STEREOCONVERGENT TRANSFORMATIONS OF CARBONYLS FOR EXPEDIENT SYNTHESIS OF STEREOCHEMICALLY COMPLEX SMALL MOLECULES

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

Chapel Hill
2016

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ABSTRACT

C. Guy Goodman: Stereoconvergent Transformations of Carbonyls for Expedient Synthesis of Stereochemically Complex Small Molecules
(Under the direction of Jeffrey S. Johnson)

I. A Primer on Dynamic Kinetic Resolutions and Extant Methods for Oxo-Ester Synthesis

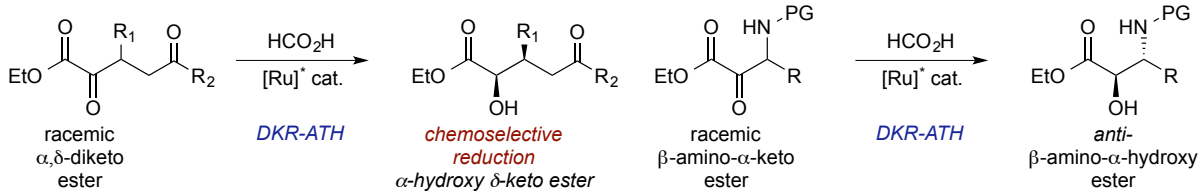
A two part overview that details: 1) the principles of dynamic kinetic resolution and its application in modern asymmetric catalysts and 2) current synthetic methods for generation of enolizable β-substituted α-keto esters and α-substituted β-oxo esters.

II. Asymmetric Transfer Hydrogenation-Dynamic Kinetic Resolution of β-Stereogenic α-Keto Esters

Two systems for dynamic kinetic resolution via asymmetric transfer hydrogenation (DKR-ATH) of racemic β-stereogenic-α-keto esters yielding optically active α-hydroxy esters are presented. In the first of these reports a previously unreported Stetter addition of ethyl gloxylate provides β-stereogenic-α,δ-diketo esters, which are reduced to α-hydroxy δ-keto esters. Stereo- and chemoselective mono-reduction provides formal glycolate Michael products.

In the second disclosure, β-amino α-keto esters are reduced to the corresponding *anti*-β-amino α-hydroxy esters. Both reports employ formic acid as

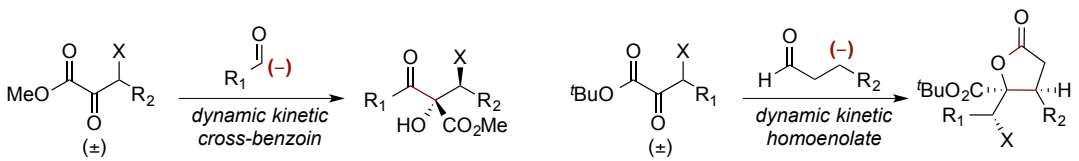
the organic reductant , and use a Ru(II)-amido complex bearing a bulky *m*-terphenylsulfonamide ligand which imparts remarkable levels of diastereo- and enantiocontrol.



III. *N*-Heterocyclic Carbene-Catalyzed Dynamic Kinetic Resolutions of β-Stereogenic α-Keto Esters

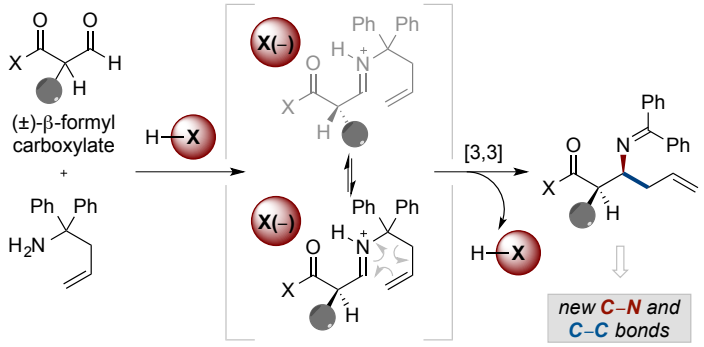
The development of two distinct *N*-Heterocyclic carbene catalyzed dynamic kinetic resolutions of β-halo-α-keto esters are discussed. In the first of these, an asymmetric cross-benzoin addition is described. The resulting fully substituted β-halo glycolic ester products are obtained with high levels of enantio- and diastereocontrol, and the reaction products undergo highly diastereoselective substrate-controlled reduction to give functionalized stereotriads. Mechanistic studies show that the high chemoselectivity observed is a result of greater electrophilicity of the α-keto ester toward the Breslow intermediate.

In the second report development of an asymmetric homoenolate ($a^3 - d^3$-*umpolung* addition) of α,β-enals, forming γ-butyrolactones with three contiguous stereocenters is described. The addition occurs with high regio-, diastereo-, and enantiocontrol and constitutes the first stereoconvergent homoenolate process.



IV. Complexity Generating Dynamic Kinetic Resolutions of β-Oxo Acid Derivatives

Dynamic kinetic resolutions of α-stereogenic-β-formyl amides in asymmetric 2-aza-Cope rearrangements are described. Chiral phosphoric acids catalyze this rare example of a non-hydrogenative DKR of a β-oxo acid derivative. The [3,3]-rearrangement occurs with high diastereo- and enantiocontrol, forming β-imino amides that can be deprotected to the primary β-amino amide or reduced to the corresponding diamine.



ACKNOWLEDGEMENTS

The most important decision I made in graduate school was to join Jeff's lab. Words don't do justice the respect I have for Jeff, but I'll pen a few anyway. Having a graduate advisor who prioritizes student education, cares about the person as much as the scientist, and has an extraordinary gift for instilling the ability to think independently was invaluable. Perhaps more instructive to the point that I am trying to make is to say that while I learned a lot about being a productive chemist from Jeff, the two most important lessons that he taught me have nothing to do with chemical synthesis. I am so grateful I was able to be a part of his group, and to have gotten the chance to know a truly unique individual.

I would like to thank Professors Jillian Dempsey, Mike Gagné, Simon Meek, and Alex Miller for serving on my final defense committee. I also acknowledge Professors Maurice Brookhart, Erik Alexanian, and Valerie Ashby for their previous committee work.

Talented co-workers have surrounded me during my time in the Johnson Group, each has been integral to this experience, and each has my thanks. I'd like to extend a specific note of thanks to Kim who helped get my feet underneath me, Justin who was so willing to spend time teaching, and to Michael who continually challenged my thinking and progressed my chemistry beyond what would have been possible otherwise. I was extremely fortunate in having been Ramsey's graduate

student as it enabled me to share in his life journey and watch him find who he wanted to be–that really was one of the best parts of graduate school. Similarly, I never thought that pushing MacKenzie to join my undergrad cohort would have such a profound benefit to myself. Her friendship, and role in getting me through the bulk of graduate school were so important.

My family and friends have been incredibly supportive throughout this process. Mom in particular has been so encouraging of my educational process, even though it kept me thousands of miles away. I've been blessed with an incredible group of friends including those who I have lived, gone to lunch, watched the Tar Heels, and spent countless Fridays at He's Not with. Carolina sports helped make this place home and Amber attended all of them with me. Since the first day of grad school Thomas has been there, I'm beyond thankful we got to take this ride together. Andrew and Javi, brought amazing levity to pretty much every situation; and have my thanks for not burning the house down (yet). Lauren and Katie were critical to making every outing better–always ensuring that food was a priority. From Pantana's on, Kelsey always provided a smile and was so integral to making the latter part of this program enjoyable, I really can't equate the value of those or so many other things. Finally, I can't express enough thanks to Ron and Sue who have welcomed me into their home, solved pretty much all of my biggest grad school crises, and somewhere along the way become family.

Dedicated to Jonell Prather who inspired joy of inquisition
and to John Bulman who illustrated the intrinsic value of learning.

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LIST OF SCHEMES

List of Abbreviations and Symbols

2D-NMR	two-dimensional nuclear magnetic resonance
2Me-THF	2-methyl tetrahydrofuran
Å	ångström
Ac	acetate
ACN	acetonitrile
Ac_2O	acetic anhydride
Ar	aryl
aq	aqueous
ATH	asymmetric transfer hydrogenation
atm	atmospheres
Aux	auxiliary
BINAP	2,2´-bis(diphenylphosphino)-1,1´-binaphthyl
Bn	benzyl
Boc	benzyloxycarbonyl
br	broad
br s	broad singlet
^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
cat	catalytic amount or catalyst
CBz	carboxybenzyl
conv	conversion

CPME	cyclopentyl methyl ether
C–C	carbon-carbon bond
d	doublet
D	dextrorotation
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
dt	doublet of triplets
ddt	doublet of doublet of triplets
$(DHQ)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DiBAL-H	diisobutyl aluminum hydride
DIPT	(+)-diisopropyl L-tartrate
DKR	dynamic kinetic resolution
DME	1,2-dimethoxyethane
DMAP	*N,N*-dimethylaminopyridine
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^+	electrophile
EE	ethoxyethyl
eq	equation
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
^{19}F NMR	fluorine nuclear magnetic resonance spectroscopy
FID	flame ionization detector
G	Gibbs free energy
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HOAc	acetic acid
HPLC	high-performance liquid chromatography

HRMS	high resolution mass spectroscopy
Hz	hertz
I	intermediate
IR	infrared spectroscopy
^{i}Pr	*iso*-propyl
J	coupling constant
k	reaction rate
KR	kinetic resolution
L	levorotation
L	liter or ligand
L-Selectride®	lithium tri-*sec*-butylborohydride
LA	Lewis acid
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
LTQ-FT	linear trap quadrapole Fourier transform
M	molarity
m	multiplet
m	*meta*
M	left-handed helix (minus)
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
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
Np	naphthyl
NR	no reaction
Nu	nucleophile
o	*ortho*
[O]	oxidation
Oxone®	potassium peroxomonosulfate
p	*para*
P	product
P	right-handed helix (plus)
PG	protecting group
*p*Ka	acid dissociation constant
Ph	phenyl
PMP	*para*-methoxyphenyl
PNBA	*para*-nitrobenzoic acid

ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
psig	pounds per square inch gage
^{i}Pr	*iso*-propyl
q	quartet
Q	quaternary ammonium salt
R	substituent
R	*Re*
R_f	retention factor
rac	racemic or racemization
rt	room temperature
Ru	ruthenium
s	singlet
S	starting material
S	*Si*
sept	septuplet
oct	octuplet
SFC	supercritical fluid chromatography
T	temperature
t	triplet
t_r	retention time
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl methylether

TBS	*tert*-butyl dimethylsilyl
TEA	triethylamine
TFA	trifluroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TS	transition state
TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
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 1

A PRIMER ON DYNAMIC KINETIC RESOLUTIONS AND EXTANT METHODS FOR OXO-ESTER SYNTHESIS

1.1 Dynamic Kinetic Resolutions

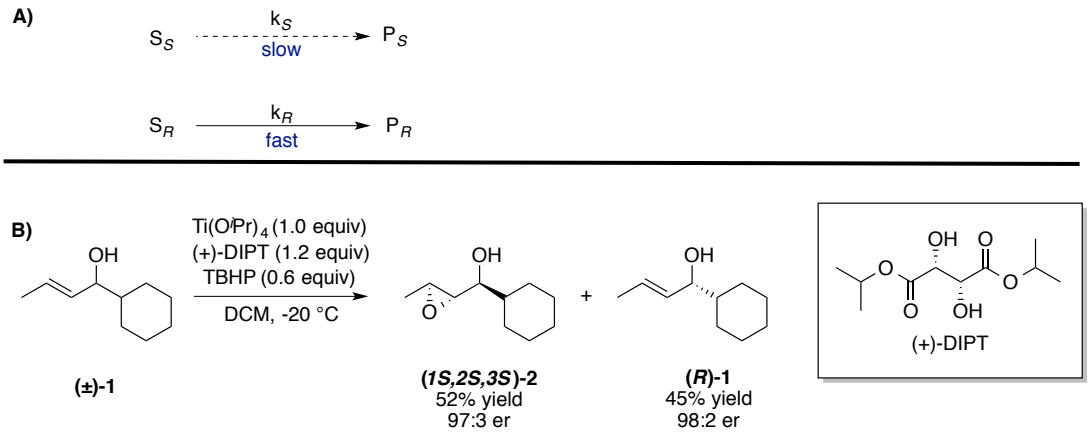
1.1.1 Key Principles

Synthetic methods that deliver enantioenriched small molecules on industrial scale are of great importance for human health. Towards this end three primary approaches to access single enantiomer therapeutics are typically employed: asymmetric catalysis, implementation of chiral feedstock provided by nature, and resolution of a pair of enantiomers. Of these, resolution strategies are particularly useful in kilogram scale synthesis due to A) cost effective access to functionalized racemic materials, B) numerous broadly applicable resolution platforms, and C) operational simplicity of those methods.

In classical resolutions, a chiral resolving agent is associatew with a racemate forming separable diastereomers, often through crystallization. In contrast, kinetic resolution (KR) relies on chiral catalyst or reagent control for the selective reaction of a single enantiomer of the racemic starting material via energy differences between diastereomeric transition states. Provided a large relative rate difference exists ($k_R >> k_{S,}$) a single enantiomer of product (P_R) and a single enantiomer of starting material (S_S) can be isolated (Scheme 1A).[1] An archetypical kinetic resolution is the Sharpless asymmetric epoxidation of

racemic allylic alcohol **1** under the control of a chiral titanium catalyst providing **(*1S,2S,3S*)-2** in 97:3 er and 52% yield (Scheme 1B) with concomitant recovery of **(*R*)-1** in 45% yield and 98:2 er.[2]

Scheme 1. Principles of Kinetic Resolutions

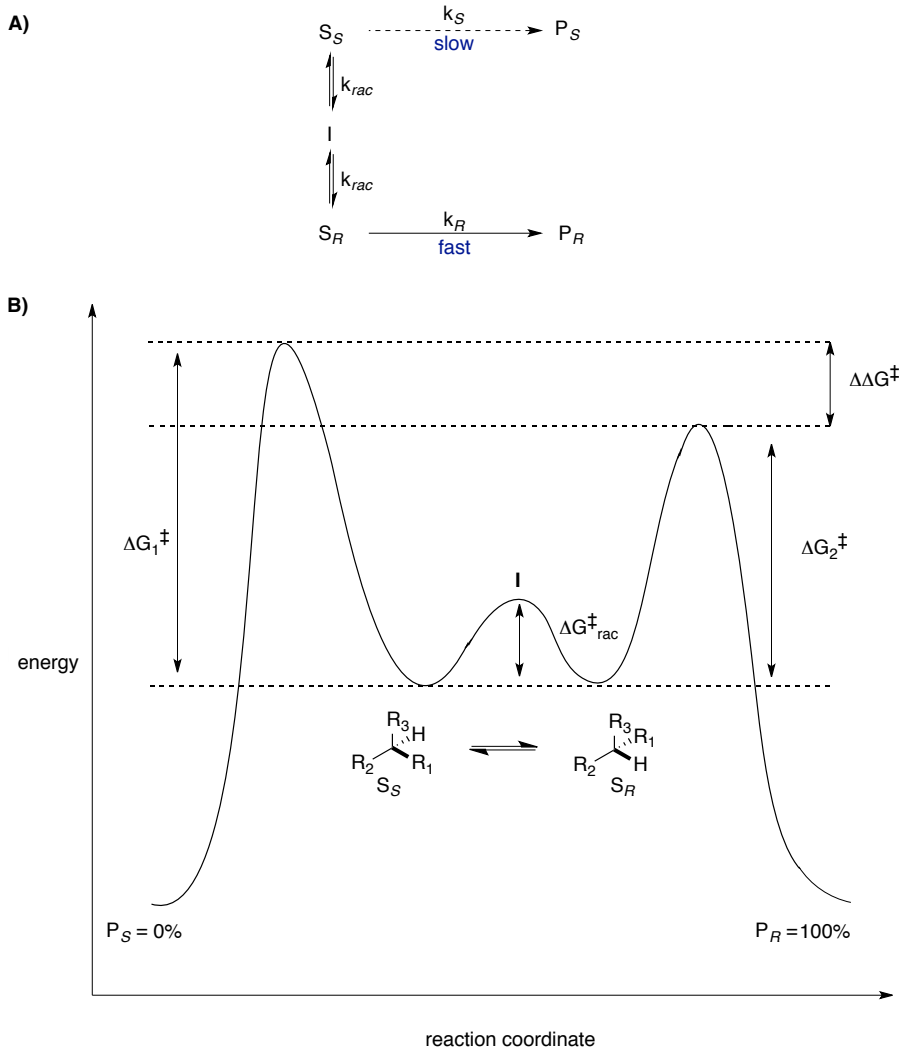


As there is no method for epimerization, typical kinetic resolutions, are inherently limited to a 50% theoretical yield of enantiomerically pure product.[3] A potential solution to this low theoretical yield is presented when a pathway for interconversion of starting material enantiomers exists. Provided that the rate of racemization through an achiral intermediate **I** is at least as fast as conversion of the faster reacting enantiomer of starting material to product (i.e., $k_{rac} \geq k_R >> k_S$) a dynamic kinetic resolution (DKR) can occur (Scheme 2A).[1] This process is governed by Curtin–Hammett kinetics where the degree of stereoselectivity is determined by the magnitude of $\Delta\Delta G^{\ddagger}$ (Scheme 2B).[3]

While in a KR $[S_S]/[S_R]$ varies as a function of time, in an efficient DKR $[S_S]/[S_R] = 1.0$ at all times. The net outcome of these principles is that under a DKR manifold, a racemic starting material can be converted to a single stereoisomeric product with 100% theoretical yield via the faster reacting

enantiomer. As a result using facile modes of racemization is critical to producing an efficacious DKR.[1,3-5]

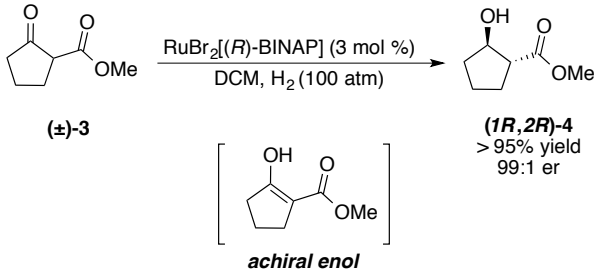
Scheme 2. Dynamic Kinetic Enantioselective Reactions



1.1.2 Racemization by Tautomerization

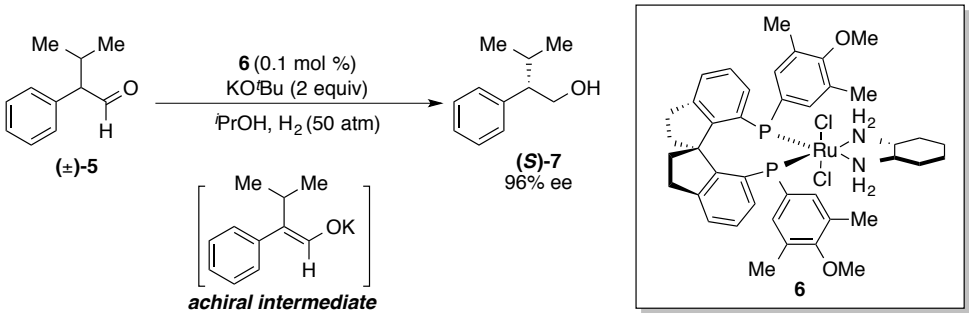
Noyori reported the first chemical DKR, converting α-alkyl-β-keto ester **3** to β-hydroxy ester **4** via asymmetric hydrogenation (Scheme 3).[6] Interconversion of **(*R*)-3** and **(*S*)-3** is through the tautomeric, achiral enol and is sufficiently facile due to the low pK_a of the α-proton.

Scheme 3. First Reported Chemical DKR with β-Keto Esters



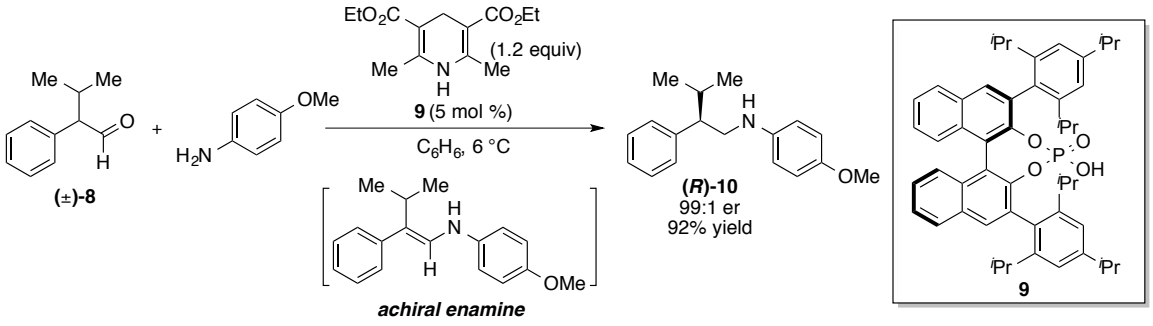
Since this seminal report, enolization as a racemization mode has been used for hydrogenative DKRs of a number of differentially substituted β-keto esters.[1,3-5,7-11] Additionally, carbonyls with α-protons having a higher pK_a than those of β-keto esters have also been shown as competent DKR substrates. Aldehydes, ketones, and azlactones have all been deployed in a number of DKR reactions including asymmetric hydrogenation,[12-16] aldol additions[17-20] and transesterifications.[21-25] For example ruthenium diamino diphosphine **6**, catalyzes the hydrogenative DKR of α-aryl aldehyde **5** forming primary alcohol **7** in 96% ee (Scheme 4).[12]

Scheme 4. Stereoconvergent Hydrogenation of α-Branched Aldehydes



Tautomerization of imines to enamines has been utilized as a similarly effective method of enantiomerization.[26-29] List has demonstrated that under chiral phosphoric acid catalysis and using Hantzsch ester **9** as an organic reductant the reductive amination of racemic aldehyde **8** occurs to provide **10** in 92% yield and 99:1 er (Scheme 5).[26]

Scheme 5. Organocatalytic Reductive Amination DKR of α-Branched Aldehydes



These selected examples represent a much larger set of DKR reactions that use tautomerization as the mechanism for racemization. This enantiomerization modality will be featured prominently in Chapters 2-4.

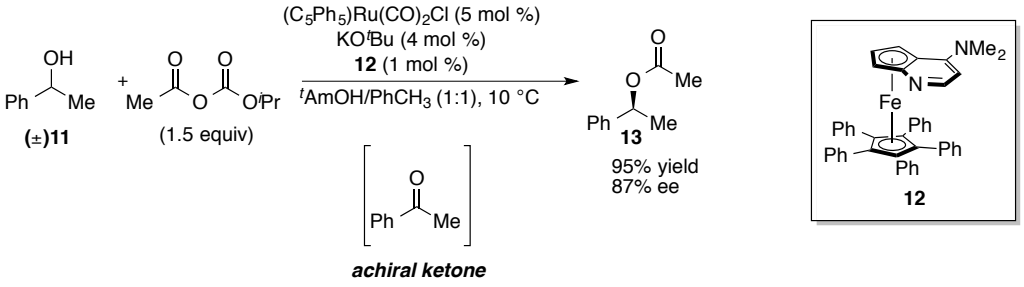
1.1.3 Additional Pathways for Enantiomerization

While the following will not be used in subsequent chapters, a number of additional modes of racemization have been applied in highly selective DKRs.

When a heteroatom is present at the stereogenic center, redox cycling through intermediate carbonyls (X = O) or imines (X = N) has been shown to effectively interconvert enantiomers as part of DKR reactions.

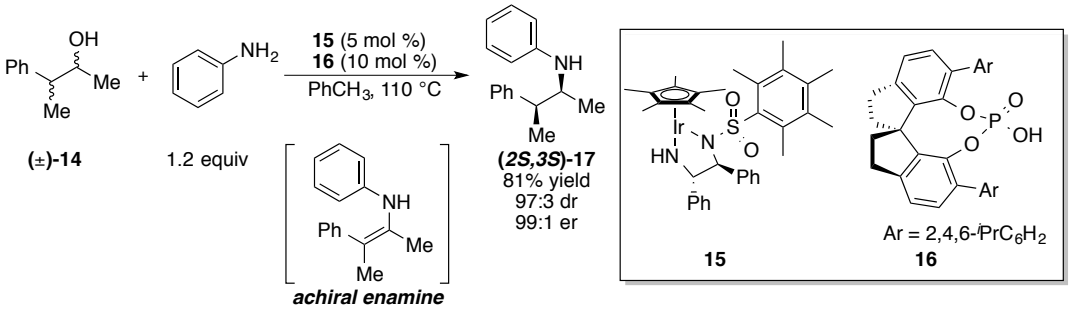
The preponderance of these methods are chemoenzymatic, utilizing metal catalysts for redox cycling and enzymes for selective substrate transformation. Enzymes are frequently employed for DKR acylations of secondary alcohols and numerous other reaction modalities. While they frequently exhibit phenomenal spatial selectivity they are typically highly specific with little substrate generality.[30] Therefore, while the significance of enzymatic DKRs is acknowledged, the focus of all subsequent discussion will be solely on the development of chemical DKRs. The first chemical acylative DKR of secondary alcohols was disclosed by Fu,[31] using $(C_5Ph_5)Ru(CO)_2Cl$ as a redox cycling catalyst in conjunction with ferrocene-based chiral *N*,*N*-dimethyl amino pyridine (DMAP) catalyst **12** providing **13** in 95% yield and 87% ee (Scheme 6). Ruthenium-promoted equilibration between acetophenone and 1-phenylethanol resulted in a rate of racemization sufficient for dynamic conversion.

Scheme 6. Acylative DKR of Alcohols by Redox Cycling



Zhao has reported a rare example where redox cycling and tautomerization are used in tandem resulting in the stereoconvergence of four isomers to a single product.[32] Subjecting alcohol **14** to a dual catalytic system consisting of iridium diamine **15** and spinol derived phosphoric acid **16** delivers reductive amination product **17** with high stereoselectivity (Scheme 7). This convergence of starting materials is the result of both redox cycling (alcohol into ketone via hydrogen borrowing) and imine/enamine racemization of the α-stereocenter.

Scheme 7. Reductive Amination DKR via Hydrogen Borrowing and Enamine Imine Tautomerization



Although less frequently used, racemization by addition-elimination and Schiff base formation are both precedented; [1,3-5] however, they are not utilized in subsequent chapters.

1.1.4 Dynamic Kinetic Asymmetric Transformations

While often used synonymously with the term DKR, a dynamic kinetic asymmetric transformation (DyKAT) is a fundamentally different process. In a DKR, enantiomerization of the stereogenic center is independent of the chiral catalyst–driven solely by the spontaneity of racemization. Conversely in a DyKAT,

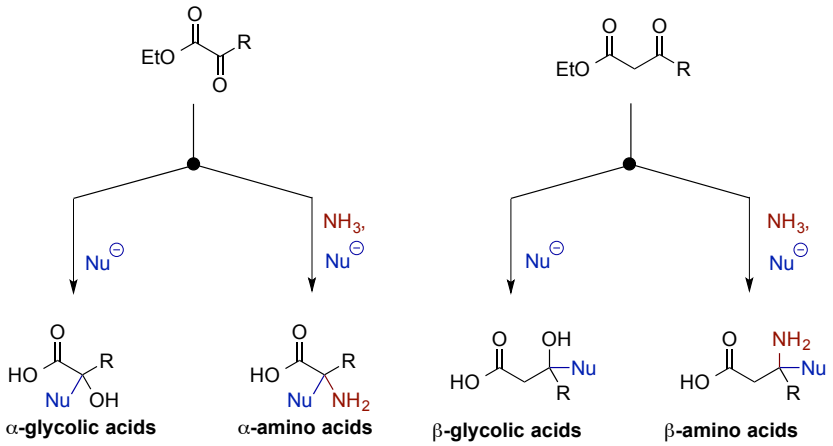
enantiomeric substrates are interconverted through diastereomeric complexes formed by association of a chiral catalyst with substrate, implying the potential for a different rate of equilibration for each enantiomer. The net effect of this is twofold: 1) unlike in a DKR a DyKAT can result in an accumulation of one enantiomer (or with catalyst associated--diastereomer) over the other; 2) interconversion of diastereomers can be more favorable than in a DKR due to the potential for an enthalpic driving force.[1] There are four classifications of DyKATs, however all following chapters will focus on only traditional DKRs; consequently, understanding the above principles is an adequate conceptual framework for the work contained herein.

1.2 Oxo-Esters

This dissertation will focus on the reactivity of stereochemically labile oxo-acid derivatives; therefore, a short discussion on the utility of their reaction products is warranted. For both α- and β-oxo acids a number of functionally rich and biologically relevant products are accessible via addition of a nucleophile or through amine condensation and subsequent nucleophile addition. Direct nucleophilic addition to an α-keto ester results in the formation of an α-glycolic acid derivative. This scaffold is present in critical therapeutics, has been utilized as a vehicle for drug delivery, and has additional roles in consumer health.[33-35] Condensation of an amine followed by addition of a nucleophile delivers α-amino acid surrogates. While natural α-amino acids are the building blocks of proteins, utilization of unnatural variants as biologic modifiers constitutes a growing sector of pharmaceuticals and plays a central role in biomedical research.[36-39] Identical

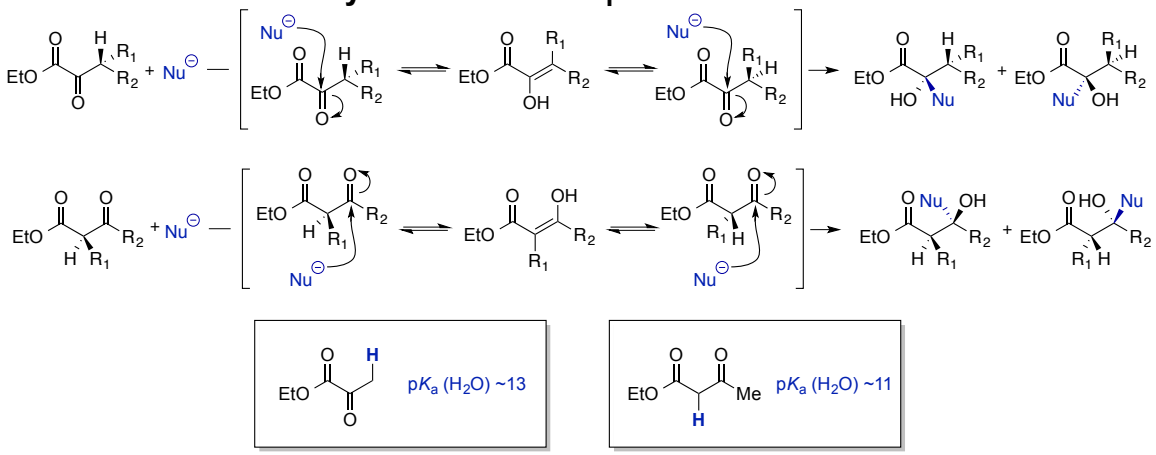
reaction platforms with β-keto esters deliver β-hydroxy acids, utilized in pharmaceuticals[40] and personal health products,[33,41] and β-amino acids which are structural motifs present in the structures of taxol,[42] cocaine,[43] and penicillin,[44] among others[45]; representing some of the most influential modern pharmaceuticals.

Scheme 8. Synthetic Utility of α- and β-Oxo Acid Addition Products.



Of particular difficulty for these important scaffolds is the generation of single enantiomer products bearing non-quaternary stereocenters vicinal to the hydroxyl or amino group. Establishing this stereocenter prior to reaction with the carbonyl is complicated by the high acidity of the carbonyl α-proton (pK_a = 11 and 13 for β-oxo esters and α-keto esters respectively)[46] as it predisposes the established stereocenter to racemization before nucleophile addition (Scheme 9). This same stereolability implicates use of these substrates in DKRs which can deliver products not prone to racemization while simultaneously establishing both both relative and absolute stereochemistry.

Scheme 9. Complications of Nucleophile Additions to Stereochemically Defined α- and β-Oxo Esters



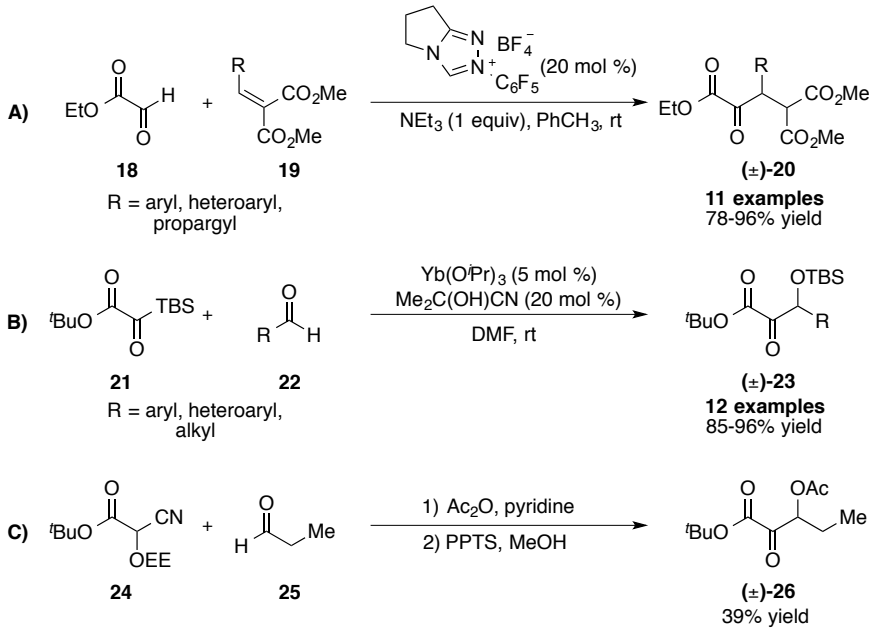
Since a DKR approach to stereochemically rich α- and β-amino or hydroxy acids requires only synthetic access to racemic, rather than enantiopure, starting oxo-acids, there is also a significant advantage in available product diversity.

1.2.1 Synthesis of Racemic β-Stereogenic α-Keto Acid Derivatives

There are numerous methods for the synthesis of non-quaternary racemic β-substituted α-keto acid derivatives that provide access to a wide array of diverse β-functionality. Many rely on the generation and subsequent addition of glyoxylate acyl anion equivalents to assorted electrophiles. Of these umpolung (polarity inversion) strategies the Stetter addition of glyoxylate to a Michael acceptor is the most efficient. Our group has described *N*-heterocyclic carbene (NHC) catalyzed addition of ethyl glyoxylate **18** to alkylidene malonate **19** delivering racemic α-keto ester **20** (Scheme 10A).[47] In a related report cyanide addition to silyl glyoxylate **21** is followed by cross-benzoin condensation with aldehyde **22** delivering β-siloxyl α-keto ester **22** (Scheme 10B).[48] Takahashi has

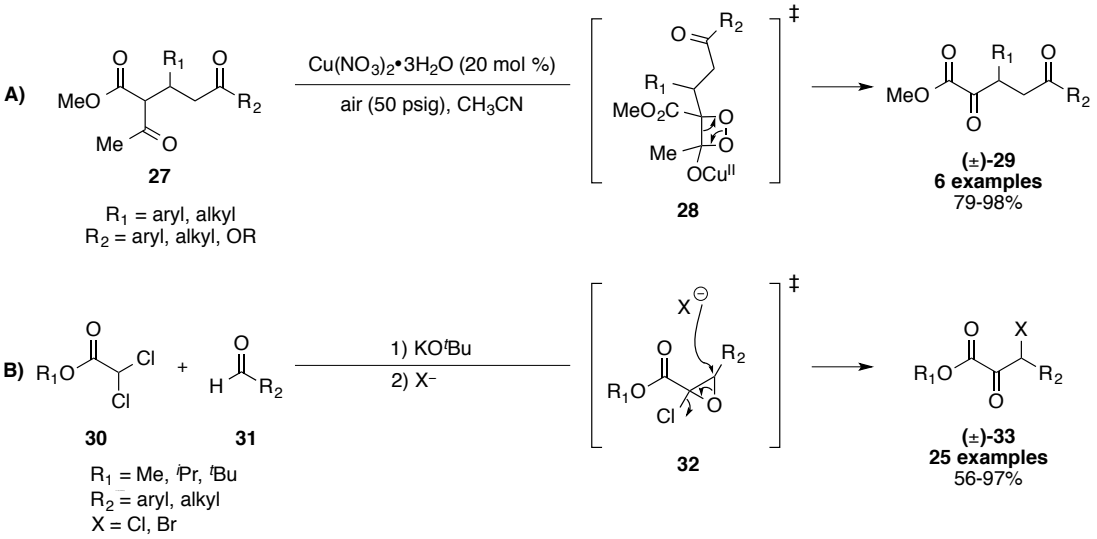
also reported the use of protected cyanohydrin **24** as a glyoxylate equivalent for the generation of β-acetoxy α-keto ester **26** (Scheme 10C).[49]

Scheme 10. Synthesis of β-Stereogenic α-Keto Esters Using Glyoxylate Equivalents



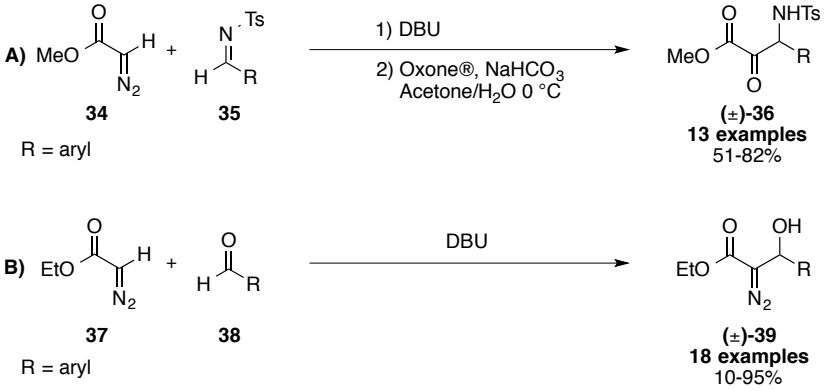
Structural reorganization to unveil racemic α-keto acid scaffolds have also been demonstrated. Our group has utilized aerobic deacylation of acetoacetate derivative **27** delivering α-keto ester **29**.[50] Mechanistically this process is proposed to proceed via enolate peroxidation followed by formation and subsequent fragmentation of endoperoxide **28** (Scheme 11A). In a distinct strategy, the Darzens reaction using dichloroacetate **30** and aldehyde **31** delivers epoxychloride **32** which upon nucleophilic ring opening eliminates chloride to form α-keto ester **33** (Scheme 11B).[51]

Scheme 11. Synthesis of β-Stereogenic α-Keto Esters via Structural Rearrangements



A number of β-substituents can be accessed using two-step protocols that terminate in oxidation of α-diazo esters to keto esters. Addition of diazo acetate **34** into tosylaldimine **35** followed by oxidation with Oxone® delivers β-amino α-keto ester **36**.[52] The use of α-diazo ester **37** for condensation with aldehyde **38** provides β-hydroxy α-diazo ester **39**.[53]

Scheme 12. Synthesis of β-Stereogenic α-Keto Esters from α-Diazo Esters



Two-step protocols that generate the α-ketone via ozonolysis have been reported including Morita-Baylis-Hillman (MBH) addition of vinyl acetates,[54] Michael addition of enol acetates,[55] and conjugate addition of methyl nitroacetate to enones.[56] Collectively, these and other transformations[57-59] encompass the synthesis of a wide variety of β-substituted α-keto acid surrogates including β-oxo, -alkyl, -allyl, -vinyl, -aryl, -amino, -thiol, -cyano, -ester, -silyl, and -acetyl groups.

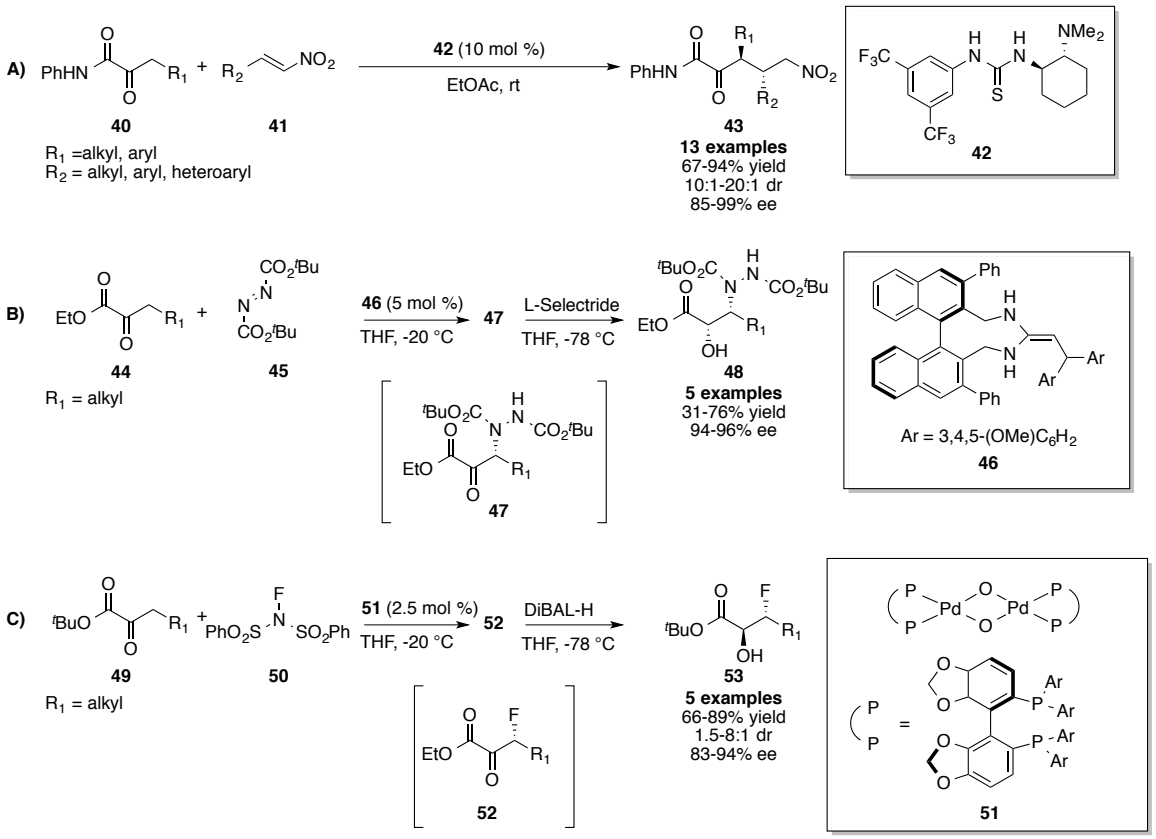
1.2.2 Asymmetric Synthesis of β-Stereogenic α-Keto Acid Derivatives

Many of the above reaction platforms have been rendered asymmetric yielding enantioenriched β-stereogenic α-keto acid derivatives. Prominent are the use of 1,2 dicarbonyl pronucleophiles in conjugate additions.[60] Multiple catalysts have been used for the addition of pyruvates such as **40** to nitro olefins.[60-64] While most of these reports are limited to β-alkyl substitution, the use of Takemoto's urea **42** as a catalyst allows formation of β-aryl and heteroaryl substituted ketone **43** (Scheme 13A).[62]

Azodicarboxylate **44** was employed with guanidine catalyst **46** for the generation of β-amino α-keto ester **47**. This product was reduced directly to the corresponding β-amino α-hydroxy ester **48** due to observed stereoablation during attempted silica-gel chromatography (Scheme 13B).[65] In a related report *N*-fluorobenzenesulfonamide **50** was used as an electrophilic source of fluorine for the synthesis of β-fluoro α-keto ester **52**, which is directly reduced to β-fluoro α-hydroxy ester **53** (Scheme 13C).[66] In both of these methods the product structural diversity is limited to β-alkyl substitution.

Mannich additions of pyruvate to aldimines have been used for the asymmetric synthesis of γ-amino α-keto acid derivatives, albeit without a method that can prevent epimerization with β-aryl substitution.[67-69]

Scheme 13. Asymmetric Synthesis of β-Stereogenic α-Keto Acid Derivatives with 1,2-Dicarbonyl Pronucleophiles.

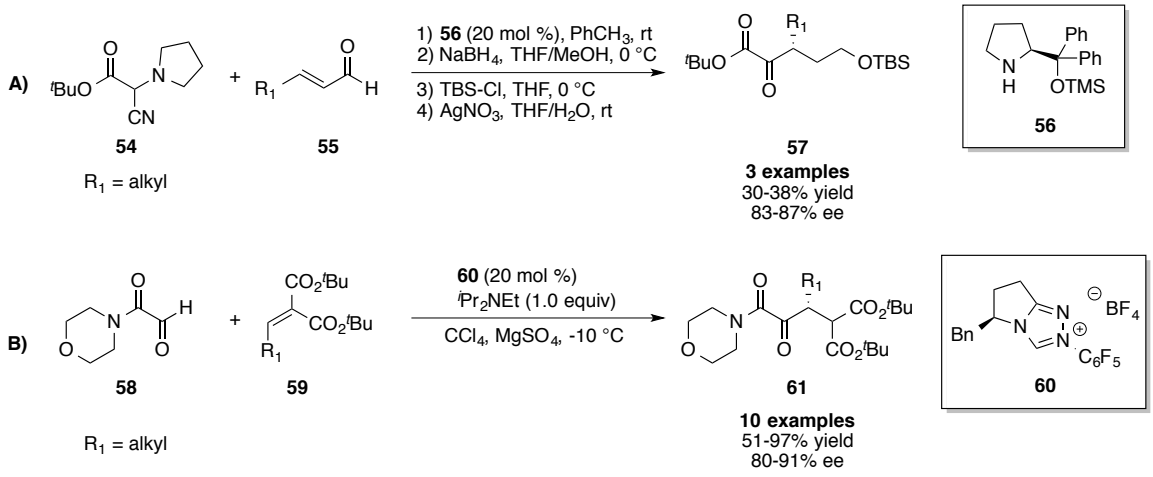


Diazoacetates can be used for asymmetric synthesis of β-oxo α-keto[70] or α-diazo esters[71] under the control of chiral Lewis acids. Additionally both Lewis acid[72-73] and guanidine–[74] catalyzed asymmetric Claisen rearrangements have been reported; however, none of these methods can tolerate β-aryl substitution.

Finally, a limited number asymmetric methods that use glyoxylate anion equivalents have been reported. Addition of aminonitrile **54** to the iminium of α,β-

unsaturated aldehyde **55** followed by aldehyde reduction, alcohol protection, and ketone deprotection provides β-alkyl α-keto ester **57** in low yields (Scheme 14A).[75] In the most atom economical route to date Rovis disclosed an asymmetric carbene catalyzed Stetter reaction using glyoxamide **58** and alkylidene malonate **59** generating β-alkyl α-keto amide **61** (Scheme 14B).[76] This method was later extended to include alkylidene ketoamide electrophiles.[77]

Scheme 14. Asymmetric Synthesis of β-Stereogenic α-Keto Acid Derivatives from Glyoxylate Equivalents.



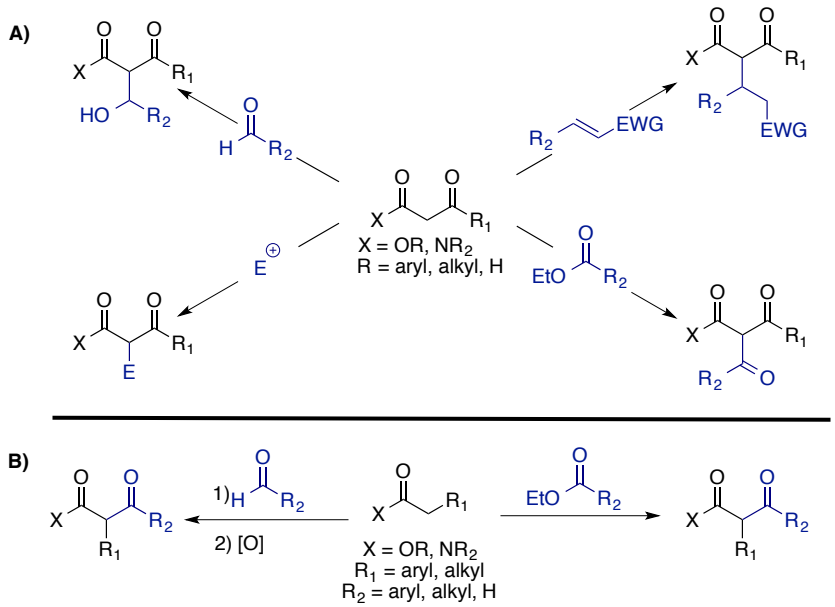
One central problem with current methods for the asymmetric synthesis of β-stereogenic α-keto esters is the limited number of β-substituents allowed. To date, there remains only a single method that generates stereoenriched β-aryl α-keto esters due to difficulty in maintaining the integrity of the established stereocenter; i.e. products are susceptible to base catalyzed racemization.

1.2.3 Synthesis of Racemic α-Stereogenic β-Keto Acid Derivatives

The low pK_a, and associated nucleophilicity, of unsubstituted 1,3-dicarbonyls allows for easy access to a wide array of diversely substituted,

racemic, and non-quaternary α-substituted β-oxo acid derivatives. Aside from simple enolate alkylation, other commonly employed pathways include Claisen condensation,[78-79] aldol condensation,[80-81] conjugate additions,[82-83] as well as enolate functionalization with other electrophilic reagents including sources of nitrogen,[84] oxygen,[85] arenes,[86] and halogens (Scheme 15A).[87-88] Claisen condensation[89] or aldol addition and subsequent oxidation[90-91] starting from simple esters can also be used to generate mono-substituted β-oxo acid derivatives (Scheme 15B).

Scheme 15. General Strategies for the Construction of Non-Quaternary Racemic α-Stereogenic β-Keto Acid Derivatives

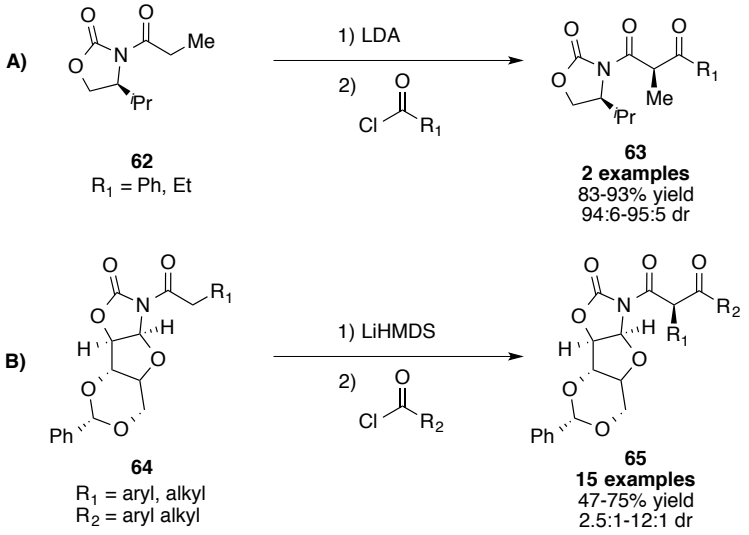


1.2.4 Asymmetric Synthesis of α-Stereogenic β-Keto Acid Derivatives

The synthesis of enantioenriched non-quaternary α-stereogenic β-oxo acid derivatives is challenging due to the ease of racemization via enol or enolate formation. The first method for asymmetric synthesis of these small molecules

was introduced by Evans in 1984, relying on the use of chiral oxazolidinone auxiliaries. Acylation of the lithium enolate of **62** resulted in highly diastereoselective formation of **63**, though this report was limited to alkyl substitution at the α-stereocenter (Figure 16A).[92] In an expansion of this work use of xylose derived oxazolidinone **64** allows for aromatic substitution at the α-stereocenter providing **65**, albeit with generally poor diastereoselection (Figure 16B).[93] The surprisingly slow rate of epimerization for these 1,3-dicarbonyls is proposed to stem from disfavored enolate formation due to developing allylic strain wherein both carbonyl π-systems must be co-planar with the methine hydrogen in order to form the enol.[92]

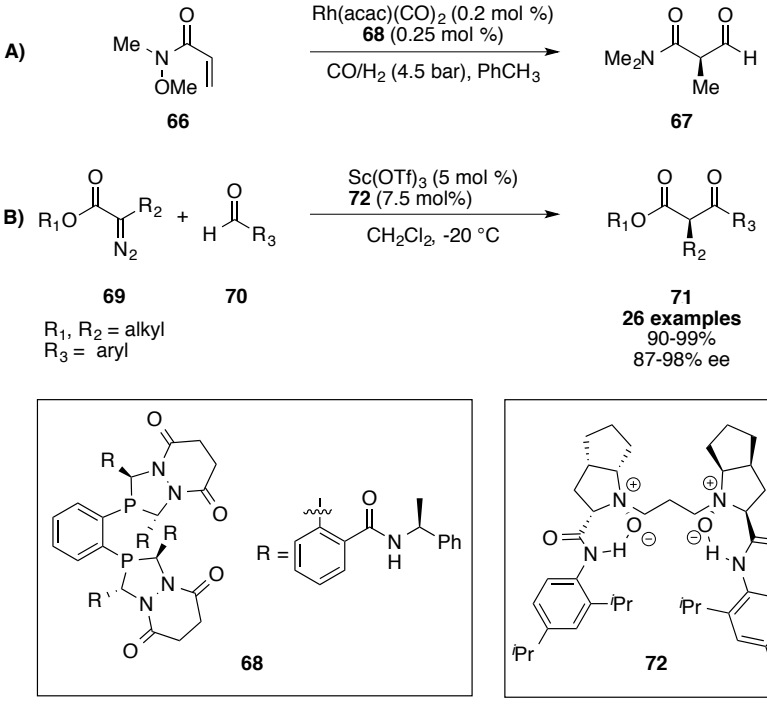
Scheme 16. Approach to the Asymmetric Synthesis of α-Stereogenic β-Keto Acid Derivatives via Chiral Auxiliaries



Despite the necessity of stoichiometric amounts of chiral auxiliaries, they remain heavily employed in the asymmetric formation of α-stereogenic β-oxo acid derivatives.[94-95]

In contrast there are only two described methods for the catalytic asymmetric synthesis of these same substrates. Hydroformylation of dialkylacrylamide **66** provides α-methyl β-formyl amide **67** in moderate enantioselectivity with product diversity limited to α-methyl substitution (Figure 17A).[96] The catalytic Roskamp reaction has been employed for access to a range of α-alkyl β-keto esters. Feng has disclosed the use of a *N,N*-dioxide-scandium (III) complex for addition of diazo-ester **69** to aldehyde **70** providing β-keto ester **71** with high yield and enantioselection (Figure 17B).[97] The Roskamp reaction has also been catalyzed by oxazaborolidiniums,[98] and under the control of a chiral camphorsultam auxillary.[99]

Scheme 17. Catalytic Asymmetric Synthesis of α-Stereogenic β-oxo Acid Derivatives



1.3 Proposed Strategy for the Synthesis of New α- and β-Hydroxy or Amino Acids

The difficulty that underlies the synthesis of both non quaternary β-stereogenic α-keto and α-stereogenic β-keto acids is linked to stereoablation by tautomerization; however, this challenge present for *stepwise* stereocenter generation with subsequent diastereoselective nucleophile addition can be rendered advantageous in the development of dynamic methods for concurrent generation of both relative and absolute stereocontrol. Our proposed area of study was the design of DKR reactions that take advantage of the high kinetic acidity of substituents, which are ineffectual in current asymmetric strategies to deliver complementary, and previously inaccessible small molecules.

1.4 REFERENCES

1) Steinreiber, J.; Faber, K.; Griengl, H. “De-racemization of enantiomers versus de-epimerization of diastereomers—classification of dynamic kinetic asymmetric transformations (DYKAT).” *Chem. Eur. J.* **2008,** *14*, 8060-8072.

2) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. “Kinetic resolution of racemic allylic alcohols by enantioselective epoxidation. A route to substances of absolute enantiomeric purity?” *J. Am. Chem. Soc.* **1981,** *103*, 6237-6240.

3) Huerta, F. F.; Minidis, A. B. E.; Backvall, J. “Racemisation in asymmetric synthesis. Dynamic kinetic resolution and related processes in enzyme and metal catalysis.” *Chem. Soc. Rev.* **2001,** *30*, 321-331.

4) Pellissier, H. “Organocatalyzed dynamic kinetic resolution.” *Adv. Synth. Catal.* **2011,** *353*, 659-676.

5) Noyori, R.; Tokunaga, M.; Kitamura, M. “Stereoselective organic synthesis via dynamic kinetic resolution.” *Bull. Chem. Soc. Jpn.* **1995,** *68*, 36-55.

6) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T. “Stereoselective hydrogenation via dynamic kinetic resolution.” *J. Am. Chem. Soc.* **1989,** *111*, 9134-9135.

7) Ros, A.; Magriz, A.; Dietrich, H.; Lassaletta, J. M.; Fernández, R. “Stereoselective synthesis of syn β-hydroxy cycloalkane carboxylates: transfer hydrogenation of cyclic β-keto esters via dynamic kinetic resolution.” *Tetrahedron* **2007,** *63*, 7532-7537.

8) Cartigny, D.; Püntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. “Highly diastereo- and enantioselective synthesis of monodifferentiated syn-1,2-diol derivatives through asymmetric transfer hydrogenation via dynamic kinetic resolution.” *Org. Lett.* **2010,** *12*, 3788-3791.

9) Prévost, S.; Gauthier, S.; de Andrade, M. C. C.; Mordant, C.; Touati, A. R.; Lesot, P.; Savignac, P.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J. “Dynamic kinetic resolution of α-chloro β-keto esters and phosphonates: hemisynthesis of Taxotere® through Ru-DIFLUORPHOS asymmetric hydrogenation.” *Tetrahedron: Asymmetry* **2010,** *21*, 1436-1446.

10) Liu, Z.; Shultz, C. S.; Sherwood, C. A.; Krska, S.; Dormer, P. G.; Desmond, R.; Lee, C.; Sherer, E. C.; Shpungin, J.; Cuff, J.; Xu, F. “Highly enantioselective synthesis of anti aryl β-hydroxy α-amino esters via DKR transfer hydrogenation.” *Tetrahedron Lett.* **2011,** *52*, 1685-1688.

11) Li, X.; Tao, X.; Ma, X.; Li, W.; Zhao, M.; Xie, X.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z. “Dynamic kinetic resolution of β′-keto-β-amino esters using Ru–DTBM–Sunphos catalyzed asymmetric hydrogenation.” *Tetrahedron* **2013,** *69*, 7152-7156.

12) Xie, J.; Zhou, Z.; Kong, W.; Zhou, Q. “Ru-catalyzed asymmetric hydrogenation of racemic aldehydes via dynamic kinetic resolution: efficient synthesis of optically active primary alcohols.” *J. Am. Chem. Soc.* **2007,** *129*, 1868-1869.

13) Wu, G.; Zhu, J.; Ding, Z.; Shen, Z.; Zhang, Y. “Dynamic kinetic resolution of racemic α-sulfonylaldehydes via asymmetric transfer hydrogenation.” *Tetrahedron Lett.* **2009,** *50*, 427-429.

14) Zhou, Z.; Xie, J.; Zhou, Q. “Enantioselective synthesis of chiral α -aryloxy alcohols by asymmetric hydrogenation of α-aryloxy aldehydes via dynamic kinetic resolution.” *Adv. Synth. Catal.* **2009,** *351*, 363-366.

15) Xie, J.; Liu, S.; Huo, X.; Cheng, X.; Duan, H.; Fan, B.; Wang, L.; Zhou, Q. “RuII-SDP-complex-catalyzed asymmetric hydrogenation of ketones. Effect of the alkali metal cation in the reaction.” *J. Org. Chem.* **2005,** *70*, 2967-2973.

16) Liu, C.; Xie, J.; Li, Y.; Chen, J.; Zhou, Q. “Asymmetric hydrogenation of α,α′-disubstituted cycloketones through dynamic kinetic resolution: an efficient construction of chiral diols with three contiguous stereocenters.” *Angew. Chem. Int. Ed.* **2013,** *52*, 593-596.

17) Reyes, E.; Córdova, A. “Amino acid-catalyzed dynamic kinetic asymmetric transformations (DYKAT): one-step de novo synthesis of polyketide sugars from racemic β-hydroxy aldehydes.” *Tetrahedron Lett.* **2005,** *46*, 6605-6609.

18) Bergeron-Brlek, M.; Teoh, T.; Britton, R. A “Tandem organocatalytic α-chlorination–aldol reaction that proceeds with dynamic kinetic resolution: a powerful tool for carbohydrate synthesis.” *Org. Lett.* **2013,** *15*, 3554-3557.

19) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. “Enantioselective direct intermolecular aldol reactions with enantiotopic group selectivity and dynamic kinetic resolution.” *Org. Lett.* **2005,** *7*, 1181-1184.

20) Ward, D. E.; Jheengut, V.; Beye, G. E.; Gillis, M.; Karagiannis, A.; Bercerril-Jimenez, F. “Enantioselective direct aldol reactions of achiral ketones with racemic enolizable α-substittued aldehydes: scope and limitations.” *Synlett,* **2011,** *4,* 508-512.

21) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Muller, T. N.; Lex, J. “Second-generation organocatalysts for the highly enantioselective dynamic kinetic resolution of azlactones.” *Chem. Commun.* **2005,** 1898-1900.

22) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. “Highly efficient dynamic kinetic resolution of azlactones by urea-based bifunctional organocatalysts.” *Angew. Chem. Int. Ed.* **2005*,*** *44*, 807-811.

23) Berkessel, A.; Mukherjee, S.; Muller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudorfl, J.; Lex, J. “Structural optimization of thiourea-based bifunctional organocatalysts for the highly enantioselective dynamic kinetic resolution of azlactones.” *Org. Biomol. Chem.* **2006*,*** *4*, 4319-4330.

24) Woong Lee, J.; Hi Ryu, T.; Suk Oh, J.; Yong Bae, H.; Bin Jang, H.; Eui Song, C. “Self-association-free dimeric cinchona alkaloid organocatalysts: unprecedented catalytic activity, enantioselectivity and catalyst recyclability in dynamic kinetic resolution of racemic azlactones.” *Chem. Commun.* **2009,** 7224-7226.

25) Yang, X.; Lu, G.; Birman, V. B. “Benzotetramisole-catalyzed dynamic kinetic resolution of azlactones.” *Org. Lett.* **2010*,*** *12*, 892-895.

26) Cheng, X.; Goddard, R.; Buth, G.; List, B. “Direct catalytic asymmetric three-component Kabachnik–Fields reaction.” *Angew. Chem. Int. Ed.* **2008*,*** *47*, 5079-5081.

27) Malkov, A.; Stončius, S.; Vranková, K.; Arndt, M.; Kočovský, P. “Dynamic kinetic resolution in the asymmetric synthesis of β-amino acids by organocatalytic reduction of enamines with trichlorosilane.” *Chem. Eur. J.* **2008*,*** *14*, 8082-8085.

28) Han, Z.; Xiao, H.; Gong, L. “Dynamic kinetic asymmetric transfer hydrogenation of racemic 2,4-diaryl-2,3-dihydrobenzo[β][1,4]diazepines catalyzed by chiral phosphoric acids.” *Bioorg. Med. Chem. Lett.* **2009*,*** *19*, 3729-3732.

29) Wakchaure, V.; Zhou, J.; Hoffmann, S.; List, B. “Catalytic asymmetric reductive amination of α-branched ketones.” *Angew. Chem. Int. Ed.* **2010*,*** *49*, 4612-4614.

30) Lee, J. H.; Han, K.; Kim, M.; Park, J. “Chemoenzymatic dynamic kinetic resolution of alcohols and amines.” *Eur. J. Org. Chem.* **2010,** 999-1015.

31) Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. “Nonenzymatic dynamic kinetic resolution of secondary alcohols via enantioselective acylation: synthetic and mechanistic studies.” *J. Am. Chem. Soc.* **2012*,*** *134*, 15149-15153.

32) Rong, Z.; Zhang, Y.; Chua, R. H. B.; Pan, H.; Zhao, Y. “Dynamic kinetic asymmetric amination of alcohols: from a mixture of four isomers to diastereo- and enantiopure α-branched amines.” *J. Am. Chem. Soc.* **2015,** *137*, 4944-4947.

33) Kornhauser, A.; Coelho, S. G.; Hearing, V. J. “Applications of hydroxy acids: classification, mechanisms, and photoactivity.” *Clin. Cosmet. Investig. Dermatol.* **2010,** *3*, 135-142.

34) Gu, X.; Wang, L.; Gao, Y.; Ma, W.; Li, Y.; Gong, P. “The synthesis of enantioenriched α-hydroxy esters.” *Tetrahedron: Asymmetry* **2014,** *25*, 1573-1580.

35) Coppola, G. M.; Schuster, H. F. “Chiral α-hydroxy acids in enantioselective syntheses” Wiley-VCH Verlag, Weinhem, **1997**.

36) Spicer, C. D.; Davis, B. G. “Selective chemical protein modification.” *Nat. Commun.* **2014***, 5*. 4740.

37) Zhang, G.; Zheng, S.; Liu, H.; Chen, P. R. “Illuminating biological processes through site-specific protein labeling.” *Chem. Soc. Rev.* **2015,** *44*, 3405-3417.

38) Sochaj, A. M.; Świderska, K. W.; Otlewski, J. “Current methods for the synthesis of homogeneous antibody–drug conjugates.” *Biotechnol. Adv.* **2015,** *33*, 775-784.

39) Werner, H. M.; Horne, W. S. “Folding and function in α/β-peptides: targets and therapeutic applications.” *Curr. Opin. Chem. Biol.* **2015,** *28*, 75-82.

40) Wong, D. T.; Bymaster, F. P.; Engleman, E. A. “Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication.” *Life Sci.* **1995,** *57*, 411-441.

41) Kornhauser, A.; Coelho, S. G.; Hearing, V. J. “Effects of cosmetic formulations containing hydroxyacids on sun-exposed skin: current applications and future developments.” *Dermatol. Res. Pract.* **2012,** *710893*.

42) Guéritte-Voegelein, F.; Guénard, D.; Potier, P. “Taxol and derivatives: a biogenetic hypothesis.” *J. Nat. Prod.* **1987,** *50*, 9-18.

43) Findlay, S. P. “The three-dimensional structure of cocaine.” *J. Am. Chem. Soc.* **1953,** *75*, 4624-4625.

44) Garrod, L. P. “Relative antibacterial activity of three penicillins.” *BMJ* **1960,** *1*, 527-529.

45) Kudo, F.; Miyanaga, A.; Eguchi, T. “Biosynthesis of natural products containing small β-amino acids.” *Nat. Prod. Rep.* **2014,** *31*, 1056-1073.

46) Guthrie, J. P. “The enol content of simple carbonyl compounds: an approach based upon pKa estimation.” *Can. J. Chem.* **1979,** *57*, 1177-1185.

47) Steward, K. M.; Gentry, E. C.; Johnson, J. S. “Dynamic kinetic resolution of α-keto esters via asymmetric transfer hydrogenation.” *J. Am. Chem. Soc.* **2012,** *134*, 7329-7332.

48) Steward, K. M.; Johnson, J. S. “Catalytic nucleophilic glyoxylation of aldehydes.” *Org. Lett.* **2010,** *12*, 2864-2867.

49) Takahashi, T.; Okano, T.; Harada, T.; Imamura, K.; Yamada, H. “Reactions of a new acyl anion equivalent; $^{-}COCO_2R$, and its use to preparation of α-ketoesters.” *Synlett,* **1994,** 121-122.

50) Steward, K. M.; Johnson, J. S. “Asymmetric synthesis of α-keto esters via Cu(II)-catalyzed aerobic deacylation of acetoacetate alkylation products: an unusually simple synthetic equivalent to the glyoxylate anion synthon.” *Org. Lett.* **2011,** *13*, 2426-2429.

51) Mamedov, V. A.; Berdnikov, E. A.; Tsuboi, S.; Hamamoto, H.; Komiyama, T.; Gorbunova, E. A.; Gubaidullin, A. T.; Litvinov, I. A. “Substituted benzaldehydes in the Darzens condensation with alkyl dihaloacetates.” *Russ. Chem. Bull.* **2006,** *55*, 1455-1463.

52) Zhao, Y.; Jiang, N.; Chen, S.; Peng, C.; Zhang, X.; Zou, Y.; Zhang, S.; Wang, J. “Concise and diastereoselective approach to *syn*- and *anti*-*N*-tosyl-α-hydroxy β-amino acid derivatives.” *Tetrahedron* **2005,** *61*, 6546-6552.

53) Jiang, N.; Wang, J. “DBU-promoted condensation of acyldiazomethanes to aldehydes and imines under catalytic conditions.” *Tetrahedron Lett.* **2002,** *43*, 1285-1287.

54) Abella, C. A. M.; Rezende, P.; Lino de Souza, M. F.; Coelho, F. “Ozonolysis of Morita–Baylis–Hillman adducts originated from aromatic aldehydes: an expeditious diastereoselective approach for the preparation of α,β-dihydroxy-esters.” *Tetrahedron Lett.* **2008,** *49*, 145-148.

55) Xian, M.; Alaux, S.; Sagot, E.; Gefflaut, T. “Chemoenzymatic synthesis of glutamic acid analogues: substrate specificity and synthetic applications of branched chain aminotransferase from *Escherichia coli*.” *J. Org. Chem.* **2007,** *72*, 7560-7566.

56) Thompson, W. J.; Buhr, C. A. “Preparation of methyl 2,5-dioxohexanoate: a highly convenient reagent for the introduction of the 2-carbalkoxy-1,5-dialkylpyrrole nucleus.” *J. Org. Chem.* **1983,** *48*, 2769-2772.

57) Skinner, G. S. “The condensation of oxalic esters with benzyl cyanide.” *J. Am. Chem. Soc.* **1933,** *55*, 2036-2039.

58) Yamagiwa, S.; Sato, H.; Hoshi, N.; Kosugi, H.; Uda, H. “New rearrangement reactions of α-phenylsulphinylacrylate derivatives.” *J. Chem. Soc., Perkin Trans. 1* **1979,** 570-583.

59) Shi, W.; Zhang, B.; Liu, B.; Xu, F.; Xiao, F.; Zhang, J.; Zhang, S.; Wang, J. “Unusual reaction of β-hydroxy α-diazo carbonyl compounds with TsNHN-CHCOCl/Et_3N.” *Tetrahedron Lett.* **2004,** *45*, 4563-4566.

60) Raimondi, W.; Bonne, D.; Rodriguez, J. “Asymmetric transformations involving 1,2-dicarbonyl compounds as pronucleophiles.” *Chem. Commun.* **2012**, 6763-6775.

61) Baslé, O.; Raimondi, W.; Duque, M. d. M. S.; Bonne, D.; Constantieux, T.; Rodriguez, J. “Highly diastereo- and enantioselective organocatalytic Michael addition of α-ketoamides to nitroalkenes.” *Org. Lett.* **2010,** *12*, 5246-5249.

62) Shi, D.; Xie, Y.; Zhou, H.; Xia, C.; Huang, H. “A highly diastereo- and enantioselective reaction for constructing functionalized cyclohexanes: six contiguous stereocenters in one step.” *Angew. Chem. Int. Ed.* **2012,** *51*, 1248-1251.

63) Du, H.; Rodriguez, J.; Bugaut, X.; Constantieux, T. “Organocatalytic enantio- and diastereoselective conjugate addition to nitroolefins: when β-ketoamides surpass β-ketoesters.” *Chem. Eur. J.* **2014,** *20*, 8458-8466.

64) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. “Diastereo- and enantioselective conjugate addition of α-ketoesters to nitroalkenes catalyzed by a chiral $Ni(OAc)_2$ complex under mild conditions.” *J. Am. Chem. Soc.* **2010,** *132*, 4036-4037.

65) Terada, M.; Amagai, K.; Ando, K.; Kwon, E.; Ube, H. “Direct enantioselective amination of α-ketoesters catalyzed by an axially chiral guanidine base.” *Chem. Eur. J.* **2011,** *17*, 9037-9041.

66) Suzuki, S.; Kitamura, Y.; Lectard, S.; Hamashima, Y.; Sodeoka, M. “Catalytic asymmetric mono-fluorination of α-keto esters: synthesis of optically active β-fluoro-α-hydroxy and β-fluoro-α-amino acid derivatives.” *Angew. Chem. Int. Ed.* **2012,** *51*, 4581-4585.

67) Juhl, K.; Gathergood, N.; Jørgensen, K. A. “Catalytic asymmetric direct Mannich reactions of carbonyl compounds with α-imino esters.” *Angew. Chem. Int. Ed.* **2001,** *40*, 2995-2997.

68) Lu, G.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. “Chiral γ-amino amide synthesis by heterobimetallic lanthanum/lithium/pybox-catalyzed direct asymmetric Mannich-type reactions of α-keto anilides.” *Angew. Chem. Int. Ed.* **2008,** *47*, 6847-6850.

69) Xu, Y.; Lu, G.; Matsunaga, S.; Shibasaki, M. “Direct *anti*-selective catalytic asymmetric Mannich-type reactions of α-ketoanilides for the synthesis of γ-amino amides and azetidine-2-amides.” *Angew. Chem. Int. Ed.* **2009,** *48*, 3353-3356.

70) Yao, W.; Wang, J. “Direct catalytic asymmetric aldol-type reaction of aldehydes with ethyl diazoacetate.” *Org. Lett.* **2003,** *5*, 1527-1530.

71) Trost, B. M.; Malhotra, S.; Fried, B. A. “Magnesium-catalyzed asymmetric direct aldol addition of ethyl diazoacetate to aromatic, aliphatic, and α–β-unsaturated aldehydes.” *J. Am. Chem. Soc.* **2009,** *131*, 1674-1675.

72) Abraham, L.; Czerwonka, R.; Hiersemann, M. “The catalytic enantioselective Claisen rearrangement of an allyl vinyl ether.” *Angew. Chem. Int. Ed.* **2001,** *40*, 4700-4703.

73) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. “The catalytic diastereo- and enantioselective Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ether.” *Adv. Synth. Catal.* **2004,** *346*, 1281-1294.

74) Uyeda, C.; Jacobsen, E. N. “Enantioselective Claisen rearrangements with a hydrogen-bond donor catalyst.” *J. Am. Chem. Soc.* **2008,** *130*, 9228-9229.

75) Enders, D.; Bonten, M. H.; Raabe, G. “Organocatalytic asymmetric conjugate nucleophilic glyoxylation.” *Synlett* **2007,** *6,* 885-888.

76) Liu, Q.; Perreault, S.; Rovis, T. “Catalytic asymmetric intermolecular Stetter reaction of glyoxamides with alkylidenemalonates.” *J. Am. Chem. Soc.* **2008,** *130*, 14066-14067.

77) Liu, Q.; Rovis, T. “Enantio- and diastereoselective intermolecular Stetter reaction of glyoxamide and alkylidene ketoamides.” *Org. Lett.* **2009,** *11*, 2856-2859.

78) Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. M. “Biomimetic total synthesis of Angelicoin A and B via a palladium-catalyzed decarboxylative prenylation-aromatization sequence.” *Org. Lett.* **2011,** *13*, 5748-5750.

79) Cordes, J.; Calo, F.; Anderson, K.; Pfaffeneder, T.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. “Total syntheses of Angelicoin A, Hericenone J, and Hericenol A via migratory prenyl- and geranylation-aromatization sequences.” *J. Org. Chem.* **2012,** *77*, 652-657.

80) Bencsik, J. R.; Xiao, D.; Blake, J. F.; Kallan, N. C.; Mitchell, I. S.; Spencer, K. L.; Xu, R.; Gloor, S. L.; Martinson, M.; Risom, T.; Woessner, R. D.; Dizon, F.; Wu, W.; Vigers, G. P. A.; Brandhuber, B. J.; Skelton, N. J.; Prior, W. W.; Murray, L. J. “Discovery of dihydrothieno- and dihydrofuropyrimidines as potent pan Akt inhibitors.” *Bioorg. Med. Chem. Lett.* **2010,** *20*, 7037-7041.

81) Clarke, P. A.; Sellars, P. B.; Mistry, N. “Diastereoselective synthesis of functionalized 2-methyltetrahydropyran-4-ones.” *Tetrahedron Lett.* **2011,** *52*, 3654-3656.

82) Christoffers, J. “Iron(III) catalysis of the Michael reaction of 1,3-dicarbonyl compounds and enones.” *Chem. Commun.* **1997,** 943-944.

83) Tsubogo, T.; Yamashita, Y.; Kobayashi, S. “Chiral calcium catalysts with neutral coordinative ligands: enantioselective 1,4-addition reactions of 1,3-dicarbonyl compounds to nitroalkenes.” *Angew. Chem. Int. Ed.* **2009,** *48*, 9117-9120.

84) Yadav, J. S.; Reddy, B. V. S.; Venugopal, C.; Padmavani, B. “$InCl_3/SiO_2$-catalyzed α-amination of 1,3-dicarbonyl compounds under microwave irradiation.” *Tetrahedron Lett.* **2004,** *45*, 7507-7509.

85) Hu, J.; Zhu, M.; Xu, Y.; Yan, J. “A novel one-pot method for α-tosyloxylation of ketones using a catalytic amount of ammonium iodide.” *Synthesis* **2012,** *8,* 1226-1232.

86) Xie, X.; Cai, G.; Ma, D. “CuI/L-proline-catalyzed coupling reactions of aryl halides with activated methylene compounds.” *Org. Lett.* **2005,** *7*, 4693-4695.

87) Okonya, J. F.; Hoffman, R. V.; Johnson, M. C. “Synthesis of 2-oxazolone-4-carboxylates from 3-nosyloxy- and 3-bromo-2-ketoesters.” *J. Org. Chem.* **2002,** *67*, 1102-1108.

88) Altuna-Urquijo, M.; Gehre, A.; Stanforth, S. P.; Tarbit, B. “A convenient synthesis of pyridine and 2,2′-bipyridine derivatives.” *Tetrahedron* **2009,** *65*, 975-984.

89) Vaswani, R. G.; Albrecht, B. K.; Audia, J. E.; Côté, A.; Dakin, L. A.; Duplessis, M.; Gehling, V. S.; Harmange, J.; Hewitt, M. C.; Leblanc, Y.; Nasveschuk, C. G.;

Taylor, A. M. “A practical synthesis of indoles via a Pd-catalyzed C–N ring formation.” *Org. Lett.* **2014,** *16*, 4114-4117.

90) Desage-El Murr, M.; Nowaczyk, S.; Le Gall, T.; Mioskowski, C. “Synthesis of pulvinic acid and norbadione A analogues by Suzuki-Miyaura cross-coupling of benzylated intermediates.” *Eur. J. Org. Chem.* **2006,** *2006*, 1489-1498.

91) Brugel, T. A.; Hudlicky, T.; Clark, M. P.; Golebiowski, A.; Sabat, M.; Endoma, M. A. A.; Bui, V.; Adams, D.; Laufersweiler, M. J.; Maier, J. A.; Bookland, R. G.; De, B. “Convergent synthesis of 2,3-bisarylpyrazolones through cyclization of bisacylated pyrazolidines and hydrazines.” *Tetrahedron Lett.* **2006,** *47*, 3195-3198.

92) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. “Asymmetric acylation reactions of chiral imide enolates. The first direct approach to the construction of chiral β-dicarbonyl synthons.” *J. Am. Chem. Soc.* **1984,** *106*, 1154-1156.

93) Lützen, A.; Köll, P. “D-xylose derived oxazolidin-2-ones as chiral auxiliaries in stereoselective acylations and halogenations.” *Tetrahedron: Asymmetry* **1997,** *8*, 29-32.

94) Lorenz, M.; Kalesse, M. “Synthesis of the C10-C32 core structure of Spirangien A.” *Org. Lett.* **2008,** *10*, 4371-4374.

95) Nguyen, H.; Ma, G.; Romo, D. “A1,3-strain enabled retention of chirality during bis-cyclization of β-ketoamides: total synthesis of (–)-salinosporamide A and (–)-homosalinosporamide A.” *Chem. Commun.* **2010,** 4803-4805.

96) Noonan, G. M.; Newton, D.; Cobley, C. J.; Suárez, A.; Pizzano, A.; Clarke, M. L. “Regioselective and enantioselective hydroformylation of dialkylacrylamides.” *Adv. Synth. Catal.* **2010,** *352*, 1047-1054.

97) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. “Catalytic asymmetric Roskamp reaction of α-rlkyl-α-diazoesters with rromatic rldehydes: highly enantioselective synthesis of α-alkyl-β-keto esters.” *J. Am. Chem. Soc.* **2010,** *132*, 8532-8533.

98) Gao, L.; Kang, B. C.; Hwang, G.; Ryu, D. H. “Enantioselective synthesis of α-alkyl-β-ketoesters: asymmetric Roskamp reaction catalyzed by an oxazaborolidinium ion.” *Angew. Chem. Int. Ed.* **2012,** *51*, 8322-8325.

99) Hashimoto, T.; Miyamoto, H.; Naganawa, Y.; Maruoka, K. “Stereoselective synthesis of α-alkyl-β-keto imides via asymmetric redox C–C bond formation between α-alkyl-α-diazocarbonyl compounds and aldehydes.” *J. Am. Chem. Soc.* **2009,** *131*, 11280-11281.

CHAPTER 2

ASYMMETRIC TRANSFER HYDROGENATION-DYNAMIC KINETIC RESOLUTION OF β-STEREOGENIC α-KETO ESTERS

2.1 Introduction

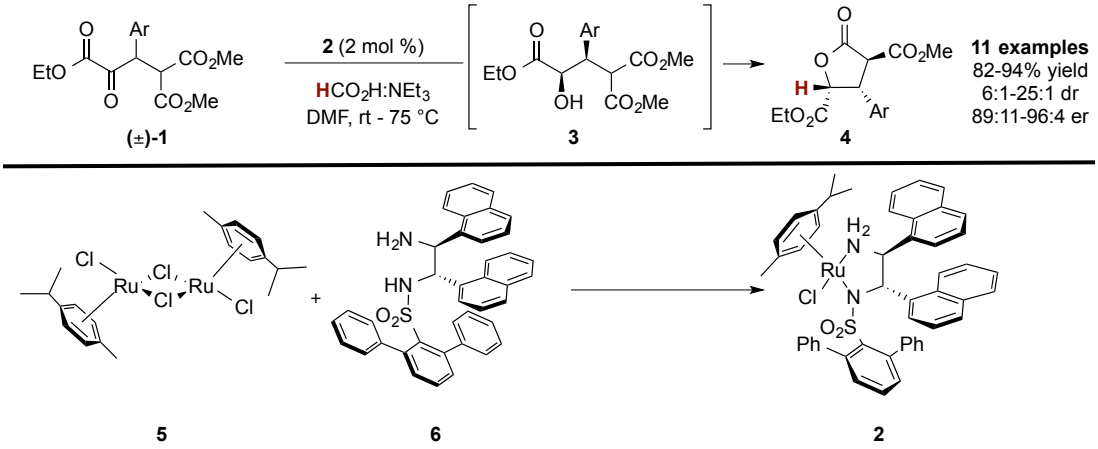
Chapter 1, demonstrated that the use of hydrogenative DKRs with α-substituted β-keto esters has been used to great effect in industrial processes, creating >100 tons of enantioenriched consumer material each year.[1] Previous to our group's involvement, the development an analogous hydrogenative DKR of β-substituted α-keto esters was limited to enzymatic catalysis.[2] In 2012 we reported a ruthenium-catalyzed asymmetric transfer hydrogenation (ATH), of the α-keto ester **1** where initial α-ketone reduction was followed by *in situ* diastereoselective lactonization of intermediate **3** providing tri-substituted γ-butyrolactone **4** in high yield and with excellent stereoselection (Scheme 1).[3]

A number of salient features of this protocol include 1) the use of formic acid as an organic reductant,[4-6] 2) generation of the requisite racemic α-keto esters by a NHC-catalyzed Stetter reaction between ethyl glyoxylate and benzylidene malonates, and 3) deployment of diamino terphenyl sulphonamide ligand **6** for use in ATH reactions.

The operational simplicity of the method is appealing as active ruthenium complex **2** is generated by simple ligation of **6** with $[RuCl_2(p\text{-cymene})]_2$ (**5**), does not require rigorous air free handling, and is stable as a precomplexed solution

for >1 month.[4] The ease of reaction setup, atom economy, and exquisite selectivity demonstrated in the formation of **4** led us to consider what other enantioenriched β-stereogenic α-hydroxy esters could accessed via this methodology. The remainder of this chapter will discuss our subsequent studies in using DKR-ATH processes catalyzed by **2** and related architectures.

Scheme 1. First Highly Enantioselective ATH-DKR of α-Keto Esters for the Formation of β-Aryl γ-Butryolactones



2.2 Chemoselective Dynamic Asymmetric Reduction of α,δ-Diketo Esters*

A primary tenant of our program was providing access to highly stereocomplex and chemically interesting small molecules by ATH-DKR; consequently, we targeted the use of α,δ-diketo ester **7**. We anticipated that under our developed ATH-DKR conditions reduction of the α-ketone followed by diastereoselective reduction of intermediate α-hydroxy δ-keto ester **8** would deliver 1,3-diol **9** (Scheme 2).

Two step conjugate addition/oxidation methods for the preparation of the requisite α,δ-diketo ester **7** were known. These reported modalities of oxidation

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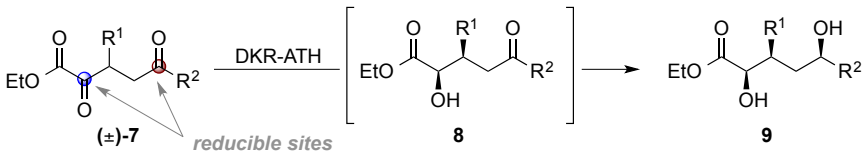
included aerobic deacylation,[7] aerobic oxidation[8] and ozonoloysis of nitronates[9] or enol acetate intermediates.[10] However, we believed that a direct one step Stetter reaction between commercial ethyl glyoxylate and α,β-enones represented the most ideal approach vector to these substrates. While this reaction was unsuccessful utilizing thiazolium carbenes,[10] our group's previous success using the triazolium carbene derived from salt **12**[11] for the formation of **(±)-1**,[4] indicated that a similar strategy might be applicable for the direct synthesis of **7**.

Scheme 2. Proposed ATH-DKR of α,δ-Diketo Esters to Form α,δ-Dihydroxy Esters

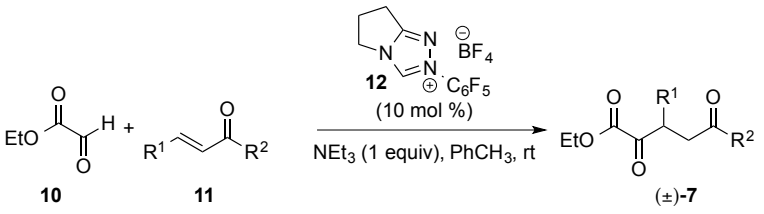


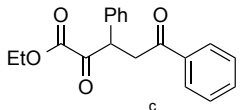
As outlined in Scheme 3, the Stetter addition of ethyl glyoxylate **10** to α,β-enone **11** was efficient, and scalable, yielding a wide array of α,δ-diketo esters **7a-n**. This method was tolerant of diverse ketonic substitution (**7a**-**f**), as well as multiple β-substituents (**7g-n**). Of particular note is that with dibenzylideneacetone **7e**, exclusive monoaddition is observed.

With appropriate substrates in hand, our investigation into the proposed DKR-ATH began with the examination of the reduction of **7a**. As shown in Table 1, our initial studies revealed unexpected chemoselectively for reduction of solely the α-ketone, providing exclusive formation of δ-keto-α-hydroxy ester **8a** as a single diastereomer.

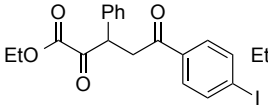
Subjection of **7a** to the previously reported reaction conditions;[4] 2 mol % of $[RuCl_2(p\text{-cymene})]_2$ and diamine ligand **6** (Ru atom:L mole ratio 1:2) in DMF at 70 °C, provided **8a** in 96% yield and a 91:9 er (Table 1, entry 1). Lower levels of selectivity were observed when the reduction was run at room temperature (Table 1, entry 2).

Scheme 3. Scope of the Glyoxylate Stetter Addition with Enones[a,b]

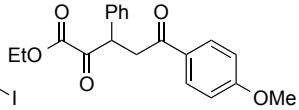




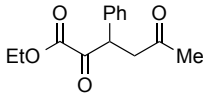
(±)-**7a**[c]
97% yield



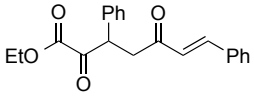
(±)-**7b**
95% yield



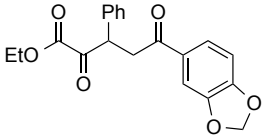
(±)-**7c**
86% yield



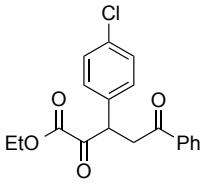
(±)-**7d**
72% yield



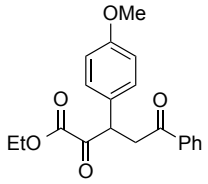
(±)-**7e**
91% yield



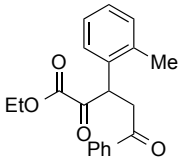
(±)-**7f**
92% yield



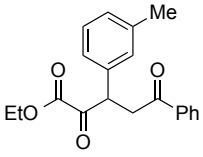
(±)-**7g**
94% yield



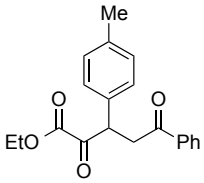
(±)-**7h**
96% yield



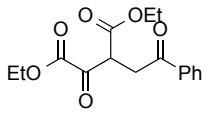
(±)-**7i**
70% yield



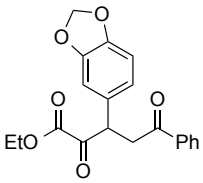
(±)-**7j**
95% yield



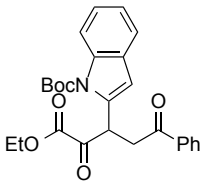
(±)-**7k**
93% yield



(±)-**7l**
92% yield



(±)-**7m**
94% yield

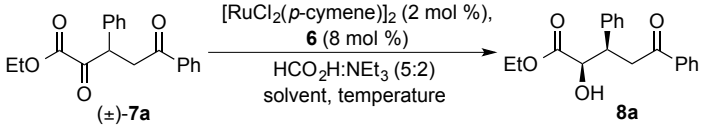


(±)-**7n**
70% yield

(a) Conditions: Unless otherwise noted, all reactions were performed on a 2.0 mmol scale in $PhCH_3$ (4 mL) at ambient temperature. (b) Yields reported are for isolated compounds. (c) Reaction performed on a 20 mmol scale.

Further optimization revealed that higher levels of enantioselectivity (97:3 er) could be obtained by running the reaction in DMSO at room temperature (Table 1, entry 6). The chemoselectivity observed is remarkable as (arene)RuCl(sulfonamide) catalysts have been extensively used for the asymmetric transfer hydrogenation of aryl ketones.[5]

Table 1: Chemoselective DKR-ATH: Reaction Optimization[a]



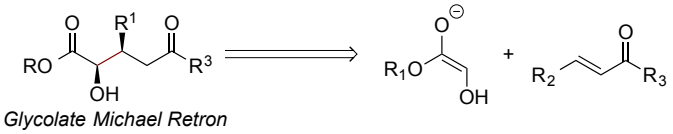
entry	solvent	temperature	yield[b]	er[c]
1	DMF	70 °C	94	91:9
2	DMF	rt	93	87:13
3	2-MeTHF	70 °C	90	65:35
4	DCE	70 °C	91	78:22
5	DMSO	70 °C	96	97:3
6	DMSO	rt	98	97:3

a) All reactions run on a 0.15 mmol scale. *b)* Isolated yield. *c)* Determined by SFC analysis.

Methods for the selective reduction of an aldehyde in the presence of less reactive carbonyls, i.e. ketones and esters, are well-established.[12] Significant progress has been made in achieving the inverse process, the selective reduction of a ketone in the presence of an aldehyde,[13-15] but examples of chemoselective ketone reductions are less documented.[16] The tactic applied in our system takes advantage of the heightened reactivity enjoyed by α-

dicarbonyls and establishes an unusually simple catalytic method for achieving the formal asymmetric glycolate Michael construct (Scheme 4).

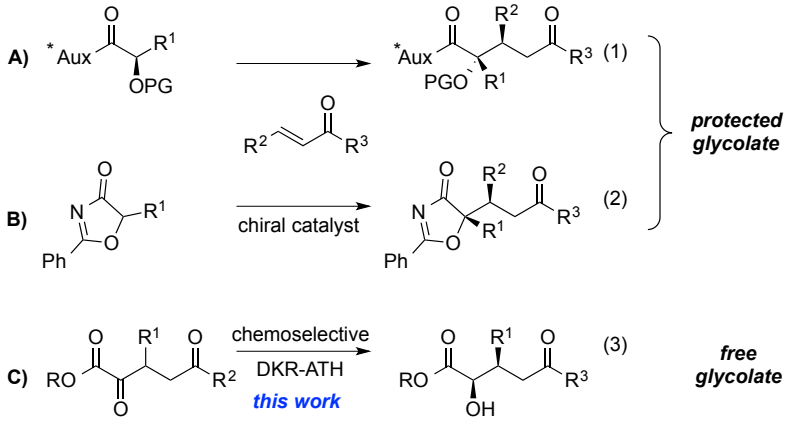
Scheme 4. ATH-DKR of α,δ-Diketo Esters Delivers Formal Glycolate Michael Products



Glycolate Michael Retron

Access to δ-oxygenated glycolic acid derivatives via asymmetric glycolate Michael reactions are limited. The most common approach to this class of compounds is the addition of stoichiometric chiral glycolate enolates to α,β-unsaturated ketones and esters;[17-19] in each case, the protected glycolate is obtained (Scheme 5). Previous to our work, only a single catalytic enantioselective variant had been disclosed using oxazolones as the α-hydroxy acid surrogate (Scheme 5B).[20]

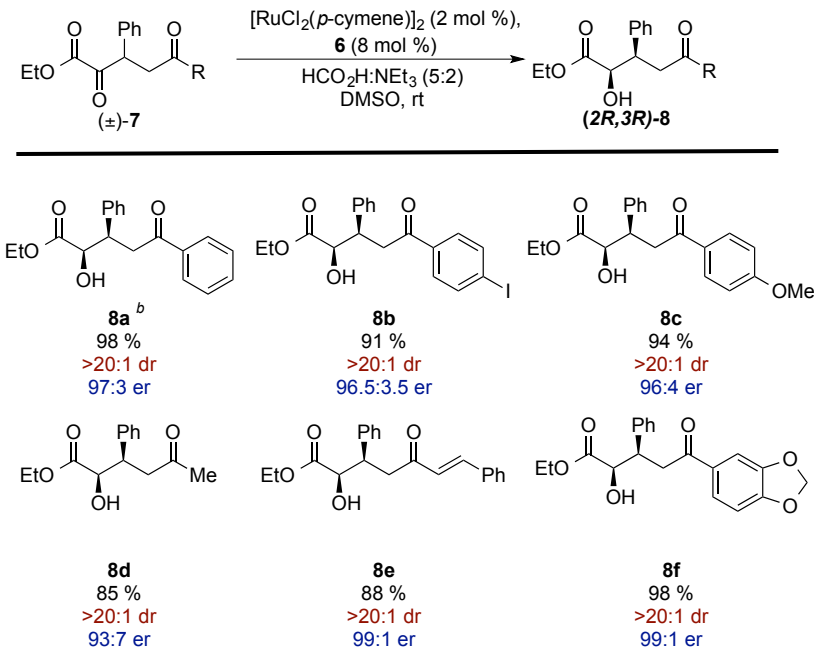
Scheme 5. Strategies to Access δ-Oxygenated Glycolic Acid Derivatives



With optimal reduction conditions to afford these formal glycolate Michael products already in hand, we next explored the generality of this chemoselective dynamic reduction. For all substrates examined, exclusive reduction of the α-keto

ester with perfect diastereoselectivity was observed, irrespective of the electronic characteristics of the δ-ketone (Scheme 6).

Scheme 6. Variation of δ-Ketone in the Chemoselective ATH-DKR of α,δ-Diketo Esters[a]

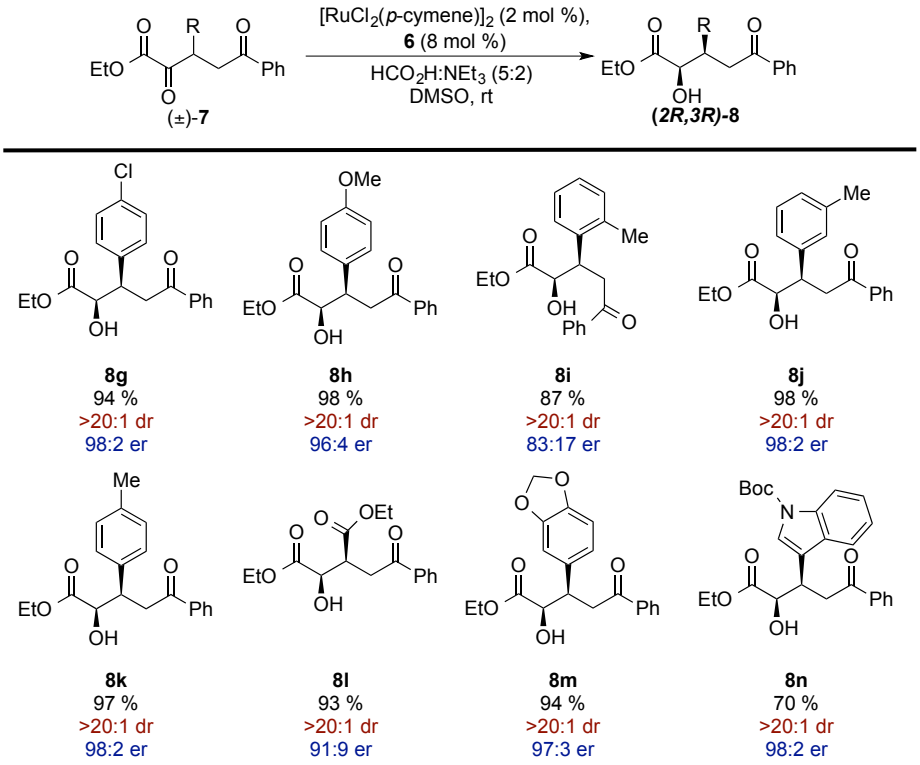


a) Yields are of isolated compounds. Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. Enantiomeric ratio determined by SFC analysis. b) Reaction performed using 0.05 mol % of $[RuCl_2(p\text{-cymene})]_2$.

High yields and enantioselectivites were obtained with both electron-poor (**8b**) and electron-rich (**8c**) aryl ketones. Use of a non-aromatic methyl ketone gave **8d** in 85% yield and 93:7 dr while enone **8e** was provided in 99:1 er with no over-reduction observed. To demonstrate the catalytic efficiency of this system, the reduction of **7a** was performed using 0.05 mol% of $[RuCl_2(p\text{-cymene})]_2$ dimer; no loss in reaction efficiency was observed as **8a** was obtained in 98:2 er.

Modulation of the β-position to include electron rich and electron poor arenes had no deleterious effects on selectivity. Sterically encumbered **8i** was obtained in 87% yield with 83:17 er. Incorporation of a nonaromatic ester at the β-position provided **8l** with 91:9 er. Changing the β-substitutent to heteroaromatic indole delivered **8n** with 98:2 er (Scheme 7).

Scheme 7. Variation of the β-Substitutent in the Chemoselective ATH-DKR of α,δ-Diketo Esters[a]

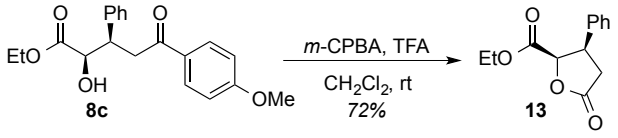


a) Yields are of isolated compounds. Diastereomeric ratio determined by ^{1}H NMR analysis of crude reaction mixture. Enantiomeric ratio determined by SFC analysis. b) Reaction performed using 0.05 mol % of [$RuCl_2$(*p*-cymene)]$_2$.

The absolute configuration and *syn*-stereochemical relationship of the α-hydroxy ester products were determined by converting **8c** to lactone **13** via a

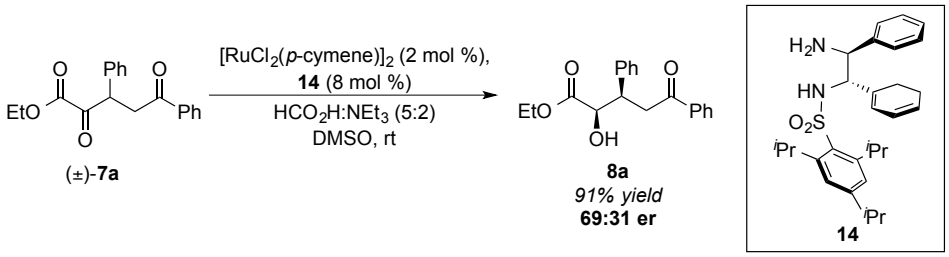
Baeyer-Villiger oxidation and subsequent *in situ* lactonization. Spectral data were in agreement with those reported in the literature (Scheme 8).[4]

Scheme 8. Stereochemical Analysis of δ-Keto α-Hydroxy Esters



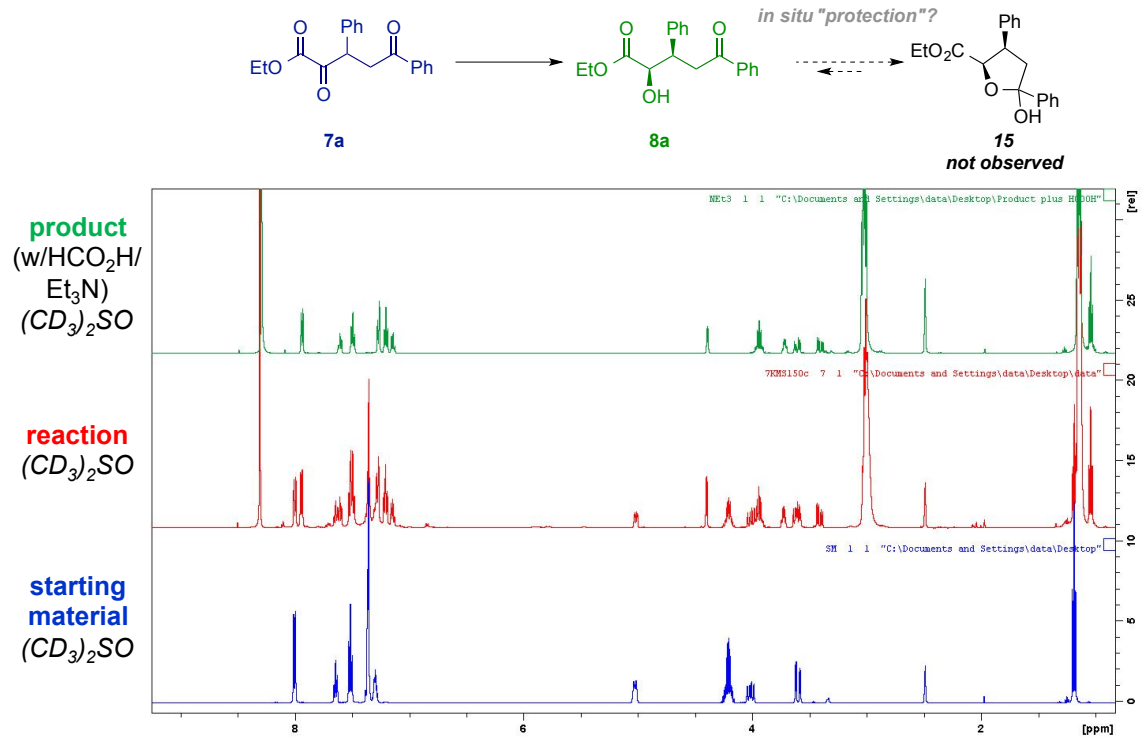
To determine if the $[RuCl_2(p\text{-cymene})]_2$/diamine **6** catalyst system was uniquely effective for the reduction of α-keto esters, the chemoselectivity of transfer hydrogenation catalysts known to reduce simple ketones was evaluated with **7a**. The use of **14** in the reduction, a known ligand for the reduction of acetophenone (this reduction was performed during the course of this study), also afforded **8a** as the sole product, albeit only 69:31 er (Scheme 9).

Scheme 9. Investigation into Observed Chemoselectivity of ATH-DKR



This result caused us to wonder if the δ-ketone was possibly undergoing *in situ* "protection" as a lactol following reduction of the α-keto ester with this intermediate masking the δ-ketone from further reduction. To test this hypothesis, the reduction was monitored by ^1H NMR spectroscopy in DMSO-d^6, but formation of lactol **15** was not detected: only the diketo ester **7a** and hydroxy ester **13a** were observed (Scheme 10).

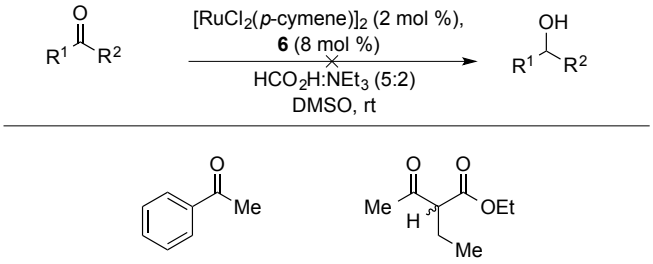
Scheme 10. ^{1}H NMR Showing Absence of *in situ* Lactol Formation



We also examined the transfer hydrogenation of several other ketone substrates using the standard reaction conditions outlined in Scheme 6. Interestingly, acetophenone and ethyl 2-ethyl-3-oxobutanoate, which are typically the test substrates for new transfer hydrogenation catalysts, are not reduced with this catalyst system (Scheme 11), suggesting the catalyst has a distinct preference for electronically activated α-keto esters.

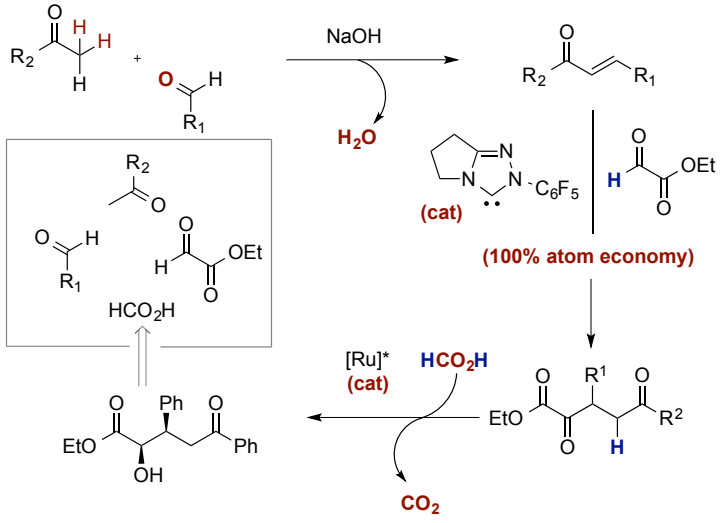
In summary, our investigations into the ATH-DKR of α,δ-diketo esters revealed a formal asymmetric glycolate Michael process via chemoselective reduction of the α-ketone. The requisite α-keto esters were prepared via a previously unreported carbene-catalyzed glyoxylate Stetter reaction. The reduction proceeds with high enantio- and diastereoselectivity for a number of electronic- and functionally rich substrates.

Scheme 11. Chemoselectivity of the [RuCl$_2$(*p*-cymene)]$_2$/Diamine 6 Catalyst System



The overall process for the generation of these β-substituted glycolates is highly atom efficient with the only stoichiometric byproducts generated being water (in the formation of the enones) and CO_2 (in the ATH-DKR). Two of the reaction steps are catalytic and the Stetter reaction proceeds with complete atom economy. Overall, the α-hydroxy ester **8** is in created in three operationally simple steps, with high ee, from four inexpensive and nontoxic starting materials (Scheme 12).

Scheme 12. Atom Economy in the Synthesis of β-Substituted α-Hydroxy Esters



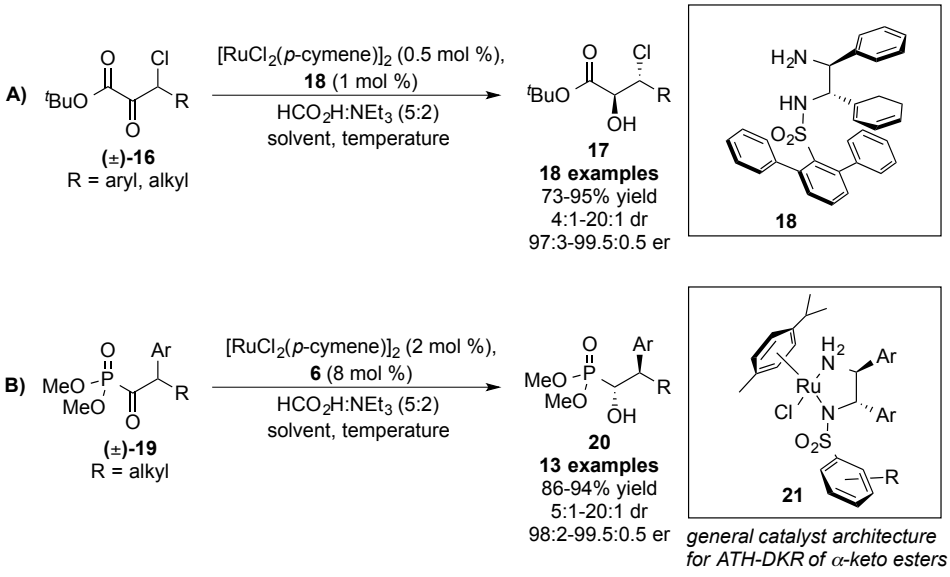
As it pertains to the origin of the observed chemoselectivity our investigations suggest that the [RuCl$_2$(*p*-cymene)]$_2$ /**6** catalyst system is uniquely

effective for the reduction of electronically activated α-keto esters, as other ketone substrates are unreactive under the standard reaction conditions.

2.3 Asymmetric Synthesis of *anti*-β-Amino-α-Hydroxy Esters via Dynamic Kinetic Resolution of β-Amino-α-Keto Esters**

Concurrent with the reduction of α,δ-diketo esters discussed in Chapter 2 Sections 2 and 3, our group also disclosed the DKR-ATH of β-chloro α-keto ester **16** to β-hydroxy ester **17**. For this substrate class the highest stereoselection was obtained using $[RuCl_2(p\text{-cymene})]_2$ in combination with diphenylethylenediamine derived ligand **18** (Scheme 13A).[21] Subsequently, we disclosed the DKR-ATH of β-aryl α-keto phosphonates using the originally disclosed ruthenium complex **3**. This transformation provides **20** with exquisite stereoselectivity; although of some curiousity is that the observed relative stereochemistry of this reduction is contrary to that observed in the reduction of β-aryl α-keto ester **1** (Scheme 13B).[22]

Scheme 13. Recent Developments in the ATH-DKR of α-Keto Esters and Congeners



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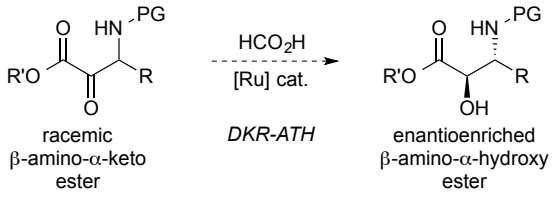
As the presence of α-hydroxy-β-amino acids in biologically important structures is well-documented,[23-27] we began studies to elucidate whether the Ru (II) catalyst system would promote the highly stereoselective reduction of β-amino α-keto esters (Scheme 14).

Scheme 14. Proposed ATH-DKR of β-Amino α-Keto Esters

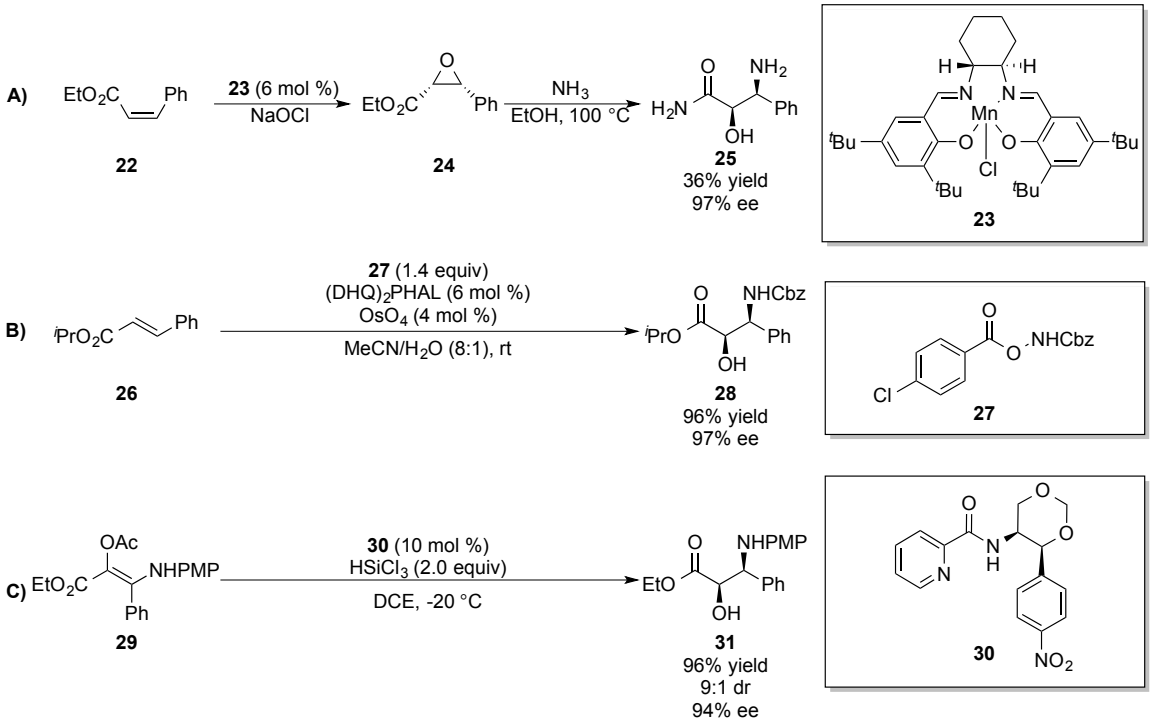


Driven by their pharmaceutical importance, multiple methods for accessing enantioenriched variants of β-amino α-hydroxy esters have been reported.[28-39] The use of alkene starting materials is common. For example, Jacobsen has reported diastereoselective nucleophile opening of chiral epoxides using manganese (III) salen **23** furnishing amino alcohol **25** via the intermediacy of chiral epoxide **24** (Scheme 15A).[28-30] Oxyamination of alkene **26** using Sharpless aminohydroxylation provides *syn* β-amino α-hydroxy ester **28** in good yield and enantioselection with hydroxycarbamate **25** serving as the source of both oxygen and nitrogen (Scheme 15B)[31-35] Zhang has reported the asymmetric hydrosilylation of α-acetoxy-β-enamino ester **29** affording *syn* α-acetoxy β-amino ester **31** (Scheme 15C).[36]

Additional synthetic routes for β-amino α-hydroxy acids, which do not utilize alkene starting materials have also been reported.[37-39] For example, Terada utilizes oxidation and subsequent reduction of chiral β-amino-α-diazo ester **32** where the enantiodetermining step is a chiral phosphoric acid catalyzed

Mannich reaction with *tert*-butyl diazoacetate. The oxidation occurs without racemization and the reduction proceeds with perfect diastereoselectivity yielding *anti* β-amino α-hydroxy ester **33** (Scheme 16A).[40] Both asymmetric[41] and diastereoselective[42] Henry reactions with subsequent nitro-group reduction have also been reported. Of these, the most efficient for both number of steps and stereoselectivity utilizes chiral glyoxylate **34** giving α-hydroxy ester **35** in 81% yield and 87:13 dr (Scheme 16B).[43]

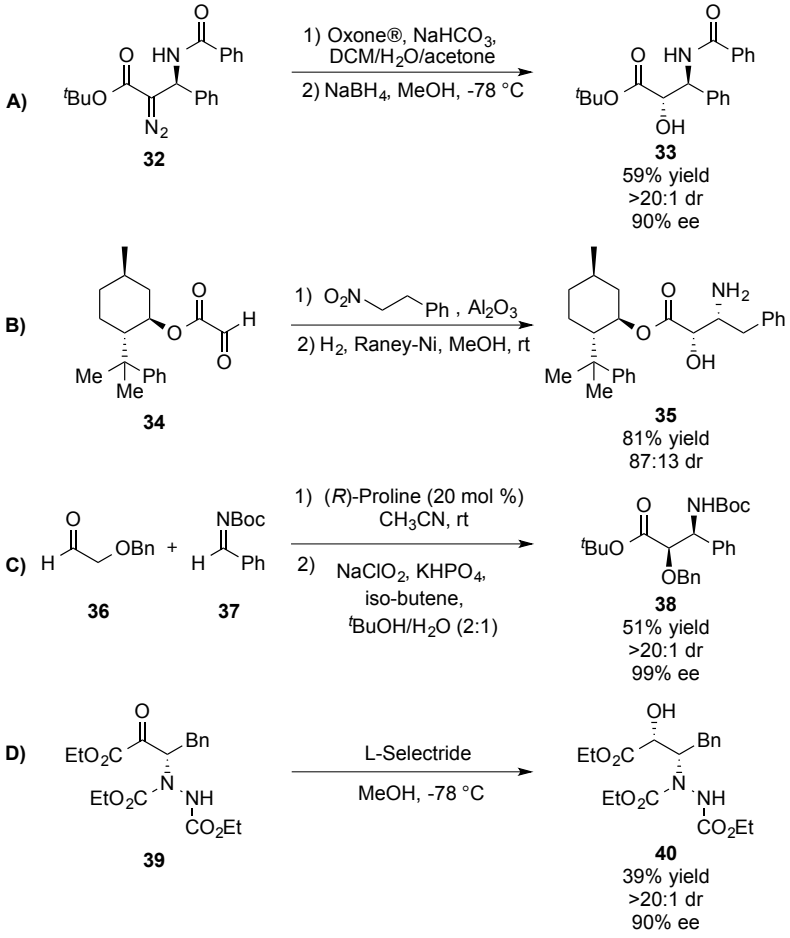
Scheme 15. Synthesis of β-Amino α-Hydroxy Esters from Alkenes



Access to β-amino α-hydroxy esters was also reported using asymmetric "glycolate" Mannich reactions where aldehyde **36** undergoes a proline catalyzed Mannich addition and subsequent Pinnick oxidation to reveal formal glycolate Mannich product **38** in 51% yield with nearly perfect stereoselectivity (Scheme 16C).[44,45] Asymmetric β-amination of α-keto esters catalyzed by chiral

bisoxazoline-copper (II) complexes provides β-amino α-oxo ester **39**, which is reduced to β-amino α-hydroxy ester **40** using L-Selectride (Scheme 16D).[46] Somfai has also disclosed synthesis of β-amino α-hydroxy esters by tosic acid cleavage of oxazolidinones (formed via 1,3 dipolar cycloadditions), however attempts to render the latter enantioselective resulted in only 24% ee.[47]

Scheme 16. Multistep Syntheses of β-Amino α-Hydroxy Esters



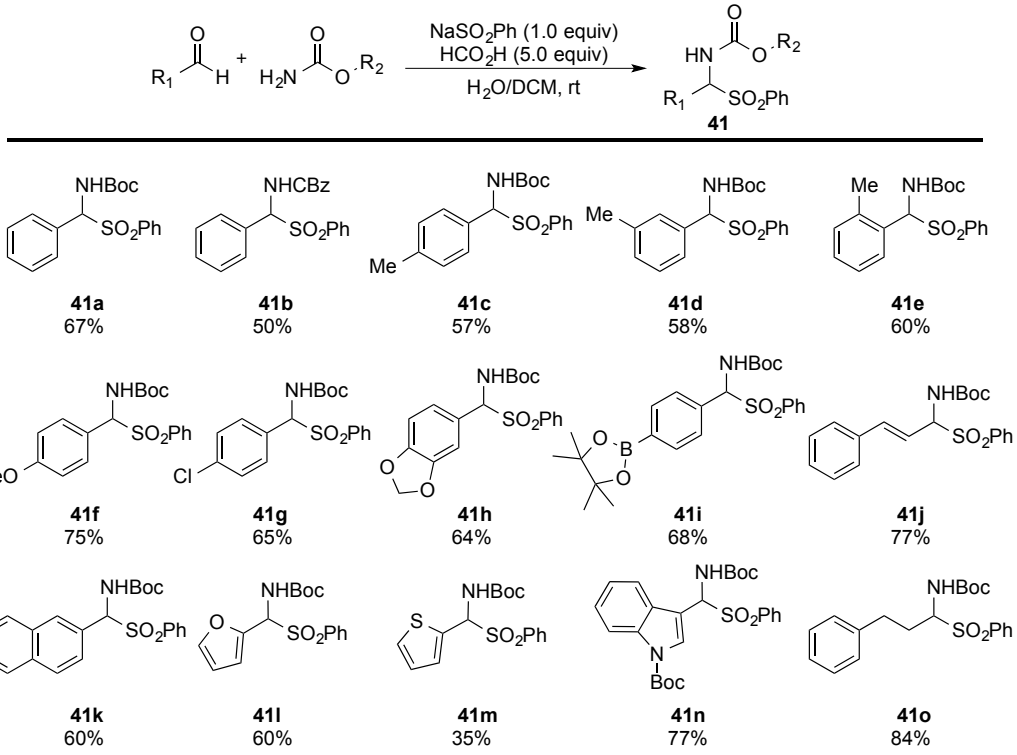
In assessing these various methods, we noticed that few afforded products with easily manipulated protecting groups while simultaneously setting both stereocenters in a single transformation. Additionally, there was a dearth of systems that gave access to enantioenriched *anti* β-amino α-hydroxy esters.[40,49-

[51] We believed that these synthetic issues could be addressed using our previously described ATH-DKR to provide facile access to enantioenriched β-amino-α-hydroxy esters from β-amino α-keto esters.

In principle, the most atom-efficient route towards the requisite β-amino-α-keto esters would be a glyoxylate aza-benzoin reaction mediated by a NHC catalyst. Suitable precedent for aza-benzoin reactions,[52,53] in combination with our recent success using NHC-catalyzed glyoxylate acyl anion equivalents[4,21] suggested that this disconnection was feasible.

Due to ease of handling and overall stability profile, we elected to use amido-sulfones **41** as a synthetic precursor to the necessary imines.

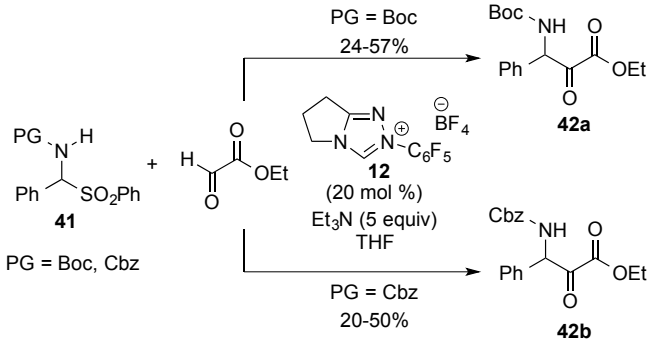
Scheme 17. Synthesis of Amido Sulfones



These masked imines are readily available via condensation of carbamate and aldehyde, followed by addition of sulfinate to the formed iminium (Scheme 17).[53,54]

With amido sulfones in hand we used the triazolium carbene derived from **12** to effect aza-benzoin addition of ethyl glyoxylate into the *in situ* formed imines (Scheme 18). However, β-amino α-keto esters **42a** and **42b** were obtained in low and variable yields and proved unstable under all silica gel purification protocols tested, making this an unsuitable method for scalable synthesis.

Scheme 18. Attempts at the Aza Benzoin Addition of Ethyl Glyoxylate into *in situ* Generated Aldimines



Despite its inefficiency, this method did provide us with sufficient amounts of the desired α-keto ester with which to examine the DKR-ATH for proof of concept. Guided by our previous works[4] we began by screening catalyst complexes **3** and **21** which arise from diarylethylene diamine monosulfonamide ligands and $[RuCl_2(p\text{-cymene})]_2$.[4,5,55,56] The use of complex **21a** for an ATH-DKR of **42** afforded complete *anti* diastereoselection but low enantioselection. Switching to complex **3** maintained high dr concurrent with high enantioselection for both Cbz- and Boc-protected amines, with Cbz providing slightly higher enantioselectivity (Table 2, entries 2 and 3). When the solvent was changed from

DMSO to DMF, an increase in selectivity for the Boc protected **43a** was observed (Table 2, entry 4).

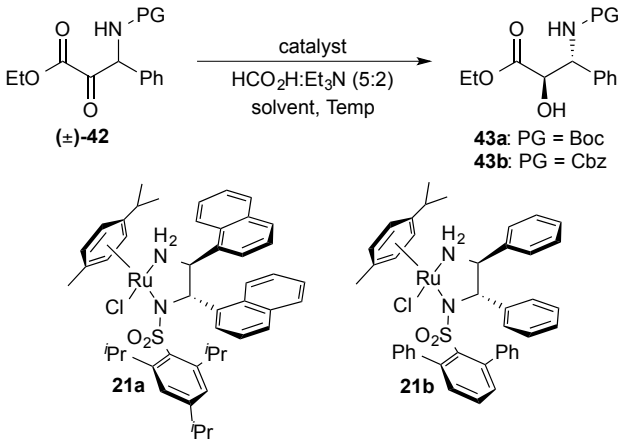
Searching for higher selectivity, we switched to complex **21b**, which gave **42a** in 99:1 er (Table 1, entry 5). Due to the observation of retro-Mannich products in the crude reaction mixture (by ^{1}H NMR) we attempted to subvert this pathway lowering the temperature to 0 °C; however, this change only resulted in decreased yield (Table 1, entry 6). This brief optimization study revealed that high levels of enantioselectivity can be obtained with two convenient carbamate protecting groups through judicious selection of catalyst. Due to the superior enantioselection using Boc-protected amine, it was selected as the protecting group for our subsequent studies. With proof of concept for the DKR-ATH established, attention returned to improving the synthesis of the requisite β-amino-α-keto esters.

A survey of the literature revealed conditions reported by Wang and coworkers, which proved effective for generation of β-sulfonamido-α-keto esters.[58] This route employs pre-generating *N*-sulfonyl imines from the corresponding amido sulfones followed by Mannich addition of ethyl diazoacetate (Scheme 19).

On the basis of precedent, subsequent oxidation was expected to furnish α-keto esters primed for reduction.[40,58] This general strategy has previously been exploited to access enantioenriched β-amino α-hydroxy esters via asymmetric Mannich addition followed by diastereoselective reduction.[40] Our hope was to

develop a method in which both stereocenters would be set during the reduction from a racemic starting material.

Table 2: DKR-ATH of β-amino α-Keto Ester Optimization

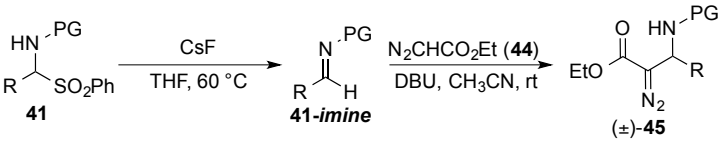


Trial	PG	Complex	Solvent	Temp (°C)	Yield[b] (%)	dr[c]	er[d]
1	Boc	**21a**	DMSO	rt	59	>20:1	77:23
2	Boc	**21b**	DMSO	rt	67	>20:1	94:6
3	Cbz	**3**	DMSO	rt	77	>20:1	97:3
4	Boc	**3**	DMF	rt	65	>20:1	97:3
5	Boc	**21b**	DMF	rt	73	>20:1	99:1
6	Boc	**21b**	DMF	0	62	>20:1	98:2
7	Cbz	**21b**	DMF	rt	71	>20:1	94:6

[a)]Reaction optimization took place using a crude mixture of compounds obtained via aza-benzoin reaction which included the desired starting material (cf. Scheme 18). [b)]Isolated yield calculated based on the assumption of pure α-keto ester starting material; actual yields are probably somewhat higher. [c)]Determined by ^{1}H NMR analysis of crude reaction mixture. [d)]Determined by chiral HPLC or SFC analysis.

The described Mannich reaction was conducted at room temperature for all aromatic substituted aldimines, and at -40 °C for aliphatic substrates to subvert enamine formation (Scheme 20). As expected the DBU catalyzed Mannich addition delivered a wide array of β-amino α-diazo esters for conversion into β-amino α-hydroxy esters.

Scheme 19. Literature Precedented Mannich Addition

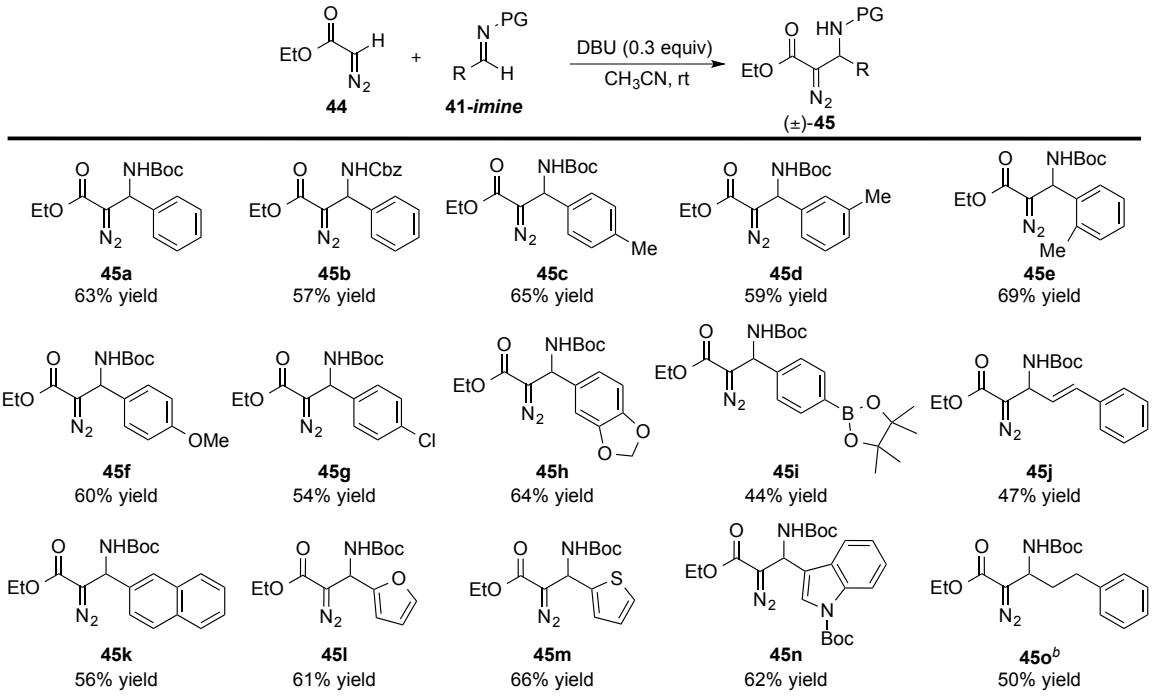


With α-diazo esters in hand, we then turned to a two-step oxidation-reduction sequence (Scheme 21). We employed previously described conditions for oxidation of α-diazo esters to their corresponding α-keto esters using commercially available Oxone®.[40] As we had anticipated using this protocol, the unchromatographed α-keto esters were sufficiently pure for direct use in the optimized reduction conditions: exposure of β-amino-α-keto esters (±)-**42** to Ru-complex **21b** and HCO_2H/Et_3N yielded products **43a-o** (Scheme 21).

Our substrate scope sought to probe both electronic and steric controls for this reaction system. Heteroaromatic (**43l-43m)** as well as electron-rich (**43f-43h)** and -poor (**43g)** aromatic systems all provide high dr and enantioselectivity. Additionally, **43j** showed only reduction of the α-ketone leaving the alkene intact, although the reaction proceeded with negligible diastereoselectivity. Products **43c-43e** showed that while steric encumbrance does affect the dr, enantioselectivity remained high. In testing **46o** for the application of this method towards aliphatic β-substitution, we observed full reduction of the ketone, albeit with low stereoselectivity.

As was already noted, this reaction is tolerant to different amine protecting groups (**4a** and **4b)** providing further flexibility in substrate design. The resultant alcohols are often solids and a single recrystallization could regularly provide er values above 99.5:0.5 (parenthetical values in Scheme 21).

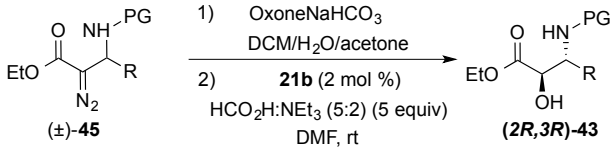
Scheme 20. Substrate Scope for the Mannich Addition of Ethyl Diazoacetate

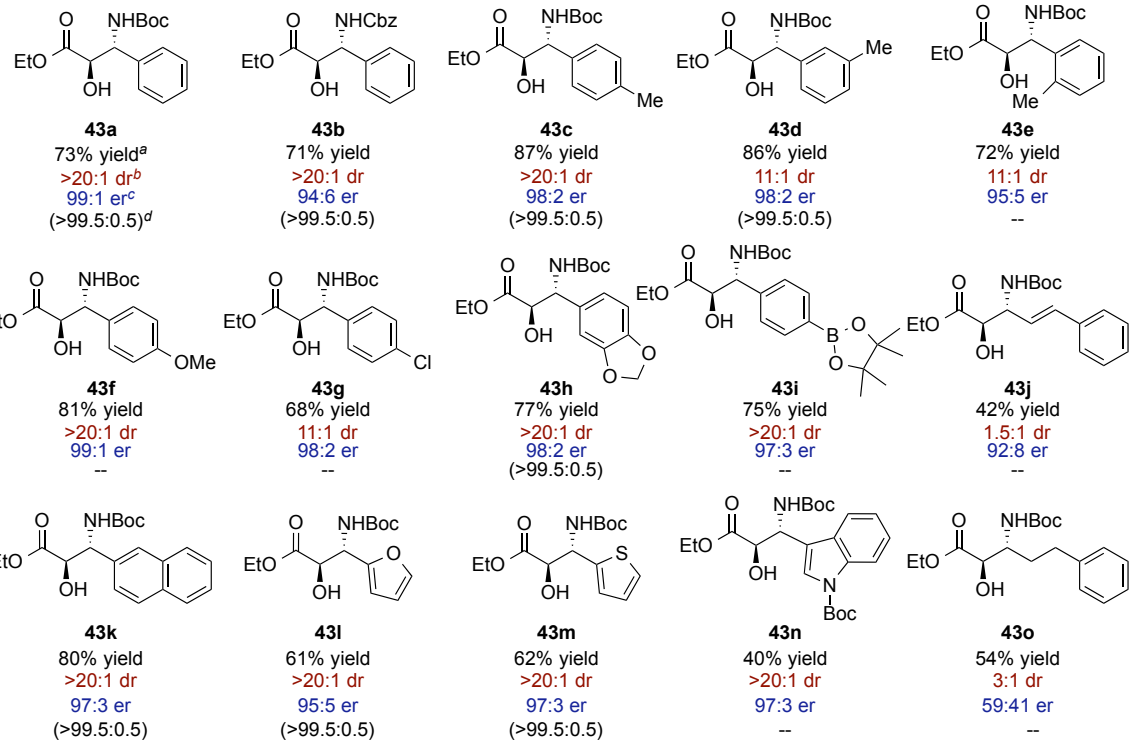


a) The imine **41** was generated from the corresponding amido sulfone (see section 2.5.3 for details). Isolated yields over the two steps are reported. *b)* Mannich addition conducted at -40 °C.

To determine the stereochemistry imparted by the DKR-ATH, (+)-**43b** was independently synthesized from the known enantioenriched epoxide **46** (Scheme 22A).[59] The stereochemistry was then assigned based on comparison of this product and (-)-**43b (**prepared by DKR-ATH, Scheme 21) using ^{1}H NMR and chiral SFC analysis. Lastly, the utility of Boc and Cbz protecting groups was demonstrated by the deprotection of **43a** under acidic conditions and **43b** with trimethylsilyl iodide, both of which resulted in free amine (-)-**47** (Scheme 22B).

Scheme 21. Substrate Scope for the ATH-DKR of β-Amino α-Keto Esters

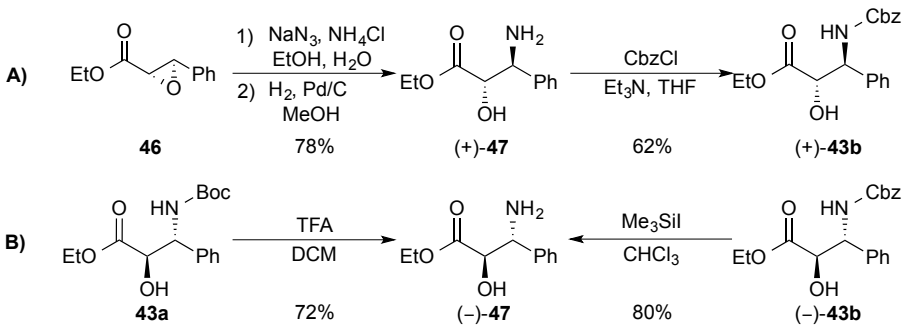




a) Isolated yields are reported. *b)*Determined by ^{1}H NMR analysis of crude reaction mixture. *c)*Determined by chiral HPLC or SFC analysis. *d)*Recrystallized er values are in parentheses

Our investigations resulted in a simple and practical implementation of racemic β-amino-α-keto esters for synthetic access to enantiomerically enriched *anti*-β-amino-α-hydroxy esters via DKR-ATH. The net effects of our studies include the expansion of the product classes that are known to be accessible via ATH-DKR using terphenyl-based catalysts **3** and **21b** while delivering a biologically relevant small molecule in a conveniently configured form.

Scheme 22. Determination of Product Stereochemistry and Synthesis of Free Amine



At this point in our study of the ATH-DKR of α-keto esters, we felt catalyst architecture **21** was proven to be both robust and general to a wide array of β-substituted α-keto esters. Therefore in order to continue to progression of the field we decided to shift focus from developing hydrogenative DKR's dynamic methods that occur via carbon nucleophile additions to β-stereogenic α-keto esters.

2.4 Experimental Data and Conditions for the Chemoselective Dynamic Asymmetric Reduction of α,δ-Diketo Esters[‡]

2.4.1 General Information

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, bs = 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, AS, OD, and WO 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 ºC. 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 Whatman or Sorbtech 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate

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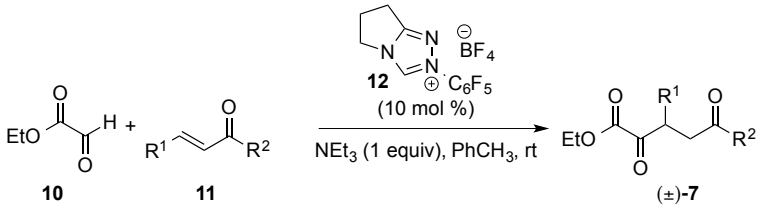
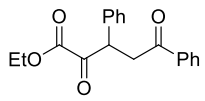
solution followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle. All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of 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: enones were prepared according to known procedures. Ethyl glyoxylate was purchased from Sigma Aldrich as a 40% solution in toluene and distilled under reduced pressure prior to use (the concentration after distillation was determined by ^{1}H NMR spectroscopy). *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 (NEt_3) 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.

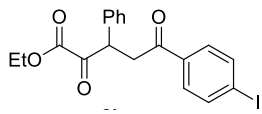
2.4.2 General Procedure A for the Preparation of β-Substituted α,δ-Diketo Esters 7a-n



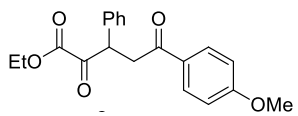
To a flame-dried 10-mL round-bottomed flask equipped with a magnetic stir bar were added enone **11** (2.0 mmol, 1.0 equiv), ethyl glyoxylate **10** (4.0 mmol, 2.0 equiv) and triazolium salt **12** (0.40 mmol, 0.20 equiv). The flask was sealed with a rubber septum and purged with nitrogen. Toluene (0.5 M concentration with respect to enone) followed by triethylamine (2.0 mmol, 1.0 equiv) were then added. The reaction was stirred at room temperature for 16 h and diluted with ethyl acetate and water. The organic layer was washed with brine and dried over sodium sulfate. Concentration *in vacuo* afforded the β-substituted α,δ-diketo esters which were purified by flash chromatography using the indicated solvent systems.



Ethyl 2,5-dioxo-3,5-diphenylpentanoate (7a): The title compound was prepared according to General Procedure A on a 20 mmol scale. Flash chromatography (20% EtOAc/hexanes) provided **7a** (6.02 g, 19.4 mmol, 97% yield) as a white solid. Analytical data for **7a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.2 Hz, 2H) 7.58-7.56 (m, 1H), 7.47-7.44 (m, 2H), 7.36-7.35 (m, 4H), 7.31-7.29 (m, 1H), 5.16 (dd, *J* = 10.8 Hz, 3.6 Hz, 1H), 4.32-4.24 (m, 2H), 4.04 (dd, *J* = 18 Hz, 10.8 Hz, 1H), 3.44 (dd, *J* = 18 Hz, 3.6 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.4, 192.2, 160.3, 135.9, 135.3, 133.5, 129.1, 128.9, 128.6, 128.2, 128.0, 62.5, 48.4, 43.2, 13.9; **IR** (thin film, cm^{-1}): 1669, 1494, 1450, 1400, 1362, 1277, 1207, 1098, 1036, 844, 751, 689, 563; **m.p.** 128-130 ºC; **TLC** (20% EtOAc/hexanes) R_f: 0.33; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{19}H_{19}O_4$: 311.1283, Found: 311.1281.

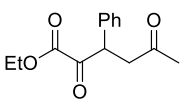


Ethyl 5-(4-iodophenyl)-2,5-dioxo-3-phenylpentanoate (7b): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7b** (0.829 g, 1.90 mmol, 95% yield) as a white solid. Analytical data for **7b**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.38-7.28 (m, 5H), 5.14 (dd, *J* = 10.8 Hz, 4.0 Hz, 1H), 4.34-4.21 (m, 2H), 3.97 (dd, *J* = 10.8 Hz, 18.2 Hz, 1H), 3.36 (dd, *J* = 18.2 Hz, 4.0 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 196.7, 192.0, 160.2, 138.0, 135.2, 135.1, 129.5, 129.2, 128.8, 128.0, 101.6, 62.6, 48.4, 42.9, 13.9; **IR** (thin film, cm^{-1}): 1728, 1681, 1581, 1494, 1455, 1394, 1274, 1204, 1097, 1037, 1002, 818, 753, 700, 560; **m.p.** 131-134 ºC; **TLC** (20% EtOAc/hexanes) R_f: 0.42; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{19}H_{18}IO_4$: 437.0250, Found: 437.0254.

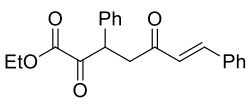


Ethyl 5-(4-methoxyphenyl)-2,5-dioxo-3-phenylpentanoate (7c): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7c** (0.585 g, 1.72 mmol, 97% yield) as a yellow solid. Analytical data for **7c**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.93 (d, *J* = 9.0 Hz, 2H), 7.35-7.33 (m, 4H), 7.30-7.28 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.13 (dd, *J* = 10.8 Hz, 3.6 Hz, 1H), 4.33-4.24 (m, 2H), 3.99 (dd, *J* = 18.0 Hz, 10.8 Hz, 1H), 3.86 (s, 3H), 3.40 (dd, *J* = 18.0 Hz, 3.6 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 195.9, 192.3, 163.8, 160.4, 135.5, 130.5, 129.1, 129.0, 127.9, 113.8, 62.5, 55.5, 48.4, 43.1, 13.9; **IR** (thin film, cm^{-1}): 2360, 1726, 1669, 1600, 1509, 1454, 1421, 1260, 1169, 1030, 833, 699; **m.p.** 118-120 ºC; **TLC** (20%

EtOAc/hexanes) R_f: 0.26; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{20}H_{21}O_5$: 341.1389, Found: 341.1392.

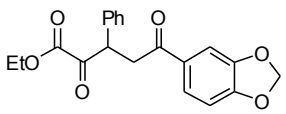


Ethyl 2,5-dioxo-3-phenylhexanoate (7d): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7d** (0.357 g, 1.44 mmol, 72% yield) as a clear oil. Analytical data for **7d**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.96 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H), 4.30-4.20 (m, 2H), 3.50 (dd, *J* = 18.0 Hz, 10.8 Hz, 1H), 2.85 (dd, *J* = 18.0 Hz, 4.2 Hz, 1H) 2.20 (s, 3H), 1.29 (t, *J* = 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 205.9, 192.2, 160.3, 135.1, 129.1, 128.8, 127.9, 62.4, 48.5, 47.0, 29.5, 13.8; **IR** (thin film, cm^{-1}): 2984, 1729, 1455, 1363, 1271, 1165, 1098, 1027, 752, 700, 516; **TLC** (20% EtOAc/hexanes) R_f: 0.28; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{14}H_{17}O_4$: 249.1127, Found: 249.1121.

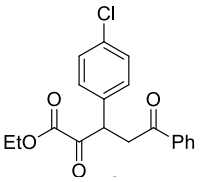


(*E*)-Ethyl 2,5-dioxo-3,7-diphenylhept-6-enoate (7e):The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7e** (0.612 g, 1.82 mmol, 91% yield) as a clear oil. Analytical data for **7e**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.57 (d, *J* = 16.2 Hz, 1 H), 7.53-7.52 (m, 2H), 7.40-7.38 (m, 3H), 7.36-7.32 (m, 4H), 7.30-7.28 (m, 1H), 6.72 (d, *J* = 16.2 Hz, 1H), 5.07 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.32-4.22 (m, 2H), 3.74 (dd, *J* = 18.0 Hz, 10.2 Hz, 1H), 3.14 (dd, *J* = 18.0 Hz, 4.2 Hz, 1H), 1.29 (t, *J* = 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.2, 192.2, 160.4, 143.6, 135.4, 134.2, 130.7, 129.1, 129.0, 128.8, 128.3, 127.9, 125.3, 62.4, 48.4, 44.6, 13.9; **IR** (thin film, cm^{-1}): 2360, 1727, 1655, 1610, 1494, 1451, 1337,

1274, 1176, 1070, 1035, 753, 699; **TLC** (20% EtOAc/hexanes) R_f: 0.34; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{21}H_{21}O_4$: 337.1440, Found: 337.1447.

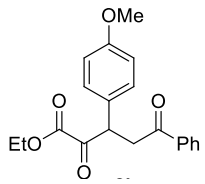


Ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2,5-dioxo-3-phenylpentanoate (7f): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7f** (0.652 g, 1.84 mmol, 92% yield) as a clear oil. Analytical data for **7f**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 1 H), 7.39 (s, 1H), 7.34-7.33 (m, 4H), 7.29-7.27 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.02 (s, 2H), 5.12 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H), 4.32-4.22 (m, 2H), 3.95 (dd, 18.0 Hz, 10.8 Hz, 1H), 3.35, (dd, *J* = 18.0 Hz, 3.6 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 195.3, 192.2, 160.3, 152.0, 148.1, 135.3, 130.7, 129.0, 128.8, 127.9, 124.5, 107.8, 107.8, 101,9, 62.4, 48.4, 43.0, 13.8; **IR** (thin film, cm^{-1}): 1727, 1670, 1603, 1488, 1444, 1365, 1254, 1091, 1036, 932, 809, 753, 700; **TLC** (20% EtOAc/hexanes) R_f: 0.29; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{20}H_{19}O_6$: 355.1182, Found: 355.1179.

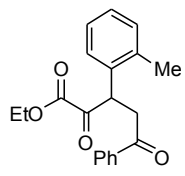


Ethyl 3-(4-chlorophenyl)-2,5-dioxo-5-phenylpentanoate (7g): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7g** (0.648 g, 1.88 mmol, 94% yield) as a clear oil. Analytical data for **7g**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.59-7.56 (m, 1H), 7.48-7.44 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.13 (dd, *J* = 10.4 Hz, 4.0 Hz, 1H), 4.36-4.23 (m, 2H), 3.99 (dd, *J* = 18.4 Hz, 10.4 Hz, 1H), 3.43 (dd, *J* = 18.4 Hz, 4.0 Hz, 1H), 1.33 (t, *J* = 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ

197.1, 191.8, 160.2, 135.7, 134.0, 133.9, 133.6, 130.2, 129.3, 128.7, 128.2, 62.7, 47.7, 43.1, 13.9; **IR** (thin film, cm^{-1}): 2983, 1729, 1681, 1596, 1490, 1449, 1273, 1207, 1092, 1037, 761, 688, 563;**TLC** (20% EtOAc/hexanes) R_f: 0.38; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{19}H_{18}ClO_4$: 345.0894, Found: 345.0894.

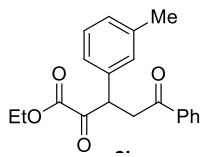


Ethyl 3-(4-methoxyphenyl)-2,5-dioxo-5-phenylpentanoate (7h): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7h** (0.653 g, 1.92 mmol, 96% yield) as a clear oil. Analytical data for **7h**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.58-7.55 (m, 1H), 7.47-7.43 (m, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.10 (dd, *J* = 10.4 Hz, 4.0 Hz, 1H), 4.34-4.21 (m, 2H), 3.99 (dd, *J* = 18.4 Hz, 10,4 Hz, 1H), 3.79 (s, 3H), 3.40 (dd, 18.4 Hz, 4.0 Hz, 1H), 1.31 (t, *J* = 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.5, 192.1, 160.4, 159.3, 136.0, 133.4, 130.0, 128.6, 128.1, 126.9, 114.5, 62.4, 55.2, 47.5, 42.9, 13.9; **IR** (thin film, cm^{-1}): 2982, 2837, 1728, 1681, 1609, 1511, 1449, 1361, 1255, 1180, 1095, 1036, 833, 796, 690, 552; **TLC** (20% EtOAc/hexanes) R_f: 0.23; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{20}H_{21}O_5$: 341.1389, Found: 341.1385.

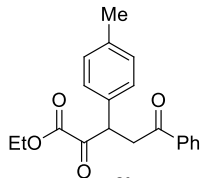


Ethyl 2,5-dioxo-5-phenyl-3-(*o*-tolyl)pentanoate (7i): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7i** (0.454 g, 1.40 mmol, 70% yield) as a clear oil. Analytical data for **7i**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.58-7.55 (m, 1H), 7.46-7.44 (m, 2H), 7.25-7.24 (m, 1H), 7.21-7.15 (m, 2H), 7.07-7.06 (m, 1H), 5.38 (dd, *J* = 10.2 Hz, 3.6 Hz, 1H),

4.25-4.11 (m, 2H), 3.93 (dd, *J* = 18.0 Hz, 10.2 Hz, 1H), 3.27 (dd, *J* = 18.0 Hz, 3.6 Hz, 1H), 2.54 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.3, 192.3, 160.5, 137.1, 136.0, 133.8, 133.4, 131.3, 128.6, 127.8, 127.5, 126.5, 62.4, 44.5, 42.2, 19.7, 13.8; **IR** (thin film, cm^{-1}): 2982, 2359, 1727, 1683, 1596, 1490, 1448, 1359, 1240, 1094, 1038, 757, 689; **TLC** (20% EtOAc/hexanes) R_f: 0.38; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{20}H_{21}O_4$: 325.1440, Found: 325.1449.

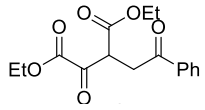


Ethyl 2,5-dioxo-5-phenyl-3-(*m*-tolyl)pentanoate (7j): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7j** (0.603 g, 1.86 mmol, 93% yield) as a clear oil. Analytical data for **7j**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.58-7.56 (m, 1H), 7.46-7.44 (m, 2H), 7.24-7.23 (m, 1H), 7.15-7.14 (m, 2H), 7.11-7.10 (m, 1H), 5.12 (dd, *J* = 10.8 Hz, 3.6 Hz, 1H), 4.34-4.24 (m, 2H), 4.03 (dd, *J* = 18.6 Hz, 10.8 Hz, 1H), 3.41 (dd, *J* = 18.6 Hz, 3.6 Hz, 1H), 2.34 (s, 3H), 1.31 (t, *J* = 6.6 Hz, 3H) ; **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.4, 192.2, 160.3, 138.8, 136.0, 135.2, 133.4, 129.4, 129.0, 128.7, 128.6, 128.1, 125.9, 62.4, 48.3, 43.1, 21.3, 13.9; **IR** (thin film, cm^{-1}): 2982, 1730, 1681, 1596, 1491, 1449, 1358, 1240, 1095, 1038, 757, 689, 560; **TLC** (20% EtOAc/hexanes) R_f: 0.40; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{20}H_{21}O_4$: 325.1440, Found: 325.1441.

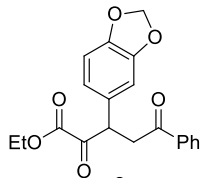


Ethyl 2,5-dioxo-5-phenyl-3-(*p*-tolyl)pentanoate (7k): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7k** (0.615

g, 1.90 mmol, 95% yield) as a clear oil. Analytical data for **7k**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.58-7.55 (m, 1H), 7.46-7.44 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.12 (dd, *J* = 10.8 Hz, 3.6 Hz, 1H), 4.33-4.23 (m, 2H), 4.01 (dd, *J* = 18.0 Hz, 10.8 Hz, 1H), 3.40 (dd, *J* = 18.0 Hz, 3.6 Hz, 1H), 2.33 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.4, 192.2, 160.4, 137.8, 136.0, 133.4, 132.2, 129.8, 128.7, 128.6, 128.1, 62.4, 48.0, 43.0, 21.0, 13.9; **IR** (thin film, cm^{-1}): 2983, 1727, 1682, 1512, 1449, 1273, 1204, 1095, 1038, 764, 689, 544; **TLC** (20% EtOAc/hexanes) R_f: 0.37; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{20}H_{21}O_4$: 325.1440, Found: 325.1440.

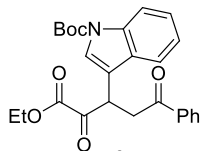


Diethyl 2-oxo-3-(2-oxo-2-phenylethyl)succinate (7l): The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7l** (0.563 g, 1.84 mmol, 92% yield) as a clear oil. Analytical data for **7l**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.89 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.60-7.56 (m, 1H), 7.48-7.45 (m, 2H), 4.91 (dd, *J* = 9.2 Hz, 4.4 Hz, 1H), 4.43-4.37 (m, 2H), 4.25-4.18 (m, 2H), 3.79 (dd, *J* = 18.0 Hz, 9.2 Hz, 1H), 3.67 (dd, 18.0 Hz, 4.4 Hz, 1H), 1.40 (t, *J* = 8.0 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.2, 188.5, 168.3, 160.2, 135.6, 133.7, 133.1, 128.7, 128.6, 128.2, 128.0, 62.8, 62.1, 48.2, 37.6, 35.8, 14.0, 13.9; **IR** (thin film, cm^{-1}): 2983, 2936, 1731, 1683, 1597, 1449, 1368, 1256, 1097, 1042, 859, 760, 690; **TLC** (20% EtOAc/hexanes) R_f: 0.26; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{16}H_{19}O_6$: 307.1182, Found: 307.1190.



Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2,5-dioxo-5-phenylpentanoate (7m): The title compound was prepared

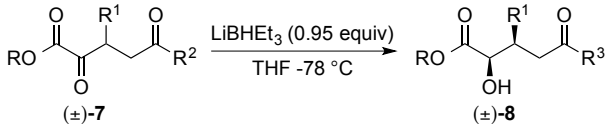
according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7m** (0.665 g, 1.88 mmol, 94% yield) as a clear oil. Analytical data for **7m**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.58-7.56 (m, 1H), 7.47-7.44 (m, 2H), 6.83 (s, 1H), 6.80-6.76 (m, 2H), 5.95 (s, 2H), 5.06 (dd, *J* = 10.8 Hz, 3.6 Hz, 1H), 4.35-4.25 (m, 2H), 3.96 (dd, *J* = 18.0 Hz, 10.8 Hz, 1H), 3.40 (dd, *J* = 18.0 Hz, 3.6 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.4, 191.9, 160.4 148.2, 147.4, 135.9, 133.5, 128.6, 128.1, 122.4, 109.1, 108.8, 101.2, 62.5, 47.9, 43.0, 13.9; **IR** (thin film, cm^{-1}): 2984, 2905, 1727, 1681, 1596, 1504, 1486, 1447, 1361, 1247, 1232, 1095, 1037, 930, 859, 811, 765, 689; **TLC** (20% EtOAc/hexanes) R_f: 0.28; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{20}H_{19}O_6$: 355.1182, Found: 355.1185.



***Tert*-butyl 3-(1-ethoxy-1,2,5-trioxo-5-phenylpentan-3-yl)-1*H*-indole-1-carboxylate (7n):** The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **7n** (0.628 g, 1.40 mmol, 70% yield) as a yellow solid. Analytical data for **7n**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.75-7.73 (m, 1H), 7.59-7.55 (m, 1H), 7.52 (s, 1H), 7.47-7.7.43 (m, 2H), 7.38-7.34 (m, 1H), 7.31-7.27 (m, 1H), 5.42 (dd, *J* = 10.8 Hz, 3.6 Hz, 1H), 4.30-4.26 (m, 2H), 4.11 (dd, *J* = 18.4 Hz, 10.8 Hz, 1H), 3.54 (dd, *J* = 18.4 Hz, 3.6 Hz, 1H), 1.67 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.4, 191.3, 160.4, 149.2, 135.7, 135.6, 133.5, 128.9, 128.6, 128.1, 124.9, 124.6, 122.9, 119.3, 115.3, 114.6, 84.0, 62.6, 42.1, 39.0, 28.2, 13.8; **IR** (thin film, cm^{-1}): 2984, 2905, 1727, 1681, 1596, 1504, 1486, 1447, 1361, 1247,

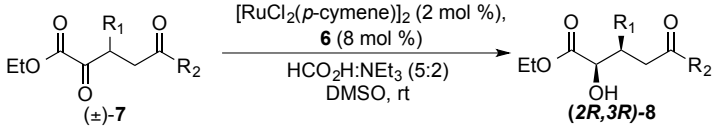
1232, 1095, 1037, 930, 859, 811, 765, 689; **TLC** (20% EtOAc/hexanes) R_f: 0.37; **HRMS** (ESI): Calculated for $[M+H]^+$ $C_{26}H_{28}NO_6$: 450.1916, Found: 450.1923.

2.4.3 General Procedure B for the Preparation of Racemic δ-Keto α-Hydroxy Esters 8a-n



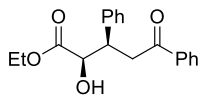
Lithium triethylborohydride (0.95 equiv, 1.0 M solution in THF) was added to a solution of β-substituted α,δ-diketo ester (1.0 equiv) in THF (0.5 M concentration) at -78 °C. The reaction was allowed to stir at this temperature for 10 minutes and quenched with saturated ammonium chloride. The reaction was further diluted with diethyl ether and water. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give δ-keto α-hydroxy esters **8** which were purified by flash chromatography using the indicated solvent systems.

2.4.4 General Procedure C for the ATH-DKR of a,δ-Diketo Esters 7a-n



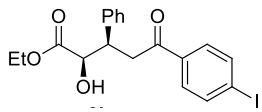
To a flame-dried 1-dram vial equipped with a magnetic stir bar were added $[RuCl_2(p\text{-cymene})]_2$ (0.02 equiv) and ligand **6** (0.08 equiv). The vial was sealed with a rubber septum and purged with nitrogen. DMSO (0.5 mL) was added and the rubber septum was quickly replaced with a PTFE-lined screw cap. The mixture was heated at 70 ºC for 30 min and cooled to ambient temperature. A solution of β-substituted α,δ-diketo ester (1.0 equiv in 1.0 mL DMSO) followed by

formic acid:triethylamine 5:2 azeotrope (5.0 equiv) were added. The vial was purged with nitrogen and the reaction was stirred at room temperature for 1-2 hours and diluted with ethyl acetate and water. The organic layer was washed with water (x2), brine, and dried over sodium sulfate. Concentration *in vacuo* afforded the δ-keto α-hydroxy esters, which were purified by flash chromatography using the indicated solvent systems.

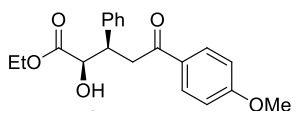


(2*R*,3*R*)-Ethyl 2-hydroxy-5-oxo-3,5-diphenylpentanoate (8a): The title compound was prepared via a modification of General Procedure C (lower catalyst loading) using α,δ-diketo ester **7a** (1.92 g, 6.20 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.0005 equiv), **6** (7.5 mg, 0.0124 mmol, 0.002 equiv), and $HCOOH:NEt_3$ 5:2 azeotrope (2.68 g, 31.0 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8a** (1.88 g, 0.601 mmol, 97% yield) as a white solid. Analytical data for **8a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.2 Hz, 2H), 7.60-7.57 (m, 1H), 7.50-7.47 (m, 2H), 7.35-7.33 (m, 2H), 7.31-7.29 (m, 2H), 7.27-7.24 (m, 1H), 4.66 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.18-4.11 (m, 2H), 3.97 (ddd, 8.4 Hz, 6.0 Hz, 3.0 Hz, 1H), 3.80 (dd, *J* = 8.4 Hz, 18.0 Hz, 1H), 3.47 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 2.92 (d, *J* = 6.0 Hz, 1H), 1.26 (t, *J* =7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.3, 173.6, 139.0, 136.9, 133.2, 128.6, 128.6, 128.3, 128.0, 127.3, 72.5, 61.7, 43.6, 40.4, 14.1; **IR** (thin film, cm^{-1}): 3503, 3029, 2981, 1733, 1684, 1597, 1579, 1495, 1449, 1369, 1267, 1212, 1103, 1022, 753, 703, 691, 554; **m.p.** 145-147 °C; **TLC** (30% EtOAc/hexanes): R_f: 0.37; **HRMS** (ESI): Calculated for [M+Na] $C_{19}H_{20}NaO_4$: 335.1259, Found: 335.1259; **SFC Analysis**: WO column, 5%

MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 9.3 min, $t_{R\ (major)}$ = 10.1 min, 98:2 er; **$[\alpha]_D^{25}$** +30.6 (*c* = 5.6, $CHCl_3$).

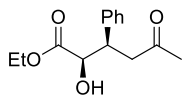


(2*R*,3*R*)-Ethyl 2-hydroxy-5-(4-iodophenyl)-5-oxo-3-phenylpentanoate (8b): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7b** (68.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and $HCOOH:NEt_3$ 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8b** (62 mg, 0.141 mmol, 91% yield) as a white solid. Analytical data for **8b**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.33-7.26 (m, 4H), 7.25-7.24 (m, 1H), 4.55 (dd, *J* = 6.0 Hz, 3.6 Hz, 1H), 4.17-4.10 (m, 2H), 3.94 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.6 Hz, 1H), 3.73 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.40 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 2.93 (d, *J* = 6.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.6, 173.5, 138.7, 137.9, 136.2, 129.4, 128.6, 128.3, 127.4, 101.2, 72.4, 61.8, 43.5, 40.3, 14.1; **IR** (thin film, cm^{-1}): 3503, 3029, 2980, 2360, 1732, 1685, 1580, 1455, 1393, 1266, 1211, 1102, 1058, 990, 813, 755, 702, 555; **m.p.** 153-155 °C; **TLC** (30% EtOAc/hexanes): R_f: 0.42; **HRMS** (ESI): Calculated for [M+Na] $C_{19}H_{19}INaO_4$: 461.0226, Found: 461.0220; **SFC Analysis**: WO column, 5% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 9.3 min, $t_{R\ (major)}$ = 10.1 min, 96:4 er; **$[\alpha]_D^{25}$** +34.3 (*c* = 12.5, $CHCl_3$).



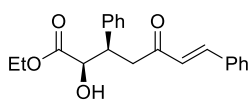
(2*R*,3*R*)-Ethyl 2-hydroxy-5-(4-methoxyphenyl)-5-oxo-3-phenylpentanoate (8b): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7c** (53.0 mg,

0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8c** (49.8 mg, 0.152 mmol, 94% yield) as a clear oil. Analytical data for **8c**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.34-7.24 (m, 5H), 6.95 (d, *J* = 8.4 Hz, 2H), 4.59 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.19-4.11 (m, 2H), 3.96 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.0 Hz, 1H), 3.89 (s, 3H), 3.74 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.40 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 2.91 (d, *J* =6.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 196.8, 173.7, 163.5, 139.0, 130.4, 130.0, 128.6, 128.3, 127.3, 113.7, 72.5, 61.8, 55.4, 43.7, 39.9, 14.1; **IR** (thin film, cm^{-1}): 3503, 2980, 2935, 2360, 1732, 1675, 1600, 1575, 1510, 1455, 1419, 1369, 1259, 1214, 1171, 1103, 1025, 991, 832, 703, 554; **TLC** (30% EtOAc/hexanes): R_f: 0.30; **HRMS** (ESI): Calculated for [M+Na] $C_{20}H_{22}NaO_5$: 365.1365, Found: 365.1364; **SFC Analysis**: WO column, 5% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 9.3 min, $t_{R\ (major)}$ = 10.1 min, 96:4 er; **$[\alpha]_D^{25}$** +47.2 (*c* = 2.7, $CHCl_3$).



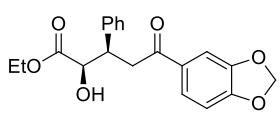
(2*R*,3*R*)-Ethyl 2-hydroxy-5-oxo-3-phenylhexanoate (8d): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7d** (38.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8d** (33.0 mg, 0.132 mmol, 85% yield) as a clear oil. Analytical data for **8d**: **^{1}H NMR** (600

MHz, $CDCl_3$): δ 7.28-7.27 (m, 2H), 7.24-7.23 (m, 3H), 4.48 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.14-4.07 (m, 2H), 3.72 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.0 Hz, 1H), 3.12 (dd, *J* = 17.7 Hz, 7.8 Hz, 1H), 2.92 (dd, *J* = 17.7 Hz, 6.0 Hz, 1H), 2.83 (d, *J* = 6.0 Hz, 1H), 2.16 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 207.0, 173.6, 138.6, 128.6, 128.3, 127.4, 72.4, 61.8, 45.3, 43.3, 30.6, 14.1; **IR** (thin film, cm^{-1}): 3502, 2983, 2937, 1731, 1717, 1494, 1455, 1366, 1213, 1165, 1106, 1025, 864, 758, 703, 542; **TLC** (30% EtOAc/hexanes): R_f: 0.22; **HRMS** (ESI): Calculated for [M+Na] $C_{14}H_{18}NaO_4$: 273.1103, Found: 273.1107; **SFC Analysis**: AS column, 7% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 6.4 min, $t_{R\ (major)}$ = 9.2 min, 93:7 er; **$[\alpha]_D^{25}$** +47.2 (*c* = 2.7, $CHCl_3$).



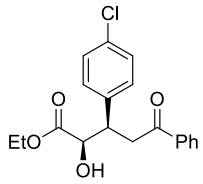
(2*R*,3*R*,*E*)-Ethyl 2-hydroxy-5-oxo-3,7-diphenylhept-6-enoate (8e): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7e** (52.1 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8e** (46.0 mg, 0.136 mmol, 88% yield) as a white solid. Analytical data for **8e**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.62, (d, *J* = 16.2 Hz, 1H), 7.57-7.55 (m, 2H), 7.43-7.41 (m, 3H), 7.33-7.29 (m, 4H), 7.27-7.24 (m, 1H), 6.76 (d, *J* = 16.2 Hz, 1H), 4.56 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.19-4.11 (m, 2H), 3.88 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.0 Hz, 1H), 3.47 (dd, *J* = 17.4 Hz, 8.4 Hz, 1H), 3.19 (dd, *J* = 17.4 Hz, 6.0 Hz, 1H), 2.94 (d, *J* = 6.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.3, 173.6, 143.0, 138.8, 134.4, 130.5, 128.9, 128.6, 128.3, 128.3,

127.3, 126.4, 72.5, 61.8, 43.7, 42.5, 14.1; **IR** (thin film, cm^{-1}): 3503, 1733, 1684, 1655, 1610, 1576, 1495, 1450, 1259, 1210, 1176, 1096, 1024, 976, 749, 703, 554; **TLC** (30% EtOAc/hexanes): R_f: 0.33; **HRMS** (ESI): Calculated for [M+Na] $C_{21}H_{22}NaO_4$: 361.1416, Found: 361.1416; **SFC Analysis**: WO column, 5% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 15.0 min, $t_{R\ (major)}$ = 16.1 min, 99:1 er; **$[\alpha]_D^{25}$** +47.3 (*c* = 5.3, $CHCl_3$).

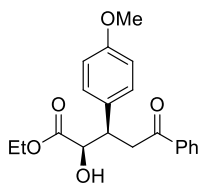


(2*R*,3*R*)-Ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxy-5-oxo-3-phenylpentanoate (8f): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7f** (55.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8f** (54.0 mg, 0.152 mmol, 98% yield) as a clear oil. Analytical data for **8f**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.48 (d, *J* = 1.8 Hz, 1H), 7.33-7.28 (m, 4H), 7.25-7.24 (m, 1H), 6.87 (d, *J* =8.4 Hz, 1H), 6.06 (s, 2H), 4.58 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.26-4.05 (m, 2H), 3.94 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.0 Hz, 1H), 3.71 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.37 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 2.89 (d, *J* = 6.0 Hz, 1H) 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 196.3, 173.7, 151.8, 148.2, 139.0, 131.9, 128.6, 128.3, 127.3, 124.4, 107.9, 107.8, 101.8, 72.5, 61.8, 43.8, 40.1, 14.1; **IR** (thin film, cm^{-1}): 3503, 2980, 1731, 1684, 1597, 1492, 1448, 1413, 1365, 1266, 1212, 1095, 1015, 785, 690, 546; **TLC** (30% EtOAc/hexanes): R_f: 0.28; **HRMS** (ESI): Calculated for [M+Na] $C_{20}H_{20}NaO_6$: 379.1158, Found: 379.1161; **SFC**

Analysis: WO column, 5% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 15.2 min, $t_{R\ (major)}$ = 16.3 min, 99:1 er; $[\alpha]_D^{25}$ +32.9 (*c* = 10.0, $CHCl_3$).

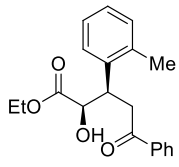


(2*R*,3*R*)-Ethyl 3-(4-chlorophenyl)-2-hydroxy-5-oxo-5-phenylpentanoate (8g): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7g** (53.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8g** (50.0 mg, 0.146 mmol, 94% yield) as a clear oil. Analytical data for **8g**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.58-7.55 (m, 1H), 7.47-7.44 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.55 (dd, *J* = 5.4 Hz, 3.0 Hz, 1H), 4.17-4.10 (m, 2H), 3.93 (ddd, *J* = 7.8 Hz, 6.6 Hz, 3.0 Hz, 1H), 3.70 (dd, *J* = 18.0 Hz, 7.8 Hz, 1H), 3.43 (dd, *J* = 18.0 Hz, 6.6 Hz, 1H), 2.91 (d, *J* = 5.4 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.3, 173.5, 137.5, 136.8, 133.3, 133.2, 130.0, 128.6, 128.4, 128.0, 72.4, 62.0, 43.0, 40.5, 14.2; **IR** (thin film, cm^{-1}): 3503, 2982, 2905, 1733, 1676, 1603, 1504, 1489, 1443, 1367, 1256, 1097, 1037, 933, 808, 757, 703, 556; **TLC** (30% EtOAc/hexanes): R_f: 0.38; **HRMS** (ESI): Calculated for [M+Na] $C_{19}H_{19}ClNaO_6$: 369.0870, Found: 369.0873; **SFC Analysis**: OD column, 10% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 8.8 min, $t_{R\ (major)}$ = 9.8 min, 98:2 er; $[\alpha]_D^{25}$ +48.4 (*c* = 4.2, $CHCl_3$).



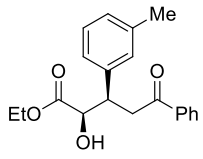
(2*R*,3*R*)-Ethyl 2-hydroxy-3-(4-methoxyphenyl)-5-oxo-5-phenylpentanoate (8h): The title compound was prepared

according to General Procedure C using α,δ-diketo ester **7h** (53.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8h** (52.0 mg, 0.152 mmol, 98% yield) as a clear oil. Analytical data for **8h**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.57-7.54 (m, 1H), 7.46-7.44 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.54 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.17-4.09 (m, 2H), 3.90 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.0 Hz, 1H), 3.76 (s, 3H), 3.71 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.41 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 2.86 (d, *J* = 6.0 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.4, 173.7, 158.7, 137.0, 133.1, 130.9, 128.6, 128.1, 113.7, 72.7, 61.8, 55.1, 42.8, 40.6, 14.2; **IR** (thin film, cm^{-1}): 3502, 2935, 1731, 1683, 1612, 1597, 1580, 1514, 1448, 1366, 1251, 1180, 1100, 1032, 837, 757, 691; **TLC** (30% EtOAc/hexanes): R_f: 0.33; **HRMS** (ESI): Calculated for [M+Na] $C_{20}H_{22}NaO_5$: 365.1365, Found: 365.1366; **SFC Analysis**: AD column, 10% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 13.2 min, $t_{R\ (major)}$ = 16.8 min, 96:4 er; **$[\alpha]_D^{25}$** +34.6 (*c* = 6.3, $CHCl_3$).



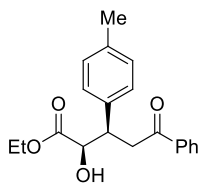
(2*R*,3*R*)-Ethyl 2-hydroxy-5-oxo-5-phenyl-3-(*o*-tolyl)pentanoate (8i): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7i** (50.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy

ester **8i** (44.0 mg, 0.135 mmol, 87% yield) as a clear oil. Analytical data for **8i**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.97 (d, *J* = 6.6 Hz, 2H), 7.56-7.51 (m, 2H), 7.46-7.43 (m, 2H), 7.15-7.08 (m, 3H), 4.63 (d, *J* = 4.2 Hz, 1H), 4.24 (ddd, *J* = 7.8 Hz, 6.0 Hz, 4.2 Hz, 1H), 4.14-4.08 (m, 1H), 4.01-3.95 (m, 1H), 3.72 (dd, *J* = 18.0 Hz, 7.8 Hz, 1H), 3.36 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 3.03 (bs, 1H), 2.41 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.5, 173.9, 138.2, 136.8, 136.2, 133.2, 130.4, 128.6, 128.1, 127.5, 126.9, 126.0, 72.4, 61.8, 41.3, 40.9, 37.7, 19.8, 13.8; **IR** (thin film, cm^{-1}): 3495, 2980, 1732, 1624, 1597, 1490, 1448, 1365, 1259, 1216, 1115, 1094, 1022, 754, 730, 690; **TLC** (30% EtOAc/hexanes): R_f: 0.40; **HRMS** (ESI): Calculated for [M+Na] $C_{20}H_{22}NaO_4$: 349.1416, Found: 349.1422; **SFC Analysis**: AD column, 10% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 14.6 min, $t_{R\ (major)}$ = 11.6 min, 83:17 er; **$[\alpha]_D^{25}$** +1.9 (*c* = 2.7, $CHCl_3$).



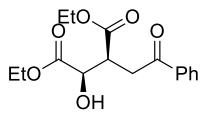
(2*R*,3*R*)-Ethyl 2-hydroxy-5-oxo-5-phenyl-3-(*m*-tolyl)pentanoate (8j): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7j** (50.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8j** (49.0 mg, 0.152 mmol, 98% yield) as a clear oil. Analytical data for **8j**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.57-7.55 (m, 1H), 7.47-7.44 (m, 2H), 7.17-7.15 (m, 1H), 7.11-7.08 (m, 1H), 7.04-7.03 (m, 1H), 4.56 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.15-4.11 (m, 2H), 3.91 (ddd, *J* = 8.4 Hz, 5.4 Hz, 3.0 Hz, 1H), 3.76 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.42 (dd, *J* = 18.0

Hz, 5.4 Hz, 1H), 2.85 (d, *J* = 6 Hz, 1H), 2.31 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.3, 173.7, 138.8, 137.8, 137.0, 133.1, 129.4, 128.6, 128.2, 128.1, 128.1, 125.6, 72.5, 61.7, 43.6, 40.3, 21.4, 14.1; **IR** (thin film, cm^{-1}): 3505, 2980, 2922, 1733, 1685, 1597, 1448, 1365, 1265, 1207, 1104, 1023, 1001, 757, 709, 691; **TLC** (30% EtOAc/hexanes): R_f: 0.43; **HRMS** (ESI): Calculated for [M+Na] $C_{20}H_{22}NaO_4$: 349.1416, Found: 349.1419; **SFC Analysis**: AD column, 10% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 9.6 min, $t_{R\ (major)}$ = 7.9 min, 98:2 er; **$[\alpha]_D^{25}$** +22.6 (*c* = 9.0, $CHCl_3$).

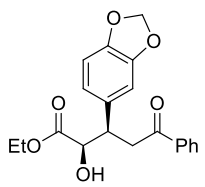


(2*R*,3*R*)-Ethyl 2-hydroxy-5-oxo-5-phenyl-3-(*p*-tolyl)pentanoate (8k): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7k** (50.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8k** (48.0 mg, 0.151 mmol, 97% yield) as a clear oil. Analytical data for **8k**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.8 Hz, 2H), 7.57-7.54 (m, 1H), 7.47-7.44 (m, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 4.55 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.17-4.09 (m, 2H), 3.91 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.0 Hz, 1H), 3.74 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.42 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 2.85 (d, *J* = 6.0 Hz, 1H), 2.29 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.3, 173.7, 137.0, 136.8, 135.8, 133.1, 129.0, 128.5, 128.4, 128.1, 72.6, 61.7, 43.2, 40.4, 21.0, 14.1; **IR** (thin film, cm^{-1}): 3509, 2981, 2923, 1731, 1684, 1597, 1515, 1448, 1336, 1265, 1210, 1100, 1022, 757, 691,

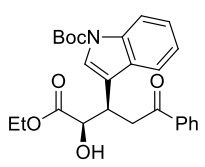
550; **TLC** (30% EtOAc/hexanes): R_f: 0.43; **HRMS** (ESI): Calculated for [M+Na] $C_{20}H_{22}NaO_4$: 349.1416, Found: 349.1422; **SFC Analysis**: AD column, 10% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 12.8 min, $t_{R\ (major)}$ = 10.6 min, 98:2 er; **$[\alpha]_D^{25}$** +32.1 (*c* = 8.0, $CHCl_3$).



(2*R*,3*S*)-Diethyl 2-hydroxy-3-(2-oxo-2-phenylethyl)succinate (8l): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7l** (47.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8l** (44.0 mg, 0.144 mmol, 93% yield) as a clear oil. Analytical data for **8l**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.60-7.56 (m, 1H), 7.49-7.46 (m, 2H), 4.37 (d, *J* = 2.8 Hz, 1H), 4.33-4.28 (m, 2H), 4.21-4.11 (m, 2H), 3.79 (ddd, *J* = 8.4 Hz, 5.6 Hz, 8.4 Hz, 1H), 3.71 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.25 (dd, *J* = 18.0 Hz, 5.6 Hz, 1H), 3.19 (bs 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 197.7, 173.3, 171.2, 136.6, 133.4, 128.6, 128.1, 70.9, 62.2, 61.2, 44.1, 36.7, 14.1, 14.0; **IR** (thin film, cm^{-1}): 3487, 2982, 1734, 1685, 1449, 1366, 1226, 1180, 1111, 1032, 861, 759, 691; **TLC** (30% EtOAc/hexanes): R_f: 0.23; **HRMS** (ESI): Calculated for [M+Na] $C_{16}H_{20}NaO_6$: 331.1158, Found: 338.1165; **SFC Analysis**: AD column, 10% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 7.3 min, $t_{R\ (major)}$ = 6.5 min, 91:9 er; **$[\alpha]_D^{25}$** +27.5 (*c* = 4.2, $CHCl_3$).



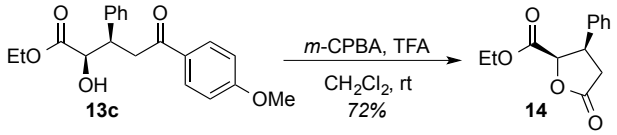
(2*R*,3*R*)-Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxy-5-oxo-5-phenylpentanoate (8m): The title compound was prepared according to General Procedure C using α,δ-diketo ester **7m** (55.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and $HCOOH:NEt_3$ 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided δ-keto α-hydroxy ester **8m** (53.0 mg, 0.149 mmol, 96% yield) as a clear oil. Analytical data for **8m**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.57-7.55 (m, 1H), 7.47-7.44 (m, 2H), 6.84 (s, 1H), 6.74-6.73 (m, 1H), 6.70-6.69 (m, 1H), 5.91 (s, 2H), 4.52 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.21-4.10 (m, 2H), 3.87 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.0 Hz, 1H), 3.67 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.41 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 2.89 (d, *J* = 6.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.2, 173.7, 147.5, 146.7, 136.9, 133.2, 132.6, 128.6, 128.1, 121.9, 109.0, 108.0, 100.9, 72.6, 61.8, 43.2, 40.6, 14.2; **IR** (thin film, cm^{-1}): 3503, 2982, 2902, 1733, 1684, 1504, 1487, 1446, 1239, 1098, 1038, 933, 811, 759, 690; **TLC** (30% EtOAc/hexanes): R_f: 0.28; **HRMS** (ESI): Calculated for [M+Na] $C_{20}H_{20}NaO_6$: 379.1158, Found: 379.1162; **SFC Analysis**: AD column, 10% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 16.5 min, $t_{R\ (major)}$ = 12.8 min, 98:2 er; **$[\alpha]_D^{25}$** +30.8 (*c* = 7.0, $CHCl_3$).



***Tert*-butyl 3-((2*R*,3*R*)-1-ethoxy-2-hydroxy-1,5-dioxo-5-phenylpentan-3-yl)-1*H*-indole-1-carboxylate (8n):** The title compound was prepared according to General Procedure C using α,δ-diketo ester **7n** (70.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$

(1.9 mg, 0.0031 mmol, 0.02 equiv), **6** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography (20% EtOAc/hexanes) provided a-hydroxy ester **8n** (60.0 mg, 0.133 mmol, 86% yield) as a clear oil. Analytical data for **8n**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 1H), 8.00-7.98 (m, 2H), 7.68-7.66 (m, 1H), 7.58-7.54 (m, 2H), 7.47-7.44 (m, 2H), 7.31-7.26 (m, 1H), 7.25-7.21 (m, 1H), 4.62 (dd, *J* = 6.0 Hz, 2.8 Hz, 1H), 4.32 (ddd, *J* = 8.4 Hz, 6.0 Hz, 2.8 Hz, 1H), 4.09-4.01 (m, 2H), 3.81 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H), 3.42 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H), 3.09 (d, *J* = 6.0 Hz, 1H), 1.67 (s, 9H), 1.15 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.2, 173.4, 136.8, 133.2, 130.0, 128.6, 128.1, 124.4, 124.0, 122.3, 119.3, 118.2, 115.2, 83.7, 71.7, 61.9, 41.0, 34.5, 28.2, 13.9; **IR** (thin film, cm^{-1}): 3502, 2979, 2932, 1732, 1685, 1452, 1375, 1309, 1256, 1217, 1157, 1107, 1090, 1020, 856, 765, 749, 690; **TLC** (30% EtOAc/hexanes): R_f: 0.40; **HRMS** (ESI): Calculated for [M+Na] $C_{26}H_{29}NNaO_6$: 474.1893, Found: 474.1899; **SFC Analysis**: AD column, 10% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 29.4 min, $t_{R\ (major)}$ = 23.5 min, 98:2 er; **$[\alpha]_D^{25}$** +21.5 (*c* = 8.7, $CHCl_3$).

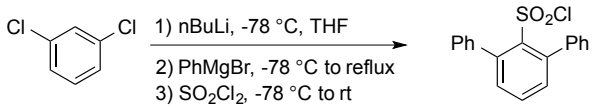
2.4.5 Baeyer-Villiger Oxidation of 8c



To a 1-dram vial equipped with a magnetic stir bar were added **8c** (34.2 mg, 0.100 mmol, 1.0 equiv), *m*-CPBA (86.3 mg, 0.500 mmol, 5.0 equiv), TFA (11.4 mg, 0.100 mmol, 1.0 equiv) and CH_2Cl_2 (1 mL). The reaction was stirred at room temperature overnight and then diluted with water and ethyl acetate. The

organic was washed with water followed by brine, dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography provided **14** (17.0 mg, 0.072 mmol, 72% yield) as a white solid whose spectral data, including $[\alpha]_D^{25}$, were in agreement with the known *cis*-lactone.[4]

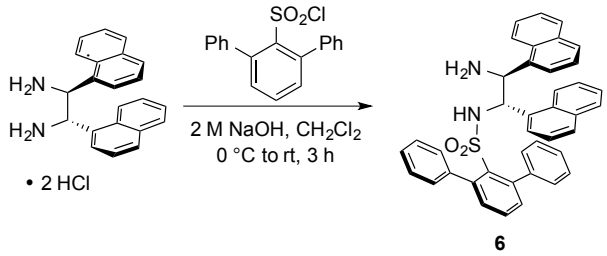
2.4.6 Preparation of *m*-Terphenyl Sulfonyl Chloride[4]



To a flame-dried 50-mL round-bottomed flask equipped with a magnetic stir bar and rubber septum were added 1,3-dichlorobenezne (1.47 g, 10.0 mmol, 1.0 equiv) and THF (25 mL). The solution was cooled to -78 ºC and ^{n}BuLi (1.6 M in hexanes, 11.0 mmol, 1.1 equiv) was added dropwise over 10 min. The resultant white slurry was stirred at -78 ºC for 1.5 hrs. While being kept at -78 ºC, this reaction mixture was then added to a room temperature solution of phenylmagnesium bromide [prepared from bromobenzene (3.14 g, 20.0 mmol, 2.0 equiv) and magnesium (578 mg, 24.0 mmol, 2.4 equiv)] in 30 mL of THF via cannula. The mixture was heated at reflux overnight, cooled to ambient temperature, and then to -78 ºC. Sulfuryl chloride (1 M in CH_2Cl_2, 20.0 mmol, 2.0 equiv) was added via syringe in a single portion and the reaction was warmed slowly to room temperature overnight. After being cooled to 0 ºC, the reaction mixture was diluted with 1 M HCl and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude brown solid was recrystallized from

hexanes and $CHCl_3$ to give the desired sulfonyl chloride (2.0 g, 6.1 mmol, 61% yield) whose spectral properties matched those reported in the literature.[4]

2.4.6 Preparation of 6[4]



6

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with (1*S*,2*S*)-1,2-di(1-naphthyl)-1,2-ethanediamine dihydrochloride (250 mg, 0.649 mmol, 1.0 equiv). Dichloromethane (3 mL) and 2 M NaOH (3 mL) were added sequentially and the biphashic mixture was cooled to 0 ºC. *m*-Terphenyl sulfonyl chloride[4] (213 mg, 0.649 mmol, 1.0 equiv) was added and the reaction was warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with ethyl acetate and water. The organic was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (50% EtOAc/hexanes) provided **6** (330 mg, 0.545 mmol, 84% yield) as a white solid. Analytical data for **6**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.72-7.67 (m, 2H), 7.66-7.02 (m, 20H), 6.97 (bs, 1H), 6.72 (bs, 1H), 5.57 (d, *J* = 6.4 Hz, 1H), 4.95 (d, *J* = 7.6 Hz), 4.68 (bs, 1H), 1.75 (bs, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 141.9, 140.9, 139.7, 137.8, 135.3, 133.8, 133.6, 131.6, 131.0, 130.7, 130.0, 129.2, 128.8, 128.6, 128.2, 127.9, 127.7, 127.7, 126.1, 126.0, 125.4, 125.3, 125.1, 125.0, 124.3, 123.6, 122.9, 122.4; **IR** (thin film, cm^{-1}): 2926, 2357, 1868, 1716, 1608, 1541,

1507, 1456, 1338, 1158, 1028, 929, 778, 759, 700, 664, 592, 529; **m.p.** 158-160 ºC; **TLC** (50% EtOAc/hexanes) R_f: 0.25; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{40}H_{33}N_2O_2S$: 605.23, Found: 605.29; $\mathbf{[\alpha]_D^{25}}$ +170.6 (*c* = 1.30, $CHCl_3$

2.5 Experimental Data and Conditions for the Asymmetric Synthesis of *anti*-β-Amino-α-Hydroxy Esters via Dynamic Kinetic Resolution of β-Amino-α-Keto Esters[‡‡]

2.5.1 General Information:

Methods: Infrared (IR) spectra were obtained using a Jasco 260 Plus fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz and ^{13}C NMR at 100 MHz or 150 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and DMSO at 2.54; ^{13}C NMR: $CDCl_3$ at 77.0 ppm and DMSO at 40.45). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, dt= doublet of triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Supercritical fluid chromatography was performed on a Berger SFC system equipped with Chiracel AD, AS, OD, and WO columns (φ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO_2 at the indicated percentage of methanol with an oven temperature of 40 °C. HPLC analysis was performed on an Agilent Technologies 1200 system equipped with Chiralpak IA, IB, and IC columns (constant flow at 1.00 mL/min). Samples were eluted with the indicated percentages of HPLC grade isopropanol in hexanes. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimiter. Mass spectra were obtained using a Finnigan linear trap quadrapole Fourier transform (LTQ-FT) spectrometer. Analytical thin layer chromatography (TLC) was performed on

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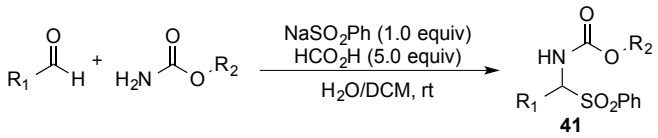
Sorbtec 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or either butanolic ninhydrin or aqueous ceric ammonium molybdate solution followed by heating. Product purification was accomplished using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Unless otherwise noted all reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the reported tables, which represent an average of at least two trials.

Materials: Amido sulfones **1a-b,**[54,55] NHC catalyst **2,**[11] ligands for complexes **5-7,**[4,21] epoxide **9,**[59] ethyl diazoacetate,[60] *tert*-butyl carbamate[61], 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde,[62] *tert*-butyl 2-formyl-1*H*-indole-1-carboxylate[63] were all prepared according to literature procedures. Ethyl glyoxylate was purchased from Sigma Aldrich as a 50% solution in toluene and distilled under reduced pressure prior to use (the concentration after distillation was determined by ^{1}H NMR spectroscopy). *N*,*N*-Dimethylformamide (DMF) was distilled from phosphorous pentoxide and stored over 3 Å molecular sieves under an atmosphere of N_2. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride and stored over 3 Å molecular sieves under an atmosphere of N_2. Triethylamine (Et_3N) was distilled from calcium hydride prior to use. Acetonitrile (CH_3CN) was distilled from calcium hydride prior to use. Methanol (MeOH) was distilled from 3 Å molecular sieves prior to use. HPLC grade chloroform ($CHCl_3$) and ethanol (EtOH) were used directly from the bottle. Dichloromethane (DCM) and tetrahydrofuran (THF) were passed 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.

2.5.2 General Procedure A for the Preparation of Amido Sulfones 41c-41o



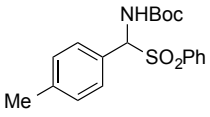
Method 1:

A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with aldehyde (10.0 mmol, 1 equiv), carbamate (10.0 mmol, 1 equiv), and THF (3.5 mL). To this solution was added H_2O (10 mL) and benzene sulfinic acid-sodium salt (10.0 mmol, 1 equiv). Formic acid (90% in H_2O) was added (50 mmol, 5.0 equiv). The reaction was stirred at room temperature for 48 hours then diluted with DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was stirred as a suspension in 20% Et_2O/Hexanes for 1 hour. Filtration with 20% Et_2O/Hexanes provided analytically pure amido sulfones.

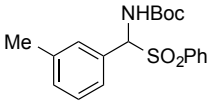
Method 2:

A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with aldehyde (10.0 mmol, 1 equiv), carbamate (10.0 mmol, 1 equiv), and DCM (10.0 mL). To this solution was added H_2O (10 mL) and benzene sulfinic acid-sodium salt (10.0 mmol, 1 equiv). Formic acid (90% in H_2O) was added last (50 mmol, 5.0 equiv). The reaction was stirred at room temperature for 48 hours then diluted with DCM and water. The organic layer was separated, and

the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was stirred as a suspension in 20% Et_2O/Hexanes for 1 h. Filtration with 20% Et_2O/Hexanes provided analytically pure amido-sulfones.

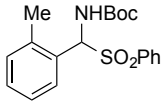


***tert*-Butyl ((phenylsulfonyl)(*p*-tolyl)methyl)carbamate (41c):** The title compound was prepared according to General Procedure A (method 1) using *para*-tolualdehyde (10.0 mmol) affording amido-sulfone **41c** (2.06 g, 5.7 mmol, 57% yield) as a white solid. Analytical data for **41c**: **mp** 175-175.6 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93-7.91 (d, *J* = 7.6 Hz, 2H), 7.63-7.62 (m, 1H), 7.55-7.51 (t, *J* = 7.6 Hz, 2H), 7.34-7.32 (d, *J* = 7.6 Hz, 2H), 7.23-7.21 (d, *J* = 7.6 Hz, 2H), 5.91-5.88, (d, *J* = 10.4 Hz, 1H), 5.79-5.76 (d, *J* = 10.4 Hz, 1H), 2.37 (s, 3 H), 1.24 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.4, 140.0, 137.0, 133.8, 129.4, 129.0, 128.7, 126.7, 81.1, 73.7, 27.9, 21.2; **IR** (thin film cm^{-1}): 3357, 2980, 1699, 1506, 1446, 1367, 1308, 1246, 1165, 1142, 1084, 603; **TLC** (25% EtOAc/hexanes): R_F 0.41; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{19}H_{23}NO_4S$: 362.1426, Found: 362.1406.

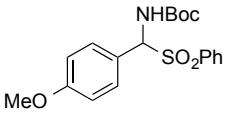


***tert*-Butyl ((phenylsulfonyl)(*m*-tolyl)methyl)carbamate (41d):** The title compound was prepared according to General Procedure A (method 1) using *meta*-tolualdehyde (10.0 mmol) affording amido-sulfone **41d** (2.09 g, 5.8 mmol, 58% yield) as a white solid. Analytical data for **41d**: **mp** 169.8-170.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94-7.93 (d, *J* = 7.6 Hz, 2H), 7.67-7.64 (m, 1H), 7.57-7.53 (m, 2H), 7.33-7.24 (m, 4H), 5.91-5.89, (d, *J* = 10.4 Hz, 1H), 5.78-5.76 (d, *J* = 10.4 Hz, 1H), 2.38 (s, 3 H), 1.26 (s, 9H); **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 138.6, 133.9, 130.7, 129.7, 129.5, 129.0, 128.6, 126.0, 81.2, 73.9, 27.9, 21.4; **IR** (thin film cm^{-1}): 3353, 2979, 1698, 1507, 1308, 1251, 1144, 1082, 716, 690, 588; **TLC** (25% EtOAc/hexanes): R_F 0.41; **HRMS** (ESI): Calcd. for $[M + NH_4]^+$ $C_{19}H_{23}NO_4S$: 379.1692, Found: 379.1716.

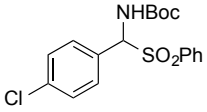


***tert*-Butyl ((phenylsulfonyl)(*o*-tolyl)methyl)carbamate** (**41e**): The title compound was prepared according to General Procedure A (method 1) using *ortho*-tolualdehyde (10.0 mmol) affording amido-sulfone **41e** (2.17 g, 6.0 mmol, 60% yield) as a white solid. Analytical data for **41e**: **mp** 141-142 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94-7.92 (d, *J* = 7.2 Hz, 2H), 7.67-7.63 (t, *J* = 7.2 Hz, 1H), 7.57-7.52 (t, *J* = 7.6 Hz, 2H), 7.46-7.43 (d, *J* = 8.0 Hz, 1H), 7.33-7.28 (m, 2H), 7.26-7.22 (m, 2H), 6.26-6.23 (d, *J* = 10.8 Hz, 1H), 5.74-5.71 (d, *J* = 10.8 Hz, 1H), 2.45 (s, 3 H), 1.26 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 153.5, 138.2, 137.2, 133.9, 130.8, 129.7, 129.3, 129.1, 129.0, 127.5, 126.5, 81.1, 69.6, 28.0, 19.7; **IR** (thin film cm^{-1}): 3349, 2979, 1704, 1517, 1496, 1447, 1393, 1368, 1248, 1163, 1083, 1046, 729; **TLC** (20% EtOAc/hexanes): R_F 0.38; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{19}H_{23}NO_4S$: 384.1246, Found: 384.1243.



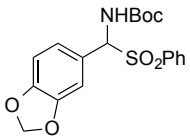
***tert*-Butyl ((4-methoxyphenyl)(phenylsulfonyl)methyl)carbamate** (**41f**): The title compound was prepared according to General Procedure A (method 1) using *para*-anisaldehyde (10.0 mmol) affording amido-sulfone **41f** (2.82 g, 7.48 mmol, 75% yield) as a white solid. Analytical data for **41f**: **mp** 115-116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95-7.93 (d, *J* = 8.0 Hz, 2H), 7.68-7.65 (t, *J* = 7.6 Hz, 1H), 7.58-7.54 (t, *J* = 7.6 Hz, 2H), 7.40-7.38 (d, *J* = 8.0 Hz, 2H), 6.98-6.96 (d, *J* =

8.0 Hz, 2H), 5.91-5.88, (d, *J* = 10.4 Hz, 1H), 5.69-5.67 (d, *J* = 10.4 Hz, 1H), 3.86 (s, 3 H), 1.28 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ163.7, 160.7, 153.5, 136.8, 133.8, 130.2, 129.7, 129.4, 129.0, 128.8, 121.5, 114.3, 114.2, 81.1, 73.5, 55.3, 55.3, 27.9; **IR** (thin film cm^{-1}): 3356, 2963, 2840, 1698, 1610, 1541, 1507, 1447, 1368, 1308, 1243, 1168, 1141, 1032, 839, 774; **TLC** (20% EtOAc/hexanes): R_F 0.45; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{19}H_{23}NO_5S$: 400.1195, Found: 400.1194.



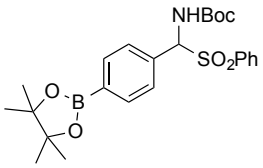
***tert*-Butyl ((4-chlorophenyl)(phenylsulfonyl)methyl)carbamate** (**41g):** The title compound was prepared according to General Procedure A (method 1) using *para*-chlorobenzaldehyde (10.0 mmol) affording amido-sulfone **41g** (2.5 g, 6.5 mmol, 65% yield) as a white solid. Analytical data for **41g**: **mp** 171-173 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95-7.93 (d, *J* = 7.2 Hz, 2H), 7.71-7.67 (t, *J* = 8.4 Hz, 1H), 7.60-7.56 (t, *J* = 7.2 Hz, 2H), 7.45-7.39 (m, 4H), 5.94-5.91 (d, *J* = 10.8 Hz, 1H), 5.70-5.67 (d, *J* = 10.8 Hz, 1H), 1.29 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 153.4, 136.5, 136.1, 134.1, 130.2, 129.4, 129.1, 129.0, 128.3, 81.4, 73.1, 27.9; **IR** (thin film cm^{-1}): 3340, 2979, 1698, 1520, 1491, 1368, 1308, 1249, 1143, 1083, 1016, 731; **TLC** (20% EtOAc/hexanes): R_F 0.35 **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{18}H_{20}ClNO_4S$: 382.0880, Found: 382.0883.

***tert*-Butyl (benzo[*d*][1,3]dioxol-5-yl(phenylsulfonyl)methyl)carbamate** (**41h):**

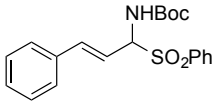


The title compound was prepared according to General Procedure A (method 1) using piperonal (10.0 mmol) affording amido-sulfone **41h** (2.50 g, 6.4 mmol, 64% yield) as a white solid. Analytical data for **41h**: **mp** 188.8-190.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.66-8.63 (d, *J* = 10.4

Hz, 1H), 7.90-7.88 (d, *J* = 7.6 Hz, 2H), 7.77-7.74 (t, *J* = 7.6 Hz, 1H), 7.63-7.59 (t, *J* = 7.6 Hz, 2H), 7.29 (s, 1H), 7.09-7.07 (d, *J* = 8.4 Hz, 1H), 6.92-6.90 (d, *J* = 8.0 Hz, 1H), 6.05 (s, 2H), 5.95-5.93, (d, *J* = 10.4 Hz, 1H), 3.32 (s, 1H), 1.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.9, 149.0, 148.1, 138.1, 134.8, 130.0, 129.9, 125.3, 124.6, 110.8, 108.8, 192.3, 80.2, 75.0, 28.7; **IR** (thin film cm^{-1}): 3356, 1713, 1490, 1445, 1369, 1302, 1248, 1145, 1040, 936, 638, 601; **TLC** (25% EtOAc/hexanes): R_F 0.20; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{19}H_{21}NO_6S$: 392.1168, Found: 392.1192.

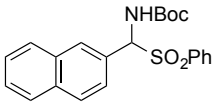


***tert*-Butyl ((phenylsulfonyl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl)carbamate** (**41i):** The title compound was prepared according to General Procedure A (method 1) using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzaldehyde[9] (10.0 mmol) affording amido-sulfone **41i** (3.22 g, 6.8 mmol, 68% yield) as a white solid. Analytical data for **41i**: **mp** 175-175.6 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97-7.82 (m, *5*H), 7.65-7.61 (t, *J*=7.6, 1H), 7.54-7.50 (m, 2H), 7.44-7.42 (m, 2H), 5.96-5.93 (d, *J* = 10.4 Hz, 1H), 5.86-5.84 (d, *J* = 10.8 Hz, 1H), 1.34 (s, 12H), 1.25 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.5, 136.8, 135.0, 133.9, 132.6, 129.4, 129.0, 128.1, 124.8, 84.0, 81.2, 74.0, 28.2, 28.0, 24.8; **IR** (thin film cm^{-1}): 3339, 2979, 1705, 1521, 1362, 1331, 1143, 1088, 857, 724, 658, 586, 536; **TLC** (25% EtOAc/hexanes): R_F 0.24; **HRMS** (ESI): Calcd. for $[M + NH_4]^+$ $C_{24}H_{32}BNO_6S$: 491.2387, Found: 491.2425.

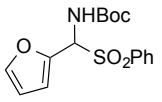


(*E*)-*tert*-Butyl (3-phenyl-1-(phenylsulfonyl)allyl)carbamate (**41j):** The title compound was prepared according to General

Procedure A (method 1) using *trans*-cinnamaldehyde (10.0 mmol) affording amido-sulfone **41j** (2.87 g, 7.7 mmol, 77% yield) as a white solid. Analytical data for **41j**: **mp** 163.2-164.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.60-7.53 (m, 3H), 7.41-7.37 (m, 2H), 7.28-7.18 (m, 3H), 7.17-7.16 (m, 2H), 6.7-6.65 (m, 1H), 6.48-6.47 (d, *J* = 8 Hz, 1 H), 5.44-5.38 (m, 1H), 4.62-4.59 (d, *J* = 9.6 Hz), 1.44 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.3, 133.5, 132.8, 131.4, 129.3, 129.2, 128.7, 128.6, 98.7, 73.5, 28.1; **IR** (thin film cm^{-1}): 3367, 2979, 1703, 1668, 1507, 1294, 1254, 1144, 1083, 962, 687, 574; **TLC** (20% EtOAc/hexanes): R_F 0.52; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{20}H_{23}NO_4S$: 374.1426, Found: 374.1440.

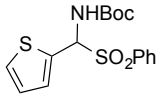


***tert*-Butyl (86aphthalene-2-yl(phenylsulfonyl)methyl)carbamate** (**41k):** The title compound was prepared according to General Procedure A (method 1) using 2-napthaldehyde (10.0 mmol) affording amido-sulfone **41k** (2.38 g, 6.0 mmol, 60% yield) as a white solid. Analytical data for **41k**: **mp** 174.4-175.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96-7.85 (m, 6H), 7.65-7.63 (m, 1H), 7.56-7.52 (m, 5H), 6.11-6.08 (d, *J* = 10 Hz, 1H), 5.89-5.86, (d, *J* = 10 Hz, 1H), 1.28 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 136.9, 134.0, 133.7, 132.9, 129.5, 129.1, 128.6, 128.3, 127.7, 127.2, 127.1, 126.7, 125.5, 74.1, 28.0; **IR** (thin film cm^{-1}): 3364, 2980, 1700, 1506, 1368, 1309, 1246, 1140, 1082, 746, 689, 649, 590; **TLC** (25% EtOAc/hexanes): R_F 0.24; **HRMS** (ESI): Calcd. for $[M + NH_4]^+$ $C_{22}H_{23}NO_4S$: 415.1692, Found: 415.1715.

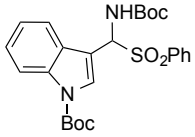


***tert*-Butyl (furan-2-yl(phenylsulfonyl)methyl)carbamate** (**41l):** The title compound was prepared according to General Procedure A

(method 1) using furfural (10.0 mmol) affording amido-sulfone **41l** (2.02 g, 6.0 mmol, 60% yield) as a white solid. Analytical data for **41l**: **mp** 159.8-161.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90-7.88 (d, *J*=7.6 Hz, 2H), 7.64-7.63 (m, 1H), 7.55-7.51 (m, 2H), 7.48 (m, 1H), 6.58-6.57 (d, *J* = 2.8 Hz, 1H), 6.44-6.43, (d, *J* = 1.6 Hz, 1H), 6.04-6.01 (d, *J* = 10.4 Hz, 1H), 5.86-5.84 (d, *J* = 10.4 Hz), 1.28 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 153.3, 144.2, 142.9, 136.4, 134.0, 129.4, 129.0, 112.3, 111.1, 81.3, 68.9, 27.9, 27.7; **IR** (thin film cm^{-1}): 3276, 2981, 1700, 1368, 1308, 1143, 1082, 1013, 759, 687, 575; **TLC** (25% EtOAc/hexanes): R_F 0.22; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{16}H_{19}NO_5S$: 338.1062, Found: 338.1081.

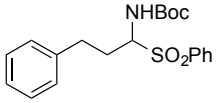


***tert*-Butyl ((phenylsulfonyl)(thiophen-2-yl)methyl)carbamate (41m):** The title compound was prepared according to General Procedure A (method 1) using 2-Thiophenecarboxaldehyde (10.0 mmol) affording amido-sulfone **41m** (1.24 g, 3.5 mmol, 35% yield) as a white solid. Analytical data for **41m**: **mp** 151.0-152.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93-7.91 (d, *J*=7.6 Hz, 2H), 7.67-7.63 (t, *J* = 7.6 Hz, 1H), 7.56-7.52 (t, *J* = 7.6 Hz, 2H), 7.42-7.41 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.27-7.26 (m, 1H), 7.08-7.06, (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 6.20-6.17 (d, *J* = 10.8 Hz, 1H), 5.66-5.64 (d, *J* = 10 Hz, 1H), 1.26 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.0, 136.6, 134.1, 131.5, 129.5, 129.0, 127.7, 127.3, 81.4, 70.2, 28.0; **IR** (thin film cm^{-1}): 3325, 2979, 1701, 1508, 1368, 1309, 1249, 1143, 853, 688, 590, 551; **TLC** (25% EtOAc/hexanes): R_F 0.24; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{16}H_{19}NO_4S_2$: 354.0833, Found: 354.0855.



***tert*-Butyl((phenylsulfonyl)(*p*-tolyl)methyl)carbamate (41n):** The title compound was prepared according to General

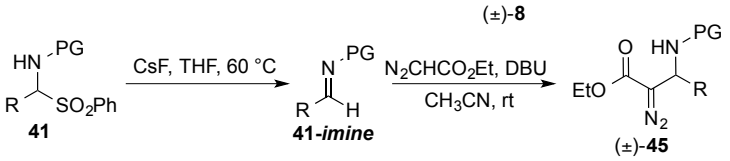
Procedure B (method 2) using *tert*-butyl 2-formyl-1*H*-indole-1-carboxylate[10] (10.0 mmol) affording amido-sulfone **41n** (2.77 g, 5.7 mmol, 57% yield) as a white solid. Analytical data for **41n**: **mp** 136-137 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19-8.17 (d, *J*=8.0 Hz, 1H), 8.01-7.89 (d, *J*=7.6 Hz, 2H), 7.88 (s,1H), 7.68-7.63 (m, 2H), 7.58-7.54 (t, *J* = 7.6 Hz, 2H), 7.38-7.34 (d, *J* = 7.6 Hz, 1H), 7.31-7.27 (t, *J* = 7.6 Hz, 1H), 6.22-6.20 (d, *J* = 10.0 Hz, 1H), 5.69-5.66 (d, *J* = 10.0 Hz, 1H), 1.68 (s, 9 H), 1.25 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 153.4, 149.1, 136.8, 135.2, 133.9, 129.5, 129.0, 128.4, 126.6, 125.1, 123.2, 119.5, 115.3, 110.4, 84.5, 81.2, 67.9, 28.0, 27.9; **IR** (thin film cm^{-1}): 3649, 3001, 2979, 2814, 1741, 1680, 1558, 1397, 1360, 1242, 1156, 1133, 1102, 760; **TLC** (20% EtOAc/hexanes): R_F 0.52; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{25}H_{30}N_2O_6S$: 509.1723, Found: 509.1762.



***tert*-Butyl((phenylsulfonyl)(*p*-tolyl)methyl)carbamate** (**41o**): The title compound was prepared according to General Procedure A (method 1) using hydrocinnamaldehyde (10.0 mmol) affording amido-sulfone **41o** (3.15 g, 8.4 mmol, 84% yield) as a white solid. Note: Carbamate **1o** shows existence of slow rotation (rotamers) in ^{1}H NMR spectra obtained at ambient temperature. Analytical data for **1o**: **mp** 128.0-128.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.92-7.90 (d, *J* = 7.6 Hz, 2H), 7.69-7.63 (m, 1H), 7.59-7.53 (m, 2H), 7.33-7.31 (m 2H), 7.29-7.28 (m, 1H), 7.27-7.19 (m, 2H), 5.11-5.08, (d, *J* = 10.8 Hz, 1H), 4.91-4.85 (dt, *J* = 10.8 Hz, 3.2 Hz, 1H), 2.93-2.86 (m, 1H), 2.80-2.72 (m, 1H), 2.68-2.60 (m, 1H), 2.14-2.06 (m, 1H), 1.25 (s, 7H), 1.08 (s, 2H); **^{1}H NMR** (600 MHz, $CDCl_3$, 55 °C): δ 7.98-7.88 (m, 2H), 7.60 (bs, 1H), 7.51 (m, 2H), 7.27-7.26 (m 2H), 7.21-7.16 (m, 3H), 4.99 (bs, 1H), 4.87

(bs,1H), 2.86 (bs, 1H), 2.75 (bs, 1H), 2.59 (bs, 1H), 2.08 (bs, 1H), 1.24-1.12 (bs, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 153.6, 139.7, 136.8, 133.8, 129.2, 129.0, 128.6, 128.4, 126.4, 80.8, 70.2, 31.4, 28.0, 27.9, 27.5; **IR** (thin film cm^{-1}): 3336, 2978, 1718, 1520, 1447, 1367, 1309, 1246, 1142, 1083, 749, 688, 598, 545; **TLC** (25% EtOAc/hexanes): R_F 0.53; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{20}H_{25}NO_4S$: 376.1582, Found: 376.1608.

2.5.3 General Procedure B for the Preparation of α-Diazo Esters 45a-o



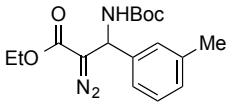
A 50 mL round-bottomed flask equipped with a magnetic stir bar and a reflux condenser was charged with CsF (6.0 mmol, 2 equiv) and heated under vacuum (~ 0.5 kPa, 95 °C) for 2 min. Amido-sulfone (2.0 mmol, 1 equiv) was then added and the flask was sealed with a rubber septum and purged with N_2. THF was added to give a solution with $[\mathbf{41}]_0$ = 0.1 M and the nitrogen line was removed. The reaction was heated at 60 °C for 12 h, filtered through celite using DCM, and concentrated *in vacuo.* The crude residue was immediately dissolved in CH_3CN (16 mL) and the reaction flask was sealed with a rubber septum and purged with N_2. Ethyl diazoacetate (2.6 mmol, 1.3 equiv) was added followed by DBU (0.6 mmol, 0.3 equiv). The reaction was stirred at room temperature for 3-6 h (monitored by TLC), then diluted with EtOAc and water. The organic layer was washed with water (3 x 50 mL), brine, and dried over Na_2SO_4. Concentration *in vacuo* afforded the α-diazo esters which were purified by flash chromatography using an eluent gradient of 7.5% EtOAc/hexanes to 15% EtOAc/hexanes.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-phenylpropanoate (**45a):** The title compound was prepared according to General Procedure B using **41a** (2.0 mmol) affording β-amino-α-diazo ester **45a** (0.41 g, 1.28 mmol, 64% yield) as a yellow oil. Analytical data for **45a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 5H), 5.66 (bs, 1H), 5.51 (bs, 1H), 4.23-4.18 (m, 2H), 1.44 (s, 9H), 1.25-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.8, 154.9, 139.0, 128.7, 128.5, 128.3, 127.9, 126.1, 125.7, 80.2, 76.7, 60.9, 51.0, 28.2, 14.3; **IR** (thin film cm^{-1}): 3346, 2979, 2095, 1698, 1496, 1247, 1168, 885, 701; **TLC** (15% EtOAc/hexanes): R_F 0.24; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{16}H_{21}N_3O_4$: 342.1430, Found: 342.1443.

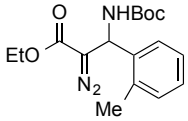
Ethyl 3-(((benzyloxy)carbonyl)amino)-2-diazo-3-phenylpropanoate (**45b):** The title compound was prepared according to General Procedure B using **41b** (2.0 mmol) affording β-amino-α-diazo ester **45b** (0.40 g, 1.18 mmol, 59% yield) as a yellow oil. Analytical data for **45b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.31 (m, 10H), 6.04 (bs, 1H), 5.81-5.79 (d, *J* = 7.2 Hz, 1H), 5.15 (s, 2H), 4.25-4.19 (m, 2H), 1.26-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.6, 138.5, 136.1, 129.0, 128.5, 128.2, 128.1, 126.1, 67.2, 61.1, 51.7, 14.3; **IR** (thin film cm^{-1}): 3330, 2096, 1697, 1523, 1497, 1454, 1372, 1244, 1103, 1027, 938, 699; **TLC** (15% EtOAc/hexanes): R_F 0.10; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{19}H_{19}N_3O_4$: 376.1274, Found: 376.1289.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-(*p*-tolyl)propanoate (**45c):** The title compound was prepared according to General Procedure B using **41c** (2.0 mmol)

affording β-amino-α-diazo ester **45c** (0.47 g, 1.42 mmol, 71% yield) as a yellow solid. Analytical data for **45c**: **mp** 70.8-71.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.22 (m, 2H), 7.17-7.15 (m, 2H), 5.64-5.62 (d, *J* = 8 Hz, 1H), 5.41 (bs, 1H), 4.22-4.20 (m, 2H), 2.33 (s, 3H), 1.45 (s, 9H) 1.26-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.8, 154.8, 137.7, 136.0, 129.4, 129.1, 126.0, 80.1, 60.9, 50.8, 28.2, 21.0, 14.3; **IR** (thin film cm^{-1}): 3352, 2950, 2931, 2014, 1699, 1513, 1369, 1291, 1247, 1169, 1100, 1020, 889, 741; **TLC** (15% EtOAc/hexanes): R_F 0.21; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{17}H_{23}N_3O_4$: 334.1767, Found: 334.1780.

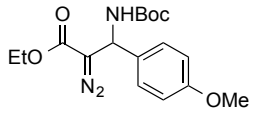


Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-(*m*-tolyl)propanoate (**45d):** The title compound was prepared according to General Procedure B using **41d** (2.0 mmol) affording β-amino-α-diazo ester **45d** (0.47 g, 1.42 mmol, 71% yield) as a yellow oil. Analytical data for **45d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24-7.22 (m, 1H), 7.14-7.09 (m, 3H), 5.64-5.62 (d, *J* = 6.8 Hz, 1H), 5.47 (bs, 1H), 4.23-4.18 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.45 (s, 9H), 1.26-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.8, 154.8, 138.9, 138.5, 128.8, 128.7, 126.8, 123.1, 80.2, 60.9, 28.2, 21.4, 14.3; **IR** (thin film cm^{-1}): 3348, 2979, 2931, 2094, 1699, 1493, 1368, 1292, 1250, 1165, 1100, 878, 779, 709; **TLC** (15% EtOAc/hexanes): R_F 0.21; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{17}H_{23}N_3O_4$: 356.1587, Found: 356.1603.

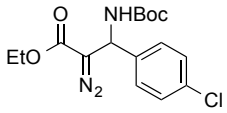


Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-(*o*-tolyl)propanoate (**45e):** The title compound was prepared according to General Procedure B using **41e** (2.0 mmol) affording β-amino-α-

diazo ester **45e** (0.46 g, 1.38 mmol, 69% yield) as a yellow solid. Analytical data for **45e**: **mp** 85-86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.30 (m, 1H), 7.22-7.19 (m, 3H), 5.81 (d, *J* = 6.8 Hz, 1H), 5.15 (bs, 1H), 4.25-4.19 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.43 (s, 9H), 1.27-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 165.7, 154.7, 137.0, 135.3, 130.9, 128.0, 126.3, 125.5, 80.2, 61.0, 47.8, 28.2, 19.1, 14.3; **IR** (thin film cm^{-1}): 3353, 2979, 2094, 1699, 1507, 1368, 1333, 1286, 1245, 1169, 1100, 1019, 888, 740; **TLC** (20% EtOAc/hexanes): R_F 0.36; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{17}H_{23}N_3O_4$: 356.1587, Found: 356.1584.

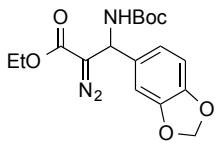


Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-(4-methoxyphenyl)propanoate (**45f):** The title compound was prepared according to General Procedure B using **41f** (2.0 mmol) affording β-amino-α-diazo ester **45f** (0.42 g, 1.20 mmol, 60% yield) as a yellow solid. Analytical data for **45f**: **mp** 97-98 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.6 (bs, 1H), 5.38 (bs, 1H), 4.22-4.19 (q, *J* = 7.2 Hz, 4H), 3.79 (s, 3H), 1.45 (s, 9H), 1.26-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 159.3, 154.8, 131.1, 127.4, 114.2, 60.94, 55.3, 50.6, 28.3, 14.4; **IR** (thin film cm^{-1}): 3353, 2979, 2934, 2361, 2094, 1698, 1513, 1369, 1294, 1249, 1168, 1100, 1032, 844, 741; **TLC** (20% EtOAc/hexanes): R_F 0.28; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{17}H_{23}N_3O_5$: 372.1536, Found: 372.1535.

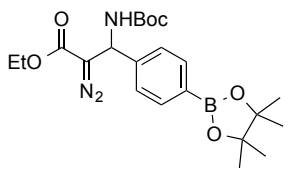


Ethyl 3-((*tert*-butoxycarbonyl)amino)-3-(4-chlorophenyl)-2-diazopropanoate (45g): The title compound was prepared according to General Procedure B using **41g** (2.0 mmol) affording β-amino-α-diazo ester **45g** (0.38 g, 1.08 mmol, 54% yield) as a yellow

solid. Analytical data for **45g**: **mp** 102-103 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.32 (d, *J* = 8.8 Hz, 1H), 7.30-7.28 (d, *J* = 8.8 Hz, 1H), 5.64-5.62 (d, *J* = 7.6 Hz, 1H), 5.44 (bs, 1H), 4.24-4.19 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.45 (s, 9H), 1.27-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 165.7, 154.9, 137.6, 133.8, 129.0, 127.6, 80.5, 61.1, 50.7, 28.3, 14.4; **IR** (thin film cm^{-1}): 3344, 2979, 2933, 2096, 1735, 1699, 1506, 1454, 1371, 1308, 1253, 1156, 1077, 1019, 766, 747; **TLC** (20% EtOAc/hexanes): R_F 0.38; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{16}H_{20}ClN_3O_4$: 376.1040, Found: 376.1039.

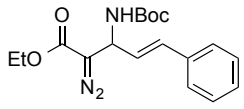


Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-3-((*tert*-butoxycarbonyl)amino)-2-diazopropanoate (**45h):** The title compound was prepared according to General Procedure B using **41h** (2.0 mmol) affording β-amino-α-diazo ester **45h** (0.52 g, 1.42 mmol, 71% yield) as a yellow solid. Analytical data for **45h**: **mp** 102-102.7 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.83-6.75 (m, 3H), 5.94 (s, 2H), 5.57-5.55 (d, *J* = 7.2 Hz, 1H), 5.39 (bs, 1H), 4.23-4.18 (q, *J* = 7.2 Hz, 2H), 1.44 (s, 9H), 1.26-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.8, 154.8, 148.1, 147.3, 133.0, 119.5, 108.3, 106.8, 101.2, 80.3, 61.0, 28.2, 14.4; **IR** (thin film cm^{-1}): 3351, 2979, 2933, 2094, 1693, 1490, 1368, 1247, 1167, 930, 741; **TLC** (15% EtOAc/hexanes): R_F 0.13; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{17}H_{21}N_3O_6$: 386.1328, Found: 386.1346.

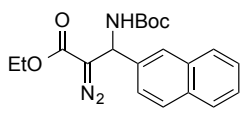


Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (**45i):** The title compound was

prepared according to General Procedure B using **41i** (2.0 mmol) affording β-amino-α-diazo ester **45i** (0.42 g, 0.94 mmol, 47% yield) as a yellow solid. Analytical data for **45i**: **mp** 51.2-53.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81-7.79 (d, *J* = 8 Hz, 2H), 7.35-7.33 (d, J = 8 Hz, 2H), 5.68-5.66 (d, *J* = 7.2 Hz, 1H), 5.40 (bs, 1H), 4.23-4.18 (q, *J* = 7.2 Hz, 2H), 1.45 (s, 9H), 1.34 (s, 12H) 1.26-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.9, 135.3, 125.4, 83.8, 61.0, 28.3, 24.8, 14.4; **IR** (thin film cm^{-1}): 3350, 2979, 2932, 2095, 1698, 1612, 1508, 1362, 1247, 1145, 1020, 888, 740; **TLC** (15% EtOAc/hexanes): R_F 0.14; **HRMS** (ESI): Calcd. for $[M + NH_4]^+$ $C_{22}H_{32}BN_3O_6$: 463.2728, Found: 463.2750.

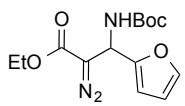


(*E*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-5-phenylpent-4-enoate (**45j):** The title compound was prepared according to General Procedure B using **41j** (2.0 mmol) affording β-amino-α-diazo ester **45j** (0.33 g, 0.96 mmol, 48% yield) as a yellow solid. Analytical data for **45i**: **mp** 76.0-76.6 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, *5*H), 6.63-6.59 (d, J = 15.6 Hz, 1H), 6.33-6.27 (dd, *J* = 16 Hz, 6.4 Hz, 1H), 5.40 (bs, 1H), 4.27-4.22 (q, *J* = 7.2 Hz, 2H), 1.46 (s, 9H), 1.29-1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.8, 135.9, 131.7, 128.5, 128.0, 126.6, 125.6, 80.2, 76.7, 60.9, 49.8, 29.2 14.4; **IR** (thin film cm^{-1}): 3345, 2979, 2933, 2094, 1696, 1496, 1369, 1292, 1168, 1016, 967, 745, 693; **TLC** (15% EtOAc/hexanes): R_F 0.20; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{18}H_{23}N_3O_4$: 346.1767, Found: 346.1781.

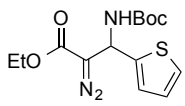


Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-(naphthalen-2-yl)propanoate (**45k):** The title compound was prepared according to General Procedure B using **41k** (2.0 mmol) affording β-

amino-α-diazo ester **45k** (0.47 g, 1.26 mmol, 63% yield) as a yellow oil. Analytical data for **45k**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86-7.80 (m, 4H), 7.51-7.44 (m, 3H), 5.85-5.83 (d, *J* = 7.2 Hz, 1H), 5.52(bs, 1H), 4.27-4.19 (m, 2H), 1.47 (s, 9H), 1.27-1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.9, 133.2, 133.0, 128.9, 128.0, 127.6, 126.4, 126.3, 125.0, 124.2, 61.1, 28.3, 14.4; **IR** (thin film cm^{-1}): 3346, 2979, 2933, 2094, 1696, 1507, 1369, 1250, 1167, 1098, 1020, 861, 745; **TLC** (15% EtOAc/hexanes): R_F 0.19; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{20}H_{23}N_3O_4$: 392.1587, Found: 392.1606.

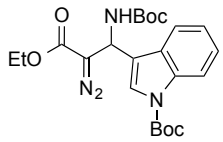


Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-(furan-2-yl)propanoate (**45l):** The title compound was prepared according to General Procedure B using **41l** (2.0 mmol) affording β-amino-α-diazo ester **45l** (0.47 g, 1.26 mmol, 63% yield) as a yellow solid. Analytical data for **45l**: **mp** 68.2-69.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 (s, 1H), 6.33-6.32 (m, 1H), 6.28-6.27 (d, *J* = 3.2 Hz, 1H), 5.70-5.68 (d, *J* = 6.8, 1H), 5.43 (bs, 1H), 4.25-4.18 (q, *J* = 7.2 Hz, 2H), 1.45 (s, 9H), 1.27-1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.6, 151.1, 142.4, 110.5, 107.0, 61.0, 28.2, 14.4; **IR** (thin film cm^{-1}): 3343, 2980, 2934, 2099, 1699, 1505, 1370, 1254, 1169, 1012, 880, 741, 598; **TLC** (15% EtOAc/hexanes): R_F 0.20; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{14}H_{19}N_3O_5$: 310.1403, Found: 310.1415.



Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-3-(furan-2-yl)propanoate (**45m):** The title compound was prepared according to General Procedure B using **41m** (2.0 mmol) affording β-amino-α-diazo ester **45m** (0.47 g, 1.26 mmol, 63% yield) as a yellow oil. Analytical data for

45m: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21-7.19 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 6.97-6.96 (dd, *J* = 2.4 Hz, 1.2 Hz, 1H), 6.93-6.91 (m, 1H), 5.86-5.84 (d, *J* = 67.6, 1H), 5.68 (bs, 1H), 4.24-4.18 (q, *J* = 7.2 Hz, 2H), 1.43 (s, 9H), 1.26-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 165.4, 154.5, 143.0, 126.9, 125.0, 124.6, 80.3, 61.0, 47.6, 28.1, 14.2; **IR** (thin film cm^{-1}): 3393, 2979, 2934, 1730, 1497, 1368, 1252, 1164, 1043, 853, 708; **TLC** (15% EtOAc/hexanes): R_F 0.10; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{14}H_{19}N_3O_4S$: 348.0994, Found: 348.0990.

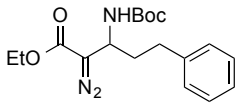


***tert*-Butyl-2-(1-((*tert*-butoxycarbonyl)amino)-2-diazo-3-ethoxy-3-oxopropyl)-1*H*-indole-1-carboxylate (45n):** The title compound was prepared according to General Procedure B using **41n** (2.0 mmol) affording β-amino-α-diazo ester **45n** (0.57 g, 1.24 mmol, 62% yield) as a yellow solid. Analytical data for **45n**: **mp** 122-123 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.56 (s, 1H), 7.52-7.50 (d, J = 8.4 Hz, 1H), 7.35-7.32 (t, J = 7.8 Hz, 1H), 7.27-7.24 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 5.88 (bs, 1H), 5.40 (bs, 1H), 4.27-4.23 (q, *J* = 7.2 Hz, 2H), 1.67 (s, 9H), 1.48 (s, 9H), 1.29-1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 154.9, 149.5, 127.9, 126.1, 124.9, 123.6, 122.9, 119.0, 115.5, 84.1, 61.1, 28.3, 28.1, 14.4; **IR** (thin film cm^{-1}): 3360, 2979, 2934, 2096, 1735, 1699, 1506, 1454, 1371, 1308, 1253, 1156, 1077, 1019, 766, 747; **TLC** (20% EtOAc/hexanes): R_F 0.38; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{23}H_{30}N_4O_6$: 481.2063, Found: 481.2068.

2.5.4 Preparation of α–Diazo Ester 45o

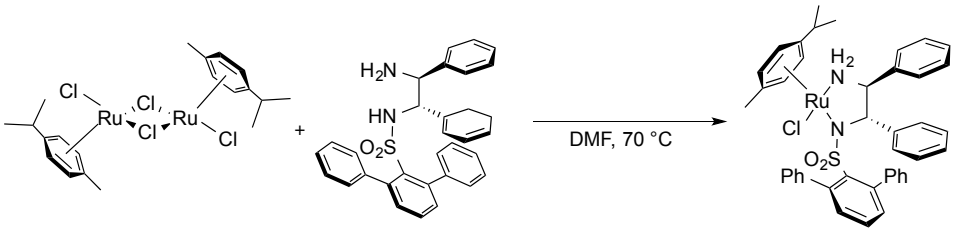
A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with $CsCO_3$ (10.0 mmol, 5 equiv) and heated under vacuum (~ 0.5 kPa,

95 °C) for 2 min. **41o** (2.0 mmol, 1 equiv) was then added and the flask was sealed with a rubber septum and purged with N_2. DCM was added to give a solution with [**41o**] = 0.1 M and the nitrogen line was removed. The reaction was heated at 45 °C for 90 min, filtered through celite using 20% DCM/hexanes, and concentrated *in vacuo.* The crude residue was immediately solvated with 16 mL of CH_3CN and the reaction flask was sealed with a rubber septum, purged with nitrogen, and cooled to -40 °C. Ethyl diazoacetate (2.6 mmol, 1.3 equiv) was added followed by DBU (0.6 mmol, 0.3 equiv). The flask was stirred at -40 °C for 52 h (monitored by TLC) then diluted with EtOAc and water. The organic layer was washed with water (3 x 30 mL), brine, and dried over Na_2SO_4. Concentration *in vacuo* afforded **45o** which was purified by flash chromatography using an eluent gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes.



Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-diazo-5-phenylpentanoate (**45o):** 2.0 mmol scale: (0.43 g, 1.16 mmol, 58% yield) as a yellow oil. Analytical data for **45o**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.27 (m, 2H), 7.19-7.17 (m, 3H), 5.15 (bs,1H), 4.33 (bs, 1H), 4.23-4.18 (q, *J* = 7.2 Hz, 2H), 2.70-2.68 (m, 2H), 2.14 (bs, 1H), 1.44 (s, 9H), 1.29-1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.1, 140.6, 128.5, 128.3, 126.1, 79.9, 60.7, 48.3, 35.0, 32.6, 28.2, 14.4; **IR** (thin film cm^{-1}): 3349, 2979, 2930, 2092, 1694, 1496, 1368, 1293, 1170, 1114, 1024, 873, 743, 700; **TLC** (15% EtOAc/hexanes): R_F 0.21; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{18}H_{25}N_3O_4$: 370.1743, Found: 370.1761.

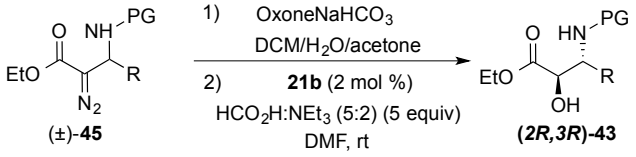
2.5.5 Preparation of complex 21b



21b

To a flame-dried 1-dram vial equipped with a magnetic stir bar were added [RuCl(arene)]$_2$ (0.005 mmol, 1.0 equiv), *N*-((1*S*,2*S*)-2-amino-1,2-diphenylethyl)-[1,1':3',1''-terphenyl]-2'-sulfonamide (0.02 mmol, 4.0 equiv), and DMF (1.0 mL). The vial was capped with a PTFE-lined screw cap, and heated to 70 °C for 30 min. Complex **7** was used without purification as a solution of DMF.

2.5.6 General Procedure C for the ATH-DKR of β-Amino-α-Keto-Esters



Method 1:

A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with Oxone® (2.5 mmol, 5 equiv), $NaHCO_3$ (10 mmol, 20 equiv), 15 mL of 1:2 (v/v) acetone/H_2O and cooled to 0 °C. To this mixture, a solution of diazo ester **45** (0.5 mmol) dissolved in DCM ([**45**]$_0$) = 0.05 M) was added and the solution was warmed to rt. Upon complete oxidation to the α-keto ester (monitored by color change and/or TLC analysis), the reaction mixture was diluted with DCM/H_2O. The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic extracts were dried over

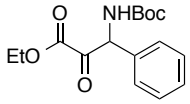
Na_2SO_4, filtered and concentrated *in vacuo* providing **46**. This crude residue was dissolved in DMF (2.5 mL) and the reaction flask was sealed with a rubber septum and purged with nitrogen. Complex **21b** (0.01 mmol, 0.02 equiv) was added as a DMF solution (see above), followed by HCO_2H:Et_3N (5:2 azeotrope, 2.5 mmol, 5 equiv). The flask was stirred at rt for 18 h (monitored by TLC) then diluted with EtOAc and water. The organic layer was washed with water (3 x 20 mL), brine, and dried over Na_2SO_4. Concentration *in vacuo* afforded the α-hydroxy esters, which were purified by flash chromatography using the indicated solvent systems. In some cases products were then recrystallized using 20% Et_2O/hexanes.

Method 2:

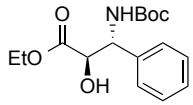
A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with Oxone® (0.6 mmol, 1.2 equiv), $NaHCO_3$ (2.5 mmol, 5 equiv), 15 mL 1:2 (v/v) acetone/H_2O and cooled to 0 °C. To this mixture, a solution of diazo ester **45** (0.5 mmol) dissolved in DCM ($[\mathbf{45}]_0$) = 0.05 M) was added and the solution was warmed to rt. Upon complete oxidation to the α-keto ester (monitored by color change and/or TLC analysis), the reaction mixture was diluted with DCM/H_2O. The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* providing **46**. The crude residue was dissolved in DMF (2.5 mL) and the reaction flask was sealed with a rubber septum and purged with nitrogen. Complex **21b** (0.01 mmol, 0.02 equiv) was added followed by HCO_2H:Et_3N (5:2 azeotrope, 2.5 mmol, 5 eqiv.). The flask was stirred at rt for 18

h (monitored by TLC) then diluted with EtOAc and water. The organic layer was washed with water (3 x 20 mL), brine, and dried over Na_2SO_4. Concentration *in vacuo* afforded the α-hydroxy-esters which were purified by flash chromatography using the indicated solvent systems. In some cases products were then recrystallized using 20% Et_2O/hexanes.

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-phenylpropanoate (**43a):** The title compound was prepared according to General Procedure C (method 1) using **45a** (0.5 mmol) affording β-amino-α-hydroxy ester **43a** (0.11 g, 0.37 mmol, 74% overall yield) as a white solid.



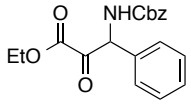
Analytical data for **42a**: **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed): δ 7.37-7.30 (m, 5H), 6.05-6.03 (d, *J* = 6.8 Hz, 1H), 5.62-5.61 (d, *J* = 5.6 Hz, 1H), 4.23-4.16 (m, 2H), 1.41 (s, 9H), 1.23-1.20 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.4, 159.6, 154.7, 133.7, 129.2, 128.9, 128.5, 80.3, 76.7, 62.7, 61.0, 28.2, 13.7.



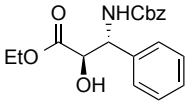
Analytical data for **43a**: **mp** 116.8-117.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed): δ 7.28-7.26 (m, 5H), 5.64-5.62 (d, *J* = 7.6 Hz, 1H), 5.12-5.10 (d, *J* = 7.2 Hz, 1H), 4.57 (bs, 1H), 4.16-4.08 (m, 2H), 2.94-2.93 (d, *J* = 6.4 Hz), 1.42 (s, 9H), 1.25-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.8, 154.9, 128.3, 128.1, 127.4, 79.8, 73.2, 62.0, 56.5, 28.3, 14.0; **IR** (thin film cm^{-1}): 3372, 1716, 1696, 1520, 1457, 1366, 1169, 1112, 700, 618, 522; **TLC** (25% EtOAc/hexanes): R_F 0.34; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{16}H_{23}NO_5$: 310.1654, Found: 310.1668. **SFC** analysis: AD column, 2% modifier,

1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 23.4 min, $t_{R\ (major)}$ = 19.0 min, 99:1 er (>99.5:0.5 recryst.); **$[\alpha]_D^{25}$** -81.5 (c = 0.3, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-(((benzyloxy)carbonyl)amino)-2-hydroxy-3-phenylpropanoate (43b): The title compound was prepared according to General Procedure C (method 1) using **45b** (0.5 mmol) affording β-amino-α-hydroxy ester **(–)-43b** (0.13 g, 0.39 mmol, 78% overall yield) as a white solid. The product was recrystallized using 20% Et_2O/hexanes.

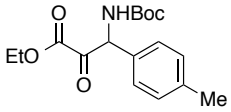


Analytical data for **42b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.34 (m, 10H), 6.14-6.13 (d, *J* = 6.8 Hz, 1H), 6.00-5.98 (d, *J* = 6.4 Hz, 1H) 5.14-5.04 (m, 2H), 4.22-4.19 (m, 2H), 1.24-1.20 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 188.8, 159.5, 155.2, 135.9, 133.4, 129.2, 129.1, 128.5, 128.4, 128.1, 128.1, 77.3, 67.1, 62.7, 61.3, 13.7.

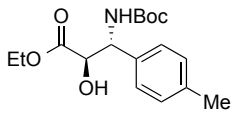


Analytical data for **(–)-43b**: **mp** 108.5-109.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 10H), 5.87-5.85 (d, *J* = 9.2 Hz, 1H), 5.18-5.14 (m, 1H), 5.11-5.04 (m, 2H), 4.61-4.58 (dd, *J* = 6.4 Hz, 3.2 Hz, 1H), 4.17-4.09 (m, 2H), 2.91-2.90 (d, *J* = 6.4 Hz, 1H), 1.26-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.7, 155.5, 136.2, 128.5, 128.4, 128.3, 127.5, 73.0, 67.0, 62.2, 56.9, 14.0; **IR** (thin film cm^{-1}): 3750, 3735, 3710, 3689, 3675, 3649, 3381, 3064, 1726, 1521, 1221, 1114, 1026, 700; **TLC** (25% EtOAc/hexanes): R_F 0.17; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{19}H_{21}NO_5$: 344.1498, Found: 344.1512. **SFC** analysis: WO column, 7% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 9.7 min, $t_{R\ (major)}$ = 12.0 min, 94:6 er (>99.5:0.5 recryst.); **$[\alpha]_D^{25}$** +6.2 (c = 0.25, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-(*p*-tolyl)propanoate (**43c**)**:** The title compound was prepared according to General Procedure C (method 1) using **45c** (0.5 mmol) affording β-amino-α-hydroxy ester **43c** (0.14 g, 0.44 mmol, 88% overall yield) as a white solid. The product was recrystallized using 20% Et_2O/hexanes.



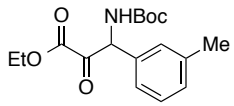
Analytical data for **42c**: **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed): δ 7.20-7.14 (m, 4H), 6.14-6.13 (d, *J* = 6.8 Hz, 1H), 6.02-6.00 (d, *J* = 6.8 Hz, 1H) 5.58-5.56 (d, *J* = 6 Hz, 1H), 4.24-4.15 (m, 2H), 2.31 (s, 3H), 1.41 (s, 9H), 1.24-1.20 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.4, 159.7, 154.7, 138.9, 130.6, 129.9, 128.4, 80.2, 76.7, 62.6, 60.7, 28.2, 21.1, 13.8.



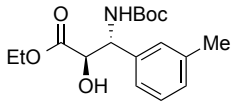
Analytical data for **43c**: **mp** 74.6-75.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed): δ 7.15-7.08 (m, 4H), 5.60-5.58 (d, *J* = 8.4 Hz, 1H), 5.08-5.07 (d, *J* = 6 Hz, 1H), 4.56 (bs, 1H), 4.18-4.09 (m, 2H), 2.89 (bs, 1H) 2.30 (s, 3H), 1.42 (s, 9H) 1.27-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.9, 155.0, 137.8, 133.8, 129.1, 127.3, 79.8, 73.2, 62.0, 56.3, 28.3, 21.1, 14.1; **IR** (thin film cm^{-1}): 3392, 2979, 1716, 1507, 1336, 1247, 1167, 1119, 1021, 882, 570; **TLC** (25% EtOAc/hexanes): R_F 0.38; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{17}H_{25}NO_5$: 324.1811, Found: 324.1825. **HPLC** analysis: Chiralpak IA, H/IPA = 90:10, flow rate = 1.0 mL/min, 210 nm; $t_{R\ (minor)}$ = 8.3 min, $t_{R\ (major)}$ = 11.1 min, 99:1 er (>99.5:0.5 recryst.); **$[\alpha]_D^{25}$** -272.6 (c = 0.28, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-(*m*-tolyl)propanoate (**43d**)**:** The title compound was prepared according to General

Procedure C (method 1) using **45c** (0.5 mmol) affording β-amino-α-hydroxy ester **43d** (0.14 g, 0.44 mmol, 88% overall yield) as a white solid. The product was recrystallized using 20% Et_2O/hexanes.



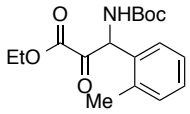
Analytical data for **42d**: **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed) : δ 7.27-7.22 (m, 2H), 7.14-7.10 (m, 2H), 6.03-6.01 (d, *J* = 6.8 Hz, 1H), 5.59-5.57 (d, *J* = 6.0 Hz, 1H) 4.26-4.17 (m, 2H), 2.33 (s, 3H), 1.42 (s, 9H), 1.26-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.5, 160.0, 154.7, 139.0, 133.5, 129.8, 129.1, 125.6, 80.3, 76.7, 62.6, 70.0, 28.2, 21.3, 13.8.



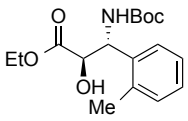
Analytical data for **43d**: **mp** 98.8-99.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed): δ 7.20-7.16 (m, 1H), 7.08-7.04 (m, 3H) 5.62-5.60 (d, *J* = 8.4 Hz, 1H), 5.08-5.07 (d, *J* = 6 Hz, 1H), 4.58-4.55 (dd, *J* = 6.4 Hz, 3.2 Hz, 1H), 4.16-4.10 (m, 2H), 2.92-2.90 (d, *J* = 7.2 Hz, 1H) 2.31 (s, 3H), 1.43 (s, 9H) 1.26-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.9, 155.0, 137.9, 136.7, 128.9, 128.3, 128.2, 124.4, 79.8, 73.2, 62.0, 56.6, 28.3, 21.4, 14.6; **IR** (thin film cm^{-1}): 3392, 2979, 2933, 1716, 1506, 1366, 1245, 1165, 1114, 1021, 864, 779, 710; **TLC** (25% EtOAc/hexanes): R_F 0.38; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{17}H_{25}NO_5$: 324.1811, Found: 324.1824. **HPLC** analysis: Chiralpak IA, H/IPA = 90:10, flow rate = 1.0 mL/min, 210 nm; $t_{R\ (minor)}$ = 6.8 min, $t_{R\ (major)}$ = 8.7 min, 98:2 er (>99.5:0.5 recryst.); **$[\alpha]_D^{25}$** -64.27 (c = 0.15, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-(*o*-tolyl)propanoate (**43e):** The title compound was prepared according to General

Procedure C (method 1) using **45e** (0.5 mmol) affording β-amino-α-hydroxy ester **43e** (0.12 g, 0.36 mmol, 72% overall yield) as a white solid.

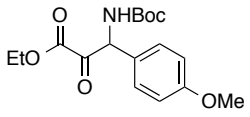


Analytical data for **42e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26-7.24 (m, 2H), 7.19-7.14 (m, 1H), 6.98-6.96 (d, *J* = 7.6 Hz, 1H), 6.29-6.27 (d, J = 7.6 Hz, 1H), 5.39-5.37 (bd, 1H) 4.26-4.13 (m, 2H), 2.59 (s, 3H), 1.45 (s, 9H), 1.24-1.20 (t, *J* = 6.8 Hz, 3H).



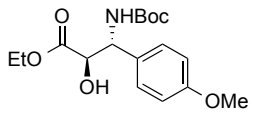
Analytical data for **43e**: **mp** 73-74 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42-7.40 (bm,1H), 7.17-7.11(m, 3H), 5.42-5.39 (bm, 2H), 4.60 (bs, 1H), 4.18-4.10 (m, 1H), 4.05-3.97 (m, 1H), 3.09-3.07 (d, *J* = 6.4 Hz, 1H), 2.42 (s, 3H), 1.42 (s, 9H) 1.16-1.12 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.2, 155.1, 136.0, 130.6, 127.9, 126.8, 126.2, 79.8, 72.7, 62.0, 51.6, 28.3, 19.5, 13.8; **IR** (thin film cm^{-1}): 3394, 3058, 2979, 2934, 1714, 1496, 1367, 1245, 1169, 1126, 1021, 880, 759, 733; **TLC** (20% EtOAc/hexanes): R_F 0.24; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{17}H_{25}NO_5$: 346.1631, Found: 346.1629. **SFC** analysis: OD column, 5 % modifier, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 8.7 min, $t_{R\ (major)}$ = 9.7 min, 95:5 er; **$[\alpha]_D^{25}$** -424.9 (c = 0.85, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-(4-methoxyphenyl)propanoate (**43f):** The title compound was prepared according to General Procedure C (method 1) using **45f** (0.5 mmol) affording β-amino-α-hydroxy ester **43f** (0.14 g, 0.41 mmol, 81% overall yield) as a white solid.



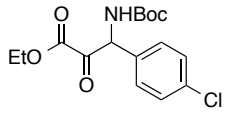
Analytical data for **42f**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24-7.21 (d, J = 8.8 Hz, 2H), 6.89-6.85 (d, J = 8.8 Hz, 2H), 6.00-

5.98 (d, *J* = 6.8 Hz, 1H), 5.56-5.54 (bd, 1H) 4.25-4.16 (m, 2H), 3.78 (s, 3H), 1.41 (s, 9H), 1.26-1.22 (t, *J* = 8.0 Hz, 3H).

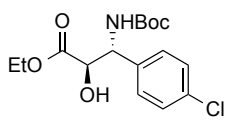


Analytical data for **43f**: **mp** 124-125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.19-7.17 (d, *J* = 8.4 Hz, 2H), 6.82-6.81 (d, *J* = 8.4 Hz, 2H 5.58 (bm, 1H), 5.07-5.04 (bm, 1H), 4.56 (bs, 1H), 4.16-4.10 (m, 2H), 3.76 (s, 3H), 2.96 (bs, 1H) 1.42 (s, 9H) 1.26-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.9, 159.3, 154.9, 128.9, 128.6, 113.7, 79.8, 73.2, 62.0, 55.9, 55.2, 55.1, 28.3, 14.1; **IR** (thin film cm^{-1}): 3392, 2979, 2935, 1715, 1613, 1512, 1366, 1299, 1249, 1167, 1118, 1031, 933, 882, 848, 735; **TLC** (20% EtOAc/hexanes): R_F 0.15; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{17}H_{25}NO_6$: 362.1580, Found: 362.1578. **SFC** analysis: WO column, 5 % modifier, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 7.3 min, $t_{R\ (major)}$ = 8.0 min, 99:1 er; **$[\alpha]_D^{25}$** -155.3 (c = 0.70, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-3-(4-chlorophenyl)-2-hydroxypropanoate (**43g**)**:** The title compound was prepared according to General Procedure C (method 1) using **45g** (0.5 mmol) affording β-amino-α-hydroxy ester **43g** (0.12 g, 0.34 mmol, 68% overall yield) as a white solid.



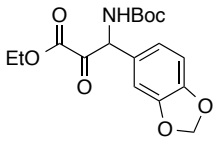
Analytical data for **42g**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.26 (d, *J* = 8.4 Hz, 2H), 7.28-7.26 (d, *J* = 8.4 Hz, 2H), 6.03-6.01 (d, *J* = 6.4 Hz, 1H), 5.67-5.65 (bd, 1H) 4.27-4.18 (m, 2H), 1.41 (s, 9H), 1.27-1.23 (t, *J* = 7.2 Hz, 3H).



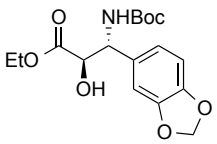
Analytical data for **43g**: **mp** 128-129 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.26 (d, *J* = 8.4 Hz, 2H), 7.22-7.19 (d, *J* = 8.4 Hz,

2H), 5.60-5.57 (d, *J* = 7.6 Hz, 1H), 5.09-5.07 (bm, 1H), 4.57-4.55 (bm, 1H), 4.19-4.10 (m, 2H), 2.91-2.89 (d, *J* = 6.0 Hz, 1H) 2.31 (s, 3H), 1.42 (s, 9H) 1.27-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.7, 154.9, 135.5, 134.0, 128.9, 128.6, 80.1, 72.9, 62.3, 55.9, 28.3, 14.1; **IR** (thin film cm^{-1}): 3385, 2979, 2933, 1716, 1492, 1392, 1367, 1249, 1168, 1116, 1015, 883, 849, 737; **TLC** (20% EtOAc/hexanes): R_F 0.24; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{16}H_{22}ClNO_5$: 366.1085, Found: 366.1082 **HPLC** analysis: Chiralpak IA, H/IPA = 96:4, flow rate = 1.0 mL/min, 210 nm; $t_{R\ (minor)}$ = 18.0 min, $t_{R\ (major)}$ = 24.7 min, 98:2 er; **$[\alpha]_D^{25}$** -242.3 (c = 0.8, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxypropanoate (**43h):** The title compound was prepared according to General Procedure C (method 1) using **45h** (0.5 mmol) affording β-amino-α-hydroxy ester **43h** (0.14 g, 0.39 mmol, 78% overall yield) as a white solid. The product was recrystallized using 20% Et_2O/hexanes.



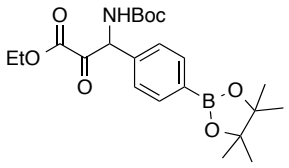
Analytical data for **42h**: **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed): δ 6.77-6.74 (m, 3H), 5.93 (bs, 3H), 5.61-5.59 (d, *J* = 5.2 Hz, 1H), 4.24-4.17 (m, 2H) 1.39 (s, 9H), 1.26-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 188.9, 159.6, 154.7, 148.2, 148.1, 127.0, 122.3, 108.7, 108.7, 101.3, 80.2, 62.6, 60.4, 30.8, 28.1, 13.7.



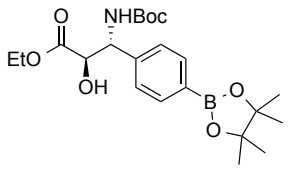
Analytical data for **43h**: **mp** 112.4-112.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed): δ 6.78 (s, 1H), 6.71 (s, 2H) 5.94-5.93 (m 2H), 5.55-5.53 (d, *J* = 8 Hz, 1H), 4.55-4.53 (t, *J* = 3.2 Hz, 1H), 4.20-4.11 (m, 2H), 2.90-2.89 (d, *J* = 6.4 Hz, 1H), 1.43 (s, 9H) 1.28-1.25 (t, *J*

= 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.8, 154.9, 147.7, 147.4, 121.0, 108.1, 107.9, 101.1, 79.9, 73.2, 62.1, 56.3, 28.3, 14.1; **IR** (thin film cm^{-1}): 3393, 2979, 1715, 1505, 1489, 1445, 1367, 1247, 1167, 1038, 933; **TLC** (25% EtOAc/hexanes): R_F 0.20; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{17}H_{23}NO_7$: 354.1553, Found: 354.1566. **HPLC** analysis: Chiralpak IA, H/IPA = 90:10, flow rate = 1.0 mL/min, 210 nm; $t_{R\ (minor)}$ = 12.4 min, $t_{R\ (major)}$ = 14.4 min, 98:2 er (>99.5:0.5 recryst.); **$[\alpha]_D^{25}$** -55.4 (c = 0.35, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (43i): The title compound was prepared according to General Procedure C (method 1) using **45i** (0.5 mmol) affording β-amino-α-hydroxy ester **43i** (0.16 g, 0.38 mmol, 76% overall yield) as a clear oil.



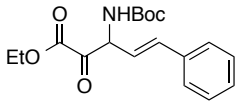
Analytical data for **42i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81-7.79 (m, 2H), 7.35-7.33 (m, 2H), 6.08-6.07 (d, *J* = 6.8 Hz, 1H), 5.67-5.66 (d, *J* = 6.0 Hz, 1H), 4.22-4.17 (m, 2H) 1.42 (s, 9H), 1.34 (s, 12H), 1.26-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 189.2, 159.5, 154.6, 136.6, 135.3, 127.7, 83.9, 80.3, 62.7, 61.2, 28.2, 24.8.



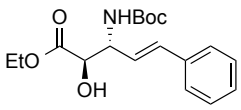
Analytical data for **43i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74-7.72 (d, *J* = 7.6 Hz, 2H), 7.26-7.24 (m, 2H), 5.66-5.64 (d, *J* = 8.4 Hz, 1H), 5.12-5.11 (d, *J* = 6 Hz, 1H), 4.55 (bs, 1H), 4.16-4.07 (m, 2H), 2.95-2.93 (d, *J* = 6.0 Hz, 1H), 1.41 (s, 9H), 1.32 (s, 12H), 1.26-1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.8, 154.9, 139.8, 134.8,

126.8, 83.8, 79.9, 73.1, 62.1, 56.6, 29.7, 28.3, 28.2, 24.9, 24.8, 14.1; **IR** (thin film cm^{-1}): 3364, 2979, 1716, 1614, 1507, 1361, 1261, 1145, 1022, 962, 858, 803, 660, 578; **TLC** (25% EtOAc/hexanes): R_F 0.28; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{22}H_{37}BNO_7$: 436.2506, Found: 436.2529. **SFC** analysis: AS column, 2% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 9.5 min, $t_{R\ (major)}$ = 12.9 min, 99:1 er; **$[\alpha]_D^{25}$** -20.53 (c = 0.40, $CHCl_3$).

(2*R*,3*R*,*E*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-5-phenylpent-4-enoate (**43j**)**:** The title compound was prepared according to General Procedure C (method 2) using **45j** (0.5 mmol) affording β-amino-α-hydroxy ester **43j** (0.07 g, 0.22 mmol, 43% overall yield) as a clear oil.



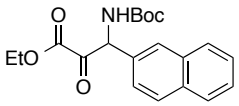
Analytical data for **42j**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 6.74-6.71 (d, *J* = 6.2 Hz, 1H), 6.10-6.07 (dd, *J* = 15.6 Hz, 4.8 Hz, 1H), 5.68 (bs, 1H), 4.38-4.31 (m, 2H) 1.45 (s, 9H), 1.36-1.33 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 189.5, 160.0, 154.7, 136.2, 135.6, 128.6, 128.5, 126.7, 121.0, 80.4, 62.9, 59.0, 28.2, 13.9.



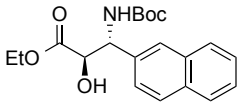
Analytical data for **43j**: **^{1}H NMR** (150 MHz, $CDCl_3$) **43j** exists as rotamers at room temperature in analogy to **1o**: δ 7.33-7.28 (m, 4H), 7.25-7.24 (m, 1H), 6.61-6.58 (d, *J* = 16.2 Hz, 1H), 6.05-6.02 (dd, *J* = 16.2 Hz, 7.8 Hz, 1H), 5.24-5.22 (d, *J* = 9 Hz, 1H), 4.73 (bs, 1H), 4.31-4.20 (m, 2H), 3.12 (bs, 1H), 1.46 (s, 9H), 1.29-1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.3, 155.1, 136.2, 133.7, 128.5, 128.0, 126.6, 123.2, 79.9, 73.0, 62.2, 55.2, 28.4, 14.2; **IR** (thin film cm^{-1}): 3383, 2979, 2931, 1716, 1497, 1367, 1247, 1168, 1101, 1020, 748, 694; **TLC** (25% EtOAc/hexanes): R_F 0.31; **HRMS** (ESI):

Calcd. for $[M + H]^+$ $C_{18}H_{25}NO_5$: 336.1811, Found: 336.1825. **SFC** analysis: OD column, 1.5% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 29.5 min, $t_{R\ (major)}$ = 32.2 min, 92:8 er; $[\alpha]_D^{25}$ -158.96 (c = 0.25, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-(naphthalen-2-yl)propanoate (**43k):** The title compound was prepared according to General Procedure C (method 1) using **45k** (0.5 mmol) affording β-amino-α-hydroxy ester **43k** (0.15 g, 0.41 mmol, 82% overall yield) as a white solid. The product was recrystallized using 20% Et_2O/hexanes.



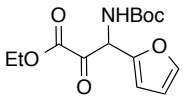
Analytical data for **42k**: **^{1}H NMR** (400 MHz, $CDCl_3$, rotamers observed): δ 7.86-7.79 (m, 4H), 7.51-7.49 (m, 2H), 7.45-7.43 (m, 1H), 6.25-6.23 (d, *J* = 6.8 Hz, 1H), 4.23-4.14 (m, 2H) 1.43 (s, 9H), 1.23-1.19 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 189.3, 159.6, 154.7, 133.3, 131.1, 129.3, 128.2, 128.1, 127.7, 126.8, 126.6, 125.6, 80.4, 62.8, 61.1, 28.3, 13.8.



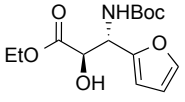
Analytical data for **43k**: **mp** 123.4-124.2 °C; (400 MHz, $CDCl_3$, rotamers observed): δ 7.81-7.77 (m, 3H), 7.73 (bs, 1H), 7.48-7.45 (m, 2H), 7.41-7.31 (m, 1H), 5.75-5.74 (d, *J* = 7.6 Hz, 1H), 5.30-5.28 (d, *J* = 8.0 Hz, 1H), 4.66-4.65 (d, *J* = 2.8 Hz, 1H), 4.15-4.09 (q, *J* = 7.2 Hz, 2H), 2.99-2.97 (d, *J* = 6 Hz, 1H), 1.43 (s, 9H), 1.25-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.8, 155.0, 134.4, 133.0, 128.1, 127.9, 127.6, 126.7, 126.2, 126.1, 125.2, 79.9, 73.3, 62.1, 56.7, 28.3, 14.1; **IR** (thin film cm^{-1}): 3393, 2979, 2934, 1714, 1499, 1367, 1248, 1166, 1020, 859, 749; **TLC** (25% EtOAc/hexanes): R_F 0.31; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{20}H_{25}NO_5$: 360.1811,

Found: 360.1827. **SFC** analysis: AS column, 3% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 12.9 min, $t_{R\ (major)}$ = 15.9 min, 97:3 er (>99.5:0.5 recryst.); **$[\alpha]_D^{25}$** -159.0 (c = 0.25, $CHCl_3$)

(2*R*,3*S*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-2-hydroxypropanoate (**43l**)**:** The title compound was prepared according to General Procedure C (method 1) using **45l** (0.5 mmol) affording β-amino-α-hydroxy ester **43l** (0.10 g, 0.33 mmol, 66% overall yield) as a white solid.

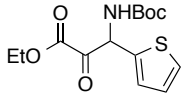


Analytical data for **42l**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36-7.26 (m, 1H), 6.36-6.33 (m, 2H), 6.19-6.18 (m, 1H), 5.56 (bs, 1H), 4.25-4.22 (m, 2H) 1.40 (s, 9H), 1.26-1.24 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 187.2, 159.5, 154.7, 146.1, 143.7, 111.0, 110.3, 80.5, 62.7, 54.7, 28.1, 13.7.

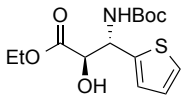


Analytical data for **43l**: **mp** 65.2-65.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.31 (m, 1H), 6.30-6.29 (m, 1H), 6.21-6.20 (d, *J* = 3.6 Hz, 1H), 5.48-5.45 (d, *J* = 8.4 Hz, 1H), 5.27-5.26 (m, 1H), 4.50 (bs,1H), 4.26-4.19 (m, 2H), 3.00 (bs, 1H), 1.45 (s, 9H), 1.28-1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.6, 154.9, 150.6, 142.3, 110.2, 107.7, 80.1, 77.2, 62.0, 51.4, 28.2, 28.1, 14.0; **IR** (thin film cm^{-1}): 3383, 2979, 2934, 1716, 1501, 1368, 1251, 1166, 1012, 875, 741, 599; **TLC** (25% EtOAc/hexanes): R_F 0.34; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{14}H_{21}NO_6$: 300.1447, Found: 300.1458. **HPLC** analysis: Chiralpak IA, H/IPA = 90:10, flow rate = 1.0 mL/min, 210 nm; $t_{R\ (minor)}$ = 12.3 min, $t_{R\ (major)}$ = 16.8 min, 95:5 er (>99.5:0.5 recryst.); **$[\alpha]_D^{25}$** = -92.2 (c = 1.1, $CHCl_3$).

(2*R*,3*S*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-3-(thiophen-2-yl)propanoate (**43m):** The title compound was prepared according to General Procedure C (method 1) using **45m** (0.5 mmol) affording β-amino-α-hydroxy ester **43m** (0.11 g, 0.35 mmol, 69% overall yield) as a white solid.



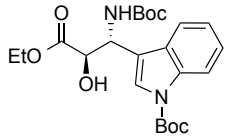
Analytical data for **42m**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.28 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 6.96-6.92 (m, 2H), 6.29-6.27 (d, *J* = 6.8 Hz, 1H), 5.61-5.60 (d, *J* = 5.6 Hz, 1H), 4.25-4.19 (m, 2H) 1.39 (s, 9H), 1.25-1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 187.7, 159.6, 154.5, 135.5, 127.6, 127.3, 127.2, 80.5, 77.2, 62.7, 55.6, 28.1, 13.7.



Analytical data for **43m**: **mp** 68.6-70.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20-7.19 (d, *J* = 4.8 Hz, 1H), 6.96-6.91 (m, 1H), 5.50-5.44 (m, 2H), 4.58-4.57 (d, *J* = 2.8 Hz, 1H), 4.18-4.13 (q, *J* = 7.2 Hz, 2H), 3.20-3.19 (d, *J* = 1.6 Hz, 1H), 1.43 (s, 9H), 1.25-1.21 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.5, 154.7, 138.9, 126.5, 126.1, 125.3, 80.1, 72.9, 62.2, 52.8, 28.3, 14.0; **IR** (thin film cm^{-1}): 3393, 2979, 2934, 1715, 1498, 1367, 1249, 1166, 1114, 1020, 877, 704; **TLC** (25% EtOAc/hexanes): R_F 0.38; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{14}H_{21}NO_5S$: 316.1218, Found: 316.1229. **SFC** analysis: AS column, 3% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 6.1 min, $t_{R\ (major)}$ = 7.3 min, 97:3 er (99:1 recryst.); **$[\alpha]_D^{25}$** -272.6 (c = 0.5, $CHCl_3$).

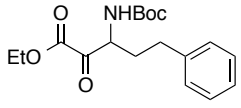
***tert*-butyl 2-((1*R*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-3-ethoxy-2-hydroxy-3-oxopropyl)-1*H*-indole-1-carboxylate** (**43n):** The title compound was prepared according to General Procedure C (method 2) using **45n** (0.5 mmol) affording β-amino-α-hydroxy ester **43n** (0.09 g, 0.20 mmol, 40% overall yield) as a white

solid. Due to partial epoxidation, β-amino-α-keto ester **42n** was never formed cleanly and the crude reaction mixture was simply subjected to the reduction conditions.



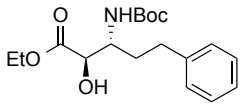
Analytical data for **43n**: **mp** 70-72 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.1 (bs, 1H), 7.66-7.64 (d, J = 7.8 Hz, 1H), 7.32-7.28 (t, J = 7.2 Hz, 1H), 7.25-7.22 (t, J = 7.2 Hz, 1H), 5. 48-5.46 (dd, J = 9.0 Hz, 1H), 5.41-5.38 (d, J = 9 Hz, J = 2.4 Hz, 1H), 4.71-4.69 (dd, J = 6.0 Hz, J = 2.4 Hz, 1H), 4.10-4.07 (m, 1H), 4.06-3.96 (m, 1H), 3.19-3.18 (d, J = 6.0 Hz, 1H), 1.66 (s, 9H), 1.44 (s, 9H), 1.17-1.14 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.0, 155.0, 124.7, 124.2, 122.6, 119.5, 115.2, 84.0, 80.0, 72.8, 62.2, 49.3, 28.3, 28.2, 13.9; **IR** (thin film cm^{-1}): 3384, 2978, 1734, 1717, 1540, 1520, 1507, 1456, 1373, 1255, 1157, 1019, 857, 748; **TLC** (20% EtOAc/hexanes): R_F 0.15; **HRMS** (ESI): Calcd. for $[M + Na]^+$ $C_{23}H_{32}N_2O_7$: 471.2108, Found: 471.2108. **SFC** analysis: WO column, 5 % modifier, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 13.0 min, $t_{R\ (major)}$ = 12.2 min, 97:3 er; **$[\alpha]_D^{25}$** -247.5 (c = 1.25, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-5-phenylpentanoate (43o): The title compound was prepared according to General Procedure C (method 1) using **45o** (0.5 mmol) affording β-amino-α-hydroxy ester **43o** (0.11 g, 0.32 mmol, 63% overall yield) as a white solid.



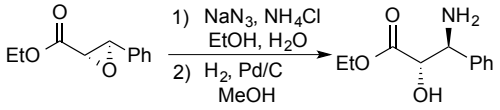
Analytical data for **42o**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.28 (m, *2*H), 7.21-7.16 (m, 3H), 5.21-5.19 (d, *J* = 8 Hz, 1H), 4.93 (bs, 1H), 4.32-4.27 (q, *J* = 7.2 Hz, 2H), 2.73-2.69 (m, 2H), 2.25-2.23 (m, 1H), 1.89-1.84 (m, 1H), 1.45 (s, 9H), 1.34-1.31 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz,

$CDCl_3$): δ 193.1, 160.4, 155.2, 140.3, 128.5, 128.3, 126.2, 80.2, 77.2, 62.5, 56.7, 32.7, 31.6, 29.6, 28.2, 13.8.



Analytical data for **43o**: **mp** 84.8-85.6 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.26 (m, 2H), 7.21-7.19 (m, 3H), 4.83-4.80 (d, *J* = 10 Hz, 1H), 4.26-4.11 (m, 4H), 3.28 (bs, 1H), 2.73-2.68 (m, 2H), 1.94-1.88 (q, *J* = 7.6 Hz, 2H), 1.41 (s, 9H), 1.32-1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.6, 155.3, 141.5, 128.4, 128.3, 125.9, 79.4, 72.2, 62.2, 52.7, 34.3, 32.4, 28.2, 14.0; **IR** (thin film cm^{-1}): 3371, 2979, 2932, 1715, 1498, 1455, 1391, 1366, 1247, 1170, 1107, 1028, 861, 754, 700; **TLC** (20% EtOAc/hexanes): R_F 0.34; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{18}H_{27}NO_5$: 338.1967, Found: 338.1983. **HPLC** analysis: Chiralpak IB, H/IPA = 95:05, flow rate = 1.0 mL/min, 210 nm; $t_{R\ (minor)}$ = 11.8 min, $t_{R\ (major)}$ = 8.2 min, 60:40 er ; **$[\alpha]_D^{25}$** +55.9 (c = 0.75, $CHCl_3$).

2.5.7 Synthesis of (+)-47 from epoxide 46

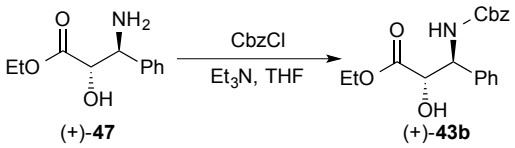


46 78% (+)-**47**

Step 1: A 1 dram vial equipped with a magnetic stir bar was charged with epoxide **46**[59] (1.0 mmol, 1 equiv), NaN_3 (2.0 mmol, 2 equiv), NH_4Cl (100 mmol, 100 equiv), and 80% EtOH/H_2O (.05 M). The reaction mixture was heated to 65 °C for 18 h then diluted with DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified via flash chromatography using 15% EtOAc/hexanes as the eluent (0.8 mmol, 80%). Spectral data for the azide matched literature reports.[11]

Step 2: A flame dried 20 mL scintillation vial equipped with a magnetic stir bar was charged with 10% Pd/C (42.0 mg). To the vial was added degassed ethanol (8 mL) and the β-azido-α-hydroxy ester (0.8 mmol, 1 equiv). The reaction vessel was purged with H_2 (3 times), then put under 1 atm of H_2 (balloon). The reaction mixture was stirred for 24 h, filtered through a plug of celite, then concentrated *in vacuo* providing **47** without need for further purification (0.78 mmol, 98% yield.) Analytical data for (2*R*,3*R*)-ethyl 3-amino-2-hydroxy-3-phenylpropanoate (+)-**47**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.26 (m, 5H), 6.96-6.91 (m, 1H), 4.45-4.44 (d, *J* = 4.0 Hz, 1H), 4.32-4.31 (d, *J* = 3.6 Hz, 1H), 4.12-4.07 (m, 2H), 2.27 (bs, 3H), 1.18-1.15 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.5, 128.6, 128.3, 127.7, 127.3, 126.9, 74.8, 61.5, 58.2, 14.0; **IR** (thin film cm^{-1}): 2924, 1733, 1558, 1541, 1507, 1457, 1209, 1073, 1024, 700; **TLC** (6% MeOH/DCM): R_F 0.19; **HRMS** (ESI): Calcd. for $[M + H]^+$ $C_{11}H_{15}NO_3$: 210.1130, Found: 210.1126.; **$[\alpha]_D^{25}$** = +200.75 (c = 0.66, $CHCl_3$).

2.5.8 Synthesis of (+)-43b from 47

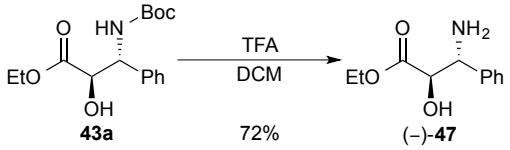


(+)-**47** (+)-**43b**

To a flame dried 1-dram vial equipped with a magnetic stir bar was added (**+)-47** (0.05 mmol, 1 equiv), THF (0.5 mL), and Et_3N (0.05 mmol, 1 equiv). The vial was cooled to 0 °C followed by the addition of benzyl chloroformate (0.05 mmol, 1 equiv). The reaction was slowly warmed to room temperature then diluted with EtOAc and water. The organic layer was washed with water (3 x 10 mL), brine,

and dried over Na_2SO_4. Concentration *in vacuo* afforded the α-hydroxy ester which was purified by flash chromatography using 30% EtOAc/Hexanes providing **43b** (0.03 mmol, 62% yield). **SFC** analysis: WO column, 7% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\ (minor)}$ = 12.0 min, $t_{R\ (major)}$ = 9.5 min, 94:6 er.

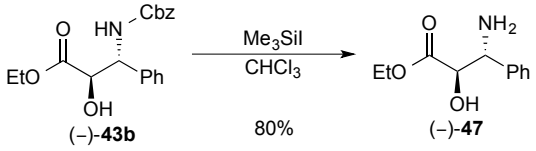
2.5.9 Boc Deprotection of 43a



43a (–)-**47**

A 1 dram vial equipped with a magnetic stir bar was charged with **43a** (0.1 mmol, 1 equiv), and DCM (.8 mL, .12 M). Trifluoroacetic acid (2.5 mmol, 25 eq) was then added and stirred at room temperature for 2 hours followed by removal of solvent *in vacuo*. Crude extracts were dissolved in EtOAc. The organic layer was washed with water (3 x 10 mL), brine, and dried over Na_2SO_4. Concentration *in vacuo* afforded the deprotected product (0.07 mmol, 72%) whose analytical properties matched those of independently synthesized (+)-**47** $[\alpha]_D^{25}$ -275.92 (c = 0.50, $CHCl_3$).

2.5.10 Cbz Deprotection of (–)-43b



(–)-**43b** (–)-**47**

To a flame dried 1 dram vial equipped with a magnetic stir bar was added with **43b** (0.1 mmol, 1 equiv), and $CHCl_3$ (1.0 mL, 0.1 M). Trimethylsilyl iodide (0.25 mmol, 2.5 equiv) was then added dropwise stirred at rt for 25 min followed by removal of solvent *in vacuo*. The product was purified via flash

chromatography using 6% MeOH/DCM as the eluent, providing amino alcohol **47** (0.8 mmol, 80%), whose analytical properties (except for rotation) matched those of independently synthesized (+)-**47.**

2.6 REFERENCES

1) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. “Developments in asymmetric hydrogenation from an industrial perspective.” *Acc. Chem. Res.* **2007,** *40,* 1385-1393.

2) Patel, R. N.; Banerjee, A.; Howell, J. M.; McNamee, D. B.; Mirfakhrae, D; Nanduri, V.; Thottathil, J. K.; Szarka, L. J. “Microbial synthesis of (*2R,3S*)-(-)-*N*-benzoyl-3-phenyl isoserine ethyl ester-α Taxol side chain synthon.” Tetrahedron Asymm. **1993,** *4,* 2069-2072.

3) Steward, K. M.; Gentry, E. C.; Johnson, J. S. “Dynamic kinetic resolution of α-keto esters via asymmetric transfer hydrogenation.” *J. Am. Chem. Soc.* **2012,** *134,* 7329-7332.

4) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. “Asymmetric transfer hydrogenation of aromatic ketones catalyzed by chiral ruthenium(ii) complexes.” *J. Am. Chem. Soc.* **1995,** *117,* 7562-7563.

5) Yoshimura, M.; Tanaka, S.; Kitamura, M. “Recent topics in catalytic asymmetric hydrogenation of ketones.” *Tetrahedron Lett.* **2014,** *55*, 3635-3640.

6) Bode, S. E.; Wolberg, M.; Müller M. “Stereoselective synthesis of 1,3-diols.” *Synthesis* **2006,** *4,* 557-588.

7) Steward, K. M.; Johnson, J. S. “Asymmetric synthesis of α-keto esters via cu(ii)-catalyzed aerobic deacylation of acetoacetate alkylation products: an unusually simple synthetic equivalent to the glyoxylate anion synthon.” *Org. Lett.* **2011,** *13,* 2426-2429.

8) Kim, S. H.; Kim, K. H.; Kim, J. N. “Construction of 1,2,5-tricarbonyl compounds using methyl cyanoacetate as a glyoxylate anion synthon combined with copper(i) iodide-catalyzed aerobic oxidation.” *Adv. Synth. Catal.* **2011,** *353*, 3335-3339.

9) Thompson, W. J.; Buhr, C. A. “Preparation of methyl 2,5-dioxohexanoate: a highly convenient reagent for the introduction of the 2-carbalkoxy-1,5-dialkylpyrrole nucleus.” *J. Org. Chem.* **1983,** *48,* 2769-2772.

10) Xian, M.; Alaux, S.; Sagot, E.; Gefflaut, T. “Chemoenzymatic synthesis of glutamic acid analogues: substrate specificity and synthetic applications of branched chain aminotransferase from Escherichia coli.” *J. Org. Chem.* **2007,** *72,* 7560-7566.

11) Vora, H. U.; Lathrop, H. P.; Reynolds, N. T.; Kerr, M. S.; Read de Alaniz, J.; Rovis, T. “Preparation of chiral and achiral triazolium salts: carbene precursors with demonstrated synthetic utility.” *Org. Synth.* **2010,** *87,* 350-361.

12) S. D. Burke, R. L. Danheiser, *Handbook of Reagents for Organic Synthesis. Oxidizing and Reducing Agents*, Wiley: Chichester, **1999**.

13) Gemal, A. L.; Luche, J. L. “Lanthanoids in organic synthesis. Selective ketalization and reduction of carbonyl groups.” *J. Org. Chem.* **1979,** *44,* 4187-4189.

14) Paradisi, M. P.; Zecchini, G. P.; Ortar, G. “A convenient one-pot procedure for the selective reduction of ketones in the presence of aldehydes.” *Tetrahedron Lett.* **1980***, 21,* 5085-5088.

15) Bastug, G.; Dierick, S.; Lebreux, F.; Markó, I. E. “Highly chemoselective reduction of carbonyl groups in the presence of aldehydes.” *Org. Lett.* **2012,** *14,* 1306-1309.

16) Bhar, S.; Guha, S. The remarkable role of water during the chemoselective reduction of ketones mediated by metallic aluminium. *Tetrahedron Lett.* **2004,** *45,* 3775-3777.

17) Calderari, G.; Seebach, D. “Asymmetrische Michael-additionen. stereoselektive alkylierung chiraler, nicht racemischer enolate durch nitroolefine. herstellung enantiomerenreiner α-aminobuttersäure- und bernsteinsäure-derivate.” *Helv. Chim. Acta* **1985,** *68,* 1592-1604.

18) Jang, D.; Chang, J.; Uang, B. “Highly diastereoselective Michael addition of α-hydroxy acid derivatives and enantioselective synthesis of (+)-crobarbatic acid.” *Org. Lett.* **2001***, 3,* 983-985.

19) Blay, G.; Fernández, I.; Monje, B.; Pedro, J. R.; Ruiz, R. “Highly diastereoselective Michael reaction of (S)-mandelic acid enolate. Chiral benzoyl carbanion equivalent through an oxidative decarboxylation of α-hydroxyacids.” *Tetrahedron Lett.* **2002***, 43,* 8463-8466.

20) Huang, H.; Zhu, K.; Wu, W.; Jin, Z.; Ye, J. “Highly diastereoselective and enantioselective Michael addition of 5H-oxazol-4-ones to α,β-unsaturated ketones catalyzed by a new bifunctional organocatalyst with broad substrate scope and applicability.” *Chem. Commun.* **2012,** *48,* 461-463.

21) Steward, K. M.; Corbett, M. T.; Goodman, C. G.; Johnson, J. S. “Asymmetric synthesis of diverse glycolic acid scaffolds via dynamic kinetic resolution of α-keto esters.” *J. Am. Chem. Soc.* **2012,** *134,* 20197-20206.

22) Corbett, M. T.; Johnson, J. S. “Diametric stereocontrol in dynamic catalytic reduction of racemic acyl phosphonates: divergence from α-keto ester congeners.” *J. Am. Chem. Soc.* **2013,** *135,* 594-597.

23) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. “The structure of bestatin.” *J. Antibiot.* **1976,** *29,* 100-101.

24) Saiki, I.; Murata, J.; Watanabe, K.; Fujii, H.; Abe, F.; Azuma, I. “Inhibition of tumor cell invasion by ubenimex (bestatin) in vitro.” *Jap. J. Cancer Res.* **1989,** *80,* 873-878.

25) Etoh, Y.; Miyazaki, M.; Saitoh, H.; Toda, N. “KRI-1314: an orally effective inhibitor of human renin.” *Jpn. J. Pharmacol.* **1993,** *63,* 109-119.

26) Nicolaou, K. C.; Dai, W.; Guy, R. K. “Chemistry and biology of Taxol.” *Angew. Chem., Int. Ed.* **1994,** *33*, 15-44.

27) Ojima, I.; Das, M. “Recent advances in the chemistry and biology of new generation taxoids.” *J. Nat. Prod.* **2009,** *72,* 554-565.

28) Deng, L.; Jacobsen, E. N. “A practical, highly enantioselective synthesis of the taxol side chain via asymmetric catalysis.” *J. Org. Chem.* **1992***, 57,* 4320-4323.

29) Righi, G.; Rumboldt, G.; Bonini, C. Stereoselective preparation of syn α-hydroxy-β-amino ester units via regioselective opening of α,β-epoxy esters: enantioselective synthesis of Taxol C-13 side chain and cyclohexylnorstatine. *J. Org. Chem.* **1996,** *61,* 3557-3560.

30) Jang, S.H.; Kim, J. Y.; Kim, M. K.; Han, J.W.; Park, K. H.; Yoon, Y. J; Lee, S-G. “Stereoselective synthesis of diverse α–hydroxy-β-amino acids and it's application for synthesis of dipeptide expecting as a protease inhibitor.” *Bull. Kor. Chem. Soc.* **2009,** *30,* 163-166.

31) Sharpless, K. B.; Chong, A. O.; Oshima, K. “Osmium-catalyzed vicinal oxyamination of olefins by Chloramine-T.” *J. Org. Chem.* **1976,** *41,* 177-179.

32) Herranz, E.; Sharpless, K. B. “Improvements in the osmium-catalyzed oxyamination of olefins by chloramine-T.” *J. Org. Chem.* **1978,** *43*, 2544-2548.

33) Li, G.; Chang, H.; Sharpless, K. B. “Catalytic asymmetric aminohydroxylation (AA) of olefins.” *Angew. Chem., Int. Ed.* **1996,** *35,* 451-454.

34) O'Brien, P. “Sharpless asymmetric aminohydroxylation: scope, limitations, and use in synthesis.” *Angew. Chem., Int. Ed.* **1999,** *38,* 326-329.

35) Harris, L.; Mee, S. P. H.; Furneaux, R. H.; Gainsford, G. J.; Luxenburger, A. “Alkyl 4-chlorobenzoyloxycarbamates as highly effective nitrogen source reagents for the base-free, intermolecular aminohydroxylation reaction.” *J. Org. Chem.* **2011,** *76,* 358-372.

36) Jiang, Y.; Chen, X.; Zheng, Y.; Xue, Z.; Shu, C.; Yuan, W.; Zhang, X. “Highly diastereoselective and enantioselective synthesis of α-hydroxy β-amino acid derivatives: lewis base catalyzed hydrosilylation of α-acetoxy β-enamino esters.” *Angew. Chem., Int. Ed.* **2011,** *50,* 7304-7307.

37) Cardillo, G.; Tomasini, C. “Asymmetric synthesis of β-amino acids and small α-substituted β-amino acids.” *Chem. Soc. Rev.* **1996,** *25,* 117-128.

38) *Enantioselective Synthesis of β-Amino Acids,* 2nd ed.; Juaristi, E.; Soloshonok, V. Ed.; Wiley: Hoboken, NJ, **2005**.

39) Sleebs, B. E.; Van Nguyen, T. T.; Hughes, A. B. “Recent advances in stereoselective synthesis and application of α-amino acids.” *Org. Prep. Proced. Int.* **2009,** *41,* 429-478.

40) Uraguchi, D.; Sorimachi, K.; Terada, M. “Organocatalytic asymmetric direct alkylation of α-diazoester via C-H Bond cleavage.” *J. Am. Chem. Soc.* **2005,** *127,* 9360-9361.

41) Kudyba, I.; Raczko, J.; Jurczak, J. “Synthesis of (−)-bestatin and the Taxotere® side-chain via nitroaldol reaction of (1*R*)-8-phenylmenthyl glyoxylate.” *Tetrahedron Lett.* **2003,** *44,* 8685-8687.

42) Borah, J. C.; Gogoi, S.; Boruwa, J.; Kalita, B.; Barua, N. C. “A highly efficient synthesis of the C-13 side-chain of taxol using Shibasaki's asymmetric Henry reaction.” *Tetrahedron Lett.* **2004,** *45,* 3689-3691.

43) Kudyba, I.; Raczko, J.; Jurczak, J. “Asymmetric nitroaldol reaction. Synthesis of Taxotere side chain and (α)-bestatin using (1*R*)-8-phenylmenthyl glyoxylate.” *J. Org. Chem.* **2004,** *69,* 2844-2850.

44) Dziedzic, P.; Vesely, J.; Córdova, A. “Catalytic asymmetric synthesis of the docetaxel (Taxotere) side chain: organocatalytic highly enantioselective synthesis of esterification-ready α-hydroxy-β-amino acids.” *Tetrahedron Lett.* **2008,** *49,* 6631-6634.

45) Dziedzic, P.; Schyman, P.; Kullberg, M.; Córdova, A. “Highly enantioselective organocatalytic addition of aldehydes to *N*-(phenylmethylene)benzamides: asymmetric synthesis of the Paclitaxel side chain and its analogues.” *Chem. Eur. J.* **2009,** *15,* 4044-4048.

46) Juhl, K.; Jørgensen, K. A. “Catalytic asymmetric direct α-amination reactions of 2-keto esters: a simple synthetic approach to optically active syn-β-amino-α-hydroxy esters.” *J. Am. Chem. Soc.* **2002,** *124,* 2420-2421.

47) Torssell, S.; Kienle, M.; Somfai, P. “1,3-Dipolar cycloadditions of carbonyl ylides to aldimines: a three-component approach to syn-α-hydroxy-β-amino esters.” *Angew. Chem., Int. Ed.* **2005,** *44,* 3096-3099.

48) Patel, R. N.; Banerjee, A.; Howell, J. M.; McNamee, C. G.; Brozozowski, D.; Mirfakhrae, D.; Nanduri, V.; Thottathil, J. K.; Szarka, L. J. “Microbial synthesis of (2*R*,3*S*)-(−)-N-benzoyl-3-phenyl isoserine ethyl ester-α-Taxol side-chain synthon.” *Tetrahedron Asymm.* **1993,** *4,* 2069-2084.

49) Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. “First one-pot copper-catalyzed synthesis of α-hydroxy-β-amino acids in water. A new protocol for preparation of optically active norstatines.” *J. Org. Chem.* **2003,** *68,* 7041-7045.

50) Sepe, V.; D’Auria, M. V.; Bifulco, G.; Ummarino, R.; Zampella, A. “Concise synthesis of AHMHA unit in perthamide C. Structural and stereochemical revision of perthamide C.” *Tetrahedron* **2010,** *66,* 7520-7526.

51) Prévost, S.; Gauthier, S.; de Andrade, M. C. C.; Mordant, C.; Touati, A. R.; Lesot, P.; Savignac, P.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J. “Dynamic kinetic resolution of α-chloro β-keto esters and phosphonates: hemisynthesis of Taxotere® through Ru-DIFLUORPHOS asymmetric hydrogenation.” *Tetrahedron Asymm.* **2010,** *21,* 1436-1446.

52) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. “Synthesis of α-amido ketones via organic catalysis: thiazolium-catalyzed cross-coupling of aldehydes with acylimines.” *J. Am. Chem. Soc.* **2001,** *123,* 9696-9697.

53) DiRocco, D. A.; Rovis, T. “Catalytic asymmetric cross-aza-benzoin reactions of aliphatic aldehydes with *N*-boc-protected imines.” *Angew. Chem., Int. Ed.* **2012,** *51,* 5904-5906.

54) Jones, C.; Dan Pantoş, G.; Morrison, A.; Smith, M. “Plagiarizing proteins: enhancing efficiency in asymmetric hydrogen-bonding catalysis through positive cooperativity.” *Angew. Chem., Int. Ed.* **2009,** *48,* 7391-7394.

55) Thirupathi, P.; Kim, S. S. “Regioselective arylations of α-amido sulfones with electron-rich arenes through friedel-crafts alkylations catalyzed by ferric chloride hexahydrate: synthesis of unsymmetrical and bis-symmetrical triarylmethanes.” *Eur. J. Org. Chem.* **2010,**1798-1808.

56) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. “Ruthenium(II)-catalyzed asymmetric transfer hydrogenation of ketones using a formic acid-triethylamine mixture.” *J. Am. Chem. Soc.* **1996,** *118,* 2521-2522.

57) Noyori, R.; Hashiguchi, S. “Asymmetric transfer hydrogenation catalyzed by chiral ruthenium complexes.” *Acc. Chem. Res.* **1997,** *30*, 97-102.

58) Zhao, Y.; Jiang, N.; Chen, S.; Peng, C.; Zhang, X.; Zou, Y.; Zhang, S.; Wang, J. “Concise and diastereoselective approach to syn- and anti-*N*-tosyl-α-hydroxy β-amino acid derivatives.” *Tetrahedron* **2005,** *61,* 6546-6552.

59) Wang, B.; Wu, X.; Wong, O. A.; Nettles, B.; Zhao, M.; Chen, D.; Shi, Y. “A diacetate ketone-catalyzed asymmetric epoxidation of olefins.” *J. Org. Chem.* **2009,** *74,* 3986-3989.

60) Womack, E. B.; Nelson, A. B. “Ethyl diazoacetate.” *Org Synth*. **1955,** *24,* 392-393.

61) Loey, B.; Kormendy, M. F.; Goodman, M. M. “t-Butyl carbamate.” *Org Synth.* **1973,** *48,* 32-34.

62) Nicolas, M.; Fabre, B.; Marchand, G.; Simonet, J. “New boronic-acid- and boronate-substituted aromatic compounds as precursors of fluoride-responsive conjugated polymer films.” *Eur. J. Org. Chem.* **2000,** 1703-1710.

63) Camp, J. E.; Craig, D.; Funai, K.; White, A. J. P. “Decarboxylative Claisen rearrangement reactions: synthesis and reactivity of alkylidene substituted indolines.” *Org. Biomol. Chem.* **2011,** *9,* 7904-7912.

64) Boruwa, J.; Borah, J. C.; Kalita, B.; Barua, N. C. “Highly regioselective ring opening of epoxides using NaN_3: A short and efficient synthesis of (-)-cytoxazone.” *Tetrahedron Lett.* **2004,** *45,* 7355-7358.

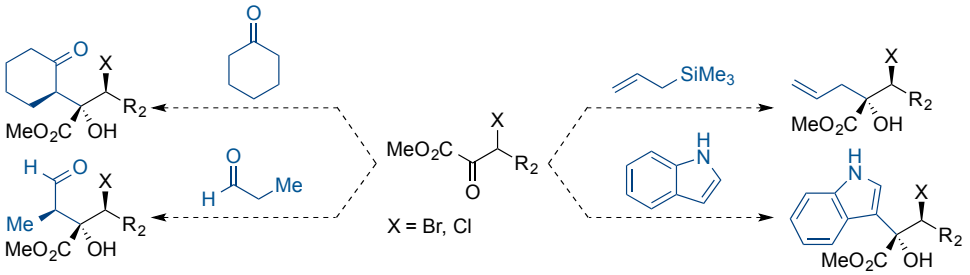
CHAPTER 3

N-HETEROCYCLIC CARBENE-CATALYZED DYNAMIC KINETIC RESOLUTIONS OF β-STEREOGENIC α-KETO ESTERS

3.1 Introduction

Our research efforts into the ATH-DKR of α-keto esters illustrated that the kinetic acidity of selected β-stereogenic α-keto esters was sufficient for reductive transformations (Chapter 2). We were cognizant that using carbon-based nucleophiles in a DKR of α-keto esters would provide expeditious access to a host of chemically diverse glycolates not available via simple hydrogenation. To this end we examined the addition of enolates, indoles, and various allylation strategies as platforms for asymmetric dynamic addition of carbon nucleophiles to β-halo α-keto esters (Scheme 1); however our efforts did not provide tractable methods for any of these additions.

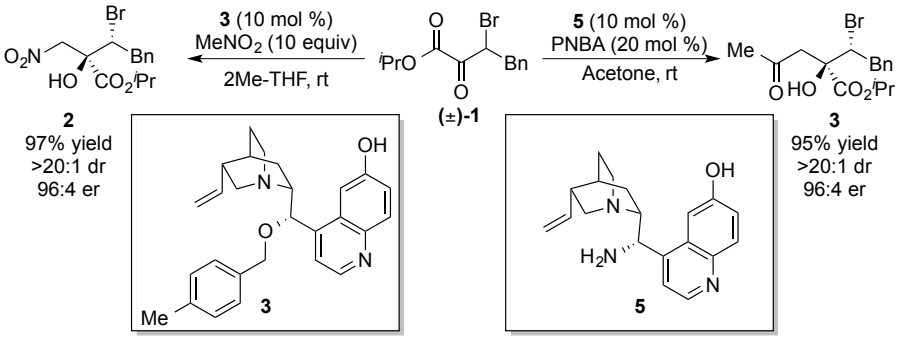
Scheme 1. Attempted Carbon Based Nucleophile Additions to β-Halo α-Keto Esters



Concurrent with these unsuccessful investigations our group was able to achieve highly stereoselective DyKAT addition of both nitromethane and acetone

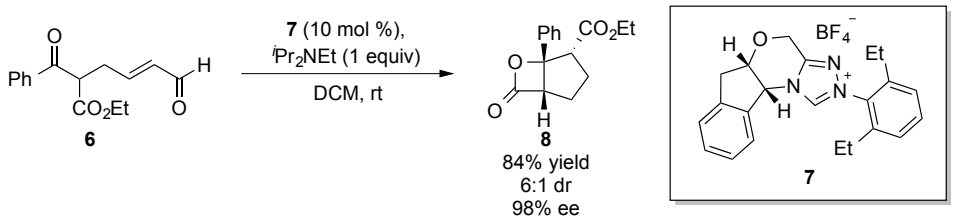
to β-bromo α-keto ester **1** under the control of cinchona alkaloid derived catalysts **3** and **5** respectively (Scheme 2).[1] As we continued evaluating potential carbon based nucleophiles our attention was drawn to the use of NHC catalysts for promoting both dynamic cross-benzoin and homoenolate couplings.

Scheme 2. DyKAT Addition of Acetone and Nitromethane to β-Bromo α-Keto Esters



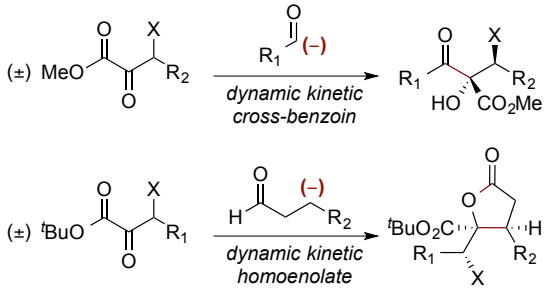
We believe these reactions to be well suited to our intended goal for a number of reasons including 1) the wide breadth of available chiral NHC catalysts, 2) the utility of the installed carbonyl functional groups, and 3) the tolerance of this catalyst class to basic conditions (advantageous for ensuring facile substrate racemization). To this latter point, NHC catalysts had previously been deployed in a successful resolution manifold where substrate enantiomerization was mandatory. Scheidt demonstrated the NHC-catalyzed DKR transformation of β-keto ester **6** forming β-lactone **8** in good yield and stereoselectivity via the intermediacy of an azolium enolate (Scheme 3).[2,3] This report was of particular interest to us as the enantiomerization of **6** occurs via Hünig's base mediated enolization. NHC-catalyzed simple kinetic resolutions were also known for both [3 + 3] and [3 + 4] cycloadditions of azomethine imines and enals.[4,5]

Scheme 3. NHC Catalyzed DKR for the Formation of β-Lactones



In light of these previous works, we began examining dynamic NHC catalyzed cross-benzoin and homoenolate couplings of aldehydes with β-halo α-keto esters (Scheme 4); these studies are the focus of this chapter.

Scheme 4. Proposed NHC catalyzed DKR of β-Halo α-Keto Esters



3.2 Dynamic Kinetic Asymmetric Cross-Benzoin Additions of β-Stereogenic α-Keto Esters*

The benzoin condensation is a carbene- or cyanide-catalyzed reaction that couples two carbonyl compounds to give α-hydroxy ketones via carbon-carbon bond formation. The reaction proceeds with concurrent generation of a stereogenic center and is the archetype of a catalytic umpolung (polarity inversion) reaction.[6-12] Its significance and widespread use largely flow from two defining characteristics: (1) its capacity to generate useful and ubiquitous α-

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hydroxy ketones, and (2) the 100% atom efficiency inherent to the reaction. As a consequence, significant research effort has been devoted to various aspects of the transformation.

A host of methods exist for the asymmetric homobenzoin reaction (the coupling of two identical aldehydes).[13-18] The union of two different carbonyls (cross-benzoin addition) poses a unique challenge in controlling the chemoselectivity of these reactions (i.e. constitutional isomer distribution), particularly in the intermolecular manifold; however, it presents the possibility of accessing a more diverse set of α-hydroxy ketones.[19-21]

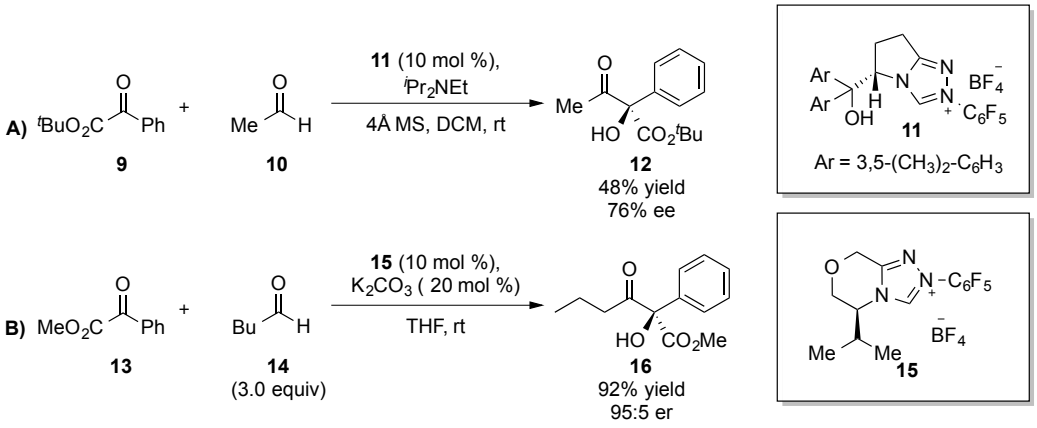
Multiple asymmetric cross-benzoin additions have been achieved through the deployment of miscellaneous strategies and reagents using enzymatic[22-27] and metallophosphite[26] catalysis. Of greater interest to us were reports which detailed the use of carbene[29-32] catalysts; in separate communications, Zeitler and Gravel reported cross-benzoin couplings with α-keto esters.

The first of these uses pyroglutamic acid derived NHC precatalyst **11** for the coupling of α-keto ester **9** and acetaldehyde providing α-hydroxy ketone **12** in 48% yield and 76% ee (Scheme 5A).[31] Subsequently it was reported that the carbene generated from salt **15** exhibited a signficant improvement in enantioselection and yield for coupling of aliphatic aldehydes and aryl α-keto esters (Scheme 5B).[32]

As we surveyed the literature we were cognizant that a limitation in all of these methods is that they generate only a single stereocenter during the C-C bond forming event. A non-enzymatic cross-benzoin coupling that generated

more than one stereocenter, and thus a higher level of complexity, had not been reported previous to our work.[33] Generating vicinal stereocenters during the cross-benzoin C–C bond construction with excellent levels of diastereo- and enantiocontrol was anticipated to be challenging.

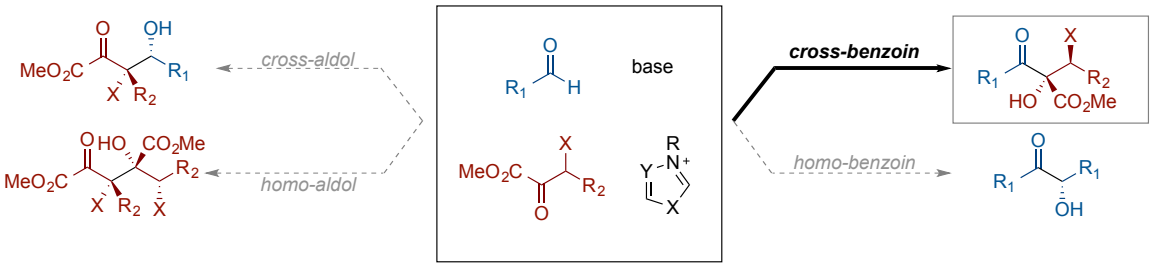
Scheme 5. NHC-Catalyzed Cross-Benzoin Couplings with α-Keto Esters



Additionally while the cross-benzoin procedures noted above do utilize α-keto esters, all previous asymmetric examples have used ketones bearing aromatic substituents, rendering them more electrophillic as well as non-enolizable.[30,31] In order for a NHC-catalyzed DKR to be achieved, the previously unknown use of enolizable α-keto esters was compulsory. Aside from potentially deleterious effects on simple electrophile reactivity, this structural change also brings with it the possibility of undesired homo- and cross-aldolization in addition to the known benzoin dimerization (Scheme 6). We were aware that our projected reaction conditions were mechanistically viable for promoting all of these processes.[15-18,34,35] Accordingly, we sought to identify conditions that would

chemoselectively deliver the cross-benzoin product while fulfilling the required parameters for a DKR.

Scheme 6. Chemoselectivity Challenges for the Coupling of Aldehydes (blue) and Enolizable α-Keto Esters (red) in the Presence of Base and Carbene



With these challenges in mind we began by examining the coupling of benzaldehyde and β-chloro-α-keto ester **17a**. Using NHC catalyst **19,**[36] glycolate **18a** was delivered with 96:4 er, and 4.5:1 dr, but only 25% conversion of **17a** (Table 1, entry 1). Using more electron-rich catalyst **20**[37] gave a marked increase in both reactivity and dr without a notable change in er (Table 1, entry 2). It is likely that the '*N*-Mesityl Effect' is important for this coupling, in that either the irreversible nature of formation, or heightened nucleophilicity, of the Breslow intermediate is critical for reactivity[38] The importance of using an electron rich catalyst was observed throughout the screening of conditions, as electron-poor catalysts **15**[30] and **22**[32] routinely gave low conversion of starting material (Table 1, entries 3, 5, 7 and 9).

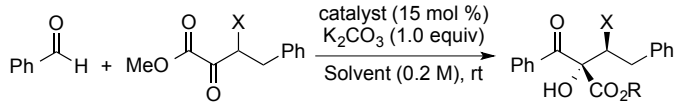
Using catalyst **20** with bromo ketone **17b** increased the observed dr with little effect on conversion or er (Table 1, entry 6). Screening the solvent and base (full details can be found In Chapter 3 Section 3.4) revealed that TBME and

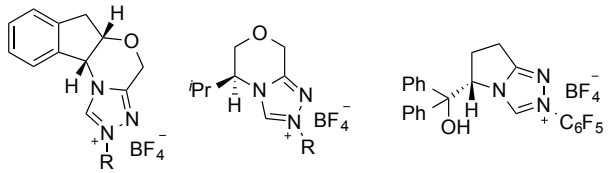
K_2CO_3 were optimal, providing tertiary alcohol **18b** with >20:1 diastereoselection and 96:4 er (Table 1, entry 10). Efforts to further increase stereoselectivity via introduction of steric bulk at the ester position only resulted in reduced reactivity and stereoselectivity (Table 1, entry 11). Under identical conditions chloro variant **17a** delivered ketone **18a** with identical enantioselectivity, but a dr of 14:1 (Table 1, entry 12). Due to the higher sense of diastereoselection, we elected to examine the scope of the reaction using β-bromo-α-keto esters.

Next we began modifying the structure of **17** in order to probe the allowable steric and electronic parameters of this cross-benzoin process (Scheme 7). Varying the arene on the α-keto ester delivered **18c** and **18e** without loss of reaction fidelity. Removing the arene as well as changing the carbon chain length provided **18d, 18f**, and **18g** cleanly with high stereoselectivity. Inclusion of a β-branch point gave product **18h** with >20:1 dr and 94:6 er, albeit in only 60% conversion of starting material (as measured by ^{1}H NMR using an internal mesitylene standard.)

Variation of the aldehyde also provided data regarding reaction generality. While both *para*- and *meta*-tolualdehyde were well tolerated (**18i** and **18j**), *ortho*-tolualdehyde proved to be too sterically encumbered, giving no reaction. Electron-rich and -poor aldehydes were slow to react providing **18l** and **18m** with good stereoselectivity but incomplete conversion after 18 h. While longer reaction time did not increase the yield, a slight increase in catalyst loading provided full conversion of the β-bromo α-keto ester (20 mol % catalyst loading was only required for substrate **17m**).[18]

Table 1: Catalyst and Substrate Optimization for the Asymmetric Cross-Benzoin



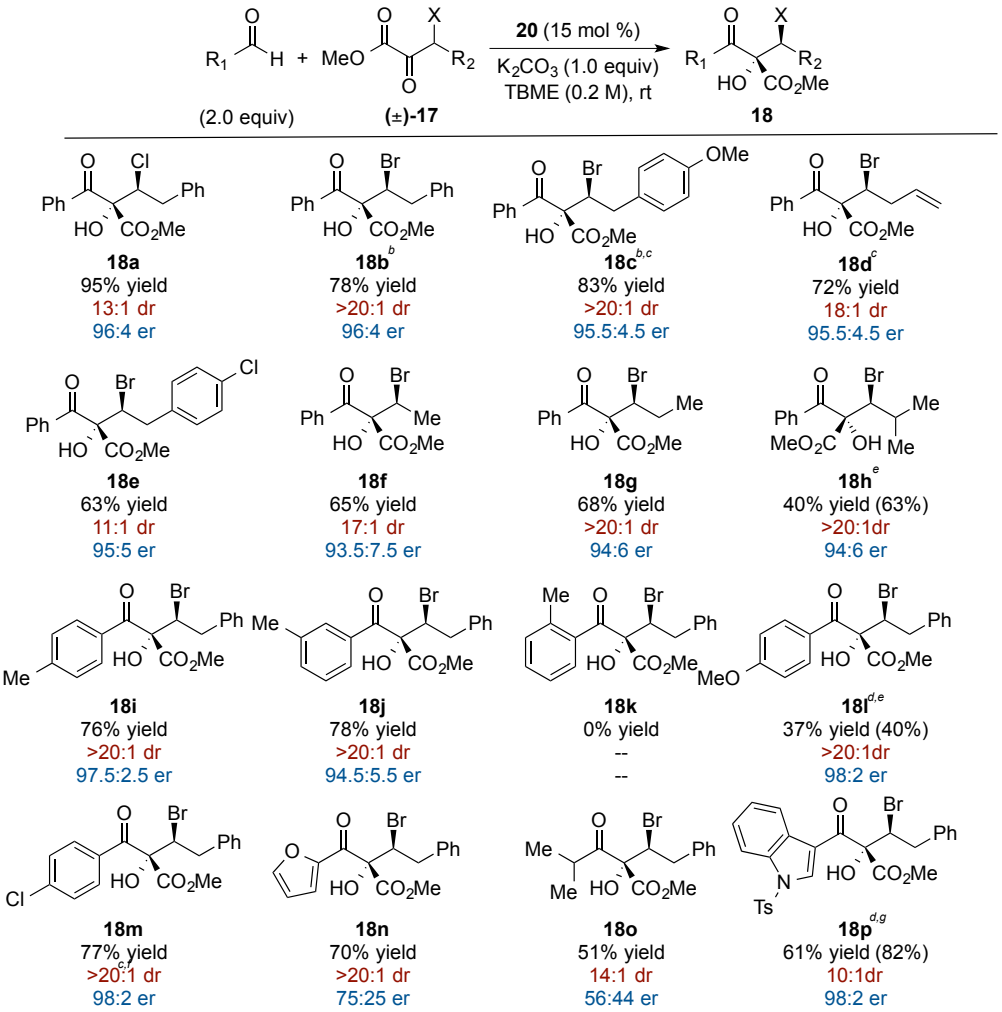


entry	X	catalyst	solvent	conv. (%)	dr[b]	er[c]
1	Cl	**19**	THF	25	4.5:1	96:4
2	Cl	**20**	THF	100	14:1	95:5
3	Cl	**15**	THF	40	1.5:1	98:2
4	Cl	**21**	THF	100	>20:1	90:10
5	Br	**19**	THF	<5	--	--
6	Br	**20**	THF	>95	>20:1	94:6
7	Br	**15**	THF	<5	--	--
8	Br	**21**	THF	30	--	--
9	Br	**22**	THF	<5	--	--
10	Br	**20**	TBME	100	>20:1	96:4
11[d]	Br	**20**	TBME	54	17:1	81:19
12	Cl	**20**	TBME	100	14:1	96:4

a) All reactions were run on a 0.10 mmol scale. *b)* Determined by ^{1}H NMR analysis of the crude reaction mixture. *c*) Determined by chiral SFC analysis. *d)* Run with the ^{i}Pr ester.

Heteroaromatic **18n** was isolated in >20:1 dr, and 75:25 er, while indole-derived **18p** was obtained with 10:1 dr and 98:2 er. One limitation of this method at the current level of development is the requirement of aromatic aldehydes in order to achieve high enantioselectivity, highlighted by the use of

Scheme 7. Cross-Benzoin Additions of Aldehydes to β-Bromo α-Keto Esters[a]

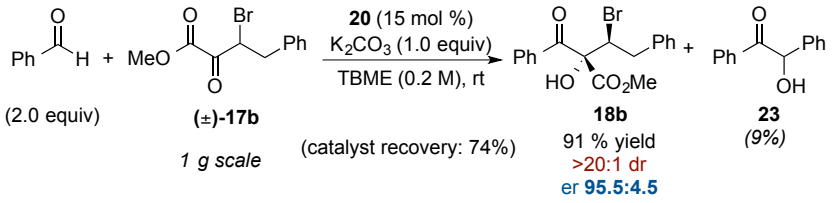


a) All reactions were run on a 0.20 mmol scale at room temperature for 16 h. Diastereomeric ratios were determined by ^{1}H NMR, enantiomeric ratios by chiral HPLC or SFC. Yields are of isolated products. *b)* Yield in parentheses represents a ^{1}H NMR yield utilizing ferrocene as an internal standard *c)* The product was reduced with $NaBH_4$ and the e.r. of the diol was analyzed. *d)* Yield in parentheses represents a ^{1}H NMR yield utilizing mesitylene as an internal standard. *e)* The mass balance is unreacted α-keto ester. *f)* Reaction was run using 20 mol % of catalyst **20.** *g)* Isolated yield is reported for the diol formed via reduction of **18p** with $NaBH_4$. The enantiomeric ratio was determined via Mosher ester analysis of the isolated diol.

isobutyraldehyde, which provided **18o** with 14:1 diastereoselectivity but only 54:46 er.

Coupling of **17b** with benzaldehyde on a 1 g scale resulted in 91% yield of **18b** without loss of stereoselectivity and with 74% catalyst recovery. Of particular note in this trial was that benzoin **23** was also isolated in 9% yield (Scheme 8).

Scheme 8. Gram Scale Reaction of 17b and Benzaldehyde

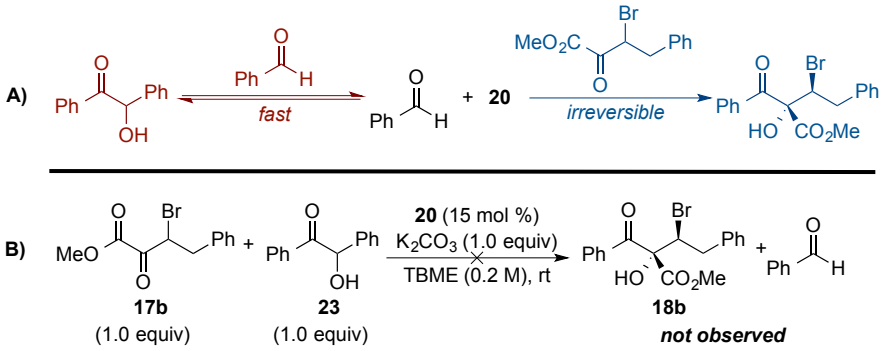


The obtention of **23** led us to consider the broader question of the chemoselectivity in the developed cross-benzoin reaction. We considered the possibility that homo-benzoin formation was the faster process, but reversible under the reaction conditions. In this scenario the cross-benzoin reaction would serve as an irreversible trap for the reversibly liberated benzaldehyde (Scheme 9A), analogous to the observations of Enders *et al*. in their study of cross-benzoin reactions with 1,1,1-trifluoromethylketones.[29] To evaluate the mechanism, we subjected **17b** and **23** to the normal reaction conditions (Scheme 9B). Neither **18b** nor benzaldehyde was observed during the course of the reaction, indicating that benzoin formation is irreversible under these conditions.

The cross-benzoin product presents four functional groups that are in principle uniquely addressable. As a first pass to probe the reactivity, selected ketones **18** were reduced with $NaBH_4$ in >20:1 diastereoselection providing the

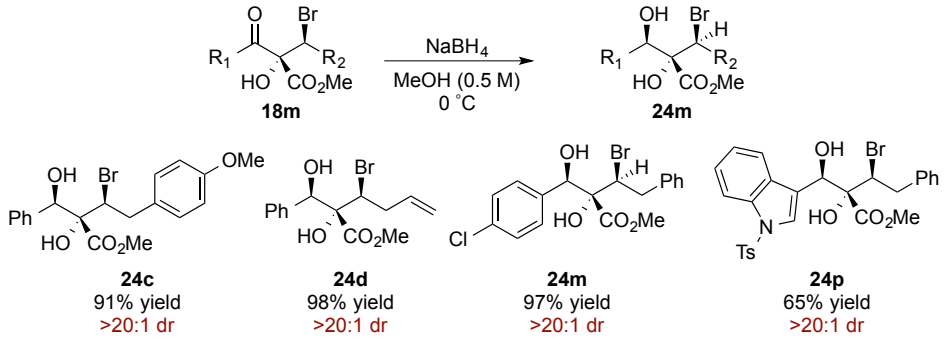
corresponding diols **24** with >20:1 diastereoselection for the reduction step (Scheme 10).[40,41]

Scheme 9. Determining the Source of the Observed Cross-Benzoin Chemoselectivity



Scheme 11 (top) shows the results of a X-ray diffraction study of **24m**, carried out to assign the relative and absolute stereochemistries as (1*R*,2*S*,3*S*).[42] By analogy the cross-benzoin adducts were assigned as (2*S*,3*S*).

Scheme 10. Reduction of the Cross-Benzoin Products

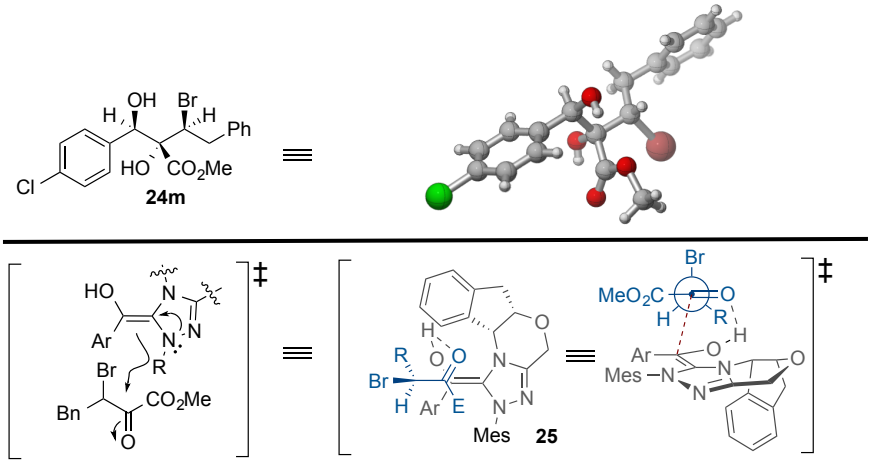


This configuration implicates the illustrated transition structure **25** as a plausible one to account for the stereochemical outcome of the benzoin addition. In this model the α-keto ester exhibits a strong polar Felkin-Ahn[43] and/or Cornforth[44,45] model diastereofacial bias. The chiral Breslow intermediate then

selects for the reactive enantiomer of the α-keto ester in part through strong facial bias imparted by the indane subunit, but also through the orienting/activating effect of the hydroxyl group.[46]

The precise orientation of the two reactants with respect to the axis of the forming bond (illustrated in red) is not known, but the gross features described above are likely to be relevant (Scheme 11 bottom).

Scheme 11. Absolute and Relative Stereochemistry and Proposed Transition State for the Dynamic-Benzoin



At the completion of these studies we had developed the first stereoconvergent cross-benzoin reaction that utilizes racemic electrophiles. The addition generates two stereocenters during the C-C bond construction via the dynamic kinetic resolution of β-halo α-keto esters. This NHC-catalyzed process generates a variety of fully substituted β-halo α-glycolic acid derivatives in high diastereo- and enantioselectivity utilizing a variety of aromatic aldehydes and α-keto esters. Subsequent diastereoselective reduction provides access to a number of highly functionalized and stereochemically-rich diols. Moreover, this investigation provided the framework and proof of concept necessary for our

subsequent investigation into the NHC-catalyzed homoenolate addition of enals to β-halo α-keto esters.

3.3 Enantioconvergent Synthesis of Functionalized y-Butyrolactones via (3+2)-Annulation**

Successful development of a NHC catalyzed dynamic cross-benzoin indicated that the proposed dynamic homoenolate addition of enals to β-halo α-keto esters (Scheme 4) might be viable providing that appropriate catalytic conditions could be identified. Developing this specific transformation was attractive to us for two primary reasons; 1) it would generate densely functionalized and stereocomplex γ-butyrolactones, and 2) it would establish three distinct stereocenters during they key C–C bond forming event (Scheme 12).

To this second point, even as the number of dynamic methodologies have grown, surprisingly few generate greater than two stereocenters. The conversion of racemic alcohols into optically pure acetates enabled by redox processing is a prototypical example of a DKR that sets one sterecenter[56] (see Chapter 1 for a thorough discussion) while most dynamic transformations of configurationally labile α- or β-oxo esters (see Chapters 1-3 for a full discussion and specific examples) establish two stereocenters.[57-61]

Stereodynamic methods that generate three stereocenters are extremely limited.[58,62-64] Further most of these methods use catalyst or substrate control to independently establish one stereocenter and dynamic bond formation to furnish the other two. Our group's dynamic reduction of β-substituted α-keto esters with

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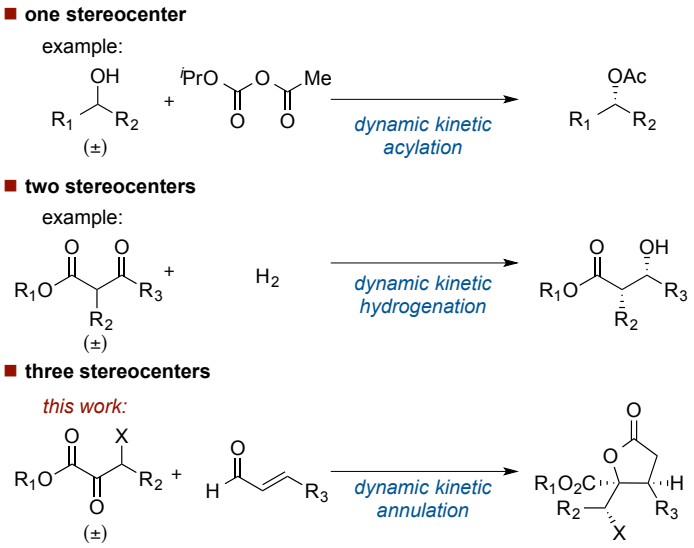
subseqent diastereoselective lactonization discussed in Chapter 2 serves as one such example.[58] Another case of this '2 + 1' type approach to dynamic stereocomplexity is sulfa-Michael addition to nitro-olefin **27** followed by dynamic Michael addition to form **30**. The initial sulfa-Michael was shown to be reversible which renders the the second Michael addition a dynamic process (Scheme 13A).[63]

Scheme 12. Levels of Stereocomplexity Present in DKR Reactions

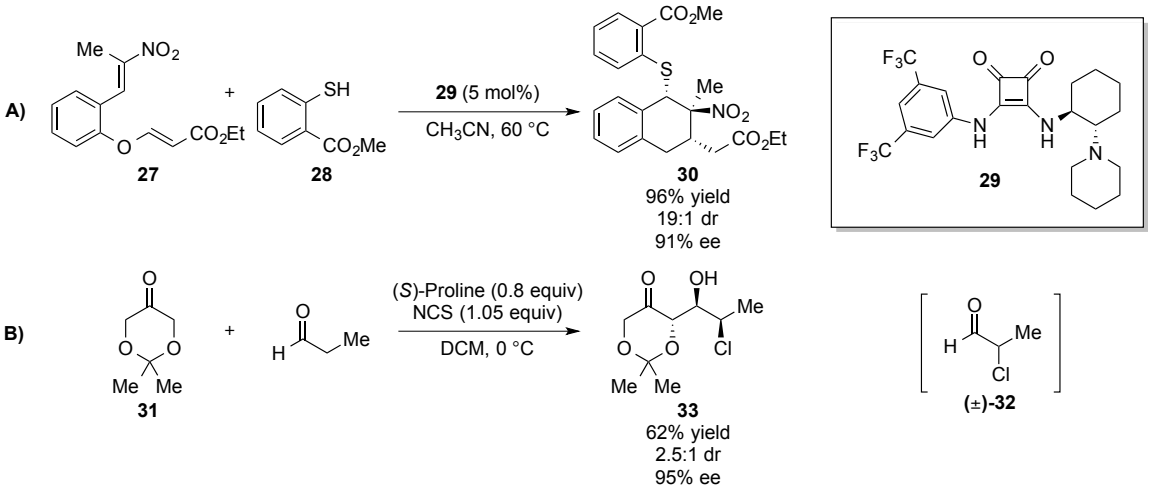


A counter-example whereby simultaneous generation of all three stereocenters occurs during the same step are reported cross-aldol to chiral racemic aldehydes.[65-68] In one report, Britton shows aldol addition of ketone **31** to *in situ* generated α-chloro aldehyde **32** producing chlorohydrin **33** in 62% yield, 2.5:1 dr and 95% ee (Scheme 13B). While proline catalyzes both the chlorination of propanal and the aldol addition, the authors took care to demonstrate that racemization of α-chloro aldehye **32** outcompetes aldol addition.

As we surveyed the litereature, the only previous example of NHC-catalyzed DKR that provides simultaneous generation of three stereocenters was the NHC catalyzed intramolecular DKR transformation of β-keto esters to β-lactones (Scheme 3) and there were no examples of stereoconvergent homoenolate reactions.[2,3]

Our synthetic plan was built on exploitation of homoenolate (d^3) nucleophiles generated by the union of NHCs and α,β-unsaturated aldehydes.[69-74] Since its simultaneous introduction by Bode and Glorius,[69,70] this method of catalytic *umpolung* (polarity inversion) has grown to include the use of imines,[75-78] carbonyls[79-84] and Michael acceptors[85-91] as electrophilic components.

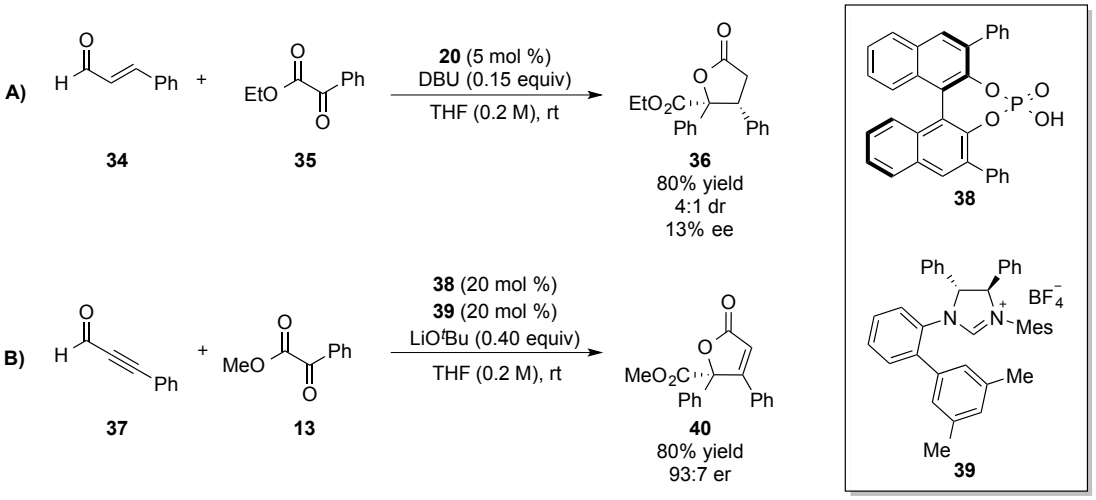
Scheme 13. DKR Reactions that Establish Three Stereocenters



Of greatest relevance to our proposed reactivity, were two reports utilizing NHC generated homoenolates in conjunction with linear α-keto ester electrophiles. The first of these from the You group demonstrated the addition of cinnamaldehyde to aryl α-keto ester **35** generating γ-butyrolactone **36** in low 1.5:1 dr and with 78% ee (Scheme 14A).[92] The issue of diastereocontrol was

indirectly addressed by the Scheidt group who utilized ynal **37** in a similar annulation to provide **40** containing only a single stereocenter with good enantioselectivity (Scheme 14B).[82]

Scheme 14. Previous Homoenolate Additions to Linear α-Keto Esters

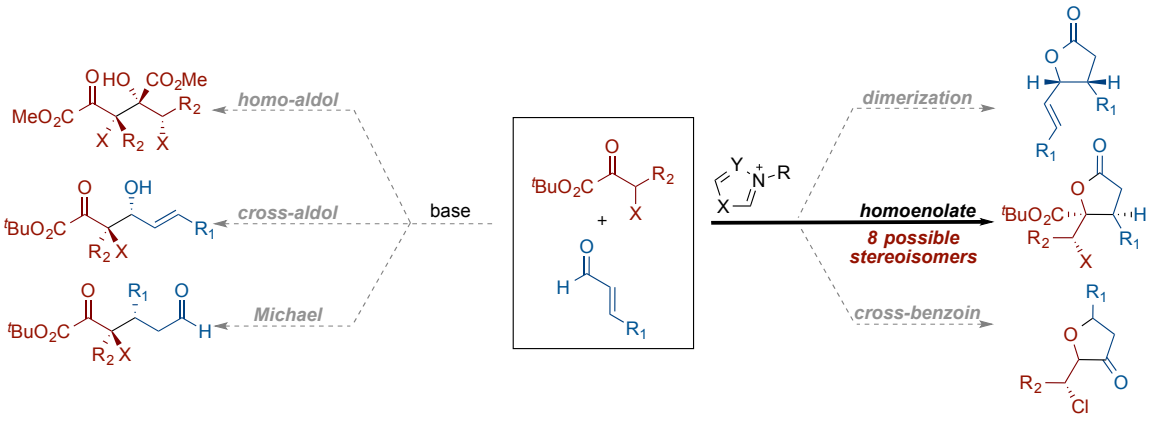


These results indicated that our proposed annulation presented a significant challenge in rate constant management. Aside from needing to select for a single stereoisomer (out of eight possibilities); by-products arising from NHC catalyzed cross-benzoin[31,32,61] or enal dimerization,[93,94] and base promoted aldol or conjugate addition pathways posed a legitimate concern (Scheme 15).[35]

With these difficulties in mind we began our studies by examining the reaction of cinnamaldehyde and α-keto ester **17a**. A preliminary screen showed that NHC catalyst **21** delivers γ-butyrolactone **42a-Me** in low regio- and diastereoselectivity (Table 2, entry 1).

Using **41a**, which has a more sterically demanding *tert*-butyl ester, in combination with catalyst **21** yielded lactone **42a** as a single product in a 6:1 diastereomeric ratio (dr) (Table 2, entry 2).

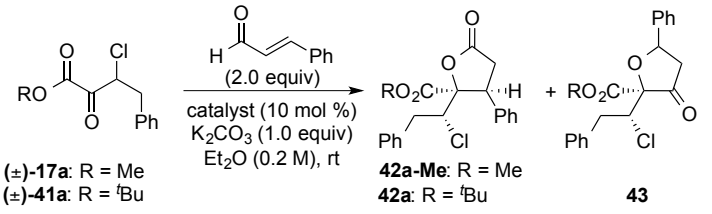
Scheme 15. Chemoselectivity Challenges for the Carbene-Catalyzed Coupling of α,β-Enals (blue) and Enolizable α-Keto Esters (red)



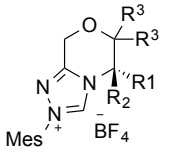
Taking this result as an indication that a sterically hindered ester was likely necessary for the efficacy of this transformation, we began a systematic screening of carbene catalysts with **41a** (complete details for the optimization of ester identity, solvent utilized, and catalysts tested can be found in Chapter 3 Section 5.7). Catalyst **44** and **45** revealed no marked increase in stereoselectivity (Table 2, entry 3-4). In tandem, these results indicated that increasing the steric bias of phenylalanine derived NHC catalysts was ineffectual to increasing reaction selectivity. Aminoindanol-derived catalyst **20** showed poor differentiation between the acyl anion and homoenolate pathway yielding a 2:1 ratio of products **42a**/**43a** (Table 2, entry 5). Catalyst **46** provided **42a** as the sole product in 3:1 dr and 78:22 er (Table 2, entry 6).

Catalyst **47**, derived from pyroglutamate, delivered exclusively **42a**, in 9:1 dr and 93:7 er (Table 2, entry 7). Implementation of catalyst **48** furnished **42a** as a single product in 33:1 dr and 99:1 er (Table 2, entry 8).

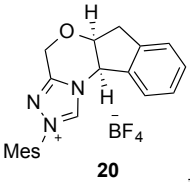
Table 2: Optimization of the Homoenolate Addition of Enals to α-Keto Esters



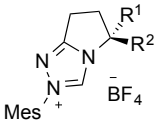
■ catalysts evaluated:



cat.	R^1	R^2	R^3
21	*i*Pr	H	H
44	Bn	H	Me
45	Bn	H	Ph



20



cat.	R^1	R^2
46	Bn	H
47	H	$C(OTMS)Ph_2$
48	H	$C(OTBS)Ph_2$

entry[a]	R	cat.	conv. (%)	**42a**:**43a**[b]	dr[b,c]	er[d]
1	Me	**21**	100	5:1	3:1	90:10
2	*t*Bu	**21**	100	>20:1	6:1	84:16
3	*t*Bu	**44**	88	>20:1	3:1	73:27
4	*t*Bu	**45**	64	3.5:1	2:1	85:15
5	*t*Bu	**20**	100	2:1	6:1	--
6	*t*Bu	**46**	100	>20:1	3:1	78:22
7	*t*Bu	**47**	100	>20:1	9:1	93:7
8	*t*Bu	**48**	100	>20:1	33:1	99:1
9[e]	*t*Bu	**48**	40	> 20:1	>20:1	--
10[f]	*t*Bu	**48**	100	>20:1	33:1	99:1

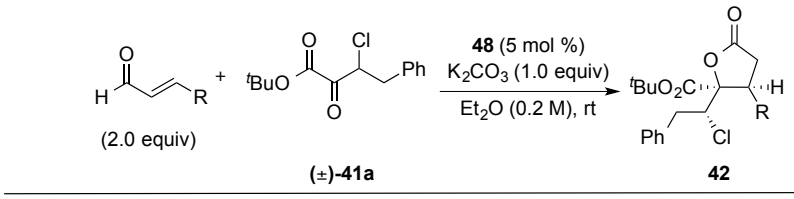
a) All reactions were run on a 0.10 mmol scale. *b)* Determined by ^{1}H NMR analysis of the crude reaction mixture. *c)* dr is only reported for homoenolate product **42a** *d*) Determined by chiral SFC analysis. *e)* Conducted on the corresponding β-bromo analog of **41a**. *f)* 5 mol % of catalyst G.

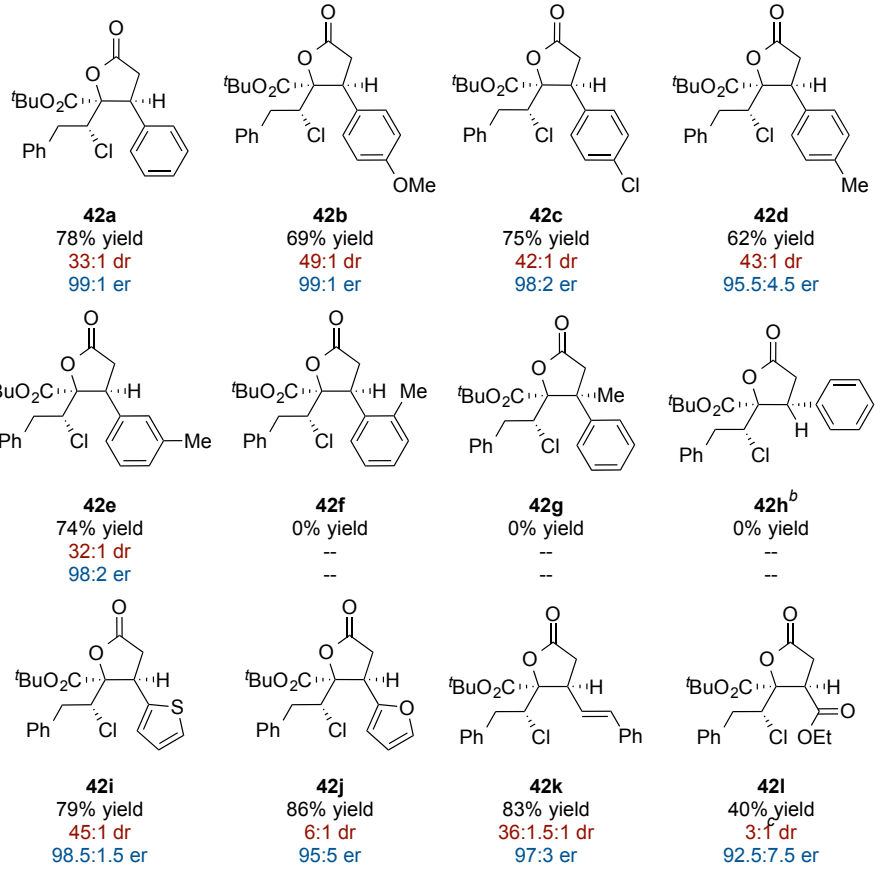
Using the β-bromo α-keto ester of **41a** under identical conditions maintained high levels of isomer selectivity but suffered from poor reactivity (Table 2, entry 9). Lowering the catalyst loading to 5 mol percent had no deleterious effects on reaction efficiency or selectivity (Table 2, entry 10).

With suitable conditions in hand we began to probe the allowable steric and electronic parameters of this annulation, initially by varying the identity of the α,β unsaturated aldehyde (Scheme 16). Changing the electronic features of the aldehyde delivered **42b** and **42c** without loss of reaction fidelity. While both *meta*- and *para*-tolyl-derived cinnamaldehydes cleanly delivered **42d** and **42e**, the heightened sense of steric encumbrance of *ortho*-substitution on the arene resulted in no reaction. Similarly, **42g** and **42h**, products that would arise from the addition of a trisubstituted alkene and (*Z*)-cinnamaldehyde respectively, were inaccessible. Heteroaromatic **42i** was isolated in 45:1 dr and 98.5:1.5 er while **42j** was obtained with 6:1 dr and 95:5 er. Products **42k** and **42l** demonstrated the viability of non-aromatic substitution, albeit with low dr for the addition of (*E*)-4-oxobut-2-enoic acid ethyl ester.

Variation of the α-keto ester also provided information regarding reaction scope (Scheme 17). Reducing the chain length of the starting α-keto ester delivered **42m** with 1.5:1 dr and 94.5:5.5 er. Similarly, **42n** was isolated with high enantioselectivity but as a 4:1 mix of isomers, while sterically encumbered **41o** resulted in no reaction.

Scheme 16. Variation of α–β Unsaturated Aldehydes in the Homoenolate Addition to β-Chloro-α-Keto Esters[a]





42a
78% yield
33:1 dr
99:1 er

42b
69% yield
49:1 dr
99:1 er

42c
75% yield
42:1 dr
98:2 er

42d
62% yield
43:1 dr
95.5:4.5 er

42e
74% yield
32:1 dr
98:2 er

42f
0% yield
--
--

42g
0% yield
--
--

42h[b]
0% yield
--
--

42i
79% yield
45:1 dr
98.5:1.5 er

42j
86% yield
6:1 dr
95:5 er

42k
83% yield
36:1.5:1 dr
97:3 er

42l
40% yield
3:1 dr
92.5:7.5 er

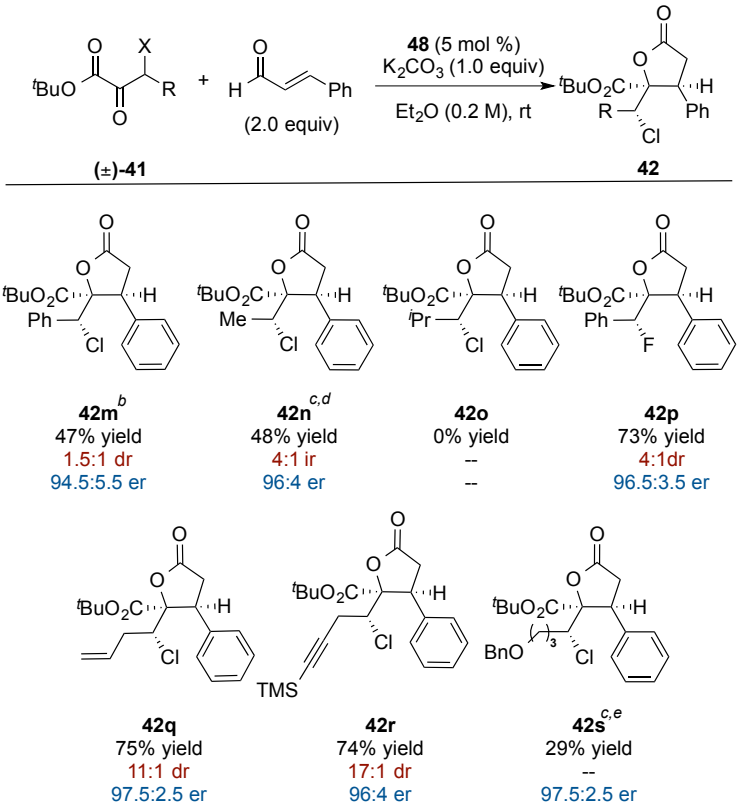
a) All reactions were run on a 0.20 mmol scale at room temperature for 14 h. No acyl anion addition was observed for any example. Diastereomeric ratios were determined by ^{1}H NMR; enantiomeric ratios by chiral SFC. Yields are of isolated products. *b*) Using (*Z*)-cinnamaldehyde.

Replacing chloride with fluoride gave **42p** in 4:1 dr and 97:3 er. Products

42q and **42r** showcase the efficacy of substrates bearing β-propargyl and β-allyl

substitution while heteroatom containing **42s** was obtained in low yield but with 97.5:2.5 er.

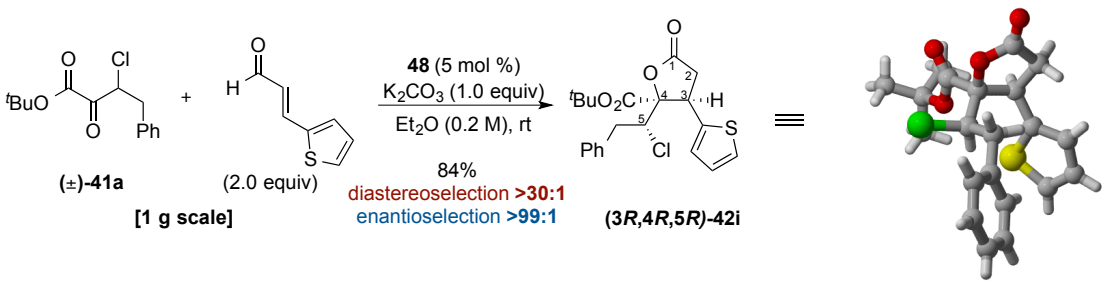
Scheme 17. Variation of β-Chloro α-Keto Esters in the Homoenolate Addition of Cinnamaldehyde[a]



a) All reactions were run on a 0.20 mmol scale at room temperature for 14 h. Diastereomeric and product ratios were determined by ^{1}H NMR; enantiomeric ratios by chiral SFC. Yields are of isolated products. *b*) Using THF as the solvent *c)* ^{1}H NMR yield utilizing mesitylene as an internal standard. *d)* Unambigious differentiation between formation of regioisomers and diastereomers was impractical, an isomeric ratio is reported. *e)* Identification of isomeric ratios was impossible. Isolation of **42s** was achieved via chromatography.

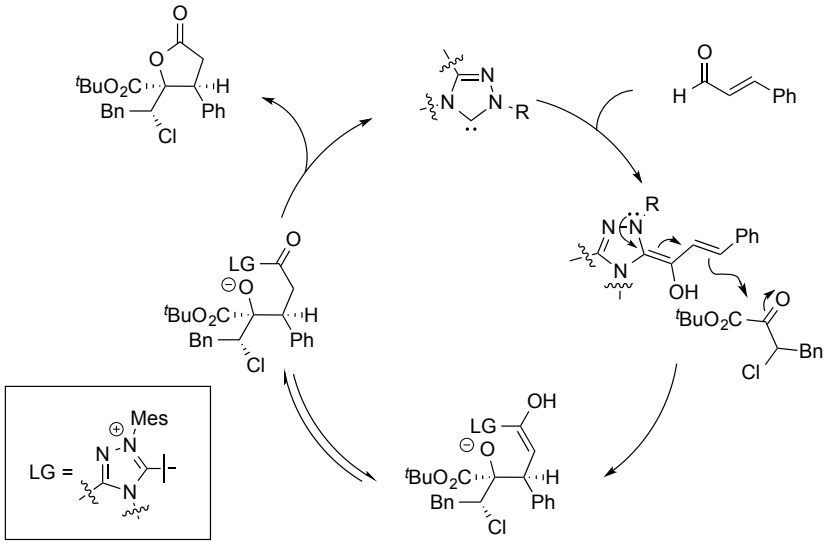
The reaction of **41a** with (*E*)-3-(thien-2-yl)acrylaldehyde on a 1 g scale resulted in 84% yield of **42i** as a single stereoisomer. An X-ray diffraction study of this product was carried out to assign the relative and absolute stereochemistries as (3*R*,4*R*,5*R*) (Scheme 18).[95]

Scheme 18. Gram Scale Reaction of 41a



Mechanistically this transformation is proposed to follow a typical homoenolate pathway where the conjugated Breslow intermediate is nucleophilic at the terminal alkene and catalyst regeneration occurs through tautomerization and alcohol acylation with concomitant carbene regeneration (Scheme 19).

Scheme 19. Proposed Mechanism of the [3 + 2] Annulation



The strong stereochemical influence of the β-chloro substitutent is manifested by the conserved *anti*-relationship between the nascent tertiary alcohol and the resident halogen. Similar to the earlier cross-benzoin addition

this outcome is consistent with diastereocontrol of the key C-C bond formation under the control of a Felkin-Anh or Cornforth model.[43-45]

The completion of this method netted the first stereoconvergent homoenolate reaction that utilizes racemic electrophiles. This NHC-catalyzed process between β-halo α-keto esters and α,β-unsaturated aldehydes constitutes a rare intermolecular dynamic kinetic resolution in which three stereocenters are established during the enantiodetermining step. The transformation results in formation of single product γ-butyrolactones bearing a fully substituted glycolic acid moiety in high diastereo- and enantioselectivity. The resultant vector between this method's successful realization and the relative dearth of complexity generating DKR's for β-oxo esters shifted our focus towards developing complexity building DKR's using β-formyl amides; this work is discussed in Chapter 4.

3.4 Experimental Data and Conditions for the Dynamic Kinetic Asymmetric Cross-Benzoin Additions of β-Stereogenic α-Keto Esters‡

3.4.1 General Information:

Methods**:** Infrared (IR) spectra were obtained using an ASI ReactIR 1000 Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz and ^{13}C NMR at 100 MHz or 150 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{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, dt = doublet of triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Supercritical fluid chromatography was performed on a Berger SFC system equipped with Chiracel AD, AS, OD, and WO columns as well as Regis Industries RegisPack (RP) column (φ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO_2 at the indicated percentage of methanol with an oven temperature of 40 °C. HPLC analysis was performed on an Agilent Technologies 1200 system equipped with Chiralpak IA, IB, and IC columns (constant flow at 1.00 mL/min). Samples were eluted with the indicated percentages of HPLC grade isopropanol in hexanes. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimiter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Samples were prepared via

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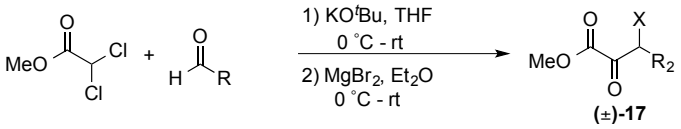
diluted with either Methanol (MeOH), 0.1 M ammonium formate (MeOH), or 0.1 M formic acid (MeOH). Analytical thin layer chromatography (TLC) was performed on Sorbtec 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or either aqueous potassium permanganate $KMnO_4$ or aqueous ceric ammonium molybdate (CAM) solution followed by heating. Product purification was accomplished using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Unless otherwise noted all reactions were carried out in flame-dried glassware with magnetic stirring. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the reported tables, which represent an average of at least two trials. In order to overlay the SFC traces for the chiral and racemic samples two separate integrations of the peaks must be taken. This results in slight discrepancies between the integration values shown in the report and seen on the trace itself. Materials**:** NHC catalysts **16, 19, 20**[47,48,32] **22,**[49] β-halo α-keto esters **17a**,[50] and 1-tosyl-1*H*-indole-3-carbaldehyde[51] were all prepared according to literature procedures. Potassium carbonate was purchased from Sigma Aldrich and dried under vacuum (5 torr) for 3 h at 110 °C. Methanol (MeOH) was distilled from 3 Å molecular sieves prior to use. HPLC grade chloroform ($CHCl_3$), ethyl acetate (EtOAc) and ethanol (EtOH) were used directly from the bottle. Dichloromethane (DCM) and tetrahydrofuran (THF) were passed through a column of neutral alumina under nitrogen prior to use. Methyl *t*butyl ether (MTBE) was distilled prior to use and stored over 4 Å molecular sieves. Benzaldehyde, *o*-tolualdehyde, *m*-tolualdehyde, *p*-tolualdehyde, *p*-anisaldehyde, furfural, and isobutyraldehyde

were all purchased from Sigma Aldrich and distilled before use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted. All racemic products were obtained via General Procedure B, Method 1 using Rovis's achiral triazolium catalyst.[48]

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

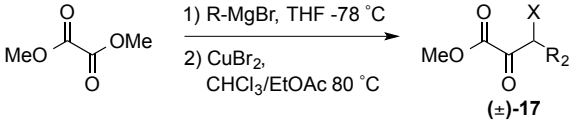


Method 1:

The following protocol was adopted from a literature procedure.[50] A 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with aldehyde (10.0 mmol, 1.0 equiv), methyl dichloroacetate (13.0 mmol, 1.3 equiv), and THF (20 mL, 0.5 M). This solution was cooled to 0 °C and potassium *tert*-butoxide (13.0 mmol, 1.3 equiv) was added in one portion. The mixture was warmed slowly to room temperature and stirred for 18 h, followed by dilution with Et_2O (60 mL) and H_2O (60 mL). The layers were separated and the organic layer was further washed with H_2O (1 x 60 mL) and brine (1 x 60 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in Et_2O (30 mL, 0.33 M) and cooled to 0 °C. To the resulting solution, magnesium bromide (10.0 mmol, 1.0 equiv) was added in one portion. The reaction was warmed slowly to room temperature and stirred for 2 h followed by dilution with Et_2O (60 mL) and H_2O (60 mL). The layers were separated and the organic layer was further washed with H_2O (1 x 60 mL) and brine (1 x 60 mL). The organic extracts were dried over $MgSO_4$, filtered and

concentrated *in vacuo*. The crude residue was purified by column chromatography using a gradient of 10-15% EtOAc/hexanes.

Method 2:



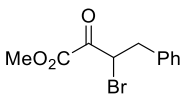
(±)-17

The following protocol was adopted from a literature procedure.[35] A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with dimethyl oxalate (10.0 mmol, 1.0 equiv) and THF (10 mL, 1.0 M). This solution was cooled to -78 °C and the required Grignard reagent (1.0 M solution in THF, 11 mL, 1.1 equiv) was added dropwise The resulting mixture was stirred at -78 °C for 2 h, quenched with saturated ammonium chloride, then diluted with Et_2O (60 mL) and 1 M HCl (60 mL). The layers were separated and the organic layer was further washed with H_2O (2 x 60 mL) and brine (1 x 60 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in EtOAc (130 mL, 0.075M) and $CHCl_3$ (67 mL, 0.15 M). Copper(II) bromide (30 mmol, 3.0 equiv) was added in one portion and the reaction was heated at reflux for 12 h. The reaction was then cooled to room temperature and filtered through celite with Et_2O. The filtrate was concentrated *in vacuo* and the crude residue was purified by column chromatography using a gradient of 10-15% EtOAc/hexanes.

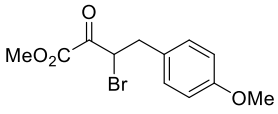
Grignard reagents were prepared according to the following procedure: a 50 mL 2-neck round-bottomed flask fitted with a reflux condenser and septa were charged with magnesium turnings (12.0 mmol, 1.2 equiv). The apparatus was

flame-dried under vacuum (<5 torr). After cooling to room temperature, THF (9 mL) was added. A small portion of alkyl bromide (11.0 mmol, 1.1 equiv) dissolved in THF (2 mL) was then added to this solution.

This solution was stirred until color change was observed, indicating reaction initiation. The remainder of the alkyl bromide was then added at a rate that maintained gentle reflux of the reaction mixture. After the addition was complete, the reaction was then aged for 1-2 h at room temperature; and used in the subsequent reaction.

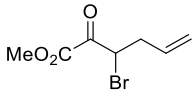


Methyl 3-bromo-2-oxo-4-phenylbutanoate (17b): The title compound was prepared according to General Procedure A (Method 1) using phenylacetaldehyde (2.2 mL, 10.0 mmol), affording **17b** (2.5 g, 4.62 mmol, 47% yield) as a yellow oil. Analytical data for **17b:** ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 7.36-7.33 (m, 2H), 7.30-7.27 (m, 3H), 5.30 (t, *J* = 7.8 Hz, 1H), 3.92 (s, 3H), 3.56 (dd, *J* = 14.4, 7.8 Hz, 1H) 3.28 (dd, *J* = 14.4, 7.8 Hz, 1H); ^{13}**C NMR** (150 MHz, $CDCl_3$): δ 184.8, 160.4, 136.3, 129.3, 128.7, 127.3, 53.4, 47.3, 38.1; **IR** (thin film): 3031, 1733,1455, 1260, 1068, 1027, 699 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.17; **LRMS** (ESI): Calcd. for $C_{11}H_{11}BrO_3$: ([M+H]): 271.00, Found: 271.12.

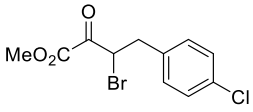


Methyl 3-bromo-4-(4-methoxyphenyl)-2-oxobutanoate (17c): The title compound was prepared according to General Procedure A (Method 2) using dimethyl oxalate (0.76 g, 5.7 mmol), affording **17c** (2.5 g, 3.27 mmol, 57% yield) as a yellow oil. Analytical data for **17c:** ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.4 Hz, 2H),

6.84 (d, *J* = 8.4 Hz, 2H), 5.22 (t, *J* = 7.8 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.48 (dd, *J* = 14.4, 7.8 Hz, 1H) 3.20 (dd, *J* = 14.4, 7.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 184.9, 160.4, 158.8, 130.4, 128.4, 114.1, 55.2, 53.4, 47.5, 37.3; **IR** (thin film): 3436, 1731, 1665, 1514, 1249, 1036 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.17; **LRMS** (ESI): Calcd. for $C_{12}H_{13}BrO_4$: ([M+NH_4]): 318.03, Found: 318.09.

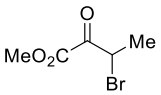


Methyl 3-bromo-2-oxohex-5-enoate (17d): The title compound was prepared according to General Procedure A (Method 2) using dimethyl oxalate (0.660 g, 5.0 mmol), affording **17d** (0.320 g, 1.55 mmol, 31% yield) as a yellow oil. Analytical data for **17d: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.79-5.74 (m, 1H), 5.21-5.16 (m, 2H), 5.06-5.04 (t, *J* = 7.8 Hz, 1H), 3.91 (s, 3H), 2.92-2.87 (m, 1H) 2.75-2.70 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 184.9, 160.7, 132.6, 119.5, 53.4, 46.2, 36.0; **IR** (thin film): 3480, 1736, 1644, 1438, 1258, 1163, 1077 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.17; **LRMS** (ESI): Calcd. for $C_7H_9BrO_3$: ([M+Na]): 239.08, Found: 239.16.

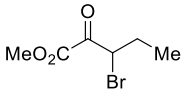


Methyl 3-bromo-4-(4-chlorophenyl)-2-oxobutanoate (17e): The title compound was prepared according to General Procedure A (Method 2) using dimethyl oxalate (0.951 g, 7.2 mmol), affording **17e** (0.66 g, 2.16 mmol, 30% yield) as a yellow oil. Analytical data for **17e: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 5.21 (t, *J* = 7.8 Hz, 1H), 3.88 (s, 3H), 3.47 (dd, *J* = 14.4, 7.8 Hz, 1H), 3.20 (dd, *J* = 14.4, 7.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 184.5, 160.3, 134.7, 133.1, 130.6, 128.7, 53.4, 46.9, 37.2; **IR** (thin film): 2955, 1735, 1493,

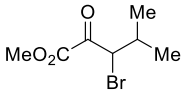
1255, 1081, 1016 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.17; **LRMS** (ESI): Calcd. for $C_6H_7BrO_3$: ([M+NH_4]): 321.98, Found: 322.12.



Methyl 3-bromo-2-oxobutanoate (17f): The title compound was prepared according to General Procedure A (Method 1) using acetaldehyde (0.56 mL, 10.0 mmol) and affording **17f** (0.5 g, 2.58 mmol, 26% yield) as a yellow oil whose spectral properties matched those previously reported.[52]

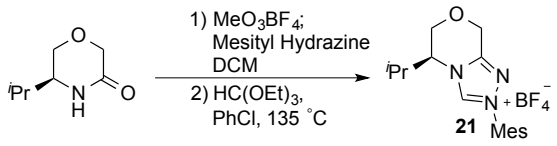


Methyl 3-bromo-2-oxopentanoate (17g): The title compound was prepared according to General Procedure A (Method 1) using propanal (0.72 mL, 10.0 mmol), affording **17g** (0.34 g, 1.62 mmol, 16% yield) as a yellow oil whose spectral properties matched those previously reported.[53]



Methyl 3-bromo-4-methyl-2-oxopentanoate (17h): The title compound was prepared according to General Procedure A (Method 1) using isobutyraldehyde (0.912 mL, 10.0 mmol), affording **17h** (0.60 g, 2.70 mmol, 27% yield) as a yellow oil whose spectral properties matched those previously reported.[5]

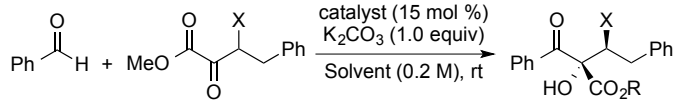
3.4.3 Preparation of Catalyst 21



This catalyst was synthesized according to the literature procedure.[48] Under N_2, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (3.6 mmol, 1.0 equiv) and

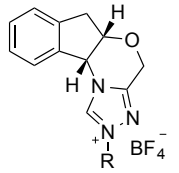
capped with a septum. DCM (20 mL, 0.2 M) was added under an atmosphere of N_2. The septum was removed and (*S*)-5-isopropylmorpholin-3-one[11] was added in a single portion. The flask was capped, put under N_2, and stirred vigorously for 14 h or until homogenous. Mesityl hydrazine[12] was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated *in vacuo* and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (20 mL, 0.2 M) and triethyl orthoformate (18.0 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated to open to the atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (18.0 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 200 mL of toluene, and concentrated *in vacuo*. The crude residue was purified by column chromatography using 5% MeOH/DCM. The resultant solid was stirred in Et_2O (100 mL) for 2 h then filtered, providing **21** (0.62 g, 1.66 mmol, 46% yield) as a tan solid. Analytical data for **21: mp** 165.2-166.2 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.76 (s, 1H), 6.99 (s, *1*H), 5.09 (d, *J* = 16.2 Hz, 1H) 4.99 (d, *J* = 16.2 Hz, 1H) 4.29-4.20 (m, 2H), 2.48-2.43 (m, 1H), 2.37 (s, 3H), 2.03 (s, 6H) 1.07 (d, *J* = 6.6 Hz, 3H) 0.98 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 150.3, 143.6, 143.5, 142.0, 131.0, 129.7, 63.7, 61.6, 60.3, 31.8, 21.2, 18.7, 17.5, 17.1; **IR** (thin film): 3507, 2927, 1796, 1692, 1599, 1226, 1151 cm^{-1}; **TLC** (5% MeOH/DCM): R_f = 0.21; **LRMS** (ESI): Calcd. for $C_{17}H_{24}N_3O$: ([M+H-BF_4]): 287.20, Found: 287.23.

3.4.4 Optimization Data for the Asymmetric Cross-Benzoin of 17a/17b with Benzaldehyde

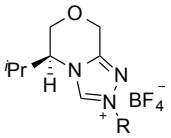


(2.0 equiv) **(±)-17a**: X = Cl; **(±)-17b**: X = Br

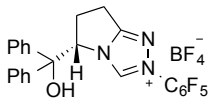
(2*S*,3*S*)-18a: X = Cl; **(2*S*,3*S*)-18b**: X = Br



19: R = C_6F_5
20: R = Mes



16: R = C_6F_5
21: R = Mes



22

General Procedure B for the Optimization of the Asymmetric Cross Benzoin Reaction

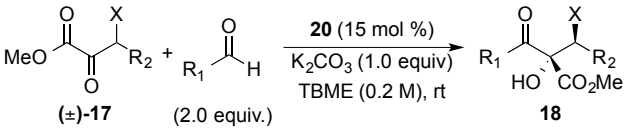
To a flame dried 1-dram vial was added catalyst, (0.03 mmol, 0.15 equiv) β-halo α-keto ester **17** (0.2 mmol, 1.0 equiv), TBME (1 mL, 0.2 M) and aldehyde (0.4 mmol, 2.0 equiv). This solution was stirred for 5 min followed by the addition of potassium carbonate (0.2 mmol, 1.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of silica gel, and concentrated *in vacuo.* The crude product was purified by column chromatography using EtOAc/hexanes.

Catalyst, base and solvent optimization table

Trial	X	cat.	base	solvent	T (°C)	conv. (%)	dr	er
1	Cl	**16**	NEt_3	DCM	rt	100	12:1	78:22
2	Cl	**19**	NEt_3	DCM	rt	100	12:1	78:22
3	Cl	**16**	NEt_3	DCM	0	100	10:1	70:30
4	Cl	**19**	NEt_3	DCM	0	100	7:1	88:12
5	Cl	**16**	NEt_3	DCM	-	45	1.4:1	99:1
6	Cl	**19**	NEt_3	DCM	-	50	5.5:1	99:1
7	Cl	**22**	NEt_3	DCM	rt	<10	5.5:1	--
8	Br	**16**	K_2CO_3	THF	rt	<5	--	--
9	Br	**19**	K_2CO_3	THF	rt	<5	--	--
10	Br	**22**	K_2CO_3	THF	rt	<5	--	--
11	Cl	**16**	K_2CO_3	THF	rt	40	1.5:1	98:2
12	Cl	**19**	K_2CO_3	THF	rt	25	4.5:1	96:4
13	Br	**21**	K_2CO_3	THF	rt	30	--	--
14	Br	**20**	K_2CO_3	THF	rt	>95	>20:1	94:6
15	Br	**20**	K_2CO_3	THF	0	60	7:1	96:4
16	Cl	**21**	K_2CO_3	THF	rt	100	>20:1	90:10
17	Cl	**20**	K_2CO_3	THF	rt	100	14:1	95:5
18	Br	**20**	K_2CO_3	2-Me THF	rt	72	>20:1	95:5
19	Br	**20**	K_2CO_3	DCM	rt	23	>20:1	--
20	Br	**20**	K_2CO_3	$CHCl_3$	rt	16	>20:1	--
21	Br	**20**	K_2CO_3	$PhCH_3$	rt	78	>20:1	92:8
22	Br	**20**	K_2CO_3	MeOH	rt	100	*	--
23	Br	**20**	K_2CO_3	EtOAc	rt	100	>20:1	95:5
24	Br	**20**	K_2CO_3	Et_2O	rt	100	>20:1	95:5
25	Br	**20**	K_2CO_3	CH_3CN	rt	100	*	--
26	Br	**20**	K_2CO_3	CPME	rt	100	>20:1	95.5:4.5
27	Br	**20**	K_2CO_3	TBME	rt	100	>20:1	96:4
28	Cl	**20**	K_2CO_3	Et_2O	rt	100	15:1	96.5:4.5
29	Cl	**20**	K_2CO_3	CPME	rt	100	15:1	97:3
30	Cl	**20**	K_2CO_3	TBME	rt	100	14:1	97.5:2.5
31	Cl	**20**	NEt_3	TBME	rt	50	20:1	97:3
32	Cl	**20**	DBU	TBME	rt	100	*	--
33	Cl	**20**	Hunig's	TBME	rt	0	--	--
34	Cl	**20**	Pyridine	TBME	rt	50	8:1	97.5:2.5
35	Cl	**20**	Cs_2CO_3	TBME	rt	100	>20:1	96:4
36	Cl	**20**	DMAP	TBME	rt	100	17:1	97:3
37	Br	**20**	NaOAc	TBME	rt	6	--	--
38	Br	**20**	$NaHCO_3$	TBME	rt	0	--	--
39	Br	**20**	Na_2CO_3	TBME	rt	10	--	--

* Reaction mixture did not contain any desired cross-benzoin product.

3.4.5 General procedure C for the Asymmetric Cross-Benzoin Procedure

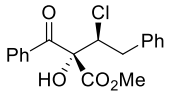


Method 1:

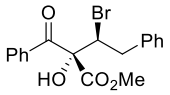
To a flame-dried 1-dram vial was added catalyst **20**, (0.03 mmol, 0.15 equiv) β-halo α-keto ester **17** (0.2 mmol, 1.0 equiv), TBME (1 mL, 0.2 M) and aldehyde (0.4 mmol, 2.0 equiv). This solution was stirred for 5 min followed by the addition of potassium carbonate (0.2 mmol, 1.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of silica gel, and concentrated *in vacuo.* The crude product was purified by column chromatography using EtOAc/hexanes.

Method 2:

To a flame dried 1-dram vial was added catalyst **20,** (0.03 mmol, 0.15 equiv) β-halo α-keto ester **17** (0.2 mmol, 1.0 equiv), and TBME (.5 mL, 0.4 M) followed by potassium carbonate (0.4 mmol, 2.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) while a 0.8 M solution of aldehyde in TBME (0.5 mL, 2.0 equiv) was added in 50 μL portions every 30 min for 5 h. Upon complete aldehyde addition the reaction was stirred an additional 9 h then filtered through a short plug of silica gel with Et_2O, and concentrated *in vacuo*. The crude residue was then purified by column chromatography using between 2.5% EtOAc/hexanes.

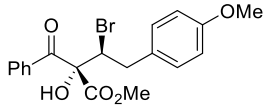


Methyl (2*S*,3*S*)-2-benzoyl-3-chloro-2-hydroxy-4-phenylbutanoate (18a): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17a** (0.045 g, 0.20 mmol), and benzaldehyde (0.04 mL, 0.40 mmol) affording **18a** (0.064 g, 0.19 mmol, 96% yield, 12:1 dr) as a clear oil. Analytical data for **18a:** **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.60-7.58 (m, 1H), 7.48-7.45 (m, 2H), 7.35-7.33 (m, 5H), 7.28-7.26 (m, 1H), 5.15 (dd, *J* = 10.7, 2.1 Hz, 1H) 4.30 (s, 1H), 3.82 (s, 3H), 3.24 (dd, *J* = 14.4, 2.2 Hz, 1H) 2.91 (dd, *J* = 14.4, 10.7 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.6, 170.4, 137.7, 134.6, 133.8, 129.8, 129.5, 128.5, 128.4, 126.9, 86.3, 67.1, 54.4, 39.1; **IR** (thin film): 3507, 2927, 1796, 1692, 1599, 1226, 1151 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.26; **LRMS** (ESI): Calcd. for $C_{18}H_{17}ClO_4$: ([M+H]): 333.09, Found: 333.21; **SFC:** Regis RP, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 3.7 min $t_{R\ (minor)}$ = 4.3 min, 96:4 er; **$[\alpha]_D$** = +45.8 (*c* = 0.03, DCM)

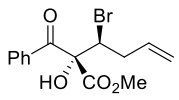


Methyl (2*S*,3*S*)-2-benzoyl-3-bromo-2-hydroxy-4-phenylbutanoate (18b): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17b** (0.054 g, 0.20 mmol), and benzaldehyde (0.04 mL, 0.40 mmol) affording **18b** (0.071 g, 0.19 mmol, 94% yield, >20:1 dr) as a clear oil. Analytical data for **18a:** **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.8 Hz, 2H), 7.61-7.58 (m, 1H), 7.47-7.45 (m, 2H), 7.34-7.19 (m, 5H), 5.22-5.20 (m, 1H) 4.37 (s,1H), 3.85 (s, 3H), 3.32-3.31 (m, 1H) 3.04-2.98 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.4, 170.5, 138.2, 134.7, 133.8, 129.8, 129.4, 128.5, 128.3, 126.9, 86.5, 60.9, 54.4, 39.9; **IR** (thin film):

3066, 2089, 2699, 1746, 1692, 1421, 1244 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.26; **LRMS** (ESI): Calcd. for $C_{18}H_{17}BrO_4$: ([M+H]): 377.23, Found: 377.15; **SFC:** Regis RP, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 4.5 min $t_{R\ (minor)}$ = 5.0 min, 96:4 er; **[α]$_D$** = +39.8 (*c* = 0.03, DCM)

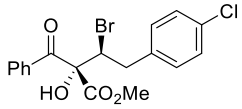


Methyl (2*S*,3*S*)-2-benzoyl-3-bromo-2-hydroxy-4-(4-methoxyphenyl)butanoate (18c): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester **17c** (0.060 g, 0.20 mmol), and benzaldehyde (0.04 mL, 0.40 mmol) affording **18c** (0.050g, 0.15 mmol, 61% yield, >20:1 dr) as a clear oil. Analytical data for **18a:** **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.8 Hz, 2H), 7.60-7.57 (m, 1H), 7.47-7.44 (m, 2H), 7.26-7.23 (m, 2H) 6.87 (d, *J* = 8.4 Hz, 2H), 5.16 (dd, *J* = 10.8, 2.3 Hz, 1H) 4.35 (s,1H), 3.82-3.81 (m, 6H), 3.24 (dd, *J* = 15.0, 2.3 Hz, 1H) 2.95 (dd, *J* = 15.0, 10.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.4, 170.5, 158.5, 134.7, 133.8, 130.4, 130.3, 129.8, 128.5, 113.7, 86.5, 61.5, 55.2, 54.4, 39.0; **IR** (thin film): 3059, 2989, 2306, 1715, 1429, 1267, 896 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.14; **LRMS** (ESI): Calcd. for $C_{19}H_{19}BrO_5$: ([M+H]): 407.05, Found: 407.08; **SFC:** Regis RP, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, **18c** could not be directly analyzed via SFC, see compound **24c** for enantiomeric analysis; **[α]$_D$** = +39.8 (*c* = 0.03, DCM)

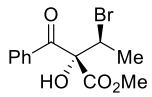


Methyl (2*S*,3*S*)-2-benzoyl-3-bromo-2-hydroxyhex-5-enoate (18d): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17d** (0.044 g, 0.20 mmol), and benzaldehyde (0.04 mL, 0.40 mmol) affording **18d** (0.046g, 0.15

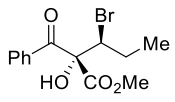
mmol, 74% yield, 17:1 dr) as a white solid. Analytical data for **18d: mp** 68.6-70.0 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.01-8.00 (m, 2H), 7.58-7.57 (m, 1H), 7.45-7.42 (m, 2H), 5.89-5.83 (m, 1H) 5.17-5.14 (m, 2H) 5.02 (dd, *J* = 10.8, 3 Hz, 1H), 4.22 (s,1H), 3.83 (s, 3H), 2.68-2.65 (m, 1H) 2.64-2.56 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.4, 170.5, 134.72, 134.70, 133.7, 129.8, 128.5, 118.2, 86.4, 58.9, 54.4, 37.8; **IR** (thin film): 3059, 2989, 2306, 1715, 1614, 1420, 1267 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.22; **LRMS** (ESI): Calcd. for $C_{14}H_{15}BrO_4$: ([M+Na]): 350.16, Found: 350.16; **18d** could not be directly analyzed via SFC, see compound **24d** for enantiomeric analysis; **[α]$_D$** = +14.8 (*c* = 0.01, DCM).



Methyl (*2S,3S*)-2-benzoyl-3-bromo-4-(4-chlorophenyl)-2-hydroxybutanoate (18e): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17e** (0.061 g, 0.20 mmol), and benzaldehyde (0.04 mL, 0.40 mmol) affording **18e** (0.050 g, 0.12 mmol, 61% yield, 12:1 dr) as a clear oil. Analytical data for **18e: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.07 (d, *J* = 4.2 Hz, 2H), 7.63-7.61 (m, 1H), 7.50-7.47 (m, 2H), 7.36-7.28 (m, 4H), 5.16-5.14 (m, 1H) 4.36 (s,1H), 3.85 (s, 3H), 3.30 (d, *J* = 15.0 Hz, 1H) 3.00 (dd, *J* = 15.0, 10.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.3, 170.4, 136.7, 134.5, 133.9, 132.7, 130.7, 129.8, 128.5, 128.5, 86.3, 60.5, 54.5, 39.3; **IR** (thin film): 3507, 3059, 2309, 1748, 1692, 1228, 1151 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.21; **LRMS** (ESI): Calcd. for $C_{18}H_{16}BrClO_4$: ([M+H]):411.00, Found: 411.14; **2e** could not be directly analyzed via SFC, see compound **24e** for enantiomeric analysis; **[α]$_D$** = +44.9 (*c* = 0.02, DCM).

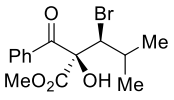


Methyl (2*S*,3*S*)-2-benzoyl-3-bromo-2-hydroxybutanoate (18f): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17f** (0.039 g, 0.20 mmol), and benzaldehyde (0.04 mL, 0.40 mmol) affording **18f** (0.042g, 0.14 mmol, 70% yield, 14:1 dr) as a clear oil. Analytical data for **18f: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.8 Hz, 2H), 7.58-7.55 (m, 1H), 7.44-7.42 (m, 2H), 5.16 (*q*, *J* = 6.6 Hz, 1H) 4.17 (s,1H), 3.83 (s, 3H), 1.72 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.0, 170.7, 134.6, 133.8, 129.8, 128.5, 86.2, 54.3, 53.4, 20.6; **IR** (thin film): 3507, 2936, 2309, 1746, 1692, 1166, 1050 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.24; **LRMS** (ESI): Calcd. for $C_{12}H_{13}BrO_4$: ([M+H]): 301.01, Found: 300.99; **SFC:** Chiracel AD, 5% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 5.7 min $t_{R\ (minor)}$ = 6.1 min, 93:7 er; **$[\alpha]_D$** = +26.1 (*c* = 0.02, DCM)

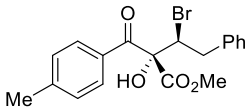


Methyl (2*S*,3*S*)-2-benzoyl-3-bromo-2-hydroxypentanoate (18g): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17g** (0.042 g, 0.20 mmol), and benzaldehyde (0.04 mL, 0.40 mmol) affording **18g** (0.046g, 0.15 mmol, 73% yield, >20:1 dr) as a white solid. Analytical data for **18g: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.01-8.00 (m, 2H), 7.58-7.55 (m, 1H), 7.44-7.42 (m, 2H), 4.92 (dd, *J* = 9, 4.2 Hz, 1H) 4.17 (s,1H), 3.83 (s, 3H), 1.87-1.82 (m, 2H), 1.11 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.7, 170.6, 134.8, 133.7, 129.8, 128.5, 86.8, 62.8, 54.4, 26.9, 12.8; **IR** (thin film): 3507, 2935, 1748, 1692, 1228, 1189 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.24; **LRMS** (ESI): Calcd. for $C_{13}H_{15}BrO_4$: ([M+H]): 315.02, Found: 315.06; **SFC:** Chiracel AD, 5% MeOH, flow rate = 1.5 mL/min, λ

= 210 nm, $t_{R\ (major)}$ = 5.9 min $t_{R\ (minor)}$ = 6.4 min, 94:6 er; **$[\alpha]_D$** = +12.5 (*c* = 0.02, DCM)

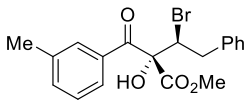


Methyl (2*R*,3*S*)-2-benzoyl-3-bromo-2-hydroxy-4-methylpentanoate (18h): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17h** (0.044 g, 0.20 mmol), benzaldehyde (0.04 mL, 0.40 mmol) and mesitylene as an internal standard (0.028 mL, 0.20 mmol) affording **18h** (0.026g, 0.08 mmol, 65% ^{1}H NMR yield, 40% isolated yield, >20:1 dr) as a clear oil. Analytical data for **18h: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.57-7.55 (m, 1H), 7.44-7.42 (m, 2H), 5.08 (d, *J* = 3 Hz, 1H) 4.22 (s,1H), 3.83 (s, 3H), 2.09-2.05 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 3H) 1.00 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.5, 170.7, 135.0, 133.5, 129.8, 128.4, 88.0, 67.2, 54.4, 31.5, 23.1, 19.8; **IR** (thin film): 3507, 2966, 1740, 1692, 1159, 409 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.29; **LRMS** (ESI): Calcd. for $C_{14}H_{17}BrO_4$: ([M+H]): 329.03, Found: 329.13; **SFC:** Regis RP, 5% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 4.0 min $t_{R\ (minor)}$ = 4.3 min, 94:6 er; **$[\alpha]_D$** = +18.3 (*c* = 0.01, DCM)

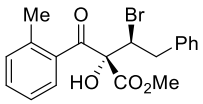


Methyl (2*S*,3*S*)-3-bromo-2-hydroxy-2-(4-methylbenzoyl)-4-phenylbutanoate (18i): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17b** (0.054 g, 0.20 mmol), and *p*-tolualdehyde (0.05 mL, 0.40 mmol) affording **18i** (0.060g, 0.15 mmol, 77% yield, >20:1 dr) as a clear oil. Analytical data for **18i: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.8 Hz, 2H), 7.36-7.28 (m, 7H), 5.23 (dd, *J* = 10.7, 2.3 Hz, 1H) 4.36 (s, 1H), 3.84 (s, 3H), 3.34 (dd, *J* = 14.6, 2.3 Hz, 1H) 3.02 (dd, *J*

= 14.6, 10.7 Hz, 1H), 2.45 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 192.7, 170.6, 145.0, 138.3, 132.0, 130.0, 129.4, 129.2, 128.3, 126.8, 86.4, 61.1, 54.3, 39.9, 21.7; **IR** (thin film): 3507, 2927, 1746, 1684, 1607, 1151 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.24; **LRMS** (ESI): Calcd. for $C_{19}H_{19}BrO_4$: ([M+H]): 391.05, Found: 391.15; **SFC:** Regis RP, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 9.7 min $t_{R\ (minor)}$ = 11.1 min, 97:3 er; **[α]$_D$** = +20.7 (*c* = 0.02, DCM)

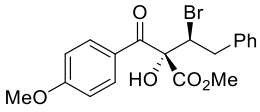


Methyl (2*S*,3*S*)-3-bromo-2-hydroxy-2-(3-methylbenzoyl)-4-phenylbutanoate (8j): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17b** (0.054 g, 0.20 mmol), and *m*-tolualdehyde (0.05 mL, 0.40 mmol) affording **18j** (0.066g, 0.17 mmol, 85% yield, >20:1 dr) as a clear oil. Analytical data for **18j: ^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.87-7.84 (m, 2H), 7.41-7.40 (m, 1H), 7.35-7.26 (m, 6H), 5.22 (m, 1H) 4.31 (s,1H), 3.82 (s, 3H), 3.31-3.28 (d, *J* = 12.6 Hz, 1H) 3.02-2.97 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.41 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$, two coincident aromatic resonances): δ 193.7, 170.5, 138.4, 138.2, 134.7, 134.6, 130.2, 129.4, 128.4, 127.0, 126.9, 86.5, 70.0, 54.4, 39.9, 21.4 (two coincident resonances); **IR** (thin film): 3507, 2927, 1746, 1692, 1607, 1143 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.24; **LRMS** (ESI): Calcd. for $C_{19}H_{19}BrO_4$: ([M+Na]): 413.04, Found: 413.12; **HPLC:** Chiralpak IC, 5% ^{i}PrOH, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 5.1 min $t_{R\ (minor)}$ = 5.7 min, 96:4 er; **[α]$_D$** = +39.8 (*c* = 0.03, DCM)

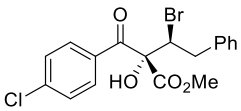


Methyl (2*S*,3*S*)-3-bromo-2-hydroxy-2-(2-methylbenzoyl)-4-phenylbutanoate (18k): No reaction was observed using

General Procedure B (Method 1) with α-keto ester **17b** (0.054 g, 0.20 mmol), and *o*-tolualdehyde (0.05 mL, 0.40 mmol).

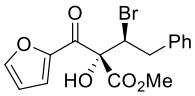


Methyl (2*S*,3*S*)-3-bromo-2-hydroxy-2-(4-methoxybenzoyl)-4-phenylbutanoate (18l): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17b** (0.054 g, 0.20 mmol), *p*-anisaldehyde (0.05 mL, 0.40 mmol), and mesitylene as an internal standard (0.028 mL, 0.20 mmol) resulting in 50% conversion of **17b** and affording **18l** (0.040 g, 0.10 mmol, 49% yield, >20:1 dr) as a clear oil. Analytical data for **18l: ^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.33-7.32 (m, 5H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.20 (dd, *J* = 10.7, 2.2 Hz, 1H) 4.33 (s,1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.33 (dd, *J* = 14.8, 2.2 Hz, 1H) 2.99 (dd, *J* = 14.8, 10.7 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 191.1, 107.8, 164.2, 138.3, 132.6, 129.4, 128.3, 127.3, 126.8, 113.8, 86.4, 61.3, 55.5, 54.3, 39.9; **IR** (thin film): 3066, 2989, 2309, 1746, 1684, 1599, 1420, 1159 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.15; **LRMS** (ESI): Calcd. for $C_{19}H_{19}BrO_5$: ([M+Na]): 429.03, Found: 429.18; **SFC:** Regis RP, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 9.7 min $t_{R\ (minor)}$ = 12.1 min, 98:2 er; **$[\alpha]_D$** = +8.23 (*c* = 0.02, DCM)



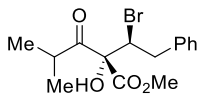
Methyl (2*S*,3*S*)-3-bromo-2-(4-chlorobenzoyl)-2-hydroxy-4-phenylbutanoate (18m): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17b** (0.054 g, 0.20 mmol), 4-Chlorobenzaldehyde (0.056 g, 0.40 mmol) and mesitylene as an internal standard (0.028 mL, 0.20 mmol) resulting in 71%

conversion of **17b** and affording **18m** (0.036 g, 0.09 mmol, 44% yield >20:1 dr) as a clear oil. With 20 mol % of catalyst **17b** went to full conversion and **18m** was obtained with identical selectivity but higher isolated yield (0.066 g, 0.16 mmol, 80% yield >20:1 dr). Analytical data for **18m:** **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34-7.33 (m, 4H), 7.29-7.26 (m, 1H), 5.17 (dd, *J* = 10.8, 1.8 Hz, 1H) 4.27 (s,1H), 3.82 (s, 3H), 3.30 (dd, *J* = 15.0, 1.8 Hz, 1H) 3.00 (dd, *J* = 15.0, 10.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 192.1, 170.4, 140.5, 138.1, 132.9, 131.4, 129.4, 128.8, 128.4, 127.0, 86.6, 60.8, 54.5, 39.9; **IR** (thin film): 3630, 3507, 3059, 2958, 2308, 1746, 1692, 1591, 1097, 1026 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.28; **LRMS** (ESI): Calcd. for $C_{18}H_{16}BrClO_4$: ([M+Na]): 411.00, Found: 411.14; **18m** could not be directly analyzed via SFC, see compound **24m** for enantiomeric analysis; **$[a]_D$** = +24.6 (*c* = 0.03, DCM)

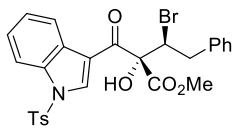


Methyl (2*S*,3*S*)-3-bromo-2-(furan-2-carbonyl)-2-hydroxy-4-phenylbutanoate (18n): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17b** (0.054 g, 0.20 mmol), and furfural (0.03 mL, 0.40 mmol) affording **2n** (0.052g, 0.14 mmol, 71% yield, >20:1 dr) as a clear oil. Analytical data for **2n:** **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.69 (d, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 3.6 Hz, 1H), 7.32-7.29 (m, 4H), 6.58 (dd, *J* = 3.6, 1.2 Hz, 1H), 5.15 (dd, *J* = 11.4, 2.4 Hz, 1H) 4.47 (s,1H), 3.81 (s, 3H), 3.28 (dd, *J* = 15.0, 2.4 Hz, 1H) 3.00 (dd, *J* = 14.4, 10.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 180.9, 169.8, 149.5, 148.2, 138.0, 129.4, 128.3, 126.9, 123.1, 112.6, 85.8, 59.7, 54.4, 39.6; **IR** (thin film): 3507, 1746, 167, 1466, 1159, 1027, 818, 617 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.35; **LRMS** (ESI): Calcd.

for $C_{16}H_{15}BrO_5$: ([M+H]): 367.02, Found: 367.02; **SFC:** Regis RP, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 4.3 min $t_{R\ (minor)}$ = 7.0 min, 75.5:25.5 er; **$[\alpha]_D$** = +4.7 (*c* = 0.02, DCM)



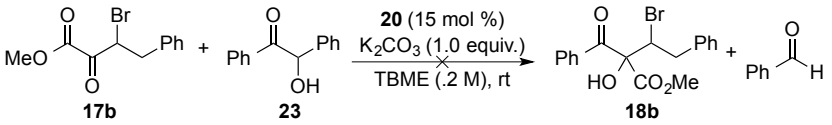
Methyl (*S*)-2-((*S*)-1-bromo-2-phenylethyl)-2-hydroxy-4-methyl-3-oxopentanoate (18o): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester **17b** (0.054 g, 0.20 mmol), and isobutyraldehyde (0.02 mL, 0.40 mmol) affording **18o** (0.039 g, 0.12 mmol, 59% yield 10:1 dr) as a clear oil. Analytical data for **18o:** **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.27-7.25 (m, 3H), 5.75 (dd, *J* = 9.0, 4.5 Hz, 1H) 3.86 (s, 3H), 3.25 (dd, *J* = 14.1, 4.5 Hz, 1H) 3.07 (dd, *J* = 14.1, 9.0 Hz, 1H) 2.61-2.57 (m, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 189.5, 176.3, 160.2, 135.3, 129.4, 128.5, 127.2, 75.7, 53.1, 36.2, 33.4, 18.64, 18.60; **IR** (thin film): 3059, 2989, 2688, 2410, 2308, 1760, 1429, 1267, 896 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.15; **LRMS** (ESI): Calcd. for $C_{15}H_{19}BrO_4$: ([M+H]): 343.05, Found: 343.04; **HPLC:** Chiralpak IC, 5% ^{i}PrOH, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 9.1 min $t_{R\ (minor)}$ = 9.9 min, 58:42 er; **$[\alpha]_D$** = +2.3 (*c* = 0.02, DCM)



Methyl (*2S,3S*)-3-bromo-2-hydroxy-4-phenyl-2-(1-tosyl-1H-indole-3-carbonyl)butanoate (18p): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **17b** (0.054 g, 0.20 mmol), and 1-tosyl-1*H*-indole-3-carbaldehyde (0.119 g, 0.40 mmol). **18a** was not isolable from 1-tosyl-1*H*-indole-3-carbaldehyde and was reduced with $NaBH_4$ **24p** (0.074 g, 0.13 mmol, 65% yield, 10:1 dr), was isolated by

column chromatography using 15% EtOAc/hexanes. See compound **24p** for all characterization data.

3.4.6 Attempting the Cross-Benzoin Reaction Using Homo-Benzoin Product 23



17b **23** **18b**

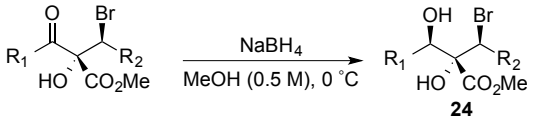
To a flame dried 1-dram vial was added catalyst **20,** (0.03 mmol, 0.15 equiv) β-halo α -keto ester **1** (0.2 mmol, 1.0 equiv), TBME (1 mL, 0.2 M) and benzoin product **23** (0.2 mmol, 1.0 equiv). This solution stirred for 5 minutes followed by the addition of potassium carbonate (0.2 mmol, 1.0 equiv). This reaction was stirred for 14 h, filtered through a short plug of silica gel with Et_2O, and concentrated *in vacuo* for analysis by ^1H NMR.

3.4.7 Procedure for the Gram Scale Asymmetric Cross-Benzoin

To a flame dried 50 mL round bottom flask was added catalyst **21,** (0.55 mmol, 0.15 equiv) β-halo α-keto ester **17b** (3.7 mmol, 1.0 equiv), TBME (19 mL, 0.2 M) and benzaldehyde (7.4 mmol, 2.0 equiv). This solution stirred for 5 minutes followed by the addition of potassium carbonate (3.7 mmol, 1.0 equiv). This reaction was stirred (rate of stirring should be >800 rpm) for 14 h, filtered through celite with DCM, and concentrated *in vacuo*. The resulting precipitate was dissolved in MeOH and quenched with (1.1 mmol, 0.3 equiv conc. HCl). The solvent was removed *in vacuo* and the crude residue was purified by column chromatography with 5% EtOAc/hexanes until **18b** (1.26 g, 91% yield, >20:1 dr, 95.5:4.5 er) had eluted from the column (TLC analysis). At this point the eluent

was changed to 2.5% MeOH/DCM in order to recover the HCl salt of catalyst **21** (0.15 g, 74% recovery based on the HCl salt).

3.4.8 General Procedure D for the Reduction of Cross-Benzoin Products



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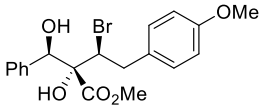
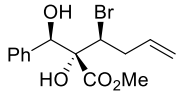
A flame dried scintillation vial was charged with cross-benzoin product **18**, diluted with MeOH (to 0.5 M), and cooled to 0 °C. $NaBH_4$ (5.0 equiv) was added and the reaction was stirred at 0 °C for 7 min, then quenched with saturated NH_4Cl and diluted with Et_2O (15 mL) and H_2O (10 mL). The layers were separated and the organic layer was further washed with brine (1 x 10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. In general no further purification was required but if necessary diols **24** could be purified by column chromatography using an eluent of 15% EtOAc/hexanes.

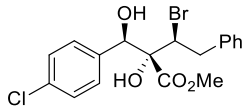


Methyl (2*S*,3*S*)-3-bromo-2-hydroxy-2-((*R*)-hydroxy(phenyl)methyl)-4-(4-methoxyphenyl)butanoate (24c): The title compound was prepared according to General Procedure C using **18c** (0.030 g, 0.074 mmol), affording **24c** (0.027 g, 0.66 mmol, 91% yield, >20:1 dr) as a white solid. Analytical data for **24c: mp** 124.5-125.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42-7.40 (m, 2H), 7.38-7.32 (m, 3H), 7.26-7.19 (m, 2H) 6.87-6.85 (m, 2H), 5.07 (d, *J* = 7.6, Hz, 1H) 4.79 (dd, *J* = 11.4, 2.0 Hz, 1H), 3.84-3.79 (m, 4H), 3.72 (s, 3H), 3.60 (s, 1H), 3.52 (d, *J* = 14.4 Hz, 1H) 2.99 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.85 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.5, 158.5, 138.7, 130.31,

130.29, 128.6, 128.2, 126.7, 113.7, 75.4, 82.7, 60.8, 55.2, 53.2, 37.2; **IR** (thin film): 2927, 2866, 1738, 1514, 803, 602 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.21; **LRMS** (ESI): Calcd. for $C_{19}H_{21}BrO_5$: ([M+H]): 409.07, Found: 409.17; **SFC:** Regis RP, 15% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 5.5 min $t_{R\ (minor)}$ = 10.8 min, 96:4 er; **[α]$_D$** = -24.8 (*c* = 0.005, DCM)



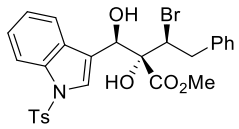
Methyl (2*S*,3*S*)-3-bromo-2-hydroxy-2-((*R*)-hydroxy(phenyl)methyl)hex-5-enoate (24d): The title compound was prepared according to General Procedure C using **18d** (0.040 g, 0.13 mmol), affording **24d** (0.039 g, 0.13 mmol, 98% yield, >20:1 dr) as a white solid. Analytical data for **24c mp** 72.1-73.0 °C**:** ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 7.38-7.30 (m, 5H), 5.92-5.85 (m, 1H), 5.19-5.15 (m, 2H) 4.99 (d, *J* = 8.4, Hz, 1H) 4.57 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.73 (s, 3H), 3.55 (s, 1H), 3.55 (s, 1H), 2.91-2.86 (m, 2H), 2.66-2.60 (m, 1H); ^{13}**C NMR** (150 MHz, $CDCl_3$): δ 172.6, 138.6, 134.9, 128.6, 128.2, 126.8, 118.0, 75.4, 82.5, 58.1, 53.2, 36.2; **IR** (thin film): 2924, 1731, 1454, 1242, 1024, 701 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.12; **LRMS** (ESI): Calcd. for $C_{14}H_{17}BrO_4$: ([M+NH_4]): 347.22, Found: 347.22;



SFC: Regis RP, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 7.7 min $t_{R\ (minor)}$ = 8.7 min, 95.5:4.5 er; **[α]$_D$** = -20.1 (*c* = 0.007, DCM)

Methyl (2*S*,3*S*)-3-bromo-2-((*R*)-(4-chlorophenyl)(hydroxy)methyl)-2-hydroxy-4-phenylbutanoate (24m): The title compound was prepared according to General Procedure C using **18m** (0.031 g, 0.075 mmol), affording **24m** (0.030 g, 0.073 mmol, 97% yield, >20:1 dr) as a white solid. This solid was then

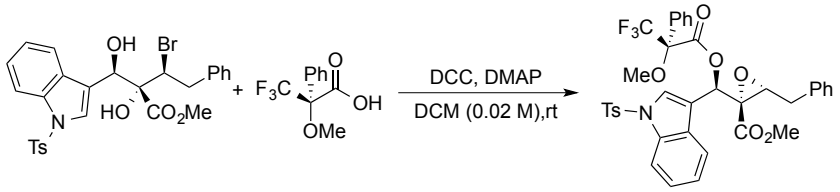
recrystallized from 5% EtOAc/hexanes. Analytical data for **24m: mp** 149.2-150.0 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.38-7.26 (m, 9H), 5.06 (d, *J* = 8.2 Hz, 1H), 4.78 (dd, *J* = 11.3, 2.6 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 1H), 3.58 (dd, *J* = 14.6, 2.6 Hz, 1H), 3.03 (dd, *J* = 22.4, 14.6 Hz, 1H) 2.98 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.4, 138.1, 137.2, 134.5, 131.0, 129.3, 128.4, 128.2, 126.9, 82.6, 74.7, 60.0, 53.4, 38.1; **IR** (thin film): 3059, 2989, 2688, 2309, 1738, 1429, 1267 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.41; **LRMS** (ESI): Calcd. for $C_{18}H_{18}BrClO_4$: ([M+Na]): 435.00, Found: 435.09; **SFC:** Regis RP, 15% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 4.4 min $t_{R\ (minor)}$ = 8.2 min, 98:2 er (>99.9:0.1 recrystallized); **$[\alpha]_D$** = -56.3 (*c* = 0.004, DCM)



Methyl (2*S*,3*S*)-3-bromo-2-hydroxy-2-((*R*)-hydroxy(1-tosyl-1H-indol-3-yl)methyl)-4-phenylbutanoate (24p): The title compound was prepared according to General Procedure C using **18p** affording **24p** (0.074 g, 0.13 mmol, 65% yield, 10:1 dr) as a white solid. Analytical data for **24p: mp** 74.8-75.2 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.73-7.68 (m, 3H), 7.35-7.25 (m, 7H), 7.18 (d, *J* = 7.8 Hz, 2H), 5.42-5.41 (m, 1H), 4.71 (d, *J* = 10.8 Hz, 1H), 3.83 (s, 1H), 3.77 (s, 3H), 3.56 (d, *J* = 14.4 Hz, 1H), 3.02-2.97 (m, 1H) 2.33 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.8, 145.1, 138.0, 135.0, 134.9, 129.9, 128.4, 126.9, 126.8, 126.7, 125.1, 124.3, 123.3, 121.4, 121.1, 113.5, 83.0, 74.7, 69.7, 59.4, 53.4, 38.3, 21.5; **IR** (thin film): 3059, 2989, 2306, 1738, 1429, 1267, 896 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.21; **LRMS** (ESI): Calcd. for $C_{27}H_{26}BrNO_6S$:

([M+Na]): 594.06, Found: 594.06; **24p** could not be directly analyzed via SFC, see compound **25** for enantiomeric analysis; $[\alpha]_D$ = -24.8 (*c* = 0.007, DCM)

3.4.9 Synthesis of the Mosher ester of 24p



24p **26**

A flame dried scintillation vial was loaded with cross-benzoin diol **24p** (0.035 mmol, 1.0 equiv)**,** (R)- α-methoxy- α-trifluoromethylphenylacetic acid (0.042 mmol, 1.2 equiv) and DCM (2.0 mL, 0.02 M). To this was added *N,N*-dicyclohexylcarboimide (0.07 mmol, 2.0 equiv) and 4-dimethylaminopyridine (0.035 mmol, 1.0 equiv) This reaction mixture was stirred at rt for 18 h then filtered through celite. The filtrate was then diluted with 1M HCl (10 mL) and EtOAc (10 mL). The layers were separated and the organic layer was further washed with 1 M NaOH (2 x 10 mL) and brine (1 x 10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The reaction mixture was purified by column chromatography using an eluent of 10% EtOAc/hexanes providing **26** as a clear oil (22 mg, 0.031 mmol, 89% yield, 98:2 er).

Analytical data for **(2*S*,3*R*)-methyl 3-benzyl-2-((*R*)-(1-tosyl-1*H*-indol-3-yl)((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)methyl)oxirane-2-carboxylate (26):** **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.57 (s, 1H), 7.40-7.39 (d, *J* = 7.8 Hz, 1H), 7.28-7.21 (m, 4H), 7.09-7.00 (m, 9H), 6.96 (s, 1H), 3.82 (s, 3H), 3.42 (s, 3H), 2.90-2.86 (m, 1H),

2.76-2.72 (m, 2H) 2.25 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 167.8, 165.3, 145.2, 135.6, 134.7, 134.5, 131.3, 129.8, 129.5, 128.8, 128.7, 128.4, 128.0, 127.5, 127.1, 126.9, 126.7, 125.0, 123.6, 121.0, 114.2, 113.4, 71.0, 63.2, 60.3, 55.5, 52.9, 33.9, 29.7 21.5 (two coincident peaks); **^{19}F NMR** (376 MHz, $CDCl_3$): δ_{major} 71.85 δ_{minor} 71.6, 98:2 er; **IR** (thin film): 3059, 2989, 2306, 1738, 1429, 1267, 896 cm^{-1}; **TLC** (15% EtOAc/hexane): R_f = 0.21

3.5 Experimental Data and Conditions for the Enantioconvergent Synthesis of Funcionalized y-Butyrolactones via (3+2)-Annulation[‡‡]

3.5.1 General Information

Methods: Infrared (IR) spectra were obtained using an ASI ReactIR 1000 Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 151 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{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, dt = doublet of triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Supercritical fluid chromatography (SFC) was performed on a Berger SFC system equipped with Chiracel AD, AS, OD, and WO columns as well as Regis Industries RegisPack (RP) column (φ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO_2 at the indicated percentage of methanol (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 polarimiter. Mass spectra were obtained using a Finnigan linear trap quadrapole Fourier transform (LTQ-FT) spectrometer. Samples were prepared via dilution with MeOH and doping with 0.1 M ammonium formate (MeOH). Analytical thin layer chromatography (TLC) was performed on Sorbtec 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or either aqueous potassium

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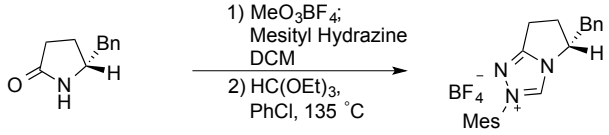
permanganate $KMnO_4$ or aqueous ceric ammonium molybdate (CAM) solution followed by heating. Product purification was accomplished using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Unless otherwise noted all reactions were carried out in flame-dried glassware with magnetic stirring. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the reported tables, which represent an average of at least two trials. In order to overlay the SFC traces for the chiral and racemic samples two separate integrations of the peaks must be taken. This results in slight discrepancies between the integration values shown in the report and seen on the trace itself.

Materials**:** NHC catalysts **20**,[61] **44,**[37] **47,**[96] β-halo α-keto ester **17a**,[35] **41m**,[97] **41p-s**[35] and α,β-unsaturated aldehydes[98,99] were all prepared according to literature procedures. Potassium carbonate was purchased from Sigma Aldrich and dried under vacuum (5 torr) for 3 h at 110 °C. HPLC grade chloroform ($CHCl_3$), ethyl acetate (EtOAc), acetonitrile (ACN), and ethanol (EtOH) were used directly from the bottle. Dichloromethane (DCM), diethyl ether (Et_2O), toluene ($PhCH_3$) and tetrahydrofuran (THF) were passed through a column of neutral alumina under nitrogen prior to use. Methyl *tert*-butyl ether (MTBE) was distilled prior to use and stored over 4 Å molecular sieves. Cinnamaldehyde was purchased from Sigma Aldrich and distilled before use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted. All racemic products were obtained via General Procedure B, using an achiral *N*-mesityl triazolium catalyst.[100]

3.5.2 Preparation of Catalyst 45

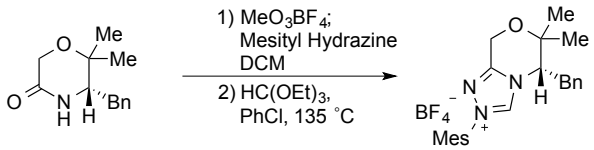


45

The following protocol is an adaptation of a literature procedure.[48] Under N_2, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (7.0 mmol, 1.0 equiv) and capped with a septum. To this flask, DCM (35 mL, 0.2 M) was added under an atmosphere of N_2. The septum was removed and (*R*)-5-benzylpyrrolidin-2-one (7.0 mmol, 1.0 equiv) [101] was added in a single portion. The flask was capped, put under N_2, and stirred vigorously for 6 h or until homogenous. Mesityl hydrazine (7.0 mmol, 1.0 equiv)[100] was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated *in vacuo* and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (35 mL, 0.2 M) and triethyl orthoformate (35.0 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated open to the atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (35.0 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 50 mL of toluene, and concentrated *in vacuo*. The crude residue was stirred in EtOAc (50 mL) for 2 h then filtered, providing **45** (0.74 g, 1.77 mmol, 25% yield) as a tan solid.

(*R*)-5-benzyl-2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium (45): Analytical data for **45:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.27 (m, 3H), 7.23-7.18 (m, 2H), 6.95 (s, 2H), 5.43-5.39 (m, 1H), 3.35-3.28 (m, 2H), 3.12-3.00 (m, 2H), 2.88-2.83 (m, 1H), 2.67-2.62 (m, 1H), 2.33 (s, 3H), 2.03 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 162.3, 141.9, 140.4, 135.0, 134.6, 129.6, 129.5, 129.0, 127.7, 61.7, 39.6, 32.0, 21.4, 21.1, 17.2; **IR** (thin film): 1056, 1035, 649, 633 cm^{-1}; **TLC** (2.5% MeOH/DCM): R_f = 0.13; **HRMS** (ESI): Calcd. for $C_{21}H_{24}BF_4N_3$: ([M+H-BF_4]): 318.1965, Found: 318.1966.

3.5.3 Preparation of Catalyst 21



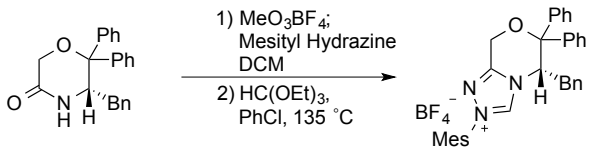
21

The following protocol is an adaptation of a literature procedure.[48] Under N_2, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (5.3 mmol, 1.0 equiv) and capped with a septum. To the flask, DCM (26 mL, 0.2 M) was added under an atmosphere of N_2. The septum was removed and (*S*)-5-isopropyl-6,6-dimethylmorpholin-3-one (5.3 mmol, 1.0 equiv)[102] was added in a single portion. The flask was capped, put under N_2, and stirred vigorously for 6 h or until homogenous. Mesityl hydrazine (5.3 mmol, 1.0 equiv)[100] was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated *in vacuo* and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (26 mL, 0.2 M) and

triethyl orthoformate (26.5 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated open to the atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (26.5 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 50 mL of toluene, and concentrated *in vacuo*. The crude residue was then purified by column chromatography using 2.5% MeOH/DCM. The resulting oil was stirred in hexanes until precipitation occurred, then filtered, providing **21** (1.50 g, 3.73 mmol, 71% yield) as a tan solid.

(*S*)-5-benzyl-2-mesityl-6,6-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium (D): Analytical data for **21:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.22 (m, 3H), 6.90 (s, 2H), 5.28 (dd, *J* = 11.8, 4.5 Hz, 1H), 5.22 (d, *J* = 17.4 Hz, 1H), 5.06 (d, *J* = 17.5 Hz, 1H), 3.51 (dd, *J* = 13.9, 4.5 Hz, 1H), 2.95 (dd, *J* = 14.0, 11.8 Hz, 1H), 2.29 (s, 3H), 1.81 (s, 9H), 1.59 (s, 3H), 1.47 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 148.7, 143.7, 142.2, 134.5, 129.7, 129.7, 129.5, 128.2, 74.0, 63.2, 56.8, 36.8, 25.0, 22.1, 21.1, 17.0; **IR** (thin film): 1085, 1063, 561 cm^{-1}; **TLC** (50% EtOAc/hexane): R_f = 0.03; **HRMS** (ESI): Calcd. for $C_{23}H_{228}BF_4N_3O$: ([M+H-BF_4]): 363.2305, Found: 363.2304.

3.5.4 Preparation of Catalyst 46



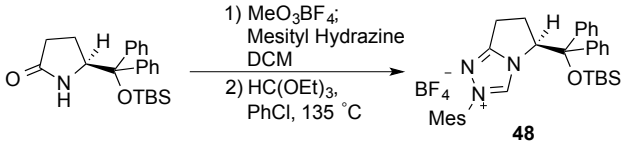
46

The following protocol is an adaptation of a literature procedure.[48] Under N_2, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (2.0 mmol, 1.0 equiv) and capped with a septum. To the flask, DCM (10 mL, 0.2 M) was added under an atmosphere of N_2. The septum was removed and (*S*)-5-isopropyl-6,6-diphenylmorpholin-3-one (2.0 mmol, 1.0 equiv)[102] was added in a single portion. The flask was capped, put under N_2, and stirred vigorously for 6 h or until homogenous. Mesityl hydrazine (2.0 mmol, 1.0 equiv)[100] was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated *in vacuo* and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (10 mL, 0.2 M) and triethyl orthoformate (10.0 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated open to the atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (10.0 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 20 mL of toluene, and concentrated *in vacuo*. The crude residue was then purified by column chromatography using 2.5% MeOH/DCM. The resulting solid was stirred in 40% EtOAc/hexanes at 70 ˚C for 1 h, then filtered, providing **46** (0.30 g, 0.57 mmol, 29% yield) as a white solid.

(*S*)-5-benzyl-2-mesityl-6,6-diphenyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium (46): Analytical data for **46**: **mp** 162.8-163.4 ˚C **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.59 (m, 4H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.37 (t, *J*

= 7.7 Hz, 2H), 7.32 – 7.30 (m, 3H), 7.27 – 7.22 (m, 4H), 6.89 (s, 2H), 6.47 (dd, *J* = 10.5, 5.3 Hz, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 4.88 (d, *J* = 17.2 Hz, 1H), 3.00 – 2.92 (m, 2H), 2.29 (s, 3H), 1.72 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 148.9, 143.4, 142.3, 140.1, 136.9, 134.3, 130.5, 129.8, 129.7, 129.6, 129.0, 128.9, 128.1, 128.1, 127.1, 81.8, 60.5, 57.7, 37.3, 21.1, 16.7; **IR** (thin film): 1739, 1365, 1228, 1217, 1204, 1085, 1064 cm^{-1}; **TLC** (50% EtOAc/hexane): R_f = 0.14; **HRMS** (ESI): Calcd. for $C_{33}H_{32}BF_4N_3O$: ([M+H-BF_4]): 487.2618, Found: 487.2611.

3.5.5 Preparation of Catalyst 48

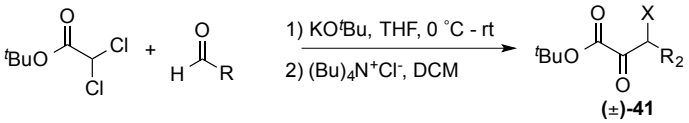


Under N_2, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (8.3 mmol, 1.0 equiv) and capped with a septum. To the flask, DCM (40 mL, 0.2 M) was added under an atmosphere of N_2. The septum was removed and (*S*)-5-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidin-2-one (8.3 mmol, 1.0 equiv)[103] was added in a single portion. The flask was capped, put under N_2, and stirred vigorously for 6 h or until homogenous. Mesityl hydrazine (8.3 mmol, 1.0 equiv)[100] was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated *in vacuo* and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (40 mL, 0.2 M) and triethyl orthoformate (41.5 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated open to the

atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (41.5 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 50 mL of toluene, and concentrated *in vacuo*. The crude residue was then purified by column chromatography using 40% EtOAc/hexanes, providing **48** (3.98 g, 6.52 mmol, 79% yield) as an off-white solid.

(*S*)-5-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)-2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium (48): Analytical data for **48: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53-7.36 (m, 9H), 6.99 (s, 2H), 6.29 (d, *J* = 9.1 Hz, 1H), 3.38 (q, *J* = 10.6, 9.6 Hz, 1H), 2.87 (dd, *J* = 17.4, 10.3 Hz, 1H), 2.34 (s, 3H), 2.07 (s, 6H), 1.85 (s, 1H), 1.67 (s, 1H), 0.92 (s, 9H), -0.31 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 163.8, 142.1, 140.3, 140.0, 131.5, 129.7, 129.0, 128.5, 82.3, 29.7, 26.1, 21.1, 21.1, 18.7, 17.26, 3.3, -3.5 (multiple coincident/broad resonances in the aryl region due to restricted rotation); **IR** (thin film): 2365, 2339, 1061, 1026, 838, 780 cm^{-1}; **TLC** (40% EtOAc/hexane): R_f = 0.14; **LRMS** (ESI): Calcd. for $C_{33}H_{42}BF_4N_3OSi$: ([M+H-BF_4]): 525.32, Found: 525.27.

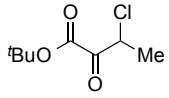
3.5.6 General Procedure A: Preparation of α-Keto Esters



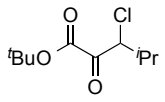
(±)-41

The following protocol was adopted from a literature procedure.[61,50] A 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with aldehyde (10.0 mmol, 1.0 equiv), *tert*-butyl dichloroacetate[97] (13.0 mmol, 1.3 equiv), and THF (20 mL, 0.5 M). This solution was cooled to 0 °C and potassium

tert-butoxide (13.0 mmol, 1.3 equiv) was added in one portion. The mixture was warmed slowly to room temperature and stirred for 18 h, followed by dilution with Et_2O (60 mL) and H_2O (60 mL). The layers were separated and the organic layer was further washed with H_2O (1 x 60 mL) and brine (1 x 60 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then filtered through a short plug of SiO_2 with 15% EtOAc/hexanes, concentrated *in vacuo,* then dissolved in THF. To the resulting solution, tetrabutylammonium chloride (1.0 mmol, 0.10 equiv) was added in one portion. The reaction was stirred for 12 h at the indicated temperature followed by dilution with H_2O (60 mL). The layers were separated and the aqueous layer was further extracted with DCM (2 x 60 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using a gradient of 5-10% EtOAc/hexanes.

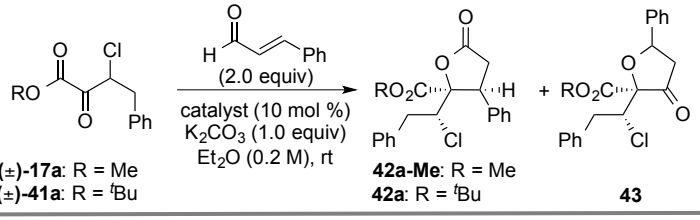


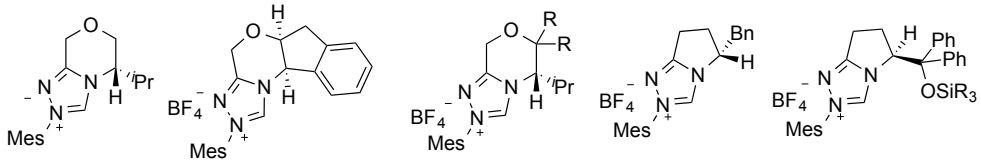
***tert*-butyl 4-chloro-2,3-dioxopentanoate (41n):** The title compound was prepared according to General Procedure A (stirred at rt after addition of tetrabutylammonium chloride) using acetaldehyde (0.56 mL, 10.0 mmol), affording **41n** (0.95 g, 4.32 mmol, 43% yield) as a yellow oil. Analytical data for **41n:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.99 (q, *J* = 6.8 Hz, 1H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.56 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 188.3, 160.2, 85.2, 54.1, 27.8, 18.7; **IR** (thin film): 2359, 2335, 1159, 668 cm^{-1}; **TLC** (5% EtOAc/hexane): R_f = 0.24; **HRMS** (ESI): Calcd. for $C_8H_{13}ClO_3$: ([M+Na+MeOH]): 247.0713, Found: 247.0710.



***tert*-butyl 4-chloro-5-methyl-2,3-dioxohexanoate (41o):** The title compound was prepared according to General Procedure A (stirred at 60 ˚C after addition of tetrabutylammonium chloride) using isobutyraldehyde (0.91 mL, 10.0 mmol), affording **41o** (0.98 g, 3.95 mmol, 40% yield) as a yellow oil. Analytical data for **1o:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.71 (d, *J* = 6.2 Hz, 1H), 2.42 (m, 1H), 1.56 (s, 9H), 1.05 (m, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 188.7, 160.5, 85.1, 30.7, 27.8, 27.6, 19.9, 17.9; **IR** (thin film): 1724, 1372 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.11; **LRMS** (ESI): Calcd. for $C_{10}H_{17}ClO_3$: ([M+NH_4]): 238.12, Found: 238.27.

3.5.7 Optimization Data for the Asymmetric Homoenolate Addition of 41a With (*E*)-PhCH=CHCHO





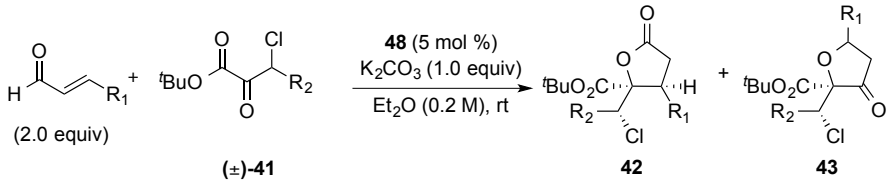
General procedure B for Optimization of the Asymmetric Homoenolate Addition of Cinnamaldehyde to 41: To a flame dried 1-dram vial was added catalyst, (0.01 mmol, 0.10 equiv) β-halo α-keto ester **1** (0.1 mmol, 1.0 equiv), solvent (0.5 mL, 0.2 M) and cinnamaldehyde (0.2 mmol, 2.0 equiv). This solution was stirred for 5 min followed by the addition of potassium carbonate (0.1 mmol, 1.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of silica gel with Et_2O, and concentrated *in vacuo.* When necessary the product was purified by column chromatography using a gradient of 5-10% EtOAc/hexanes.

Ester, catalyst, base, and solvent optimization table:

Entry	R =	X =	Cat	Solvent	Base	Conv. (%)	42a:43a	dr[a]	er[a]
1	Me	Cl	**21**	DCM	K_2CO_3	100	6:1	5:1	75:25
2	Me	Cl	**44**	DCM	K_2CO_3	100	5:1	3:1	76:24
3	Me	Cl	**21**	$PhCH_3$	K_2CO_3	55	5.5:1	2:1	--
4	Me	Cl	**21**	Et_2O	K_2CO_3	100	5:1	3:1	90:10
5	Me	Cl	**21**	THF	EtN^iPr_2	57	5:1	2:1	80:20
6	Me	Cl	**21**	THF	DMAP[a]	76	10:1	3:1	80:20
7	Me	Cl	**21**	THF	NEt_3	0	--	--	--
8	Me	Cl	**21**	THF	TMG	100	5.5:1	1:1	--
9	Me	Cl	**21**	Et_2O	K_2CO_3	100	>20:1	6:1	84:16
10	^{t}Bu	Br	**21**	Et_2O	K_2CO_3	100	>20:1	2:1	--
11	^{t}Bu	Cl	**44**	Et_2O	K_2CO_3	100	2:1	6:1	--
12	^{t}Bu	Cl	**45**	Et_2O	K_2CO_3	100	>20:1	3:1	78:22
13	^{t}Bu	Cl	**20**	Et_2O	K_2CO_3	88	>20:1	3:1	73:27
14	^{t}Bu	Cl	**46**	Et_2O	K_2CO_3	64	3.5:1	2:1	85:15
15	^{t}Bu	Cl	**47**	Et_2O	K_2CO_3	100	>20:1	9:1	93:7
16	^{t}Bu	Br	**48**	Et_2O	K_2CO_3	40	>20:1	>20:1	--
17	^{t}Bu	Cl	**48**	Et_2O	K_2CO_3	100	>20:1	33:1	99:1

a) Only reported for product **42a**.

3.5.8 General procedure B: Asymmetric (3+2)-Annulation



Method 1:

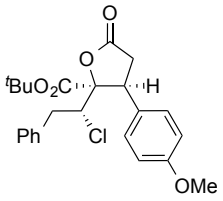
To a flame-dried 1-dram vial was added catalyst **48**, (0.01 mmol, 0.05 equiv) β-halo α-keto ester **1** (0.2 mmol, 1.0 equiv), Et_2O (1 mL, 0.2 M) and α,β-unsaturated aldehyde (0.4 mmol, 2.0 equiv). This solution was stirred for 5 min followed by the addition of potassium carbonate (0.2 mmol, 1.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of silica gel with Et_2O, and concentrated *in vacuo.* The crude product was purified by column chromatography using EtOAc/hexanes. In certain instances minor impurities remained after purification, in these cases a ^1H NMR yield utilizing mesitylene (0.20 mmol) as an internal standard is provided.
Method 2: For instances where product **42** and unreacted α,β-unsaturated aldehyde are inseparable by chromatography.

To a flame-dried 1-dram vial was added catalyst **48**, (0.01 mmol, 0.05 equiv) β-halo α-keto ester **1** (0.2 mmol, 1.0 equiv), Et_2O (1 mL, 0.2 M) and α,β-unsaturated aldehyde (0.4 mmol, 2.0 equiv). This solution was stirred for 5 min followed by the addition of potassium carbonate (0.2 mmol, 1.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) for 14 h,

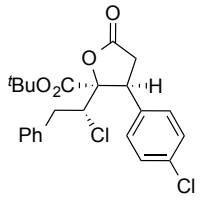
filtered through a short plug of silica gel with Et_2O, and concentrated *in vacuo.* The crude product was dissolved in MeOH (1 mL) then cooled to -78 ˚C. $NaBH_4$ (5.0 equiv) was added and the reaction was stirred at -78 ˚C for 10 min, then quenched with saturated NH_4Cl and diluted with Et_2O (15 mL) and H_2O (10 mL). The layers were separated and the organic layer was further washed with brine (1 x 10 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using EtOAc/hexanes.

(2*R*,3*S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (42a): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **41a** (0.054 g, 0.20 mmol), and (*E*)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording **42a** (0.070 g, 0.18 mmol, 87% yield, 33:1 dr) as a white solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.60 (minor diastereomer) and δ 4.34 (major diastereomer). Analytical data for **42a: mp** 133.2-133.4 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38-7.32 (m, 5H), 7.22-7.18 (m, 3H), 6.92 (dd, 2H), 4.29 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.88 (dd, *J* = 11.4, 2.0 Hz, 1H), 3.17 (dd, *J* = 14.5, 2.0 Hz, 1H), 3.09 (dd, *J* = 17.9, 8.8 Hz, 1H), 2.82 (dd, *J* = 18.0, 3.0 Hz, 1H), 2.75 (dd, *J* = 14.5, 11.5 Hz, 1H), 1.61 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.8, 167.5, 136.9, 136.4, 129.2, 128.9, 128.6, 128.4, 128.2, 126.8, 90.3, 84.6, 62.0, 46.7, 38.9, 36.1, 27.9; **IR** (thin film): 2360, 2339, 1794, 1515, 1366, 1228, 1216 cm^{-1}; **TLC** (10%

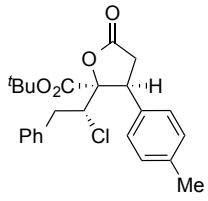
EtOAc/hexane): R_f = 0.24; **HRMS** (ESI): Calcd. for $C_{23}H_{25}ClO_4$: ([M+NH_4]): 418.1785, Found: 418.1784; **SFC** OD, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 6.3 min $t_{R\ (minor)}$ = 10.2 min, 99:1 er; **[α]$_D$** = +18.6 (*c* = 0.01, DCM).



(2*R*,3*S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-3-(4-methoxyphenyl)-5-oxotetrahydrofuran-2-carboxylate (42b): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester **41a** (0.054 g, 0.20 mmol), and (*E*)-3-(4-methoxyphenyl)acrylaldehyde (0.066 g, 0.40 mmol) affording **42b** (0.052 g, 0.12 mmol, 60% yield, 49:1 dr) as a colorless oil. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.59 (minor diastereomer) and δ 4.35 (major diastereomer). Analytical data for **42b: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24-7.17 (m, 4H), 6.97-6.96 (m, 2H), 6.89-6.86 (m, 2H), 4.24 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.84 (dd, *J* = 11.3, 2.1 Hz, 1H), 3.79 (s, 3H), 3.20 (dd, *J* = 14.5, 2.0 Hz, 1H), 3.07 (dd, *J* = 17.9, 8.9 Hz, 1H), 2.80-2.71 (m, 2H). 1.60 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.9, 167.6, 159.5, 137.1, 129.8, 129.3, 128.3, 126.8, 114.2, 90.5, 84.5, 62.1, 55.3, 46.1, 39.1, 36.4, 28.0 (two coincident resonances); **IR** (thin film): 1794, 1735, 1515, 1369, 1229, 1216 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.11; **HRMS** (ESI): Calcd. for $C_{24}H_{27}ClO_5$: ([M+NH_4]):448.1891, Found: 448.1890; **SFC** OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 7.6 min $t_{R\ (minor)}$ = 12.0 min, 99:1 er; **[α]$_D$** = +3.9 (*c* = 0.01, DCM).



2*R*,3*S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-3-(4-chlorophenyl)-5-oxotetrahydrofuran-2-carboxylate (42c): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester **41a** (0.054 g, 0.20 mmol), and (*E*)-3-(4-chlorophenyl)acrylaldehyde (0.066 g, 0.40 mmol) affording **42c** (0.060 g, 0.14 mmol, 69% yield, 34:1 dr) as a colorless oil. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.55 (minor diastereomer) and δ 4.38 (major diastereomer). Analytical data for **42c: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.27-7.20 (m, 5H), 7.00 (d, *J* = 7.0 Hz, 2H), 4.28 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.76 (dd, *J* = 11.4, 2.0 Hz, 1H), 3.29 (dd, *J* = 14.6, 2.0 Hz, 1H), 3.09 (dd, *J* = 20.8, 11.4 Hz, 1H), 2.79-2.71 (m, 2H), 1.61 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.4, 167.1, 136.8, 135.2, 134.4, 130.0, 129.2, 129.1, 128.4, 127.0, 90.1, 84.8, 61.7, 46.3, 39.3, 36.5, 28.0; **IR** (thin film): 1795, 1735, 1515, 1368, 1228, 1217 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.26; **HRMS** (ESI): Calcd. for $C_{23}H_{24}Cl_2O_4$: ([M+NH_4]): 452.1396, Found: 452.1395; **SFC** OD, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 4.8 min $t_{R\ (minor)}$ = 7.1 min, 97.5:2.5 er; **[α]$_D$** = +2.4 (*c* = 0.008, DCM).

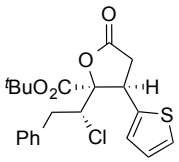


(2*R*,3*S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-5-oxo-3-(p-tolyl)tetrahydrofuran-2-carboxylate (42d): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **41a** (0.054 g, 0.20 mmol), and (*E*)-3-(p-tolyl)acrylaldehyde (0.58 g, 0.40 mmol) affording **42d** (0.062 g, 0.15 mmol, 73%

yield, 43:1 dr) as a colorless oil. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.61 (minor diastereomer) and δ 4.31 (major diastereomer). Analytical data for **42d: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23-7.16 (m, 7H), 6.96-6.94 (m, 2H), 4.25 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.88 (dd, *J* = 11.4, 2.0 Hz, 1H), 3.19 (dd, *J* = 14.5, 2.1 Hz, 1H), 3.08 (dd, *J* = 17.9, 8.9 Hz, 1H), 2.81-2.74 (m, 2H), 2.34 (s, 3H), 1.61 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.9, 167.6, 138.2, 137.1, 133.4, 129.6, 129.3, 128.5, 128.2, 126.8, 90.4, 84.5, 62.0, 46.5, 39.0, 36.2, 27.93, 21.0; **IR** (thin film): 1795, 1735, 1369, 1228, 1216 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.27; **HRMS** (ESI): Calcd. for $C_{24}H_{27}ClO_4$: ([M+NH_4]): 432.1942, Found: 432.1941; **SFC** OD, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 6.0 min $t_{R\ (minor)}$ = 9.7 min, 97.5:2.5 er; **[α]$_D$** = +9.4 (*c* = 0.02, DCM).

(2*R*,3*S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-5-oxo-3-(m-tolyl)tetrahydrofuran-2-carboxylate (42e): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **41a** (0.054 g, 0.20 mmol), and (*E*)-3-(m-tolyl)acrylaldehyde (0.58 g, 0.40 mmol) affording **42e** (0.062 g, 0.15 mmol, 73% yield, 32:1 dr) as a white solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.60 (minor diastereomer) and δ 4.30 (major diastereomer). Analytical data for **42e: mp** 116.0-116.6 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28-7.12 (m, 7H), 6.93-6.92 (m, 2H), 4.25 (dd, *J* = 8.9,

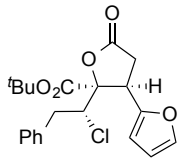
3.1 Hz, 1H), 3.93 (dd, *J* = 11.4, 2.0 Hz, 1H), 3.15 (dd, *J* = 14.5, 2.0 Hz, 1H), 3.08 (dd, *J* = 18.0, 8.9 Hz, 1H), 2.82 (dd, *J* = 18.0, 3.1 Hz, 1H), 2.76 (dd, *J* = 14.5, 11.4 Hz, 1H), 2.35 (s, 3H), 1.62 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.8, 167.6, 138.7, 137.1, 136.4, 129.4, 129.2, 129.2, 128.8, 128.2, 126.8, 125.5, 90.4, 84.5, 62.1, 46.8, 38.9, 36.0, 27.9, 21.4; **IR** (thin film): 1795, 1734, 1369, 1158, 839, 750, 699 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.24; **HRMS** (ESI): Calcd. for $C_{24}H_{27}ClO_4$: ([M+NH_4]): 432.1942, Found: 432.1940; **SFC** OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 4.1 min $t_{R\ (minor)}$ = 6.7 min, 98.5:1.5 er; **$[\alpha]_D$** = +16.7 (*c* = 0.03, DCM).



(2*R*,3*S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-5-oxo-3-(thiophen-2-yl)tetrahydrofuran-2-carboxylate (42i): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **41a** (0.054 g, 0.20 mmol), and (*E*)-3-(thiophen-2-yl)acrylaldehyde (0.055 g, 0.40 mmol) affording **42i** (0.069 g, 0.17 mmol, 85% yield, 50:1 dr) as a white solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.38 (minor diastereomer) and δ 4.27 (major diastereomer). Analytical data for **42i: mp** 161.8-162.1 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 5.1 Hz, 1H), 7.25-7.20 (m, 3H), 7.13 (d, *J* = 3.5 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.91 (d, *J* = 6.5 Hz, 2H), 4.54 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.20 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.20-3.13 (m, 1H), 3.15-3.09 (m, 1H), 2.98 (dd, *J* = 17.9, 6.0 Hz, 1H), 2.72 (m, 1H), 1.61 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.2, 167.2, 137.9, 136.8, 129.2, 128.3, 127.4, 127.3, 126.9,

125.9, 89.8, 84.9, 62.7, 42.4, 38.6, 36.6, 27.9; **IR** (thin film): 1796, 1751, 1369, 1158, 755, 700 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.18; **HRMS** (ESI): Calcd. for $C_{21}H_{23}ClO_4S$: ([M+NH_4]): 424.1350, Found: 424.1348; **SFC** OD, 10% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 3.7 min $t_{R\ (minor)}$ = 8.5 min, 99.5:0.5 er; **[α]$_D$** = +24.0 (*c* = 0.03, DCM).

(2*R*,3*S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-3-(furan-2-yl)-5-oxotetrahydrofuran-2-carboxylate (42j): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester **41a** (0.045 g, 0.20 mmol), and (*E*)-3-(furan-2-yl)acrylaldehyde (0.49 g, 0.40 mmol) affording **42j** (0.070 g, 0.18 mmol, 89% yield, 6:1 dr) as a white solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.26 (minor diastereomer) and δ 4.06 (major diastereomer). Analytical data for **42j: mp** 143.2-144.0 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 1.8 Hz, 1H), 7.27-7.20 (m, 3H), 7.03 (dd, *J* = 6.8, 1.7 Hz, 2H), 6.42-6.40 (m, 2H), 4.33 (dd, *J* = 8.3, 6.2 Hz, 1H), 4.00 (dd, *J* = 11.5, 2.1 Hz, 1H), 3.08 (dd, *J* = 14.4, 2.1 Hz, 1H), 2.99 (m, 2H), 2.74 (m, 1H), 1.58 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.4, 167.0, 149.1, 142.8, 136.9, 129.2, 128.3, 126.9, 111.0, 110.2, 89.8, 84.6, 62.8, 40.9, 38.4, 33.4, 27.9; **IR** (thin film): 1797, 1735, 1370, 1155, 1133 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.12; **HRMS** (ESI): Calcd. for $C_{21}H_{23}ClO_5$: ([M+NH_4]): 408.1578, Found: 408.1576; **SFC** OD, 3.9% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 4.3 min $t_{R\ (minor)}$ = 9.7 min, 96:4 er; **[α]$_D$** = +25.9 (*c* = 0.02, DCM).

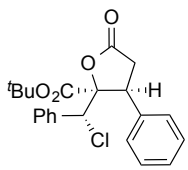


(*2R,3S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-5-oxo-3-((E)-styryl)tetrahydrofuran-2-carboxylate (42k): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **41a** (0.054 g, 0.20 mmol), and (2*E*,4*E*)-5-phenylpenta-2,4-dienal (0.063 g, 0.40 mmol) affording **42k** (0.067 g, 0.15 mmol, 74% yield, 40:1.5:1 dr) as a white solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.75 (minor diastereomer), δ 4.62 (minor diastereomer), and δ 4.41 (major diastereomer). Analytical data for **42k: mp** 133.2-133.4 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40-7.34 (m, 4H), 7.31-7.22 (m, 4H), 7.16-7.15 (m, 2H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.33 (dd, *J* = 15.9, 7.9 Hz, 1H), 4.32 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.82 (q, *J* = 7.8 Hz, 1H), 3.31 (dd, *J* = 14.3, 2.0 Hz, 1H), 2.95-2.86 (m, 2H), 2.74 (dd, *J* = 17.9, 6.5 Hz, 1H), 1.58 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.7, 167.3, 136.6, 135.7, 135.1, 129.3, 128.8, 128.5, 128.4, 127.1, 126.4, 122.9, 89.7, 84.4, 63.2, 44.7, 39.0, 34.5, 27.9; **IR** (thin film): 1796, 1735, 1370, 1197, 1157, 1133, 749, 700 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.14; **HRMS** (ESI): Calcd. for $C_{25}H_{27}ClO_4$: ([M+NH_4]): 444.1942, Found: 444.1946; **SFC** Regis RP, 2.5% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 13.4 min $t_{R\ (minor)}$ = 16.3 min, 97:3 er; **[α]$_D$** = -48.6 (*c* = 0.03, DCM).

(*2R,3S*)-*tert*-butyl 2-((*R*)-1-chloro-2-phenylethyl)-5-oxo-3-((E)-styryl)tetrahydrofuran-2-carboxylate (42l): The title compound

was prepared according to General Procedure B (Method 1) using α-keto ester **1a** (0.045 g, 0.20 mmol), and (*E*)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording **42l** (0.052 g mix of diastereomers + aldehyde dimerization, 43% ^{1}H NMR yield, >20:1 dr) as a colorless oil. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.77 (minor diastereomer) and δ 4.55 (major diastereomer). Analytical data for **42l: ^{1}H NMR** (600 MHz, $CDCl_3$) **major diastereomer:** δ 7.36-7.23 (m, 5H), 4.50 (dd, *J* = 11.4, 2.1 Hz, 1H), 4.30-4.19 (m, 2H), 3.79-3.75 (m, 1H), 3.39 (dd, *J* = 14.2, 2.0 Hz, 1H), 2.91-2.82 (m, 3H), 1.56 (s, 9H), 1.29-1.24 (m, 3H); **minor diastereomer:** δ 7.36-7.23 (m, 5H), 4.73 (dd, *J* = 11.2, 2.3 Hz, 1H), 4.30-4.19 (m, 2H), 3.57 (dd, *J* = 14.6, 2.3 Hz, 1H), 3.20 (dd, *J* = 18.0, 10.4 Hz, 1H), 2.91-2.82 (m, 3H), 1.50 (s, 9H), 1.34 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR major diastereomer** (151 MHz, $CDCl_3$): δ 172.5, 169.9, 166.3, 136.8, 129.4, 128.5, 127.1, 87.9, 84.9, 62.2, 61.9, 46.3, 39.2, 32.9, 27.9, 14.0; **IR** (thin film): 1800, 1734, 1369, 1259, 1197, 1153, 750 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.30; **HRMS** (ESI): Calcd. for $C_{20}H_{25}ClO_6$: ([M+NH_4]): 414.1684, Found: 414.1700; **SFC** Regis OD, 2-8% MeOH gradient, linear ramp rate, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 8.9 min $t_{R\ (minor)}$ = 12.3 min, 94:6 er; **$[\alpha]_D$** = +14.4 (*c* = 0.03, DCM).

Synthesis of (*2R,3S*)-*tert*-butyl 2-((*R*)-chloro(phenyl)methyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (42m) and (2*R*)-2-(tert-butoxy)-2-((*R*)-chloro(phenyl)methyl)-5-phenyldihydrofuran-



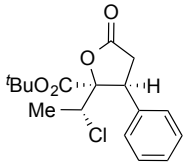
3(2H)-one (43m): The title compounds were prepared according to General Procedure B (Method 1) using α-keto ester **41m** (0.051 g, 0.20 mmol), (*E*)-cinnamaldehyde (0.04 mL, 0.40 mmol), and THF as the solvent (1.0 mL, 0.2 M) affording both the major and minor diastereomers of **42m major** (0.036 g , 0.09 mmol, 47% yield, >30:1 dr) and **42m minor** (0.020 g, 0.05 mmol, 26% yield) in a 1.5:1 ratio as white solids.

The diastereomeric ratio of **42m** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.47 (minor diastereomer), and δ 4.79 (major diastereomer).

Analytical data for **42m major: mp** 153.8-154.0 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.0 Hz, 2H), 7.47-7.39 (m, 5H), 7.27-7.26 (m, 3H), 4.74 (s,1H), 3.98 (dd, *J* = 12.4, 9.9 Hz, 1H), 3.50 (dd, *J* = 17.6, 12.4 Hz, 1H), 2.92 (dd, *J* = 17.6, 10.0 Hz, 1H), 1.14 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.2, 167.3, 137.5, 133.1, 129.5, 129.0, 128.9, 128.7, 128.6, 128.4, 89.3, 84.0, 63.2, 49.2, 34.1, 27.3; **IR** (thin film): 2364, 2341, 1796, 1753, 1369, 1125, 700 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.15; **HRMS** (ESI): Calcd. for $C_{22}H_{23}ClO_4$: ([M+NH_4]): 404.1629, Found: 404.1627; **SFC** OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 5.0 min $t_{R\ (minor)}$ = 6.9 min, 97:3 er; **$[\alpha]_D$** = +76.5 (*c* = 0.01, DCM).

Analytical data for **2m minor: mp** 109.8-110.2 ˚C **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.39-7.27 (m, 8H), 5.41 (s, 1H), 4.33 (t, *J* = 9.6 Hz, 1H), 3.13 (dd, *J* = 17.7, 9.3 Hz, 1H), 3.06 (dd, *J* = 17.7, 9.7 Hz, 1H), 0.77 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.4, 165.3, 137.0, 136.0, 129.2, 129.1, 128.9, 128.5,

128.4, 128.2, 91.2, 84.0, 64.4, 48.0, 34.0, 26.9; **IR** (thin film): 1735, 1365, 1228, 1217, 529, 519 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.22; **HRMS** (ESI): Calcd. for $C_{22}H_{23}ClO_4$: ([M+NH_4]): 404.1629, Found: 404.1627; **SFC** OD, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 6.8 min $t_{R\ (minor)}$ = 8.9 min, 95:5 er; **[α]$_D$** = -11.6 (*c* = 0.01, DCM).

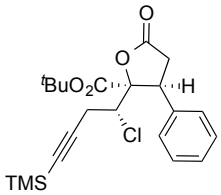


(2*R*,3*S*)-*tert*-butyl 2-((*R*)$^{-1}$-chloroethyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (42n): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester **41n** (0.038 g, 0.20 mmol), and (*E*)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording **42n** (0.032 g 4:1 mix of isomers, 52% ^{1}H NMR yield) as a colorless oil. The isomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.45 (minor product), and δ 4.25 (major product) in conjunction with the resonances at δ 1.77 (minor product), and δ 1.43 (major product). Analytical data for **42n: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 3H), 7.29-7.26 (m, 2H), 4.22 (dd, *J* = 8.7, 2.7 Hz, 1H), 3.84 (q, *J* = 6.7 Hz, 1H), 3.03 (dd, *J* = 17.9, 8.7 Hz, 1H), 2.74 (dd, *J* = 17.9, 2.7 Hz, 1H), 1.57 (s, 9H), 1.40 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.9, 167.5, 128.8, 128.7, 128.3, 128.1, 90.6, 84.4, 55.4, 46.8, 36.4, 27.9, 20.0; **IR** (thin film): 2363, 1792, 1734, 1457, 1369, 1228, 1205, 1134 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.22; **HRMS** (ESI): Calcd. for $C_{17}H_{21}ClO_4$: ([M+NH_4]): 342.1472, Found: 342.1469; **SFC** OD, 2.5% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 2.3 min $t_{R\ (minor)}$ = 2.7 min, 97:3 er; **[α]$_D$** = +19.0 (*c* = 0.008, DCM).

(2R,3S) *tert*-butyl-2-((R)-fluoro(phenyl)methyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (42p): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester **41p**[35] (0.048 g, 0.20 mmol), and (*E*)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording **42p** (0.055 g, 0.15 mmol, 74% yield, 4:1 dr) as a white solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.94 (minor diastereomer) and δ 5.43 (major diastereomer). Analytical data for **42p: mp** 98.8-99.4 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48-7.39 (m, 8H), 7.33-7.29 (m, 2H), 5.41 (d, *J* = 43.3 Hz, 1H), 3.93 (dd, *J* = 12.6, 9.4 Hz, 1H), 3.37-3.32 (m, 1H), 2.93-2.88 (m, 1H), 1.26 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.0, 166.6 (d, $J_{C\text{-}F}$ = 10.6 Hz), 133.6, 133.3 (d, $J_{C\text{-}F}$ = 10.6 Hz), 129.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 128.9 (d, $J_{C\text{-}F}$ = 6.0 Hz), 128.7, 128.6, 128.1, 92.6 (d, $J_{C\text{-}F}$ = 181.2 Hz), 88.6 (d, $J_{C\text{-}F}$ = 21.1 Hz), 84.0, 49.5, 34.2, 27.6; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -180.13; **IR** (thin film): 1797, 1756, 1130, 768, 521 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.08; **LRMS** (ESI): Calcd. for $C_{22}H_{23}FO_4$: ([M+NH_4]): 388.19, Found: 388.31; **SFC** OD, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 5.3 min $t_{R\ (minor)}$ = 6.7 min, 97:3 er; **[α]$_D$** = +42.1 (*c* = 0.02, DCM).

(2R,3S) *tert*-butyl -2-((R)-1-chlorobut-3-en-1-yl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (42q): The title compound was prepared according to General Procedure B (Method 1) using

α-keto ester **41q**[35] (0.044 g, 0.20 mmol), and (*E*)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording **42q** (0.053 g, 0.15 mmol, 76% yield, 11:1 dr) as a white solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.46 (minor diastereomer) and δ 4.28 (major diastereomer). Analytical data for **42q: mp** 120.0-120.6 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37-7.33 (m, 3H), 7.28-7.27 (m, 2H), 5.64-5.57 (m, 1H), 5.01-4.93 (m, 2H), 4.24 (d, *J* = 7.8 Hz, 1H), 3.64 (d, *J* = 11.1 Hz, 1H), 3.03 (dd, *J* = 17.8, 8.7 Hz, 1H), 2.75-2.72 (m, 1H), 2.59-2.55 (m,1H), 2.35-2.29 (m, 1H), 1.57 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.8, 167.35, 136.7, 133.4, 128.8, 128.6, 128.4, 118.2, 90.3, 84.5, 60.0, 46.9, 37.4, 36.3, 27.9; **IR** (thin film): 2979, 1731, 1246, 1152, 1126, 698 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.18; **LRMS** (ESI): Calcd. for $C_{19}H_{23}ClO_4$: ([M+NH_4]): 368.16, Found: 368.31; **SFC** OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 2.2 min $t_{R\ (minor)}$ = 2.6 min, 97.2:2.5 er; **[α]$_D$** = +35.2 (*c* = 0.03, DCM).



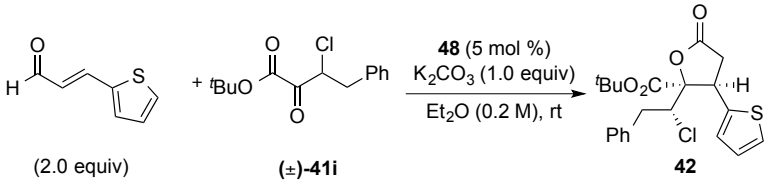
(2R,3S) *tert*-butyl -2-((R)-1-chloro-4-(trimethylsilyl)but-3-yn-1-yl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (42r): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester **41r**[35] (0.058 g, 0.20 mmol), and (*E*)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording **42r** (0.065 g, 0.15 mmol, 77% yield, 17:1 dr) as a white solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.71 (minor diastereomer) and δ 4.32 (major diastereomer). Analytical data for **42r: mp** 124.8-125.4 ˚C; **^{1}H**

NMR (600 MHz, $CDCl_3$) δ 7.40-7.36 (m, 3H), 7.27-7.26 (m, 2H), 4.28 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.72 (dd, *J* = 10.7, 2.6 Hz, 1H), 3.04 (dd, *J* = 17.9, 8.6 Hz, 1H), 2.88 (dd, *J* = 17.7, 2.6 Hz, 1H), 2.70 (dd, *J* = 17.9, 2.2 Hz, 1H), 2.62 (dd, *J* = 17.7, 10.7 Hz, 1H), 1.55 (s, 9H), 0.09 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.5, 166.7, 136.7, 129.0, 128.6, 128.4, 101.65, 89.8, 87.3, 84.8, 58.1, 46.6, 36.6, 27.9, 25.6, -0.2; **IR** (thin film): 2980, 1799, 1734, 1248, 1151, 1122, 841, 699 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.17; **LRMS** (ESI): Calcd. for $C_{22}H_{29}ClO_4Si$: ([M+NH_4]): 438.19, Found: 438.33; **SFC** OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 2.1 min $t_{R\ (minor)}$ = 2.4 min, 96.5:3.5 er; **[α]$_D$** = +27.6 (*c* = 0.02, DCM).

(2R,3S) *tert*-butyl -2-((R)-2-(benzyloxy)-1-chloroethyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (42s): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester **41s**[35] (0.065 g, 0.20 mmol), and (*E*)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording **42s** (0.030 g isomeric mix of products, 28% ^{1}H NMR yield) as a colorless oil. The exact isomer ratio was not possible to determine. For product purity a second chromatographic purification using an eluent gradient of 7.5-10% Et_2O/Hexanes was run after initial purification using EtOAc/Hexanes. Analytical data for **42s: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 4.43-4.38 (m, 2H), 4.22-4.21 (m, 1H), 3.68 (d, *J* = 10.9 Hz, 1H), 3.33-3.31 (m, 2H), 3.09-2.98 (m, 1H), 2.74-2.71 (m, 1H), 2.02-1.86 (m, 2H), 1.80-1.69 (m, 2H), 1.56 (s, 9H), 1.43-1.39 (m, 2H).; **^{13}C NMR** (151 MHz, $CDCl_3$): δ 174.9, 167.5, 138.4, 128.7, 128.7, 128.3, 128.3, 128.3, 127.5, 127.5,

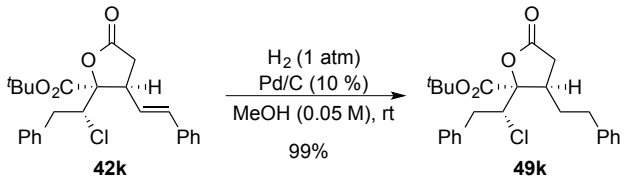
90.5, 84.3, 72.8, 69.2, 46.9, 36.3, 30.1, 27.9, 27.2, 26.9; **IR** (thin film): 2980, 1795, 1729, 1157, 1124, 697 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.12; **LRMS** (ESI): Calcd. for $C_{26}H_{31}ClO_5$: ([M+NH_4]): 476.22, Found: 476.28; **SFC** OD, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 8.1 min $t_{R\ (minor)}$ = 9.0 min, 98.5:1.5 er; $[\alpha]_D$ = +23.9 (*c* = 0.02, DCM).

3.5.9 Procedure for the Gram Scale Asymmetric (3+2)-Annulation



To a flame dried 50 mL round bottom flask was added catalyst **G,** (0.19 mmol, 0.05 equiv) β-halo α-keto ester **1i** (3.5 mmol, 1.0 equiv), Et_2O (19 mL, 0.2 M) and cinnamaldehyde (7.0 mmol, 2.0 equiv). This solution stirred for 5 min followed by the addition of potassium carbonate (3.5 mmol, 1.0 equiv). This reaction was stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of SiO_2 with 20% EtOAc/hexanes, and concentrated *in vacuo*. The resultant crude material was then stirred with 20% Et_2O/hexanes and filtered providing **2i** (1.20 g, 84% yield, >30:1 dr, >99.5:0.5 er) as a white solid which was recrystallized from a 1:1 solution of DCM/MeOH by slow solvent evaporation providing crystals suitable for X-Ray diffraction**.**

3.5.10 Procedure for the Hydrogenation of 42k



Step 2: A flame dried 20 mL scintillation vial equipped with a magnetic stir bar was charged with 10% Pd/C (3.0 mg). To the vial was added degassed ethanol (2 mL) and **42k** (0.08 mmol, 1 equiv). The reaction vessel was purged with H_2 (3 times), then put under 1 atm of H_2 (balloon). The reaction mixture was stirred for 24 h, filtered through a plug of celite, then concentrated in vacuo providing **49k** without need for further purification (0.35g, 0.08 mmol, 99% yield). Analytical data for **49k: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35-7.22 (m, 8H), 7.17 (d, *J* = 7.5 Hz, 2H), 4.32-4.30 (m, 1H), 3.30-3.28 (m, 1H), 2.90-2.80 (m, 3H), 2.77-2.72 (m, 1H), 2.60-2.55 (m, 1H), 2.50 (dd, *J* = 17.6, 6.9 Hz, 1H), 2.39-2.34 (m, 1H), 1.83-1.76 (m, 1H), 1.48 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.9, 167.3, 139.9, 136.6, 129.3, 128.7, 128.5, 128.3, 127.2, 126.6, 89.4, 84.1, 77.2, 77.0, 76.8, 62.4, 41.2, 39.4, 34.2, 33.8, 30.1, 27.8; **IR** (thin film): 1790, 1752, 1128, 573 cm^{-1}; **TLC** (10% EtOAc/hexane): R_f = 0.08; **LRMS** (ESI): Calcd. for $C_{25}H_{29}ClO_4$: ([M+NH_4]): 446.21, Found: 446.34; **$[\alpha]_D$** = -6.1 (*c* = 0.01, DCM).

3.6 REFERENCES

1) Corbett, M. T.; Johnson, J. S. “Dynamic kinetic asymmetric transformations of β-stereogenic α-ketoesters by direct aldolization. *Angew. Chem., Int. Ed.* **2014,** *53*, 255-259.

2) Cohen, D. T.; Eichman, C. C.; Phillips, E. M.; Zarefsky, E. R.; Scheidt, K. A. “Catalytic dynamic kinetic resolutions with *N*-heterocyclic carbenes: asymmetric synthesis of highly substituted β-lactones.” *Angew. Chem. Int. Ed.* **2012,** *51,* 7309-7313.

3) Johnston, R. C.; Cohen, D. T.; Eichman, C. C.; Scheidt, K. A.; Cheong, P. H-Y. “Catalytic kinetic resolution of a dynamic racemate: highly stereoselective β-lactone formation by *N*-heterocyclic carbene catalysis.” *Chem. Sci.* **2014,** *5,* 1974-1982.

4) Chan, A.; Scheidt, K.A. “Highly stereoselective formal [3 + 3] cycloaddition of enals and azomethine Imines catalyzed by *N*-heterocyclic carbenes.” *J. Am. Chem. Soc.* **2007,** *129,* 5334-5335.

5) Wang, M.; Huang, Z.; Xu, J.; Chi, Y. R. “*N*-Heterocyclic carbene-catalyzed [3+4] cycloaddition and kinetic resolution of azomethine imines.” *J. Am. Chem. Soc.* **2014,** *136,* 1214-1217.

6) Liebig, J.; Wöhler, F. “Untersuchungen über das radikal der benzoesäure.**”***Ann. Pharm.,* **1832,** *3,* 249-282.

7) Hassner, A, Rai, K. M. "The benzoin and related acyl anion equivalent reactions." In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1; pp 541-577.

8) Ide, W.S.; Buck, J.S. *Org. React*. **1948**, *4,* 269-304.

9) Bugaut, X.; Glorius, F. “Organocatalytic umpolung: *N*-heterocyclic carbenes and beyond.” *Chem. Soc. Rev.* **2012,** *41,* 3511-3522.

10) Johnson, J. S. “Catalyzed reactions of acyl anion equivalents.” *Angew. Chem., Int. Ed.* **2004,** *43,* 1326-1328.

11) DiRocco, D. A.; Rovis, T. "Asymmetric benzoin and Stetter reactions." In *Stereoselective Synthesis 2: Stereoselective Reactions of Carbonyl and Imino Groups*; Molander, G. A., Ed.; Georg Thieme Verlag: Stuttgart-New York; Vol. 2011; pp 835-862.

12) O'Bryan, E. A.; Scheidt, K. A. "Acyloin coupling reactions." In *Comprehensive Organic Synthesis II*; Knochel, P., Molander, G. S., Eds.; Elsevier, **2014**; Vol. 3; pp 621-655.

13) Enders, D.; Bruer, K.; Teles J. H. "A novel asymmetric benzoin reaction catalyzed by a chiral triazolium salt. Preliminary communication." *Helv. Chim. Acta* **1996,** *79,* 1217-1221.

14) Knight, R. L.; Leeper, F. J. "Comparison of chiral thiazolium and triazolium salts as asymmetric catalysts for the benzoin condensation." *J. Chem. Soc. Perkin Trans. 1* **1998,** *12,* 1891-1893.

15) Enders, D.; Kallfass, U. "An efficient nucleophilic carbene catalyst for the asymmetric benzoin condensation." *Angew. Chem., Int. Ed.* **2002,** *41,* 1743-1745.

16) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. "From mono-triazolium salt to bis-triazolium salt: improvement of the asymmetric intermolecular benzoin condensation." *Adv. Synth. Catal.* **2008,** *350,* 2645-2651.

17) Enders, D.; Han, J. "Synthesis of enantiopure triazolium salts from pyroglutamic acid and their evaluation in the benzoin condensation." *Tetrahedron: Asymmetry* **2008,** *19,* 1367-1371.

18) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. "Highly enantioselective benzoin condensation reactions involving a bifunctional protic pentafluorophenyl-substituted triazolium precatalyst." *J. Org. Chem.* **2009,** *74,* 9214-9217.

19) Rose, C. A.; Gundala, S.; Connon, S. J.; Zeitler, K. "Chemoselective crossed acyloin condensations: catalyst and substrate control." *Synthesis* **2011,** 190-198.

20) Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. "Switching regioselectivity in crossed acyloin condensations between aromatic aldehydes and acetaldehyde by altering *N*-heterocyclic carbene catalysts." *Org. Lett.* **2011,** *13,* 880-883.

21) Langdon, S. M.; Wilde, M. D.; Thai, K.; Gravel, M. "Chemoselective *N*-heterocyclic carbene-catalyzed cross-benzoin reactions: importance of the fused ring in triazolium salts." *J. Am. Chem. Soc.,* **2014,** *136,* 7539-7542.

22) Iding, H.; Dünnwald, T.; Greiner, L.; Liese, A.; Müller, M.; Siegert, P.; Grötzinger, J.; Demir, A. S.; Pohl, M. "Benzoylformate decarboxylase from *pseudomonas putida* as stable catalyst for the synthesis of chiral 2-hydroxy ketones." *Chem.-Eur. J.,* **2000,** *6*, 1483-1495.

23) Demir, A. S.; Pohl, M.; Janzen, E.; Müller, M. “Enantioselective synthesis of hydroxy ketones through cleavage and formation of acyloin linkage. Enzymatic kinetic resolution *via* C–C bond cleavage.” *J. Chem. Soc., Perkin Trans. 1,* **2001,** 633-635.

24) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. “Development of a donor−acceptor concept for enzymatic cross-coupling reactions of aldehydes: the first asymmetric cross-benzoin condensation.” *J. Am. Chem. Soc.* **2002,** *124,* 12084-12085.

25) Pohl, M.; Lingen, B.; Müller, M. “Thiamin-diphosphate-dependent enzymes: new aspects of asymmetric C C Bond formation.” *Chem.-Eur. J.* **2002,** *8,* 5288-5295.

26) Lehwald, P.; Richter, M.; Röhr, C.; Liu, H.; Müller, M. “Enantioselective intermolecular aldehyde–ketone cross-coupling through an enzymatic carboligation reaction.” *Angew. Chem., Int. Ed.* **2010,** *49*, 2389-2392.

27) Beigi, M.; Waltzer, S.; Fries, A.; Eggeling, L.; Sprenger, G. A.; Müller, M. “TCA cycle involved enzymes SucA and Kgd, as well as MenD: efficient biocatalysts for asymmetric C–C Bond formation.” *Org. Lett.* **2013,** *15,* 452-455.

28) Linghu, X.; Potnick, J. R.; Johnson, J. S. “Metallophosphites as umpolung catalysts: the enantioselective cross silyl benzoin reaction.” *J. Am. Chem. Soc.* **2004,** *126,* 3070-3071.

29) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. “*N*-heterocyclic carbene catalysed asymmetric cross-benzoin reactions of heteroaromatic aldehydes with trifluoromethyl ketones.” *Chem. Commun.* **2010,** *46,* 6282-6284.

30) O’Toole, S. E.; Rose, C. A.; Gundala, S.; Zeitler, K.; Connon, S. J. “Highly chemoselective direct crossed aliphatic−aromatic acyloin condensations with triazolium-derived carbene catalysts.” *J. Org Chem.* **2011,** *76,* 347-357.

31) Rose, C. A.; Gundala, S.; Fagan, C. –L.; Franz, J. F.; Connon, S. J.; Zeitler, K. “NHC-catalysed, chemoselective crossed-acyloin reactions.” *Chem. Sci.* **2012,** *3,* 735-740.

32) Thai, K.; Langdon, S. M.; Bilodeau, F.; Gravel, M. “Highly chemo- and enantioselective cross-benzoin reaction of aliphatic aldehydes and α-ketoesters.” *Org. Lett.,* **2013,** *15,* 2214-2217.

33) Müller, C. R.; Pérez-Sanchez, M.; Dominguez de Maria, P. “Benzaldehyde lyase-catalyzed diastereoselective C–C bond formation by

simultaneous carboligation and kinetic resolution." *Org. Biomol. Chem.* **2013,** *11,* 2000-2004.

34) O'Toole, S. E.; Connon, S. J. "The enantioselective benzoin condensation promoted by chiral triazoliumprecatalysts: stereochemical control *via* hydrogen bonding." *Org. Biomol. Chem.* **2009,** *7,* 3584-3593.

35) Steward, K. M.; Corbett, M. T.; Goodman, C. G.; Johnson, J. S. "Asymmetric synthesis of diverse glycolic acid scaffolds via dynamic kinetic resolution of α-keto esters." *J. Am. Chem. Soc.* **2012***, 134*, 20197-20206.

36) Kerr, M. S.; Rovis, T. "Enantioselective synthesis of quaternary stereocenters via a catalytic asymmetric stetter reaction." *J. Am. Chem. Soc.* **2004,** *126,* 8876-8877.

37) He, M.; Struble, J. R.; Bode, J. W. "Highly enantioselective azadiene Diels−Alder reactions catalyzed by chiral *N*-heterocyclic carbenes." *J. Am. Chem. Soc.* **2006,** *128,* 8418-8420.

38) *Mahatthananchai, J.; Bode, J. W. "*On the mechanism of *N*-heterocyclic carbene-catalyzed reactions involving acyl azoliums*." Acc. Chem. Res.,* **2014,** *47*, 696-707.

39) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J.; Reider, P. J. "Synthesis of α-amido ketones via organic catalysis: thiazolium-catalyzed cross-coupling of aldehydes with acylimines." *J. Am. Chem. Soc.* **2001,** *123,* 9696-9697.

40) Drutu, I.; Krygowski, E. S.; Wood, J. L. "Reactive enols in synthesis 2. synthesis of (+)-latifolic acid and (+)-latifoline." *J. Org. Chem.,* **2001,** *66,* 7025-7029.

41) Nagase, R.; Oguni, Y.; Ureshino, S.; Mura, H.; Misaki, T.; Tanabe, Y. "Asymmetric Ti-crossed Claisen condensation: application to concise asymmetric total synthesis of alternaric acid." *Chem. Commun.,* **2013,** *49,* 7001-7003.

42) CCDC 1009331 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif. The structure in Scheme 11 was generated with CYLview: Legault, C. Y. CYLview, version 1.0b; Université de Sherbrooke: Sherbrooke, QC, 2009; http://www.cylview.org.

43) Mengel, A.; Reiser, O. "Around and beyond Cram's rule." *Chem. Rev.* **1999**, *99*, 1191-1224.

44) Evans, D. A.; Siska, S. J.; Cee, V. J. “Resurrecting the Cornforth model for carbonyl addition: studies on the origin of 1,2-asymmetric induction in enolate additions to heteroatom-substituted aldehydes.” *Angew. Chem., Int. Ed.* **2003**, *42*, 1761-1765.

45) Cee, V. J.; Cramer, C. J.; Evans, D. A. “Theoretical investigation of enolborane addition to α-heteroatom-substituted aldehydes. relevance of the Cornforth and polar Felkin−Anh models for asymmetric induction.” *J. Am. Chem. Soc.* **2006**, *128*, 2920-2930.

46) Dudding, T.; Houk, K. N. “Computational predictions of stereochemistry in asymmetric thiazolium- and triazolium-catalyzed benzoin condensations.” *Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101,* 5770-5775.

47) Vora, H. U.; Lathrop, H. P.; Reynolds, N. T.; Kerr, M. S.; Read de Alaniz, J.; Rovis, T. “Preparation of chiral and achiral triazolium salts: carbene precursors with demonstrated synthetic utility.” *Org. Synth.* **2010**, *87*, 350-361.

48) Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, I. “Organocatalytic enantioselective synthesis of nitrogen-substituted dihydropyran-2-ones, a key synthetic intermediate of 1β-methylcarbapenems.” *Org. Lett.* **2009,** *11,* 3934-3937.

49) Massey, R. S.; Collett, C. J.; Lindsay, A. G.; Smith, A. D.; O’Donoghue, A. C. “Proton transfer reactions of triazol-3-ylidenes: kinetic acidities and carbon acid pK_a values for twenty triazolium salts in aqueous solution.” *J. Am. Chem. Soc.* **2012,** *134,* 20421-20432.

50) Saifina, D. F.; Ganieva, V. R.; Mamedov, V. A. “Darzens reaction in the synthesis of 3-(α-chloroalkyl)quinoxalin-2(1*H*)-ones.” *Russ. J. Org. Chem.* **2009,** *45,* 1244-1247.

51) Yang, L.; Deng, G.; Wang, D-X.; Huang, Z-T.; Zhu, J-P.; Wang, M-X. “Highly efficient and stereoselective n-vinylation of oxiranecarboxamides and unprecedented 8-*endo*-epoxy-arene cyclization: expedient and biomimetic synthesis of some *Clausena* alkaloids.” *Org. Lett.* **2007,** *9*, 1387-1390

52) Rothman, J. H. “Syntheses of heterocyclic ethenyl *c*-nucleosides for recognition of inverted base pairs within the dna triple helix by stereoselective intramolecular cyclization and olefin metathesis.” *J. Org. Chem.* **2009,** *74,* 925-928.

53) Cornwall C.; Dell, C. P.; Knight D. W. “Regioselectivity in the lithiation of methyl-substituted thiazole- and oxazole-carboxylic acids and carboxamides: general methods for the elaboration of trisubstituted thiazoles and oxazoles.” *J. Chem. Soc., Perkin Trans. 1* **1991,** *2417-2428*.

54) Nagasaki, A.; Adachi, Y.; Yonezawa, Y.; Shin, C-G. “Useful synthesis of various thiazole and polythiazolyl derivatives from thiocarboxamide and β-bromoacyl compound.” *Heterocycles,* **2003,** *60,* 321-335.
.

55) Medine, J. R.; Becker, C. J.; Blackledge, C. W.; Duquenne, C.; Feng, Y.; Grant, S. W.; Heerding, D.; Li, W. H.; Miller, W. H.; Romeril, S. P.; Scherzer, D.; Shu, A.; Bobko, M. A.; Chadderton, A. R.; Dumble, M.; Gardiner, C. M.; Gilbert, S.; Liu, Q.; Rabindran, S. K.; Sudakin, V.; Xiang, H.; Brady, P. G.; Campobasso, N.; Ward, P.; Axten, J. M. “Structure-based design of potent and selective 3-phosphoinositide-dependent kinase-1 (pdk1) inhibitors.” *J. Med. Chem.* **2011,** *54,* 1871-1895.

56) Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. “Nonenzymatic dynamic kinetic resolution of secondary alcohols via enantioselective acylation: synthetic and mechanistic studies.” *J. Am. Chem. Soc.* **2012***, 134*, 15149-15153.

57) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T. “Stereoselective hydrogenation via dynamic kinetic resolution.” *J. Am. Chem. Soc.* **1989***, 111*, 9134-9135.

58) Steward, K. M.; Gentry, E. C.; Johnson, J. S. “Dynamic kinetic resolution of α-keto esters via asymmetric transfer hydrogenation.” *J. Am. Chem. Soc.* **2012***, 134*, 7329-7332.

59) Steward, K. M.; Corbett, M. T.; Goodman, C. G.; Johnson, J. S. “Asymmetric synthesis of diverse glycolic acid scaffolds via dynamic kinetic resolution of α-keto esters.” *J. Am. Chem. Soc.* **2012***, 134*, 20197-20206.

60) Goodman, C.G.; Do, D. T.; Johnson J. S. “Asymmetric synthesis of anti-β-amino-α-hydroxy esters via dynamic kinetic resolution of β-amino-α-keto esters.**”** *Org Lett,* **2013,** *15,* 2446-2449.

61) Goodman, C. G.; Johnson, J. S. “Dynamic kinetic asymmetric cross-benzoin additions of β-stereogenic α-keto esters.” *J. Am. Chem. Soc*. **2014**, *136*, 14698-14701.

62) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. “Organocatalytic asymmetric sulfa-Michael/Michael addition reactions: a strategy for the synthesis of highly substituted chromans with a quaternary stereocenter.” *Angew. Chem., Int. Ed.* **2010,** *49,* 8379-8383.

63) Yang, W.; Yang, Y.; Du, D-M. “Squaramide–tertiary amine catalyzed asymmetric cascade sulfa-Michael/Michael addition via dynamic kinetic

resolution: access to highly functionalized chromans with three contiguous stereocenters." *Org. Lett.* **2013,** *15,* 1190-1193.

64) Meninno, S.; Croce, G.; Lattanzi, A. "Asymmetric synthesis of trisubstituted tetrahydrothiophenes bearing a quaternary stereocenter via double Michael reaction involving dynamic kinetic resolution." *Org. Lett.* **2013,** *15*, 3436-3439.

65) Reyes, E.; Córdova, A. "Amino acid-catalyzed dynamic kinetic asymmetric transformations (DYKAT): one-step de novo synthesis of polyketide sugars from racemic β-hydroxy aldehydes." *Tetrahedron Lett*. **2005,** *46,* 6605−6609.

66) Ward, D. E.; Jheengut, V.; Aokinnusi, O. T. "Enantioselective direct intermolecular aldol reactions with enantiotopic group selectivity and dynamic kinetic resolution." *Org. Lett.* **2005,** *7,* 1181−1184.

67) Ward, D. E.; Jheengut, V.; Beye, G. E.; Gillis, H. M.; Karagiannis, A.; Becerril-Jimenez, F. "Enantioselective direct aldol reactions of achiral ketones with racemic enolizable α-substituted aldehydes: scope and limitations." *Synlett* **2011,** 508−512.

68) Bergeron-Brlek, M.; Teoh, T.; Britton, R. "A tandem organocatalytic α-chlorination–aldol reaction that proceeds with dynamic kinetic resolution: a powerful tool for carbohydrate synthesis." *Org. Lett.* **2013,** *15,* 3554−3557.

69) Burstein, C.; Glorius, F. "Organocatalyzed conjugate umpolung of α,β-unsaturated aldehydes for the synthesis of γ-butyrolactones." *Angew. Chem., Int. Ed.* **2004,** *43,* 6205-6208.

70) Sohn, S. S.; Rosen, E. L.; Bode, J. W. "*N*-heterocyclic carbene-catalyzed generation of homoenolates: γ-butyrolactones by direct annulations of enals and aldehydes." *J. Am. Chem. Soc.* **2004,** *126,* 14370-14371.

71) Enders, D.; Niemeier, O.; Henseler, A. "Organocatalysis by *N*-heterocyclic carbenes." *Chem. Rev.* **2007,** *107,* 5606-5655.

72) Nair, V.; Vellalath, S.; Babu, B. P. "Recent advances in carbon–carbon bond-forming reactions involving homoenolates generated by NHC catalysis." *Chem. Soc. Rev.* **2008,** *37,* 2691-2698.

73) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. "Employing homoenolates generated by NHC catalysis in carbon–carbon bond-forming reactions: state of the art." *Chem. Soc. Rev.* **2011,** *40,* 5336-5346.

74) Vora, H. U.; Wheeler, P.; Rovis, T. “Exploiting acyl and enol azolium intermediates *via N*-hetero- cyclic carbene-catalyzed reactions of α-reducible aldehydes.” *Adv. Synth. Catal.* **2012,** *354,* 1617-1639.

75) Rommel, M.; Fukuzumi, T.; Bode, J. W. “Cyclic ketimines as superior electrophiles for nhc-catalyzed homoenolate additions with broad scope and low catalyst loadings.” *J. Am. Chem. Soc.* **2008,** *130,* 17266-17267.

76) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. “Cooperative catalysis by carbenes and Lewis acids in a highly stereoselective route to γ-lactams.” *Nature Chem.* **2010,** *2,* 766-771.

77) Zhang, B.; Feng, P.; Sun, L-H.; Cui, Y.; Ye, S.; Jiao, N. “*N*-heterocyclic carbene-catalyzed homoenolate additions with *N*-aryl ketimines as electrophiles: efficient synthesis of spirocyclic γ-lactam oxindoles.” *Chem. Eur. J.* **2012,** *18,* 9198-9203.

78) Lv, H.; Tiwari, B.; Mo, J.; Xing, C.; Chi, Y. R. “Highly enantioselective addition of enals to isatin-derived ketimines catalyzed by *N*-heterocyclic carbenes: synthesis of spirocyclic γ-lactams.” *Org. Lett,* **2012,** *14,* 5412-5415.

79) Sun, H.-L.; Shen, L.-T.; Ye, S. “Highly diastereo- and enantioselective NHC-catalyzed [3+2] annulation of enals and isatins.” *Chem. Commun.,* **2011,** *47,* 10136-10138.

80) Dugal-Tessier, J.; O’Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. “An *N*-heterocyclic carbene/Lewis acid strategy for the stereoselective synthesis of spirooxindole lactones.” *Angew. Chem., Int. Ed.* **2012,** *51,* 4963-4967.

81) Jang, K. P.; Hutson, G. E.; Johnston, R. C.; McCusker, E. O.; Cheong, P. H-Y.; Scheidt, K. A. “Asymmetric homoenolate additions to acyl phosphonates through rational design of a tailored *N*-heterocyclic carbene catalyst.” *J. Am. Chem. Soc.* **2014,** *136,* 76-79.

82) Lee, A.; Scheidt, K. A. “A cooperative *N*-heterocyclic carbene/chiral phosphate catalysis system for allenolate annulations.” *Angew. Chem., Int. Ed.* **2014,** *53,* 7594-7598.

83) Li, J-L.; Sahoo, B.; Daniliuc, C-G.; Glorius, F. “Conjugate umpolung of β,β-disubstituted enals by dual catalysis with an *N*-heterocyclic carbene and a Brønsted acid: facile construction of contiguous quaternary stereocenters.” *Angew. Chem., Int. Ed.* **2014,** *53,* 10515-10519.

84) Zheng, C.; Yao, W.; Zhang, Y.; Ma, C. “chiral spirooxindole–butenolide synthesis through asymmetric *N*-heterocyclic carbene-catalyzed formal (3 + 2) annulation of 3-bromoenals and isatins.” *Org. Lett.* **2014,** *16,* 5028-5031.

85) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. “Cooperative *N*-heterocyclic carbene/Lewis acid catalysis for highly stereoselective annulation reactions with homoenolates.” *J. Am. Chem. Soc.* **2010,** *132,* 5345-5347.

86) Cohen, D. T.; Cardinal-David, B.; Roberts, J. M.; Sarjeant, A. A.; Scheidt, K. A. “NHC-catalyzed/titanium(iv)−mediated highly diastereo- and enantioselective dimerization of enals.” *Org. Lett.* **2011,** *13,* 1068-1071.

87) Cohen, D. T.; Cardinal-David, B.; Scheidt, K. A. “Lewis acid activated synthesis of highly substituted cyclopentanes by the *N*-heterocyclic carbene catalyzed addition of homoenolate equivalents to unsaturated ketoester.” *Angew. Chem., Int. Ed.* **2011,** *50,* 1678-1682.

88) Izquierdo, J.; Orue, A.; Scheidt, K. A. “A dual Lewis base activation strategy for enantioselective carbene-catalyzed annulations.” *J. Am. Chem. Soc.* **2013,** *135,* 10634-10637.

89) Lv, H.; Jia, W-Q.; Sun, L-H.; Ye, S. “*N*-heterocyclic carbene catalyzed [4+3] annulation of enals and *o*-quinone methides: highly enantioselective synthesis of benzo-ε-lactones.” *Angew. Chem., Int. Ed.* **2013,** *52,* 8607-8610.

90) White, N. A.; DiRocco, D. A.; Rovis, T. “Asymmetric *N*-heterocyclic carbene catalyzed addition of enals to nitroalkenes: controlling stereochemistry via the homoenolate reactivity pathway to access δ-lactams.” *J. Am. Chem. Soc.* **2013,** *135,* 8504-8507.

91) Guo, C.; Schedler, M.; Daniliuc, C. G.; Glorius, F. “*N*-heterocyclic carbene catalyzed formal [3+2] annulation reaction of enals: an efficient enantioselective access to spiro-heterocycles.” *Angew. Chem., Int. Ed.* **2014,** *53,* 10232-10236.

92) Li, Y.; Zhao, Z-A.; He, H.; You, S.-L. “Stereoselective synthesis of γ-butyrolactones *via* organocatalytic annulations of enals and keto esters.” *Adv. Synth. Catal.* **2008,** *350,* 1885-1890.

93) Sohn, S. S.; Bode, J. W. “Catalytic generation of activated carboxylates from enals: a product-determining role for the base.” *Org. Lett.* **2005,** *7,* 3873-3876

94) Cohen, D. T.; Scheidt, K. A. “Cooperative Lewis acid/*N*-heterocyclic carbene catalysis.” *Chem. Sci.* **2012,** *3,* 53-57.

95) CCDC 1023584 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

96) Huang, X-L.; He, L.; Shao, P-L.; Ye, S. "[4+2] Cycloaddition of ketenes with *N*-benzoyldiazenes catalyzed by *N*-heterocyclic carbenes." *Angew. Chem., Int. Ed.* **2009,** *48,* 192-195.

97) Marmedov, V. A.; Berdnikov, E. A.; Tsuboi, S.; Hamamoto, H.; Komiyama, T.; Gorbunova, E. A.; Gubaidullin, A. T.; Litvinov, I. A. "Substituted benzaldehydes in the darzens condensation with alkyl dihaloacetates." *Russ. Chem Bull., Int. Ed.* **2006,** *55,* 1455-1463.

98) Patil, N. T.; Singh, V. "Synthesis of 1,3,5-trisubstituted pyrazolines *via*Zn(II)-catalyzed doublehydroamination of enynes with aryl hydrazines." *Chem. Commun.* **2011,** *47,* 11116-11118.

99) Chandra, A.; Pigza, J. A.; Han, J-S.; Mutnick, D.; Johnston, J. N. "Total synthesis of the *lycopodium* alkaloid (+)-Serratezomine A." *J. Am. Chem. Soc.* **2009,** *131,* 3470-3471.

100) Ling, K. B.; Smith, A. D. "α-Aroyloxyaldehydes: scope and limitations as alternatives to α-haloaldehydes for NHC-catalysed redox transformations." *Chem. Commun.* **2011,** *47,* 373-375.

101) Kerr, M. S.; Read de Alaniz, J. Rovis, T. "An efficient synthesis of achiral and chiral 1,2,4-triazolium salts: bench stable precursors for *N*-heterocyclic carbenes." *J. Org. Chem.* **2005,** *70,* 5725-5728.

103) Zhang, Y-R.; He, L.; Wu, X.; Shao, P-L.; Ye, S. "Chiral *N*-heterocyclic carbene catalyzed Staudinger reaction of ketenes with imines: highly enantioselective synthesis of *N*-boc β-lactams." *Org. Lett.* **2008,** *10,* 277-280.

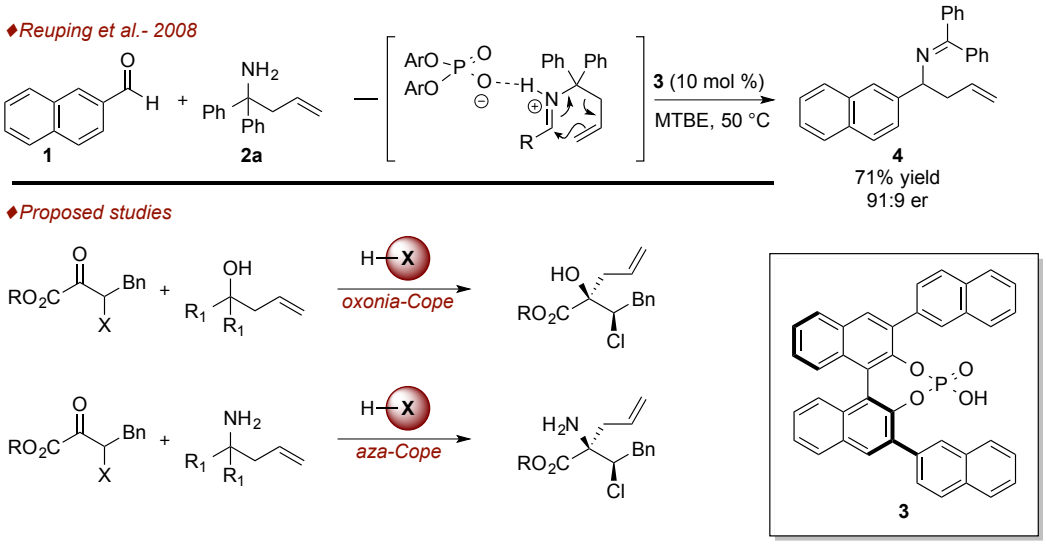
CHAPTER 4

COMPLEXITY GENERATING DYNAMIC KINETIC RESOLUTIONS OF β-OXO ACID DERIVATIVES

4.1 Introduction

As our investigations targeting DKRs that employ β-stereogenic α-keto esters progressed, we focused on sigmatropic rearrangements as a DKR platform. Inspired by the Reuping group's report of chiral acid catalyzed aza-allylation of aldehyde **1** using amino-allyl donor **2a** (Scheme 1 top),[1-2] we noted that the development of a chiral phosphoric acid catalyzed dynamic [3,3]-aza-Cope or [3,3]-oxonia-Cope would deliver functionally useful and stereochemically rich products (Scheme 1 bottom).

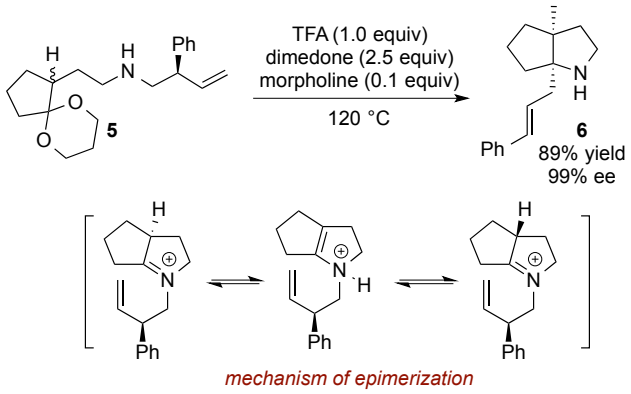
Scheme 1. Stereoconvergent Sigmatropic Processes



Preliminary studies indicated that the development of an aza-Cope was more promising proposal based on lack of reactivity in initial oxonia-Cope rearrangement trials; our focus centered solely on the development of the aza-Cope rearrangement.

While catalytic asymmetric sigmatropic rearrangements are well-established,[3-5] examples of enantioselective 2-aza-Cope rearrangements are limited.[1,2] Of some note was the Overman lab's report of a dynamic 2-aza-Cope utilizing stereochemically defined aminoallyl reagent **5** to generate amino allyl **6** (Figure 2), where epimerization occurs via enamine-iminium tautomerization.[6-7] However, previous to our work there were no examples of a 2-aza-Cope reaction where enantiocontrol was imparted via chiral catalyst.

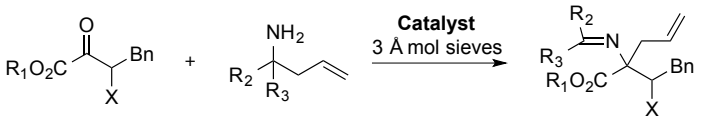
Scheme 2. Previous 2-Aza-Cope DKR



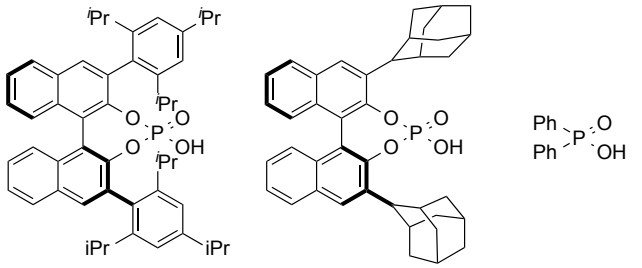
Our initial investigations were conducted using α-keto ester (±)-**7** in combination with allyl amine **2a** in the presence of a phosphoric acid catalyst.[8-13] Using achiral phosphinic acid **11** as the catalyst, we observed no reactivity with **7a** (Table 1, entry 1) and 30% conversion using **7b** (Table 1, entry 2). We switched to salicylaldehyde derived **2b** as the allyl amine source, due to potential activating and orienting effects (via hydrogen bonding) of the distal hydroxyl

group. This modification did enhance reactivity as 50% of **7a** was converted to **8a**, but in low dr (Table 1, entry 3). Employing BINOL derived chiral phosphoric acids **10**[14] and **11**[15] increased reactivity; without appreciable stereoselectivity (Table 1, entries 5,6). We thought that using a sterically encumbering *tert*-butyl ester might impart higher stereoselectivity; however, it had only detrimental effects on reactivity (Tabe 1 entries 6,7).

Table 1: Attempts to Effect the 2-Aza-Cope Transformation Using β-Stereogenic α-Keto Esters[a]



♦Catalysts utilized



9 10 11

Trial	R_1	R_2	R_3	X	catalyst	solvent	T (˚C)	conv (%)	dr[b]	er[c]
1	Me	Ph	Ph	Br	**11**	$CHCl_3$	80	*	--	--
2	Me	Ph	H	Cl	**11**	$CHCl_3$	80	30	--	--
3	Me	2-OH-C_6H_3	H	Cl	**11**	$CHCl_3$	80	50	2:1	--
4	Me	2-OH-C_6H_3	H	Cl	**9**	$PhCH_3$	70	100	4:1	53:47
5	Me	2-OH-C_6H_3	H	Cl	**10**	$PhCH_3$	70	100	2:1	55:45
6	^{t}Bu	2-OH-C_6H_3	H	Cl	**9**	$PhCH_3$	70	20	3:1	55:45
7	^{t}Bu	2-OH-C_6H_3	H	Cl	**10**	$PhCH_3$	70	40	2:1	53:47

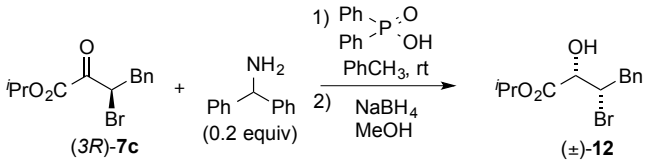
* reaction mixture is complex by ^{1}H NMR *a)* All reactions were run on a 0.10 mmol scale. *b)* Determined by ^{1}H NMR analysis of the crude reaction mixture. *c*) Determined by chiral HPLC analysis.

We were cognizant that in all of our group's previously successful DKRs, base was present in the reaction mixture (NEt_3 for the hydrogenations and K_2CO_3

for the carbene catalyzed reactions) and was likely critical for substrate racemization. In light of this, we questioned whether the rate of racemization was suitable for a DKR to occur under the buffered conditions provided by **2** and phosphoric acids.

A racemization study of enantioenriched **7** revealed that under the reaction conditions full enantiomerization to the racemate takes > 18 h, indicating that racemization via tautomerization is likely slower than the rate of sigmatropic rearrangement (Table 2).

Table 2: Racemization Study of β-Bromo α-Keto Ester 7c Under the Proposed Reaction Conditions[a]



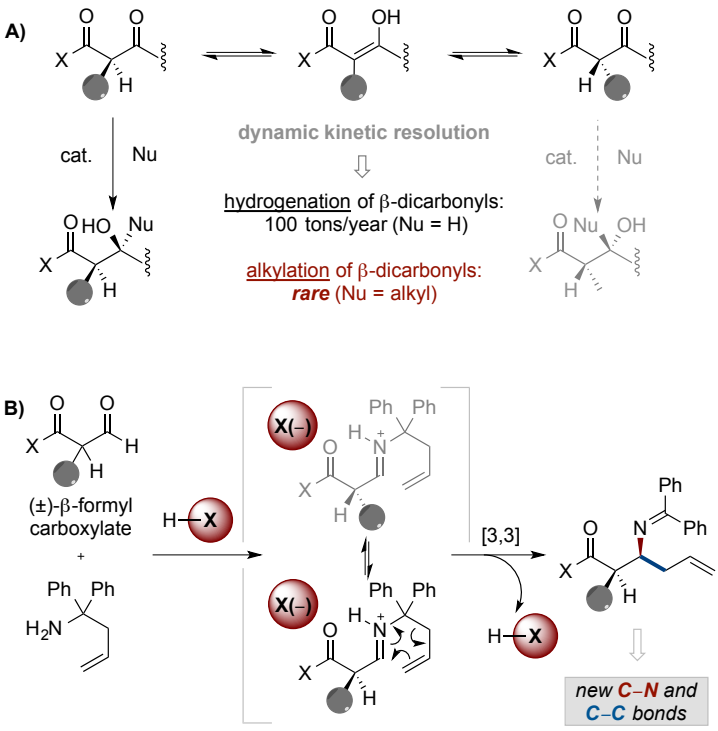
time (h)	er
0	83.5:16.5
0.25	83:17
0.5	83:17
0.75	82.5:17.5
1	82.5:17.5
2	80:20
18	66:34

a) 0.07 mmol aliquots of the reaction mixture were drawn at the indicated timepoints, diluted with MeOH and reduced with $NaBH_4$. The reduction proceeds with >20:1 diastereoselectivity. Chiral SFC was used to analyze er values.

We were still interested in effecting a dynamic aza-Cope; however, due to the inability of **7** to achieve kinetically useful enantiomerization, we shifted to the use of β-formyl acid derivatives. We anticipated this would enhance the rate of enantiomer conversion relative to **7** by favoring enamine formation.

We were also cognizant that the use of β-formyl esters as opposed to α-keto esters presented a unique opportunity to expand the range of carbon-based nucleophiles in DKRs of β-oxo esters. As discussed in Chapter 1 the hydrogenative DKR of β-oxo esters is an indispensable synthetic technology used to generate hectoton quantities of optically enriched β-hydroxy esters annually (Scheme 3A),[16] yet non-hydride based enantioconvergent methods for these substrates remain scarce.

Scheme 3. Impact of Developing a 2-Aza-Cope of β-Oxo Acid Derivatives



Of those that have been reported the most pertinent are, enzymatic Baeyer-Villiger oxidative cleavage,[17] NHC catalyzed intramolecular aldol addition (for a full discussion see Chapter 3 Section 1),[18,19] and enzymatic hydrocyanation[20] of β-keto esters. Dynamic aldol addition at the α-ketone of α,γ-

diketo esters has also been reported.[21,22] A 2-aza-Cope reaction using racemic β-oxo acid derivatives represents an advance in the field of non-hydrogenative DKRs as it establishes new C-N and C-C bonds and vicinal stereogenic centers, generating new $\beta^{2,3}$-amino acid derivatives (Scheme 3B).[23]

4.2 Asymmetric Synthesis of β-Amino Amides by Catalytic Enantioconvergent 2-Aza-Cope Rearrangement*

Our studies using β-formyl acid derivatives began with β-formyl ester **13** and achiral phosphinic acid **11** as the catalyst; however, neither elevated temperature nor the use of hydrogen bonding solvents resulted in any product other than enamine **14** (Table 3, entries 1-4). As our studies progressed it became clear that **14** was impervious to [3,3]-rearrangement under any conditions that could be rendered catalytic. The use of triflic acid under thermal conditions was required before appreciable amounts of rearranged product were observable (Table 3 entry 7,8). We attributed this circumstance to a debilitating thermodynamic preference for the unreactive enamine relative to the needed iminium ion **14•H$^+$** (Scheme 4).

Considering our inadvertant overcorrection, we speculated that replacing the ester with a more sterically demanding dialkyl amide might provide a proper balance by destabilizing the enamine tautomer through A(1,3) strain[24,25] while still maintaining a faster rate of enantiomerization than was observed with α-keto ester **7** (Scheme 4).

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Table 3: Attempts to Effect the 2-Aza-Cope Transformation Using α-Stereogenic β-Formyl Esters[a]

(±)–**13** **14** **15**

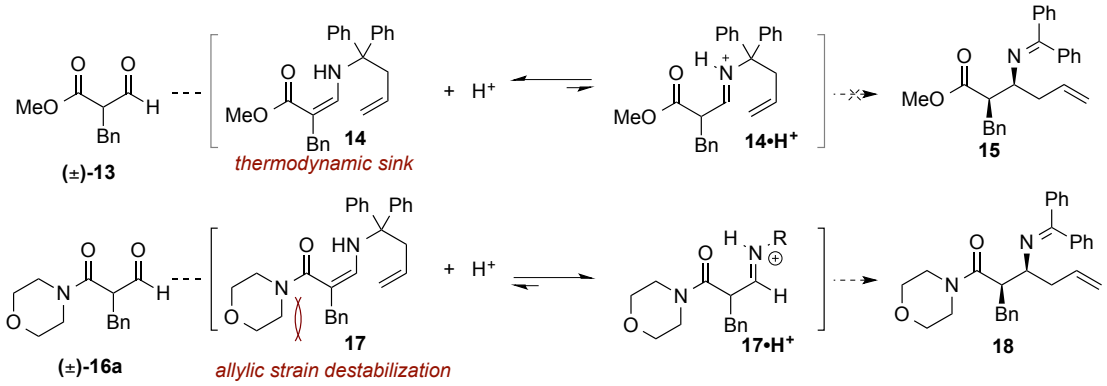
Trial	R_1	R_2	cat	solvent	temp (˚C)	14:15[b]
1	2-OH-C_6H_3	H	**11**	$PhCH_3$	75	>50:1
2	Ph	Ph	**11**	$PhCH_3$	120	>50:1
3	Ph	Ph	**11**	MeOH	70	>20:1
4	Ph	Ph	**11**	H_2O	70	>20:1
5	Ph	Ph	TsOH	$PhCH_3$	80	6:1
6	Ph	Ph	TsOH	MeOH	80	12:1
7	Ph	Ph	TfOH	$PhCH_3$	80	1:6
8	Ph	Ph	TfOH	MeOH	80	2:3

a) All reactions were run on a 0.10 mmol scale using 0.1 mmol of catalyst. *b)* Determined by ^{1}H NMR analysis of the crude reaction mixture.

Of potential concern is a reasonable body of literature demonstrating stereoselective addition reactions of enantiopure α-stereogenic-β-oxo amides and imides that do not epimerize (or racemize) at the α-carbon.[26-] As previously discussed the use of these sterically encumbering dialkyl amides provides one of the most common routes to stereochemically defined non-quaternary α-stereogenic β-keto esters (see Chapter 1 Section 2.4 for a full discussion.)

In order to test our hypothesis against this literature precedent we subjected β-formyl amide (±)-1**6a** and allyl amine **2a** to chiral phosphoric acid **9**, forming β-amino amide **18a** in 7:1 dr and 96:4 er (Table 4, entry 1). A screen of chiral phosphoric acids revealed **9** and **19**[18] as the best candidates for further optimization (full details of these trials can be found in Chapter 4 Section 3.6).

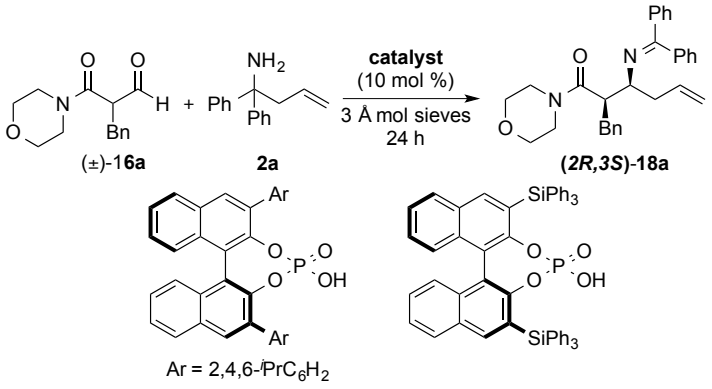
Scheme 4. Proposal for Achieving Facile Racemization



Elevating the reaction temperature increased the reaction rate with little loss of stereoselection (Table 4, entry 3 and 4). Using cyclopentyl methyl ether (CPME) as a solvent increased the stereoselectivity for both catalyst **9** and **19** (Table 1, entry 5 and 6). With catalyst **9** and $CHCl_3$ as the solvent, ketimine **18a** was obtained in 10:1 dr and 97:3 er (Table 4, entry 7). Lowering the catalyst loading to 2.5 mol % had no detrimental effects on reactivity or selectivity (Table 4, entry 9).

We used modified conditions for a crossed-Claisen condensation synthesizing diverse β-formyl amides in order to test the tolerance of our optimized 2-aza-Cope rearrangement to various substrates (Scheme 5).[32,33] An array of β-formal amides **16** were synthesized in 37-85% yield; however, a complication of these synthetic procedures was that many of the formed aldehydes were inseparable from various impurities using SiO_2 chromatography. These impurities did not impinge upon the rearrangement, but to compensate we opted for a reaction stoichiometry of 1.0:1.2 (**2**:**16**) and calculated yields based on the amine component.

Table 4: Optimization of Aza-Allylation Conditions[a]



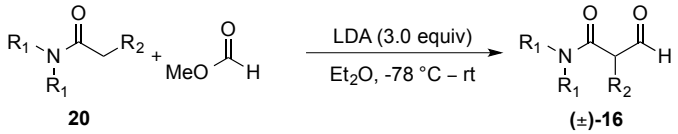
entry	**cat.**	T (º C)	solvent	conv (%)	dr[b]	er[c]
1	**9**	rt	$PhCH_3$	100	7:1	96:4
2	**19**	rt	$PhCH_3$	50	--	--
3	**9**	80	$PhCH_3$	100	7:1	95:5
4	**19**	80	$PhCH_3$	100	20:1	87:13
5	**9**	60	CPME	100	8:1	98:2
6	**19**	60	CPME	100	>20:1	89:11
7	**9**	60	$CHCl_3$	100	10:1	97:3
8	**19**	60	$CHCl_3$	100	>20:1	93:7
9[d]	**9**	60	$CHCl_3$	100	10:1	97:3

a) All reactions were run on a 0.10 mmol scale. *b)* Determined by ^{1}H NMR analysis of the crude reaction mixture. *c*) Determined by chiral HPLC analysis. *d)* 2.5 mol % of catalyst.

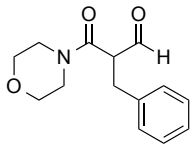
With an array of β-formyl amides in hand and suitable reaction conditions determined, we began to probe the allowable steric and electronic parameters of this rearrangement, initially by studying the effects of substrate variation at α-substituent (Scheme 6).

The phenylacetic acid derivative **18b** was obtained in 1.1:1 dr and 85:15 er. An α-allyl aldehyde provided **18c** in 8:1 dr and 91.5:8.5 er, while inclusion of a pendant heteroatom provided **18d** in 2:1 dr and 90.5:9.5 er.

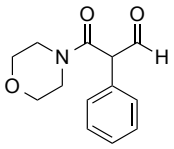
Scheme 5. Synthesis of α-Stereogenic β-Formyl Amides[a]



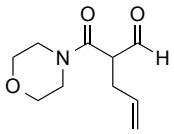
20 **(±)-16**



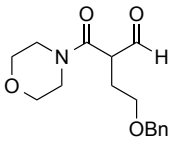
(±)-16a[b]
63% yield



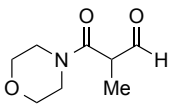
(±)-16b[b,c]
83% yield



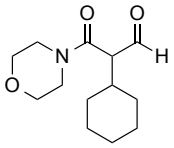
(±)-16c[b]
55% yield



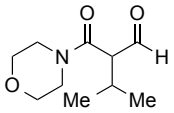
(±)-16d[b]
53% yield



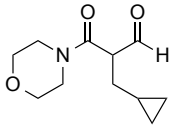
(±)-16e
67% yield



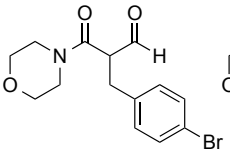
(±)-16f[b]
85% yield



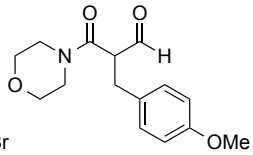
(±)-16g[b]
83% yield



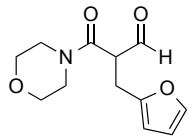
(±)-16h[b]
82% yield



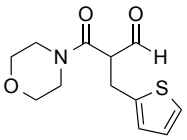
(±)-16i
81% yield



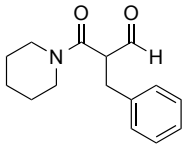
(±)-16j
37% yield



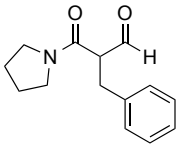
(±)-16k
41% yield



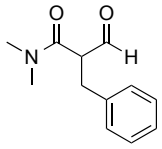
(±)-16l
39% yield



(±)-16m[b]
83% yield



(±)-16n[b]
59% yield



(±)-16o
82% yield

a) Reactions were run on a 1.0-2.0 mmol scale. Isolated yields are reported *b)* Yield determined by ^{1}H NMR using 0.1 mmol of 2,4,6-$(OMe)_3C_6H_3$ as an internal standard. *c*) Synthesized according to an alternate protocol employing 2.5 equiv $TiCl_4$, 3.5 equiv NEt_3, and 10.0 equiv ethyl formate.

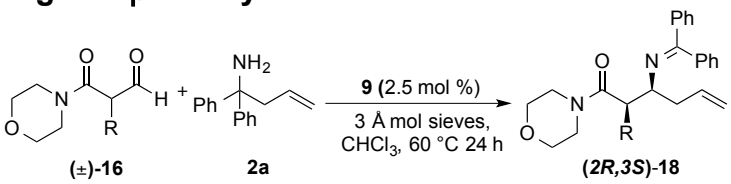
The less sterically demanding α-methyl substitution gave **18e** in 3:1 dr and 82:18 er. The use of larger α-substituents, as represented by **18f** (R = ^{c}Hex) and **18g** (R = ^{i}Pr), restored higher levels of stereoselection.

Electronically differentiated benzyls provided **18i** and **18j** with >10:1 dr and 97:3 er. Using 2-furyl and 2-thenyl instead of benzyl derivatives yielded products **18k** and **18l** with high stereocontrol.

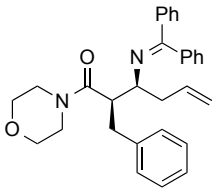
Cognizant that modifying the amide identity would result in differentiated diamines after amide reduction, we next examined structural variation at that position (Scheme 7). The β-amino amides generated from piperidine **18m**, pyrrolidine **18n**, and dimethyl amine **18o** were all formed in high yield and stereoselectivity. We also probed the allowed variance of the allyl amine donor. Internally substituted allyl amine **2b** provided the formal aza-methallylation adduct **18p** in 60% yield with 5:1 dr and 80:20 er. Terminally substituted allyl amine donors condensed with the β-formyl amide **16**, but did not undergo [3,3]-rearrangement, results we attribute to greater steric encumbrance at the reaction site. Product stereochemistry was determined by X-ray diffraction of **18g** (Scheme 8) to be (*2R,3S*).[34]

For our final investigations we turned our attention to assessing the reactivity of the product β-imino amides. Hydrolysis of **18a** to form primary amine **20** proceeded under mild conditions and in 99% yield (Scheme 9A).

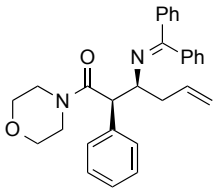
Scheme 6. Variation of the α-Substituent in the [3,3]-Rearrangement of α-Stereogenic-β-Formyl Esters[a]



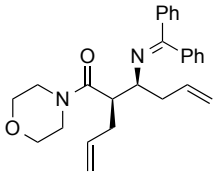
(±)-16 2a (2R,3S)-18



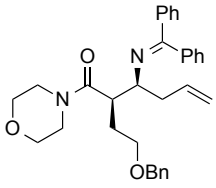
18a[b]
87% yield
10:1 dr
97:3 er
isolated dr >20:1



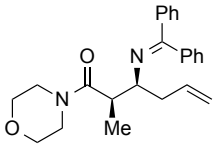
18b[c]
31% yield
1.1:1 dr
85:15 er
isolated dr >20:1



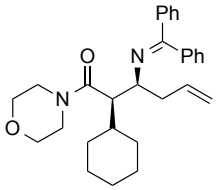
18c
80% yield
8:1 dr
91.5:8.5 er
isolated dr >20:1



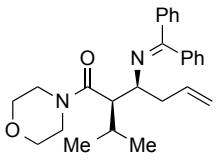
18d[b]
65% yield
2:1 dr
90.5:9.5 er
isolated dr >20:1



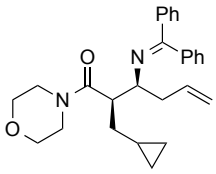
18e[b]
61% yield
3:1 dr
82:18 er
isolated dr 3:1



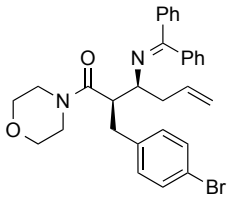
18f
79% yield
>20:1 dr
95.5:4.5 er
isolated dr >20:1



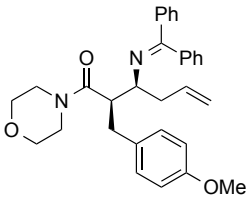
18g
52% yield
13:1 dr
94:6 er
isolated dr >20:1



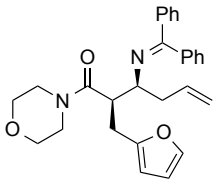
18h
90% yield
11:1 dr
92:8 er
isolated dr 11:1



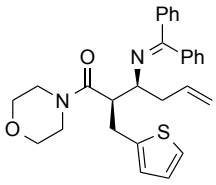
18i[b]
84% yield
11:1 dr
97:3 er
isolated dr >20:1



18j[b,d]
75% yield
12:1 dr
97:3 er
isolated dr >20:1



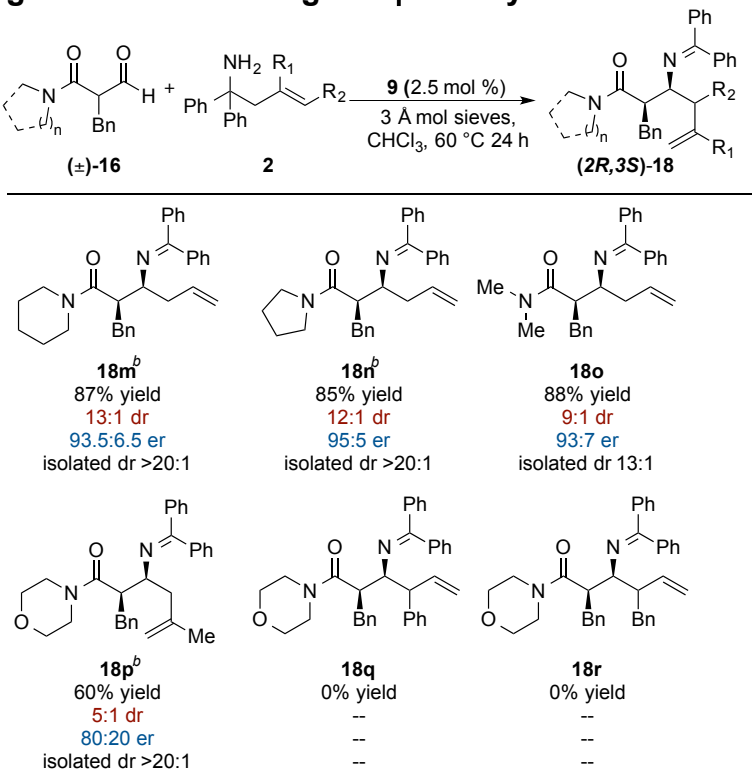
18k[b]
86% yield
10:1 dr
94:6 er
isolated dr >20:1



18l[b,d]
85% yield
20:1 dr
95:5 er
isolated dr >20:1

a) All reactions were run on a 0.20 mmol scale at 60 ºC for 24 h. Diastereomeric ratios were determined by ^{1}H NMR or HPLC analysis of the crude reaction mixture; enantiomeric ratios by chiral SFC or HPLC. Yields are of isolated products. *b*) Yield reported is of the primary amine after hydrolysis of the benzophenone imine. c) Run at 130 ºC under microwave irradiation for 6 h. d) Run on a 0.10 mmol scale.

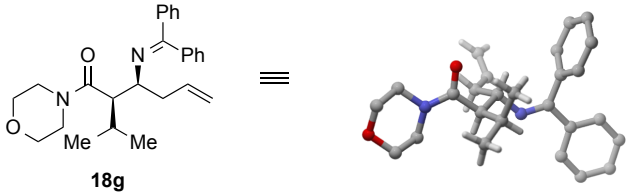
Scheme 7. Variation of Amide and Allyl Amine Identity in the [3,3]-Rearrangement of α-Stereogenic-β-Formyl Esters[a]



a) All reactions were run on a 0.20 mmol scale at 60 ºC for 24 h. Diastereomeric ratios were determined by ^{1}H NMR or HPLC analysis of the crude reaction mixture; enantiomeric ratios by chiral SFC or HPLC. Yields are of isolated products. *b*) Yield reported is of the primary amine after hydrolysis of the benzophenone imine.

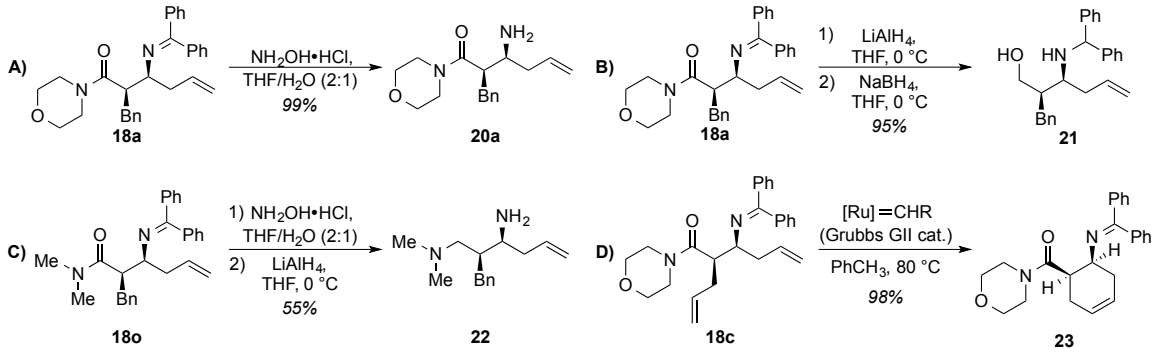
Initial reduction of **18a** with $LiAlH_4$ results in an intermediate aldehyde which can be further reduced by sodium borohydride to form benzhydryl-protected amino alcohol **21** in 95% yield (Scheme 9B). If the benzophenone imine is cleaved prior to reduction, the diamine **22** is obtained in good yield (Scheme 9C). Finally, diene **18c** underwent facile ring-closing metathesis with Grubb's 2nd generation catalyst to provide cyclohexene **23** in 98% yield (Scheme 9D).

Scheme 8. Determination of Relative and Absolute Stereochemistry of the [3,3]-Aza Cope Rearrangement



The completion of these studies netted a stereoconvergent 2-aza-Cope reaction employing stereocontrol from a chiral organic acid catalyst. This DKR between homoallylic amines and α-stereogenic-β-formyl amides constitutes a rare example of a non-hydrogenative DKR reaction of β-oxo acid derivatives and delivers new β-amino amides in high diastereo- and enantioselectivity. Using β-formyl amides was critical to providing the rate of racemization necessary for stereoconvergence, striking a balance between kinetic acidity and confomational preference. Additionally the rearranged products can be readily converted into an array of functional small molecule building blocks.

Scheme 9. Chemical Transformation of Aza-Cope Products



Mechanistic studies delineating the factors that lead to the observed stereoselectivity and the use of this information in the development of other

stereoconvergent reactions of racemization-prone β-oxo carboxylic acid derivatives are of interest for future studies.

4.3 Experimental Data and Conditions for the Asymmetric Synthesis of β-Amino Amides by Catalytic Enantioconvergent 2-Aza-Cope Rearrangement‡

4.3.1 General Information

Methods: Infrared (IR) spectra were obtained using an ASI ReactIR 1000 Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 151 MHz) or a Bruker model 500 (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{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 doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, m = multiplet), coupling constants (Hz), and integration. Supercritical fluid chromatography (SFC) was performed on a Berger SFC system equipped with Chiracel AD, AS, OD, and WO columns as well as a Regis Industries RegisPack (RP) column (φ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO_2 at the indicated percentage of methanol (MeOH) with an oven temperature of 40 °C. High pressure liquid chromatography (HPLC) was performed on a Perkin Elmer flexar photodiode array (PDA) system equipped with Daicel IA, IB, IC, and ID columns (φ 4.6 mm x 250 mm) Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimiter. Mass spectra were obtained using a Finnigan linear trap

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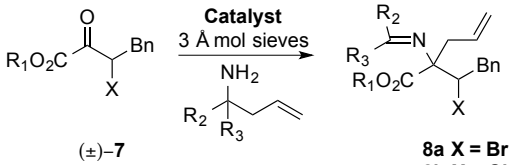
quadrapole Fourier transform (LTQ-FT) spectrometer. Samples were prepared via dilution with MeOH. Analytical thin layer chromatography (TLC) was performed on Sorbtec 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or either aqueous potassium permanganate $KMnO_4$ or aqueous ninhydrin solution followed by heating. Product purification was accomplished using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Microwave irradiation was performed using a CEM Discover microwave (50/60 Hz, 300 W). Unless otherwise noted all reactions were carried out in flame-dried glassware with magnetic stirring. Yields, diastereomeric- (dr) and enantiomeric ratios (er) are reported for a specific experiment and as a result may differ slightly from those found in the reported tables, which represent an average of at least two trials. In order to overlay the SFC traces for the chiral and racemic samples two separate integrations of the peaks must be taken. This results in slight discrepancies between the integration values shown in the report and seen on the trace itself.

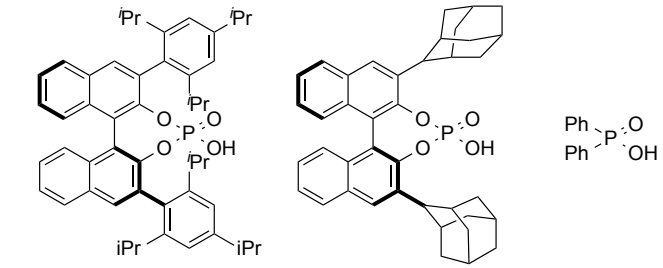
Materials: Phosphoric acid catalysts **9**,[14] **10**,[15] **19**,[31] **24**,[33] **25-26**,[34] **27**,[15] morpholine amides,[35] **7**,[36] **2a**,[1] and **13**[37] were all prepared according to literature procedures. 3 Å molecular sieves were purchased from Sigma Aldrich and dried for 24 h at 180 °C before use. Chloroform ($CHCl_3$), acetonitrile (ACN), 2-methyl tetrahydrofuran (2-Me THF), cyclopentyl methyl ether (CPME), Methyl *tert*-butyl ether (MTBE), and dichloroethane (DCE) were purchased from Sigma Aldrich and used directly from the bottle. Dichloromethane (DCM), diethyl ether (Et_2O), toluene ($PhCH_3$) and tetrahydrofuran (THF) were passed through a column of

neutral alumina under nitrogen prior to use. Triethylamine (TEA) was distilled from calcium hydride prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted. All racemic products were obtained via General Procedure E, using diphenylphosphinic acid.

4.3.2 Complete Reaction Data for the Asymmetric 2-Aza Cope Rearrangement of β-halo α-Keto Esters



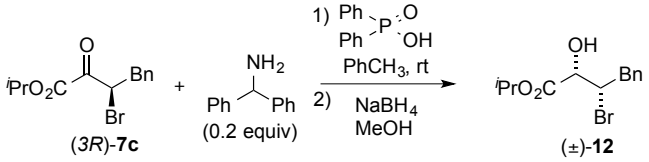
♦Catalysts utilized



General procedure A for developing the asymmetric 2-aza Cope rearrangement of β-halo-α-keto esters: To a 1-dram vial was added catalyst, (0.01 mmol, 0.10 equiv) β-formyl amide **7** (0.14 mmol, 1.4 equiv), solvent (0.5 mL, 0.2 M) 3 Å molecular sieves (50 mg), and allyl amine (0.1 mmol, 1.0 equiv). This solution was stirred at the indicated temperature for 24 h filtered through a short plug of silica with DCM, and concentrated *in vacuo.*

R_1	R_2	R_3	X	cat.	solvent	T (˚C)	conv (%)	dr	er
Me	Ph	Ph	Br	**11**	$PhCH_3$	80	mess	--	--
Me	Ph	Ph	Br	**11**	$CHCl_3$	80	mess	--	--
Me	Ph	Ph	Cl	**11**	$PhCH_3$	80	36	--	--
Me	Ph	Ph	Cl	**11**	$CHCl_3$	80	17	--	--
Me	Ph	Ph	Cl	**11**	THF	60	27	--	--
Me	Ph	Ph	Cl	**11**	CH_3CN	60	37	--	--
Me	2-OH-C_6H_3	H	Cl	**11**	$CHCl_3$	80	50	2:1	--
^{t}Bu	2-OH-C_6H_3	H	Cl	**11**	$PhCH_3$	80	mess	--	--
^{t}Bu	2-OH-C_6H_3	H	Cl	**9**	$PhCH_3$	80	mess	--	--
^{t}Bu	2-OH-C_6H_3	H	Cl	**10**	$PhCH_3$	80	mess	--	--
Me	2-OH-C_6H_3	H	Cl	**9**	$PhCH_3$	70	100	4:1	53:47
Me	2-OH-C_6H_3	H	Cl	**10**	$PhCH_3$	70	100	2:1	55:45
^{t}Bu	2-OH-C_6H_3	H	Cl	**9**	$PhCH_3$	70	20	3:1	55:45
^{t}Bu	2-OH-C_6H_3	H	Cl	**10**	$PhCH_3$	70	40	2:1	53:47

4.3.3 Racemization Study of Enantioenriched α-Halo-β-Keto Esters Under Buffered Conditions



time (h)	er
0	83.5:16.5
0.25	83:17
0.5	83:17
0.75	82.5:17.5
1	82.5:17.5
2	80:20
18	66:34

A flame dried scintillation vial was loaded with enantioenriched **7**[38] (0.33 mmol, 1.0 equiv), diphenylmethanamine (0.06 mmol, 0.20 equiv), phosphinic acid (0.03 mmol, 0.10 equiv), 3 Å molecular sieves (500 mg), followed by $PhCH_3$ (3.5 mL). The mixture was stirred at room temp with 0.5 mL aliquots of reaction mixture being drawn at the indicated time-points. These aliquots were immediately diluted with MeOH (2 mL) and cooled to 0 ˚C followed by addition of a single portion of

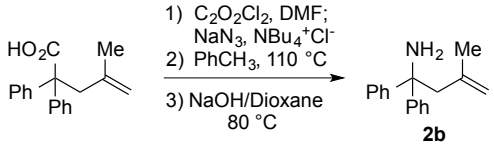
$NaBH_4$ (0.1 mmol, 2.0 equiv). (This reduction proceeds with >20:1 diastereoselectivity.)[38] This solution was stirred for 5 min, quenched with saturated NH_4Cl (2 mL) and partitioned between EtOAc (10 mL) and H_2O (10 mL). The layers were separated and the organic layer was washed with H_2O (2 x 10 mL), brine (1 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo.* The er of the crude alcohol was analyzed by chiral SFC without further purification. 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.

4.3.4 Tested Reaction Conditions to Promote the 2-Aza Cope Rearrangement of α-Substituted-β-Formyl Esters

General procedure B for development of the 2-aza Cope rearrangement of α-substituted-β-formyl esters: To a 1-dram vial were added catalyst, (0.10 mmol, 1.0 equiv) β-formyl amide **13**[37] (0.14 mmol, 1.4 equiv), 3 Å molecular sieves (50 mg), solvent (0.5 mL, 0.2 M) and allyl amine **2a** (0.1 mmol, 1.0 equiv). This solution was stirred at the indicated temperature for 24 h, filtered through a short plug of silica with DCM, and concentrated *in vacuo* for analysis.

R_1	R_2	acid	solvent	T (˚C)	5:12
2-OH-C_6H_3	H	Ph_2PO_2H	$PhCH_3$	75	>50:1
Ph	Ph	Ph_2PO_2H	$PhCH_3$	70	>50:1
Ph	Ph	Ph_2PO_2H	$PhCH_3$	120	>50:1
Ph	Ph	Ph_2PO_2H	MeOH	70	>20:1
Ph	Ph	Ph_2PO_2H	H_2O	70	>20:1
Ph	Ph	Ph_2PO_2H	CH_3CN	70	>20:1
Ph	Ph	TsOH	$PhCH_3$	80	6:1
Ph	Ph	TsOH	MeOH	80	12:1
Ph	Ph	TfOH	$PhCH_3$	80	1:6
Ph	Ph	TfOH	MeOH	80	2:3

4.3.5 Preparation of Allyl Amine 2b

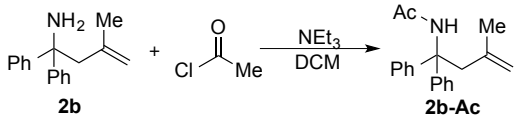


A 25 mL round-bottomed flask equipped with a magnetic stir bar was flame dried and cooled to rt under an atmosphere of N_2. The flask was charged with 4-methyl-2,2-diphenylpent-4-enoic acid (2.0 mmol, 1.0 equiv), DMF (0.1 mmol, 0.05 equiv), and DCM (10 mL, 0.2 M) then cooled to 0 ˚C. Oxalyl chloride (2.2 mmol, 1.1 equiv) was added dropwise and the resulting mixture was warmed slowly to rt and stirred for 1 h. The reaction mixture was concentrated *in vacuo*, then redissolved in DCM (10 mL) and cooled to 0 ˚C. Sodium azide (6.0 mmol, 3.0 equiv) and tetrabutylammonium chloride (0.1 mmol, 0.05 equiv) were added successively and the reaction mixture was stirred at rt for 2 h. The mixture was then partitioned between H_2O (20 mL) and Et_2O (20 mL). The layers were separated and the organic layer was washed with H_2O (2 x 20 mL) and brine (1 x

20 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude azide was redissolved in $PhCH_3$ (5 mL) and heated, open to air, at 110 ˚C for 5 h. The solvent was removed *in vacuo,* the crude isocyanate was redissolved in a 1:1 solution of 2 M NaOH/dioxane (4 mL, 0.5 M) and heated to 80 ˚C for 1 h. The mixture was partitioned between H_2O (10 mL) and EtOAc (10 mL), the layers were separated and the organic layer was further washed with H_2O (2 x 10 mL) and brine (1 x 10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using a gradient of 10-15% acetone/hexane affording **2b** (0.22 g, 0.92 mmol, 46% yield) as a clear oil. Note: amine **2b** shows existence of slow rotation (rotamers) in ^{1}H NMR spectra obtained at ambient temperature.

Analytical data for **2b: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 4H), 7.35-7.32 (m, 4H), 7.27 – 7.24 (m, 2H), 4.97 (s, 1H), 4.79 (s, 1H), 3.12 (s, 2H), 2.98 (s, 2H), 1.23 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 148.1, 142.2, 127.9, 126.7, 126.3, 116.2, 59.7, 50.5, 24.1; **IR** (thin film): 1492, 1445, 1032, 899 cm^{-1}; **TLC** (5% EtOAc/hexane): R_f = 0.16; **LRMS** (ESI): Calcd. for $C_{17}H_{19}N$: ([M+Na]): 260.14, Found: 260.27.

Acylation of **2b** to form **2b-Ac** eliminates the observed rotamers.

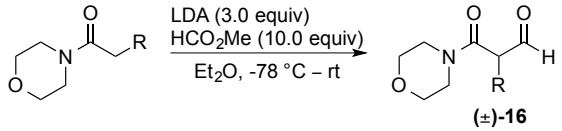


A 1-dram vial equipped with a magnetic stir bar was flame dried and cooled to rt under an atmosphere of N_2. The flask was charged with **2b** (0.1 mmol, 1.0 equiv) and DCM (1.0 mL) then cooled to 0 ˚C. TEA (0.1 mmol, 2.0 equiv) was added to

the solution followed by dropwise addition of acetyl chloride (0.12 mmol, 1.2 equiv). The reaction mixture was slowly warmed to rt and stirred for 18 h. The mixture was then partitioned between H_2O (20 mL) and EtOAc (20 mL), the layers were separated and the organic layer was further 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 using a gradient of 15-30% acetone/hexane affording **2b-Ac** (0.022 g, 0.08 mmol, 79% yield) as a clear oil. Analytical data for **2b-Ac:** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 8H), 7.24-7.21 m, 2H), 6.41 (s, 1H), 4.99 (s, 1H), 4.67 (s, 1H), 3.30 (s, 2H), 2.04 (s, 3H), 1.26 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.0, 144.6, 142.1, 128.0, 126.9, 126.8, 116.3, 63.7, 46.9, 24.4, 24.1; **IR** (thin film): 1655, 1526, 1493, 1446, 697 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.22; **HRMS** (ESI): Calcd. for $C_{19}H_{21}NO$: ([M+H]): 280.1678, Found: 280.1702.

4.3.6 General Procedure C: Preparation of β-Formyl Amide 16

Method 1:

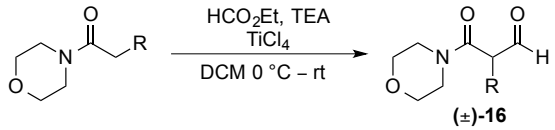


(±)-16

A 25 mL round-bottomed flask equipped with a magnetic stir bar was flame dried and cooled to rt under an atmosphere of N_2. The flask was cooled to -78 ˚C and then charged with freshly prepared 0.7 M LDA (4.3 mL, 3.0 equiv). The morpholine amide (1.0 mmol, 1.0 equiv) was added dropwise and stirred at -78 ˚C for 10 min then 0 ˚C for 1 h. The mixture was cooled to -78 ˚C followed by dropwise addition of methyl formate (10.0 mmol, 10.0 equiv). The solution was

warmed slowly to room temperature, then stirred for 12 h, followed by careful quenching with 2 M HCl (10 mL) and dilution with DCM (30 mL). The layers were separated and the aqueous layer was further extracted with DCM (3 x 30 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography using a gradient of 15-30% acetone/hexane. The β-formyl amide products were often inseparable from unidentified byproducts. In these cases a ^1H NMR yield of the crude reaction mixture, using 1,3,5-trimethoxybenzene (0.2 mmol) as an internal standard, is reported.

Method 2:

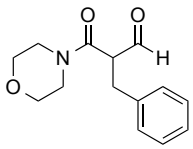


(±)-16

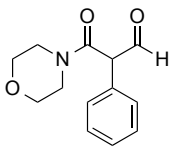
A 1-dram vial equipped with a magnetic stir bar was flame dried and cooled to rt under an atmosphere of N_2. The flask was charged with morpholine amide (1.0 mmol, 1.0 equiv), ethyl formate (10.0 mmol, 10.0 equiv), and DCM (0.3 mL) then cooled to 0 ˚C. To this solution $TiCl_4$ (2.5 mmol, 2.5 equiv) in DCM (0.3 mL) was added by syringe pump (30 min) followed by syringe pump addition of triethylamine (3.5 mmol, 3.5 equiv) over 30 min. The reaction mixture was slowly warmed to rt and stirred for 18 h, followed by quenching with 2 M HCl (10 mL) and dilution with DCM (30 mL). The layers were separated and the aqueous layer was further extracted with DCM (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography using a gradient of 15-30% acetone/hexane.

The β-formyl amide products were often inseparable from unidentified byproducts. In these cases a ^{1}H NMR yield of the crude reaction mixture, using 1,3,5-trimethoxybenzene (0.2 mmol) as an internal standard, is reported.

2-benzyl-3-morpholino-3-oxopropanal (16a): The title compound was prepared according to General Procedure C (Method 1) using 1-morpholino-3-phenylpropan-1-one (0.44 g, 2.0 mmol), affording **16a** (0.36 g, 1.44 mmol, ~95% purity, 63% ^{1}H NMR yield) as a clear oil. Analytical data for **16a: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.74 (d, *J* = 2.4 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.29-7.27 (m, 1H), 7.26-7.22 (m, 2H), 3.76-3.73 (m, 1H), 3.70 (ddd, *J* = 12.7, 6.2, 2.4 Hz, 1H), 3.63 (ddd, *J* = 11.1, 6.0, 2.4 Hz, 1H), 3.56 – 3.41 (m, 3H), 3.32-3.28 (m, 1H), 3.25 (m, 2H), 3.03-2.99 (m, 1H), 2.96-2.92 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.3, 167.1, 137.3, 129.0, 128.8, 127.1, 66.5, 66.1, 56.5, 46.2, 42.2, 34.4; **IR** (thin film): 1724, 1635, 1441, 1113 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.16; **HRMS** (ESI): Calcd. for $C_{14}H_{17}NO_3$: ([M+H]): 248.1286, Found: 248.1282.



3-morpholino-3-oxo-2-phenylpropanal (16b): The title compound was prepared according to General Procedure C (Method 2) using 1-1-morpholino-2-phenylethan-1-one (0.21 g, 1.0 mmol), affording **16b** (0.20 g, 0.86 mmol, ~75% purity, 83% ^{1}H NMR yield) as a clear oil. Analytical data for **16b: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.82 – 9.81 (m, 1H), 7.41 – 7.38 (m, 2H), 7.35 – 7.29 (m, 2H), 7.15 – 7.14 (m, 1H), 4.50 (d, *J* = 3.4 Hz, 1H), 3.75 – 3.72 (m, 1H), 3.68 – 3.65 (m, 1H), 3.57 – 3.48 (m, 4H), 3.36-3.32 (m, 2H), 3.21 – 3.14 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 196.1, 167.3, 131.1, 129.4,



128.3, 128.2, 66.3, 65.8, 60.9, 45.6, 41.7; **IR** (thin film): 1725, 1635, 1440, 1113 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.17; **HRMS** (ESI): Calcd. for $C_{13}H_{15}NO_3$: ([M+H]): 234.1130, Found: 234.1126.

2-(morpholine-4-carbonyl)pent-4-enal (16c): The title compound was prepared according to General Procedure C (Method 1) using 1-1-morpholinopent-4-en-1-one (0.17 g, 1.0 mmol), affording **16c** (0.13 g, 0.66 mmol, ~92% purity, 55% ^{1}H NMR yield) as a clear oil. Analytical data for **16c: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, *J* = 2.2 Hz, 1H), 5.79-5.68 (m, 1H), 5.13 – 5.06 (m, 2H), 3.70 – 3.42 (m, 8H), 2.66 (t, *J* = 7.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.1, 166.6, 133.6, 118.0, 66.7, 66.6, 54.5, 46.2, 42.3, 31.6; **IR** (thin film): 1642, 1595, 1432, 1171 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.17; **HRMS** (ESI): Calcd. for $C_{10}H_{15}NO_3$: ([M+H]): 198.1130, Found: 198.1126.

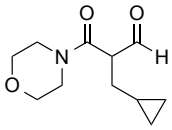
4-(benzyloxy)-2-(morpholine-4-carbonyl)butanal (16d): The title compound was prepared according to General Procedure C (Method 1) using 4-(benzyloxy)-1-morpholinobutan-1-one (0.26 g, 1.0 mmol), affording **16d** as a 4:1 mixture of **16d** to unreacted morpholine amide (0.23 g, 0.79 mmol, ~69% purity, 53% ^{1}H NMR yield) as a clear oil. Analytical data for **6d: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.60 (d, *J* = 2.4 Hz, 1H), 7.34 – 7.26 (m, 5H), 4.48 – 4.42 (m, 2H), 3.75-3.42 (m, 9H), 2.31-2.225 (m, 1H), 2.17-2.11 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 198.1, 167.0, 137.7, 128.2, 127.5, 127.4, 72.8, 67.0, 66.5, 66.4, 52.0, 46.0, 42.0, 27.6.; **IR** (thin film): 1724, 1635, 1437, 1113 cm^{-1}; **TLC** (22.5% acetone/hexane): R_f = 0.11; **HRMS** (ESI): Calcd. for $C_{16}H_{21}NO_4$: ([M+H]): 292.1549, Found: 292.1545.

2-methyl-3-morpholino-3-oxopropanal (16e): The title compound was prepared according to General Procedure C (Method 1) using 1-morpholinopropan-1-one (0.21 g, 1.5 mmol), affording **16e** (0.17 g, 01.0 mmol, 67% yield) as a clear oil. Analytical data for **16e:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.62 (d, *J* = 2.2 Hz, 1H), 3.73–3.65 (m, 5H), 3.58 – 3.43 (m, 4H), 1.40 (d, *J* = 7.2, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.5, 168.1, 66.8, 66.6, 49.2, 46.2, 42.2, 11.8; **IR** (thin film): 1725, 1625, 1436, 1225, 1113, 1030 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.13; **HRMS** (ESI): Calcd. for $C_8H_{13}NO_3$: ([M+Na]): 194.0793, Found: 194.0788.

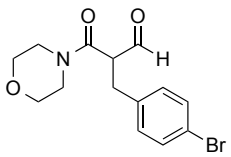
2-cyclohexyl-3-morpholino-3-oxopropanal (16f): The title compound was prepared according to General Procedure C (Method 1) using 2-cyclohexyl-1-morpholinoethan-1-one (0.21 g, 1.0 mmol), affording **16f** (0.18 g, 0.75 mmol, ~97% purity, 85% ^{1}H NMR yield) as a clear oil. Analytical data for **16f:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.57 (d, *J* = 4.6 Hz, 1H), 3.68 – 3.43 (m, 8H), 3.16 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.29 – 2.22 (m, 1H), 1.72 – 1.62 (m, 6H), 1.30-1.20 (m, 2H), 1.14 – 1.06 (m, 1H), 1.01-0.86 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 200.5, 166.7, 66.8, 66.6, 61.6, 46.2, 42.2, 37.8, 30.9, 30.6, 25.9, 25.8; **IR** (thin film): 1721, 1629, 1433, 1115 cm^{-1}; **TLC** (22.5% acetone/hexane): R_f = 0.26; **HRMS** (ESI): Calcd. for $C_{13}H_{21}NO_3$: ([M+H]): 240.1599, Found: 240.1595.

3-methyl-2-(morpholine-4-carbonyl)butanal (16g): The title compound was prepared according to General Procedure C (Method 1) using 3-methyl-1-morpholinobutan-1-one (0.17 g, 1.0

mmol), affording **16g** (0.17 g, 0.86 mmol, ~90% purity, 70% ^{1}H NMR yield) as a clear oil. Analytical data for **16g: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.56 (d, *J* = 4.4 Hz, 1H), 3.70 – 3.51 (m, 7H), 3.47-3.44 (m, 1H), 3.10 (dd, *J* = 9.3, 4.4 Hz, 1H), 2.56-2.50 (m, 1H), 0.96-0.94 (m, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 200.2, 166.8, 66.8, 66.6, 62.4, 46.2, 42.2, 28.5, 20.7, 19.9.; **IR** (thin film): 1723, 1635, 1440, 1263, 1117 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.27; **HRMS** (ESI): Calcd. for $C_{10}H_{17}NO_3$: ([M+H]): 200.1286, Found: 200.1282.



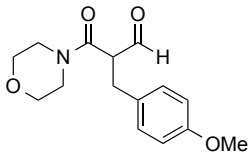
2-(cyclopropylmethyl)-3-morpholino-3-oxopropanal (16h): The title compound was prepared according to General Procedure C (Method 1) using 3-cyclopropyl-1-morpholinopropan-1-one (0.18 g, 1.0 mmol), affording **16h** (0.20 g, 0.86 mmol, ~95% purity) as a clear oil. Analytical data for **16h: ^{1}H NMR** (600 MHz, $CDCl_3$) δ ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.56 (d, J = 3.1 Hz, 1H), 3.72 – 3.49 (m, 8H), 3.45-3.37 (m, 2H), 1.91-1.87 (m, 2H), 1.34 – 1.21 (m, 2H), 0.87 (t, J = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 199.1, 167.2, 66.7, 66.6, 55.2, 46.1, 42.2, 29.2, 27.2, 22.5, 13.7; **IR** (thin film): 1631, 1436, 1269, 1115 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.35; **LRMS** (ESI): Calcd. for $C_{11}H_{17}NO_3$: ([M+Na]): 234.11, Found: 234.30.



2-(4-bromobenzyl)-3-morpholino-3-oxopropanal (16i): The title compound was prepared according to General Procedure C (Method 1) using 3-(4-bromophenyl)-1-morpholinopropan-1-one (0.60 g, 2.0 mmol), affording **16i** (0.59 g, 1.8 mmol, ~90% purity) as a clear oil. Analytical data for **16i: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.61 (d, J = 2.3 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.04 (d, J = 8.1 Hz, 2H), 3.70-3.66 (m, 1H), 3.60 – 3.43

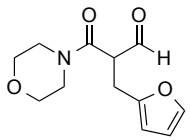
(m, 6H), 3.33 – 3.28 (m, 2H), 3.19 – 3.01 (m, 4H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 197.5, 166.4, 136.3, 131.7, 130.6, 120.8, 66.5, 66.1, 56.3, 46.1, 42.2, 33.2; **IR** (thin film): 1625, 1488, 1115, 1071, 760 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.18; **LRMS** (ESI): Calcd. for $C_{14}H_{16}BrNO_3$: ([M+Na]): 348.02, Found: 348.25.

2-(4-methoxybenzyl)-3-morpholino-3-oxopropanal (16j):



The title compound was prepared according to General Procedure C (Method 1) using 3-(4-methoxyphenyl)-1-morpholinopropan-1-one (0.50 g, 2.0 mmol), affording **16j** (0.23 g, 0.82 mmol, ~90% purity) as a clear oil. Analytical data for **16j: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.69 (d, J = 2.7 Hz, 1H), 7.11 – 7.08 (m, 2H), 6.89 – 6.53 (m, 2H), 3.77 (s, 3H), 3.69 – 3.55 (m, 4H), 3.55-3.41 (m., 4H), 3.36 – 3.26 (m, 2H), 3.17-3.15 (m, 2H), 3.05-2.98 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.6, 167.2, 130.1, 129.2, 114.18, 66.61, 66.21, 56.84, 55.29, 46.20, 42.22, 33.65; **IR** (thin film): 1628, 1513, 1247, 1114, 1031, 749 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.07; **HRMS** (ESI): Calcd. for $C_{15}H_{19}NO_4$: ([M+Na]): 300.12, Found: 300.29.

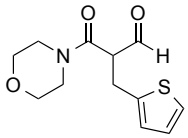
2-(furan-2-ylmethyl)-3-morpholino-3-oxopropanal (16k): The title compound



was prepared according to General Procedure C (Method 1) using 3-(furan-2-yl)-1-morpholinopropan-1-one (0.20 g, 1.0 mmol), affording **16k** (0.11 g, 0.45 mmol, ~90% purity) as a clear oil. Analytical data for **16k: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.62 (d, J = 2.2 Hz, 1H), 7.30 (m, 1H), 6.28-6.27 (m, 1H), 6.09-6.08 (m, 1H), 3.87 – 3.84 (m, 1H), 3.64 – 3.55 (m, 5H), 3.48 – 3.40 (m, 2H), 3.36 – 3.24 (m, 2H), 3.21-3.16 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 197.4, 197.4, 166.6, 151.1, 141.9, 110.7, 107.6, 66.7, 66.5, 53.8, 46.3,

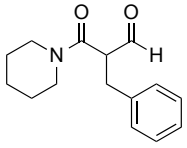
42.4, 26.4; **IR** (thin film): 1621, 1443, 1114, 1070, 1012 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.11; **HRMS** (ESI): Calcd. for $C_{12}H_{15}NO_4$: ([M+Na]): 260.09, Found: 260.35.

3-morpholino-3-oxo-2-(thiophen-2-ylmethyl)propanal (16l):



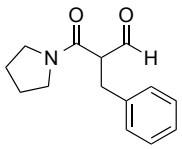
The title compound was prepared according to General Procedure C (Method 1) using 1-morpholino-3-(thiophen-2-yl)propan-1-one (0.23 g, 1.0 mmol), affording **16l** (0.11 g, 0.43 mmol,~90% purity) as a clear oil. Analytical data for **16l: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.63 (d, J = 2.4 Hz, 1H), 7.16-7.15 (m, 1H), 6.92-6.91 (m, 1H), 6.85 – 6.81 (m, 1H), 3.78 (td, J = 7.4, 2.4 Hz, 1H), 3.68 – 3.51 (m, 5H), 3.47 – 3.39 (m, 3H), 3.27-3.17 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 197.36, 166.38, 139.29, 127.17, 126.36, 124.63, 66.58, 66.32, 56.86, 46.30, 42.37, 28.02; **IR** (thin film): 1624, 1437, 1269, 1112, 1067, 1025 cm^{-1}; **TLC** (30% acetone/hexane): R_f = 0.16; **HRMS** (ESI): Calcd. for $C_{12}H_{15}NO_3S$: ([M+H]): 276.06, Found: 276.30.

2-benzyl-3-oxo-3-(piperidin-1-yl)propanal (16m): The title compound was

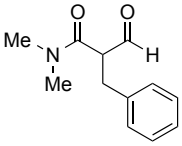


prepared according to General Procedure C (Method 1) using 3-phenyl-1-(piperidin-1-yl)propan-1-one (0.20 g, 1.0 mmol), affording **16m** (0.23 g, 0.95 mmol,~90% purity, 83% ^{1}H NMR yield) as a clear oil. Analytical data for **16m: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.6 Hz, 1H), 7.30-7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 3.80 (td, *J* = 7.5, 2.6 Hz, 1H), 3.63-3.59 (m, 1H), 3.46-3.42 (m, 1H), 3.23-3.19 (m, 3H), 3.11-3.06 (m, 1H), 1.54-1.48 (m, 4H), 1.43 – 1.33 (m, 1H), 1.01 – 0.95 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.6, 166.5, 137.6, 128.9, 128.6, 126.7, 56.8, 46.9, 43.0, 34.2, 25.9, 25.3, 24.1.;

IR (thin film): 1723, 1635, 1444, 700 cm^{-1}; **TLC** (22.5% acetone/hexane): R_f = 0.20; **HRMS** (ESI): Calcd. for $C_{15}H_{19}NO_2$: ([M+H]): 246.1494, Found: 246.1490.



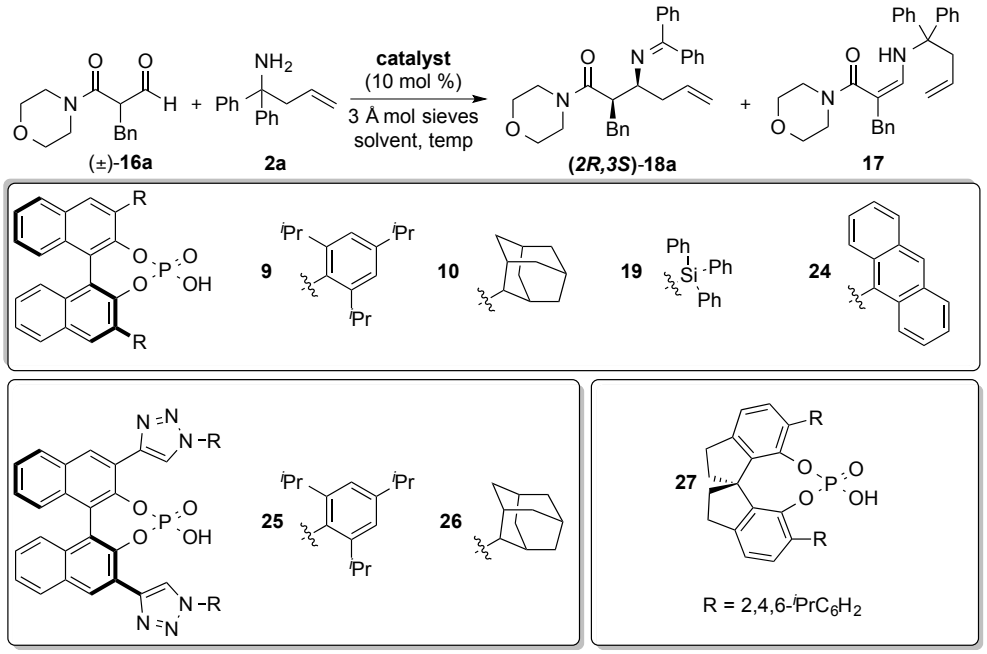
2-benzyl-3-oxo-3-(pyrrolidin-1-yl)propanal (16n): The title compound was prepared according to General Procedure C (Method 1) using 3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (0.22 g, 1.0 mmol), affording **16n** (0.16 g, 0.67 mmol, ~83% purity, 59% ^{1}H NMR yield) as a clear oil. Analytical data for **16n: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.73 (d, *J* = 2.8 Hz, 1H), 7.29 – 7.20 (m, 5H), 3.59 (ddd, *J* = 9.0, 5.9, 2.8 Hz, 1H), 3.47 – 3.37 (m, 2H), 3.32 – 3.23 (m, 2H), 3.18 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.78-2.74 (m, 1H), 1.81 – 1.76 (m, 2H), 1.73-1.67 (m, 1H), 1.65 – 1.60 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.7, 166.6, 137.6, 128.8, 128.5, 126.7, 59.7, 46.5, 45.7, 34.1, 25.7, 24.1.; **IR** (thin film): 1629, 1604, 1455, 1072 cm^{-1}; **TLC** (22.5% acetone/hexane): R_f = 0.26; **HRMS** (ESI): Calcd. for $C_{14}H_{17}NO_2$: ([M+H]): 232.1337, Found: 232.1332.



2-benzyl-N,N-dimethyl-3-oxopropanamide (16o): The title compound was prepared according to General Procedure C (Method 1) *N*,*N*-dimethyl-3-phenylpropanamide (0.18 g, 1.0 mmol), affording **16o** (0.17 g, 0.82 mmol, 82% yield) as a clear oil. Analytical data for **16o: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.70 (d, *J* = 2.7 Hz, 1H), 7.31-7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 3.79 (td, *J* = 7.5, 2.7 Hz, 1H), 3.23 (d, *J* = 7.5 Hz, 2H), 2.92 (s, 3H), 2.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 198.5, 168.4, 137.6, 128.9, 128.6, 126.8, 57.3, 37.1, 35.5, 34.2.; **IR** (thin film): 1723, 1635, 1497, 1401 cm^{-1};

TLC (22.5% acetone/hexane): R_f = 0.08; **HRMS** (ESI): Calcd. for $C_{12}H_{15}NO_2$: ([M+H]): 206.1181, Found: 206.117

4.3.7 Full Optimization Data for the Asymmetric 2-aza Cope Rearrangement of β-Formyl Amides



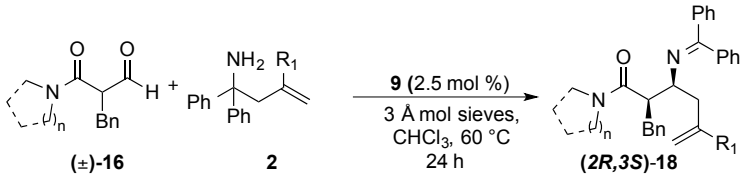
General procedure D for optimization of the asymmetric 2-aza Cope rearrangement of β-formyl amides: To a 1-dram vial were added catalyst, (0.01 mmol, 0.10 equiv) β-formyl amide **16a** (0.14 mmol, 1.4 equiv), 3 Å molecular sieves (50 mg), solvent (0.5 mL, 0.2 M) and allyl amine **2a** (0.1 mmol, 1.0 equiv). This solution was stirred at the indicated temperature for the indicated time, filtered through a short plug of celite with DCM, and concentrated *in vacuo*

Trial	Catalyst	solvent	T (˚C)	time (h)	18a:17	dr	er
1	**9**	$PhCH_3$	rt	24	1:1	--	92:8
2	**10**	$PhCH_3$	rt	24	1:5	--	91:9
3	**19**	$PhCH_3$	rt	24	1:1.5	--	68:32
4	**24**	$PhCH_3$	rt	24	3:1	--	85:15
5	**25**	$PhCH_3$	rt	24	1:1.5	--	66:34
6	**26**	$PhCH_3$	rt	24	1:1.5	--	68:32
7	**27**	$PhCH_3$	rt	24	<1:50	--	--
8	**27**	$PhCH_3$	80	12	1:2	--	70:30
9	**9**	$PhCH_3$	80	12	>20:1	7:1	95.5:4.5
10	**19**	$PhCH_3$	80	12	>20:1	20:1	86.5:13.5
11	**9**	$PhCH_3$	rt	48	>20:1	7:1	95:5
12	**19**	$PhCH_3$	rt	48	1:1	--	--
13	**9**	$CHCl_3$	60	12	>20:1	10:1	97:3
14	**19**	$CHCl_3$	60	12	>20:1	>20:1	93:7
15	**9**	DCE	60	12	>20:1	10:1	95:5
16	**19**	DCE	60	12	>20:1	>20:1	88:12
17	**9**	MTBE	60	12	>20:1	7:1	97:3
18	**19**	MTBE	60	12	3:1	--	--
19	**9**	CPME	60	12	>20:1	8:1	98:2
20	**19**	CPME	60	12	>20:1	>20:1	89:11
21	**9**	CH_3CN	60	12	>20:1	2.5:1	92:8
22	**19**	CH_3CN	60	12	mess	--	--
23	**9**	THF	60	12	>20:1	1.4:1	97.5:2.5
24	**19**	THF	60	12	mess	--	--
25	**9**	2-Me THF	60	12	>20:1	7:1	95:5
26	**19**	2-Me THF	60	12	5:1	--	--
27	**9**[a]	$CHCl_3$	60	12	>20:1	10:1	97:3
28	**9**[b]	$CHCl_3$	60	24	>20:1	10:1	97:3
29	**9**[c]	$CHCl_3$	60	24	4:1	--	--

a) Using 5 mol % of **9** *b)* Using 2.5 mol % of **9** *c)* Using 1 mol % of **9**

4.3.8 General procedure E for the Asymmetric 2-Aza Cope Rearrangement of β-Formyl Amides

Note: As indicated above, the aldehyde is often carried forward with some quantity of inseparable impurities. In practice these impurities did not interfere with the subsequent rearrangement, but for the purposes of simplifying yield calculations, a slight excess of the aldehyde was used relative to the homoallyl amine and the yield was calculated based on the latter.



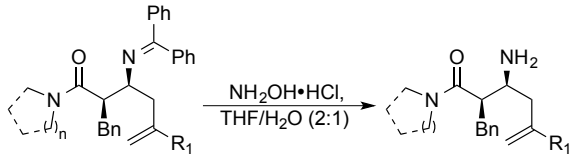
(±)-16 2 (2R,3S)-18

Method 1: To a 1-dram vial were added catalyst, (0.005 mmol, 0.025 equiv) β-formyl amide **16** (0.24 mmol, 1.2 equiv), 3 Å molecular sieves (100 mg), solvent (1.0 mL, 0.2 M) and homoallyl amine **2** (0.2 mmol, 1.0 equiv). This solution was stirred at 60 °C for 18 h then filtered through a short plug of celite with DCM, and concentrated *in vacuo.* The crude residue was purified by column chromatography using a gradient of 10-15% acetone/hexane. The rearranged α-stereogenic-β-amino amide products were often inseparable from unidentified byproducts by chromatography. In these cases products were either recrystallized from 0.5% EtOAc/hexane or deprotected to the corresponding primary amine according to General Procedure F. Note: all er values are of material prior to recrystallization.

Method 2: To a microwave vial was added catalyst, (0.005 mmol, 0.025 equiv) β-formyl amide **16** (0.24 mmol, 1.2 equiv), 3 Å molecular sieves (100 mg), solvent (1.0 mL, 0.2 M) and homoallyl amine **2** (0.2 mmol, 1.0 equiv). This solution was

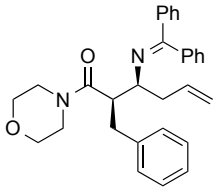
stirred under microwave irradiation at 130 ˚C for 6 h then filtered through a short plug of celite with DCM, and concentrated *in vacuo.* The crude residue was purified by column chromatography using a gradient of 10-15% acetone/hexane. The rearranged α-stereogenic-β-amino amide products were often inseparable from unidentified byproducts by chromatography. In these cases products were recrystallized from 0.5% EtOAc/hexane. Note: all er values of material prior to recrystallization.

General procedure F for the Hydrolysis of β-Amino Amide 18



18 **20**

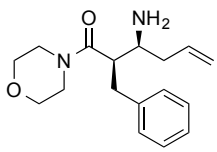
To a 1-dram vial was added **18**, (0.2 mmol, 1.0 equiv) hydroxylamine hydrochloride (1.0 mmol, 5.0 equiv), and 2:1 THF:H_2O (2.0 mL, 0.1 M). This solution was stirred at rt for 18 h then partitioned between 2 M HCl (10 mL) and Et_2O (10 mL). The aqueous layer was washed with Et_2O (3 x 10 mL), basified to pH 14 with 2 M NaOH, extracted with DCM (3x 50 mL), dried over $MgSO_4$, filtered then concentrated *in vacuo* to provide primary amine **20** without need for further purification.



(*2R,3S*)-2-benzyl-3-((diphenylmethylene)amino)-1 morpholinohex-5-en-1-one (18a): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16a** (0.059 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18a** whose diastereomer ratio was determined as

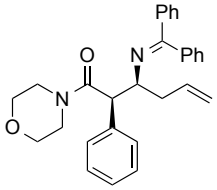
10:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.20-5.11 (minor diastereomer) and δ 5.06-5.00 (major diastereomer). As product **18a** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20a** (0.050 g, 0.17 mmol, 87% yield, >20:1 dr) for final characterization.

Analytical data for **18a:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 – 7.69 (m, 2H), 7.49 – 7.37 (m, 6H), 7.28 – 7.18 (m, 7H), 5.86-5.79 (m, 1H), 5.06 – 5.00 (m, 2H), 3.94-3.90 (m, 1H), 3.75 – 3.72 (m, 1H), 3.57 – 3.54 (m, 1H), 3.34 – 3.22 (m, 4H), 3.18-3.14 (m, 1H), 2.92-2.88 (m, 2H), 2.72 (t, *J* = 12.1 Hz, 1H), 2.51-2.47 (m, 1H), 2.31-2.29 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.1, 168.5, 140.1, 139.8, 136.9, 135.5, 129.9, 129.2, 128.5, 128.4, 128.3, 128.3, 128.0, 127.9, 126.4, 117.0, 66.6, 66.0, 63.7, 48.7, 46.1, 41.78, 39.5, 37.9.; **IR** (thin film): 1742, 1630, 1259, 1015, 701 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.14; **HRMS** (ESI): Calcd. for $C_{30}H_{32}N_2O_2$: ([M+H]): 453.2542, Found: 453.2533; **HPLC** ID, 97% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 12.6 min $t_{R\ (minor)}$ = 18.2 min, 97:3 er; **$[\alpha]_D$** = +34.6 (*c* = 0.03, DCM).



Analytical data for **20a:** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.35 – 7.19 (m, 3H), 5.84-5.75 (m, 1H), 5.17-5.14 (m, 2H), 3.76-3.75 (m, 1H), 3.56 (dd, *J* = 8.7, 5.1 Hz, 1H), 3.34-3.31 (m, 1H), 3.28 – 3.20 (m, 3H), 3.16 – 3.06 (m, 2H), 2.96-2.81 (m, 3H), 2.52 (ddd, *J* = 11.3, 8.2, 2.9 Hz, 1H), 2.33-2.31 (m, 1H), 2.08-2.02 (m, 1H), 1.63 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.8, 139.7, 135.2, 129.2,

128.5, 126.5, 118.2, 66.6, 66.1, 52.6, 51.8, 49.1, 46.1, 41.9, 35.6.; **IR** (thin film): 1738, 1618, 1445, 1365, 1231, 1113 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.40; **HRMS** (ESI): Calcd. for $C_{17}H_{24}N_2O_2$: ([M+H]): 289.1916, Found: 289.1910; **$[\alpha]_D$** = -6.4 (*c* = 0.003, DCM).

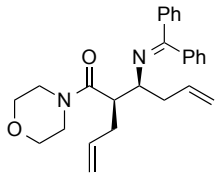


(*2R,3S*)-3-((diphenylmethylene)amino)-1-morpholino-2-phenylhex-5-en-1-one (18b): The title compound was prepared according to General Procedure E (Method 2) using β-formyl amide **16b** (0.056 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18b** (0.028 g, 0.06 mmol, 31% yield, >20:1 dr) as a white solid after recrystallization. The crude diastereomer ratio was determined as 1.1:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 6.01-5.94 (minor diastereomer) and δ 5.66-5.61 (major diastereomer).

Analytical data for **18b: mp:** 121.4-122.2 ˚C **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.43 (m, 2H), 7.35 – 7.17 (m, 12H), 6.39 (d, *J* = 7.3 Hz, 2H), 6.01-5.93 (m, 1H), 5.13 – 5.09 (m, 2H), 4.15-4.13 (m, 2H), 3.72 – 3.63 (m, 2H), 3.57-3.50 (m, 4H), 3.40-3.35 (m, 1H), 3.19-3.14 (m, 1H), 2.61-2.52 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.27, 137.43, 136.59, 136.03, 129.49, 129.13, 128.30, 128.24, 127.91, 127.78, 127.76, 127.74, 127.03, 117.02, 66.73, 66.36, 64.61, 53.23, 46.10, 42.07, 40.03; **IR** (thin film): 1640, 1432, 1114, 699 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.15; **HRMS** (ESI): Calcd. for $C_{29}H_{30}N_2O_2$: ([M+H]): 439.2385, Found: 439.2377; **HPLC** IC, 96% hexanes/IPA, flow rate = 1.0 mL/min,

λ = 230 nm, $t_{R\ (major)}$ = 7.1 min $t_{R\ (minor)}$ = 8.5 min, 84.5:15.5 er; **[α]$_D$** = +96.7 (*c* = 0.03, DCM).

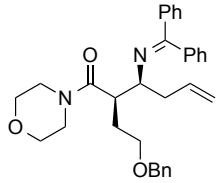
(*2R,3S*)-2-allyl-3-((diphenylmethylene)amino)-1-morpholinohex-5-en-1-one



(18c): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16c** (0.056 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18c** (0.072 g, 0.16 mmol, 80% yield, >20:1 dr) as a white solid after recrystallization. The crude diastereomer ratio was determined as 8:1 by UHPLC analysis of the crude reaction mixture by comparison of the peaks at 7.7 min (minor diastereomer) and 7.9 min (major diastereomer).

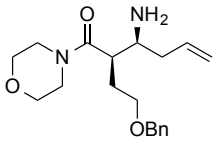
Analytical data for **18c: mp:** 118.0-118.4 ˚C **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.82 (m, 2H), 7.45 – 7.31 (m, 6H), 7.14-7.12 m, 2H), 5.76-5.64 (m, 2H), 5.08 – 4.96 (m, 4H), 3.79 – 3.49 (m, 8H), 3.14-3.10 (m, 1H), 2.34-2.26 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.3, 168.4, 140.0, 136.8, 135.9, 135.5, 129.9, 128.4, 128.4, 128.3, 128.0, 127.9, 117.1, 116.8, 67.0, 66.8, 63.4, 46.4, 45.86, 42.0, 39.3, 35.3; **IR** (thin film): 1625, 1444, 1232, 1115, 916, 697 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.14; **HRMS** (ESI): Calcd. for $C_{26}H_{30}N_2O_2$: ([M+H]): 403.2385, Found: 403.2378; **HPLC** IC, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 5.8 min $t_{R\ (minor)}$ = 7.7 min, 92:8 er; **[α]$_D$** = +40.5 (*c* = 0.03, DCM).

(*2R,3S*)-2-(2-(benzyloxy)ethyl)-3-((diphenylmethylene)amino)-1-



morpholinohex-5-en-1-one (18d): The title compound was prepared according to General Procedure E (Method 1) using β-

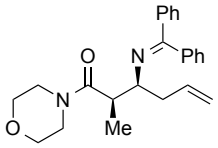
formyl amide **16d** (0.070 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18d** whose diastereomer ratio was determined as 2:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 7.56-7.55 (minor diastereomer) and δ 7.62-7.61 (major diastereomer). As product **18d** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20d** (0.043 g, 0.13 mmol, 65% yield, >20:1 dr) for final characterization. Analytical data for **18d: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63-7.62 (m, 2H), 7.46 – 7.28 (m, 11H), 7.16 – 7.15 (m, 2H), 5.75 – 5.68 (m, 1H), 5.05-5.02 (m, 2H), 4.52 – 4.43 (m, 2H), 3.80-3.76 (m, 1H), 3.69 – 3.60 (m, 2H), 3.59-3.51 (m, 7H), 3.41-3.37 (m, 1H), 3.33-3.29 (m, 1H), 2.35-2.32 (m, 2H), 1.95-1.90 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.7, 168.0, 140.0, 138.2, 136.8, 135.61, 129.9, 128.5, 128.3, 128.3, 128.2, 127.9, 127.9 127.5, 127.4, 117.1, 72.7, 68.1, 66.9, 66.7, 63.7, 46.3, 42.5, 41.9, 39.2, 30.5; **IR** (thin film): 1625, 1444, 1115, 749, 697 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.10; **HRMS** (ESI): Calcd. for $C_{32}H_{36}N_2O_3$: ([M+H]): 497.2804, Found: 497.2794; **HPLC** IC, 85% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 9.8 min $t_{R\ (minor)}$ = 13.4 min, 91:9 er; **[α]$_D$** = +15.9 (*c* = 0.03, DCM).



Analytical data for **20d: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 5.78 – 5.71 (m, 1H), 5.12 – 5.09 (m, 2H), 4.49 – 4.41 (m, 2H), 3.67-3.62 (m, 1H), 3.59 – 3.48 (m, 8H), 3.40-3.36 (m, 1H), 3.03 – 3.00 (m, 1H), 2.92-2.88 (m, 1H), 2.326 – 2.22 (m, 1H), 2.04-1.94 (m, 3H), 1.57 (bs, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.4, 138.2, 135.4, 128.3,

127.6, 127.5, 118.0, 72.8, 68.1, 67.0, 66.8, 52.8, 46.3, 42.6, 42.0, 40.2, 28.4; **IR** (thin film): 1632, 1495, 705 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.37; **HRMS** (ESI): Calcd. for $C_{19}H_{28}N_2O_3$: ([M+H]): 333.2178, Found: 333.2169; **$[\alpha]_D$** = +2.77 (*c* = 0.013, DCM).

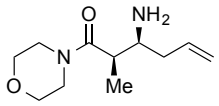
(*2R,3S*)-3-((diphenylmethylene)amino)-2-methyl-1-morpholinohex-5-en-1-one (18e): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16e** (0.04 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18e** as a clear oil. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 1.18 (minor diastereomer) and δ 1.13 (major diastereomer). As product **18e** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20e** (0.028 g, 0.13 mmol, 66% yield, 3:1 dr) for final characterization.



Analytical data for **18e: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.64-7.62 (m, 2H), 7.48 – 7.29 (m, 6H), 7.19-7.16 (m, 2H), 5.82-5.73 (m, 1H), 5.08-5.04 (m, 2H), 3.82 – 3.77 (m, 1H), 3.73 – 3.52 (m, 9H), 3.38 – 3.30 (m, 1H), 3.011-3.06 (m, 1H), 1.13 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.6, 168.1, 140.2, 137.0, 135.3, 129.8, 128.4, 128.3, 128.3, 128.0, 128.0, 117.0, 66.7, 63.6, 46.1, 41.9, 40.1, 39.4, 15.6; **IR** (thin film): 1626, 1432, 1115, 783 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.12; **HRMS** (ESI): Calcd. for $C_{24}H_{28}N_2O_2$: ([M+H]): 377.2229, Found: 377.2217; **SFC** OD, 3% MeOH, flow rate = 3.0 mL/min, λ =

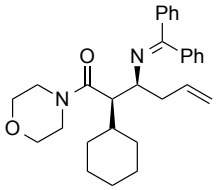
210 nm, $t_{R\ (major)}$ = 9.0 min $t_{R\ (minor)}$ = 8.2 min, 82:18 er; **$[\alpha]_D$** = +34.1 (*c* = 0.02, DCM).

Analytical data for **20e:** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.82 – 5.72 (m, 1H), 5.15 –



5.08 (m, 2H), 3.68-3.60 (m, 6H), 3.51-3.48 (m, 2H), 3.10-3.06 (m, 1H), 2.66 – 2.61 (m, 1H), 2.23 – 2.18 (m, 1H), 2.07-2.01 (m, 1H), 1.62 (bs, 2H), 1.13 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.4, 135.4, 117.8, 67.0, 66.7, 52.4, 46.1, 41.9, 40.0, 39.8, 12.4; **IR** (thin film): 1622, 1466, 1444, 1116 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.16; **HRMS** (ESI): Calcd. for $C_{11}H_{20}N_2O_2$: ([M+H]): 213.1578, Found: 289.213.1595; **$[\alpha]_D$** = -2.8 (*c* = 0.008, DCM).

(*2R,3S*)-2-cyclohexyl-3-((diphenylmethylene)amino)-1-



morpholinohex-5-en-1-one (18f): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **6f** (0.057 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18f** (0.071 g, 0.16 mmol, 80% yield, >20:1 dr) as a white solid after recrystallization. A single diastereomer was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Analytical data for **18f: mp:** 127.8-128.1 ˚C **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.58 (m, 2H), 7.45 – 7.30 (m, 6H), 7.12 – 7.11 (m, 2H), 5.72 – 5.64 (m, 1H), 4.99 – 4.95 (m, 2H), 3.85-3.82 (m, 1H), 3.76 – 3.60 (m, 4H), 3.58 – 3.43 (m, 4H), 2.78 (t, *J* = 6.9 Hz, 1H), 2.52-2.46 (m, 1H), 2.40-2.35 (m, 1H), 1.76-1.69 (m, 1H), 1.64 – 1.58 (m, 4H), 1.53-1.50 (m, 1H), 1.21 – 1.04 (m, 3H), 0.84 – 0.76 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.9, 166.9, 139.8, 136.7, 136.4, 129.9, 128.4, 128.3,

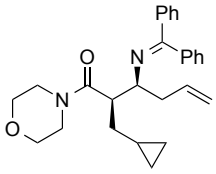
128.3, 128.0, 127.7, 116.6, 67.2, 66.7, 61.2, 50.4, 46.9, 41.8, 38.1, 37.6, 31.6, 30.3, 26.5, 26.4, 26.2.; **IR** (thin film): 1625, 1444, 1115, 769, 698 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.21; **HRMS** (ESI): Calcd. for $C_{29}H_{36}N_2O_2$: ([M+H]): 445.2855, Found: 445.2847; **HPLC** ID, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 6.6 min $t_{R\ (minor)}$ = 10.8 min, 95.5:4.5 er; **$[\alpha]_D$** = +30.8 (*c* = 0.04, DCM).

(*2R,3S*)-3-((diphenylmethylene)amino)-2-isopropyl-1-morpholinohex-5-en-1-one (18g): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16g** (0.046 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18g** (0.042 g, 0.10 mmol, 52% yield, >20:1 dr) as a white solid after recrystallization. The crude diastereomer ratio was determined as 13:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.19-5.07 (minor diastereomer) and δ 5.00-4.92 (major diastereomer).

Analytical data for **18g: mp:** 127.8-128.1 ˚C **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.59 (m, 2H), 7.45 – 7.35 (m, 4H), 7.35 – 7.30 (m, 2H), 7.14 – 7.12 (m, 2H), 5.73-5.65 (m, 1H), 4.99 – 4.96 (m, 2H), 3.84-3.80 (m, 1H), 3.76-3.67 (m, 2H), 3.65 – 3.46 (m, 6H), 2.77-2.74 (t, *J* = 6.9 Hz, 1H), 2.47 – 2.35 (m, 2H), 2.09-2.03 (m, 1H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.8, 167.0, 139.7, 136.7, 136.3, 129.9, 128.4, 128.3, 128.0, 127.8, 116.6, 67.2, 66.7, 61.9, 51.1, 46.9, 41.8, 37.8, 28.4, 21.1, 20.0; **IR** (thin film): 1625, 1444, 1225, 910, 697 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.11; **HRMS**

(ESI): Calcd. for $C_{26}H_{32}N_2O_2$: ([M+H]): 405.2542, Found: 405.2535; **HPLC** IC, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 8.7 min $t_{R\ (minor)}$ = 9.4 min, 94:6 er; **[α]$_D$** = +16.7 (*c* = 0.01, DCM).

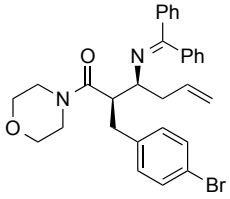
(2R,3S)-2-(cyclopropylmethyl)-3-((diphenylmethylene)amino)-1-



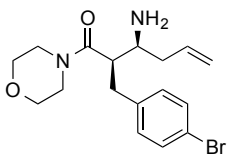
morpholinohex-5-en-1-one (18h): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16h** (0.050 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol,) affording **18h** (0.072 g, 0.18 mmol, 86% yield, 12:1 dr) as clear oil. The crude diastereomer ratio was determined ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.42-5.40 (minor diastereomer) and δ 5.69-5.68 (major diastereomer).

Analytical data for **18h: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 – 7.60 (m, 2H), 7.59 – 7.28 (m, 6H), 7.16 – 7.14 (m, 2H), 5.74-5.68 (m, 1H), 5.03-5.0 (m, 2H), 3.77 – 3.61 (m, 8H), 3.07 – 3.04 (m, 1H), 2.32 – 2.29 (m, 1H), 1.65 – 1.62 (m, 1H), 1.55-1.50 (m, 1H), 1.31-1.21 (m, 2H), 1.13-1.10 (m, 1H) 0.87 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.1, 140.1, 136.9, 135.7, 129.8, 128.4, 128.3, 128.0, 126.5, 126.3, 117.0, 67.1, 66.8, 63.8, 46.5, 45.8, 42.0, 39.3, 30.8, 29.8, 22.9, 14.0; **IR** (thin film): 1638, 1445, 1227, 1115 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.19; **LRMS** (ESI): Calcd. for $C_{27}H_{32}N_2O_2$: ([M+H]): 439.24, Found: 439.40; **HPLC** ID, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 8.5 min $t_{R\ (minor)}$ = 18.0 min, 92:8 er; **[α]$_D$** = +35.8 (*c* = 0.03, DCM).

(2R,3S)-2-(4-bromobenzyl)-3-((diphenylmethylene)amino)-1-morpholinohex-5-en-1-one (18i): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16i** (0.078 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18i** as clear oil. The diastereomer ratio was determined as 13:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.06-5.00 (minor diastereomer) and δ 5.32-5.28 (major diastereomer). As product **18i** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20i** (0.061 g, 0.17 mmol, 83% yield, >20:1 dr) for final characterization.

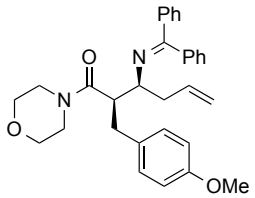


Analytical data for **18i: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 – 7.64 (m, 2H), 7.47 – 7.34 (m, 8H), 7.17 – 7.15 (m, 2H), 7.05 – 7.03 (m, 2H), 5.77 (ddt, J = 17.2, 10.2, 7.2 Hz, 1H), 5.18 – 4.81 (m, 2H), 3.87-3.84 (m, 1H), 3.64-3.60 (m, 1H), 3.58 – 3.53 (m, 1H), 3.39 – 3.17 (m, 5H), 2.92 – 2.81 (m, 2H), 2.73 – 2.68 (m, 2H), 2.29-2.26 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.75, 168.59, 139.91, 138.86, 136.75, 135.31, 131.30, 130.91, 129.96, 128.45, 128.41, 128.32, 128.00, 127.79, 120.08, 117.18, 66.62, 66.09, 63.49, 48.40, 46.07, 41.75, 39.35, 36.97 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.12; **LRMS** (ESI): Calcd. for $C_{30}H_{31}BrN_2O_2$: ([M+Na]): 553.15, Found: 553.33; **HPLC** ID, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 10.7 min $t_{R\ (minor)}$ = 20.5 min, 97:3 er; **$[\alpha]_D$** = +39.3 (*c* = 0.02, DCM).



Analytical data for **20i: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 2H), 7.04-3.52 (m, 1H), 3.42 – 3.23 (m, 3H), 3.18-3.12

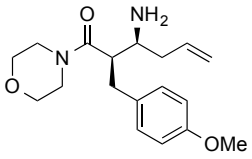
(m, 2H), 2.98-2.95 (m, 1H), 2.89-2.85 (m, 2H), 2.81-2.78 (m, 1H), 2.74-2.71 (m, 1H), 2.28-2.24 (m, 1H), 2.02-1.98 (m, 1H), 1.88-1.84 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.3, 138.6, 134.9, 131.3, 130.8, 120.1, 118.3, 66.6, 66.1, 52.4, 48.7, 46.0, 41.8, 40.0, 34.8; **IR** (thin film): 1620, 1479, 1115, 1011 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.24; **LRMS** (ESI): Calcd. for $C_{17}H_{23}BrN_2O2$: ([M+H]): 367.10, Found: 367.25; **$[\alpha]_D$** = +9.8 (*c* = 0.01, DCM).



((2R,3S)-3-((diphenylmethylene)amino)-2-(4-methoxybenzyl)-1-morpholinohex-5-en-1-one (18j): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16j** (0.033 g, 0.12 mmol), and homoallyl amine **2a** (0.022 g, 0.10 mmol) affording **18j** as clear oil. The diastereomer ratio was determined as 14:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 6.87-6.86 (minor diastereomer) and δ 6.81-6.80 (major diastereomer). As product **18j** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20j** (0.046 g, 0.14 mmol, 72% yield, >20:1 dr) for final characterization.

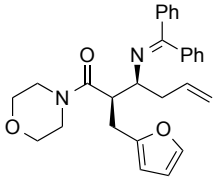
Analytical data for **18j: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 – 7.57 (m, 2H), 7.49 – 7.29 (m, 6H), 7.21 – 7.13 (m, 2H), 7.12 – 6.96 (m, 2H), 6.92 – 6.45 (m, 2H), 5.87 – 5.66 (m, 1H), 5.01-4.97 (m, 2H), 3.94 – 3.82 (m, 1H), 3.77 (s, 3H), 3.66-3.63 (m, 1H), 3.53-3.52 (m, 1H), 3.34 – 3.23 (m, 4H), 3.19-3.15 (m, 1H), 2.90 – 2.80 (m, 2H), 2.66 – 2.60 (m, 2H), 2.27 – 2.75 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.3, 168.5, 140.1, 137.0, 135.6, 131.8, 130.1, 129.9, 128.5, 128.3, 128.0,

127.9, 117.0, 113.7, 66.6, 66.1, 63.6, 55.3, 48.8, 46.1, 41.8, 39.5, 36.9; **IR** (thin film): 1629, 1511, 1259, 1029, 809 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.12; **LRMS** (ESI): Calcd. for $C_{31}H_{34}N_2O_3$: ([M+Na]): 505.25, Found: 505.35; **HPLC** IC, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 16.9 min $t_{R\ (minor)}$ = 28.3 min, 94:6 er; **[α]$_D$** = +20.8 (*c* = 0.02, DCM).



Analytical data for **20j:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.08 (dd, J = 8.5, 1.8 Hz, 2H), 6.79 (dd, J = 8.5, 1.8 Hz, 2H), 5.80 – 5.73 (m, 1H), 5.14 – 5.11 (m, 2H), 3.77 (s, 3H), 3.69-3.67 (m, 1H), 3.55 – 3.53 (m, 1H), 3.35 – 3.29 (m, 3H), 3.17 – 3.13 (m, 2H), 2.99-2.97 (m, 1H), 2.90 – 2.80 (m, 2H), 2.79 – 2.76 (m, 1H), 2.68-2.64 (m, 1H), 2.30 – 2.27 (m, 1H), 2.03-2.00 (m, 1H), 1.66 (bs, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.8, 158.2, 135.2, 131.5, 130.1, 118.2, 113.8, 66.7, 66.2, 55.2, 52.5, 49.2, 46.0, 41.8, 40.2, 34.7; **IR** (thin film): 1622, 1453, 1248, 703 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.19; **LRMS** (ESI): Calcd. for $C_{18}H_{26}N_2O$: ([M+H]): 319.20, Found: 319.37; **[α]$_D$** = +12.9 (*c* = 0.01, DCM).

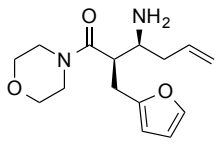
(2R,3S)-3-((diphenylmethylene)amino)-2-(furan-2-ylmethyl)-1-morpholinohex-5-en-1-one (18k): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16k** (0.057 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18h** as clear oil. The diastereomer ratio was determined as 10:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.19-5.11 (minor diastereomer) and δ 5.06-5.01 (major diastereomer). As product **18k** was



inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20k** (0.049 g, 0.18 mmol, 88% yield, >20:1 dr) for final characterization.

Analytical data for **18k:** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 – 7.63 (m, 2H), 7.46 – 7.28 (m, 7H), 7.16 – 7.13 (m, 2H), 6.25 (dd, J = 3.2, 1.9 Hz, 1H), 5.99 (d, J = 3.1 Hz, 1H), 5.80-5.73 (m, 1H), 5.04 – 4.99 (m, 2H), 3.86-3.84 (m, 1H), 3.69-3.65 (m, 1H), 3.61-3.57 (m, 1H), 3.50 – 3.32 (m, 5H), 3.21-3.20 (m, 1H), 3.14-3.11 (m, 1H), 2.91 – 2.79 (m, 2H), 2.30 – 2.27 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.1, 168.6, 153.5, 141.0, 139.9, 136.8, 135.4, 130.0, 128.5, 128.3, 128.0, 127.8, 117.2, 66.8, 66.4, 63.3, 46.1, 45.4, 41.9, 39.4, 29.7; **IR** (thin film): 1642, 1443, 1114, 1008, 699 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.12; **LRMS** (ESI): Calcd. for $C_{28}H_{30}N_2O_3$: ([M+Na]): 465.21, Found: 465.25; **HPLC** ID, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 21.7 min $t_{R\ (minor)}$ = 24.8 min, 94.5:5.5 er; **$[\alpha]_D$** = +26.2 (*c* = 0.03, DCM).

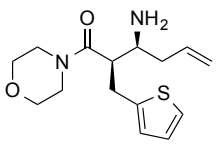
Analytical data for **20k:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 (m, 1H), 6.26-6.25 (m,



1H), 6.02-6.01 (m, 1H), 5.78-5.71 (m, 1H), 5.313 –5.09 (m, 2H), 3.71-3.68 (m, 1H), 3.62-3.58 (m, 1H), 3.52 – 3.50 (m, 1H), 3.46 – 3.31 (m, 3H), 3.20-3.16 (m, 2H), 3.12 – 3.10 (m, 1H), 3.07 – 2.97 (m, 3H), 2.27-2.24 (m, 1H), 2.04-2.00 (m, 1H), 1.55 (s, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ172.9, 153.4, 141.2, 135.0, 118.3, 110.6, 66.8, 66.5, 52.4, 46.1, 45.6, 45.6, 42.0, 40.2, 27.6; **IR** (thin film): 1624, 1442, 1114, 1009 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.21; **LRMS** (ESI): Calcd. for $C_{15}H_{22}N_2O_3$: ([M+H]): 279.17, Found: 279.22; **$[\alpha]_D$** = +3.0 (*c* = 0.02, DCM).

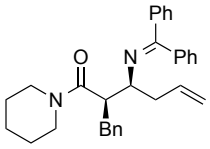
(2R,3S)-3-((diphenylmethylene)amino)-1-morpholino-2-(thiophen-2-ylmethyl)hex-5-en-1-one (18l): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16l** (0.030 g, 0.12 mmol), and homoallyl amine **2a** (0.022 g, 0.10 mmol) affording **18l** as clear oil. The diastereomer ratio was determined as 20:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.17-5.49 (minor diastereomer) and δ 5.80-5.74 (major diastereomer). As product **18l** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20h** (0.027 g, 0.09 mmol, 92% yield, >20:1 dr) for final characterization.

Analytical data for **18l: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65-7.63 m, 2H), 7.46 – 7.33 (m, 5H), 7.16 – 7.09 (m, 3H), 6.89-6.88 (m, 1H), 6.78 (d, J = 3.3 Hz, 1H), 5.77-5.72 (m, 1H), 5.04 – 4.99 (m, 2H), 3.85-3.82 (m, 1H), 3.78-3.74 (m, 1H), 3.60-3.56 (m, 1H), 3.44-3.40 (m, 1H), 3.37 – 3.24 (m, 4H), 3.18 – 3.15 (m, 1H), 3.04 (d, J = 2.7 Hz, 2H), 2.84-2.80 (m, 1H), 2.29 – 2.27 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.9, 168.8, 141.9, 140.0, 136.8, 135.3, 130.0, 128.5, 128.4, 128.0, 127.9, 126.9, 125.9, 123.8, 117.3, 66.7, 66.3, 63.5, 48.9, 46.3, 42.0, 39.4, 31.4; **IR** (thin film): 1742, 1630, 1443, 1114 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.11; **LRMS** (ESI): Calcd. for $C_{28}H_{30}N_2O_2S$: ([M+Na]): 481.19, Found: 481.30; **HPLC** IC, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 10.13 min $t_{R\ (minor)}$ = 13.33 min, 95:5 er; **[α]$_D$** = +39.3 (*c* = 0.02, DCM).



Analytical data for **20l: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.11-7.10 (m, 1H), 6.90-6.88 (m, 1H), 6.79 (d, J = 3.4 Hz, 1H), 5.75 (dddd,

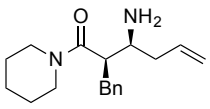
J = 16.6, 10.7, 8.2, 6.1 Hz, 1H), 5.15-5.11 (m, 2H), 3.81-3.77 (m, 1H), 3.61-3.59 (m, 1H), 3.46-3.44 (m, 1H), 3.38 – 3.22 (m, 5H), 3.17 – 3.12 (m, 2H), 2.91 – 2.86 (m, 2H), 2.30 – 2.27 (m, 1H), 2.05-2.01 (m, 1H), 1.87 (d, J = 10.7 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.6, 141.8, 135.0, 127.0, 125.9, 123.8, 118.4, 66.8, 66.4, 52.5, 49.3, 46.3, 46.3, 42.0, 40.2, 29.4.; **IR** (thin film): 1620, 1443, 1114, 644 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.24; **LRMS** (ESI): Calcd. for $C_{15}H_{22}N_2O_2S$: ([M+H]): 295.14, Found: 295.29; **$[\alpha]_D$** = +3.3 (*c* = 0.02, DCM).



(*2R,3S*)-2-benzyl-3-((diphenylmethylene)amino)-1-(piperidin-1-yl)hex-5-en-1-one (18m): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16m** (0.073 g, 0.24 mmol), and homoallyl amine **2a** (0.045 g, 0.20 mmol) affording **18m** as clear oil. The diastereomer ratio was determined as 13:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.17-5.12 (minor diastereomer) and δ 5.04-5.01 (major diastereomer). As product **7h** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20m** (0.050 g, 0.17 mmol, 87% yield, >20:1 dr) for final characterization. Analytical data for **18m: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 – 7.69 (m, 2H), 7.49 – 7.36 (m, 6H), 7.28 – 7.16 (m, 7H), 5.78-5.75 (m, 1H), 5.04 – 5.00 (m, 2H), 3.92-3.88 (m, 1H), 3.69-3.65 (m, 1H), 3.41-3.36 (m, 1H), 3.21-3.17 (m, 1H), 3.07-2.86 (m, 2H), 2.87 (dd, *J* = 12.4, 3.5 Hz, 1H), 2.77 (t, *J* = 12.0 Hz, 1H), 2.32-2.30 (m, 2H), 1.42-1.36 (m, 3H), 1.26 – 1.18 (m, 2H), 0.54-0.47 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.5, 168.4, 140.2, 140.1, 137.0, 135.8, 129.8, 129.2, 128.4,

128.4, 128.2, 128.1, 128.0, 127.9, 126.0, 116.9, 63.8, 48.8, 46.7, 42.5, 39.4, 37.8, 25.7, 25.4, 24.3; **IR** (thin film): 1627, 1444, 1228, 697 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.27; **HRMS** (ESI): Calcd. for $C_{31}H_{34}N_2O$: ([M+H]): 451.2749, Found: 451.2743; **HPLC** IC, 92% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 9.0 min $t_{R\ (minor)}$ = 6.8 min, 94:6 er; **$[\alpha]_D$** = +29.5 (*c* = 0.05, DCM).

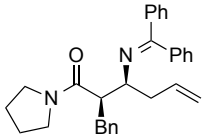
Analytical data for **20m:** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.20-



7.17 (m, 3H), 5.80 (dddd, *J* = 16.9, 10.7, 8.4, 6.1 Hz, 1H), 5.18 – 5.14 (m, 2H), 3.70-3.66 (m, 1H), 3.24 – 3.15 (m, 2H), 3.06 – 2.89 (m, 5H), 2.34 – 2.

30 (m, 1H), 2.08-2.02 (dt, *J* = 13.8, 8.2 Hz, 1H), 1.68 (bs, 2H), 1.45-1.39 (m, 3H), 1.27 – 1.19 (m, 2H), 0.63-0.56 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.3, 140.0, 135.5, 129.2, 128.3, 126.1, 118.0, 52.7, 49.0, 46.7, 42.7, 40.2, 35.3, 25.9, 25.5, 24.3.; **IR** (thin film): 1622, 1453, 1248, 703 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.32; **HRMS** (ESI): Calcd. for $C_{18}H_{26}N_2O$: ([M+Na]): 309.1898, Found: 309.1928; **$[\alpha]_D$** = +3.3 (*c* = 0.02, DCM).

(*2R,3S*)-2-benzyl-3-((diphenylmethylene)amino)-1-

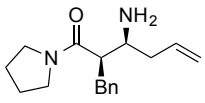


(pyrrolidin-1-yl)hex-5-en-1-one (18n): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16n** (0.055 g, 0.24 mmol), and allyl amine **2a** (0.045 g, 0.20 mmol) affording **18n** as clear oil. The crude diastereomer ratio was determined as 11:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.17-5.12 (minor diastereomer) and δ

5.04-5.01 (major diastereomer). As product **18n** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20n** (0.046 g, 0.17 mmol, 84% yield, >20:1 dr) for final characterization.

Analytical data for **18n:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 – 7.66 (m, 2H), 7.45 – 7.34 (m, 6H), 7.26 – 7.14 (m, 7H), 5.82-5.75 (m, 1H), 5.00 – 4.97 (m, 2H), 3.91-3.87 (m, 1H), 3.32-3.25 (m, 2H), 3.22-3.18 (m, 1H), 3.10-3.06 (m, 1H), 2.83 (dd, *J* = 12.5, 3.6 Hz, 1H), 2.73 (t, *J* = 12.1 Hz, 1H), 2.38 – 2.32 (m, 3H), 1.66-1.57 (m, 2H), 1.54-1.49 (m, 1H), 1.37-1.33 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 171.9, 168.3, 140.2, 140.0, 137.0, 135.9, 129.8, 129.1, 128.4, 128.4, 128.2, 128.0, 128.0, 128.0, 126.1, 116.8, 63.6, 52.5, 46.3, 45.3, 39.5, 37.6, 25.7, 24.1; **IR** (thin film): 1629, 1445, 765, 697 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.16; **HRMS** (ESI): Calcd. for $C_{30}H_{32}N_2O$: ([M+H]): 437.2593, Found: 437.2584; **HPLC** ID, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 11.6 min $t_{R\ (minor)}$ = 8.7 min, 95:5 er; **[α]$_D$** = +48.6 (*c* = 0.04, DCM).

Analytical data for **20n:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 – 7.14 (m, 5H), 5.81–



5.75 (m, 1H), 5.13 – 5.10 (m, 2H), 3.33-3.25 (m, 2H), 3.18 – 3.08 (m, 2H), 2.99 – 2.91 (m, 2H), 2.65 – 2.61 (m, 1H), 2.44-2.40 (m, 1H), 2.34-2.30 (m, 1H), 2.20-2.05 (m, 1H), 1.68-1.60 (m, 4H), 1.55-1.49 (m, 1H), 1.42-1.35 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.7, 139.9, 135.5, 129.0, 128.2, 126.2, 118.0, 52.3, 52.2, 46.3, 45.3, 40.2, 35.0, 25.7, 24.1; **IR** (thin film): 1620, 1452 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.35; **HRMS** (ESI): Calcd. for $C_{17}H_{24}N_2O$: ([M+H]): 273.1978, Found: 273.1960; **[α]$_D$** = +47.0 (*c* = 0.01, DCM).

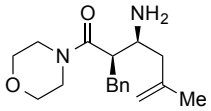
(*2R,3S*)-2-benzyl-3-((diphenylmethylene)amino)-N,N-dimethylhex-5-enamide (18o): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16o** (0.049 g, 0.24 mmol), and allyl amine **2a** (0.045 g, 0.20 mmol) affording **18o** (0.072 g, 0.17 mmol, 87% yield, 13:1 dr) as clear oil. The diastereomer ratio was determined as 8:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.18-5.14 (minor diastereomer) and δ 5.05-5.01 (major diastereomer).

Analytical data for **18o: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 2H), 7.46 – 7.34 (m, 6H), 7.26 – 7.14 (m, 8H), 5.78 – 5.75 (m, 1H), 5.03 – 4.97 (m, 2H), 3.91-3.87 (m, 1H), 3.32 (ddd, *J* = 12.0, 8.7, 3.5 Hz, 1H), 2.86 (dd, *J* = 12.5, 3.5 Hz, 1H), 2.75-2.71 (m, 4H), 2.41 (s, 3H), 2.32-2.29 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.5, 168.4, 140.2, 134.0, 137.0, 135.8, 129.8, 129.0, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 126.1, 116.9, 63.7, 49.5, 39.4, 37.7, 36.9, 35.2; **IR** (thin film): 1637, 1445, 913, 765, 698 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.16; **HRMS** (ESI): Calcd. for $C_{28}H_{30}N_2O$: ([M+H]): 411.2436, Found: 411.2428; **HPLC** IC, 90% hexanes/IPA, flow rate = 1.0 mL/min, λ = 230 nm, $t_{R\ (major)}$ = 7.6 min $t_{R\ (minor)}$ = 6.6 min, 93:7 er; **$[\alpha]_D$** = +53.7 (*c* = 0.03, DCM).

(*2R,3S*)-2-benzyl-3-((diphenylmethylene)amino)-5-methyl-1-morpholinohex-5-en-1-one (18p): The title compound was prepared according to General Procedure E (Method 1) using β-formyl amide **16a** (0.059 g, 0.24 mmol), and allyl amine **2b** (0.047 g, 0.20 mmol) affording **18p** as clear oil. The crude diastereomer ratio

was determined as 5:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 7.57-7.55 (minor diastereomer) and δ 7.68-7.67 (major diastereomer). As product **18p** was inseparable from minor unidentified impurities it was deprotected using General Procedure F to amine **20p** (0.036 g, 0.12 mmol, 60% yield, >20:1 dr) for final characterization.

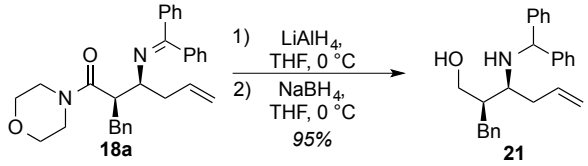
Analytical data for **18p: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68-7.67 (m, 2H), 7.47 – 7.36 (m, 6H), 7.30-7.17 (m, 7H), 4.79-4.60 (m, 2H), 3.97-3.94 (m, 1H), 3.73-3.67 (m, 1H), 3.57-3.53 (m, 1H), 3.33 – 3.23 (m, 4H), 3.19 – 3.15 (m, 1H), 2.97-2.92 (m, 2H), 2.84-2.80 (m, 1H), 2.57-2.53 (m, 1H), 2.30 (dd, *J* = 13.0, 8.2 Hz, 1H), 2.18 (dd, *J* = 13.0, 3.5 Hz, 1H), 1.45 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.0, 168.2, 142.7, 140.2, 139.9, 136.7, 129.8, 129.2, 128.5, 128.3, 128.3, 128.3, 128.2, 128.0, 126.3, 113.8, 66.6, 66.1, 62.6, 49.0, 46.1, 43.4, 41.8, 37.8, 23.0; **IR** (thin film): 1736, 1625, 1444, 1228, 1114, 700 cm^{-1}; **TLC** (15% acetone/hexane): R_f = 0.18; **HRMS** (ESI): Calcd. for $C_{31}H_{34}N_2O_2$: ([M+H]): 467.2698, Found: 467.2690; **[α]$_D$** = -7.4 (*c* = 0.03, DCM).



Analytical data for **20p: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.03 – 7.24 (m, 2H), 7.23 – 7.19 (m, 3H), 4.91 (s, 1H), 4.84 (s, 1H), 3.77-3.74 (m, 1H), 3.60 – 3.55 (m, 1H), 3.35 – 3.23 (m, 4H), 3.15 (ddd, *J* = 13.3, 8.2, 3.2 Hz, 1H), 3.08 (dd, *J* = 12.4, 3.7 Hz, 1H), 2.98 – 2.90 (m, 2H), 2.86-2.82 (m, 1H), 2.54 (ddd, *J* = 11.3, 8.1, 2.9 Hz, 1H), 2.23 (dd, *J* = 13.3, 4.2 Hz, 1H), 1.98 (dd, *J* = 13.3, 9.6 Hz, 1H), 1.76 (s, 3H), 1.69 (bs, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.8, 142.8, 139.7, 129.2, 128.5, 126.5, 113.6, 66.7, 66.1,

50.5, 49.3, 46.1, 44.2, 41.9, 35.5, 21.8, **IR** (thin film): 1114 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.35; **HRMS** (ESI): Calcd. for $C_{18}H_{26}N_2O_2$: ([M+H]): 303.2078, Found: 303.2065; **HPLC** ID, 30% hexanes/IPA, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 11.5 min $t_{R\ (minor)}$ = 9.0 min, 80:20 er; **$[\alpha]_D$** = +9.6 (*c* = 0.006, DCM).

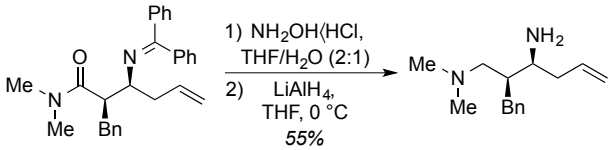
4.3.9 Procedure for the Generation of Amino Alcohol 21



A flame dried 1-dram vial equipped with a magnetic stir bar was charged with **18a** (0.025 g, 0.06 mmol, 1.0 equiv) and THF (0.6 mL) then cooled to 0 ˚C. A single portion of $LiAlH_4$ (0.22 mmol, 4.0 equiv) was added to the mixture which was slowly warmed to rt then stirred for 1 h. The solution was then cooled to 0 ˚C, quenched by slow addition of 2 M NaOH (0.2 mL), filtered through a short plug of celite with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. The crude aldehyde was dissolved in MeOH and cooled to 0 ˚C. A single portion of $NaBH_4$ (0.12 mmol, 2.0 equiv) was added to the mixture, stirred for 10 min, quenched with saturated NH_4Cl (3 mL), then partitioned between EtOAc (10 mL) and H_2O (10 mL). The layers were separated and the organic layer was further washed with H_2O (2 x 10 mL) and brine (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude residue was purified by column chromatography using a gradient of 15% acetone/hexane affording **21** (0.020 g, 0.05 mmol, 98% yield). Analytical data for **21: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 11H), 7.11-7.06 (m, 4H), 5.52-5.43 (m, 1H), 5.18 – 5.11 (m, 2H), 4.99

(s, 1H), 3.78 (dd, *J* = 10.8, 8.8 Hz, 1H), 3.67 (dd, *J* = 10.8, 3.6 Hz, 1H), 2.76 (td, *J* = 6.9, 2.6 Hz, 1H), 2.53 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.43 – 2.32 (m, 4H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 142.5, 142.4, 140.1, 135.5, 128.8, 128.5, 128.5, 128.4, 127.6, 127.4, 127.2, 127.1, 126.0, 118.5, 64.9, 63.2, 56.1, 41.0, 33.6, 33.5.; **IR** (thin film): 1708, 1360, 1221, 703 cm^{-1}; **TLC** (40% EtOAc/hexane): R_f = 0.18; **HRMS** (ESI): Calcd. for $C_{26}H_{29}NO$: ([M+H]): 372.2327, Found: 372.2320; **$[\alpha]_D$** = -2.8 (*c* = 0.009, DCM).

4.3.10 Procedure for the Generation of 1,3-Diamine 22

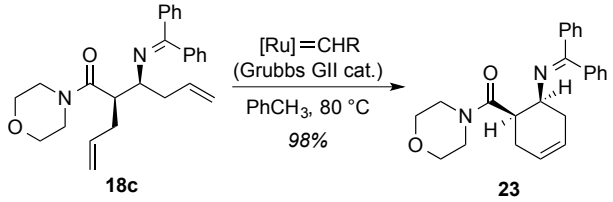


18o **22**

To a 1-dram vial was added **18o**, (0.030 g, 0.07 mmol, 1.0 equiv) hydroxylamine hydrochloride (035 mmol, 5.0 equiv), and 2:1 THF:H_2O (0.7 mL, 0.1 M). This solution was stirred at rt for 18 h then partitioned between 2M HCl (10 mL) and Et_2O (10 mL). The aqueous layer was washed with Et_2O (3 x 10 mL), basified to pH 12 with 2M NaOH, extracted with DCM (3x 50 mL), dried over $MgSO_4$ then concentrated *in vacuo*. The remaining residue was then dissolved in THF (0.6 mL) and cooled to 0 ˚C. A single portion of $LiAlH_4$ (0.22 mmol, 4.0 equiv) was added to the mixture which was slowly warmed to rt then stirred for 1 h. The solution was then cooled to 0 ˚C, quenched by slow addition of 2 M NaOH (0.2 mL), filtered through a short plug of celite with DCM, dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The crude residue was purified by column chromatography using a gradient of 2.5-10% MeOH/DCM (with 0.1% AcOH

modifier) affording **22** (0.009 g, 0.04 mmol, 53% yield, >20:1 dr). Analytical data for **10: ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 2H), 7.22 – 7.19 (m, 3H), 5.92-5.84 (m, 1H), 5.26 – 5.23 (m, 2H), 4.27 (bs, 2H), 3.38-3.34 (m, 1H), 2.81-2.80 (m, 1H), 2.73-2.70 (m, 1H), 2.61 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.50-2.46 (m, 1H), 2.34-2.20 (m, 8H), 2.00-1.99 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 138.3, 133.2, 128.9, 128.7, 126.6, 119.9, 60.3, 53.9, 45.4, 37.2, 36.1, 33.3, 29.8; **IR** (thin film): 1495, 1454, 1229, 911, 699 cm^{-1}; **TLC** (10% MeOH/DCM): R_f = 0.36; **HRMS** (ESI): Calcd. for $C_{15}H_{24}N_2$: ([M+H]): 233.2017, Found: 233.2012; **$[\alpha]_D$** = 35.52 (*c* = 0.003, DCM).

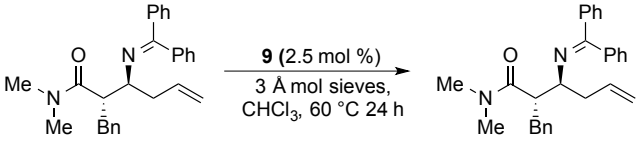
4.3.11 Procedure for the Generation of Cyclohexene 23



To a flame dried 1-dram vial under an atmosphere of N_2 was added Grubb's second generation catalyst,[39] (0.001 g, 0.003 mmol, 0.05 equiv), **18c** (0.020 g, 0.05 mmol, 1.0 equiv) and $PhCH_3$ (1.0 mL, 0.05 M). This solution was stirred at 80 ˚C for 2 h then loaded directly onto a short plug of SiO_2 and eluted with a gradient of 10-25% acetone/hexane providing **23** (0.018 g, 0.05 mmol, 97% yield) without need for further purification. Analytical data for **23: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61-7.59 (d, *J* = 7.4 Hz, 2H), 7.50 – 7.41 (m, 3H), 7.36 – 7.29 (m, 4H), 7.15 – 7.14 (m, 2H), 5.94-5.91 (m, 1H), 5.74 – 5.71 (m, 1H), 3.94-3.93 (m, 1H), 3.71 – 3.55 (m, 3H), 3.44 – 3.35 (m, 2H), 3.28 – 3.22 (m, 2H), 3.16-3.11 (m, 1H), 2.94 – 2.87 (m, 2H), 2.44-2.39 (m, 1H), 2.20 – 2.16 (m, 1H), 2.10-2.06 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.69, 167.15, 140.23, 136.91, 129.79, 128.86, 128.38, 128.07, 127.92, 126.53, 123.23, 66.69, 66.21, 56.08, 56.05, 45.75, 41.74, 40.78, 33.04, 24.43; **IR** (thin film): 1641, 1443, 1114 cm^{-1}; **TLC** (25% EtOAc/hexane): R_f = 0.09; **HRMS** (ESI): Calcd. for $C_{24}H_{26}N_2O_2$: ([M+H]): 375.2072, Found: 375.2065; **$[\alpha]_D$** = -9.6 (*c* = 0.01, DCM).

4.3.12 Testing for Reversibility of [3,3]-Aza Cope Rearrangement



7o - minor
>20:1 dr

7o - minor
>20:1 dr

To eliminate speculation that the aza-Cope might be a reversible process the minor diastereomer of product **18o** (0.013 g, 0.03 mmol) was isolated in 20:1 dr and stirred with catalyst **9** (0.001g, 0.001 mmol) and $CDCl_3$ (0.3 mL, 0.1 M) at 60 °C for 24 hours. Direct ^{1}H NMR analysis of the reaction mixtures showed no change in diastereomeric ratio implicating a non-reversible [3 , 3] process.

4.4 REFERENCES

1) Rueping, M.; Antonchick, A. P. “Catalytic asymmetric aminoallylation of aldehydes: a catalytic enantioselective aza-Cope rearrangement.” *Angew. Chem. Int. Ed.* **2008,** *47,* 10090-10093.

2) Ren, H.; Wulff, W. D. “Direct catalytic asymmetric aminoallylation of aldehydes: synergism of chiral and nonchiral brønsted acids.” *J. Am. Chem. Soc.* **2011,** *133,* 5656-5659.

3) Nubbemeyer, U. “Recent advances in asymmetric [3,3]-sigmatropic rearrangements." *Synthesis,* **2003,** *7*, 961-1008.

4) Castro A. M. M. “Claisen rearrangement over the past nine decades.” *Chem. Rev.* **2004,** *104,* 2939-3002.

5) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. “Catalysis of the Claisen rearrangement.” *Tetrahedron* **2008,** *64,* 597-643.

6) Ito, T.; Overman, L. E.; Wang, J. “Enantioselective synthesis of angularly substituted 1-azabicyclic ring systems: dynamic kinetic resolution using aza-Cope rearrangements.” *J. Am. Chem. Soc.* **2010,** *132,* 3272-3273.

7) Aron, Z. D.; Ito, T.; May, T. L.; Overman, L. E.; Wang, J. “Enantioselective synthesis of angularly substituted 1-azabicylic rings: coupled dynamic kinetic epimerization and chirality transfer.” *J. Org. Chem.* **2013,** *78,* 9929-9948.

8) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. “Enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid.” *Angew. Chem., Int. Ed.* **2004,** *43,* 1566-1568.

9) Uraguchi, D.; Terada, M. “Chiral Brønsted acid-catalyzed direct Mannich reactions via electrophilic activation.” *J. Am. Chem. Soc.* **2004,** *126,* 5356-5357.

10) Terada, M. “Chiral phosphoric acids as versatile catalysts for enantioselective transformations.” *Synthesis* **2010,** *12,* 1929-1982.

11) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. “Chiral BINOL-derived phosphoric acids: privileged Brønsted acid organocatalysts for C–C bond formation reactions.” *Org. Biomol. Chem.* **2010,** *8,* 5262-5276.

12) Rueping, M.; Kuenkel, A.; Atodiresei, I. “Chiral Brønsted acids in enantioselective carbonyl activations – activation modes and applications.” *Chem. Soc. Rev.* **2011,** *40,* 4539-4549.

13) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. “Complete field guide to asymmetric BINOL-phosphate derived Brønsted acid and metal catalysis: history and classification by mode of activation; Brønsted acidity, hydrogen bonding, ion pairing, and metal phosphates.” *Chem. Rev.* **2014,** *114,* 9047-9153.

14) Hoffman, S.; Seayad, A. M.; List, B. “A powerful Brønsted acid catalyst for the organocatalytic asymmetric transfer hydrogenation of imines.” *Angew. Chem. Int. Ed.* **2005,** *44,* 7424-7427.

15) Yang, J.; Wu, S.; Chen, F.-X. “Chiral sodium phosphate catalyzed enantioselective 1,4-addition of TMSCN to aromatic enones.” *Synlett,* **2010,** *18,* 2725-2728.

16) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. “Developments in asymmetric hydrogenation from an industrial perspective.” *Acc. Chem. Res.* **2007,** *40,* 1385-1393.

17) Rioz-Martínez A.; Cuetos, A.; Rodríguez, C.; de Gonzalo, G.; Lavandera, I.; Fraaije, M. W.; Gotor, V. “Dynamic kinetic resolution of α-substituted β-ketoesters catalyzed by Baeyer–Villiger monooxygenases: access to enantiopure α-hydroxy esters.” *Angew. Chem. Int. Ed.* **2011,** *50,* 8387-8390.

18) Cohen, D. T.; Eichman, C. C.; Phillips, E. M.; Zarefsky, E. R.; Scheidt, K. A. “Catalytic dynamic kinetic resolutions with *N*-heterocyclic carbenes: asymmetric synthesis of highly substituted β-lactones.” *Angew. Chem. Int. Ed.* **2012,** *51,* 7309-7313.

19) Johnston, R. C.; Cohen, D. T.; Eichman, C. C.; Scheidt, K. A.; Cheong, P. H-Y. “Catalytic kinetic resolution of a dynamic racemate: highly stereoselective β-lactone formation by *N*-heterocyclic carbene catalysis.” *Chem. Sci.* **2014,** *5,* 1974-1982.

20) Kobler, C.; Effenberger, F. “Hydroxynitrile lyase-catalyzed addition of HCN to 2-substituted cyclopentanones.” *Tetrahedron: Asymmetry* **2004,** *15,* 3731-3742.

21) Wang, Y.; Shen, Z.; Li, B.; Zhang, Y.; Zhang, Y. “Dynamic kinetic resolution of 2-oxo-3-aryl-succinates by organocatalyzed aldolization.” *Chem. Commun.* **2007,** 1284-1286.

22) Yang, J.; Wang, T.; Ding, Z.; Shen, Z.; Zhang, Y.” Highly diastereo- and enantioselective organocatalytic addition of acetone to β-substituted α-ketoesters *via* dynamic kinetic resolution.” *Org. Biomol. Chem.* **2009,** *7,* 2208-2213.

23) Kiss, L.; Cherepanova, M.; Fülöp, F. “Recent advances in the stereoselective syntheses of acyclic disubstituted $\beta^{2,3}$-amino acids.” *Tetrahedron* **2015,** *71,* 2049-2069.

24) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. “Asymmetric acylation reactions of chiral imide enolates. The first direct approach to the construction of chiral β-dicarbonyl synthons.” *J. Am. Chem. Soc.* **1984,** *106,* 1154-1156.

25) Nguyen, H.; Ma, G.; Romo, D. “$A^{1,3}$-strain enabled retention of chirality during bis-cyclization of β-ketoamides: total synthesis of (−)-Salinosporamide A and (−)-Homosalinosporamide A.” *Chem. Commun.* **2010,** *46,* 4803-4805.

26) Fujita, M.; Hiyama, T. “Highly stereoselective reduction of α-substituted β-keto amides by means of hydrosilane-fluoride ion and hydrosilane-acid reagent. A practical approach to aldols of both threo and erythro configurations.” *J. Am. Chem. Soc.* **1985,** *107,* 8294-8296.

27) Roush, W. R.; Palkowitz, A. D. “Synthesis of the C(1)-C(15) segment of Streptovaricin D.” *J. Org. Chem.* **1989,** *54,* 3009-3011.

28) Soucy, F.; Grenier, L.; Behnke, M. L.; Destree, A. T.; McCormack, T. A.; Adams, J.; Plamondon, L. “A novel and efficient synthesis of a highly active analogue of *clasto*-Lactacystin β-lactone.”*J. Am. Chem. Soc.* **1999,** *121,* 9967-9976.

29) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. “Application of complex aldol reactions to the total synthesis of Phorboxazole B.” *J. Am. Chem. Soc.* **2000,** *122,* 10033-10046.

30) Flores-Morales, V.; Fernández-Zertuche M.; Ordóñez, M. “Highly diastereoselective addition of Et_2AlCN to β-keto amides derived from (*S*)-4-isopropyl-2-oxazolidinone.” *Tetrahedron: Asymmetry* **2003,** *14,* 2693-2698.

31) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2006,** *128,* 84-86.

32) CCDC 1423130 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

33) Romanov-Michailidis F.; Guénée L.; Alexakis, A. “Enantioselective Organocatalytic Iodination-Initiated Wagner–Meerwein Rearrangement.” *Org. Lett.* **2013,** *15,* 5890-5893.

34) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. “Asymmetric Cross-Dehydrogenative Coupling Enabled by the Design and Application of Chiral Triazole-Containing Phosphoric Acids.” *J. Am. Chem. Soc.* **2013,** *135,* 14044-14047.

35) Clark, C. T.; Milgram, B. C.; Scheidt, K. A. “Efficient synthesis of acylsilanes using morpholine amides.” *Org. Lett.* **2004,** *6,* 3977-3980.

36) Saifina, D. F.; Ganieva, V. R.; Mamedov, V. A. “Darzens reaction in the synthesis of 3-α-chloroalkyl)quinoxalin-2(1*H*)-ones.” *Russ. J. Org. Chem.* **2009,** *45,* 1244-1247.

37) Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. “Efficient synthesis of acylsilanes using morpholine amides.” *Tetrahedron Lett.* **1999,** *40,* 4227-4230.

38) Corbett, M. T.; Johnson J. S. “Dynamic kinetic asymmetric transformations of β-stereogenic α-ketoesters by direct aldolization.” *Angew. Chem., Int. Ed.* **2013,** *53,* 255-259.

39) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. “Synthesis and activity of a new generation of ruthenium-based olefin metathesis catalysts coordinated with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligands.” *Org. Lett.* **1999,** *1,* 953-956. Sigma Aldrich catalog number 569747.