

**I. ENANTIOSELECTIVE METALLOPHOSPHITE-CATALYZED AZA-BENZOIN REACTION BETWEEN ACYL SILANES AND NITRONES**

**II. LANTHANUM TRICYANIDE-CATALYZED ACYL SILANE-KETONE BENZOIN ADDITIONS AND KINETIC RESOLUTION OF RESULTANT  $\alpha$ -SILYLOXYKETONES**

**III. BIS-FUNCTIONALIZATION OF GLYOXYLATE FOR THE SYNTHESIS OF FULLY SUBSTITUTED GLYCOLIC ACIDS**

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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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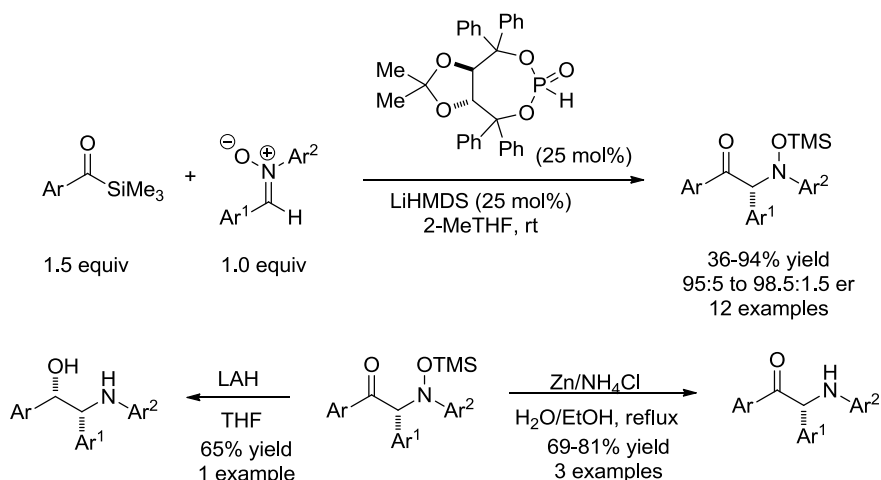
## ABSTRACT

JAMES CHRISTOPHER TARR:

- I. Enantioselective Metallophosphite-Catalyzed Aza-Benzoin Reaction Between Acyl Silanes and Nitrones
  - II. Lanthanum Tricyanide-Catalyzed Acyl Silane-Ketone Benzoin Additions and Kinetic Resolution of Resultant  $\alpha$ -Silyloxyketones
  - III. Bis-Functionalization of Glyoxylate for the Synthesis of Fully Substituted Glycolic Acids
- (Under the direction of Professor Jeffrey Scott Johnson)

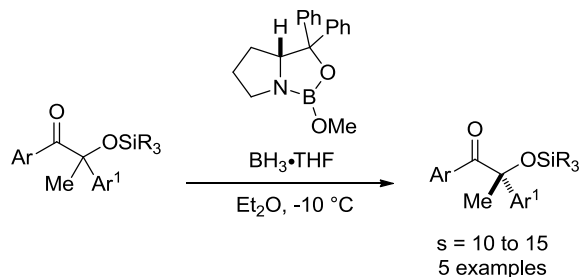
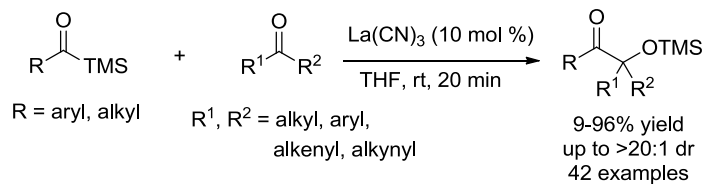
### **I. Enantioselective Metallophosphite-Catalyzed Aza-Benzoin Reaction Between Acyl Silanes and Nitrones**

The asymmetric *C*-acylation of nitrones was developed. TADDOL-derived metallophosphites catalyze the enantioselective addition of acyl silanes to nitron electrophiles. The product  $\alpha$ -*N*-silyloxyamino ketones were obtained in 36-94% yield and greater than 95:5 er. The methodology is scalable, as the yield and er of the products were essentially constant as the scale of the reaction was increased over three orders of magnitude. The products can be further elaborated by reduction of the N–O bond and ketone functionality with negligible loss of optical purity. The nitron oxygen is essential in facilitating the silyl transfer necessary for catalyst turnover. This reaction constitutes the first example of *C*-acylation of nitrones and the most highly enantioselective methodology to date for the addition of acyl anion equivalents to azomethine electrophiles.



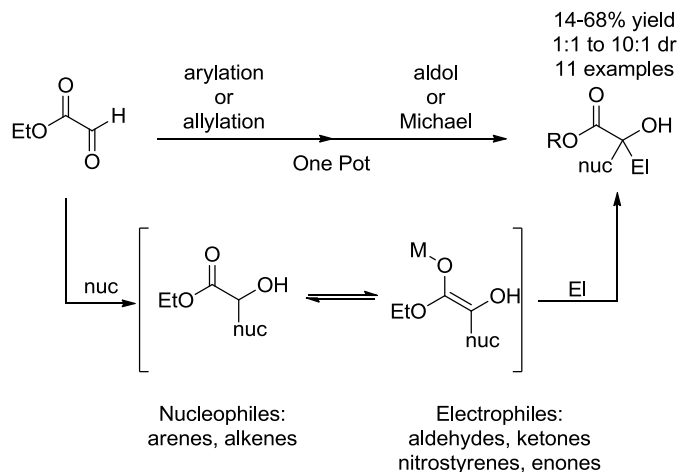
## II. Lanthanum Tricyanide-Catalyzed Acyl Silane-Ketone Benzoin Additions and Kinetic Resolution of Resultant $\alpha$ -Silyloxyketones

An intermolecular cyanide-catalyzed coupling of acyl silanes and ketones has been developed. The reaction scope encompasses alkyl and aryl acyl silanes and aryl-alkyl, alkyl-alkyl, aryl-aryl, alkenyl-alkyl, and alkynyl-alkyl ketones. In cyclic systems, good to excellent diastereocontrol is observed for equatorial attack. The reaction conditions can be tuned so that either the Felkin-Ahn or chelation-controlled product is obtained when acyclic protected  $\alpha$ -hydroxyketones are employed. The resultant  $\alpha$ -silyloxyketones can be resolved with selectivity factors ranging from 10 to 15 via CBS reduction.



### III. Bis-Functionalization of Glyoxylate for the Synthesis of Fully Substituted Glycolic Acids

Current progress towards the development of ethyl glyoxylate as a conjunctive reagent in the three component coupling between ethyl glyoxylate, a nucleophile, and an electrophile is described. The addition of unactivated arene and alkene nucleophiles followed by one-pot electrophilic trapping with aldehydes, Michael acceptors, and ketones has been demonstrated.



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## TABLE OF CONTENTS

<b>LIST OF TABLES .....</b>	<b>xii</b>
<b>LIST OF FIGURES AND SCHEMES .....</b>	<b>xiii</b>
<b>LIST OF ABBREVIATIONS AND SYMBOLS .....</b>	<b>xvii</b>
<b>CHAPTER I    ENANTIOSELECTIVE METALLOPHOSPHITE-                  CATALYZED AZA-BENZOIN REACTION                  BETWEEN ACYL SILANES AND NITRONES .....</b>	<b>1</b>
1.1    Introduction.....	1
1.2 $\alpha$ -Amino Ketones .....	7
1.3    Preliminary Results .....	12
1.4    Results and Discussion .....	15
1.4.1    Optimization of aza-Benzoin Reaction.....	15
1.4.2    Substrate Scope .....	21
1.4.3    Further Synthetic Manipulations.....	26
1.5    Alternative Acyl Donors .....	29
1.6    Conclusions.....	30
1.7    Experimental Section.....	31
1.8    References .....	50
<b>CHAPTER II    LANTHANUM TRICYANIDE-CATALYZED                  ACYL SILANE-KETONE BENZOIN                  ADDITIONS AND KINETIC RESOLUTION                  OF RESULTANT <math>\alpha</math>-SILYLOXYKETONES.....</b>	<b>54</b>
2.1    Introduction.....	54
2.2    Background .....	56

2.3	Results and Discussion .....	59
2.3.1	Discovery and Optimization of Acyl Silane-Ketone Silyl Benzoin Reactions .....	59
2.3.2	Scope: Ketone Partner.....	61
2.3.3	Diastereoselectivity of Reaction .....	65
2.3.4	Scope: Enones .....	70
2.3.5	Scope: Acyl Silane .....	73
2.3.6	Retro-Benzoin Reaction.....	75
2.3.7	Kinetic Resolution .....	77
2.4	Conclusions.....	81
2.5	Experimental Section .....	81
2.6	References .....	125
 <b>CHAPTER III BIS-FUNCTIONALIZATION OF GLYOXYLATE FOR THE SYNTHESIS OF FULLY SUBSTITUTED GLYCOLIC ACIDS .....</b>		 <b>128</b>
3.1	Introduction.....	128
3.2	Background .....	133
3.3	Results and Discussion .....	138
3.3.1	Addition of Organometallic Reagents to Ethyl Glyoxylate.....	138
3.3.2	Addition of Nucleophiles to Ethyl Glyoxylate Without Prior Functionalization or Activation .....	142
3.3.3	Attempts for Stepwise Aldol Reaction under Basic Conditions .....	147
3.3.4	Development of Stepwise Aldol Reaction under Lewis Acidic Conditions .....	151
3.3.5	Development of One-Pot Protocols for Bis- Functionalization of Ethyl Glyoxylate.....	153

3.4	Conclusions.....	161
3.5	Experimental Section.....	163
3.6	References.....	194

## LIST OF TABLES

Table 1.1	Screen of Bases in Aza-Benzoin Reaction.....	17
Table 1.2	Screen of Amine Ligands in Aza-Benzoin Reaction .....	18
Table 1.3	Slow Addition of Nitron.....	20
Table 2.1	Optimization of M(CN) <sub>3</sub> Catalyst.....	61
Table 2.2	Optimization of Chelation Control in Addition to Protected Acetoin .....	67
Table 2.3	Optimization of Felkin-Ahn Control in Addition to Protected Acetoin .....	68
Table 2.4	Scope of $\alpha,\beta$ -Unsaturated Coupling Partners.....	72
Table 3.1	Optimization of PhMgBr Addition to Ethyl Glyoxylate.....	139
Table 3.2	Scope of Addition of Organometallic Reagents to Ethyl Glyoxylate .....	140
Table 3.3	Scope of Addition of Organometallic Reagents to <i>tert</i> -Butyl Glyoxylate .....	141
Table 3.4	Friedel-Crafts Reaction of Arenes and Ethyl Glyoxylate .....	143
Table 3.5	Screening of Carbonyl-ene Reaction of $\alpha$ -Methyl Styrene and Ethyl Glyoxylate .....	145
Table 3.6	Variety of Alkenes Able to Undergo Carbonyl-ene Reaction .....	146
Table 3.7	Optimization of Addition of Allyl Trimethylsilane to Ethyl Glyoxylate .....	147
Table 3.8	Optimization of One-Pot Friedel-Crafts Alkylation/Aldol Reaction .....	154
Table 3.9	Lewis Acid Screen for Aldol Reaction of Ethyl Mandelate .....	159

## LIST OF FIGURES AND SCHEMES

Figure 1.1	Seebach's Analysis of Heteroatom Substituted Chains .....	2
Figure 1.2	Retro-Synthesis of Aldol, Michael, Benzoin, and Stetter Products .....	3
Scheme 1.1	Electrophilic Acylation <i>via</i> Dithiane .....	3
Scheme 1.2	Mechanism of Cyanide-Catalyzed Benzoin Reaction .....	4
Scheme 1.3	Benzoin and Stetter Reactions Catalyzed by <i>N</i> -Heterocyclic Carbenes .....	5
Scheme 1.4	Mechanism of Cyanide-Catalyzed Silyl Benzoin Reaction .....	6
Scheme 1.5	Metallophosphite-Catalyzed Cross Silyl Benzoin and Sila-Stetter Reactions .....	7
Figure 1.3	Biologically Active Molecules Bearing $\alpha$ -Amino Ketones or Derivatives Thereof .....	8
Scheme 1.6	Racemic and Asymmetric Imine Acylation <i>via</i> NHC Catalysis .....	9
Scheme 1.7	Mechanistic Studies on NHC-Catalyzed Imine Acylation .....	10
Scheme 1.8	Scheidt's Imine Acylation with Acyl Silanes .....	11
Scheme 1.9	Proposed Metallophosphite-Catalyzed Imine Acylation .....	12
Figure 1.4	Energetics of Silyl Transfer: Imine vs. Nitron .....	13
Scheme 1.10	Phosphite-Nitron Redox Reaction .....	14
Scheme 1.11	Initial Success in Aza-Benzoin Reaction .....	15
Figure 1.5	Screen of Nitron <i>N</i> -Substituents .....	16
Scheme 1.12	Optimized Conditions for Aza-Benzoin Reaction .....	21
Figure 1.6	Substrate Scope for Aza-Benzoin Reaction .....	22
Figure 1.7	Problematic Substrates in Aza-Benzoin Reaction .....	24
Scheme 1.13	Aza-Benzoin Reaction to Yield <b>34j</b> of 10-gram Scale .....	26

Figure 1.8	X-ray Crystal Structure of <b>34j</b> .....	26
Scheme 1.14	Synthetic Manipulations of Aza-Benzoin Products <b>34</b> .....	28
Scheme 1.15	Attempts to Employ Benzil as an Acyl Donor.....	30
Scheme 2.1	Proposed Mechanistic Pathway for Acyl Silane-Ketone Benzoin Reaction and Possible Side Reactions .....	55
Scheme 2.2	NHC-Catalyzed Retro-Benzoin Reaction of Tertiary $\alpha$ -Hydroxyketone .....	56
Scheme 2.3	Intramolecular Ketone-Benzoin Reaction.....	57
Scheme 2.4	Demir's Intermolecular Acyl Phosphonate Ketone-Benzoin Reaction .....	58
Scheme 2.5	Electrophiles Previously Acylated Using Acyl Silanes .....	59
Figure 2.1	Scope of Ketone Coupling Partner .....	62
Figure 2.2	Addition of Acyl Silane to Diaryl Ketones.....	64
Figure 2.3	NOESY Analysis to Determine Equatorial Attack.....	65
Figure 2.4	NOESY Analysis to Confirm Felkin-Ahn and Chelation Controlled Addition.....	68
Scheme 2.6	Optimized Conditions for Achieving Felkin-Ahn or Chelation Control .....	69
Scheme 2.7	Proposed Tandem Aldehyde-Ketone Acylation .....	69
Scheme 2.8	Results from Felkin-Ahn Controlled Addition to Propiophenone Derivatives.....	70
Figure 2.5	Scope of Acyl Silane Coupling Partner .....	74
Figure 2.6	Incompatible Acyl Silane Coupling Partners.....	75
Scheme 2.9	Retro-Benzoin Crossover Experiment .....	75
Scheme 2.10	La(CN) <sub>3</sub> -Catalyzed Retro-Benzoin Reaction.....	76
Scheme 2.11	Mechanistic Rationale for Retro-Benzoin Observations .....	77

Figure 2.7	Chiral Catalysts and Co-Catalysts Screened for Ketone-Benzoin Reaction .....	78
Scheme 2.12	Resolution of <b>5a</b> with <i>R</i> - $\alpha$ -Methylbenzylamine.....	79
Figure 2.8	Kinetic Resolution of $\alpha$ -Silyloxy Ketones via CBS Reduction.....	80
Scheme 2.13	Synthesis of <i>ent</i> - <b>20d</b> to Determine Absolute Stereochemistry.....	81
Scheme 3.1	Brook Rearrangement of Acyl Silanes and Silyl Glyoxylates .....	129
Scheme 3.2	Different Reactivity Patterns of Acyl Silanes and Silyl Glyoxylates .....	130
Scheme 3.3	Multi-Component Couplings Achieved with Silyl Glyoxylates.....	131
Figure 3.1	Natural Products Targeted by Silyl Glyoxylate Coupling Reactions .....	132
Scheme 3.4	Application of Silyl Glyoxylate Coupling to Total Synthesis of Zaragozic Acid C .....	132
Scheme 3.5	Synthesis of Silyl Glyoxylate.....	133
Scheme 3.6	Routes to Access $\alpha$ -Hydroxy or $\alpha$ -Silyloxy Carbonyl Compounds .....	134
Figure 3.2	Nucleophiles to be Evaluated for Tandem Functionalization of Glyoxylates .....	135
Scheme 3.7	Aldol Reactions of Aryl and Allyl Glycolic Esters .....	136
Scheme 3.8	Methods for Asymmetric Aldol Reactions of $\alpha$ -Hydroxy Ketones and Protected Glycine Derivatives .....	137
Scheme 3.9	Goals for Tandem Functionalization of Ethyl Glyoxylate.....	138
Scheme 3.10	Attempts to Add Terminal Alkyne to Ethyl Glyoxylate .....	144
Scheme 3.11	Proposed Strategy for Trapping <b>41</b> with Electrophile .....	148

Figure 3.3	Electrophiles Examined in the Tandem Addition/Electrophilic Trapping Reactions .....	148
Scheme 3.12	One-Pot Functionalization of Ethyl Glyoxylate Through Nucleophilic Addition/Deprotonation/Aldol Sequence .....	150
Scheme 3.13	Attempts to Perform Aldol Reaction Under Phase Transfer Conditions .....	151
Scheme 3.14	Ti(O <sup><i>i</i></sup> Pr) <sub>4</sub> -Promoted Addition of Ethyl Mandelate to Electrophiles .....	152
Scheme 3.15	Ti(O <sup><i>i</i></sup> Pr) <sub>4</sub> -Promoted Aldol Reaction of Aryl Substituted Glycolic Esters .....	153
Scheme 3.16	Scope of One-Pot SnCl <sub>4</sub> -Promoted Arylation/ Ti(O <sup><i>i</i></sup> Pr) <sub>4</sub> -Promoted Aldol Reaction with Ethyl Glyoxylate .....	157
Scheme 3.17	Attempts to Perform Aldol Reaction with Alkyl and Allyl Substituents .....	158
Scheme 3.18	Bu <sub>2</sub> BOTf-Promoted Aldol Reaction of Aliphatic Glycolic Esters .....	160
Scheme 3.19	One-Pot Allylation/Aldol Reactions .....	161
Scheme 3.20	Current Progress on Protocols for Bis-Functionalization of Ethyl Glyoxylate .....	162



## LIST OF ABBREVIATIONS AND SYMBOLS

18-cr-6	18-crown-6 ether
Ac	acetate
Anal.	elemental analysis
Ar	aryl
aq	aqueous
BINOL	1,1'-bi-2-naphthol
box	bisoxazoline
Bn	benzyl
br	broad
bs	broad singlet
<sup>n</sup> Bu	<i>normal</i> -butyl
<sup>t</sup> Bu	<i>tert</i> -butyl
<sup>13</sup> C NMR	carbon nuclear magnetic resonance spectroscopy
C–C	carbon-carbon bond
calcd.	Calculated
CBS	Corey-Bakshi-Shibata
CAN	ceric ammonium nitrate
cat	catalytic amount or catalyst
conv	conversion
Cp	cyclopentadienyl
d	doublet
dd	doublet of doublet

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethyl amine (Hunig's base)
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dr	diastereomeric ratio
<i>E</i>	<i>entgegen</i>
EDG	electron donating group
El	electrophile
<i>ent</i>	enantiomer of
eq	equation
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et <sub>2</sub> O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FID	flame ionization detector
GC	gas chromatography
h	hour
<sup>1</sup> H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high performance liquid chromatography

HRMS	high resolution mass spectroscopy
Hz	hertz
<i>i</i> Pr	isopropyl
IR	infrared spectroscopy
<i>J</i>	coupling constant
kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L*	chiral ligand
L <sub><i>n</i></sub>	ligand
Ln	lanthanide
L.A.	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LRMS	low resolution mass spectroscopy
M	metal or molarity
m	multiplet
Me	methyl
Mes	mesityl
MeOH	methanol
2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	megahertz

min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl protecting group
mp	melting point
MTBE	methyl <i>tert</i> -butyl ether
<i>n</i>	<i>normal</i> or number of atoms or counterions
NaHMDS	sodium hexamethyldisilazide
NBS	<i>N</i> -bromosuccinimide
nd	not determined
NDP	no desired product
NHC	<i>N</i> -heterocyclic carbene
NMP	<i>N</i> -methyl pyrrolidinone
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
nr	no reaction
Nuc	nucleophile
<i>o</i> -	<i>ortho</i>
OMP	<i>ortho</i> -methoxyphenyl
op	optical purity
<i>p</i> -	<i>para</i>
PG	protecting group
Ph	phenyl

PMP	<i>para</i> -methoxyphenyl
ppm	parts per million
<i>i</i> Pr	<i>iso</i> -propyl
pybox	pyridine-2,6-bis(oxazoline)
q	quartet
qn	quintuplet
R	substituent
R <sub>f</sub>	retention factor
R <sub>large</sub>	large substituent
R <sub>small</sub>	small substituent
r.s.m.	recovered starting material
<i>rac</i>	racemic
rt	room temperature
s	singlet
sept	septuplet
SFC	supercritical fluid chromatography
s.m.	starting material
T	temperature
t	triplet
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
TBABr	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl

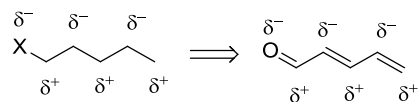
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	tri-isopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethyl ethylenediamine
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
triflate	trifluoromethanesulfonate
Tr	trityl
Ts	<i>para</i> -toluenesulfonyl
UV	ultraviolet
X	anionic ligand, halide, substituent, or number
Z	<i>zusammen</i>
Å	Ångstrom
[α]	optical rotation
Δ	heat
δ	chemical shift or partial charge
μL	microliter
μm	micrometer

## CHAPTER I

# ENANTIOSELECTIVE METALLOPHOSPHITE-CATALYZED AZA-BENZON REACTION BETWEEN ACYL SILANES AND NITRONES<sup>1</sup>

### 1.1 Introduction: Polarity Umpolung

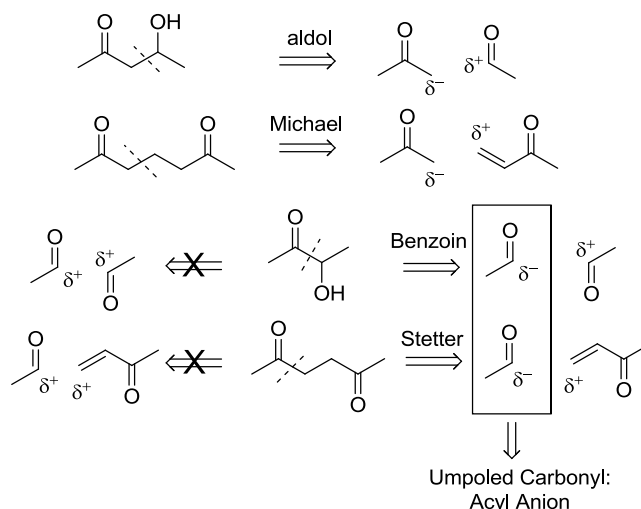
Many of the most common and powerful carbon-carbon bond forming reactions in the organic chemist's synthetic toolkit can be described as polar coupling reactions; i.e. attack by a nucleophile onto an electrophile. Such polar coupling reactions form the basis for the aldol, Michael, Mannich, Henry, Wittig and numerous other reactions. Hence, a crucial component of developing a synthetic strategy to access a target molecule is to identify sites of latent nucleophilicity and electrophilicity that may be utilized in a bond-forming event *via* a dipolar addition. Seebach developed a simple yet powerful retro-synthetic tool for determining the latent electronic character of carbons in a heteroatom-substituted chain (Figure 1.1).<sup>2</sup> Since commonly occurring heteroatoms (N, O, halides) are more electronegative than carbon, inductive polarization places a  $\delta^-$  charge on the heteroatom, a  $\delta^+$  charge on the *ipso* carbon, a  $\delta^-$  charge on the  $\alpha$ -carbon, and so forth. Incorporation of  $\pi$ -bonds in the carbon chain that can delocalize the partial charges can transmit *via* resonance these electronic effects to more remote carbons in the chain.



**Figure 1.1.** Seebach's Analysis of Heteroatom Substituted Chains

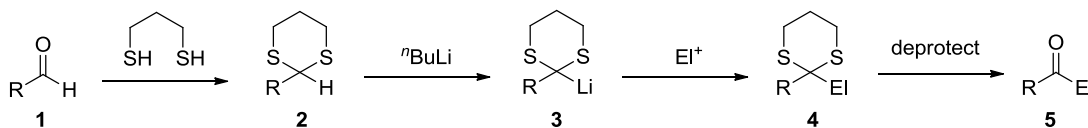
Applying this analysis to the aldol and Michael reactions, one can see that the polarization of the carbonyl reagents is identical to that needed for desired productive coupling (Figure 1.2). Therefore, conventional enolate chemistry gives rise to carbon frameworks with 1,3 and 1,5 heteroatom substitution patterns. Other substitution patterns, however, may require a modified synthetic approach.<sup>2,3</sup> For example,  $\alpha$ -hydroxyketones cannot be synthesized with a straight-forward dipolar coupling strategy as this would require the coupling of two electrophilic sites. This illustrates the need for a polarity reversal, or umpolung, strategy whereby a normally electrophilic site can be rendered nucleophilic or vice versa.<sup>4</sup> In an umpoled carbonyl group, the carbonyl carbon would act as a nucleophile, or acyl anion equivalent. This switch in polarity would allow it to be coupled to an electrophile through a polar addition. As acyl anions and other umpoled reagents are often not stable or accessible (i.e. an acyl anion cannot be generated by deprotonation of an aldehyde), it is often necessary to mask umpoled functionality with a synthetically equivalent group.





**Figure 1.2.** Retro-Synthetic Analysis of Aldol, Michael, Benzoin, and Stetter Products

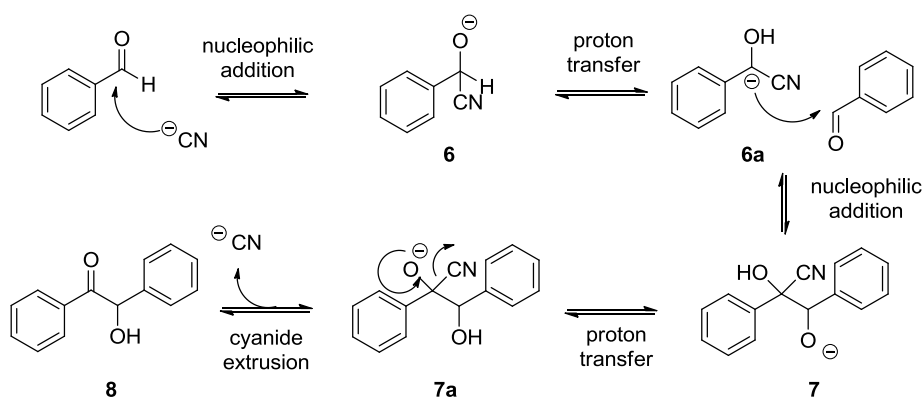
A classic illustration of a polarity umpolung strategy *via* a synthetically equivalent group is the protection of an aldehyde as the dithiane (**1**  $\rightarrow$  **2**) followed by deprotonation and subsequent trapping with an electrophile (Scheme 1.1).<sup>5</sup> As the carbonyl carbon typically bears a partial positive charge, it is usually a site of nucleophilic attack. However, the two anion-stabilizing sulfur atoms of dithiane **2** stabilize formation of an  $\alpha$ -carbanion, making the dithiane proton sufficiently acidic to be deprotonated by a strong base. The intermediate carbanion **3** can then react with an electrophile. Deprotection of dithiane **4** regenerates the initially present carbonyl functionality in product **5** and yields the formal acylation of an electrophile.



**Scheme 1.1.** Electrophile Acylation *via* Dithiane

One of the most widely studied and utilized reactions that proceeds with umpoled reactivity of one of the reagents is the benzoin reaction, the coupling of two aldehydes to yield an  $\alpha$ -hydroxyketone (**8**) in the presence of a nucleophilic catalyst (Scheme 1.2).<sup>6</sup>

The reaction was first described in 1832 when it was found that dimerization of aryl aldehydes was catalyzed by the presence of cyanide anion.<sup>7</sup> A mechanism was later proposed by Lapworth where the metal cyanide adds to the aldehyde yielding **6**.<sup>8</sup> The methine proton of the resultant cyanohydrin is sufficiently acidic to be deprotonated, generating carbon nucleophile **6a**. Nucleophile **6a** can then productively add to a second equivalent of aldehyde. Proton transfer and expulsion of the cyanide catalyst yields the  $\alpha$ -hydroxyketone (or benzoin) (**8**).

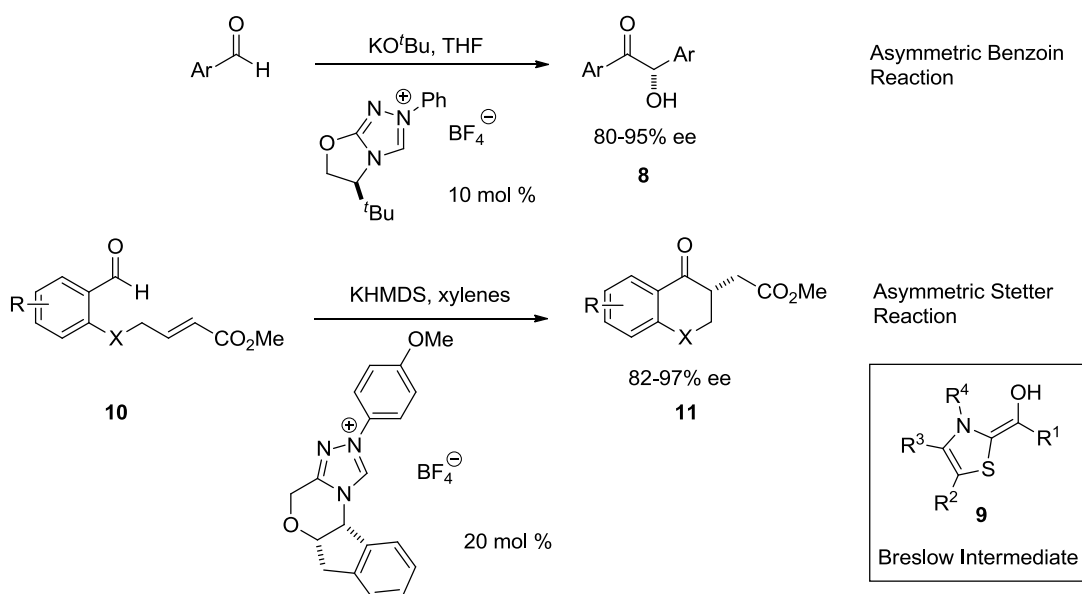


**Scheme 1.2.** Mechanism of Cyanide-Catalyzed Benzoin Reaction

Alternative catalysts to promote benzoin and benzoin-type reactions have been sought in order to impart asymmetric induction to the reaction as well as provide safer alternatives to cyanide catalysts. At various times throughout the catalytic cycle, cyanide or any other viable catalyst must fulfill three roles: 1) a nucleophile; 2) an anion-stabilizing group; 3) a leaving group. Both *N*-heterocyclic carbenes and metallophosphites are capable of meeting each of these requirements and have emerged as scaffolds for asymmetric catalysis in reactions of acyl anion equivalents.

Thiazolium and triazolium salts were found to catalyze the benzoin reaction via a carbene mechanism proposed by Breslow.<sup>9</sup> Treatment of the thiazolium or triazolium salt with a base generates a nucleophilic carbene. Attack of the carbene on an aldehyde

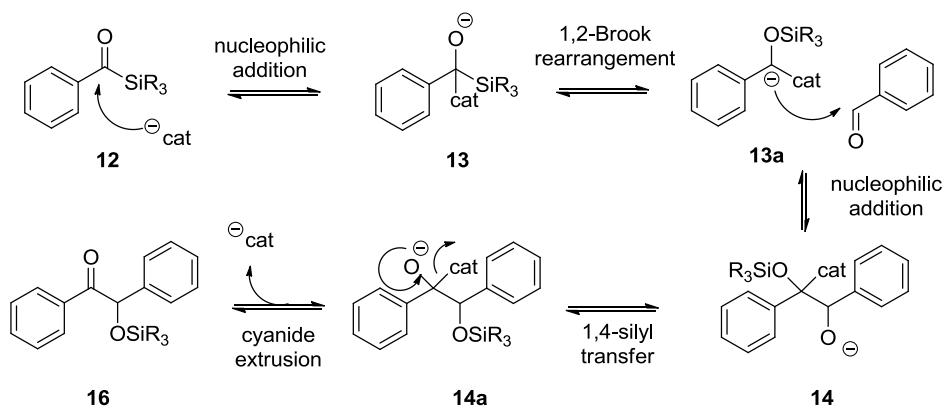
generates a nucleophilic enamine known as the Breslow intermediate (**9**) (Scheme 1.3). Incorporation of a stereodefined R group on the carbene catalyst can result in asymmetric induction in the products. Nucleophilic carbene catalysis has been successfully employed in both the asymmetric benzoin reaction<sup>10</sup> and the asymmetric intra-<sup>11</sup> and intermolecular<sup>12</sup> Stetter reactions (conjugate addition of acyl nucleophile). The inherent advantage of employing *N*-heterocyclic carbenes as asymmetric catalysts is the ability to use aldehydes as the acyl donor, as this avoids synthetic steps to pre-functionalize or mask the acyl anion (Scheme 1.3).



**Scheme 1.3.** Benzoin and Stetter Reactions Catalyzed by *N*-Heterocyclic Carbenes

Acyl silanes<sup>13</sup> can serve as aldehyde surrogates where the aldehyde hydrogen has been replaced by a silyl group and are also capable of undergoing benzoin-type condensations with electrophiles via nucleophilic catalysis. Our group has demonstrated the utility of acyl silanes in the racemic cyanide-catalyzed cross-silyl benzoin reaction (Scheme 1.4).<sup>14</sup> Prefunctionalization of one coupling partner as the acyl silane addresses the longstanding challenge for performing a cross-benzoin reaction between two different

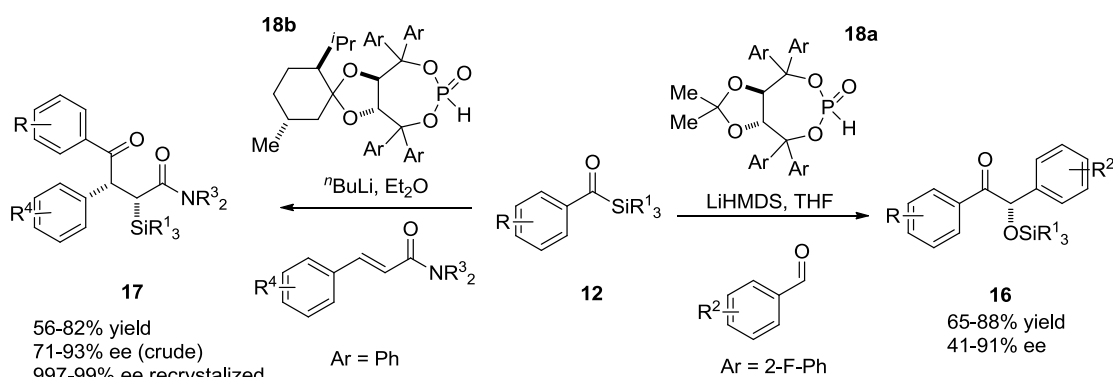
aldehydes with complete regiocontrol. The mechanism for the silyl benzoin reaction is analogous to that for the cyanide-catalyzed benzoin reaction (Scheme 1.4).<sup>14</sup> Upon nucleophilic addition of the catalyst to acyl silane **12**, oxy-anion **13** is formed. Subsequent intramolecular 1,2-silyl migration from carbon to oxygen, known as a [1,2]-Brook rearrangement,<sup>15</sup> furnishes carbanion **13a**. The driving force for the Brook rearrangement is the formation of the strong Si-O bond at the expense of the relatively weak C-Si bond.<sup>16</sup> The Brook rearrangement is further facilitated by electron-withdrawing groups  $\alpha$  to the carbanion and by coordinating solvents. Compound **14** is formed upon attack of **13a** on an electrophile. Following intramolecular 1,4-silyl migration, alkoxide **14a** is formed, which can then extrude the catalyst to regenerate the carbonyl functionality and allow for catalyst turnover. Acyl silanes offer the advantage over aldehydes of allowing the cross silyl benzoin reaction to be conducted with complete regioselectivity. Additionally, acyl silanes are uniquely suitable for undergoing metallophosphite-catalyzed reactions.



**Scheme 1.4.** Mechanism of Cyanide-Catalyzed Silyl Benzoin Reaction

Our group has explored TADDOL-derived metallophosphites as nucleophilic catalysts in the cross silyl benzoin reaction between acyl silanes and aldehydes to achieve

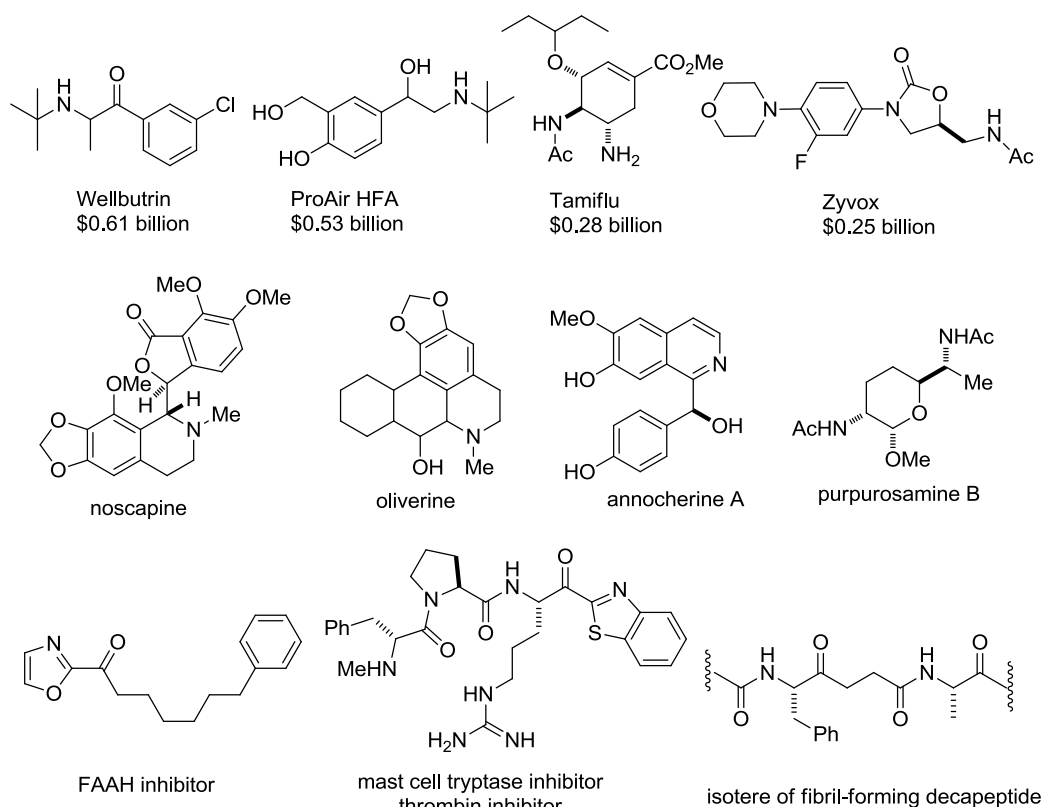
high yields and er's (Scheme 1.5).<sup>17</sup> These catalysts are uniquely effective with acyl silanes, as they do not promote benzoin condensation with other acyl donors (aldehydes,<sup>18</sup> acyl phosphonates,<sup>19</sup> and benzil). The acyl silane/metallophosphite system has also been successfully employed in the intermolecular sila-Stetter reaction between acyl silanes and  $\alpha$ ,  $\beta$ -unsaturated amides (Scheme 1.5).<sup>20</sup> Given these prior successes in nucleophilic acylation, we wished to examine whether the acyl silane/metallophosphite chemistry could be expanded to include C=N acylation in an aza-benzoin-type reaction.



**Scheme 1.5.** Metallophosphite-Catalyzed Cross Silyl Benzoin and Sila-Stetter Reactions

## 1.2 $\alpha$ -Amino Ketones

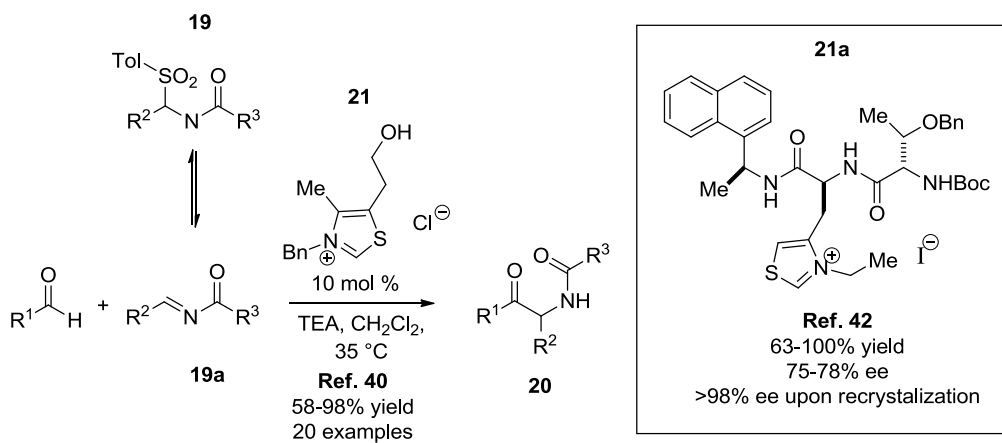
$\alpha$ -Amino ketones are desirable synthetic targets as they serve as useful synthetic building blocks as well as possess interesting biological activities.<sup>21, 22</sup> They can be elaborated into a wide variety of heterocycles.<sup>21, 23</sup> In addition to heterocycle synthesis,  $\alpha$ -amino ketones serve as convenient precursors to amino alcohols, a structural motif that is ubiquitous in ligand architecture as well as biologically active molecules. A survey of pharmaceutical agents, natural products, and enzyme inhibitors demonstrates the vast range of effects  $\alpha$ -aminoketones and their derivatives can impart on biological systems (Figure 1.3).<sup>24-31</sup>



**Figure 1.3.** Biologically Active Molecules Bearing  $\alpha$ -Amino Ketones or Derivatives Thereof

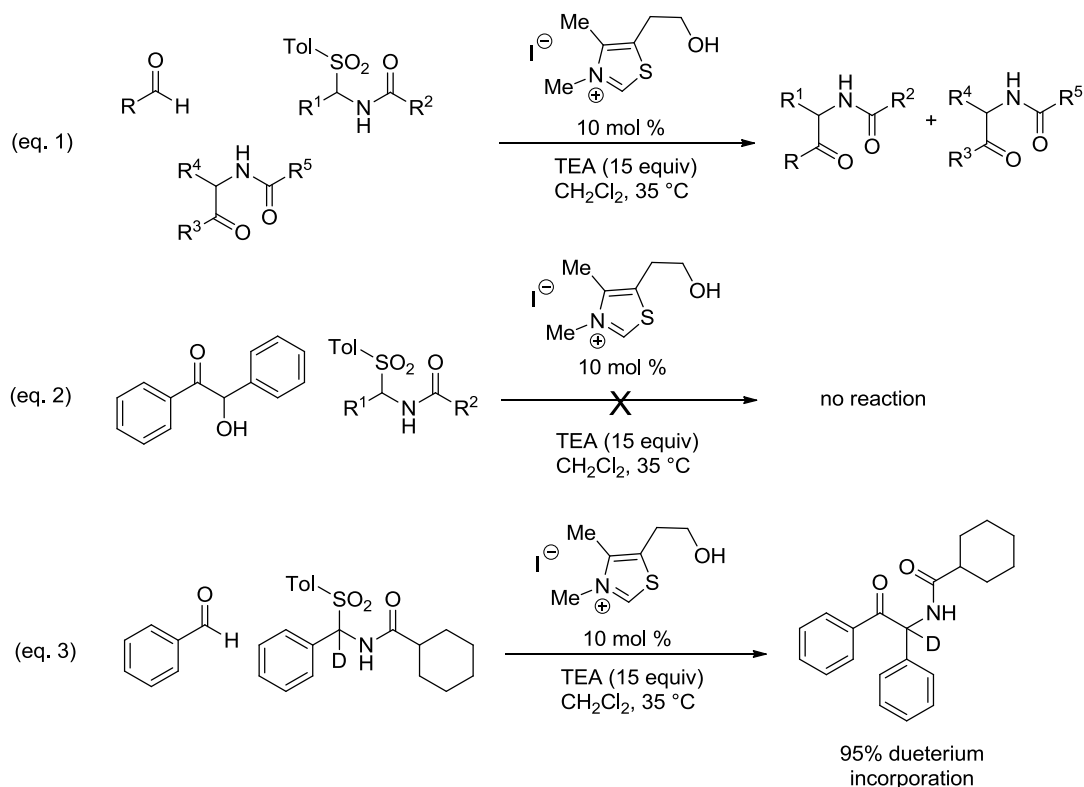
A number of stoichiometric methods exist for the synthesis of  $\alpha$ -amino ketones, with the most common method being the addition of an organometallic agent to a suitably protected amino acid derivative.<sup>32</sup> The Fukuyama,<sup>33</sup> Rovis,<sup>34</sup> and Liebeskind<sup>35</sup> groups have all recently contributed to the development of mild conditions and improvement upon the functional group tolerance for organometallic addition to the amino acid derivatives. However, the products are still limited by the availability of a given amino acid. The *de novo* synthesis of  $\alpha$ -amino ketones has been accomplished by the 1,3-dipolar cycloaddition of aryl azirines,<sup>36</sup> Lewis-acid catalyzed addition of acyl zirconocenes to imines,<sup>37</sup> allylation of imines with geminal dialkoxy zirconocenes,<sup>38</sup> and the addition of lithiodithianes to chiral imines.<sup>39</sup>

In 2001, Murry and Frantz reported the first catalytic approach to coupling acyl anion equivalents with C=N  $\pi$ -bond electrophiles (Scheme 1.6).<sup>40</sup> Employing 10 mol % of thiazolium catalyst **21**, they were able to couple aryl, heteroaryl, and alkyl aldehydes with an *in situ* derived *N*-acyl imine (**19a**) to furnish *N*-acyl  $\alpha$ -amino ketones (**20**).



**Scheme 1.6.** Racemic and Asymmetric Imine Acylation *via* NHC Catalysis

In the course of their studies, they made a number of key mechanistic observations. The products were formed irreversibly, as demonstrated in a crossover experiment. When one amino ketone product was added to a second reaction between different coupling partners, no cross products were isolated (Scheme 1.7, eq. 1). They also observed no benzoin coupling of the aldehyde acyl donor, and  $\alpha$ -hydroxy ketones did not undergo a retro-benzoin reaction to generate the Breslow intermediate to participate in imine coupling (Scheme 1.7, eq. 2). In a key labeling experiment, when deuterium was incorporated at the aldimine site of the imine it was incorporated with high fidelity in the product, indicating that it may be possible to avoid product racemization and that a catalytic asymmetric reaction was plausible (Scheme 1.7, eq. 3).



**Scheme 1.7.** Mechanistic Studies on NHC-Catalyzed Imine Acylation

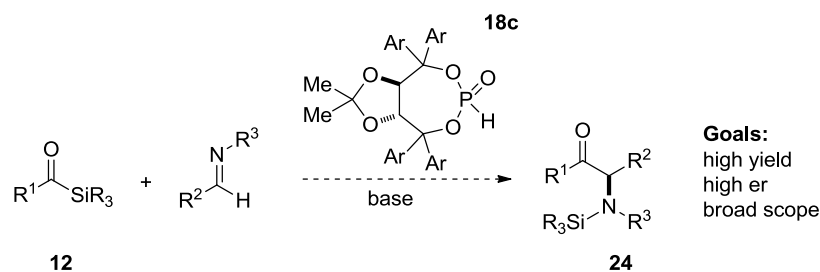
Scheidt reported the first coupling of acyl silanes with phosphoryl imines to access products analogous to those achieved by Murry and Frantz (Scheme 1.8).<sup>41</sup> Scheidt asserted it is necessary to employ the acyl silane to avoid unproductive benzoin condensation, although Murry and Frantz report never observing the benzoin by-product when aldehydes were employed in similar reaction conditions. An important mechanistic aspect is use of an alcoholic solvent, which is postulated to intercept the silylated Breslow intermediate **9b** to afford the desilylated Breslow intermediate **9a** generated in the Murry and Frantz chemistry.





### 1.3 Preliminary Results

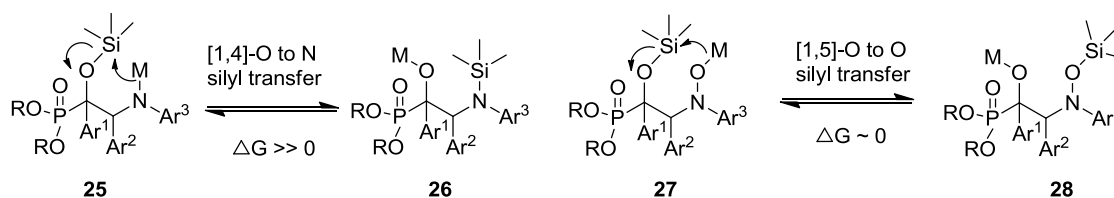
It was our hope that we could bring the metallophosphite-catalyzed acyl silane chemistry to bear on this reaction. We reasoned that metallophosphites, which possess high nucleophilicity while maintaining a low basicity, would be capable of promoting the silyl aza-benzoin reaction without leading to racemization of the products (Scheme 1.9). We believed that we could contribute to this field by extending the reaction to a wider class of substrates, most notably electron-rich and electron-neutral acyl donors. We were also optimistic that we could achieve *er*'s sufficiently high that a post-reaction recrystallization would not be necessary in order to achieve synthetically useful *er*'s.



**Scheme 1.9.** Proposed Metallophosphite-Catalyzed Imine Acylation

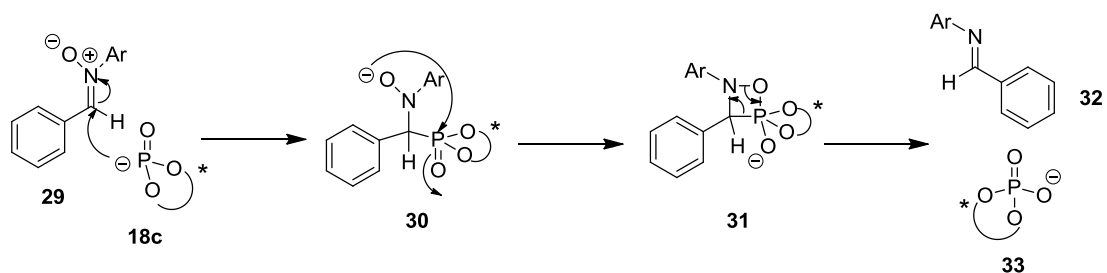
Initial results from our laboratory identified two crucial considerations for a metallophosphite-catalyzed silyl aza-benzoin reaction as compared to an NHC-catalyzed aldehyde/imine aza-benzoin. The first consideration is the intramolecular 1,4-silyl transfer step of the mechanism (Figure 1.4). Analogous to the silyl benzoin reaction, a silyl transfer after addition to the electrophile is required to generate the metal alkoxide intermediate capable of expelling the catalyst and turning over the catalytic cycle. When an aldehyde is employed as the electrophile, the resultant 1,4 O-to-O transfer is thermoneutral.<sup>16</sup> However, silicon forms a uniquely strong bond with oxygen. Therefore, the 1,4 O-to-N silyl transfer that arises from imine electrophiles is

endothermic (Figure 1.4, **25**  $\rightarrow$  **26**).<sup>16</sup> This was corroborated by the fact that all attempts to couple acyl silanes with imines have been unsuccessful using a variety of catalysts (metallophosphite, KCN,  $\text{La}(\text{CN})_3$ ). An intriguing solution to this problem was developed: using nitrones as imine surrogates. Now the requisite silyl-transfer becomes a 1,5 O-to-O transfer, which is again thermoneutral (**27**  $\rightarrow$  **28**). This mechanistic proposal was validated as nitrones were found to be viable coupling partners with acyl silanes.



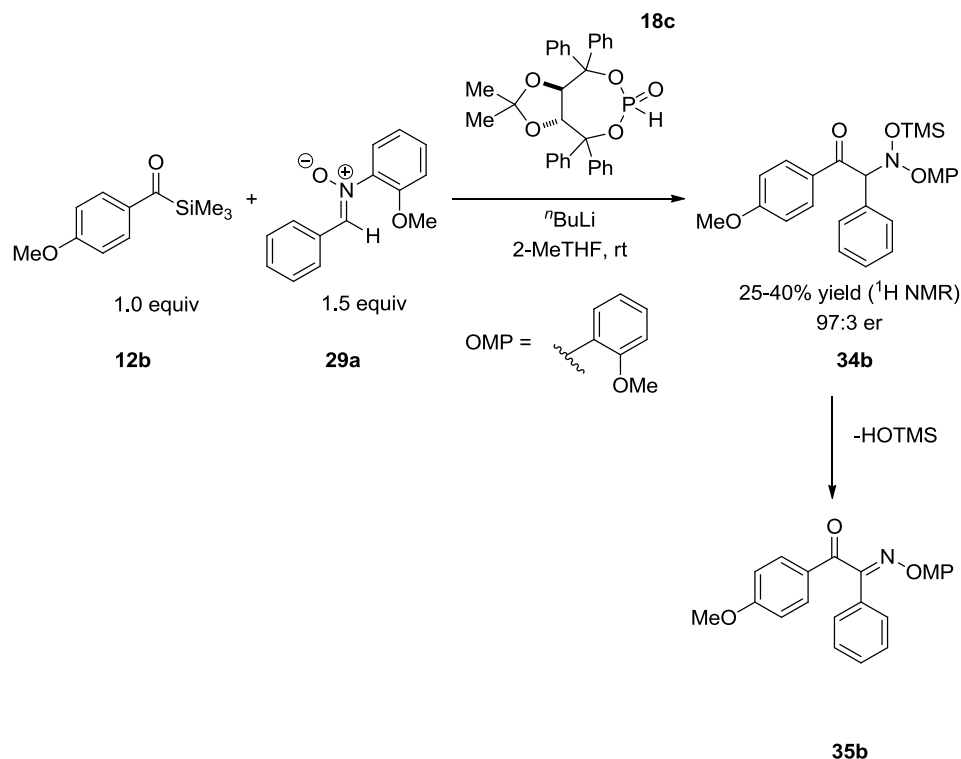
**Figure 1.4.** Energetics of Silyl Transfer: Imine vs. Nitron

A second challenge unique to the metallophosphite catalyst/nitrone reaction system was the occurrence of an irreversible redox pathway (Scheme 1.10). Rather than adding the acyl silane, the metallophosphite could instead add to the nitrone to yield **30**. Subsequent attack of the oxygen on the phosphorus would lead to the formation of intermediate **31**. Collapse of the intermediate as shown would produce reduced imine **32** and oxidized phosphate **33**, which is incapable of promoting the aza-benzoin. Catalyst degradation through this pathway was validated by reacting the metallophosphite with a nitrone in the absence of acyl silane, which resulted in isolation of the reduced imine and catalyst decomposition.



**Scheme 1.10.** Phosphite-Nitron Redox Reaction

Following initial screening, suitable conditions were found to deliver the desired coupling product (Scheme 1.11). Treatment of acyl silane **12b** and aryl nitron **29a** with *R,R*-TADDOL phosphite catalyst **18c** and *n*BuLi in 2-MeTHF afforded the silyloxyamino ketone **34b** in variable yields between 25-40% with incomplete conversions (~40%) and in 97:3 er. Flash column chromatography on silica gel resulted in silyloxy elimination to form imine **35b**. Pre-treatment of the silica gel with 5% TEA/petroleum ether retarded the elimination. While the initial er was excellent, the incomplete conversion and low chemical yield needed to be addressed.



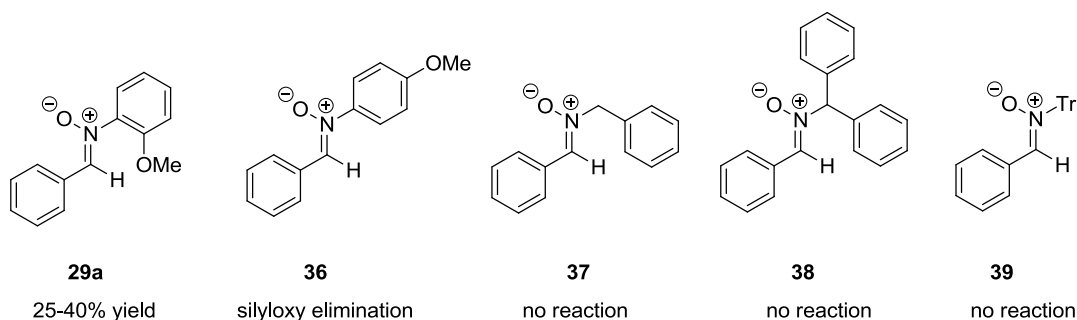
**Scheme 1.11.** Initial Success in Aza-Benzoin Reaction

## 1.4 Results and Discussion

### 1.4.1 Optimization of aza-Benzoin Reaction

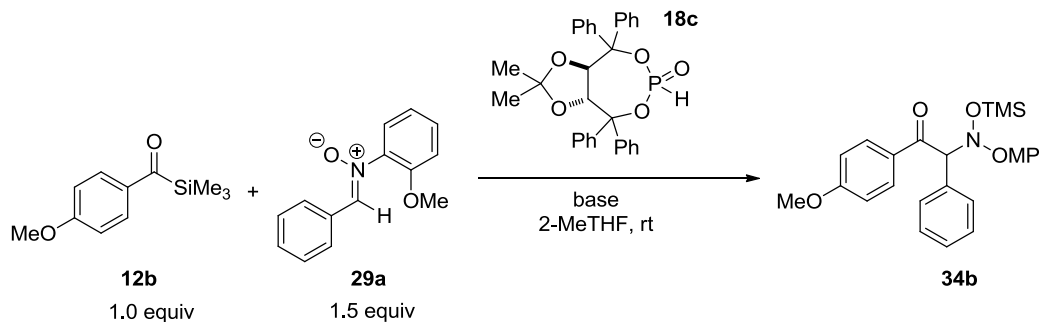
Before examining the generality of the metallophosphite-catalyzed aza-benzoin reaction, it was necessary to find conditions that would afford higher yields without decreasing the efficiency of asymmetric control. The primary goal was to find conditions to disfavor the irreversible redox reaction between the metallophosphite catalyst and the nitronium. Initial attempts were aimed at varying the nitrogen substituent of the nitronium to a less activating group. Unfortunately, this route never met with success as less activating groups (benzyl (**37**), diphenylmethyl (**38**), and trityl (**39**)) all failed to undergo coupling with the acyl silane. These results highlight the intricate balance that must be struck in achieving the desired coupling. If the nitronium component is too electrophilic, then the

metallophosphite will add to it preferentially and irreversibly decompose the catalyst. If the nitron is not sufficiently electrophilic, the (silyloxy)nitrile anion will not attack and instead it will dimerize with another equivalent of acyl silane. Being limited to *N*-aryl substituents and wishing to preserve the methoxy functionality as a handle for eventually cleaving the *N*-aryl bond, we sought other ways to modulate the two competing reaction pathways.



**Figure 1.5.** Screen of Nitron *N*-Substituents

We drew an analogy between the undesired phosphite oxidation reaction and the Wittig reaction. It has been reported that various metal additives and the identity of the base can favor or disfavor the formation of the oxetane ring in the Wittig reaction.<sup>43</sup> We hoped that by employing other bases or additives, we could prevent oxetane formation and the resultant catalyst degradation. Using acyl silane **12b** and nitron **29a** as the model system, we investigated the role of other reaction variables (Table 1.1). Upon screening a variety of bases, we found that only lithium-derived metallophosphites provided any desired product with magnesium, sodium, potassium, and amine bases giving no desired product. <sup>n</sup>BuLi and LiHMDS provided the best results of the lithium bases, with yields approaching 50% yield by <sup>1</sup>H NMR with LiHMDS. Due to the stability and ease of handling, the use of LiHMDS was preferable over <sup>n</sup>BuLi.

**Table 1.1.** Screen of Bases in Aza-Benzoin Reaction<sup>a</sup>

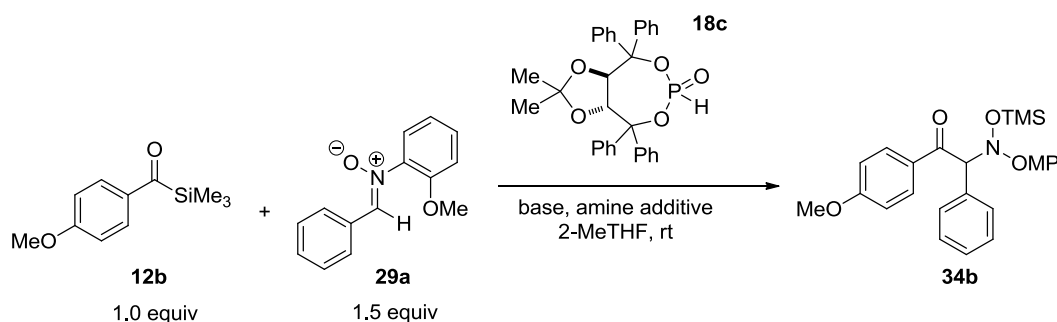
Entry	Base	Time	Temp	Yield. <sup>b</sup>
1	BrMgEt	1 h	rt	NDP <sup>c</sup>
2	DBU	1 h	rt	NDP
3	NaHMDS	1 h	rt	NDP
4	KHMDS	2 h	rt	NDP
5	KO <sup>t</sup> Bu	1.5 h	rt	NDP
6	NaO <sup>t</sup> Bu	1.5 h	rt	NDP
7	MeMgI	30 min	rt	NDP
8	EtMgCl	1 h	rt	NDP
9	<sup>sec</sup> BuLi	1 h	rt	8%
10	<sup>t</sup> BuLi	1 h	rt	10%
11	LDA	1 h	rt	6%
12	LiHMDS	1 h	rt	51%
13	LiHMDS	30 min	0 °C	30%
14	LiHMDS	10 min	50 °C	50%

<sup>a</sup> Standard reaction conditions (see Experimental section). <sup>b</sup> Yields determined by <sup>1</sup>H NMR spectroscopy with a mesitylene internal standard. <sup>c</sup> No desired product.

Being constrained to lithium bases, we subsequently examined metal salt and Lewis base additives. Organolithium compounds are known to form aggregates, which can affect their reactivity.<sup>44</sup> Metal salts and amine ligands can prevent aggregation, leading to a more reactive species.<sup>45</sup> In a screen of metal halides, lithium salts were found to shut

down the reaction, while potassium salts resulted in essentially no change in the yield. Employing known ligands for organolithium species (TMEDA, NMP, DMPU, *N*-ethyl piperidine) provided generally lower yields (Table 1.2). One exception was one equivalent of NMP, which provided a marginal increase to 54% yield with LiHMDS as the base (entry 6). However, when the equivalents of NMP were increased, the reaction was shut down (entry 7).

**Table 1.2.** Screen of Amine Ligands in Aza-Benzoin Reaction<sup>a</sup>



Entry	Base	Additive	Time	Yield <sup>b</sup>
1	<i>n</i> BuLi	TMEDA	30 min	27%
2	<i>n</i> BuLi	NMP	30 min	41%, 53%
3	<i>n</i> BuLi	ethyl piperidine <sup>c</sup>	15 min	NDP <sup>e</sup>
4	<i>n</i> BuLi	TMEDA <sup>c</sup>	15 min	NDP
5	LiHMDS	TMEDA	15 min	51%
6	LiHMDS	NMP	15 min	54%
7	LiHMDS	NMP <sup>d</sup>	15 min	NDP
8	LiHMDS	DMPU	30 min	35%
9	LiHMDS	ethyl piperidine <sup>c</sup>	15 min	38%
10	LiHMDS	TMEDA <sup>c</sup>	15 min	28%

<sup>a</sup> Standard reaction conditions (see Experimental section). <sup>b</sup> Yields determined by <sup>1</sup>H NMR spectroscopy with a mesitylene internal standard. <sup>c</sup> distilled prior to use. <sup>d</sup> 10 equivalents used <sup>e</sup> No desired product.

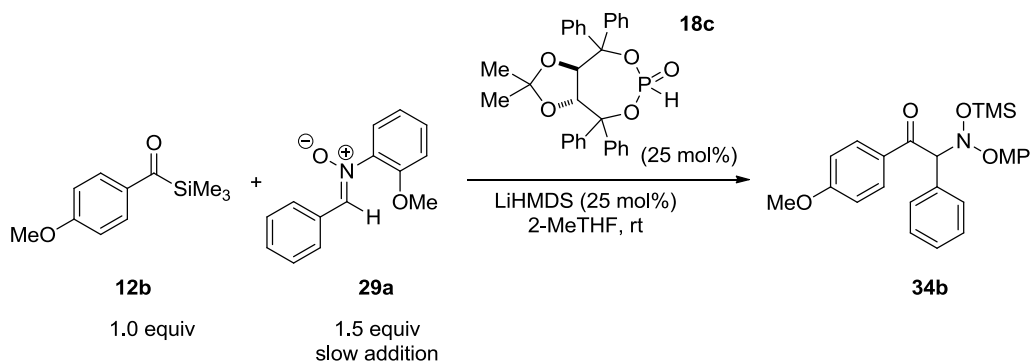


After attempts to increase the yield of the reaction through additives and choice of base met with little success, we endeavored to engineer the reaction protocol to increase the yield. Examination of the tolerance of the reaction to temperature showed that heating to 50 °C provided no increase in yield, while cooling to 0 °C resulted in a decreased <sup>1</sup>H NMR yield of 30%. The reaction was completely shut down at temperatures below 20 °C. Surprisingly, we found the order of addition played a crucial role in the reaction. If the reaction was run to 40-50% conversion using 20 mol % of catalyst **18c** and the typical reaction conditions, addition of a second 20 mol % of metallophosphite catalyst to the reaction mixture failed to lead to any additional product formation, despite the presence of both unreacted nitron and acyl silane. Furthermore, when the acyl silane and metallophosphite were pre-mixed followed by a slow addition of the nitron, no desired product was obtained. These results again underscore the delicate balance between productive heterocoupling and deleterious homocouplings of the reagents. In the absence of the nitron electrophile, the acyl silane simply dimerizes or polymerizes. This was corroborated by treating the acyl silane with the metallophosphite catalyst at -78 °C, a temperature at which Brook-rearrangement and therefore dimerization does not occur, for 1 hr. Subsequent addition of the nitron partner and warming to room temperature resulted in the formation of  $\alpha$ -silyloxyamino ketone **34b** in 40% yield (<sup>1</sup>H NMR).

During subsequent attempts involving slow addition of the nitron, we met with a fortuitous discovery. We hoped to initiate the reaction with a substoichiometric amount of nitron, and then add the remainder at a rate such that the reaction proceeded, but the concentration of nitron remained low to avoid outcompeting the acyl silane for

metallophosphite addition. The yields in these reactions were found to be approximately equal to the amount of nitron initially present in the reaction (Table 1.3).

**Table 1.3.** Slow Addition of Nitron<sup>a</sup>

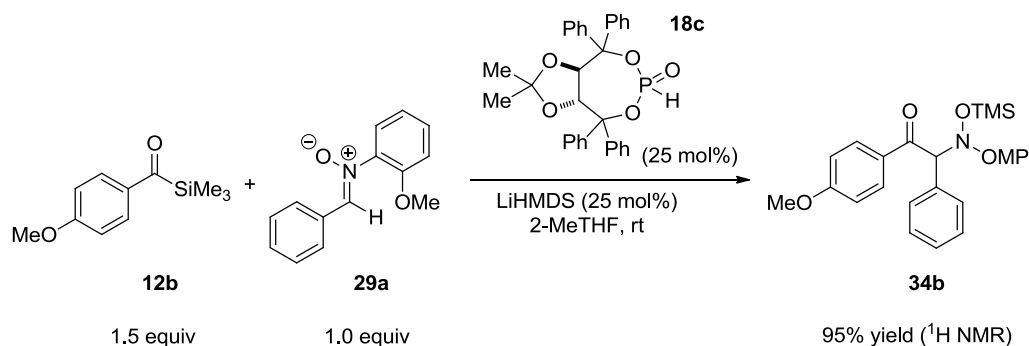


Entry	[ <b>29a</b> ] <sub>0</sub>	Conversion <sup>b</sup>
1	0 mol%	6%
2	10 mol%	10%
3	25 mol%	23%
4	25 mol%	40% <sup>c</sup>

<sup>a</sup> Conditions: **12b** (0.1 mmol), **18c** (0.025 mmol), LiHMDS (0.025 mmol), 3 mL of 2-MeTHF. The remainder of nitron **29a** added as a 2-MeTHF solution over 5 min. <sup>b</sup> Conversions determined by <sup>1</sup>H NMR spectroscopy with a mesitylene internal standard. <sup>c</sup> Remainder of nitron **29a** added as 2-MeTHF solution over 1 min.

We postulated that the initial nitron present reacted almost quantitatively, while the subsequently added nitron was added too slowly and failed to react. This prompted us to alter the stoichiometry of the reaction and use 2.0 equivalents of acyl silane to 1.0 equivalent of nitron rather than a slow addition of the nitron. This resulted in 95% <sup>1</sup>H NMR yield with complete consumption of the nitron starting material. We found that 1.5 equivalents of acyl silane was sufficient to obtain a 95% <sup>1</sup>H NMR yield and complete conversion; a smaller excess led to incomplete conversion and lower yields (Scheme

1.12). A portion of the excess acyl silane (~25 mol%) could be recovered as unreacted starting material.

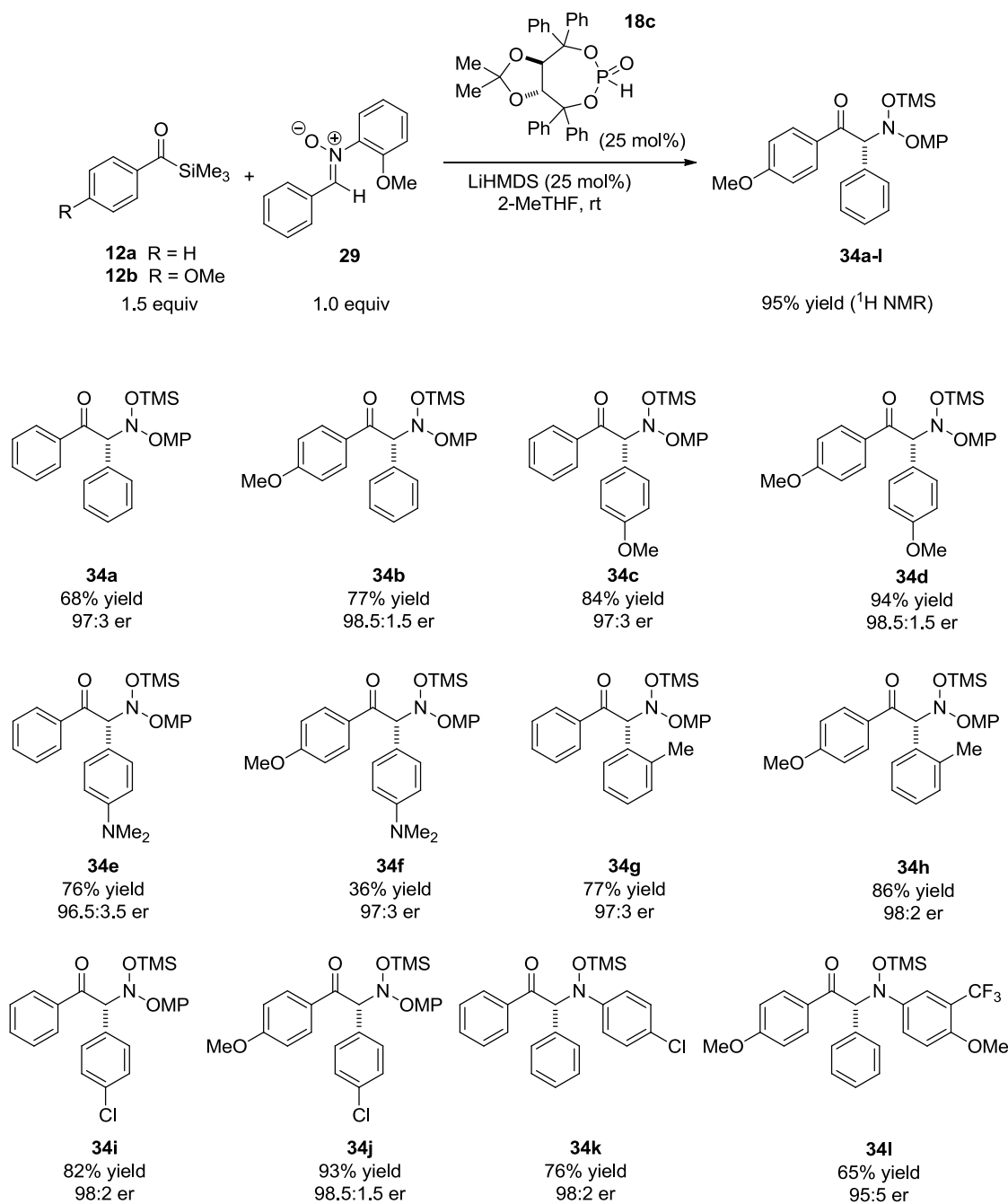


**Scheme 1.12.** Optimized Conditions for Aza-Benzoin Reaction

#### 1.4.2 Substrate Scope

With optimized coupling conditions in hand, we wished to examine the scope of the asymmetric aza-benzoin reaction. In general, the reaction was quite rapid (< 20 min) and proceeded with complete conversion for the substrates shown in Figure 1.6. The lower yield observed for some of the substrates (**34a**, **34f**, **34i**) is a result of facile elimination to the imine upon column chromatography even after deactivation of the SiO<sub>2</sub> with TEA. Both electron-rich and electron-neutral acyl silanes performed quite well in the reaction, providing a complementary methodology to Miller's reaction conditions which employ electron-deficient acyl donors.<sup>41</sup> As has been observed in the previously reported sila-Stetter reaction, the electron-rich acyl silane **12b** reacted more efficiently, affording moderately higher yields and er than the electron-neutral silane **12a**.<sup>19</sup> The nitron partner could be varied to include a variety of electron-rich, -neutral, and -deficient C-aryl groups. Ortho substitution was also tolerated as evidenced by compounds **34g** and **34h**. Both electron-rich and electron-deficient *N*-aryl groups were tolerated. In all cases,

er's were above 95:5, obviating the need for recrystallization to obtain synthetically useful er's.

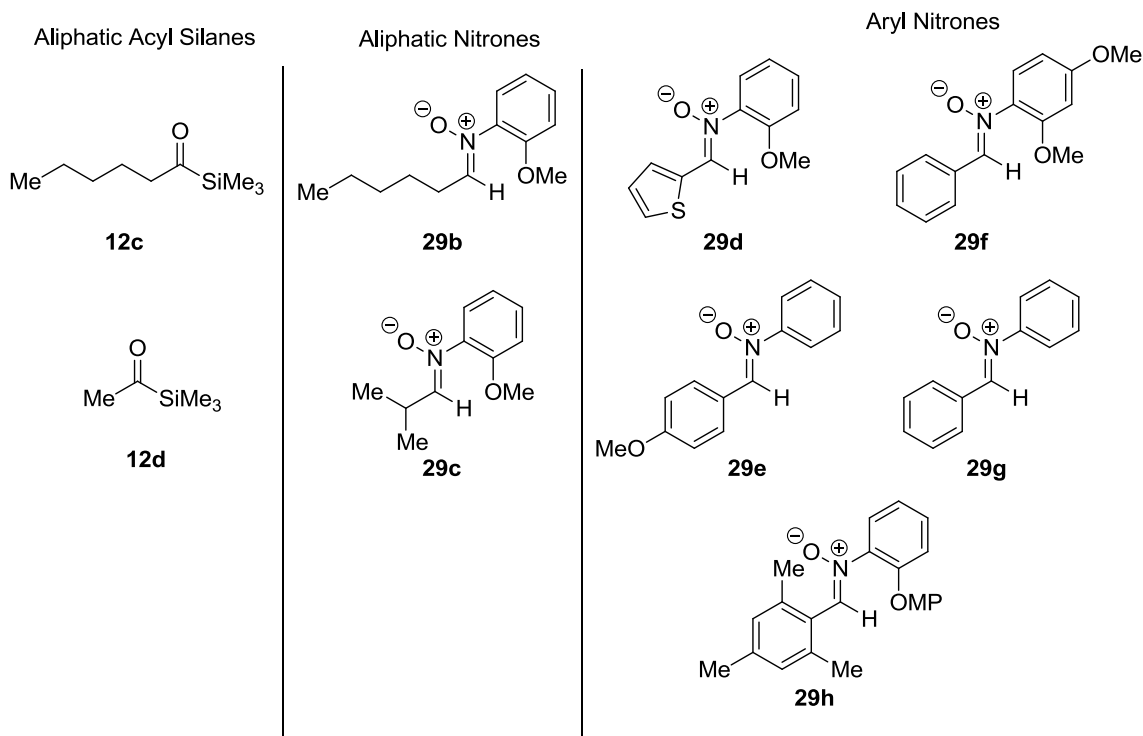


**Figure 1.6.** Substrate Scope for Aza-Benzoin Reaction

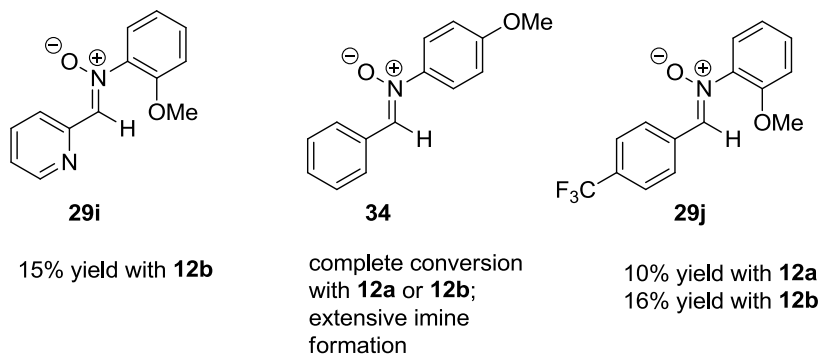
Limitations were encountered in conducting the substrate scope, however. The conditions are only applicable to aryl acyl silanes and *C*- and *N*-aryl nitrones (Figure 1.7).

The reaction conditions yielded no desired product for substrates where alkyl groups when introduced in any of the three possible positions (Figure 1.7, **12c**, **12d**, **29b**, **29c**). C-Heteroaryl substituted nitrones also failed to efficiently couple, with nitrone **29d** yielding no desired product and **29i** affording only low yields and incomplete conversions when reacted with **12a** or **12b**. While a single ortho substituent was tolerated on the C-aryl terminus of the nitrone partner, the C-mesityl group proved too sterically encumbering (**29h**). Some *N*-aryl groups failed to undergo the aza-benzoin reaction (**29e-g**), with no clear trend emerging as electron-poor and electron-rich *N*-aryl groups performed well while electron-neutral *N*-aryl substituents typically did not. Nitrone **29j** again illustrates that if the nitrone becomes too electrophilic, then low yields are obtained due to catalyst degradation *via* addition to the nitrone over the acyl silane.

No Desired Product Observed



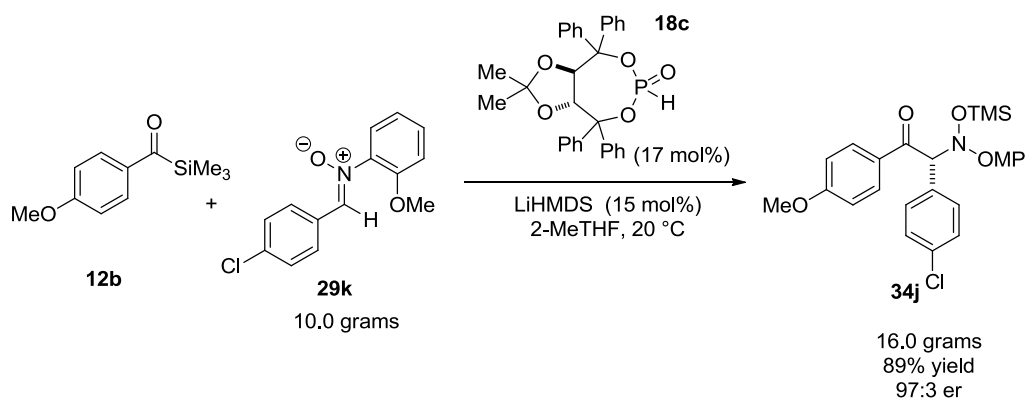
Low Yields of Desired Product Observed



**Figure 1.7.** Problematic Substrates in Aza-Benzoin Reaction

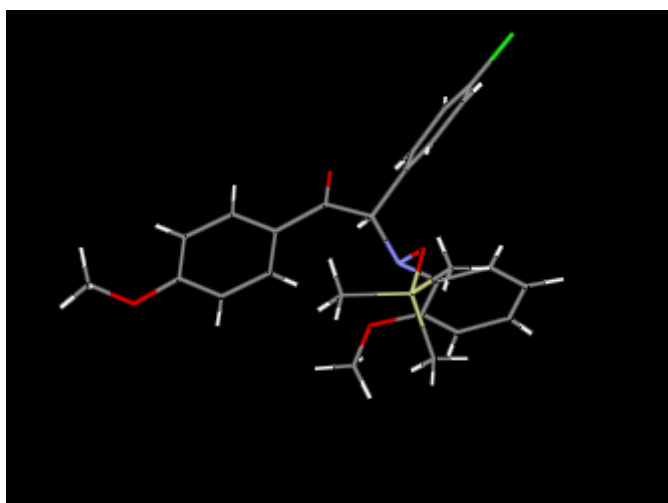
In order to determine the utility of the metallophosphite-catalyzed aza-benzoin reaction as a preparative procedure, we attempted to perform the reaction on a 10-gram scale. We chose silyloxyamino ketone **34j** as our model reaction as it was formed in excellent yield and er when the reaction was conducted on the 0.1-gram scale. An initial scale-up to 1 gram of nitron led to formation of desired product **34j** with complete

conversion and no loss in enantioselectivity. Attempts to lower the catalyst loading on a 1-gram scale proved moderately successful. The catalyst loading was decreased from 25 mol% to 17 mol% while maintaining complete conversion. A further decrease to 10 mol% of phosphite **18c** resulted in only 35% conversion. With these encouraging results, the reaction was carried out on a 10-gram scale. Unfortunately, silyloxyamino ketone **34j** was isolated in only 53% yield following flash column chromatography, along with 39% yield of the imine elimination product. Examination of the  $^1\text{H}$  NMR spectrum of the crude reaction mixture indicated that elimination occurred during purification, presumably due to a longer residence time on the larger column. Given that the combined yield for the **34j** and the imine exceeded 90%, efficient coupling was still being achieved. In order to address imine formation during chromatography, the product was split into two smaller batches for chromatography, reducing the residence time on the column to approximately 20 to 30 minutes as opposed to 60 to 90 minutes. Additionally, an exotherm was observed for the reaction on this scale. To address this issue, a 20 °C bath was used to maintain a constant temperature. Repeating the 10-gram reaction with the modifications to the purification and temperature in place afforded  $\alpha$ -silyloxyamino ketone **34j** in 89% yield and 97:3 er (Scheme 1.13). Additionally, 23 mol % of the excess acyl silane employed could be recovered on this scale. These results illustrate the robust nature of this methodology; with minute changes in the experimental procedure, nearly identical yields and enantioselectivities can be obtained on scales varying by a factor of 1000.



**Scheme 1.13.** Aza-Benzoin Reaction to Yield **34j** on 10-gram Scale

The material from the 10-gram scale reaction was crystallized from Et<sub>2</sub>O to afford the product in greater than 99:1 er. Single crystal X-ray diffraction established the absolute stereochemistry as *R* (Figure 1.8).<sup>46</sup> This result is interesting as the *R,R*-TADDOL derived metallophosphite exhibits the opposite facial selectivity for aldehyde electrophiles in the asymmetric cross silyl benzoin reaction.<sup>16</sup>



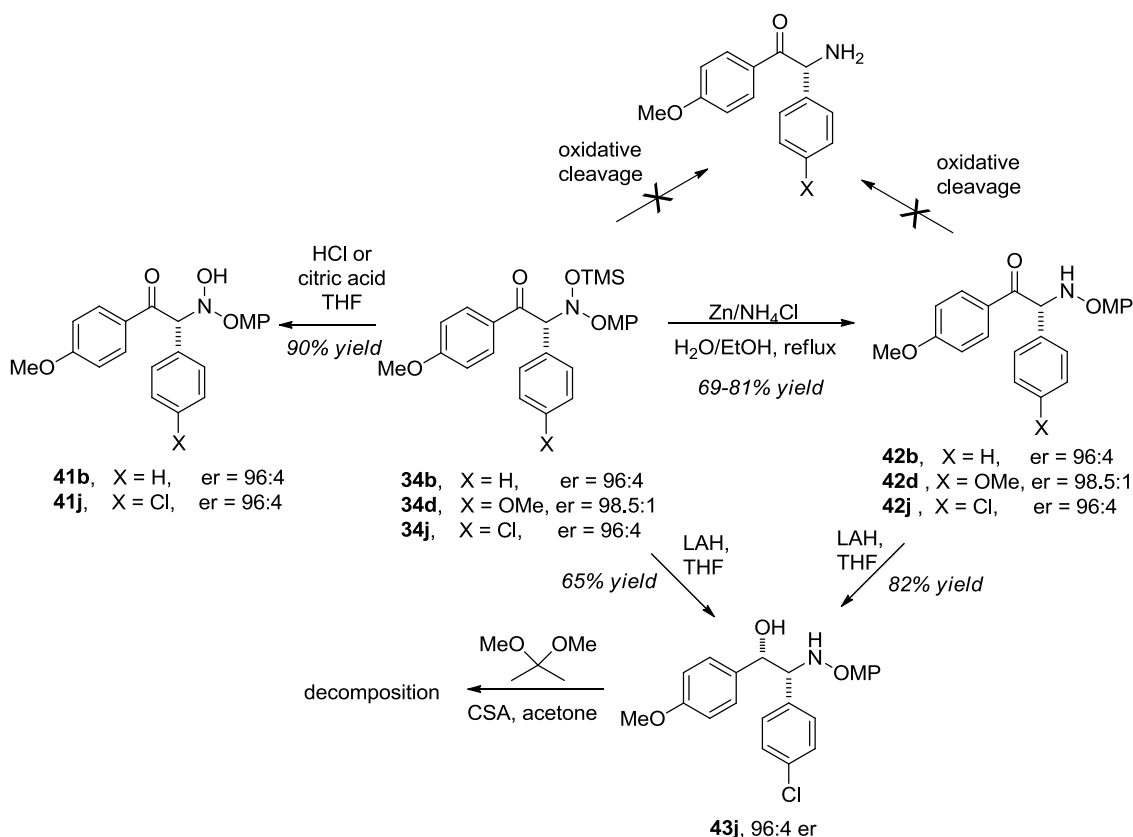
**Figure 1.8.** X-ray Crystal Structure of **34j**

*1.4.3 Further Synthetic Manipulations*

We next sought conditions to deprotect the amine functionality by cleavage of the OTMS group (Scheme 1.14). Treatment of the silyloxy amine **34** with dilute HCl or



citric acid in THF at 0 °C cleanly provided the hydroxylamine **41** with retention of stereochemistry. A number of conditions were examined to cleave the N–O bond. Reduction with Zn/HOAc<sup>47</sup> and with lithium naphthalenide<sup>48</sup> resulted in elimination of trimethylsilanol to give the achiral imine, which itself could be reduced to yield the racemic secondary amine. Cleavage with Pd/C/NH<sub>4</sub>CO<sub>2</sub>H could furnish the desired secondary amine; however, yields and er were variable.<sup>49</sup> The optimal conditions were determined to be refluxing with Zn/NH<sub>4</sub>Cl in EtOH/H<sub>2</sub>O.<sup>50</sup> This could be performed on either the free hydroxylamine or the silyloxyamine obtained directly from the aza-benzoin reaction. This mild and operationally simple procedure yielded between 69 and 81% of three representative secondary amines (**42**) with almost complete retention of stereochemistry. It should be noted that the secondary amines were significantly more robust than the corresponding silyloxyamine. Not only were the secondary amines stable to flash column chromatography without deactivation of the SiO<sub>2</sub> with TEA, but even stirring several hours at room temperature with TEA or DBU failed to racemize the secondary amines.



**Scheme 1.14.** Synthetic Manipulations of Aza-Benzoin Products **34**

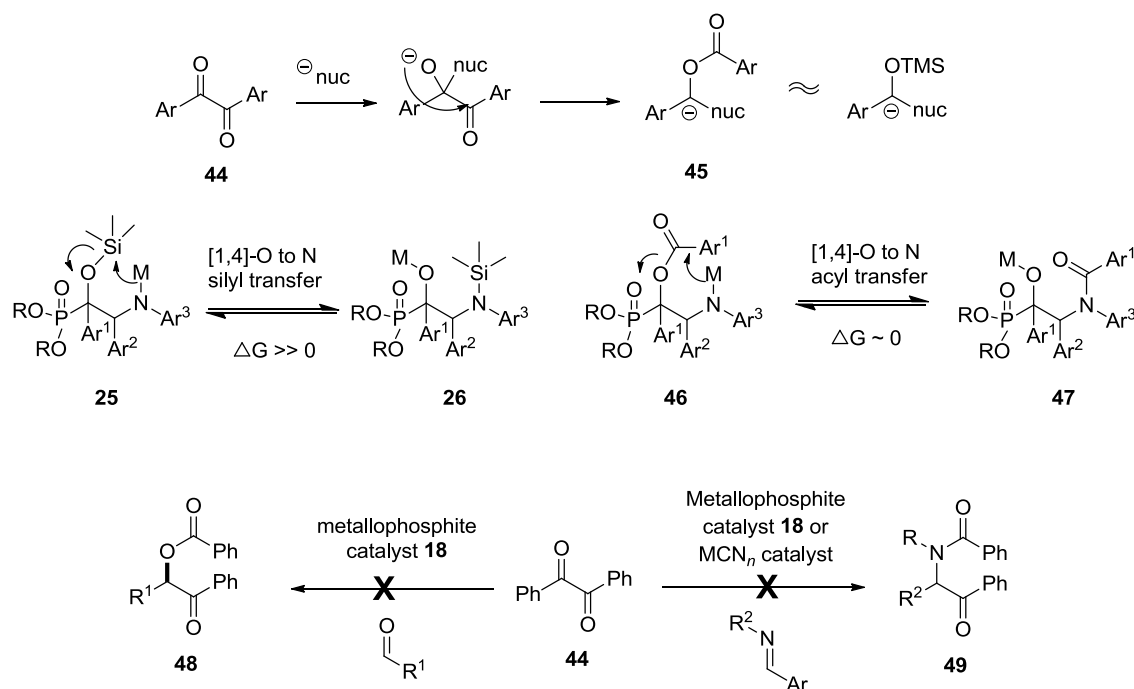
Attempts to cleave the secondary aryl amine to the primary free amine were unsuccessful. We had incorporated a methoxy group onto the *N*-aryl group for most substrates with hopes to develop an oxidative cleavage following the aza-benzoin. The most commonly employed *N*-aryl protecting group for oxidative cleavage is 2,4-dimethoxyphenyl.<sup>51</sup> However, nitrones prepared with this *N*-aryl group failed to undergo aza-benzoin coupling. Our attempts to cleave the *N*-aryl bond with CAN, hypervalent iodide, and ammonium persulfate resulted in imine formation followed by hydrolysis to the benzil product.<sup>52-54</sup>

The  $\alpha$ -silyloxyamino ketones could also be reduced to yield vicinal amino alcohols. Treatment of either the silyloxyamine or the reduced secondary amine with LAH yielded the amino alcohol **43j** as a single diastereomer in 65% and 82% yield, respectively. The

resultant amino alcohol was much less stable, undergoing decomposition under acidic ketalization conditions as well as in chloroform at room temperature over 72 hours. Being unable to ketalize amino alcohol **43j** to determine the relative stereochemistry by nOe, it has tentatively been assigned as the *anti* reduction product based on an analogous reduction.<sup>55</sup> Treatment of the vicinal amino alcohol **43j** with typical cleavage conditions (CAN, ammonium persulfate, hypervalent iodine) resulted in decomposition as well.

## 1.5 Alternative Acyl Donors

We were interested extending the C=N acylation chemistry to other acyl donors (Scheme 1.15). Commercially available benzil (**44**) is known to undergo a 1,2 C-O acyl shift upon the addition of a nucleophile, generating an intermediate analogous to the carbanion formed by Brook-rearrangement of the acyl silane (**45**).<sup>56</sup> Additionally, the benzoyl group that is transferred would allow a more thermoneutral oxygen to nitrogen transfer than a silyl group, and allow for the reaction to be conducted with imines rather than nitrones. Unfortunately, we were unable to achieve desired coupling between **44** and a variety of imines or nitrones to yield products such as **49**. A variety of solvents (ether, THF, DMF, DMSO), multiple classes of catalysts (metallophosphites, 18-crown-6/KCN, La(CN)<sub>3</sub>), *N*-protecting groups, and temperatures were examined. The problem appears to be a lower reactivity of intermediate **45** as compared to the silyl-derivative. This was evidenced by the inability of benzil to undergo metallophosphite-catalyzed coupling with aldehydes.



**Scheme 1.15.** Attempts to Employ Benzil as an Acyl Donor

## 1.6 Conclusions

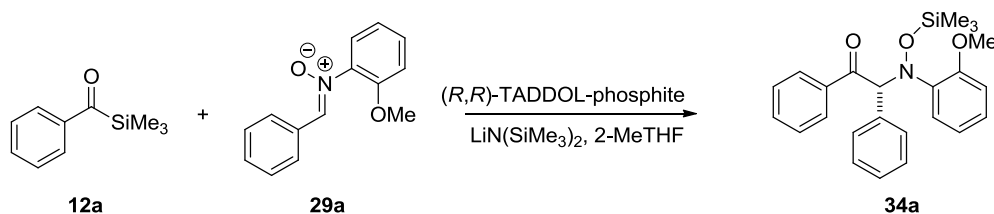
In summary, we have developed the first catalytic asymmetric nitron acylation. The methodology extends the scope and utility of the metallophosphite-catalyzed coupling of acyl silanes couplings to include C=N  $\pi$ -electrophiles. The use of nitrones provides an energetically favorable pathway that allows for successful catalyst turnover. The reactions proceed in high yield and exceptionally high er for organocatalysis to yield *N*-arylamino ketones. The substrate scope encompasses electron-rich and electron-neutral acyl donors, which had been incompatible with other imine acylation methodology. The resultant  $\alpha$ -silyloxyamino ketones can undergo further synthetic manipulation without loss of optical purity. The methodology is also scalable over three orders of magnitude with no decrease in yield or er.

## 1.7 Experimental Section

**Materials and Methods: General.** Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra ( $^1\text{H}$  and  $^{13}\text{C}$  NMR) were recorded on the following instruments: Bruker model Avance 400 ( $^1\text{H}$  NMR at 400 MHz and  $^{13}\text{C}$  NMR at 100 MHz) and Varian Gemini 300 ( $^1\text{H}$  NMR at 300 MHz and  $^{13}\text{C}$  at 75 MHz) spectrometers with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm and  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet), coupling constants (Hz), and integration. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Mass spectra were obtained on a Micromass Quattro II Triple Quadrupole Spectrometer using ESI ionization. X-ray diffraction was performed using a Bruker Smart 1K Single Crystal CCD Diffractometer with a MoK source. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and aqueous ceric ammonium nitrate molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent Technologies silica gel 60 (32-63  $\mu\text{m}$ ). All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Reagents were massed out in the glovebox. Yield refers to isolated yield of analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Diethyl ether was dried by passage through a column of neutral alumina under nitrogen prior to use.<sup>57</sup> Acyl silanes<sup>58-60</sup> and nitrones<sup>61</sup> were prepared by

literature methods. TADDOL-phosphites were synthesized *via* the method reported in a previous communication.<sup>16</sup>

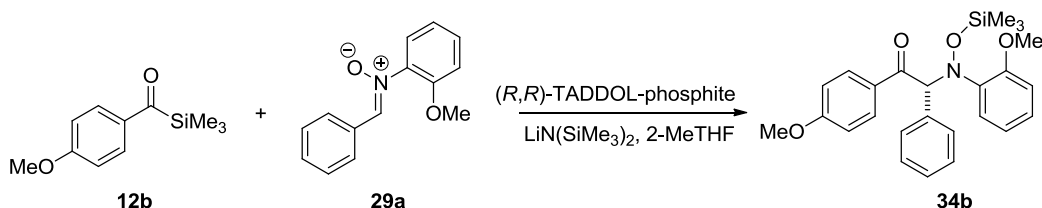
**General procedure (A) for the reaction of acyl silanes with nitrones.** In the glovebox, 0.38 mmol of the nitrone, 0.57 mmol (1.5 equiv) of the acyl silane, 0.097 mmol (0.25 equiv) of the TADDOL-phosphite, and 0.097 mmol (0.25 equiv) of LHMDS was added to a dry round-bottomed flask with magnetic stir bar. The flask was removed from the glovebox and 6.0 mL of 2-MeTHF was added and the resulting solution was stirred under N<sub>2</sub> at room temperature until starting material was consumed (TLC analysis). The solvent was removed *in vacuo*, then purified by flash chromatography on SiO<sub>2</sub> deactivated by 5% Et<sub>3</sub>N in hexanes and eluting with the indicated solvent system to afford the pure *N*-silyloxy- $\alpha$ -amino ketone. The enantioselectivity of the reaction was determined by CSP-SFC analysis by the specified conditions.



**2-((2-methoxyphenyl)(trimethylsilyloxy)amino)-1,2-diphenylethanone (34a,**

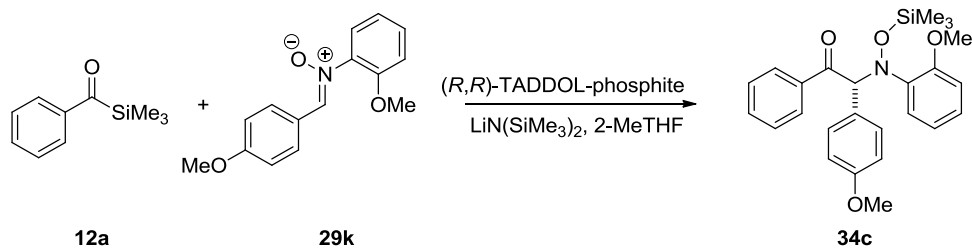
**Scheme 1.11).** The title compound was prepared according to General Procedure A using 100.0 mg of nitrone, 135.0 mg of acyl silane, 56.0 mg of phosphite, 17.0 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica

gel eluting with 15% EtOAc in hexanes to afford 115 mg (62%) of the product as a thick, pale yellow oil in 95.5:4.5 e.r. as determined by CSP-SFC ((*S,S*)-Chiralpak AS, 5.0% MeOH, 2.0 mL/min, 200 bar, 25 °C, 240 nm) analysis ( $t_{\text{r-major}}$  3.2 min,  $t_{\text{r-minor}}$  3.8 min)  $[\alpha]_{\text{D}}^{25}$  -16.5 ( $c = 0.95$ ,  $\text{CH}_2\text{Cl}_2$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3064, 3029, 2958, 2835, 1700, 1597, 1490, 1448, 1251, 1208, 1116, 1026, 902, 845, 753;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 (d,  $J = 7.6$  Hz, 2H), 7.52-7.49 (m, 1H), 7.45-7.38 (m, 4H), 7.27-7.25 (m, 1H), 7.22-7.20 (m, 3H), 6.97 (t,  $J = 8.0$  Hz, 1H), 6.81 (d,  $J = 8.0$  Hz, 1H), 6.77 (t,  $J = 8.0$  Hz, 1H), 6.20 (s, 1H), 3.93 (s, 3H), -0.19 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.5, 150.3, 140.8, 136.9, 134.1, 132.6, 131.4, 129.3, 128.2, 127.8, 127.5, 124.8, 122.8, 120.6, 111.3, 73.6, 55.7, -0.61 (four sets of coincidental signals); TLC (40% EtOAc in hexanes)  $R_f$  0.78; **Anal.** Calcd for  $\text{C}_{24}\text{H}_{27}\text{NO}_3\text{Si}$ : C, 71.08; H, 6.71; N, 3.45. Found: C, 71.34; H, 6.67; N, 3.44.



**1-(4-methoxyphenyl)-2-((2-methoxyphenyl)(trimethylsilyloxy)amino)-2-phenylethanone (**34b**, Scheme 1.11).** The title compound was prepared according to General Procedure A using 100.0 mg of nitrone, 160.0 mg of acyl silane, 56.0 mg of phosphite, 17.0 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica gel eluting with 15% EtOAc in hexanes to afford 151.0 mg (80%) of the product as a thick, pale yellow oil in 97:3 e.r. as determined by

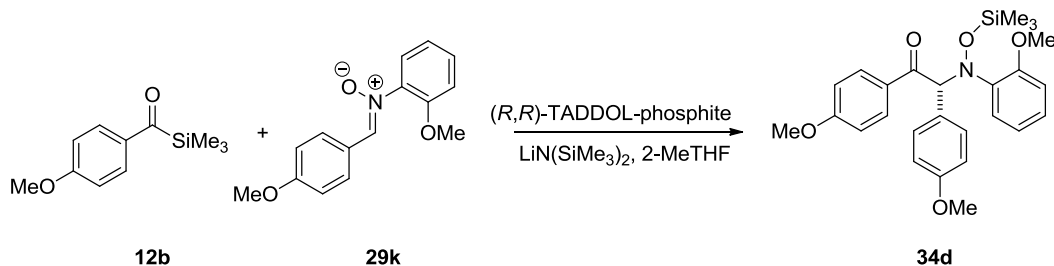
CSP-SFC ((*S,S*)-Chiralpak-AS, 7.0% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) analysis ( $t_{\text{r-major}}$  4.0 min,  $t_{\text{r-minor}}$  5.3 min);  $[\alpha]_{\text{D}}^{25}$  +33.0 ( $c = 0.96$ ,  $\text{CH}_2\text{Cl}_2$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2959, 2838, 1684, 1600, 1510, 1490, 1456, 1420, 1308, 1255, 1171, 1117, 1028, 905, 841, 751;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (d,  $J = 8.4$  Hz, 2H), 7.40-7.38 (m, 2H), 7.25-7.19 (m, 4H), 6.96 (t,  $J = 8.0$  Hz, 1H), 6.91 (d,  $J = 8.8$  Hz, 2H), 6.81 (d,  $J = 8.0$  Hz, 1H), 6.75 (t,  $J = 7.6$  Hz, 1H), 6.15 (s, 1H), 3.94 (s, 3H), 3.85 (s, 3H), -0.21 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  193.9, 163.1, 150.3, 141.0, 134.4, 131.6, 131.4, 130.0, 127.7, 127.4, 124.7, 122.8, 120.6, 113.4, 111.3, 73.4, 55.7, 55.3, -0.57 (four sets of coincidental signals); TLC (40% EtOAc in hexanes)  $R_f$  0.72; **Anal.** Calcd for  $\text{C}_{25}\text{H}_{29}\text{NO}_4\text{Si}$ : C, 68.93; H, 6.71; N, 3.22. Found: C, 68.64; H, 6.72; N, 3.17.



**2-(4-methoxyphenyl)-2-((2-methoxyphenyl)(trimethylsilyloxy)amino)-1-phenylethanone (34c, Scheme 1.11).** The title compound was prepared according to General Procedure A using 99.8 mg of nitronium, 103.8 mg of acyl silane, 49.9 mg of phosphite, 16.3 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica gel with 5% EtOAc in hexanes to afford 148.7 mg (88%) of the product as a pale yellow thick oil in 97:3 e.r. as determined by CSP-SFC

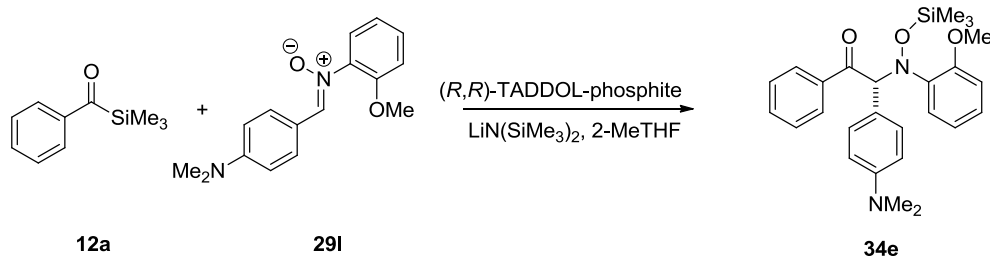


((*S,S*)-Chiralpak AS, 7.0% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) analysis ( $t_{\text{r-major}}$  3.7 min,  $t_{\text{r-minor}}$  4.6 min);  $[\alpha]_{\text{D}}^{25}$  -13.3 ( $c = 0.085$ ,  $\text{CH}_2\text{Cl}_2$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3056, 2961, 2838, 1695, 1609, 1512, 1490, 1265, 1250, 1178, 1029, 906, 847, 737;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 (d,  $J = 7.2$  Hz, 2H), 7.51 (t,  $J = 7.6$  Hz, 1H), 7.43 (t,  $J = 7.2$  Hz, 2H), 7.39 (m, 3H), 7.02-6.94 (m, 1H), 6.85-6.72 (m, 4H), 6.14 (s, 1H), 3.92 (s, 3H), 3.73 (s, 3H), -0.17 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.7, 159.1, 150.2, 140.8, 136.9, 132.6, 132.5, 129.2, 128.2, 126.1, 124.8, 122.8, 120.6, 112.8, 111.2, 73.0, 55.7, 55.0, -0.59 (four sets of coincidental signals); TLC (40% EtOAc in hexanes)  $R_f$  0.79; **Anal.** Calcd for  $\text{C}_{25}\text{H}_{29}\text{NO}_4\text{Si}$ : C, 68.93; H, 6.71; N, 3.22. Found: C, 69.22; H, 6.69; N, 3.24.



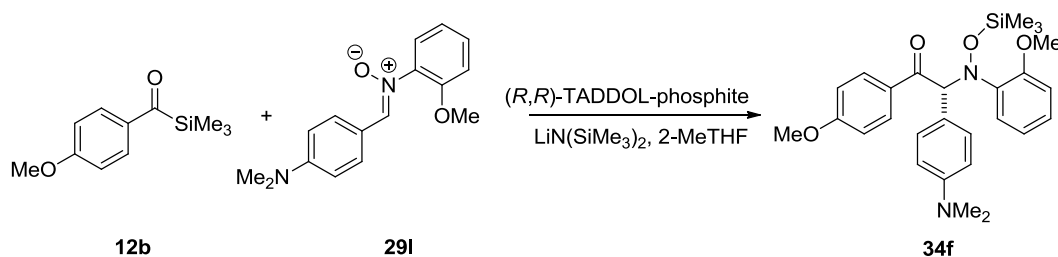
**1,2-bis(4-methoxyphenyl)-2-((2-methoxyphenyl)(trimethylsilyloxy)amino)-ethanone (34d, Scheme 1.11).** The title compound was prepared according to General Procedure **A** using 99.5 mg of nitron, 121.0 mg of acyl silane, 49.9 mg of phosphite, 16.2 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography with 5% EtOAc in hexanes to afford 174.4 mg (97%) of the product as a pale yellow, thick, oil in 98.5:1.5 e.r. as determined by CSP-SFC ((*S,S*)-Chiralpak AS, 7.0% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) analysis ( $t_{\text{r-major}}$  4.8 min,  $t_{\text{r-minor}}$  6.7 min);  $[\alpha]_{\text{D}}^{25}$  +27.3 ( $c$

= 1.1, CH<sub>2</sub>Cl<sub>2</sub>). Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 3054, 2938, 2839, 1684, 1601, 1577, 1490, 1260, 1172, 1113, 1031, 908, 846, 738; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.28 (d, *J* = 8.4 Hz, 2H), 7.35-7.20 (m, 3H), 7.02-6.90 (m, 3H), 6.87-6.72 (m, 4H), 6.08 (s, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H), -0.18 (s, 9H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 194.2, 163.1, 159.1, 150.2, 141.0, 132.5, 131.6, 130.1, 126.5, 124.7, 122.8, 120.6, 113.3, 112.8, 111.2, 72.8, 55.7, 55.3, 55.0, -0.53 (four sets of coincidental signals); TLC (40% EtOAc in hexanes) *R<sub>f</sub>* 0.55; **Anal.** Calcd for C<sub>26</sub>H<sub>31</sub>NO<sub>5</sub>Si: C, 67.07; H, 6.71; N, 3.01. Found: C, 67.30; H, 6.74; N, 3.01.



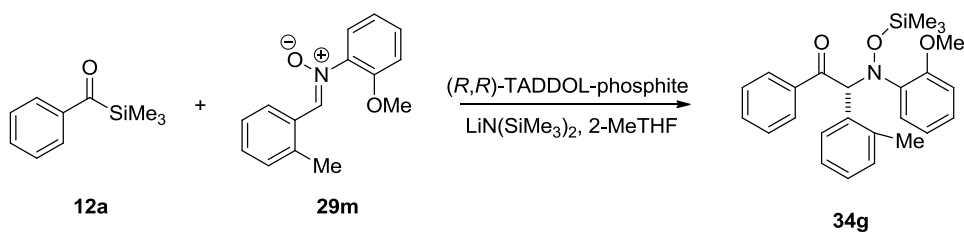
**2-(4-(dimethylamino)phenyl)-2-((2-methoxyphenyl)(trimethylsilyloxy)amino)-1-phenylethanone (34e, Scheme 1.11).** The title compound was prepared according to General Procedure A using 100.0 mg of nitronium, 101.0 mg of acyl silane, 47.0 mg of phosphite, 15.0 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica gel eluting with 20% EtOAc in hexanes to afford 147.5 mg (89%) of the product as a thick, pale yellow oil in 95.5:4.5 e.r. as determined by CSP-SFC ((*S,S*)-Chiralpak-AS, 7.0% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) analysis (*t<sub>r-major</sub>* 4.5 min, *t<sub>r-minor</sub>* 6.0 min); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -96.9 (*c* = 1.08, CH<sub>2</sub>Cl<sub>2</sub>). Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 3070, 2959, 2840, 1694, 1612, 1523, 1489, 1448,

1355, 1249, 1165, 1116, 1025, 842, 760;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.17 (d,  $J = 8.0$  Hz, 2H), 7.48-7.45 (m, 1H), 7.39 (t,  $J = 7.6$  Hz, 2H), 7.34-7.32 (m, 1H), 7.21 (d,  $J = 8.4$  Hz, 2H), 6.97-6.94 (m, 1H), 6.81-6.78 (m, 2H), 6.56 (d,  $J = 8.4$  Hz, 2H), 6.10 (s, 1H), 3.88 (s, 3H), 2.88 (s, 6H), -0.16 (s, 9H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  196.0, 150.5, 150.1, 141.3, 137.2, 132.3, 132.1, 129.1, 128.1, 124.7, 123.1, 121.7, 120.6, 111.6, 111.4, 73.4, 55.7, 40.4, -0.53 (five sets of coincidental signals); TLC (40% EtOAc in hexanes)  $R_f$  0.78; **Anal.** Calcd for  $\text{C}_{20}\text{H}_{21}\text{NO}_3$ : C, 69.61; H, 7.19; N, 6.24. Found: C, 69.61; H, 7.45; N, 6.28.



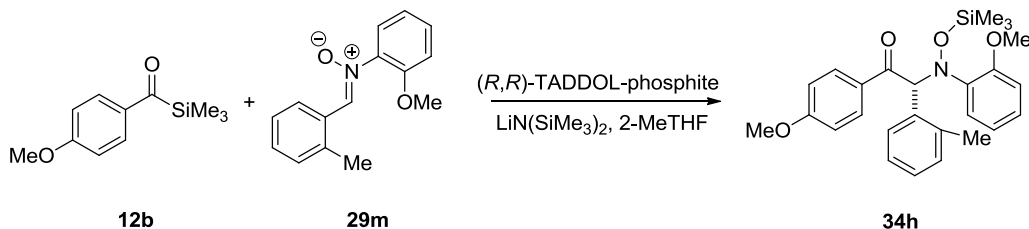
**2-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)-2-((2methoxyphenyl)(trimethylsilyloxy)amino)ethanone (34f, Scheme 1.11).** The title compound was prepared according to General Procedure A using 105 mg of nitronium, 115.0 mg of acyl silane, 47.0 mg of phosphite, 15.0 mg of LHMDs, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica gel eluting with 20% EtOAc in hexanes to afford 71.4 mg (38%) of the product as a thick, pale yellow oil in 97.5:2.5 e.r. as determined by CSP-SFC ((*S,S*)-Chiralpak-AS, 7.0% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) analysis ( $t_{\text{r-major}}$  5.8 min,  $t_{\text{r-minor}}$  9.2 min);  $[\alpha]_{\text{D}}^{25}$  -34.8 ( $c = 0.65$ ,  $\text{CH}_2\text{Cl}_2$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3067, 2956, 2835, 1687, 1600,

1511, 1463, 1252, 1170, 1029, 907, 842, 750; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.35-7.32 (m, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.95 (t, *J* = 6.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 7.6 Hz, 2H), 6.56 (d, *J* = 8.4 Hz, 2H), 6.06 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 2.87 (s, 6H), -0.14 (s, 9H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 194.4, 162.7, 149.9, 141.2, 132.0, 131.3, 130.1, 124.4, 122.9, 122.0, 120.5, 113.1, 111.5, 111.2, 72.9, 55.6, 55.2, 40.3, -0.61 (five sets of coincidental signals); TLC (40% EtOAc in hexanes) *R<sub>f</sub>* 0.74; **Anal.** Calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>3</sub>: C, 67.75; H, 7.16; N, 5.85. Found: C, 67.46; H, 7.44; N, 5.71.



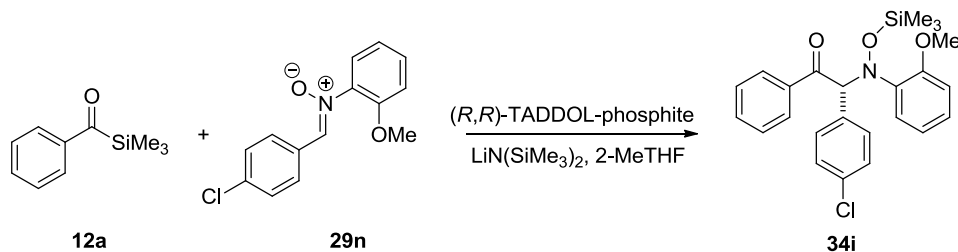
**2-((2-methoxyphenyl)(trimethylsilyloxy)amino)-1-phenyl-2-*o*-tolylethanone (34g, Scheme 1.11).** The title compound was prepared according to General Procedure A using 100.0 mg of nitronium, 110.8 mg of acyl silane, 53.1 mg of phosphite, 17.3 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography with 5% EtOAc in hexanes to afford 149.6 mg (86%) of the product as thick, yellow oil in 96:4 e.r. by CSP-SFC analysis ((*S,S*)-Whelk-O1, 5.0% MeOH, 2.0 mL/min, 200 bar, 25 °C, 240 nm) (*t<sub>r</sub>*-major 10.3 min, *t<sub>r</sub>*-minor 5.2 min); [α]<sub>D</sub><sup>25</sup> -204.2 (c = 2.8, CH<sub>2</sub>Cl<sub>2</sub>). Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 3061, 2956, 2837, 1699, 1596, 1490, 1448, 1249, 1214, 1028, 844, 748; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.93-7.76 (m, 2H), 7.72-7.59 (m, 1H), 7.56-7.24 (m, 4H), 7.19-7.05 (m, 3H), 7.01-6.86 (m, 2H), 6.68 (s, 1H), 3.89 (s, 3H), -0.29

(s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  196.4, 149.4, 141.0, 137.8, 136.9, 133.9, 132.45, 132.39, 130.4, 128.4, 128.3, 128.1, 125.3, 124.1, 123.0, 120.6, 111.0, 68.6, 55.6, -1.0 (two sets of coincidental signals); TLC (40% EtOAc in hexanes)  $R_f$  0.76; **Anal.** Calcd for  $\text{C}_{25}\text{H}_{29}\text{NO}_3\text{Si}$ : C, 71.56; H, 6.97; N, 3.34. Found: C, 71.69; H, 6.95; N, 3.37.

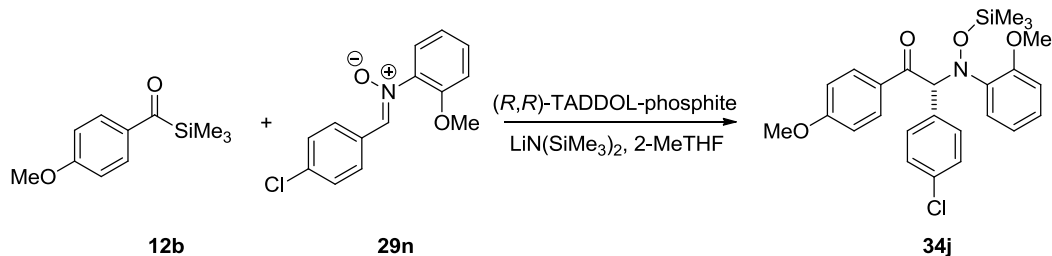


**1-(4-methoxyphenyl)-2-((2-methoxyphenyl)(trimethylsilyloxy)amino)-2-phenylethanone (34h, Scheme 1.11).** The title compound was prepared according to General Procedure A using 100.0 mg of nitron, 130.0 mg of acyl silane, 63.0 mg of phosphite, 20.0 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography with 20% EtOAc in hexanes to afford 150.9 mg (81%) of the product as thick, yellow oil in 97:3 e.r. by CSP-SFC analysis ((*S,S*)-Whelk-O1, 10.0% MeOH, 2.0 mL/min, 200 bar, 25 °C, 240 nm) ( $t_{\text{r-major}}$  19.7 min,  $t_{\text{r-minor}}$  7.8 min);  $[\alpha]_{\text{D}}^{25}$  -150.3 ( $c$  = 0.45,  $\text{CH}_2\text{Cl}_2$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3065, 2958, 2838, 1687, 1600, 1510, 1490, 1464, 1249, 1170, 1118, 1028, 908, 842, 750;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87-7.84 (m, 2H), 7.64 (d,  $J$  = 6.4 Hz, 1H), 7.54 (d,  $J$  = 7.2 Hz, 1H), 7.14-7.08 (m, 3H), 6.98-6.93 (m, 1H), 6.89 (t,  $J$  = 7.6 Hz, 1H), 6.81-6.78 (m, 3H), 6.63 (s, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 2.49 (s, 3H), -0.30 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  194.7, 162.7, 149.3, 140.9, 137.4, 133.7, 132.3, 130.6, 130.5, 130.2, 129.8, 127.8, 125.1, 123.9, 122.9, 120.5, 113.6, 113.3, 110.9, 68.1, 55.4, 55.2, 19.4, -1.07 (two

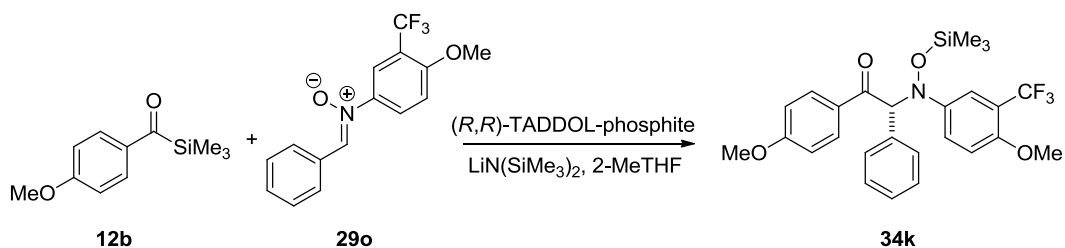
sets of coincidental signals); TLC (40% EtOAc in hexanes)  $R_f$  0.72; **Anal.** Calcd for  $C_{26}H_{31}NO_4Si$ : C, 69.45; H, 6.95; N, 3.12. Found: C, 69.27; H, 7.10; N, 3.18.



**2-(4-chlorophenyl)-2-((2-methoxyphenyl)(trimethylsilyloxy)amino)-1-phenylethanone (34i, Scheme 1.11).** The title compound was prepared according to General Procedure A using 100.4 mg of nitrosonium ylide, 102.2 mg of acyl silane, 39.3 mg of phosphite, 10.8 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica gel with 5% EtOAc in hexanes to afford 124.2 mg (74%) of the product in 97.5:2.5 e.r. as determined by CSP-SFC analysis ((*S,S*)-Chiralpak-AS, 7.0% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) ( $t_{R\text{-major}}$  3.5 min,  $t_{R\text{-minor}}$  4.9 min);  $[\alpha]_D^{25} +15.8$  ( $c = 0.35$ ,  $CH_2Cl_2$ ). Analytical data for title compound: **IR** (thin film,  $cm^{-1}$ ) 3054, 2964, 2839, 1695, 1594, 1490, 1449, 1265, 1208, 1091, 1017, 905, 848, 742;  **$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta$  8.35 (d,  $J = 7.6$  Hz, 2H), 7.62-7.42 (m, 3H), 7.32 (d,  $J = 8.4$ , 2H), 7.23-7.09 (m, 3H), 7.04-6.95 (m, 1H), 6.97 (d,  $J = 7.2$  Hz, 1H), 6.80-6.70 (m, 1H), 3.97 (s, 3H), -0.20 (s, 9H);  **$^{13}C$  NMR** (100 MHz,  $CDCl_3$ )  $\delta$  195.1, 150.0, 140.5, 136.7, 133.8, 132.8, 132.4, 129.5, 128.3, 127.6, 125.0, 122.5, 120.7, 111.1, 72.8, 55.7, -0.60 (four sets of coincidental signals); TLC (40% EtOAc in hexanes)  $R_f$  0.63; **Anal.** Calcd for  $C_{24}H_{26}NO_3Si$ : C, 65.51; H, 5.96; N, 3.18. Found: C, 65.67; H, 5.82; N, 3.17.

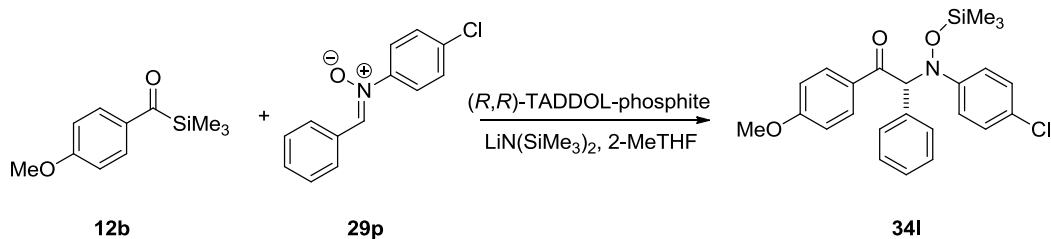


**2-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-((2-methoxyphenyl)(trimethylsilyloxy)-amino)ethanone (34j, Scheme 1.12).** The title compound was prepared according to General Procedure A using 99.9 mg of nitron, 119.3 mg of acyl silane, 40.0 mg of phosphite, 10.7 mg of LHMDS, and 6 mL of 2-MeTHF. After 5 min at 25 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica gel with 5% EtOAc in hexanes to afford 149.1 mg (83%) of the product in 98.5:1.5 e.r. as determined by CSP-SFC analysis ((*S,S*)-Chiralpak-AS, 7.0% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) ( $t_{\text{r-major}}$  4.5 min,  $t_{\text{r-minor}}$  6.9 min);  $[\alpha]_{\text{D}}^{25} +55.0$  ( $c = 0.95$ ,  $\text{CH}_2\text{Cl}_2$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3056, 2959, 2840, 1684, 1601, 1577, 1512, 1490, 1264, 1172, 1117, 1092, 1029, 909, 845, 740;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.36 (d,  $J = 8.8$  Hz, 2H), 7.31 (d,  $J = 8.0$ , 2H), 7.21-7.08 (m, 3H), 7.01-6.90 (m, 3H), 6.83 (d,  $J = 8.0$  Hz, 1H), 6.73 (t,  $J = 7.6$  Hz, 1H), 6.08 (s, 1H), 3.97 (s, 3H), 3.88 (s, 3H), -0.20 (s, 9H);  **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  193.5, 163.3, 149.9, 140.6, 133.7, 132.8, 132.6, 131.9, 129.8, 127.5, 124.9, 122.4, 120.7, 113.4, 111.2, 72.5, 55.7, 55.4, -0.55 (four sets of coincidental signals); TLC (40% EtOAc in hexanes)  $R_f$  0.67; **Anal.** Calcd for  $\text{C}_{25}\text{H}_{28}\text{ClNO}_4\text{Si}$ : C, 63.88; H, 6.00; N, 2.98. Found: C, 64.09; H, 6.04; N, 2.97.



**2-[(4-methoxy-3-trifluoromethylphenyl)(trimethylsiloxy)-amino]-1-(4-methoxyphenyl)-2-phenyl-ethanone (34k, Scheme 1.12).** The title compound was prepared according to General Procedure A using 100.0 mg of nitronium, 106.0 mg of acyl silane, 43.0 mg of phosphite, 11.0 mg of LHMDS, and 9 mL of 2-MeTHF. After 3 min at 0 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica gel with 30% Et<sub>2</sub>O in petroleum ether to afford 147 mg (86%) of the product in 98:2 e.r. as determined by CSP-SFC analysis ((*S,S*)-Chiralpak-AS, 2.5% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) (*t*<sub>R-major</sub> 5.4 min, *t*<sub>R-minor</sub> 6.8 min); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -25.7 (*c* = 1.45, CH<sub>2</sub>Cl<sub>2</sub>). Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 3012, 2964, 2842, 1686, 1602, 1576, 1501, 1459, 1424, 1322, 1258, 1171, 1113, 1055; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.96 (d, *J* = 8.8 Hz, 2H), 7.37 (2, 3H), 7.31-7.26 (m, 4H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 1H), 5.75 (s, 1H), 3.84 (s, 6H), -0.01 (s, 9H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  193.9, 163.4, 154.7, 144.8, 134.4, 130.8, 130.6, 129.9, 128.6, 128.4, 128.1, 122.0, 118.0, 117.7, 113.7, 111.2, 78.3, 56.0, 55.4, -0.39 (four sets of coincidental signals); **MS** *m/z* = 503.17; **TLC** (20% EtOAc in petroleum ether) *R*<sub>f</sub> 0.66.

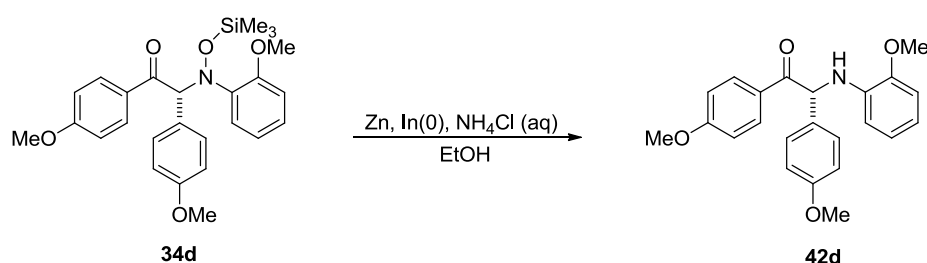




**2-[(4-Chlorophenyl)-(trimethylsiloxy)-amino]-1-(4-methoxyphenyl)-2-phenyl-ethanone (34l, Scheme 1.12).** The title compound was prepared according to General Procedure A using 100 mg of nitron, 137 mg of acyl silane, 55.0 mg of phosphite, 15.0 mg of LHMDS, and 9 mL of 2-MeTHF. After 2 min at 0 °C, the reaction was complete and the product was concentrated and purified by flash chromatography on deactivated silica gel with 30% Et<sub>2</sub>O in petroleum ether to afford 121.8 mg (64%) of the product in 94.5:5.5 e.r. as determined by CSP-SFC analysis ((*S,S*)-Chiralpak-AS, 7.0% MeOH, 2.0 mL/min, 150 bar, 25 °C, 240 nm) (*t*<sub>r-major</sub> 3.8 min, *t*<sub>r-minor</sub> 6.1 min); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -64.1 (*c* = 0.75, CH<sub>2</sub>Cl<sub>2</sub>). Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 3055, 2960, 2840, 1686, 1602, 1578, 1509, 1484, 1459, 1420, 1252, 1169, 845, 750; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.95 (d, *J* = 8.8 Hz, 2H), 7.38-7.36 (m, 2H), 7.27-7.26 (m, 3H), 7.11-7.09 (m, 4H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.81 (s, 1H), 3.84 (s, 3H), -0.01 (s, 9H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  193.8, 163.3, 151.2, 134.4, 130.9, 130.7, 129.9, 129.8, 128.5, 128.4, 128.0, 123.5, 113.7, 77.9, 55.4, -0.41 (six sets of coincidental signals); MS *m/z* = 439.14; TLC (20% EtOAc in petroleum ether) *R*<sub>f</sub> 0.73.

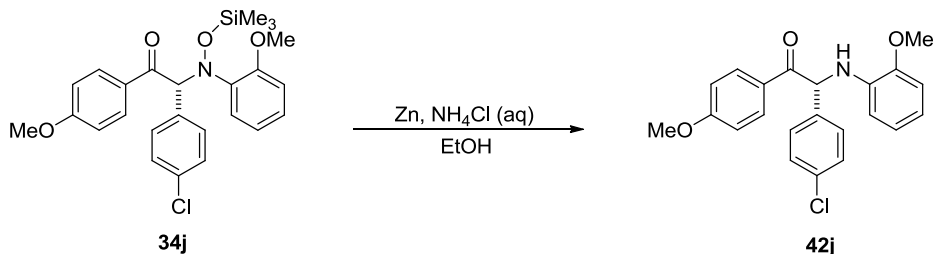
**General procedure (B) for the N–O bond cleavage of *N*-silyloxy- $\alpha$ -amino ketone.** This procedure was adapted from the literature.<sup>62</sup> In a round-bottomed flask with stir bar, 0.21 mmol of the *N*-silyloxy- $\alpha$ -amino ketone was dissolved in 12.3 mL of ethanol. The solution was stirred magnetically as 6.2 mL of NH<sub>4</sub>Cl saturated aqueous solution, (0.62

mmol, 3.0 equiv) zinc, and (0.21 mmol, 1.0 equiv) of indium powder were added. A cold-water condenser was then affixed to the top of the flask and the reaction was heated to reflux overnight. Approximately 15 mL of CH<sub>2</sub>Cl<sub>2</sub> was added to the reaction and stirred for 15 minutes. The reaction is then filtered through Celite and transferred to a separatory funnel with CH<sub>2</sub>Cl<sub>2</sub>, washed with water (2x) and with brine (2x). The organic layer is then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The resultant oil is purified by flash chromatography on SiO<sub>2</sub> eluting with 20% EtOAc in hexanes to afford the pure  $\alpha$ -amino ketone. The enantioselectivity of the reaction was determined by CSP-SFC analysis ((*S,S*)-Whelk-O1, 10% MeOH, 2.0 mL/min, 200 bar, 40 °C, 240 nm).

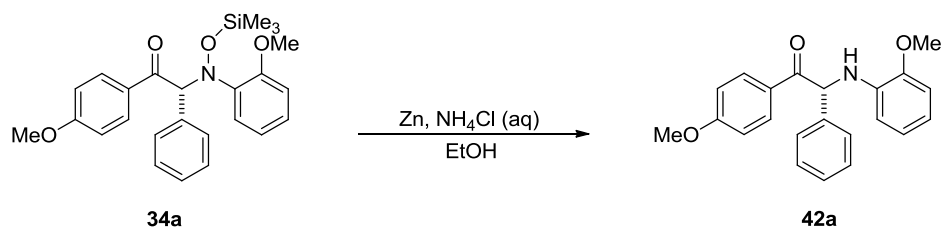


**1,2-bis(4-methoxyphenyl)-2-(2-methoxyphenylamino)ethanone (40d).** The title compound was prepared according to General Procedure **B** using 96.1 mg of *N*-silyloxy- $\alpha$ -amino ketone, 40.5 mg of zinc, and 23.7 mg of indium powder. Flash chromatography with 20% EtOAc in hexanes to afford 77.9 mg (82%) of the product as a pale yellow, solid in 98.5:1.5 e.r. as determined by CSP-SFC ( $t_{\text{r-major}}$  13.8 min,  $t_{\text{r-minor}}$  12.8 min);  $[\alpha]_{\text{D}}^{25}$  -77.2 ( $c = 0.72$ , CH<sub>2</sub>Cl<sub>2</sub>). Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 3019, 3065, 2840, 1674, 1603, 1511, 1265, 737, 705; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.02 (d,  $J = 9.2$  Hz, 2H), 7.39 (d,  $J = 8.8$  Hz, 2H), 6.91 (d,  $J = 9.2$  Hz, 2H), 6.81 (d,  $J = 8.4$  Hz, 2H), 6.80-6.70 (m, 2H), 6.68-6.62 (m, 1H), 6.58-6.50 (m, 1H), 5.95 (s, 1H), 5.85 (s (br), 1H),

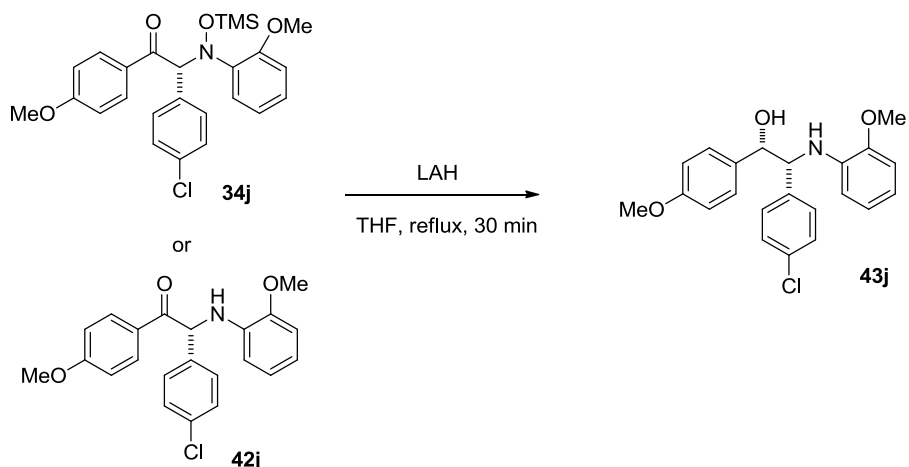
3.88 (s, 3H), 3.84 (s, 3H), 3.72 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.4, 163.6, 159.1, 147.1, 136.2, 131.1, 130.1, 129.2, 127.9, 120.8, 116.8, 114.3, 113.8, 110.5, 109.5, 61.3, 55.38, 55.36, 55.1 (four sets of coincidental signals); MS  $m/z$  = 377.16; TLC (40% EtOAc in hexanes)  $R_f$  0.49.



**2-(4-Chloro-phenyl)-1-(4-methoxy-phenyl)-2-(2-methoxy-phenylamino)-ethanone (42j).** The title compound was prepared according to General Procedure **B** using 158 mg of *N*-silyloxy-  $\alpha$ -amino ketone and 85 mg of zinc. Flash chromatography with 20% EtOAc in hexanes to afford 104 mg (81%) of the product as a pale yellow, solid in 91:9 e.r. as determined by CSP-SFC ( $t_{\text{r-major}}$  10.3 min,  $t_{\text{r-minor}}$  9.5 min);  $[\alpha]_{\text{D}}^{25}$  -17.7 ( $c$  = 1.05,  $\text{CH}_2\text{Cl}_2$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3066, 2975, 2824, 1675, 1600, 1509, 1457, 1420, 1314, 1256, 1169, 1115;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.01 (d,  $J$  = 6.9 Hz, 2H), 7.42 (d,  $J$  = 8.4 Hz, 2H), 7.25 (d,  $J$  = 10.0 Hz, 2H), 6.93 (d,  $J$  = 10.0 Hz, 2H), 6.80-6.73 (m, 2H), 6.69-6.66 (m, 1H), 6.50 (d,  $J$  = 7.8 Hz, 1H), 5.97 (s, 1H), 5.90 (s (br), 1H), 3.89 (s, 3H), 3.82 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  194.9, 163.9, 147.1, 136.9, 135.9, 133.7, 131.1, 129.3, 129.1, 127.7, 120.9, 117.2, 113.9, 110.6, 109.7, 61.3, 55.4 (five sets of coincidental signals); MS  $m/z$  = 381.3; TLC (20% EtOAc in hexanes)  $R_f$  0.38.



**1-(4-Methoxy-phenyl)-2-(2-methoxy-phenylamino)-2-phenyl-ethanone (42a).** The title compound was prepared according to General Procedure **B** using 145 mg of *N*-silyloxy- $\alpha$ -amino ketone and 81 mg of zinc. Flash chromatography with 20% EtOAc in hexanes to afford 86 mg (74%) of the product as a pale yellow, oil in 97:3 e.r. as determined by CSP-SFC ( $t_{\text{r-major}}$  19.2 min,  $t_{\text{r-minor}}$  16.7 min);  $[\alpha]_{\text{D}}^{25}$  -59.2 ( $c = 1.00$ ,  $\text{CH}_2\text{Cl}_2$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3062, 2962, 2840, 1675, 1602, 1513, 1455, 1322, 1258, 1169;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (d,  $J = 8.8$  Hz, 2H), 7.51 (d,  $J = 7.4$  Hz, 2H), 7.35-7.21 (m, 3H), 6.94 (d,  $J = 8.6$  Hz, 2H), 6.84-6.76 (m, 2H), 6.69-6.65 (m, 1H), 6.57 (d,  $J = 7.4$  Hz, 1H), 5.97 (s, 1H), 5.85 (s (br), 1H), 3.91 (s, 3H), 3.87 (s, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.4, 163.8, 147.2, 138.3, 136.3, 131.3, 129.0, 128.1, 128.0, 121.0, 117.0, 113.9, 113.8, 110.6, 109.6, 62.1, 55.5, 53.47 (four sets of coincidental signals); **MS**  $m/z = 347.15$ ; TLC (20% EtOAc in petroleum ether)  $R_f$  0.56.

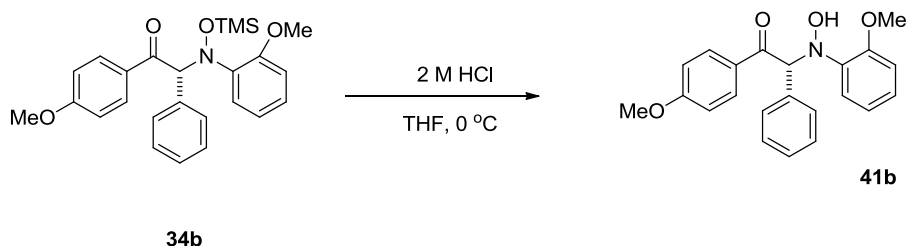


**(1*S*,2*R*)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-((2-methoxyphenyl)amino)ethanol (Scheme 1.14, 43j)**

In a flame-dried 10-mL round-bottomed flask under an atmosphere of N<sub>2</sub>, a stir bar and *N*-silyloxy- $\alpha$ -amino ketone (100 mg 0.210 mmol), were charged, followed by 5 mL of dry THF. Lithium aluminum hydride (0.15 mL, 1.0 M, 0.16 mmol) was added *via* syringe at room temperature. A condenser was then attached and the reaction heated to reflux for 1 hr. The reaction was cooled to room temperature, and extracted into Et<sub>2</sub>O. The organic layer was washed with saturated aqueous NH<sub>4</sub>Cl, NaHCO<sub>3</sub>, and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The resultant oil was purified by flash chromatography and obtained in 65% yield (55 mg) from **34j**; the title compound was accessible in 82% yield from amine **42j**. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.17 (d, *J* = 8.7 Hz, 2H), 7.05-6.99 (m, 3H), 6.92-6.82 (m, 3H), 6.76-6.70 (m, 4H), 5.32 (d, *J* = 9.9 Hz, 1H), 4.33 (d, *J* = 9.9 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H).

### General Procedure (C) for Cleavage of Silyl Protecting Group

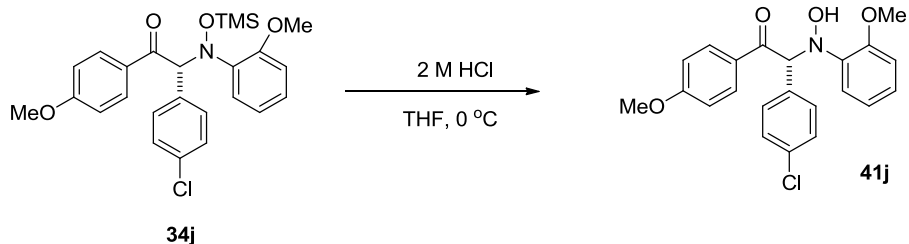
In a 10-mL round-bottomed flask, the crude *N*-silyloxy- $\alpha$ -amino ketone was dissolved in THF. The reaction was cooled to 0 °C, and 4 drops of 2 M aqueous HCl were added. The reaction was stirred for 5 minutes at 0 °C and monitored by TLC. Upon completion, the reaction was portioned between 1:1 Et<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub> and the organic layer separated. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated.



### (*R*)-2-(hydroxy(2-methoxyphenyl)amino)-1-(4-methoxyphenyl)-2-phenylethanone

#### (Scheme 1.14, **41b**)

The title compound was prepared by General Procedure C using 20 mg of crude *N*-silyloxy- $\alpha$ -amino ketone **34b**. Flash chromatography with 20% EtOAc in hexanes to afford 15 mg (91%) of the product as a pale colorless oil. Enantiomeric ratios were not determined by SFC, but reduction to secondary amine **42b** proceeds in 96:4 er whether the silyloxy or hydroxyl amine is employed, demonstrating that no racemization occurs in this step. Analytical data for title compound: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.88 (d, *J* = 8.8 Hz, 2H), 7.22-7.18 (m, 3H), 7.09-7.02 (m, 4H), 6.82-6.73 (m, 4H), 6.27 (s, 1H), 3.89 (s, 1H), 3.87 (s, 3H), 3.77 (s, 3H).



**(*R*)-2-(4-chlorophenyl)-2-(hydroxy(2-methoxyphenyl)amino)-1-(4-methoxyphenyl)ethanone (Scheme 1.14, 41j)**

The title compound was prepared by General Procedure C using 50 mg of crude *N*-silyloxy- $\alpha$ -amino ketone **34j**. Flash chromatography with 20% EtOAc in hexanes to afford 36 mg (89%) of the product as a pale colorless oil. Enantiomeric ratios were not determined by SFC, but reduction to secondary amine **42j** proceeds in 96:4 er whether the silyloxy or hydroxyl amine is employed, demonstrating that no racemization occurs in this step. Analytical data for title compound:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (d,  $J = 8.8$  Hz, 2H), 7.16 (d,  $J = 8.4$  Hz, 2H), 7.09-7.00 (m, 4H), 6.87-6.81 (m, 4H), 6.22 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H).

## 1.8 References

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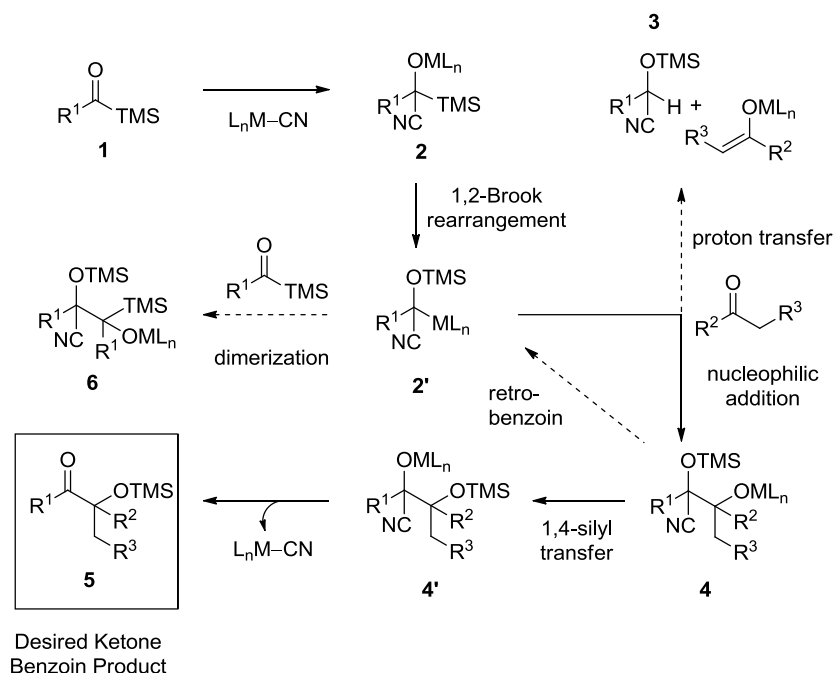
# **CHAPTER II**

## **LANTHANUM TRICYANIDE-CATALYZED ACYL SILANE-KETONE BENZOIN ADDITIONS AND KINETIC RESOLUTION OF RESULTANT $\alpha$ -SILYLOXYKETONES<sup>1</sup>**

### **2.1 Introduction**

In recent years polarity umpolung strategies have evolved into powerful synthetic tools for constructing otherwise challenging carbon-carbon bonds.<sup>2</sup> The benzoin reaction, the archetypical example of polarity umpolung, has recently become the subject of intense study which has led to the development of the asymmetric benzoin<sup>3</sup> and cross silyl benzoin<sup>4</sup> reactions promoted by NHC and metallophosphite catalysts, respectively. In moving beyond the acylation of aldehydes, methodologies have been developed for alkene acylation in the asymmetric Stetter<sup>5</sup> and sila-Stetter<sup>6</sup> reactions and, as discussed in the previous chapter, aldimine<sup>7</sup> and nitron<sup>8</sup> electrophiles have also been successfully utilized in umpolung acylation strategies. However, despite these advances in the benzoin reaction, a general catalytic procedure for the coupling of acyl donors to ketone electrophiles has remained a largely unmet challenge.

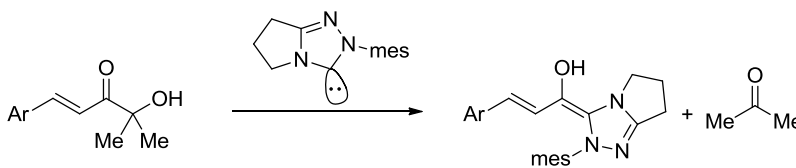
As can be inferred from the relative dearth of literature precedent, the ketone-benzoin reaction poses significant challenges compared to the parent aldehyde-benzoin reaction. Some of the potential pitfalls are illustrated in Scheme 2.1 below. The root of these challenges lies in the lower reactivity of ketones relative to aldehydes due to the extra steric demand posed by the second carbonyl substituent. This reduced reactivity allows side reactions to become competitive with the desired coupling process.



**Scheme 2.1.** Proposed Mechanistic Pathway for Acyl Silane-Ketone Benzoin Reaction and Possible Side Reactions

Productive reactivity arises from cyanide addition to the acyl silane, followed by [1,2]-Brook rearrangement ( $1 \rightarrow 2 \rightarrow 2'$ ). This intermediate undergoes nucleophilic attack on the ketone electrophile. The added steric hindrance of ketones relative to aldehydes can lead to dimerization of intermediate  $2'$  with a second equivalent of acyl silane leading to **6** rather than addition to the ketone. For ketones that possess acidic protons, deprotonation can lead to the quenched silyl cyanohydrins **3**. Once the desired carbon-carbon bond has been formed, the added steric hindrance between the two vicinal

quaternary centers in **4** can facilitate the retro-benzoin reaction back to **2'**. Intramolecular 1,4-silyl transfer followed by expulsion of cyanide furnishes the desired ketone-benzoin product **5**. Even if the desired product is formed, it may still be susceptible to undergoing retro-benzoin reaction as evidenced by Bode's recent report of an NHC-catalyzed retro-benzoin reaction of  $\alpha,\alpha$ -dimethyl- $\alpha$ -hydroxyketones as a strategy to mask unstable enal functionality (Scheme 2.2).<sup>9</sup>

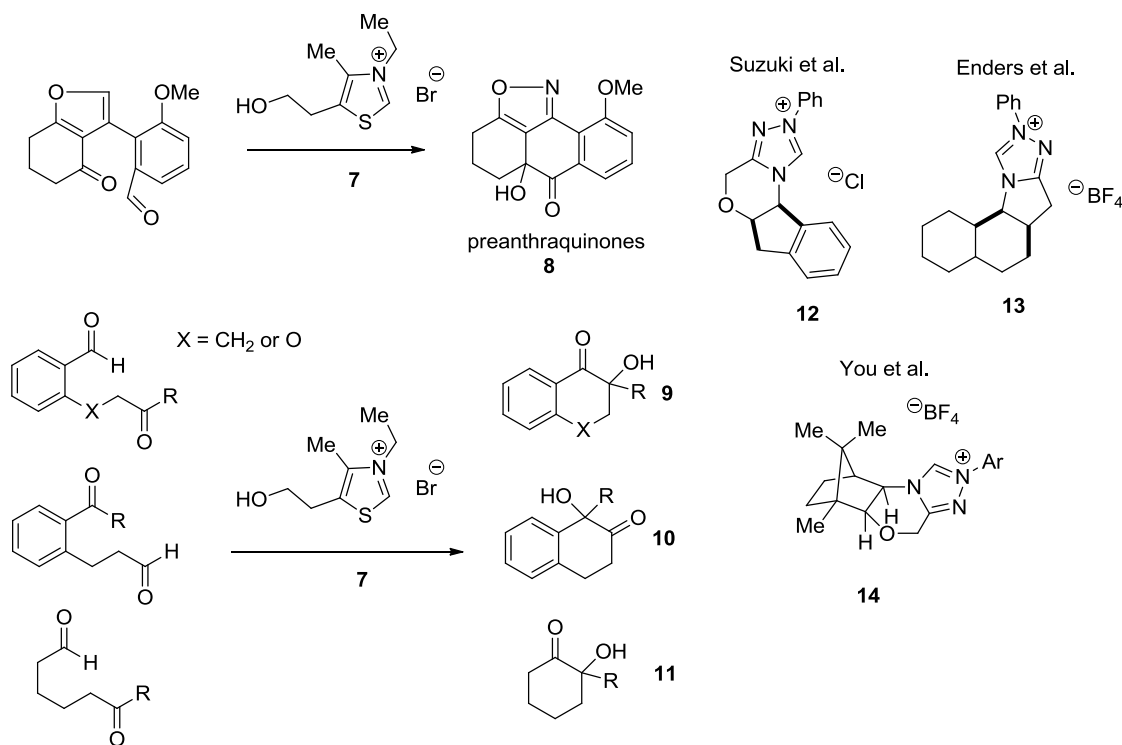


**Scheme 2.2.** NHC-Catalyzed Retro-Benzoin Reaction of Tertiary  $\alpha$ -Hydroxyketone

## 2.2 Background

Stoichiometric methods for generating acyl anion equivalents, such as deprotonation of dithianes or protected cyanohydrins, have been successfully employed in ketone acylation reactions.<sup>10</sup> However, there is no general strategy for accomplishing these reactions in an asymmetric fashion. Furthermore, we found that deprotection of tertiary  $\alpha$ -hydroxy dithianes results in an almost 1:1 mixture of the hydroxyl ketone and the alkene elimination product. In a seminal advance, Suzuki reported the first example of a catalytic aldehyde-ketone benzoin coupling.<sup>11</sup> Employing a thiazolium NHC catalyst **7**, Suzuki and co-workers were able to access the preanthraquinone skeleton **8** in good yields. Following the initial discovery, both the Suzuki and the Enders laboratories expanded the scope of the racemic ketone-benzoin to include less constrained intramolecular systems and were successful in incorporating alkyl and aryl ketones and

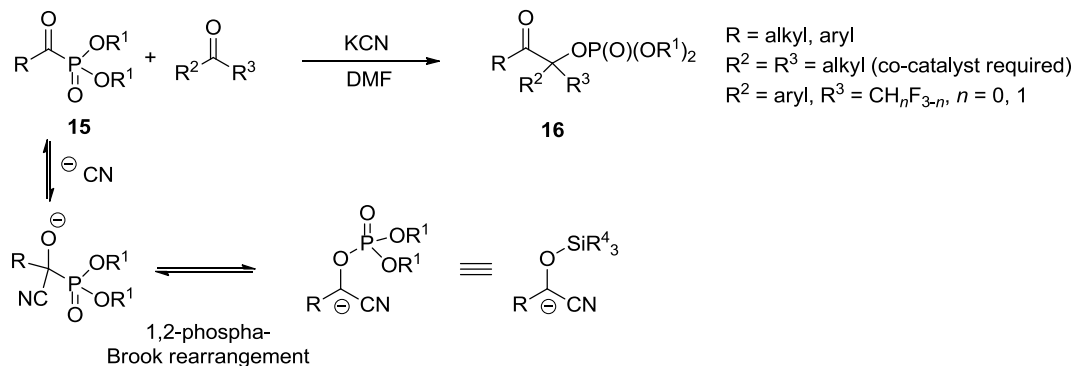
aldehydes (**9-11**).<sup>12, 13</sup> Subsequent efforts from Suzuki,<sup>14</sup> Enders,<sup>15</sup> and You<sup>16</sup> revealed that catalysts **12**, **13**, and **14** were competent in promoting the asymmetric intramolecular ketone-benzoin reaction and were able to afford enantiomerically enriched products of the type **9-11**.



**Scheme 2.3.** Intramolecular Ketone-Benzoin Reaction

The first example of an intermolecular catalytic ketone acylation was reported by Demir and coworkers, who were able to develop a cyanide-catalyzed coupling between acyl phosphonates and ketones in yields ranging from 41-95% (Scheme 2.4).<sup>17</sup> Acyl phosphonates are analogous to acyl silanes in their ability to serve as acyl anion synthetic equivalents by nucleophilic attack followed by 1,2-phospha-Brook rearrangement.<sup>18</sup> While this system is remarkable as the first example of the intermolecular ketone-benzoin reaction, the reaction is hampered by a limited substrate scope. Most of the examples employed electron-deficient aryl ketones and enolizable protons were often replaced with

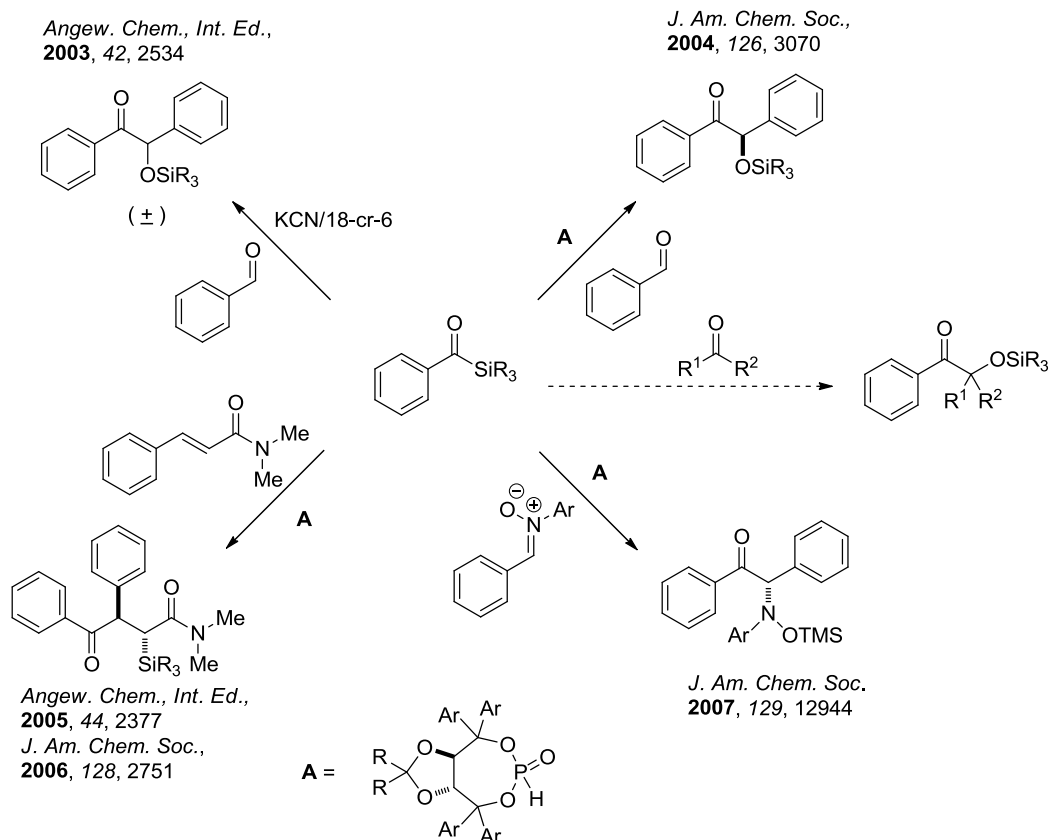
fluorine atoms. Most notably, the reaction was incompatible with ortho-substituted aryl ketones and most methyl aryl ketones. While the authors were able to use a limited number of aliphatic ketones, the reaction conditions required a case-by-case modification, including the addition of various co-catalysts such as  $\text{Cu}(\text{OTf})_2$  and a thiourea to activate the ketone.



**Scheme 2.4.** Demir's Intermolecular Acyl Phosphonate Ketone-Benzoin Reaction

Our laboratory has successfully employed acyl silanes as acyl donors for a variety of electrophiles including aldehydes,<sup>4</sup> alkenes,<sup>6</sup> and nitrones<sup>8</sup> (Scheme 2.5). It was our goal to extend this methodology to include the ketone electrophiles. We wished to develop a general catalytic procedure for the coupling of acyl silanes and a wide variety of ketones, without having to optimize the catalysts and reagents on a case-by-case basis. Additionally, we sought to develop a platform that could yield enantiomerically enriched products.





**Scheme 2.5.** Electrophiles Previously Acylated Using Acyl Silanes

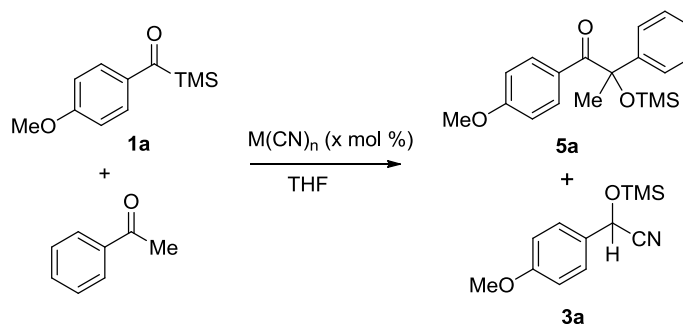
## 2.3 Results and Discussion

### 2.3.1 Discovery and Optimization of Acyl Silane-Ketone Silyl Benzoin Reactions

To initiate our investigations into the ketone-benzoin reaction, we chose to examine lanthanum tricyanide as a catalyst.<sup>19</sup> Previous work in our group had identified La(CN)<sub>3</sub> as a particularly effective catalyst in promoting the cross silyl benzoin reaction. This catalyst promoted challenging alkyl silane-alkyl aldehyde couplings that failed to proceed with other cyanide catalysts.<sup>20</sup> We hoped that this highly reactive system would allow us to overcome the inherent difficulties of the intermolecular ketone-benzoin. Gratifyingly, we found that acyl silane **1a** reacted with one equivalent of acetophenone in the presence of 20 mol % of La(CN)<sub>3</sub> in THF to deliver the desired α-silyloxyketone product in

approximately 40% yield within 20 minutes. Additionally, we observed no desired product formation when using KCN, 18-cr-6/KCN, TMSCN/TBAF as the catalyst in a variety of solvents including DMF.

Competing with desired product formation in our model reaction was proton transfer from acetophenone leading to the quenched silyl cyanohydrin (**3a**), as well as retro-benzoin reaction of the desired product. Empirically, we determined that employing two equivalents of ketone was optimal, as the product **5a** was obtained in greater than 90% yield when these conditions were applied. In a screen of metal cyanide catalysts, we found that numerous  $M(CN)_n$  species effectively promoted the reaction and gave complete conversion (Table 2.1); however,  $La(CN)_3$  provided the highest ratio of desired product (**5a**) to the quenched cyanohydrin (**3a**). Optimization of the catalyst loading showed that the benzoin product could be obtained in up to 95% yield with 10 mol % catalyst loading. Lowering the catalyst loading to 5 mol % provided the product with no change to the conversion or yield. Upon further reduction of the catalyst loading to 2 mol % and 1 mol %, the reaction stalled with incomplete conversion after 24 h.

**Table 2.1.** Optimization of  $M(CN)_3$  Catalyst<sup>a</sup>

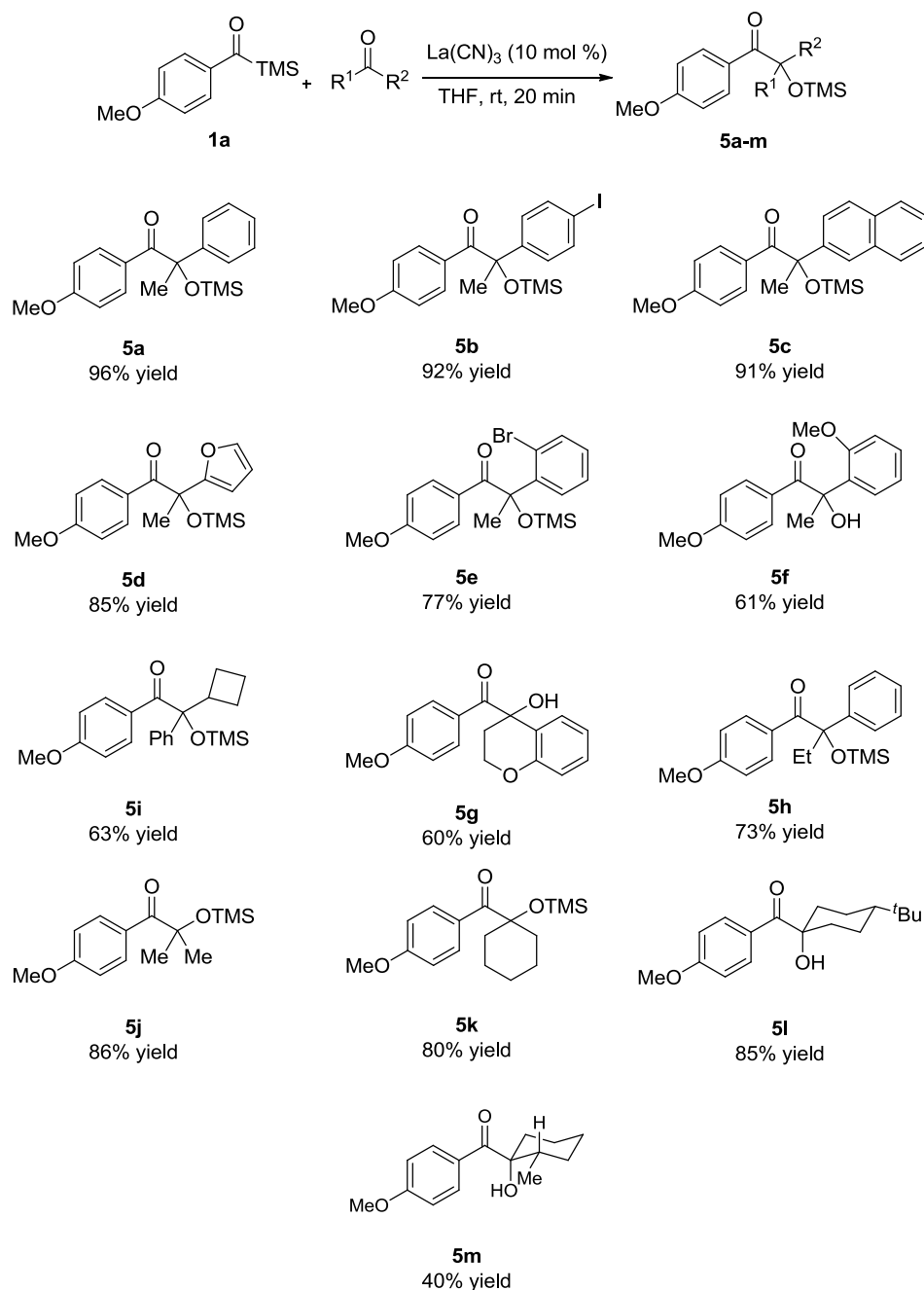
entry	catalyst	x mol %	convn (%) <sup>b</sup>	5a:3a <sup>b</sup>	yield (%) <sup>c</sup>
1	Ce(CN) <sub>3</sub>	20	100	3.2:1	nd
2	Y(CN) <sub>3</sub>	20	100	4.5:1	nd
3	Yb(CN) <sub>3</sub>	20	100	6.5:1	nd
4	Sc(CN) <sub>3</sub>	20	100	6.8:1	nd
5	Er(CN) <sub>3</sub>	20	100	8.0:1	nd
6	Hf(CN) <sub>4</sub>	20	100	8.6:1	nd
7	La(CN) <sub>3</sub>	20	100	10.5:1	nd
8	La(CN) <sub>3</sub>	10	100	nd	95
9	La(CN) <sub>3</sub>	5	100	nd	94
10	La(CN) <sub>3</sub>	2	62	nd	nd
11	La(CN) <sub>3</sub>	1	7	nd	nd

<sup>a</sup> Conditions: 1.0 equiv of **1a**, 2.0 equiv of ketone, 0.10 equiv of La(CN)<sub>3</sub>, THF, [**1a**]<sub>0</sub> = 0.04 M, rt, 20 min. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> Yields of analytically pure material after SiO<sub>2</sub> column chromatography.

### 2.3.2 Scope: Ketone Partner

The scope of the reaction was first probed in terms of the ketone coupling partner with acyl silane **1a**. The results of this screen are shown in Figure 2.1. The reactions all proceeded with complete consumption of acyl silane with isolated yields ranging from 40-95%. The major byproduct in all cases was the quenched cyanohydrin, which accounts for most of the remaining mass balance. For some substrates, it was convenient to deprotect the silyl ether to the alcohol using TBAF at 0 °C in order to separate the benzoin product from the ketone starting material. In all cases, this desilylation

proceeded smoothly within 10 minutes, and elimination to the alkene was never observed.

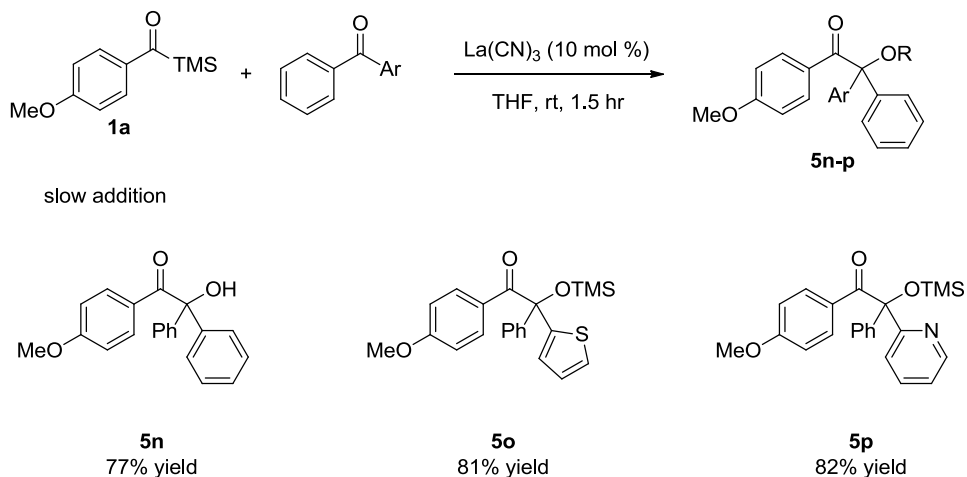


**Figure 2.1.** Scope of Ketone Coupling Partner

Our initial screen of ketone substrates revealed a reaction that was quite general. Both aryl-alkyl and alkyl-alkyl ketones resulted in high isolated yields. The new

methodology addresses a number of limitations in the Demir system.<sup>17</sup> All of the ketones examined possess enolizable protons and a potential source of silylcyanohydrin quenching. Aryl-methyl ketones performed exceedingly well, as did both *ortho*-substituted aryl groups and electron-rich and electron-neutral aryl groups. Furthermore, no changes in the reaction conditions or additional co-catalysts were necessary to achieve the desired coupling. The reaction does seem to be fairly sensitive to the steric environment of alkyl ketones as well as the pK<sub>a</sub> of the  $\alpha$ -protons. The major byproduct obtained in all of the coupling reactions was the protonated silyl cyanohydrin resulting from ketone enolization. While methyl and ethyl groups were well tolerated, tertiary carbons at the  $\alpha$ -position typically introduce too much steric repulsion for productive coupling. Both isobutyrophenone and cyclopentyl-methyl ketone provided the desired product in less than 10% yield, and pinacolone yielded no desired coupling (not shown). Compound **5i** shows just how sensitive the reaction can be to even small changes in the steric environment at the  $\alpha$ -position. The benzoin coupling of acyl silane **1a** with cyclobutyl phenyl ketone yielded **5i** in 63% yield, despite possessing a very similar steric environment to isobutyrophenone. The difference in yields appears to be steric in origin rather than  $\alpha$ -proton acidity for alkyl ketones. The pK<sub>a</sub> for propiophenone is 24.4 yet **5h** is obtained in 73% yield, whereas the pK<sub>a</sub> of isobutyrophenone is 26.3, but the desired product is obtained in less than 10% yield.<sup>21</sup> Methyl pyruvate, whose attempted coupling yielded only quenched cyanohydrin, represents the single example where enolization rather than steric hindrance proves to be more detrimental to the achieving the desired reaction.

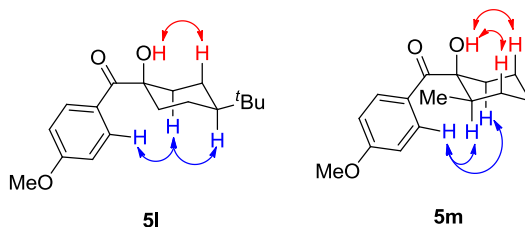
We next endeavored to couple acyl silanes with diaryl ketones. While lacking enolizable protons, the additional steric constraints of these ketones make this a challenging transformation. Initial attempts at employing benzophenone under the normal reaction conditions led to less than 20% yield of the desired coupling product. In addition to cyanohydrin formation (presumably from adventitious water), acyl silane dimerization and desilylation of the acyl silane also accounted for significant decreases in the yield. We found that freshly distilling the benzophenone prior to use provided a marginal improvement. Employing a slow addition of the acyl silane via syringe pump over fifty minutes allowed us to isolate the desired product in 80% yield after silyl deprotection and flash column chromatography. This procedure works for both carbocyclic and heterocyclic diaryl ketones, as evidenced by compounds **5n-p** in Figure 2.2.



**Figure 2.2.** Addition of Acyl Silane to Diaryl Ketones

### 2.3.3 Diastereoselectivity of Reaction

Products **5l** and **5m** demonstrate the high degree of stereoselectivity possible in the reaction with cyclic ketones, each being isolated as a single diastereomer. In order to determine the relative stereochemistry between the existing alkyl group and the newly introduced acyl group, 2-D NOESY was employed (Figure 2.3). In **5l**, a nOe was observed between the hydroxyl proton and the two axial  $\gamma$ -protons, as well as between the ortho aryl protons and the axial  $\beta$ -protons on the cyclohexane ring. Similar nOe's were observed for compound **5m**. This leads us to propose the illustrated stereochemistry with the hydroxyl group *cis* to the existing alkyl group. The observed stereochemistry arises from an equatorial attack of the acyl silane to avoid 1,3-diaxial interactions, even in the case of 2-methylcyclohexanone, where the vicinal methyl group also occupies the equatorial position.

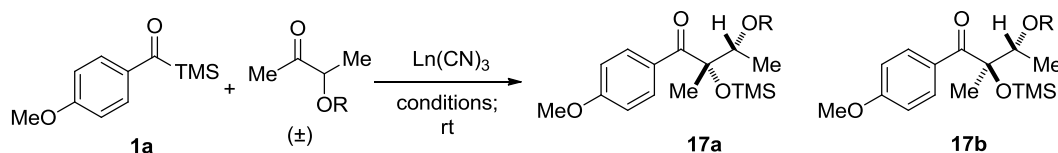


**Figure 2.3.** NOESY Analysis to Determine Equatorial Attack

After achieving such high levels of diastereocontrol with cyclic electrophiles, we sought to determine if we could extend this control to acyclic systems. We hoped that we could use an  $\alpha$ -stereocenter to exert either Felkin-Ahn<sup>22</sup> or chelation<sup>23</sup> diastereocontrol on the ketone-benzoin coupling. To our knowledge, this is first example of utilizing an  $\alpha$ -stereocenter to control the diastereoselectivity of the benzoin reaction. We found that acyl silane **1a** did couple with various protected acetoin to yield  $\alpha,\beta$ -dihydroxy ketones.

As with the diaryl ketone substrates, a slow addition of the acyl silane to a suspension of the ketone and catalyst provided increased yields. We screened a number of hydroxyl protecting groups and reaction conditions, summarized in Table 2.2. While we achieved minimal ketone facial selectivity with the benzyl protecting group, we found that the MOM group afforded moderate levels of diastereocontrol (2.7:1) favoring the chelation product (MOM =  $\text{CH}_2\text{OCH}_3$ ). A solvent screen identified  $\text{Et}_2\text{O}$  and MTBE as giving similar diastereoselectivity; however,  $\text{Et}_2\text{O}$  afforded higher yields in the reaction. We were uncertain as to the effectiveness of  $\text{La}(\text{CN})_3$  as a chelating catalyst. The  $\text{La}(\text{CN})_3$  is heterogeneous, and it is unknown what portion is soluble and available for substrate chelation. Believing a more soluble metal catalyst may lead to higher diastereoselectivities, we screened a variety of  $\text{Ln}(\text{CN})_3$  catalysts, as well as a number of soluble lanthanide and Lewis acid additives. Unfortunately, none of these conditions led to higher observed diastereoselectivities.



**Table 2.2.** Optimization of Chelation Control in Addition to Protected Acetoins<sup>a</sup>

entry	R	$\text{Ln}(\text{CN})_3$	solvent	additive	yield	<b>17a:17b</b> <sup>b</sup>
1 <sup>c</sup>	Bn	$\text{La}(\text{CN})_3$	THF	none	49	1:1.4
2 <sup>c</sup>	Bn	$\text{La}(\text{CN})_3$	$\text{Et}_2\text{O}$	none	45	1.1:1
3	MOM	$\text{La}(\text{CN})_3$	THF	none	42	1.4:1
4	MOM	$\text{La}(\text{CN})_3$	$\text{Et}_2\text{O}$	none	80	2.7:1
5	MOM	$\text{La}(\text{CN})_3$	$\text{MeO}^c\text{C}_5\text{H}_9$	none	10	1.2:1
6	MOM	$\text{La}(\text{CN})_3$	$\text{MeO}^t\text{Bu}$	none	71	2.1:1
7	MOM	$\text{La}(\text{CN})_3$	$\text{Et}_2\text{O}$	LiCl	70	2.1:1
8	MOM	$\text{La}(\text{CN})_3$	$\text{Et}_2\text{O}$	$\text{MgBr}_2$	NDP <sup>d</sup>	---
9	MOM	$\text{La}(\text{CN})_3$	$\text{Et}_2\text{O}$	$\text{ZnBr}_2$	NDP <sup>d</sup>	---
10	MOM	$\text{Ce}(\text{CN})_3$	$\text{Et}_2\text{O}$	none	76	2.0:1
11	MOM	$\text{Er}(\text{CN})_3$	$\text{Et}_2\text{O}$	none	72	1.8:1
12	MOM	$\text{Yb}(\text{CN})_3$	$\text{Et}_2\text{O}$	none	49	1.2:1

<sup>a</sup> Conditions: 1.0 equiv of **1a** added via slow addition, 2.0 equiv of ketone, 0.10 equiv of  $\text{La}(\text{CN})_3$ , THF,  $[\mathbf{1a}]_0 = 0.04 \text{ M}$ . <sup>b</sup> Yields and dr determined by  $^1\text{H}$  NMR. <sup>c</sup> **1a** added via normal addition. <sup>d</sup> NDP = no desired product.

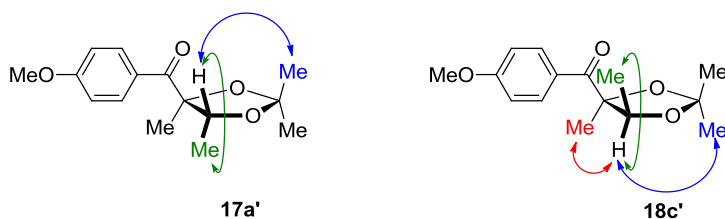
To investigate the feasibility of obtaining the opposite (Felkin-Ahn) diastereomer, we investigated non-chelating silyl protecting groups (Table 2.3). As expected, we found that as the size of the silyl group was increased from TMS to TES to TBS, the dr likewise increased (this trend did not extend to the TIPS group). Upon varying the reaction temperature, we found that we could increase the dr of the reaction up to 10:1 by running the reaction at  $-20^\circ\text{C}$ ; however, the diastereoselectivity came at the expense of yield as competing side reactions could not be suppressed even with slow addition of **1a** at the lower temperature. To verify chelation and Felkin-Ahn controlled products were formed under the respective conditions, the products were converted to the free diols and then to the corresponding acetonides. 2D-NOESY analysis of the resultant acetonides confirmed

that **17a** was indeed the *syn*-diol arising from chelation control and **18c** was consistent with the *anti*-diol and Felkin-Ahn control (Figure 2.4). Scheme 2.6 shows the final optimized conditions, yields, and diastereomer ratios for both the chelation and Felkin-Ahn controlled ketone benzoin reactions.

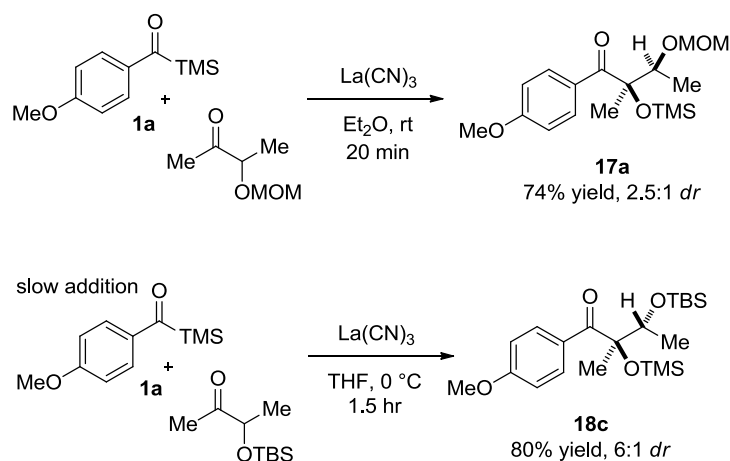
**Table 2.3.** Optimization of Felkin-Ahn Control in Addition to Protected Acetoins<sup>a</sup>

entry	R	T (°C)	yield (%) <sup>b</sup>	<b>18c:18d</b> <sup>b</sup>
1	TMS	0	65	2:1
2	TES	0	70	4:1
3	TBS	0	80	6:1
4	TIPS	0	74	3.5:1
5	TBS	-20	48	10:1

<sup>a</sup> Conditions: 1.0 equiv of **1a**, 2.0 equiv of ketone, 0.10 equiv of La(CN)<sub>3</sub>, THF, [**1a**]<sub>0</sub> = 0.04 M. <sup>b</sup> Yields and dr were determined by <sup>1</sup>H NMR.

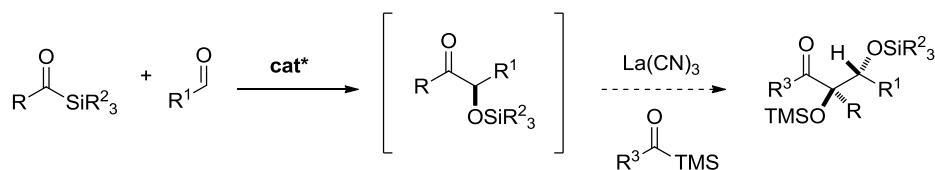


**Figure 2.4.** NOESY Analysis to Confirm Felkin-Ahn and Chelation Controlled Addition



**Scheme 2.6.** Optimized Conditions for Achieving Felkin-Ahn or Chelation Control

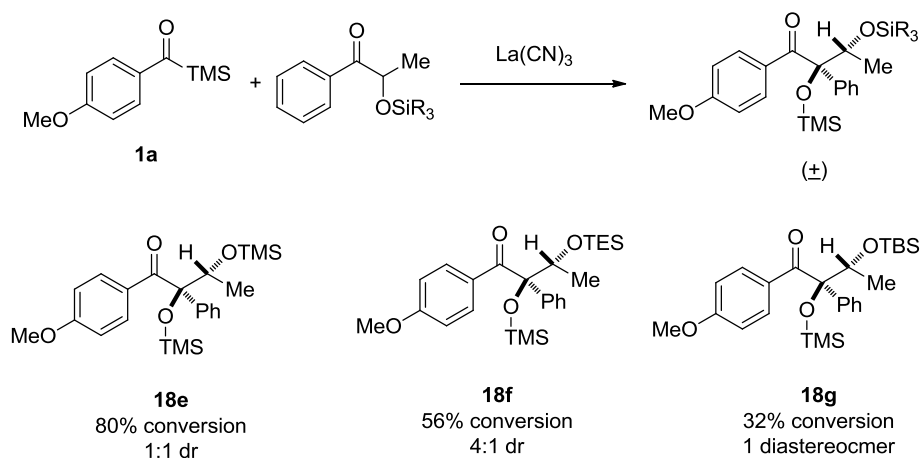
The  $\alpha$ -silyloxy ketone substrates employed as electrophiles in the Felkin-Ahn controlled ketone-benzoin reaction could potentially arise from a cross silyl aldehyde-benzoin reaction themselves. This raised the intriguing possibility of conducting a cross silyl benzoin reaction followed by a ketone-benzoin reaction in one pot (Scheme 2.7). As the metallophosphite catalyst is capable of controlling the asymmetric cross silyl benzoin, this strategy could also provide access to enantiomerically enriched products.



**Scheme 2.7.** Proposed Tandem Aldehyde-Ketone Acylation

Despite examining several potential coupling partners, we were unfortunately never able to realize this tandem sequence. The benzoin products that we were able to access with the metallophosphite catalyst were too sterically encumbered to undergo subsequent ketone-benzoin reaction (the metallophosphite catalyst proved ineffective for generating acetoin products). Additionally, any amount of ketone-benzoin product that was formed was inseparable from the cross silyl benzoin product. The only non-acetoin derived

substrates that underwent any measurable degree of coupling arose from phenyl-methyl benzoin products, which were accessed via a Rubottom oxidation of propiophenone. As was observed with the protected acetoin, the diastereoselectivity of the reaction increased with the bulk of the silyl protecting group, at the expense of the conversion. We were unable to strike a compromise where both the conversion and dr reached synthetically useful levels; the results of these efforts are shown in Scheme 2.8 below.



**Scheme 2.8.** Results from Felkin-Ahn Controlled Addition to Propiophenone Derivatives

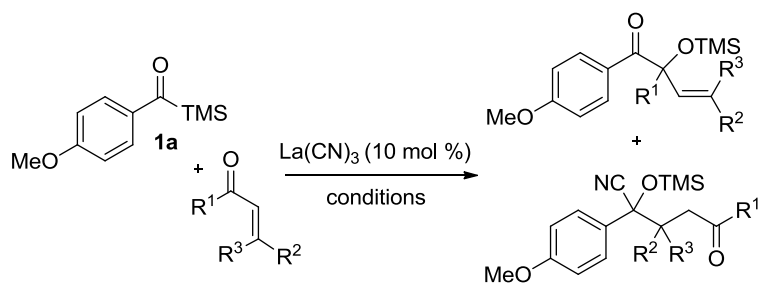
#### 2.3.4 Scope: Enones

After expanding the scope of the reaction to include alkyl-alkyl, aryl-alkyl, and aryl-aryl ketones, we turned our attention to enones and ynones. Choosing cyclohexenone as our initial model system, we were disappointed to isolate only a small amount (9%) of the desired product. The major product in the reaction was the 4-silyloxycyanohydrin ketone resulting from Stetter-type 1,4-addition to the enone (Table 2.4, entry 1).<sup>24</sup> In the Stetter-type reaction, the resultant enolate was not sufficiently nucleophilic to undergo silyl transfer and initiate catalyst turnover. This is consistent with previous work in our lab on the metallophosphite-catalyzed sila-Stetter reaction, where it was necessary to use  $\alpha,\beta$ -

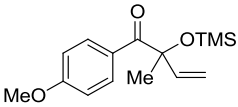
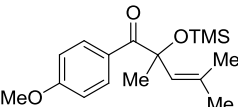
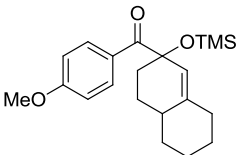
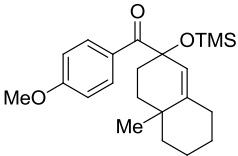
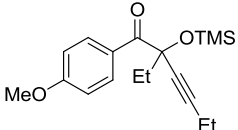
unsaturated amides as the electrophile. The enolates derived from enones and esters were not sufficiently nucleophilic to initiate silyl transfer and achieve catalyst turnover.<sup>6</sup> Thus, the reactions between acyl silanes and some enones required stoichiometric cyanide to achieve complete conversion in the cases where substantial 1,4-addition occurred. The silyl cyanohydrins exist as inseparable mixtures of diastereomers. Cleavage of the silyl group with TBAF converted both diastereomers to the 1,4-diketone.

Fortunately, we found that the yield of the 1,2-addition product increased when enones with more steric hindrance at the  $\beta$ -position were employed. In cyclohexene-derived enones,  $\gamma$ -substitution was particularly effective at preventing conjugate addition as the substituents extend above or below the plane of the alkene to block the incoming nucleophile. Additionally, acyclic enones gave more of the 1,2-addition product than comparably substituted cyclic alkenes. An ynone was also found to be a competent coupling partner as evidenced by the formation of **19j**. No conjugate addition product was observed with this substrate. We observed a marked decrease in the diastereoselectivity for addition to fused-decalin enone systems as compared to saturated cyclohexanone scaffolds. Decalin products **19h** and **19i** were obtained in a 2.5:1 and a 2.7:1 dr respectively, as compared to the single diastereomer that was isolated from 4-*t*Bu-cyclohexanone.

**Table 2.4.** Scope of  $\alpha,\beta$ -Unsaturated Coupling Partners<sup>a</sup>



entry		product	% yield (dr) <sup>b</sup>
1 <sup>c</sup>	<b>19a</b>		9
1 <sup>c,d</sup>	<b>19a'</b>		71
2 <sup>c</sup>	<b>19b</b>		35
2 <sup>c,d</sup>	<b>19b'</b>		29
3 <sup>c</sup>	<b>19c</b>		45
3 <sup>c,d</sup>	<b>19c'</b>		33
4 <sup>c</sup>	<b>19d</b>		41
5	<b>19e</b>		82

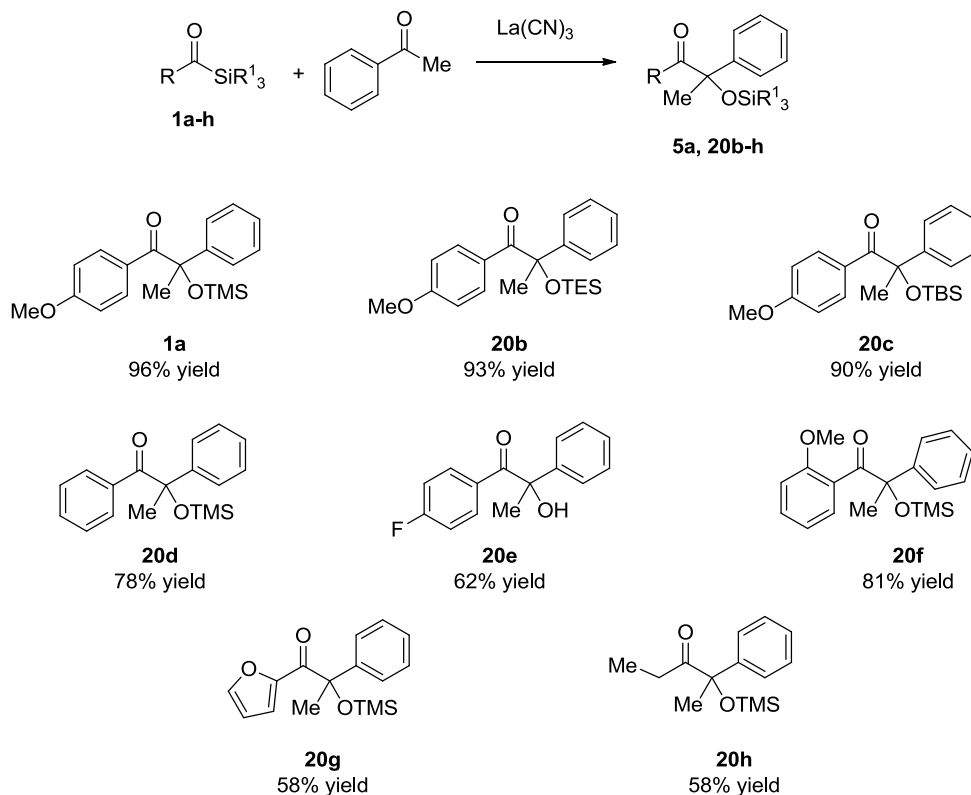
6 <sup>c</sup>	<b>19f</b>		34
7	<b>19g</b>		69
8	<b>19h</b>		74 (2.5:1)
9	<b>19i</b>		83 (2.7:1)
10	<b>19j</b>		86

<sup>a</sup> Conditions: 1.0 equiv of **1a**, 2.0 equiv of ketone, 0.10 equiv of La(CN)<sub>3</sub>, THF, [**1a**]<sub>0</sub> = 0.04 M, rt, 20 min. <sup>b</sup> Yields of analytically pure material after SiO<sub>2</sub> column chromatography, dr determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> Stoichiometric cyanide was employed. <sup>d</sup> Product was treated with 1.0 equiv TBAF at 0 °C for 10 min to provide diketone which was used for characterization. Yield refers to yield of the silylcyanohydrin.

### 2.3.5 Scope: Acyl Silane

In addition to varying the ketone component, we examined the reaction's tolerance with respect to the variation of the acyl silane coupling partner. The results of this survey are shown in Figure 2.5. Electron-rich acyl silanes deliver a more nucleophilic (silyloxy)nitrile anion intermediate and performed the best, as expected.<sup>6,17</sup> Yields of the coupling product decreased as a function of electron density on the aryl ring, as evidenced by compounds **5a**, **20d**, and **20e**. The effect of steric hindrance in the acyl silane component was examined with **1f**, which delivered the desired product **20f** with a

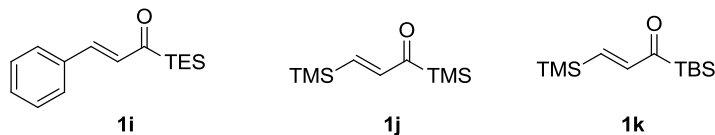
slight decrease in yield. In addition to aromatic acyl silanes, both heteroaromatic and aliphatic silanes were tolerated. The more sterically demanding TES and TBS groups were also tolerated with almost no decrease in yield (**20b** and **20c**).



**Figure 2.5.** Scope of the Acyl Silane Coupling Partner

$\alpha,\beta$ -Unsaturated acyl silanes represent the one major class of substrates that was not tolerated in the silyl ketone-benzoin reaction. All alkenyl silanes we examined yielded a complex mixture of compounds. While somewhat speculative, it is most likely that the more reactive vinyl silanes (specifically compounds **1j** and **1k**)<sup>25</sup> are undergoing dimerization/polymerization rather than productive coupling with the less reactive ketones.

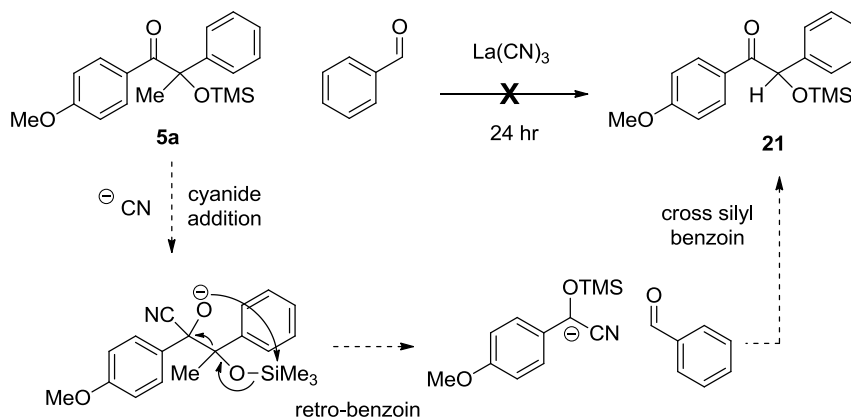




**Figure 2.6.** Incompatible Acyl Silane Coupling Partners

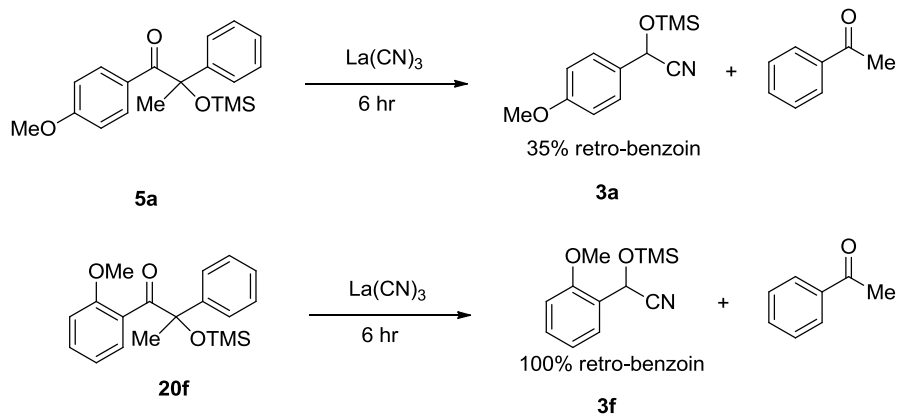
### 2.3.6 Retro-Benzoin Reaction

After defining the breadth and limitations of the reaction scope, we endeavored to explore the mechanism in more detail, specifically in terms of the retro-benzoin reaction. Our interest in the retro-benzoin reaction arose from the possibility of employing a chiral nucleophilic catalyst to perform a kinetic resolution of the racemic product by inducing retro-benzoin degradation of one enantiomer.<sup>9</sup> In our initial probe, we subjected compound **5a** to  $\text{La}(\text{CN})_3$  and excess benzaldehyde. If retro-benzoin reaction did occur, then at least a portion of the product should be trapped as the cross silyl benzoin product, **21**. After 24 hr, only starting material **5a** was recovered from the reaction.



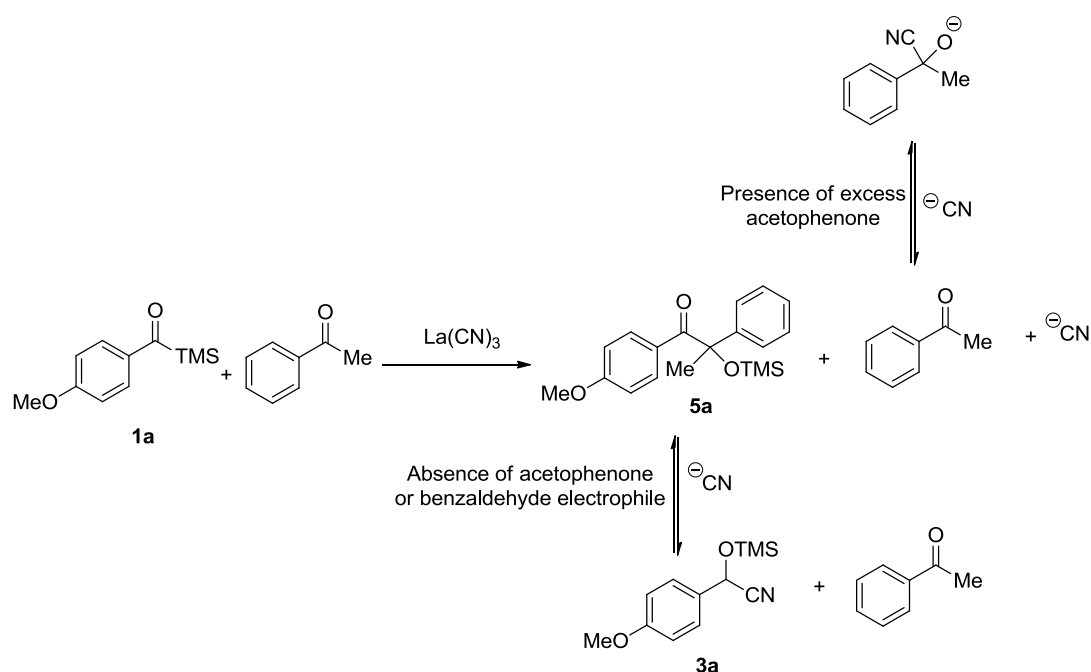
**Scheme 2.9.** Retro-Benzoin Crossover Experiment

However, we obtained contradictory results when we subjected either compound **5a** or **20f** to  $\text{La}(\text{CN})_3$  in the absence of benzaldehyde: partial or complete degradation to acetophenone and the corresponding silyl cyanohydrin.



**Scheme 2.10.**  $\text{La(CN)}_3$ -Catalyzed Retro-Benzoin Reaction

We explain these observations with the following rationale: the retro-benzoin pathway operates in competition with desired product formation. However, the resultant  $\alpha$ -silyloxyketone is quite sterically hindered. We believe that when excess ketone is used, the cyanide adds to the excess ketone rather than to the product silyloxyketone. This reduces the concentration of free cyanide in the reaction solution and retards the rate of the retro-benzoin pathway. In the crossover experiment described, benzaldehyde performs the same function. However, in the absence of a more accessible electrophile, the cyanide can add to the silyloxyketone and initiate a retro-benzoin reaction. This rationale also explains why 1.5 to 2 equivalents of the ketone were necessary for optimal conversions. While we were able to initiate the retro-benzoin reaction using  $\text{La(CN)}_3$  as the catalyst, we were unable to achieve the same results with thiourea NHC catalysts.



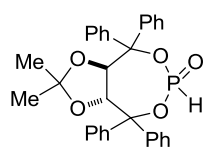
**Scheme 2.11.** Mechanistic Rationale for Retro-Benzoin Observations

### 2.3.7 Kinetic Resolution

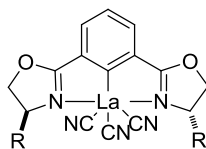
We next directed our attention towards developing a catalytic asymmetric platform to accomplish the ketone-benzoin reaction. The metallophosphite catalyst developed by our laboratory (Figure 2.7, **A1**) proved ineffective at promoting the ketone-benzoin under a variety of conditions including increased temperature, longer reaction times, and the use of  $\alpha,\alpha,\alpha$ -trifluoroacetophenone, a substrate with no enolizable protons. The lack of reactivity is presumably due to steric congestion. We were encouraged by Demir's observation that both Lewis and Brønsted acid co-catalysts were capable of accelerating the intermolecular coupling of acyl phosphonates and ketones, and felt these scaffolds may provide a source of enantiocontrol.<sup>17</sup> We observed that addition of a thiourea co-catalysts **D1** and **D2** did increase the relative rate of the reaction at  $-30\text{ }^\circ\text{C}$  compared to just  $\text{La}(\text{CN})_3$ ; however, no asymmetric induction was observed in the products. Likewise, use of  $(\text{box})\text{La}(\text{CN})_3$  and  $(\text{pybox})\text{La}(\text{CN})_3$  (**B1** and **B2**) yielded racemic

product. Employing chiral (box)Cu(OTf)<sub>2</sub> complexes **C** also failed to yield any asymmetric induction.

Chiral Catalysts



**A1**

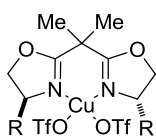


**B1**

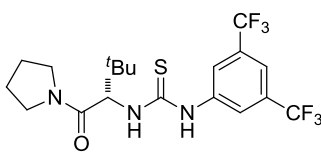


**B2**

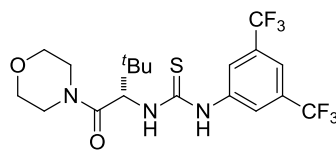
Chiral Co-Catalysts



**C**



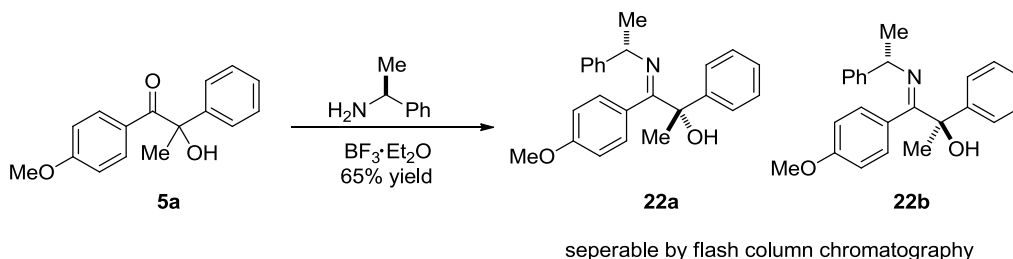
**D1**



**D2**

**Figure 2.7.** Chiral Catalysts and Co-Catalysts Screened for Ketone-Benzoin Reaction

Given the elusiveness achieving the catalytic asymmetric ketone-benzoin reaction, we explored other possibilities for obtaining optically enriched products. We were initially able to resolve the two enantiomers with a chiral amine. We found that condensation of the  $\alpha$ -hydroxyketone products with *R*- $\alpha$ -methylbenzylamine led to the formation of diastereomeric imines that could be separated by flash chromatography, providing a stoichiometric approach to resolution. While methylbenzylamine may offer a stoichiometric route to separate the enantiomers at a reasonable cost, we still wished to effect a catalytic transformation for obtaining enantioenriched products.



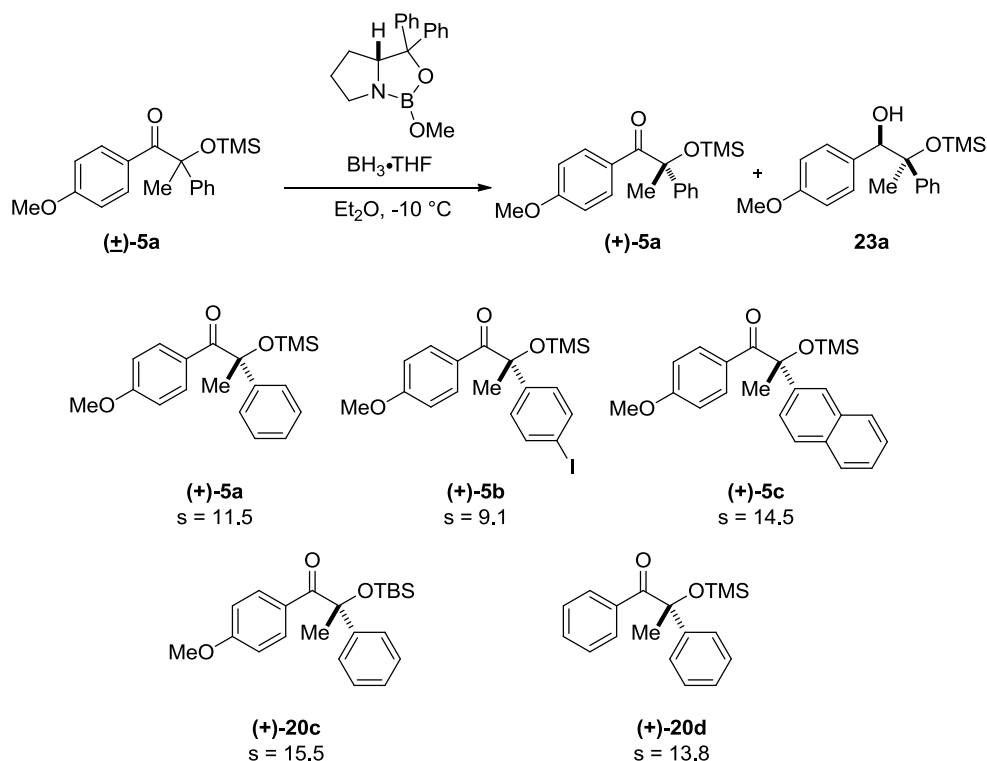
**Scheme 2.12.** Resolution of **5a** with *R*- $\alpha$ -Methylbenzylamine

We were pleased to find that when the silyloxyketone product **5a** was subjected to a CBS reduction, the recovered starting material was enriched in one enantiomer.<sup>26</sup> Thus, we decided to employ the CBS reduction to achieve a kinetic resolution of the  $\alpha$ -silyloxyketones.<sup>27</sup> Choosing silyloxyketone **5a** as a model substrate for optimization, the role of the protecting group was investigated. We found that the silyl-protected hydroxyketones seem uniquely suited to undergo kinetic resolution; when the reaction was conducted with the free hydroxyl group no rate difference was observed for the two enantiomers. Thus, the acyl silane-ketone benzoin reaction directly furnishes the substrate necessary for the resolution. It stands to reason that the tertiary carbinol acts as  $R_{\text{large}}$ , with the aryl group functioning as  $R_{\text{small}}$ , as increasing the steric bulk of the silyl group from TMS to TBS led to an increase in the selectivity factor.

Upon screening a variety of reaction variables we found the optimal borane source to be  $\text{BH}_3 \cdot \text{THF}$ . The reaction could be conducted with a catalyst loading as low as 10 mol% of the oxaborolidine catalyst without loss of the reaction efficiency. It was optimal to employ two equivalents of the borane, as lower loadings resulted in the reaction stalling at low conversion. We were able to obtain higher selectivity factors at lower temperatures; however, the reaction was impractically slow at  $-30\text{ }^\circ\text{C}$ . We found the optimum compromise between rate and resolution to be  $-10\text{ }^\circ\text{C}$ . While both aromatic and

ethereal solvents provided the desired product, Et<sub>2</sub>O provided the fastest reaction times while still maintaining high selectivity factors.

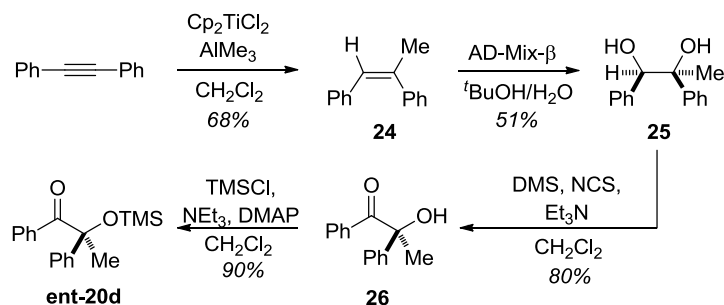
With the optimized conditions in hand, we sought to explore the generality of the kinetic resolution. Selectivity factors obtained with methy-aryl ketones were between 10 and 15 (Figure 2.8). The reaction is fairly general for aryl-methyl ketones; unfortunately, other substrates (including dialkyl, vinyl-alkyl, and alkynyl-alkyl) resulted in very little discrimination between enantiomers. The bulkier TBS group can be substituted for the TMS protecting group which results in a slightly higher selectivity factor.



**Figure 2.8.** Kinetic Resolution of  $\alpha$ -Silyloxy Ketones via CBS Reduction

The absolute stereochemistry of the product  $(+)$ -20d was determined to be *R* by comparison to a sample of independently prepared *ent*-20d. Synthesis of *ent*-20d commenced with carbometallation of diphenyl acetylene to yield *Z*-alkene **24**.<sup>28</sup> Sharpless asymmetric dihydroxylation,<sup>29</sup> oxidation,<sup>30</sup> and silylation followed to yield *ent*-

**20d**, whose analytical data was identical to (+)-**20d** prepared by the ketone benzoin reaction, except it provided the opposite optical rotation. The remaining absolute configurations were assigned by analogy.



**Scheme 2.13.** Synthesis of *ent*-**20d** to Determine Absolute Stereochemistry

## 2.4 Conclusion

In conclusion, we have developed a broadly applicable and operationally simple method for intermolecular ketone acylation through a  $\text{La}(\text{CN})_3$ -catalyzed silyl benzoin reaction. Various ketone classes including aryl-alkyl, alkyl-alkyl, aryl-aryl, enones, and ynones have been employed. The reaction can be done in a diastereoselective fashion on both cyclic and acyclic systems. In cyclic systems, equatorial attack is favored, and in acyclic systems both chelation and Felkin-Ahn products can be selected by judicious choice of protecting group and solvent with acetoin electrophiles. Products arising from aryl-methyl ketones can be resolved through a novel kinetic resolution that makes use of the CBS reduction.

## 2.5 Experimental Section

**Materials and Methods: General.** Infrared (IR) spectra were obtained using a Nicolet 460-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra

( $^1\text{H}$  and  $^{13}\text{C}$  NMR) were recorded on a Bruker model Avance 400 ( $^1\text{H}$  NMR at 400 MHz and  $^{13}\text{C}$  NMR at 100 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm and  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, sep = septet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with a Chiradex B-DM column (30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250 °C) with helium gas as carrier. Supercritical fluid chromatography was performed on a Berger SFC system equipped with a Chiralpack OD or AD column. HPLC separations were performed on a Varian SD-1 HPLC with a Berger CYANO 60A 6u column (150 x 21.2 mm). Optical rotations were measured using a 2.0 mL cell with a 1.0 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained on a Micromass Quattro II Triple Quadrupole Spectrometer using ESI ionization. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 200  $\mu\text{m}$  silica G TLC plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Silia-P flash silica gel (40-63  $\mu\text{m}$ ) purchased from Silicycle. All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Reagents were massed out in the glovebox. Yield refers to isolated yield of analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Tetrahydrofuran was dried by passage through a column of neutral alumina under



nitrogen prior to use.<sup>31</sup> Acyl silanes<sup>32-34</sup> and  $\text{La}(\text{CN})_3$ <sup>18b</sup> were prepared by literature methods. Ketones were purchased from Sigma Aldrich, Fisher Scientific, or Matheson, Coleman, and Bell. Acetophenone, 2'-methoxyacetophenone, acetone, cyclohexanone, and benzophenone were distilled prior to use. Compound **6a'** has also been previously prepared.<sup>35</sup>

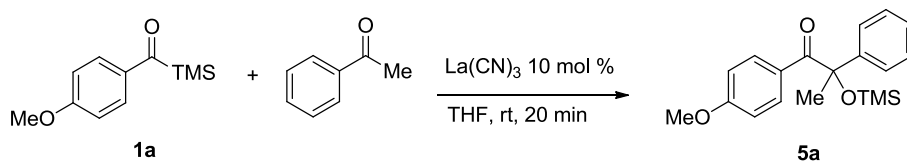
#### **General Procedure for $\text{La}(\text{CN})_3$ -Catalyzed Ketone Benzoin Reaction (A)**

In the glovebox, a 25-mL round bottomed flask was charged with  $\text{LaCl}_3$  (12 mg, 0.049 mmol), a stir bar, and THF (3 mL). A second 10-mL flask was charged with 0.48 mmol of acyl silane, 1.00 mmol of ketone, and 8 mL of THF. The flasks were capped with a septum, removed from the glovebox, and placed under positive pressure of  $\text{N}_2$ . The suspension of  $\text{LaCl}_3$  was cooled to  $-78\text{ }^\circ\text{C}$  for 5 min, then  $n\text{BuLi}$  (1.4 M in hexanes, 105  $\mu\text{L}$ , 0.147 mmol) was added. The cloudy suspension was stirred for 10 min at  $-78\text{ }^\circ\text{C}$  and warmed to  $0\text{ }^\circ\text{C}$  for 15 minutes.  $\text{TMSCN}$  was added as a solution in THF ( $\sim 0.5\text{ M}$ , 15 mg, 0.152 mmol). The catalyst suspension was stirred at  $0\text{ }^\circ\text{C}$  for 10 min and allowed to warm to rt over 30 min. After the catalyst suspension reached room temperature, the solution of acyl silane (0.48 mmol, 1 equiv) and ketone (0.96 mmol, 2 equiv) was added via syringe. The reaction was monitored by TLC (20%  $\text{EtOAc}$ /petroleum ether) and all substrates showed complete consumption of starting material within 20 min. Upon completion, the reaction mixture was poured into 40 mL of 1:1  $\text{Et}_2\text{O}/\text{H}_2\text{O}$  in a separatory funnel. The layers were separated and the aqueous layer was extracted with two 20 mL portions of  $\text{Et}_2\text{O}$ . The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered, and concentrated on a rotary evaporator. Column chromatography of the crude material on silica gel using 5:95  $\text{Et}_2\text{O}$ /petroleum ether as the eluent furnished the desired product in

analytically pure form or as a mixture of product and ketone starting material (see General Procedure for Deprotection of  $\alpha$ -Silyloxyketones).

### General Procedure for Deprotection of $\alpha$ -Silyloxyketones (B)

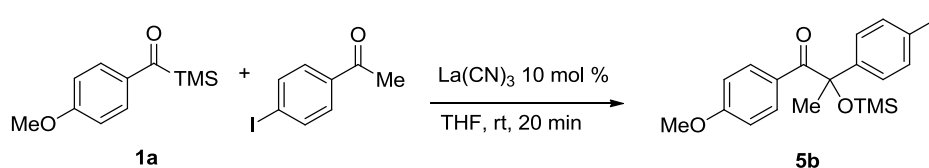
The title compound was dissolved in dry THF (10 mL) in a 100-mL flame dried round bottomed flask and cooled to 0 °C. Tetrabutylammonium fluoride (0.50 mL, 1.0 M solution in THF, 1.0 equivalents based on 100% yield from initial coupling) was added. The reaction turned yellow and rapidly faded to colorless. The reaction was monitored by TLC (20% EtOAc/petroleum ether) and was complete within 10 min for all substrates. The reactions were poured into 1:1 Et<sub>2</sub>O/H<sub>2</sub>O (40 mL), and the aqueous layer was extracted with two 20 mL portions of Et<sub>2</sub>O. The organic extracts were combined, dried over MgSO<sub>4</sub>, and concentrated on a rotary evaporator. The crude material was purified by flash chromatography on silica gel using 3:7 Et<sub>2</sub>O/petroleum ether as the eluent to furnish the desired product in analytically pure form. Yields for these products are reported over two steps.



### 1-(4-methoxyphenyl)-2-phenyl-2-(trimethylsilyloxy)propan-1-one (Figure 2.1, 5a)

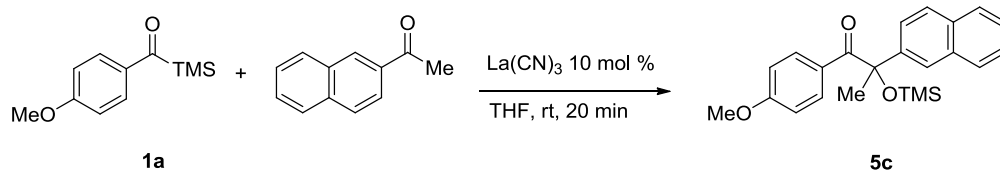
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 120 mg of acetophenone, 12 mg LaCl<sub>3</sub>, 105  $\mu$ L of <sup>n</sup>BuLi, and 15 mg of TMSCN in 11 mL of THF. After chromatography, 151 mg (96% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 2959, 1675, 1600, 1508, 1253, 1175, 1154, 1127, 868, 844; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.93

(dd,  $J = 6.8, 2.0$  Hz, 2H), 7.48-7.46 (m, 2H), 7.33-7.29 (m, 2H), 7.23-7.19 (m, 1H), 6.74 (dd,  $J = 6.8, 2.0$  Hz, 2H), 3.78 (s, 3H), 1.76 (s, 3H), 0.06 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.1, 162.7, 145.5, 133.3, 128.4, 127.6, 127.0, 124.1, 112.9, 83.5, 55.2, 30.2, 1.8; TLC (20% EtOAc/petroleum ether)  $R_f = 0.44$ , (5%  $\text{Et}_2\text{O}$ /petroleum ether)  $R_f = 0.29$ ; LRMS (ESI) Calcd for  $\text{C}_{19}\text{H}_{25}\text{O}_3\text{Si}$ , 329.2; Found, 329.0.



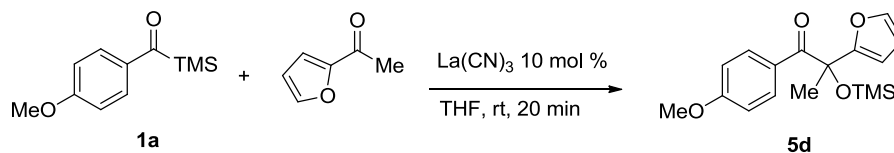
**2-(4-iodophenyl)-1-(4-methoxyphenyl)-2-(trimethylsilyloxy)propan-1-one (Figure 2.1, 5b)**

The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 237 mg of 4'-iodoacetophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 205 mg (94% yield) of the title compound was isolated as a yellow oil. Analytical data for title compound: IR (thin film,  $\text{cm}^{-1}$ ) 2958, 1675, 1600, 1508, 1482, 1253, 1174, 1127, 1001, 844;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (dd,  $J = 6.8, 2.4$  Hz, 2H), 7.63 (dd,  $J = 6.8, 2.0$  Hz, 2H), 7.21 (dd,  $J = 8.4, 2.0$  Hz, 2H), 6.75 (dd,  $J = 7.2, 2.0$  Hz, 2H), 3.79 (s, 3H), 1.72 (s, 3H), 0.05 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  198.6, 162.9, 145.4, 137.5, 133.3, 127.2, 126.3, 113.0, 92.6, 83.3, 55.3, 30.1, 1.8; TLC (20% EtOAc/petroleum ether)  $R_f = 0.46$ , (5%  $\text{Et}_2\text{O}$ /petroleum ether)  $R_f = 0.34$ ; LRMS (ESI) calc. for  $[\text{M}+\text{Na}] = 477.05$ , found 477.04.



**1-(4-methoxyphenyl)-2-(naphthalen-1-yl)-2-(trimethylsilyloxy)propan-1-one (Figure 2.1, 5c)**

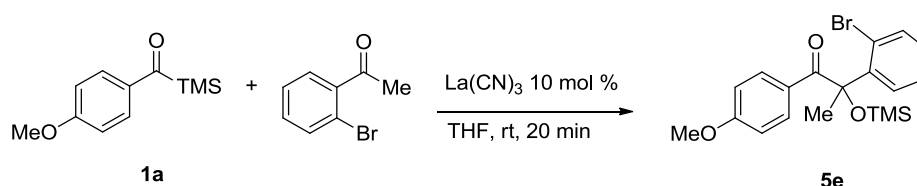
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 165 mg of 2-acetonaphthone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 169 mg (93% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: IR (thin film,  $\text{cm}^{-1}$ ) 2959, 1674, 1600, 1508, 1254, 1175, 1126, 1016, 842;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84-7.82 (m, 3H), 7.80-7.78 (m, 3H), 7.56 (d,  $J = 8.4$  Hz, 1H), 7.46-7.43 (m, 2H), 6.71 (d,  $J = 9.2$  Hz), 3.75 (s, 3H), 1.83 (s, 3H), 0.11 (s, 9H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.2, 162.7, 143.0, 133.4, 132.6, 128.3, 128.2, 127.6, 126.1, 125.8, 122.8, 122.6, 112.9, 83.7, 55.2, 30.3, 1.9; TLC (20% EtOAc/petroleum ether)  $R_f = 0.46$ , (5%  $\text{Et}_2\text{O}$ /petroleum ether)  $R_f = 0.27$ ; LRMS (ESI) calc. for  $[\text{M}+\text{Na}] = 401.15$ , found 401.15.



**2-(furan-2-yl)-1-(4-methoxyphenyl)-2-(trimethylsilyloxy)propan-1-one (Figure 2.1, 5d)**

The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 106 mg of 2-furylmethyl ketone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 137 mg (90% yield) of the title

compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2959, 2854, 1680, 1601, 1509, 1460, 1308, 1254, 1175, 1017, 844;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (dd,  $J = 8.4, 2.0$  Hz, 2H), 7.33 (s, 1H), 6.84 (dd,  $J = 8.4, 2.0$  Hz, 2H), 6.35 (t,  $J = 2$  Hz, 2H), 3.84 (s, 3H), 1.86 (s, 3H), 0.02 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.7, 162.9, 156.4, 141.8, 132.9, 127.9, 113.0, 110.5, 106.7, 79.8, 55.3, 26.4, 1.5; TLC (20% EtOAc/petroleum ether)  $R_f = 0.44$ , (5%  $\text{Et}_2\text{O}$ /petroleum ether)  $R_f = 0.27$ ; **LRMS** (ESI) calc. for  $[\text{M}+\text{H}] = 269.08$ , found 269.08 (MS data calculated for free alcohol, TMS group cleaved during sample preparation).

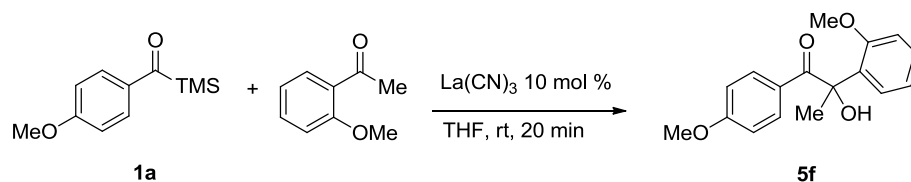


**2-(2-bromophenyl)-1-(4-methoxyphenyl)-2-(trimethylsilyloxy)propan-1-one (Figure 2.1, 5e)**

The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 191 mg of 2'-bromoacetophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 156 mg (80% yield) of the title compound was isolated as a white solid (mp 70-72  $^\circ\text{C}$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3067, 2957, 1681, 1600, 1508, 1463, 1252, 1175, 1151, 1126, 1028, 1004, 845;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (d,  $J = 8.0$  Hz, 1H), 7.84 (dd,  $J = 7.2, 1.6$  Hz, 2H), 7.41-7.35 (m, 2H), 7.08 (t,  $J = 7.6$  Hz), 6.70 (dd,  $J = 7.2, 1.6$  Hz, 2H), 3.77 (s, 3H), 1.86 (s, 3H), 0.12 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  195.8, 162.5, 145.5, 134.2, 132.6, 128.7, 128.3, 127.6, 127.2, 120.1, 112.8, 82.4, 55.2, 26.2, 1.9;

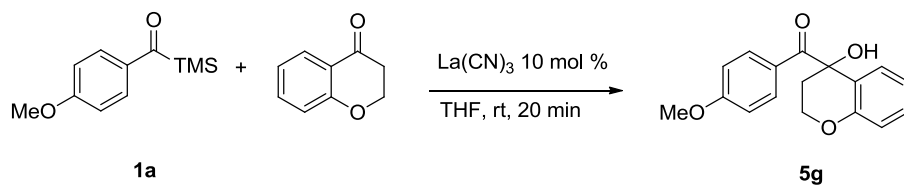
TLC (20% EtOAc/petroleum ether)  $R_f$  = 0.43, (5% Et<sub>2</sub>O/petroleum ether)  $R_f$  = 0.27;

**LRMS** (ESI) calc. for [M+Na] = 429.05, found 429.05.



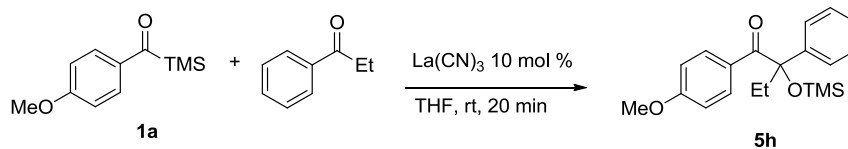
**2-hydroxy-2-(2-methoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (Figure 2.1, 5f)**

The title compound was prepared according to General Procedure A, followed by General Procedure B, using 100 mg of acyl silane, 145 mg of 2'-methoxyacetophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 84 mg (61% yield) of the title compound was isolated as a white solid (mp 89-90 °C). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the title compound are available in Section S4. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3435, 2965, 2932, 1667, 1600, 1509, 1489, 1464, 1251, 1174, 1123, 1026, 965, 844;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J$  = 8.8 Hz, 2H), 7.66 (d,  $J$  = 7.6 Hz, 1H), 7.30 (t,  $J$  = 8.0 Hz, 1H), 7.06 (t,  $J$  = 7.2 Hz, 1H), 6.79-6.73 (m, 3H), 4.98 (s, 1H), 3.79 (s, 3H), 3.49 (s, 3H), 1.85 (s, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.4, 163.1, 157.0, 132.5, 131.6, 129.6, 126.2, 121.1, 113.3, 112.1, 76.7, 55.3, 55.2, 26.2; TLC (20% EtOAc/petroleum ether)  $R_f$  = 0.12, (30% Et<sub>2</sub>O/petroleum ether)  $R_f$  = 0.11; **LRMS** (ESI) calc. for [M+Na] = 309.1, found 309.1.



**(4-hydroxychroman-4-yl)(4-methoxyphenyl)methanone (Figure 2.1, 5g)**

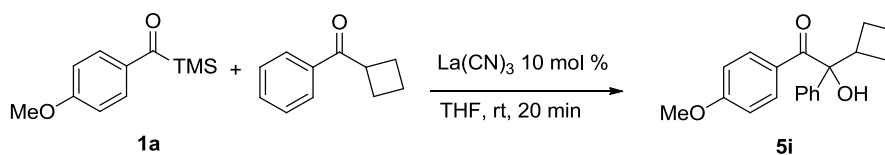
The title compound was prepared according to General Procedure A, followed by General Procedure B, using 100 mg of acyl silane, 140 mg of chromanone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 120 mg (74% yield) of the title compound was isolated as a white solid (mp 77-78  $^{\circ}\text{C}$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3435, 2965, 2918, 1660, 1600, 1509, 1488, 1451, 1261, 1223, 1173, 1119, 1048, 901, 839;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 (d,  $J = 8.8$  Hz, 2H), 7.27-7.22 (m, 1H), 7.00 (d,  $J = 8.8$  Hz, 1H), 6.88-6.83 (m, 2H), 6.77 (d,  $J = 8.8$  Hz, 2H), 5.42 (s, 1H), 4.48-4.36 (m, 2H), 3.80 (s, 3H), 2.65 (td,  $J = 12.8, 4.4$  Hz, 1H), 1.93 (d,  $J = 14.0$  Hz, 1H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.8, 163.7, 154.3, 132.9, 130.0, 129.0, 124.6, 124.3, 121.6, 117.8, 113.8, 73.2, 63.1, 55.4, 36.8; TLC (20%  $\text{EtOAc}$ /petroleum ether)  $R_f = 0.20$ , (30%  $\text{Et}_2\text{O}$ /petroleum ether)  $R_f = 0.22$ ; **LRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 307.1$ , found 307.1.



**1-(4-methoxyphenyl)-2-phenyl-2-(trimethylsilyloxy)butan-1-one (Figure 2.1, 5h)**

The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 130 mg of propiophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 164 mg (74% yield) of the title compound was

isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2965, 2839, 1673, 1600, 1509, 1446, 1251, 1173, 1148, 884, 840 ;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (d,  $J = 7.6$  Hz, 2H), 7.90 (d,  $J = 9.2$  Hz, 2H), 7.54 (t,  $J = 7.2$  Hz, 1H), 7.47-7.40 (m, 4H), 7.30 (t,  $J = 7.2$  Hz, 2H), 7.20 (t,  $J = 7.2$  Hz, 1H), 3.78 (s, 3H), 2.41-2.32 (m, 1H), 2.09-2.00 (m, 1H), 0.63 (t,  $J = 7.2$  Hz, 3H), 0.01 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.1, 162.6, 142.7, 133.3, 128.2, 128.0, 126.9, 124.9, 112.9, 86.1, 55.2, 32.7, 7.4, 1.7; TLC (20% EtOAc/petroleum ether)  $R_f = 0.51$ , (5% Et<sub>2</sub>O/petroleum ether)  $R_f = 0.34$ ; **LRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 365.15$ , found 365.16.

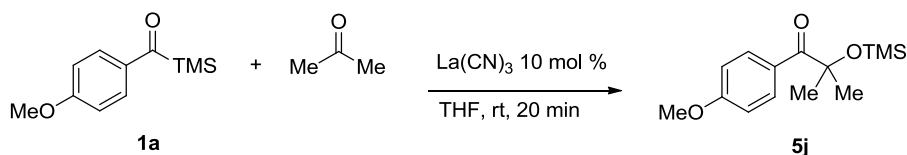


### 2-cyclobutyl-2-hydroxy-1-(4-methoxyphenyl)-2-phenylethanone (Figure 2.1, 5i)

The title compound was prepared according to General Procedure A, followed by General Procedure B, using 100 mg of acyl silane, 154 mg of cyclobutyl phenyl ketone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{-BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 94 mg (66% yield) of the title compound was isolated as a white solid (mp 97-98  $^{\circ}\text{C}$ ). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3426, 2938, 2860, 1657, 1600, 1509, 1447, 1359, 1309, 1256, 1174, 1141, 1078, 1029, 984, 946, 838;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (d,  $J = 6.8$  Hz, 2H), 7.35 (d,  $J = 4.4$  Hz, 4H), 7.30-7.26 (m, 1H), 6.75 (d,  $J = 6.8$  Hz, 2H), 5.13 (s, 1H), 3.79 (s, 3H), 3.47 (qt,  $J = 8.4$  Hz, 1H), 2.49-2.42 (m, 1H), 2.24-2.17 (m, 1H), 1.92-1.89 (m, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.3, 163.3, 142.1, 132.4, 128.9, 127.9, 126.9, 113.5, 81.8, 55.4, 40.9, 23.8,

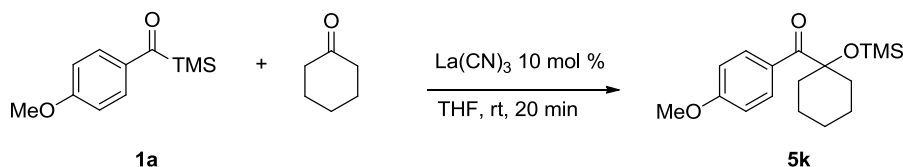


21.4, 18.1; TLC (20% EtOAc/petroleum ether)  $R_f$  = 0.27, (30% Et<sub>2</sub>O/petroleum ether)  $R_f$  = 0.34; **LRMS** (ESI) calc. for [M+Na] = 319.13, found 319.14.



**1-(4-methoxyphenyl)-2-methyl-2-(trimethylsilyloxy)propan-1-one (Figure 2.1, 5j)**

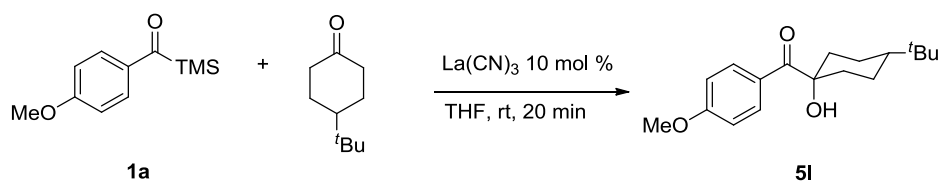
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 57 mg of acetone, 12 mg LaCl<sub>3</sub>, 105  $\mu$ L of <sup>n</sup>BuLi, and 15 mg of TMSCN in 11 mL of THF. After chromatography, 113 mg (88% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 2972, 1672, 1601, 1497, 1455, 1255, 1161, 1033, 885, 841; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.24 (d,  $J$  = 8.0 Hz, 2H), 6.89 (d,  $J$  = 8.0 Hz, 2H), 3.87 (s, 3H), 1.56 (s, 6H), 0.04 (s, 9H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  202.3, 162.8, 132.9, 127.7, 113.0, 80.5, 55.3, 29.1, 1.9; TLC (20% EtOAc/petroleum ether)  $R_f$  = 0.51, (5% Et<sub>2</sub>O/petroleum ether)  $R_f$  = 0.34; **LRMS** (ESI) calc. for [M+Na] = 289.12, found 289.13.



**(4-methoxyphenyl)(1-(trimethylsilyloxy)cyclohexyl)methanone (Figure 2.1, 5k)**

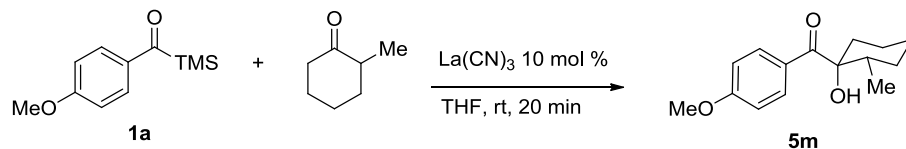
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 94 mg of cyclohexanone, 12 mg LaCl<sub>3</sub>, 105  $\mu$ L of <sup>n</sup>BuLi, and 15 mg of TMSCN in 11 mL of THF. After chromatography, 120 mg (82% yield) of the title compound was

isolated as a white solid (mp 88-90 °C). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2934, 2857, 1671, 1600, 1508, 1450, 1308, 1251, 1172, 1156, 1090, 1051, 972, 842;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 (d,  $J = 9.0$  Hz, 2H), 6.91 (d,  $J = 9.0$  Hz, 2H), 3.88 (s, 3H), 1.99-1.88 (m, 4H), 1.76-1.71 (m, 2H), 1.57-1.55 (m, 3H), 1.35-1.33 (m, 1H), 0.02 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  201.9, 162.8, 132.9, 127.9, 113.0, 81.7, 55.3, 36.6, 25.6, 22.1, 1.9; TLC (20% EtOAc/petroleum ether)  $R_f = 0.49$ , (5% Et<sub>2</sub>O/petroleum ether)  $R_f = 0.37$ ; **LRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 329.15$ , found 329.15.



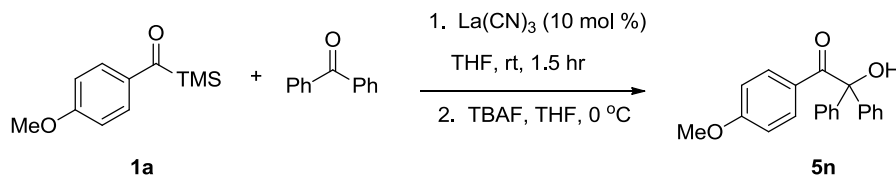
**(4-tert-butyl-1-hydroxycyclohexyl)(4-methoxyphenyl)methanone (Figure 2.1, 5I)**

The title compound was prepared according to General Procedure A, followed by General Procedure B, using 100 mg of acyl silane, 150 mg of 4-*tert*-butylcyclohexanone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 123 mg (88% yield) of the title compound was isolated as a white solid (mp 106-107 °C). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3451, 2954, 2865, 1654, 1600, 1508, 1459, 1364, 1308, 1252, 1173, 1031, 954, 838;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (d,  $J = 7.2$  Hz, 2H), 6.93 (d,  $J = 7.2$  Hz, 2H), 3.87 (s, 3H), 3.75 (s, 1H), 2.08 (t,  $J = 13.6$  Hz, 2H), 1.82-1.73 (m, 4H), 1.59-1.51 (m, 2H), 1.16 (t,  $J = 9.6$  Hz, 1H), 0.91 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  203.5, 163.1, 127.1, 132.4, 113.5, 78.1, 55.4, 47.5, 36.3, 32.6, 27.5, 22.5; TLC (20% EtOAc/petroleum ether)  $R_f = 0.34$ , (5% Et<sub>2</sub>O/petroleum ether)  $R_f = 0.15$ ; **LRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 313.2$ , found 313.2.



**(1-hydroxy-2-methylcyclohexyl)(4-methoxyphenyl)methanone (Figure 2.1, 5m)**

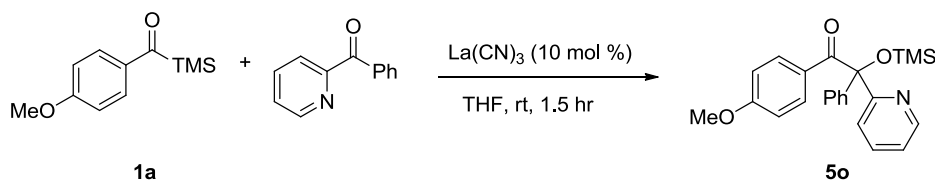
The title compound was prepared according to General Procedure A, followed by General Procedure B, using 100 mg of acyl silane, 110 mg of 2-methylcyclohexanone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 52 mg (44% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2931, 1650, 1600, 1509, 1460, 1306, 1261, 1175, 1150, 1018, 933, 839;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09 (d,  $J = 8.8$  Hz, 2H), 6.94 (d,  $J = 8.8$  Hz, 2H), 4.20 (s, 1H), 3.88 (s, 3H), 2.3-2.24 (m, 1H), 2.09-2.03 (m, 1H), 1.84-1.64 (m, 4H), 1.57-1.42 (m, 3H), 0.67 (d,  $J = 6.8$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  203.6, 163.3, 132.0, 127.1, 113.6, 80.7, 55.4, 38.4, 37.1, 30.2, 26.0, 21.3, 15.7; TLC (20% EtOAc/petroleum ether)  $R_f = 0.32$ , (30% Et<sub>2</sub>O/petroleum ether)  $R_f = 0.42$ ; **LRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 271.13$ , found 271.13.



**2-hydroxy-1-(4-methoxyphenyl)-2,2-diphenylethanone (Figure 2.2, 5n)**

The title compound was prepared by a modification to General Procedure A using 100 mg of acyl silane, 175 mg of benzophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 13 mL of THF. After the catalyst suspension was prepared via General

Procedure A, the ketone was added as a THF solution (5 mL) at rt. The acyl silane was then added via syringe pump over 1 hr as a THF solution (5 mL). Upon complete addition, the reaction was stirred an additional 30 minutes. Upon completion, the reaction was quenched, extracted, and purified according to General Procedure A. The crude oil was subjected to General Procedure B to furnish the free alcohol. After chromatography, 116 mg (76% yield) of the title compound was isolated as a colorless waxy solid. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3436, 3025, 2839, 1661, 1598, 1509, 1446, 1310, 1250, 1172, 1054, 1028, 980, 839, 796, 741, 701;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J = 8.8$  Hz, 2H), 7.44-7.41 (m, 4H), 7.36-7.31 (m, 6H), 6.76 (d,  $J = 9.2$  Hz, 2H), 5.31 (s, 1H), 3.80 (s, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  198.8, 163.4, 142.4, 133.6, 128.4, 128.3, 128.0, 127.5, 113.4, 84.6, 55.4; **TLC** (10% EtOAc/petroleum ether)  $R_f = 0.09$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 341.1154$ , found 341.1181.

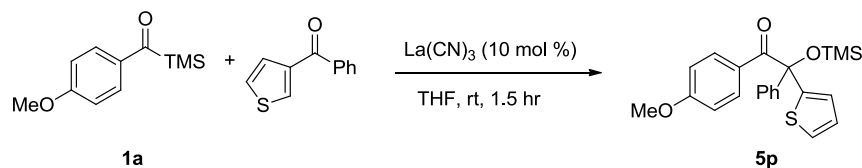


### 1-(4-methoxyphenyl)-2-phenyl-2-(pyridin-2-yl)-2-((trimethylsilyl)oxy)ethanone

#### (Figure 2.2, 5o)

The title compound was prepared by a modification to General Procedure A using 100 mg of acyl silane, 176 mg of 2-benzoylpyridine, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 13 mL of THF. After the catalyst suspension was prepared via General Procedure A, the ketone was added as a THF solution (5 mL) at rt. The acyl silane was

then added via syringe pump over 1 hr as a THF solution (5 mL). Upon complete addition, the reaction was stirred an additional 30 minutes. Upon completion, the reaction was quenched, extracted, and purified according to General Procedure A. After chromatography, 158 mg (84% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2839, 2360, 1675, 1599, 1574, 1509, 1436, 1309, 1247, 1173, 1129, 1075, 1030, 884, 839, 753, 703;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.58 (dd,  $J = 4.4$  Hz, 1.6 Hz, 1H), 7.97 (d,  $J = 8.8$  Hz, 2H), 7.59 (td,  $J = 8.0$  Hz, 2.0 Hz, 1H), 7.54 (d,  $J = 6.8$  Hz, 2H), 7.38-7.28 (m, 3H), 7.18-7.15 (m, 2H), 6.78 (d,  $J = 9.2$  Hz, 2H), 3.80 (s, 3H), -0.05 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  198.7, 162.7, 162.0, 147.9, 142.5, 136.0, 133.3, 128.7, 128.1, 127.7, 127.3, 123.1, 122.3, 112.9, 89.0, 55.3, 2.3; **TLC** (10% EtOAc/petroleum ether)  $R_f = 0.14$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 414.1501$ , found 414.1516.

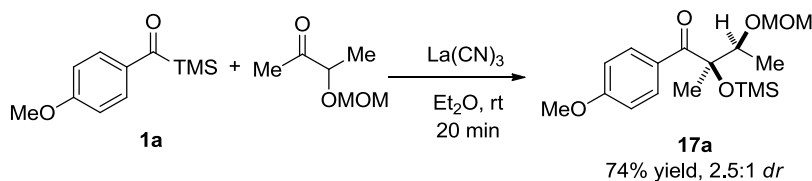


### 1-(4-methoxyphenyl)-2-phenyl-2-(thiophen-2-yl)-2-((trimethylsilyl)oxy)ethanone

#### (Figure 2.2, 5p)

The title compound was prepared by a modification to General Procedure A using 100 mg of acyl silane, 180 mg of 2-benzoylthiophene, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 13 mL of THF. After the catalyst suspension was prepared via General Procedure A, the ketone was added as a THF solution (5 mL) at rt. The acyl silane was then added via syringe pump over 1 hr as a THF solution (5 mL). Upon complete addition, the reaction was stirred an additional 30 minutes. Upon completion, the

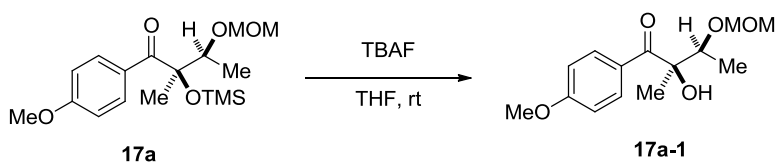
reaction was quenched, extracted, and purified according to General Procedure A. After chromatography, 160 mg (84% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 3066, 3006, 2957, 2839, 1677, 1599, 1573, 1508, 1458, 1446, 1419, 1310, 1252, 1173, 1103, 1071, 1028, 884, 842, 751, 730, 700;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (d,  $J = 9.2$  Hz, 2H), 7.60 (d,  $J = 8.0$  Hz, 2H), 7.34 (t,  $J = 7.2$  Hz, 2H), 7.29-7.27 (m, 2H), 6.95-6.92 (m, 2H), 6.80 (d,  $J = 8.8$  Hz, 2H), 3.80 (s, 3H), -0.15 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.5, 162.9, 147.1, 143.9, 133.4, 128.5, 128.3, 128.0, 127.8, 126.2, 126.0, 113.0, 84.9, 55.3, 1.1; **TLC** (10% EtOAc/petroleum ether)  $R_f = 0.31$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 419.1113$ , found 419.1120.



### 3-(methoxymethoxy)-1-(4-methoxyphenyl)-2-methyl-2-((trimethylsilyl)oxy)butan-1-one (Scheme 2.6, **17a**)

The title compound was prepared by a modification to General Procedure A using 100 mg of acyl silane, 120 mg of MOM-protected acetoin, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of  $\text{Et}_2\text{O}$ . The reaction was conducted in  $\text{Et}_2\text{O}$  rather than THF to obtain the chelation-controlled product. After chromatography, 126 mg (77% yield, 2.7:1 dr) of the compound was isolated as a colorless oil. The diastereomers were then separated by HPLC chromatography (15 mL/min flow rate, 15% EtOAc/PE). The

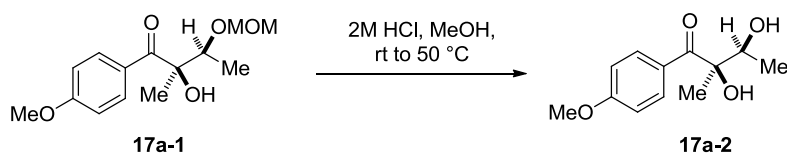
major diastereomer was characterized and further derivatized to **4a'** to determine the relative stereochemistry. Analytical data: **IR** (thin film,  $\text{cm}^{-1}$ ) 2954, 2895, 2840, 1672, 1600, 1573, 1508, 1460, 1418, 1375, 1306, 1254, 1206, 1156, 1109, 1033, 938, 884, 842, 756;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.16 (d,  $J = 9.2$  Hz, 2H), 6.88 (d,  $J = 9.2$  Hz, 2H), 4.73 (d,  $J = 6.8$  Hz, 1H), 4.64 (d,  $J = 6.8$  Hz, 1H), 4.15 (q,  $J = 6.4$  Hz, 1H), 4.13 (s, 3H), 3.28 (s, 3H), 1.47 (s, 3H), 1.08 (d,  $J = 6.4$  Hz, 3H), -0.02 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  202.9, 162.8, 132.8, 129.3, 112.9, 96.1, 86.7, 78.2, 55.5, 55.3, 21.4, 15.0, 1.9; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.28$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 363.1604$ , found 363.1627.



### 2-hydroxy-3-(methoxymethoxy)-1-(4-methoxyphenyl)-2-methylbutan-1-one (**17a-1**)

The title compound was prepared by charging a 10-mL round-bottomed flask with the ketone (**4a**) (33 mg, 0.097 mmol, 1.0 equiv.), a stir bar, and 3 mL of THF. The solution was cooled to 0 °C, and tetrabutylammonium fluoride (1.0 M in THF, 0.15 mL, 1.5 equiv.) was added. The reaction monitored by TLC and complete within 5 minutes. The reactions were then poured into 1:1  $\text{Et}_2\text{O}/\text{H}_2\text{O}$  (20 mL), and the aqueous layer was extracted with two 10 mL portions of  $\text{Et}_2\text{O}$ . The organic extracts were combined, dried over  $\text{MgSO}_4$ , and concentrated on a rotary evaporator. The crude material (**4a-1**) (24 mg, 92% yield) was carried through the next reaction without purification. Analytical data for title compound:  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (d,  $J = 8.8$  Hz, 2H), 6.92 (d,  $J = 8.8$  Hz, 2H), 4.58 (d,  $J = 7.2$  Hz, 1H), 4.41 (d,  $J = 7.2$  Hz, 1H), 4.36 (q,  $J = 6.4$  Hz, 1H), 3.87

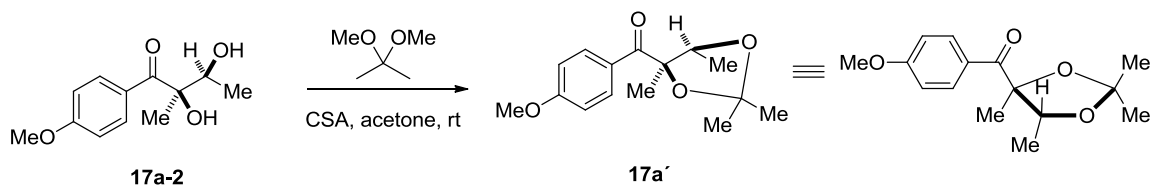
(s, 3H), 3.08 (s, 3H), 1.49 (s, 3H), 1.28 (d,  $J = 6.4$  Hz, 3H); **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.17$ .



### 2,3-dihydroxy-1-(4-methoxyphenyl)-2-methylbutan-1-one (**17a-2**)

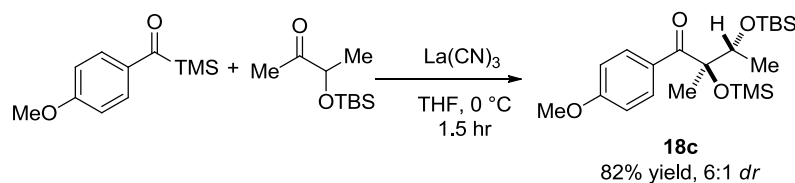
The title compound was prepared by charging a 10-mL round-bottomed flask with the ketone (**4a-1**) (24 mg, 0.089 mmol, 1.0 equiv.), a stir bar, and 2 mL of MeOH. Aqueous HCl was added (1M, 1.0 mL) at rt, and the reaction was monitored by TLC. After incomplete conversion after 12 hr, the reaction was heated to 50 °C for 3 hr. Upon completion, the reaction was diluted in Et<sub>2</sub>O (20 mL) and washed with H<sub>2</sub>O (10 mL) then brine (**4a-2**) (10 mL). Organic layer was dried over MgSO<sub>4</sub> the concentrated. The crude product (15 mg, 74% yield) was carried forward to the next step without purification. Analytical data for title compound: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.12 (d,  $J = 9.2$  Hz, 2H), 6.95 (d,  $J = 8.8$  Hz, 2H), 4.41-4.36 (m, 1H), 3.88 (s, 3H), 1.52 (s, 3H), 1.31 (d,  $J = 6.4$ , 2H); **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.09$ .





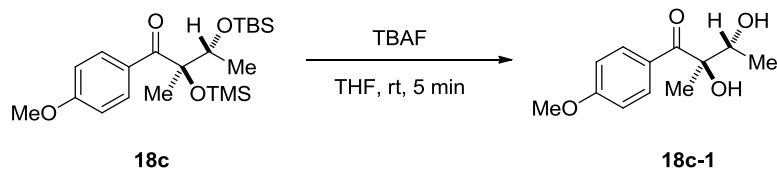
**(4-methoxyphenyl)(2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)methanone (Figure 2.4, 17a')**

The title compound was prepared by charging a dry 10-mL round bottomed flask with the diol (**4a-2**) (15 mg, 0.067 mmol, 1.0 equiv.), a stir bar, and dl-camphorsulfonic acid (10 mg, 0.043 mmol, 0.65 equiv.). Solids were dissolved in acetone (1.5 mL) and 2,2-dimethoxypropane (0.75 mL). Reaction was monitored by TLC and complete within 1 hr. Upon completion, reaction was concentrated *in vacuo*, and the red-brown residue was purified by flash chromatography (10% Et<sub>2</sub>O/petroleum ether eluent). After chromatography, 15 mg (85% yield) of the desired product (**4a'**) was obtained. Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 2985, 2936, 1666, 1600, 1573, 1509, 1458, 1419, 1371, 1257, 1217, 1152, 1101, 1030, 935, 862, 840, 766; **<sup>1</sup>H NMR** (100 MHz, CDCl<sub>3</sub>) δ 8.25 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.55 (q, *J* = 6.4 Hz, 1H), 3.87 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.20 (s, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 200.8, 163.4, 132.9, 127.7, 113.3, 107.9, 87.5, 75.8, 55.4, 28.6, 25.8, 21.9, 15.6; **TLC** (10% EtOAc/ petroleum ether) *R<sub>f</sub>* = 0.31; **HRMS** (ESI) calc. for [M+Na] = 287.1259, found 287.1247.



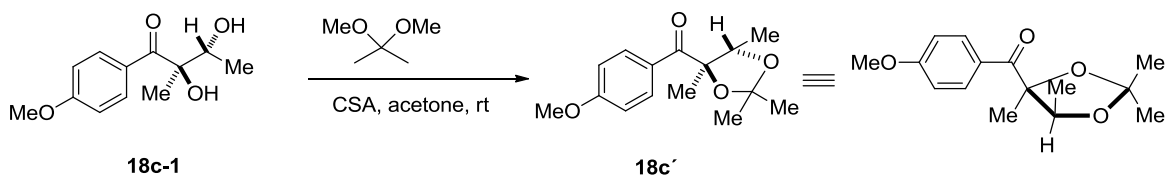
**3-((tert-butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)-2-methyl-2-((trimethylsilyl)oxy)butan-1-one (Scheme 2.6, 18c)**

The title compound was prepared by a modification to General Procedure A using 100 mg of acyl silane, 180 mg of OTBS-protected acetoin, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. The OTBS-protected acetoin was added to the catalyst suspension in THF (3 mL) at 0 °C. The acyl silane was added in THF (8 mL) via syringe pump over 1 hr. After complete addition, the reaction was allowed to stir an additional 20 min., then subjected to the standard workup. After chromatography, 162 mg (82% yield, 6.0:1 *dr*) of the compound was isolated as a colorless oil. The diastereomers were then separated by HPLC chromatography (15 mL/min flow rate, 15% EtOAc/PE). The major diastereomer was characterized and further derivatized to **5c'** to determine the relative stereochemistry. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2956, 2897, 2857, 1678, 1600, 1573, 1508, 1462, 1371, 1308, 1252, 1206, 1174, 1156, 1119, 1037, 1003, 976, 876, 838, 812, 775;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (d,  $J = 9.2$  Hz, 2H), 6.86 (d,  $J = 9.2$  Hz, 2H), 4.31 (q,  $J = 6.0$  Hz, 1H), 3.85 (s, 3H), 1.43 (s, 3H), 1.19 (d,  $J = 6.0$  Hz, 3H), 0.75 (s, 9H), 0.04 (s, 9H), -0.11 (s, 3H), -0.41 (s, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.7, 162.6, 132.9, 132.8, 128.6, 112.9, 112.8, 85.2, 73.3, 55.3, 30.0, 25.9, 25.7, 19.5, 17.8, 1.9, 1.8, -4.3, -5.4; TLC (10% EtOAc/petroleum ether)  $R_f = 0.47$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 433.2206$ , found 433.2199.



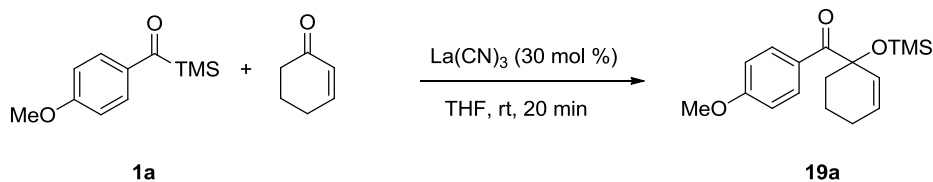
### 2,3-dihydroxy-1-(4-methoxyphenyl)-2-methylbutan-1-one (**18c-1**)

The title compound was prepared by charging a 10-mL round-bottomed flask with the bis(siloxy)ketone (**5c**) (40 mg, 0.098 mmol, 1.0 equiv.), a stir bar, and 3 mL of THF. The solution was cooled to 0 °C, and tetrabutylammonium fluoride (1.0 M in THF, 0.30 mL, 3.0 equiv.) was added. The reaction monitored by TLC and complete within 5 minutes. The reactions were then poured into 1:1 Et<sub>2</sub>O/H<sub>2</sub>O (20 mL), and the aqueous layer was extracted with two 10 mL portions of Et<sub>2</sub>O. The organic extracts were combined, dried over MgSO<sub>4</sub>, and concentrated on a rotary evaporator. The crude material was purified by flash chromatography on silica gel using 2:3 EtOAc/petroleum ether as the eluent. After chromatography, 16 mg (73% yield) of the desired product (**5c-1**) was obtained as a colorless oil. Analytical data for title compound: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.11 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.52 (s, 1H), 4.23-4.20 (m, 1H), 3.89 (s, 3H), 2.40 (d, J = 9.6 Hz, 1H), 1.68 (s, 3H), 0.98 (d, J = 6.4 Hz, 3H); TLC (1:9 EtOAc/petroleum ether) R<sub>f</sub> = 0.05.



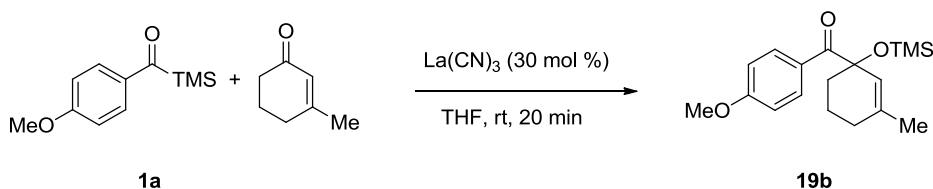
**(4-methoxyphenyl)(2,2,4,5-tetramethyl-1,3-dioxolan-4-yl)methanone (Figure 2.4, 18c')**

The title compound was prepared by charging a dry 10-mL round bottomed flask with the diol (**5c-1**) (16 mg, 0.071 mmol, 1.0 equiv.), a stir bar, and dl-camphorsulfonic acid (10 mg, 0.043 mmol, 0.60 equiv.). Solids were dissolved in acetone (1.5 mL) and 2,2-dimethoxypropane (0.75 mL). Reaction was monitored by TLC and complete within 2 hr. Upon completion, reaction was concentrated *in vacuo*, and the red-brown residue was purified by flash chromatography (10% Et<sub>2</sub>O/petroleum ether eluent). After chromatography, 14 mg (75% yield) of the desired product (**5c'**) was obtained. Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 2984, 1671, 1600, 1509, 1460, 1374, 1254, 1169, 1030, 842, 766; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.02 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.17 (q, *J* = 6.4, 1H), 3.85 (s, 3H), 1.62 (s, 3H), 1.46 (s, 3H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.28 (s, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 202.8, 162.7, 132.0, 130.7, 112.9, 109.1, 88.9, 81.7, 55.3, 27.5, 27.0, 25.4, 16.4; TLC (10% EtOAc/petroleum ether) *R<sub>f</sub>* = 0.35; **HRMS** (ESI) calc. for [M+Na] = 287.1259, found 287.1246.



**(4-methoxyphenyl)(1-((trimethylsilyl)oxy)cyclohex-2-en-1-yl)methanone (Table 2.4, 19a)**

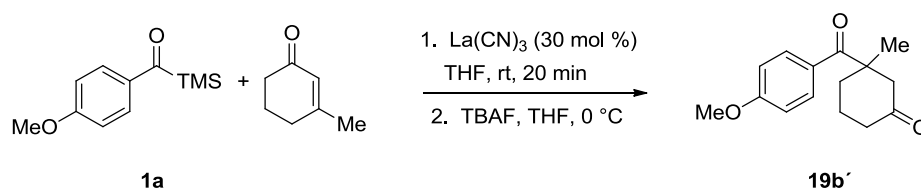
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 93 mg of cyclohexenone, 36 mg  $\text{LaCl}_3$ , 315  $\mu\text{L}$  of  $n\text{BuLi}$ , and 45 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 13 mg (13% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2955, 1671, 1599, 1573, 1458, 1308, 1254, 1168, 1113, 1078, 1030, 902, 885, 841, 754;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 (d,  $J = 8.8$  Hz, 2H), 6.91 (d,  $J = 8.8$  Hz, 2H), 6.01 (s, 2H), 3.89 (s, 3H), 2.10-2.04 (m, 4H), 1.95-1.91 (m, 1H), 1.76-1.70 (m, 1H), 0.07 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.6, 162.9, 132.8, 131.5, 129.6, 128.1, 113.1, 79.3, 55.3, 35.5, 24.8, 18.5, 2.0; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.32$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 327.1392$ , found 327.1387.



**(4-methoxyphenyl)(3-methyl-1-((trimethylsilyl)oxy)cyclohex-2-en-1-yl)methanone (Table 2.4, 19b)**

The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 106 mg of 3-methylcyclohex-2-enone, 36 mg  $\text{LaCl}_3$ , 315  $\mu\text{L}$  of  $n\text{BuLi}$ , and 45 mg

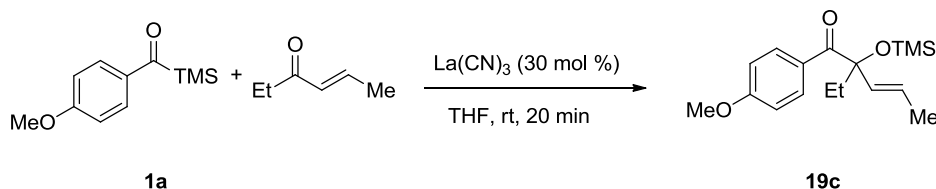
of TMSCN in 11 mL of THF. After chromatography, 58 mg (38% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2956, 2838, 1673, 1599, 1508, 1443, 1307, 1253, 1166, 1145, 1105, 1078, 1036, 908, 887, 841, 804, 753;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (d,  $J = 8.8$  Hz, 2H), 6.89 (d,  $J = 9.2$  Hz, 2H), 5.71 (s, 1H), 3.86 (s, 3H), 1.98-1.80 (m, 5H), 1.74 (s, 4H), 0.02 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.9, 162.8, 139.5, 132.8, 128.2, 124.2, 113.0, 80.0, 55.3, 35.1, 29.8, 24.0, 18.9, 1.9; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.32$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 341.1549$ , found 341.1504.



### 3-(4-methoxybenzoyl)-3-methylcyclohexanone (Table 2.4, 19b')

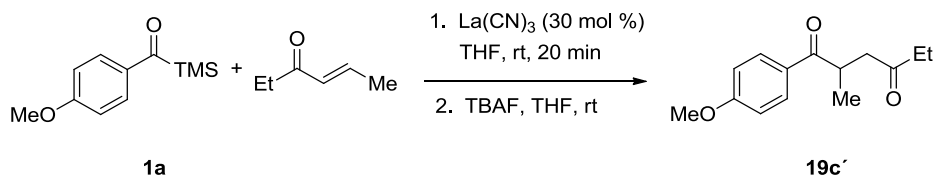
The silylcyanohydrin of the title compound was prepared according to General Procedure A using 100 mg of acyl silane, 106 mg of 3-methylcyclohex-2-enone, 36 mg  $\text{LaCl}_3$ , 315  $\mu\text{L}$  of  $n\text{BuLi}$ , and 45 mg of TMSCN in 11 mL of THF. After chromatography, 51 mg (37% yield) of the silylcyanohydrin of the title compound was isolated as a colorless oil. The silylcyanohydrin is isolated as an inseparable mixture of diastereomers. For characterization, the crude material deprotected according to General Procedure B to afford the 1,4-diketone, which was purified by flash chromatography. The diketone product was isolated in low yields (<10%), which precluded obtaining an adequate  $^{13}\text{C}$  spectrum. Analytical data: **IR** (thin film,  $\text{cm}^{-1}$ ) 2925, 1713, 1659, 1599, 1509, 1457, 1307, 1256, 1159, 1028, 957, 841;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (d,  $J = 8.8$  Hz,

2H), 6.91 (d,  $J = 8.8$  Hz, 2H), 3.86 (s, 3H), 2.89 (d,  $J = 14.8$ , 1H), 2.39-2.34 (m, 2H), 2.27-2.17 (m, 2H), 2.04-1.97 (m, 2H), 2.85-2.65 (m, 1H), 1.49 (s, 3H); **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.35$ ; **HRMS** (ESI) calc. for  $[M+Na] = 269.1154$ , found 269.1132.



**(E)-2-ethyl-1-(4-methoxyphenyl)-2-((trimethylsilyl)oxy)pent-3-en-1-one (Table 2.4, 19c)**

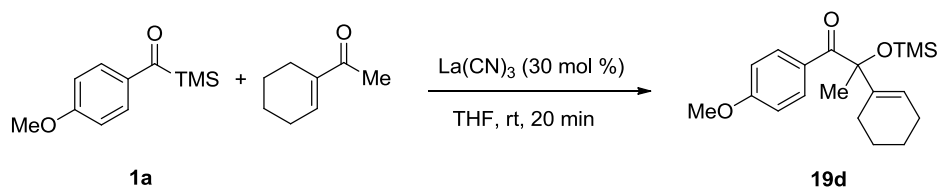
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 94 mg of (E)-hex-4-en-3-one, 36 mg  $\text{LaCl}_3$ , 315  $\mu\text{L}$  of  $n\text{BuLi}$ , and 45 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 66 mg (45% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2964, 1676, 1600, 1574, 1508, 1460, 1418, 1376, 1306, 1249, 1172, 1142, 1086, 1033, 970, 912, 840, 754;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (d,  $J = 8.8$  Hz, 2H), 6.86 (d,  $J = 8.8$  Hz, 2H), 5.79-5.73 (m, 1H), 5.66-5.62 (m, 1H), 3.85 (s, 3H), 2.07-1.92 (m, 2H), 1.71 (d,  $J = 6.4$  Hz, 3H), 0.86 (t,  $J = 7.2$  Hz, 3H), 0.01 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.4, 162.7, 134.0, 132.9, 128.8, 126.4, 112.9, 85.5, 55.3, 31.8, 17.8, 8.0, 2.0; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.36$ ; **HRMS** (ESI) calc. for  $[M+Na] = 329.1549$ , found 329.1525.



### 1-(4-methoxyphenyl)-2-methylhexane-1,4-dione (Table 2.4, 19c')

The silylcyanohydrin of the title compound was prepared according to General Procedure A using 100 mg of acyl silane, 94 mg of (E)-hex-4-en-3-one, 36 mg  $\text{LaCl}_3$ , 315  $\mu\text{L}$  of  $n\text{BuLi}$ , and 45 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 57 mg (36% yield) of the title compound was isolated as a colorless oil. The silylcyanohydrin is isolated as an inseparable mixture of diastereomers. For characterization, the crude material deprotected according to General Procedure B to afford the 1,4-diketone, which was purified by flash chromatography. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2971, 2937, 2842, 1712, 1672, 1600, 1574, 1509, 1458, 1418, 1376, 1353, 1308, 1258, 1238, 1173, 1143, 1114, 1029, 975, 842, 760;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (d,  $J = 8.4$  Hz, 2H), 6.96 (d,  $J = 8.4$  Hz, 2H), 3.97-3.94 (m, 1H), 3.88 (s, 3H), 3.13 (dd,  $J = 18.0, 8.4$  Hz, 1H), 2.55-2.44 (m, 3H), 1.19 (d,  $J = 7.2$  Hz, 3H), 1.03 (t,  $J = 8.4$  Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  210.0, 201.9, 163.5, 130.7, 129.0, 113.8, 55.4, 45.7, 36.1, 35.8, 18.0, 7.7; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.06$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 257.1154$ , found 257.1131.

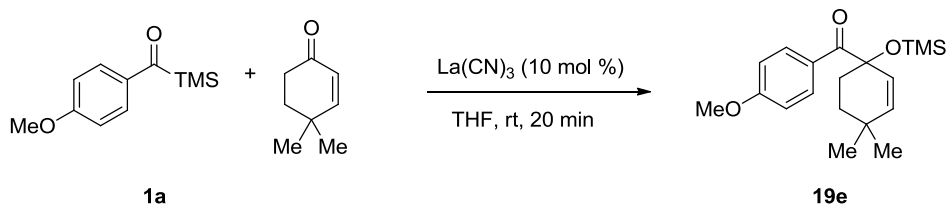




**2-(cyclohex-1-en-1-yl)-1-(4-methoxyphenyl)-2-((trimethylsilyl)oxy)propan-1-one**

**(Table 2.4, 19d)**

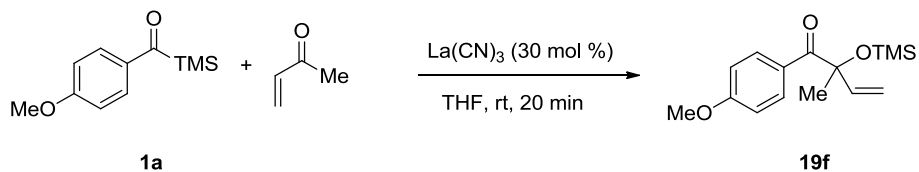
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 120 mg of 1-(cyclohex-1-en-1-yl)ethanone, 36 mg  $\text{LaCl}_3$ , 315  $\mu\text{L}$  of  $n\text{BuLi}$ , and 45 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 65 mg (41% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2934, 2857, 2838, 1676, 1625, 1599, 1573, 1508, 1457, 1418, 1366, 1309, 1248, 1174, 1145, 1121, 1032, 1005, 963, 943, 839, 808, 795;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (d,  $J = 8.8$  Hz, 2H), 6.82 (d,  $J = 9.2$  Hz, 2H), 5.92 (s, 1H), 3.83 (s, 3H), 2.04-2.00 (m, 3H), 1.75-1.70 (m, 1H), 1.59-1.49 (m, 7H), -0.03 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.1, 162.7, 140.8, 132.8, 128.3, 121.1, 112.8, 84.4, 55.3, 26.3, 25.1, 24.1, 22.9, 22.3, 1.8; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.44$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 355.1705$ , found 355.1702.



**(4,4-dimethyl-1-((trimethylsilyl)oxy)cyclohex-2-en-1-yl)(4-methoxyphenyl)**

**methanone (Table 2.4, 19e)**

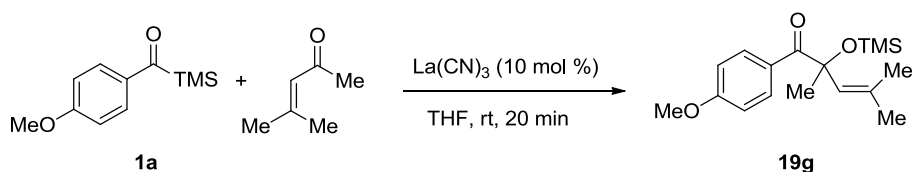
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 120 mg of 4,4-dimethylcyclohexenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 131 mg (82% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2957, 2865, 1672, 1600, 1508, 1459, 1309, 1258, 1169, 1111, 1069, 1031, 1010, 873, 841, 756, 695;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (d,  $J = 9.2$  Hz, 2H), 6.89 (d,  $J = 9.2$  Hz, 2H), 5.85 (d,  $J = 10.0$  Hz, 1H), 5.68 (d,  $J = 10.0$  Hz, 1H), 3.86 (s, 3H), 2.06-2.02 (m, 2H), 1.84-1.77 (m, 1H), 1.54-1.49 (m, 1H), 1.05 (s, 3H), 0.97 (s, 3H), 0.04 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.5, 162.9, 141.3, 132.8, 128.1, 126.8, 113.1, 79.2, 55.3, 32.9, 31.7, 29.4, 27.8, 2.0; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.42$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 355.1705$ , found 355.1709.



**1-(4-methoxyphenyl)-2-methyl-2-((trimethylsilyl)oxy)but-3-en-1-one (Table 2.4, 19f)**

The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 70 mg of methyl vinyl ketone, 36 mg  $\text{LaCl}_3$ , 315  $\mu\text{L}$  of  $n\text{BuLi}$ , and 45 mg of

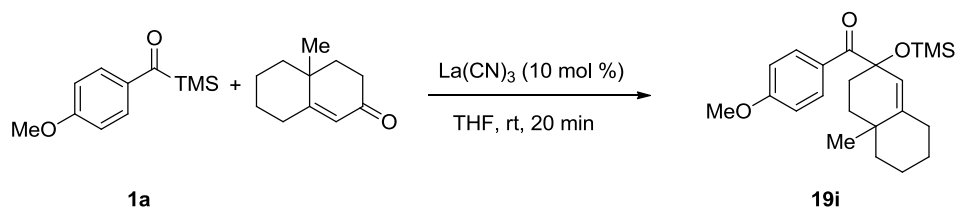
TMSCN in 11 mL of THF. After chromatography, 44 mg (33% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2961, 2936, 2840, 1671, 1600, 1509, 1458, 1419, 1366, 1310, 1254, 1172, 1132, 1032, 929, 880, 841, 768;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (d,  $J = 8.8$  Hz, 2H), 6.86 (d,  $J = 8.8$  Hz, 2H), 6.07 (dd,  $J = 17.2$  Hz, 10.4 Hz, 1H), 5.44 (d,  $J = 17.2$  Hz, 1H), 5.17 (d,  $J = 10.4$  Hz, 1H), 3.85 (s, 3H), 1.60 (s, 3H), 0.03 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.7, 162.9, 143.0, 133.1, 127.9, 113.8, 112.9, 83.2, 55.3, 26.7, 1.8; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.42$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 301.1236$ , found 301.1230.



**1-(4-methoxyphenyl)-2,4-dimethyl-2-((trimethylsilyl)oxy)pent-3-en-1-one (Table 2.4, 19g)**

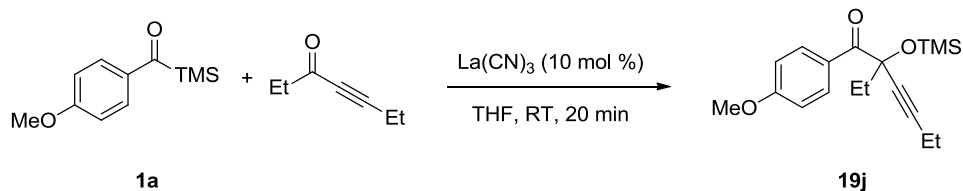
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 95 mg of mesityl oxide, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 106 mg (72% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2961, 2935, 2839, 1677, 1600, 1573, 1508, 1443, 1419, 1370, 1253, 1172, 1113, 1032, 1014, 901, 842, 755, 688;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (d,  $J = 8.8$  Hz, 2H), 6.88 (d,  $J = 9.2$  Hz, 2H), 5.58 (s, 1H), 3.87 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H), 1.53 (s, 3H), 0.02 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.7, 162.7, 133.7, 132.9, 131.1, 127.7, 122.9, 81.4,





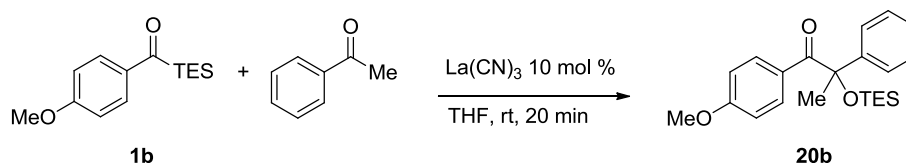
**(4-methoxyphenyl)(4a-methyl-2-((trimethylsilyl)oxy)-2,3,4,4a,5,6,7,8-octahydro-naphthalen-2-yl)methanone (Table 2.4, 19i)**

The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 158 mg of 4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of  $\text{TMSCN}$  in 11 mL of THF. After chromatography, 156 mg (87% yield, 2.7:1 dr) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2929, 2854, 1671, 1599, 1509, 1444, 1308, 1257, 1171, 1064, 1029, 892, 874, 755;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 (d,  $J = 8.8$  Hz, 2H), 6.90 (d,  $J = 8.8$  Hz, 2H), 5.56 (s, 1H), 3.87 (s, 3H), 2.29-2.19 (m, 2H), 2.04-2.00 (m, 1H), 1.94-1.87 (m, 1H), 1.78-1.75 (m, 1H), 1.65-1.52 (m, 4H), 1.44-1.40 (m, 1H), 1.30-1.24 (m, 2H), 1.14 (s, 3H), 0.05 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.4, 162.7, 149.0, 132.9, 128.3, 122.5, 113.0, 80.7, 55.3, 41.0, 36.3, 34.9, 32.7, 31.7, 28.3, 23.7, 22.2, 2.1; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.40$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 395.2018$ , found 395.1972.



### 2-ethyl-1-(4-methoxyphenyl)-2-((trimethylsilyl)oxy)hex-3-yn-1-one (Table 2.4, 19j)

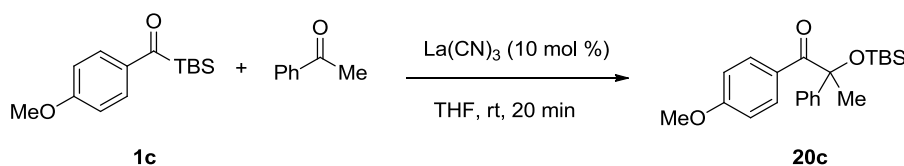
The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 110 mg of hept-4-yn-3-one, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 135 mg (88% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2974, 2938, 2841, 1682, 1600, 1573, 1509, 1461, 1419, 1375, 1310, 1249, 1171, 1139, 1082, 1031, 967, 873, 840, 753, 686;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (d,  $J = 9.2$  Hz, 2H), 6.88 (d,  $J = 9.2$  Hz, 2H), 3.86 (s, 3H), 2.28 (q,  $J = 7.6$  Hz, 2H), 2.01 (q,  $J = 7.6$  Hz, 2H), 1.15 (t,  $J = 7.2$  Hz, 3H), 1.00 (t,  $J = 7.2$  Hz, 3H), 0.14 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  196.3, 163.0, 132.8, 127.4, 113.0, 90.4, 80.0, 79.0, 55.3, 35.2, 13.4, 12.6, 8.4, 1.6; **TLC** (10% EtOAc/ petroleum ether)  $R_f = 0.40$ ; **HRMS** (ESI) calc. for  $[\text{M}+\text{Na}] = 341.1549$ , found 341.1510.



### 1-(4-methoxyphenyl)-2-phenyl-2-(triethylsilyloxy)propan-1-one (Figure 2.5, 20b)

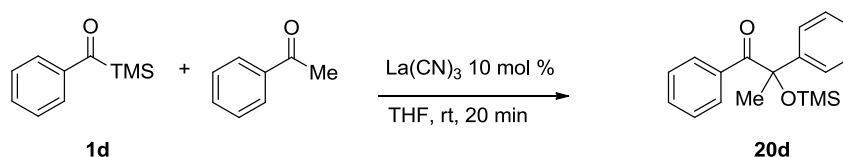
The title compound was prepared according to General Procedure A using 120 mg of acyl silane, 116 mg of acetophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 165 mg (93% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2955,

2876, 1674, 1600, 1509, 1459, 1418, 1368, 1310, 1255, 1175, 1153, 1128, 1014, 951, 857; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.91 (d, J = 8.8 Hz, 2H), 7.48-7.46 (m, 2H), 7.33-7.30 (m, 2H), 7.23-7.20 (m, 1H), 6.73 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 1.76 (s, 3H), 0.92-0.88 (m, 9H), 0.63-0.49 (m, 6H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 298.9, 162.7, 145.8, 133.3, 128.5, 127.5, 127.0, 124.0, 112.9, 83.2, 55.2, 30.1, 7.0, 6.5; TLC (20% EtOAc/petroleum ether) R<sub>f</sub> = 0.51, (5% Et<sub>2</sub>O/petroleum ether) R<sub>f</sub> = 0.34; **LRMS** (ESI) calc. for [M+Na] = 393.19, found 393.19.



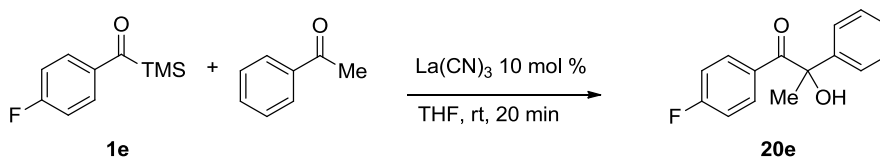
**2-((tert-butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)-2-phenylpropan-1-one (Figure 2.5, 20c)**

The title compound was prepared according to General Procedure A using 120 mg of acyl silane, 120 mg of acetophenone, 12 mg LaCl<sub>3</sub>, 105 µL of <sup>n</sup>BuLi, and 15 mg of TMSCN in 11 mL of THF. After chromatography, 160 mg (90% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 2955, 2931, 2857, 1675, 1600, 1509, 1462, 1445, 1310, 1256, 1175, 1149, 1126, 1004, 951, 843, 777; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.84 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.27-7.24 (m, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.78 (s, 3H), 1.76 (s, 3H), 0.87 (s, 9H), 0.19 (s, 3H), -0.17 (s, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 198.7, 162.7, 146.2, 133.4, 128.5, 127.7, 127.0, 124.0, 112.9, 83.2, 55.2, 30.6, 26.1, 18.5, -1.8, -3.3; **TLC** (10% EtOAc/ petroleum ether) R<sub>f</sub> = 0.38; **HRMS** (ESI) calc. for [M+Na] = 393.1862, found 393.1853.



### 1,2-diphenyl-2-(trimethylsilyloxy)propan-1-one (Figure 2.5, 20d)

The title compound was prepared according to General Procedure A using 86 mg of acyl silane, 116 mg of acetophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 117 mg (81% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: IR (thin film,  $\text{cm}^{-1}$ ) 3061, 2959, 1685, 1598, 1446, 1369, 1254, 1216, 1162, 1128, 1075, 1011, 952, 865, 842;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (d,  $J = 7.2$ , 2H), 7.49 (d,  $J = 7.2$ , 2H), 7.39-7.24 (m, 5H), 1.77 (s, 3H), 0.03 (2, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.8, 145.0, 134.8, 132.2, 130.9, 128.5, 127.7, 127.1, 124.2, 83.6, 30.1, 1.8; TLC (20% EtOAc/petroleum ether)  $R_f = 0.54$ , (5% Et<sub>2</sub>O/petroleum ether)  $R_f = 0.49$ ; LRMS (ESI) calc. for  $[\text{M}+\text{Na}] = 321.13$ , found 321.13.

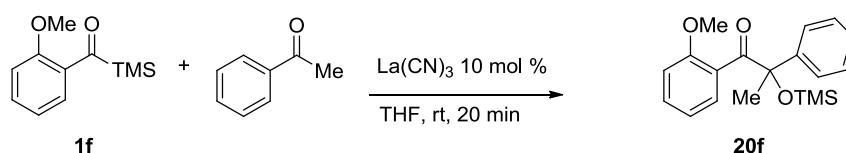


### 1-(4-fluorophenyl)-2-hydroxy-2-phenylpropan-1-one (Figure 2.5, 20e)

The title compound was prepared according to General Procedure A, followed by General Procedure B, using 94 mg of acyl silane, 116 mg of acetophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 74 mg (62% yield) of the title compound was isolated as a yellow oil. Analytical data for title compound: IR (thin film,  $\text{cm}^{-1}$ ) 3458, 3065, 2980, 1680, 1599, 1505, 1447, 1362, 1238,

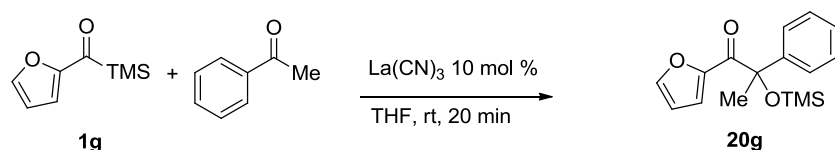


1158, 1027, 1014, 980, 914, 852; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.78-7.75 (m, 2H), 7.45-7.43 (m, 2H), 7.40-7.36 (m, 2H), 7.33-7.30 (m, 1H), 6.96 (t, *J* = 8.4 Hz, 2H), 4.62 (s, 1H), 1.88 (s, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 200.2, 166.7, 164.1, 142.5, 133.1 (d, *J*<sub>C-F</sub> = 9.1 Hz), 129.8, 129.0, 128.2, 125.7, 115.4 (d, *J*<sub>C-F</sub> = 21.7 Hz), 79.2, 26.5; TLC (20% EtOAc/petroleum ether) *R*<sub>f</sub> = 0.32, (30% Et<sub>2</sub>O/petroleum ether) *R*<sub>f</sub> = 0.37; **LRMS** (ESI) calc. for [M+Na] = 267.08, found 267.08.



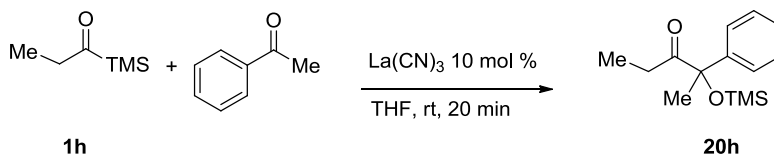
#### 1-(2-methoxyphenyl)-2-phenyl-2-(trimethylsilyloxy)propan-1-one (Figure 2.5, 20f)

The title compound was prepared according to General Procedure A using 100 mg of acyl silane, 120 mg of acetophenone, 12 mg LaCl<sub>3</sub>, 105 μL of <sup>n</sup>BuLi, and 15 mg of TMSCN in 11 mL of THF. After chromatography, 129 mg (82% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film, cm<sup>-1</sup>) 2957, 2836, 1710, 1597, 1488, 1461, 1446, 1434, 1252, 1167, 1076, 1011, 955, 867, 841; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.53 (d, *J* = 7.6 Hz, 2H), 7.38-7.28 (m, 4H), 6.97 (d, *J* = 6.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 3.73 (s, 3H), 1.87 (s, 3H), 0.03 (s, 9H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 206.1, 157.2, 144.2, 131.1, 129.3, 128.5, 128.0, 127.1, 125.4, 119.3, 110.9, 84.1, 55.3, 28.0, 1.9; TLC (20% EtOAc/petroleum ether) *R*<sub>f</sub> = 0.42, (5% Et<sub>2</sub>O/petroleum ether) *R*<sub>f</sub> = 0.26; **LRMS** (ESI) calc. for [M+Na] = 328.14, found 328.15.



### 1-(furan-2-yl)-2-phenyl-2-(trimethylsilyloxy)propan-1-one (Figure 2.5, 20g)

The title compound was prepared according to General Procedure A using 80 mg of acyl silane, 116 mg of acetophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 78 mg (57% yield) of the title compound was isolated as a white solid (mp 64-66 °C). Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2959, 1672, 1560, 1492, 1462, 1388, 1370, 1253, 1218, 1155, 1075, 1029, 1008, 959, 865;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51-7.46 (m, 3H), 7.31 (t,  $J = 7.6$  Hz, 2H), 7.24-7.20 (m, 1H), 7.12-7.11 (m, 1H), 6.37-6.36 (m, 1H), 1.81 (s, 3H), 0.14 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  189.4, 149.7, 146.2, 144.4, 128.3, 127.3, 124.5, 121.2, 11.6, 82.7, 28.0, 1.8; TLC (20% EtOAc/petroleum ether)  $R_f = 0.46$ , (5% Et<sub>2</sub>O/petroleum ether)  $R_f = 0.27$ ; **LRMS** (ESI) calc. for  $[\text{M}+\text{H}] = 289.13$ , found 289.13.



### 2-phenyl-2-(trimethylsilyloxy)pentan-3-one (Figure 2.5, 20h)

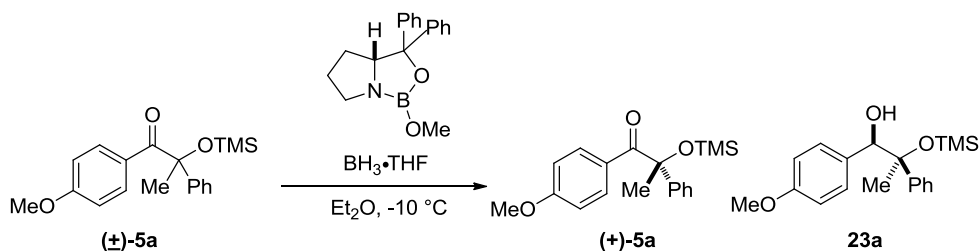
The title compound was prepared according to General Procedure A using 63 mg of acyl silane, 116 mg of acetophenone, 12 mg  $\text{LaCl}_3$ , 105  $\mu\text{L}$  of  $n\text{BuLi}$ , and 15 mg of TMSCN in 11 mL of THF. After chromatography, 74 mg (61% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: **IR** (thin film,  $\text{cm}^{-1}$ ) 2959, 1719, 1447, 1253, 1154, 1075, 1035, 993, 959, 864, 841;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$

7.41 (d,  $J = 7.6$  Hz, 2H), 7.32 (t,  $J = 7.6$  Hz, 2H), 7.26-7.23 (m, 1H), 2.70-2.60 (m, 1H), 2.43-2.33 (m, 1H), 1.72 (s, 3H), 0.90 (t,  $J = 7.2$  Hz, 3H), 0.17 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ ; 212.6, 143.7, 128.2, 127.3, 125.1, 83.5, 29.0, 26.0, 8.1, 2.0; TLC (20% EtOAc/petroleum ether)  $R_f = 0.54$ , (5% Et<sub>2</sub>O/petroleum ether)  $R_f = 0.39$ ; LRMS (ESI) calc. for  $[\text{M}+\text{Na}] = 273.1$ , found 273.1.

### III. Procedures and Analytical Data for Kinetic Resolution

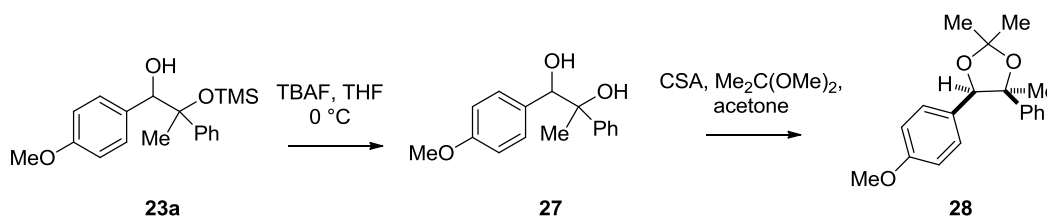
#### General Procedure for Kinetic Resolution of $\alpha$ -Silyloxyketones (C)

The  $\alpha$ -silyloxyketone was massed into a dry Teflon coated screw-cap vial with a stir bar, and purged with N<sub>2</sub>. Diethyl ether (2 mL) was added, and the reaction was capped and brought into the glovebox. A 0.1 M toluene solution of the CBS catalyst (10 mol %) was added, and the reaction was capped and removed from the glovebox. The reaction was then cooled to -10 °C, and a 1.0 M THF solution of BH<sub>3</sub>•THF was added to the reaction. The reaction was monitored by quenching aliquots in MeOH. To stop the reaction, MeOH was added, and the contents were poured into 1:1 Et<sub>2</sub>O/saturated NH<sub>4</sub>Cl. The organic layer was separated, washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The resolved material was separated from the monosilylated diol by column chromatography on silica gel with 1:9 Et<sub>2</sub>O/petroleum ether as the eluent.



**(*R*)-1-(4-methoxyphenyl)-2-phenyl-2-((trimethylsilyl)oxy)propan-1-one (Figure 2.8, (+)-5a)**

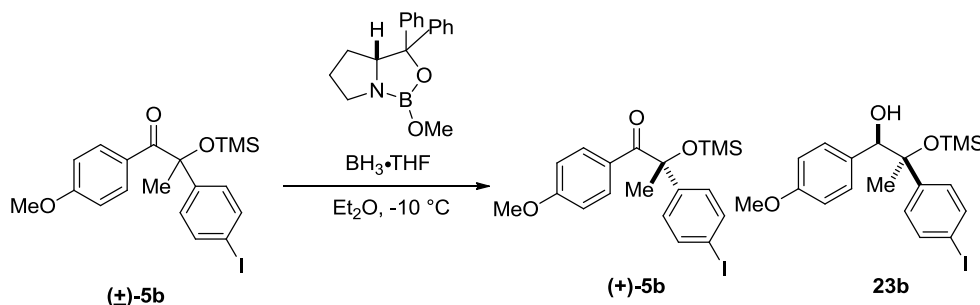
The title compound was prepared according to General Procedure C using 30 mg of ( $\pm$ )-**5a**, 100  $\mu$ L of the CBS catalyst as a 0.1 M solution in toluene, and 75  $\mu$ L of  $\text{BH}_3\cdot\text{THF}$  as a 1.0 M solution in THF. The reaction was stopped at partial conversion after 3 hr. Conversion was determined by  $^1\text{H}$  NMR spectroscopy and the enantiomeric excess of the recovered starting material was determined by SFC (OD column, 150 psi, 1.5 mL/min, and 0.5% MeOH modifier,  $t_{\text{major}} = 12.9$  min,  $t_{\text{minor}} = 13.5$  min). The SFC traces of the racemic and enantioenriched samples are shown below. The reaction was stopped 31% conversion and the starting material was recovered in 36% ee, with a selectivity factor of  $s = 12.9$ . The crude starting material was separated from the diol by flash chromatography. Analytical data is identical to ( $\pm$ )-**5a**,  $[\alpha]_{\text{D}}^{25} = 136.0$  ( $c = 3.30$ ,  $\text{CH}_2\text{Cl}_2$ ). Deprotection of (+)-**5a** with TBAF cleanly yielded the free hydroxyl product,  $[\alpha]_{\text{D}}^{25} = -30.4$  ( $c = 0.70$ ,  $\text{CH}_2\text{Cl}_2$ ). Absolute stereochemistry was assigned by analogy.



**Determination of Diol Stereochemistry by Conversion of **23a** to (4*S*,5*R*)-5-(4-methoxyphenyl)-2,2,4-trimethyl-4-phenyl-1,3-dioxolane (**28**)**

Compound **23a** (25 mg, 0.76 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. TBAF (1.3 equiv.) was added and the reaction was complete by TLC in 5 min. The reaction was diluted in 1:1  $\text{Et}_2\text{O}$ /brine (30 mL), separated, the organic layer dried over

MgSO<sub>4</sub>, filtered, and concentrated. The crude material was dissolved 2:1 acetone:dimethoxypropane (3 mL). Camphorsulfonic acid (5 mg) was added and the reaction was complete after 2 hr. The crude reaction mixture was concentrated to a red oil and subjected to flash column chromatography (20% EtOAc/PE eluent), affording the title compound in 84% overall yield. Analytical data: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.38-7.28 (mult., 5H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.93 (s, 1H), 3.84 (s, 3H), 1.74 (s, 3H), 1.63 (s, 3H), 1.27 (s, 3H). 2D-NOESY was taken and cross peaks were observed between the *p*-OMePh, Ph, and one acetonide methyl group; and between the methine proton and the non-acetonide methyl group, leading to the assignment of the aryl rings as *cis*. A copy of the <sup>1</sup>H NMR and 2D-NOESY is available in Section S5 and S6, respectively.

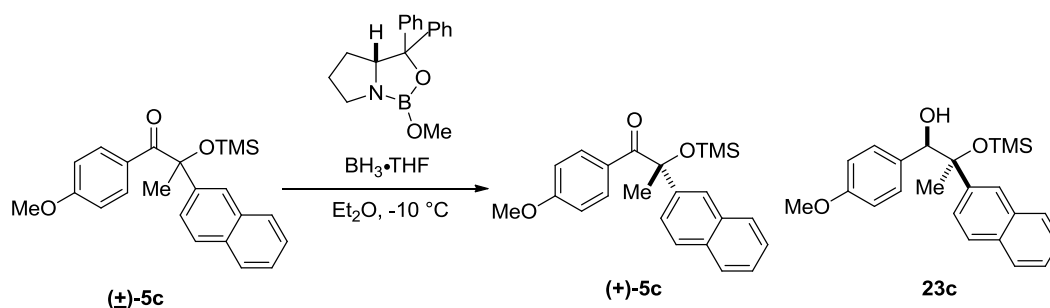


**(R)-2-(4-iodophenyl)-1-(4-methoxyphenyl)-2-((trimethylsilyl)oxy)propan-1-one**

**(Figure 2.8, (+)-5b)**

The title compound was prepared according to General Procedure C using 50 mg of (+)-5b, 100 μL of the CBS catalyst as a 0.1 M solution in toluene, and 100 μL of BH<sub>3</sub>·THF as a 1.0 M solution in THF. The reaction was stopped at partial conversion after 3 hr. Conversion was determined by <sup>1</sup>H NMR spectroscopy and the enantiomeric excess of the recovered starting material was determined by SFC (OD column, 150 psi, 1.5 mL/min,

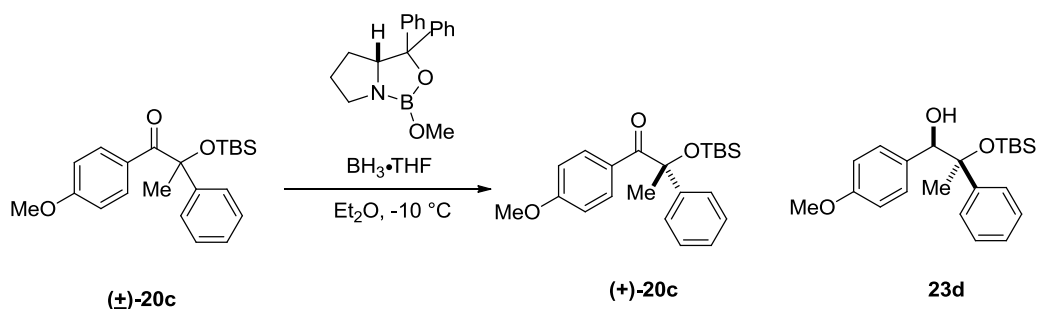
and 0.5% MeOH modifier,  $t_{\text{major}} = 23.9$  min,  $t_{\text{minor}} = 26.3$  min). The reaction was stopped 35% conversion and the starting material was recovered in 39% ee, with a selectivity factor of  $s = 9.1$ . The crude starting material was separated from the diol by flash chromatography. Analytical data is identical to **(±)-5b**,  $[\alpha]_{\text{D}}^{25} = 49.2$  ( $c = 0.95$ ,  $\text{CH}_2\text{Cl}_2$ ). Absolute stereochemistry was assigned by analogy.



**(R)-1-(4-methoxyphenyl)-2-(naphthalen-2-yl)-2-((trimethylsilyl)oxy)propan-1-one**

**(Figure 2.8, (+)-5c)**

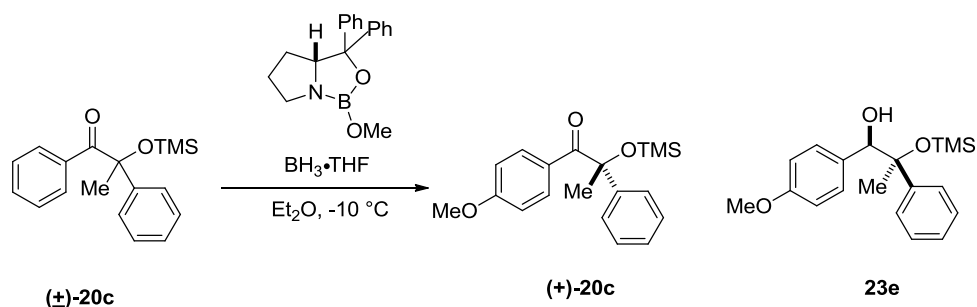
The title compound was prepared according to General Procedure C using 20 mg of **(±)-5c**, 100  $\mu\text{L}$  of the CBS catalyst as a 0.1 M solution in toluene, and 65  $\mu\text{L}$  of  $\text{BH}_3 \cdot \text{THF}$  as a 1.0 M solution in THF. The reaction was stopped at partial conversion after 3 hr. Conversion was determined by  $^1\text{H}$  NMR spectroscopy and the enantiomeric excess of the recovered starting material was determined by SFC (AD column, 200 psi, 1.5 mL/min, and 4.0% MeOH modifier,  $t_{\text{major}} = 6.6$  min,  $t_{\text{minor}} = 7.7$  min). The reaction was stopped 42% conversion and the starting material was recovered in 56% ee, with a selectivity factor of  $s = 13.6$ . The crude starting material was separated from the diol by flash chromatography. Analytical data is identical to **(±)-5c**,  $[\alpha]_{\text{D}}^{25} = 53.9$  ( $c = 0.20$ ,  $\text{CH}_2\text{Cl}_2$ ). Absolute stereochemistry was assigned by analogy.



**(R)-2-((tert-butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)-2-phenylpropan-1-one**

**(Figure 2.8, (+)-20c)**

The title compound was prepared according to General Procedure C using 30 mg of  $(\pm)\text{-20c}$ , 100  $\mu\text{L}$  of the CBS catalyst as a 0.1 M solution in toluene, and 75  $\mu\text{L}$  of  $\text{BH}_3\cdot\text{THF}$  as a 1.0 M solution in THF. The reaction was stopped at partial conversion after 3 hr. Conversion was determined by  $^1\text{H}$  NMR spectroscopy and the enantiomeric excess of the recovered starting material was determined by SFC (OD column, 200 psi, 2.0 mL/min, and 5.0% MeOH modifier,  $t_{\text{major}} = 19.1$  min,  $t_{\text{minor}} = 17.9$  min). The reaction was stopped 50% conversion and the starting material was recovered in 75% ee, with a selectivity factor of  $s = 15.5$ . The crude material was treated with TBAF then the starting material was separated from the diol by flash chromatography. Analytical data is identical to silyl deprotected  $(\pm)\text{-20c}$ ,  $[\alpha]_{\text{D}}^{25} = -32.9$  ( $c = 0.20$ ,  $\text{CH}_2\text{Cl}_2$ ). Absolute stereochemistry was assigned by analogy.

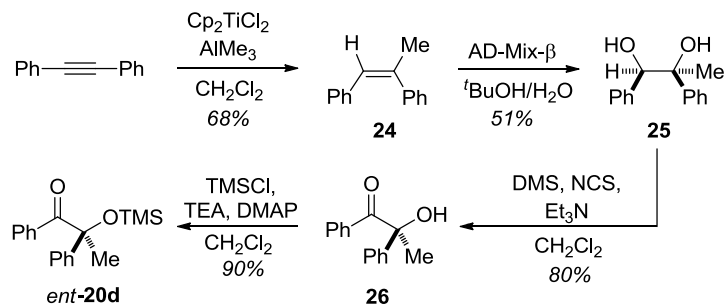


**(*R*)-1-(4-methoxyphenyl)-2-phenyl-2-((trimethylsilyl)oxy)propan-1-one (Figure 2.8, (+)-20d)**

The title compound was prepared according to General Procedure C using 30 mg of ( $\pm$ )-**20d**, 100  $\mu\text{L}$  of the CBS catalyst as a 0.1 M solution in toluene, and 75  $\mu\text{L}$  of  $\text{BH}_3\cdot\text{THF}$  as a 1.0 M solution in THF. The reaction was stopped at partial conversion after 3 hr. Conversion was determined by  $^1\text{H}$  NMR spectroscopy and the enantiomeric excess of the recovered starting material was determined by GC (oven temp. = 140  $^\circ\text{C}$ ,  $t_{\text{major}} = 109.5$  min,  $t_{\text{minor}} = 111.2$  min). The reaction was stopped 58% conversion and the starting material was recovered in 91% ee, with a selectivity factor of  $s = 14.5$ . The crude starting material was separated from the diol by flash chromatography. Analytical data is identical to ( $\pm$ )-**20d**,  $[\alpha]_{\text{D}}^{25} = 122.8$  ( $c = 0.40$ ,  $\text{CH}_2\text{Cl}_2$ ). Absolute stereochemistry was assigned by comparison to *ent*-**20d** which was prepared by Sharpless asymmetric dihydroxylation.



## Independent Synthesis of ent-7d



### (Z)-prop-1-ene-1,2-diylidibenzene (**24**)

The title compound was prepared by the literature method of Negishi et al in 68% yield following flash column chromatography.<sup>27</sup> Physical properties of the synthesized material are consistent with the literature values.

### (1*R*,2*S*)-1,2-diphenylpropane-1,2-diol (**25**)

The title compound was prepared by following the literature method of Rosini et al in 51% yield following flash column chromatography.<sup>28</sup> Physical properties of the synthesized material are consistent with the literature values.

### (S)-2-hydroxy-1,2-diphenylpropan-1-one (**26**)

The title compound was prepared by following the literature method of Corey et al. following flash chromatography.<sup>29</sup> Physical properties of the synthesized material are consistent with the literature values.

**(S)-1,2-diphenyl-2-((trimethylsilyl)oxy)propan-1-one (ent-20d)**

The title compound was prepared by charging a 10-mL round bottomed flask with hydroxyketone (**11**) (16 mg, 0.071 mmol, 1.0 equiv.), a stir bar, and CH<sub>2</sub>Cl<sub>2</sub>. Trimethylsilyl chloride (1.5 equiv.), triethylamine (2.0 equiv.) and 4-dimethylaminopyridine (0.2 equiv.) were added and the reaction was monitored by TLC and determined to be complete after 3 hr. The reaction was diluted in 10 mL of CH<sub>2</sub>Cl<sub>2</sub>, washed with sat aq. NH<sub>4</sub>Cl and brine. The organic layer was dried over MgSO<sub>4</sub> then concentrated. Following flash chromatography, *ent*-**20d** was obtained in 90% yield. The analytical data for *ent*-**20d** matches that of **20d** prepared by the ketone-benzoin coupling reaction. Enantiomeric ratio of *ent*-**20d** was determined by GC (140 °C, t<sub>major</sub> = 111.26 min., t<sub>minor</sub> = 109.4 min.) and found to be 66:34, [α]<sub>D</sub><sup>25</sup> = -30.0 (c = 0.95, CH<sub>2</sub>Cl<sub>2</sub>).

## 2.6 References

- (1) Portions of the work described herein have been published and reprinted in part with permission from Tarr, J. C.; Johnson, J. S. *Org. Lett.* **2009**, *11*, 3870-3873, © 2009 American Chemical Society and Tarr, J. C.; Johnson, J. S. *J. Org. Chem.* **2010**, *75*, 3317-3325, © 2010 American Chemical Society.
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# CHAPTER III

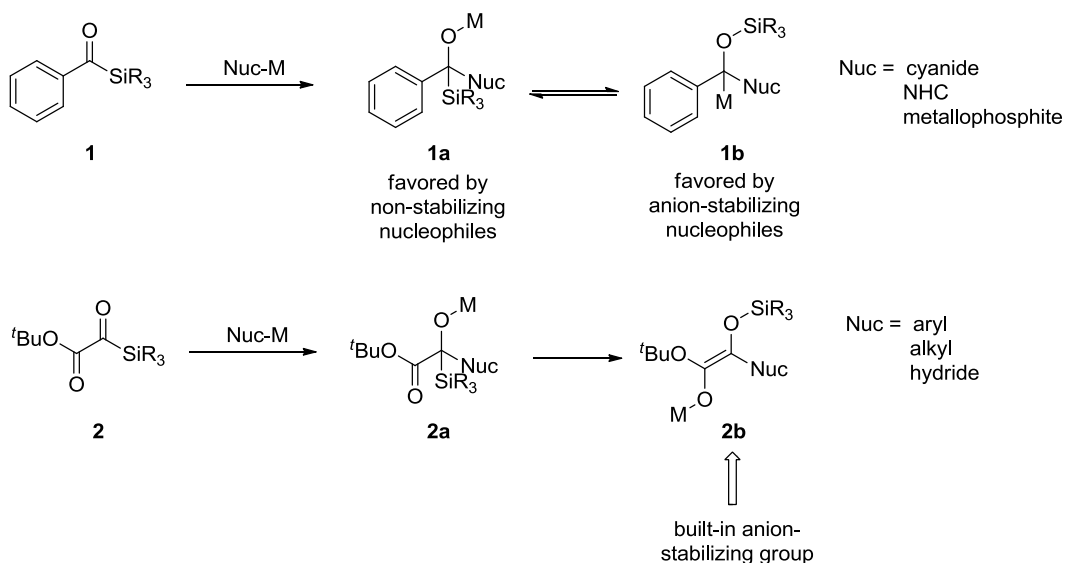
## BIS-FUNCTIONALIZATION OF GLYOXYLATE FOR THE SYNTHESIS OF FULLY SUBSTITUTED GLYCOLIC ACIDS

### 3.1 Introduction

Multi-component coupling reactions can provide efficient access to complex molecular architectures through the rapid construction of multiple carbon-carbon bonds.<sup>1</sup> Achieving multiple bond forming events in one pot is attractive as it can increase the overall yield of a series of transformations and reduce the amount of time and resources necessary to isolate and purify each intermediate. Hence, the development of multi-component coupling strategies is attractive across a broad range of disciplines ranging from green chemistry to industrial/process chemistry to classical total syntheses.

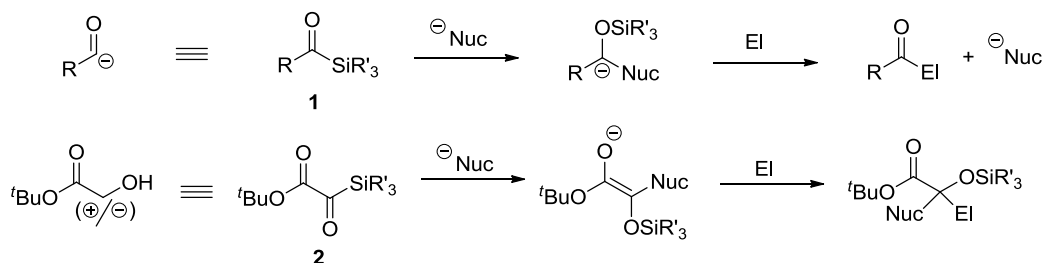
Our group has developed silyl glyoxylates as a special class of acyl silanes that can be used as a linchpin for multi-component coupling reactions.<sup>2</sup> As discussed in Chapter 1, nucleophilic addition to acyl silanes can trigger a [1,2]-Brook rearrangement to reveal a site of latent nucleophilicity (Scheme 3.1).<sup>3</sup> However, when aryl or alkyl acyl silanes (**1**) are employed, it is typically necessary to use an electron-withdrawing nucleophile that can stabilize an  $\alpha$ -carbanion to promote Brook rearrangement, limiting the types of products that can be accessed. Silyl glyoxylates, ester-substituted acyl

silanes, incorporate the electron-withdrawing functionality into the structure of the acyl silane, allowing a wide range of nucleophiles, including aryl and alkyl organometallics and hydride, to initiate the Brook rearrangement (**2a**→**2b**, Scheme 3.1).



### Scheme 3.1. Brook Rearrangement of Acyl Silanes and Silyl Glyoxylates

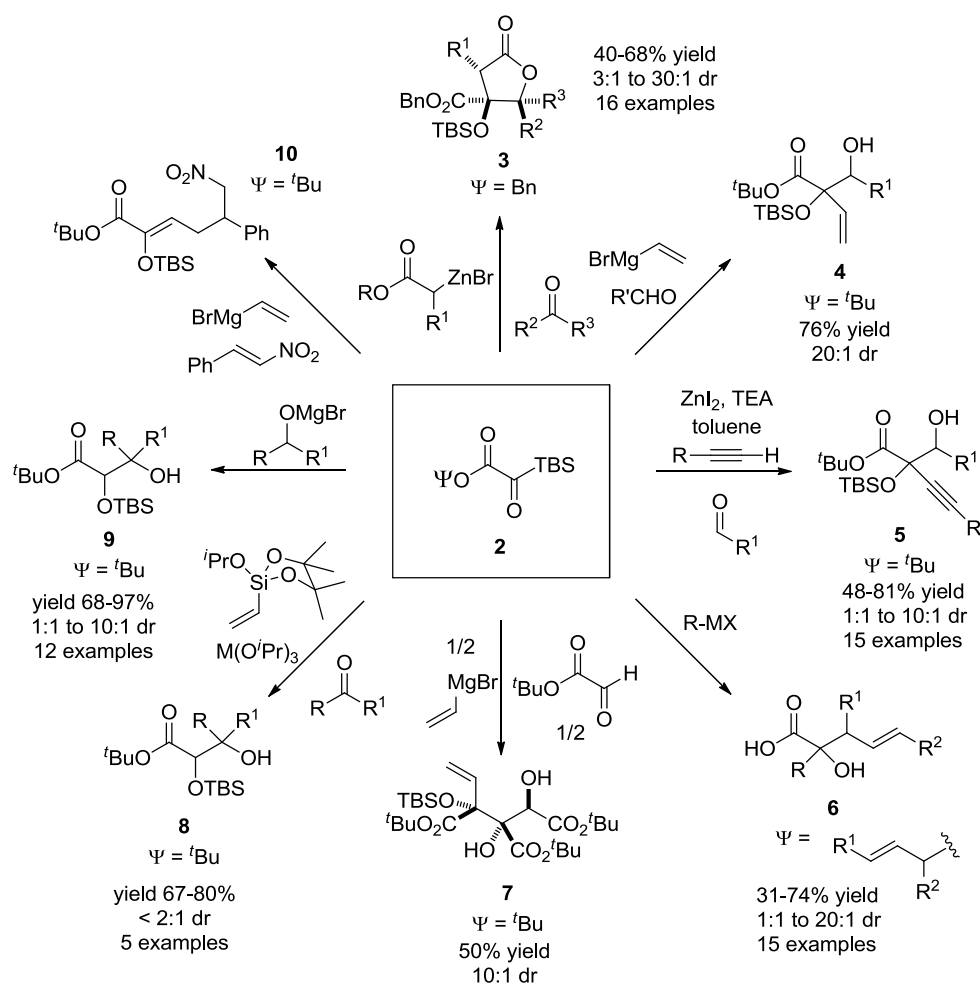
Since the typical nucleophiles that are used with silyl glyoxylates are poor leaving groups, they are not expelled following addition of an electrophile but are retained in the product. Silyl glyoxylates, therefore, typically function as ambiphilic conjunctive reagents for coupling a nucleophile and an electrophile at a glycolic acid junction rather than acyl anion synthetic equivalents.<sup>4</sup> This leads to a divergence in product types between acyl silanes and silyl glyoxylates: acyl silanes provide an acylated electrophile, whereas silyl glyoxylates yield disubstituted glycolic acid derivatives (Scheme 3.2).



**Scheme 3.2.** Different Reactivity Patterns of Acyl Silanes and Silyl Glyoxylates

Silyl glyoxylates are versatile reagents capable of undergoing a variety of reactions to access different functionalized glycolic acids. The extant methodologies developed by our lab are illustrated in Scheme 3. Both alkynylzinc and Grignard reagents been used to trigger Brook rearrangement and subsequent trapping with an aldehyde electrophile (**4**, **5**, and **7**).<sup>2, 5</sup> Reformatsky reagents were successfully employed as the nucleophilic component and subsequently trapped by ketone electrophiles in high yield and dr (**3**).<sup>6</sup> Michael acceptors have been successfully engaged as electrophiles by coupling with  $\text{CH}_2=\text{CHMgBr}$  via  $\gamma$ -addition (**10**).<sup>7</sup> The use of an allyl ester group allows for trapping of the enolate intermediate via an Ireland-Claisen reaction (**6**).<sup>8</sup> Hydride nucleophiles have also been employed to trigger reductive aldol reactions between silyl glyoxylate and an aldehyde (**8**, **9**).<sup>9, 10</sup>

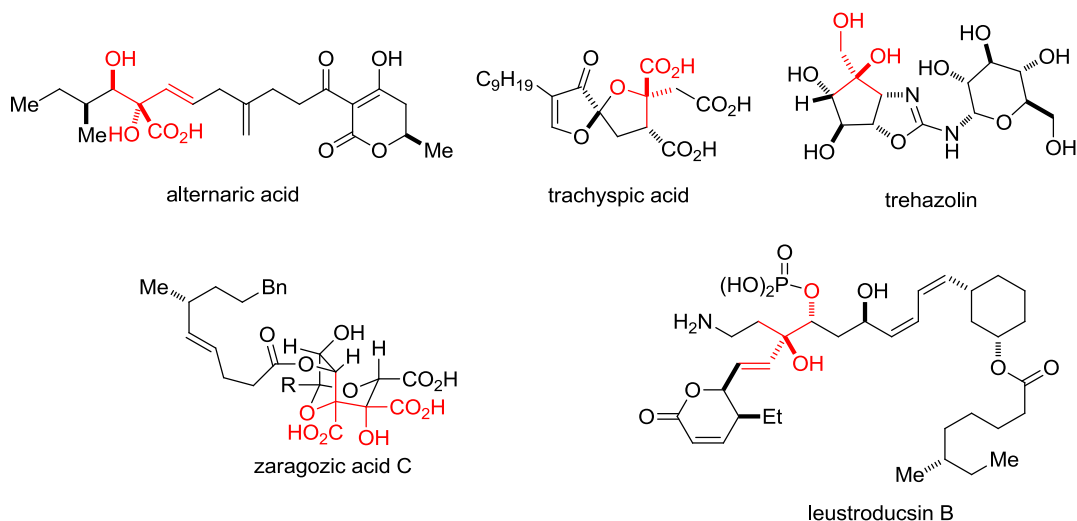




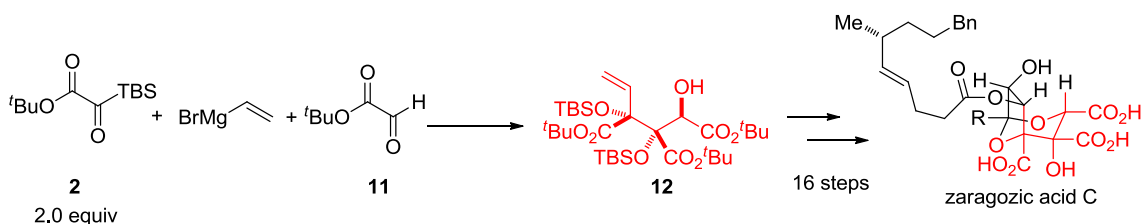
**Scheme 3.3.** Multi-Component Couplings Achieved with Silyl Glyoxylates

The methodologies that have stemmed from silyl glyoxylate-derived couplings have provided access to a variety of useful synthetic building blocks with applications to total synthesis. The glycolic acid functionality is present in numerous natural products and biologically active agents. Some of the natural products that our group has targeted using silyl glyoxylate couplings as an entry point to the synthesis are zaragozic acid C,<sup>5</sup> alternaric acid,<sup>11</sup> leustroducsin B,<sup>12</sup> trachyspic acid,<sup>13</sup> and trehazolin. These targets, with the functionalized glycolic acid subunits highlighted, are shown in Figure 3.1 below. Currently, zaragozic acid C is the only target that has yielded to total synthesis. A controlled oligomerization of silyl glyoxylate initiated by the addition of vinylmagnesium

bromide and terminated by electrophilic capping with *tert*-butyl glyoxylate provided most of the core of zaragozic acid C (Scheme 3.4). Employing this efficient multi-component coupling reaction in the initial step enabled the completion of the shortest synthesis of this challenging molecule to date.



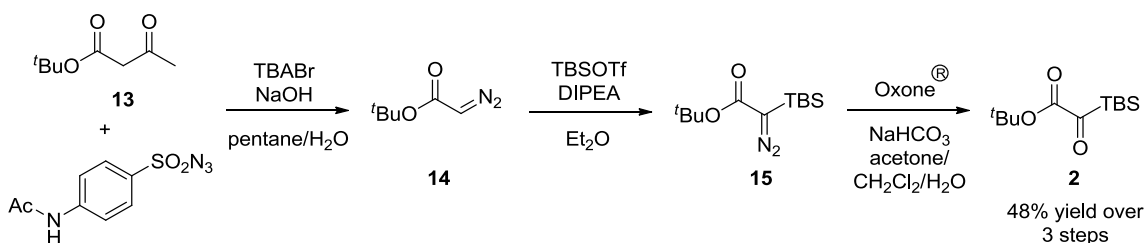
**Figure 3.1.** Natural Products Targeted by Silyl Glyoxylate Coupling Reactions



**Scheme 3.4.** Application of Silyl Glyoxylate Coupling to Total Synthesis of Zaragozic Acid C

Silyl glyoxylates are prepared in three steps from *tert*-butyl acetoacetate (**13**, Scheme 3.5).<sup>14</sup> The synthesis commences with a diazo transfer reaction and concomitant deacylation conducted under phase transfer conditions to afford the diazo ester **14**. Silylation with TBSOTf and Hünig's base at -30 °C provides the silylated diazo compound **15**. Oxidation with Oxone<sup>®</sup> furnishes *tert*-butyl *tert*-

butyldimethylsilyl glyoxylate (**2**) in 48% overall yield. The reaction can be carried out on a 20-gram scale with no detriment to the yield. A single purification is required after the oxidation to **2**; however, this step requires flash column chromatography and is the throughput-limiting step on a laboratory scale. While the synthesis is scalable and practical on a laboratory scale, it does pose drawbacks, especially for larger scales: three steps (and work-ups) are required, the second and third steps must be conducted at low temperatures, and the final purification is a chromatographic separation. The silyl group that is introduced in the product will almost always require removal to obtain the desired product. Additionally, silyl triflates are more expensive than desirable for a functionality destined to be removed from the final product (TBSOTf is ~\$200/mol from Oakwood Products, Inc., or \$1950/mol from Sigma Aldrich).<sup>15</sup> Perhaps due to these drawbacks in the preparation, silyl glyoxylates have yet to gain a foothold as general reagents for organic synthesis.

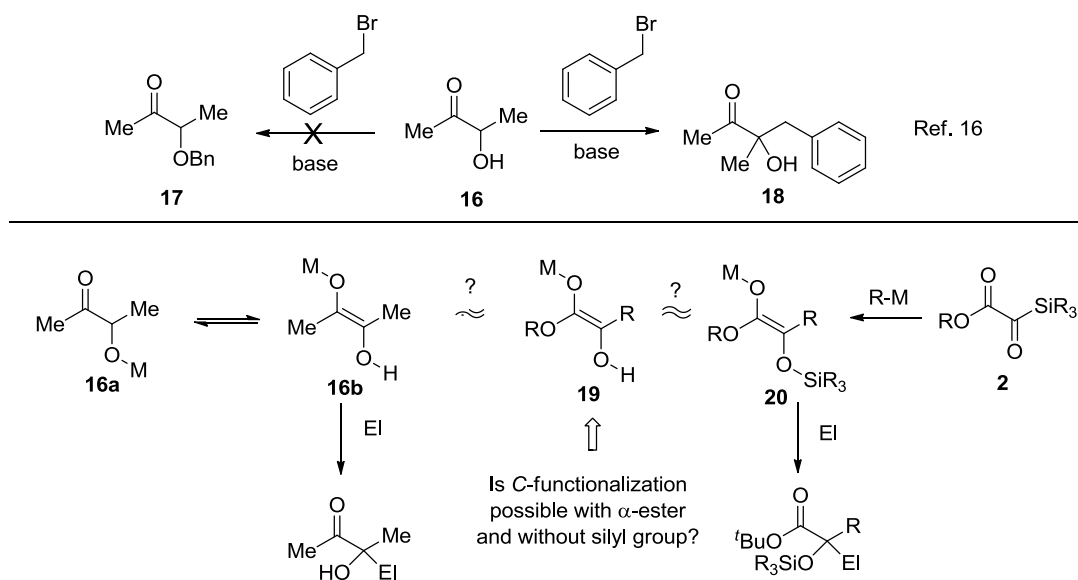


**Scheme 3.5.** Synthesis of Silyl Glyoxylate

## 3.2 Background

In the course of our studies on the chelation-controlled addition of acyl silanes to ketones (Chapter 2), we wished to examine a benzyl protected acetoin derivative. Surprisingly, treatment of acetoin with a base and benzyl bromide does not furnish the

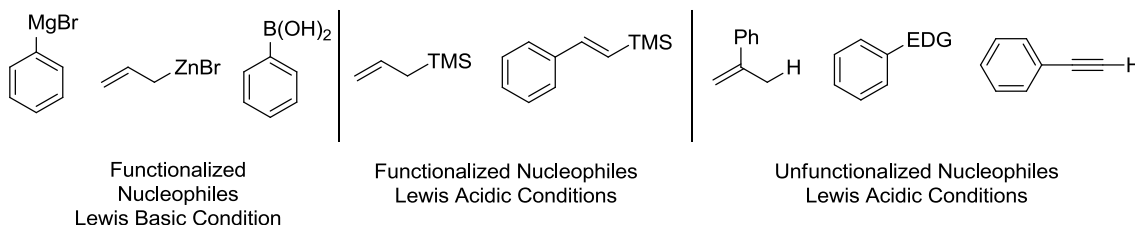
protected hydroxyl group but instead yields the *C*-alkylated product (**17**, Scheme 3.6), indicating that the reaction proceeds through intermediate **16b** rather than **16a**.<sup>16</sup> The intermediate that undergoes *C*-alkylation (**16b**) is quite analogous to the one accessed from nucleophilic addition to ethyl glyoxylate with the difference being an  $\alpha$ -keto substituent rather than an  $\alpha$ -ester. This prompted us to ask whether *C*-functionalization could be accomplished from intermediate **19**, which would arise from nucleophilic addition to commercially available ethyl glyoxylate. The analogous reaction with silyl glyoxylate is known; however, reaction *via* the alkoxide is prevented by protecting it as the silyl ether (**20**).



**Scheme 3.6.** Routes to Access  $\alpha$ -Hydroxy or  $\alpha$ -Silyloxy Carbonyl Compounds

Nucleophilic addition to glyoxylates is well precedented, as the  $\alpha$ -ester group makes the aldehyde exceptionally reactive. Their high reactivity enables addition of not only more reactive organometallic species such as Grignard<sup>17</sup> and organozinc<sup>18</sup> reagents, but milder nucleophiles as well. Aryl boronic acids have been added in a palladium-catalyzed Suzuki reaction.<sup>19</sup> Both allyl and vinyl silanes have been shown to undergo

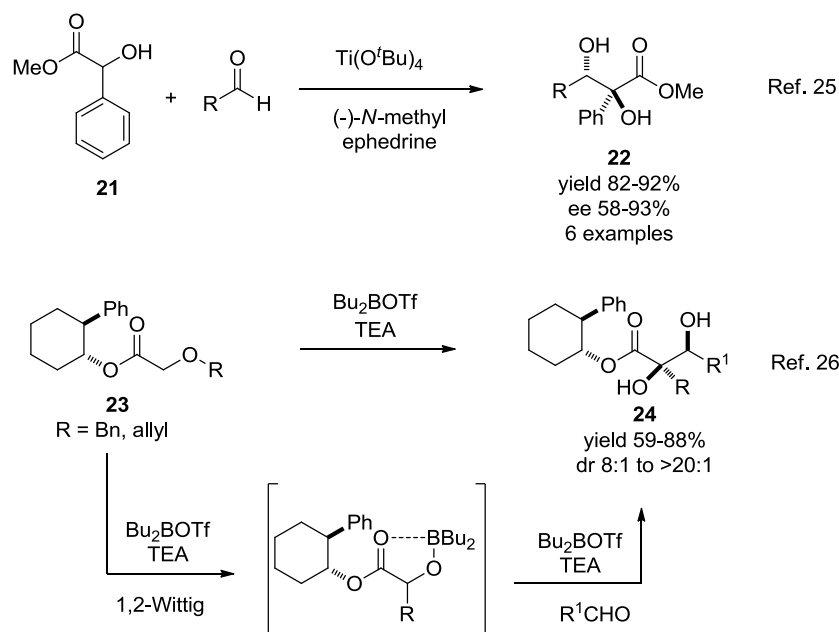
addition to ethyl glyoxylate under Lewis acidic conditions.<sup>20, 21</sup> Unfunctionalized nucleophiles have been reported to add in both Lewis acid-catalyzed Friedel-Crafts reactions<sup>22</sup> between arenes and ethyl glyoxylate, and carbonyl-ene reactions<sup>23</sup> with alkenes and ethyl glyoxylate. Potentially suitable nucleophiles whose addition to ethyl glyoxylate we plan to examine are shown in Figure 3.2. The major challenge associated with this facet of the project will be elucidating conditions for the initial coupling step that will be compatible in the second electrophilic trapping step. For example, a number of the reported additions to ethyl glyoxylate achieve synthetically useful yields by using the ethyl glyoxylate in excess, which will likely be problematic if we wish to introduce a different electrophile in the second step. Another anticipated challenge is solvent choice, as some of the targeted methodologies proceed best in ethereal solvents which may coordinate to and shut down Lewis acid-promoted pathways.



**Figure 3.2.** Nucleophiles to be Evaluated for Tandem Functionalization of Glyoxylates

While numerous methods exist for nucleophilic additions to glyoxylates, methods for enolate generation of  $\alpha$ -hydroxy esters are rarer. While deprotonation can be accomplished with stoichiometric amounts of an amide base,<sup>24</sup> this approach does not allow for asymmetric induction and has not been evaluated in a one-pot sequence. Mahrwald has demonstrated that mandelic acid derivatives can undergo direct aldol reaction with aryl and alkyl aldehydes in the presence of  $\text{Ti(OR)}_4$  and an amine base (Scheme 3.7).<sup>25</sup> Use of two equivalents of *N*-methyl ephedrine as the amine base resulted

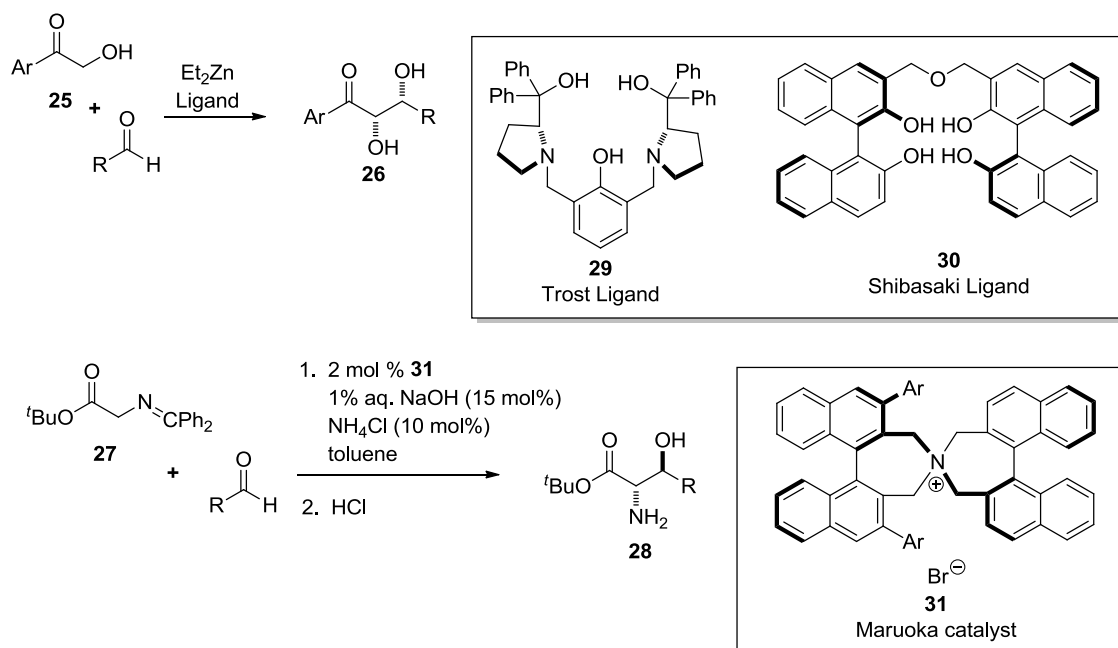
in good levels of asymmetric induction. Wolfe has also developed an aldol reaction between an *in situ* generated allylated glycolate and an aldehyde (Scheme 3.7).<sup>26</sup> Wolfe was able to access enantioenriched products through the use of a chiral auxiliary. While these two reactions are attractive starting points, both rely on the use of a full equivalent (or more) of the Lewis acid, a catalytic asymmetric variant has not been reported, and the scope of products that can be accessed is currently limited. Additionally, the enolization methodology employed must also be compatible with the conditions for the initial nucleophile addition.



**Scheme 3.7.** Aldol Reactions of Aryl and Allyl Glycolic Esters

Catalytic asymmetric methodologies for electrophilic substitution of similar compounds have been reported and may find application in our chemistry. The catalytic asymmetric aldol reaction between  $\alpha$ -hydroxy ketones has been reported by Trost<sup>27</sup> and Shibasaki,<sup>28</sup> who both employ a chiral zinc base. Due to the more acidic nature of the  $\alpha$ -hydroxy ketone, it is unknown whether these catalysts will be basic enough to

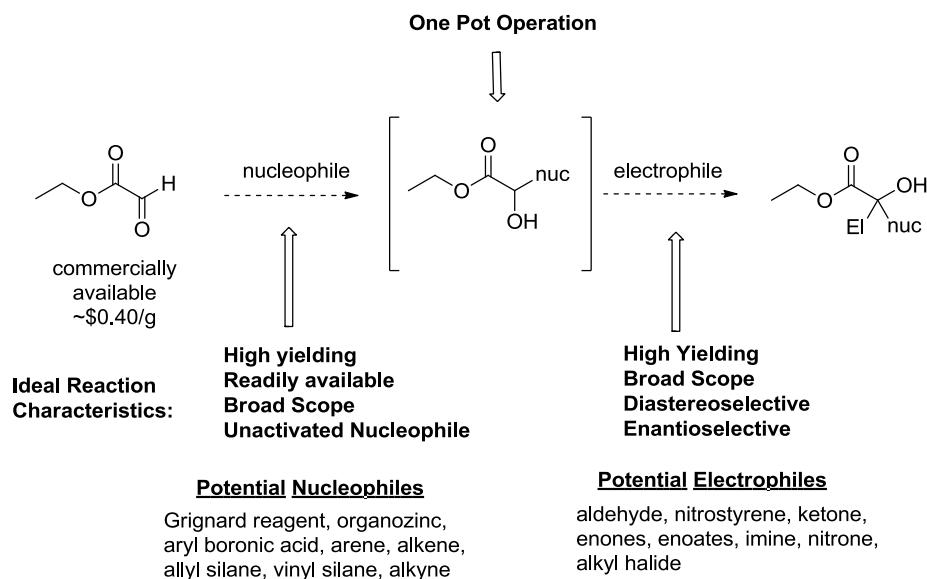
deprotonate the  $\alpha$ -hydroxy ester intermediate. Maruoka has also reported a chiral phase transfer catalyst for the catalytic aldol reaction between protected glycine esters and aldehydes; however, no reports have been published evaluating its use with  $\alpha$ -hydroxy esters.<sup>29</sup>



**Scheme 3.8.** Methods for Asymmetric Aldol Reaction of  $\alpha$ -Hydroxy Ketones and Protected Glycine Derivatives

Given the absence of any similar reaction in the literature, we have elected to pursue a strategy for employing ethyl glyoxylate as an ambiphilic linchpin for synthesizing fully substituted glycolic acids. The facile manner in which a variety of synthetically useful building blocks could be accessed would make the development of such a method quite desirable. We also anticipate that this approach will allow us to access the rich chemistry that our lab has already developed using silyl glyoxylates with commercially available feedstock reagents, rendering the methodology considerably more practical and attractive as a general synthetic method. In order to achieve these goals, the new methodology must meet a number of challenging criteria (Scheme 3.9). Both functionalization steps

must proceed in the same pot with high yields and good diastereocontrol. The scope should also be broad enough to access a range of differently functionalized products. Given the high reactivity of ethyl glyoxylate, the ideal reaction would use bench stable, commercially available reagents that do not require pre-functionalization. Lastly, the methodology needs to possess some mechanism for asymmetric induction.



**Scheme 3.9.** Goals for Tandem Functionalization of Ethyl Glyoxylate

### 3.3 Results and Discussion

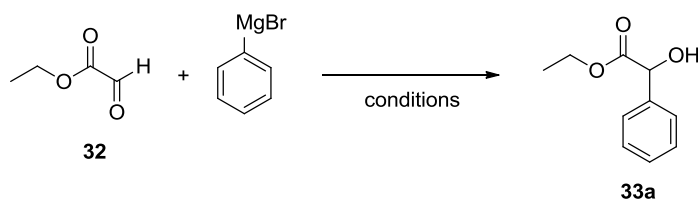
#### 3.3.1 Addition of Organometallic Reagents to Ethyl Glyoxylate

Our efforts began with the investigation of the addition of organometallic reagents to ethyl glyoxylate. Choosing PhMgBr as our model nucleophile, we found that this reaction proceeded with surprisingly poor efficiency in our hands. The major product in the reaction arises from oligomerization of ethyl glyoxylate, which accounts for 60-70% of the mass balance. The results of our optimization studies are summarized in Table 3.1 below. After screening various solvents, temperatures, and reaction times, we found that the optimum conditions were an inverse addition of ethyl glyoxylate to a PhMgBr



solution at -78 °C in THF for 15 min (entry 3). The slow addition of the ethyl glyoxylate to PhMgBr provided marginally higher yields than addition of the Grignard reagent to the ethyl glyoxylate; however, the yield was not synthetically useful. The highest yields that we were able to obtain were 30-40%.

**Table 3.1.** Optimization of PhMgBr Addition to Ethyl Glyoxylate<sup>a</sup>



Entry	Solvent	Time (min)	Temp (°C)	Yield (%) <sup>b</sup>
1	THF	15	rt	22
2	THF	15	0	35
3	THF	15	-78	40
4	THF	45	-78	30
5 <sup>c</sup>	THF	15	-78	26
6	Et <sub>2</sub> O	15	-78	34
7	toluene	15	-78	30

<sup>a</sup> Conditions: 1.0 equiv of **32**, 1.1 equiv of PhMgBr (1.0 M in THF) in 5 mL of solvent.

<sup>b</sup> Isolated yields. <sup>c</sup> PhMgBr (1.0 M in THF) was added to THF solution of ethyl glyoxylate.

Requiring a more efficient nucleophilic addition in the first bond-forming event, other nucleophiles were examined, and the results are tabulated below (Table 3.2). Transmetalation to zinc provided no improvement in the yield. Vinyl magnesium bromide, MeMgBr, and <sup>n</sup>BuLi provided disappointing yields as well, although product volatility may account for some loss in yield. Addition of a less sterically hindered nucleophile, phenyl acetylene, proved more promising, as the adduct was isolated in 65%

yield upon transmetallation to the organozinc. Allylzinc bromide provided the best results, as the coupling proceeded quite efficiently with complete conversion and isolation of the product in 85% yield.

**Table 3.2.** Scope of Addition of Organometallic Reagents to Ethyl Glyoxylate<sup>a</sup>

CCOC(=O)C=O (32) + R-M  $\xrightarrow{\text{THF, -78 } ^\circ\text{C}}$  CCOC(=O)C(O)R (33a-e)

Entry	Reagent	Yield (%) <sup>b</sup>
1		40
2		35
3	<sup>n</sup> BuLi	<20 <sup>c</sup>
4	MeMgBr	<20 <sup>c</sup>
5		40 <sup>c</sup>
6		57
7		65
8		85

<sup>a</sup> Conditions: 1.0 equiv of **32**, 1.1 equiv of organometallic reagent in 5 mL THF, -78 °C, 15 min. See section 3.5 for detailed experimental procedures. <sup>b</sup> Isolated yields unless otherwise noted. <sup>c</sup> <sup>1</sup>H NMR yield.

In drawing an analogy to the silyl glyoxylate chemistry, we hypothesized that a bulkier ester group might prove beneficial. The *tert*-butyl silyl glyoxylate is commonly employed rather than other esters to avoid dimerization of the silyl glyoxylate.<sup>2</sup> *tert*-Butyl glyoxylate is available *via* ozonolysis of *tert*-butyl fumarate or periodate cleavage of *tert*-butyl tartrate.<sup>4, 30</sup> While not commercially available, it is still readily and

economically accessible. Results from the addition of various organometallic reagents to *tert*-butyl glyoxylate are tabulated below (Table 3.3). *tert*-Butyl glyoxylate underwent considerably more efficient coupling with various organometallic reagents than did the ethyl ester, and the results are shown below in Table 3.3. Addition of PhMgBr proceeds in a 70% yield with *tert*-butyl glyoxylate, as compared to 40% yield with ethyl glyoxylate. Transmetallation to zinc resulted in a quantitative addition to **34** to give *tert*-butyl mandelate **35a**. Phenyl acetylide addition was also more efficient, proceeding in 90% yield. Even alkyl and vinyl Grignard and organolithium reagents produced more promising yields. Efforts are currently underway to evaluate the subsequent aldol reaction of the *tert*-butyl mandelate products from this reaction.

**Table 3.3.** Scope of Addition of Organometallic Reagents to *tert*-Butyl Glyoxylate<sup>a</sup>

$$\text{tBuO}-\text{C}(=\text{O})-\text{CH}=\text{O} + \text{R}-\text{M} \xrightarrow{\text{THF, } -78\text{ }^{\circ}\text{C}} \text{tBuO}-\text{C}(=\text{O})-\text{CH}(\text{OH})-\text{R}$$

**34**  **35a-d**

Entry	Reagent	Yield (%) <sup>b</sup>
1		70
2		>95
3	<sup>n</sup> BuLi	34
4		42
5		90

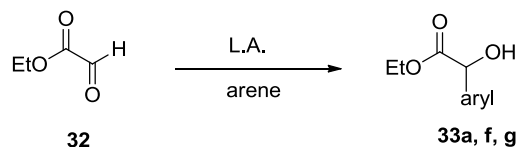
<sup>a</sup> Conditions: 1.0 equiv of **34**, 1.1 equiv of organometallic reagent, 5 mL THF, -78 °C, 1 h. See section 3.5 for detailed experimental procedures. <sup>b</sup> Isolated yields.

### 3.3.2 Addition of Nucleophiles to Ethyl Glyoxylate Without Prior Functionalization or Activation

It was also possible to couple ethyl glyoxylate to nucleophiles without the need to prefunctionalize the nucleophile as an organometallic reagent. These strategies provide the potential to use a catalytic amount of a metal catalyst to promote the desired coupling. Electron-rich and electron-neutral aryl rings underwent Friedel-Crafts alkylation with ethyl glyoxylate,<sup>21</sup> the results of which are tabulated below (Table 3.4). The Friedel-Crafts reaction with toluene promoted by SnCl<sub>4</sub> proceeded quite efficiently at room temperature with either a full equivalent or a catalytic amount of SnCl<sub>4</sub>. We were able to generate ethyl mandelate from the Friedel-Crafts reaction with benzene in quantitative yields, although it was necessary to heat the reaction to 80 °C for 6 h for the reaction to go to completion. It was also necessary obtain the ethyl glyoxylate as free from toluene as possible. Ethyl glyoxylate is sold as a 50% wt. solution of the trimer in toluene. Cracking the trimer followed by distillation yields a solution of ethyl glyoxylate in toluene. When a 50% mixture of distilled toluene/ethyl glyoxylate was employed, a 1:2 inseparable mixture of the benzene adduct and the toluene adduct were formed. Employing a solution that was 90% wt. ethyl glyoxylate and heating to 80 °C furnished the benzene adduct in a greater than 20:1 ratio to the toluene adduct. Friedel-Crafts coupling with anisole could be accomplished at lower temperatures and shorter reaction times; however, further reaction optimization is necessary as the yield suffers from competing double arylation. With both toluene and anisole, only the *para*-addition product was observed. *tert*-Butyl glyoxylate proved to be unsuitable for SnCl<sub>4</sub>-promoted Friedel-Crafts reactions as cleavage of the *tert*-butyl group proceeded more rapidly than

arylation. Examination of milder Lewis acids may lead to the identification of suitable conditions for use with *tert*-butyl glyoxylate.

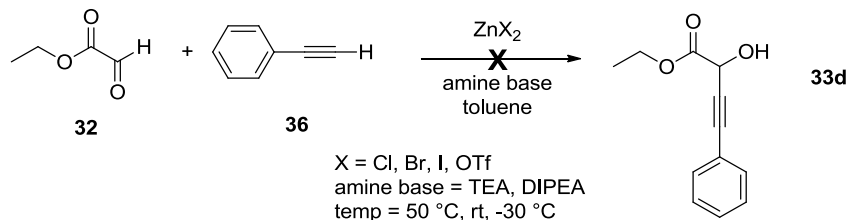
**Table 3.4.** Friedel-Crafts Reaction of Arenes and Ethyl Glyoxylate<sup>a</sup>



Entry	Arene	Lewis Acid	Cat. mol%	Yield (%) <sup>b</sup>
1	toluene	SnCl <sub>4</sub>	100	>95%
2	toluene	Ti(OiPr) <sub>4</sub>	100	NDP
3	toluene	Yb(OTf) <sub>3</sub>	20	NDP
4	toluene	Zn(OTf) <sub>2</sub>	20	NDP
5	anisole	SnCl <sub>4</sub>	100	40%
6	anisole	SnCl <sub>4</sub>	30	66%
7 <sup>c</sup>	benzene	SnCl <sub>4</sub>	100	30%
8 <sup>d</sup>	benzene	SnCl <sub>4</sub>	100	>95%

<sup>a</sup> Conditions: 1.0 equiv of **32**, excess arene, see section 3.5 for detailed experimental procedure. <sup>b</sup> Isolated yield. <sup>c</sup> 50% wt. solution of ethyl glyoxylate, 80 °C. <sup>d</sup> 90% wt. solution of ethyl glyoxylate, 80 °C.

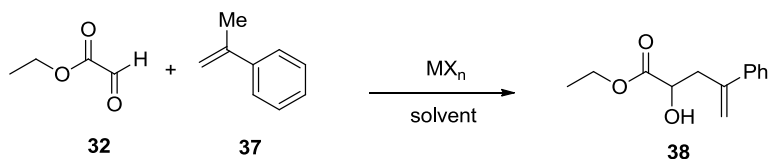
In an attempt to broaden the scope of the Lewis acid-mediated addition of unactivated nucleophiles we examined alkynes, which offer a more convenient functional handle than arenes. Carreira has developed methodology to add an alkyne to aldehydes without generation of a stoichiometric organometallic reagent.<sup>31</sup> Unfortunately, we were unable to successfully apply Carreira's conditions to the alkynylation of ethyl glyoxylate. The desired product was never isolated in spite of trying a variety of catalytic or stoichiometric zinc salts, amine bases, or temperatures (Scheme 3.10).



**Scheme 3.10.** Attempts to Add Terminal Alkyne to Ethyl Glyoxylate

In addition to aryl nucleophiles, allylation from unactivated nucleophiles could also be accomplished through a carbonyl-ene reaction.<sup>23</sup> Choosing  $\alpha$ -methyl styrene as the model nucleophile, a screen of metal catalysts identified  $\text{ZnBr}_2$  as the most effective catalyst for this coupling. With 20 mol % catalyst loading, after 12 h the reaction was extracted and concentrated to give almost quantitative yield of analytically pure material. The catalyst loading could be reduced to as low as 5% (entry 10); however, longer reaction times were necessary. The reaction worked equally well in toluene and  $\text{CH}_2\text{Cl}_2$ , but incomplete conversions were obtained in THF.

**Table 3.5.** Screening of Carbonyl-ene Reaction of  $\alpha$ -Methyl Styrene and Ethyl Glyoxylate<sup>a</sup>

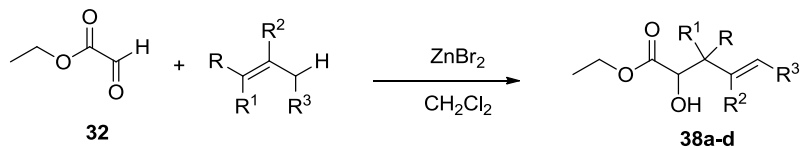


Entry	Lewis Acid	Solvent	Yield <sup>b</sup>
1	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	28%
2	Sn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	35%
3	ZnBr <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	>95% <sup>c</sup>
4	ZnBr <sub>2</sub>	toluene	>95%
5	ZnI <sub>2</sub>	toluene	>95%
6	Zn(OTf) <sub>2</sub>	toluene	80%
7	ZnBr <sub>2</sub>	THF	nd <sup>d</sup>
8	ZnI <sub>2</sub>	THF	nd <sup>d</sup>
9	Zn(OTf) <sub>2</sub>	THF	nd <sup>d</sup>
10	ZnBr <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	>95% <sup>c,e</sup>

<sup>a</sup> Conditions: 1.0 equiv of **32**, 1.0 equiv of **37**, 20 mol % Lewis acid, 3 mL of solvent. See section 3.5 for detailed experimental procedure. <sup>b</sup> Yield determined by <sup>1</sup>H NMR. <sup>c</sup> Isolated yield. <sup>d</sup> After 24 h, reactions did not reach completion. <sup>e</sup> 5% catalyst loading.

The scope of the carbonyl-ene allylation was examined with a variety of diversely functionalized alkenes in addition to  $\alpha$ -methyl styrene. A range of alkenes proved to be viable coupling partners in the reaction; the results of a short alkene screen are shown in Table 3.6 below. The yields reported are from the initial screen; no attempts at optimization have yet been made.

**Table 3.6.** Variety of Alkenes Able to Undergo Carbonyl-ene Reaction<sup>a</sup>

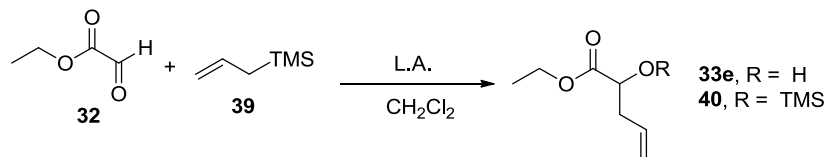


Entry		Alkene	Product	Yield <sup>b</sup>
1	<b>38a</b>			>95%
2	<b>38b</b>			44% <sup>c</sup>
3	<b>38c</b>			41% <sup>c, d</sup>
4	<b>38d</b>			26% <sup>c</sup>

<sup>a</sup> Conditions: 1.0 equiv of **32**, 1.0 equiv of alkene, 20 mol % of ZnBr<sub>2</sub>, 3 mL of CH<sub>2</sub>Cl<sub>2</sub>. See section 3.5 for detailed experimental procedure. <sup>b</sup> Isolated yield. <sup>c</sup> Reaction stopped prior to complete conversion. <sup>d</sup> Product obtained in 3:1 dr.

Since it was not convenient to use propene in the carbonyl-ene reaction due to its volatility, allyl trimethylsilane was examined as a reagent to introduce the unsubstituted allyl group to ethyl glyoxylate.<sup>20</sup> Treatment of ethyl glyoxylate and allyl trimethylsilane with a number of Lewis acids provided product **33e** or **40**. The highest yields were obtained with a stoichiometric amount of BF<sub>3</sub>•OEt<sub>2</sub>, which results in desilylation and isolation of the free hydroxyl group. Catalytic BF<sub>3</sub>•OEt<sub>2</sub> can be employed to give the silyl-protected species **40**, but the yield is lower. Other Lewis acids (Cu, Sc, Yb) also promoted the reaction to give the silyl-protected glycolic ester, but less cleanly. The reaction was not amenable to running in THF.



**Table 3.7.** Optimization of Addition of Allyl Trimethylsilane to Ethyl Glyoxylate<sup>a</sup>

Entry	Lewis Acid	Solvent	Yield (%) <sup>b</sup>
1	BF <sub>3</sub> •OEt <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	>95 ( <b>33e</b> )
2	BF <sub>3</sub> •OEt <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	85 ( <b>40</b> )
3	Yb(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	82 ( <b>40</b> )
4	Yb(OTf) <sub>3</sub>	THF	nd <sup>c</sup>
5	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	70 ( <b>40</b> )
6	Cu(OTf) <sub>2</sub>	THF	NDP <sup>d</sup>
7	Sc(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	69 ( <b>40</b> )
8	Sc(OTf) <sub>2</sub>	THF	NDP <sup>d</sup>

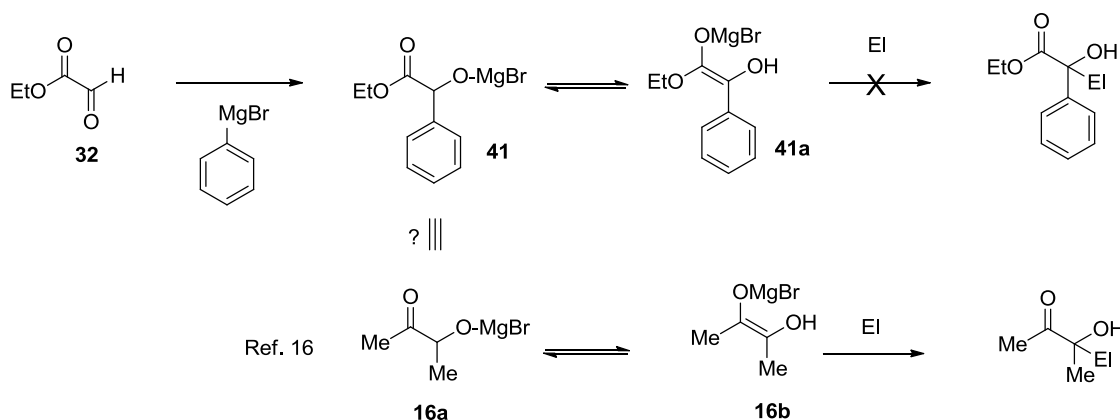
<sup>a</sup> Conditions: 1.0 equiv **32**, 1.2 equiv **39**, 3 mL of solvent. See section 3.5 for detailed experimental procedures. <sup>b</sup> Isolated yield. <sup>c</sup> Not determined. Reaction had only reached low conversion after 48 h. <sup>d</sup> Reaction components polymerized to form gel.

At this point, the feasibility of a variety of approaches for the nucleophilic addition had been explored. We found that we could efficiently generate both aryl and allylated products using either a stoichiometric amount of an organometallic reagent or the coupling of an unfunctionalized arene or alkene *via* a Lewis acid catalyst. This gave us the necessary flexibility in the design of the second electrophilic trapping step, as we found complementary conditions for addition of the nucleophile that should be amenable to either a basic or Lewis acid-mediated enolization reaction.

### 3.3.3. Attempts for Stepwise Aldol Reaction under Basic Conditions

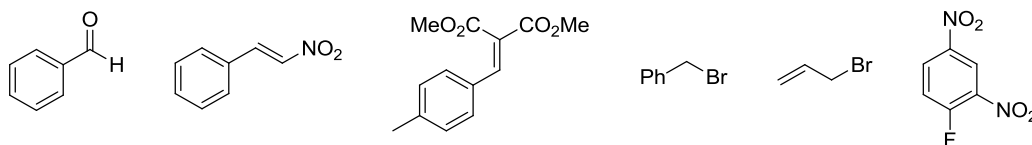
We began our studies on the electrophilic trapping step by investigating basic conditions for the enolization of the various glycolic esters we could prepare. Our initial

approach was to intercept metal alkoxide **41**, which would result from the addition of an organometallic species to ethyl glyoxylate, with an electrophile (Scheme 3.11). As the analogous ketone underwent exclusive *C*-alkylation,<sup>16</sup> we hoped to observe the same trend.



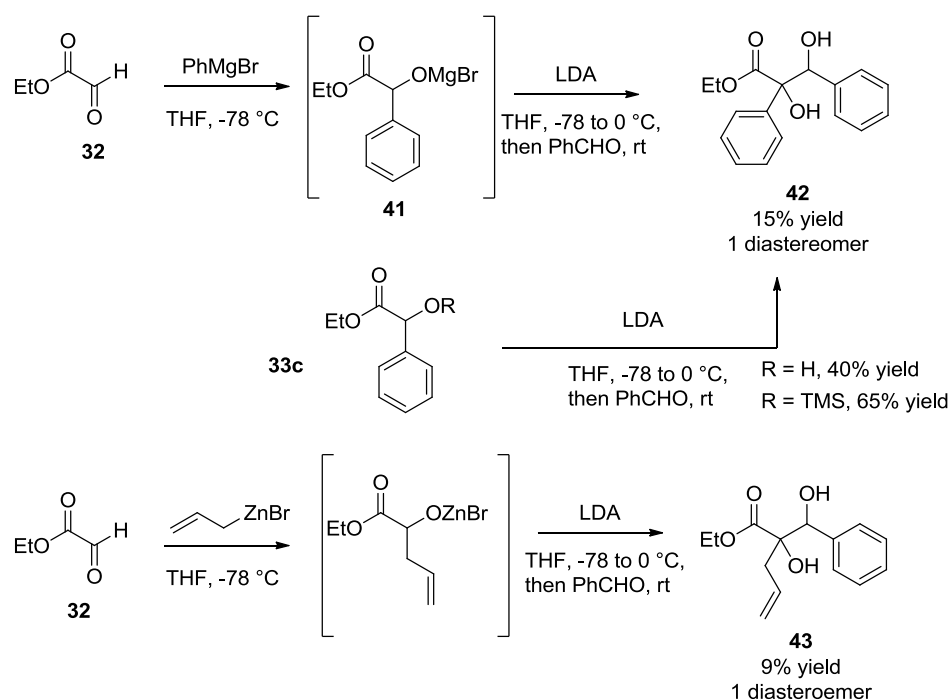
**Scheme 3.11.** Proposed Strategy for Trapping **41** with Electrophile

Following the addition of PhMgBr or allylzinc bromide to ethyl glyoxylate, we examined numerous electrophiles for *C*-functionalization (vide infra, Figure 3.3). Unfortunately, none of the electrophiles examined yielded the desired product. This observation likely stems from the lower pK<sub>a</sub> of the  $\alpha$ -protons of the  $\alpha$ -hydroxy ketone relative to the ester. To verify this as the cause for our lack of productive coupling, we examined the addition of an extra equivalent of base to the reaction after nucleophilic addition of the organometallic (Scheme 3.13).



**Figure 3.3.** Electrophiles Examined in the Tandem Addition/Electrophilic Trapping Reactions

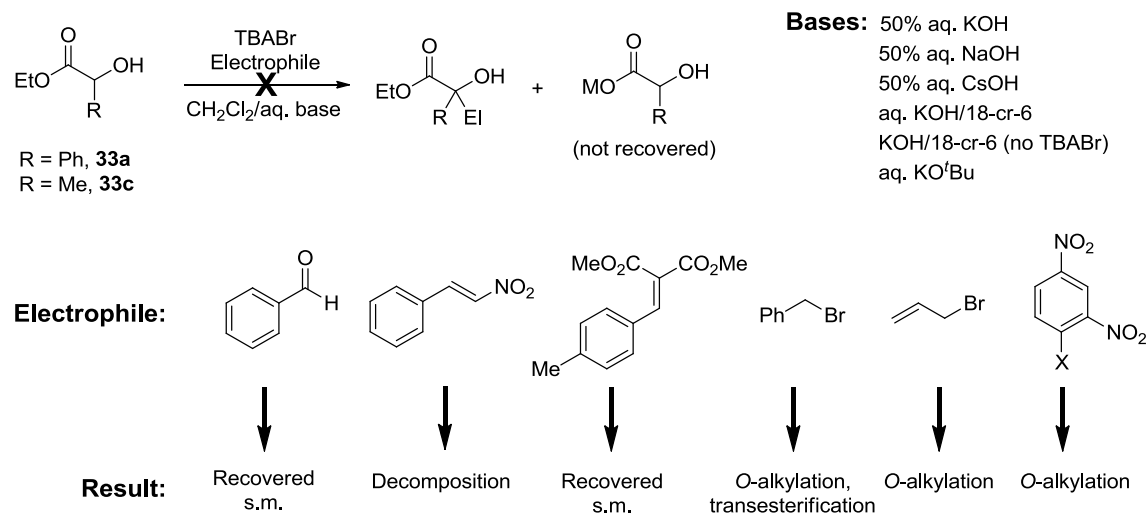
Treating ethyl glyoxylate with PhMgBr followed by deprotonation with 1.5 equivalents of LDA and subsequent trapping with benzaldehyde as the terminal electrophile provided the desired product **42**, although in a disappointing 15% yield (Scheme 3.12). The primary culprit for the low yield is the inefficient addition of PhMgBr, which only proceeds in 40% yield; however, the isolated two-step yield is still significantly lower. Extensive Cannizzaro reaction<sup>32</sup> was observed with benzaldehyde. Treatment of ethyl mandelate with LDA and benzaldehyde yielded aldol product in only 40% isolated yield of a single diastereomer in our hands. Treatment of the less hindered ethyl lactate with identical reaction conditions resulted in similar yields but a 1:1.5 dr. Allylation followed by deprotonation and trapping with benzaldehyde in a two-step one-pot procedure yielded 9% of a single diastereomer. We found that TMS protection of the free hydroxyl group of **33c** resulted in suppression of the Cannizzaro reaction and a higher yield. This may give some insight as to why silyl glyoxylates, which generate the  $\alpha$ -silyloxy ester upon Brook rearrangement, are capable of efficiently undergoing Grignard addition followed by trapping with aldehydes.



**Scheme 3.12.** One-Pot Functionalization of Ethyl Glyoxylate Through Nucleophilic Addition/Deprotonation/Aldol Sequence

While generation of the glycolate enolate with LDA did allow for preparation of the fully substituted glycolic esters, poor overall yield and lack of an opportunity for asymmetric induction led us to examine phase transfer conditions. For simplicity, the reaction was evaluated independently from the initial nucleophilic addition step. Substituted glycolic esters ethyl mandelate (**33a**) and ethyl lactate (**33c**) were treated with a variety of electrophiles under basic biphasic conditions. As can be seen from Scheme 3.13, we have thus far been unable to obtain the desired fully substituted glycolic esters with this strategy regardless of the R group, the base, or the electrophile employed. Benzyl bromide, allyl bromide, and di-nitrofluorobenzene<sup>33</sup> provided the *O*-alkylated products. Saponification was problematic in all cases, as the mass balances were consistently low due to loss of the free acid upon workup. *tert*-Butyl mandelate, which

should be considerably less prone to saponification, is currently being assessed in this reaction.

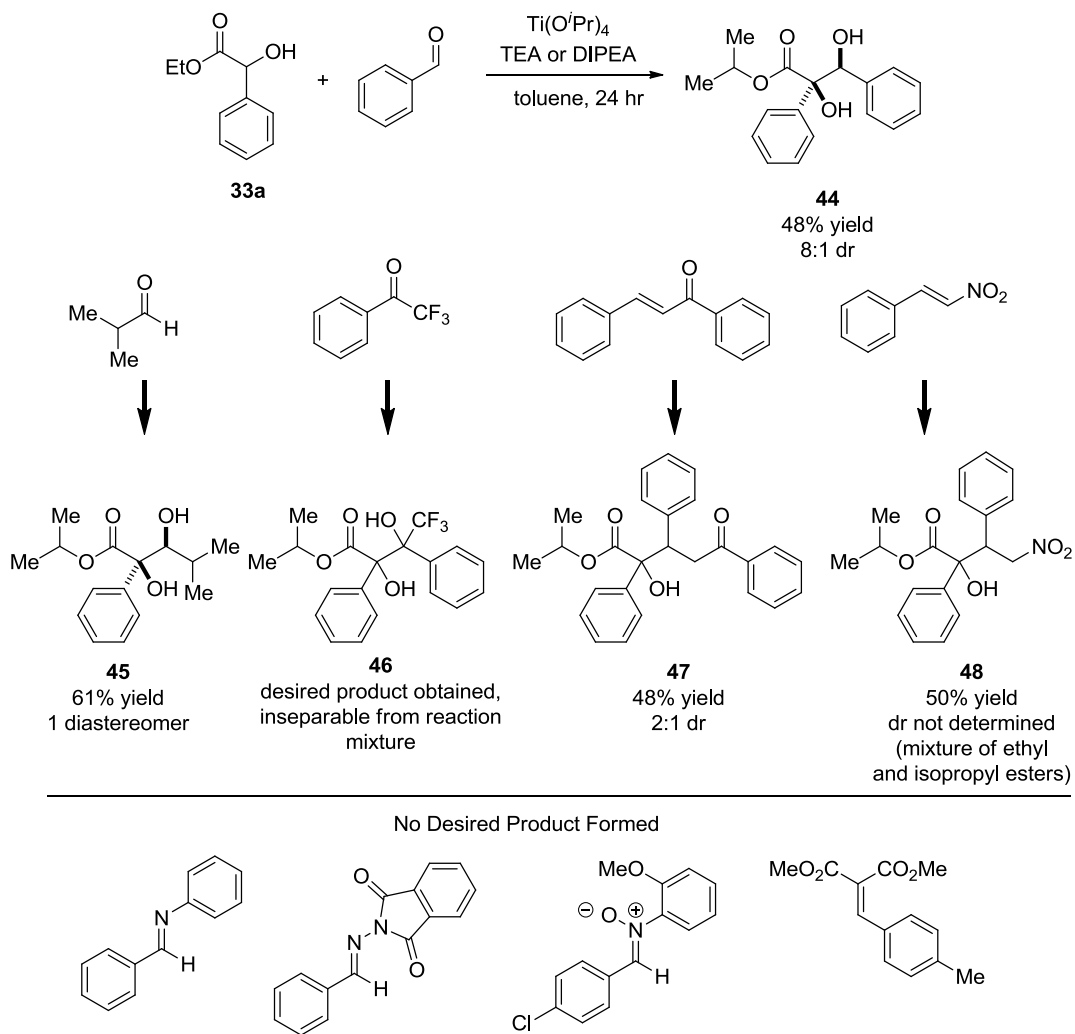


**Scheme 3.13.** Attempts to Perform Aldol Reaction Under Phase Transfer Catalysis

#### 3.3.4. Development of Stepwise Aldol Reaction under Lewis Acidic Conditions

After encountering setbacks in the development of basic enolization conditions, we shifted our focus to Lewis acid-mediated reactions to generate the fully substituted glycolic acid products.<sup>25, 26</sup> Beginning with Mahrwald's Ti(OR)<sub>4</sub>/TEA catalyst system,<sup>25</sup> we investigated the aldol reaction of ethyl mandelate with benzaldehyde. We obtained the expected aldol product **44** and observed transesterification to the isopropyl ester (Scheme 3.14). In our hands, the reaction took considerably longer than the 1-2 h reported by Mahrwald. For the aldol reaction with benzaldehyde, after 24 h the reaction had only reached 60% conversion. The remainder of the mass balance was accounted for by the isopropyl mandelate. In addition to the reported aryl and aliphatic aldehydes (**44** and **45**), we found that other electrophiles could be successfully engaged. Addition to  $\alpha,\alpha,\alpha$ -trifluoroacetophenone demonstrated that ketones are viable electrophiles (**46**). Conjugate addition was also achieved, with both chalcone and  $\beta$ -nitrostyrene providing

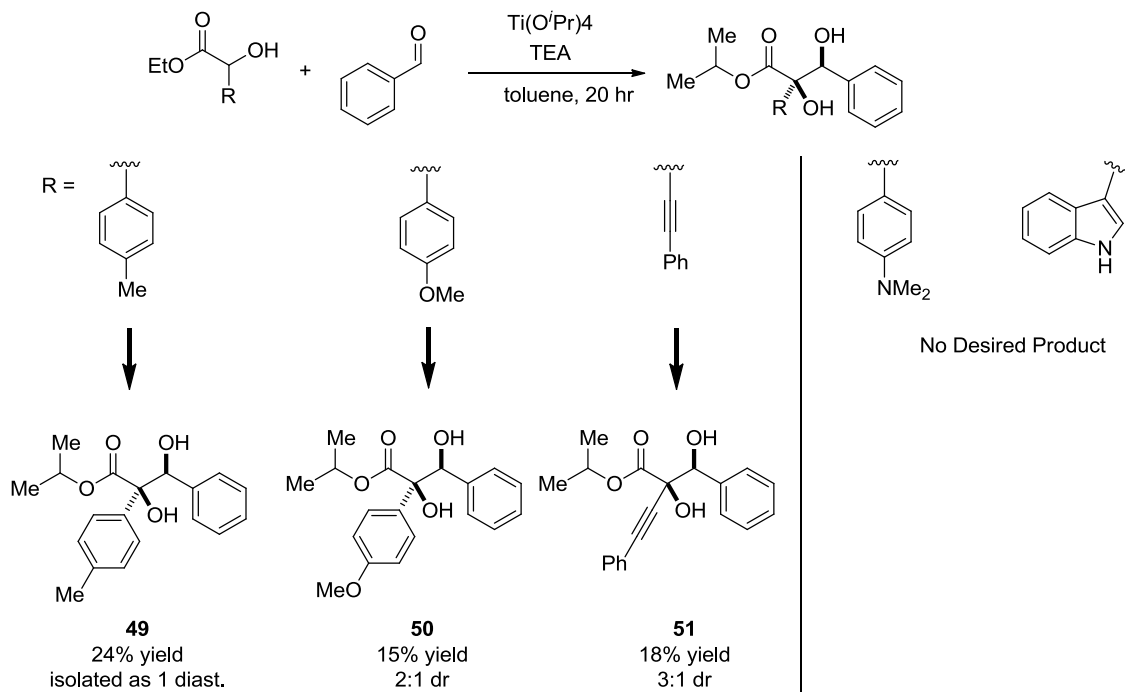
products **47** and **48** in promising yields. The benzylidene malonate derivative failed to deliver the desired coupling product. Nitrogen-derived  $\pi$ -electrophiles failed to undergo coupling with an imine, an imide, and a nitron all failing to productively couple.



**Scheme 3.14.**  $\text{Ti}(\text{O}^i\text{Pr})_4$ -Promoted Addition of Ethyl Mandelate to Electrophiles

After identifying which electrophiles showed promise for further study, we turned our attention to what substitution patterns on the glycolic ester would be tolerated. It was unknown how general the  $\text{Ti}(\text{O}^i\text{Pr})_4/\text{TEA}$  reaction would prove to be, as Mahrwald had only examined mandelic esters. Electron-rich arenes were better suited for the Friedel-Crafts reaction; however, they may mitigate the acidity of the methine proton to the

extent that the aldol reaction no longer proceeds. An initial screen of aryl glycolic esters we could prepare *via* the Friedel-Crafts reaction, as well as one alkynyl example, demonstrated that the aldol reaction could proceed in the presence of electron-rich aryl groups (Scheme 3.15). The yields reported below are from an exploratory screen and were not optimized.



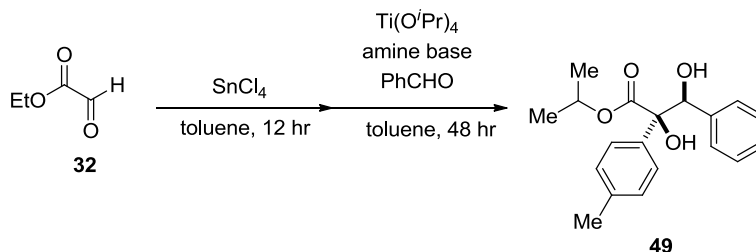
**Scheme 3.15.**  $\text{Ti}(\text{O}^i\text{Pr})_4$ -Promoted Aldol Reaction of Aryl Substituted Glycolic Esters

### 3.3.5. Development of One-Pot Protocols for Bis-Functionalization of Ethyl Glyoxylate

With procedures in hand for nucleophilic attack and subsequent capture of an electrophile, we sought to perform the tandem Friedel-Crafts alkylation/aldol in a single pot. Selecting toluene as the model nucleophile, we subjected ethyl glyoxylate (**32**) to  $\text{SnCl}_4$  in a solution of toluene. After 12 h, the amine base,  $\text{Ti}(\text{O}^i\text{Pr})_4$ , and benzaldehyde were added. Gratifyingly, this yielded the desired product **49**, which was isolated in 35%

yield and as a single diastereomer. Our efforts to optimize this result are summarized below (Table 3.8).

**Table 3.8.** Optimization of One-Pot Friedel-Crafts Alkylation/Aldol Reaction<sup>a</sup>



Entry	Base (equiv)	SnCl <sub>4</sub> equiv	Yield (%) <sup>b</sup>	dr
1	TEA (1.5)	1.0	35 <sup>c</sup>	1 diast.
2	DIPEA (1.5)	1.0	40 <sup>c</sup>	10:1
3	TEA (1.0)	0.5	25	nd
4	TEA (0.75)	0.25	19	nd
5	DIPEA (1.0)	0.5	32	nd
6	DIPEA (0.75)	0.25	>10	nd
7	TEA (1.0)	1.0	26	nd
8	TEA (2.0)	1.0	38	nd
9	TEA (3.0)	1.0	45 <sup>c</sup>	1 diast.
10	DIPEA (1.0)	1.0	17	nd
11	DIPEA (3.0)	1.0	68 <sup>c</sup>	10:1
12	DIPEA (3.0)	0.5	53 <sup>c</sup>	nd
13 <sup>d</sup>	DIPEA (1.5)	1.0	34 <sup>c</sup>	nd
14 <sup>e</sup>	(-)- <i>N</i> -Me-ephedrine	1.0	17 <sup>c</sup>	nd

<sup>a</sup> Conditions: 1.0 equiv of **32**, excess toluene, 1.0 equiv of Ti(O<sup>*i*</sup>Pr)<sub>4</sub>, 1.5 equiv of PhCHO in 3 mL of toluene. See section 3.5 for detailed experimental procedure. <sup>b</sup> Yield determined by <sup>1</sup>H NMR unless otherwise specified. <sup>c</sup> Isolated yield. <sup>d</sup> No Ti(O<sup>*i*</sup>Pr)<sub>4</sub> was added to the reaction. <sup>e</sup> *er* was determined by chiral SFC analysis.

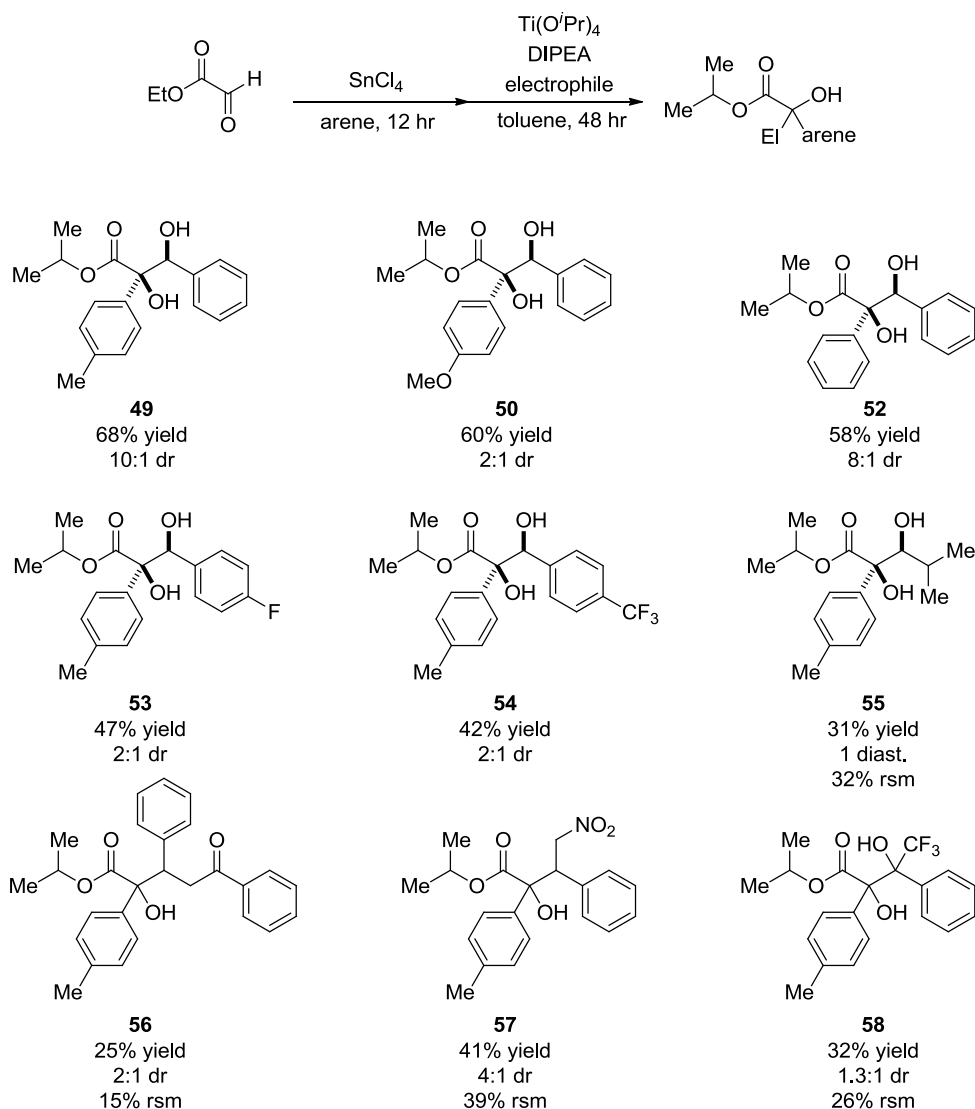


As can be seen from the table, use of DIPEA provided higher yields, while TEA gave a somewhat higher diastereoselectivity. At this point, we have chosen to use DIPEA for future reactions. Increasing the equivalents of the amine base proved beneficial to the reaction yield, with three equivalents providing the highest yield. We have not examined higher stoichiometries of base to see if the trend for the increase in yield continues. Observing that higher yields were obtained when a full equivalent of  $\text{SnCl}_4$  was used prompted us to explore omitting the  $\text{Ti}(\text{O}^i\text{Pr})_4$  from the reaction. Addition of DIPEA to the  $\text{SnCl}_4$  solution results in the formation of an oily precipitate producing a biphasic system. When the  $\text{Ti}(\text{O}^i\text{Pr})_4$  is added, it solubilizes the precipitate to produce a homogenous solution. The aldol reaction still proceeds in the absence of  $\text{Ti}(\text{O}^i\text{Pr})_4$ , establishing that the  $\text{SnCl}_4$  also promotes the aldol reaction, although the efficiency is higher when  $\text{Ti}(\text{O}^i\text{Pr})_4$  is also employed (entry 13). In light of these findings, it is not surprising that when chiral amine (-)-*N*-methyl ephedrine was used as the base in the reaction, the product that was obtained was racemic (entry 14).

We thought we might be able to expand the substrate scope of the arene nucleophile if it were introduced as an organometallic species. Attempts to introduce the aryl group as a Grignard or an organozinc reagent followed by the  $\text{Ti}(\text{O}^i\text{Pr})_4$ /DIPEA aldol reaction failed to deliver the desired product. Addition of a proton source to generate the free hydroxyl group for the subsequent aldol also failed to activate our desired pathway.

In an effort to determine the scope of the  $\text{SnCl}_4$ / $\text{Ti}(\text{O}^i\text{Pr})_4$ -mediated bis-functionalization of glyoxylates, we sought to vary both the nucleophile and the electrophile in one-pot procedures. Scheme 3.16 summarizes the results we have obtained in this vein. The arene can be varied to include a range of electron-rich to

electron-neutral substituents. Electron-rich and -neutral aryl aldehydes both performed comparably. It should be noted that compounds **53** and **54** were prepared using unoptimized reaction conditions (1.5 equiv DIPEA). More challenging carbonyl electrophiles including aliphatic aldehydes and a ketone (albeit a reactive one with no enolizable protons) also underwent the coupling reaction. Conjugate addition has been demonstrated in the addition to both  $\beta$ -nitrostyrene and chalcone. It should be noted that these yields were all obtained without alteration to the reaction conditions that were optimized in the model system. We are optimistic that further tailoring of the conditions to each substrate class will produce higher yields.

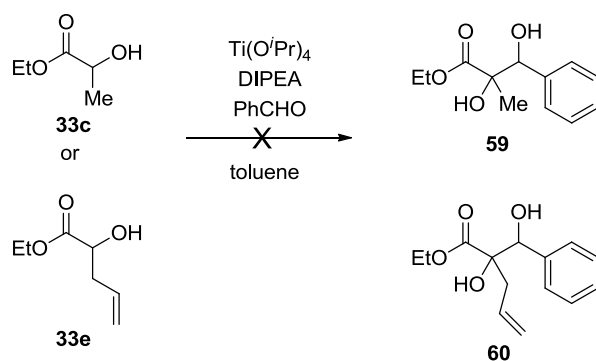


**Scheme 3.16.** Scope of One-Pot  $\text{SnCl}_4$ -Promoted Arylation/ $\text{Ti}(\text{O}^i\text{Pr})_4$ -Promoted Aldol Reaction with Ethyl Glyoxylate

The reaction we developed is quite attractive from a preparative standpoint. The product contains a tertiary alcohol and two adjacent oxygenated stereocenters that can be formed with high diastereocontrol. The starting materials for the reaction, ethyl glyoxylate, toluene, and benzaldehyde, are all feedstock chemicals, the most expensive of which is ethyl glyoxylate at \$0.40/gram.<sup>15</sup> The other reactants,  $\text{SnCl}_4$ ,  $\text{Ti}(\text{O}^i\text{Pr})_4$ , and DIPEA, are also inexpensive reagents. The reaction is operationally simple, requiring no

cooling or heating and no precautions to exclude air or water other than placing the reaction container in the oven prior to use.

All of the examples described thus far in the one-pot bisfunctionalization reaction possess an aryl substituent (or conjugated arene) on the glycolic ester. Attempts to carry out the Mahrwald aldol reaction on alkyl and allyl substituted glycolic acids was unsuccessful, as the acidity of the  $\alpha$ -proton is insufficient for the  $\text{Ti}(\text{O}^i\text{Pr})_4/\text{DIPEA}$  system (Scheme 3.17).

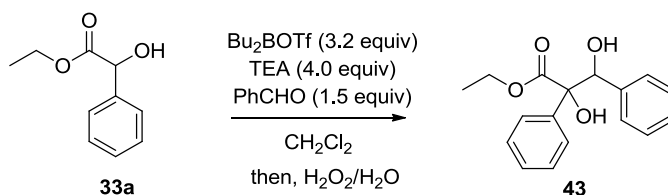


**Scheme 3.17.** Attempts to Perform Aldol Reaction with Alkyl and Allyl Substituents

Due to the synthetic utility of the allyl group as a functional handle for subsequent elaboration and the highly efficient manner in which it can be introduced into the glycolic ester moiety, we sought conditions that would allow **33e** to undergo the tandem aldol reaction. For screening purposes, we employed ethyl lactate as a model for all aliphatic and allyl glycolic esters. We first examined the use of alternative amine bases. TEA, DIPEA, and DBU all failed to promote the aldol reaction at room temperature or 60 °C. Incorporation of a more electron withdrawing ester group ( $\text{CF}_3\text{CH}_2\text{O}$ ) also failed to facilitate enolization. We next decided to conduct a Lewis acid screen to find suitable conditions. We postulated that if we could find a more oxophilic or electron-poor Lewis acid than  $\text{Ti}(\text{O}^i\text{Pr})_4$ , then we may render the  $\alpha$ -proton sufficiently acidic for enolization to

occur. The Lewis acids of interest were initially screened against ethyl mandelate, as we reasoned that any Lewis acid that would promote the aldol reaction of an aliphatic glycolic ester should also promote the aldol reaction of the mandelate derivative (Table 3.9). The results of this screen are tabulated below. While almost every Lewis acid that we examined failed to give any desired product, we were pleased to find that Bu<sub>2</sub>BOTf/TEA did promote the desired aldol reaction in 60% yield. The other Lewis acids employed in stoichiometric quantities yielded transesterification products, while the lanthanum alkoxides gave no reaction even after heating to 50 °C for 48 h.

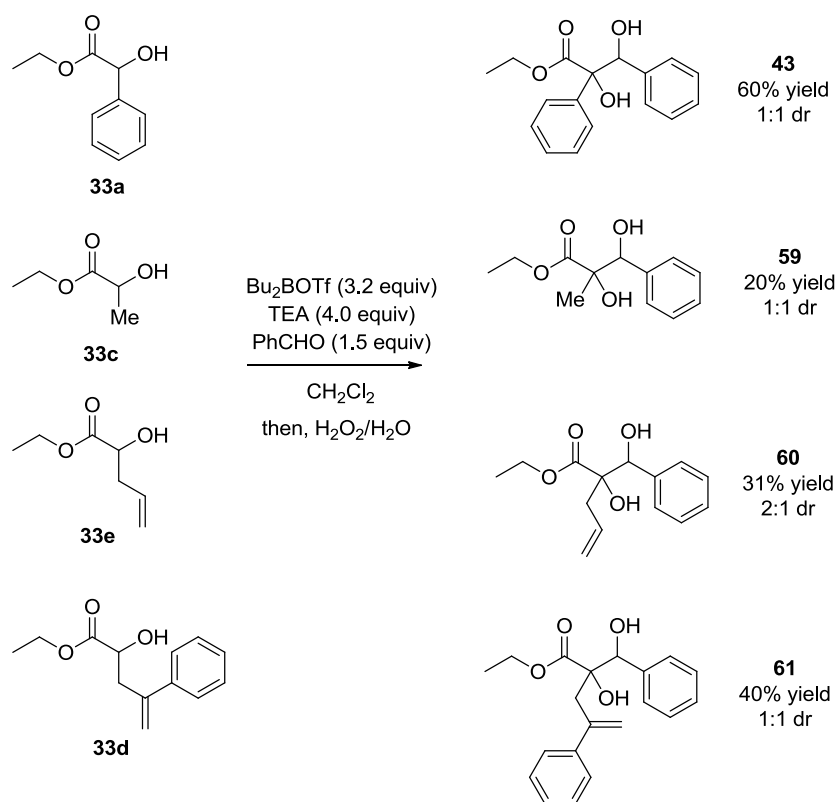
**Table 3.9.** Lewis Acid Screen for Aldol Reaction of Ethyl Mandelate<sup>a</sup>



Entry	Lewis Acid	Loading (mol %)	Result
1	Ti(O <sup><i>i</i></sup> Pr) <sub>4</sub>	100	NDP <sup>b</sup>
2	Al(O <sup><i>i</i></sup> Pr) <sub>3</sub>	100	NDP <sup>b</sup>
3	Zr(O <sup><i>i</i></sup> Pr) <sub>4</sub>	50	NDP <sup>b</sup>
4	Er(O <sup><i>i</i></sup> Pr) <sub>3</sub> <sup>c</sup>	20	NR <sup>d</sup>
5	Yb(O <sup><i>i</i></sup> Pr) <sub>3</sub> <sup>c</sup>	20	NR <sup>d</sup>
6	Ba(O <sup><i>i</i></sup> Pr) <sub>2</sub> <sup>c</sup>	30	NR <sup>d</sup>
7	BF <sub>3</sub> •Et <sub>2</sub> O	100	NR <sup>d</sup>
8	SnCl <sub>4</sub>	100	NR <sup>d</sup>
9	Bu <sub>2</sub> BOTf	300	60% yield <sup>e</sup>

<sup>a</sup> Conditions: 1.0 equiv **33a**, 1.5 equiv of PhCHO, see section 3.5 for detailed experimental details. <sup>b</sup> **33a** was converted to the isopropyl ester. <sup>c</sup> After 48 h at rt, reactions were heated to 60 °C for 24 h. <sup>d</sup> No reaction was observed at either rt or 60 °C. <sup>e</sup> Isolated yield.

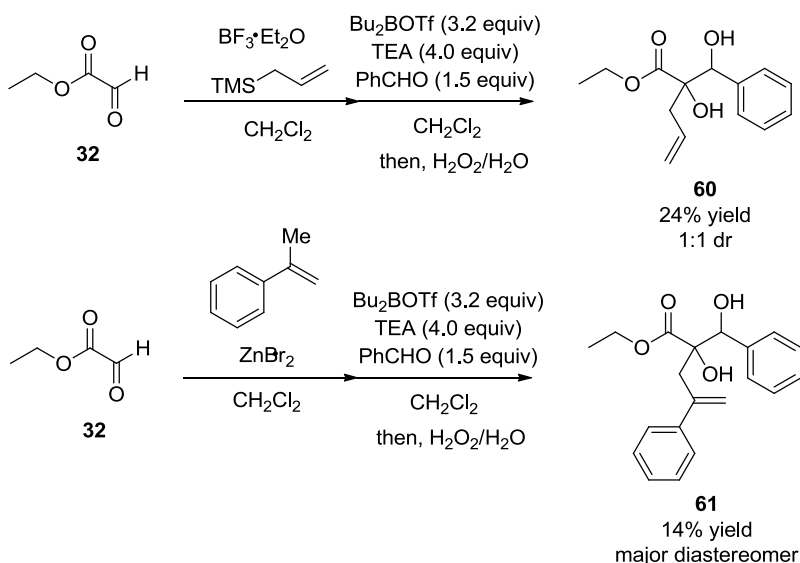
Upon examining the Bu<sub>2</sub>BOTf/TEA system with glycolic esters **33c**, **33d**, and **33e**, we were pleased to find that we were able to induce the aldol reaction with non-aryl substituted glycolic esters (Scheme 3.18). The yields for ethyl lactate were somewhat lower than for the allylated esters. The reaction proceeds with poor diastereoselectivity, and the diastereomers of the methylated and allylated products **59**, **60**, and **61** were inseparable by flash column chromatography. The yields reported for these reactions are unoptimized and employed conditions directly from Wolfe's Wittig/aldol cascade. Optimization of the reaction conditions as well as evaluation of other electrophiles is currently underway.



**Scheme 3.18.** Bu<sub>2</sub>BOTf-Promoted Aldol Reaction of Aliphatic Glycolic Esters

While significant room for improvement still exists for the Bu<sub>2</sub>BOTf-promoted aldol, we wished to demonstrate its use in a tandem allylation/aldol reaction with ethyl

glyoxylate. Using allyl trimethylsilane and  $\alpha$ -methyl styrene as the allylating agents, we carried out the tandem reactions shown in Scheme 3.19. The efficiency for the synthesis of **60** was comparable to that seen in the two-step process, but the yield of **61** was significantly lower. Efforts to optimize the yield obtained in these reactions are currently underway. We expect these yields to improve as more effective aldol conditions are elucidated.

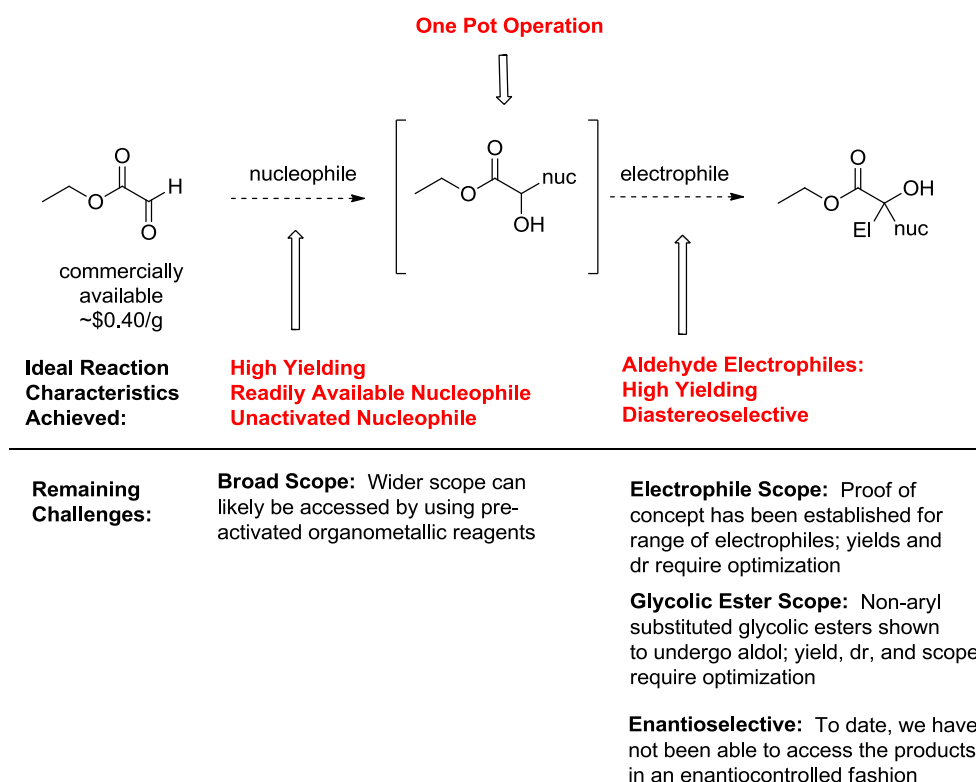


**Scheme 3.19.** One-Pot Allylation/Aldol Reactions

### 3.4 Conclusion

When we embarked on this project, we set forth a number of objectives we wished to accomplish. A critical assessment of our current progress reveals that we have succeeded in a number of our goals, especially in the Friedel-Crafts/aldol cascade (Scheme 3.20). In this arena, we can employ unactivated arene nucleophiles and aryl aldehyde electrophiles, and preliminary results suggest that the reaction scope will be fairly general in regards to both the arene and aldehyde partner. Proof of concept has been established for other electrophiles including enones, nitrostyrenes, and ketones, whose unoptimized yields are

quite promising. Additionally, a one-pot procedure has also been established for tandem allylation/aldol reactions, although substantial optimization of this reaction is still necessary in order to reach synthetically useful yields. Limited efforts to carry out the reaction in an asymmetric fashion have thus far been unsuccessful, and accomplishing this represents a major challenge remaining to be met in this methodology.



**Scheme 3.20.** Current Progress on Protocols for Bis-Functionalization of Ethyl Glyoxylate

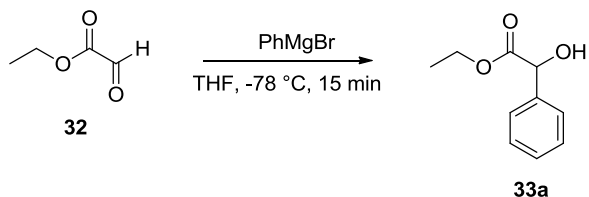


### 3.5 Experimental Section

**Materials and Methods: General.** Proton and carbon nuclear magnetic resonance spectra ( $^1\text{H}$  and  $^{13}\text{C}$  NMR) were recorded on either a Bruker model Avance 400 ( $^1\text{H}$  NMR at 400 MHz and  $^{13}\text{C}$  NMR at 100 MHz) or Varian Gemini 300 ( $^1\text{H}$  NMR at 300 MHz and  $^{13}\text{C}$  NMR at 75 MHz) spectrometer with solvent resonance as the internal standard ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm and  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.0 ppm).  $^1\text{H}$  NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, sep = septet, m = multiplet), coupling constants (Hz), and integration. Supercritical fluid chromatography was performed on a Berger SFC system equipped with a Chiralpack OD or AD column. HPLC separations were performed on a Varian SD-1 HPLC with a Berger CYANO 60A 6u column (150 x 21.2 mm). Optical rotations were measured using a 2.0 mL cell with a 1.0 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained on a Micromass Quattro II Triple Quadrupole Spectrometer using ESI ionization. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 200  $\mu\text{m}$  silica G TLC plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Silia-P flash silica gel (40-63  $\mu\text{m}$ ) purchased from Silicycle. Yield refers to isolated yield of analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Toluene, THF,  $\text{Et}_2\text{O}$ , and methylene chloride were dried by passage through a column of neutral alumina under nitrogen prior to use;<sup>34</sup> benzene was distilled from Na/benzophenone ketyl.

### General Procedure for Addition Organometallic Reagents to Ethyl Glyoxylate (A)

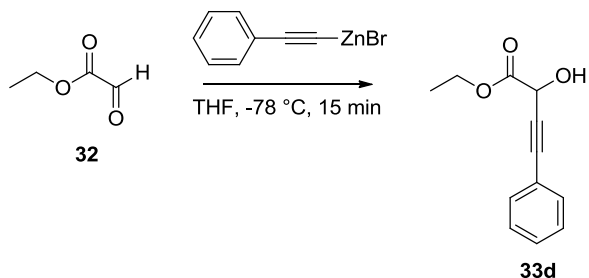
In a flame-dried 10-mL round bottomed flask, PhMgBr (1.0 M in THF, 1.0 mL, 1.0 mmol) was added to 2 mL of THF and cooled to -78 °C. Ethyl glyoxylate (**32**) was distilled immediately prior to use and collected as a solution of the cracked monomer in toluene. The concentration of ethyl glyoxylate was determined by  $^1\text{H}$  NMR spectroscopy and typically ranged between 40% to 60% by weight. The ethyl glyoxylate (**32**) (100 mg, 0.98 mmol) was dissolved in 2 mL of THF and added dropwise to the solution of PhMgBr over 15 min. Upon complete addition, the reaction was monitored by TLC with an eluent system of 30% EtOAc/petroleum ether (It can be difficult to determine when complete conversion is achieved. By TLC, the oligomerized by-product overlaps with the ethyl glyoxylate starting material; however, in all cases, no appreciable amount of ethyl glyoxylate was observed in the crude  $^1\text{H}$  NMR spectrum after 15 min at -78 °C). Upon completion (typically within ~15 min), the reaction was poured into 30 mL of a 1:1 mixture of Et<sub>2</sub>O and saturated aqueous ammonium chloride. The organic layer was separated, and the aqueous layer was extracted with an additional 20 mL of Et<sub>2</sub>O. The organic layers were combined, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*.



### Ethyl 2-hydroxy-2-phenylacetate (**33a**, Table 3.1)<sup>19</sup>

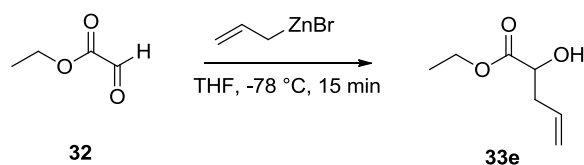
The title compound was prepared according to General Procedure A. The following flash column chromatography on SiO<sub>2</sub> gel using 30% EtOAc/petroleum ether as the eluent, 69

mg (40% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.31 (m, 5H), 5.21 (s, 1H), 4.29-4.20 (m, 2H), 4.02 (br s, 1H), 1.24 (t,  $J = 6.9$  Hz, 3H).



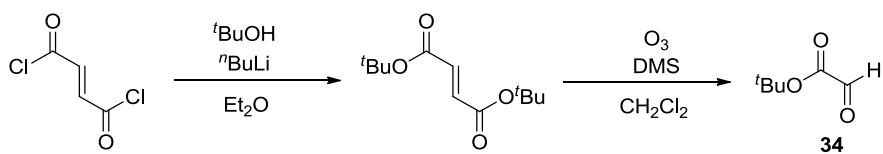
### Ethyl 2-hydroxy-4-phenylbut-3-ynoate (33d, Table 3.2, entries 5-7)<sup>35</sup>

The title compound was prepared by a modification to General Procedure A. Phenyl acetylene (112 mg, 110 mmol) was massed into a flame dried round-bottomed flask equipped with a stir bar and under  $\text{N}_2$ . Tetrahydrofuran (3 mL) was added, followed by cooling to 0  $^\circ\text{C}$  and addition of 1.0 mmol of either  $^n\text{BuLi}$  or  $\text{EtMgBr}$ . The reaction was allowed to warm from 0  $^\circ\text{C}$  to rt and stir for a period of time ( $^n\text{BuLi}$   $t = 1$  h;  $\text{EtMgBr}$ ,  $t = 4$  h). To generate the alkynyl zinc, the alkynyl lithium was transferred via cannula to a flask containing zinc bromide (225 mg, 1.0 mmol) in 2 mL of THF. The resultant solution was then stirred for 1 h at room temperature. Following generation of the desired organometallic species, ethyl glyoxylate (32) was added following General Procedure A. Following flash column chromatography on  $\text{SiO}_2$  gel using 30%  $\text{EtOAc}$ /petroleum ether as the eluent, 130 mg (65% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 (d,  $J = 6.0$  Hz, 2H), 7.36-7.31 (m, 3H), 5.31 (s, 1H), 5.07 (d,  $J = 5.4$  Hz, 1H), 4.37 (q,  $J = 5.4$  Hz, 2H), 3.14 (d,  $J = 5.7$  Hz, 1H), 1.37 (t,  $J = 5.1$  Hz, 3H).



### Ethyl 2-hydroxypent-4-enoate (33e, Table 3.2, entry 8)<sup>20a</sup>

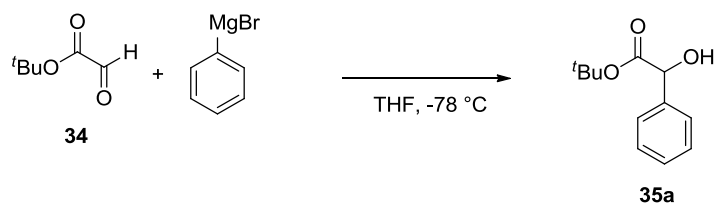
The title compound was prepared by a modification to General Procedure A. Allyl zinc bromide was prepared by massing  $\text{Zn}^0$  (80 mg, 1.25 mmol) into a dry 10-mL round bottomed flask in the glovebox. The flask was then removed and placed under  $\text{N}_2$ . THF (3 mL),  $\text{TMSCl}$  (1 drop), dibromoethane (1 drop), and allyl bromide (125 mg, 1.03 mmol) were added to the flask. The suspension was stirred for at least 1 h to generate the allylzinc bromide, which can be observed by the lightening of the color of the reaction from a dark to light gray. Upon generation of the allylzinc bromide, ethyl glyoxylate (**32**) was added according to General Procedure A. Following flash column chromatography on  $\text{SiO}_2$  gel using 30% EtOAc/petroleum ether as the eluent, 120 mg (85% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.85-5.76 (m, 1H), 5.19-5.14 (m, 2H), 4.28-4.22 (m, 2H), 3.05 (s, 1H), 2.61 (m, 1H), 2.57 (m, 1H), 2.48-2.42 (m, 1H), 1.30 (t,  $J = 6.8$  Hz, 3H).



### Synthesis of *tert*-Butyl Glyoxylate:<sup>5</sup>

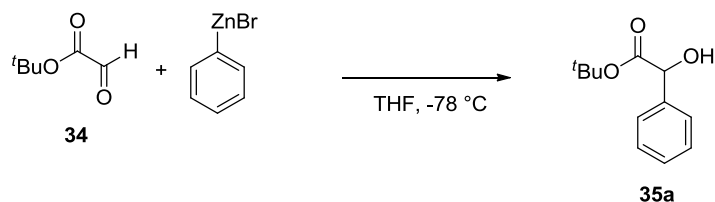
*tert*-Butyl glyoxylate (**34**) was prepared as reported by Nicewicz et al. In a flame-dried 250-mL flask, *tert*-butanol (22 mL, 234 mmol) was dissolved in 50 mL of  $\text{Et}_2\text{O}$  and

cooled to 0 °C. A slurry formed as the *tert*-butanol solidified at 0 °C. <sup>n</sup>Butyllithium (1.6 M in hexanes, 74 mL, 118 mmol) was added over 20 min. After 15 min, the fumaryl chloride (6.4 mL, 59.5 mmol) was added in a solution of 25 mL of Et<sub>2</sub>O over 30 min. The reaction was allowed to warm to room temperature and stir for 12 h. The reaction mixture was quenched with aqueous NaHCO<sub>3</sub> and poured into 200 mL of a 1:1 mixture of Et<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub> solution. The organic layer was separated and the aqueous layer was extracted with an additional 100 mL of Et<sub>2</sub>O. The organic layers were combined, washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The product can be purified by either crystallization from hexanes or flash column chromatography using 10% EtOAc/petroleum ether as the eluent. Following purification, the *tert*-butyl fumarate was dissolved in 100 mL of CH<sub>2</sub>Cl<sub>2</sub> in a 250-mL round bottomed flask and cooled to -78 °C. Ozone was bubbled through the solution until the starting material was consumed and the reaction turned blue (~2 h). The solution was then sparged with O<sub>2</sub> then N<sub>2</sub>. Dimethyl sulfide (5.0 equiv) was added and the reaction was allowed to slowly warm to room temperature, after which time it was allowed to stir for an additional 24 h. The reaction was then concentrated *in vacuo* behind a blast shield. The resultant oil was distilled under reduced pressure (25 mbar, 62 °C b.p.) to afford *tert*-butyl glyoxylate (**34**), which was used immediately.



***tert*-Butyl 2-hydroxy-2-phenylacetate (**35a**, Table 3.3, entry 1)<sup>36</sup>**

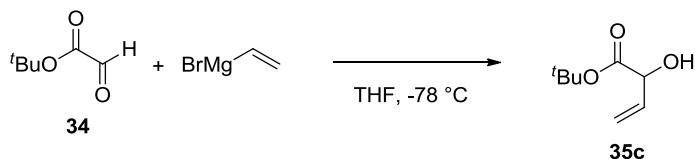
The title compound was prepared according to General Procedure A using *tert*-butyl glyoxylate (**34**) (130 mg, 1.0 mmol) in place of ethyl glyoxylate (**32**). The reaction was allowed to stir for 1 h following addition of the *tert*-butyl glyoxylate (**34**) to reach completion as determined by TLC analysis. Following flash column chromatography on SiO<sub>2</sub> gel using 10% EtOAc/petroleum ether as the eluent, 145 mg (70% yield) of the title compound was isolated as a colorless waxy solid. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43-7.30 (m, 5H), 5.06 (s, 1H), 3.65 (s, 1H), 1.41 (s, 9H).



***tert*-Butyl 2-hydroxy-2-phenylacetate (**35a**, Table 3.3, entry 2)**

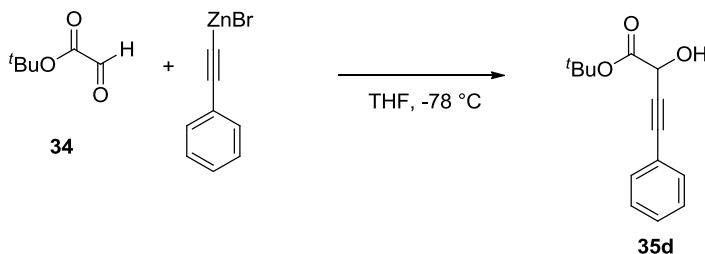
The title compound was prepared according to General Procedure A using *tert*-butyl glyoxylate (**34**) (130 mg, 1.0 mmol) in place of ethyl glyoxylate (**32**) and PhZnBr in place of PhMgBr. Transmetalation was accomplished by reacting PhMgBr with ZnBr<sub>2</sub> (1:1) in 5 mL of THF for 1 h at room temperature. The reaction was allowed to stir for 1 h after addition of the *tert*-butyl glyoxylate (**34**) to the PhZnBr. Following flash column chromatography on SiO<sub>2</sub> gel using 10% EtOAc/petroleum ether as the eluent, 200 mg

(96% yield) of the title compound was isolated as a colorless waxy solid. Analytical data was identical to material prepared by addition of PhMgBr to *tert*-butyl glyoxylate.



***tert*-Butyl 2-hydroxybut-3-enoate (**35c**, Table 3.3, entry 4)**

The title compound was prepared according to General Procedure A using *tert*-butyl glyoxylate (**34**) (130 mg, 1.0 mmol) in place of ethyl glyoxylate (**32**) and vinyl magnesium bromide in place of PhMgBr. The reaction was allowed to stir for 1 h after addition of the *tert*-butyl glyoxylate (**34**) to the vinyl magnesium bromide. Following flash column chromatography on SiO<sub>2</sub> gel using 20% EtOAc/petroleum ether as the eluent, 64 mg (40% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.92-5.86 (m, 1H), 5.46 (dd, *J* = 17.1 Hz, 3.0 Hz, 1H), 5.21 (dd, *J* = 10.5 Hz, 3.0 Hz, 1H), 4.52 (dd, *J* = 4.0 Hz, 1.8 Hz, 1H), 1.46 (s, 9H).



***tert*-Butyl 2-hydroxy-4-phenylbut-3-ynoate (**35d**, Table 3.3, entry 5)**

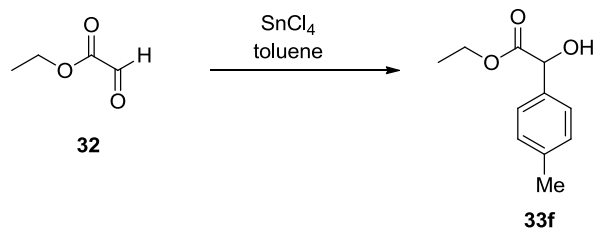
The title compound was prepared according to General Procedure A using *tert*-butyl glyoxylate (**34**) (130 mg, 1.0 mmol) in place of ethyl glyoxylate (**32**) and zinc

phenylacetylide in place of PhMgBr. The zinc acetylide was prepared as previously described. The reaction was allowed to stir for 1 h after addition of the *tert*-butyl glyoxylate (**34**) to the zinc acetylide. Following flash column chromatography on SiO<sub>2</sub> gel using 20% EtOAc/petroleum ether as the eluent, 207 mg (90% yield) of the title compound was isolated as a colorless waxy solid. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46-7.41 (m, 2H), 7.32-7.27 (m, 3H), 4.96 (s, 1H), 4.25 (br s, 1H), 1.53 (s, 9H).

### **General Procedure for Friedel-Crafts Alkylation of Moderately Nucleophilic Arenes (B)**

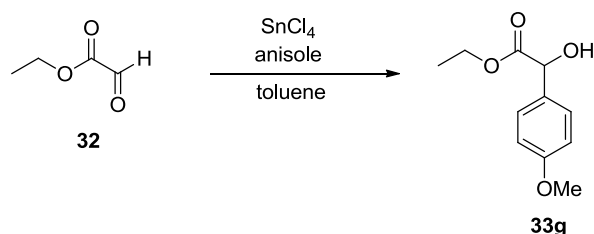
In a flame-dried 3-mL screw cap vial with a stir bar, ethyl glyoxylate (**32**) (100 mg, 0.98 mmol) was charged under N<sub>2</sub>. The vial was then charged with 2 mL of solvent (CH<sub>2</sub>Cl<sub>2</sub>, toluene, or benzene) and the arene (if different). Tin (IV) chloride (115 μL, 1.0 mmol) was then added at room temperature, and the reaction was monitored by TLC. Upon completion, the reaction was poured into 30 mL of a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub> and water. The layers were separated and the aqueous layer was extracted with 2 x 20 mL of CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were combined, washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*.





**Ethyl 2-hydroxy-2-(*p*-tolyl)acetate (33f, Table 3.4, entry 1)<sup>22a</sup>**

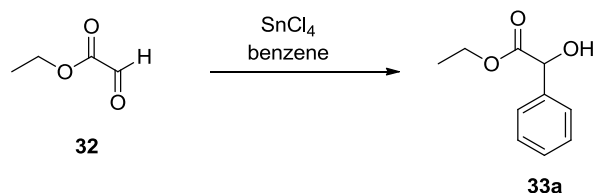
The title compound was prepared according to General Procedure B. The reaction was conducted with toluene as the solvent and arene nucleophile. Following flash column chromatography on SiO<sub>2</sub> gel using 20% EtOAc/petroleum ether as the eluent, 185 mg (95% yield) of the title compound was isolated as a tan solid. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 5.17 (s, 1H), 4.41 (s, 1H), 4.32-4.15 (m, 2H), 2.36 (s, 3H), 1.23 (t, *J* = 6.9 Hz, 3H).



**Ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (33g, Table 3.4, entry 6)<sup>19</sup>**

The title compound was prepared according to General Procedure B. The reaction was conducted with toluene as the solvent, anisole (350 mg, 3.2 mmol) as the arene nucleophile, and SnCl<sub>4</sub> (35 μL, 0.3 mmol) as the Lewis acid. Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 138 mg (66% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.34 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.4 Hz,

2H), 5.11 (d,  $J = 5.7$  Hz, 1H), 4.30-4.14 (m, 2H), 3.81 (s, 3H), 3.40 (d,  $J = 5.7$  Hz, 1H), 1.23 (t,  $J = 7.2$  Hz, 3H).



### Ethyl 2-hydroxy-2-phenylacetate (33a, Table 3.4, entry 8)<sup>19</sup>

The title compound was prepared according to General Procedure B. The reaction was conducted with benzene as the solvent and the arene nucleophile. Upon addition of all reagents, the reaction was heated to 60 °C for 6 h. Following flash column chromatography on  $\text{SiO}_2$  gel using 20%  $\text{Et}_2\text{O}$ /petroleum ether as the eluent, 170 mg (95% yield) of the title compound was isolated as a colorless oil. Analytical data was identical to **33a** prepared via General Procedure A.

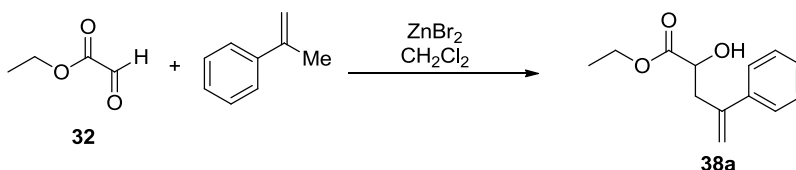
### General Procedure for Carriera Alkynylation Attempts (C)

In a flame-dried 10-mL round bottomed flask equipped with a stir bar, the zinc halide (Br, I, OTf) was massed in the glovebox. The flask was stoppered then removed from the glovebox. Toluene (3 mL) was then added to the reaction. Subsequently, ethyl glyoxylate (**32**) (100 mg, 0.98 mmol), phenyl acetylene (**37**) (150 mg, 1.50 mmol), and an amine base were added at various temperatures. Upon consumption of the starting material by TLC analysis, the reactions were poured into 30 mL of a 1:1 mixture of  $\text{Et}_2\text{O}$  and  $\text{NH}_4\text{Cl}$ . The layers were separated, and the aqueous layer was extracted with an additional 20 mL of  $\text{Et}_2\text{O}$ . The organic layers were combined, dried over  $\text{MgSO}_4$ , and

concentrated. The reaction yielded a complex mixture, from which the desired product was never isolated.

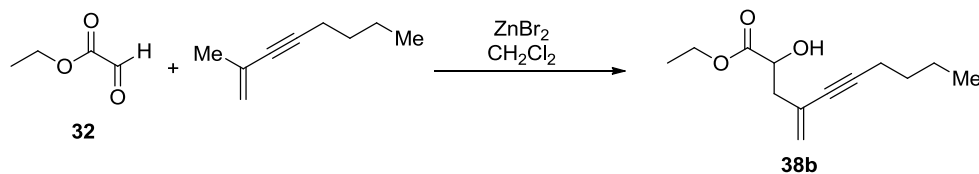
### General Procedure for Ene-reaction (D)

In the glovebox, a flame dried 3-mL screw cap vial was charged with a stir bar and ZnBr<sub>2</sub> (50 mg, 0.25 mmol). The vial was capped and removed from the glovebox. Freshly distilled ethyl glyoxylate (100 mg, 0.98 mmol) was added to the vial followed by addition of 2 mL of solvent (CH<sub>2</sub>Cl<sub>2</sub> or toluene) by quickly removing the cap. The alkene (1.0 mmol) was then added via syringe. The reaction was allowed to stir at room temperature and monitored by TLC. Upon complete consumption of the starting material, the reaction was poured into a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O. The organic layer was separated, and the aqueous layer was extracted with 2 x 20 mL CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were combined, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*.



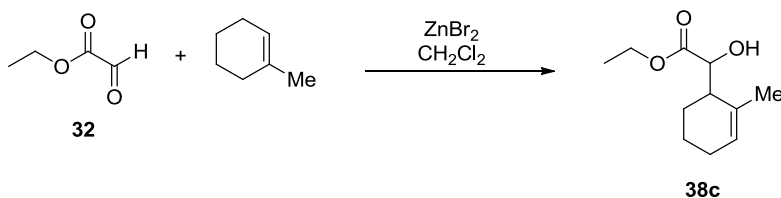
### Ethyl 2-hydroxy-4-phenylpent-4-enoate (38a, Table 3.6, entry 1)<sup>23b</sup>

The title compound was prepared according to General Procedure D. Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 210 mg (96% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44-7.28 (m, 5H), 5.41 (s, 1H), 5.22 (s, 1H), 4.29-4.26 (m, 1H), 4.13-4.03 (m, 2H), 3.08 (dd, *J* = 14.4 Hz, 4.2 Hz, 1H), 2.85 (dd, *J* = 14.4 Hz, 7.5 Hz, 1H), 1.70 (d, *J* = 6.3 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H).



**Ethyl 2-hydroxy-4-methylenedec-5-ynoate (38b, Table 3.6, entry 2)**

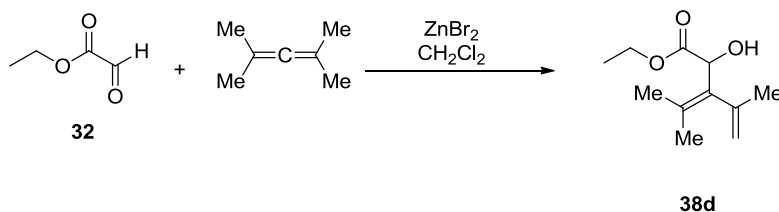
The title compound was prepared according to General Procedure D. The reaction was worked up after 12 h, prior to complete conversion. Following flash column chromatography on  $\text{SiO}_2$  gel using 20%  $\text{Et}_2\text{O}$ /petroleum ether as the eluent, 99 mg (44% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.36 (s, 1H), 5.24 (s, 1H), 4.44-4.38 (m, 1H), 4.23 (q,  $J = 7.2$  Hz, 2H), 2.86 (d,  $J = 6.0$  Hz, 1H), 2.64 (dd,  $J = 13.8$  Hz, 3.9 Hz, 1H), 2.44 (dd,  $J = 13.8$  Hz, 8.1 Hz, 1H), 2.29 (t,  $J = 6.0$  Hz, 2H), 1.53-1.36 (m, 4H), 1.27 (t,  $J = 7.2$ , 3H), 0.90 (t,  $J = 7.2$  Hz, 3H).



**Ethyl 2-hydroxy-2-(2-methylcyclohex-2-en-1-yl)acetate (38c, Table 3.6, entry 3)**

The title compound was prepared according to General Procedure D. The reaction was worked up after 12 h, prior to complete conversion. Following flash column chromatography on  $\text{SiO}_2$  gel using 20%  $\text{Et}_2\text{O}$ /petroleum ether as the eluent, 81 mg (41% yield, 3:1 dr) of the title compound was isolated as a colorless oil. Analytical data for title compound:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.52 (s, 1H), 4.28-4.13 (m, 2H), 2.95 (d,

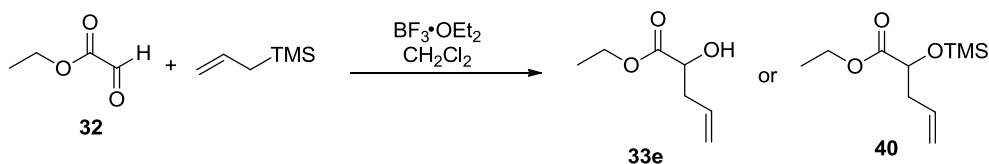
$J = 4.8$  Hz, 1H), 2.58 (s, 1H), 1.91 (br s, 1H), 1.65 (s, 3H), 1.63-1.41 (m, 5H), 1.23 (t,  $J = 5.4$  Hz, 3H).



**Ethyl 2-hydroxy-5-methyl-3-(propan-2-ylidene)hex-4-enoate (38d, Table 3.6, entry 4)**

The title compound was prepared according to General Procedure D. The reaction was worked up after 12 h, prior to complete conversion. Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 81 mg (41% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.08-5.05 (m, 2H), 4.62 (s, 1H), 4.24-4.19 (m, 2H), 2.98 (d,  $J = 5.1$  Hz, 1H), 1.84 (s, 3H), 1.79 (s, 3H), 1.73 (s, 3H), 1.28 (t,  $J = 7.2$  Hz, 3H).

**General Procedure for the Allylation of Ethyl Glyoxylate with Allyl Silane (E)<sup>20a</sup>**



A flame dried 3-mL screw cap vial equipped with a stir bar was charged with ethyl glyoxylate (**32**) (100 mg, 0.98 mmol), allyl trimethylsilane (**39**) (120 mg, 1.05 mmol), and 2 mL of CH<sub>2</sub>Cl<sub>2</sub>. Boron trifluoride etherate (140 mg, 1.0 mmol) was added at room

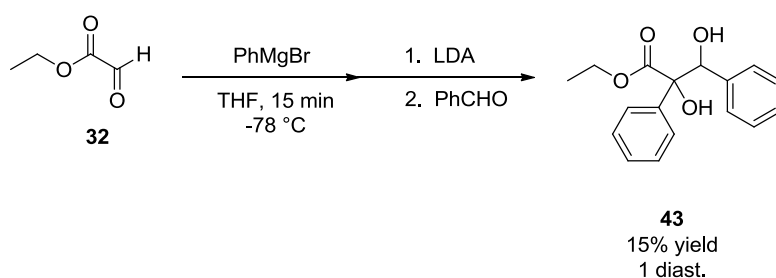
temperature. The reaction was monitored by TLC. Upon completion, the reaction was poured into 30 mL of a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O. The organic layer was separated, and the aqueous layer was extracted with 2 x 20 mL CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were combined, washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The analytical data for **33e** was consistent with material prepared by addition of allylzinc bromide to ethyl glyoxylate. Analytical data for **40**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.85-5.78 (m, 1H), 5.14-5.08 (m, 2H), 4.24-4.15 (m, 2H), 2.53-2.42 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.14 (s, 9H).

#### **General Procedure for One-Pot Grignard Addition/Electrophilic Trap (F)**

In a flame-dried 10-mL round bottomed flask, PhMgBr (1.0 M in THF, 1.0 mL, 1.0 mmol) was added to 2 mL of THF and cooled to -78 °C. Freshly distilled ethyl glyoxylate (**32**) (100 mg, 0.98 mmol) was dissolved in 2 mL of THF and added dropwise to the solution of PhMgBr over 15 min. The reaction was monitored by TLC (30% EtOAc/petroleum ether eluent) and upon completion, the secondary electrophile was added to the flask. The reaction was allowed to slowly warm to room temperature and was stirred until the mandelate intermediate was consumed. The reaction was quenched by pouring into 30 mL of a 1:1 mixture of Et<sub>2</sub>O and saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with 2 x 20 mL of Et<sub>2</sub>O. The organic layers were then combined, washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*.

### General Procedure Nucleophilic Addition/Deprotonation with LDA/Electrophilic Trapping: (G)

In a flame-dried 10-mL round-bottomed flask, PhMgBr (1.0 M, 1.00 mL, 1.00 mmol) was added to 2 mL of dry THF. The solution was cooled to -78 °C, and a second solution of freshly distilled ethyl glyoxylate (~50% in toluene by weight, 100 mg (ethyl glyoxylate), 0.98 mmol) in 2 mL of THF was added over 15 min. The reaction was monitored by TLC and the starting material was consumed after 15 min. The reaction was then transferred via cannula into a solution of freshly prepared LDA (1.5 equiv in THF) at -78 °C. The reaction was allowed to warm to 0 °C over ~2-3 h. Upon reaching 0 °C, the reaction was stirred for 30 min., then cooled to -78 °C. Benzaldehyde (150 µL, 1.5 mmol) was added, and the reaction was allowed to stir for 20 h at room temperature. After 20 h, the reaction was poured into a 1:1 mixture of Et<sub>2</sub>O/saturated aqueous NH<sub>4</sub>Cl (30 mL) and the layers separated. The aqueous layer was washed with 2 x 20 mL of Et<sub>2</sub>O and the organic layers combined. The organic layers were washed with brine, the dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*.



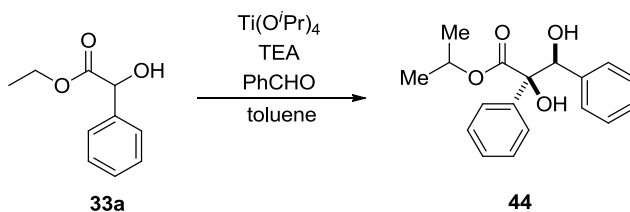
### Ethyl 2,3-dihydroxy-2,3-diphenylpropanoate (43, Scheme 3.13)

The title compound was prepared according to General Procedure G. Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 42

mg (15% yield) of the title compound was isolated as a white solid. Analytical data for title compound:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52-7.50 (m, 2H), 7.26-7.21 (m, 3H), 7.15-7.08 (m, 5H), 5.42 (d,  $J = 8.4$  Hz, 1H), 4.39 (q,  $J = 7.2$  Hz, 2H), 4.05 (s, 1H), 2.93 (d,  $J = 8.1$  Hz, 1H), 1.39 (t,  $J = 6.9$  Hz, 3H).

### General Procedure for $\text{Ti}(\text{O}^i\text{Pr})_4/\text{TEA}$ -Promoted Aldol with Ethyl Mandelate (**H**)

In an oven-dried 3-mL screw cap vial equipped with a stir bar, the aryl glycolic ester was massed then dissolved in toluene. Titanium (IV) isopropoxide was then added to the reaction and allowed to stir for 10 min, followed by addition of TEA. After stirring an additional 10 min, the electrophile was added to the reaction. The reaction was allowed to stir for 24-48 h. After this time, the reaction was added to 15 mL of 1:1  $\text{CH}_2\text{Cl}_2$  : saturated aqueous solution of Rochelle salt. The vial was rinsed with an additional 3 mL of  $\text{CH}_2\text{Cl}_2$ . The resultant emulsion was allowed to stir until two phases separated (~2 h). The reaction mixture was then diluted into a 1:1 mixture of  $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$  (30 mL), extracted into  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL). The organic layers were combined, dried over  $\text{MgSO}_4$ , filtered, and then concentrated *in vacuo*.

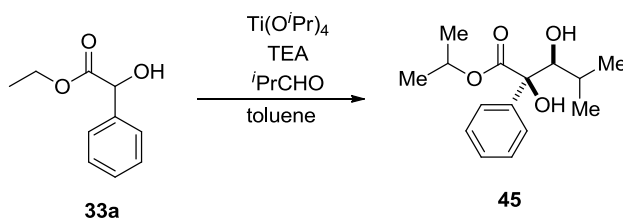


### Isopropyl 2,3-dihydroxy-2,3-diphenylpropanoate (**44**, Scheme 3.14)<sup>25</sup>

The title compound was prepared according to General Procedure H using ester **33a** (50 mg, 0.278 mmol), benzaldehyde (45 mg PhCHO, 0.417 mmol),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (80  $\mu\text{L}$ , 0.273

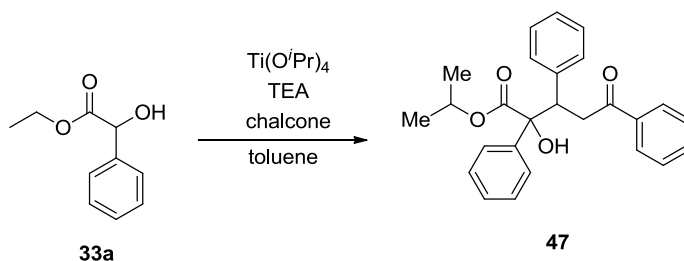


mmol), and TEA (20  $\mu$ L, 0.144 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 38 mg (48% yield) of the title compound was isolated as a white solid. Analytical data for title compound: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.54-7.47 (m, 2H), 7.37-7.33 (m, 1H), 7.24-7.22 (m, 2H), 7.12 (s, 5H), 5.40 (d, *J* = 7.6 Hz, 1H), 5.20 (sept, *J* = 6.4 Hz, 1H), 4.12 (s, 1H), 3.08 (d, *J* = 7.6 Hz, 1H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.33 (d, *J* = 6.0 Hz, 3H).



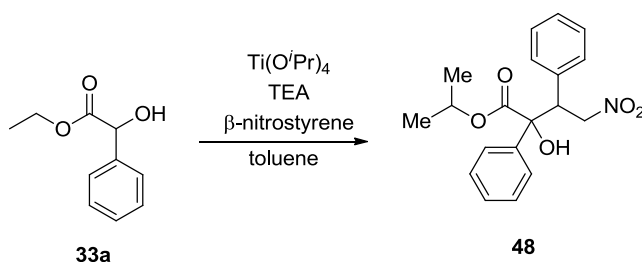
#### Isopropyl 2,3-dihydroxy-4-methyl-2-phenylpentanoate (**45**, Scheme 3.14)<sup>25</sup>

The title compound was prepared according to General Procedure H using ester **33a** (50 mg, 0.278 mmol), isobutyraldehyde (30 mg PhCHO, 0.417 mmol), Ti(O<sup>*i*</sup>Pr)<sub>4</sub> (80  $\mu$ L, 0.273 mmol), and TEA (20  $\mu$ L, 0.144 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 43 mg (61% yield) of the title compound was isolated as a colorless oil. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.66 (d, *J* = 7.2 Hz, 2H), 7.38-7.26 (m, 3H), 5.07 (sept, *J* = 6.3 Hz, 1H), 4.25 (dd, *J* = 11.1, 2.4 Hz, 1H), 4.09 (s, 1H), 2.26 (d, *J* = 11.4 Hz, 1H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H).



### Isopropyl 2-hydroxy-5-oxo-2,3,5-triphenylpentanoate (**47**, Scheme 3.14)

The title compound was prepared according to General Procedure H using ester **33a** (50 mg, 0.278 mmol), chalcone (85 mg PhCHO, 0.417 mmol), Ti(O<sup>*i*</sup>Pr)<sub>4</sub> (80 μL, 0.273 mmol), and TEA (20 μL, 0.144 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 52 mg (48% yield, 2:1 dr) of the title compound was isolated as a colorless oil. Analytical data for title compound (major diastereomer): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 6.9 Hz, 2H), 7.48-7.16 (m, 9H), 4.76 (sept, *J* = 6.3 Hz, 1H), 4.42 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.09 (s, 1H), 3.71 (dd, *J* = 17.7, 10.8 Hz, 1H), 2.87 (dd, *J* = 17.7, 2.4 Hz, 1H), 1.10 (d, *J* = 6.3 Hz, 3H), 1.06 (d, *J* = 6.3 Hz, 3H).



### Isopropyl 2-hydroxy-4-nitro-2,3-diphenylbutanoate (**48**, Scheme 3.14)

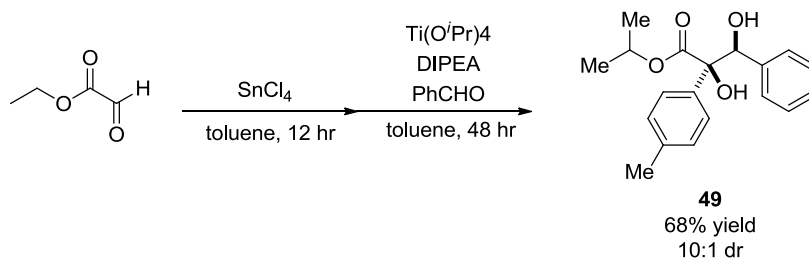
The title compound was prepared according to General Procedure H using ester **33a** (50 mg, 0.278 mmol), β-nitrostyrene (60 mg PhCHO, 0.417 mmol), Ti(O<sup>*i*</sup>Pr)<sub>4</sub> (80 μL, 0.273 mmol), and TEA (20 μL, 0.144 mmol). Following flash column chromatography on SiO<sub>2</sub>

gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 92 mg (50% yield) of the title compound was isolated as a colorless oil (yield corresponds to sum of diastereomers and esters). The major diastereomer of the isopropyl ester was obtained in 31% yield (29 mg). Analytical data for title compound (major diastereomer): **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.86 (d, *J* = 6.9 Hz, 2H), 7.55-7.31 (m, 8H), 4.85-4.76 (m, 2H), 4.43-4.29 (m, 2H), 4.11 (s, 1H), 1.09 (d, *J* = 6.3 Hz, 3H), 1.06 (d, *J* = 6.3 Hz, 3H). The minor diastereomer of the isopropyl ester and major diastereomer of the ethyl ester were isolated as an inseparable mixture. Peaks that are sufficiently resolved are given: major diastereomer, ethyl ester: **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 4.83 (dd, *J* = 13.2 Hz, 11.4 Hz, 1H), 4.06 (s, 1H), 4.04-3.96 (m, 2H); minor diastereomer, isopropyl ester: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.19 (sept, *J* = 6.3 Hz, 1H), 5.00 (dd, *J* = 12.9 Hz, 10.2 Hz, 1H), 4.67 (dd, *J* = 12.9 Hz, 3.9 Hz, 1H), 3.91 (d, *J* = 1.2 Hz, 1H).

### **General Procedure for One-Pot Friedel-Craft/Aldol Reaction (I)**

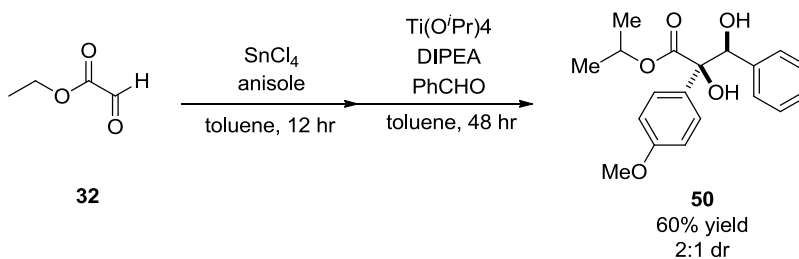
An oven dried 3-mL screw cap vial was charged with a stir bar and freshly distilled ethyl glyoxylate (100 mg, 0.98 mmol, toluene solution). The vial was flushed with N<sub>2</sub>, 2 mL of toluene was added via syringe, and the vial was capped. Tin (IV) chloride (115 µL, 1.00 mmol) was added via syringe by quickly removing the cap. The resultant solution was stirred for 12-16 h at room temperature during which time a white precipitant forms. The reaction progress was checked by TLC analysis after this time to ensure complete conversion. Hünig's base (0.5 mL, 3.00 mmol) was added to the reaction and allowed to stir for 15 min. Titanium (IV) isopropoxide (300 µL, 1.00 mmol) was then added and the reaction stirred an additional 15 min. The electrophile (1.5 mmol) was added and the

reaction was allowed to stir at room temperature for 48 h. After this time, the reaction was added to 15 mL of a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub> and a saturated aqueous solution of Rochelle salt. The vial was rinsed with an additional 3 mL of CH<sub>2</sub>Cl<sub>2</sub>. The resultant emulsion was allowed to stir until the two phases separated (~2 h). The reaction mixture was then diluted into a 1:1 mixture of H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (30 mL), extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered, and then concentrated *in vacuo*.



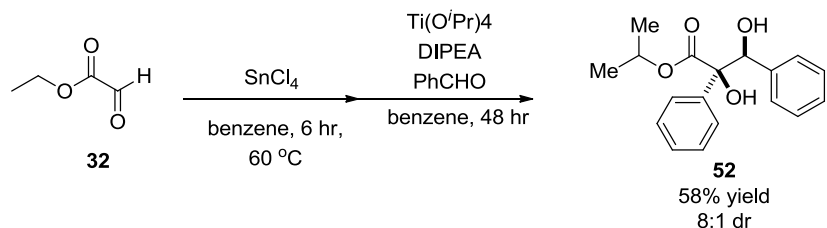
### Isopropyl 2,3-dihydroxy-3-phenyl-2-(p-tolyl)propanoate (**49**, Scheme 3.16)

The title compound was prepared according to General Procedure I using benzaldehyde (156 mg, 1.5 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 210 mg (68% yield, 10:1 dr) of the title compound was isolated as a white solid. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40 (d, *J* = 8.1 Hz, 2H), 7.14 (s, 5H), 7.04 (d, *J* = 8.1 Hz, 2H), 5.38 (d, *J* = 8.4 Hz, 1H), 5.18 (sept, *J* = 6.3 Hz, 1H), 4.05 (s, 1H), 2.97 (d, *J* = 8.4 Hz, 1H), 2.28 (s, 3H), 1.40 (d, *J* = 6.3 Hz, 3H), 1.32 (d, *J* = 6.3 Hz, 3H).



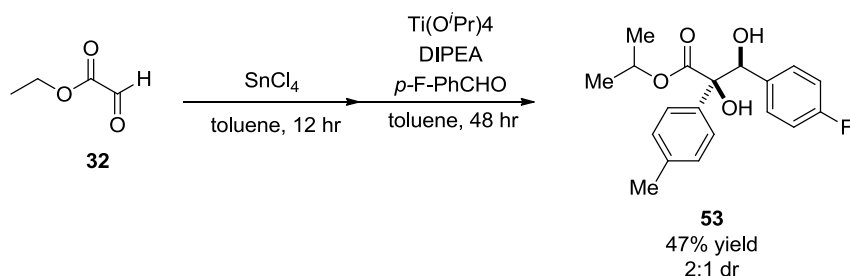
**Isopropyl 2,3-dihydroxy-2-(4-methoxyphenyl)-3-phenylpropanoate (50, Scheme 3.16)**

The title compound was prepared according to General Procedure I using anisole as the arene nucleophile (325 mg, 3.0 mmol) and benzaldehyde (156 mg, 1.5 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 198 mg (60% yield, 2:1 dr) of the title compound was isolated as a white solid. Analytical data for title compound: major diastereomer: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.41 (d, *J* = 9.0 Hz, 2H), 7.16-7.10 (m, 5H), 6.50 (d, *J* = 9.0 Hz, 2H), 5.35 (d, *J* = 8.4 Hz, 1H), 5.19 (sept, *J* = 6.3, *J* = 1H), 4.01 (s, 1H), 3.75 (s, 3H), 2.85 (d, *J* = 8.7 Hz, 1H), 1.40 (d, *J* = 6.3 Hz, 3H), 1.32 (d, *J* = 6.3 Hz, 3H); minor diastereomer: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.71 (dd, *J* = 6.9 Hz, 2.1 Hz, 2H), 7.46-7.43 (m, 2H), 7.34-7.31 (m, 3H), 6.94 (dd, *J* = 6.9 Hz, 2.1 Hz, 2H), 5.32 (d, *J* = 6.6 Hz, 1H), 4.88 (sept, *J* = 6.3 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 1H), 2.65 (d, *J* = 6.6 Hz, 1H), 1.20 (t, *J* = 6.0 Hz, 3H), 1.08 (d, *J* = 6.0 Hz, 3H).



### Isopropyl 2,3-dihydroxy-2,3-diphenylpropanoate (52, Scheme 3.16)

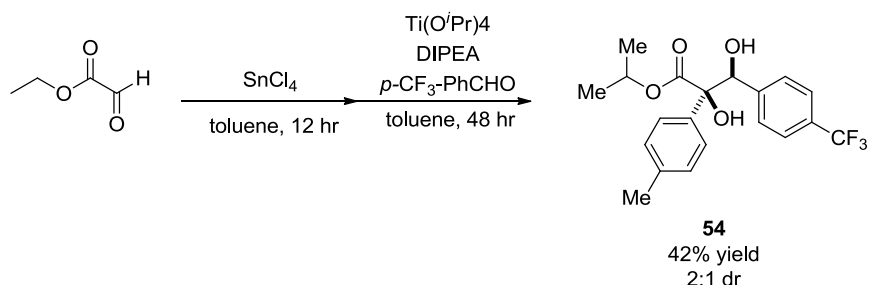
The title compound was prepared according to General Procedure I using benzene as the solvent and arene nucleophile and benzaldehyde (156 mg, 1.5 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 173 mg (62% yield, 8:1 dr) of the title compound was isolated as a white solid. Analytical data for title compound (major diastereomer): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.54-7.47 (m, 2H), 7.37-7.33 (m, 1H), 7.24-7.22 (m, 2H), 7.12 (s, 5H), 5.40 (d, *J* = 7.6 Hz, 1H), 5.20 (sept, *J* = 6.4 Hz, 1H), 4.12 (s, 1H), 3.08 (d, *J* = 7.6 Hz, 1H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.33 (d, *J* = 6.0 Hz, 3H).



### Isopropyl 3-(4-fluorophenyl)-2,3-dihydroxy-2-(*p*-tolyl)propanoate (53, Scheme 3.16)

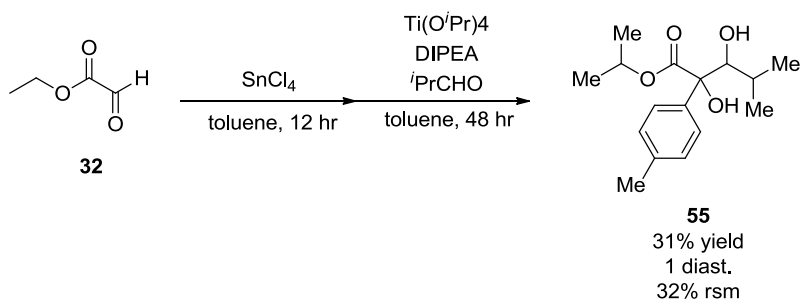
The title compound was prepared according to General Procedure I using *p*-fluorobenzaldehyde (180 mg, 1.5 mmol) and DIPEA (260 μL, 1.5 mmol) (NOTE: the title compound was prepared using 1.5 equiv of DIPEA, not the optimized conditions in General Procedure I). Following flash column chromatography on SiO<sub>2</sub> gel using 20%

Et<sub>2</sub>O/petroleum ether as the eluent, 147 mg (47% yield, 2:1 dr) of the title compound was isolated as a white solid. Analytical data for title compound (major diastereomer): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.36 (d, *J* = 8.1 Hz, 2H), 7.11-7.05 (m, 4H), 6.81 (t, *J* = 8.7 Hz, 2H), 5.35 (s, 1H), 5.18 (sept, *J* = 6.3 Hz, 1H), 4.05 (s, 1H), 2.28 (s, 3H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.32 (d, *J* = 6.3 Hz, 3H). The minor diastereomer was unable to be isolated in sufficient purity to characterize.



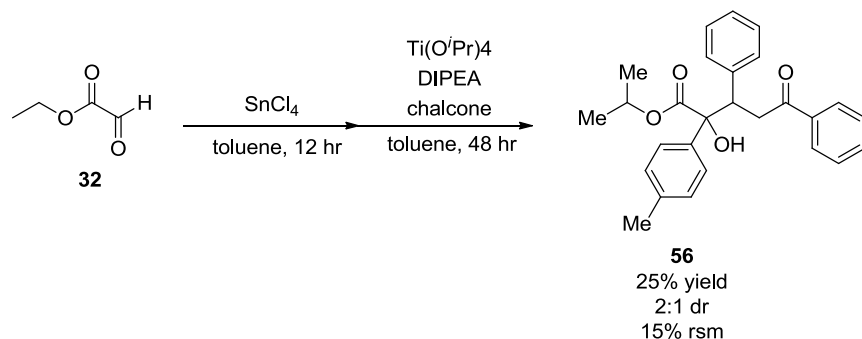
**Isopropyl 2,3-dihydroxy-2-(*p*-tolyl)-3-(4-(trifluoromethyl)phenyl)propanoate (54, Scheme 3.16)**

The title compound was prepared according to General Procedure I using *p*-trifluoromethyl- benzaldehyde (250 mg, 1.5 mmol) and DIPEA (260 μL, 1.5 mmol) (NOTE: the title compound was prepared using 1.5 equiv of DIPEA, not the optimized conditions in General Procedure I). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 152 mg (42% yield, 2:1 dr) of the title compound was isolated as a white solid. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.64-7.56 (m, 4H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 5.42 (d, *J* = 8.7 Hz, 1H), 5.19 (sept, *J* = 6.0 Hz, 1H), 4.06 (s, 1H), 3.02 (d, *J* = 8.7 Hz, 1H), 2.29 (s, 3H), 1.40 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H).



### Isopropyl 2,3-dihydroxy-4-methyl-2-(p-tolyl)pentanoate (**55**, Scheme 3.16)

The title compound was prepared according to General Procedure I using isobutyraldehyde (100 mg, 1.5 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 85 mg (31% yield) of the title compound was isolated as a colorless oil and 66 mg (32% yield) of the glycolic ester **33f** was also recovered. Analytical data for title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 5.06 (sept, *J* = 6.0 Hz, 1H), 4.23 (dd, *J* = 11.1 Hz, 2.7 Hz, 1H), 4.06 (s, 1H), 2.35 (s, 3H), 2.27 (d, *J* = 11.1 Hz, 1H), 1.58 (dt, *J* = 6.6 Hz, 2.7 Hz, 1H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.34 (t, *J* = 6.3 Hz, 6H).

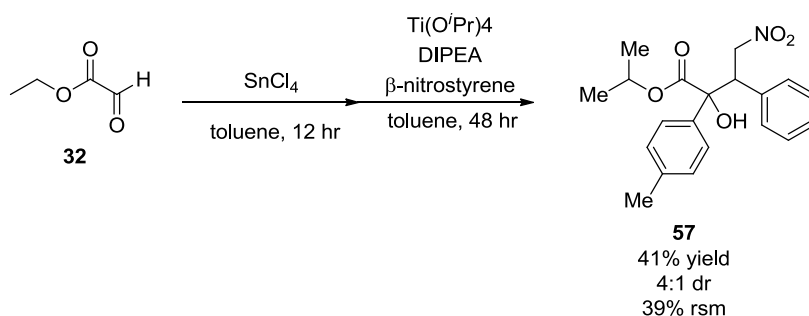


### Isopropyl 2-hydroxy-5-oxo-3,5-diphenyl-2-(p-tolyl)pentanoate (**56**, Scheme 3.16)

The title compound was prepared according to General Procedure I using chalcone (300 mg, 1.5 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20%



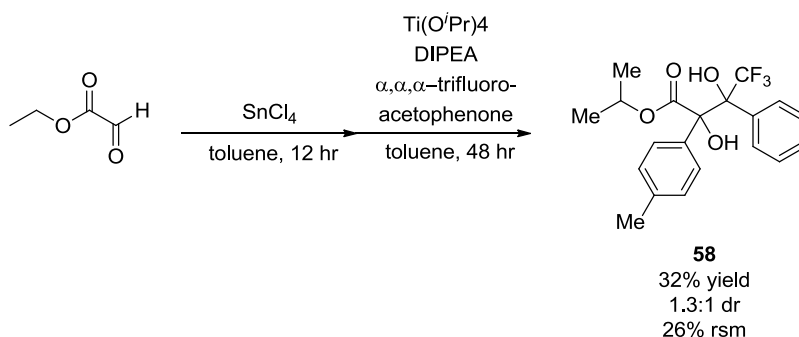
Et<sub>2</sub>O/petroleum ether as the eluent, the desired product was isolated as a mixture of diastereomers, excess chalcone, and other impurities. Purification on HPLC (20% EtOAc/hexanes eluent) afforded each diastereomer cleanly enough that diagnostic peaks can be determined. The diagnostic peaks that are sufficiently resolved are listed in the analytical data. The yield of the title compound for the reaction (102 mg, 25% yield, 2:1 dr) was determined by <sup>1</sup>H NMR with mesitylene as an internal standard. The glycolic ester **33f** (30 mg, 15% yield) was also recovered. Analytical data for title compound (diagnostic peaks): major diastereomer: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.75 (sept, *J* = 6.0 Hz, 1H), 4.40 (dd, *J* = 10.8 Hz, 2.4 Hz, 1H), 4.07 (s, 1H), 3.71 (dd, *J* = 17.7 Hz, 10.8 Hz, 1H), 3.89 (dd, *J* = 18.0 Hz, 2.7 Hz, 1H), 2.34 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H); minor diastereomer: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.11 (sept, *J* = 6.3 Hz, 1H), 4.44 (d, *J* = 10.5 Hz, 1H), 3.99 (s, 1H), 3.98-3.89 (m, 1H), 3.08 (dd, *J* = 17.4 Hz, 3.0 Hz, 1H), 2.23 (s, 3H), 1.31 (d, *J* = 8.7 Hz, 3H), 1.26 (d, *J* = 7.5 Hz, 3H).



### Isopropyl 2-hydroxy-4-nitro-3-phenyl-2-(p-tolyl)butanoate (**57**, Scheme 3.16)

The title compound was prepared according to General Procedure I using  $\beta$ -nitrostyrene (220 mg, 1.5 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 145 mg (41% yield, 4:1 dr) of the title compound was isolated as a colorless oil and 81 mg (39% yield) of the glycolic ester **33f** was also

recovered. Analytical data for title compound: major diastereomer:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31-7.27 (m, 2H), 7.20-7.17 (m, 2H), 7.11-7.19 (m, 3H), 6.98 (d,  $J = 8.4$  Hz, 2H), 5.17 (sept,  $J = 6.3$  Hz, 1H), 4.99 (dd,  $J = 12.6$  Hz, 9.9 Hz, 1H), 4.65 (dd,  $J = 12.9$  Hz, 3.9 Hz, 1H), 4.43 (dd,  $J = 9.9$  Hz, 3.6 Hz, 1H), 3.88 (s, 1H), 2.23 (s, 3H), 1.40 (d,  $J = 6.3$  Hz, 3H), 1.31 (d,  $J = 6.3$  Hz, 3H); minor diastereomer:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J = 8.1$  Hz, 2H), 7.55-7.52 (m, 2H), 7.36-7.29 (m, 3H), 7.25 (d,  $J = 8.1$  Hz, 2H), 4.85-4.75 (m, 2H), 4.41-4.31 (m, 2H), 4.09 (s, 1H), 2.39 (s, 3H), 1.09 (d,  $J = 6.0$  Hz, 3H), 1.05 (d,  $J = 6.3$  Hz, 3H).



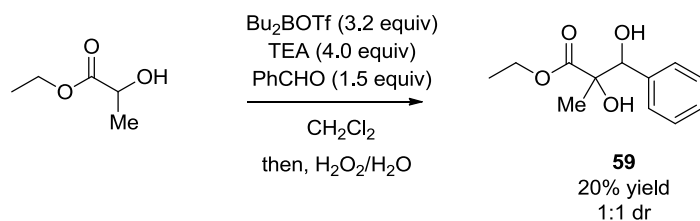
### Isopropyl 4,4,4-trifluoro-2,3-dihydroxy-3-phenyl-2-(p-tolyl)butanoate (**58**, Scheme 3.16)

The title compound was prepared according to General Procedure I using  $\alpha,\alpha,\alpha$ -trifluoroacetophenone (270 mg, 1.5 mmol). Following flash column chromatography on  $\text{SiO}_2$  gel using 20%  $\text{Et}_2\text{O}$ /petroleum ether as the eluent, 124 mg (32% yield) of the title compound was isolated as a colorless oil and 54 mg (26% yield) of the glycolic ester **33f** was also recovered. Analytical data for title compound: major diastereomer:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (d,  $J = 7.2$  Hz, 2H), 7.33-7.28 (m, 2H), 7.20-7.13 (m, 3H), 6.91 (d,  $J = 8.1$  Hz, 2H), 5.96 (s, 1H), 5.25 (sept,  $J = 6.3$  Hz, 1H), 3.96 (s, 1H), 2.21 (s,

3H), 1.39 (d,  $J = 6.0$  Hz, 3H), 1.22 (d,  $J = 6.0$  Hz, 3H); minor diastereomer:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J = 8.4$  Hz, 2H), 7.55 (d,  $J = 8.4$  Hz, 2H), 7.36-7.29 (m, 3H), 7.12 (d,  $J = 8.4$  Hz, 2H), 4.92 (sept,  $J = 6.0$  Hz, 1H), 4.35 (s, 1H), 4.00 (s, 1H), 2.35 (s, 3H), 1.15 (d,  $J = 6.3$  Hz, 3H), 1.07 (d,  $J = 6.3$  Hz, 3H).

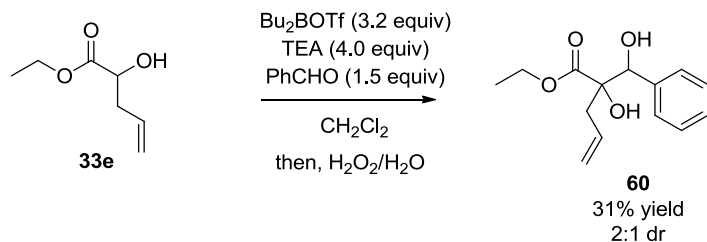
### **General Procedure for $\text{Bu}_2\text{BOTf/TEA}$ -Promoted Aldol of Aliphatic Glycolic Esters (J)**

In a flame-dried 10-mL round bottomed flask equipped with a stir bar,  $\text{Bu}_2\text{BOTf}$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ , 1.2 mL, 1.2 mmol) was added to a solution of TEA (125  $\mu\text{L}$ , 0.898 mmol) in 1 mL of  $\text{CH}_2\text{Cl}_2$  at 0  $^\circ\text{C}$ . The solution was allowed to stir for 15 min at rt, then cooled to 0  $^\circ\text{C}$ . The glycolic ester (0.278 mmol) was added as a 2 mL solution of  $\text{CH}_2\text{Cl}_2$ . After stirring an additional 15 min at 0  $^\circ\text{C}$ , PhCHO (50 mg, 0.472 mmol) was added and the reaction was allowed to warm to rt and stir for 24 h. After 24 h, 0.5 mL of 0.1 M pH 7 buffer was added, followed by 2 mL of MeOH and  $\text{H}_2\text{O}_2$  (1.5 mL, 30% wt.). The reaction was stirred at rt for 1 h then extracted into  $\text{Et}_2\text{O}$  (2 x 20 mL). The organic layers were combined and washed with saturated aqueous  $\text{FeSO}_4$  until green color persisted. The organic layer was then washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*.



### Ethyl 2,3-dihydroxy-2-methyl-3-phenylpropanoate (**59**, Scheme 3.18)<sup>37</sup>

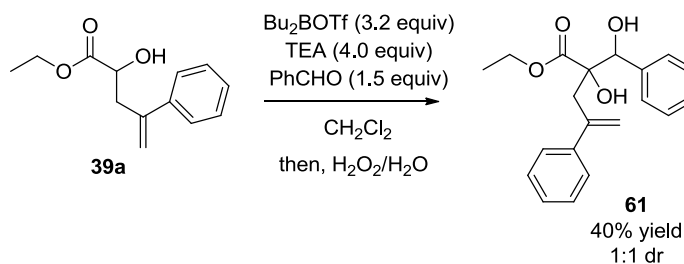
The title compound was prepared according to General Procedure J using ethyl lactate (33 mg, 0.277 mmol). Following flash column chromatography on  $\text{SiO}_2$  gel using 20%  $\text{Et}_2\text{O}$ /petroleum ether as the eluent, 13 mg (20% yield, 1:1 dr) of the title compound was isolated as a colorless oil. Analytical data for title compound: major diastereomer:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.29 (m, 5H), 4.84 (s, 1H), 4.32 (q,  $J = 7.2$  Hz, 2H), 3.53 (s, 1H), 2.45 (s, 1H), 1.58 (s, 3H), 1.33 (t,  $J = 7.2$  Hz, 3H).; minor diastereomer: 7.40-7.29 (m, 5H), 4.75 (s, 1H), 4.11-4.05 (m, 2H), 3.32 (s, 1H), 2.95 (s, 1H), 1.22-1.17 (m, 6H).



### Ethyl 2-hydroxy-2-(hydroxy(phenyl)methyl)pent-4-enoate (**60**, Scheme 3.18)

The title compound was prepared according to General Procedure J using **33e** (40 mg, 0.277 mmol). Following flash column chromatography on  $\text{SiO}_2$  gel using 20%  $\text{Et}_2\text{O}$ /petroleum ether as the eluent, 22 mg (31% yield, 1:1 dr) of the title compound was isolated as a colorless oil. Analytical data for title compound (major diastereomer):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 -7.31 (m, 5H), 5.74-5.60 (m, 1H), 5.12-5.02 (m, 2H),

4.85 (d,  $J = 6.6$  Hz, 1H), 4.37-4.34 (m, 2H), 3.56 (s, 1H), 2.71 (d,  $J = 7.5$  Hz, 1H), 2.42 (dd,  $J = 13.8$  Hz, 8.4 Hz, 1H), 2.00 (dd,  $J = 14.4$  Hz, 6.3 Hz, 1H), 1.33 (t,  $J = 6.3$  Hz, 3H).

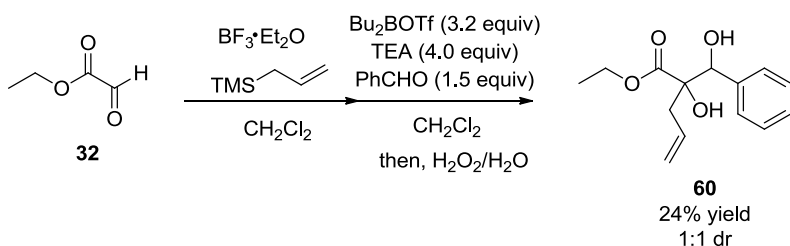


**Ethyl 2-hydroxy-2-(hydroxy(phenyl)methyl)-4-phenylpent-4-enoate (61, Scheme 3.19)**

The title compound was prepared according to General Procedure J using **39a** (60 mg, 0.277 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 36 mg (40% yield, 1:1 dr) of the title compound was isolated as a colorless oil. Analytical data for title compound: major diastereomer: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.48-7.35 (m, 5H), 7.33-7.27 (m, 5H), 5.26 (s, 1H), 5.09 (s, 1H), 4.88 (s, 1H), 3.97-3.91 (m, 1H), 3.62-3.56 (m, 1H), 3.46 (s, 1H), 2.97 (d,  $J = 13.8$  Hz, 1H), 2.92 (s, 1H), 2.37 (d,  $J = 13.8$  Hz, 1H), 1.11 (t,  $J = 7.2$  Hz, 3H); minor diastereomer: 7.41-7.21 (m, 10H), 5.32 (s, 1H), 5.21 (s, 1H), 4.80 (s, 1H), 3.68-3.64 (m, 1H), 3.51-3.46 (m, 2H), 3.35 (d,  $J = 13.8$  Hz, 1H), 3.23-3.17 (m, 2H), 0.98 (t,  $J = 7.2$  Hz, 3H).

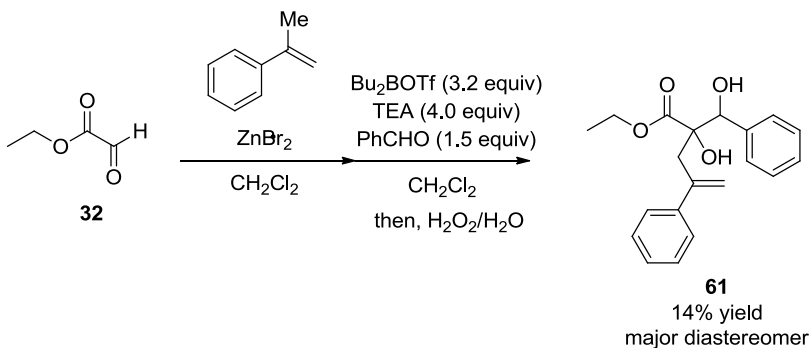
### General Procedure for One-Pot Allylation/Aldol Reaction (K)

The tandem allylation/aldol reaction was accomplished by employing General Procedure E or D without work-up to generate the desired allylated glycolic ester. The crude reaction mixture was then subjected to General Procedure J to accomplish the aldol reaction. The work-up employed is identical to that detailed in General Procedure J.



### Ethyl 2-hydroxy-2-(hydroxy(phenyl)methyl)pent-4-enoate (**60**, Scheme 3.19)

The title compound was prepared according to General Procedure K using **32** (50 mg, 0.49 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 29 mg (24% yield, 1:1 dr) of the title compound was isolated as a colorless oil. Analytical data for the title compound was identical to material prepared using General Procedure J.



**Ethyl 2-hydroxy-2-(hydroxy(phenyl)methyl)-4-phenylpent-4-enoate (61, Scheme 3.19)**

The title compound was prepared according to General Procedure J using **32** (50 mg, 0.277 mmol). Following flash column chromatography on SiO<sub>2</sub> gel using 20% Et<sub>2</sub>O/petroleum ether as the eluent, 22 mg (14% yield, only major diastereomer isolated) of the title compound was isolated as a colorless oil. Analytical data for the title compound was identical to material prepared using General Procedure J.

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