NiBr_2$	**37**	<5
4	$CuBr_2$	**37**	<5
5	$Ni(OAc)_2$	**39**	<5
6	$Ni(OAc)_2$	**40**	51

[a]Reactions were performed on 0.20 mmol scale in 2-propanol (2 mL) employing a precomplexed catalyst unless otherwise noted. [b]Isolated yield of analytically pure product.

We next began to investigate a variety of diamine ligands in order to determine if structure and electronics could influence the yield of **38a** in the chlorination reaction (**Table 3-2**). The presence of a ligand was critical for solvation as employing unligated $Ni(OAc)_2 \cdot 4H_2O$ resulted in no reaction due to the poor solubility of the free Ni(II) salt in 2-propanol (entry 1). Since (±)-**L1** worked well in the reaction, we attempted the chlorination utilizing acyclic 1,2-diamine **L2**; however, a drop in yield was observed suggesting that the rigidity provided by the cyclohexyl moiety is structurally important (entry 3). Tetramethylethylenediamine (**L3**) was found to completely shut down the reaction providing evidence that a free N–H bond may be

required for effective reactivity; however, both 2,2'-bipyridine (**L4**) and 1,10-phenanthroline (**L5**) provided **38a** in low yield (entries 4-6).

Table 3-2. Screening Diamine Ligands in Catalytic Direct β-Chlorination of α-Keto Esters[a]



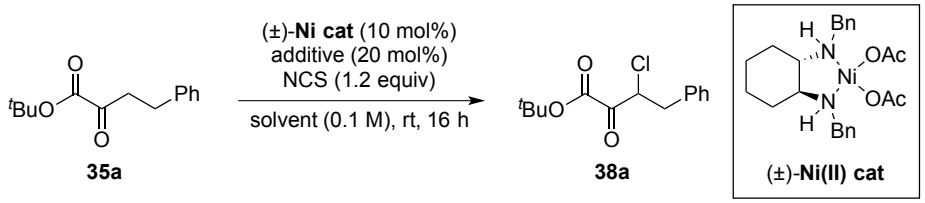
entry	ligand	yield (%)[b]
1[c]	none	0[d]
2	(±)-**L1**	48
3	**L2**	35
4	**L3**	0[d]
5	**L4**	24
6	**L5**	23

[a]Reactions were performed on 0.20 mmol scale in 2-propanol (2 mL) employing a precomplexed catalyst unless otherwise noted. [b]Isolated yield of analytically pure product. [c]Employing $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) as the catalyst. [d]No reaction was observed.

Since structural deviations from Sodeoka's $Ni(OAc)_2$-**L1** complex were largely unsuccessful, we turned our attention to an optimization of reaction conditions to improve the efficiency of the direct catalytic β-chlorination of α-keto esters (**Table 3-3**). Addition of Et_3N (20 mol%) as an exogenous base provided little improvement in the yield of **38a** (entry 2). Since Sodeoka reported that DME provided comparable results to 2-propanol in the direct Michael addition of α-keto esters into nitroolefins, we examined its application and observed an increase in yield of **38a** to 62% (entry 3). An examination of base additives was conducted and revealed,

that although addition of Et_3N provided only trace product, both KOAc and $NaHCO_3$ provided an increase in the yield of **38a** to 72% (entries 4-6 and 8). In reactions utilizing base additives, significant formation of dimerization byproduct **41** was observed (~10-15% yield by NMR). This product results from aldol dimerization/cyclization of the α-keto ester starting material (**Scheme 3-19**).[27] Inclusion of acid additives, such as trichloroacetic acid (TCA), resulted in only trace conversion suggesting that acid was inhibiting the catalyst (entry 7). Given the formation of **41** in the presence of exogenous base, we turned our attention to the effect of solvent in the chlorination reaction as a means of improving the yield of **38a**. Diglyme and CH_2Cl_2 both provided low yields of **38a** (entries 9 and 10). Other ethereal solvents such as THF and Et_2O provided a boost in yield to 78% and 73%, respectively (entries 11 and 12). Optimized conditions were realized by employing THF at 0 °C for 4 h before allowing the reaction to room temperature overnight in order to reduce the amount of dichlorination observed (entry 13).

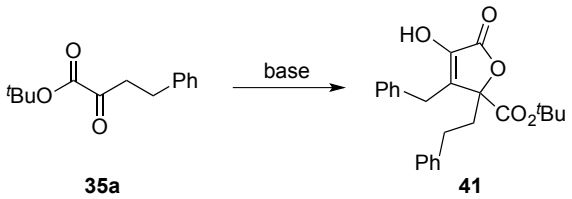
Table 3-3. Optimization of Ni(II)-Catalyzed Direct β-Chlorination of α-Keto Esters[a]



entry	additive (mol%)	solvent	yield (%)[b]
1	none	2-propanol	48
2	Et_3N (20)	2-propanol	51
3	none	DME	62
4	Et_3N (20)	DME	<5
5	KOAc (20)	DME	72
6	$NaHCO_3$ (20)	DME	72
7	TCA (20)	DME	<5
8[c]	KOAc (20)	DME	71
9	none	diglyme	23
10	none	CH_2Cl_2	37
11	none	THF	78
12	none	Et_2O	73
13[d]	none	THF	85

[a]Reactions were performed on 0.2 mmol scale unless otherwise noted. [b]Isolated yield of analytically pure product. [c]Reaction performed at 45 °C for 16 h. [d]Reaction performed at 0 °C for 4 h before being warmed to room temperature for 12 h.

Scheme 3-19. Byproduct Generated via Dimerization of α-Keto Ester **35a**

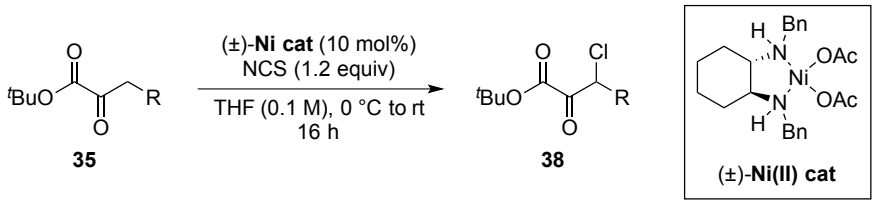


3.3.3 Scope of Ni(II)-Catalyzed Direct β-Chlorination of α-Keto Esters

With optimized reaction conditions in hand, we probed the scope of this methodology in the direct catalytic β-chlorination of α-keto esters (**Table 3-4**). A variety of aliphatic α-keto esters were found to be competent reaction partners in the chlorination reaction providing

products in high yield and good, selectivity for the singly halogenated product. Functional group compatibility was good allowing for incorporation of alkene, alkyne, and benzyloxy functionality in the products (entries 6, 7, and 9). Despite the generality observed for aliphatic substrates, the reaction resulted in selective dichlorination of aryl substrates due to their elevated acidity (entry 10). In order to further demonstrate the utility of this method, β-chlorination of **35a** was performed on multigram scale providing **38a** with little loss in efficiency or selectivity (entry 2).

Table 3-4. Scope of Ni(II)-Catalyzed Direct β-Chlorination of α-Keto Esters[a]



entry	R	38	mono:di[b]	yield (%)[c]
1	$-CH_2Ph$	**38a**	10:1	85
2[d]	$-CH_2Ph$	**38a**	9:1	81
3	$-CH_2$-*p*-ClPh	**38b**	10:1	83
4	$-CH_2$-*p*-MeOPh	**38c**	12:1	84
5	$-(CH_2)_2Ph$	**38d**	8:1	78
6	$-CH_2CH{=}CH_2$	**38e**	13:1	86
7	$-CH_2C{\equiv}CTMS$	**38f**	10:1	79
8	$-(CH_2)_2CH_3$	**38g**	13:1	87
9	$-(CH_2)_3OBn$	**38h**	13:1	86
10	–Ph	**38i**	1:>20	<5[b]

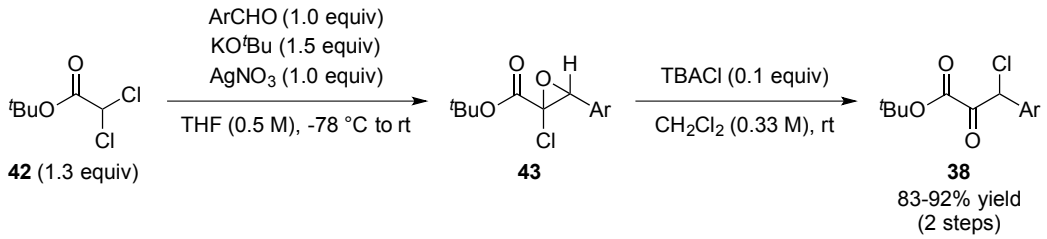
[a]Reactions were performed on 1.0 mmol scale unless otherwise noted. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yield of analytically pure monochlorination product. [d]Reaction performed on 8.0 mmol scale.

3.3.4 Preparation of β-Aryl-β-Chloro-α-Keto Esters via Darzens Reaction

Since aryl substrates were not compatible with our Ni(II)-catalyzed chlorination, we elected to modify a Darzens strategy developed by Mamedov to access the requisite β-aryl-β-

chloro-α-keto esters (**Scheme 3-20**).[28] Darzens condensation of *tert*-butyl dichloroacetate (**42**) with an aryl aldehyde using KO^{t}Bu as the base resulted in the clean formation of 2-chloroglycidic ester **43**, which can be isolated via column chromatography in high yield. The addition of $AgNO_3$ was necessary to precipitate AgCl from the reaction since free chloride ion was found to partially convert **43** to **38** during the Darzens condensation. The desired aryl β-chloro-α-keto ester **38** was found to be unstable to column chromatography so we needed to identify a method for the conversion of **43** to **38** that obviated purification via chromatography. Conversion of 2-chloroglycidic ester **43** to β-chloro-α-keto ester **38** was originally examined using Tsuboi's conditions (PPh_3, benzene, reflux);[29] however, these conditions were incompatible with our *tert*-butyl esters, resulting in decomposition of starting material. Given the propensity of chloride ions to rearrange **43** to **38** during the Darzens reaction, we reasoned that the addition of chloride to the reaction would effect the desired rearrangement. Treating **43** with a catalytic amount of tetrabutylammonium chloride (TBACl) provided clean isomerization of **43** to **38** in quantitative yield following removal of the tetrabutylammonium salt via aqueous washes.

Scheme 3-20. Preparation of β-Aryl-β-Chloro-α-Keto Esters via Darzens Reaction

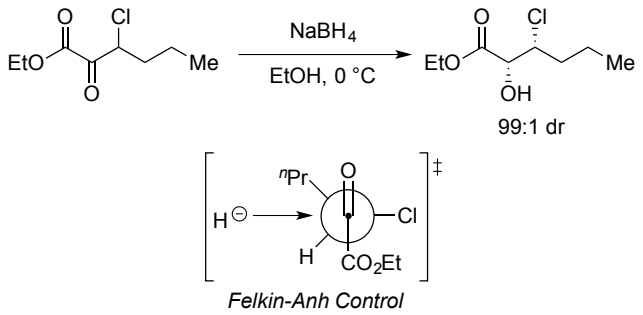


3.3.5 Optimization and Ligand-Controlled Switch in Diastereoselectivity of DKR-ATH

Having identified methods for the preparation of both aliphatic and aryl β-chloro-α-keto esters, we commenced our studies into the realization of a DKR-ATH reaction employing (arene)RuCl(monosulfonamide) complexes. During the kinetic resolution of *syn*-chloroalcohols

via enzymatic acylation, Tsuboi observed that the reduction of β-chloro-α-keto esters with $NaBH_4$ proceeded with high *syn*-selectivity due to Felkin–Anh control (**Scheme 3-21**).[7a] We hoped that the propensity of β-halo-α-keto esters to undergo Felkin–Anh controlled diastereoselective nucleophilic addition would be retained in our proposed dynamic reduction.

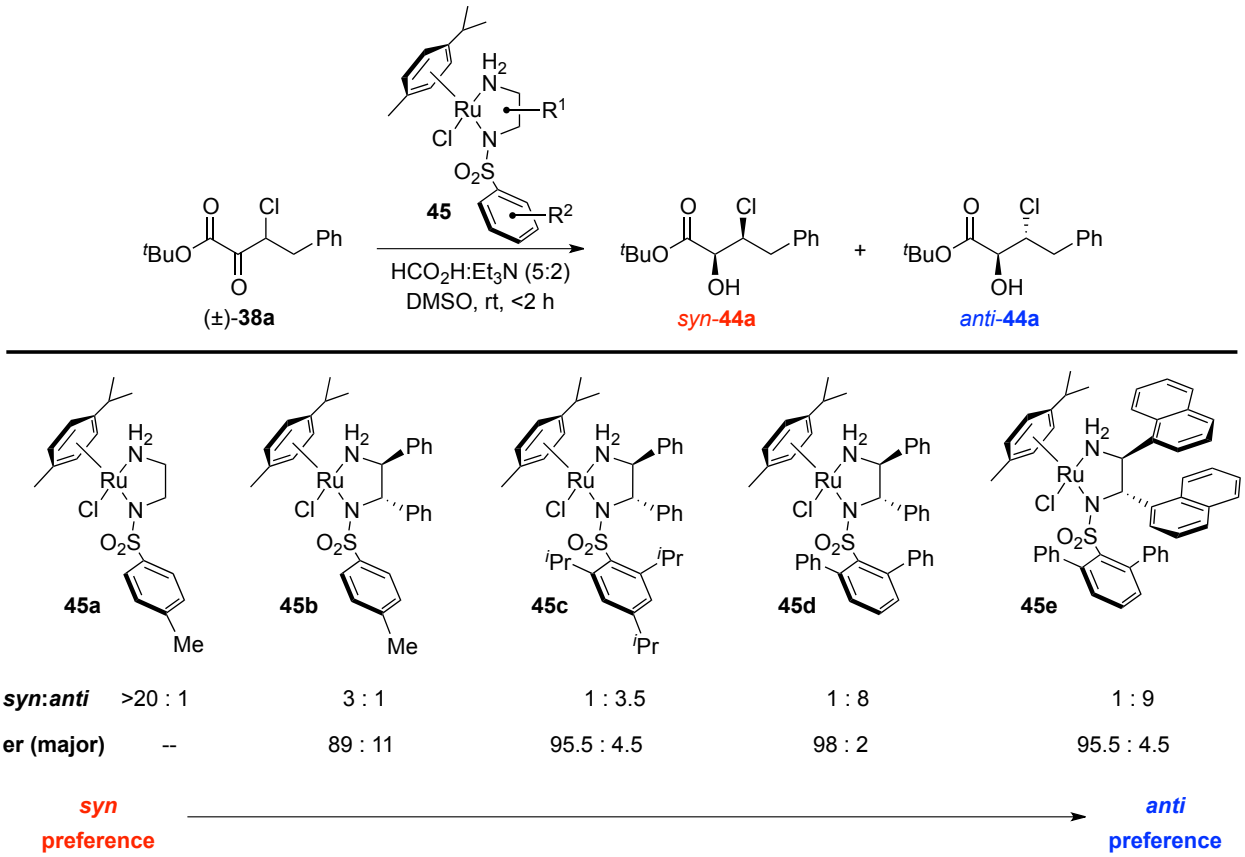
Scheme 3-21. Felkin–Anh Control in the Reduction of β-Chloro-α-Keto Esters



We commenced our studies by subjecting β-chloro-α-keto ester (±)-**38a** to a series of (arene)RuCl(monosulfonamide) complexes **45** bearing sterically-distinct ligands in DMSO at room temperature employing a mixture of formic acid:triethylamine (5:2) as the organic reductant (**Scheme 3-22**). Achiral ethylenediamine-derived **45a** afforded excellent levels of *syn*-selectivity in the reduction of (±)-**38a**, which was consistent with Tsuboi's observation. Upon switching to Noyori's parent (*S*,*S*)-TsDPEN complex **45b**, a significant erosion in *syn*-diastereoselection to 3:1 dr was observed, although *syn*-**44a** was obtained with promising levels of enantioselectivity (89:11 er). Application of a (*S*,*S*)-DPEN ligand bearing the bulkier triisopropylphenyl sulfonamide (**45c**) resulted in a switch in diastereoselectivity favoring *anti*-**44a** in 3.5:1 dr with improved enantiocontrol. Given the success of the *m*-terphenylsulfonamide in our seminal work (**Scheme 3-15**), we applied (*S*,*S*)-DPEN-derived complex **45d** to the dynamic reduction of (±)-**38a**, which resulted in the formation of *anti*-**44a** with 8:1 dr and excellent levels of enantioselectivity (98:2 er). Further amplification of this remarkable ligand-

controlled diastereoselection was explored through the use of the (*S*,*S*)-α-naphthyl backbone which provided *anti*-**44a** with slightly higher levels of diastereoselection albeit with a small erosion in enantioselectivity. Considering diastereoselectivity only, the continuum expressed by ligands **45a** and **45e** (>20:1 *syn*:*anti* → 1:9 *syn*:*anti* at 298 K) represents approximately 2.5 kcal/mol modulation of diastereomeric transition states through simple substituent modifications on a common ligand framework.

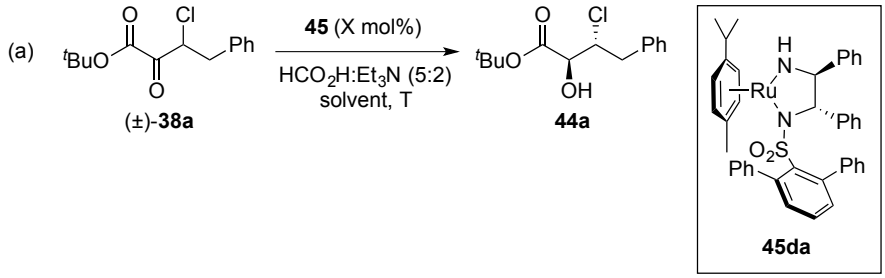
Scheme 3-22. Screening Ligands in the DKR-ATH of β-Chloro-α-Keto Esters[a]



[a]Reactions performed on 0.155 mmol scale employing **45** (4 mol%) and 5 equivalents of HCO_2H:Et_3N (5:2) in DMSO (1.5 mL) at room temperature unless otherwise noted. Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. Enantiomeric ratio was determined by chiral SFC analysis.

Although (arene)RuCl(monosulfonamide) complex **45d** already provided **44a** in good diastereoselectivity and excellent enantioselectivity, we explored catalyst loading, solvent, and temperature in order to further increase activity and selectivity in the dynamic reduction (**Table 3-5**). Switching to DMF as the solvent provided comparable results to DMSO (entry 2); however, DMF's lower freezing point provides more flexibility to explore the role of temperature in the reduction. Decreasing the temperature to 0 °C resulted in an increase in diastereo- and enantioselectivity, whereas increasing the temperature to 40 °C provided **44a** in lower diastereoselectivity than at room temperature (entries 2 and 3). Content with the high levels of diastereoselectivity observed in the reduction at 0 °C, we turned our attention to increasing the TON of the transformation by decreasing the catalyst loading. We also began to explore using the active bench-stable 16-electron amide complex **45da** directly in the reduction in order to facilitate the operational simplicity of the reaction. We were pleased to observe that dropping the catalyst loading of **45da** to 1 mol% (TON = 100) or 0.5 mol% (TON = 200) provided identical levels of selectivity, although the reaction took 10 and 24 h, respectively, to reach full conversion at 0 °C (entries 6 and 7).

Table 3-5. Optimization of DKR-ATH of β-Chloro-α-Keto Esters[a]



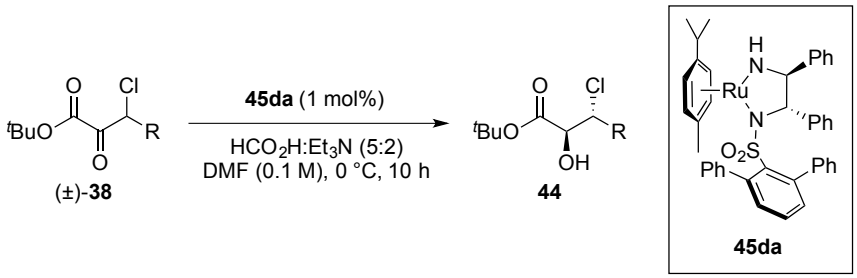
entry	45 (mol%)	solvent	T (°C)	t (h)	dr[b]	er[e]
1	**45d** (4)	DMSO	23	2	9:1	98:2
2	**45d** (4)	DMF	23	2	8:1	97.5:2.5
3	**45d** (4)	DMF	0	6	12:1	98.5:1.5
4	**45d** (4)	DMF	40	1	6:1	97.5:2.5
5	**45d** (1)	DMF	0	10	12:1	98.5:1.5
6	**45da** (1)	DMF	0	10	12:1	99:1
7	**45da** (0.5)	DMF	0	24	12:1	99:1

[a]Reactions performed on 0.155 mmol scale employing 5 equivalents of HCO_2H:Et_3N (5:2) in solvent (1.5 mL) unless otherwise noted. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by chiral SFC analysis.

3.3.6 Scope of the DKR-ATH of β-Chloro-α-Keto Esters

With optimized reaction conditions in hand the relationship between α-keto ester structure and reaction stereoselectivity was assayed (**Table 3-6**). A variety of aliphatic substrates were found to be amenable to the reaction conditions providing β-chloro-α-hydroxy esters **44** with excellent levels of diastereo- and enantioselection. Alkene, alkyne, and benzyloxy functionality was tolerated under the reaction conditions offering value-added functional handles that are incompatible with extant methods (entries 6, 7, and 9). The method was also scalable with no observed loss in activity or selectivity (entry 2). The efficiency of these aliphatic substrates under the DKR-ATH reaction conditions is a marked structural departure from the β-aryl requirements in antecedent work from our group.

Table 3-6. Scope of β-Aliphatic-β-Chloro-α-Keto Esters in the DKR-ATH[a]

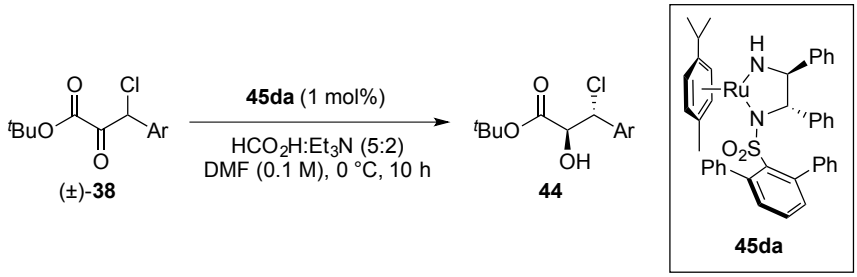


entry	R	44	yield (%)[b]	dr[c]	er[d]
1	$-CH_2Ph$	**44a**	90	12:1	99:1
2[e]	$-CH_2Ph$	**44a**	89	12:1	99:1
3	$-CH_2$-*p*-ClPh	**44b**	90	16:1	99.5:0.5
4	$-CH_2$-*p*-MeOPh	**44c**	93	20:1	98.5:1.5
5	$-(CH_2)_2Ph$	**44d**	93	16:1	98.5:1.5
6	$-CH_2CH{=}CH_2$	**44e**	95	>20:1	98:2[f]
7[g]	$-CH_2C{\equiv}CTMS$	**44f**	91	>20:1	96.5:3.5[f]
8	$-(CH_2)_2CH_3$	**44g**	94	>20:1	98.5:1.5[f]
9	$-(CH_2)_3OBn$	**44h**	91	18:1	98:2

[a]Reactions performed on 0.155 mmol scale employing 5 equivalents of HCO_2H:Et_3N (5:2) in DMF (1.5 mL) at 0 °C for 10 h unless otherwise noted. [b]Isolated yield of *anti*-diastereomer. [c]Determined by ^1H NMR analysis of the crude reaction mixture. [d]Determined by chiral SFC/HPLC analysis. [e]Performed on 6.5 mmol scale. [f]Determined following benzoylation of the product. [g]Performed at 23 °C for 10 h.

Compatibility with β-aryl substrates was also demonstrated under the optimized reaction conditions, providing adducts **44** with excellent levels of enantioselectivity (**Table 3-7**). The electronic character of the aromatic ring was found to significantly impact the diastereoselectivity of the reaction. Electron-releasing groups engendered excellent diastereocontrol (entries 2, 3, and 10) whereas electron-withdrawing groups provided somewhat lower diastereoselection (entries 4, 7, and 8).

Table 3-7. Scope of β-Aryl-β-Chloro-α-Keto Esters in the DKR-ATH[a]



entry	Ar	44	yield (%)[b]	dr[c]	er[d]
1	Ph	**44i**	93	14:1	99.5:0.5
2	*o*-MeOPh	**44j**	95	>20:1	99:1
3	*m*-MeOPh	**44k**	94	19:1	99.5:0.5
4	*m*-NO_2Ph	**44l**	74	5:1	97.5:2.5
5	*p*-ClPh	**44m**	85	10:1	98.5:1.5
6	*p*-CF_3Ph	**44n**	80	8:1	98.5:1.5
7[g]	*p*-CNPh	**44o**	82	6:1	98:2
8	*p*-NO_2Ph	**44p**	73	4:1	99:1
9	*p*-MePh	**44q**	91	14:1	99.5:0.5
10	*p*-MeOPh	**44r**	93	>20:1	99:1

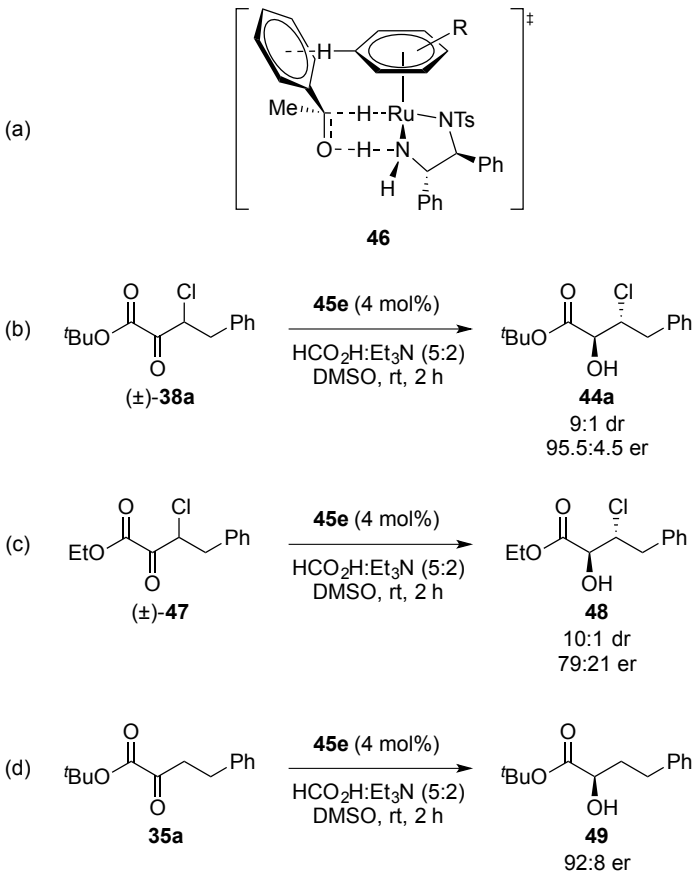
[a]Reactions performed on 0.155 mmol scale employing 5 equivalents of HCO_2H:Et_3N (5:2) in DMF (1.5 mL) at 0 °C for 10 h unless otherwise noted. [b]Isolated yield of *anti*-diastereomer. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by chiral SFC/HPLC analysis.

3.3.7 Selectivity in the DKR-ATH of β-Chloro-α-Keto Esters

Detailed studies by Noyori into the origin of enantioselectivity in the ATH of aryl ketones catalyzed by (*S*,*S*)-TsDPEN **45b** revealed that the enantioselection results from attractive C–H/π interactions between the η^6-arene and the aryl group in the substrate (**Scheme 3-23a**).[30] In the hydrogen-bonding coordination of acetophenone to form the six-membered pericyclic transition state **46**, enantiotopic discrimination of the two faces of the carbonyl is achieved by the alignment of a C–H on the η^6-arene into the center of the phenyl ring to effect stabilization of the transition state. Given the need for strong attractive interactions to control the enantiofacial approach of the carbonyl to the ruthenium complex, we were surprised to observe high levels of

enantioselectivity in the reductions of (±)-**38e-g**, substrates lacking aryl functionality (**Table 3-6**). In order to better understand the strucutral requirements necessary to obtain high levels of enantioselectivity in the DKR-ATH of β-chloro-α-keto esters, we compared the selectivities obtained from (±)-**38a**, (±)-**47**, and **35a** (**Scheme 3-23b-d**). Decreasing the steric bulk of the ester group from *tert*-butyl to ethyl resulted in a large drop in enantioselectivity suggesting that the α-keto ester's approach occurs as to minimize catalyst/ester interactions; however, **44a** and **48** were obtained in nearly identical diastereoselectivity. The role of the chlorine atom was found to be unsubstantial in governing facial selectivity in the reduction, as **49** was obtained in only slightly lower enantioselectivity.

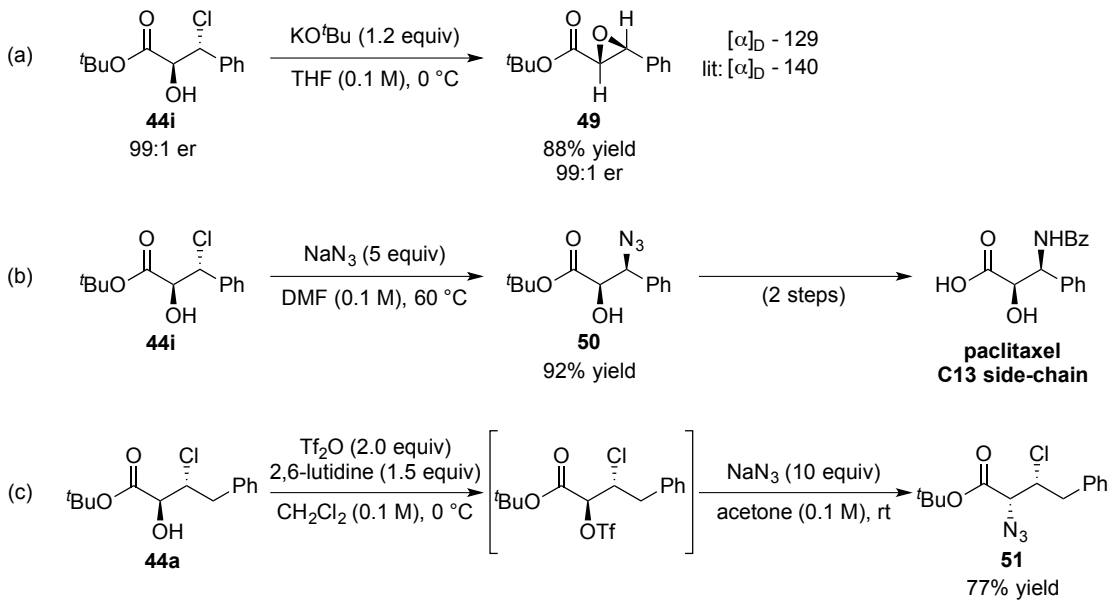
Scheme 3-23. Origin of Enantioselectivity in the DKR-ATH of β-Chloro-α-Keto Esters



3.3.8 Secondary Transformations of Chlorohydrin Products

To highlight the synthetic utility of the enantioenriched chlorohydrins as synthetic building blocks, illustrative secondary transformations were pursued. Exposure of chlorohydrin (2*S*,3*R*)-**44i** to KO^{t}Bu provides access to glycidic ester (2*R*,3*S*)-**49** in 88% yield (**Scheme 3-24a**). The absolute stereochemistry of the products was determined by comparing the optical rotation of glycidic ester (2*R*,3*S*)-**49** to the literature value and other products were assigned by analogy.[31] Treatment of chlorohydrin **44i** with NaN_3 afforded the azido alcohol **50** representing a formal synthesis of the paclitaxel C13 side-chain (**Scheme 3-24b**).[32] Notably, the *syn*-product **50** is stereocomplementary to the *anti* diastereomer obtained from the glycidic esters that one might derive from Darzens or Weitz-Scheffer reactions. Following triflate formation of chloroalcohol **44a**, chemoselective displacement with NaN_3 affords α-azido-β-chloro ester **51** providing access to β-chloro amino acid derivatives (**Scheme 3-24c**).

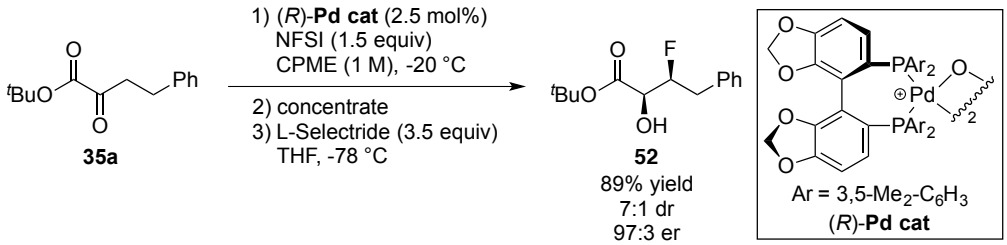
Scheme 3-24. Secondary Transformations of Chlorohydrin Products



3.3.9 Application to Other β-Halo-α-Keto Esters

During the development of our DKR-ATH of β-chloro-α-keto esters, Sodeoka reported a method for the preparation of β-fluoro-α-hydroxy esters from α-keto esters (**Scheme 3-25**).[25d] Employing a two-step asymmetric fluorination/diastereoselective reduction sequence, α-keto ester **35a** was converted to fluorohydrin **52** in high yield with 9:1 dr and 97:3 er. Despite the high levels of enantioselectivity obtained in the Pd-catalyzed fluorination, conditions to provide high diastereocontrol in the reduction of the intermediate β-fluoro-α-keto esters proved challenging. Although **52** was obtained in 7:1 dr, most substrates were only obtained in moderate diastereoselection (<5:1 dr).

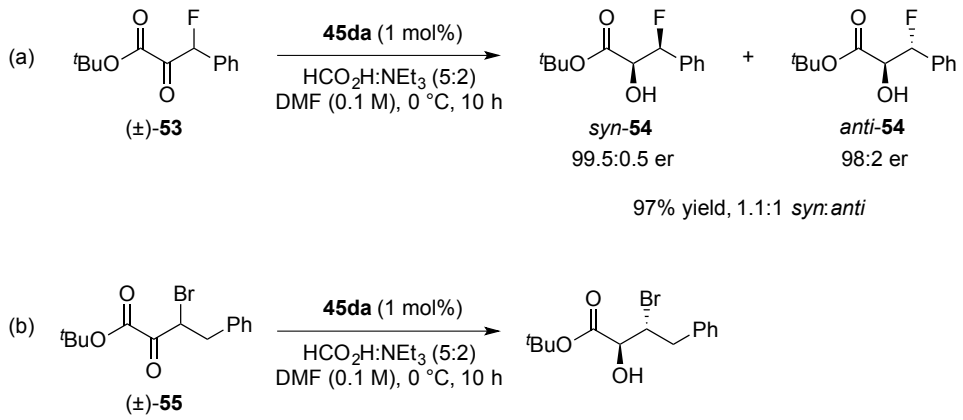
Scheme 3-25. Synthesis of Optically Active Fluorohydrins



We wondered if we could access enantiopure fluorohydrins with higher levels of diastereocontrol from racemic β-fluoro-α-keto esters utilizing our newly developed DKR-ATH protocol. Preliminary investigations have revealed that ketone (±)-**53** can be reduced under the optimized reaction conditions to afford the derived fluorohydrin **54** in excellent yield as a mixture of diastereomers (**Scheme 3-26a**). Despite the lack of diastereocontrol in the reaction, excellent levels of enantioinduction were observed for both diastereomers. This initial finding is quite encouraging in light of the responsiveness of diastereocontrol to ligand structure in this reaction family (*vide supra*). However, our complementary methodology did not initially provide

any improvements on the diastereoselectivities observed by Sodeoka. Early experiments examining the potential use of β-bromo-α-keto esters in the DKR-ATH were largely unsuccessful (**Scheme 3-26b**). Subjecting (±)-**55** to typical reaction conditions led to complete consumption of starting material with only trace product detected by crude ^{1}H NMR. This is attributed to the increased lability of bromine relative to chlorine or fluorine leading to deleterious pathways such as C–Br cleavage under the hydrogenation conditions.[33]

Scheme 3-26. DKR-ATH of β-Halo-α-Keto Esters



3.4 Conclusion

This chapter has described a highly stereoselective synthesis of β-chloro-α-glycolic acid derivatives via asymmetric transfer hydrogenation. A Ni(II)-catalyzed β-chlorination of aliphatic α-keto esters was developed to provide the requisite β-chloro-α-keto esters under mild reaction conditions. In the reduction of these ketones, careful catalyst tuning allowed for a remarkable ligand-controlled inversion of the preference for *syn*-selectivity to provide access to *anti*-chlorohydrins. The DKR-ATH proceeded with high levels of diastereo- and enantioselectivity for a number of aliphatic and aromatic substrates. The obtained chlorohydrins are versatile chemical building blocks for valuable secondary transformations.

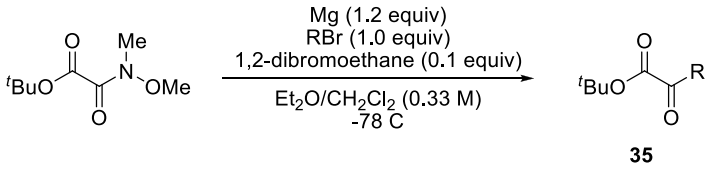
3.5 Experimental Details

Methods: Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 100 MHz or 150 MHz, and ^{19}F NMR at 376 MHz or 565 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, sept = septuplet, oct = octuplet, m = multiplet), coupling constants (Hz), and integration. Supercritical fluid chromatography was performed on a Berger SFC system equipped with Chiralcel AD and WO columns (φ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH. HPLC analysis was performed on an Agilent Technologies 1200 System equipped with Chiralpak IA, IB, and IC columns (φ 4.6 mm x 250 mm, constant flow at 1.00 mL/min). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization (Note: All samples prepared in acetonitrile or methanol). Analytical thin layer chromatography (TLC) was performed on Whatman or Sorbtech 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle. All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and

diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

Materials: $Ni(OAc)_2$-diamine complex from **L1** ((±)-**S1**),[26] α-keto esters **35a-e** and **35g**,[25d,26,34] and β-aryl-β-chloro-α-keto esters **38i-l**, **38p**, and **38r**[28,35] were prepared according to literature procedures. *N*-Chlorosuccinimide (NCS) was recrystallized from toluene.[36] *N*,*N*-Dimethylformamide (DMF) was distilled from phosphorous pentoxide and stored under nitrogen over 3Å molecular sieves. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride and stored under nitrogen over 3Å molecular sieves. Triethylamine (Et_3N) was freshly distilled from calcium hydride prior to use. Toluene ($PhCH_3$), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and tetrahydrofuran (THF) were dried by passage through a column of neutral alumina under nitrogen prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

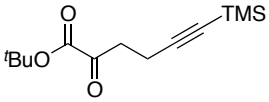
General Procedure A for the Preparation of α-Keto Esters 35



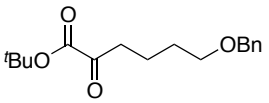
A 3-neck round-bottomed flask affixed with a reflux condenser and addition funnel was charged with magnesium turnings (12 mmol, 1.2 equiv). The apparatus was flame-dried under high vacuum. Upon cooling to room temperature, the apparatus was placed under an atmosphere of nitrogen and diethyl ether (6 mL) was added. The solution was heated to reflux. 1,2-Dibromoethane (1 mmol, 0.1 equiv) was added dropwise over 5 min to the refluxing solution. Following addition, the solution was allowed to cool to room temperature. A solution of the alkyl bromide (10 mmol, 1.0 equiv) in diethyl ether (4 mL) was added dropwise from the addition

funnel over 30 min. The reaction was allowed to age for 1 h at room temperature following addition.

A flame-dried round-bottomed flask affixed with an addition funnel was charged with mono-*tert*-butyloxalic acid-*N*-methoxy-*N*-methylamide[26] (10 mmol, 1.0 equiv) in methylene chloride (20 mL) under a nitrogen atmosphere. The solution was cooled to -78 ºC. The previously prepared Grignard solution (~1M, 1.0 equiv) was added dropwise to the reaction over 30 min. Following addition, the reaction was allowed to stir for 90 min at -78 ºC. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The obtained residue was purified by column chromatography on silica gel eluting with 5% ethyl acetate:hexanes to afford the α-keto ester **35**.



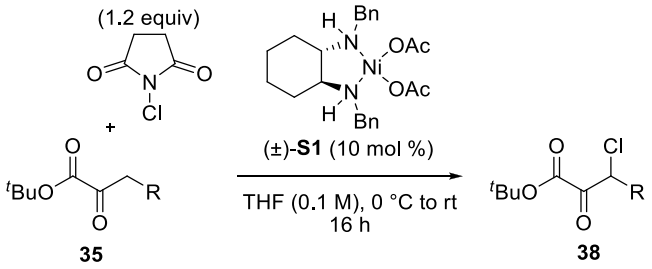
***tert*-Butyl 2-oxo-6-(trimethylsilyl)hex-5-ynoate (35f):** The title compound was prepared according to General Procedure A using (4-bromobut-1-yn-1-yl)trimethylsilane[37] (2.05 g, 10 mmol) affording α-keto ester **35f** (1.74 g, 6.8 mmol, 68% yield) as a pale yellow oil. Analytical data for **35f**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.97 (t, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 6.7 Hz, 2H), 1.49 (s, 9H), 0.07 (s, 9H); **^{13}C NMR** (101 MHz) δ 193.1, 159.9, 104.6, 85.3, 84.0, 38.3, 27.7, 13.7, -0.1; **IR** (thin film) 2983, 2359, 2178, 1735, 1718, 1646, 1371, 1252, 1140, 1077, 842 cm^{-1}; **TLC** (5% EtOAc:Hexanes) R_f = 0.23; **LRMS** (ESI) Calcd. for $C_{14}H_{26}NaO_4Si$ ($[M+MeOH+Na]^+$): 309.15, Found: 309.20.



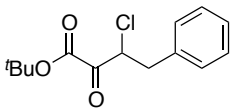
***tert*-Butyl 6-(benzyloxy)-2-oxohexanoate (35h):** The title compound was prepared according to General Procedure A using ((4-bromobutoxy)methyl)benzene[38] (2.43 g, 10 mmol) affording α-keto ester **35h** (2.07 g, 7.1 mmol,

71% yield) as a pale yellow oil. Analytical data for **35h**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.33 (m, 5H), 4.49 (s, 2H), 3.48 (t, *J* = 6.1 Hz, 2H), 2.80 (t, *J* = 7.1 Hz, 2H), 1.77-1.62 (m, 4H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz) δ 195.2, 160.6, 138.3, 128.1, 127,4, 127.3, 83.5, 72.6, 69.6, 38.6, 28.7, 27.6, 19.7; **IR** (thin film) 2359, 1752, 1721, 1646, 1370, 1161, 698 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.31; **LRMS** (ESI) Calcd. for $C_{18}H_{28}NaO_5$ ([M+MeOH+Na]$^+$): 347.18, Found: 347.28.

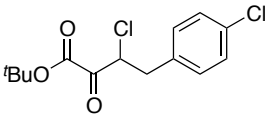
General Procedure B for the Ni(II)-Catalyzed Chlorination of α-Keto Esters



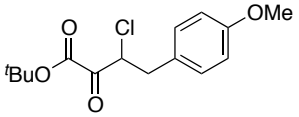
A round-bottomed flask was charged with α-keto ester **35** (1.0 mmol, 1.0 equiv) and Ni(II)-diamine complex (±)-**S1** (47.2 mg, 0.1 mmol, 0.1 equiv) in THF (10 mL). The solution was cooled to 0 ºC. *N*-Chlorosuccinimide (160.2 mg, 1.2 mmol, 1.2 equiv) was added to the reaction, which was allowed to stir for 4 h at 0 ºC before being allowed to warm to room temperature overnight. The reaction was diluted with Et_2O (20 mL) and quenched by the addition of H_2O (20 mL). The layers were separated the organic layer was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The obtained residue was purified by column chromatography on silica gel to afford the β-chloro-α-keto ester **38**.



***tert*-Butyl 3-chloro-2-oxo-4-phenylbutanoate (38a):** The title compound was prepared according to General Procedure B using α-keto ester **35a** (1.87 g, 8.0 mmol) affording β-chloro-α-keto ester **38a** (1.75 g, 6.50 mmol, 81% yield) as a pale yellow oil. Analytical data for **38a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.22 (m, 5H), 5.08 (dd, *J* = 8.2, 6.2 Hz, 1H), 3.41 (dd, J = 14.3, 6.2 Hz, 1H), 3.11 (dd, *J* = 14.3, 8.2 Hz, 1H), 1.52 (s, 9H); **^{13}C NMR** (101 MHz) δ 187.7, 159.6, 135.7, 129.4, 128.6, 127.3, 85.2, 58.8, 38.8, 27.3; **IR** (thin film) 2917, 2089, 1753, 1726, 1646, 1456, 1371, 1260, 1157, 699 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.24; **LRMS** (ESI) Prepared in MeCN, Calcd. for $C_{14}H_{18}ClO_3$ ([M+H]$^+$): 269.09, Found: 269.03.

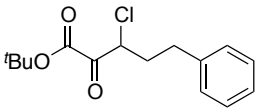


***tert*-Butyl 3-chloro-4-(4-chlorophenyl)-2-oxobutanoate (38b):** The title compound was prepared according to General Procedure B using α-keto ester **35b** (269 mg, 1.0 mmol) affording β-chloro-α-keto ester **38b** (251 mg, 0.83 mmol, 83% yield) as a white crystalline solid (mp: 51-54 ºC). Analytical data for **38b**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 5.06 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.39 (dd, *J* = 14.4, 6.2 Hz, 1H), 3.10 (dd, *J* = 14.4, 8.2 Hz, 1H), 1.55 (s, 9H); **^{13}C NMR** (101 MHz) δ 187.3, 159.6, 134.2, 133.2, 130.8, 128.8, 85.4, 58.5, 38.0, 27.7; **IR** (thin film) 2941, 1753, 1731, 1645, 1491, 1372, 1260, 1158, 1093, 1016, 751 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.19; **LRMS** (ESI) Prepared in MeCN, Calcd. for $C_{14}H_{16}Cl_2NaO_3$ ([M+Na]$^+$): 325.04, Found: 325.06.

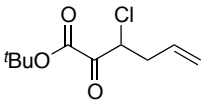


***tert*-Butyl 3-chloro-4-(4-methoxyphenyl)-2-oxobutanoate (38c):** The title compound was prepared according to General Procedure B using α-keto ester **35c** (264 mg, 1.0 mmol) affording β-chloro-α-keto ester **38c** (251 mg, 0.84 mmol, 84% yield) as a pale yellow oil. Analytical data for **38c**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.05 (dd, *J* = 7.9, 6.7 Hz, 1H), 3.79 (s, 3H), 3.37 (dd, *J* =

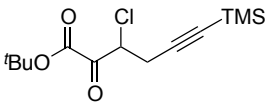
14.4, 6.5 Hz, 1H), 3.08 (dd, J = 14.4, 8.0 Hz, 1H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz) δ 187.8, 159.6, 158.8, 130.5, 127.6, 114.0, 85.2, 59.0, 55.2, 38.0, 27.7; **IR** (thin film) 2983, 2360, 1751, 1717, 1653, 1515, 1457, 1252, 750 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.22; **LRMS** (ESI) Calcd. for $C_{16}H_{23}ClNaO_5$ ([M+MeOH+Na]$^+$): 353.11, Found: 353.08.



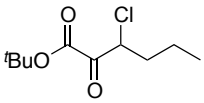
***tert*-Butyl 3-chloro-2-oxo-5-phenylpentanoate (38d):** The title compound was prepared according to General Procedure B using α-keto ester **35d** (248 mg, 1.0 mmol) affording β-chloro-α-keto ester **38d** (219 mg, 0.78 mmol, 78% yield) as a pale yellow oil. Analytical data for **38d**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.25-7.20 (m, 3H), 4.83 (dd, J = 9.0, 4.8 Hz, 1H), 2.92-2.85 (m, 1H), 2.82-2.75 (m, 1H), 2.40-2.31 (m, 1H), 2.25-2.15 (m, 1H), 1.55 (s, 9H); **^{13}C NMR** (101 MHz) δ 188.2, 160.0, 139.8, 128.6, 128.5, 126.4, 85.2, 58.4, 33.9, 31.8, 27.7; **IR** (thin film) 2983, 2360, 1732, 1713, 1647, 1541, 1456, 1372, 1157, 700 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.24; **LRMS** (ESI) Calcd. for $C_{16}H_{23}ClNaO_4$ ([M+MeOH+Na]$^+$): 337.12, Found: 337.09.



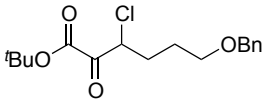
***tert*-Butyl 3-chloro-2-oxohex-5-enoate (38e):** The title compound was prepared according to General Procedure B using α-keto ester **35e** (184 mg, 1.0 mmol) affording β-chloro-α-keto ester **38e** (162 mg, 0.74 mmol, 74% yield) as a pale yellow oil. Analytical data for **38e**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85-5.75 (m, 1H), 5.20 (d, J = 17.2 Hz, 1H), 5.18 (d, J = 9.6 Hz, 1H), 4.91 (t, J = 6.9 Hz, 1H), 2.85-2.79 (m, 1H), 2.69-2.61 (m, 1H), 1.57 (s, 9H); **^{13}C NMR** (101 MHz) δ 187.7, 159.9, 131.9, 119.5, 85.2, 57.8, 36.7, 27.8; **IR** (thin film) 2991, 2358, 2091, 1736, 1725, 1646, 1539, 1452, 1259 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.24; **LRMS** (ESI) Calcd. for $C_{11}H_{19}ClNaO_4$ ([M+MeOH+Na]$^+$): 273.09, Found: 273.10.



***tert*-Butyl 3-chloro-2-oxo-6-(trimethylsilyl)hex-5-ynoate (38f):** The title compound was prepared according to General Procedure B using α-keto ester **35f** (254 mg, 1.0 mmol) affording β-chloro-α-keto ester **38f** (205 mg, 0.71 mmol, 71% yield) as a pale yellow oil. Analytical data for **38f**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.99 (t, *J* = 6.9 Hz, 1H), 2.99 (dd, *J* = 17.3, 6.6 Hz, 1H), 2.83 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.57 (s, 9H), 0.14 (s, 9H); **^{13}C NMR** (101 MHz) δ 186.3, 159.3, 100.0, 88.7, 85.4, 55.5, 27.8, 24.3, -0.18; **IR** (thin film) 2692, 2183, 1751, 1728, 1371, 1252, 1157, 1091, 844, 761 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.16; **LRMS** (ESI) Calcd. for $C_{14}H_{26}ClO_4Si$ ([M+MeOH+H]$^+$): 321.13, Found: 321.17.



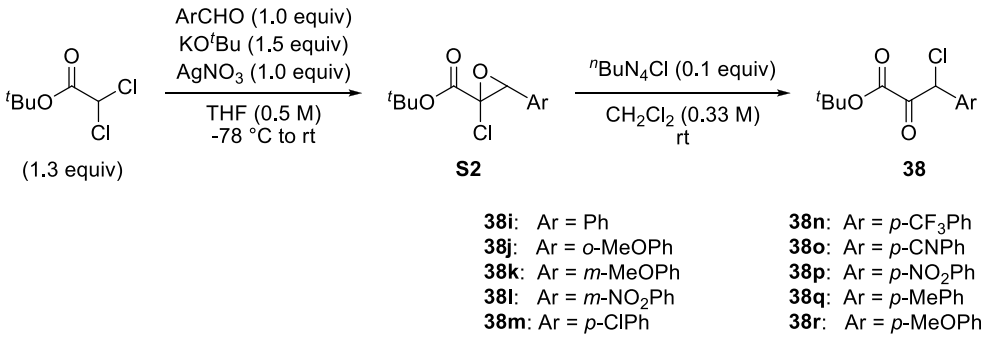
***tert*-Butyl 3-chloro-2-oxohexanoate (38g):** The title compound was prepared according to General Procedure B using α-keto ester **35g** (186 mg, 1.0 mmol) affording β-chloro-α-keto ester **38g** (192 mg, 0.87 mmol, 87% yield) as a pale yellow oil. Analytical data for **38g**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.86 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.05-1.96 (m, 1H), 1.91-1.81 (m, 1H), 1.56 (s, 9H), 1.54-1.44 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz) δ 188.4, 160.2, 85.1, 59.0, 34.3, 27.8, 19.1, 13.3; **IR** (thin film) 1747, 1723, 1647, 1457, 1371, 1258, 1159, 1060 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.22; **LRMS** (ESI) Calcd. for $C_{11}H_{21}ClNaO_4$ ([M+MeOH+Na]$^+$): 275.10, Found: 275.14.



***tert*-Butyl 6-(benzyloxy)-3-chloro-2-oxohexanoate (38h):** The title compound was prepared according to General Procedure B using α-keto ester **35h** (292 mg, 1.0 mmol) affording β-chloro-α-keto ester **38h** (280 mg, 0.86 mmol, 86% yield) as a pale yellow oil. Analytical data for **38h**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 4.96 (dd, *J* = 8.3, 5.6 Hz, 1H), 4.49 (s, 2H), 3.56-3.47 (m, 2H), 2.26-2.17 (m, 1H), 2.04-1.95 (m, 1H), 1.90-1.71 (m, 2H), 1.55 (s, 9H); **^{13}C NMR** (101 MHz) δ 188.0, 160.0, 138.2, 128.4,

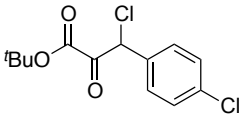
127.6, 85.1, 72.9, 69.1, 58.8, 29.5, 27.7, 26.1; **IR** (thin film) 2866, 1743, 1724, 1641, 1455, 1371, 1258, 1160, 1117 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.19; **LRMS** (ESI) Calcd. for $C_{18}H_{27}ClNaO_5$ ($[M+MeOH+Na]^+$): 381.14, Found: 381.22.

General Procedure C for the Synthesis of β-Aryl-β-Chloro-α-Keto Esters

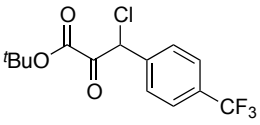


A flame-dried round-bottomed flask was charged with *tert*-butyl 2,2-dichloroacetate[28] (0.74 g, 4.0 mmol, 1.3 equiv), aldehyde (3.0 mmol, 1.0 equiv), and $AgNO_3$ (0.51 g, 3.0 mmol, 1.0 equiv) in THF (6 mL). The solution was cooled to -78 ºC. KO^{t}Bu (0.50 g, 4.5 mmol, 1.5 equiv) was added. The reaction was allowed to stir for 10 h as it slowly warmed to room temperature. The reaction was diluted with Et_2O (20 mL) and quenched by the addition of H_2O (20 mL). The layers were separated and the organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude glycidic ester was filtered through a short plug of silica gel eluting with 20% EtOAc:hexanes to afford pure glycidic ester **S2**, which was immediately dissolved in CH_2Cl_2 (10 mL) in a flame-dried round-bottomed flask. Tetrabutylammonium chloride (83 mg, 0.3 mmol, 0.1 equiv) was added and the reaction stirred at room temperature for 2 h. The reaction was concentrated *in vacuo*. The crude residue was partitioned between Et_2O (20 mL) and H_2O (20 mL). The layers were separated and the organic layer was washed with H_2O (2 x 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the pure β-chloro-α-keto ester **38**.

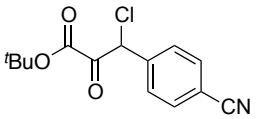
Note: The β-aryl-β-chloro-α-keto esters **38** were found to exist in equilibrium with a dimeric aldol adduct when the aryl group was electron-poor. The mixture was found to readily interconvert back to the β-chloro-α-keto ester **38** under the reduction conditions.



***tert*-Butyl 3-chloro-3-(4-chlorophenyl)-2-oxopropanoate (38m):** The title compound was prepared according to General Procedure C using 4-chlorobenzaldehyde (422 mg, 3.00 mmol) affording β-chloro-α-keto ester **38m** (796 mg, 2.75 mmol, 92% yield) as a pale yellow oil. Analytical data for **38m**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.03 (s, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz) δ 185.4, 159.1, 135.7, 131.9, 130.2, 129.2, 85.6, 61.3, 27.6; **IR** (thin film) 2360, 1747, 1721, 1642, 1491, 1369, 1158, 776 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.48; **LRMS** (ESI) Calcd. for $C_{14}H_{18}Cl_2NaO_4$ ($[M+MeOH+Na]^+$): 343.05, Found: 343.14.

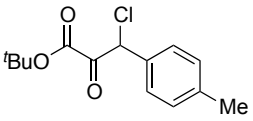


***tert*-Butyl 3-chloro-2-oxo-3-(4-(trifluoromethyl)phenyl)propanoate (38n):** The title compound was prepared according to General Procedure C using 4-(trifluoromethyl)benzaldehyde (522 mg, 3.00 mmol) affording β-chloro-α-keto ester **38n** (853 mg, 2.64 mmol, 88% yield) as a pale yellow oil. Analytical data for **38n**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 6.09 (s, 1H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz) δ 185.3, 159.1, 137.4, 129.3, 127.5 (q, *J* = 125.7 Hz), 125.9 (q, *J* = 3.7 Hz), 85.8, 61.0, 27.6; **IR** (thin film) 2987, 2363, 1751, 1728, 1627, 1372, 1129, 1068, 839 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.45; **LRMS** (ESI) Calcd. for $C_{15}H_{19}ClF_3O_4$ ($[M+MeOH+H]^+$): 355.09, Found: 355.05.



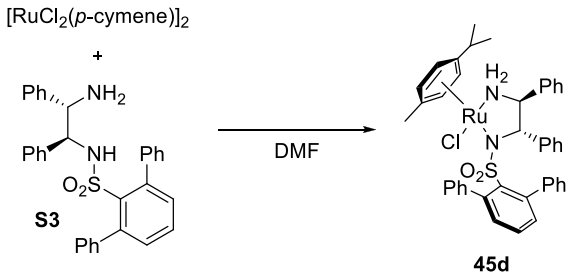
***tert*-Butyl 3-chloro-3-(4-cyanophenyl)-2-oxopropanoate (38o):** The title compound was prepared according to General Procedure C using 4-formylbenzonitrile (393 mg, 3.00 mmol) affording β-chloro-α-keto ester **38o** (769 mg, 2.75

mmol, 92% yield) as a pale yellow oil. Analytical data for **38o**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 6.06 (s, 1H), 1.47 (s, 9H); **^{13}C NMR** (101 MHz) δ 184.9, 158.9, 138.5, 132.6, 129.6, 117.9, 113.4, 86.0, 60.6, 27.6; **IR** (thin film) 2985, 2232, 1747, 1731, 1372, 1258, 1156, 838 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.28; **LRMS** (ESI) Calcd. for $C_{15}H_{19}ClNO_4$ ([M+MeOH+H]$^+$): 312.10, Found: 312.10.



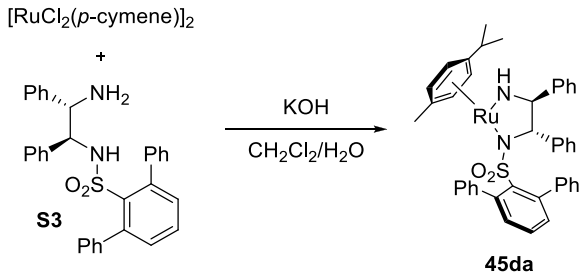
***tert*-Butyl 3-chloro-2-oxo-3-(*p*-tolyl)propanoate (38q):** The title compound was prepared according to General Procedure C using *p*-tolualdehyde (360 mg, 3.00 mmol) affording β-chloro-α-keto ester **38q** (674 mg, 2.51 mmol, 83% yield) as a pale yellow oil. Analytical data for **38q**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.04 (s, 1H), 2.36 (s, 3H), 1.42 (s, 9H); **^{13}C NMR** (101 MHz) δ 186.0, 159.5, 139.8, 130.4, 129.8, 128.9, 85.3, 62.6, 27.7, 21.3; **IR** (thin film) 2981, 1750, 1725, 1371, 1253, 1157, 1058, 840, 741 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.23; **LRMS** (ESI) Calcd. for $C_{15}H_{22}ClO_4$ ([M+MeOH+H]$^+$): 301.12, Found: 301.12.

<u>Procedure for the *in situ* Formed Ru-complex 45d</u>



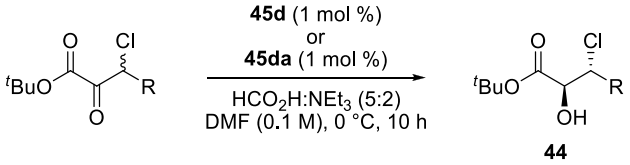
A flame-dried 1-dram vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 1.0 equiv) and **S3** (3.4 mg, 0.0068 mmol, 2.2 equiv) in DMF (2 mL). The vial was purged with N_2, capped, and stirred at 60 ºC for 30 min. The reaction was cooled to room temperature to afford a 1.55 mM solution of the Ru-complex **45d** in DMF, which was immediately used.

Procedure for the Preparation of Preformed Ru-complex 45da



A 1-dram vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (23.7 mg, 0.039 mmol, 1.0 equiv) and **S3** (39.2 mg, 0.078 mmol, 2.0 equiv) in CH_2Cl_2 (1 mL). A solution of KOH (61.1 mg, 1.088 mmol, 18.0 equiv) in H_2O (1 mL) was added. The biphasic solution was vigorously stirred for 1 h at room temperature. The reaction was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the Ru-complex **45da** as a brown powder that could be stored on the bench top under nitrogen.

General Procedure D for the DKR-ATH of β-Chloro-α-Keto Esters



Note: Identical results were obtained employing both the preformed (Method A) and *in situ* generated (Method B) catalysts and can be used interchangeably in the title reaction.

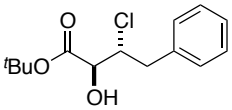
Method A:

A flame-dried 1-dram vial was charged with the β-chloro-α-keto ester **38** (0.1550 mmol, 1.00 equiv) and preformed Ru-complex **45da** (1.2 mg, 0.0016 mmol, 0.01 equiv) in DMF (1.5

mL). The solution was cooled to 0 ºC. Formic acid:triethylamine (5:2) (67 mg, 0.7750 mmol, 5.00 equiv) was added to the reaction. The vial was purged with N_2, capped, and stirred at 0 ºC for 10 h. The reaction was diluted with EtOAc (20 mL) and washed with H_2O (2 x 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The crude residue was purified by column chromatography on silica gel to afford the β-chloro-α-hydroxy ester **44**.

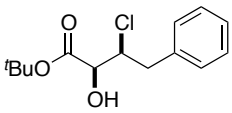
Method B:

A flame-dried 1-dram vial was charged with the β-chloro-α-keto ester (0.1550 mmol, 1.00 equiv) in DMF (1.0 mL). A 1.55 mM solution of *in situ* generated Ru-complex **45da** (0.5 mL, 0.0016 mmol, 0.01 equiv) was added to the reaction. The solution was cooled to 0 ºC. Formic acid:triethylamine (5:2) (67 mg, 0.7750 mmol, 5.00 equiv) was added to the reaction. The vial was purged with N_2, capped, and stirred at 0 ºC for 10 h. The reaction was diluted with EtOAc (20 mL) and washed with H_2O (2 x 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The crude residue was purified by column chromatography on silica gel to afford the β-chloro-α-hydroxy ester **44**.

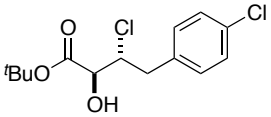


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-4-phenylbutanoate (*anti*-44a): The title compound was prepared according to General Procedure D using **38a** (1.75 g, 6.50 mmol) affording β-chloro-α-hydroxy ester ***anti*-44a** (1.56 g, 5.76 mmol, 89% yield) as a pale yellow oil. Analytical data for ***anti*-44a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-731 (m, 2H), 7.28-7.24 (m, 3H), 4.34 (dt, *J* = 6.4, 2.7 Hz, 1H), 4.29 (dd, *J* = 6.1, 2.6 Hz, 1H), 3.32 (d, *J* = 6.2 Hz, 1H), 3.20 (dd, *J* = 14.3, 6.4 Hz, 1H), 3.13 (dd, *J* = 14.3, 8.4 Hz, 1H), 1.57 (s, 9H); **^{13}C**

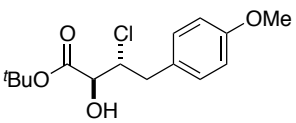
NMR (101 MHz) δ 170.3, 137.2, 129.3, 128.6, 127.0, 84.0, 73.2, 64.6, 40.0, 28.1; **IR** (thin film) 3435, 2983, 2363, 1725, 1641, 1369, 1245, 1154, 780 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.23; **LRMS** (ESI) Calcd. for $C_{14}H_{19}ClNaO_3$ ($[M+Na]^+$): 293.09, Found: 293.09; **SFC** AD Column, 5% MeOH, flow rate = 1.5 mL/min, 150 bar, λ = 210 nm, 6.1 min (major isomer), 8.1 min (minor isomer), 99:1 er; $[\alpha]_D$ -27 (*c* = 0.8, $CHCl_3$).



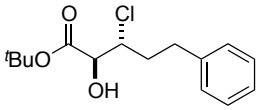
(2*S*,3*S*)-*tert*-Butyl 3-chloro-2-hydroxy-4-phenylbutanoate (*syn*-44a): Analytical data for ***syn*-44a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 4.33 (t, *J* = 7.8 Hz, 1H), 4.06 (d, *J* = 6.2 Hz, 1H), 3.21 (dd, *J* = 13.7, 7.6 Hz, 1H), 3.13 (br s, 1H), 3.13 (dd, *J* = 15.0, 7.1 Hz, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz) δ 170.9, 137.1, 129.5, 128.6, 127.1, 83.6, 71.2, 63.8, 41.0, 27.9; **TLC** (10% EtOAc:Hexanes) R_f = 0.33.



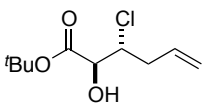
(2*S*,3*R*)-*tert*-Butyl 3-chloro-4-(4-chlorophenyl)-2-hydroxybutanoate (44b): The title compound was prepared according to General Procedure D using **38b** (47.0 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44b** (42.5 mg, 0.139 mmol, 90% yield) as a pale yellow oil. Analytical data for **44b**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.29-4.26 (m, 2H), 3.31 (d, *J* = 5.9 Hz, 1H), 3.14 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.09 (dd, *J* = 14.5, 8.5 Hz, 1H), 1.55 (s, 9H); **^{13}C NMR** (101 MHz) δ 170.1, 135.6, 132.9, 130.7, 128.7, 84.2, 73.3, 64.2, 39.3, 28.1; **IR** (thin film) 3436, 2979, 2359, 1731, 1640, 1492, 1369, 1156, 1097, 839 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.21; **LRMS** (ESI) Calcd. for $C_{14}H_{18}Cl_2NaO_3$ ($[M+Na]^+$): 327.05, Found: 327.10; **SFC** AD Column, 5% MeOH, flow rate = 1.5 mL/min, 150 bar, λ = 210 nm, 9.7 min (minor isomer), 12.3 min (major isomer), 99.5:0.5 er; $[\alpha]_D$ -14 (*c* = 1.6, $CHCl_3$).



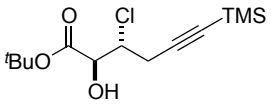
(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-4-(4-methoxyphenyl)butanoate (44c): The title compound was prepared according to General Procedure D using **38c** (46.3 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44c** (43.2 mg, 0.144 mmol, 93% yield) as a pale yellow oil. Analytical data for **44c**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.31-4.27 (m, 2H), 3.79 (s, *3*H), 3.29 (br s, 1H), 3.14 (dd, *J* = 14.3, 6.7 Hz, 1H), 3.07 (dd, *J* = 14.3, 8.4 Hz, 1H), 1.56 (s, 9H); **^{13}C NMR** (101 MHz) δ 170.3, 158.6, 130.3, 129.2, 114.0, 84.0, 73.1, 65.0, 55.2, 39.2, 28.1; **IR** (thin film) 3435, 2976, 2356, 1732, 1641, 1514, 1365, 1248, 1159, 1039 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.15; **LRMS** (ESI) Calcd. for $C_{15}H_{21}ClNaO_4$ ($[M+Na]^+$): 323.10, Found: 323.15; **SFC** AD Column, 5% MeOH, flow rate = 1.5 mL/min, 150 bar, λ = 210 nm, 8.9 min (minor isomer), 12.5 min (major isomer), 99:1 er; **$[\alpha]_D$** -21 (*c* = 1.7, $CHCl_3$).



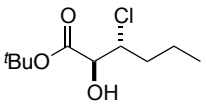
(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-5-phenylpentanoate (44d): The title compound was prepared according to General Procedure D using **38d** (43.8 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44d** (41.1 mg, 0.144 mmol, 93% yield) as a pale yellow oil. Analytical data for **44d**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.23-7.19 (m, 3H), 4.27 (br s, 1H), 4.05 (dt, *J* = 10.8, 2.9 Hz, 1H), 3.21 (br s, 1H), 2.97-2.90 (m, 1H), 2.78-2.71 (m, 1H), 2.28-2.18 (m, 1H), 1.95-1.89 (m, 1H), 1.43 (s, 9H); **^{13}C NMR** (101 MHz) δ 170.3, 140.5, 128.6, 128.5, 126.2, 83.7, 74.4, 62.9, 34.6, 32.3, 27.9; **IR** (thin film) 3433, 2983, 2360, 2344, 1729, 1641, 1365, 1249, 1154 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.23; **LRMS** (ESI) Calcd. for $C_{15}H_{21}ClNaO_3$ ($[M+Na]^+$): 307.11, Found: 307.16; **SFC** AD Column, 1.5% MeOH, flow rate = 1.5 mL/min, 150 bar, λ = 210 nm, 19.5 min (major isomer), 22.5 min (minor isomer), 98.5:1.5 er; **$[\alpha]_D$** -27 (*c* = 1.4, $CHCl_3$).



(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxyhex-5-enoate (44e): The title compound was prepared according to General Procedure D using **38e** (33.9 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44e** (32.4 mg, 0.147 mmol, 95% yield) as a pale yellow oil. Analytical data for **44e**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.87-5.80 (m, 1H), 5.17 (d, *J* = 16.1 Hz, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 4.28 (d, *J* = 2.5 Hz, 1H), 4.13 (ddd, *J* = 8.6, 6.0, 2.7 Hz, 1H), 3.26 (br s, 1H), 2.64-2.55 (m, 2H), 1.52 (s, 9H); **^{13}C NMR** (151 MHz) δ 170.2, 133.6, 118.6, 83.9, 73.5, 63.1, 38.1, 28.0; **IR** (thin film) 3435, 2986, 2359, 1725, 1643, 1369, 1298, 1244, 1157 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.26; **LRMS** (ESI) Calcd. for $C_{10}H_{17}ClNaO_3$ ([M+Na]$^+$): 243.08, Found: 243.05; **[α]$_D$** -4 (*c* = 1.4, $CHCl_3$).

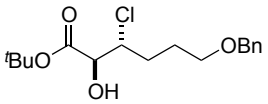


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-6-(trimethylsilyl)hex-5-ynoate (44f): The title compound was prepared according to General Procedure D using **38f** (44.8 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44f** (40.9 mg, 0.141 mmol, 91% yield) as a pale yellow oil. Analytical data for **44f**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.44 (br s, 1H), 4.19 (dt, *J* = 7.5, 3.0 Hz, 1H), 3.30 (d, *J* = 3.9 Hz, 1H), 2.87 (dd, *J* = 17.2, 7.7 Hz, 1H), 2.81 (dd, *J* = 17.2, 7.6 Hz, 1H), 1.53 (s, 9H), 0.16 (s, 9H); **^{13}C NMR** (101 MHz) δ 169.9, 101.4, 87.9, 84.1, 72.7, 61.1, 28.0, 26.2, -0.1; **IR** (thin film) 3505, 2960, 2179, 1738, 1370, 1252, 1160, 1119, 844, 760 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.41; **LRMS** (ESI) Calcd. for $C_{13}H_{23}ClNaO_3Si$ ([M+Na]$^+$): 313.10, Found: 313.15; **[α]$_D$** -4 (*c* = 1.4, $CHCl_3$).

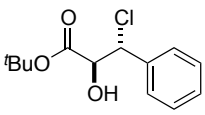


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxyhexanoate (44g): The title compound was prepared according to General Procedure D using **38g** (34.2 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44g** (32.5 mg, 0.146 mmol, 94% yield) as a pale yellow oil. Analytical data for **44g**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 6.5, 3.5 Hz, 1H), 4.12 (dt, *J* = 10.0, 3.3 Hz, 1H), 3.20 (d, *J* = 6.5 Hz, 1H), 1.92-1.81 (m, 1H), 1.71-1.56 (m, 2H),

1.51 (s, 9H), 1.48-1.41 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz) δ 170.4, 83.7, 74.3, 64.0, 35.4, 28.0, 19.8, 13.4; **IR** (thin film) 3442, 2964, 2877, 2363, 1731, 1460, 1370, 1246, 1159, 1089, 836 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.26; **LRMS** (ESI) Prepared in MeCN, Calcd. for $C_{10}H_{19}ClNaO_3$ ([M+Na]$^+$): 245.09, Found: 245.08; **[α]$_D$** -3 (c = 1.2, $CHCl_3$).

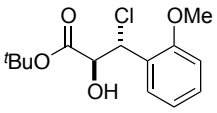


(2*S*,3*R*)-*tert*-Butyl 6-(benzyloxy)-3-chloro-2-hydroxyhexanoate (44h): The title compound was prepared according to General Procedure D using **38h** (50.7 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44h** (46.5 mg, 0.142 mmol, 91% yield) as a pale yellow oil. Analytical data for **44h**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 4.50 (s, 2H), 4.27 (dd, J = 6.5, 3.0 Hz, 1H), 4.17-4.13 (m, 1H), 3.56-3.46 (m, 2H), 3.23 (d, J = 6.5 Hz, 1H), 1.97-1.89 (m, 3H), 1.76-1.70 (m, 1H), 1.49 (s, 9H); **^{13}C NMR** (101 MHz) δ 170.3, 138.3, 128.3, 127.5, 83.7, 74.2, 72.9, 69.3, 64.2, 30.2, 28.0, 27.0, one carbon not found due to overlap; **IR** (thin film) 3435, 2976, 2934, 2360, 1730, 1634, 1456, 1365, 1158, 731 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.18; **LRMS** (ESI) Calcd. for $C_{17}H_{25}ClNaO_4$ ([M+Na]$^+$): 351.13, Found: 351.16; **HPLC** Chiralpak IA, H/IPA = 99:1, flow rate = 1.0 mL/min, λ = 210 nm, 23.3 min (major isomer), 25.2 min (minor isomer), 98:2 er; **[α]$_D$** -2 (c = 1.2, $CHCl_3$).

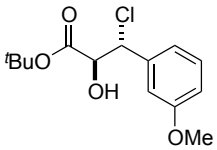


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-3-phenylpropanoate (44i): The title compound was prepared according to General Procedure D using **38i** (39.5 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44i** (36.9 mg, 0.144 mmol, 93% yield) as a pale yellow oil. Analytical data for **44i**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.35-7.32 (m, 3H), 5.21 (d, J = 3.7 Hz, 1H), 4.54 (dd, J = 6.3, 3.8 Hz, 1H), 3.15 (d, J = 6.5 Hz, 1H), 1.39 (s, 9H); **^{13}C NMR** (101 MHz) δ 169.7, 136.2, 128.8, 128.2, 128.2, 83.8, 75.2, 63.2, 27.8; **IR** (thin film) 3435, 1731, 1643, 1373, 1162, 1117, 704 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.29; **LRMS** (ESI) Calcd. for $C_{13}H_{17}ClNaO_3$ ([M+Na]$^+$): 279.08, Found: 279.08; **HPLC** Chiralpak IC,

H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.0 min (minor isomer), 8.5 min (major isomer), 99.5:0.5 er; **[α]$_D$** -74 (*c* = 1.6, $CHCl_3$).

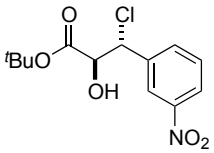


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-3-(2-methoxyphenyl)propanoate (44j): The title compound was prepared according to General Procedure D using **38j** (44.1 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44j** (42.1 mg, 0.147 mmol, 95% yield) as a pale yellow oil. Analytical data for **44j**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.1 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.68 (d, *J* = 4.0 Hz, 1H), 4.58 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.87 (s, 3H), 3.35 (d, *J* = 7.6 Hz, 1H), 1.33 (s, 9H); **^{13}C NMR** (151 MHz) δ 170.2, 155.9, 129.8, 129.6, 124.9, 120.5, 110.1, 83.1, 73.9, 58.7, 55.5, 27.7; **IR** (thin film) 3434, 1732, 1639, 1491, 1249, 1158, 1033 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.46; **LRMS** (ESI) Calcd. for $C_{14}H_{20}ClO_4$ ([M+H]$^+$): 287.11, Found: 287.11; **HPLC** Chiralpak IC, H/IPA = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 13.7 min (minor isomer), 21.6 min (major isomer), 99:1 er; **[α]$_D$** -94 (*c* = 0.9, $CHCl_3$).

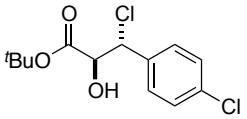


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-3-(3-methoxyphenyl)propanoate (44k): The title compound was prepared according to General Procedure D using **38k** (44.1 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44k** (41.7 mg, 0.146 mmol, 94% yield) as a pale yellow oil. Analytical data for **44k**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (t, *J* = 8.5 Hz, 1H), 7.04 (s, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.17 (d, *J* = 3.8 Hz, 1H), 4.53 (dd, *J* = 6.6, 3.9 Hz, 1H), 3.80 (s, 3H), 3.13 (d, *J* = 6.7 Hz, 1H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz) δ 169.7, 159.4, 137.6, 129.2, 120.5, 114.2, 114.1, 83.8, 75.2, 63.1, 55.2, 27.9; **IR** (thin film) 3433, 2979, 1729, 1644, 1491, 1369, 1263, 1156, 1048 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.46; **LRMS** (ESI) Calcd. for $C_{14}H_{19}ClNaO_4$

([M+Na]$^+$): 309.09, Found: 309.14; **HPLC** Chiralpak IC, H/IPA = 9:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.9 min (minor isomer), 9.8 min (major isomer), 99.5:0.5 er; $[\alpha]_D$ -65 (*c* = 1.7, $CHCl_3$).

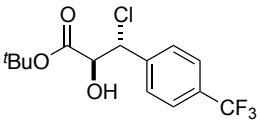


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-3-(3-nitrophenyl)propanoate (44l): The title compound was prepared according to General Procedure D using **38l** (46.5 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44l** (34.7 mg, 0.115 mmol, 74% yield) as a pale yellow oil. Analytical data for **44l**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.30 (t, *J* = 1.9 Hz, 1H), 8.20 (ddd, *J* = 8.2, 2.0, 0.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 5.30 (d, *J* = 3.4 Hz, 1H), 4.57 (dd, *J* = 5.5, 3.5 Hz, 1H), 3.24 (d, *J* = 5.6 Hz, 1H), 1.41 (s, 9H); **^{13}C NMR** (151 MHz) δ 169.4, 147.8, 138.3, 134.6, 129.3, 123.7, 123.3, 84.7, 74.8, 61.8, 27.9; **IR** (thin film) 3435, 1729, 1640, 1531, 1351, 1253, 1155, 1116 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.38; **LRMS** (ESI) Calcd. for $C_{13}H_{16}ClNNaO_5$ ([M+Na]$^+$): 324.06, Found: 324.07; **HPLC** Chiralpak IC, H/IPA = 85:15, flow rate = 1.0 mL/min, λ = 230 nm, 7.9 min (minor isomer), 8.8 min (major isomer), 97.5:2.5 er; $[\alpha]_D$ -36 (*c* = 1.3, $CHCl_3$).

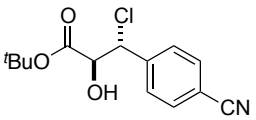


(2*S*,3*R*)-*tert*-Butyl 3-chloro-3-(4-chlorophenyl)-2-hydroxypropanoate (44m): The title compound was prepared according to General Procedure D using **38m** (44.8 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44m** (38.5 mg, 0.132 mmol, 85% yield) as a pale yellow oil. Analytical data for **44m**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.18 (d, *J* = 3.6 Hz, 1H), 4.52 (dd, *J* = 6.1, 3.7 Hz, 1H), 3.15 (d, *J* = 6.1 Hz, 1H), 1.40 (s, 9H); **^{13}C NMR** (151 MHz) δ 169.6, 134.75, 134.71, 129.7, 128.4, 84.1, 72.0, 62.3, 27.9; **IR** (thin film) 3435, 1725, 1643, 1494, 1373, 1249, 1158, 1014 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.29; **LRMS** (ESI) Calcd. for $C_{13}H_{16}Cl_2NaO_3$ ([M+Na]$^+$): 313.04, Found: 313.09; **SFC** AD Column, 2% MeOH, flow rate = 1.5 mL/min, 150

bar, λ = 210 nm, 17.3 min (major isomer), 21.2 min (minor isomer), 98.5:1.5 er; **[α]$_D$** -56 (*c* = 1.3, $CHCl_3$).

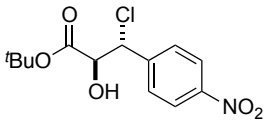


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-3-(4-(trifluoromethyl)phenyl)propanoate (44n): The title compound was prepared according to General Procedure D using **38n** (50.0 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44n** (40.2 mg, 0.124 mmol, 80% yield) as a pale yellow oil. Analytical data for **44n**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.9 Hz, 2H), 5.25 (d, *J* = 3.6 Hz, 1H), 4.56 (dd, *J* = 6.1, 3.7 Hz, 1H), 3.20 (d, *J* = 6.2 Hz, 1H), 1.39 (s, 9H); **^{13}C NMR** (151 MHz) δ 169.5, 140.2, 130.9 (q, $J_{C\text{-}F}$ = 32.6 Hz), 128.8, 125.2 (q, $J_{C\text{-}F}$ = 4.2 Hz), 123.8 (q, $J_{C\text{-}F}$ = 272.3 Hz), 84.3, 75.0, 62.3, 27.9; **IR** (thin film) 3435, 2987, 1736, 1615, 1418, 1326, 1253, 1123, 844 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.24; **LRMS** (ESI) Calcd. for $C_{14}H_{16}ClF_3NaO_3$ ([M+Na]$^+$): 347.06, Found: 347.15; **HPLC** Chiralpak IB, H/IPA = 99:1, flow rate = 1.0 mL/min, λ = 230 nm, 9.1 min (minor isomer), 9.9 min (major isomer), 98.5:1.5 er; **[α]$_D$** -56 (*c* = 1.0, $CHCl_3$).

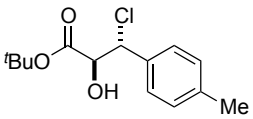


(2*S*,3*R*)-*tert*-Butyl 3-chloro-3-(4-cyanophenyl)-2-hydroxypropanoate (44o): The title compound was prepared according to General Procedure D using **38o** (43.4 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44o** (35.9 mg, 0.128 mmol, 82% yield) as a pale yellow oil. Analytical data for **44o**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 5.22 (d, *J* = 3.7 Hz, 1H), 4.54 (dd, *J* = 5.8, 3.7 Hz, 1H), 3.24 (d, *J* = 5.9 Hz, 1H), 1.39 (s, 9H); **^{13}C NMR** (151 MHz) δ 169.3, 141.4, 131.9, 129.1, 118.2, 112.6, 84.4, 74.8, 62.1, 27.8; **IR** (thin film) 3435, 2231, 1732, 1644, 1369, 1286, 1257, 1162, 1139 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.35; **LRMS** (ESI) Calcd. for $C_{28}H_{32}Cl_2N_2NaO_6$ ([2M+Na]$^+$): 585.15, Found: 585.18; **HPLC** Chiralpak IC, H/IPA = 9:1, flow rate = 1.0 mL/min,

λ = 250 nm, 11.3 min (minor isomer), 12.0 min (major isomer), 98:2 er; $[\alpha]_D$ -53 (*c* = 0.8, $CHCl_3$).

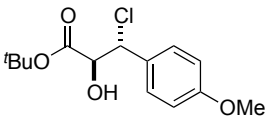


(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-3-(4-nitrophenyl)propanoate (44p): The title compound was prepared according to General Procedure D using **38p** (46.5 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44p** (34.0 mg, 0.113 mmol, 73% yield) as a pale yellow oil. Analytical data for **44p**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 5.27 (d, *J* = 3.6 Hz, 1H), 4.57 (dd, *J* = 5.8, 3.6 Hz, 1H), 3.23 (d, *J* = 5.8 Hz, 1H), 1.40 (s, 9H); **^{13}C NMR** (151 MHz) δ 169.3, 147.9, 143.2, 129.4, 123.3, 84.6, 74.8, 61.7, 27.9; **IR** (thin film) 3446, 2981, 1732, 1524, 1348, 1156, 1117, 836 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.43; **LRMS** (ESI) Calcd. for $C_{13}H_{16}ClNNaO_5$ ($[M+Na]^+$): 324.06, Found: 324.13; **HPLC** Chiralpak IC, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 254 nm, 16.6 min (minor isomer), 17.5 min (major isomer), 99:1 er; $[\alpha]_D$ -44 (*c* = 1.1, $CHCl_3$).



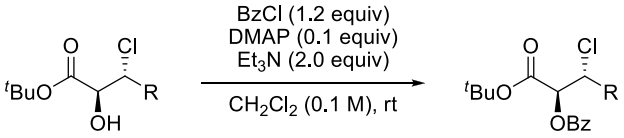
(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-3-(*p*-tolyl)propanoate (44q): The title compound was prepared according to General Procedure D using **38q** (41.7 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44q** (38.0 mg, 0.140 mmol, 91% yield) as a pale yellow oil. Analytical data for **44q**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.18 (d, *J* = 3.8 Hz, 1H), 4.52 (dd, *J* = 6.6, 3.8 Hz, 1H), 3.08 (d, *J* = 6.7 Hz, 1H), 2.33 (s, 3H), 1.41 (s, 9H); **^{13}C NMR** (151 MHz) δ 169.6, 138.7, 133.2, 128.9, 128.2, 83.7, 75.3, 63.1, 27.9, 21.1; **IR** (thin film) 3448, 2983, 1732, 1649, 1370, 1249, 1156, 1119, 844 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.29; **LRMS** (ESI) Calcd. for $C_{14}H_{19}ClNaO_3$ ($[M+Na]^+$): 293.09, Found: 293.09; **HPLC** Chiralpak IC, H/IPA = 19:1, flow rate

= 1.0 mL/min, λ = 210 nm, 7.4 min (minor isomer), 9.1 min (major isomer), 99.5:0.5 er; $[\alpha]_D$ -50 (c = 1.3, $CHCl_3$).



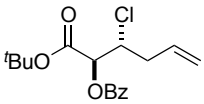
(2*S*,3*R*)-*tert*-Butyl 3-chloro-2-hydroxy-3-(4-methoxyphenyl)propanoate (44r): The title compound was prepared according to General Procedure D using **38r** (44.1 mg, 0.155 mmol) affording β-chloro-α-hydroxy ester **44r** (41.4 mg, 0.144 mmol, 93% yield) as a pale yellow oil. Analytical data for **44r**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.18 (d, J = 3.8 Hz, 1H), 4.52 (dd, J = 6.2, 3.8 Hz, 1H), 3.80 (s, 3H), 3.07 (d, J = 6.3 Hz, 1H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz) δ 169.9, 159.9, 129.6, 128.3, 113.6, 83.8, 75.3, 62.9, 55.3, 27.9; **IR** (thin film) 3450, 2359, 1730, 1683, 1599, 1251, 1143, 1025, 836 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.40; **LRMS** (ESI) Calcd. for $C_{14}H_{20}ClO_4$ ($[M+H]^+$): 287.11, Found: 287.11; **HPLC** Chiralpak IC, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 230 nm, 10.4 min (minor isomer), 13.1 min (major isomer), 99:1 er; $[\alpha]_D$ -31 (c = 0.5, $CHCl_3$).

<u>General Procedure E for the Benzoylation of β-Chloro-α-Hydroxy Esters</u>

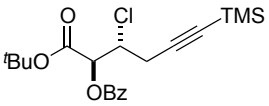


A flame-dried 1-dram vial was charged with the alcohol (1.0 equiv) in CH_2Cl_2. To the stirred solution was sequentially added benzoyl chloride (1.2 equiv), 4-dimethylaminopyridine (0.1 equiv), and triethylamine (2.0 equiv). After stirring for 30 minutes at room temperature, the reaction was quenched with sat. aq. NH_4Cl (5 mL). The aqueous layer was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with

brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford the β-chloro-α-benzoyloxy ester.

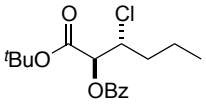


(2*S*,3*R*)-1-(*tert*-Butoxy)-3-chloro-1-oxohex-5-en-2-yl benzoate (44ea): The title compound was prepared according to General Procedure E using **44e** (32.4 mg, 0.147 mmol) affording β-chloro-α-benzoyloxy ester **44ea** (44.9 mg, 0.138 mmol, 94% yield) as a pale yellow oil. Analytical data for **44ea**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 5.95-5.83 (m, 1H), 5.23 (d, *J* = 3.5 Hz, 1H), 5.20 (d, *J* = 15.4 Hz, 1H), 5.52 (d, *J* = 7.8 Hz, 1H), 4.42-4.37 (m, 1H), 2.75-2.72 (m, 2H), 1.50 (s, 9H); **^{13}C NMR** (101 MHz) δ 165.6, 165.5, 133.5, 133.2, 129.9, 129.2, 128.5, 118.9, 83.4, 75.3, 59.3, 38.2, 27.9; **IR** (thin film) 2938, 1754, 1729, 1642, 1448, 1373, 1275, 1110, 712 cm^{-1}; **TLC** (5% EtOAc:Hexanes) R_f = 0.21; **LRMS** (ESI) Calcd. for $C_{17}H_{21}ClNaO_4$ ($[M+Na]^+$): 347.10, Found: 347.09; **HPLC** Chiralpak IC, H/IPA = 99:1, flow rate = 1.0 mL/min, λ = 230 nm, 10.4 min (minor isomer), 13.1 min (major isomer), 99:1 er; **$[\alpha]_D$** -3 (*c* = 0.8, $CHCl_3$).



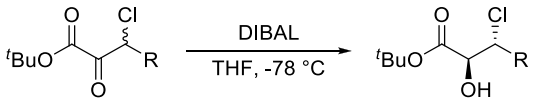
(2*S*,3*R*)-1-(*tert*-Butoxy)-3-chloro-1-oxo-6-(trimethylsilyl)hex-5-yn-2-yl benzoate (44fa): The title compound was prepared according to General Procedure E using **44f** (40.9 mg, 0.141 mmol) affording β-chloro-α-benzoyloxy ester **44fa** (51.2 mg, 0.130 mmol, 92% yield) as a pale yellow oil. Analytical data for **44fa**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.1 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 5.52 (d, *J* = 3.7 Hz, 1H), 4.43 (dt, *J* = 6.9, 3.7 Hz, 1H), 2.95 (d, *J* = 7.0 Hz, 2H), 1.50 (s, 9H), 0.17 (s, 9H); **^{13}C NMR** (101 MHz) δ 165.4, 165.2, 133.5, 129.9, 129.0, 128.5, 101.0, 88.3, 83.6, 74.6, 57.6, 27.9, 26.2, -0.1; **IR** (thin film) 2979, 2359, 2178, 1753, 1729, 1641, 1365, 1248, 840 cm^{-1}; **TLC** (5% EtOAc:Hexanes) R_f = 0.21; **LRMS** (ESI) Calcd. for $C_{40}H_{54}Cl_2NaO_8Si_2$ ($[2M+Na]^+$): 811.26,

Found: 811.29; **HPLC** Chiralpak IC, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 230 nm, 10.4 min (minor isomer), 13.1 min (major isomer), 99:1 er; $[\alpha]_D$ -5 (*c* = 0.3, $CHCl_3$).



(2*S*,3*R*)-1-(*tert*-Butoxy)-3-chloro-1-oxohexan-2-yl benzoate (44ga): The title compound was prepared according to General Procedure E using **44g** (32.5 mg, 0.146 mmol) affording β-chloro-α-benzoyloxy ester **44ga** (45.6 mg, 0.139 mmol, 96% yield) as a pale yellow oil. Analytical data for **44ga**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 5.45 (d, *J* = 3.4 Hz, 1H), 4.39 (dt, *J* = 10.4, 3.4 Hz, 1H), 2.07-1.97 (m, 1H), 1.86-1.78 (m, 1H), 1.74-1.64 (m, 1H), 1.53-1.46 (m, 1H), 1.49 (s, 9H), 0.98 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz) δ 165.8, 165.6, 133.4, 129.9, 129.3, 128.4, 83.3, 76.0, 59.9, 35.4, 28.0, 19.7, 13.3; **IR** (thin film) 2965, 1755, 1730, 1642, 1452, 1370, 1270, 1110, 711 cm^{-1}; **TLC** (5% EtOAc:Hexanes) R_f = 0.23; **LRMS** (ESI) Calcd. for $C_{17}H_{23}ClNaO_4$ ($[M+Na]^+$): 349.12, Found: 349.13; **HPLC** Chiralpak IC, H/IPA = 99:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.1 min (major isomer), 7.0 min (minor isomer), 98.5:1.5 er; $[\alpha]_D$ -1 (*c* = 1.8, $CHCl_3$).

<u>General Procedure F for the Racemic Reduction of β-Chloro-α-Keto Esters</u>

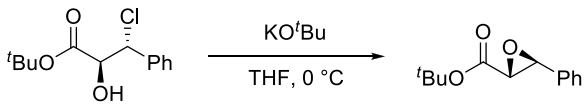


A flame-dried round-bottomed flask was charged with the β-chloro-α-keto ester (0.15 mmol, 1.0 equiv) in THF (1.5 mL). The reaction was cooled to -78 ºC. A 1M solution of diisobutylaluminum hydride (DIBAL) in THF (0.45 mL, 0.45 mmol, 3.0 equiv) was added dropwise. The reaction was allowed to stir for 1 hour at -78 ºC before being quenched by the dropwise addition of acetone (5 mL). After warming to room temperature, the reaction was diluted with Et_2O (10 mL) and sat. aq. Rochelle's salt (10 mL). The reaction stirred at room

temperature for 30 minutes. The layers were separated (1 M HCl was added to help break the emulsion). The aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford the racemic chlorohydrin as a mixture of diastereomers.

Note: Other reducing agents ($NaBH_4$ (>20:1 dr), LTBA (11:1 dr), and Super-Hydride (>20:1 dr)) all provided a strong preference for the *syn* diastereomer. Only DIBAL was found to provide a ~1:1 mixture of diastereomers.

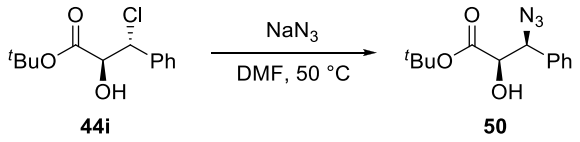
Conversion of Chlorohydrin 44a to Glycidic Ester 49



(2*R*,3*S*)-*tert*-Butyl 3-phenyloxirane-2-carboxylate (49): A flame-dried 1-dram vial was charged with the chlorohydrin **44i** (51.3 mg, 0.200 mmol, 1.0 equiv) in THF (2.0 mL). The solution was cooled to 0 ºC. A freshly prepared 1 M solution of KO^{t}Bu in THF (0.240 mL, 0.240 mmol, 1.2 equiv) was added dropwise and the reaction was allowed to stir for a further 1 h at 0 ºC. The reaction was quenched with sat. aq. NH_4Cl (1 mL) and diluted with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 5% EtOAc:hexanes to afford the glycidic ester **49** (38.9 mg, 0.177 mmol, 88% yield) as a white crystalline solid (mp: 64-65 ºC). Analytical data for **49**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 4.03 (d, J = 1.6 Hz, 1H), 3.41 (d, J = 1.8 Hz, 1H), 1.52 (s, 9H); **^{13}C NMR** (101 MHz) δ 167.1, 135.2, 128.8, 128.5,

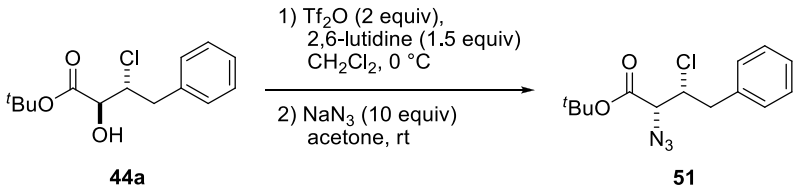
125.8, 82.5, 57.5, 57.3, 27.9; **IR** (thin film) 2979, 1746, 1541, 1507, 1418, 1246, 1155, 745, 696 cm^{-1}; **TLC** (5% EtOAc:Hexanes) R_f = 0.23; **LRMS** (ESI) Calcd. for $C_{13}H_{17}O_3$ ($[M+H]^+$): 221.12, Found: 221.08; **SFC** AD Column, 2% MeOH, flow rate = 1.5 mL/min, 150 bar, λ = 210 nm, 6.3 min (major isomer), 9.0 min (minor isomer), 99:1 er; $[\alpha]_D$ -129 (*c* = 0.9, $CHCl_3$).

Synthesis of β-Azido-α-Hydroxy Ester 50 from 44i



(2*R*,3*S*)-*tert*-Butyl 3-azido-2-hydroxy-3-phenylpropanoate (50): A flame-dried 1-dram vial was charged with the chlorohydrin **44i** (51.3 mg, 0.200 mmol, 1.0 equiv) in DMF (2.0 mL). NaN_3 (65.0 mg, 1.000 mmol, 5.0 equiv) was added and the reaction was warmed to 50 ºC where it was left to stir for 40 h. The reaction was cooled to room temperature and diluted with EtOAc (20 mL). The organic layer was extracted with H_2O (2 x 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 10% EtOAc:hexanes to afford β-azido-α-hydroxy ester **50** (48.3 mg, 0.183 mmol, 92% yield) as a pale yellow oil. Analytical data for **50**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47-7.34 (m, 5H), 4.76 (d, *J* = 3.4 Hz, 1H), 4.28 (dd, *J* = 6.3, 3.4 Hz, 1H), 3.17 (d, *J* = 6.3 Hz, 1H), 1.48 (s, 9H); **^{13}C NMR** (101 MHz) δ 171.0, 135.8, 128.7, 128.7, 127.9, 83.7, 74.0, 67.4, 27.9; **IR** (thin film) 3436, 2104, 1735, 1645, 1456, 1257, 1155, 700 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.32; **LRMS** (ESI) Calcd. for $C_{13}H_{17}N_3NaO_3$ ($[M+Na]^+$): 286.12, Found: 286.12; $[\alpha]_D$ +109 (*c* = 0.8, $CHCl_3$).

Synthesis of α-Azido-β-Chloro Ester 51 from 44a

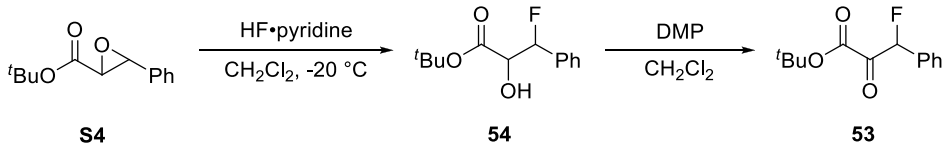


A flame-dried round-bottomed flask was charged with the chloroalcohol **44a** (54.2 mg, 0.200 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL). The solution was cooled to 0 ºC. Tf_2O (67 µL, 0.400 mmol, 2.0 equiv) and 2,6-lutidine (35 µL, 0.300 mmol, 1.5 equiv) were sequentially added dropwise. The resulting solution was allowed to stir for 1 h at 0 ºC. The reaction was quenched by addition of 0.5 M HCl (5 mL). Following dilution with CH_2Cl_2 (8 mL), the layers were separated and the organic phase was washed with 0.5 M HCl (2 x 5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to afford the crude triflate as a pale yellow oil.

A round-bottomed flask was charged with the crude triflate in acetone (2 mL). NaN_3 (130.0 mg, 2.00 mmol, 10.0 equiv) was added and the heterogeneous mixture was stirred for 16 h at room temperature. The crude reaction mixture was filtered through Celite eluting with Et_2O and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 2.5% EtOAc:hexanes to afford (2*R*,3*R*)-*tert*-butyl 2-azido-3-chloro-4-phenylbutanoate (**51**) (45.7 mg, 0.155 mmol, 77% yield) as a white solid (mp: 81-82 ºC). Analytical data for **51**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.29-7.28 (m, 2H), 4.57 (ddd, *J* = 8.6, 6.7, 2.7 Hz, 1H), 3.85 (d, *J* = 2.7 Hz, 1H), 3.24 (dd, *J* = 13.6, 6.7 Hz, 1H), 3.21 (dd, *J* = 13.6, 8.5 Hz, 1H), 1.54 (s, 9H); **^{13}C NMR** (151 MHz) δ 166.7, 136.4, 129.3, 128.9, 127.4, 84.1, 63.8, 62.3, 41.6, 27.9; **IR** (thin film) 2979, 2359, 2116,

1744, 1455, 1370, 1261, 1152, 703 cm^{-1}; **TLC** (5% EtOAc:Hexanes) R_f = 0.20; **LRMS** (ESI) Calcd. for $C_{28}H_{36}Cl_2N_6NaO_4$ ($[2M+Na]^+$): 613.21, Found: 613.24; $[\alpha]_D$ +64 (*c* = 1.1, $CHCl_3$).

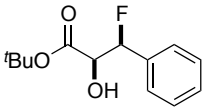
Synthesis of β-Fluoro-α-Keto Ester 53 and Reduction to Fluorohydrin 54



Using a procedure adapted from Yang and coworkers,[39] a 20-mL Nalgene scintillation vial was charged with *tert*-butyl 3-phenyloxirane-2-carboxylate (**S4**) (440 mg, 2.00 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). The solution was cooled to -20 ºC. A solution of HF/pyridine (70%, 0.2 mL) was added dropwise. After stirring for a further 15 min at -20 ºC, the reaction was carefully quenched by the dropwise addition of sat. aq. NH_4Cl (5 mL). The reaction was further diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 10% EtOAc:hexanes to afford β-fluoro-α-hydroxy ester (±)-**54** (268 mg, 1.12 mmol, 56% yield, 1:1 dr) as a pale yellow oil along with recovered **S4** (164 mg, 0.74 mmol, 37% yield).

A round-bottomed flask was charged with β-fluoro-α-hydroxy ester (±)-**54** (240 mg, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). Dess–Martin periodinane (DMP) (1.27 g, 3.00 mmol, 3.0 equiv) was added to the reaction. After stirring for 1 h at room temperature, the reaction was quenched with sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1:1, 10 mL). The reaction was diluted with Et_2O (50 mL) and the layers were separated. The aqueous layer was washed with sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1:1, 2 x 25 mL) and brine (25 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford *tert*-butyl 3-fluoro-2-oxo-3-phenylpropanoate (**53**)

(228 mg, 0.96 mmol, 96% yield) as a pale yellow oil that was used without further purification. Analytical data for **53**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (s, 5H), 6.35 (d, J = 47.4 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR** (151 MHz) δ 188.5 (d, $J_{C\text{-}F}$ = 24.3 Hz), 159.1, 131.7 (d, $J_{C\text{-}F}$ = 19.9 Hz), 130.1 (d, $J_{C\text{-}F}$ = 2.0 Hz), 129.0, 128.0 (d, $J_{C\text{-}F}$ = 5.1 Hz), 93.5 (d, $J_{C\text{-}F}$ = 187.4 Hz), 85.4, 27.6; **^{19}F NMR** (565 Hz) δ -183.5; **IR** (thin film) 2981, 2349, 1753, 1726, 1456, 1371, 1259, 1157, 1013, 698 cm^{-1}; **TLC** (30% EtOAc:Hexanes) R_f = 0.36; **LRMS** (ESI) Calcd. for $C_{14}H_{20}FO_4$ ([M+MeOH+H]$^+$): 271.13, Found: 271.12.



(2*S*,3*S*)-*tert*-Butyl 3-fluoro-2-hydroxy-3-phenylpropanoate (54): The title compound was prepared according to General Procedure D using **53** (36.9 mg, 0.1550 mmol) affording β-fluoro-α-hydroxy ester **54** (36.1 mg, 0.150 mmol, 97% yield, 1.1:1 dr) as a pale yellow oil. Analytical data for **54**: **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ 7.41-7.34 (m, 5H), 5.79 (d, J = 2.4 Hz, 1H), 4.32 (ddd, J = 27.6, 6.3, 2.3 Hz, 1H), 3.12 (d, J = 6.4 Hz, 1H), 1.50 (s, 9H), *minor diastereomer* δ 7.41-7.34 (m, 5H), 5.67 (d, J = 2.2 Hz, 1H), 4.32 (ddd, J = 18.0, 6.9, 3.1 Hz, 1H), 3.04 (d, J = 7.1 Hz, 1H), 1.39 (s, 9H); **^{13}C NMR** (101 MHz) *major diastereomer* δ 170.4 (d, $J_{C\text{-}F}$ = 3.7 Hz), 135.9 (d, $J_{C\text{-}F}$ = 20.6 Hz), 128.6, 128.3,126.0 (d, $J_{C\text{-}F}$ = 7.6 Hz), 93.5 (d, $J_{C\text{-}F}$ = 180.2 Hz), 83.7, 73.7 (d, $J_{C\text{-}F}$ = 23.6 Hz), 27.9, *minor diastereomer* δ 169.8 (d, $J_{C\text{-}F}$ = 9.5 Hz), 135.1 (d, $J_{C\text{-}F}$ = 21.0 Hz), 128.7, 128.1, 126.1 (d, $J_{C\text{-}F}$ = 7.9 Hz), 94.1 (d, $J_{C\text{-}F}$ = 181.2 Hz), 83.6, 73.8 (d, $J_{C\text{-}F}$ = 24.4 Hz), 27.8; **^{19}F NMR** (376 MHz) *major diastereomer* δ -194.2, *minor diastereomer* δ -189.6; **IR** (thin film) 3437, 1732, 1649, 1456, 1369, 1258, 1162, 1018 cm^{-1}; **TLC** (10% EtOAc:Hexanes) R_f = 0.27; **LRMS** (ESI) Prepared in MeCN, Calcd. for $C_{13}H_{17}FNaO_3$ ([2M+Na]$^+$): 503.22, Found: 503.22; **HPLC** Chiralpak IA, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 8.9 min (minor diastereomer, major isomer), 9.5 min (minor diastereomer, minor isomer), 11.0 min (major diastereomer, major isomer), 13.5

min (major diastereomer, minor isomer), 99.5:0.5 er (major), 98:2 er (minor); $[\alpha]_D$ -31 (c = 0.7, $CHCl_3$).

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CHAPTER FOUR: DYNAMIC KINETIC REDUCTION OF RACEMIC ACYL PHOSPHONATES*

4.1 Introduction

A strategy for the preparation of β-stereogenic-α-hydroxy phosphonic acid derivatives via dynamic kinetic resolution via asymmetric transfer hydrogenation (DKR-ATH) of racemic α-aryl acyl phosphonates is discussed in this chapter (**Scheme 4-1**). An (arene)RuCl(monosulfonamide) complex bearing a bulky *m*-terphenylsulfonamide ligand provided excellent levels of diastereo- and enantiocontrol in the reduction. Interestingly, an unexpected dichotomy was observed in the title reaction, which was determined to proceed from the opposite face relative to that observed in the analogous reduction of β-stereogenic-α-keto esters providing pseudo-diastereomeric products. This methodology was extended to the catalytic enantioselective reduction of acyl phosphonates to provide complementary access to challenging Pudovik adducts.

Scheme 4-1. Preparation of β-Stereogenic-α-Hydroxy Phosphonic Acid Derivatives via Dynamic Kinetic Reduction

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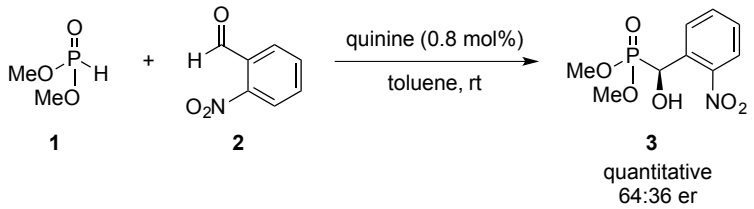
4.2 Background

4.2.1 Preparation of Optically Active α-Hydroxy Phosphonates via Pudovik Reaction

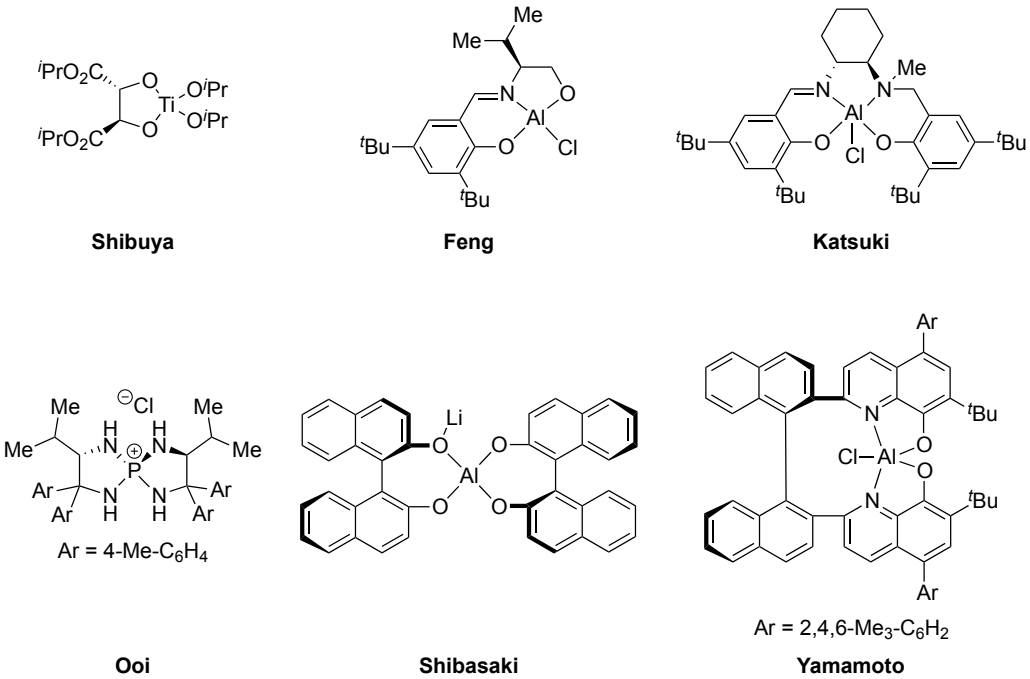
The leading methodology in the literature for the preparation of α-hydroxy phosphonates is the addition of dialkyl phosphites to carbonyl compounds under acid or base catalysis via C–P bond formation (Pudovik reaction). Wynberg reported the first asymmetric Pudovik reaction between dimethyl phosphite (**1**) and 2-nitrobenzaldehyde (**2**) under chiral base catalysis (**Scheme 4-2**).[1] Although **3** was obtained with low enantiomeric ratio (64:36), this pioneering work illustrated the potential to induce asymmetry through the addition of phosphorus-centered nucleophiles to prochiral electrophiles.

Scheme 4-2. Quinine-Catalyzed Pudovik Reaction



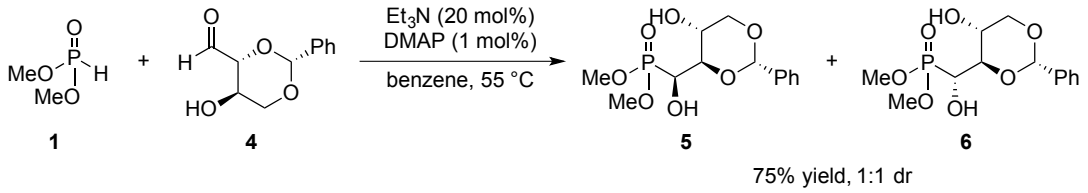
Since Wynberg's seminal work, a number of groups have developed highly selective chiral Lewis acid and Brønsted base catalysts to achieve enantioselective Pudovik reaction of dialkyl phosphites to aldehydes (**Scheme 4-3**).[2] A majority of the developed systems employ chiral Schiff base architectures for aluminum and titanium metal centers with a single report utilizing a chiral base catalyst to achieve high levels of asymmetric induction. Although these systems achieve excellent levels of enantiocontrol in the addition of dialkyl phosphites to aryl aldehydes, the complementary product class prepared via addition into aliphatic aldehydes was obtained with substantial erosion in enantiofacial bias even at cryogenic temperatures.

Scheme 4-3. Chiral Catalysts Employed in Enantioselective Pudovik Reactions



Despite its synthetic utility as a C–P bond-forming reaction, the absence of a diastereoselective variant has hindered its incorporation in complex-molecule synthesis. A number of groups have investigated the development of diastereoselective Pudovik reactions into α-chiral aldehydes; however, these methodologies are often substrate specific and succumb to racemization under the reaction conditions.[3] An early example by Wróblewski examined the addition of dimethyl phosphite (**1**) to 2,4-*O*-benzylidene-D-erythrose (**4**) under Et_3N/DMAP catalysis (**Scheme 4-4**).[4] Although the Pudovik reaction provided the desired α-hydroxy phosphonates in good combined yield, no diastereoselectivity was observed yielding equimolar quantities of **5** and **6**.

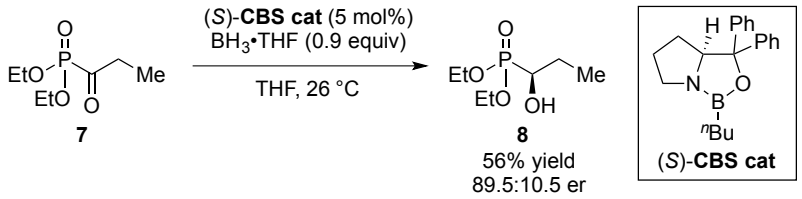
Scheme 4-4. Diastereoselective Pudovik Reactions



4.2.2 Preparation of Optically Active α-Hydroxy Phosphonates via Asymmetric Hydrogenation

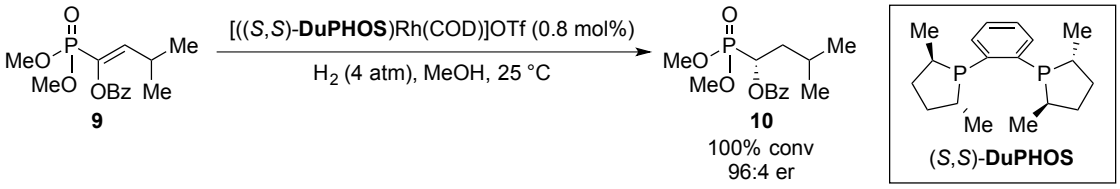
In principle, a complementary approach to the enantioselective Pudovik reaction for the synthesis of enantiopure α-hydroxy phosphonates is the asymmetric reduction of acyl phosphonates, which are readily prepared via Michaelis–Arbuzov reaction of trialkyl phosphites and acyl chlorides. Their ease of synthesis renders them versatile building blocks for the construction of optically active phosphorous-containing compounds. Gajda first demonstrated the applicability of acyl phosphonates to serve as competent substrates in asymmetric reductions utilizing a Corey–Bakshi–Shibata (CBS)[5] oxazaborolidine-mediated borane reduction (**Scheme 4-5**).[6] Subjection of acyl phosphonate **7** to CBS reduction conditions resulted in the formation of α-hydroxy phosphonate **8** in moderate yield with high levels of enantioselectivity at room temperature. Stereochemical analysis of **8** confirmed that the stereochemistry obtained via CBS reduction of **7** was consistent with the mechanism proposed by Corey for the reduction of ketones.

Scheme 4-5. Enantioselective CBS Reduction of Acyl Phosphonates



Despite the early success of strategies for the synthesis of α-hydroxy phosphonates via CBS reduction, asymmetric hydrogenation methodologies remained largely unexplored. In 1999, Burk reported the first method for the preparation of α-hydroxy phosphonate derivatives via catalytic asymmetric hydrogenation utilizing a cationic rhodium complex (**Scheme 4-6**).[7] Employing enolbenzoate phosphonate **9**, hydrogenation proceeded under mild hydrogenation conditions to provide α-benzoyloxy phosphonate **10** in 96:4 er, which can be deprotected upon treatment with K_2CO_3/MeOH. This methodology worked well for alkyl substrates providing products in high enantioselectivity; however, use of aryl substrates resulted in diminished levels of selectivity. Since Burk's seminal report, a number of groups have developed even more efficient and selective ligands for application in catalytic asymmetric hydrogenations of enol phosphonates employing cationic rhodium catalyst complexes.[8]

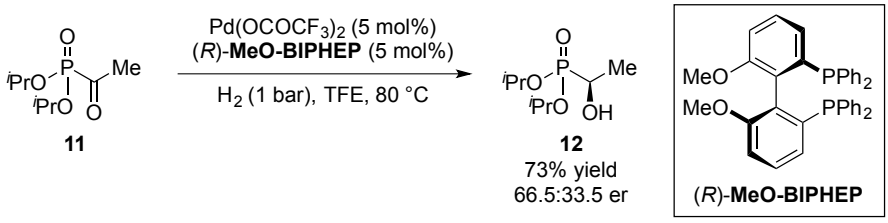
Scheme 4-6. Catalytic Asymmetric Hydrogenation of Enol Phosphonates



Catalytic enantioselective hydrogenation of acyl phosphonates in their native form to directly access α-hydroxy phosphonates remained a long-standing challenge for synthetic chemists. Recently, Goulioukina and Beletskaya reported the first catalytic asymmetric hydrogenation of acyl phosphonates employing a chiral palladium complex (**Scheme 4-7**).[9] Subjection of **11** to their optimized hydrogenation conditions resulted in the isolation of **12** in good yield with moderate levels of enantioselectivity. Their efforts demonstrate the potential to directly access optically active α-hydroxy phosphonates via hydrogenation while highlighting the

need for the development of new catalysts to achieve reduction with high levels of enantioselectivity.

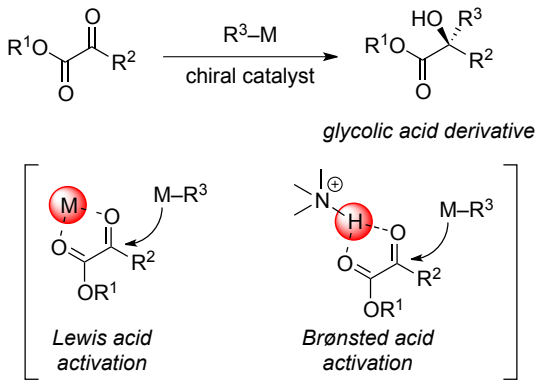
Scheme 4-7. Catalytic Asymmetric Hydrogenation of Acyl Phosphonates



4.2.3 Acyl Phosphonates as Structural Congeners of α-Keto Esters

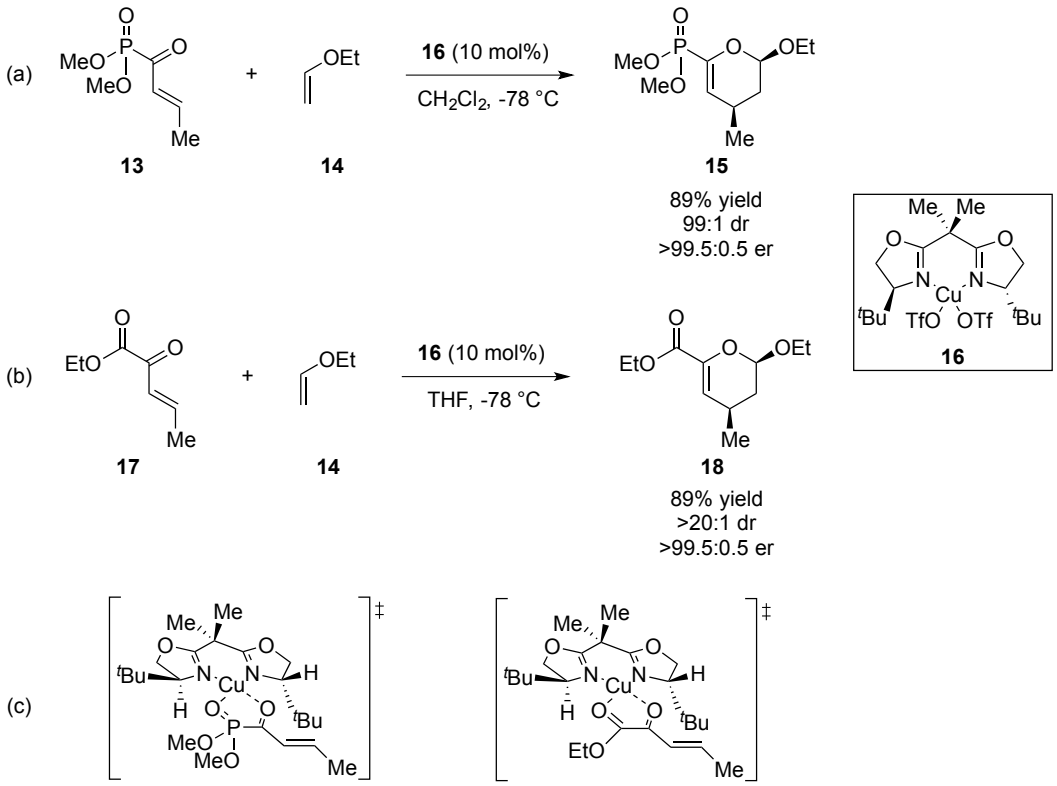
Asymmetric catalysis relies on the fundamental paradigm that privileged catalysts generate well-defined chiral spaces, which provide an environment capable of effectively directing similarly structured small molecules for enantiofacial discrimination.[10] This principle has led to the interchangeable application of catalysts and reaction modes developed for α-keto esters and their structural congeners, acyl phosphonates, due to their structural and electronic similarities. The activation of α-keto esters has been primarily achieved through the generation of a tight five-membered chelate with a Lewis or Brønsted acid catalyst via coordination to the 1,2-dicarbonyl moiety (**Scheme 4-8**). This well-defined chelate often allows for high levels of enantiocontrol to be realized in the addition of a nucleophile.

Scheme 4-8. Activation Modes of α-Keto Esters for Nucleophilic Attack



Given their structural similarity, Evans and Jørgensen were able to interchangeably utilize α-keto esters and acyl phosphonates in the bis(oxazoline)Cu(II)-catalyzed asymmetric hetero-Diels–Alder reaction to vinyl ethers (**Scheme 4-9**). The [4+2]-cycloaddition of acyl phosphonate **13** and ethyl vinyl ether (**14**) catalyzed by **16** afforded enantiopure **15** in 89% yield as a single diastereomer (**Scheme 4-9a**).[11] Similarly, treatment of α-keto ester **17** and ethyl vinyl ether (**14**) with **16** provided enantiopure **18** in identical yield also as a single diastereomer (**Scheme 4-9b**).[12] The products **15** and **18** were obtained with identical stereoinduction highlighting the interchangeability of α-keto esters and acyl phosphonates and the potential generality of these substrate classes in asymmetric catalysis by utilizing a common activation mode (**Scheme 4-9c**). Although sparingly utilized relative to α-keto esters, acyl phosphonates have been broadly employed as electrophiles in asymmetric methodologies.[11-13]

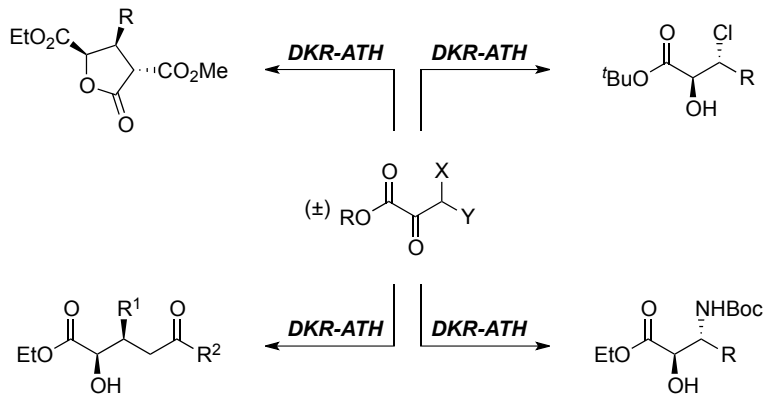
Scheme 4-9. Common Reactivity of α-Keto Esters and Acyl Phosphonates



4.2.4 DKR-ATH Strategy for the Synthesis of Optically Active α-Hydroxy Phosphonates

As described in Chapter Three, our group has been actively involved in the development of novel dynamic kinetic resolutions[14] via asymmetric transfer hydrogenation (DKR-ATH) for the preparation of β-stereogenic-α-glycolic acid derivatives. Utilizing (arene)RuCl(monosulfonamide) complexes bearing a bulky *m*-terphenylsulfonamide, the dynamic reduction of β-aryl-, β-chloro-, and β-amino-α-keto esters provides direct access to a diverse class of products with excellent levels of diastereo- and enantioselectivity (**Scheme 4-10**).[15]

Scheme 4-10. Synthesis of β-Stereogenic-α-Glycolic Acid Derivatives via DKR-ATH



The generality of this reaction manifold for the reduction of β-stereogenic-α-keto esters led us to consider the potential extrapolation of this precedent to the reduction of racemic α-stereogenic acyl phosphonates (**Scheme 4-11**). Given the aforementioned studies by Evans and Jørgensen, we proposed that the dynamic reduction of acyl phosphonates could be achieved through the application of our previously developed catalyst architectures to provide a flexible entry point into new β-stereogenic-α-hydroxy phosphonates with high levels of absolute and relative stereocontrol. Enantiopure α-hydroxy phosphonic acid subunits appear in compounds exhibiting antibacterial, antiviral, antibiotic, pesticidal, and anticancer properties;[16] however, prior art designed to access this structural motif bearing a β-stereogenic center efficiently are scarce.[17]

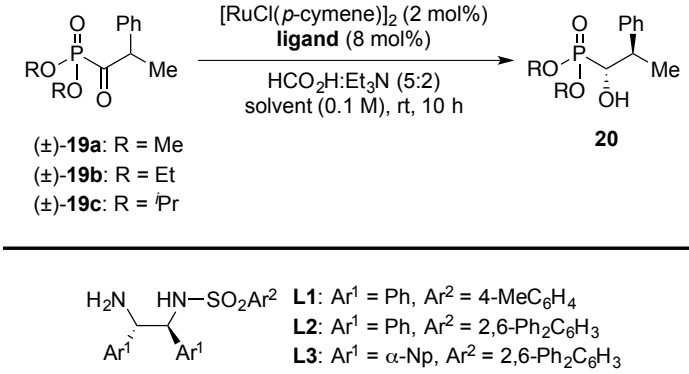
Scheme 4-11. Synthesis of β-Stereogenic-α-Hydroxy Phosphonic Acid Derivatives via DKR-ATH

4.3 Results and Discussion

4.3.1 Optimization of DKR-ATH of Racemic α-Aryl Acyl Phosphonates

We began our studies by examining the reduction of racemic α-aryl acyl phosphonates **19** with our library of (arene)RuCl(monosulfonamide) catalysts employing a mixture of HCO_2H:NEt_3 (5:2) as our organic reductant (**Table 4-1**). Employing α-phenyl acyl phosphonate **19b** as a test substrate, Noyori's (*p*-cymene)RuCl[(*S*,*S*)-TsDPEN] complex[18] was found to provide α-hydroxy phosphonate **20b** with modest *anti*/*syn* selectivity, but with excellent levels of enantiocontrol for both diastereomers (entry 1). Based on our group's recent success in tuning the diastereoselectivity of the DKR-ATH of β-chloro-α-keto esters through the application of a bulky *m*-terphenylsulfonamide ligand,[15b] aminosulfonamide **L2** was employed in the reduction of **19b** in *N*,*N*-dimethylformamide (DMF) delivering a marked increase in diastereoselectivity to 14:1 dr (entry 2). Changing the solvent to dimethyl sulfoxide (DMSO) resulted in a boost in diastereoselection up to 20:1 (entry 3). α-Naphthyl ethylenediamine-derived **L3** was tested and found to engender even higher levels of diastereocontrol with optimized reaction conditions being realized with DMSO as the solvent (entries 4 and 5). Both dimethyl and diethyl phosphonates were found to provide comparable levels of reactivity and selectivity (entries 5 and 6); however, the bulkier diisopropyl phosphonate **19c** suffered from reduced reactivity presumably due to its increased steric requirements (entry 7).

Table 4-1. Optimization of Ligand and Substrate in DKR-ATH of Racemic α-Aryl Acyl Phosphonates[a]



entry	19	L	solvent	conv. (%)[b]	dr[b]	er[c]
1	**19b**	**L1**	DMSO	>95	3:1	>99.5:0.5 (98.5:1.5)[d]
2	**19b**	**L2**	DMF	>95	14:1	99:1
3	**19b**	**L2**	DMSO	>95	20:1	>99.5:0.5
4	**19b**	**L3**	DMF	>95	22:1	>99.5:0.5
5	**19b**	**L3**	DMSO	>95 (93)[e]	29:1	>99.5:0.5
6	**19a**	**L3**	DMSO	>95 (91)[e]	>30:1	>99.5:0.5
7	**19c**	**L3**	DMSO	19	–	–

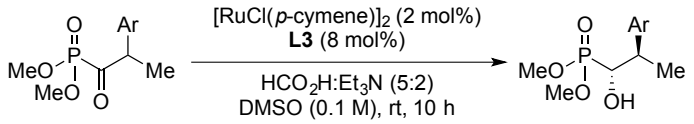
[a]Reactions were performed on 0.155 mmol scale employing 5 equiv of $HCO_2H:Et_3N$ (5:2). [b]Determined by ^{31}P NMR analysis of the crude reaction mixture. [c]Determined by chiral HPLC analysis. [d]The value in parentheses is the enantiomeric ratio for the *syn* isomer. [e]The value in parentheses is the isolated yield of analytically pure product.

4.3.2 Examination of Substrate Scope in DKR-ATH of Racemic α-Aryl Acyl Phosphonates

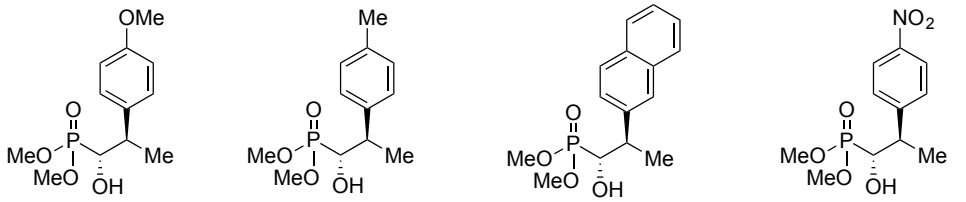
With optimized reaction conditions in hand, the reaction scope was next examined (**Table 4-2**). A variety of electron-releasing and electron-withdrawing aryl groups were tolerated providing products **20d-i** in uniformly high yield and selectivity. Heteroaromatic substituents were also amenable to the reaction providing the *N*-Ts indoyl product **20k** in 94% yield with excellent levels of diastereo- and enantiocontrol. *Ortho*-substituents resulted in reduced reactivity necessitating elevated temperatures (45 °C) and longer reaction times to provide **20j** in 6:1 dr and 98.5:1.5 er. Under the standard reaction conditions, **19j** proceeded to 28% conversion

providing **20j** in 11:1 dr demonstrating that the elevated reaction conditions required in the reduction led to reduced selectivity.

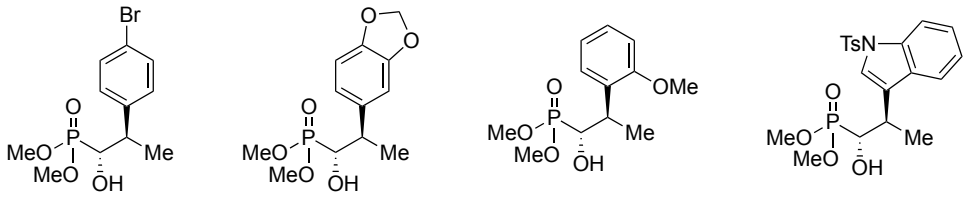
Table 4-2. Examination of Aromatic Substrate Scope[a]



(±)-**19** → **20**



20d	**20e**	**20f**	**20g**
92% yield	90% yield	93% yield	86% yield
>20:1 dr	>20:1 dr	>20:1 dr	19:1 dr
>99.5:0.5 er	>99.5:0.5 er	>99.5:0.5 er	>99.5:0.5 er



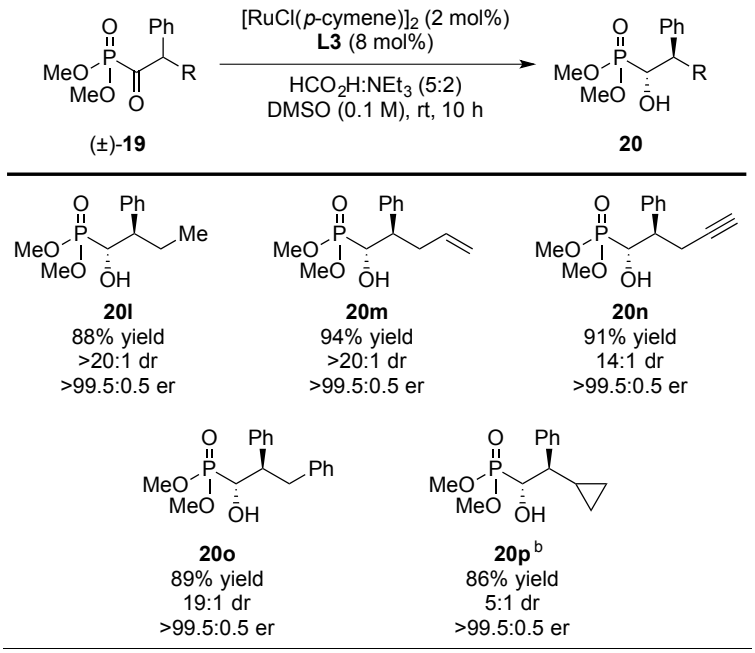
20h	**20i**	**20j**[b]	**20k**
93% yield	93% yield	84% yield	94% yield
>20:1 dr	>20:1 dr	6:1 dr	>20:1 dr
>99.5:0.5 er	>99.5:0.5 er	97.5:2.5 er	>99.5:0.5 er

[a]Reactions were performed on 0.155 mmol scale employing 5 equiv of $HCO_2H:Et_3N$ (5:2) in DMSO (1.5 mL) at room temperature for 10 h. Isolated yields of analytically pure material are reported. Diastereomeric ratios were determined by ^{31}P NMR analysis of the crude reaction mixture; enantiomeric ratios were determined by chiral HPLC analysis. [b]Reaction was performed at 45 °C for 20 h.

The identity of the α-aliphatic substituent was also investigated to probe the steric sensitivity of the system (**Table 4-3**). Linear aliphatic substituents were tolerated, providing products **20l-o** in equally high yield and selectivity and allowing for the incorporation of alkene and alkyne functional handles. The sterically demanding cyclopropyl acyl phosphonate reacted

slower under the reactions conditions, requiring 36 h to provide **20p** in 5:1 dr while retaining excellent enantiocontrol.

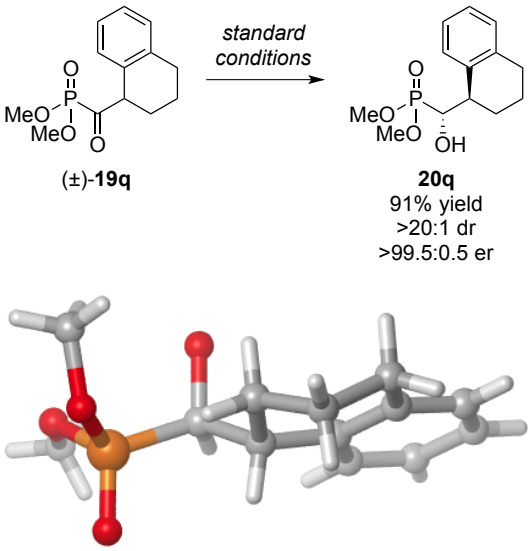
Table 4-3. Examination of Aliphatic Substrate Scope[a]



[a]Reactions were performed on 0.155 mmol scale employing 5 equiv of $HCO_2H:Et_3N$ (5:2) in DMSO (1.5 mL) at room temperature for 10 h. Isolated yields of analytically pure material are reported. Diastereomeric ratios were determined by ^{31}P NMR analysis of the crude reaction mixture; enantiomeric ratios were determined by chiral HPLC analysis. [b]Reaction was performed at room temperature for 36 h.

To further probe the utility of this reaction, the bicyclic substrate **19q** was subjected to the reduction conditions affording **20q** in high yield and comparable levels of selectivity as the acyclic examples (**Scheme 4-12**). In contrast to *ortho*-substituted **20j**, α-hydroxy phosphonate **20q** was obtained with excellent levels of diastereoselectivity suggesting that the *ortho*-substituent occupies a sterically encumbering conformation when unconstrained causing nonideal substrate-catalyst interactions. The absolute stereochemistry of the products was established as (1*R*,2*R*) via x-ray crystallographic analysis of **20e** and **20q** confirming the *anti* orientation of the alcohol and aryl groups.[19]

Scheme 4-12. DKR-ATH of Cyclic α-Aryl Acyl Phosphonate **19q**

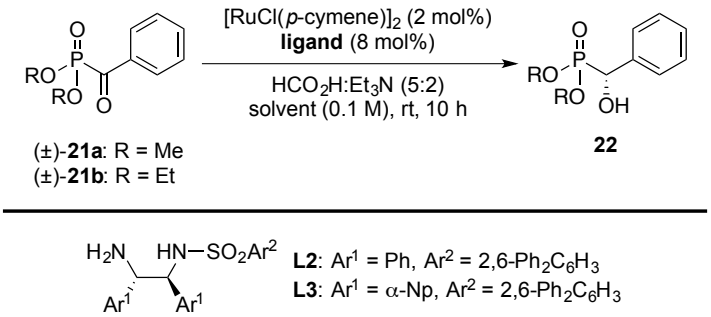


4.3.3 Application of ATH Methodology to the Reduction of Simple Acyl Phosphonates

As previously outlined, a number of highly efficient catalysts have been developed for application in the Pudovik reaction (**Scheme 4-3**); however, we envisioned that our reduction methodology was an attractive strategy to provide complementary access to optically active α-hydroxy phosphonates. A majority of the reported asymmetric Pudovik reactions require cryogenic temperatures, whereas our ATH methodology provides high levels of enantioinduction at room temperature increasing its synthetic practicality. To this end, we examined the reduction of aryl acyl phosphonates **21** with our (arene)RuCl(monosulfonamide) catalysts (**Table 4-4**). Under the previously optimized conditions for the dynamic reduction of α-aryl acyl phosphonates, **22a** was obtained in quantitative yield with 88.5:11.5 er (entry 1). The high level of enantioselectivity initially obtained was encouraging, so a screen of solvents was conducted with **L3** (entries 2-4). Although *N*-methyl-2-pyrrolidone (NMP) resulted in the complete decomposition of **21a**, both *N*,*N*-dimethylacetamide (DMA) and DMF provided slight increases in enantioselectivity to 89.5:10.5 er and 91.5:8.5 er, respectively. Reducing the temperature of

the reduction to 0 °C was found to be ineffective at increasing the levels of enantioselection providing **22a** in 91:9 er (entry 5). Changing the phosphonate ester identity from methyl to ethyl had little effect on the stereochemical outcome of the reaction (entry 6). Reverting to a (*S*,*S*)-DPEN backbone (**L2**) led to comparable enantioselectivities in DMF and DMSO (entries 7 and 8); however, reaction in DMF led to the isolation of (*R*)-**22a**[20] in 95% yield with 92:8 er.

Table 4-4. Optimization of Ligand and Substrate in ATH of Acyl Phosphonates[a]



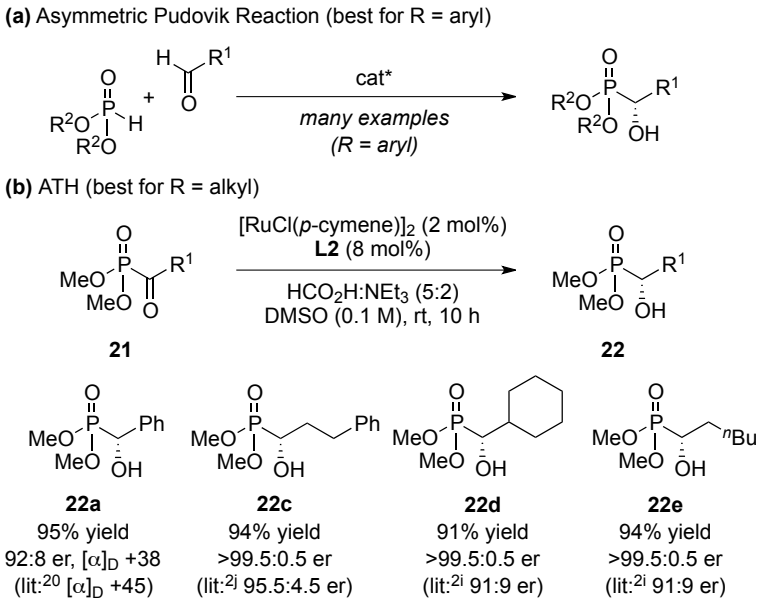
entry	21	L	solvent	conv. (%)[b]	er[c]
1	**21a**	**L3**	DMSO	>95	88.5:11.5
2	**21a**	**L3**	DMF	>95	91.5:8.5
3	**21a**	**L3**	DMA	>95	89.5:10.5
4	**21a**	**L3**	NMP	>95[d]	–
5[e]	**21a**	**L3**	DMF	>95	91:9
6	**21b**	**L3**	DMF	>95	89.5:10.5
7	**21a**	**L2**	DMF	>95 (95)[f]	92:8
8	**21a**	**L2**	DMSO	>95	90:10

[a]Reactions were performed on 0.155 mmol scale employing 5 equiv of $HCO_2H:Et_3N$ (5:2). [b]Determined by ^{31}P NMR analysis of the crude reaction mixture. [c]Determined by chiral HPLC analysis. [d]The reaction resulted in the complete decomposition of starting material with no desired product observed. [e]Reaction was performed at 0 °C for 10 h. [f]The value in parentheses is the isolated yield of analytically pure product.

The levels of enantioselection achieved with aryl acyl phosphonate **21a** were found to be uncompetitive with those observed via known Pudovik methods into aryl aldehydes (**Scheme 4-13a**). Upon consideration of the structural differences between **19a** and **21a**, we wondered if our catalyst system was more effective and selective in the enantiofacial discrimination of aliphatic

acyl phosphonates. Interestingly, the presence of a α-substituent was found to be unnecessary for high levels of enantioselectivity in the reduction of aliphatic acyl phosphonates providing enantiopure products **22c-e** in high yield (**Scheme 4-13b**). The excellent levels of enantiocontrol observed for **22c-e** are a marked improvement over Pudovik-based methodologies, highlighting the potential utility and complementarity of this transfer hydrogenation in the preparation of enantiopure aliphatic α-hydroxy phosphonic acids bearing one stereocenter.

Scheme 4-13. ATH of Aliphatic Acyl Phosphonates

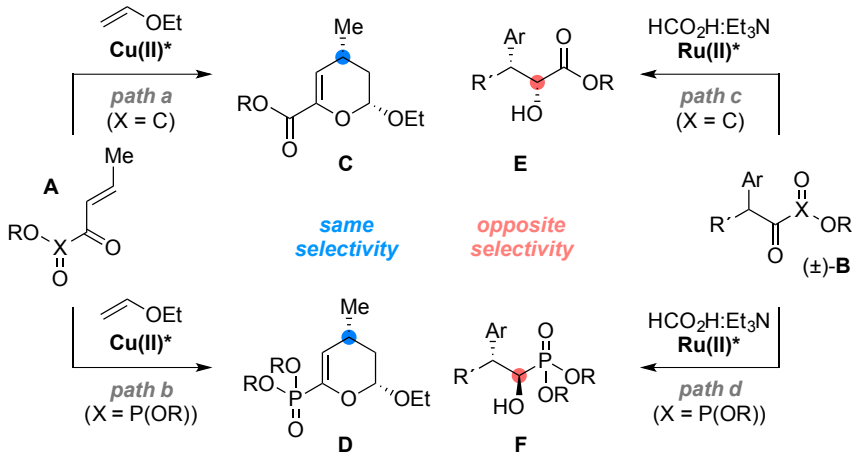


4.3.4 Diametric Stereocontrol in α-Keto Ester and Acyl Phosphonate Reductions

The characteristic that well-defined homogenous catalysts are expected to engender complimentary enantiofacial selectivity for structurally similar compounds is practically useful insofar as a seminal advance can pave the way for useful extensions based on structurally related congeners. For instance, Evans and Jørgensen found that dihydropyrans **C** and **D** were obtained with identical stereochemistry irrespective of the identity of the starting material **A** (**Scheme 4-14**, paths a and b). Deviations from this principle are rare and important in understanding

substrate-catalyst interactions.[21] In our analysis of x-ray crystal structures obtained of the α-hydroxy phosphonate products **F**, it was shown that the reduction of the acyl phosphonates (path d) was proceeding from the opposite face of the carbonyl than observed with their α-keto ester congeners which afford α-hydroxy esters **E** (path c).

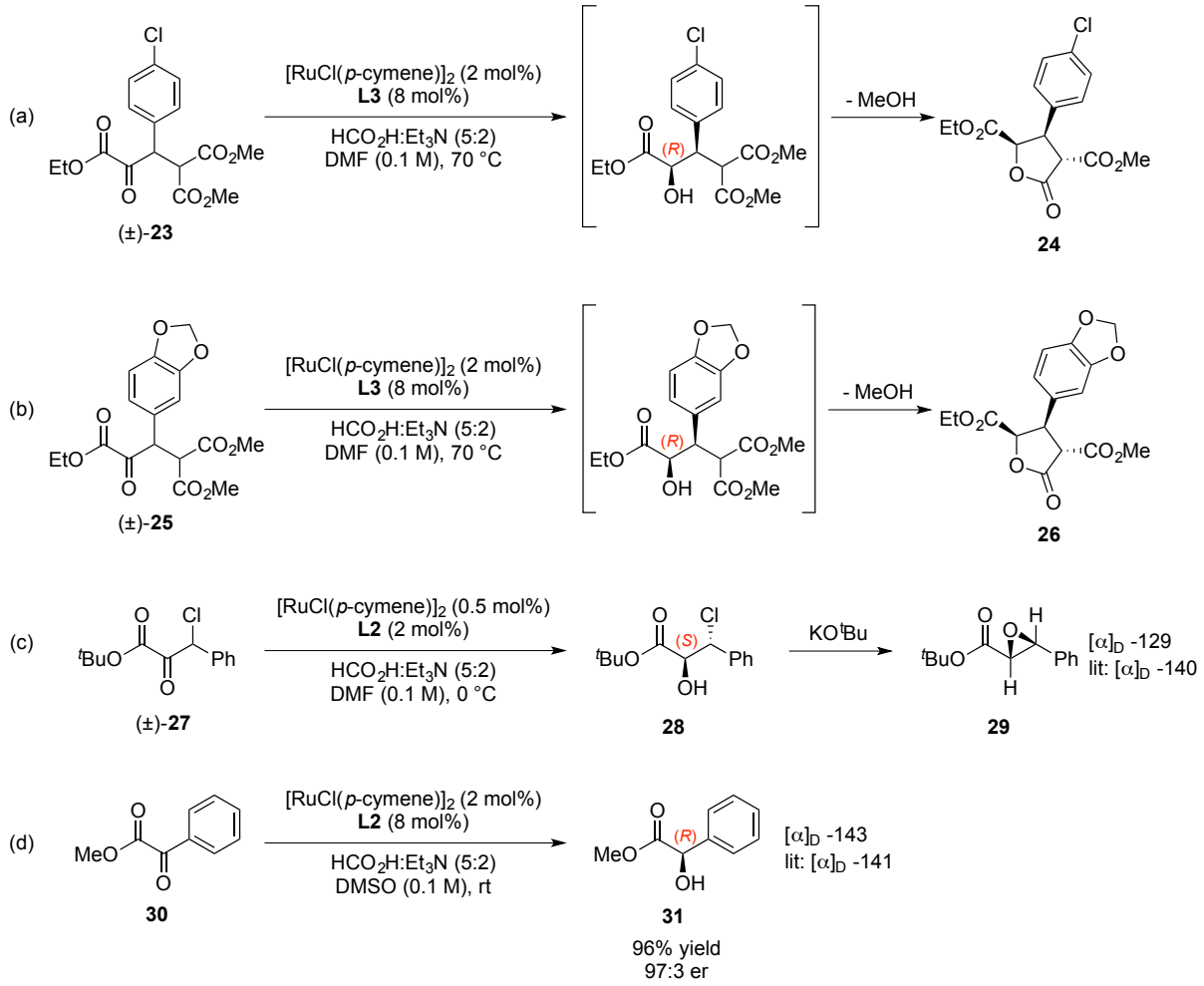
Scheme 4-14. Reversal in Enantiofacial Selectivity



In order to determine the generality of this observed dichotomy, representative substrates were reduced whose absolute stereochemistries were either reported in the literature or determined by x-ray crystallographic analysis. During the course of our prior studies in the DKR-ATH of β-aryl-α-keto esters,[15a,15b] the absolute stereochemistries of γ-butyrolactones **24** and **26** were determined by x-ray crystallographic analysis,[19] indicating that the reduction of α-keto esters (±)-**23** and (±)-**25** proceeds from the *Si*-face (**Scheme 4-15a-b**). This enantiofacial selectivity was further confirmed in the asymmetric reduction of β-chloro-α-ester (±)-**27** to **28**, which was stereospecifically transformed into the known glycidic ester **29** (**Scheme 4-15c**). Upon comparison of the optical rotation of (2*R*,3*S*)-**29** to that reported in the literature,[22] it was concluded that the reduction of (±)-**27** proceeded from the *Re*-face (**Note:** This reduction occurs on the same diastereotopic face as (±)-**23** and (±)-**25**; substituent Cahn–Ingold–Prelog priorities

have switched due to the presence of the chlorine atom). Methyl benzoylformate (**30**) was subjected to the standard reduction conditions affording methyl mandelate (**31**) in high yield and excellent enantioselectivity (**Scheme 4-15d**). The absolute stereochemistry of (*R*)-**31** was determined by comparison of optical rotations to those reported in the literature,[23] confirming that aliphatic and aryl α-keto esters undergo reduction from the same face of the carbonyl.

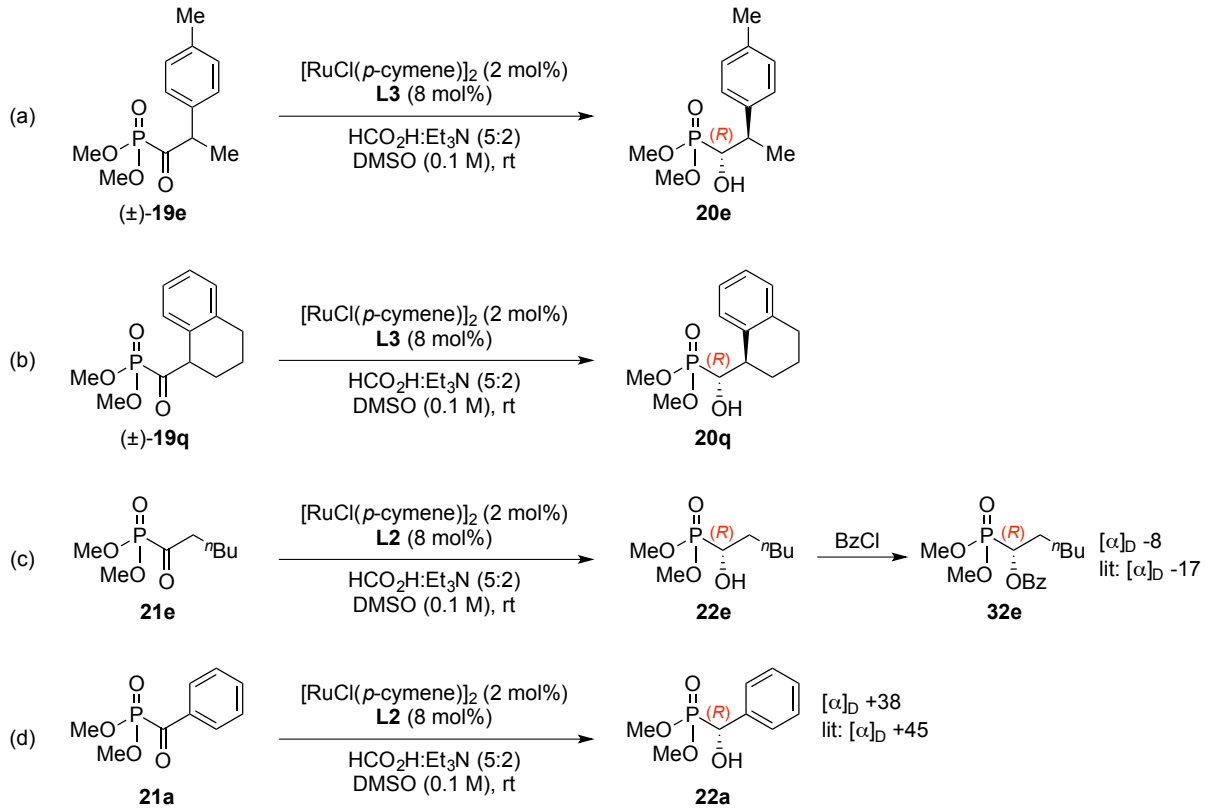
Scheme 4-15. Facial Selectivity in the ATH of α-Keto Esters



During the course of the present study, the absolute stereochemistry of products obtained from the DKR-ATH of α-aryl acyl phosphonates was determined by x-ray crystallographic

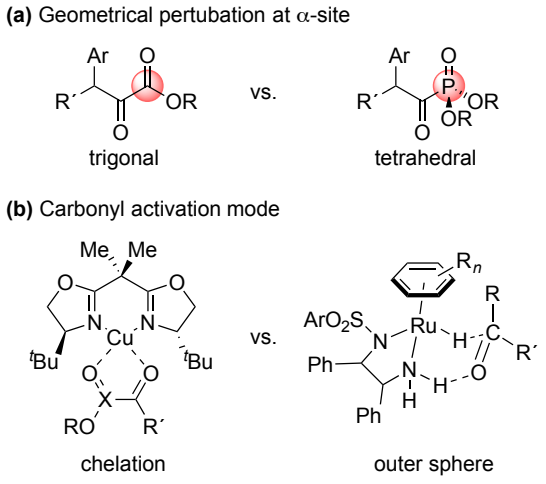
analysis of **20e** and **20q** (**Scheme 4-16a-b**). Both reductions proceeded with diastereofacial selectivity *opposite* of what was observed in the preparation of **24** and **26**. This facial selectivity is not dependent on the presence of a α-substituent since the reduction of **21e** proceeds to afford **22e** (**Scheme 4-16c**); the configuration of the latter was determined by comparison of the optical rotation of the derived benzoate (*R*)-**32e** with that reported in the literature.[7] (**Note:** In reference 7, there is a mistake in the structure corresponding to **32e** (one extra carbon) for that paper. The Supporting Information shows the correct structure consistent with the provided analytical data.) The reduction of aryl acyl phosphonate **21** proceeded to provide (*R*)-**22a** based on comparison of the optical rotation to that reported in the literature (**Scheme 4-16d**).[20]

Scheme 4-16. Facial Selectivity in the ATH of Acyl Phosphonates



Given these collective data, it can be concluded that the Ru-catalyzed asymmetric transfer hydrogenation of both aliphatic and aryl acyl phosphonates proceeds from the *opposite* face observed in the reduction of α-keto esters. Obtaining a full understanding of the reversal in stereoselectivity will require further investigation, but some initial observations that are relevant can be offered. Despite being electronic congeners of α-keto esters, acyl phosphonates are tetrahedral rather than trigonal at the α-center to the carbonyl, a circumstance that alters the steric environment of the ketone undergoing reduction (**Scheme 4-17a**). The impact of this geometric change is probably compounded by the fact that the outersphere carbonyl activation mode in the (amido)Ru(II) complex is dramatically different than in the bis(oxazoline)Cu(II) systems (**Scheme 4-9** and **Scheme 4-17b**).

Scheme 4-17. Potential Variables to Account for Stereoselectivity Inversion



The inner-sphere chelation control invoked by chiral Lewis acids causes α-keto esters and acyl phosphonates to experience identical influence from the C_2-symmetric chiral framework. Facial selectivity in bifunctional outersphere activation by the Ru–H complex is governed by the approach of the ketone through substrate-catalyst discrimination of the R and R´ groups. The

length of the P–C bond (1.84 Å) found in the acyl phosphonate moiety is significantly longer than the C–C bond (1.54 Å) possessed by α-keto esters. This effect can be substantial when considering the potential penalties incurred due to substrate-catalyst interactions by the ester and phosphonate groups. Therefore, another possible explanation is that the ester and phosphonate moieties do not occupy the same chiral space in the six-membered transition state required for transfer hydrogenation.

4.4 Conclusion

An unexpected reversal in facial selectivity was observed in the (arene)RuCl(monosulfonamide)-mediated asymmetric transfer hydrogenation of acyl phosphonates from their structural mimics, α-keto esters. This dichotomy in reactivity was exploited in the development of an extremely selective dynamic kinetic resolution of α-aryl acyl phosphonates providing β-stereogenic-α-hydroxy phosphonic acid derivatives. The first highly selective catalytic reduction of acyl phosphonates also provides complementary access to challenging Pudovik adducts. Substrate-catalyst interactions, reactant orientations, and activation modes are proposed to be influential in providing the observed facial divergence between α-keto esters and acyl phosphonates.

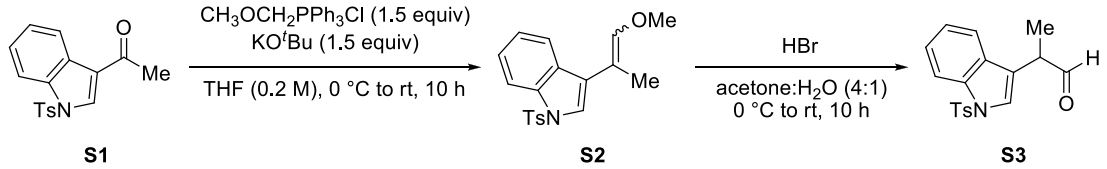
4.5 Experimental Details

Methods: Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, and ^{31}P NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 100 MHz or 150 MHz, and ^{31}P NMR at 162 MHz or 243 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). Chemical shifts for ^{31}P NMR are reported in ppm from H_3PO_4 resonance (0.00 ppm) as the external standard. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, sept = septuplet, oct = octuplet, m = multiplet), coupling constants (Hz), and integration. HPLC analysis was performed on an Agilent Technologies 1200 System equipped with Chiralpak IA, IB, and IC columns (φ 4.6 mm x 250 mm, constant flow at 1.00 mL/min). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization (Note: All samples prepared in methanol). Analytical thin layer chromatography (TLC) was performed on Sorbtech 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle. All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted.

Materials: α-Aryl aldehydes,[24] ligands **L1-3**,[15a,15b] acyl phosphonates **21a-e**,[7,25] and Dess–Martin periodinane (DMP)[26] were prepared according to known procedures. Dimethyl

sulfoxide (DMSO) was distilled from calcium hydride and stored under nitrogen over 3Å molecular sieves. Triethylamine (Et_3N) was freshly distilled from calcium hydride prior to use. Diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and tetrahydrofuran (THF) were dried by passage through a column of neutral alumina under nitrogen prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

Preparation of S3

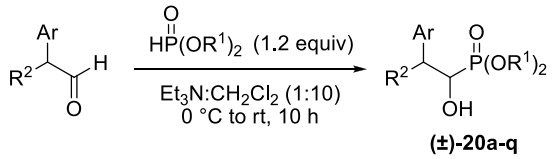


A flame-dried 50-mL round-bottomed flask equipped with a magnetic stir bar was charged with methoxymethyl(triphenyl)phosphonium chloride (1.54 g, 4.50 mmol, 1.5 equiv) in Et_2O (15 mL). KO^{t}Bu (0.50 g, 4.50 mmol, 1.5 equiv) was added to the stirring suspension. After 30 min, the blood red solution was cooled to 0 °C in an ice bath. Ketone **S1** (0.94 g, 3.00 mmol, 1.0 equiv) was added and the resulting solution was allowed to warm to room temperature and stir for 10 h. The reaction was quenched with H_2O (30 mL) and diluted with Et_2O (30 mL). The layers were separated and the organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was filtered through a plug of silica eluting with 30% ethyl acetate:hexanes to afford the crude enol ether **S2** as an *E*/*Z* mixture, which was used without further purification.

A 25-mL round-bottomed flask equipped with a magnetic stir bar was charged with the crude enol ether **S2** in acetone:H_2O (4:1) (5 mL). The solution was cooled to 0 °C in an ice bath. HBr (48%) (1 mL) was carefully added to the reaction. After stirring at 0 °C for 30 min, the ice bath was removed and the reaction was allowed to stir for 10 h at room temperature. The reaction

was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 30% ethyl acetate:hexanes to afford 2-(1-tosyl-1*H*-indol-3-yl)propanal (**S3**) (0.78 g, 2.38 mmol, 79% yield) as a viscous yellow oil. Analytical data for **S3**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.62 (d, *J* = 1.9 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.50 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.26-7.21 (m, 3H), 3.82 (dq, *J* = 7.1, 0.9 Hz, 1H), 2.32 (s, 3H), 1.52 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.7, 145.1, 135.2, 134.9, 129.9, 129.6, 126.7, 125.1, 123.7, 123.3, 119.5, 119.0, 113.7, 44.0, 21.4, 13.3; **IR** (thin film): 1730, 1653, 1448, 1370, 1174, 1130, 1089 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.35; **LRMS** (ESI): Calcd. for $C_{19}H_{21}NaNO_4S$ ([M+MeOH+Na]$^+$): 360.13, Found: 360.17.

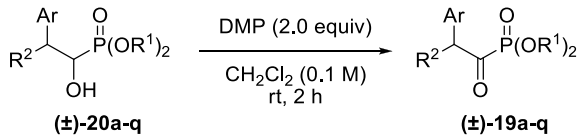
<u>General Procedure A for the Preparation of Racemic β-Aryl-α-Hydroxy Phosphonates 20a-q</u>



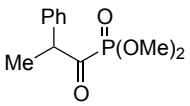
A 25-mL round-bottomed flask equipped with a magnetic stir bar was charged with dialkyl phosphite (2.40 mmol, 1.2 equiv) in Et_3N:CH_2Cl_2 (1:10) (5.0 mL). The solution was cooled to 0 °C in an ice bath. α-Aryl aldehyde (2.00 mmol, 1.0 equiv) was added dropwise. After stirring at 0 °C for 30 min, the ice bath was removed and the reaction was stirred for 10 h at room temperature. The reaction was diluted with Et_2O (40 mL) and sequentially washed with 1 M HCl (1 x 20 mL), H_2O (2 x 20 mL), and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column

chromatography on silica gel eluting with a 30% to 50% acetone:hexanes gradient to afford to racemic β-aryl-α-hydroxy phosphonate **20** as an inseparable mixture of diastereomers.

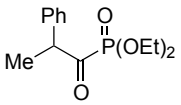
General Procedure B for the Preparation of α-Aryl Acyl Phosphonates 19a-q



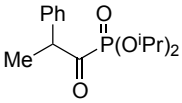
A 25-mL round-bottomed flask equipped with a magnetic stir bar was charged with β-aryl-α-hydroxy phosphonate **20** (0.50 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL). Dess-Martin periodinane (424 mg, 1.00 mmol, 2.0 equiv) was added and the reaction stirred 2 h at room temperature. The reaction was diluted with Et_2O (25 mL) and washed with sat. aq. $NaHCO_3$:sat. aq. $Na_2S_2O_3$ (1:1) (3 x 10 mL) and brine (1 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford α-aryl acyl phosphonate **19**, which was used in the reduction without further purification.



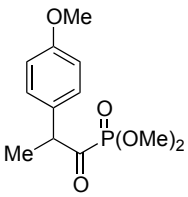
Dimethyl (2-phenylpropanoyl)phosphonate (19a): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20a** (122 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19a** (120 mg, 99% yield) as a pale yellow oil. Analytical data for **19a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.32 (m, 2H), 7.29-7.24 (m, 2H), 4.38 (q, J = 6.9 Hz, 1H), 3.70 (d, J = 10.7 Hz, 3H), 3.39 (d, J = 10.9 Hz, 3H), 1.44 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.7 (d, $J_{P\text{-}C}$ = 161.8 Hz), 136.6, 128.82, 128.81, 127.6, 53.8 (d, $J_{P\text{-}C}$ = 7.3 Hz), 53.1 (d, $J_{P\text{-}C}$ = 6.9 Hz), 52.7 (d, $J_{P\text{-}C}$ = 54.6 Hz), 16.6 (d, $J_{P\text{-}C}$ = 3.2 Hz); **^{31}P NMR** (151 MHz, $CDCl_3$): δ -0.64; **IR** (thin film): 2959, 1692, 1454, 1258, 1032, 837, 701 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.35; **LRMS** (ESI): Calcd. for $C_{11}H_{15}NaO_4P$ ([M+Na]$^+$): 265.06, Found: 265.02.



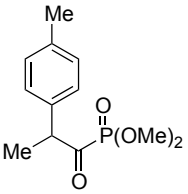
Diethyl (2-phenylpropanoyl)phosphonate (19b): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20b** (136 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19b** (131 mg, 97% yield) as a pale yellow oil. Analytical data for **19b**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31-7.28 (m, 2H), 7.24-7.21 (m, 3H), 4.39 (q, J = 7.0 Hz, 1H), 4.11-3.97 (m, 2H), 3.82-3.68 (m, 2H), 1.41 (d, J = 7.0 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 210.4 (d, $J_{P\text{-}C}$ = 162.2 Hz), 137.0, 128.73, 128.71, 127.5, 63.6 (d, $J_{P\text{-}C}$ = 6.9 Hz), 63.0 (d, $J_{P\text{-}C}$ = 7.1 Hz), 52.5 (d, $J_{P\text{-}C}$ = 53.9 Hz), 16.8 (d, $J_{P\text{-}C}$ = 2.9 Hz), 16.1 (d, $J_{P\text{-}C}$ = 5.7 Hz), 15.9 (d, $J_{P\text{-}C}$ = 6.0 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$): δ -2.15; **IR** (thin film): 1685, 1646, 1254, 1021, 700 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.40; **LRMS** (ESI): Calcd. for $C_{13}H_{20}O_4P$ ([M+H]$^+$): 271.11, Found: 271.12.



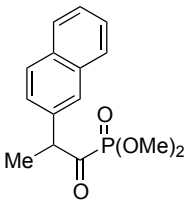
Diisopropyl (2-phenylpropanoyl)phosphonate (19c): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20c** (150 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19c** (137 mg, 92% yield) as a pale yellow oil. Analytical data for **19c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.22-7.18 (m, 3H), 4.63 (dq, J = 12.6, 6.3 Hz, 1H), 4.47-4.36 (m, 2H), 1.40 (d, J = 7.0 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.2 Hz, 3H), 1.06 (d, J = 6.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 211.1 (d, $J_{P\text{-}C}$ = 166.0 Hz), 137.5, 128.7, 128.6, 127.3, 72.6 (d, $J_{P\text{-}C}$ = 7.5 Hz), 72.4 (d, $J_{P\text{-}C}$ = 7.6 Hz), 52.1 (d, $J_{P\text{-}C}$ = 54.3 Hz), 23.9 (d, $J_{P\text{-}C}$ = 3.6 Hz), 23.8 (d, $J_{P\text{-}C}$ = 5.4 Hz), 23.5 (d, $J_{P\text{-}C}$ = 4.8 Hz), 23.4 (d, $J_{P\text{-}C}$ = 5.4 Hz), 17.0 (d, $J_{P\text{-}C}$ = 2.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -3.89; **IR** (thin film): 2981, 1695, 1653, 1455, 1387, 1254, 993 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.46; **LRMS** (ESI): Calcd. for $C_{15}H_{24}O_4P$ ([M+H]$^+$): 299.14, Found: 299.14.



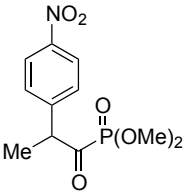
Dimethyl (2-(4-methoxyphenyl)propanoyl)phosphonate (19d): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20d** (143 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19d** (134 mg, 98% yield) as a pale yellow oil. Analytical data for **19d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.14 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.30 (q, J = 6.9 Hz, 1H), 3.74 (s, 1H), 3.68 (d, J = 10.7 Hz, 3H), 3.39 (d, J = 10.9 Hz, 3H), 1.38 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.6 (d, $J_{P\text{-}C}$ = 160.6 Hz), 159.1, 130.0, 128.3, 114.2, 55.1, 53.8 (d, $J_{P\text{-}C}$ = 7.2 Hz), 53.2 (d, $J_{P\text{-}C}$ = 6.8 Hz), 51.9 (d, $J_{P\text{-}C}$ = 54.5 Hz), 16.5 (d, $J_{P\text{-}C}$ = 3.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 0.12; **IR** (thin film): 1730, 1683, 1653, 1509, 1253, 1179, 1030 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.24; **LRMS** (ESI): Calcd. for $C_{12}H_{17}NaO_5P$ ([M+Na]$^+$): 295.07, Found: 295.07.



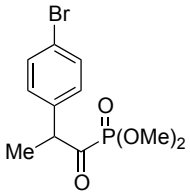
Dimethyl (2-(*p*-tolyl)propanoyl)phosphonate (19e): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20e** (129 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19e** (119 mg, 93% yield) as a pale yellow oil. Analytical data for **19e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.12-7.08 (m, 4H), 4.30 (dq, J = 6.9, 0.9 Hz, 1H), 3.66 (d, J = 10.7 Hz, 3H), 3.37 (d, J = 10.9 Hz, 3H), 2.27 (s, 3H), 1.37 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.6 (d, $J_{P\text{-}C}$ = 161.3 Hz), 137.3, 133.4, 129.4, 128.6, 53.7 (d, $J_{P\text{-}C}$ = 7.2 Hz), 53.1 (d, $J_{P\text{-}C}$ = 7.1 Hz), 52.2 (d, $J_{P\text{-}C}$ = 54.5 Hz), 20.8, 16.5 (d, $J_{P\text{-}C}$ = 3.3 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -0.56; **IR** (thin film): 2959, 1732, 1698, 1515, 1497, 1248, 1038 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.33; **LRMS** (ESI): Calcd. for $C_{12}H_{18}O_4P$ ([M+H]$^+$): 257.10, Found: 257.12.



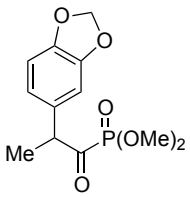
Dimethyl (2-(naphthalen-2-yl)propanoyl)phosphonate (19f): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20f** (147 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19f** (141 mg, 96% yield) as a pale yellow oil. Analytical data for **19f**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.83-7.79 (m, 3H), 7.73 (s, 1H), 7.48-7.44 (m, 2H), 7.35 (dd, J = 8.5, 1.7 Hz, 1H), 4.57 (q, J = 6.9 Hz, 1H), 3.70 (d, J = 16.7 Hz, 3H), 3.32 (d, J = 16.9 Hz, 3H), 1.53 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 209.7 (d, $J_{P\text{-}C}$ = 161.7 Hz), 134.0, 133.3, 132.6, 128.6, 127.9, 127.7, 127.5, 126.29, 126.28, 126.1, 53.9 (d, $J_{P\text{-}C}$ = 6.9 Hz), 53.2 (d, $J_{P\text{-}C}$ = 7.1 Hz), 52.8 (d, $J_{P\text{-}C}$ = 54.7 Hz), 16.7 (d, $J_{P\text{-}C}$ = 3.0 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$): δ -0.57; **IR** (thin film): 1716, 1698, 1558, 1457, 1254, 1034 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.31; **LRMS** (ESI): Calcd. for $C_{15}H_{18}O_4P$ ([M+H]$^+$): 293.10, Found: 293.16.



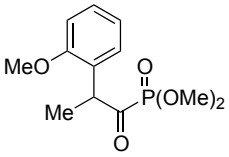
Dimethyl (2-(4-nitrophenyl)propanoyl)phosphonate (19g): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20g** (137 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19g** (133 mg, 97% yield) as a pale yellow oil. Analytical data for **19g**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.49 (dq, J = 7.0, 0.8 Hz, 1H), 3.76 (d, J = 10.8 Hz, 3H), 3.58 (d, J = 10.9 Hz, 3H), 1.48 (d, J = 7.0, 0.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.2 (d, $J_{P\text{-}C}$ = 177.4 Hz), 147.3, 144.5, 129.5, 123.9, 54.1 (d, $J_{P\text{-}C}$ = 7.5 Hz), 53.7 (d, $J_{P\text{-}C}$ = 7.4 Hz), 52.3 (d, $J_{P\text{-}C}$ = 54.7 Hz), 16.7 (d, $J_{P\text{-}C}$ = 1.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -1.50; **IR** (thin film): 1716, 1698, 1605, 1521, 1348, 1038 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.21; **LRMS** (ESI): Calcd. for $C_{11}H_{15}NO_6P$ ([M+H]$^+$): 288.07, Found: 288.10.



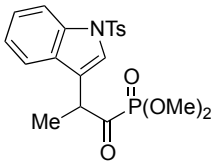
Dimethyl (2-(4-bromophenyl)propanoyl)phosphonate (19h): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20h** (162 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19h** (157 mg, 98% yield) as a pale yellow oil. Analytical data for **19h**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.46 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 4.34 (q, J = 7.0 Hz, 1H), 3.73 (d, J = 10.7 Hz, 3H), 3.49 (d, J = 10.9 Hz, 3H), 1.42 (dd, J = 7.0, 0.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 209.5 (d, $J_{P\text{-}C}$ = 162.9 Hz), 135.9, 132.0, 130.4, 121.8, 54.0 (d, $J_{P\text{-}C}$ = 6.9 Hz), 53.4 (d, $J_{P\text{-}C}$ = 6.8 Hz), 52.1 (d, $J_{P\text{-}C}$ = 54.2 Hz), 16.6 (d, $J_{P\text{-}C}$ = 2.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -1.01; **IR** (thin film): 1732, 1652, 1507, 1457, 1258, 1030 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.31; **LRMS** (ESI): Calcd. for $C_{11}H_{15}BrO_4P$ ([M+H]$^+$): 320.99, Found: 320.99.



Dimethyl (2-(benzo[*d*][1,3]dioxol-5-yl)propanoyl)phosphonate (19i): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20i** (144 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19i** (137 mg, 96% yield) as a pale yellow oil. Analytical data for **19i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.73 (dd, J = 6.6, 1.9 Hz, 1H), 6.68 (s, 1H), 6.67 (dd, J = 6.6, 1.7 Hz, 1H), 5.89 (s, 2H), 4.25 (dq, J = 6.9, 0.8 Hz, 1H), 3.70 (d, J = 10.7 Hz, 3H), 3.47 (d, J = 10.9 Hz, 3H), 1.35 (dd, J = 7.0, 0.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.5 (d, $J_{P\text{-}C}$ = 161.5 Hz), 148.0, 147.1, 130.1, 122.3, 108.8, 108.4, 101.0, 53.8 (d, $J_{P\text{-}C}$ = 7.3 Hz), 53.3 (d, $J_{P\text{-}C}$ = 7.0 Hz), 52.1 (d, $J_{P\text{-}C}$ = 54.6 Hz), 16.6 (d, $J_{P\text{-}C}$ = 3.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -0.63; **IR** (thin film): 1716, 1685, 1558, 1506, 1488, 1035 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.22; **LRMS** (ESI): Calcd. for $C_{12}H_{15}NaO_6P$ ([M+Na]$^+$): 309.05, Found: 309.14.

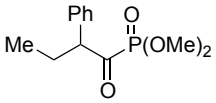


Dimethyl (2-(2-methoxyphenyl)propanoyl)phosphonate (19j): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20j** (137 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19j** (133 mg, 97% yield) as a pale yellow oil. Analytical data for **19j**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (dt, *J* = 8.2, 1.7 Hz, 1H), 7.08 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.90 (dt, *J* = 7.5, 0.6 Hz, 1H), 6.84 (dd, *J* = 8.2, 0.6 Hz, 1H), 4.48 (dq, *J* = 7.0, 1.3 Hz, 1H), 3.76 (s, 3H), 3.63 (d, *J* = 10.7 Hz, 3H), 3.52 (d, *J* = 10.8 Hz, 3H), 1.37 (dd, *J* = 7.0, 0.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 210.1 (d, $J_{P\text{-}C}$ = 163.2 Hz), 156.7, 128.9, 128.7, 126.1, 120.6, 110.5, 55.2, 53.5 (d, $J_{P\text{-}C}$ = 7.3 Hz), 53.2 (d, $J_{P\text{-}C}$ = 7.3 Hz), 46.9 (d, $J_{P\text{-}C}$ = 56.3 Hz), 14.7 (d, $J_{P\text{-}C}$ = 2.3 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -0.46; **IR** (thin film): 1698, 1653, 1541, 1495, 1247, 1029 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.28; **LRMS** (ESI): Calcd. for $C_{12}H_{18}O_5P$ ($[M+H]^+$): 273.09, Found: 273.10.

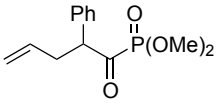


Dimethyl (2-(1-tosyl-1*H*-indol-3-yl)propanoyl)phosphonate (19k): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20k** (219 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19k** (216 mg, 99% yield) as a pale yellow oil. Analytical data for **19k**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.54 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.31-7.28 (m, 2H), 7.22-7.19 (m, 3H), 4.52 (q, *J* = 7.1 Hz, 1H), 3.59 (d, *J* = 10.8 Hz, 3H), 3.37 (d, *J* = 10.9 Hz, 3H), 2.29 (s, 3H), 1.53 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 209.0 (d, $J_{P\text{-}C}$ = 162.9 Hz), 144.9, 134.94, 134.87, 129.7, 129.3, 126.8, 125.0, 124.9, 123.3, 119.5, 118.0, 113.6, 53.8 (d, $J_{P\text{-}C}$ = 7.2 Hz), 53.3 (d, $J_{P\text{-}C}$ = 7.2 Hz), 43.8 (d, $J_{P\text{-}C}$ = 56.0 Hz), 21.4, 15.4; **^{31}P NMR** (243 MHz, $CDCl_3$): δ -0.83; **IR** (thin film): 1695, 1653, 1597, 1448,

1372, 1260, 1175, 1034 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.18; **LRMS** (ESI): Calcd. for $C_{20}H_{23}NO_6PS$ ($[M+H]^+$): 436.10, Found: 436.14.

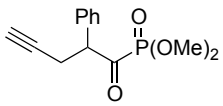


Dimethyl (2-phenylbutanoyl)phosphonate (19l): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20l** (129 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19l** (123 mg, 96% yield) as a pale yellow oil. Analytical data for **19l**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.23-7.18 (m, 3H), 4.15 (t, J = 7.4 Hz, 1H), 3.66 (d, J = 10.7 Hz, 3H), 3.33 (d, J = 10.9 Hz, 3H), 2.10-2.00 (m, 1H), 1.77-1.66 (m, 1H), 0.79 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.6 (d, $J_{P\text{-}C}$ = 161.3 Hz), 134.9, 129.2, 128.7, 127.6, 60.2 (d, $J_{P\text{-}C}$ = 52.2 Hz), 53.8 (d, $J_{P\text{-}C}$ = 7.3 Hz), 53.0 (d, $J_{P\text{-}C}$ = 6.8 Hz), 24.5 (d, $J_{P\text{-}C}$ = 3.4 Hz), 11.6; **^{31}P NMR** (162 MHz, $CDCl_3$): δ -0.77; **IR** (thin film): 2693, 1696, 1653, 1456, 1259, 1033 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.33; **LRMS** (ESI): Calcd. for $C_{12}H_{18}O_4P$ ($[M+H]^+$): 257.10, Found: 257.12.

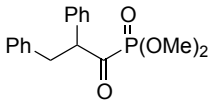


Dimethyl (2-phenylpent-4-enoyl)phosphonate (19m): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20m** (135 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19m** (132 mg, 98% yield) as a pale yellow oil. Analytical data for **19m**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.29-7.23 (m, 3H), 5.68-5.58 (m, 1H), 5.00 (d, J = 26.2 Hz, 1H), 4.97 (d, J = 19.3 Hz, 1H), 4.39 (t, J = 7.5 Hz, 1H), 3.69 (d, J = 10.8 Hz, 3H), 3.36 (d, J = 10.9 Hz, 3H), 2.86-2.78 (m, 1H), 2.51-2.44 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 208.9 (d, $J_{P\text{-}C}$ = 162.8 Hz), 134.5, 134.4, 129.3, 128.8, 127.8, 117.2, 58.1 (d, $J_{P\text{-}C}$ = 53.1 Hz), 53.9 (d, $J_{P\text{-}C}$ = 7.1 Hz), 53.1 (d, $J_{P\text{-}C}$ = 6.9 Hz), 35.4 (d, $J_{P\text{-}C}$ = 3.6 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -0.98; **IR** (thin film): 2958, 1693,

1644, 1496, 1456, 1261, 1032 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.29; **LRMS** (ESI): Calcd. for $C_{13}H_{18}O_4P$ ($[M+H]^+$): 269.10, Found: 269.09.

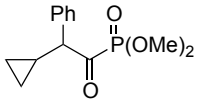


Dimethyl (2-phenylpent-4-ynoyl)phosphonate (19n): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20n** (134 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19n** (126 mg, 95% yield) as a pale yellow oil. Analytical data for **19n**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35-7.33 (m, 2H), 7.29-7.27 (m, 1H), 7.24-7.22 (m, 2H), 4.50 (t, *J* = 7.4 Hz, 1H), 3.67 (d, *J* = 10.8 Hz, 3H), 3.35 (d, *J* = 11.0 Hz, 3H), 2.88 (ddd, *J* = 16.9, 7.4, 2.6 Hz, 1H), 2.60-2.55 (m, 1H), 1.91 (t, *J* = 2.6 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 207.8 (d, J_{P-C} = 166.7 Hz), 133.4, 129.2, 129.0, 128.3, 80.7, 70.2, 57.4 (d, J_{P-C} = 54.4 Hz), 54.0 (d, J_{P-C} = 7.2 Hz), 53.3 (d, J_{P-C} = 6.6 Hz), 20.9 (d, J_{P-C} = 4.2 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$): δ -0.78; **IR** (thin film): 3292, 2958, 1696, 1653, 1456, 1262, 1031 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.25; **LRMS** (ESI): Calcd. for $C_{13}H_{16}O_4P$ ($[M+H]^+$): 267.08, Found: 267.11.

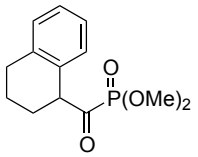


Dimethyl (2,3-diphenylpropanoyl)phosphonate (19o): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20o** (160 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19o** (151 mg, 95% yield) as a pale yellow oil. Analytical data for **19o**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.11 (m, 8H), 7.05 (d, *J* = 7.2 Hz, 2H), 4.63 (t, *J* = 7.4 Hz, 1H), 3.57 (d, *J* = 10.8 Hz, 3H), 3.43 (dd, *J* = 13.9, 7.4 Hz, 1H), 3.32 (d, *J* = 10.9 Hz, 3H), 2.98 (ddd, *J* = 13.9, 7.4, 1.6 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.1 (d, J_{P-C} = 162.6 Hz), 138.4, 134.4, 129.4, 128.9, 128.8, 128.2, 127.8, 126.2, 77.2, 60.3 (d, J_{P-C} = 53.0 Hz), 53.7 (d, J_{P-C} = 7.0 Hz), 53.1 (d, J_{P-C} = 6.7 Hz), 37.6 (d, J_{P-C} = 3.6 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -1.66; **IR** (thin film): 2853, 1716, 1691, 1495, 1454,

1263, 1031, 699 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.30; **LRMS** (ESI): Calcd. for $C_{17}H_{20}O_4P$ ($[M+H]^+$): 319.11, Found: 319.14.



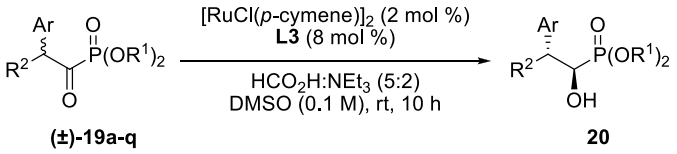
Dimethyl (2-cyclopropyl-2-phenylacetyl)phosphonate (19p): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20p** (135 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19p** (129 mg, 96% yield) as a pale yellow oil. Analytical data for **19p**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.22 (m, 5H), 3.65 (d, J = 10.7 Hz, 3H), 3.47 (d, J = 9.9 Hz, 1H), 3.41 (d, J = 10.9 Hz, 3H), 1.48-1.40 (m, 1H), 0.69-0.62 (m, 1H), 0.53-0.46 (m, 1H), 0.34-0.28 (m, 1H), 0.17-0.11 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.7 (d, J_{P-C} = 159.7 Hz), 135.2, 128.9, 128.7, 127.6, 63.3 (d, J_{P-C} = 53.4 Hz), 53.8 (d, J_{P-C} = 7.2 Hz), 53.2 (d, J_{P-C} = 6.9 Hz), 12.3 (d, J_{P-C} = 4.2 Hz), 4.9, 3.4 (d, J_{P-C} = 1.1 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ -0.83; **IR** (thin film): 3006, 1696, 1653, 1456, 1258, 1034 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.35; **LRMS** (ESI): Calcd. for $C_{13}H_{18}O_4P$ ($[M+H]^+$): 269.10, Found: 269.09.



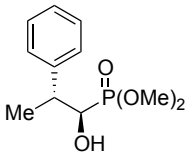
Dimethyl (1,2,3,4-tetrahydronaphthalene-1-carbonyl)phosphonate (19q): The title compound was prepared according to General Procedure B using β-aryl-α-hydroxy phosphonate **20q** (135 mg, 0.50 mmol) affording α-aryl acyl phosphonate **19q** (131 mg, 97% yield) as a pale yellow oil. Analytical data for **19q**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17-7.09 (m, 3H), 6.95 (d, J = 8.6 Hz, 1H), 4.41 (q, J = 6.2 Hz, 1H), 3.78 (d, J = 10.7 Hz, 3H), 3.76 (d, J = 10.8 Hz, 3H), 2.81-2.73 (m, 2H), 2.27-2.21 (m, 1H), 2.14-2.09 (m, 1H), 1.84-1.73 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 211.3 (d, J_{P-C} = 159.4 Hz), 137.9, 131.0 (d, J_{P-C} = 4.0 Hz), 129.5, 129.4, 127.1, 125.7, 77.2, 53.8 (d, J_{P-C} = 7.5 Hz), 53.7 (d, J_{P-C} = 7.4 Hz), 52.3 (d, J_{P-C} = 55.2 Hz), 28.7, 24.5, 19.8; **^{31}P NMR** (162 MHz, $CDCl_3$): δ -0.85; **IR**

(thin film): 2955, 1694, 1558, 1496, 1456, 1254, 1183 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.60; **LRMS** (ESI): Calcd. for $C_{13}H_{18}O_4P$ ($[M+H]^+$): 269.10, Found: 269.09.

General Procedure C for the DKR-ATH of α-Aryl Acyl Phosphonates 19a-q

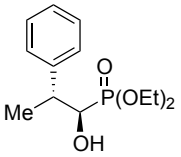


A flame-dried 1-dram vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv) and **L3** (7.5 mg, 0.0124 mmol, 0.08 equiv) in DMSO (0.5 mL). The vial was purged with N_2, capped, and stirred at 60 ºC for 30 min. After cooling to room temperature, a solution of α-aryl acyl phosphonate **19** (0.1550 mmol, 1.00 equiv) in DMSO (1.0 mL) and formic acid:triethylamine (5:2) (67 mg, 0.7750 mmol, 5.00 equiv) were added to the reaction. The vial was purged with N_2, capped, and stirred at room temperature for 10 h. The reaction was diluted with EtOAc (20 mL) and washed with H_2O (2 x 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{31}P NMR analysis of the crude residue. The crude residue was purified by column chromatography on silica gel to afford β-aryl-α-hydroxy phosphonate **20**.

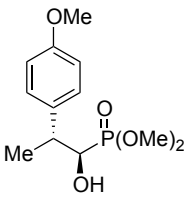


Dimethyl ((1*R*,2*R*)-1-hydroxy-2-phenylpropyl)phosphonate (20a): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19a** (37.5 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20a** (34.3 mg, 91% yield) as a pale yellow oil. Analytical data for **20a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.29 (m, 4H), 7.25-7.19 (m, 1H), 4.06 (t, J = 6.4 Hz, 1H), 3.66 (d, J = 10.4 Hz, 3H), 3.60 (d, J = 10.4 Hz, 3H), 3.42 (br s, 1H), 3.28-3.20 (m, 1H), 1.45 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.6 (d, $J_{P\text{-}C}$ = 10.2 Hz), 128.4, 127.8, 126.7, 72.3 (d, $J_{P\text{-}C}$

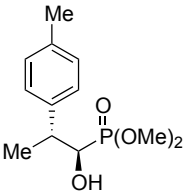
= 158.8 Hz), 53.0 (d, $J_{P\text{-}C}$ = 7.5 Hz), 52.9 (d, $J_{P\text{-}C}$ = 7.5 Hz), 41.2 (d, $J_{P\text{-}C}$ = 3.2 Hz), 16.4 (d, $J_{P\text{-}C}$ = 7.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 26.23; **IR** (thin film): 3289, 2359, 1219, 1044, 700 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.36; **LRMS** (ESI): Calcd. for $C_{13}H_{22}O_4P$ ($[M+H]^+$): 245.10, Found: 245.08; **HPLC** Chiralpak IC, H:IPA = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 13.3 min (major diastereomer, major isomer), 15.8 min (minor diastereomer), 24.0 min (major diastereomer, minor isomer), 25.8 min (minor diastereomer), >99.5:0.5 er; **$[\alpha]_D$** +1 (*c* = 1.3, $CHCl_3$).



Diethyl ((1*R*,2*R*)-1-hydroxy-2-phenylpropyl)phosphonate (20b): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19b** (41.9 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20b** (39.4 mg, 93% yield) as a pale yellow oil. Analytical data for **20b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.28 (m, 4H), 7.23-7.18 (m, 1H), 4.08-3.91 (m, 5H), 3.57 (br s, 1H), 3.28-3.19 (m, 1H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 144.0 (d, $J_{P\text{-}C}$ = 10.1 Hz), 128.3, 127.8, 126.6, 72.4 (d, $J_{P\text{-}C}$ = 158.8 Hz), 62.4 (d, $J_{P\text{-}C}$ = 7.4 Hz), 41.2 (d, $J_{P\text{-}C}$ = 3.0 Hz), 16.6 (d, $J_{P\text{-}C}$ = 7.1 Hz), 16.31 (d, $J_{P\text{-}C}$ = 5.1 Hz), 16.26 (d, $J_{P\text{-}C}$ = 5.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 24.02; **IR** (thin film): 3429, 2925, 1645, 1454, 1216, 1026, 700 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.50; **LRMS** (ESI): Calcd. for $C_{11}H_{18}O_4P$ ($[M+H]^+$): 273.11, Found: 273.10; **HPLC** Chiralpak IC, H:IPA = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, 5.8 min (major diastereomer, major isomer), 6.4 min (minor diastereomer), 7.4 min (major diastereomer, minor isomer), 8.5 min (minor diastereomer), >99.5:0.5 er; **$[\alpha]_D$** +1 (*c* = 1.4, $CHCl_3$).

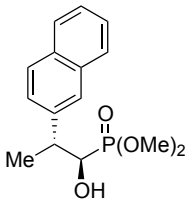


Dimethyl ((1*R*,2*R*)-1-hydroxy-2-(4-methoxyphenyl)propyl)phosphonate (20d): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19d** (42.2 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20d** (39.2 mg, 92% yield) as a pale yellow oil. Analytical data for **20d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.01 (t, J = 6.2 Hz, 1H), 3.78 (s, 3H), 3.67 (d, J = 10.4 Hz, 3H), 3.61 (d, J = 10.4 Hz, 3H), 3.32 (t, J = 7.0 Hz, 1H), 3.25-3.16 (m, 1H), 1.42 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.3, 135.6 (d, $J_{P\text{-}C}$ = 10.4 Hz), 128.8, 113.7, 72.5 (d, $J_{P\text{-}C}$ = 158.1 Hz), 55.2, 53.0 (d, $J_{P\text{-}C}$ = 7.4 Hz), 52.9 (d, $J_{P\text{-}C}$ = 7.3 Hz), 40.3 (d, $J_{P\text{-}C}$ = 3.1 Hz), 16.5 (d, $J_{P\text{-}C}$ = 7.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 26.34; **IR** (thin film): 3320, 1514, 1247, 1039, 832, 759 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.28; **LRMS** (ESI): Calcd. for $C_{12}H_{19}NaO_5P$ ($[M+Na]^+$): 297.09, Found: 297.04; **HPLC** Chiralpak IC, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 13.9 min (major diastereomer, major isomer), 16.8 min (minor diastereomer), 23.2 min (major diastereomer, minor isomer), 24.9 min (minor diastereomer), >99.5:0.5 er; **$[\alpha]_D$** +5 (c = 1.0, $CHCl_3$).

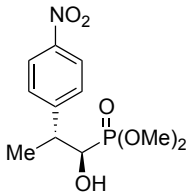


Dimethyl ((1*R*,2*R*)-1-hydroxy-2-(*p*-tolyl)propyl)phosphonate (20e): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19e** (39.7 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20e** (36.2 mg, 90% yield) as a white solid (mp: 62-64 °C). Analytical data for **20e**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.18 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 4.03 (t, J = 6.2 Hz, 1H), 3.68 (br s, 1H), 3.66 (d, J = 10.4 Hz, 3H), 3.59 (d, J = 10.4 Hz, 3H), 3.23-3.19 (m, 1H), 2.31 (s, 3H), 1.43 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 140.6 (d, $J_{P\text{-}C}$ = 10.1 Hz), 136.2, 129.0, 127.6, 72.3 (d, $J_{P\text{-}C}$ = 158.2 Hz), 53.0 (d, $J_{P\text{-}C}$ = 7.1 Hz), 52.9 (d, $J_{P\text{-}C}$ = 6.9 Hz), 40.7 (d, $J_{P\text{-}C}$ = 3.6 Hz), 21.0, 16.4 (d, $J_{P\text{-}C}$ = 6.9 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$): δ 27.05; **IR**

(thin film): 3324, 2956, 1515, 1456, 1218, 1042, 823 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.38; **LRMS** (ESI): Calcd. for $C_{12}H_{20}O_4P$ ($[M+H]^+$): 259.11, Found: 259.09; **HPLC** Chiralpak IB, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 10.8 min (major diastereomer, major isomer), 12.8 min (major diastereomer, minor isomer), 13.9 min (minor diastereomer), 15.5 min (minor diastereomer), >99.5:0.5 er; $[\alpha]_D$ +7 (*c* = 1.5, $CHCl_3$).

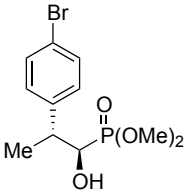


Dimethyl ((1*R*,2*R*)-1-hydroxy-2-(naphthalen-2-yl)propyl)phosphonate (20f): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19f** (45.3 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20f** (42.4 mg, 93% yield) as a pale yellow oil. Analytical data for **20f**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81-7.78 (m, 3H), 7.75 (s, 1H), 7.47-7.41 (m, 3H), 4.17 (br s, 1H), 3.77 (br s, 1H), 3.64 (d, *J* = 10.4 Hz, 3H), 3.56 (d, *J* = 10.4 Hz, 3H), 3.47-3.39 (m, 1H), 1.55 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 141.2 (d, J_{P-C} = 10.4 Hz), 133.4, 132.4, 127.9, 127.7, 127.5, 126.3, 126.2, 125.9, 125.5, 72.2 (d, J_{P-C} = 159.2 Hz), 53.0 (d, J_{P-C} = 7.5 Hz), 52.9 (d, J_{P-C} = 7.6 Hz), 41.3 (d, J_{P-C} = 6.5 Hz), 16.3 (d, J_{P-C} = 7.0 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 26.21; **IR** (thin film): 3300, 1218, 1050, 824, 753 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.38; **LRMS** (ESI): Calcd. for $C_{15}H_{20}O_4P$ ($[M+H]^+$): 295.11, Found: 295.13; **HPLC** Chiralpak IC, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 11.0 min (major diastereomer, major isomer), 13.8 min (minor diastereomer), 15.9 min (major diastereomer, minor isomer), 20.2 min (minor diastereomer), >99.5:0.5 er; $[\alpha]_D$ +8 (*c* = 1.6, $CHCl_3$).

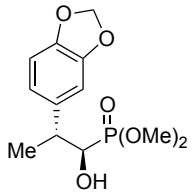


Dimethyl ((1*R*,2*R*)-1-hydroxy-2-(4-nitrophenyl)propyl)phosphonate (20g): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19g** (44.5 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20g** (38.6 mg, 86% yield, 19:1 dr) as a pale yellow oil. Analytical data for **20g**: **^{1}H**

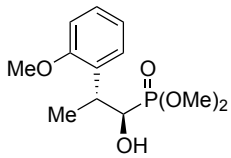
NMR (600 MHz, $CDCl_3$): δ 8.16 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 4.05 (t, J = 6.1 Hz, 1H), 4.00 (br s, 1H), 3.69 (d, J = 10.4 Hz, 6H), 3.36-3.31 (m, 1H), 1.47 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 151.6 (d, $J_{P\text{-}C}$ = 11.6 Hz), 146.8, 128.7, 123.5, 71.5 (d, $J_{P\text{-}C}$ = 159.0 Hz), 53.3 (d, $J_{P\text{-}C}$ = 7.7 Hz), 53.2 (d, $J_{P\text{-}C}$ = 7.9 Hz), 41.2 (d, $J_{P\text{-}C}$ = 3.2 Hz), 16.1 (d, $J_{P\text{-}C}$ = 6.3 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$): δ 21.59; **IR** (thin film): 3397, 1519, 1349, 1217, 1039, 857 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.30; **LRMS** (ESI): Calcd. for $C_{11}H_{17}NO_6P$ ($[M+H]^+$): 290.08, Found: 290.07; **HPLC** Chiralpak IB, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 30.5 min (major diastereomer, major isomer), 33.3 min (major diastereomer, minor isomer), 36.4 min (minor diastereomer), 40.7 min (minor diastereomer), >99.5:0.5 er; **[α]$_D$** +4 (c = 1.0, $CHCl_3$).



Dimethyl ((1*R*,2*R*)-2-(4-bromophenyl)-1-hydroxypropyl)phosphonate (20h): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19h** (49.8 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20h** (46.7 mg, 93% yield) as a pale yellow oil. Analytical data for **20h**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 4.17 (br s, 1H), 3.98 (t, J = 6.4 Hz, 1H), 3.65 (d, J = 10.4 Hz, 3H), 3.61 (d, J = 10.4 Hz, 3H), 3.22-3.14 (m, 1H), 1.41 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 142.8 (d, $J_{P\text{-}C}$ = 10.4 Hz), 131.3, 129.6, 120.3, 71.9 (d, $J_{P\text{-}C}$ = 159.3 Hz), 53.1 (d, $J_{P\text{-}C}$ = 7.3 Hz), 53.0 (d, $J_{P\text{-}C}$ = 7.1 Hz), 40.7 (d, $J_{P\text{-}C}$ = 3.7 Hz), 14.4 (d, $J_{P\text{-}C}$ = 7.1 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 26.55; **IR** (thin film): 3429, 2153, 1646, 1488, 1407, 1217, 1039, 1010 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.39; **LRMS** (ESI): Calcd. for $C_{11}H_{17}BrO_4P$ ($[M+H]^+$): 323.01, Found: 323.02; **HPLC** Chiralpak IB, H:IPA = 93:7, flow rate = 1.0 mL/min, λ = 230 nm, 10.0 min (major diastereomer, major isomer), 11.0 min (major diastereomer, minor isomer), 12.0 min (minor diastereomer), 12.9 min (minor diastereomer), >99.5:0.5 er; **[α]$_D$** +8 (c = 1.9, $CHCl_3$).

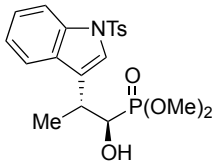


Dimethyl ((1*R*,2*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-1-hydroxypropyl)phosphonate (20i): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19i** (44.4 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20i** (41.6 mg, 93% yield) as a pale yellow oil. Analytical data for **20i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.81 (s, 1H), 6.73 (s, 2H), 5.91 (s, 2H), 3.99 (q, *J* = 6.9 Hz, 1H), 3.69 (d, *J* = 10.4 Hz, 3H), 3.65 (d, *J* = 10.5 Hz, 3H), 3.58 (t, *J* = 7.0 Hz, 1H), 3.21-3.12 (m, 1H), 1.39 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.5, 146.1, 137.7 (d, $J_{P\text{-}C}$ = 11.1 Hz), 120.8, 108.2, 108.0, 100.8, 72.3 (d, $J_{P\text{-}C}$ = 158.3 Hz), 53.1 (d, $J_{P\text{-}C}$ = 7.6 Hz), 53.0 (d, $J_{P\text{-}C}$ = 7.0 Hz), 40.8 (d, $J_{P\text{-}C}$ = 3.5 Hz), 16.4 (d, $J_{P\text{-}C}$ = 6.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 26.19; **IR** (thin film): 3299, 1489, 1440, 1244, 1038, 930, 834 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.30; **LRMS** (ESI): Calcd. for $C_{12}H_{18}O_6P$ ($[M+H]^+$): 289.09, Found: 289.14; **HPLC** Chiralpak IC, H:IPA = 80:20, flow rate = 1.0 mL/min, λ = 230 nm, 11.6 min (major diastereomer, major isomer), 13.6 min (minor isomer), 14.7 min (major diastereomer, minor isomer), 24.4 min (minor isomer), >99.5:0.5 er; **$[\alpha]_D$** +8 (*c* = 0.9, $CHCl_3$).

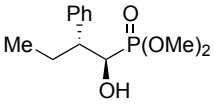


Dimethyl ((1*R*,2*R*)-1-hydroxy-2-(2-methoxyphenyl)propyl)phosphonate (20j): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19j** (42.2 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20j** (35.7 mg, 84% yield, 6:1 dr) as a pale yellow oil. Analytical data for **20j**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.21-7.18 (m, 1H), 6.95-6.87 (m, 1H); 6.84 (d, *J* = 8.1 Hz, 1H), 4.26-4.23 (m, 1H), 3.81 (s, 3H), 3.69 (d, *J* = 10.4 Hz, 3H), 3.65 (d, *J* = 10.4 Hz, 3H), 3.65-3.58 (m, 1H), 3.52 (t, *J* = 7.5 Hz, 1H), 1.41 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 156.6, 131.6 (d, $J_{P\text{-}C}$ = 12.2 Hz), 128.9, 127.6, 120.6, 110.4, 70.6 (d, $J_{P\text{-}C}$ = 158.7 Hz), 55.3, 53.0 (d, $J_{P\text{-}C}$ = 7.1 Hz), 52.8 (d, $J_{P\text{-}C}$ = 6.8 Hz), 35.1, 14.4 (d, $J_{P\text{-}C}$

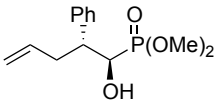
= 5.6 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$): δ 26.68; **IR** (thin film): 3314, 2955, 1493, 1457, 1241, 1032, 833 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.32; **LRMS** (ESI): Calcd. for $C_{12}H_{20}O_5P$ ($[M+H]^+$): 275.11, Found: 275.14; **HPLC** Chiralpak IB, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 6.9 min (major diastereomer, major isomer), 7.6 min (major diastereomer, minor isomer), 9.3 min (minor diastereomer), 16.3 min (minor diastereomer), 98.5:1.5 er; **$[\alpha]_D$** -15 (*c* = 0.5, $CHCl_3$).



Dimethyl ((1*R*,2*R*)-1-hydroxy-2-(1-tosyl-1*H*-indol-3-yl)propyl)phosphonate (20k): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19k** (67.5 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20k** (63.9 mg, 94% yield) as a white solid (mp: 134-136 °C). Analytical data for **20k**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 6.5 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.23-7.17 (m, 3H), 4.17 (br s, 1H), 3.86 (t, *J* = 7.0 Hz, 1H), 3.63 (d, *J* = 10.4 Hz, 6H), 3.53-3.45 (m, 1H), 2.30 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 144.7, 135.1 (d, J_{P-C} = 15.2 Hz), 129.8, 129.7, 126.7, 125.1, 124.9, 124.6, 123.6, 123.0, 119.5, 113.7, 70.4 (d, J_{P-C} = 160.6 Hz), 53.1 (d, J_{P-C} = 7.4 Hz), 53.0 (d, J_{P-C} = 7.0 Hz), 32.1 (d, J_{P-C} = 4.2 Hz), 21.5, 14.8 (d, J_{P-C} = 4.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 25.89; **IR** (thin film): 3286, 1597, 1447, 1366, 1215, 1174, 1035, 748 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.40; **LRMS** (ESI): Calcd. for $C_{20}H_{24}NaNO_6PS$ ($[M+Na]^+$): 460.10, Found: 460.09; **HPLC** Chiralpak IC, H:IPA = 65:35, flow rate = 1.0 mL/min, λ = 210 nm, 15.8 min (major diastereomer, major isomer), 18.2 min (minor diastereomer), 28.1 min (minor diastereomer), 36.8 min (major diastereomer, minor isomer), >99.5:0.5 er; **$[\alpha]_D$** -19 (*c* = 3.1, $CHCl_3$).

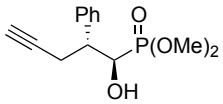


Dimethyl ((1*R*,2*R*)-1-hydroxy-2-phenylbutyl)phosphonate (20l): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19l** (39.7 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20l** (35.2 mg, 88% yield) as a pale yellow oil. Analytical data for **20l**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H), 4.07 (t, J = 7.1 Hz, 1H), 4.05 (br s, 1H), 3.64 (d, J = 10.4 Hz, 3H), 3.50 (d, J = 10.5 Hz, 3H), 2.99-2.92 (m, 1H), 2.29-2.19 (m, 1H), 1.78-1.67 (m, 1H), 0.77 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 141.1 (d, $J_{P\text{-}C}$ = 7.4 Hz), 128.7, 128.2, 126.7, 72.0 (d, $J_{P\text{-}C}$ = 158.9 Hz), 53.0 (d, $J_{P\text{-}C}$ = 7.2 Hz), 52.8 (d, $J_{P\text{-}C}$ = 7.2 Hz), 49.2 (d, $J_{P\text{-}C}$ = 3.1 Hz), 23.8 (d, $J_{P\text{-}C}$ = 9.2 Hz), 11.7; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 26.60; **IR** (thin film): 3301, 2957, 1227, 1051, 835 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.39; **LRMS** (ESI): Calcd. for $C_{12}H_{20}O_4P$ ([M+H]$^+$): 259.11, Found: 259.09; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 19.7 min (major diastereomer, major isomer), 24.7 min (minor diastereomer), 36.4 min (minor diastereomer), 38.4 min (major diastereomer, minor isomer), >99.5:0.5 er; **$[\alpha]_D$** -4 (c = 1.6, $CHCl_3$).

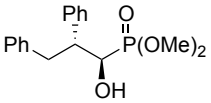


Dimethyl ((1*R*,2*R*)-1-hydroxy-2-phenylpent-4-en-1-yl)phosphonate (20m): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19m** (41.6 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20m** (39.2 mg, 94% yield) as a pale yellow oil. Analytical data for **20m**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H), 5.66-5.55 (m, 1H), 4.96 (d, J = 35.5 Hz, 1H), 4.93 (d, J = 28.6 Hz, 1H), 4.23 (br s, 1H), 4.10 (t, J = 6.9 Hz, 1H), 3.61 (d, J = 10.4 Hz, 3H), 3.49 (d, J = 10.5 Hz, 3H), 3.20-3.13 (m, 1H), 2.97-2.91 (m, 1H), 2.58-2.50 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.7 (d, $J_{P\text{-}C}$ = 6.7 Hz), 136.1, 128.8, 128.2, 126.8, 116.5, 71.7 (d, $J_{P\text{-}C}$ = 159.4 Hz), 53.0 (d, $J_{P\text{-}C}$ = 7.1 Hz), 52.9 (d, $J_{P\text{-}C}$ = 7.2 Hz), 47.4 (d, $J_{P\text{-}C}$ = 3.6 Hz), 35.4 (d, $J_{P\text{-}C}$ = 9.4 Hz); **^{31}P**

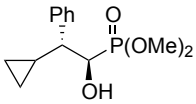
NMR (162 MHz, $CDCl_3$): δ 26.26; **IR** (thin film): 3431, 1646, 2135, 1217, 1054 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.36; **LRMS** (ESI): Calcd. for $C_{13}H_{20}O_4P$ ($[M+H]^+$): 271.11, Found: 271.12; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 18.0 min (major diastereomer, major isomer), 20.2 min (minor diastereomer), 25.4 min (minor diastereomer), 32.0 min (major diastereomer, minor isomer), >99.5:0.5 er; $[\alpha]_D$ -7 (*c* = 0.3, $CHCl_3$).



Dimethyl ((1*R*,2*R*)-1-hydroxy-2-phenylpent-4-yn-1-yl)phosphonate (20n): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19n** (41.3 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20n** (37.9 mg, 91% yield, 14:1 dr) as a pale yellow oil. Analytical data for **20n**: ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 7.38-7.31 (m, 4H), 7.28-7.25 (m, 1H), 4.51 (dd, *J* = 7.2, 4.4 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 1H), 3.60 (d, *J* = 10.5 Hz, 3H), 3.47 (d, *J* = 10.5 Hz, 3H), 3.32 (ddd, *J* = 16.9, 9.7, 3.6 Hz, 1H), 2.96 (dt, *J* = 16.9, 3.6 Hz, 1H), 2.78 (ddd, *J* = 16.9, 9.7, 2.5 Hz, 1H), 1.91 (t, *J* = 2.6 Hz, 1H); ^{13}**C NMR** (101 MHz, $CDCl_3$): δ 140.0 (d, J_{P-C} = 5.7 Hz), 128.6, 128.2, 127.3, 82.3, 70.6 (d, J_{P-C} = 161.4 Hz), 70.2, 53.1 (d, J_{P-C} = 7.3 Hz), 53.0 (d, J_{P-C} = 7.3 Hz), 46.0 (d, J_{P-C} = 4.3 Hz), 21.6 (d, J_{P-C} = 11.0 Hz); ^{31}**P NMR** (162 MHz, $CDCl_3$): δ 25.83; **IR** (thin film): 3289, 2955, 1684, 1219, 1055, 834 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.35; **LRMS** (ESI): Calcd. for $C_{13}H_{18}O_4P$ ($[M+H]^+$): 269.10, Found: 269.09; **HPLC** Chiralpak IC, H:IPA = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 14.0 min (minor diastereomer), 16.0 min (minor diastereomer), 18.7 min (major diastereomer, major isomer), 25.8 min (major diastereomer, minor isomer), >99.5:0.5 er; $[\alpha]_D$ +11 (*c* = 1.1, $CHCl_3$).

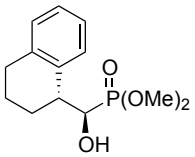


Dimethyl ((1*R*,2*R*)-1-hydroxy-2,3-diphenylpropyl)phosphonate (20o): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19o** (49.3 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20o** (44.3 mg, 89% yield, 19:1 dr) as a pale yellow oil. Analytical data for **20o**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.07 (m, 8H), 6.97-6.95 (m, 2H), 4.74 (br s, 1H), 4.19 (t, J = 6.6 Hz, 1H), 3.65 (d, J = 10.4 Hz, 3H), 3.67-3.59 (m, 1H), 3.39 (d, J = 10.2 Hz, 3H), 3.43-3.33 (m, 1H), 2.93 (dd, J = 13.3, 11.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.4 (d, $J_{P\text{-}C}$ = 5.9 Hz), 139.8, 129.3, 128.9, 128.0, 127.8, 126.7, 125.6, 71.5 (d, $J_{P\text{-}C}$ = 159.9 Hz), 53.2 (d, $J_{P\text{-}C}$ = 7.1 Hz), 52.8 (d, $J_{P\text{-}C}$ = 7.5 Hz), 49.8 (d, $J_{P\text{-}C}$ = 4.9 Hz), 37.8 (d, $J_{P\text{-}C}$ = 10.0 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$): δ 26.57; **IR** (thin film): 3276, 3028, 1603, 1454, 1222, 1057, 831 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.42; **LRMS** (ESI): Calcd. for $C_{17}H_{21}NaO_4P$ ([M+Na]$^+$): 343.11, Found: 343.14; **HPLC** Chiralpak IC, H:IPA = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 10.8 min (major diastereomer, major isomer), 11.6 min (minor diastereomer), 14.7 min (minor diastereomer), 16.3 min (major diastereomer, minor isomer), >99.5:0.5 er; **$[\alpha]_D$** -52 (c = 2.5, $CHCl_3$).



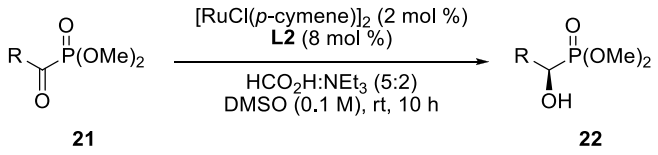
Dimethyl ((1*R*,2*R*)-2-cyclopropyl-1-hydroxy-2-phenylethyl)phosphonate (20p): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19p** (41.6 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20p** (36.1 mg, 86% yield, 5:1 dr) as a pale yellow oil. Analytical data for **20p**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35-7.28 (m, 4H), 7.24-7.20 (m, 1H), 4.23 (t, J = 6.4 Hz, 1H), 3.68 (d, J = 10.4 Hz, 3H), 3.52 (d, J = 10.5 Hz, 3H), 3.38 (br s, 1H), 2.44-2.39 (m, 1H), 1.38-1.32 (m, 1H), 0.74-0.70 (m, 1H), 0.53-0.49 (m, 1H), 0.47-0.43 (m, 1H), 0.02-(-)0.02 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 141.8 (d, $J_{P\text{-}C}$ = 9.2 Hz), 128.4, 128.2, 126.7, 72.4 (d, $J_{P\text{-}C}$ = 159.8 Hz), 53.1 (d, $J_{P\text{-}C}$ = 7.6 Hz), 52.6 (d, $J_{P\text{-}C}$ = 6.9 Hz), 51.9 (d, $J_{P\text{-}C}$ = 3.6 Hz), 12.0 (d, $J_{P\text{-}C}$ = 8.2 Hz), 6.8,

3.0; **^{31}P NMR** (243 MHz, $CDCl_3$): δ 25.42; **IR** (thin film): 3420, 1218, 1036, 701 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.36; **LRMS** (ESI): Calcd. for $C_{13}H_{19}NaO_4P$ ([M+Na]$^+$): 293.09, Found: 293.09; **HPLC** Chiralpak IB, H:IPA = 96:4, flow rate = 1.0 mL/min, λ = 210 nm, 15.2 min (major diastereomer, major isomer), 16.2 min (minor diastereomer), 17.4 min (major diastereomer, minor isomer), 22.8 min (minor diastereomer), >99.5:0.5 er; **[α]$_D$** -13 (*c* = 0.3, $CHCl_3$).

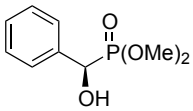


Dimethyl ((*R*)-hydroxy((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)phosphonate (20q): The title compound was prepared according to General Procedure C using α-aryl acyl phosphonate **19q** (41.6 mg, 0.1550 mmol) affording β-aryl-α-hydroxy phosphonate **20q** (38.2 mg, 91% yield) as a white solid (mp: 105-106 °C). Analytical data for **20q**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 1H), 7.17-7.07 (m, 3H), 4.54 (d, *J* = 10.8 Hz, 1H), 3.80 (d, *J* = 10.4 Hz, 3H), 3.78 (d, *J* = 10.5 Hz, 3H), 3.36-3.30 (m, 1H), 2.82-2.68 (m, 3H), 2.13-1.97 (m, 3H), 1.72-1.65 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.5, 135.9 (d, J_{P-C} = 15.2 Hz), 129.4, 127.5, 126.2, 126.0, 71.7 (d, J_{P-C} = 162.0 Hz), 53.2 (d, J_{P-C} = 7.2 Hz), 53.0 (d, J_{P-C} = 7.3 Hz), 39.5 (d, J_{P-C} = 4.4 Hz), 29.6, 23.7 (d, J_{P-C} = 3.6 Hz), 21.5; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 26.47; **IR** (thin film): 3292, 1541, 1466, 1217, 1038, 833 cm^{-1}; **TLC** (50% acetone:hexanes): R_f = 0.38; **LRMS** (ESI): Calcd. for $C_{13}H_{19}NaO_4P$ ([M+Na]$^+$): 293.09, Found: 293.09; **HPLC** Chiralpak IC, H:IPA = 88:15, flow rate = 1.0 mL/min, λ = 210 nm, 10.7 min (major diastereomer, major isomer), 12.8 min (minor isomer), 14.1 min (major diastereomer, minor isomer), 19.7 min (minor isomer), >99.5:0.5 er; **[α]$_D$** -36 (*c* = 0.7, $CHCl_3$).

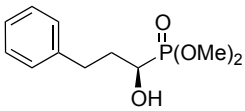
General Procedure D for the ATH of Acyl Phosphonates 21a-d



A flame-dried 1-dram vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv) and **L2** (6.3 mg, 0.0124 mmol, 0.08 equiv) in DMSO (0.5 mL). The vial was purged with N_2, capped, and stirred at 60 ºC for 30 min. After cooling to room temperature, a solution of acyl phosphonate **21** (0.1550 mmol, 1.00 equiv) in DMSO (1.0 mL) and formic acid:triethylamine complex (5:2) (67 mg, 0.7750 mmol, 5.00 equiv) were added to the reaction. The vial was purged with N_2, capped, and stirred at room temperature for 10 h. The reaction was diluted with EtOAc (20 mL) and washed with H_2O (2 x 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford α-hydroxy phosphonate **22**.

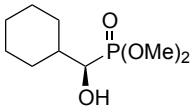


(*R*)-Dimethyl (hydroxy(phenyl)methyl)phosphonate (22a): The title compound was prepared according to General Procedure D using acyl phosphonate **21a** (33.2 mg, 0.1550 mmol) affording α-hydroxy phosphonate **22a** (31.8 mg, 95% yield) as a white solid (mp: 92-93 °C) whose spectral properties matched those reported in the literature.[5] Analytical data for **22a**: **HPLC** Chiralpak IC, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 24.1 min (minor isomer), 24.6 min (major isomer), 92:8 er; $[\alpha]_D$ +38 (*c* = 0.3, $CHCl_3$).

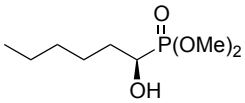


(*R*)-Dimethyl (1-hydroxy-3-phenylpropyl)phosphonate (22b): The title compound was prepared according to General Procedure D using acyl phosphonate **21b** (37.5 mg, 0.1550 mmol) affording α-hydroxy phosphonate **22b** (35.6 mg, 94%

yield) as a pale yellow oil whose spectral properties matched those reported in the literature.[2g] Analytical data for **22b**: **HPLC** Chiralpak IC, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 10.3 min (major isomer), 11.2 min (minor isomer), >99.5:0.5 er; $[\alpha]_D$ -16 (*c* = 0.8, $CHCl_3$).

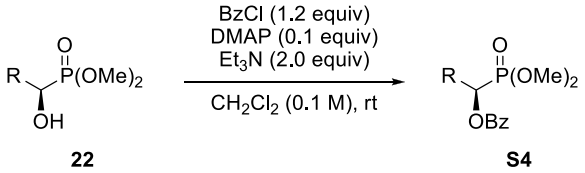


(*R*)-Dimethyl (cyclohexyl(hydroxy)methyl)phosphonate (22c): The title compound was prepared according to General Procedure D using acyl phosphonate **21c** (34.1 mg, 0.1550 mmol) affording α-hydroxy phosphonate **22c** (31.4 mg, 91% yield) as a pale yellow oil whose spectral properties matched those reported in the literature.[27]



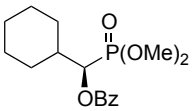
(*R*)-Dimethyl (1-hydroxyhexyl)phosphonate (22d): The title compound was prepared according to General Procedure D using acyl phosphonate **21d** (32.3 mg, 0.1550 mmol) affording α-hydroxy phosphonate **22d** (30.5 mg, 94% yield) as a pale yellow oil whose spectral properties matched those reported in the literature.[7] Analytical data for **22d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91-3.82 (m, 1H), 3.79 (d, *J* = 10.3 Hz, 3H), 3.78 (d, *J* = 10.3 Hz, 3H), 1.75-1.59 (m, 3H), 1.43-1.24 (m, 5H), 0.87 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 67.6 (d, $J_{P\text{-}C}$ = 160.8 Hz), 53.2 (d, $J_{P\text{-}C}$ = 7.8 Hz), 53.1 (d, $J_{P\text{-}C}$ = 7.7 Hz), 31.3 (d, $J_{P\text{-}C}$ = 13.3 Hz), 25.3, 25.2, 22.4, 13.9; **^{31}P NMR** (162 MHz, $CDCl_3$): δ 27.08.

<u>General Procedure E for the Benzoylation of α-Hydroxy Phosphonates 22</u>

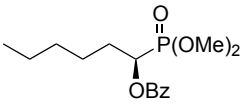


A flame-dried 1-dram vial was charged with α-hydroxy phosphonate **22** (1.0 equiv) in CH_2Cl_2. To the stirred solution was sequentially added benzoyl chloride (1.2 equiv), 4-dimethylaminopyridine (0.1 equiv), and triethylamine (2.0 equiv). After stirring for 2 h at room temperature, the reaction was quenched with sat. aq. NH_4Cl (5 mL). The aqueous layer was

diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford benzoate **S4**.

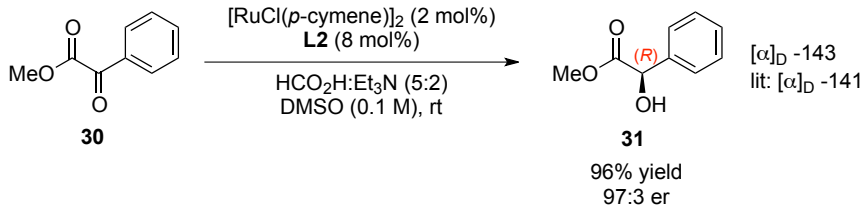


(*R*)-Cyclohexyl(dimethoxyphosphoryl)methyl benzoate (S4c): The title compound was prepared according to General Procedure E using α-hydroxy phosphonate **22c** (34.1 mg, 0.14 mmol) affording benzoate **S4c** (40.7 mg, 89% yield) as a pale yellow oil. Analytical data for **S4c**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 5.38 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.73 (d, *J* = 10.7 Hz, 3H), 3.72 (d, *J* = 10.6 Hz, 3H), 2.06-2.00 (m, 1H), 1.93 (d, *J* = 12.5 Hz, 1H), 1.87 (d, *J* = 12.5 Hz, 1H), 1.70 (d, *J* = 13.0 Hz, 2H), 1.59 (d, *J* = 13.0 Hz, 1H), 1.28-1.05 (m, 5H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 165.3 (d, $J_{P\text{-}C}$ = 5.1 Hz), 133.3, 129.7, 129.1, 128.4, 71.7 (d, $J_{P\text{-}C}$ = 164.7 Hz), 53.2 (d, $J_{P\text{-}C}$ = 7.6 Hz), 52.8 (d, $J_{P\text{-}C}$ = 6.2 Hz), 38.4, 29.7 (d, $J_{P\text{-}C}$ = 7.9 Hz), 28.1 (d, $J_{P\text{-}C}$ = 7.6 Hz), 25.8, 25.7, 25.6; **^{31}P NMR** (243 MHz, $CDCl_3$): δ 22.55; **IR** (thin film): 2930, 1725, 1253, 1109, 1027, 710 cm^{-1}; **TLC** (30% acetone:hexanes): R_f = 0.30; **LRMS** (ESI): Calcd. for $C_{16}H_{24}O_5P$ ([M+H]$^+$): 327.14, Found: 327.16; **HPLC** Chiralpak IA, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 230 nm, 11.5 min (major isomer), 12.6 min (minor isomer), >99.5:0.5 er; **$[\alpha]_D$** -1 (*c* = 1.3, $CHCl_3$).



(*R*)-1-(Dimethoxyphosphoryl)hexyl benzoate (S4d): The title compound was prepared according to General Procedure E using a-hydroxy phosphonate **22d** (30.5 mg, 0.15 mmol) affording benzoate **S4d** (41.2 mg, 91% yield) as a pale yellow oil whose spectral properties matched those reported in the literature.[7] Analytical data for **S4d**: **HPLC** Chiralpak IA, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 9.8 min (major isomer), 10.8 min (minor isomer), >99.5:0.5 er; **$[\alpha]_D$** -8 (*c* = 3.1, $CHCl_3$).

ATH of Methyl Benzoylformate (30)



A flame-dried 1-dram vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv) and **L2** (6.3 mg, 0.0124 mmol, 0.08 equiv) in DMSO (0.5 mL). The vial was purged with N_2, capped, and stirred at 60 ºC for 30 min. After cooling to room temperature, a solution of methyl benzoylformate (**30**) (25.4 mg, 0.1550 mmol, 1.00 equiv) in DMSO (1.0 mL) and formic acid:triethylamine complex (5:2) (67 mg, 0.7750 mmol, 5.00 equiv) were added to the reaction. The vial was purged with N_2, capped, and stirred at room temperature for 10 h. The reaction was diluted with EtOAc (20 mL) and washed with H_2O (2 x 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford methyl mandelate (**22**). The absolute stereochemistry of (*R*)-**22** was determined by comparison to that reported in the literature.[23] Analytical data for **22**: **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 15.3 min (major isomer), 17.0 min (minor isomer), 97:3 er; $\mathbf{[\alpha]_D}$ -143 (*c* = 1.2, $CHCl_3$).

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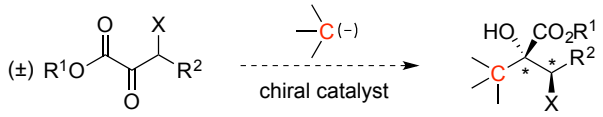
CHAPTER FIVE: DYNAMIC KINETIC ALDOLIZATION OF CONFIGURATIONALLY LABILE ELECTROPHILES*

5.1 Introduction

Deracemization is a valuable method for the generation of chiral molecules from simple racemic starting materials.[1] While there are a plethora of reported dynamic kinetic processes, most are arguably either complexity-neutral transformations (hydrogenation, acylation, etc.) or generate a single chiral center. Dynamic kinetic asymmetric transformations (DyKATs) that utilize a C–C bond forming step in the construction of multiple stereocenters are highly valuable synthetic strategies.[2] In this chapter, we describe DyKATs of racemic β-bromo-α-keto esters through direct aldolization of nitromethane and acetone, providing access to fully-substituted α-glycolic acid derivatives bearing a β-stereocenter (**Scheme 5-1**). Mechanistic studies revealed that the reactions proceed via facile catalyst-mediated racemization of the β-bromo-α-keto esters under a DyKAT Type I manifold.

Scheme 5-1. Dynamic Kinetic Asymmetric Transformations of Configurationally Labile Electrophiles



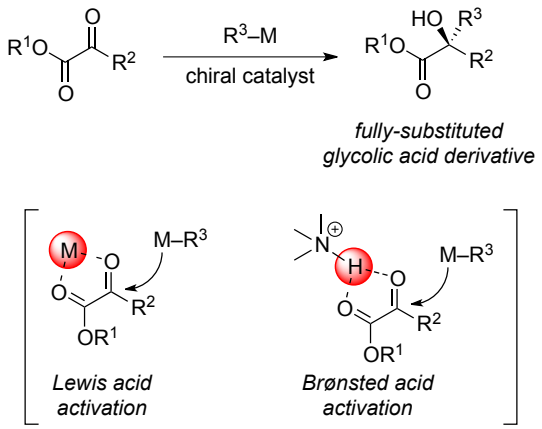
* Reproduced in part by permission of Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim: Corbett, M. T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2013**, *52*, (DOI: 10.1002/anie.201306873).

5.2 Background

5.2.1 Catalytic, Asymmetric Addition of Carbon Nucleophilies to α-Keto Esters

Methods for the catalytic enantioselective addition of carbon nucleophiles to α-keto esters have been extensively developed during the past 15 years as a strategy to directly access fully-substituted α-glycolic acid derivatives (**Scheme 5-2**). In addition to enhancing the electrophilicity of the ketone through inductive effects, the ester moiety provides a 1,2-dicarbonyl motif that is well suited for activation by Lewis or Brønsted acids through chelation. The generation of a five-membered chelate provides a method to directly control the chiral environment of the α-keto ester allowing for enantioselective approach of the carbon nucleophile.

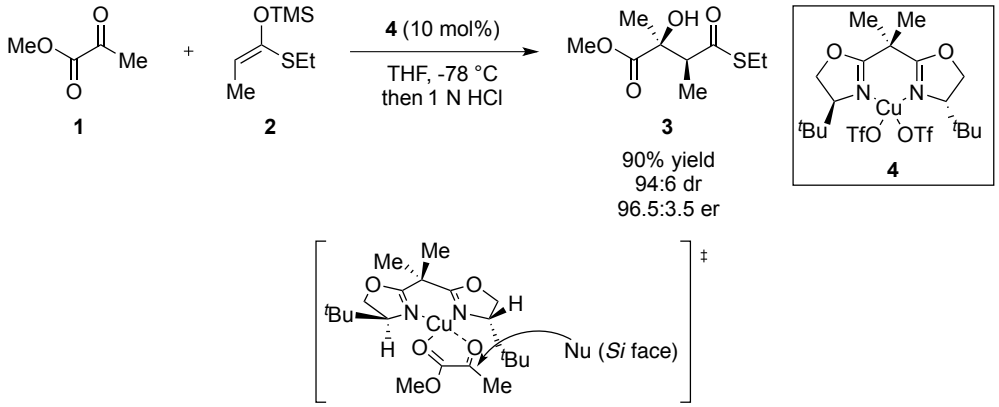
Scheme 5-2. Preparation of Fully-Substituted Glycolates via Nucleophilic Addition to α-Keto Esters



This concept was first developed by Evans as an extension of earlier work in the activation of α-oxy aldehydes.[3] Employing C_2-symmetric (*S*,*S*)-Cu(II) complex **4**, the catalytic enantioselective Mukaiyama aldol addition of silyl enol ethers to pyruvates was developed providing access to fully-substituted glycolic acid derivatives (**Scheme 5-3**).[4] Addition of (*Z*)-silylketene acetal **2** to methyl pyruvate (**1**) afforded **3** in excellent yield with high diastereo- and enantiocontrol. Upon chelation to pyruvate, the C_2-symmetric Cu(II)-complex effectively

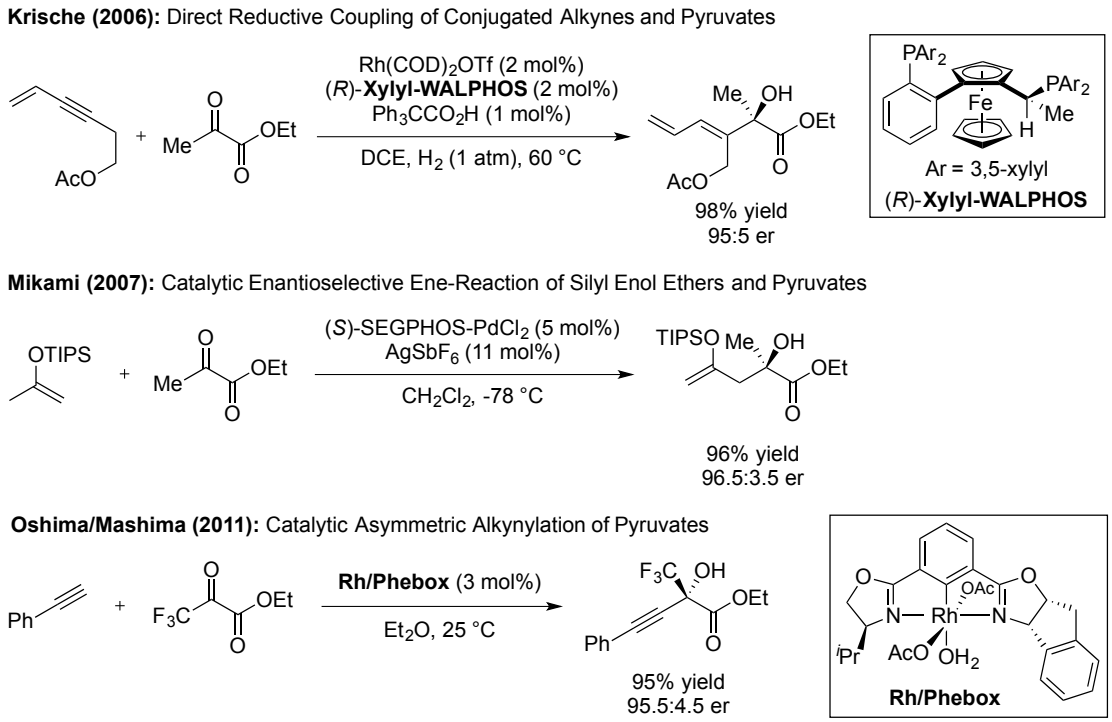
directed addition of the nucleophile to the *Si* face of the carbonyl to avoid approach over the bulky *tert*-butyl group. This activation mode has also found applicability in the vinylogous Mukaiyama aldolization of dienosilanes to α-keto esters.[5]

Scheme 5-3. Catalytic Asymmetric Mukaiyama Aldolization of Pyruvates

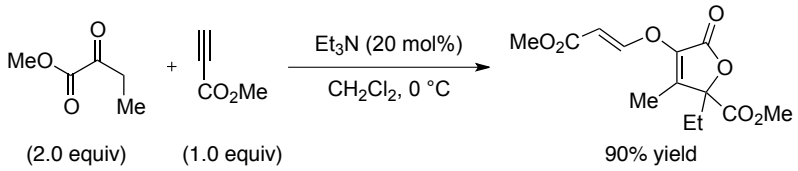


In addition to silyl enol ether nucleophiles, numerous examples have since been reported for the addition of carbon nucleophiles to α-keto esters. Leading examples include Henry additions,[6] direct aldolizations,[7] Alder–ene reactions,[8] arylations,[9] alkynylations,[10] reductive couplings,[11] Friedel–Crafts alkylations,[12] among others[13] (**Scheme 5-4**). These methods largely rely on the use of pyruvates or aryl α-keto esters in order to avoid deleterious side reactions resulting from α-keto ester dimerization, which is facile under basic reaction conditions (**Scheme 5-5**).[14]

Scheme 5-4. Representative Catalytic Enantioselective Additions of Carbon Nucleophiles to α-Keto Esters



Scheme 5-5. Dimerization of α-Keto Esters via Aldol/Cyclization Pathway

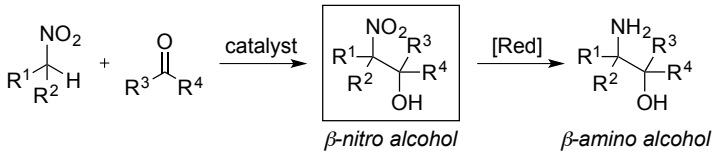


5.2.2 Catalytic Enantioselective Henry Additions to α-Keto Esters

The Henry reaction (or nitroaldol reaction) is a widely employed method for the construction of β-nitro alcohols via addition of nitroalkanes to aldehydes or ketones under acid or base catalysis (**Scheme 5-6**).[15] The products can be reduced to generate valuable β-amino alcohol derivatives.[16] Despite this utility, asymmetric Henry additions into simple un-activated ketones are difficult due to their reversibility under basic reaction conditions limiting methods for their preparation to kinetic resolution strategies.[17] To circumvent reversibility, alternative approaches

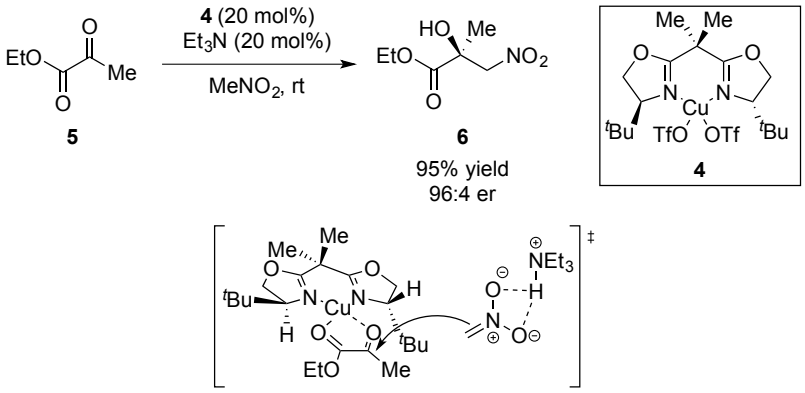
have utilized activated carbonyls, such as α-keto esters[6] or trifluoromethyl ketones,[18] to access chiral tertiary nitroladol adducts.

Scheme 5-6. Preparation of β-Amino Alcohols via Henry Addition



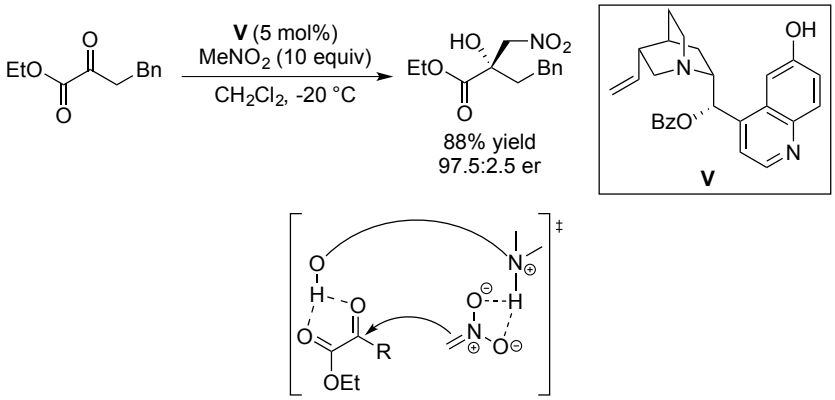
In 2001, Jørgensen reported the first example of an asymmetric Henry addition of nitromethane to ethyl pyruvate (**5**) to provide β-nitro-α-hydroxy ester **6** in excellent yield and enantioselectivity (**Scheme 5-7**).[6a,6b] Activation of the pyruvate was achieved through the use of the same C_2-symmetric (*S*,*S*)-Cu(II) complex **4** that Evans employed in the Mukaiyama aldol reaction with pyruvates (**Scheme 5-3**); however, catalytic amount of triethylamine was added in order to generate the reactive nitronate species. Since this initial report, a number of methods have been reported for the asymmetric Henry addition to pyruvates under chiral acid and base catalysis.[6c-6l]

Scheme 5-7. Catalytic Enantioselective Henry Addition into Pyruvates



Despite the multitude of methods developed for the addition of nitroalkanes to pyruvates, there is limited precedent for the addition into non-pyruvic alkyl α-keto esters and β-branched substrates.[6f,6g] Deng developed the first organocatalytic Henry reaction to α-keto esters using a bifunctional cinchona alkaloid-derived catalyst **V** (**Scheme 5-8**).[6f] Under mild reaction conditions, a variety of simple α-keto esters underwent productive reaction to afford the desired Henry adducts in excellent yield and enantioselectivity. Bifunctional catalyst **V** serves as a chiral base to generate the reactive nitronate species, which can react with the α-keto ester that is concomitantly activated by the acidic phenol moiety through hydrogen-bonding through a pseudo-intramolecular process. Notably, no byproducts associated with α-keto ester dimerization were observed (**Scheme 5-5**).

Scheme 5-8. Organocatalytic Henry Addition into α-Keto Esters

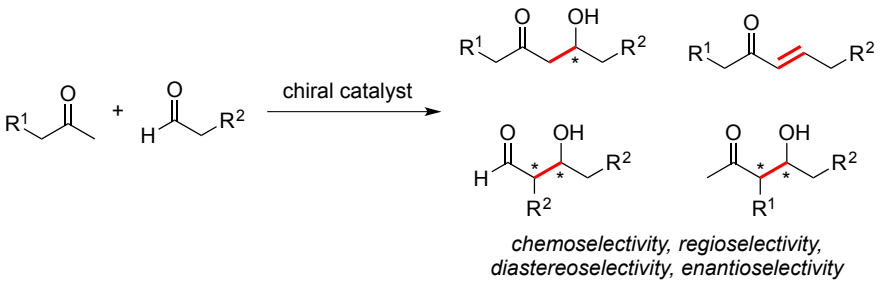


5.2.3 Direct Catalytic Acetone Aldolizations of α-Keto Esters

The direct catalytic asymmetric aldol reaction has long stood as an effective method for the construction of carbon–carbon bonds enroute to β-hydroxy carbonyls (**Scheme 5-9**).[19] Key challenges to the direct asymmetric cross-aldol reaction are the chemo-, regio-, diastereo-, and enantioselectivity observed in the reaction of two nonequivalent carbonyls. Judicious selection of

catalyst and substrate can circumvent a majority of the challenges associated with the selective generation of a single enol(ate) or enamine species in the presence of other carbonyl species. The electronic and steric properties of α-keto esters render them particularly attractive substrates for direct aldol reactions under primary and secondary amine catalysis. The inductive effects of the ester moiety render the ketone more electrophilic than a normal ketone; however, it is more sterically encumbered than a simple ketone, such as cyclohexanone, due to the proximity of a large ester group. Furthermore, the generated enamine is a poor nucleophile since it is deactivated by the electron-withdrawing nature of the proximal ester functionality.[20] These two attributes render α-keto esters amenable to serve as electrophiles in direct aldolizations with simple ketone nucleophiles.

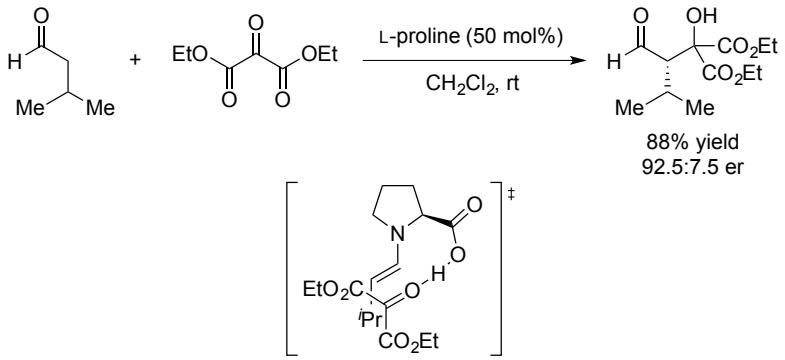
Scheme 5-9. Selectivity Issues in Direct Catalytic Asymmetric Aldolizations



Although catalytic Mukaiyama-type aldolizations of α-keto esters were previously demonstrated by Evans (**Scheme 5-3)**, the first direct catalytic aldol addition of aldehydes to α-keto esters was reported by Jørgensen (**Scheme 5-10**).[21] Under proline-catalysis, aliphatic aldehydes were found to be competent nucleophiles in the addition to highly activated ketomalonates affording β-hydoxy aldehydes in high yield and enantioselectivity. The high levels of enantioinduction were attributed to strong hydrogen-bonding interactions between the carboxylic acid of the L-proline enamine and ketone generating a well-defined transition state.

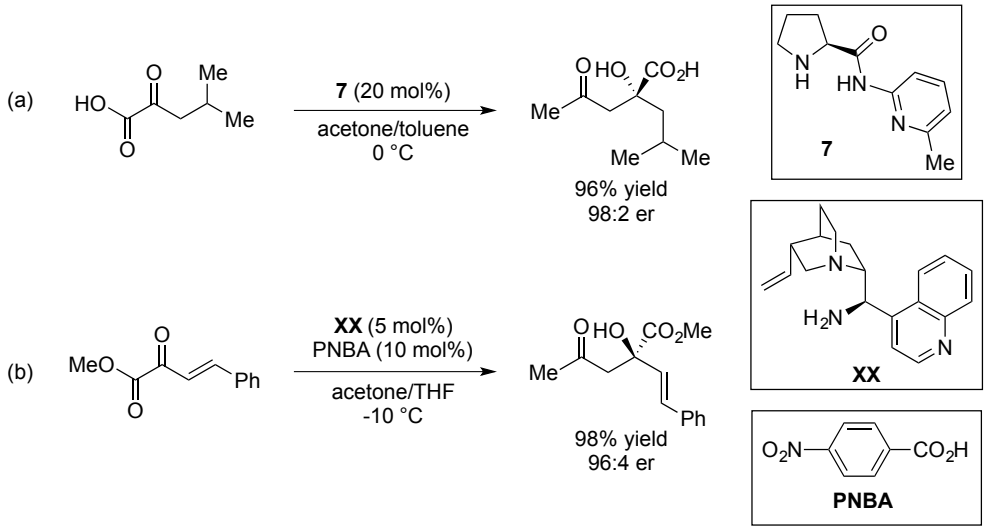
This proposed transition state was supported by experiments employing L-proline methyl ester as the catalyst, which afforded racemic product.

Scheme 5-10. Proline-Catalyzed Direct Catalytic Asymmetric Aldolizations



Extension of this aldolization methodology to less activated α-keto ester substrates employing cyclic and acyclic ketone nucleophiles has been subsequently developed.[7] Of particular relevance in the present context is the development of direct acetone aldolizations of α-keto esters under both chiral primary and secondary amine catalysis. Gong developed a direct aldolization of acetone to α-keto acids with excellent levels of selectivity utilizing a proline-derived secondary amine catalyst **7**, which served to activate the 1,2-dicarbonyl moiety through molecular recognition (**Scheme 5-11a**).[7b] Similarly, Chan and Kwong demonstrated that cinchona alkaloid primary amine catalyst **XX** efficiently promoted the direct aldolization of β,γ-unsaturated-α-keto esters with high regio- and enantioselectivity (**Scheme 5-11b**).[7h]

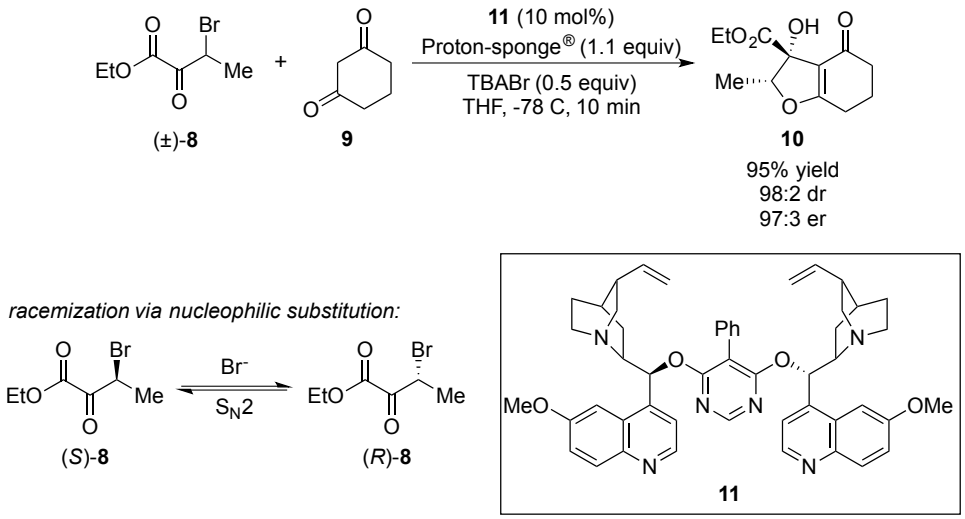
Scheme 5-11. Amine-Catalyzed Direct Acetone Aldolization of α-Keto Esters



5.2.4 Resolution of Configurationally Labile α-Stereogenic Carbonyls

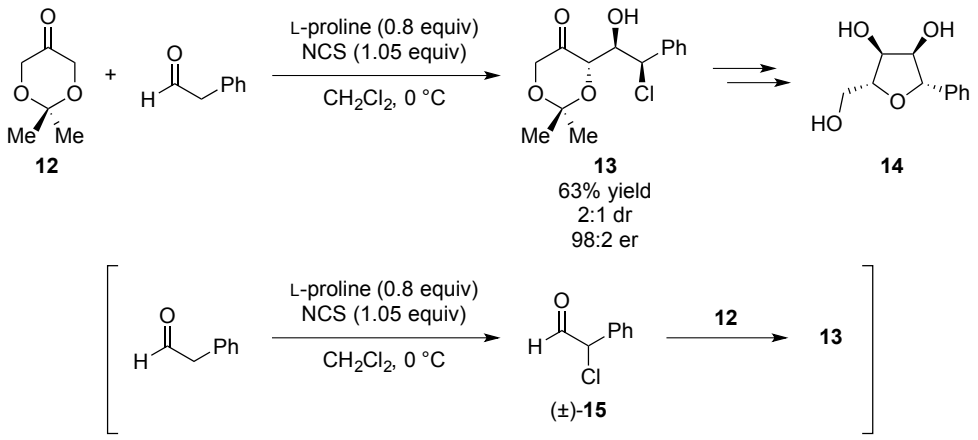
The dynamic kinetic resolution of a diverse range of α-stereogenic carbonyls and imines has been achieved through hydrogenation and transfer hydrogenation protocols;[22] however, the use of carbon-centered nucleophiles is relatively underdeveloped with only a handful of examples in the literature.[23] A pertinent example is the "interrupted" Feist−Bénary reaction of racemic β-bromo-α-keto esters and 1,3-diketones developed by Calter (**Scheme 5-12**).2[3a] Employing pyrimidinyl-linked bis(quinidine) catalyst **11**, 1,3-cyclohexanedione (**9**) underwent aldolization with β-bromo-α-keto ester **8** followed by a subsequent intramolecular *O*-alkylation to afford bicycle **10** with excellent enantio- and diastereocontrol. The reaction was rendered dynamic via the inclusion of exogenous bromide to promote a nucleophilic substitution racemization pathway. Addition of the 1,3-diketone was effectively directed by the chiral catalyst **11** to achieve selective addition into one enantiomer of the starting material **8**.

Scheme 5-12. Asymmetric "Interrupted" Feist−Bénary Reaction of β-Bromo-α-Keto Esters



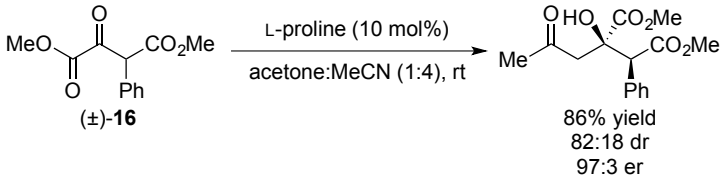
More recently, Britton described a method for the direct addition of ketones to α-chloro aldehydes (**Scheme 5-13**).[23c] Employing a protocol developed by MacMillan for the L-proline catalyzed α-chlorination of aliphatic aldehydes,[24] the labile α-chloro aldehyde (±)-**15** could be prepared *in situ* employing the same reagent that would effect the desired aldolization with dioxanone **12**. The resultant chlorohydrin **13** is obtained in good yield with excellent enantioselectivitity albeit with poor diastereoselection. Mechanistic studies revealed that the intermediate α-chloro aldehyde **15** is configurationally labile under the reaction conditions allowing for dynamic kinetic resolution to occur. The products can be easily transformed into carbohydrate analogues, such as **14**, in short order; however, the present method requires long reaction times and nearly stoichiometric amounts of chiral reagent to obtain synthetically useful yields and selectivities.

Scheme 5-13. Tandem α-Chlorination/Aldolization of Aliphatic Aldehydes



In 2007, Zhang reported a dynamic kinetic resolution of 2-oxo-3-aryl-succinates employing a direct acetone aldolization catalyzed by L-proline (**Scheme 5-14**).[25] The addition of acetone into (±)-**16** was found to occur with high enantioselectivity, but low diastereoselectivity. Due to its heightened acidity, (±)-**16** existed in its enol form removing any challenges with developing a racemization pathway to render the reaction dynamic. This work was later extended to the development of a DKR of β,γ-diketo esters via direct acetone aldolization employing catalyzed by L-proline.[26]

Scheme 5-14. Dynamic Kinetic Resolution of 2-Oxo-3-Aryl-Succinates

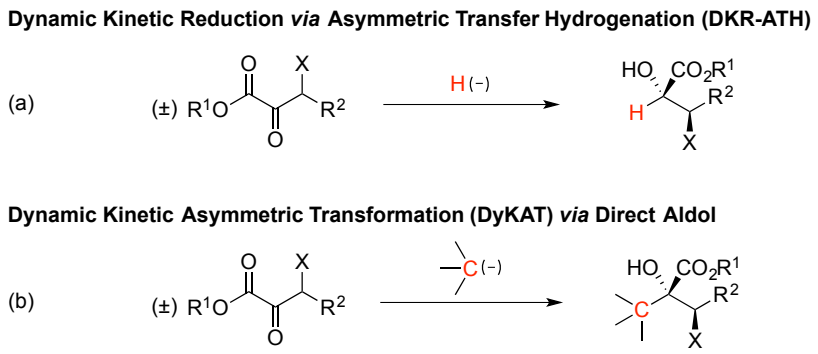


5.2.5 β-Stereogenic-α-Keto Esters as Configurationally Labile Electrophiles

As described in Chapters Three and Four, we have recently disclosed a protocol for the Ru(II)-catalyzed dynamic kinetic reduction via asymmetric transfer hydrogenation (DKR-ATH)

of β-stereogenic-α-keto esters affording secondary glycolic acid derivatives (**Scheme 5-15a**).[22f,22g,27] Our group's longstanding interest in the synthesis of complex fully-substituted glycolates,[28] however, prompted us to investigate reaction manifolds for the dynamic addition of carbon nucleophiles to β-stereogenic-α-keto esters to provide access to products of this type (**Scheme 5-15b**). We postulated that under judiciously selected reaction conditions, starting material racemization could be achieved via keto-enol(ate) tautomerism to render the β-stereocenter labile. Catalyst controlled diastereo- and enantioeelective addition of a carbon nucleophile to one of the two β-stereogenic-α-keto ester enantiomers would allow for the preparation of fully-substituted α-glycolic acid derivatives bearing a β-stereocenter.

Scheme 5-15. Synthesis of β-Stereogenic-α-Glycolic Acid Derivatives from α-Keto Esters



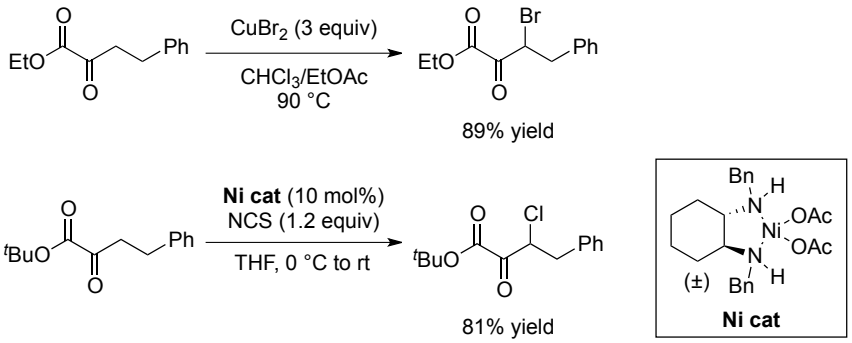
5.3 Results and Discussion

5.3.1 Synthesis and Properties of β-Halo-α-Keto Esters

We postulated that the identity of the β-substituent of the α-keto ester would be important in promoting the desired reactivity due to its direct impact on both the β-C–H acidity and steric environment about the ketone. Based on these considerations, we were drawn to β-halo-α-keto esters to investigate this potential reactivity profile due to their previous success in our group's Ru-catalyzed DKR-ATH reactions as well as Calter's "interrupted" Feist–Bénary reaction

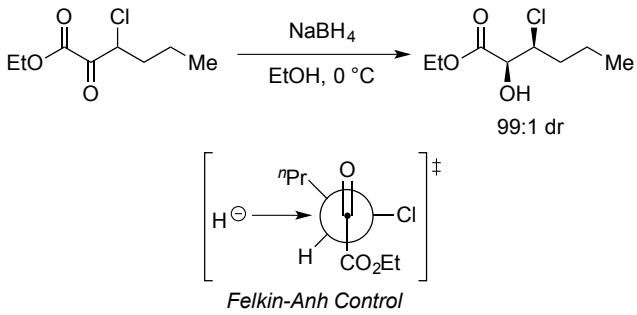
(**Scheme 5-12**).[23a,27a] The requisite β-halo-α-keto esters can be prepared directly from their parent α-keto esters in high yield employing extant methodologies providing access to bromo and chloro derivatives (**Scheme 5-16**).[27a,29]

Scheme 5-16. Methods for the Synthesis of β-Halo-α-Keto Esters



In addition to their facile synthesis, β-halo-α-keto esters have an attractive reactivity profile that engenders high diastereocontrol in the addition of nucleophiles to the ketone moiety. Tsuboi found that the reduction of β-chloro-α-keto esters with $NaBH_4$ proceeded with high *syn*-selectivity due to Felkin–Anh control.[30] We reasoned that we could take advantage of this affinity for β-halo-α-keto esters to undergo Felkin–Anh controlled addition of nucleophiles to control the reactive conformation of the electrophile in our desired addition reactions.

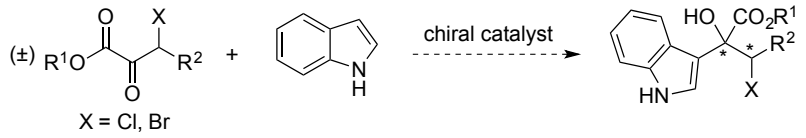
Scheme 5-17. Diastereoselectivity in the Reduction of β-Halo-α-Keto Esters



5.3.2 Development of a Catalytic Friedel–Crafts Alkylation of Indoles with β-Halo-α-Keto Esters

Based on prior art by Franz and Deng, we believed that the addition of indoles to β-stereogenic-α-keto esters could be realized under mild reaction conditions.[12,31] Although both of these reports were limited to the use of α-keto esters and isatins lacking a β-proton, we sought to adapt their previously reported reaction conditions to incorporate a racemization pathway to allow for the development of a highly diastereo- and enantioselective variant. To this end, we sought to examine both Lewis acid and Brønsted base catalysis modes to examine the potential development of a dynamic addition of indole to racemic β-halo-α-keto esters (**Scheme 5-18**).

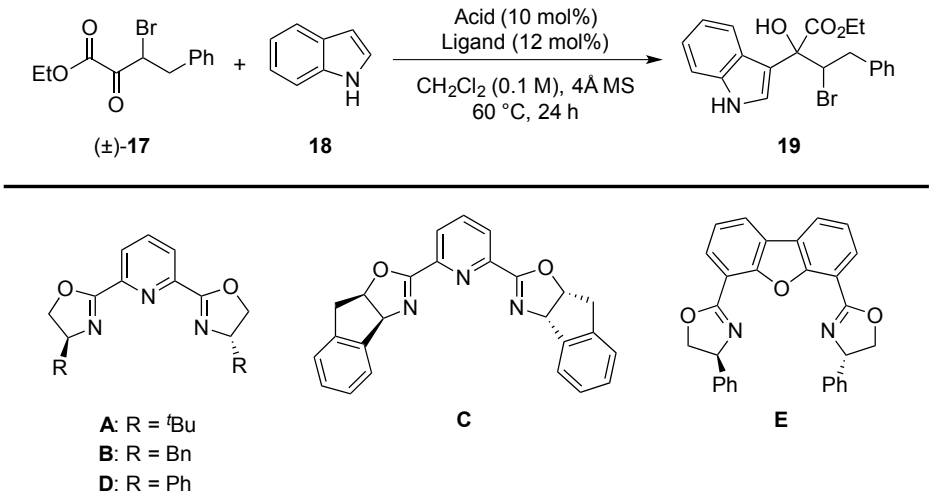
Scheme 5-18. Dynamic Addition of Indole to β-Halo-α-Keto Esters



Initial studies focused on the application of chiral Lewis acids to activate the α-keto ester moiety through chelation, while also providing a mechanism for enolization.[32] Exposure of β-bromo-α-keto ester **17** and indole (**18**) to $Cu(OTf)_2$ in CH_2Cl_2 resulted in no reaction after 24 h at both room temperature and 60 °C (**Table 5-1**, entries 1 and 2). Switching to $Sc(OTf)_3$ or $In(OTf)_3$ led to the slow formation of the desired product **19** as a single diastereomer (entry 3 and 4). Application of Pybox ligands was subsequently investigated to ascertain the potential to develop an enantioselective variant.[33] Although ligand **A** was too bulky to affect the transformation, ligands **B** and **C** provided **19** as a single diastereomer after moderate conversion (entries 5-7). Since Indapybox (**C**) afforded promising levels of enantioselection (67.5:32.5 er) in the Friedel–Crafts alkylation, we turned our attention to increasing the conversion of the reaction.

Employing 3.0 equivalents of indole effectively increased the rate of the reaction catalyzed by $Sc(OTf)_3$/**C** providing **19** in 89% isolated yield after 24 h, but with a significant drop in enantioselectivity to 53:47 er (entry 9). Further attempts employing an $In(OTf)_3$/**C** or $Sc(OTf)_3$/**D** catalyst system resulted in low conversions in the Friedel–Crafts alkylation (entries 10 and 12). Since enriched product is obtained at partial conversion (entry 7) and racemic product is obtained at full conversion (entries 9 and 11), we presumed that this reaction is proceeding through a classical kinetic resolution. In order to promote racemization and render the reaction dynamic, exogenous bases, such as 2,6-lutidine or Hünig's base, were added; however, they inhibited the reaction and resulted in only trace conversion after 24 h (entries 13 and 14).

Table 5-1. Optimization of Lewis Acid-Catalyzed Friedel–Crafts Alkylation of Indole[a]



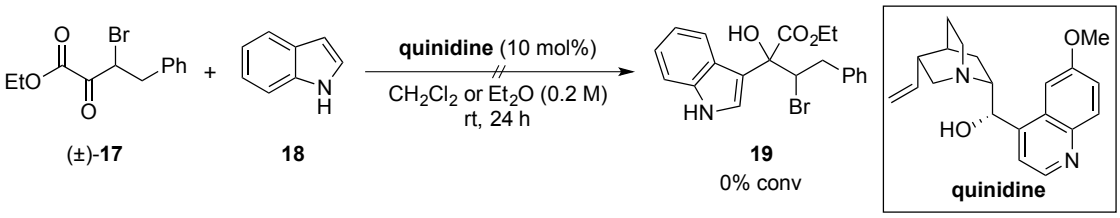
entry	18 (equiv)	Acid	Ligand	conv (%)[b]	dr[b]	er[c]
1[d]	1.3	$Cu(OTf)_2$	–	0	–	–
2	1.3	$Cu(OTf)_2$	–	0	–	–
3	1.3	$Sc(OTf)_3$	–	44	>20:1	–
4	1.3	$In(OTf)_3$	–	56	>20:1	–
5	1.3	$Sc(OTf)_3$	**A**	0	–	–
6	1.3	$Sc(OTf)_3$	**B**	46 (42)	>20:1	58:42
7	1.3	$Sc(OTf)_3$	**C**	49 (39)	>20:1	67.5:32.5
8	3.0	$Sc(OTf)_3$	–	83	>20:1	–
9	3.0	$Sc(OTf)_3$	**C**	>95 (89)	>20:1	53:47
10	3.0	$In(OTf)_3$	**C**	<10	>20:1	N/D
11	3.0	$Sc(OTf)_3$	**D**	>95	>20:1	51.5:48.5
12	3.0	$Sc(OTf)_3$	**E**	12	>20:1	N/D
13[e]	1.3	$Sc(OTf)_3$	**C**	14	>20:1	N/D
14[f]	1.3	$Sc(OTf)_3$	**C**	19	>20:1	N/D

[a]Reactions were performed on 0.20 mmol scale with 4Å MS (50 mg), unless otherwise noted. [b]Determined by ^{1}H NMR analysis of crude reaction mixture; numbers in parentheses represent isolated yield of analytically pure product. [c]Determined by chiral SFC analysis. [d]Reaction performed at room temperature for 24 h. [e]Reaction performed with 2,6-lutidine (20 mol%) as an additive. [f]Reaction performed with Hünig's base (20 mol%) as an additive.

Despite obtaining **19** in high yield and as a single diastereomer, early attempts to develop a dynamic Friedel–Crafts alkylation of indole was found to be unsuccessful under Lewis acid catalysis. In order to identify a catalyst system that would promote racemization of β-bromo-α-keto ester **17**, we turned our attention to Brønsted base catalysts that could enolize the starting

material. Deng has previously demonstrated that cinchona alkaloid-derived organocatalysts effectively promoted the Friedel–Crafts alkylation of indoles with a variety of carbonyl and imine electrophiles in high enantioselectivity.[12,34] Attempts employing quinidine in the addition of indole to **17** were unsuccessful, resulting in no reaction (**Scheme 5-19**).

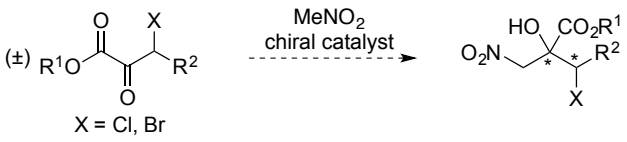
Scheme 5-19. Attempted Organocatalytic Friedel–Crafts Alkylation of Indole



5.3.3 Identification and Optimization of a Catalytic Direct Henry Aldolization of β-Halo-α-Keto Esters

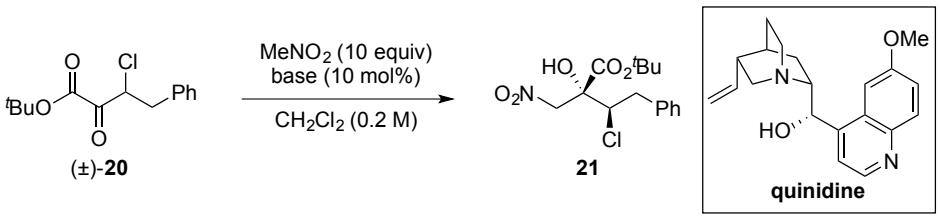
Concurrent to the development of Lewis acid-catalyzed alkylations of indoles, we began to pursue the Henry addition of nitromethane to β-halo-α-keto esters under Brønsted base catalysis. Based on seminal work by Deng (**Scheme 5-8**),[6f] we saw the potential to develop an asymmetric synthesis of β-halo-β′-nitro glycolic acid derivatives (**Scheme 5-20**). Although conditions required for the addition of indole to β-halo-α-keto esters suffered from a static environment, we believed that β-halo-α-keto esters possessed the necessary C–H acidity to promote a protonation/deprotonation racemization pathway under the basic conditions already required for the generation of the reactive nitronate species.

Scheme 5-20. Dynamic Addition of Nitromethane to β-Halo-α-Keto Esters



We commenced our investigations with β-chloro-α-keto ester **20**, which had found previous success in our Ru-catalyzed DKR-ATH methodologies.[27a] Treatment of (±)-**20** and nitromethane (10 equiv) with Hünig's base in CH_2Cl_2 resulted in the rapid formation of **21** in quantitative yield, but in low diastereoselectivity (**Table 5-2**, entry 1). Application of the chiral base quinidine resulted in the isolation of **21** in only 3:1 dr and 56.5:43.5 er at room temperature (entry 2). Cooling the reaction to 0 °C led to a slight boost in enantioselectivity to 64:36 er, but the Henry reaction was still proceeding with poor diastereocontrol (entry 3). Attempts to further reduce the temperature of the reaction to increase the selectivity were unsuccessful as the reaction was not operational at -50 °C (entry 4).

Table 5-2. Henry Addition of Nitromethane to β-Chloro-α-Keto Esters[a]



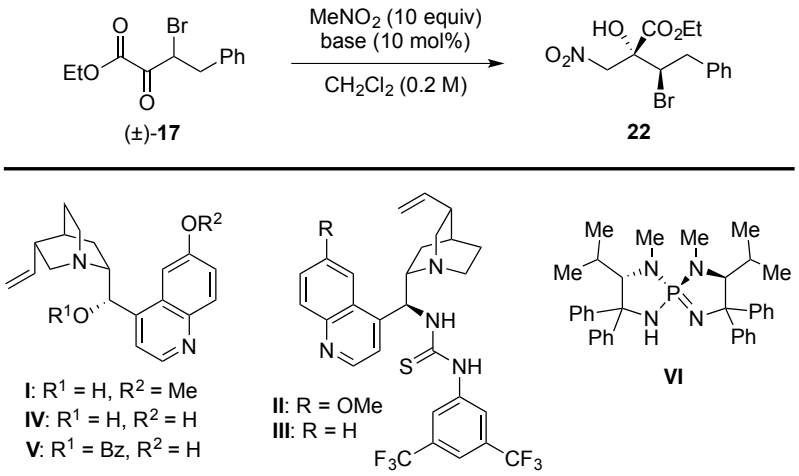
entry	base	T (°C)	t (h)	conv (%)[b]	dr[b]	er[c]
1	Hünig's base	23	4	>95	3:1	–
2	quinidine	23	4	>95	3:1	56.5:43.5
3	quinidine	0	12	>95	3:1	64:36
4	quinidine	-50	24	0	–	–

[a]Reactions were performed on 0.20 mmol scale, unless otherwise noted. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]Determined by chiral SFC analysis.

The poor diastereocontrol observed in the Henry addition of nitromethane to β-chloro-α-keto ester **20** led us to investigate β-bromo-α-keto ester **17**, which provided high diastereocontrol in the addition of indole (**Table 5-1**). Upon reacting (±)-**17** and nitromethane with Hünig's base in CH_2Cl_2 resulted in the slow formation of **22** reaching only 48% conversion after 18 h at room temperature (**Table 5-3**, entry 1). Despite this reduced reactivity, we were pleased to observe that

the Henry addition was proceeding in 8:1 dr. Employing quinidine (**I**) as the catalyst, the reaction proceeded to full conversion in 18 h affording the Henry adduct **22** in quantitative yield with 13:1 dr and 62:38 er (entry 2). Although lowering the reaction temperature to 0 °C increased the diastereoselectivity to 18:1 dr, there was no improvement in enantioselectivity (entries 3). Examination of bifunctional cinchona alkaloid-derived thiourea catalysts **II** and **III** resulted in low conversions and poor selectivities in the Henry reaction (entries 4 and 5); however, cupreidine (**IV**)[35] was found to provide a boost in enantioselection up to 72:28 er (entries 6 and 7). Adding steric bulk to the secondary alcohol of cupreidine resulted in a further increase in selectivity generating **22** in 80:20 er (entry 8). Iminophosphorane (*P*,*S*)-**VI** provided slow conversion to **22** in high diastereoselectivity and moderate enantioselectivity (entry 9).

Table 5-3. Initial Catalyst Screen in Henry Addition of Nitromethane to β-Bromo-α-Keto Esters[a]



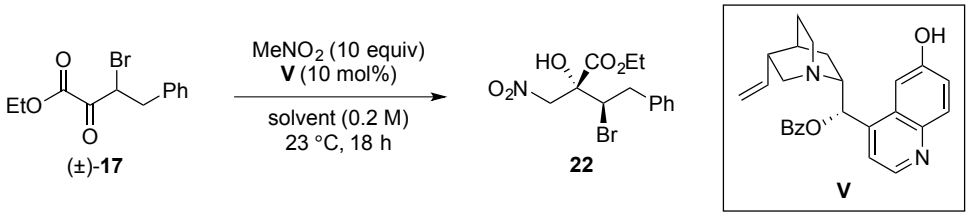
entry	base	T (°C)	t (h)	conv (%)[b]	dr[b]	er[c]
1	Hünig's base	23	18	48	8:1	–
2	**I**	23	18	>95	13:1	62:38
3	**I**	0	12	94	18:1	62.5:37.5
4	**II**	0	24	47	5:1	46.5:53.5
5	**III**	0	24	84	7:1	48.5:51.5
6	**IV**	0	18	86	15:1	72:28
7	**IV**	23	18	>95	12:1	72:28
8	**V**	23	18	>95	11:1	80:20
9[d]	**VI**	23	18	32	18:1	30.5:69.5

[a]Reactions were performed on 0.20 mmol scale, unless otherwise noted. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]Determined by chiral SFC analysis. [d]Reaction performed with THF as solvent.

Having identified a general catalyst structure that imparts good levels of enantioselectivity in the Henry addition of nitromethane to (±)-**17**, we turned our attention to an examination of solvents in the reaction (**Table 5-4**). Although both EtOAc and THF provided the product as a single diastereomer with significant increase in enantioselection to 89:11 and 92:8 er, respectively, the reactions were very slow at room temperature providing only partial conversion after 18 h (entries 2 and 4). Toluene and MeCN both provided small increases in diastereoselectivity, but did not improve the enantioselection (entries 3 and 5). Since the highest

enantioselectivity was observed with THF, a screen of ethereal solvents was conducted and showed that methyl *tert*-butyl ether (MTBE) provided **22** as a single diastereomer in quantitative yield with 92.5:7.5 er (entry 9). An enantiomeric ratio of 94.5:5.5 was obtained with cyclopentyl methyl ether (CPME); however, only partial conversion was observed after 18 h at room temperature.

Table 5-4. Initial Solvent Screen in Henry Addition of Nitromethane to β-Bromo-α-Keto Esters[a]



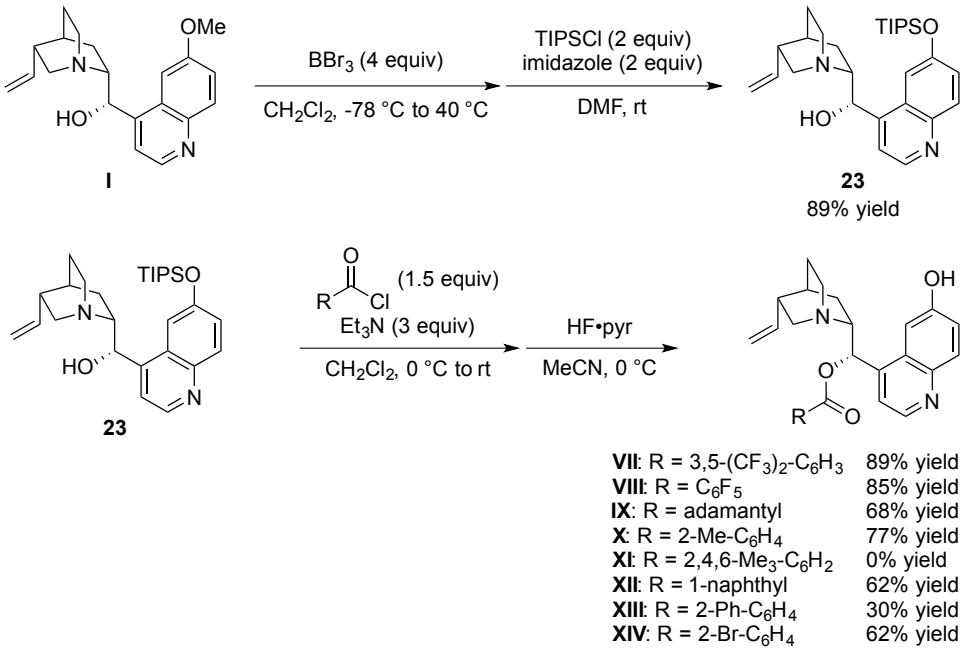
entry	solvent	conv (%)[b]	dr[b]	er[c]
1	CH_2Cl_2	>95	12:1	80:20
2	THF	17	>20:1	92:8
3	Toluene	>95	16:1	80.5:19.5
4	EtOAc	51	>20:1	89:11
5	MeCN	>95	>20:1	88:12
6	CPME	48	>20:1	94.5:5.5
7	DME	60	18:1	91.5:8.5
8	2Me-THF	15	>20:1	91:9
9	MTBE	>95	>20:1	92.5:7.5

[a]Reactions were performed on 0.20 mmol scale, unless otherwise noted. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]Determined by chiral SFC analysis.

Although conditions were identified with catalyst **V** to provide the product in high yield and diastereoselectivity, we were interested in the identification of a catalyst that would provide slightly higher levels of enantioselectivity. A survey of the literature identified a report by Bandini and Umani-Ronchi that utilized modified *C*9-benzoylcupreines, structural derivatives of **V**, to achieve the highly enantioselective Henry reaction of nitromethane with fluoromethyl ketones.[36] Based on their success with catalyst derivatization, we set out to synthesize a library

of catalysts based on the *C*9-acylcupreidine framework **V** (**Scheme 5-21**). Demethylation of quinidine (**I**) with BBr_3 provided cupreidine (**IV**), which was subsequently TIPS-protected to afford silyl ether **23** in 89% yield over two steps. Acylation of the secondary alcohol followed by cleavage of the silyl ether with HF•pyr provides *C*9-acylcupreidine derivatives **VII-XIV** in good yield over two steps. Acylation of **23** with 2,4,6-trimethylbenzoyl chloride, however, proved challenging due to its steric requirements resulting in no reaction.

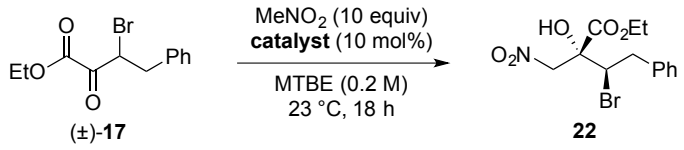
Scheme 5-21. Synthesis of *C*9-Acylcupreidine Catalysts

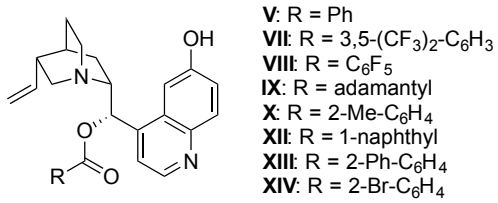


With a library of catalysts in hand, the Henry addition of nitromethane to (±)-**17** was reinvestigated (**Table 5-5**). Catalysts **VII** and **VIII** bearing electron-withdrawing groups on the benzoyl moiety provided comparable enantioselectivities to the parent catalyst **V** (entries 2 and 3). Adamantyl-derived catalyst **IX** provided **22** in reduced enantioselectivity suggesting that the aryl group was important for high levels of selectivity (entry 4). The *o*-toluoyl-derived catalyst **X**

provided a small increase in enantioselection to 93:7 er (entry 5); however, an examination of other *ortho*-substituted aryl groups resulted in no further improvement in selectivity (entries 6-8).

Table 5-5. Screening of *C*9-Acylcupreidine Catalysts in Henry Addition of Nitromethane to β-Bromo-α-Keto Esters[a]





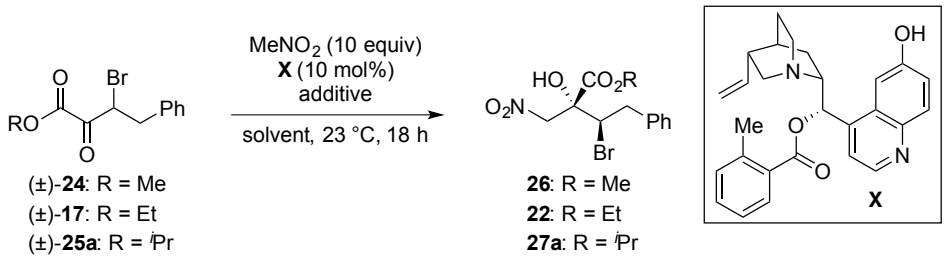
entry	catalyst	conv (%)[b]	dr[b]	er[c]
1	**V**	>95	>20:1	92.5:7.5
2	**VII**	>95	>20:1	92:8
3	**VIII**	>95	>20:1	92:8
4	**IX**	>95	>20:1	87.5:12.5
5	**X**	>95	>20:1	93:7
6	**XII**	>95	>20:1	89:11
7	**XIII**	>95	>20:1	89.5:10.5
8	**XIV**	>95	>20:1	92:8

[a]Reactions were performed on 0.20 mmol scale, unless otherwise noted. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]Determined by chiral SFC analysis.

Having identified an optimal catalyst structure, an examination of reaction parameters was conducted to further optimize the enantioselectivity of the reaction (**Table 5-6**). Addition of $LiClO_4$ to the reaction resulted in a drastic drop in enantioselection to 63.5:36.5 er suggesting that the Li^+ ions were interfering with hydrogen-bonding required for high levels of enantioselectivity to be observed (entry 1). Since Calter saw an increase in diastereo- and enantiocontrol upon addition of TBABr in the "interrupted" Feist−Bénary reaction of β-bromo-α-keto esters, we investigated the addition of varying amounts of exogenous bromide in our

Henry addition. Although 10 mol% of TBABr provided no change in the reaction, further increasing the loading to 50 mol% caused a noticeable decrease in selectivity to 83.5:16.5 er (entries 2 and 3). Attempts to increase enantioselectivity by decreasing or increasing the concentration or adjusting the equivalencies of nitromethane were largely unsuccessful (entries 4-6). The identity of the ester group was important since the methyl ester resulted in a drop in selectivity to 88.5:11.5 er, but the isopropyl ester led to comparable levels of selectivity (entries 7 and 8). Gratifyingly, reexamination of ethereal solvents with the isopropyl ester led to the identification of optimized conditions providing **27a** in 97% yield as a single diastereomer with 96:4 er (entries 9-11).

Table 5-6. Final Optimization of Conditions for Henry Addition of Nitromethane to β-Bromo-α-Keto Esters[a]



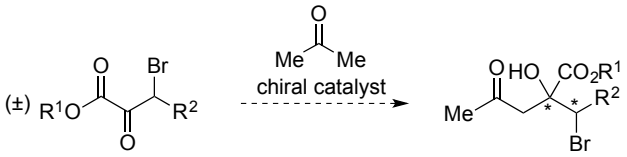
entry	R	additive (mol%)	solvent ([M])	conv (%)[b]	dr[b]	er[c]
1	Et	$LiClO_4$ (10)	MTBE (0.2)	>95	>20:1	63.5:36.5
2	Et	TBABr (10)	MTBE (0.2)	>95	>20:1	93:7
3	Et	TBABr (50)	MTBE (0.2)	89	>20:1	83.5:16.5
4	Et	–	MTBE (0.1)	84	>20:1	95:5
5	Et	–	MTBE (0.5)	>95	>20:1	90:10
6[d]	Et	–	MTBE (0.2)	>95	>20:1	93.5:6.5
7	Me	–	MTBE (0.2)	>95	>20:1	88.5:11.5
8	^{i}Pr	–	MTBE (0.2)	>95	>20:1	92:8
9	^{i}Pr	–	CPME (0.2)	>95	>20:1	93.5:6.5
10	^{i}Pr	–	2Me-THF (0.2)	>95 (97)	>20:1	96:4
11	^{i}Pr	–	THF (0.2)	>95	>20:1	94.5:5.5

[a]Reactions were performed on 0.20 mmol scale, unless otherwise noted. [b]Determined by ^{1}H NMR analysis of crude reaction mixture; numbers in parentheses represent isolated yield of analytically pure product. [c]Determined by chiral SFC analysis. [d]Reaction performed with $MeNO_2$ (5 equiv) for 36 h.

5.3.4 Identification and Optimization of a Catalytic Direct Acetone Aldolization of β-Bromo-α-Keto Esters

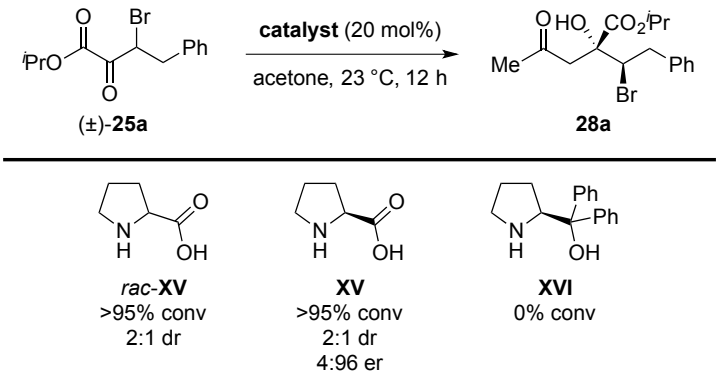
During the course of our optimization of Henry conditions, we also became interested in the potential application of ketones, such as acetone, in the dynamic aldolization reaction of β-bromo-α-keto esters to access β-bromo-γ′-oxo glycolic acid derivatives (**Scheme 5-22**). We saw a potential to utilize primary or secondary amine catalysts to not only generate a nucleophilic enamine species, but to also promote the racemization of the β-bromo-α-keto ester starting material if deployed under acidic or basic reaction conditions.

Scheme 5-22. Dynamic Addition of Acetone to β-Bromo-α-Keto Esters



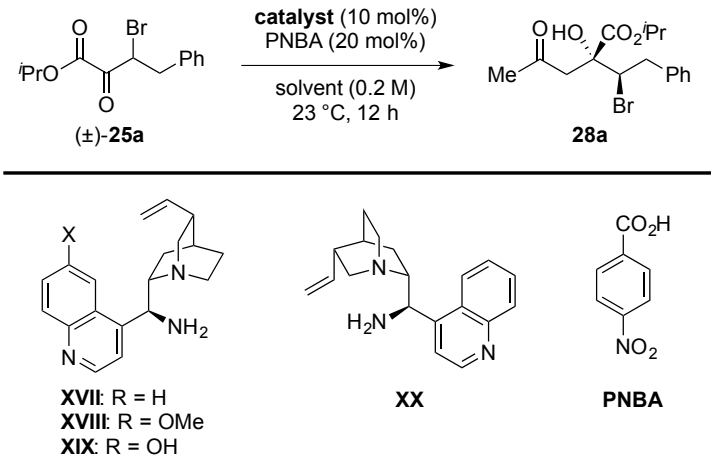
We initially found that treating a solution of β-bromo-α-keto ester (±)-**25a** in acetone with D/L-proline (*rac*-**XV**) resulted in the formation of aldol adduct **28a** in quantitative yield in 2:1 dr (**Scheme 5-23**). Despite this poor diastereoselectivity in the aldolization, L-proline (**XV**) afforded *ent*-**28a** in 96:4 er. Other hydrogen-bonding secondary amine catalysts, such as diphenylprolinol **XVI**, did not catalyze the reaction. Based on these results, we were encouraged by the high levels of enantioinduction observed with L-proline, but felt that different catalyst structures would need to be probed to introduce higher levels of diastereoselection in the transformation.

Scheme 5-23. Secondary Amine Catalysts for Acetone Aldolization of β-Bromo-α-Keto Esters[a]



Based on our earlier success with cinchona alkaloid-catalysts for the Henry addition, we considered examining primary amine catalysts derived from the cinchona alkaloids.[37] Cinchonidine-derived primary amine catalyst **XVII** with *p*-nitrobenzoic acid (PNBA) as cocatalyst[7h] in acetone:dioxane (1:9) delivered *ent*-**28a** in good diastereo- and enantioselection (**Table 5-7**, entry 1). An examination of other polar solvents did not provide satisfactory improvement (entries 2-5); however, reaction with **XVII** run in acetone as the solvent provided *ent*-**28a** in 95.5:4.5 er as a single diastereomer (entry 6). Attempts to further increase the enantioselectivity employing either **XVII** or **XIX** proved ineffective (entries 7 and 8), but pseudo-enantiomeric **XX** provided slight improvement delivering **28a** quantitatively with 96:4 er as a single diastereomer (entry 9).

Table 5-7. Optimization of Direct Acetone Aldolization of β-Bromo-α-Keto Esters[a]



entry	catalyst	solvent	conv (%)[b]	dr[b]	er[c]
1	**XVII**	acetone:dioxane (1:9)	>95	14:1	12:88
2	**XVII**	acetone:EtOAc (1:9)	>95	6:1	19.5:80.5
3	**XVII**	acetone:DMSO (1:9)	>95[d]	–	–
4	**XVII**	acetone:DMF (1:9)	>95	9:1	9.5:90.5
5	**XVII**	acetone:MeCN (1:9)	>95	5:1	16:84
6	**XVII**	acetone	>95 (96)	>20:1	4.5:95.5
7	**XVIII**	acetone	>95	>20:1	10.5:89.5
8	**XIX**	acetone	>95	>20:1	14.5:85.5
9	**XX**	acetone	>95 (95)	>20:1	96:4

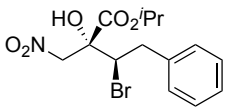
[a]Reactions were performed on 0.20 mmol scale, unless otherwise noted. [b]Determined by ^{1}H NMR analysis of crude reaction mixture; numbers in parentheses represent isolated yield of analytically pure product. [c]Determined by chiral SFC analysis. [d]Obtained a complex mixture.

5.3.5 Scope of Direct Aldolizations of β-Bromo-α-Keto Esters

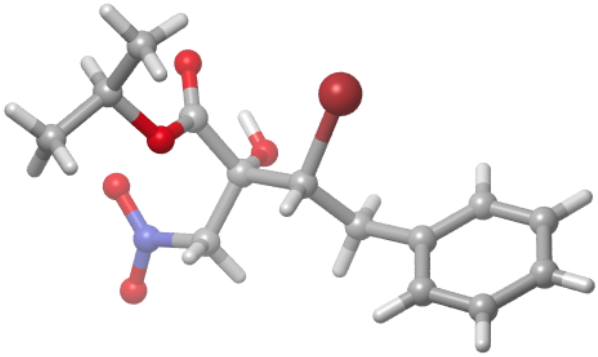
With optimized reaction conditions in hand, we probed the scope of both the direct Henry and acetone aldolization DyKATs of β-bromo-α-keto esters (**Table 5-8**). In addition to phenyl (**27a** and **28a**), the reactions were tolerant of both *ortho*- and *para*-substituted aryl groups at the γ-position providing aldol adducts **27b-d** and **28b-d** in high yield and selectivity. Heteroaryl (±)-**25e** also reacted efficiently under the reaction conditions cleanly providing **27e** and **28e**. A range of linear alkyl substrates underwent aldolization with no loss in selectivity providing **27f-28h** and **27f-28h** in similarly high efficiency suggesting that aromatic interactions between substrate

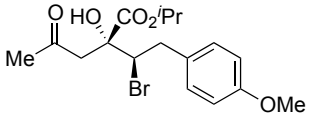
and catalyst are not required for high levels of selectivity. The increased steric requirements of γ-branching resulted in low diastereoselectivity and moderate enantioselectivity in the formation of **27i** and **28i**. The absolute configuration of (2*R*,3*R*)-**27a** and (2*R*,3*R*)-**28d** was in each case determined by x-ray crystallography and the other products were assigned by analogy (**Scheme 5-24**).[38]

Scheme 5-24. Determination of Absolute Configuration of (2*R*,3*R*)-**27a** and (2*R*,3*R*)-**28d**



(2*R*,3*R*)-**27a**





(2*R*,3*R*)-**28d**

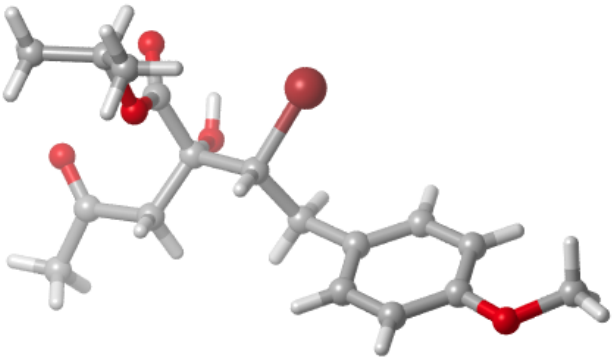
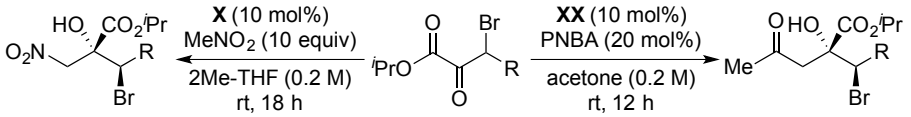
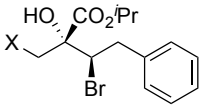
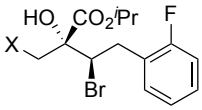
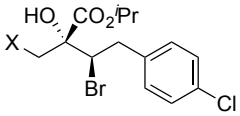
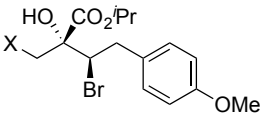
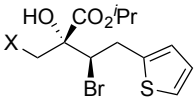
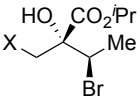
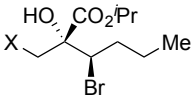
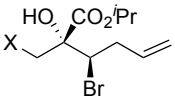
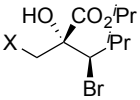


Table 5-8. Substrate Scope for Direct Aldolization of β-Bromo-α-Keto Esters[a]



27 (±)-**25** **28**

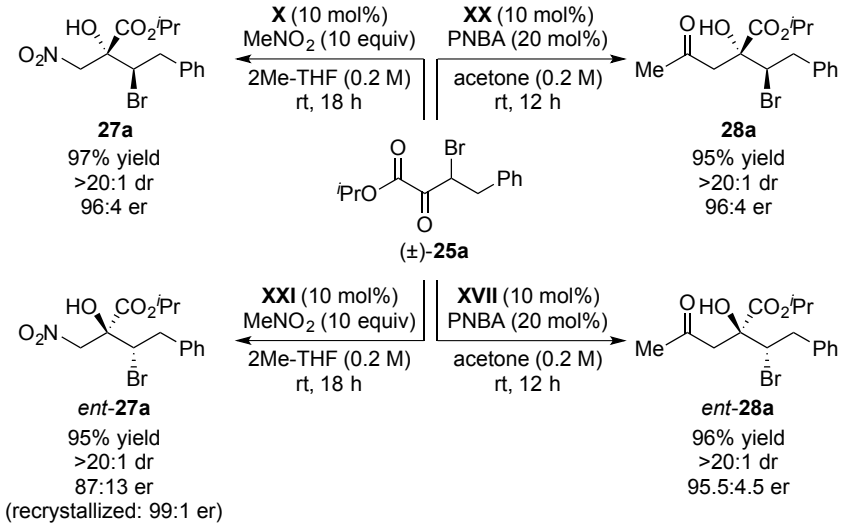
27a: X = NO_2 97% yield >20:1 dr 96:4 er		**28a**: X = Ac 95% yield >20:1 dr 96:4 er
27b: X = NO_2 97% yield >20:1 dr 92:8 er		**28b**: X = Ac 95% yield >20:1 dr 95.5:4.5 er
27c: X = NO_2 98% yield >20:1 dr 95.5:4.5 er		**28c**: X = Ac 97% yield >20:1 dr 96.5:3.5 er
27d: X = NO_2 98% yield >20:1 dr 96:4 er		**28d**: X = Ac 93% yield >20:1 dr 96:4 er
27e: X = NO_2 92% yield >20:1 dr 94.5:5.5 er		**28e**: X = Ac 96% yield >20:1 dr 95.5:4.5 er
27f: X = NO_2 95% yield >20:1 dr 94:6 er		**28f**: X = Ac 96% yield >20:1 dr 95.5:4.5 er
27g: X = NO_2 96% yield 17:1 dr 93:7 er		**28g**: X = Ac 94% yield >20:1 dr 95.5:4.5 er
27h: X = NO_2 98% yield >20:1 dr 94.5:5.5 er		**28h**: X = Ac 95% yield >20:1 dr 96:4 er
27i:[b] X = NO_2 95% yield 5:1 dr 87:13 er		**28i**: X = Ac 90% yield 2.5:1 dr 90:10 er

[a]Reactions were performed on 0.20 mmol scale. Yield of isolated product reported. Diastereomeric ratio (dr) determined by ^{1}H NMR analysis of crude reaction mixture. Enantiomeric ratio (er) determined by chiral HPLC analysis. [b]Reaction performed for 42 h.

5.3.6 Accessing Both Enantiomeric Series of Products in the Direct Aldolization of β-Bromo-α-Keto Esters

Since catalysts **X** and **XX** are derived from cinchona alkaloids, their pseudo-enantiomeric catalysts **XXI** and **XVII** are readily available and provide access to both enantiomeric series of Henry and acetone aldolization adducts (**Scheme 5-25**). Although **XXI** provides *ent*-**27a** in only 87:13 er, a single recrystallization provides enantioenrichment to 99:1 er. The utility of these reactions is highlighted not only by the mild, operationally simple reaction conditions, but by the near quantitative yield of products obtained following a simple filtration of the crude reaction mixtures through a plug of silica gel obviating the need for aqueous workup.

Scheme 5-25. Accessing Both Enantiomeric Series of Aldol Adducts

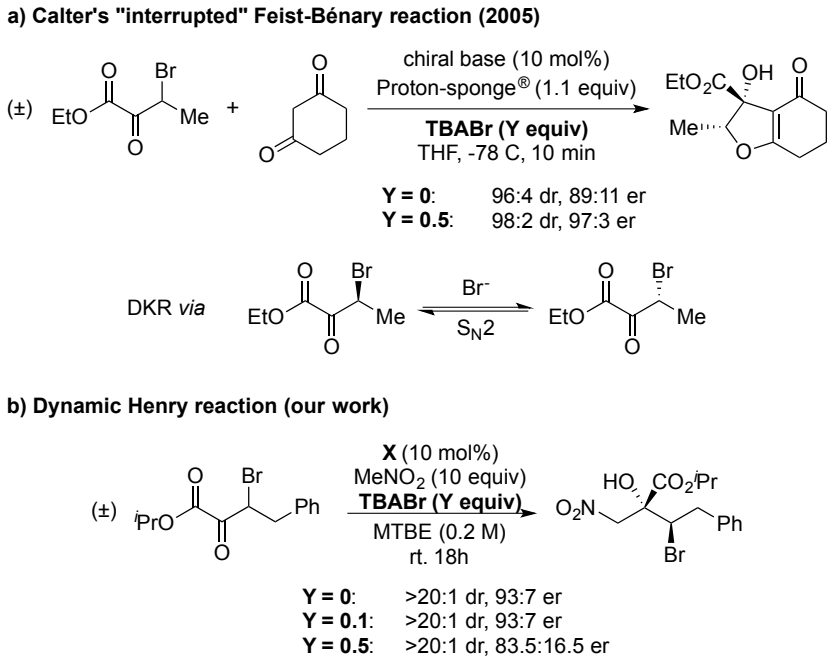


5.3.7 Mechanistic Divergence from Calter's "Interrupted" Feist−Bénary Reaction

In order to better understand the mechanistic nuances of our direct aldolization reactions, we sought to elucidate the racemization pathway of β-bromo-α-keto esters in our work. During the development of an "interrupted" Feist−Bénary reaction, Calter proposed that the addition of 1,3-diketones to β-bromo-α-keto esters proceeds via DKR, where halide S_N2 displacement is

promoted by TBABr or TBAI (**Scheme 5-26a**).[23a,23b] Since our reactions do not generate stoichiometric bromide and addition of TBABr provided no improvement (**Scheme 5-26b**), we sought to examine the nature of our dynamic reaction by studying the Henry reaction as a representative system.

Scheme 5-26. Dynamic Kinetic Resolution via Nucleophilic Displacement

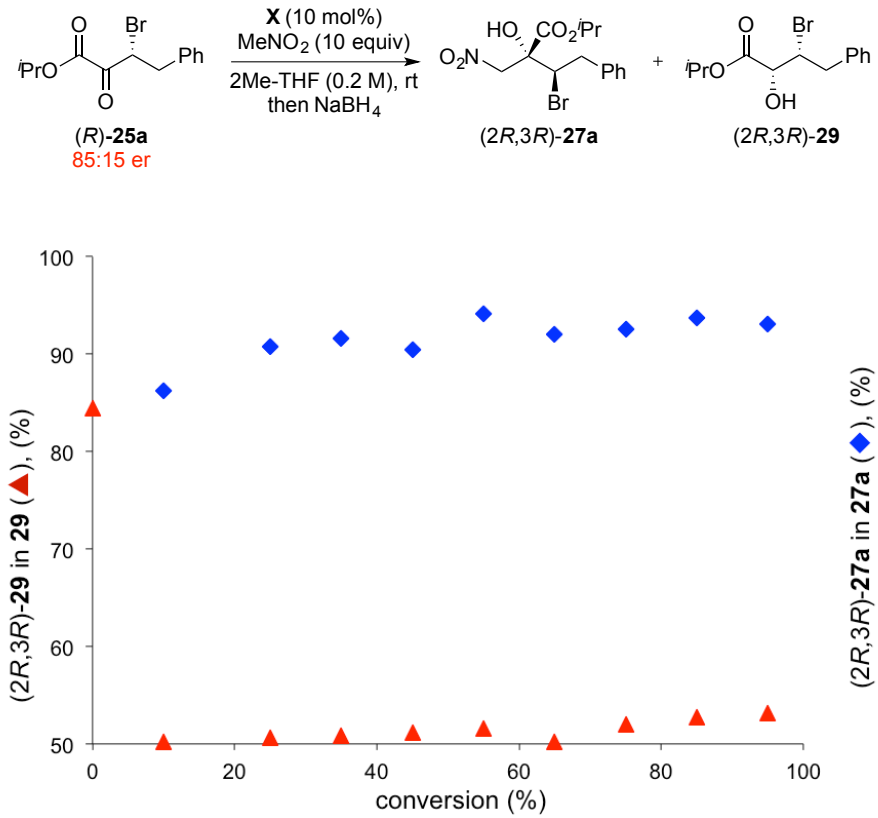


5.3.8 Racemization Studies of Henry Reaction

Since our Henry addition of nitromethane into β-bromo-α-keto esters is proceeding to convert a racemate into a single enantiomer of product, we concluded that a deracemization process was operational. As described in Chapter One, deracemization can be achieved through a variety of pathways requiring careful experimentation to elucidate the operative pathway for a particular transformation. To this end, we conducted experiments to determine if substrate racemization was indeed occurring and, if so, what the racemization mechanism was.

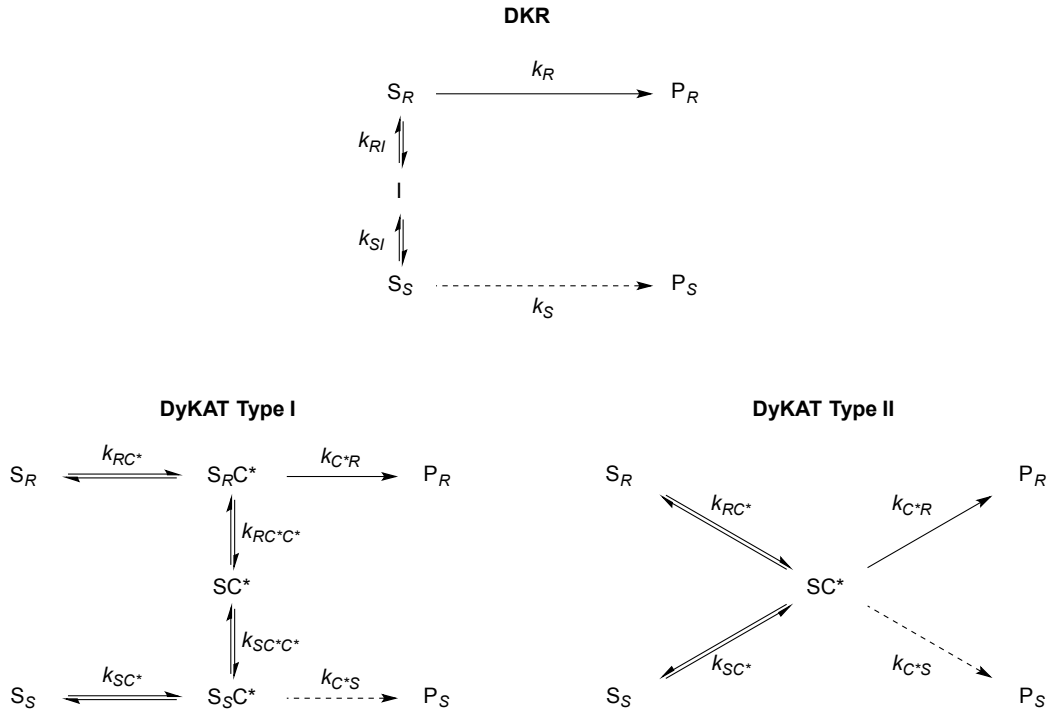
We began our studies by monitoring the enantiomeric compositions of both starting material (▲) and product (◆) during the course of the reaction of (*R*)-**25a** (**Figure 5-1**). While substrate racemization is obligatory to successful dynamic kinetic resolutions and certain DyKAT subtypes, this assay is seldom performed.[39] The enantiomeric composition of unreacted starting material was most easily assayed by subjecting reaction aliquots to stereoselective $NaBH_4$ reduction, thereby converting (*R*)-**25a** to (2*R*,3*R*)-**29** (diastereoselection >20:1). This study confirmed that (2*R*,3*R*)-**27a** is obtained in uniform selectivity and that **25a** remains racemic throughout the entire course of the reaction. Since a racemization pathway is operative under the reaction conditions, this eliminates the possibility that the Henry reaction is an enantioconvergent transformation.

Figure 5-1. Enantiomeric Composition of **29** and (2*R*,3*R*)-**27a** as a Function of Conversion



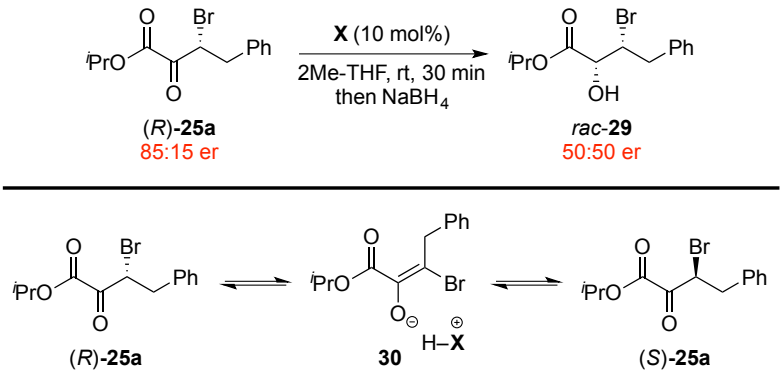
Based on the results from this experiment, we assumed that the reaction was operating as either a DKR or a matched DyKAT (Type I or II) since the starting material was being deracemized in a process that delivered product in uniform enantioselectivity (**Scheme 5-27**). In a mismatched DyKAT, the enantioselectivity of the product would decrease at higher conversions due to a build-up of the undesired enantiomer of starting material due to inefficient racemization. Although DKR and DyKAT are similar, a distinct different between these two processes is the identity of the catalyst/reagent that induces racemization and the identity of the intermediate that is formed during racemization. In a DKR, racemization is generally promoted by an achiral catalyst/reagent that is not involved in the enantiodetermining step, which leads to an intermediate (I) that is achiral. Alternatively, in a DyKAT racemization is mediated by the chiral catalyst/reagent generating a chiral complex between substrate and catalyst (SC*).

Scheme 5-27. Deracemization Methods



To determine if the chiral catalyst **X** was responsible for racemization, as to distinguish between DKR and DyKAT mechanisms, (*R*)-**25a** was treated with **X** in 2Me-THF at room temperature (**Scheme 5-28**). Notably, (*R*)-**25a** is racemized in less than 30 min to (±)-**29** highlighting the configurational lability of β-bromo-α-keto esters under base catalysis. Since **X** effectively promoted the racemization of (*R*)-**25a** in the absence of nitromethane, we proposed that the quinuclidine moiety of **X** was capable of enolizing the starting material to generate a chiral ammonium complex with the enolate of **25a**. The generated onium salt **30** is chiral due to its intimate ion-pairing with the chiral catalyst suggesting that the Henry reaction is occurring through a DyKAT pathway.

Scheme 5-28. Catalyst-Mediated Racemization of (*R*)-**25a**



5.3.9 Elucidating the Type of DyKAT for the Henry Addition into β-Bromo-α-Keto Esters

Having elucidated a DyKAT mechanism, we turned our attention to determining if the Henry reaction was proceeding under a Type I or Type II manifold. In DyKAT Type I, the reactive species **25a** would serve as the resting state for the reaction and undergo direct nucleophilic attack by the nitronate. If this pathway were operative, then a reaction run with CD_3NO_2 in place of CH_3NO_2 would not necessarily have full D incorporation at the β-position of the product. In DyKAT Type II, however, the onium salt **30** generated during the reaction would

serve as the reactive intermediate and undergo direct addition by *aci*-nitromethane through an ene-type mechanism. This pathway would lead to complete D incorporation at the β-position of the product in a deuterium labeling experiment. Conducting the catalyzed Henry addition with CD_3NO_2 resulted in a primary kinetic isotope effect (k_H/k_D = 2.8) and only 36% D incorporation at the β-position (**Scheme 5-29**, **Figure 5-2**).

Scheme 5-29. Deuterium-Labeling Studies in Direct Henry Addition

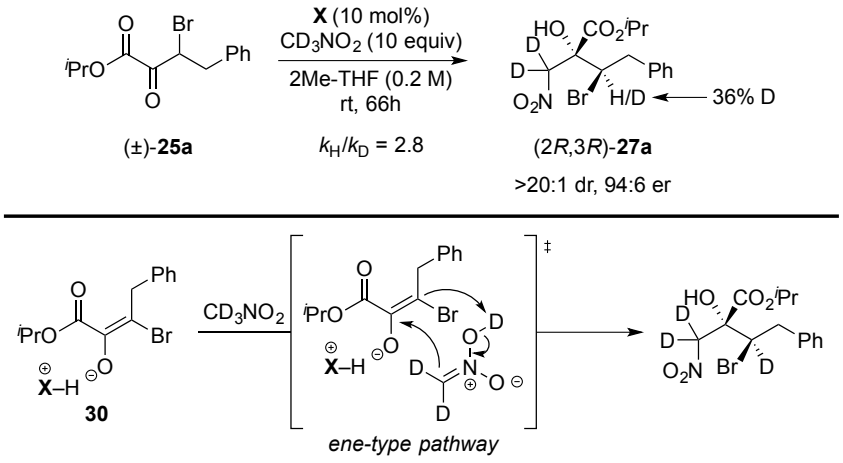
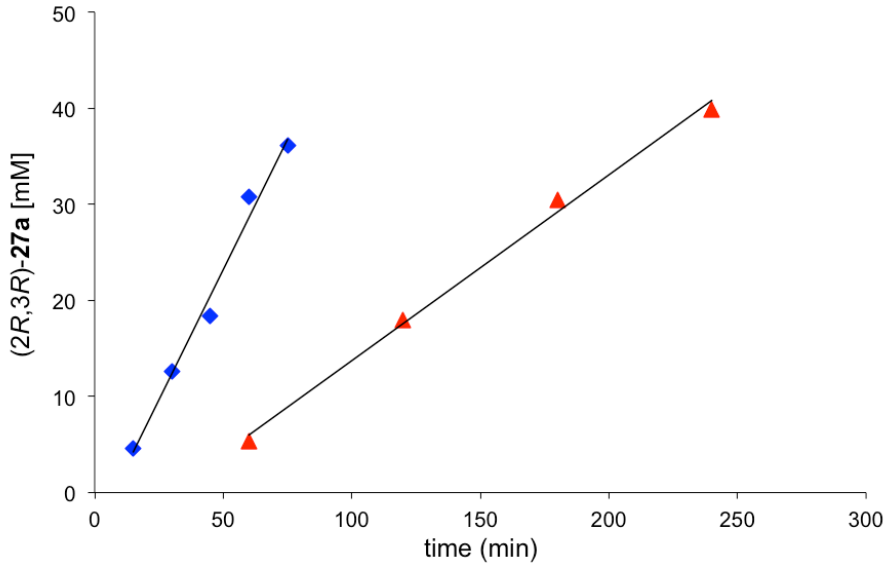
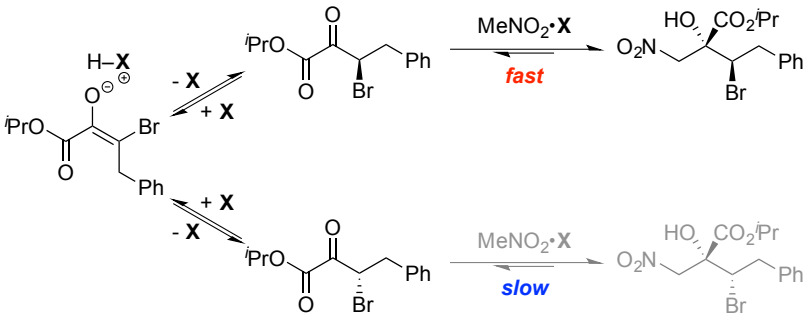


Figure 5-2. Initial Rates of Formation of **27a** in Direct Henry Addition of CH_3NO_2 (◆) and CD_3NO_2 (▲) to Determine Kinetic Isotope Effect



These data suggest that racemization is at least partially an intimate ion process with protonation from the ammonium salt (protonated catalyst) rather than nitromethane, and generation of the reactive nitronate species contributes to the overall reaction rate. Furthermore, *in situ* monitoring of the reaction by No-D ^{1}H NMR spectroscopy[40] in 2-MeTHF revealed no intermediates, confirming that the catalyst resting state is the neutral amine and corroborating that nitronate formation is an uphill process. The moderate deuterium incorporation excludes a DyKAT Type II mechanism wherein the chiral onium enolate would directly participate in an ene-type reaction with *aci*-nitromethane. Based on these collective data, we propose that the reaction proceeds through a DyKAT Type I manifold (**Scheme 5-30**).

Scheme 5-30. Proposed DyKAT Mechanism for Direct Henry Addition

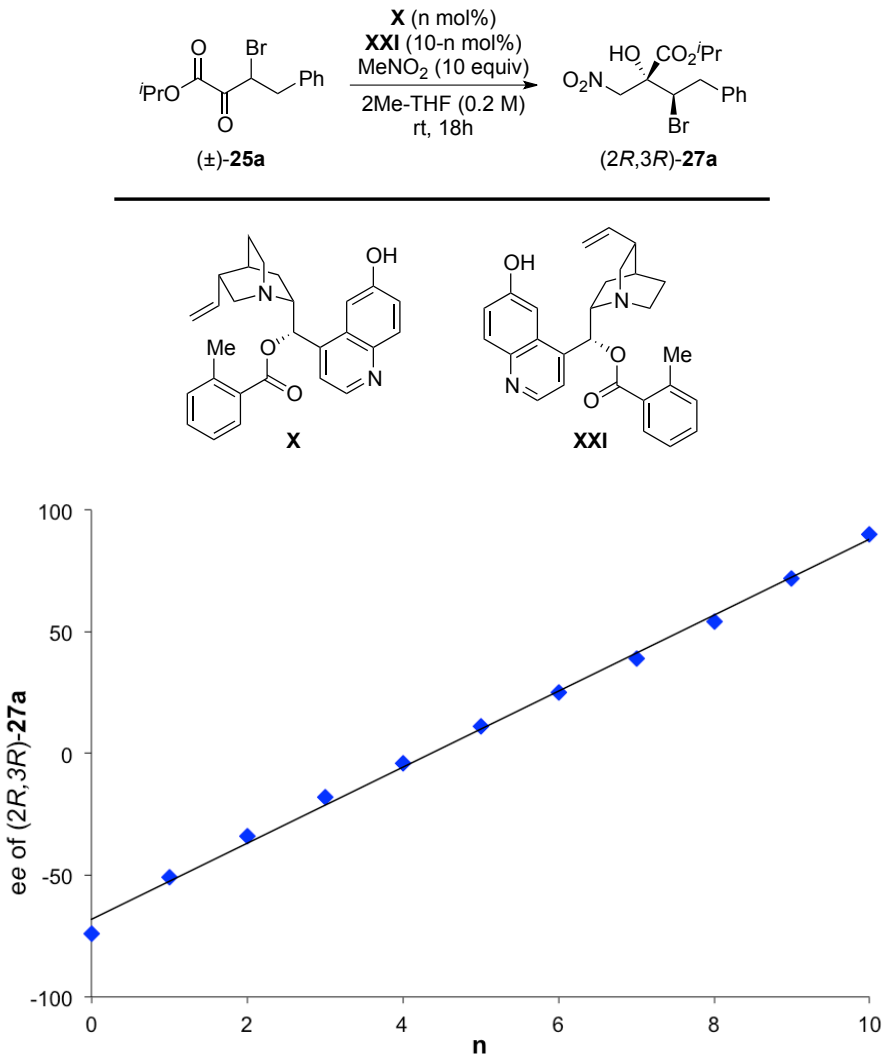


5.3.10 Non-Linear Effects in the Direct Henry Addition

Although not explicitly discussed in their work, Calter employed a pyrimidinyl-bridged bis(quinidine) catalyst in their "interrupted" Feist−Bénary reaction to overcome poor selectivities observed with quinidine itself suggesting that both chiral amines in the catalyst structure may be involved in the enantio-determining step (**Scheme 5-12**). Non-linear effects have been sparingly studied with cinchona-derived catalysts.[41] To elucidate if a non-linear effect was observed in our Henry reaction, we employed a mixture of pseudo-enantiomeric catalysts **X** and **XXI**. The Henry reaction was found to exhibit a linear relationship between catalyst diastereomeric composition

and reaction enantioselectivity (R^2 = 0.997), eliminating the possibility of a dimeric catalyst species with concomitant activation of electrophile and nucleophile (**Figure 5-3**).

Figure 5-3. Examination of Non-Linear Effects in Direct Henry Reaction



5.4 Conclusion

In conclusion, dynamic kinetic asymmetric transformations of β-bromo-α-keto esters have been developed employing direct aldolization of nitromethane and acetone. The fully-substituted β-bromo-α-glycolic acid derivatives are obtained with high levels of diastereo- and

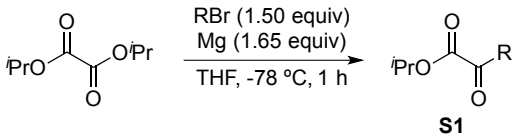
enantioselectivity in near quantitative yield. The operationally simple protocols offer rapid generation of molecular complexity through formation of vicinal stereocenters in a single C–C bond forming event. Mechanistic studies provide evidence for a DyKAT Type I manifold in the Henry addition of nitromethane into β-bromo-α-keto esters. The mechanistic insight gained in this work will serve as the basis for the design and development of new dynamic reaction manifolds employing α-labile carbonyls, which will explore the use of more complex nucleophile/electrophile pairings.

5.5 Experimental Details

Methods: Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 101 MHz or 151 MHz, and ^{19}F NMR at 376 or 565 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, sept = septuplet, oct = octuplet, m = multiplet), coupling constants (Hz), and integration. HPLC analysis was performed on an Agilent Technologies 1200 System equipped with Chiralpak IA, IB, and IC columns (φ 4.6 mm x 250 mm, constant flow at 1.00 mL/min). Supercritical fluid chromatography (SFC) was performed on a Berger SFC system equipped with Chiralpak AD, AS, and OD columns (φ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH with an oven temperature of 40 °C. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Thermo Scientific LTQ FT Ultra instrument with electrospray ionization. Analytical thin layer chromatography (TLC) was performed on Sorbtech 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle. All reactions were carried out with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

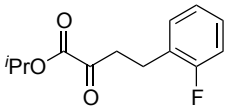
Materials: Catalysts were prepared according to known literature procedures.[6f,42] α-Keto esters **S1a**,[43] **S1f**,[44] **S1h**,[45] and **S1i**[46] were prepared according to General Procedure A and matched spectral data reported in the literature. β-Bromo-α-keto esters **25f**[47] and **25i**[47] were prepared according to General Procedure B and matched spectral data reported in the literature. Triethylamine (Et_3N) was freshly distilled from calcium hydride prior to use. 2Me-THF was freshly distilled from lithium aluminum hydride prior to use. Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

General Procedure A for the Preparation of α-Keto Esters S1

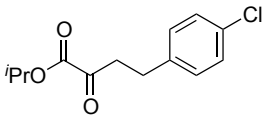


A 100-mL 3-neck round-bottomed flask affixed with a reflux condenser and addition funnel was charged with magnesium turnings (400 mg, 16.5 mmol, 1.65 equiv). The apparatus was flame-dried under high vacuum. Upon cooling to room temperature, the apparatus was placed under an atmosphere of nitrogen and THF (10 mL) was added. A solution of the alkyl bromide (15 mmol, 1.5 equiv) in THF (5 mL) was added dropwise from the addition funnel over 15 min. The reaction was allowed to age for 1 h at room temperature following addition. The solution was cooled to -78 ºC. A solution of diisopropyl oxalate (1.74 g, 10 mmol, 1.0 equiv) in THF (10 mL) was added dropwise. Following addition, the reaction was allowed to stir for 1 h at -78 ºC. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 30

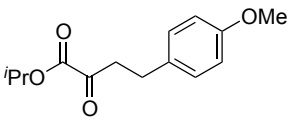
mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The obtained residue was purified by column chromatography on silica gel to afford α-keto ester **S1**.



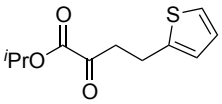
Isopropyl 4-(2-fluorophenyl)-2-oxobutanoate (S1b): The title compound was prepared according to General Procedure A using 1-(2-bromoethyl)-2-fluorobenzene (3.05 g, 15.0 mmol) affording **S1b** (2.23 g, 94% yield) as a pale yellow oil. Analytical data for **S1b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22-7.14 (m, 2H), 7.06-6.97 (m, 2H); 5.11 (sept, J = 6.3 Hz, 1H), 3.15 (t, J = 7.6 Hz, 1H), 2.96 (t, J = 7.4 Hz, 1H), 1.32 (d, J = 6.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.5, 162.2, 160.0 (d, $J_{C–F}$ = 46.2 Hz), 130.7 (d, $J_{C–F}$ = 4.8 Hz), 128.1 (d, $J_{C–F}$ = 8.2 Hz), 126.9 (d, $J_{C–F}$ = 15.8 Hz), 124.0 (d, $J_{C–F}$ = 3.6 Hz), 115.2 (d, $J_{C–F}$ = 21.9 Hz), 70.6, 39.4, 22.7, 22.6, 21.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -118.3; **IR** (thin film): 1725, 1493, 1456, 1376, 1255, 1231, 1072 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.47; **HRMS** (ESI): Calcd. for $C_{13}H_{16}FO_3$ ([M+H]$^+$): 239.1084, Found: 239.1078.



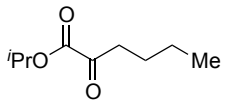
Isopropyl 4-(4-chlorophenyl)-2-oxobutanoate (S1c): The title compound was prepared according to General Procedure A using 1-(2-bromoethyl)-4-chlorobenzene (3.29 g, 15.0 mmol) affording **S1c** (2.37 g, 93% yield) as a pale yellow oil. Analytical data for **S1c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 5.12 (sept, J = 6.3 Hz, 1H), 3.14 (t, J = 7.4 Hz, 2H), 2.92 (t, J = 7.4 Hz, 2H), 1.33 (d, J = 6.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.6, 160.4, 138.6, 132.1, 129.8, 128.6, 70.8, 40.7, 28.3, 21.5; **IR** (thin film): 1724, 1646, 1491, 1456, 1257, 1106 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.43; **HRMS** (ESI): Calcd. for $C_{13}H_{15}ClNaO_3$ ([M+Na]$^+$): 277.0608, Found: 277.0602.



Isopropyl 4-(4-methoxyphenyl)-2-oxobutanoate (S1d): The title compound was prepared according to General Procedure A using 1-(2-bromoethyl)-4-methoxybenzene (3.23 g, 15.0 mmol) affording **S1d** (2.17 g, 87% yield) as a pale yellow oil. Analytical data for **S1d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.12 (sept, *J* = 6.3 Hz, 1H), 3.78 (s, 3H), 3.12 (t, *J* = 7.5 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.32 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.0, 160.5, 158.1, 132.1, 129.3, 113.9, 70.6, 55.2, 41.2, 28.1, 21.5; **IR** (thin film): 1727, 1651, 1492, 1378, 1231, 1102 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.35; **HRMS** (ESI): Calcd. for $C_{14}H_{18}NaO_4$ ([M+Na]$^+$): 273.1103, Found: 273.1097.



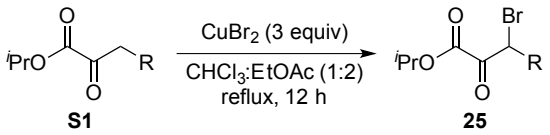
Isopropyl 2-oxo-4-(thiophen-2-yl)butanoate (S1e): The title compound was prepared according to General Procedure A using 2-(2-bromoethyl)thiophene (2.87 g, 15.0 mmol) affording **S1e** (2.02 g, 89% yield) as a yellow oil. Analytical data for **S1e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.91 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.83 (d, *J* = 3.3 Hz, 1H), 5.13 (sept, *J* = 6.3 Hz, 1H), 3.24-3.15 (m, 4H), 1.34 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 193.3, 160.3, 142.6, 126.9, 124.9, 123.6, 70.8, 41.1, 23.2, 21.5; **IR** (thin film): 1725, 1651, 1491, 1377, 1255, 1183, 1016 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.43; **HRMS** (ESI): Calcd. for $C_{11}H_{14}NaO_3S$ ([M+Na]$^+$): 249.0562, Found: 249.0556.



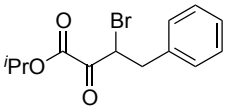
Isopropyl 2-oxo-4-(thiophen-2-yl)butanoate (S1g): The title compound was prepared according to General Procedure A using 1-bromobutane (2.06 g, 15.0 mmol) affording **S1g** (1.51 g, 88% yield) as a yellow oil. Analytical data for **S1g**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.08 (sept, *J* = 6.3 Hz, 1H), 2.76 (t, *J* = 7.4 Hz, 2H), 1.60-1.52 (m, 2H), 1.36-1.25 (m, 2H), 1.30 (d, *J* = 6.3 Hz, 6H), 0.87 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz,

$CDCl_3$): δ 195.0, 160.9, 70.3, 38.8, 25.0, 22.0, 21.4, 13.6; **IR** (thin film): 1717, 1647, 1541, 1466, 1376, 1279, 1106 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.61; **HRMS** (ESI): Calcd. for $C_9H_{16}NaO_3$ ($[M+Na]^+$): 195.0997, Found: 195.0991.

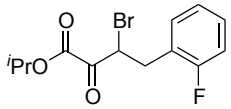
General Procedure B for the Preparation of β-Bromo-α-Keto Esters 25



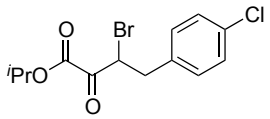
A 200-mL round-bottomed flask affixed with a reflux condenser was charged with α-keto ester **S1** (4.0 mmol, 1.0 equiv) in $CHCl_3$:EtOAc (1:2, 60 mL). $CuBr_2$ (2.7 g, 12.0 mmol, 3.0 equiv) was added in one portion. The reaction was allowed to stir at a gentle reflux for 12 h. The reaction was cooled to room temperature and filtered through a pad of Celite® washing with EtOAc (3 x 20 mL). The filtrate concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford β-bromo-α-keto ester **25**.



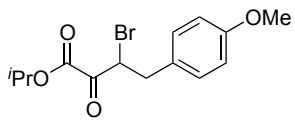
Isopropyl 3-bromo-2-oxo-4-phenylbutanoate (25a): The title compound was prepared according to General Procedure B using **S1a** (0.88 g, 4.0 mmol) affording **25a** (1.09 g, 91% yield) as a yellow oil. Analytical data for **25a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.24 (m, 5H); 5.25 (t, *J* = 7.5 Hz, 1H), 5.17 (sept, *J* = 6.3 Hz, 1H), 3.53 (dd, *J* = 14.5, 7.3 Hz, 1H), 3.24 (dd, *J* = 14.5, 7.7 Hz, 1H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.34 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.6, 159.7, 136.5, 129.3, 128.6, 127.3, 71.5, 47.8, 38.2, 21.5, 21.4; **IR** (thin film): 1730, 1698, 1653, 1456, 1376, 1283, 1089 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.44; **HRMS** (ESI): Calcd. for $C_{13}H_{15}BrNaO_3$ ($[M+Na]^+$): 321.0103, Found: 321.0107.



Isopropyl 3-bromo-4-(2-fluorophenyl)-2-oxobutanoate (25b): The title compound was prepared according to General Procedure B using **S1b** (0.95 g, 4.0 mmol) affording **25b** (1.21 g, 95% yield) as a yellow oil. Analytical data for **25b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H), 7.11-7.03 (m, 2H), 5.32 (t, J = 7.3 Hz, 1H), 5.18 (sept, J = 6.3 Hz, 1H), 3.53 (dd, J = 14.6, 6.9 Hz, 1H), 3.31 (dd, J = 14.6, 8.1 Hz, 1H), 1.36 (d, J = 6.3 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.5, 162.5, 159.8 (d, $J_{C–F}$ = 40.3 Hz), 132.0 (d, $J_{C–F}$ = 4.3 Hz), 129.3 (d, $J_{C–F}$ = 8.2 Hz), 124.2 (d, $J_{C–F}$ = 3.5 Hz), 123.4 (d, $J_{C–F}$ = 15.4 Hz), 115.4 (d, $J_{C–F}$ = 21.7 Hz), 71.6, 46.3 (d, $J_{C–F}$ = 1.6 Hz), 32.1 (d, $J_{C–F}$ = 1.8 Hz), 21.5, 21.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -117.5; **IR** (thin film): 1731, 1655, 1492, 1377, 1291, 1257, 1104 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.39; **HRMS** (ESI): Calcd. for $C_{14}H_{18}BrFNaO_4$ ([M+Na+MeOH]$^+$): 371.0270, Found: 371.0263.

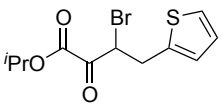


Isopropyl 3-bromo-4-(4-chlorophenyl)-2-oxobutanoate (25c): The title compound was prepared according to General Procedure B using **S1c** (1.02 g, 4.0 mmol) affording **25c** (1.16 g, 87% yield) as a yellow oil. Analytical data for **25c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 5.23-5.13 (m, 2H), 3.48 (dd, J = 14.6, 7.2 Hz, 1H), 3.21 (dd, J = 14.6, 7.7 Hz, 1H), 1.35 (d, J = 6.3 Hz, 3H), 1.34 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.4, 159.7, 134.9, 133.3, 130.7, 128.9, 71.7, 47.3, 37.5, 21.49, 21.46; **IR** (thin film): 1732, 1698, 1647, 1541, 1457, 1259, 1015 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.29; **HRMS** (ESI): Calcd. for $C_{14}H_{18}BrClNaO_4$ ([M+Na+MeOH]$^+$): 386.9975, Found: 386.9968.

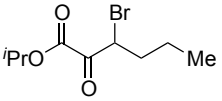


Isopropyl 3-bromo-4-(4-methoxyphenyl)-2-oxobutanoate (25d): The title compound was prepared according to General Procedure B using **S1d** (1.00 g, 4.0 mmol) affording **25d** (1.28 g, 97% yield) as a yellow oil. Analytical data for

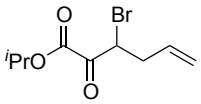
25d: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.22-5.11 (m, 2H), 3.78 (s, 3H), 3.47 (dd, *J* = 14.5, 7.6 Hz, 1H), 3.18 (dd, *J* = 14.5, 7.4 Hz, 1H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.34 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.7, 159.7, 158.8, 130.4, 128.5, 114.0, 71.5, 55.2, 48.0, 37.4, 21.5, 21.4; **IR** (thin film): 1725, 1697, 1647, 1514, 1457, 1251, 1180 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.31; **HRMS** (ESI): Calcd. for $C_{15}H_{21}BrNaO_5$ ([M+Na+MeOH]$^+$): 383.0470, Found: 383.0463.



Isopropyl 3-bromo-2-oxo-4-(thiophen-2-yl)butanoate (25e): The title compound was prepared according to General Procedure B using **S1e** (0.91 g, 4.0 mmol) affording **25e** (1.17 g, 96% yield) as an orange oil. Analytical data for **25e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.95-6.92 (m, 2H), 5.25-5.15 (m, 2H), 3.75 (dd, *J* = 15.4, 7.7 Hz, 1H), 3.47 (dd, *J* = 15.4, 6.9 Hz, 1H), 1.36 (d, *J* = 6.2 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.3, 159.6, 138.2, 127.1, 127.0, 125.0, 71.6, 46.8, 32.4, 21.49, 21.46; **IR** (thin film): 1727, 1647, 1466, 1374, 1293, 1235, 1104 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.34; **HRMS** (ESI): Calcd. for $C_{12}H_{17}BrNaO_4S$ ([M+Na+MeOH]$^+$): 358.9929, Found: 358.9922.

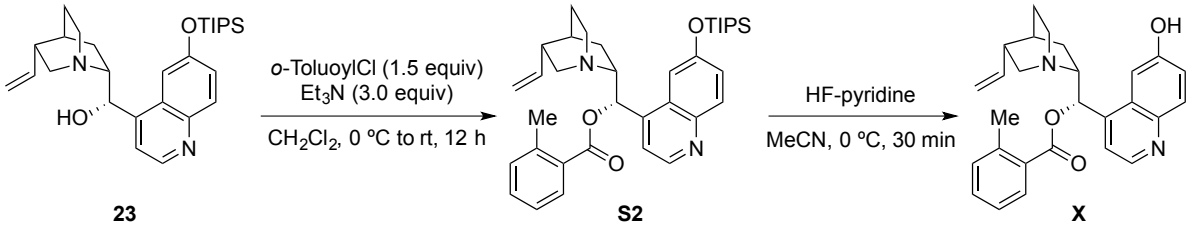


Isopropyl 3-bromo-2-oxohexanoate (25g): The title compound was prepared according to General Procedure B using **S1g** (0.69 g, 4.0 mmol) affording **25g** (0.88 g, 88% yield) as a yellow oil. Analytical data for **25g**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.18 (sept, *J* = 6.3 Hz, 1H), 5.01 (dd, *J* = 8.4, 6.0 Hz, 1H), 2.09-1.92 (m, 2H), 1.61-1.51 (m, 1H), 1.47-1.31 (m, 1H), 1.36 (d, *J* = 6.3 Hz, 6H), 0.96 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 186.2, 160.3, 71.4, 48.3, 33.8, 21.49, 21.47, 20.3, 13.4; **IR** (thin film): 1731, 1698, 1645, 1457, 1376, 1279, 1058 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.54; **HRMS** (ESI): Calcd. for $C_{10}H_{19}BrNaO_4$ ([M+Na+MeOH]$^+$): 305.0365, Found: 305.0359.



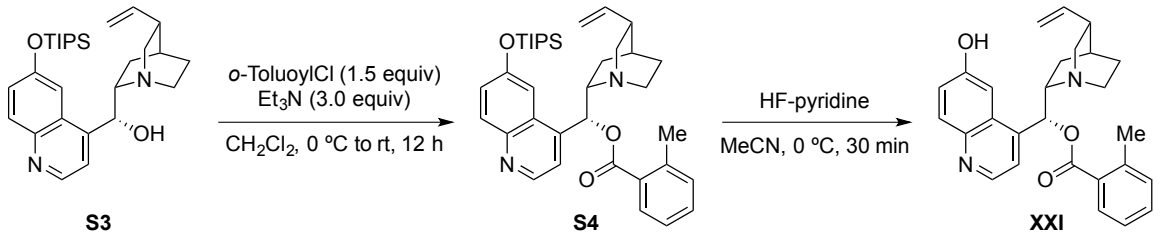
Isopropyl 3-bromo-2-oxohex-5-enoate (25h): The title compound was prepared according to General Procedure B using **S1h** (0.68 g, 4.0 mmol) affording **25h** (0.81 g, 81% yield) as a yellow oil. Analytical data for **25h**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.81-5.74 (m, 1H), 5.21-5.16 (m, 3H), 5.04 (t, *J* = 7.6 Hz, 1H), 2.91-2.86 (m, 1H), 2.74-2.69 (m, 1H), 1.36 (d, *J* = 6.2 Hz, 3H), 1.35 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 185.6, 159.9, 132.7, 119.4, 71.5, 46.6, 36.1, 21.48, 21.45; **IR** (thin film): 1735, 1697, 1636, 1490, 1237, 1105 cm^{-1}; **TLC** (15% ethyl acetate:hexanes): R_f = 0.48; **HRMS** (ESI): Calcd. for $C_{10}H_{17}BrNaO_4$ ([M+Na+MeOH]$^+$): 303.0208, Found: 303.0201.

Synthesis of Bifunctional Catalysts X and XXI



(*S*)-(6-hydroxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl 2-methylbenzoate (X): A flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was charged with alcohol **23**[6f] (934 mg, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). The solution was cooled to 0 ºC in an ice bath. 2-Methylbenzoyl chloride (460 µL, 3.0 mmol, 1.5 equiv) and Et_3N (840 µL, 6.0 mmol, 3.0 equiv) were added sequentially. The reaction was allowed to stir overnight as it slowly warmed to room temperature. After 12 h, the reaction was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude **S2**.

A 50-mL Nalgene® Erlenmeyer flask equipped with a magnetic stir bar was charged with crude **S2** in MeCN (20 mL). The solution was cooled to 0 ºC in an ice bath. HF-Pyridine (~70% HF, 1 mL) was added dropwise. The reaction was allowed to stir for 30 min at 0 ºC before being carefully quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was diluted with EtOAc (30 mL) and the layers were separated. The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with EtOAc:MeOH:Et_3N (50:2:1) to afford bifunctional catalyst **X** (689 mg, 80% yield) as an off-white solid (mp: 201-203 ºC). Analytical data for **X**: **^{1}H NMR** (600 MHz, CD_3OD): δ 8.61 (d, *J* = 4.6 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 9.1 Hz, 1H), 7.56 (d, *J* = 4.6 Hz, 1H), 7.51-7.48 (m, 2H), 7.41-7.35 (m, 2H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 4.6 Hz, 1H), 6.08-6.02 (m, 1H), 5.13-5.07 (m, 2H), 3.58-3.57 (m, 1H), 3.23-3.19 (m, 1H), 3.11-3.03 (m, 2H), 2.93-2.88 (m, 1H), 2.50 (s, 3H), 2.51-2.45 (m, 1H), 2.25-2.21 (m, 1H), 1.92 (br s, 1H), 1.72-1.70 (m, 2H), 1.62-1.57 (m, 1H), 1.31-1.27 (m, 1H), 1.15-1.09 (m, 1H); **^{13}C NMR** (151 MHz, CD_3OD): δ 167.1, 158.1, 147.5, 144.6, 144.4, 142.1, 140.2, 134.0, 133.1, 131.8, 131.7, 129.7, 128.4, 127.2, 123.6, 119.8, 116.2, 105.2, 60.1, 50.8, 50.1, 39.8, 32.8, 28.8, 26.1, 23.7, 23.3, 21.8, 17.6, 14.5, 14.4, 13.0, 12.9; **IR** (thin film): 3430, 2125, 1732, 1636, 1520, 1472, 1418, 1243, 1067 cm^{-1}; **TLC** (40:2:1 ethyl acetate:methanol:triethylamine): R_f = 0.45; **HRMS** (ESI): Calcd. for $C_{27}H_{29}N_2O_3$ ($[M+H]^+$): 429.2179, Found: 429.2170; **$[\alpha]_D$** -4 (*c* = 0.5, $CHCl_3$).

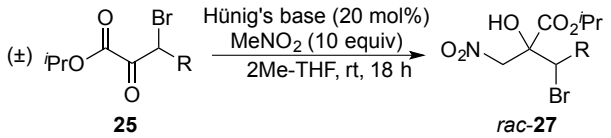


(*R*)-(6-hydroxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl 2-methylbenzoate (XXI): A flame-dried 25-mL round-bottomed flask equipped with a magnetic stir bar was charged with alcohol **S3**[6f] (934 mg, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). The solution was cooled to 0 ºC in an ice bath. 2-Methylbenzoyl chloride (460 µL, 3.0 mmol, 1.5 equiv) and Et_3N (840 µL, 6.0 mmol, 3.0 equiv) were added sequentially. The reaction was allowed to stir overnight as it slowly warmed to room temperature. After 12 h, the reaction was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude **S4**.

A 50-mL Nalgene® Erlenmeyer flask equipped with a magnetic stir bar was charged with crude **S4** in MeCN (20 mL). The solution was cooled to 0 ºC in an ice bath. HF-Pyridine (~70% HF, 1 mL) was added dropwise. The reaction was allowed to stir for 30 min at 0 ºC before being carefully quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was diluted with EtOAc (30 mL) and the layers were separated. The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with EtOAc:MeOH:Et_3N (50:2:1) to afford bifunctional catalyst **XXI** (787 mg, 92% yield) as an off-white solid (mp: 203-205 ºC). Analytical data for **XXI**: **^{1}H NMR** (600 MHz, DMSO-d_6): δ 8.63 (br s, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.57 (s, 1H),

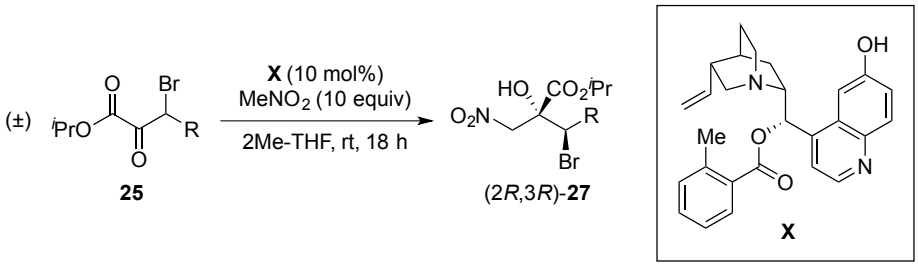
7.51 (d, J = 12.8 Hz, 1H), 7.36-7.32 (m, 3H), 6.42 (d, J = 6.2 Hz, 1H), 5.96-5.93 (m, 1H), 5.00 (dd, J = 20.3, 10.1 Hz, 2H), 3.48 (br s, 1H), 3.09 (br s, 1H), 2.85-2.84 (m, 1H), 2.45 (s, 3H), 2.50-2.42 (m, 1H), 2.22 (br s, 1H), 1.97 (br s, 1H), 1.77 (br s, 1H), 1.66 (br s, 1H), 1.50-1.47 (m, 2H), 1.13 (br s, 1H); **^{13}C NMR** (151 MHz, DMSO-d_6): δ 165.9, 155.7, 146.7, 143.3, 142.3, 139.7, 132.7, 131.9, 131.4, 130.3, 128.6, 127.2, 126.3, 121.7, 114.5, 104.6, 59.4, 55.9, 48.6, 45.6, 41.7, 27.3, 27.2, 25.3, 21.2; **IR** (thin film): 3419, 2132, 1734, 1647, 1576, 1541, 1472, 1436, 1244, 1069 cm^{-1}; **TLC** (40:2:1 ethyl acetate:methanol:triethylamine): R_f = 0.50; **HRMS** (ESI): Calcd. for $C_{27}H_{29}N_2O_3$ ([M+H]$^+$): 429.2179, Found: 429.2169; **[α]$_D$** +67 (c = 0.5, $CHCl_3$).

<u>General Procedure C for the Preparation of *rac*-27</u>

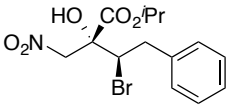


A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester **25** (0.20 mmol, 1.0 equiv) and $MeNO_2$ (110 µL, 2.00 mmol, 10.0 equiv) in 2Me-THF (1.0 mL, 0.2 M). Hünig's base (7 µL, 0.04 mmol, 0.2 equiv) was added, the vial was capped, and the reaction was allowed to stir for 18 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The crude residue was purified by column chromatography on silica gel to afford *rac*-**27** as a mixture of diastereomers.

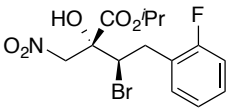
General Procedure D for the Henry Aldolization



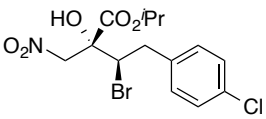
A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester **25** (0.20 mmol, 1.0 equiv) and $MeNO_2$ (110 µL, 2.00 mmol, 10.0 equiv) in 2Me-THF (1.0 mL, 0.2 M). Catalyst **X** (8.6 mg, 0.02 mmol, 0.1 equiv) was added, the vial was capped, and the reaction was allowed to stir for 18 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) and concentrated *in vacuo* to afford analytically pure **27**. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue.



Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-2-(nitromethyl)-4-phenylbutanoate (27a): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25a** (59.8 mg, 0.20 mmol) affording **27a** (69.9 mg, 97% yield, >20:1 dr) as a white solid (mp: 113-116 ºC). Analytical data for **27a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.23 (m, 5H), 5.27 (sept, J = 6.3 Hz, 1H), 5.03 (d, J = 13.2 Hz, 1H), 4.71 (d, J = 13.2 Hz, 1H), 4.24 (dd, J = 10.7, 3.4 Hz, 1H), 4.18 (br s, 1H), 3.42 (dd, J = 10.7, 7.4 Hz, 1H), 2.98 (dd, J = 14.6, 10.7 Hz, 1H), 1.38 (d, J = 6.3 Hz, 3H), 1.36 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.7, 137.2, 129.1, 128.6, 127.3, 79.0, 77.2, 72.5, 56.3, 38.9, 21.6, 21.4; **IR** (thin film): 3445, 1735, 1717, 1647, 1374, 1235, 1059 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.41; **HRMS** (ESI): Calcd. for $C_{14}H_{18}BrNNaO_5$ ([M+Na]$^+$): 382.0266, Found: 382.0260; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 17.2 min, $t_{R\ (minor)}$ 22.2 min, 96:4 er; **[α]$_D$** -28 (c = 1.2, $CHCl_3$).

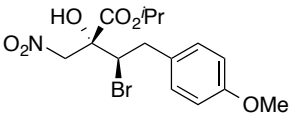


Isopropyl (2*R*,3*R*)-3-bromo-4-(2-fluorophenyl)-2-hydroxy-2-(nitromethyl)butanoate (27b): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25b** (63.4 mg, 0.20 mmol) affording **27b** (74.2 mg, 98% yield, >20:1 dr) as a white solid (mp: 90-92 ºC). Analytical data for **27b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.23 (m, 2H), 7.14-7.04 (m, 2H), 5.26 (sept, J = 6.3 Hz, 1H), 5.04 (d, J = 13.2 Hz, 1H), 4.83 (d, J = 13.2 Hz, 1H), 4.29 (dd, J = 11.0, 2.9 Hz, 1H), 4.16 (br s, 1H), 3.45 (dd, J = 14.3, 1.8 Hz, 1H), 3.02 (dd, J = 14.7, 11.1 Hz, 1H), 1.37 (d, J = 6.3 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.6, 161.2 (d, $J_{C–F}$ = 246.0 Hz), 132.0 (d, $J_{C–F}$ = 4.2 Hz), 129.3 (d, $J_{C–F}$ = 8.2 Hz), 124.2 (d, $J_{C–F}$ = 3.5 Hz), 123.4 (d, $J_{C–F}$ = 15.4 Hz), 115.4 (d, $J_{C–F}$ = 21.7 Hz), 71.6, 46.3 (d, $J_{C–F}$ = 1.6 Hz), 32.1 (d, $J_{C–F}$ = 1.8 Hz), 21.5, 21.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -118.4; **IR** (thin film): 3451, 1733, 1717, 1645, 1451, 1281, 1105 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.39; **HRMS** (ESI): Calcd. for $C_{14}H_{17}BrFNNaO_5$ ($[M+Na]^+$): 400.0172, Found: 400.0165; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 17.5 min, $t_{R\ (minor)}$ 19.2 min, 92:8 er; **$[\alpha]_D$** -20 (c = 1.1, $CHCl_3$).

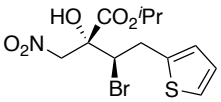


Isopropyl (2*R*,3*R*)-3-bromo-4-(4-chlorophenyl)-2-hydroxy-2-(nitromethyl)butanoate (27c): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25c** (66.7 mg, 0.20 mmol) affording **27c** (77.3 mg, 98% yield, >20:1 dr) as a white solid (mp: 96-98 ºC). Analytical data for **27c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 5.26 (sept, J = 6.3 Hz, 1H), 5.07 (d, J = 13.2 Hz, 1H), 4.72 (d, J = 13.2 Hz, 1H), 4.21 (br s, 1H), 4.17 (dd, J = 11.1, 3.1 Hz, 1H), 3.38 (dd, J = 14.7, 3.1 Hz, 1H), 2.92 (dd, J = 14.7, 3.1 Hz, 1H), 1.37 (d, J = 6.3 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.6, 135.6, 133.1, 130.5,

128.8, 78.9, 77.0, 72.6, 56.0, 38.1, 21.6, 21.4; **IR** (thin film): 3471, 1733, 1716, 1647, 1374, 1235, 1061 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.38; **HRMS** (ESI): Calcd. for $C_{14}H_{17}BrClNNaO_5$ ($[M+Na]^+$): 415.9877, Found: 415.9870; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 15.9 min, $t_{R\ (minor)}$ 21.0 min, 95.5:4.5 er; **[α]$_D$** -35 (*c* = 1.2, $CHCl_3$).

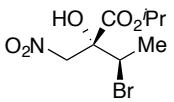


Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-4-(4-methoxyphenyl)-2-(nitromethyl)butanoate (27d): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25d** (65.8 mg, 0.20 mmol) affording **27d** (76.2 mg, 98% yield, >20:1 dr) as a pale yellow oil. Analytical data for **27d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.25 (sept, *J* = 6.3 Hz, 1H), 5.01 (d, *J* = 13.2 Hz, 1H), 4.69 (d, *J* = 13.2 Hz, 1H), 4.20 (dd, *J* = 10.6, 3.6 Hz, 1H), 4.17 (br s, 1H), 3.80 (s, 3H), 3.35 (dd, *J* = 14.8, 3.6 Hz, 1H), 2.93 (dd, *J* = 14.8, 2.6 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.35 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.7, 158.8, 130.2, 129.2, 114.0, 79.0, 77.2, 72.4, 56.9, 55.2, 38.1, 21.6, 21.4; **IR** (thin film): 3446, 1733, 1717, 1653, 1515, 1457, 1249, 1178 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.30; **HRMS** (ESI): Calcd. for $C_{15}H_{20}BrNNaO_6$ ($[M+Na]^+$): 412.0372, Found: 412.0366; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 27.5 min, $t_{R\ (minor)}$ 37.2 min, 96:4 er; **[α]$_D$** -28 (*c* = 1.1, $CHCl_3$).

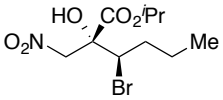


Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-2-(nitromethyl)-4-(thiophen-2-yl)butanoate (27e): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25e** (61.0 mg, 0.20 mmol) affording **27e** (68.3 mg, 93% yield, >20:1 dr) as an off-white solid (mp: 77-79 ºC). Analytical data for **27e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 5.0 Hz, 1H), 6.98-6.94 (m, 2H), 5.25 (sept, *J* = 6.3 Hz, 1H), 5.00 (d,

J = 13.3 Hz, 1H), 4.67 (d, J = 13.3 Hz, 1H), 4.17 (dd, J = 10.0, 3.8 Hz, 1H), 4.16 (br s, 1H), 3.61 (dd, J = 15.7, 3.8 Hz, 1H), 3.27 (dd, J = 15.7, 10.0 Hz, 1H), 1.37 (d, J = 6.3 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.5, 139.3, 127.0, 126.9, 124.9, 78.8, 77.1, 72.6, 55.8, 33.6, 21.6, 21.4; **IR** (thin film): 3445, 1732, 1716, 1653, 1541, 1457, 1374, 1253 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.38; **HRMS** (ESI): Calcd. for $C_{12}H_{16}BrNNaO_5S$ ([M+Na]$^+$): 387.9831, Found: 387.9825; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 19.5 min, $t_{R\ (minor)}$ 24.5 min, 95.5:4.5 er; **[α]$_D$** -37 (c = 1.1, $CHCl_3$).

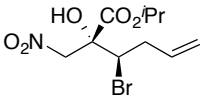


Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-2-(nitromethyl)butanoate (27f): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25f** (44.6 mg, 0.20 mmol) affording **27f** (54.1 mg, 95% yield, >20:1 dr) as a white solid (mp: 57-59 ºC). Analytical data for **27f**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.23 (sept, J = 6.3 Hz, 1H), 4.93 (d, J = 13.1 Hz, 1H), 4.64 (d, J = 13.1 Hz, 1H), 4.22 (q, J = 6.8 Hz, 1H), 3.98 (br s, 1H), 1.73 (d, J = 6.8 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H), 1.33 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.8, 78.5, 77.1, 72.3, 49.2, 21.6, 21.4, 19.9; **IR** (thin film): 3517, 1732, 1717, 1698, 1515, 1450, 1298, 1106 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.35; **HRMS** (ESI): Calcd. for $C_8H_{14}BrNNaO_5$ ([M+Na]$^+$): 305.9953, Found: 305.9947; **HPLC** Chiralpak IC, H:IPA = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 10.0 min, $t_{R\ (major)}$ 10.9 min, 94:6 er; **[α]$_D$** -15 (c = 0.9, $CHCl_3$).

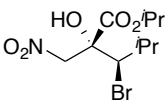


Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-2-(nitromethyl)hexanoate (27g): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25g** (50.2 mg, 0.20 mmol) affording **27g** (60.1 mg, 96% yield, 17:1 dr) as a white solid (mp: 37-38 ºC). Analytical data for **27g**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.22 (sept, J = 6.3 Hz, 1H), 5.01 (d, J = 13.2 Hz, 1H), 4.70 (d, J = 13.2 Hz, 1H), 4.04 (br s, 1H), 4.07 (dd, J =

9.6, 3.8 Hz, 1H), 1.81-1.67 (m, 3H), 1.43-1.31 (m, 1H), 1.35 (d, J = 6.3 Hz, 3H), 1.33 (d, J = 6.3 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.8, 79.1, 77.2, 72.3, 56.2, 34.1, 21.6, 21.4, 21.0, 13.1; **IR** (thin film): 3417, 1735, 1715, 1683, 1541, 1335, 1298, 1191 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.45; **HRMS** (ESI): Calcd. for $C_{10}H_{18}BrNNaO_5$ ($[M+Na]^+$): 334.0266, Found: 334.0260; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 13.3 min, $t_{R\ (major)}$ 13.9 min, 92.5:7.5 er; **$[\alpha]_D$** -42 (c = 1.0, $CHCl_3$).



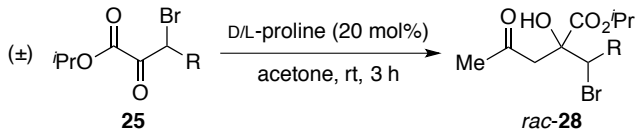
Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-2-(nitromethyl)hex-5-enoate (27h): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25h** (49.8 mg, 0.20 mmol) affording **27h** (60.8 mg, 98% yield, >20:1 dr) as a pale yellow oil. Analytical data for **27h**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.87-5.77 (m, 1H), 5.26-5.16 (m, 3H), 5.01 (d, J = 13.2 Hz, 1H), 4.73 (d, J = 13.2 Hz, 1H), 4.06 (br s, 1H), 4.03 (dd, J = 10.6, 3.2 Hz, 1H), 2.77-2.71 (m, 1H), 2.57-2.49 (m, 1H), 1.36 (d, J = 6.3 Hz, 3H), 1.34 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.6, 133.9, 118.8, 78.9, 77.1, 72.4, 54.7, 36.8, 21.6, 21.4; **IR** (thin film): 3451, 1736, 1717, 1653, 1558, 1457, 1374, 1105 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.42; **HRMS** (ESI): Calcd. for $C_{11}H_{20}BrNNaO_6$ ($[M+Na+MeOH]^+$): 364.0372, Found: 364.0383; **HPLC** Chiralpak IB, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 7.5 min, $t_{R\ (major)}$ 8.0 min, 92.5:7.5 er; **$[\alpha]_D$** -30 (c = 1.1, $CHCl_3$).



Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-4-methyl-2-(nitromethyl)pentanoate (27i): The title compound was prepared according to General Procedure D using β-bromo-α-keto ester **25i** (50.2 mg, 0.20 mmol) affording **27i** (59.3 mg, 95% yield, 5:1 dr) as a pale yellow oil. Analytical data for **27i**: **^{1}H NMR** (600 MHz, $CDCl_3$): *major diastereomer* δ 5.25-5.17 (m, 1H), 4.96 (d, J = 13.6 Hz, 1H), 4.73 (d, J = 13.6 Hz, 1H), 4.17 (d, J = 1.7 Hz, 1H), 4.02 (br s, 1H), 2.01-1.96 (m, 1H), 1.26-1.32 (m, 6H), 1.06-0.99 (m, 6H), *minor diastereomer* δ

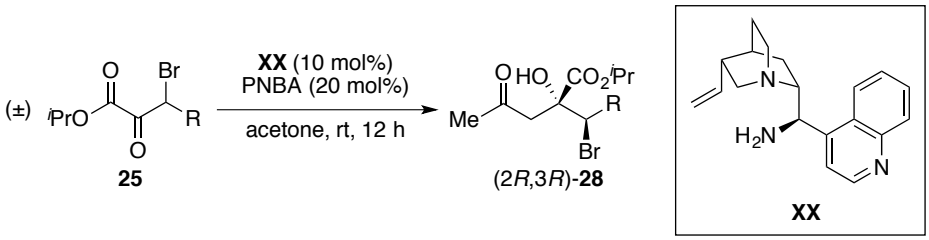
5.25-5.17 (m, 1H), 5.10 (d, J = 13.6 Hz, 1H), 4.80 (d, J = 13.6 Hz, 1H), 4.07 (d, J = 1.4 Hz, 1H), 3.79 (br s, 1H), 1.76-1.71 (m, 1H), 1.26-1.32 (m, 6H), 1.06-0.99 (m, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$): *major diastereomer* δ 170.3, 79.3, 77.7, 72.3, 64.5, 29.7, 29.5, 23.4, 21.5, 21.4, 17.6, *minor diastereomer* δ 169.8, 172.4, 81.9, 78.4, 72.3, 64.0, 31.2, 21.5, 21.4, 18.2; **IR** (thin film): 3416, 1734, 1716, 1698, 1559, 1418, 1243, 1102 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.49; **HRMS** (ESI): Calcd. for $C_{10}H_{18}BrNNaO_5$ ([M+Na]$^+$): 334.0266, Found: 334.0260; **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 13.3 min, $t_{R\ (minor)}$ 14.9 min, 87:13 er; **$[\alpha]_D$** -14 (c = 1.1, $CHCl_3$).

<u>General Procedure E for the Preparation of *rac*-28</u>

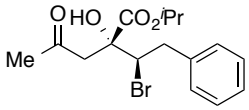


A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester **25** (0.20 mmol, 1.0 equiv) in acetone (1.0 mL, 0.2 M). D/L-Proline (4.6 mg, 0.04 mmol, 0.2 equiv) was added, the vial was capped, and the reaction was allowed to stir for 3 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) and concentrated *in vacuo* to afford analytically pure *rac*-**28**. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The diastereomers were separated by column chromatography on silica gel.

General Procedure F for the Acetone Aldolization

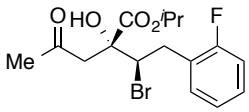


A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester **25** (0.20 mmol, 1.0 equiv) in acetone (1.0 mL, 0.2 M). Catalyst **XX** (5.9 mg, 0.02 mmol, 0.1 equiv) and PNBA (6.7 mg, 0.04 mmol, 0.2 equiv) were added, the vial was capped, and the reaction was allowed to stir for 12 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) and concentrated *in vacuo* to afford analytically pure **28**. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The diastereomers were separated by column chromatography on silica gel (if applicable).

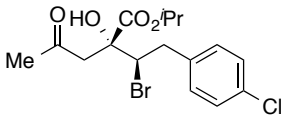


Isopropyl (*R*)-2-((*R*)-1-bromo-2-phenylethyl)-2-hydroxy-4-oxopentanoate (28a): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25a** (59.8 mg, 0.20 mmol) affording **28a** (67.9 mg, 95% yield, >20:1 dr) as a white solid (mp: 103-105 ºC). Analytical data for **28a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 5H), 5.16 (sept, J = 6.3 Hz, 1H), 4.25 (dd, J = 11.2, 2.8 Hz, 1H), 4.10 (br s, 1H), 3.42 (dd, J = 10.8, 2.8 Hz, 1H), 3.11 (dd, J = 20.8, 16.6 Hz, 2H), 2.99 (dd, J = 14.8, 11.2 Hz, 1H), 2.20 (s, 3H), 1.31 (d, J = 6.3 Hz, 3H), 1.29 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 205.1, 171.7, 138.1, 129.2, 128.4, 126.9, 70.7, 60.7, 48.9, 38.7, 31.0, 21.57, 21.55; **IR** (thin film): 3446, 1732, 1684, 1541, 1450, 1376, 1141 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.41; **HRMS** (ESI): Calcd. for $C_{16}H_{21}BrNaO_4$ ([M+Na]$^+$): 379.0521,

Found: 379.0514; **HPLC** Chiralpak IA, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 7.3 min, $t_{R\ (major)}$ 8.6 min, 96:4 er; $[\alpha]_D$ +1 (*c* = 1.1, $CHCl_3$).

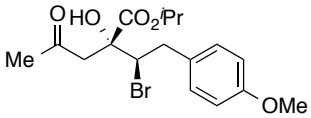


Isopropyl (*R*)-2-((*R*)-1-bromo-2-(2-fluorophenyl)ethyl)-2-hydroxy-4-oxopentanoate (28b): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25b** (63.4 mg, 0.20 mmol) affording **28b** (71.2 mg, 95% yield, >20:1 dr) as a pale white solid (mp: 64-65 ºC). Analytical data for **28b**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 9.7 Hz, 1H), 5.15 (sept, *J* = 6.2 Hz, 1H), 4.29 (dd, *J* = 11.3, 2.1 Hz, 1H), 4.05 (br s, 1H), 3.49 (d, *J* = 14.6 Hz, 1H), 3.15 (dd, *J* = 31.0, 16.7 Hz, 2H), 2.99 (dd, *J* = 14.6, 11.3 Hz, 1H), 2.21 (s, 3H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 204.9, 171.7, 161.2 (d, $J_{C–F}$ = 244.8 Hz), 132.2 (d, $J_{C–F}$ = 4.4 Hz), 128.9 (d, $J_{C–F}$ = 6.8 Hz), 125.0 (d, $J_{C–F}$ = 14.9 Hz), 123.9 (d, $J_{C–F}$ = 3.3 Hz), 115.2 (d, $J_{C–F}$ = 21.3 Hz), 70.8, 59.1, 48.7, 32.8, 30.9, 21.6, 21.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -118.5; **IR** (thin film): 3445, 1734, 1653, 1561, 1494, 1376, 1235, 1102 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.43; **HRMS** (ESI): Calcd. for $C_{16}H_{20}BrFNaO_4$ ($[M+Na]^+$): 397.0427, Found: 397.0421; **HPLC** Chiralpak IA, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 7.8 min, $t_{R\ (major)}$ 8.6 min, 95.5:4.5 er; $[\alpha]_D$ +6 (*c* = 1.2, $CHCl_3$).

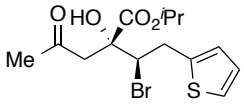


Isopropyl (*R*)-2-((*R*)-1-bromo-2-(4-chlorophenyl)ethyl)-2-hydroxy-4-oxopentanoate (28c): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25c** (66.7 mg, 0.20 mmol) affording **28c** (75.9 mg, 97% yield, >20:1 dr) as a pale yellow oil. Analytical data for **28c**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 5.15 (sept, *J* = 6.2 Hz, 1H), 4.18 (dd, *J* = 11.5, 2.6 Hz, 1H), 4.10 (br s, 1H), 3.38 (dd, *J* = 14.8, 2.5 Hz, 1H), 3.11 (dd, *J* = 35.8, 16.6 Hz, 2H), 2.94 (dd, *J* = 14.8, 11.5 Hz, 1H), 2.20 (s, 3H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.2 Hz,

3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 205.0, 171.6, 136.5, 132.7, 130.5, 128.5, 76.8, 70.8, 60.3, 48.9, 37.9, 31.0, 21.57, 21.55; **IR** (thin film): 3457, 1734, 1647, 1561, 1494, 1243, 1141, 1101 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.35; **HRMS** (ESI): Calcd. for $C_{16}H_{20}BrClO4$ ($[M+Na]^+$): 413.0131, Found: 413.0125; **HPLC** Chiralpak IA, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 8.1 min, $t_{R\ (major)}$ 9.4 min, 96.5:3.5 er; **$[\alpha]_D$** -2 (*c* = 1.4, $CHCl_3$).

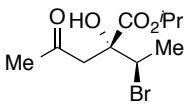


Isopropyl (*R*)-2-((*R*)-1-bromo-2-(4-methoxyphenyl)ethyl)-2-hydroxy-4-oxopentanoate (28d): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25d** (65.8 mg, 0.20 mmol) affording **28d** (72.1 mg, 93% yield, >20:1 dr) as a white solid (mp: 107-108 ºC). Analytical data for **28d**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.15 (sept, *J* = 6.2 Hz, 1H), 4.20 (dd, *J* = 11.3, 2.8 Hz, 1H), 4.08 (br s, 1H), 3.79 (s, 3H), 3.34 (dd, *J* = 14.9, 2.6 Hz, 1H), 3.11 (dd, *J* = 18.7, 16.7 Hz, 2H), 2.92 (dd, *J* = 14.8, 11.3 Hz, 1H), 2.20 (s, 3H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 205.2, 171.8, 158.5, 130.1, 130.0, 113.8, 77.2, 70.7, 61.4, 55.2, 48.9, 37.8, 31.0, 21.57, 21.56; **IR** (thin film): 3444, 1733, 1646, 1541, 1514, 1377, 1249 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.33; **HRMS** (ESI): Calcd. for $C_{17}H_{23}BrNaO_5$ ($[M+Na]^+$): 409.0627, Found: 409.0619; **HPLC** Chiralpak IA, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 8.8 min, $t_{R\ (major)}$ 10.7 min, 96:4 er; **$[\alpha]_D$** -3 (*c* = 1.3, $CHCl_3$).

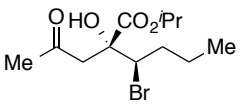


Isopropyl (*R*)-2-((*R*)-1-bromo-2-(thiophen-2-yl)ethyl)-2-hydroxy-4-oxopentanoate (28e): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25e** (61.0 mg, 0.20 mmol) affording **28e** (69.8 mg, 96% yield, >20:1 dr) as a yellow oil. Analytical data for **28e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21-7.20 (m, 1H), 6.97-6.93 (m, 2H), 5.15 (sept, *J* = 6.2 Hz, 1H), 4.21 (dd, *J* = 10.8, 2.8 Hz,

1H), 4.09 (br s, 1H), 3.60 (dd, J = 11.4, 2.3 Hz, 1H), 3.28 (dd, J = 15.7, 10.8 Hz, 1H), 3.08 (dd, J = 31.4, 16.6 Hz, 2H), 2.19 (s, 3H), 1.31 (d, J = 6.2 Hz, 3H), 1.28 (d, J = 6.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 205.0, 171.5, 140.3, 126.8, 126.6, 124.4, 77.2, 70.8, 60.2, 48.8, 33.4, 31.0, 21.60, 21.57; **IR** (thin film): 3456, 1732, 1697, 1542, 1507, 1375, 1233 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.40; **HRMS** (ESI): Calcd. for $C_{14}H_{19}BrNaO_4S$ ([M+Na]$^+$): 385.0085, Found: 385.0078; **HPLC** Chiralpak IA, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 9.2 min, $t_{R\ (minor)}$ 13.1 min, 95.5:4.5 er; **[α]$_D$** -15 (c = 1.7, $CHCl_3$).

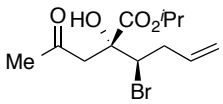


Isopropyl (*R*)-2-((*R*)-1-bromoethyl)-2-hydroxy-4-oxopentanoate (28f): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25f** (44.6 mg, 0.20 mmol) affording **28f** (54.0 mg, 96% yield, >20:1 dr) as a pale yellow oil. Analytical data for **28f**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.12 (sept, J = 6.3 Hz, 1H), 4.21 (q, J = 6.8 Hz, 1H), 3.85 (br s, 1H), 2.94 (br s, 2H), 2.16 (s, 3H), 1.71 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 204.9, 172.0, 77.1, 70.5, 53.5, 48.3, 30.9, 21.6, 21.5, 19.9; **IR** (thin film): 3445, 1733, 1642, 1558, 1457, 1276, 1159 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.35; **HRMS** (ESI): Calcd. for $C_{10}H_{17}BrNaO_4$ ([M+Na]$^+$): 303.0208, Found: 303.0203; **HPLC** Chiralpak IA, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 6.4 min, $t_{R\ (minor)}$ 7.1 min, 95.5:4.5 er; **[α]$_D$** +28 (c = 0.9, $CHCl_3$).

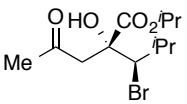


Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-2-(2-oxopropyl)hexanoate (28g): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25g** (50.2 mg, 0.20 mmol) affording **28g** (58.3 mg, 94% yield, >20:1 dr) as a pale yellow oil. Analytical data for **28g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (sept, J = 6.3 Hz, 1H), 4.04 (dd, J = 7.0, 6.7 Hz, 1H), 3.96 (br s, 1H), 3.00 (br s, 2H), 2.16 (s, 3H), 1.83-1.64 (m, 3H), 1.42-1.33 (m, 1H), 1.29 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 0.93 (t, J = 7.4 Hz,

3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 205.4, 171.9, 77.4, 70.5, 60.6, 48.7, 48.3, 34.1, 30.9, 21.6, 21.5, 21.2, 13.2; **IR** (thin film): 3451, 1736, 1653, 1542, 1452, 1376, 1249 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.47; **HRMS** (ESI): Calcd. for $C_{12}H_{22}BrO_4$ ($[M+H]^+$): 309.0702, Found: 309.0695; **HPLC** Chiralpak IA, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 8.3 min, $t_{R\ (major)}$ 10.2 min, 95.5:4.5 er; **$[\alpha]_D$** -4 (*c* = 1.2, $CHCl_3$).



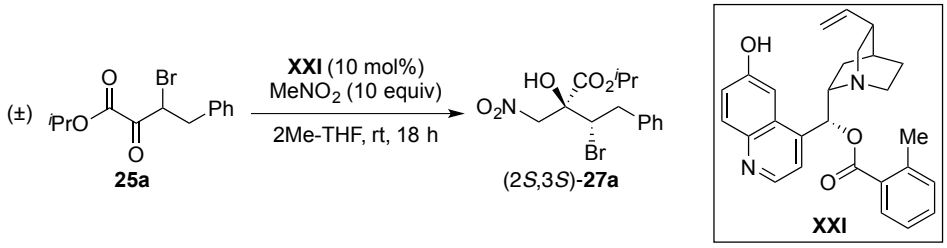
Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-2-(2-oxopropyl)hex-5-enoate (28h): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25h** (49.8 mg, 0.20 mmol) affording **28h** (58.6 mg, 95% yield, >20:1 dr) as a pale yellow oil. Analytical data for **28h**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.88-5.81 (m, 1H), 5.17-5.09 (m, 3H), 4.05 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.97 (br s, 1H), 3.03 (br s, 2H), 2.76-2.72 (m, 1H), 2.58-2.52 (m, 1H), 2.17 (s, 3H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 205.0, 171.7, 134.8, 118.0, 77.2, 70.7, 59.1, 48.7, 36.7, 30.9, 21.6, 21.5; **IR** (thin film): 3444, 1733, 1646, 1560, 1457, 1376, 1248, 1147 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.44; **HRMS** (ESI): Calcd. for $C_{12}H_{19}BrNaO_4$ ($[M+Na]^+$): 329.0365, Found: 329.0359; **HPLC** Chiralpak IA, H:IPA = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 7.0 min, $t_{R\ (major)}$ 8.8 min, 96:4 er; **$[\alpha]_D$** -4 (*c* = 0.9, $CHCl_3$).



Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-4-methyl-2-(2-oxopropyl)pentanoate (28i): The title compound was prepared according to General Procedure F using β-bromo-α-keto ester **25i** (50.2 mg, 0.20 mmol) affording **28i** (55.7 mg, 90% yield, 2.5:1 dr) as a pale yellow oil. Analytical data for **28i**: **^{1}H NMR** (400 MHz, $CDCl_3$): *major diastereomer* δ 5.15-5.05 (m, 1H), 4.16 (d, *J* = 1.8 Hz, 1H), 3.80 (br s, 1H), 3.04 (d, *J* = 16.3 Hz, 1H), 2.96 (d, *J* = 16.3 Hz, 1H), 2.15 (s, 3H), 2.11-2.04 (m, 1H), 1.30-1.23 (m, 6H), 1.04 (d, *J* = 3.2 Hz, 3H), 1.02 (d, *J* = 3.2 Hz, 3H), *minor diastereomer* δ 5.15-5.05 (m, 1H), 4.04 (d, *J* = 1.8 Hz, 1H), 3.82

(br s, 1H), 3.38 (d, J = 17.4 Hz, 1H), 2.98 (d, J = 17.4 Hz, 1H), 2.13 (s, 3H), 1.77-1.71 (m, 1H), 1.30-1.23 (m, 6H), 1.05 (d, J = 2.6 Hz, 3H), 0.97 (d, J = 2.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): *major diastereomer* δ 204.6, 172.4, 77.9, 70.6, 68.6, 30.9, 29.5, 23.6, 21.5, 17.8, *minor diastereomer* δ 206.7, 172.0, 78.6, 70.4, 68.6, 31.1, 30.7, 21.49, 21.45, 18.5; **IR** (thin film): 3446, 1734, 1684, 1560, 1489, 1376, 1250, 1102 cm^{-1}; **TLC** (30% ethyl acetate:hexanes): R_f = 0.54; **HRMS** (ESI): Calcd. for $C_{12}H_{21}BrNaO_4$ ([M+Na]$^+$): 331.0521, Found: 331.0515; **HPLC** Chiralpak IA, H:IPA = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 6.0 min, $t_{R\ (major)}$ 7.3 min, 90:10 er; **[α]$_D$** +11 (c = 1.4, $CHCl_3$).

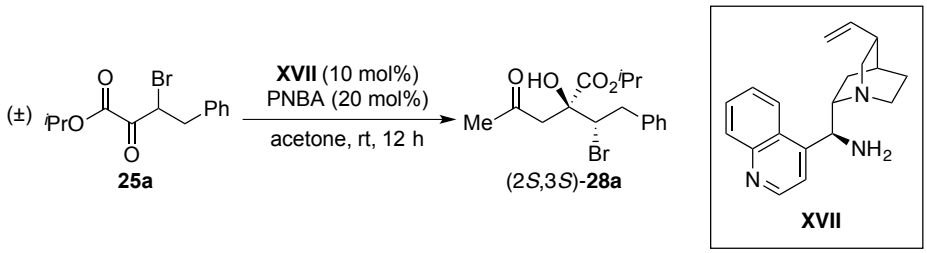
<u>Synthesis of *ent*-27a</u>



Isopropyl (2*S*,3*S*)-3-bromo-2-hydroxy-2-(nitromethyl)-4-phenylbutanoate (*ent*-27a): A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester **25a** (59.8 mg, 0.20 mmol, 1.0 equiv) and $MeNO_2$ (110 µL, 2.00 mmol, 10.0 equiv) in 2Me-THF (1.0 mL, 0.2 M). Catalyst **XXI** (8.6 mg, 0.02 mmol, 0.1 equiv) was added, the vial was capped, and the reaction was allowed to stir for 18 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) and concentrated *in vacuo* to afford analytically pure *ent*-**27a** (65.5 mg, 95% yield, >20:1 dr) as a white solid (mp: 114-116 ºC). The product was recrystallized in a 20-mL scintillation vial by dissolving the crude residue in acetone (0.2 mL). Hexanes (3.8 mL) was carefully layered on top of the acetone solution. The vial was capped and carefully transferred to a freezer. The biphasic mixture was left to slowly diffuse in the freezer

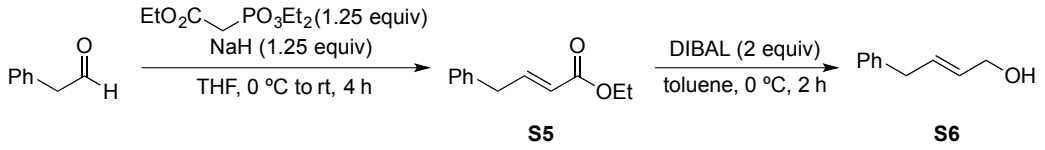
overnight. The obtained crystals were collected and washed with hexanes. Spectral data is consistent with that reported for **27a**. Analytical data for *ent*-**27a**: **HPLC** Chiralpak IC, H:IPA = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 17.2 min, $t_{R\ (major)}$ 22.2 min, 99:1 er; $[\alpha]_D$ +21 (c = 1.3, $CHCl_3$).

Synthesis of *ent*-28a



Isopropyl (*S*)-2-((*S*)-1-bromo-2-phenylethyl)-2-hydroxy-4-oxopentanoate (*ent*-28a): A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester **25a** (59.8 mg, 0.20 mmol, 1.0 equiv) in acetone (1.0 mL, 0.2 M). Catalyst **XVII** (5.9 mg, 0.02 mmol, 0.1 equiv) and PNBA (6.7 mg, 0.04 mmol, 0.2 equiv) were added, the vial was capped, and the reaction was allowed to stir for 12 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) and concentrated *in vacuo* to afford analytically pure *ent*-**28a** (66.4 mg, 96% yield, >20:1 dr) as a white solid (mp: 102-105 ºC). Spectral data is consistent with that reported for **28a**. Analytical data for *ent*-**28a**: **HPLC** Chiralpak IA, H:IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 7.3 min, $t_{R\ (minor)}$ 8.6 min, 95.5:4.5 er; $[\alpha]_D$ -1 (c = 0.9, $CHCl_3$).

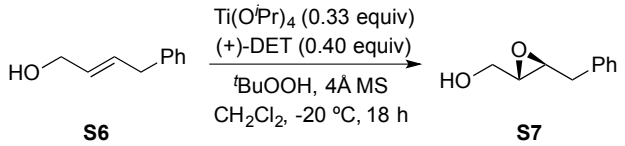
Enantioselective Synthesis of (*R*)-25a



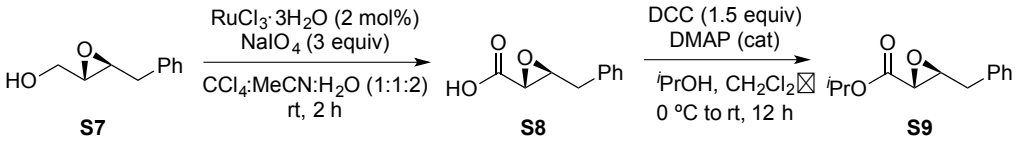
(*E*)-4-phenylbut-2-en-1-ol (S6): A flame-dried 500-mL round-bottomed flask equipped with a stir bar was charged with triethyl phosphonoacetate (12.4 mL, 62.5 mmol, 1.25 equiv) in THF (125 mL). The solution was cooled to 0 ºC in an ice bath. NaH (60%, 2.5 g, 62.5 mmol, 1.25 equiv) was added portionwise over 10 min. The reaction was allowed to stir for 30 min at 0 ºC. Phenylacetaldehyde (6.5 mL, 50.0 mmol, 1.00 equiv) was added dropwise at 0 ºC. Following addition, the ice bath was removed and the reaction was allowed to stir for 4 h as it slowly warmed to room temperature. The reaction was cooled to 0 ºC and quenched with sat. aq. $NaHCO_3$ (75 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude ester **S5** (5:1 *E*/*Z*) as a pale yellow oil.

A flame-dried 1-L round-bottomed flask equipped with a stir bar was charged with ester **S5** (5:1 *E*/*Z*) in toluene (200 mL). The solution was cooled to 0 ºC in an ice bath. DIBAL (17.8 mL, 100 mmol, 2.00 equiv) was added dropwise to maintain the internal temperature of the reaction at 0-10 ºC. Following addition, the reaction was allowed to stir at 0 ºC for 2 h. The reaction was quenched by sequential addition of acetone (20 mL) and 1 *N* HCl (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel

eluting with 20% ethyl acetate:hexanes to afford allyl alcohol **S6** (5.76 g, 70% yield, >20:1 *E*/*Z*) as a colorless oil whose spectral properties matched those reported in the literature.[48]



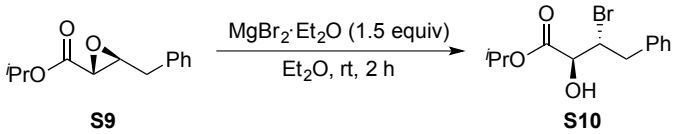
((2*S*,3*S*)-3-benzyloxiran-2-yl)methanol (S7): A flame-dried 250-mL round-bottomed flask equipped with a stir bar was charged with activated powdered 4Å molecular sieves (1.5 g) in CH_2Cl_2 (50 mL). The suspension was cooled to -20 ºC. Titanium isopropoxide (1.5 mL, 5 mmol, 0.33 equiv) and (+)-diethyl L-tartrate (1.0 mL, 6 mmol, 0.40 equiv) were added sequentially. *tert*-Butyl hydroperoxide solution (~5.5 M in decane, 6.5 mL, 36 mmol, 2.40 equiv) was added dropwise and the mixture was allowed to stir at -20 ºC for 30 min. A solution of allyl alcohol **S6** (2.46 g, 15 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) was added dropwise and the reaction was allowed to stir at -20 ºC for 18 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (20 mL) and was allowed to stir at room temperature for 30 min. The emulsion was filtered through a pad of Celite® rinsing with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 30% ethyl acetate:hexanes to afford alcohol **S7** (2.12 g, 70% yield, 84.5:14.5 er) as a colorless oil whose spectral properties matched those reported in the literature.[49] The enantiomeric ratio of **S7** was determined by analysis of **S10** (*vide infra*).



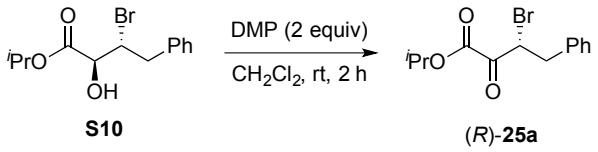
Isopropyl (2*R*,3*S*)-3-benzyloxirane-2-carboxylate (S9): A 250-mL round-bottomed flask equipped with a stir bar was charged with alcohol **S7** (1.55 g, 9.4 mmol, 1.00 equiv) in CCl_4 (20 mL). $NaIO_4$ (6.00 g, 28.2 mmol, 3.00 equiv), MeCN (20 mL), and H_2O (40 mL), and $RuCl_3 \cdot 3H_2O$ (50 mg, 0.2 mmol, 0.02 equiv) were added sequentially. The reaction was vigorously stirred at room temperature for 2 h. The suspension was filtered through a pad of Celite® rinsing with Et_2O. The layers are separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude carboxylic acid **S8** as a purple oil.

A flame-dried 250-mL round-bottomed flask equipped with a stir bar was charged with crude carboxylic acid **S8** in CH_2Cl_2 (50 mL). The solution was cooled to 0 ºC in an ice bath. DCC (2.91 g, 14.1 mmol, 1.50 equiv), isopropanol (2.9 mL, 37.6 mmol, 4.00 equiv), and DMAP (50 mg) were added sequentially. The reaction was allowed to stir overnight as it slowly warmed to room temperature. The suspension was filtered through a pad of Celite® rinsing with CH_2Cl_2. The crude residue was purified by column chromatography on silica gel eluting with 10% ethyl acetate:hexanes to afford glycidic ester **S9** (1.42 g, 69% yield) as a pale orange oil. Analytical data for **S9**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.27-7.24 (m, 3H), 5.08 (sept, *J* = 6.3 Hz, 1H), 3.39 (ddd, *J* = 6.4, 1.8, 1.0 Hz, 1H), 3.23 (d, *J* = 1.8 Hz, 1H), 2.99 (dd, *J* = 14.8, 4.6 Hz, 1H), 2.91 (dd, *J* = 14.8, 5.8 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.4, 135.8, 129.0, 128.5, 126.9, 69.2, 58.0, 52.8, 37.5, 21.63, 21.57; **IR** (thin film): 1725, 1455, 1435, 1374, 1288, 1204, 1107, 984 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f =

0.44; **HRMS** (ESI): Calcd. for $C_{13}H_{16}NaO_3$ ([M+Na]$^+$): 243.0997, Found: 243.0993; **[α]$_D$** -15 (*c* = 0.9, $CHCl_3$).

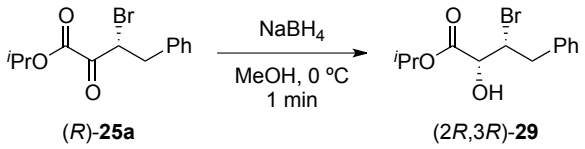


Isopropyl (2*S*,3*R*)-3-bromo-2-hydroxy-4-phenylbutanoate (S10): A flame-dried 50-mL round-bottomed flask equipped with a stir bar was charged with glycidic ester **S9** (660 mg, 3.0 mmol, 1.00 equiv) in Et_2O (18 mL). $MgBr_2 \cdot Et_2O$ (1.16 g, 4.5 mmol, 1.50 equiv) was added and the reaction was allowed to stir at room temperature for 2 h. The reaction was diluted with Et_2O (20 mL) and washed with H_2O (2 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 15% ethyl acetate:hexanes to afford *anti*-bromohydrin **S10** (819 mg, 91% yield) as a pale yellow oil. Analytical data for S11: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 5H), 5.14 (sept, *J* = 6.3 Hz, 1H), 4.45 (ddd, *J* = 6.9, 2.7, 1.4 Hz, 1H), 4.37 (dd, *J* = 6.2, 2.8 Hz, 1H), 3.36-3.22 (m, 3H), 1.36 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.6, 137.6, 129.2, 128.5, 127.1, 73.1, 70.7, 56.6, 40.6, 21.9, 21.8; **IR** (thin film): 3460, 1732, 1496, 1455, 1387, 1266, 1224, 1103, 1031 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.32; **HRMS** (ESI): Calcd. for $C_{13}H_{17}BrNaO_3$ ([M+Na]$^+$): 323.0259, Found: 323.0259; **SFC** Chiralpak AS, 3% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 7.3 min, $t_{R\ (minor)}$ 8.1 min, 84.5:15.5 er; **[α]$_D$** -15 (*c* = 1.0, $CHCl_3$).



Isopropyl (*R*)-3-bromo-2-oxo-4-phenylbutanoate ((*R*)-25a): A 20-mL scintillation vial equipped with a stir bar was charged with bromohydrin **S10** (301 mg, 1.0 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL). Dess-Martin periodinane (828 mg, 2.0 mmol, 2.00 equiv) was added and the reaction was allowed to stir at room temperature for 2 h. The reaction was diluted with Et_2O (30 mL) and washed with sat. aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$ (1:1) (3 x 15 mL) and brine (1 x 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford analytically pure (*R*)-**25a** (296 mg, 99% yield) as a pale yellow oil whose spectral properties matched those obtained via General Procedure B. The enantiomeric ratio of (*R*)-**25a** was determined via stereoselective reduction to (2*R*,3*R*)-**29** employing $NaBH_4$ (*vide infra*). Analytical data for (*R*)-**25a**: $[\alpha]_D$ +90 (*c* = 0.9, $CHCl_3$).

<u>Stereospecific Stereoselective Reduction of (*R*)-25a to (2*R*,3*R*)-29</u>



Isopropyl (2*R*,3*R*)-3-bromo-2-hydroxy-4-phenylbutanoate ((2*R*,3*R*)-29): A 20-mL scintillation vial equipped with a stir bar was charged with β-bromo-α-keto ester (*R*)-**25a** (59.8 mg, 0.20 mmol, 1.00 equiv) in MeOH (4 mL). The solution was cooled to 0 ºC in an ice bath. $NaBH_4$ (15.1 mg, 0.40 mmol, 2.00 equiv) was added and the reaction was allowed to stir at 0 ºC for 1 min. The reaction was carefully quenched with sat. aq. NH_4Cl (4 mL). The reaction was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4,

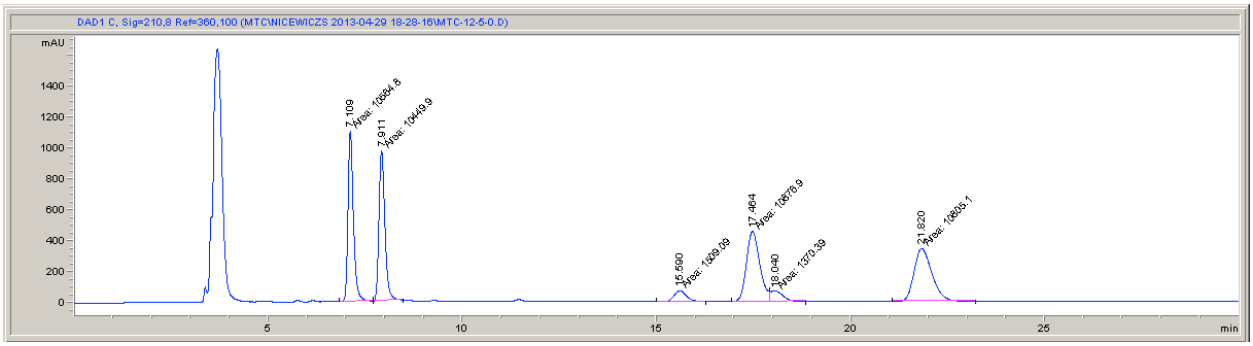
filtered, and concentrated *in vacuo* to afford analytically pure (2*R*,3*R*)-**29** (59.3 mg, 98% yield, >20:1 dr) as a pale yellow oil. Analytical data for (2*R*,3*R*)-**29**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.13 (sept, *J* = 6.3 Hz, 1H), 4.49 (ddd, *J* = 8.9, 7.0, 1.2, 1H), 4.12 (dd, *J* = 7.0, 1.2 Hz, 1H), 3.38 (dd, *J* = 13.8, 8.9 Hz, 1H), 3.29 (dd, *J* = 13.8, 7.0 Hz, 1H), 3.24 (d, *J* = 7.0 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.4, 137.6, 129.4, 128.7, 127.1, 70.9, 70.5, 56.4, 41.7, 21.7, 21.6; **IR** (thin film): 3445, 1734, 1653, 1505, 1375, 1288, 1106, 997 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.34; **HRMS** (ESI): Calcd. for $C_{13}H_{17}BrNaO_3$ ($[M+Na]^+$): 323.0259, Found: 323.0259; **SFC** Chiralpak AS, 3% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ 5.0 min, $t_{R\ (minor)}$ 6.3 min, 84.5:15.5 er; $\mathbf{[\alpha]_D}$ -14 (*c* = 0.9, $CHCl_3$).

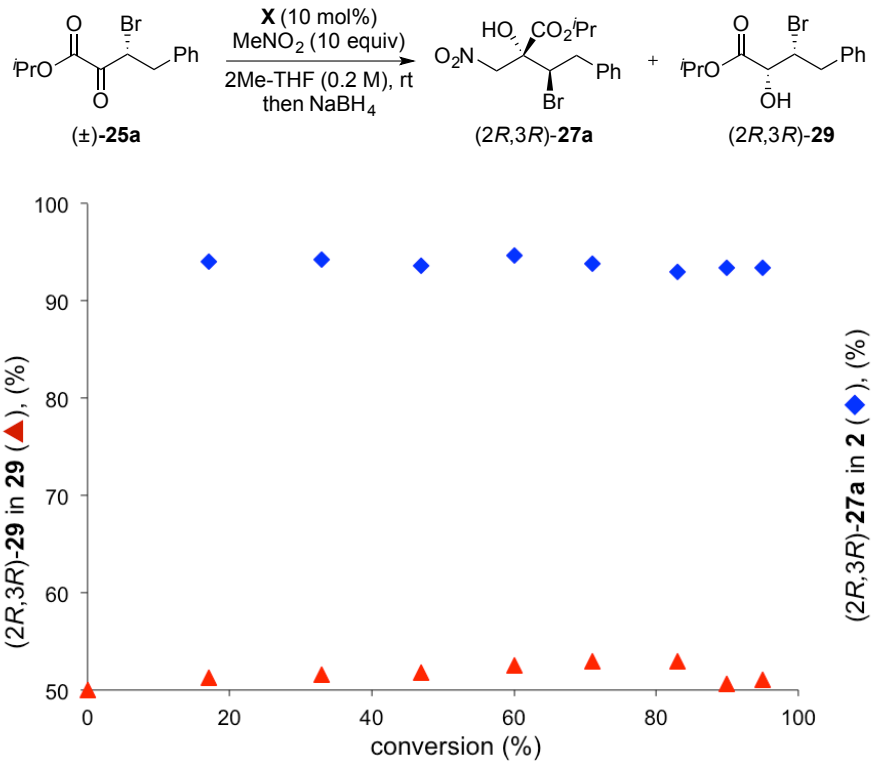
<u>Monitoring the Enantiomeric Composition of Species in Henry Aldolization</u>

Procedure: A 20-mL scintillation vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester (±)-**25a** (239 mg, 0.80 mmol, 1.0 equiv), mesitylene (120.2 mg, 1.00 mmol), and $MeNO_2$ (430 μL, 8.00 mmol, 10.0 equiv) in 2Me-THF (4.0 mL, 0.2 M). Catalyst **X** (34.3 mg, 0.08 mmol, 0.1 equiv) was added, the vial was capped, and the reaction was allowed to stir at room temperature. Aliquots (250 μL) were removed at various time points during the course of the reaction.

Analysis: The aliquot was added to a 1-dram vial equipped with a magnetic stir bar was charged with MeOH (1.5 mL) at 0 ºC. A spatula tip of $NaBH_4$ (~5 mg) is added to the reaction at 0 ºC (Note: Quenching at 0 ºC is imperative for accurate data). After 1 min, the reaction was quenched with sat. aq. NH_4Cl (0.5 mL). The reaction was diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The

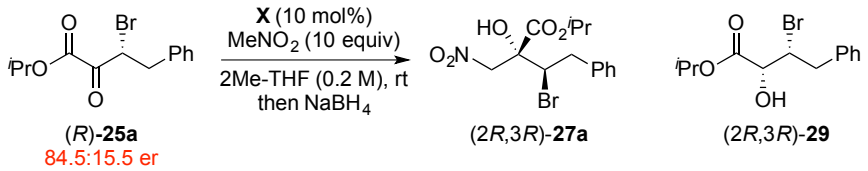
resulting residue was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) to remove the catalyst and concentrated *in vacuo* to afford a mixture of **27a** and **29**. The diastereomeric ratio of **27a** and conversion (comparison with mesitylene internal standard) was determined by ^{1}H NMR analysis of the crude residue. The enantiomeric excess of **27a** and **29** were determined by chiral HPLC analysis: **HPLC** Chiralpak IA, H:IPA = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, *syn*-**29**: t_R 7.1 min, t_R 7.9 min, *anti*-**27a**: t_R 15.6 min, t_R 18.0 min, *syn*-**27a**: t_R 17.5 min, t_R 21.8 min.

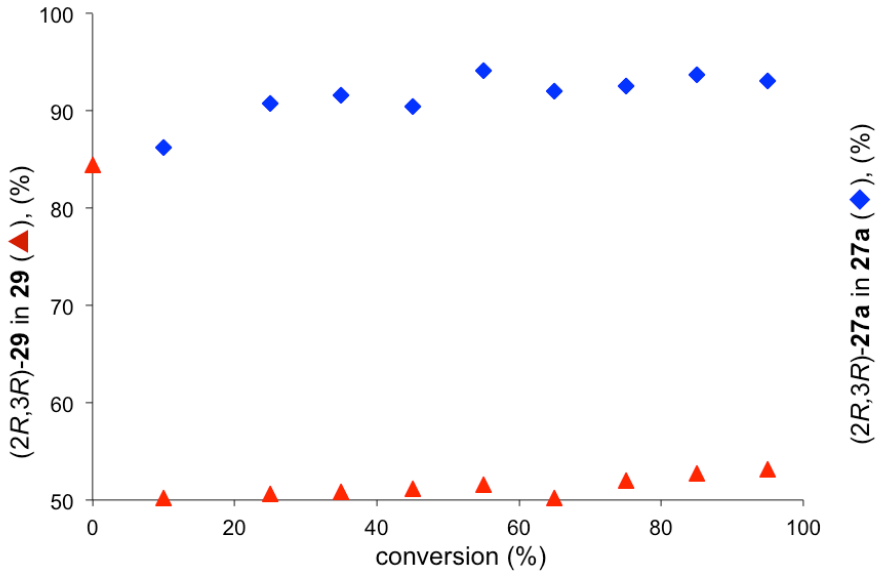




Aliquot	Conversion (%)	Enantiomeric Composition of 27a	Enantiomeric Composition of 29
1	17	94	51
2	33	94	52
3	47	94	52
4	60	95	53
5	71	94	53
6	83	93	53
7	90	94	51
8	95	94	51

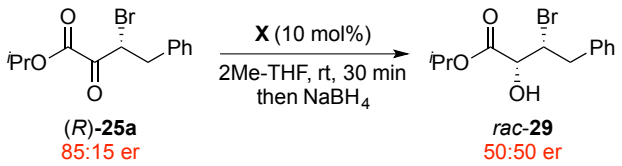
Procedure: A 20-mL scintillation vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester (*R*)-**25a** (239 mg, 0.80 mmol, 1.0 equiv), mesitylene (120.2 mg, 1.00 mmol), and $MeNO_2$ (430 µL, 8.00 mmol, 10.0 equiv) in 2Me-THF (4.0 mL, 0.2 M). Catalyst **X** (34.3 mg, 0.08 mmol, 0.1 equiv) was added, the vial was capped, and the reaction was allowed to stir at room temperature. Aliquots (250 µL) were removed at various time points during the course of the reaction and analyzed as previous described.





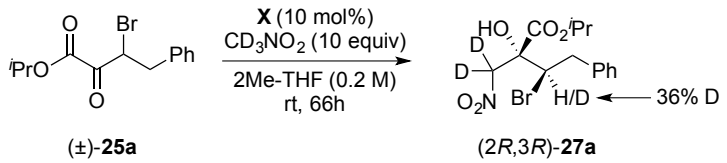
Aliquot	Conversion (%)	Enantiomeric Composition of 27a	Enantiomeric Composition of 29
1	0	-	84.5
2	9	86	50
3	24	91	51
4	35	92	51
5	46	91	51
6	56	94	52
7	64	92	50
8	73	93	52
9	84	94	53
10	95	93	53

Racemization Studies with (*R*)-25a



A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester (*R*)-**25a** (15.0 mg, 0.05 mmol, 1.0 equiv) in 2Me-THF (250 µL, 0.2 M). Catalyst **X** (2.1 mg, 0.005 mmol, 0.1 equiv) was added, the vial was capped, and the reaction was allowed to stir for 30 min at room temperature. The reaction was cooled to 0 ºC in an ice bath and diluted with MeOH (1.5 mL). A spatula tip of $NaBH_4$ (~5 mg) is added to the reaction at 0 ºC. After 1 min, the reaction was quenched with sat. aq. NH_4Cl (0.5 mL). The reaction was diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was filtered through a 2 cm pad of SiO_2, washing with Et_2O (5 x 2 mL) to remove the catalyst, and concentrated *in vacuo* to afford *rac*-**29** (14.7 mg, 98% yield, >20:1 dr) as a pale yellow oil. Spectral properties were consistent with those reported for (2*R*,3*R*)-**29**. Analytical data for *rac*-**29**: **SFC** Chiralpak AS, 3% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 4.8 min, $t_{R\ (major)}$ 6.0 min, 50:50 er.

Deuterium Labeling Studies with CD_3NO_2 in Henry Aldolization



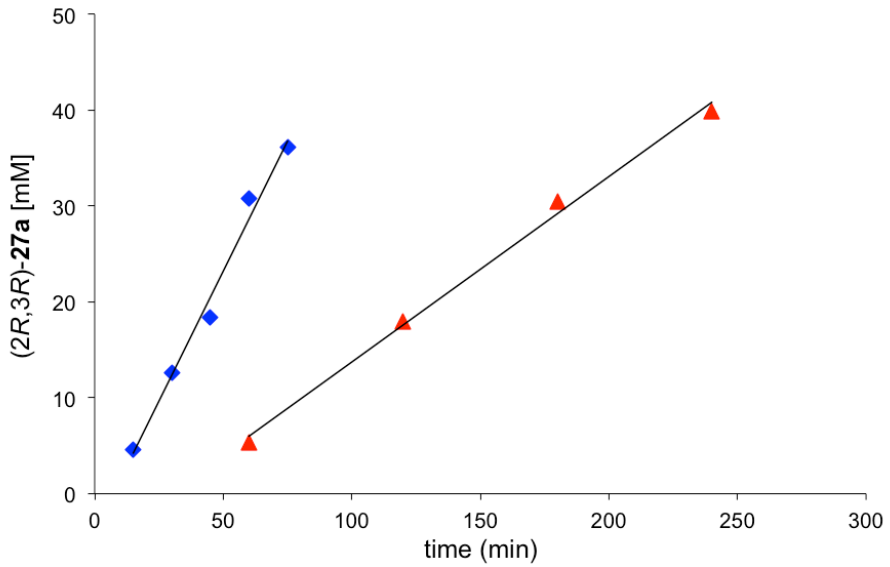
A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester (±)-**25a** (59.8 mg, 0.20 mmol, 1.0 equiv) and CD_3NO_2 (110 µL, 2.00 mmol, 10.0 equiv) in 2Me-THF (1.0 mL, 0.2 M). Catalyst **X** (8.6 mg, 0.02 mmol, 0.1 equiv) was added, the vial was capped, and the reaction was allowed to stir for 66 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) and concentrated *in vacuo* to afford analytically pure **27a** (69.2 mg, 96% yield, >20:1 dr). The deuterium incorporation was determined by ^{1}H NMR analysis of the crude residue.

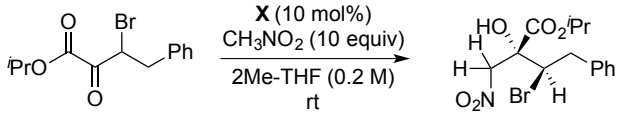
Determination of Initial Rates and Kinetic Isotope Effect

Procedure: A 20-mL scintillation vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester (±)-**25a** (239 mg, 0.80 mmol, 1.0 equiv), mesitylene (120.2 mg, 1.00 mmol), and $MeNO_2$ or CD_3NO_2 (430 µL, 8.00 mmol, 10.0 equiv) in 2Me-THF (4.0 mL, 0.2 M). Catalyst **X** (34.3 mg, 0.08 mmol, 0.1 equiv) was added, the vial was capped, and the reaction was allowed to stir at room temperature. Aliquots (250 µL) were removed at the indicated time points.

Analysis: The aliquot was added to a 1-dram vial equipped with a magnetic stir bar was charged with MeOH (1.5 mL) at 0 ºC. A spatula tip of $NaBH_4$ (~5 mg) is added to the reaction at 0 ºC (Note: Quenching at 0 ºC is imperative for accurate data). After 1 min, the reaction was quenched sat. aq. NH_4Cl (0.5 mL). The reaction was diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The

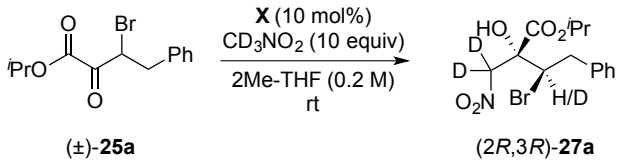
resulting residue was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 x 2 mL) to remove the catalyst and concentrated *in vacuo* to afford a mixture of **27a** and **29**. The conversion and concentration of (2*R*,3*R*)-**27a** was determined by comparison with mesitylene internal standard by ^{1}H NMR analysis of the crude residue.





CH_3NO_2 (◆)
y = 0.2710x – 1.9473
R^2 = 0.98548

time (min)	conversion (%)	(2*R*,3*R*)-27a [mM]
15	2.3	4.6
30	6.3	12.6
45	9.2	18.3
60	15.4	30.8
75	18.1	36.2

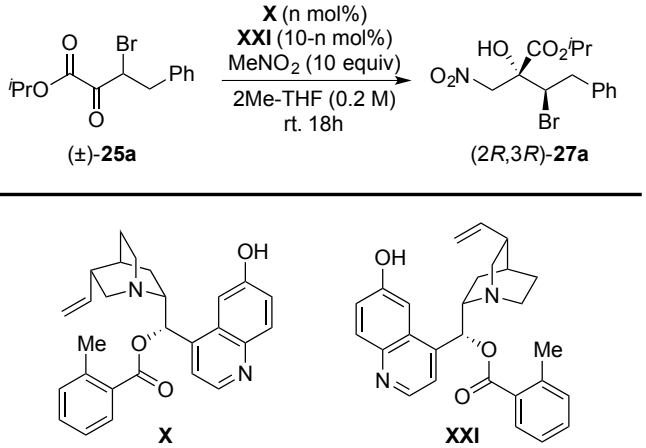


CD_3NO_2 (▲)
y = 0.0967x – 2.8049
R^2 = 0.99528

time (min)	conversion (%)	(2*R*,3*R*)-27a [mM]
60	2.7	5.3
120	9.0	18.0
180	15.2	30.5
240	19.9	39.8

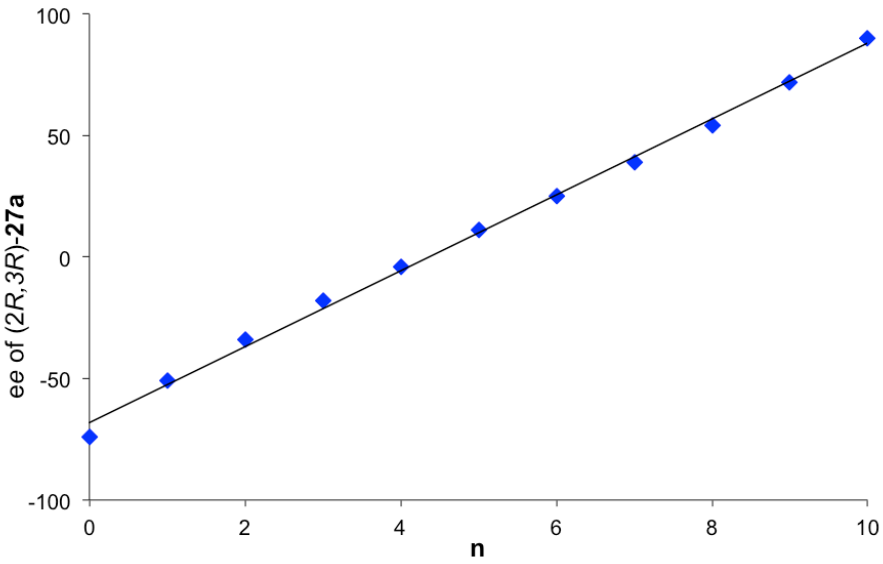
$$k_H/k_D = (0.2710/0.0967) = 2.8$$

Non-Linear Effects in Henry Aldolization



Procedure: Stock solutions (0.2 M in 2Me-THF) of catalysts **X** (42.9 mg, 1.00 mmol) and **XXI** (42.9 mg, 1.00 mmol) were prepared in 20-mL scintillation vials. A 1-dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester (±)-**25a** (59.8 mg, 0.20 mmol, 1.0 equiv) and $MeNO_2$ (110 μL, 2.00 mmol, 10.0 equiv). Solutions of catalyst **X** (n x 100 μL) and catalyst **XXI** ((10-n) x 100 μL) was added, the vial was capped, and the reaction was allowed to stir for 18 h at room temperature. The reaction was filtered through a 2 cm pad of

SiO_2 washing with Et_2O (5 x 2 mL) and concentrated *in vacuo* to afford analytically pure **27a**. The enantiomeric ratio was determined by HPLC analysis.



$R^2 = 0.99715$

n	0.2 M X (µL)	0.2 M XXI (µL)	*ee* of (2*R*,3*R*)-2b
0	1000	0	91
1	900	100	72
2	800	200	54
3	700	300	39
4	600	400	25
5	500	500	11
6	400	600	-4
7	300	700	-18
8	200	800	-34
9	100	900	-51
10	0	1000	-74

5.6 References

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38) CCDC 951438 ((2*R*,3*R*)-**27a**) and 951439 ((2*R*,3*R*)-**28d**) contain the supplementary crystallographic data for this chapter. These data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif. The structures in **Scheme 5-24** were generated with CYLview: Legault, C. Y. CYL*view*, version 1.0b; Université de Sherbrooke: Sherbrooke, QC, 2009; http://www.cylview.org.

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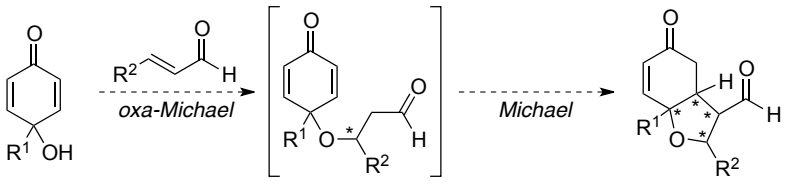
CHAPTER SIX: ENANTIOSELECTIVE SYNTHESIS OF HINDERED CYCLIC DIALKYL ETHERS VIA ORGANOCATALYTIC OXA-MICHAEL/MICHAEL DESYMMETRIZATION*

6.1 Introduction

Sterically hindered dialkyl ethers are ubiquitous in natural products; however, efficient and selective methods for their stereocontrolled preparation remain a challenge to the synthetic community. Modern approaches to the asymmetric synthesis of dialkyl ethers through C–O bond formation rely largely on the use of metal-mediated alkene functionalizations where a single α-stereocenter is generated in the etherification. In this chapter, we report a tractable metal-free approach to the synthesis of *tert*/*sec* ethers employing an oxa-Michael/Michael desymmetrization strategy involving achiral tertiary carbinols and α,β-unsaturated aldehydes (**Scheme 6-1**). The present art provides direct access to densely functionalized bicycles with the concomitant formation of four stereocenters including both α-stereocenters of the ether linkage.

Scheme 6-1. Oxa-Michael/Michael Desymmetrization Strategy



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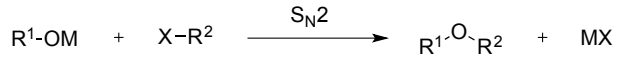
6.2 Background

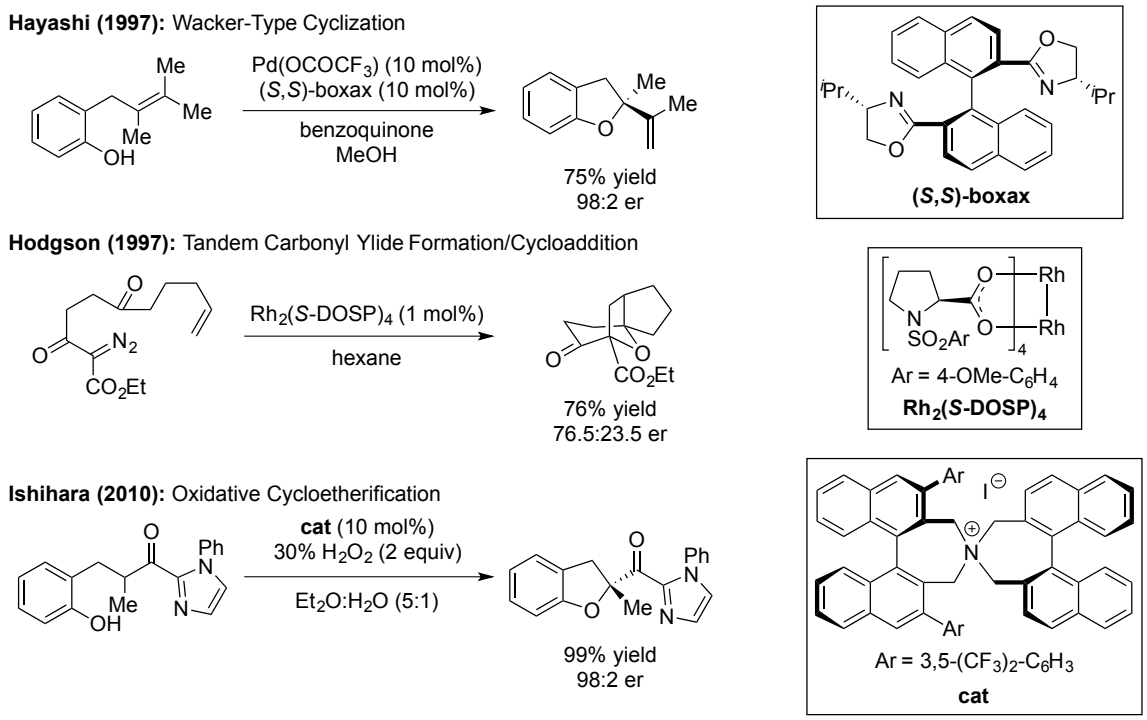
6.2.1 Extant Methods for the Synthesis of Hindered Ethers

The Williamson ether synthesis is a fundamental chemical transformation for the preparation of ethers via S_N2 displacement of an alkyl halide with an alkoxide (**Figure 6-1**).[1] Despite its utility in the synthesis of simple acyclic and cyclic ethers, the harsh reaction conditions of the Williamson ether synthesis render it incompatible to asymmetric synthesis due to competitive racemization/epimerization and elimination pathways. To address these limitations, myriad methods for the construction of chiral tertiary ethers via C–O bond formation have been developed through the use of metal-mediated alkene functionalizations,[2] carbonyl ylide cycloadditions,[3] among others (**Scheme 6-2**).[4] Despite significant advancement, these methods are largely limited to metal-mediated intramolecular reactions and generally result in the formation of a single α-stereocenter.

Figure 6-1. Williamson Ether Synthesis



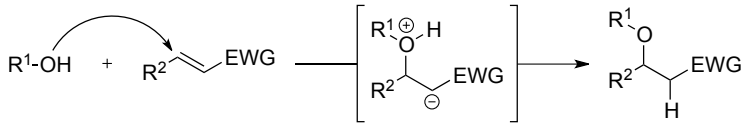
Scheme 6-2. Representative Catalytic Asymmetric Hindered Ether Syntheses



6.2.2 Applications of Hindered Nucleophiles in Oxa-Michael Additions

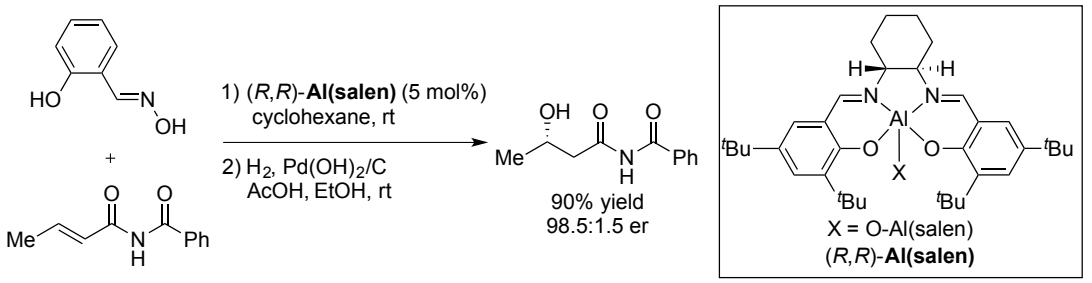
The oxa-Michael reaction is a powerful method for the construction of C–O bonds through the 1,4-conjugate addition of an alcohol (or alkoxide) to a Michael acceptor (**Figure 6-2**).[5] Although underdeveloped relative to the Michael addition of carbon nucleophiles, the oxa-Michael addition is amenable to application of commonly employed organocatalysts due to its similar reactivity mode to the parent transformation.[6] Nucleophile activation can be achieved through application of chiral organic bases, generating a chiral nucleophile through ion-pairing. Alternatively, electrophile activation can be achieved through hydrogen-bonding (i.e., thiourea/squaramide activation of nitroolefins) or covalent coordination (iminium-ion activation of carbonyls).

Figure 6-2. Mechanism of Oxa-Michael Reaction



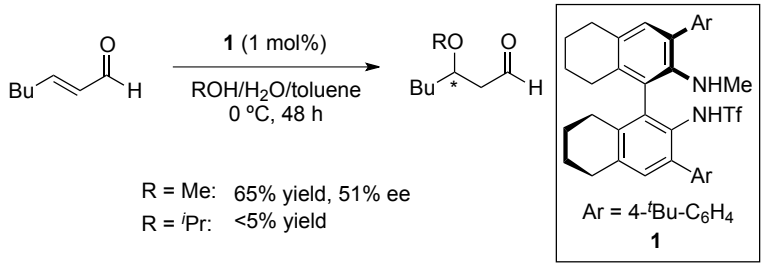
Despite the potential utility of this reactivity profile, poor nucleophilicity of oxygen nucleophiles, competitive acetal/ketal formation, and reversibility have hindered its broad application in asymmetric synthesis.[5] As a result of these limitations, early applications of oxa-Michael additions in the literature have employed oximes or phenols due to their enhanced reactivity providing access to alcohols or aryl ethers, respectively.[8] In 2004, Jacobsen demonstrated the potential of the oxa-Michael addition of oximes to serve as a valuable method for the construction of β-hydroxy carboxylic acid derivatives following N–O bond cleavage (**Scheme 6-3**).[7b] The utility of the oxa-Michael reaction in the preparation of hindered alkyl ethers has been comparatively underdeveloped with limited examples of secondary and tertiary alcohol nucleophiles.[8] Furthermore, starting material stereogenicity is an additional challenge with secondary and tertiary alcohol nucleophiles that limits either the substrate scope or reaction class (kinetic resolution) (*vide infra*).

Scheme 6-3. Formal Enantioselective Hydration of α,β-Unsaturated Imides



Early efforts by Marouka highlighted the challenges associated with the development of an efficient asymmetric intermolecular oxa-Michael addition (**Scheme 6-4**).[8b] Employing bifunctional secondary amine catalyst **1**, the oxa-Michael addition of methanol to α,β-unsaturated aldehydes proceeded in good yield with moderate enantioselectivity. Although methanol was a competent nucleophile in formation of β-methoxy aldehydes with no observed competitive acetal formation, more hindered nucleophiles, such as 2-propanol, were incompatible with the developed system. This observed difference in reactivity could arise from either reduced nucleophilicity of the more hindered alcohol or a competitive retro-Michael pathway that favors elimination over proton-transfer.

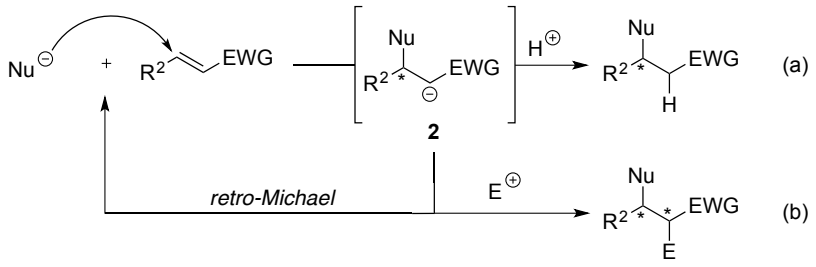
Scheme 6-4. Catalytic Asymmetric Oxa-Michael Addition of Hindered Alcohols



A mechanistic nuance of the Michael reaction (**Scheme 6-5a**) is the generation of a transient enolate equivalent **2** that can be harnessed in a secondary bond forming reaction allowing for the construction of multiple stereocenters in a single operation (**Scheme 6-5b**).[9] As defined by Tietze, a domino (or cascade) reaction is "any process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step" under static reaction conditions without the addition of additional reagents/catalysts.[10] The stepwise nature of the Michael reaction renders it amenable to complexity-building domino reaction manifolds where β- and α-

functionalization of the Michael acceptor can be realized. By harnessing the transient enolate equivalent **2** in favorable constructive pathways, competitive retro-Michael pathways are repressed allowing for the development of highly efficient Michael additions.

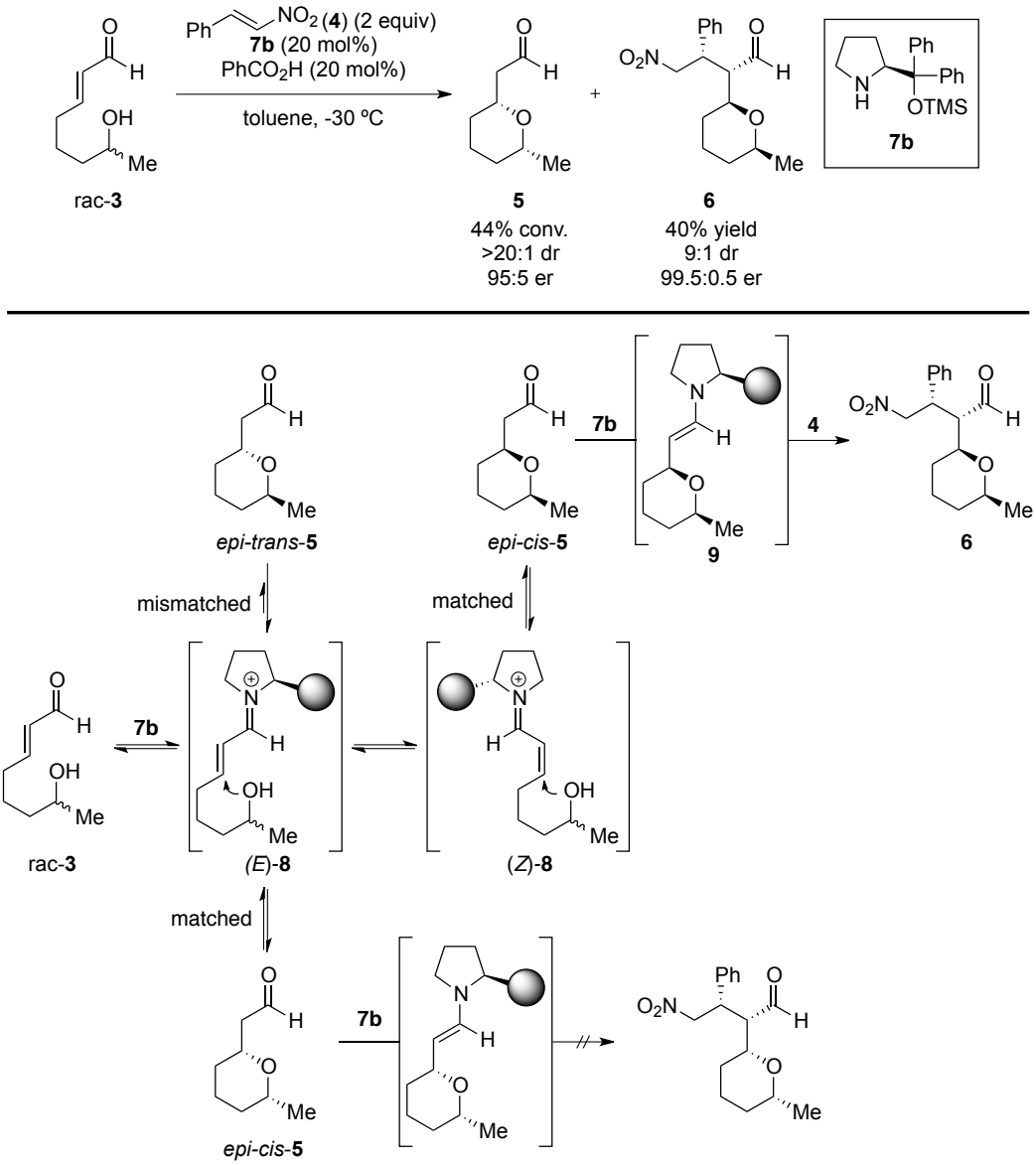
Scheme 6-5. Michael Addition Triggered Domino Reactions



In 2011, Brenner-Moyer applied this concept in the development of an oxa-Michael/Michael organocascade kinetic resolution of racemic secondary alcohols to afford enantioenriched tetrahydropyrans **5** and **6** (Scheme **6-6**).[8d] The intramolecular oxa-Michael addition of (*E*)-**8** was found to be reversible under secondary amine catalysis employing Hayashi's catalyst **7b**, allowing for a kinetic resolution to be realized via intermolecular Michael addition of transient enamine **9** to β-nitrostyrene (**4**). Although the retro-oxa-Michael addition was not explicitly observed, experimental observations strongly suggest retro-oxa-Michael is facile under the reaction conditions. Analysis of product stereochemical information led to the assumption that oxa-Michael addition occurs through the higher-energy iminium species (*Z*)-**8** providing access to the necessary tetrahydropyran *epi-cis*-**5**. This realization is based on the well-studied reactivity profiles of Jørgensen–Hayashi catalysts that have substantial precedent to direct nucleophilic attack to the face opposite of the catalyst's steric bulk, which would lead to the formation of tetrahydropyran *epi-trans*-**5**. Since both **5** and **6** are *cis*-tetrahydropyrans, *epi-trans*-**5** cannot a productive intermediate in the catalytic cycle. Despite a facile retro-oxa-

Michael, subsequent Michael addition to afford **6** effectively drove the reaction to completion suggesting that sterically hindered oxygen nucleophiles are competent reaction partners when the reaction is driven through domino processes.

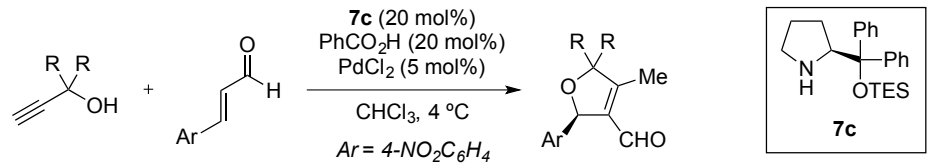
Scheme 6-6. Oxa-Michael/Michael Kinetic Resolution of Secondary Alcohols



The same year, Córdova reported an oxa-Michael/carbocyclization domino reaction for the preparation of dihydrofurans (**Scheme 6-7**).[8c] Intermolecular oxa-Michael addition of

propargyl alcohol (**10a**) to an α,β-unsaturated aldehyde was achieved via iminium-ion activation employing Jørgensen–Hayashi catalyst **7c** followed by intramolecular carbocyclization mediated by $PdCl_2$ to afford **11a** in high yield and excellent enantioselectivity. Notably, tertiary alcohol **10b** was found to be compatible with the reaction affording the *tert*/*sec*-dihydrofuran **11b** in slightly reduced yield and selectivity. The success of **10b** was attributed to facile intramolecular carbocylization; effectively funneling material away from the deleterious retro-Michael pathway. Furthermore, Córdova's work provides strong evidence that sterically encumbered secondary amine catalysts, such as **7c**, can effectively direct the intermolecular approach of bulky oxygen-centered nucleophiles in the oxa-Michael addition.

Scheme 6-7. Synthesis of Dihydrofurans via Oxa-Michael/Carbocyclization Cascade



10a: R = H
10b: R = Me

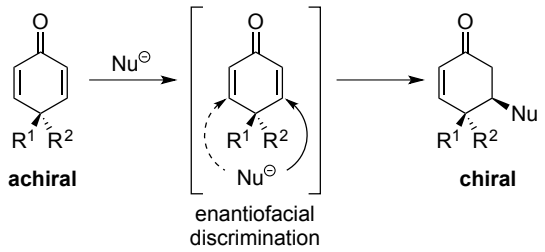
11a: 77% yield, 96.5:3.5 er
11b: 40% yield, 91.5:8.5 er

6.2.3 Cyclohexadienone Desymmetrization

As defined in Chapter One, asymmetric desymmetrization is an efficient, direct method for the conversion of achiral/meso compounds into functionally-rich chiral building blocks. Catalytic enantioselective desymmetrization of achiral cyclohexadienones has emerged as a powerful method for the construction of highly functionalized enantioenriched cyclohexanone derivatives (**Figure 6-3**).[11] Dearomatization of readily available 4-substituted phenols provides rapid access to cyclohexadienones bearing enantiotopic π-groups.[12] 4,4-Disubstituted cyclohexadienones can undergo enantiofacial selective 1,4-conjugate addition by an appropriate

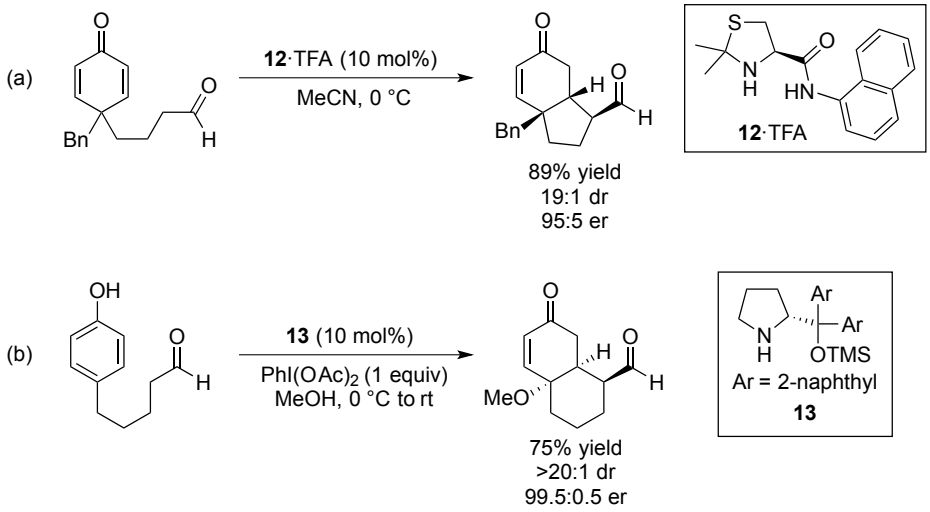
nucleophile to provide access to chiral cyclohexanone derivatives bearing malleable enone functionality that can be deployed in secondary transformations.

Figure 6-3. Enantioselective Desymmetrization of 4,4-Disubstituted Cyclohexadienones



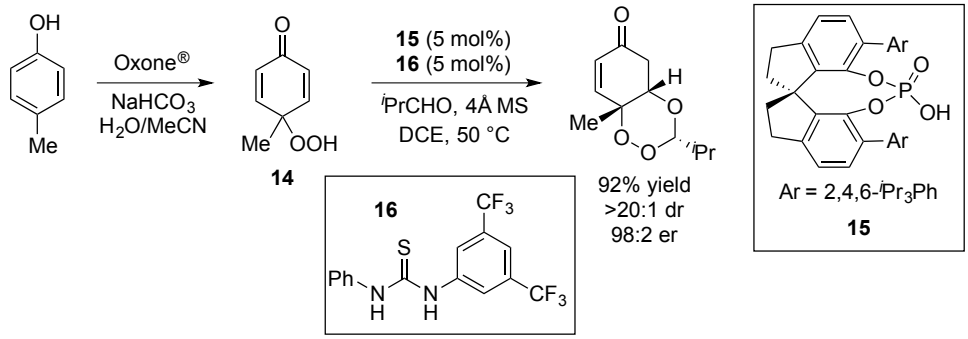
Although a number of desymmetrizations of cyclohexadienones have been reported, of particular relevance in the present context are prior art by Hayashi and Gaunt. In 2005, Hayashi disclosed an intramolecular Michael addition of aldehydes to 4-alkyl cyclohexadieneones under secondary amine catalysis (**Scheme 6-8a**).[11d] The cysteine-derived amine **12**·TFA affectively promoted the reaction providing high levels of diastereo- and enantiocontrol. This mechanistic paradigm was extended by Gaunt through the development of a one-pot oxidative dearomatization/Michael cascade reaction of 4-substituted phenols (**Scheme 6-8b**).[11f] $PhI(OAc)_2$ promoted the oxidative dearomatization of the phenol moiety to the transient cyclohexadienone that underwent intramolecular Michael addition catalyzed by Jørgensen–Hayashi catalyst **13** to provide the bicyclic products in good yield with excellent levels of stereocontrol.

Scheme 6-8. Desymmetrization of Cyclohexadieneones via Asymmetric Michael Addition



Despite a number of reported intramolecular desymmetrizations of cyclohexadienones, multicomponent intermolecular examples are rare.[11m] Rovis developed a domino process for the conversion of *p*-peroxyquinols **14** to 1,2,4-trioxanes via an acetalization/oxa-Michael cascade reaction under chiral Brønsted acid catalysis (**Scheme 6-9**). The *p*-peroxyquinols were prepared in one-step via treatment of 4-substituted phenols with singlet oxygen in aqueous media (*vide infra*).[13] Although *p*-peroxyquinol dimerization via oxa-Michael addition is mechanistically feasible under the reaction conditions,[14] acetalization was determined to outcompete this mechanistic pathway giving selective formation of the desired endoperoxides.

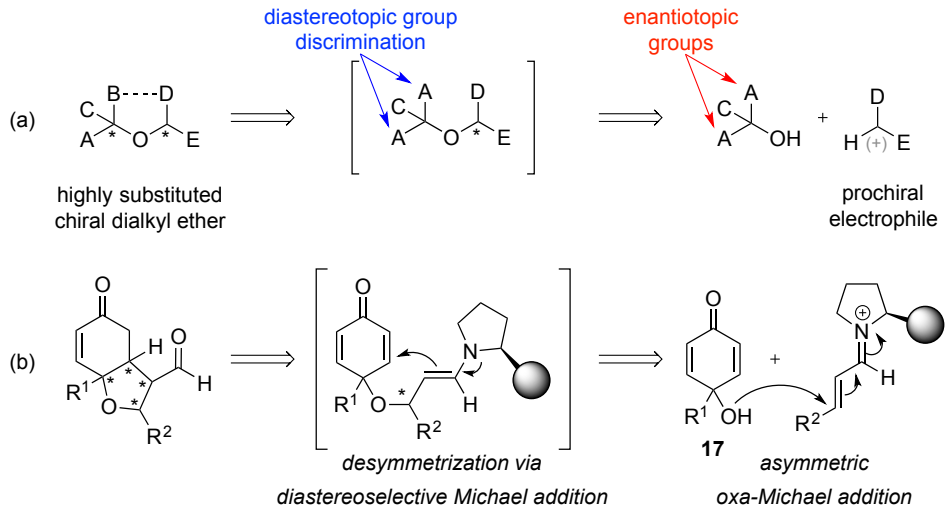
Scheme 6-9. Acetalization/Oxa-Michael Cascade of *p*-Peroxyquinols



6.2.4 Desymmetrization Approach to Hindered Ether Synthesis

We sought to design a method for the asymmetric synthesis of hindered *tert*/*sec* ethers where both α-stereocenters of the ether linkage could be set in a single operation. Our approach would parlay an asymmetric C–O bond construction involving achiral tertiary carbinols bearing enantiotopic π-groups with a subsequent diastereoselective desymmetrization to establish the tertiary stereogenic center (**Scheme 6-10a**). We proposed that *p*-quinols, a structurally unique subclass of cyclohexadienones readily available via oxidative dearomatization of phenols,[13] possessed the requisite structural attributes to achieve the illustrated (3+2)-annulation.[15] *p*-Quinols **17** feature a tertiary alcohol moiety tethered to enantiotopic π-electrophiles and serve as an attractive embodiment of this strategy (**Scheme 6-10b**). Iminium-ion activation of an α,β-unsaturated aldehyde would trigger the requisite asymmetric oxa-Michael addition of *p*-quinol **17**, which could then be harnessed in a subsequent diastereoselective Michael addition to establish the tertiary ether stereocenter via desymmetrization. This process would allow for the concomitant formation of both α-stereocenters of the dialkyl ether in a single operation.

Scheme 6-10. Asymmetric Approach to Hindered Ether Synthesis

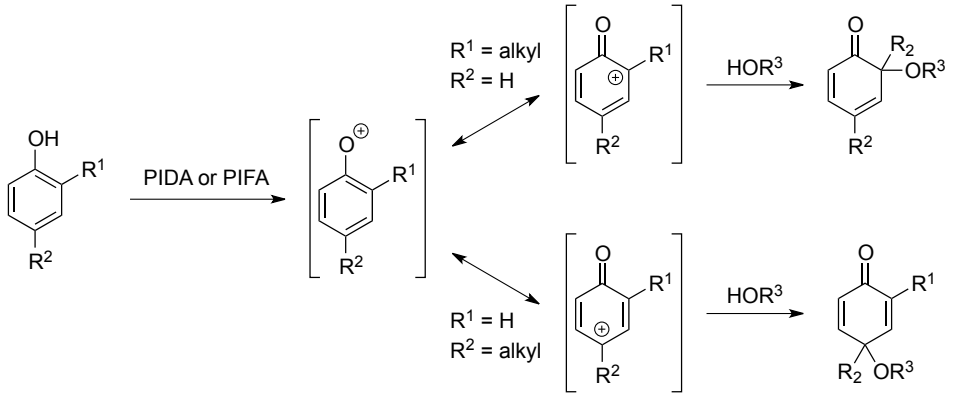


6.3 Results and Discussion

6.3.1 Synthesis of *p*-Quinols via Oxidative Dearomatization

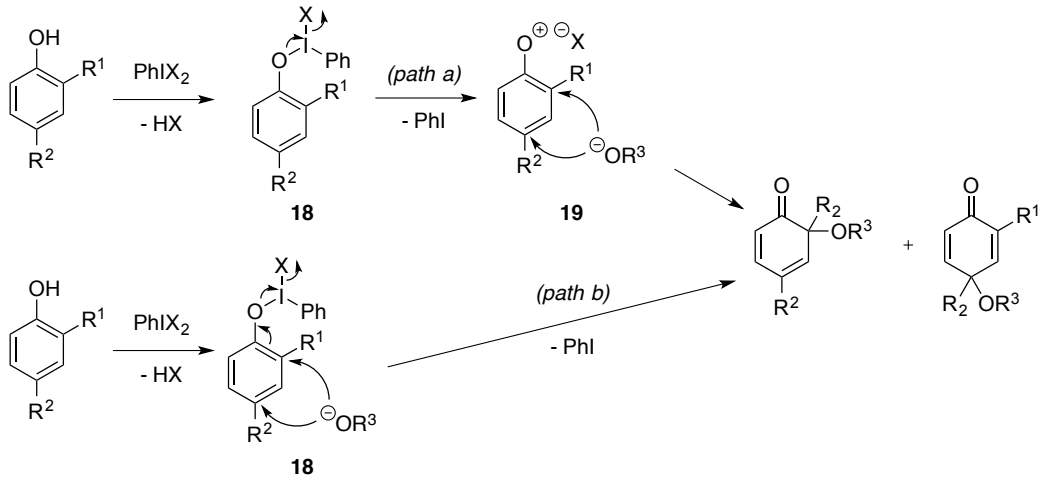
Phenols are commodity chemicals that are readily prepared on industrial scale and serve as valuable intermediates in organic synthesis.[16] In addition to their inherent utility, phenols are susceptible to oxidative dearomatization with oxygen-centered nucleophiles providing direct access to benzoquinones and quinols. Traditionally employed $Pb(OAc)_4$ protocols for the oxidation of phenols have since been replaced by metal-free hypervalent iodine reagents, such as phenyliodine diacetate (PIDA) and phenyliodine bis(trifluoroacetate) (PIFA).[12] For intramolecular and intermolecular reactions, the regioselectivity of the dearomatization (*ortho* vs. *para*) is dictated by the substitution pattern on the phenol where nucleophilic attack occurs at the most stable carbenium ion (**Scheme 6-11**). This observed regioselectivity allows for the selective preparation of *p*-quinols via oxidative dearomatization of 4-substituted phenols in the presence of H_2O.

Scheme 6-11. Regioselectivity in Oxidative Dearomatization of Phenols by Hypervalent Iodine Reagents



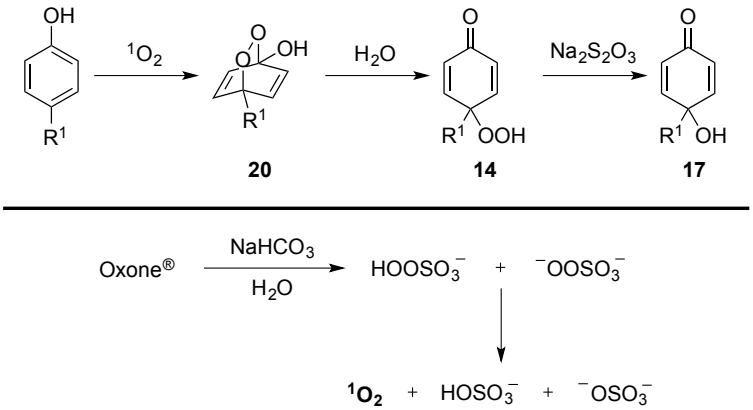
As originally described by Antus and Pelter, coordination of the phenol to the hypervalent iodine reagent generates the reactive aryloxyiodonium(III) intermediate **18** (**Scheme 6-12**).[17] From **18**, two pathways are possible: 1) dissociation to generate phenoxenium ion **19** that undergoes direct nucleophilic attack that is controlled by electronic effects (path a); or 2) direct nucleophilic attack on **18** that is governed by sterics (path b). Although dissociation to **19** was originally proposed to be the dominant pathway based on observed regioselectivities, the success of elegantly designed chiral hypervalent iodine reagents by Kita and Ishihara strongly suggest that an associative pathway (path b) can be active based on the observed chiral induction that can only be rationalized through covalent coordination of the hypervalent iodine reagent to the phenol in the enantiodetermining step.[18]

Scheme 6-12. Mechanism of Oxidative Dearomatization of Phenols by Hypervalent Iodine Reagents



An alternative synthesis of *p*-peroxyquinols and *p*-quinols from 4-substituted phenols employs singlet oxygen ($^1O_2$), which is generated by irradiation of gaseous oxygen with UV light in the presence of a sensitizer.[19] A more attractive approach for the generation of singlet oxygen for the preparation of *p*-quinols was developed by Carreño through the use of Oxone®, which decomposes in aqueous basic media to generate $^1O_2$ (**Scheme 6-13**).[13,20] Electron-rich 4-substituted phenols undergo [4+2]-cycloaddition with $^1O_2$ to generate the 1,4-endoperoxide **20**, which rapidly decomposes in the presence of H_2O to form the desired *p*-peroxyquinol **14**. One-pot reductive work-up in the presence of $Na_2S_2O_3$ cleanly provides the *p*-quinol **17** in near quantitative yield. Based on its operational simplicity, scalability and greenness, we chose to prepare our requisite alkyl *p*-quinols employing Carreño's Oxone®-based strategy over more established hypervalent iodine reagent methods. 2,2′-Disubstituted-4-methyl *p*-quinols, however, necessitated PIDA-mediated oxidation conditions.

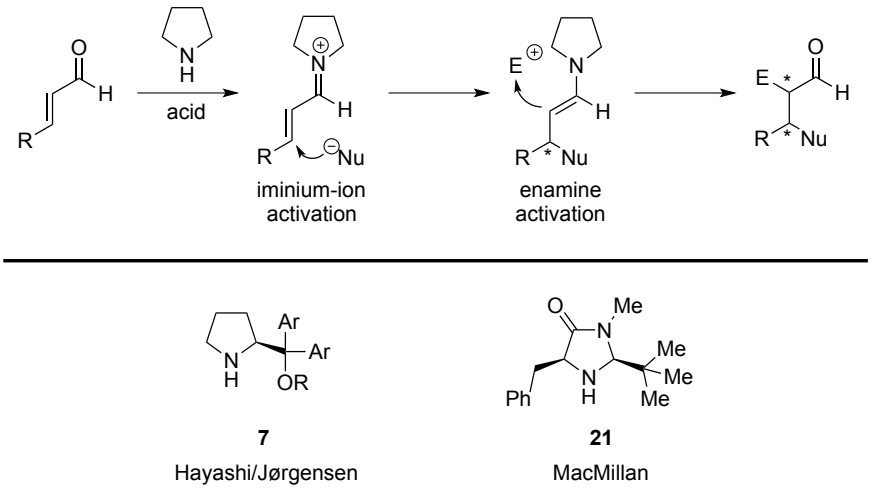
Scheme 6-13. Oxidative Dearomatization of Phenols by Singlet Oxygen ($^1O_2$)



6.3.2 Identification of Secondary Amine Catalysts

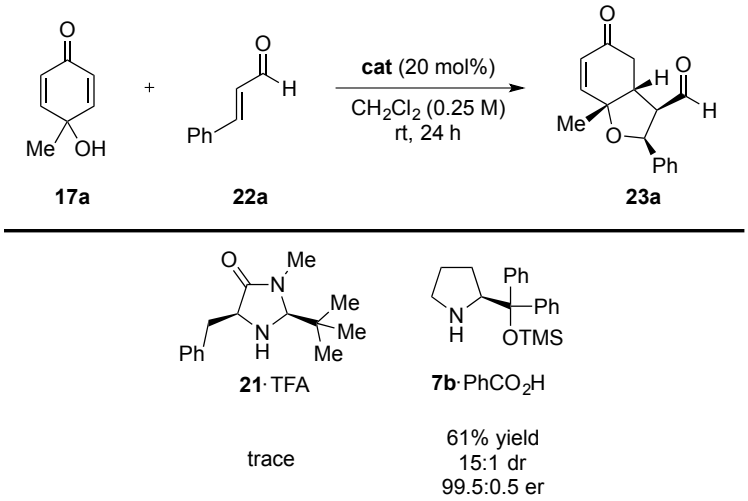
In order to achieve the proposed domino reactivity, iminium-ion/enamine activation of α,β-unsaturated aldehydes was investigated using secondary amine catalysis (**Scheme 6-14**). Since Langenbeck's pioneering work,[21] a variety of chiral secondary amine catalysts have been shown to achieve LUMO-lowering activation of α,β-unsaturated carbonyls through iminium-ion formation.[22] Based on their prior success in catalytic asymmetric transformations of enals, diarylprolinol ether catalysts **7** developed by Hayashi and Jørgensen and imidazolidinone catalysts **21** developed by MacMillan were selected for initial screening.[23] Both of these catalyst architectures have been shown to provide excellent levels of enantioselectivity in 1,4-conjugate addition reactions of α,β-unsaturated aldehydes through chiral control where bulky groups on the secondary amine control iminium-ion geometry and effectively shield one face of the extended π-system.

Scheme 6-14. Secondary Amine Activation of α,β-Unsaturated Carbonyls



We commenced our investigation by examining the reaction of *p*-quinol **17a** with cinnamaldehyde (**22a**) under secondary amine catalysis in the presence of acid additives (**Scheme 6-15**). Although MacMillan's imidazolidinone catalyst **21**·TFA provided only trace product after 24 h, Hayashi's catalyst **7b**·$PhCO_2H$ efficiently catalyzed the reaction providing the desired (3+2)-annulation adduct **23a** in 61% yield with 15:1 dr (**23a**:Σothers) and 99.5:0.5 er. The excellent levels of enantioselectivity observed in the annulation suggest that the oxa-Michael addition proceeds with excellent facial selectivity due to steric control provided by the bulky amine catalyst.

Scheme 6-15. Screening of Chiral Secondary Amine Catalysts

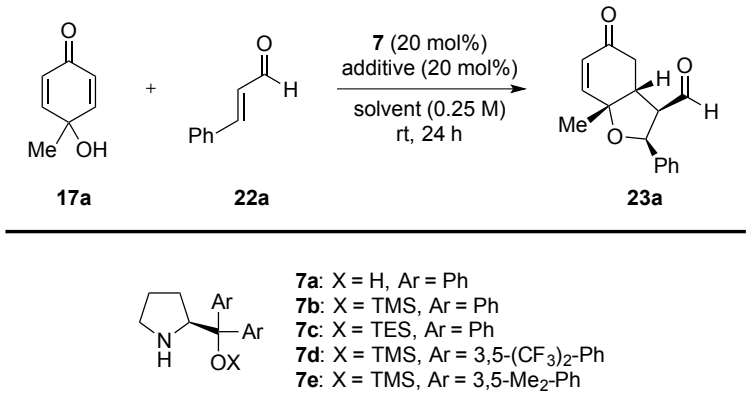


6.3.3 Optimization of Catalyst Structure and Reaction Conditions

Having identified an efficient catalyst for the oxa-Michael/Michael desymmetrization, we turned our attention to screening catalysts and conditions to optimize both reaction efficiency and selectivity (**Table 6-1**). The use of basic additives like $NaHCO_3$ was found to be detrimental to the reaction (entry 2). Although running the reaction in EtOAc or Et_2O resulted in dramatic drops in diastereoselection (entries 3 and 4), switching the solvent to toluene and utilizing 4-nitrobenzoic acid (PNBA) increased the yield to 82% with no loss in stereocontrol (entry 7). Although high levels of enantioselectivity were observed in the initial oxa-Michael addition, efforts to increase the diastereoselection of the subsequent intramolecular Michael addition through structural modifications of the catalyst **7** were largely unsuccessful. Both diphenylprolinol (**7a**) and Jørgensen's catalyst **7d** completely shut down the reaction (entries 8 and 10). Catalysts possessing a bulkier TES group (**7c**) or 3,5-Me_2-Ph aryl groups (**7e**) provided **23a** in good yield, but lower levels of diastereoselection (entries 9 and 11). Optimized conditions

were realized using commercially available **7b** with 1.5 equivalents of cinnamaldehyde (**22a**) affording **23a** in 81% yield with 15:1 dr and >99.5:0.5 er (entry 12).

Table 6-1. Reaction Optimization[a]



entry	7	additive	solvent	yield (%)[b]	dr[c]	er[d]
1	**7b**	$PhCO_2H$	CH_2Cl_2	61	15:1	99.5:0.5
2	**7b**	$NaHCO_3$	CH_2Cl_2	trace[c]	–	–
3	**7b**	$PhCO_2H$	EtOAc	N/D	6:1	N/D
4	**7b**	$PhCO_2H$	Et_2O	N/D	2:1	N/D
5	**7b**	$PhCO_2H$	CH_2Cl_2:H_2O (10:1)	68	10:1	>99.5:0.5
6	**7b**	$PhCO_2H$	toluene	78	15:1	>99.5:0.5
7	**7b**	PNBA	toluene	82	16:1	>99.5:0.5
8	**7a**	PNBA	toluene	0	–	–
9	**7c**	PNBA	toluene	72	7:1	>99.5:0.5
10	**7d**	PNBA	toluene	0	–	–
11	**7e**	PNBA	toluene	75	9:1	>99.5:0.5
12[e]	**7b**	PNBA	toluene	81	15:1	>99.5:0.5

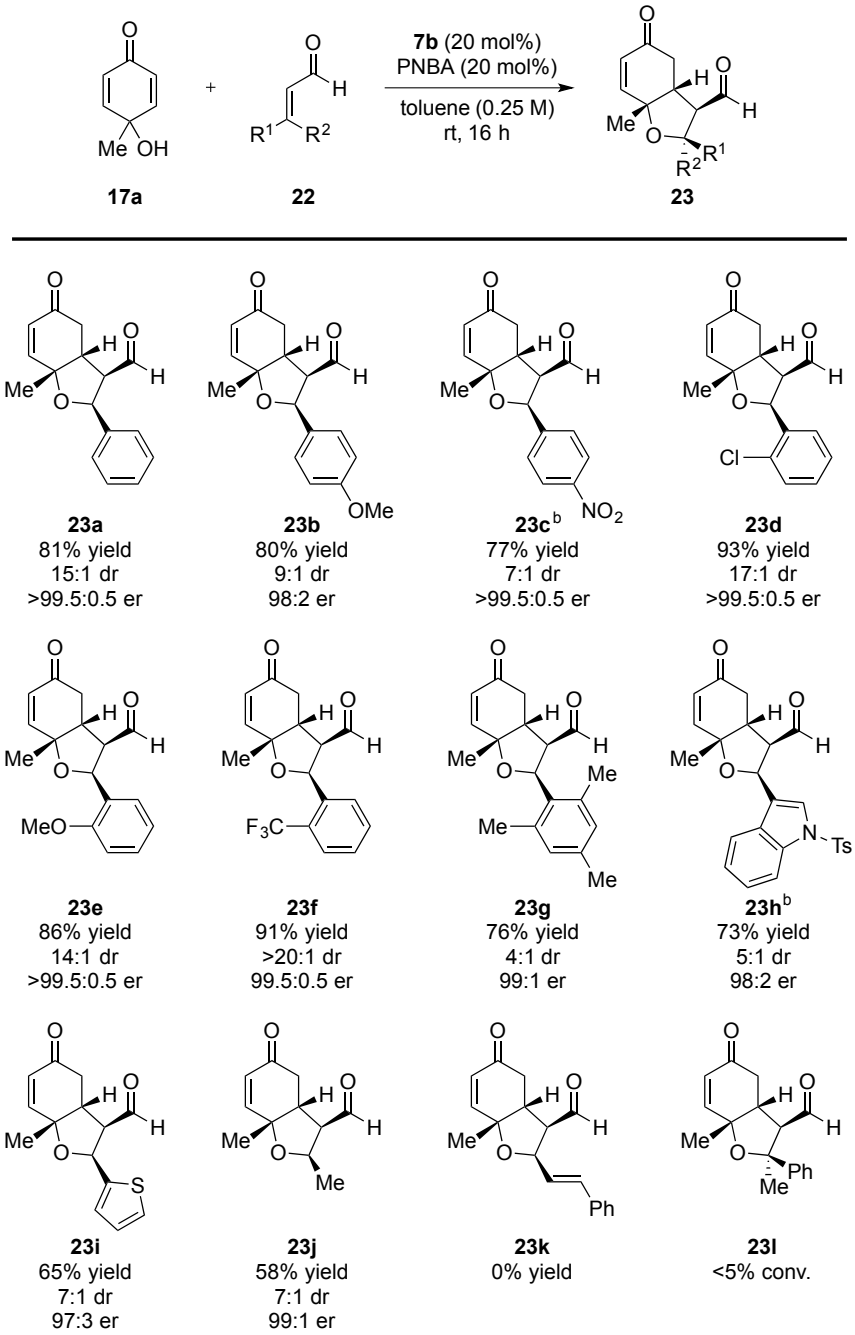
[a]Reactions were performed on 0.30 mmol scale, using 3.0 equiv. aldehyde unless otherwise noted. [b]Isolated yield of major diastereomer. [c]Determined by ^{1}H NMR analysis of crude reaction mixture. [d]Determined by chiral SFC analysis. [e]Employing 1.5 equiv. aldehyde.

6.3.4 Reaction Scope

The feasibility of employing other *p*-quinol and aldehyde reactants was examined as the reaction's scope was probed (**Tables 6-2** and **6-3**). Notably, excellent levels of enantioselection were observed for all substrates irrespective of the steric and electronic features of the nucleophile and electrophile. In addition to the parent product **23a**, products can be obtained

bearing strongly electron-releasing and withdrawing *para*-substituents on the aldehyde with slightly reduced diasterecontrol (**23b** and **23c**). Aromatic aldehydes bearing *ortho*-substituents were found to provide excellent levels of diastereocontrol regardless of electronic features (**23d**, **23e**, and **23f**). The bulky mesityl-group could be incorporated providing **23g** in good chemical yield and enantioselectivity, but with low diastereocontrol (4:1 dr). Thien-2-yl and indol-3-yl functionality was amenable to the reaction providing access to heteroaromatic substrates **23h** and **23i**. Aldehydes bearing a γ-enolizable site are also compatible under the reaction conditions as crotonaldehyde provides access to Me-substituted **23j** in 58% yield and 7:1 dr with 99:1 enantioselection. Only trace byproducts were observed from undesired dienamine formation. Although 1,4-conjugate addition pathways predominate in acyclic α,β-γ,δ-unsaturated aldehyde systems, attempts at employing 2,4-dienals resulted in a complex reaction mixture (**23k**).[24] β-Disubstituted α,β-unsaturated aldehydes were found to be unreactive under the reaction conditions suggesting that they are too sterically encumbered for the oxa-Michael addition of tertiary carbinols (**23l**).

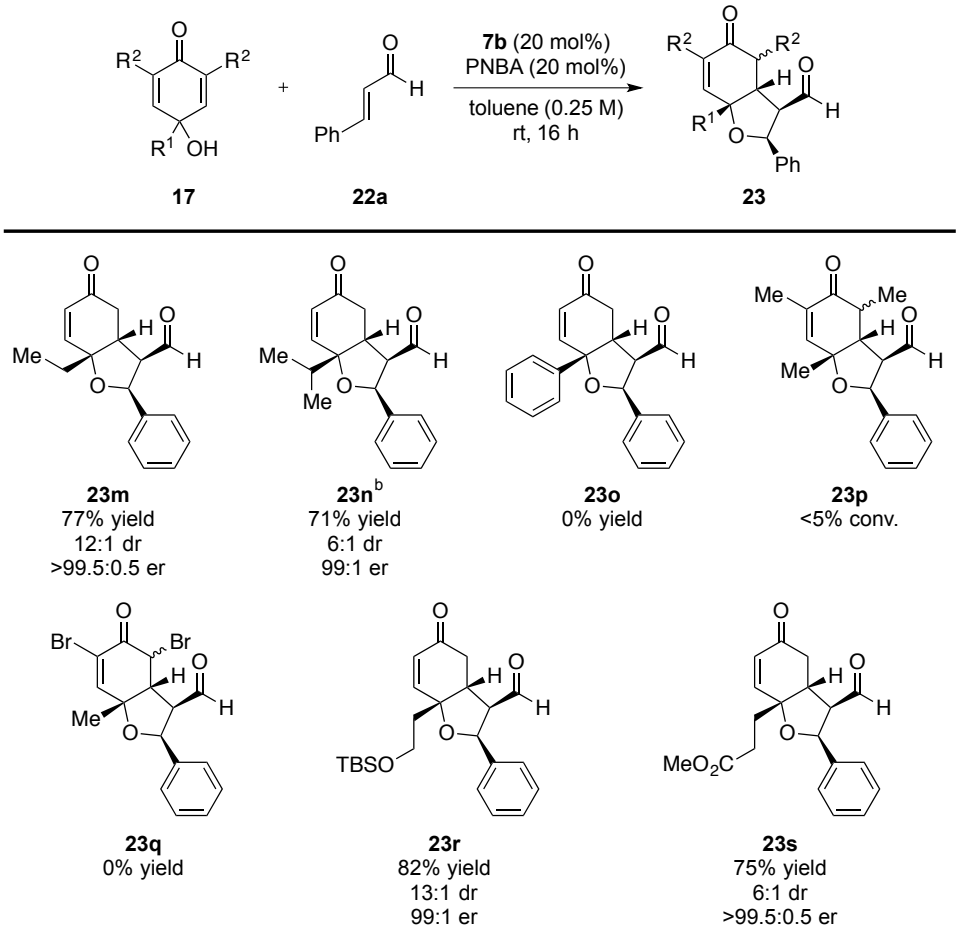
Table 6-2. Scope of Aldehydes[a]



[a]Reactions were performed on 1.00 mmol scale, using 1.5 equiv aldehyde. Isolated yields of analytically pure major diastereomer are reported. Diastereomer ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures; enantiomer ratios were determined by chiral HPLC/SFC analysis. [b]toluene:CH_2Cl_2 (1:1) (0.25 M).

In addition to methyl-substituted **17a**, a variety of *p*-quinols bearing linear aliphatic substituents were tolerated in the addition to cinnamaldehyde (**22a**) allowing for the incorporation of pendant siloxy and ester functionality (**23m**, **23r**, and **23s**). The bulkier ^{i}Pr-derived *p*-quinol provided **23n** in 71% yield, but with modest diastereoselection in the intramolecular Michael addition. The Ph-substituted *p*-quinol afforded a complex mixture in the reaction (**23o**). Examination of 2,2´-disubtititued-4-methyl *p*-quinols in the reaction was pursued to install an additional stereocenter thereby increasing molecular complexity; however, attempted annulations were unfruitful (**23p** and **23q**).

Table 6-3. Scope of *p*-Quinols[a]

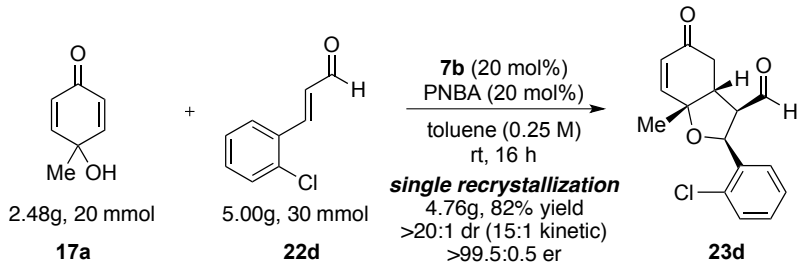


[a]Reactions were performed on 1.00 mmol scale, using 1.5 equiv aldehyde. Isolated yields of analytically pure major diastereomer are reported. Diastereomer ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures; enantiomer ratios were determined by chiral HPLC/SFC analysis. [b]Isolated yield of 10:1 dr mixture.

6.3.5 Reaction Scalability

In order to further highlight the potential applicability of this methodology, the reaction of **17a** and **22d** was performed on 20 mmol scale employing commercially available catalyst **7b** with technical grade reagents under ambient atmosphere providing **23d** in 82% yield after a single recrystallization (**Scheme 6-16**).

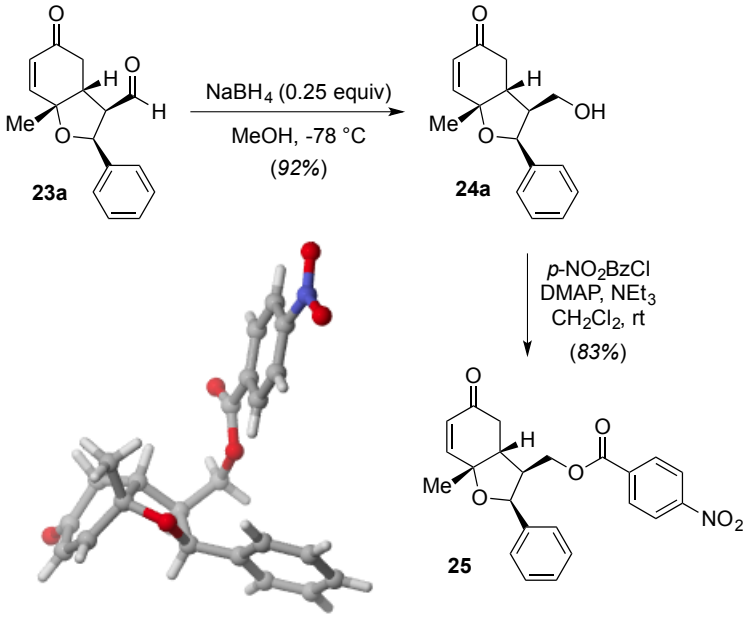
Scheme 6-16. Gram-scale Synthesis



6.3.6 Determination of Absolute Stereochemistry and Secondary Transformations of Products

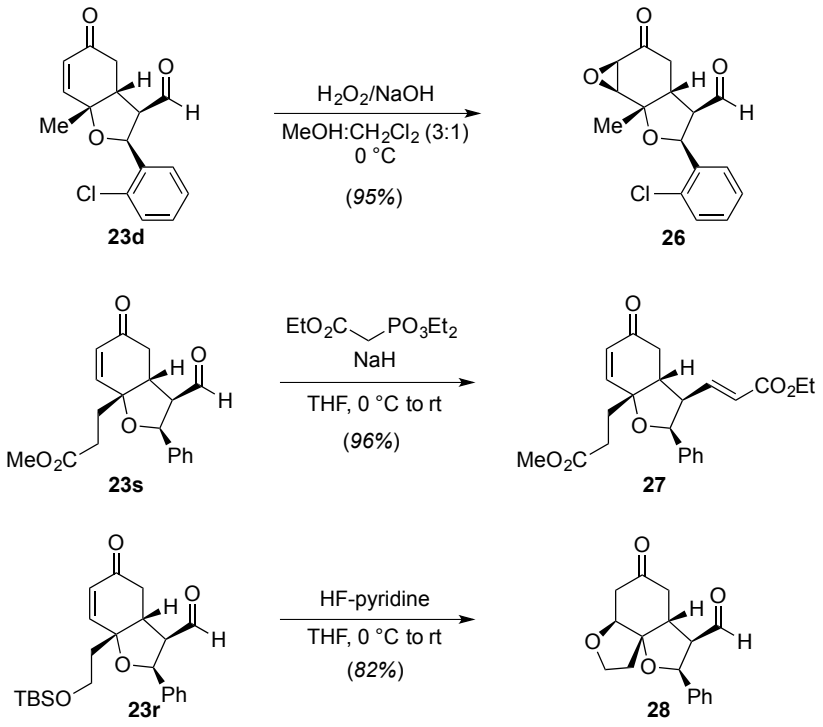
In addition to providing complex fused bicyclic frameworks with good stereocontrol, the products contain synthetically useful aldehyde and enone functional handles for further orthogonal manipulations. Chemoselective reduction of aldehyde **23a** afforded alcohol **24a** (92% yield), which was subsequently converted to the *p*-nitrobenzoate **25** (**Scheme 6-17**). The absolute stereochemistry of the product was assigned by an X-ray diffraction study of (2*S*,3*S*,3a*R*,7a*R*)-**25** and other products were assigned by analogy.[25]

Scheme 6-17. Determination of Absolute Stereochemistry



The illustrated X-ray structure reveals interesting topology that was projected to engender excellent stereocontrol in manipulations of π-functional groups (**Scheme 6-18**). Indeed, Weitz-Scheffer reaction of **23d** afforded epoxide **26** as a single diastereomer bearing six contiguous stereocenters. Chemoselective Horner-Wadsworth-Emmons olefination of **23s** provided diester **27** in 96% yield. A one-pot TBS-cleavage/oxa-Michael cyclization of **23r** gave access to aldehyde **28** bearing a tricyclic framework found in the physalins.[26]

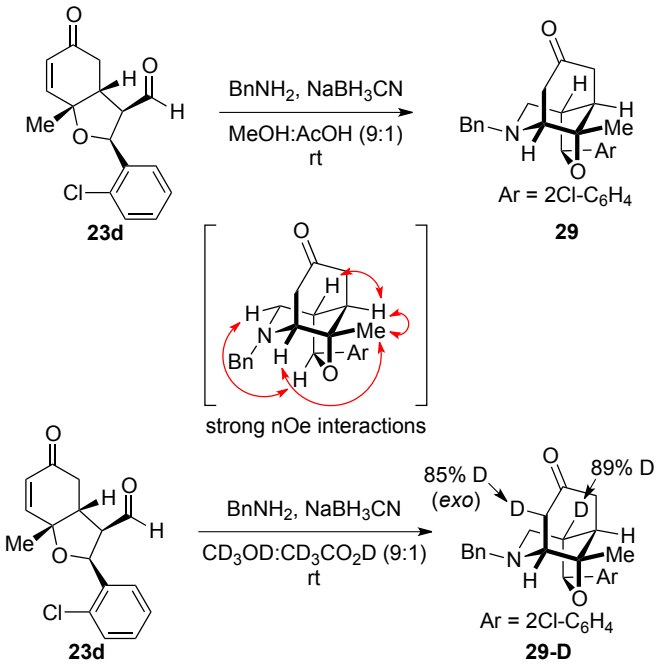
Scheme 6-18. Complexity-Building Secondary Transformations



Exposure of **23d** to benzylamine and $NaBH_3CN$ generated tricycle **29** presumably via sequential epimerization, reductive amination, and intramolecular aza-Michael addition from the concave surface of the bicyclic enone (**Scheme 6-19**). The structure **29** was supported by 2D-NMR analysis of nOe interactions as well as mechanistic observations. Based on deuterium incorporation α-aldehyde, it can be assumed that under the acidic conditions epimerization occurs via enamine/iminum tautomerization. This observation is also consistent with experimental observations related to the time required for condensation/epimerization to occur. When the aldehyde and amine are premixed for shorter periods of time before $NaBH_3CN$ is added, the yield of **29** is lower with the remaining mass being the formation of **24d** via direct reduction of the aldehyde. Deuterium incorporation α-ketone is consistent with protonation

following aza-Michael addition, with protonation of the enol from the convex face preferentially (85% D for *exo* and <5% D for *endo*).

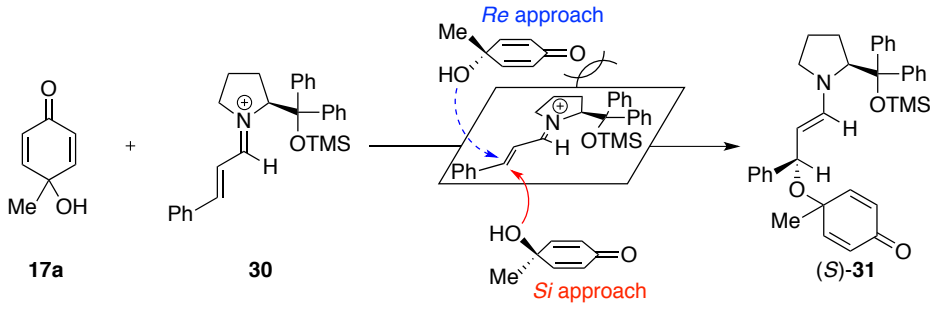
Scheme 6-19. Reductive Amination/Aza-Michael Cascade



6.3.7 Origin of Stereoselectivity in Oxa-Michael/Michael Domino Reaction

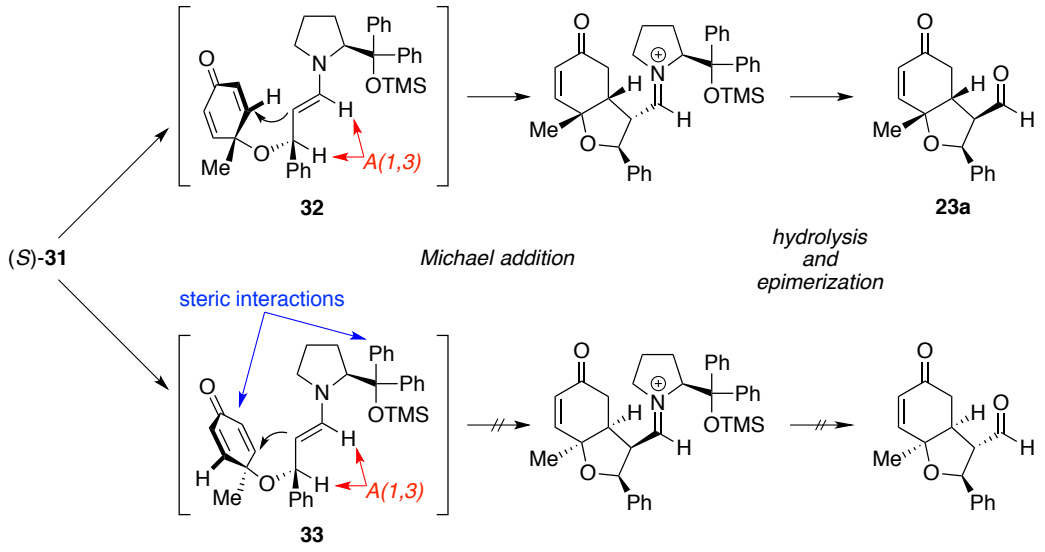
The stereochemistry obtained in the reaction can be rationalized through a careful examination of the individual oxa-Michael and Michael steps in the domino reaction enroute to bicyclic tetrahydrofurans. The oxa-Michael addition is presumed to be the enantiodetermining step in the reaction sequence. Therefore, 1,4-conjugate addition of *p*-quinol **17a** to iminium-ion activated (*E*)-**30** needs to occur with high facial selectivity (**Scheme 6-20**). The chiral secondary amine catalyst blocks the top face of the conjugated system preventing *Re* approach of *p*-quinol **17a** due to unfavorable steric interactions with the catalyst. Alternatively, *Se* approach of **17a** can occur with minimal steric penalties providing intermediate enamine (*S*)-**31** with high enantiocontrol following proton-transfer.

Scheme 6-20. Model for Asymmetric Induction in Oxa-Michael Addition



The resultant enamine (*S*)-**31** is well positioned to undergo intramolecular diastereoselective Michael addition into the quinol moiety. Following minimization of allylic strain through bond rotation, the quinol moiety is positioned away from the steric bulk of the catalyst (**Scheme 6-21**). In order for high diastereoselectivity to be observed in the final product **23a**, discrimination of diastereotopic π-groups is necessary in the Michael addition. Based on the stereochemistry established during the oxa-Michael addition, two possible diastereomeric transition states (**32** and **33**) for the Michael addition are possible. In transition state **32**, the steric bulk of the quinol moiety is directed below the plane of the chiral catalyst. Michael addition from transition state **32** provides the correct *syn*-relationship between the Me and Ph groups observed in the products. The aldehyde stereochemistry is incorrect following hydrolysis, but epimerization under the acidic reaction conditions is proposed to be favorable in order to move from the concave to convex surfaces of the molecule to provide the stereochemistry observed in the isolated product **23a**. Transition state **33**, however, is expected to undergo slow Michael addition due to unfavorable steric interactions between the quinol moiety and the chiral catalyst that occupy the same plane. Michael addition would afford an *anti*-relationship between the Me and Ph groups not observed in the products.

Scheme 6-21. Model for Diasterocontrol in Michael Addition



6.4 Conclusion

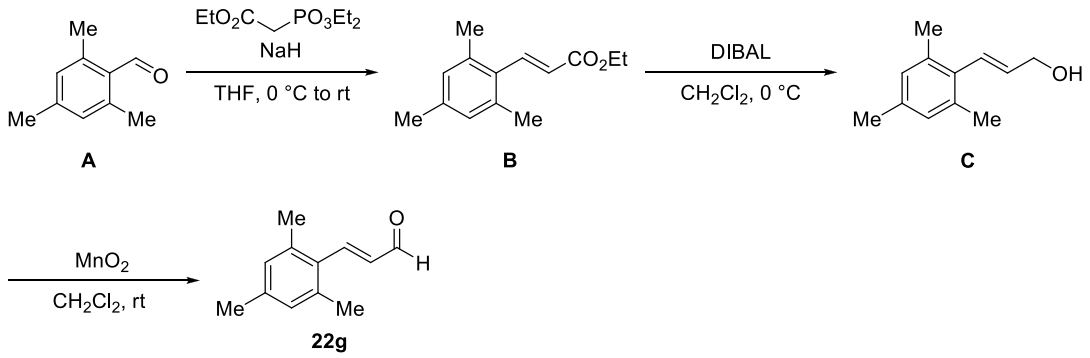
In conclusion, we have developed an asymmetric synthesis of hindered cyclic dialkyl ethers via intermolecular oxa-Michael addition of *p*-quinols and α,β-unsaturated aldehydes under secondary amine catalysis. Iminium-ion activation of α,β-unsaturated aldehydes promotes intermolecular oxa-Michael addition of achiral tertiary carbinols, which can undergo desymmetrization via intramolecular Michael addition to afford the (3+2)-annulation adducts in high diastereoselectivity and excellent enantioselectivity. The reaction sequence provides rapid access to complex bicyclic frameworks with the concomitant formation of four contiguous stereocenters. Furthermore, the reaction is a rare example of a reaction sequence that establishes both α-stereocenters of a dialkyl ether in a single operation. Rapid construction of molecular complexity in the domino reaction provides products that contain malleable enone and aldehyde functionality that can be orthogonally manipulated. We have also demonstrated that the products can undergo a range of complexity-building secondary transformations providing access to complex, highly functionalized tricyclic frameworks of interest to the synthetic community.

6.5 Experimental Details

Methods: Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 101 MHz or 151 MHz, and ^{19}F NMR at 565 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, sept = septuplet, oct = octuplet, m = multiplet), coupling constants (Hz), and integration. HPLC analysis was performed on an Agilent Technologies 1200 System equipped with Chiralpak IA, IB, and IC columns (φ 4.6 mm x 250 mm, constant flow at 1.00 mL/min). Supercritical fluid chromatography (SFC) was performed on a Berger SFC system equipped with Chiralpak AD, AS, and OD columns (φ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH with an oven temperature of 40 °C. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Thermo Scientific LTQ FT Ultra instrument with electrospray ionization. Analytical thin layer chromatography (TLC) was performed on Sorbtech 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. All reactions were carried out with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

Materials: *p*-Quinols **17**,[13,27] α,β-unsaturated aldehydes **22**,[28] and Jørgensen–Hayashi catalysts **7**[23b] were prepared according to known literature procedures. Triethylamine (Et_3N) was freshly distilled from calcium hydride prior to use. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were dried by passage through a column of neutral alumina under nitrogen prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

Synthesis of (*E*)-3-Mesitylacrylaldehyde (22g)

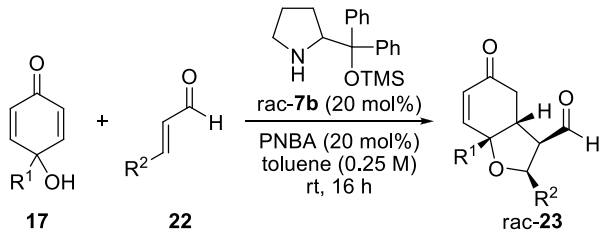


A flame-dried 100-mL round-bottom flask equipped with a magnetic stir bar was charged with NaH (60%) (0.5 g, 12.5 mmol, 1.25 equiv) suspended in THF (25 mL). The suspension was cooled to 0 ºC. Triethyl phosphonoacetate (2.5 mL, 12.5 mmol, 1.25 equiv) was added dropwise. The homogenous solution was allowed to stir at 0 ºC for 20 min before mesitaldehyde (**A**) (1.5 mL, 10.0 mmol, 1.00 equiv) was added dropwise. The ice bath was removed and the resulting solution was allowed to stir for 3 h as it slowly warmed to room temperature. The reaction was cooled to 0 ºC and quenched with sat. aq. NH_4Cl (25 mL). The reaction was diluted with Et_2O (100 mL) and washed with H_2O (40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford analytically pure unsaturated ester **B**, which was used without further purification.

A flame-dried 250-mL round-bottom flask equipped with a magnetic stir bar was charged with unsaturated ester **B** in CH_2Cl_2 (100 mL). The solution was cooled to 0 ºC. DIBAL (4.0 mL, 22.0 mmol, 2.20 equiv) was added dropwise. The reaction was allowed to stir at 0 ºC for 2 h. The reaction was quenched by sequential addition of acetone (25 mL) and 1 N HCl (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford analytically pure allyl alcohol **C**, which was used without further purification.

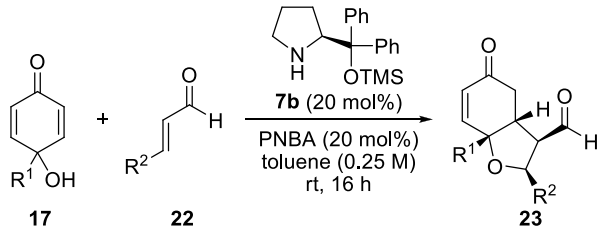
A flame-dried 250-mL round-bottom flask equipped with a magnetic stir bar was charged with allyl alcohol **C** in CH_2Cl_2 (100 mL). Activated MnO_2 (4.4 g, 50.0 mmol, 5.00 equiv) was added and the reaction was allowed to stir at room temperature for 16 h. The reaction was filtered through a pad of Celite® rinsing with CH_2Cl_2 (3 x 50 mL). The filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford (*E*)-3-mesitylacrylaldehyde (**22g**) (1.27 g, 73% yield) as a white solid (mp 72-73 ºC). Analytical data for **22g**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.70 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 16.3 Hz, 1H), 6.94 (s, 2H), 6.41 (dd, *J* = 16.3, 7.7 Hz, 1H), 2.36 (s, 6H), 2.31 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 194.32,† 194.28,‡ 151.5, 139.5, 137.1, 133.5, 130.0, 129.5, 21.2, 21.1 (†Rotomer A, ‡Rotomer B); **IR** (thin film): 1662, 1626, 1136, 1020, 984, 845 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.49; **HRMS** (ESI): Calcd. for $C_{12}H_{15}O$ ($[M+H]^+$): 175.1124, Found: 175.1117.

General Procedure A for the Preparation of rac-23



A 20-mL scintillation vial equipped with a magnetic stir bar was charged with α,β-unsaturated aldehyde **22** (1.50 mmol, 1.5 equiv), rac-**7b** (70.5 mg, 0.20 mmol, 0.2 equiv), and 4-nitrobenzoic acid (33.4 mg, 0.20 mmol, 0.2 equiv) in toluene (4.0 mL, 0.25 M). The solution was stirred for 5 min at room temperature until homogeneous. *p*-Quinol **17** (1.00 mmol, 1.0 equiv) was added, the vial was capped, and the reaction was allowed to stir for 16 h at room temperature. The reaction was diluted with EtOAc (30 mL) and sequentially washed with sat. aq. $NaHCO_3$ (1 x 15 mL), H_2O (1 x 15 mL), and brine (1 x 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The crude residue was purified by column chromatography on silica gel to afford rac-**23**.

General Procedure B for the Preparation of 23



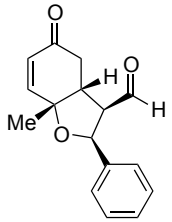
17a: R^1 = Me
17b: R^1 = Et
17c: R^1 = ^{i}Pr
17d: R^1 = CH_2CH_2OTBS
17e: R^1 = $CH_2CH_2CO_2Me$

22a: R^2 = C_6H_5
22b: R^2 = 4-$OMeC_6H_4$
22c: R^2 = 4-$NO_2C_6H_4$
22d: R^2 = 2-ClC_6H_4
22e: R^2 = 2-$OMeC_6H_4$

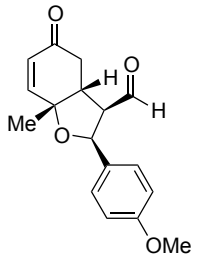
22f: R^2 = 2-$CF_3C_6H_4$
22g: R^2 = 2,4,6-$Me_3C_6H_2$
22h: R^2 = *N*-Ts-indol-3-yl
22i: R^2 = thien-2-yl
22j: R^2 = Me

Note: No precautions were taken to preclude water or air from the reactions. Reactions were performed in non-flame-dried glassware using reagent grade solvents as received under ambient atmosphere. Reactions can be performed employing CH_2Cl_2 or $CHCl_3$ in place of toluene with comparable levels of selectivity, but in slightly reduced yields.

A 20-mL scintillation vial equipped with a magnetic stir bar was charged with α,β-unsaturated aldehyde **22** (1.50 mmol, 1.5 equiv), **7b** (70.5 mg, 0.20 mmol, 0.2 equiv), and 4-nitrobenzoic acid (33.4 mg, 0.20 mmol, 0.2 equiv) in toluene (4.0 mL, 0.25 M). The solution was stirred for 5 min at room temperature until homogeneous. *p*-Quinol **17** (1.00 mmol, 1.0 equiv) was added, the vial was capped, and the reaction was allowed to stir for 16 h at room temperature. The reaction was diluted with EtOAc (30 mL) and sequentially washed with sat. aq. $NaHCO_3$ (1 x 15 mL), H_2O (1 x 15 mL), and brine (1 x 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The crude residue was purified by column chromatography on silica gel to afford **23**. The enantiomeric ratio was determined following reduction to **24** (with subsequent benzoate formation for **23h** and **23j**) or olefination to **27**.

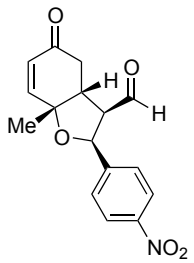


(2*S*,3*R*,3a*R*,7a*R*)-7a-Methyl-5-oxo-2-phenyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23a): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22a** (198 mg, 1.50 mmol) affording a 15:1 (**23a**:Σothers) mixture of diastereomers. Purification provided **23a** (207 mg, 81% yield, >20:1 dr) as a pale yellow oil. The enantiomeric ratio was determined following reduction to **24a**. Analytical data for **23a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.99 (d, *J* = 1.7 Hz, 1H), 7.36-7.33 (m, 2H), 7.29-7.27 (m, 3H), 6.71 (dd, *J* = 10.3, 1.5 Hz, 1H), 6.08 (d, *J* = 10.3 Hz, 1H), 5.23 (d, *J* = 9.7 Hz, 1H), 3.14 (dt, *J* = 9.5, 1.7 Hz, 1H), 3.06-3.03 (m, 1H), 2.70 (dd, *J* = 17.4, 5.4 Hz, 1H), 2.55 (d, *J* = 17.4 Hz, 1H), 1.67 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.9, 196.4, 152.0, 136.9, 129.8, 128.8, 128.4, 126.3, 79.6, 79.1, 60.4, 43.0, 37.3, 23.2; **IR** (thin film): 2973, 1718, 1679, 1494, 1455, 1122, 1045, 703 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.50; **HRMS** (ESI): Calcd. for $C_{16}H_{17}O_3$ ([M+H]$^+$): 257.1178, Found: 257.1173; **[α]$_D$** -116 (*c* = 1.9, $CHCl_3$).

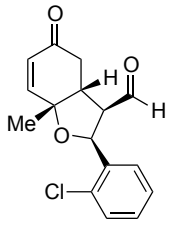


(2*S*,3*R*,3a*R*,7a*R*)-2-(4-Methoxyphenyl)-7a-methyl-5-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23b): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22b** (243 mg, 1.50 mmol) affording a 9:1 (**23b**:Σothers) mixture of diastereomers. Purification provided **23b** (223 mg, 78% yield, >20:1 dr) as a pale yellow oil. The enantiomeric ratio was determined following reduction to **24b**. Analytical data for **23b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.02 (d, *J* = 1.8 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.72 (dd, *J* = 10.3, 1.8 Hz, 1H), 6.08 (d, *J* = 10.3 Hz, 1H), 5.19 (d, *J* = 9.3 Hz, 1H), 3.78 (s, 3H), 3.14-3.04 (m, 2H), 2.70 (dd, *J* = 17.4, 5.2 Hz, 1H), 2.55 (d, *J* = 17.4 Hz, 1H), 1.66 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 199.1, 196.5, 159.5, 152.1, 129.8,

128.9, 127.7, 114.2, 79.3, 78.9, 60.4, 55.2, 42.9, 37.3, 23.2; **IR** (thin film): 2930, 1717, 1682, 1612, 1513, 1249, 1032, 836 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.36; **HRMS** (ESI): Calcd. for $C_{17}H_{19}O_4$ ($[M+H]^+$): 287.1284, Found: 287.1279; $[\alpha]_D$ -87 (*c* = 1.6, $CHCl_3$).

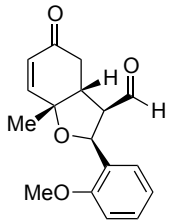


(2*S*,3*R*,3a*R*,7a*R*)-7a-Methyl-2-(4-nitrophenyl)-5-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23c): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22c** (266 mg, 1.50 mmol) affording a 17:1 (**23c**:Σothers) mixture of diastereomers. Purification provided **23c** (214 mg, 77% yield, >20:1 dr) as a pale yellow oil. The enantiomeric ratio was determined following reduction to **24c**. Analytical data for **23c**: ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 9.02 (d, *J* = 2.5 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 6.72 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.13 (dd, *J* = 10.3, 1.0 Hz, 1H), 5.32 (d, *J* = 9.6 Hz, 1H), 3.25 (dt, *J* = 9.5, 2.5 Hz, 1H), 3.08-3.03 (m, 1H), 2.73 (dd, *J* = 17.4, 5.4 Hz, 1H), 2.56 (ddd, *J* = 17.4, 2.1, 1.1 Hz, 1H), 1.71 (s, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$): δ 198.0, 195.9, 151.2, 147.8, 144.2, 130.3, 127.2, 124.1, 80.3, 78.3, 60.5, 43.4, 37.2, 23.3; **IR** (thin film): 2089, 1716, 1681, 1645, 1520, 1457, 1348, 529 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.24; **HRMS** (ESI): Calcd. for $C_{16}H_{16}NO_5$ ($[M+H]^+$): 302.1029, Found: 302.1019; $[\alpha]_D$ -115 (*c* = 0.5, $CHCl_3$).



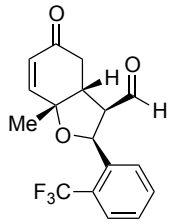
(2*S*,3*R*,3a*R*,7a*R*)-2-(2-Chlorophenyl)-7a-methyl-5-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23d): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22d** (250 mg, 1.50 mmol) affording a 17:1 (**23d**:Σothers) mixture of diastereomers. Purification provided **23d** (273 mg, 94% yield, >20:1 dr) as an off-white solid (mp 150-153 ºC). The enantiomeric ratio was determined following

reduction to **24d**. Analytical data for **23d**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.09 (d, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.25-7.22 (m, 1H), 6.71 (dd, *J* = 10.3, 1.9 Hz, 1H), 6.12 (d, *J* = 10.3 Hz, 1H), 5.47 (d, *J* = 9.5 Hz, 1H), 3.35 (dt, *J* = 9.5, 2.0 Hz, 1H), 3.01-2.98 (m, 1H), 2.69 (dd, *J* = 17.5, 5.5 Hz, 1H), 2.56 (dd, *J* = 17.5, 1.0 Hz, 1H), 1.68 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.6,† 198.5,‡ 196.4, 151.7, 135.0, 131.3, 130.4, 129.4, 129.3, 127.34, 127.29, 79.5, 75.9, 58.6, 43.0, 37.3, 23.1 (†Rotomer A, ‡Rotomer B); **IR** (thin film): 2089, 1717, 1682, 1653, 1474, 1374, 1120, 1049 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.51; **HRMS** (ESI): Calcd. for $C_{16}H_{16}ClO_3$ ([M+H]$^+$): 291.0789, Found: 291.0785; **[α]$_D$** -205 (*c* = 1.4, $CHCl_3$).

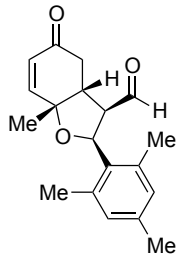


(2*S*,3*R*,3a*R*,7a*R*)-2-(2-Methoxyphenyl)-7a-methyl-5-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23e): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22e** (243 mg, 1.50 mmol) affording a 14:1 (**23e**:Σothers) mixture of diastereomers. The enantiomeric ratio was determined following reduction to **24e**. Purification provided **23e** (247 mg, 86% yield, >20:1 dr) as a white solid (mp 101-103 ºC). Analytical data for **23e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.00 (d, *J* = 2.5 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 1H), 7.23 (dt, *J* = 8.0, 1.6 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 10.3, 1.9 Hz, 1H), 6.68 (dd, *J* = 10.3, 1.9 Hz, 1H), 6.06 (dd, *J* = 10.3, 0.7 Hz, 1H), 5.36 (d, *J* = 9.3 Hz, 1H), 3.77 (s, 3H), 3.35 (dt, *J* = 9.2, 2.5 Hz, 1H), 2.89-2.84 (m, 1H), 2.65 (dd, *J* = 17.4, 5.4 Hz, 1H), 2.52 (d, *J* = 17.4 Hz, 1H), 1.63 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 199.5, 196.6, 155.1, 152.2, 129.9, 129.0, 126.1, 125.5, 120.7, 109.8, 79.1, 74.5, 58.6, 55.0, 43.1, 37.2, 23.1; **IR** (thin film): 2839, 1717, 1684, 1490, 1296, 1116, 1046, 757 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.46;

HRMS (ESI): Calcd. for $C_{17}H_{19}O_4$ ([M+H]$^+$): 287.1284, Found: 287.1279; **[α]$_D$** -182 (*c* = 1.8, $CHCl_3$).

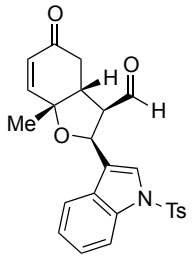


(2*S*,3*R*,3a*R*,7a*R*)-7a-Methyl-5-oxo-2-(2-(trifluoromethyl)phenyl)-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23f): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22f** (300 mg, 1.50 mmol) affording a >20:1 (**23f**:Σothers) mixture of diastereomers. Purification provided **23f** (295 mg, 91% yield, >20:1 dr) as a white solid (mp 99-100 ºC). The enantiomeric ratio was determined following reduction to **24f**. Analytical data for **23f**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.95 (d, *J* = 1.1 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 6.73 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.12 (d, *J* = 10.3 Hz, 1H), 5.52 (d, *J* = 9.8 Hz, 1H), 3.21 (t, *J* = 9.5 Hz, 1H), 3.10-3.07 (m, 1H), 2.70 (dd, *J* = 17.5, 5.4 Hz, 1H), 2.53 (dt, *J* = 17.5, 1.1 Hz, 1H), 1.68 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.4,† 198.3,‡ 196.3, 151.5, 135.8, 132.6, 130.4, 128.5, 128.0, 127.1 (q, $J_{C–F}$ = 30.2 Hz), 125.8 (q, $J_{C–F}$ = 6.0 Hz), 124.0 (q, $J_{C–F}$ = 273.3 Hz), 79.6, 74.61,† 74.60,‡ 60.5, 42.6, 37.3, 23.1 (†Rotomer A, ‡Rotomer B); **^{19}F NMR** (565 MHz, $CDCl_3$): δ -59.3; **IR** (thin film): 2089, 1717, 1683, 1653, 1314, 1165, 1121, 770 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.49; **HRMS** (ESI): Calcd. for $C_{17}H_{16}F_3O_3$ ([M+H]$^+$): 325.1052, Found: 325.1048; **[α]$_D$** -127 (*c* = 0.8, $CHCl_3$).



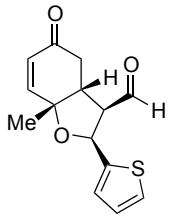
(2*S*,3*R*,3a*R*,7a*R*)-2-Mesityl-7a-methyl-5-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23g): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22g** (261 mg, 1.50 mmol) affording a 4:1 (**23g**:Σothers) mixture of diastereomers. Purification provided **23g** (215 mg, 72% yield, >20:1 dr)

as a pale yellow oil. The enantiomeric ratio was determined following reduction to **24g**. Analytical data for **23g**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.04 (d, *J* = 1.3 Hz, 1H), 6.79 (br s, 2H), 6.68 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.11 (dd, *J* = 10.3, 0.8 Hz, 1H), 5.47 (d, *J* = 10.5 Hz, 1H), 3.18-3.15 (m, 1H), 3.04 (dt, *J* = 8.9, 1.3 Hz, 1H), 2.73 (dd, *J* = 17.3, 5.3 Hz, 1H), 2.60 (dd, *J* = 17.3, 0.9 Hz, 1H), 2.27 (br s, 6H), 2.22 (s, 3H), 1.63 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.0, 196.8, 152.4, 137.7, 136.2,† 135.3,‡ 131.6,† 130.5, 129.4,‡ 128.7, 79.2, 76.3, 59.02,† 58.98, 43.2,† 43.1,‡ 37.8, 22.7, 22.1,† 20.8,‡ 20.71,† 20.68‡ (†Rotomer A, ‡Rotomer B); **IR** (thin film): 2929, 1732, 1684, 1653, 1558, 1507, 1220, 1124 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.56; **HRMS** (ESI): Calcd. for $C_{19}H_{23}O_3$ ([M+H]$^+$): 299.1648, Found: 299.1643; **[α]$_D$** -81 (*c* = 1.5, $CHCl_3$).

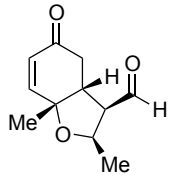


(2*S*,3*R*,3a*R*,7a*R*)-7a-Methyl-5-oxo-2-(1-tosyl-1*H*-indol-3-yl)-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23h): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22h** (488 mg, 1.50 mmol) affording a 5:1 (**23h**:Σothers) mixture of diastereomers. Purification provided **23h** (328 mg, 73% yield, >20:1 dr) as a viscous pale yellow oil. The enantiomeric ratio was determined following reduction and benzoate formation to **S1a**. Analytical data for **23h**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.00 (d, *J* = 2.0 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.22-7.19 (m, 3H), 6.70 (dd, *J* = 10.3, 1.7 Hz, 1H), 6.11 (d, *J* = 10.3 Hz, 1H), 5.40 (d, *J* = 8.6 Hz, 1H), 3.18-3.08 (m, 2H), 2.73 (dd, *J* = 17.9, 5.1 Hz, 1H), 2.57 (d, *J* = 17.1 Hz, 1H), 2.31 (s, 3H), 1.69 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 198.3, 196.2, 151.5, 145.2, 135.3, 134.8, 130.4, 129.9, 127.7, 126.7, 125.3, 124.2, 123.6, 119.7, 118.7, 113.8, 79.6, 77.2, 73.1, 59.6, 43.3, 37.3, 23.2, 21.5; **IR** (thin film): 2917, 1717, 1698, 1684, 1507, 1457,

1373, 1174 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.29; **HRMS** (ESI): Calcd. for $C_{50}H_{47}N_2O_{10}S_2$ ($[2M+H]^+$): 899.2673, Found: 899.2696; **[α]$_D$** -98 (*c* = 1.2, $CHCl_3$).

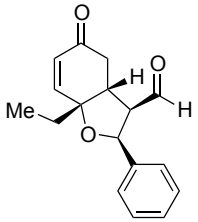


(2*S*,3*R*,3a*R*,7a*R*)-7a-Methyl-5-oxo-2-(thiophen-2-yl)-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23i): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22i** (207 mg, 1.50 mmol) affording a 7:1 (**23i**:Σothers) mixture of diastereomers. Purification provided **23i** (171 mg, 65% yield, >20:1 dr) as a pale yellow oil. The enantiomeric ratio was determined following reduction to **24i**. Analytical data for **23i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.17 (d, *J* = 1.9 Hz, 1H), 7.28-7.26 (m, 1H), 6.97-6.96 (m, 2H), 6.69 (dd, *J* = 10.3, 1.9 Hz, 1H), 6.04 (dd, *J* = 10.3, 0.9 Hz, 1H), 5.57 (d, *J* = 9.3 Hz, 1H), 3.15 (dt, *J* = 9.8, 1.9 Hz, 1H), 3.10-3.05 (m, 1H), 2.71 (dd, *J* = 17.5, 5.2 Hz, 1H), 2.58 (ddd, *J* = 17.5, 2.0, 1.1 Hz, 1H), 1.65 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 198.2, 196.2, 151.7, 141.2, 129.4, 127.2, 125.9, 125.0, 79.9, 75.4, 60.0, 42.9, 36.9, 23.5; **IR** (thin film): 2973, 1868, 1717, 1683, 1558, 1457, 1374, 1120 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.39; **HRMS** (ESI): Calcd. for $C_{14}H_{15}O_3S$ ($[M+H]^+$): 263.0743, Found: 263.0736; **[α]$_D$** -90 (*c* = 1.3, $CHCl_3$).

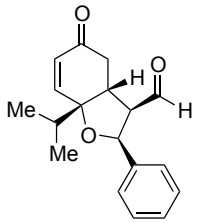


(2*R*,3*R*,3a*R*,7a*R*)-2,7a-Dimethyl-5-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23j): The title compound was prepared according to General Procedure B using *p*-quinol **17a** (124 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22j** (105 mg, 1.50 mmol) affording a 7:1 (**23j**:Σothers) mixture of diastereomers. Purification provided **23j** (116 mg, 60% yield, >20:1 dr) as a pale yellow oil. The enantiomeric ratio was determined following reduction and benzoate formation to **S1b**. Analytical data for **23j**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.72 (d, *J* = 2.1 Hz, 1H), 6.60 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.99 (d, *J* = 10.3 Hz, 1H), 4.32 (dq, *J* = 6.6, 2.2 Hz, 1H), 2.96-2.94 (m, 1H), 2.90 (dt, *J* = 9.0, 2.0 Hz, 1H),

2.64 (dd, J = 17.3, 5.4 Hz, 1H), 2.51 (d, J = 17.3 Hz, 1H), 1.52 (s, 3H), 1.27 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 200.10,† 200.06,‡ 196.7, 152.5, 129.4, 78.9, 73.7, 59.2, 43.1, 37.3, 23.5, 18.0 (†Rotomer A, ‡Rotomer B); **IR** (thin film): 3420, 1716, 1683, 1653, 1541, 1457, 1367, 709 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.29; **HRMS** (ESI): Calcd. for $C_{11}H_{15}O_3$ ([M+H]$^+$): 195.1022, Found: 195.0995; **[α]$_D$** -38 (c = 0.7, $CHCl_3$).

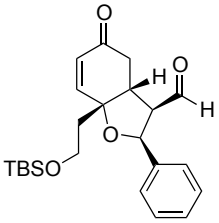


(2*S*,3*R*,3a*R*,7a*R*)-7a-Ethyl-5-oxo-2-phenyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23m): The title compound was prepared according to General Procedure B using *p*-quinol **17b** (138 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22a** (198 mg, 1.50 mmol) affording a 12:1 (**23m**:Σothers) mixture of diastereomers. Purification provided **23m** (212 mg, 78% yield, >20:1 dr) as a pale yellow oil. The enantiomeric ratio was determined following reduction to **24m**. Analytical data for **23m**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.02 (d, J = 2.7 Hz, 1H), 7.39-7.29 (m, 5H), 6.77 (dd, J = 15.5, 2.5 Hz, 1H), 6.18 (d, J = 15.5 Hz, 1H), 5.24 (d, J = 13.3 Hz, 1H), 3.21-3.13 (m, 2H), 2.71 (dd, J = 26.4, 7.9 Hz, 1H), 2.55 (d, J = 26.4 Hz, 1H), 2.13-1.93 (m, 2H), 1.20 (t, J = 11.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 199.0, 196.6, 151.4, 137.0, 130.6, 128.8, 128.3, 126.3, 81.6, 78.8, 60.7, 40.3, 37.6, 29.8, 8.1; **IR** (thin film): 2972, 1718, 1683, 1576, 1507, 1457, 1396, 1219 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.55; **HRMS** (ESI): Calcd. for $C_{17}H_{19}O_3$ ([M+H]$^+$): 271.1335, Found: 271.1329; **[α]$_D$** -110 (c = 1.3, $CHCl_3$).



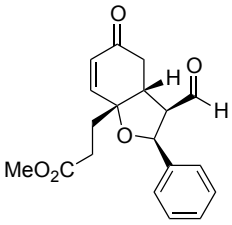
(2*S*,3*R*,3a*R*,7a*R*)-7a-Isopropyl-5-oxo-2-phenyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23n): The title compound was prepared according to General Procedure B using *p*-quinol **17c** (152 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22a** (198 mg, 1.50 mmol) affording a 6:1 (**23n**:Σothers) mixture of diastereomers. Purification provided **23n** (202 mg, 71% yield, 10:1 dr)

as a pale yellow oil. The enantiomeric ratio was determined following reduction to **24n**. Analytical data for **23n**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.02 (d, *J* = 2.0 Hz, 1H), 7.39-7.29 (m, 5H), 6.75 (dd, *J* = 10.4, 1.7 Hz, 1H), 6.28 (d, *J* = 10.4 Hz, 1H), 5.19 (d, *J* = 9.3 Hz, 1H), 3.34-3.31 (m, 1H), 3.12-3.07 (m, 1H), 2.74 (dd, *J* = 17.7, 6.0 Hz, 1H), 2.53 (d, *J* = 17.7 Hz, 1H), 2.34-2.23 (m, 1H), 1.21 (dd, *J* = 10.1, 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 199.0, 197.1, 150.5, 136.8, 131.9, 128.9, 128.4, 126.4, 83.6, 78.6, 62.1, 39.1, 38.2, 35.4, 18.0, 17.1; **IR** (thin film): 2967, 2089, 1717, 1683, 1636, 1457, 1268, 1222 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.60; **HRMS** (ESI): Calcd. for $C_{18}H_{21}O_3$ ([M+H]$^+$): 285.1491, Found: 285.1486; **[α]$_D$** -122 (*c* = 0.8, $CHCl_3$).



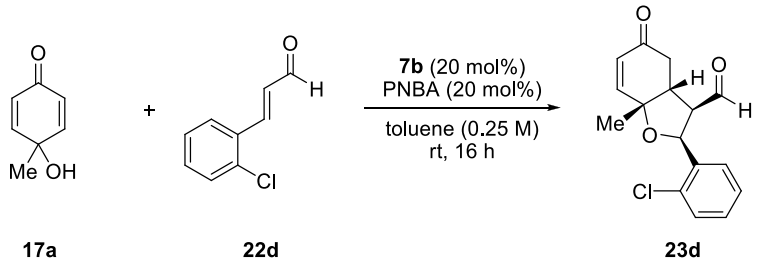
(2*S*,3*R*,3a*R*,7a*R*)-7a-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5-oxo-2-phenyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (23r): The title compound was prepared according to General Procedure B using *p*-quinol **17d** (268 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22a** (198 mg, 1.50 mmol) affording a 13:1 (**23r**:Σothers) mixture of diastereomers. Purification provided **23r** (329 mg, 82% yield, >20:1 dr) as a pale yellow oil. The enantiomeric ratio was determined following reduction to **24r**. Analytical data for **23r**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.99 (d, *J* = 2.3 Hz, 1H), 7.36-7.34 (m, 2H), 7.30-7.27 (m, 3H), 6.75 (dd, *J* = 10.3, 1.9 Hz, 1H), 6.12 (d, *J* = 10.3 Hz, 1H), 5.22 (d, *J* = 9.8 Hz, 1H), 4.03-3.99 (m, 1H), 3.91-3.87 (m, 1H), 3.37-3.34 (m, 1H), 3.13 (dt, *J* = 9.6, 2.3 Hz, 1H), 2.83 (dd, *J* = 17.5, 5.5 Hz, 1H), 2.53 (dd, *J* = 17.5, 1.1 Hz, 1H), 2.24-2.19 (m, 1H), 2.15-2.11 (m, 1H), 0.90 (s, 9H), 0.08 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.0, 197.1, 151.6, 137.0, 130.2, 128.9, 128.5, 126.4, 81.1, 79.0, 60.5, 58.4, 41.4, 39.9, 37.4, 25.8, 18.1, -5.5; **IR** (thin film): 2953, 2856, 1717, 1684, 1472, 1255, 1089, 837

cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.69; **HRMS** (ESI): Calcd. for $C_{23}H_{33}O_4Si$ ([M+H]$^+$): 401.2149, Found: 401.2144; **[α]$_D$** -69 (*c* = 1.2, $CHCl_3$).



Methyl 3-((2*S*,3*R*,3a*R*,7a*R*)-3-formyl-5-oxo-2-phenyl-2,3,3a,4,5,7a-hexahydrobenzofuran-7a-yl)propanoate (23s): The title compound was prepared according to General Procedure B using *p*-quinol **17e** (196 mg, 1.00 mmol) and α,β-unsaturated aldehyde **22a** (198 mg, 1.50 mmol) affording a 6:1 (**23s**:Σothers) mixture of diastereomers. Purification provided **23s** (246 mg, 75% yield, >20:1 dr) as a pale yellow oil. The enantiomeric ratio was determined following olefination to **27**. Analytical data for **23s**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 7.36-7.22 (m, 5H), 6.71 (d, *J* = 10.4 Hz, 1H), 6.14 (d, *J* = 10.3 Hz, 1H), 5.19 (dd, *J* = 14.8, 1.8 Hz, 1H), 3.68 (s, 3H), 3.15-3.09 (m, 2H), 2.73-2.62 (m, 3H), 2.52 (d, *J* = 17.4 Hz, 1H), 2.38-2.22 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 198.6, 196.3, 173.2, 150.3, 136.6, 131.0, 128.9, 128.5, 126.4, 80.5, 79.1, 60.3, 51.8, 40.6, 37.3, 31.4, 28.4; **IR** (thin film): 2952, 1733, 1717, 1683, 1636, 1200, 1028, 755 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.32; **HRMS** (ESI): Calcd. for $C_{19}H_{21}O_5$ ([M+H]$^+$): 329.1390, Found: 329.1385; **[α]$_D$** -78 (*c* = 0.9, $CHCl_3$).

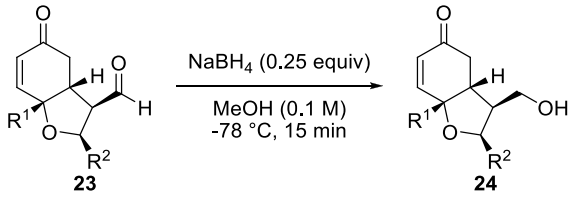
<u>Gram Scale Synthesis of 23d</u>



A 250-mL round bottom flask equipped with a magnetic stir bar was charged with α,β-unsaturated aldehyde **22d** (5.00 g, 30.0 mmol, 1.5 equiv), **7b** (1.41 g, 4.0 mmol, 0.2 equiv), and

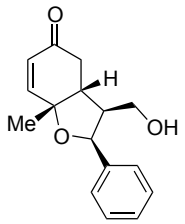
4-nitrobenzoic acid (0.67 g, 4.0 mmol, 0.2 equiv) in toluene (80.0 mL, 0.25 M). The solution was stirred for 5 min at room temperature until homogeneous. *p*-Quinol **17a** (2.48 g, 20.0 mmol, 1.0 equiv) was added and the reaction was allowed to stir for 16 h at room temperature. The reaction was diluted with EtOAc (400 mL) and sequentially washed with sat. aq. $NaHCO_3$ (1 x 100 mL), H_2O (1 x 100 mL), and brine (1 x 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude residue. The crude residue was purified by column chromatography on silica gel eluting with 20% ethyl acetate:hexanes. The obtained solid was recrystallized from 10% ethyl acetate:hexanes to afford **23d** (4.76 g, 82% yield, >20:1 dr, >99.5:0.5 er) as colorless crystals (mp 150-153 ºC).

<u>General Procedure C for the Reduction of Aldehydes 23 to Alcohols 24</u>

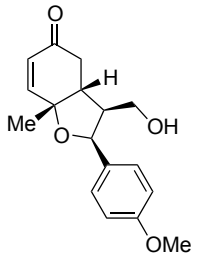


A 10-mL round-bottom flask equipped with a magnetic stir bar was charged with aldehyde **23** (1.00 equiv) in MeOH (0.1 M). The solution was cooled to -78 ºC. $NaBH_4$ (0.25 equiv) was added and the reaction was allowed to stir for 15 min at -78 ºC. The reaction was quenched with sat. aq. NH_4Cl (2 mL) at -78 ºC and allowed to warm to room temperature. After stirring at room temperature for 30 min, the reaction was partitioned between CH_2Cl_2 (15 mL) and H_2O (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in*

vacuo. The crude residue was purified by column chromatography on silica gel to afford alcohol **24**.

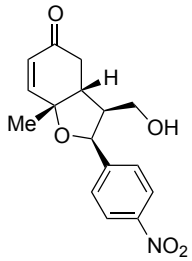


(2*S*,3*S*,3a*R*,7a*R*)-3-(Hydroxymethyl)-7a-methyl-2-phenyl-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24a): The title compound was prepared according to General Procedure C using aldehyde **23a** (90 mg, 0.35 mmol) and $NaBH_4$ (3.3 mg, 0.09 mmol) affording **24a** (83 mg, 92% yield) as a pale yellow oil. Analytical data for **24a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35-7.32 (m, 2H), 7.30-7.27 (m, 3H), 6.68 (dd, *J* = 10.3, 1.4 Hz, 1H), 6.02 (d, *J* = 10.3 Hz, 1H), 5.00 (d, *J* = 8.4 Hz, 1H), 3.25-3.19 (m, 2H), 2.71 (d, *J* = 17.2 Hz, 1H), 2.65 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.46-2.39 (m, 2H), 1.62 (s, 3H), 1.40 (br s, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 197.7, 152.8, 138.6, 129.0, 128.3, 127.8, 126.4, 80.3, 79.0, 62.5, 49.7, 46.7, 37.9, 23.4; **IR** (thin film): 3445, 2937, 1683, 1456, 1387, 1027, 703 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.38; **HRMS** (ESI): Calcd. for $C_{32}H_{36}NaO_6$ ([2M+Na]$^+$): 539.2410, Found: 539.2419; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 13.6 min, $t_{R\ (major)}$ 14.7 min, >99.5:0.5 er; **$[\alpha]_D$** -117 (*c* = 1.2, $CHCl_3$).

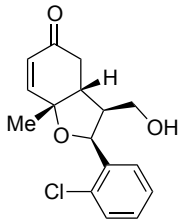


(2*S*,3*S*,3a*R*,7a*R*)-3-(Hydroxymethyl)-2-(4-methoxyphenyl)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24b): The title compound was prepared according to General Procedure C using aldehyde **23b** (129 mg, 0.45 mmol) and $NaBH_4$ (4.1 mg, 0.11 mmol) affording **24b** (108 mg, 83% yield) as a pale yellow oil. Analytical data for **24b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 7.7 Hz, 2H), 6.67 (d, *J* = 10.2 Hz, 1H), 6.01 (d, *J* = 10.2 Hz, 1H), 4.97 (d, *J* = 7.6 Hz, 1H), 3.77 (s, 3H), 3.24-3.23 (m, 2H), 2.72-2.61 (m, 2H), 2.43-2.38 (m, 2H), 1.60 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.7, 159.1, 152.9, 130.6, 129.0, 127.6, 113.7, 80.0, 78.9, 62.5,

55.2, 49.8, 46.6, 37.8, 23.5; **IR** (thin film): 3420, 2928, 1671, 1514, 1248, 1174, 1033, 835 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.24; **HRMS** (ESI): Calcd. for $C_{17}H_{20}NaO_4$ ([M+Na]$^+$): 311.1260, Found: 311.1255; **HPLC** Chiralpak IC, H:IPA = 55:45, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 16.0 min, $t_{R\ (minor)}$ 20.7 min, 98:2 er; **[α]$_D$** -99 (*c* = 1.0, $CHCl_3$).

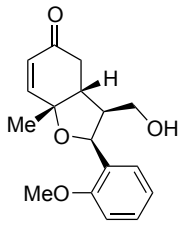


(2*S*,3*S*,3a*R*,7a*R*)-3-(Hydroxymethyl)-7a-methyl-2-(4-nitrophenyl)-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24c): The title compound was prepared according to General Procedure C using aldehyde **23c** (135 mg, 0.45 mmol) and $NaBH_4$ (4.1 mg, 0.11 mmol) affording **24c** (109 mg, 80% yield) as a white solid (mp 135-137 ºC). Analytical data for **24c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 6.68 (dd, *J* = 10.2, 1.7 Hz, 1H), 6.03 (d, *J* = 10.2 Hz, 1H), 5.11 (d, *J* = 9.0 Hz, 1H), 3.24-3.16 (m, 2H), 2.74-2.63 (m, 2H), 2.58-2.50 (m, 1H), 2.42-2.39 (m, 1H), 1.65 (s, 3H), 1.59 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.4, 152.3, 147.3, 146.4, 129.3, 127.6, 123.2, 79.6, 79.6, 62.3, 49.8, 46.9, 37.9, 23.5; **IR** (thin film): 3431, 2088, 1671, 1520, 1347, 1231, 1121, 1047 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.22; **HRMS** (ESI): Calcd. for $C_{16}H_{17}NNaO_5$ ([M+Na]$^+$): 326.1005, Found: 326.0999; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 26.1 min, $t_{R\ (major)}$ 28.4 min, >99.5:0.5 er; **[α]$_D$** -98 (*c* = 1.5, $CHCl_3$).

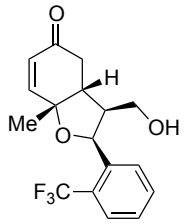


(2*S*,3*S*,3a*R*,7a*R*)-2-(2-Chlorophenyl)-3-(hydroxymethyl)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24d): The title compound was prepared according to General Procedure C using aldehyde **23d** (250 mg, 0.86 mmol) and $NaBH_4$ (8.1 mg, 0.21 mmol) affording **24d** (234 mg, 93% yield) as a white solid (mp 147-148 ºC). Analytical data for **24d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33-7.19 (m, 3H), 6.67 (dd, *J* = 10.2, 1.1 Hz, 1H), 6.09 (dd, *J* = 10.2, 1.0 Hz, 1H), 5.20

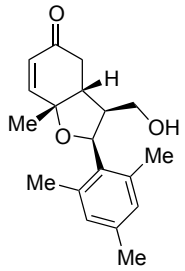
(dd, J = 13.8, 5.8 Hz, 1H), 3.32-3.29 (m, 1H), 3.16-3.13 (m, 1H), 2.77 (d, J = 17.3 Hz, 1H), 2.67 (dd, J = 17.3, 5.3 Hz, 1H), 2.58-2.50 (m, 2H), 1.63 (s, 3H), 1.30 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.9, 152.3, 136.6, 131.9, 130.2, 129.2, 128.7, 127.4, 126.8, 78.8, 76.8, 62.9, 48.5, 47.3, 38.4, 23.3; **IR** (thin film): 3420, 1683, 1558, 1473, 1374, 1121, 1049, 748 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.38; **HRMS** (ESI): Calcd. for $C_{16}H_{18}ClO_3$ ([M+H]$^+$): 293.0945, Found: 293.0939; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 10.2 min, $t_{R\ (major)}$ 13.1 min, >99.5:0.5 er; **[α]$_D$** -201 (c = 0.7, $CHCl_3$).



(2*S*,3*S*,3a*R*,7a*R*)-3-(Hydroxymethyl)-2-(2-methoxyphenyl)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24e): The title compound was prepared according to General Procedure C using aldehyde **23e** (200 mg, 0.70 mmol) and $NaBH_4$ (6.7 mg, 0.17 mmol) affording **24e** (176 mg, 87% yield) as a white solid (mp 124-126 ºC). Analytical data for **24e**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.51 (d, J = 7.4 Hz, 1H), 7.30-7.27 (m, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.71 (dd, J = 10.2, 1.1 Hz, 1H), 6.08 (d, J = 10.3 Hz, 1H), 5.26 (d, J = 7.9 Hz, 1H), 3.82 (s, 3H), 3.25 (br s, 2H), 2.74-2.67 (m, 2H), 2.53-2.48 (m, 2H), 1.62 (s, 3H), 1.36 (br s, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.0, 155.5, 153.0, 129.5, 128.6, 127.3, 126.2, 120.8, 110.1, 78.5, 75.2, 62.5, 55.29,† 55.25,‡ 49.2, 46.1, 38.1, 23.4 (†Rotomer A, ‡Rotomer B); **IR** (thin film): 3446, 2929, 1682, 1491, 1244, 1125, 1046, 756 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.30; **HRMS** (ESI): Calcd. for $C_{17}H_{20}NaO_4$ ([M+Na]$^+$): 311.1260, Found: 311.1254; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 10.9 min, $t_{R\ (major)}$ 12.0 min, >99.5:0.5 er; **[α]$_D$** -175 (c = 1.5, $CHCl_3$).

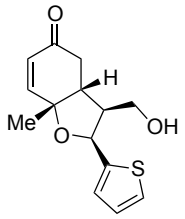


(2*S*,3*S*,3a*R*,7a*R*)-3-(Hydroxymethyl)-7a-methyl-2-(2-(trifluoromethyl)phenyl)-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24f): The title compound was prepared according to General Procedure C using aldehyde **23f** (195 mg, 0.60 mmol) and $NaBH_4$ (5.6 mg, 0.15 mmol) affording **24f** (161 mg, 82% yield) as a white solid (mp 133-135 ºC). Analytical data for **24f**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 6.68 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.08 (dd, *J* = 10.3, 0.9 Hz, 1H), 5.23 (d, *J* = 9.0 Hz, 1H), 3.18 (dd, *J* = 10.9, 5.0 Hz, 1H), 3.08-3.05 (m, 1H), 2.80 (ddd, *J* = 17.5, 2.0, 1.1 Hz, 1H), 2.66 (d, *J* = 17.3 Hz, 1H), 2.50-2.47 (m, 1H), 2.42-2.37 (m, 1H), 1.64 (s, 3H), 1.63 (br s, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.0, 152.3, 136.7, 131.6, 130.2, 128.1, 127.8, 127.4 (q, $J_{C–F}$ = 30.4 Hz), 125.7 (q, $J_{C–F}$ = 5.6 Hz), 124.0 (q, $J_{C–F}$ = 274.2 Hz), 79.0, 75.8, 63.7, 49.7, 48.5, 38.5, 23.3; **^{19}F NMR** (565 MHz, $CDCl_3$): δ -59.2; **IR** (thin film): 3432, 2931, 1677, 1313, 1163, 1123, 1035, 771 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.37; **HRMS** (ESI): Calcd. for $C_{17}H_{17}F_3NaO_3$ ($[M+Na]^+$): 349.1028, Found: 349.1020; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 5.3 min, $t_{R\ (major)}$ 6.6 min, 99.5:0.5 er; **$[\alpha]_D$** -124 (*c* = 1.5, $CHCl_3$).

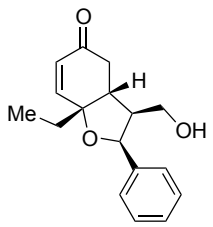


(2*S*,3*S*,3a*R*,7a*R*)-3-(Hydroxymethyl)-2-mesityl-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24g): The title compound was prepared according to General Procedure C using aldehyde **23g** (142 mg, 0.48 mmol) and $NaBH_4$ (4.5 mg, 0.12 mmol) affording **24g** (127 mg, 88% yield) as a pale yellow oil. Analytical data for **24g**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.80 (s, 1H), 6.77 (s, 1H), 6.66 (dd, *J* = 10.3, 1.9 Hz, 1H), 6.07 (d, *J* = 10.3 Hz, 1H), 5.24 (d, *J* = 9.3 Hz, 1H), 3.31-3.28 (m, 2H), 2.78 (d, *J* = 17.2 Hz, 1H), 2.66 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.48-2.43 (m, 1H), 2.45 (s, 3H), 2.38-

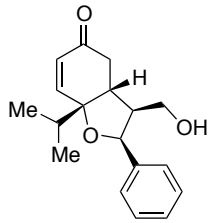
2.36 (m, 1H), 2.22 (s, 3H), 2.18 (s, 3H), 1.35 (br s, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 197.9, 153.0, 136.9, 136.4, 135.5, 131.4, 130.3, 130.0, 129.2, 78.7, 77.67,† 77.66,‡ 63.5, 49.3, 48.2, 38.4, 22.9,† 22.8,‡ 20.70,† 20.69,‡ 20.67,† 20.66‡ (†Rotomer A, ‡Rotomer B); **IR** (thin film): 3444, 2925, 1673, 1457, 1371, 1126, 1052, 754 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.42; **HRMS** (ESI): Calcd. for $C_{19}H_{25}O_3$ ([M+H]$^+$): 301.1804, Found: 301.1799; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 10.1 min, $t_{R\ (major)}$ 12.1 min, 99:1 er; **[α]$_D$** -136 (*c* = 1.5, $CHCl_3$).



(2*S*,3*S*,3a*R*,7a*R*)-3-(Hydroxymethyl)-7a-methyl-2-(thiophen-2-yl)-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24i): The title compound was prepared according to General Procedure C using aldehyde **23i** (95 mg, 0.36 mmol) and $NaBH_4$ (3.4 mg, 0.09 mmol) affording **24i** (83 mg, 87% yield) as a white solid (mp 99-101 ºC). Analytical data for **24i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.26 (m, 1H), 7.00-6.96 (m, 2H), 6.67 (dd, *J* = 10.2 Hz, 1H), 5.97 (d, *J* = 10.2 Hz, 1H), 5.39 (d, *J* = 7.9 Hz, 1H), 3.44 (br s, 2H), 2.74-2.63 (m, 2H), 2.57-2.46 (m, 2H), 1.62 (s, 3H), 1.37 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.2, 152.7, 143.3, 128.3, 126.9, 125.1, 124.4, 79.7, 77.5, 61.8, 49.7, 45.6, 37.3, 23.8; **IR** (thin film): 3430, 2924, 1672, 1374, 1236, 1115, 1027, 708 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.32; **HRMS** (ESI): Calcd. for $C_{14}H_{16}O_3NaS$ ([M+Na]$^+$): 287.0718, Found: 287.0713; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 16.8 min, $t_{R\ (major)}$ 18.6 min, 97:3 er; **[α]$_D$** -77 (*c* = 1.2, $CHCl_3$).

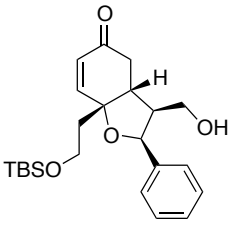


(2*S*,3*S*,3a*R*,7a*R*)-7a-Ethyl-3-(hydroxymethyl)-2-phenyl-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24m): The title compound was prepared according to General Procedure C using aldehyde **23m** (189 mg, 0.70 mmol) and $NaBH_4$ (6.6 mg, 0.18 mmol) affording **24m** (141 mg, 74% yield) as a pale yellow oil. Analytical data for **24m**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 6.72 (dd, *J* = 10.3, 1.8 Hz, 1H), 6.11 (d, *J* = 10.3 Hz, 1H), 5.01 (d, *J* = 8.7 Hz, 1H), 3.27-3.19 (m, 2H), 2.71 (dd, *J* = 17.3, 1.5 Hz, 1H), 2.64 (dd, *J* = 17.4, 1.1 Hz, 1H), 2.52-2.40 (m, 2H), 2.08-1.86 (m, 2H), 1.49 (br s, 1H), 1.16 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 198.1, 152.2, 138.6, 130.0, 128.3, 127.7, 126.4, 81.0, 79.8, 77.2, 62.7, 50.1, 44.3, 38.4, 30.1, 8.1; **IR** (thin film): 3420, 2925, 1683, 1558, 1457, 1027, 703 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.34; **HRMS** (ESI): Calcd. for $C_{17}H_{20}NaO_3$ ($[M+Na]^+$): 295.1310, Found: 295.1305; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 12.5 min, $t_{R\ (major)}$ 14.6 min, >99.5:0.5 er; **$[\alpha]_D$** -126 (*c* = 1.6, $CHCl_3$).



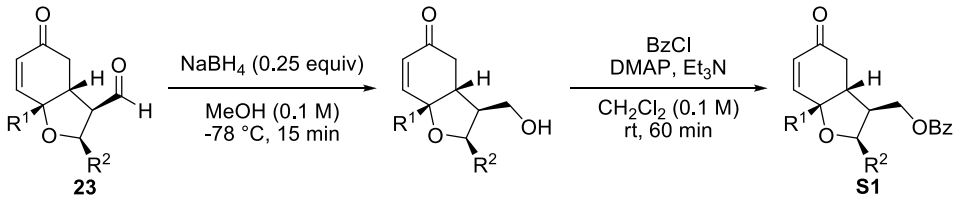
(2*S*,3*S*,3a*R*,7a*R*)-3-(Hydroxymethyl)-7a-isopropyl-2-phenyl-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24n): The title compound was prepared according to General Procedure C using aldehyde **23n** (108 mg, 0.38 mmol) and $NaBH_4$ (3.6 mg, 0.09 mmol) affording **24n** (81 mg, 74% yield) as a pale yellow oil. Analytical data for **24n**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 6.69 (dd, *J* = 10.4, 1.4 Hz, 1H), 6.23 (d, *J* = 10.4 Hz, 1H), 4.97 (d, *J* = 8.5 Hz, 1H), 3.32-3.24 (m, 2H), 2.69-2.59 (m, 3H), 2.40-2.32 (m, 1H), 2.27-2.17 (m, 1H), 1.16 (dd, *J* = 12.4, 6.9 Hz, 6H), 0.92 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 198.2, 150.9, 138.4, 131.5, 128.5, 127.9, 126.3, 82.9, 79.1, 62.7, 51.8, 42.2, 39.8, 35.6, 18.0, 17.1; **IR** (thin film): 3420, 2963, 1683, 1558, 1387, 1265, 1051, 714 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.41; **HRMS** (ESI): Calcd. for

$C_{18}H_{22}NaO_3$ ([M+Na]$^+$): 309.1467, Found: 309.1461; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (minor)}$ 11.2 min, $t_{R\ (major)}$ 13.9 min, 99:1 er; **[α]$_D$** -131 (*c* = 2.0, $CHCl_3$).



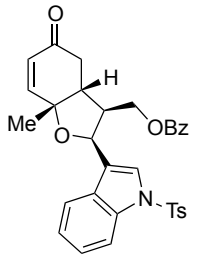
(2*S*,3*S*,3a*R*,7a*R*)-7a-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-(hydroxymethyl)-2-phenyl-2,3,3a,4-tetrahydrobenzofuran-5(7a*H*)-one (24r): The title compound was prepared according to General Procedure C using aldehyde **23r** (274 mg, 0.68 mmol) and $NaBH_4$ (6.5 mg, 0.17 mmol) affording **24r** (238 mg, 87% yield) as a pale yellow oil. Analytical data for **24r**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 6.72 (dd, *J* = 10.3, 1.8 Hz, 1H), 6.07 (d, *J* = 10.3 Hz, 1H), 5.03 (d, *J* = 9.0 Hz, 1H), 4.02-3.97 (m, 1H), 3.93-3.87 (m, 1H), 3.27 (t, *J* = 5.3 Hz, 2H), 2.78 (dd, *J* = 17.5, 5.6 Hz, 1H), 2.69-2.64 (m, 2H), 2.49-2.41 (m, 1H), 2.22-2.07 (m, 2H), 0.97 (br s, 1H), 0.89 (s, 9H), 0.08 (d, *J* = 3.4 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 198.0, 152.1, 138.7, 129.6, 128.4, 127.9, 126.5, 80.4, 80.0, 62.5, 58.6, 50.0, 44.9, 40.4, 38.0, 25.8, 18.1, -5.43, -5.44; **IR** (thin film): 3444, 2953, 2084, 1671, 1472, 1255, 1091, 836 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.50; **HRMS** (ESI): Calcd. for $C_{23}H_{34}O_4NaSi$ ([M+Na]$^+$): 425.2124, Found: 425.2119; **SFC** Chiralpak AD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ 7.7 min, $t_{R\ (minor)}$ 9.3 min, 99:1 er; **[α]$_D$** -71 (*c* = 1.0, $CHCl_3$).

General Procedure D for the Conversion of 23h and 23j to S1a and S1b

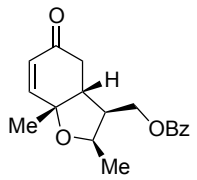


A 10-mL round-bottom flask equipped with a magnetic stir bar was charged with aldehyde **23** (1.00 equiv) in MeOH (0.1 M). The solution was cooled to -78 ºC. $NaBH_4$ (0.25 equiv) was added and the reaction was allowed to stir for 15 min at -78 ºC. The reaction was quenched with sat. aq. NH_4Cl (2 mL) at -78 ºC and allowed to warm to room temperature. After stirring at room temperature for 30 min, the reaction was partitioned between CH_2Cl_2 (15 mL) and H_2O (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude alcohol, which was used without further purification.

A flame-dried 10-mL round-bottom flask equipped with a magnetic stir bar was charged with the crude alcohol (1.00 equiv) in CH_2Cl_2 (0.1 M). 4-Dimethylaminopyridine (0.10 equiv), benzoyl chloride (1.20 equiv), and triethylamine (3.00 equiv) were added sequentially. The reaction was allowed to stir for 60 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl (2 mL). The reaction was partitioned between CH_2Cl_2 (15 mL) and H_2O (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford benzoate **S1**.



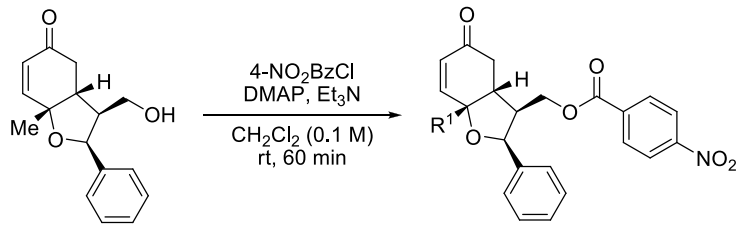
((2*S*,3*S*,3a*R*,7a*R*)-7a-Methyl-5-oxo-2-(1-tosyl-1*H*-indol-3-yl)-2,3,3a,4,5,7a-hexahydrobenzofuran-3-yl)methyl benzoate (S1a): The title compound was prepared according to General Procedure D using aldehyde **23h** (300 mg, 0.67 mmol) affording **S1a** (193 mg, 52% yield) as a viscous pale yellow oil. Analytical data for **S1a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.64 (s, 1H), 7.54 (d, *J* = 7.1 Hz, 2H), 7.48-7.45 (m, 2H), 7.31-7.27 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.70 (dd, *J* = 10.3, 1.7 Hz, 1H), 6.14 (d, *J* = 10.3 Hz, 1H), 5.29 (d, *J* = 8.4 Hz, 1H), 4.04 (dd, *J* = 11.3, 7.4 Hz, 1H), 3.90 (dd, *J* = 11.3, 6.8 Hz, 1H), 2.81-2.72 (m, 3H), 2.49-2.47 (m, 1H), 2.23 (s, 3H), 1.67 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 196.9, 165.8, 151.8, 144.9, 135.0, 134.7, 132.8, 130.2, 129.7, 129.2, 128.9, 128.2, 126.5, 124.9, 123.8, 123.7, 123.4, 119.7, 119.5, 113.8, 78.8, 73.8, 64.74, 64.68,† 64.6,‡ 48.3, 46.7, 38.2, 23.5, 21.42,† 21.39‡ (†Rotomer A, ‡Rotomer B); **IR** (thin film): 2974, 1716, 1683, 1372, 1271, 1174, 1120, 750 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.26; **HRMS** (ESI): Calcd. for $C_{64}H_{58}N_2NaO_{12}S_2$ ([2M+Na]$^+$): 1133.3330, Found: 1133.3330; **SFC** Chiralpak AD, 10% MeOH, pressure = 150 bar, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ 18.8 min, $t_{R\ (minor)}$ 27.4 min, >99.5:0.5 er; **[α]$_D$** -52 (*c* = 1.6, $CHCl_3$).



((2*R*,3*S*,3a*R*,7a*R*)-2,7a-Dimethyl-5-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-yl)methyl benzoate (S1b): The title compound was prepared according to General Procedure D using aldehyde **23j** (90 mg, 0.46 mmol) affording **S1b** (32 mg, 23% yield) as a pale yellow oil. Analytical data for **S1b**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.02 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47-7.44 (m, 2H), 6.62 (dd, *J* = 10.3, 1.8 Hz, 1H), 6.01 (dd, *J* = 10.3, 0.7 Hz, 1H), 4.41 (dd, *J* = 11.2, 6.9 Hz, 1H), 4.30 (d, *J* = 11.2, 7.0 Hz, 1H), 4.22-4.17 (m, 1H), 2.75 (dd, *J* = 17.2, 1.0 Hz, 1H), 2.67 (dd, *J* = 17.2, 5.4 Hz, 1H),

2.51-2.46 (m, 1H), 2.35-2.32 (m, 1H), 1.51 (s, 3H), 1.28 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 197.3, 166.4, 152.9, 133.2, 129.6, 129.5, 128.9, 128.5, 78.3, 74.31,† 74.28,‡ 64.3, 47.6, 45.3, 37.9, 24.1, 16.7 (†Rotomer A, ‡Rotomer B); **IR** (thin film): 2973, 1717, 1684, 1456, 1273, 1114, 713 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.31; **HRMS** (ESI): Calcd. for $C_{18}H_{20}NaO_4$ ([M+Na]$^+$): 323.1260, Found: 323.1252; **SFC** Chiralpak AD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ 6.4 min, $t_{R\ (minor)}$ 8.1 min, 99.5:0.5 er; **[α]$_D$** -9 (c = 1.4, $CHCl_3$).

<u>Synthesis of Benzoate 25 from 24a</u>



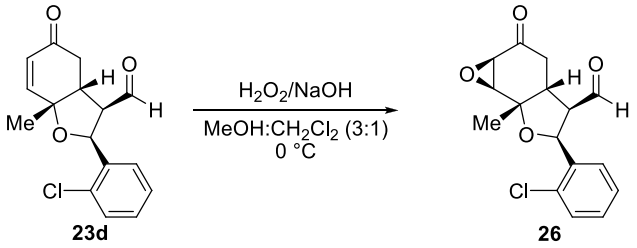
24a **25**

((2*S*,3*S*,3a*R*,7a*R*)-7a-Methyl-5-oxo-2-phenyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-yl)methyl 4-nitrobenzoate (25): A flame-dried 10-mL round-bottom flask equipped with a magnetic stir bar was charged with alcohol **24a** (77 mg, 0.30 mmol, 1.00 equiv) in CH_2Cl_2 (3 mL, 0.1 M). 4-Dimethylaminopyridine (3.7 mg, 0.03 mmol, 0.10 equiv), 4-nitrobenzoyl chloride (67 mg, 0.36 mmol, 1.20 equiv), and triethylamine (125 mL, 0.90 mmol, 3.00 equiv) were added sequentially. The reaction was allowed to stir for 60 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl (2 mL). The reaction was partitioned between CH_2Cl_2 (15 mL) and H_2O (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford benzoate **25** (102 mg, 83% yield) as a white solid (mp 125-126 ºC). Analytical data for **25**: **^{1}H**

NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.9 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.26-7.10 (m, 5H), 6.64 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.99 (d, *J* = 10.2 Hz, 1H), 5.03 (d, *J* = 8.8 Hz, 1H), 3.95-3.83 (m, 2H), 2.74-2.64 (m, 3H), 2.38-2.35 (m, 1H), 1.58 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.8, 164.0, 152.4, 150.5, 137.8, 134.9, 130.5, 129.3, 128.3, 128.0, 126.5, 123.5, 80.2, 79.2, 65.6, 47.8, 46.7, 38.0, 23.6; **IR** (thin film): 2975, 2097, 1725, 1683, 1529, 1371, 1279, 1171, 1133 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.33; **HRMS** (ESI): Calcd. for $C_{46}H_{42}N_2NaO_{12}$ ($[2M+Na]^+$): 837.2636, Found: 837.2626; **$[\alpha]_D$** -50 (*c* = 0.5, $CHCl_3$)**.**

X-ray suitable crystals were grown by dissolving **25** (100 mg) in a minimal amount of acetone (~0.2 mL) in a 20-mL scintillation vial. Without disturbing the acetone layer, hexanes (~4 mL) was carefully pipetted on top to form a second layer. The vial was capped and carefully transferred to a freezer (-10 ºC) where it was left to age overnight.

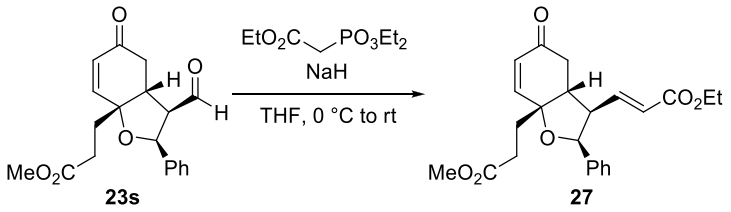
Synthesis of Epoxide 26 from 23d



(1a*R*,3a*R*,4*R*,5*S*,6a*S*,6b*S*)-5-(2-Chlorophenyl)-6a-methyl-2-oxooctahydrooxireno[2,3-*g*]benzofuran-4-carbaldehyde (26): A 10-mL round-bottom flask equipped with a magnetic stir bar was charged with aldehyde **23d** (116 mg, 0.40 mmol, 1.0 equiv) in MeOH:CH_2Cl_2 (3:1) (1.6 mL, 0.25 M). The solution was cooled to 0 ºC. H_2O_2 (30 wt. % in H_2O) (0.8 mL) and NaOH (20 wt. % in H_2O) (0.2 mL) were sequentially added. The reaction was allowed to at 0 ºC for 12 h. The reaction was carefully quenched with sat. aq. $Na_2S_2O_3$ (5 mL) to remove excess peroxides. The reaction was partitioned between CH_2Cl_2 (15 mL) and H_2O (30 mL). The layers were

separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford epoxide **26** (117 mg, 95% yield, >20:1 dr) as a white solid (mp 73 ºC). Analytical data for **26**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.03 (d, *J* = 1.4 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.30-7.24 (m, 2H), 5.54 (d, *J* = 8.3 Hz, 1H), 3.50 (dd, *J* = 3.7, 1.8 Hz, 1H), 3.41 (dd, *J* = 3.7, 0.7 Hz, 1H), 3.33-3.31 (m, 1H), 3.13-3.10 (m, 1H), 3.07 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.07 (ddd, *J* = 13.8, 2.6, 0.9 Hz, 1H), 1.77 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 206.0, 197.9, 134.1, 131.3, 129.5, 129.4, 127.4, 127.2, 78.2, 76.8, 64.3, 58.7, 55.7, 46.1, 35.3, 23.0; **IR** (thin film): 2978, 1720, 1684, 1653, 1541, 1473, 1375, 1127, 1034 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.28; **HRMS** (ESI): Calcd. for $C_{32}H_{30}Cl_2NaO_8$ ([2M+Na]$^+$): 635.1216, Found: 635.1217; **[α]$_D$** -104 (*c* = 1.3, $CHCl_3$).

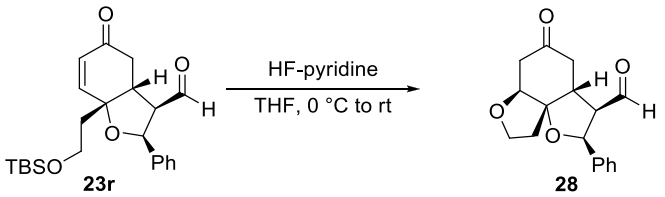
Synthesis of Diester 27 from 23s



(*E*)-Ethyl 3-((2*S*,3*R*,3a*R*,7a*R*)-7a-(3-methoxy-3-oxopropyl)-5-oxo-2-phenyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-yl)acrylate (27): A flame-dried 10-mL round-bottom flask equipped with a magnetic stir bar was charged with NaH (60%) (23 mg, 0.57 mmol, 1.25 equiv) suspended in THF (2 mL). The suspension was cooled to 0 ºC. Triethyl phosphonoacetate (115 mL, 0.57 mmol, 1.25 equiv) was added dropwise. The homogenous solution was allowed to stir at 0 ºC for 20 min before a solution of aldehyde **23s** (150 mg, 0.46 mmol, 1.00 equiv) in THF (0.5 mL) was added dropwise. The ice bath was removed and the resulting solution was allowed

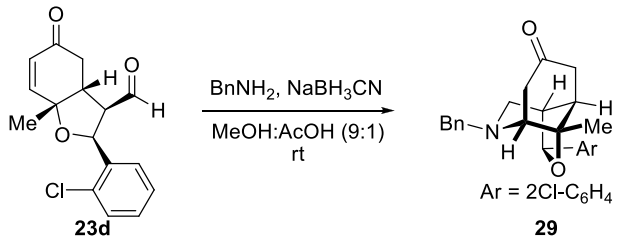
to stir for 3 h as it slowly warmed to room temperature. The reaction was cooled to 0 ºC and quenched with sat. aq. NH_4Cl (5 mL). The reaction was diluted with Et_2O (30 mL) and washed with H_2O (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford diester **27** (176 mg, 96% yield, >20:1 *E*:*Z*) as a pale yellow oil. Analytical data for **27**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.4 Hz, 2H), 7.26-7.23 (m, 1H), 7.17 (d, *J* = 7.4 Hz, 2H), 6.78 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.12-6.08 (m, 2H), 5.65 (d, *J* = 15.5 Hz, 1H), 5.13 (d, *J* = 9.1 Hz, 1H), 4.10-3.99 (m, 2H), 3.70 (s, 3H), 3.06 (q, *J* = 9.7 Hz, 1H), 2.74-2.61 (m, 3H), 2.49 (d, *J* = 17.8 Hz, 1H), 2.46-2.43 (m, 1H), 2.38-2.26 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 196.3, 173.4, 165.4, 150.9, 145.7, 138.0, 130.1, 128.4, 127.9, 126.3, 123.2, 81.7, 80.9, 60.3, 52.1, 51.9, 47.2, 36.1, 32.4, 28.6, 14.0; **IR** (thin film): 1734, 1716, 1683, 1456, 1387, 1248, 1175, 1028 cm^{-1}; **TLC** (50% ethyl acetate:hexanes): R_f = 0.50; **HRMS** (ESI): Calcd. for $C_{23}H_{26}NaO_6$ ($[M+Na]^+$): 421.1627, Found: 421.1622; **SFC** Chiralpak OD, 9% MeOH, pressure = 150 bar, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ 9.4 min, $t_{R\ (minor)}$ 10.4 min, >99.5:0.5 er; **$[\alpha]_D$** -17 (*c* = 1.6, $CHCl_3$).

Synthesis of bis(Tetrahydrofuran) 28 from 23r



(3a*S*,5*S*,6*R*,6a*R*,9a*S*)-8-Oxo-5-phenyloctahydro-2*H*-benzo[1,2-*b*:2,3-*b'*]difuran-6-carbaldehyde (28): A 20-mL Nalgene® scintillation vial equipped with a magnetic stir bar was charged with silyl ether **23r** (400 mg, 1.00 mmol, 1.00 equiv) in THF (10 mL, 0.1 M). The solution was cooled to 0 ºC. HF-pyridine (70% HF) (4 mL) was slowly added to the reaction. The ice bath was removed and the resulting solution was allowed to stir for 3 h as it slowly warmed to room temperature. The reaction was quenched by carefully pipetting the reaction mixture into a beaker containing sat. aq. $NaHCO_3$ (60 mL). The biphasic solution was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford tricycle **28** (235 mg, 82% yield, >20:1 dr) as a pale yellow oil. Analytical data for **28**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.05 (s, 1H), 7.38-7.34 (m, 2H), 7.31-7.28 (m, 3H), 5.47 (d, *J* = 8.5 Hz, 1H), 4.17 (t, *J* = 5.4 Hz, 1H), 4.07 (dt, *J* = 8.6, 3.1 Hz, 1H), 3.98 (q, *J* = 8.9 Hz, 1H), 3.20 (q, *J* = 6.0 Hz, 1H), 3.09 (t, *J* = 7.2 Hz, 1H), 2.70-2.57 (m, 3H), 2.55-2.49 (m, 1H), 2.43-2.34 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 207.3, 198.8, 136.7, 128.8, 128.4, 125.9, 89.1, 80.4, 80.1, 66.5, 60.6, 43.1, 40.8, 38.9, 38.3; **IR** (thin film): 1716, 1653, 1636, 1541, 1457, 1397, 1209, 1065 cm^{-1}; **TLC** (40% ethyl acetate:hexanes): R_f = 0.25; **HRMS** (ESI): Calcd. for $C_{17}H_{18}NaO_4$ ([M+Na]$^+$): 309.1103, Found: 309.1100; **$[\alpha]_D$** -72 (*c* = 1.2, $CHCl_3$)**.**

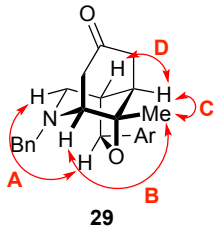
Synthesis of Tricycle 29 from 23d



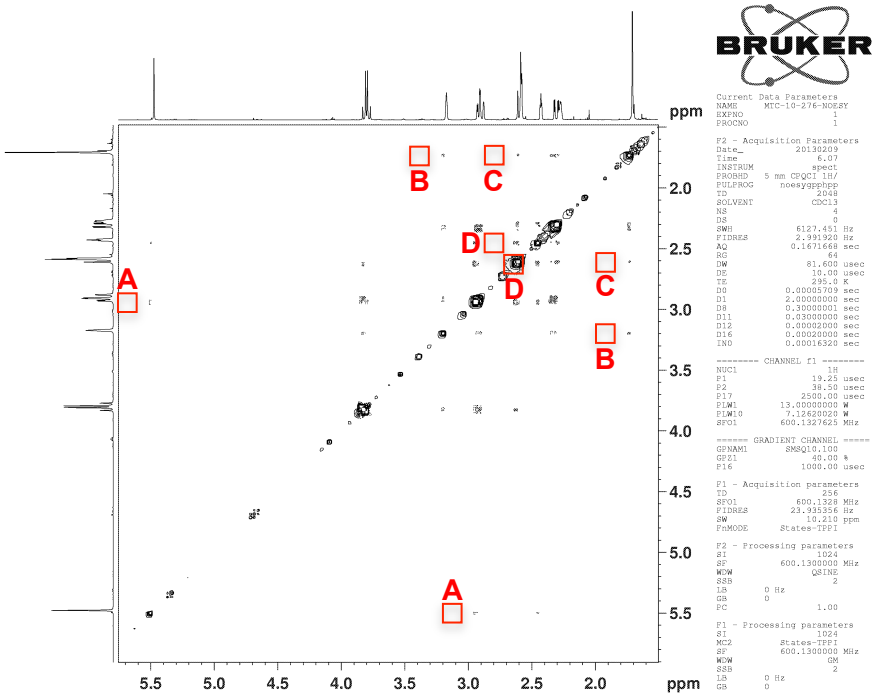
(2*S*,3*R*,3a*R*,7*R*,7a*S*)-8-Benzyl-2-(2-chlorophenyl)-7a-methylhexahydro-7,3-(epiminomethano)benzofuran-5(6*H*)-one (29): A 10-mL round-bottom flask equipped with a magnetic stir bar was charged with aldehyde **23d** (116 mg, 0.40 mmol, 1.00 equiv) and benzylamine (86 mg, 0.80 mmol, 2.00 equiv) in MeOH:AcOH (9:1) (4 mL, 0.1 M). The solution was allowed to stir at room temperature for 4 h. $NaBH_3CN$ (50 mg, 0.80 mmol, 2.00 equiv) was added in one portion resulting in vigorous gas formation. After stirring at room temperature for 30 min, the reaction was quenched with sat. aq. $NaHCO_3$ (4 mL). The reaction was partitioned between CH_2Cl_2 (15 mL) and sat. aq. $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford tricycle **29** (136 mg, 89% yield, >20:1 dr) as a pale yellow oil. Analytical data for **29**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.34-7.28 (m, 4H), 7.27-7.24 (m, 1H), 7.20 (dt, *J* = 7.7, 1.4 Hz, 1H), 5.48 (s, 1H), 3.80 (dd, *J* = 22.4, 13.7 Hz, 2H), 3.17 (bs, 1H), 2.93-2.88 (m, 2H), 2.61-2.58 (m, 3H), 2.43 (t, *J* = 3.8 Hz, 1H), 2.30 (dd, *J* = 17.3, 3.8 Hz, 1H), 2.29-2.27 (m, 1H), 1.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 209.5, 141.0, 138.3, 131.3, 129.3, 128.4, 128.3, 128.0, 127.0, 126.4, 80.7, 79.7, 62.4, 57.1, 47.7, 46.9, 40.3, 38.7, 38.5, 22.0; **IR** (thin film): 2905, 2813, 1707, 1558, 1457, 1338,

1121, 751 cm^{-1}; **TLC** (20% ethyl acetate:hexanes): R_f = 0.28; **HRMS** (ESI): Calcd. for $C_{23}H_{27}ClNO_2$ ($[M+H]^+$): 382.1575, Found: 382.1568; $[\alpha]_D$ +38 (c = 1.1, $CHCl_3$).

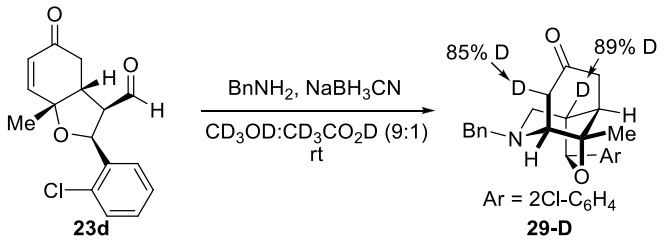
NOESY of Tricycle 29



29



Deuterium Labeling Experiment and Structure Determination



A 10-mL round-bottom flask equipped with a magnetic stir bar was charged with aldehyde **23d** (58 mg, 0.20 mmol, 1.00 equiv) and benzylamine (43 mg, 0.40 mmol, 1.00 equiv) in CD_3OD:CD_3CO_2D (9:1) (2 mL, 0.1 M). The solution was allowed to stir at room temperature for 4 h. $NaBH_3CN$ (25 mg, 0.40 mmol, 2.00 equiv) was added in one portion resulting in vigorous gas formation. After stirring at room temperature for 30 min, the reaction was quenched with sat. aq. $NaHCO_3$ (2 mL). The reaction was partitioned between CH_2Cl_2 (15 mL) and sat. aq. $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford tricycle **29-D** (64 mg, 84% yield, >20:1 dr) as a pale yellow oil.

6.6 References

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25) CCDC 926927 contains the supplementary crystallographic data for this chapter. This data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.c.uk/data_request/cif. The structure in **Scheme 6-17** was generated with CYLview: Legault, C. Y. CYL*view*, version 1.0b; Université de Sherbrooke: Sherbrooke, QC, 2009; http://www.cylview.org.

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