STRATEGIES FOR THE SYNTHESIS AND USE OF β-STEREOGENIC α-KETO ESTERS

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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.

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ABSTRACT

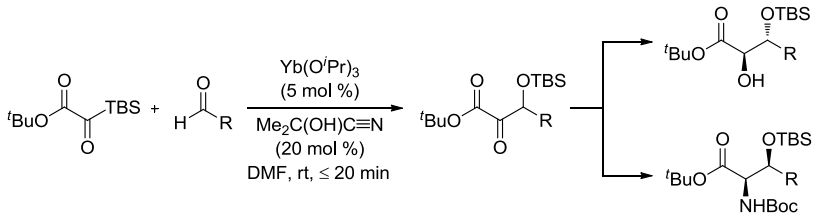
KIMBERLY MICHELLE STEWARD: Strategies for the Synthesis and Use of β-Stereogenic α-Keto Esters
(Under the direction of Jeffrey S. Johnson)

I. Extant Methods for the Preparation of α-Keto Esters

An overview of the synthetic methods to prepare α-keto esters is presented, with a particular focus on strategies to incorporate a stereocenter at the β-position.

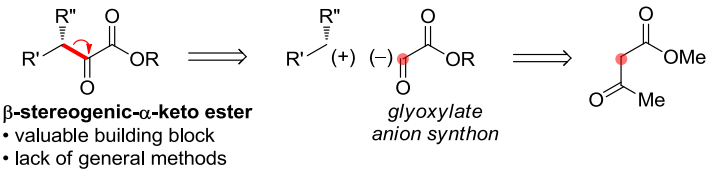
II. Catalytic Nucleophilic Glyoxylation of Aldehydes

The synthesis of β-silyloxy α-keto esters via a cyanide catalyzed benzoin-type reaction with silyl glyoxylates and aldehydes is described. Critical to the success of the reaction was identifying $Yb(O^iPr)_3$ and acetone cyanohydrin as a mild source of cyanide to prevent isomerization of the products to the corresponding α-silyloxy β-keto esters. Several secondary transformations add to the utility to the α-keto ester products. Of the methods available to prepare β-hydroxy α-keto acid derivatives, this method provides the most direct route and displays the broadest substrate scope.



III. Asymmetric Synthesis of α-Keto Esters via Cu(II)-Catalyzed Aerobic Deacylation of Acetoacetate Alkylation Products

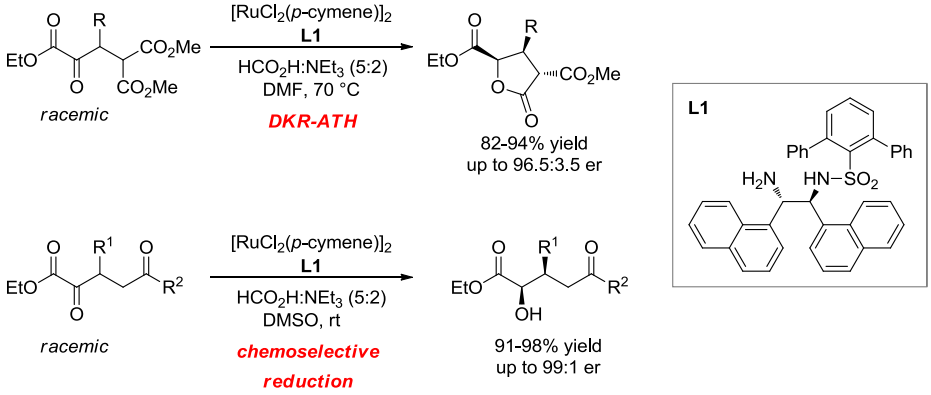
A simple and efficient method for the preparation of β-stereogenic α-keto esters is described using a copper(II)-catalyzed aerobic deacylation of substituted acetoacetate esters. The substrates for the title process arise from catalytic, enantioselective conjugate addition and alkylation reactions of acetoacetate esters. The mild conditions do not induce racemization of the incipient enolizable α-keto ester. The reaction is tolerant of a number esters, certain ketones, ketals and nitro groups and establishes synthetic equivalency between acetoacetate esters and the glyoxylate anion synthon.



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

The development of the first highly selective dynamic kinetic resolution of β-stereogenic α-keto esters via asymmetric transfer hydrogenation using a newly designed (arene)Ru(monosulfonamide) catalyst is described. For substrates incorporating a diester at the γ-postion, spontaneous lactonization of the nascent α-hydroxyl group onto the pendant ester occurs to provide trisubstituted γ-butyrolactones with complete diastereocontrol.

Extension of this method to β-substituted α,δ-diketo esters results in chemoselective dynamic reduction of the α-keto ester providing highly enriched δ-keto α-hydroxy esters.



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To my family
and
in loving memory of my grandmother
Erma R. Durden
(1931–2011)

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LIST OF ABBREVIATIONS AND SYMBOLS

2D-NMR	two-dimensional nuclear magnetic resonance
Ac	acetate
Ar	aryl
aq	aqueous
ATH	asymmetric tranfer hydrogenation
atm	atmospheres
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
BOC	benzyloxycarbonyl
br	broad
br s	broad singlet
^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CSA	camphorsulfonic acid
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
C–C	carbon-carbon bond
cat	catalytic amount or catalyst
conv	conversion
COSY	correlated spectroscopy
*m*CPBA	*meta*-chloroperoxybenzoic acid

d	doublet or days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
dd	doublet of doublet
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
ddt	doublet of doublet of triplets
DIBAL–H	diisobutylaluminum hydride
dq	doublet of quartet
DMAP	4-*N,N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DKR	dyamic kinetic resolution
dr	diastereomeric ratio
dt	doublet of triplet
E^+ or El	electrophile
eq	equation
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FID	flame ionization detector
h	hour

^{1}H NMR	proton nuclear magnetic resonance spectroscopy
n-hexanal	*normal*-hexanal
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie
L or Ln	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LRMS	low resolution mass spectroscopy
M	metal or molarity
m	multiplet
Me	methyl
MeCN	acetonitrile
Menth	menthyl
MeOH	methanol
2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mp	melting point

MPM	*para*-methoxybenzyl
MPV	Meerwein-Ponndorf-Verley
n	number of atoms or counterions
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NBSH	*o*-nitrobenzenesulfonylhydrazide
nd	not determined
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
nr	no reaction
Nu	nucleophile
OO	Oppenauer Oxidation
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
ppm	parts per million
PPTS	pyrdinium *p*-toluenesulfonate
^{i}Pr	*iso*-propyl
q	quartet
R	substituent
R_f	retention factor
rac	racemic
RCHO	aldehyde
rt	room temperature

s	singlet
SFC	supercritical fluid chromatography
S_N2	bimolecular nucleophilic substitution
T	temperature
t	triplet
$t_{1/2}$	half-life
t_r	retention time
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TEA	triethylamine
TEMPO	tetramethylpiperidine-*N*-oxide
TES	triethylsilyl
TMS	trimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tr	trityl or triphenylmethyl
triflate	trifluoromethanesulfonate
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	anionic ligand, halide, substituent, or number
X_c^*	chiral auxiliary
Z	*zusammen*

Å	Ångstrom
[α]	optical rotation
δ	chemical shift or partial charge
μL	microliter

CHAPTER ONE

EXTANT METHODS FOR THE PREPARATION OF α-KETO ESTERS

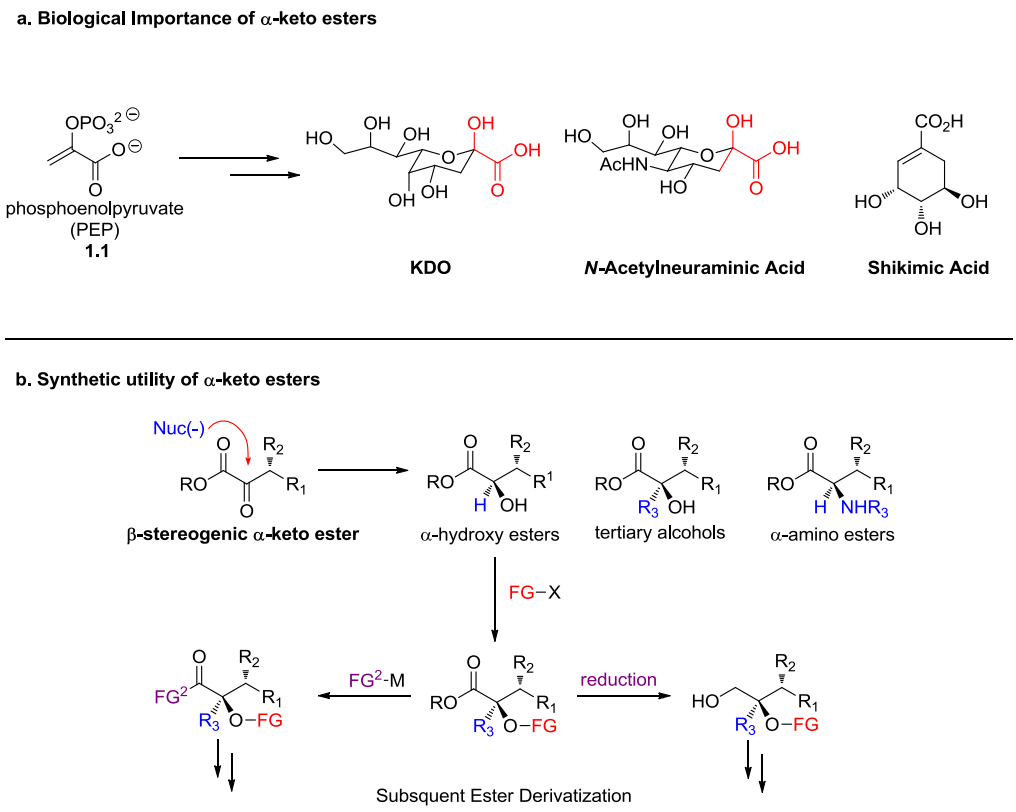
1.1 Introduction

α-Keto acids are of considerable importance in biological systems as they play integral roles in various metabolic and biosynthetic pathways.[1] Pyruvic acid is the simplest derivative, which in its active form as phosphoenol pyruvate (PEP) **1.1**, undergoes aldolase-catalyzed C–C bond formation to aldehydes in the biosynthesis of the sialic and ulosonic acids (Figure 1a).[2] Important natural products including *N*-acetylneuraminic acid (NeuAc), 3-deoxy-D-*manno*-2-octulosonic acid (KDO), and 3-deoxy-D-arabino-2-heptulosonic acid 7-phosphate (DAHP) are produced in this manner. These are distinct classes of carbohydrates which exhibit a wide range of biological activity due to their participation in cell surface interactions. Accordingly, the α-keto acid subunit has been incorporated into peptidic molecules to generate potent inhibitors of proteolytic enzymes such as α-chymotrypsin and the cysteine proteinase calpain.[3] The ability to prepare these and other synthetic analogues to evaluate structure-activity relationships hinges upon convenient synthetic methods for the direct incorporation of the α-keto acid moiety.

For the synthetic chemist, the α-keto ester presents itself as a unique and versatile functional group.[4-5] Due the inductive effects of the adjacent ester and opportunities for chelation, α-keto esters display an enhanced electrophilicity relative to a normal ketone.[6] As

a result, they react readily with nucleophiles, providing access to a number of useful organic building blocks including α-hydroxy[7] and α-amino esters[8] (Figure 1b). In addition, subsequent derivatization of the pendant ester permits additional opportunities to introduce molecular complexity; however, despite these useful attributes, the development of a general method for the de novo introduction of the α-keto ester functionality has not been realized, particularly for those α-keto esters bearing a β-stereogenic center. The purpose of this initial chapter is to provide an overview of the synthetic methods available for the preparation of α-keto esters, with a particular focus on strategies to incorporate a stereocenter at the β-position.

Figure 1-1. Synthetic Utility of α-Keto Esters

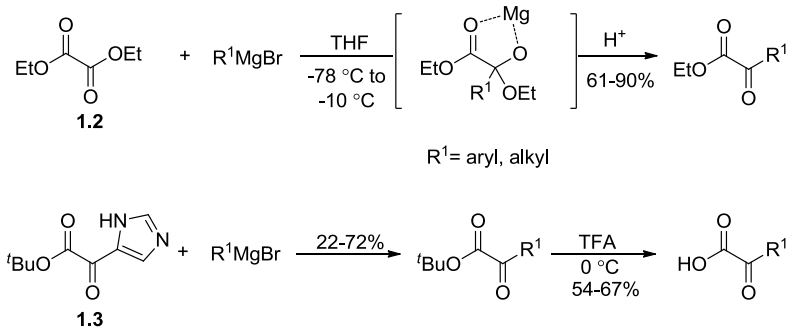


1.2 Synthetic Strategies for the Preparation of Achiral α-Keto Esters

1.2.1 Oxalic Acid Derivatives

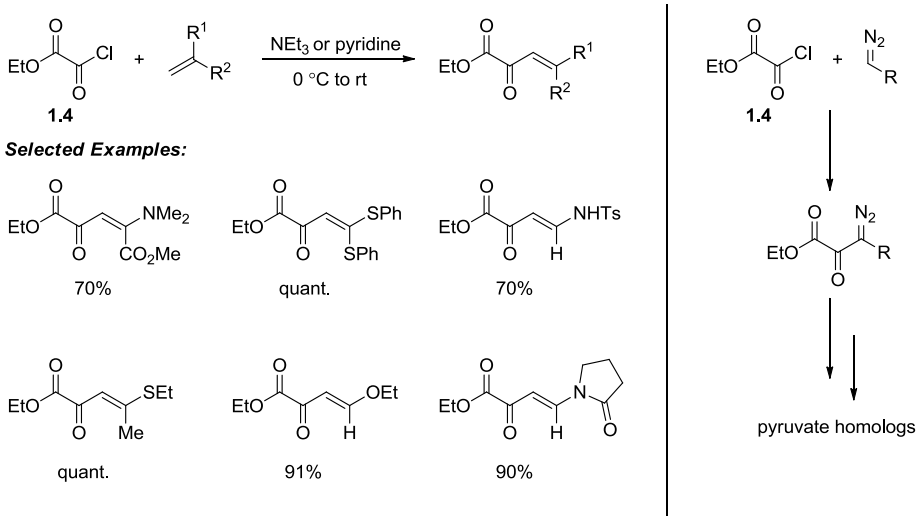
The most direct and widely used method for the preparation of simple aryl and alkyl α-keto esters is the addition of an organometallic to diethyl oxalate **1.2** (Scheme 1-1). This approach was first disclosed by Wieland[9] using Grignard nucleophiles, but the reaction was reported to proceed in low yield. A number of modified procedures have since been developed that deliver synthetically useful yields and the method that is commonly employed uses a slight excess of Grignard reagent (1.2 equivalents) at low temperatures.[10] Notably, over-addition to the ester is not observed; this is attributed to the chelation-stabilized tetrahedral intermediate allowing the ketone to only be exposed after hydrolytic work-up. The isolated yields for alkyl α-keto esters tend to be lower than aryl derivatives due to the volatility of the products. This methodology is not limited to diethyl oxalate and Grignards; dimethyl and dibenzyl oxalates and organolithium, –sodium, and –potassium nucleophiles are also commonly used. If the α-keto acid is desired, *tert*-butyl oxalyl imidazole[11] **1.3** is used due to the facile acid-catalyzed cleavage of the *tert*-butyl ester.

Scheme 1-1. α-Keto Ester Synthesis Using Diethyl Oxalate



The Friedel-Crafts acylation with ethyl oxalyl chloride **1.4** has found widespread use in the preparation of a variety of α-keto ester substrates (Scheme 1-2). In addition to aryl nucleophiles, activated 1-alkenes, including dithio acetals, vinyl sulfides, and *N*-vinylamides, readily react to provide β,γ-unsaturated α-keto esters;[12] enol ethers[13] and enamines[14] react analogously to give α,γ-dioxoesters and β,γ-enamino esters respectively. This methodology has been proven to be particularly useful for the acylation of diazoalkanes[15] which gives access to pyruvate and its higher homologues and has been strategically used in the chain elongation of diazo sugar derivatives.[16]

Scheme 1-2. α-Keto Ester Synthesis via Friedel-Crafts Acylations with Ethyl Oxalyl Chloride



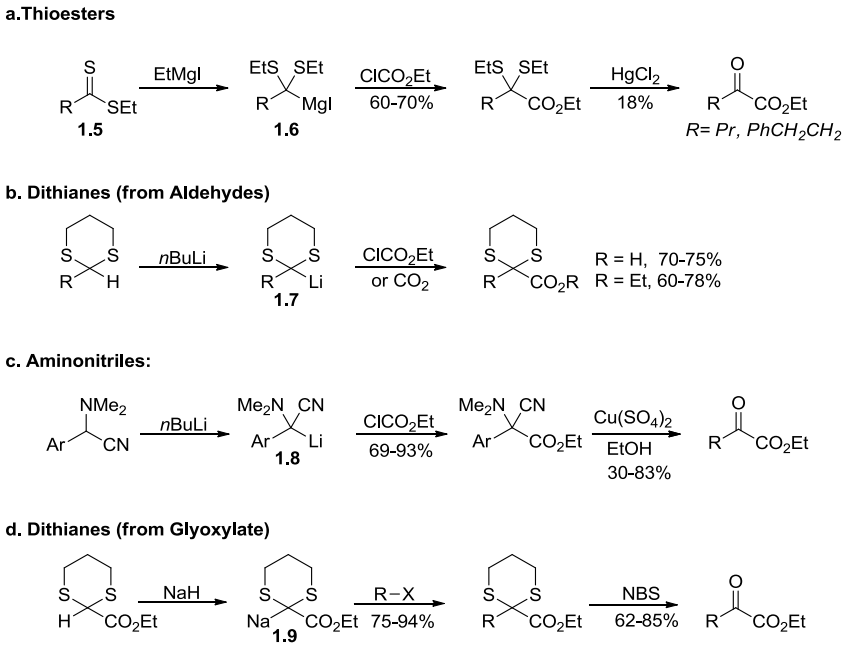
1.2.2 Acylation Reactions

1.2.2.1 Umpolung Reagents

The acylation of acyl anion equivalents with ethyl chloroformate is another common approach to α-keto ester synthesis (Scheme 1-3). Meyers has shown that thioesters **1.5**

display umpolung reactivity (polarity reversal of functional groups) following thiophilic addition of Grignard reagents to furnish magnesio dithio acetals **1.6** (Scheme 1-3a).[17] These intermediates readily react with ethyl chloroformate to provide the corresponding α-keto ester following deprotection. Corey and Seebach[18] have demonstrated that lithiated dithianes **1.7** derived from aldehydes react in a similar manner and the α-keto acid can be obtained directly using carbon dioxide as the terminal electrophile (Scheme 1-3b). Comparable reactivity of lithiated dimethylamino nitriles **1.8** has been reported by Reutrakul[19] (Scheme 1-3c). Additionally, the "inverse" of these reactions has been reported by Eliel[20] who demonstrated that 1,3-dithiane-2-sodium-2-carboxylates **1.9** (glyoxylate anion equivalents) undergo alkylation with various alkyl halides (Scheme 1-3d).

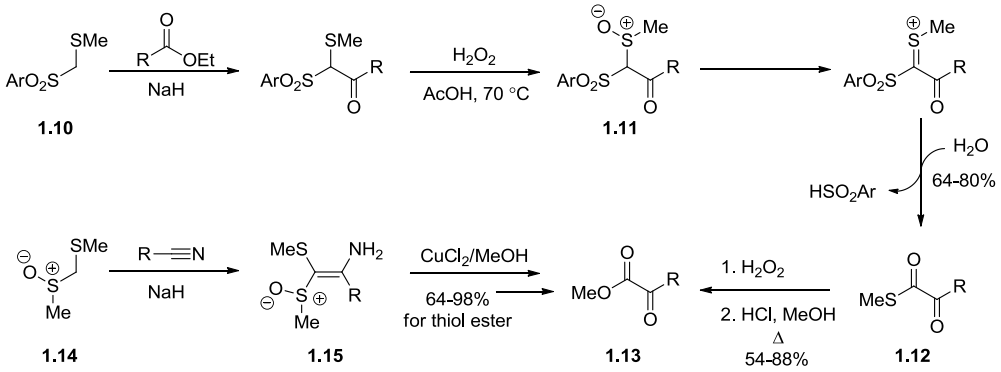
Scheme 1-3. Acylation of Acyl Anion Equivalents with Ethylchloroformate



1.2.2.2 Pummerer Rearrangement

Ogura has established (methylthio)methyl *p*-tolyl sulfones **1.10** as α-keto ester surrogates following acylation with aromatic and aliphatic carboxylic esters (Scheme 1-4).[21] Oxidation of the methyl thiol to the sulfone **1.11** with hydrogen peroxide and acetic acid induces a Pummerer rearrangement with concomitant elimination of *p*-tolyl sulfinic acid yielding the corresponding α-keto thiol ester **1.12**. The methyl ester **1.13** is obtained following further oxidation of the thiol and subsequent treatment with hydrogen chloride in refluxing methanol. Alternatively, enamine **1.15**, derived from the treatment of (methylthio)methyl sulfoxide **1.14** with sodium hydride and the appropriate nitrile, can be oxidatively transformed to the corresponding α-keto ester upon treatment with copper(II) chloride and methanol via a similar reaction pathway (hydrolysis followed by a Pummerer rearrangement and subsequent elimination of methanethiol).[22]

Scheme 1-4. Pummerer Rearrangement of (Methylthio)Methyl Sulfoxides

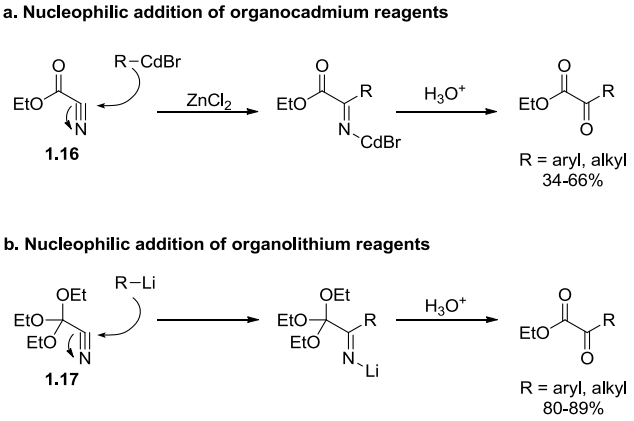


1.2.2.3 Divergent Reactivity of Ethyl Cyanoformate

Nucleophilic addition to ethyl cyanoformate **1.16** typically occurs at the carbonyl site to give simple esters. However, Sakamoto has shown that zinc chloride activation of **1.16**

results in addition to the nitrile with organocadmium reagents (prepared by transmetallation of Grignards with cadmium bromide), which upon hydrolysis affords the α-keto ester (Scheme 1-5a).[23] This difference in reactivity is explained in terms of hard and soft nucleophilicity. Organocadmium reagents are softer than Grignards, and in a screen with organomagnesium, –zinc, and –mercury reagents, organocadmium nucleophiles proved to be superior in all cases.[24] Axiotis has prepared α-keto esters in a similar manner from the addition of organolithium reagents to triethoxyacetonitrile **1.17** (Scheme 1-5b).[25]

Scheme 1-5. Nucleophilic Addition to Ethyl Cyanoformate

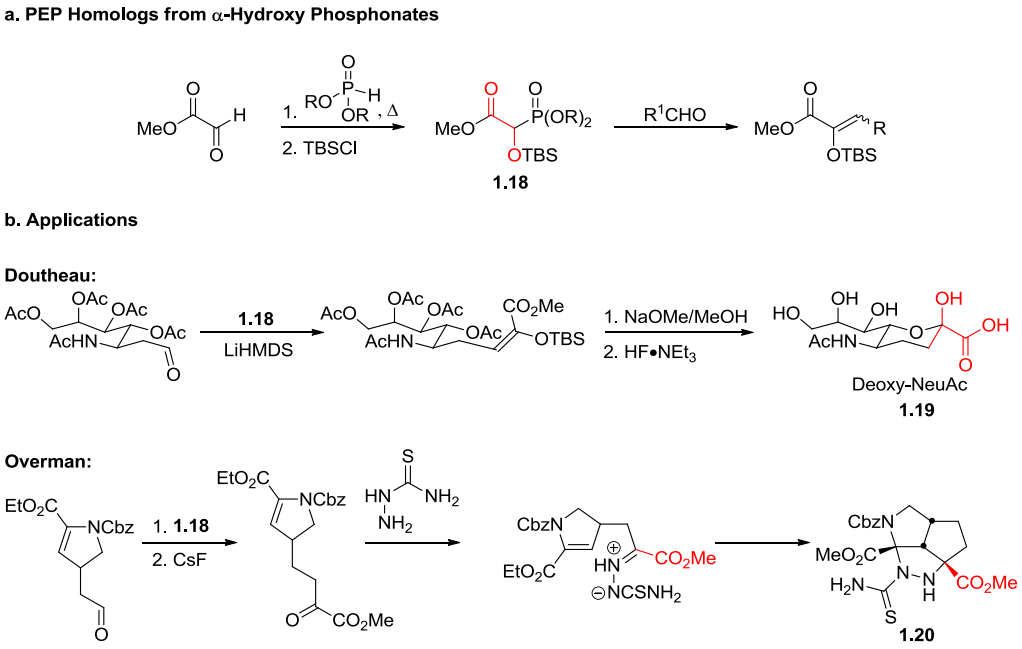


1.2.3 PEP Equivalents

Due to the importance of PEP in biological systems, the development of chemical equivalents to transfer pyruvate units directly to electrophiles has been an active area of research. The one carbon homologation of aldehydes via Horner-Wadsworth-Emmons reaction with α-hydroxy phosphonacetates **1.18**, disclosed by Nakamura in 1981,[26] is the most widely used method to prepare enol ether derivatives (Scheme 1-6). The α-keto ester can be revealed upon treatment with acid or undergo silylation to remain protected as the

silyl enol ether. This strategy has been applied towards the synthesis of biologically active natural products. Doutheau used this method to directly introduce the α-keto acid moiety in the total synthesis of deoxy-NeuAc **1.19**.[27] This approach has also been utilized by Overman in the assembly of the central *cis*-3-azobicyclo [3.3.0]octane core **1.20** of the structurally complex natural products palau'amine and styloguanidine.[28] The key step involves an intramolecular cycloaddition with imine dipoles generated from the condensation of the α-keto ester and thiosemicarbazide.

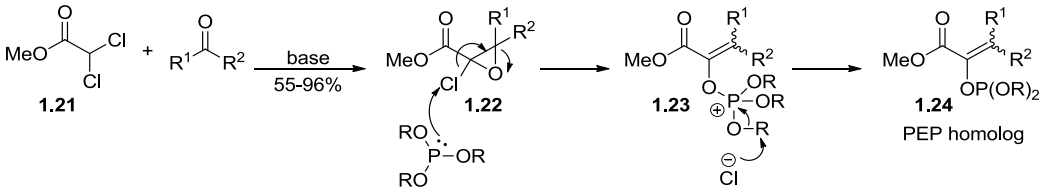
Scheme 1-6. PEP Homologs Derived from α-Hydroxy Phosphonates



Phosphoenolpyruvate homologs can be directly obtained by treating α-chloro glycidic esters **1.22**, readily available from the Darzens condensation of dichloroacetate **1.21**, with trialkyl phosphites (Scheme 1-7).[29] Nucleophilic opening of these intermediates typically gives β-substituted α-keto esters (Section 1.3.1). To account for this divergent reactivity,

Bodalski proposes that nucleophilic acttack of the phosphite on the chlorine, rather than the epoxide occurs. This opens the oxirane to form chlorophosphonium enolate **1.23** which gives PEP equivalent **1.24** upon dealkylation.

Scheme 1-7. PEP Homologs Derived from α-Chloro Glycidic Esters



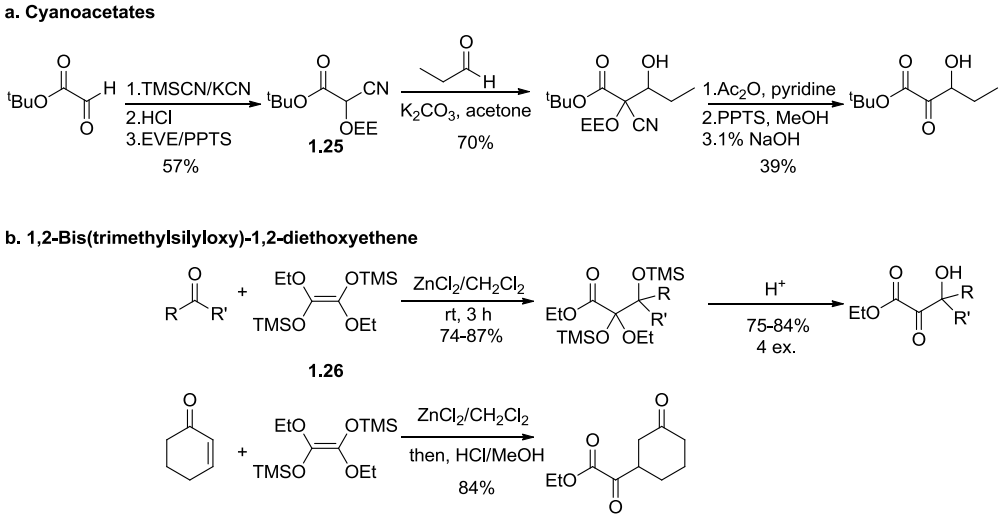
1.3 Synthetic Strategies for the Preparation of β-Stereogenic α-Keto Esters

1.3.1 Racemic Methods

The majority of the aforementioned methods for the preparation of α-keto esters (acylations and nucleophilic additions) are not viable for the introduction of a β-stereogenic center. The most direct approach to access this class of compounds is the addition of reagents that function as glyoxylate anion equivalents to π-electrophiles. This strategy has been used in several methods for the preparation of β-hydroxy α-keto esters (Scheme 1-8). Takahashi has shown that 2-metallo-2-alkoxy-2-cyanoacetates **1.25** undergo a facile reaction with aldehydes,[30] but significant functional group manipulation is required to reveal the α-keto ester functionality: deprotection of the protected cyanohydrin to unmask the ketone first requires protection of the β-hydroxyl group (Scheme 1-8a). Reetz has demonstrated that reacting 1,2-bis(trimethylsilyloxy)-1,2-diethoxyethene **1.26** with aldehydes and ketones under Lewis acidic conditions furnishes complimentary products (Scheme 1-8b).[31] In

addition, **1.26** undergoes 1,4-conjugate addition to α,β-unsaturated ketones to provide β-alkyl substrates.

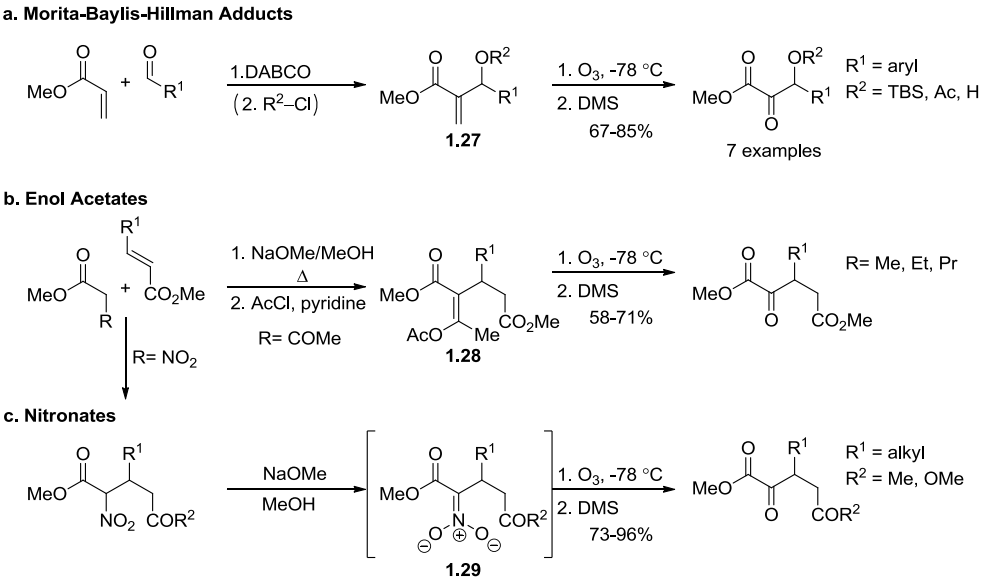
Scheme 1-8. Synthesis of β-Hydroxy α-Keto Esters Using Glyoxylate Anion Equivalents



Another popular technique that indirectly affords β-stereogenic α-keto esters is the ozonolysis of α-methylene esters (Scheme 1-9). Coelho has shown the oxidation of Morita-Baylis-Hillman (MBH) adducts **1.27** provides access to both β-silyloxy and β-hydroxy substrates and displays a broader substrate scope than the abovementioned methods (Scheme 1-9a).[32] In studies directed toward developing new therapeutic glutamic acid analogs, Gefflaut developed a similar method in which enol acetates **1.28** derived from α-substituted β-keto esters are cleaved to provide β-alkyl derivatives (Scheme 1-9b).[33] Furthermore, Thompson disclosed that β-aryl α-keto esters can be accessed using this strategy via ozonolysis of substituted nitronates **1.29** (Scheme 1-9c).[34] The α-aryl nitro esters were prepared by conjugate addition of methyl nitroacetate to enones. Conversion of these

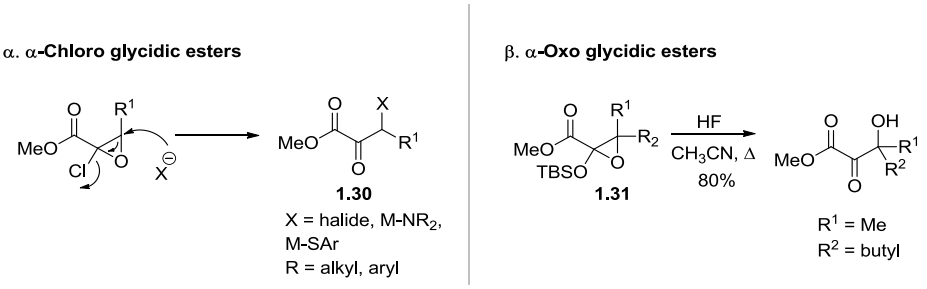
products to the α-keto ester was initially attempted using the Nef reaction, but this proved unsuccessful; the desired products were obtained by deprotonation to generate the nitronate anions followed by *in situ* ozonolysis.

Scheme 1-9. α-Keto Ester Synthesis via Ozonolysis



α-Chloro glycidic esters are most commonly used for the preparation of β-halo α-keto esters **1.30** by the addition of exogenous halide (Scheme 1-10a).[35] These substrates are particularly useful intermediates as they are immediately amenable to secondary transformations via S_N2 displacement. Additionally, in contrast to trialkyl phosphites, the addition of nitrogen[36] and sulfur[37] nucleophiles to **1.22** provides β-amino and β-sulfenyl α-keto esters respectively. β-hydroxy α-keto esters can also be obtained from α-oxo glycidic esters **1.31** derived from **1.24** upon treatment with aqueous hydrofluoric acid in acetonitrile (Scheme 1-10b).[38]

Scheme 1-10. β-Hetero α-Keto Esters From Nucleophilic Opening of Glycidic Esters



1.3.2 Asymmetric Methods

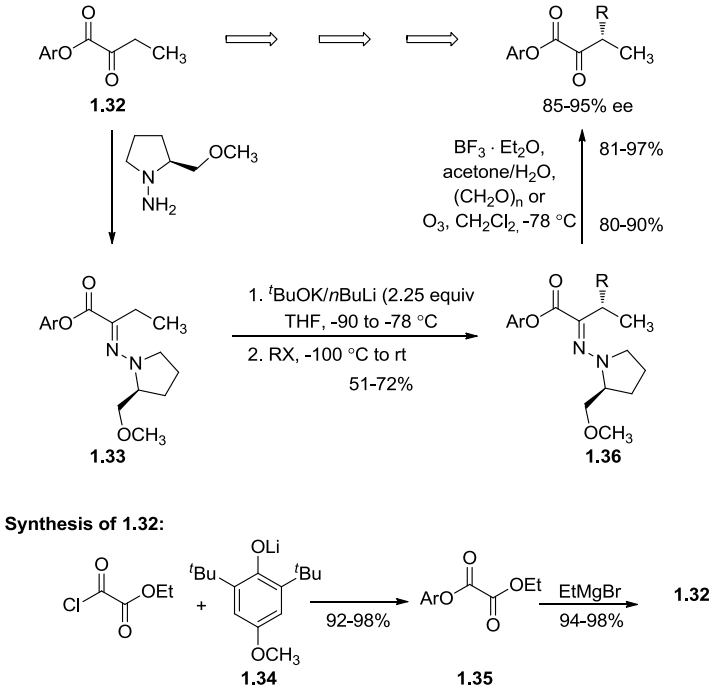
The preparation of enantioenriched β-stereogenic α-keto esters is inherently challenging due to their high C–H acidity, which renders these products susceptible to racemization under both acidic and basic conditions. Additionally, the asymmetric methods that have been developed to access these products do not have widespread applicability due to case-dependent disadvantages and/or limitations. Of the known enantioselective procedures, only one allows for the direct incorporation of the glyoxylate unit and many require a chiral auxiliary to control the stereochemistry at the β-stereocenter.

1.3.2.1 Chiral Enolates

The first enantioselective α-keto ester synthesis was reported by Enders who utilized pyruvate derived RAMP/SAMP hydrazones (chiral PEP equivalents) **1.33** which undergo alkylation with a number of alkyl halides (Scheme 1-11).[39] The α-keto ester precursors **1.32** were prepared by esterification of ethyl oxalyl chloride with the lithium salt of 2,6-di-*tert*-butyl-4-methoxyphenol **1.34**, followed by the chemoselective nucleophilic addition of ethyl Grignard to the unsymmetrical ethyl aryl oxalate **1.35**. The presence of a sterically demanding aryl group on the ester was necessary due to the observed self-acylation of azaenolates derived from methyl and *tert*-butyl pyruvate homologs. Alkylation of metalated hydrazones derived from **1.33** proceeded with high diastereoselectivity (85 to >95% de) and

the resulting alkylated products **1.36** were converted to the corresponding β-alkyl α-keto esters by either oxidative cleavage with ozone or treatment with boron trifluoride-ether/paraformaldehyde with no loss in optical purity.

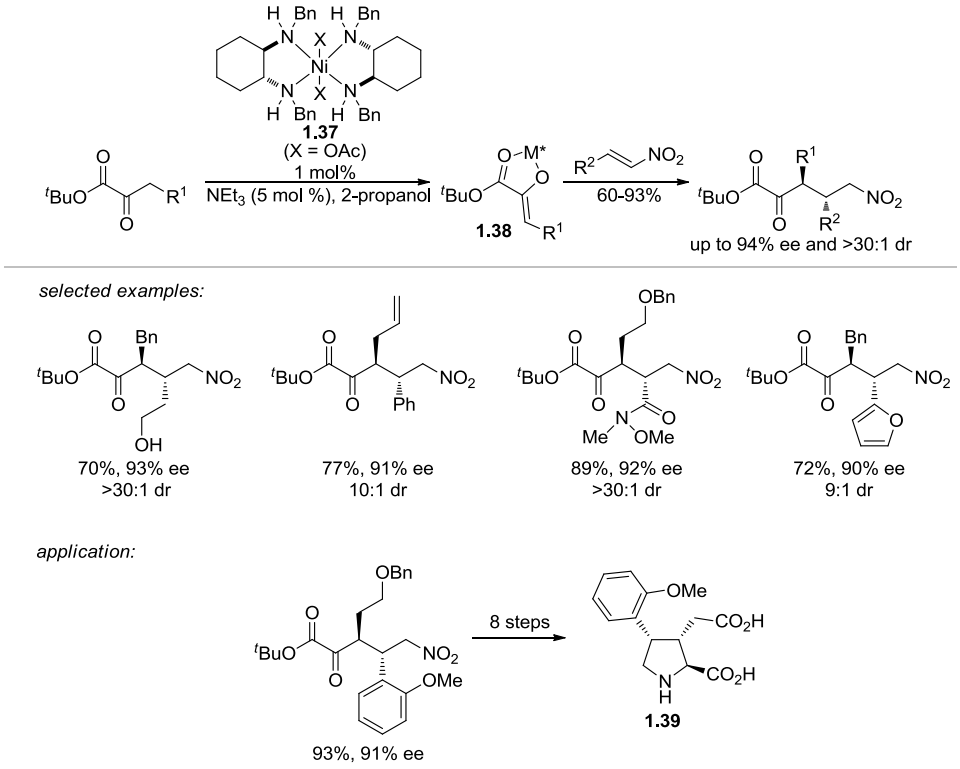
Scheme 1-11. Chiral α-Keto Esters Using RAMP/SAMP Hydrazones



Sodeoka recently reported a similar strategy in a *catalytic* enantio- and diastereoselective (up to 94% ee and >30:1 dr) conjugate addition of α-keto esters to nitroalkenes (Scheme 1-12).[40] The α-keto ester precursors were prepared in one step from commercial di-*tert*-butyl oxalate and the corresponding alkyl Grignard according to the procedure developed by Weinstock[10] (Section 1.2.1). Mild activation of the α-keto ester was achieved with nickel(II) acetate-diamine complex **1.37** to effectively generate a chiral metal enolate **1.38** which reacts with nitroalkenes in a stereoselective manner. The reaction

proceeds using only 1 mol % of catalyst and 5 mol % triethylamine (to facilitate formation of the enolate) and displays broad generality with respect to the α-keto ester and nitroalkene; however, the scope is also limited to alkyl substituents at the β-stereocenter. The synthetic utility of the β,γ-disubstituted α-keto esters was demonstrated in the asymmetric synthesis of the biologically interesting kainic acid analogue **1.39**, a potent glutamate receptor agonist.

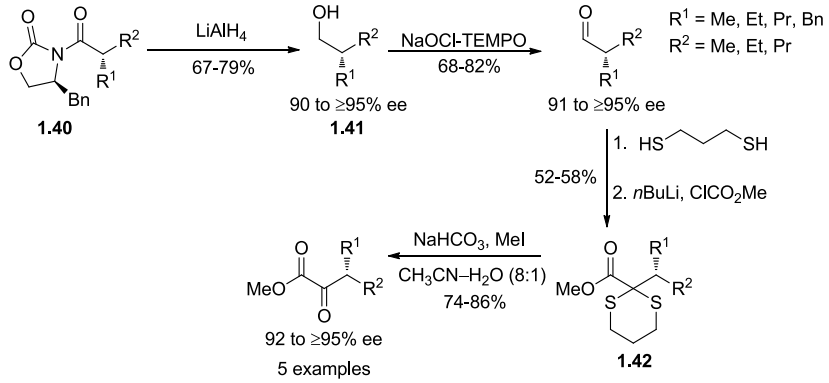
Scheme 1-12. Chiral α-Keto Esters via Asymmetric Conjugate Addition to Nitroalkenes



The use of chiral dithianes to prepare enantioenriched α-keto esters has been reported by Tyrell (Scheme 1-13).[41] The β-stereocenter was installed via alkylation of a chiral enolate using Evans' auxiliary **1.40**. Following cleavage of the auxiliary, primary alcohol **1.41** was obtained. Oxidation to the aldehyde with NaOCl-TEMPO and treatment with 1,3-

propanedithiol afforded chiral dithiane **1.42** with no significant loss in enantiopurity. Acylation with methyl chloroformate followed by dethioacetalization provided the desired chiral α-keto esters. This method has limited practicality due the redox manipulations required to unmask the α-keto ester moiety (amide to alcohol to aldehyde to ketone).

Scheme 1-13. Chiral α-Keto Esters via Chiral Dithianes

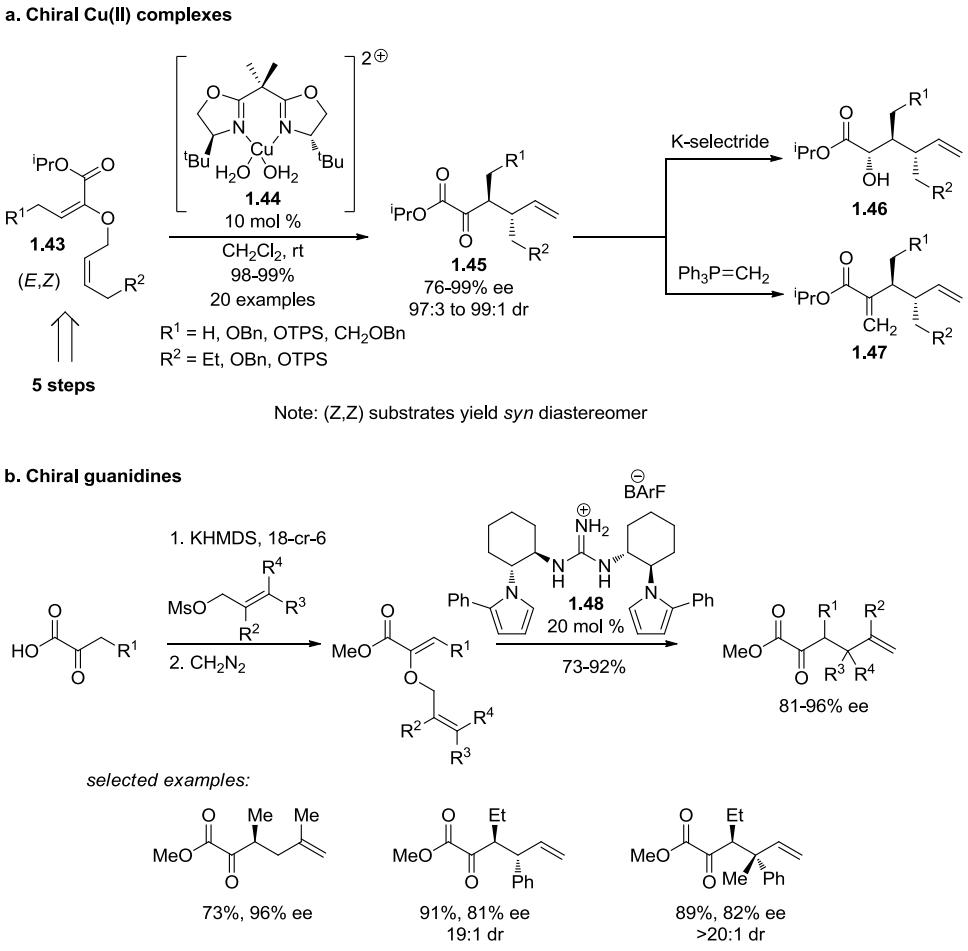


1.3.2.2 Asymmetric Claisen Rearrangement

The first catalytic asymmetric synthesis of β-alkyl α-keto esters was reported by Hiersemann in a Cu(II)-bis(oxazoline) catalyzed enantioselective Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers (Scheme 1-14a).[42-43] The reactant substrates **1.43** include two stereogenic double bonds which provides access to highly functionalized β-γ substituted α-keto esters **1.45** with high yield (>95%) and remarkable enantio- and diastereoselectivity (up to 99:1 er and 99:1 de). The synthetic utility of the α-keto ester products is highlighted by the ability of **1.45** to undergo a diastereoselective reduction to the α-hydroxy ester **1.46** and Wittig methylenation to provide highly functionalized α,β-unsaturated ester **1.47**. While there is no argument against the usefulness of the title reaction,

it should be noted that five synthetic steps, each requiring purification (three steps overnight), are necessary for the preparation of the 2-alkoxycarbonyl-substituted allyl vinyl ethers.[44] Jacobsen later demonstrated that C_2-symmetrical guanidinium catalyst **1.48** induced an asymmetric Claisen rearrangement (via hydrogen bonding) with similar substrates albeit with lower levels of enantioselectivity (Scheme 1-14b).[45] Nevertheless, only three synthetic steps to access the starting materials employed are required.

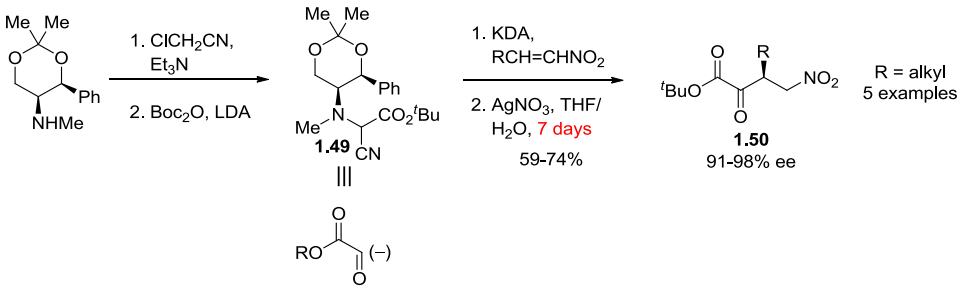
Scheme 1-14. Chiral α-Keto Esters via an Asymmetric Clasien Rearrangement



1.3.2.3 Asymmetric Nucleophilic Glyoxylation

The first formal asymmetric nucleophilic glyoxylation was accomplished by Enders utilizing the chiral metalated α-aminonitrile **1.49** in addition reactions to nitroalkenes providing γ-nitro β-alkyl α-keto esters **1.50** (Scheme 1-15).[46] The initial Michael addition proceeded with good diastereoselectivities (75-96% de crude, >98% after column chromatography), but cleavage of the aminonitrile to unmask the ketone proved difficult; subjection of the Michael adduct to a solution of 2.0 M silver nitrate for seven days was necessary to obtain reasonable conversions (89-94%) affording the α-keto ester products in modest yields (59-74%). In addition this method displays a limited substrate scope (5 examples), as only alkyl substituents at the β-position are tolerated due the tendency of β-aryl products to readily eliminate nitrous acid on silica gel to form β,γ-unsaturated α-keto esters (vide infra).

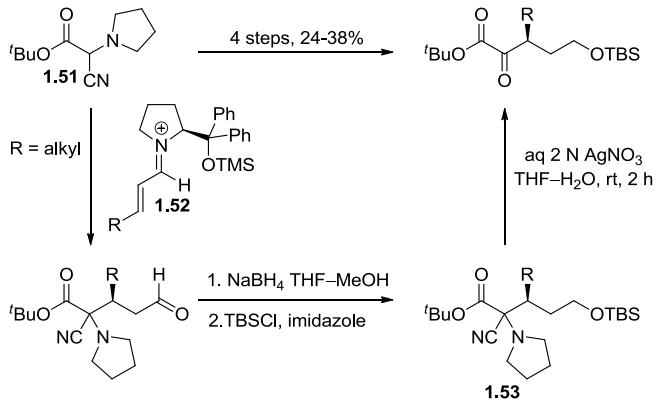
Scheme 1-15. Chiral α-Keto Esters Using Chiral Aminonitriles



Enders took a similar approach by employing an achiral aminonitrile **1.51** in an organocatalytic nucleophilic glyoxation of α,β-unsaturated aldehydes via iminium activation with trimethylsilyl protected diphenylprolinol (**1.52**, Scheme 1-16);[47] however, cleavage of the aminonitrile **1.53** to the ketone with silver nitrate first required reduction of the aldehyde

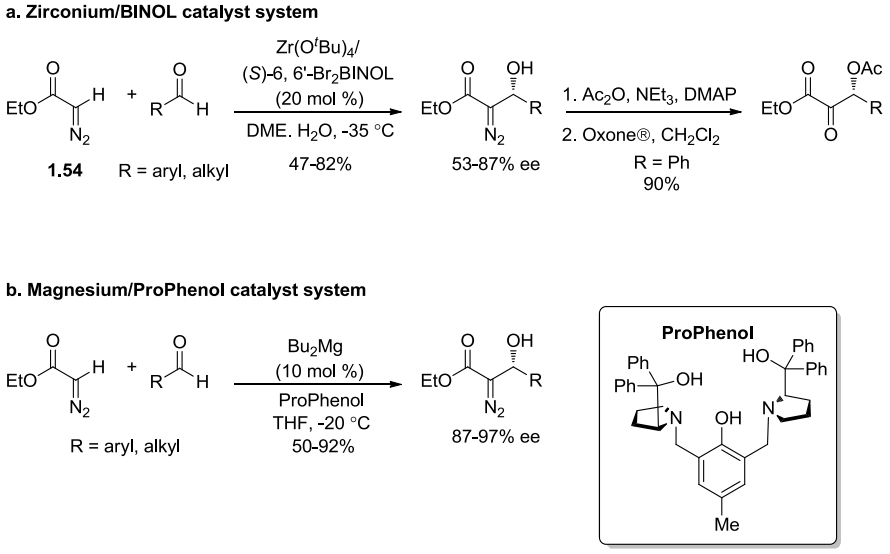
with sodium borohydride followed by protection with *tert*-butyldimethylsilyl chloride. This requirement resulted in low isolated yields of the δ-alkoxy α-keto ester products. Only alkyl α,β-unsaturated aldehydes gave reasonable enantioselectivities as their aromatic counterparts were readily racemized under the reaction conditions.

Scheme 1-16. Chiral α-Keto Esters via Organocatalysis



Commercial ethyl diazoacetate **1.54** has been utilized as a glyoxylate anion equivalent in an asymmetric direct aldol reaction with aldehydes providing access to enantioenriched β-hydroxy α-keto ester derivatives following oxidation (Scheme 1.15a). This method was first disclosed by Wang[7] who utilized Kobayashi's zirconium-BINOL catalyst which facilitates the reaction by activating both the aldehyde and ethyl diazoacetate. A variety of aromatic and aliphatic aldehydes are viable reaction partners affording the corresponding β-hydroxy α-diazo esters with modest enantioselectivity (53-87% ee). No loss in enantiopurity is observed upon oxidation of the diazo group with Oxone®. Higher enantioselectivities for the title reaction were later reported by Trost using a di-*n*-butylmagnesium/(*S*,*S*)-Prophenol catalyst system (Scheme 1.15b).[48]

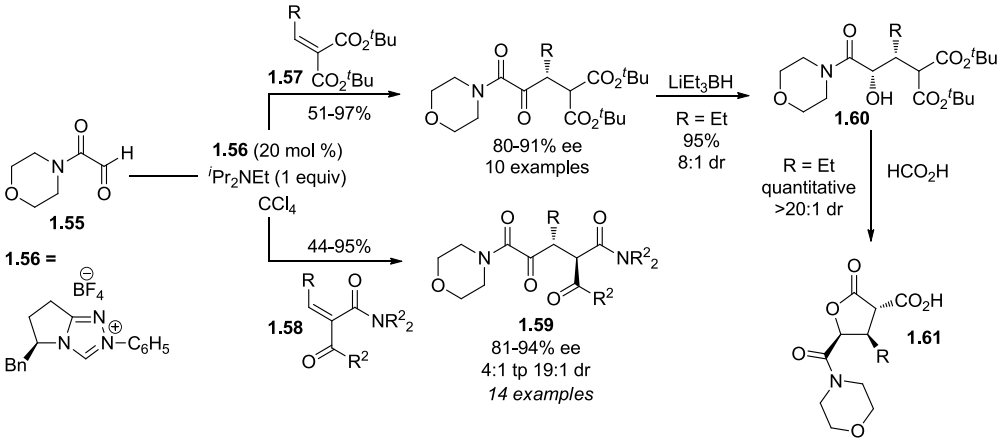
Scheme 1-17. Ethyl Diazoacetate as a Glyoxylate Anion Equivalent



The asymmetric intermolecular Stetter reaction with glyoxamides and alkylidene malonates developed by Rovis is the most direct method for the preparation of β-stereogenic α-keto acid derivatives, as the glyoxylate unit is directly incorporated into the product (Scheme 1-18).[49] High enantioselectivities in the addition of morpholine-derived glyoxamide **1.55** to a series of *tert*-butyl alkylidene malonates **1.57** were observed by using the chiral triazolium **1.56**. To avoid racemization of the α-keto amide products, it was necessary to conduct the reaction at low temperature and use a bulky base, diisopropylethylamine, to generate the active carbene; again, the scope is limited to β-alkyl derivatives due to ready racemization of β-aryl derivatives. This method was later extended to alkylidene ketoamides[50] **1.58** which incorporates four differentiated carbonyl groups in the α-keto amide products **1.59**. The asymmetric Stetter reaction proceeded with high enantioselectivity; the excellent level of diastereoselectivity observed is due to the highly diastereoselective protonation of the tertiary β-ketoamide following 1,4-addition. The synthetic utility of the

products is highlighted by their ease of conversion to α-hydroxy amides **1.60** with high diastereoselectivity and subsequent lactonization to trisubstituted γ-butyrolactones **1.61**.

***Scheme* 1-18.** Enantioselective Glyoxylate Stetter with Alkylidene Malonates and Ketoamides



1.4 Summary and Outlook

The biological importance and synthetic utility of α-keto acids and their derivatives has led to the development of various methods for their preparation. While there are a number of practical procedures in place for the synthesis of achiral α-keto esters, a general synthetic method for the introduction of a stereocenter at the β-position remains elusive. The current strategies that are available to access this important class of compounds, particularly asymmetric methods, suffer from several major drawbacks. With the exception of Wang and Trost, the reaction scopes are restricted to alkyl substituents at the β-position due to the vulnerability of enolization at this site. From a practicality standpoint, in many cases, the α-keto ester moiety is not introduced in the key asymmetric C–C bond forming step and

significant functional group manipulation to reveal the α-keto ester is required, and/or the starting materials are not readily available. The methods described in the following chapters seek to address these deficiencies by introducing three simple reagents that function as glyoxylate anion equivalents to provide access to diverse classes of β-stereogenic α-keto esters. Additionally, the facile racemization of these substrates is capitalized on in the development of the first dynamic kinetic resolution of α-keto esters.

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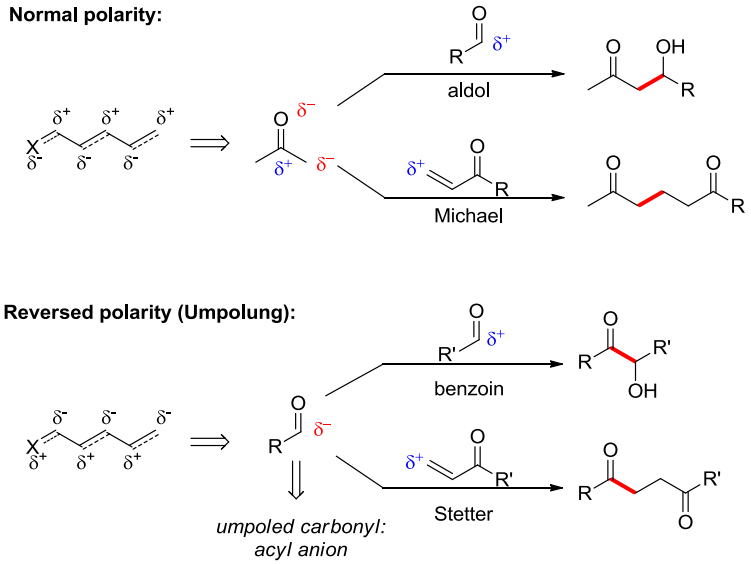
CHAPTER TWO
CATALYTIC NUCLEOPHILIC GLYOXYLATION OF ALDEHYDES

2.1 Introduction

2.1.1 Umpolung Reactivity

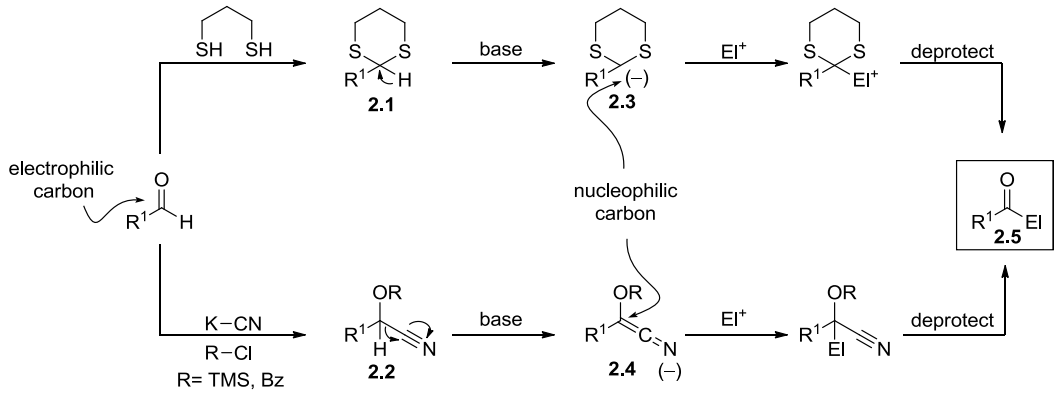
The term umpolung is defined as "any process by which the normal alternating donor and acceptor reactivity pattern of a chain, which is due to the presence of O or N heteroatoms, is interchanged."[1] This concept was first introduced by Seebach to describe the latent electronic character at carbon in a heteroatom substituted framework, in which the inductive polarization of the more electronegative heteroatom (O, N, etc.) places a δ^+ on the *ipso* carbon and a δ^- on the α-position (Figure 2-1). [2] The incorporation of π-bonds allows further delocalization of the partial charges via resonance to more remote sites. Based on this analysis, the normal polarity mode of carbonyls provides access to β-hydroxy carbonyl (aldol reaction), β-amino carbonyl (Mannich reaction), and 1,5-dicarbonyl (Michael reaction) motifs. However, access to the complementary class of products, α-hydroxy carbonyl, α-amino carbonyl, and 1,4-dicarbonyls, requires an inversion of the standard polarity of carbonyl reagents (electrophilic to nucleophilic). As acyl anions and other umpolung reagents are often not stable or accessible (i.e. an acyl anion cannot be generated by deprotonation of an aldehyde), it is often necessary to mask umpoled functionality with a synthetically equivalent group.

Figure 2-1. Normal vs. Umpolung Reactivity



The conversion of an aldehyde into an umpolung reagent is typically accomplished through dithiane[3] and protected cyanohydrin[4] derivatives (Scheme 2-1). The two anion-stabilizing sulfur atoms of dithiane **2.1** and the electron-withdrawing properties of the nitrile in **2.2** allow these intermediates to be converted to the corresponding α-carbanion (**2.3** and **2.4**) with a strong base; this renders the electrophilic carbonyl carbon nucleophilic. The intermediate carbanion can then react with an electrophile and the deprotection of the dithiane or cyanohydrin regenerates the initially present carbonyl functionality in **2.5,** yielding the formal acylation of an electrophile. While these tactics have proven to be useful in a number of circumstances, they lack the step economy and convenience of their enolate counterparts (generated from a normal polarity mode).

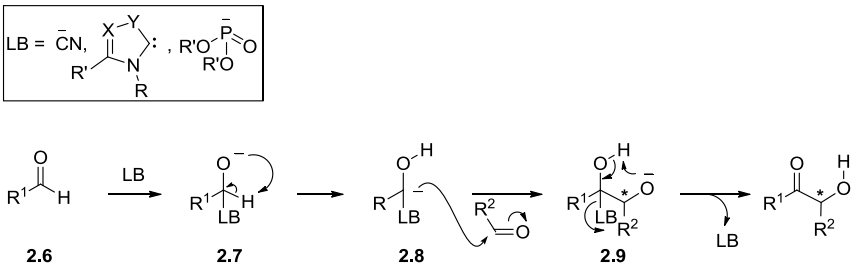
Scheme 2-1. Acylation of Electrophiles with Acyl Anion Equivalents



2.1.2 Acyl Anion Catalysis

The above shortcomings have been circumvented with the development of reaction manifolds that do not necessitate the stoichiometric generation of the acyl anion equivalent, viz., the benzoin reaction.[5] This reaction is mediated by cyanide or heteroazolium carbenes and allows the *direct* coupling of two aldehydes to afford α-hydroxy ketones.[6] The mechanism for this reaction, proposed by Lapworth,[7] is shown in Scheme 2-2. The conversion of the aldehyde **2.6** into the requisite nucleophilic reagent **2.8** involves nucleophilic addition of the Lewis basic catalyst (LB) to the carbonyl followed by migration of hydrogen from carbon to oxygen (**2.7**→**2.8**). The key productive bond construction is the interception of **2.8** with another aldehyde component. Catalysis is achieved via proton transfer to the terminus of the electrophile and collapse of the tetrahedral intermediate **2.9** to expel the catalyst and regenerate the carbonyl.

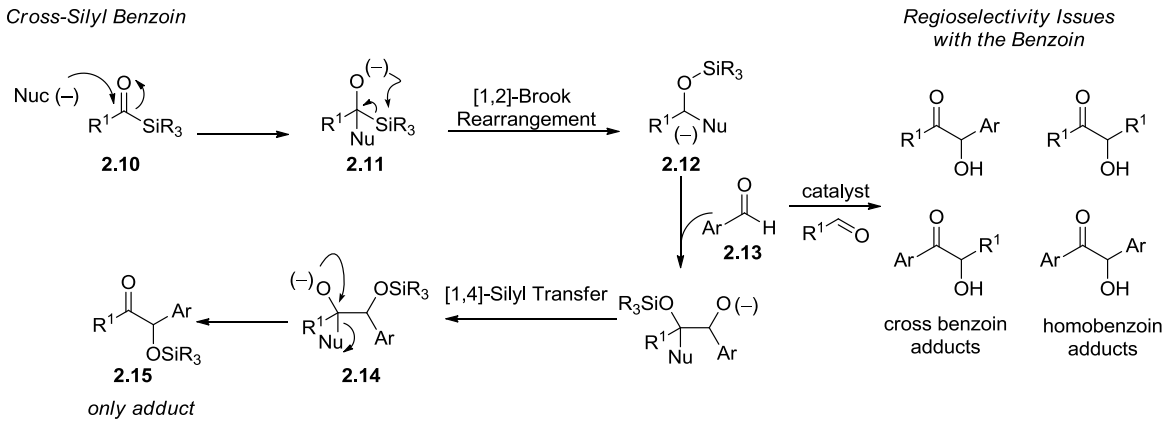
Scheme 2-2. General Mechanism for Acyl Anion Catalysis



The utility of the traditional benzoin reaction is well documented, but its major limitation arises when coupling two different aldehydes (cross benzoin). The observed product distribution is thought to be determined by the relative stability of the four possible products, which typically results in product mixtures and/or inaccessibility to the higher energy regioisomer (Scheme 2-3). Our group has shown that the reaction can effectively be placed under kinetic control by generation of the acyl anion equivalent from acyl silanes[8] **2.10** (aldehyde surrogate) in the cyanide-catalyzed cross silyl benzoin reaction.[9] The addition of a nucleophilic catalyst (cyanide or metallophosphite) to **2.10** triggers a [1,2]-Brook rearrangement,[10] the migration of silicon from carbon to oxygen (**2.11**→**2.12**), which generates (silyloxy)nitrile anion **2.12**. The driving force for the Brook rearrangement is the formation of the stronger silicon−oxygen bond at the expense of the weaker silicon−carbon bond,[11] and is facilitated by electron-withdrawing groups α to the carbanion. Addition of **2.12** to aldehyde **2.13** followed by 1,4-silyl migration gives the alkoxide intermediate **2.14**. Catalyst expulsion leads to the α-silyloxy ketone product **2.15** to complete the catalytic cycle. The noteworthy features of this reaction are: 1) *in situ* protection of the secondary hydroxyl group, 2) no competing homobenzoin products are observed and 3) either

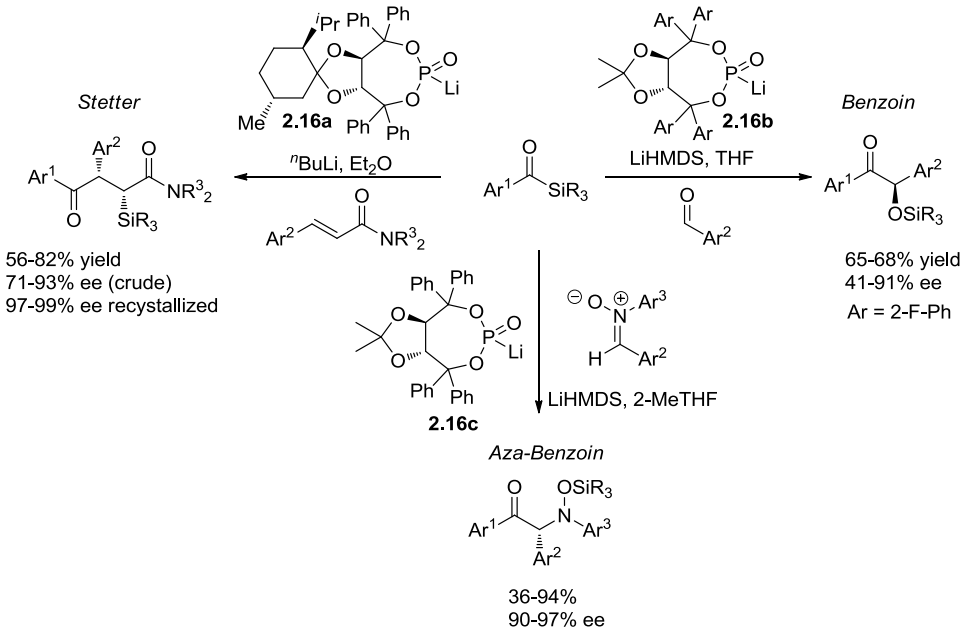
regioisomeric benzoin product can be accessed through the judicious choice of acyl silane and aldehyde.

Scheme 2-3. Cross Silyl Benzoin Reaction Mechanism



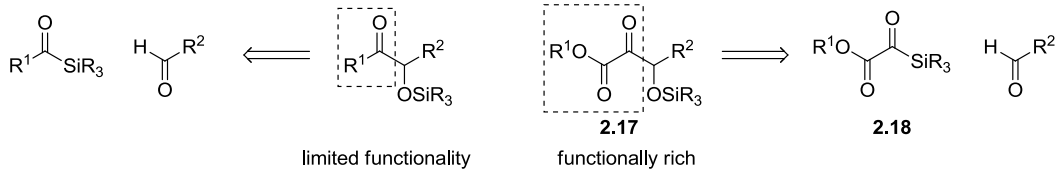
Additionally, we have identified TADDOL-based metallophosphites **2.16** as viable nucleophilic catalysts which led to the development of the first nonenzymatic enantioselective synthesis of unsymmetrical benzoins (Scheme 2-4).[12] These catalysts are uniquely effective with acyl silanes, as they do not promote the benzoin reaction with other acyl donors (aldehydes, acyl phosphonates, and benzil). The acylsilane/metallophosphite system has since been extended to aza-benzoin[13] and Stetter-type[14] reactions using aryl nitrones and α,β-unsaturated amides respectively.

Scheme 2-4. Metallophosphite-Catalyzed Cross Silyl Benzoin and Sila-Stetter Reactions



While each of these reactions display a broad substrate scope, the acyl donors tend to be relatively simple and devoid of functionality for further derivatization. Therefore, the introduction of carboxyl functionality adjacent to the ketone would be highly desirable and significantly expand the product types delivered by this reaction class. This chapter delineates the development of a glyoxylate benzoin reaction utilizing silyl glyoxylates **2.18** that provides facile access to a variety of β-silyoxy α-keto esters **2.17**.

Figure 2-2. Inspiration for the Development of Glyoxylate Benzoin

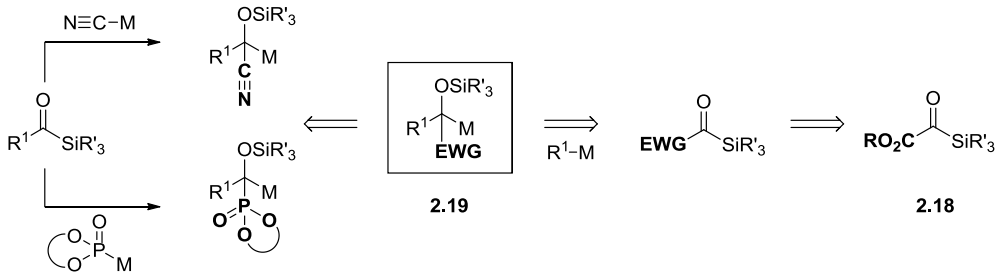


2.2 Background

2.2.1 Development of Silyl Glyoxylates

Acyl silanes provide a center of reactivity for both nucleophiles and electrophiles by way of the [1,2]-Brook rearrangement. The key (silyloxy)anion intermediate **2.19** in the above catalytic reactions is generated upon silyl migration and is facilitated by stabilization of the nascent carbanion by the nitrile or phosphonate groups, which are introduced into the molecule as the nucleophilic catalyst. It was speculated that silyl migration could also be promoted by incorporating an electron-withdrawing moiety directly into the acyl silane, thereby broadening the scope for the type of nucleophiles that can participate in this reaction manifold. Accordingly, silyl glyoxylates[15] **2.18** were identified as reagents that could fulfill this role.

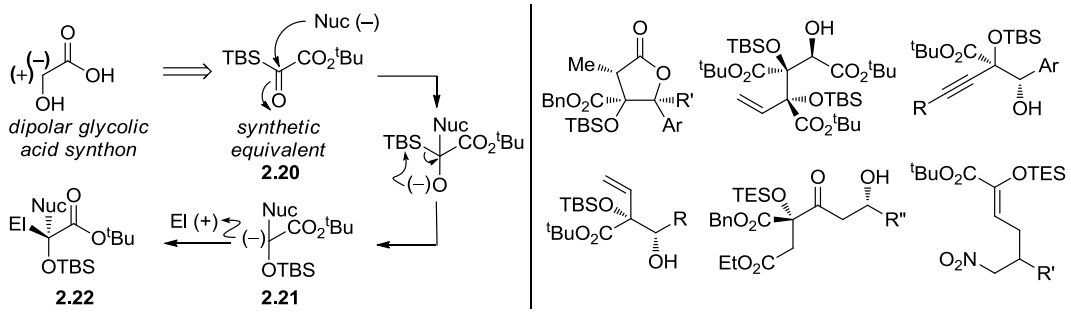
Scheme 2-5. Development of Silyl Glyoxylates



The representative silyl glyoxylate **2.20**,[16] prepared in two steps from the corresponding diazoacetate (silylation followed by oxidation of the diazo group) has been shown to be a useful conjunctive reagent for one-pot geminal coupling of nucleophilic and electrophilic species to a glycolic acid junction (Scheme 2-6). These reactions proceed by nucleophilic addition which triggers a [1,2]-Brook rearrangement to generate glycolate enolate **2.21**, followed by electrophilic trapping to yield fully substituted glycolic acid

derivatives **2.22**. In most cases, the secondary electrophile and the silyl glyoxylate are present in the reaction simultaneously, exemplifying the unique reactivity of this α-dicarbonyl. Highly reactive electrophiles such as aldehydes and nitroalkenes do not compete with **2.20** for nucleophilic addition and the latent glycolate intermediate reacts with the desired secondary electrophile rather than another molecule of **2.20**. Scheme 2-6 illustrates the diversity of complex building blocks that can arise from this multicomponent coupling strategy.[17]

Scheme 2-6. Synthetic Utility of Silyl Glyoxylates in Three-Component Couplings

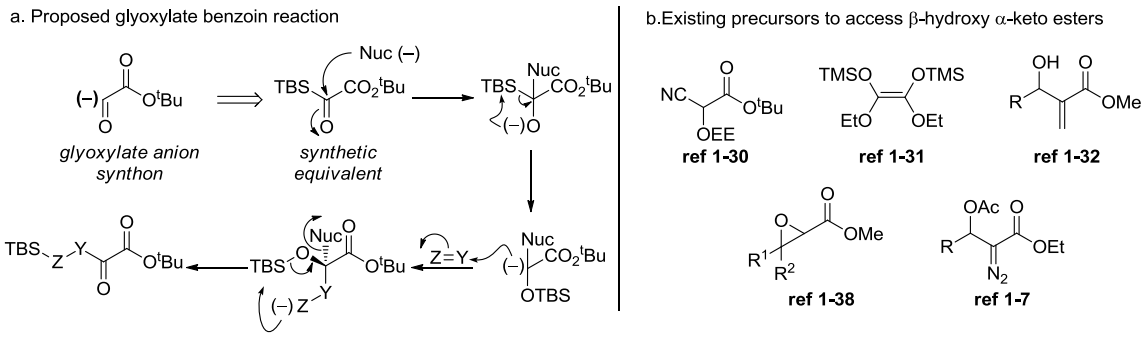


2.2.2 Origin of the Title Reaction

All of the reported reactions involving silyl glyoxylates incorporate the nucleophile as a stoichiometric component. It was postulated that divergent reactivity could be achieved in the presence of a nucleophilic catalyst and aldehyde to access β-silyloxy α-keto esters via a silyl benzoin reaction mechanism (Scheme 2-7a). In this context, silyl glyoxylates would function as a synthetic equivalent for the glyoxylate anion synthon. Alternate methods for the preparation of β-hydroxy α-keto acid derivatives were discussed in the previous chapter and are summarized again in Scheme 2-7b. In each case, the α-keto ester is not directly

incorporated into the product so the implementation of this method would constitute the first catalytic, and hence most direct, method for the preparation of this class of α-keto esters.

Scheme 2-7. Silyl Glyoxylates as Glyoxylate Anion Equivalents

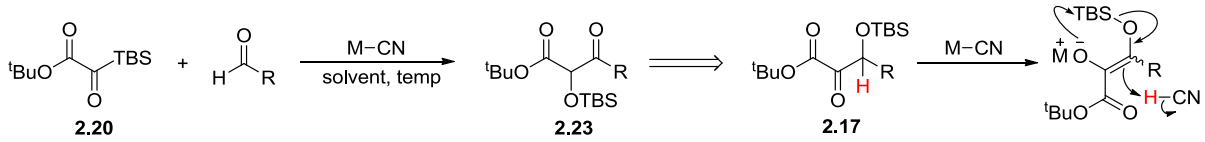


2.3 Results and Discussion

2.3.1 Identification of a Viable Nucleophilic Catalyst

To assess the viability of the proposed reaction, various metal cyanides were evaluated as the nucleophilic catalyst with silyl glyoxylate **2.20** and benzaldehyde as the test substrate. Sodium cyanide, potassium cyanide, and potassium cyanide/18-crown-6 complex were initially screened. Under a variety of reaction conditions, the desired α-keto ester **2.17** was not obtained; instead, the reaction yielded α-silyoxy β-keto ester **2.23** (Table 2-1). This product is likely derived from isomerization of the initially formed β-silyloxy α-keto ester **2.17** under the basic reaction conditions and occurs independent of solvent identity and temperature (entries 2, 3, and 5). To probe the propensity of this isomerization, several aldehyde substrates were examined, but the derived β-keto ester was obtained in each case (entries 6-9). A less basic source of cyanide was desired that could potentially stop at the desired ketone product.

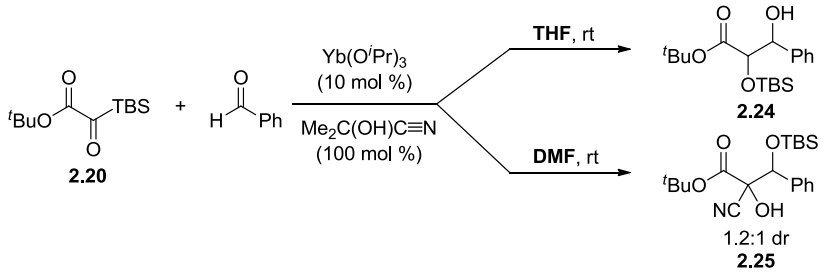
Table 2-1. Evaluation of Metal Cyanides



entry	R	M–CN	solvent	temp	% yield (**2.23**)
1	Ph	NaCN	DMF	rt	53
2	Ph	NaCN	DMF	0 ºC	ND
3	Ph	NaCN	DMF	-78 ºC	ND
4	Ph	KCN	DMF	rt	ND
5	Ph	[18]crown6/KCN	THF	rt	ND
6	4Cl-Ph	NaCN	DMF	rt	45
7	2-furyl	NaCN	DMF	rt	40
8	2-thienyl	NaCN	DMF	rt	42
9	^{i}Pr	NaCN	DMF	rt	35

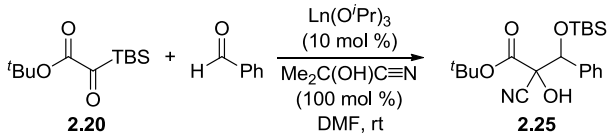
Lanthanide isopropoxides have been reported as efficient catalysts in the transhydrocyanation from acetone cyanohydrin to aldehydes and ketones.[18] Subjection of silyl glyoxylate and benzaldehyde to the reported reaction conditions, 10 mol % Yb(O^{i}Pr)$_3$ and one equivalent of acetone cyanohydrin in THF, resulted in a known Oppenauer oxidation/Brook rearrangement/aldolization sequence to give **2.24**.[19] A number of solvents were screened and DMF provided the desired reactivity, yielding the cyanohydrin adduct **2.25** in a 1.2:1 dr. Although this product was not desired, it could potentially be useful as the nitrile offers a valuable functional handle, provided **2.25** could be obtained with higher levels of diastereoselectivity.

Scheme 2-8. Initial Studies with Ytterbium Isopropoxide/Acetone Cyanohydrin Catalyst System

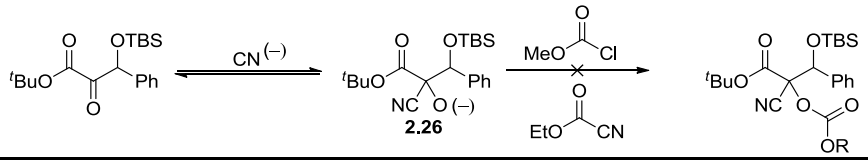


We initially screened all available lanthanide isopropoxides and the results are summarized in Table 2-2. With the exception of dysprosium (entry 7), all the lanthanides were efficient in promoting the reaction; however, the highest diastereomeric ratio observed was 1.4:1 (entries 8-9). Decreasing the temperature to 0 ºC had no effect (entry 9) and at -78 ºC no reaction was observed (entry 10). Using catalytic quantities of $Yb(O^iPr)_3$ (20 mol %) yielded a 5:1 mixture of the desired α-keto ester **2.17a** and the cyanohydrin, albeit in a 1.2:1 dr. It was conjectured that cyanation and retrocyanation of the α-keto ester were in rapid equilibrium which could deteriorate the diastereoselectivity. We then attempted to trap the alkoxide **2.26** formed following 1,4-silyl migration with acylating reagents. The introduction of methyl chloroformate to the reaction yielded a complex mixture of products, and in the presence of ethyl cyanoformate and quinuclidine, cyanation followed by acylation of benzaldehyde occurred.

Table 2-2. Evaluation of Lanthanide Isopropoxides

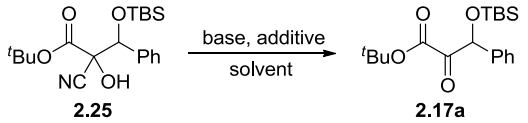


entry	Ln(O^{i}Pr)$_3$	temperature	d.r.
1	Yb(O^{i}Pr)$_3$	rt	1.2 : 1
2	Y(O^{i}Pr)$_3$	rt	1 : 1
3	Er(O^{i}Pr)$_3$	rt	1 : 1
4	Gd(O^{i}Pr)$_3$	rt	1.4 : 1
5	Nd(O^{i}Pr)$_3$	rt	1.2 : 1
6	Sm(O^{i}Pr)$_3$	rt	1.4 : 1
7	Dy(O^{i}Pr)$_3$	rt	NR
8	Pr(O^{i}Pr)$_3$	rt	1.4 : 1
9	Pr(O^{i}Pr)$_3$	0 °C	1.4 : 1
10	Pr(O^{i}Pr)$_3$	-78 °C	NR

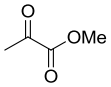


Having determined a successful means of promoting the desired reactivity, conditions for retrocyanation to deliver the desired β-silyoxy α-keto ester **2.17a** were explored. Initial efforts employed traditional methods by subjecting cyanohydrin **2.25** to basic conditions, but either starting material was recovered (entry 1) or decomposition occurred (entry 2). It is likely that cyanide expulsion occurs in the presence of potassium carbonate, but in the absence of a "cyanide sponge", addition back into the ketone is inevitable. Several potential cyanide scavengers were evaluated (entries 3, 5-6) and the most promising results were observed with silver nitrate[20] which produced the desired ketone product in a 2.5:1 ratio (entry 6). Most optimally, **2.17a** was obtained directly from **2.20** using 20 mol % of Yb(O^{i}Pr)$_3$ by simply quenching the reaction with 1 mL of 2M aqueous silver nitrate.

Table 2-3. Retrocyanation Attempts



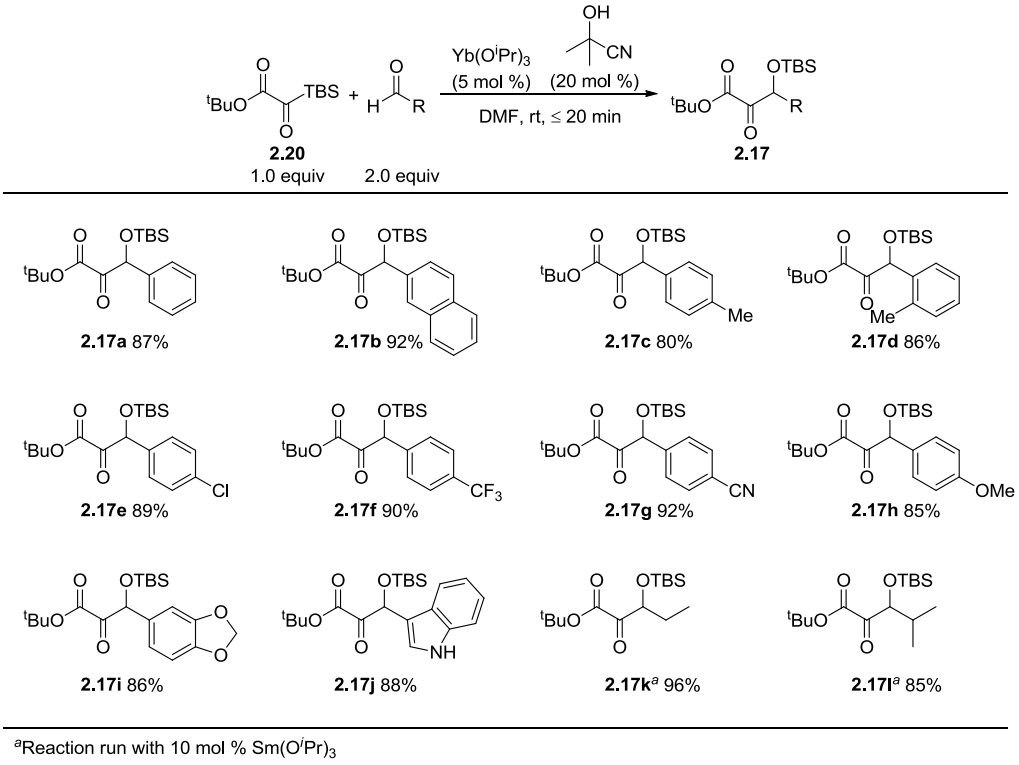
2.25 **2.17a**

entry	base	additive	solvent	observed product(s)
1	K_2CO_3	none	MeOH	S.M.
2	NEt_3	none	MeOH	Decomposition
3	none	Ag_2CO_3	$PhCH_3$	S.M.
4	1% NaOH	none	THF	Decomposition
5	2,6-lutidine		EtOH	2 : 1 (48 hrs) (S.M. : ketone)
6	2,6-lutidine	$AgNO_3$	EtOH	2.5 : 1 (7 hrs)

2.3.2 Reaction Scope

With the optimal conditions in hand, 20 mol % acetone cyanohydrin, 5 mol% $Yb(O^iPr)_3$ and two equivalents of aldehyde, the scope of the electrophiles amenable to the reaction was investigated (Scheme 2-7). Electron-rich, electron-poor, and heteroaromatic aldehydes all performed well with yields ranging from 80 to 92%. The reaction was also tolerant of aliphatic aldehydes (**2.17k** and **2.17l**), but required $Sm(O^iPr)_3$ as the catalyst to achieve full conversion. This method has steric limitations as pivaldehyde failed to provide any desired product. It is notable that all reactions were complete within twenty minutes, and in most cases the silyl glyoxylate was completely consumed upon addition of all reagents. Additionally, the products were obtained in analytically pure form after passing the crude reaction mixture through a short silica plug and removing the excess aldehyde under reduced pressure. Extension of this reaction to include ketones was unsuccessful which may be due to their lower reactivity and increased steric demand.

Scheme 2-9. Scope of Aldehyde Glyoxylation

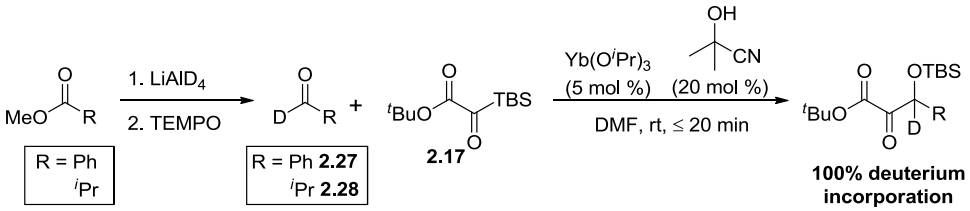


[a]Reaction run with 10 mol % $Sm(O^iPr)_3$

2.3.3 Efforts Toward an Enantioselective Catalytic Reaction

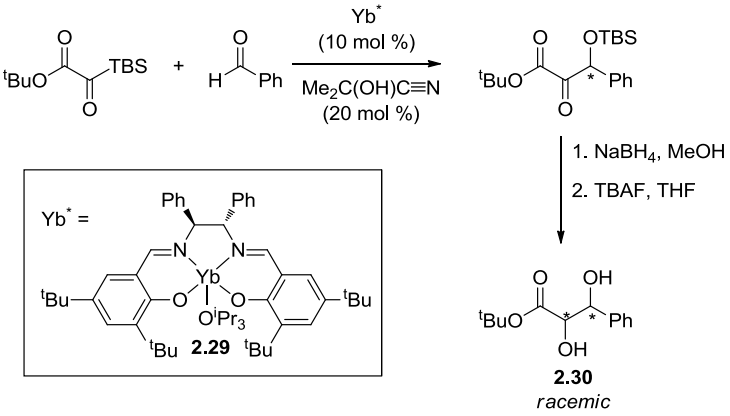
The isomerization of **2.17** that was observed in the presence of metal cyanides indicates the lability of the newly formed stereocenter. To determine the stability of this center in the presence of $Yb(O^iPr)_3$ and acetone cyanohydrin, deuterium labeling studies were performed (Scheme 2-8). Deuterated benzaldehyde **2.27** and isobutyraldehyde **2.28** were prepared by reduction of the corresponding methyl esters with deuterated lithium aluminum hydride ($LiAlD_4$), followed by a TEMPO oxidation (Scheme 2-8). When the reaction was run with these electrophiles, full deuterium incorporation at the methine was observed, suggesting that the product is stable toward enolization under the silyl benzoin conditions. This implicates the title reaction should be amenable to enantioselective catalysis.

Scheme 2-10. Deuterium Labeling Studies



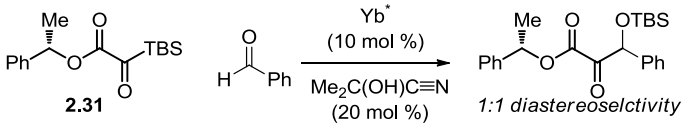
We presumed the enantiodetermining step to be the addition of the glycolate enolate to the aldehyde so the ideal chiral catalyst would need to both facilitate the transhydrocyanation and direct the facial selectivity in the subsequent aldol reaction. Our group had previously developed an enantioselective cyanation and acylation of acylsilanes using chiral (salen)metal,[21] so this was our point of departure for this study (Scheme 2-9). We first evaluated the use of chiral complex **2.29**, but racemic product was obtained as determined after conversion to diol **2.30**. This result implies that either the catalyst is completely non-selective, or an achiral catalyst is generated by disproportionation of the (salen)-Yb complex to generate $Yb(CN)_3$ as the active catalyst.

Scheme 2-11. Asymmetric Attempts Using Yb(salen)-Complex



Chiral silyl glyoxylate **2.31** was employed as another potential option to introduce asymmetry; however, a 1:1 diastereoselectivity was observed. As a final attempt, chiral metallophosphites **2.16** were examined given their success in a number of asymmetric umpolung reactions (Scheme 2-4). Under a variety of reaction conditions, no desired product was observed.

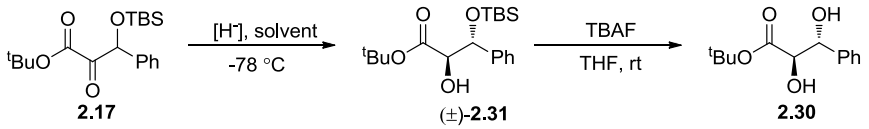
Scheme 2-12. Chiral Silyl Glyoxylates



2.3.4 Subsequent Transformations of β-Silyloxy α-Keto Esters

To highlight the synthetic utility of the products, several secondary derivatizations were examined. Reduction of the α-keto ester **2.17a** with sodium borohydride in methanol at -78 ºC provided orthogonally protected diol **2.32** in a 2.3:1 diastereomeric ratio. In an effort to increase the diastereoselectivity, other reducing reagents were evaluated, but no significant increase was observed (Table 2-4). The favored diastereomer was determined to be the *anti*-isomer following deprotection of the *tert*-butyldimethyl silyl group with tetrabutylammonium fluoride to diol **2.30**, whose spectral data was compared to that reported in the literature.[22]

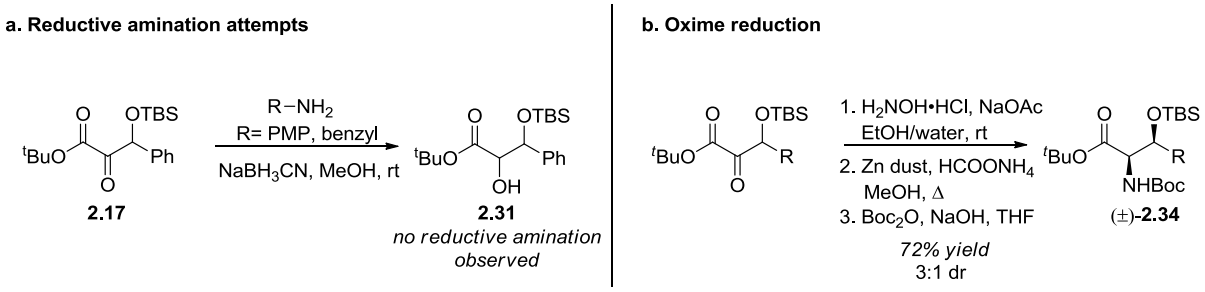
Table 2-4. α-Keto Ester Reduction Optimization



entry	reducing agent	solvent	d.r.
1	$NaBH_4$	MeOH	2.3:1
2	$NaBH_4/CeCl_3$	MeOH	2:1
3	L-selectride	THF	2.5:1
4	DIBAL-H	$PhCH_3$	no reaction
5	Red-Al	THF	1:1

The α-keto esters may also be converted to their derived β-silyloxy α-amino esters **2.33** (Scheme 2-11). Under standard reductive amination conditions (*p*-methoxy aniline and sodium cyanoborohydride), competitive ketone reduction was observed.[23] To obtain the desired product first required conversion of **2.17a** to the derived oxime. This intermediate was then reduced with zinc and ammonium formate to give the α-amino ester **2.34** in a 3:1 dr, which was isolated following Boc protection in 72% yield over the three steps. Preference for the *syn*-diastereomer was observed.[24]

Scheme 2-13. Synthesis of β-Silyloxy α-Amino Esters



2.4 Conclusion

We have demonstrated that silyl glyoxylates can function as glyoxylate anion equivalents in a silyl benzoin reaction with aldehydes to provide β-silyloxy α-keto esters. The reaction proceeds in excellent yield for both aryl and aliphatic aldehydes. Critical to our success was identifying $Yb(O^iPr)_3$ and acetone cyanohydrin as a source of cyanide mild enough to prevent isomerization of the products to the corresponding α-silyloxy β-keto ester. The secondary transformations of the products add to the synthetic utility of this methodology. Deuterium labeling studies suggests an asymmetric variant is possible, but preliminary studies with chiral ytterbium complexes and chiral silyl glyoxylates displayed no selectivity. Of the methods available to prepare β-hydroxy α-keto acid derivatives, this method provides the most direct route and displays the broadest substrate scope.

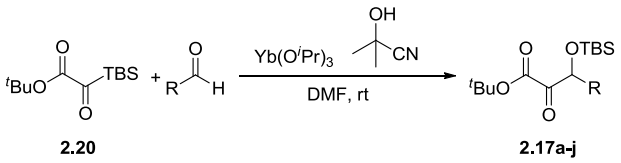
2.5 Experimental Details

Methods. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 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, br d = broad doublet, t = triplet, br t = broad triplet, q = quartet, sept = septuplet, oct = octuplet, m = multiplet), coupling constants (Hz), and integration. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-

63μm) purchased from Silicycle. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization (Note: All samples prepared in methanol). All reactions were carried out under an atmosphere of nitrogen in oven-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. Enantiomeric excesses were obtained using a Supercritical Fluid Chromatograph equipped with a UV-Vis detector using a Chiralcel Chiralpak AD HPLC column. Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH.

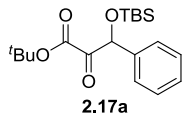
Materials: General. *N*,*N*-Dimethylformamide was distilled from P_2O_5 and stored under N_2 over 3Å molecular sieves. Benzaldehyde, *p*-anisaldehyde, 4-methylbenzaldehyde, and 2-methylbenzaldehyde were purified by the following procedure: The neat aldehydes were washed sequentially with a 1 M sodium hydroxide solution and a saturated aqueous sodium bicarbonate solution, dried with magnesium sulfate, and distilled under reduced pressure. 4-Chlorobenzaldehyde was sublimed under reduced pressure. Isobutyraldehyde and propionaldehyde were dried over $CaSO_4$ and distilled under N_2 prior to use. Silyl glyoxylate **1** was prepared according to the published procedure. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

General Procedure A for the Yb(O^{i}Pr)$_3$ catalyzed nucleophilic glyoxylation of aryl aldehydes to afford β-siloxy-α-ketoesters 4a-j:



In an inert atmosphere glovebox, a 10-mL round-bottomed flask containing a magnetic stir bar was charged with Yb(O^{i}Pr)$_3$ (0.05 equiv). The flask was sealed with a rubber septum and removed from the glovebox. To this flask was added DMF (1 mL), and this solution was allowed to stir until complete dissolution of the Yb(O^{i}Pr)$_3$ occurred. A shell vial containing silyl glyoxylate (1.0 equiv), aldehyde (2.0 equiv) and acetone cyanohydrin (0.20 equiv) in DMF ([**2.20**]$_0$ = 0.20 M) was transferred to the round-bottomed flask *via* cannula. Upon the disappearance of the silyl glyoxylate (as indicated by TLC analysis: 10% EtOAc/hexanes), the reaction was quenched with 2 M aqueous silver nitrate (1 mL).[1] The resultant silver salts were removed via filtration through a pad of silica gel with EtOAc (20 mL). The organic layer was washed with water (3x), brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting α-ketoesters were obtained in analytically pure form after the removal of the excess aldehyde as described below.

***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-oxo-3-phenylpropanoate (2.17a):**

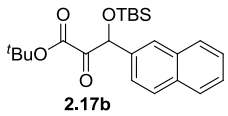


The title compound was prepared according to General Procedure A using **2.20** (1.00 g, 4.09 mmol, 1.0 equiv), benzaldehyde (0.868 g, 8.18 mmol, 2.0 equiv), acetone cyanohydrin (0.070 g, 0.818 mmol, 0.20 equiv), Yb(O^{i}Pr)$_3$ (0.072 g,

[1] This was necessary to remove all trace amounts of the cyanohydrin product **3**.

0.205 mmol, 0.05 equiv) and DMF (10 mL). The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup and removal of the excess aldehyde *in vacuo* (<1 mm Hg), **2.17a** (1.20 g, 3.57 mmol, 87% yield) was obtained as a clear yellow oil. Analytical data for **2.17a**: **IR** (thin film, cm^{-1}) 2956, 2931, 2857, 1748, 1725, 1472, 1257, 1132, 872, 838, 426; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.42 (m, 5H), 5.56 (s, 1H), 1.43 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), -0.010 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.7, 162.2, 137.0, 128.5, 127.3, 84.2, 78.3, 27.9, 25.7, 18.3, -5.0; **TLC** (10% EtOAc/hexanes) R_f 0.46; **LRMS** (ESI) Calcd. For $C_{19}H_{30}O_4SiNa + CH_3OH$): 405.21. Found: 405.20.

***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-3-(naphthalen-2-yl)-2-oxopropanoate (2.17b)**:

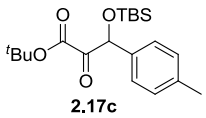


2.17b

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), 2-napthaldehyde (0.064 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035 g, 0.0102 mmol, 0.05 equiv) and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup and purification by flash chromatography (10% EtOAC/hexanes), **2.17b** (0.076 g, 0.188 mmol, 92% yield) was obtained as a clear colorless oil. Analytical data for **2.17b**: **IR** (thin film, cm^{-1}) 2955, 2931, 2886, 2857, 1747, 1724, 1370, 1255, 1164, 1127, 839, 782; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83-7.87 (m, 4H), 7.48-7.55 (m, 3H), 5.74 (s, 1H), 1.42 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.007 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.7, 162.3, 134.5, 133.4, 133.2, 128.4, 128.1, 127.8, 126.8, 126.4, 126.3, 124.7, 84.3, 78.4, 27.9, 25.7, 18.4, -

4.9; **TLC** (10% EtOAc/hexanes) R_f 0.42; **LRMS** (ESI) Calcd. For $C_{23}H_{32}O_4SiNa$ + CH_3OH: 455.22. Found: 455.21.

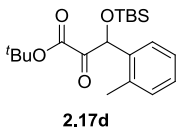
***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-oxo-3-*p*-tolylpropanoate (2.17c):**



2.17c

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), *p*-tolualdehyde (0.049 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035g, 0.0102 mmol, 0.05 equiv) and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup and removal of the excess aldehyde *in vacuo* (<1 mm Hg), **2.17c** (0.060 g, 0.164 mmol, 80% yield) was obtained as a clear colorless oil. Analytical data for **2.17c**: **IR** (thin film, cm^{-1}) 2957, 2930, 2858, 1721, 1462, 1369, 1254, 1151, 1103, 838, 779; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 5.52 (s, 1H), 2.34 (s, 3H), 1.44 (s, 9H), 0.90 (s, 9H), 0.095 (s, 3H), -0.018 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.8, 162.3, 138.3, 134.0, 129.2, 127.3, 84.1, 78.2, 27.9, 25.7, 21.1, 18.3, -4.99; **TLC** (10% EtOAc/hexanes) R_f 0.49; **LRMS** (ESI) Calcd. For $C_{20}H_{32}O_4SiNa$ + CH_3OH: 419.22 Found: 419.22.

***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-oxo-3-*o*-tolylpropanoate (2.17d):**

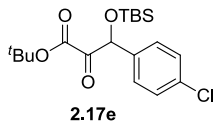


2.17d

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), *o*-tolualdehyde (0.049 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035g, 0.0102 mmol, 0.05 equiv) and DMF (2 mL).The reaction was complete

immediately upon the addition of all reagents as determined by TLC analysis. After workup and removal of the excess aldehyde *in vacuo* (<1 mm Hg), **2.17d** (0.064 g, 0.176 mmol, 86% yield) was obtained as a clear colorless oil. Analytical data for **2.17d**: **IR** (thin film, cm^{-1})2955, 2931, 2858, 1747, 1725, 1462, 1370, 1257, 1132, 838, 780, 746; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.37 (m, 1H), 7.14-7.22 (m, 3H), 5.69 (s, 1H), 2.36 (s, 3H), 1.39 (s 9H), 0.89 (s, 9H), 0.11 (s, 3H), -0.048 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.0, 162.7, 136.7, 135.1, 130.8, 129.1, 128.6, 126.0, 84.1, 77.3, 27.8, 25.7, 19.2, 18.2, -4.99, -5.03; **TLC** (10% EtOAc/hexanes) R_f 0.49; **LRMS** (ESI) Calcd. For $C_{20}H_{32}O_4SiNa + CH_3OH$: 419.22 Found: 419.22.

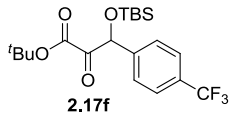
***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-3-(4-chlorophenyl)-2-oxopropanoate (2.17e):**



2.17e

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.058 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035g, 0.0102 mmol, 0.05 equiv)and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup and removal of the excess aldehyde *in vacuo* (<1 mm Hg), **2.17e** (0.070 g, 0.182 mmol, 89% yield) was obtained as a clear colorless oil. Analytical data for **2.17e**: **IR** (thin film, cm^{-1}) 2955, 2931, 2887, 2859, 1749, 1725, 1490, 1371, 1257, 1132, 1089, 869, 839; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 5.51 (s, 1H), 1.46 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), -0.009 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.3, 162.0, 135.7, 134.5, 128.7, 128.5, 84.5, 77.6, 27.9, 25.7, 18.3, -5.02; **TLC** (10% EtOAc/hexanes) R_f 0.41; **LRMS** (ESI) Calcd. For $C_{19}H_{29}ClO_4SiNa + CH_3OH$: 439.17. Found: 439.15.

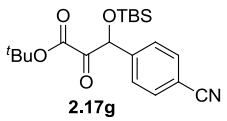
***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-oxo-3-(4-(trifluoromethyl)phenyl)propanoate (2.17f):**



2.17f

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), 4-(trifluoromethyl)benzaldehyde (0.071 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035g, 0.0102 mmol, 0.05 equiv) and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup and removal of the excess aldehyde *in vacuo* (<1 mm Hg), **2.17f** (0.077g, 0.185 mmol, 90% yield) was obtained as a clear colorless oil. Analytical data for **2.17f**: **IR** (thin film, cm^{-1}) 2956, 2933, 2889, 2860, 1750, 1726, 1326, 1258, 1167, 1131, 1067, 870, 839, 782; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 5.58 (s, 1H), 1.46 (s, 9H), 0.91 (s, 9H), 0.12 (s, 3H), 0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.1, 161.9, 141.2, 127.4, 125.5, 84.7, 77.8, 27.9, 25.7, 18.3, -5.00, -5.03; **TLC** (10% EtOAc/hexanes) R_f 0.43; **LRMS** (ESI) Calcd. For $C_{20}H_{29}F_3O_4SiNa + CH_3OH$: 473.19. Found: 473.17.

***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-3-(4-cyanophenyl)-2-oxopropanoate (2.17g):**

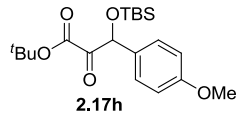


2.17g

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), 4-cyanobenzaldehyde (0.054 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035g, 0.0102 mmol, 0.05 equiv) and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup and purification by flash chromatography (10% EtOAC/hexanes), **2.17g** (0.071 g, 0.189

mmol, 92% yield) was obtained as a clear colorless oil. Analytical data for **2.17g**: **IR** (thin film, cm^{-1}) 2955, 2931, 2859, 2230, 1750, 1730, 1502, 1394, 1257, 1133, 868, 840, 783; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8 Hz, 2H), 7.56 (d *J* = 8 Hz, 2H), 5.55 (s, 1H), 1.46 (s, 9H), 0.91 (s, 9H), 0.12 (s, 3H), 0.010 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.7, 161.7, 142.5, 132.3, 127.6, 118.4, 112.5, 84.9, 77.7, 27.9, 25.6, 18.3, -5.01, -5.06; **TLC** (10% EtOAc/hexanes) R_f 0.25; **LRMS** (ESI) Calcd. For $C_{20}H_{29}NO_4SiNa$ + CH_3OH: 430.20. Found: 430.18.

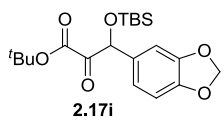
***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-3-(4-methoxyphenyl)-2-oxopropanoate (2.17h)**:



2.17h

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), *p*-anisaldehyde (0.056 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035g, 0.0102 mmol, 0.05 equiv), 2,6-lutidine (0.022 g, 0.205 mmol, 1.0 equiv) and DMF (2 mL). After stirring 20 min, the reaction was complete as determined by TLC analysis. After workup and removal of the excess aldehyde *in vacuo* (<1 mm Hg), **2.17h** (0.066 g, 0.174 mmol, 85% yield) was obtained as a clear colorless oil. Analytical data for **2.17h**: **IR** (thin film, cm^{-1}) 2955, 2932, 2856, 1748, 1723, 1611, 1512, 1464, 1303, 1254, 1171, 1130, 1033, 870, 838, 781; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* =8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz), 5.52 (s, 1H), 3.80 (s, 3H), 1.45 (s, 9H), 0.89 (s, 9H), 0.094 (s, 3H), -0.024 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.7, 162.4, 159.9, 129.1, 128.8, 114.0, 84.1, 77.9, 55.3, 27.9, 25.7, 18.3, -4.95; **TLC** (10% EtOAc/hexanes) R_f 0.35; **LRMS** (ESI) Calcd. For $C_{20}H_{32}O_5SiCs$ + CH_3OH: 545.13. Found: 545.11.

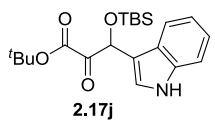
***tert*-Butyl 3-(benzo[d][1,3]dioxol-5-yl)-3-(*tert*-butyldimethylsilyloxy)-2-oxopropanoate (2.17i):**



2.17i

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), piperonal (0.062 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035g, 0.0102 mmol, 0.05 equiv) and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup and removal of the excess aldehyde *in vacuo* (<1 mm Hg), **2.17i** (0.069 g, 0.176 mmol, 86% yield) was obtained as a clear colorless oil. Analytical data for **2.17i**: **IR** (thin film, cm^{-1}) 2955, 2931, 2895, 2856, 1747, 1725, 1489, 1445, 1371, 1252, 1143, 1040, 873, 839, 782; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.86 (s, *J* = 8 Hz, 2H), 6.77 (d, *J* = 8 Hz, 2H), 5.96 (s, 2H), 5.47 (s, 1H), 1.47 (s, 9H), 0.90 (s, 1H), 0.098 (s, 3H), -0.005 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.5, 162.3, 147.9, 131.0, 121.2, 108.2, 107.7, 101.2, 84.3, 77.9, 27.9, 25.7, 18.3, -4.96, -4.99; **TLC** (10% EtOAc/hexanes) R_f 0.36; **LRMS** (ESI) Calcd. For $C_{20}H_{30}O_6SiNa + CH_3OH$: 449.20. Found: 449.15.

***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-3-(1H-indol-3-yl)-2-oxopropanoate (2.17j):**

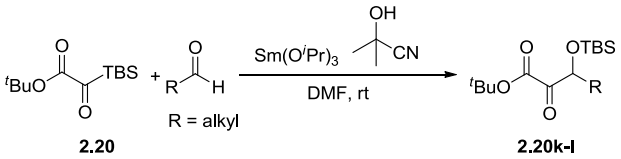


2.17j

The title compound was prepared according to General procedure A using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), indole-3-carboxaldehyde (0.060 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g, 0.041 mmol, 0.20 equiv), $Yb(O^iPr)_3$ (0.0035g, 0.0102 mmol, 0.05 equiv) and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup and removal of the excess aldehyde by treatment with hexanes and filtration, **2.17j** (0.070 g,

0.180 mmol, 88% yield) was obtained as a light brown oil. Analytical data for **2.17j**: **IR** (thin film, cm^{-1}) 2955, 2931, 2857, 1755, 1668, 1537, 1461, 1395, 1370, 1255, 1149, 839, 783; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.30-8.33 (m, 1H), 7.96 (s, 1H), 7.47-7.49 (m, 1H), 7.31-7.33 (m, 2H), 6.02 (s, 1H), 1.38 (s, 9H), 0.91 (s, 9H), 0.18 (s, 3H), -0.004 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.0, 166.2, 136.2, 136.1, 125.5, 124.2, 123.3, 122.3, 119.4, 110.8, 83.6, 79.2, 27.8, 25.4, 18.1, -5.26, -5.31; **TLC** (10% EtOAc/hexanes) R_f 0.14; **LRMS** (ESI) Calcd. For $C_{21}H_{31}NO_4SiNa$: 412.19. Found: 412.18.

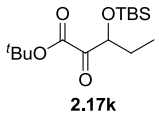
General Procedure B for the Sm(O^{i}Pr)$_3$ catalyzed nucleophilic glyoxylation of aliphatic aldehydes to afford β-siloxy-α-ketoesters 2.17k-l:



2.20 **2.20k-l**

These substrates were prepared in the same manner described in General Procedure A except 10 mol % Sm(O^{i}Pr)$_3$ was substituted for Yb(O^{i}Pr)$_3$.

***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-oxopentanoate (2.17k):**

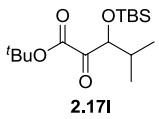


2.17k

The title compound was prepared according to General procedure B using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), propionaldehyde (0.024 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035, g 0.041 mmol, 0.20 equiv), Sm(O^{i}Pr)$_3$ (0.0067 g, 0.0205 mmol, 0.10 equiv) and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup, **2.17k** (0.060 g, 0.197 mmol, 96% yield) was obtained as a clear colorless oil. Analytical data for **2.17k**: **IR** (thin film, cm^{-1}) 2958, 2932, 2885, 2859, 1746, 1722, 1472, 1463, 1371, 1256, 1147, 1111,

862, 839, 780; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.47 (t, *J* = 6.4 Hz, 1H), 1.71-1.86 (m, 2H), 1.70 (s, 9H), 0.962 (t, *J* = 7.6 Hz, 3H), 0.91 (s, 9H), 0.081 (s, 3H), 0.066 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.0, 162.8, 84.2, 77.32, 28.0, 27.3, 25.7, 18.3, 9.3, -4.81, -5.14; **TLC** (10% EtOAc/hexanes) R_f 0.48; **LRMS** (ESI) Calcd. For $C_{15}H_{30}O_4SiNa$ + CH_3OH: 357.21. Found: 357.20.

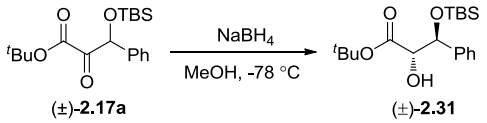
***tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-4-methyl-2-oxopentanoate (2.17l):**



2.17l

The title compound was prepared according to General procedure B using **2.20** (0.050 g, 0.205 mmol, 1.0 equiv), isobutyraldehyde (0.030 g, 0.410 mmol, 2.0 equiv), acetone cyanohydrin (0.0035 g 0.041 mmol, 0.20 equiv), $Sm(O^iPr)_3$ (0.0067 g, 0.0205 mmol, 0.10 equiv) and DMF (2 mL).The reaction was complete immediately upon the addition of all reagents as determined by TLC analysis. After workup, **2.17l** (0.055 g, 0.174 mmol, 85% yield) was obtained as a clear colorless oil. Analytical data for **2.17l**: **IR** (thin film, cm^{-1}) 2960, 2932, 2859, 1745, 1722, 1472, 1371, 1255, 1147, 1073, 863, 839, 780; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.33 (d, *J* = 5.2 Hz, 1H), 2.11-2.17 (m, 1H), 1.54 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.049 (s, 3H), 0.038 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.9, 162.6, 84.1, 80.6, 31.8, 27.9, 25.8, 19.0, 18.3, 17.0, -4.74, -5.31; **TLC** (10% EtOAc/hexanes) R_f 0.50; **LRMS** (ESI) Calcd. For $C_{16}H_{32}O_4SiNa$ + CH_3OH: 371.22. Found: 371.24.

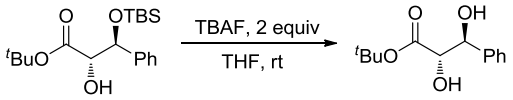
Preparation of β-Silyloxy α-Hydroxy Ester 2.31



(±)-**2.17a** (±)-**2.31**

Sodium borohydride (1.0 equiv) was added to a solution of β-silyloxy α-keto ester **2.17a** (1.0 equiv) in methanol (0.5 M concentration) at -78 ºC. When gas evolution ceased, 1 mL saturated ammonium chloride was added and the reaction was further diluted with diethyl ether and water. The organic layer was washed with brine and dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (10% EtOAc/hexanes) provided **2.31** as a clear colorless oil in a 2.5:1 dr, as determined by ^{1}HNMR analysis. Analytical data for **2.31**: **IR** (thin film, cm^{-1}) 2958, 2930, 2857, 1726, 1368, 1252, 1161, 1119, 935, 837, 778, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) major: δ 7.24-7.36 (m, 5H), 5.05 (d, *J* = 2.4 Hz), 4.24 (dd, *J* = 2.8 Hz, 8 Hz), 3.18 (d, *J* = 7.2 Hz), 1.46 (s, 9H), 0.93 (s, 9H), 0.11 (s, 3H), -0.045 (s, 3H) minor: δ 7.24-7.36 (m, 5H), 4.95 (d, *J* = 2.4 Hz), 4.03 (dd, *J* = 2.8 Hz, 8 Hz), 2.99 (d, *J* = 8.8 Hz), 1.58 (s, 9H), 0.89 (s, 9H), 0.043 (s, 3H), -0.22 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) major: δ 171.0, 140.4, 127.8, 127.2, 126.4, 77.3, 27.9, 25.9, 18.3, -4.8, -5.0 minor: 171.5, 141.0, 128.0, 127.0, 82.3, 76.3, 28.1, 25.8, 18.1, -4.5, -5.1; **TLC** (10% EtOAc/hexanes) R_f major: 0.43, minor: 0.38; **LRMS** (ESI) Calcd. For $C_{19}H_{32}O_4SiNa$: 375.20. Found: 375.18.

Determination of Diastereomer Identity

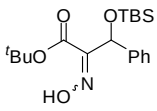


2.31 **2.30**

***tert*-Butyl 2,3-dihydroxy-3-phenylpropanoate (30):** The title compound was prepared by dissolving **6** (0.040 g, 0.113 mmol, 1.0 equiv) in THF (2 mL) followed by addition of TBAF trihydrate (0.071 g, 0.226 mmol, 2.0 equiv). After stirring five minutes, TLC analysis (10% EtOAc/hexanes) showed that deprotection was complete (R_f(diol) ≈ 0). The reaction mixture was passed through a plug of silica gel with EtOAc (30 mL) and filtrate was concentrated. The spectroscopic data matched that in the literature.

Preparation of β-silyoxy-α-aminoester 2.34

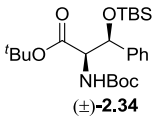
***tert*-butyl 3-(*tert*-butyldimethylsilyloxy)-2-(hydroxyimino)-3-phenylpropanoate**



Hydroxylamine hydrochloride (0.396 g, 5.70 mmol, 10.0 equiv) and sodium acetate (0.468 g, 5.70 mmol, 10.0 equiv) were dissolved separately in the minimum amount of water (~ 0.5 mL) and added sequentially to a solution of **2.17a** (0.200 g, 0.570 mmol, 1.0 equiv) in ethanol (5 mL). The reaction was allowed to stir overnight and diluted with EtOAc. The layers were separated and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was passed through a plug of silica gel using 20% EtOAc/hexanes to afford the oxime (0.194 g, 0.531 mmol, 93% yield) as a clear colorless oil (d.r. 5:1). Analytical data: **IR** (thin film, cm^{-1}) 2955, 2930, 2887, 2858, 1736, 1369, 1256, 1148, 869, 838, 780, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) major: δ 11.0 (bs, 1H),

7.24-7.50 (m, 5H), 5.54 (s, 1H), 1.33(s, 9H), 0.95 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H) minor δ 7.24-7.50 (m, 5H), 6.30 (s, 1H), 1.42 (s, 9H), 0.94 (s, 9H), 0.109 (s, 3H), 0.07 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) major: δ 161.6, 152.2, 140.4, 127.9, 127.2, 126.0, 84.0, 74.0, 66.7, 27.9, 25.8, 18.21, -4.8, -5.2; minor: δ 160.9, 154.7, 140.2, 127.4, 125.8, 82.6, 66.7, 29.7, 27.9, 25.7, 18.2, -4.8, -5.2; **TLC** (10% EtOAc/hexanes) R_f major: 0.45, minor: 0.34; **LRMS** (ESI) Calcd. For $C_{19}H_{31}NO_4SiNa$: 388.19. Found: 388.18.

***tert*-Butyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropanoate (2.34):**



(±)-**2.34**

To a 10-mL round-bottomed flask was added zinc dust (0.173 g, 2.65 mmol, 5.0 equiv) and ammonium formate (0.167 g, 2.65 mmol, 5.0 equiv). A solution of the oxime (0.194 g, 0.530 mmol, 1.0 equiv) in MeOH (5 mL) was added and the reaction was heated at reflux overnight. After cooling to room temperature, the reaction was filtered through a pad of celite. The pad was washed with MeOH (20 mL) and the filtrate was concentrated. The crude material was dissolved in EtOAc, washed with saturated $NaHCO_3$, water, brine, dried over Na_2SO_4, and concentrated. The crude material was dissolved in THF (3 mL) and (^{t}BuOC)$_2$O (0.231 g, 1.06 mmol, 2.0 equiv) was added. Sodium hydroxide (0.042 g, 1.06 mmol, 2.0 equiv) in water (2 mL) was added and the reaction was allowed to stir overnight. The reaction was diluted with water and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (eluting with 5% EtOAc/hexanes) afforded **7** (0.155 g, 0.410 mmol, 72% yield over three steps) as a clear colorless oil. The spectroscopic data matched that in the literature.

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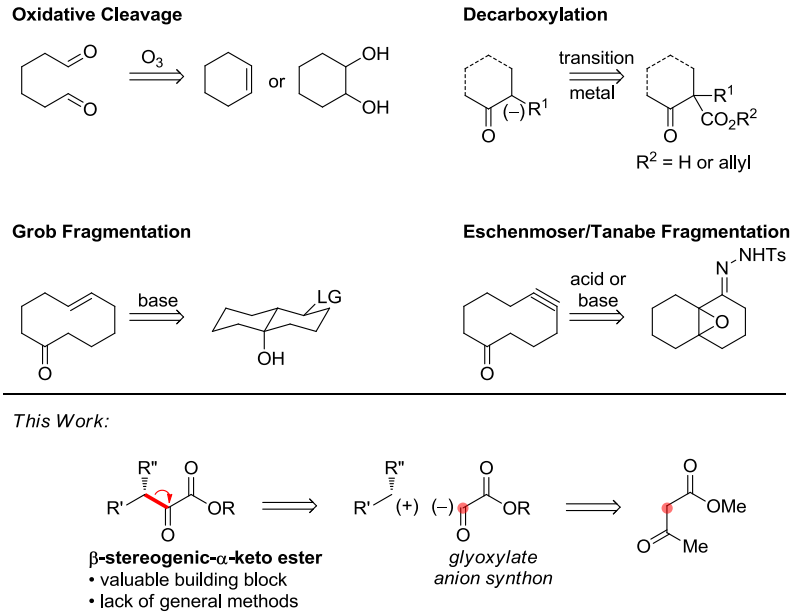
CHAPTER THREE

ASYMMETRIC SYNTHESIS OF α-KETO ESTERS VIA CU(II)-CATALYZED AEROBIC DEACYLATION OF ACETOACETATE ALKYLATION PRODUCTS

3.1 Introduction

The development of methods for the creation of carbon–carbon bonds is essential for the construction of complex molecules and is exemplified by the continual efforts directed toward identifying novel and selective bond-forming reactions. However, the complementary process, carbon–carbon bond cleavage, has received considerably less attention despite the tremendous potential it holds.[1] These reactions are not always obvious retrosynthetic disconnections, but can efficiently provide useful synthetic intermediates as they often unmask latent functional groups (Figure 3-1). Important examples include oxidative cleavage of 1,2-diols[2] and ozonolysis of alkenes[3] to provide (di)carbonyl compounds, transition-metal catalyzed decarboxylations[4-8] to generate reactive carbanionic species, and the Grob[9] and Eschenmoser-Tanabe fragmentations[10] to yield alkenyl and alkynyl ketones respectively. Moreover, the oxidative cleavage of enol acetates,[11] nitronates,[12] and MBH adducts[13] via ozonolysis introduces the α-keto ester functionality (Chapter 1). Introduced in this chapter is a copper(II)-catalyzed oxidative cleavage of substituted acetoacetates as a simple and efficient method for the preparation of diverse β-stereogenic α-keto esters, establishing synthetic equivalency between acetoacetate esters and the glyoxylate anion in the context of asymmetric synthesis.

Figure 3-1. C–C Bond Cleavage Strategies in Organic Synthesis

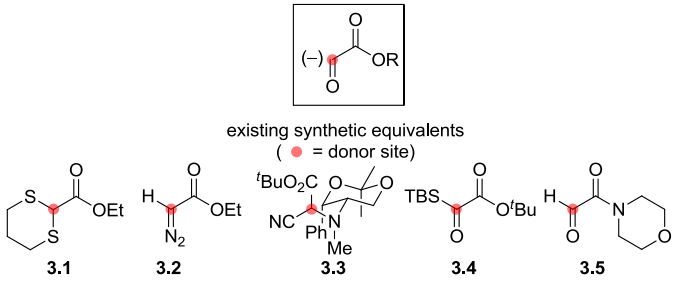


3.2 Background

Formal nucleophilic glyoxylation of π-functional groups through the application of glyoxylate anion equivalents in principle defines a direct entry into α-keto esters. The existing reagents and strategies discussed in the previous chapters, which are highlighted in Figure 3-2, are not amenable to widespread adoption of the "glyoxylate anion" tactic in organic synthesis due to case-dependent disadvantages and/or limitations. Application of these methods to access enantioenriched substrates is particularly challenging and the only two examples of direct asymmetric "glyoxylate anion" catalysis employ glyoxamides as the glyoxylate donor.[14-15] Additionally, the substrate scopes of these methods and others (see Chapter 1) are confined to alkyl substituents at the β-stereocenter (with the exception of **3.2**), display limited functional group tolerance, and several require a chiral auxiliary to achieve acceptable levels of enantioselectivity. No *single* reagent has been developed to provide access to enantioenriched, structurally diverse α-keto esters. Due to the importance of this

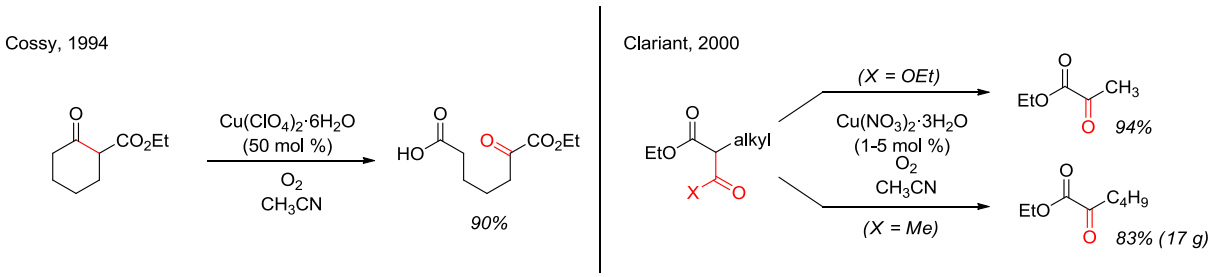
class of compounds and the lack of general methods for their preparation, we sought to identify a family of enantioselective reactions that would deliver products to serve as the α-keto ester progenitor.

Figure 3-2. Notable Glyoxylate Anion Equivalents



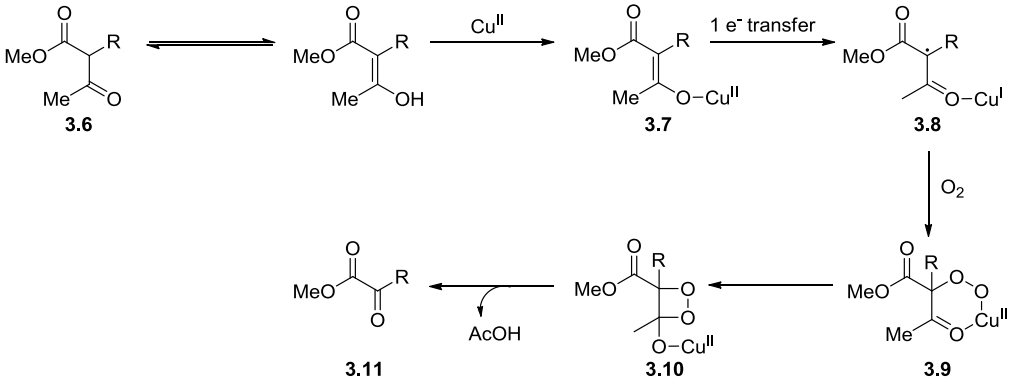
The conversion of α-substituted β-keto esters and malonates to the corresponding α-keto ester using oxygen and catalytic quantities of a Cu(II) or Fe(III) salt was disclosed in the patent literature by Clariant in 2000;[16] this reaction is related to prior oxidative ring cleavage reactions of cycloalkanones disclosed by Cossy and co-workers[17] (Scheme 3-1). Although the products reported by Clariant are achiral and unfunctionalized, the transformation is noteworthy for its simplicity, scalability, and use of cheap, unmodified catalysts.

Scheme 3-1. Oxidative cleavage of β-Keto Esters



The mechanism for this transformation has not been studied in detail but what has been proposed is shown in Scheme 3-2. Key to the success of this reaction is enolization of the β-dicarbonyl **3.6** to generate copper enolate **3.7**. The enolate is then oxidized via a one electron transfer yielding radical species **3.8**. Reaction with dioxygen delivers hydroperoxide **3.9** which undergoes cyclization to give dioxetane **3.10** that readily eliminates acetic acid as the only presumed byproduct to deliver the α-keto ester product **3.11**.

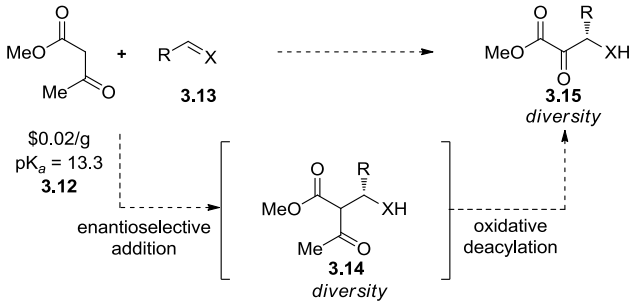
Scheme 3-2. Proposed Mechanism for the Oxidative Cleavage of α-Substituted β-Keto Esters



The appeal of using α-substituted β-dicarbonyls **3.14** as precursors to α-keto esters **3.15** stems from the range of chiral catalysts that are available to mediate enantioselective enolate-based carbon−carbon bond constructions with β-dicarbonyl nucleophiles **3.12** and π-electrophiles **3.13** (Scheme 3-3). These reactions offer significant practical advantages since the pronucleophiles are commercially available and inexpensive. Moreover, activation can be achieved under mild and convenient reaction conditions due to the low pK_a of the carbon acid. Subjection of these chiral intermediates to a second-stage oxidative deacylation would

parlay the established advantages of enolate-based reactions into syntheses of many families of α-keto esters that have not been previously prepared and would not be accessible via a glyoxylate anion catalysis manifold.

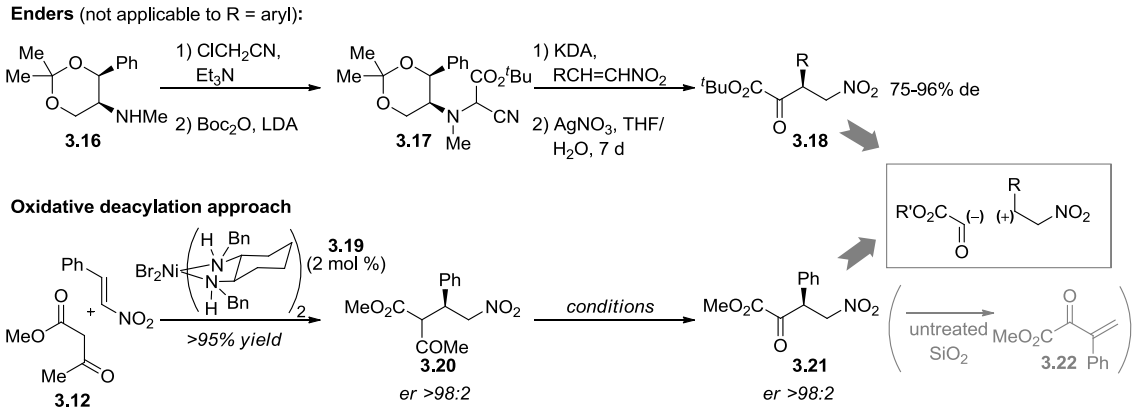
Scheme 3-3. Proposed Strategy to Access Enantioenriched α-Keto Esters



3.3 Preliminary Studies

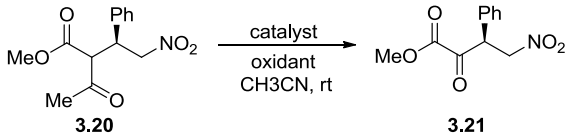
For our preliminary studies we purposely chose a challenging substrate. The oxidative deacylation shown in Scheme 3-4 is an ideal inquiry into the efficiency, mildness and functional group compatibility of the title reaction. The proposed conversion of the Michael addition product **3.20** to the derived α-keto ester **3.21** would give a product of formal alkene nucleophilic glyoxylation. The state of the art in this area comes from Enders[18] which requires the synthesis of a noncommercial chiral auxiliary (**3.16→3.17**) and four overall steps to arrive at the glyoxylation products **3.18**. Additionally, this method was found to be incompatible with nitrostyrenes due to their tendency to readily eliminate nitrous acid (HNO_2) on silica gel to form the corresponding β,γ-unsaturated α-keto ester **3.22**.

Scheme 3-4. Formal Alkene Nucleophilic Glyoxylation: Nitrostyrenes



The asymmetric addition of methyl acetoacetate **3.12** to nitrostyrene was accomplished using the chiral nickel diamine complex **3.19** developed by Evans, providing **3.20** in >98:2 er.[19] The oxidative deacylation was initially conducted under 1 atm of O_2 using 5 mol % $Cu(NO_3)_2 \cdot 3H_2O$, and after 48 h 60% conversion to the α-keto ester was observed. Further optimization (Table 1) revealed that pressurized air (50 psig in a standard Fisher-Porter bottle) and 20 mol % of $Cu(NO_3)_2 \cdot 3H_2O$ provided the best results, affording **3.21** in 83% yield and in >98:2 er; pretreating the silica gel with 5% acetic acid prevents elimination of HNO_2 during purification. The fact that this elimination does not occur during the course of the reaction underscores the mildness of these oxidation conditions. Most importantly, despite the C–H acidity of the product **3.21**[20] and the accompanying possibility of racemization, no loss in enantiopurity is observed allowing enantioenriched β-*aryl* α-keto esters to be prepared for the first time.

Table 3-1. Optimization of Oxidative Deacylation Reaction Conditions

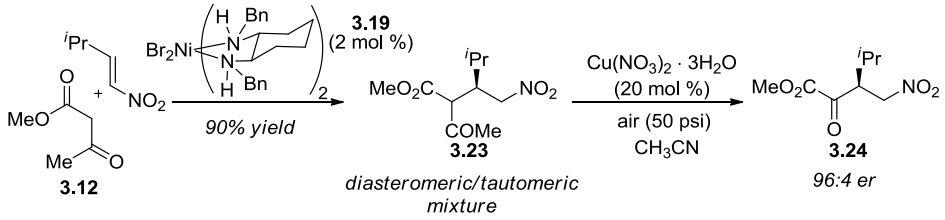


entry	catalyst	oxidant	% conversion[a]	time (h)
1	$Cu(NO_3)_2{\cdot}3H_2O$ (5 mol %)	O_2	60	48
2	$Cu(NO_3)_2{\cdot}3H_2O$ (10 mol %)	O_2	63	23
3	$Cu(NO_3)_2{\cdot}3H_2O$ (20 mol %)	O_2	56	18
4	$FeCl_3$	O_2	43	24
5	$Cu(NO_3)_2{\cdot}3H_2O$ (20 mol %)	air (50 psig)	72	4
6	$Cu(NO_3)_2{\cdot}3H_2O$ (20 mol %)	air (50 psig)	100	24

[a] Determined by ^{1}HNMR spectroscopy.

Conjugate adduct **3.23** was not previously described using catalyst **3.19**, but efficient enantioselective catalysis was observed and aerobic deacylation of the crude tautomeric and stereoisomeric mixture provided α-keto ester **3.24** in good yield (80%) without measurable racemization (96:4 er) (Scheme 3-5).

Scheme 3-5. Formal Alkene Nucleophilic Glyoxylation: Alkyl Nitroolefins

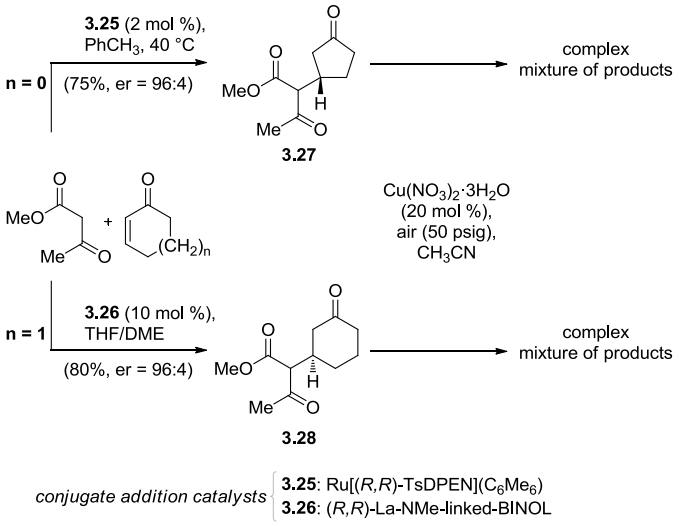


3.4 Reaction Scope

With the goal of diversifying available product classes, attention was directed to finding other cases that might be amenable to aerobic deacylation. Conjugate glyoxylation of cyclic enones has previously been described by Reetz using 1,2-bis(trimethylsilyloxy)-1,2-

diethoxyethene,[21] albeit in racemic form. Asymmetric addition of methyl acetoacetate to both 2-cyclopenten-1-one[22] and 2-cyclohexen-1-one[23] were performed using the chiral catalysts developed by Ikariya (**3.25**) and Shibasaki (**3.26**), respectively. However, subjection of these substrates (**3.27** and **3.28**) directly to the optimized oxidation conditions afforded a complex mixture of products (Scheme 3-6). This observation was attributed to undesired reactivity in the presence of the ketone functionality; therefore, reaction conditions to allow a site-selective ketalization were examined.

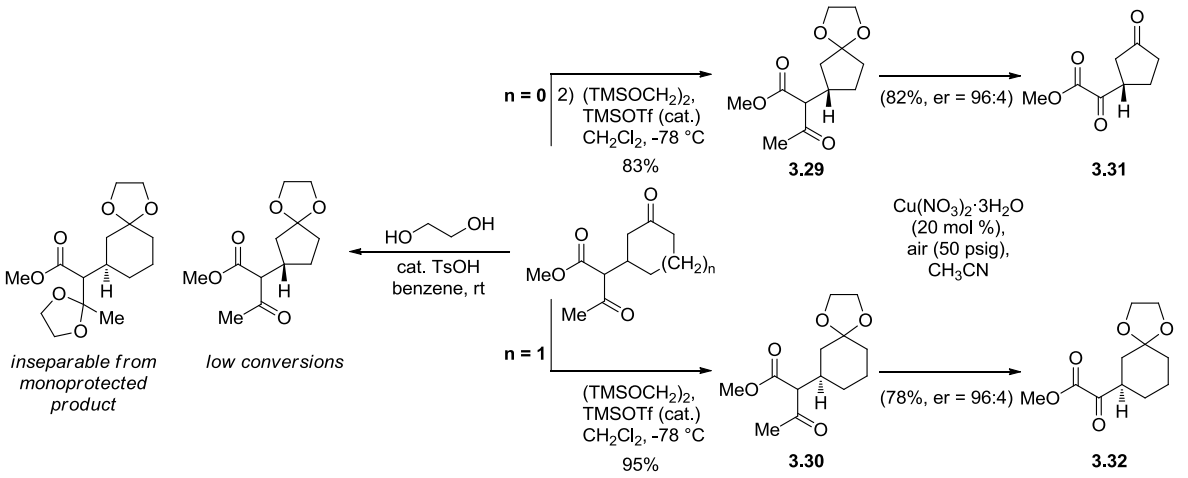
Scheme 3-6. Initial Conjugate Glyoxylation Studies



Initial attempts were made using one equivalent of ethylene glycol and catalytic quantities of *p*-TsOH (Scheme 3-7). For substrate **3.28**, an inseparable mixture of the desired mono-protected and undesired di-protected ketone was obtained, and for **3.27**, very low conversions were observed. This roadblock was overcome by performing the ketalization under the aprotic conditions developed by Noyori[24] using two equivalents of 1,2-bis(trimethylsiloxy)ethane and catalytic quantities of TMSOTf at -78 ºC. The aerobic

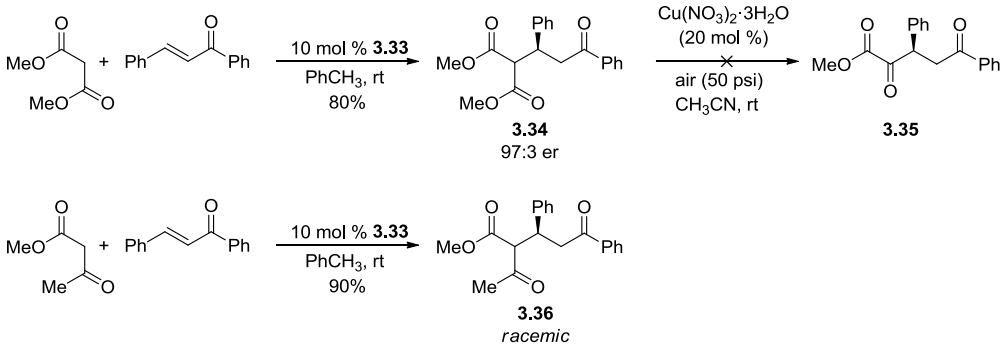
deacylation of the protected substrates **3.29** and **3.30** proceeded cleanly. Concomitant ketal deprotection was observed for **3.29** yielding dione **3.31** in 82% yield and 96:4 er. Conversely, the ketal remained intact for the cyclohexanone derivative **3.30**, which afforded **3.32** (78%, er 96:4) with all three oxygenated functional groups differentiated.

Scheme 3-7. Site Selective Ketalization/Deacylation of Cyclic Enones



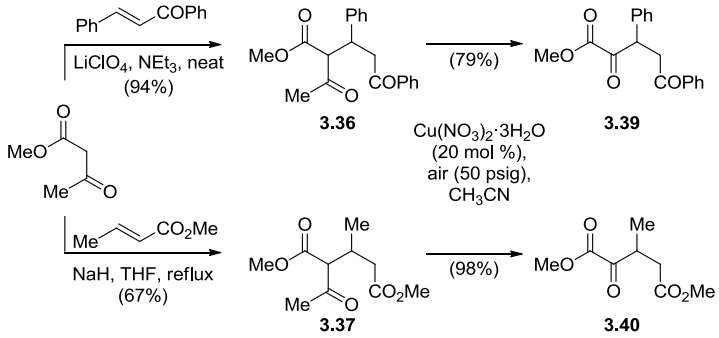
Extension of this method to achieve formal asymmetric glyoxylation of acyclic Michael acceptors was desired, but surprisingly enantioselective acetoacetate additions to acyclic α,β-unsaturated carbonyls have yet to be developed. Kobayashi has reported the asymmetric conjugate addition of dimethyl malonate to chalcones using chiral strontium complex **3.33** (Scheme 3-8).[25] The Clariant patent described the aerobic cleavage of simple linear malonates, but the oxidative cleavage of the branched and more highly functionalized malonate derivative **3.34** to the α-keto ester **3.35** has to date been unsuccessful. Unfortunately, the use of catalyst **3.33** with methyl acetoacetate afforded racemic product **3.36**.

Scheme 3-8. Formal Asymmetric Conjugate Glyoxylation Attempts with Malonate Derivatives



Nonetheless, conjugate adducts (±)-**3.36**[26] and (±)-**3.37**[11] are easily accessible and provide their derived α-keto esters **3.39** and **3.40** in good yields in the presence of Cu(II)/air. This is a more practical method to prepare this class of α-keto esters than those previously described which require conversion to either the nitronate or enol acetate followed by ozonolysis.

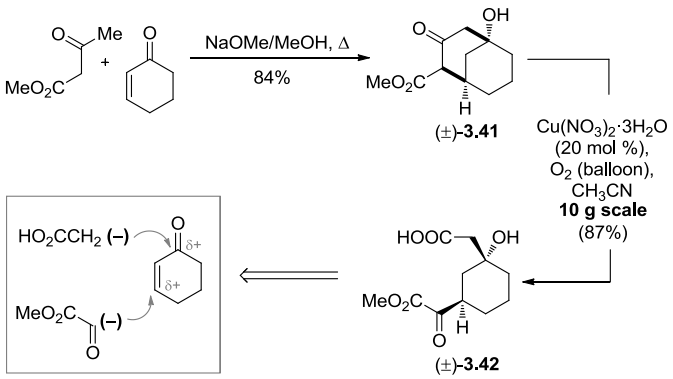
Scheme 3-9. Formal Conjugate Glyoxylation of Acyclic Michael Acceptors



Even more value-added products can be accessed by utilizing the second nucleophilic site on methyl acetoacetate. With an ambident electrophile such as 2-cyclo-hexen-1-one,

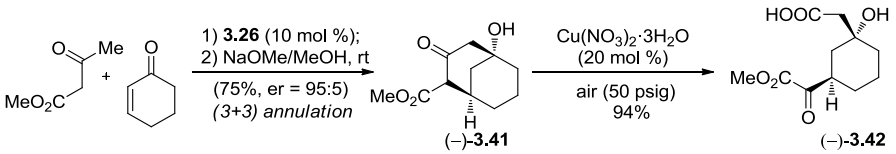
methyl acetoacetate undergoes a (3+3)-annulation providing bicyclo[3.3.1]nonanone **3.41**.[27] Oxidative deacylation of (±)-**3.41** led to a ring-cleavage reaction[17] yielding cyclohexanol **3.42** as single isomer with all *four* oxygenated functional groups differentiated. Notably, the product is the synthetic equivalent of two challenging reactions: enone conjugate glyoxylation and diastereoselective ketone acetate aldolization. The scalability of the aerobic cleavage was highlighted as this reaction was trivially performed on a 10 g scale without the need of chromatography; the product was isolated in pure form by precipitation from diethyl ether with hexanes as the antisolvent.

Scheme 3-10. Formal Racemic Conjugate Glyoxylation/Ketone Acetate Adolization Sequence



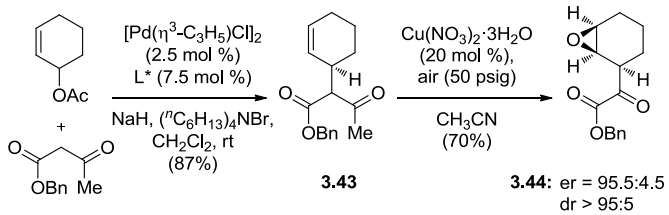
The acetoacetate/cyclohexanone (3+3)-annulation has only been reported in racemic form, but subjection the enantioenriched 1,4-conjugate adduct **3.28** to a second stage aldolization (NaOMe and MeOH) provided (–)-**3.41** in good yield. It was critical to run the aldol cyclization at room temperature to avoid loss in enantioputirty via a retro-Michael/Michael sequence. Aerobic deacylation provided (–)-**3.42** with no loss in enantiopurity (95:5 er).

Scheme 3-11. Formal Asymmetric Conjugate Glyoxylation/Ketone Acetate Adolization Sequence



Dual functionalization was also achieved with unsaturated β-keto ester **3.43**. The asymmetric allylic alkylation of cyclohexen-3-yl acetate has been reported with malonate esters, but the analogous asymmetric reaction with acetoacetate esters to the best our knowledge remained unknown. We have found that benzyl acetoacetate is a competent nucleophile for asymmetric allylic alkylations,[28] affording β-keto ester **3.43** in 95.5:4.5 er. Subjection of **3.43** to the standard oxidative conditions resulted in both aerobic deacylation and epoxidation of the alkene providing **3.44** with >95:5 diastereoselection. The *syn*-stereochemical relationship strongly implicates participation of the α-keto ester or a precursor thereto in the epoxidation.[29]

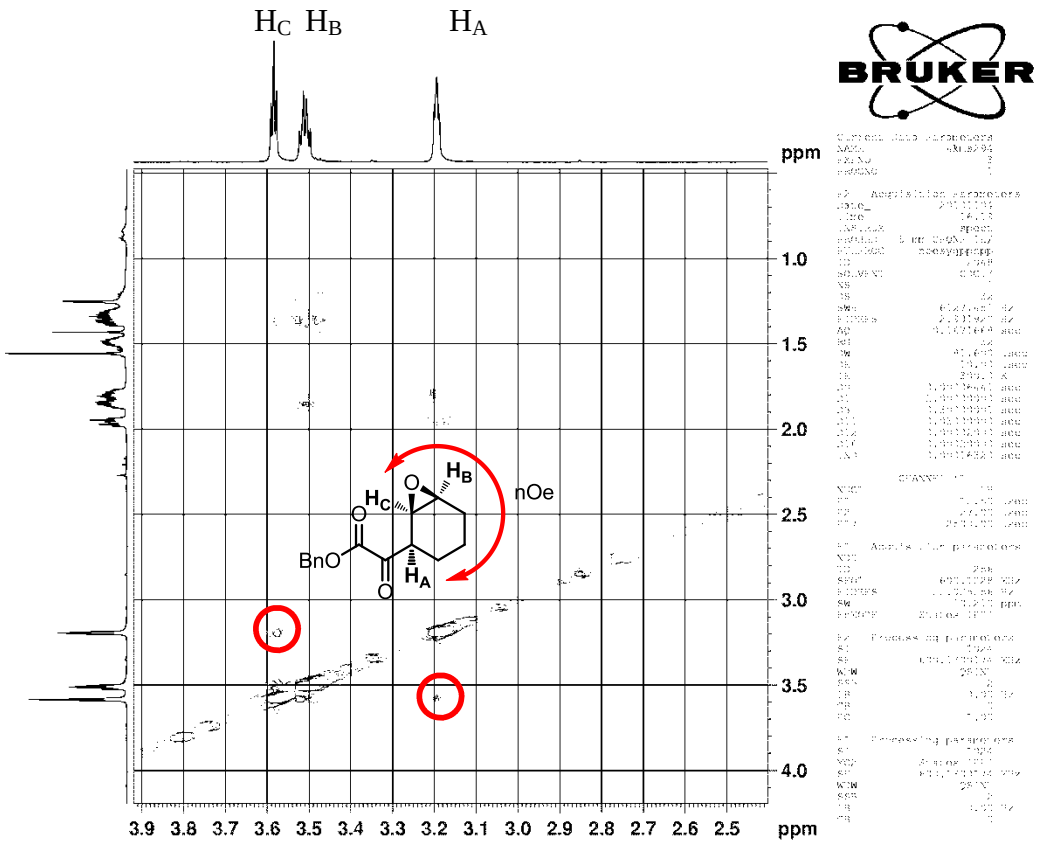
Scheme 3-12. Merged Aerobic Deacylation/Epoxidation



L* = *N*,*N*′-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(2-(diphenylphosphino)benzamide)

3.5 Stereochemical Analysis of 3.44

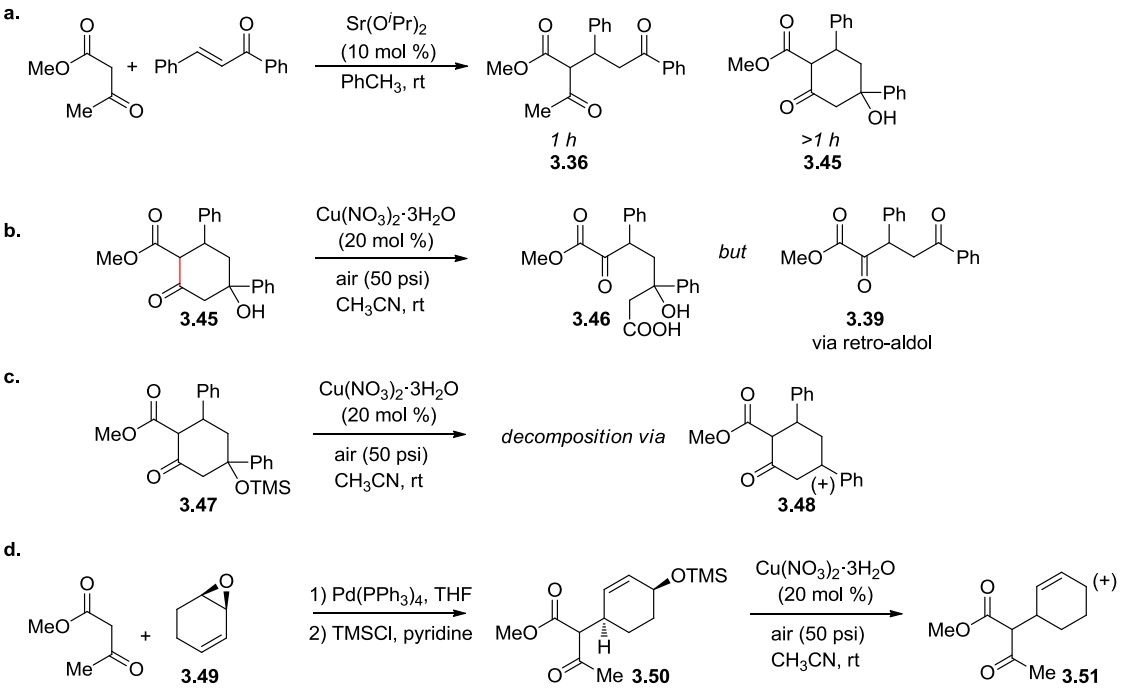
The *syn*-stereochemical relationship of the epoxide and α-keto ester was based on the expectations of the vicinal coupling constant/diehedral angle relationship of H_A and H_C as described by Davies and Whitman for a closely related compound (Figure 3-3).[30] COSY analysis allowed assignment of H_C for which no interactions with the cyclohexane methylenes were observed. NOESY analysis allowed for the assignment of H_A (nOE with H_C but not with H_B) and H_B. If H_A and H_C were *trans*, the coupling constant would be expected to be ~0 Hz (90º dihedral angle) and H_C would appear as a doublet; however, H_C appears as a doublet of doublets which is consistent with a *syn*-relationship.



3.6 Problematic Substrates

While investigating the asymmetric addition of methyl acetoacetate to chalcone, it was observed if the reaction was allowed to run longer than one hour, a (3+3) annulation occurred, affording cyclohexanol **3.45** (Scheme 3-13a). Upon subjection of this substrate to the oxidative conditions, the ring cleavage product **3.46** was expected, however, a retro-aldol reaction was found to be operative and provided Michael adduct **3.39** (Scheme 3-13b). In an attempt to avoid this reactivity, the tertiary alcohol was protected as the trimethylsilyl ether **3.47**. However, decomposition of **3.47** occurred in the presence of Cu(II)/air, perhaps due to the formation of the benzylic carbocation **3.48** (Scheme 3-13c). Similar results were obtained with substrate **3.50**, which was prepared by allylic alkylation of epoxide **3.49** (Scheme 3-13d).[31] Subjection of the free alcohol to the reaction conditions resulted in low conversion to the α-keto ester and the allylic silyl ether derivative underwent decomposition, presumably through a similar pathway (formation of allylic carbocation **3.51**). Addressing these limitations and extending the scope of the deacylation are current areas of interest.

Scheme 3-13. Problematic Substrates for the Aerobic Deacylation



3.7 Conclusions

A simple protocol for the preparation of β-stereogenic α-keto esters has been established through the aerobic deacylation of substituted acetoacetate derivatives. A heretofore underdeveloped relationship between chiral β-keto esters and α-keto esters has been realized that dramatically simplifies the glyoxylate anion problem. The strategy described herein captures many of the characteristics that are often described in "ideal" synthetic methods: aerobic deacylation is operationally simple and scalable, employs starting materials that are commercially available and cheap, generates an innocuous byproduct, provides product diversity, and is compatible with a number of useful functional groups.

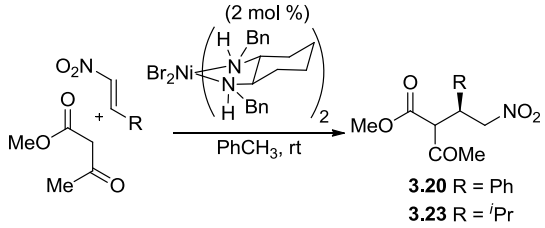
3.8 Experimental Details

Methods. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and C_6D_6 at 7.15 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, br d = broad doublet, t = triplet, br t = broad 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 a Chiralcel WO column. Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH. HPLC analysis was performed on an Agilent Technologies 1200 System equipped with Chiralpak IA, IB, and IC columns (constant flow at 1.00 mL/min). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization (Note: All samples prepared in methanol). Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and

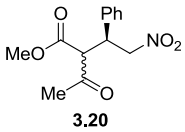
diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

Materials. Tetrahydrofuran and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. 1,1-Dimethoxyethane was purchased from Sigma Aldrich and used without further purification. Copper(II) nitrate trihydrate, 1,2-bis(trimethylsiloxy)ethane and acetonitrile were purchased from Fisher Scientific and used without further purification. The 3 oz. Fisher-Porter bottle was purchased from Andrew Glass Co.

Preparation of Substrates 3.20 and 3.23



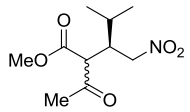
(3*S*)-methyl 2-acetyl-4-nitro-3-phenylbutanoate (3.20):



3.20

The title compound was prepared on a 1 mmol scale according to the procedure described by Evans. Addition of hexanes to the crude reaction mixture afforded **3.20** as a white solid (95% yield) whose spectral properties matched those reported in the literature (dr ~1:1).[1] **SFC analysis**: (Chiralcel, WO, 1.0% MeOH, 1.5 mL/min, 150 bar, 210 nm) > 98:2 er, $t_{R\text{-major-1}}$ 8.8 min, $t_{R\text{-minor-1}}$ 9.5 min; $t_{R\text{-major-2}}$ 10.4 min, $t_{R\text{-minor-2}}$ 10.6 min.

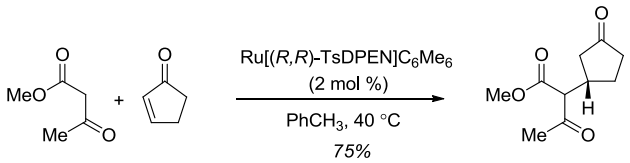
(3*S*)-Methyl 2-acetyl-4-methyl-3-(nitromethyl)pentanoate (3.23):



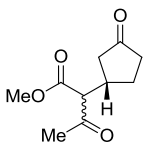
3.23

The title compound was prepared on a 1 mmol scale according to the procedure described by Evans.[1] The reaction afforded **3.23** as a tautomeric and diastereomeric mixture (94% yield). The enantiomeric excess was determined to be 97:3 via conversion to **3.24**. The crude material was used directly in the oxidative deacylation.

Preparation of 3.27



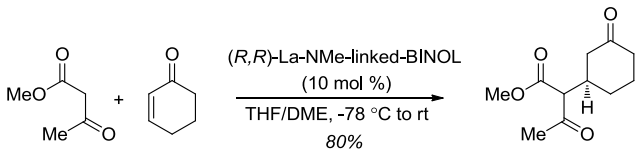
(*S*)-3-Oxo-2-(3-oxo-cyclopentyl)butyric acid methyl ester (3.27):



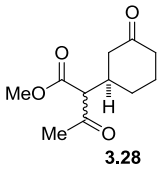
3.27

The title compound was prepared according to the procedure described by Watanabe. Diketone **3.27** was obtained in 75% yield. The spectral properties matched those reported in the literature. The enantiomeric excess was determined via conversion to (*R*)-3-(2-oxopropyl)cyclopentanone. **HPLC Analysis** for that compound: (Chiralcel, IC, 15% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210nm) 96:4 er, $t_{R\text{-major}}$ 28.6 min, $t_{R\text{-minor}}$ 27.1 min.

Preparation of 3.28



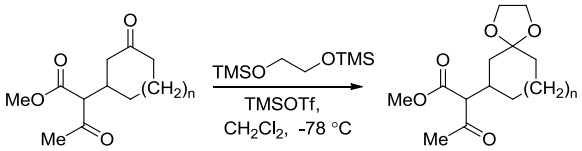
***(R)*-3-Oxo-2-(3-oxo-cyclohexyl)butyric acid methyl ester (3.28):**



3.28

The title compound was prepared according to the procedure described by Shibasaki. Diketone **3.28** was obtained in 80% yield. The spectral properties matched those reported in the literature.[3] The enantiomeric excess was determined by conversion to (*R*)-1-(1,4-dioxaspiro[4.5]decan-7-yl)propan-2-one. **GC Analysis** for that compound: (Chiradex B-DM column, 80 kPa, 0.6 mL/min, 120 ºC) 96:4 er, $t_{R\text{-minor}}$ 77.9 min, $t_{R\text{-major}}$ 74.2 min.

General Procedure for the Ketalization of Substrates 3.27 and 3.28

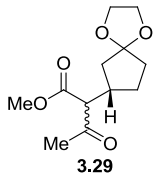


3.27 n=0
3.28 n=1

3.29 n=0
3.30 n=1

An oven-dried flask was charged with the β-ketoester (1 equiv), 1,2-bis(trimethylsiloxy)ethane (2 equiv), and dichloromethane (0.20 M in the β-ketoester) and cooled to -78 ºC. TMSOTf (0.10 equiv) was added and the reaction was allowed to stir at this temperature until the disappearance of starting material was confirmed by TLC analysis (30% EtOAc/hexanes as the mobile phase). The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The layers were separated and the organic was dried over Na_2SO_4. Concentration *in vacuo* afforded the ketals which were purified by flash chromatography using the indicated solvent system.

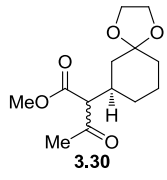
Methyl 3-oxo-2-((*R*)-1,4-dioxaspiro[4.5]nonan-7-yl)butyric acid methyl ester (3.29):



3.29

The title compound was prepared using (*R*)-3-oxo-2-(3-oxo-cyclopentyl)butyric acid methyl ester **(3.27**, 142 mg, 0.717 mmol, 1.0 equiv), 1,2-bis(trimethylsilyoxy)ethane (296 mg, 1.43 mmol, 2.0 equiv) and TMSOTf (16.0 mg, 0.0717 mmol, 0.1 equiv); reaction time = 4 h. Flash chromatography provided **3.29** (145 mg, 0.598 mmol, 83% yield, dr 1:1) as a clear oil. Analytical data for **3.29**: **IR** (thin film cm^{-1}) 2954, 2881, 1743, 1714, 1434, 1357, 1210, 1145, 1025; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.90-3.83 (m, 8H), 3.71 (s, 3H), 3.70 (s, 3H), 3.39 (d, *J* = 2.8 Hz, 1H), 3.37 (d, *J* = 2.8 Hz, 1H), 2.75-2.63 (m, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 2.09-1.94 (m, 2H), 1.91-1.75 (m, 6H), 1.54-1.23 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) 202.0, 169.2, 169.2, 116.9, 116.7, 65.0, 64.1, 64.1, 52.1, 40.5, 40.5, 36.4, 36.3, 35.4, 35.3, 29.0, 28.9, 28.1, 28.1; **TLC** (30% EtOAc/hexanes) R_f 0.32; **LRMS** (ESI) Calcd. for $C_{12}H_{18}O_5Na$: 265.11, Found: 265.15.

Methyl 3-oxo-2-((*R*)-1,4-dioxaspiro[4.5]decan-7-yl)butyric acid methyl ester (5b):

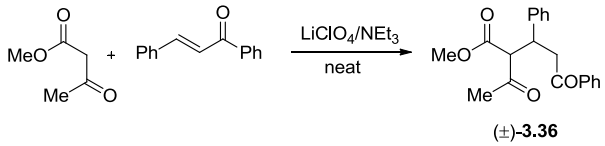


3.30

The title compound was prepared using (*R*)-3-oxo-2-(3-oxo-cyclohexyl)butyric acid methyl ester **(3.28**, 104 mg, 0.490 mmol, 1.0 equiv), 1,2-bis(trimethylsilyoxy)ethane (121 mg, 0.588 mmol, 1.2 equiv) and TMSOTf (11 mg, 0.0490 mmol, 0.10 equiv); reaction time = 1 h. Flash chromatography provided **3.30** (119 mg, 0.47 mmol, 95%, dr 1:1) as a clear oil. Analytical data for **3.30**: **IR** (thin film cm^{-1}) 2946, 1743, 1714, 1434, 1358, 1169, 1147, 1072, 1032, 924; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.92 (brs, 8H), 3.71 (s, 6H), 3.34-3.29 (m, 2H), 2.47-2.41 (m, 2H), 2.21 (s, 6H), 1.74-1.52 (m, 10H), 1.48-1.40 (m, 2H), 1.31-1.20 (m, 2H), 1.04-0.96 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.3, 202.3, 169.1, 169.0, 108.3, 65.4, 65.3, 64.1, 52.0, 38.8,

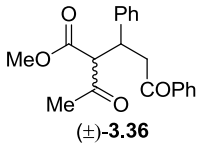
38.5, 35.4, 35.4, 34.5, 29.2, 29.1, 29.0, 28.9, 22.5, 22.4; **TLC** (30% EtOAc/hexanes) R_f 0.26; **LRMS** (ESI) Calcd. for $C_{12}H_{20}O_5Na$: 279.12, Found: 279.17.

Preparation of Substrate 3.36



(±)-**3.36**

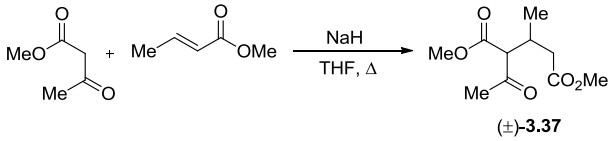
Methyl 2-acetyl-5-oxo-3,5-diphenylpentanoate (3.36):



(±)-**3.36**

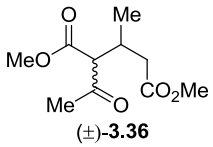
The title compound was prepared according to the procedure described by Saidi. After 1 h, the reaction mix solidified and the resultant white solid was washed with hexanes affording **3.36** as a white solid (95% yield) whose spectral properties matched those reported in the literature.

Preparation of Substrate 3.37



(±)-**3.37**

Dimethyl 2-acetyl-3-methylpentanedioate (8b)

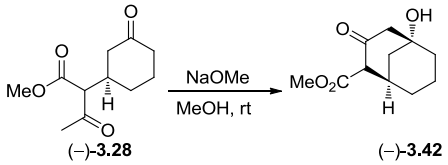


(±)-**3.36**

An oven-dried 100-mL round-bottomed flask equipped with a magnetic stir bar was charged with sodium hydride (0.400 g, 10.0 mmol, 2.0 equiv) and THF (15 mL). The flask was fitted with a condenser and purged with nitrogen. Methyl acetoacetate (1.20 g, 10.0 mmol, 2.0 equiv) was added and the solution was

stirred for 15 minutes. Methyl crotonate (0.500 g, 5.0 mmol, 1.0 equiv) was added and the reaction was heated at reflux for 48 h and then cooled to rt. The reaction was quenched with saturated ammonium chloride (5 mL) and diluted with water and ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (30% EtOAc/hexanes) provided **3.36** (649 mg, 3.0 mmol, 60% yield, dr 1:1) as a clear oil whose spectral properties matched those reported in the literature.

Preparation of Substrate (–)-3.24



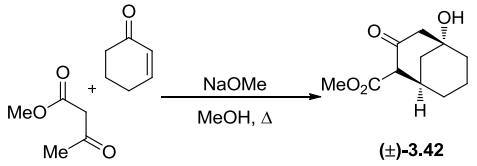
(–)-**3.28** (–)-**3.42**

(1*R*, 2*S*, 5*R*)-methyl 5-hydroxy-3-oxobicyclo[3.3.1]nonane-2-carboxylate (–)-3.42:

A flame-dried 1-dram vial equipped with a magnetic stir bar was charged with (–)-**3.28** (100 mg, 0.471 mmol, 1 equiv), NaOMe (31 mg, 0.565 mmol, 1.2 equiv), and methanol (2 mL). The vial was sealed with a PTFE-lined screw cap and the reaction mixture was allowed to stir at rt. After 20 min, the reaction mixture turned brown; stirring was continued for 15 h. The reaction was quenched with water and neutralized with 1 M HCl. The aqueous layer was extracted with ethyl acetate three times and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting brown oil was purified by flash chromatography (30% EtOAc/hexanes, R_f 0.32) and (–)-**3.42** (94 mg, 0.442 mmol, 94%) was obtained as a clear viscous oil whose spectral properties matched those reported in the literature. The enantiomeric ratio was determined to be 95:5 by HPLC analysis

(Chiralpak, IB, 5% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; $t_{R\text{-major}}$ 17.0 min, $t_{R\text{-minor}}$ 18.4 min); $[\alpha]_D^{26}$ = -52.2.

Scale-Up of (±)-3.42

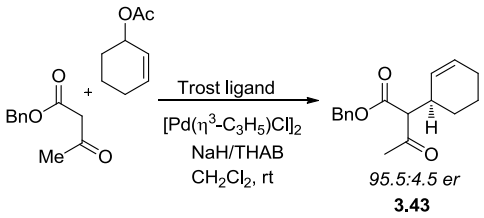


The title compound was prepared on a 55 mmol scale according to the procedure of Momose and Muraoka with the following modifications:

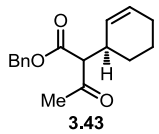
1. Instead of refluxing for 36 h, TLC analysis (30% EtOAc/hexanes) showed the reaction was complete in 15 h.

2. Instead of purification via distillation, the crude material was purified via flash chromatography (30% EtOAc/hexanes), affording the title compound (84% yield) as a clear viscous oil whose spectral properties matched those reported in the literature.

Preparation of 3.43



Benzyl 2-((*R*)-cyclohex-2-en-1-yl)-3-oxobutanoate (3.43)



3.43

An oven-dried 25-mL round bottomed flask equipped with a stir bar was charged with sodium hydride (0.124 g, 3.1 mmol, 3.1 equiv) and dichloromethane (15 mL). Benzyl acetoacetate (0.577 g, 3.0 mmol, 3 equiv) followed by tetrahexylammonium bromide (1.35 g, 3.1 mmol, 3.1 equiv) were added and stirred for 20 minutes. [Note: The reaction does not become homogeneous.] In an inert atmosphere glovebox, a 50-mL round bottomed flask equipped with a stir bar was charged with allylpalladium dimer (0.0091 g, 0.025 mmol, 0.025 equiv), *N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(2-(diphenylphosphino)benzamide (0.0518 g, 0.075 mmol, 0.075 equiv) and dichloromethane (2 mL). The flask was sealed with a septum, removed from the box and stirred under nitrogen. After 5 min, 2-cyclohexenyl acetate (0.140 g, 1.0 mmol, 1 equiv) was added. The solution of tetrahexylammonium benzyl acetoacetate was transferred via cannula into the reaction mix over 5 min. The reaction was allowed to stir for 15 h at rt and was quenched with saturated ammonium chloride and diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (2x) and the combined organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (10% EtOAc/hexanes) provided **3.43** (240 mg, 0.88 mmol, 88% yield, dr 1:1) as a clear oil. The enantiomeric ratio was determined to be 95.5:4.*5* via conversion to **3.44.** Analytical Data for **3.43**: **IR** (thin film, cm^{-1}) 2360, 2341, 1743, 1715, 1135; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 10H), 5.76-5.75 (m, 2H), 5.49-5.44 (m, 2H), 3.44-3.40 (m, 2H), 2.97-2.95 (m, 2H), 2.20 (s, 3H), 2.19 (s, 3H), 1.98-1.97 (m, 4H), 1.75-1.66 (m, 4H), 1.58-1.55 (m, 2H), 1.30-1.27 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) 202.5, 202.4, 168.6, 168.5, 135.3, 129.8, 129.5, 128.5, 128.4, 128.3, 128.3, 128.2, 127.4, 127.1, 67.0, 65.0, 35.1, 35.0, 29.8, 29.5, 26.6,

26.5, 24.9, 24.8, 20.8, 20.7; **TLC** (20% EtOAc/hexanes) R_f 0.48; **LRMS** (ESI) Calcd. for $C_{17}H_{20}O_3Na$: 295.13, Found: 295.19.

Preparation of (±)-3.43

An oven-dried 25-mL round bottomed flask equipped with a stir bar was charged with sodium hydride (0.120 g, 3.0 mmol, 3 equiv) and THF (5 mL). Benzyl acetoacetate (0.577 g, 3.0 mmol, 3 equiv) was added and the suspension was stirred for 10 minutes. A solution of palladium(II) acetate (0.0067 g, 0.030 mmol, 0.030 equiv) and triphenylphosphine (0.024 g, 0.090 mmol, 0.090 equiv) in 2.5 mL THF was added via cannula followed by 2-cyclohexenyl acetate (0.140 g, 1.0 mmol, 1.0 equiv) in 2.5 mL THF. The reaction was heated at reflux for 16 h and worked up and purified as above to provide (±)-**3.43** (0.250 g, 0.92 mmol, 92% yield).

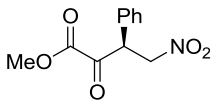
General Procedure A: Aerobic Deacylation with Oxygen as the Oxidant

A round-bottomed flask was charged with the β-keto ester (1 equiv), copper(II) nitrate trihydrate (0.20 equiv), and acetonitrile (1 mL/100 mg β-keto ester). Oxygen was bubbled through the reaction solution for 10 min. The reaction was stirred at rt under 1 atm of oxygen (balloon) for the indicated time and then diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (2x) and the combined organic extracts were washed with brine and dried over Na_2SO_4. Concentration *in vacuo* afforded the α-keto esters which were purified by flash chromatography using the indicated solvent systems.

General Procedure B: Aerobic Deacylation with Air as the Oxidant

A 3 oz. Fisher-Porter bottle was charged with the β-ketoester (1.0 equiv), copper(II) nitrate trihydrate (0.20 equiv) and acetonitrile (1 mL/100 mg of β-ketoester). A pressure gauge was attached and the vessel pressurized with air (50 psig). The reaction was stirred at rt for 15-24 h and diluted with ethyl acetate and water.The aqueous layer was extracted with ethyl acetate (2x) and the combined organic extracts were washed with brine and dried over Na_2SO_4. Concentration *in vacuo* afforded the α-keto esters which were purified by flash chromatography using the indicated solvent systems.

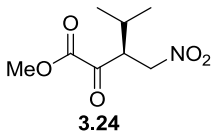
(*S*)-methyl 4-nitro-2-oxo-3-phenylbutanoate (3.21):



3.21

The title compound was prepared according to General Procedure B using (3*S*)-methyl 2-acetyl-4-nitro-3-phenylbutanoate (**3.20**, 0.100 g, 0.377 mmol, 1 equiv); reaction time = 24 h. Flash chromatography (97% (30% EtOAc/hexanes)/3 % AcOH) provided **3.21** (0.076 g, 0.320 mmol, 85% yield) as a clear oil in >98:2 er as determined by SFC analysis (Chiralcel, WO, 1.0% MeOH, 1.5 mL/min, 150 bar, 210 nm; $t_{R\text{-minor}}$ 8.4 min, $t_{R\text{-major}}$ 9.0 min). Analytical data for **3.21**: **IR** (thin film, cm^{-1}) 1731, 1553, 1377, 1257, 1150, 1074, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.39 (m, 3H), 7.29-7.27 (m, 2H), 5.38 (dd, *J* = 10, 4.8 Hz, 1H), 5.20 (dd, *J* = 14.8, 10 Hz, 1H), 4.64 (dd, *J* = 14.8, 4.8 Hz, 1H), 3.84 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.8, 160.0, 130.3, 129.7, 129.3, 129.0, 74.6, 53.3, 50.8; **TLC** (30% EtOAc/hexanes) R_f 0.30; **LRMS** (ESI) Calcd. for $C_{11}H_{11}NO_5Na$ + CH_3OH: 292.08, Found: 292.06; $[\alpha]_D^{25}$ = -213.6 (*c* = 0.500, $CHCl_3$). [Note: If AcOH is omitted during the chromatographic purification, elimination to enone **3.22** results.]

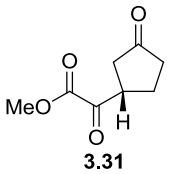
(*S*)-methyl 4-methyl-3-(nitromethyl)-2-oxopentanoate (3.24):



3.24

The title compound was prepared according to General Procedure B using (3*S*)-methyl 2-acetyl-4-methyl-3-(nitromethyl)pentanoate **(3.23**, 0.100 g, 0.432 mmol, 1.0 equiv); reaction time = 16 h. Flash chromatography (20% EtOAc/hexanes) provided **3b** (0.070 g, 0.345 mmol, 80% yield) as a clear oil in 97:3 er as determined by HPLC analysis (Chiralpak, IA, 5% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; $t_{R\text{-minor}}$ 15.2 min, $t_{R\text{-major}}$ 16.7 min). Analytical data for **3.24**: **IR** (thin film, cm^{-1}) 1729, 1555, 1375, 1243, 1061; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 14.8, 10.8 Hz, 1H), 4.52 (dd, *J* = 14.8, 3.6 Hz, 1H), 4.07-4.02 (m, 1H), 3.93 (s, 3H). 2.20-2.11 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 1H), 0.92 (d, *J* = 6.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.0, 160.8, 72.8, 53.3, 49.8, 28.5, 20.4, 19.0; **TLC** (30% EtOAc/hexanes) R_f 0.42; **LRMS** (ESI) Calcd. for $C_8H_{18}NO_5Na$ + CH_3OH: 258.10, Found: 258.07; $[\alpha]_D^{25}$ = -89.6 (c = 0.700, $CHCl_3$).

(*R*)-Methyl 2-oxo-2-(3-oxocyclopentyl)acetate (3.31):

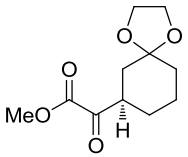


3.31

The title compound was prepared according to General Procedure B using methyl 3-oxo-2-((*R*)-1,4-dioxaspiro[4.5]nonan-7-yl)butyric acid methyl ester (**3.29**, 0.077 g, 0.318 mmol, 1 equiv); reaction time =24 h. Flash chromatography (20% EtOAc/hexanes) provided **3.31** (0.044 g, 0.259 mmol, 81% yield) in 96:4 er as determined by HPLC anlaysis (Chiralpak, IC, 15% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; $t_{R\text{-minor}}$ 10.3 min, $t_{R\text{-major}}$ 11.7 min). Analytic data for **3.31**: **IR** (thin film cm^{-1}); **^{1}H NMR** (400 MHz, C_6D_6) δ 3.19 (s, 3H), 3.07-3.01 (m, 1H), 2.16-2.07 (m, 1 H), 1.88-1.83 (m, 1H), 1.77-1.74 (m, 1H), 1.54-1.50 (m, 2H), 1.36-1.34 (m, 1H); **^{13}C NMR** (150

MHz) δ 215.3, 193.7, 161.0, 53.3, 44.2, 39.4, 37.3, 25.4; **TLC** (30% EtOAc/hexanes) R_f 0.28 (20% EtOAc/hexanes); **LRMS** (ESI) Calcd. for $C_8H_{10}O_4Na$ + CH_3OH: 225.07, Found: ; $[\alpha]_D^{25}$ = -9.00 (c = 0.75) .

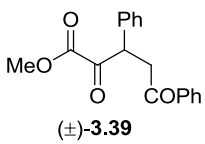
(*R*)-Methyl 2-oxo-2-(1,4-dioxaspiro[4.5]decan-7-yl)acetate (3.32):



3.32

The title compound was prepared according to General Procedure B using methyl 3-oxo-2-((*R*)-1,4-dioxaspiro[4.5]decan-7-yl)butyric acid methyl ester (**3.30**, 0.0610 g, 0.238 mmol, 1.0 equiv); reaction time = 15 h. Flash chromatography (30% EtOAc/hexanes) provided **3.32** (0.0430 g, 0.188 mmol, 79% yield) in 96:4 er as determined by HPLC analysis (Chiralpak, IC, 5% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; $t_{R\text{-minor}}$ 10.7 min, $t_{R\text{-major}}$ 11.4 min). Analytical data for **3.32**: **IR** (thin film cm^{-1}) 2950, 1731, 1454, 1250, 1164, 1073, 1020, 947; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.95 (s, 4H), 3.87 (s, 3H), 3.37-3.31 (m, 1H), 1.95-1.82 (m, 3H), 1.75-1.62 (m, 3H), 1.57-1.50 (m, 1H), 1.48-1.38 (m, 1H); **^{13}C NMR** (100 MHz) δ 195.9, 161.9, 108.3, 64.4, 52.7, 44.7, 35.6, 34.6, 26.4, 22.5; **TLC** (30% EtOAc/hexanes) R_f 0.34; **LRMS** (ESI) Calcd. for $C_{11}H_{16}O_5Na$ + CH_3OH: 283.12, Found: 283.17; $[\alpha]_D^{28}$ = -20.1 (c = 0.850, $CHCl_3$).

Methyl 2,5-dioxo-3,5-diphenylpentanoate (3.39):

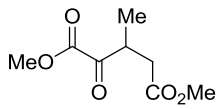


(±)-**3.39**

The title compound was prepared according to General Procedure B using methyl 2-acetyl-5-oxo-3,5-diphenylpentanoate (**3.36**, 0.100 g, 0.206 mmol, 1.0 equiv); reaction time = 20 h. Flash chromatography (30% EtOAc/hexanes) provided **3.39** as clear oil. Analytical data for **3.39**: **IR** (thin film cm^{-1})

1730, 1679, 1449, 1261, 1037, 751, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8 Hz, 2H), 7.57 (d, *J* = 7.2, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.36-7.30 (m, 5H), 5.16 (dd, *J* = 10.4, 2.8 Hz 1H), 4.05 (dd, *J* = 18.4, 10.8 Hz, 1H), 3.85 (s, 3H), 3.46 (dd, *J* = 18.4, 2.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.3, 191.8, 160.8, 136.0, 135.3, 133.5, 129.2, 128.8, 128.6, 128.2, 128.0, 52.9, 48.4, 43.3; **TLC** (30% EtOAc/hexanes) R_f 0.43; **LRMS** (ESI) Calcd. for $C_{18}H_{16}O_4Na$: 319.09, Found: 319.07.

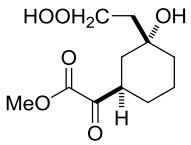
Dimethyl 3-methyl-2-oxopentanedioate (3.40):



(±)-**3.40**

The title compound was prepared according to General Procedure B using dimethyl 2-acetyl-3-methylpentanedioate (**3.36**, 0.336 g, 1.55 mmol, 1 equiv); reaction time = 15 h. Concentration *in vacuo* provided **3.39** (0.283 g, 1.50 mmol, 97% yield) as a clear oil. Analytical data for **3.39**: **IR** (thin film cm^{-1}) 2360, 2337, 1732, 1261, 1172; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.89 (s. 3H), 3.73-3.69 (m, 1H), 3.66 (s, 3H), 2.84 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.51 (dd *J* = 16.8, 5.2 Hz, 1H) 1.21 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 195.8, 172.1, 161.1, 52.9, 51.9, 38.2, 36.7, 15.8; **TLC** (30% EtOAc/hexanes) R_f 0.38; **LRMS** (ESI) Calcd. for $C_8H_{12}O_5Na$: 211.06, Found: 211.04.

2-((1*R*,3*R*)-1-hydroxy-3-(2-methoxy-2-oxoacetyl)cyclohexyl)acetic acid (3.42):

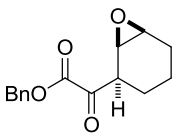


3.42

The title compound was prepared according to General Procedure B (3 oz. Fisher Porter bottle unable to accommodate this scale) using (1*R*, 2*S*, 5*R*)-methyl 5-hydroxy-3-oxobicyclo[3.3.1]nonane-2-carboxylate (**3.41**, 0.106 g, 0.500 mmol, 1.0 equiv); reaction time = 15 h. Flash chromatography (50% EtOAc/hexanes) provided **11** (0.115 g, 0.470 mmol, 94% yield) as a clear viscous oil in 95:5 er as determined

by HPLC analysis (Chiralpak, IC, 25% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; $t_{R\text{-minor}}$ 17.2 min, $t_{R\text{-major}}$ 19.4 min). Analytical data for **3.42**: **IR** (thin film, cm^{-1}) 2942, 1725, 1437, 1406, 1254, 968, 632; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.58-3.50 (m, 1H), 2.55 (s, 2H), 2.04-2.00 (m, 2H), 1.98-1.86 (m, 2H), 1.83-1.79 (m, 1H), 1.70-1.67 (m, 1H), 1.45-1.38 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 196.9, 177.4, 161.7, 69.4, 52.9, 46.1, 42.0, 37.1, 36.0, 27.2, 20.4; **TLC** (50% EtOAc/hexanes) R_f 0.28; **LRMS** (ESI) Calcd. for $C_{11}H_{16}O_6Na$ + CH_3OH: 299.11, Found: 299.13. $[\alpha]_D^{26}$ = -9.74. (±)-**11** was prepared according to General Procedure A using methyl 5-hydroxy-3-oxobicyclo[3.3.1]nonane-2-carboxylate (**(±)-3.41,** 10.0 g, 47.1 mmol, 1.0 equiv) in a 250-mL round bottomed flask; reaction time = 15 h. The material was dissolved in 50 mL diethyl ether and the product precipitated out upon the addition of 150 mL of hexanes. The off-white solid was collected by filtration to provide (±)-**3.42** (10.0 g, 40.9 mmol, 87% yield, mp 85-87 °C).

Benzyl 2-((1*R*,2*R*,6*S*)-7-oxabicyclo[4.1.0]heptan-2-yl)-2-oxoacetate (3.44):



3.44

The title compound was prepared according to General Procedure B using benzyl 2-((*R*)-cyclohex-2-en-1-yl)-3-oxobutanoate (**3.43**, 0.100 g, 0.367 mmol, 1.0 equiv); reaction time = 16 h. Flash chromatography (10% EtOAc/hexanes) provided **3.44** (0.064 g, 0.246 mmol, 67% yield) as a clear oil in 95.5: 4.5 er as determined by HPLC analysis (Chiralpak, IB, constant flow at 1.00 mL/min, 210 nm; $t_{R\text{-major}}$ 12.7 min, $t_{R\text{-minor}}$ 15.3 min). Analytical data for **3.44**: **IR** (thin film, cm^{-1}) 2918, 1731, 1456, 1246, 1065, 1032, 976, 753, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 5H), 5.33 (m, 2H), 3.59-3.58 (t, *J* = 4.0 Hz, 1H), 3.52-3.50 (dt, *J* = 9.6, 5.6 Hz 1H), 3.20-3.19 (dt, *J* = 4.0, 1.4 Hz, 1H), 1.99-1.88 (m, 1H), 1.86-1.80 (m, 2H), 1.51-1.49 (m, 1H), 1.40-1.32 (m,

2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 192.5, 161.2, 134.5, 128.7, 128.7, 128.5, 68.0, 51.8, 51.0, 43.7, 23.5, 20.1, 17.3; **TLC** (20% EtOAc/hexanes) R_f 0.29; **LRMS** (ESI) Calcd. for $C_{15}H_{16}O_4Na + CH_3OH$: 315.12, Found: 315.12; $[\alpha]_D^{25}$ = -38.3.

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CHAPTER FOUR

DYNAMIC KINETIC RESOLUTION OF α-KETO ESTERS VIA ASYMMETRIC TRANSFER HYDROGENATION

4.1 Introduction

The preparation of enantioenriched organic molecules is an increasingly important objective in organic synthesis due to the growing need and interest in such compounds in the pharmaceutical and agrochemical industries.[1] Many essential biomolecules exist in homochiral form. Examples include carbohydrates, which are involved in cell signaling and recognition processes, and amino acids, which are the primary constituents of structural proteins, enzymes, and receptors; as a result, biological activity is highly enantiomer dependent. This makes the advancement of drug candidates as racemates increasingly difficult to justify, as one enantiomeric form can be inactive and/or have adverse effects. Therefore, the development of methods to access enantiopure compounds is of considerable importance.

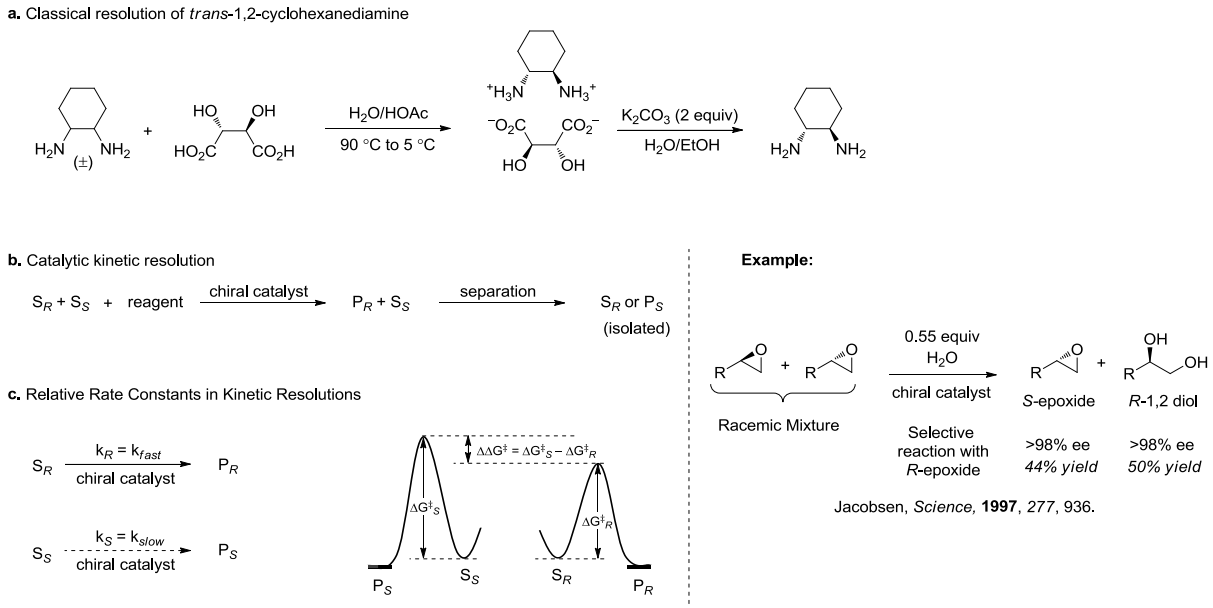
The majority of methods used for the preparation of enantiomerically enriched compounds can be classified into three distinct strategies: the use of enantiopure compounds provided by Nature (chiral pool), enantioselective synthesis and the resolution of a pair of enantiomers. There are a number of instances where the chiral pool approach is unbeatable, but the range of compounds provided by Nature is limited in regards to structure and stereochemistry; for this reason asymmetric synthesis and the resolution of racemates are important strategies for accessing enantiopure substances.

Significant advances have been made over the past several decades in asymmetric synthesis,[2-3] particularly in the development of catalytic enantioselective reactions. The advantages associated with this approach are well-recognized and include: 1) access to either enantiomer of product based on which enantiomer of reagent/auxiliary/catalyst is employed; 2) the use of readily available achiral starting materials; and 4) the minimization of waste typically associated with resolution processes (vide infra). Additionally, a number of factors influence the practicality of an asymmetric process and the characteristics that generally describe an ideal enantioselective transformation include, but are not limited to: 1) the products are obtained in near quantitative yield in high enantiomeric excess; 2) the chiral reagent or catalyst is inexpensive and does not contribute to the overall cost; 3) the reaction can be applied reliably and reproducibly on any scale; and 4) there is minimal generation of byproducts and waste. While there are a few asymmetric catalytic methodologies that make it as convenient to prepare highly enantioenriched materials as it is to prepare racemic mixtures (i.e. 1,2 diols, epoxy alcohols, and certain hydrogenation products), there are a far greater number of circumstances where it is much easier and cost effective to access racemates. As a result, resolution strategies are commonly evaluated against asymmetric methods.

There are two commonly used resolution techniques, classical and kinetic. Classical resolutions involve the use of a stoichiometric amount of a chiral resolving reagent which associates to the substrate, either covalently or non-covalently, to generate a pair of diastereomers. The diastereomers are then separated, and through a separate chemical transformation, the substrate is released from the resolving reagent. This approach has proven to be especially useful for the resolution of amines and carboxylic acids through salt formation (Scheme 4-1a). Kinetic resolutions involve the use of a chiral catalyst or reagent to

promote the selective reaction of one enantiomer in a racemic substrate (S) over the other yielding a mixture of enantioenriched starting material and product (P), from which the desired component is then isolated (Scheme 4-1b). The relative rates of reaction for the substrate enantiomers, typically expressed as $k_{rel} = k_{fast}/k_{slow}$, are dictated by the magnitude of $\Delta\Delta G^{\ddagger}$. This corresponds to the difference in energies between the diastereomeric transition states in the selectivity-determining step of the catalytic reaction (Scheme 4-1c). Although numerous methods exist which are highly efficient in terms of enantio-discrimination for each of the above resolutions, the maximum theoretical yield is only 50% for each enantiomer, which places a low ceiling on the productivity of such processes.

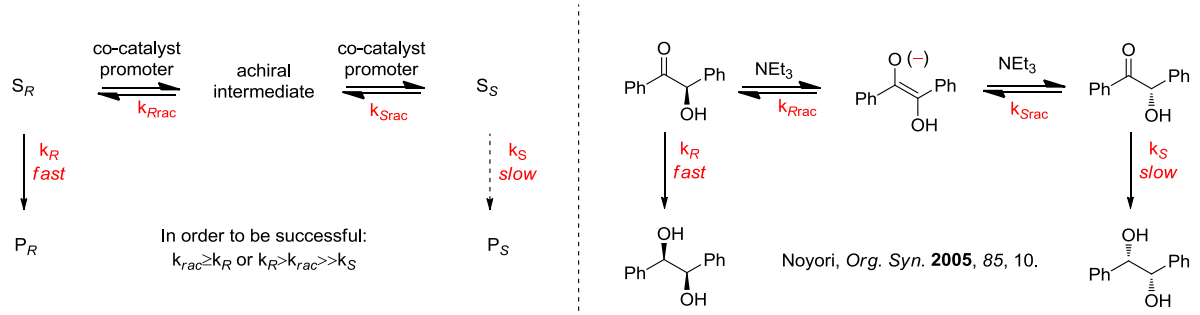
Scheme 4-1. Classical and Kinetic Resolutions



In some special circumstances, it is possible to induce substrate racemization under the conditions of a kinetic resolution, which allows the "undesired" resolution byproduct to

be converted back to the reactive enantiomer. It then becomes possible, in principle, to convert 100% of the racemate to the desired product (Scheme 4-2); this process is known as a dynamic kinetic resolution (DKR).[5] While DKRs also rely on differential reactivity of substrate enantiomers (S_R/S_S), they are distinct from standard kinetic resolutions since the catalyst is always encountering a racemic, or nearly racemic substrate. As the faster acting enantiomer is depleted during the course of the reaction, the equilibrium of S_R/S_S is readjusted by racemization of the slower reacting counterpart S_S. The kinetic balance of the two concurring reactions (racemization and product formation) is of crucial importance for the success of a DKR (Scheme 4-2). The rate constants for racemization (k_{rac}) and the transformation of the more reactive enantiomer (k_R) have to match each other, specifically, k_{rac} should be equal to or greater than k_R. If k_{rac} is smaller than k_R, k_{rac} needs to be much greater than the transformation of the less reactive enantiomer k_S ($k_R > k_{rac} \gg k_S$). This system is an example of a reaction under Curtin-Hammett control in which the composition of the products is determined by the free energies of the transition states and not the composition of the starting materials.[6]

Scheme 4-2. Kinetics of a Dynamic Kinetic Resolution

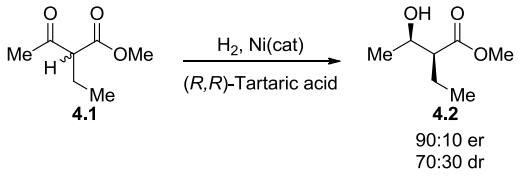


The simplest and hence most widely used method for in situ racemization involves acid/base-catalyzed enol(ate) formation.[7] As such, a number of α-substituted carbonyl compounds have successfully been dynamically resolved in this manner. The propensity of β-stereogenic α-keto esters to racemize under acidic and basic reaction conditions has been highlighted in previous chapters. While this process is undesired for enantioselective syntheses, it is favorable when considering opportunities for dynamic asymmetric reaction development. The work reported herein describes the development of the first highly selective dynamic kinetic resolution of several classes of α-keto esters via asymmetric transfer hydrogenation.

4.2 Background

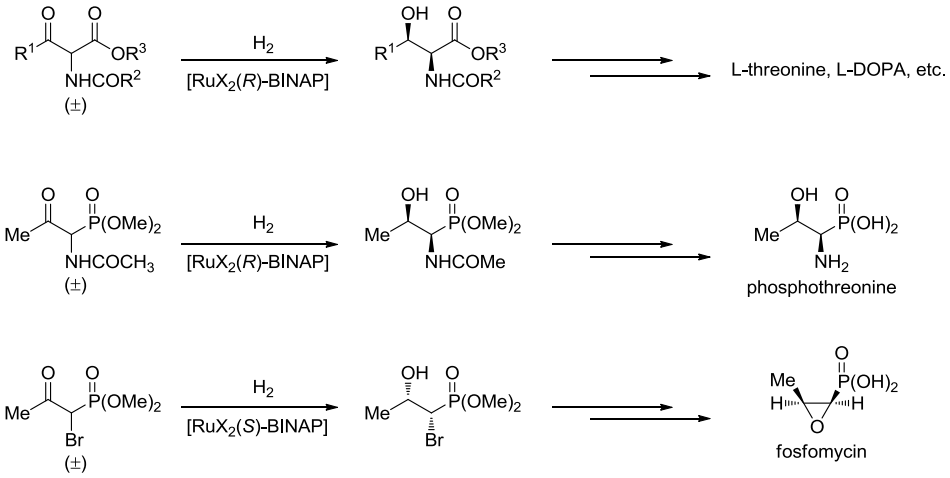
The enantioselective hydrogenation of configurationally labile α-substituted-β-keto esters is the archetypal dynamic kinetic resolution which is used to create greater than 100 tons of chiral material each year.[8] The high impact of this transformation flows from (1) the ready availability of the starting materials, (2) the use of H_2 as the stoichiometric reductant, and (3) the ability to simultaneously control two stereogenic centers in a useful product. As previously mentioned, the success of the reaction relies upon the acidity of the carbon acid that facilitates enantiomer interconversion via the achiral enol. The first example of this dynamic process was described by Tai and co-workers in 1979 for the hydrogenation of methyl 2-ethyl-3-oxobutyrate **4.1** with a chiral nickel catalyst (Scheme 4-3).[9] Addition of hydrogen from the catalyst surface in the preferentially bound 2*S*-**4.1** complex furnished the 2*S*,3*R*-**4.2** *syn*-product in a 70:30 dr and 90:10 er.

Scheme 4-3. First Example of DKR of β-Keto Esters



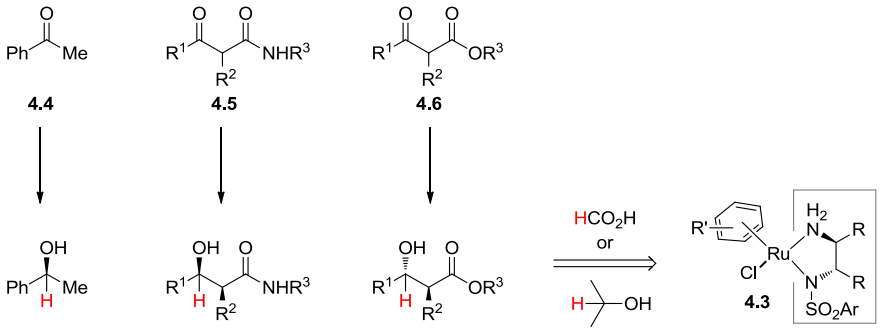
Seminal work by Noyori using homogenous Ru(II) hydrogenation catalysts allows for high levels of enantio- and diastereocontrol to be achieved, greatly extending the synthetic utility of this method.[10] Notably, this dynamic kinetic resolution has been used on industrial scale for the synthesis of biologically important compounds including threonine,[11] phosphothreonine,[12] and fosfomycin[13] (Scheme 4-4). A variety of chiral variants have been developed and BINAP-based catalysts have particularly displayed excellent stereoinductive properties. However, no single catalyst can be universal due to the structurally diverse array of ketonic substrates. This hydrogenation system has the flexibility to cope with such diverse situations through modification of the catalyst structure and reaction conditions. A wide range of chiral ruthenium catalysts can be prepared by different combinations of chiral phosphane and diamine ligands.[14]

Scheme 4-4. Synthetic Applications of Ru(II) Catalyzed DKR of β-Keto Esters



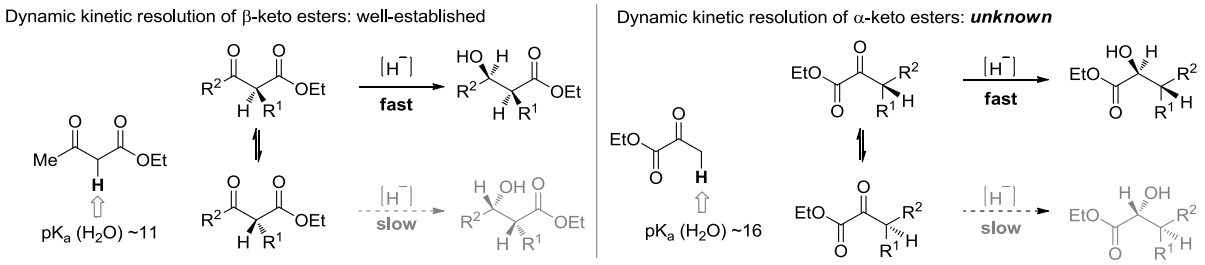
Due to the air and moisture sensitivity of the above ruthenium(II) catalysts and the high pressures that are required for certain substrates, catalytic reductions that do not require molecular hydrogen have been developed. The (arene)RuCl(monosulfonamide) catalyst scaffold **4.3** developed by Noyori has proven to be highly efficient for the asymmetric transfer hydrogenation of simple ketones[15] **4.4** and the dynamic reduction of α-substituted-β-keto esters[16] **4.5** and amides[17] **4.6** (Scheme 4-5). This process has practical advantages due to its operational simplicity and use of either isopropanol or formic acid as the organic reductant.

Scheme 4-5. **(Dynamic) Asymmetric Transfer Hydrogenation of Ketones**



While the dynamic kinetic resolution of β-keto esters is well-established, the analogous reaction for α-keto esters is an unknown process, despite its enormous potential synthetic utility and complementary nature of the derived products (Scheme 4-6). The C–H acidity of β-silyoxy α-keto esters **4.7** was first realized when we observed isomerization of these products to the corresponding α-silyloxy β-keto ester under basic reaction conditions (Chapter 2). We sought to capitalize upon this reactivity in developing a dynamic kinetic resolution via asymmetric reduction to afford orthogonally protected 1,2-diols **4.8** (vide infra, Scheme 4-7), a common structural motif in many natural products.

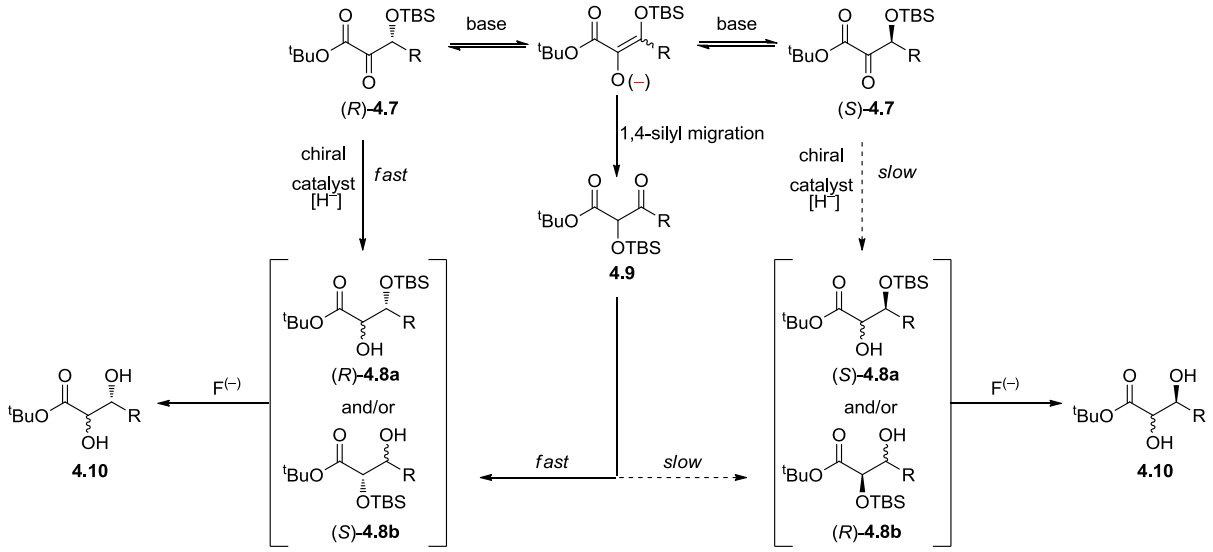
Scheme 4-6. Proposed Dynamic Kinetic Resolution of α-Keto Esters



4.3 Early Investigations

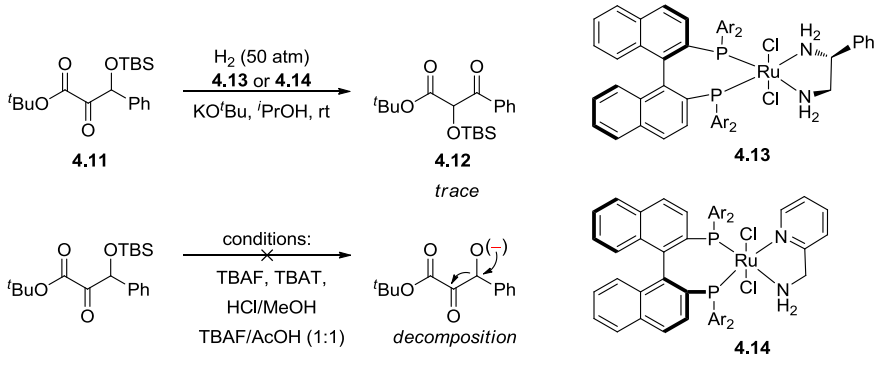
Based on the observed isomerization, we recognized that two reaction pathways could be operative to arrive at the desired 1,2-diol (**4.8**, Scheme 4-7). Dynamic reduction of the α-keto ester would lead to regioisomer **4.8a**; alternatively, the dynamic reduction of the β-keto ester **4.9**, which could potentially be formed under the basic reaction conditions, would lead to regioisomer **4.8b.** While both isomers can be converted to the same 1,2-diol **4.10** upon silyl deprotection, the reduction would need to proceed with the same level of enantio- and diatereocontrol to be productive. Ideally, one reaction pathway would need to predominate.

Scheme 4-7. Competing Pathways for the DKR of β-Silyoxy α-Keto Esters



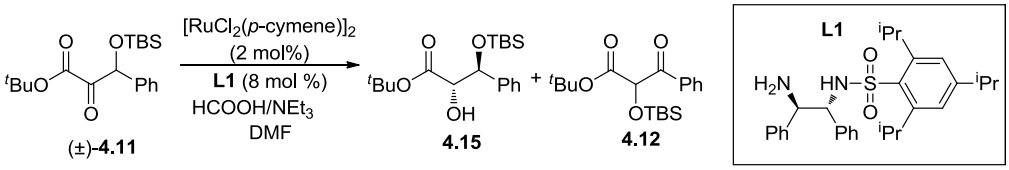
We chose **4.11** as our test substrate and initially examined the use of the Ru(II)-BINAP(diamine) complex **4.13,** which has previously been shown to have success with α-alkoxy ketones,[18] but only trace amounts of α-alkoxy β-keto ester **4.12** were observed and **4.11** remained untouched. This lack of reactivity was attributed to the steric bulk of the TBS protected alcohol. Noyori developed hydrogenation catalyst **4.14** specifically for the reduction of sterically encumbered ketones,[19] but the same results were obtained. All attempts to remove the silyl group led to decomposition, perhaps through retro-aldol reaction.

Scheme 4-8. Attempted DKR of β-Silyloxy α-Keto Esters via Asymmetric Hydrogenation



Attention was then turned to developing a dynamic kinetic asymmetric transfer hydrogenation (DKR-ATH) with $[RuCl_2(p\text{-cymene})]_2$ and **L1** using triethylamine as the base and formic acid as the organic reductant (Table 4-1).[20] Running the reaction in DMF at room temperature afforded the desired product **4.15**, albeit with low enantioselectivity (67:33 er) and moderate *anti*-diastereoselectivity (5:1 dr) (entry 1). As anticipated, the basic reaction conditions also facilitated the formation of the isomerized product **4.12**, and interestingly, this ketone is not reduced under the reaction conditions. Exclusive formation of regioisomer **4.15** was confirmed by ^{1}H NMR analysis. Increasing the equivalents of base led to higher enantioselectivities (entry 3), and this result can possibly be attributed to more rapid racemization of the starting material; however, this also led to an increased ratio of the isomerized product relative to the desired diol. It was speculated that fine-tuning the basicity of the reaction conditions could suppress silyl transfer, so a number of formate salts as well as other bases in combination with formic acid were screened (entries 4-12). The results in Table 4-1 reveal that the degree of isomerization is base-dependant and the most favorable outcome was observed with sodium formate at 40 ºC (entry 5). Unfortunately, these reaction conditions only afforded **4.15** in a 72:28 er and 3:1 dr. While these results indicate the potential of α-keto esters to undergo a DKR-ATH, further optimization with a simpler system (i.e. non-base sensitive substrates) was desired.

Table 4-1. Dynamic Kinetic Resolution of β-Silyoxyl α-Keto Esters via Asymmetric Transfer Hydrogenation



entry	[H⁻]/base (equiv)	conv (%)[a] (**4.15** : **4.12**)	er[b] (*anti*)	dr[c] *anti*:*syn*
1	$HCOOH/NEt_3$ (3.2/4.4)	88 : 12	67 : 33	5 : 1
2	$HCOOH/NEt_3$ (12.5/5.0)	79 : 21	67 : 33	4 : 1
3	$HCOOH/NEt_3$ (3.2/10.0)	35 : 65	78 : 22	4 : 1
4[d]	HCOONa (5.0)	97 : 0	67 : 33	3 : 1
5[e]	HCOONa (5.0)	93 : 7	71 : 29	3 : 1
6	HCOONa (5.0)	92 : 8	72 : 28	3 : 1
7	HCOOH/DIEA (3.2/10.0)	67 : 33	75 : 25	2 : 1
8	$HCOOH/Cs_2CO_3$ (3.2/10.0)	91 : 9	70 : 30	3 : 1
9	$HCOOH/Li_2CO_3$ (3.2/10.0)	73 : 27	70 : 30	3 : 1
10	$HCOOH/BaCO_3$ (3.2/10.0)	46 : 2	70 : 30	3 : 1
11	$HCOOH/CdCO_3$ (3.2/10.0)	51 : 5	76 : 24	3 : 1
12	HCOOCs (5.0)	89 : 6	70 : 30	3 : 1

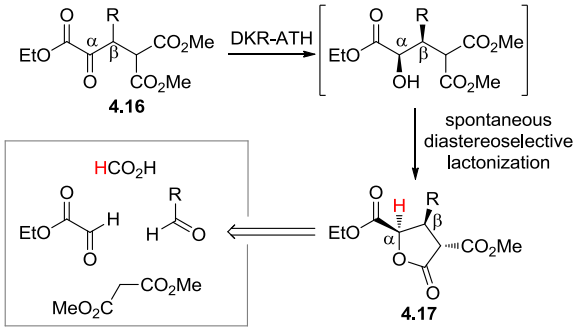
[a] Conversion determined by ^{1}H NMR spectroscopy. [b]Enantiomeric excess determined by SFC. [c] Diastereomeric excess determined by ^{1}H NMR spectroscopy. [d] Reaction run at 0 °C. [e]Reaction run at 40 °C

4.4 Development of the Glyoxylate Stetter Reaction

At the reaction design stage, we not only wanted to establish a convenient and scalable route to the α-keto ester precursors, but also to strategically incorporate structural elements that would allow us to productively merge a dynamic process with downstream complexity-building events. With the functionality presented in α-keto ester **4.16**, we envisioned a diastereoselective dynamic reduction to create the α- and β-stereocenters; the incorporation of a diester at the γ-position was projected to facilitate substrate synthesis and allow a third stereocenter to be established by concomitant lactonization of the nascent hydroxyl group (Figure 4-1). Retrosynthetic analysis of **4.16** constitutes the addition of a

glyoxylate anion equivalent to readily available benzylidene malonate derivatives. While acetoacetate addition followed by oxidative deacylation would be a viable option (Chapter 3),[21] the most direct route to this class of α-keto esters would be a catalytic Stetter reaction with ethyl glyoxylate. The implementation of this strategy would provide direct access to synthetically useful enantioenriched γ-butyrolactones **4.17**, which notably would arise from four commercial reagents (aldehyde, dimethyl malonate, ethyl glyoxylate, and formic acid) and three catalytic steps (Knoevenagel, Stetter, DKR/lactonization).

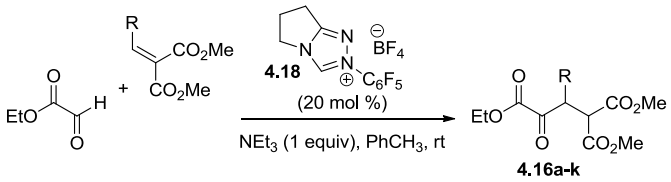
Figure 4-1. DKR-ATH of α-Keto Esters—Modular, Green, *de novo* Approach to Enantioenriched γ-Butyrolactones



The glyoxamide Stetter with alkylidene malonates has previously been reported by Rovis,[22] but the analogous reaction with ethyl glyoxylate would be considerably more convenient, as it is commercially available, and obviate the need to manipulate an amide after the reaction of interest. As shown in Table 4-2, the glyoxylate Stetter catalyzed by triazolium carbene[23] **4.18** is efficient for a number of substrates and can be performed on a multigram scale (entry 7). The β-aryl α-keto esters **4.16a-k** cannot be accessed in enantioenriched form using the method developed by Rovis due to the high configurational vulnerability of the β-

stereocenter.[22a] This is a major problem associated with stereoselective umpolung catalysis, but is rendered moot here since the racemate is the desired product.

Table 4-2. Scope of the Glyoxylate Stetter Reaction with Benzylidene Malonates[a]



Entry	R	Product	% yield[b]
1	C_6H_5	**4.16a**	96
2	4Cl-C_6H_5	**4.16b**	95
3	4Me-C_6H_5	**4.16c**	92
4	4MeO-C_6H_5	**4.16d**	93
5	4NC-C_6H_5	**4.16e**	90
6	2Me-C_6H_5	**4.16f**	78
7[c]	piperonyl	**4.16g**	91
8	2-furyl	**4.16h**	87
9	3-*N*-TsIndole	**4.16i**	89
10	3-*N*-BocIndole	**4.16j**	84
11	CH_2CHPh	**4.16k**	93

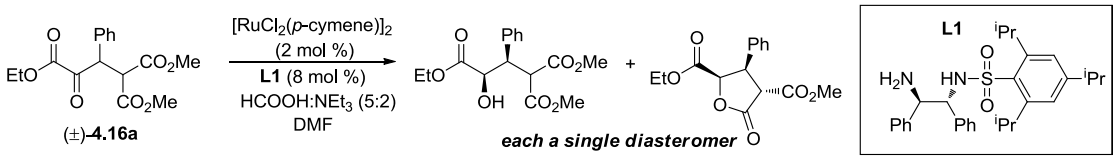
[a] Conditions: Unless otherwise noted, all reactions were performed on a 2.0 mmol scale in $PhCH_3$ (4 mL) at ambient temperature for 16 h. [b] Isolated yield. [c] Reaction performed on a 10 mmol scale.

4.5 Preliminary Studies on the DKR-ATH of β-Aryl α-Keto Esters

Our point of departure with respect to catalyst development was Noyori's (arene)RuCl(monosulfonamide) scaffold using HCOOH:NEt_3 (5:2 azeotrope) as the organic reductant/base, and **4.16a** as the test substrate (Table 4-3). Subjection of **4.16a** to 2 mol % of $[RuCl_2(p\text{-cymene})]_2$ and ligand **L1** (Ru atom: **L** mole ratio 1:2) in DMF at room temperature afforded a mixture of the α-hydroxy ester **4.19** and desired γ-butyrolactone **4.17a** in a 1:2 ratio, each as a single diastereomer. Heating the reaction to 70 ºC yielded **4.17a** as the sole product in 70:30 er with complete diastereocontrol; this is the same level of enantiocontrol

observed with **4.11**. Varying the arene ligand on ruthenium identified *p*-cymene to be optimal (entry 3).

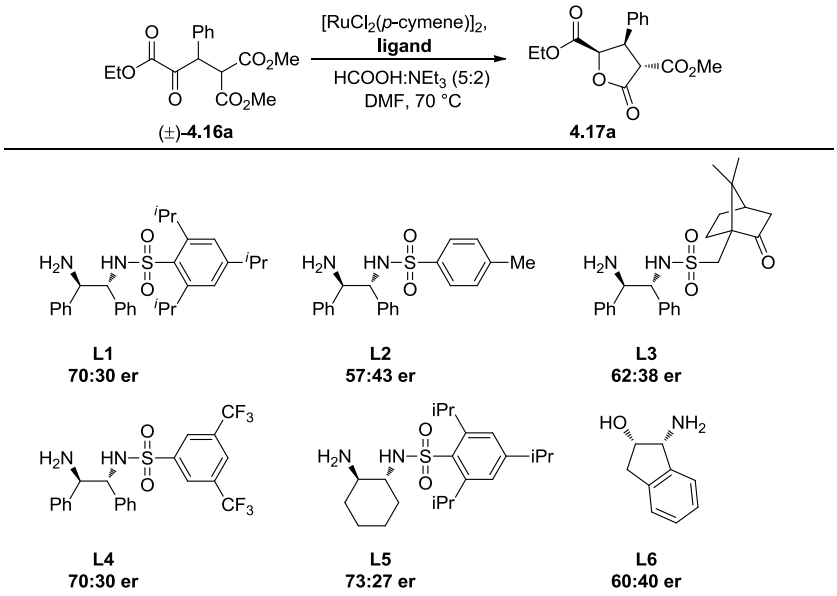
Table 4-3. Optimization of the DKR-ATH Reaction Conditions



entry	arene	temperature	ratio **4.19**:**4.17**	er
1	hexamethylbenzene	rt	1:2	57:43
2	hexamethylbenzene	70 ºC	0:100	62:38
3	*p*-cymene	70 ºC	0:100	70:30
4	benzene	70 ºC	0:100	71:29

Having identified ideal reaction conditions to obtain γ-butryolactone **4.17**, a number of chiral 1,2-diaminoethane monosulfonamide ligands were evaluated for selectivity (Table 4-4). The ease of preparation and proven utility of these ligands in asymmetric reactions as diverse as cycloaddition,[24] epoxidation,[25] conjugate addition,[26] carbonyl alkylation[27] and others, allowed us to narrow our focus to ruthenium complexes derived from this class. While all the ligands catalyzed the title reaction to high conversion and diastereoselectivity, enantioselectivities were poor in all cases; the identity of the sulfonamide was shown to have a significant effect on the level of enatiocontrol (**L1** vs **L2**). Employing 1,2-diaminocyclohexane **L5** and 1,2-aminoindaonol **L6** to serve as the chiral backbone yielded comparable results.

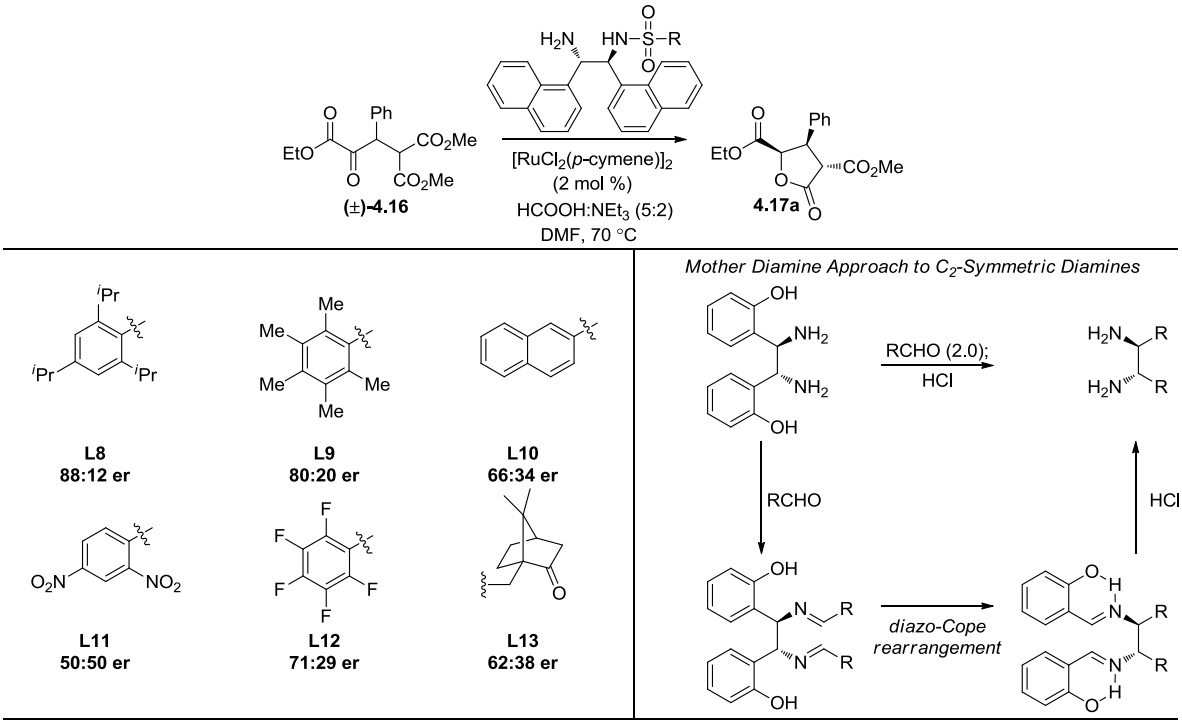
Table 4-4. Evaluation of Chiral Diamine Ligands



4.6 Further Ligand Development

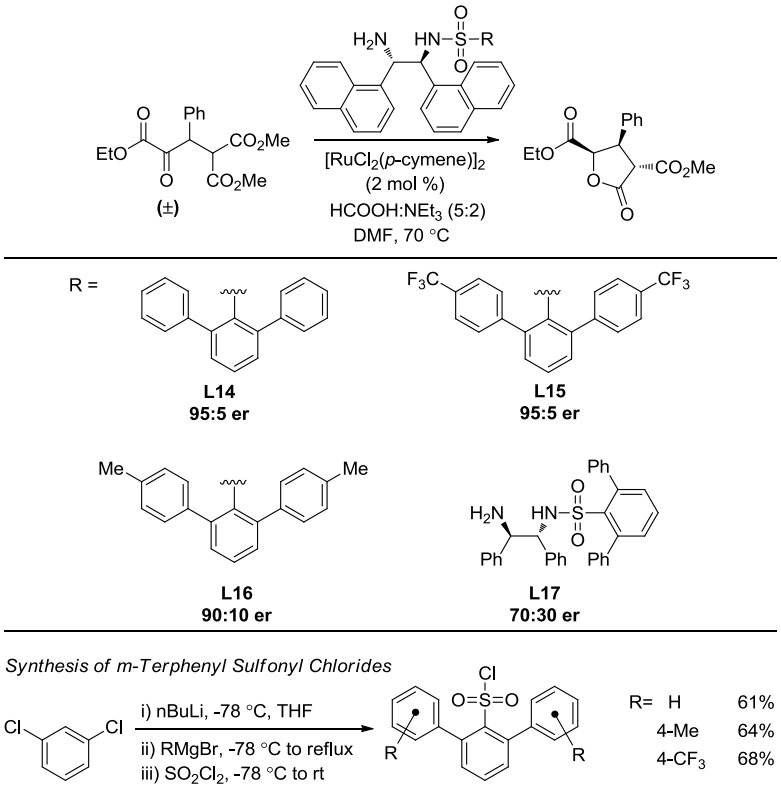
Based on these observations, it was clear that a new chiral ligand would need to be identified to achieve high levels of enantiocontrol. The development of the "mother diamine"/diazo-Cope approach to the synthesis of C_2-symmetric 1,2-diamines allowed facile screening of several diamine backbones (Scheme 4-9).[29] From this evaluation, we found the α-naphthyl/triisopropylbenzenesulfonamide ligand **L7** considerably increased the selectivity (88:12 er). To further optimize the ligand structure, pertubations of the sulfonamide were examined due to its apparent ability to directly impact the chiral environment. However, after screening a number of sulfonamide derivatives (**L8-13**) prepared from commercially available sulfonyl chlorides, no significant increase in enantioselectivity was observed.

Scheme 4-9. Evaluation of α-Naphthyl Diamine Ligands



We were able to access a number of diverse sulfonyl chlorides through a one-pot double alkylation/sulfonylation of 1,3-dichlorobenzene following a modified procedure developed by Hart (Scheme 4-10).[29] The simplest *m*-terphenylsulfonamide variant **L14**, distinguished itself as being uniquely effective for providing high levels of enantioselectivity, providing **4.17a** in 94:6 er. The α-naphthyl backbone and *m*-terphenylsulfonamide operate synergistically; no improvement in enantiocontrol with DPEN/*m*-terphenylsulfonamide ligand **L17** was observed. It is noteworthy that the α-naphthyl ethylenediamine backbone has been used sporadically in asymmetric synthesis,[30] and the current study is to the best of our knowledge the first use of the *m*-terphenylsulfonamide for enantioselective catalysis.[31]

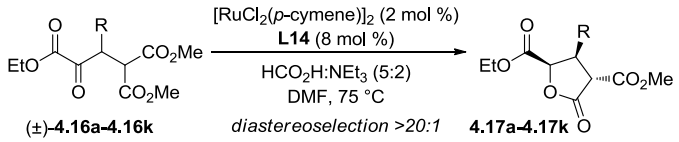
Scheme 4-10. Synthesis and Evaluation of *m*-Terphenyl Sulfonamide Ligands

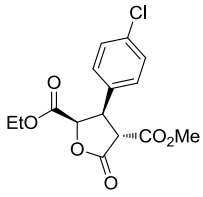


4.7 Reaction Scope

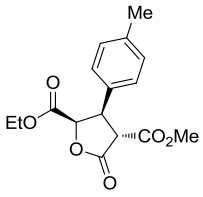
As outlined in Table 4-5, this DKR-ATH was found to be broad in scope for a number of β-aryl α-keto esters. High yields and enantioselectivities (up to 94% yield and 96.5:3.5 er) were obtained for substrates incorporating electron-rich, electron-poor, and heteroaryl substituents at the β-position. α-Keto ester **4.16k** bearing an alkyl substituent was not a successful substrate as the derived γ-butyrolactone **4.17k** was obtained in a 67:33 er and this is possibly due to insufficient racemization. The *syn,anti*-relationship of the trisubstituted γ-butyrolactone products **4.17a-k** was determined by NOESY experiments, and the absolute configuration was established by single X-ray crystallographic analysis of **4.17b**.

Table 4-5. DKR-ATH Substrate Scope[a]

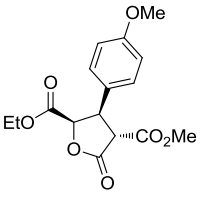




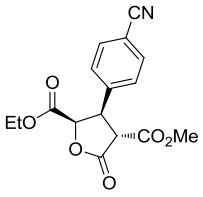
4.17b, 94%, 96:4 er



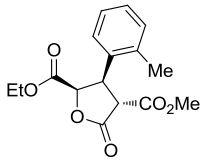
4.17c, 84%, 95.5:4.5 er



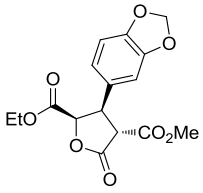
4.17d, 90%, 95:5 er



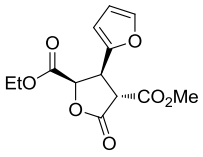
4.17e, 88%, 95:5 er



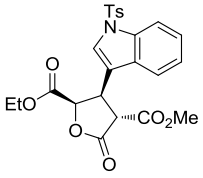
4.17f, 82%, 89:11 er



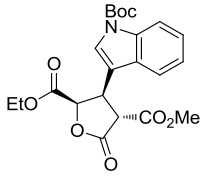
4.17g, 83%, 96:4 er



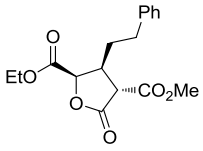
4.17h, 91%, 95:5 er



4.17i, 91%, 96.5:3.5 er



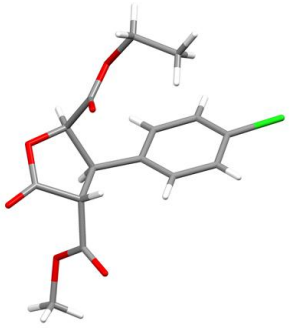
4.17j, 88%, 96:4 er

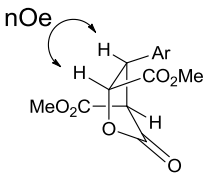


4.17k, 91%, 67:33 er

[a]Conditions: **4.16** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.02 equiv), **L** (0.08 equiv), $[\mathbf{4.16}]_0$ = 0.1 M in DMF, 70 ºC, 16 h

Figure 4-2. Absolute Stereochemical Determination of γ-Butyrolactones through Single X-Ray Diffraction Analysis of **4.17b** and Key nOe Interactions

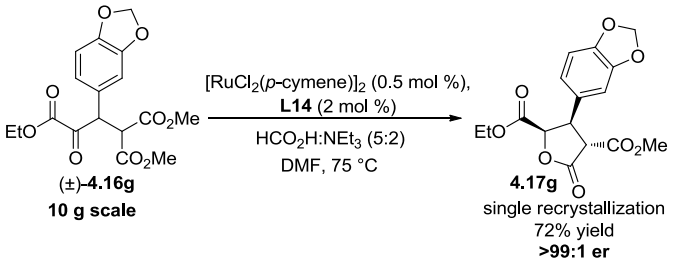




4.8 Reaction Scalability and Catalyst Efficiency

To demonstrate the synthetic utility and catalytic efficiency of this method, the reaction was performed on multigram scale (Scheme 4-11). Additional experimentation revealed that the catalyst loading could be lowered to 1 mol % with no loss in reaction efficiency. The reduction was trivially performed on a 10 g scale with **4.16g**, yielding lactone **4.17g** in 95:5 er. The product lactones exhibit high incidence of crystallinity; recrystallization of **4.17g** yielded enantiomerically pure lactone in 72% yield.

Scheme 4-11. Catalyst Efficiency and Scalability

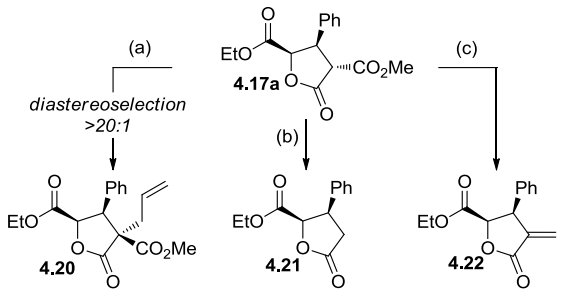


4.9 Secondary Transformations

The reduction products present functionality immediately amenable to further manipulation (Scheme 4-12). Lactone **4.17a** undergoes facile diastereoselective alkylation upon treatment with allyl bromide and DBU, yielding tetrasubstitued lactone **4.20** bearing an all-carbon quaternary center (94% yield). Krapcho decarboxylation[32] afforded α-unsubstituted lactone **4.21** (86% yield), which is primed to undergo further enolate-based bond constructions. Of particular importance, alkylation with dibromomethane followed by dehalodecarboxylation[33] afforded α-alkylidene γ-butyrolactone **4.22**. This substructure is featured in 3% of all known natural products, and members of this subclass exhibit a wide

range of biological activity. Due to the versatility of the product classes obtainable, it is expected this method will be of significant value in the areas of both natural product and medicinal agent synthesis.

Scheme 4-12. Synthetic Utility of Lactone Products



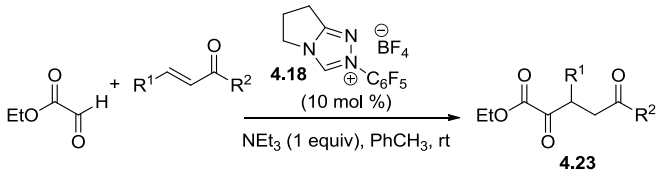
Conditions: (a) allyl bromide (2 equiv), DBU (2 equiv), THF, rt, 2h, 94%. (b) LiCl, DMSO, 140 ºC, 87%. (c) i) K_2CO_3, dibromomethane, 84%. ii) LiCl, DMSO, 140 ºC, 87%.

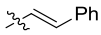
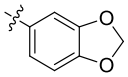
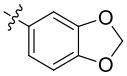
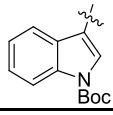
4.10 Chemoselective DKR-ATH of α,δ-Diketo Esters

4.10.1 Origin of the Title Reaction

We next sought to extend this method to include β-stereogenic α,δ-diketo esters **4.23**. We and others have previously reported indirect methods to access this class of compounds, but we have found the Stetter reaction with ethyl glyoxylate and enones to be highly efficient for their preparation (Table 4-6). The glyoxylate Stetter is tolerant of a number of ketonic substrates and substituents at the β-position. Notably, with the doubly activated enone, dibenzylideneacetone, exclusive mono-addition was observed (entry 5).

Table 4-6. Glyoxylate Stetter Scope with Enones[a]



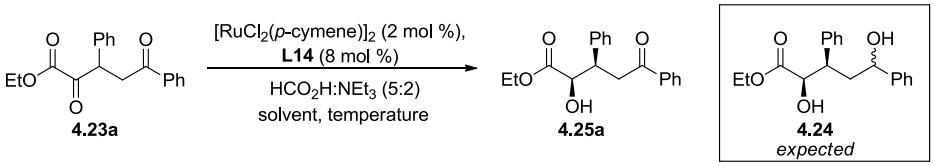
entry	R^1	R^2	product	yield[b]
1	C_6H_5	C_6H_5	**4.23a**	97
2	C_6H_5	4I-C_6H_4	**4.23b**	95
3	C_6H_5	4MeO-C_6H_4	**4.23c**	86
4	C_6H_5	Me	**4.23d**	72
5	C_6H_5		**4.23e**	91
6	C_6H_5		**4.23f**	92
7	4Cl-C_6H_5	C_6H_5	**4.23g**	94
8	4MeO-C_6H_5	C_6H_5	**4.23h**	96
9	2Me-C_6H_5	C_6H_5	**4.23i**	70
10	3Me-C_6H_5	C_6H_5	**4.23j**	93
11	4Me-C_6H_5	C_6H_5	**4.23k**	95
12	CO_2Et	C_6H_5	**4.23l**	92
13		C_6H_5	**4.23m**	94
14		C_6H_5	**4.23n**	70

[a]Conditions: Unless otherwise noted, all reactions were performed on a 2.0 mmol scale in $PhCH_3$ (4 mL) at ambient temperature. [b]Isolated yield.

With this substrate class we envisioned a dynamic diastereoselective reduction of the α-keto ester to set the α- and β-stereocenters followed by a diastereoselective reduction of the δ-ketone to afford enantionriched 1,4 diols **4.24**. We began this study by subjecting **4.23a** to the standard reaction conditions and observed exclusive reduction of the α-keto ester affording α-hydroxy ester **4.25a** as a single diastereomer in 96% yield and 91:9 er. This was an unexpected result as (arene)RuCl(sulfonamide) catalysts have been extensively used for the asymmetric transfer hydrogenation of ketones. We proceeded to capitalize upon this

unique reactivity and further optimized the reaction conditions (Table 4-7). A short screen of solvents and reaction temperatures revealed that high levels of selectivity (97:3 er) could be obtained by running the reaction in DMSO at room temperature (entry 6).

Table 4-7. Optimization of the Reaction Conditions

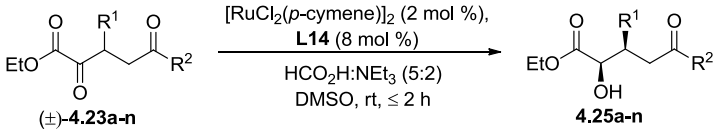


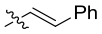
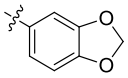
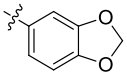
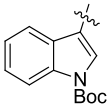
entry	solvent	temperature	yield	er
1	DMF	70 ºC	94	91:9
2	DMF	rt	93	87:13
3	2-MeTHF	70 ºC	90	65:35
4	DCE	70 ºC	91	78:22
5	DMSO	70 ºC	96	97:3
6	DMSO	rt	98	97:3

4.10.2 Reaction Scope

Next, we explored the generality of this chemoselective dynamic reduction. For all substrates examined, exclusive reduction of the α-keto ester was observed, irrespective of the electronic characteristics of the δ-ketone (Table 4-8). High yields and enantioselectivites were obtained in each case (up to 98% yield and 99:1 er). The level of selectivity for **4.25l** is noteworthy as this demonstrates that the scope is not limited to substrates that contain a β-aryl substituent. Additionally, the α,β-unsaturated moiety in **4.25e** remained intact, providing a useful functional handle for further derivatization.

Table 4-8. Chemoselective Dynamic Reduction Scope[a]



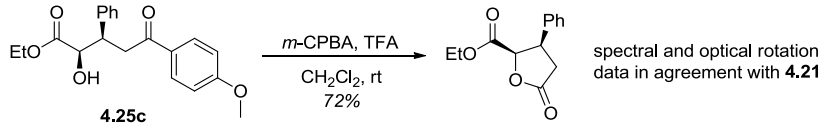
entry	R^1	R^2	product	yield[b]	er[c]
1	C_6H_5	C_6H_5	**4.25a**	98	97:3
2	C_6H_5	4I-C_6H_4	**4.25b**	91	96.5:3.5
3	C_6H_5	4MeO-C_6H_4	**4.25c**	94	96:4
4	C_6H_5	Me	**4.25d**	85	93:7
5	C_6H_5		**4.25e**	88	99:1
6	C_6H_5		**4.25f**	98	99:1
7	4Cl-C_6H_5	C_6H_5	**4.25g**	94	98:2
8	4MeO-C_6H_5	C_6H_5	**4.25h**	98	96:4
9	2Me-C_6H_5	C_6H_5	**4.25i**	87	83:17
10	3Me-C_6H_5	C_6H_5	**4.25j**	98	98:2
11	4Me-C_6H_5	C_6H_5	**4.25k**	97	98:2
12	CO_2Et	C_6H_5	**4.25l**	93	91:9
13		C_6H_5	**4.25m**	96	97:3
14		C_6H_5	**4.25n**	--	98:2

[a]Conditions: **4.25** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.02 equiv), **L** (0.08 equiv), $[\mathbf{4.25}]_0$ = 0.1 M in DMSO, rt, 1-2 h. [b]Isolated yield. [c]Determined by SFC analysis.

4.10.3 Stereochemical Analysis

The absolute and relative stereochemistry of α-hydroxy esters **4.19** were determined by converting **4.25c** to **4.21** via a Bayer Villiger oxidation followed by *in situ* lactonization (Scheme 4-13). The spectral and optical rotation data were in agreement indicating the catalyst exhibits the same enantio- and diastereomeric preference for this substrate class.

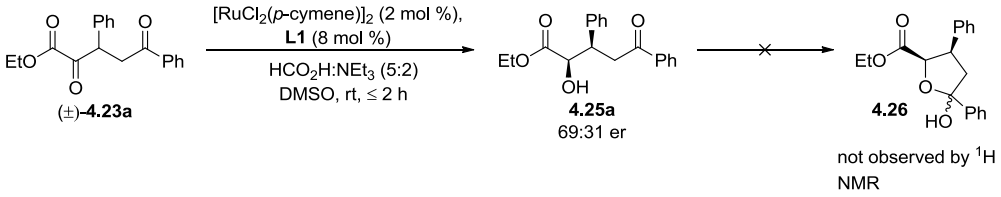
Scheme 4-13. Stereochemical Analysis



4.10.4 Origin of Selectivity

To determine if the $[RuCl_2(p\text{-cymene})]_2$/**L14** catalyst system was uniquely effective for the reduction of α-keto esters, the selectivity of transfer hydrogenation catalysts known to reduce simple ketones were evaluated with **4.23a** (Scheme 4-14). Running the reaction with ligand **L1**, which is known to reduce acetophenone, also afforded **4.25a** as the sole product, albeit with lower levels of enantioselectivity (69:31 er). This result suggested that the δ-ketone could possibly be protected as the lactol **4.26** following the reduction of the α-keto ester. To test this hypothesis, the reaction was monitored by ^{1}H NMR in DMSO-d^6 (using **L14**), but **4.26** was not detected. This implicates that the observed chemoselectivity may be substrate dependent.

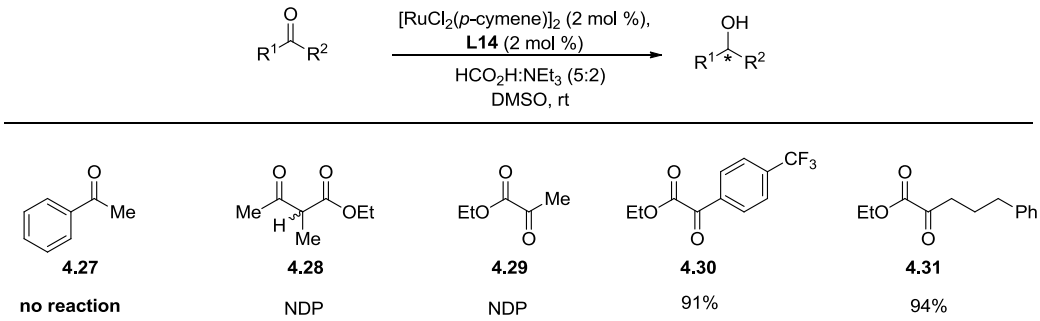
Scheme 4-14. Probing the Selectivity of **L14**



The above results prompted us to examine the transfer hydrogenation of several other ketone substrates using the standard reaction conditions in outlined in Table 4-8 (Scheme 4-14). Surprisingly, acetophenone **4.27**, which is typically the test substrate for new transfer

hydrogenation catalysts, was not reduced with this catalyst system. However, aryl and alkyl glyoxylates **4.30** and **4.31** readily afforded the corresponding α-hydroxy ester. This suggests the catalyst has a distinct preference for α-keto esters. Furthermore, ethyl pyruvate **4.28** did not provide desired product which implies a branch point at the β-position is also necessary for the reduction to proceed (**4.29** vs **4.31**). Further mechanistic studies to understand the origin of selectivity are ongoing.

Scheme 4-15. Transfer Hydrogenation of Other Ketone Substrates Using **L14**



4.11 Conclusions

We have designed a new asymmetric transfer hydrogenation catalyst that has led to the successful development of the first dynamic kinetic resolution of β-aryl α-keto esters. For substrates **4.17a-4.17k**, spontaneous lactonization of the α-hydroxyl group onto the pendent ester occurs to provide trisubstituted γ-butyrolactones with complete diastereocontrol. With respect to the rubric of green chemistry, it is instructive to inventory the three steps that lead to the lactones **4.17**: (i) the Knoevagel condensation is amine-catalyzed and generates water as the by-product; (ii) the glyoxylate Stetter addition is carbene-catalyzed and 100% atom economical, generating no stoichiometric byproducts; (iii) the DKR-ATH reaction uses a

chiral ruthenium catalyst and formic acid as the reductant and generates only CO_2 and CH_3OH as byproducts. Extension of this method to β-stereogenic α,δ-diketo esters revealed that this catalyst system is selective for α-keto esters exclusively providing α-hydroxy esters **4.25a-4.25n**; other ketonic substrates are unreactive under the standard reaction conditions. Additional studies to understand the catalyst-substrate interactions to account for the high levels of selectivity for α-keto esters as well as identification of other green, dynamic transformations of β-stereogenic α-keto esters are current areas of interest.

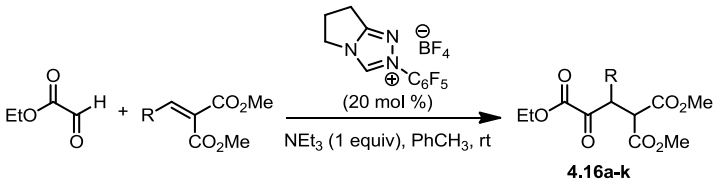
4.12 Experimental Details

Methods: Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR 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 ^{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 a Chiralcel WO column. Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH. HPLC analysis was performed on an Agilent Technologies 1200 System equipped with Chiralpak IA, IB, and IC columns (constant flow at 1.00 mL/min). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Low resolution mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with

nanoelectrospray ionization. (Note: All samples prepared in methanol). High resolution mass spectra were obtained using an Agilent Technologies 6520, Accurate—Mass QTOF LCMS, Series 1200 LC with dual spray electrospray ionization. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle. All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

Materials: Benzylidene malonates and α,β-unsaturated ketones 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). *N*,*N*-Dimethylformamide (DMF) was distilled from phosphorous pentoxide and stored under nitrogen over 3Å molecular sieves. Anhydrous DMSO was purchased from Sigma Aldrich and used as received. Triethylamine (NEt_3) was freshly distilled from calcium hydride prior to use. Toluene ($PhCH_3$) and tetrahdyrofuran (THF) were dried by passage through a column of neutral alumina under nitrogen prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

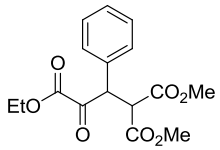
General Procedure A for the Preparation of β-Substituted α-Keto Esters 4.16a-4.16k



4.16a-k

To a flame-dried 10-mL round-bottomed flask equipped with a magnetic stir bar were added benzylidene malonate (2.0 mmol, 1.0 equiv), ethyl glyoxylate (4.0 mmol, 2.0 equiv) and triazolium salt (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 benzylidene malonate) 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-keto esters which were purified by flash chromatography using the indicated solvent systems.

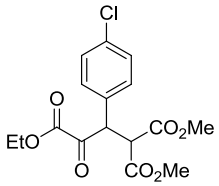
3-Ethyl 1,1-dimethyl 3-oxo-2-phenylpropane-1,1,3-tricarboxylate (4.16a):



4.16a

The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **4.16a** (0.618 g, 1.92 mmol, 96% yield) as a colorless oil. Analytical data for **4.16a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31-7.27 (m, 3H), 7.25-7.24 (m, 2H), 5.22 (d, *J* = 12 Hz, 1H), 4.30 (d, *J* = 12 Hz, 1H), 4.26-4.19 (m, 2H), 3.74 (s, 3H), 3.46 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 190.2, 168.2, 167.4, 159.5, 131.4, 129.4, 129.1, 128.6, 62.7, 54.5, 53.2, 52.7, 52.6, 13.8; **IR** (thin film cm^{-1}): 2956, 1731, 1495, 1435, 1256, 1153, 1103, 1052, 854, 753, 700; **TLC** (20% EtOAc/hexanes): R_f : 0.27; **LRMS** (ESI): Calculated for $[M + H]^+$ $C_{16}H_{18}O_7$: 323.11, Found: 323.07.

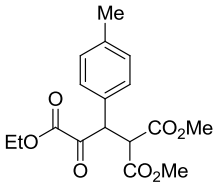
3-Ethyl 1,1-dimethyl 2-(4-chlorophenyl)-3-oxopropane-1,1,3-tricarboxylate (4.16b):



4.16b

The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **4.16b** (0.660 g, 1.9 mmol, 95% yield) as a colorless oil. Analytical data for **4.16b**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.22 (d, *J* = 12 Hz, 1H), 4.29 (d, *J* = 12 Hz, 1H), 4.28-4.22 (m, 2H), 3.75 (s, 3H), 3.51 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 189.9, 168.0, 167.2, 159.4, 134.8, 130.7, 130.1, 129.4, 62.9, 54.5, 53.3, 52.7, 51.8, 13.9; **IR** (thin film, cm^{-1}): 3649, 2956, 1732 1491, 1435, 1258, 1154, 1094, 1051, 936, 854, 717, 597; **TLC** (20% EtOAc/hexanes): R_f : 0.32; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{16}H_{18}ClO_7$: 357.07, Found: 357.02.

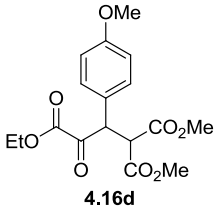
3-Ethyl 1,1-dimethyl 3-oxo-2-(p-tolyl)propane-1,1,3-tricarboxylate (4.16c):



4.16c

The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **4.16c** (0.618 g, 1.84 mmol, 92% yield) as a colorless oil. Analytical data for **4.16c**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.12 (m, 4H), 5.19 (d, *J* = 12 Hz, 1H), 4.29 (d, *J* = 12 Hz, 1H), 4.27-4.18 (m, 2H), 3.75 (s, 3H), 3.49 (s, 3H), 2.30 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 190.2, 168.3, 167.5, 159.6, 138.5, 129.9, 129.3, 128.2, 62.7, 54.5, 53.1, 52.6, 52.3, 21.1, 13.9; **IR** (thin film, cm^{-1}): 3649, 2956, 1731, 1513, 1436, 1257, 1153, 1100, 1053, 854, 801, 718, 601; **TLC** (20% EtOAc/hexanes): R_f : 0.32; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{17}H_{21}O_7$: 337.13, Found: 337.15.

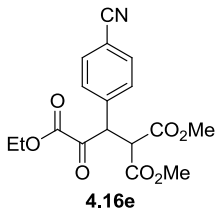
3-Ethyl 1,1-dimethyl 2-(4-methoxyphenyl)-3-oxopropane-1,1,3-tricarboxylate (4.16d):



4.16d

The title compound was prepared according to General Procedure A. Flash chromatography (30% EtOAc/hexanes) provided **4.16d** (0.655 g, 1.86 mmol, 93% yield) as a colorless oil. Analytical data for **4.16d**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.16 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.17 (d, *J* = 12 Hz, 1H), 4.27 (d, *J* = 12 Hz, 1H), 4.26-4.19 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 3.49 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 190.0, 168.2, 167.5, 159.7, 159.6, 130.6, 123.0, 114.6, 62.7, 55.2, 54.4, 53.1, 52.6, 51.8, 13.9; **IR** (thin film, cm^{-1}): 2956, 1731, 1609, 1511, 1436, 1304, 1256, 1180, 1153, 1099, 1052, 1031, 832, 741, 602; **TLC** (30% EtOAc/hexanes): R_f : 0.34; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{17}H_{21}O_8$: 353.12, Found: 353.17.

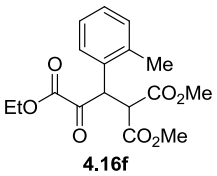
3-Ethyl 1,1-dimethyl 2-(4-cyanophenyl)-3-oxopropane-1,1,3-tricarboxylate (4.16e):



4.16e

The title compound was prepared according to General Procedure A. Flash chromatography (30% EtOAc/hexanes) provided **4.16e** (0.625 g, 1.80 mmol, 90% yield) as a white solid. Analytical data for **4.16e**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 2H), 5.29 (d, *J* = 12 Hz, 1 H), 4.32 (d, *J* = 12 Hz, 1H), 4.30-4.23 (m, 2H), 3.75 (s, 3H), 3.50 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 189.5, 167.8, 166.9, 159.2, 137.3, 132.7, 130.1, 118.0, 112.7, 63.1, 54.5, 53.4, 52.8, 52.2, 13.8; **IR** (thin film, cm^{-1}): 2957, 2230, 1732, 1506, 1436, 1259, 1156, 1097, 1051, 836; **m.p.** 71-73 ºC; **TLC** (30% EtOAc/hexanes): R_f: 0.32; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{17}H_{18}NO_7$: 348.11, Found: 348.14.

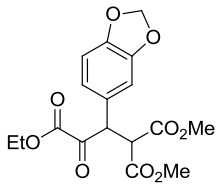
3-Ethyl 1,1-dimethyl 3-oxo-2-(o-tolyl)propane-1,1,3-tricarboxylate (4.16f):



4.16f

The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **4.16f** (0.524 g, 1.56 mmol, 78% yield) as a colorless oil. Analytical data for **4.16f**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.18-7.12 (m, 3H), 7.11-7.01 (m, 2H), 5.47 (d, *J* = 11.6 Hz, 1H), 4.29 (d, *J* = 11.6 Hz, 1H), 4.25-4.16 (m, 2H), 3.76 (s, 3H), 3.42 (s, 3H), 2.54 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.3, 168.3, 167.6, 159.8, 138.5, 131.4, 129.7, 128.5, 128.2, 126.5, 62.7, 54.4, 53.1, 52.4, 48.3, 19.6, 13.8; **IR** (thin film, cm^{-1}): 3578, 2964, 1734, 1523, 1441, 1264, 1148, 1110, 1057, 852, 806, 714, 605; **TLC** (20% EtOAc/hexanes): R_f : 0.33; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{17}H_{21}O_7$: 337.13, Found: 337.14.

3-Ethyl 1,1-dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-3-oxopropane-1,1,3-tricarboxylate (4.16g):

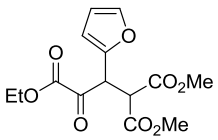


4.16g

The title compound was prepared according to General Procedure A on a 10 mmol scale. Flash chromatography (30% EtOAc/hexanes) provided **4.16g** (3.33 g, 9.10 mmol, 91% yield) as a viscous yellow oil. Analytical data for **4.16g**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.74-6.70 (m, 3H), 5.95 (bs, 2H), 5.14 (d, *J* = 12 Hz, 1H), 4.24 (d, *J* = 12 Hz, 1H), 4.29-4.22 (m, 2H), 3.74 (s, 3H), 3.54 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 189.9, 168.2, 167.4, 159.6, 148.2, 147.9, 124.6, 123.2, 109.5, 108.8, 101.4, 62.8, 54.6, 53.2, 52.7, 52.0, 13.9; **IR** (thin film, cm^{-1}): 2956, 2360, 1731, 1505, 1489, 1440, 1249, 1225, 1153, 1095, 1037, 932,

857, 812, 638; **TLC** (30% EtOAc/hexanes): R_f : 0.35; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{17}H_{19}O_9$: 367.10, Found: 367.01

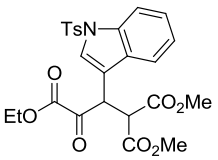
3-Ethyl 1,1-dimethyl 2-(furan-2-yl)-3-oxopropane-1,1,3-tricarboxylate (4.16h):



4.16h

The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **1h** (0.543 g, 1.74 mmol, 87% yield) as an orange oil. Analytical data for **1h**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.37 (s, 1H), 6.32-6.30 (m, 2H), 5.40 (d, *J* = 12 Hz, 1H), 4.36 (d, *J* = 12 Hz, 1H), 4.33-4.25 (m, 2H), 3.75 (s, 3H), 3.62 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 187.3, 167.9, 167.3, 159.5, 145.0, 143.9, 111.0, 110.7, 62.9, 53.2, 52.9, 52.4, 46.5, 13.9; **IR** (thin film, cm^{-1}): 2957, 1736, 1499, 1436, 1252, 1153, 1100, 1051, 1014, 749, 599; **TLC** (20% EtOAc/hexanes): R_f : 0.27; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{14}H_{17}O_8$: 313.09, Found: 313.13.

3-Ethyl 1,1-dimethyl 3-oxo-2-(1-tosyl-1H-indol-3-yl)propane-1,1,3-tricarboxylate (4.16i):

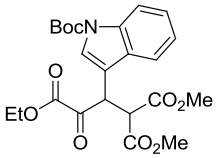


4.16i

The title compound was prepared according to General Procedure A. Flash chromatography (30% EtOAc/hexanes) provided **4.16i** (0.918 g, 1.78 mmol, 89% yield) as a viscous yellow oil. Analytical data for **4.16i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.67 (m, 1H), 7.51 (s,1H), 7.33-7.30 (m, 2H), 7.23-7.21 (m, 2H), 5.48 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.21-4.12 (m, 2H), 3.77 (s, 3H), 3.25 (s, 3H), 2.33 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H);); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 188.9, 168.0, 167.2, 159.5, 145.1, 135.1, 134.9,

129.9, 126.8, 126.4, 125.4, 123.7, 119.9, 113.6, 113.4, 62.8, 53.9, 53.2, 52.5, 43.5, 21.5, 13.7; **IR** (thin film, cm^{-1}): 2955, 1732, 1596, 1447, 1372, 1286, 1251, 1176, 1123, 1093, 1050, 979, 814, 748, 704, 669, 573, 538; **TLC** (30% EtOAc/hexanes): R_f : 0.25; **LRMS** (ESI): Calculated for [M+Na] $C_{25}H_{25}NO_9SNa$ + MeOH: 570.14, Found: 570.03.

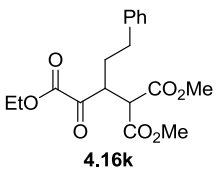
3-Ethyl 1,1-dimethyl 2-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-3-oxopropane-1,1,3-tricarboxylate (4.16j):



4.16j

The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **4.16j** (0.775 g, 1.68 mmol, 84% yield) as a pale yellow solid. Analytical data for **4.16j**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.0 Hz, 1H) 7.70-7.68 (m, 1H), 7.45 (s, 1H), 7.35-7.27 (m, 2H), 5.53 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.25-4.15 (m, 2H), 3.78 (s, 3H), 3.43 (s, 3H), 1.65 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 188.9, 168.2, 167.2, 159.5, 149.1, 135.5, 128.7, 125.9, 125.0, 123.0, 119.3, 115.2, 111.0, 84.3, 62.8, 54.0, 53.2, 52.7, 43.3, 28.1, 13.7; **IR** (thin film, cm^{-1}): 2980, 1733, 1453, 1367, 1257, 1154, 1083, 1051, 748; **m.p.** 96-97.5 ºC; **TLC** (20% EtOAc/hexanes) R_f : 0.29; **LRMS** (ESI): Calculated for [M+Na] $C_{23}H_{17}NO_9Na$ + MeOH: 516.18, Found: 516.21.

3-Ethyl 1,1-dimethyl 3-oxo-2-phenethylpropane-1,1,3-tricarboxylate (4.16k):

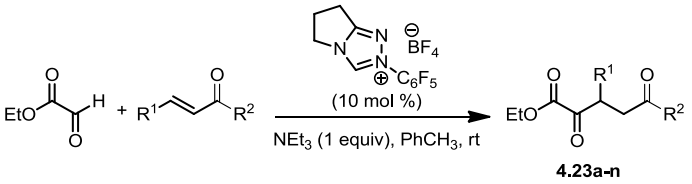


4.16k

The title compound was prepared according to General Procedure A. Flash chromatography (20% EtOAc/hexanes) provided **4.16k** (0.775 g, 1.86 mmol, 93% yield) as a colorless oil. Analytical data for **4.16k**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29-7.26 (m, 2H), 7.21-7.18 (m, 1H), 7.12-7.11 (m, 2H), 4.41-

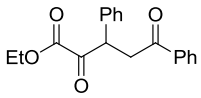
4.33 (m, 2H), 4.13 (ddd, *J* = 10.8, 8.4, 4.2 Hz, 1H), 3.97 (d, *J* = 10.8 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 2.59-2.56 (m, 2H), 1.99-1.87 (m, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 194.8, 168.6, 168.1, 140.6, 128.5, 128.3, 126.3, 62.7, 54.2, 53.1, 52.9, 45.2, 32.4, 31.7, 14.0; **IR** (thin film, cm^{-1}): 2955, 1797, 1730, 1603, 1496, 1455, 1436, 1257, 1155, 1097, 1064, 752, 700; **TLC** (20% EtOAc/hexanes) R_f : 0.29; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{18}H_{23}O_7$: 351.14, Found: 351.16.

General Procedure B for the Preparation of β-Aryl α-Keto Esters 4.23a-4.23n



To a flame-dried 10-mL round-bottomed flask equipped with a magnetic stir bar were added α,β-unsaturated ketone (2.0 mmol, 1.0 equiv), ethyl glyoxylate (4.0 mmol, 2.0 equiv) and triazolium salt (0.20 mmol, 0.10 equiv). The flask was sealed with a rubber septum and purged with nitrogen. Toluene (0.5 M concentration with respect to α,β-unsaturated ketone) 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.

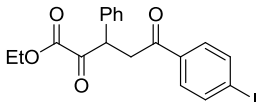
Ethyl 2,5-dioxo-3,5-diphenylpentanoate (4.23a):



4.23a

The title compound was prepared according to General Procedure B on a 20 mmol scale. Flash chromatography (20% EtOAc/hexanes) provided **4.23a** (6.02 g, 19.4 mmol, 97% yield) as a white solid. Analytical data for **4.23a**: **^{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.** 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.

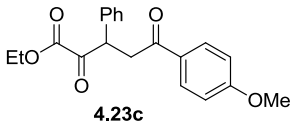
Ethyl 5-(4-iodophenyl)-2,5-dioxo-3-phenylpentanoate (4.23b):



4.23b

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23b** ().829 g, 1.90 mmol, 95% yield) as a white solid. Analytical data for **4.23a**: **^{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.** 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.

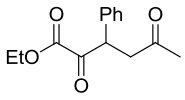
Ethyl 5-(4-methoxyphenyl)-2,5-dioxo-3-phenylpentanoate (4.23c):



4.23c

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23c** (0.585 g, 1.72 mmol, 97% yield) as a yellow solid. Analytical data for **4.23c**: **^{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.** 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.

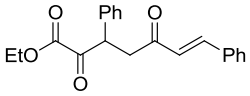
Ethyl 2,5-dioxo-3-phenylhexanoate (4.23d):



4.23d

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23d** (0.357 g, 1.44 mmol, 72% yield) as a clear oil. Analytical data for **4.23d**: **^{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.

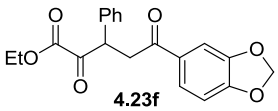
(E)-Ethyl 2,5-dioxo-3,7-diphenylhept-6-enoate (4.23e):



4.23e

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23e** (0.612 g, 1.82 mmol, 91% yield) as a clear oil. Analytical data for **4.23e**: **^{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 (4.23f):

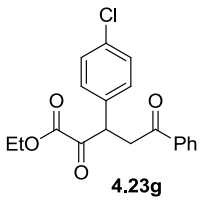


4.23f

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23f** (0.652 g, 1.84 mmol, 92% yield) as a clear oil. Analytical data for **4.23f**: **^{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.

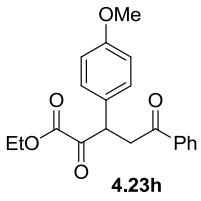
Ethyl 3-(4-chlorophenyl)-2,5-dioxo-5-phenylpentanoate (4.23g):



4.23g

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23g** (0.648 g, 1.88 mmol, 94% yield) as a clear oil. Analytical data for **4.23g**: **^{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 (4.23h):

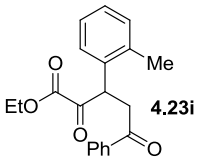


4.23h

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23h** (0.653 g, 1.92 mmol, 96% yield) as a clear oil. Analytical data for **4.23h**: **^{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.

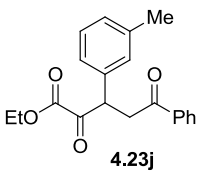
Ethyl 2,5-dioxo-5-phenyl-3-(o-tolyl)pentanoate (4.23i):



4.23i

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23i** (0.454 g, 1.40 mmol, 70% yield) as a clear oil. Analytical data for **4.23i**: **^{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 (4.23j):

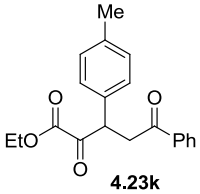


4.23j

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23j** (0.603 g, 1.86 mmol, 93% yield) as a clear oil. Analytical data for **4.23j**: **^{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.

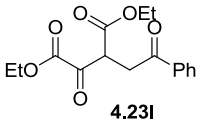
Ethyl 2,5-dioxo-5-phenyl-3-(p-tolyl)pentanoate (4.23k):



4.23k

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23k** (0.615 g, 1.90 mmol, 95% yield) as a clear oil. Analytical data for **4.23k**: **^{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 (4.23l):

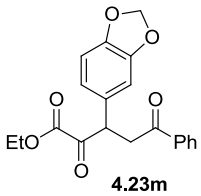


4.23l

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23l** (0.563 g, 1.84

mmol, 92% yield) as a clear oil. Analytical data for **4.23l**: **^{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.

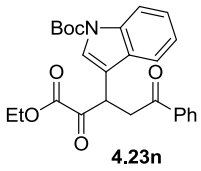
Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2,5-dioxo-5-phenylpentanoate (4.23m):



4.23m

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23m** (0.665 g, 1.88 mmol, 94% yield) as a clear oil. Analytical data for **4.23m**: **^{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.

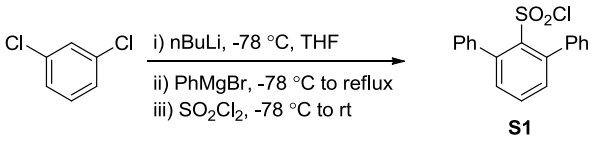
***Tert*-butyl 3-(1-ethoxy-1,2,5-trioxo-5-phenylpentan-3-yl)-1H-indole-1-carboxylate (4.23n):**



4.23n

The title compound was prepared according to General Procedure B. Flash chromatography (20% EtOAc/hexanes) provided **4.23n** (0.628 g, 1.40 mmol, 70% yield) as a yellow solid. Analytical data for **4.23n**: **^{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, 28.1, 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.

<u>Preparation of *m*-Terphenyl Sulfonyl Chloride S1</u>

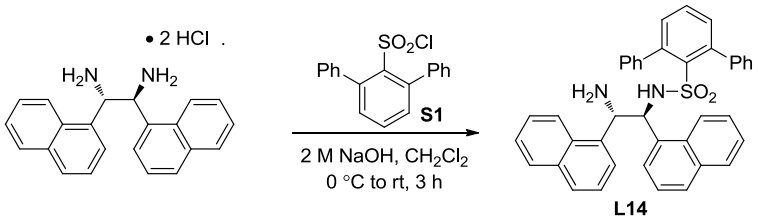


S1

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 nBuLi (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 bromobenzne (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.[34]

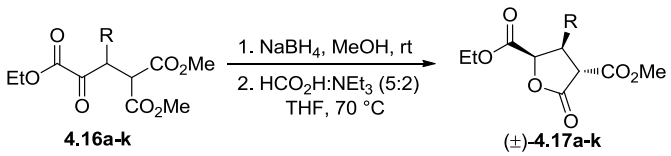
Preparation of L14



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 **S1** (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 **L14** (330 mg, 0.545 mmol, 84% yield) as a white solid. Analytical data for **L14**: **^{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; **$[\alpha]_D^{25}$** +170.6 (*c* = 1.30, $CHCl_3$).

General Procedure C for the Preparation of Racemic γ-Butyrolactones 4.16a-4.17k

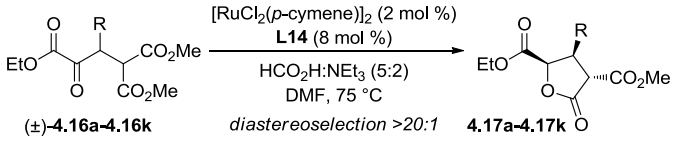


4.16a-k (±)-**4.17a-k**

Sodium borohydride (1.0 equiv) was added to a solution of β-aryl α-keto ester (1.0 equiv) in methanol (0.5 M concentration) at room temperature. When gas evolution ceased, 1 mL saturated ammonium chloride was added. 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 a mixture of α-hydroxy ester and γ-butyrolactone. The crude reaction mixture was dissolved in tetrahydrofuran (0.5 M concentration) and formic

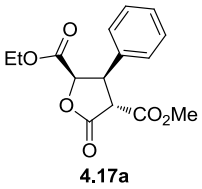
acid:triethylamine 5:2 azeotrope (1.0 equiv) was added. The reaction heated at 70 ºC for 1 hour, at which point the reaction mixture was allowed to cool to ambient temperature and diluted with diethyl ether and water. The organic layer was washed with brine and dried over sodium sulfate. Concentration *in vacuo* afforded the γ-butyrolatones which were purified by flash chromatography using the indicated solvent systems.

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



To a flame-dried 1-dram vial equipped with a magnetic stir bar were added [$RuCl_2$(*p*-cymene)]$_2$ (0.02 equiv) and ligand (0.08 equiv). The vial was sealed with a rubber septum and purged with nitrogen. DMF (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-aryl α-keto ester (1.0 equiv in 1.0 mL DMF) followed by formic acid:triethylamine 5:2 azeotrope (5.0 equiv) were added. The vial was purged with nitrogen and the reaction was heated at 70 ºC for 16 h, at which point the reaction mixture was allowed to cool to ambient temperature 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 γ-butyrolactones which were purified by flash chromatography using the indicated solvent systems.

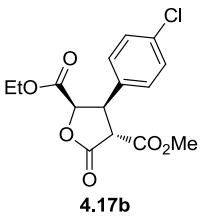
(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 5-oxo-3-phenyltetrahydrofuran-2,4-dicarboxylate (4.17a):



4.17a

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16a** (50 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 γ-butyrolactone **4.17a** (42.0 mg, 0.143 mmol, 92% yield) as a white solid. Analytical data for **4.17a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35-7.32 (m, 3H), 7.22-7.20 (m, 2H), 5.18 (d, *J* = 8.4 Hz, 1H), 4.52 (dd, *J* = 12, 8.4 Hz, 1H), 4.25 (d, *J* = 12 Hz, 1H), 3.92-3.87 (m, 1H), 3.87 (s, 3H), 3.86-3.74 (m, 1H), 0.84 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 170.5, 167.7, 167.2, 132.6, 129.0, 128.7, 127.4, 78.9, 61.7, 53.4, 48.7, 47.8, 13.5; **IR** (thin film, cm^{-1}): 2963, 1797, 1742, 1455, 1437, 1382, 1280, 1218, 1133, 1075, 994, 940, 751, 699; **m.p.** 100-102 ºC; **TLC** (20% EtOAc/hexanes) R_f :0.26; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{15}H_{17}O_6$: 293.10, Found: 293.16 **SFC Analysis**: WO column, 2% MeOH, 1.5 mL/min, 150 bar, 210 nm; t_{minor} = 12.5 min t_{major} = 14.5, 95:5 er; **$[\alpha]_D^{25}$** -150.9 (*c* = 1.70, $CHCl_3$).

(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 3-(4-chlorophenyl)-5-oxotetrahydrofuran-2,4-dicarboxylate (4.17b):

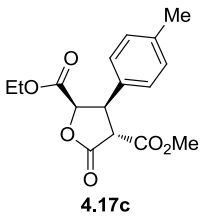


4.17b

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16b** (55 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 provided γ-butyrolactone **4.17b** (47.6 mg, 0.146 mmol, 94%

yield) as a white solid. Analytical data for **4.17b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 5.16 (d, *J* = 8.4 Hz, 1H), 4.48 (dd, *J* = 11.2, 8.4 Hz, 1H), 4.18 (d, *J* = 11.2 Hz, 1H), 3.98-3.90 (m, 1H), 3.87-3.82 (m, 1H), 3.81 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.0, 167.6, 167.0, 134.8, 131.3, 129.6, 129.2, 128.9, 128.5, 78.6, 61.9, 53.5, 48.9, 47.2, 13.6; **IR** (thin film, cm^{-1}): 2957, 1796, 1741, 1437, 1382, 1302, 1213, 1128, 1060, 840, 708, 564; **m.p.** 94-94 ºC; **TLC** (20% EtOAc/hexanes) R_f: 0.31; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{15}H_{16}ClO_6$: 327.06, Found: 327.10; **SFC Analysis**: WO column, 2% MeOH, 1.5 mL/min, 150 bar, 210 nm; t_{minor} = 13.4 min t_{major} = 17.3, 96:4 er; **$[\alpha]_D^{25}$** -143.1 (*c* = 1.5, $CHCl_3$).

(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 5-oxo-3-(p-tolyl)tetrahydrofuran-2,4-dicarboxylate (4.17c):

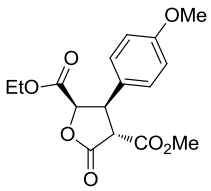


4.17c

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16c** (52 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 provided γ-butyrolactone **4.17c** (40 mg, 0.130 mmol, 84% yield) as a white solid. Analytical data for **4.17c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.15 (d, *J* = 8.8 Hz, 1H), 4.47 (dd, *J* = 11.2, 8 Hz, 1H), 4.21 (d, *J* = 11.2 Hz, 1H), 3.93-3.89 (m, 1H), 3.82-3.78 (m, 1H), 3.79 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.5, 167.8, 167.3, 138.5, 129.6, 127.3, 79.0, 61.7, 53.3, 49.0, 47.6, 21.0, 13.5; **IR** (thin film, cm^{-1}): 2957, 1796, 1742, 1519, 1438, 1381, 1306, 1213, 1131, 1058, 828, 517; **m.p.** 85-86 ºC; **TLC** (30% EtOAc/hexanes) R_f: 0.38; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{16}H_{19}O_6$: 307.12, Found: 307.16; **HPLC Analysis**:

Chiralpak IB,10% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; t_{minor} = 12.5 min t_{major} = 15.8 min, 95.5:4.5 er; $[\alpha]_D^{25}$ -191.3 (*c* = 1.7, $CHCl_3$).

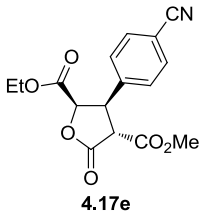
(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 3-(4-methoxyphenyl)-5-oxotetrahydrofuran-2,4-dicarboxylate (4.17d):



4.17d

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16d** (55 mg, 0.155 mmol, 1.0 equiv), [$RuCl_2$(*p*-cymene)]$_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 provided γ-butyrolactone **4.17d** (45 mg, 0.140 mmol, 90% yield) as a white solid. Analytical data for **2d**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.13 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.14 (d, *J* = 8.4 Hz, 1H), 4.45 (dd, *J* = 11.4, 8.4 Hz, 1H), 4.19 (d, *J* = 11.4 Hz, 1H), 3.95-3.80 (m, 1H), 3.84-3.8 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 170.5, 167.8, 167.3, 159.8, 128.6, 124.5, 114.3, 79.0, 61.7, 55.3, 53.4, 49.1, 47.2, 13.6; **IR** (thin film, cm^{-1}): 2958, 1796, 1742, 1613, 1518, 1440, 1382, 1256, 1218, 1182, 1132, 1096, 1058, 1030, 835, 750, 683; **m.p.** 106-107 ºC; **TLC** (30% EtOAc/hexanes) R_f : 0.31; **LRMS** (ESI): Calculated for [M+Na] $C_{16}H_{18}O_7Na$: 345.10, Found: 345.18; **HPLC Analysis**: Chiralpak IB,10% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; t_{minor} = 18.7 min t_{major} = 23.6 min, 95:5 er; $[\alpha]_D^{25}$ -179.2 (*c* = 1.9, $CHCl_3$).

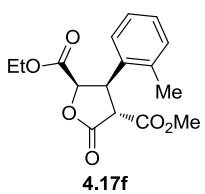
(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 3-(4-cyanophenyl)-5-oxotetrahydrofuran-2,4-dicarboxylate (4.17e):



4.17e

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16e** (54 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 provided γ-butyrolactone **4.17e** (43 mg, 0.136 mmol, 88% yield) as a white solid. Analytical data for **4.17e**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.21 (d, *J* = 8.8 Hz, 1H), 4.56 (dd, *J* = 11.2, 8.8 Hz, 1H), 4.21 (d, *J* = 11.2 Hz, 1H), 3.96-3.90 (m, 1H), 3.85-3.79 (m, 1H), 3.82 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.4, 167.3, 166.7, 138.2, 132.7, 128.4, 117.9, 112.8, 78.1, 62.1, 53.6, 48.6, 47.6, 13.6; **IR** (thin film, cm^{-1}): 2360, 2333, 1796, 1742, 1312, 1271, 1134, 995, 836, 670; **m.p.** 104-107 ºC; **TLC** (30% EtOAc/hexanes) R_f : 0.25; **LRMS** (ESI): Calculated for [M+Na] $C_{16}H_{15}NO_6Na$: 340.08, Found: 340.18; **HPLC Analysis**: Chiralpak IB, 25% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; t_{minor} = 18.6 min t_{major} = 22.4 min, 95:5 er; **$[\alpha]_D^{25}$** -177.4 (*c* = 1.7, $CHCl_3$).

(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 5-oxo-3-(o-tolyl)tetrahydrofuran-2,4-dicarboxylate (4.17f):

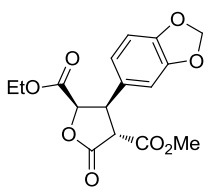


4.17f

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16f** (52 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 provided γ-butyrolactone **4.17d** (39 mg, 0.127 mmol, 82% yield) as a white

solid. Analytical data for **4.17f**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.21 (m, 2H), 7.19-7.16 (m, 1H), 7.09-7.07 (m, 1H), 5.24 (d, *J* = 8.8 Hz, 1H), 4.72 (dd, *J* = 12, 8.8 Hz, 1H), 4.34 (d, *J* = 12 Hz, 1H), 3.86-3.81 (m, 1H), 3.79 (s, 3H), 3.74-3.7 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.5, 167.7, 167.3, 137.4, 131.0, 130.7, 128.5, 126.5, 125.0, 77.3, 61.6, 53.3, 48.3, 44.8, 19.6, 13.4; **IR** (thin film, cm^{-1}): 2359, 2341, 1797, 1742, 1440, 1381, 1317, 1212, 1135, 1021, 752, 538; **m.p.** 103-104 ºC; **TLC** (20% EtOAc/hexanes) R_f: 0.29; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{16}H_{19}O_6$: 307.12, Found: 307.16; **HPLC Analysis**: Chiralpak IB, 10% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; t_{minor} = 12.1 min t_{major} = 15.0 min, 89:11 er; **$[\alpha]_D^{25}$** -136.4 (*c* = 1.4, $CHCl_3$).

(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 3-(benzo[*d*][1,3]dioxol-5-yl)-5-oxotetrahydrofuran-2,4-dicarboxylate (4.17g):

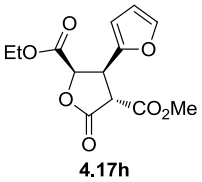


4.17g

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16g** (57 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 provided γ-butyrolactone **4.17d** (43 mg, 0.129 mmol, 83% yield) as a white solid. Analytical data for **4.17g**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.4 Hz, 1H), 6.68-6.67 (m, 2H), 5.96 (s, 2H), 5.12 (d, *J* = 8.4 Hz, 1H), 4.41 (dd, *J* = 11.6, 8.4 Hz, 1H), 4.14 (d, *J* = 11.6 Hz, 1H), 4.05-3.87 (m, 2H), 3.80 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.3, 167.7, 167.2, 148.2, 147.9, 126.2, 120.9, 108.6, 107.8, 101.4, 78.9, 61.8, 53.3, 49.2, 47.7, 13.7; **IR** (thin film, cm^{-1}): 2906, 2363, 2349, 1797, 1740, 1506, 1494, 1446, 1304, 1256, 1237, 1142, 1093, 1037, 931, 801; **m.p.** 86-87 ºC; **TLC**

(30% EtOAc/hexanes) R_f : 0.31; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{16}H_{17}O_8$: 337.09, Found: 337.09; **HPLC Analysis**: Chiralpak IB, 10% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; t_{minor} = 21.8 min t_{major} = 25.8 min, 96:4 er; $\mathbf{[\alpha]_D^{25}}$ -206.3 (*c* = 2.1, $CHCl_3$).

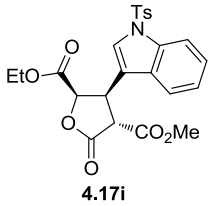
(2*R*,3*S*,4*R*)-2-ethyl 4-methyl 3-(furan-2-yl)-5-oxotetrahydrofuran-2,4-dicarboxylate (4.17h):



4.17h

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16h** (48 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 provided □-butyrolactone **4.17h** (40 mg, 0.141 mmol, 91% yield) as a clear oil. Analytical data for **4.17h**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.37 (m, 1H), 6.34-6.33 (m, 1H), 6.28-6.27 (m, 1H), 5.14 (d, *J* = 8.4 Hz, 1H), 4.56 (dd, *J* = 11.6, 8.4 Hz, 1H), 4.16 (d, *J* = 11.6, 1H), 4.10-4.04 (m, 1H), 3.99-3.92 (m, 1H), 3.82 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.6, 167.6, 166.8, 146.7, 143.2, 110.7, 109.0, 77.2, 62.2, 53.5, 48.2, 41.9, 13.7; **IR** (thin film, cm^{-1}): 2963, 1797, 1743, 1440, 1382, 1305, 1215, 1133, 1061, 841, 708, 560; **TLC** (20% EtOAc/hexanes) R_f : 0.21; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{13}H_{15}O_7$: 283.08, Found: 283.03; **HPLC Analysis**: Chiralpak IA, 10% ^{i}PrOH/hexanes, constant flow at 1.00 mL/min, 210 nm; t_{minor} = 11.4 min t_{major} = 12.5 min, 95:5 er; $\mathbf{[\alpha]_D^{25}}$ -52.3 (*c* = 1.2, $CHCl_3$).

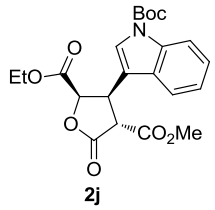
(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 5-oxo-3-(1-tosyl-1H-indol-3-yl)tetrahydrofuran-2,4-dicarboxylate (4.17i):



4.17i

The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16i** (80 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 provided γ-butyrolactone **4.17i** (68 mg, 0.141 mmol, 91% yield) as a white solid. Analytical data for **4.17i**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 7.37-7.35 (m, 1 H), 7.32-7.30 (m, 1H), 7.54-7.23 (m, 1H), 5.30 (d, *J* = 8.4 Hz, 1H), 4.64 (dd, *J* =11.6, 8.4 Hz, 1H), 4.20 (d, *J* = 11.6 Hz, 1H), 3.82 (s, 3H), 3.64-3.56 (m, 1H), 3.36-3.28 (m, 1H), 2.35 (s, 3H), 0.41 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.8, 167.6, 167.0, 145.3, 135.0, 134.8, 130.0, 129.2, 126.9, 125.6, 123.6, 123.4, 119.5, 115.5, 113.7, 77.6, 61.4, 53.5, 48.4, 39.9, 30.2, 21.5, 12.9; **IR** (thin film, cm^{-1}): 2978, 2348, 1800, 1742, 1595, 1449, 1373, 1290, 1215, 1175, 1139, 1092, 1075, 1021, 974, 912, 816, 762, 747, 703, 680, 655; **m.p.** 99-100 ºC **TLC** (30% EtOAc/hexanes) R_f : 0.28; **LRMS** (ESI): Calculated for [M+Na] $C_{24}H_{23}NO_8SNa$: 508.10, Found: 508.10; **SFC Analysis**: WO column, 10% MeOH, 1.5 mL/min, 150 bar 210 nm; t_{minor} = 16.5 min t_{major} = 22.5 min, 96.5:3.5 er; **$[\alpha]_D^{25}$** -81.2 (*c* = 1.7, $CHCl_3$).

(2*R*,3*R*,4*R*)-2-ethyl 4-methyl 3-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-5-oxotetrahydrofuran-2,4-dicarboxylate (4.17j):



2j

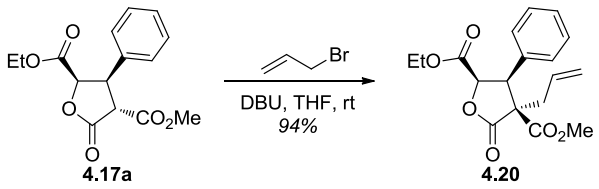
The title compound was prepared according to General Procedure D using β-aryl α-keto ester **4.16j** (71.5 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (7.5 mg, 0.0124 mmol, 0.08 equiv), and HCOOH:NEt_3 5:2 azeotrope (67 mg, 0.775 mmol, 5.0 equiv). Flash chromatography provided γ-butyrolactone **4.17j** (59 mg, 0.136 mmol, 88% yield) as a white solid. Analytical data for **4.17j**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.57-7.55 (m, 1H), 7.44 (s, 1H), 7.37-7.30 (m, 2H), 5.35 (d, *J* = 8.4 Hz, 1H), 4.70 (dd, *J* =11.6, 8.4 Hz, 1H), 4.24 (d, *J* = 11.6, 1H), 3.85-3.80 (m, 2H), 3.82 (s, 3H), 0.69 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.1, 167.9, 167.2, 149.2, 135.4, 129.0, 125.3, 123.2, 123.0, 118.9, 115.4, 113.5, 84.5, 77.9, 61.7, 53.4, 48.8, 40.0, 28.1, 13.2; **IR** (thin film, cm^{-1}): 2979, 1800, 1739, 1454, 1375, 1338, 1310, 1273, 1258, 1220, 1155, 1078, 1018, 857, 840, 763, 748; **m.p.** 84-85 ºC; **TLC** (30% EtOAc/hexanes): R_f : 0.4; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{22}H_{26}NO_8$: 432.17, Found: 432.18; **HPLC Analysis**: Chiralpak IB, 10% ^{i}PrOH/hexanes, constant flow at 1.0 mL/min, 210 nm; t_{minor} = 11.7 min t_{major} = 12.6 min, 96:4 er; **$[\alpha]_D^{25}$** -75.7 (*c* =2.3, $CHCl_3$).

<u>Large Scale Preparation of γ-Butyrolactone 4.17g</u>

To a flame-dried 250-mL round-bottomed flask were added $[RuCl_2(p\text{-cymene})]_2$ (83.6 mg, 0.137 mmol, 0.005 equiv), **L14** (330 mg, 0.546 mmol, 0.020 equiv) and 50 mL of DMF. The mixture was heated at 70 ºC under nitrogen for 45 min and cooled to ambient temperature. A solution of β-aryl α-keto ester **4.16g** (10.0 g, 27.3 mmol, 1.0 equiv) in 20 mL DMF was

added via syringe and the reaction mixture was further diluted with 66 mL DMF. Formic acid:triethylamine 5:2 azeotrope (11.8 g, 136.5 mmol, 5.0 equiv) was added in a single portion and the reaction was heated at 70 ºC for 16 h, at which point the reaction was cooled to ambient temperature and diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (x2) and the combined organics were washed with water (x3) followed by brine (x1), dried over sodium sulfate and concentrated *in vacuo.* A 150-mL frit funnel (7 cm diameter) was charged with silica gel (4 cm in height). The crude reaction mixture was dissolved in the minimum amount of dichloromethane and passed through the pad of silica gel using 150 mL of 30% EtOAc/hexanes; the filtrate was concentrated *in vacuo*. The resultant residue was dissolved in the minimum amount of diethyl ether. Hexanes were added until the solution became cloudy. This solution was stored in the freezer overnight. The crystals were collected by filtration to yield enantiopure **4.17g** (6.61 g, 19.6 mmol, 72% yield).

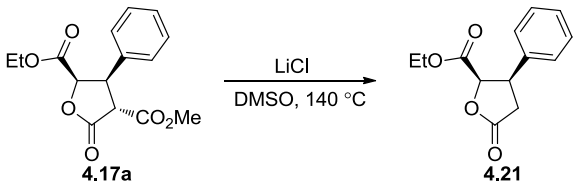
Preparation of γ-Butyrolactone 4.20



To a 1-dram vial equipped with a magnetic stir bar were added **4.17a (**29.2 mg, 0.100 mmol, 1.0 equiv), allyl bromide (24.2 mg, 0.200 mmol, 2.0 equiv) and THF (1 mL). DBU (30.4 mg, 0.200 mmol, 2.0 equiv) was added and the reaction was stirred at room temperature for 2 h 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 **4.20** (31.2 mg, 0.940 mmol, 94% yield) as a white solid. Analytical data for **3a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.25-7.24 (m, 3H), 7.15-7.13 (m, 2H), 5.90-5.85 (m, 1H), 5.35-5.30 (m, 2H), 5.22 (d, *J* = 7.2 Hz, 1H), 3.91-3.81 (m, 2H), 3.89 (d, *J* = 7.2 Hz, 1H), 3.22 (s, 3H), 2.97 (dd, *J* = 14.1, 7.2 Hz, 1H), 2.85 (dd, *J* = 14.1, 7.2 Hz, 1H), 0.83 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.6, 167.6, 166.3, 134.8, 130.5, 128.6, 128.4, 128.2, 121.5, 77.3, 61.6, 60.4, 53.6, 52.1, 40.1, 13.5; **IR** (thin film, cm^{-1}): 2921, 2359, 1797, 1759, 1740, 1436, 1221, 1168, 1125, 1087, 1028, 929, 705; **m.p.** 100-101.5 ºC; **TLC** (20% EtOAc/hexanes) R_f : 0.22; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{18}H_{21}O_6$: 333.13, Found: 333.16; **$[\alpha]_D^{25}$** -35.5 (*c* =6.5, $CHCl_3$).

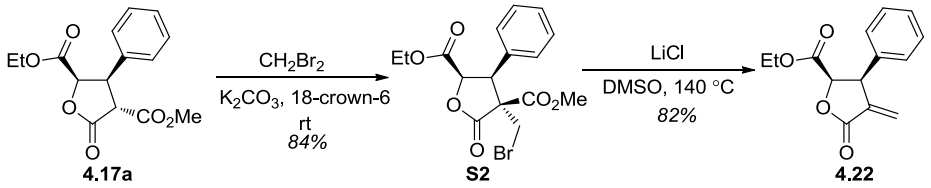
Preparation of γ-Butyrolactone 4.21



To a 1-dram vial equipped with a magnetic stir bar were added **4.17a** (45.0 mg, 0.155 mmol, 1.0 equiv), lithium chloride (71.0 mg, 0.310 mmol, 2.0 equiv), and DMSO (1 mL). The vial was fitted with a PTFE screw-cap and heated in an oil bath at 140 ºC for 16 h, at which point the reaction was cooled to ambient temperature and diluted with water and ethyl acetate. The organic layer was washed with water (x2) followed by brine (x1), dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (20% EtOAc/hexanes) provided **4.21** (31.2

mg, 0.133 mmol, 86% yield) as a colorless oil. Analytical data for **3b**: : **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.30 (m, 3H), 7.22-7.20 (m, 2H), 5.13 (d, *J* = 8.4 Hz, 1H), 4.13-4.06 (m, 1H), 3.91-3.83 (m, 1H), 3.80-3.72 (m, 1H), 3.09 (dd, *J* = 17.2, 10 Hz, 1H), 2.84 (dd, *J* = 17.2, 8.8 Hz, 1H), 0.86 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.2, 167. 9, 134.9, 128.8, 128.3, 127.5, 80.1, 61.4, 44.1, 32.2, 13.5; **IR** (thin film, cm^{-1}): 2985, 2359, 2342, 1793, 1742, 1498, 1455, 1381, 1214, 1151, 1094, 1074, 1051, 700, 544; **TLC** (20% EtOAc/hexanes) R_f : 0.19; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{13}H_{15}O_4$: 235.10, Found: 235.08; **$[\alpha]_D^{25}$** -68.4 (*c* =1.6, $CHCl_3$).

Preparation of α-methylene γ-Butyrolactone 4.22

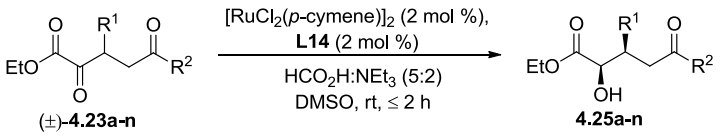


To a flame-dried 1-dram vial equipped with a magnetic stir bar were added **4.17a** (29.2 mg, 0.100 mmol, 1.0 equiv) and dibromomethane (0.125 mL). 18-crown-6 (1.30 mg, 0.005 mmol, 0.05 equiv) and potassium carbonate (35 mg, 0.25 mmol, 2.5 equiv) were added sequentially and the reaction was stirred at ambient temperature for 36 h. The reaction was diluted with water and ethyl acetate and the organic was washed with water followed by brine, dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (30% EtOAc/hexeanes) provided **S2** (32 mg, 0.084 mmol, 84% yield) as a white solid. Analytical data for **S2**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.26 (m, 3H), 7.17-7.15 (m, 2H), 5.42 (d, *J*

= 8.4 Hz, 1H), 4.20 (d, *J* = 8.4 Hz, 1H), 4.01 (d, *J* = 10.8 Hz, 1H), 3.94 (d, *J* = 10.8 Hz, 1H), 3.92-3.86 (m, 2H), 3.30 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.3, 166.2, 134.2, 128.9, 128.7, 128.3, 78.2, 61.8, 61.6, 52.8, 52.7, 33.2, 13.5; **IR** (thin film, cm^{-1}): 2360, 1795, 1751, 1736, 1232, 1146, 1086, 1041, 709; **m.p.** 161-162 ºC; **TLC** (30% EtOAc/hexanes) R_f : 0.32; **LRMS** (ESI): Calculated for [M+Na] $C_{16}H_{17}BrO_6Na$: 407.01, Found: 407.01; **$[\alpha]_D^{25}$** = -37.3 (*c* =2.0, $CHCl_3$).

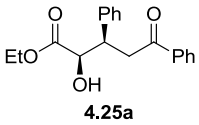
To a 1-dram vial equipped with a magnetic stir bar were added **S2** (26 mg, 0.067 mmol, 1.0 equiv), lithium chloride (6.0 mg, 0.134 mmol, 2.0 equiv) and DMSO (1 mL). The vial was fitted with a PTFE screw-cap and heated in an oil bath at 140 ºC for 16 h, at which point the reaction was cooled to ambient temperature and diluted with water and ethyl acetate. The organic was washed with water (x2) followed by brine (x1), dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (20% EtOAc/hexanes) provided **4.22** (14 mg, 0.057 mmol, 85% yield) as a white solid. Analytical data for **3c**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.33-7.30 (m, 3H), 7.21-7.19 (m, 2H), 6.54 (d, *J* = 3 Hz, 1H), 5.63 (d, *J* = 3 Hz, 1H), 5.18 (d, *J* = 9 Hz, 1H), 4.62-4.59 (dt, *J* = 9.6, 3 Hz 1H), 3.85-3.80 (m, 1H), 3.68-3.63 (m, 1H), 0.84 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.3, 167.7, 135.8, 135.3, 129.0, 128.8, 128.4, 125.1, 78.4, 61.5, 48.6, 13.5; ; **IR** (thin film, cm^{-1}): 2983, 2359, 1780, 1747, 1402, 1188, 1095, 1067, 757, 702; **m.p.** 113-114 ºC; **TLC** (20% EtOAc/hexanes) R_f : 0.25; **LRMS** (ESI): Calculated for $[M+H]^+$ $C_{14}H_{15}O_4$: 247.10, Found: 247.12; **$[\alpha]_D^{25}$** -62.3 (*c* =2.2, $CHCl_3$).

General Procedure E for the ATH-DKR of β-Substituted α,δ-Diketo Esters



To a flame-dried 1-dram vial equipped with a magnetic stir bar were added [$RuCl_2$(*p*-cymene)]$_2$ (0.02 equiv) and ligand (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 DMF) 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 α-hydroxy esters which were purified by flash chromatography using the indicated solvent systems.

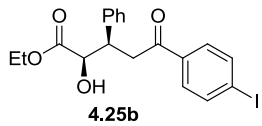
(2*R*,3*R*)-Ethyl 2-hydroxy-5-oxo-3,5-diphenylpentanoate (4.25a):


4.25a

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23a** (48.0 mg, 0.155 mmol, 1.0 equiv), [$RuCl_2$(*p*-cymene)]$_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25a** (47 mg, 0.152 mmol, 98% yield) as a white solid. Analytical data for **4.25a**: **^{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.**; **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_{minor} = 9.3 min t_{major} = 10.1 min, 97:3 er; **$[\alpha]_D^{25}$** +30.56 (*c* = 5.6, $CHCl_3$).

(2*R*,3*R*)-Ethyl 2-hydroxy-5-(4-iodophenyl)-5-oxo-3-phenylpentanoate (4.25b):

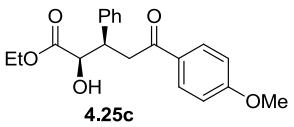


4.25b

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23b** (68.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25b** (62 mg, 0.141 mmol, 91% yield) as a white solid. Analytical data for **4.25b**: **^{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.**; **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_{minor} = 9.3 min t_{major} = 10.1 min, 96.5:3.5 er; **$[\alpha]_D^{25}$** +34.32 (*c* = 12.5, $CHCl_3$).

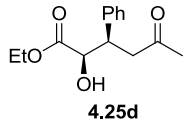
(2*R*,3*R*)-Ethyl 2-hydroxy-5-(4-methoxyphenyl)-5-oxo-3-phenylpentanoate (4.25c):



4.25c

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23c** (53.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25c** (49.8 mg, 0.152 mmol, 94% yield) as a clear oil. Analytical data for **4.25c**: **^{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_{minor} = 9.3 min t_{major} = 10.1 min, 96:4 er; **$[\alpha]_D^{25}$** +47.15 (*c* = 2.7, $CHCl_3$).

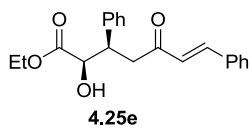
(2*R*,3*R*)-Ethyl 2-hydroxy-5-oxo-3-phenylhexanoate (4.25d):



4.25d

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23d** (38.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25d** (33.0 mg, 0.132 mmol, 85% yield) as a clear oil. Analytical data for **4.25d**: **^{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_{minor} = 6.4 min t_{major} = 9.2 min, 93:7 er; **$[\alpha]_D^{25}$** +47.15 (*c* = 2.7, $CHCl_3$).

(2*R*,3*R*,*E*)-Ethyl 2-hydroxy-5-oxo-3,7-diphenylhept-6-enoate (4.25e):

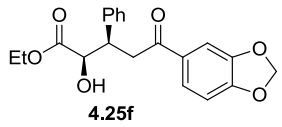


4.25e

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23e** (52.1 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25e** (46.0 mg, 0.136

mmol, 88% yield) as a white solid. Analytical data for **4.25e**: **^{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_{minor} = 15.0 min t_{major} = 16.1 min, 99:1 er; **$[\alpha]_D^{25}$** +47.32 (*c* = 5.3, $CHCl_3$).

(2*R*,3*R*)-Ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxy-5-oxo-3-phenylpentanoate (4.25f):

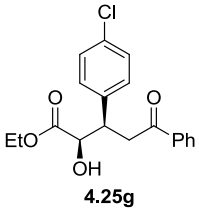


4.25f

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23f** (55.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25f** (54.0 mg, 0.152 mmol, 98% yield) as a clear oil. Analytical data for **4.25f**: **^{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_{minor} = 15.2 min t_{major} = 16.3 min, 99:1 er; **$[\alpha]_D^{25}$** +32.94 (*c* = 10.0, $CHCl_3$).

(2*R*,3*R*)-Ethyl 3-(4-chlorophenyl)-2-hydroxy-5-oxo-5-phenylpentanoate (4.25g):

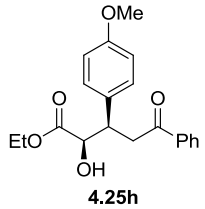


4.25g

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23g** (53.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25g** (50.0 mg, 0.146 mmol, 94% yield) as a clear oil. Analytical data for **4.25g**: **^{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_{minor} = 8.8 min t_{major} = 9.8 min, 98:2 er; $[\alpha]_D^{25}$ +48.4 (*c* = 4.2, $CHCl_3$).

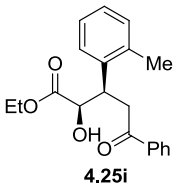
(2*R*,3*R*)-Ethyl 2-hydroxy-3-(4-methoxyphenyl)-5-oxo-5-phenylpentanoate (4.25h):



4.25h

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23h** (53.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25h** (52.0 mg, 0.152 mmol, 98% yield) as a clear oil. Analytical data for **4.25h**: **^{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_{minor} = 13.2 min t_{major} = 16.8 min, 96:4 er; $[\alpha]_D^{25}$ +34.6 (*c* = 6.3, $CHCl_3$).

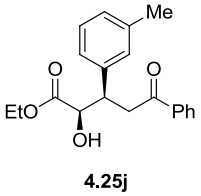
(2*R*,3*R*)-Ethyl 2-hydroxy-5-oxo-5-phenyl-3-(o-tolyl)pentanoate (4.25i):



4.25i

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23i** (50.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25i** (44.0 mg, 0.135 mmol, 87% yield) as a clear oil. Analytical data for **4.25i**: **^{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_{minor} = 14.6 min t_{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 (4.25j):

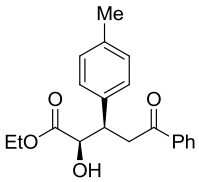


4.25j

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23j** (50.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25j** (49.0 mg, 0.152 mmol, 98% yield) as a clear oil. Analytical data for **4.25j**: **^{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_{minor} = 9.6 min t_{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 (4.25k):

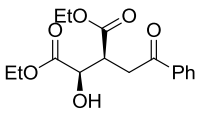


4.25k

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23k** (50.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25k** (48.0 mg, 0.151 mmol, 97% yield) as a clear oil. Analytical data for **4.25k**: **^{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_{minor} = 12.8 min t_{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 (4.25l):

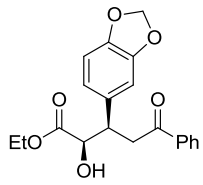


4.25l

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23l** (47.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25l** (44.0 mg, 0.144 mmol, 93% yield) as a clear oil. Analytical data for **4.25l**: **^{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_{minor} = 7.3 min t_{major} = 6.5 min, 91:9 er; $[\alpha]_D^{25}$ +27.5 (*c* = 4.2, $CHCl_3$).

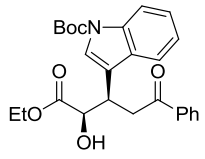
(2*R*,3*R*)-Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxy-5-oxo-5-phenylpentanoate (4.25m):



4.25m

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23m** (55.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25m** (53.0 mg, 0.149 mmol, 96% yield) as a clear oil. Analytical data for **4.25m**: **^{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_{minor} = 16.5 min t_{major} = 12.8 min, 98:2 er; $[\alpha]_D^{25}$ +30.8 (*c* = 7.0, $CHCl_3$).

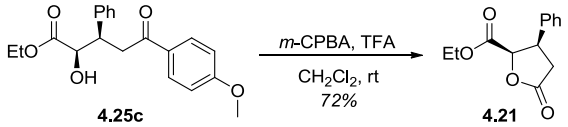
***Tert*-butyl 3-((2R,3R)-1-ethoxy-2-hydroxy-1,5-dioxo-5-phenylpentan-3-yl)-1H-indole-1-carboxylate (4.25n):**



4.25n

The title compound was prepared according to General Procedure E using α,δ-diketo ester **4.23n** (70.0 mg, 0.155 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (1.9 mg, 0.0031 mmol, 0.02 equiv), **L14** (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 α-hydroxy ester **4.25n** (60.0 mg, 0.133 mmol, 86% yield) as a clear oil. Analytical data for **4.25n**: **^{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_{minor} = 29.4 min t_{major} = 23.5 min, 98:2 er; **$[\alpha]_D^{25}$** +21.5 (*c* = 8.7, $CHCl_3$).

Bayer Villiger Oxidation of 4.25c



To a 1-dram vial equipped with a magnetic stir bar were added **4.25c** (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 **4.21** (17.0 mg, 0.072 mmol, 72% yield) as a white solid whose spectral data were in agreement with the cis-lactone.

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