COMPLEXITY-BUILDING TRANFORMATIONS ENABLED BY BRØNSTED BASE ORGANOCATALYSIS AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF THE *VERATRUM* ALKALOIDS JERVINE, CYCLOPAMINE, AND VERATRAMINE

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

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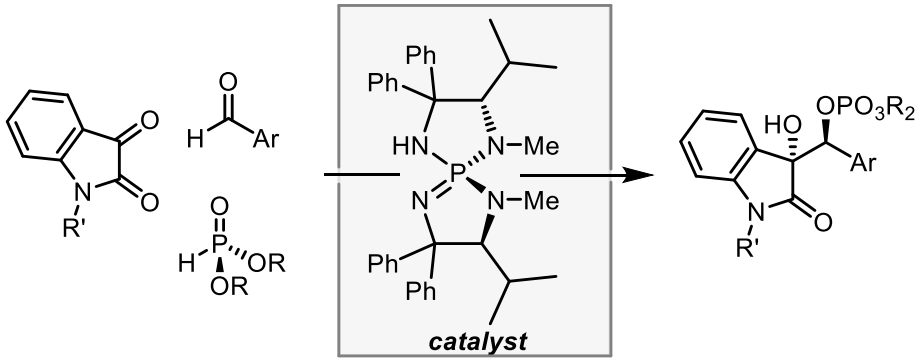
ABSTRACT

MATTHEW ALLAN HORWITZ: COMPLEXITY-BUILDING TRANFORMATIONS ENABLED BY BRØNSTED BASE ORGANOCATALYSIS
AND
PROGRESS TOWARD THE TOTAL SYNTHESIS OF THE *VERATRUM* ALKALOIDS JERVINE, CYCLOPAMINE, AND VERATRAMINE
(Under the direction of Jeffrey S. Johnson)

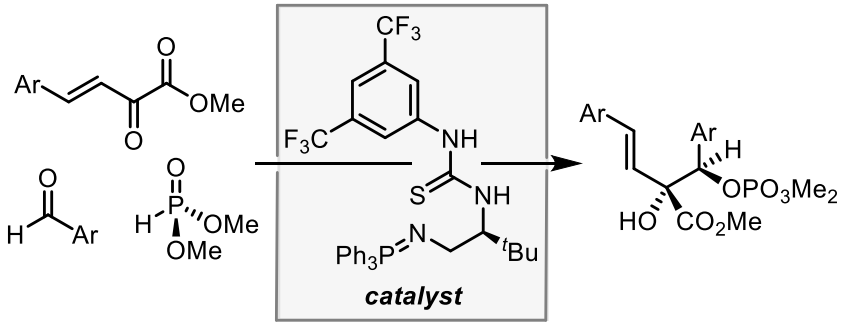
I. Asymmetric Organocatalytic Reductive Coupling Reactions between Isatins and Aldehydes

A fully organic phosphite-mediated stereoselective reductive coupling reaction between isatins and aldehydes was developed. A Pudovik-phospha-Brook sequence was used to invert the polarity of the isatin, which allowed the formation of an enolate intermediate. Subsequent aldol-type addition into aldehydes provided a new carbon-carbon bond and two new stereocenters with high yields and stereoselectivities using a chiral triaminoiminophosphorane organocatalyst. Using this novel *umpolung* reaction, chemically differentiated diols were formed and a new two-electron pathway for reductive coupling of carbonyl reaction partners was demonstrated.



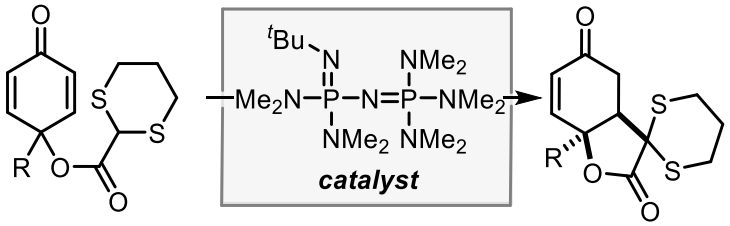
II. Asymmetric Organocatalytic Reductive Coupling Reactions between Benzylidene Pyruvates and Aldehydes

Utilizing the previously developed two-election reductive coupling mechanism, dimethyl phosphite was used as an organic reductant to reductively couple benzylidene pyruvates and aldehydes. Though a larger number of selectivity issues were present in this case, the desired mode of carbonyl coupling was enabled in a stereoselective fashion using a chiral triaryliminophosphorane catalyst. Using this reaction manifold, a range of highly functionalized stereodyads were generated in high diastereoselectivity, enantioselectivity, and yield. The reaction was demonstrated to work on gram scale.



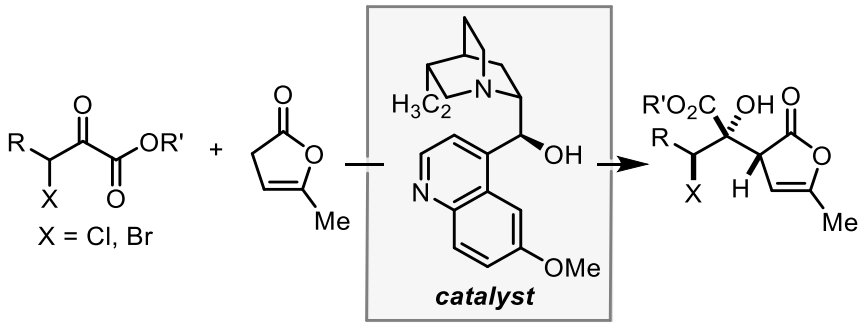
III. Phosphazene-catalyzed Desymmetrization of Cyclohexadienones by Intramolecular Dithiane Addition

A phosphazene-catalyzed desymmetrization reaction of dithiane-tethered cyclohexadienones is established. Using the ester-bound dithiane nucleophile, a conjugate addition reaction was found to be possible using catalytic P2-^{t}Bu phosphazene base. A series of products containing two nascent stereocenters was synthesized in a racemic sense. Chiral iminophosphorane catalysts were studied but were found to not give enantioenrichment in the product. Deprotection of the dithiane and desulfurization were studied but proved unsuccessful. An independent synthesis of the α-ketolactone that would result from dithiane deprotection also failed using an oxidative deacylation strategy, suggesting an inherent product stability issue.



IV. Diastereoselective Organocatalytic Addition of α-Angelica Lactone to β-Halo-α-ketoesters

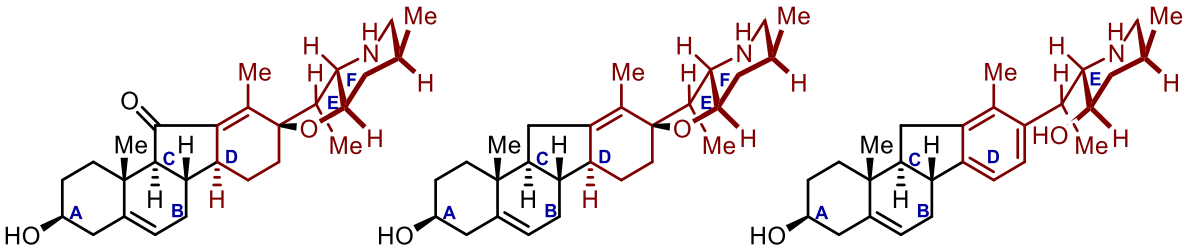
A diastereoselective addition of α-angelica lactone to β-halo-α-ketoesters is discussed. Using commercial quinidine as an organocatalyst, three contiguous stereocenters were set in a relative sense. The scope of the reaction demonstrated that high diastereoselectivity was possible in several cases with either a β-bromo or β-chloro substituent on the α-ketoester, though yields were moderate. A stereochemical model was developed to explain the observed outcome. Though α-angelica lactones are most commonly nucleophilic at the γ-position, this reaction was found to proceed with an observed α-nucleophilicity of the α-angelica lactone. Hydrogenation of the product was found to result in a diastereoselective formation of a fourth stereocenter by delivery of hydrogen to the least hindered face of the alkene.



V. Progress Toward the Total Synthesis of the *Veratrum* Alkaloids Jervine, Cyclopamine, and Veratramine

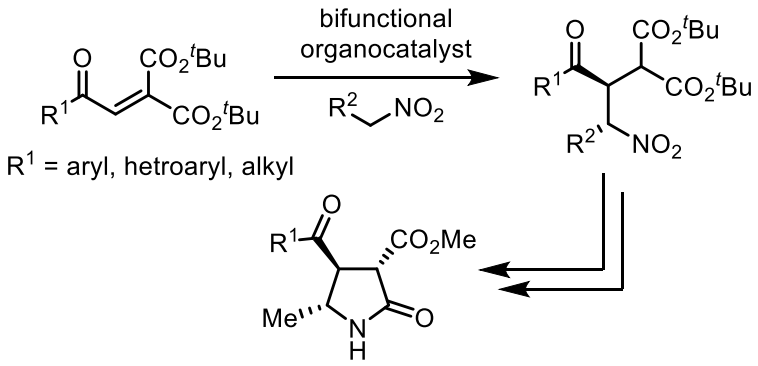
Efforts toward a *de novo* total synthesis of the *Veratrum* alkaloids jervine, cyclopamine, and veratramine are presented. A novel synthetic approach relying on oxidative dearomatization of a tyrosine derivative and local desymmetrization of a cyclohexadienone was developed. Starting

from a known racemic β-methyltyrosine derivative with two stereocenters set in a relative sense, a third stereocenter in the E ring of jervine and cyclopamine was conveniently set with a borohydride reduction. The oxidative dearomatization sequence was found to lead to the desired 6-5 framework necessary for the DE ring system of jervine and cyclopamine, but a competitive cyclization process necessitated further revisions to the route.



VI. Enantio- and Diastereoselective Organocatalytic Conjugate Additions of Nitroalkanes to Enone Diesters

A conjugate addition of nitroalkanes to enone diester electrophiles was used to provide two new stereocenters in polyfunctionalized products. A one-pot procedure for the synthesis of the starting materials from diazo compounds and Wittig reagents was developed and used to generate a wide range of substrates. A triaryliminophosphorane organocatalyst enabled high stereoselectivity in the conjugate addition reaction. Reduction of the nitro group and diastereoselective cyclization led to the formation of a third stereocenter in the lactam products.



For My Grandfather,
Allan Loosemore
&
My Parents,
James and Deanna Horwitz
&
My Brothers,
Joshua and Daniel Horwitz

ACKNOWLEDGEMENTS

I would like to begin by thaking my research advisor and mentor, Jeff Johnson. Of all the chemists and professors I have interacted with in my life, I have to say that Jeff is the most humble. He has inspired creativity in myself as well as all the students that have worked in his lab over the years. His ideas possess a certain ideality and he also has a sharp sense what for reactions "should be" possible, given time and effort. Additionally, as projects progress and face seemingly insurmountable difficulties, he has – time and time again- demonstrated a sympathetic and reasonable attitude that shows respect for the work his students do. Sympathy is not even a strong enough word. Every project I have worked on has hit some kind of wall that I have felt might stop it from being completed, but these have been the key moments when Jeff's wisdom and experience have shown through to balance out my cynicism with an enthusiastic yet pragmatic attitude. My sometimes broken spirit often found solace in his office. He has been a strong role model for myself and his research group, and I cannot thank him enough for his time and patience.

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2-MeTHF	2-methyl tetrahydrofuran
Å	ångström
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
^{i}Bu	*iso*-butyl
^{s}Bu	*sec*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
C-C	carbon-carbon bond
Comins' reagent	*N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide)
conv.	conversion
m-CPBA	*meta*-chloroperoxybenzoic acid
CPME	cyclopentyl methyl ether
d	doublet
DCC	*N*,*N*'-dicyclohexylcarbodiimide

DCCSO	8,8-dichlorocamphoryl-sulfonyl oxaziridine
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMSO	dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide
dr	diastereomeric ratio
dt	doublet of triplets
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
equiv	equivalents
er	enantiomeric ratio
EtOAc	ethyl acetate
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
^{19}F NMR	fluorine nuclear magnetic resonance spectroscopy
g	gram
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
Hex	hexanes
Hh	Hedgehog

HMDS	hexamethyldisilazide
HPLC	high-pressure liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
KO^{t}Bu	potassium *tert*-butoxide
LDA	lithium diisopropylamide
M	molarity
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimole
mp	melting point
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
nm	nanometer
NMO	*N*-methylmorpholine *N*-oxide
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy

Nu	nucleophile
P2-^{t}Bu	1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^{5},4λ^{5}-catenadi(phosphazene)
^{31}P NMR	phosphorus nuclear magnetic resonance spectroscopy
PDA	photodiode array
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
^{i}Pr	*iso*-propyl
^{i}PrOH	*iso*-propanol
psi	pounds per square inch
R_f	retention factor
RaNi	Raney nickel
rt	room temperature
s	singlet
Smo	Smoothened
Super-Hydride®	lithium triethylborohydride
t	triplet
TBME	*tert*-butyl methyl ether
TBOx	tethered bis(8-quinolinolato)
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine

temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl
UV	ultraviolet
[α]	optical rotation
δ	chemical shift or parital charge
λ	wavelength
μL	microliter

CHAPTER ONE:
ASYMMETRIC ORGANOCATALYTIC REDUCTIVE COUPLING REACTIONS BETWEEN ISATINS AND ALDEHYDES*

1.1 Introduction

The synthetic toolbox that is available to organic chemists is constantly expanding as a result of innovation in reaction methodology. Consquently, new avenues in the field of natural product synthesis are developing, which in turn will lead to a larger amount of biological screening and translational applications. Retrosynthetic analysis in natural product synthesis relies on polarity relationships, which are related to the placement of carbon-heteroatom bonds in target molecules. While many canonical reactions (including additions into carbonyls, enolate chemistry, and conjugate additions) rely on traditional polarity relationships, a larger synthetic toolbox invoking *umpolung* (polarity reversal) reactions would allow a plethora of new approaches in natural product synthesis. Traditional polarity relationships in retrosynthetic analysis allow consonant disconnections, while *umpolung* relationships allow dissonant disconnections. One of the most common dissonant disconnections is a 1,2-diol motif, which can be achieved through a reductive coupling of carbonyl reaction partners. Well-established methods for accomplishing this transformation normally require stoichiometric or superstoichiometric amounts of metal reagents, and result in non-stereoselective formation of non-chemically differentiated diols. Here, we

* Reprinted in part with permission from The Royal Society of Chemistry. Horwitz, M. A.; Tanaka, N.; Yokosaka, T.; Uraguchi, D.; Johnson, J. S.; Ooi, T. *Chem. Sci.* **2015,** *6*, 6086. – Published by The Royal Society of Chemistry.

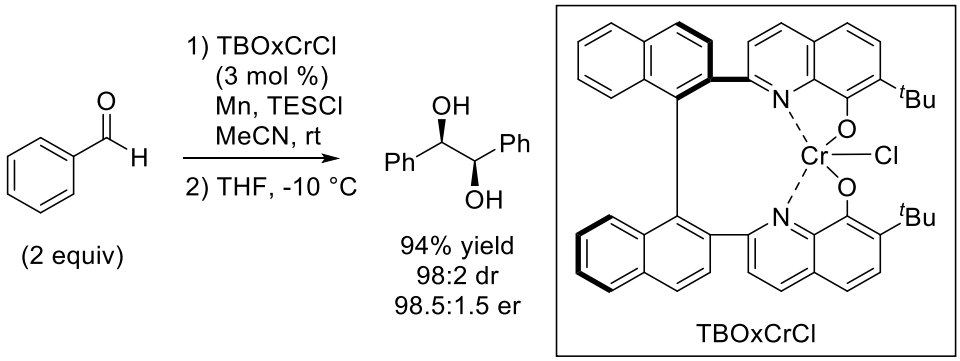
develop a reductive coupling reaction between isatins and aldehydes using commercial dialkylphosphites as the organic reductant and a chiral triaminoiminophosphorane catalyst to establish the two new stereocenters with high diastereo- and enantioselectivity.

1.2 Background

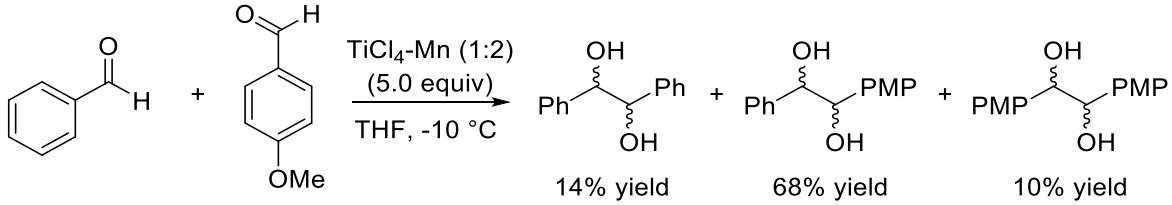
1.2.1 Extant Approaches to Reductive Coupling of Carbonyls

Reductive coupling of unsaturated functional groups has enabled the rapid construction of new chemical bonds in a large number of reaction manifolds. In addition to the bonds created through this process, the stereochemistry that results from the formation of new tetrahedral centers adds value to the process. Under the umbrella of carbonyl reductive coupling process lie several mechanistic categories.[1] The pinacol reaction makes manifest the ketyl radical coupling mechanistic pathway. Utilization of low-valent metals in this transformation has enabled this single-electron mechanism to proceed in many different contexts.[2-6] For example, low-valent titanium species can be utilized to promote pinacol couplings between distinct aldehyde reaction partners. In a foundational example from the Yamamoto group, the chiral chromium complex TBOxCrCl was used to enable the homocoupling of aldehydes in high yields and stereoselectivities (Scheme 1-1).[4w] In 2009, Duan and coworkers were able to obtain the cross-coupled diol as the major product of a pinacol reaction (Scheme 1-2).[4x]

Scheme 1-1. Yamamoto's Stereoselective Homocoupling of Aldehydes



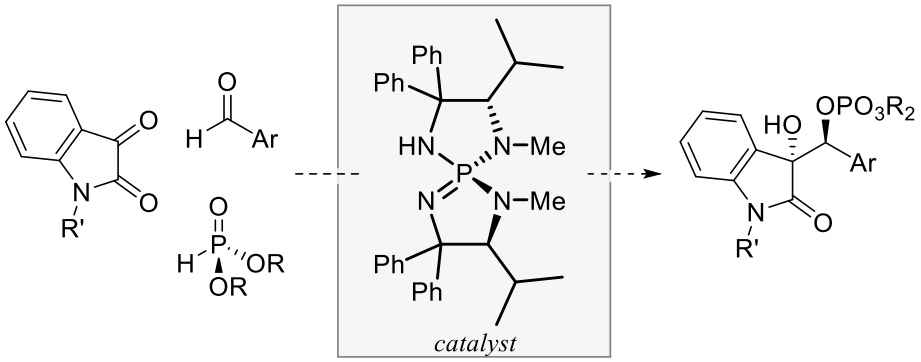
Scheme 1-2. Pinacol Coupling with Distinct Aldehyde Partners



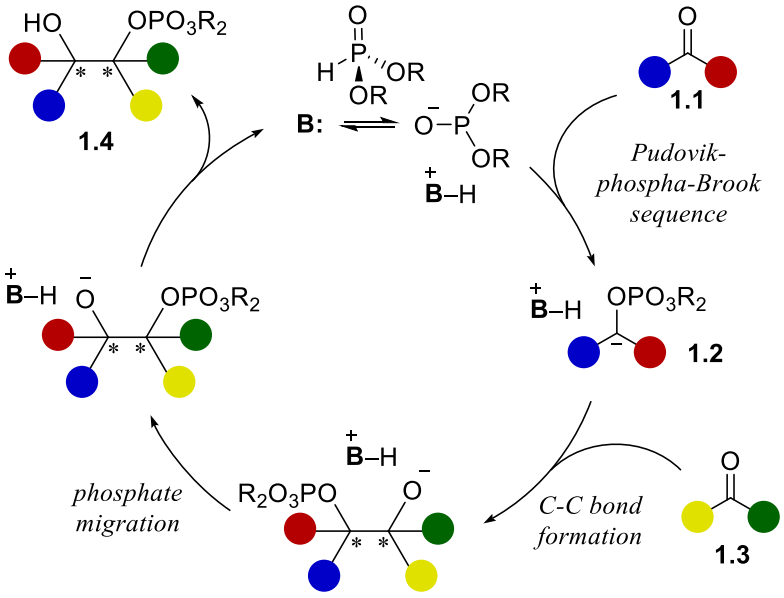
However, a broader perspective of these advances highlights a number of common shortcomings: stoichiometric or superstoichiometric metal reagents are generally needed (with a few exceptions).[4n-4r] Moreover, the nature of the mechanism can render it difficult to control both chemoselectivity (homo- *versus* cross-coupling) and stereoselectivity, and the lack of differentiation of the nascent alcohols can be nettlesome. These precedents collectively informed our interest in developing an alternative, potentially generalizable reductive coupling strategy that utilizes a polar two-electron reaction mechanism for addressing the aforementioned issues. The purpose of this research direction is to detail a new base-catalyzed cross coupling of carbonyls mediated by an economical organic reductant, diethyl phosphite; the stereochemical outcome of this multicomponent process is precisely controlled by a chiral triaminoiminophosphorane (Figure 1-1a).[7,8]

Figure 1-1. Stereoselective Reductive Coupling Reactions

(a) Enantioselective three-component reductive coupling



(b) Mechanistic proposal for asymmetric reductive coupling reaction



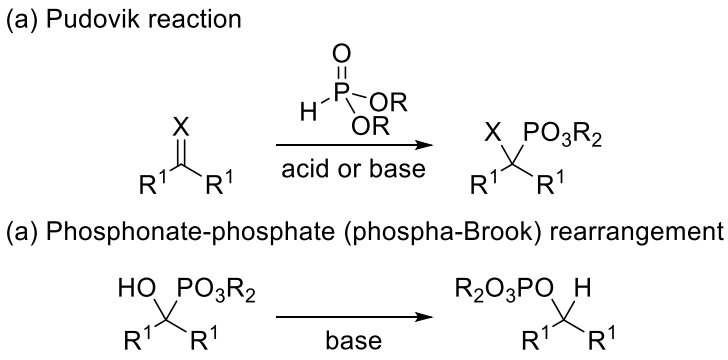
1.2.2 Precedents for Phosphite-mediated Reductive Coupling

At the outset, we envisaged the possibility of catalytic generation of an α-oxycarbanion from a carbonyl substrate and its rapid and selective trapping with another carbonyl compound to form 1,2-diols. For substantiating this hypothesis, polarity reversal of a particular carbonyl group is of critical importance and we sought to take advantage of the phosphonate–phosphate (phospha-Brook) rearrangement to achieve this requisite process. Thus, a base-catalyzed sequence of Pudovik addition and phosphonate–phosphate rearrangement between ketone **1.1** and dialkyl

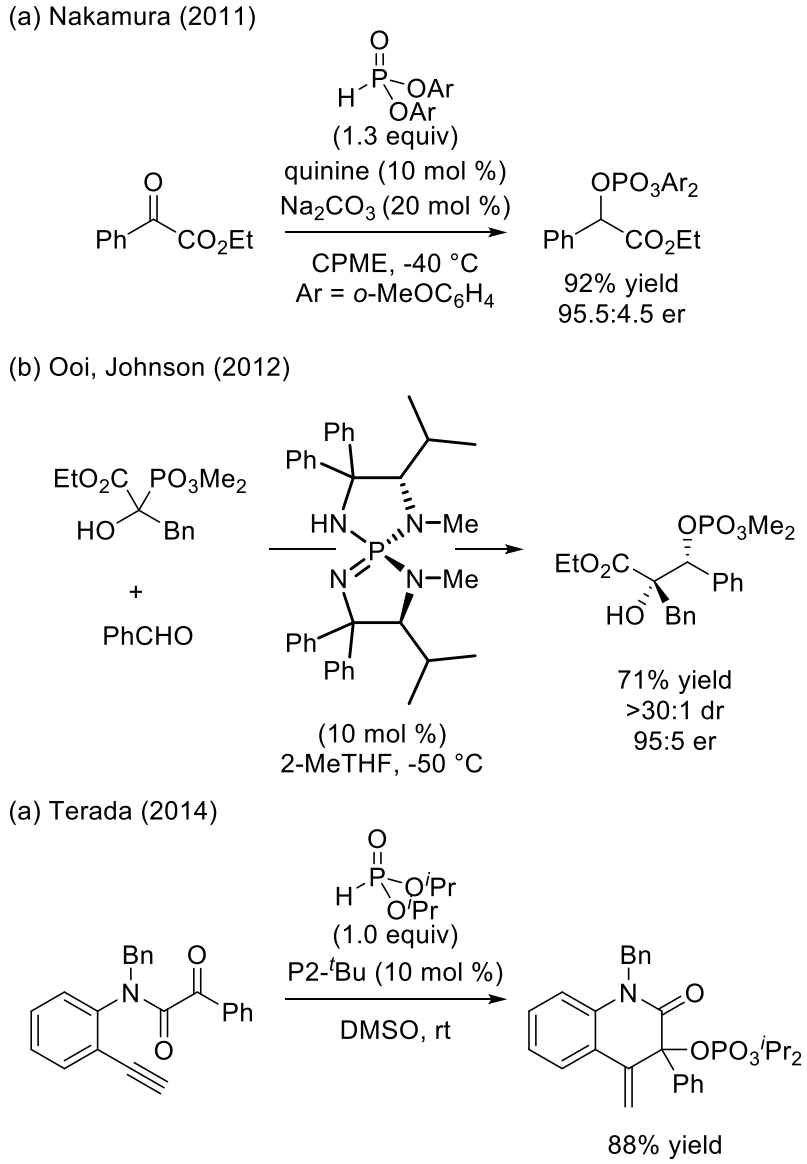
phosphite was projected to lead to carbanion **1.2**. The interception of this key intermediate by aldehyde **1.3** would afford mono-protected diol **1.4** through dialkoxyphosphinyl migration (Figure 1-1b).[9]

The overall electron flow proposed in the phosphite-mediated reductive coupling was a conceptual outgrowth of extant mechanistic precedents utilizing the Pudovik reaction (Scheme 1-3a) and the phosphonate-phosphate (phospha-Brook) rearrangement (Scheme 1-3b). In 2011, Nakamura applied these motifs in a Pudovik-phospha-Brook-protonation cascade that provided enantioenriched phosphates in high yield using commercial quinine as the Brønsted basic organocatalyst (Scheme 1-4a).[9e] Following this development, the Ooi and Johnson groups reported a phospha-Brook-aldol sequence that allowed a carbon-carbon bond formation to give two adjacent stereocenters with good yields and excellent stereselectivities (Scheme 1-4b).[9c] The Terada group subsequently developed a Pudovik-phospha-Brook-addition sequence that allowed an intramolecular cyclization to proceed in a racemic sense with P2-^{t}Bu phosphazene (Scheme 1-4c).[9d]

Scheme 1-3. Pudovik Reaction and Phospha-Brook Rearrangement



Scheme 1-4. Mechanistic Precedents for the Title Reaction



A crucial departure from prior art is the fully intermolecular nature of the coupling and the need for the phosphite to exhibit complete selectivity between the two carbonyl reactants. We reasoned that the crucial chemoselectivity issue underlying this mechanistic framework, *viz.* the selective generation of α-oxycarbanion **1.2** from ketone **1.1**, would be ensured by the inherent reversibility of the Pudovik reaction and the reluctance of the aldehyde Pudovik product to undergo phospha-Brook rearrangement. In addition, absolute stereochemical guidance in the C–C bond-

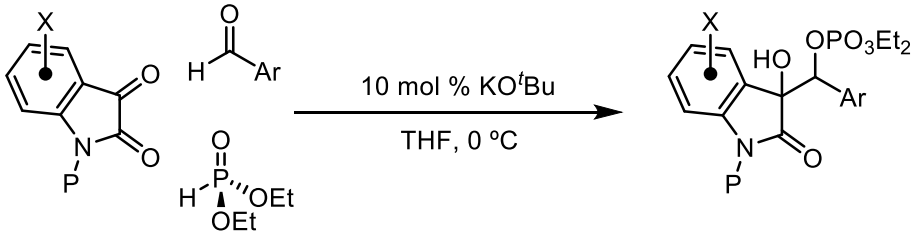
forming event could be provided by the conjugate acid of a suitable chiral base. In providing the conceptual blueprint for this scenario, we focused our attention on the exceptional electrophilicity and utility of α-dicarbonyls.[9d–g,10]

1.3 Results and Discussion

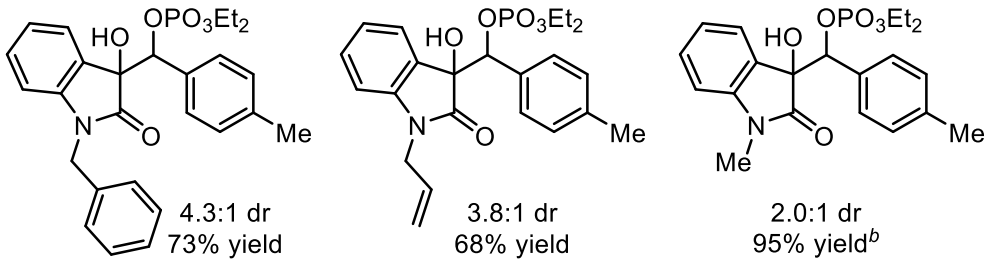
1.3.1 Development of Racemic Phosphite-mediated Reductive Coupling Reaction

Steps were initially taken to assess the feasibility of the proposed reaction in a racemic sense using achiral bases such as potassium tert-butoxide (KO^{t}Bu). Initial trials with diethyl phosphite as the stoichiometric reductant indicated that the reaction proceeds most cleanly and efficiently when a protecting group is used on the isatin. Benzyl, allyl, and methyl protecting groups were examined using 20 mol % KO^{t}Bu in THF at 0 ºC (Table 1-1, **(±)-1.4a**–**(±)-1.4c**). Under these conditions, the reactions were complete in minutes with no observable intermediates (if the aldehyde is omitted from the reaction, the Pudovik-phospha-Brook product can be observed, however).[9f] These experiments revealed that the benzyl protecting group provided the highest isolated yield and diastereoselectivity. We subsequently verified that *para*-tolualdehyde is not capable of phospha-Brook rearrangement when treated with diethyl phosphite and 20 mol % KO^{t}Bu: only the Pudovik adduct was observed, implying that it is the isatin that is undergoing polarity reversal as we expected. We then briefly studied the scope of the racemic reaction. The reaction gives consistently good yields for various aryl aldehydes incorporating substituents of different electronic properties (Table 1-1, **(±)-1.4d**–**(±)-1.4g**). At the current level of optimization, alkyl aldehydes and Boc-protected imine electrophiles were not well tolerated and only provided messy reactions.[11] The substitution pattern of the isatin was also examined; we found that the racemic reaction is reasonably flexible in terms of isatin electronics (**(±)-1.4h**–**(±)-1.4k**).

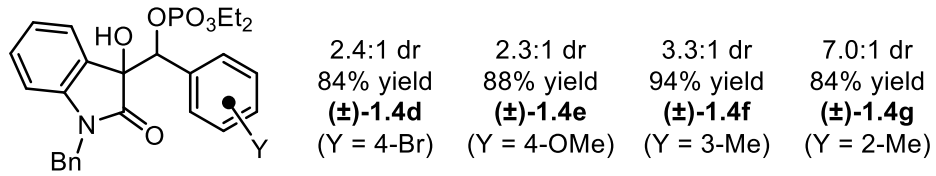
Table 1-1. Three Component Reductive Coupling: Racemic[a]



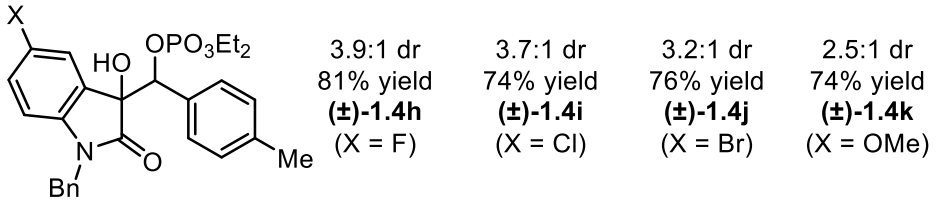
_N_-protecting groups (Ar = 4-tol, X = H)**:**



Aldehydes (P = Bn, X = H)**:**



Isatin Electronics (Ar = 4-tol, P = Bn)**:**



[a] All reactions were run on 0.2 mmol scale, using 1.1 equiv of dialkylphosphite and 5.0 equivalents of aldehyde. % Yields refer to isolated yields. All dr and % yield values are the averages of two trials. Reactions were run until complete as adjudged by TLC. [b] % Yield determined by crude ^{1}H NMR spectroscopy using mesitylene as an internal standard. Products

derived from apparent retro-reaction significantly diminished the isolated yield; therefore, this substrate was not selected for further study.

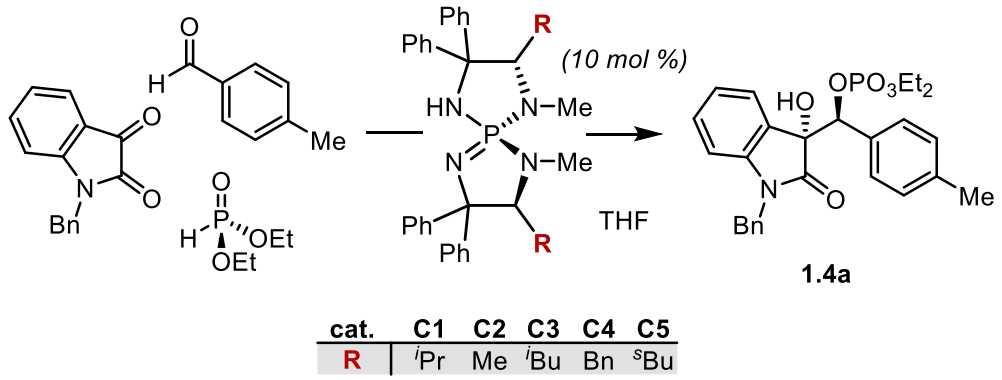
1.3.2 Development of Asymmetric Reaction

Efforts were next directed to the development of the enantioselective variant.[12] We were encouraged to find that when we used the chiral iminophosphorane (**C1**), we obtained the secondary phosphate **1.4a** with appreciable enantioenrichment (er 89.5:10.5), although the diastereoselectivity was poor (Table 1-2, entry 1). Gratifyingly, we found that upon lowering the temperature to -78 ºC, phosphate **1.4a** was obtained in 82% yield, 15:1 diastereoselectivity and an er of 96.5:3.5 (entry 2). Using the same temperature, we proceeded to evaluate the effect of the catalyst structure (entries 3 to 6), but ultimately concluded that α-branching in ligand substituent R is essential for promoting the desired transformations and the valine-derived iminophosphorane **C1** was optimal in terms of stereoselectivity and chemical yield.

1.3.3 Crossover Experiments Probing the Reversibility of Asymmetric Reaction

The disparity between the stereoselectivities at 0 ºC and -78 ºC prompted us to investigate the reversibility of the carbon-carbon bond formation via crossover experiments in that temperature range (Table 1-3). When racemic phosphate **(±)-1.4a** was subjected to standard conditions in the presence of 4-fluorobenzaldehyde, significant incorporation of that component in the form of phosphate **1.4a–F** was observed at 0 ºC and 40 ºC, but no crossover was observed at -78 ºC. These data support the hypothesis that the increase in enantioselectivity at -78 ºC is not only a consequence of more rigorous facial discrimination of both substrates but also shutting down a stereoablative retro-aldol process that is operative at higher temperatures.

Table 1-2. Optimization of the Catalytic Asymmetric Reductive Coupling[a]



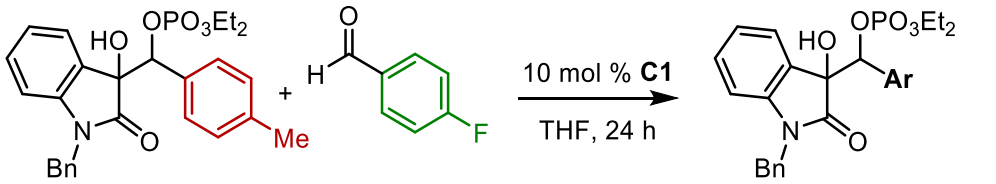
entry	T (°C)	catalyst	dr	er	% conv.
1	0	**C1**	3.4:1	89.5:10.5	96
2	–78	**C1**	15:1	96.5:3.5	82
3	–78	**C2**	n.a.	n.a.	18
4	–78	**C3**	n.a.	n.a.	15
5	–78	**C4**	n.a.	n.a.	12
6	–78	**C5**	7.9:1	86:14	80

[a] All reactions were conducted on a 0.1 mmol scale, using 1.1 equiv of dialkylphosphite and 5.0 equiv of ArCHO. Argon was used to purge the reaction flasks. All dr, er, and % conversion values are the average of two trials. n.a. = not analyzed.

1.3.4 Substrate Scope for Asymmetric Reaction

Using the optimized conditions, we evaluated the scope of the asymmetric reaction by initially looking at various isatins. While electron-deficient 5-halogenated isatins were well accommodated under the optimized conditions, use of dimethyl phosphite was indispensable for completion of the reactions with 5-methyl and methoxy isatins probably because of the slow phospha-Brook rearrangement (Table 1-4, **1.4h**–**1.4m**).[13] 6-Chloro and 7-fluoro isatins were also smoothly converted into the reductive coupling products of high stereochemical purity using appropriate phosphite (**1-4n** and **1-4o**).

Table 1-3. Crossover Experiments Establish Reversibility[a]



(±)-1.4a
3.2:1 dr

4.0 equiv

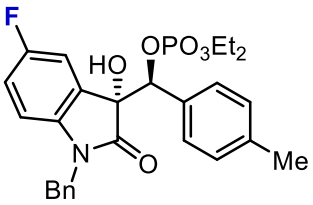
***recov*-1.4a** (**Ar** = 4-MeC_6H_4)
+
1.4a-F (**Ar** = 4-FC_6H_4)

entry	T (°C)	catalyst	dr	er	% conv.
1	0	**C1**	3.4:1	89.5:10.5	96
2	–78	**C1**	15:1	96.5:3.5	82
3	–78	**C2**	n.a.	n.a.	18
4	–78	**C3**	n.a.	n.a.	15
5	–78	**C4**	n.a.	n.a.	12
6	–78	**C5**	7.9:1	86:14	80

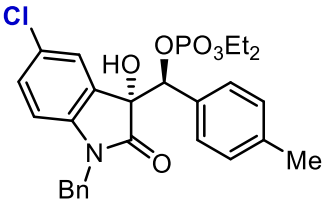
[a] Product distributions were determined by ^{1}H NMR analysis (800 MHz) of the crude mixture. n.a. = not analyzed.

For exploration of aldehyde generality, we selected 5-bromo isatin as a coupling partner in consideration of its high reactivity and advantage of having an additional functional handle. As included in Table 1-4, various para substituted aromatic aldehydes were tolerated and relatively electron rich aldehydes exhibited higher reactivity and selectivity (**1.4p**–**1.4t**). Hetero-substituents at the meta-position slightly affected the stereochemical outcome (**1.4u**–**1.4w**). For sterically demanding ortho-substituted aldehydes, dimethyl phosphite was needed to accelerate the reaction and virtually complete stereocontrol could be achieved (**1.4x**–**1.4z**).

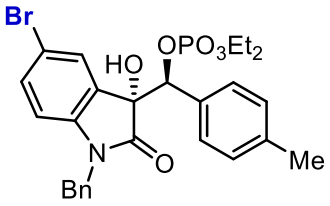
Table 1-4. Scope of Asymmetric Reductive Coupling Reaction with Isatins and Aldehydes[a]



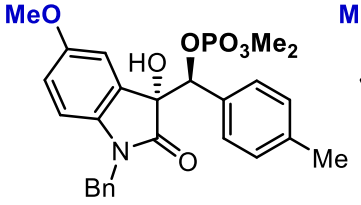
48 h, 19:1 dr
96:4 er
91% yield
1.4h[b]



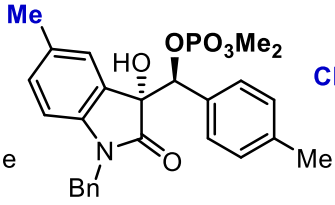
48 h, 10:1 dr
96.5:3.5 er
99% yield
1.4i[b]



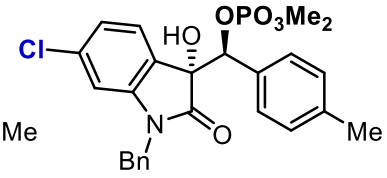
36 h, > 20:1 dr
98.5:1.5 er
94% yield
1.4j



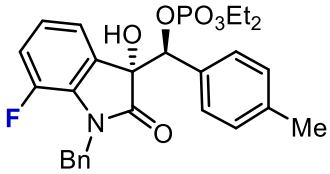
24 h, 5:1 dr
95:8 er
84% yield
1.4l



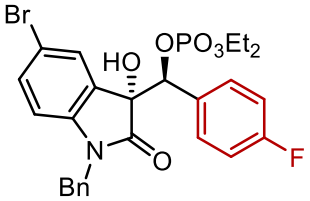
24 h, 10:1 dr
92.5:7.5 er
73% yield
1.4m



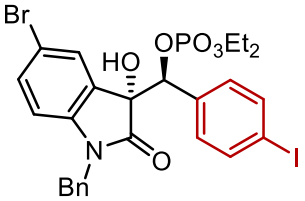
24 h, 12:1 dr
94.5:5.5 er
98% yield
1.4n



48 h, 11:1 dr
95:5 er
99% yield
1.4o

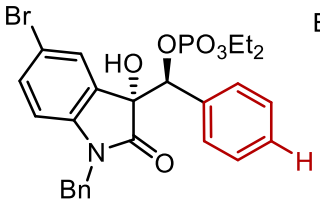


72 h, 10:1 dr
93.5:6.5 er
78% yield
1.4p

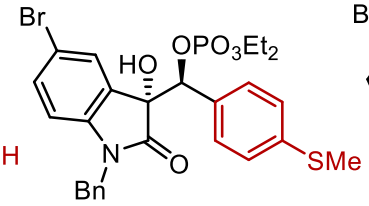


81 h, 15:1 dr
92.5:7.5 er
59% yield
1.4q

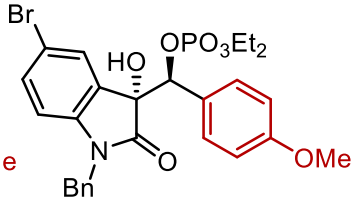
Table 1-4, cont.



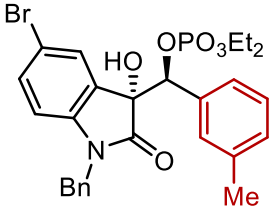
48 h, 12:1 dr
97.5:2.5 er
90% yield
1.4r



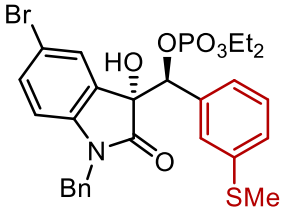
48 h, 13:1 dr
96:4 er
90% yield
1.4s



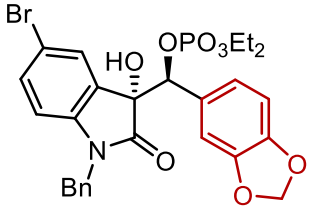
24 h, > 20:1 dr
99:1 er
85% yield
1.4t



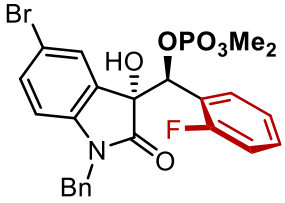
24 h, 19:1 dr
97.5:2.5 er
89% yield
1.4u



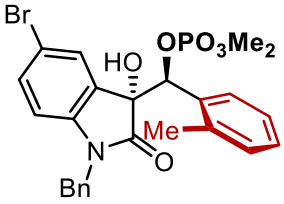
48 h, 10:1 dr
93.5:6.5 er
78% yield
1.4v



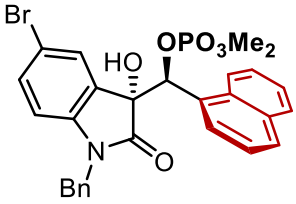
48 h, 7:1 dr
95:5 er
92% yield
1.4w



24 h, 18:1 dr
99:1 er
73% yield
1.4x[c]



24 h, > 20:1 dr
98:2 er
90% yield
1.4y



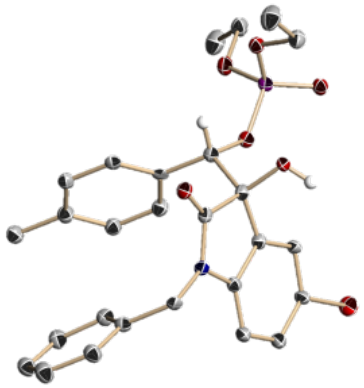
24 h, > 20:1 dr
99:1 er
77% yield
1.4z

[a] All reactions were conducted on a 0.1 mmol scale, using 1.1 equiv of dialkylphosphite and 5.0 equiv of ArCHO. Argon was used to purge the reaction flasks. % Yields refer to isolated yields. All dr, er, and % yield values are the average of two trials. [b] 15 mol % of catalyst was used. [c] 2.2 equiv of dialkylphosphite was used.

1.3.5 Determination of Absolute Configuration

The absolute stereochemistry furnished in the product series was determined by an X-ray diffraction study of phosphate **1.4j** (Figure 1-2).[14]

Figure 1-2. ORTEP Diagram of **1.4j**[a]



[a] Ellipsoids displayed at 50% probability. Calculated hydrogen atoms except for that attached to the stereogenic carbon atom are omitted for clarity. Black: carbon, Red: oxygen, Purple: phosphorous, Blue: nitrogen, Vermilion: bromine, White: hydrogen.

1.4 Conclusion

In summary, we have developed a highly stereoselective, fully organic multicomponent coupling reaction between isatins and aldehydes with dialkyl phosphite as an economical reductant. The advantages of extending the reductive coupling into a two-electron manifold are manifest, and the mechanistic framework established herein may be applicable to other stereoselective reductive carbon–carbon bond constructions.

1.5 Experimental Details

Methods: Infrared (IR) spectra were obtained using an Jasco 460 Plus Fourier transform infrared spectrometer or a Shimadzu IRAffinity-1 spectrometer. Magnetic resonance spectra (^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR) were recorded on a Bruker model DRX 400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz, ^{19}F NMR at 376 MHz, and ^{31}P NMR at 162 MHz), a Bruker model DRX 600 (^{1}H NMR at 600 MHz, ^{13}C NMR at 151 MHz, and ^{31}P NMR at 243 MHz), a JEOL JNM-ECS400 (^{1}H NMR at 400 MHz, ^{19}F NMR at 376 MHz, and ^{31}P NMR at 162 MHz), ECA-800 (^{1}H NMR at 800 MHz),

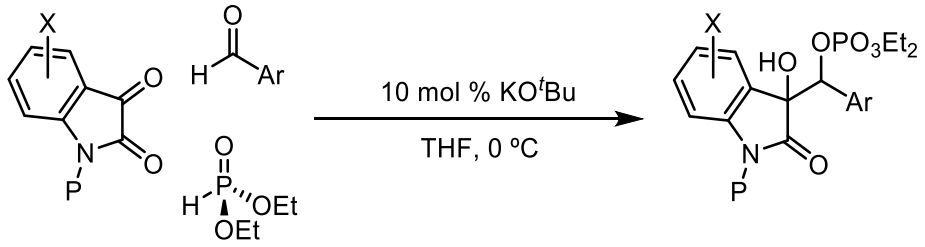
a Bruker AVANCE III-OneBay500 (^{13}C NMR at 126 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.16 ppm), or benzotrifluoride (^{19}F NMR: -64.0 ppm) and H_3PO_4 (^{31}P NMR: 0.0 ppm) resonances as the external standard. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br = broad, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were obtained with a Thermo Fisher Scientific Exactive, Finnigan™ LTQ-ICR FT™, or Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization (all samples prepared in methanol). Melting points were obtained using a Stanford Research Systems OptiMelt MPA100 or Thomas Hoover UniMelt Capillary Melting Point Apparatus. Analytical thin layer chromatography was carried out using Whatman 0.25 mm silica gel 60 plates, Sorbent Technologies 0.20 mm Silica Gel TLC plates, or Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Visualization was allowed by UV light, phosphomolybdic acid in ethanol, or aqueous ceric ammonium nitrate solution. HPLC analysis was performed on a Shimadzu SPD-M20A PDA detector with a Shimadzu SPD20AD eluent system using DAICEL CHIRALPAK IA or AD3 columns (ϕ 4.6 mm x 250 mm, constant flow at 1.00 mL/min), using hexane, 2-propanol, and ethanol as eluents. To perform HPLC trials at 4 ºC, a Shimadzu LC-2010C HT unit was used. Asymmetric reactions were carried out under an atmosphere of argon, in oven-dried glass with magnetic stirring, using a UC Reactor (Techno Sigma) or a PSL-1810 (EYELA) reactor. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle, or silica gel 60 (spherical, 40-50 μm) from Kanto Chemical Co., Inc. Yields refer to isolated yields after flash column chromatography; some samples contain residual minor diastereomers. Since all results are the

averages of two trials, the stereochemical outcomes listed in the above tables may not exactly match those represented in the NMR and HPLC data below.

Materials: Tetrahydrofuran (THF) was supplied from Kanto Chemical Co., Inc. as "Dehydrated solvent system" and further purified by passing through neutral alumina under nitrogen atmosphere. Isatins were purchased from Acros Organics or Wako Chemical Co. and alkylated according to literature procedures.[15] Triaminoiminophosphorane catalysts **C1**-**C5** were prepared according to literature procedures.[8b] Commercially available dimethyl phosphite, diethyl phosphite, and diisopropyl phosphite were distilled using a Kügelrohr apparatus prior to use. Commerically available aldehydes were freshly distilled directly before the reactions. Potassium *tert*-butoxide was purchased from Sigma Aldrich and used as is.

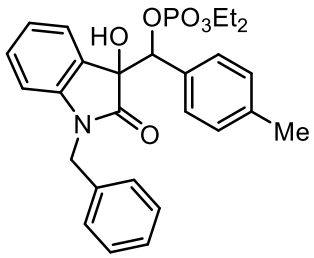
Experimental Procedures:

General procedure for the three component reaction using KO^{t}Bu:



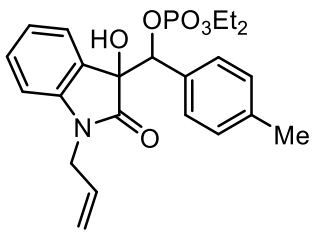
To a stirred solution of isatin derivative (0.20 mmol), diethyl phosphite (30.4 mg, 0.22 mmol, 1.1 equiv) and aldehyde (1.0 mmol, 5.0 equiv) in THF (2.0 mL) at 0 °C was added KO^{t}Bu (2.2 mg, 0.02 mmol, 10 mol %). The reaction was allowed to proceed at the same temperature and was followed by TLC. Once the isatin was fully consumed (typically 5-10 minutes), the reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in*

vacuo. The residue was purified by silica gel column chromatography to give the desired products **1.4**.



1-Benzyl-3-((((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-3-hydroxyindolin-2-one ((±)-1.4a):

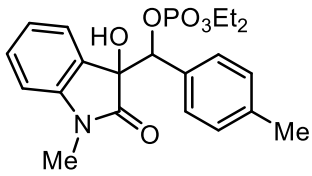
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.73 (major diastereomer) and δ 4.44 (minor diastereomer). White solid (mp 166-167 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.2 Hz, 1H), 7.07-7.18 (m, 5H), 6.89-6.94 (m, 4H), 6.56 (d, *J* = 7.6 Hz, 2H), 6.37 (d, *J* = 7.6 Hz, 1H), 5.77 (d, *J* = 8.8 Hz, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 4.38 (s, 1H), 4.28 (d, *J* = 16.0 Hz, 1H), 3.97-4.22 (m, 4H), 2.30 (s, 3H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.22 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 175.0, 143.3, 138.7, 134.8, 131.1 (d, *J* = 3.6), 130.1, 128.7, 128.4, 127.9, 127.2, 126.6, 126.5, 126.3, 123.0, 109.4, 83.6 (d, *J* = 5.7 Hz), 79.1 (d, *J* = 4.5 Hz), 64.5 (*d*, J = 5.7 Hz), 64.3 (d, *J* = 5.9 Hz), 43.7, 21.3, 16.1 (d, *J* = 7.2 Hz), 16.0 (d, *J* = 6.9 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ -0.3; IR (thin film) ν 3420, 2928, 1721, 1615, 1469, 1368, 1250, 1123, 1081, 1029, 909 cm^{-1}; **HRMS** (ESI^+) cald for $C_{27}H_{30}NO_6P$ 496.1889 ($M+H^+$) found 496.1893. **TLC** (2:1 EtOAc/Hexanes): R_f = 0.33.



1-Allyl-3-((((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-3-hydroxyindolin-2-one ((±)-1.4b):

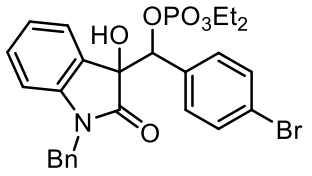
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction

mixture by comparison of the resonances at δ 6.58 (minor diastereomer) and δ 6.53 (major diastereomer). Clear oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.3 Hz, 1H), 7.30-7.27 (m, 1H), 7.16-7.13 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 7.7 Hz, 1H), 5.72 (d, *J* = 8.6 Hz, 1H), 5.28-5.22 (m, 1H), 4.87 (d, *J* = 10.4 Hz, 1H), 4.48-4.44 (m, 2H), 4.29-4.20 (m, 2H), 4.14-4.01 (m, 2H), 3.78-3.75 (m, 1H), 2.24 (s, 3H), 1.35-1.29 (m, 3H), 1.28-1.20 (m, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.5, 143.2, 138.7, 130.9, 130.4, 130.0, 128.4, 127.6, 126.2, 122.8, 118.1, 116.8, 109.0, 83.5 (d, *J* = 5.6 Hz), 79.3 (d, *J* = 4.5 Hz), 64.5 (d, *J* = 5.7 Hz), 64.3 (d, *J* = 5.9 Hz), 42.0, 21.0, 16.1-16.0 (m, 2C); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.23; **IR** (thin film) ν 3288, 2984, 1725, 1614, 1469, 1368, 1257, 1029, 754, 663 cm^{-1}; **HRMS** (ESI^+) cald for $C_{23}H_{28}NNaO_6P$ 468.155197 ($M+Na^+$) found 468.1565. **TLC** (2:1 EtOAc/Hexanes): R_f = 0.17.



3-((((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-3-hydroxy-1-methylindolin-2-one ((±)-1.4c):

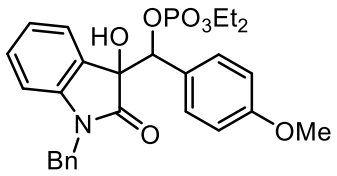
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.59 (minor diastereomer) and δ 6.51 (major diastereomer). The product was found to be unstable to silica gel chromatography.The percent yield was calculated by ^{1}H NMR spectroscopy using mesitylene as an internal standard.



1-Benzyl-3-((4-bromophenyl)(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)methyl)-3-hydroxyindolin-2-one ((±)-1.4d):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the

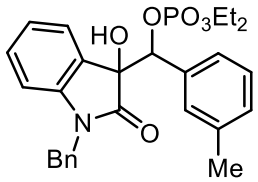
resonances at δ 4.92 (minor diastereomer) and δ 4.83 (minor diastereomer). White solid (mp 168-169 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.2 Hz, 1H), 7.16-7.26 (m, 6H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.55-6.57 (m, 2H), 6.42 (d, *J* = 8.0 Hz, 1H), 5.78 (d, *J* = 8.8 Hz, 1H), 5.00 (d, *J* = 16.0 Hz, 1H), 4.71 (s, 1H), 4.28 (d, *J* = 16.0 Hz, 1H), 3.94-4.25 (m, 4H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.20 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.8, 143.2, 134.6, 133.3 (d, J_{P-C} = 3.5 Hz), 131.2, 130.3, 129.7 ,128.7, 127.5, 126.5, 126.3, 126.0, 123.2, 123.1, 109.5, 82.9 (d, *J* = 5.7 Hz), 78.9 (d, *J* = 4.7 Hz), 64.6 (d, *J* = 5.6 Hz), 64.4 (d, *J* = 5.6 Hz), 43.8, 16.1 (d, *J* = 7.2 Hz), 16.0 (d, *J* = 6.6 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$) δ -0.6; **IR** (thin film) ν 3403, 2984, 1720, 1614, 1489, 1369, 1252, 1029, 1008, 972 cm^{-1}; **HRMS** (ESI^+) cald for $C_{26}H_{27}BrNO_6P$ 560.0838 ($M+H^+$) found 560.0820. **TLC** (2:1 EtOAc/Hexanes): R_f = 0.33.



1-Benzyl-3-((((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(4-methoxyphenyl)methyl)-3-hydroxyindolin-2-one ((±)-1.4e):

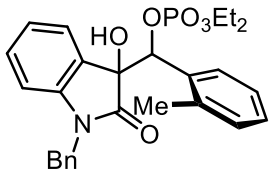
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.76 (major diastereomer) and δ 5.71 (minor diastereomer).White solid (mp 157-158 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 1H), 7.05-7.21 (m, 5H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 7.6 Hz, 2H), 6.37 (d, *J* = 7.6 Hz, 1H), 5.78 (d, *J* = 8.8 Hz, 1H), 4.99 (d, *J* = 16.0 Hz, 1H), 4.76 (s, 1H), 4.24 (d, *J* = 16.0 Hz, 1H), 3.91-4.21 (m, 4H), 3.73 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) 174.9, 160.1, 143.3, 134.7, 130.1, 129.4, 128.4, 127.3, 126.5, 126.4, 126.3, 126.2 (d, *J* = 4.1 Hz), 123.0, 113.4, 109.4, 83.4 (d, *J* = 6.2 Hz), 79.2 (d, *J* = 5.0 Hz), 64.4 (d, *J* = 5.6 Hz), 64.3 (d, *J* = 5.6 Hz), 55.1, 43.6, 16.1 (d, *J* = 7.2 Hz), 16.0 (d, *J* = 6.9 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$) δ -0.5; **IR**

(thin film) ν 3416, 2983, 2931, 1721, 1614, 1515, 1441, 1368, 1251, 1028 cm^{-1}; **HRMS** (ESI^+) cald for $C_{27}H_{30}NO_7P$ 512.1838 ($M+H^+$) found 512.1803. **TLC** (2:1 EtOAc/Hexanes): R_f = 0.19.



1-benzyl-3-((((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(m-tolyl)methyl)-3-hydroxyindolin-2-one ((±)-1.4f):

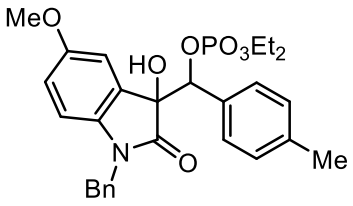
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.24 (major diastereomer) and δ 4.46 (minor diastereomer). White solid (mp 109-110 °C); **^1H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 6.8 Hz, 1H), 6.89-7.19 (m, 7H), 6.82 (s, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 2H), 6.33 (d, *J* = 7.6 Hz, 1H), 5.77 (d, *J* = 8.4 Hz, 1H), 4.96 (d, *J* = 16.4 Hz, 1H), 4.89 (br-s, 1H), 3.95-4.27 (m, 5H), 2.10 (s, 3H), 1.26 (t, *J* = 6.8 Hz, 3H), 1.19 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) 174.9, 143.3, 137.7, 134.7, 133.9 (d, *J* = 3.0 Hz), 130.0, 129.7, 128.7, 128.6, 127.9, 127.2, 126.4, 126.3, 126.3, 125.0, 123.0, 109.4, 83.7 (d, *J* = 6.0 Hz), 79.2 (d, *J* = 4.5 Hz), 64.5 (d, *J* = 6.0 Hz), 64.4 (d, *J* = 6.0 Hz), 43.6, 21.2, 16.1 (d, *J* = 6.0 Hz), 16.0 (d, J_{P-C} = 7.6 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ -0.6; **IR** (thin film) ν 3290, 1724, 1614, 1468, 1366, 1251, 1028, 753, 699 cm^{-1}; **HRMS** (ESI^+) cald for $C_{27}H_{30}NO_6P$ 496.1889 ($M+H^+$) found 496.1815. **TLC** (2:1 EtOAc/Hexanes): R_f = 0.25.



1-benzyl-3-((((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(o-tolyl)methyl)-3-hydroxyindolin-2-one ((±)-1.4g):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 4.86 (major diastereomer) and δ 4.54 (minor diastereomer).White solid (mp 170-

171 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.2 Hz, 1H), 7.04-7.26 (m, 7H), 6.82 (t, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.39-6.46 (m, 3H), 6.13 (d, *J* = 8.8 Hz, 1H), 5.06 (d, *J* = 16.0 Hz, 1H), 4.61 (s, 1H), 3.88-4.22 (m, 5H), 2.45 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) 175.0, 143.4, 137.4, 134.8, 132.7 (d, *J* = 4.5 Hz), 130.5, 130.2, 128.9, 128.7, 127.8, 127.2, 126.6, 126.4, 126.3, 125.5, 123.1, 109.4, 79.1 (d, *J* = 4.5 Hz), 78.9 (d, *J* = 6.0 Hz), 64.3 (d, 4.5 Hz), 64.1 (d, 6.0 Hz), 43.7, 19.8, 16.0 (d, *J* = 7.6 Hz), 15.9 (d, *J* = 7.6 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ -0.5; **IR** (thin film) ν 3264, 2982, 2341, 1716, 1613, 1468, 1362, 1241, 1016, 753 cm^{-1}; **HRMS** (ESI^+) cald for $C_{27}H_{30}NO_6P$ 496.1889 ($M+H^+$) found 496.1812. **TLC** (2:1 EtOAc/Hexanes): R_f = 0.29.

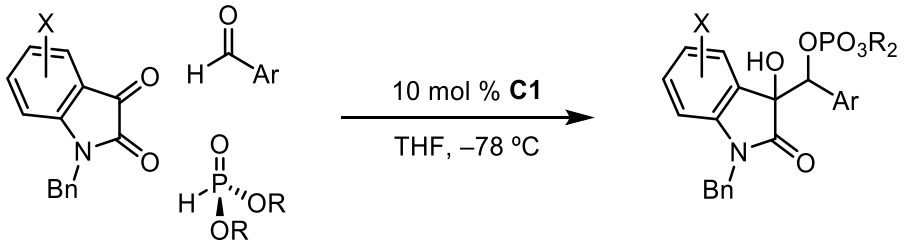


1-Benzyl-3-((((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-5-methoxy-3-hydroxyindolin-2-one ((±)-1.4k):

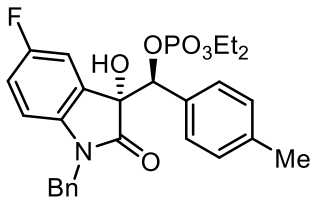
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.24 (minor diastereomer) and δ 6.15 (major diastereomer). White solid (mp 128-129 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 2.4 Hz, 1H), 7.05-7.26 (m, 3H), 6.90-6.95 (m, 4H), 6.67 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 2H), 6.25 (d, *J* = 8.8 Hz, 1H), 5.77 (d, *J* = 8.8 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H), 4.76 (s, 1H), 3.91-4.25 (m, 5H), 3.79 (s, 3H), 2.30 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.7, 156.1, 138.7, 136.5, 134.9, 131.1 (d, *J* = 3.8 Hz), 128.7, 128.4, 128.0, 127.7, 127.2, 126.6, 114.6, 113.4, 109.8, 83.6 (d, *J* = 5.6 Hz), 79.5 (d, *J* = 4.4 Hz), 64.4 (d, *J* = 5.6 Hz), 64.3 (d, *J* = 6.0 Hz), 55.8, 43.8, 21.3, 16.1 (d, *J* =6.8 Hz), 16.0 (d, *J* = 6.8 Hz); **^{31}P NMR** (243 MHz, $CDCl_3$) δ -0.3; **IR** (thin

film) ν 3402, 2986, 1717, 1605, 1494, 1370, 1351, 1253, 1183, 1028 cm^{-1}; **HRMS** (ESI^+) cald for $C_{28}H_{32}NO_7P$ 526.1995 ($M+H^+$) found 526.1944. **TLC** (2:1 EtOAc/Hexanes): R_f = 0.19.

General procedure for three component reaction using chiral iminophosphorane:



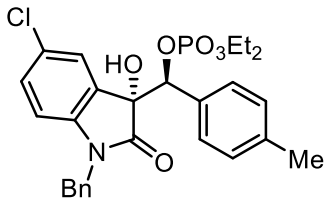
An oven-dried test tube was evacuated and filled with argon, then charged sequentially with the isatin substrate and THF (0.5 mL), followed by the dialkylphosphite and the aldehyde. THF (0.5 mL) was then added and used to wash the residual solids on the sides of the test tube to the bottom. The reaction was stirred at -78 ºC in a cryogenic cooling apparatus, then the iminophosphorane catalyst **C1** was added. The reaction was then stirred at -78 ºC and monitored by TLC until the reaction was complete. Trifluoroacetic acid in toluene (40μL of a 0.5 M solution) was added to quench the reaction and the reaction was concentrated on a rotatory evaporator. The crude materials thusly obtained were purified using flash column chromatography, with a gradient from 1:1 hexanes/EtOAc to 1:2 hexanes/EtOAc.



(*R*)-1-Benzyl-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-5-fluoro-3-hydroxyindolin-2-one (1.4h):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.79 (major diastereomer) and δ 5.70 (minor diastereomer). White solid; **^{1}H NMR**

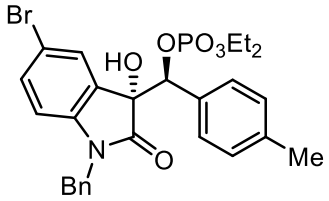
(400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 2.8, 7.8 Hz, 1H), 7.18-6.84 (m, 8H), 6.51 (d, *J* = 7.3 Hz, 2H), 6.28 (d, *J* = 4.1 Hz, 1H), 5.79 (d, *J* = 8.7 Hz, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 4.28-4.09 (m, 3H), 4.04-3.97 (m, 2H), 2.31 (s, 3H), 1.34-1.29 (m, 3H), 1.25-1.18 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.8, 160.2, 158.3, 139.2 (d, *J* = 1.8 Hz), 138.9, 134.5, 130.8, 128.8, 128.5, 127.8, 127.4, 126.6, 116.3 (d, *J* = 23.6 Hz), 114.4 (d, *J* = 25.0 Hz, 110.0 (d, *J* = 8.2 Hz), 83.4 (d, *J* = 5.5 hz), 79.4 (d, *J* = 4.6 Hz), 64.6 (d, *J* = 5.5 Hz), 64.4 (d, *J* = 5.5 Hz), 43.8, 21.3, 16.1 (d, *J* = 7.3 Hz), 16.0 (d, *J* = 7.3 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.48. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −119.6. **IR** (thin film) ν 3275, 2980, 2247, 1715, 1620, 1485, 1258, 1177, 1007, 903 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{27}H_{29}FNNaO_6P$ ([M+Na^+]): 536.1614, found 536.1605. **HPLC** Chiralpak IA column, Hex/^{i}PrOH/EtOH = 95:4:1, flow rate = 1.0 mL/min, λ = 210 nm, 28.5 min (minor isomer), 44.2 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.38.



(*R*)-1-Benzyl-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-5-chloro-3-hydroxyindolin-2-one (1.4i):

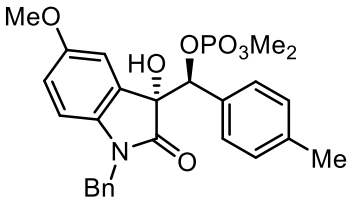
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.80 (major diastereomer) and δ 5.72 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.22-6.91 (m, 8H), 6.50 (d, *J* = 7.3 Hz, 2H), 6.27 (d, *J* = 8.2 Hz, 1H), 5.78 (d, *J* = 9.2 Hz, 1H), 4.97 (d, *J* = 16.0 Hz, 1H), 4.28-4.10 (m, 3H), 4.05-3.95 (m, 2H), 2.32 (s, 3H), 1.35-1.29 (m, 3H), 1.26-1.17 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.7, 141.9, 139.0, 134.5, 130.9, 130.0, 128.9, 128.8, 128.6, 128.5, 128.4, 128.0, 127.5, 126.8, 126.7, 110.5, 83.4 (d, *J* = 6.4 Hz), 79.4 (d, *J* = 4.6 Hz), 64.8 (d, *J* = 5.5 Hz), 64.6 (d, *J* = 6.4 Hz), 43.9, 21.4,

16.2 (d, J = 8.6 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.51. **IR** (thin film) ν 3269, 2988, 2245, 1726, 1613, 1483, 1254, 1173, 1007, 783 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{27}H_{29}ClNNaO_6P$ ([M+Na$^+$]): 522.1319, found 552.1309. **HPLC** Chiralpak IA column, Hex/^{i}PrOH/EtOH = 95:4:1, flow rate = 1.0 mL/min, λ = 210 nm, 28.8 min (minor isomer), 43.3 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.41.



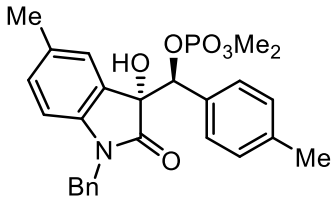
(*R*)-1-Benzyl-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-5-bromo-3-hydroxyindolin-2-one (1.4j):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.78 (major diastereomer) and δ 5.69 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, J = 1.8 Hz, 1H), 7.31-6.90 (m, 7H), 6.50 (d, J = 7.8 Hz, 2H), 6.23 (d, J = 8.7 Hz, 1H), 5.77 (d, J = 8.7 Hz, 1H), 4.96 (d, J = 16.0 Hz, 1H), 4.29-4.11 (m, 3H), 4.05-3.95 (m, 2H), 2.32 (s, 3H), 1.37-1.30 (m, 3H), 1.25-1.17 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) 174.6, 142.4, 139.1, 134.4, 133.0, 130.9 (2C), 130.8, 129.6, 129.0, 128.0, 127.5, 126.7, 115.8, 111.0, 83.4 (d, J = 6.4 Hz), 79.4 (d, J = 4.6 Hz), 64.8 (d, J = 5.5 Hz), 64.6 (d, J = 5.5 Hz), 43.9, 21.5, 16.2 (d, J = 7.3 Hz), 16.1 (d, J = 6.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.67. **IR** (thin film) ν 3293, 2983, 2909, 2245, 1726, 1609, 1479, 1248, 1028, 733 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{27}H_{29}BrNNaO_6P$ ([M+Na$^+$]): 596.0814, found 596.0809. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 11.3 min (minor isomer), 15.3 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.44.



(*R*)-1-Benzyl-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-5-methoxy-3-hydroxyindolin-2-one (1.4l):

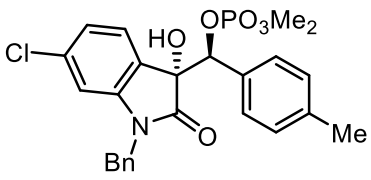
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.77 (major diastereomer) and δ 5.74 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.3 Hz, 1H), 7.22-6.92 (m, 7H), 6.69 (dd, *J* = 8.6 Hz, 2.5 Hz, 1H), 6.54 (d, *J* = 7.3 Hz, 2H), 6.28 (d, *J* = 8.9 Hz, 1H), 5.77 (d, *J* = 8.7 Hz, 1H), 4.99 (d, *J* = 16.0 Hz, 1H), 4.40 (br, 1H), 4.25 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H), 3.78 (d, *J* = 11.4 Hz, 3H), 3.64 (d, *J* = 11.5 Hz, 3H), 2.31 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.9, 152.2, 138.9, 136.8, 135.0, 131.2, 128.9, 128.7, 128.5, 128.1, 127.7, 127.3, 127.1, 126.7, 114.7, 113.7, 110.0, 83.9 (d, *J* = 5.5 Hz), 79.5 (d, *J* = 4.6 Hz), 56.0, 54.8 (d, *J* = 5.5 Hz), 54.6 (d, *J* = 6.4 Hz), 43.9, 21.4; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.55. **IR** (thin film) ν 3300, 2951, 2243, 1713, 1605, 1487, 1258, 1163, 1026, 810 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{26}H_{28}NNaO_7P$ ([M+Na$^+$]): 520.1501, found 520.1499. **HPLC** Chiralpak IA column, Hex/^{i}PrOH/EtOH = 90:5:5, flow rate = 1.0 mL/min, λ = 210 nm, 34.2 min (minor isomer), 45.4 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.17.



(*R*)-1-Benzyl-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-5-methyl-3-hydroxyindolin-2-one (1.4m):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.76 (major diastereomer) and δ 5.72 (minor diastereomer). White solid; **^{1}H NMR**

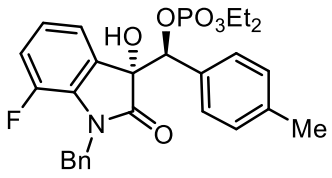
(400 MHz, $CDCl_3$) δ 7.54, 7.17–6.91 (m, 8H), 6.54 (d, *J* = 6.1 Hz, 2H), 6.27 (d, *J* = 7.8 Hz, 1H), 5.75 (d, *J* = 8.7 Hz, 1H), 4.26 (d, *J* = 16.0 Hz, 1H), 3.74 (d, *J* = 11.0 Hz, 3H), 3.66 (d, *J* = 11.4 Hz, 3H), 2.36 (s, 3H), 2.31 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.1, 141.0, 138.9, 135.0, 132.7, 131.2 (d, *J* = 3.6 Hz), 130.5, 128.9, 128.5, 128.1, 127.3, 127.1, 126.7, 126.4, 109.3, 84.0 (d, *J* = 6.4 Hz), 79.2 (d, *J* = 5.5 Hz), 54.8 (d, *J* = 5.5 Hz), 54.6 (d, *J* = 5.5 Hz), 43.8, 21.4, 21.3; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.55. **IR** (thin film) ν 3337, 2924, 2851, 2243, 2116, 1715, 1620, 1493, 1260, 1032 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{26}H_{28}NNaO_6P$ ([M+Na^+]): 504.1552, found 504.1547. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 13.4 min (minor isomer), 16.5 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.23.



(*R*)-1-Benzyl-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-6-chloro-3-hydroxyindolin-2-one (1.4n):

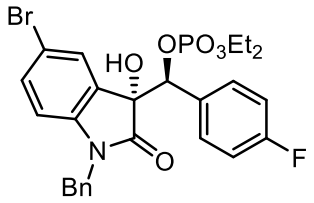
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.80 (major diastereomer) and δ 5.74 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.16-7.20 (m, 1H), 7.08-7.12 (m, 3H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.53 (d, 7.3 Hz, 2H), 6.38 (d, 1.8 Hz, 1H), 5.77 (d, *J* = 9.2 Hz, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 4.24 (d, *J* = 16.5 Hz, 1H), 3.76 (d, *J* = 11.4 Hz, 3H), 3.65 (d, *J* = 11.4 Hz 3H), 2.32 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.1, 144.7, 139.2, 136.1, 134.3, 130.8 (d, *J* = 2.36 Hz), 129.1, 128.7, 127.9, 127.6, 127.5, 126.7, 125.0, 123.1, 83.8 (d, *J* = 4.1 Hz), 78.9 (d, *J* = 2.9 Hz), 54.9 (d, *J* = 11.7 Hz), 43.9, 21.5; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.55. **HRMS** (ESI): Calcd. For $C_{25}H_{25}ClNNaO_6P$ ([M+Na^+]): 524.1006, found 524.1003. **IR** (thin film) ν 3302,

2957, 2247, 1726, 1609, 1454, 1252, 1180, 1025, 731 cm^{-1}. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 90.9:9.1, flow rate = 1.0 mL/min, λ = 210 nm, 20.5 min (minor isomer), 30.6 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.41.



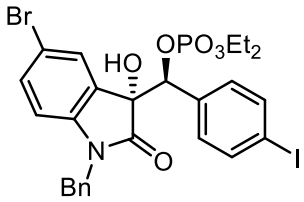
(*R*)-1-Benzyl-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(*p*-tolyl)methyl)-7-fluoro-3-hydroxyindolin-2-one (1.4o):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.75 (major diastereomer) and δ 5.67 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.55-7.53 (m, 1H), 7.18-7.04 (m, 4H), 6.99-6.86 (m, 5H), 6.70 (d, *J* = 7.3 Hz, 2H), 5.74 (d, *J* = 8.7 Hz, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 4.21-4.15 (m, 2H), 4.10-3.96 (m, 2H), 2.28 (s, 3H), 1.32-1.27 (m, 3H), 1.23-1.19 (m, 3H) ; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.7, 148.3, 146.3, 139.0, 136.2, 130.7 (d, *J* = 3.6 Hz), 129.6 (d, *J* = 8.2 Hz), 128.9, 128.4, 127.9, 127.2, 126.8 (d, *J* = 1.8 Hz), 123.9 (d, *J* = 6.4 Hz), 122.4 (d, *J* = 3.6 Hz), 118.5, 118.4, 79.1-79.1 (m), 64.6 (d, *J* = 5.5 Hz), 64.5 (d, *J* = 5.5 Hz), 45.3 (d, *J* = 4.5 Hz), 21.4, 16.2-16.0 (m, 2C); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.46; ^{19}F NMR (376 MHz, $CDCl_3$) δ −133.6. **IR** (thin film) ν 3296, 2986, 2237, 1730, 1632, 1487, 1248, 1022, 910, 733 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{27}H_{29}FNNaO_6P$ ([M+Na^+]): 536.1614, found 536.1608. **HPLC** Chiralpak IA column, Hex/^{i}PrOH/EtOH = 85:5:10, flow rate = 1.0 mL/min, λ = 210 nm, 9.3 min (minor isomer), 12.5 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.38.



(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((diethyλ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(4-fluorophenyl)methyl)-3-hydroxyindolin-2-one (1.4p):

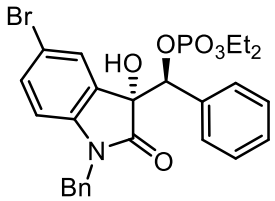
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.81 (major diastereomer) and δ 5.75 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.84 Hz, 1H), 7.33-6.81 (m, 8H), 6.54 (d, *J* = 7.4 Hz, 2H), 6.29 (d, *J* = 8.7 Hz, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 4.89 (br s, 1H), 4.28 (d, *J* = 16.5 Hz, 1H), 4.25-4.13 (m, 2H), 4.06-3.95 (m, 2H), 1.80 (br, 1H), 1.38-1.31 (m, 3H), 1.25-1.18 (m, 3H**)**; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 164.2, 162.2, 142.4, 134.3, 133.2, 130.0 (d, *J* = 8.2 Hz), 129.6, 128.8, 127.8, 126.6, 115.9, 115.3 (d, *J* = 21.8 Hz), 111.1, 82.7 (d, *J* = 6.4 Hz), 79.3 (d, *J* = 4.6 Hz), 64.9 (d, *J* = 5.5 Hz), 64.9 (d, *J* = 5.5 Hz), 64.6 (d, *J* = 5.5 Hz), 43.9, 16.3 (d, *J* = 13.4 Hz), 16.1 (d, *J* = 6.3 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.27; **^{19}F NMR** (376 MHz, $CDCl_3$) δ −111.6. **IR** (thin film) ν 3252, 2986, 2245, 1726, 1607, 1510, 1479, 1346, 1229, 1022 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{26}H_{26}BrFNNaO_6P$ ([M+Na$^+$]): 600.0563, found 600.0552. **HPLC** Chiralpak IA column, Hex/^{i}PrOH/EtOH = 95:4:1, flow rate = 1.0 mL/min, λ = 210 nm, 29.6 min (minor isomer), 43.8 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.45.



(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(4-iodophenyl)methyl)-3-hydroxyindolin-2-one (1.4q):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the

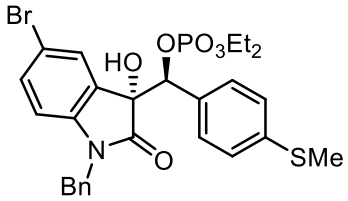
resonances at δ 5.76 (major diastereomer) and δ 5.69 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.8 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.32-7.23 (m, 4H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.56-6.54 (m, 2H), 6.28 (d, *J* = 8.7 Hz, 1H), 5.75 (d, *J* = 8.7 Hz, 1H), 4.99 (d, *J* = 16.0 Hz, 1H), 4.28-4.15 (m, 3H), 4.07-3.99 (m, 2H), 1.38-1.35 (m, 3H), 1.26-1.19 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 142.4, 137.5, 134.2, 133.6, 133.2, 129.8, 129.6, 128.3, 127.8, 126.6, 115.9, 111.2, 95.5, 82.8 (d, *J* = 5.5 Hz), 79.1 (d, *J* = 5.3 Hz), 65.0 (d, *J* = 6.4 Hz), 64.7 (d, *J* = 4.6 Hz), 44.0, 16.3-16.1 (m, 2C); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.56. **IR** (thin film) ν 3291, 2980, 2243, 1730, 1607, 1481, 1371, 1254, 1024, 910 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{26}H_{26}BrINNaO_6P$ ([M+Na^+]): 707.9623, found 707.9618. **HPLC** Chiralpak AD3 column, Hex/EtOH = 88:12 (4 ºC), flow rate = 1.0 mL/min, λ = 210 nm, 18.9 min (minor isomer), 29.7 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.47.



(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(phenyl)methyl)-3-hydroxyindolin-2-one (1.4r):

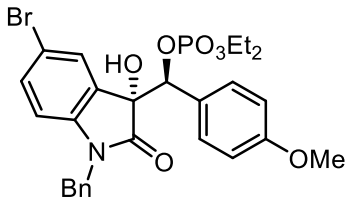
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.82 (major diastereomer) and δ 5.77 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.32-7.26 (m, 3H), 7.18-7.14 (m, 3H), 7.11-7.04 (m, 4H), 6.46 (d, *J* = 7.8 Hz, 2H), 6.21 (d, *J* = 8.2 Hz, 1H), 5.81 (d, *J* = 9.2 Hz, 1H), 5.06 (br, 1H), 4.90 (d, *J* = 16.5 Hz, 1H), 4.29-4.11 (m, 2H), 4.05-3.98 (m, 2H), 1.36-1.30 (m, 3H), 1.26-1.16 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 142.4, 134.4, 133.9, 133.0, 129.6, 129.2, 128.8, 128.7 (d, *J* = 2.7 Hz), 128.3, 128.1, 127.5, 126.6, 115.8, 111.1, 83.5 (d, *J* = 6.4 Hz), 79.4 (d, *J* = 4.6 Hz), 64.9

(d, J = 5.5 Hz), 65.6 (d, J = 5.5 Hz), 43.9, 16.3-16.1 (m, 2C); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.48. **HRMS** (ESI): Calcd. For $C_{26}H_{27}BrNNaO_6P$ ([M+Na^+]): 582.0657, found 582.0652. **IR** (thin film) ν 3283, 2978, 2247, 1726, 1715, 1607, 1454, 1348, 1254, 725 cm^{-1}. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 18.1 min (minor isomer), 28.0 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.44.



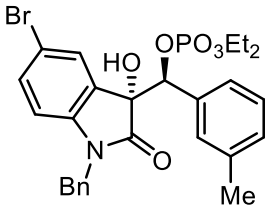
(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(4-(methylthio)phenyl)methyl)-3-hydroxyindolin-2-one (1.4s):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.78 (major diastereomer) and δ 5.71 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, J = 1.8 Hz, 1H), 7.30-6.93 (m, 8H), 6.47-6.45 (m, 2H), 6.24 (d, J = 8.2 Hz, 1H), 5.77 (d, J = 9.2 Hz, 1H), 5.77 (d, J = 9.2 Hz, 1H), 5.01 (d, J = 16.0 Hz, 1H), 4.30-4.13 (m, 3H), 4.06-3.95 (m, 2H), 2.42 (s, 3H), 1.38-1.35 (m, 3H), 1.25-1.18 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 142.4, 134.2, 133.1, 130.2, 130.2, 129.6, 128.9, 128.8, 128.6, 128.5, 127.7, 126.5, 125.4, 115.8, 111.1, 83.2 (d, J = 5.5 Hz), 79.3 (d, J = 4.6 Hz), 64.9 (d, J = 5.5 Hz), 64.6 (d, J = 5.5 Hz), 43.9, 16.3 (d, J = 7.3 Hz), 16.1 (d, J = 6.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.54. **HRMS** (ESI): Calcd. For $C_{27}H_{29}BrNNaO_6PS$ ([M+Na^+]): 628.0534, found 628.0526. **IR** (thin film) ν 3306, 2986, 2247, 1730, 1607, 1483, 1250, 1134, 1020, 731 cm^{-1}. HPLC Chiralpak IA column, Hex/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 13.7 min (minor isomer), 20.7 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.42.



(*R*)-1-benzyl-5-Bromo-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(4-methoxyphenyl)methyl)-3-hydroxyindolin-2-one (1.4t):

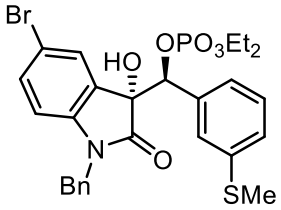
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.78 (major diastereomer) and δ 5.71 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.8 Hz), 7.31-7.07 (m, 4H), 6.94 (d, *J* = 9.2 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.47 (d, *J* = 7.8 Hz, 2H), 6.24 (d, *J* = 8.7 Hz, 1H), 5.76 (d, *J* = 9.2 Hz, 1H), 4.98 (d, *J* = 16.5 Hz, 1H), 4.88 (br, 1H), 4.28-4.14 (m, 3H), 4.05-3.98 (m, 2H), 3.76 (s, 3H), 1.38-1.34 (m, 3H), 1.25-1.21 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 160.3, 142.5, 134.3, 133.0, 129.5, 129.4, 128.6, 127.6, 126.6, 115.8, 113.7, 111.0, 83.2 (d, *J* = 5.5 Hz), 79.4 (d, *J* = 4.6 Hz), 64.8 (d, *J* = 5.5 Hz), 64.6 (d, *J* = 5.5 Hz), 55.2, 43.8, 16.3 (d, *J* = 7.3 Hz), 16.1 (d, *J* = 6.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.83. **IR** (thin film) ν 3314, 2976, 2353, 2245, 1730, 1613, 1514, 1485, 1250, 1024 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{27}H_{29}BrNNaO_7P$ ([M+Na$^+$]): 612.0763, found 612.0754. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 13.4 min (minor isomer), 18.9 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.39.



(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(m-tolyl)methyl)-3-hydroxyindolin-2-one (1.4u):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.76 (major diastereomer) and δ 5.71 (minor diastereomer). White solid; **^{1}H NMR**

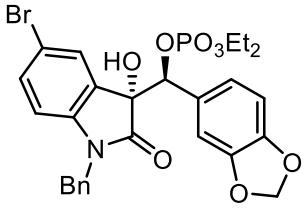
(400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.8 Hz, 1H), 7.32-7.02 (m, 6H), 6.86 (s, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 7.3 Hz, 2H), 6.2 (d, *J* = 8.0 Hz, 1H), 5.75 (d, *J* = 8.7 Hz, 1H), 4.94 (d, *J* = 16.5 Hz, 1H), 4.86 (br, 1H), 4.30-4.12 (m, 3H), 4.07-3.98 (m, 2H), 2.16 (s, 3H), 1.38-1.31 (m, 3H), 1.26-1.18 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 142.5, 138.0, 134.5, 133.7, 133.0, 130.0, 129.6, 128.8, 128.2, 127.6, 126.5, 125.0, 115.8, 111.0, 83.5 (d, *J* = 5.5 Hz), 79.4 (d, *J* = 3.6 Hz), 64.9 (d, *J* = 6.4 Hz), 64.6 (d, *J* = 8.6 Hz), 43.9, 21.4, 16.3 (d, *J* = 7.3 Hz), 16.1 (d, *J* = 6.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.67. **IR** (thin film) ν 3266, 2932, 2934, 1730, 1714, 1609, 1454, 1250, 1130, 1020 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{27}H_{29}BrNNaO_6P$ ([M+Na^+]): 596.0814, found 596.0795. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 90.9:9.1, flow rate = 1.0 mL/min, λ = 210 nm, 14.5 min (minor isomer), 24.7 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.45.



(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(3-(methylthio)phenyl)methyl)-3-hydroxyindolin-2-one (1.4v):

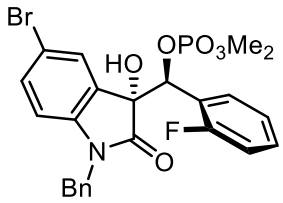
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.78 (major diastereomer) and δ 5.72 (minor diastereomer).White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.30-7.03 (m, 7H), 6.87-6.81 (m, 1H), 6.49 (d, *J* = 7.3 Hz, 2H), 6.24 (d, *J* = 8.7 Hz, 1H), 5.78 (d, *J* = 8.7 Hz, 1H), 5.09 (br, 1H), 4.93 (d, *J* = 16.5 Hz, 1H), 4.31-4.13 (m, 3H), 4.07-3.98 (m, 2H), 2.14 (s, 3H), 1.38-1.34 (m, 3H), 1.25-1.21 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.4, 142.4, 139.1, 134.7 (2C), 134.3, 133.0, 129.6, 128.9, 128.5, 127.9, 127.6, 126.5, 125.0, 124.9, 115.8, 111.2, 83.1 (d, *J* = 5.5 Hz), 79.3 (d, *J* = 4.6 Hz), 64.9 (d, *J* = 6.4 Hz), 64.7 (d, *J* = 6.4 Hz), 43.9, 16.3 (d, *J* = 6.4 Hz), 16.1 (d, *J* = 6.4 Hz), 15.6; **^{31}P NMR** (162

MHz, $CDCl_3$) δ 0.48. **HRMS** (ESI): Calcd. For $C_{27}H_{29}BrNNaO_6PS$ ([M+Na^+]): 628.0534, found 628.0530. **IR** (thin film) ν 3256, 2984, 2363, 1730, 1607, 1479, 1256, 1018, 972, 895 cm^{-1}. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 90.9:9.1, flow rate = 1.0 mL/min, λ = 210 nm, 19.4 min (minor isomer), 34.1 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.41.



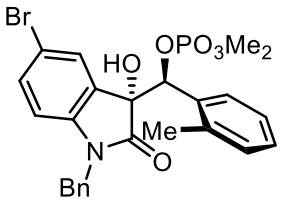
(*R*)-3-((*S*)-Benzo[d][1,3]dioxol-5-yl(((diethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)methyl)-1-benzyl-5-bromo-3-hydroxyindolin-2-one (1.4w):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.72 (major diastereomer) and δ 5.64 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 1.8 Hz, 1H), 7.38-7.14 (m, 4H), 6.64-6.59 (m, 4H), 6.40 (s, 1H), 6.32 (d, *J* = 8.7 Hz, 1H), 5.89 (d, *J* = 1.4 Hz, 1H), 5.88 (d, *J* = 1.4 Hz, 1H), 5.71 (d, *J* = 8.7 Hz, 1H), 5.01 (d, *J* = 16.0 Hz, 1H), 4.31-4.13 (m, 3H), 4.08-3.97 (m, 2H), 1.40-1.32 (m, 3H), 1.27-1.20 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 148.4 (d, *J* = 1.8 Hz), 147.5, 142.5, 134.6, 133.1, 129.5, 128.7, 127.7, 126.8, 122.4, 115.9, 111.0, 108.2, 108.1, 101.3, 83.3 (d, *J* = 5.5 Hz), 79.4 (d, *J* = 4.6 Hz), 64.9, 64.7, 43.9, 16.3 (d, *J* = 7.3 Hz), 16.1 (d, *J* = 7.3 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 0.56. **HRMS** (ESI): Calcd. For $C_{27}H_{27}BrNNaO_8P$ ([M+Na^+]): 626.0555, found 626.0550. **IR** (thin film) ν 3281, 2990, 2249, 1726, 1609, 1483, 1445, 1244, 1018, 733 cm^{-1}. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 90.9:9.1, flow rate = 1.0 mL/min, λ = 210 nm, 26.2min (minor isomer), 43.4 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.39.



(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((dimethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(2-fluorophenyl)methyl)-3-hydroxyindolin-2-one (1.4x):

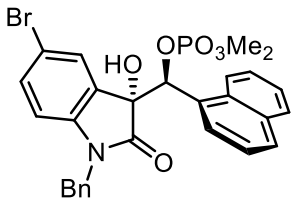
The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.21 (major diastereomer) and δ 6.16 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.35-6.90 (m, 10H), 6.65 (d, *J* = 7.3 Hz, 2H), 6.35 (d, *J* = 8.2 Hz, 1H), 6.14 (d, *J* = 9.2 Hz, 1H), 5.01 (d, *J* = 16.5 Hz, 1H), 4.33 (d, *J* = 16.0 Hz, 1H), 3.75 (d, *J* = 11.4 Hz, 3H), 3.68 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.1, 161.0, 159.0, 142.5, 134.6, 133.4, 131.2 (d, 8.3 Hz), 129.6, 128.9, 127.7, 126.7, 124.1 (d, *J* = 3.6 Hz), 121.5 (d, *J* = 3.6 Hz), 121.4 (d, *J* = 3.6 Hz), 115.9, 115.8, 111.1, 78.5 (d, *J* = 5.5 Hz), 76.0-75.9 (m, 1C), 55.0 (d, *J* = 6.4 Hz), 54.9 (d, *J* = 6.4 Hz), 44.0; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.39; **^{19}F NMR** (376 MHz, $CDCl_3$) δ −114.0. **IR** (thin film) ν 3273, 2355, 1730, 1609, 1483, 1454, 1344, 1263, 1180, 1028 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{24}H_{22}BrFNNaO_6P$ ([M+Na$^+$]): 572.0250, found 572.0245. **HPLC** Chiralpak IA column, Hex/^{i}PrOH/EtOH = 93:5:2 (4 ºC), flow rate = 1.0 mL/min, λ = 210 nm, 76.3 min (minor isomer), 92.1 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.42.



(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((dimethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(o-tolyl)methyl)-3-hydroxyindolin-2-one (1.4y):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the

resonances at δ 6.15 (major diastereomer) and δ 6.04 (minor diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.34-7.06 (m, 6H), 6.90-6.87 (m, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.42 (d, *J* = 6.9 Hz, 2H), 6.30-6.28 (m, 1H), 6.14 (d, *J* = 8.7 Hz, 1H), 5.05 (d, *J* = 16.0 Hz, 1H), 4.18 (d, *J* = 16.5 Hz, 1H), 3.74 (dd, *J* = 11.5 Hz, 1.8 Hz, 3H), 3.57 (dd, *J* = 11.4 Hz, 1.4 Hz, 3H), 2.44 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.7, 142.6, 137.6, 134.4, 133.2, 132.4 (d, *J* = 2.7 Hz), 130.8, 129.8, 129.3, 128.9, 128.7, 127.7, 127.5, 126.4, 125.9, 116.0, 111.0, 79.2 (d, *J* = 6.4 Hz), 79.0 (d, *J* = 6.4 Hz), 54.8 (d, *J* = 5.5 Hz), 54.5 (d, *J* = 5.5 Hz), 43.9, 19.8; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.60. **IR** (thin film) ν 3204, 2957, 2245, 1725, 1607, 1454, 1346, 1223, 1003, 812 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{25}H_{25}BrNNaO_6P$ ([M+Na^+]): 596.0501, found 596.0495. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 90.9:9.1, flow rate = 1.0 mL/min, λ = 210 nm, 15.9 min (minor isomer), 21.6 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.40.



(*R*)-1-Benzyl-5-bromo-3-((*S*)-(((dimethyl-λ^3-oxidanyl)(λ^1-oxidanyl)phosphoryl)oxy)(naphthalen-1-yl)methyl)-3-hydroxyindolin-2-one (4z):

The title compound was prepared according to general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.41 (minor diastereomer) and δ 6.17 (major diastereomer). White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 2.3 Hz, 1H), 7.82 (dd, *J* = 5.0, 8.2 Hz, 2H), 7.59-7.51 (m, 1H), 7.49-7.46 (m, 1H), 7.30 (dd, *J* = 1.4, 8.7 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.09-7.05 (m, 2H), 6.96-6.93 (m, 2H), 6.76 (d, *J* = 8.7 Hz, 1H), 6.22 (d, *J* = 8.2 Hz, 1H), 6.12, (m, 2H), 4.81 (d, *J* = 16.0 Hz, 1H), 4.65 (br, 1H), 4.01 (d, *J* = 16.0 Hz, 1H), 3.75 (dd, *J* = 1.8, 9.6 Hz, 3H), 3.57 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 142.7, 134.3, 133.5, 133.2,

130.8, 130.0, 129.7, 129.6, 129.0, 128.8, 128.7, 128.6, 127.5, 127.0, 126.6, 126.4, 126.2, 124.7, 123.5, 115.9, 110.9, 79.4 (d, J = 4.5 Hz), 55.0 (d, J = 5.5 Hz), 54.7 (d, J = 6.4 Hz), 43.9; **^{31}P NMR** (162 MHz, $CDCl_3$) 2.84. **IR** (thin film) ν 3277, 2955, 2247, 1730, 1609, 1481, 1260, 1175, 1026, 731 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{28}H_{25}BrNNaO_6P$ ([M+Na^+]): 604.0501, found 604.0496. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 16.3 min (minor isomer), 30.0 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.38.

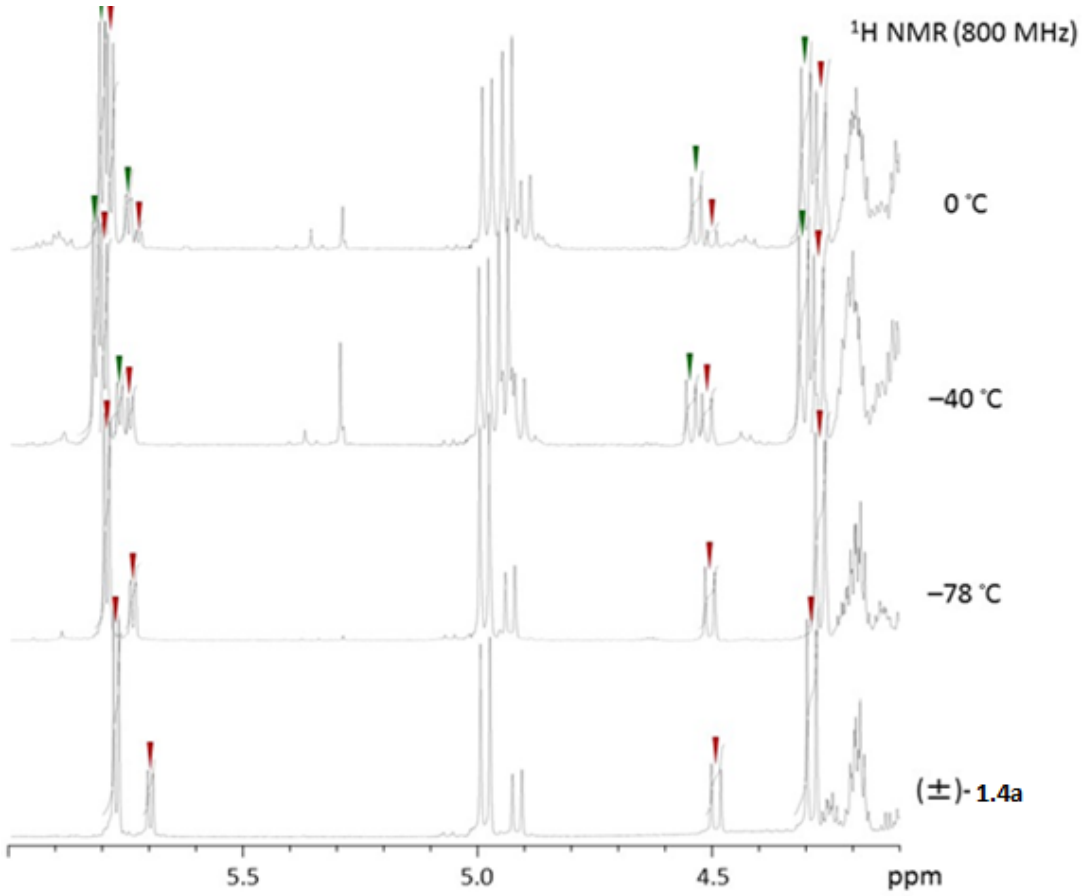
Details of crossover experiment:

Three oven-dried test tubes were evacuated and filled with argon, then charged sequentially with the cross pinacol product **(±)-1.4a** and THF (0.5 mL), followed by 4-fluorobenzaldehyde (4.0 equiv). THF (0.5mL) was then added and used to collect residual solids on the sides of the test tube. The reaction was stirred at 0 ºC, or -40 ºC, or -78 ºC in an appropriate cooling apparatus, then the iminophosphorane catalyst **C1** was added. The reaction was then stirred at the same temperatures and monitored by TLC until the reaction was complete. Trifluoroacetic acid in toluene (40μL of a 0.5 M solution) was added to quench the reaction and the reaction was concentrated on a rotatory evaporator.

Analysis of crossover experiment:

The reactions were analyzed by ^{1}H NMR spectroscopy on an 800 MHz spectrometer. The ^{1}H NMR trace show below details the results of the above crossover experiment. The trace on bottom shows racemic starting material (3.2:1 dr, **1.4a**). The major and minor diastereomer peaks of the starting material are identified with red wedges. As the temperature is increased from -78 ºC to -40 ºC, crossover starts to occur; the major and minor diastereomers of the crossover product are identified with green wedges. Additionally, at 0 ºC the dr of the starting material was observed

to sharply increase; we attribute this to a relatively rapid retro reaction of the minor diastereomer of starting material (which could also be responsible for the low diastereoselectivity of crossover product at that temperature). These results suggest that the crossover process shuts down between -40 ºC and -78 ºC.



REFERENCES

[1] (a) Ramirez, F.; Desai, N. B.; Ramanathan, N. *Tetrahedron Lett.* **1963,** *4*, 323. (b) Mukaiyama, T.; Sugimura, H.; Ohno, T.; Kobayashi, S. *Chem. Lett.* **1989,** *18*, 1401. (c) Greszler, S. N.; Johnson, J. S. *Org. Lett.* **2009,** *11*, 827.

[2] Reviews: (a) Terra, B. S.; Macedo, F., Jr. *Arkivoc* **2012,** 134. (b) Chatterjee, A.; Joshi, N. N. *Tetrahedron* **2006,** *62*, 12137.

[3] Initial papers on cross pinacol reactions with low-valent metal reagents: (a) McMurry, J. E.; Krepski, L. R. *J. Org. Chem.* **1976,** *41*, 3929. (b) McMurry, J. E. *Chem. Rev.* **1989,** *89*, 1513.

[4] Developments toward using aldehydes as coupling partners in stereoselective reductive coupling reactions: (a) Takahara, P. M.; Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *Tetrahedron Lett.* **1989,** *30*, 7177. (b) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J.Am. Chem. Soc.* **1989,** *111*, 8014. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P. *Tetrahedron: Asymmetry* **1990,** *1*, 355. (d) Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P.; Benaglia, M. *Tetrahedron* **1991,** *47*, 5737. (e) Annunziata, R.; Benaglia, M.;Cinquini, M.; Cozzi, F.; Giaroni, P. *J. Org. Chem.* **1992,** *57*, 782. (f) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1990,** *55*, 4506. (g) Konradi, A. W. ; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994,** *116*, 1316. (h) Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990,** *55*, 5924. (i) Askham, F. R.; Carroll, K. M. *J. Org. Chem.* **1993,** *58*, 7328. (j) Yoda, H.; Matsuda, K.; Nomura, H; Takabe, K. *Tetrahedron Lett.* **2000,** *41*, 1775. (k) Takai, K.; Nittaand, K.; Utimoto, K. *Tetrahedron Lett.* **1988,** *29*, 5263. (l) Takai, K.; Morita, R.; Toratsu, C. *Angew. Chem., Int. Ed.* **2001,** *40*, 1116. (m) Takai, K.; Morita, R.; Matsushita, H.; Toratsu, C. *Chirality*, **2003,** *15*, 17. (n) Boeckman, R. K., Jr.; Hudack, R. A., Jr. *J. Org. Chem.*, **1998,** *63*, 3524. (o) Jung, M. Groth, U. *Synlett*, **2002,** 2015. (p) Groth, U.; Jung, M.; Vogel, T. *Chem. Eur. J.*, **2005,** *11*, 3127. (q) Fischer, S.; Groth, U.; Jung, M.; Lindenmaier, M.; Vogel, T. *Tetrahedron Lett.* **2005,** *46*, 6679. (r) Miyoshi, N.; Fukuma, T.; Wada, M. *Chem. Lett.* **1995,** *24*, 999. (s) Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetrahedron Lett.* **2004,** *45*, 3869. (t) Nair, V.; Ros, S.; Jayanand, C. N.; Rath, N. P. *Tetrahedron Lett.* **2002,** *43*, 8967. (u) Yang, Y.-S.; Shen, Z.-L.; Loh, T.-P. *Org. Lett.* **2009,** *11* ,2213. (v) Kise, N.; Shiozawa, Y.; Ueda, N. *Tetrahedron* **2007,** *63*, 5415. (w) Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004,** *126*, 13198. (x) Duan, X.-F.; Feng, J.-X.; Zi, G.-F.; Zhang, Z.-B. *Synthesis* **2009,** *2*, 277.

[5] Fittig, R. *Justus Liebigs Ann. Chem.* **1859,** *110*, 23.

[6] Recent developments in using ketones in pinacol reactions: (a) Matsukawa, S.; Hinakubo, Y. *Org. Lett.* **2003,** *5*, 1221. (b) Shi, L.; Fan, C.-A.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M. *Tetrahedron*, **2004,** *60*, 2851. (c) Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005,** *7*, 1919.

[7] (a) Uraguchi, D.; Ito, T.; Ooi, T. *J. Am. Chem. Soc.* **2009,** *131*, 3836. (b) Uraguchi, D.; Ito, T.; Nakamura, S.; Ooi, T. *Chem. Sci.* **2010,** *1*, 488.

[8] (a) Uraguchi, D.; Ooi, T. *J. Synth. Org. Chem., Jpn.* **2010,** *68*, 1185. (b) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012,** *134*, 19370. (c) Uraguchi, D.; Tsutsumi, R.; Ooi, T. *J. Am. Chem. Soc.* **2013,** *135*, 8161. (d) Uraguchi, D.; Nakamura, S.; Sasaki, H.; Konakade, Y.; Ooi, T. *Chem. Commun.* **2014,** *50*, 3491. (e) Krawczyk, H.; Dzięgielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, Ł. *Chem. Eur. J.* **2015,** *21*, 10268.

[9] Phosphonate–phosphate rearrangement from acyl phosphonates: (a) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal.* **2005,** *347*, 1207. (b) Demir, A. S.; Reis, Ö.; İğdir, A. Ç.; Esiringü, İ; Eymur, S. *J. Org. Chem.* **2005,** *70*, 10584. Phosphonate–phosphate rearrangements from a-hydroxy trialkyl phosphonoacetates; (c) Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2012,** *51*, 4685. Addition of phosphite to a-keto amides followed by phosphonate–phosphate rearrangement and intramolecular trapping; (d) Kondoh, A.; Aoki, T.; Terada, M. *Org. Lett.* **2014,** *16*, 3528. Phosphite addition and rearrangement with protonation; (e) Hayashi, M.; Nakamura, S. *Angew. Chem., Int. Ed.* **2011,** *50*, 2249. (f) Wang, L.; Yao, Z.; Xu, F.; Shen, Q. *Heteroat. Chem.* **2012,** *23*, 449. (g) Fang, W.; Liu, G.-G.; Huang, X.-F.; Jia, J.; Wang, X.-W. *Chin. J. Org. Chem.* **2014,** *34*, 1177.

[10] For example: (a) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982,** 989. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999,** *121*, 686. (c) Peng, L.; Wang, L.-L.; Bai, J.-F.; Jia, L.-N.; Yang, Q.-C.; Huang, Q.-C.; Xu, X.-Y.; Wang, L.-X. *Tetrahedron Lett.* **2011,** *52*, 1157. (d) Goodman, C.G.; Walker, M. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2015,** *137*, 122.

[11] With respect to aldehyde electrophiles, we examined linear and alpha-branched alkyl aldehydes and observed slow conversion affording a mixture of unidentified products, together with a certain amount of the aldehyde Pudovik product and the desired mono-protected diol.

[12] We studied a number of cinchona alkaloid-derived catalysts, as well as hydrogen-bonding catalysts of other types (ureas, thioureas, cyclopropyl imines) and found low levels of stereoselectivity and unacceptable isolated yields.

[13] Pudovik adduct formation was detected with larger phosphites, implicating steric effects as being important in determining the rate of phosphonate– phosphate rearrangement.

[14] Crystallographic data (excluding structure factors) for phosphate **1.4j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1055582.

[15] (a) Overman, L. E.; Peterson, E. A. *Tetrahedron*, **2003,** *59*, 6905. b) Vyas, D. J.; Froehlich, R.; Oestreich, M. *J. Org. Chem.* **2010,** *75*, 6720. c) Bouhfid, R.; Joly, N.; Essassi, E. M.; Lequart, V.; Massoui, M.; Martin, P. *Synth. Comm.* **2011,** *41*, 2096.

CHAPTER TWO:
ASYMMETRIC ORGANOCATALYTIC REDUCTIVE COUPLING REACTIONS BETWEEN BENZYLIDENE PYRUVATES AND ALDEHYDES[†]

2.1 Introduction

Following the development of the asymmetric organocatalytic reductive coupling reaction between isatins and aldehydes, we sought to extend the same mechanistic manifold to a wider array of chemical systems. The eventual endpoint of these developments would be arriving at a catalytic asymmetric system that is capable of furnishing the core of natural products. With this goal in mind, we aimed to utilize more complex substrates than we did in our initial work. In the work presented in this chapter, the mechanistic framework from Chapter One is further developed in order to advance the state of the reaction using a new substrate class. While more selectivity issues were present in this new system, we were ultimately able to resolve them by deploying a chiral triaryliminophosphorane organocatalyst, allowing a stereocontrolled reductive coupling reaction between benzylidene pyruvates and aldehydes.

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2.2 Background

2.2.1 Extension of the Phosphite-mediated Reductive Coupling Mechanism to Benzylidene Pyruvates and Aldehydes

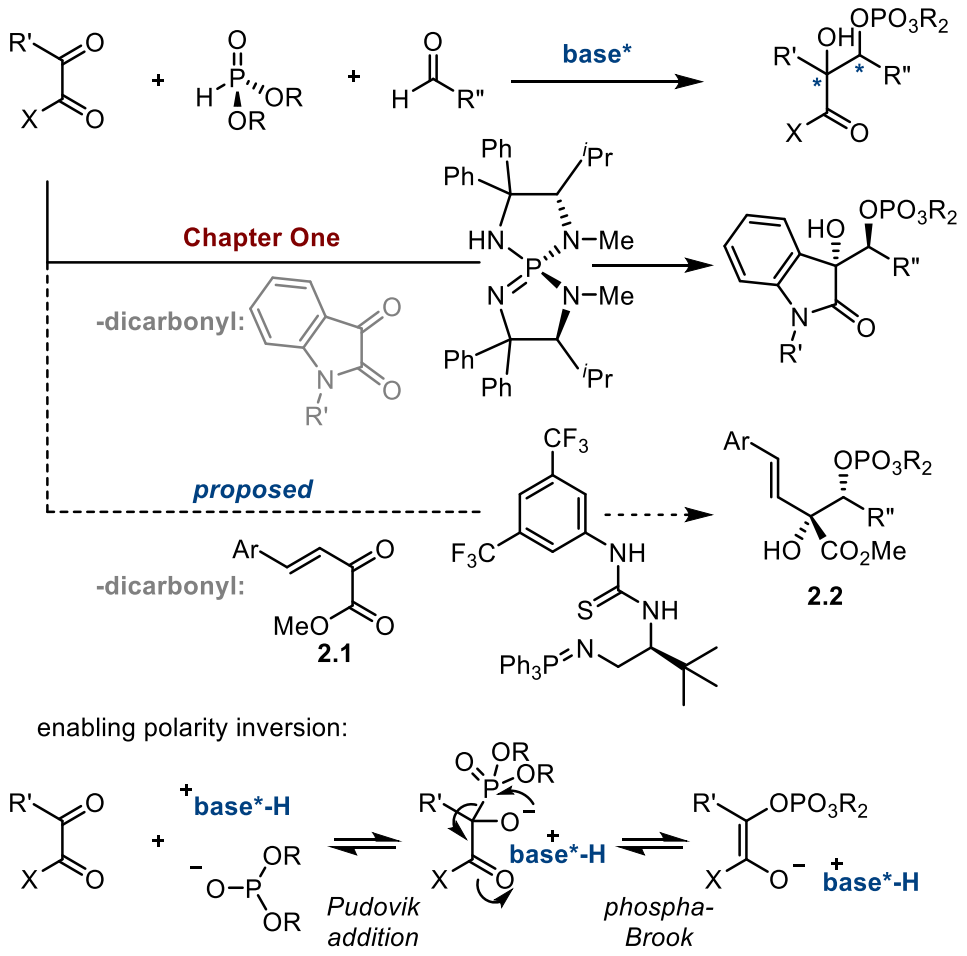
The reductive union of two prochiral starting materials into products bearing vicinal stereogenic centers builds molecular complexity and as such is an actively sought transformation in chemical synthesis. Pinacol-type reductive coupling reactions deliver vicinal diols,[1-5] but drawbacks remain. Commonly used single-electron transfer methods rely on stoichiometric amounts of low-valent metal[3n-3r] and stereocontrol can be challenging.[5b,5c] In the methodologies that have successfully achieved selectivity in the reductive coupling reaction, the challenge of achieving orthogonal reactivity in downstream transformations of the vicinal alcohols remains.[3g] Some of these issues were addressed in Chapter One through the use of a base-catalyzed, phosphite mediated asymmetric reductive coupling of two different carbonyls.[6,7] In this mechanistic manifold, a Pudovik addition of a dialkylphosphite to an isatin triggers phospha-Brook rearrangement and subsequent catalyst controlled trapping of the resultant enolate with an aldehyde.[6-9] In this chapter, we extend this reaction framework and report a highly stereoselective phosphite-mediated reductive coupling reaction between benzylidene pyruvates and aryl aldehydes (Scheme 2-1).

2.2.2 Chemoselectivity Challenges Associated with Phosphite-mediated Reductive Coupling of Benzylidene Pyruvates and Aldehydes

Our goal of introducing a higher level of functionality into the product carries with it challenges not faced in our prior work (Scheme 2-2). In order to achieve a stereoselective cross-coupled product from ambident benzylidene pyruvates and aryl aldehydes, it is necessary to be able to control (a) the chemoselectivity of the phosphite addition (pyruvate vs. aldehyde; Scheme 2-3a),[10] (b) the regioselectivity of the phosphite addition (1,2- vs. 1,4-addition; Scheme 2-3b),[11]

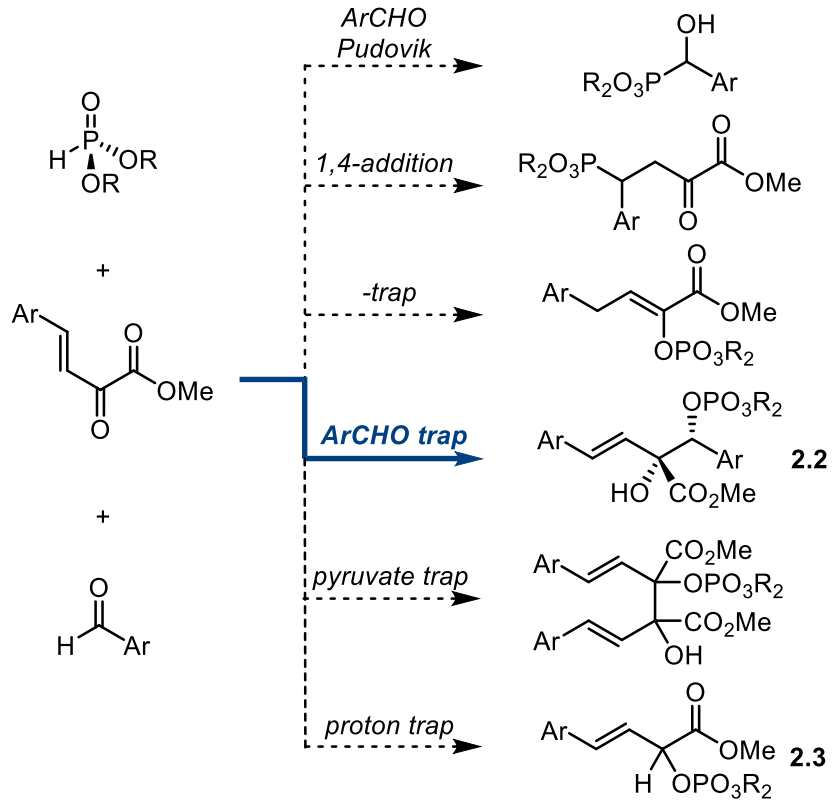
(c) the nucleophilicity of the nascent enolate (α- vs. γ-trapping; Scheme 2-3c),[12] (d) the chemoselectivity of the enolate trap (proton vs. pyruvate vs. aldehyde; Scheme

Scheme 2-1. Asymmetric Reductive Multicomponent Reactions



2-3d),[12,13] and (e) the stereoselectivity of the enolate addition into the aryl aldehyde. Fortunately, the relative electron deficiency of the benzylidene pyruvates made the chemo- and regioselectivity issues manageable. Furthermore, the chiral triaryliminophosphoranes developed by Dixon and coworkers[14] guided the stereodefining C-C bond construction with excellent levels of diastereo- and enantiocontrol.

Scheme 2-2. Chemoselectivity Issues



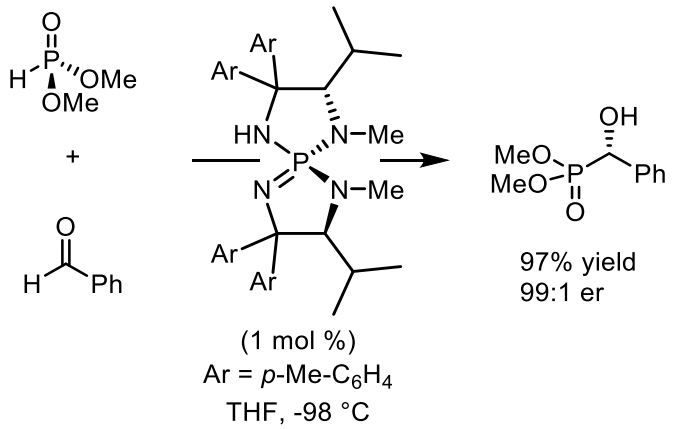
2.3 Results and Discussion

2.3.1 Discovery and Optimization of Asymmetric Reaction

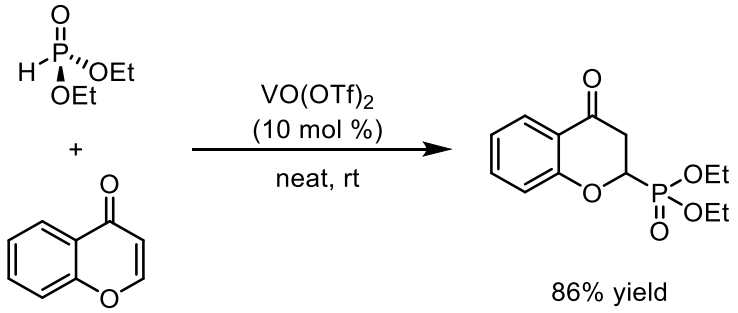
Initially, we studied the dimethyl phosphite-mediated reductive coupling of benzylidene pyruvate **1a** with *para*-bromobenzaldehyde (Table 2-1). Using 10 mol % KO^{t}Bu at 0 ºC, the reaction was complete in minutes and hydroxy phosphate **2a** was formed exclusively (1.2:1 dr). Having found that the enolate formed by the Pudovik-phospha-Brook sequence was both nucleophilic at the correct position and capable of being trapped by aryl aldehydes, we turned our attention to the development of the asymmetric variant.

Scheme 2-3. Precedents for Undesired Modes of Reactivity

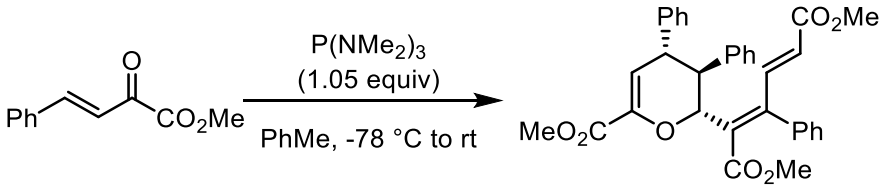
a) Ooi



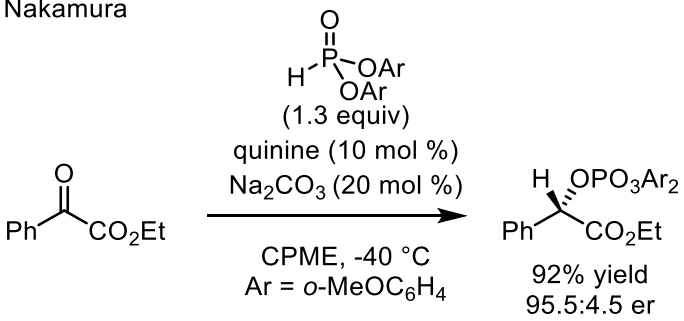
b) Chen



c) Radosevich



d) Nakamura



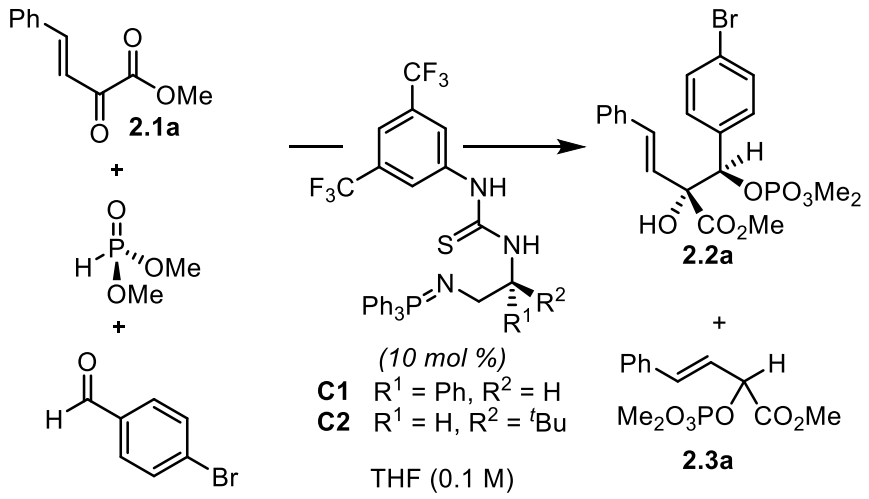
In our previous experience with this type of reductive coupling reaction, we demonstrated through crossover experiments that a stereoablative retro aldol process becomes possible somewhere in the

cryogenic range;[7] therefore, we sought to carry out the reactions at as low a temperature as possible. We observed that cinchona alkaloid-derived thiourea catalysts were not basic enough to permit the reaction to proceed at cryogenic temperatures, which caused us to move toward other catalyst families. The evaluation of chiral triaryliminophosphorane **C1** revealed that after 48 h at -60 ºC, the starting material was completely consumed and a 6:1 ratio of products was obtained arising from aldehyde trapping (**2.2a**) relative to proton trapping (**2.3a**), the former with a diastereomer ratio of 13:1. This encouraging result led us to synthesize and evaluate catalyst **C2**, which gave a >20:1 ratio of **2.2a**:**2.3a**, with 17:1 dr and 97:3 er.

2.3.2 Scope of Reaction

The application of catalyst **C2** to a broader range of reaction partners was then undertaken (Table 2-2). The reaction proceeds with electron-withdrawing groups on the benzylidene pyruvate; placing the electron-withdrawing group on the *ortho* (**2.2f**, **2.2g**) or *para* (**2.2b**-**2.2d**) positions on the benzylidene pyruvate led to comparable yields and stereoselectivities to the unsubstituted case, but we found that using a *meta*-bromo benzylidene pyruvate gave only 5.4:1 dr. Additionally, while substrates with *meta* and *para* electron-withdrawing groups gave upwards of 96:4 er, we observed enantioselectivities of 90.5:9.5 for **2.2f** and 93:7 for **2.2g** (*o*-bromo and *o*-fluoro, respectively). Using a 4-methyl substituted benzylidene pyruvate we observed that the reaction was complete in 24 h (**2.2h**), though with stronger electron-donating groups on the ring, the reaction is slower likely due to depressed rate of Pudovik addition (**2.2i-2.2j**).

Table 2-1. Reaction Optimization for Reductive Coupling Reaction with Benzylidene Pyruvates

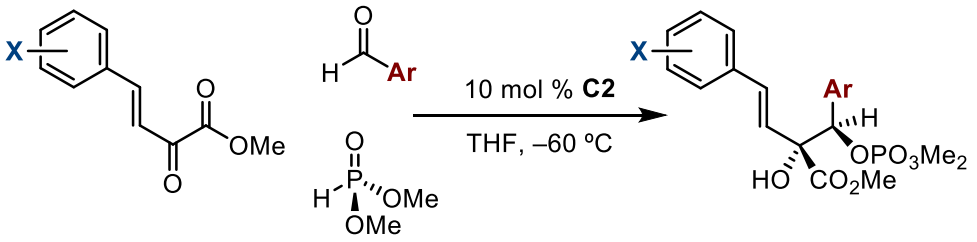


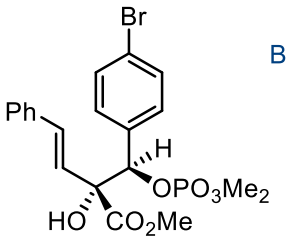
entry	temp (°C)	catalyst	dr	er	2.2a:2.3a
1[a]	0	KO^{t}Bu	1.2:1	50:50	100:0
2[b]	–60	**C1**	13:1	9:91	6:1
3[b]	–60	**C2**	17:1	97:3	>20:1

[a] Reaction was conducted on 1.0 mmol scale, using 1.1 equiv of dimethylphosphite and 5.0 equiv of ArCHO; reaction was complete in minutes. [b] Reactions were conducted on 0.2 mmol scale, using 1.1 equiv of dimethylphosphite and 5.0 equiv of ArCHO. Reactions were run for 24 h.

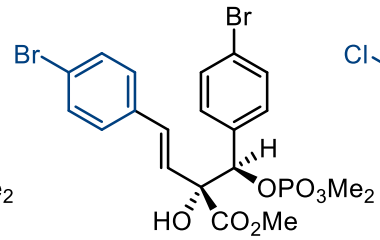
Using the 2-thienylidene pyruvate gave **2.2k** in >20:1 dr, with 87% yield and 92:8 er, but extending the conjugation of the starting material as in **2.2l** gave 14:1 dr and 92:8 er, with 74% yield. The reaction was found to proceed with other electron-deficient aryl aldehydes as well (**2.2m**-**2.2r**), either in the *para* or *meta* position, although there was a noticeable drop in stereoselectivity with *para*-nitrobenzaldehyde. We attempted to use benzaldehyde as a coupling partner, but observed that the major product formed in that reaction was **2.3**.[15]

Table 2-2. Scope of Asymmetric Reductive Coupling Reaction with Benzylidene Pyruvates and Aldehydes[a]

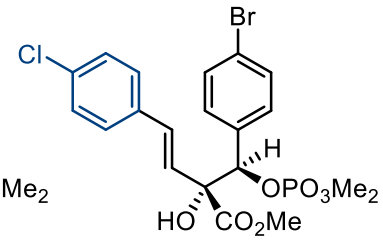




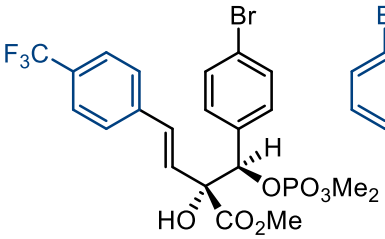
18:1 dr
94:6 er
81% yield
2.2a



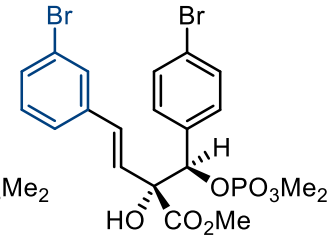
18:1 dr
98.5:1.5 er
72% yield
2.2b[b]



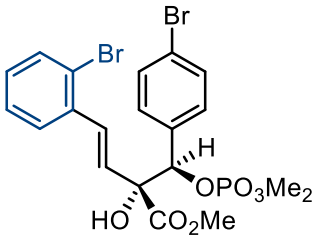
15:1 dr
96:4 er
66% yield
2.2c[b]



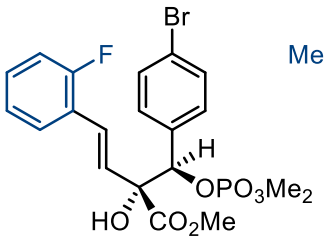
17:1 dr
97.5:2.5 er
68% yield
2.2d[b]



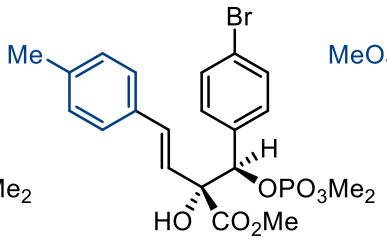
5.4:1 dr
96:4 er
67% yield
2.2e[b]



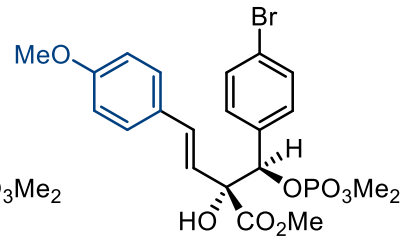
10:1 dr
90.5:9.5 er
65% yield
2.2f



14:1 dr
93:7 er
68% yield
2.2g

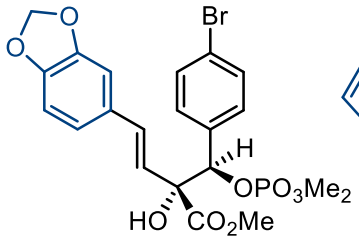


17:1 dr
93.5:6.5 er
84% yield
2.2h

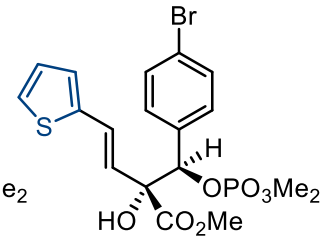


13:1 dr
93:7 er
59% yield
2.2i[b]

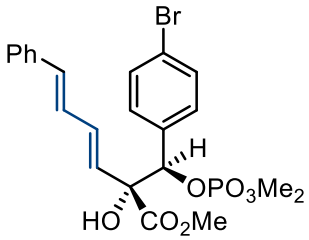
Table 2-2, cont.



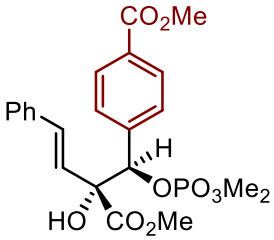
16:1 dr
96.5:3.5 er
56% yield
2.2j[b]



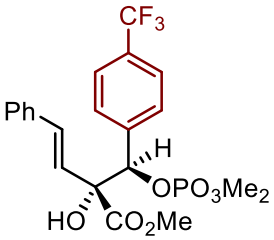
>20:1 dr
92:8 er
87% yield
2.2k



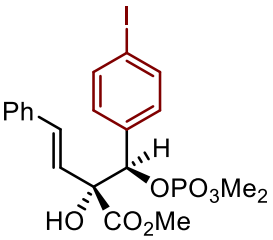
14:1 dr
92:8 er
74% yield
2.2l



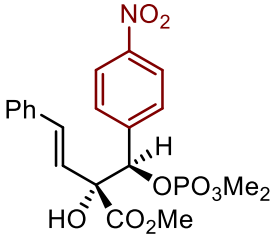
14:1 dr
97:3 er
70% yield
2.2m



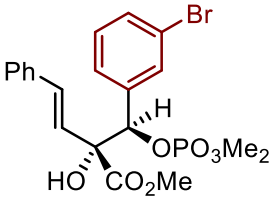
9:1 dr
94.5:5.5 er
53% yield
2.2n



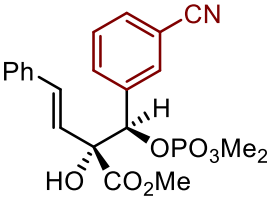
16:1 dr
96:4 er
78% yield
2.2o



4:1 dr
82:18 er
43% yield
2.2p



15:1 dr
94:6 er
70% yield
2.2q



10:1 dr
96:4 er
55% yield
2.2r

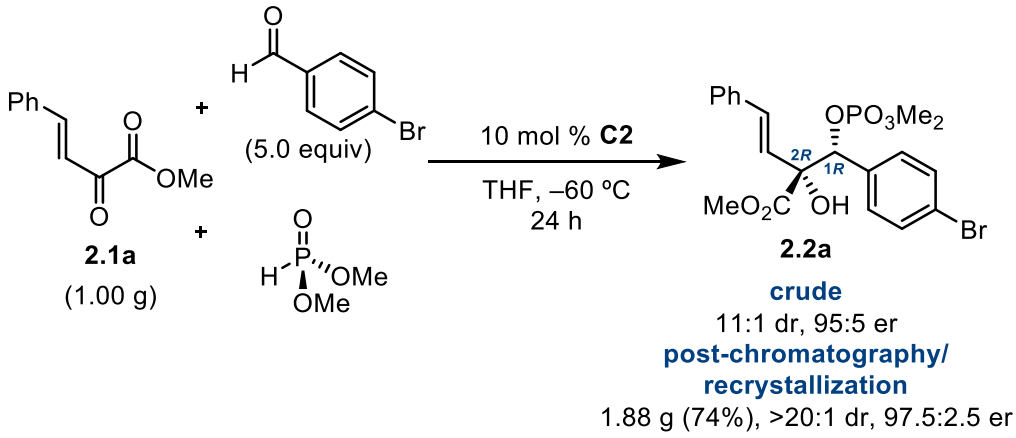
[a] All reactions were conducted on 0.1 mmol scale, using 1.1 equiv of dimethyl phosphite and 5.0 equiv of ArCHO. % yields refer to isolated yields. All dr, er, and % yields are the averages of two trials. [b] Reaction time = 48 h.

2.3.2 Gram-scale Reductive Coupling Reaction

The asymmetric reductive coupling reaction on gram scale works comparably to those reactions conducted on smaller scale. Figure 2 illustrates the conversion of 1 g of **1a** to 1.88 g of

the derived coupled product **2a** with >20:1 dr and 97.5:2.5 er after a single recrystallization. An x-ray diffraction study of this material revealed the absolute configuration of the coupled product to be (*1R*,2*R*) (Scheme 2-4).

Scheme 2-4. Asymmetric Reductive Coupling Reaction on Gram-Scale and X-Ray Diffraction Study of **2.2a**[a]



[a] The reaction was conducted using 1.1 equiv of dimethyl phosphite and 5.0 equiv of ArCHO. % yield refers to isolated yield. Reaction was run for 24 h.

2.4 Conclusion

The work described in this chapter expands on the organic reductant-based organocatalytic reductive coupling developed in Chapter One. The title process exhibits high levels of chemo- and stereoselectivity in the face of multiple potential reaction pathways. Specifically, this work presents new possibilities for the coupling partners that can participate in this reaction.

2.5 Experimental Details

Methods: Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz,

^{13}C NMR at 101 MHz or 151 MHz, ^{19}F NMR at 376 MHz and ^{31}P NMR at 162 MHz or 243 MHz), or a Bruker AVANCE III-OneBay500 (^{13}C NMR at 235 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br-s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were obtained with a Thermo Fisher Scientific Exactive or Finnigan™ LTQ-ICR FT™ (all samples prepared in methanol). Melting points were obtained using a Thomas Hoover UniMelt Capillary Melting Point Apparatus. Analytical thin layer chromatography was carried out using Whatman 0.25 mm silica gel 60 plates, Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was allowed by UV light, phosphomolybdic acid in ethanol, or aqueous ceric ammonium nitrate solution. HPLC analysis was performed on a Perkin Elmer flexar photodiode array (PDA) system equipped with Daicel IA, IC, AD, and OD-H columns. Asymmetric reactions were carried out in a Thermo NESLAB CB-80 immersive cryogenic cooler with stirring. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40- 63μm) purchased from Silicycle. Yields refer to isolated yields after flash column chromatography; some samples contain residual minor diastereomers. Since all results are the averages of two trials, the stereoisomer ratios listed in the tables may not exactly match those represented in the NMR and HPLC data below.

Materials: Tetrahydrofuran (THF) was passed through a column of neutral alumina under nitrogen prior to use. Benzylidene pyruvates were prepared according to literature procedures.[16] Triaryliminophosphorane catalysts **C1-C2** were prepared according to literature procedures.[14] Commercially available dimethyl phosphite and potassium *tert*-butoxide were used as received. Commercially available liquid aldehydes were freshly distilled directly before the reactions. The

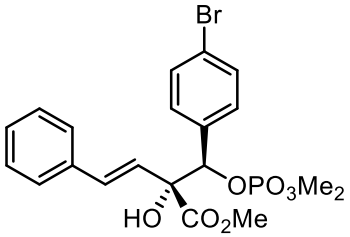
literature method for the racemic three-component coupling was used to generate racemic standards.[7]

Experimental Procedures:

General procedure for three component reaction using chiral iminophosphorane:

A test tube was charged sequentially with dimethyl phosphite (0.11 mmol, 1.1 equiv), aldehyde (0.5 mmol, 5.0 equiv), and α–keto ester (0.1 mmol, 1.0 equiv), followed by THF (1.0 mL), which was used to wash the residual solids and liquids on the sides of the test tube to the bottom. The reaction was stirred at -60 ºC in a cryogenic cooling apparatus for 30 minutes, then the iminophosphorane catalyst **C2** was added. The reaction was then stirred at -60 ºC and monitored by TLC until the reaction was complete. The crude reaction mixture was then flowed through a short silica plug and flushed through with diethyl ether, then concentrated *in vacuo*. The crude materials thusly obtained were purified using flash column chromatography, with a gradient from 60:40 hexanes/EtOAc to 40:60 hexanes/EtOAc.

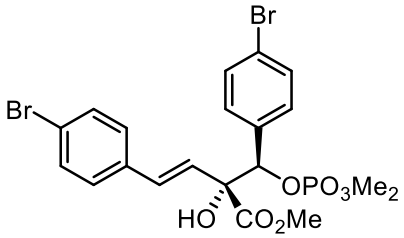
Characterization data for new compounds:



Methyl (*R*,*E*)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxy-4-phenylbut-3-enoate (2.2a):

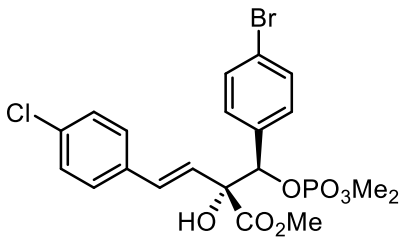
The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.46 (major diastereomer) and δ 6.18 (minor diastereomer). White solid (40.1 mg), mp 136-137 °C (decomp); **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.38-7.28 (m, 5H), 7.04 (d, *J* = 16.0 Hz, 1H), 6.47 (d, 16.0 Hz, 1H), 5.71 (d, J = 9.6 Hz, 1H), 3.78 (s, 3H), 3.59 (d, *J* = 11.2 Hz, 3H), 3.49 (d, *J* = 11.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.1, 135.9, 134.3 (d, *J* = 2.4 Hz), 132.7, 131.4, 129.6, 128.7, 128.3, 126.9, 126.0, 123.4, 81.5 (d, *J* = 5.4 Hz), 80.3 (d, *J* = 6.5 Hz), 54.6 (d, *J* = 6.0 Hz), 54.3 (d, *J* = 6.0 Hz), 53.5; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.97. **IR** (thin film) ν 2917, 2360, 1741, 1489, 1257, 1034, 906, 852, 507 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{22}BrO_7P$ ($[M+H^+]$): 485.0359, found 485.0367. **HPLC** Chiralpak OD-H column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 18.1 min (minor isomer), 25.0 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.13. **$[\alpha]_D$** = -14.9 (c = 3.0, CH_2Cl_2).

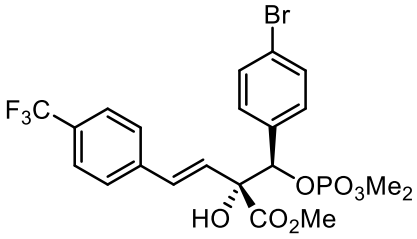


Methyl (*R*,*E*)-4-(4-bromophenyl)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxybut-3-enoate (2.2b): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 48 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.46 (major diastereomer) and δ 6.18 (minor diastereomer). White solid (45.3 mg), mp 148-153 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.33-7.30 (m, 4H), 6.96 (d, *J* = 15.7 Hz, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.69 (d, *J* = 9.6 Hz, 1H), 3.78 (s, 3H), 3.58 (d, *J* = 11.4 Hz, 3H), 3.48 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.9, 134.8, 134.1 (d, *J* = 2.3 Hz), 131.9, 131.5, 131.4, 129.5, 128.4, 126.9, 123.5, 122.1, 81.3 (d, *J* = 5.4 Hz), 80.2 (d, *J* = 6.5 Hz), 54.6 (d, *J* = 6.0 Hz), 54.3 (d, *J* = 6.0 Hz), 53.6; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.96. **IR** (thin film) ν 2954, 1742, 1590, 1488, 1251, 1149, 1036, 1009, 905, 851 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{21}Br_2O_7P$ ($[M+H^+]$):

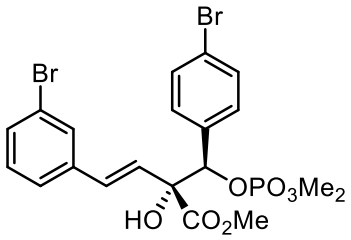
562.9464, found 562.9475. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 42.0 min (minor isomer), 53.0 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.14. **[α]$_D$** = -10.2 (c = 4.6, CH_2Cl_2).



Methyl (*R*,*E*)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-4-(4-chlorophenyl)-2-hydroxybut-3-enoate (2.2c): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 48 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.45 (major diastereomer) and δ 6.16 (minor diastereomer). White solid (44.4 mg), mp 137-141 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.33-7.30 (m, 4H), 6.98 (d, *J* = 15.7 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 5.70 (d, *J* = 9.8 Hz, 1H), 3.79 (s, 3H), 3.58 (d, *J* = 11.2 Hz, 3H), 3.48 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.9, 134.4, 134.1 (d, *J* = 2.6 Hz), 133.9, 131.5, 131.4, 129.5, 128.9, 128.1, 126.7, 123.5, 81.4 (d, *J* = 5.3 Hz), 80.2 (d, *J* = 6.6 Hz), 54.6 (d, *J* = 6.2 Hz), 54.3 (d, *J* = 6.2 Hz), 53.6; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.99. **IR** (thin film) ν 1740, 1492, 1249, 1036 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{21}BrClO_7P$ ([M+H$^+$]): 518.9970, found 518.9976. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 28.8 min (minor isomer), 62.8 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.36. **[α]$_D$** = -5.5 (c = 2.9, CH_2Cl_2).

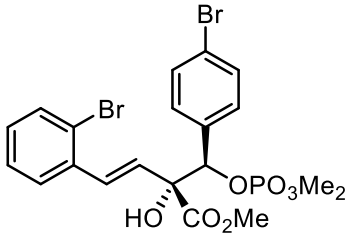


Methyl (*R*,*E*)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxy-4-(4-(trifluoromethyl)phenyl)but-3-enoate (2.2d): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 48 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.59 (major diastereomer) and δ 6.30 (minor diastereomer). White solid (40.9 mg), mp 134-140 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 16.0 Hz, 1H), 6.58 (d, *J* = 15.7 Hz, 1H), 5.72 (d, *J* = 102. Hz, 1H), 3.79 (s, 3H), 9. 3.59 (d, *J* = 11.4 Hz, 3H), 3.49 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.8, 139.4, 134.0 (d, *J* = 2.3 Hz), 131.5, 131.4, 130.1, 129.9, 129.5, 128.8, 127.0, 125.7 (q, *J* = 3.9 Hz), 123.5, 81.3 (d, *J* = 5.3 Hz), 80.3 (d, *J* = 6.5 Hz), 54.6 (d, *J* = 6.0 Hz, 54.3 (d, *J* = 6.3 Hz), 53.6; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.95; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.6. **IR** (thin film) ν 1739, 1326, 1123, 1045 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{21}BrF_3O_7P$ ([M+H$^+$]): 553.0233, found 553.0244. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 22.3 min (minor isomer), 51.9 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.32. **$[\alpha]_D$** = -6.6 (c = 3.6, CH_2Cl_2).



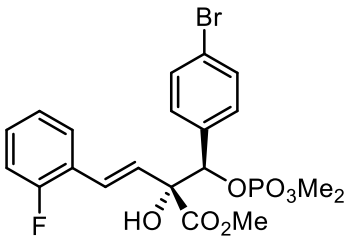
Methyl (*R*,*E*)-4-(3-bromophenyl)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxybut-3-enoate (2.2e): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 48 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of

the crude reaction mixture by comparison of the resonances at δ 6.48 (major diastereomer) and δ 5.05 (minor diastereomer). White solid (42.9 mg), mp 128-131 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 5.69 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.60 (d, *J* = 11.4 Hz, 3H), 3.49 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.9, 138.1, 134.1 (d, *J* = 2.4 Hz), 131.5, 131.4, 131.1, 130.3, 129.7, 129.5, 127.6, 125.5, 123.5, 122.9, 81.4 (d, *J* = 5.6 Hz), 80.2 (d, *J* = 6.6 Hz), 54.6 (d, *J* = 6.0 Hz), 54.3 (d, *J* = 5.9 Hz), 53.6; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.97. **IR** (thin film) ν 2955, 2349, 1742, 1591, 1563, 1269, 1153, 1037, 1067, 905 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{21}Br_2O_7P$ ([M+H^+]):562.9464, found 562.9476. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 28.5 min (minor isomer), 63.1 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.30. **$[\alpha]_D$** = -2.4 (c = 2.8, CH_2Cl_2).



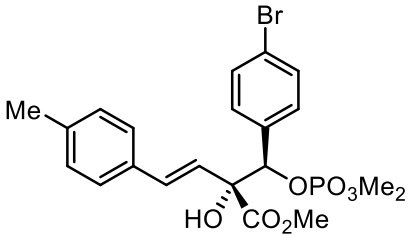
Methyl (*R*,*E*)-4-(2-bromophenyl)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxybut-3-enoate (2.2f): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.44 (major diastereomer) and δ 6.09 (minor diastereomer). White solid (40.9 mg), mp 122-126 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.35-7.31 (m, 3H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 5.72 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 3H), 3.64 (d, *J* = 11.2 Hz, 3H), 3.49 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.8, 135.9, 134.1 (d, *J* = 2.6 Hz), 133.0, 131.6, 131.4, 129.6, 129.5, 129.2, 127.7,

127.5, 124.0, 123.5, 81.2 (d, J = 5.6 Hz), 80.4 (d, J = 6.3 Hz), 54.7 (d, J = 6.5 Hz), 54.3 (d, J = 6.2 Hz), 53.6; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.83. **IR** (thin film) ν 1741, 1268, 1028, 553 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{21}Br_2O_7P$ ([M+H^+]): 562.9464, found 562.9474. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 23.7 min (minor isomer), 57.3 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.27. **$[\alpha]_D$** = +6.6 (c = 3.5, CH_2Cl_2).

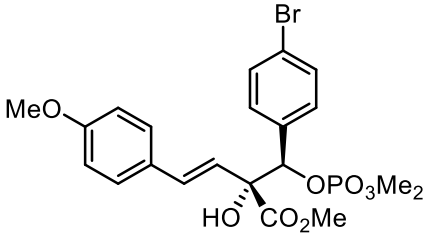


Methyl (*R*,*E*)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-4-(2-fluorophenyl)-2-hydroxybut-3-enoate (2.2g): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.54 (major diastereomer) and δ 6.68 (minor diastereomer). White solid (36.2 mg), mp 126-130 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.54-7.50 (m, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.29-7.24 (m, 1H), 7.19 (d, J = 15.9 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 7.08-7.05 (m, 1H), 6.58 (d, J = 15.6 Hz, 1H), 5.71 (d, J = 9.6 Hz, 1H), 3.78 (s, 3H), 3.62 (d, J = 11.4 Hz, 3H), 3.49 (d, J = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.9, 161.2, 159.6, 134.2 (d, J = 1.8 Hz), 131.4, 129.6, 128.7 (d, J = 5.0 Hz), 128.1 (d, J = 3.2 Hz), 125.5 (d, J = 3.2 Hz), 124.3 (d, J = 3.5 Hz), 123.7 (d, J = 12.1 Hz), 123.4, 115.9 (d, J = 22.0 Hz), 81.4 (d, J = 5.3 Hz), 80.4 (d, J = 6.6 Hz), 54.6 (d, J = 5.7 Hz), 54.3 (d, J = 6.5 Hz), 53.5; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.86; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.0. **IR** (thin film) ν 3649, 3956, 1748, 1507, 1489, 1457, 1289, 1270, 1231, 1039 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{21}BrFO_7P$ ([M+H^+]): 503.0265, found 503.0272. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 96:4, flow rate = 1.0

mL/min, λ = 210 nm, 34.1 min (minor isomer), 87.9 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.25. **$[\alpha]_D$** = -1.0 (c = 4.0, CH_2Cl_2).

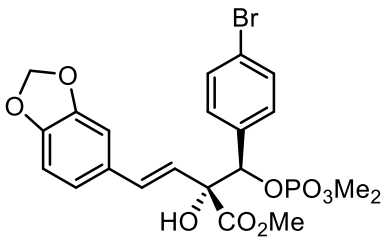


Methyl (*R*,*E*)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxy-4-(*p*-tolyl)but-3-enoate (2.2h): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.37 (major diastereomer) and δ 6.54 (minor diastereomer). White solid (42.7 mg), mp 129 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 15.6 Hz, 1H), 6.41 (d, *J* = 15.6 Hz, 1H), 5.70 (d, *J* = 9.6 Hz), 3.77 (s, 3H), 3.59 (d, *J* = 11.4 Hz, 3H), 3.48 (d, *J* = 11.4 Hz, 3H), 2.36 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.1, 138.2, 134.3 (d, *J* = 2.4 Hz), 133.1, 132.5, 131.4, 129.6, 129.4, 126.8, 125.0, 123.3, 81.5 (d, *J* = 5.4 Hz), 80.3 (d, *J* = 6.6 Hz), 54.6 (d, *J* = 6.0 Hz), 54.3 (d, *J* = 6.0 Hz), 53.4 21.3; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.95. **IR** (thin film) ν 3853, 3649, 3345, 2954, 2854, 2360, 1741, 1593, 1514, 1488 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{24}BrO_7P$ ([M+H^+]): 499.0516, found 499.0524. **HPLC** Chiralpak IC column, Hex/^{i}PrOH = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 27.0 min (minor isomer), 58.0 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.29. **$[\alpha]_D$** = -24.2 (c = 4.0, CH_2Cl_2).



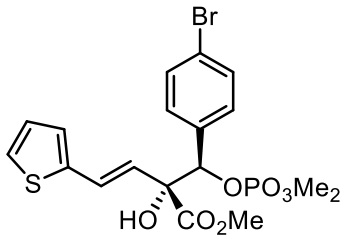
Methyl (*R*,*E*)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxy-4-(4-methoxyphenyl)but-3-enoate (2.2i): The title

compound was prepared according to the general procedure; the reaction was allowed to proceed for 48 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.31 (major diastereomer) and δ 6.55 (minor diastereomer). White solid (31.3 mg), mp 115-129 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 15.7 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 15.7 Hz, 1H), 5.70 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.59 (d, *J* = 11.4 Hz, 3H), 3.48 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.2, 159.7, 134.3 (d, *J* = 2.1 Hz), 132.1, 131.4, 129.6, 128.6, 128.1, 123.7, 123.3, 114.1, 81.5 (d, *J* = 5.6 Hz), 80.2 (d, *J* = 6.6 Hz), 55.3, 54.6 (d, *J* = 6.0 Hz), 54.3 (d, *J* = 6.2 Hz), 53.4; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.96. **IR** (thin film) ν 2955, 1740, 1606, 1513, 1488, 1456, 1253, 1176, 1032, 1008 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{24}BrO_8P$ ([M+H$^+$]): 515.0465, found 515.0472. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 18.6 min (minor isomer), 36.6 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.09. **$[\alpha]_D$** = -30.4 (c = 2.5, CH_2Cl_2).



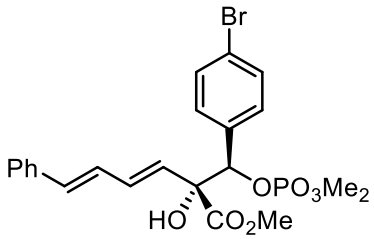
Methyl (*R*,*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxybut-3-enoate (2.2j): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 48 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.28 (major diastereomer) and δ 6.51 (minor diastereomer). White solid (31.5 mg), mp 118-120 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 1.5 Hz, 1H), 6.92 (d, *J* = 15.7 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 5.98 (s, 2H), 5.68 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 3.61 (d, *J* = 10.8 Hz, 3H), 3.49 (d, *J* = 11.4 Hz, 3H); **^{13}C**

NMR (151 MHz, $CDCl_3$) δ 172.1, 148.1, 147.7, 134.3, 132.3, 131.4, 130.3, 129.6, 124.1, 123.4, 121.8, 108.4, 106.0, 101.2, 81.5 (d, J = 5.4 Hz), 80.2 (d, J = 6.6 Hz), 54.6 (d, J = 6.0 Hz), 54.3 (d, J = 6.0 Hz), 53.4; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.94. **IR** (thin film) ν 1740, 1490, 1446, 1252, 1037, 852 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{22}BrO_9P$ ([M+H^+]): 529.0258, found 529.0267. **HPLC** Chiralpak OD-H column, Hex/^{i}PrOH = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 41.4 min (minor isomer), 47.7 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.31. **$[\alpha]_D$** = -14.7 (c = 2.1, CH_2Cl_2).

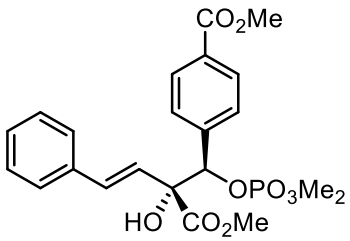


Methyl (*R*,*E*)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxy-4-(thiophen-2-yl)but-3-enoate (2.2k): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.26 (major diastereomer) and δ 6.03 (minor diastereomer). White solid (43.0 mg), mp 119-124 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 5.4 Hz, 1H), 7.15 (d, J = 15.0 Hz, 1H), 7.05 (d, J = 3.0 Hz, 1H), 6.99 (dd, J = 3.6 Hz, 1.8 Hz), 6.27 (d, J = 15.0 Hz, 1H), 5.65 (d, J = 9.6 Hz, 1H), 3.78 (s, 3H), 3.63 (d, J = 10.8 Hz, 3H), 3.50 (d, J = 11.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9, 140.8, 134.2, 131.4, 129.6, 127.6, 127.0, 126.0, 125.3, 125.2, 123.4, 81.5 (d, J = 4.4 Hz), 80.0 (d, J = 5.6 Hz), 54.6 (d, J = 4.8 Hz), 54.3 (d, J = 4.9 Hz), 53.5; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.95. **IR** (thin film) ν 3323, 2954, 2360, 1741, 1488, 1435, 1261, 1203, 1146, 1036 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{18}H_{20}BrO_7PS$ ([M+H^+]): 490.9923, found 490.9930. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 90:10, flow rate = 1.0 mL/min, λ = 210

nm, 18.1 min (minor isomer), 36.5 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.14. $[\alpha]_D$ = -18.1 (c = 5.2, CH_2Cl_2).

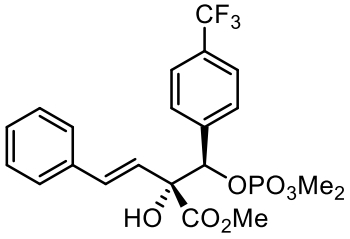


Methyl (R,3*E*,5*E*)-2-((*R*)-(4-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxy-6-phenylhexa-3,5-dienoate (2.2l): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.07 (major diastereomer) and δ 5.77 (minor diastereomer). White solid (43.1 mg), mp 132-137 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.36-7.26 (m, 5H), 6.89-6.80 (m, 2H), 6.65 (d, *J* = 14.4 Hz, 1H), 6.07 (d, *J* = 14.3 Hz, 1H), 5.64 (d, *J* = 9.7 Hz, 1H), 3.78 (s, 3H), 3.71 (d, *J* = 11.4 Hz, 3H), 3.49 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.0, 136.8, 134.6, 134.3 (d, *J* = 2.3 Hz) 133.2, 131.4, 129.6, 129.5, 128.7, 128.0, 127.1, 126.6, 123.4, 81.4 (d, *J* = 5.3 Hz), 80.1 (d, *J* = 6.6 Hz), 54.8 (d, *J* = 6.0 Hz), 54.3 (d, *J* = 6.2 Hz), 53.5; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.87. **IR** (thin film) ν 2954, 1754, 1289, 1029, 1008, 851, 692 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{22}H_{24}BrO_7P$ ([M+H^+]): 511.0516, found 511.0530. **HPLC** Chiralpak OD-H column, Hex/^{i}PrOH = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 35.7 min (major isomer), 45.7 min (minor isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.27. $[\alpha]_D$ = -5.7 (c = 3.9, CH_2Cl_2).



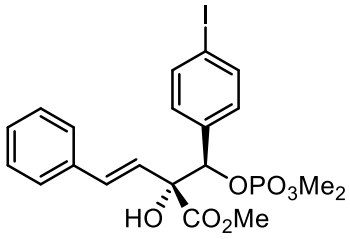
Methyl 4-((1*R*,2*R*,*E*)-1-((dimethoxyphosphoryl)oxy)-2-hydroxy-2-(methoxycarbonyl)-4-phenylbut-3-en-1-yl)benzoate (2.2m): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric

ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.46 (major diastereomer) and δ 6.56 (minor diastereomer). White solid (36.7 mg), mp 139-140 (decomp) °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3 Hz), 7.53 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.4, 2H), 7.37-7.29 (m, 3H), 7.05 (d, *J* = 15.6 Hz, 1H), 6.48 (d, *J* = 16.2 Hz, 1H), 5.80 (d, *J* = 9.6 Hz, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.60 (d, *J* = 10.8 Hz, 3H), 3.48 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.0, 166.6, 140.1 (d, *J* = 2.4 Hz), 135.8, 132.8, 130.8, 129.4, 128.7, 128.3, 127.9, 126.9, 125.9, 81.7 (d, *J* = 5.3 Hz), 80.3 (d, *J* = 6.5 Hz), 54.6 (d, *J* = 6.2 Hz), 54.3 (d, *J* = 6.2 Hz), 53.5, 52.3; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.96. **IR** (thin film) ν 2955, 1719, 1437, 1283, 1112, 1035, 853 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{22}H_{25}O_9P$ ($[M+H^+]$): 465.1309, found 465.1316. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 23.4 min (minor isomer), 44.3 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.15. **$[\alpha]_D$** = -1.0 (c = 6.3, CH_2Cl_2).

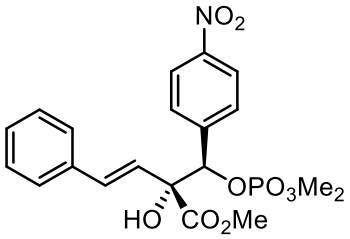


Methyl (*R*,*E*)-2-((*R*)-((dimethoxyphosphoryl)oxy)(4-(trifluoromethyl)phenyl)methyl)-2-hydroxy-4-phenylbut-3-enoate (2.2n): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.47 (major diastereomer) and δ 6.60 (minor diastereomer). White solid (27.7 mg), mp 128-129 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.38-7.30 (m, 3H), 7.05 (d, *J* = 16.2 Hz, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 5.81 (d, *J* = 10.2 Hz, 1H), 3.80 (s, 3H), 3.61 (d, *J* = 10.8 Hz, 3H), 3.51 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.0, 139.2, 135.8, 132.9, 131.2 (d, *J* = 32.8 Hz), 128.7, 128.3, 126.9, 125.8, 125.1, 124.8, 123.0, 81.4 (d, *J* = 5.3 Hz),

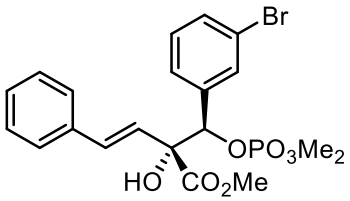
80.3 (d, J = 6.6 Hz), 54.7 (d, J = 6.0 Hz), 54.3 (d, J = 6.0 Hz), 53.6; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.98; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.7. **IR** (thin film) ν 2957, 1743, 1327, 1251, 1126, 1038, 693 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{22}F_3O_7P$ ([M+H^+]): 475.1128, found 475.1134. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 20.3 min (minor isomer), 46.5 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.29. **$[\alpha]_D$** = -4.4 (c = 2.8, CH_2Cl_2).



Methyl (*R*,*E*)-2-((*R*)-((dimethoxyphosphoryl)oxy)(4-iodophenyl)methyl)-2-hydroxy-4-phenylbut-3-enoate (2.2o): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.77 (major diastereomer) and δ 5.03 (minor diastereomer). White solid (49.2 mg), mp 137-141 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 7.4 Hz, 2H), 7.37-7.34 (m, 2H), 7.30-7.28 (m, 1H), 7.19 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 15.7 Hz, 1H), 6.47 (d, J = 15.6 Hz, 1H), 5.70 (d, J = 10.2 Hz, 1H), 3.78 (s, 3H), 3.59 (d, J = 10.8 Hz, 3H), 3.49 (d, J = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.1, 137.3, 136.9, 134.9 (d, J = 2.6 Hz), 132.7, 129.7, 128.7, 128.3, 126.9, 126.0, 95.3, 81.6 (d, J = 5.6 Hz), 80.3 (d, J = 6.6 Hz), 54.6 (d, J = 6.0 Hz), 54.3 (d, J = 6.0 Hz), 53.5; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.98. **IR** (thin film) ν 3750, 3649, 2349, 1541, 704, 514 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{22}IO_7P$ ([M+H^+]): 533.0221, found 533.0232. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 15.1 min (minor isomer), 33.4 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.33. **$[\alpha]_D$** = -7.8 (c = 2.0, CH_2Cl_2).

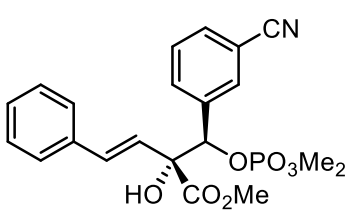


Methyl (*R*,*E*)-2-((*R*)-((dimethoxyphosphoryl)oxy)(4-nitrophenyl)methyl)-2-hydroxy-4-phenylbut-3-enoate (2.2p): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.44 (major diastereomer) and δ 6.22 (minor diastereomer). White solid (20.0 mg), mp 141-142 (decomp) °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.25 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 7.4 Hz, 2H), 7.37-7.28 (m, 3H), 7.04 (d, J = 15.6, 1H), 6.45 (d, J = 15.6 Hz, 1H), 5.83 (d, J = 9.6 Hz, 1H), 3.82 (s, 3H), 3.62 (d, J = 11.4 Hz, 3H), 3.53 (d, J = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.9, 148.3, 142.4, 135.7, 133.2, 128.9, 128.8, 128.4, 126.9, 125.4, 123.3, 81.1 80.2, 54.8, 54.4, 53.7; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.92. **IR** (thin film) 3853, 3735, 3649, 3566, 1749, 1716, 1558, 1541, 1507, 1457 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{22}NO_9P$ ([M+H$^+$]): 452.1105, found 452.1108. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 24.1 min (minor isomer), 55.4 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.18. **$[\alpha]_D$** = -7.1 (c = 1.3, CH_2Cl_2).



Methyl (*R*,*E*)-2-((*R*)-(3-bromophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxy-4-phenylbut-3-enoate (2.2q): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.46 (major diastereomer) and δ 6.19 (minor diastereomer). White solid (35.4 mg), mp 105-110 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 (s, 1H),

7.51 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.36-7.24 (m, 5H), 7.04 (d, *J* = 15.7 Hz, 1H), 6.48 (d, *J* = 15.7 Hz, 1H), 5.72 (d, *J* = 9.8 Hz, 1H), 3.80 (s, 3H), 3.59 (d, *J* = 11.2 Hz, 3H), 3.51 (d, *J* = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.0, 137.4 (d, *J* = 1.8 Hz), 135.9, 132.8, 132.2, 131.0, 129.8, 128.7, 128.3, 126.9, 126.5, 126.0, 122.3, 81.3 (d, *J* = 5.4 Hz), 80.4 (d, *J* = 6.6 Hz), 54.6 (d, *J* = 6.2 Hz), 54.3 (d, *J* = 6.2 Hz), 53.5; **^{31}P NMR** (203 MHz, $CDCl_3$) δ 0.88. **IR** (thin film) ν 1741, 1252, 1036, 698 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{22}BrO_7P$ ([M+H^+]): 485.0359, found 485.0364. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 210 nm, 25.9 min (minor isomer), 36.3 min (major isomer). **TLC** (1:4 EtOAc/Hexanes): R_f = 0.19. **$[\alpha]_D$** = -22.8 (c = 3.1, CH_2Cl_2).



Methyl (*R*,*E*)-2-((*R*)-(3-cyanophenyl)((dimethoxyphosphoryl)oxy)methyl)-2-hydroxy-4-phenylbut-3-enoate (2.2r): The title compound was prepared according to the general procedure; the reaction was allowed to proceed for 24 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 6.44 (major diastereomer) and δ 6.59 (minor diastereomer). Some minor diastereomer and trace Pudovik-Brook adduct is present in isolated sample. White solid (26.8 mg), mp 116-119 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.69-7.66 (m, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 15.7 Hz, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 5.77 (d, *J* = 9.8Hz, 1H), 3.81 (s, 3H), 3.61 (d, *J* = 11.3 Hz, 3H), 3.52 (d, J = 11.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.9, 137.0 (d, *J* = 2.4 Hz) 135.7, 133.1, 132.7, 132.3, 131.6, 129.0, 128.8, 128.4, 126.9, 125.6, 118.4, 112.5, 80.9 (d, *J* = 5.3 Hz), 80.2 (d, *J* = 6.6 Hz), 54.7 (d, *J* = 6.0 Hz), 54.4 (d, *J* = 6.0 Hz), 53.7; **^{31}P NMR** (243 MHz, $CDCl_3$) δ 0.89. **IR** (thin film) ν 2956, 1741, 1255, 1035, 695 cm^{-1}. **HRMS**

(ESI): Calcd. For $C_{21}H_{22}NO_7P$ ([M+H$^+$]): 432.1207, found 432.1211. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 90:10, flow rate = 1.0 mL/min, λ = 210 nm, 22.2 min (minor isomer), 33.4 min (major isomer). **TLC** (1:1 EtOAc/Hexanes): R_f = 0.10. $\mathbf{[\alpha]_D}$ = -7.8 (c = 3.4 CH_2Cl_2).

REFERENCES

[1] Reviews: (a) Terra, B. S.; Macedo, F., Jr. *Arkivoc* **2012,** 134. (b) Chatterjee, A.; Joshi, N. N. *Tetrahedron* **2006,** *62*, 12137.

[2] Seminal papers on cross pinacol reactions with low-valent metal reagents: (a) McMurry, J. E.; Krepski, L. R. *J. Org. Chem.* **1976,** *41*, 3929. (b) McMurry, J. E. *Chem. Rev.* **1989,** *89*, 1513.

[3] Developments toward using aldehydes as coupling partners in stereoselective reductive coupling reactions: (a) Takahara, P. M.; Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *Tetrahedron Lett.* **1989,** *30*, 7177. (b) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989,** *111*, 8014. (c) Annunziata, R.;Cinquini, M.; Cozzi, F.; Giaroni, P. *Tetrahedron: Asymmetry* **1990,** *1*, 355. (d) Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P.; Benaglia, M. *Tetrahedron* **1991,** *47*, 5737. (e) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Giaroni, P.; *J. Org. Chem.* **1992,** *57*, 782. (f) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1990,** *55*, 4506. (g) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F.; *J. Am. Chem. Soc.* **1994,** *116*, 1316. (h) Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990,** *55*, 5924. (i) Askham, F. R.; Carroll, K. M. *J. Org. Chem.* **1993,** *58*, 7328. (j) Yoda, H.; Matsuda, K.; Nomura, H.; Takabe, K. *Tetrahedron Lett.* **2000,** *41*, 1775. (k) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988,** *29*, 5263. (l) Takai, K.; Morita, R.; Toratsu, C. *Angew. Chem. Int. Ed.* **2001,** *40*, 1116. (m) Takai, K.; Morita, R.; Matsushita, H.; Toratsu, C. *Chirality* **2003,** *15*, 17. (n) Boeckman, R. K., Jr.; Hudack, R. A., Jr. *J. Org. Chem.* **1998,** *63*, 3524. (o) Jung, M.; Groth, U. *Synlett* **2002,** 2015. (p) Groth, U.; Jung, M.; Vogel, T. *Chem. Eur. J.* **2005,** *11*, 3127 (q) Fischer, S.; Groth, U.; Jung, M.; Lindenmaier, M.; Vogel, T. *Tetrahedron Lett.* **2005,** *46*, 6679. (r) Miyoshi, N.; Fukuma, T.; Wada, M. *Chem. Lett.* **1995,** *24*, 999. (s) Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetrahedron Lett.* **2004,** *45*, 3869. (t) Nair, V.; Ros, S.; Jayan, C. N.; Rath, N. P. *Tetrahedron Lett.* **2002,** *43*, 8967. (u) Yang, Y.-S.; Shen, Z.-L.; Loh, T.-P. *Org. Lett.* **2009,** *11*, 2213. (v) Kise, N.; Shiozawa, Y.; Ueda, N. *Tetrahedron* **2007,** *63*, 5415. (w) Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004,** *126*, 13198. (x) Duan, X.-F.; Feng, J.-X.; Zi, G.-F.; Zhang, Z.-B. *Synthesis* **2009,** 277.

[4] Fittig, R. *Justus Liebigs Ann. Chem.* **1859,** *110*, 23.

[5] Recent developments in using ketones in pinacol reactions: (a) Matsukawa, S.; Hinakubo, Y. *Org. Lett.* **2003,** *5*, 1221. (b) Shi, L.; Fan, C.-A.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M. *Tetrahedron* **2004,** *60*, 2851. (c) Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005,** *7*, 1919.

[6] Phosphonate-phosphate rearrangements starting from α-hydroxy trialkyl phosphonoacetates: Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2012,** *51*, 4685.

[7] Asymmetric reductive coupling of isatins and aldehydes: Horwitz, M. A.; Tanaka, N.; Yokosaka, T.; Uraguchi, D.; Johnson, J. S.; Ooi, T. *Chem. Sci.* **2015,** *6*, 6086.

[8] Addition of phosphite to α-keto amides followed by phosphonate-phosphate rearrangement and intramolecular trapping: Kondoh, A.; Aoki, T.; Terada, M. *Org. Lett.* **2014,** *16*, 3528.

[9] Developments in phosphonate-phosphate rearrangement using acyl phosphonates as starting materials: (a) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal.* **2005,** *347*, 1207. (b) Demir, A. S.; Reis, Ö.; İğdir, A. Ç.; Esiringü, İ.; Eymur, S. *J. Org. Chem.* **2005,** *70*, 10584.

[10] Phosphite additions to aldehydes catalyzed by iminophosphoranes: Uraguchi, D.; Ito, T.; Ooi, T. *J. Am. Chem. Soc.*, **2009,** *131*, 3836.

[11] Phospha-Michael additions to enones and ynones with dialkylphosphite nucleophiles: (a) Li, G.; Wang, L.; Yao, Z.; Xu, F. *Tetrahedron: Asymmetry* **2014,** *25*, 989. (b) Lin, Y.-D.; Kao, J.-Q.; Chen, C.-T. *Org. Lett.* **2007,** *9*, 5195. (c) Zhang, A.; Cai, L.; Yao, Z.; Xu, F.; Shen, Q. *Heteroat. Chem.* **2013,** *24*, 345. (d) Yavari, I.; Hossaini, Z.; Alizadeh, A. *Monatsh. Chem.* **2006,** *137*, 1083. (e) Zhao, D.; Yuan, Y. Chan, A.; Wang, R. *Chem. Eur. J.* **2009,** *15*, 2738. (f) Wang, F.; Wang, S.; Zhu, X.; Zhou, S.; Miao, H.; Gu, X.; Wei, Y.; Yuan, Q. *Organometallics* **2013,** *32*, 3920. (g) Oehler, E.; Zbiral, E. *Liebigs Ann. Chem.* **1991,** *3*, 229. (h) Touil, S.; Zantour, H. *Phosphorus, Sulfur Silicon Relat. Elem*. **1997,** *131*, 183. (i) Galkin, V. I.; Khabibullina, A. B.; Bakhtiyarova, I. V.; Cherkasov, R. A.; Pudovik, A. N. *Zh. Obshch. Khim.* **1988,** *58*, 1002; (j) Galkin, V. I.; Galkina, I. V.; Khabibullina, A. B.; Kurdi, K. A.; Cherkasov, R. A.; Pudovik, A. N. *Dokl. Akad. Nauk SSSR Ser. Khim.* **1990,** *314*, 1408. (k) Vysotskii, V. I.; Prikhod'ko, Y. V.; Pavel', G. V.; Tilichenko, M. N. *Zh. Obshch. Khim.* **1983,** *53*, 2675. (l) Khidre, M. D.; Abou-Yousef, H. M.; Mahran, M. R. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000,** *160*, 181.

[12] Radosevich and Wang have demonstrated that similar enolates are α-nucleophilic instead of γ-nucleophilic, and are also capable of homodimerization: Wang, S. R.; Radosevich, A. T.; *Org. Lett.* **2013,** *15*, 1926.

[13] Nakamura and Hayashi have shown that related enolates are subject to enantioselective protonation: Hayashi, M.; Nakamura, S. *Angew. Chem. Int. Ed.* **2011,** *50*, 2249.

[14] Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013,** *135*, 16348.

[15] Alkylidene pyruvates also undergo the reaction, but the products are not stable to column chromatography.

[16] (a) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2000,** *65*, 4487. (b) Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2006,**

71, 6592. (c) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M.. *Chem. Eur. J.* **2007,** *13*, 9478. (d) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem. Eur. J.* **2008,** *14*, 3630. (e) Faita, G.; Mella, M.; Toscanini, M.; Desimoni, G. *Tetrahedron*. **2010,** *66*, 3024. (f) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011,** *133*, 2714. (g) Allais, C.; Lieby-Muller, F.; Rodriguez, J.; Constantieux, T. **2013,** *19*, 4131. (h) Matsumura, Y.; Suzuki, T.; Sakakura, A.; Ishihara, K. *Angew. Chem. Int. Ed.* **2014,** *53*, 6131. (i) Zhang, S.; Xu, K.; Guo, F.; Hu, Y.; Zha, Z.; Wang, Z. *Chem. Eur. J.* **2014,** *20*, 979.

CHAPTER THREE:
PHOSPHAZENE-CATALYZED DESYMMETRIZATION OF CYCLOHEXADIENONES BY INTRAMOLECULAR DITHIANE ADDITION [‡]

3.1 Introduction

The application of desymmetrization methodologies to the expedient synthesis of natural products has had a profound impact on the field. Of the scaffolds that have been studied in stereoselective organocatalytic desymmetrization reactions, the cyclohexadienone system is a noteworthy case and has received increased attention in recent years. The cyclohexene products that result from using desymmetrizing addition reactions on cyclohexadienones frequently map onto biologically active substructures. By applying the inherent efficiency of desymmetrization processes to this important structural unit, a large number of polyfunctionalized synthetic building blocks can be accessed in a small number of operations.

3.2 Background

3.2.1 Synthetic Value of Cyclohexadienone Desymmetrization Reactions

Desymmetrization has become a well-developed strategy for the construction of complex molecular frameworks.[1-6] Cyclohexadienones are multipurpose synthetic building blocks that have found a central role in desymmetrization methodologies. The functional groups present in these symmetrical molecules allow for a wide array of downstream transformations and they are all

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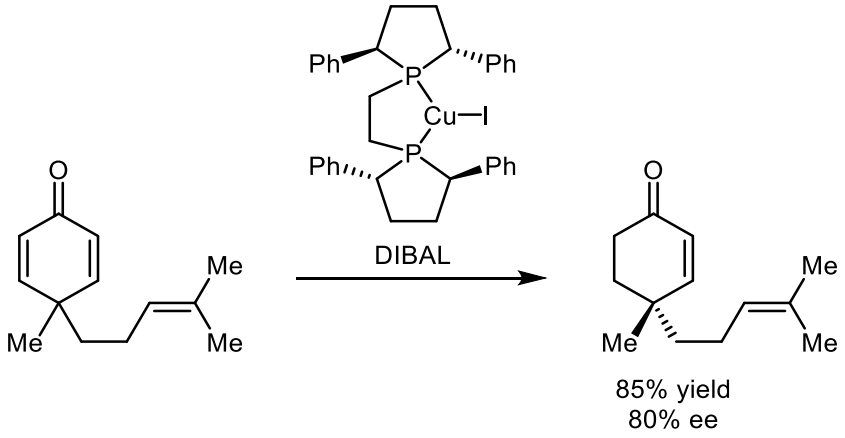
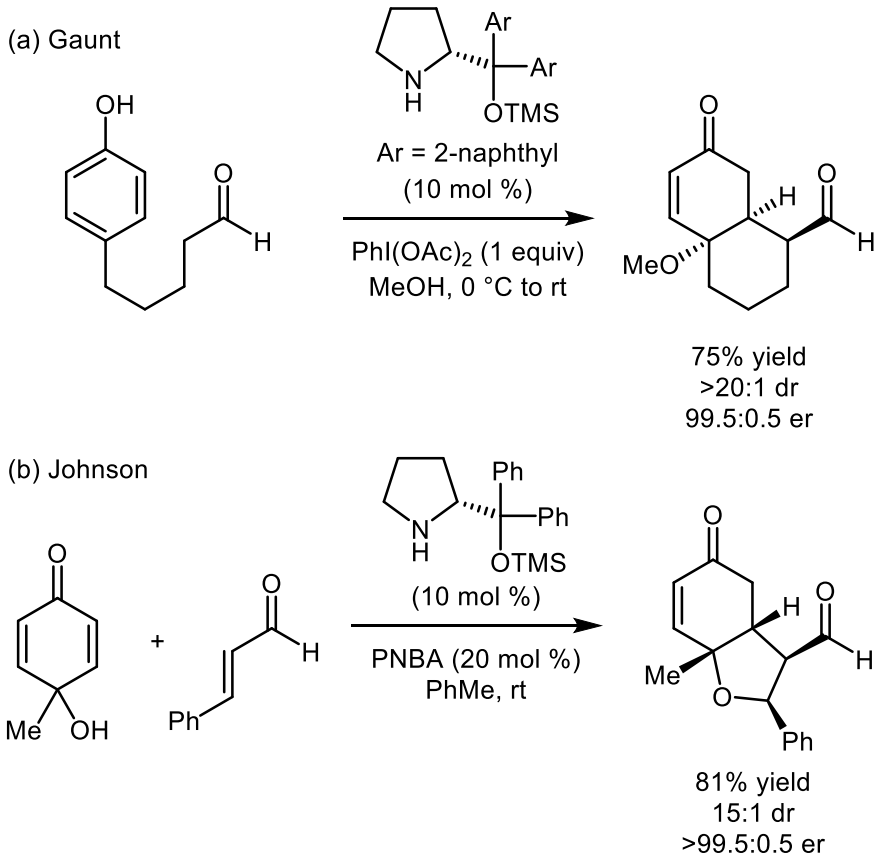
formed through a single reaction from cheap and readily available aromatic feedstocks.[7-11] These substrates have been successfully employed in a number of stereoselective desymmetrization reaction manifolds. Recent work by the Corey group has enabled the enantioselective conjugate reduction of prochiral cyclohexadienones using copper hydride generated *in situ* (Scheme 3-1).[12] Using this methodology, the authors were able to access enantioenriched cyclohexenones.

Scheme 3-1. Asymmetric Synthesis of Cyclohexenones by Enantioselective Desymmetrization



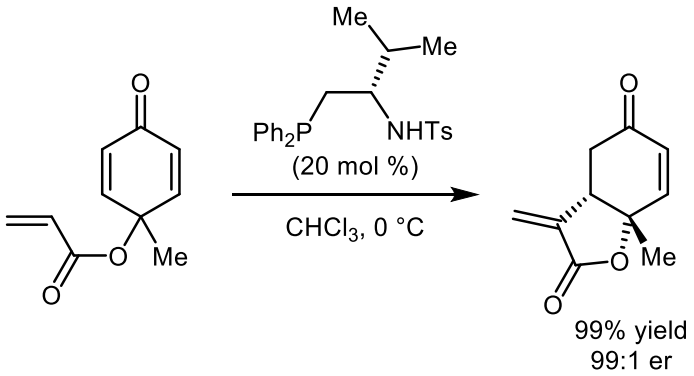
Outside the "simple" context of utilizing asymmetric desymmetrization of cyclohexadienones to access enantioenriched products with a single stereocenter, there have been numerous examples that provide multiple contiguous stereocenters. Michael additions *via* enamine intermediates have been studied by the Gaunt[13] (Scheme 3-2a) and Johnson groups[14] (Scheme 3-2b); in the former case, the cyclohexadienone is formed *in situ*. The intermolecularity of the latter case is particularly noteworthy due to the hindered nature of the *para*-quinol nucleophile; this fact speaks strongly to the electrophilicity of the iminium electrophile. Using these systems, it was possible to obtain bicyclic systems with three or four contiguous stereocenters.

Scheme 3-2. Desymmetrization of Cyclohexadienones *via* Enamine Addition



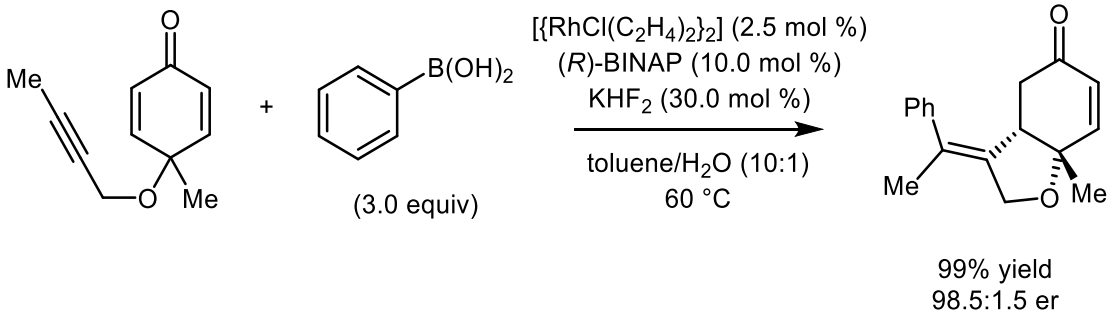
There are ample additional examples of desymmetrizing additions to achiral cyclohexadienones. The You group has disclosed methods for the intramolecular addition of amine[15] and bisphenylsulfonyl[16] nucleophiles using bifunctional cinchona alkaloid catalysts. The Sasai and Enders groups used a phosphinosulfonamide organocatalyst to enable a Rauhut-Currier reaction to form bicyclic enones (Scheme 3-3).[17] These examples provided good precedents for organocatalytic ring closure to form hindered bicyclic systems by desymmetrization.

Scheme 3-3. Desymmetrization of Cyclohexadienones by Rauhut-Currier Reaction

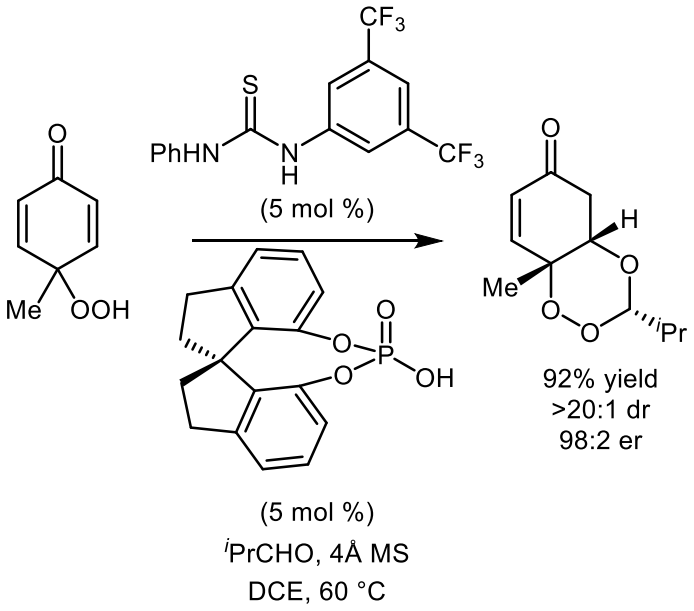


Further catalytic modes for cyclohexadienone desymmetrization have been well established, including transition-metal catalyzed cyclizations and Brønsted acid catalysis cascades. The Tian and Lin group used alkyne-tethered cyclohexadienones in an arylrhodation/conjugate addition sequence that enantioselectively delivered oxabicyclo[4.3.0]nonanes (Scheme 3-4).[18] In that work, the authors surveyed a large number of sophisticated chiral ligands and determined that the simple BINAP ligand conveniently offered the highest yields and enantioselectivities. The Lautens and Lan groups have also contributed to the further development of this reaction.[19,20] The Rovis group employed cyclohexadienone hydroperoxides in a chiral phosphoric acid-catalyzed [1,2]/[1,4]-addition cascade [21] (Scheme 3-5). The same group also developed an acyl anion addition promoted by *N*-heterocyclic carbenes (NHC) that furnishes bicyclic furanones *via* Stetter addition;[22] later, the You group developed an extension of this theme using the same catalytic manifold in a new bicyclic substrate class.[23]

Scheme 3-4. Desymmetrization of Cyclohexadienones by Arylrhodation/Conjugate Addition



Scheme 3-5. Desymmetrization of Cyclohexadienones by Acetalization/Oxy-Michael Cascade



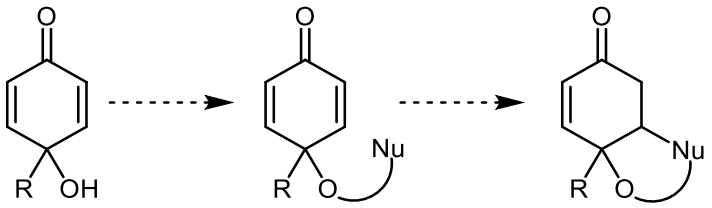
Inspired by these advances, we sought to develop an alternative and complementary method invoking the dithiane moiety as an established and easily accessible glyoxylate anion surrogate.[24-29] This would in principle provide access to highly functionalized products with orthogonally protected carbonyl groups in a novel glycolic acid scaffold.

3.2.2 Reaction Design for Desymmetrization by Intramolecular Dithiane Addition

We envisioned utilizing *para*-quinol derivatives featuring a tethered nucleophile as desymmetrization substrates, with the intention of implementing a Brønsted base organocatalyzed addition (Scheme 3-6). This reaction would lead to bicyclic systems with the salient attribute of

having a convex-concave facial differentiation, allowing subsequent diastereoselective transformations. With the aim of using a dithiane nucleophile, we selected 1,3-dithiane-2-carboxylic acid because of its relatively low pK_a (compared with non-carboxylate substituted analogs) and the possibility of using an ester linkage as a tether.

Scheme 3-6. Desymmetrization of Cyclohexadienone by Tethered Nucleophile



3.3 Results and Discussion

3.3.1 Synthesis of Dithiane-tethered Cyclohexadienones

We found that the heretofore unknown dicyclohexylcarbodiimide (DCC) mediated coupling between *para*-quinols and 1,3-dithiane-2-carboxylic acid proceeds in a straightforward manner in cases where R is unbranched (though it does work for R = Ph). Using this method, diversely functionalized dithiane-linked *para*-quinols were generated to study the intramolecular cyclization.

3.3.2 Discovery and Scope of Intramolecular Dithiane Addition

Based on a prior report[31] demonstrating the efficacy of phosphazene bases in deprotonating carboxylate dithianes, we selected the commercially available achiral superbase P2-^{t}Bu phosphazene to initiate the ring closure (Table 3-1).[33,34] We found that in the simplest case, with the methyl-substituted *para*-quinol ester (**3.1a**), the reaction was complete in 30 min at ambient temperature with 20 mol % catalyst.[35] Extending the length of the alkyl chain, the reaction proceeded similarly, even in the presence of a methyl ester or a TBS-protected primary alcohol (**3.1b-d**); a comparable result was observed with a phenyl substituent (**3.1e**). We considered that

if a nucleophilic group were appended to the *para*-quinol, it would be possible to construct a 5-6-5 fused ring system. Indeed, when R = CH_2CH_2NHBoc (**3.1f**), the desired tricyclic product **3.2f** was obtained. In all cases only a single diastereomer was observed. In a substrate where a β-methyl group is present on the cyclohexadienone (**3.1g**), the reaction proved to be completely regioselective, only allowing conjugate addition to the less substituted position.

Table 3-1. Scope of the Intramolecular Dithiane Conjugate Addition Reaction

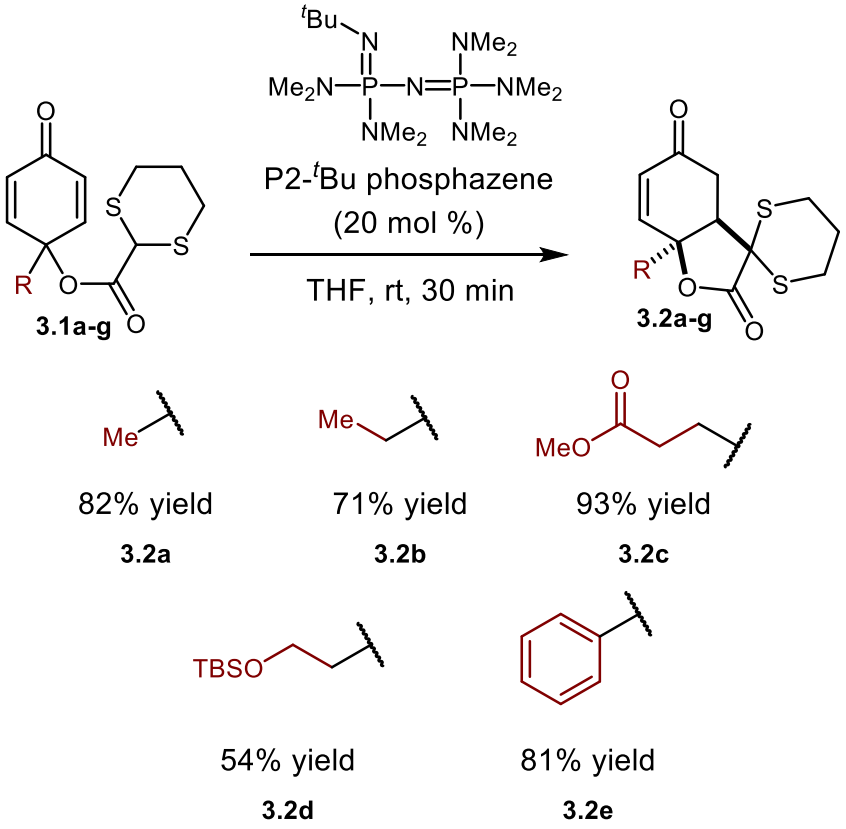
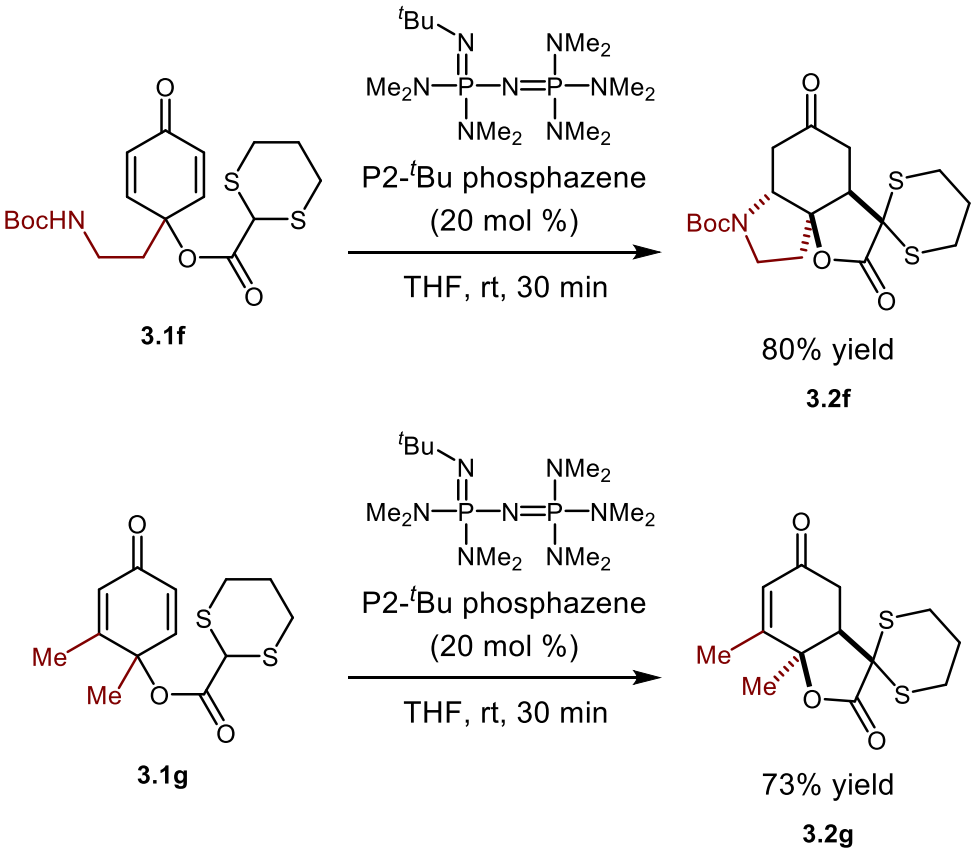


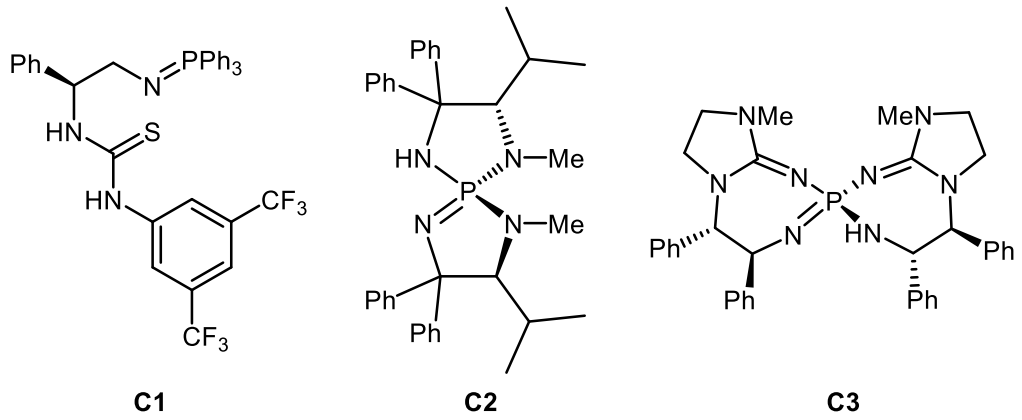
Table 3-1, cont.



3.3.3 Studies on the Asymmetric Intramolecular Dithiane Addition

We attempted to render the reaction enantioselective using chiral iminophosphoranes (Figure 1) structurally related to P2-^{t}Bu phosphazene, which are known to be substantially more basic than trialkylamines.[36] With **C1**[36-40] and **C2**[41-57],we observed no product formation, presumably due to insufficient basicity. Though **C3**[30-32] led to partial conversion of starting material, no appreciable enantioselectivity was observed.

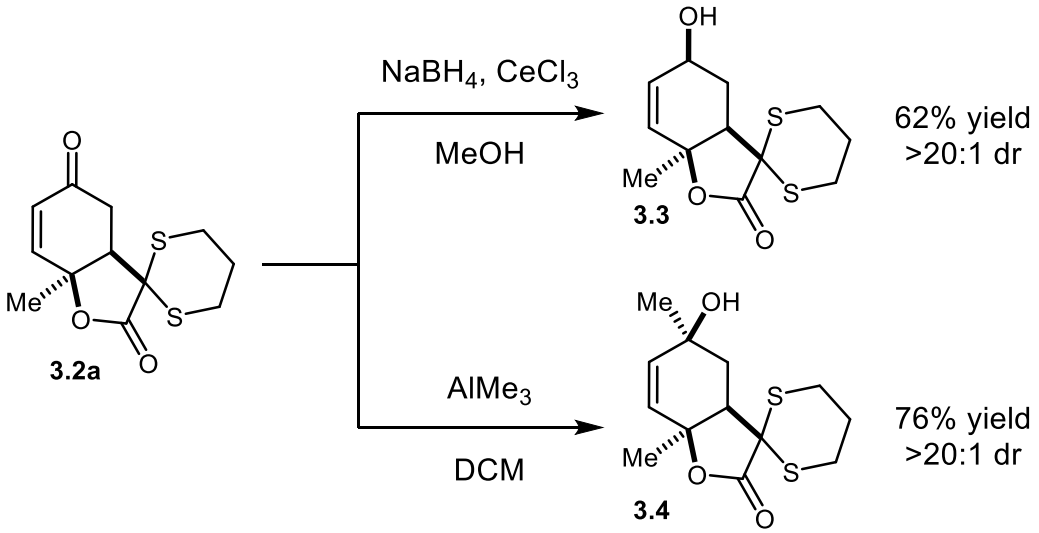
Figure 3-1. Chiral Iminophosphorane Catalysts Surveyed for Dithiane Addition



3.3.4 Studies on Convex-facial Additions to Cyclized Products

To investigate the feasibility of a convex-facial addition, we subjected **3.2a** to Luche reduction conditions (Scheme 3-7). We found this transformation to be completely diastereoselective, and an X-ray diffraction study[58] of the product confirmed our hypothesis regarding the facial selectivity, as the hydride was delivered to the convex face. An analogous reaction occurs when **3.2a** is treated with $AlMe_3$, affording the 1,2-addition product (Scheme 3-3).[59-63]

Scheme 3-7. Convex-facial Additions to Desymmetrized Bicycles



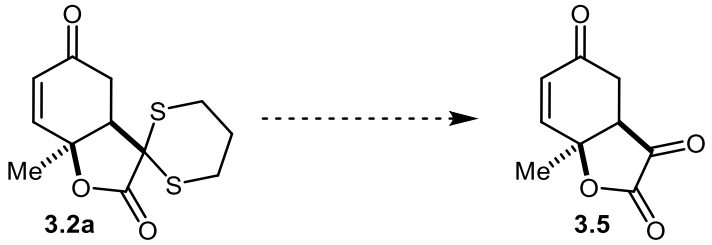
3.3.5 Studies on the Attempted Deprotection of Dithiane Conjugate Addition Adducts

We next sought to establish the glyoxylate anion equivalency of the dithiane substructure in our system. In order to reveal the masked carbonyl functionality, we rigorously applied reported dithiane deprotection conditions to **3.2a** (Table 3-2). Despite extensive investigations, none of our efforts were fruitful, resulting in either no conversion, side reactions,[64] or decomposition. We rationalize these disappointing results considering: 1) the crowded steric environment surrounding the dithiane moiety on the concave face of the bicycle, 2) the sensitive nature of this class of compounds, which stems from the highly reactive functional groups present, and 3) the strained character of the five-membered α-ketolactone (**3.5**) that would result from deprotection. In order to minimize the observed side reactions, we sought to apply the deprotection conditions to allylic alcohol **3.3**. However, both the use of NBS and $HgCl_2$/HgO were unsuccessful.

3.3.6 Attempted Independent Synthesis of Desired α-Ketolactone by Oxidative Deacylation

We attempted to synthesize **3.5** *via* an alternative route using Cu(II)-catalyzed aerobic oxidative deacylation[76] of the β-keto ester **3.6** (Scheme 3-8).[77] The fact that this reaction also leads to decomposition of the starting material is cause for general concern about the feasibility of easily reaching the target substructure.

Table 3-2. Carbonyl Deprotection Conditions

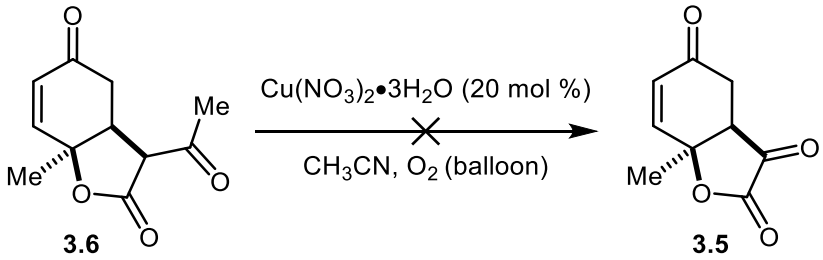


[a]

Entry	Conditions	Result
1[65]	NBS - MeCN/H_2O, 0 °C, 10 min[a]	Side reaction
2[66]	NBS, $AgNO_3$ - MeCN /H_2O, 0 °C, 5 min[b]	Side reaction
3[67]	$PhI(OAc)_2$ - MeCN /CH_2Cl_2/H_2O, 50 °C, 18 h	No reaction[c]
4[68]	$Hg(ClO_4)_2$ - MeOH/CH_2Cl_2, rt, 2 h	Side reaction
5[69]	$HgCl_2$,HgO - MeOH/H_2O, 55°C, 18 h[d]	No reaction
6[70]	MeI - MeCN /H_2O, reflux, 18 h	No reaction
7[71]	*m*-CPBA - MeCN, rt, 18 h, then 1M HCl, reflux, 4 h	Decomposition
8[72]	$SbCl_5$ - CH_2Cl_2, 0 °C, 1 h	Decomposition
9[73]	I_2, $NaHCO_3$ - acetone/H_2O, 50 °C, 18 h	No reaction
10[74]	CAN - acetone/H_2O, 50 °C , 18 h	No reaction
11[75]	Chloramine T - MeOH/H_2O, 70 °C, 18 h	No reaction

Different solvent systems, such as acetone/H_2O and DMSO were used, stoichiometry was varied and the reaction was run also at rt and for longer times (4 and 18 h) but in none of the cases was the desired product obtained. [b] The reaction was also run at rt for 18 h, but the desired product was not obtained. [c] Decomposition products were also observed. [d] The system MeCN/H_2O was also used and the reaction was also run at rt and reflux, but in none of the cases was the desired product obtained.

Scheme 3-8. Attempted Oxidative Deacylation

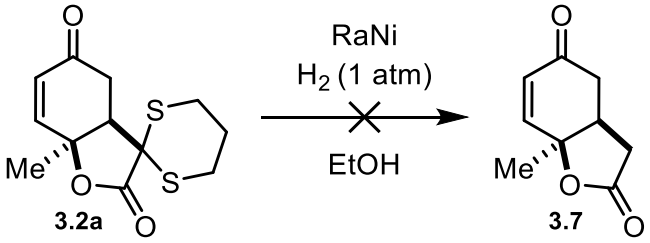


3.3.7 Attempted Desulfurization of Dithiane Conjugate Addition Adducts

We further investigated removal of the dithiane moiety *via* Raney nickel-promoted desulfurization (Scheme 3-9). To observe any substrate conversion, it was necessary to use a

hydrogen atmosphere. Under those conditions, though the dithiane function was removed, degradation occurred.

Scheme 3-9. Attempted Desulfurization with Raney Nickel



3.4 Conclusion

In this chapter, we have developed a desymmetrizing intramolecular conjugate addition of a tethered dithiane moiety to cresol-derived cyclohexadienones. The substrates are easily accessible from cheap starting materials and the reaction provides functionalized bicyclic lactones as a single diastereomer. The products of the reaction were able to undergo diastereoselective convex-facial additions. The carbonyl deprotection was unsuccessful and we hope that our efforts can serve as a cautionary tale for future synthetic planning involving related structures.

3.5 Experimental Details

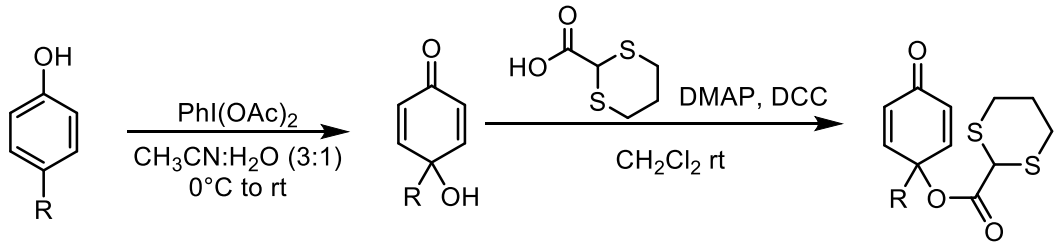
Methods: Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 101 MHz or 151 MHz, or a Bruker AVANCE III-OneBay500 (^{13}C NMR at 235 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br-s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were obtained with a Thermo Fisher Scientific Exactive or Finnigan^{TM} LTQ-ICR FT^{TM} (all

samples prepared in methanol). Melting points were obtained using a Thomas Hoover UniMelt Capillary Melting Point Apparatus. Analytical thin layer chromatography was carried out using Whatman 0.25 mm silica gel 60 plates, Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was allowed by UV light, phosphomolybdic acid in ethanol, or aqueous ceric ammonium nitrate solution. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40- 63μm) purchased from Silicycle. Yields refer to isolated yields after flash column chromatography. Since all results are the averages of two trials, the yields listed in the tables may not exactly match those listed below.

Materials: THF and DCM were purified by passing the solvent through a column of aluminum oxide under nitrogen. Dearomatization of phenol derivatives was carried out according to literature procedures.[7-11] 1,3-dithiane-2-carboxylic acid was prepared according to literature procedure.[31] Phosphazene base P_2-^{t}Bu solution (~2.0 M in THF) and DMAP were purchased from Sigma-Aldrich and used as received. (Diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene, and DCC were purchased from Oakwood Chemical and used as received.

General procedure for substrate synthesis:

The substrates were prepared through a two-step synthesis on gram scale.



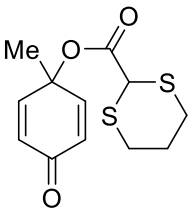
STEP 1 – Dearomatization of phenols[7-11]

The phenol (1 equiv) was dissolved in MeCN (3 mL for 1 mmol) and H_2O (1 mL for 1 mmol); the solution was cooled to 0 °C and $PhI(OAc)_2$ (1.1 equiv) was slowly added as a solid. The reaction mixture was allowed stirred at ambient temperature for 18 h. The mixture was diluted with EtOAc and washed with water and brine. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude materials thusly obtained were purified using flash column chromatography on silica gel.

STEP 2 – DCC coupling between *para*-quinols and 1,3-dithiane-2-carboxylic acid

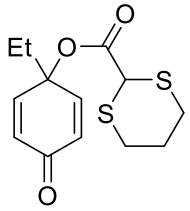
The desired *p*-quinols (1 equiv) and 1,3-dithiane-2-carboxylic acid (1.5 equiv) were dissolved in CH_2Cl_2 ($[quinol]_0 = 1.0$ M); 4-(dimethylamino)pyridine (DMAP) (1 equiv) was then added to the mixture. The reaction mixture was cooled to 0 °C and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (1.1 equiv) was added. The reaction mixture was allowed to warm to rt and stirred for 18 h. After that period, the mixture was filtered through a short plug of silica gel and washed with CH_2Cl_2.The solvent was removed under reduced pressure. The crude materials thusly obtained were purified using flash column chromatography on silica gel.

Characterization of substrates:

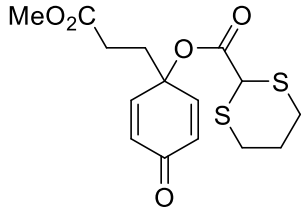


1-Methyl-4-oxocyclohexa-2,5-dien-1-yl 1,3-dithiane-2-carboxylate (3.1a): The title compound was obtained in 61% yield. White solid, mp 88-90 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.96 (d, J = 10.2 Hz, 2H), 6.31 (d, J = 10.2 Hz, 2H), 4.12 (s, 1H), 3.43-3.39 (m, 2H), 2.61-2.57 (m, 2H), 2.19-2.14 (m, 1H), 2.06-1.99 (m, 1H), 1.62 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 184.8, 168.3, 148.6, 128.5, 75.3, 39.0, 26.4, 25.5, 24.8; **IR** (thin film) ν 2931, 1735, 1667, 1631, 1608, 1393, 1285, 1138, 1052, 857 cm^{-1}; **HRMS** (ESI):

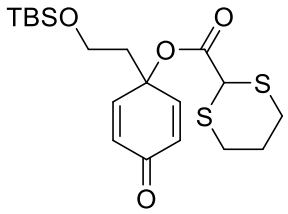
Calcd. For $C_{12}H_{14}NaO_3S_2^+$ ([M+Na$^+$]): 293.0277, found 293.0275; **TLC** (1:4 EtOAc/hexanes): R_f = 0.33.



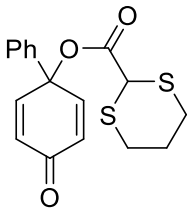
1-Ethyl-4-oxocyclohexa-2,5-dien-1-yl 1,3-dithiane-2-carboxylate (3.1b): The title compound was obtained in 49% yield. Yellow oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.88 (d, *J* = 10.2 Hz, 2H), 6.36 (d, *J* = 10.2 Hz, 2H), 4.14 (s, 1H), 3.40 (ddd, *J* = 14.3, 12.2, 2.5 Hz, 1H), 2.60-2.57 (m, 1H), 2.18-2.14 (m 1H), 2.06-1.99 (m, 1H), 1.94 (q, *J* = 7.5 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 185.1, 168.3, 147.6, 129.6, 78.4, 39.2, 32.2, 25.5, 24.8, 7.7; **IR** (thin film) ν 2935, 1736, 1667, 1631, 1282, 1138, 1063, 995, 915, 853 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{13}H_{16}NaO_3S_2^+$ ([M+Na$^+$]): 307.0433, found 307.0428; **TLC** (1:4 EtOAc/hexanes): R_f = 0.38.



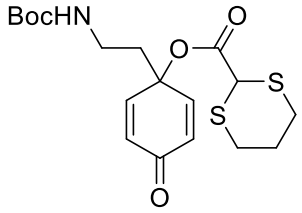
1-(3-methoxy-3-oxopropyl)-4-oxocyclohexa-2,5-dien-1-yl 1,3-dithiane-2-carboxylate (3.1c): The title compound was obtained in 49% yield. Light yellow solid, mp 79-80 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.85 (d, *J* = 10.2 Hz, 2H), 6.34 (d, *J* = 10.1 Hz, 2H), 4.10 (s, 1H), 3.66 (s, 3H), 3.39-3.34 (m, 2H), 2.58-2.54 (m, 2H), 2.36-2.33 (m, 2H), 2.26-2.23 (m, 2H), 2.16-2.12 (m, 1H), 2.04-1.97 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 184.6, 172.5, 168.0, 146.7, 129.9, 52.0, 39.0, 33.8, 28.1, 25.5, 24.8; **IR** (thin film) ν 2949, 2360, 1734, 1670, 1654, 1521, 1473, 1281, 1136, 990 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{15}H_{18}NaO_5S_2^+$ ([M+Na$^+$]): 365.0488, found 365.0478; **TLC** (1:4 EtOAc/hexanes): R_f = 0.25.



1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-oxocyclohexa-2,5-dien-1-yl 1,3-dithiane-2-carboxylate (3.1d): The title compound was obtained in 55% yield. Clear oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.98 (d, *J* = 10.2 Hz, 2H), 6.29 (d, *J* = 10.2 Hz, 2H), 4.11 (s, 1H), 3.75 (t, *J* = 9.0 Hz, 2H), 3.42-3.35 (m, 2H), 2.59-2.55 (m, 2H), 2.18-2.16 (m, 1H), 2.08 (t, *J* = 6.1 Hz, 2H), 2.04-1.95 (m, 1H), 0.87 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 185.1, 168.1, 147.9, 128.6, 57.7, 42.7, 39.2, 25.8, 25.5, 24.8, 18.1; **IR** (thin film) ν 2929, 2855, 1739, 1670, 1635, 1508, 1472, 1256, 1097, 838 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{19}H_{30}NaO_4S_2Si^+$ ([M+Na^+]): 437.1247, found 437.1233; **TLC** (1:4 EtOAc/hexanes): R_f = 0.32.

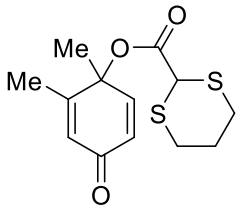


4-Oxo-[1,1'-biphenyl]-1(4H)-yl 1,3-dithiane-2-carboxylate (3.1e): The title compound was obtained in 18% yield. Orange solid, mp 113-114 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41-7.46 (m, 2H), 7.41-7.34 (m, 3H), 7.06 (d, *J* = 10.1 Hz, 2H), 6.38 (d, *J* = 10.1 Hz, 2H), 4.26 (s, 1H), 3.37 (td, *J* = 12.0, 6.1 Hz, 2H), 2.60-2.57 (m, 2H), 2.15-2.12 (m, 1H), 2.06-1.99 (m, 1H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 185.3, 167.7, 146.8, 136.2, 129.2, 129.0, 128.5, 125.2, 39.6, 25.6, 24.8; **IR** (thin film) ν 2920, 2360, 1739, 1669, 1277, 1126, 994, 849, 698 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{17}H_{16}NaO_3S_2^+$ ([M+Na^+]): 355.0433, found 355.0425; **TLC** (1:4 EtOAc/hexanes): R_f = 0.44.



1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-4-oxocyclohexa-2,5-dien-1-yl 1,3-dithiane-2-carboxylate (3.1f): The title compound was obtained in 17% yield. White solid, mp 107-109 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.91 (d, *J* = 10.1 Hz, 2H), 6.32 (d, *J* = 10.1 Hz, 2H), 4.68 (bs, 1H), 4.10 (s, 1H), 3.22-3.21 (m, 2H), 3.22-3.21 (m, 2H), 2.58-2.54 (m, 2H), 2.14-2.11 (m, 1H), 2.08-2.05 (m, 2H), 2.03-1.95 (m, 1H), 1.41 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 184.6, 168.0, 155.6, 147.0, 129.5, 79.7, 39.6,

39.3, 35.7, 33.9, 28.4, 25.6, 24.8; **IR** (thin film) ν 3354, 2975, 2929, 1738, 1668, 1517, 1366, 1274, 1169, 859 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{18}H_{25}NNaO_5S_2^+$ ([M+Na^+]): 422.1066, found 422.1054; **TLC** (1:4 EtOAc/hexanes): R_f = 0.24.

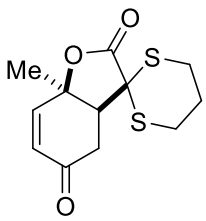


1,2-Dimethyl-4-oxocyclohexa-2,5-dien-1-yl 1,3-dithiane-2-carboxylate (3.1g): The title compound was obtained in 67% yield. White solid, mp 120-121 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.91 (d, *J* = 10.2 Hz, 1H), 6.29 (dd, *J* = 9.9, 2.4 Hz, 1H), 6.16 (s, 1H), 4.13 (s, 1H), 3.48-3.36 (m, 2H), 2.61-2.56 (m, 2H), 2.20-2.15 (m, 1H), 2.07-1.99 (m, 1H), 2.04 (d, *J* = 1.2 Hz, 3H), 1.57 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 185.3, 168.0, 158.8, 149.4, 128.1, 126.8, 38.4, 26.4, 25.3, 25.3, 24.8, 17.8; ; **IR** (thin film) ν 2933, 1734, 1668, 1613, 1433, 1391, 1293, 1134, 1056, 885 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{13}H_{16}NaO_3S_2^+$ ([M+Na^+]): 307.0433, found 307.0431; **TLC** (1:4 EtOAc/hexanes): R_f = 0.25.

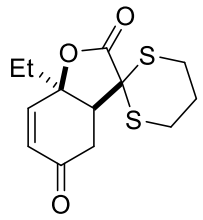
General procedure for intramolecular conjugate addition of dithiane:

A flame-dried 1 dram vial was charged sequentially with the dithiane-tethered cyclohexadienone (0.1 mmol, 1.0 equiv), followed by THF (1.0 mL), and then P2-^{t}Bu phosphazene (0.02 mmol, 20 mol %). The reaction was stirred at room temperature for 30 min. The reaction was quenched with saturated ammonium chloride, and the layers were separated. The aqueous layer was extracted three times with ethyl acetate, and then the combined organic phases were dried with sodium sulfate, and concentrated *in vacuo*. The crude materials thusly obtained were purified using flash column chromatography on silica gel using a hexane/EtOAc system (typically EtOAc/hexanes 1:9).

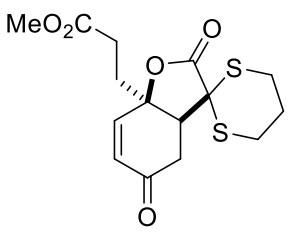
Characterization of products:



7a-Methyl-3a,7a-dihydro-2*H*-spiro[benzofuran-3,2'-[1,3]dithiane]-2,5(4*H*)-dione (3.2a): The title compound was prepared by the general procedure. White solid, mp 185-187 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 10.5 Hz, 1.8 Hz, 1H), 6.10 (d, *J* = 10.2 Hz, 1H), 3.99-3.94 (m, 1H), 3.42-3.37 (m, 1H), 2.99 (d, *J* = 18.6 Hz, 1H), 2.87 (d, *J* = 7.2 Hz, 1H), 2.69 (dd, *J* = 18.6 Hz, 7.8 Hz, 1H), 2.63-2.61 (m, 2H), 2.17-2.13 (m, 1H), 1.87-1.80 (m, 1H), 1.68 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.4, 171.9, 147.7, 130.0, 78.8, 52.5, 49.5, 33.4, 27.4, 26.6, 25.9, 23.6; ; **IR** (thin film) ν 2920, 1761, 1681, 1275, 1194, 1104, 1067, 972, 787, 734 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{12}H_{15}O_3S_2^+$ ([M+H$^+$]): 271.0457, found 271.0457: **TLC** (2:8 EtOAc/hexanes): R_f = 0.13.

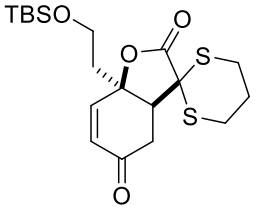


7a-Ethyl-3a,7a-dihydro-2*H*-spiro[benzofuran-3,2'-[1,3]dithiane]-2,5(4*H*)-dione (3.2b): The title compound was prepared by the general procedure. White solid, mp 109-110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 10.5 Hz, 1H), 6.18 (d, *J* = 10.6 Hz, 1H), 4.02-3.94 (m, 1H), 3.45-3.38 (m, 1H), 3.01 (d, *J* = 18.9 Hz, 1H), 2.89 (d, *J* = 8.0 Hz, 1H), 2.68-2.61 (m, 3H), 2.20-2.13 (m, 1H), 2.04-1.98 (m, 1H), 1.94-1.89 (m, 1H), 1.87-1.81 (m, 1H), 1.09 (t, *J* = 5.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.8, 172.0, 147.0, 130.8, 81.2, 50.1, 49.7, 33.8, 32.8, 27.3, 26.0, 23.7, 7.8 **IR** (thin film) ν 3425, 2970, 1757, 1681, 1388, 1223, 1187, 1116, 978, 9321 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{13}H_{16}NaO_3S_2^+$ ([M+Na$^+$]): 307.0433, found 307.0433; **TLC** (2:8 EtOAc/hexanes): R_f = 0.28.

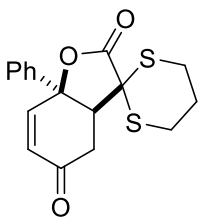


Methyl 3-(2,5-dioxo-4,5-dihydro-2*H*-spiro[benzofuran-3,2'-[1,3]dithian]-7a(3a*H*)-yl)propanoate (3.2c): The title compound was prepared by the general procedure. White solid, mp 114-115 °C; **^{1}H NMR**

(600 MHz, $CDCl_3$) δ 6.78 (dd, J = 10.5,1.6 Hz, 1H), 6.17 (d, *J* = 10.6 Hz, 1H), 3.98-3.93 (m, 1H), 3.72 (s, 3H), 3.42-3.37 (m, 1H), 3.00 (d, *J* = 18.9 Hz, 1H), 2.89 (d, *J* = 7.7 Hz, 1H), 2.69 (dd, *J* = 18.8, 7.8 Hz, 1H), 2.64-2.61 (m, 2H), 2.59-2.51 (m, 2H), 2.35-2.30 (m, 1H), 2.25-2.20 (m, 1H), 2.18-2.14 (m, 1H), 1.88-1.81 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.3, 172.5, 171.6, 146.0, 131.1, 79.8, 52.2, 50.5, 49.3, 34.4, 33.4, 28.0, 27.3, 26.0, 23.6; **IR** (thin film) ν 2923, 2852, 1760, 1735, 1685, 1435, 1166, 1079, 972, 932 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{15}H_{19}O_5S_2Si^+$ ([M+H^+]): 343.0668, found 343.0663; **TLC** (3:7 EtOAc/hexanes): R_f = 0.14.

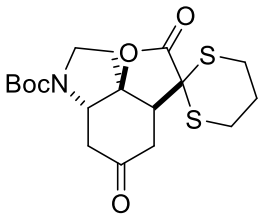


7a-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3a,7a-dihydro-2*H*-spiro[benzofuran-3,2'-[1,3]dithiane]-2,5(4*H*)-dione (3.2d): The title compound was prepared by the general procedure. White solid, mp 135-137 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.78 (d, *J* = 10.5 Hz, 1H), 6.15 (d, *J* = 10.5 Hz, 1H), 3.97 (td, *J* = 13.6, 2.4 Hz, 1H), 3.89-3.86 (m, 1H), 3.80-3.76 (m, 1H), 3.43-3.93 (m, 1H), 3.35 (d, *J* = 7.8 Hz, 1H), 2.96 (d, *J* = 18.8 Hz, 1H), 2.81 (dd, *J* = 18.8, 7.7 Hz, 1H), 2.63-2.60 (m, 1H), 2.18-2.14 (m, 1H),2.08-2.04 (m, 1H), 2.88-2.81 (m, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 194.3, 172.2, 147.4, 130.5, 80.7, 57.7, 50.0, 49.5, 41.6, 33.5, 27.3, 26.0, 25.8, 23.7, 18.1, -5.5, -5.5; **IR** (thin film) ν 23434, 2953, 1761, 1642, 1407, 1248, 1182, 1095, 778 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{19}H_{31}O_4S_2Si^+$ ([M+H^+]): 415.1428, found 415.1420; **TLC** (2:8 EtOAc/hexanes): R_f = 0.37.

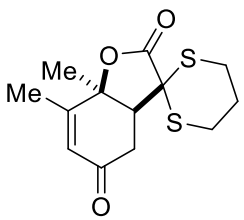


7a-Phenyl-3a,7a-dihydro-2*H*-spiro[benzofuran-3,2'-[1,3]dithiane]-2,5(4*H*)-dione (3.2e): The title compound was prepared by the general procedure. White solid, mp 171-172 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46-7.42 (m, 5H), 6.87 (d, *J* = 10.2 Hz, 1H), 6.40 (d, *J* = 10.2 Hz, 1H), 4.02 (t, *J* = 13.2 Hz, 1H), 3.50 (t, *J* = 14.4 Hz, 1H), 3.03 (d, *J* = 7.2 Hz, 1H), 2.99 (d, *J* = 18.6 Hz, 1H), 2.72-2.64 (m, 3H), 2.20

(m, 1H), 1.87 (q, *J* = 13.2 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.8, 172.0, 145.3, 138.8, 131.5, 129.3, 129.2, 124.6, 81.7, 54.6, 49.4, 33.0, 27.4, 26.0, 23.7; **IR** (thin film) ν 2971, 2361, 1769, 1684, 1540, 1507, 1224, 1170, 997, 799 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{17}H_{17}O_3S_2^+$ ([M+H$^+$]): 333.0614, found 333.0608; **TLC** (3:7 EtOAc/hexanes): R_f = 0.38.



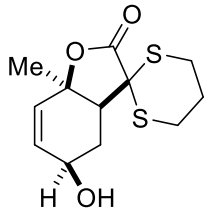
***Tert*-butyl 2,5-dioxohexahydro-2*H*-spiro[furo[2,3-d]indole-3,2'-[1,3]dithiane]-7(3a*H*)-carboxylate (3.2f):** The title compound was prepared by the general procedure. Two rotamers were observed in a 56:44 ratio in the ^{1}H NMR spectrum. White solid, mp 196-197 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.32-4.04 (m, 1H for the minor rotamer), 4.28-4.25 (m, 1H for the major rotamer) 3.77-3.58 (m, 4H), 3.19 (dd, *J* = 17.2, 5.8 Hz, 1H for the minor rotamer), 3.02 (dd, *J* = 17.1, 5.7 Hz, 1H for the major rotamer)., 2.80-2.75 (m, 1H), 2.75-2.73 (m, 4H), 2.63-2.59 (m, 1H), 2.32-2.26 (m, 1H), 2.24-2.19 (m, 1H), 2.10-1.99 (m, 1H), 1.96-1.89 (m, 1H), 1.48 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.0, 204.7, 171.2, 153.8, 153.5, 88.7, 88.0, 80.7, 60.6, 60.5, 49.3, 48.3, 48.2, 44.4, 44.0, 43.6, 42.9, 37.3, 37.2, 35.7, 34.8, 28.5, 28.4, 27.6, 27.5, 26.4, 26.3, 23.8; **IR** (thin film) ν 2974, 2927, 1764, 1721, 1691, 1399, 1249, 1174, 1136 975 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{18}H_{25}NNaO_5S_2$ ([M+Na$^+$]): 422.1067, found 422.1077; **TLC** (1:1 EtOAc/hexanes): R_f = 0.50.



7,7a-Dimethyl-3a,7a-dihydro-2*H*-spiro[benzofuran-3,2'-[1,3]dithiane]-2,5(4*H*)-dione (3.2g): The title compound was prepared by the general procedure. Impurity present in the δ 2.73-2.67 muliplet makes integral appear as 3H. Orange-brown solid, mp 169-179 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.96 (s, 1H), 3.96 (t, *J* = 13.8 Hz, 1H), 3.35 (t, *J* = 13.8 Hz, 1H), 2.98 (d, *J* = 19.2 Hz, 1H), 2.87 (d, *J* = 9.0 Hz, 1H), 2.73-2.67 (m, 1H), 2.63-2.60 (m, 2H), 2.17-2.14 (m, 1H), 2.09 (s, 3H), 1.83 (q, *J* = 13.2 Hz, 1H), 1.69 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.2, 171.9, 159.3, 128.5, 81.0,

53.2, 49.5, 33.1, 27.1, 26.1, 25.7, 23.7, 18.4; **IR** (thin film) ν 2920, 1266, 1760, 1671, 1425, 1228, 1190, 1098, 970, 935 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{13}H_{17}O_3S_2$ ([M+Na^+]): 285.0614, found 285.0611; **TLC** (2:8 EtOAc/hexanes): R_f = 0.13.

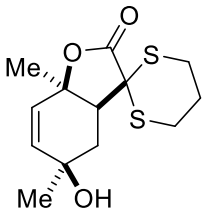
Procedure for the preparation of 5-hydroxy-7a-methyl-3a,4,5,7a-tetrahydro-2*H*-spiro[benzofuran-3,2'-[1,3]dithian]-2-one (3.3) via Luche reduction of enone 3.2a: $CeCl_3$•$7H_2O$ (1.2 equiv) and $NaBH_4$ (5.3 equiv) were added to a solution of the substrate (**3.2a**; 0.80 mmol) in MeOH (0.2 M) at -10 °C. The reaction mixture was stirred at the same temperature for 40 min. After this period, it was quenched with 1 M HCl and extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using EtOAc/hexanes 3:7 as the eluent.



White solid, mp 97-99 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.95 (d, *J* = 10.2 Hz, 1H), 5.79 (d, *J* = 10.2 Hz, 1H), 4.20-4.16 (br, 1H), 4.00 (t, *J* = 13.8 Hz, 1H), 3.62 (t, *J* = 18.3 Hz, 1H), 2.68-2.64 (m, 2H), 2.46-2.43 (d, *J* = 12.0, 5.4 Hz, 1H), 2.41-2.37 (m, 1H), 2.22-2.18 (m, 1H), 1.98-1.90 (m, 1H), 1.86 (d, *J* = 7.2 Hz, 1H), 1.77-1.70 (m, 1H), 1.67 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.6, 134.7, 129.6, 65.4, 49.9, 49.8, 49.8, 31.3, 29.0, 28.2, 26.5, 24.3; **IR** (thin film) ν 3035, 2926, 1752, 1423, 1276 1189, 1148, 1061, 956, 732 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{12}H_{17}O_3S_2$ ([M+Na^+]): 273.0614, found 273.0610; **TLC** (6:4 EtOAc/hexanes): R_f = 0.34.

Procedure for the preparation of 5-hydroxy-5,7a-dimethyl-3a,4,5,7a-tetrahydro-2*H*-spiro[benzofuran-3,2'-[1,3]dithian]-2-one (3.4) via 1,2-addition of $AlMe_3$: A solution of the substrate (**3.2a**; 0.09 mmol) in dry CH_2Cl_2 (1.0 mL) was added to a solution of $AlMe_3$ (2.0 M in toluene, 4 equiv) in dry CH_2Cl_2 (1.0 mL) at 0 °C. The reaction mixture was allowed to rt and kept

under stirring for 3 h. After this period, it was quenched with MeOH and extracted with CH_2Cl_2 and EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure.



Light yellow solid, mp 179-180 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 10.1, 1.4 Hz, 1H), 5.67 (d, *J* = 10.1 Hz, 1H), 4.06-4.01 (m, 1H), 3.62-3.57 (m, 1H), 2.71-2.65 (m, 3H), 2.50 (dd, *J* = 12.7, 5.6 Hz, 1H), 2.23-2.16 (m, 2H), 1.95-1.91 (m, 2H), 1.70 (s, 3H), 1.28 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.7, 137.9, 128.0, 79.1, 68.9, 50.0, 36.7, 29.3, 28.3, 26.5, 26.4, 24.4; **IR** (thin film) ν 3433, 2960, 2088, 1752, 1643, 1373, 1280, 1193, 1151, 1055 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{13}H_{18}NaO_3S_2$ ($[M+Na^+]$): 309.0590, found 309.0593; **TLC** (4:6 EtOAc/hexanes): R_f = 0.43.

REFERENCES

[1] Schreiber, S. L.; Poss, C. S. *Acc. Chem. Res.* **1994**, *27*, 9.

[2] Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167

[3] García-Urdiales, E.; Alfonso, I; Gotor, V. *Chem. Rev.* **2005**, *105*, 313.

[4] Wang, M.; Feng, M.; Tang, B.; Jiang, X. *Tetrahedron Lett.* **2014**, *55*, 7147.

[5] Borissov, A.; Davies, T.Q.; Ellis, S. R.; Fleming, T. A.; Richardson, M. S. W.; Dixon, D. J. *Chem. Soc. Rev.* **2016**, *45*, 5474.

[6] Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330.

[7] Felpin, F.-X. *Tetrahedron Lett.* **2007**, *48*, 409.

[8] McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1*, **1994**, *15*, 2047.

[9] Jepsen, T. J.; Jensen, A. A.; Lund, M. H.; Glibstrup, E.; Kristensen, J. L. *ACS Med. Chem. Lett.* **2014**, *5*, 766.

[10] Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175.

[11] Brown, P. D.; Willis, A. C.; Sherburn, M. S.; Lawrence, A. L. *Org. Lett.* **2012**, *14*, 4537.

[12] Han, Y.; Breitler, S.; Zheng, S.-L.; Corey, E. J. *Org. Lett.* **2016**, *18*, 6172.

[13] Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404.

[14] Corbett, M. T.; Johnson, J. S. *Chem. Sci.* **2013**, *4*, 2828.

[15] Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, 1519.

[16] Gu, Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 5192.

[17] Takizawa, S.; Nguyen, T. M.-N.; Grossman, A.; Enders, D.; Sasai, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 5423.

[18] He, Z.-T.; Tian, B.; Fukui, Y.; Tong, X.; Tian, P.; Lin, G.-Q. *Angew. Chem. Int. Ed.* **2013**, *52*, 5314.

[19] Keilitz, J.; Newman, S. G.; Lautens, M. *Org. Lett.* **2013**, *15*, 1148.

[20] Yu, Z.; Qi, X.; Li, Y.; Liu, S.; Lan, Y. *Org. Chem. Front.* **2016**, *3*, 209.

[21] Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554.

[22] Liu, Q.; Rovis, T. *Org. Process Res. Dev.* **2007**, *11*, 598.

[23] Jia, M.-Q.; Liu, C.; You, S.-L. *J. Org. Chem.* **2012**, *77*, 10996.

[24] Eliel, E.; Hartmann, A. *J. Org. Chem.* **1972**, *37*, 505.

[25] Takahashi, T.; Okano, T.; Harada, T.; Imamura, K.; Yamada, H. *Synlett* **1994**, *38*, 121.

[26] Takahashi, T.; Tsukamoto, H.; Kurosaki, M.; Yamada, H. *Synlett* **1997**, *41*, 1065.

[27] Enders, D.; Bonten, M. H.; Raabe, G. *Synlett* **2007**, *51*, 885.

[28] Enders, D.; Bonten, M. H.; Raabe, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2314.

[29] Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc*. **2008**, *130*, 14066.

[30] Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306.

[31] Kondoh, A.; Oishi, M.; Takeda, T.; Terada, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 15836.

[32] Takeda, T.; Kondoh, A.; Terada, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 4734.

[33] A significant increase in the dithiane carboxylate acidity is observed when the substrate is derivatized to an activated thioester: Massolo, E; Benaglia, M; Genoni, A.; Annunziata, R.; Celentano, G.; Gaggero, N.; *Org. Biomol. Chem*, **2015**, *13*, 5591.

[34] Massolo, E.; Brenna, D.; Cozzi, F.; Raimondi, L.; Gaggero, N.; Benaglia , M. *Synlett* **2016**, *27*, 2716.

[35] Under the same reaction conditions, we observed that triethylamine was unable to promote the transformation and tetramethylguanidine provided only trace amounts of desired product after 13 h.

[36] Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348.

[37] Goldys, A. M.; Dixon, D. J. *Macromolecules* **2014**, *47*, 1277.

[38] Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992.

[39] Robertson, G. P.; Farley, A. J. M.; Dixon, D. J. *Synlett* **2016**, *27*, 21.

[40] Horwitz, M. A.; Zavesky, B. P.; Martinez-Alvarado, J. I.; Johnson, J. S. *Org. Lett.* **2016**, *18*, 36.

[41] Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088.

[42] Uraguchi, D.; Ito, T.; Ooi, T. *J. Am. Chem. Soc.* **2009**, *131*, 3836.

[43] Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120.

[44] Uraguchi, D.; Ito, T.; Nakamura, S.; Sakaki, S.; Ooi, T. *Chem. Lett.* **2009**, *38*, 1052.

[45] Uraguchi, D.; Ito, T.; Nakamura, S.; Ooi, T. *Chem. Sci.* **2010**, *1*, 488.

[46] Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 7562.

[47] Uraguchi, D.; Ueki, Y.; Ooi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 3681.

[48] Uraguchi, D.; Ueki, Y.; Ooi, T. *Chem. Sci.* **2012**, *3*, 842.

[49] Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 4685.

[50] Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 19370.

[51] Uraguchi, D.; Ueki, Y.; Sugiyama, A.; Ooi, T. *Chem. Sci.* **2013**, *4*, 1308.

[52] Uraguchi, D.; Tsutsumi, R.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 8161.

[53] Uraguchi, D.; Tsutsumi, R.; Ooi, T. *Tetrahedron* **2014**, *70*, 1691.

[54] Tsutsumi, R.; Kim, S.; Uraguchi, D.; Ooi, T. *Synthesis* **2014**, *46*, 871.

[55] Uraguchi, D.; Nakamura, S.; Sasaki, H.; Konakade, Y.; Ooi, T. *Chem. Comm.* **2014**, *50*, 3491.

[56] Uraguchi, D.; Yamada, K.; Ooi, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 9954.

[57] Horwitz, M. A.; Tanaka, N.; Yokosaka, T.; Uraguchi, D.; Johnson, J. S.; Ooi, T. *Chem. Sci.* **2015**, *6*, 6086.

[58] CCDC1511800 contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge from the Cambridge Crystallographic Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[59] Carreño, M. C.; González, M. P.; Ribagorda, M. *J. Org. Chem.* **1996**, *61*, 6758.

[60] Carreño, M. C.; González, M. P.; Ribagorda, M. *J. Org. Chem.* **1998**, *63*, 3687.

[61] Carreño, M. C.; Ribagorda, M.; Somoza, Á.; Urbano, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 2755.

[62] Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, Á.; Urbano, A. *Org. Lett.* **2005**, *7*, 1419.

[63] Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, Á.; Urbano, A. *Chem Eur. J.* **2007**, *13*, 1064.

[64] When NBS was used, the unpurified ^{1}H NMR spectrum was suggestive of bromination at the ketone α-position, although the product was not isolable by column chromatography. With $Hg(ClO_4)_2$, an unidentified rearomatized product was observed.

[65] Corey, E. J.; Erickson, B. W. *J. Org. Chem.*, **1971**, *36*, 3553.

[66] Burks, E. A.; Johnson, W. H.; Whitman, C: P. *J. Am. Chem. Soc.* **1998**, *120*, 7665.

[67] Gao, A. X; Hamada, T.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 10301.

[68] Tsuboi, K.; Ichikawa, Y.; Jiang, Y.; Naganawa, A.; Isobe, M.; *Tetrahedron* **1997,** *53*, 5123.

[69] Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *Angew. Chem. Int. Ed*. **2004**, *43*, 2652.

[70] Fetizon, M.; Jurion M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.

[71] Smith, A. B.; Dorsey, B. D.; Visnick, M.; Maeda, T.; Malamas, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 3110.

[72] Kamata, M.; Otogawa, H.; Hasegawa, E. *Tetrahedron Lett.* **1991,** *32*, 7421.

[73] Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 599.

[74] La Claire, J. J.; Lansbury, P. T.; Zhi, B.; Hoogsteen, K. *J. Org. Chem.* **1995**, *60*, 4822.

[75] Emerson, D. W.; Wynberg, H. *Tetrahedron Lett.* **1971,** *12*, 3445.

[76] Steward, K. M.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 2426.

[77] Tello-Aburto, R.; Kalstabakken, K. A.; Volp, K. A.; Harned, A. M. *Org. Biomol. Chem.* **2011**, *9*, 7849.

CHAPTER FOUR:
DIASTEREOSELECTIVE ORGANOCATALYTIC ADDITION OF α-ANGELICA LACTONE TO β-HALO-α-KETOESTERS[§]

4.1 Introduction

The glycolic acid structural unit presents diverse possibilities as a synthetic intermediate and appears in many natural product frameworks. The proximity of functional groups in this moiety allows for a large number of potential chemical elaborations. Thus, methods for the direct construction of this motif have intrinsic value and are desirable from a complexity-building standpoint. One of the most straightforward approaches to forming a glycolic acid subunit is to carry out a nucleophilic addition into an α-ketoester. With the goal of increasing the number of contiguous stereocenters that can be set during this process, we selected a more complex nucleophile than has previously been used for this type of process. In this chapter, we develop a diastereoselective addition of α-angelica lactone into β-halo-α-ketoesters using commercial quinidine as the organocatalyst.

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4.2 Background

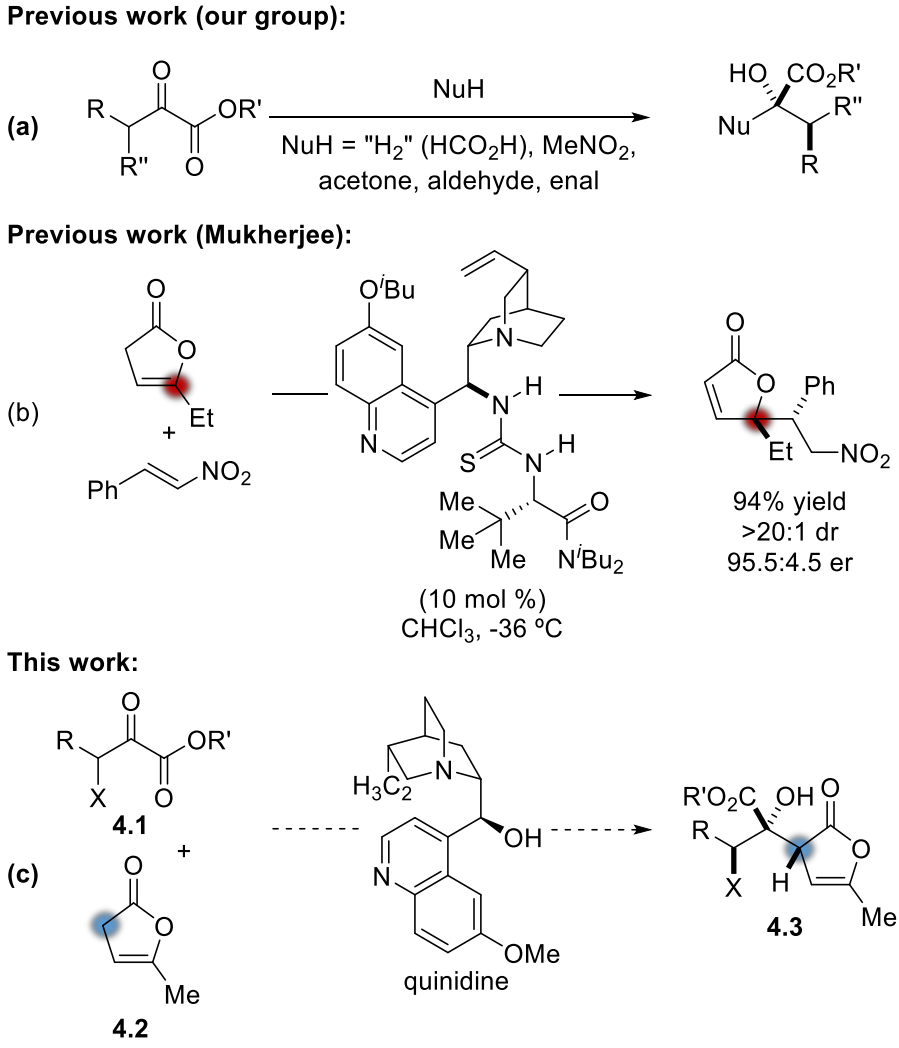
4.2.1 Construction of Glycolic Acid Scaffolds

The construction of contiguous stereogenic polyads is an ongoing challenge in organic synthesis. In this context, β-stereogenic α-ketoesters (**4.1**) are molecules of interest due to their appreciable electrophilicity and their available functional handles for downstream transformations.[1] Previously, our group has developed a number of methods for their synthesis,[2] as well as their application in complexity-building transformations encompassing a variety of reaction manifolds (i.e., transfer hydrogenation, Henry reaction, acetone aldol, benzoin addition, and homoenolate addition; Scheme 4-1a).[3b-3i] While these methods have provided access to a wide array of fully substituted glycolic acid scaffolds, there are few examples of the addition of prochiral nucleophiles.[3a,3f, 3g] The application of α-angelica lactone (**4.2**) as a nucleophile presents an interesting opportunity to build more stereochemically complex products.

4.2.2 Established Reactivity Pattern of α-Angelica Lactone

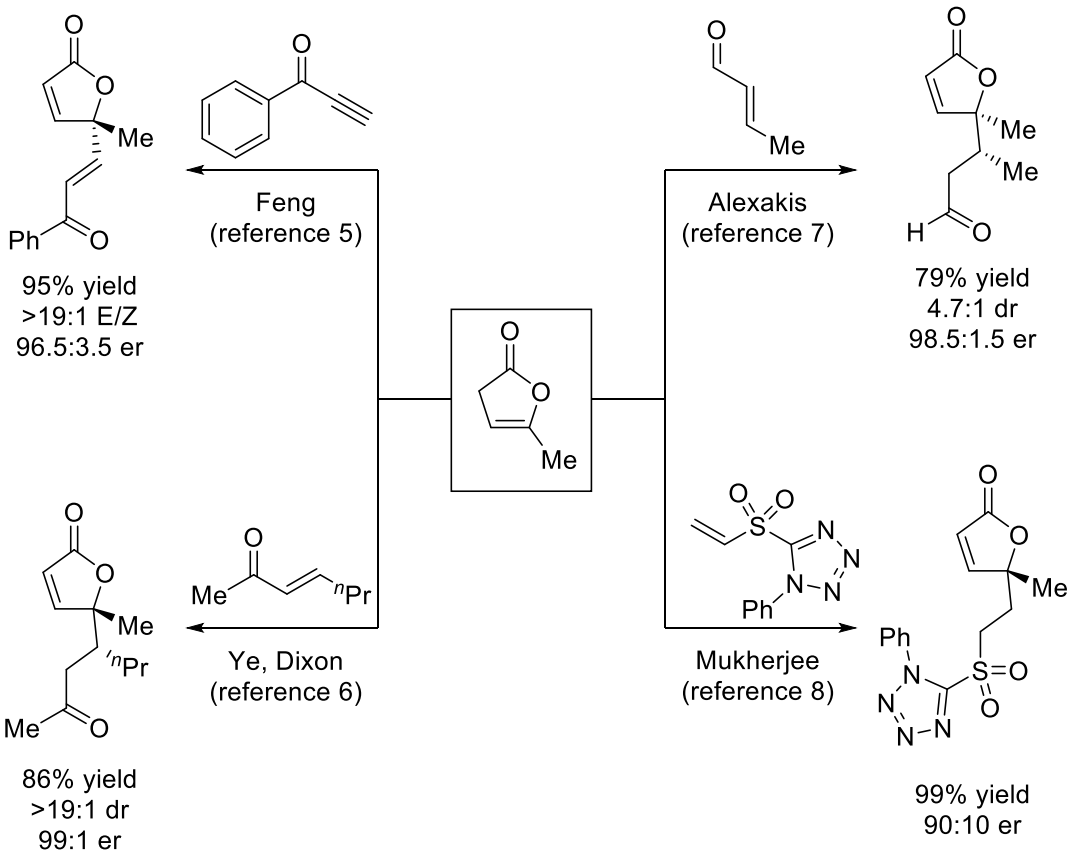
Unlike previously deployed pro-nucleophiles, α-angelica lactone (**4.2**) poses additional challenges with respect to (1) reactivity due to the imposition of increased steric bulk; (2) regioselectivity (α- vs γ-nucleophilicity of the dienolate); and (3) stereoselectivity (eight stereoisomers are possible in the α-addition mode). This class of nucleophile has been studied in the stereoselective addition to nitrostyrenes and other prochiral electrophiles using cinchona alkaloid-derived thiourea organocatalysts (Scheme 4-1b).[4a] Herein, we describe initial studies toward the creation of complex stereotriads in the form of a quinidine-catalyzed diastereoselective aldol addition of α-angelica lactone (**4.2**) to β-halo-α-ketoesters (**4.1**) (Scheme 4-1c).

Scheme 4-1. Proposed Addition of α-Angelica Lactone to Stereogenic α-Ketoester



Other additions to nitrostyrenes,[4] aldimines,[5] enones,[6] enals,[7] and vinyl sulfones[8] have also been studied (examples in Scheme 4-2). In all of these cases, the α-angelica lactone exhibited electrophilic trapping at the γ-carbon. A rare example from Boukouvalas achieved α-trapping with α-angelica lactones via *in situ* generation of tin or boron dienolates for addition into aldehydes.[9]

Scheme 4-2. Extant Aysmmetric Additions with α-Angelica Lactone



4.3 Results and Discussion

4.3.1 Reaction Optimization and Studies Toward Rendering the Reaction Asymmetric

Based on the high levels of Felkin-Ahn diastereoselectivity observed with β-halo-α-ketoesters (**4.1**) previously,[3b, 3d-3f] we selected this substrate class for our investigation. Initially, a screen of bases in THF (Table 4-1, entries 1-5) demonstrated that quinidine was the best base for the reaction. Then, by studying the reaction in different solvents (Table 4-1, entries 5-10), we found 2-MeTHF to be optimal. We observed that there was no improvement when the reaction time was extended to 24 h, either at -20 ºC (Table 4-1, entry 11) or room temperature (Table 4-1, entry 12). Although a low level of enantioselectivity (16% ee) was observed with **QN-1** (Table 4-2, entry 1),

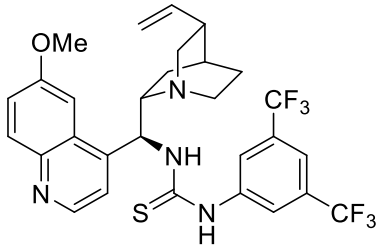
no enantioselectivity (0% ee) was observed with quinidine (Table 4-2, entry 6). In cases where the reactions worked, no minor diastereomers were observed.

Table 4-1. Reaction Optimization for α-Angelica Lactone Addition: Base and Solvent Screen[a]

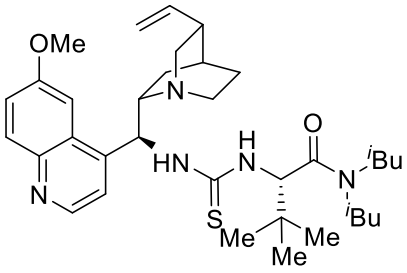
Entry	**Conditions**	**% Yield (^{1}H NMR)**	**dr**[b]
1	10 mol % KO^{t}Bu, THF, 6 h, rt	0	-
2	10 mol % DBU, THF, 6 h, rt	0	-
3	10 mol % TEA, THF, 6 h, rt	Trace product	-
4	10 mol % TMG, THF, 6 h, rt	Trace product	-
5	10 mol % quinidine, THF, 6 h, rt	61	>20:1
6	10 mol % quinidine, EtOAc, 6 h, rt	66	>20:1
7	10 mol % quinidine, DMSO, 6 h, rt	23	n.d.
8	10 mol % quinidine, TBME, 6 h, rt	45	>20:1
9	10 mol % quinidine, Et_2O, 6 h, rt	46	>20:1
10	*10 mol % quinidine, 2-MeTHF, 6 h, rt*	*91*	*>20:1*
11	10 mol % quinidine, 2-MeTHF, 24 h, -20 ºC	43	>20:1
12	10 mol % quinidine, 2-MeTHF, 24 h, rt	53	>20:1

[a] Optimized conditions are italicized. [b] In general, we started by looking in the crude NMR spectra to see if anything that could be a diastereomer could be identified. Some cases were more clear than others. The most definitive method that we found to identify diastereomers or γ-addition products was to flash the crude material and then flush the column with x+10% more polar solvent system (where x was the gradient that allowed the product to elute cleanly) in an EA/hexanes gradient for >10 fractions. We then concentrated all fractions on each side of the desired product (more polar and less polar) and if we found anything (^{1}H NMR analysis), we went back to the crude spectra and calculated the dr. It is possible that a minor diastereomer or γ-addition product for some cases might be not isolable due to instability, but this procedure was the best readout feasible with the available data.

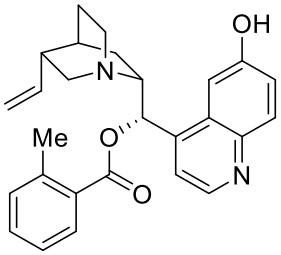
Table 4-2. Enantioselectivity Data for Chiral Catalysts



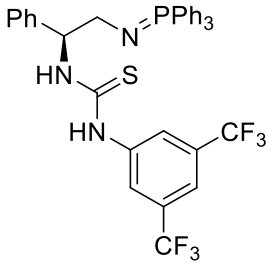
QN-1



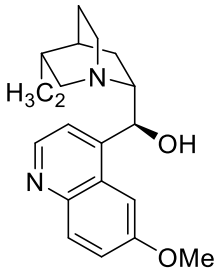
QN-2



QD-1



Ph-Dixon



quinidine

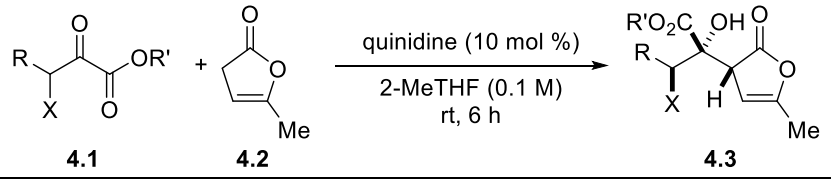
Entry	Conditions	er
1	10 mol % **QN-1**, THF, 21 h, rt	58.0:42.0
2	10 mol % **QN-2**, THF, 6 h, rt	53.5:46.5
3	10 mol % **QD-1**, 2-MeTHF, 6 h, rt	54.0:42.0
4	10 mol % **Ph-Dixon**, THF, 19 h, rt	52.5:47.5
5	10 mol % **Ph-Dixon**, THF, 16 h, -40 ºC	55.5:44.5
6	10 mol % quinidine, THF, 6 h, rt	50.5:49.5

After performing the above aldol reactions and studying varations of base (whether chiral or achiral) and solvent, our results indicated that quinidine was an optimal catalyst for the diastereoselective addition. Quinidine provides a racemic product and to date the maximum enantioselectivity observed for the title reaction with any catalyst is 58:42 er.

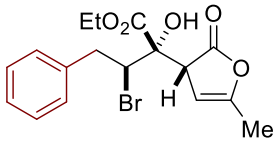
4.3.2 Scope of Reaction

Intriguingly, in all cases we studied, capture of the electrophile at the α-position of the lactone was the dominant mode of reactivity. We speculate that this divergence may arise from the more demanding steric environment imposed by the α-ketoester, as compared with those used in previous reports.[4-8] Additionally, for the most part, substitution at the β-position of the α-ketoesters does not affect the intrinsically high diastereoselectivity of the reaction. Using β-halo-β-benzyl α-ketoesters, catalyzed addition of α-angelica lactone provided the aldol products **4.3a-4.3c** in modest yields in >20:1 dr (Table 4-3). By comparing β-bromo-substituted **4.3a** with β-chloro-substituted **4.3b**, we found that the identity of the halogen has no impact on diastereoselectivity. Benzyl-substituted substrates **4.3d** and **4.3e** gave >20:1 dr; however, *para*-chlorophenyl-substituted **4.3d** gave an elevated 73% yield while *ortho*-fluoro-substituted **4.3c** gave 55% yield. Changing the *ortho*-tolyl group (**4.3e**) to a *meta*-tolyl group (**4.3f**) resulted in a dramatic loss of diastereoselectivity; the reason for this decrease in stereoselectivity is unclear. Aliphatic products **4.3g** and **4.3h** were formed diastereoselectively in 41% and 48% yield, respectively. While the branched product **4.3j** was formed in higher yield relative to other aliphatic substrates, a significantly lower diastereoselectivity was observed (4.0:1 dr). We found that the reaction to give **4.3i** was also diastereoselective, though low yielding (primarily due to product instability on column purification).

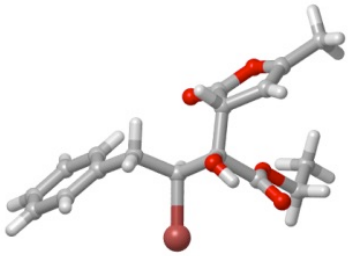
Table 4-3. Scope of the Diastereoselective Addition of α-Angelica Lactone to β-Halo-α-ketoesters



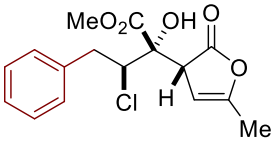
4.1 **4.2** **4.3**



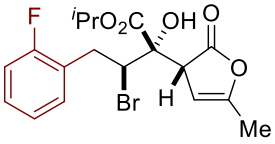
40% yield
>20:1 dr
4.3a



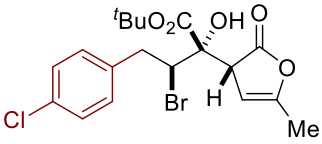
4.3a



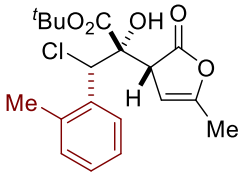
31% yield
>20:1 dr
4.3b[b]



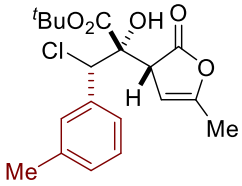
55% yield
>20:1 dr
4.3c[b]



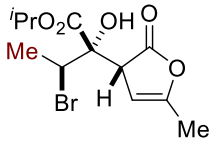
73% yield
>20:1 dr
4.3d



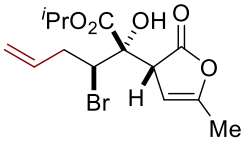
42% yield
>20:1 dr
4.3e



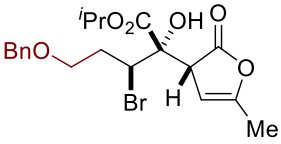
38% yield
1.2:1 dr
4.3f



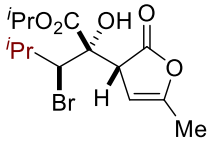
41% yield
>20:1 dr
4.3g



48% yield
>20:1 dr
4.3h



30% yield
>20:1 dr
4.3i



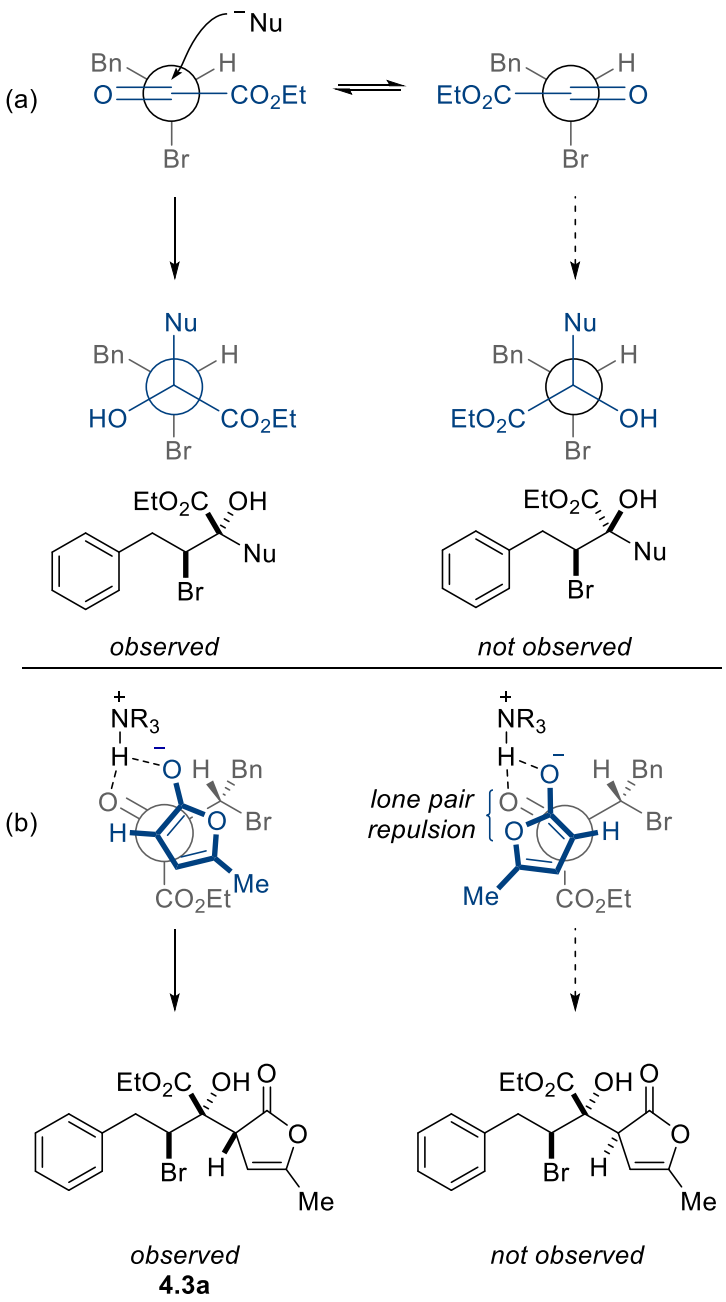
56% yield
4.0:1 dr
4.3j

[a] Reaction was conducted on 0.1 mmol scale, using 2.0 equiv of α-angelica lactone. [b] Yield was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

4.3.3 Determination of Relative Configuration and Stereochemical Model for Observed Relative Stereochemistry

The relative stereochemistry afforded by the reaction was determined by an X-ray diffraction study performed on the lactone product **4.3a** (Table 4-3).[10] In order to rationalize the observed stereochemical outcome of the reaction, the Felkin-Anh (or Cornforth) model[11] for the approach of the nucleophile to the β-halo-α-ketoester can be used, whereby the nucleophile approaches *anti* to the large β-halo substituent (Scheme 4-3a). In this model, the angelica lactone attacks at the Bürgi-Dunitz angle over the smallest β-substituent while the carbonyl is orthogonal to the β-halo group, thereby controlling the relationship between secondary halogen-bearing stereocenter and the tertiary alcohol. Governance of the lactone stereocenter could arise from the trajectory of the α-angelica lactone that minimizes repulsion between the lone pairs on the furanyl oxygen and the carbonyl oxygen (Scheme 4-3b). We propose that hydrogen-bonding with the catalyst facilitates this step, although stereochemical transmission from the chiral catalyst is poor at our current level of optimization.

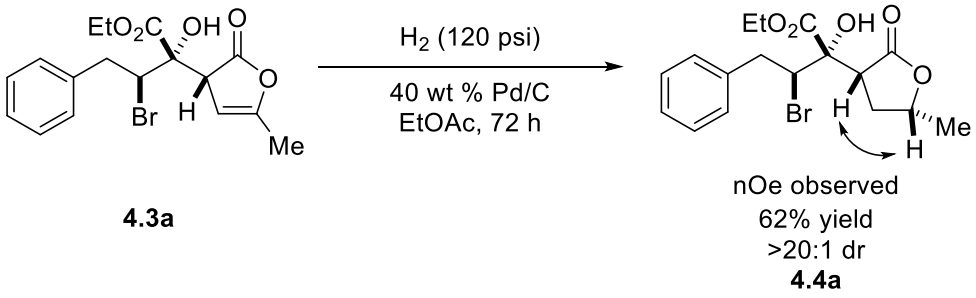
Scheme 4-3. Stereochemical Model for Addition of α-Angelica Lactone to β-Halo-α-ketoesters



4.3.4 Hydrogenation of Alkene in Aldol Adduct

Having developed conditions for the diastereoselective generation of **4.3**, we sought to extend our stereochemical arrays using downstream reduction of the dihydrofuranone. In the event, the resultant stereocenter was provided in >20:1 dr through catalytic hydrogenation (Scheme 4-4). A *syn* relationship between the lactone methine protons was determined through NOESY analysis, which is consistent with hydrogenation from the less hindered face of the lactone.

Scheme 4-4. Hydrogenation of α-Angelica Lactone Addition Product



4.3a

4.4a

4.4 Conclusion

Drawing inspiration from prior work on α-angelica lactones and α-ketoesters, this work presents new opportunities for accessing glycolic acid scaffolds. This reaction proceeded diastereoselectively for a variety of α-ketoester derivatives. This method represents a convenient way to diastereoselectively produce three contiguous stereocenters using a commercial organocatalyst. Additionally, this method represents a rare case where α-angelica lactone behaves as a regioselective α-nucleophile. Future directions for this work include investigations into the regioselectivty phenomenon and an expanded study of more complex α-angelica lactone nucleophiles.[12]

4.5 Experimental Details

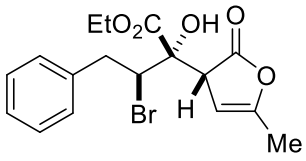
Methods: Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR) were recorded at the following frequencies: ^{1}H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 101 MHz or 151 MHz, ^{19}F NMR at 376 MHz and ^{31}P NMR at 162 MHz or 243 MHz with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br-s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a Finnigan linear trap quadrapol Fourier transform (LTQ-FT) spectrometer. TLC visualization was accomplished with UV light, phosphomolybdic acid in ethanol, or aqueous ceric ammonium nitrate solution. Yields refer to isolated yields after flash column chromatography; some samples contain residual minor diastereomers. Since all results are the averages of two trials, the stereoisomer ratios listed in the tables may not exactly match those represented in the NMR data below.

Materials: 2-MeTHF and α-angelica lactone were purchased and used as received. β-halo-α-ketoesters were prepared according to literature procedures.[3b-3e] Commercially available quinidine was used as received. Since dr and % yield values reported in the tables reflect an average of two trials, they may not exactly match the isolated yields reported below.

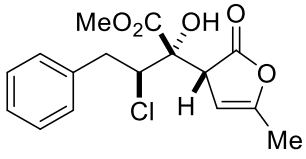
General procedure for addition of α-angelica lactone to β-halo-α-ketoester:

A 1 dram vial was charged sequentially with β-halo-α-ketoester (0.1 mmol, 1.0 equiv), followed by 2-MeTHF (1.0 mL), and finally the α-angelica lactone (0.2 mmol, 2.0 equiv). The reaction was stirred at room temperature for one min. Quinidine (0.01 mmol, 10 mol %) was added in one portion. The reaction was stirred at room temperature for 6 h, then concentrated *in vacuo*. The

crude materials thusly obtained were purified using flash column chromatography, with a gradient from 95:5 hexanes/EtOAc to 80:20 hexanes/EtOAc.

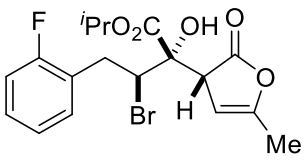


(±)-Ethyl 3-bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-4-phenylbutanoate (4.3a): The title compound was prepared according to the general procedure; 18.1 mg (47%) was isolated. No minor diastereomer was observed. Light yellow solid, mp 114-116 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H) 5.29 (s, 1H), 5.05 (dd, *J* = 11.4, 2.4 Hz, 1H), 4.35-4.30 (m, 1H), 4.26-4.21 (m, 1H), 3.98 (s, 1H), 3.91 (br, 1H), 3.61 (dd, *J* = 14.4, 2.4 Hz, 1H), 3.03 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.03 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.0, 171.2, 154.4, 137.9, 129.6, 128.4, 126.9, 100.7, 80.5, 63.4, 58.5, 50.3, 38.2, 14.1, 13.9; **IR** (thin film) ν 3433, 2359, 1794, 1747, 1647, 1541, 1456, 1237, 1122, 944, 777 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{17}H_{19}BrNaO_5^+$ ([M+Na^+]): 405.0308, found 405.0296; **TLC** (1:5 EtOAc/hexanes): R_f = 0.51.

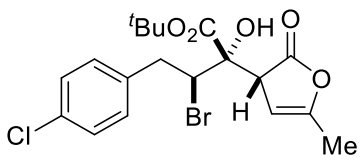


(±)-Methyl 3-chloro-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-4-phenylbutanoate (4.3b): The title compound was prepared according to the general procedure; some impurities remained after repeated silica gel column chromatography; NMR yields were calculating using 1,3,5-trimethoxybenzene as an internal standard and using the signal of the desired product at δ 5.27 in the crude ^{1}H NMR spectrum. The product was obtained in 49% ^{1}H NMR yield. No minor diastereomer was observed. White solid, mp 70-72 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 5.27 (s, 1H), 4.88 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.92 (s, 1H), 3.90 (t, *J* = 2.4 Hz, 1H), 3.83 (s, 3H), 3.50 (dd, *J* = 13.8, 2.4 Hz), 3.89 (dd, *J* = 13.8, 2.4 Hz), 2.04 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.1, 171.7, 154.7, 137.2,

129.7, 128.4, 127.0, 100.2, 80.9, 64.5, 53.6, 50.5, 37.7, 14.0; **IR** (thin film) ν 3461, 1752, 1636, 1455, 1254, 1140, 1084, 703, 641, 523 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{16}H_{17}ClNaO_5^+$ ([M+Na^+]): 347.0675, found 347.0648; **TLC** (1:5 EtOAc/hexanes): R_f = 0.10.

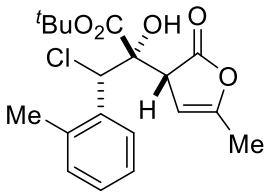


(±)-Isopropyl 3-bromo-4-(2-fluorophenyl)-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)butanoate (4.3c): The title compound was prepared according to the general procedure; some impurities remained after repeated silica gel column chromatography; NMR yields were calculating using 1,3,5-trimethoxybenzene as an internal standard and using the signal of the desired product at δ 5.29 in the crude ^{1}H NMR spectrum. The product was obtained in 57% ^{1}H NMR yield. No minor diastereomer was observed. White solid, mp 92-94 °C, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.8 Hz, 1H), 7.30-7.26 (m, 1H), 7.17-1.15 (m, 1H), 7.09-7.06 (m, 1H), 5.29 (s, 1H), 5.12-5.08 (m, 2H), 4.00 (s, 1H), 3.88 (s, 1H), 3.46 (d, *J* = 14.4 Hz, 1H), 3.34 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.02 (s, 3H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H)**; ^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.9, 170.6, 162.1, 154.3, 131.5 (d, *J* = 4.1 Hz), 128.7 (d, *J* = 8.0 Hz), 125.0 (d, *J* = 15.3 Hz), 124.1 (d, *J* = 3.8 Hz), 115.4 (d, *J* = 22.2 Hz), 100.7, 79.9, 72.1, 56.5, 50.3, 31.0 (d, *J* = 2.1 Hz), 21.4, 21.3,14.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.1; **IR** (thin film) ν 3853, 3750, 3649, 3437, 2349, 1653, 1558, 1507, 1457, 716, 578 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{18}H_{20}BrFNaO_5^+$ ([M+Na^+]): 437.0370, found 437.0356; **TLC** (1:5 EtOAc/hexanes): R_f = 0.57.

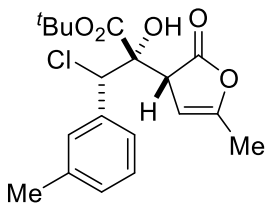


(±)-Isopropyl 3-bromo-4-(4-chlorophenyl)-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)butanoate (4.3d): The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography; 30.0 mg (70%) was isolated. No minor diastereomer was observed. Yellow solid, 117-120 °C, **^{1}H NMR** (600 MHz,

$CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 5.28 (s, 1H), 5.09 (m, 1H), 4.97 (s, 1H), 5.00 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.98 (s, 1H), 3.86 (t, *J* = 2.4 Hz, 1H), 3.55 (dd, *J* = 14.4, 1.8 Hz, 1H), 3.02 (dd, *J* = 14.4, 2.4 Hz, 1H), 2.03 (s, 3H), 1.27 (dd, 12.6, 6.6 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.1, 170.6, 154.4, 136.4, 132.8, 131.1, 128.5, 100.7, 80.0, 72.1, 58.2, 50.2, 37.6, 21.4 (d, *J* = 8.9 Hz), 14.1; **IR** (thin film) ν 3421, 2359, 1794, 1741, 1635, 1495, 1102, 944, 813, 536 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{18}H_{20}BrClNaO_5^+$ ([M+Na$^+$]): 453.0075, found 453.0068; **TLC** (1:5 EtOAc/hexanes): R_f = 0.30.

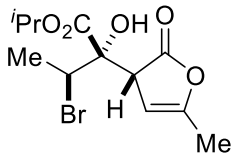


(±)-*Tert*-butyl 3-chloro-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-3-(*o*-tolyl)propanoate (4.3e): The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography; 15.8 mg (43%) was isolated. No minor diastereomer was observed. White solid, mp 143-144 °C, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 (br, 1H), 7.21-7.20 (m, 2H), 7.14 (m, 1H), 6.40 (s, 1H), 5.30 (s, 1H), 4.14 (s, 1H), 4.12 (t, *J* = 3.6 Hz, 1H), 2.49 (s, 3H), 2.02 (s, 3H), 1.16 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.4, 169.5, 153.8, 136.1, 135.5, 103.2, 129.0, 128.9, 126.7, 100.4, 85.7, 80.3, 55.7, 51.3, 27.2, 19.6, 14.1; **IR** (thin film) ν 3853, 3839, 3734, 3649, 3446, 2390, 1653, 1558, 1540, 1507, 578, 508 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{19}H_{23}ClNaO_5^+$ ([M+Na$^+$]): 389.1126, found 389.1114; **TLC** (1:5 EtOAc/hexanes): R_f = 0.57.

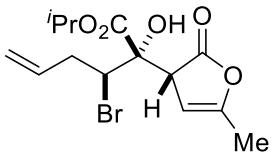


(±)-*Tert*-butyl 3-chloro-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-3-(*m*-tolyl)propanoate (4.3f): The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography; 16.0 mg (44%) was isolated. The diastereoselectivity was determined by comparing the signals at δ 5.86 (major) and δ 5.81 (minor).

Trace amounts of both diastereomers of the γ–addition product were also observed in the crude ^{1}H NMR spectrum, and were identified after separation by column chromatography. White solid, mp 133-135 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (d, J = 7.8 Hz, 1H), 7.29 (s, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.14 (d, J = J = 7.8 Hz, 1H), 5.87 (s, 1H), 5.28 (s, 1H), 4.16 (t, J = 2.4 Hz, 1H), 3.82 (s, 1H), 2.35 (s, 3H), 2.02 (s, 3H), 1.32 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.2, 169.4, 153.6, 137.7, 135.9, 129.9, 129.7, 128.1, 126.2, 100.5, 85.8, 80.2, 62.1, 50.9, 27.5, 21.4, 14.1; **IR** (thin film) ν 3853, 3837, 3801, 3734, 3627, 2360, 2341, 1683, 1539, 1244, 791, 668 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{19}H_{23}ClNaO_5^+$ ([M+Na$^+$]): 389.1126, found 389.1114; **TLC** (1:5 EtOAc/hexanes): R_f = 0.62.

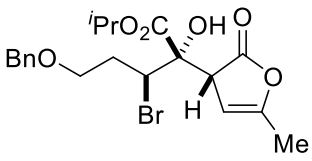


(±)-Isopropyl 3-bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)butanoate (4.3g): The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography; 14.0 mg (44%) was isolated. No minor diastereomer was observed. White solid, mp 84-85 °C, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.25 (s, 1H), 5.10 (m, 1H), 4.98 (q, 1H), 3.81 (s, 1H), 3.64 (t, 1H), 2.00 (s, 3H), 1.87 (d, J = 6.6 Hz, 1H), 1.28 (dd, J = 33.6, 6.0 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.9, 170.9, 154.1, 100.7, 79.9, 71.8, 50.7, 50.1, 21.5, 21.3,19.7, 14.0; **IR** (thin film) ν 3446, 2393, 1740, 1653, 1287, 1102, 782, 579, 519, 503 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{12}H_{17}BrNaO_5^+$ ([M+Na$^+$]): 343.0152, found 343.0146; **TLC** (1:5 EtOAc/hexanes): R_f = 0.39.

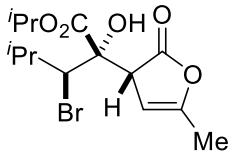


(±)-Isopropyl 3-bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)hex-5-enoate (4.3h): The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography; 18.0 mg (54%) was isolated. No minor diastereomer was observed. Clear oil, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.60-5.93 (m, 1H), 5.27-5.21

(m, 3H), 5.10 (quintet, J = 6.0 Hz, 1H), 4.83 (dd, J = 10.8, 3.0 Hz, 1H), 3.89 (s, 1H), 3.79 (br, 1H), 2.95-2.91 (m, 1H), 2.69-2.64 (m, 1H), 2.00 (s, 3H), 1.31 (d, J = 6.6 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.9, 170.6, 154.2, 134.6, 118.3, 100.6, 79.9, 72.0, 56.3, 50.2, 36.5, 21.5, 21.3, 14.1; **IR** (thin film) ν 3448, 1797, 1739, 1646, 1249, 1182, 1102, 945, 607, 505 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{14}H_{19}BrNaO_5^+$ ([M+Na$^+$]): 369.0308, found 369.0297; **TLC** (1:5 EtOAc/hexanes): R_f = 0.35.

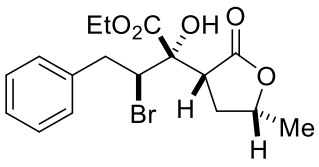


(±)-Isopropyl 5-(benzyloxy)-3-bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)pentanoate (4.3i): The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography; 13.3 mg (30%) was isolated. No minor diastereomer was observed. Clear oil, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 5.25 (s, 1H), 5.14-5.09 (m, 1H), 4.98 (dd, J = 11.1, 2.4 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 11.1 Hz, 1H), 4.00 (s, 1H), 3.80-3.79 (m, 2H), 2.48-2.43 (m, 1H), 2.19-2.13 (m, 1H), 2.00 (s, 3H), 1.39-1.35 (m, 1H), 1.32 (d, J = 6.0 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.8, 170.7, 154.2, 138.3, 128.4, 127.7, 127.6, 100.6, 80.0, 72.9, 71.9, 68.0, 54.1, 50.4, 32.0, 21.5, 21.4, 14.1; **IR** (thin film) ν 3464, 2389, 1738, 1640, 1102, 788, 699, 607, 526^{-1}; **HRMS** (ESI): Calcd. For $C_{20}H_{25}BrNaO_6^+$ ([M+Na$^+$]): 463.0727, found 463.0708; **TLC** (1:5 EtOAc/hexanes): R_f = 0.27.



(±)-Isopropyl 3-bromo-2-hydroxy-4-methyl-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)pentanoate (4.3j): The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography; 20.0 mg (57%) was isolated. The diastereoselectivity was determined by comparing the signals at δ 4.82 (major) and δ 5.04 (minor). White solid, mp 150-

152 °C, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.25 (s, 1H), 5.08 (m, 1H), 4.82 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 1H), 3.81 (t, *J* = 2.4 Hz, 1H), 2.37 (m, 1H), 2.0 (s, 3H), 1.28 (dd, *J* = 37.2, 6.0 Hz, 6H), 1.15 (dd, *J* = 26.4, 6.6 Hz, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.9, 171.2,154.0, 100.9, 80.9, 71.9, 65.3, 50.7, 29.8, 23.2, 21.4, 21.3, 18.0, 14.0; **IR** (thin film) ν 3459, 2968, 1796, 1736, 1647, 1388, 1271, 1104, 942, 780 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{14}H_{21}BrNaO_5^+$ ([M+Na$^+$]): 371.0465, found 371.0453; **TLC** (1:5 EtOAc/hexanes): R_f = 0.52.



(±)-Ethyl 3-bromo-2-hydroxy-2-(5-methyl-2-oxotetrahydrofuran-3-yl)-4-phenylbutanoate (4.4a): A 1 dram vial was charged with 10% Pd/C (40 w/w %) and flushed with nitrogen. A solution of ethyl 3-bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-4-phenylbutanoate (**3a**) (0.1 mmol, 1.0 equiv) dissolved in EtOAc (1 mL) was added. The solution was sparged with H_2 for 5 min. The reaction was then allowed to stir for 72 h in a high-pressure reactor under 120 psi H_2. The reaction mixture then was filtered through a Celite® plug, rinsing with ethyl acetate, and concentrated *in vacuo.* The crude materials thusly obtained were purified using flash column chromatography, with a gradient from 95:5 hexanes/EtOAc to 80:20 hexanes/EtOAc to yield 25.0mg (64%) desired product in >20:1 dr. Clear oil, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.59-4.55 (m, 1H), 4.46-4.42 (m, 3H), 4.04 (br, 1H), 3.77 (dd, *J* = 12.0, 9.0 Hz, 1H), 3.55 (d, *J* = 14.4 Hz, 1H), 2.70 (dd, *J* = 14.1, 12.0 Hz, 1H), 2.63-2.58 (m, 1H), 1.88-1.83 (m, 1H), 1.46 (d, *J* = 6.0 Hz, 3H), 1.41 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.5, 171.9, 138.0, 129.3, 128.4, 127.0, 78.4, 75.0, 63.4, 58.0, 48.1, 38.6, 32.2, 20.9, 14.2; **IR** (thin film) ν 3776, 3453, 2391, 2349, 1767, 1642, 1260, 749, 543 cm^{-1}; **HRMS** (ESI): Calcd. For $C_{17}H_{21}BrNaO_5^+$ ([M+Na$^+$]): 407.0465, found 407.0454; **TLC** (1:5 EtOAc/hexanes): R_f = 0.24.

REFERENCES

[1] (a) Eftekhari-Sis, B.; Zirak, M. *Chem. Rev.* **2015,** *115*, 151.

[2] (a) Steward, K. M.; Johnson, J. S. *Org. Lett.* **2010,** *12*, 2864. (b) Steward, K. M.; Johnson, J. S. *Org. Lett.* **2011,** *13*, 2426.

[3] (a) Calter, M. A.; Phillips, R. M.; Flaschenriem, C. *J. Am. Chem. Soc.* **2005,** *127*, 14566. (b) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012,** *134*, 7329. (c) Steward, K. M.; Corbett, M. T.; Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2012,** *134*, 20197. (d) Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2013,** 15, 2446. (e) Corbett, M. T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2014,** *53*, 255. (f) Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2014,** *136*, 14698. (g) Goodman, C. G.; Walker, M. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2015**, *137*, 122. (h) Horwitz, M. A.; Tanaka, N.; Yokosaka, T.; Uraguchi, D.; Johnson, J. S.; Ooi, T. *Chem. Sci.* **2015,** *6*, 6086 (i) Horwitz, M. A.; Zavesky, B. P.; Martinez-Alvarado, J. I.; Johnson, J. A. *Org. Lett.* **2016,** *18*, 36.

[4] Examples of α-angelica lactone acting as a γ-nucleophile while adding to nitrostyrenes: (a) Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012,** *48*, 5193. (b) Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2016,** *18*, 646.

[5] Examples of α-angelica lactone acting as a γ-nucleophile while adding to aldimines: Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011,** *13*, 3056.

[6] Examples of α-angelica lactone acting as a γ-nucleophile while adding to enones: Li, X.; Lu, M.; Dong, Y.; Wu, W.; Qian, Q.; Ye, J.; Dixon, D. J. *Nat. Commun.* **2014,** DOI: 10.1038/ncomms5479.

[7] Examples of α-angelica lactone acting as a γ-nucleophile while adding to enals: Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011,** *13*, 1540.

[8] Examples of α-angelica lactone acting as a γ-nucleophile while adding to vinyl sulfones: Simlandy, A. K.; Mukherjee, S. *Org. Biomol. Chem.* **2016,** *14*, 5659.

[9] Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.* **1988,** 1595.

[10] CCDC1511793 contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999,** *99*, 1191. (b) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003,** *42*, 1761. (c) Cee, V. J.; Cramer, C. J.; Evans, D. A. J. Am. Chem. Soc. **2006,** *128*, 2920.

[12] Synthesis of more complex α-angelica lactone nucleophiles: Wu, Y.; Singh, R. P.; Deng, L. *J. Am. Chem. Soc.* **2011,** *133*, 12458.

CHAPTER FIVE:
PROGRESS TOWARD THE TOTAL SYNTHESIS OF THE *VERATRUM* ALALOIDS JERVINE, CYCLOPAMINE, AND VERATRAMINE

5.1 Introduction

The utility of studying natural product synthesis can be viewed from several distinct vantage points. The most common reason for this challenging pursuit is to access druglike molecules in the smallest number of steps possible. While this is a noble and worthy reason in and of itself, the counterargument is that a large number of total syntheses that are published result in milligram or sub-milligram quanities of material and contain steps that would be unattractive on larger scale, or simply contain too many steps to result in a translational breakthrough. Taking these practical considerations to heart, recent efforts in natural product synthesis groups have sought to oppose the lengthy, "finish at all costs" style total synthesis and have placed emphasis on efficiency and ideality; an optimist may look to this trend and see the possibility for rejuvenation and advancement for this field.

From another standpoint, natural product synthesis represents one of the most robust ways to train chemists to solve hard problems. In this vein, we can see there is great didactic value provided by challenges that often are much harder and less predictable than even a research adviser could intentionally devise. While methodology projects focus on optimization of a reaction by changing any variables of our choosing (making structural or electronic modifications to our substrates, changing the catalyst or ligand, studying the effect solvent and temperature and time),

we generally do not have that luxury in natural product synthesis. The structural and stereochemical constraints imposed by synthetic targets from nature are uncompromising. These challenges make the total synthesis of natural products an invaluable tool for chemists to test the limits of methodologies and synthetic tactics in practice.

In this chapter, we describe progress toward the total synthesis of three alkaloids from the *Veratrum* genus: jervine, cyclopamine, and veratramine. These targets possess desirable biological activities and have numerous structural features that have necessitated creative synthetic strategies. The work presented in this chapter will serve as a blueprint for the completion of the final targets using the dearomatization-desymmetrization approach that we will propose in this chapter.

5.2 Background

5.2.1 Biological Activity of the *Veratrum* Alkaloids

The abundance of natural products with unique and desirable biological properties provides chemists with a diverse array of challenges and inspiration for the development of new synthetic strategies and tactics. Jervine (**5.6**), cyclopamine (**5.21**), and veratramine (**5.11**) are representative members of the *Veratrum* steroidal alkaloids,[1] which are most conspicuously known as antagonists of Smoothened (Smo), a Hedgehog (Hh) signaling protein; dysregulation of this cell signaling pathway is often implicated in rhabdomyosarcoma, medulloblastoma, basal cell carcinoma, and pancreatic, breast, and prostate cancers.[2] Hedgehog signaling inhibition allows improved delivery of chemotherapeutics for pancreatic cancer in a mouse model.[3] A semisynthetic analogue of cyclopamine called IPI-926 (saridegib) is a drug candidate that has been evaluated in clinical trials.[4] By utilizing a late-stage functionalization of cyclopamine, a kilogram-scale approach to the synthesis of saridegib has been developed.[4d] In addition to these exciting developments, it has been shown that introducing structural modifications to the parent structure of cyclopamine can allow

increased stability as well as improved Hh signal inhibition.[5] With these possibilities in mind, a *de novo* synthesis is attractive as it might allow modifications in different regions of the parent structure and potentially provide a more diverse array of analogues. Others[6,7] have taken this approach, although *de novo* routes have not yet been completed to date and reliance on the chiral pool has left room for exploration of other tactics.

5.2.2 Overview of Extant Synthetic Work on *Veratrum* Alkaloids

Early synthetic efforts to access this family of compounds were successful in providing a conceptual framework to obtain these molecules, though the routes began from steroidal starting materials and suffered from high step counts; a synopsis of these efforts is outlined below.[8] Subsequent studies expanded on that work and led to completed syntheses of verarine, veratramine, jervine, and veratrobasine.[9] More recent work established a novel skeletal rearrangement for the transformation of 12β-hydroxy steroids (containing a 6-6-6-5 ABCD ring system) into C-*nor*-D-homo-steroids (containing a 6-6-5-6 ABCD ring system), allowing a new path to the Veratrum alkaloids.[10] After construction of the steroidal portion, installation of a spirocyclic lactone facilitated elaboration to the fused tetrahydrofuran and piperidine rings.

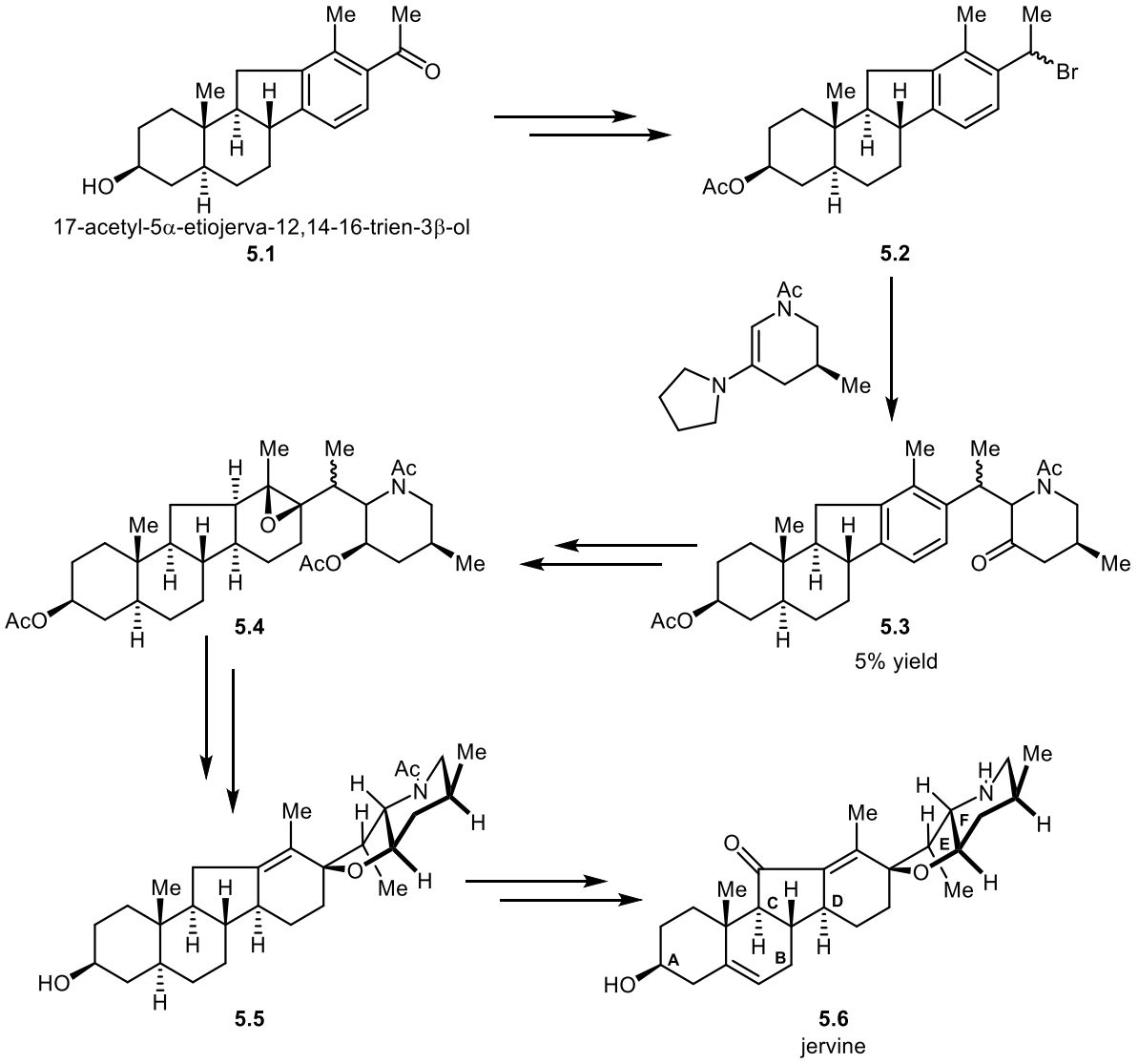
A model study directed toward a *de novo* synthesis of the DEF ring system achieved a high level of efficiency,[11] but several key issues remained: the methyl group of the piperidine was not incorporated, the tetrahydrofuran contained a methyl group in the wrong oxidation state (and with incorrect relative stereochemistry), and the synthesis was racemic. Recently, our group has developed a research focus on developing efficient synthetic routes toward steroidal alkaloids using local desymmetrization (diastereotopic group selection).[12] In this chapter, we present a *de novo* route that attempts to address challenges associated with the spirocylic tetrahydrofuran

subunit of the Veratrum alkaloids using a merged oxidative dearomatization-local desymmetrization approach.

5.2.3 Masamune Synthesis of Jervine

In 1967, Masamune and coworkers reported a synthesis of jervine (Scheme 5-1).[8a] Their approach began with 17-acetyl-5α-etiojerva-12,14-16-trien-3β-ol (**5.1**), which was accessible by synthetic means from Hagemann's ester[13] or *via* degradation of hecogenin[14]. The early steps of the synthesis converted the methyl ketone into a mixture of diastereomeric benzylic bromides **5.2**, which were alkylated with a pyrrolidine enamine nucleophile. Unfortunately, this key fragment coupling reaction only afforded a 5% yield of the steroidal alkaloid product **5.3**. A Birch reduction and epoxidation furnished intermediate **5.4**, which was further elaborated to the hexacyclic alkaloid **5.5** through an epoxide-opening/dehydration sequence. Late-stage oxidation in the C ring and installation of the unsaturation in the B ring led to completion of the synthesis of jervine.

Scheme 5-1. Overview of Masamune Synthesis of Jervine



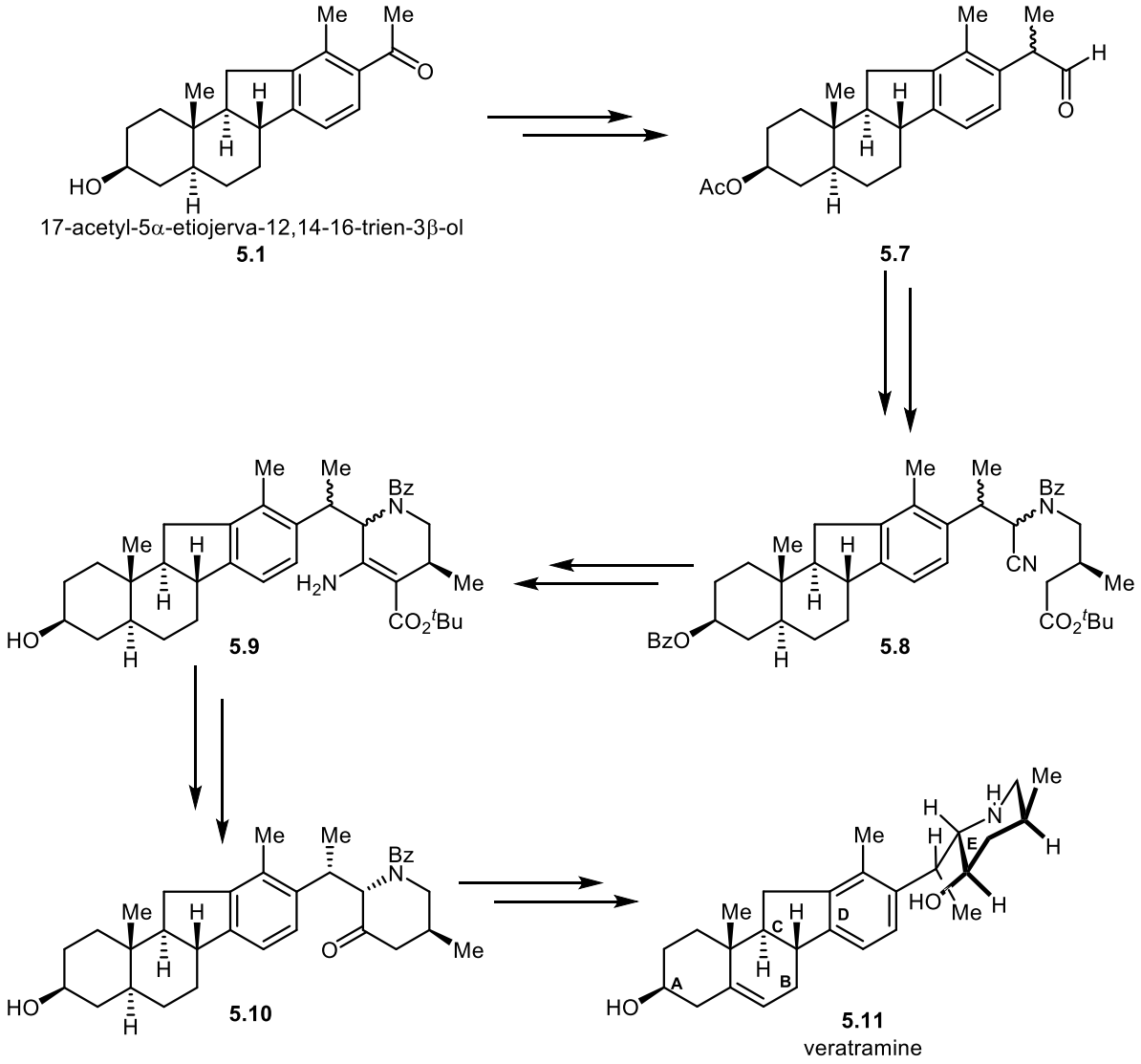
The Masamune synthesis was a foundational effort which, while not practical in many respects, represents a fundamental analytical mindset that has persevered for several decades. In this route, we see a convergent approach to coupling a "steroid" and an "alkaloid" while expending much time and energy constructing the unique features present the tetrahydrofuran core of this complex target.

5.2.4 Johnson Synthesis of Veratramine

In the same year that Manamune and coworkers disclosed their synthesis of jervine (**5.6**), W. S. Johnson disclosed a synthesis of veratramine (**5.11**) which began from the same intermediate.[8b] They began by homologating the methyl ketone present in **5.1** into an aldehyde by performing a Corey-Chaykovsky epoxidation, followed by Lewis acid-mediated epoxide opening. The aldehyde **5.7** was obtained as an epimeric mixture, which was carried through a Strecker reaction to obtain **5.8** as a mixture of stereoisomers. Cyclization under basic conditions provided enamine **5.9**, which was hydrolyzed under acid conditions to ketone **5.10**. Subsequent reduction of the ketone, installation of the alkene in the A ring, and global deprotection yielded veratramine (**5.11**).

By its nature, this synthesis has many similarities to the Masamune approach to jervine. In both routes, we see a strong focus on taking an established steroidal building block and utilizing it to construct the alkaloid portion of the molecule. The amount of work these routes represent reinforces the idea that these targets are particularly difficult to attack from the standpoint of convergency. Moreover, they underscore the importance of designing reactions that exhibit high levels of stereocontrol in order to preserve valuable late-stage material.

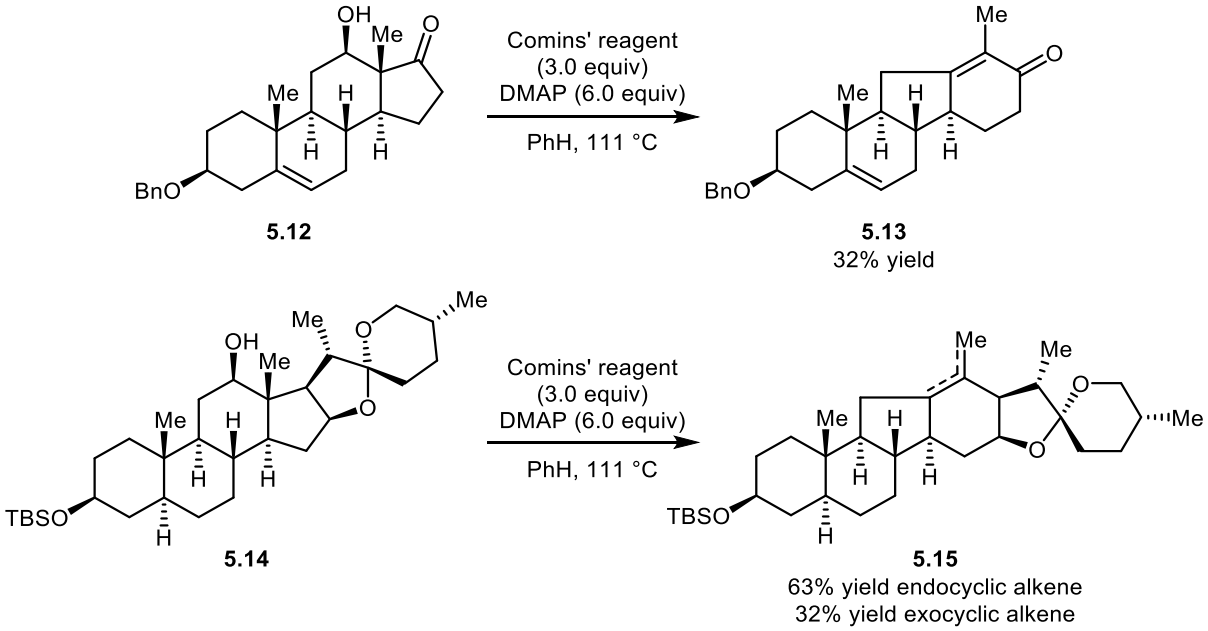
Scheme 5-2. Overview of Johnson Synthesis of Veratramine



5.2.5 Giannis Synthesis of Cyclopamine

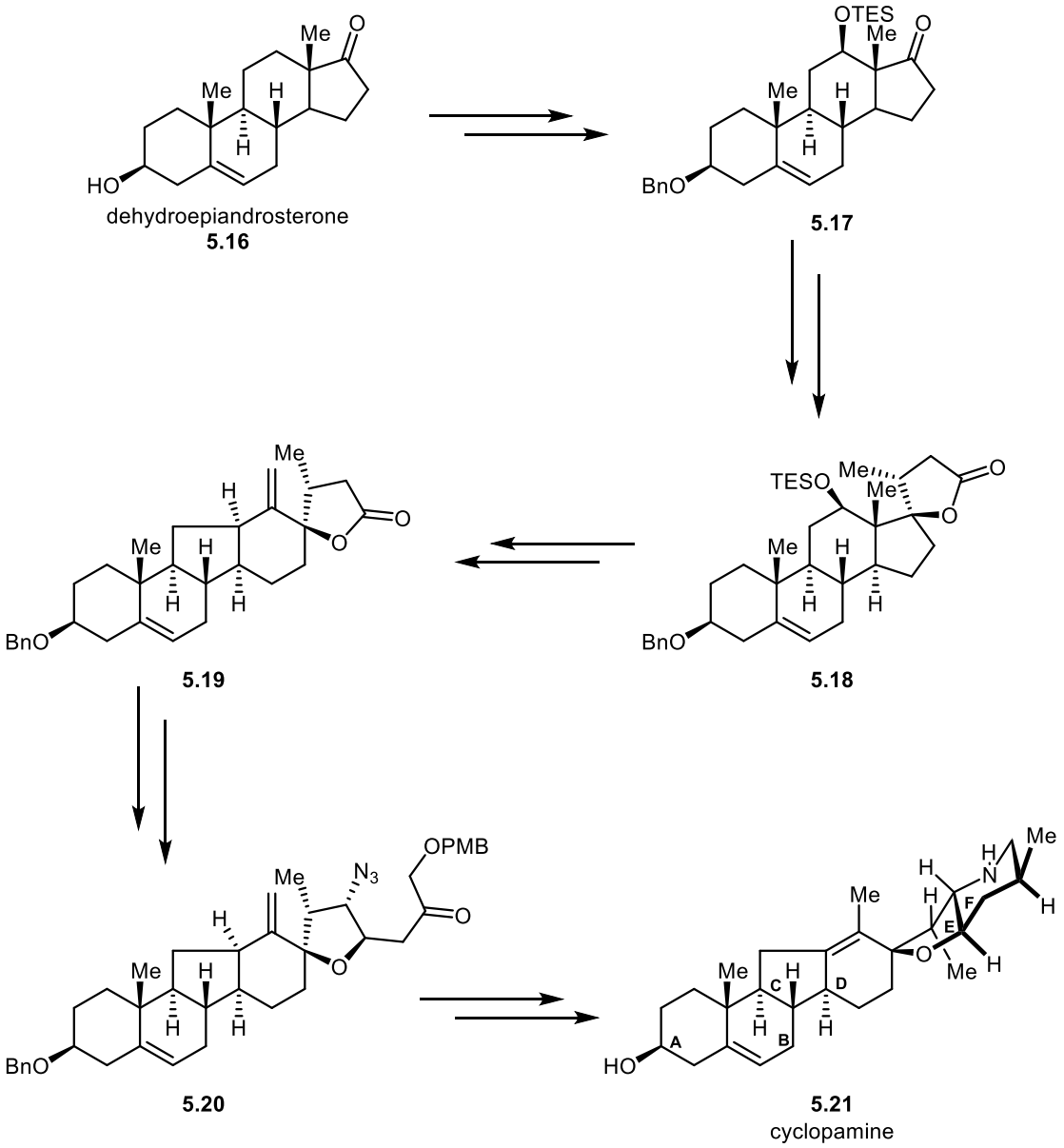
The Giannis group has reported a creative rearrangement of 6-6-6-5 ring systems into the 6-6-5-6 ring system of C-*nor*-D-*homo*-steroids.[10b] Using Comins' reagent as a triflate source allowed the authors to convert the secondary alcohol present in 12β-hydroxy steroids into a nucleofuge, which enabled the Wagner-Meerwein rearrangement to occur in a number of complex contexts (Scheme 5-3). With this methodology, the authors were able to convert **5.12** into **5.13** in 32% yield, and **5.14** into a mixture of endocyclic and exocyclic alkenes favoring the former.

Scheme 5-3. Approach to C-*nor*-D-*homo*-Steroids Developed by the Giannis Group



This rearrangement tactic was applied in the synthesis of cyclopamine from dehydroepiandrosterone.[10a] From the intial 6-6-6-5 steroid, a C-H functionalization protocol enabled installiation of the 12β-hydroxyl group in **5.17**. A sequence of diastereoselective organometallic additions allowed subsequent elaboration of the ketone into the key spirocyclic lactone **5.18**. The key rearrangement of **5.18** into **5.19** proceeded through deprotection with hydrogen fluoride and treatment with triflic anhydride to give a 7:3 mixture of alkenes (endocyclic:exocyclic). The authors were only able to carry out the downstream piperidine closure using the exocyclic alkene. The nitrogen was installed by reacting the lactone enolate with trisyl azide. Subequent Horner-Wadsworth-Emmons olefination set the stage for an annulative Mitsunobu reaction to provide the piperidine F ring. The location of the alkene in the D ring was corrected using an Alder-ene reaction with *N*-sulfinylbenzenesulfonamide followed by treatment with Raney nickel. The synthesis of cyclopamine was completed shortly thereafter.

Scheme 5-4. Overview of Giannis Synthesis of Cyclopamine

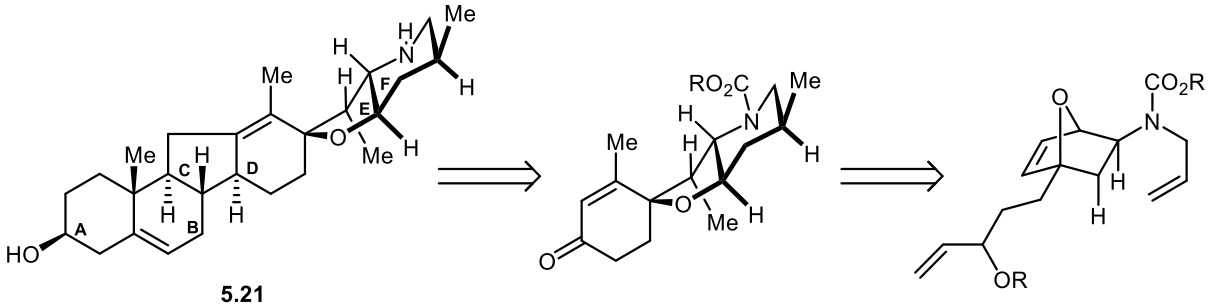


The Giannis approach to cylcopamine is primarily noteworthy because it makes a significant advance towards realistic accessibility of this difficult family of natural products. Additionally, there are many system-specific lessons from this work that will inform future efforts. However, while this route possesses the conceptual novelty of starting from a 6-6-6-5 system, it ultimately rests on the availability of a steroidal starting material. This weakness, combined with the overall length of the route, leave room for improvement.

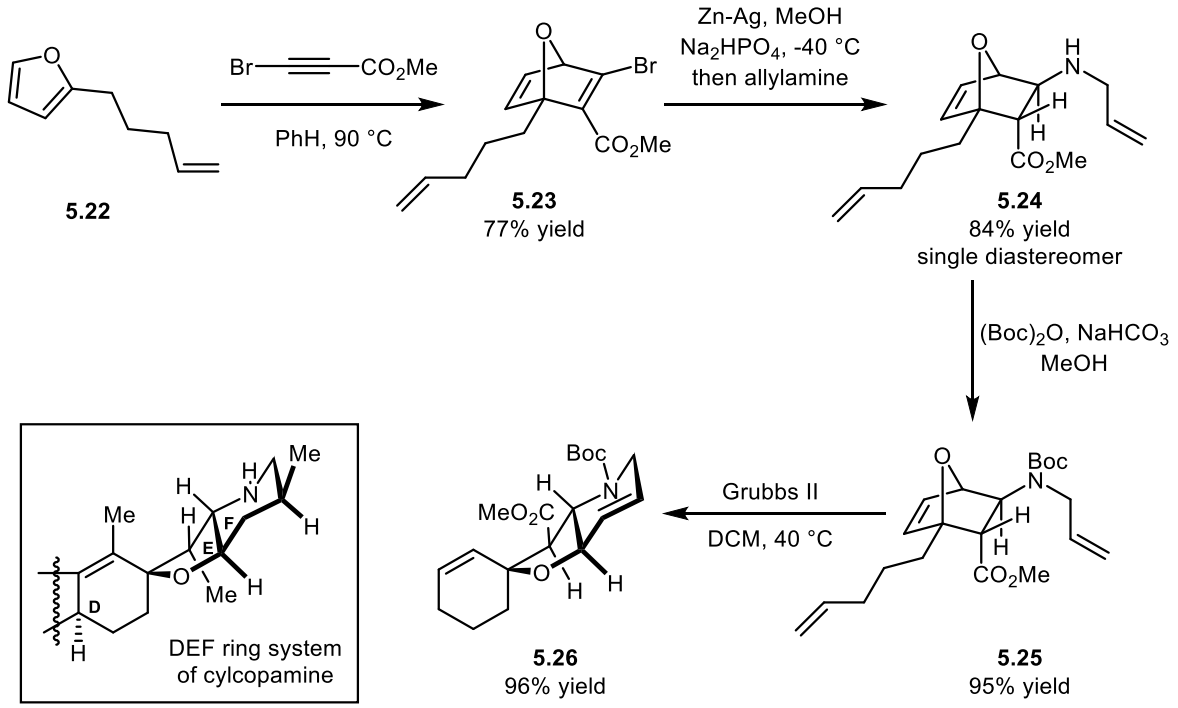
5.2.6 Wright Approach to the *Veratrum* Alkaloid Core

In 2011, the Wright group described a domino olefin methathesis approach to the synthesis of the DEF ring system of jervine and cyclopamine.[11] In their retrosynthetic analysis of cyclopamine, they envisioned using a key domino olefin metathesis reaction on a bicyclic furan with tethered terminal alkenes to simultaneously close the D and F rings of the target (Scheme 5-5). The authors began their endeavor using the monosubstituted furan **5.22** in a Diels-Alder reaction to from **5.23** in 77% yield (Scheme 5-6). Subsequent dehalogenation and aza-Michael addition with allylamine gave **5.25**, formed as a single diastereomer. Finally a domino metathesis reaction with Grubbs second generation catalyst provided **5.26** in 96% yield.

Scheme 5-5. Retrosynthetic Analysis in Wright Approach



Scheme 5-6. Wright's Domino Metathesis Approach



Though this approach to the DEF ring system is incredibly efficient at constructing a model scaffold, there are several shortcomings that prevent it from being applied to a full route to the target molecule. At present, the route is racemic and would require a mechanism for enantiocontrol in the Diels-Alder reaction. The methyl ester in **5.26** would need to be transformed into a methyl group; it also has the wrong relative stereochemistry for the target molecule. Additionally, it is not immediately obvious how the alkene moieties can be elaborated into useful functional handles for a full route. These drawbacks collectively informed our decision to avoid this type of domino metathesis approach in our own investigations.

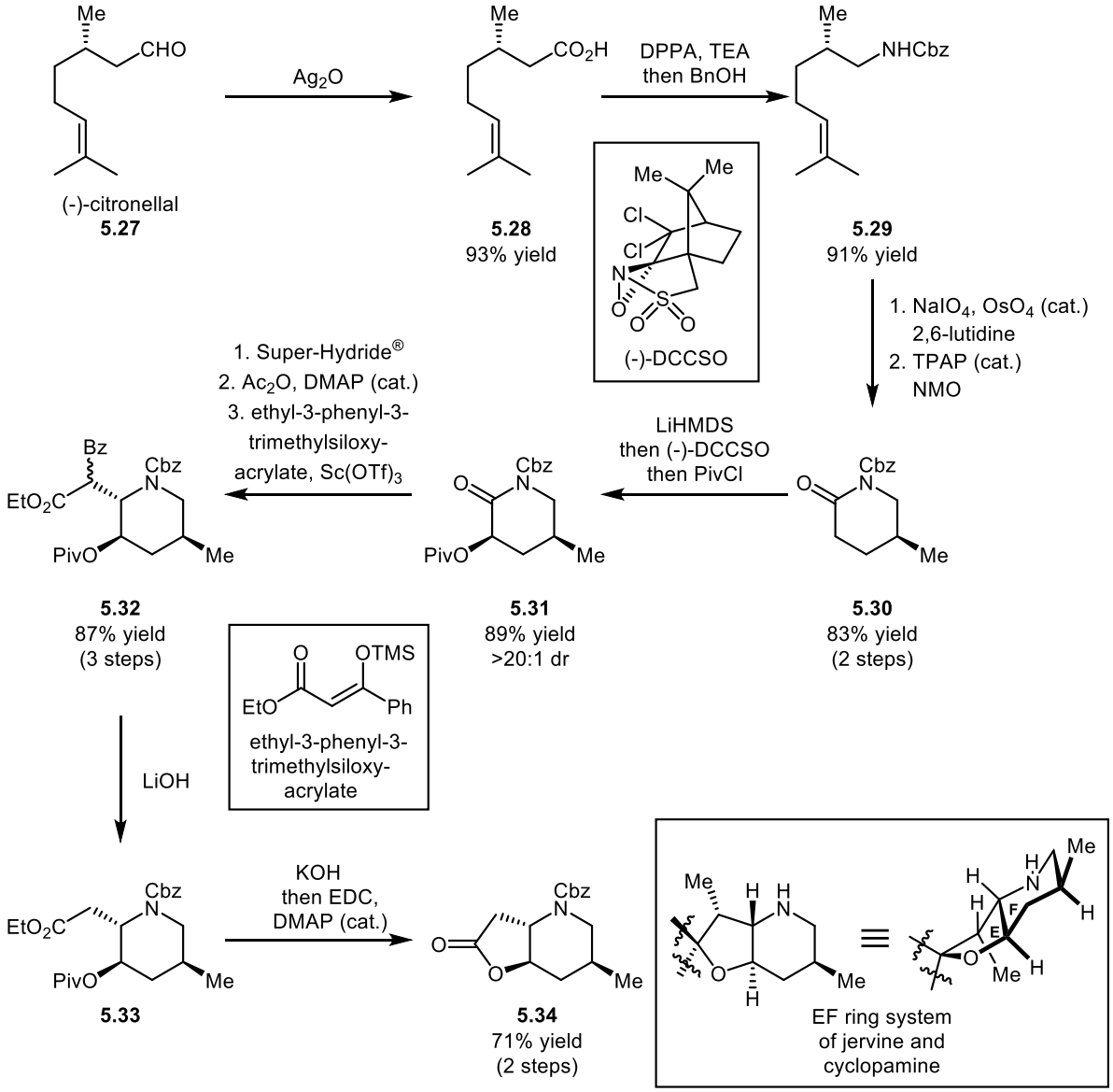
5.2.7 Other *De Novo* Approaches to the Synthesis of the *Veratrum* Alkaloid Core

Giannis developed a synthetic approach that enabled access to all diastereomers of the cyclopamine alkaloid substructure in 2009 (Scheme 5-7).[6] In this work, the authors used the stereochemistry present in (-)-citronellal (**5.27**) to construct the core EF ring system of jervine and

cyclopamine. After oxidizing **5.27** to carboxylic acid **5.28** with silver oxide, DPPA was used to promote a Curtius rearrangement to form **5.29** in 91% yield. Oxidative cleavage and cyclization provided **5.30**, which was used to form an enolate and react with chiral oxaziridine (-)-DCCSO to obtain **5.31** in >20:1 dr. Subsequent elaboration into **5.32** was possible by adding an enol silane into a derivative of **5.31**. Retro-Claisen reaction with LiOH and esterification provided the chiral building block **5.34**. This chiral pool approach only suffers from a few oxidation/reduction steps. The principal drawbacks to this route are that it does not incorporate a methyl group in the lactone (E ring) and it fails to demonstrate that a lactone is an appropriate surrogate for a spirocyclic stereocenter.

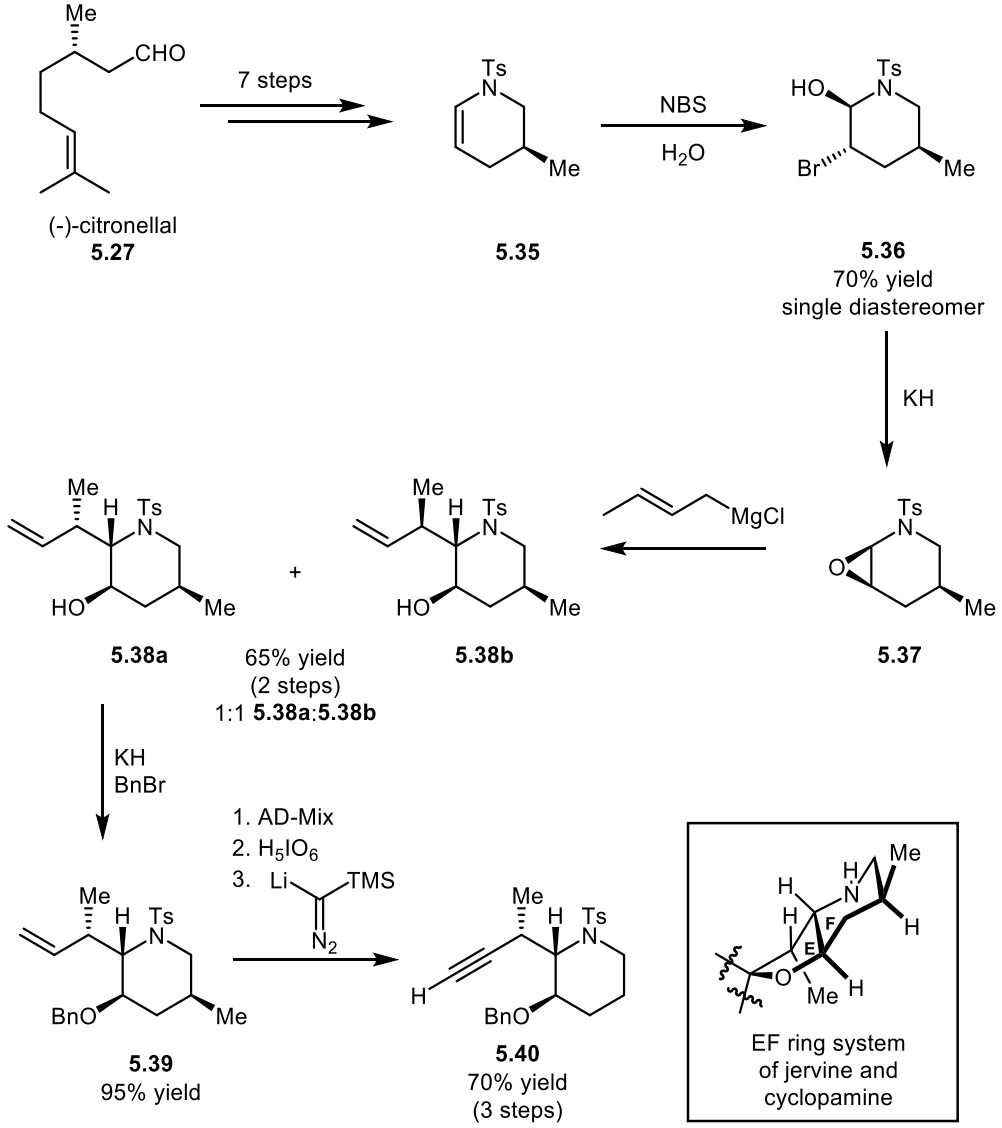
Later work on a *de novo* approach was reported by DeMatteo and Taber in a 2012 paper,[7a] where the authors focused on the same region of the target molecules. Using chemistry similar to the work by Giannis (Scheme 5-7) to convert (-)-citronellal to a piperidine, they arrived at **5.35**. Subsequent halohydration allowed epoxide formation to give **5.37**, which was found to react with a 2-butenyl Grignard reagent to give a 1:1 diastereomeric mixture of **5.38**. Benzyl protection of the alcohol and conversion of the alkene to an alkyne by a three-step sequence furnished **5.40**. As compared to the Giannis chiral pool approach, this route has the advantage of incorporating the methyl group in the E ring, though it has not been demonstrated that the ring can be closed. In a separate route where Taber merged his approach with that of Giannis, the authors reported an unoptimized alkylation of **5.34** to give **5.35** with the stereochemistry required for the targets (Scheme 5-9).

Scheme 5-7. *De Novo* Approach of Giannis

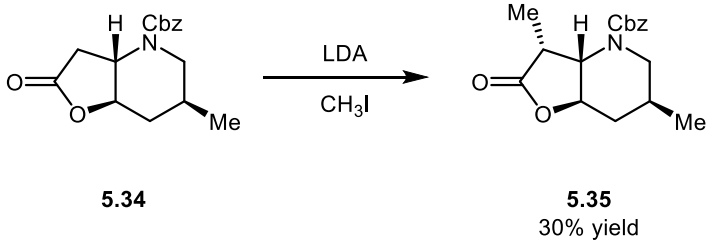


Both of these *de novo* approaches are significant developments toward a more ideal route to the *Veratrum* alkaloids. In spite of this, it deserves note that (a) they both rely on the chiral pool for starting materials, (b) they are, arguably, not concise routes, and (c) they would require converting a lactone into a spirocyclic stereocenter. With these considerations in mind, we envisioned the following retrosynthetic analysis of the target molecules.

Scheme 5-8. *De Novo* Approach of Taber



Scheme 5-9. Taber's Alkylation of the Alkaloid Core



5.2.8 Retrosynthetic Analysis for Dearomatization/Local Desymmetrization Approach

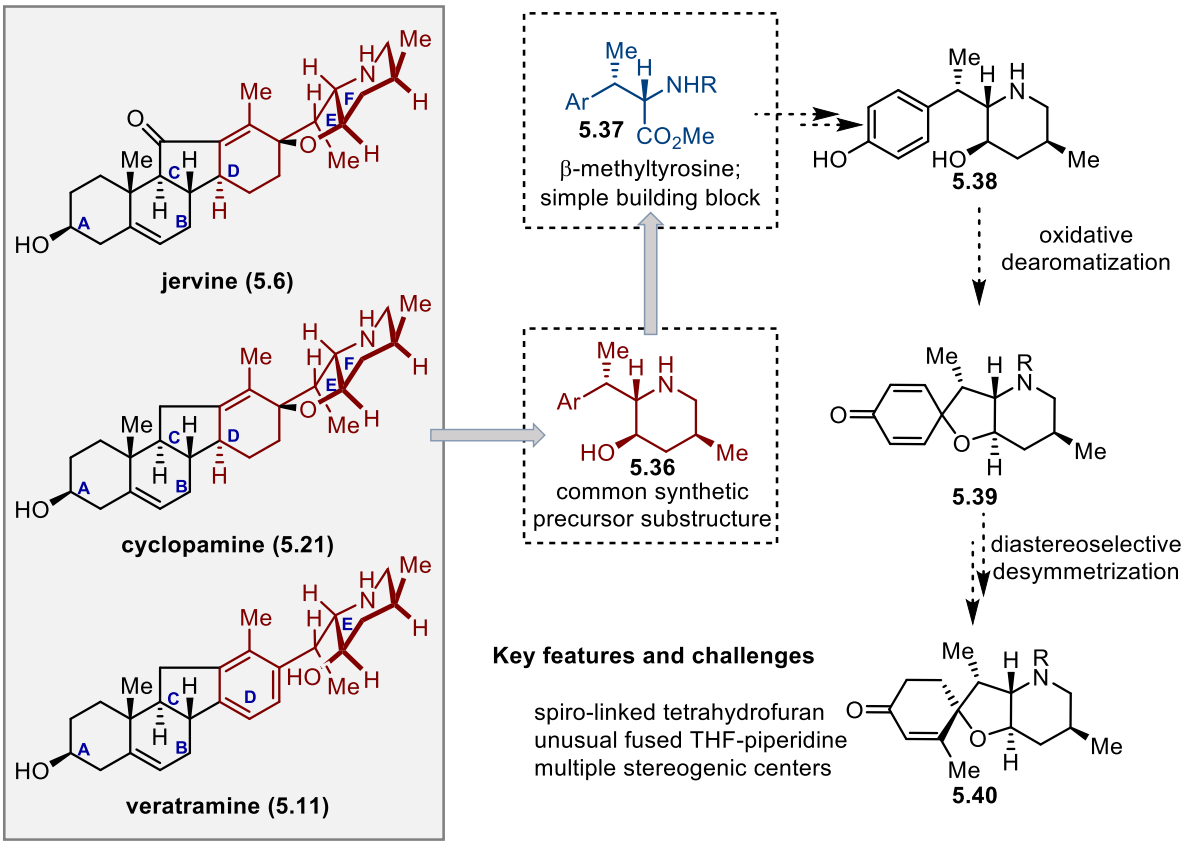
Our retrosynthetic analysis of the target molecules placed an emphasis on the construction of the alkaloid core, which possesses several challenging structural features, including a unique fused tetrahydrofuran/piperidine ring system (Scheme 5-10). We envisioned that all three alkaloids might arise from a common synthetic intermediate type resembling piperidine **5.36**. We considered that by having a synthetic strategy that furnishes a functionalized aromatic D ring, we might be able to access veratramine using a substitution pattern that is well suited for steroid-alkaloid coupling. Alternatively, for jervine and cyclopamine, we imagined using a phenol (**5.38**) in an oxidative dearomatization[15] to provide a cyclohexadienone; such a cyclohexadienone intermediate (**5.39**) would allow a local desymmetrization via diastereotopic group discrimination to define the spirocyclic stereocenter (as in **5.40**). With these considerations in mind, we made it our goal to synthesize the stereochemical array of the common intermediate **5.36**.

5.3 Results and Discussion

5.3.1 Synthesis of Stereotriad from β-Methyltyrosine Derivative

As a first investigation into the feasibility of this synthetic plan, we aimed to study a simplified model system for the intramolecular oxidative dearomatization. We began by synthesizing the known racemic β-methyltyrosine derivative **5.41**,[16] which was obtained in three steps from 4-methoxyacetophenone and hippuric acid (and can be produced on decagram scale in a single batch) (Scheme 5-11). Weinreb amide formation proceeded smoothly in 70% yield, providing amide **5.42** in >20:1 dr after recrystallization.

Scheme 5-10. Retrosynthetic Analysis and Overall Synthetic Plan



Grignard addition of **5.43** furnished ketone **5.44**, which could be diastereoselectively reduced to afford triad **5.45** in 57% yield over two steps. The ability of the nitrogen-bearing stereocenter to control the stereochemical outcome at the adjacent carbon is an attractive aspect of this synthetic route.[17]

5.3.2 Synthesis of Dearomatization Substrate from Stereotriad

Aiming to study the dearomatization in a model system, we minimized the number of reactive functional groups present by hydrogenating the terminal alkene to obtain **5.46** in 51% yield. Attempts to carry out hydroboration on the 1,1-disubstituted alkene (with substrate-controlled or reagent-controlled diastereoselectivity) in **5.45** were unsuccessful. Other efforts to utilize the terminal alkene in **5.45** for epoxide formation and epoxide-opening ring closure

sequences were similarly fruitless. Demethylation of ether **5.46** using BBr_3 resulted in the target oxidative dearomatization substrate, phenol **5.47**.

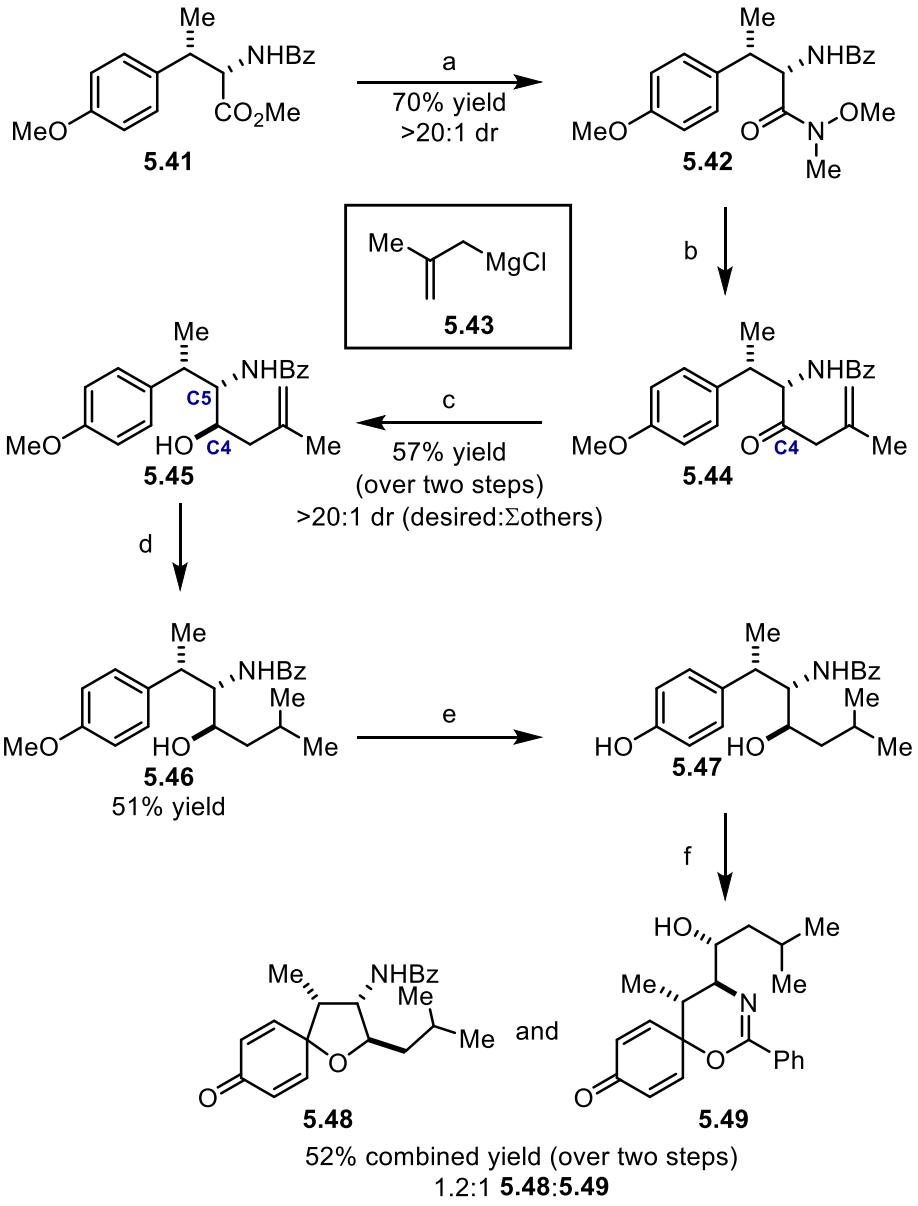
5.3.3 Dearomatization of Phenol to Cyclohexadienone

Guided by prior studies utilizing $PhI(OAc)_2$ in TFA,[15e] dearomatization of the phenol **5.47** under these conditions led to the expected spiro-tetrahydrofuran **5.48** and the undesired dihydrooxazine **5.49**[18] in a combined yield of 52% over two steps. Unfortunately, the two dearomatization products were inseparable; however, this model system provided a useful lesson that it is important to transform the benzamide into a non-reactive functionality prior to dearomatization.

5.3.4 Discussion of Competitive Cyclization and Proposed Revisions to Route

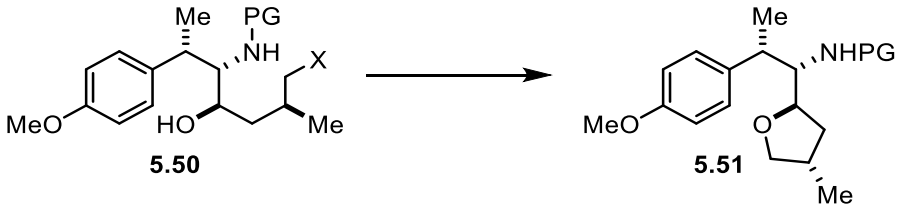
In view of the competitive cyclization pathways that are observed during the oxidative dearomatization of **5.47**, it appears that the options available are (a) close the piperidine first, with the idea of preventing participation of the benzoyl group, or (b) use a different protecting group on the nitrogen. Because the benzoyl protecting group is necessary for isolating a single alkene isomer in the synthesis of β-methyltyrosine derivative **5.41**, pursuing option (b) would necessarily involve removal of the protecting group from **5.41** (or a downstream intermediate) and attaching a different protecting group which cannot participate in the competitive cyclization. Seeking to avoid protecting group manipulations, we first investigated option (a). However, in a number of studies that ended only in synthetic dead ends, we learned that it is difficult to close the piperidine prior to tetrahydrofuran formation due to another competitive cyclization process (Scheme 5-12). We observed that tetrahydrofuran formation can outcompete piperidine formation in several contexts, even when the nitrogen protected group is benzyl.

Scheme 5-11. Synthesis of Spirocyclic Tetrahydrofuran Core



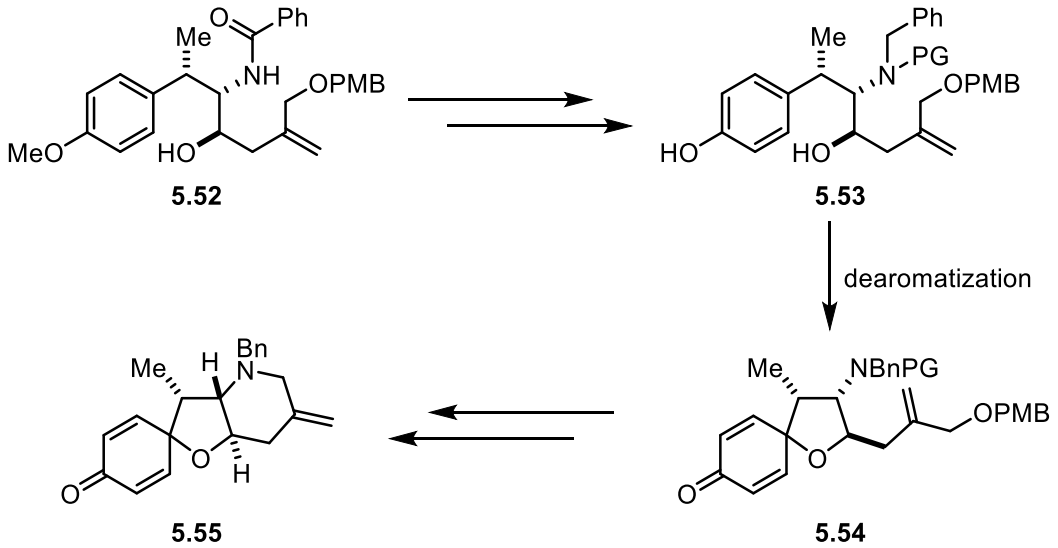
(a) CH_3NHOCH_3•HCl, $AlMe_3$, CH_2Cl_2, rt; (b) **5.43**, THF, 0 ºC to rt; (c) $NaBH_4$, MeOH, 0 ºC to rt; (d) H_2 (1 atm), Pd/C, MeOH, rt; (e) BBr_3, DCM, -78 ºC to 0 ºC; (f) $PhI(OAc)_2$, TFA, DCM, 0 ºC to rt.

Scheme 5-12. Common Competive Tetrahydrofuran Formation



With this added challenge in mind, we have elected to pursue option (b). We intend to implement a protecting group manipulation on stereotriad **5.52** to create a scenario where the nitrogen protecting groups cannot participate in the type of dearomative cyclization that led to **5.49**. We anticipate that using this strategy, as well as a more functionalized methallyl group, will allow us to close both the spirocyclic tetrahydrofuran and the piperidine. We are optimistic that our proposed revisions to the existing route will allow us to arrive at an intermediate resembling **5.54**, which will serve as a crucial building block for the completion of the synthesis of jervine and cyclopamine.

Scheme 5-13. Plan for Future Work



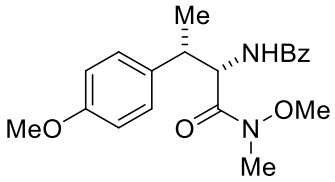
5.4 Conclusion

A key building block for the alkaloid core of jervine, cyclopamine, and veratramine has been synthesized in a short sequence that utilizes high yielding transformations. The unresolved issues for this synthetic approach, going forward, will be (1) finding a nitrogen protecting group that does not participate in the competitive dearomative cyclization, (2) executing a local desymmetrization of the D ring after dearomatization, and (3) rendering the synthesis asymmetric by employing an enantioselective hydrogenation in the synthesis of **5.41**. We are optimistic that these issues are resolvable and will present exciting opportunities for reaction development and synthetic planning. Studies toward these ends are ongoing in our laboratory.

5.5 Experimental Details

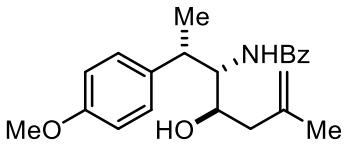
General Comments. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and 13C NMR) were recorded with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). 1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were obtained via Fourier transform mass spectrometry (FTMS) with electrospray ionization (ESI) and external calibration in positive ion mode (all samples prepared in methanol). Melting points were obtained using a capillary melting point apparatus. Visualization for thin layer chromatography (TLC) was allowed by UV light, phosphomolybdic acid in ethanol, or aqueous ceric ammonium nitrate solution. Purification of the reaction products was carried out by using silica gel (40- 63μm). Reagents, catalysts, and ligands were purchased and used as received. Solvents were purified by

passage through an aluminum oxide column using nitrogen. Methyl ester **5.41**[16] was made according to literature procedure.



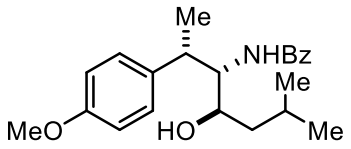
(±)-*N*-(1-(methoxy(methyl)amino)-3-(4-methoxyphenyl)-1-oxobutan-2-yl)benzamide (5.42): A 2 L round-bottomed flask with a stir bar was charged with N,O-dimethylhydroxylamine hydrochloride (16.68 g, 171.0 mmol, 3.0 equiv) and DCM (340 mL). The flask was cooled in an ice bath and placed under an atmosphere of N_2. Trimethylaluminum (2.0 M solution in heptane, 85.5 mL, 171.0 mmol, 3.0 equiv) was added in a dropwise fashion. The ice bath was removed and the reaction was stirred for 30 min at room temperature. A solution of methyl ester **5.41** (18.66 g, 57.0 mmol, 1.0 equiv) in DCM (170 mL) was added dropwise. The reaction was allowed to stir for 24 h. Once complete, the reaction was cooled in an ice bath and, while stirring, quenched with saturated sodium potassium tartrate in a dropwise fashion until the reaction stopped bubbling. The quenched reaction was allowed to continue stirring for 1 h. The reaction mixture was filtered through a Celite® pad using DCM and the filtrate was concentrated in vacuo. The crude material was purified by silica gel chromatography (30:70 to 60:40 ethyl acetate/hexanes) and subsequently recrystallized from EtOAc/hexanes to obtain the desired product as a white solid (14.26 g, 70%). The product was obtained in >20:1 dr, which was determined by comparing the signals at δ 5.51 (minor) and δ 5.46 (major) in the ^{1}H NMR spectrum. Analytical data: mp 128-130 ºC; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.48-7.46 (m, 1H), 7.40-7.37 (m, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.59 (d, *J* = 8.5 Hz, 1H), 5.47-5.45 (m, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.33-3.30 (m, 1H), 3.28 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.0, 167.1, 158.6, 134.1, 133.6, 131.6, 128.8, 128.5, 127.0, 113.9, 61.8, 55.2, 53.7, 42.0, 32.1, 18.7; **IR** (thin film) ν 3310, 2935, 1636, 1509, 1249, 1179, 1036, 987, 912, 834 cm^{-1};

HRMS (ESI): Calcd. for $C_{20}H_{24}N_2NaO_4^+$ ([M+Na^+]): 379.1628, found 379.1623; **TLC** (60:40 EtOAc/hexanes): R_f = 0.42.



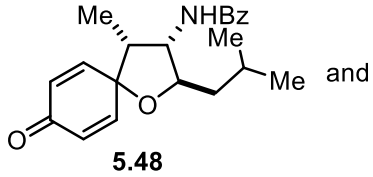
(±)-*N*-(4-hydroxy-2-(4-methoxyphenyl)-6-methylhept-6-en-3-yl)benzamide (5.45): A flame dried 1 L round-bottomed flask was charged with Weinreb amide **5.42** (534.6 mg, 1.5 mmol, 1.0 equiv) and THF (6.0 mL). The reaction was placed under N_2 and stirred in an ice bath. A commercial solution of methallylmagnesium chloride (0.5 M, 9.0 mL, 4.5 mmol, 3.0 equiv) was added slowly as a steady stream. The reaction was stirred at room temperature for 14 h, at which point the reaction was quenched by addition of saturated aqueous ammonium chloride solution with cooling in an ice bath. The solution was transferred to a separatory funnel and extracted three times with diethyl ether. The combined organic phases were dried with sodium sulfate and concentrated in vacuo to afford the crude product, which was recrystallized from ethyl acetate and hexanes to obtain the desired product (the conjugated enone formed by isomerization was also present as an impurity). The material was carried on without further purification (when silica gel chromatography was attempted in other trials, the alkene was found to isomerize during the purification, which prevented clean isolation). Methallyl ketone **5.44** was dissolved in MeOH (7.5 mL) and cooled in an ice bath. $NaBH_4$ (192.9 mg, 5.1 mmol, 3.4 equiv with respect to **5.42**) was added carefully. The reaction was stirred for 2 h under N_2 and slowly allowed to warm to room temperature. The reaction was then quenched with 1 M HCl (aqueous) and concentrated in vacuo to remove MeOH. The crude residue was partitioned between ethyl acetate and 1 M HCl and the layers were separated. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with sodium sulfate and concentrated in vacuo to afford the crude product, which was purified by silica gel chromatography (20:80 to 40:60 ethyl

acetate/hexanes) to obtain the desired product as a white solid (300.8 mg, 57% over the two steps from 10 to 13). The product was obtained in >20:1 dr, which was determined by comparing the signals at δ 4.85 (major) and δ 4.77 (C5 epimer) in the ^{1}H NMR spectrum. No C4 epimer was observed. Analytical data: mp 89-90 ºC, **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.54-7.51 (m, 1H), 7.45-7.42 (m, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.81 (d, *J* = 9.3 Hz, 1H), 4.92 (s, 1H), 4.85 (s, 1H), 4.32-4.28 (m, 1H), 3.85 (s, 3H), 3.58-3.51 (m, 2H), 2.68 (br s, 1H), 2.29-2.20 (m, 2H), 1.71 (s, 3H), 1.39 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.7, 158.6, 142.6, 134.1, 133.5, 131.7, 129.3, 128.7, 126.8, 114.1, 114.1, 69.1, 58.8, 55.3, 42.6, 38.0, 22.4, 18.9; IR (thin film) ν 3423, 2965, 1646, 1513, 1249, 1179, 1035, 835, 712, 559 cm^{-1}; **HRMS** (ESI): Calcd. for $C_{22}H_{28}NO_3^+$ ([M+H$^+$]): 354.2064, found 354.2060; TLC (20:80 EtOAc/hexanes): Rf = 0.07.



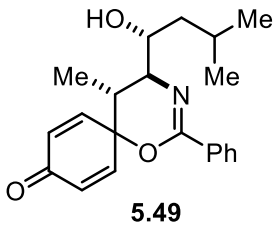
(±)-*N*-(4-hydroxy-2-(4-methoxyphenyl)-6-methylheptan-3-yl)benzamide (5.46): Alcohol **5.45** (277.0 mg, 0.79 mmol, 1.00 equiv) was added to a scintillation vial, followed by 10% Pd/C (55.4 mg, 20 w/w %). The flask was placed under an atmosphere of N_2, and then MeOH (7.9 mL) was added slowly. The solution was sparged with H_2 for 15 min, then the exit line was removed and the reaction was allowed to stir for 2 h at room temperature under a balloon of H_2. Once complete, the reaction was flowed through a pad of Celite® with additional methanol, and the filtrate was concentrated in vacuo. The crude product was purified by silica gel chromatography (20:80 to 40:60 ethyl acetate/hexanes) to obtain the desired product as a white solid (140.7 mg, 51%). Analytical data: mp 70-72 ºC, **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.50-7.48 (m, 3H), 7.40-7.38 (m, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.86 (d, *J* = 7.7 Hz, 1H), 4.31-4.28 (m, 1H), 3.83 (s, 3H), 3.81-3.79 (m, 1H), 3.33 (d, *J* = 7.4 Hz, 1H), 3.19-3.14 (m, 1H), 1.94-1.88 (m, 1H), 1.49-1.44 (m, 1H), 1.40 (d, *J* = 7.0

Hz, 3H), 1.24-1.20 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.4, 158.6, 134.6, 134.0, 131.7, 128.8, 128.6, 126.9, 114.4, 70.8, 60.6, 55.3, 41.9, 39.4, 24.4, 24.1, 21.6, 20.0; **IR** (thin film) ν 3426, 2956, 1644, 1514, 1304, 1285, 1250, 1179, 1038, 733 cm^{-1}; **HRMS** (ESI): Calcd. for $C_{22}H_{30}NO_3^+$ ([M+H$^+$]): 356.2220, found 356.2213; **TLC** (40:60 EtOAc/hexanes): Rf = 0.35.



5.48

and



5.49

(±)-*N*-(2-isobutyl-4-methyl-8-oxo-1-oxaspiro[4.5]deca-6,9-dien-3-yl)benzamide (5.48) and **(±)-4-(1-hydroxy-3-methylbutyl)-5-methyl-2-phenyl-1-oxa-3-azaspiro[5.5]undeca-2,7,10-trien-9-one (5.49):** Alcohol **5.46** (287 mg, 0.81 mmol, 1.0 equiv) was added to a flame dried 100 mL round-bottomed flask, followed by DCM (8.0 mL). The reaction was cooled to -78 ºC in a dry ice/acetone bath and placed under nitrogen before adding BBr_3 (0.23 mL, 2.42 mmol, 3.0 equiv) dropwise. Then the reaction was placed in an ice water bath and allowed to stir for 1 h. Once complete, the reaction was quenched by adding MeOH dropwise. Then water was added and the layers were separated. The aqueous layer was extracted three times with DCM. The combined organic layers were dried with sodium sulfate and concentrated in vacuo to afford the crude phenol **5.47**, which was carried on without further purification. $PhI(OAc)_2$ (390 mg, 1.21 mmol, 1.5 equiv with respect to **5.46**) was dissolved in DCM (28.8 mL), cooled to 0 ºC in an ice bath, and then TFA (0.14 mL, 1.9 mmol, 2.3 equiv) was added dropwise. After stirring for 15 min at room temperature, the solution was added dropwise to a solution of the crude phenol **5.47** in DCM (28.8 mL) at 0 °C. The reaction was then allowed to warm to room temperature slowly and stir for 3 h. $NaHCO_3$ (339 mg, 4.0 mmol, 5.0 equiv) was added and the reaction was allowed to continue stirring for 10 min before concentration in vacuo.

The crude residue was purified by silica gel chromatography (10:90 to 30:70 ethyl acetate/hexanes) to obtain an inseparable mixture of the two products as a red-brown foam (142.7 mg, 52% over two steps); the composition (by ^{1}H NMR analysis) was found to be **5.48**:**5.49** = 1.2:1. ^{1}H NMR signals were assigned to **5.48** and **5.49**, though assignments were not made for ^{13}C NMR. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$) **5.48**: δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.60-7.57 (m, 1H), 7.52-7.49 (m, 2H, overlaps with **5.49**), 6.88-6.85 (m, 1H, overlaps with **5.49**), 6.78-6.76 (m, 1H, overlaps with **5.49**), 6.28-6.26 (m, 1H), 6.24-6.22 (m, 1H), 6.20 (d, *J* = 7.7 Hz, 1H), 4.71-4.68 (m, 1H), 4.22-4.19 (m, 1H), 2.76-2.71 (m, 1H), 1.90-1.85 (m, 1H, overlaps with **5.49**), 1.72-1.67 (m, 1H), 1.62-1.58 (m, 1H), 1.00-0.96 (m, 6H, overlaps with **5.49**), 0.92-0.89 (m, 3H, overlaps with **5.49**); **5.49**: δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.52-7.49 (m, 1H, overlaps with **5.48**), 7.44-7.41 (m, 2H), 6.88-6.85 (m, 1H, overlaps with **5.48**), 6.78-6.76 (m, 1H, overlaps with **5.48**), 6.45-6.43 (m, 1H), 6.42-6.40 (m, 1H), 3.99-3.97 (m, 1H), 3.56 (dd, *J* = 11.3, 4.0 Hz, 1H), 2.02-1.98 (m, 1H), 1.90-1.85 (m, 1H, overlaps with **5.48**), 1.35-1.31 (m, 1H), 1.00-0.96 (m, 6H, overlaps with **5.48**), 0.92-0.89 (m, 3H, overlaps with **5.48**); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 185.4, 185.0, 167.5, 154.3, 150.8, 147.1, 146.4, 142.8, 133.9, 132.4, 132.1, 131.2, 131.1, 130.9, 129.2, 128.9, 128.4, 128.2, 127.3, 126.9, 83.1, 81.3, 75.6, 68.7, 59.9, 58.5, 45.8, 44.6, 39.7, 34.4, 25.1, 24.2, 24.1, 23.3, 22.1, 21.4, 11.4, 9.5; **IR** (thin film) ν 3317, 2956, 1669, 1532, 1490, 1385, 1291, 1178, 862, 732 cm^{-1}; **HRMS** (ESI): Calcd. for $C_{21}H_{26}NO_{3+}$ ($[M+H^+]$): 340.1907, found 340.1904; **TLC** (30:70 EtOAc/hexanes): Rf = 0.35 (**5.48**), 0.46 (**5.49**).

REFERENCES

[1] (a) Wright, C. R. A.; Luff, A. P. *J. Chem. Soc., Trans.* **1879,** *35*, 405. (b) Wintersteiner, O.; Hosansky, N. *J. Am. Chem. Soc.* **1952,** *74*, 4474. (c) Wintersteiner, O.; Moore, M. *J. Org. Chem.* **1964,** *29*, 262. (d) Keeler, R. F.; Binns, W. *Proc. Soc. Exp. Biol. Med.* **1964,** *116*, 123. (e) Kupchan, S. M.; Suffness, M. I. *J. Am. Chem. Soc.* **1968,** *90*, 2730. (f) Chen, J. K.; Taipale, J.; Cooper, M. K.; Beachy, P. A. *Genes Dev.* **2002,** *16*, 2743. (g) Heretsch, P.; Tzagkaroulaki, L.; Giannis, A. *Angew. Chem., Int. Ed.* **2010,** *49*, 3418. (h) Chen, J. K. *Nat. Prod. Rep.* **2016,** *33*, 595.

[2] (a) Borzillo, G. V.; Lippa, B. *Curr. Top. Med. Chem.* **2005,** *5*, 147. (b) Scales, S. J.; de Sauvage, F. J. *Trends Pharmacol Sci.* **2009,** *30*, 303. (c) Tremblay, M.; McGovern, K. Cyclopamine and Its Derivatives for Cancer Therapeutics. In *Hedgehog Signaling Activation in Human Cancer and its Clinical Application*; Xie, J. Ed.; Spinger Science + Business Multimedia, LLC: New York, 2011; pp 187.

[3] Olive, K. P.; Jacobetz, M. A.; Davidson, C. J.; Gopinathan, A.; McIntyre, D.; Honess, D.; Madhu, B.; Goldgraben, M. A.; Caldwell, M. E.; Allard, D.; Frese, K. K.; DeNicola, G.; Feig, C.; Combs, C.; Winter, S. P.; Ireland-Zecchini, H.; Reichelt, S.; Howat, W. J.; Chang, A.; Dhara, M.; Wang, L.; Rückert, F.; Grützmann, R.; Pilarsky, C.; Izeradjene, K.; Hingorani, S. R.; Huang, P.; Davies, S. E.; Plunkett, W.; Egorin, M.; Hruban, R. H.; Whitebread, N.; McGovern, K.; Adams, J.; Iacobuzio-Donahue, C.; Griffiths, J.; Tuveson, D. A. *Science* **2009,** *324*, 1457.

[4] (a) Tremblay, M. R.; Nevalainen, M.; Nair, S. J.; Porter, J. R.; Castro, A. C.; Behnke, M. L.; Yu, L.-C.; Hagel, M.; White, K.; Faia, K.; Grenier, L.; Campbell, M. J.; Cushing, J.; Woodward, C. N.; Hoyt, J.; Foley, M. A.; Read, M. A.; Sydor, J. R.; Tong, J. K.; Palombella, V. J.; McGovern, K.; Adams, J. *J. Med. Chem.* **2008,** *51*, 6646. (b) Tremblay, M. R.; Lescarbeau, A.; Grogan, M. J.; Tan, E.; Lin, G.; Austad, B. C.; Yu, L.-C.; Behnke, M. L.; Nair, S. J.; Hagel, M.; White, K.; Conley, J.; Manna, J. D.; Alvarez-Diez, T. M.; Hoyt, J.; Woodward, C. N.; Sydor, J. R.; Pink, M.; MacDougall, J.; Campbell, M. J.; Cushing, J.; Ferguson, J.; Curtis, M. S.; McGovern, K.; Read, M. A.; Palombella, V. J.; Adams, J.; Castro, A. C. *J. Med. Chem.* **2009,** *52*, 4400. (c) Jimeno, A.; Weiss, G. J.; Miller, W. H., Jr.; Gettinger, S.; Eigl, B. J. C.; Chang, A. L. S.; Dunbar, J.; Devens, S.; Faia, K.; Skliris, G.; Kutok, J.; Lewis, K. D.; Tibes, R.; Sharfman, W. H.; Ross, R. W.; Rudin, C. M. *Clin. Cancer Res.* **2013,** *19*, 2766. (d) Austad, B. C.; Hague, A. B.; White, P.; Peluso, A.; Nair, S. J.; Depew, K. M.; Grogan, M. J.; Charette, A. B.; Yu, L.-C.; Lory, C. D.; Grenier, L.; Lescarbeau, A.; Lane, B. S.; Lombardy, R.; Behnke, M. L.; Koney, N.; Porter, J. R.; Campbell, M. J.; Shaffer, J.; Xiong, J.; Helble, J. C.; Foley, M. A.; Adams, J.; Castro, A. C.; Tremblay, M. R. *Org. Process Res. Dev.* **2016,** *20*, 786.

[5] (a) Heretsch, P.; Büttner, A.; Tzagkaroulaki, L.; Zahn, S.; Kirchner, B.; Giannis, A. *Chem. Commun.* **2011,** *47*, 7362. (b) Moschner, A.; Chentsova, A.; Eilert, N.; Rovardi, I.; Heretsch, P.; Giannis, A. *Beilstein J. Org. Chem.* **2013,** *9*, 2328. (c) Rabe, S.; Moschner, J.; Bantzi, M.; Heretsch, P.; Giannis, A. *Beilstein J. Org. Chem.* **2014,** *10*, 1564.

[6] Heretsch, P.; Rabe, S.; Giannis, A. *Org. Lett.* **2009,** *11*, 5410.

[7] (a) Taber, D. F.; DeMatteo, P. W. *J. Org. Chem.* **2012,** *77*, 4235. (b) Taber, D. F.; Berry, J. F. *J. Org. Chem.* **2013,** *78*, 8437.

[8] (a) Masamune, T.; Takasugi, M.; Murai, A.; Kobayashi, K. *J. Am. Chem. Soc.* **1967,** *89*, 4521. (b) Johnson, W. S.; deJongh, H. A. P.; Coverdale, C. E.; Scott, J. W.; Burckhardt, U. *J. Am. Chem. Soc.* **1967,** *89*, 4523.

[9] (a) Kutney, J. P.; By, A.; Cable, J.; Gladstone, W. A. F.; Inaba, T.; Leong, S. Y.; Roller, P.; Torupka, E. J.; Warnock, W. D. C. *Can. J. Chem.* **1975,** *53*, 1775. (b) Kutney, J. P.; Cable, J.; Gladstone, W. A. F.; Hanssen, H. W.; Nair, G. V.; Torupka, E. J.; Warnock, W. D. C. *Can. J. Chem.* **1975,** *53*, 1796.

[10] (a) Giannis, A.; Heretsch, P.; Sarli, V.; Stöβel, A. *Angew. Chem., Int. Ed.* **2009,** *48*, 7911. (b) Heretsch, P.; Rabe, S.; Giannis, A. *J. Am. Chem. Soc.* **2010,** *132*, 9968.

[11] Oblak, E. Z.; G-Dayanandan, N.; Wright, D. L. *Org. Lett.* **2011,** *13*, 2433.

[12] (a) Malinowski, J. T.; Sharpe, R. J.; Johnson. J. S. *Science* **2013,** *340*, 180. (b) Sharpe, R. J.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013,** *135*, 17990. (c) Sharpe, R. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2015,** *137*, 4968. (d) Sharpe, R. J.; Johnson, J. S. *J. Org. Chem.* **2015,** *80*, 9740. (e) Horwitz, M. A.; Johnson, J. S. *Eur. J. Org. Chem.* **2017,** *2017*, 1381.

[13] Johnson, W. S.; Cox, J. M.; Graham, D. W.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1967,** *89*, 4524.

[14] (a) Mitsuhashi; Shibata, K. *Tetrahedron Lett.* **1964,** 2281. (b) Johns, W. F.; Laos, I. *J. Org. Chem.* **1965,** *30*, 4220.

[15] (a) Hutinec, A.; Ziogas, A.; El-Mobayed, M.; Rieker, A. *J. Chem. Soc., Perkin Trans. 1*, **1998,** 2201. (b) Quideau, S.; Lebon, M.; Lamidey, A.-M. *Org. Lett.* **2002,** *4*, 3975. (c) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005,** *127*, 225-235. (d) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008,** *47*, 6650. (e) Cha, J. Y.; Huang, Y.; Pettus, T. R. R. *Angew. Chem., Int. Ed.* **2009,** *48*, 9519. (f) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009,** *11*, 5394. (g) Yokosaka, T.; Nemoto, T.; Hamada, Y. *Tetrahedron Lett.* **2013,** *54*, 1562.

[16] Tourwé, D.; Mannekens, E.; Diem, T. N. T.; Verheyden, P.; Jaspers, H.; Tóth, G.; Péter, A.; Kertész, I.; Török, G.; Chung, N. N.; Schiller, P. W. *J. Med. Chem.* **1998,** *41*, 5167.

[17] Wang, D.; Schwinden, M. D.; Radesca, L.; Patel, B.; Kronenthal, D.; Huang, M.-H.; Nugent, W. A. *J. Org. Chem.* **2004,** *69*, 1629.

[18] This mode of reactivity is known for similar systems: (a) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991,** *56*, 435. (b) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans. 1*, **1996,** 1385.

CHAPTER SIX:
ENANTIO- AND DIASTEREOSELECTIVE ORGANOCATALYTIC CONJUGATE ADDITION OF NITROALKANES TO ENONE DIESTERS

6.1 Introduction

The advent of organocatalysis has led to the development of catalysts which operate *via* a number of distinct activation modes. Hydrogen-bonding catalysis in particular has experienced a surge in popularity in the last two decades, largely as a result of the incorporation of thioureas and related hydrogen-bond donor motifs into complex catalyst architectures. In the last five years, a family of bifunctional thiourea-iminophosphorane organocatalysts has been demonstrated to have promising possibilities for enabling new reactivity in a stereoselective manner, such as the asymmetric reductive coupling reaction discussed in Chapter Two. In this chapter, we discuss a stereoselective conjugate addition of nitroalkanes to enone diester electrophiles. Using the conjugate addition reaction as a means of incorporating nitrogen stereoselectively into small molecules, we are able to generate small polyads *via* this synthetic framework.

6.2 Background

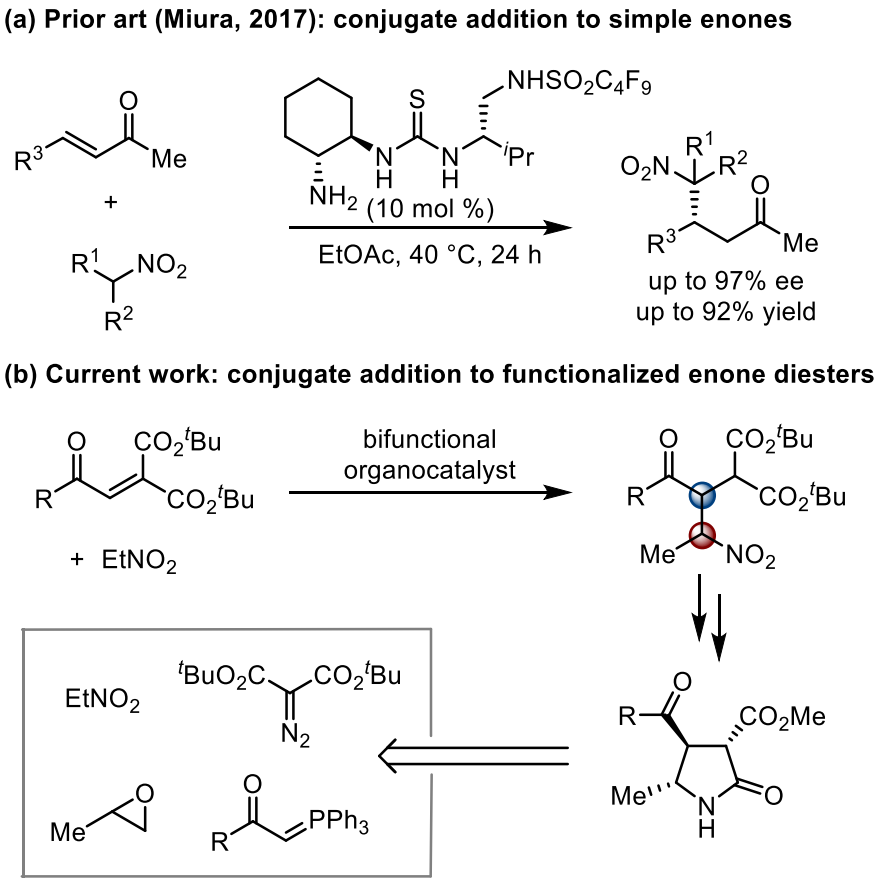
6.2.1 Organocatalytic Conjugate Additions of Nitroalkanes

The prevalence of nitrogen-containing acyclic and heterocyclic scaffolds in bioactive molecules provides opportunities for the development of methodologies for their efficient construction. Asymmetric organocatalytic conjugate additions of nitroalkanes have enabled the rapid construction of small polyads possessing numerous functional handles for downstream transformations. Previous approaches utilizing Brønsted base organocatalysis have accomplished this transformation in a stereoselective manner.[1]

6.2.2 The Challenge of Diastereoselectivity in Nitroalkane Conjugate Additions

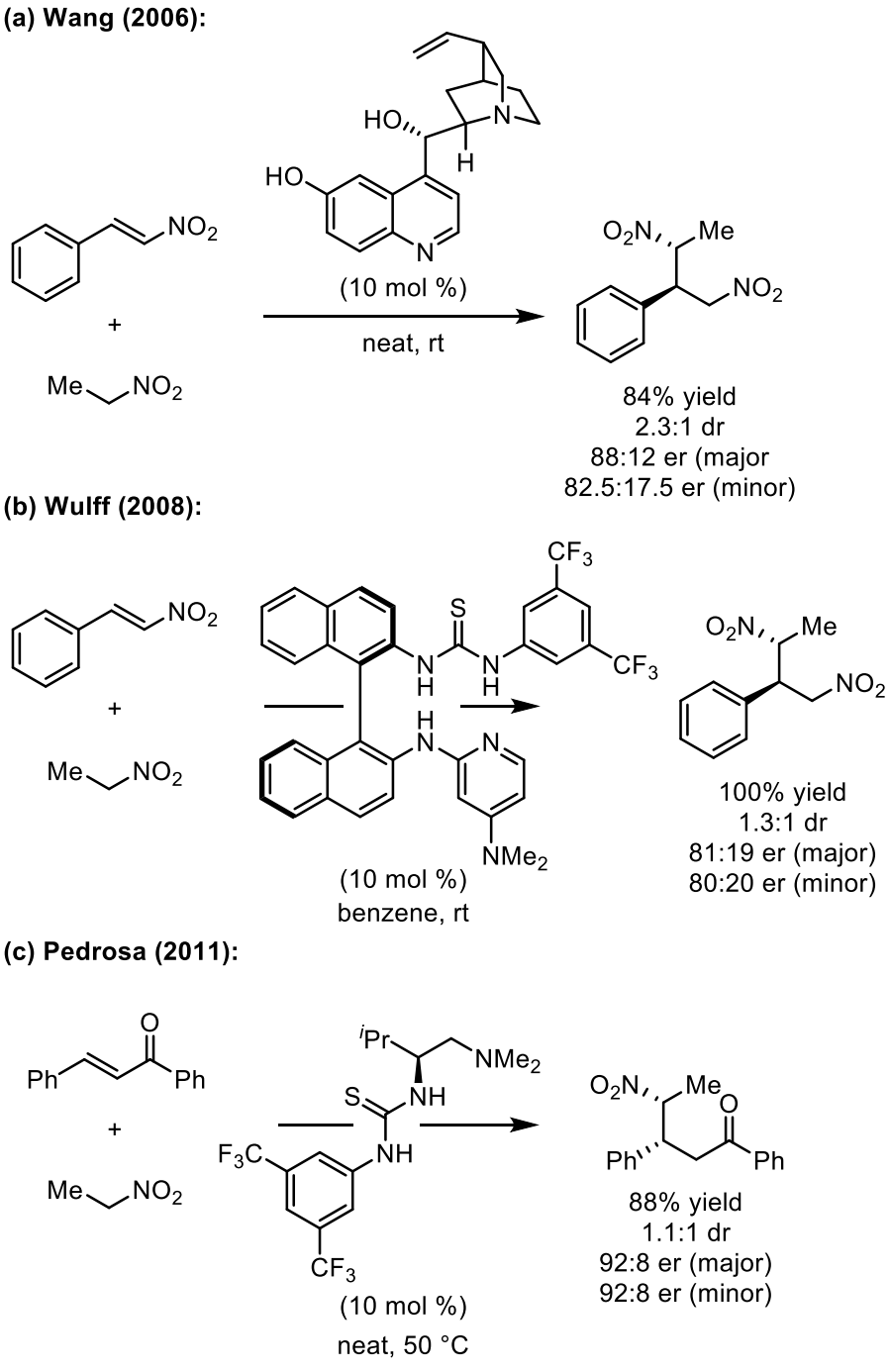
Although methods have been developed for the enantioselective addition of nitromethane (Scheme 6-1a), diastereocontrol with homologs has proven challenging in many contexts because of prochirality in both reaction partners.[22] For example, in nitroethane conjugate addition reactions developed by Wang (Scheme 6-2a) and Wulff (Scheme 6-2b) using a nitrostyrene electrophile, diastereoselectivity was universally poor. In a case where Pedrosa used chalcones as electrophiles (Scheme 6-2c), the same problem resulted. These studies indicate that, even when the chiral catalyst contains functional groups necessary to interact with both the nucleophile and the electrophile, it is difficult to create a situation where only a single prochiral face of each component is displayed to the other.

Scheme 6-1. Asymmetric Conjugate Additions of Nitroalkanes



We sought to meet this challenge by using a bifunctional organocatalyst to stereoselectively orient and unite extended nitroalkanes with functionalized Michael acceptors, starting from simple building blocks. In this chapter, we report the enantio- and diastereoselective conjugate addition of nitroethane and nitropropane to enone diester electrophiles (Scheme 6-1b).

Scheme 6-2. The Challenge of Diastereoselectivity in Nitroalkane Conjugate Additions

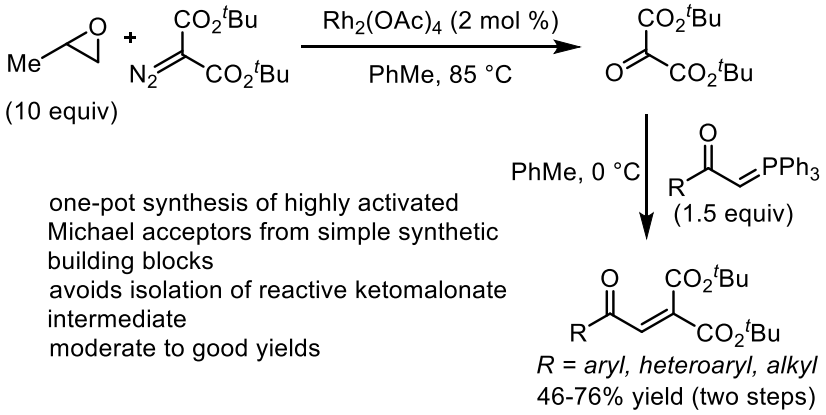


6.3 Results and Discussion

6.3.1 Synthesis of Starting Materials by One-pot Sequence

With the aim of exploiting these highly activated substrates and delivering useful functionality in the derived products, we initiated conjugate addition reaction studies with enone diester **6.1a**. The preparation of this electrophile was achieved by a one-pot reaction wherein di-*tert*-butyl 2-diazomalonate was subjected to oxo transfer under the action of Rh(II)/propylene oxide, and the resulting ketone underwent Wittig olefination with a stabilized ylide (Scheme 6-3).[3-4] The telescoped sequence avoided the problematic hydration issues associated with isolating ketomalonates.[5] Using this reaction sequence, we synthesized a variety of enone diesters in moderate to good yields.

Scheme 6-3. One-pot Synthesis of Enone Diesters



6.3.2 Optimization of Conjugate Addition Reaction

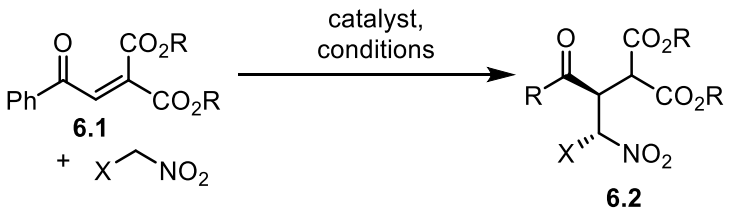
Having established a synthetic path to access enone diesters **6.1**, we began optimization of the stereoselective addition of nitroalkanes. By screening chiral Brønsted bases known to enable this transformation, we identified triaryliminophosphorane **C3**, a bifunctional compound

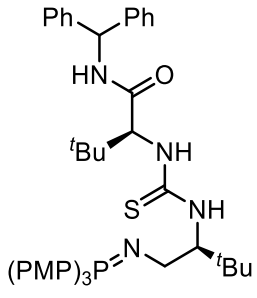
pioneered in the Dixon laboratory, as a suitable catalyst.[6] Evaluating the effect of solvent and the identity of the diester present in **6.1** allowed us to maximize the stereoselectivity and yield. Using catalyst **C1** we observed poor reactivity at cryogenic temperatures (and even at room temperature; entries 1-2). A promising er of 13:87 was obtained with **C2** at -60 ºC. The yield and enantioselectivity was improved by switching to **C3** (entry 3). A solvent screen (entries 4-8) allowed us to identify diethyl ether as the optimal solvent for the reaction. Switching the ester groups of the substrate to ^{t}Bu esters (entry 9) and using nitroethane (entry 10) allowed us into achieve our highest yields and stereoselectivities.

6.3.3 Reaction Scope

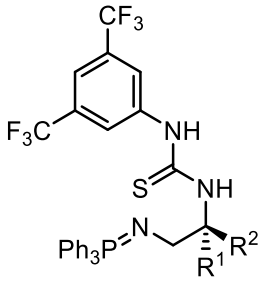
Applying the optimized conditions to the parent substrate **6.1a**, the reaction proceeds with >20:1 diastereoselection and 97:3 er, with 88% isolated yield (Table 6-2). We observed similar reaction outcomes with halogen-substituted arenes **6.2b**-**6.2d**. X-ray diffraction analysis of **6.2d** allowed us to determine the absolute stereochemical outcome of the reaction.[7] Other electron-deficient enone diesters **6.1e**-**6.1g** provided the desired products in high stereoselectivity and yield. When we turned our attention to the electron-donating substituents present in **6.1h**-**6.1j** (4-methoxy, 3-methoxy, piperonyl), we found similar results regardless of the specific substitution pattern. A study into furan (**6.1k**), thiophene (**6.1l**), and pyridine heterocycles (**6.1m**) also provided products with nearly perfect stereoselectivities and high yields. Aliphatic enones **6.1n** and **6.1o** performed well in the reaction, giving >20:1 dr, with high enantioselectivities and good yields. Finally, we investigated whether homologous nitroalkanes could be employed. A nitropropane addition product was prepared in high stereoselectivity and chemical yield (**6.2p**). On 1 g scale, the reaction of enone diester **6.1a** provided the adduct **6.2a** in nearly perfect stereoselectivity with 86% isolated yield (Scheme 6-4).

Table 6-1. Optimization of Asymmetric Conjugate Addition Reaction





C1

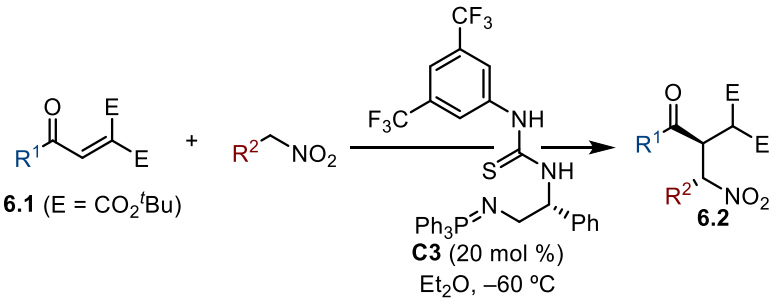


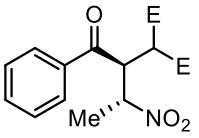
C2 R^1 = H, R^2 = ^{t}Bu
C3 R^1 = Ph, R^2 = H

entry	X (equiv)	R	solvent	catalyst (equiv)	Time (h)	dr	er	Yield[a]
1	H (10.0)	Et	THF	**C1** (0.10)	21	n.a.	n.a.	trace
2[b]	H (10.0)	Et	THF	**C1** (0.10)	19	n.d.	n.d.	(30)
3	H (10.0)	Et	THF	**C2** (0.10)	21	n.a.	13:87	(41)
4	H (10.0)	Et	THF	**C3** (0.10)	21	n.a.	88:12	(62)
5	H (10.0)	Et	EtOAc	**C3** (0.10)	21	n.a.	85.5:14.5	(45)
6	H (10.0)	Et	CH_2Cl_2	**C3** (0.10)	21	n.a.	78:22	(46)
7	H (10.0)	Et	PhMe	**C3** (0.10)	21	n.a.	81:19	(48)
8	H (10.0)	Et	Et_2O	**C3** (0.10)	21	n.a.	89:11	(54)
9	H (10.0)	^{t}Bu	Et_2O	**C3** (0.10)	22	n.a.	93.5:6.5	(47)
10[c]	Me (20.0)	^{t}Bu	Et_2O	**C3** (0.20)	24	>20:1	97:3	88

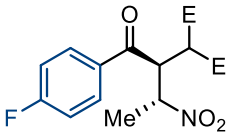
[a] Yields in parentheses represent ^{1}H NMR yields determined using 1,3,5-trimethoxybenzene as an internal standard. [b] Reaction was run at room temperature [c] The dr, er, and yield values for this entry are an average of two trials. n.a. = not applicable, n.d. = not determined.

Table 6-2. Reaction Scope for Asymmetric Conjugate Addition of Nitroalkanes[a]

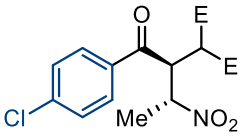




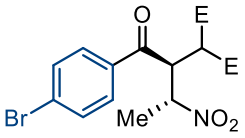
>20:1 dr
97:3 er
88% yield
6.2a[b]



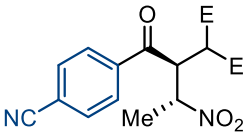
>20:1 dr
97.5:2.5 er
85% yield
6.2b



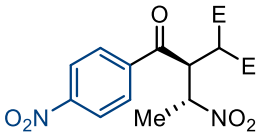
>20:1 dr
99:1 er
89% yield
6.2c



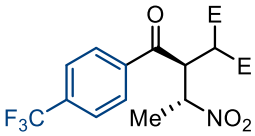
>20:1 dr
98.5:1.5 er
85% yield
6.2d



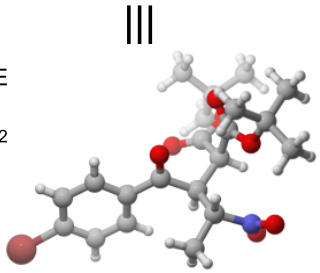
>20:1 dr
96.5:3.5 er
96% yield
6.2e



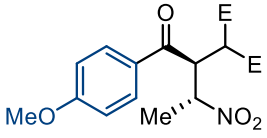
>20:1 dr
97:3 er
91% yield
6.2f



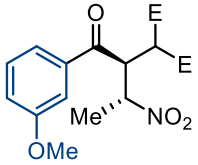
>20:1 dr
99:1 er
94% yield
6.2g



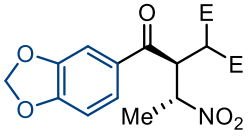
6.2d



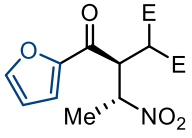
>20:1 dr
96.5:3.5 er
88% yield
6.2h



>20:1 dr
99:1 er
84% yield
6.2i

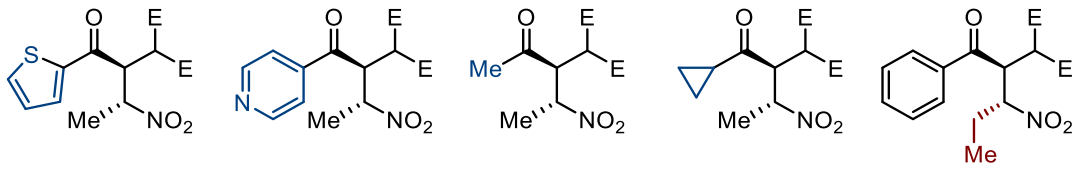


>20:1 dr
98:2 er
80% yield
6.2j



>20:1 dr
99:1 er
95% yield
6.2k

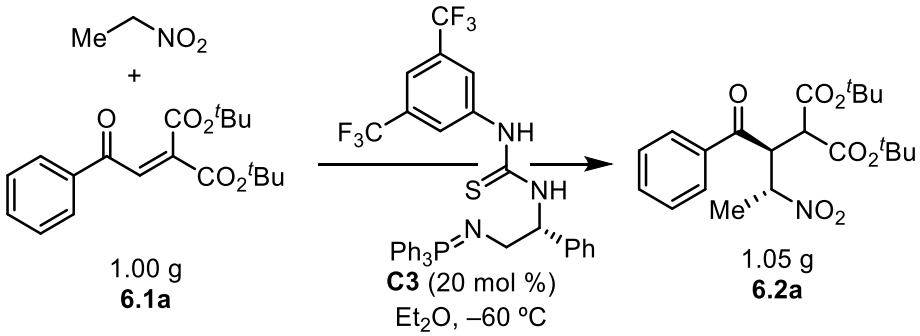
Table 6-2, cont.



>20:1 dr	>20:1 dr	>20:1 dr	>20:1 dr	>20:1 dr
99.5:0.5 er	>99.5:0.5 er	96.5:3.5 er	98:2 er	96.5:3.5 er
92% yield	85% yield	78% yield	83% yield	95% yield
6.2l	**6.2m**	**6.2n**	**6.2o**	**6.2p**

[a] All reactions were conducted on 0.1 mmol scale, using 21.0 equiv $EtNO_2$ or 20.2 equiv *n*-$PrNO_2$. % yields refer to isolated yields. All dr, er, and % yields are the averages of two trials. [b] er was determined by derivatization to dimethyl malonate **6.4a**.

Scheme 6-4. Asymmetric Conjugate Addition Reaction on Gram-Scale



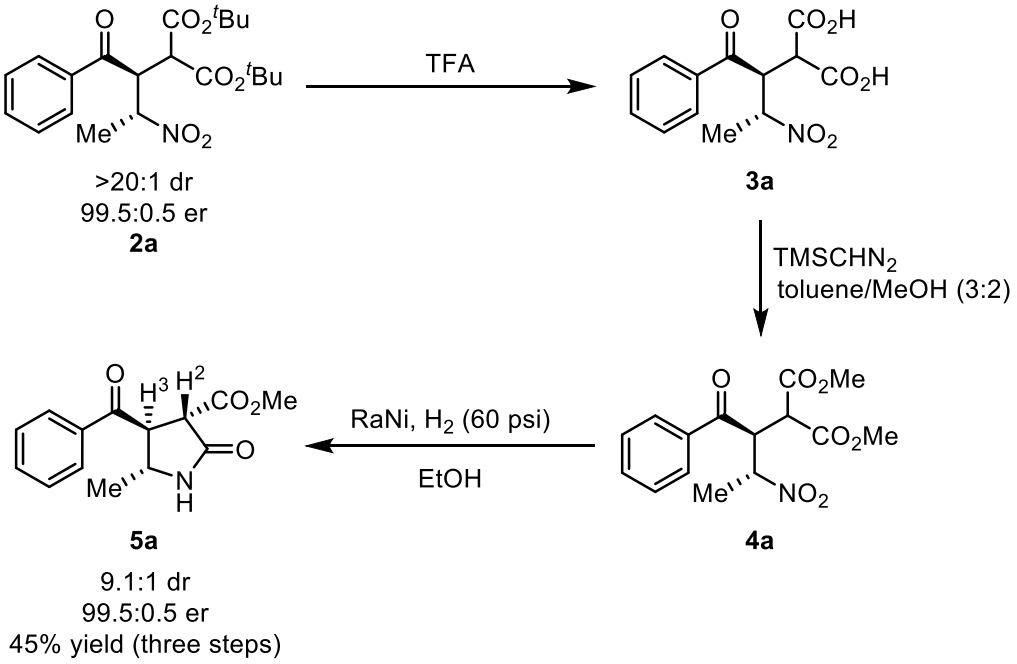
[a] The reaction was conducted using 20.8 equiv $EtNO_2$. % yield refers to isolated yield. Reaction was run for 24h.

6.3.4 Synthesis of Lactam Stereotriad *via* Diastereotopic Group Discrimination

Seeking to take advantage of the diastereotopic ester groups, we developed a three-step local desymmetrization[8] protocol that enables the formation of a new stereocenter with concomitant lactamization (Scheme 6-5). It was necessary to transform the di-*tert*-butyl malonate moiety into a dimethyl malonate to achieve ring closure during the nitro group reduction. The

final lactam **6.5a** was obtained in 9.1:1 dr and 45% yield over three steps while maintaining the same level of enantiopurity as the starting material **6.2a**. Based on the absence of a H^2-H^3 nOe, the three bond coupling constant of 7.5 Hz in CD_3OD (or 8.2 Hz in $CDCl_3$), and strong literature precedent,[9] the benzoyl group and methyl ester were assigned as *trans* on the γ-butyrolactam ring.

Scheme 6-5. Local Desymmetrization *via* Transesterification and Diastereoselective Lactamization



6.4 Conclusion

In summary, we have developed asymmetric organocatalytic conjugate additions of extended nitroalkanes to enone diester electrophiles. A chiral bifunctional iminophosphorane enabled the creation of two adjacent stereocenters with high levels of enantio- and diastereoselectivity. Through subsequent diastereotopic group selection, the establishment of a third stereocenter during formation of a polyfunctional lactam was demonstrated.

6.5 Experimental Details

General Information:

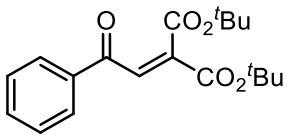
Methods: Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, ^{19}F NMR) were recorded on a Bruker model DRX 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 101 MHz or 151 MHz, 19F NMR at 376 MHz with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet , m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were obtained with a Thermo Fisher Scientific Finnigan^{TM} LTQ-ICR FT^{TM} (all samples prepared in methanol). Melting points were obtained using a Thomas Hoover UniMelt Capillary Melting Point Apparatus. Analytical thin layer chromatography was carried out using Whatman 0.25 mm silica gel 60 plates, Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was allowed by UV light, phosphomolybdic acid in ethanol, or aqueous ceric ammonium nitrate solution. HPLC analysis was performed on a Perkin Elmer flexar photodiode array (PDA) system equipped with Daicel IA, IC, AD, and OD-H columns. Asymmetric reactions were carried out in a Thermo Sigma UCR-150N aluminum block UC reactor with stirring. Purification of the reaction products was carried out by using Siliaflash-P60 silica gel (40- 63μm) purchased from Silicycle. Yields refer to isolated yields after flash column chromatography; some samples contain residual minor diastereomers. Since all asymmetric trial results are the averages of two trials, the stereoisomer ratios listed in the tables may not exactly match those represented in the NMR and HPLC data below.

Materials: Diethyl ether (Et_2O) was passed through a column of neutral alumina under nitrogen prior to use. Wittig reagents were prepared according to a literature procedure.[10] Triaryliminophosphorane catalysts **C1-C3** were prepared according to literature procedures.[6a] Commercially available nitroethane and nitropropane were used as received. Raney®-Nickel 2800 (W.R. Grace and Co. Raney®) slurry in H_2O was used as received.

General procedure for synthesis of enone diesters:

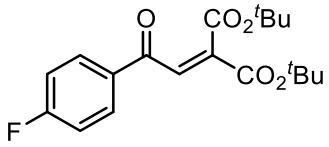
A modified literature procedure was used.[3-4] A flame-dried 100 mL round-bottomed flask equipped with a reflux condenser was charged with $Rh_2(OAc)_4$ (0.046 mmol, 0.02 equiv), toluene (10 mL), and propylene oxide (22.4 mmol, 10.0 equiv). The mixture was heated to 85 ºC in an oil bath for 10 min. Afterwards, a solution of di-*tert*-butyl 2-diazomalonate (2.25 mmol, 1.0 equiv) in toluene (2 mL) was added dropwise. An additional volume of toluene (1 mL) was used to quantitatively transfer. The reaction was stirred at 85 ºC for 1 h before removing the oil bath and allowing the reaction to return to room temperature. The reaction flask was then placed in an ice bath. $MgSO_4$ (500 mg) was added to the reaction, followed by the appropriate Wittig reagent (3.37 mmol, 1.5 equiv). The reaction was allowed to slowly warm to room temperature and was stirred for 16 h. The crude mixture was filtered through a short silica plug with CH_2Cl_2 and concentrated *in vacuo*. The crude materials thusly obtained were purified using flash column chromatography, with the gradient noted below.

Characterization data for enone diesters:

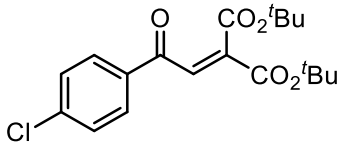


Di-*tert*-butyl 2-(2-oxo-2-phenylethylidene)malonate (6.1a): The title compound was prepared according to the general procedure. 35.0 mmol di-*tert*-butyl 2-diazomalonate was used and all components of the general procedure were scaled appropriately. The crude materials were purified using flash column

chromatography, with a gradient from 95:5 hexanes/EtOAc to 85:15 hexanes/EtOAc. Yellow solid (8.53 g), mp 89-90 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.01-7.99 (m, 2H), 7.68 (s, 1H), 7.65-7.62 (m, 1H), 7.53-7.51 (m, 2H), 1.57 (s, 9H), 1.49 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 189.6, 163.7, 162.2, 138.9, 136.3, 134.0, 133.2, 128.9, 128.9, 83.3, 83.0, 27.9, 27.8. **IR** (thin film) ν 2979, 1724, 1673, 1450, 1369, 1278, 1257, 1156, 1069, 866 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{19}H_{24}NaO_5^+$ ($[M+Na^+]$): 355.1516, found 355.1509. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.32.

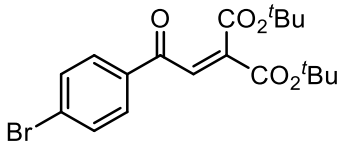


Di-*tert*-butyl 2-(2-(4-fluorophenyl)-2-oxoethylidene)malonate (6.1b): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 95:5 hexanes/EtOAc. Yellow oil (544.0 mg); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.04-8.02 (m, 2H), 7.64 (s, 1H), 7.20-7.18 (m, 2H), 1.56 (s, 9H), 1.50 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.0, 166.3 (d, J = 256.8 Hz), 163.6, 162.1, 139.1, 132.9, 132.8 (d, J = 3.0 Hz), 131.6 (d, J = 9.4 Hz), 116.1 (d, J = 22.1 Hz), 83.4, 83.1, 27.9, 27.8; **^{19}F NMR** (565 MHz, $CDCl_3$) δ -103.18. **IR** (thin film) ν 3437, 2980, 1724, 1673, 1598, 1541, 1369, 1279, 1155, 1070 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{19}H_{23}FNaO_5^+$ ($[M+Na^+]$): 373.1422, found 373.1413. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.34.

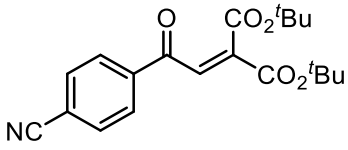


Di-*tert*-butyl 2-(2-(4-chlorophenyl)-2-oxoethylidene)malonate (6.1c): The title compound was prepared according to the general procedure. The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 95:5 hexanes/EtOAc. Yellow solid (528.0 mg), mp 63-64 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 (d, J = 8.6 Hz, 2H), 7.63 (s, 1H), 7.49 (d, J = 8.6 Hz, 2H), 1.56 (s, 9H), 1.50 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.3, 163.6, 162.1, 140.6, 139.4, 134.7, 132.5, 130.2,

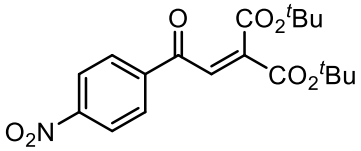
129.2, 83.5, 83.2, 27.9, 27.8. **IR** (thin film) ν 2979, 2934, 1725, 1673, 1589, 1369, 1258, 1158, 1092, 847 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{19}H_{23}ClNaO_5^+$ ([M+Na^+]): 389.1126, found 389.1119. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.34.



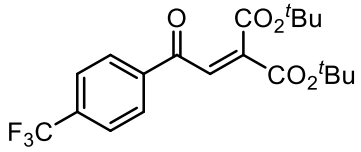
Di-*tert*-butyl 2-(2-(4-bromophenyl)-2-oxoethylidene)malonate (6.1d): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 95:5 hexanes/EtOAc. Light yellow solid (626.6 mg), mp 73-74 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.62 (s, 1H), 1.56 (s, 9H), 1.50 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.5, 163.6, 162.0, 139.5, 135.1, 132.4, 132.2, 130.3, 129.4, 83.5, 83.2, 27.9, 27.8. **IR** (thin film) ν 2979, 2933, 1725, 1672, 1586, 1569, 1369, 1278, 1159, 1071 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{19}H_{23}BrNaO_5^+$ ([M+Na^+]): 433.0621, found 433.0611. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.38.



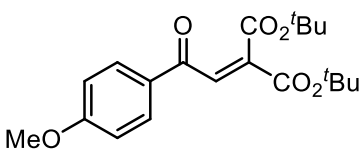
Di-*tert*-butyl 2-(2-(4-cyanophenyl)-2-oxoethylidene)malonate (6.1e): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 90:10 hexanes/EtOAc. Yellow solid (407.2 mg), mp 72-73 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.62 (s, 1H), 1.56 (s, 9H), 1.51 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.3, 163.3, 161.8, 140.4, 139.2, 132.7, 131.6, 129.2, 117.8, 117.1, 83.7, 83.5, 27.9, 27.8. **IR** (thin film) ν 2980, 2935, 2232, 1725, 1677, 1370, 1279, 1158, 1071, 847 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{23}NNaO_5^+$ ([M+Na^+]): 380.1468, found 380.1463. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.14.



Di-*tert*-butyl 2-(2-(4-nitrophenyl)-2-oxoethylidene)malonate (6.1f): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 85:15 hexanes/EtOAc. Yellow solid (598.1 mg), mp 77-78 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.16 (d, *J* = 8.9 Hz, 2H), 7.65 (s, 1H), 1.57 (s, 9H), 1.52 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.0, 163.3, 161.8, 150.7, 140.7, 140.5, 131.5, 129.8, 124.1, 83.8, 83.5, 27.9, 27.8. **IR** (thin film) ν 2980, 2360, 1725, 1678, 1530, 1370, 1347, 1278, 1157, 847 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{19}H_{23}NNaO_7^+$ ([M+Na^+]): 400.1367, found 400.1358. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.28.

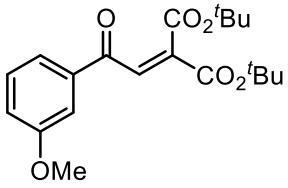


Di-*tert*-butyl 2-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethylidene)malonate (6.1g): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 90:10 hexanes/EtOAc. Yellow oil (550.6 mg); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.66 (s, 1H), 1.60 (s, 9H), 1.51 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.6, 163.4, 161.9, 140.0, 139.0, 135.1 (q, *J* = 32.8 Hz), 132.0, 129.1, 125.9 (m), 123.4 (d, *J* = 273.0 Hz), 83.6, 83.3, 27.9, 27.8; **^{19}F NMR** (565 MHz, $CDCl_3$) δ -63.19. **IR** (thin film) ν 2981, 1726, 1678, 1370, 1326, 1279, 1258, 1161, 1067, 1032 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{23}F_3NaO_5^+$ ([M+Na^+]): 423.1390, found 423.1383. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.34.

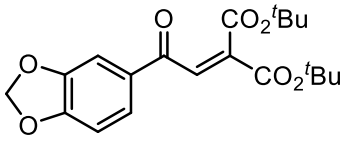


Di-*tert*-butyl 2-(2-(4-methoxyphenyl)-2-oxoethylidene)malonate (6.1h): The title compound was prepared according to the general procedure. The crude materials were

purified using flash column chromatography, with a gradient from pure hexanes to 90:10 hexanes/EtOAc. White solid (612.8 mg), mp 93-94 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 2H), 7.67 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H), 1.56 (s, 9H), 1.50 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 187.9, 164.3, 163.9, 162.4, 138.3, 133.5, 131.3, 129.5, 114.1, 83.2, 82.8, 55.6, 27.9, 27.8. **IR** (thin film) ν 2979, 1724, 1666, 1599, 1512, 1369, 1281, 1257, 1161, 847 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{26}NaO_6^+$ ([M+Na^+]): 385.1622, found 385.1613. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.14.

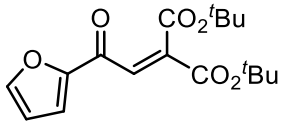


Di-*tert*-butyl 2-(2-(3-methoxyphenyl)-2-oxoethylidene)malonate (6.1i): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 90:10 hexanes/EtOAc. Yellow oil (617.3 mg); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.58-7.56 (m, 1H), 7.52-7.51 (m, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.19-7.17 (m, 1H), 3.88 (s, 3H), 1.56 (s, 9H), 1.50 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 189.3, 163.7, 162.2, 160.0, 139.0, 137.7, 133.1, 129.8, 121.8, 121.0, 112.4, 83.3, 83.0, 55.5, 27.9, 27.8. **IR** (thin film) ν 2979, 1724, 1672, 1597, 1456, 1369, 1278, 1157, 1032, 848 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{26}NaO_6^+$ ([M+Na^+]): 385.1622, found 385.1612. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.25.

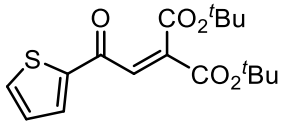


Di-*tert*-butyl 2-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoethylidene)malonate (6.1j): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 80:20 hexanes/EtOAc. Yellow solid (506.0 mg), mp 55-56 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.59 (d, *J* = 8.2, 1H), 7.48 (s, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.09 (s, 2H), 1.56 (s, 9H), 1.51

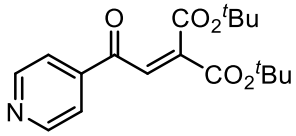
(s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 187.5, 163.8, 162.3, 152.7, 148.6, 138.5, 133.4, 131.3, 126.0, 108.1, 108.1, 102.1, 83.2, 82.9, 27.9, 27.8. **IR** (thin film) ν 2979, 2933, 1723, 1664, 1603, 1505, 1446, 1369, 1259, 1161 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{24}NaO_7^+$ ([M+Na^+]): 399.1414, found 399.1405. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.21.



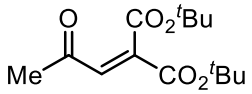
Di-*tert*-butyl 2-(2-(furan-2-yl)-2-oxoethylidene)malonate (6.1k): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 80:20 hexanes/EtOAc. White solid (389.0 mg), mp 67-68 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (m, 1H), 7.58 (s, 1H), 7.36 (d, J = 3.7 Hz, 1H), 6.62 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 1.59 (s, 9H), 1.55 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 175.8, 163.9, 162.0, 152.7, 147.9, 140.0, 129.8, 119.6, 113.0, 83.4, 83.1, 27.9, 27.9. **IR** (thin film) ν 2979, 1732, 1669, 1558, 1465, 1370, 1258, 1158, 1071, 846 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{17}H_{22}NaO_6^+$ ([M+Na^+]): 345.1309, found 345.1302. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.17.



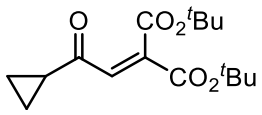
Di-*tert*-butyl 2-(2-oxo-2-(thiophen-2-yl)ethylidene)malonate (6.1l): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 90:10 hexanes/EtOAc. Off-white solid (485.8 mg), mp 84-85 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.83 (dd, J = 3.9, 1.0 Hz, 1H), 7.76 (dd, J = 4.9, 1.0 Hz, 1H), 7.58 (s, 1H), 7.19 (dd, J = 4.9, 3.8 Hz, 1H), 1.56 (s, 18H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 180.7, 163.7, 162.1, 144.2, 139.4, 135.8, 133.7, 131.2, 128.6, 83.4, 83.1, 27.9, 27.9. **IR** (thin film) ν 2979, 1726, 1656, 1516, 1415, 1369, 1282, 1257, 1156, 1066 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{17}H_{22}NaO_5S^+$ ([M+Na^+]): 361.1080, found 361.1073. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.18.



Di-*tert*-butyl 2-(2-oxo-2-(pyridin-4-yl)ethylidene)malonate (6.1m): The title compound was prepared according to the general procedure, but best results were obtained on larger scale. 12.4 mmol di-*tert*-butyl 2-diazomalonate was used and all components of the general procedure were scaled appropriately. The crude materials were purified using flash column chromatography, with a gradient from 95:5 hexanes/EtOAc to 40:60 hexanes/EtOAc. Low-melting red-brown solid (2.23 g); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.87 (br s, 2H), 7.78 (br s, 2H), 7.61 (s, 1H), 1.57 (s, 9H), 1.52 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 188.8, 163.3, 161.8, 151.2, 142.1, 140.7, 130.9, 121.4, 83.8, 83.5, 27.9, 27.8. **IR** (thin film) ν 2979, 1725, 1682, 1370, 1279, 1223, 1158, 1072, 1032, 847 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{18}H_{23}NNaO_5^+$ ([M+Na$^+$]): 356.1468, found 356.1452. **TLC** (40:60 EtOAc/Hexanes): R_f = 0.35.



Di-*tert*-butyl 2-(2-oxopropylidene)malonate (6.1n): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 95:5 hexanes/EtOAc. Clear oil (282.4 mg); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.97 (s, 1H), 2.35 (s, 3H), 1.58 (s, 9H), 1.52 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.4, 163.9, 162.0, 138.1, 133.5, 83.4, 83.1, 30.8, 27.9 (2C). **IR** (thin film) ν 2980, 2935, 1730, 1703, 1369, 1274, 1254, 1159, 1075, 848 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{14}H_{22}NaO_5^+$ ([M+Na$^+$]): 293.1359, found 293.1356. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.24.



Di-*tert*-butyl 2-(2-cyclopropyl-2-oxoethylidene)malonate (6.1o): The title compound was prepared according to the general procedure. The crude materials were purified using flash column chromatography, with a gradient from pure hexanes to 95:5 hexanes/EtOAc. Clear oil (342.4 mg); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.11 (s, 1H), 2.14-2.09

(m, 1H), 1.56 (s, 9H), 1.53 (s, 9H), 1.22-1.19 (m, 2H), 1.07-1.04 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.7, 164.0, 162.2, 137.4, 133.6, 83.2, 82.9, 27.9, 27.9, 22.2, 12.6. **IR** (thin film) ν 2979, 1729, 1686, 1391, 1369, 1256, 1159, 1087, 1062, 917 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{16}H_{24}NaO_5^+$ ([M+Na^+]): 319.1516, found 319.1510. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.29.

General procedure for asymmetric conjugate addition of nitroalkanes:

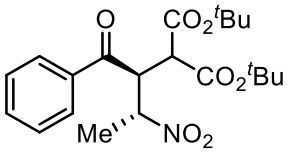
A flame-dried test tube was charged sequentially with enone diester (0.1 mmol, 1.0 equiv), Et_2O (1.0 mL), and nitroethane (2.1 mmol, 21.0 equiv). The reaction was stirred at -60 ºC in a cryogenic cooling apparatus for 15 min, then triaryliminophosphorane catalyst **C1** (0.02 mmol, 0.20 equiv) was added. The reaction was then stirred at -60 ºC for 24 h. After this period, the reaction was quenched with a TFA solution in toluene (50 μL, 0.5 M solution) at the same temperature. Additional Et_2O was used to flush the reaction through a short plug of silica and the filtrate was concentrated *in vacuo*. The crude materials thusly obtained were purified using flash column chromatography with a gradient from 97.5:2.5 hexanes/EtOAc to 90:10 hexanes/EtOAc unless otherwise noted.

Gram scale asymmetric conjugate addition reaction:

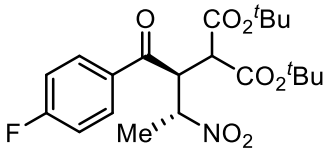
A flame-dried 100 mL round-bottomed flask was charged sequentially with enone diester **1a** (1.00 g, 3.01 mmol, 1.0 equiv), Et_2O (30.0 mL), and nitroethane (4.50 mL, 62.6 mmol, 20.8 equiv). The reaction was stirred at -60 ºC in a cryogenic cooling apparatus for 15 min, then triaryliminophosphorane catalyst **C1** (401.7 mg, 0.60 mmol, 0.20 equiv) was added. The reaction was then stirred at -60 ºC for 24 h. After this period, the reaction was quenched with a TFA solution in toluene (1.5 mL, 0.5 M solution) at the same temperature. Additional Et_2O was used to flush the reaction through a short plug of silica and the filtrate was concentrated *in vacuo*. The crude materials thusly obtained were purified using flash column chromatography with a gradient from

97.5:2.5 hexanes/EtOAc to 90:10 hexanes/EtOAc, yielding 1.05 g (86%) **6.2a** as a white solid in >20:1 dr and >99.5:0.5 er.

Characterization data for conjugate addition products:

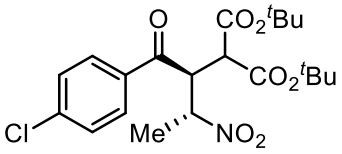


Di-*tert*-butyl 2-(3-nitro-1-oxo-1-phenylbutan-2-yl)malonate (6.2a): The title compound was prepared according to the general procedure. No minor diastereomer was observed in the crude ^{1}H NMR. White solid (34.7 mg), mp 93-94 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.61 (t, 7.4 Hz, 1H), 7.5 (t, *J* = 7.8 Hz, 2H), 4.92-4.86 (m, 2H), 3.87 (d, *J* = 9.8 Hz, 1H), 1.52 (s, 9H), 1.47 (d, 6.7 Hz, 3H), 1.35 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.3, 166.8, 166.2, 137.1, 133.9, 128.8, 128.6, 83.2, 83.0, 82.4, 55.0, 46.5, 27.8, 27.7, 15.3. **IR** (thin film) ν 2979, 1729, 1682, 1557, 1370, 1257, 1143, 842, 734, 692 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{29}NNaO_7^+$ ([M+Na$^+$]): 430.1842, found 430.1831. **HPLC** Derivatized to **4a** for determination of enantiopurity. **TLC** (10:90 EtOAc/Hexanes): R_f = 0.25. **$[\alpha]_D$** = +80.2 (c = 1.5, $CHCl_3$).

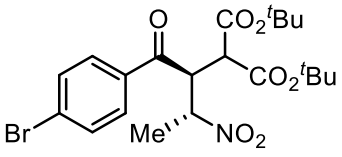


Di-*tert*-butyl 2-(1-(4-fluorophenyl)-3-nitro-1-oxobutan-2-yl)malonate (6.2b): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 3.92 (minor diastereomer) and δ 3.86 (major diastereomer). The crude materials were purified using flash column chromatography, with a gradient from 97.5:2.5 hexanes/EtOAc to 95:5 hexanes/EtOAc. White solid (34.9 mg), mp 89-90 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.17 (t, *J* = 8.6 Hz, 2H), 4.88-4.83 (m, 2H), 3.87 (d, *J* = 9.9 Hz, 1H), 1.53 (s, 9H), 1.48 (d, *J* = 6 Hz, 3H), 1.36 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.7, 166.7, 166.2, 166.2 (d, *J* = 256.7 Hz), 133.6, 131.3 (d, *J* = 9.1 Hz), 116.0 (d, *J* = 21.14 Hz), 83.29,

83.06, 82.37, 54.9, 46.4, 27.8, 27.8, 15.0; **^{19}F NMR** (565 MHz, $CDCl_3$) δ -103.8. **IR** (thin film) ν 2980, 1729, 1683, 1599, 1557, 1394, 1370, 1257, 1158, 848 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{28}FNNaO_7^+$ ([M+Na^+]): 448.1748, found 448.1729. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 98:2, flow rate = 1.0 mL/min, λ = 210 nm, 9.0 min (minor isomer), 16.4 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.16. **$[\alpha]_D$** = +75.2 (c = 1.5, $CHCl_3$).

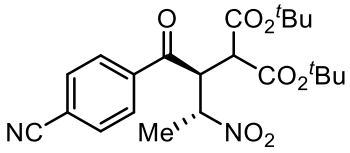


Di-*tert*-butyl 2-(1-(4-chlorophenyl)-3-nitro-1-oxobutan-2-yl)malonate (6.2c): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 3.92 (minor diastereomer) and δ 3.87 (major diastereomer). The crude materials were purified using flash column chromatography, with a gradient from 97.5:2.5 hexanes/EtOAc to 95:5 hexanes/EtOAc. White solid (39.0 mg), mp 83-84 °C (decomp); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 4.89-4.81 (m, 2H), 3.86 (d, *J* = 9.9 Hz, 1H), 1.52 (s, 9H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.36 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.1, 166.6, 166.2, 140.4, 135.5, 130.0, 129.1, 83.3, 83.1, 82.4, 55.0, 46.4, 27.8, 27.7, 15.1. **IR** (thin film) ν 2980, 1728, 1683, 1557, 1370, 1258, 1163, 1093, 846, 736 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{28}ClNNaO_7^+$ ([M+Na^+]): 464.1452, found 464.1435. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 98:2, flow rate = 1.0 mL/min, λ = 210 nm, 9.1 min (minor isomer), 21.8 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.28. **$[\alpha]_D$** = +68.6 (c = 1.5, $CHCl_3$).

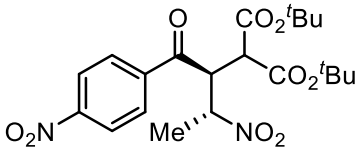


Di-*tert*-butyl 2-(1-(4-bromophenyl)-3-nitro-1-oxobutan-2-yl)malonate (6.2d): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at

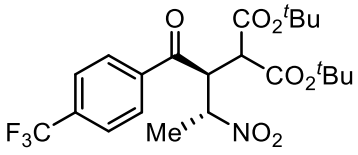
δ 3.92 (minor diastereomer) and δ 3.86 (major diastereomer). Some residual minor diastereomer was still present in the isolated material. The crude materials were purified using flash column chromatography, with a gradient from 97.5:2.5 hexanes/EtOAc to 95:5 hexanes/EtOAc. White solid (41.1 mg), mp 80-81 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 4.88-4.81 (m, 2H), 3.86 (d, J = 10.1 Hz, 1H), 1.52 (s, 9H), 1.48 (d, J = 6.7 Hz, 3H), 1.36 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.4, 166.6, 166.2, 135.9, 132.1, 130.1, 129.3, 83.3, 83.1, 82.4, 55.0, 46.4, 27.8, 27.7, 15.1. **IR** (thin film) ν 2979, 1728, 1683, 1557, 1370, 1258, 1144, 1072, 845, 738 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{28}BrNNaO_7^+$ ([M+Na$^+$]): 508.0947, found 508.0928. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 98:2, flow rate = 1.0 mL/min, λ = 210 nm, 12.9 min (minor isomer), 32.9 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.31. **$[\alpha]_D$** = +61.4 (c = 1.5, $CHCl_3$).



Di-*tert*-butyl 2-(1-(4-cyanophenyl)-3-nitro-1-oxobutan-2-yl)malonate (6.2e): The title compound was prepared according to the general procedure. No minor diastereomer was observed in the crude ^{1}H NMR. White solid (41.3 mg), mp 116-117 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 4.86-4.81 (m, 2H), 3.89 (d, J = 10.1 Hz, 1H), 1.54 (s, 9H), 1.50 (d, J = 6.7 Hz, 3H), 1.37 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.5, 166.4, 166.3, 140.1, 132.6, 128.9, 117.9, 116.8, 83.6, 83.4, 82.3, 55.1, 46.4, 27.8, 27.7, 14.8. **IR** (thin film) ν 2980, 2360, 1727, 1688, 1557, 1370, 1294, 1257, 1143, 848 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{22}H_{28}N_2NaO_7^+$ ([M+Na$^+$]): 455.1794, found 455.1782. **HPLC** Chiralpak IC column, Hex/^{i}PrOH = 99:1, flow rate = 1.0 mL/min, λ = 254 nm, 41.1 min (minor isomer), 43.2 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.11. **$[\alpha]_D$** = +47.5 (c = 1.5, $CHCl_3$).

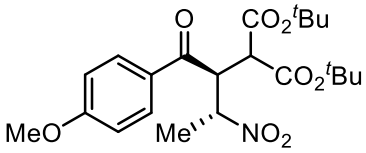


Di-*tert*-butyl 2-(3-nitro-1-(4-nitrophenyl)-1-oxobutan-2-yl)malonate (6.2f): The title compound was prepared according to the general procedure. No minor diastereomer was observed in the crude ^{1}H NMR. White solid (42.1 mg), mp 109-110 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.7 Hz, 2H), 4.86 (d, *J* = 8.8 Hz, 2H), 3.90 (d, *J* = 10.1 Hz, 1H), 1.54 (s, 9H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.38 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.4, 166.4, 166.3, 150.5, 141.6, 129.6, 123.9, 83.6, 83.5, 82.3, 55.1, 46.7, 27.8, 27.7, 14.8. **IR** (thin film) ν 2980, 2936, 2349, 1727, 1530, 1346, 1258, 1144, 850, 734 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{21}H_{28}N_2NaO_9^+$ ([M+Na$^+$]): 475.1693, found 475.1681. **HPLC** Chiralpak OD-H column, Hex/^{i}PrOH = 99:1, flow rate = 1.0 mL/min, λ = 254 nm, 11.8 min (major isomer), 13.9 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.28. **$[\alpha]_D$** = +47.2 (c = 1.5, $CHCl_3$).

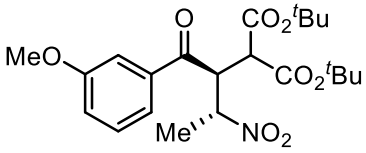


Di-*tert*-butyl 2-(3-nitro-1-oxo-1-(4-(trifluoromethyl)phenyl)butan-2-yl)malonate (6.2g): The title compound was prepared according to the general procedure. No minor diastereomer was observed in the crude ^{1}H NMR. Yellow solid (46.0 mg), mp 68-69 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.16 Hz, 2H), 4.87 (d, *J* = 7.7 Hz, 2H), 3.89 (d, 9.8 Hz, 1H), 1.53 (s, 9H), 1.50 (d, *J* = 6.1 Hz, 3H), 1.37 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.7, 166.5, 166.3, 139.8, 134.8 (q, *J* = 33.2 Hz), 128.9, 125.8 (q, *J* = 3 Hz), 123.5 (q, *J* = 273.3 Hz), 83.4, 83.3, 82.3, 55.0, 46.6, 27.8, 27.7, 15.0; **^{19}F NMR** (565 MHz, $CDCl_3$) δ -63.2. **IR** (thin film) ν 2981, 2937, 1728, 1689, 1558, 1371, 1325, 1169, 1067, 850 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{22}H_{28}F_3NNaO_7^+$ ([M+Na$^+$]): 498.1716, found 498.1696. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 98:2, flow rate = 1.0 mL/min, λ = 215 nm, 6.5 min

(minor isomer), 20.0 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.29. **$[\alpha]_D$** = +67.1 (c = 1.5, $CHCl_3$).

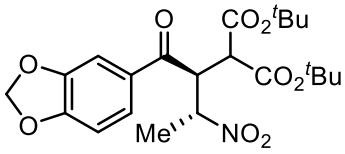


Di-*tert*-butyl 2-(1-(4-methoxyphenyl)-3-nitro-1-oxobutan-2-yl)malonate (6.2h): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 5.05-4.99 (minor diastereomer) and δ 4.90-4.83 (major diastereomer). Some residual minor diastereomer was still present in the isolated material. White solid (37.6 mg), mp 63-64 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.89-4.84 (m, 2H), 3.89 (s, 3H), 3.86 (d, *J* = 9.7 Hz, 1H), 1.52 (s, 9H), 1.47 (d, *J* = 6.5 Hz, 3H), 1.34 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.3, 166.9, 166.2, 164.2, 131.0, 130.1, 114.0, 83.1, 82.8, 82.6, 55.5, 54.9, 46.3, 27.8, 27.7, 15.2. **IR** (thin film) ν 2979, 2360, 1729, 1672, 1601, 1556, 1263, 1168, 1030, 846 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{22}H_{31}NNaO_8^+$ ([M+Na^+]): 460.1948, found 460.1926. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 98:2, flow rate = 1.0 mL/min, λ = 210 nm, 20.3 min (minor isomer), 29.0 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.17. **$[\alpha]_D$** = +77.9 (c = 1.5, $CHCl_3$).

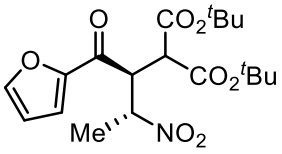


Di-*tert*-butyl 2-(1-(3-methoxyphenyl)-3-nitro-1-oxobutan-2-yl)malonate (6.2i): The title compound was prepared according to the general procedure. No minor diastereomer was observed in the crude ^{1}H NMR. White solid (37.1 mg), mp 80-81 °C (decomp); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.49 (s, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.91-4.84 (m, 2H), 3.88 (s, 3H), 3.85 (d, signal overlap prevents *J* value calculation, 1H), 1.52 (s, 9H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.35 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.9, 166.8, 166.2, 159.8,

138.3, 129.8, 121.4, 120.6, 112.5, 83.2, 83.0, 82.4, 55.5, 55.0, 46.7, 27.8, 27.7, 15.4. **IR** (thin film) ν 2979, 2937, 1729, 1683, 1557, 1456, 1370, 1270, 1144, 840 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{22}H_{31}NNaO_8^+$ ([M+Na^+]): 460.1948, found 460.1926. **HPLC** Chiralpak OD-H column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 205 nm, 25.3 min (major isomer), 50.5 min (minor isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.17. **$[\alpha]_D$** = +38.3 (c = 1.5, $CHCl_3$).

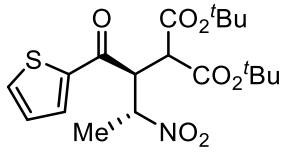


Di-*tert*-butyl 2-(1-(benzo[d][1,3]dioxol-5-yl)-3-nitro-1-oxobutan-2-yl)malonate (6.2j): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 3.93 (minor diastereomer) and δ 3.85 (major diastereomer). White solid (35.8 mg), mp 91-92 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.08 (s, 2H), 4.88-4.83 (m, 1H), 4.79 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.85 (d, *J* = 10.2 Hz, 1H), 1.52 (s, 9H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.37 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 194.9, 166.8, 166.2, 152.6, 148.4, 131.9, 125.4, 108.2, 108.1, 102.1, 83.2, 82.9, 82.5, 55.0, 46.4, 27.8, 27.7, 15.2. **IR** (thin film) ν 3443, 2937, 2349, 1728, 1673, 1556, 1444, 1260, 1144, 1038 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{22}H_{29}NNaO_9^+$ ([M+Na^+]): 474.1740, found 474.1717. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 96:4, flow rate = 1.0 mL/min, λ = 205 nm, 13.9 min (minor isomer), 18.5 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.22. **$[\alpha]_D$** = +77.5 (c = 1.5, $CHCl_3$).

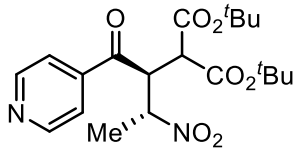


Di-*tert*-butyl 2-(1-(furan-2-yl)-3-nitro-1-oxobutan-2-yl)malonate (6.2k): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 3.93

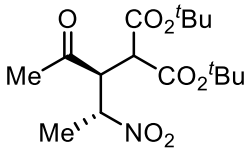
(minor diastereomer) and δ 3.81 (major diastereomer). White solid (38.0 mg), mp 88-89 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.65 (app s, 1H), 7.31 (d, *J* = 3.6 Hz, 1H), 6.59 (dd, *J* = 3.5, 2.7 Hz, 1H), 4.91-4.86 (m, 1H), 4.62 (dd, *J* = 10.4, 5.1 Hz, 1H), 3.82 (d, *J* = 10.4 Hz, 1H), 1.52 (d, signal overlap prevents *J* value calculation, 3H), 1.51 (s, 9H), 1.37 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 184.6, 166.5, 166.0, 152.5, 147.6, 118.9, 112.9, 83.2, 83.0, 82.3, 54.2, 47.6, 27.8, 27.7, 15.0. **IR** (thin film) ν 2980, 2359, 1730, 1674, 1558, 1466, 1296, 1144, 842, 768 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{19}H_{27}NNaO_8^+$ ([M+Na^+]): 420.1635, found 420.1623. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 96:4, flow rate = 1.0 mL/min, λ = 210 nm, 10.4 min (minor isomer), 11.8 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.15. **$[\alpha]_D$** = +65.2 (c = 1.5, $CHCl_3$).



Di-*tert*-butyl 2-(3-nitro-1-oxo-1-(thiophen-2-yl)butan-2-yl)malonate (6.2l): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 3.93 (minor diastereomer) and δ 3.83 (major diastereomer). White solid (39.4 mg), mp 100-101 °C (decomp); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 3.8, 0.8 Hz, 1H), 7.72 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.16 (dd, *J* = 4.8, 4.0 Hz, 1H), 4.94-4.87 (m, 1H), 4.66 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.82 (d, *J* = 10.2 Hz, 1H), 1.53 (d, *J* = 7.2 Hz, 3H), 1.51 (s, 9H), 1.35 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 189.0, 166.6, 165.9, 144.4 135.7, 133.5, 128.6, 83.3, 83.0, 82.5, 54.6, 48.6, 27.8, 27.6, 15.2. **IR** (thin film) ν 2980, 1730, 1660, 1557, 1415, 1370, 1256, 1144, 838, 733 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{19}H_{27}NNaO_7S^+$ ([M+Na^+]): 436.1406, found 436.1394. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 98:2, flow rate = 1.0 mL/min, λ = 215 nm, 14.1 min (minor isomer), 22.6 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.23. **$[\alpha]_D$** = +80.6 (c = 1.5, $CHCl_3$).

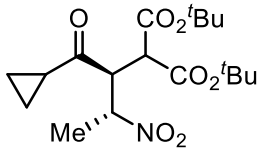


Di-*tert*-butyl 2-(3-nitro-1-oxo-1-(pyridin-4-yl)butan-2-yl)malonate (6.2m): The title compound was prepared according to the general procedure. No minor diastereomer was observed in the crude ^{1}H NMR. The crude materials were purified using flash column chromatography with a gradient from 90:10 hexanes/EtOAc to 60:40 hexanes/EtOAc. White solid (35.3 mg), mp 95-96 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4.6 Hz, 2H), 7.76 (d, *J* = 4.6 Hz, 2H), 4.88-4.84 (m, 1H), 4.79 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.88 (d, *J* = 10.4 Hz, 1H), 1.53 (s, 9H), 1.51 (d, *J* = 6.9 Hz, 3H), 1.37 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.3, 166.4, 166.2, 151.0, 143.0, 121.3, 83.5 (2C), 82.3, 55.1, 46.4, 27.8, 27.7, 15.1. **IR** (thin film) ν 3438, 2980, 2935, 1727, 1696, 1557, 1370, 1257, 1144, 845 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{20}H_{29}N_2O_7^+$ ([M+H$^+$]): 409.1974, found 409.1958. **HPLC** Chiralpak IC column, Hex/^{i}PrOH = 95:5, flow rate = 1.0 mL/min, λ = 225 nm, 12.1 min (minor isomer), 18.3 min (major isomer). **TLC** (20:80 EtOAc/Hexanes): R_f = 0.19. **$[\alpha]_D$** = +55.5 (c = 1.5, $CHCl_3$).

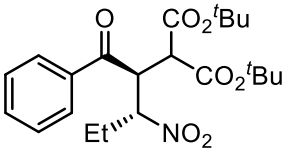


Di-*tert*-butyl 2-(2-nitro-4-oxopentan-3-yl)malonate (6.2n): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 3.66 (minor diastereomer) and δ 3.60 (major diastereomer). The crude materials were purified using flash column chromatography, with a gradient from 97.5:2.5 hexanes/EtOAc to 95:5 hexanes/EtOAc. Low-melting white solid (26.3 mg); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.73-4.69 (m, 1H), 4.02 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.62 (d, *J* = 10.4 Hz, 1H), 2.30 (s, 3H), 1.50 (s, 12H), 1.45 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.5, 166.6, 166.4, 83.2, 83.0, 82.0, 54.6, 52.0, 32.5, 27.8 (2C), 14.7. **IR** (thin film) ν 2980, 1724, 1557, 1477, 1458, 1395, 1316, 1144, 1256, 847 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{16}H_{27}NNaO_7^+$

([M+Na$^+$]): 368.1685, found 368.1671. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 99:1, flow rate = 1.0 mL/min, λ = 210 nm, 6.3 min (minor isomer), 10.2 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.34. **[α]$_D$** = +30.8 (c = 1.5, $CHCl_3$).



Di-*tert*-butyl 2-(1-cyclopropyl-3-nitro-1-oxobutan-2-yl)malonate (6.2o): The title compound was prepared according to the general procedure. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the resonances at δ 3.77 (minor diastereomer) and δ 3.62 (major diastereomer). The crude materials were purified using flash column chromatography, with a gradient from 97.5:2.5 hexanes/EtOAc to 95:5 hexanes/EtOAc. White solid (33.3 mg), mp 64-65 °C (decomp); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.76-4.72 (m, 1H), 4.32 (dd, *J* = 10.6, 4.7 Hz, 1H), 3.64 (d, *J* = 10.7 Hz, 1H), 2.02-1.98 (m, 1H), 1.50 (s, 9H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 1.17-1.12 (m, 1H), 1.05-1.01 (m, 2H), 0.98-0.95 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.2 166.7, 166.3, 83.1, 82.7, 81.7, 54.2, 53.3, 27.8 (2C), 22.7, 14.6, 13.3, 12.9. **IR** (thin film) ν 2980, 2359, 1730, 1556, 1393, 1370, 1294, 1256, 1146, 843 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{18}H_{29}NNaO_7^+$ ([M+Na$^+$]): 394.1842, found 394.1826. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 99:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.9 min (minor isomer), 30.1 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.36. **[α]$_D$** = +36.5 (c = 1.5, $CHCl_3$).

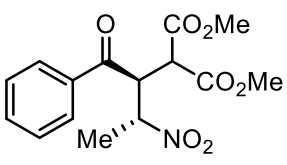


Di-*tert*-butyl 2-(3-nitro-1-oxo-1-phenylpentan-2-yl)malonate (6.2p): The title compound was prepared according to the general procedure. No minor diastereomer was observed in the crude ^{1}H NMR. White solid (41.7 mg), mp 99-100 °C (decomp); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.4 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 4.79 (dd, *J* = 9.4, 6.0 Hz, 1H), 4.73-4.68 (m, 1H), 3.87 (d,

J = 9.4 Hz, 1H), 1.94-1.82 (m, 1H), 1.78-1.68 (m, 1H), 1.51 (s, 9H), 1.35 (s, 9H), 0.88 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.3, 166.7, 166.2, 137.2, 133.8, 128.8, 128.6, 89.9, 83.1, 83.0, 55.2, 46.4, 27.8, 27.7, 23.5, 10.8. **IR** (thin film) ν 2979, 1741, 1683, 1556, 1370, 1258, 1144, 845, 735, 692 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{22}H_{31}NNaO_7^+$ ([M+Na$^+$]): 444.1999, found 444.1981. **HPLC** Chiralpak AD column, Hex/^{i}PrOH = 98:2, flow rate = 1.0 mL/min, λ = 210 nm, 11.1 min (minor isomer), 14.1 min (major isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.27. **$[\alpha]_D$** = +78.3 (c = 1.5, $CHCl_3$).

Procedure for transesterification of 6.2a:

A one dram vial with a stir bar was charged with di-*tert*-butyl ester **6.2a** (0.058 mmol, 1.0 equiv) and trifluoroacetic acid (0.5 mL). The reaction was stirred for 30 min, then placed under a stream of nitrogen to evaporate volatiles. The residue was dissolved in 3:2 toluene:MeOH (1 mL, 0.06 M) and cooled in an ice bath. A solution of $TMSCHN_2$ (2.0 M in Et_2O) was added dropwise until a yellow color persisted. The reaction was stirred for 30 min at room temperature then quenched dropwise with glacial acetic acid; the acid was added until the yellow color disappeared. After stirring for 30 min, ethyl acetate was used to dilute the crude reaction and the organic layer was washed with an aqueous saturated sodium bicarbonate solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude materials thusly obtained were purified using flash column chromatography with a gradient from 97.5:2.5 hexanes/EtOAc to 90:10 hexanes/EtOAc.



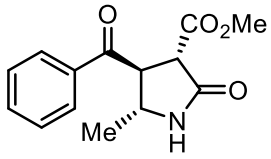
Dimethyl 2-(3-nitro-1-oxo-1-phenylbutan-2-yl)malonate (6.4a): The diastereomeric ratio of the isolated material was determined by ^{1}H NMR spectroscopic analysis by comparison of the resonances at δ 4.22 (minor diastereomer) and δ 4.08 (major diastereomer). Clear oil (16.4 mg); **^{1}H NMR** (600 MHz, $CDCl_3$)

δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.65-7.63 (m, 1H), 7.54-7.51 (m, 2H), 4.98 (dd, *J* = 9.2, 6.5 Hz, 1H), 4.96-4.91 (m, 1H), 4.08 (d, *J* = 9.2 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 1.47 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.3, 167.8, 167.7, 136.8, 134.1, 128.9, 128.7, 82.3, 53.3, 53.2, 52.6, 46.7, 16.5. **IR** (thin film) ν 2956, 1738, 1682, 1596, 1579, 1437, 1281, 1198, 968, 698 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{15}H_{17}NNaO_7^+$ ([M+Na^+]): 346.0897, found 346.0893. **HPLC** Chiralpak IC column, Hex/^{i}PrOH = 97:3, flow rate = 1.0 mL/min, λ = 210 nm, 27.3 min (major isomer), 44.1 min (minor isomer). **TLC** (10:90 EtOAc/Hexanes): R_f = 0.07. **$[\alpha]_D$** = +58.8 (c = 0.5, $CHCl_3$).

Local desymmetrization sequence for transesterification/lactamization of 6.2a:

A scintillation vial with a stir bar was charged with di-*tert*-butyl ester **6.2a** (0.25 mmol, 1.0 equiv) and cooled in an ice bath. Trifluoroacetic acid (1.25 mL) was added slowly and the reaction was stirred for 30 min in the ice bath. The reaction was then placed under a stream of nitrogen to evaporate volatiles. The residue was dissolved in 3:2 toluene:MeOH (2.5 mL, 0.1 M) and cooled in an ice bath. A solution of $TMSCHN_2$ (2.0 M in Et_2O) was added dropwise until a yellow color persisted. The reaction was stirred for 30 min at room temperature and then cooled in an ice bath while it was quenched dropwise with glacial acetic acid; the acid was added until the yellow color disappeared. The reaction was allowed to return to room temperature and stir for 30 min. Ethyl acetate was used to dilute the crude reaction and the organic layer was washed with an aqueous saturated sodium bicarbonate solution. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were dried with sodium sulfate, filtered, and concentrated *in vacuo*. ^{1}H NMR analysis of this crude material indicated that it was >20:1 dr. The material was concentrated into a scintillation vial, where it was dissolved in EtOH (2.0 mL) and treated with Raney®-Nickel 2800 slurry in H_2O (250 mg). The reaction was placed in a high pressure Parr reactor under H_2 (60 psi); the vessel was filled and purged three times before finally refilling and

allowing the reaction to stir for 24 h at room temperature. The crude reaction was flowed through a Celite® plug with EtOH and concentrated *in vacuo*. The diastereomeric ratio could not be discerned from the crude ^{1}H NMR. The crude materials were purified using flash column chromatography, with a gradient from 60:40 hexanes/EtOAc to 40:60 hexanes/EtOAc to obtain the lactam product.



Methyl 4-benzoyl-5-methyl-2-oxopyrrolidine-3-carboxylate (6.5a): The title compound was prepared according to the above procedure. The diastereoselectivity could not be determined from the crude ^{1}H NMR. Once isolated, the product was found to be 9.1:1 dr, which was determined by compared the signals in the ^{1}H NMR at δ 1.38 (major) and δ 1.34 (minor). Clear oil (29.3 mg); **^{1}H NMR** (600 MHz, CD_3OD) δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.70-7.67 (m, 1H), 7.58-5.55 (m, 2H), 4.38 (dd, *J* = 7.4, 6.0 Hz, 1H), 3.89 (d, *J* = 7.5 Hz, 1H), 3.88-3.85 (m, 1H), 3.75 (s, 3H), 1.38 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, CD_3OD) δ 197.8, 171.1, 169.8, 135.9, 133.7, 128.7, 128.4, 52.0, 51.9, 51.7, 51.7, 20.3. **IR** (thin film) ν 3231, 2954, 2359, 1705, 1596, 1448, 1381, 1264, 1219, 697 cm^{-1}. **HRMS** (ESI): Calcd. For $C_{14}H_{15}NNaO_4^+$ ([M+Na$^+$]): 284.0893, found 284.0895. **HPLC** Chiralpak IA column, Hex/^{i}PrOH = 92:8, flow rate = 1.0 mL/min, λ = 210 nm, 16.8 min (minor isomer), 22.7 min (major isomer). **TLC** (50:50 EtOAc/Hexanes): R_f = 0.19. **$[\alpha]_D$** = +3.15 (c = 1.25, $CHCl_3$).

REFERENCES

[1] (a) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005,** *7*, 1967. (b) Dong, X.-Q.; Teng, H.-L.; Wang, C.-J. *Org. Lett.* **2009,** *11*, 1265. (c) Dai, Q.; Arman, H.; Zhao, J. C.-G. *Chem. Eur. J.* **2013,** *19*, 1666. (d) Kwiatkowski, P.; Cholewiak, A.; Kasztelan, A. *Org. Lett.* **2014,** *16*, 5930. (e) Li, N.; Liu, G.-G.; Chen, J.; Pan, F.-F.; Wu, B.; Wang, X.-W. *Eur. J. Org. Chem.* **2014,** *2014*, 2677. (f) Zhang, G.; Zhu, C.; Liu, D.; Pan, J.; Zhang, J.; Hu, D.; Song, B. *Tetrahedron* **2017,** *73*, 129.

[2] Examples of diastereoselectivity challenges in conjugate addition reactions of extended nitroalkanes: (a) Crossley, M. J.; Fung, Y. M.; Potter, J. J.; Stamford, A. W. *J. Chem. Soc., Perkin Trans. 1* **1998,** *6*, 1113. (b) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2006,** *348*, 2047. (c) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008,** *130*, 13524. (d) Yang, W.; Du, D.-M. *Org. Lett.* **2010,** *12* 5450. (e) Manzano, R.; Andrés, J. M.; Álvarez, R.; Muruzábal, M. D.; de Lera, Á., R.; Pedrosa, R. *Chem. Eur. J.* **2011,** *17*, 5931. (f) Deng, Y.-Q.; Zhang, Z.-W.; Feng, Y.-H.; Chan, A. S. C.; Lu, G. *Tetrahedron: Asymmetry* **2012,** *23*, 1647. (g) Kawada, M.; Nakashima, K.; Hirashima, S.-i.; Yoshida, A.; Koseki, Y.; Miura, T. *J. Org. Chem.* **2017,** *82*, 6986.

[3] Stachel, H.-D.; Schorp, M.; Zoukas, T. *Liebigs Ann. Chem.* **1992,** *1992*, 1039.

[4] Okuro, K.; Alper, H. *J. Org. Chem.* **2012,** *77*, 4420.

[5] (a) Dei, T.; Morino, K.; Sudo, A.; Endo, T. *J. Polym. Sci. A Polym. Chem.* **2011,** *49*, 2245. (b) Santos, M. S.; Coelho, F. *RSC Adv.* **2012,** *2*, 3237. (c) Sivan, A.; Deepthi, A. *Tetrahedron Lett.* **2014,** *55*, 1890.

[6] Development of catalyst family and recent applications: (a) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013,** *135*, 16348. (b) Goldys, A. M.; Dixon, D. J. *Macromolecules* **2014,** *47*, 1277. (c) Goldys, A. M.; Núñez, M. G.; Dixon, D. J. *Org. Lett.* **2014,** *16*, 6294. (c) Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015,** *137*, 15992. (d) Robertson, G. P.; Farley, A. J. M.; Dixon, D. J. *Synlett* **2016,** *27*, 21. (e) Horwitz, M. A.; Zavesky, B. P.; Martinez-Alvarado, J. I.; Johnson, J. S. *Org. Lett.* **2016,** *18*, 36. (f) Yang, J.; Farley, A. J. M.; Dixon, D. J. *Chem. Sci.* **2017,** *8*, 606.

[7] CCDC1563042 contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.ui/data_request/cif.

[8] Horwitz, M. A.; Johnson, J. S. *Eur. J. Org. Chem.* **2017,** *2017*, 1381.

[9] (a) Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006,** *8*, 2183. (b) Wang, J.; Li, W.; Liu, Y.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2010,** *12*, 1280. (c) Chowdhury, R.; Vamisetti, G. B.; Ghosh, S. K. *Tetrahedron: Asymmetry* **2014,** 516. (d)

Montoya-Balbás, I. J.; Valentín-Guevara, B.; López-Mendoza, E.; Linzaga-Elizalde, I.; Ordoñez, M.; Román-Bravo, P. *Molecules* **2015,** *20*, 22028.

[10] Matviitsuk, A.; Taylor, J. E.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Chem. Eur. J.* **2016,** *22*, 11748.