NEW COMPLEXITY-BUILDING REACTIONS OF ALPHA-KETO ESTERS

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ABSTRACT

Samuel Lee Bartlett: New Complexity-Building Reactions of α-Keto Esters
(Under the direction of Jeffrey S. Johnson)

I. Introduction: Importance of Asymmetric Catalysis and the Reactivity Patterns of α-Keto Esters

II. Synthesis of Complex Tertiary Glycolates by Enantioconvergent Arylation of Stereochemically Labile α-Keto Esters

Enantioconvergent arylation reactions of boronic acids and racemic β-stereogenic α-keto esters have been developed. The reactions are catalyzed by a chiral (diene)Rh(I) complex and provide a wide array of β-stereogenic tertiary aryl glycolate derivatives with high levels of diastereo- and enantioselectivity. Racemization studies employing a series of sterically differentiated tertiary amines suggest that the steric nature of the amine base additive exerts a significant influence on the rate of substrate racemization.
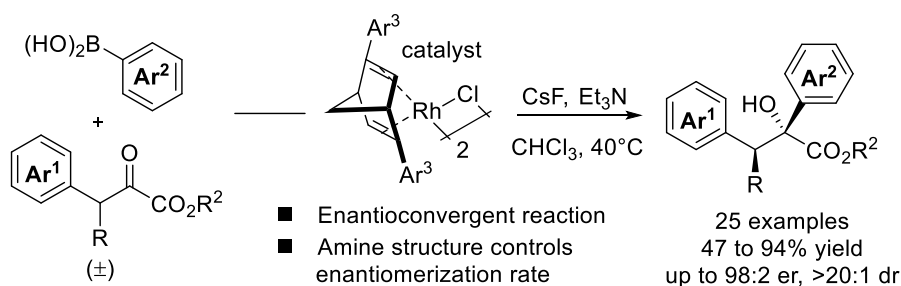
**III. Palladium-Catalyzed β-Arylation of α-Keto Esters**

A catalyst system derived from commercially available $Pd_2(dba)_3$ and P^tBu_3 has been applied to the coupling of α-keto ester enolates and aryl bromides. The reaction provides access to an array of β-stereogenic α-keto ester derivatives. When the air stable

ligand precursor P^{t}Bu$_3$·HBF$_4$ is employed, the reaction can be carried out without use of a glovebox. The derived products are of broad interest given the prevalence of the α-keto acid substructure in biologically important molecules.
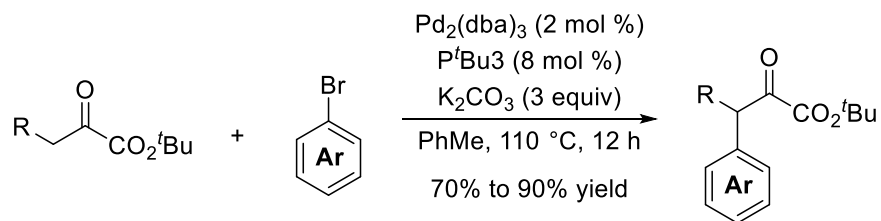
IV. Catalytic Enantioselective [3+2] Cycloaddition of α-Keto Ester Enolates and Nitrile Oxides

An enantioselective [3+2] cycloaddition reaction between nitrile oxides and transiently generated enolates of α-keto esters has been developed. The catalyst system was found to be compatible with *in situ* nitrile oxide generation conditions. A versatile array of nitrile oxides and α-keto esters could participate in the cycloaddition, providing novel 5-hydroxy-2-isoxazolines in high chemical yield with high levels of diastereo- and enantioselectivity. Notably, the optimal reaction conditions circumvented concurrent reaction via *O*-imidoylation and hetero-[3+2] pathways.

high chemo-, diastereo- and enantioselectivity
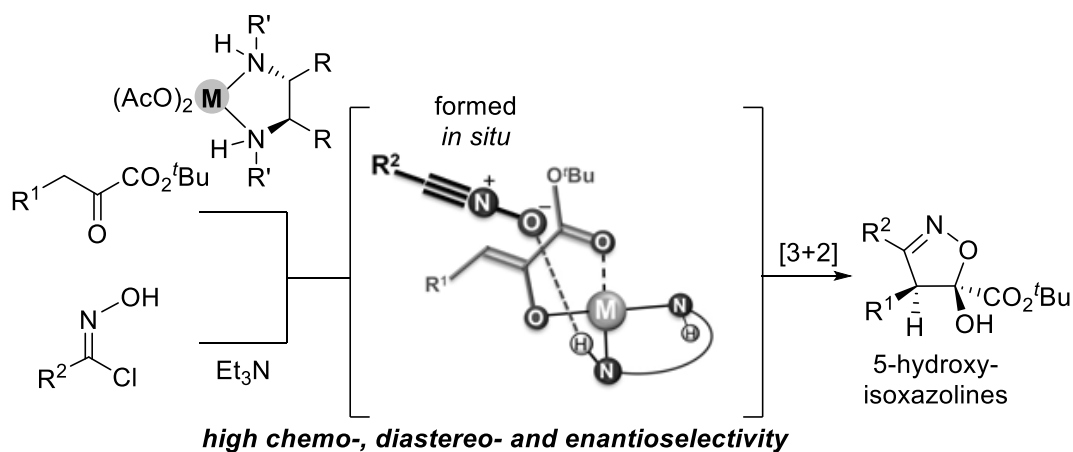
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First and foremost, I would like to thank my doctoral advisor Jeff Johnson. Jeff's mentoring style can be characterized as "hands-off" and he grants his students an extraordinary level of independence and trust from the moment they join the lab. Nevertheless, he is continuously available for discussion, and on numerous occasions, I can say ,with utmost confidence, that my research would not have progressed without his wisdom and insight. I am particularly grateful for the sacrifices he has made to maintain his availability during his transition to department chairperson. Jeff is extremely dedicated to the current and future success of every person that steps foot in his lab. It is clear now that his mentoring style is designed to enable maximum development of budding scientists and I believe it has uniquely prepared me for my future endeavors. Jeff truly lets his students define their own path through graduate school and I am thankful that he granted me extended leave to carry out research in Japan; this experience was immensely important to my personal development.

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UNC for a few months, was an inspiration in terms of his productivity, creativity, and dedication to research. I am grateful for his continued friendship and his eagerness to show me around Japan. The research output from Jeff's lab in many cases rivals or surpasses much larger groups. This is a testament to the drive and creativity of the people that join the lab. Considering the current group, I'm certain this trend will continue. All lab members have demonstrated unremitting commitment to extremely challenging research problems. I am particularly thankful for the friendship of Kendrick Smith and Blane Zavesky. Kendrick's encyclopedic knowledge of chemistry, jazz music, and the operational nuances of public transportation systems is especially impressive. Our friendship outside of lab has been a highlight of my time in Chapel Hill. Blane has a rare capability to remain positive during all phases of his research. He approaches new and uncertain research ideas the same way he approaches ordering chemicals from obscure companies, without fear, and his ability to gain insight (or $700 in company credit) from negative results is inspiring. I enjoyed our time working together on the enolate arylation project. Finally, I would like to acknowledge Kimberly Keiter for her dedication and haard work on the nitrone rearrangement project.

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LIST OF ABBREVIATIONS AND SYMBOLS

^{13}C	carbon-13
^{19}F	fluorine-19
^{1}H	proton
$A_{1,3}$	allylic 1,3
Ac	acetyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
CAM	ceric ammonium nitrate
d	doublet
dba	dibenzylideneacetone
DIPEA	diisopropylethylamine
DKR	Dynamic Kinetic Resolution
DMF	dimethylformamide
dr	diastereomeric ratio
DyKAT	Dynamic Kinetic Asymmetric Transformation
E	entgegen
equiv	equivalents
er	enantiomeric ratio
eV	electron volt
FMO	frontier molecular orbitals
h	hours

HOMO	highest occupied molecular orbital
HPLC	high-performance
HRMS	high resolution mass spectrometry
Hz	hertz
iPr	iso-propyl
IR	infrared
LUMO	lowest unoccupied molecular orbital
m	meta
m	multiplet
Me	methyl
MHz	megahertz
min	minutes
ml	milliliter
mmol	millimolar
mmol	millimeter
mol	molar
NMR	nuclear magnetic resonance
NS5A	nonstructural protein 5A
o	ortho
p	para
Ph	phenyl
PTEF	polytetrafluoroethylene

q	quartet
R	rectus
S	sinister
s	singlet
t	triplet
tBu	tertiary-butyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
uL	microliter
UV	ultraviolet
Z	zusammen

Chapter I Introduction

1.1 Enantioselective Catalysis: Implications for Human Health

The key role played by stereochemistry in biological molecular recognition events is now well understood. Related to the the development of small molecule pharmaceuticals, one enantiomer might possess desirable therapeutic properties, while the opposite antipode may be inherently detrimental. For instance (*R*)-levamisole is known to cause emesis.[1] Alternatively, a member of an enantiomeric pair may simply be inactive. In such cases its presence may complicate the determination of precise dose-response relationships and lessen the therapeutic window.[2] These considerations underwrite the recent ascendancy of the single-enantiomer therapeutics, which now account for sales of over $100 billion.[3] As a striking example, ledipasvir, an NS5A inhibitor of the hepatitis C virus, was the 2nd greatest selling pharmaceutical in 2016.[4] Considering the unremitting pressure on human health from factors including cancer and increasing microbial resistance to existing antibiotics, the development of novel organic transformations leading to diverse architecturally complex molecular frameworks with potential biological activity is an imperative scientific objective. Enantioselective catalysis of organic transformations is perhaps the most strategic and straightforward method to produce new organic scaffolds in enantioenriched form.[5] A striking illustration of this can be found in the recent synthesis of idasanutlin **1**, an MDM2 inhibitor currently in clinical trials, by Hoffman-La Roche.[6] The process relies on a chiral Cu(I) complex-catalyzed azomethine ylide cycloaddition between readily accessed dipolarophile **2** and azomethine

ylide precursor **3**. This methodology enables assembly of the molecules formidably complex framework, including three of four stereocenters, in a single step (**Scheme 1-1**).

Scheme 1-1 Catalytic Enantioselective Synthesis of Idasanutlin
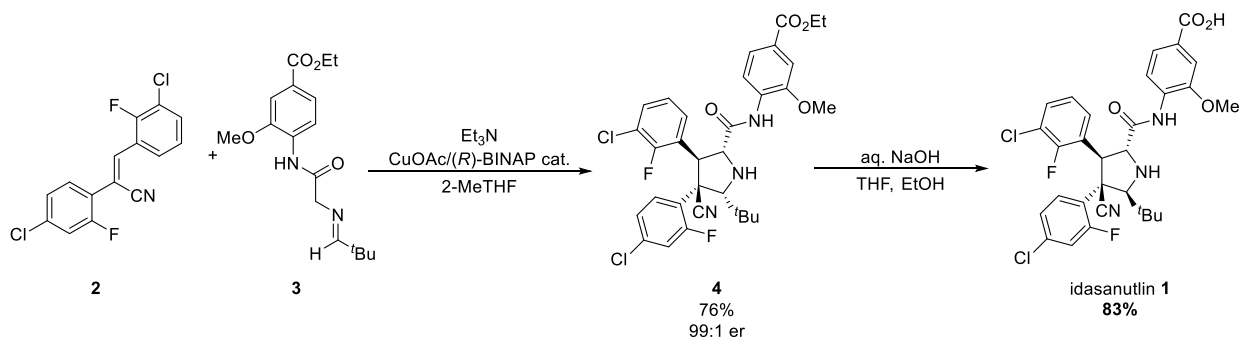
Within the realm of asymmetric catalysis, a handful of compound classes enjoy privileged status due to enabling reactivity features and the prevalence of derived products in biologically active organic structures. Among these privileged compounds, α-keto acid derivatives are particularly important due to the pervasiveness of the amino acid and glycolic acid substructure in pharmaceuticals and medicinally active natural products (**5-10**, **Scheme 1-2**).[7]

Scheme 1-2 Selected Examples of Medicinal Compounds Bearing the Amino Acid or Glycolic Acid Substructure

paclitaxel **5**
anticancer

penicillin **6**
antibiotic

fluticasone propionate **7**
anti-inflammatory

sofosbuvir **8**
antiviral

echinosporin **9**
anticancer

zaragozic acid C **10**
cholesterol lowering
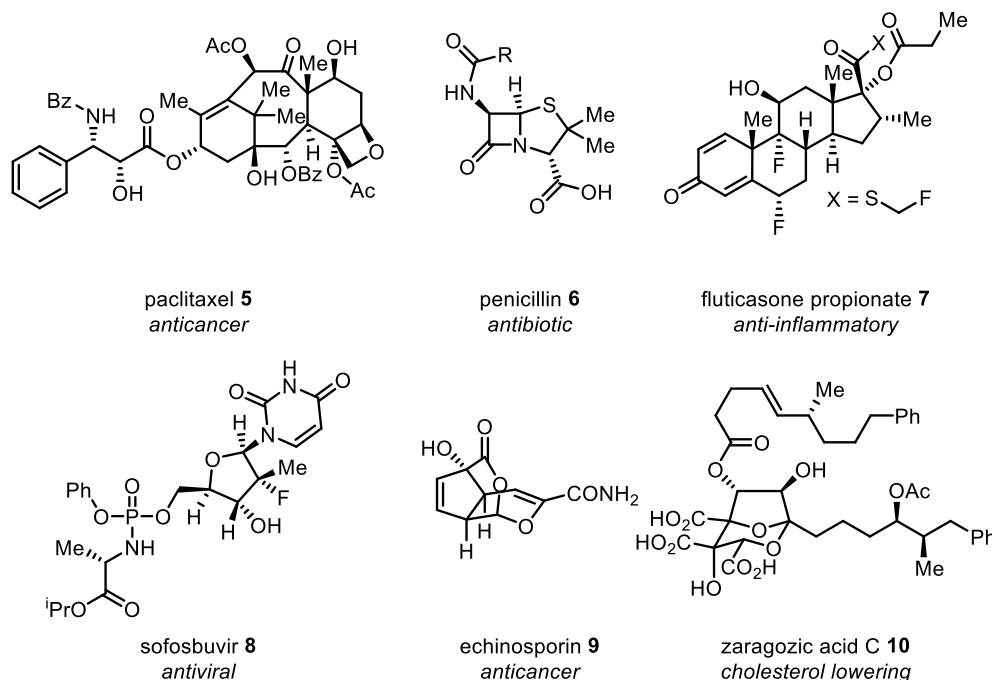
1.2 Reactivity of α-Keto Esters

With regards to their utility in synthesis, α-keto acid derivatives, including α-keto esters **11**, are unique due to their dual electrophilic[8] and nucleophilic[9] modes of reactivity. The versatile reactivity of α-keto acid derivatives enables their transformation to diverse glycolates and amino acids (**Scheme 1-3**) The presence of an adjacent electron accepting ester functionality activates the keto functionality toward electrophilic reactivity, while simultaneously acidifying the β-proton, thereby promoting enolization and subsequent nucleophilic reactivity. As a point of comparison DFT calculations (B3LYP, 6-31+G(d,p))

show that the LUMO (lowest unoccupied molecular orbital) of ethyl pyruvate (11, R^1 = H, R^2 = ethyl) is considerably lower in energy than acetone ($LUMO_{pyruvate}$ = -2.35 eV, $LUMO_{AcMe}$ = -0.74 eV).[10] As a result, ethyl pyruvate is approximately three orders of magnitude more acidic than acetone in aqueous solution and is expected to be more reactive in nucleophilic additions.[11]

Scheme 1-3. Ambiphilic Reactivity of α-Keto Esters.
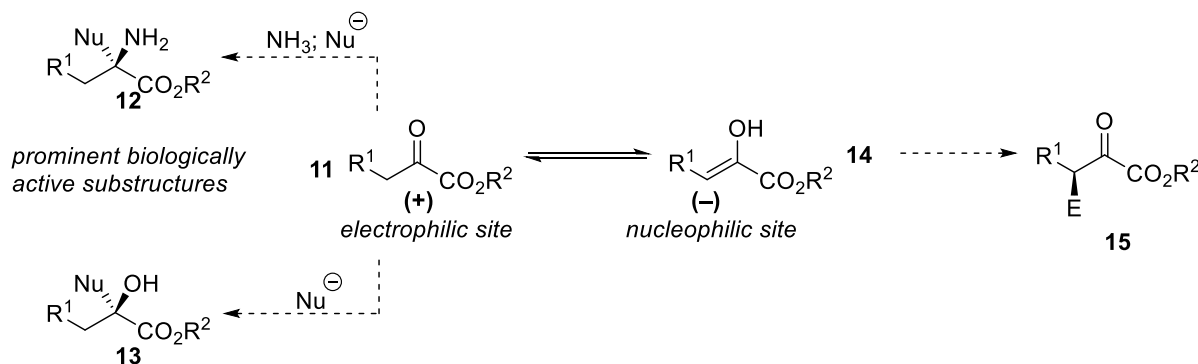
The unique reactivity profile of α-keto acids is also of importance to numerous biological processes. For instance, α-keto acids give rise to amines via transaminase-catalyzed amine transposition of the coenzyme pyridoxal phosphate **Scheme 1-4**, eq. 1).[12] In this process, the condensation of pyridoxalamine **16** to form imine intermediate **18** is likely aided by the electrophilicity of the α-keto acid, while the key protoropic shift is driven by the presence of the adjacent electron withdrawing carboxylate functionality. The conversion of pyruvic acid **21** to the building block acetyl-CoA **22** during the Krebs cycle constitutes a second important biological process involving α-keto acids (**Scheme 1-4,** eq. 2).[12] Finally, the biological synthesis of N-acetylneuraminic acid **23**, an important structural component of gangliosides, involves the aldolase-catalyzed condensation of pyruvic acid **21** and N-acetylmannosamine **24** (**Scheme 1-4**, eq. 3).[13] This

transformation is a notable example of the nucleophilic reactivity of α-keto acids in a biological process.

The enantioconvergent arylation methodology[14] to be described herein exploits the electrophilic activity of α-keto esters and the starting materials for this reaction can be synthesized using a newly developed palladium-catalyzed β-arylation that harnesses the nucleophilic activity of α-keto esters.[15] Finally, we will discuss the development of an enantioselective [3+2] cycloaddition of α-keto ester enolates and nitrile oxides that simultaneously relies on both manifolds of reactivity.[16]

Scheme 1-4 Reactivity of α-Keto Acids in Biological Processes

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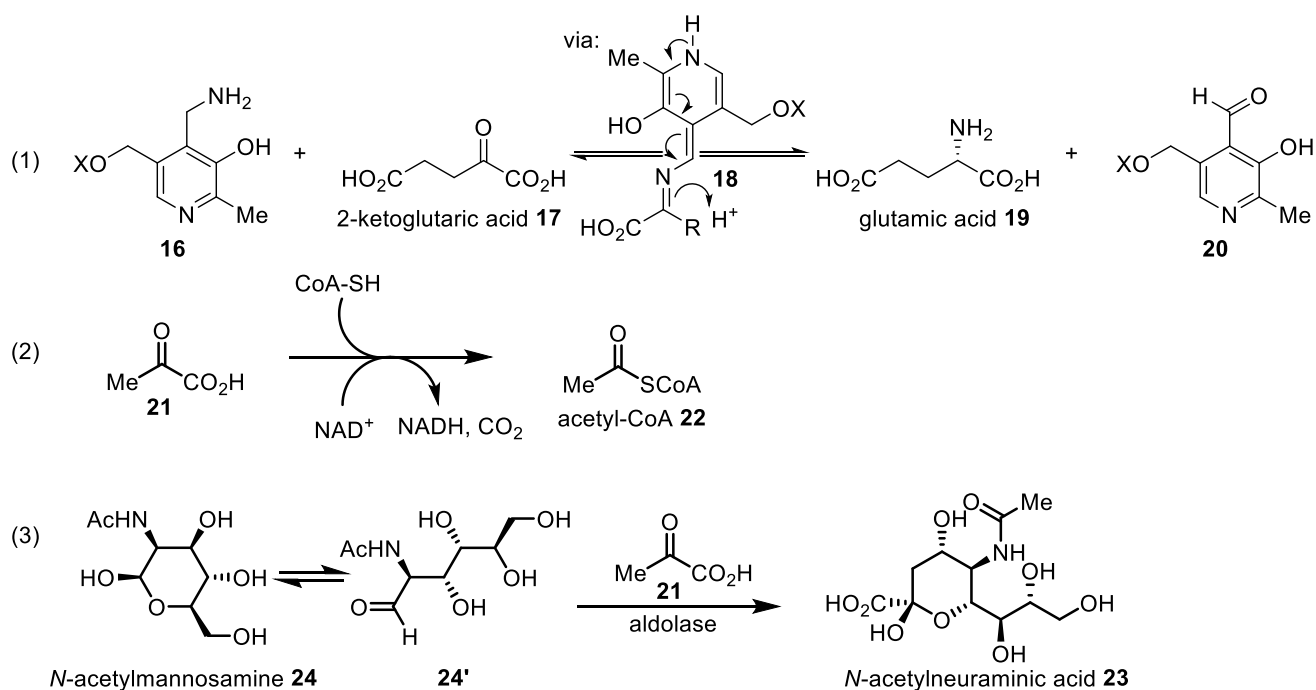
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Chapter II Synthesis of Complex Tertiary Glycolates by Enantioconvergent Arylation of Stereochemically Labile α-Keto Esters

2.1 Synthesis of Alcohols by Enantioconvergent Addition Reactions

Nucleophilic addition to α-stereogenic carbonyl derivatives is a robust strategy for the synthesis of complex alcohols.[1] The requisite chiral electrophiles are readily prepared by the functionalization of enolate derivatives (i.e. the β-arylation methodology to be described herein). The addition of acyl anion equivalents to prochiral electrophiles constitutes an alternative approach that can be deployed in the synthesis of α-stereogenic carbonyls.[2,3] Both strategies require basic reaction conditions and the inclination of optically active carbonyls bearing acidic protons to racemize via enolization can pose a significant challenge.[4]

Scheme 2-1 Noyori's Pioneering Dynamic Kinetic Hydrogenation
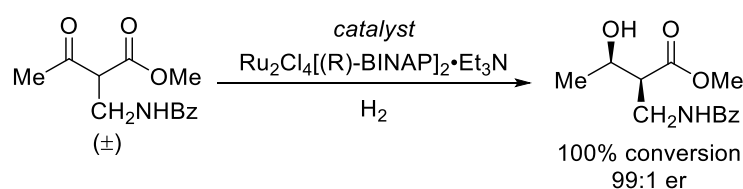
Enantioconvergent catalysis represents a powerful solution to this problem.[5] Disclosed by Noyori and co-workers in their foundational report of a dynamic kinetic hydrogenation, the ability to channel configurationally labile starting materials through stereoconvergent reaction pathways. (**Scheme 2-1**), represents a significant advancement in organic

synthesis.[6] Racemization, typically viewed as an undesired process, can be harnessed to achieve streamlined syntheses of complex molecular frameworks. [7]

Enantioconvergent additions are classified as either dynamic kinetic resolutions (DKRs) or Type I dynamic kinetic asymmetric transformations (DyKATs).[5,8] In a DKR the racemization is independent of the chiral catalyst (**Scheme 2-2**) and the stereoselectivity is affected by the rate of racemization, which generally must be greater than the rate of reaction for the fast reacting enantiomer. In a Type I DyKAT, racemization is promoted by the chiral catalyst. The rates of formation and transformation of epimeric catalyst/substrate complexes and their concentrations influence stereoselectivity. Processes that fall within these mechanistic paradigs can be described according to Curtin−Hammett kinetics. (**Scheme 2-2**).

Scheme 2-2 Mechanistic Considerations
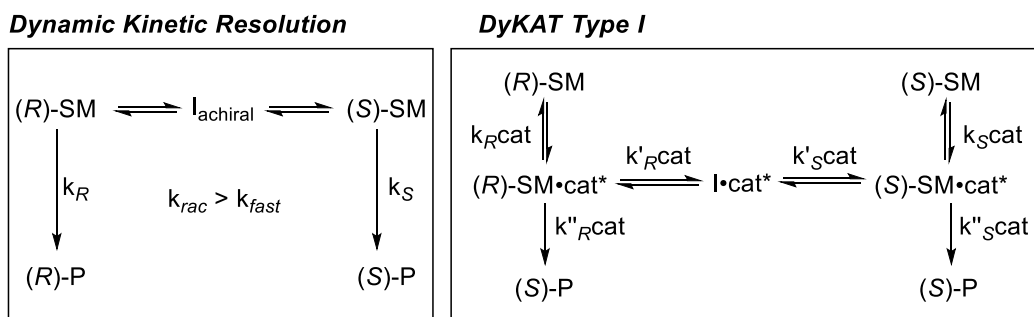
Numerous tranformations that operate under these mechanistic paradigms have been developed.[5] The complexity found in the products ascends according to the number of stereocenters centers formed and the reagents coupled in the enantioselective step. Beginning with enantioconvergent reactions that furnish a single stereocenter,[9,10] the next stratum of complexity includes Noyori-type hydrogenations that establish two chiral centers.[6,11,12] As discussed above, facile substrate enantiomerization is a prerequisite for obtaining high stereoselectivity in certain enantioconvergent reactions;[5,8] therefore, β-

oxo ester derivatives have emerged as the factotum substrate class for dynamic kinetic hydrogenations (**Scheme 2-2**, eq. 2). In contrast, by capitalizing on the inherent tunability of the basic Ru(II)-sulfonamide framework developed by Noyori, our lab identified a novel terphenylsulfonamide variant that made possible chemo- and enantioselective reduction of the α-keto ester moiety (**Scheme 2-2**, eq. 3). Non-hydrogenative transformations that establish two chiral centers constitute the third echelon of complexity.[13] In this realm our lab has developed organocatalytic dynamic kinetic aldolizations of β-halogenated α-keto esters and dynamic kinetic aminoallylations of β-formyl amides. The final echelon of complexity comprises a handful of reactions that involve the addition of prochiral nucleophiles and create three chiral centers, including an enantioconvergent homoenolate addition developed by our lab that furnishes stereochemically complex glycolate architectures (**Scheme 2-3**, eq. 5).[14]

Scheme 2-3 Evolution of Complexity in Enantioconvergent Addition Reactions

†All transformations shown employ racemic starting materials.
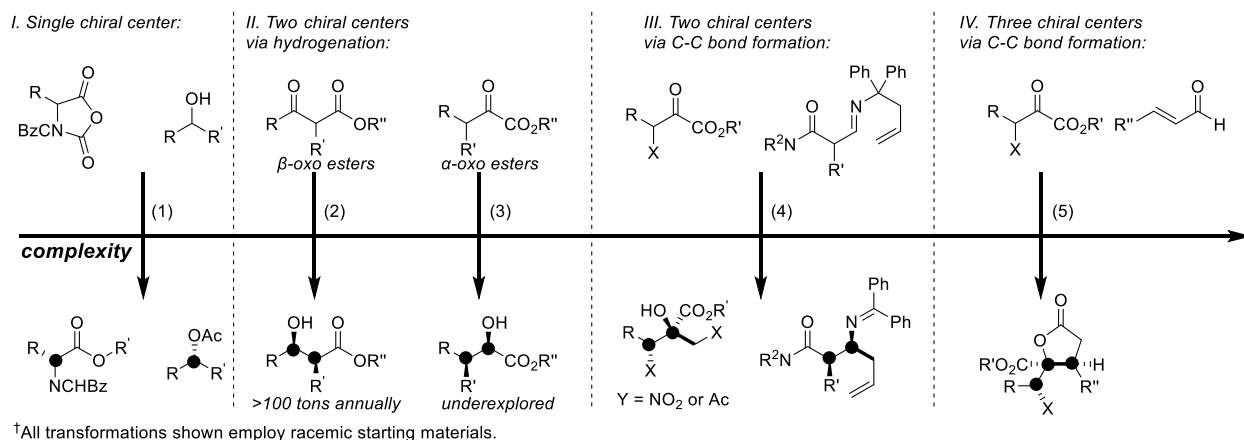
2.2 Enantioconvergent Arylation: Introduction

The recognition that the basic additives or catalysts employed in the above transformations likely mediate substrate enantiomerization has been key to the *de novo*

design of enantioconvergent processes in our laboratory. Accordingly, the transition metal-catalyzed addition of nonstabilized carbon nucleophiles to ketones emerged as a compelling opportunity to generate complex tertiary alcohols not accessible

Scheme 2-4 Proposed Enantioconvergent Hayashi–Miyaura-Type Reactions
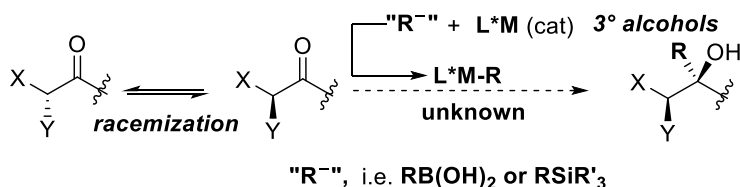
through other methods (**Scheme 2-4**). The Hayashi–Miyaura type reactions typically rely on the base-promoted transmetallation of an organoboron or organosilicon pro-nucleophile to a chiral metal complex.[15] As an example, the enantioselective addition of arylboronic acids to carbonyl derivatives, including α-keto esters, has been widely developed.[16] Zhou and co-workers reported the asymmetric addition of arylboronic acids to arylglyoxylates such as **1** under the action of a complex comprising rhodium(I) and chiral phosphite **2**, while Ready and co-workers developed a novel hybrid phosphine-allene catalyst **5** for an analogous transformation (**Scheme 2-5**).

Scheme 2-5 Enantioselective α-Keto Ester Arylations

Zhou, 2008

PhB(OH)$_2$ (2 equiv), LiF
2 (6 mol %)
[RhCl(C$_2$H$_4$)$_2$]$_2$ (3 mol %)
H$_2$O/DCE (4:1), rt

1

3
81% yield
95:5 er

2
Ar = (4-OMe)C$_6$H$_4$

Ready, 2011

PhB(OH)$_2$ (2 equiv)
5 (2 mol %), KF
^{i}PrOH/H$_2$O (5:1), rt

4

6
81% yield
97.5:2.5 er

5
Ar = (3,5-CF$_3$)C$_6$H$_3$
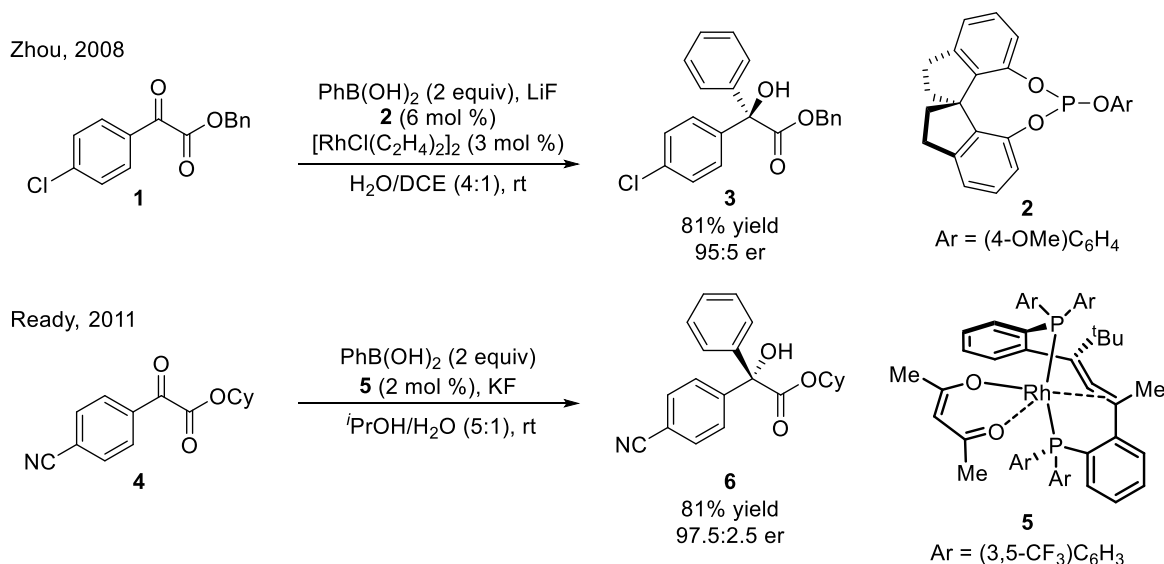
Considering their chemical stability, ease of handling and broad commercial availability,[17] we envisioned the deployment of arylboronic acids in an enantioconvergent addition to racemic α-keto ester electrophiles electrophiles would facilitate the production of diverse, stereochemically complex glycolate architectures.

2.3 Optimization Studies

Carbonyl electrophiles and their derivatives lacking electron withdrawing functionality (i.e. ketone, ester, or halogen) at the chiral α center are underutilized in dynamic kinetic resolutions (DKR). List and Zhao have reported a dynamic kinetic reductive aminations employing α-alkyl, aryl branched imines that presumably racemize via enamine intermediates.[18] In addition, the cyclohexanecarboxaldehyde derivatives utilized by Ward and co-workers likely racemize via an analogous pathway.[19] Finally, dynamic kinetic hydrogenations of nonactivated aldehydes and ketones have been shown to occur in the presence of *tert*-butoxide bases.[20] Nevertheless, considering that facile

racemization is essential, the execution of DKRs employing compounds of lower acidity is inherently more challenging.[8] However, in this context the use of less activated substrates would allow access to heretofore unknown glycolate architectures.

In light of the considerations described above, the β-alkyl, aryl substituted α-keto ester derivative **7a** was chosen as a model substrate for this transformation (**Table 2-1**). Our group has previously developed dynamic kinetic resolutions of α-keto esters that occur in the presence of tertiary amines;[11b-e] therefore, we reasoned that an amine base would promote substrate racemization. Sterically hindered Hünig's base (^{i}Pr$_2$NEt) was initially selected to abate potential interference of the Rh(I)-catalyst through nonproductive binding. A substoichiometric quantity of potassium hydroxide was employed because analogous conditions promote the Hayashi–Miyaura arylation of

Table 2-1 Optimization of Enantioconvergent Arylation

catalyst (2.5 mol%)
PhB(OH)$_2$ (2.0 equiv)
organic base (3.0 equiv)
inorganic base (0.3 equiv)
CH$_2$Cl$_2$, 40 °C, 24 h

(±)-**7a** → **8a**
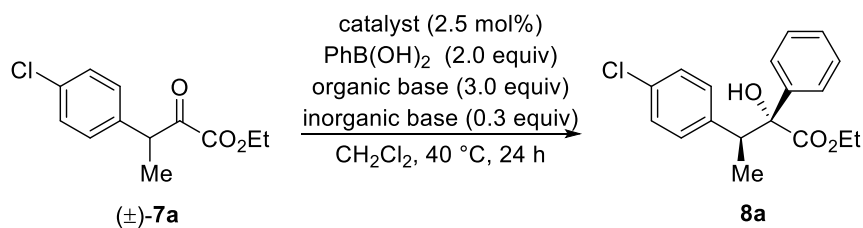
entry[a]	cat.	org. base	inorg. base	conv (%)[b]	dr[b]	er[c]
1	9	DIPEA	KOH	59	>20:1	80:20
2	10	DIPEA	KOH	56	>20:1	90:10
3	11	DIPEA	KOH	40	>20:1	90:10
4[d]	12	DIPEA	KOH	61	2.7:1	43:57
5[e]	11	DIPEA	CsF	>95	>20:1	70:30
6[e]	11	Et$_3$N	CsF	>95	20:1	89:11
7[e,f]	11	Et$_3$N	CsF	85	>20:1	92:8
8[e,f,g,h]	11	Et$_3$N	CsF	>95	>20:1	94:6
9[e,f,g,h]	10	Et$_3$N	CsF	>95	>20:1	94:6
10[e,f,g,h,i]	10	Et$_3$N	CsF	>95	>20:1	94:6
11[j,k,e,f,g,h]	11	Et$_3$N	CsF	>95	>20:1	93:7
12[j,l,e,f,g]	11	Et$_3$N	CsF	>95	14:1	91:9
13[e,g,h,j]	13	Et$_3$N	CsF	trace	-	-
14[e,g,h,j]	14	Et$_3$N	CsF	trace	-	-

catalysts:
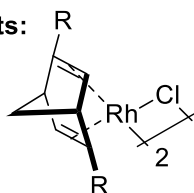
9: R = C$_6$H$_5$
10: R = 4-CF$_3$C$_6$H$_4$
11: R = 3,5-(CF$_3$)$_2$C$_6$H$_3$
12: R = Bn

13: {[Rh(C$_2$H$_2$)$_2$Cl]$_2$ + (PhO)$_3$P}
14: [Rh((S)-BINAP)OH]$_2$

a) All reactions were conducted on a 0.10 mmol scale. b) Determined by ^{1}H NMR analysis of the crude reaction mixture. c) Determined by HPLC using a chiral stationary phase. d) Reaction time = 36 h. e) 3.0 equiv CsF. f) 6.0 equiv of Et$_3$N. g) CHCl$_3$ as solvent. h) Reaction time = 48 h. i)

Reaction was run at 60 °C. j) 3.0 equiv PhB(OH)$_2$, k) Substrate ester = ^{t}Bu. l) Substrate ester = CH$_2$Ph

isatins and **7** is sensitive to stoichiometric hydroxide base.[21] An initial evaluation of ligands revealed that rhodium complex **9** bearing a Ph-substituted norbornadiene derived ligand, developed by Hayashi and co-workers, provided promising levels of enantioselectivity,[22] although low conversion was observed under these conditions (entry 1). Further screening showed the 4-CF$_3$C$_6$H$_4$- and 3,5-(CF$_3$)$_2$C$_6$H$_3$-substituted analogues **10** and **11** provided higher levels of enantioselection; however, conversion remained low (**Table 2-1**, entries 2 and 3). The supposed low acidity of these substrates caused us to wonder if a simple kinetic resolution was occurring under these conditions, but this possibility was ruled out by isolation of racemic unreacted **7a** from entry 3. Interestingly, the benzyl substituted ligand **12** provided low enantioselectivity slightly in favor of opposite enantiomer, while also exhibiting drastically lower levels of diastereocontrol over the formation of **8a** (entry 4). Switching the inorganic base promoter from potassium hydroxide to CsF while increasing the loading to 3.0 equiv promoted full conversion to the desired aryl glycolate, albeit with a striking decline in enantioselectivity (entry 5). Simply replacing Hünig's base with triethylamine restored the previously observed levels of enantioselectivity (entry 6). Further increasing the amount of triethylamine to 6.0 equiv provided higher levels of enantioselectivity (entry 7), although a longer reaction time was necessary to achieve full conversion under these conditions. Satisfactory levels of enantioselectivity were achieved when chloroform was used as solvent in place of methylene chloride (entry 8). At this stage of optimization it was noted that both the 4-CF$_3$C$_6$H$_4$- and 3,5-(CF$_3$)$_2$C$_6$H$_3$-substituted norbornadiene complexes **10** and **11** provided identical levels of enantioselectivity (entries 8 and 9). Furthermore,

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conducting the reaction at 60 °C does not influence the enantio- or diastereoselectivity of the process (entry 10). Substituting the ethyl ester of **7a** with bulkier *t*Bu or Bn groups (entries 11 and 12, respectively) did not result in improved enantioselectivity. Finally, although phosphine and phosphite based ligands have been utilized in Hayashi–Miyaura-type arylation (**Scheme 2-5**) reactions of α-keto esters, a complex of triphenylphosphite (**13**, entry 13) as well as hydroxy[(*S*)-BINAP]rhodium(I) dimer (**14**, entry 14) failed to catalyze this transformation.

The superiority of the chiral(diene)Rh(I) catalysts merits further discussion. The original Miyaura arylation of aldehydes utilized an arylphosphine-Rh(I) catalyst system.[15a] In contrast, arylations of α-keto esters have relied on ligand systems characterized by higher π- accepting ability.[16] For instance, although the ligand system reported by Ready and co-workers contains a bisphosphine motif (**Scheme 2-5**), X-ray crystallographic analysis revealed that the rhodium center interacts with the central π acidic allene.[16b] The systems reported by Zhou, Xu, and Yamamoto employ a phosphite, a sulfur-olefin hybrid, and a bisphosphoramidite ligand, respectively.Diene ligands are characterized by several features which likely manifest in their effectiveness for the title reaction.[23] The aptitude of diene ligands to form ridged chelates underwrites the stability of the derived Rh(I) complexes; in contrast to arylphosphine-Rh(I) systems, the majority of chiral(diene)Rh(I) complexes, including those reported herein, are air tolerant and are stable to silica gel chromatography.[22] Diene ligands exhibiting a greater degree of geometric strain are found to form more stable complexes due to binding induced pyramidalization (**Scheme 2-6**).[24] The Dewar–Chatt–Duncanson accounts for the unique electronic properties of chiral(diene)Rh(I) catalysts; simultaneous σ donation and π back donation occurs between the ligand π system and the metal center.[25] The large

change in chemical shift between the free and complexed ligand vinyl resonance upon formation of complex **10** provides evidence for these effects: the unbound ligand exhibits a vinyl resonance at δ 7.18 and this signal is shifted to 4.24 in complex **10**. These unique electronic features may be important for activation of the bound α-keto ester electrophile which is more sterically hindered than the aldehydes originally reported by Miyaura. Finally, a feature inherent to Hayashi's original design is the ability of the square planar chiral(diene)Rh(I) complexes to mimic the way analogous complexes of C2-symmetric bisphosphines relay chirality in asymmetric transformations (vide infra)

Scheme 2-6 Binding Strength of Diene Ligands and the Dewar –Chatt–Duncanson Model

Complex Stability and Strain   Dewar–Chatt–Duncanson

3   :   2   :   1

σ donation   π back donation
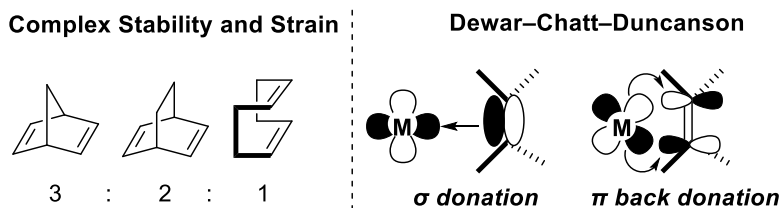
2.4 Influence of Base Structure on Substrate Racemization

At this juncture we sought to understand the large contribution to product enantioselectivity associated with the superficially similar structure of the amine base additive. We hypothesize that this difference arises from a faster rate of starting material racemization under the action of triethylamine. Using Hünig's base in conjunction with low inorganic base concentration resulted in high levels of product enantioselectivity and the unreacted starting material recovered from the reaction was not enantioenriched (entry 3, Table 1), suggesting that an efficient dynamic kinetic resolution is occurring under these conditions. We postulate that under conditions of low inorganic base concentration the arylation reaction is slow relative to Hünig's base promoted

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racemization ($k_{rac} > k_{fast}$)[8] resulting in a dynamic kinetic resolution. However, in entry 5 the higher loading of CsF results in a faster arylation reaction for both substrate enantiomers, presumably due to higher rates of transmetallation, while the rate of racemization by Hünig's base occurs too slowly for efficient dynamic kinetic resolution. Rovis and co-workers noted a similar effect during the development of an enantioselective glyoxamidation reaction.[26] To gain further insight into this phenomenon and to provide support for our hypothesis we studied the rate of racemization of **7** using an array of tertiary amine bases (**Figure 2-1**). At room temperature racemization with triethylamine was rapid; within eight minutes the extent of racemization had reached 87% and complete racemization occurred after 20 min. Tri-*n*-butylamine exhibited a noticeably slower racemization profile, but racemization was still nearly complete within 20 min. In contrast to triethylamine and tri-*n*-butylamine, the alkyl branched Hünig's base displayed a slow racemization profile, and **7a** was still

Figure 2-1 Influence of Base Structure on Racemization Rate
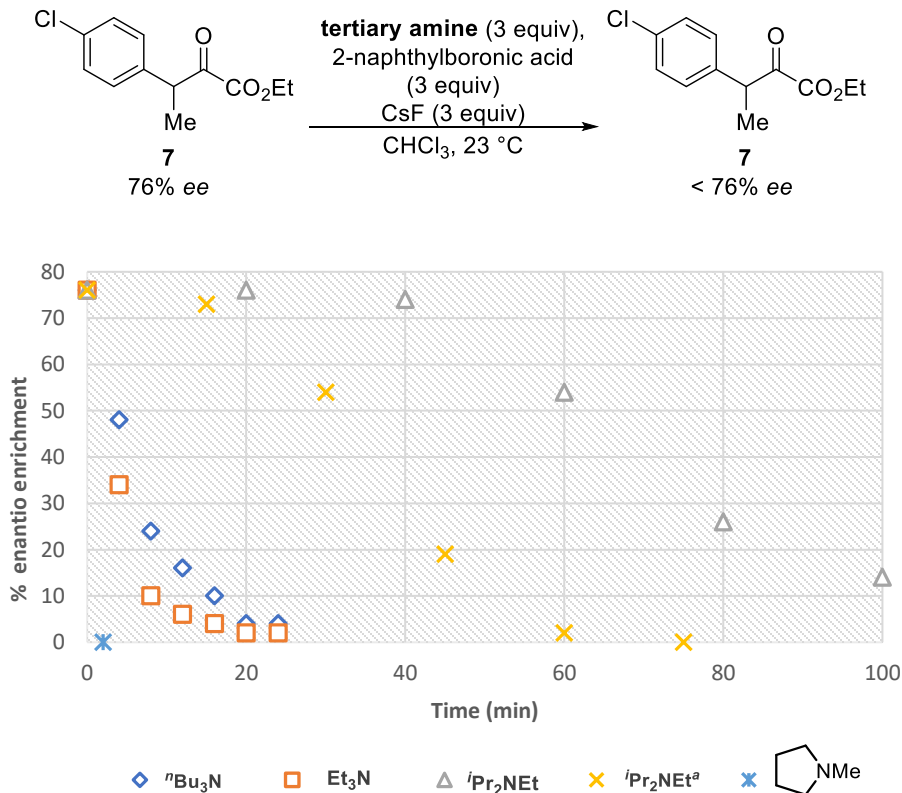
a) Trial conducted at 40 °C. 6.0 equiv Hünig's base.

measurably enriched after 100 min at room temperature. When studied at 40 °C in the presence of 6 equiv of Hünig's base, racemization of **7** was enhanced but complete racemization only occurred after 60 min. Thus, although Hünig's base exhibits greater thermodynamic basicity than triethylamine it is less effective at promoting the racemization of **7a**.[27] Finally, *N*-methylpyrroldine, which possesses lower thermodynamic basicity than triethylamine,[28] displayed the fastest racemization profile, promoting complete racemization of **7** in under two minutes. The observed trend suggests the kinetic basicity of the tertiary amine exerts a larger influence on the racemization of

7a than its thermodynamic basicity. This observation may prove to be generally important in the *de novo* design novel dynamic kinetic resolutions involving enolizable carbonyl substrates.[29]

2.5 Scope of the Enantioconvergent Arylation Reaction

   With optimal reaction conditions in hand we began to study the scope of the process with respect to the arylboronic acid component (**Scheme 2-7**). It should be noted that while catalysts **10** and **11** provide identical levels of selectivity for product **8**, in certain cases it was found that one catalyst was more selective for a particular substrate. Ultimately, electron-rich arylboronic acids were found to be suitable reaction partners as the *p*-tolyl adduct **8b** was formed in high yield with high levels of diastereo- and enantiocontrol. Electron-poor arylboronic acids could also be used; however, in the case of *p*-fluoro- and *p*-chlorophenylboronic acid a larger excess was required to achieve good yields. Nevertheless, high levels of diastereo- and enantioselectivity were still observed for addition products **8c** and **8d**. Substitution of the arylboronic acid at the *m*-position was also tolerated. For instance, the *m*-methoxy and *m*-tolyl adducts **8e** and **8f** were obtained in good yield, with high levels of stereocontrol. Electron-withdrawing substituents were also tolerated at this position and the use of *m*-chlorophenylboronic acid afforded the desired arylation product **8g** in good yield with high levels of stereocontrol. Polyaromatic boronic acids were also suitable substrates for this transformation, as the 2-naphthyl adduct **8h** could be obtained in good yield with similarly high levels of diastereo- and enantiocontrol. The sterically demanding *o*-

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methoxy adduct **8i** was formed in good yield with high levels of enantiocontrol, although in this instance a relatively large excess of the boronic acid substrate was required to achieve full conversion. Finally, we found that even unprotected 6-indoylboronic acid could be employed, furnishing adduct **8j**, while maintaining reaction efficiency. It should be noted that at this stage of optimization certain electron poor arylboronic acid

Scheme 2-7 Scope of Reaction: Boronic Acids
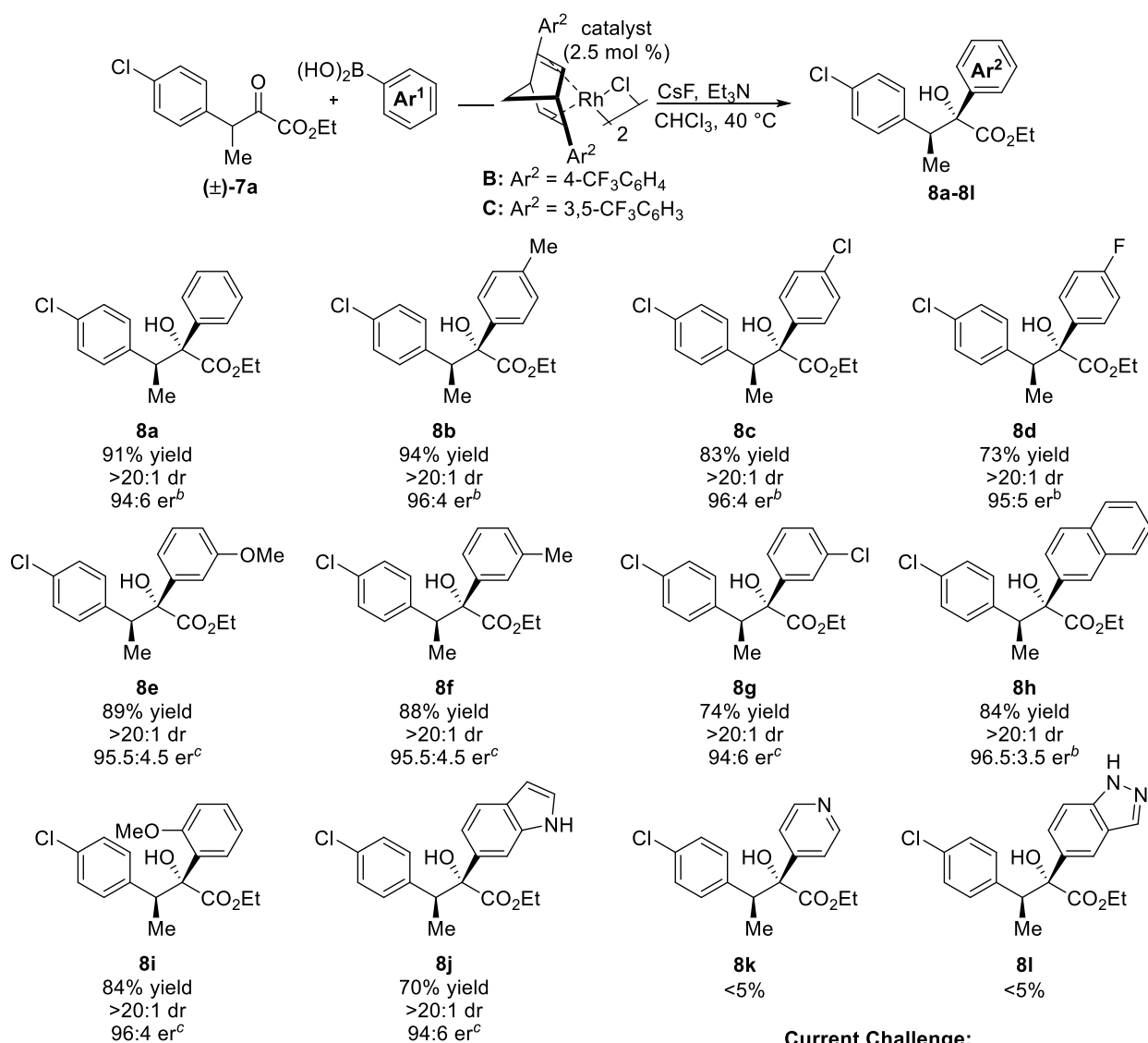
B: $Ar^2 = 4\text{-}CF_3C_6H_4$
C: $Ar^2 = 3,5\text{-}CF_3C_6H_3$

(±)-**7a**

8a-8l

8a
91% yield
>20:1 dr
94:6 er[b]

8b
94% yield
>20:1 dr
96:4 er[b]

8c
83% yield
>20:1 dr
96:4 er[b]

8d
73% yield
>20:1 dr
95:5 er[b]

8e
89% yield
>20:1 dr
95.5:4.5 er[c]

8f
88% yield
>20:1 dr
95.5:4.5 er[c]

8g
74% yield
>20:1 dr
94:6 er[c]

8h
84% yield
>20:1 dr
96.5:3.5 er[b]

8i
84% yield
>20:1 dr
96:4 er[c]

8j
70% yield
>20:1 dr
94:6 er[c]

8k
<5%

8l
<5%

Current Challenge:
Electron Poor Heteroaromatics

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a) Reactions run on 0.1 mmol scale for 48 h or 60 h (see SI for individual reaction times and boronic acid equivalents), reported yields and er values are averages of two runs. Values in parentheses represent recrystallized yields and enantiomeric ratios. b) Catalyst **10** employed. c) Catalyst **11** employed.

substrates cannot be used, as the 4-pyridyl and 5-indazole adducts **8k** and **8l** were not formed. In addition, the reaction with 2-thienylboronic acid only reached 11% conversion after 36 h under the optimized reaction conditions (not shown). Efforts to address these limitations are currently underway in our laboratory.

   Next, we explored the scope of the reaction with respect to the α-keto ester reaction partner (**Scheme 2-8**). Substrates bearing electron donating substituents at the *para*-position of the aryl ring were suitable reaction partners. For example, the *p*-tolyl substituted product **8m** was obtained in good yield with high levels of stereocontrol. Higher levels of enantioselectivity were observed with this substrate when 2-naphthylboronic acid was employed as a nucleophile furnishing the addition product **8n**. Apparently, the electron-rich *p*-methoxy substituted substrate was subject to facile racemization under the reaction conditions, as product **8o** could also be obtained in good yield with high levels of stereocontrol. An *ortho*-F substituted α-keto ester was subject to phenylboronic acid addition, producing **8p** in acceptable yield and high diastereoselectivity and decent levels of enantiocontrol. The *o*-tolyl product **8q** was afforded in 57% yield, and 94:6 er, while the *m*-tolyl product **8r** was formed in 88% yield with 96:4 er, suggesting that the steric nature of the α-keto ester aryl component has a

slight impact on reaction efficiency and enantioselectivity. A 2-naphthyl substituted α-keto ester could also be used, affording

Scheme 2-8 Scope of Reaction: α-Keto Esters

B: Ar^3 = 4-CF$_3$C$_6$H$_4$
C: Ar^3 = 3,5-CF$_3$C$_6$H$_3$

8m
89% yield
>20:1 dr
93:7 er[c]

8n
83% yield
>20:1 dr
97:3 er[c]

8o
81% yield
>20:1 dr
94:6 er[c]

8p
66% yield
>20:1 dr
92:8 er[c]

8q
57% yield
>20:1 dr
94:6 er[c]

8r
88% yield
>20:1 dr
96:4 er[c]

8s
73% yield (48%)
>20:1 dr
94:6 er[c] (97.5:2.5)

8t
71% yield
>20:1 dr
96:4 er[c]

8u
78% yield (49%)
>20:1 dr
93:7 er[c] (>99.5:0.5)

8v
47% yield
>20:1 dr
96.5:3.5 er[b]

8w
82% yield (43%)
>20:1 dr
90.5:9.5 er[c] (>99.5:0.5)

8x
67% yield (23%)
>20:1 dr
98:2 er[c] (>99.5:0.5 er)

a) Reactions run on 0.1 mmol scale for 48 h or 60 h (see SI for individual reaction times and boronic acid equivalents), reported yields and er values are averages of two runs.

Values in parentheses represent recrystallized yields and enantiomeric ratios. b) Catalyst **10** employed. c) Catalyst **11** employed.

addition product **8s** with high levels of enantio- and diastereoselectivity. Product **3s** could be enriched to 97.5:2.5 er following a single crystallization. Notably, arylation of an unprotected 3-indole substituted α-keto ester with 6-indoleboronic acid afforded bis(indole) adduct **8t** in good yield with high levels of selectivity. The use of 2-naphthyl and *m*-tolylboronic acid was also successful with this α-keto ester (see supporting information). Larger alkyl substituents at the β-position were tolerated and the β-ethyl substituted product **8u** was obtained in good yield with acceptable levels of enantiocontrol. Product **8u** could be obtained as a single enantiomer in acceptable yield following a single recrystallization. The arylation reaction exhibited functional group chemoselectivity in the presence of competing functionality as the bromoaryl and β-allyl substituted product **8v** was obtained in acceptable yield with high levels of stereocontrol. Notably, less than 10% of Heck-type co-products were observed during formation of **8v**.[30] The branched diester product was formed in excellent yield. Although lower levels of enantiocontrol were observed in this reaction, product **8w** can be accessed as a single enantiomer in acceptable yield following a single crystallization. Finally, although pyridine containing boronic acids are not successful reaction partners at this stage of optimization, a 3-pyridyl substituted α-keto ester was tolerated under the reaction conditions and afforded arylation product **8x** in good yields with high diastereo- and enantiocontrol. Product **8x** could also be recovered as a single enantiomer, albeit in lower

yield, after a single crystallization. Substrates bearing only aliphactic substitution at the β-position have not been tested at this juncture; presumably these substrates are less acidic and would be challenging to implement under the present reaction conditions.

2-6 1 Mmol Scale Reaction and Stereochemical Model

Having investigated the scope of the DKR arylation process, we sought to examine the effect of increasing the scale of the reaction while simultaneously decreasing the catalyst loading (**Scheme 2-9**). The 4-bromo substituted α-keto ester **7y** underwent arylation with 2-naphthylboronic acid on 1 mmol scale using 0.5 mol % of the catalyst (1 mol % Rh) to afford **8y** in good yield with high levels of diastereo- and enantiocontrol. Product **8y** could be recrystallized to 99:1 er allowing the absolute stereochemistry of **8y** to be determined via X-ray crystallography. The configuration of the other arylation products **8a**-**8x** were assigned by analogy.

Scheme 2-9 Mmol Scale Arylation and Stereochemical Model

(2R,3S)-**8y**
77% yield (51%)
>20:1 dr
97:3 er (99:1 recryst.)
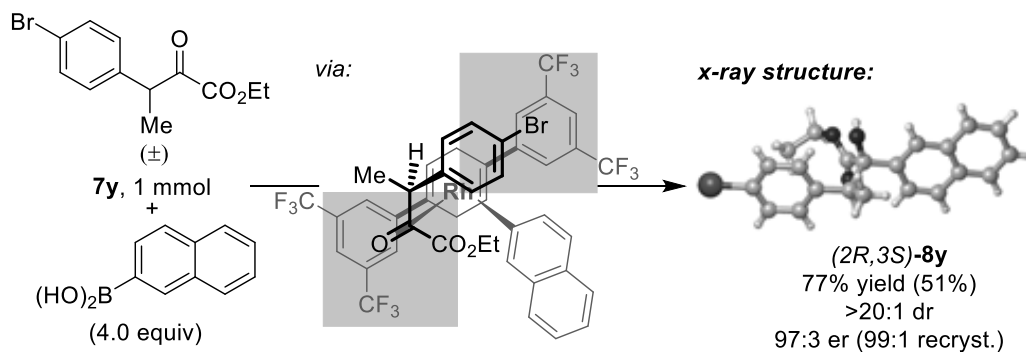
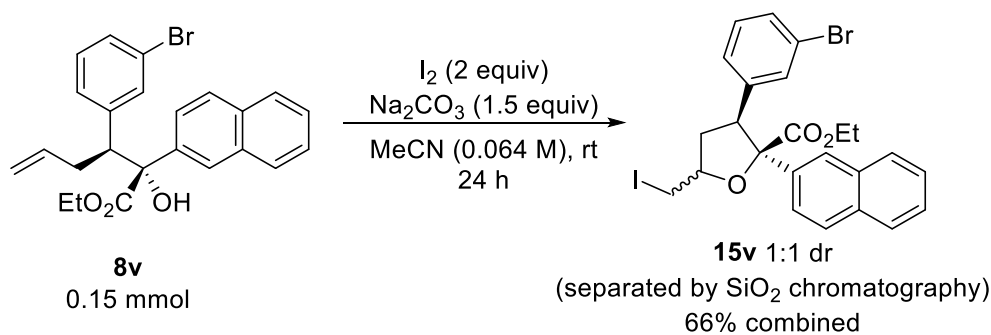[a]Conditions: 0.5 mol % catalyst C, 4.0equiv CsF CHCl3, 40 °C, 72 h

The observed stereochemistry can be attributed to the C2-symmetric nature of (*R,R*)-catalyst **11** which enforces high levels of enantiocontrol in this reaction by effectively blocking the shaded quadrants in the stereochemical model shown in **Scheme 2-9**; the bulky *sp3* center is guided to the top left quadrant and the reaction of

the *S* configured starting material is favored.[31] Aromatic interactions appear to be important for achieving high levels of enantio- and diastereoselectivity as evidenced by the inferior results using the benzyl substituted catalyst **12**.

2.7 Iodoetherification of β-Allyl Substituted Aryl Glycolate

Finally, considering the sterically encumbered nature of the tertiary alcohol installed in the arylation reaction we wondered if this functionality could be leveraged in downstream transformations. Preliminary findings have been promising. For instance, unsaturated alcohol **8v** undergoes iodoetherification to tetrahydrofuran **15v** in 66% yield, albeit without diastereoselectivity. The diastereomers of **15v** were easily separated by silica gel column chromatography.

Scheme 2-10 Iodoetherification of 8v

I$_2$ (2 equiv)
Na$_2$CO$_3$ (1.5 equiv)
MeCN (0.064 M), rt
24 h

8v
0.15 mmol

15v 1:1 dr
(separated by SiO$_2$ chromatography)
66% combined

2.8 Conclusion

In summary, we have developed an enantioconvergent arylation of racemic β-alkyl substituted α-keto esters catalyzed by a chiral rhodium-diene complex. A wide range of complex aryl glycolate derivatives could be obtained in good yields with high levels of stereocontrol. Notably, despite the longstanding use of transition metal catalysts in dynamic kinetic hydrogenations, this is the first use of analogous catalysts for the installation of C-C bonds in a dynamic kinetic addition to carbonyl electrophiles.

Considering the substantial number of commercially available arylboronic acid derivatives and the well-recognized biological activity of the glycolic acid substructure,[32] this chemistry opens the door to a diverse array of interesting building blocks. Although racemizationis central to efficient dynamic kinetic resolutions[8] it is rarely discussed or studied in detail. Here we have shown that the racemization of less acidic β-alkyl/aryl substituted α-keto esters is strongly linked to the steric size of a tertiary amine additive. Preliminary results show that the products of this reaction can be utilized in additional downstream transformations including the synthesis of valuable tetrahydrofuran derivatives. Extension of this work to other classes of nonstabilized carbon centered nucleophiles is currently underway in our laboratory and will be reported in due course.

2.9 Experimental Details

All air sensitive reactions were carried out under an atmosphere of nitrogen. Thin layer chromatography (TLC) was performed on Sorbtech plastic-backed 0.20 mm silica gel 60 plates. Visualization was accomplished with UV light and either an aqueous ceric ammonium molybdate (CAM) or potassium permanganate ($KMnO_4$) solution, followed by heating. Flash chromatography was performed under positive nitrogen pressure using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Semipreparative thin layer chromatography was employed for the generation of pure racemic samples for HPLC analysis and was conducted on 250 μm glass backed TLC plates. An Analtech 1000 μm/silica gel GF glass backed preparative thin layer chromatography plate was used for the purification of **30**. Yields and enantiomeric ratios reported for the enantioconvergent arylation reactions represents the average of two trials.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on either a Bruker model DRX 500 or 600 (cryoprobe equipped) spectrometer. The spectra were calibrated using residual solvent resonances: ^{1}H NMR ($CDCl_3$ at 7.26 ppm), 13C NMR ($CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, qt = quintet, and m =

multiplet), coupling constant (Hz) and integration. High resolution mass spectrometry (HRMS) was performed using a Thermo Scientific LTQ FT Ultra mass spectrometer S2 with direct infusion in either the positive or negative ion mode. Samples were prepared in HPLC grade methanol. High performance liquid chromatography (HPLC) was performed on a Perkin Elmer Flexar® HPLC system. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier Transform Infrared Spectrometer.

Chloroform was washed several times with water to remove the ethanol stabilizer, dried over $MgSO_4$, then distilled from $MgSO_4$ and stored in a Schlenk flask wrapped in aluminum foil in an N_2 filled glovebox. All other solvents were purified by passage through a column packed with activated aluminum under N_2 pressure. Phenylboronic acid was recrystallized from water. All other boronic acids were used as received. All boronic acids were stored in an N_2 filled glovebox. All 1-(phenyl)ethanol derivatives used in the synthesis of racemic a-keto esters are known compounds and were prepared according to literature methods.

Procedure for Optimization Experiments: The α-keto ester was massed directly into a flame dried 1 dram vial equipped with a stir bar and red PTEF/silicone cap. This vial was taken into a glovebox, under an N_2 atmosphere, where the organic base, arylboronic acid, and inorganic base were added successively to the vial containing the α-keto ester substrate. Next, the catalyst was transferred from a separate 1 dram vial using 1.0 mL of reaction solvent. The reaction vial was removed from the glovebox, sealed with electrical tape and heated at the indicated temperature for the specified duration, after which time the crude reaction mixture was passed through a silica gel plug (5.75 in, 4 mL capacity pipette filled ~ ½ full of silica gel) using ethyl acetate to rinse (10 mL) and concentrated. The diastereomeric ratio of the product and percent conversion [(prod./(prod. + starting material))*100] were determined by ^{1}H NMR analysis of the entire crude reaction mixture. Around 150 μL of the 700 μL solution of crude material in $CDCl_3$ was applied to the base of a 3.5 x 8 inch glass TLC plate (thickness of silica gel = 250 μm) and purified by semi-preparative thin layer chromatography, using 5% ethyl acetate/hexanes to elute, so that pure material for chiral HPLC analysis could be obtained.

Note: In all screening experiments listed in table Table 2-1, with exception of entry 13, the chloro(diene)rhodium (I) dimer isolated by silica gel column chromatography was employed. In entry 13 the catalyst was prepared in situ.

Procedure for Preparation of Racemic Standards: The α-keto ester substrate (0.042 mmol) was massed directly into a flame dried 1 dram vial equipped with a stir bar and a cap with a red PTFE/silicone septum. The vial was brought into a glovebox, under an N_2 atmosphere, and chloro(1,5-cyclooctadiene)rhodium (I) dimer (2.5 mol %, 0.51 mg) was added, followed by the arylboronic acid (2.0 equiv) and potassium carbonate (3.0 equiv, 17.2 mg). Finally, toluene (0.50 mL) was added and the vial was removed from the glovebox, sealed with electrical tape and heated to 40 °C for 24 h before being filtered through a silica gel plug using ethyl acetate to rinse. The crude sample was dissolved in 1.0 mL of methylene chloride and approximately ¼ of the solution was applied to a 3.5 x 8 inch glass TLC plate (thickness of silica gel = 250 μm) and purified by semi-preparative thin layer chromatography, using 5% ethyl acetate/hexanes to elute, so that pure material for chiral HPLC analysis could be obtained.

Preparation of α-Keto Ester Starting Materials
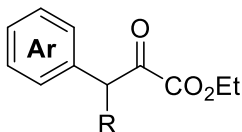
Prepared According to Method A:
7a Ar = 4-ClC$_6$H$_4$, R = Me
7m Ar = 4-MeC$_6$H$_4$, R = Me
7o Ar = 4-OMeC$_6$H$_4$, R = Me
7p Ar = 2-FC$_6$H$_4$, R = Me
7q Ar = 2-MeC$_6$H$_4$
7r Ar = 3-MeC$_6$H$_4$
7s Ar = 2-naphthyl
7u Ar = C$_6$H$_5$, R = Et
7y Ar = 4-BrC$_6$H$_4$, R = Me

Prepared According to Method B:
7t Ar = 3-indole, R = Me

Prepared According to Method C:
7v Ar = 3-BrC$_6$H$_4$, R = allyl

Prepared According to Method D:
**7w** Ar = Ph, R = CH$_2$CH(CO$_2$Me)$_2$

Prepared According to Method E:
7x Ar = 3-pyridyl, R = CH$_2$C$_6$H$_5$
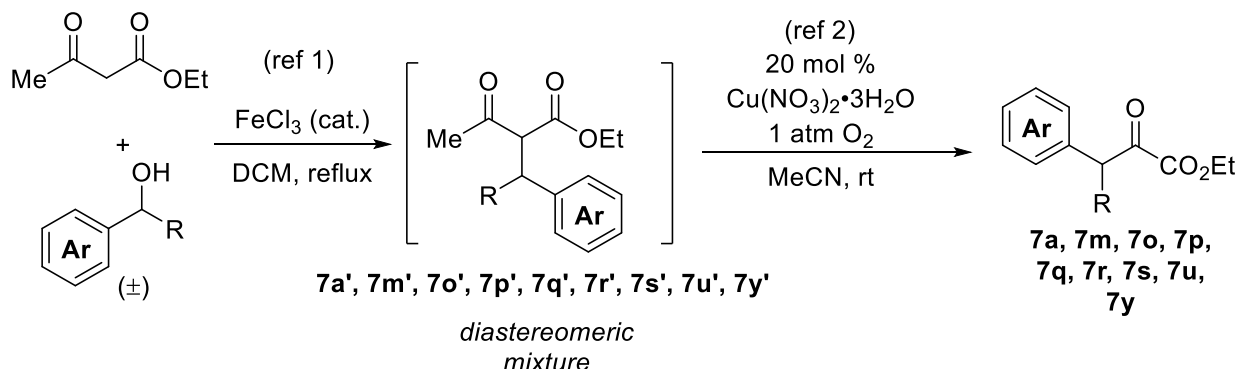
Method A for the Preparation of β-Methyl and β-Ethyl Substituted Substrates

7a,7m,7o,7p,7q and 7r, 7s, 7u, 7y: The listed substrates were prepared via a modified

literature method.[33,34] As noted by Ishii and co-workers , symmetrical dibenzyl ethers

were sometimes observed as intermediates in the alkylation procedure detailed below; in

some cases it was necessary to employ higher loadings of FeCl$_3$ and longer reaction times

to promote full conversion of these intermediates to the desired ethyl acetoacetate

alkylation product.
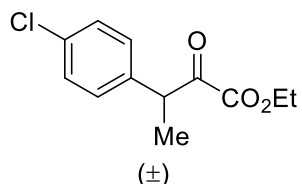
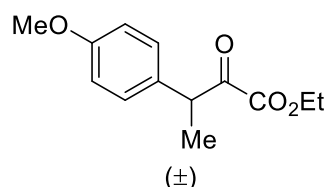**Ethyl 3-(4-chlorophenyl)-2-oxobutanoate: Step 1:** Ethyl acetoacetate (1.47 mL, 1.50 g, 11.50 mmol) and (±)-1-(4-chlorophenyl)ethanol (2.01 g, 12.8 mmol) were combined with 46.0 mL (0.25 M) of anhydrous methylene chloride in a 100 mL round-bottomed flask equipped with a reflux condenser . Next, iron(III) chloride (467 mg, 2.88 mmol, black anhydrous form) was added and the reaction was heated to reflux (external bath at 50 °C). Analysis of a reaction aliquot by ^{1}H NMR spectroscopy indicated completion after 20 h; the reaction mixture was subsequently filtered through a pad of silica gel using 70/30 hexanes/ethyl acetate and concentrated. In this case, purification by silica gel chromatography yielded ethyl 2-acetyl-3-(4-chlorophenyl)butanoate **7a'** as a yellow oil (10.3 mmol, 89% yield)**^{1}H NMR data for 7a**' (1:1 mixture of diastereomers**):** (600 MHz, CDCl$_3$): δ 7.27–7.24 (m, 4H), 7.16–7.13 (m, 4H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.92–3.89 (m, 2H), 3.75–3.69 (m, 2H), 3.56–3.49 (m, 2H), 2.30 (s, 3H), 1.97 (s, 3H), 1.30–1.26 (m, 6H), 1.21 (d 1.21, *J* = 6.9 Hz, 3H), 0.99 (t, 7.1 Hz, 3H). **Step 2:** Ethyl 2-acetyl-3-(4-chlorophenyl)butanoate **7a'** (2.77 g, 10.3 mmol) was dissolved in MeCN (27.7 mL, 1 mL/100 mg). Next, Cu(NO$_3$)$_2$·3H$_2$O (498 mg, 2.06 mmol, 0.2 equiv) was added and the resulting green homogenous solution was sparged with O$_2$ gas (O$_2$ balloon attached to penetration needle) for 10 min. The reaction was stirred for 44 h at room temperature under an atmosphere of oxygen, at which point NMR analysis indicated full consumption of the starting β-keto ester. The reaction mixture was diluted with water and extracted three times with ethyl acetate (20 mL per extraction), the combined organic extracts were then washed with brine and dried over MgSO$_4$ and concentrated. Purification of the resulting residue by silica gel column chromatography (**1st column:** 2.5% ethyl acetate/hexanes as eluent, **2nd column:** methylene chloride as eluent) afforded **7a** as a

clear oil (2.48 g, 5.1 mmol, 49% yield). **Analytical Data for 7a: ^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.31–7.29 (m, 2H), 7.18–7.15 (m, 2H), 4.48 (q, J = 7.0 Hz, 1H), 4.24-4.16 (m, 2H), 1.44 (d, J = 7.0 Hz, 3H), 1.24 (t, J = 7.1 Hz); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 193.5, 161.0, 136.2, 133.6, 129.8, 129.2, 62.5, 47.7, 16.8, 13.9; **IR** (thin film): 3434, 2064, 1732, 1697, 1647, 1636, 1522, 1507, 1374, 1268 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{12}$H$_{13}$ClO$_3$: ([M+Na]): 263.0451, Found: 263.0450; **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3. **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): t_{R1} = 7.1 min, t_{R2} = 7.6 min.
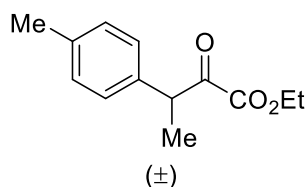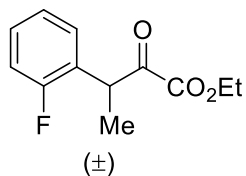

Ethyl 2-oxo-3-(*p*-tolyl)butanoate (7m): The title compound was prepared according to Method A with the following modifications: **Step 1:** ethyl acetoacetate (4.82 g, 37.0 mmol, 1.0 equiv), (±)-1-(4-methylphenyl)ethanol (5.04 g, 37.0 mmol, 1.0 equiv), and anhydrous FeCl$_3$ (601 mg, 3.7 mmol, 0.10 equiv) were used. Methylene chloride (40.0 mL, 0.93 M) was used as solvent. The reaction time was 24 h. In this case the product from Step 1 was not purified by silica gel column chromatography and was taken on to step 2 in crude form. **Step 2:** Cu(NO$_3$)$_2$·3H$_2$O (2.19 g, 9.1 mmol, 0.24 equiv with respect to ethyl acetoacetate) was used and the reaction was run in acetonitrile (40.0 mL, 0.93 M with respect to ethyl acetoacetate) for 60 h. The crude material from step 2 was purified by silica gel column chromatography (**1st column:** 2.5% ethyl acetate/hexanes acetate as eluent, **2nd column:** methylene chloride as eluent) affording **7m** as a clear oil (4.55 g, 20.6 mmol, 56% yield over two steps). **Analytical data for 7m: ^{1}H NMR** (600 MHz, CDCl$_3$): 7.14–7.10 (m, 4H), 4.45 (q, J = 7.0 Hz, 1H), 4.22–4.13 (m, 2H), 2.32 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 194.1, 161.4, 137.4, 134.6, 129.7, 128.3, 62.2, 48.0, 21.1, 16.8, 13.8; **IR** (thin film): 3445, 2982, 2937,

2360, 1731, 1646, 1636, 1540, 1508, 1457, 1269 cm⁻¹; **HRMS** (ESI+): Calcd. for: $C_{13}H_{16}O_3$

([M+1]): 221.1178, Found: 221.1174. **TLC** (90:10 hexanes: ethyl acetate): R_f = 0.3.

Ethyl 3-(4-methoxyphenyl)-2-oxobutanoate (70): The title compound was prepared according to Method A with the following modifications: **Step 1:** ethyl acetoacetate (4.27 g, 32.8 mmol, 1.0 equiv) and (±)-1-(4-methoxyphenyl)ethanol (5.0 g, 32.8 mmol, 1.0 equiv), and FeCl₃ (532 mg, 3.28 mmol, 0.10 equiv) were used. Methylene chloride (40.0 mL, 0.82 M) was used as solvent. The reaction time was 24 h. In this case the product from step 1 was not purified by silica gel column chromatography and was taken on to step 2 in crude form. **Step 2:** Cu(NO₃)₂·3H₂O (1.94 g, 8.0 mmol, 0.24 equiv) was used and the reaction was run in acetonitrile (40.0 mL, 0.82 M) for 60 h. The crude material from Step 2 was purified by silica gel column chromatography (**1st column:** 2.5% ethyl acetate/hexanes as eluent, **2nd column:** methylene chloride as eluent) affording **70** as a clear oil (2.76 g, 11.7 mmol, 36% yield over two steps). **Analytical data for 70: ¹H NMR** (600 MHz, CDCl₃): δ 7.15–7.13 (m, 2H), 6.86–6.85 (m, 2H), 4.44 (q, J = 7.0 Hz, 1H), 4.22–4.14 (m, 2H), 3.78 (s, 3H), 1.43 (d, J = 7.0 Hz, 3H), 1.22 (t, J = 7.1 Hz); **¹³C NMR** (151 MHz, CDCl₃): δ 194.0, 162.0, 159.0, 129.6, 129.4, 114.4, 62.2, 55.2, 47.5, 16.7, 13.9; **IR** (thin film): 3431, 2982, 2360, 2341, 1771, 1731, 1647, 1636, 1510, 1457, 1253, 1034 cm⁻¹; HRMS (ESI+): Calcd. for $C_{13}H_{16}O_4$: ([M+Na]): 259.0946, Found: 259.0943. **TLC** (90:10 hexanes: ethyl acetate): R_f = 0.3.
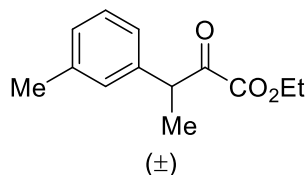
Ethyl 3-(2-fluorophenyl)-2-oxobutanoate (7p): The title compound was prepared according to Method A with the following modifications: **Step 1:** ethyl acetoacetate (4.76 g, 36.6 mmol, 1.0 equiv), (±)-1-(2-fluorophenyl)ethanol (5.13 g, 36.6 mmol, 0.10 equiv), and $FeCl_3$ (2.97 g, 18.3 mmol. 0.5 equiv) were used. Methylene chloride (40.0 mL, 0.92 M) was used as solvent. The reaction time was 36 h. In this case the product from step 1 was not purified by silica gel column chromatography and the crude material was taken on to step 2. **Step 2:** $Cu(NO_3)_2 \cdot 3H_2O$ (2.16 g, 9.0 mmol, 0.24 equiv) was used and the reaction was run in acetonitrile (40.0 mL, 0.92 M) for 60 h. The crude material from step 2 was purified by silica gel column chromatography (**1st column:** 2.5% ethyl acetate/hexanes as eluent, **2nd column:** methylene chloride as eluent) affording **7p** as a clear oil (3.88 g, 17.3 mmol, 47% yield over two steps). **Analytical data for 7p:** **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.28–7.24 (m, 1H), 7.13–7.09 (m, 2H), 7.09–7.06 (m, 1H), 4.70 (q, J = 7.0 Hz, 1H), 4.23–4.16 (m, 2H), 1.46 (d, J = 7.0 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 193.6, 161.1, 160.4 (d, $J_{19F-13C}$ = 247.6 Hz), 129.3 (d, $J_{19F-13C}$ = 24.3 Hz), 129.2 (d, $J_{19F-13C}$ = 19.8), 125.5 (d, $J_{19F-13C}$ = 15.4 Hz), 124.6 (d, $J_{19F-13C}$ = 3.4 Hz), 115.8 (d, $J_{19F-13C}$ = 22.5 Hz), 62.3, 41.8 (d, $J_{19F-13C}$ = 1.9 Hz), 15.8, 13.8; **^{19}F NMR** (376 MHz, CDCl$_3$): δ -117.5; **IR** (thin film): 3446. 2985, 2940, 1732, 1698, 1653, 1636, 1507, 1492, 1456, 1233 cm^{-1}; **HRMS** (ESI+): Calcd. for $C_{12}H_{13}FO_3$: ([M+1]): 225.0927, Found: 225.0924. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.
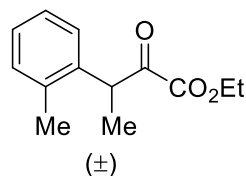
Ethyl 2-oxo-3-(o-tolyl)butanoate (7q): The title compound was prepared according to Method A with the following modifications: Step 1: ethyl acetoacetate (1.93 g, 14.8 mmol, 1.0 equiv), (±)-1-(o-tolyl)ethan-1-ol (2.02 g, 14.8 mmol, 1.0 equiv), and $FeCl_3$ (1.20 g, 7.42 mmol, 0.50 equiv) were used. Methylene chloride (16.0 mL, 0.93 M) was used as solvent. The reaction time was 21.3 h. In this case the product from step 1 was not purified by silica gel column chromatography and the crude material was taken on to Step 2. **Step 2:** $Cu(NO_3)_2 \cdot 3H_2O$ (877 mg, 2.97 mmol, 0.20 equiv) was used and the reaction was run in acetonitrile (16.0 mL, 0.92 M) for 75 h. The crude material from step 2 was purified by silica gel column chromatography (**1st column:** 2.5% ethyl acetate/hexanes as eluent, **2nd column:** methylene chloride as eluent) affording **7q** as a light yellow oil (700 mg, 3.18 mmol, 21% yield over two steps). **Analytical data for 7q: ^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.22–7.20 (m, 2H), 7.18–7.12 (m, 2H), 6.93–6.90 (m, 1H), 4.64 (q, J = 6.8 Hz, 1H), 4.18–4.10 (m, 1H), 2.44 (s, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): 194.5, 161.5, 136.5, 136.4, 131.1, 127.6, 127.1, 126.6, 62.2, 44.7, 19.5, 16.2, 13.8; **IR** (thin film): 3750, 3734, 3649, 3566, 2359, 2330, 1771, 1748, 1733, 1653, 1558, 1541, 1521, 1507, 1457, 1270, 761 cm^{-1}; HRMS (ESI+): Calcd. for C$_{13}$H$_{16}$O$_3$: ([M+1]): 221.1178, Found: 221.1176. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.
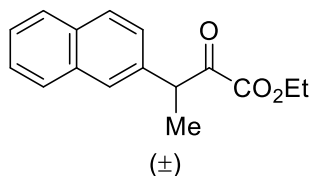
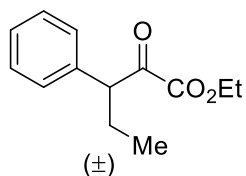**Ethyl 2-oxo-3-(m-tolyl)butanoate (7r):** The title compound was prepared according to Method A with the following modifications: **Step 1:** ethyl acetoacetate (5.46 g, 41.9 mmol, 1.1 equiv) and (±)-1-(m-tolyl)ethan-1-ol (5.19 g, 38.1 mmol, 1.0 equiv), and $FeCl_3$ (3.09 g, 0.50 equiv) were used. Methylene chloride (152 mL, 0.25 M) was used as solvent. The

reaction time was 21 h. In this case the crude material from step 1 was taken on without purification. **Step 2:** Cu(NO$_3$)$_2$·3H$_2$O (1.84 g, 7.62 mmol, 0.20 equiv) was used and the reaction was run in acetonitrile (47.3 mL,   0.81 M) for 94.5 h. The crude material from step 2 was purified by silica gel column chromatography (**1st column:** 2.5% ethyl acetate/hexanes as eluent, **2nd column:** methylene chloride as eluent) affording **7r** as a light yellow oil (4.52 g, 54% yield over two steps). **Analytical data for 7r: ^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.21 (app t, J = 8.0 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 7.03 –7.00 (m, 2H), 4.45 (1, J = 7.0 Hz, 1H), 4.22–4.13 (m, 2H), 2.32 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H); **^{13}C NMR:** (151 MHz, CDCl$_3$): δ 194.1, 161.4, 138.7, 137.6, 129.1, 128.9, 128.4, 125.5, 62.2, 48.3, 21.4, 16.8, 13.8; ; **IR** (thin film): 3767, 3750, 3734, 3649, 3050, 2980, 2936, 2875, 2358, 2322, 1771, 1742, 1715, 1581, 1473, 1270, 1174, 1038, 787 cm^{-1} ; **HRMS** (ESI+): Calcd. for C$_{13}$H$_{16}$O$_3$: ([M+1]): 221.1178, Found: 221.1178. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.

Ethyl 3-(naphthalen-2-yl)-2-oxobutanoate (7s): The title compound was prepared according to Method A with the following modifications: **Step 1:** ethyl acetoacetate (5.74 g, 44.1 mmol, 1.50 equiv) and (±)-1-(naphthalen-2-yl)ethan-1-ol (5.00 g, 29.4 mmol, 1.0 equiv) and FeCl$_3$ (2.38 g, 14.7 mmol, 0.5 equiv) were used. Methylene chloride (40.0 mL, 0.74 M) was used as solvent. The reaction time was 48 h. In this case the crude material from step 1 was used without further purification. **Step 2:** Cu(NO$_3$)$_2$·3H$_2$O (1.42 g, 5.88 mmol, 0.2 equiv) was used and the reaction was run in acetonitrile (40.0 mL, 0.74 M) for 72 h. The crude material from step 2 was purified by silica gel column chromatography (**1st column:** 2.5% ethyl acetate/hexanes as eluent, **2nd column:** methylene chloride as eluent) affording **7s** as a light yellow oil (2.65 g, 10.3 mmol, 35% yield over two steps).

Analytical data for 7s: ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.84 − 7.78 (m, 3H), 7.66 (s, 1H), 7.50−7.45 (m, 2H), 7.36 (dd, J = 8.5, 1.8 Hz, 1H), 4.67 (q, J = 7.0 Hz, 1H), 4.19−4.10 (m, 2H), 1.55 (d, J = 7.0 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}**C NMR:** (151 MHz, CDCl$_3$): δ 193.8, 161.3, 135.1, 133.5, 132.7, 128.9, 127.8, 127.6, 127.5, 126.3, 126.3, 126.2, 62.3, 48.4, 16.9, 13.8, **IR** (thin film): 3767, 3750, 3734, 3587, 3566, 3056, 2979, 2934, 2353, 2321, 1771, 1748, 1732, 1717, 1558, 1541, 1521, 1507, 1269, 1037, 748 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{16}$H$_{16}$O$_3$: ([M+1]): 257.1178, Found: 257.1176. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.


Ethyl 2-oxo-3-phenylpentanoate (7u): The title compound was prepared according to Method A with the following modifications: **Step 1:** ethyl acetoacetate (37.1 mmol, 4.83 g, 1.0 equiv), (±)-1-phenyl-1-propanol (37.1 mmol, 5.05 g, 1.0 equiv), and FeCl$_3$ (3.01 g, 18.5 mmol, 0.5 equiv) were used. Methylene chloride (40.0 mL, 0.93 M) was used as solvent. The reaction time was 36 h. In this case the product from Step 1 was not purified by silica gel column chromatography and the crude material was taken on to step 2. **Step 2:** Cu(NO$_3$)$_2$·3H$_2$O was used (2.192 g, 9.1 mmol, 0.24 equiv) and the reaction was run in acetonitrile (40.0 mL, 0.93 M). The crude material from Step 2 was purified by silica gel column chromatography (**1st column:** 2.5% ethyl acetate/hexanes as eluent, **2nd column:** methylene chloride as eluent) affording **7u** as a light yellow oil (3.05 g, 13.8 mmol, 37% yield over two steps). **Analytical data for 7u: ^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.33−7.31 (m, 2H), 7.27−7.25 (m, 1H), 7.22−7.20 (m, 2H), 4.29−2.27 (m, 1H), 4.22−4.14 (m, 2H), 2.14−2.07 (m, 1H), 1.82−1.76 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}**C NMR** (151 MHz, CDCl$_3$): δ 193.6, 161.3, 136.1, 129.0, 128.9, 127.6, 62.3, 55.8, 24.7, 13.8,

11.8; **IR** (thin film): 3420, 2969, 2936, 2876, 2360, 2341, 1771, 1732, 1558, 1540, 1522, 1507, 1457, 1248 cm^{-1}; **HRMS** (ESI+): Calcd. for $C_{13}H_{16}O_3$: ([M+1]): 221.1178, Found: 221.1174. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.
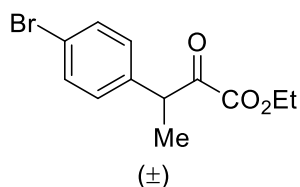
ethyl 3-(4-bromophenyl)-2-oxobutanoate (7y): The title compound was prepared according to Method A with the following modifications: **Step 1:** ethyl acetoacetate (4.31 g, 33.2 mmol, 1.5 equiv), (±)-1-(4-methylphenyl)ethanol (4.44g, 22.1 mmol, 1.0 equiv), and FeCl$_3$ (10.5 mmol, 1.70 g, 0.50 equiv) were used. Methylene chloride (24.0 mL, 0.92 M) was used as solvent. After 48 h the reaction was incomplete, an additional 1.70 g of FeCl$_3$ and 2.16 g ethyl acetoacetate were added and the reaction was ran for an additional 96 h before being filtered through silica gel and concentrated. The resulting material was subjected to the next step without further purification. Step 2: Cu(NO$_3$)$_2$·3H$_2$O was used (1.07 g, 4.42 mmol, 0.20 equiv based on (±)-1-(4-methylphenyl)ethanol) and the reaction was run in acetonitrile (22.0 mL) for 60 h. The crude material from step 2 was purified by silica gel column chromatography (1st **column:** 2.5% ethyl acetate/hexanes as eluent, **2nd column:** methylene chloride as eluent) affording **7y** as a clear oil (3.19 g, 11.2 mmol, 51% yield over two steps). **Analytical data for 7y:** ^{1}**H NMR** (600 MHz, CDCl$_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.47 (q, *J* = 7.0 Hz, 1H), 4.24–4.16 (m, 1H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, CDCl$_3$): δ 193.4, 161.0, 136.8, 132.1, 130.1, 121.7, 62.5, 47.7, 16.7, 13.9; **IR** (thin film): 3446, 2981, 2937, 1792, 1731, 1647, 1636, 1507, 1489, 1457, 1266 cm^{-1}; **HRMS** (ESI+): Calcd. for $C_{12}H_{13}BrO_3$: ([M+Na]): 306.9946, Found: 306.9948. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.
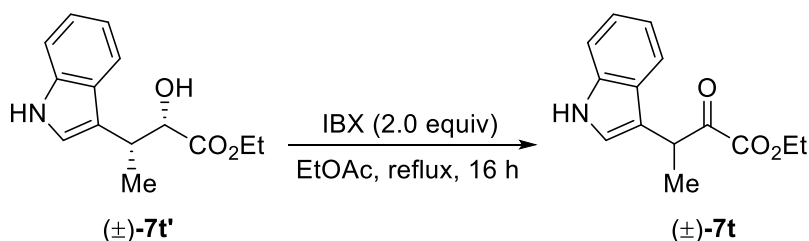
Method B for the Preparation of Ethyl 3-(1H-indol-3-yl)-2-oxobutanoate (7t):[35]

The known compound, *syn*-(±)-ethyl 2-hydroxy-3-(1H-indol-3-yl)butanoate **7t'** (2.12 g, 8.59 mmol, 1.0 equiv) was dissolved in ethyl acetate (43.0 mL, 0.2 M) in a round-bottomed flask equipped with a reflux condenser. Next, o-iodoxybenzoic acid (IBX) was added and the mixture was heated at reflux for 16 h. Upon completion, the reaction was cooled to room temperature and the crude mixture was passed through a pad of silica gel using ethyl acetate to rinse. Upon concentration, the crude residue was subjected to silica gel column chromatography (15% ethyl acetate/hexanes followed by 20% ethyl acetate hexanes) affording **7t** as a slightly brown oil (2.11 g, 8.59 mmol, >99% yield). **Analytical data for 7t:** ^{1}H NMR (600 MHz, CDCl$_3$): δ 8.18 (br s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.22–7.20 (m, 1H), 7.17–7.14 (m, 1H), 7.06 (br s, 1H), 4.80 (q, J = 7.0 Hz, 1H), 4.16–4.08 (m, 2H), 1.56 (d, J = 7.0 Hz, 3H), 1.13 (t, J = 7.1 Hz); ^{13}**C NMR** (151 MHz, CDCl$_3$): δ 193.6, 162.0, 136.2, 126.3, 123.1, 122.5, 120.0, 119.0, 112.1, 111.3, 62.1, 39.3, 16.2, 13.8; **IR** (thin film): 3502, 3408, 3058, 2980, 2936, 1792, 1770, 1726, 1684, 1541, 1472, 1457, 1421, 1339, 1258, 1102, 1037, 744 cm^{-1} ; **HRMS** (ESI+): Calcd. for C14H15NO3: ([M+1]): 246.1130, Found: 246.1126. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.1.

Method C for the Preparation of β-allyl Substituted Substrate 1v:
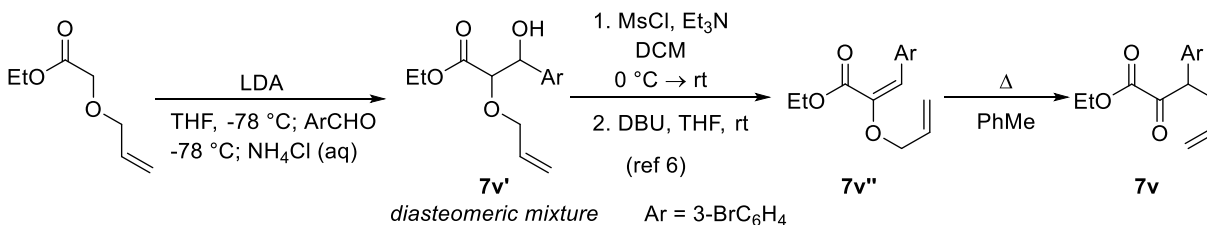
**Ethyl 2-(allyloxy)-3-(3-bromophenyl)-3-hydroxypropanoate (7v') Step 1:**[36] *n*-BuLi (7.27 mL, 1.72 M, 12.5 mmol, 1.2 equiv) was added dropwise to a solution of diisopropylamine (1.37 g, 1.91 mL, 13.5 mmol, 1.3 equiv) in THF (21 mL) cooled to -78 °C. After the resulting solution had stirred for 10 minutes, ethyl 2-(allyloxy)acetate (1.5 g, 10.4 mmol, 1.0 equiv) was added dropwise as a solution in THF (15.0 mL, 0.7 M) and the reaction was stirred for 15 minutes at -78 °C. Next, 3-bromobenzaldehyde (2.50 g, 13.5 mmol, 1.3 equiv) was added dropwise in THF (10 mL). The reaction was stirred for an additional 45 minutes at -78 °C before being quenched with sat. NH_4Cl (aq). The aqueous layer was extracted three times with methylene chloride (15 mL per extraction) and the combined organic layers were dried over $MgSO_4$. Concentration and purification of the residue by silica gel column chromatography using gradient elution from 10% to 20% ethyl acetate/hexanes provided ethyl 2-(allyloxy)-3-(3-bromophenyl)-3-hydroxypropanoate **7v'** as a clear oil (2.4:1 mixture of diastereomers, 2.13 g, 6.5 mmol, 62% yield). **Analytical data for 7v' ¹H NMR:** (reported as 2.4:1 mixture of diastereomers normalized to the methine resonance corresponding to the minor diastereomer at δ 4.91 (500 MHz, CDCl₃): δ 7.55 (s, 3.4H), 7.46–7.41 (m, 3.4H), 7.31–7.30 (m, 3.4H), 7.24–7.19 (m, 3.4H), 5.82–5.76 (m, 3.4H), 5.24–5.19 (m, 6.8H), 4.99–

4.97 (m, 2.4H), 4.91–4.91 (m, 1H), 4.18–4.06 (m, 10.6), 4.06 (d, J = 5.7 Hz, 2.4H), 3.98 (d, J = 5.3 Hz, 1H), 3.96– 3.88 (m, 3.4H), 3.05–3.03 (m, 3.4H), 1.18 – 1.14 (m, 10.2H); **13C NMR** (151 MHz, C_6D_6): δ 170.7, 170.5, 143.7, 143.5, 134.6, 134.5, 131.7, 131.6, 131.0, 130.8, 130.5, 130.3, 126.5, 126.2, 125.7, 123.2, 123.1, 118.3, 118.1, 83.3, 82.8, 74.9, 74.3, 72.4, 72.4, 61.5, 61.4, 14.6, 14.6.

Ethyl 2-(allyloxy)-3-(3-bromophenyl)acrylate (7v") Step 2:[36] To a solution of ethyl 2-(allyloxy)-3-(3-bromophenyl)-3-hydroxypropanoate **7v'** (2.13 g, 6.5 mmol, 1.0 equiv) and triethylamine (850 mg, 1.2 mL, 8.40 mmol, 1.3 equiv) in methylene chloride (20 mL, 0.3 M) cooled to 0 ° C was added methanesulfonyl chloride (889 mg, 0.60 mL, 7.8 mmol, 1.2 equiv) dropwise. The resulting solution was allowed to warm to room temperature slowly and was then stirred for an additional 12h before being quenched with sat. $NaHCO_3$ (aq). The aqueous layer was extracted three times with methylene chloride (15 mL per extraction) and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude mesylate was dissolved in tetrahydrofuran (12.9 mL, 0.5 M) and treated with 1,8-diazabicycloundec-7-ene (2.95 g, 2.89 mL, 19.4 mmol, 3.0 equiv) at room temperature. The reaction was stirred for 12 h before being diluted with water (2 mL/ mmol substrate, 13.0 mL). The aqueous layer was extracted three times with methylene chloride (15 mL per extraction) and the combined organic layers were dried over $MgSO_4$. The crude residue was purified by silica gel column chromatography (5% then 10% ethyl acetate/hexanes) affording ethyl 2-(allyloxy)-3-(3-bromophenyl)acrylate **7v"** as a pale yellow oil (1.47 g, 4.71 mmol, 73% yield over two steps). **Analytical data for 7v":1H NMR** (600 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 7.92 Hz, 1H), 6.90 (s, 1H), 6.04–5.98 (m, 1H), 5.36 (dd, J = 17.2, 1.3 Hz, 1H),

5.26 (d, J = 10.4 Hz, 1H), 4.51 (d, J = 6.1 Hz, 2H), 4.31 (q, J = 14.3, 7.1 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 164.0, 145.2, 135.6, 133.2, 132.7, 131.6, 129.9, 128.6, 122.5, 122.3, 118.8, 72.7, 61.4, 14.3.

Ethyl 3-(3-bromophenyl)-2-oxohex-5-enoate (7v, Step 3):[37] Ethyl 2-(allyloxy)-3-(3-bromophenyl)acrylate **7v''** (1.47 g, 4.71 mmol) was dissolved in toluene (11.8 mL, 0.4 M) in a sealed reaction tube equipped with a stir bar and heated to 95 °C for 6 h, after which concentration provided ethyl 3-(3-bromophenyl)-2-oxohex-5-enoate **10** in quantitative yield (ca 94% pure, containing toluene). **Analytical data for 7v: ^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.42–7.39 (m, 2H), 7.22–7.19 (m, 1H), 7.17–7.15 (m, 1H), 5.69–5.62 (m, 1H), 5.06–5.03 (m, 1H), 5.01 (dd, J = 10.2, 1.3 Hz, 1H), 4.47 (t, J = 7.6 Hz, 1H), 4.26–4.17 (m, 2H), 2.84–2.79 (m, 1H), 2.51–2.47 (m, 1H), 1.27–1.25 (m, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 192.2, 160.6, 137.9, 134.2, 131.9, 131.0, 130.5, 127.5, 122.9, 117.8, 62.6, 53.2, 35.7, 13.8; **IR** (thin film): 3446, 3080, 2982, 2938, 1793, 1731, 1646, 1569, 1559, 1489, 1474, 1428, 1271, 1236; HRMS (ESI-): Calcd. for C$_{14}$H$_{15}$BrO$_3$ ([M-1]): 309.0126, Found: 309.0133. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.
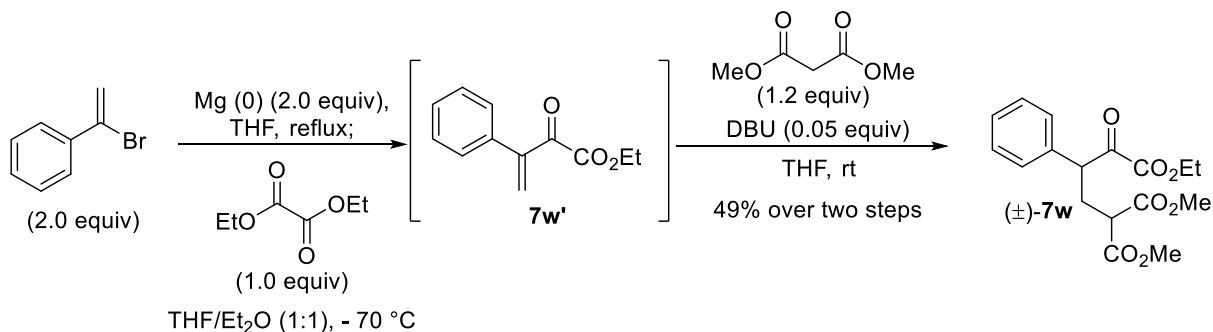
Method D for the preparation of (±)-4-ethyl 1,1-dimethyl 4-oxo-3-phenylbutane-1,1,4-tricarboxylate 7w: Step 1:[38] Magnesium turnings (333 mg, 13.7 mmol, 2.0 equiv) were added to a flame dried round-bottomed flask equipped with a reflux condenser and stir bar under N_2. The magnesium turnings were then activated by holding the flame of a Bunsen burner to the bottom of the flask for 1-2 min with stirring. Upon cooling to room temperature, tetrahydrofuran (13.7 mL) was added, followed by α-bromostyrene (2.51 g, 13.7 mmol, 2.0 equiv). After approximately 10 min the reaction began to reflux after an additional 30 min the Grignard formation was complete as evidenced by consumption of the magnesium turnings and cessation of the reflux. Upon cooling to room temperature the resulting Grignard solution was added dropwise (manually) to a solution of diethyl oxalate (1.00 g, 6.84 mmol, 1.0 equiv) cooled to -70 °C using a dry ice/acetone bath. After complete addition of the Grignard reagent the resulting reaction was allowed to stir for 2.2 h at -70 °C before being quenched at this temperature with saturated aqueous ammonium chloride solution. The reaction was further diluted with water until the resulting salts had dissolved. The aqueous layer was extracted three times with ethyl acetate (50 mL per extraction) and the combined organic layers were dried over $MgSO_4$ and concentrated. The resulting α,β-unsaturated α-keto ester **7w'** was found to be unstable to silica gel column chromatography as well as prolonged storage at low temperature and was therefore used directly without purification. **Step 2:** Crude **7w'** was dissolved in tetrahydrofuran (15.2 mL), dimethylmalonate (1.09 g, 8.21 mmol, 1.2 equiv) was added followed by 1,8-diazobicyclo(5.4.0)undec-7-ene (DBU, 52.1 mg, 0.342 mmol, 0.05 equiv). The reaction was stirred for 13.5 h and concentrated. Silica gel column chromatography 10% ethyl acetate/hexanes delivered the desired product as a yellow oil (1.11 g, 3.32 mmol, 49% yield

over two steps, ~86% pure). **Analytical data for 7w:** **¹H NMR** (600 MHz, CDCl₃): δ 7.35–7.32 (m, 2H), 7.30–7.27 (m, 1H), 7.19–7.18 (m, 1H), 4.50 (dd, J = 8.6, 6.7 Hz, 1H), 4.21–4.12 (m, 2H), 3.76 (s, 3H), 3.67 (s, 3H), 3.25 (dd, J = 8.8 Hz, 6.2 Hz, 1H), 2.64 (ddd, J = 14.3, 8.8, 6.6 Hz, 1H), 7.37 (ddd, J = 14.3, 8.6, 6.3 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H); **¹³C NMR** (151 MHz, CDCl₃): δ 192.0, 169.3, 169.2, 160.5, 134.5, 129.3, 129.1, 128.3, 62.5, 52.7, 52.7, 51.4, 48.9, 30.1, 13.8; **IR** (thin film): 3750, 3734, 3566, 2955, 2359, 2341, 1792, 1748, 1733, 1558, 1541, 1507, 1456, 1436, 1273, 1236, 1038, 701 cm⁻¹ ; **HRMS** (ESI+): Calcd. for $C_{17}H_{20}O_7$:[(M+Na)]: 359.1107, Found: 359.1818. **TLC** (90:10 hexanes: ethyl acetate): R_f = 0.1.
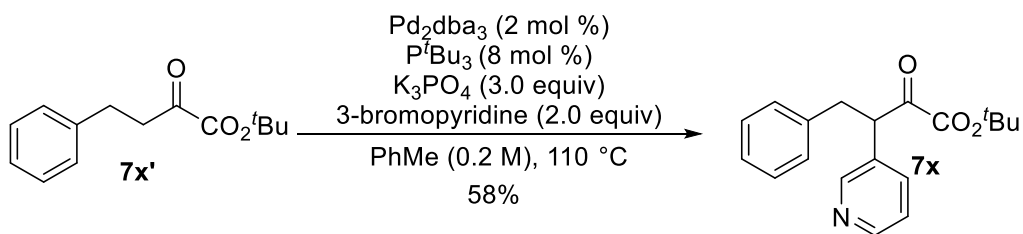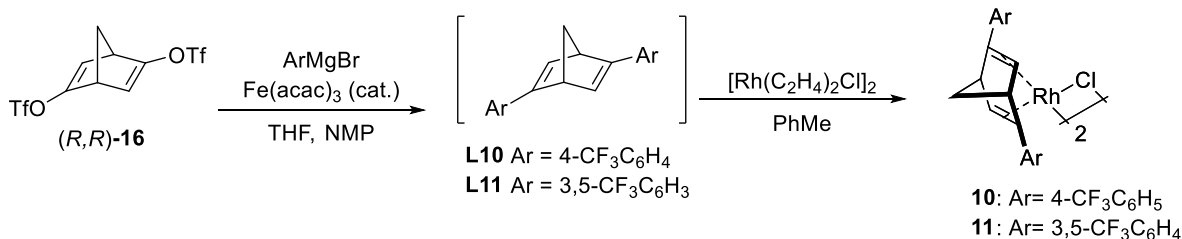

Method E for the preparation of tert-butyl 2-oxo-4-phenyl-3-(pyridin-3-yl)butanoate 7x:[38]

In an N₂ filled glovebox a solution of the known[9] α-keto ester **1x'** (70.3 mg, 0.30 mmol, 1.0 equiv) and 3-bromopyridine (94.8 mg, 0.60 mmol, 2.0 equiv) was added in toluene (1.5 mL, 0.2 M) to a flame dried 1 dram vial containing Pd₂dba₃ (5.49 mg, 0.006 mmol, 0.02 equiv), tri-*tert*-butylphosphine (0.024 mmol,24.0 μL, 1.0 M PhMe, 0.08 equiv), and K₃PO₄ (191 mg, 0.90 mmol, 3.0 equiv). The vial was capped (red silicone/PTFE septum cap), removed from the glovebox, and heated at 110 °C for 12 h. Upon cooling to room temperature, the reaction was quenched by the addition of 1 mL of saturated aqueous ammonium chloride and the mixture was allowed to stir for 20 minutes at room temperature until two separate homogenous phases were observed. The mixture was

further diluted with methylene chloride and water and the aqueous phase was etracted several times using methylene chloride. The combined organic layers were dried over $MgSO_4$ and concentrated. Silica gel column chromatography (70:30 hexanes/ethyl acetate) afforded the desired compound as a yellowish solid (54.0 mg, 0.17 mmol, 58% yield). **Analytical data for 7x: ^{1}H NMR** (600 MHz, CDCl$_3$): δ 8.50 (d, J = 3.7 Hz, 1H), 8.38 (s, 1H), 7.50–7.49 (m, 1H), 7.27–7.15 (m, 4H), 7.03 (d, J = 7.1 Hz, 2H), 4.63 (dd, J = 8.0 Hz, 7.1 Hz, 1H), 3.44 (dd, J = 13.9, 6.7 Hz, 1H), 2.97 (dd, J = 13.9 Hz, 8.4 Hz, 1H), 1.36 (s, 9H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 193.3, 159.8, 150.5, 148.9, 137.8, 136.0, 132.0, 129.0, 128.5, 126.6, 123.6, 84.6, 53.4, 37.7, 27.6; **HRMS** (ESI+): Calcd. for $C_{19}H_{21}NO_3$: ([M+1]): 312.1600, Found: 312.1597. **TLC** (70: 30 hexanes: ethyl acetate): R$_f$ = 0.2.

Catalyst Preparation

L10 Ar = 4-CF$_3$C$_6$H$_4$
L11 Ar = 3,5-CF$_3$C$_6$H$_3$

10: Ar= 4-CF$_3$C$_6$H$_5$
11: Ar= 3,5-CF$_3$C$_6$H$_4$

Method F for the Preparation of Chiral Rhodium Catalysts: The (chiraldiene)rhodium(I) dimers **10** and **11** were prepared starting from known bis(triflate) (*R,R*)-**16** according to the Kumada coupling method reported by Hayashi and co-workers for the synthesis of complex **9**.[22b] As noted by Hayashi, the norbornadiene derived ligands reported here were sensitive and were directly complexed without purification. We have provided the crude ^{1}H NMR spectra of the ligands **L10** and **L11** corresponding to catalysts **10** and **11** below as a reference.

Ar

Rh–Cl

2

Ar

Ar = 4-CF$_3$C$_6$H$_4$
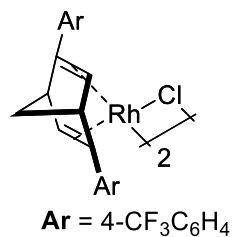
Preparation of Catalyst 10: To a suspension of magnesium turnings (187 mg, 7.7 mmol, 6.0 equiv) in THF (3.0 mL) in a flame dried round-bottomed flask equipped with a reflux condenser under N$_2$ was added 1-bromo-4-(trifluoromethyl)benzene (1.74 g, 7.7 mmol, 6.0 equiv) in THF (3.0 mL) once the ensuing reflux had subsided and complete consumption of the magnesium turnings was observed the resulting deep red solution was added slowly to a solution of bis(triflate) **16** (499 mg, 1.30 mmol), Fe(acac)$_3$ (22.7 mg, 0.06 mmol, 0.05 equiv) , and NMP (130 μL) in THF (6.0 mL) cooled to 0 °C (ice bath). The reaction was allowed to warm to room temperature and stirred for 20 h before being quenched with water (15 mL). The aqueous phase was extracted three times with ethyl acetate (15 mL per extraction) and dried over K$_2$CO$_3$. Upon concentration the residue was passed through a silica plug using 5/95 ethyl acetate/hexanes and concentrated. **¹H NMR Data for L10** (400 MHz, CDCl$_3$) δ 7.58 (d, J = 8.3 Hz, 4H), 7.51 (d, J = 8.0 Hz, 4H), 7.18 (s, 2H), 4.11 (s, 2H), 2.32 (s, 2H), see crude spectrum below. **Complexation:** In an N$_2$ filled glovebox the crude diene ligand was dissolved in PhMe (2.0 mL) in a scintillation vial equipped with a stir bar. Next, di-μ-chlorotetraethylene dirhodium(I) (250 mg, 0.64 mmol, 0.5 equiv) was added and the mixture was allowed to stir at room temperature for 2 h. The reaction was concentrated and the crude residue was purified by silica gel column chromatography (pressurized with N$_2$, gradient elution, 25/75 DCM/hexanes then 50/50 DCM/hexanes, followed by DCM), yielding catalyst **10** as a red solid (200 mg, 0.19 mmol, 30% yield). **Analytical data for catalyst 10:** **¹H NMR** (600 MHz, CDCl$_3$) δ 7.61 (d, J = 8.2 Hz, 8H), 7.54 (d, J = 8.2 Hz, 8H), 4.24 (m, 1H), 3.80 (s, 1H), 1.43 (s, 1H); **¹³C NMR** (151 MHz, CDCl$_3$): δ 142.1, 129.3 (q, $J_{19F-13C}$ = 32.6 Hz), 127.7, 125.2 (q, $J_{19F-13C}$ = 3.5 Hz), 124.3 (q, $J_{19F-13C}$ = 272.0 Hz), 64.4 (d, $J_{Rh103-13C}$ = 10.3 Hz), 58.3 (d, $J_{Rh103-13C}$ = 5.5 Hz),

53.1, 42.5 (d, $J_{Rh103-13C}$ = 10.3 Hz); **¹⁹F NMR** (565 MHz, CD₂Cl₂) δ -62.8. **TLC** (90:10 hexanes: ethyl acetate): R_f = 0.2, red spot. Crystals suitable for X-ray analysis were obtained by adding catalyst **10** (15.0 mg) in hexanes (1 mL), heating the resulting suspension to reflux while adding chloroform dropwise until a homogenous red solution was observed and allowing the resulting solution to sit at room temperature for 48 h.
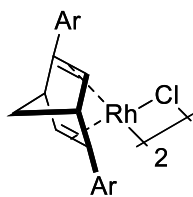

Ar = 4-CF₃C₆H₄

Preparation of Catalyst 11: To a round-bottomed flask equipped with a reflux condenser containing a suspension of magnesium turnings under N₂ atmosphere (226 mg. 9.3 mmol) in THF (5.0 mL) was added 1,3-Bis(trifluoromethyl)-5-bromobenzene (2.72 g, 9.3 mmol). After the ensuing reflux had subsided and the magnesium turnings were completely consumed the resulting Grignard solution was added slowly to a solution of bis(triflate) **16** (400 mg, 1.03 mmol), Fe(acac)₃ (18.2 mg, 0.05 mmol, .05 equiv), and NMP (291 μL) in THF (5.2 mL) cooled to 0 °C (ice bath). After 5 minutes TLC analysis showed complete consumption of bis(triflate) **16** and the reaction was quenched with water (12 mL) and extracted three times with ethyl acetate (15 mL per extraction). The combined organic layers were dried over K₂CO₃ before being concentrated. The crude residue was passed through a plug of silica gel using 5/95 ethyl acetate/hexanes and concentrated. **¹H NMR Data for Ligand 11:** (500 MHz, CDCl₃) δ 7.82 (s, 4H), 7.71 (s, 2H), 7.33 (s, 2H), 4.19 (s, 2H), 2.39 (s, 2H), see crude spectrum below. In an N₂ filled glovebox the crude diene ligand was dissolved in PhMe (3.0 mL) in a scintillation vial equipped with a stir bar. Next, di-μ-chlorotetraethylene dirhodium(I) was added and the mixture was allowed to stir at room temperature for 6 h. The reaction was concentrated and the residue was purified by silica gel column chromatography (N₂ used to pressurize, 25/75 DCM/hexanes

as eluent) yielding catalyst **C** as a red solid (252 mg, 0.19 mmol, 37% yield). **Analytical data for catalyst 11:** **¹H NMR** (600 MHz, CDCl$_3$) δ 7.90 (s, 4H), 7.84 (s, 8H), 4.30 (s, 4H), 3.87 (s, 4H), 1.49 (s, 4H); **¹³C NMR** (151 MHz, CDCl$_3$) δ 140.5, 132.1 (q, $J_{19F-13C}$ = 34.0 Hz), 127.0, 123.0 (q, $J_{19F-13C}$ = 273.1 Hz), 121.1, 64.0 (d, $J_{Rh103-C13}$ = 10.5 Hz), 58.7 (d, $J_{Rh103-13C}$ = 5.2 Hz), 53.4, 42.9 (d, $J_{Rh103-13C}$ = 10.2 Hz); **¹⁹F NMR** (565 MHz, CDCl$_3$): δ -63.2. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4, red spot. Crystals suitable for X-ray analysis were obtained by adding catalyst **11** (10.0 mg) in hexanes (1 mL), heating the resulting suspension to reflux while adding ethyl acetate dropwise until a homogenous red solution was observed and allowing the resulting solution to sit at room temperature for 72 h.

Method G for Dynamic Kinetic Arylation Reaction:

To a flame dried 1 dram vial equipped with a stir bar and red PTFE/silicone cap was added (in an N_2 filled glovebox) triethylamine (0.6 mmol, 6.0 equiv), the arylboronic acid (3.0-6.0 equiv, see below for individual loadings), and cesium fluoride (3.0-6.0 equiv, see below for individual loadings). Next, 0.50 mL of chloroform was added to a separate flame dried vial containing the chiral(diene)chlororhodium(I) dimer (.0025 mmol, 2.5 mol %) and the resulting solution was transferred to a third vial containing the α-keto ester substrate (0.1 mmol). The combined solution was transferred to the original stir bar, triethylamine, arylboronic acid, and cesium fluoride containing vial. The transfer process described above was repeated with an additional 0.50 mL of chloroform bringing the total reaction volume to 1.0 mL (.10 M). The reaction vial was capped tightly, removed from the glovebox, sealed with electrical tape and heated at 40 °C (external bath temperature, LabArmor® aluminum heating beads) with stirring (1100-1200 rpm) for the specified time. Upon completion, the reaction was allowed to cool to room temperature, 1.0 mL of sat. NH_4Cl (aq) was added and the mixture was stirred until two homogenous layers were produced. The resulting mixture was transferred to a 30 mL separatory funnel using 5 mL of ethyl acetate. Next, 5-6 mL of water was added and the layers were separated. The aqueous phase was extracted three times (5 mL ethyl acetate per extraction) and the combined organic layers were washed with 6-8 mL of sat. NaCl (aq) and dried over $MgSO_4$. The crude arylation products were purified by silica gel column chromatography, with the exception of product **8o** which was purified using preparatory thin layer chromatography (see below for individual eluent systems).
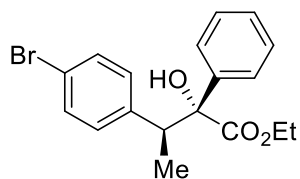
Method H for the 1 Mmol Scale Arylation of 7y: Ethyl(2R,3S)-3-(4-bromophenyl)-2-hydroxy-2-phenylbutanoate: Triethylamine (607 mg, 6.00 mmol, 6.0 equiv), 2-naphthylboronic acid (688 mg, 4.0 mmol, 4.0 equiv), and cesium fluoride (608 mg, 4.0 mmol, 4.0 equiv), and 5.0 mL of chloroform were combined in a flame dried 20.0 mL reaction tube equipped with a stir bar in the glovebox. Next, 2.0 mL of chloroform was used to transfer catalyst **C** (6.55 mg, 0.005 mmol, .005 equiv) and α-keto ester **7y**, which were contained in separate vials, to the reaction tube. Finally, the vials containing the catalyst and substrate were rinsed with an additional 3.0 mL of chloroform and the reaction tube was removed from the glovebox, sealed with electrical tape, and heated for 72 h. The reaction was cooled to room temperature, 500 μL of ethanol was added and the mixture was allowed to stir for 5 min before being filtered through a pad of silica gel using ethyl acetate to rinse. The crude reaction mixture was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes as eluent affording **8y** as an amorphous white solid (average yield of two runs = 77%). **Recrystallization of 8y:** The product could be recrystallized by titrating a hot suspension of **8y** in hexanes with ethyl acetate and allowing the resulting solution to stand at room temperature which afforded **8y** enriched to 99:1 er in the form of needles suitable for x-ray crystal diffraction studies.
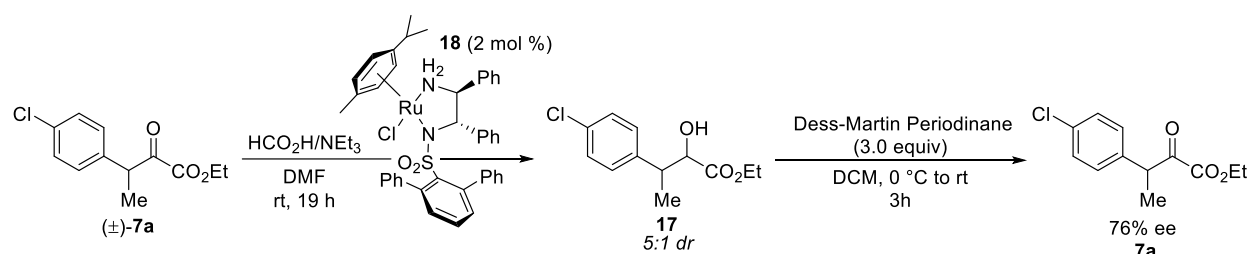
Method I for the Synthesis of Enantioenriched 7a:

Step 1: DKR-ATH of (±)-7a[11b]

Dichloro(p-cymene)ruthenium(II) dimer (25.4 mg, 0.0415 mmol, 0.02 equiv) and *N*-[(1R,2R)-2-amino-1,2-diphenyl-ethyl]-2,6-diphenyl-benzenesulfonamide[10] were massed into a flame dried 1 dram vial equipped with a stir bar in an N_2 filled glovebox, DMF (2.0 mL) was added and the mixture was heated to 70 °C for 30 minutes. Upon cooling to room temperature the solution of complexed catalyst was transferred to a solution of the α-keto ester (±)-7a in DMF (18.8 mL) in a 150 mL pressure vessel. The reaction was stirred for 19 h at room temperature. Upon completion the reaction mixture was diluted with water and ethyl acetate. The organic layer was washed twice with brine and dried over magnesium sulfate and concentrated. The crude residue was purified by silica gel column chromatography affording α-hydroxyester **17** as a 5:1 mixture of diastereomers (406 mg, 1.67 mmol, 81%). **¹H NMR data for 17** (500 MHz, CDCl$_3$, major diastereomer): δ 7.26 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 4.31 (dd, *J* = 6.0, 3.7 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.29–3.24 (m, 1H), 2.79 (d, *J* = 6.0 Hz, 1H), 1.44 (d, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). **HPLC** (98:2 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): t_{R1} = min ; t_{R2} = min.

Step 2: DMP oxidation of 17:

Ethyl 3-(4-chlorophenyl)-2-hydroxybutanoate **17** (mixture of diastereomers, 406 mg, 1.67 mmol, 1.0 equiv) was dissolved in methylene chloride (11.1 mL, 0.15 M) and the resulting solution was cooled to 0 °C. Next, Dess–Martin Periodinane (2.13 g, 5.02 mmol, 3.0 equiv) was added and the reaction was stirred for 3 h while warming to room temperature. Upon completion the reaction mixture was diluted with water and methylene chloride and filtered through a pad of celite, rinsing with methylene chloride. The aqueous phase was extracted with methylene chloride and the combined organic layers were dried over $MgSO_4$. Silica gel column chromatography (2.5% ethyl acetate in hexanes) afforded optically active **7a** (357 mg, 1.48 mmol, 89%, 88:12 er).
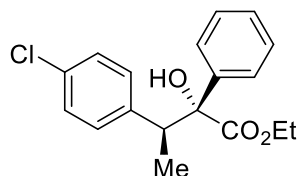
Racemization Studies:

A solution of optically active **7a** (24.1 mg, 0.1 mmol) was transferred in chloroform (1.0 mL 0.1 M) to a flame dried 1 dram vial containing the tertiary amine base, 2-naphthylboronic acid, CsF, and a stir bar and the mixture was stirred at the indicated temperature. Aliquots were removed (100-200 µL) at the specified times and delivered to a scintillation vial containing a stir bar and methanol (1.0 mL). Sodium borohydride (~20 mg) was immediately added and the resulting solution was diluted with water and extracted with ethyl acetate. The resulting α-hydroxy ester **7a'** was directly analyzed by chiral HPLC analysis.

 Note: racemic **17** was prepared via an analogous procedure starting from (±)-**7a**.

Table 2-2 Racemization Studies.

Time (min)	$^nBu_3N$ (% ee)	Et_3N (% ee)	$^iPr_2NEt$, rt (% ee)	$^iPr_2Net$, 40 ˚C (% ee)	NMP(%ee)
0	76	76	76	76	76
2					0
4	48	34			
8	24	10			
12	16	6			
15				73	
16	10	4			
20	4	2	76		
24	4	2			
30				54	
40			74		
45				19	
60			54	2	
75				0	
80			26		
100			14		

Analytical Data for Arylation Products

Ethyl (2*R*,3*S*)-3-(4-chlorophenyl)-2-hydroxy-2-phenylbutanoate (8a): The title compound was prepared according to Method G using 3.0 equiv phenylboronic acid and 3.0 equiv cesium fluoride. The reaction time was 48 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8a** as a clear oil (27.3 mg, .086 mmol, 86% yield) **Analytical data for 8a: ^{1}H NMR** (500 MHz, CDCl$_3$) δ = 7.80 (d, J = 8.0 Hz, 2H), 7.41–7.38 (m, 4H), 7.34–7.31 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 4.04–3.98 (m, 2H), 3.77 (s, 1H), 3.68 (q, J = 7.1 Hz, 1H), 1.17 (t, J = 7.2 Hz, 3H), 1.07 (d, 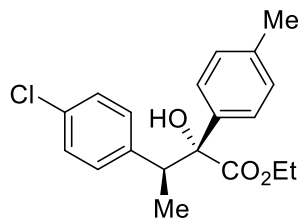J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CHCl$_3$): δ 174.4, 132.7, 130.4, 128.2, 128.1, 127.7, 126.1, 80.5, 62.5, 47.1, 15.2, 13.9; **IR** (thin film): 3501, 2935, 1727, 1490, 1248, 1014 cm^{-1}; HRMS (ESI+): Calcd. for C$_{18}$H$_{19}$ClO$_3$ ([M+Na]): 341.0920, Found: 341.0923; **HPLC** (99:1 hexanes:*i*PrOH, Daicel CHIRALPAK IC): 94:6 er, $t_{R \text{ (major)}}$ = 4.78 min, $t_{R \text{ (minor)}}$ = 5.86 min; **[α]$_D$** = -50.1 (c = 0.02, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.
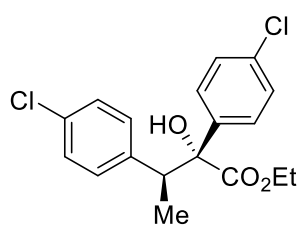

Ethyl (2*R*,3*S*)-3-(4-chlorophenyl)-2-hydroxy-2-(p-tolyl)butanoate (8b): The title compound was prepared according to Method G using 3.0 equiv of *p*-tolylboronic acid and 3.0 equiv of cesium fluoride. The reaction time was 48 h. The diastereoselectivity was

determined by analysis of the crude ¹H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8b** as an amorphous white solid (30.9 mg, .093 mmol, 93% yield). **Analytical data for 3b: ¹H NMR** (500 MHz, CDCl$_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.0 Hz), 4.04−3.95 (m, 2H), 3.74 (s, 1H), 3.65 (q, J = 7.1 Hz, 1H), 2.37 (s, 3H), 1.65 (t, J = 7.2 Hz, 3H), 1.07 (d, J = 7.2 Hz, 3H); ¹³C NMR (151 MHz, CDCl$_3$): δ 174.5, 140.5, 137.4, 137.4, 132.6, 130.4, 128.9, 128.0, 126.0, 80.4, 62.4, 47.0, 21.0, 15.2, 13.9; **IR** (thin film): 3502, 3030, 2980, 2936, 2874, 1725, 1508, 1492, 1248, 1138, 1041, 1016 cm⁻¹; **HRMS** (ESI+): Calcd. for C$_{19}$H$_{21}$ClO$_3$ ([M+Na]): 355.1077, Found: 355.1080; **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 96:4 er, $t_{R\ (major)}$ = 5.28 min, $t_{R\ (minor)}$ = 7.45 min; **[α]**$_D$ = -57.7 (c = 0.01, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.
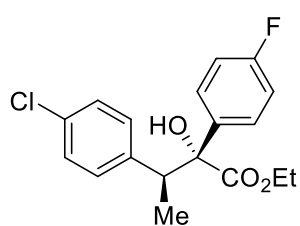

Ethyl (2R,3S)-2,3-bis(4-chlorophenyl)-2-hydroxybutanoate (8c): The title compound was prepared according to Method G using 5.0 equiv p-chlorophenylboronic acid and 5.0 equiv cesium fluoride. The reaction time was 48 h. The diastereoselectivity was determined by analysis of the crude ¹H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8c** as an amorphous white solid (28.6 mg, 0.081 mmol, 81% yield). **Analytical data for 8c: ¹H NMR** (500 MHz, CDCl$_3$) δ 7.73 (d, J = 8.6 Hz, 2H), 7.38−7.35 (m, 4H), 7.27 (d, J = 8.4 Hz, 2H), 4.06−3.97 (m, 2H), 3.76 (s, 1H), 3.61 (q,

J = 7.1 Hz), 1.17 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, CDCl$_3$):

δ 174.0, 140.0, 138.9, 133.7, 130.3, 128.3, 128.1, 127.7, 80.3, 62.7, 47.1, 15.06, 13.9; **IR**

(thin film): 3494, 2980, 2937, 2359, 1730, 1490, 1473, 1249, 1138, 1093; **HRMS** (ESI+):

Calcd. for C$_{18}$H$_{18}$Cl$_2$O$_3$ ([M+Na]): 375.0531, Found: 375.0538; **HPLC** (99:1

hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 96:4 er, $t_{R\ (major)}$ = 4.70 min, $t_{R\ (minor)}$ = 5.58 min;

**[α]$_D$** = -58.0 (c = .01, CHCl$_3$). TLC (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.

Ethyl (2R,3S)-3-(4-chlorophenyl)-2-(4-fluorophenyl)-2-hydroxybutanoate (8d): The title compound was prepared according to Method G using 5.0 equiv p-fluorophenylboronic acid and 5.0 equiv cesium fluoride. The procedure was modified for this product as follows: upon completion the reaction was allowed to cool to room temperature and 50 μL of ethanol were added, the resulting mixture was allowed to stir for 10 minutes before being filtered through a plug of silica gel using ethyl acetate to rinse and concentrated. When the work-up according to Method G was employed a large amount of inhomogenous material resulted, complicating extraction and crude ^{1}H NMR analysis. The reaction time was 48 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8d** as a clear oil (27.0 mg, .080 mmol, 80% yield). **Analytical data for 8d: ^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.76 (dd, J = 8.8, 5.4 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.08 (t, J = 8.7 Hz, 2H), 4.06−3.97 (m, 2H), 3.76 (s, 1H), 3.62 (q, J = 7.1 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (151MHz, CDCl$_3$) δ 174.2, 162.2 (d,

$J_{19F-13C}$ = 247 Hz), 140.1, 136.1 (d, $J_{19F-13C}$ = 3.1 Hz), 130.4, 128.1, 128.0 (d, $J_{19F-13C}$ = 8.1

Hz), 115.0 (d, $J_{19F-13C}$ = 71.6 Hz), 80.2, 62.7, 47.2, 15.1, 13.9; **19F NMR** (376 MHz, CDCl$_3$):

δ 115.2; **IR** (thin film): 3495, 2981, 2937, 1726, 1603, 1506, 1493, 1250, 1136, 1041, 1015

cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{18}$H$_{18}$ClFO$_3$ ([M+Na]): 359.0826, Found: 359.0832;

HPLC (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 95:5 er, $t_{R\ (major)}$ = 4.8, $t_{R\ (minor)}$ = 5.6

min; **[α]$_D$** = -54.8 (c = 0.01, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.5.
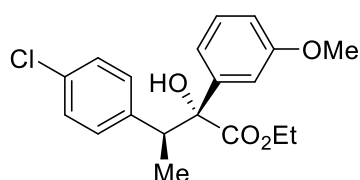
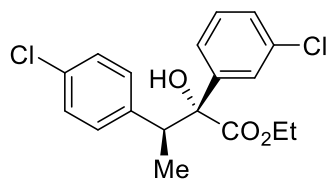**Ethyl (2R,3S)-3-(4-chlorophenyl)-2-hydroxy-2-(3-methoxyphenyl)butanoate (8e):** The title compound was prepared according to Method G using 3.0 equiv of *m*-methoxyphenylboronic acid and 3.0 equiv of cesium fluoride. The reaction time was 60

h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum.

The reaction was run in duplicate; the reported yields and enantioselectivities are

averages of two runs. The crude product was purified by silica gel column

chromatography using 2.5% ethyl acetate in hexanes affording **8e** as a clear oil (30.8 mg,

.088 mmol, 88% yield). **Analytical data for 8e:** ^{1}**H NMR** (500 MHz, CDCl$_3$) δ 7.39–

7.37 (m, 4H), 7.33–7.30 (m, 1H), 7.27 –7.25 (m, 2H), 6.88–6.86 (m, 1H), 4.06–3.97 (m,

2H), 3.85 (s, 3H), 3.77 (s, 1H), 3.65 (q, J = 7.1 Hz, 1H), 1.18 (t, J = 7.1 Hz, 3H), 1.08 (d, J

= 7.2 Hz, 3H); ^{13}**C NMR** (151 MHz, CDCl$_3$): δ 174.3, 159.5, 142.2, 140.4, 132.7, 130.4,

129.1, 128.0, 118.5, 112.9, 112.1; **IR** (thin film): 3502, 2979, 2936, 2835, 2360, 1725, 1600,

1583, 1491, 1457, 1255, 1136, 1041, 1015; **HRMS** (ESI+): Calcd. for C$_{19}$H$_{21}$ClO$_4$ ([M+Na]):

371.1026, Found: 371.1031; **HPLC** (98:2 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 96:4

er, $t_{R\ (major)}$ = 6.0 min, $t_{R\ (minor)}$ = 12.6 min; **[α]$_D$** = -35.6 (c = 0.01, CHCl$_3$). **TLC** (90:10

hexanes: ethyl acetate): R$_f$ = 0.3.
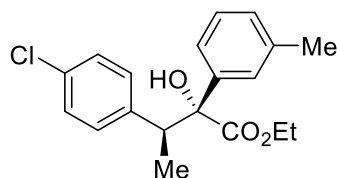
Ethyl (2R,3S)-3-(4-chlorophenyl)-2-hydroxy-2-(m-tolyl)butanoate (8f): The title compound was prepared according to Method G using 3.0 equiv of *m*-tolylboronic acid and 3.0 equiv of cesium fluoride. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8f** as a clear oil (30.0 mg, .090 mmol, 90% yield). **Analytical data for 8f: ^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.61–7.57 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.30–7.26 (m, 3H), 7.14 (d, *J* = 7.4 Hz, 1H), 4.04–3.96 (m, 2H), 3.76 (s, 1H), 3.68 (q, *J* = 7.1 Hz, 1H), 2.41 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 174.4, 140.5, 140.3, 137.8, 132.6, 130.4, 128.4, 128.1, 128.0, 126.7, 123.2, 62.5, 46.9, 21.7, 15.3, 13.9; **IR** (thin film): 3502, 2979, 2936, 2360, 2341, 1771, 1717, 1698, 1558, 1540, 1490, 1457, 1254, 1231, 1134, 1093 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{19}$H$_{21}$ClO$_3$ ([M+Na]): 355.1077, Found: 355.1079; **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 96:4 er, *t*$_{R (major)}$ = 4.48, *t*$_{R (minor)}$ = 5.53 min; **[α]$_D$** = -44.5 (c = 0.01, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.
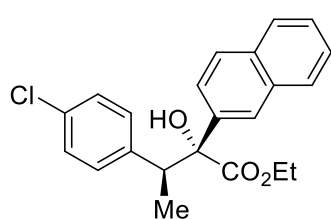
Ethyl (2R,3S)-2-(3-chlorophenyl)-3-(4-chlorophenyl)-2-hydroxybutanoate (8g): The title compound was prepared according to Method G using 6.0 equiv of 3-chlorophenylboronic acid and 6.0 equiv of cesium fluoride. The reaction was run for 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum.
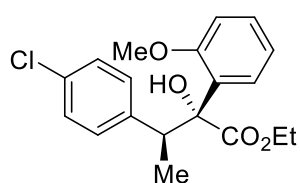
The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8g** as a clear oil (25.5 mg, 0.072 mmol, 72% yield). **Analytical data for 8g:** **¹HNMR** (500 MHz, CDCl$_3$): δ 7.82 (s, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.39–7.28 (m, 6H), 4.09–4.02 (m, 2H), 3.81 (s, 1H), 3.63 (q, J = 7.1 Hz, 1H), 1.20 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 7.1 Hz, 3H); **¹³C NMR** (151 MHz, CDCl$_3$): 173.8, 142.6, 139.9, 134.3, 132.9, 130.4, 129.4, 128.1, 127.9, 126.5, 124.4, 80.3, 62.8, 47.2, 15.1, 13.9; **IR** (thin film): 3524, 3502, 3481, 2979, 2936, 2359, 2340, 1748, 1732, 1717, 1698, 1569, 1558, 1541, 1507, 1418, 1248, 1139, 1015 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{18}$H$_{18}$Cl$_2$O$_3$: ([M+Na]): 375.0531, Found: 375.0542; **HPLC** (99:1 hexanes: ^{i}PrOH, Daicel CHIRALPAK IC): 94: 6 er, t$_{R\ (major)}$ = 4.55 min, t$_{R\ (minor)}$ = 5.90 min; **[α]$_D$** = -90.5 (c = 0.01, CHCl$_3$); **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.

Ethyl (2R,3S)-3-(4-chlorophenyl)-2-hydroxy-2-(naphthalen-2-yl)butanoate (8h): The title compound was prepared according to Method G using 3.0 equiv 2-naphthylboro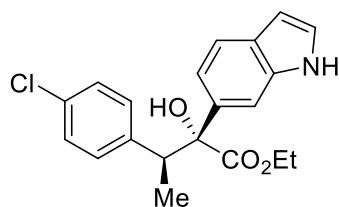nic acid and 3.0 equiv of CsF. The reaction was run for 48 h. The diastereoselectivity was determined by analysis of the crude ¹H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8h** as a white amorphous solid (30.3 mg, .082 mmol, 82% yield). **Analytical data for 8h**: **¹H NMR** (500 MHz, CDCl$_3$) δ 8.30 (s, 1H), 7.92–7.86 (m, 4H), 7.52–7.51 (m, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.91 (s, 1H), 3.83 (q, J = 7.1 Hz, 1H), 1.19

(t, J = 7.1 HZ, 3H), 1.10 (d, J = 7.2 Hz, 3H); **13C NMR** (151 MHz, CDCl$_3$): δ 174.3, 140.3, 137.7, 133.0, 132.8, 132.7, 130.5, 128.4, 128.1, 127.9, 127.4, 126.3, 126.2, 125.6, 124.0; **IR** (thin film): 3502, 3058, 2980, 2935, 2359, 1725, 1491, 1256, 1240, 1132 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{22}$H$_{21}$ClO$_3$ ([M+Na]): 391.1077, Found: 391.1084; **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 96.5:3.5 er, $t_{R\ (major)}$ = 4.8 min, $t_{R\ (minor)}$ = 6.9 min; **[α]$_D$** = -48.9 (c = 0.02, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.

Ethyl (2R,3S)-3-(4-chlorophenyl)-2-hydroxy-2-(2-methoxyphenyl)butanoate (8i): The title compound was prepared according to Method G using 6.5 equiv of 2-methoxyphenylboronic acid and 6.5 equiv of cesium fluoride. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using gradient elution from 2.5% ethyl acetate in hexanes to 5% ethyl acetate in hexanes affording **8i** as a clear oil. **Analytical data for 8i: ^{1}H NMR** (600 MHz, CDCl$_3$): δ (dd, J = 7.8, 1.0 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.32–7.30 (m, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.05– 7.03 (m, 1H), 6.92 (d, J = 8.2 Hz, 1H), 4.70 (s, 1H), 3.93 (q, J = 7.0 Hz, 1H), 3.89– 3.80 (m, 5H), 1.39 (d, J = 7.1 Hz, 3H), 0.99 (t, J = 7.1 Hz, 3H); **13C NMR** (151 MHz, CDCl$_3$): δ 173.7, 157.7, 140.7, 132.5, 131.0, 129.2, 129.0, 128.0, 127.8, 120.9, 111.7, 80.2, 61.3, 55.5, 43.4, 16.4, 13.8; **IR** (thin film): 2360.4, 1742.4, 1490, 1247, 1121, 1028 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{19}$H$_{21}$ClO$_4$ ([M+Na]): 371.1026, Found: 371.1027; **HPLC** (98:2 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 95.5:4.5 er, $t_{R\ (major)}$ = 8.2 min, $t_{R\ (minor)}$ = 11.7 min; **[α]$_D$** = -74.5 (c = 0.01, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.2.
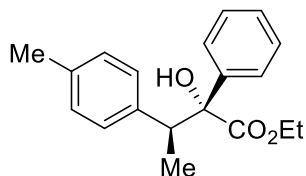
Ethyl (2R,3S)-3-(4-chlorophenyl)-2-hydroxy-2-(1H-indol-6-yl)butanoate (8j): The title compound was prepared according to Method G using 3.5 equiv of 6-indolylboronic acid and 3.5 equiv of cesium fluoride. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. **Note**: The reaction was run in triplicate and two of the trials were averaged; during the second trial it was noticed the reaction was not stirring due to the low solubility of 6-indoylboronic acid under the reaction conditions and in this run what is presumably the opposite diastereomer was observed in the crude ^{1}H NMR spectrum and the enantioselectivity was lower (89:11 er). Thus a third trial was run in a 20 mL scintillation with a larger stir bar (instead of a 1 dram vial) to promote stirring. The results from the third trial closely matched those obtained in the first trial. In this case the results from the first and third trial were averaged. This is the only instance where the first and second trials yielded inconsistent selectivities. The crude product was purified by silica gel column chromatography using 20% ethyl acetate in hexanes as eluent providing **8j** as a clear oil (24.4 mg, .068 mmol, 68% yield). **Analytical data for 8j:** ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.25 (br s, 1H), 7.87 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.54 (dd, J = 8.4, 1.3 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.25–7.24 (m, 1H), 6.56 (br s, 1H), 4.00 (q, J = 7.1 Hz, 2H), 3.85 (s, 1H), 3.78 (q, J = 14.3, 7.1 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 174.9, 140.7, 135.8, 134.4, 132.6, 130.5, 128.0, 127.1, 124.9, 120.3, 118.1, 109.1, 102.3, 80.8, 62.4, 47.1, 15.3, 13.9; **IR** (thin film): 3750, 2820, 2360, 2341, 1771, 1748, 1558, 1541, 1507, 1497, 1457, 1396; **HRMS** (ESI+): Calcd. for C$_{20}$H$_{20}$ClNO$_3$ ([M+1]): 358.1210, Found: 358.1218; **HPLC** (97:3

hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 94:6 er, $t_{R\ (major)}$ = 13.6 min, $t_{R\ (minor)}$ = 15.8 min;

[α]$_D$: -45.7 (c = .01, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.1.

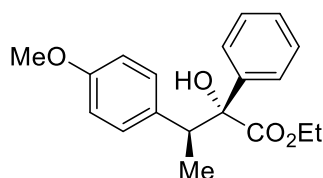**Ethyl (2R,3S)-2-hydroxy-2-phenyl-3-(p-tolyl)butanoate (8m):** The title compound was prepared according to Method G using 3.0 equiv of phenylboronic acid and 3.0 equiv of cesium fluoride. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8m** as an amorphous white solid (28.3 mg, .095 mmol, 95% yield). **Analytical data for 3m: ^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.83–7.82 (m, 2H), 7.41– 7.39 (m, 2H), 7.33–7.31 (m, 3H), 7.12–7.11 (d, J = 7.9 Hz, 2H), 4.04–3.96 (m, 2H), 3.74 (s, 1H), 3.69 (q, J = 7.1 Hz, 1H), 2.33 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 174.6, 140.6, 138.6, 136.5, 128.9, 128.7, 128.1, 127.5, 126.3, 80.8, 62.3, 47.2, 21.1, 15.1, 13.9; **IR** (thin film): 3501, 2361, 1731, 1535, 1496, 1457, 1240, 1157, 1031 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{19}$H$_{22}$O$_3$ ([M+Na]): 321.1467, Found: 321.1465; **HPLC** (99:1 hexanes:EtOAc, Daicel CHIRALPAK IA): 95:5 er, $t_{R\ (major)}$ = 8.3 min, $t_{R\ (minor)}$ = 7.6 min; **[α]$_D$** = -50.1 (c = 0.01, CHCl$_3$); **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.
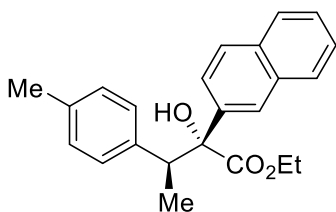
Ethyl (2R,3S)-2-hydroxy-2-(naphthalen-2-yl)-3-(p-tolyl)butanoate (8n): The title compound was prepared according to Method G using 3.0 equiv of 2-naphthylboronic acid and 3.0 equiv of cesium fluoride. The reaction time was 60
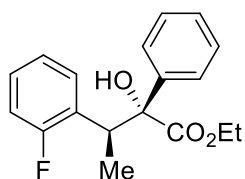
h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8n** as an amorphous white solid (28.6 mg, .082 mmol, 82%). **Analytical data for 8n: ^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.32 (s, 1H), 7.97–7.86 (m, 4H), 7.53–7.49 (m, 2H), 7.38 (d, J = 7.9, 2H), 7.15 (d, J = 7.8 Hz, 2H), 4.03 (q, J = 7.2 Hz, 2H), 3.87–3.83 (m, 3H), 2.35 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 174.6, 138.5, 137.9, 136.6, 133.0, 132.7, 128.9, 128.7, 128.4, 127.7, 127.4, 126.1, 126.1, 125.7, 124.3, 81.0, 62.4, 47.0, 21.1, 15.1, 13.9; **IR** (thin film): 3502, 3057, 2979, 2934, 2360, 1722, 1507, 1373, 1257, 1240, 1156, 1132, 1022, 824 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{23}$H$_{24}$O$_3$ ([M+Na]): 371.1623, Found: 371.1630; **HPLC** (98:2 hexane:^{i}PrOH, Daicel CHIRALPAK IC): 96:4 er, $t_{R\ (major)}$ = 5.7 min, $t_{R\ (minor)}$ = 7.1 min; **[α]$_D$** = -67.6 (c = 0.01, CHCl$_3$). **TLC** (90:10 hexanes; ethyl acetate): R$_f$ = 0.4.

Ethyl (2R,3S)-2-hydroxy-3-(4-methoxyphenyl)-2-phenylbutanoate (8o): The title compound was prepared according to Method G using 3.5 equiv of phenylboronic acid and 3.5 equiv of cesium fluoride. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using a gradient elution of 2.5% ethyl acetate in hexanes then 5% ethyl acetate in hexanes affording **8o** as a clear oil (25.5 mg,

0.081 mmol, 81% yield). **Analytical data for 8o:** ^{1}**H NMR** (500 MHz, CDCl$_3$) δ 7.81 (d, J = 7.6 Hz, 2H), 7.41–7.30 (m, 5H), 6.84 (d, J = 8.7 Hz, 2H), 4.03–3.97 (m, 2H), 3.80 (s, 3H), 3.74 (s, 1H), 3.68 (q, J = 7.1 Hz, 1H), 1.18 (t, J = 7.2 Hz, 3H), 1.07 (d, J = 7.2 Hz, 3H); ^{13}**C NMR** (600 MHz, CDCl$_3$): δ 174.6, 158.5, 140.6, 133.8, 130.0, 128.1, 127.5, 126.2, 113.3, 80.8, 62.4, 55.1, 46.8, 15.2, 13.9; **IR** (thin film): 3724, 2835, 1868, 1733, 1716, 1558, 1541, 1509, 1457, 1246; **HRMS** (ESI+): Calcd. for C$_{19}$H$_{22}$O$_4$ ([M+Na]): 337.1416, Found: 337.1416; **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 94:6 er, $t_{R\ (major)}$ = 10.6 min, $t_{R\ (minor)}$ = 12.6 min; **[α]$_D$:** -74.5 (c = 0.01, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.
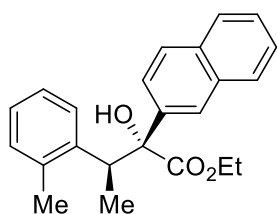
Ethyl (2R,3S)-3-(2-fluorophenyl)-2-hydroxy-2-phenylbutanoate (8p): The title compound was prepared according to Method G using 3.0 equiv of phenylboronic acid and 3.0 equiv of cesium fluoride. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8p** as a clear oil (20.7 mg, .069 mmol, 69% yield). **Analytical data for 8p:** ^{1}**H NMR** (500 MHz, CDCl$_3$): δ 7.83 (d, J = 7.7 Hz, 2H), 7.77–7.74 (m, 1H), 7.41 (app t, J = 7.5 Hz, 2H), 7.34–7.31 (m, 1H), 7.22–7.18 (m, 1H), 7.11 (app t, J = 7.6 Hz, 1H), 7.03–6.99 (m, 1H), 4.20 (q, J = 7.2 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 3.92 (s, 1H), 1.12 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 7.2 Hz); ^{13}**C NMR** (151 MHz, CDCl$_3$): δ 174.8, 160.0 (d, $J_{^{19}F-^{13}C}$ = 245.3 Hz), 140.6, 130.2 (d, $J_{^{19}F-^{13}C}$ = 3.4 Hz), 129.2 (d, $J_{^{19}F-^{13}C}$ = 14.2 Hz), 128.2 (d, $J_{^{19}F-^{13}C}$ = 8.5 Hz), 128.1, 127.7, 126.2, 124.0 (d, $J_{^{19}F-^{13}C}$ = 3.4 Hz), 114.8 (d, $J_{^{19}F-^{13}C}$ = 23.9 Hz), 80.4, 62.7,

38.1 (d, $J_{19F-13C}$ = 2.6 Hz), 15.2, 13.5; **19F NMR** (376 MHz, CDCl$_3$): δ 117.9; **IR** (thin film): 3649, 2360, 1867, 1733, 1716, 1558, 1541, 1507, 1489, 1457; **HRMS** (ESI+): Calcd. for C$_{18}$H$_{19}$FO$_3$ ([M+Na]): 325.1216, Found: 325.1214; **HPLC** (98:2 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 92:8 er, $t_{R\ (major)}$ = 4.4 min, $t_{R\ (minor)}$ = 4.7 min; **[α]$_D$** = -37.7 (c = 0.01, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.
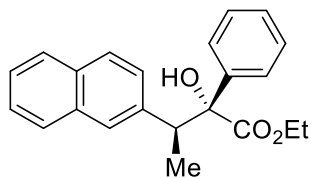

Ethyl (2R,3S)-2-hydroxy-2-(naphthalen-2-yl)-3-(o-tolyl)butanoate (8q): The title compound was prepared according to Method G using 3.50 equiv of 2-naphthylboronic acid and 3.50 equiv of cesium fluoride. The reaction was run for 48 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. Note in this instance the reaction did not reach full conversion. One trial reached 80% conversion while the other reached 84% conversion by analysis of the crude ^{1}H NMR spectrum. Further optimization of the reaction parameters for this substrate was not pursued. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8q** as a light yellow oil (19.0 mg, .055 mmol, 55% yield). **Analytical data for 8q:** ^{1}**H NMR** (500 MHz, CDCl$_3$): δ 8.33 (s, 1H), 7.95−7.86 (m, 5H), 7.53− 7.49 (m, 2H), 7.21−7.11 (m, 3H), 4.13 (s, 1H), 4.07 (q, J = 7.1 Hz, 1H), 3.98− 3.87 (m, 2H), 2.53 (s, 3H), 1.10 (d, J = 7.1 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H); **13C NMR** (151 MHz, CDCl$_3$): 174.7, 141.4, 138.8, 135.5, 133.0, 132.7, 130.0, 128.5, 127.8, 127.6, 127.4, 126.5, 126.2, 126.2, 126.1, 125.6, 124.0, 81.1, 62.4, 41.8, 20.1, 15.8, 13.5; **IR** (thin film): 3565.7; 3545.5, 2966, 2930, 2319, 1771, 1733, 1716, 1558, 1541, 1521, 1507, 1457, 1256, 1241, 1021 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{23}$H$_{24}$O$_3$: ([M+Na]): 371.1623, Found:

371.1624; **HPLC** (99:1 hexanes:*i*PrOH, Daicel CHIRALPAK IC): 94:6 er, t$_{R\ (major)}$ = 6.2 min, t$_{R\ (minor)}$ = 9.2 min; **[α]$_D$** = -14.7 (c = 0.01, CHCl$_3$); **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.
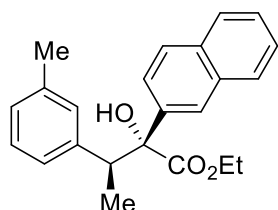
Ethyl (2R,3S)-2-hydroxy-2-(naphthalen-2-yl)-3-(m-tolyl)butanoate (8r): The title compound was prepared according to Method G using 3.50 equiv of 2-naphthylboronic acid and 3.50 equiv of CsF. The reaction was run for 48 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8r** as an amorphous solid (29.7 mg, .085 mmol, 85% yield). **Analytical data for 8r:** ^{1}**H NMR** (500 MHz, CDCl$_3$): δ 8.32 (s, 1H), 7.96 −7.86 (m, 4H), 7.53–7.49 (m, 2H), 7.29–7.27 (m, 2H), 7.23–7.20 (m, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 4.05–3.98 (m, 2H), 3.86–3.81 (m, 2H), 2.37 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.2 Hz, 3H); ^{13}**C NMR** (151 MHz, CDCl$_3$)**:** δ 174.5, 141.5, 137.9, 137.40, 133.0, 132.7, 129.9, 128.4, 127.9, 127.8, 127.7, 127.4, 126.1, 126.1, 126.0, 125.7, 124.2, 80.9, 62.4, 47.4, 21.5, 15.1, 13.9; **IR** (thin film): 3587, 3566, 3502, 2978, 2933, 2359, 2330, 1748, 1732, 1717, 1558, 1541, 1507, 1457, 1258, 1238, 1131, 1023 cm^{-1} **HRMS** (ESI+): Calcd. for C$_{23}$H$_{24}$O$_3$: ([M+Na]): 371.1623, Found: 371.1631; **[α]$_D$** = -63.2 (c = 0.02, CHCl$_3$); **HPLC** (99:1 hexanes:*i*PrOH, Daicel CHIRALPAK IC): 96.5:3.5 er, t$_{R\ (major)}$ = 6.7 min, t$_{R\ (minor)}$ = 8.7 min; **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.
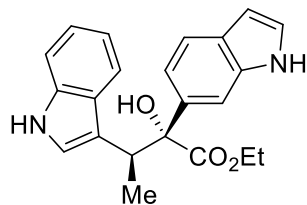
Ethyl (2R,3S)-2-hydroxy-3-(naphthalen-2-yl)-2-phenylbutanoate (8s): The title compound was prepared according to Method G using 3.50 equiv of phenylboronic acid and 3.50 equiv of cesium fluoride. The reaction was run for 48 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8s** as an amorphous solid (24.5 mg, 0.073 mmol, 73% yield). **Recrystallization:** A suspension of **8s** (24.5 mg) in hexanes was heated until complete dissolution was observed. Allowing the resulting solution to stand at room temperature for 24 h provided crystalline **8s** (16.1 mg, 0.048 mmol, 48% yield) enriched to 97.5:2.5 er. Analytical data for 3s: **^{1}H NMR** (500 MHz, CDCl$_3$): 7.89–7.78 (m, 6H), 7.64–7.62 (m, 1H), 7.49–7.42 (m, 4H), 7.36–7.33 (m, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.90 (q, J = 7.1 Hz, 1H), 3.84 (s, 1H), 1.20 (d, J = 7.1 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): 174.5, 140.6, 139.4, 133.2, 132.6, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 126.2, 125.8, 125.5, 80.9, 62.4, 47.8, 15.2, 13.9; **IR** (thin film): 3524, 3502, 3481, 3460, 3057, 2979, 2935, 2874, 2359, 2340, 2089, 1770, 1718, 1698, 1519, 1507, 1489, 1446, 1249, 1137, 1023 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{22}$H$_{22}$O$_3$: ([M+Na]): 357.1467, Found: 357.1468; **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 94:6 er, t$_{R\ (major)}$ = 9.7 min, t$_{R\ (minor)}$ = 12.4 **[α]$_D$** = -85.2 (c = 0.01, CHCl$_3$); **mp** 94 – 96 °C. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4

Ethyl (2R,3S)-2-hydroxy-3-(1H-indol-3-yl)-2-(1H-indol-6-yl)butanoate (8t): The title compound was prepared according to Method G using 3.50 equiv 1H-indol-6-ylboronic acid and 3.50 equiv of cesium fluoride. The procedure was modified for this product as follows: upon completion the reaction was allowed to cool to room temperature and 200 µL of ethanol were added, the resulting mixture was allowed to stir for 10 minutes before being filtered through a plug of silica gel using ethyl acetate to rinse and concentrated. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 20% ethyl acetate in hexanes followed by 40% ethyl acetate in hexanes affording **8t** as an off white solid (26.7 mg, 0.074 mmol, 74% yield). **Analytical data for 8t: ^{1}H NMR** (600 MHz, CDCl$_3$): δ 8.30 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.71–7.66 (m, 2H), 7.36–7.34 (m, 2H), 7.24–7.23 (m, 1H), 7.21–7.15 (m, 2H), 6.58–6.58 (m, 1H), 4.26 (q, J = 7.1 Hz, 1H), 4.07 (s, 1H), 3.87–3.82 (m, 1H), 3.73–3.68 (m, 1H), 1.18 (d, J = 7.2 Hz, 3H), 0.94 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): 175.6, 135.8, 135.5, 134.7, 127.2, 127.0, 124.8, 122.9, 121.7, 120.2, 119.3, 119.0, 118.4, 117.0, 111.0, 109.2, 102.2, 81.2, 62.2, 38.5, 16.3, 13.5; **IR** (thin film): 3459, 3413, 2978, 2934, 2359, 2340, 1733, 1716, 1699, 1521, 1507, 1497, 1456, 1339, 1259, 1016 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{22}$H$_{22}$N$_2$O$_3$: ([2M+Na]): 747.3159, Found: 747.3187; **HPLC** (80:20 hexanes:^{i}PrOH, Daicel CHIRALPAK IA): 96:4 er, t$_{R (major)}$ = 10.9 min, t$_{R (minor)}$ = 20.4 min; **[α]$_D$** = -21.0 (c = 0.01). **TLC** (70:30 hexanes:ethyl acetate): R$_f$ = 0.1.
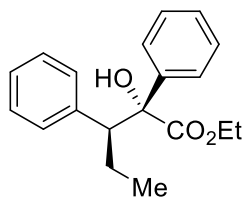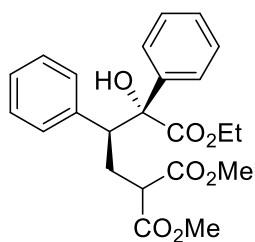
Ethyl (2R,3S)-2-hydroxy-2,3-diphenylpentanoate (8u): The title compound was prepared according to Method G Procedure C using 3.5 equiv of phenylboronic acid and 3.5 equiv of cesium fluoride. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 2.5% ethyl acetate in hexanes affording **8u** as a clear oil (22.4 mg, .075 mmol, 75% yield). **Analytical data for 3u:** ^{1}**H NMR** (500 MHz, CDCl$_3$): δ 7.83–7.82 (m, 2H), 7.44– 7.39 (m, 4H), 7.34–7.29 (m, 3H), 7.25–7.23 (m, 1H), 3.99–3.89 (m, 2H), 3.86 (s, 3H), 3.38 (dd, J = 11.8, 3.0 Hz, 1H), 1.81–1.71 (m, 1H), 1.45–1.37 (m, 1H), 1.13 (t, J = 7.2 Hz, 3H), 0.60 (t, J = 7.4 Hz); ^{13}**C NMR** (151 MHz, CDCl$_3$): δ 174.5, 140.8, 139.6, 129.8, 128.1, 127.9, 127.5, 127.0, 126.3, 80.9, 62.4, 55.6, 21.8, 13.8, 12.3; **IR** (thin film): 3649, 2963, 1717, 1558, 1541, 1507, 1246, 1133 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{19}$H$_{22}$O$_3$ ([M+Na]): 321.1467, Found: 321.1467; **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALCEL OJ-H): 93:7 er, $t_{R\,(major)}$ = 7.5 min, $t_{R\,(minor)}$ = 6.2 min; **[α]$_D$** = -60.3 (c = 0.01, CHCl$_3$); **mp** 80 – 82 °C. **TLC** (90:10 hexanes: ethyl acetate): 0.4.
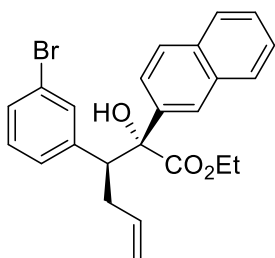
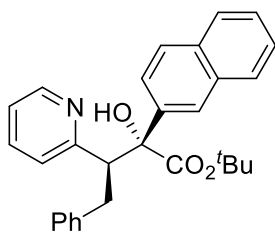**Ethyl (2R,3S)-3-(3-bromophenyl)-2-hydroxy-2-(naphthalen-2-yl)hex-5-enoate (8v):** The title compound was prepared according to Method G using 3.0 equiv of 2-naphthylboronic acid and 3.0 equiv of cesium fluoride. The reaction time was 60 h. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by preparatory thin layer chromatography on silica gel using 5% ethyl acetate in hexanes as aluent affording **8v** as a clear oil (19.9 mg, .045 mmol, 45% yield). Note: This yield is based off of starting material that contained ~6% toluene as an impurity. **Analytical data for 8v**: **¹H NMR** (600 MHz, CDCl$_3$) δ 8.30 (s, 1H), 7.92−7.85 (m, 4H), 7.62 (s, 1H), 7.54−7.50 (m, 2H), 7.44 (d, J = 7.7 Hz, 1H), 7.40−7.39 (m, 1H), 7.20 (app t, J = 7.8 Hz, 1H), 5.42−5.35 (m, 1H), 4.77−4.74 (m, 2H), 4.07−3.98 (m, 2H), 3.68 (dd, J = 11.9, 3.2 Hz, 1H), 2.56−2.50 (m, 1H), 2.14− 2.10 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H); **¹³C NMR** (151 MHz, CDCl$_3$): δ 174.0, 141.5, 137.4, 136.0, 133.2, 133.0, 132.8, 130.2, 129.6, 128.5, 128.4, 128.0, 127.4, 126.4, 126.3, 125.7, 123.8, 122.0, 116.4, 80.8, 62.9, 53.0, 33.3, 13.9; **IR** (thin film): 3649, 3628, 3502, 2979, 2360, 1733, 1717, 1698, 1558, 1540, 1507, 1237 cm^{-1}; **HRMS** (ESI+): Calcd. forC$_{24}$H$_{23}$BrO$_3$: ([M+Na]): 461.0728, Found: 461.0743; **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 97:3 er, $t_{R\ (major)}$ = 5.5 min, $t_{R\ (minor)}$ = 7.9 min; **[α]$_D$** = -55.3 (c = 0.01, CHCl$_3$). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3.

4-Ethyl 1,1-dimethyl (3S,4R)-4-hydroxy-3,4-diphenylbutane-1,1,4-tricarboxylate (8w): The title compound was prepared according to Method G using 3.50 equiv of phenylboronic acid and 3.50 equiv of cesium fluoride. The reaction

was run for 48 h. The diastereoselectivity was determined by ¹H NMR analysis of the crude reaction mixture. The reaction was run in duplicate, the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using a gradient of 5% to 10% to 20% ethyl acetate in hexanes affording **8w** as an amorphous white solid (34.1 mg, 0.0823 mmol, 82% yield, based off of ~86% pure starting material). **Recrystallization:** A suspension of **8w** (34.2 mg) in hexanes was gradually heated while titrating with ethyl acetate until complete dissolution was observed. The resulting solution was allowed to stand at room temperature for 36 h affording crystalline **8w** (17.8 mg, 0.043 mmol, 43%) enriched to >99.5:0.5 er.

Analytical data for 3w: ¹H NMR (500 MHz, CDCl₃): δ 7.81– 7.79 (m, 2H), 7.43–7.40 (m, 4H), 7.34–7.25 (m, 4H), 3.96–2.86 (m, 3H), 3.67–3.64 (m, 4H), 3.53 (s, 3H), 2.95 (dd, J = 11.5, 3.8 Hz, 1H), 2.36–2.30 (m, 1H), 2.05–1.99 (m, 1H), 1.09 (t, J = 7.2Hz, 3H), **¹³C NMR:** δ 174, 169.7, 169.4, 139.8, 137.7, 129.8, 128.3, 128.2, 127.9, 127.7, 126.3, 80.6, 62.6, 52.4, 52.2, 50.5, 49.4, 28.3, 13.8; **IR** (thin film): 3524, 3502, 3481, 3059, 3030, 2980, 2953, 2845, 2357, 2328, 2089, 1770, 1749, 1717, 1569, 1558, 1507, 1456, 1241, 1025 cm⁻¹; **HRMS** (ESI+): Calcd. for $C_{23}H_{26}O_7$: ([M+Na]): 437.2576, Found: 437.1593; **HPLC** (85:15 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 90:10 er, t$_{R\ (major)}$ = 7.8 min, t$_{R\ (minor)}$ = 22.5 min; **[α]**$_D$ = -55.1 (c = 0.02); **Mp**: 108 – 110 °C. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.1.
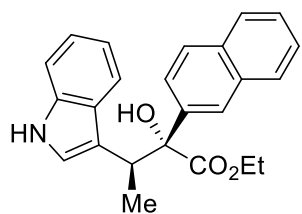

***Tert*-butyl (2R,3S)-2-hydroxy-2-(naphthalen-2-yl)-4-phenyl-3-(pyridin-3-yl)butanoate (8x):** The title compound was prepared according to Method G using 4.0 equiv of 2-naphthylboronic acid and 4.0 equiv of CsF. The procedure was

modified for this product as follows: upon completion the reaction was allowed to cool to room temperature and 200 μL of ethanol were added, the resulting mixture was allowed to stir for 10 minutes before being filtered through a plug of silica gel using ethyl acetate to rinse and concentrated. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 20% ethyl acetate in hexanes affording **8x** as an off white amorphous solid (30.4 mg, 0.069 mmol, 69% yield). **Recrystallization:** A suspension of **8x** in hexanes was gradually heated while titrating with ethyl aetate until complete dissolution was observed. The resulting solution was allowed to stand at room temperature for 36 h affording crystalline **8x** (10.1 mg, 0.023 mmol, 23%) enriched to >99.5: 0.5 er. **Analytical data for 8x: ^{1}H NMR** (500 MHz, CDCl$_3$): 8.45–8.39 (m, 3H), 8.02–7.90 (m, 5H), 7.55–7.54 (m, 2H), 7.25–7.22 (m, 1H), 7.04–6.99 (m, 2H), 4.29 (s, 1H), 3.80 (d, J = 11.6 Hz, 1H), 2.96–2.78 (m, 2H), 1.21 (s, 9H); **^{13}C NMR** (151 MHz, CDCl$_3$): 172.9, 151.8, 148.4, 139.5, 138.1, 136.9, 135.2, 133.1, 132.9, 128.8, 128.5, 128.1, 128.0, 127.5, 126.4, 126.3, 125.9, 125.8, 123.6, 123.0, 84.2, 81.0, 53.2, 36.1, 27.5; **IR** (thin film): 3566, 3545, 3027, 2977, 2930, 2353, 2321, 1733, 1716, 1698, 1558, 1521, 1507, 1457, 1372, 1269, 1151, 1028 cm^{-1}; **HRMS** (ESI+): C$_{29}$H$_{29}$NO$_3$: ([M+1]): 440.2226, Found: 440.2214; **HPLC** (87.5:12.5 hexanes:^{i}PrOH, Daicel CHIRALPAK IA): 98.5:1.5 er, t$_{R (major)}$ = 6.8 min, t$_{R (minor)}$ = 10.9 min; **[α]$_D$** = -27.9 (c = 0.02); **Mp** 159 − 161 °C. **TLC** (70:30 hexanes: ethyl acetate): R$_f$ = 0.2.

Ethyl (2R,3S)-3-(4-bromophenyl)-2-hydroxy-2-(naphthalen-2-yl)butanoate (8y): The title compound was prepared according to Method G. **Analytical data for**

8y: **¹H NMR** (600 MHz, CDCl$_3$): δ 8.28 (s, 1H), 7.91–7.85 (m, 4H), 7.53–7.49 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.88 (s, 1H), 3.81 (q, J = 7.1 Hz, 1H), 1.18 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 7.1 Hz, 3H); **¹³C NMR** (151 MHz, CDCl$_3$): δ 174.3, 140.8, 137.7, 133.0, 132.7, 131.1, 130.9, 130.8, 128.4, 127.8, 127.4, 126.2, 126.2, 125.6, 123.9, 120.9, 80.7, 62.6, 46.9, 15.2, 13.9; **IR** (thin film): 3750, 3734, 2360, 1868, 1845, 1733, 1716, 1698, 1558, 1541, 1507, 1497, 1457, 1240; **HRMS** (ESI+): Calcd. for C$_{22}$H$_{21}$BrO$_3$ ([M+Na]): 435.0572, Found: 435.0582; **HPLC** (99:1 hexanes:^{i}PrOH, Daicel CHIRALPAK IC), 97:3 er, $t_{R\ (major)}$ = 6.8 min, $t_{R\ (minor)}$ = 10.9 min; **[α]$_D$** = -46.0 (c = 0.01, CHCl$_3$); **Mp** 118 – 120 °C. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.4.

Ethyl   (2R,3S)-2-hydroxy-3-(1H-indol-3-yl)-2-(naphthalen-2-yl)butanoate (19):

The title compound was prepared according to Method G using 3.50 equiv 2-naphthylboronic acid and 3.50 equiv of cesium fluoride. The procedure was modified for this product as follows: upon completion the reaction was allowed to cool to room temperature and 200 μL of ethanol were added, the resulting mixture was allowed to stir for 10 minutes before being filtered through a plug of silica gel using ethyl acetate to rinse and concentrated. The reaction time was 60 h. The diastereoselectivity was determined by analysis of the crude ¹H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using 10:90 followed by 20% ethyl acetate= in hexanes affording **19** as an amorphous solid (27.3 mg, 0.073 mmol, 73%).

Analytical data for 19: **¹H NMR** (500 MHz, CDCl₃): δ 8.37 (s, 1H), 8.12 (s, 1H), 8.04–8.02 (m, 1H), 7.95–7.83 (m, 4H), 7.54–7.49 (m, 2H), 7.37–7.35 (m, 2H), 7.22–7.16 (m, 2H), 4.30 (q, J = 7.1 Hz, 1H), 4.08 (s, 1H), 3.91–3.84 (m, 1H), 3.76–3.70 (m, 1H), 1.18 (d, J = 7.2 Hz, 3H), 0.97 (t, J = 7.1 Hz, 3H); **¹³C NMR** (500 MHz, CDCl₃): δ 175.0, 138.1, 135.6, 133.1, 132.7, 128.4, 127.7, 127.4, 127.1, 126.1, 126.1, 125.6, 124.3, 122.9, 121.8, 119.3, 119.1, 116.7, 111.0, 81.1, 62.3, 38.4, 16.2, 13.5; **IR** (thin film): 3566, 3545, 3420, 2977, 2932, 2358, 2323, 1733, 1716, 1698, 1558, 1541, 1507, 1457, 1259, 1242, 1017 cm⁻¹; **HRMS** (ESI+): Calcd. for C₂₄H₂₃NO₃: ([M+1]): 374.1756, Found: 374.1758; HPLC (87.5:12.5 hexanes:^{i}PrOH, Daicel CHIRALPAK IA): 96:4 er, t$_R$ (major) = 9.3 min, t$_R$ (minor) = 26.4 **[α]$_D$** = -36.9 (c = 0.01). **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.1.
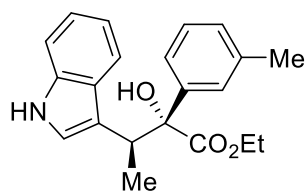
Ethyl (2R,3S)-2-hydroxy-3-(1H-indol-3-yl)-2-(m-tolyl)butanoate (20):

The title compound was prepared according to Method G using 3.50 equiv m-tolylboronic acid and 3.50 equiv of cesium fluoride. The procedure was modified for this product as follows: upon completion the reaction was allowed to cool to room temperature and 200 μL of ethanol were added, the resulting mixture was allowed to stir for 10 minutes before being filtered through a plug of silica gel using ethyl acetate to rinse and concentrated. The reaction time was 48 h. The diastereoselectivity was determined by analysis of the crude ¹H NMR spectrum. The reaction was run in duplicate; the reported yields and enantioselectivities are averages of two runs. The crude product was purified by silica gel column chromatography using a gradient of 5% to 10% to 20% ethyl acetate in hexanes affording **20** as a light yellow oil (21.5 mg, 0.064 mmol, 64% yield). **Analytical data for 20:** **¹H NMR** (500 MHz, CDCl₃): 8.08 (s, 1H), 7.80 (d, J =

7.7 Hz, 1H), 7.69–7.67 (m, 2H), 7.35–7.30 (m, 3H), 7.19–7.13 (m, 3H), 4.14 (q, J = 7.2 Hz, 1H), 3.94 (s, 1H), 3.88–3.81 (m, 1H), 3.71–3.65 (m, 1H), 2.43 (s, 3H), 1.15 (d, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (500 MHz, CDCl$_3$): δ 175.2, 140.6, 137.7, 135.5, 128.2, 128.0, 127.2, 126.9, 123.4, 122.8, 121.7, 119.3, 119.0, 116.8, 111.0, 80.9, 62.2, 38.5, 21.7, 16.3, 13.5; **IR** (thin film): 3502, 3414, 2977, 2931, 2360, 2341, 1716, 1683, 1539, 1506, 1487, 1456, 1256, 1233, 1153, 1017 cm^{-1}; **HRMS** (ESI+): Calcd. for C$_{21}$H$_{23}$NO$_3$: ([M+1]): 338.1756, Found: 338.1760; HPLC (97:3 hexanes:^{i}PrOH, Daicel CHIRALPAK IC): 94.8:5.2 er, t$_{R\ (major)}$ = 16.2 min, t$_{R\ (minor)}$ = 14.8 min; **[α]$_D$** = -17.5 (c = 0.01, CDCl$_3$); **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.1.

Iodoetherification to form 15v:

Ethyl   (*2R,3S*)-3-(3-bromophenyl)-2-hydroxy-2-(naphthalen-2-yl)hex-5-enoate   8**3v** (67.0 mg, 0.153 mmol) was dissolved in acetonitrile (2.40 mL, 0.064M) in a round-bottomed flask equipped with a stir bar. Sodium carbonate (24.2 mg, 0.229 mmol, 1.5 equiv) was added and the flask was covered with aluminum foil. Iodine (77.4 mg, 0.31 mmol, 2.0 equiv) was added and the reaction was stirred at room temperature under an atmosphere of N$_2$ for 24 h before being quenched with saturated aqueous Na$_2$S$_2$O$_3$ until a colorless solution was observed. The mixture was diluted further with water (20.0 mL) and extracted three times with methylene chloride (12.0 mL per extraction). The combined organic layers were dried over anhydrous MgSO$_4$. Upon concentration the crude residue was analyzed by ^{1}H NMR analysis, indicating the formation of an equimolar mixture of diastereomers. The residue was purified by silica gel column chromatography (2.5% ethyl acetate/hexanes then 5% ethyl acetate/hexanes) which enabled separation of the diastereomeric mixture (diastereomer 1: 29.3 mg, diastereomer 2: 27.4 mg, 0.10 mmol

combined, 66% combined yield). **Analytical data for diastereomer 1: ^{1}H NMR** (500 MHz, CDCl$_3$): δ 8.10 (s, 1H), 7.89–7.85 (m ,3H), 7.66–7.64 (m, 1H), 7.54 – 7.50 (m, 3H), 7.44–7.43 (m, 1H), 7.32 –7.31 (m, 1H), 7.24–7.21, 4.43–4.37 (m, 1H), 4.00 (app t, 1H), 3.85 (q, J = 7.1 Hz, 2H), 3.70 (dd, J = 9.7, 4.8 Hz, 1H), 3.50 (app t, 1H), 2.71–2.66 (m, 1H), 2.18–2.12, (m, 1H), 0.91 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 170.1, 142.9, 137.6, 132.8, 132.8, 131.4, 130.4, 130.1, 128.4, 128.0, 127.5, 127.1, 126.4, 126.3, 124.9, 124.4, 122.4, 91.6, 78.3, 61.4, 55.3, 40.8, 13.6, 7.2; **HRMS** (ESI+): Calcd. for C$_{24}$H$_{22}$BrIO$_3$: ([M+1]): 564.9875, Found: 564.9881. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.3. **Analytical data for diastereomer 2: ^{1}H NMR** (600 MHz, CDCl$_3$): δ 8.19 (s, 1H), 7.90–7.85 (m, 3H), 7.76–7.75 (m, 1H), 7.55–7.51 (m, 3H), 7.44–7.43 (m, 1H), 7.32–7.31 (m, 1H), 7.24–7.22 (m, 1H); 4.91–4.86 (m, 1H), 4.13 (dd, J = 7.6, 3.7 Hz, 1H), 3.91–3.82 (m, 2H), 3.61 (dd, J = 9.4, 4.2 Hz, 1H), 3.06 (app t, 1H), 2.53–2.49 (m, 1H), 2.11–2.07 (m, 1H), 0.89 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 170.32, 142.6, 138.2, 132.9, 132.7, 131.2, 130.4, 130.2, 128.4, 127.9, 127.5, 126.7, 126.6, 126.4, 125.2, 124.1, 122.6, 92.0, 79.8, 61.4, 54.6, 39.6, 13.6, 9.7; **HRMS** (ESI+): Calcd. for C$_{24}$H$_{22}$BrIO$_3$: ([M+1]): 564.9875, Found: 564.9872. **TLC** (90:10 hexanes: ethyl acetate): R$_f$ = 0.2.

Note on structural assignment: Both compounds exhibit ^{13}C resonances above 10.0 ppm, this is consistent with the heavy atom effect and a primary alkyl iodide. The methine resonances at ca. 4.40 ppm for diastereomer 1 and 4.85 ppm for diastereomer 2 do not show correlation to these upfield ^{13}C signals in an HSQC experiment but instead correlate with ^{13}C signals at 78.3 ppm and 79.8 ppm, respectively. This data suggests tetrahydrofurans bearing primary alkyl iodides rather than tetrahydropyrans containing secondary alkyl iodides.

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Chapter III Palladium-Catalyzed β-Arylation of α-Keto Esters

3.1 Introduction

In the previous chapter a chiral (diene)rhodium(I) complex catalyzed enantioconvergent arylation of α-keto esters was described.[1] The reduced activity of highly electron deficient boronic acids prevented access to heteroaryl tertiary glycolates. Heteroaromatic rings, especially pyridine derivatives, are encountered frequently as important structural units of small molecule therapeutics.[2] Therefore, we sought to incorporate this functionality in the α-keto ester precursor. Initial attempts to access a pyridyl-substituted α-keto ester via the aerobic deacylation used for analogous carbocyclic starting compounds failed (**Scheme 3-1**, eq. 1).[3] Similarly, oxidation of the corresponding α-hydroxy ester failed to deliver the targeted α-keto esters (**Scheme 3-1**, eq. 2).

**Scheme 3-1** Challenges During Synthesis of Pyridyl Substrates
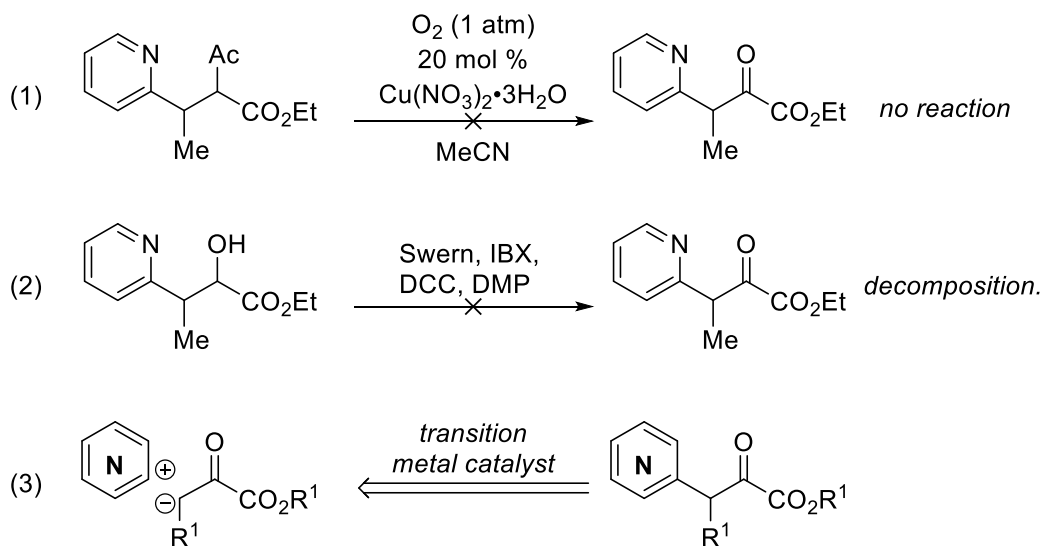
Considering the limitations with known methods, the development of a novel route toward β-heteroaryl α-keto esters was necessary. Harnessing the nucleophilic nature of α-keto esters by reaction with a heteroaryl electrophile would constitute an underutilized strategy for the synthesis of these compounds.

Scheme 3-2 Semmelhack's Seminal Report of an Enolate Arylation Reaction
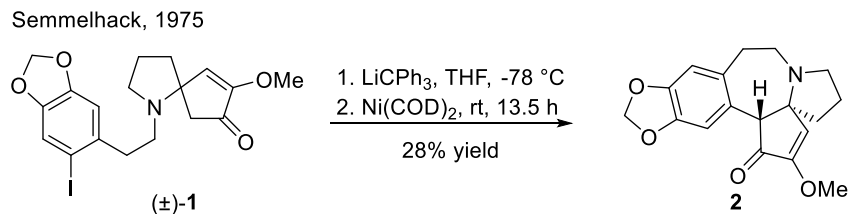

Since Semmelhack's pioneering report of a transition metal-catalyzed carbonyl arylation,[4] which described the synthesis of cephalotaxinone **2** using a preformed enolate derived from iodoketone **1** (**Scheme 3-2**), the scope of this general transformation has dramatically expanded. The reaction has grown to include the use of ketones, aldehydes, amides, esters, amino acids, nitriles, and activated methylene compounds as substrates.[5-10] The mechanism of this transformation is shown below (**Scheme 3-3**). Modern variants employ Pd[0]/phosphine derived catalysts and proceed via direct enolization under the action of inorganic bases.

Scheme 3-3 Mechanism of Transition Metal-Catalyzed Enolate Coupling
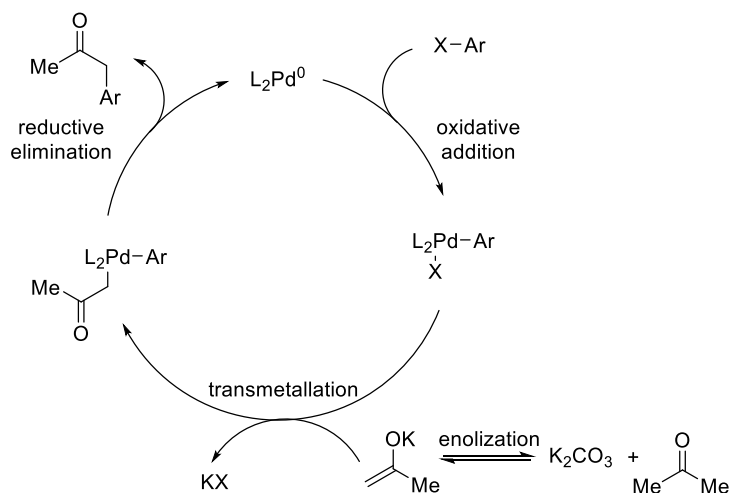
While the relatively high acidity of α-keto esters would be an enabling feature, we perceived several challenges associated with our reaction design. First, a slow reductive elimination from a Pd-enolate species could lead to competitive β-hydride elimination in the case of *n*-alkyl α-keto esters.[11] Furthermore, we, as well as others, have observed that α-keto esters **3** with enolizable protons form isotetronic acid derivatives **4** via a homoaldol/lactonization pathway in the presence of inorganic bases such as K_2CO_3.[12]

Scheme 3-4 Sensitivity of Linear α-Keto Esters Toward Base
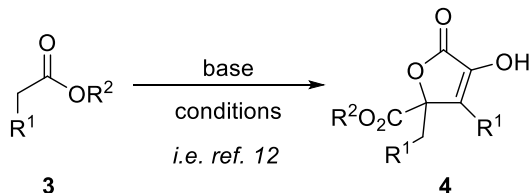
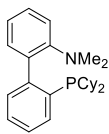Neverthless, if successful, this method would allow for a variety of electronically diverse β-aryl α-keto esters to be generated in short order from feedstock chemicals.

3.2 Optimization Studies

With the goal of suppressing the competitive homo-aldol process in mind, the *tert*-butyl α-keto ester **5a** (**Table 3-1**) was chosen as a model substrate. We first chose to probe the effect of the supporting ligand, beginning with the electron rich and sterically hindered ligand tricyclohexylphosphine (entry 1), shown previously to be an effective ligand in Pd-catalyzed enolate arylation reactions.[13] When no appreciable quantity of desired coupled product **7a** was obtained, we moved on to the more sterically encumbered ligand cataCXium A®, which delivered keto ester **7a** in reasonable yield (entry 2). Encouraged by this result, we switched to the Buchwald-type ligand DavePhos (entry 3), which is also well-precedented to work in this reaction.[14] When a slight decrease in yield was observed, we took inspiration from Hartwig's arylation of malonate derivatives, employing tri-*tert*-butylphosphine.[15] This ligand provided product **7a** in an isolated yield of 85% (entry 4).

Table 3-1 Optimization Studies

entry	base	ligand	temp ($^{\circ}$C)	NMR yield (isolated yield)
1	K_3PO_4	PCy_3	110	< 5
2	K_3PO_4	$PAd_2{}^nBu$ (cataCXium® A)	110	50
3	K_3PO_4	(DavePhos)	110	43
4	K_3PO_4	P^tBu_3	110	85 (85)
5	KO^tBu	P^tBu_3	110	< 5
6	K_2CO_3	P^tBu_3	110	99 (95)
7[b]	K_2CO_3	P^tBu_3	110	89

[a]Reaction conditions: 1.0 equiv of **5a**, 2.0 equiv of **6a**, 3.0 equiv of base, 2 mol % Pd_2dba_3, 8 mol % ligand, 110 °C, PhMe ($[\mathbf{5a}]_0$ = 0.2 M), 12 h.
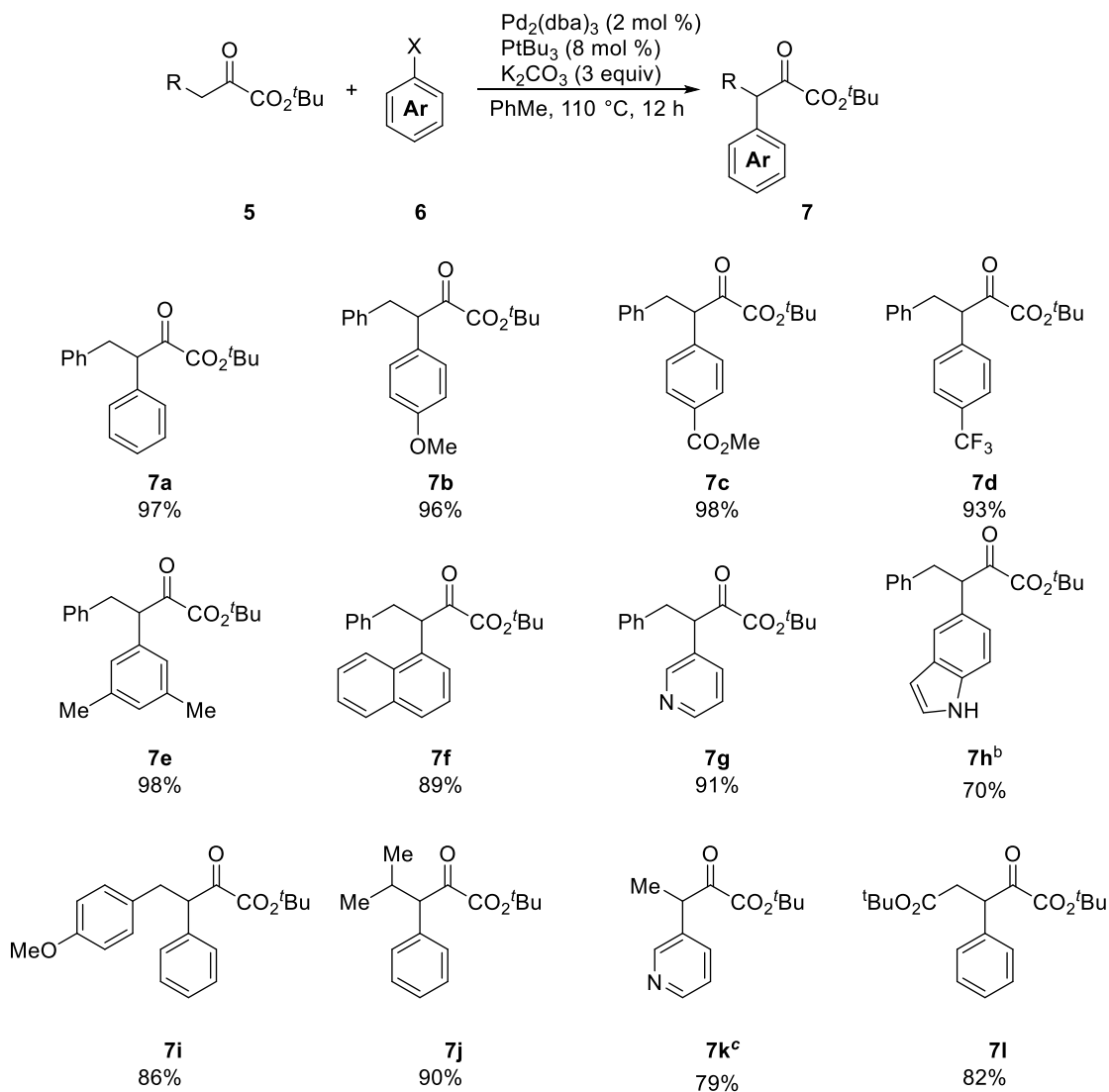
[b]Reaction conducted with 1 mol % $Pd_2(dba)_3$ and 4 mol % P^tBu_3.

Further optimization led to the discovery that less basic potassium carbonate improved the isolated yield of the reaction to 95% (entry 6). Notably, product **7a** was still formed in high yield when 2 mol % of palladium was employed. (1 mol % Pd_2dba_3, entry 7). Furthermore, the known dimerization product **4** was not observed, which suggests that the desired pathway is faster than this side reaction under the optimal catalytic conditions.

3.3 Scope of Palladium-Catalyzed Arylation Reaction

With optimal conditions in hand, we next turned to analyzing the scope of the Pd-catalyzed β-arylation reaction (**Scheme 3-5**). First, a variety of aryl bromides were tested. Both electron-rich and electron-poor aryl groups gave excellent results, including α-keto esters **7c** and **7d**, which would have been difficult compounds to access using previous routes. The reaction also tolerated various types of aryl groups, allowing the synthesis of products with *meta*-substituents (**7e**) and *ortho*-substituents (**7f**). Of particular interest to us was the use of heterocyclic aryl bromides. We were pleased to find that 3-bromopyridine and unprotected 5-bromoindole proved to be viable coupling partners (**7g** and **7h**). The use of alkenyl halides resulted in decomposition of the starting materials (not shown). In addition to the parent substrate **5a**, other α-keto esters were evaluated in the enolate arylation reaction. As seen with product **7j**, this method allowed facile entry to α-keto esters with bulky β-alkyl substituents. Additionally, decreasing the size of the β-alkyl substituent did not significantly decrease yields (**7k**). Finally, in order to test the chemoselectivity of this reaction, a substrate containing both an ester and an α-keto ester was tested. Product **7l** was generated without any noticeable formation of a bis-arylated product, highlighting the gentle nature of these reaction conditions. When β-disubstituted α-keto esters were used in this reaction, decomposition of the starting materials and low conversion to the quaternary β-substituted product was observed (not shown).

**Scheme 3-5** Scope of Pd-Catalyzed β-Arylation Reaction

7a 97%	**7b** 96%	**7c** 98%	**7d** 93%
7e 98%	**7f** 89%	**7g** 91%	**7h**[b] 70%
7i 86%	**7j** 90%	**7k**[c] 79%	**7l** 82%

[a]Reaction conditions: 1.0 equiv of **5**, 2.0 equiv of **6**, 3.0 equiv of K_2CO_3, 2 mol % Pd_2dba_3, 8 mol % P^tBu_3, PhMe (0.2 M), 110 °C, 12 h. [b]Reaction gave 69% yield when scale was increased to 2.7 mmol. [c]Reaction conducted on 1 g scale.

3.4 Gram Scale arylation Reaction and Glovebox-Free Conditions

The syntheses of products **7k** (**Scheme 3-5**) and **7g** (**Scheme 3-6**, eq. 1) were accomplished on one-gram scale with yields almost identical to those obtained in experiments on a smaller scale. Furthermore, the reaction could be carried out without the use of a glovebox when $P^tBu_3 \cdot HBF_4$ was used in place of the air sensitive P^tBu_3 (**Scheme 3-6**, eq 2.).[16] The former can be synthesized in house from cheap starting materials.[17]

Scheme 3-6 Large Scale and Glovebox Free Syntheses
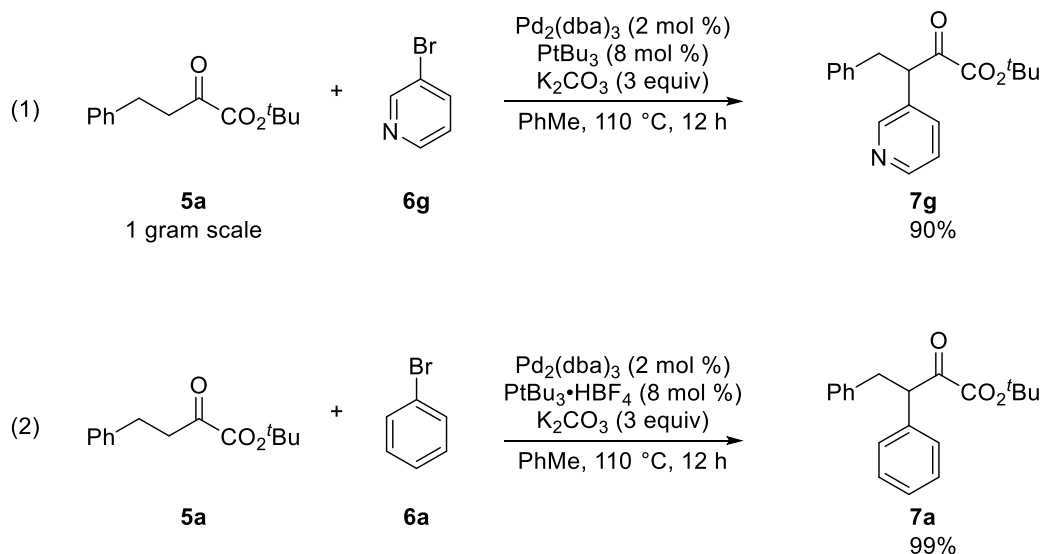
^{a}$Pd_2(dba)_3$, $P^tBu_3 \cdot HBF_4$, K_2CO_3, and PhMe were mixed for 2 h prior to addition of **5a** and **6a**. See experimental details for full procedure.

3.5 Conclusion

In conclusion, we have developed a Pd-catalyzed β-arylation reaction of α-keto esters that allows for the generation of a wide array of aryl pyruvate derivatives. These reactions

typically proceed in excellent yield, and provide access to previously inaccessible β-heteroaryl derivatives. Finally, the reaction can be conducted without the use of a glovebox.

3.6 Experimental Details

Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 (^{19}F NMR at 376 MHz), Bruker Avance III 500 (^{1}H NMR at 500 MHz), or a Bruker Avance III 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 151 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: CDCl$_3$ at 7.26 ppm; ^{13}C NMR: CDCl$_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, app t = apparent triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a Thermo LTqFT mass spectrometer with electrospray introduction and external calibration. All samples were prepared in methanol. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was accomplished with UV light, KMnO$_4$, and/or Seebach's stain (2.5 g phosphomolybdic acid, 1.0 g Ce(SO$_4$)$_2$, 6.0 mL conc. H$_2$SO$_4$, 94 mL H$_2$O) followed by heating. Purification of the reaction products was carried out by flash column chromatography using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle. Unless otherwise noted, all reactions were carried out under an atmosphere of dry nitrogen in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of pure material unless otherwise noted. Yields are

reported for a specific experiment and as a result may differ slightly from those found in figures, which are averages of at least two experiments.

Tetrahydrofuran (THF), diethyl ether (Et$_2$O), methylene chloride (CH$_2$Cl$_2$), and toluene (PhMe) were dried by passage through a column of neutral alumina under nitrogen prior to use. Tri-*tert*-butylphosphonium tetrafluoroborate,[17] **5i**,[18] and **5l** [19]and were synthesized according to known procedures.

General Procedure for the Synthesis a-Keto Ester Substrates: The addition of Grignard reagents to di-*tert*-butyl oxalate is a modification of a procedure published by Sodeoka.[2] A flame-dried 2-neck round-bottomed flask equipped with a stirbar and reflux condenser was cooled under a stream of N$_2$, and charged with magnesium turnings (1.9 equiv), a crystal of iodine, and enough THF to cover the magnesium turnings. A small portion of the alkyl bromide (typically less than 0.1 equiv) was then added dropwise until the yellow color of the reaction mixture turned to clear and colorless, indicating initiation of the Grignard reagent. Additional THF was added to the mixture ([magnesium turnings]$_0$ = 1.5 M), and the rest of the alkyl bromide (1.8 equiv in total) was added dropwise, while maintaining a gentle reflux. The reaction mixture was stirred for 1 h at rt. A separate flame-dried round-bottomed flask equipped with a stirbar was cooled under a stream of N$_2$, and charged with di-*tert*-butyl oxalate (1.0 equiv), and a 5:3 mixture of methylene chloride:THF (to give a solution with [di-*tert*-butyl oxalate] = 0.37 M). The solution was cooled to -78 °C, and the solution of Grignard reagent was added to it dropwise. The reaction mixture was stirred for 4 h at -78 °C, then quenched with saturated aqueous NH$_4$Cl (3 mL/mmol substrate) and diluted with methylene chloride (1.5 mL/mmol substrate). The biphasic mixture was added to a separatory funnel, and the layers were separated. The aqueous layer was extracted with methylene chloride (2 x 3

mL/mmol substrate). The combined organic extracts were dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel.
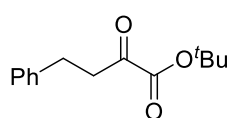
tert-Butyl 2-oxo-4-phenylbutanoate (5a): The general procedure was employed for the reaction of (2-bromoethyl)benzene (2.5 mL, 18.0 mmol) and di-*tert*-butyl oxalate (2.20 g, 10.0 mmol). The crude material was purified by column chromatography (methylene chloride/hexane = 30/70 to 70/30) to afford 2.34 g (57%) of the title compound as a white solid. Spectroscopic properties were identical to those previously reported:[2] **¹H NMR** (400 MHz, CDCl$_3$) d = 7.32-7.25 (m, 2 H), 7.23-7.18 (m, 3 H), 3.12 (t, *J* = 8.0 Hz, 2 H), 2.94 (t, *J* = 7.6 Hz, 2 H), 1.53 (s, 9 H).
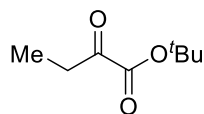
tert-Butyl 2-oxo-4-phenylbutanoate (5k): The general procedure was employed for the reaction of bromoethane (4.0 mL, 54.0 mmol) and di-*tert*-butyl oxalate (6.07 g, 30.0 mmol). The crude material was purified by column chromatography (methylene chloride/hexane = 30/70 to 70/30) to afford 4.75 g (44%) of the title compound as a clear and colorless liquid. Spectroscopic properties were identical to those previously reported: **¹H NMR** (400 MHz, C$_6$D$_6$) d = 2.36 (q, *J* = 7.2 Hz, 2 H), 1.28 (s, 9H), 0.81 (t, *J* = 7.3 Hz, 3H).
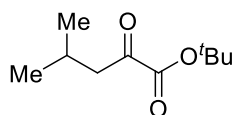
tert-Butyl 4-methyl-2-oxopentanoate (5j): A flame-dried round-bottomed flask equipped with a stirbar was cooled under a stream of N$_2$, and charged with ethyl 4-methyl-2-oxopentanoate[20] (4.51 g, 28.5 mmol, 1.0 equiv), methanol (91 mL, 0.31 M), and water (30 mL, 0.94 M). Powdered KOH (9.60 g, 171.0

mmol, 6.0 equiv) was added to the solution portion-wise in order to control the resulting exotherm. The solution was stirred for 30 min at rt before being concentrated *in vacuo* to remove the methanol. The reaction mixture was cooled to 0 °C, then diluted with concentrated HCl until pH = 1 was reached. The mixture was diluted with methylene chloride (40 mL), and added to a separatory funnel. The layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude carboxylic acid intermediate.

The crude carboxylic acid, methylene chloride (57 mL, [carboxylic acid]$_0$ = 0.5 M), and DMF (44 mL, 0.6 mmol, 0.02 equiv) were added to a flame-dried round-bottom flask equipped with a stirbar. The solution was cooled to 0 °C, and oxalyl chloride (4.9 mL, 57.0 mmol, 2.0 equiv) was added dropwise at a rate such that gas evolution was controlled. The solution was warmed to rt slowly overnight. The solution was then concentrated *in vacuo*, taking care to ensure that all residual oxalyl chloride was removed.

The crude acid chloride was dissolved in methylene chloride (43 mL, [acid chloride]$_0$ = 0.67 M) and cooled to 0 °C. *tert*-Butyl alcohol (5.4 mL, 57.0 mmol, 2.0 equiv) was added dropwise to the solution. Pyridine (2.3 mL, 28.5 mmol, 1.0 equiv) was added dropwise to the solution. The solution was stirred at 0 °C for 6 h, after which time it was quenched by water (30 mL). The biphasic mixture was added to a separatory funnel, and the layers were separated. The aqueous layer was extracted with methylene chloride (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc/hexane = 2.5/97.5) afforded 1.98 g (37% over 3 steps) of the title compound as a clear and colorless liquid.[21] Analytical data for **5j**: **¹H NMR** (400 MHz, CDCl$_3$) d = 2.64 (d, *J* = 6.8 Hz, 2 H), 2.21-2.12 (m, 1 H),

1.54 (s, 9 H), 0.96 (d, J = 6.7 Hz, 6 H); **¹³C NMR** (151 MHz, CDCl3) d 195.5, 160.9, 83.8, 47.7, 27.8, 24.2, 22.5; **IR** (thin film): 2962, 2936, 2874, 1722.1, 1395, 1272, 1138, 1052 cm⁻¹; **HRMS:** (ESI+): Calcd. for $C_{10}H_{18}O_3$: ([M+Na]): 209.1154, Found: 209.1145. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.5.

General Procedure for the Pd-Catalyzed Arylation of a-Keto Ester Enolates:

A flame-dried 1-dram vial was cooled under a stream of N₂, and charged with the appropriate a-keto ester (0.2 mmol, 1.0 equiv) and aryl halide (0.4 mmol, 2.0 equiv). This vial and a separate flame-dried 1-dram vial equipped with a stirbar were transferred to a N₂-filled glovebox. The vial equipped with only a stirbar was charged with Pd₂(dba)₃ (0.004 mmol, 0.02 equiv), a 1.0 M solution of P^{t}Bu₃ in toluene (0.016 mmol, 0.08 equiv), and K₂CO₃ (0.6 mmol, 3.0 equiv). To the 1-dram vial containing the a-keto ester and aryl halide was added toluene (1 mL, [a-keto ester]₀ = 0.2 M). This solution was transferred to the 1-dram vial containing the base and catalyst. The vial was capped with a red PTFE/silicone cap, removed from the N₂ filled glovebox, and heated at 110 °C (external oil bath temperature) for 12 h. The reaction mixture was transferred to a separatory funnel filled with methylene chloride (50 mL/mmol substrate) and saturated aqueous NH₄Cl (50 mL/mmol substrate). The 1-dram vial was washed with methylene chloride (2 x 5 mL/mmol substrate), saturated aqueous NH₄Cl (1 x 5 mL/mmol substrate), and methylene chloride (2 x 5 mL/mmol substrate). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 50 mL/mmol substrate). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel.
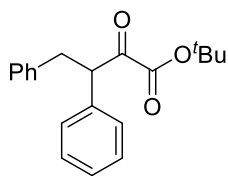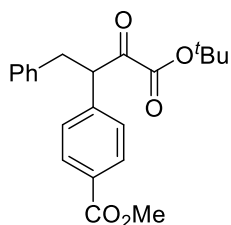
***tert*-Butyl 2-oxo-3,4-diphenylbutanoate (7a):** The general procedure was employed for the coupling of **5a** (46.9 mg, 0.2 mmol) and bromobenzene (62.8 mg, 42 mL, 0.4 mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 1/99 to 2.5/97.5) to afford 62.0 mg (99%) of the title compound as an off-white amorphous solid. Analytical data for **7a**: **^{1}H NMR** (400 MHz, CDCl$_3$) d 7.32–7.14 (m, 8 H), 7.07–7.02 (m, 2 H), 4.55 (app t, J = 7.4 Hz, 1 H), 3.44 (dd, J = 13.9, 6.9 Hz, 1 H), 2.96 (dd, J = 13.9, 7.9 Hz, 1 H), 1.31 (s, 9 H); **^{13}C NMR** (151 MHz, CDCl$_3$) d 193.9, 160.4, 138.8, 135.9, 129.1, 128.8, 128.2, 127.6, 126.2, 84.0, 56.2, 37.6, 27.5; **IR** (thin film): 2981, 2932, 1742, 1722, 1455, 1160 cm^{-1}; **HRMS:** (ESI+): Calcd. for C$_{20}$H$_{22}$O$_3$: ([M+Na]): 333.1467, Found: 333.1453. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.45.
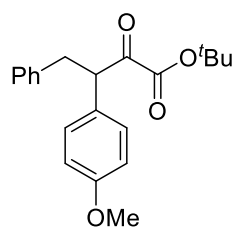
***tert*-Butyl 3-(4-methoxyphenyl)-2-oxo-4-phenylbutanoate (7b):** The general procedure was employed for the coupling of **5a** (46.9 mg, 0.2 mmol) and 1-bromo-4-methoxybenzene (74.8 mg, 50 mL, 0.4 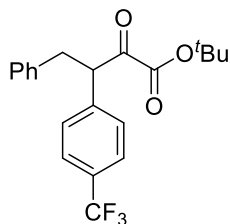mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 2.5/97.5 to 5/95) to afford 65.3 mg (96%) of the title compound as a light-yellow amorphous solid. Analytical data for **7b**: **^{1}H NMR** (400 MHz, CDCl$_3$) d 7.23–7.10 (m, 3 H), 7.07–7.01 (m, 4 H), 6.84–6.79 (m, 2 H), 4.51 (app t, J = 7.4 Hz, 1 H), 3.78 (s, 3 H), 3.40 (dd, J = 13.9, 6.8 Hz, 1 H), 2.94 (dd, J = 13.9, 8.1 Hz, 1 H), 1.34 (s, 9 H); **^{13}C NMR** (151 MHz, CDCl$_3$) d 193.8, 160.6, 159.0, 138.9, 130.2, 129.1, 128.2, 127.6, 126.2, 114.2, 83.9, 55.2, 55.2, 37.6, 27.6; **IR** (thin film): 2980, 2934, 2837, 1721, 1609, 1511, 1253 cm^{-1}; **HRMS:** (ESI+): Calcd. for C$_{21}$H$_{24}$O$_4$: ([M+Na]): 363.1573, Found: 363.1558. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.35.

Methyl 4-(4-(*tert*-butoxy)-3,4-dioxo-1-phenylbutan-2-yl)benzoate (7c): The general procedure was employed for the coupling of **5a** (46.9 mg, 0.2 mmol) and methyl 4-bromobenzoate (86.0 mg, 0.4 mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 2.5/97.5 to 5/95) to afford 70.5 mg (96%) of the title compound as an off-white amorphous solid. Analytical data for **7c**: **¹H NMR** (400 MHz, CDCl$_3$) d 7.98–7.93 (m, 2 H), 7.22–7.11 (m, 5 H), 7.03–6.99 (m, 2 H), 4.63 (dd, J = 8.4, 6.6 Hz, 1 H), 3.90 (s, 3 H), 3.43 (dd, J = 13.9, 6.6 Hz, 1 H), 2.97 (dd, J = 13.9, 8.4 Hz, 1H), 1.33 (s, 9 H); **¹³C NMR** (151 MHz, CDCl$_3$) d 193.3, 166.6, 159.9, 141.2, 138.1, 130.0, 129.4, 129.1, 129.0, 128.3, 126.4, 84.4, 56.1, 52.2, 37.7, 27.5; **IR** (thin film): 2981, 2953, 1723, 1608, 1282, 1112 cm^{-1}; **HRMS:** (ESI+): Calcd. for C$_{22}$H$_{24}$O$_5$: ([M+Na]): 391.1522, Found: 391.1510. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.3.
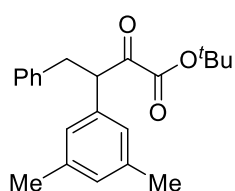
tert-Butyl 2-oxo-4-phenyl-3-(4-(trifluoromethyl)phenyl)butanoate (7d): The general procedure was employed for the coupling of **5a** (46.9 mg, 0.2 mmol) and 1-bromo-4-(trifluoromethyl)benzene (90.0 mg, 55 mL, 0.4 mmol). The crude material was purified by column chromatography (column 1: EtOAc/hexanes = 1/99 to 2.5/97.5, column 2: methylene chloride) to afford 74.5 mg (98%) of the title compound as an off-white amorphous solid. Analytical data for **7d**: **¹H NMR** (600 MHz, CDCl$_3$) d 7.55 (d, J = 8.1 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.24-7.19 (m, 2 H), 7.19-7.15 (m, 1 H), 7.05-7.01 (m, 2 H), 4.67 (dd, J = 8.2, 6.8 Hz, 1 H), 3.44 (dd, J = 13.9, 6.8 Hz, 1 H), 2.97 (dd, J = 13.9, 8.2 Hz, 1 H), 1.35 (s, 9H); **¹³C NMR** (151 MHz, CDCl$_3$) d 193.3, 159.9, 140.2 (d, $J_{13C-19F}$ = 1.7 Hz), 138.0, 129.9 (q, $J_{13C-19F}$ = 32.4 Hz), 129.3, 129.0, 128.4, 126.5, 125.7 (q,

$J_{13C-19F}$ = 3.9 Hz), 123.9 (q, $J_{13C-19F}$ = 270.3 Hz), 84.5, 55.8, 37.8, 27.5; **IR** (thin film): 2982, 2935, 1723, 1327, 1165, 1126, 1068 cm^{-1}; **HRMS:** (ESI+): Calcd. for $C_{21}H_{21}F_3O_3$: ([M+Na]): 401.1341, Found: 401.1325. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.45.

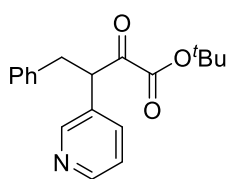***tert*-Butyl 3-(3,5-dimethylphenyl)-2-oxo-4-phenylbutanoate (7e):** The general procedure was employed for the coupling of **5a** (46.9 mg, 0.2 mmol) and 1-bromo-3,5-dimethylbenzene (74.0 mg, 54 mL, 0.4 mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 2.5/97.5) to afford 66.8 mg (99%) of the title compound as an off-white amorphous solid. Analytical data for **7e**: **¹H NMR** (400 MHz, CDCl$_3$) d 7.24-7.13 (m, 3 H), 7.19-7.15 (m, 1 H), 7.12-7.06 (m, 2 H), 6.88 (s, 1 H), 6.76 s, 2 H) 4.50 (app t, J = 7.3 Hz, 1 H), 3.43 (dd, J = 14.0, 7.6 Hz, 1 H), 2.94 (dd, J = 13.9, 7.1 Hz), 2.26 (s, 6 H), 1.32 (s, 9 H); **¹³C NMR** (151 MHz, CDCl$_3$) d 193.9, 160.5, 139.1, 138.3, 135.7, 129.3, 129.1, 128.2, 126.8, 126.2, 83.8, 56.0, 37.5, 27.5, 21.2; **IR** (thin film): 2980, 2921, 1743, 1722, 1160, 700 cm^{-1}; **HMRS:** (ESI+): Calcd. for $C_{22}H_{26}O_3$: ([M+Na]): 361.1780, Found: 361.1765. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.45.
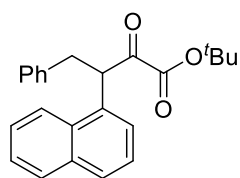
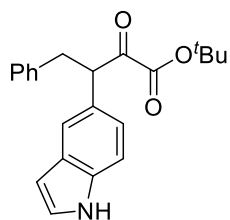***tert*-Butyl 3-(naphthalen-1-yl)-2-oxo-4-phenylbutanoate (7f):** The general procedure was employed for the coupling of **5a** (46.9 mg, 0.2 mmol) and 1-bromonaphthalene (82.8 mg, 56 mL, 0.4 mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 2.5/97.5) to afford 65.2 mg (89%) of the title compound as a light-yellow liquid. Analytical data for **7f**: **¹H NMR** (400 MHz, CDCl$_3$) d 8.01-7.95 (m, 1 H), 7.88-7.82 (m, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.52-7.45 (m, 2 H), 7.44-7.38 (m, 1 H), 7.20-7.10 (m, 6 H), 5.33-5.23 (m, 1 H),

3.60 (dd, J = 13.9, 7.6 Hz, 1 H), 3.04 (dd, J = 13.9, 6.4 Hz, 1 H), 1.04 (s, 9 H); **¹³C NMR** (151 MHz, CDCl₃) d 194.0, 160.3, 139.2, 134.1, 133.0, 131.5, 129.1, 128.9, 128.4, 128.3, 126.5, 126.3, 125.9, 125.4, 123.2, 83.8, 51.9, 37.7, 27.2; **IR** (thin film): 3061, 3029, 2980, 2932, 1742, 1724, 1153 cm⁻¹; **HRMS:** (ESI+): Calcd. for $C_{24}H_{24}O_3$: ([M+Na]): 383.1623, Found: 383.1608. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.5.

***tert*-Butyl 2-oxo-4-phenyl-3-(pyridin-3-yl)butanoate (7g):** The general procedure was employed for the coupling of **5a** (46.9 mg, 0.2 mmol) and 3-bromopyridine (63.2 mg, 39 mL, 0.4 mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 20/80 to 30/70) to afford 58.6 mg (94%) of the title compound as a light-yellow amorphous solid, existing as a 93:7 mixture of ketone:enol tautomers. Analytical data for **7g**: **¹H NMR** (400 MHz, CDCl₃) d 8.52 (d, J = 4.8 Hz, 1 H), 8.41 (s, 1 H), 7.53-7.48 (m, 1 H), 7.30-7.14 (m, 4 H), 7.07-7.02 (m, 2 H), 4.65 (dd, J = 8.4, 6.7 Hz, 1 H), 3.46 (dd, J = 13.9, 6.7 Hz, 1 H), 2.99 (dd, J = 13.9, 8.4 Hz, 1 H) 1.38 (s, 9 H); **¹³C NMR** (151 MHz, CDCl₃) d 193.3, 159.8, 150.5, 148.9, 137.8, 136.0, 132.0, 129.0, 128.5, 126.6, 123.6, 84.6, 53.4, 37.7, 27.6; **IR** (thin film): 3061, 3030, 2980, 2933, 1723 cm⁻¹; **HRMS:** (ESI+): Calcd. for $C_{19}H_{21}NO_3$: ([M+H⁺]): 312.1600, Found: 312.1597. **TLC** (EtOAc/hexane = 30/70): R$_f$ = 0.3.

***tert*-Butyl 3-(1*H*-indol-5-yl)-2-oxo-4-phenylbutanoate (7h):** The general procedure was employed for the coupling of **5a** (46.9 mg, 0.2 mmol) and 5-bromo-1*H*-indole (78.4 mg, 0.4 mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 10/90 to 15/85) to afford 52.5 mg (75%) of the title compound as an off-white amorphous

solid. Analytical data for **7h**: **¹H NMR** (400 MHz, CDCl₃) d 8.16 (br s, 1 H), 7.43 (s, 1 H), 7.30 (d, J = 8.4 Hz, 1 H), 7.22-7.06 (m, 6 H), 6.98-6.94 (m, 1 H), 6.51-6.47 (m, 1 H), 4.66 (app t, J = 7.4 Hz, 1 H), 3.50 (d, J = 13.9, 7.1 Hz, 1 H), 3.04 (d, J = 13.9, 7.6 Hz, 1 H), 1.28 (s, 9 H); **¹³C NMR** (151 MHz, CDCl₃) d 194.1, 160.8, 139.4, 135.2, 129.1, 128.2, 128.2, 126.8, 126.1, 124.8, 123.2, 121.4, 111.4, 102.6, 83.7, 56.1, 37.9, 27.5; **IR** (thin film): 3420 (br), 2980, 2931, 1723, 1156, 1091 cm⁻¹; **HRMS:** (ESI+): Calcd. for $C_{22}H_{23}NO_3$: ([M+Na]): 372.1576, Found: 372.1561. **TLC** (EtOAc/hexane = 20/80): R$_f$ = 0.35.
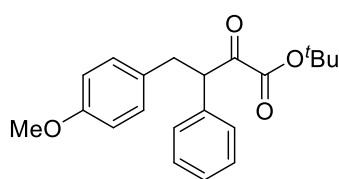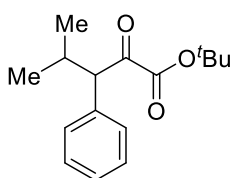

***tert*-butyl** **4-(4-methoxyphenyl)-2-oxo-3-phenylbutanoate (7i):** The general procedure was employed for the coupling of **5i** (52.9 mg, 0.2 mmol) and bromobenzene (62.8 mg, 42 mL, 0.4 mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 2.5/97.5 to 5/95) to afford 57.9 mg (85%) of the title compound as a light-yellow liquid. Analytical data for **7i**: **¹H NMR** (400 MHz, CDCl₃) d 7.31-7.22 (m, 3 H), 7.15-7.11 (m, 2 H), 6.96 (d, J = 8.6 Hz, 2 H), 6.74 (d, J = 8.6 Hz, 2 H), 4.51 (app t, J = 7.4 Hz, 1 H), 3.75 (s, 3 H), 3.37 (dd, J = 14.0, 6.9 Hz, 1 H), 2.91 (dd, J = 14.0, 7.9 Hz, 1 H), 1.32 (s, 9 H); **¹³C NMR** (151 MHz, CDCl₃) d 194.0, 160.4, 158.0, 136.0, 130.8, 130.0, 129.1, 128.8, 127.6, 113.6, 83.9, 56.5, 55.1, 36.8, 27.5; **IR** (film) 2980, 2934, 2836, 1722, 1513, 1248.7 cm⁻¹; **HRMS:** (ESI+): Calcd. for $C_{21}H_{24}O_4$: ([M+Na]): 363.1573, Found: 363.1818. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.35.


***tert*-Butyl** **4-methyl-2-oxo-3-phenylpentanoate** **(7j):** The general procedure was employed for the coupling of **5j** (37.3 mg, 0.2 mmol) and bromobenzene (62.8 mg, 42 mL, 0.4 mmol). The crude
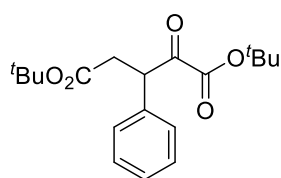
material was purified by column chromatography (EtOAc/hexanes = 1/99 to 2.5/97.5) to afford 47.3 mg (90%) of the title compound as a clear, colorless liquid. Analytical data for **7j**: **¹H NMR** (400 MHz, CDCl₃) d 7.36-7.24 (m, 3 H), 7.23-7.18 (m, 2 H), 4.03 (d, J = 9.8 Hz, 1 H), 2.52-2.39 (m, 1 H), 1.39 (s, 9 H), 1.04 (d, J = 6.5 Hz, 3 H), 0.74 (d, J = 6.7 Hz, 3 H); **¹³C NMR** (151 MHz, CDCl₃) d 194.6, 160.8, 135.5, 129.6, 128.7, 127.5, 83.8, 61.6, 29.8, 27.6, 21.5, 20.1; **IR** (thin film): 2977, 2935, 2873, 1742, 1724, 1370, 1256 cm⁻¹; **HRMS:** (ESI+): Calcd. for $C_{16}H_{22}O_3$: ([M+Na]): 285.1467, Found: 285.1454. **TLC** (EtOAc/hexane = 10/90): R_f = 0.55.
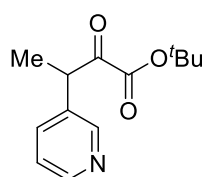
***tert*-butyl 2-oxo-3-(pyridin-3-yl)butanoate (7k):** The general procedure was employed for the coupling of **7k** (31.6 mg, 0.2 mmol) and 3-bromopyridine (63.2 mg, 39 mL, 0.4 mmol). The crude material was purified by column chromatography (EtOAc/hexanes = 30/70 to 40/60) to afford 37.9 mg (81%) of the title compound as a light-yellow amorphous solid. Analytical data for **7k**: **¹H NMR** (400 MHz, CDCl₃) d 8.55-8.51 (m, 2 H), 7.55-7.50 (m, 1 H), 7.30-7.25 (m, 1 H), 4.42 (q, J = 7.0 Hz, 1 H), 1.48 (d, J = 7.1 Hz, 3 H), 1.39 (s, 9 H); **¹³C NMR** (151 MHz, CDCl₃) d 194.3, 160.3, 150.1, 148.8, 135.5, 134.0, 123.7, 84.5, 46.0, 27.6, 16.7; **IR** (thin film): 2981, 2936, 1723, 1576, 1479, 1455 cm⁻¹; **HRMS:** (ESI+): Calcd. for $C_{13}H_{17}NO_3$: ([M+H⁺]): 236.1287, Found: 236.1282. **TLC** (EtOAc/hexane = 30/70): R_f = 0.2.

Di-*tert*-butyl 2-oxo-3-phenylpentanedioate (7l): The general procedure was employed for the coupling of **5l** (51.7 mg, 0.2 mmol) and bromobenzene (62.8 mg, 42 mL, 0.4 mmol). The crude material was purified by column chromatography (column 1: EtOAc/hexanes = 1/99 to 2.5/97.5,

column 2: EtOAc/hexanes = 1/99 to 2.5/97.5) to afford 56.9 mg (85%) of the title compound as a clear and colorless liquid. Analytical data for **7l**: **^{1}H NMR** (500 MHz, CDCl$_3$) d 7.36-7.26 (m, 3 H), 7.24-7.17 (m, 2 H), 4.79 (dd, J = 9.5, 5.6 Hz, 1 H), 3.12 (dd, J = 16.8, 9.5 Hz, 1 H), 2.61 (dd, J = 16.8, 5.7 Hz, 1 H), 1.41 (s, 9 H), 1.38 (s, 9 H); **^{13}C NMR** (151 MHz, CDCl$_3$) d 193.1, 170.5, 159.8, 135.2, 129.0, 128.9, 127.9, 84.0, 81.1, 50.2, 37.7, 27.9, 27.6; **IR** (thin film): 2980, 2933, 1727, 1369, 1255, 1157 cm^{-1}; **HRMS:** (ESI+): Calcd. for C$_{19}$H$_{26}$O$_5$: ([M+Na]): 357.1678, Found: 357.1662. **TLC** (EtOAc/hexane = 10/90): R$_f$ = 0.45.

Procedure for the Gram Scale Pd-Catalyzed Arylation: A flame-dried 150 mL pressure vessel equipped with a stirbar was cooled under a stream of N$_2$, and charged with **5a** (1.00 g, 4.27 mmol, 1.0 equiv) and 3-bromopyridine (1.35 g, 820 mL, 8.54 mmol, 2.0 equiv). The vessel was transferred to a N$_2$ filled glovebox. The vessel was then charged with Pd$_2$(dba)$_3$ (78 mg, 0.09 mmol, 0.02 equiv), a 1.0 M solution of P^{t}Bu$_3$ in toluene (340 mL, 0.34 mmol, 0.08 equiv), K$_2$CO$_3$ (1.77 g, 12.8 mmol, 3.0 equiv), and toluene (21 mL, [**5a**]$_0$ = 0.2 M). The vessel was capped, removed from the N$_2$ filled glovebox, and heated at 110 °C (external oil bath temperature) for 12 h. The reaction mixture was transferred to a separatory funnel filled with diethyl ether (30 mL) and saturated aqueous NH$_4$Cl (30 mL). The pressure vessel was washed with diethyl ether (2 x 5 mL), saturated aqueous NH$_4$Cl (1 x 5 mL), and diethyl ether (2 x 5 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 40 mL). The organic extracts were combined, washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (EtOAc/hexanes = 20/80 to 30/70) to afford 1.33 g (90%) of **7g** as a white amorphous solid.

Procedure for the Air-Tolerant Pd-Catalyzed Arylation: A flame-dried 1-dram vial was cooled under a stream of N_2, and charged with $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol, 0.02 equiv), tri-*tert*-butylphosphonium tetrafluoroborate (4.6 mg, 0.016 mmol, 0.08 equiv), K_2CO_3 (83 mg, 0.6 mmol, 3.0 equiv), and toluene (1 mL, $[K_2CO_3]_0$ = 0.6 M). The reaction mixture was purged under a stream of N_2, capped with a red PTFE/silicone cap, and stirred at rt for 2 h. The cap was removed, and the vial was charged with **5a** (47 mg, 0.2 mmol, 1.0 equiv) and bromobenzene (62.8 mg, 42 mL, 0.4 mmol, 2.0 equiv). The reaction mixture was purged under a stream of N_2, capped, and stirred at 110 °C (external oil bath temperature) for 12 h. The reaction mixture was transferred to a separatory funnel filled with methylene chloride (20 mL) and saturated aqueous NH_4Cl (20 mL). The 1-dram vial was washed with methylene chloride (2 x 1 mL), saturated aqueous NH_4Cl (1 x 1 mL), and methylene chloride (2 x 1 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (EtOAc/hexanes = 1/99 to 2.5/97.5) to afford 62.0 mg (99%) of **7a** compound as an off-white amorphous solid.

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Chapter IV Catalytic Enantioselective [3+2] Cycloaddition of α-Keto Ester Enolates and Nitrile Oxides

4.1 Introduction to Soft Enolization

The stereoselective functionalization of enolate derivatives is a venerable, time-honored strategy for the assembly of complex molecular frameworks.[1] Historically, the preparation of enolates has involved the use of group I metal-amides as thermodynamically strong bases. In these reactions, stereoselectivity has often relied on pre-installed chiral auxiliaries.[2] More recently, it has been shown that complexation of a Lewis acid to the non-bonding electrons of a carbonyl pro-nucleophile can lower the energy of its π system, leading to enhanced acidity, which thereby enables enolization under milder conditions.[3] This process has been referred to as *soft enolization* In an early report, Mukaiyama and co-workers developed an aldol reaction between ketone nucleophiles and aldehyde electrophiles promoted by $Sn(OTf)_2$ and a trialkylamine base (**Scheme 4-1**, eq 1).[4] Prior to this work the same lab had developed direct cross-aldol reactions employing boron enolates formed under the action of a trialkylamine and $^nBu_2OTf$.[5] An early catalytic version of this process was disclosed by Evans and co-workers.[6] They showed that a magnesium halide salt in conjunction with a trialkylamine base, could catalyze the diastereoselective aldol reaction of chiral acyloxazolidinone nucleophiles (**Scheme 4-1**, eq 2). This finding set the stage for the development of asymmetric reactions proceeding by direct enolization catalyzed by chiral metal complexes. In 1992, Shibasaki and coworkers reported a direct asymmetric Henry reaction catalyzed by a rare earth metal-

binolate complex.[7] Several years later they reported the first direct asymmetric aldol reaction catalyzed by a related chiral lanthanum-binolate complex (**Scheme 4-1**, eq. 3).[8]

Scheme 4-1. Exemplary Soft Enolization Reactions
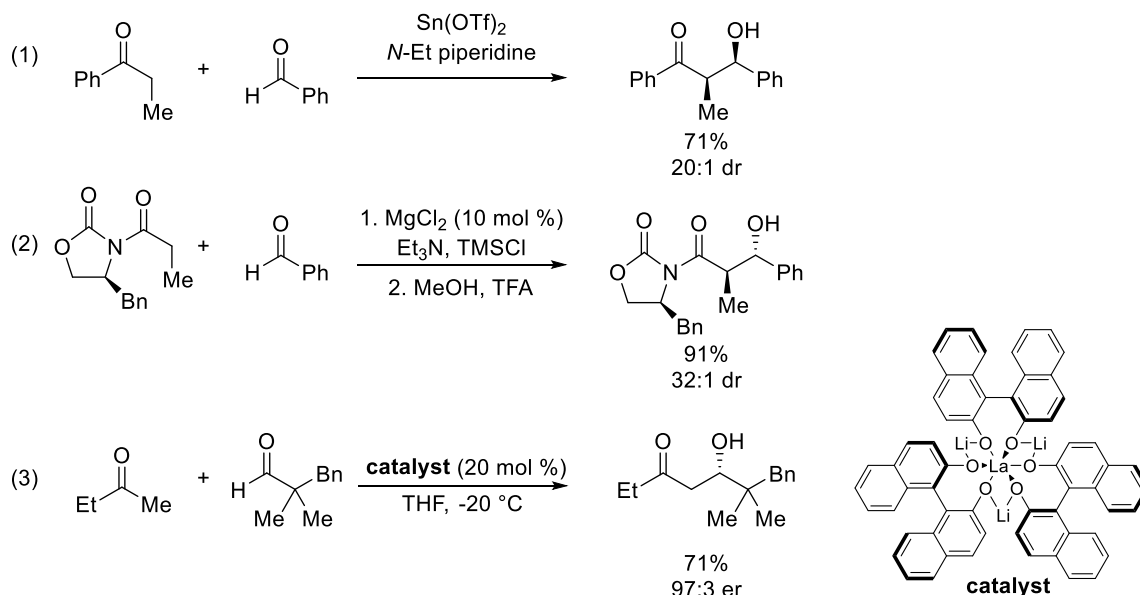
A number of research groups have since reported that chiral late transition metal complexes act as catalysts for reactions that proceed via soft enolization of carbonyl compounds.[9] Transformations developed under this paradigm include Michael,[9a] halogenation,[9b,c] Mannich,[9d] and aldol[9e] reactions of β-keto esters, as well as Michael[9f] additions and halogenations[9g-i] using α-keto esters as pro-nucleophiles. Substrates, that are capable of forming strong chelates with the chiral metal catalyst perform particularly well in these reactions. Consequently, α-keto esters have emerged as a privileged substrate class. The chiral Ni(II)-diamine catalyzed 1,4-addition of α-keto ester pro-nucleophiles and nitroolefins, disclosed by the Sodeoka laboratory, is an important example of a direct asymmetric addition via a soft enolization reaction manifold.[9f] This reaction proceeds via the intermediacy of a chiral (*Z*)-Ni(II)-enolate **4** which evades

destabilizing $A_{1,3}$ interactions between the β-substituent and *t*Bu group of the α-keto ester present in the opposite geometrical isomer (**Scheme 4-2**).

Scheme 4-2. Sodeoka's Ni(II)-Diamine Catalyzed Michael Addition of α-Keto Esters and Nitroolefins.
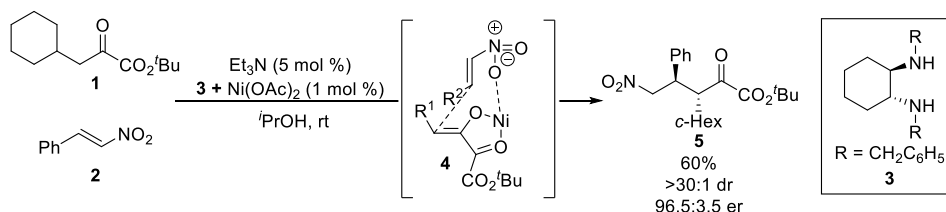

4.2 Reaction Design

The integration of unconventional electrophiles under the mechanistic construct discussed above carries with it the possibility to create heretofore unknown compounds: 1,3-dipolar synthons emerged as attractive targets. Sustmann classified 1,3-dipolar cycloadditions based on the relevant FMO interactions:[10] Type I cycloadditions are controlled by the homo of the dipole and LUMO of the dipolarophile. In type II cycloadditions the orbital energy levels of the dipole and dipolarophile are effectively matched. Finally, type III cycloadditions are controlled by the HOMO of the dipolarophile and the LUMO of the dipole (**Scheme 4-3**) The cycloaddition of an electron rich vinyl ether **6** and a nitrile oxide **7** constitutes a type III cycloaddition.[11]

Scheme 4-3. Sustmann's Frontier Orbital Control Classification Scheme for Dipolar Cycloadditions
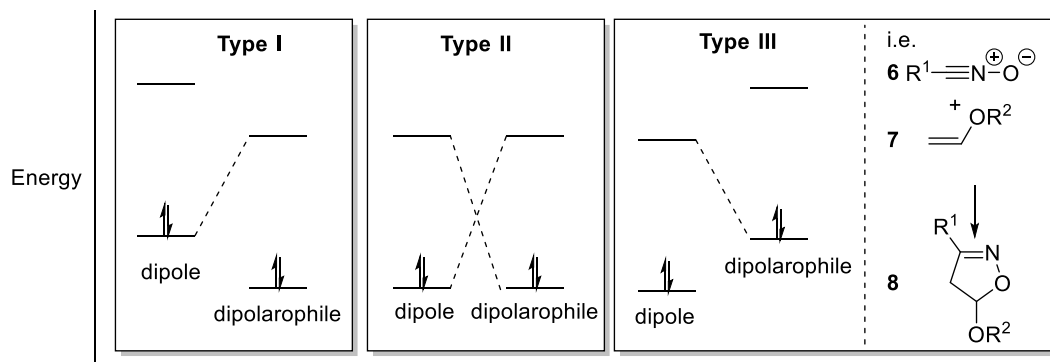

Drawing a parallel with electron-rich dipolarophiles[12] we postulated that transition metal enolates could similarly engage dipoles in [3+2] cycloadditions. Precedent for achieving catalytic asymmetric dipolar cycloadditions by way of HOMO raising activation exists. Yanagisawa and coworkers reported the cycloaddition of nitrones and alkenyl acetates and proposed the intermediacy of catalytically formed tin(IV) enolates.[13] Additionally, enamine catalysis has been used to facilitate asymmetric [3+2] cycloadditions of aldehydes and azomethine imines.[14,15] Building on this concept, the Sodeoka laboratory recently developed a catalytic asymmetric [3+2] cycloaddition of nitrones **9** and enolates derived from α-keto esters **10** that was inspired by the structural characterization of a Ni(II)–diamine catalyst that merges Ni(II)–enolate and hydrogen-bonding activation modes (**Scheme 4-4**).[16] However, the scope of the process was limited to isolable (*E*)-nitrones, specifically dihydroquinoline derivatives.

Scheme 4-4. Sodeoka's [3+2] Cycloaddition of Nitrones and α-Keto Ester Enolates.
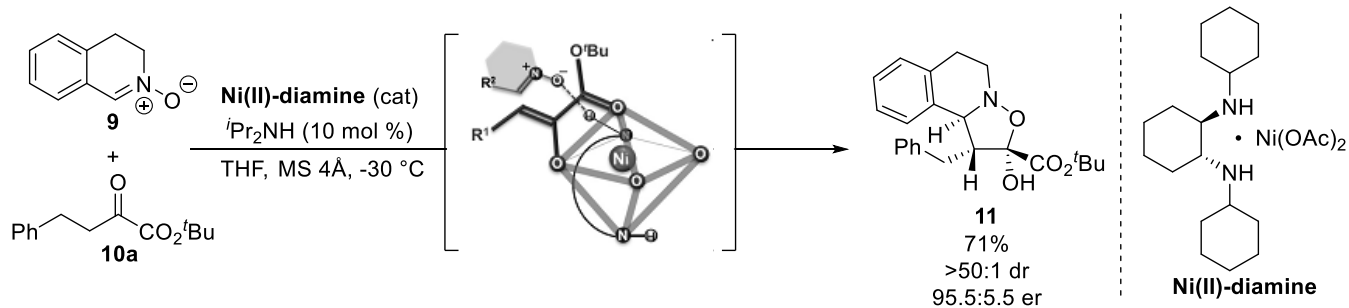
The generation of heretofore unknown isoxazolines via the reaction of an ephemeral metalloenolate with a transient nitrile oxide emerged as an attractive, yet challenging next step (**Scheme 4-5**).[17]

Scheme 4-5 Proposed [3+2] Cycloaddition and Competitive Reactions.
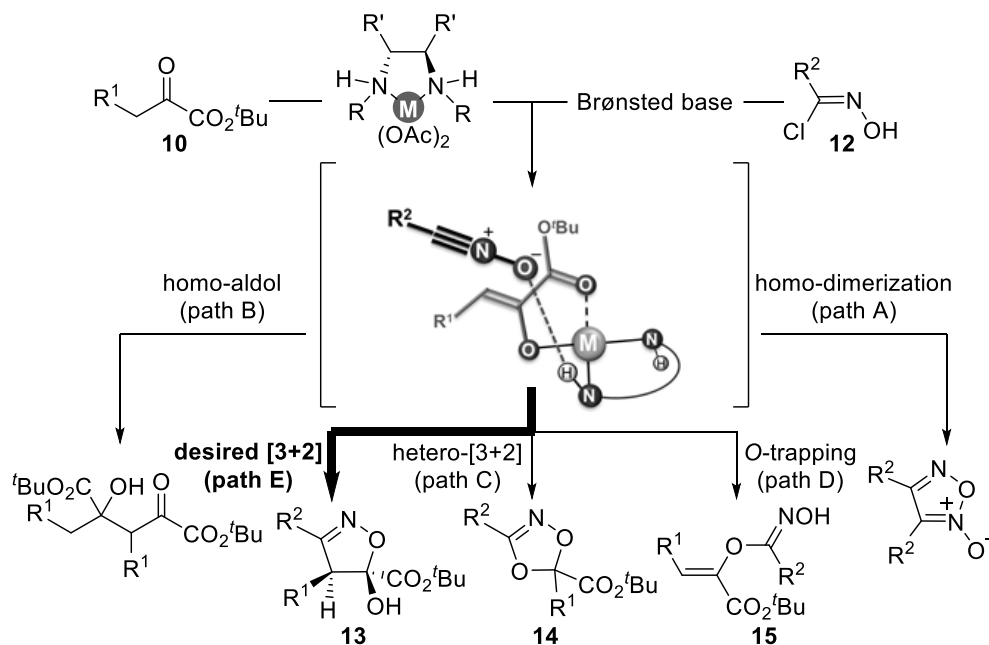
At the outset, we perceived several unique challenges to our reaction plan. Foremost among these is the inherent instability of nitrile oxides toward dimerization (**Scheme 4-5**, path A)[11b,18] and the need to generate them *in situ* via base mediated

dehydrohalogenation of the corresponding hydroximoyl chloride, or by the dehydration of nitroalkanes.[19] Additionally, our labs have observed that α-keto esters **10** react via homo-aldol (path B) in the absence of other viable pathways. The known hetero [3+2] cycloaddition of nitrile oxides with α-keto esters defines a third relative rate concern (path C),[20] especially since the latter will be present in great excess relative to the derived metalloenolate. Finally, the inherent competition of *O*- versus *C*-trapping of metalloenolates (path D vs. E) must be effectively managed for a successful outcome.
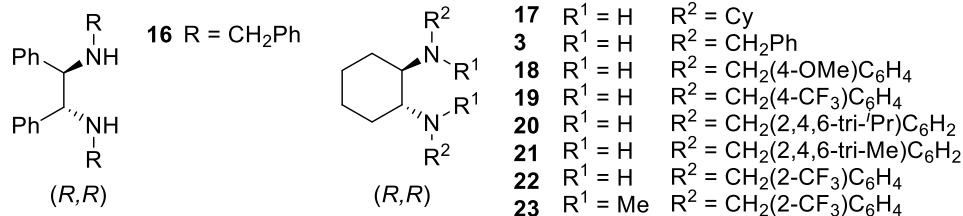
4.3 Reaction Optimization

We hypothesized that the Ni(II)-catalyst developed for the cycloaddition of nitrones with α-keto ester **10a**[16] would display similar efficiency with nitrile oxides and running the reaction at −40 °C would preclude the undesired dioxazole coproduct **14** (**Table 4-1**). Catalytic amounts of tertiary amine bases have been shown to accelerate reactions involving Ni(II)−enolates of α-keto esters,[9f] thus nitrile oxides were generated *in situ* from hydroximoyl chlorides using triethylamine. Hydroximoyl chloride **12a** was chosen as a model substrate. As shown in entries 1 and 2, utilizing Ni(OAc)$_2$ complexes of ligands **16** and **17**, these conditions did not favor formation of the desired 5-hydroxy-2-isoxazoline **13a**. In addition to the anticipated dioxazole coproduct **14a**, the intervention of the *O*-imidoylation pathway was concurrently observed (**15a**);[21] however, we were encouraged by the promising levels of stereoselectivity observed for **13a** (**Table 4-1**, entry 1: −82% ee, 11:1 dr and entry 2: −53% ee, 11:1 dr) without interference by the forecasted homo-dimerization (path A) and homo-aldol adducts (path B). A solvent screen (entries 3-5) revealed that the chemoselectivity could be dramatically improved (**Table 4-1**, entry 5: 10:1 **13a:15a**) if *N,N*-dimethylformamide was employed as solvent. In contrast, the use of

ⁱPrOH as solvent induced a preference for **15a** (Table 4-1, entry 6, 1:2 **13a:15a**). Further

screening of conditions with Ni(II) failed to yield satisfactory results.

Table 4-1 Reaction Optimization Studies
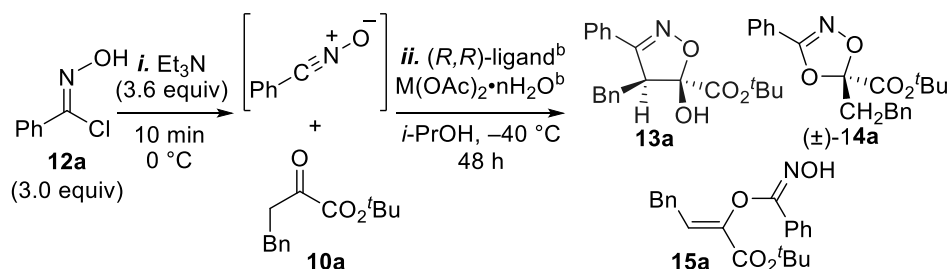
entry	lig-and	M(OAc)₂	solvent	yield **13a** [%][c]	ratio[d] **13:14:15**	dr **(13a)**[d]	ee major [%][e]
1[f]	**16**	Ni(OAc)₂	THF	34	1:0.3:1	11:1 [g]	–82
2[f]	**17**	Ni(OAc)₂	THF	20	1:1:1	11:1 [g]	–53
3[f]	**16**	Ni(OAc)₂	DCM	22	1:0.3:1	18:1	n.d.
4[f]	**16**	Ni(OAc)₂	PhMe	25	1:0.6:1	13:1	n.d.
5[f]	**16**	Ni(OAc)₂	DMF	65	10:1:1	11:1	–58
6[f]	**16**	Ni(OAc)₂	ⁱPrOH	24	1:_:2	13:1	–78
7[h]	**17**	Cu(OAc)₂	THF	<17	1:5:_	11:1 [g]	54
8[h]	**3**	Cu(OAc)₂	THF	15	1:4:_	12:1	74
9[h]	**3**	Cu(OAc)₂	DCM	16	1:5:_	12:1	74
10[h]	**3**	Cu(OAc)₂	PhMe	38	1.6:1:_	10:1	70
11[h]	**3**	Cu(OAc)₂	ⁱPrOH	77	>20:1:_	11:1	70
12[h]	**18**	Cu(OAc)₂	ⁱPrOH	86	8:1:_.	9:1	66
13[h]	**19**	Cu(OAc)₂	ⁱPrOH	72	>20:1:_	10:1	64
14[h]	**20**	Cu(OAc)₂	ⁱPrOH	79	>20:1:_	10:1	83
15[h]	**21**	Cu(OAc)₂	ⁱPrOH	82	>20:1:_	10:1	91
16[i]	**21**	Cu(OAc)₂	ⁱPrOH	75	>20:1:_	13:1	90
17[i,j]	**21**	Cu(OAc)₂	ⁱPrOH	83	>20:1:_	13:1	91
18[i,j]	**22**	Cu(OAc)₂	ⁱPrOH	86	>20:1:_	11:1	92
19[j,k]	**23**	Cu(OAc)₂	ⁱPrOH	9	1:3:0.2	12:1	8

16 R = CH$_2$Ph

(R,R)

|			
17	R^1 = H	R^2 = Cy	
3	R^1 = H	R^2 = CH$_2$Ph	
18	R^1 = H	R^2 = CH$_2$(4-OMe)C$_6$H$_4$	
19	R^1 = H	R^2 = CH$_2$(4-CF$_3$)C$_6$H$_4$	
20	R^1 = H	R^2 = CH$_2$(2,4,6-tri-^{i}Pr)C$_6$H$_2$	
21	R^1 = H	R^2 = CH$_2$(2,4,6-tri-Me)C$_6$H$_2$	
22	R^1 = H	R^2 = CH$_2$(2-CF$_3$)C$_6$H$_4$	
23	R^1 = Me	R^2 = CH$_2$(2-CF$_3$)C$_6$H$_4$	

(R,R)

a) Reactions were run on 0.1 mmol scale; M(OAc)$_2$ refers to hydrate. *b*) 20 mol % ligand and metal acetate were used unless otherwise noted. *c*) Isolated yield. *d*) Determined by ^{1}H NMR analysis of crude reaction mixture, unless noted otherwise; _ = not observed *e*) HPLC analysis using chiral stationary phase, n.d. = not determined. *f*) Isolated complex used. *g*) Isolated dr. *h*) Catalyst complexed *in situ. i*) 5 mol % of isolated complex used. *j*) 1.5 equiv **2**, 2.5 equiv Et$_3$N. *k*) 0.2 mmol scale. Catalyst complexed *in situ*; 5 mol % loading.

Switching to Cu(OAc)$_2$·H$_2$O as the metal source in THF completely eliminated the *O*-addition byproduct while favoring the opposite enantiomer of **13a** (**Table 4-1**, entry 7: 54% ee, 11:1 dr),[22] although the concurrence of the undesired hetero-[3+2] pathway was still observed. Diamine complexes of Ni(II) and Cu(II) exhibit distinct coordination geometries,[23] thereby leading to different coordination modes for the derived enolates. We postulate that these differences manifest in opposite enantiofacial selectivity in the present system. The differences in coordination geometry may also result in preferential chiral recognition of geometrically distinct nitrones (trigonal) and nitrile oxides (linear) by the Ni(II) and Cu(II) complexes, respectively, via hydrogen bonding with the H-bond donating diamine ligand. These considerations could account for the unique ability of the Cu(II) complexes to provide high enantioselectivity with nitrile oxides while the previously developed Ni(II) complexes perform poorly (**Scheme 4-6**). Along these lines,

the inclination of Ni(II) enolates to undergo *O*-trapping may, in part, result from a kinetic preference for this pathway induced by the distinct geometry of Ni(II)-enolates.

Scheme 4-6 Rationale for Stereodivergence Observed with Ni(II) and Cu(II)
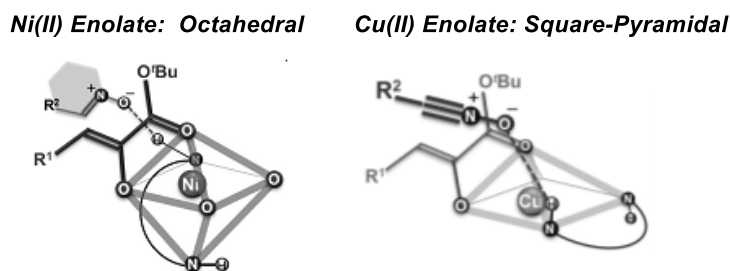
While exchanging the cyclohexyl substituted ligand **17** with the benzyl-type ligand **3** did not lead to an improvement in chemoselectivity, a noticeable enhancement in enantioselectivity was observed (**Table 4-1**, entry 8: 74% ee). Further solvent screening was performed; while no improvement in chemoselectivity occurred in DCM (**Table 4-1**, entry 9: 1:5 **13a:14a**), **13a** was favored slightly in PhMe (**Table 4-1**, entry 10: 1.6:1 **13a:14a**). We and others have noted that reactions involving transition metal enolates display enhanced rates in alcoholic solvent.[9f,24] In fact, the use of *i*PrOH gave >20:1 preference for the desired product **13a**, (**Table 4-1**, entry 11: 77% yield, 70% ee, 11:1 dr). The protic solvent may promote fragmentation of less active catalyst oligomers, or catalyst turnover from the Cu(II)-alkoxide intermediate proceeding [3+2]-cycloaddition via protonolysis.[25]

Having overcome the issue of low chemical yield, we shifted our focus toward the influence of ligand structure on enantioselectivity. The electronic features of the of the benzyl-type ligands **18** and **19** have little influence on enantioselection (**Table 4-1**, entry 12: 66% ee and Table 1, entry 13: 64% ee); however, the results with ligand **20** suggest that non-bonding interactions are important (**Table 4-1**, entry 14: 83% ee). Ligand **21** provided satisfactory levels of enantioselectivity (entry 15, 91% ee) and we were pleased to find that the catalyst loading could be reduced to 5 mol % without adversely influencing reactivity or selectivity (entry 16). Additionally, the amount of hydroximoyl chloride 1**2a** and Et_3N could be reduced to 1.5 equiv and 2.5 equiv, respectively (entry 17). The 2-CF_3 substituted benzyl-type ligand **22** also provided high selectivity for this substrate and was later found to be uniquely suited for achieving high enantioselectivity with 2-substituted benzenenitrile oxides (entry 18, 92% ee). Finally, the reduced yield and stereocontrol obtained with *N*-Me ligand **23** suggests the secondary diamine as a key design feature of the present catalyst system (entry 19, 9% yield, 8% ee).
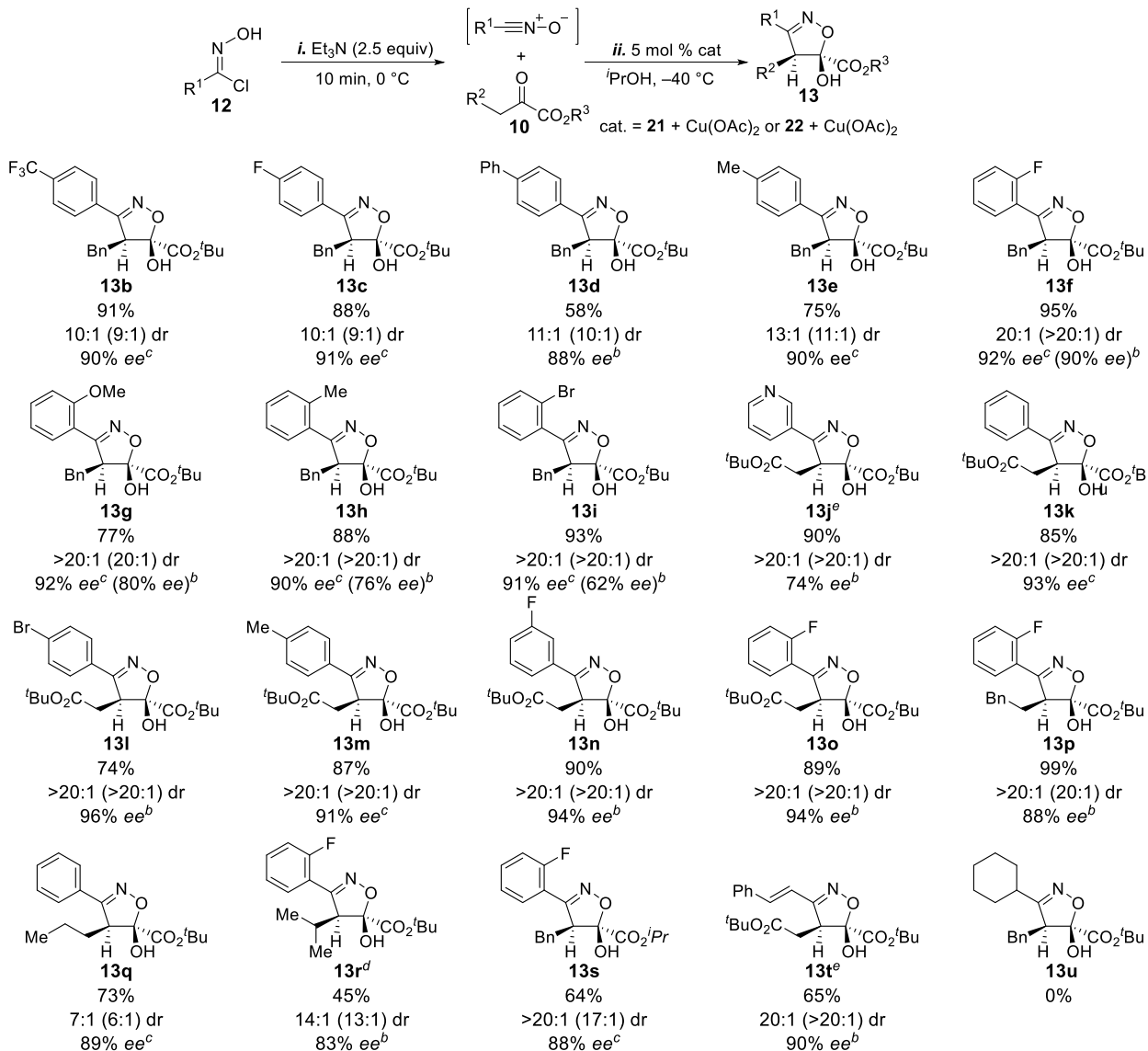
4.4 Scope of Enantioselective [3+2] Cycloaddition

With suitable reaction conditions in hand, we sought to investigate how the steric and electronic parameters of the reaction partners might affect the process (**Scheme 4-7**). Nitrile oxides bearing electron withdrawing groups in the 4-position were tolerated under the optimized conditions, for instance 4-$CF_3C_6H_4$ substituted **13b** and 4-FC_6H_4 substituted **13c** were obtained in good chemical yield with high levels of diastereo- and enantioselectivity (**Scheme 4-7**, **13b**: 91% yield, 90% ee, 10:1 dr and **13c**: 88% yield, 91% ee, 10:1 dr). Electron-rich aromatic nitrile oxides also participated and 4- PhC_6H_4 substituted **13d** and 4-MeC_6H_4 substituted **13e** were obtained with similarly high levels of diastereo- and enantioselectivity (**Scheme 4-7**, **13d**: 58% yield, 88% ee, 11:1 dr and

116

13e: 75% yield, 90% ee, 13:1 dr). Mesityl ligand **21** displayed lower levels of enantioselection when 2-substituted aryl nitrile oxides were used, however, the 2-CF$_3$ analogue **22** promoted high selectivity with these substrates. This effect was not as marked with smaller substituents as 2-FC$_6$H$_4$ **13f** was obtained in high levels of enantioselectivity using both catalysts (**Scheme 4-7**, lig. **21**: 90% ee and lig. **22**: 92% ee). The difference in selectivity increased upon moving from 2-OMe to larger 2-Me substitution (**Scheme 4-7**, **13g**: 80% ee vs. 92% ee and **13h**: 76% ee vs. 90% ee). The enantioselectivity difference was accentuated in the case of 2-BrC$_6$H$_4$ substituted **13i**, which was obtained in 62% ee using the mesityl substituted ligand **21**, while the 2-CF$_3$C$_6$H$_4$ substituted ligand **22** provided 91 % ee. Heteroaromatic nitrile oxides were compatible with the optimized reaction conditions; the 2-keto glutaric acid derived 3-pyridyl substituted **3j** could be formed, albeit with lower enantioselectivity (Table 2, **3j**: 90% yield, 74% ee). Cycloadduct **13k** was obtained in good yield, excellent diastereoselectivity, with high levels of enantioselectivity (**Scheme 4-7**, **13k**: 85% yield, 93% ee). The absolute stereochemistry of **13k** was determined via X-ray crystallography and the configurations of the remaining products are assigned by analogy. Other electronically diverse nitrile oxides reacted well with this α-keto ester (**13l-o**). The homobenzyl substituted α-keto ester furnished the corresponding cycloadduct **13p** in 88% ee with high diastereoselection when the 2-FC$_6$H$_4$ substituted hydroxyimidoyl chloride was employed. In contrast, the *n*-propyl substituted product **13q** was formed with lower levels of diastereoselectivity. A γ-branched α-keto ester could be employed when the catalyst loading was increased to 20 mol % (**Scheme 4-7**, **13r**: 45% yield, 14:1 dr, 83% ee). A β-aryl substituted α-keto ester (R^2 = 3-tolyl) provided low diastereo- and enantiocontrol during the formation of the derived cycloadduct (59% yield, 1.3:1 dr, 62%

ee and 68% ee. Similarly, lower levels of enantiocontrol were observed for a product, derived from a Me substituted α-keto ester (R^2 = Me) and 2-fluorobenzonitrile oxide, although satisfactory levels of diastereocontrol were maintained (79% yield, 54% ee, 7:1 dr. The isoxazoline, derived from *tert*-butyl pyruvate (R^2 = H), was furnished in racemic form (58% yield, 2% ee). The identity of the ester influenced enantiocontrol as lower levels of enantioselectivity were obtained for product **13s** using the *i*-propyl substituted analogue of our model α-keto ester **10a** (**Scheme 4-7**, 88% ee). Finally, alkenyl nitrile oxides are viable partners under the reaction conditions and the styryl isoxazoline **13t** was obtained in good yield, as a single diastereomer, with high levels of enantioselectivity (**Scheme 4-7**, 65% yield, 20:1 dr, 90% ee). Unfortunately, aliphatic nitrile oxides are not compatible at this stage of optimization (i.e. **13u**). Aliphatic nitrile oxides are less stable than their sp^2-carbon-substituted counterparts[15] and we believe that competitive decomposition is to blame.

Scheme 4-7 Scope of Reaction

13b	**13c**	**13d**	**13e**	**13f**
91%	88%	58%	75%	95%
10:1 (9:1) dr	10:1 (9:1) dr	11:1 (10:1) dr	13:1 (11:1) dr	20:1 (>20:1) dr
90% ee^c	91% ee^c	88% ee^b	90% ee^c	92% ee^c (90% $ee)^b$
13g	**13h**	**13i**	**13j**^{e}	**13k**
77%	88%	93%	90%	85%
>20:1 (20:1) dr	>20:1 (>20:1) dr	>20:1 (>20:1) dr	>20:1 (>20:1) dr	>20:1 (>20:1) dr
92% ee^c (80% $ee)^b$	90% ee^c (76% $ee)^b$	91% ee^c (62% $ee)^b$	74% ee^b	93% ee^c
13l	**13m**	**13n**	**13o**	**13p**
74%	87%	90%	89%	99%
>20:1 (>20:1) dr	>20:1 (>20:1) dr	>20:1 (>20:1) dr	>20:1 (>20:1) dr	>20:1 (20:1) dr
96% ee^b	91% ee^c	94% ee^b	94% ee^b	88% ee^b
13q	**13r**^{d}	**13s**	**13t**^{e}	**13u**
73%	45%	64%	65%	0%
7:1 (6:1) dr	14:1 (13:1) dr	>20:1 (17:1) dr	20:1 (>20:1) dr	
89% ee^c	83% ee^b	88% ee^c	90% ee^b	

a) The reactions were run on 0.2 mmol scale, see SI for reaction times. Yields are for isolated products. Diastereomeric ratio (dr) values were determined by ^{1}H NMR analysis of crude reaction mixture, isolated dr values were written in parentheses. The enantiomeric excess (ee) values were determined by HPLC using chiral stationary phase. b) Ligand **21** employed. c) Ligand **22** employed. d) 20 mol % of

Cu(OAc)$_2$–diamine employed. *e*) 3.0 equiv of hydroximoyl chloride, 3.6 equiv of Et$_3$N.

4.5 Gram Scale Reaction and Isoxazoline Reduction

Having established the scope of this transformation, we sought to study the reactivity of the C=N bond installed during the cycloaddition reaction (**Scheme 4-8**). We found that the 2-ketoglutaric acid derived cycloadduct **13k** could be prepared on gram scale (2.5 mol % catalyst). Under the action of NaBH$_4$/NiCl$_2$,[26] **13k** (90% ee) was converted to γ-lactam **24k** containing three vicinal stereocenters (2.5 mmol scale). Lactam **24k** was moderately enriched upon recrystallization and the structure of this product was obtained via X-ray crystallography.

Scheme 4-8 Gram Scale Reaction and Isoxazoline Reduction
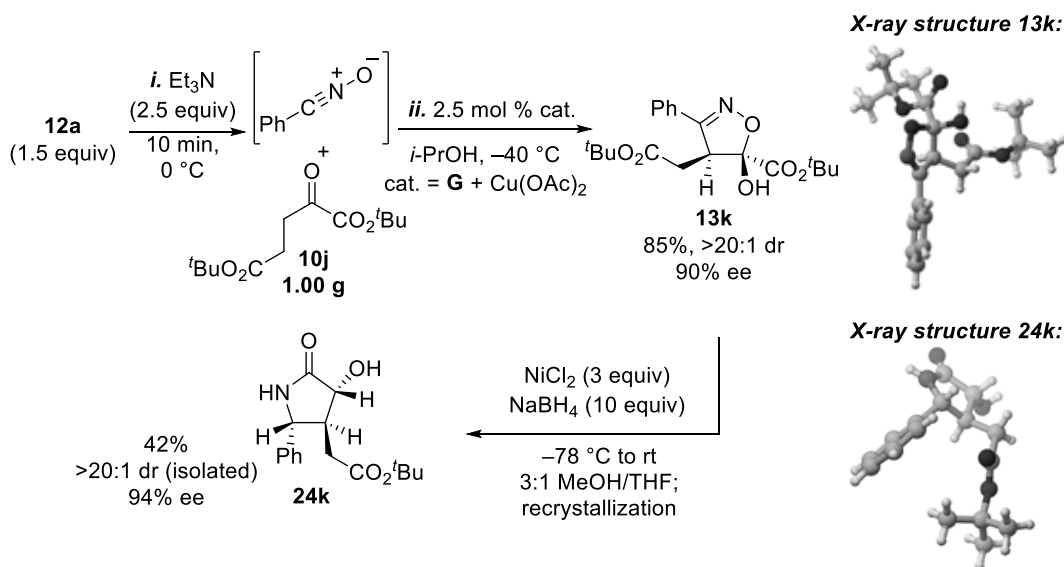
4.6 Unusual Configurational Stability of Products

The isoxazoline products delivered by the title reaction are hemiacetals that could in principle coexist with their ring-opened acyclic γ-oximo-β-keto ester isomers (**25**, **Scheme 4-9**). Such structures would appear to be quite vulnerable toward racemization

via facile keto-enol tautomerization due to high C-H acidity for the methine proton (**25** ⇆ **26**). The obtention of isoxazoline adducts **3** and a downstream adduct like **24k** with high enantiomeric enrichment allows us to draw conclusions regarding the intervention of the equilibria depicted in **Scheme 4-9**. We postulate that the lack of racemization stems from the high stability of the isoxazoline hemiacetal that disfavors ring-opening. Circumstantial evidence against formation of the acyclic oxime **25** is the constant product diastereomeric ratio as a function of time: ring opening/ring closure would presumably change the diastereomeric composition. The kinetic reluctance to form the oxime **25** may stem from the system's preference to avoid creation of a highly electrophilic α-keto ester in the presence of multiple electronegative atoms/functional groups. The isoxazoline hemiacetal thus insulates a potentially labile stereocenter from undesired racemization.

Scheme 4-9 Izoxazoline Hemiacetals do not Racemize via Tautomerization
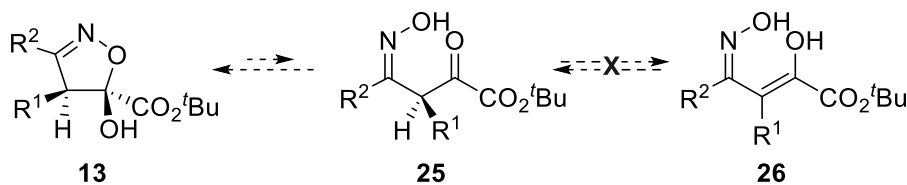
4.7 Conclusion

In summary, we have developed an enantioselective [3+2] cycloaddition reaction between nitrile oxides and transiently generated enolates of α-keto esters catalyzed by a chiral copper(II)–diamine complex. The catalyst system was found to be compatible with *in situ* nitrile oxide generation. This constitutes the first catalytic enantioselective preparation of this unique class of heterocycles, which can be transformed into interesting lactams. With this data in hand we are currently assessing the reactivity of the 5-hydroxy-

2-isoxazolines in other downstream transformations in addition to studying the mechanism of this transformation in detail. These results will be reported in due course.

4.8 Experimental Details

All air and or moisture sensitive transformations were performed in a flame dried flask or sealed Schlenk tube under a positive pressure of argon or nitrogen. Dichloromethane, toluene, and tetrahydrofuran were purified by passage through a column of activated alumina, anhydrous isopropyl alcohol was purchased and used without further purification. All commercial reagents were purchased and used without further purification. Non-commercial starting compounds and title products were purified using silica gel column chromatography with Siliaflash-P60 (40-63 μm) or silica gel N 60 (40-100 μm) silica gel. Racemic standards were purified using semi-preparative thin layer chromatography (silica gel 60 F_{254}). TLC analysis (0.25 mm silica gel 60 F_{254} precoated glass plates) employing UV light and phosphomolybdic acid or ceric ammonium molybdate stains.

Infrared spectra were recorded using a Thermo Nicolet iS5. ESI-MS spectra were obtained using a Bruker microTOF-QII-RSL. ^{1}H and ^{13}C NMR spectra were recorded at room temperature using a JEOL JNM-ECS-400 (^{1}H at 400 MHz and ^{13}C at 100 MHz), a Bruker DRX 600 (^{1}H at 600 MHz and ^{13}C at 151 MHz), and a Bruker 500 (^{1}H at 500 MHz and ^{13}C at 125 MHz). Proton and carbon chemical shifts are reported relative to $CHCl_3$ as an internal reference (^{1}H at 7.26 ppm and ^{13}C at 77.0 ppm).^{1}H NMR data are listed by chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, app t = apparent triplet, dt = doublet of triplets, m = multiplet), coupling constants, and normalized integration. Enantiomeric ratios of enantioenriched products were determined by chiral HPLC

analysis using a chiral stationary phase (Daicel CHIRALPAK IA) on a JASCO HPLC system or a Perkin Elmer flexar photodiode array (PDA) system.

α-Keto Esters **10** and hydroximoyl chlorides **12** and were prepared according to literature procedures. Triethylamine was purified by distillation and stored over 4Å molecular sieves. Ligands **3**, and **16-23** were prepared via known literature methods. In all transformations M(OAc)$_2$ refers to the hydrate: Ni(OAc)$_2$·4H$_2$O or Cu(OAc)$_2$·H$_2$O were purchased and used without further purification.

Density functional theory (DFT) calculations were performed for singlet configurations using the Gaussian 09 program package.[27] All geometry optimizations and vibrational analyses were carried out using the M06-2X functional with the 6-311+G(d) basis set.[28]

We recently reported that the (*E*)-cyclic nitrone and (*E*)-aliphatic nitrone serve as the 1,3-dipole in the [3+2] cycloaddition of a-keto ester enolate using Ni(II)–diamine catalyst.[16] To broaden the available 1,3-dipolalopihle in our catalytic strategy using metal–diamine–acetate complex, we performed DFT calculations. Initial theoretical calculations suggest that the both HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of **DFT-nitrile oxide** (HOMO: −8.12 eV and LUMO: −0.816 eV) is between those of **DFT-(*E*)-cyclic nitrone** (HOMO: −7.09 eV and LUMO: −0.831 eV) and **DFT-(*E*)-aliphatic nitrone** (HOMO: −8.19 and LUMO: −1.06 eV). On the basis of these preliminary results, we planned to apply the nitrile oxide, which can be prepared from *N*-hydroxyimidoyl chloride **12**, in the catalytic asymmetric [3+2] cycloaddition of α-keto ester enolate.

DFT-(*E*)-Cyclic nitrone　　**DFT-(*E*)-Aliphatic nitrone**　　**DFT-Nitrile oxide**
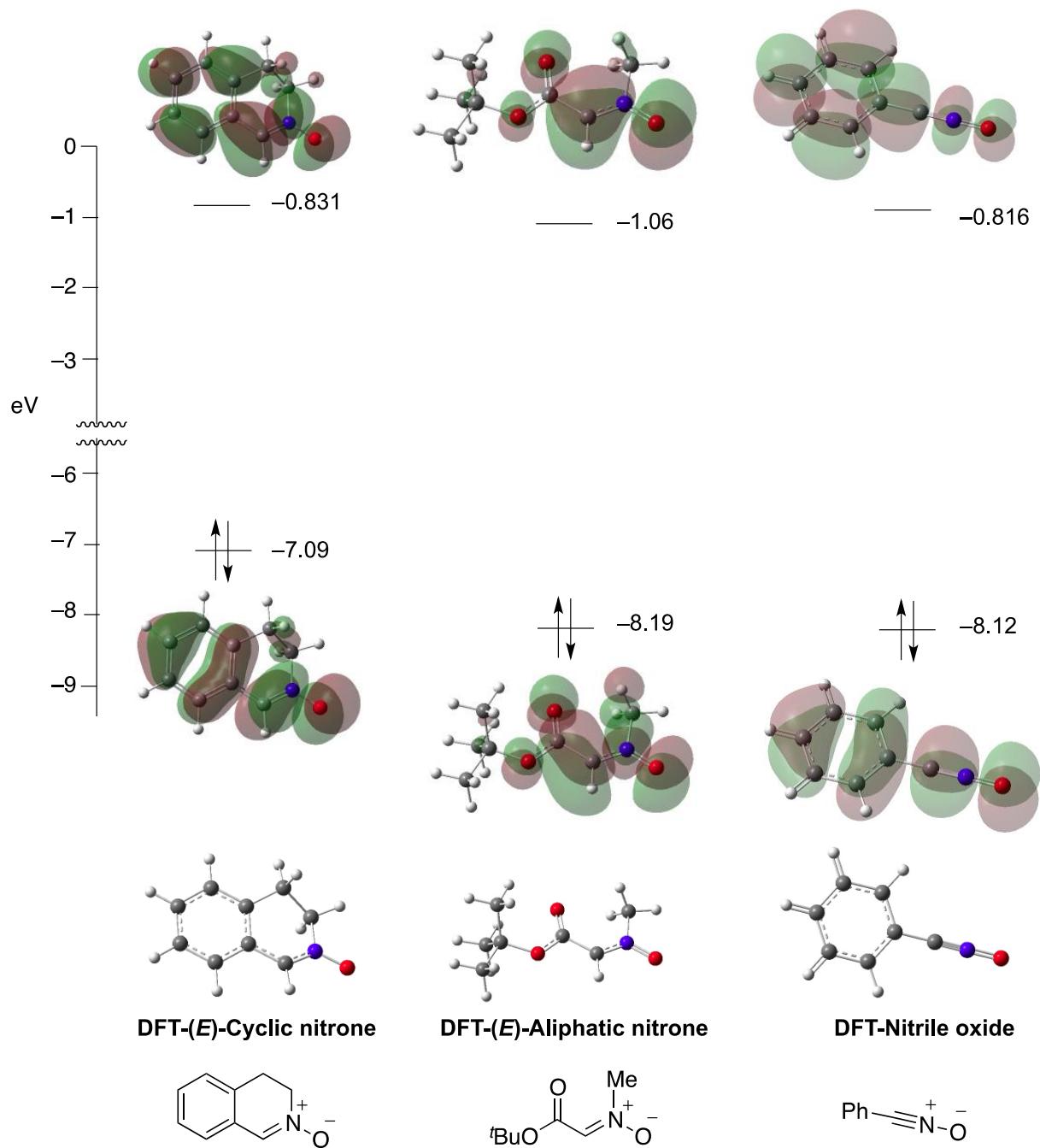
Cartesian coordinates (in Å) and energy of DFT-(*E*)-cyclic nitrone

SCF Done: E(RM062X) = −478.203232680 A.U.

			Coordinates (Angstroms)		
Center	Atomic	Atomic			
number	number	type	X	Y	Z

1	6	0	2.922814	0.383181	0.094680
2	6	0	2.705703	-0.991316	0.101682
3	6	0	1.413192	-1.492112	0.011215
4	6	0	0.326763	-0.619201	-0.086461
5	6	0	0.547528	0.766311	-0.107669
6	6	0	1.842464	1.256079	-0.013401
7	6	0	-1.032338	-1.132314	-0.178781
8	7	0	-2.074896	-0.376467	0.026379
9	6	0	-1.872710	1.050441	0.397731
10	6	0	-0.662088	1.641377	-0.302281
11	8	0	-3.271945	-0.777295	0.004779
12	1	0	3.930291	0.775847	0.169878
13	1	0	3.543611	-1.674352	0.181284
14	1	0	1.239796	-2.563308	0.023139
15	1	0	2.010599	2.328551	-0.030586
16	1	0	-1.247255	-2.174674	-0.377007
17	1	0	-1.763601	1.066419	1.485770
18	1	0	-2.803222	1.543955	0.128730
19	1	0	-0.484147	2.652169	0.070643
20	1	0	-0.874212	1.724353	-1.375023

Cartesian coordinates (in Å) and energy of DFT-(*E*)-aliphatic nitrone

SCF Done: E(RM062X) = −554.849139711 A.U.

Center number	Atomic number	Atomic type	X	Y	Z
1	8	0	0.285081	-1.302380	-0.004865
2	6	0	0.289075	-0.092934	-0.003426
3	8	0	-0.802577	0.680119	-0.002377
4	6	0	1.472069	0.773757	-0.002792
5	7	0	2.705508	0.327118	0.000607
6	8	0	3.692146	1.092210	-0.000254
7	6	0	-2.141861	0.095245	0.000863
8	6	0	-3.042865	1.322246	-0.000627
9	6	0	-2.358343	-0.730046	-1.262967
10	6	0	-2.353233	-0.723541	1.269731
11	6	0	3.025052	-1.124120	0.004035
12	1	0	1.365207	1.847844	-0.005266
13	1	0	-4.091050	1.017194	0.003657
14	1	0	-2.854230	1.935413	0.882483
15	1	0	-2.859830	1.929177	-0.889231
16	1	0	-3.409795	-1.020349	-1.325589
17	1	0	-1.749344	-1.632138	-1.265035

18	1	0	-2.118445	-0.135862	-2.147865
19	1	0	-2.113688	-0.123577	2.150822
20	1	0	-3.403439	-1.017440	1.336120
21	1	0	-1.741109	-1.623575	1.275455
22	1	0	2.578085	-1.592779	0.876529
23	1	0	4.108196	-1.171127	0.024799
24	1	0	2.614319	-1.585837	-0.890069

Cartesian coordinates (in Å) and energy of DFT-(E)-nitrile oxide

SCF Done: E(RM062X) = −399.567943760 A.U.

Center number	Atomic number	Atomic type	Coordinates (Angstroms)		
			X	Y	Z

1	8	0	3.832095	0.000201	0.000115
2	7	0	2.626621	-0.000092	-0.000012
3	6	0	1.472116	-0.000321	-0.000146
4	6	0	0.040804	-0.000403	-0.000119
5	6	0	-0.658599	-1.212208	0.000009
6	6	0	-2.046497	-1.205384	0.000017
7	6	0	-2.741692	0.000356	0.000048
8	1	0	-2.586617	-2.144876	0.000053
9	1	0	-3.825500	0.000597	0.000109

10	6	0	-2.045927	1.205822	0.000016
11	6	0	-0.658071	1.211874	0.000007
12	1	0	-2.585635	2.145556	0.000062
13	1	0	-0.108557	2.145558	-0.000030
14	1	0	-0.109605	-2.146217	-0.000029

Table 4-2 Additional Screening Experiments with Ni(II)[a]
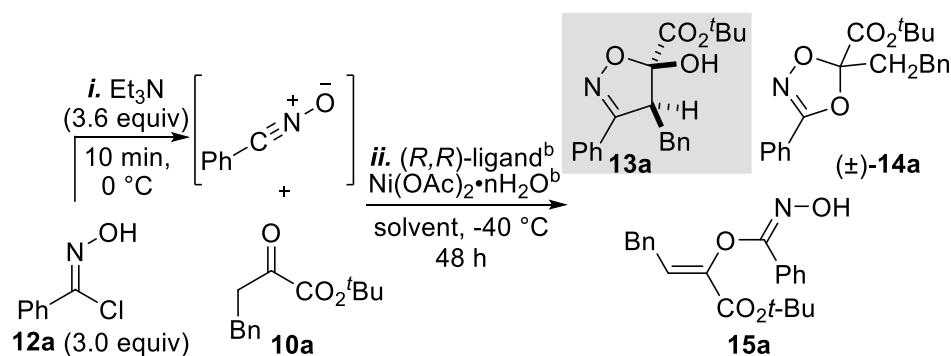
entry	ligand	solvent	yield **3a** [%][c]	Ratio[d] **3:4:5**	dr (**3a**)[d]	ee major [%][e]
1[f]	16	THF	34	1:0.3:1	11:1[g]	−82
2[f]	17	THF	20	1:1:1	11:1[g]	−53
3[f]	16	DCM	22	1:0.3:1	18:1	n.d.
4[f]	16	PhMe	25	1:0.6:1	13:1	n.d.
5[f]	16	DMF	65	10:1:1	11:1	−58
6[f]	16	iPrOH	24[j]	1:_:2	13:1	−78
7[f,i,]	16	DMF/THF[k]	51[j]	4:1:0.3	12:1	−66
8[f,i,]	16	MeCN	51[j]	2:_:1	11:1	−76
9[f,i]	16	MeOH	40[j]	2:1:0.5	11:1	−66
10[f,i]	16	DMF/NMP[k]	67[j]	11:_:1	14:1	−64
11[f,i]	16	DMF/iPrOH[k]	71[j]	11:_:1	9:1	−60
12[f,i]	16	DMF/H₂O[k]	< 13[j]	1:6:0.5	>10:1	−60
13[f,i]	16	DMF/TBME[k]	< 57[j]	2:1:0.5	10:1	−64
14[f,i,l]	16	DMF/THF[k]	n.d.	n.d.	n.d.	−60
15[f,i,m]	16	DMF/THF[k]	61[j]	12:1:1	11:1	−66
16[f,i,n]	16	DMF/THF[k]	20[j]	10:_:1	n.d.	−60
17[f,i,o]	16	DMF/THF[k]	<25[j]	1:1:_	n.d.	0
18[f,i,p]	16	DMF/THF[k]	trace	n.d.	n.d.	n.d.
19[i,q]	27	DMF	22[j]	1:2:1	14:1	−12
20[i,q]	28	DMF	47[j]	5:1:1	11:1	−44
21[i,q]	29	DMF	63[j]	11:_:1	11:1	−58
22[i,q]	30	DMF	54[j]	10:_:1	17:1	−62

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23[f,i]	3	DMF/MeCN[k]	< 80[j]	4:_:1	12:1	−30
24[i,q]	21	THF	24	1:0.2:1	13:1[g]	−60
25[i,q]	31	THF	25	2:1:1	10:1[g]	−40

a) Reactions were run on 0.1 mmol scale; Ni(OAc)$_2$ refers to hydrate. *b*) 20 mol % ligand and Ni(OAc)$_2$ were used unless otherwise noted. *c*) Isolated yield unless otherwise noted. *d*) Determined by ^{1}H NMR analysis of crude reaction mixture, unless noted otherwise, n.d. = not determined. *e*) HPLC analysis using chiral stationary phase, n.d. = not determined. *f*) Isolated complex used. *g*) Isolated dr. *h*) _ = not observed *i*) 24 h reaction time. *j*) NMR yield using mesitylene as internal standard. k) DMF/solv = 1:1 *l*) 3.6 equiv Hünig's base used in place of Et$_3$N. *m*) 3.6 equiv ^{i}Pr$_2$NH used in place of Et$_3$N. *n*) 3.6 equiv of DBU used in place of Et$_3$N *o*) 3.6 equiv TMEDA used in place of Et$_3$N. *p*) 3.6 equiv equiv 2,6-lutidine used in place of Et$_3$N. *q*) Catalyst complexed *in situ*.

(R,R)
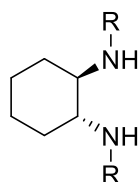
17 R = Cy
3 R = CH$_2$Ph
20 R = CH$_2$(2,4,6-tri-iPr)C$_6$H$_2$
31 R = CH$_2$(9-anthryl)

(R,R)
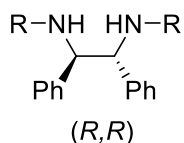
27 R = CH$_2$(2,4,6-tri-Me)C$_6$H$_2$
28 R = CH$_2$(1-naphthyl)
29 R = CH$_2$(2-naphthyl)
30 R = CH$_2$(3-Me)C$_6$H$_4$
16 R = CH$_2$Ph

Discussion: DMF afforded a large enhancement in chemoselectivity for the desired [3+2] over the *O*-imidoylation pathway. Mixed solvent systems employing DMF with less polar solvents afforded high chemoselectivity and the enantioselectivity was higher than when DMF was used alone as solvent. Unfortunately, further screening of parameters including

the identity of the amine base and chiral ligand failed to provide satisfactory enhancements in enantioselectivity.

IV. Preparation of a-Keto Esters

General procedure A :[9f]**Step 1:** To a solution of oxalyl chloride (distilled, 1.02 equiv) in THF (0.63 M relative to alcohol) was added alcohol (1.0 equiv) at 0 °C under an N_2 atmosphere. The mixture was stirred for 1 h at 0 °C, then *N,O*-dimethylhydroxylamine hydrochloride (1.02 equiv) and triethylamine (3.0 equiv) were added, and the solution was further stirred for 2 h. The reaction was quenched with saturated NH_4Cl_{aq}, and THF in the resulting mixture was evaporated under reduced pressure. The aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give *N*-methoxy-*N*-methylamide. **Step 2:** To a solution of magnesium turnings (972 mg, 40.0 mmol) in diethyl ether were added pieces of iodine. A solution of alkyl bromide (1.5 equiv.) in diethyl ether was added dropwise over 30 min at 0 °C. The reaction mixture was stirred for 1 h to give the Grignard solution. The Grignard solution was added dropwise to a solution of *N*-methoxy-*N*-methylamide (1.0 equiv), which prepared in step 1, in dichloromethane over 30 min at −78 °C. The mixture was stirred at −78 °C for 1.5 h and then the reaction was quenched with saturated aqueous NH_4Cl_{aq}. The aqueous layer was extracted with dichloromethane (50 mL x 3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The

residue was purified by column chromatography, and distilled or recrystallized to give the a-keto ester.
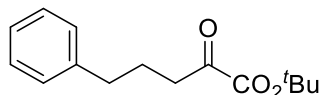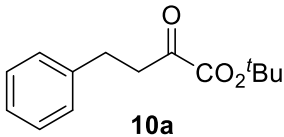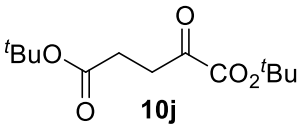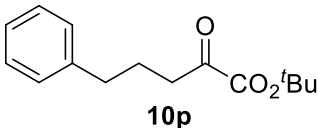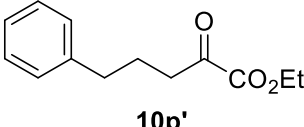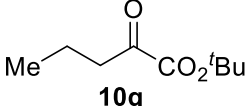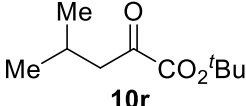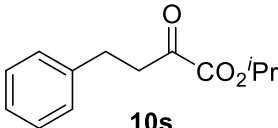
Procedure B: Synthesis of *tert*-butyl 2-oxo-5-phenylpentanoate (10p): Step 1:[29] Ethyl 2-oxo-5-phenylpentanoate **1p'** (1.00 g, 4.54 mmol) was dissolved in methanol (4.0 mL). Next, 3 M sodium hydroxide (4.0 mL) was added at room temperature resulting in an exotherm and solidification of the reaction mixture, which was left to stand for 12 h. The mixture was quenched with 3M HCl (5.0 mL), extracted with methylene chloride, and dried over anhydrous magnesium sulfate. **Step 2:** The crude α-keto acid from step 1 was dissolved in tetrahydrofuran (9.1 mL) and a small drop of *N,N*-dimethylformamide was added. The resulting solution was cooled to 0 °C using an ice bath and oxalyl chloride (0.58 mL, 864 mg, 6.81 mmol) was slowly added. The reaction was stirred for 12 h at room temperature and concentrated. **Step 3**: The crude α-keto acid chloride from step 2 was slowly added to a solution of *t*BuOH (1.01 g, 13.6 mmol) and pyridine (0.73 mL, 718 mg, 9.08 mmol) in methylene chloride (9.1 mL) cooled to 0 °C using an ice bath. The reaction was stirred for 24 h and diluted with water. The aqueous phase was extracted several times with ethyl acetate and the combined organic layers were dried over anhydrous magnesium sulfate. Silica gel column chromatography (2.5% ethyl acetate/hexanes as eluent) afforded the desired product as colorless oil (437 mg, 1.76 mmol, 39% yield over 3 steps). **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.31–7.28 (m, 2H), 7.21–7.17 (m, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 1.98–1.92 (m, 2H), 1.53 (s, 9H).
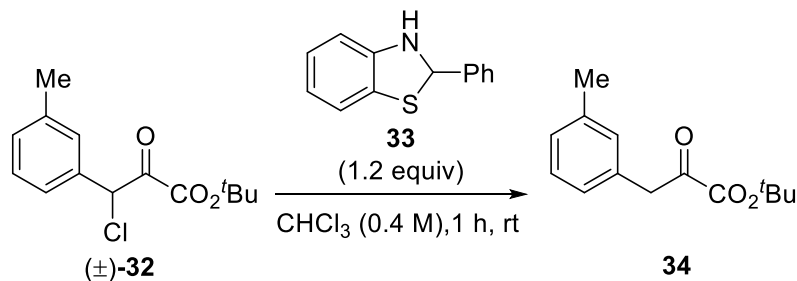
Preparation of *tert*-butyl 2-oxo-3-(m-tolyl)propanoate: *tert*-Butyl 3-chloro-2-oxo-3-(m-tolyl)propanoate **32** (640 mg, 2.38 mmol) was dissolved in chloroform (6.0 mL) in a 20 mL scintillation vial equipped with a stir bar. Benzothiazoline **33** was added (610 mg, 2.86 mmol, 1.2 equiv). The homogenous solution was stirred at room temperature for 1 h and concentrated. Silica gel column using DCM as eluent afforded the title compound **34** as a light yellow oil (482 mg, 2.06 mmol, 86% yield, approximately 90% purity). The product is depicted as the keto form, but exists as a tautomeric mixture of enol and keto isomers. Analytical data for **34**: **¹H NMR**: (2.5:1 keto:enol, benzyl methylene of keto normalized to 2H, 500 MHz, CDCl₃): δ 7.58 − 7.56 (m, 2H, enol), 7.28−7.2 (m, 2H, enol), 7.10−7.01 (m, 4H, keto), 6.55 (s, 1H, enol), 6.40 (s, 1H, enol), 4.0 (s, 2H, keto), 2.36 (s, 3H, enol), 2.33 (s, 3H, keto), 1.58 (s, 9H, enol), 1.47 (s, 9H, keto); **¹³C NMR** (2.5:1 keto: enol): CDCl₃, 150 MHz)**:** 192.7, 165.4, 160.5, 140.0, 138.4, 137.9, 135.3, 134.2, 131.8, 130.5, 130.4, 128.6, 128.5, 128.3, 128.1, 126.9, 126.8, 109.7, 84.2, 83.3, 45.8, 28.0, 27.7, 21.5, 21.3; **HRMS** (ESI): Calcd. for $C_{14}H_{18}O_3$ ([M+Na]): 257.1154, Found: 257.1147.
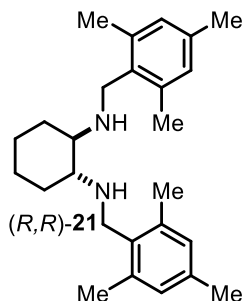
References describing preparation of known substrates and their corresponding analytical data are found below. α-Keto esters are numbered in accord with which product described in the main text they first appear in:
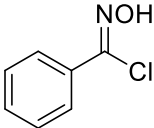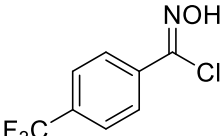
  10a	*Prepared via general procedure A* Reference 9f
  ${}^tBuO$ $CO_2{}^tBu$ **10j**	*Prepared via modified literature procedure from 2-ketoglutaric acid:* Reference 30
   $CO_2{}^tBu$ **10p**	*Prepared via Procedure B starting from the corresponding known ethyl ester.* *Procedure B adapted from:* Reference 29
  CO_2Et **10p'**	*Prepared via general procedure A* Reference 31
 Me $CO_2{}^tBu$ **10q**	*Prepared via general procedure A* 9f
 Me O Me $CO_2{}^tBu$ **10r**	*Prepared via known literature procedure:* Reference 32
  $CO_2{}^iPr$ **10s**	*Prepared via general procedure A* Reference 33
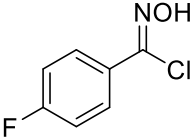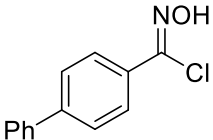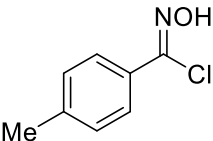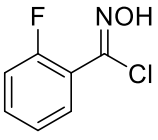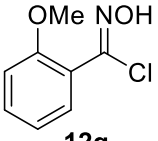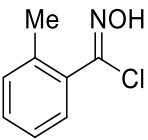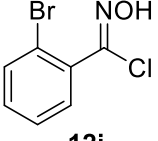
Structure	Reference
Me ... O ... CO$_2^t$Bu ... Cl ... (±)-**32**	Reference 9i
H ... N ... Ph ... S ... **33**	Reference 34
Me ... O ... CO$_2^t$Bu ... (±)-**34**	*Prepared as described above.*
O ... Me ... CO$_2^t$Bu ... **36**	Reference 9f
O ... Me ... CO$_2^t$Bu ... **38**	Reference 35
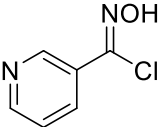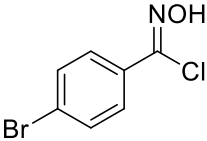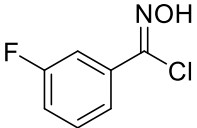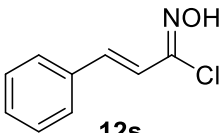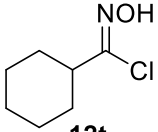
General procedure C: preparation of hydroximoyl chlorides: All hydroximoyl chlorides are known compounds that were synthesized from commercially available aldehydes according to the procedure that follows. **Step 1:** aldehyde (1.0 equiv) was added to a solution of sodium acetate (3.0 equivalents) and hydroxylamine hydrochloride in 1:1 ethanol:water (0.5 M relative to aldehyde) at room temperature. The solution was stirred at this temperature until completion was indicated by TLC. The reaction was then diluted with water and extracted three times with methylene chloride. The combined organic extracts were dried over MgSO$_4$ and concentrated. **Note:** In the case of

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hydroximoyl chlorides **12d**, **12j** and **12l** the oxime precipitated from the reaction mixture in step 1 and was collected via filtration in lieu of an aqueous work-up. **Step 2:** Without further purification, the resulting material was dissolved in DMF (1.2 M relative to aldehyde) and cooled in an ice bath. Next, *N*-chlorosuccinimide was added in a single portion and the reaction was stirred for 12-14 h. Upon completion, as indicated by TLC, the reaction mixture was diluted with ether or ethyl acetate. The organic layer was then washed three times with water, and three times with brine to remove succinimide and DMF. The organic layer was dried over MgSO$_4$ and concentrated to afford the corresponding *N*-hydroxyimidoyl chloride as an off white solid that could be used in the title reaction without further purification.

References describing preparation of known substrates and their corresponding analytical data are found below. *N*-Hydroxyimidoyl chlorides are numbered in accord with which product described in the main text they first appear in:

12a	*Prepared via general procedure C* Reference 36
12b	*Prepared via general procedure C* Reference 37

12c	*Prepared via general procedure C* Reference 38
12d	*Prepared via general procedure C* Reference 39
12e	*Prepared via general procedure C* Reference 37
12f	*Prepared via general procedure C* Reference 40
12g	*Prepared via general procedure C* Reference 36
2h	*Prepared via general procedure C* Reference 37
12i	*Prepared via general procedure C* Reference 36

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 12j	*Prepared via general procedure C* Reference 41
 12l	*Prepared via general procedure C* Reference 42
 12n	*Prepared via general procedure C* Reference 37
 12s	*Prepared via general procedure C* Reference 36
 12t	*Prepared via general procedure C*

Ligand 21: (1*R*,2*R*)-diaminocyclohexane (512 mg, 4.48 mmol) was dissolved in MeOH, mesitaldehyde (1.395 g, 9.42 mmol, 1.39 mL) was then added and the solution was heated to reflux for 17.5 h. Once the solution had reached room temperature, sodium borohydride was added in portions. Once cessation of gas evolution occurred, the solution was heated to reflux for an additional 6 h and diluted with water. Finally, the resulting solid was collected by filtration, while rinsing with H₂O, and purified by recrystallization from methanol
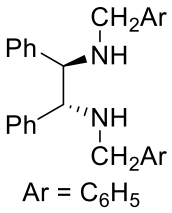
affording (1*R*,2*R*)-*N*1,*N*2-bis(2,4,6-trimethylbenzyl)cyclohexane-1,2-diamine **21** as a white solid (995 mg, 2.63 mmol, 59% yield). The spectral data for this compound were in agreement with reported literature values.
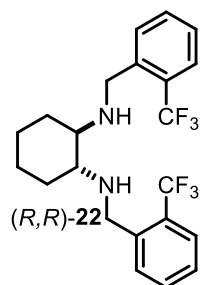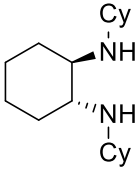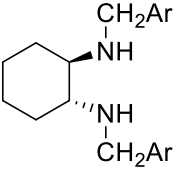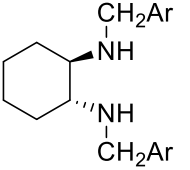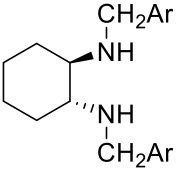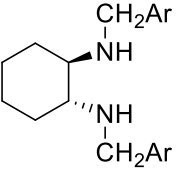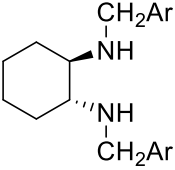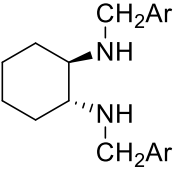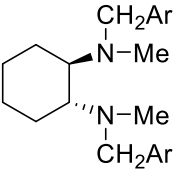
Ligand 22: Diamine ligand **22** is a known compound that can be prepared using the procedure that follows: (1*R*,2*R*)-Diaminocyclohexane (300 mg, 2.63 mmol) was dissolved in MeOH (20.0 mL). Next, 2-trifluoromethylbenzaldehyde (938 mg, 711 μL, 5.39 mmol) was added and the solution was heated at reflux for 3 h. The solution was then cooled to room temperature and sodium borohydride (298 mg, 7.88 mmol) was added in portions. Once all the sodium borohydride had been added and the evolution of gas had ceased the reaction was heated at 40 °C for 12 h, cooled to room temperature and diluted with water (100 mL). The aqueous layer was extracted three times with DCM (20 mL each extraction) and the combined organic layers dried over Na$_2$SO$_4$. Concentration of the organic layers and purification of the residue by silica gel column chromatography (50% hexane:ethyl acetate) afforded (1*R*,2*R*)-*N*1,*N*2-bis(2-(trifluoromethyl)benzyl)cyclohexane-1,2-diamine **22** as a colorless oil (501 mg, 1.16 mmol, 44% yield). The spectral data for this compound was in agreement with reported literature values.
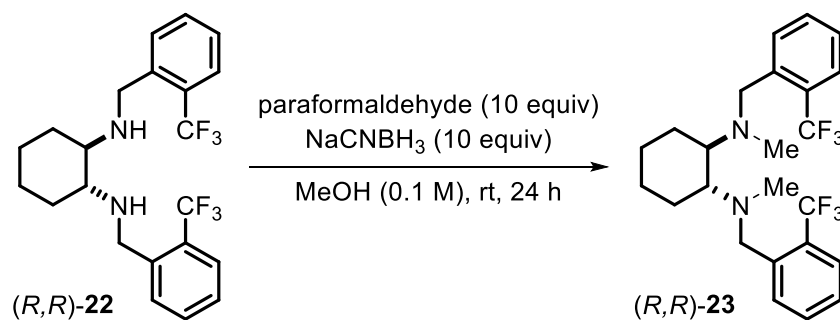
Ligand 23: Ligand **22** (343 mg, 0.80 mmol) was dissolved in MeOH (8.0 mL, 0.1 M), in a 25 mL round-bottomed flask under an N_2 atmosphere, paraformaldehyde (239 mg, 8.0 mmol, 10 equiv) was added followed by $NaCNBH_3$ (501 mg, 0.80 mmol, 10 equiv). The mixture was stirred for 48 h at room temperature. Upon complete consumption of ligand **22**, as indicated by TLC analysis, 10.0 mL of saturated aqueous $NaHCO_3$ was added and the resulting solution was extracted several times with ethyl acetate. The combined organic phase was washed with brine and dried over sodium sulfate. The crude material was purified by silica gel column chromatography (2.5% MeOH/DCM) affording Ligand **23** as a clear oil (165 mg, 0.36 mmol, 45% yield). Analytical data for ligand **23**: **¹H NMR** ($CDCl_3$, 500 MHz): δ 8.01 (d, J = 7.9 Hz, 2H), 7.62 (d, J = 7.9 Hz, 2H), 7.47–7.44 (m, 2H), 7.32–7.29 (m, 2H), 3.97 (d, J = 15.4 Hz, 2H), 3.87 (d, J = 15.3 Hz, 2H), 2.73–2.67 (m, 2H), 2.23 (s, 6H), 2.05–2.02 (m, 2H), 1.82–1.80 (m, 2H), 1.37– 1.33 (m, 2H), 1.26–1.20 (m, 2H); **¹³C NMR** ($CDCl_3$, 125 MHz): δ 140.0, 131.6, 130.3, 128.1 (q, $J_{19F-13C}$ = 29.9 Hz), 126.2, 125.2 (q, $J_{19F-13C}$ = 5.7 Hz), 124.7 (q, $J_{19F-13C}$ = 272.3 Hz), 64.9, 54.3, 35.7, 26.1, 25.8; **HRMS** (ESI): Calcd. for $C_{24}H_{28}F_6N_2$ ([M+H]): 459.2235, Found: 459.2200.

|	
CH₂Ar Ph NH Ph '''NH CH₂Ar Ar = C₆H₅ ligand **16**	Reference 43 **Note:** We advise using the procedure described in reference 23 for 1,2-diphenylethylene diamine derived benzyl-type ligands; *racemization is*

	observed when the reductive amination procedure is employed.
Cy NH (cyclohexane-1,2-diamine backbone) NH Cy ligand **17**	Reference 16
CH$_2$Ar NH (cyclohexane-1,2-diamine backbone) NH CH$_2$Ar Ar = C$_6$H$_5$ ligand **3**	Reference 44, Reference 9f
CH$_2$Ar NH (cyclohexane-1,2-diamine backbone) NH CH$_2$Ar Ar = 4-OMeC$_6$H$_4$ ligand **18**	Reference 45
CH$_2$Ar NH (cyclohexane-1,2-diamine backbone) NH CH$_2$Ar Ar = 4-CF$_3$C$_6$H$_4$ ligand **19**	Reference 45
CH$_2$Ar NH (cyclohexane-1,2-diamine backbone) NH CH$_2$Ar Ar = 2,4,6-tri-^{i}PrC$_6$H$_2$ ligand **20**	Reference 9h

	Reference 45
CH$_2$Ar NH ''NH CH$_2$Ar Ar = Mesityl ligand **21**	
CH$_2$Ar NH ''NH CH$_2$Ar Ar = 2-CF$_3$C$_6$H$_4$ ligand **22**	Reference 46
CH$_2$Ar N−Me ''N−Me CH$_2$Ar Ar = 2-CF$_3$C$_6$H$_4$ ligand **23**	Reference 47
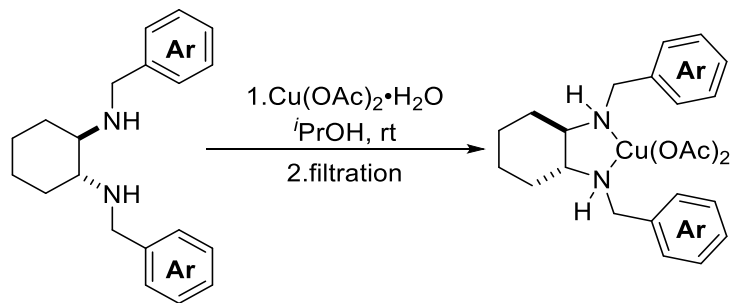
Ligand **21** or **22** (1.0 equiv) was dissolved in *^{i}*PrOH (0.05 M). Copper(II) acetate monohydrate (1.0 equiv) was then added and the resulting suspension was stirred for 4

to 6 h at room temperature, eventually producing a homogenous blue solution which was filtered through celite with DCM and concentrated to yield blue powder. Isolated 1:1 complexes of ligands **21** and **22** were air and moisture tolerant and both could be stored on the bench for months without noticeable decline in appearance or catalytic performance.

Ligand **G** + Cu(OAc)$_2$•H$_2$O

Ligand **H** + Cu(OAc)$_2$•H$_2$O
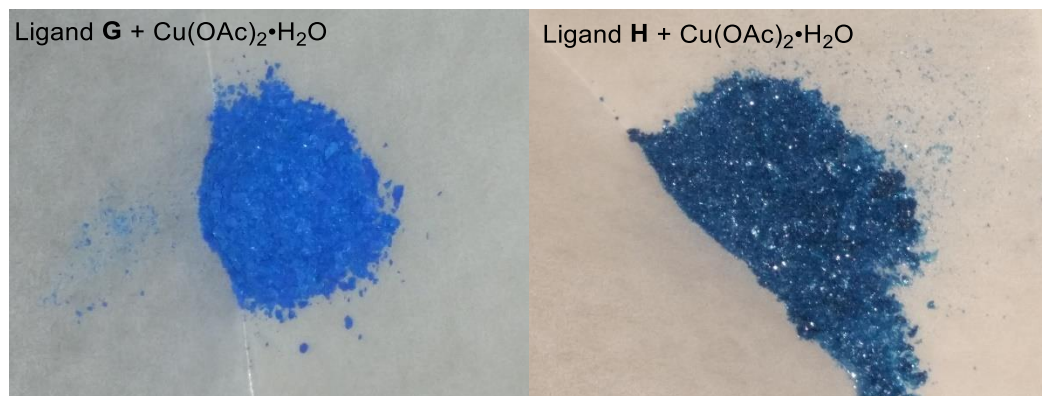
General Procedure E: Asymmetric [3+2] cycloaddition (solid α-keto esters):

To a flame dried Schlenk tube under N$_2$ was added ^{i}PrOH (2.0 mL) followed by the *N*-hydroxyimidoyl chloride (1.5 equiv, 0. 30 mmol). The resulting solution was cooled to 0 °C using an ice bath. Triethylamine (2.5 equiv, 0.5 mmol, 70 μL) slowly added (usually resulting in immediate precipitation of triethylammonium chloride) and the solution was stirred for 10 min at 0 °C. The resulting nitrile oxide was cooled to −78 °C using a dry ice/acetone bath and the solid α-keto ester (0.2 mmol) and copper complex (0.01 mmol)* were added successively. The reaction was warmed to −40 °C and stirred under an atmosphere of nitrogen or argon while monitoring periodically for completion by TLC analysis using phosphomolybdic acid to stain. Upon completion the reaction mixture was passed through a thin plug of silica gel, concentrated, and purified by silica gel column chromatography. Individual reaction times are indicated along with the analytical data below.

General Procedure F: Asymmetric [3+2] cycloaddition (liquid/oil α-keto esters): To a flame dried Schlenk tube under N_2 was added ^{i}PrOH (1.0 mL) followed by the *N*-hydroxyimidoyl chloride (1.5 equiv, 0. 30 mmol). The resulting solution was cooled to 0 °C using an ice bath. Triethylamine (2.5 equiv, 0.5 mmol, 70 µL) slowly added (usually resulting in immediate precipitation of triethylammonium chloride) and the solution was stirred for 10 min at 0 °C. Next, the resulting nitrile oxide was cooled to −78 °C using a dry ice/acetone bath and the α-keto ester (0.2 mmol, 0.2 M solution in ^{i}PrOH) and copper complex (0.01 mmol)* were added successively. The reaction was warmed to −40 °C and stirred under an atmosphere of nitrogen or argon while monitoring periodically for completion by TLC analysis using phosphomolybdic acid to stain. Upon completion the reaction mixture was passed through a thin plug of silica gel, concentrated, and purified by silica gel column chromatography. Individual reaction times are indicated along with the analytical data below.

*Calculated assuming complexation of $Cu(OAc)_2 \cdot H_2O$ (1 equiv) with ligand **21** and **22** (1 equiv) results in complexes with formulae $C_{30}H_{44}CuN_2O_4$ and $C_{26}H_{30}CuF_6N_2O_4$, respectively. Inclusion of a molecule of water into the formula for ligand **21** and ligand **22** changes the mass by 3.11% and 2.86%, respectively. Calculating catalyst loading on the basis of either formula should not significantly influence reaction performance.
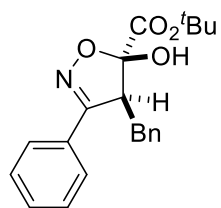
***tert*-butyl (4*S*,5*S*)-4-benzyl-5-hydroxy-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (13a):** The title compound was prepared according to General Procedure E on 0.1 mmol scale. Reaction

times = 48 h (Table 1, entries 16 and 17). The diastereoselectivity was determined by analysis of the crude ^{1}H NMR spectrum by the relative integration of the methine resonances at δ 4.45 (major diastereomer) and δ 4.32 (minor diastereomer): 11:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate yielded a colorless oil, isolated dr = 11:1. The diastereomers of **13a** were inseparable. Analytical data for **13a** (major): **^{1}H NMR** (400 MHz, CDCl$_3$, major diastereomer): δ 7.61–7.68 (m, 2H), 7.45–7.49 (m, 3H), 7.17– 7.28, 4.79 (br s, 1H), 4.10–4.49 (m, 1H), 3.03–3.11 (m, 2H), 1.30 (s, 9H); **^{13}C NMR** (100 MHz, CDCl$_3$, major diastereomer): δ 167.4, 159.9, 138.8, 130.2, 128.8, 128.6, 128.8, 128.4, 127.7, 126.5, 103.0, 84.8, 54.6, 30.7, 27.4; **IR** (thin film): 3468, 2980, 1729, 1497, 1476, 1140, 1066, 895 cm^{-1}; **TLC** (70:30 hexanes:EtOAc): R$_f$ = 0.50; **HRMS** (ESI): Calcd. for C$_{21}$H$_{23}$NO$_4$: ([M+Na]): 376.1525, Found: 376.1525; **HPLC**: IA, 90:10 hexanes/EtOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\ (major)}$ = 34.0 min, $t_{R\ (minor)}$ = 11.0 min, ligand **22**: 96:4 er, ligand **21** 95.5:4.5 er; **[α]$_D$** = 85.4 (*c* = 1.33, CHCl$_3$, 92% ee, 11:1 diastereomeric mixture).
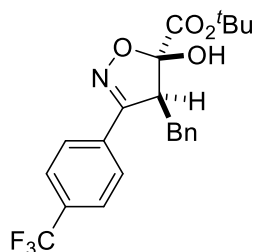
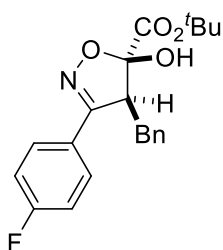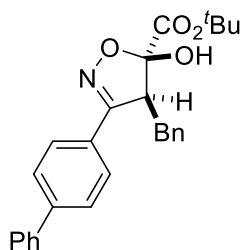***tert*-butyl (4*S*,5*S*)-4-benzyl-5-hydroxy-3-(4-(trifluoromethyl)phenyl)-4,5-dihydroisoxazole-5-carboxylate (13b):** The title compound was prepared according to General Procedure C. Reaction time = 48 h. The diasteroselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine

resonances at δ 4.45 (major diastereomer) and δ 4.28 (minor diastereomer): 10:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate

afforded a white solid, isolated dr = 9:1. The diastereomers of **13b** were inseparable. Analytical data for **13b** (major): mp = 110 °C; **¹H NMR** (400 MHz, CDCl₃, major diastereomer): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.17–7.29 (m, 5H), 4.89 (br s, 1H), 4.45 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.10 (dd, *J* = 14.2, 11.3 Hz, 1H), 3.02 (dd, *J* = 14.2, 4.1 Hz, 1H), 1.32 (s, 9H); **¹³C NMR** (150 MHz, CDCl₃, major diastereomer): δ 167.1, 159.0, 138.3, 132.2, 131.9 (q, $J_{19F-13C}$ = 32.6 Hz), 128.7, 128.5, 128.0, 126.7, 125.7 (q, $J_{19F-13C}$ = 4.5 Hz), 123.7 (q, $J_{19F-13C}$ = 270.7 Hz), 103.4, 85.1, 54.2, 30.6, 27.4; **IR** (thin film): 3469, 2982, 1732, 1165, 1073, 842 cm⁻¹; **TLC** (70:30 hexanes/EtOAc): R*f* = 0.53; **HRMS** (ESI): Calcd. for $C_{22}H_{22}F_3NO_4$: ([M+Na]): 444.1399, Found: 444.1369; **HPLC**: IA, 95:5 hexanes/*i*PrOH, flow rate = 1.0 mL/min, λ = 254 nm, *t*R (major) = 33.2 min, *t*R (minor) = 22.7 min, Ligand **22**: 95:5 er; **[α]**D = 99.7 (*c* = 1.14, CHCl₃, 90% ee, 9:1 diastereomeric mixture).

***tert*-butyl (4*S*,5*S*)-4-benzyl-3-(4-fluorophenyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (13c)**: The title compound was prepared according to General Procedure E. Reaction time = 48 h. The diastereoselectivity was determined by analysis of the crude ¹H NMR by the relative integration of the methine resonances at δ 4.42 (major diastereomer) and δ 4.25 (minor diastereomer): 10:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr = 9:1. The diastereomers of **13c** were inseparable. Analytical data for **13c** (major): **¹H NMR** (400 MHz, CDCl₃, major diastereomer): δ 7.60–7.66 (m, 2H), 7.13–7.27 (m, 7H), 4.42 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.00–3.13 (m, 2H), 1.31 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃, major diastereomer): δ 167.3, 163.8 (d, $J_{19F-13C}$ = 248.7 Hz), 159.0, 138.58, 129.68 (d, $J_{19F-13C}$ = 8.0 Hz), 128.7, 128.5, 126.6, 124.8 (d, $J_{19F-13C}$ = 3.5 Hz), 116.0 (d, $J_{19F-13C}$ = 21.8 Hz), 103.1,

84.9, 54.5, 30.7, 27.4; **IR** (thin film): 1731, 1603, 1157, 837 cm⁻¹; **TLC** (70:30 hexanes/EtOAc): R_f = 0.50; **HRMS** (ESI): Calcd. for $C_{21}H_{22}FNO_4$: ([M+Na]): 394.1431, Found: 394.1406; **HPLC**: IA, ligand **22**: 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\ (major)}$ = 34.5 min, $t_{R\ (minor)}$ = 25.4 min, 95.5:4.5 er; **[α]$_D$** = 84.7 (c = 1.48, CHCl$_3$, 91% ee, 9:1 diastereomeric mixture).
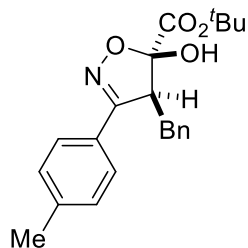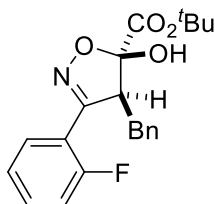

***tert*-butyl (4*S*,5*S*)-3-([1,1'-biphenyl]-4-yl)-4-benzyl-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (13d):** The title compound was prepared according to General Procedure E. Reaction time = 72 h. The diastereoselectivity was determined by analysis of the crude ¹H NMR by the relative integration of the methine resonances at δ 4.50 (major diastereomer) and δ 4.36 (minor diastereomer): 11:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr = 10:1. The diastereomers of **13d** were inseparable. Analytical data for **13d** (major): **¹H NMR** (400 MHz, CDCl$_3$, major diastereomer): δ 7.69–7.76 (m, 4H), 7.60–7.69 (m, 2H), 7.37– 7.51 (m, 3H), 7.19–7.31 (m, 5H), 4.50 (m, 1H), 3.09–3.19 (m, 1H), 1.33 (s, 9H); **¹³C NMR** (100 MHz, CDCl$_3$, major diastereomer): δ 167.4, 159.6, 143.0, 140.1, 138.8, 138.0, 128.9, 128.8, 128.4, 128.1, 127.9, 127.4, 127.1, 126.5, 103.1, 84.8, 54.6, 30.8, 27.4; **IR** (thin film): 3854, 3735, 3473, 2981, 2342, 1729, 1071, 840 cm⁻¹; **TLC** (70:30 hexanes/EtOAc): R_f = 0.53; **HRMS** (ESI): Calcd. for $C_{27}H_{27}NO4$: ([M+Na]): 452.1838, Found: 452.1881; ; **HPLC**: IA, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\ (major)}$ = 50.1 min, $t_{R\ (minor)}$ = 37.5 min, ligand **21**: 94:6 er; ; **[α]$_D$** = 85.6 (c = 1.64, CHCl$_3$, 88% ee, 10:1 diastereomeric mixture).

tert-butyl (4_S_,5_S_)-4-benzyl-5-hydroxy-3-(p-tolyl)-4,5-dihydroisoxazole-5-carboxylate (13e): The title compound was prepared according to General Procedure E. Reaction times = 72 h (Table 2, entry 5) and 48h (Table 2, entry 6). The diastereoselectivity was determined by analysis of the crude ¹H NMR by the relative integration of the methine resonances at δ 4.43 (major diastereomer) and δ 4.31 (minor diastereomer): 13:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr = 11:1. The diastereomers of **13e** were inseparable. Analytical data for **13e** (major): **¹H NMR** (400 MHz, CDCl₃, major diastereomer): δ 7.50−7.58 (m, 2H), 7.22−7.40 (m, 7H), 4.78 (br s, 1H), 4.39−4.49 (m, 1H), 3.00−3.13 (m, 2H), 2.41 (s, 3H), 1.30 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃, major diastereomer): δ 167.5, 159.8, 140.42, 138.9, 129.5, 128.8, 128.4, 127.6, 126.5, 125.7, 102.9, 84.7, 54.7, 30.8, 27.4, 21.4; **IR** (thin film): 1734, 1663, 1313, 1159, 822 cm⁻¹; **TLC** (70:30 hexanes/EtOAc): R_f = 0.47; **HRMS** (ESI): Calcd. for $C_{22}H_{25}NO_4$: ([M+Na]): 390.1681, Found: 390.1692; **HPLC**: IA, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\ (major)}$ = 22.4 min, $t_{R\ (minor)}$ = 15.0 min, ligand **21**: 95:5 er; ; **[α]$_D$** = 83.8 (_c_ = 1.33, CHCl₃, 90% ee, 11:1 diastereomeric mixture).

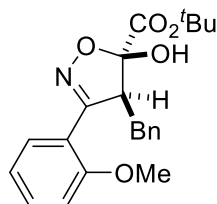**_tert_-butyl (4_S_,5_S_)-4-benzyl-3-(2-fluorophenyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (13f):** The title compound was prepared according to General Procedure E. Reaction times = 44 h (ligand **21**) and 48 h (ligand **22**). The diastereoselectivity was determined by analysis of the crude ¹H NMR by the relative integration of the methine resonances at δ 4.54 (major diastereomer) and δ 4.48 (minor diastereomer): >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil,

isolated dr >20:1. Analytical data for **13f**: **¹H NMR** (400 MHz, CDCl₃, major): δ 7.68–7.74 (m, 1H), 7.45–7.52 (m, 1H), 7.15–7.30 (m, 7H), 4.85 (br s, 1H), 4.54 (ddd, J = 11.9, 2.9, 2.9 Hz, 1H), 3.00 (dd, J = 13.6, 12.0 Hz, 1H), 2.90 (ddd, J = 13.6, 3.3, 2.0 Hz, 1H), 1.27 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃, major): δ 167.3, 159.9 (d, $J_{19F-13C}$ = 247.7 Hz), 157.7, 138.8, 132.3 (d, $J_{19F-13C}$ = 8.5 Hz), 130.6 (d, $J_{19F-13C}$ = 3.5 Hz), 128.8, 128.3, 126.4, 124.9 (d, $J_{19F-13C}$ = 3.5 Hz), 116.8 (d, $J_{19F-13C}$ = 13.1 Hz), 116.1 (d, $J_{19F-13C}$ = 21.2 Hz), 103.0, 84.7, 56.2 (d, $J_{19F-13C}$ = 3.6 Hz), 30.3 (d, $J_{19F-13C}$ = 2.4 Hz), 27.3; **IR** (thin film): 3467, 2980, 1731, 1240, 1141, 859 cm⁻¹; **TLC** (70:30 hexanes/EtOAc): R$_f$ = 0.67; **HRMS** (ESI): Calcd. for C₂₁H₂₂FNO₄: ([M+Na]): 394.1431, Found: 394.1402; **HPLC**: IA, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R (major)}$ = 28.7 min, $t_{R (minor)}$ = 20.6 min, ligand **22**: 96:4 er; **[α]**$_D$ = 108.8 (c = 1.06, CHCl₃, 92% ee, >20:1 dr).

***tert*-butyl (4*S*,5*S*)-4-benzyl-5-hydroxy-3-(2-methoxyphenyl)-4,5-dihydroisoxazole-5-carboxylate (13g):** The title compound was prepared according to General Procedure E. Reaction times = 48 h (ligands **21** and **22**). The diastereo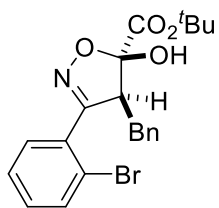selectivity was determined by analysis of the crude ¹H NMR by the relative integration of the methine resonances at δ 4.65 (major diastereomer) and δ 4.37 (minor diastereomer): >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr = 20:1 dr. Analytical data for **13g**: **¹H NMR** (400 MHz, CDCl₃, major diastereomer): δ 7.59 (dd, J = 7.5, 1.6 Hz, 1H), 7.42–7.47 (m, 1H), 7.12–7.27 (m, 5H), 7.01–7.07 (m, 1H), 6.97 (d, J = 8.3 Hz, 1H), 4.68 (br s, 1H), 4.65 (dd, J = 11.8, 3.5 Hz, 1H), 3.94 (s, 1H), 2.92 (dd, J = 13.5, 11.8 Hz, 1H), 2.79 (dd, 13.5, 3.5 Hz, 1H), 1.28 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃, major diastereomer): δ 167.5, 160.5, 157.0, 139.4, 131.7, 130.8, 128.7, 128.3, 126.2, 121.1, 117.7, 110.9, 102.7, 84.4, 56.5, 55.5, 30.3, 27.3; **IR** (thin film):

3467, 2979, 1728, 1601, 1142, 1063, 982 cm⁻¹; **TLC** (90:10 hexanes/EtOAc): R_f = 0.15; **HRMS** (ESI): Calcd. for $C_{22}H_{25}NO_5$: ([M+Na]): 406.1630, Found: 406.1648; **HPLC**: IA, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\,(major)}$ = 17.3 min, $t_{R\,(minor)}$ = 23.0min, ligand **22**: 96:4 er; **[α]$_D$** = 74.8 (c =1.33, CHCl₃, 92% ee, 20:1 dr).
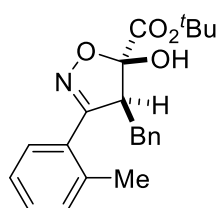
***tert*-butyl (4*S*,5*S*)-4-benzyl-5-hydroxy-3-(o-tolyl)-4,5-dihydroisoxazole-5-carboxylate (13h):** The title compound was prepared according to General Procedure E. Reaction times = 48 h (ligand **21**) and 60 h (ligand 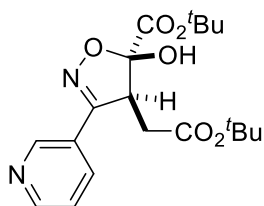**22**). The diastereoselectivity was determined by analysis of the crude ¹H NMR by the relative integration of the methine resonances at δ 4.42 (major diastereomer) and δ 4.32 (minor diastereomer): >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr >20:1. Analytical data for **13h** (major): **¹H NMR** (400 MHz, CDCl₃, major diastereomer): δ 7.11– 7.38 (m, 9H), 4.74 (br s, 1H), 4.42 (dd, J = 12.1, 3.6 Hz, 1H), 2.99 (dd, J = 13.9, 12.1 Hz, 1H), 2.70 (dd, J = 13.9, 3.6 Hz, 1H), 2.47 (s, 3H), 1.30 (s, 9H) ; **¹³C NMR** (100 MHz, CDCl₃, major diastereomer): δ 167.4, 160.7, 138.62, 137.2, 130.9, 129.6, 128.9, 128.7, 128.4, 128.0, 126.4, 125.9, 102.3, 84.6, 57.0, 30.3, 27.4, 20.3; **IR** (thin film): 3467, 2979, 2361, 1730, 1142, 1065, 893 cm⁻¹; **TLC** (70:30hexanes/EtOAc): R_f = 0.56; **HRMS** (ESI): Calcd. for $C_{22}H_{25}NO_4$: ([M+Na]): 390.1681, Found: 390.1661; **HPLC**: IA, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\,(major)}$ = 28.3 min, $t_{R\,(minor)}$ = 15.0 min, ligand **22**: 95:5 er; **[α]$_D$** = 83.1 (c = 1.45, CHCl₃, 90% ee, >20:1 dr).

***tert*-butyl (4*S*,5*S*)-4-benzyl-3-(2-bromophenyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (13i)**: The title compound was prepared according to General Procedure E. Reaction times = 48 h (ligands **21** and **22**). The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ 4.85 (major diastereomer) and δ 4.68 (minor diastereomer): >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr >20:1. Analytical data for 1**3i:** [1]**H NMR** (400 MHz, CDCl$_3$, major): 7.64–7.69 (m, 1H), 7.48–7.53 (m, 1H), 7.38–7.43 (m, 1H), 7.31–7.37 (m, 1H), 7.21–7.23 (m, 4H), 7.13–7.18 (m, 1H), 4.86 (dd, *J* = 12.2, 3.5 Hz, 1H), 4.80 (br s, 1H), 2.88–2.94 (m, 1H), 2.72 (dd, *J* = 13.7, 3.5 Hz); [13]**C NMR** (100 MHz, CDCl$_3$, major): δ 167.3, 161.4, 138.6, 133.4, 132.1, 131.6, 130.3, 128.9, 128.5, 127.9, 126.6, 122.0, 103.0, 84.9, 56.2, 30.2, 27.5; **IR** (thin film): 3469, 2980, 1731, 1143, 1062, 835 cm^{-1}; **TLC** (70:30 hexanes/EtOAc): R$_f$ = 0.50; **HRMS** (ESI): Calcd. for C$_{21}$H$_{22}$BrNO$_4$: ([M+Na]): 454.0630, Found: 454.0623; **HPLC**: IA, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, *t*R (major) = 25.4 min, *t*R (minor) = 30.1 min, ligand **22**: 95.5:4.5 er; **[α]**D = 54.5 (*c* = 1.15, CHCl$_3$, 91% ee, >20:1 dr).

***tert*-butyl (4*S*,5*S*)-4-(2-(*tert*-butoxy)-2-oxoethyl)-5-hydroxy-3-(pyridin-3-yl)-4,5-dihydroisoxazole-5-carboxylate (13j):** The title compound was prepared according to General Procedure F. Reaction time = 168 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ 4.51 (major diastereomer) and δ 4.14 (minor diastereomer): >20:1. Purification by silica gel column chromatography using 80:20 hexanes/ethyl acetate followed by 70:30

hexanes: EtOAc afforded a white solid, isolated dr >20:1. Analytical data for **13j:** mp = 135-137 °C ; **¹H NMR** (600 MHz, CDCl₃, major diastereomer): δ 8.78 (d, J = 1.5 Hz, 1H), 8.66 (dd, J = 4.8, 1.5 Hz, 1H), 7.93–7.96(m, 1H), 7.37 (dd, J = 7.6, 4.8 Hz, 1H), 5.60 (br s, 1H), 4.51 (dd, J = 11.6, 4.1 Hz, 1H), 2.68 (dd, J = 17.2, 11.6 Hz, 1H), 2.61 (dd, 17.2, 4.1 Hz, 1H), 1.55 (s, 9H), 1.38 (s, 9H); **¹³C NMR** (151 MHz, CDCl₃, major diastereomer): δ 170.3, 167.5, 156.1, 151.0, 147.9, 134.8, 124.8, 123.7, 103.8, 84.8, 81.4, 48.5, 31.6, 27.8, 27.7; **IR** (thin film): 1733, 1679, 1489, 1395, 1153, 2359 cm⁻¹; **HRMS** (ESI): Calcd. for C₁₉H₂₆N₂O₆: ([M+H]): 379.1869, Found: 379.1866; **TLC** (70:30hexanes/EtOAc): R$_f$ = 0.17; **HPLC**: IA, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R \text{ (major)}}$ = 11.6 min, $t_{R \text{ (minor)}}$ = 14.7 min, ligand **21**: 87:13 er; **[α]**$_D$ = 158.2 (c = 3.42, CHCl₃, 74% ee, >20:1 dr).
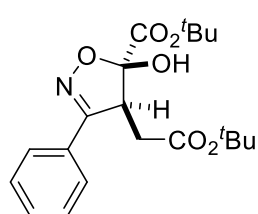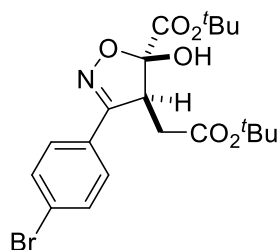

***tert*-butyl (4*S*,5*S*)-4-(2-(*tert*-butoxy)-2-oxoethyl)-5-hydroxy-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (13k)**: The title compound was prepared according to General Procedure F on 0.2 on 0.2 mmol scale. Reaction time = 24 h. No resonances corresponding to the minor diastereomer were detected in the crude ¹HNMR for **13k**: >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes: EtOAc afforded a white solid, isolated dr > 20:1. Crystals suitable for x-ray analysis were produced by titrating a suspension of **13k** in hot hexanes with ethyl acetate and allowing the resulting homogenous solution to stand at room temperature for 24 h. Analytical data for **13k:** mp = 147-149 °C; **¹H NMR** (400 MHz, CDCl₃, major diastereomer): δ 7.55 − 7.60 (m, 2H), 7.40 − 7.44 (m, 3H), 5.06 (br s, 1H), 4.46–4.56 (m, 1H), 2.62–2.72 (m, 2H), 1.57 (s, 9H), 1.39 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃, major diastereomer): δ 170.8, 168.0, 158.5, 130.2, 128.8, 128.4, 127.3, 103.3, 84.7, 81.2, 48.9, 31.9, 27.9, 27.7; **IR** (thin film): 3424, 2985, 2360, 2342, 1730, 1705, 1252, 1232, 1110, 842 cm⁻¹; **TLC** (70:30

hexanes/EtOAc): R$_f$ = 0.6; **HRMS** (ESI): Calcd. for C$_{20}$H$_{27}$NO$_6$: ([M+Na]): 400.1736, Found: 400.1727; **HPLC**: IA, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\,(major)}$ = 9.2, $t_{R\,(minor)}$ = 13.0 min, ligand **22**: 96.5:3.5 er; **[α]$_D$** = 79.5 (*c* = 1.43, CHCl$_3$, 90% ee, >20:1 dr). **Note:** the difference in enantiomeric ratio between the material used for optical rotation and the reported value (entry 14, Table 2) is due to the fact that this material was generated with ligand **21**.

***tert*-butyl (4*S*,5*S*)-3-(4-bromophenyl)-4-(2-(*tert*-butoxy)-2-oxoethyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (13l):** The title compound was prepared according to General Procedure F. Reaction time = 72 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ 4.46 (major diastereomer) and δ 4.29 (minor diastereomer): >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a white solid, isolated dr >20:1. Analytical data for **13l:** mp = 129-131 °C; **^{1}H**
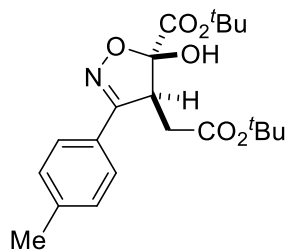

NMR (400 MHz, CDCl$_3$, >20:1 dr): δ 7.54−7.58 (m, 2H), 7.43−7.47 (m, 2H), 5.06 (br s, 1H), 4.46 (dd, *J* = 11.2, 4.4 Hz Hz, 1H), 2.66 (dd, *J* = 17.2, 11.2 Hz, 1H), 2.58 (dd, *J* = 17.2, 4.4 Hz, 1H), 1.56 (s, 9H), 1.39 (s, 9H); **^{13}C NMR** (100 MHz, CDCl$_3$, >20:1 dr): δ 170.6, 167.8, 157.7, 132.2, 128.8, 127.4, 124.7, 103.6, 84.9, 81.4, 48.6, 31.8, 27.9, 27.7; **IR** (thin film): 3459, 2984, 1736, 1719, 1368, 1143, 1010, 844 cm^{-1}; **TLC** (90:10 hexanes/EtOAc): 0.2; **HRMS** (ESI): Calcd. for C$_{20}$H$_{26}$BrNO$_6$: ([M+Na]): 478.0841, Found: 478.0814;

HPLC: IA, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\ (major)}$ = 15.3, t_R (minor) = 11.1 min, ligand **21**: 98:2 er; **[α]**$_D$ = 62.7 (c = 1.64, CHCl$_3$, 96% ee, >20:1 dr).
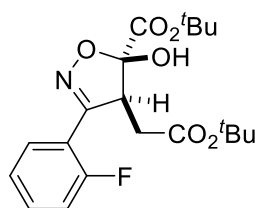
***tert*-butyl (4*S*,5*S*)-4-(2-(*tert*-butoxy)-2-oxoethyl)-5-hydroxy-3-(p-tolyl)-4,5-dihydroisoxazole-5-carboxylate (13m):** The title compound was prepared according to General Procedure F. Reaction time = 60 h. No resonances corresponding to the minor diastereomer of **13m** were detected by analysis of the crude ^{1}H NMR spectrum: >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a white solid, isolated dr >20:1. Analytical data for **13m** (major): mp = 143-155 °C; **^{1}H NMR** (400 MHz, CDCl$_3$, major diastereomer): δ 7.47 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 5.02 (br s, 1H), 4.44–4.54 (m, 1H), 2.61–2.70 (m, 2H), 2.38 (s, 3H), 1.57 (s, 9H), 1.39 (s, 9H); **^{13}C NMR** (100 MHz, CDCl$_3$, major diastereomer): δ 170.8, 168.1, 158.5, 140.5, 129.5, 127.3, 125.5, 103.2, 84.7, 81.1, 48.9, 32.0, 27.9, 27.7, 21.4; **IR** (thin film): 3460, 2980, 2360, 1729, 1394, 1302, 913 cm^{-1}; **TLC** (70:30 hexanes/EtOAc): 0.50; **HRMS** (ESI): Calcd. for C$_{21}$H$_{29}$NO$_6$: ([M+Na]): 414.1893, Found: 414.1948; **HPLC**: IA, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\ (major)}$ = 24.3, $t_{R\ (minor)}$ = 20.3 min, ligand **22**: 95.5:4.5 er; **[α]**$_D$ = 80.3 (c = 1.57, CHCl$_3$, 91% ee, >20:1 dr).
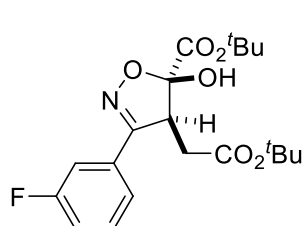
***tert*-butyl (4*S*,5S)-4-(2-(*tert*-butoxy)-2-oxoethyl)-3-(3-fluorophenyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (13n):** The title compound was prepared according to General Procedure F. Reaction time = 35 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ 4.46 (major diastereomer) and δ 4.21 (minor diastereomer): >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a white solid, isolated dr >20:1. Analytical data for **13n**

(major): mp = 125-127 °C; **¹H NMR** (400 MHz, CDCl$_3$, major diastereomer): δ 7.29–7.43 (m, 3H), 7.11–7.16 (m, 1H), 5.08 (br s, 1H), 4.46 (dd, J = 10.7, 4.9 Hz, 1H), 2.59–2.72 (m, 2H), 1.57 (s, 9H), 1.40 (s, 9H); **¹³C NMR** (100 MHz, CDCl$_3$, major diastereomer): δ 170.6, 167.8, 162.7 (d, $J_{19F-13C}$ = 245.2 Hz), 157.6, 130.6 (d, $J_{19F-13C}$ = 8.3 Hz), 130.5 (d, 8.2 Hz), 123.1 (d, $J_{19F-13C}$ = 3.3 Hz), 117.3 (d, $J_{19F-13C}$ = 21.1 Hz), 114.3 (d, 22.9 Hz), 103.6, 84.9, 81.4, 48.6, 31.7, 27.9, 27.7; IR (thin film): 1731, 1700, 1541, 1369, 1147; **TLC** (70:30 hexanes/EtOAc): 0.52; **HRMS** (ESI): Calcd. for C$_{20}$H$_{26}$FNO$_5$: ([M+Na]): 418.1642, Found: 418.1636; **HPLC**: IA, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R (major)}$ = 10.1, $t_{R (minor)}$ = 19.6 min, ligand **21**: 97:3 er; **[α]$_D$** = 73.2 (c = 0.81, CHCl$_3$, 94% ee, >20:1 dr).

***tert*-butyl (4*S*,5*S*)-4-(2-(tert-butoxy)-2-oxoethyl)-3-(2-fluorophenyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (130)**: The ti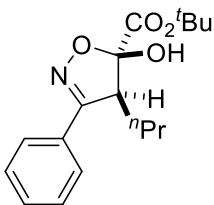tle compound was prepared according to General Procedure F. Reaction time = 37 h. The diastereoselectivity was determined by analysis of the crude ¹H NMR by the relative integration of the methine resonances at δ 4.57 (major diastereomer) and δ 4.22 (minor diastereomer): >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a white solid, isolated dr >20:1. Analytical data for **130** (major): mp = 113-115 °C; **¹H NMR** (400 MHz, CDCl$_3$, major diastereomer): δ 7.67 (td, J = 7.5, 1.8 Hz, 1H), 7.41–7.46 (m, 1H), 7.20 (td, J = 7.5, 1.0 Hz, 1H), 7.13 (dd, J = 10.8, 0.9 Hz, 1H), 5.07 (br s, 1H), 4.57 (ddd, J = 11.6, 4.0 Hz, 2.5 Hz, 1H), 2.62 (dd, J = 17.0, 11.6 Hz, 1H), 2.52 (17.0, 4.0 Hz, 1H), 1.58 (s, 9H), 1.38 (s, 9H); **¹³C NMR** (100 MHz, CDCl$_3$, major diastereomer): δ 170.6, 167.9, 159.9 (d, $J_{19F-13C}$ = 248.4 Hz), 155.9 (d, $J_{19F-13C}$ = 1.6 Hz), 132.2 (d, $J_{19F-13C}$ = 8.5 Hz), 130.4 (d, $J_{19F-13C}$ = 3.5 Hz), 124.8 (d, $J_{19F-13C}$ = 3.5 Hz), 116.6 (d, $J_{19F-13C}$ = 12.9 Hz),

116.2 (d, $J_{19F-13C}$ = 21.3 Hz), 103.5, 84.8, 81.1, 50.2, 31.4, 27.9, 27.7; **IR** (thin film): 2980, 1729, 1599, 1394, 1233, 867, 844 cm^{-1}; **TLC** (70:30 hexanes/EtOAc): 0.47; **HRMS** (ESI): Calcd. for $C_{20}H_{26}FNO_5$: ([M+Na]): 418.1642, Found: 418.1648; **HPLC**: IA, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R (major)}$ = 8.0 min, $t_{R (minor)}$ = 13.1 min, ligand **22**: 97:3 er; **[α]$_D$** = 81.0 (c = 1.21, CHCl$_3$, 94% ee, >20:1 dr).
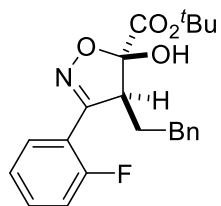
***tert*-butyl (4*S*,5*S*)-3-(2-fluorophenyl)-5-hydroxy-4-phenethyl-4,5-dihydroisoxazole-5-carboxylate (13p):** The title compound was prepared according to general procedure F. Reaction time = 48 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by integration of the methane resonance at δ 4.25 and the absence of an analogous resonance corresponding to the minor diastereomer >20:1 dr. Purification by silica gel column chromatography afforded an amorphous off white solid, isolated dr = 20:1. Analytical data for **13p**: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.68 − 7.65 (m, 1H), 7.48− 7.44 (m, 1H), 7.30−7.27 (m, 2H), 7.24−7.19 (m, 2H); 7.17−7.13 (m, 3H), 4.88 (br s, 1H), 4.25 (dt, J = 11.4, 2.58 Hz, 1H), 2.74−2.59 (m, 2H), 2.13−2.06 (m, 1H), 1.89−1.84 (m, 1H), 1.58 (s, 9H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 168.4, 159.9 (d, $J_{19F-13C}$ = 250.8 Hz), 157.7, 141.1, 132.1 (d, $J_{19F-13C}$ = 8.3 Hz), 132.1 (d, $J_{19F-13C}$ = 3.2 Hz), 128.3 (d, $J_{19F-13C}$ = 13.3 Hz), 126.1, 124.7 (d, $J_{19F-13C}$ = 3.2 Hz), 116.8 (d, $J_{19F-13C}$ = 13.2 Hz), 116.1 (d, $J_{19F-13C}$ = 21.7), 103.5, 85.1, 53.0 (d, $J_{19F-13C}$ = 3.4 Hz), 33.9, 27.7, 27.0; **IR** (thin film): 3468, 2985, 1732, 1243, 1141, 1080, 859 cm^{-1}; **TLC** (70:30 hexanes/EtOAc): R_f = 0.7; **HRMS** (ESI): Calcd. for $C_{22}H_{24}FNO_4$: ([M+1]): 386.1768, Found: 386.1767; HPLC: IA, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R (major)}$ = 27.1 min, $t_{R (minor)}$ = 22.8 min, ligand **21**: 94:6 er; **[α]$_D$** = 52.0 (c = 0.40, CHCl$_3$, 88% ee, 20:1 dr).
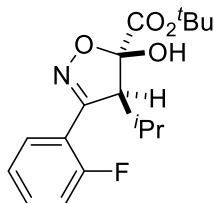
***tert*-butyl (4*S*,5*S*)-5-hydroxy-3-phenyl-4-propyl-4,5-dihydroisoxazole-5-carboxylate (13q):** The title compound was prepared according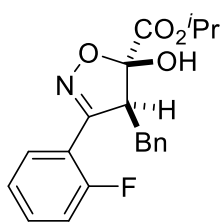 to General Procedure F. Reaction time = 36 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ 4.07(major diastereomer) and δ 3.74 (minor diastereomer): 7:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr = 6:1. The major and minor diastereomer of **13q** were inseparable. Analytical data for **13q** (major): **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.56−7.59 (m, 2H), 7.42−7.45 (m, 3H), 4.69 (br s, 1H), 4.07 (dd, *J* = 11.4, 3.1 Hz), 1.61−1.85 (m, 3H), 1.55 (s, 9H), 1.23−1.45 (m, 2H), 0.91 (dd, *J* = 9.2, 9.2 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 168.6, 160.6, 130.2,129.0, 128.8, 127.6, 103.6, 85.0, 52.2, 27.8, 27.4, 21.2, 14.1; **IR** (thin film): 3468, 2962, 2874, 2360, 1728, 1245, 1031, 837; **TLC** (70:30 hexanes/EtOAc): 0.56; **HRMS** (ESI): Calcd. for C$_{17}$H$_{23}$NO$_4$: ([M+Na]): 328.1525, Found: 328.1563; **HPLC**: IA, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\text{ (major)}}$ = 31.5 min, $t_{R\text{ (minor)}}$ = 10.6 min, ligand **22**: 94.5:5.5 er; **[α]$_D$** = 68.4 (*c* = 1.96, CHCl$_3$, 94% ee, 6:1 mixture of diastereomers).

***tert*-butyl (4S,5S)-3-(2-fluorophenyl)-5-hydroxy-4-isopropyl-4,5-dihydroisoxazole-5-carboxylate (13r):** The title compound was prepared according to General Procedure F. Reaction time = 48 h. The diastereoselectivity was

determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ 4.02 (major diastereomer) and δ 3.80 (minor diastereomer): 14:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr = 13:1. Analytical data for **13r** (major): **^{1}H NMR** (500 MHz, CDCl$_3$, major diastereomer): δ 7.65-7.62 (m, 1H), 7.45–7.41 (m, 1H), 7.23–7.20 (m, 1H), 7.13–7.10 (m, 1H), 4.80 (s, 1H), 4.03–4.02 (m, 1H), 2.25–2.18 (m, 1H), 1.54 (s, 9H), 0.98 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 169.0, 160.4 (d, $J_{19F-13C}$ = 250.1 Hz), 157.8, 131.9 (d, $J_{19F-13C}$ = 8.5 Hz), 130.2 (d, $J_{19F-13C}$ = 3.4 Hz), 124.8 (d, $J_{19F-13C}$ = 3.4 Hz), 118.5 (d, $J_{19F-13C}$ = 13.3 Hz), 116.0 (d, $J_{19F-13C}$ = 21.5 Hz), 105.2, 84.9, 57.5 (d, $J_{19F-13C}$ = 3.2 Hz), 27.7, 26.4, 19.9, 19.3; **IR** (thin film): 3464, 3071, 2969, 2936, 2342, 1731, 1617, 1342, 1302, 1261, 842 cm^{-1}; **TLC** (70:30 hexanes/EtOAc): 0.60; HRMS (ESI): Calcd. for C$_{17}$H$_{22}$FNO$_4$: ([M+Na]): 346.1431, Found: 346.1433; HPLC: IC, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R(major)}$ = 8.7 min, $t_{R(minor)}$ = 11.1 min, ligand G: 91.5:8.5 er **[α]$_D$** = 45.3 (c = 0.95, CHCl$_3$, 83% ee, 13:1 mixture of diastereomers)
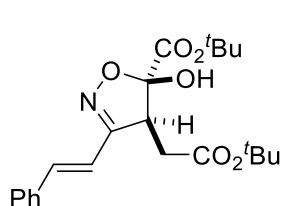

isopropyl (4S,5S)-4-benzyl-3-(2-fluorophenyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (13s): The title compound was prepared according to General Procedure F. Reaction time = 24 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ 4.57 (major diastereomer) and δ 4.46 (minor diastereomer): >20:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded a colorless oil, isolated dr = 17:1. Analytical data for **13r** (major): **^{1}H NMR** (400 MHz, CDCl$_3$, major diastereomer): δ 7.72 (m, 1H), 7.49 (m, 1H), 7.15–7.27 (m, 7H), 4.85 (sept, J = 6.3 Hz, 1H), 4.79 (br s, 1H),

4.57 (dt, J = 11.8, 3.0 Hz, 1H), 2.90–3.05 (m, 2H), 1.18 (d, J = 6.3 Hz, 3H), 0.98 (d, 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$, major diastereomer): δ 167.9, 159.9 (d, $J_{19F-13C}$ = 247.8 Hz), 157.7 (d, $J_{19F-13C}$ = 1.5 Hz), 138.6, 132.3 (d, $J_{19F-13C}$ = 8.5 Hz), 130.6 (d, $J_{19F-13C}$ = 3.5 Hz), 128.8, 128.3, 126.5, 124.9 (d, $J_{19F-13C}$ = 3.5 Hz), 116.7 (d, $J_{19F-13C}$ = 13.2 Hz), 116.1 (d, $J_{19F-13C}$ = 21.2 Hz), 102.8, 71.9, 56.3 (d, $J_{19F-13C}$ = 3.46 Hz), 30.2 (d, $J_{19F-13C}$ = 2.5 Hz), 21.3, 21.1; **IR** (thin film): 3463, 2984, 2360, 1740, 1238, 1063, 858 cm^{-1}; **TLC** (70:30 hexanes/EtOAc): 0.41; **HRMS** (ESI): Calcd. for C$_{20}$H$_{21}$FNO$_4$: ([M+Na]): 380.1274, Found: 380.1256; **HPLC**: IA, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, $t_{R\text{ (major)}}$ = 20.8 min, $t_{R\text{ (minor)}}$ = 18.6 min, ligand **22**: 94:6 er; **[α]$_D$** = 97.7 (c = 1.02, CHCl$_3$, 88% ee, 17:1 dr)

tert-butyl (4S,5S)-4-(2-(_tert_-butoxy)-2-oxoethyl)-5-hydroxy-3-((_E_)-styryl)-4,5-dihydroisoxazole-5-carboxylate (13t): The title compound was prepared according to General Procedure F. Reaction time = 48 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ 4.27 (major diastereomer) and δ 3.94 (minor diastereomer): 20:1 dr. Purification by silica gel column chromatography using 95:5 followed by 90:10 hexanes/ethyl acetate afforded a white solid, >20:1 dr. Analytical data for **13s** (major): mp = 122 to 124 °C; **^{1}H NMR** (500 MHz, CDCl$_3$): δ7.47 (m, 2H), 7.31–7.39 (m, 3H), 6.95 (d, J = 16.8 Hz, 1H), 6.86 (d, J = 16.8, 1H), 5.02 (br s, 1H), 4.23–4.31 (m, 1H), 2.74–2.82 (m, 2H), 1.56 (s, 9H), 1.44 (s, 9H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 170.9, 167.9, 158.2, 136.4, 135.4, 129.2, 128.9, 127.0, 116.3, 103.8, 84.8, 81.4, 47.9, 32.1, 27.9, 27.7; **IR** (thin film): 1732, 1473, 1396, 1151 cm^{-1}; **TLC** (70:30 hexanes/EtOAc): R$_f$ = 0.45; **HRMS** (ESI): Calcd. for C$_{22}$H$_{29}$NO$_6$: ([M+H]): 404.2073, Found: 404.2071; **HPLC**: IA, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ

= 210 nm, $t_{R \text{ (major)}}$ = 18.9 min, $t_{R \text{ (minor)}}$ = 17.6 min, ligand **21**: 95:5 er; **[α]$_D$** = 141.3 (c = 1.43, CHCl$_3$, 90% ee, >20:1 dr).
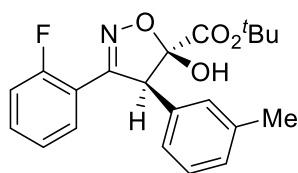
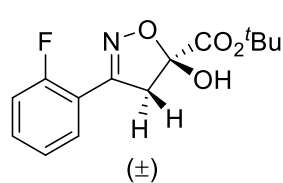**_tert_-butyl (4S,5S)-3-(2-fluorophenyl)-5-hydroxy-4-(m-tolyl)-4,5-dihydroisoxazole-5-carboxylate (35):** The title compound was prepared according to General Procedure F. Reaction time = 36 h. The diastereoselectivity was determined by analysis of the crude ^{1}H NMR by the relative integration of the methine resonances at δ = 5.40 (major diastereomer) and 5.03 (minor diastereomer): 1.3:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded **35** as a clear oil (43.6 mg, 0.12 mmol, 59% yield). Product **35** epimerized during chromatography to afford a 1.7:1 mixture favoring the opposite diastereomer. The fact that this product was still isolated via chromatography with significant levels of enantioenrichment for both diastereomers suggests the ring open form is not involved in this process. The increased acidity of this species due to conjugation with the aryl ring may promote epimerization via an alkoxyenamine intermediate. The absolute stereochemical assignment for **35** is tentative. Analytical data for **35**: **^{1}H NMR** (CDCl$_3$, 500 MHz): Distinguishing aryl protons of diastereomers was not possible, the assignment that follows includes only non aromatic resonances: δ 5.40 (s, 1H, minor), 5.03 (s, 1H, major), 4.77 (s, 1H, major), 4.45 (s, 1H, minor), 2.26 (s, 3H, major), 2.26 (s, 3H, minor), 1.59 (s, 9H, minor), 1.06 (s, 9H, major); **^{13}C NMR:** (CDCl$_3$, 150 MHz): δ 167.5, 166.8, 160.0 (d, $J_{19F-13C}$ = 252.9 Hz), 159.9 (d, $J_{19F-13C}$ = 251.7 Hz), 157, 155, 138.1, 137.9, 132.7, 132.1 (d, $J_{19F-13C}$ = 8.4), 132.0 (d, $J_{19F-13C}$ = 8.5 Hz), 131.2, 130.4, 130.0 (d, $J_{19F-13C}$ = 3.0 Hz), 129.7 (d, $J_{19F-13C}$ = 3.6 Hz), 129.6824, 128.5, 128.1, 126.8, 126.2, 124.5, 124.5, 117.0 (d, $J_{19F-13C}$ = 12.2 Hz), 116.6 (d, $J_{19F-13C}$ = 21.9 Hz), 116.5 (d, $J_{19F-13C}$ = 8.9 Hz), 116.2 (d, $J_{19F-13C}$ = 21.3 Hz), 106.2, 104.2, 85.2, 84.3, 65.6 (d,

$J_{19F-13C}$ = 5.0 Hz), 59.8 (d, $J_{19F-13C}$ = 4.3 Hz), 27.8, 27.0, 21.3, 21.3; IR (thin film): **HRMS** (ESI): Calcd. for $C_{21}H_{22}FNO_4$ **HRMS** (ESI): Calcd. for: ([M+H]): 372.1611, Found: 372.1608; **HPLC**: IC, 85:15 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 210 nm, major diastereomer: $t_{R\,(major)}$ =14.3 min, $t_{R\,(minor)}$ = 23.8 min, minor diastereomer: $t_{R\,(major)}$ = 10.0 min, $t_{R\,(minor)}$ = 21.0 min, Ligand **21**: 81:19 er (major diastereomer), 84:16 er (minor diastereomer).
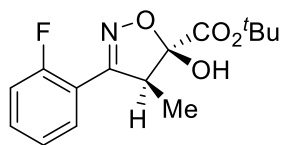
***tert*-butyl (4*S*,5*S*)-3-(2-fluorophenyl)-5-hydroxy-4-methyl-4,5-dihydroisoxazole-5-carboxylate (37):** The title compound was prepared according to General Procedure F. Reaction time = 36 h. The diastereoselectivity was determined by the relative integration of the methane resonances at δ 4.23 and δ 3.96: 7:1 dr. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded **37** as an amorphous white solid (46.9 mg, 0.16 mmol, 79% yield), 8:1 dr. Analytical data for **37** (major): **¹H NMR** (CDCl$_3$, 500 MHz): δ 7.82–7.79 (m, 1H), 7.46–7.42 (m 1H), 7.22–7.19 (m, 1H), 7.15–7.12 (m, 1H), 4.69 (s, 1H), 4.23 (q, *J* = 7.4 Hz, 1H), 1.55 (s, 9H), 1.17 (d, *J* = 7.5 Hz, 3H); **¹³C NMR** (CDCl$_3$, 150 MHz): δ 168.0, 160.0 (d, $J_{19F-13C}$ = 249.4 Hz), 158.7, 132.1 (d, $J_{19F-13C}$ = 8.6 Hz), 130.4 (d, $J_{19F-13C}$ = 3.3 Hz), 124.7 (d, $J_{19F-13C}$ = 3.2 Hz), 116.7 (d, $J_{19F-13C}$ = 12.7 Hz), 116.1 (d, $J_{19F-13C}$ = 21.6), 104.2, 85.0, 48.2 (d, $J_{19F-13C}$ = 3.7 Hz), 27.7, 9.7 (d, $J_{19F-13C}$ = 1.7 Hz); **HRMS** (ESI): Calcd. for $C_{15}H_{18}FNO_4$: ([M+H]): 296.1298, Found: 296.1289; **HPLC**: IC, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R\,(major)}$ = 10.3 min, $t_{R\,(minor)}$ = 17.0 min, Ligand **21**: 77:23 er.

***tert*-butyl**   **(±)-3-(2-fluorophenyl)-5-hydroxy-4,5-dihydroisoxazole-5-carboxylate (39):** The title compound was prepared according to General Procedure F. Reaction time = 36 h. Purification by silica gel column chromatography using 90:10 hexanes/ethyl acetate afforded **39** as a colorless oil (32.8 mg, 0.12 mmol, 58% yield) Analytical data for **39**: **¹H NMR** (CDCl$_3$, 500 MHz): δ 7.93–7.90 (m, 1H), 7.43–7.40 (m, 1H), 7.21–7.18 (m, 1H), 7.14–7.10 (m, 1H), 4.70 (s, 1H), 3.98 (d, J = 18.1, 1H), 3.48 (dd, *J* = 18.1 Hz, J_{19F-1H} = 2.6 Hz, 1H), 1.54 (s, 9H); **¹³C NMR** (CDCl$_3$, 150 MHz): δ = 167.2, 160.4 (d, $J_{19F-13C}$ = 250.7 Hz), 153.0 (d, $J_{19F-13C}$ = 2.5 Hz), 132.2 (d, $J_{19F-13C}$ = 8.3 Hz), 129.0 (d, $J_{19F-13C}$ = 2.3 Hz), 124.6 (d, $J_{19F-13C}$ = 3.2 Hz), 116.8 (d, $J_{19F-13C}$ = 11.4 Hz), 116.4 (d, $J_{19F-13C}$ = 21.9 Hz), 103.4 (d, $J_{19F-13C}$ = 2.4 Hz), 85.0, 45.2 (d, $J_{19F-13C}$ = 7.7 Hz), 27.7; **HRMS** (ESI): Calcd. for C$_{14}$H$_{16}$FNO$_4$: ([M+H]): 282.1142, Found: 282.1135; **HPLC:** OJ-H, 91:9 hexanes/^{i}PrOH, flow rate 1.0 mL/min, λ = 210 nm, $t_{R\ (major)}$ = 8.2 min, $t_{R\ (minor)}$ = 9.1 min, Ligand **21**: 51:49 er.
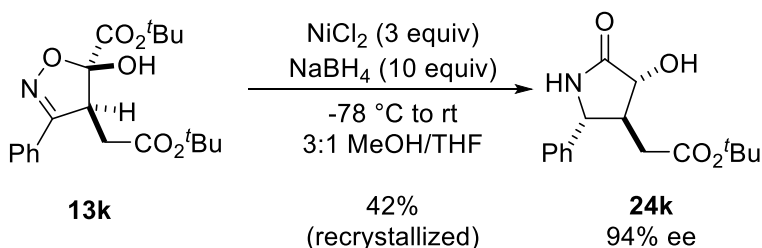
Isoxazoline **13k** (954 mg, 2.53 mmol, 90% ee) was dissolved in MeOH (12.7 mL) and THF (4.21 mL) in a 300 mL RBF. NiCl$_2$·6H$_2$O (1.80 g, 7.58 mmol) was added and the resulting solution was cooled to −78 °C using a dry ice/acetone bath. Sodium borohydride (956 mg, 25.3 mmol) was added in several portions (each addition immediately produced a black soot-like material, presumed to be nickel boride). After complete addition of NaBH$_4$ a septum was placed on the flask, which was then sealed with electrical tape. The

suspension was allowed to stir at −78 °C for 7.5 h and then warmed to room temperature slowly, and stirred for an additional 22 h before being quenched with ammonium hydroxide (50 mL). The resulting biphasic mixture was filtered through a thin pad of silica gel using ethyl acetate to rinse. The aqueous layer was further extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated. The resulting material was then purified by recrystallization from ethyl acetate/hexanes affording **24k** (white solid, 314 mg, 1.08 mmol, 94% ee, >20:1 dr, 42% yield). The higher level of enantioenrichment for **24k** relative to **13k** is most likely due to enrichment upon crystallization. The crude er of **24k** was not measured due to the presence of co-products and impurities. Analytical data for **24k**: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.33–7.41 (m, 5H), 6.13 (br s, 1H), 4.32 (d, J = 9.3 Hz, 1H), 4.26 (d, J = 8.6 Hz, 1H), 4.00 (br s, 1H), 2.43–2.6 (m, 3H), 1.38 (s, 9H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 175.3, 171.5, 138.9, 129.1, 128.8, 126.9, 81.9, 74.0, 59.2, 50.4, 35.5, 27.9; **IR** (thin film): 3278, 2979, 2360, 1708, 1392, 1152 cm^{-1}; **HRMS** (ESI): Calcd. for C$_{16}$H$_{22}$NO$_4$: ([M+H]): 292.1549, Found: 292.1544; **HPLC**: IC, 80:20 hexanes/EtOH, flow rate = 1.0 mL/min, λ = 210 nm, $t_{R \text{ (major)}}$ = 13.7 min, $t_{R \text{ (minor)}}$ = 17.2 min; **[α]$_D$** = -12.8 (c = 3.42, CHCl$_3$, 94% ee).

Single crystal X-ray diffraction data were collected with a Rigaku RAXIS-RAPID imaging-plate diffractometer (**13k**) and a Bruker APEX-II CCD diffractometer (**24k**).
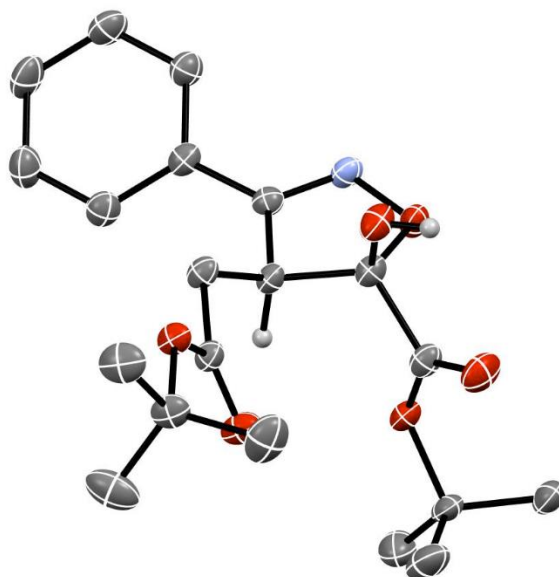
ORTEP drawing of 13k (CCDC 1476444). H atoms except for those on chiral carbon and on alcohol are omitted for the sake of clarity.

Crystallographic data of 13k (CCDC 1476444).

Molecular formula	$C_{20}H_{27}NO_6$
Formula weight	377.42
T (K)	90
Wavelength (Å)	1.54184
Color	Colourless
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	10.67160(19)
b (Å)	11.1383(2)

|	
c (Å)	34.5954(6)
V (Å³)	4112.13 (13)
Z	8
Density (Mg/m³)	1.219
Absorption coefficient (mm⁻¹)	0.742
F (000)	1616
Crystal size (mm³)	0.495 x 0.492 x 0.224
Theta range for data collection	4.170 to 68.251
(°)	84980
Reflections collected	7535
Independent reflections	SHELXL-2014/7
Software for refinements	1.087
Goodness of fit on F^2	0.0338, 0.0725
R_1, wR_2 [$I>2\sigma(I)$]	0.0351, 0.0730
R_1, wR_2 (all data)	-0.02(4)
Flack parameter	
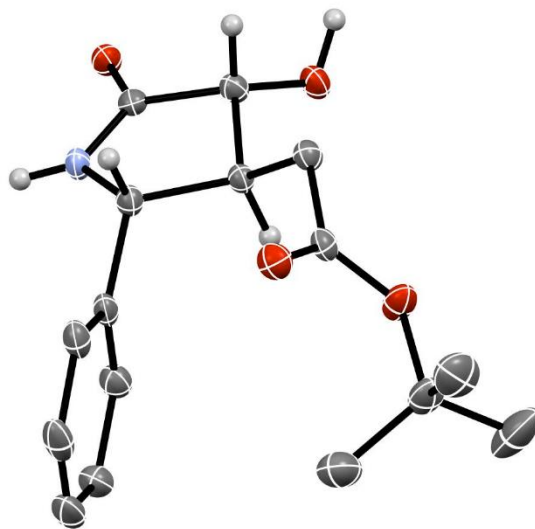
ORTEP drawing of 24k (CCDC 1476445). H atoms except for those on chiral carbons, amine and alcohol are omitted for the sake of clarity.

Crystallographic data of 24k (CCDC 1476445).

Molecular formula	$C_{16}H_{21}NO_4$
Formula weight	291.34
T (K)	100
Wavelength (Å)	1.54178
Color	Colourless
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	6.0729(3)
b (Å)	8.3117(5)
c (Å)	30.5846(17)

V (Å³)	1543.79(15)
Z	4
Density (Mg/m³)	1.253
Absorption coefficient (mm⁻¹)	0.736
F (000)	624
Crystal size (mm³)	0.341 x 0.206 x 0.038
Theta range for data collection (°)	2.890 to 74.348
	23787
Reflections collected	3121
Independent reflections	Olex2 1.2
Software for refinements	1.085
Goodness of fit on F^2	0.0320, 0.0725
R_1, wR_2 [$I>2\sigma(I)$]	0.0323, 0.0835
R_1, wR_2 (all data)	-0.02(4)
Flack parameter	

As we described in Table 1, in the main text, we found the unique metal-dependent enantioswitching using (*R,R*)-diamine as a chiral ligand in the [3+2] cycloaddition of a-keto ester enolate with nitrile oxide. The Ni(II)–(*R,R*)-diamine complex gave (*R,R*)-**13a** as the major product (Table 1, entries 1, 2 and 5), while Cu(II)–(*R,R*)-diamine complex mainly afforded (*S,S*)-**13a** (Table 1, entries 6–17). The enantioselectivity trend [Ni(II):

(R,R)-selective vs. Cu(II): (S,S)-selective] is general regardless the substituents (R and R')

on the (R,R)-diamine and solvents we used.
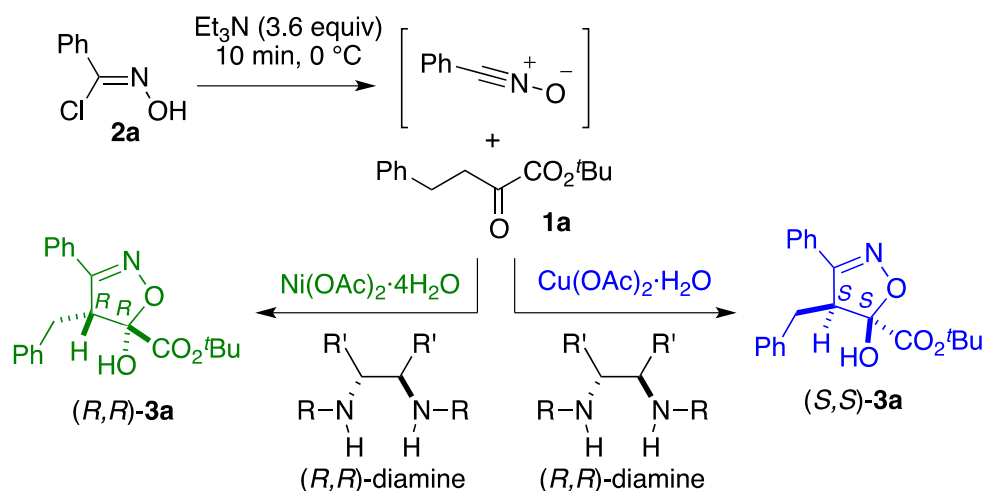
On the basis of a series of structural analyses in both the solid and solution states, supported by DFT calculations, we proposed a model that enables the merger of enolate formation and H-bonding activation with amine ligand (Sohtome, Y.; Nakamura, G.; Muranaka, A.; Hashizume, D.; Lectard, S.; Tsuchimoto, T.; Uchiyama, M.; Sodeoka, M. *Nature Commun.*, **2017**, *8,* 14875.). In this model, the carbonyl group in the ester in **1** coordinates to Ni(II) at the pseudoapical position. The H-bonding activation of the (*E*)-nitrone would be a key driving force for the major pathway in the [3+2] cycloadditions of a-keto ester enolates with (*E*)-nitrones. Analogically, the (R,R)-selectivity of the [3+2] cycloaddition of a-keto ester enolates with nitrile oxides using the Ni(II) complex can be well explained.

Ni–O1: 2.140(1) Å
Ni–O2: 2.101(1) Å
Ni–O3: 2.045(1) Å
Ni–O4: 2.302(1) Å

Ni–N1: 2.091(1) Å
Ni–N2: 2.109(1) Å

CCDC 1482739
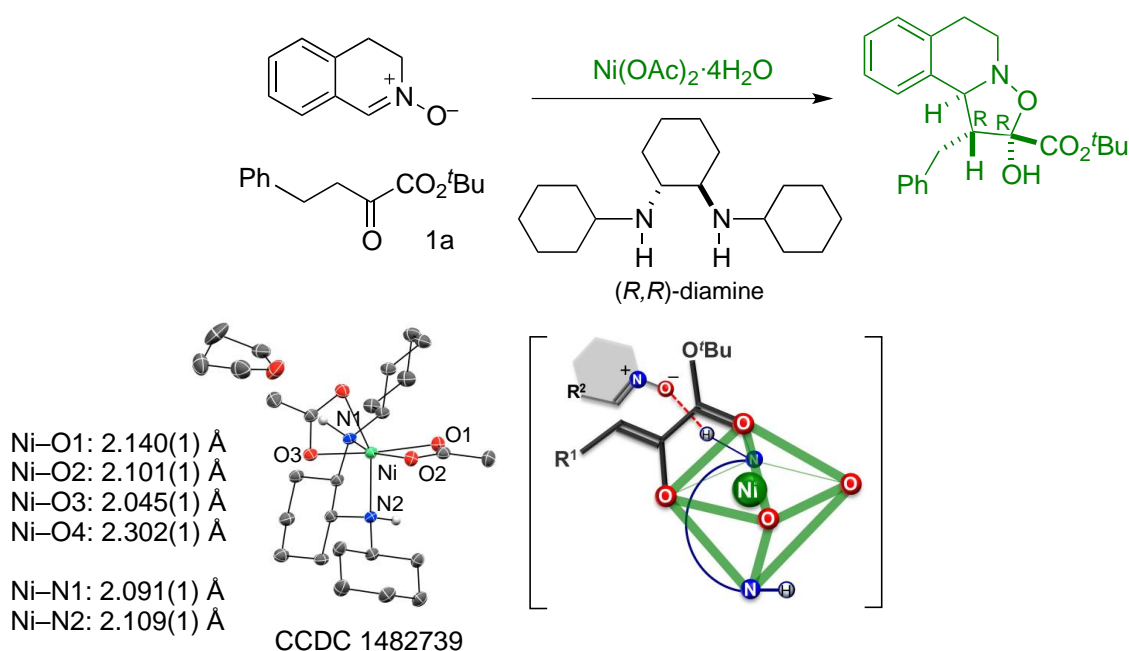
In contrast to the distorted octahedral Ni(II)–diamine–acetate complex, the Cu(II)–diamine–acetate complex exhibits the distorted square-pyramidal geometry (ex. CCDC 299401: Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2006**, 616–618. CCDC 665454: Zhang, G.; Yashima, E. Woggon, W.-D. *Adv. Synth. Catal.* **2009**, *351*, 1255–1262. CCDC 894524: Tanaka, K.; Asakura, A.; Muraoka, T.; Kalicki, P.; Urbanczyk-Lipkowska, *New J. Chem.* **2013**, *37*, 2851–2855.). As shown in the stick illustration below, the diamine ligand occupies the equatorial plane in the Cu(II) complex. One of the acetates coordinates to the Cu(II)-center in the apical-equatorial mode. In contrast, the other acetate coordinates to the Cu(II)-center in a monodentate fashion. A feature in the distorted square-pyramidal Cu(II) complex is the distance between Cu(II) and pseudoapical O(2) [2.78(1) Å], which is significantly longer than other Cu(II)–O and Cu(II)–N distances [1.907(8)–2.054(8) Å], suggesting weak coordination. We can find the similar structural features with other related Cu(II)–diamine–acetate

complexes (CCDC 665454 and CCDC 894524). Based on these structural features in the Cu(II)–diamine–acetate complexes as well as our structural investigation of Ni(II)–diamine–acetate complex (Sohtome, Y.; Nakamura, G.; Muranaka, A.; Hashizume, D.; Lectard, S.; Tsuchimoto, T.; Uchiyama, M.; Sodeoka, M. *Nature Commun.*, **2017**, *8*, 14875.), we speculate that a Cu(II)–enolate, in which the carbonyl group in the ester coordinates to Cu(II) at the pseudoapical position, is generated. Considering that the N–H functionality on the Cu(II)–diamine complex can act as Brønsted acid (CCDC 1038527: Tanaka, K.; Iwashita, T.; Yoshida, E.; Ishikawa, T.; Otuka, S.; Urbanczyk-Lipkowska, Z.; Takahashi, H. *Chem. Commun.* **2015**, *51*, 7907.), we assume that the H-bonding activation of the nitrile oxide with amine ligand is a reasonable mechanistic scenario to explain the obtained absolute stereochemistry of **13a**. Further mechanistic studies are ongoing.

Cu–O1: 1.966(8) Å
Cu–O2: 2.78(1)   Å
Cu–O3: 1.907(8) Å

Cu–N1: 2.054(8) Å
Cu–N2: 1.999(8) Å
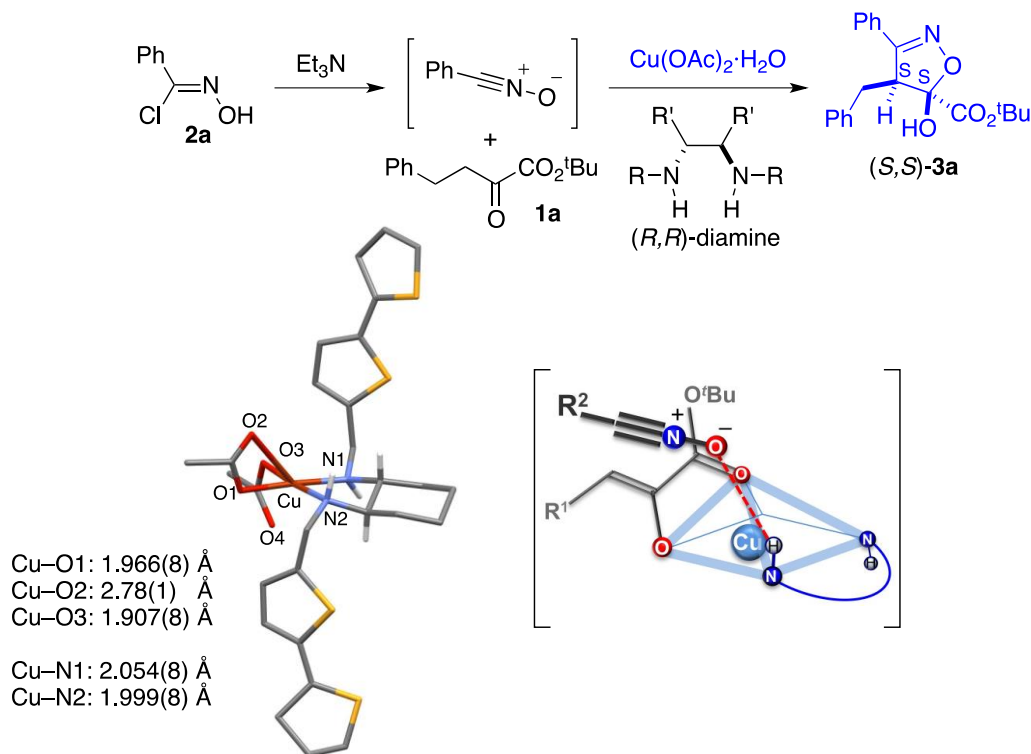
Mirror inverted image was drawn using GaussView
from CCDC 299401

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