SYNTHESIS, STUDY AND APPLICATION OF SILYL KETENE IMINES IN LEWIS BASE CATALYZED CARBONYL ADDITION REACTIONS

BY

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DISSERTATION

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Abstract

The activation of Lewis acids by chiral Lewis bases has allowed for the development of a robust and highly selective catalyst system for the addition of silylated nucleophiles to carbonyl compounds. In general, aldolate-type products containing secondary and tertiary stereogenic centers are obtained in high yield and with excellent stereoselectivities. Despite the breadth of reactivity that has been observed for additions to aldehydes under this mode of catalysis certain structural motifs, such as quaternary carbons and tertiary alcohols have remained unsolved problems. This deficiency is further underscored by the dearth of general methods for the catalytic, asymmetric preparation of fully substituted stereogenic carbon centers. To address these challenges, and empower Lewis base catalysis for the asymmetric synthesis of tetrasubstituted carbons a range of disubstituted *N*-silyl ketene imines has been investigated as latent nucleophiles for additions to carbonyl compounds. In the presence of silicon tetrachloride and a catalytic amount of chiral bis-phosphoramide, *N*-silyl ketene imines underwent extremely rapid additions to aldehydes, providing aldol products containing quaternary stereogenic centers in excellent yields and stereoselectivities. Further extension of this chemistry to catalytic, enantioselective Michael-type reactions and vinylogous aldol additions has also been realized, by introduction of a double bond into the aldehyde acceptor or *N*-silyl ketene imine donor. The reactions of these unsaturated species occurred with excellent site selectivity and provide products with a 1,5-disposition of oxygen and nitrogen heteroatoms in moderate to excellent enantioselectivity. Finally, a new class of *N*-silyl oxyketene imines derived from protected cyanohydrins has been developed. These nucleophiles serve as acyl anion equivalents in Lewis base catalyzed aldol addition reactions and allow for the preparation of cross-benzoin and glycolate-aldol products in high yield and with exceptional diastereo- and enantioselectivities.

Dedicated to my parents,
Beau and Kate

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The work embodied in this thesis would not have been possible without the support and encouragement of my family, friends and co-workers. I would like to give special thanks to my parents, for emboldening a love of the sciences and a passion for discovery in my early years. Also, a great gratitude is owed to my brother, who has been such a good friend to me over the years and provided a great deal of support during my undergraduate studies. A significant recognition is bestowed to my wife, Tiffany, who continues to be my best friend and dearest companion. Her unwavering support and reassurances provided me with the will to push through the difficult times encountered in graduate school. As we close one chapter of our lives, I look forward to the new challenges and adventures that we will share together in the future.

A number of senior members from the Denmark group aided me as a young graduate student and deserve accolades; I would like to especially thank Dr. Edwards and Dr. Eklov for providing me with experimental and theoretical expertise during my early years. I have also been exceptionally fortunate to share a lab with some outstanding scientist and would like to acknowledge Dr. Collins, Dr. Chung and Dr. Vogler for helpful insights and endless discussions. Overall there are too many people from the Denmark group to mention individually, but I would like to express my overwhelming gratitude to all the group members for their friendships, support and help over the past seven years.

Finally, I would like to express a tremendous amount of appreciation to my Advisor, Scott E. Denmark, for his steadfast support, insights and encouragement throughout my graduate studies. Prof. Denmark leads by example, and his passion for science and dedication to the field of organic chemistry is truly contagious and has provided me with a model that I will continue to strive towards for the rest of my career

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Chapter 1: Theory and Applications of Lewis Base Catalysis In Organic Synthesis

1.1 Theory of Lewis Acids and Bases. In the early 20th century, Gilbert N. Lewis unified the theory of acids and bases by recognizing a base simply as an electron pair donor and an acid as an electron pair acceptor.wilson[1] Previous definitions of Arrhenius and Brønsted-Lowry relied on physical observables, such as production of protons or hydronium ions in the reaction medium. The power of Lewis's theory was to recast the definitions of acid and bases in terms of electron sharing and the formation of dative chemical bonds.[2] In the classic monograph published in 1923, Lewis states, "*it seems to me that with complete generality we may say that a basic substance is one which has a lone pair of electrons which may be used to complete the stable group of another atom and that an acid substance is one which can employ a lone pair from another molecule in completing the stable group of one of its own atoms. In other words, the basic substance furnishes a pair of electrons for a chemical bond: the acid substance accepts such a pair.*" This revolutionary theory of Lewis acids and bases has come to be one of the primary axioms of modern chemistry and plays a central role in our understanding of reactivity and bonding in both transition and main-group chemistry.

One of the guiding principles in Lewis acid-base chemistry is the octet rule,[3] which states that an atom is in its most stable state when it has a full valence of electrons (*i.e.* eight electrons for main group elements). Filling the valence shell of an atom provides a thermodynamic driving force for the chemical reaction between Lewis acids and bases and, in many cases, results in the formation of a more stable Lewis acid-base adduct. However, the interactions between Lewis

acids and bases do not necessarily result in reduced reactivity, even though the overall formation of an adduct may be stabilizing.

Countless examples from the literature reveal cases where stable Lewis acid-base adducts exhibit increased reactivity. Most notably, strong Lewis bases, such as hexamethylphosphoric triamide (HMPA), are known to have a dramatic accelerating effect on the rates of chemical reactions ranging from organolithium alkylations to samarium diiodide reductions.[4] Furthermore, the use of Lewis basic ligands in transition-metal catalyzed processes has allowed for the fine-tuning of reactivity and selectivity for a range of different transformations.[5] More recently, the interaction of a sterically hindered Lewis acid-base pair, unable to form a dative bond, has been exploited for unprecedented types of reactivity, such as heterolytic bond cleavage and activation of dihydrogen.[6]

1.2. Jensen's Orbital Analysis for Lewis Acid-Base Adducts. The influence of Lewis acids and bases on a chemical reaction can vary from nucleophilic or electrophilic activation of substrates, to modulation of electrochemical properties, to the heterolytic cleavage of covalent bonds. To better understand how the interactions of Lewis acids and bases can influence such a diverse range of chemical reactivity, it is helpful to classify the different types of interactions in terms of the molecular orbitals involved. Jensen proposed a classification system for Lewis acid-base adducts based on the combination of three different types of donor orbitals with three kinds of acceptor orbitals (Table 1).[2a]

Table 1. Orbital analysis for Lewis acid-base pairs

Donor	Acceptor		
	n*	σ*	π*
n	n–n*	n–σ*	n–π*
σ	σ–n*	σ–σ*	σ–π*
π	π–n*	π–σ*	π–π*

Jensen's analysis of molecular orbital interactions leads to nine possible bonding phenomenon that can account for Lewis acid-base adduct formation. Although each of the nine different types of orbital combinations could lead to a productive Lewis-acid base complex, only three have been widely utilized in activation or catalysis. The three most common modes all involve interaction of the non-bonding pair with: (1) vacant non-bonding orbitals (n-n*), (2) anti-bonding orbitals with σ-character (n-σ*), and (3) anti-bonding orbitals with π-character (n-π*).

1.3 General Classes of Activation Employed by Lewis Acids and Bases. Jensen's orbital analysis for bond formation applies to all Lewis acid-base adducts. However, the fundamental ways in which Lewis acids and Lewis bases activate a substrate molecule (S) are very distinct. The inherent differences between these classes of activation can be organized into three main types, depending on the manner of electron density flow in the newly formed adduct, *i.e*. either away from or towards the substrate (Figure 1).

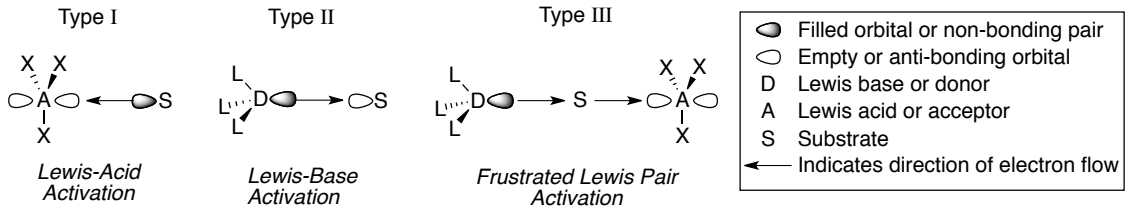


Figure 1. Common types of activation for Lewis acid-base pairs

In Lewis acid activation (Figure 1, Type I), a substrate containing either a filled orbital or non-bonding pair in the highest occupied molecular orbital (HOMO) donates electron density to

the lowest unoccupied orbital of a Lewis acid (LUMO). The net flow of electron-density is away from the substrate resulting in an overall increase in its electrophilicity. This mode of interaction has developed into Lewis-acid catalysis, and has found wide spread use and success in both stoichiometric and catalytic processes.[7]

The second general type of activation involves the donation of electron density from a non-bonding or filled orbital of a Lewis base to an empty or anti-bonding orbital in the substrate (Figure 1, Type II). In this case the net flow of electron density is towards the substrate and can result in the enhancement of either nucleophilic or electrophilic character, depending on how the electron density is distributed among the constituent atoms. This mode of activation is fundamentally distinct from that of Lewis acids and has led to the development of Lewis base-catalyzed processes.[8]

The final type of activation was developed only recently and involves the use of Lewis acid-base pairs that are sterically precluded from quenching each other. This relationship creates a large chemical potential that can be used to heterolytically cleave appropriate substrate molecules, to achieve neutralization in the frustrated pair. Remarkably, this unique arrangement of a Lewis acid-base pair has been shown to be the first non-metallic system able to reversibly take-up and release dihydrogen, allowing for catalytic hydrogenation of imines.[9] This method does not represent a fundamentally distinct mode of activation from that of Lewis acids or bases, but offers very distinctive types of reactivity.[6]

Although not as easily identified as Lewis acid catalysis, Lewis base activation is quite common in organic chemistry and is central to the chemistry reported in this document. The remaining sections of this introduction will focus on the theory of Lewis base catalysis and its uses for activation of silicon-based Lewis acids.

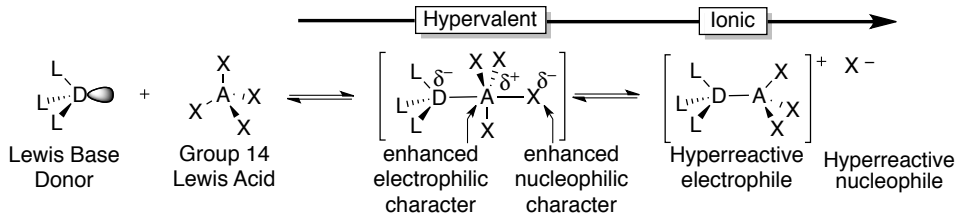
1.4 Lewis Base Catalysis. In contrast to traditional Lewis acid catalysis, in which the mode of activation is always electrophilic in nature, Lewis bases are effective at promoting reactions by enhancement of either nucleophilic or electrophilic character in a substrate. This disparity in activation modes is most easily reconciled by identifying that in Lewis base catalysis electron density flows towards the substrate or reactant. The mode of activation (*e.g.* electrophilic or nucleophilic) depends on how the additional electron density is distributed among the constituent atoms in the substrate. In Lewis acid catalysis, electron density always flows out of the substrate, resulting in an enhancement of the substrate's electrophilicity. Lewis base catalysis has recently been defined in very general terms as any process in which an electron pair donor increases the rate of a given chemical transformation by interacting with an acceptor atom in one of the reagents or substrates. Furthermore, the Lewis base should not be consumed or altered in the reaction, which is a requirement of any catalytic process.[8]

1.4.1 Lewis Base Activation of Silicon Lewis Acids. The ability of Group 14 Lewis acids to expand their coordination sphere and engage in hypervalent bonding has made them an attractive target for Lewis base activation. In particular, the Lewis base activation of silicon-containing substrates has flourished, due to the favorable characteristics of organosilicon compounds, such as: high stability, low-toxicity, ease-of-preparation and commercial-availability. Furthermore, Lewis base activation of organosilicon compounds provides a concrete example of how the interaction of a Lewis base can lead to enhancement of both nucleophilic and electrophilic character.

1.4.2 General Considerations and Model for Lewis Base Activation of Silicon. In the proposed model for activation of a silicon Lewis acid with a Lewis base, the base donates a pair of electrons from a non-bonding orbital (n) to the anti-bonding orbital (σ^*) of the silicon Lewis

acid (Scheme 1). Overall, the electron density in the acceptor fragment is increased; however, it is not equally distributed among the constituent atoms. Rehybridization of the silicon center to accommodate the additional ligand results in polarization and lengthening of the adjacent bond. As a result of the hybridization change, the electron density at the silicon atom decreases, while the electron density at the peripheral ligands increases. The newly formed hypervalent species displays a unique pattern of reactivity, showing increased electrophilicity at the central atom as well as increased nucleophilicity at the peripheral ligands. In extreme cases, with strong donors, polarization of the adjacent bond by the Lewis base can result in ionization, yielding a reactive cationic Lewis acid/anionic nucleophile pair.

Scheme 1



1.4.3 Hypervalent Bonding Analysis. The increase in electrophilic character of the silicon Lewis acid that results upon binding of a Lewis base is counter-intuitive because overall, the electron density on the Lewis acid fragment increases. However, this can be understood by considering the nature of the hypervalent bonds present in the Lewis base/Lewis acid complex.[10] The interaction between the non-bonding orbital of the Lewis base and the σ* orbital of silicon requires the formation of a hypervalent bond. The ability of silicon and other main group elements to participate in hypervalent bonding has generated some controversy in the literature. Earlier models suggested that silicon and other 3rd row elements employed vacant d-orbitals to engage in hypervalent bonding, in a similar manner to transition metals. Later studies suggested that the d-orbitals of the 3rd row elements were far too diffuse and high energy to engage in

productive bonding.[11] Today, it is generally accepted that main group elements expand their valency by engaging a filled p orbital in a highly polarized, electron-rich three-center-four-electron (3C-4E) bond.[12]

For silicon to engage in hypervalent bonding requires that a p-orbital be available to engage in 3C-4E bonding; this is accomplished by rehybridization of the central silicon atom from sp^3 to sp^2. Changing the hybridization state of silicon from sp^3 to sp^2 lowers the energy of the hybrid orbitals involved in covalent bonding, by increasing the amount of s-character, and alters the overall geometry of the structure from tetrahedral to trigonal bipyramidal (Figure 2a).[8] A second p-orbital can be made available for hypervalent 3C-4E bonding by rehybridization of the central atom to sp, resulting in a hexa-coordinate silicon complex (SiL_6) displaying octahedral geometry.

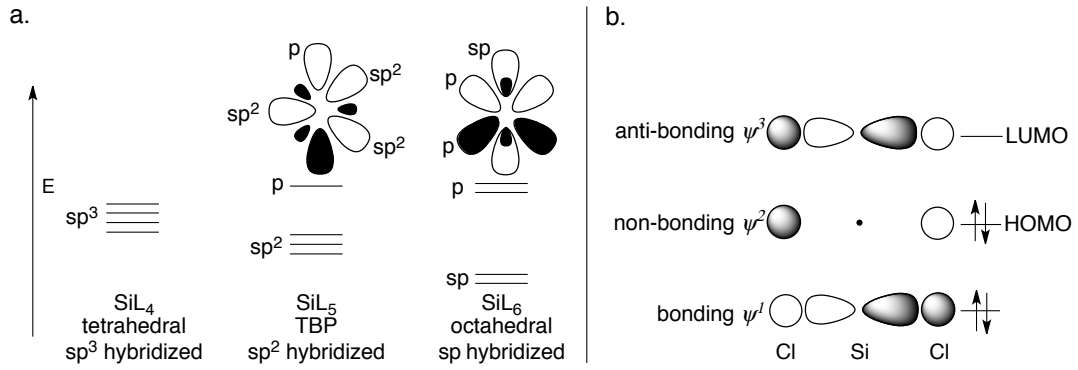


Figure 2. (a) Hybridization scheme for hypervalent penta- and hexa-valent silicon complexes. (b) Molecular orbital diagram for 3-center-4-electron bonding.

The 3C-4E, hypervalent bonding is accomplished by mixing the available p-orbital of the silicon atom with the atomic orbitals from two other ligands (L). From the perspective of molecular orbital (MO) theory, combination of the three atomic orbitals results in the formation of three molecular orbitals: bonding (Ψ^1), non-bonding (Ψ^2) and anti-bonding (Ψ^3), as illustrated in Figure 2b. Filling in the four electrons required for bonding shows that, in the HOMO the

electron density is localized at the periphery atoms with a node at silicon. This MO diagram provides a sound rationale for how the binding of a Lewis base can result in enhancement of both electrophilic and nucleophilic character at different atomic positions within the n-σ* adduct.

1.4.4 Support from X-ray Crystallographic Studies. The redistribution of electron density that occurs upon binding of a Lewis base to a Lewis acid results in observable changes in the bond lengths throughout the complex. This phenomenon has been thoroughly scrutinized by Guttmann for the Lewis acid-base complex resulting from the addition of tetrachloroethylene carbonate to antimony pentachloride (Figure 3).[13] Careful examination of the X-ray crystallographic data for the antimony complex, reveals that coordination of the Lewis base results in a lengthening of the Sb-Cl bonds. Importantly, Guttmann hypothesized that the observed changes in bond length were a manifestation of the electron density being distributed to the more electronegative periphery atoms.

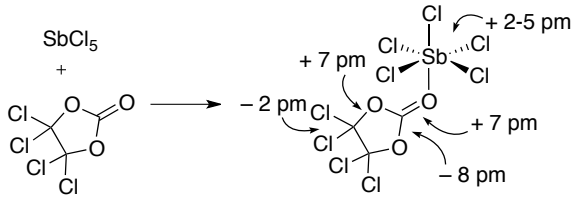
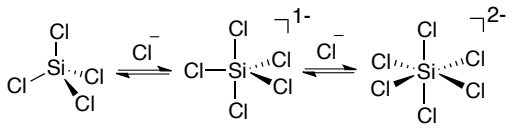


Figure 3. Observable bond length changes in $SbCl_5$-Lewis base adduct

1.4.5 Support from Computational Studies. X-ray crystallography provides an excellent tool for examining the structural changes that are induced upon Lewis base binding. Unfortunately, the diffraction patterns only give information about the absolute positions of the nuclei in the complex and not the actual fractional charges of electron density residing on the atom. To gain information about the perturbations to the electron density, which occur within Lewis acid-base complexes, requires computational methods. Gordon and co-workers have computationally determined the change in Mulliken charges that results upon formation of penta-

and hexa-coordinate silicates, from the addition of chloride anions to $SiCl_4$ (Figure 4).[14] The results agree with the hypervalent-bonding model as shown by the increase in partial positive charge (+0.101) at silicon upon coordination of a chloride ion. Within the ligand sphere of the silicon atom, the distribution of electron density at the axial chlorides was highest, which is also consistent with the highly polarized, electron-rich nature of 3C-4E bonds. Similar trends have been observed for other silicates; for example, the series SiF_4, SiF_5^{-1}, SiF_6^{-2} has respective Mulliken charges at silicon of +1.19, +1.14, +2.12.[15]



	$SiCl_4$	$SiCl_5^{-1}$	$SiCl_6^{-2}$
q (Si)	+ 0.178	+ 0.279	+ 0.539
q (Cl)	– 0.045	– 0.139_{eq}	– 0.423
		– 0.430_{ax}	

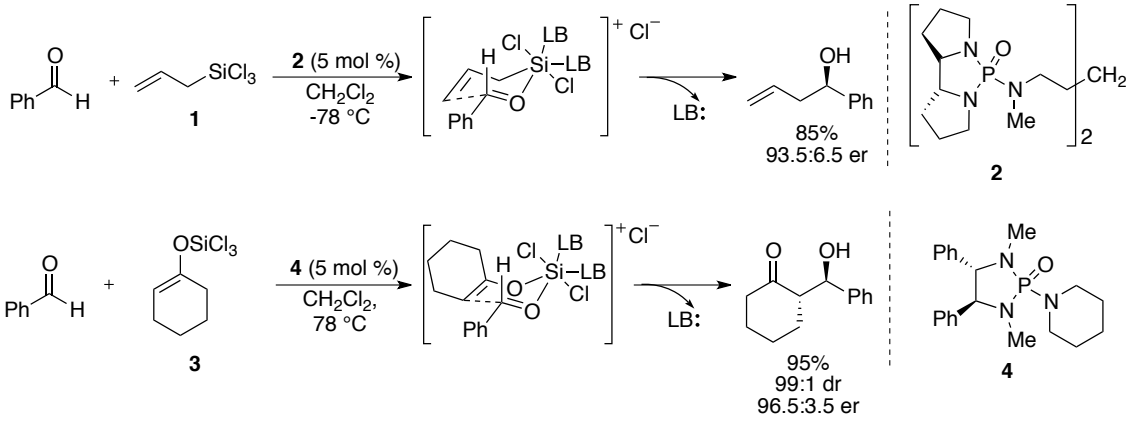
Figure 4. Mulliken charges for $SiCl_x$ series calculated at 6-311^{++}G(d,p) level.

1.5 Lewis Base Activation of Organosilicon Reagents in Synthesis. The capacity of silicon to expand its coordination sphere and undergo n-σ* activation with Lewis bases presents unique opportunities for developing catalytic processes. An enormous amount of flexibility is allowed in the types of reactions that are susceptible to this catalysis, by the ability of Lewis bases to enhance both the electrophilicity of the silicon center and the nucleophilicity of the periphery ligands. Researchers have utilized this dual activation of organosilicon compounds for the development of a diverse range of Lewis base-catalyzed transformations, including trifluoromethylation, cyanation, allylation and aldolization.[8,16] The Lewis bases used in these reactions are either anionic or neutral and are most commonly used for nucleophilic enhancement of the organosilane reagent.

1.5.1 Lewis Base Activation of Polyhalosilane Reagents in Synthesis. A class of silicon reagents that have monopolized the ability of Lewis bases to enhance both the

electrophilicity of the silicon and the nucleophilicity of the ligands are the polyhalosilanes. The presence of electronegative halogens in these compounds render polyhalosilanes more Lewis acidic than alkylsilanes, and hence, more susceptible to Lewis base coordination. Previous studies from these laboratories have shown that chiral phosphoramides are effective catalysts for enantioselective allylations and aldolizations of aldehydes using allyltrichlorosilanes (**1**),[17] and trichlorosilyl enolates (**3**),[18] respectively (Scheme 2). In these reactions, binding of the Lewis basic phosphoramides (**2** or **4**) to the trichlorosilicon Lewis acid leads to polarization of the periphery silicon ligands, and eventually, ionization of a chloride. The resulting highly reactive electrophilic silicon center binds the aldehyde and provides an organizational center for the reactive intermediates. The addition reaction of the activated nucleophile occurs through a closed, six-member transition structure, and gives the products in excellent yield and high enantioselectivity. Mechanistic studies have shown that both one- and two-phosphoramide catalyzed pathways can be operative, but that the highest selectivities result from a pathway involving activation by two-phosphoramides.[19]

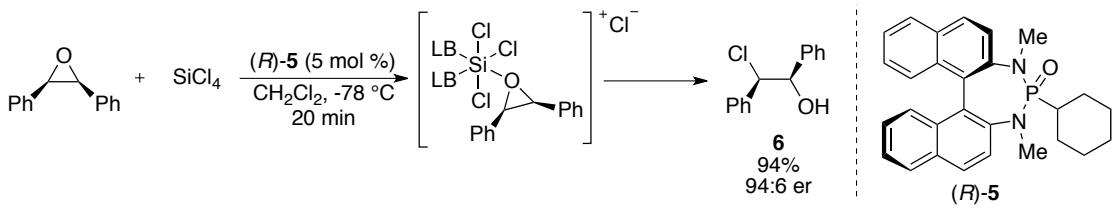
Scheme 2



1.5.2 Lewis Base Activation of Lewis Acids. Although Lewis base catalysis with allyltrichlorosilanes and trichlorosilylenolates allows for dual activation of both electrophilic and

nucleophilic character of these reagents, the major drawback to this method is the need to prepare, store and handle extremely hydrolytically sensitive reagents (*i.e*. trichlorosilanes). This shortfall led the Denmark group to explore the use of Lewis base-catalyzed, $SiCl_4$-mediated processes, in which the role of the nucleophile and silicon Lewis acid could be disconnected. The role of the Lewis base in this process would be to bind the weak Lewis acid $SiCl_4$ and, through ionization of chloride, yield a hyper-reactive Lewis base-trichlorosilyl complex. This activated Lewis acid could then bind a substrate and allow for the subsequent enantioselective addition of a nucleophile to occur. This initial hypothesis for the activation of $SiCl_4$ by Lewis bases was supported by earlier studies on the ring opening reaction of meso-epoxides with $SiCl_4$ (Scheme 3).[20] In this study, it was found that the combination of $SiCl_4$ and 5 mol % of a chiral Lewis base phosphoramide **5**, resulted in the chloride opening of *cis*-stilbene oxide in good yield and enantioselectivity. The proposed intermediate in this reaction was a chiral Lewis base activated trichlorosilyl cation, which could activate the epoxide and allow for enantiotopic group selection in the meso-epoxide. Importantly, control experiments showed that if the reaction was performed in the absence of Lewis base, less than 5% of the chlorohydrin product **6** was observed in the time frame of the catalytic reaction.

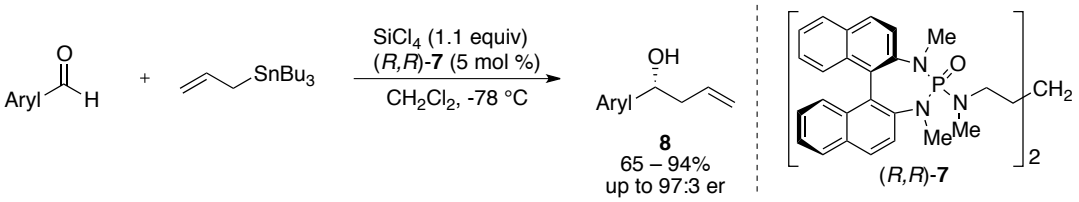
Scheme 3



The success of the meso-epoxide opening demonstrates the ability of Lewis bases to activate $SiCl_4$ and form chiral Lewis acids, exhibiting much higher reactivity than the nascent species. Tied to this overall process is the ionization of chloride, which could potentially

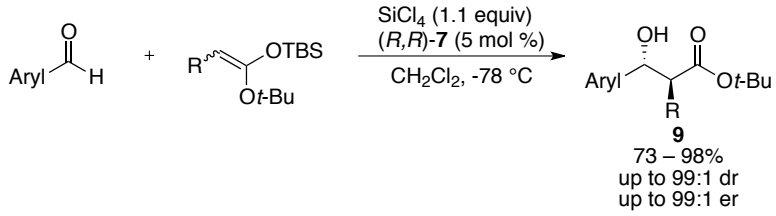
outcompete the addition of any externally added nucleophile. To further examine this catalyst system and the role of the ionized chloride, Denmark and Wynn studied the addition of allylstannanes to aldehydes in the presence of stoichiometric $SiCl_4$ and 5 mol % of chiral bis-phosphoramide (*R,R*)-**7** (Scheme 4).[21] For aromatic aldehydes, excellent yields and good enantioselectivities were obtained for the homoallyl product **8**, proving that external nucleophiles could outcompete the chloride anion.

Scheme 4



Following up on the promising results obtained with allyltributyltin, Denmark and co-workers reported the Mukaiyama aldol-type reactions of acetate- and propionate-derived silyl ketene acetals.[22] Under similar reaction conditions, the desired β-hydroxy esters **9** were obtained in high yields and good to excellent stereoselectivities (Scheme 5). Remarkably, the catalytic action of (*R,R*)-**7**/$SiCl_4$ was found to be a stereoconvergent *anti*-aldol process, as indicated by the high selectivities obtained from the addition of either *E* or *Z*-propionate derived-silyl ketene acetals.

Scheme 5



Detailed spectroscopic analysis of the intermediates and in situ rapid injection NMR kinetic rate studies have allowed for determination of the resting state of the catalyst and the rate equation for the overall process.[23] These studies have culminated in the proposal of a catalytic cycle for Lewis base-catalyzed, $SiCl_4$-mediated aldol reactions (Figure 5). The proposed catalytic cycle commences with the binding of the bis-phosphoramide Lewis base to the weak Lewis acid silicon tetrachloride. This complexation of the Lewis base leads to the formation of a dimeric resting state, as indicated by the observed ½ order rate dependence upon catalyst. The resting state may be in equilibrium with the active trichlorosilyl cation, or the aldehyde could break up the dimer, giving the aldehyde catalyst complex **10**. Enantioselective addition of the silyl ketene acetal to the activated aldehyde though an open transition structure produces oxocarbenium ion intermediate **11**. Irreversible desilylation of this reactive species by nucleophilic chloride and subsequent regeneration of the Lewis base catalyst delivers aldol product **12** as the trichlorosilyl ether. The β-hydroxy ketone products (**13**) are isolated in high yield and selectivity following aqueous workup with $NaHCO_3$ and KF. The aldol reaction shows attenuated addition rates for aliphatic aldehydes, typically requiring up to 24 h to go to full conversion. This reduced reactivity has been attributed to and verified by ^1H NMR studies to the formation of an α-chlorotrichlorosilylether (**14**). Finally, in the catalytic cycle each molecule of $SiCl_4$ that enters the reaction is incorporated into the aldol product, and the species that is turning over is the Lewis base. Therefore, these reactions can best be classified as Lewis base-catalyzed, $SiCl_4$-mediated reactions.

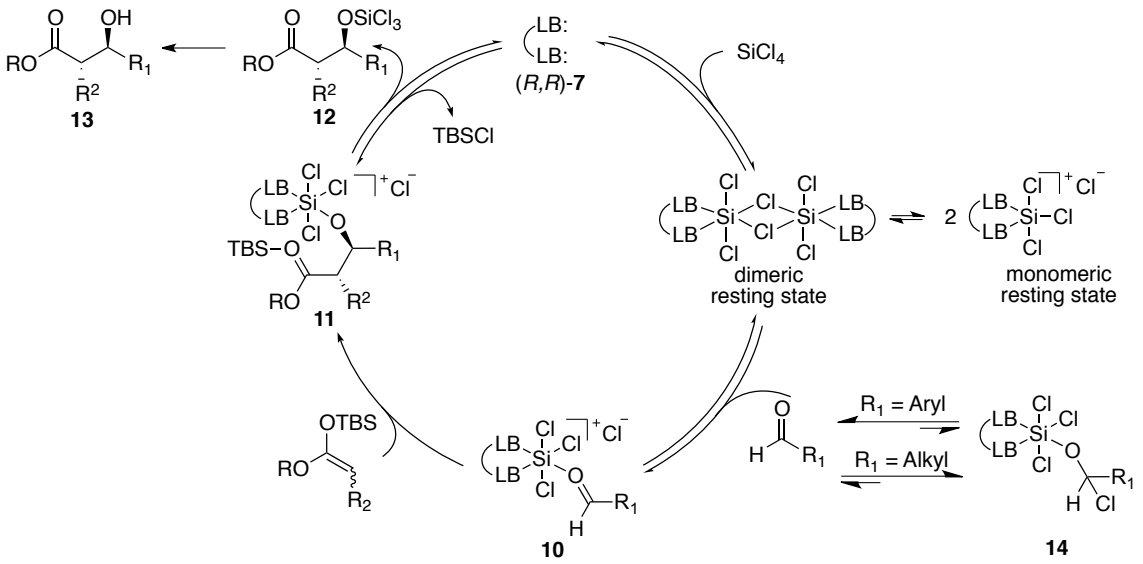
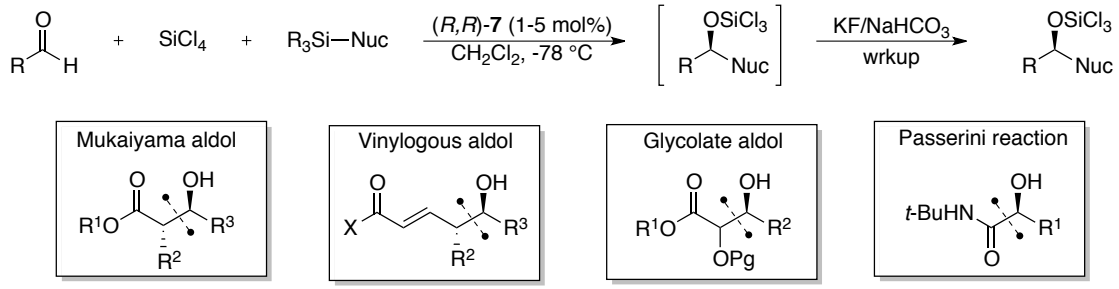


Figure 5. Proposed catalytic cycle for $SiCl_4$-mediated, Lewis base catalyzed aldol reactions.

The utility and generality of this catalyst system has been realized by the diversity of silylated nucleophiles that will participate in these Lewis base-catalyzed, enantioselective carbonyl addition reactions (Scheme 6). Thus far, catalytic enantioselective reactions of enol silanes derived from aldehydes,[24] ketones,[25] and esters[23b] have been developed for normal 1,3-aldol type relationships. The extension of this chemistry to highly γ-selective vinylogous aldol reactions has been accomplished with conjugated silyl ketene acetals,[26] and amides.[27] The selective preparation of glycolate aldol products containing either *syn* or *anti* stereogenic secondary diols has been achieved using variably protected glycolate silyl ketene acetals.[28] Finally, addition of isonitriles has allowed for enantioselective Passerini reactions, giving either α-hydroxy esters or amides depending on the reaction workup.[29] Overall the additions to aromatic aldehydes are characterized by high yields, good substrate scope, and excellent stereoselectivities. The addition to aliphatic aldehydes requires longer reaction times, and higher catalyst loadings; good results have been observed for the more reactive nucleophile classes such as silyl ketene acetals and amides.

Scheme 6



1.5.3 Current Challenges in Lewis Base Catalyzed Carbonyl Addition Reactions. Despite the widespread success observed in Lewis base-catalyzed, $SiCl_4$-mediated carbonyl addition reactions, some noteworthy challenges still remain. The formation of quaternary stereogenic centers in this catalyst system, and in general for any aldol process, presents a formidable task. This is mainly due to the difficulties in obtaining geometrically defined enolates, as well as overcoming the steric requirements associated with forming quaternary centers. A second, related difficulty is the synthesis of tetrasubstituted carbons containing a tertiary alcohol using glycolate-aldol type reactions. Finally, the ability to achieve inverse polarity relationships, such as cross-benzoin or homo-aldol products, in high selectivity is a long-standing problem in synthetic organic methods development. The goal of this thesis research is to address these challenges by using Lewis base-catalyzed additions of silyl ketene imines, which are introduced in the following chapter.

Chapter 2: Synthesis, Structure and Uses of Silyl Ketene Imines In Organic Synthesis

2.1 General Considerations

Silyl ketene imines (SKIs) are a class of silylated nucleophiles derived from the selective trapping of nitrile anions with electrophilic silylating reagents. SKIs belong to a broader class of compounds known as cumulenes, which are molecules processing at least two or more cumulative double bonds.[30] The characteristic feature of SKIs is the pair of orthogonal substituent planes, which impart an axis of chirality whenever R^1 and R^2 are dissimilar.

SKIs are more generally related to enoxysilane nucleophiles, which are derived from the selective *O*-silylation of enolates (Figure 6). Enoxysilanes have found extensive use as nucleophiles in catalytic, enantioselective reactions such as Mukaiyama-type carbonyl addition reactions.[31] From an elementary viewpoint, SKIs can simply be seen as the nitrile analogs of ester or amide derived enoxysilanes. However, the unique structure of SKIs offers significant advantages over enoxysilanes, especially in the realm of asymmetric quaternary carbon synthesis.

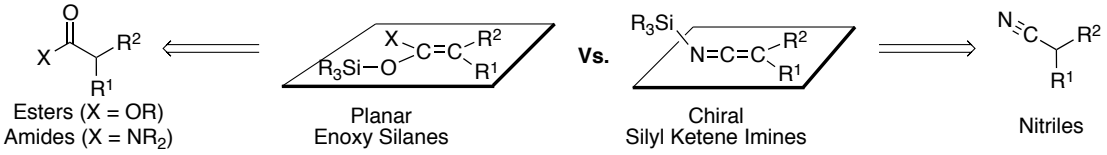


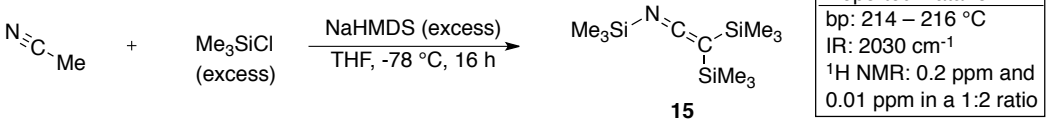
Figure 6. General comparison of enoxysilane and silyl ketene imine structures.

The following chapters of this thesis will focus on the implementation of SKIs in Lewis base-catalyzed carbonyl addition reactions. However, the goal of the current chapter is to provide an introduction to silyl ketene imines regarding their synthesis, structure and isolation, as well as some preliminary applications of these nucleophiles in synthesis.

2.2 Synthesis and Structure of Silyl Ketene Imines.

2.2.1 Initial Preparation and Characterization of Silyl Ketene Imines. The first reported synthesis, isolation and characterization of a silyl ketene imine was by Kruger and Rocher in 1963 (Scheme 7).[32] The authors were studying the reaction of acetonitrile with excess sodium hexamethyldisilazide (NaHMDS) and reported isolation of an ether-insoluble white solid. Subsequent reaction of the solid with excess trimethylsilyl chloride yielded a high boiling liquid in low yield and with spectroscopic data consistent with tris(trimethylsilyl)ketene imine **1**. The authors remarked on the surprising stability and isolation of this SKI and concluded that the white solid was a trianion of acetonitrile (Na_3CCN). West and Gornowicz, later repeated these studies and determined that the white solid was actually the monosodium salt of acetonitrile ($NaCH_2CN$).[33] The authors proposed that the tris(silyl) ketene imine **15** was formed by multiple deprotonations and silylations of $NaCH_2CN$, aided by the acidifying effect of silicon on the α-proton. Neither of the authors of these initial disclosures reported any applications or further study of this new compound.

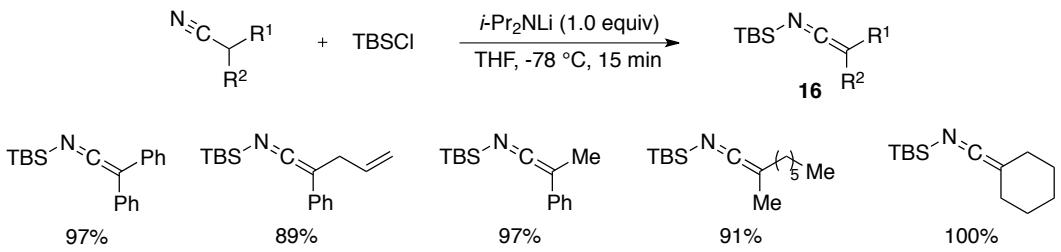
Scheme 7



2.2.2 Factors Influencing *N*- Versus *C*-Silylation in the Preparation of Silyl Ketene Imines. Watt reported the first synthetically useful procedures for preparing silyl ketene imines as well as determining some of the factors that influence *N*- versus *C*-silylation.[34] The metalation of nitriles with strong amide bases gives ambident anions, which can undergo reactions with electrophiles at either carbon or nitrogen. Previous studies from Watt had shown that, with

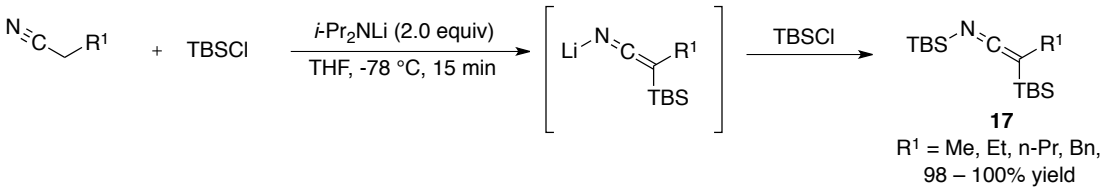
carbon-based electrophiles, nitrile anions reacted with high selectivity to give *C*-alkylation products.[34-35] Following on this report, Watt examined the product distributions for reactions of various nitrile anions with trialkylsilyl chlorides. Interestingly, the opposite site selectivity was observed in these reactions, yielding selectively *N*-silyl ketenes (**16**) in excellent yields (Scheme 8).

Scheme 8



The study also demonstrated the importance of disubstitution for obtaining high selectivities and yields of the silyl ketene imines. Mono-substituted nitriles yielded SKIs only after initial *in-situ* α-C-silylation (Scheme 9), and conditions had to be re-optimized to favor this isomer (2.0 eqiuv of LDA and 2.0 equiv of TBSCl). The author noted that with mono-substituted nitriles, reducing the amount of LDA and TBSCl did not result in isolation of mono-substituted silyl ketene imine, but rather just reduced yields of α-silyl ketene imines **17**.

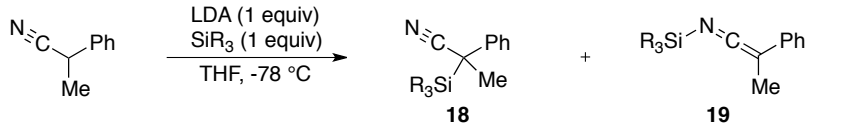
Scheme 9



Watt[35] and others[36] have also studied how the size of the trialkylsilyl chloride influences the site of silylation of nitrile anions derived from disubstituted nitriles. For example, lithiation

of 2-phenylpropionitrile with LDA at low temperature, followed by trapping of the anion with the less sterically encumbered trimethylsilyl chloride affords the *C*-silyl nitrile **18** in excellent yield and selectivity (Scheme 10). This is in stark contrast to the results obtained with the sterically bulky TBSCl, which gives exclusively the *N*-silyl ketene imine **19** in high yield. In some cases, silyl ketene imines are known to isomerize to the *C*-silylated isomers upon heating. These observations are consistent with the *C*-silyl isomer being the more thermodynamically favored isomer. Sterically hindered silylating agents likely favor reaction at nitrogen, because the C=N subunit in the nitrile anion is relatively unencumbered.

Scheme 10

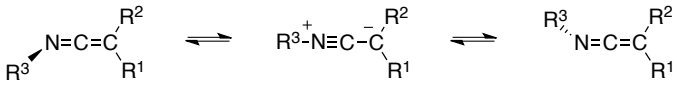


2.2.3 Stereoisomerization of Silyl Ketene Imines. The perpendicular substituent planes present in SKIs impart an axis of chirality whenever the alkyl substituents are dissimilar. The configurational stability of the SKIs plays an important role in developing catalytic, enantioselective processes, because each enantiomer could react at different rates in the catalyzed pathway. To study the racemization of SKIs would require a spectroscopic tool that could observe two distinct diastereotopic signals from the chiral compound at a particular temperature. The energy required for racemization could then be calculated by monitoring the temperature at which the two signals coalesce. This is typically done using variable temperature ^{1}HNMR; unfortunately, silyl ketene imines do not exhibit signals for diastereotopic protons even at temperatures as low as -78 °C, making determination of the configurational stability extremely

difficult. However, related studies on the configurational stability of *N*-alkyl ketene imines have been performed and can be used for comparison.

Jochims and co-workers have studied the stereoisomerization of both *N*-alkyl and *N*-aryl ketene imines by observing the coalescence temperature of diastereotopic methyl groups or benzylic protons in the ketene imine.[37] The results demonstrate that both *N*-aryl and *N*-alkyl ketene imines racemize quickly in solution at room temperature with experimentally determined energy barriers ranging from 30 – 60 kJ/mol. The computational studies also reported by Jochims and co-workers suggest a mechanism that involves intermediate **20**, containing a linear C-C≡N-R^+ fragment (Scheme 11). A similar mechanism for topomerization of imines has been suggested, with experimentally determined values in the range of 57 – 64 kJ/mol.[38]

Scheme 11



20

N-Alkyl ketene imines are typically on the higher end of the racemization barriers, and the authors have noted that, in general, the energies are lowered by electron attracting substituents at either *N* or *C*. Furthermore, *N*-aryl ketene imines give a linear Hammett correlation with σ^- constants for meta- and para-substituted aromatic rings. For these reasons, *N*-silyl ketene imines likely have inversion barriers closer to those observed for *N*-alkyl ketene imines in the range of 40 – 60 kJ/mol.

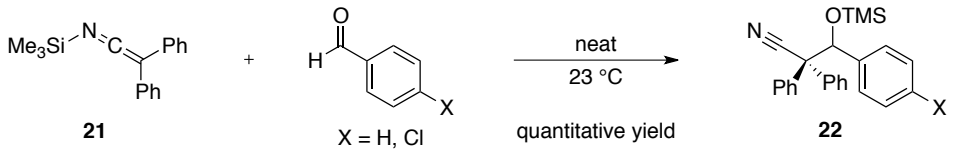
2.3 Silyl Ketene Imines as Nucleophiles in Uncatalyzed, Achiral Reactions. Despite the early reports on the synthesis and characterization of SKIs by Kruger in 1963, and the later improvements by Watt, very few examples on the uses of SKIs as nucleophiles have appeared.

Surprisingly, the related enoxysilane nucleophiles derived from ketones, esters and amides were concurrently being developed for uses in a variety of synthetic transformations.

2.3.1 Aldol and Michael Reactions of Silyl Ketene Imines. One of the important early studies on the chemistry of SKI is that of Frainnet and co-workers, who studied carbonyl addition reactions.[39] The authors established that SKIs were competent carbon nucleophiles for the addition reactions to a variety of different carbonyl electrophiles, including aromatic aldehydes, α,β-unsaturated aldehydes, ketones and acid halides.

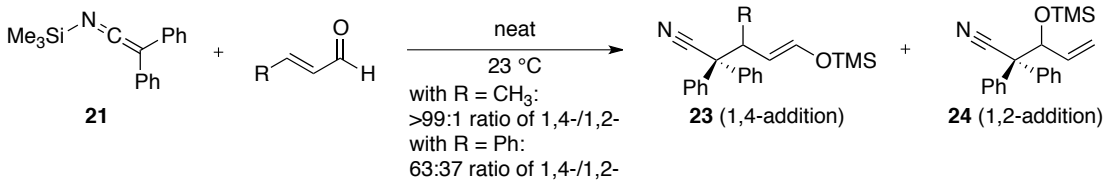
In their first report, the authors demonstrated that, when *N*-trimethylsilyldiphenylketeneimine (**21**) was added neat to benzaldehyde, an exothermic reaction ensued, and the corresponding β-silyloxy nitrile product **22** could be isolated in high yield (Scheme 12).[39] An electron-poor aromatic aldehyde, 4-chlorobenzaldhyde, also underwent addition in high yield, but no further studies on the scope of this reaction, with respect to nucleophile or other aromatic aldehydes, were reported.

Scheme 12



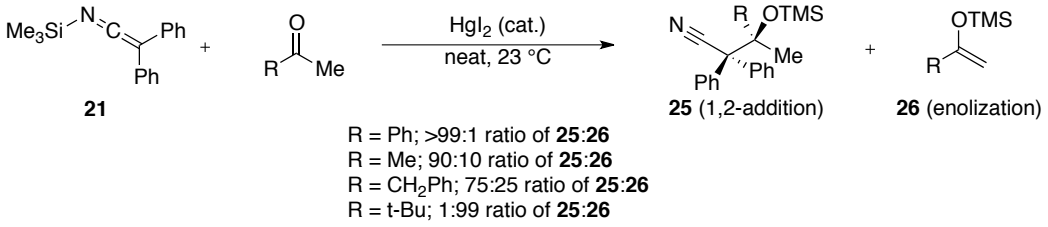
Interestingly, Frainnet and co-workers observed a competitive 1,4-additon pathway when olefinic aldehydes were examined under identical reaction conditions (Scheme 13).[39] For the addition of SKI **21** to cinnamaldehyde, a 63:37 ratio of 1,4- to 1,2-addition products (**23** and **24**, respectively) was observed. However, when crotonaldehyde was examined, the addition proceeded exclusively through the 1,4-pathway giving an aldehyde product in high yield following protonation of the trimethylsilyl enol ether.

Scheme 13



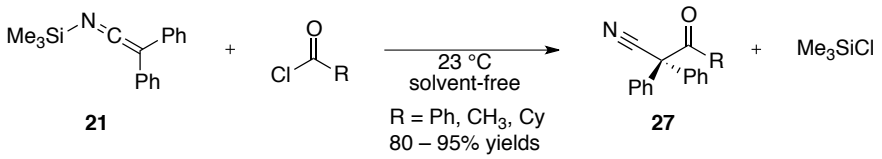
The authors next examined the addition of SKI **21** to a variety of ketones. Unlike the reactions with aldehydes, which proceeded in the absence of any promoters, ketones required sub-stoichiometric amounts of HgI_2 to undergo the reaction. Additionally, enolization of the ketone to yield trimethylsilyl enol ether **26** was found to be a competitive process for many of the ketones studied, limiting the overall scope of this process (Scheme 14).

Scheme 14



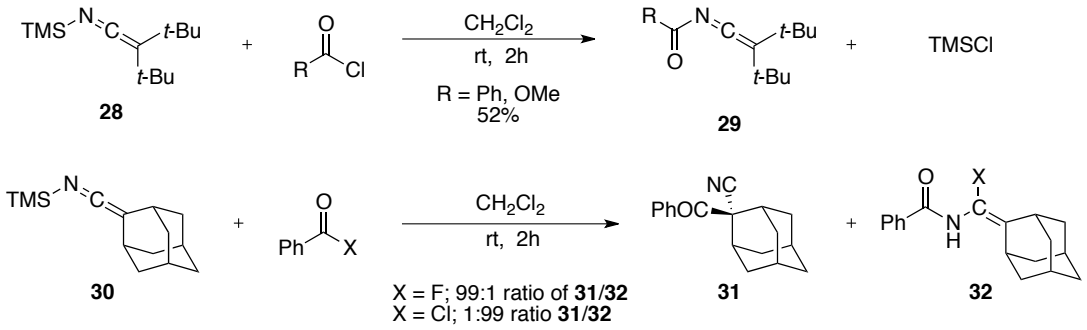
2.3.2 Acylation Reactions of Silyl Ketene Imines. A subsequent publication by Frainnet and co-workers briefly examined the addition of SKI **21** to a number of different acid chlorides.[40] The reactions were run in the absence of promoter or solvent and proceeded in high yields to give β-keto nitriles **27** (Scheme 15).

Scheme 15



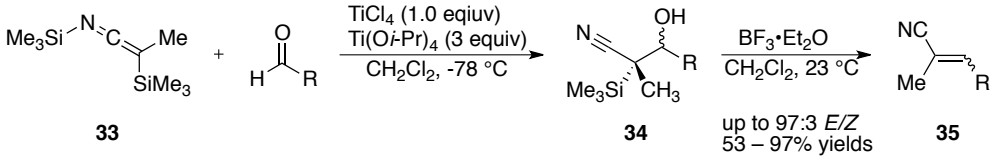
Meier and Wurthwein followed up on the initial work of Frainnet with a more detailed investigation on the acylation of SKIs .[41] Remarkably, the authors observed competitive *N*-acylation in cases where extremely hindered SKIs were employed. For example, reaction of di-*t*-butyl silyl ketene imine **28** with benzoyl chloride yields selectively *N*-benzoyl ketene imine **29** in 52% yield (Scheme 16). Slightly less sterically encumbered ketene imines gave mixture of *C*- and *N*-acylation depending on the type of acylating reagent employed. The reaction of adamantyl ketene imine **30** proceeds with high selectivity to give the *C*-acylation product **31** with benzoyl fluoride; however, when the reaction is repeated with benzoyl chloride the *N*-acylation product **32** is isolated after protonolysis of the trimethylsilyl group.

Scheme 16



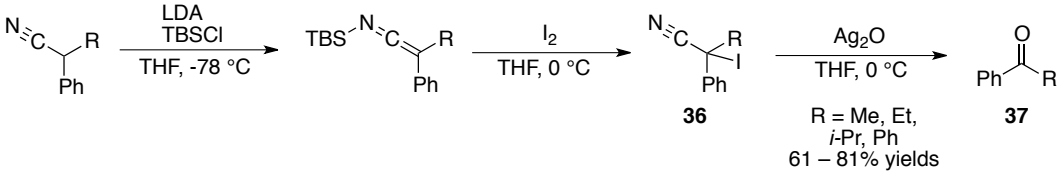
2.3.3 Aldol-type Addition Followed by Peterson Elimination. Matsuda and co-workers have examined the addition of *bis*-trimethylsilyl ketene imine **33** to aldehydes in the presence of various Lewis acids.[42] The direct aldolization product of this reaction is β-silylcarbinol **34**, which undergoes Peterson-type elimination in the presence of boron trifluoride yielding (*E*)-2-alkenenitrile **35** in moderate to good yields and high selectivity (Scheme 17). Importantly, the authors were able to identify a mixed titanium Lewis acid catalyst that allowed for the isolation of the aldol products in excellent *anti/syn* diastereoselectivity. Ketones also underwent the addition/elimination reaction, but with reduced yields and selectivity.

Scheme 17



2.3.4 Oxidative Decyanation of Silyl Ketene Imines. Watt and co-workers envisioned a procedure that would allow for conversion of secondary nitriles to ketones.[35,43] This process would render alkyl nitriles as acyl anion equivalents, greatly extending the utility of the nitrile functional group. To achieve umpolung reactivity of a nitrile, secondary nitriles were first converted to silyl ketene imines and then iodinated at the α-carbon with iodine in THF (Scheme 18). The α-iodo nitriles (**36**) underwent decyanation in the presence of silver oxide to give the desired ketone products (**37**) in moderate to good overall yields.

Scheme 18

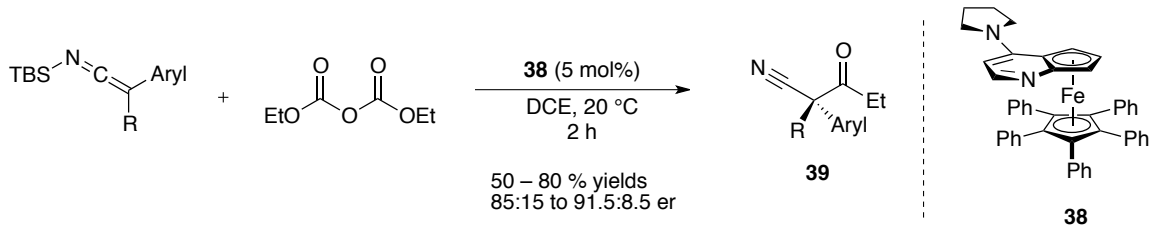


2.4 Enantioselective Reactions of Silyl Ketene Imines.

2.4.1 Catalytic, Enantioselective Acylations of Silyl Ketene Imines. In spite of the fact that SKIs are demonstrably competent nucleophiles in the additions to carbonyl electrophiles, it was not until 2005 that the first catalytic, asymmetric reaction employing a silyl ketene imine was reported by Fu and co-workers.[44] The authors showed that a planar chiral PPY (4-(pyrrolidino)pyridine) derivative **38** catalyzed the acylation of a number of different SKIs producing enantioenriched β-keto nitrile products **39** in good yields and moderate to good enantioselectivities (Scheme 19). The reaction showed excellent substrate scope for aryl

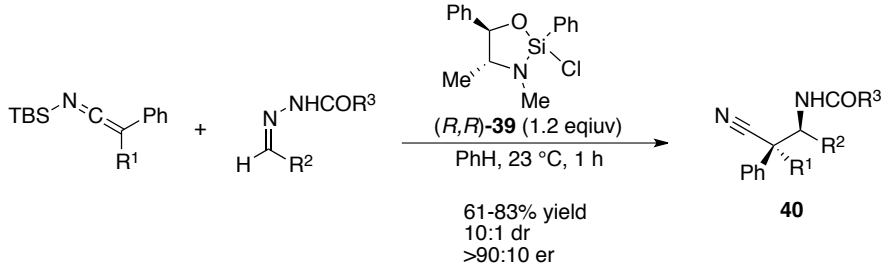
substituted silyl ketene imines reacting with propionic anhydride. SKIs derived from dialkyl nitriles did not undergo acylation under the optimized reaction conditions.

Scheme 19



2.4.2 Enantioselective Mannich Reactions of Silyl Ketene Imines to Acyl Hydrazones. Subsequent to the work reported in this thesis, Leighton and co-workers reported on the addition of silyl ketene imines to acyl hydrazones catalyzed by stoichiometric quantities of the chiral silicon Lewis acid (*R,R*)-**39**.[45] The Mannich reaction allows access to β-amino nitriles (**40**) containing a quaternary stereogenic center in moderate to good yields and with good diastereo- and enantioselectivities (Scheme 20). Importantly, the authors showed that disubstituted silyl ketene acetals were unreactive under the reaction conditions, demonstrating the enhanced reactivity of silyl ketene imines for the synthesis of quaternary stereogenic centers.

Scheme 20



Chapter 3: Lewis Base Catalyzed Aldol Addition Reactions of Silyl Ketene Imines for the Synthesis of Quaternary Stereogenic Centers

3.1 Introduction

The aldol reaction is one of the most well studied, powerful and reliable tools a synthetic chemist has for the stereoselective construction of carbon-carbon bonds. In the classic reaction an aldehyde or ketone is rendered nucleophilic at the α-carbon by pretreatment with a Brønsted or Lewis base. This activated species then undergoes addition to the π* orbital of a second carbonyl compound giving rise to a β-hydroxy carbonyl product. A stereochemical analysis of this process reveals that when the reacting partners are both prochiral substrates, four possible stereoisomers can form (Figure 7). Focusing on the facial addition to the aldehyde shows that the enantiomeric pairs in the tetrad arise from addition of the nucleophile to either the *pro-R* or *pro-S* face of the aldehyde. The *syn/anti* diastereomers would then result from addition of one of the two-prochiral faces of the nucleophile to the aldehyde. Indeed, the primary focus over the past 30 years of research in aldol methodology has been on the development of catalytic, enantioselective methods for selectively obtaining single stereoisomers from this tetrad of compounds. Largely these challenges have been met by very inspired and elegant solutions and the aldol reaction has provided a useful testing ground for the development of modern asymmetric catalysis.[46] Despite these recent successes a few key challenges for the aldol reaction still remain unsolved problems, for example the synthesis of aldol adducts containing quaternary stereogenic carbon centers.

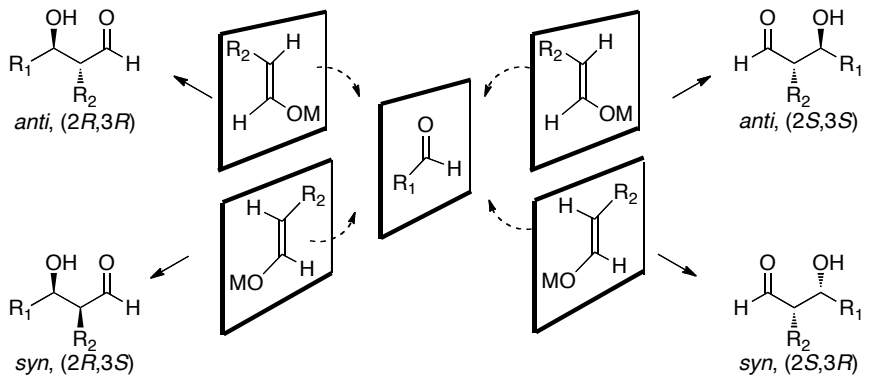


Figure 7. Stereochemical tetrad resulting from the combination of two prochiral substrates.

The development of catalytic, enantioselective methods for the construction of quaternary stereogenic centers represents an ongoing challenge to organic chemists.[47] The difficulty in forming these centers arises from the high degree of steric repulsion that is encountered in the transition state during the key C-C bond-forming event. Furthermore, achieving high levels of enantiotopic face selectivity is difficult because of the relatively similar steric environments presented by the non-hydrogen substituents. Although a number of different catalytic, enantioselective reactions have been reported, very few exhibit generality over a wide range of carbon architectures. Meanwhile, the need for more general methods is underscored by a growing number of biologically active natural products and pharmaceutical targets that possess quaternary stereogenic carbon atoms.

The aldol addition of α,α–disubstituted enolates to aldehydes provides a potential method for generating quaternary centers and, given the edifice of work on catalytic, enantioselective aldol-type reactions, this strategy seems logical. However, this approach is limited by the need for and inability to prepare geometrically defined α,α–disubstituted enolate or enolate equivalents. Therefore, to successfully utilize the aldol reaction for the asymmetric

synthesis of quaternary centers, one must either address this deficiency or develop other nucleophile classes.

3.2 Background

3.2.1 Stereoselective Synthesis of *E*- and *Z*-Substituted Enolates. The ability to selectively control enolate geometry is paramount to the success of achieving stereocontrol in the aldol reaction. The additions proceed through either chairlike (Zimmerman-Traxler)[48] or open transition structures depending on the nature of the enolate and the reaction conditions employed (Figure 8). In both cases, the transition structures are well ordered and insufficient stereocontrol in the enolate geometry can be directly reflected by poor *anti/syn* diastereoselectivity in the product. For this reason, much work has been dedicated to developing reliable and robust methods for achieving highly selective enolizations. Pioneering studies by Ireland and co-workers showed that for monosubstituted ketones and esters, the *E/Z* selectivity can be dramatically influenced by the choice of base, temperature, solvent and additives such as HMPA.[4d] Subsequently, these observations led to the development of protocols for achieving either *E* or *Z*-monosubstituted enolates by judicious choice of reaction conditions.[49] Despite this important body of work very few methods have been realized for achieving control with disubstituted enolates.[50]

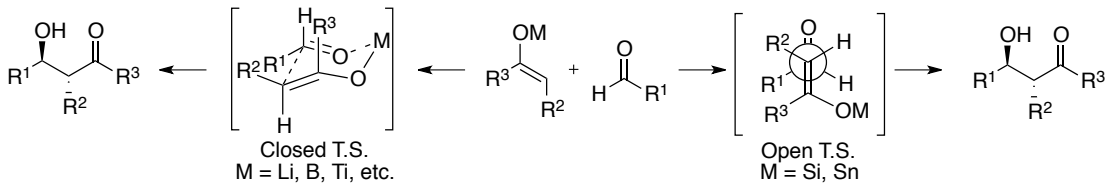
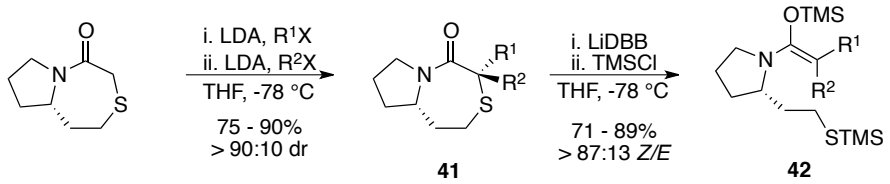


Figure 8. Limiting transition structures for aldol addition reactions with various enolates

3.2.2 Stereoselective Synthesis of Disubstituted Enolates and Their Application in Diastereoselective Aldol Reactions. Gleason and Manthorpe reported an innovative method for

the synthesis of both *E*- and *Z*-disubstituted amide enolates by the reduction of bicyclic thioglycolate lactams.[51] The design relies on the rigidity present in the bicyclic lactams, such that the sulfur atom is constrained to reside on only one face of the carbonyl plane. Upon two-electron reduction of the disubstituted thioglycolate lactams **41** with lithium di-*tert*-butylbiphenylide (LiDBB), the carbon-sulfur bond is cleaved and an enolate dianion is formed. Trapping of this intermediate with two equivalents of trimethylsilyl chloride (TMSCl) gave the silyl ketene aminals **42** in good yield and high diastereoselectivity (Scheme 21). Importantly, either *E*- or *Z*-enolates can be made using this method by simply changing the order in which the R-groups are introduced onto the thioglycolate lactam.

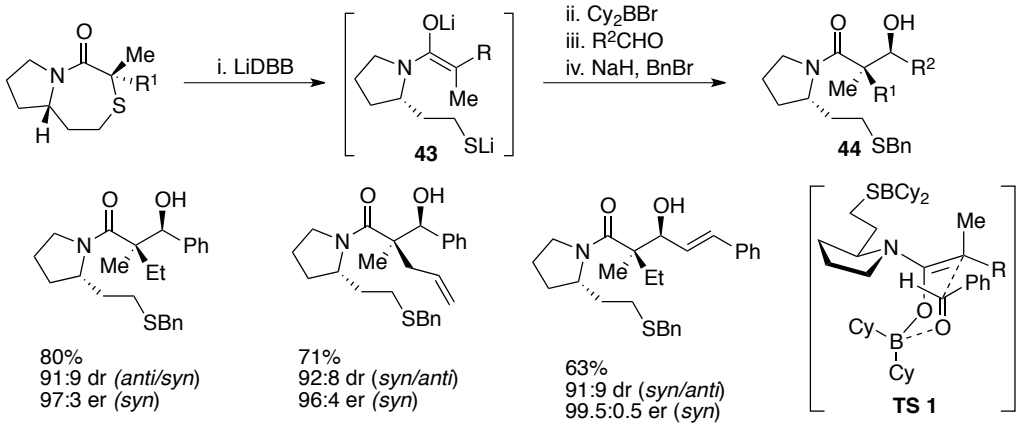
Scheme 21



With the ability to selectively access fully substituted amide enolates, Gleason was next able to extend this method toward a diastereoselective aldol reaction for the synthesis of quaternary stereogenic centers.[52] The success of this reaction relies on the ability to transmetalate lithium enolate **43**, obtained directly from the reduction with LiDBB, to a boron enolate using dicylcohexylboron bromide. The *in-situ* formed boron enolate then undergoes diastereoselective *syn* aldol additions with aromatic and olefinic aldehydes in good yield and excellent stereoselectivities. The absolute and relative configuration of the aldol product (**44**) was established by X-ray crystallographic analysis on one of the parent amides. The authors propose a closed transition structure that minimizes steric interactions between the pyrrolidine ring side-chain and the enolate (Scheme 22, TS 1). In extension of this early work, Gleason and co-

workers have also reported an enantioselective Mannich-type addition with benzenesulfonyl imines.[53]

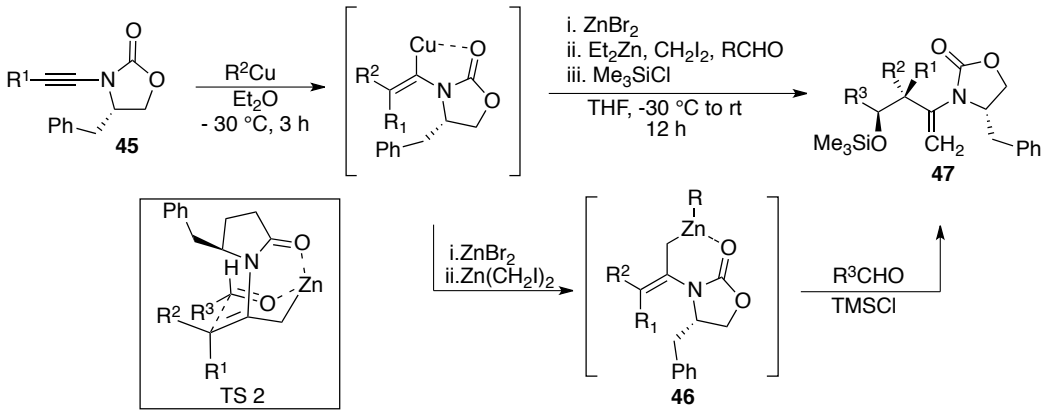
Scheme 22



Traditionally methods for enolate formation have relied on the deprotonation of preexisting carbon skeletons. Recently, Marek and co-workers have challenged this paradigm and developed an alternative strategy for the synthesis of disubstituted enolates that involves the regio and stereoselective creation of three new carbon-carbon bonds in a single vessel.[54] The synthetic route begins with the suprafacial carbometalation of an oxazolidinone modified ynamide **45** followed by homologation of the vinylcopper species with the Simmons-Smith-Furukawa carbenoid ($Zn(CH_2I)_2$). Finally, the allylzinc reagent **46** can undergo nucleophilic additions to a range of different aldehydes giving enamine products (**47**), after trapping with TMSCl. With a chirally modified oxazolidinone the enamide products are isolated in good yields and excellent stereoselectivities (Scheme 23). The absolute and relative configuration of the products is established by X-ray crystallographic analysis after derivatization of the enamine product. The observed configuration is consistent with a chair-like transition structure in which the benzyl group of the oxazolidinone shields one face of the allylzinc species and also forces the R-group

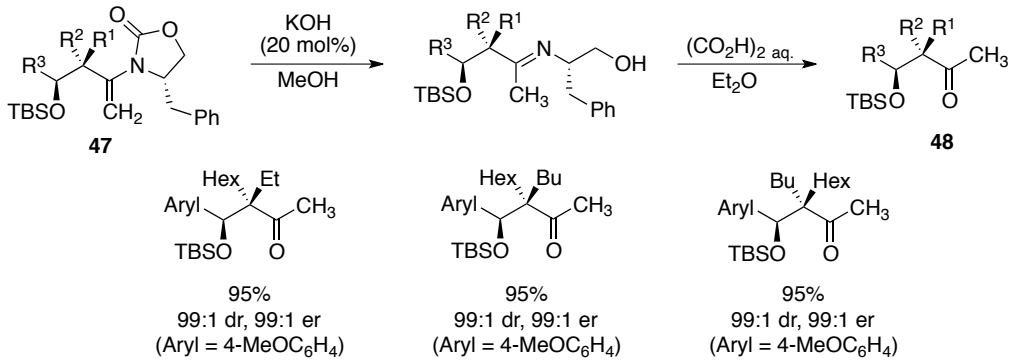
of the aldehyde to occupy a pseudo equatorial position in the chair (Scheme 23, TS 2). These interactions are further rigidified by coordination of the oxazolidinone oxygen to zinc.

Scheme 23



Although the key nucleophilic species does resemble an enamine, it is unlikely that much overlap exists between the amide nitrogen and the π-system. For this reason, the reaction is more correctly viewed as an allylation rather then an aldol addition. However, the authors also demonstrate that aldol-type products can be revealed by a two-step process that involves: (1) basic hydrolysis of the enamide to imine **47**, followed by (2) acidic hydrolysis to ketone **48** (Scheme 24). The two-step process allows access to β-hydroxy ketone products containing an α-stereogenic quaternary center in excellent yield and with high diastereo- and enantioselectivities. This method has also been extended to the addition of imines allowing for asymmetric synthesis of β-amino carbonyl compounds in good yields and enantioselectivities.

Scheme 24

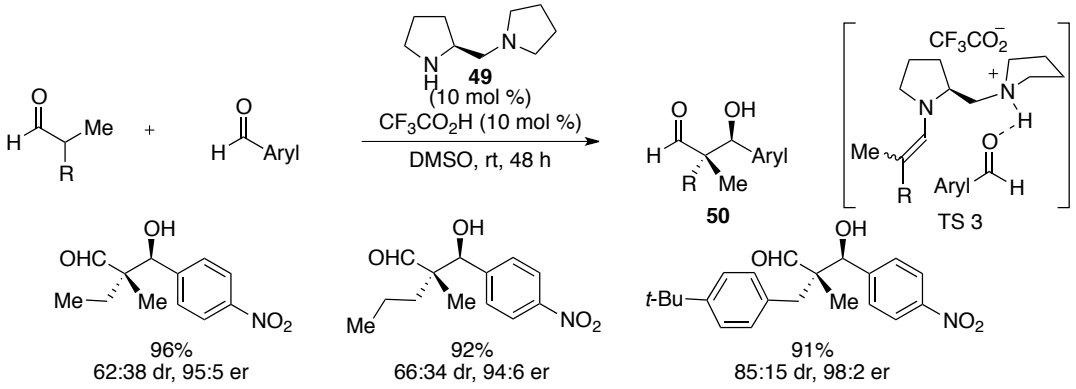


3.2.3 Catalytic, Enantioselective Aldol Reactions for the Synthesis of Quaternary Stereogenic Centers. Although high enantioselectivities for the aldol addition could be achieved with the methods discussed above, both relied on the use of a chiral auxiliary as the stereocontrolling unit. Ultimately the reliance on chiral auxiliaries limits the overall utility of these strategies, and provides an opportunity for chemists to develop more practical methods based on the principles of asymmetric catalysis. The next section will examine two initial investigations on catalytic, enantioselective aldol reactions for setting quaternary carbon centers. Each example employs a very distinct mode of catalysis, the first being based on pyrrole-type Lewis base catalysts, and the second involving organotransition metal chemistry. However, both examples can be classified as direct aldol additions, in which a separate pre-activation step of the carbonyl nucleophile is avoided. This evades the issues of having to prepare geometrically defined α,α-disubstituted enolates, but places an additional element of stereocontrol on the catalyst.

An amine-catalyzed, direct aldol addition of α,α-dialkylaldehydes donors with aromatic aldehydes acceptors was identified using a high-throughput florescence-based screening method, by Barbas and co-workers.[55] The authors screened various chiral amines and acid co-catalysts and found that with 10 mol % each of chiral diamine **49** and trifluoroacetic acid, quaternary

carbon containing aldol products **50** could be obtained in good yield and enantioselectivity (Scheme 25). The products are isolated with poor diastereomeric ratios, suggesting that the amine catalyst is unable to discriminate between the two possible enamine intermediates. Furthermore, this method seems to be limited to electron poor aromatic aldehydes, as no other substrates were disclosed in the report. The *S* absolute configuration of the products is established by derivation to the Mosher ester and is consistent with an attack of the enamine to the *Re* face of the aromatic aldehyde. The authors propose a transition state in accord with previously reported L-proline catalyzed direct aldol additions (Scheme 25, TS3). Similar work has also been described by the Barbas group for the enantioselective Mannich reactions of protected α-imino ethyl glycolates, catalyzed by L-proline.[56]

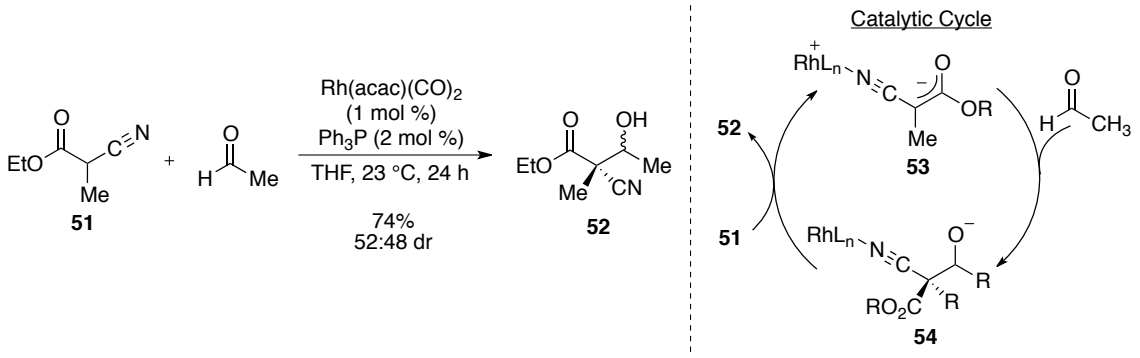
Scheme 25



A mechanistically distinct direct aldol reaction for the asymmetric synthesis of quaternary carbons using catalytic amounts of an organotransition metal complex was described by Ito and co-workers.[57] Preliminary studies showed that the aldol addition between ethyl 2-cyanopropionate (**51**) and acetaldehyde could be catalyzed by sub-stoichiometric amounts of an *in-situ* generated rhodium complex, to give the corresponding α-cyano-β-hydroxycarboxylates **52** in good yield and low diastereoselectivity (Scheme 26). The key intermediate in the proposed

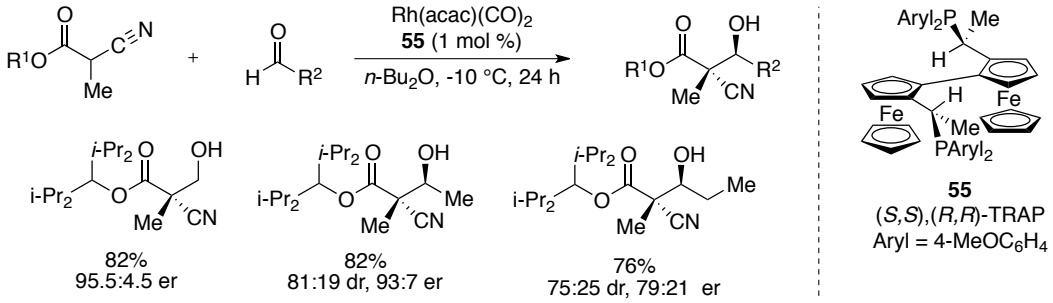
catalytic cycle is a zwitterionic rhodium enolate (**53**), which results from deprotonation of the α-cyanoester by the acetylacetonate anionic ligand on rhodium. This rhodium enolate can then react with an aldehyde to give the rhodium bound aldolate intermediate **54**. Turnover of the rhodium enolate is accomplished by deprotonation of another α-cyanoester by the aldolate intermediate and release of the alcohol product.

Scheme 26



In the same communication the authors report a catalytic, enantioselective aldol reaction based on this catalytic cycle by evaluating various chiral phosphine ligands. The highest levels of enantioselectivity are achieved with a *trans*-chelating biferrocene TRAP ligand **55** and a bulky diisopropyl methyl substituted ester group (Scheme 27). Under these reaction conditions nitrile products containing a α-stereogenic quaternary centers could be prepared in good yield and with moderate to good diastereo- and enantioselectivities. Unfortunately, the scope of this reaction is limited to unhindered aliphatic aldehydes; the authors noted that when aromatic aldehydes are tested, low conversions are observed and purification of the products is complicated by their thermodynamic instability toward retro-aldol reactions.

Scheme 27

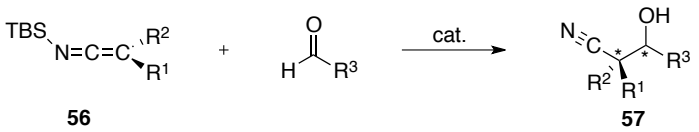


Despite the promising initial results reported by the research groups of Barbas and Ito on catalytic, enantioselective aldol reactions for synthesizing quaternary stereogenic carbons, the generality of these systems remains limited. An analysis of the results from the previous researchers reveals two central challenges that continue to impede the development of this reaction: (1) controlling the enolate geometry of α,α-disubstituted enolates, and (2) achieving high enough reactivity in the enolate to overcome the intrinsic steric repulsions encountered in the formation of quaternary carbons. The development of a successful method for the synthesis of quaternary carbons using the aldol addition must address these two challenges.

3.3 Research Objectives

Silyl ketene imines (**56**) are a class of α,α-disubstituted nucleophiles that avoid the issues associated with enolate geometry. The key structural feature in these species is the pair of orthogonal substituent planes, which imparts an axis of chirality when R^1 and R^2 are dissimilar. This unique geometry also places a significant portion of the steric bulk in a plane perpendicular to and distal from the nucleophilic carbon, which should alleviate some of the steric interactions encountered in the transition state for quaternary carbon formation. Aldol-type reactions of these nucleophiles would generate synthetically useful β-hydroxy nitriles (**57**) containing a α-quaternary stereogenic center (Scheme 28).

Scheme 28



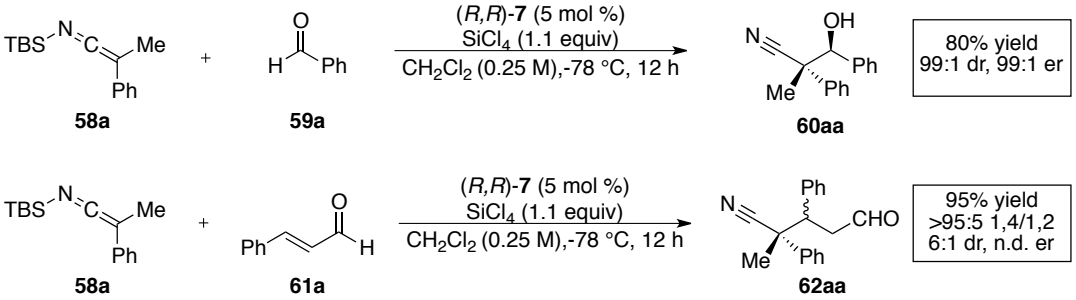
Although the preparation and characterization of silyl ketene imines (SKIs) are well known, only a few reports have documented their use as nucleophiles. Early work by Frainnett and co-workers establish that silyl ketene imines will undergo exothermic additions to aldehydes; however, subsequent studies on catalytic, enantioselective variants have not been realized. Previous studies in the Denmark laboratories on the Lewis base catalyzed, silicon tetrachloride mediated additions of silyl ketene acetals and ketone derived silyl enol ethers have attested to the sensitivity of this catalyst system to minor changes in nucleophile structure. This suggests that the asymmetric environment provided by this catalyst system would be well suited for discriminating the two carbon substituents of a silyl ketene imine. Despite these promising attributes very little is known about the stability and reactivity of silyl ketene imines toward the $SiCl_4$/phosphoramide catalyst system. Therefore the first goals of this project were to test the compatibility and background reactions of silyl ketene imines with simple aromatic aldehydes. The long-term goals of the study were to develop a general, and highly selective aldol reaction for setting quaternary stereogenic centers.

3.4 Results

3.4.1 Proof of Principle Studies on the Addition of Silyl Ketene Imines to Aromatic and Olefinic Aldehydes. The initial investigations, conducted by a Dr. John Heemstra, tested the compatibility and reactivity of silyl ketene imines under the standard reaction conditions previously developed for the additions of silyl ketene acetals to aldehydes. Reaction of silyl

ketene imine **58a** with both an aromatic and an olefinic aldehyde was examined (Scheme 29). The results were very promising showing not only that the silyl ketene imine was stable under the reaction conditions, but also that addition products were isolated in high yield for both aldehydes. Moreover, in the addition to benzaldehyde, the β-hydroxy nitrile product **60aa** was isolated with high diastereo- and enantioselectivity. The addition to cinnamaldehyde (**61a**) showed high 1,4 site-selectivity, which is in agreement with earlier experiments conducted by Frainnet and co-workers. However, the aldehyde product **62aa** was isolated with moderate diastereoselectivity and the enantioselectivity was not determined due to poor separation of the four stereoisomers by chiral stationary phase liquid chromatography. These initial results demonstrate that high diastereo- and enantioselectivity can be obtained in the addition of silyl ketene imine **58a** to benzaldehyde (**59a**), promoted by the bis-phosphoramide catalyst (*R,R*)-**7**. However, long reaction times were required because little was known about the reactivity of the silyl ketene imine. Encouraged by these proof of principle experiments further studies were undertaken to establish the rates of both the background and catalyzed reactions for the addition to aromatic aldehydes.

Scheme 29



3.4.2. In Situ IR Monitoring of the Background and Catalyzed Reaction Rates. The reaction rate was determined by monitoring the loss of aldehyde signal by in-situ IR kinetic

analysis for the addition of silyl ketene imine **58a** to 1-naphthaldehyde (**59b**) in the presence of 5 mol % (*R,R*)-**7** and 1.1 equiv of $SiCl_4$ at –65 °C. A slower-reacting, hindered aromatic aldehyde was chosen for this study to allow for the maximal resolution on the React-IR instrument, which has a pulsing limit of about 1 scan/10 sec. The plot of the aldehyde absorbance at 1700 cm^{-1} vs. reaction time for the catalyzed reaction (red line) is shown in Figure 9, and indicates that the reaction is complete within 3 minutes of SKI **58** addition. Furthermore, upon quenching the reaction into a saturated aqueous solution of $KF/NaHCO_3$, and following aqueous workup and purification by column chromatography, the nitrile **60ab** was isolated in 70% overall yield and in excellent diastereo- and enantioselectivity.

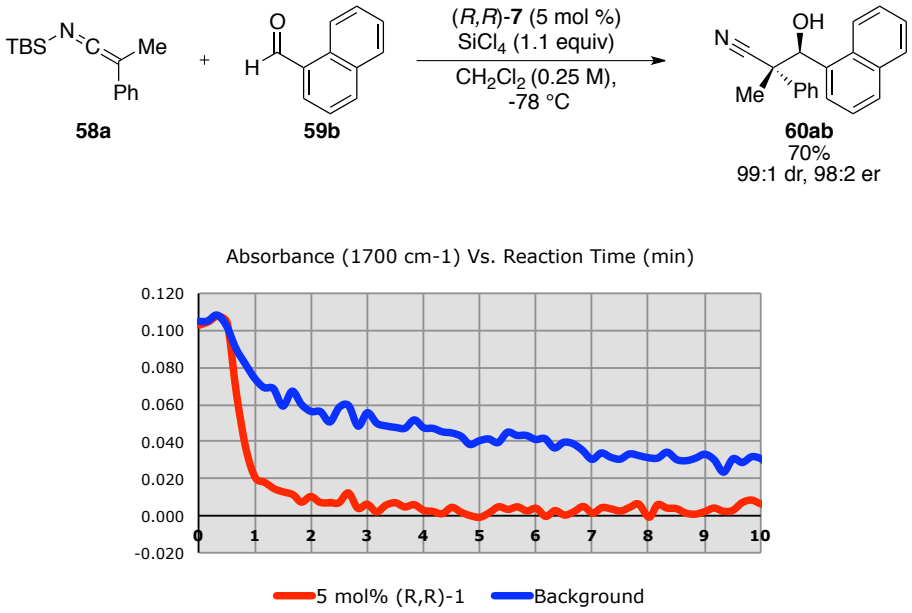


Figure 9. In situ IR kinetic data for catalyzed and background reactions of SKI **58a** addition to 1-naphthaldehyde

Having established the reaction rate for the catalyzed process, the achiral background reaction was next examined. To monitor this rate the same experimental procedure was followed, except the Lewis base catalyst (*R,R*)-**7** was not added. Surprisingly, a significant background

reaction was observed showing about 70% conversion of the aldehyde in only 10 minutes (blue line, Figure 9). The achiral reaction does not appear to interfere with the catalyzed process since the nitrile product is obtained with excellent asymmetric induction.

3.4.3 In Situ IR Rate Comparison of Silyl Ketene Imines and Silyl Ketene Acetals. The extremely facile reaction rates observed in both the catalyzed and uncatalyzed addition of SKI **58** to 1-naphthaldehyde was unexpected and prompted further study. To elucidate how the unique geometry of the SKI may be affecting the observed reaction rates, a comparative rate study between silyl ketene imines and analogously substituted ketene acetals was conducted. Silyl ketene acetals were chosen for this study because they are the ester analogs of ketene imines and have the same oxidation state at the α and β carbons. Structurally though, ketene acetals differ from ketene imines because they lack an orthogonal substituent plane, and a majority of the steric bulk resides in the same plane as the reacting carbon. Additionally, mono-substituted silyl ketene acetals have been extensively studied within this catalyst system and are known to be excellent substrates for the addition to aromatic aldehydes.

To test the rate difference, silyl ketene acetal **63** was prepared (by lithiation of methyl 2-phenylpropionate followed by trapping with TBSCl) and its reactivity was assayed by in situ IR kinetic analysis in the addition to 1-naphthaldehyde using the same experimental conditions as described for SKIs. The React-IR data for each nucleophile is plotted in Figure 10 and the observed difference in reaction rates is dramatic. Under identical reaction conditions, silyl ketene acetal **63** is nearly unreactive, whereas, silyl ketene imine **58a** goes to completion in less than 3 minutes.

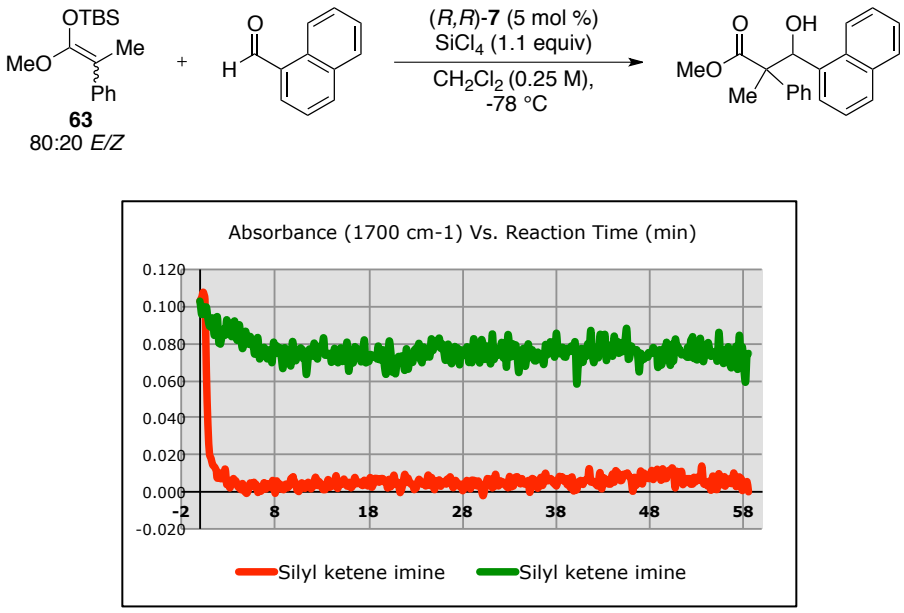
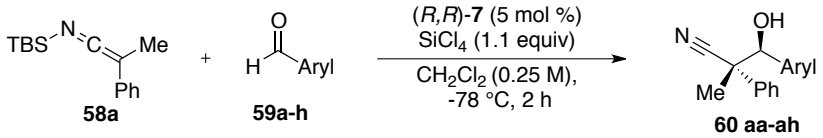


Figure 10. React-IR rate study comparing silyl ketene acetals and silyl ketene imines in the addition to 1-naphthaldehyde

3.4.4 Survey of Aldehyde Structure in the Addition of a Silyl Ketene Imine. Motivated by the promising results obtained from the in-situ IR rate studies, a more thorough study of the scope of this process with respect to the aldehyde structure was conducted. A wide range of aromatic aldehydes, including electron neutral, electron rich, electron deficient, and heteroaromatic, were surveyed in the addition of SKI **58a** and overall consistently high selectivities and yields were observed for the nitrile products (Table 2). The series of electron neutral aromatic aldehydes: benzaldehyde, 4-bromobenzaldehyde, and 1-naphthaldehyde reacted with comparable rates and selectivities (Table 2, entries 1-3). Furthermore, only a slight drop in the enantioselectivity was observed for addition to the more sterically encumbered aldehyde, 1-naphthaldehyde (Table 2, entry 2). Electron-poor and electron-rich aromatic aldehydes reacted with similar rates and selectivities to benzaldehyde (Table 2, entries 4-6). Finally, only a slight decrease in the enantioselectivity was observed for reaction with the electron-rich heteroaromatic aldehyde, 2-furaldehyde (Table2, entry 9).

Table 2. Lewis Base Catalyzed Aldol Addition of α-Phenylpropionitrile-Derived SKI **58a** with Aromatic Aldehydes (**59a-h**).



Entry	Aryl	Product	Yield (%)[b]	dr[c]	er[c]
1	C_6H_5 (**59a**)	**60aa**	87	95:5	98.5:1.5
2	1-naphthyl (**59b**)	**60ab**	76	> 99/1	98.4:1.6
3	4-BrC_6H_4 (**59c**)	**60ac**	93	99/1	98.9:1.1
4	4-$CF_3C_6H_4$ (**59d**)	**60ad**	88	> 99/1[d]	99.3:0.7
5	4-$CH_3CO_2C_6H_4$ (**59e**)	**60ae**	93	> 99/1	98.6:1.4
6	4-$CH_3OC_6H_4$ (**59f**)	**60af**	78	96/4	96.6:3.4
7	2-$CH_3C_6H_4$ (**59g**)	**60ag**	84	> 99/1	99.2:0.8
8	2-furyl (**59h**)	**60ah**	92	99/1	94.9:5.1

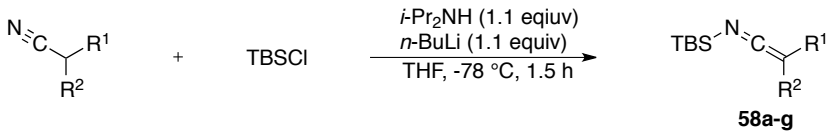
[a]Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of silyl ketene imine, 0.05 equiv of (*R,R*)-**7** at 0.25 M in CH_2Cl_2 at –78 °C for 2h. [b]Yield of analytically pure material. [c]Determined by CSP-SFC. [d]Determined by ^{1}H NMR Analysis.

Although good generality has been observed for the addition of silyl ketene imine **58a** to aromatic aldehydes, addition to aliphatic aldehydes has proven much more challenging. For example, when hydrocinnamaldehyde and silyl ketene imine **58a** were allowed to stir in the presence of 5 mol % of (*R,R*)-**7** and 1.1 equiv of $SiCl_4$ at –78 °C for 24 hours, only trace amounts of addition products were observed in the crude reaction mixture by ^{1}H-NMR analysis.

3.4.5 Synthesis of Silyl Ketene Imines from Disubstituted Nitriles. To further probe the scope of the Lewis base catalyzed aldol additions of SKIs, a thorough survey of the ketene imine structure was conducted. A number of relevant questions can be raised with respect to the nucleophile scope in these reactions. For example, how much steric differentiation in the alkyl groups of the ketene imine is required to retain high levels of diastereoselectivity in the aldol addition? Also, how will the reactivity and stability of aryl vs. dialkyl substituted ketene imines compare under the current reaction conditions? This question is especially relevant since only a small number of dialkyl silyl ketene imines have been reported in the literature. Before these questions could be addressed a number of different silyl ketene imines needed to be synthesized.

Although only a few reports have described the reactions of silyl ketene imines, their preparation is straightforward and well documented in the literature. The general procedure, first reported by Watt and co-workers, involves metalation of a α,α-disubstituted nitrile with lithium diisopropylamide followed by trapping with *tert*-butyldimethylsilyl chloride (TBSCl).[34] Isolation of the silyl ketene imine product is then achieved by distillation of the reaction mixture, first at ambient pressure to remove solvent and then at reduced pressure to obtain the SKI. A modified procedure of this initial report was developed for the synthesis of ketene imines in this study. After lithiation and trapping of the nitrile with TBSCl the reaction solvent was removed under reduced pressure and the LiCl salts were removed by precipitation with pentanes and anhydrous filtration. The product ketene imines were then obtained in high yield and purity by simply concentrating the pentane solution under reduced pressure. Following this general protocol, a number of silyl ketene imines were prepared from their respective nitrile precursors (Table 3).

Table 3. Synthesis of *ter*t-Butyldimethylsilyl Ketene Imines from α,α-Disubstituted Nitriles.



58a-g

Entry	R^1	R^2	Product	Yield,%[b]
1	Ph	Me	**58a**	95 (73[c])
2	Ph	Et	**58b**	96
3	Ph	*i*-Bu	**58c**	98
4	Ph	*i*-Pr	**58d**	98
5	Ph	Allyl	**58e**	96
6	$(CH_2)_5$	/	**59f**	90
7	Me	*i*-Pr	**59g**	92

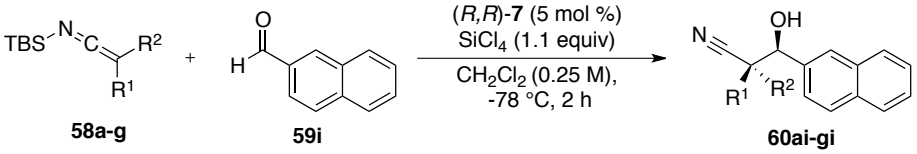
[a]All reactions employed 1.0 equiv of diisopropyl amine, 1.0 equiv of *n*-BuLi and 1.2 equiv of TBSCl. [b]Yield of crude material, purity judged to be > 95% by 1H NMR (500 MHz) analysis of the crude reaction mixture. [c]Yield reported after short-path distillation under reduced pressure.

Both α–phenyl (Table 3, entries 1-5) and α–alkyl (Table 3, entries 6-7) nitriles reacted similarly, producing silyl ketene imines in high yields and greater than 98% purity as judged by

^{1}H-NMR analysis of the crude reaction mixtures. Whereas some of these nucleophiles are stable to distillation (Table 3, entry 1), no significant differences in the yield or selectivity of the aldol addition reactions have been observed when crude silyl ketene imines were used.

3.4.6 Survey of Silyl Ketene Imine Structure in the Additions to 1-Naphthaldehyde. To test what role the nucleophile structure plays on the selectivity of the reaction, the addition of silyl ketene imines **58a-g** to 2-naphthaldehyde were surveyed in the presence of 5 mol % of (*R,R*)-**7** and 1.1 equiv of $SiCl_4$ (Table 4). First, α-alkylbenzylnitrile-derived ketene imines **58a-e** were tested in the aldol addition. The results showed that, although steric bulk can be well tolerated at this position, the presence of an α-branched substituent leads to a drop in both the diastereomeric and enantiomeric purity of the product (Table 4, compare entries 1-3 to entry 4). More importantly, a synthetically useful allyl substituted silyl ketene imine **58e** was well tolerated in the reaction providing a nitrile product in good yield and high selectivity (Table 4, entry 5). To further expand the nucleophile scope, two dialkyl substituted SKIs that do not contain an aryl ring were prepared and tested in the addition to 2-naphthaldehyde. The cyclohexane-derived ketene imine **58f** provided an aldol product with a non-stereogenic quaternary carbon in good yield and enantioselectivity (Table 4, entry 6). Silyl ketene imine **58g,** containing disparate alkyl groups, reacted to give a 60:40 mixture of enantiomerically enriched diastereomers in good yield (Table 4, entry 7). The high enantiomeric ratio observed within each diastereomer suggests that source of low dr was insufficient steric differentiation in the alkyl substituents of the ketene imine.

Table 4. Lewis Base Catalyzed Aldol Addition Reaction of α,α-Disubstituted Silyl Ketene Imines with 2-Naphthaldehyde.[a]



Entry	SKI	R^2	R^3	Product	Yield,%[b]	dr[c]	er[d]
1	**58a**	Ph	Me	**60ai**	90	98:2	98.7:1.3
2	**58b**	Ph	Et	**60bi**	78	97:3	92.7:7.3
3	**58c**	Ph	*i*-Bu	**60ci**	90	99:1	99.6:0.4
4	**58d**	Ph	*i*-Pr	**60di**	73[c]	61:39	78.9:21.1[e]
5	**58e**	Ph	Allyl	**60ei**	79	94:6	97.5:2.5
6	**58f**	–$(CH_2)_5$–		**60fi**	85	N/A	91.2:8.8
7	**58g**	i-Pr	Me	**60gi**	92	60:40	92.1:7.9[f]

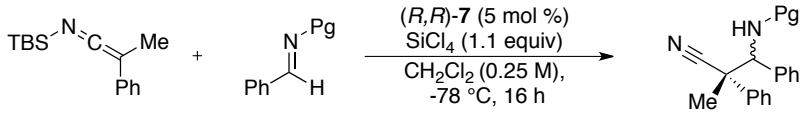
[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of silyl ketene imine, 0.05 equiv of (*R*,*R*)-**5** at 0.25 M in CH_2Cl_2 at –78 °C for 2h. [b]Yield of analytically pure material. [c]Yield of chromatographically homogenous material. [d]Determined by CSP-SFC on the major diastereomer. [e]Enantiomeric ratio of the minor diasteromer was 71.4:28.6. [f]Enantiomeric ratio of the minor diasteromer was 96.6:3.4.

3.4.7 Lewis Base Catalyzed Addition of a Silyl Ketene Imine to Aromatic Imines.

The extremely facile reaction rates observed for SKI additions to aromatic aldehydes prompted an investigation into other classes of electrophilic acceptors. Related to aldol chemistry, the Mannich-type reactions of SKIs with alkyl or aromatic imines would provide access to valuable β-amino nitriles. In general, imines represent a more difficult class of acceptors due to the reduced electrophilicity of the imine carbon.[58] However, the electrophilicity of imines can be augmented by selection of an appropriate electron-withdrawing *N*-substituent, which has greatly increased the utility of imines in a number of different addition reactions. With this strategy in mind, three different phenyl imines were prepared and tested in the addition of SKI **58a**, under the standard conditions developed for aromatic aldehydes (Table 5). Overall the reactivity trends

for SKI **58a** addition follow the electrophilicity scales that have been experimentally determined by Mayr and co-workers.[58] The less electrophilic *N*-4-methoxyphenyl imine **64a** was unreactive under the reaction conditions, but more reactive imines such as *N*-phosphinoyl imine **64b** and *N*-sulfonyl imine **64c** underwent additions. The β-amino nitriles products (**65ab-ac**) were isolated in moderate to good yield and diastereoselectivity, but no asymmetric induction was observed.

Table 5. Lewis Base Catalyzed Mannich Reaction of SKI **58** with Various Phenyl Imines.[a]



58a **64a-c** **65aa-ac**

Entry	R	Product	Yield, %[b]	dr[c]	er[d]
1	4-$CH_3OC_6H_4$– (**64a**)	**65aa**	nr	na	na
2	$(C_6H_5)_2P(O)$– (**64b**)	**65ab**	67	70:30	50:50 (major)[f]
3	4-$CH_3C_6H_4SO_2$– (**64c**)	**65ac**	96[e]	70:30	50:50 (major)[f]

[a]Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of silyl ketene imine, 0.05 equiv of (*R*,*R*)-**3.21** at 0.25 M in CH_2Cl_2 at –78 °C for 16h. [b]Yield of chromatographically homogenious material. [c]Determined by ^{1}H NMR (500 MHz) integration of the crude material. [d]Determined by CSP-SFC analysis on the major diastereomer. Reaction run at -25 °C for 24 h. [f]Enantiormeric ratio of the minor diastereomer was also 50:50.

3.4.8 Determination of Relative and Absolute Configuration for the Aldol Products.

The β-hydroxy nitrile products prepared in this study had not been previously reported and consequently the absolute configurations could not be determined by comparison of the optical rotations to known compounds. Furthermore, given the current challenges for preparing aldol-type products containing a quaternary stereogenic center it became difficult to even find suitable literature compounds that could be arrived at by functional group manipulation of the nitrile. Therefore, the absolute and relative configuration of the products was established by single crystal X-ray crystallography on nitrile product **60ac** (Figure 11). The *S* configuration at the alcohol center (C(3)) confirms that the nucleophile adds to the *Re* face of the aldehyde and is in

agreement with the sense of asymmetric induction observed in other reaction manifolds reported for this catalyst system.[23b]

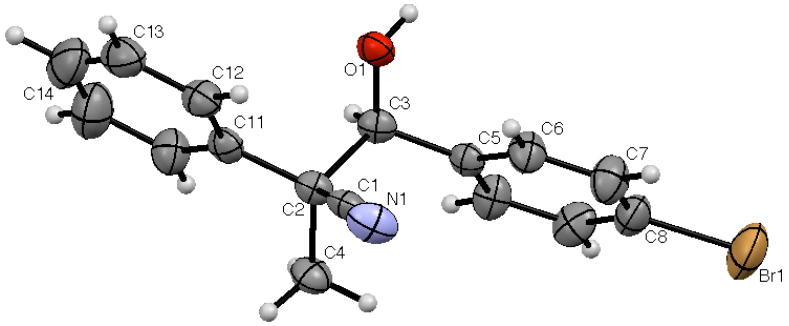


Figure 11. X-ray crystallographic structure obtained for nitrile product **60ac**

3.5 Discussion

3.5.1 Trends in Reactivity with Respect to Silyl Ketene Imine Structure. The extremely facile addition rate exhibited by silyl ketene imines under the $SiCl_4$/bis-phosphoramide catalyst system is truly remarkable and has allowed for the synthesis of quaternary carbon containing aldol products in high yields and stereoselectivities for the first time. To probe how the structure of silyl ketene imines could be accounting for the observed reaction rates a comparative study of silyl ketene acetals and silyl ketene imines was conducted. The results of these experiments showed that silyl ketene imines were orders of magnitude more reactive than silyl ketene acetals in this catalyst system. This large disparity in observed reactivity between silyl ketene imines and ketene acetals most likely results from both steric and electronic differences that exist between these two nucleophile classes. However, the steric component may play a more dominant role in these reactions due to the congestion associated with the formation of a quaternary center. This is especially apparent when comparing the open-transition state models, which have been proposed to explain the stereochemical outcome for addition of

silyl ketene acetals to aldehydes with the (*R,R*)-**7**/$SiCl_4$ catalyst system (Figure 12). Previous mechanistic and computational studies have suggested that the active catalytic species in these reactions is a phosphoramide-bound trichlorosilyl cation. This highly electrophilic chiral Lewis acid activates the aldehyde through coordination to the lone pair of the carbonyl and then controls the relative and absolute topicity for the combination of two prochiral reactants. The high diastereoselectivity observed for these additions can then be rationalized by minimizing steric interactions between the approaching nucleophile and the sizable trichlorosilyl cation. Comparing the antiperiplanar open transition structures leading to the *anti*-aldol product for the addition of disubstituted silyl ketene acetals and silyl ketene imines show dramatic differences. For example, the transition structure for the addition of either *E* or *Z* SKA **63** to benzaldehyde both suffer from unfavorable steric interactions with the alkoxy substituents of the SKA and the phenyl ring of the aldehyde (Figure 12). This space is completely open in the transition state proposed for the addition of silyl ketene imine **58a** to benzaldehyde. Furthermore, the bulky TBS substituent of the silyl ketene imine can occupy a position in space perpendicular to the plane of the aldehyde and away from the congestion of the newly forming quaternary center.

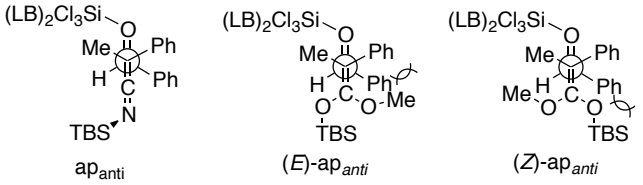
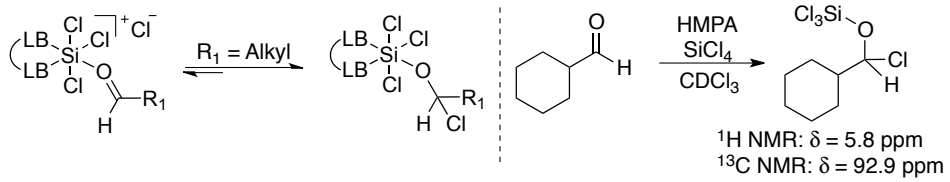


Figure 12. Open transition structures comparing addition of silyl ketene imines and acetals to benzaldehyde

3.5.2 Trends in Reactivity with Respect to Aliphatic Aldehyde Structure. Despite the high reaction rates observed in the additions of silyl ketene imines to aromatic aldehydes, these nucleophiles remained inert toward aliphatic aldehydes. The reduced reactivity of aliphatic aldehydes is well known within this catalyst system, and may be attributed to an unfavorable

equilibrium that exists between the activated aldehyde complex and an inactive α-chloro trichlorosilyl ether (Scheme 30).[23b] Experimental evidence supporting this hypothesis has previously been obtained by ^{1}HNMR studies with aliphatic aldehydes. Because of the low equilibrium concentration of activated aldehyde complex, only powerful nucleophiles, such as ethyl propionate- and methyl acetate-derived silyl ketene acetals, react with appreciable rates. Although silyl ketene imines appeared to have enough reactivity to overcome this unfavorable equilibrium, significant quantities of addition products have not been observed for a variety of different reaction conditions. A possible explanation for this is that although silyl ketene imines are more reactive than α,α-disubstituted silyl ketene acetals, they may not be as reactive as the mono- and unsubstituted acetal derivatives. Although this difference in reactivity could in principle be discerned by comparing the rates of addition for each of these nucleophiles to aromatic aldehydes, currently, these reactions are too fast to be distinguished by in situ IR kinetic analysis. To overcome this problem of reaction monitoring, one needs to either slow down the reaction rates or use an instrument with better temporal resolution, such as RI-NMR.[59]

Scheme 30



3.5.3 Reactivity Trends with Respect to Aromatic Imines. In the addition of silyl ketene imine **58a** to various *N*-substituted phenyl imines, good conversions and yields could only be obtained with highly electrophilic imines, such as *N*-phosphinoyl (**64b**) and *N*-sulfonoyl (**64c**). Unfortunately, the Mannich products from these additions were isolated with only moderate diastereoselectivities and no enantiomeric induction. Although the reactivity trends follow

experimentally determined values for phenyl imines, further comment on the lack of enantioselectivity in these additions is warranted. Two possible mechanistic scenarios could account for the poor selectivities obtained in the addition to *N*-sulfonyl and *N*-phosphinoyl imines and both center around the nature of the activating group on the imine. First, each of these imines contains a fairly strong Lewis basic moiety, which can competitively bind the $SiCl_4$ and promote an achiral background reaction. The amount this achiral reaction contributes to the loss in enantioselectivity will depend on the relative Lewis basicity of the activating group compared to the catalyst, their respective affinities for $SiCl_4$, and the concentration of each in solution. The second consequence of having a strongly Lewis basic activating group on the imine is that it places the electrophilic carbon of the imine further away from the chiral information of the catalyst. This arrangement makes it more challenging for the catalyst to exert a strong influence over addition of the nucleophile to one of the prochiral faces of the electrophile.

3.5.4 Rationale for the Observed Diastereoselectivity with Aromatic Aldehydes. The current results for the addition of silyl ketene imines to aldehydes illustrate the high level of control that the catalyst structure exerts over approach of the nucleophile to a single face of the prochiral aldehyde. Furthermore, the reactions are characterized by high levels of diastereoselectivity, suggesting the catalyst structure is also providing a framework to discriminate between the two faces of the approaching silyl ketene imine. Previous studies on the additions of silyl ketene acetals to aldehydes catalyzed by the (*R,R*)-**7**/$SiCl_4$ catalyst system have suggested that the active catalytic species is a phosphoramide-bound trichlorosilyl cation complex.[23] This activated Lewis acid binds and activates the aldehyde and the diastereoselectivity of these reactions can be rationalized through analysis of open-transition structure models. Under the assumption that the silyl ketene imines are also reacting through an

open transition structure, a similar analysis can lead to prediction of the configuration in the nitrile products. However, before the diastereoselectivity of the reaction can be analyzed, the stereochemistry of the silyl ketene imine needs to be discussed.

Similar to allenes, silyl ketene imines contain an axis of chirality whenever the two carbon substituents R^1 and R^2 are non-equivalent. For example, silyl ketene imines **58a-e** are chiral/racemic, whereas **58f** is achiral. Because the silyl ketene imines were generated from an achiral base, they will be present in the reaction in racemic form, and additional open-transition state models need to be considered.

The four possible antiperiplanar (ap) transition structures for the addition of racemic silyl ketene imine **58a** to benzaldehyde are shown in Figure 13 (for clarity only ap transition structures are depicted, but similar arguments can be made for synclinal (sc) arrangements). Each transition structure takes into account the stereochemistry of the silyl ketene imine; hence, there are two structures that lead to *anti* products ((*S*)-ap_{anti} and (*R*)-ap_{anti}) and two that lead to *syn* products ((*S*)-ap_{syn} and (*R*)-ap_{syn}). The most apparent difference between the transition structures that lead to *anti* products and those that lead to *syn* products is the position of the phenyl substituent of the silyl ketene imine. For the *syn* pathway, the phenyl ring lies in a more sterically crowded region, adjacent to the bound trichlorosilyl cation (LB_2Cl_3Si-), whereas in the *anti* pathway, the phenyl ring resides in a relatively open region of space, co-planar with the aldehydic phenyl ring. The high levels of diastereoselectivity observed in these reactions likely results from the unfavorable steric interaction that exists between the phenyl substituent of the silyl ketene imine and the sizeable silyl cation in the *syn* transition structures.

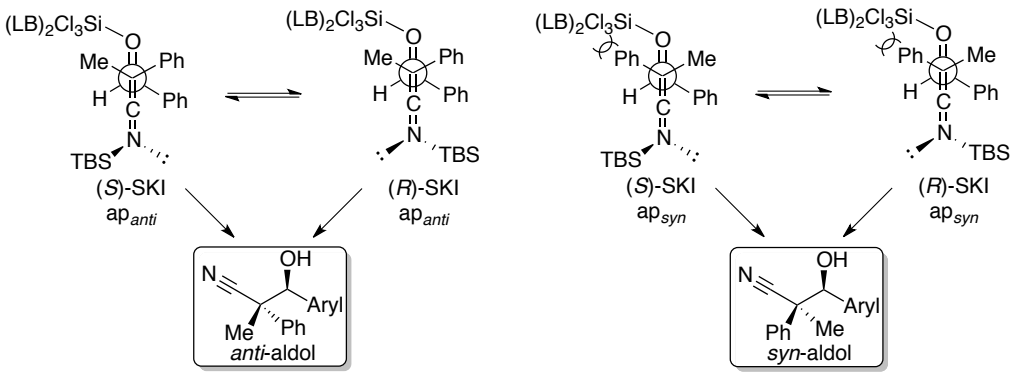


Figure 13. Open antiperiplanar transition structures accounting for stereochemistry of SKI

Another noteworthy observation from the open transition structures is that, within each set (*anti* or *syn*), two different diastereomeric transition structures lead to the same product. This discrepancy has an interesting consequence, because if the energy difference between the two transition structures is substantial, then one enantiomer of the silyl ketene imine will react faster than the other. This rate difference will lead to enrichment in the enantiomeric composition of the racemic silyl ketene imine and reduced yields of the observed product. However, since the products are isolated in high yield and with diastereo- and enantiomeric ratios greater than 98:2, it seems unlikely that the energy difference between the two transition structures has any bearing on the course of the reaction. Alternatively, if the energy difference between the conformations were significant, then invoking a racemization of the silyl ketene imine could also explain the observed yields and stereoselectivities. The configurationally stability of silyl ketene imines has never been studied or determined, however, both aryl and alkyl ketene imines are known to have a low barrier to racemization.[37]

If silyl ketene imines are able to undergo racemization under the reaction conditions then it is reasonable to also consider synclinal (sc) open transition states to rationalize the observed diastereoselectivity (Figure 14). These transition states would only be favorable if the silyl

ketene imine could attack in a geometry that placed the bulky silyl group away from the plane of the aldehyde-catalyst complex. Of the four possible synclinal transition states, the (–)-synclinal geometries could be highly favored due the ability to place sterically unencumbered ketene imine in the sector occupied by the Lewis base-trichlorosilyl cation. The observed *anti* diastereoselectivity could then be rationalized by avoidance of an unfavorable interaction between the phenyl substituent of the SKI and the lone pair of the carbonyl group in the (–)sc_{syn} transition structure.

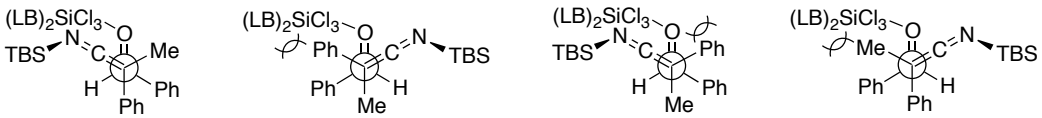


Figure 14. Possible open synclinal transition structures for SKI **58a** addition to benzaldehyde

3.5.5 Rationale for the Observed Enantioselectivity with Aromatic Aldehydes. The structure of the Lewis base activated complex between (*R,R*)-**7** and $SiCl_4$ has been of much interest, and kinetic studies have suggested that the catalytically active species involves a hexacoordinate silicate bound by two phosphoramide moieties.[23a] Direct evidence for the hexacoordinate silicon complex *via* X-ray crystallography has been elusive due to the transient nature of the phosphoramide-silicon bond. However, hexacoordinate complexes of $SiCl_4$ with hexamethylphosphoramide[60] and $SnCl_4$ with bis-phosphoramides[61] have been observed and characterized by X-ray crystallography in these laboratories. These results have aided in the development of a working computational model of the trichlorosilyl cation where both the chiral bis-phosphoramide and a substrate aldehyde are bound to the silicon center (Figure 15).[23b] In the minimized structure, the aldehyde binds *trans* to one of the phosphoramides due to the nature of the hypervalent bonds in the ligand field around silicon. This geometry places the aldehyde close

to one of the binaphthyl rings of the Lewis base catalyst, possibly stabilized by an edge to face π–π interaction. The *N*-methyl group on the binaphthyl ring of the catalyst protrudes far into the binding pocket, effectively shielding the *Si*-face of the aldehyde and leaving the *Re* face exposed for nucleophilic attack.

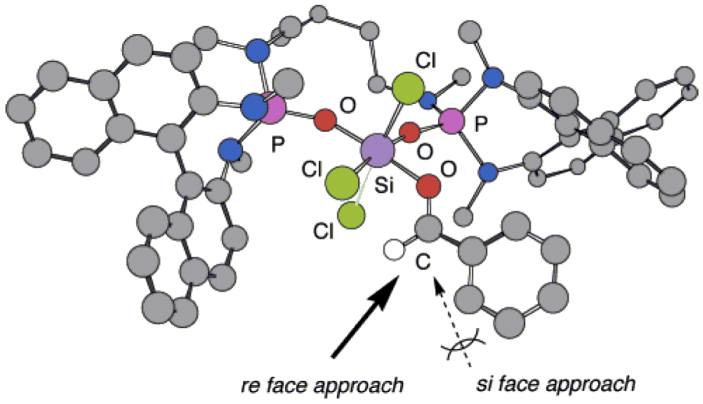


Figure 15. Calculated model of the benzaldehyde-silyl cation complex optimized with PM3 basis set using GAMESS(UC) QC package and visualized using Chem3d.

The absolute configuration for the nitrile products derived from silyl ketene imine additions to aromatic aldehydes catalyzed by (*R,R*)-**7** are also consistent with this stereochemical model. The *S* configuration of the alcohol center confirmed that SKI underwent addition to the *Re* face of the aldehyde and open transition state models based on minimizing interactions between the silyl cation and phenyl substituents of the SKI are consistent with the observed relative configuration. These findings provide further support for the current stereochemical model.

3.6 Conclusions and Outlook

A novel, Lewis base catalyzed aldol reaction for the synthesis of quaternary centers *via* the addition of silyl ketene imines to aromatic aldehydes has been described. The products of the reaction are isolated in high yield and with excellent levels of both diastereo- and

enantioselectivity. Furthermore, the reaction exhibits broad substrate scope in both the silyl ketene imine and the aromatic aldehyde. Future work will focus on new classes of silyl ketene imine nucleophiles and extending the scope of the electrophile acceptors.

Chapter 4: Lewis Base Catalyzed Conjugate Additions of Silyl Ketene Imines to α,β-Unsaturated Aldehydes and Ketones

4.1 Introduction

The catalytic, enantioselective synthesis of compounds containing quaternary stereogenic carbon centers continues to provide organic chemists with challenges for catalyst design and reaction development.[47,62] The key issue in the construction of these centers is to identify catalyst systems that can overcome the substantial steric encumbrance encountered in the carbon-carbon bond-forming event, while still providing an effective environment for obtaining high asymmetric induction. Although a number of elegant solutions have recently been devised for achieving this goal, certain types of reaction frameworks still present significant obstacles and provide platforms for novel catalyst design and innovation in synthetic methods.

An important transformation that presents promising opportunities for setting quaternary stereogenic centers is the Michael reaction (Figure 16a).[47c,63] This venerable process has long been recognized as one the most reliable methods for carbon-carbon bond formation as it allows for the preparation of the synthetically useful class of 1,5-dicarbonyl compounds. Moreover, the high exothermicity of the catalytic Michael reaction may provide the energy needed to overcome the steric strain of setting a quaternary center. The successful implementation of a catalytic, enantioselective variant of this reaction,[64] requires a catalyst that can control both the site selectivity of the addition (*1,4*- vs. 1,2-, Figure 16a) as well as the relative and absolute topicity for the combination of two fully substituted sp^2 centers. Moreover, for activation of the nucleophile, the catalyst has to control the configuration of a disubstituted enolate. On the other hand, activation of the electrophile requires the catalyst to be coordinated selectively at one of

the binding sites of the Lewis basic oxygen (*anti* vs. *syn,* Figure 16b) and also control the conformation of the conjugated double bonds in the acceptor (*s-cis* vs. *s-trans,* Figure 16b).[65]

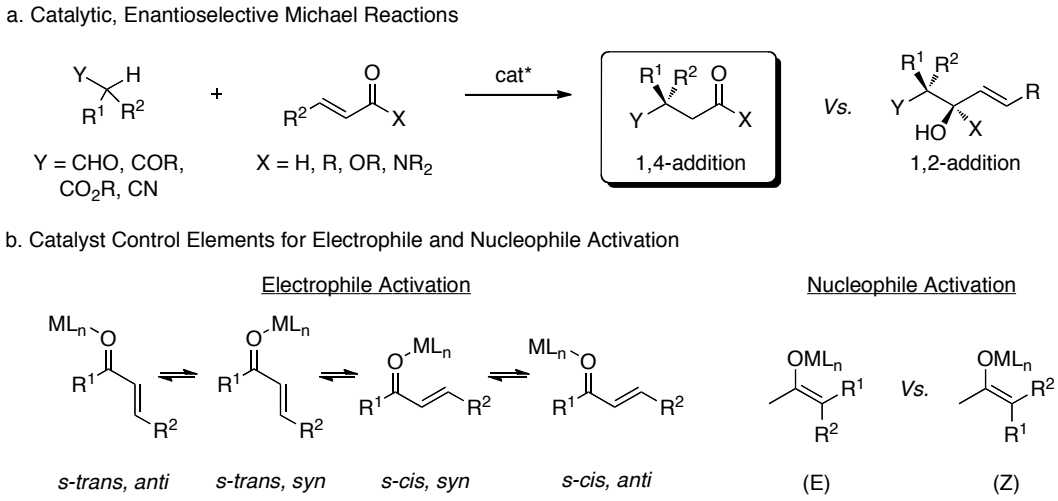


Figure 16. Catalytic, enantioselective Michael reactions and catalyst control elements.

In recent years, creative solutions to these challenges have appeared that provide Michael addition products containing quaternary stereogenic carbons in good yield and high selectivity.[47c,63]

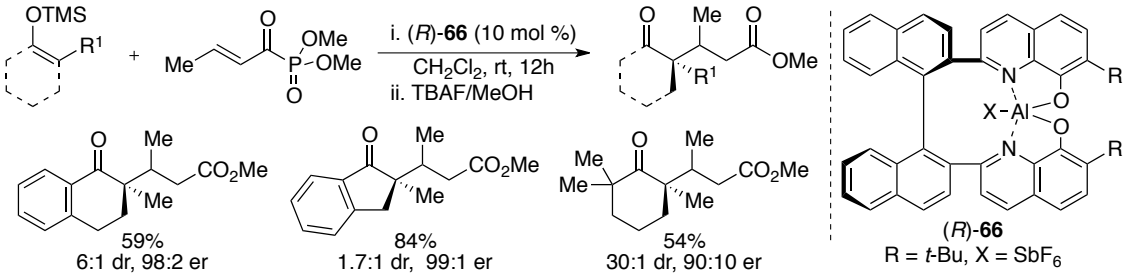
Despite these achievements some limitations still exist for certain combinations of donors and acceptors. For example, existing methods are limited to readily enolizable carbonyl compounds, such as β-keto esters, α-cyano ketones, and β-diketones in combination with acyclic and cyclic ketones. The addition of simple ketones, esters or nitriles to α,β-unsaturated aldehydes or ketones finds no general solution for the synthesis of quaternary stereogenic carbon centers due the inherent problems of controlling enolate geometry.[51,54] The following chapter details the application of SKIs in Lewis-base catalyzed, enantioselective Michael-type reactions with α,β-unsaturated aldehydes and ketones for the construction of stereogenic quaternary centers.

4.2 Background

4.2.1 Catalytic, Enantioselective Mukaiyama-Michael Reactions. The catalytic, asymmetric Mukaiyama-Michael (MM) reaction of enoxysilane nucleophiles with activated acceptor olefins has developed as a powerful strategy for the synthesis of enantioenriched 1,5-dicarbonyl compounds.[66] The use of silylated nucleophiles in these reactions provides an attractive alternative over conventional metalloenolate processes, owing to the milder reaction conditions and the superior selectivities normally exhibited by these donors for 1,4-addition. Whereas numerous catalyst systems have been reported for the preparation of secondary and tertiary centers, the preparation of quaternary centers have received little attention.

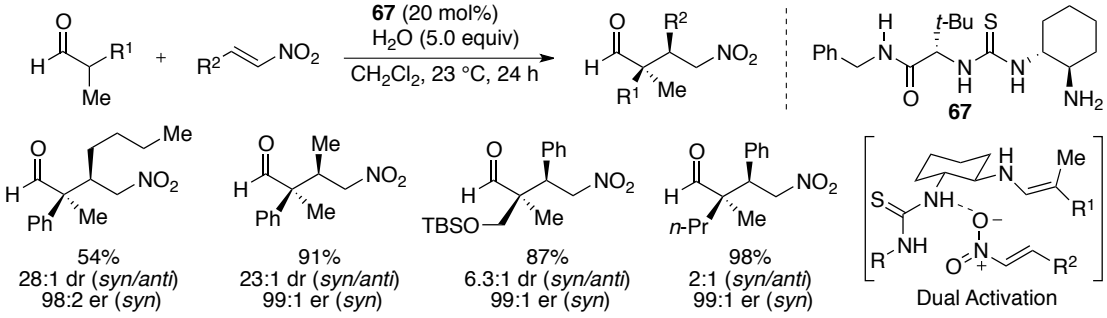
4.2.2 Catalytic, Enantioselective Mukaiyama-Michael Reactions for the Synthesis of Quaternary Stereogenic Centers. One notable exception is the work of Yamamoto *et. al.* on the Michael addition of silyl enol ethers to α,β-unsaturated acyl phosphonates catalyzed by tethered bis-(8-quinolato)aluminum complexes (Scheme 31).[67] In this report, the authors obtained 1,5-dicarbonyl compounds containing a quaternary stereogenic center in moderate to good yield and with high enantioselectivity. The Al(III) based catalyst (*R*)-**66** was able overcome the reduced reactivity observed for silyl enol ethers as compared to silyl ketene acetals, however, the reaction scope was limited to cyclic enol ethers. Additionally, the reaction requires the use of specialized acyl phosphonates for coordination and activation of the acceptor by the Lewis acidic aluminum. This single achievement notwithstanding, no methods for the catalytic, enantioselective MM addition of acyclic disubstituted nucleophiles to simple unsaturated aldehydes or ketones, are on record.

Scheme 31



Jacobson and co-workers describe the use of simple acyclic α,α-disubstituted aldehydes as nucleophiles in catalytic, asymmetric Michael reactions without the need for preformation of enoxy silanes.[68] The chiral primary amine thiourea **67** acts as a bifunctional catalyst in the process by activating both the aldehyde donor through enamine formation as well as the nitroalkene acceptor by hydrogen bonding (Scheme 32). The reaction allows for preparation of a diverse range of γ-nitroaldehyde products containing quaternary stereogenic centers in moderate yields and excellent enantioselectivities. Aldehydes that had only a minimal degree of steric differentiation between the two α-substituents reacted with reduced diastereoselectivity.

Scheme 32



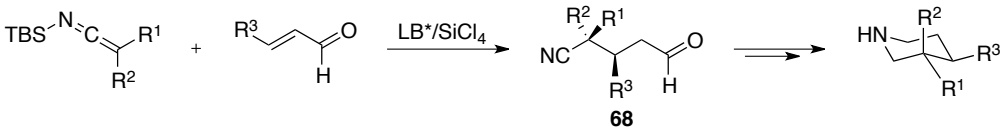
4.3 Research Objectives

Recent studies from these laboratories[69] and others[44] have documented the use of silyl ketene imines (SKIs) for the catalytic, enantioselective construction of quaternary stereogenic carbon centers. These nucleophiles possess a pair of orthogonal substituent planes that place the

bulky silyl group in a region perpendicular and distal to the reactive carbon. Because of this unique geometry, SKIs are less hindered than carbonyl derived enolates and are thus very reactive nucleophiles. In addition, the orthogonal planes obviate the problems of producing geometrically defined, disubstituted enoxysilane nucleophiles.[51,54] More interestingly, some of the earliest studies on silyl ketene imines carbonyl addition reactions demonstrated the tendency of this nucleophile to undergo selective 1,4-additions with α,β-unsaturated aldehydes such as crotonaldehyde and cinnamaldehyde.[39] However, no subsequent reports have appeared on the enantioselective 1,4-additions of SKIs to conjugated carbonyl compounds.

The overarching goal of this study is to develop Lewis base catalyzed, enantioselective Michael-type reactions of disubstituted silyl ketene imines for the synthesis of γ-cyanocarbonyl compounds **68** containing a quaternary stereogenic carbon center (Scheme 33). These substances could be extremely valuable synthetic intermediates, as manipulation of the aldehyde and nitrile functional groups could provide access to chiral lactones, lactams and piperdines.[12] Given the complex nature of this type of catalysis, the initial goal was to establish the reactivity, and site-selectivity of the silyl ketene imines with various α,β-unsaturated electrophiles using the bis-phosphoramide/$SiCl_4$ catalyst system.

Scheme 33

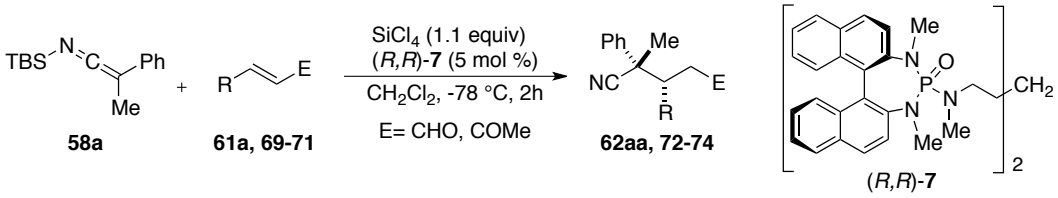


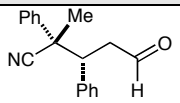
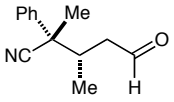
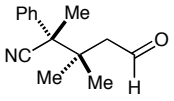
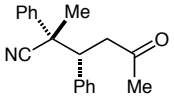
4.4 Results and Discussion

4.4.1 Electrophile Survey in the Lewis Base Catalyzed Conjugate Addition of a Silyl Ketene Imine. The combination of $SiCl_4$ and a chiral, nonracemic bis-phosphoramide is a highly

effective catalyst system for the enantioselective 1,2-addition of a number of different silylated nucleophiles with aldehydes.[23b,26-29,70] Although α,β-unsaturated aldehydes are known to be effective electrophiles under these reaction conditions, selective 1,4-addition has rarely been observed with this catalyst system.[27b] To test the ability of SKIs to participate in a MM-type addition, SKI **58a** was prepared by lithiation of the nitrile followed by trapping with TBSCl and its reactivity was assayed in the addition to cinnamaldehyde under the catalytic action of $SiCl_4$ and bis-phosphoramide (*R,R*)-**7** (Table 6, entry 1).

Table 6. Electrophile Survey in the Addition of SKI **58a**.



Entry	Product	Yield (%)[a]	1,4:1,2[b]	dr[c]	er[d]
1	 **62aa**	84	92:8	82:18	72:28
2	 **72**	74	92:8	84:16	51:49
3	 **73**	78	48:52	n.a.	55:45
4	 **74**	80	99:1	54:46	80:20[e]

[a] Overall yield of chromatographically homogeneous material.[b,c] determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by CSP-SFC analysis of the alcohol resulting after $NaBH_4$ reduction. [e] Minor diastereomer er was 54:46

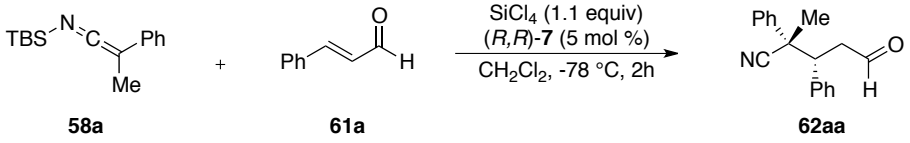
Gratifyingly, the major product obtained by hydrolysis of the *in-situ* formed trichlorosilyl enol ether, resulted from selective 1,4-addition (92:8) and was produced in good yield and with moderate selectivity. On the basis of this encouraging result, a broader survey of α,β-unsaturated

electrophiles was carried out (Table 6). Both α,β-unsaturated aldehydes and ketones bearing either aliphatic or aromatic substituents underwent highly site-selective 1,4-additions in good yield (Table 6, entries 1-4). However, the stereoselectivity of the reactions were poor for the cases of aliphatic enals such as (*E*)-crotonaldehyde (Table 6, entry 2). Moreover, when the β-disubstituted electrophile 3-methyl-2-butenal (**70**) was tested, competitive 1,2-addition was observed, suggesting that steric effects greatly influence the site of addition in this reaction (Table 6, entry 3). The aromatic enone (*E*)-4-phenyl-3-buten-2-one (**71**) reacted exclusively via 1,4-addition, and the resulting ketone product **74** was isolated in good yield, but poor diastereoselectivity (Table 6, entry 4). Interestingly, the enantioselectivity differed greatly within each diastereomer; moderate er was obtained for the favored *syn*-diastereomer, whereas the minor *anti*-diastereomer was racemic. This result suggests that each diastereomer arises from different enone-catalyst bound complexes.[18] Other classes of conjugated electrophiles, including α,β-unsaturated esters, nitriles, and nitroalkenes were also tested, but proved unreactive under these reaction conditions.

4.4.2 In Situ IR Rate Studies for the Catalyzed and Uncatalyzed Addition of a Silyl Ketene Imine to Cinnamaldehyde. The results from the electrophile survey identified α,β-unsaturated aromatic aldehydes as suitable substrates for site selective 1,4-addition of SKI **58a**. The initial results showed high selectivity for the 1,4-addition pathway, however, the observed diastereo- and enantioselectivities of the aldehyde product were modest. Prompted by these findings, the next goal was to establish the catalyzed and background reaction rates for the addition of silyl ketene imine **58a** to cinnamaldehyde.

Experimentally, the reaction kinetics for the addition were measured by monitoring the loss of the IR absorption band for the carbonyl resonance of cinnamaldehyde at 1642 cm^{-1} in the

presence and absence of Lewis base catalyst (*R,R*)-**7**. The R-IR plots of this data show an extremely rapid addition rate of the silyl ketene imine to the enal for both the catalyzed (Figure 17, blue line) and uncatalyzed (Figure 17, red line) pathways. Although IR cannot distinguish between 1,4- versus 1,2-addition, quenching of the reaction mixtures and analysis of the crude products by H NMR confirmed selective 1,4-additions (1,4:1,2 ratios >90:10) for each reaction.



58a **61a** **62aa**

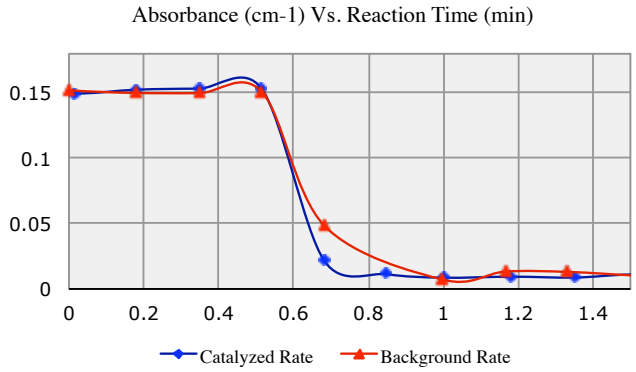
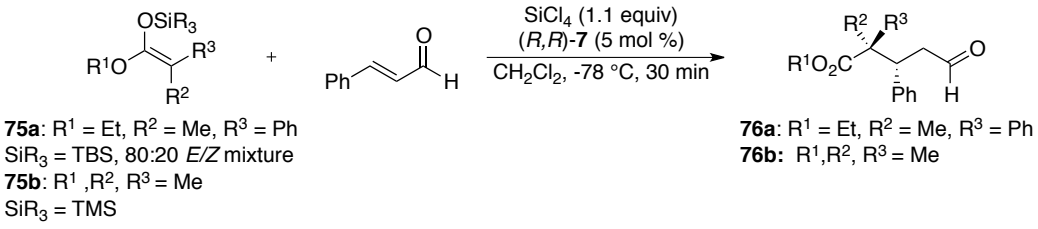


Figure 17. In situ IR data for catalyzed and background 1,4-addition of SKI **58a** and cinnamaldehyde.

4.4.3 In Situ IR Rate Studies Comparing 1,4-Additions of Silyl Ketene Imine and Silyl Ketene Acetals. Previous studies on the Lewis base catalyzed aldol reactions of SKI **58a** clearly demonstrated the enhanced reactivity these nucleophiles exhibit as compared to their ester-derived silyl ketene acetal counterparts. This rate difference was rationalized by the ability of SKIs to avoid unfavorable steric interactions that develop in the transition structure for addition of disubstituted SKAs. Many of these steric interactions are avoided in the conjugate addition pathway because the electrophilic carbon is remote to the site of activation in the enal (*i.e.* the lone pair electrons of the carbonyl fragment). This observation raised an intriguing

question as to whether this same disparity in reaction rates for SKIs and SKAs would be borne out in Lewis base catalyzed conjugate addition reactions.

To address this question, a comparative rate study between analogously substituted silyl ketene acetals and imines was conducted. Silyl ketene acetal **75a,** prepared from methyl 2-phenylpropionate (80/20 mixture of *E/Z* isomers), was assayed by In Situ IR analysis in the addition to cinnamaldehyde using identical experimental conditions as described for SKI **58a** (Figure 18, green line).



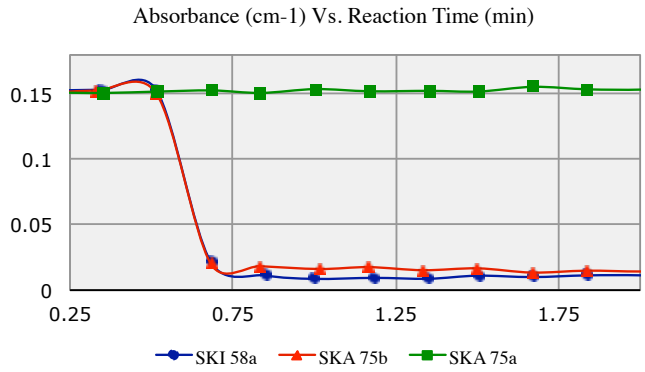


Figure 18. In Situ IR-rate data for comparison of silyl ketene imines and silyl ketene acetals.

Similar to results observed in the aldol reaction, SKI **58a** showed a marked increase in reaction rate for 1,4-addition to cinnamaldehyde as compared to SKA **75a**. To further probe the reactivity differences between SKAs and SKIs, the more nucleophilic *gem*-dimethyl SKA **75b** was also evaluated in the Lewis base catalyzed 1,4-addition to cinnamaldehyde (Figure 18, red line). Interestingly, within the scanning time of this experiment (~10 s) no difference between the addition rates of SKA **75b** and SKI **58a** (Figure 18, red vs. blue line) could be discerned.

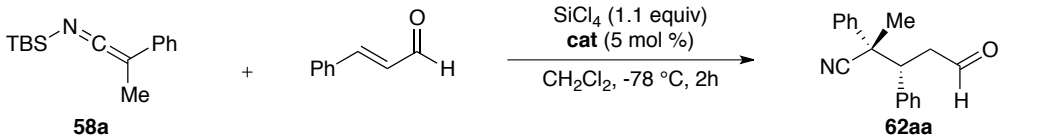
Furthermore, this disubstituted silyl ketene acetal underwent highly selective 1,4-addition to cinnamaldehyde to give aldehyde **76b** in good yield. This result suggests that the major factor influencing the 1,4/1,2-selectivity is simply unfavorable steric interactions encountered with the catalyst.

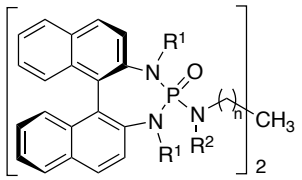
4.4.4 Phosphoramide Lewis Base Catalyst Survey in the Conjugate Addition of Silyl Ketene Imine to Cinnamaldehyde. To optimize the selectivity of the reaction, a survey of the Lewis base catalysts was performed (Table 7). The series of catalysts tested in the 1,4-addition examined the sensitivity of the reaction to a number of different structural features of the parent phosphoramide catalyst (*R,R*)-**7**, including: (1) the alkyl group on the nitrogen of both the binaphthyl-diamine and the diamine tether (Table 7, entries 2-4), (2) the tether length (Table 7, entry 1), (3) monomeric catalyst (Table 7, entry 6), and (4) the dihedral angle of the biaryl unit (Table 7, entry 5 and entries 7-8). Unfortunately, none of the structural modifications resulted in a significant increase in the enantioselectivity of the addition. Surprisingly though, both the reduced dimeric catalyst and the biphenyl-derived catalysts afforded the 1,4-addition products in similar yields, site selectivities, and enantioselectivities, but with increased diastereoselectivities.

To rule out whether the poor enantioselectivity was arising from a competitive achiral background reaction, the addition was carried out at higher catalyst loading (Table 7, entry 9). Performing the reaction with 15 mol % of (*R,R*)-**7** afforded the 1,4-product in similar yield and selectivities as compared to previous runs with 5 mol % catalyst. The result demonstrates that even at 3x the loading of (*R,R*)-**7**, no significant change in the enantioselectivity of the reaction is observed, suggesting that the low selectivity is not solely resulting from an uncatalyzed pathway. Alternative explanations that could account for the moderate enantioselectivity are that the

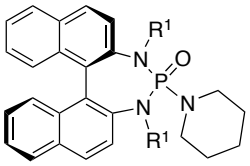
catalyst modifications are not far reaching enough to influence addition at the β-carbon of the enal, and/or the reaction is proceeding through multiple catalyst-acceptor complexes.

Table 7. Catalyst survey for the addition of SKI **58a** to cinnamaldehyde.

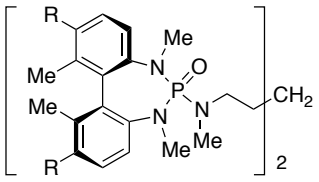




(*R,R*)-**7** (R^1,R^2= Me, n= 2)
(*R,R*)-**77** (R^1,R^2= Me, n= 1)
(*R,R*)-**78** (R^1= Et, R^2= Me, n= 2)
(*R,R*)-**79** (R^1= *i*-Pr, R^2= Me, n= 2)
(*R,R*)-**80** (R^1= Me, R^2= Et, n= 2)
(*S,S*)-**81** (R^1,R^2= Me n= 2, H_8-BINAM)



(R)-**82**



(*S,S*)-**83** (R = H)
(*R,R*)-**84** (R = 3,5-$(CH_3)_2C_6H_3$)

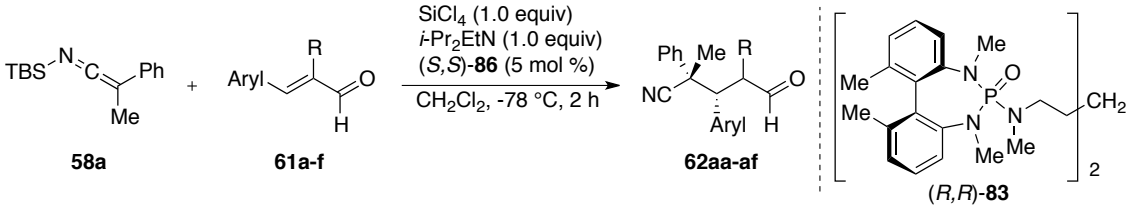
Entry	Catalyst	1,4:1,2[b]	dr[c]	er[c]
1	(*R,R*)-**77**	94:6	82:18	64:26
2	(*R,R*)-**78**	80:20	80:20	65:35
3	(*R,R*)-**79**	75:25	78:22	52:48
4	(*R,R*)-**80**	91:9	82:18	69:31
5	(*R,R*)-**81**	92:8	90:10	65:35
6	(*R*)-**82**	92:8	85:15	60:40
7	(*S,S*)-**83**	94:6	91:9	68:32
8	(*R,R*)-**84**	92:8	90:10	70:30
9	(*R,R*)-**7**	92:8	90:10	74:26[d]

[a,b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by CSP-SFC analysis of the alcohol resulting after $NaBH_4$ reduction. [d] Reaction ran with 15 mol % catalyst

4.4.5 Survey of Aromatic α,β-Unsaturated Aldehydes in the Addition of Silyl Ketene Imine. The final study examined the scope of the reaction with respect to the aryl substituent of the α,β-unsaturated aldehyde (Table 8). In view of the beneficial effect of the biphenyl-based catalyst on the diastereoselectivity, reactions were carried out with 5 mol % of bis-phosphoramide (*R,R*)-**7**. Additionally, *N,N*-diisopropylethylamine was employed in these reactions to scavenge any adventitious HCl (formed by hydrolysis of $SiCl_4$), which could be

acting as a promoter for an achiral background reaction. Under this new set of reaction conditions the addition of SKI **58a** to a variety of commercially available β-aryl enals was conducted (Table 8). The results of this study show that both electron-rich and heteroaromatic enals undergo selective 1,4-addition in good yield and with moderate to good diastereo- and enantioselectivity. One intriguing result that the survey revealed is that substitution pattern on the aryl ring affects the enantioselectivity of the reaction. This influence was suggested by the difference in enantiomeric ratio observed for the addition to (*E*)-3-(2-methoxyphenyl)propenal (Table 8, entry 4, 86:14 er) vs. (*E*)-3-(4-methoxyphenyl)propenal (Table 8, entry 2, 72:28 er). The addition to α-methylcinnamaldehyde illustrates the ability of this reaction to set multiple stereogenic centers in a single reaction (Table 8, entry 6). Furthermore, this example demonstrates that protonation of the *in-situ* formed trichlorosilyl enol ether occurs with fairly high diastereoselectivity and suggests that tandem processes could be developed that harness the reactivity of the direct product formed under the reaction conditions.

Table 8. Survey of α,β-Unsaturated Aromatic Aldehydes in the Additon of SKI **58a**



Entry	Aryl	R	Product	Yield (%)[a]	1,4:1,2[b]	dr[c]	er[d]
1	C_6H_5	H	**62aa**	84	92:8	90:10	70:30
2	4-$CH_3OC_6H_4$	H	**62ab**	79	95:5	91:9	72:28
3	4-$(CH_3)_2NC_6H_4$	H	**62ac**	94	95:5	68:32	59:41
4	2-$CH_3OC_6H_4$	H	**62ad**	83	95:5	68:32	86:14[e]
5	2-furyl	H	**62ae**	78	92:8	81:19	79:21
6	C_6H_5	Me	**62af**	86	93:7	84:10:4:2	69:31[f]

[a] Overall yield of chromatographically homogeneous material. [b,c]Determined by ^{1}H NMR analysis of the crude mixture. [d]Determined by CSP-SFC analysis of the alcohol resulting after $NaBH_4$ reduction of the major diastereomer. [e]Minor diastereomer er was 73:27. [f]82:18 er obtained with (*R,R*)-**7.**

4.4.6 Determination of Relative and Absolute Configuration for the Michael Products.

The *syn* relative configuration of the major diastereomer resulting from 1,4-addition of SKI **58a** to cinnamaldehyde was unambiguously established by single crystal X-ray analysis of the product (Figure 19). However, the depicted absolute configuration is assumed from a *Re*-face addition of the SKI to the enal bound in an *s-cis* conformation to the Lewis base catalyst complex. Although this assignment employs the stereochemical model developed from previous mechanistic and computational studies on 1,2-additions to aldehydes catalyzed by (*R,R*)-**7**/$SiCl_4$, it has not been unequivocally confirmed for this reaction.

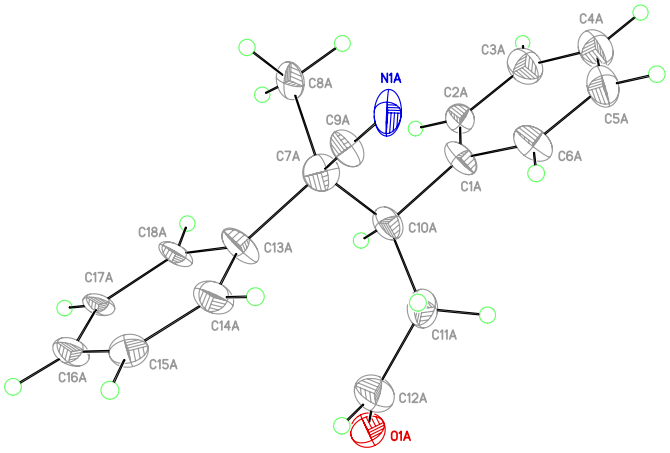


Figure 19. X-ray crystallographic coordinates for nitrile **62aa**

4.5 Conclusions and Outlook

A novel Lewis base catalyzed Mukaiyama-Michael reaction for the generation of quaternary stereogenic carbon centers via the 1,4-addition of silyl ketene imines to α,β-unsaturated aldehydes and ketones has been described. The reactions are selective for 1,4-addition and yield aldehyde or ketone products in moderate to good yield and diastereoselectivity and with moderate enantioselectivity. Future work will focus on mechanistic studies to elucidate

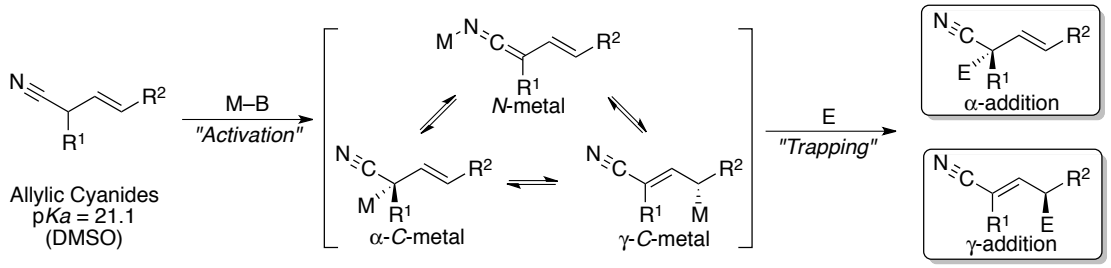
the confirmation of the bound electrophile-catalyst complex as well as new Lewis base catalyst architectures that can engender higher stereoselectivities.

Chapter 5: Lewis Base Catalyzed Vinylogous Aldol Additions of N-Silyl Vinylketene Imines

5.1 Introduction

The anions derived from metalation of allylic cyanides represent a promising class of nucleophiles for carbon-carbon bond formation. The reactions of these nucleophiles with carbon electrophiles can proceed through either α- or γ- addition of the allylic anion and provides access to synthetically useful compounds containing both cyano and alkene groups (Scheme 34).

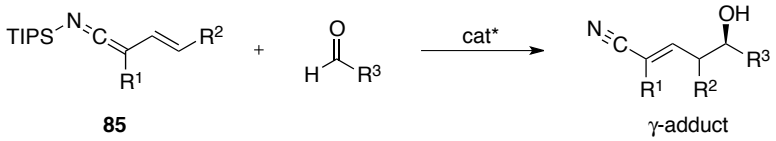
Scheme 34



Achieving site-selectivity in these reactions present significant challenges, especially when considering the number of metalated intermediates that can form upon activation of the allylic cyanide. Furthermore, the use of anionic intermediates in catalytic, enantioselective reactions can hamper catalyst turnover and lead to increased reaction rates for competitive achiral processes involving the nascent metalated nucleophile. Despite these challenges some recent inspiring work on the activation of allyl cyanide by a soft Lewis acid and a hard Brønsted base has allowed for the first examples of catalytic, enantioselective reactions of this nucleophile class.[71] However, significant challenges in terms of nucleophile scope and the implementation of base-sensitive electrophilic acceptors remain as unsolved problems.

A related strategy for accessing nucleophilic allylic cyanides that avoids the use of anionic intermediates would be to employ *N*-silyl vinylketene imines (**85**). These nucleophiles could be prepared by selectively *N*-silylating the allylic cyanide anion. Applying these nucleophiles in catalytic vinylogous aldol additions could then generate useful α,β-unsaturated nitriles (Scheme 35). Interestingly, despite the ubiquity and success of the vinylogous Mukaiyama aldol reactions for controlling site-, diastereo-, and enantioselectivity no analogous reactions of nitrile anions have been reported.[72]

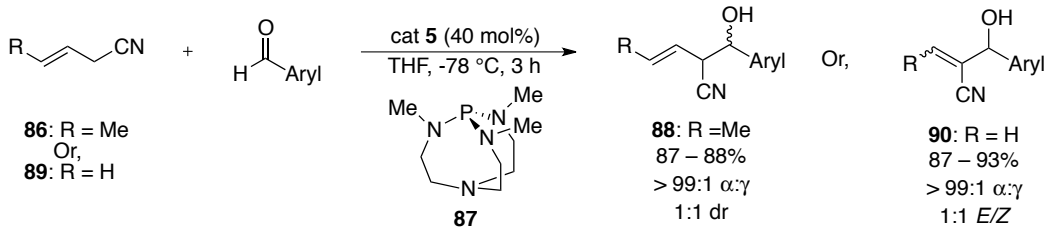
Scheme 35



5.2 Background

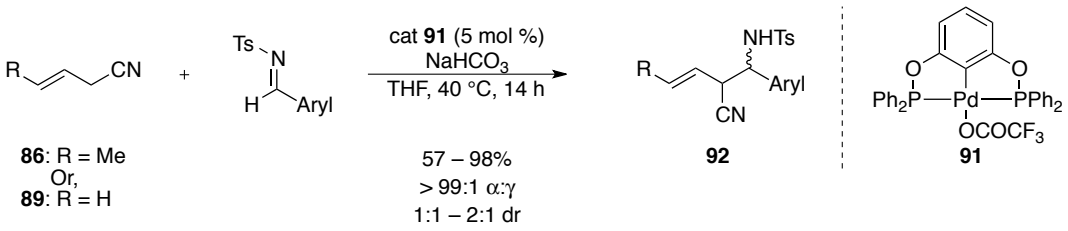
5.2.1 Achiral Addition Reactions of Allylic Cyanides. Verkade and Kisanga reported the addition of crotyl cyanide (**86**) to aromatic aldehydes, catalyzed by proazaphosphatrane **87** (Scheme 36).[73] Nitrile products **88** derived from selective α-addition of the allylic anion were isolated in good yields, but as 1:1 mixtures of *anti/syn* diastereomers. Allyl cyanide (**1**) also underwent selective α-addition to aromatic aldehydes in good yields; however, in these cases Bayliss-Hillman type products **90** were obtained after isomerization of the alkene into conjugation with the nitrile

Scheme 36



Methods for achieving nucleophilic addition of allylic cyanides that circumvent the need for strong bases have also been realized. Szabo and Aydin recently communicated a strategy based on allylic C-H bond activation of allyl and crotyl cyanide using catalytic palladium-pincer complexes (Scheme 37).[74] Treatment of the allylic cyanides with Pd pincer catalyst **91** and trapping with various sulfonimines yielded aminonitriles **92** in good yields and moderate to poor diastereoselectivity. The reactions were characterized by very high selectivities for α-addition of the allylic cyanides and good substrate scope in the imine acceptor (e.g. aromatic, olefinic and aliphatic). Computational studies support the intermediacy of a η^1-allylpalladium intermediate over an *N*-bound palladium ketene imine structure.

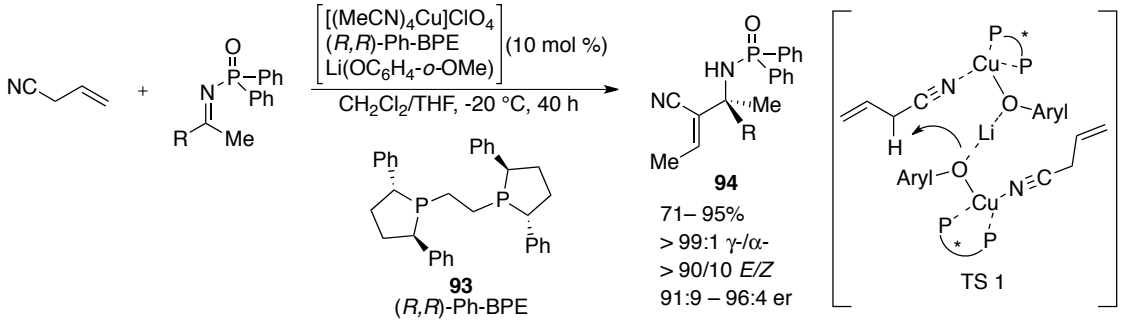
Scheme 37



5.2.2. Catalytic, Enantioselective Addition Reactions of Allylic Cyanides. Despite the utility that nucleophilic allylic cyanides offer in carbon-carbon bond forming reactions, asymmetric processes involving these species are rather rare. To date only a single strategy for the catalytic, enantioselective additions of allylic cyanides has been disclosed. The method

reported by Shibasaki and co-workers involves the cooperative catalytic action of a soft Lewis acid (Cu^I), hard Brønsted base (LiOAryl), and a chiral phosphine ligand (*R,R*)-**93** to achieve activation/deprotonation of allyl cyanide (Scheme 38, TS1).[71d] The enantioselective α-addition of the resulting chiral copper allylic cyanide anion to aliphatic and aromatic imines occurs with good yields and moderate to high enantioselectivities. The direct nitrile products **94** of the α-addition are not stable under the reaction condition and undergo isomerization to α,β-unsaturated nitriles.

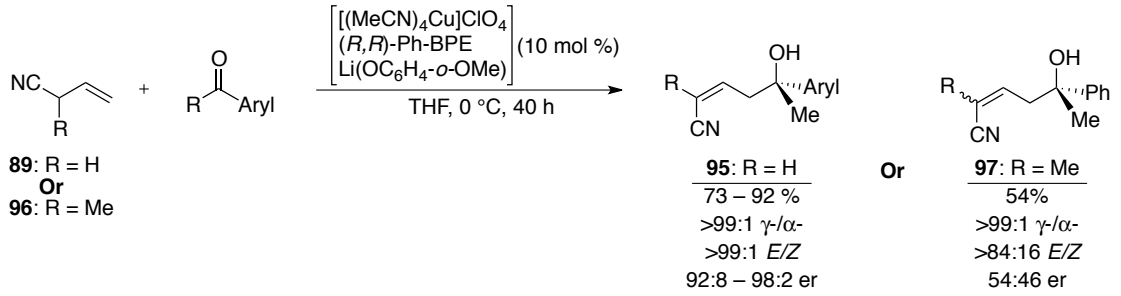
Scheme 38



A subsequent report from Shibasaki and co-workers detailed the catalytic, enantioselective additions of ally cyanide to ketones.[71b,71c] Interestingly, the observed products for ketone addition resulted from selective γ-addition of allyl cyanide (**89**) giving tertiary alcohols **95** with a pendant (*Z*)-configured unsaturated nitrile in good yield and excellent enantioselectivity (Scheme 39). The authors propose that the change in site selectivity is due to the imine binding to copper through the phosphinoyl oxygen, but do not provide much mechanistic support. The reactions show good substrate scope for various methyl-substituted aromatic ketones, however the enantioselectivity dramatically decreased with other types of allylic nitriles. For example, 2-methyl 3-butenenitrile (**96**) afforded the alcohol product **97** in 54% yield and with a depleted enantiomeric ratio of 54:46 (Scheme 39, R = Me). Finally, the

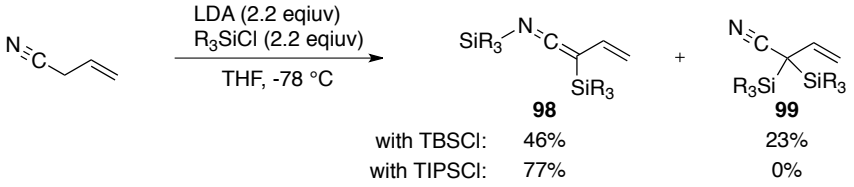
reactions seem to be limited ketone and ketoimine electrophiles, compounds that do not readily undergo base catalyzed self-condensations reactions.

Scheme 39



5.2.3 Silyl Ketene Imines Derived from Allylic Cyanides. The synthesis, isolation and application of silyl ketene imines from alkyl nitriles are well documented. However, only a single report describes the synthesis of a *N*-silyl vinylketene imines derived from allylic cyanide compounds. Ghosez and co-workers developed a method for converting allyl cyanide selectively to the *N*-silyl vinylketene imine isomer **98** in good yields and high selectivity for *N*- over *C*-silylation (Scheme 40).[75] The synthesis involves the double lithiation of allyl cyanide with excess LDA followed by trapping of the dianion with excess triisopropylsilyl chloride (TIPSCl). The authors note that even with bulky silylating agents such as *tert*-butyldimethylsilyl chloride (TBSCl) competitive C-silylation to give **99** is observed.

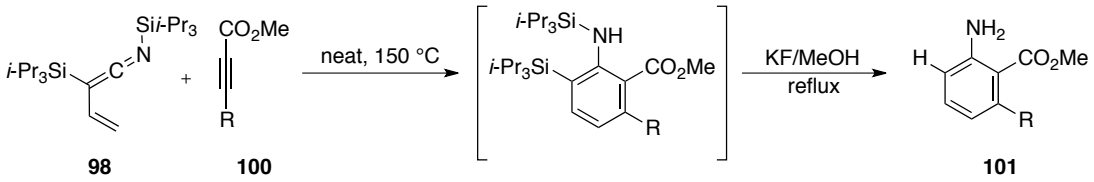
Scheme 40



In the same communication, the authors report the use of *N*-silyl vinylketene imine **98** as a diene in cycloaddition reactions with acetylenic esters **100**. Typically the ketene imine is

heated to 150 °C in the presence of an equimolar amount of alkynyl dienophile to yield substituted aniline **101** after desilylation with KF in refluxing MeOH (Scheme 41). To date, this single report is the only study detailing the synthesis or reactivity of *N*-silyl vinylketene imines.

Scheme 41



5.3 Research Objectives

Initial studies directed toward the application of allylic cyanides for carbon-carbon bond forming reactions have primarily relied on base-mediated processes, wherein metallo allylic anions are generated. Despite some very impressive results on the application of these nucleophiles for site-selective, enantioselective additions to ketone and ketoimines, significant limitations in the substrate scope of both the nucleophile and electrophile are observed. Primarily, these issues arise from the reliance on moderately strong Brønsted bases for the production of metalated allylic cyanides intermediates in the reaction. *N*-Silyl vinylketene imines present a potential solution to this problem by circumventing the need for generating anionic species in the presence of base-sensitive substrate electrophiles. However, only preliminary studies on the preparation and synthetic applications of silyl ketene imines derived from allylic cyanides have been documented. Therefore the first goal of the current research was to develop a robust and reliable method for the selective *N*-silylation of an allylic anion derived from the metalation of a readily available allyl cyanide derivative. The next phase of the study was to examine the uses of *N*-silyl vinylketene imines in Lewis base-catalyzed, $SiCl_4$-mediated aldol additions.[23b] Here focus shifted to the factors controlling α- vs. γ-site selectivity, as well as relative configuration of

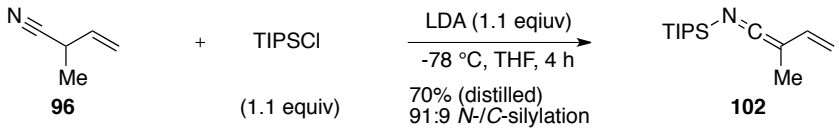
the unsaturated nitrile and enantioselectivity. Finally, Lewis base catalyzed additions of *N*-silyl vinlyketene imines to a wide variety of carbonyl electrophiles was tested under the reaction conditions. Special attention was placed on more base-sensitive electrophiles such as aliphatic aldehydes, which have challenged the established methods for allylic cyanide additions.

5.4 Results

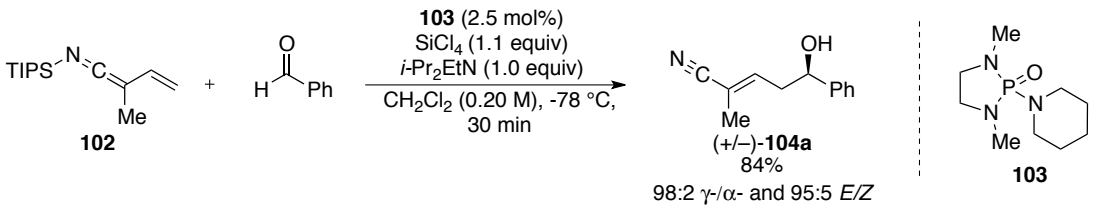
5.4.1. Synthesis of *N*-Silyl Vinylketene Imines. The inherent challenge faced for the synthesis of silyl vinylketene imines is achieving selective *N*- over α-*C*- or γ-*C*-silylation of the allylic cyanide. Foregoing studies have documented the tendency of metalated nitriles to undergo competitive *C*-silylation, however the use of bulkier silylating agents can result in kinetically controlled silylation at the less hindered nitrogen atom.[35,75] The work of Ghosez et. al. supports this overall trend, as was noted in their preliminary studies on the selective synthesis of *N*-silyl vinylketene imines with TIPSCl. Cognizant of the aforementioned precedent, studies aimed at the preparation of *N*-silyl vinylketene imines with allylic cyanide derivatives were initiated.

2-Methyl-3-butenenitrile (**96**) was chosen as a valuable pronucleophile because it is a readily available and inexpensive starting material (13 ¢/gram, TCI) and the methyl substituent at C(2) should inhibit competitive α-C-silylation. Gratifyingly, it was found that the *N*-silyl vinylketene imine **102** could be prepared in good yield and selectivity by addition of **96** to a pre-cooled solution of lithium diisopropylamide and TIPSCl in THF (Scheme 42). The ketene imine product was isolated as a thermally-stable, yellow liquid, which could be purified by distillation and handled in air without significant hydrolysis. When stored at -10 °C *N*-silyl vinylketene imine **102** exhibited excellent stability, showing little decomposition even after storage for 8 months.

Scheme 42



5.4.2. In Situ IR Rate Study For *N*-Silyl Vinylketene Imine Additions. With a convenient preparation of *N*-silyl vinylketene imine **102** established, studies were initiated to test the reactivity of this nucleophile in Lewis base catalyzed aldol reactions. The reaction rate for the addition of **102** to benzaldehyde in the presence of stoichiometric quantities of $SiCl_4$ and 10 mol % of achiral Lewis base **103** were investigated by in situ IR analysis (Figure 20). Not surprisingly, an extremely rapid rate of addition (< 30 sec) was observed by monitoring the loss of the carbonyl absorption at 1700 cm^{-1}, even at sub-ambient temperatures. The unsaturated nitrile **104** resulting from selective γ-addition to benzaldehyde was isolated in good yield and high diastereoselectivity following workup and chromatographic purification.



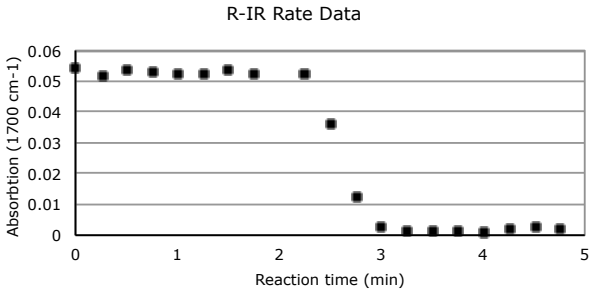
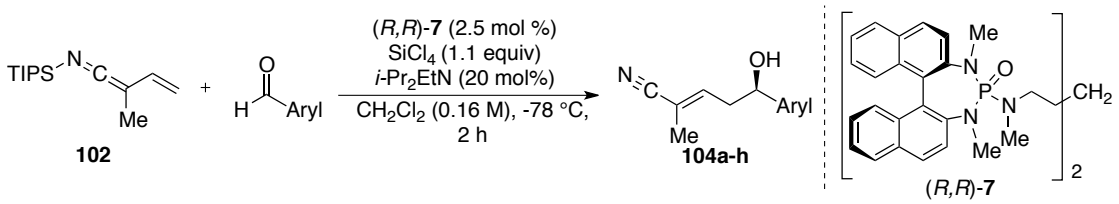
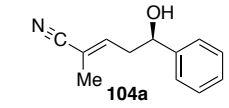
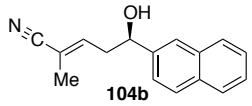
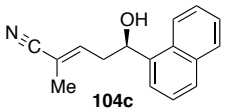
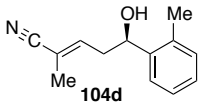
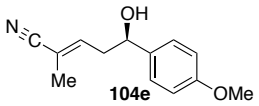
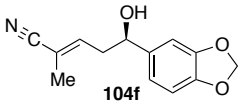
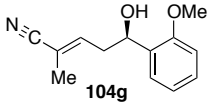
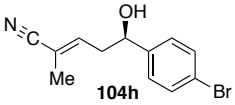
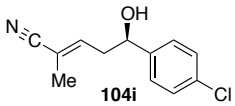
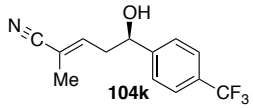


Figure 20. In situ IR data for addition of **102** to benzaldehyde catalyzed by Lewis base **103**

5.4.3. *N*-Silyl Vinylketene Imine Addition to Aromatic Aldehydes. The initial result obtained from the IR rate study demonstrated that excellent control over the site-selectivity of addition as well as double bond geometry in the unsaturated nitrile is obtained. However, it was still unclear if enantioselective versions of this process could be affected using chiral Lewis bases. To determine the efficacy of *N*-silyl vinylketene imines in Lewis base catalyzed, enantioselective additions, nucleophile **102** was combined with benzaldehyde using a stoichiometric quantity of $SiCl_4$ and only 2.5 mol % of chiral, non-racemic bis-phosphoramide (*R,R*)-**7.** Under these reaction conditions, the (*E*)-nitrile **104a** resulting from selective γ-addition was obtained in high yield and with good enantioselectivity (Table 9, entry 1). To establish the generality of this reaction with respect to the aromatic residue, various electron-rich, electron-poor and hindered aromatic aldehydes were investigated (Table 9). In general, unsaturated nitriles (**104a-k**) derived from selective γ-addition of SKI **102** were obtained in excellent yield and with high levels of both diastereo- and enantioselectivity. Electron neutral aromatic aldehydes such as benzaldehyde, 2-naphthaldehyde and 4-brombenzaldehyde underwent addition in high yield and good enantioselectivities (Table 9, entries 1-2 and 8). Throughout the study electron-rich aromatic aldehydes exhibited the highest enantiomeric ratios, for example addition of SKI **102** to 4-methoxybenzaldehyde gave nitrile product **104e** with 97:3 er (Table 9, entry 5). Whereas highly electron-deficient aromatic aldehydes reacted with high selectivities, electron poor substrates, such as 4-trifluromethylbenzaldehyde, reacted with reduced enantioselectivity (Table 9, entry 10). However, addition to slightly less electron poor aromatic aldehydes produced nitrile products in good yield and enantioselectivity (*e.g.* 4-chlorobenzaldehyde, Table 9, entry 9).

Table 9. Aromatic Aldehyde Survey in the addition of SKI **15** catalyzed by (*R,R*)-18



Entry	Product	Yield, (%)[b]	γ:α[c]	*E*:*Z*[c]	er[d]
1	 **104a**	97	98:2	99:1	93.4:6.6
2	 **104b**	97	99:1	99:1	92:9:7.1
3	 **104c**	84	95:5	93:7	59.5:40.5 (*E*) 94.3:5.7 (*Z*)
4	 **104d**	87	95:5	98:2	92.3:7.7
5	 **104e**	91	99:1	99:1	97.0:3.0
6	 **104f**	93	99:1	97:3	92.9:7.1
7	 **104g**	93	95:5	98:2	94.5:5.5
8	 **104h**	95	97:3	98:2	92.6:7.4
9	 **104i**	91	97:3	97:3	91.4:8.6
10	 **104k**	93	92:8	99:1	77.2:22.8

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.15 equiv of silyl ketene imine, 0.2 equiv of *i*-Pr_2EtN 0.025 equiv of (*R,R*)-**5** at 0.15 M in CH_2Cl_2 at –78 °C for 2h. [b]Yield of analytically pure material. [c]Determined by ^{1}HNMR (500 MHz) analysis of crude reaction mixture. [d]Determined by CSP-SFC analysis.

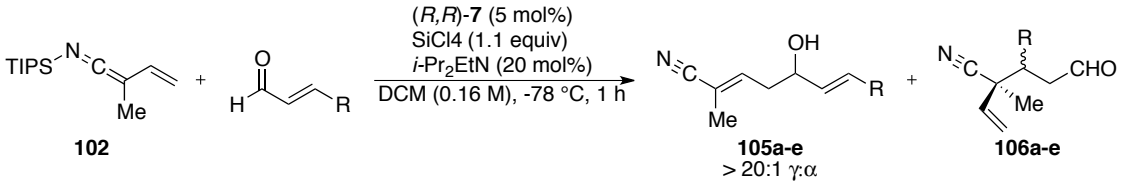
The lowest enantioselectivity observed in the survey was for the addition to the sterically hindered aromatic aldehyde, 1-naphthaldehyde. Interestingly, in this case a large disparity was observed in the enantiomeric ratios for the isolated (*E*)- and (*Z*)-nitriles (Table 9, entry 3). Previous studies with this catalyst system have also noted higher observed enantioselectivities for the minor diastereomer, but the difference is typically not as dramatic. Importantly, additions to slightly less hindered aromatic aldehydes such as 2-methyl benzaldehyde and 2-methoxybenzaldehdye, yielded nitrile products in good diastereo- and enantioselectivity.

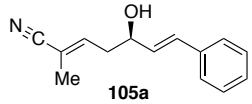
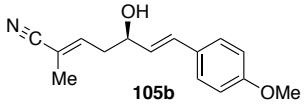
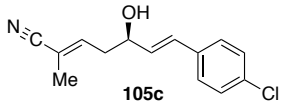
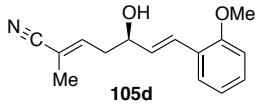
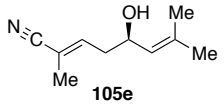
5.4.4. *N*-Silyl Vinylketene Imine Addition to Olefinic Aldehydes. To further elaborate the electrophile scope of the reaction, a survey of olefinic aldehydes was conducted. This substrate class presents additional challenges because the catalyst has to dictate the site selectivity for addition in both the nucleophile (N_α/N_γ) and the electrophile ($E_{1,2}/E_{1,4}$). The pairwise combination of these two variables leads to a total of four different constitutional isomers that can result from the addition of SKI **102** to a α,β-unsaturated aldehyde. Further analysis of the stereochemistry for this process reveals four possible stereoisomers within each constitutional isomer; therefore to achieve selectivity in this system requires the production of one out of sixteen possible isomers.

Initial studies for the reaction of *N*-silyl vinylketene imine **102** with an α,β-unsaturated aldehyde was conducted using conditions similar to those employed for additions to aromatic aldehydes. However, the catalyst loading was increased to 5 mol % because preliminary rate studies revealed, an extremely fast reaction even in the absence of Lewis base catalyst (see, Experimental Section). Under these conditions, the addition of SKI **102** to cinnamaldehyde was examined (Table 10, entry 1). Analysis of the crude reaction mixture by ^{1}H NMR showed high

constitutional selectivity for γ-attack of nucleophile **102** to the carbonyl of the enal (1,2-addition) giving diene **105a** in good yield and high enantioselectivity.

Table 10. Olefinic aldehyde survey in the addition of SKI **102** catalyzed by (*R,R*)-**7**



Entry	Product	Yield, (%)[b]	1,2:1,4[c]	*E*:*Z*[c]	Er[d]
1	 **105a**	83	92:8	99:1	92.4:7.6
2	 **105b**	79	93:7	98:2	92.7:7.3
3	 **105c**	83	92:8	99:1	91.7:8.3
4	 **105d**	78	90:10	94:6	94.0:6.0
5	 **105e**	63	85:15	99:1	72.0:28.0

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.15 equiv of silyl ketene imine, 0.2 equiv of *i*-Pr_2EtN, 5 mol % of (*R,R*)-**7** at 0.16 M in CH_2Cl_2 at –78 °C for 2h. [b]Yield of analytically pure material. [c]Determined by ^{1}H NMR (500 MHz) analysis of crude reaction mixture. [d]Determined by CSP-SFC analysis

In response to the promising result obtained from addition to cinnamaldehyde, other commercially available aromatic enals were evaluated in the reaction and overall diene products (**105a-d**) were isolated in good yield, excellent geometrical purity and good enantioselectivity (Table 10, entries 1-4). In line with the results observed in the addition to aromatic aldehydes, the highest enantioselectivities were achieved for reactions with electron rich aromatic enals, such as 2- and 4-methoxycinnamaldehyde (Table 10, entries 2 and 4, respectively). Furthermore,

electron poor aromatic enal, 4-chlorocinnamaldehyde, also underwent addition with good site- and enantioselectivity (Table 10, entry 3).

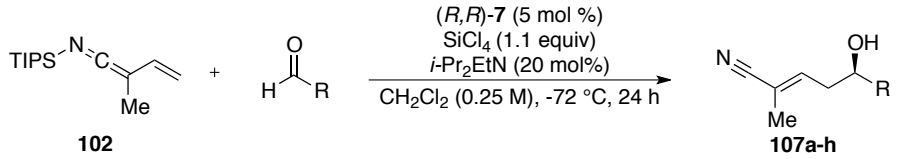
Continuing to examine the scope of this reaction, an aliphatic enal was also tested in the addition. Reaction of SKI **102** with 3-methyl-2-butenal exhibited good constitutional selectivity, but the diene product **105e** was isolated with attenuated yield and enantioselectivity (Table 10, entry 5). This result suggests that these more reactive substrates are undergoing competitive achiral background reactions with $SiCl_4$, but more conclusive studies need to be conducted. Interestingly, the observed aldehyde side products for the additions of SKI **102** to enals always resulted from α-addition of the nucleophile regardless of the substitution of the α,β-unsaturated aldehyde.

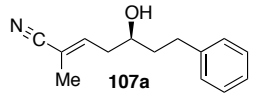
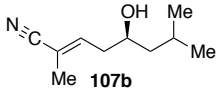
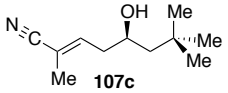
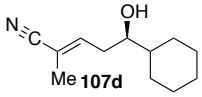
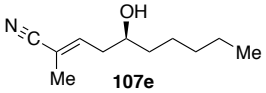
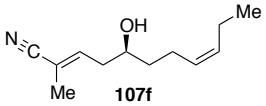
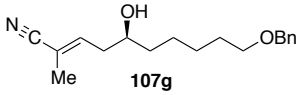
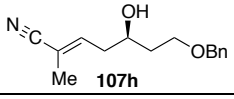
5.4.5. *N*-Silyl Vinylketene Imine Addition to Aliphatic Aldehydes. Although high selectivities and good isolated yields have been observed with the addition of SKI **102** to aromatic and olefinic aldehydes, for this nucleophile to be broadly applicable, it must also be able to combine with aliphatic aldehydes. Past studies on Lewis base catalyzed aldol additions with (*R,R*)-**7**/$SiCl_4$ have shown attenuated reactivity for aliphatic aldehydes as compared to aromatic or olefinic substrates.[23b] This disparity in reactivity has been attributed to the formation of an α-chloro trichlorosilyl ether, resulting from addition of an ionized chloride to the aldehyde after the Lewis base-trichlorosilyl cation has activated it. Due to the unfavorable equilibrium that exists between the activated aldehyde and the unreactive chloride addition product, reactions with aliphatic aldehydes generally require more reactive nucleophiles and extended reaction times. With regard to Lewis base catalyzed silyl ketene imine additions to aliphatic aldehydes has been an unattainable goal due to the added strain energy accrued during the formation of a quaternary carbon. However, *N*-silyl vinylketene imines have generated renewed interest in this

substrate class because reaction through the γ-C position of the ketene imine is relatively free of steric hindrance. To test this hypothesis, SKI **102** was combined with hydrocinnamaldehyde using conditions similar to those previously reported for the addition of silyl dienolates derived from α,β-unsaturated esters. Gratifyingly, the reaction selectively afforded the (*E*)-γ-addition product **107a** in moderate yield and excellent enantioselectivity (Table 11, entry 1). Optimization studies revealed that the moderate yields in the addition to hydrocinnamaldehyde arise from incomplete consumption of the aldehyde. Employing slightly elevated temperatures (–55 °C) eliminated this problem and synthetically useful yields of nitrile product **107a** were obtained with only minor reductions in the enantioselectivity. A range of aliphatic aldehydes was tested to explore how the reaction responds to various substitution patterns, as well as its functional group tolerance. Overall, the addition was highly selective for formation of the (*E*)-γ-unsaturated nitriles in moderate to good isolated yields and with good to excellent enantioselectivities. Aldehydes containing a β-branching substituent gave nitrile products (**107a-c**) with the highest levels of enantiopurity (Table 11 entries 1-3), whilst aldehydes containing a linear aliphatic chain, reacted with moderate to good enantioselectivity (Table 11, entries 5-8). To examine functional group compatibility in the addition of SKI **102**, aliphatic aldehydes containing either isolated olefins or benzlyoxy ethers were tested. Overall high functional group tolerance was observed, as noted by the good yields, site selectivities and enantioselectivities obtained for these γ-nitrile products (**107f-h**). However, for the aldehydes containing ethereal linkages, the reaction was sensitive to the position of the oxygen in the chain. For example, reaction with 3-benzyloxypropanal (Table 11, entry 8) resulted in reduced enantiomeric ratios as compared to 5-benzylxoxyhexanal (Table 11, entry 7). Surprisingly, even more hindered aliphatic aldehydes containing an α-substituent, such as cyclohexanecarboxaldehyde, effectively underwent addition

to give (*E*)-γ-unsaturated nitrile **107d** in moderate yield and excellent enantioselectivity (Table 11, entry 4).

Table 11. Aliphatic Aldehyde Survey in the addition of SKI **102** catalyzed by (*R,R*)-**7**



Entry	Product	Yield, (%)[b]	γ:α[c]	*E*:*Z*[c]	er[d]
1	 **107a**	65 (82)[e]	96:4	99:1	93.4:6.6 (94:6)[e]
2	 **107b**	57 (86)[e]	98:2	99:1	98.5:1.5 (98.0:2.0)[e]
3	 **107c**	82	98:2	99:1	96.0:4.0
4	 **107d**	64	98:2	99:1	98.5:1.5
5	 **107e**	75 (81)[e]	97:3	98:2	92:8 (90:10)[e]
6	 **107f**	55 (86)[e]	96:4	99:1	88:12 (87:13)[e]
7	 **107g**	74	96:4	99:1	90:10
8	 **107h**	54 (78)[e]	96:4	99:1	78:22 (76:24)[e]

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.15 equiv of silyl ketene imine, 0.2 equiv of *i*-Pr_2EtN, 5 mol % of (*R,R*)-**7** at 0.25 M in CH_2Cl_2 at –72 for 2h. [b]Yield of analytically pure material. [c]Determined by ^1H NMR (500 MHz) analysis of crude reaction mixture. [d]Determined by CSP-SFC analysis. [e] Reaction run at -55 °C for 24 h.

5.4.6. Determination of the Absolute and Relative Configuration of the Nitrile Products. The relative configuration of the olefin geometry in the α,β-unsaturated nitriles was unambiguously determined to be *E* by single crystal X-ray crystallographic of compound **104b**, resulting from addition of SKI **15** to 2-naphthaldyde (Figure 21). Correlation of the *E*-double

bond geometry to nitriles derived from other classes of aldehydes (e.g. olefinic and aliphatic) was done by comparison of the ^{13}C and ^{1}H NMR chemical shifts in the alkene subunit (see experimental section).

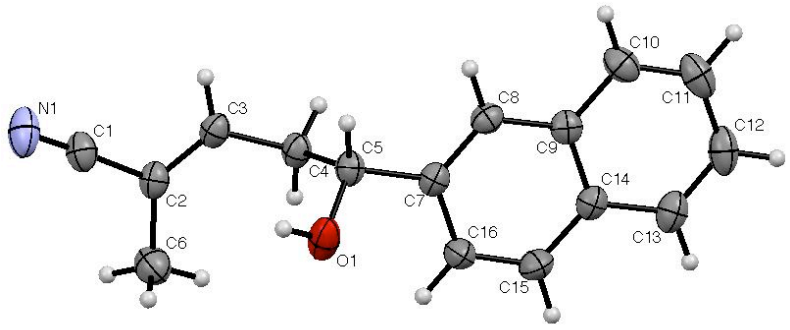


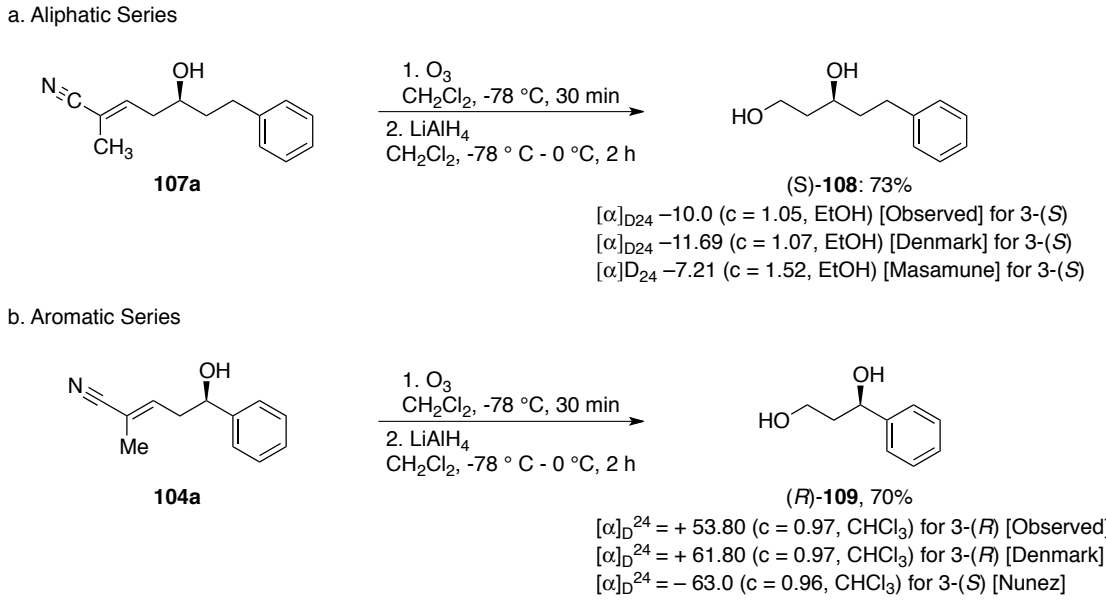
Figure 21. X-ray crystal structure of nitrile **104b** showing *E* double bond geometry of α,β-unsaturated nitrile subunit

The absolute configuration of the products was determined by conversion to a known compounds and then comparison of the optical rotations. Hence, nitrile product **107a** was subjected to ozonolysis followed by reduction with $LiAlH_4$ to afford the expected diol product **108** in good yield. Comparison of the optical rotation for the diol with those reported in literature assured an *S* absolute configuration at the C(3) stereogenic center (Scheme 43a).[27b,102] This configuration confirms a *Re* face attack of SKI **102** to the aldehyde and is consistent with all previous reports for this catalyst system.

Independent conformation of the absolute configuration for the nitrile products derived from the addition SKI **102** to aromatic aldehydes was also confirmed by conversion to a known compound and comparison of the optical rotations.[27b,102] Following the same route, nitrile **104a** underwent ozonolysis followed by reduction with $LiAlH_4$ to give diol product **109** in good yield (Scheme 43b). Optical rotation data comparison for the diol with literature reported values

confirmed the *R* absolute configuration of the product which is also consistent with *Re* face attack of the SKI to the aldehyde.

Scheme 43



5.5 Discussion

5.5.1 Trends in Reactivity for Additions of *N*-Silyl Vinylketene Imine. In the previous chapters on Lewis base catalyzed aldol and Michael additions, direct comparisons of the reactions rates for silyl ketene imines (SKIs) and silyl ketene acetals (SKAs) were made by *in-situ* IR analysis. These studies revealed remarkable rate accelerations for the addition of SKIs in comparison to analogously substituted SKAs. The increased reaction rates were attributed to the unique geometry of the silyl ketene imines, which allows for much of the steric bulk of the nucleophile to reside in a plane perpendicular to and distal from the reacting carbon. This geometry also plays a crucial role in the formation of quaternary centers, where steric factors become exacerbated. However, for the vinylogous additions studied in this chapter steric consideration should play a less dominate role because the addition occurs at the γ-carbon distal

to the steric hindrance imposed by the bulky silyl groups. Interestingly, comparison of the reaction rates between SKIs and SKAs in these γ-additions may speak more to the inherent electronic differences that exist between these two nucleophile classes.

Previous studies conducted in these laboratories by Dr. Greg Beutner and Dr. John Heemstra have already established a baseline rate of reactivity for α-methyl substituted silyl dienol ethers[25] derived from esters and amides.[27] Interestingly, these studies already show a dramatic rate difference between the nucleophilicity of silyl ketene acetal **110** and silyl ketene aminal **111** in the addition to hydrocinnamaldehyde. Under very similar reaction conditions, the ester-derived nucleophile shows no reaction in the addition to hydrocinnamaldehyde, whereas, the morpholine amide-derived silyl dienolate yields vinylogous aldol product **112** in low yield but with excellent enantioselectivity (Figure 22).

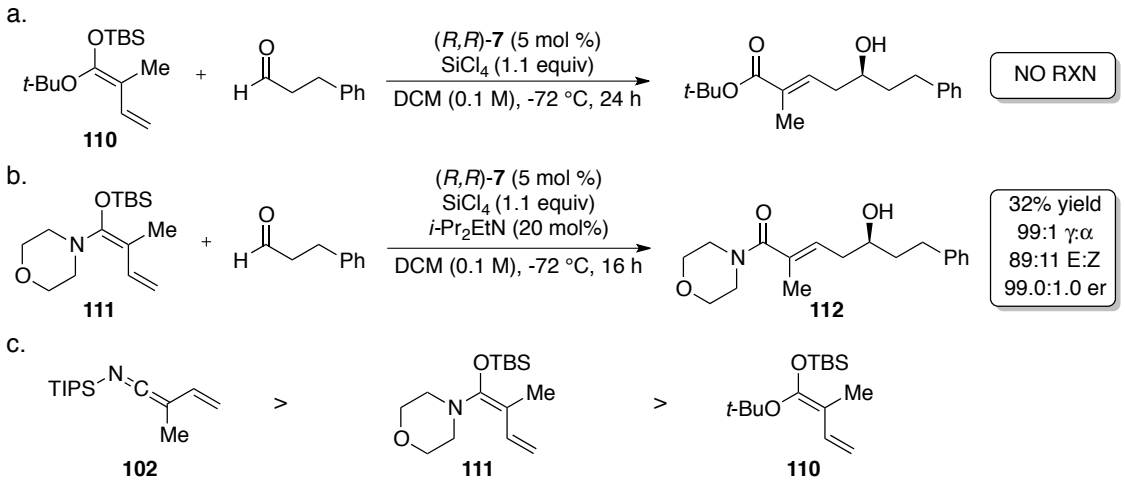


Figure 22. (a) Addition of ester derived silyl ketene acetal **110** to hydrocinnamaldehyde. (b) Addition of amide derived silyl ketene aminal **111** to hydrocinnamaldehyde. (c) Qualitative ordering of the nucleophilicity observed for silyl ketene imine, aminal, and acetal in Lewis base catalyzed vinylogous aldol reaction

Comparing the results for addition of silyl ketene acetals and aminals with those obtained in the current study suggests that silyl ketene imines are the most reactive nucleophile of the three classes. This is supported by the findings observed for the addition of SKI **102** to aliphatic

aldehydes, which showed a 65% yield and 96:4 er for the reaction with hydrocinnamaldehyde (Table 11, entry 1). However, this is only a qualitative analysis based on isolated yields collected from different researchers. Independent rate studies conducted under identical conditions have not been performed.

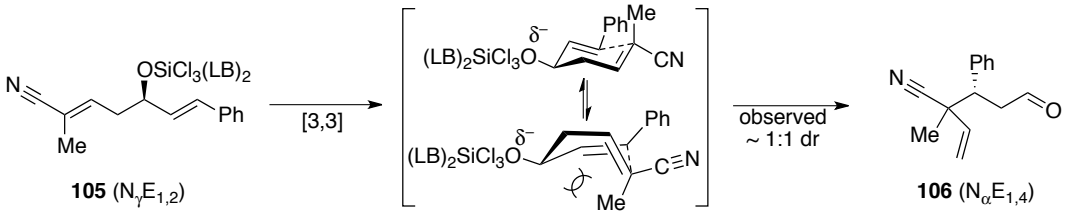
5.5.2 Trends in Site-Selectivity for Additions of *N*-Silyl Vinylketene Imine. The addition of *N*-vinyl silylketene imine **102** to a wide variety of aldehydes showed extremely high selectivity for γ-addition. Computational studies on related silyl dienolates derived from unsaturated esters and amides have shown that both the HOMO orbital coefficient and the electrophilic susceptibility parameter are highest at C(4), which is consistent with the highly selective γ-additions observed for these nucleophiles.[72b] Although direct computational studies have yet to be performed on silyl ketene imines derived from unsaturated nitriles, similar trends in the orbital coefficients and electron density are predicted.

Another factor that will influence the site of reactivity in the addition is the steric influence provided by the substantial phosphoramide bound silyl cation. Previous studies from theses laboratories have revealed the sensitivity of the (*R,R*)-**7**/$SiCl_4$ catalyst system to the steric environment around the nucleophile. In general, addition at the less hindered γ-carbon of unsaturated nucleophiles is favored since this avoids repulsive steric interactions between the Lewis base/silyl cation and alkoxy substituents of the nucleophile. In the case of silyl ketene imine **102**, steric consideration should also play an important role in the site selectivity because addition at the α-carbon (C(2)) leads to the formation of quaternary center.

An interesting observation from the reactions of *N*-silyl vinylketene imine **102** with α,β-unsaturated aldehydes was the selectivity for α-addition observed in the minor product resulting from 1,4-additon of the SKI to the enal. Even though steric interactions with the catalyst will be

less influential at this remote position of the electrophile, exclusive α-attack of the more hindered site in the nucleophiles is surprising. A possible explanation to explain this outcome is that the minor side product **106** results from an oxy-Cope [3,3] rearrangement of the major γ-nitrile **105** (Scheme 44). Neutral oxy-Cope rearrangements require a very high activation barrier, however the rate can be enormously accelerated by increasing the negative charge at oxygen for example through deprotonation (*e.g.* anionic oxy-Cope).[76] A similar increase in rate could be observed for the oxy-Cope rearrangement proposed here, because coordination of the Lewis base to the trichlorosilyl ether will lead polarization and hence enhancement of the electron density at the oxygen. Contrary to this hypothesis is the observation of both *syn* and *anti* diastereomers of the aldehyde product **106** in nearly equivalent amounts. This observation requires that the reaction proceeds through an equal populations of both chair and boat transition structures in the [3,3] rearrangement, because the γ-adduct **105** was formed with high selectivity as the (*E,E*)-diene. Furthermore, the oxy-Cope rearrangement is predicted to be thermodynamically uphill in this case, due to a loss in conjugation of the alkene double bonds of the starting material.

Scheme 44



5.5.3 Trends in Diastereoselectivity for Additions of *N*-Silyl Vinylketene Imine. The addition of *N*-silyl vinylketene imine **102** showed very high selectivity for formation of the (*E*)-nitrile regardless of the class of aldehyde or its substitution pattern. The observed *E* double geometry in the products relays information about the orientation in which the silyl ketene imine

attacks the aldehyde-catalyst complex. Formation of the *E*-double bond requires attack of the nucleophile in an *s-trans* conformation, whereas, a *Z*-double bond would necessitate an *s-cis* arrangement. The extremely high selectivity for formation of the *E*-isomer can be rationalized by considering open transition structure models for the addition of SKI **102** to an aldehyde activated by the silyl cation/Lewis base complex (Figure 23). The antiperiplanar transition structure in which SKI attacks in an *s-trans* orientation allows for the most minimization of unfavorable steric and dipole-dipole interactions ($ap_{s\text{-}trans}$). Alternatively, the transition structure leading to the formation of the (*Z*)-nitrile requires the ketene imine fragment to come in close proximity of the sizable Lewis base activated trichlorosilyl cation ($ap_{s\text{-}cis}$). Furthermore, the *s-cis* geometry of the silyl ketene shows unfavorable allylic strain ($A_{1,2}$) between the α-methyl substituent and the vinyl hydrogen.

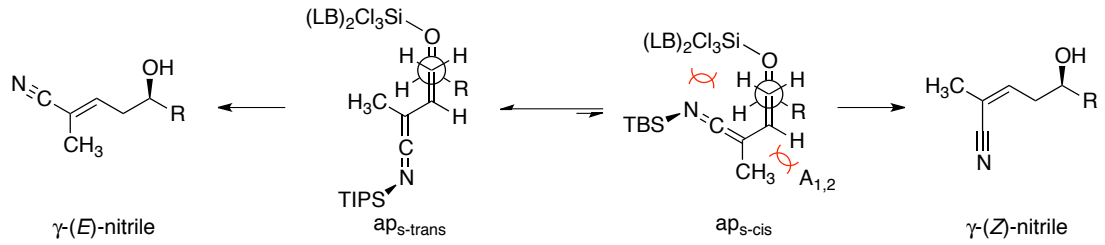


Figure 23. Open transition structures and conformation of SKI **102**

5.5.4 Trends in Enantioselectivity for Additions of *N*-Silyl Vinylketene Imine. Overall (*R,R*)-**7** was a very effective catalyst for the additions of SKI **102** to aldehydes allowing the isolation of nitrile products with good to high enantioselectivities. With aromatic aldehydes, the highest selectivities were achieved with electron-rich aromatic rings. However, extremely electron-poor substrates such as, 4-trifluromethylbenzaldehyde, reacted with moderate enantioselectivity (72:28 er). This observation is consistent with a competitive achiral background promoted by unactivated $SiCl_4$. Good enantioselectivities with electron-poor

aromatic aldehydes have been reported for the addition of amide and ester derived silyl dienolates within this catalyst system. A competitive achiral background reaction for *N*-silyl vinylketene imine **102** is further supported by the observation that these nucleophiles are more reactive then their ester or amide analogs.

For additions of SKI **102** to aliphatic aldehydes, the highest enantioselectivities were observed for substrates containing a β-substituent. Aldehydes containing a linear alkyl-chain reacted with moderate to good enantioselectivity in the addition of SKI **102**. This difference in selectivity could be attributed to an increased degree of conformational freedom available to linear aliphatic aldehydes in the binding pocket. Similar trends with respect to aliphatic aldehydes have been noted in earlier studies using this catalyst system.[27b]

The lowest enantioselectivity in the aliphatic series were observed for linear substrates containing a benzyloxy substituent proximal to the carbonyl group. In this case, the Lewis basic oxygen of the benzyloxy group could be binding the activated trichlorosilyl cation though a favorable six-membered chelate. This would block one of the coordination sites on the silicon typically occupied by one of the phosphoramide Lewis bases, and lead to a less selective addition.

5.6 Conclusions and Outlook

In conclusion, a novel Lewis base catalyzed aldol addition reaction of an N-silyl vinyl ketene imines has been reported. This stable, storable silylated nucleophile is easily prepared in a single step from 2-methyl-3-butene nitrile and addresses some of the current challenges associated with the reactions of allylic cyanide anions. The reactions show exceptionally high site-selectivity for γ-addition of the nucleophile to a diverse range of aldehyde acceptors including: aromatic, olefinic and aliphatic. The resulting α,β-unsaturated nitrile products are obtained in good to high yield and with excellent selectivity for formation of the (*E*)-double bond

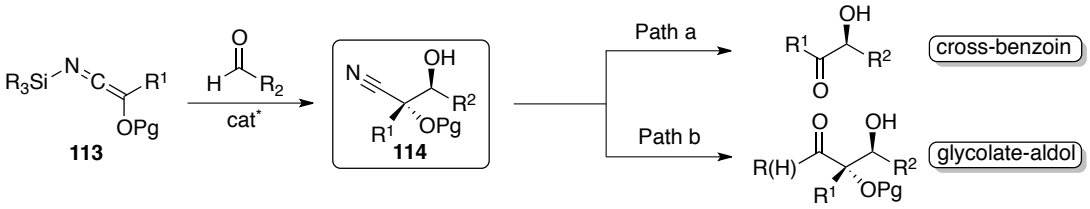
isomer. Furthermore, the nitrile products could be prepared with good to excellent enantioselectivity by employing Lewis base catalyst (*R,R*)-**7** in loadings as low as 0.025 equivalents. Future studies will focus on extending the scope of this reaction with respect to the *N*-silyl vinyl ketene imine as well as exploring the reactivity of other classes of electrophiles such as ketones and imines. Additionally, the synthetic utility of the products will be explored by examining useful transformations of the α,β-unsaturated nitrile.

Chapter 6: Synthesis and Application of N-Silyl Oxyketene Imines in Lewis Base Catalyzed, Enantioselective Carbonyl Addition Reactions

6.1 Introduction

The deprotonation of protected cyanohydrins and the subsequent reactions of the resulting metallo ketene imines with carbon-based electrophiles is a well-established method for constructing carbon-carbon bonds.[77] When applied to carbonyl additions, extremely versatile β-hydroxy cyanohydrins **114** are obtained (Scheme 45). The usefulness of these products arises from the ability of cyanide to act as either a leaving group through deprotection/retrocyanation (path a, Scheme 45), or to be revealed as a carbonyl compound through hydrolysis, reduction or organometallic addition (path b, Scheme 45). Unfortunately, the generation of metalated ketene imines requires stoichiometric quantities of strong amide or alkyllithium bases which severely limits the extension of this process to a catalytic, enantioselective variant. The following chapter describes the development of a new class of stable, isolable *N*-silyl oxyketene imines **113** derived from protected cyanohydrins. These latent nucleophiles harness the reactivity of a metallo ketene imine and allow for the catalytic, enantioselective synthesis of β-hydroxy cyanohydrins and their subsequent application to cross-benzoin and glycolate aldol reactions.

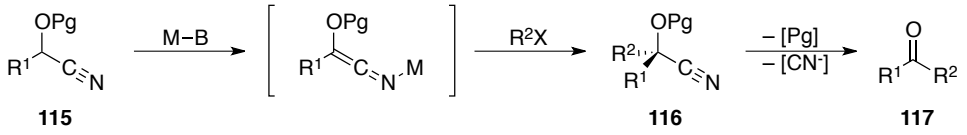
Scheme 45



6.2 Background

6.2.1 Stoichiometric Methods for Generating Nucleophilic Cyanohydrins. Stork and Maldonado were the first to recognize the utility nucleophilic cyanohydrins offer for carbon-carbon bond formation. In their seminal paper, protected cyanohydrins **115** are rendered nucleophilic by deprotonation with a strong base (Scheme 46).[77b] Capture of these anionic ketene imine intermediates with various electrophiles gives chiral cyanocarbinols **116**, which can subsequently be revealed as new ketone products **117** after deprotection and retrocyanation. Because the protected cyanohydrins are readily prepared from aldehydes, the overall transformation provides a convenient method for achieving polarity inversion of the carbonyl function. Despite useful extensions of this work by others,[78] as well as numerous implementations of the strategy in synthesis,[77a] little is known about enantioselective versions of this process that aim to preserve the stereochemical attributes of the cyanocarbinol products **116**.

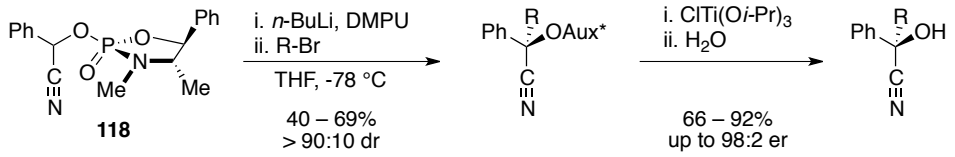
Scheme 46



115 **116** **117**

6.2.2 Enantioselective Reactions of Nucleophilic Cyanohydrins – Chiral Auxiliary Methods. The potential benefits that nucleophilic cyanohydrins offer in asymmetric addition reactions have been recognized in recent years. The earliest examples have relied on the use of auxiliary based methods wherein the alkoxy substituent of the cyanohydrin is modified with a chiral, non-racemic group. For example, Schrader has developed a chiral-auxiliary-based method in which benzaldehyde cyanohydrin, modified with an ephedrine-derived *O*-phosphate (**118**) undergoes highly diastereoselective alkylations and Michael reactions (Scheme 47).[79]

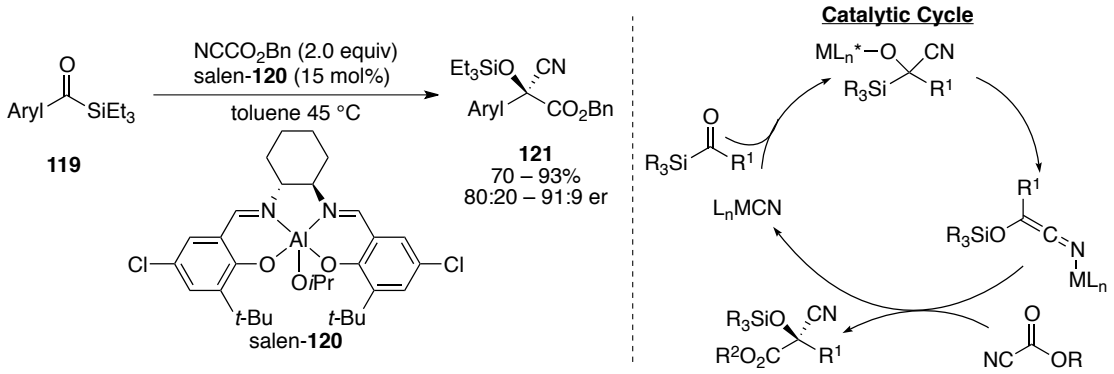
Scheme 47



In a related field of chemistry, Enders and co-workers have developed useful auxiliary-based methods for the asymmetric Michael-type additions of nucleophilic α-aminonitriles.[80] Similar to cyanohydrin reactions, challenging umpolung relationships, such as 1,4-dicarbonyl compounds, can be prepared in high enantiomeric purity after retrocyanation and hydrolysis of the α-aminonitrile. The obvious drawbacks to these methods are the use of stoichiometric amounts of alkyllithium bases and the additional steps required for removal and recovery of the auxiliary.

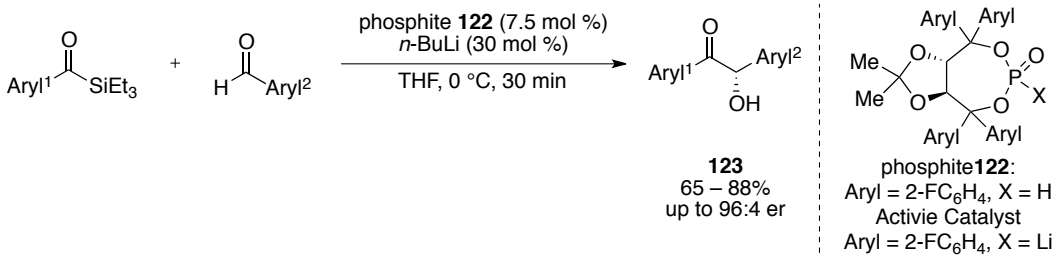
6.2.3 Enantioselective Reactions of Nucleophilic Cyanohydrins – Catalytic, Enantioselective Methods. A novel strategy for accessing the anions of protected cyanohydrins that circumvents the need for strong bases is the cyanide promoted 1,2-Brook rearrangement,[81] of acyl silanes **119** (Scheme 48).[82] Johnson and co-workers have successfully applied this process to catalytic, enantioselective acylations of cyanohydrins by employing a chiral (salen)aluminium alkoxide catalyst **120** and benzyl cyanoformate as both the source of cyanide and the acylating reagent.[83] Although this reaction represents a benchmark for asymmetric reactions of metalated cyanohydrins, the observed enantioselectivities of the product cyano esters **121** were highly substrate dependent and reach a maximum at 91:9 er.

Scheme 48



In a related study, Johnson and co-workers reported the catalytic, enantioselective cross-benzoin reaction of acyl silanes with aldehydes catalyzed by TADDOL-derived metallophosphite **122** (Scheme 49).[84] These reactions also proceed through a nucleophile promoted 1,2-Brook rearrangement, but do not involve the intermediacy of a cyanohydrin anion. Cross-benzoin adducts **123** comprised of two different aromatic aldehydes are obtained in good yield and enantioselectivity (91:9 to 96.5:4.5 er), but the yields and selectivities were significantly reduced with aliphatic aldehydes or acyl silanes. Although limitations in substrate scope are observed for this catalyst system, the method represents a current state-of-the-art for achieving non-enzymatic, catalytic, enantioselective cross-benzoin reactions.[85]

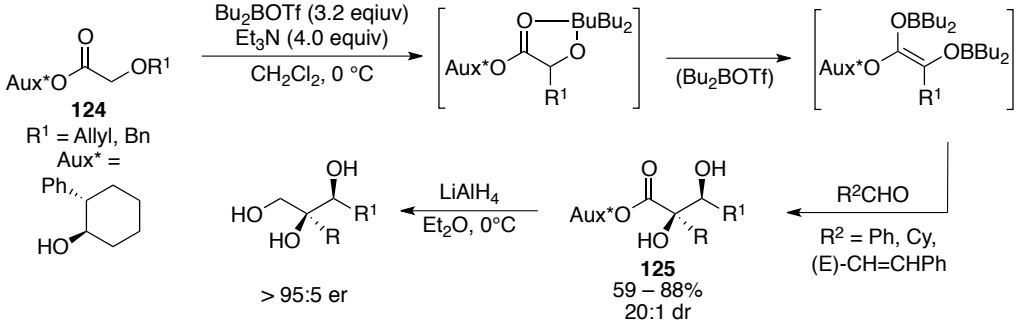
Scheme 49



6.2.4 Synthesis of Glycolate Aldol Products Containing a Tertiary Alcohol – Chiral Auxiliary Methods. Among all of the useful addition reactions of cyanohydrin-derived anions, curiously, the aldol process remains underdeveloped. The products of these reactions are

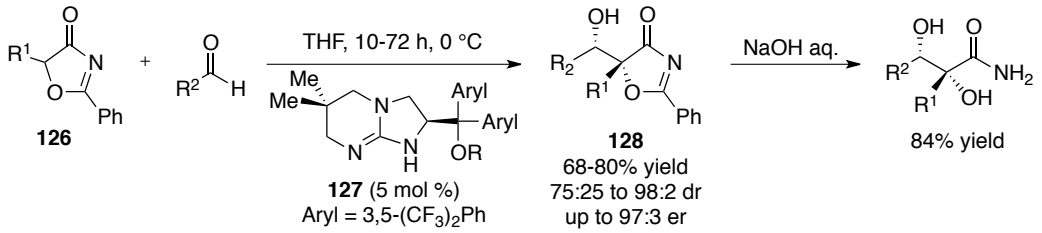
analogous to the aldol additions of α-substituted glycolate enolates and possess a fully substituted α-stereogenic center. Very few methods are capable of delivering this structure in a stereocontrolled fashion. Wolfe and co-workers have reported a chiral auxiliary method in which a boron enolate is generated by the 1,2-Wittig rearrangement of an *O*-alkylglycolates **124**, derived from a chiral alcohol (Scheme 50).[86] The authors demonstrate the utility of the boron enolates through reactions with aromatic, aliphatic or olefinic aldehydes to give diol products **125** in good yields and excellent diastereoselectivities.

Scheme 50



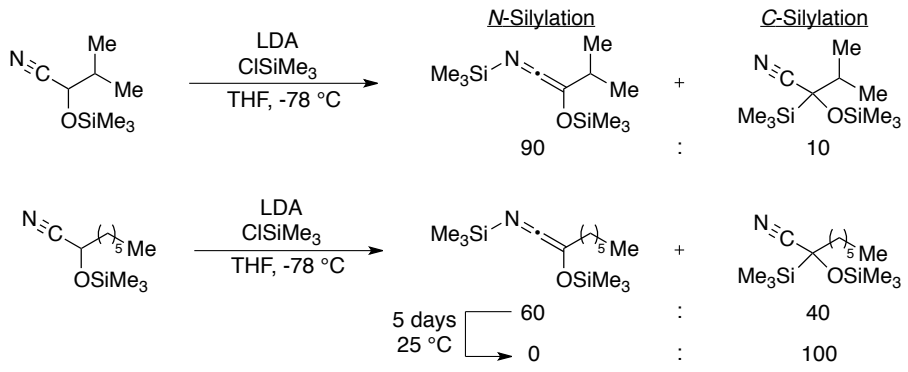
6.2.5 Synthesis of Glycolate Aldol Products Containing a Tertiary Alcohol – Catalytic, Enantioselective Methods. Sugimura and co-workers have described the catalytic, enantioselective additions of 5H-oxazole-4-ones **126** with aldehydes catalyzed by chiral guanidines **127** (Scheme 51).[87] The glycolate aldol products **128** are obtained in good yield and enantioselectivity, but the diastereoselectivity is highly dependent on the substrates. Additionally, the reaction is limited to cyclic donors, which further emphasizes the challenges inherent in controlling enolate geometry for acyclic disubstituted substrates.[51,54] Although the preparation of secondary alcohols by catalytic, enantioselective glycolate aldol additions are known,[28,88] Sugimura's method is the first in which tetrasubstituted stereogenic centers are obtained.

Scheme 51



6.2.6 Synthesis of *N*-Silyl Oxyketene Imines. Previous studies from these laboratories[69] and others[44] have documented the advantages that silyl ketene imines offer in the catalytic, enantioselective synthesis of compounds containing quaternary stereogenic centers. These nucleophiles are readily prepared in high yield and purity by the deprotonation of disubstituted alkyl or aryl nitriles, followed by trapping of the resulting anion with an appropriate trialkylsilyl chloride. Surprisingly, the analogous reactions of protected cyanohydrins are practically unknown. A single account by Cunico and Kuan on the deprotonation of trimethylsilyl-protected cyanohydrins by lithium diisopropylamide and subsequent trapping with trimethylsilyl chloride appeared in 1992 (Scheme 52).[36] This study reveals that the site of silylation of the metallo ketene imine is highly responsive to the size of the alkyl substituent of the cyanohydrin. For example, cyanohydrin derived from acetaldehyde gave exclusively *C*-silylated nitrile, whereas, cyanohydrin derived from isobutyraldehyde gave primarily *N*-silylated ketene imine (90:10 ratio, *N*- to *C*-silylation). Intermediate results are observed with cyanohydrin prepared from 1-hexanal (60:40 ratio, *N*- to *C*-silylation), but interestingly the ratio changes in favor of *C*-silylation upon standing for 5 days at 25 °C (16:84 ratio, *N*- to *C*-silylation). These results suggest that the initial product distribution is, at least partially under kinetic control, and that the *C*-silylated isomer is the thermodynamically more stable product. Despite these promising findings, no subsequent reports on the preparation and/or utilization of silyl ketene imines derived from protected cyanohydrins are on record.

Scheme 52



6.3 Research Objectives

Chapter 3 detailed the use of silyl ketene imines derived from α,α-disubstituted nitriles for the Lewis base catalyzed, $SiCl_4$-mediated aldol reactions with aromatic aldehydes. The reactions were characterized by exceptionally facile addition rates, good isolated yields, and excellent diastereo- and enantioselectivities. Motivated by the successful application of silyl ketene imines in this catalyst system, research was directed towards the development of analogous reactions of silyl ketene imines derived from protected cyanohydrins. The first goal of the study was to identify suitable protecting groups for the cyanohydrins that would allow for the preparation of *N*-silyl oxyketene imines with high selectivity for *N*- vs. *C*-silylation. After a suitable protecting group is chosen and a procedure for the synthesis of oxyketene imines is developed, focus will shift to the application of these nucleophiles in Lewis base catalyzed aldol additions. The products of these reactions will be the nitrile analogs of glycolate aldol products containing a stereogenic tertiary alcohol. The final goals of the current research will be to develop useful transformations that capitalize on the ability of cyanide to act as either a leaving group or to be revealed as a carbonyl compound through functional group manipulation.

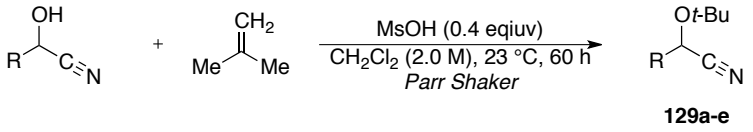
6.4 Results

6.4.1 Synthesis of *t*-Butyl Protected Cyanohydrins. The work of Cunico and Kuan demonstrates the crucial role that sterics effects play in obtaining *N*-silyl oxyketene imines versus the more thermodynamically favored *C*-silylated isomer. Therefore, the first goal of the current study was to identify and synthesize a suitably protected cyanohydrin that would allow for the selective formation of the ketene imine. Specifically, an *O*-protecting group was sought that met the following criteria: (1) sterically bulky so that silylation at the less encumbered *N*-terminus will be favored, (2) able to be installed under acidic conditions because of the sensitivity of cyanohydrins to basic media, (3) stable to alkyllithium and amide bases, and (4) high yielding, robust and scalable procedures for the preparation and removal.

The *tert*-butyl group embodies all of these characteristics; however, methods for installing this moiety on a cyanohydrin are very rare. A single example by Watt and coworkers describes a scalable process for the protection of formaldehyde cyanohydrin using isobutylene and a catalytic amount of sulfuric acid.[89] Following this precedent, *tert*-butyl protected cyanohydrins derived from aliphatic aldehydes could be obtained reproducibly in 30-40% yields and on multigram scale. Careful inspection of the ^{1}H NMR spectra of the crude reaction mixtures revealed that the low yields were primarily due to a competitive Ritter process[90] which consumed one equivalent of the cyanohydrin and yielded the corresponding *tert*-butyl amide. In the mechanism of the Ritter reaction, water is required to hydrolyze the *tert*-butyl nitrilium ion intermediate, thus rigorous exclusion of moisture from these reactions should prevent this side process from occurring. To this end, a new procedure was employed wherein the crude cyanohydrins were thoroughly dried with $MgSO_4$ and then distilled prior to use. Additionally, anhydrous methanesulfonic acid was employed as the acid catalyst and the loading was raised to

increase the reaction rate. Under these optimized reaction conditions, analytically pure *tert*-butyl protected cyanohydrins **129a-e** were obtained in moderate to good yield and on multi-gram scale after distillation (Table 12). With a practical, convenient and scaleable route for the preparation of various *tert*-butoxy nitriles, studies aimed at the synthesis of *N*-silyl oxyketene imines were undertaken.

Table 12. Synthesis of *t*-Butyl Protected Cyanohydrins



129a-e

Entry	R^2	Product	Yield,%[b]
1	H	**129a**	65
2	Me	**129b**	50
3	Et	**129c**	57
4	*i*-Bu	**129d**	52
5	Bn	**129e**	60

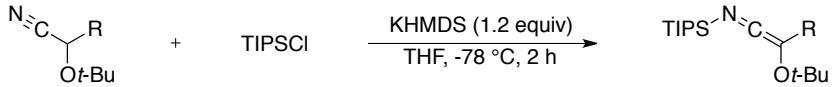
[a]All reactions employed 25 eqiuv of isobutylene and 0.4 eqiuv of methanesulfonic acid in dichloromethane. [c]Yield of analytically pure material, reported after short-path distillation under reduced pressure.

6.4.2 Synthesis of *N*-silyl Oxyketene Imines. The ability of metalated nitriles to undergo competitive *C*-silylation is well documented and previous studies have shown that the size of the silylating agent has a large influence on the sight of silylation.[34-35,91] In the case of protected cyanohydrins, the smaller size of the intervening oxygen atom could attenuate the influence of the protecting group and result in a higher degree of *C*-silylation, relative to disubstituted alkyl or aryl nitriles. In this case, the steric bulk of the silylating agent could play an important role in the selective synthesis of *N*-silyl oxyketene imines.

Accordingly, triisopropylsilyl chloride (TIPSCl) was selected as the silylating agent and the deprotonation/silylation of *tert*-butyl protected cyanohydrins under various conditions was studied. Gratifyingly, it was found that *N*-silyl oxyketene imines **130b-f** could be prepared in

excellent yield and selectivity by the use of KHMDS as the base at -78 °C in THF (Table 13).[27a] The products were obtained as liquids in high purity by simple filtration through Celite and removal of the volatile materials under vacuum. The silyl ketene imines were stable for months when stored at 4 °C, although partial isomerization to the *C*-silylated nitrile was observed upon distillation. Additionally, the compounds were surprisingly resilient to hydrolysis and could be filtered and handled in air without significant decomposition.

Table 13. Preparation of *N*-Silyl Oxyketene Imines from *tert*-Butyl Protected Cyanohydrins



129b-f **130b-f**

Entry	R	Product	Yield, %[b]	υ max, (cm-1)[c]
1	Me	**130b**	94	2037
2	Et	**130c**	94	2033
3	*i*-Bu	**130d**	93	2036
4	Bn	**130e**	93	2039
5	Allyl[d]	**130f**	97	2037

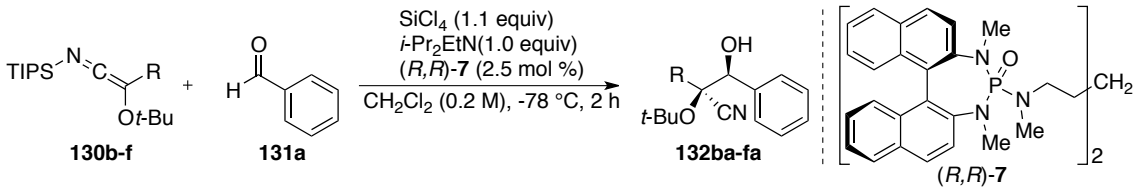
[a]All reactions employed 1.2 eqiuv of KHMDS and 1.1 eqiuv of TIPSCl in THF. [b]Yield of crude ketene imine obtained after filtration and removal of volatiles by high vacuum. [b]FT-IR of neat liquids on NaCl plates. [d]Starting material prepared by alkylation of *tert*-butyl protected formaldehyde cyanohydrin.

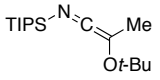
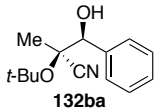
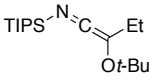
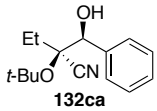
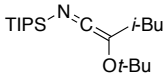
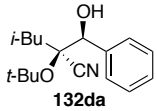
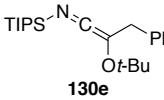
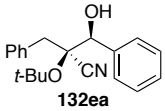
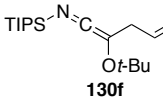
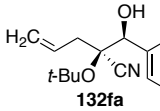
Analysis of the liquids by IR revealed an intense band at 2030 cm^{-1}, which is a characteristic feature of the ketene imine architecture (Table 13). The exclusive formation the *N*-silyl isomer highlight the importance of the *O*-*tert*-butyloxy and *N*-triisopropylsilyl groups, especially when compared to the previous work of Cunico and Kuan, who showed that *C*-silylation absolutely predominates for TMS-protected cyanohydrins derived from simple aldehydes such as acetaldehyde.

6.4.3 Aldol Reactions of *N*-Silyl Oxyketene Imines – Survey of Nucleophile Structure. Although the selective synthesis of *N*-silyl oxyketene imines represents a significant advance in ketene imine chemistry, the ability of these compounds to participate in catalytic,

enantioselective carbonyl addition reactions was unknown. Studies reported previously from these laboratories, have shown that a large array of different silylated nucleophiles,[22,27a,28a,70] including silyl ketene imines,[69,92] are susceptible to Lewis base catalyzed,[8] $SiCl_4$-mediated aldol additions. To determine if *N*-silyl oxyketene imines would be competent nucleophiles in this system, ketene imine **130b** was combined with benzaldehyde (**131a**), 2.5 mol% of (*R,R*)-**7** and a stoichiometric quantity of $SiCl_4$. Under these conditions the desired diol product **132ba** was produced in good yield and excellent diastereo- and enantioselectivity (Table 14, entry 1).

Table 14. Survey of *N*-Silyl Oxyketene Imines in the Addition to Benzaldehyde[a]



entry	nucleophile	product	yield (%)[b]	dr[c]	er[d]
1	 **130b**	 **132ba**	84	96:4	> 99:1[e]
2	 **130c**	 **132ca**	92	98:2	> 99:1
3	 **130d**	 **132da**	92	98:2	> 99:1
4	 **130e**	 **132ea**	93	99:1	> 99:1
5	 **130f**	 **132fa**	90	99:1	> 99:1

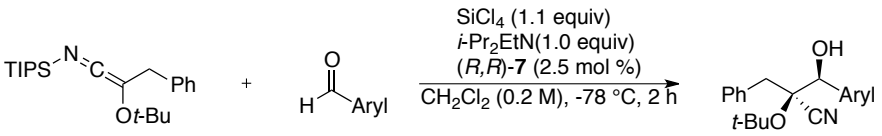
[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.20 equiv of silyl ketene imine, 1.0 equiv of *i*-Pr_2EtN, 2.5 mol % of (*R,R*)-**7** at 0.20 M in CH_2Cl_2 at –78 for 2h. [b] Yield of analytically pure material. [c] Determined by ^1H NMR analysis of the crude reaction mixture [d] Determined by chiral stationary phase supercritical fluid chromatography (CSP-SFC). [e] Determined by CSP-SFC analysis after conversion to the 3,5-dinitrobenzoyl ester .

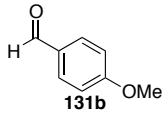
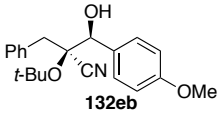
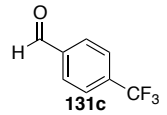
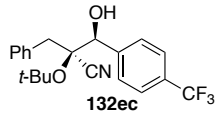
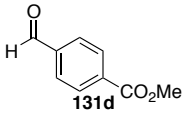
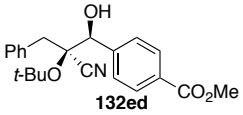
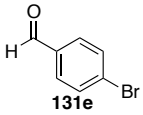
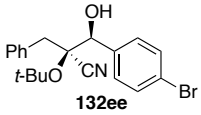
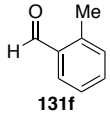
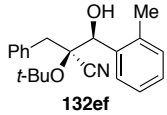
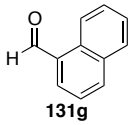
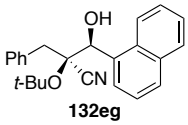
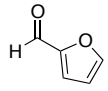
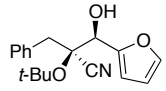
In response to this impressive result, other *N*-silyl oxyketene imines were evaluated in the addition to benzaldehyde. In general, the resulting diol products were obtained in high yield and with exceptional diastereo- and enantioselectivities for a number of different *N*-silyl oxyketene imines (Table 14, entries 2-5). The diastereoselectivity for the addition was responsive to the size of the alkyl substituent of the ketene imine such that the dr increased with more sterically demanding groups. Importantly, a synthetically versatile allyl-substituted diol product **132fa** was produced in excellent yield and stereoselectivity (Table 14, entry 4).

6.4.4 Aldol Reactions of *N*-Silyl Oxyketene Imines – Survey of Aldehyde Structure. To further explore the scope of this aldol process a number of different aromatic aldehydes were examined in the addition of phenylacetaldehyde-derived ketene imine **130e** (Table 15). Reactions with electron-rich, electron-poor, sterically hindered and heteroaromatic aldehydes all afforded diol products in high yield, and excellent diastereo- and enantioselectivities. The electron-rich aromatic aldehyde, 4-methoxybenzaldehyde, underwent addition to give diol product **132eb** in >99:1 er (Table 15, entry 1). Furthermore, electron-poor aromatic aldehydes reacted with similar rates and selectivities (Table 15, entries 2 and 3). The only case in which a moderate reduction in the enantioselectivity was observed is for the addition to 1-naphthaldehyde (Table 15, entry 6, 93.5:6.5 er); however, other hindered aromatic aldehydes such as 2-tolualdehyde participated with high enantioselectivity (Table 15, entry 5, 98.9:1.1 er). Importantly, heteroaromatic aldehydes also participated in the glycolate aldol reaction, affording diols in excellent yield and enantioselectivity (Table 15, entry 7). The reaction rates for the addition of *N*-silyl oxyketene imines to aliphatic aldehydes were attenuated, compared to aromatic aldehydes and studies aimed at increasing this rate are ongoing. Interestingly, α,β-

unsaturated aldehydes undergo highly site-selective 1,4-additions; however, the current catalyst structure is not optimal for achieving even modest stereoselectivities at this remote position.

Table 15. Survey of Aromatic Aldehydes in the Addition of *N*-silyl oxyketene imine **130e**[a]



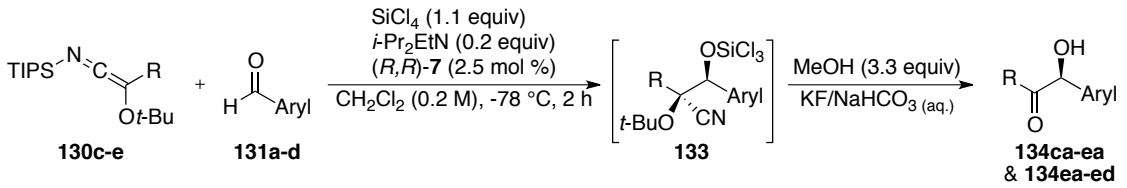
Entry	Aldehyde	Product	Yield (%)[b]	dr[c]	er[d]
1	 **131b**	 **132eb**	93	98:2	> 99:1
2	 **131c**	 **132ec**	93	99:1	> 99:1
3	 **131d**	 **132ed**	91	98:2	98.6:1.4
4	 **131e**	 **132ee**	95	98:2	> 99:1
5	 **131f**	 **132ef**	93	99:1	98.9:1.1
6	 **131g**	 **132eg**	89	99:1	93.5:6.5
7	 **131h**	 **132eh**	93	99:1	> 99:1

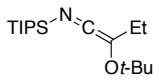
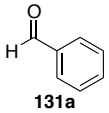
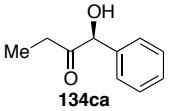
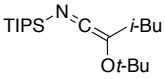
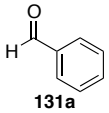
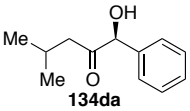
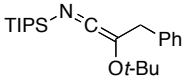
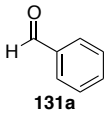
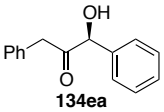
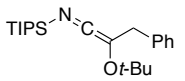
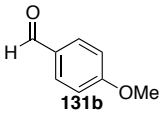
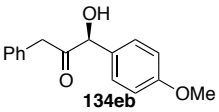
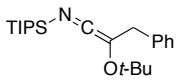
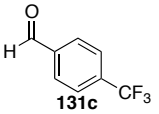
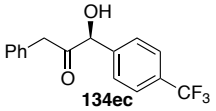
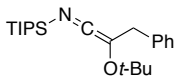
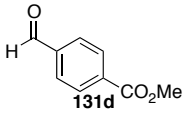
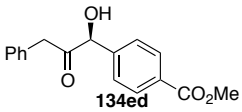
[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.20 equiv of silyl ketene imine, 1.0 equiv of *i*-Pr_2EtN, 2.5 mol % of (*R,R*)-**7** at 0.20 M in CH_2Cl_2 at –78 for 2h. [b] Yield of analytically pure material. [c] Determined by ^1H NMR analysis of the crude reaction mixture.[d] Determined by CSP-SFC analysis.

6.4.5 Cross-Benzoin Reactions of *N*-Silyl Oxyketene Imines. On the basis of the now classic studies by Stork,[77b] it was initially imagined that cross-benzoin products would be obtained by deprotection of the isolated aldol product **132** under acidic conditions, followed by

basic work-up to trigger retrocyantion. Although this route should be viable, it was envisioned that cross-benzoin adducts could also be obtained more directly, by taking advantage of the immediate product of the reaction, trichlorosilyl ether **133**. The hydrolytically labile trichlorosilyl ether could be utilized for in-situ deprotection (through the release of HCl) and then the cross-benzoin products could be obtained following a basic work-up. To test this hypothesis, the aldol addition of propionaldehyde-derived *N*-silyl oxyketene imine **130c** with benzaldehyde was performed and the reaction was quenched with 3.3 equiv of methanol. To our delight, the corresponding cross-benzoin product **134ca** was obtained in good yield and excellent enantioselectivity after the standard basic work-up with aqueous KF/$NaHCO_3$ (Table 16, entry 1). Following this encouraging result, other combinations of silyl ketene imines and aromatic aldehydes were examined to test the generality of this novel process (Table 16, entries 2-6). The resulting α-hydroxy carbonyl compounds were isolated in good yield and excellent enantioselectivities. Importantly, good correlations were observed between the enantiomeric ratios of the aldol products **132** and the corresponding cross-benzoin adducts **134** (e.g. entry 2, Table 16 vs. entry 3, Table 14). This correlation demonstrates that the stereogenic center in the cross-benzoin product does not undergo significant epimerization during the basic work-up. Only in the cases of strongly electronegative aryl substituents (Table 16, entries 5-6), were minor losses in the enantioselectivity of the cross-benzoin products observed; nevertheless, enantiomerically pure compounds could easily be obtained by a single recrystallization from toluene. To our knowledge, this represents the first example of a catalytic, enantioselective cross-benzoin reaction that involves an aliphatic aldehyde as one of the coupling partners

Table 16. Cross-Benzoin Reactions of *N*-Silyl Oxyketene Imines with Aromatic Aldehydes[a]



entry	nucleophile	aldehyde	product	yield (%)	er[c]
1	 **130c**	 **131a**	 **134ca**	79[b]	> 99:1
2	 **130d**	 **131a**	 **134da**	82[b]	98.9:1.1
3	 **4e**	 **131a**	 **134ea**	84[c]	> 99:1[d]
4	 **130e**	 **131b**	 **134eb**	75[c]	> 99:1[d]
5	 **130e**	 **131c**	 **134ec**	77[c]	> 99:1[d,e]
6	 **130e**	 **131d**	 **134ed**	78[c]	> 99:1[d,f]

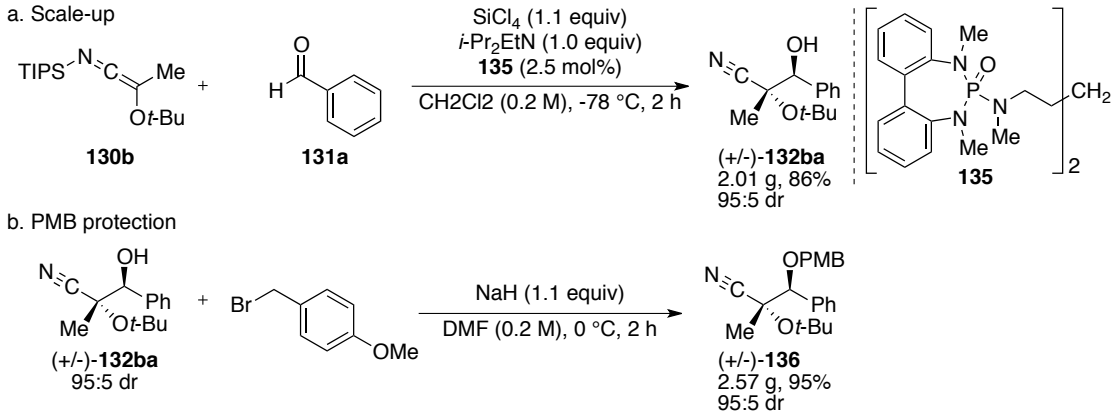
[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.20 equiv of silyl ketene imine, 1.0 equiv of *i*-Pr_2EtN, 2.5 mol % of (*R,R*)-**7** at 0.20 M in CH_2Cl_2 at –78 for 2h followed by 3.3 eqiuv of MeOH.[b] Yield of chromatographically homogeneous material. [c] Yield of analytically pure material after recrystallization. [d] Determined by CSP-SFC analysis after single recrystallization from toluene. [e] 96.1:3.9 er was obtained prior to recrystallization. [f] 96.5:3.5 er was obtained prior to recrystallization .

6.4.6 Transformations of the Aldol Products. The ability to access cross-benzoin products in high yield and enantioselectivity through deprotection and retrocyanation of the β-hydroxy cyanohydrins demonstrates the highly versatile nature of these products. Other useful pathways available to these compounds are by transformation of the nitrile via reduction or organometallic addition. The potential advantage to these manipulations is that the stereochemically defined tertiary alcohol, which was set in the aldol addition, is preserved. The products would allow access to stereochemically complex polyols and amino alcohols, which

could be relevant synthetic intermediates en route to biologically active compounds. Although the functional group manipulations of nitriles are well described,[93] the application to hindered nitriles is not trivial. For this reason a thorough examination of these transformations for the nitrile products relevant to this work was undertaken.

Nitrile product **132ba** was chosen for the current study and was prepared in high diastereoselectivity and on multi-gram scale by the addition of *N*-silyl oxyketene imine **130b** with benzaldehyde, catalyzed by racemic biphenyl-derived bisphosphoramide **135** (Scheme 53a). Because **132ba** was obtained with high diastereoselectivity any evidence for epimerization in the subsequent transformations could easily be secured by inspection of the ^{1}H NMR spectra, for the crude reaction mixtures. The first reaction investigated was for the protection of the secondary alcohol of the aldol product as its 4-methoxybenzyl ether. Treatment of the sodium salt of **132ba** with 4-methoxybenzyl bromide afforded **136** in high yield and with no change in the diastereomeric composition (Scheme 53b).

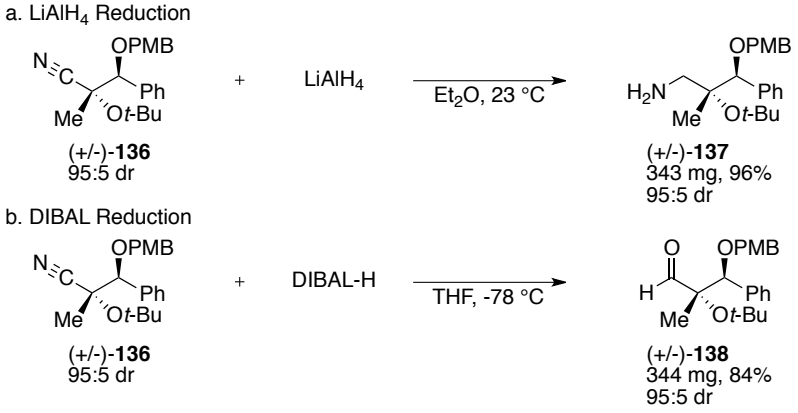
Scheme 53



Next, the reduction of nitrile **136** with two different metal hydride agents was studied (Scheme 54). Reduction of the nitrile to the corresponding protected amino alcohol **137** was accomplished with $LiAlH_4$. No epimerization was observed and analytically pure amine was

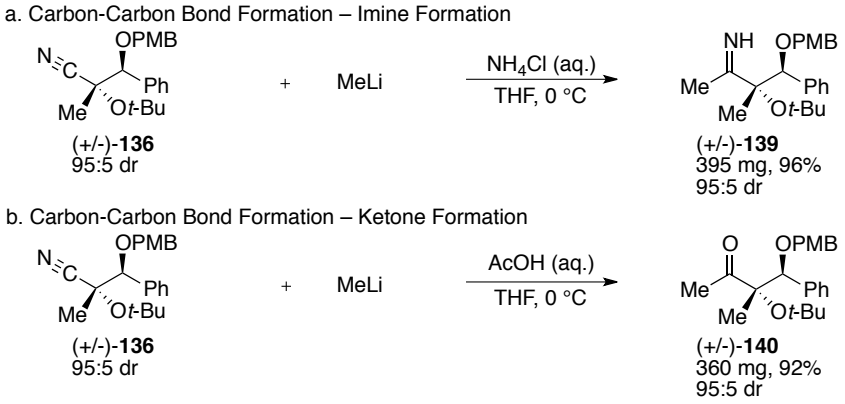
conveniently obtained in excellent yield after distillation (Scheme 54a). Partial reduction of nitrile **136** with diisobutylaluminum hydride and hydrolysis of the resulting imine afforded aldehyde **138** in good yield and high diastereoselectivity (Scheme 54b).

Scheme 54



Finally, the addition of organometallic reagents to **136** was studied. These reactions are highly valuable as they allow for the creation of new carbon-carbon bonds with a variety of nucleophilic species. Preliminary investigations with methylmagnesium bromide showed a slow rate of addition (>24 h), however, the analogous reaction with methyllithium showed complete consumption of **136** in less than 2 hours. Interestingly, quenching the reaction with aqueous NH_4Cl solution resulted in the isolation of analytical pure imine **139** in high yield after distillation (Scheme 55a). Although the isolation of imines is uncommon for nitrile addition reactions, it is not unprecedented for cases where sterically hindered nitriles are employed.[94] The methyl ketone product **140** could also be obtained in similar yield by simply changing the conditions of the hydrolysis to the use of concentrated aqueous acetic acid (Scheme 55b). Importantly, both imine **139** and ketone **140** were obtained without loss in diastereoselectivity.

Scheme 55



6.4.7 Determination of Absolute and Relative Configuration. The absolute and relative configuration of the aldol products was unambiguously assigned by single crystal X-ray diffraction analysis of **132da**, obtained by addition of ketene imine **130d** to benzaldehyde (Figure 24). Independent assignment of the absolute configuration for the cross-benzoin products was achieved by comparison of the optical rotation of **134ca** to a known compound.[95] Both methods confirmed an *S* absolute configuration at the secondary alcohol and verify that the aldehyde undergoes addition to the *Re* face. This sense of asymmetric addition is in agreement with previous reports on $SiCl_4$ mediated aldehyde additions catalyzed by (*R,R*)-**7**.

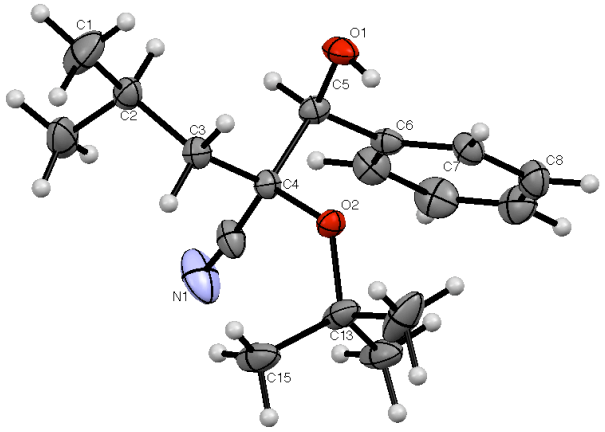


Figure 24. X-ray crystal structure of *t*-butyl protected diol product **132da**

6.5 Discussion

6.5.1 Trends with Respect to Reactivity. In-situ kinetic analysis (IR-spectroscopy) for the addition of *N*-silyl oxyketene imines to benzaldehyde in the presence of stoichiometric quantities of $SiCl_4$ have revealed that in the absence of the Lewis base, no appreciable background reaction is occurring ($t_{1/2} > 4$ h, see experimental section). Alternatively, executing the reaction with 2.5 mol % of a bisphosphoramide catalyst and 1.1 equiv of $SiCl_4$, an extremely facile addition is observed as noted by loss of the aldehyde absorbance at 1702 cm^{-1} ($t_{1/2} < 2$ min). The rate data is striking when compared to our previous studies on Lewis base catalyzed aldol additions of silyl ketene imines. In that case, significant background reactions were observed in the addition to benzaldehyde, although the relative catalyzed rates were still competitive enough to achieve high enantioselectivities.

To rationalize the enantioselectivities in the current study requires knowledge of the catalytic cycle for $SiCl_4$ mediated Lewis base catalyzed processes (Figure 25). The proposed catalytic cycle commences with the binding of the bisphosphoramide Lewis base to the weak Lewis acid $SiCl_4$. The complexation of the Lewis base leads to polarization in the Lewis acid and eventually ionization of a chloride ion to generate a chiral trichlorosilyl cation **140**. Coordination of the aldehyde to the activated Lewis acid gives complex **141** and enantioselective addition of the *N*-silyl oxyketene imine leads to the nitrilium ion intermediate **142**. Desilylation of the nitrilium by nucleophilic chloride and subsequent regeneration of the Lewis base catalyst delivers aldol product **133** as the trichlorosilyl ether. The extraordinary enantioselectivities observed in the current study might be ascribed to the absence of an achiral background reaction promoted by unactivated $SiCl_4$. This scenario is ideal for achieving high enantioselectivities because reaction can only occur when the Lewis base is bound to the weakly Lewis acidic $SiCl_4$.

This mode of catalysis ensures that the chiral information from the Lewis base is present during the stereochemistry-determining step of the reaction and showcases the power of Lewis base catalysis.

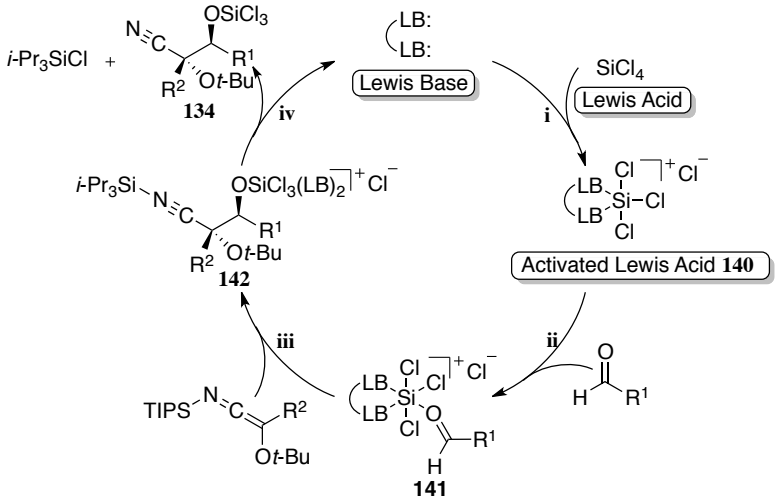


Figure 25. Proposed catalytic cycle for *N*-silyl oxyketene imine additions to aldehydes

6.5.2 Trends with Respect to Stereoselectivity. The major diastereomer obtained from the addition of *N*-silyl oxyketene imines to aromatic aldehydes using the SiC_4/(*R,R*)-**7** catalyst system showed a relative *anti* relationships in the diol fragment. Previous mechanistic and computational studies for the addition of silyl ketene acetals to aromatic aldehydes have suggested that the active catalytic species in these reactions is a Lewis base bound trichlorosilyl cation (**140**). Working under the assumption that *N*-silyl oxyketene imines follow an analogous mechanistic pathway, then analysis of open transition state models for the addition to the aldehyde/$SiCl_3(LB)_2$ cation complex **141** should allow for rationalization of the observed diastereoselectivity. However before analyzing the possible open transition state models, one caveat regarding the stereochemistry of *N*-silyl oxyketene imines needs to be addressed.

N-Silyl oxyketene imines are present in solution as chiral, racemic mixtures and this could have significant implications on the course of the catalytic reaction. If these, nucleophiles

are configurationally stable under the reaction conditions then each enantiomer could react at different rates in the catalyzed pathways, leading to a kinetic resolution of the ketene imine and reduced yields of the aldol products. This is not consistent with the results obtained from the Lewis base catalyzed reactions of *N*-silyl oxyketene imines because no reductions in yields or selectivities are observed when the additions are quenched at early time points. Furthermore, diastereotopic protons have never observed in the ^{1}HNMR spectra for *N*-silyl oxyketene imines. These observations suggest that *N*-silyl oxyketene imines are not configurationally stable under the reaction conditions. Further, support for this conclusion is provided by studies on related *N*-alkyl and *N*-aryl ketene imines, which show a low barrier to racemization.

Under the assumption that *N*-silyl oxyketene imines can undergo racemization in solution, six possible open transition structures can be considered for formation of the major and minor diastereomers (Figure 26). Analysis of the steric interactions incurred during the approach of the nucleophile show that the most favorable transition structure leading to the observed *anti*-product is the (–)-synclinal ((–)-sc_{anti}) orientation. This geometry places the sterically unencumbered ketene imine in the quadrant containing the sizable Lewis-base activated trichlorosilyl cation and also minimizes interactions between the bulky *t*-butoxide group and the aldehyde. The high *anti/syn* diastereoselectivities observed for these reactions likely result from the unfavorable steric interactions between the *t*-butoxide group of the ketene imine and the carbonyl oxygen of the aldehyde noted in the (–)-synclinal transition structure leading to the *syn* diastereomer.

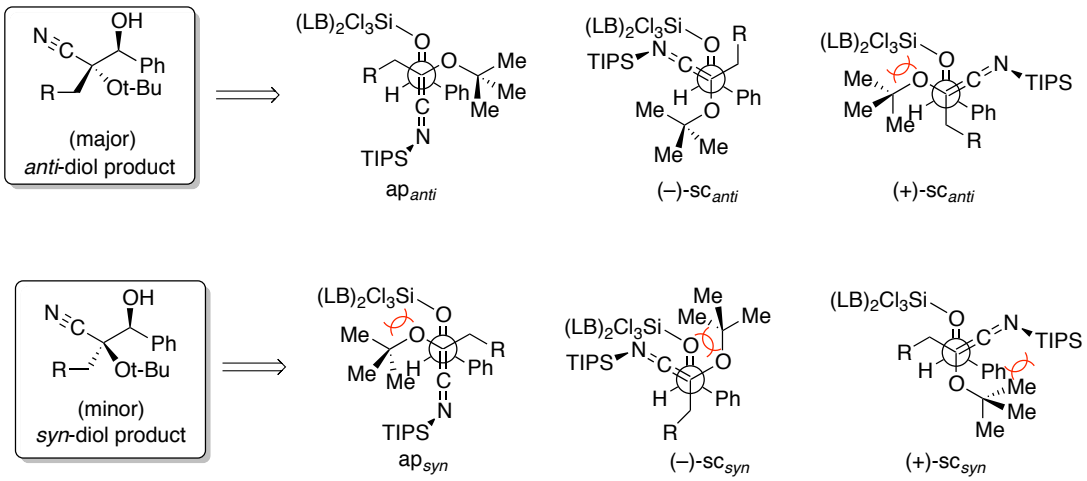


Figure 26. Open transition state models leading to *anti* or *syn* diol products

The *S* absolute configuration of the product confirms that the (*R,R*)-**7** Lewis base catalyst is blocking addition to the *Si* face of the aldehyde in the trichlorosilyl cation complex. This observation is consistent with previously developed computational models for this catalyst system, which show that nucleophilic addition is favored at the *Re* face of the aldehyde.

6.6 Conclusions and Outlook

In conclusion, a new class of silyl ketene imines derived from *tert*-butyl protected cyanohydrins has been described. Utilization of these nucleophiles in Lewis base catalyzed aldol additions affords β-hydroxy cyanohydrins in good yields, high diastereoselectivities and exceptional enantioselectivities. The ability of *N*-silyl oxyketene imines to act as acyl anion equivalents was also demonstrated by merely altering the conditions of the reaction work-up. This modification allowed for the preparation of cross-benzoin products derived from aliphatic aldehydes in good yields and excellent enantioselectivities. The versatility of the β-hydroxy cyanohydrins was highlighted by three different transformations of the nitrile group. These functional group manipulations allowed access to aminoalcohols and α-hydroxy aldehydes or ketones containing a stereogenic tertiary alcohol in good yields and high selectivity. Future work

will focus on the application of this novel class of nucleophiles to other classes of umpolung reactions such as Stetter-type additions and homoenolate chemistry.

Chapter 7: Experimental

7.1 General Experimental

All reactions were performed in oven dried (140 °C) and/or flame dried glassware under an atmosphere of dry argon, unless noted. Internal temperatures of low temperature reactions were measured using Teflon coated thermocouples unless otherwise noted.

Boiling points for Kugelrohr distillations correspond to uncorrected air bath temperatures (ABT). Melting points were obtained in vacuum-sealed capillary tubes and are corrected. Analytical thin-layer chromatography was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV (254), or potassium permanganate ($KMnO_4$), or ceric ammonium molybdate (CAM). Column chromatography was performed using Merck silica 60 (40-63 μm particle size) gel purchased from Aldrich.

Kinetic data was obtained on a Mettler Toledo React-IR 4000 instrument with a 10 mm DiComp React-IR probe. Analytical supercritical fluid chromatography (CSP-SFC) was performed on a Berger Instruments SFC with spectrophotometric detector (220 nm) using Daicel Chiralpak OD, OJ, OB, AD and AS columns as well as a Regis Whelk-O1 column. Optical rotations were measured using a Jasco DIP-360 digital polarimeter in Fischer ACS reagent grade $CHCl_3$ containing approximately 0.75% EtOH as a preservative and are reported as follows: concentration (c = g/dL), and solvent.

^1H NMR Spectra and ^{13}C NMR spectra were acquired in $CDCl_3$ at 500 MHz and referenced to residual $CHCl_3$ at 7.26 and 77.00 ppm respectively or in C_6D_6 and referenced to residual C_6D_5H at 7.15 and 128.00 ppm respectively. Assignments were obtained by reference to COSY, HMQC and HMBC correlations as well as by comparison to calculated structures obtained from MestReNova software package (Version 6.0.3). Chemical shifts are reported in

ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), hep (heptet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz.

Mass spectroscopy was performed by the University of Illinois Mass Spectrometer Center. EI mass spectra were performed on a 70-VSE instrument. ESI mass specta were performed on a Waters Q-Tof Ulitima instrument. Data are reported in the form of (m/z) versus intensity. Infrared spectra (IR) were recorded on a Mattson Galaxy 5020 spectrophotometer in KBr pellets or NaCl cells (film). Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 67-100%); m (medium, 34-66%); w (weak, 0-33%). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory and Robertson Microlit Laboratories, Inc. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus.

7.2 Commercial Chemicals

Reaction solvents tetrahydrofuran (Fisher, HPLC grade), diethyl ether (Fisher, BHT stabilized ACS grade), and CH_2Cl_2 (Fisher, unstabilized HPLC grade) were dried by passage through two columns of neutral alumina in a solvent dispensing system. Reaction solvents hexane (Fisher, Optima grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, in a solvent dispensing system. Reaction solvent *N,N*-dimethylformamide (Fisher, HPLC grade) was dried by percolation through a column packed with molecular sieves in a solvent dispensing system. Solvents for chromatography, filtration and recrystallization were CH_2Cl_2 (Aldrich, ACS grade), ethyl acetate (Fisher, ACS grade), diethyl ether (Fisher, ACS grade), hexane (Fisher, Optima) and toluene (Aldrich, Optima) and were used as received.

Silicon tetrachloride (Aldrich) was heated at reflux for 24 hr and distilled prior to use. *N,N*-Diisopropylethylamine (Alfa-Aesar, 99%) and pyridine (Aldrich, ACS grade) were freshly distilled over CaH_2. Methanol (Fisher, ACS grade) was distilled from magnesium. Benzaldehyde (Aldrich, 99%), 2-tolualdehyde (Aldrich, 98%), 4-trifluoromethylbenzaldehyde (Oakwood, **5c**), 1-napthaldehyde (Aldrich, 95%), 2-furfuraldehyde (Aldrich, 95%), isovaleraldehyde (Aldrich, 97%), propionaldehyde (Aldrich, 97%), 4-methoxybenzyl alcohol (Aldrich, 98%) and triisopropylsilyl chloride (Gelest, >95%) were distilled under reduced pressure before use. Piperonal (Aldrich, 97%), Methyl 4-formylbenzoate (Alfa-Aesar, 98%), 4-bromobenzaldehyde (Aldrich, 98%), 4-chlorobenzaldehyde (Aldrich, 98%) were sublimed under high vacuum and stored in a glove box prior to use. Sodium cyanide (Aldrich, ACS Reagent), 2-methylpropene (S.J. Smith, C.P. grade), sodium bisulfite (Aldrich, ReagentPlus), 4-methoxycinnamaldehyde (Aldrich, 95%), 4-chlorocinnamaldehyde (Aldrich, 98%), 2-methoxycinnamaldehyde (Aldirch, 95%), 4-dimethylaminocinnamaldehyde (Alrich, 95%), 3,5-dinitrobenzoylchloride (Aldrich, 98+%), potassium fluoride (GFS Chemical, 98%), triethylamine (Fisher, Reagent Grade), acetaldehyde (Aldrich, ReagentPlus), phenylacetaldehyde (Aldrich, 90+%), paraformaldehyde (Fisher, Laboratory Grade), diisobutylaluminum hydride (Aldrich, 1.0 M in hexanes), potassium bis(trimethylsilyl)amide (Aldrich, 95%), phosphorus tribromide (Aldrich, 97%), allyl bromide (Aldrich, 99%) and lithium aluminum hydride (Aldrich, 95%) cyclohexanecarboxaldehyde (Aldrich, 97%), cinnamaldehyde (Aldrich, 95%), hydrocinnamaldehyde (Aldrich, 98%), 1-hexanal (Aldrich, 99%), 2,2-dimethylbutryaldehyde (Aldrich, 99%), 4-*cis*-heptenal (Aldrich, 93%), 3-methyl-2-butenenitrile (TCI America, 92%) were used as received.

"Brine" refers to a saturated aqueous solution of sodium chloride. Catalyst (*R,R*)-**7** was obtained from Obiter Research, LLC and used as received. Racemates for all reported products

can be prepared by following the listed general procedures, but employing 1 equiv of dried and distilled hexamethylphosphoramide (HMPA) instead of chiral catalyst.

7.3 Literature Preparations

2–Phenylpropanenitrile,[96] 2-phenylbutanenitrile,[43] 2-phenyl-pent-4-enenitrile,[96] 3-methyl-2-phenyl-butanenitirle,[43] 4-methyl-2-phenylpentanenitrile,[43] 2,3-dimethyl-butanenitrile[97] were prepared according to the general procedure of Watt except di-isopropylamine was used in place of N-isopropylcyclohexaneylamine. Silyl ketene imines **58a-e** were known compounds and prepared according to the general procedure of Fu and coworkers except cannula filtration was substituted for filtration in a glove box.[44]

Formaldehyde cyanohydrin was prepared according to the procedure of Watt and was stabilized with a few drops of conc. HCl and distilled under vacuum prior to use,[89] Acetaldehyde cyanohydrin,[98] isovaleraldehyde cyanohydrin,[99] and propionaldehyde cyanohydrin[100] were prepared according to the general procedure of Heathcock and co-workers and were stabilized with a few drops of conc. HCl and distilled under reduced pressure prior to use. Phenylacetaldehyde cyanohydrin was also prepared by the method of Heathcock and co-workers and was purified by column chromatography prior to use.[100] 4-Methoxybenzyl bromide was prepared according to the procedure of Maier and co-workers and distilled under reduced pressure prior to use.[101]

Caution! *Sodium cyanide and cyanohydrins are extremely toxic and great care should be taken when handling these reagents. All reactions should be performed in a well-ventilated fume-hood and the appropriate protective clothing should be worn at all times. Distillations of cyanohydrins should be perfumed with a vacuum placed is in a ventilated cabinet or fume-hood and care should be taken when empting liq.* N_2 *cold traps.*

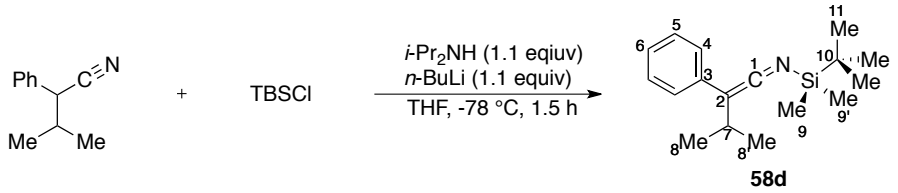
7.4 Experimental Procedures

7.4.1 Enantioselective Aldol Addition of Silyl Ketene Imines.

7.4.1.1 Preparation of Silyl Ketene Imines.

General Procedure 1. Preparation of Silyl Ketene Imines.

Preparation of 1-(1,1-Dimethylethyl)-1,1-dimethyl-*N*-(3-methyl-2-phenyl-1-buten-1-ylidene)silanamine (58d) (Table 3, entry 4)



n-Butyllithium (2.6 M in hexanes, 2.26 mL, 5.98 mmol, 1.0 equiv) was added via syringe to a flame-dried, 50-mL, Schlenk flask containing a –78 °C (dry ice/acetone bath, internal temp) solution of 0.60 g diisopropylamine (5.98 mmol, 1.0 equiv) in 6 mL of THF. The reaction mixture was stirred for 10 min at –78 °C and then a solution of 0.95 g (5.98 mmol) 3-methyl-2-phenylbutanenitrile in 4 mL of THF was added to the reaction *via* cannula. The resultant yellow solution was stirred for 5 min at –78 °C and then a solution of 0.99 g of TBSCl (6.59 mmol, 1.1 equiv) in 4 mL of THF was added via cannula. The solution was allowed to warm to room temperature and was stirred for 1 h. The solvent was removed under high vacuum (0.3 mm Hg), and the residue taken up in 30 mL of anhydrous pentane and was then filtered *via* cannula into a flame dried, 100-mL, round bottomed flask. Removal of the solvent under vacuum (0.3 mmHg) afforded 1.59 g (98%) of **58d** as a yellow liquid, which was used in the subsequent addition reactions without further purification.

Data for **58d**:

^{1}H-NMR: (500 MHz, C_6D_6)

7.27-7.22 (m, 4 H, HC(4) and HC(5)), 6.95-6.91(m, 1 H, HC(6)), 2.69 (qq, *J* = 6.7, 6.7, 1 H, HC(7)), 1.20 (d, *J* = 6.8, 6 H, $H_3C(8)$ and $H_3C(9')$), 0.92 (s, 6 H, $H_3C(9)$ and $H_3C(9')$, 0.10 (s, 9H, $H_3C(11)$

^{13}C-NMR: (126 MHz, $CDCl_3$)

185.95 (C(1)), 138.33 (C(4)), 129.02 (C(5)), 123.75 (C(6)), 122.55 (C(5)), 62.33 (C(2)), 25.59 (C(11)), 24.76 (C(7)) , 22.82 (C(8, 8')), 17.70 (C(10)), -4.77(C(9, 9'))

IR: (neat)

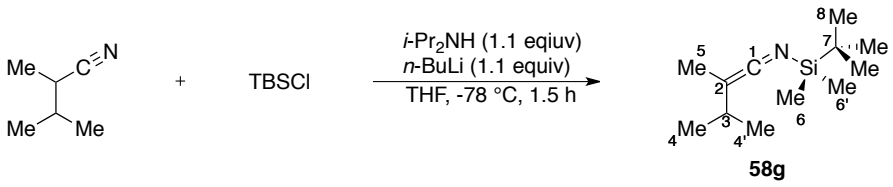
3022 (w), 2955 (s), 2929 (s), 2859 (m), 2030 (s), 1595 (s), 1495 (s), 1463 (m), 1251 (s), 1071 (m), 976 (m), 840 (s), 822 (s), 784 (s), 752 (s), 732 (m), 692 (m)

MS: (EI, 70ev)

73 (77), 135 (20), 161 (18), 207 (16), 275 (100)

HRMS: Calcd for $C_{17}H_{27}NSi$: 273.1913, found: 275.1913

Preparation of 1-(1,1-Dimethylethyl)-1,1-dimethyl-*N*-(3-methyl-2-methyl-1-buten-1-ylidene)silanamine (58g) (Table 3, entry 7)



58g

Following General Procedure 1, *i*-Pr_2NH (2.90 mL, 20.6 mmol, 1.0 equiv), THF (15 mL), 2.6 M *n*-BuLi in hexanes (7.9 mL 1.0 equiv), 2,3-dimethylbutanenitrile (2.06 g, 20.6 mmol) in 8 mL of THF and a solution of TBSCl (3.42 g, 1.1 equiv, 20.6 mmol) in 8 mL of THF were combined to afford 3.27 g (77%) of **58g** after vacuum distillation at 3 mmHg.

Data for **59g**:

mp: 62-63 °C (3 mmHg)

^{1}H-NMR: (500 MHz, C_6D_6)

2.08 (qq, J = 6.6, 6.6, 1 H, HC(1)), 1.068 (d, J = 6.6 Hz, 6 H, H_3C(4) and H_3C(4')), 0.96 (s, 9 H, H_3C(8)), -0.12 (s, 6 H, H_3C(6) and H_3C(6'))

^{13}C-NMR: (126 MHz, $CDCl_3$)

192.56 (C(1)), 49.11 (C(2)), 28.85 (C(5)), 25.76 (C(8)), 22.25 (C(4, 4')), 17.17 (C(7)), 12.36 (C(3)), -5.04 (C(8, 8'))

IR: (neat)

2956 (s), 2929 (s), 2886 (s), 2858 (s), 2036 (s), 1471 (m), 1390 (m), 1377 (m), 1360 (m), 1303 (m), 1251 (m), 1074 (w), 1005 (w) 882 (m), 838 (s), 823 (s), 810 (s), 782 (s), 742 (s), 679 (s)

MS: (ESI)

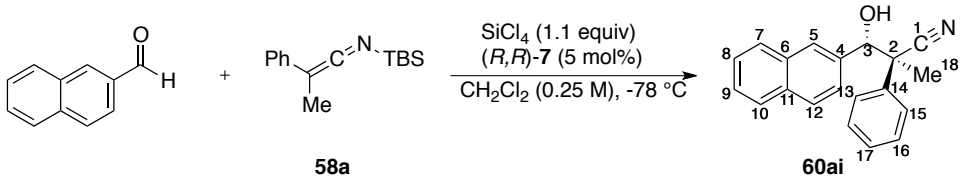
211.2 (28.2), 211.1 (28.2), 196.2 (58.1), 196.0 (53.9), 73.0 (100.0), 59.0 (11.4)

HRMS: Calcd for $C_{12}H_{25}NSi$: 211.1756, found: 211.1757

7.4.1.2 Silyl Ketene Imine Survey in the Addition to 2-Naphthaldehyde.

General Procedure 2. Addition of Silyl Ketene Imines to 2-Naphthaldehyde

Preparation of (2*R*,3*S*)-3-Hydroxy-2-methyl-3-(2-naphthyl)-2-phenylpropanenitrile (60ai) (Table 4, entry 1)



58a **60ai**

To a flame-dried, 10-mL, Schlenk flask equipped with a magnetic stir bar, a thermocouple, a gas inlet tube and a septum were added (*R,R*)-**7** (42 mg, 0.05 mmol, 0.05 equiv), 2-naphthaldehyde (156 mg, 1.0 mmol) and CH_2Cl_2 (4.0 mL, 0.25 M in aldehyde). The solution was stirred, cooled to –78 °C (internal temp) in a dry ice-acetone bath and 126 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) was added to the reaction mixture. The resulting bright yellow solution was allowed to stir for 5 min at –74 °C and then 0.85 mL of a 1.41 M solution of silyl ketene imine **58a** in CH_2Cl_2 (1.2 mmol, 1.2 equiv) was added dropwise via syringe over 5 min. The resulting reaction mixture was allowed to stir at –78 °C for 2 h and was then quenched by pouring the cold solution into a 125mL Erlenmeyer flask containing a rapidly stirring solution of sat. aq. KF (20 mL) and sat. aq. $NaHCO_3$ solutions (20 mL). The biphasic mixture was vigorously stirred for 3 h at ambient temperature and then was filtered through a pad of Celite (ca. 7 g) using a 60 mL, coarse glass fritted, Buchner funnel. The filtrate was transferred to a 250 mL separatory funnel and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and then the organic layers were combined and washed with brine (1 x 40 mL). The aqueous washes were back-extracted with EtOAc (1 x 40 mL) and then the organic layers were combined and dried over $MgSO_4$ (ca. 2 g), filtered and concentrated *in vacuo (*25 °C, 15 mmHg). The residue was purified by column chromatography (SiO_2 (30 g), 3 cm diam., CH_2Cl_2/hexanes, 9/1 to CH_2Cl_2/EtOAc, 9/1) to afford 252 mg (88%) of **60ai** as a white solid.

Data for **60ai**:

mp: 133-135 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.85-7.51 (m, 4 H, HC(aryl)), 7.51-7.48 (m, 4 H, 3 X HC(aryl) and HC(15)), 7.43-7.38 (m, 4 H, 1 x HC(aryl), HC(16), and HC(17)), 5.03 (s, 1 H, HC(3)), 2.47

(br s, 1 H, OH), 1.64 (s, 3 H, $H_3C(14)$)

^{13}C-NMR: (126 MHz, $CDCl_3$)

137.6 (C(15)), 135.4 (C(4)), 133.6 (C(6, 11)), 132.8 (C(6, 11)), 129.0 (C(16, 17)), 128.6 (C(aryl)), 128.4 (C(aryl)), 127.9 (C(aryl)), 127.8 (C(aryl)), 127.2 (C(5, 13)), 126.9 (C(16, 17)), 126.6 (C(aryl)), 126.5 (C(aryl)), 125.1 (C(5,13)), 122.0 (C(1)), 80.1 (C(3)), 49.6 (C(2)), 22.6 (C(14))

IR: (KBr pellet)

3434 (s), 3058 (m), 3023 (m), 2987 (m), 2883 (m), 2246 (m), 1599 (m), 1506 (m), 1497 (s), 1446 (s), 1381 (m), 1272 (m), 1168 (m), 1074 (m), 1048 (s), 1027 (s), 898 (m), 863 (m), 827 (s), 776 (s), 754 (s), 723 (s), 696 (s)

MS: (ESI)

402.2 (100), 401.2 (20), 310.1 (8), 305.2 (21), 271.1(13)

HRMS: calcd for $C_{20}H_{17}NONa$: 310.1208, found 310.1219

TLC: R_f 0.14 (hexanes/EtOAc, 4/1)[UV (254 nm)]

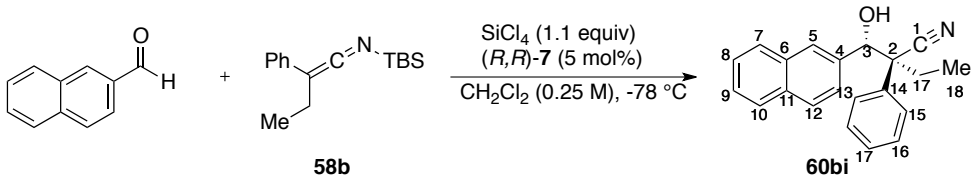
SFC: (2*R/S*,3*R/S*)-**60ai**, t_R 9.8 min (1.3%); (2*S*,3*R*)-**60ai**, t_R 14.8 min (1.0%); (2*R/S*,3*R/S*)-**60ai**, t_R 17.3 min (0.9%); (2*R*,3*S*)-**60ai**, t_R 23.8 min (96.8%) (Chiralpak OJ, 150 bar, 40 °C, 2.75 mL/min, 9% MeOH in CO_2, 2.5 mL/min, 220

Opt. Rot.: $[\alpha]_D^{24}$ – 87 (c = 0.52, $CHCl_3$)

Analysis: $C_{20}H_{17}NO$ (287.36)

Calcd:	C, 83.59;	H, 5.96;	N, 4.87%
Found:	C, 83.42;	H, 5.83;	N, 4.97%

Preparation of (2*R*,3*S*)-3-Hydroxy-2-ethyl-3-(2-naphthyl)-2-phenylpropanenitrile (60bi) (Table 4, entry 2).



Following General Procedure 2, 156 mg of 2-naphthaldehyde (1.0 mmol) was combined with 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv), and 0.94 mL of a 1.27 M solution of silyl ketene imine **58b** in CH_2Cl_2 (1.2 mmol, 1.2 equiv) to yield after column chromatography (SiO_2 (30 g), 3 cm diam., hexanes/EtOAc, 4/1) 264 mg of a white solid, that was recrystallized from hot EtOAc (ca. 0.5 mL) and hexanes (ca. 1 - 0.5 mL) to yield 234 mg (77%) of **60bi** as white needles.

Data for **6bi**:

mp: 138-139 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.85-7.78 (m, 4 H, HC(aryl)), 7.53-7.37 (m, 8 H, HC(aryl)), 5.05 (s, 1 H, HC(3)), 2.36 (s, 1 H, OH), 2.08 (dq, *J* = 7.2, 7.2, 1 H, HC(18)), 1.86 (dq, *J* = 7.2, 7.2, 1 H, HC(18)), 0.82 (dd, *J* = 7.3, 7.3, 3 H, HC(19))

^{13}C-NMR: (126 MHz, $CDCl_3$)

135.8 (C(4)), 135.4 C(14)), 133.7 (C(11)), 132.9 (C(6)), 129.1 (C(15/16)), 128.5 (C(aryl)), 128.4 (C(17)), 128.0 (C(aryl)), 127.8 (C(aryl)), 127.5 (C(15/16)), 127.4 (C(aryl)), 127.6 (C(aryl)), 126.4 (C(aryl)), 125.2 (C(aryl)), 120.6 (C(1)), 80.0 (C(3)), 56.7 (C(2)), 28.8 (C(18)), 9.4 (C(19))

IR: (KBr pellet)

3580 (s), 3056 (s), 2979 (s), 2930 (s), 2878 (s), 2237 (s), 1599 (s), 1506 (m), 1498 (s), 1466 (s), 1446 (s), 1380 (m), 1362 (s), 1272 (m), 1245 (m), 1193 (m), 1170 (s), 1123 (s), 1053 (s), 955 (s), 916 (s), 864 (s), 791(s), 757 (s), 669 (s)

MS: (ESI)

325.1 (16), 324.1 (100)

HRMS: calcd for $C_{21}H_{19}NONa$: 324.1364, found 324.1364

TLC: R_f 0.17 (hexanes/EtOAc, 4/1)[UV (254 nm)]

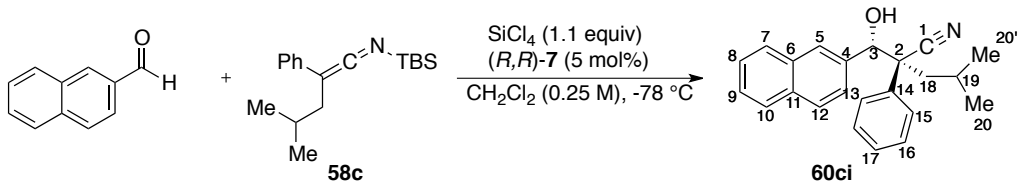
SFC: (2*R/R*,3*S/S*)-**60bi**, t_R 11.4 min (1.7%); (2*S*,3*R*)-**60bi**, t_R 13.3 min (1.2%); (2*R/R*,3*S/S*)-**60bi**, t_R 14.1 min (1.3%); (2*R*,3*S*)-**60bi**, t_R 15.0 min (95.8%) (Chiralpak OD, 125 bar, 40 °C, 10% MeOH in CO_2, 3.0 mL/min, 220 nm)

Opt. Rot.: $[\alpha]_D^{24}$ 48.4 (0.55, $CHCl_3$)

Analysis: $C_{21}H_{19}NO$ (301.38)

Calcd:	C, 83.69;	H, 6.35;	N, 4.65%
Found:	C, 83.51;	H, 6.27;	N, 4.73%

Preparation of (2*R*,3*S*)-3-Hydroxy-2-(2-methylpropyl)-3-(2-naphthyl)-2-phenylpropanenitrile (60ci) (Table 4, entry 3)



Following General Procedure 2, 156 mg of 2-naphthaldehyde (1.0 mmol) was combined with 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv), and 0.75

mL of a 1.59 M solution of silyl ketene imine **58c** in CH_2Cl_2 (1.2 mmol, 1.2 equiv) to yield after column chromatography (SiO_2 (30 g), 3 cm diam., CH_2Cl_2/hexanes, 7/1 to CH_2Cl_2/EtOAc, 7/1) 297 mg (90%) of **60ci** as a white, amorphous solid.

Data for **60ci**:

mp: 154-156 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.87-7.82 (m, 4 H, 4 x HC(aryl)), 7.56-7.49 (m, 5 H, 2 x HC(15), 3 x HC(aryl)), 7.46-7.38 (m, 3 H, 2 x HC(16), HC(17)), 5.00 (s, 1 H, HC(3)), 2.30 (br s, 1 H, OH), 2.07 (dd, *J* = 14.1, 5.0, 1 H, HC(18)), 1.64 (dd, *J* = 14.2, 7.8, 1 H, HC(18)), 1.54 (m, 1 H, HC(19)), 0.88 (d, *J* = 6.4, 3 H, HC(20)), 0.66 (d, *J* = 6.6, 3 H, HC(20'))

^{13}C-NMR: (126 MHz, $CDCl_3$)

135.9 (C(14)), 135.6 (C(4)), 133.7 (C(6/11)), 132.9 (C(6/11)), 129.1 (C(16)), 128.5 (C(17)), 128.0 (C(aryl)), 127.8 (C(aryl)), 127.6 (C(aryl)), 127.6 (C(15)), 126.6 (C(aryl)), 126.4 (C(aryl)), 125.4 (C(aryl)), 121.1 (C(1)), 81.0 (C(3)), 54.5 (C(20)), 43.6 (C(18)), 25.6 (C(19)), 24.2 (C(20')), 22.9 (C(20))

IR: (KBr pellet)

3578 (s), 3058 (s), 3023 (m), 2958 (s), 2869 (s), 2236 (s), 1600 (s), 1507 (m), 1497 (s), 1469 (s), 1387 (m), 1364 (s), 1273 (m), 1243 (m), 1170 (s), 1123 (s), 1069 (s), 1045 (s), 1017 (s), 953 (m), 864 (s), 775 (s), 751 (s), 720 (s), 698 (s)

MS: (ESI)

352.2 (10), 348.2 (11), 347.2 (65), 313.2 (35), 312.2 (100)

HRMS: calcd for $C_{23}H_{23}NONa$: 352.1688, found 353.1677

TLC: R_f 0.21 (hexanes/EtOAc, 4/1)[UV (254 nm)]

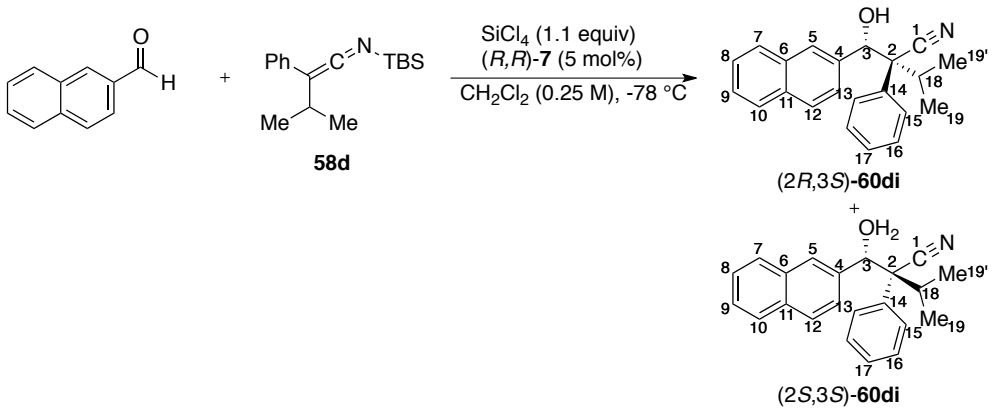
SFC: (2*R/R*,3*S/S*)-**60ci**, t_R 11.4 min (1.7%); (2*S*,3*R*)-**60ci**, t_R 13.3 min (1.2%); (2*R/R*,3*S/S*)-**60ci**, t_R 14.1 min (1.3%); (2*R*,3*S*)-**60ci**, t_R 15.0 min (95.8%) (Chiralpak OD, 150 bar, 40 °C, 16% MeOH in CO_2, 3.0 mL/min, 220 nm)

Opt. Rot.: $[\alpha]_D^{24}$ –107.1 (c = 0.52, $CHCl_3$)

Analysis: $C_{23}H_{23}NO$ (329.43)

Calcd:	C, 83.85;	H, 7.04;	N, 4.25%
Found:	C, 83.88;	H, 6.94;	N, 4.44%

Preparation of (2*R*,3*S*)-3-Hydroxy-2-(1-methylethyl)-3-(2-naphthyl)-2-phenyl propanenitrile (60di) (Table 4, entry 4)



Following General Procedure 2, 156 mg of 2-naphthaldehyde (1.0 mmol) was combined with 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv), and 0.71 mL of a 1.68 M solution of silyl ketene imine **58d** in CH_2Cl_2 (1.2 mmol, 1.2 equiv) to yield after column chromatography (SiO_2 (30 g), 3 cm diam., CH_2Cl_2/hexanes, 6/1 to CH_2Cl_2/hexanes/EtOAc, 6/1/1) 294 mg of a white solid. The material was further purified by column chromatography (SiO_2 (30 g), 3 cm diam., toluene to toluene/EtOAc 9/1)) to yield 81 mg

(26%) of (2*S*,3*S*)-**60di** as a white foam and 149 mg (47%) of (2*R*,3*S*)-**60di**, also as a white foam. The diastereo- and enantiomeric ratio was determined by SFC-analysis prior to separation of the diastereomers by further chromatography.

Data for (2*R*,3*S*)-**60di**:[8]

mp: 61-63 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.76-7.74 (m, 1 H, HC(Aryl)), 7.68-7.66 (m, 1 H, HC(Aryl)), 7.61 (d, *J* = 8.6, 1 H, HC(Aryl)), 7.47-7.43 (m, 3 H, HC(Aryl)), 7.23-7.17 (m, 3 H, HC(Aryl)), 7.11-7.01 (m, 2 H, HC(Aryl)), 7.06 (d, *J* = 8.6, 1 H, HC(Aryl)), 5.47 (s, 1 H, HC(3)), 2.71-2.40 (m, 2 H, OH, HC(18)), 1.40 (d, *J* = 6.6, 3 H, H_3C(19)), 0.960 (d, *J* = 6.6, 3 H, H_3C(19))

^{13}C-NMR: (126 MHz, $CDCl_3$)

136.4 (C(4)), 133.6 (C(14)), 133.4 (C(11,6)), 132.7 (C(11,6)), 129.0 (C(15,16)), 128.4 (C(aryl)), 128.2 (C(aryl)), 128.0 (C(15,16)), 127.7 (C(aryl)), 127.6 (C(aryl)), 127.4 (C(aryl)), 126.6 (C(aryl)), 126.4 (C(Aryl)), 125.4 (C(aryl)), 121.0 (C(1)), 76.2 (C(3)), 60.6 (C(2)), 33.3 (C(18)), 19.8 (C(19, 19')), 19.2 (C(19, 19'))

IR: (KBr pellet)

3446 (s), 3054 (s), 2967 (s), 2873 (s), 2237 (m), 1600 (m), 1495 (m), 1448 (m), 391 (s), 1369 (s), 1297 (m), 1271 (m), 1165 (m), 1137 (m), 1124 (s), 1063 (s), 1033 (s), 953 (m), 894 (m), 859 (s), 820 (s), 748 (s), 711 (s)

MS: (EI, 70 eV)

315.0 (2.2), 159.0 (25.3), 158.0 (15.0), 157.0 (100.0), 156.0 (38.2), 155.0 (34.7), 144.0 (13.8), 129.0 (38.5), 128.0 (24.5), 127.0 (32.9), 117.0 (44.0), 90.0 (5.1),

89.0 (6.3), 63.0 (5.2)

HRMS: (ESI)

calcd for $C_{22}H_{21}NONa$: 338.1521, found 338.1531

TLC: 0.10 R_f (CH_2Cl_2/hexanes, 6/1)[UV (254 nm)]

SFC: (2*S*,3*S*)-**60di**, t_R 9.38 min (27.9%); (2*S*,3*R*)-**60di**, t_R 11.3 min (12.9%); (2*R*,3*R*)-**60di**, t_R 12.5 min (11.2%); (2*R*,3*S*)-**60di**, t_R 13.8 min (48.0%) (Chiralpak OD, 125 bar, 40 °C, 10% MeOH in CO_2, 3.0 mL/min, 220 nm)

Opt. Rot.: $[\alpha]_D^{24}$ +67.7 (c = 0.50, CH_3Cl)

Analysis: $C_{22}H_{21}NO$ (315.41)

Calcd:	C, 83.78;	H, 6.71;	N, 4.44%
Found:	C, 83.43;	H, 6.73;	N, 4.50%

Data for (2*S*,3*S*)-**60di**:

mp: 61-63 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.75-737 (m, 1 H, HC(Aryl)), 7.67-7.65 (m, 1 H, HC(Aryl)), 7.57 (d, *J* = 8.6, 1 H, HC(Aryl)), 7.46-7.40 (m, 3 H, HC(Aryl)), 7.30-7.21 (m, 5 H, HC(Aryl)), 6.92 (dd, *J* = 8.6, 1.5, 1 H, HC(Aryl)), 5.45 (s, 1 H, HC(3)), 2.92 (qq, *J* = 6.8, 6.6, 1 H, HC(18)), 2.18 (br s, 1 H, OH), 1.41 (d, *J* = 6.6, 3 H, H_3C(19)), 0.90 (d, *J* = 6.8, 3 H, H_3C(19'))

^{13}C-NMR: (126 MHz, $CDCl_3$)

136.7 (C(4)), 133.9 (C(14)), 133.3 (C(11,6)), 132.6 (C(11,6)), 128.6 (C(15,16)), 128.3 (C(Aryl)), 128.2 (C(Aryl)), 128.1 (C(15,16)), 127.6 (C(Aryl)), 127.4 (C(Aryl)), 127.2 (C(Aryl)), 126.4 (C(Aryl)), 126.2 (C(Aryl)), 125.0 (C(Aryl)),

119.9 (C(1)), 75.9 (C(3)), 60.2 (C(2)), 32.3 (C(18)), 19.4 (C(19, 19')), 18.6 (C(19, 19'))

IR: (KBr pellet)

3447 (s), 3054 (s), 2968 (s), 2930 (s), 2868 (m), 2237 (m), 1600 (m), 1507 (m), 1495 (m), 1468 (m), 1448 (m), 1390 (m), 1369 (m), 1271 (m), 1170 (s), 858 (s), 820 (s), 747 (s), 710 (s)

MS: (EI, 70 eV)

315.0 (1.3), 159.0 (23.2), 158.0 (14.2), 157.0 (100.0), 156.0 (25.0), 155.0 (26.7), 144.0 (17.7), 129.0 (62.7), 128.0 (34.2), 127.0 (43.2), 117.0 (51.2), 116.0 (10.2), 75.0 (7.8)

HRMS: (ESI)

calcd for $C_{22}H_{21}NONa$: 338.1521, found 338.1528

TLC: R_f 0.20 (CH_2Cl_2/hexanes, 6/1)[UV (254 nm)]

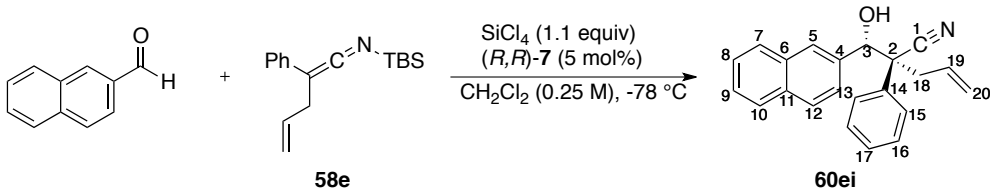
SFC: (2*S*,3*S*)-**60di**, t_R 9.38 min (27.9%); (2*S*,3*R*)-**60di**, t_R 11.3 min (12.9%); (2*R*,3*S*)-**60di**, t_R 12.5 min (11.2%); (2*R*,3*S*)-**60di**, t_R 13.8 min (48.0%) (Chiralpak OD, 125 bar, 40 °C, 10% MeOH in CO_2, 3.0 mL/min, 220 nm)

Opt. Rot.: $[\alpha]_D^{24}$ +96.4 (c = 0.63, $CHCl_3$)

Analysis: $C_{22}H_{21}NO$ (315.41)

Calcd:	C, 83.78;	H, 6.71;	N, 4.44%
Found:	C, 83.43;	H, 6.73;	N, 4.50%

Preparation of (2*R*,3*S*)-3-Hydroxy-2-(3-propenyl)-3-(2-naphthyl)-2-phenylpropanenitrile (6bh) (Table 2, entry 5)



58e **60ei**

Following general Procedure 2, 156 mg of 2-naphthaldehyde (1.0 mmol) was combined with 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv), and 0.68 mL of a 1.76 M solution of silyl ketene imine **58e** in CH_2Cl_2 (1.2 mmol, 1.2 equiv) to yield after column chromatography (SiO_2 (30 g), 3 cm diam., CH_2Cl_2/hexanes, 7/1 to CH_2Cl_2/EtOAc, 7/1) 264 mg of a white solid, which was recrystallized from hot EtOAc (ca. 0.5 mL) and hexanes (ca. 1 - 0.5 mL) to yield 248 mg (79%) of **60ei** as white needles.

Data for **60ei**:

mp: 138-139 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.85-7.78 (m, 2 H, HC(aryl)), 7.71 (s, 1 H, HC(5)), 7.53-7.49 (m, 2 H, HC(aryl)), 7.45-7.43 (m, 2 H, 1 x HC(15), 1 x HC(aryl)), 7.42-7.34 (m, 4 H, HC(aryl)), 5.56 (dddd, *J* = 17.2, 10.2, 7.1, 7.1, 1 H, HC(19)), 5.10 (s, 1 H, HC(3)), 5.13 (dd, *J* = 17.4, 1.4, 1 H, HC(20)) 5.05 (dd, *J* = 10.7, 1.4, 1 H, HC(20)), 2.85 (dd, *J* = 14.2, 6.6, 1 H, HC(18)), 2.65 (dd, *J* = 14.2, 7.6, 1 H, HC(18)), 2.51 (br s, 1 H, OH)

^{13}C-NMR: (126 MHz, $CDCl_3$)

135.5 (C(4)), 134.9 (C(14)), 133.6 (C(11)), 132.8 (C(6)), 131.5 (C(19)), 128.8 (C(16)), 128.5 (C(17)), 128.4 (C(13)), 127.9 (C(aryl)), 127.8 (C(15)), 127.8 (C(naph)), 127.4 (C(5)), 126.6 (C(aryl)), 126.4 (C(aryl)), 125.2 (C(13)), 120.5

(C(1)), 120.3 (C(20)), 79.3 (C(3)), 55.3 (C(2)), 39.6 (C(18))

IR: (KBr pellet)

3578 (s), 3058 (m), 2978 (m), 2930 (w), 2240 (m), 1600 (m), 1506 (m), 1498 (m), 1449 (m), 1359 (s), 1273 (m), 1249 (m), 1167 (m), 1122 (m), 1042 (s), 1018 (m), 983 (s), 922 (s), 867 (s), 829 (s), 779 (m), 755 (s), 726 (s), 696 (s)

MS: (ESI)

454.2 (12), 453.2 (50.0), 336.1 (9), 331.2 (15), 297.1 (32), 296.1 (100), 279.1 (8.0)

HRMS: calcd for $C_{22}H_{19}NONa$: 336.1364, found 336.1373

TLC: R_f 0.19 (hexanes/EtOAc, 4/1)[UV (254 nm)]

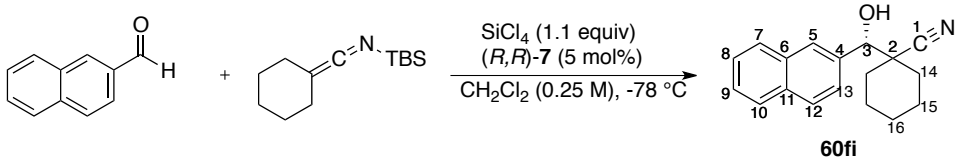
SFC: (2*R*,3*S*)-**6bh**, t_R 17.2 min (91.7%); (2*S*,3*R*)-**6bh**, t_R 21.7 min (2.3%); (2*R*/*R*, 3*S*/*S*)-**6bh**, t_R 24.9 min (6.0%) (Chiralpak AS, 150 bar, 40 °C, 6.5% MeOH in CO_2, 2.2 mL/min, 220 nm)

Opt. Rot.: $[\alpha]_D^{24}$ 31.8 (c = 0.5, $CHCl_3$)

Analysis: $C_{22}H_{19}NO$ (313.39)

Calcd:	C, 84.31;	H, 6.11;	N, 4.47%
Found:	C, 84.16;	H, 5.96;	N, 4.64%

Preparation of (3*S*)-2-Cyclohexaneyl-3-hydroxy-3-(2-naphthyl)propanenitrile (60fi) (Table 4, entry 6)



58f **60fi**

Following General Procedure 2, 156 mg of 2-naphthaldehyde (1.0 mmol) was combined with 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv), and 0.65 mL of a 1.83 M solution of silyl ketene imine **58f** in CH_2Cl_2 (1.2 mmol, 1.2 equiv) to yield after column chromatography (SiO_2 (30 g), 3 cm diam., CH_2Cl_2/hexanes, 9/1) 247 mg of a white solid, which was recrystallized from hot EtOAc (ca. 0.5 mL) and hexanes (ca. 1 - 0.5 mL) to yield 224 mg (85%) of **60fi** as white needles.

Data for **60fi**:

mp: 176-178 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.86-7.83 (m, 4 H, HC(5, 7, 10, 12)), 7.580 (dd, J = 8.4, 1.83, 1 H, HC(13)), 7.52-7.49 (m, 2 H, HC(8, 9)), 4.66 (s, 1 H, HC(3)), 2.52 (s, 1 H, OH), 2.33 (dd, *J* = 13.3, 1.5, 1 H, HC(14 or 18)), 1.79-1.75 (m, 1 H, HC(15 or 17)), 1.72-1.58 (m, 4 H, HC(14, 18)), 1.56-1.47 (m, 1 H, HC(15 or 17)), 1.43-1.37 (m, 1 H, HC(14 or 18)), 1.33-1.28 (m, 1 H, HC(14 or 18)), 1.15-1.06 (m, 1 H, HC(16))

^{13}C-NMR: (126 MHz, $CDCl_3$)

136.6 (C(4)), 133.6 (C(11)), 132.9 (C(6)), 128.3 (C(12, 7, 10)), 128.2 (C(12, 7, 10)), 127.8 (C(12, 7, 10)), 126.9 (C(5)), 126.5 (C(8, 9)), 126.5 (C(8, 9)), 125.1 (C(13)), 122.1 (C(1)), 79.4 (C(3)), 46.1 (C(2)), 33.1 (C(14, 18)), 31.8 (C(14, 18)), 25.3 (C(16)), 22.9 (C(15, 17)), 22.71 (C(15, 17))

IR: (KBr pellet)

3435 (s), 3054 (m), 3023 (w), 2943 (s), 2888 (s), 2857 (s), 2242 (s), 1600 (m), 1509 (m), 1448 (s), 1367 (s), 1274 (m), 1243 (s), 1162 (m), 1124 (s), 1075 (s), 1048 (s), 958 (m), 936 (m), 912 (s), 872 (s), 824 (s), 778 (s), 760 (s),

MS: (ESI)

288.1 (10), 283.2 (15), 249.1 (13), 248.1 (100)

HRMS: calcd for $C_{18}H_{19}NONa$: 288.1375, found 288.1364

TLC: R_f 0.16 (hexanes/EtOAc, 4/1)[UV (254 nm)]

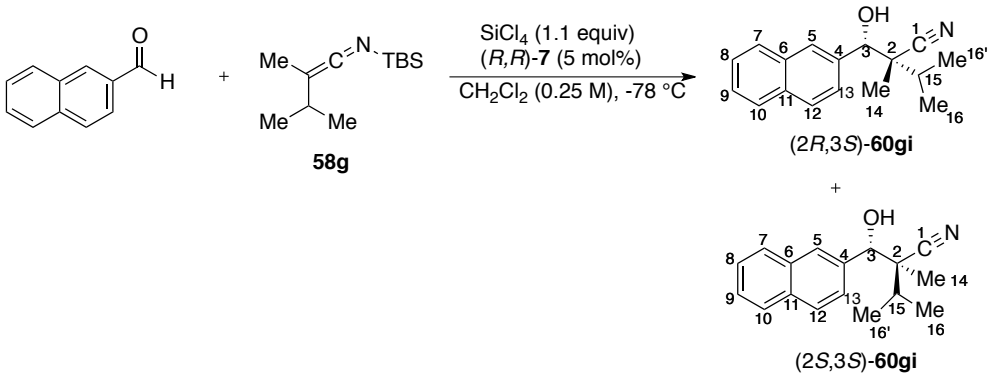
SFC: (3*R*)-**60fi**, t_R 6.3 min (8.7%); (3*S*)-**60fi**, t_R 8.2 min (91.3%) (Chiralpak OD, 125 bar, 40 °C, 15% MeOH in CO_2, 3.0 mL/min, 220 nm)

Opt. Rot.: $[\alpha]_D^{24}$ -161.7 (c = 0.52, $CHCl_3$)

Analysis: $C_{18}H_{19}NO$ (265.35)

Calcd:	C, 81.47;	H, 7.22;	N, 5.28%
Found:	C, 81.32;	H, 7.31;	N, 5.41%

Preparation of (2*R*,3*S*)-3-Hydroxy-2-methyl-2-(1-methylethyl)-3-(2naphthyl)propanenitrile (60gi) (Table 4, entry 7)



Following General Procedure 2, 156 mg of 2-naphthaldehyde (1.0 mmol) was combined with 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv), and 0.48 mL of a 2.5 M solution of silyl ketene imine **58f** in CH_2Cl_2 (1.2 mmol, 1.2 equiv) to yield after column chromatography (SiO_2 (30 g), 3 cm diam., CH_2Cl_2/hexanes, 9/1 to

CH_2Cl_2/hexanes/EtOAc, 9/1/1) 254 mg of a white solid. The material was further purified by column chromatography (SiO_2 (30 g), 3 cm diam., toluene to 9/1 toluene/EtOAc)) to yield 232 mg (92%) of **60gi** as an amorphous white powder. The diastereomeric mixture was separated by column chromatography (SiO_2 (30 g), 3 cm diam., CH_2Cl_2/hexanes, 9/1 to CH_2Cl_2/hexanes/EtOAc, 9/1/1) prior to characterization. The diastereo- and enantiomeric ratio was determined by SFC-analysis prior to separation of the diastereomers.

Data for (2*R*,3*S*)-**60gi**:

mp: 129-131 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.92 (s, 1 H, HC(5)), 7.87-7.84 (m, 3 H, HC(Aryl)), 7.64 (dd, *J* = 8.6, 1.6, 1 H, HC(Aryl)), 7.52-7.50 (m, 2 H, HC(Aryl)), 4.98 (s, 3H, HC(3)), 2.22 (br s, 1 H, OH), 1.94 (qq, *J* = 6.8, 6.8, 1 H, HC(15)), 1.35 (s, 3 H, H_3C(14)), 1.16 (d, *J* = 6.8, 3 H, H_3C(16, 16')), 1.04 (d, *J* = 6.8, 3 H, H_3C(16, 16'))

^{13}C-NMR: (126 MHz, $CDCl_3$)

137.3 (C(4)), 133.5 (C(6)), 133.0 (C(7)), 128.3 (C(12, 10, 7)), 128.2 (C(12,10, 7)), 127.8 (C(12,10,7)), 126.8 (C(5)), 126.6 (C(9, 8)), 126.5 (C(9,8)), 125.0 (C(13)), 122.2 (C(1)), 75.6 (C(3)), 47.9 (C(2)), 31.9 (C(15)), 18.9 (C(16, 16')), 17.8 (C(16, 16')), 16.3 (C(14))

IR: (KBr Pellet)

3400 (s), 3059 (m), 2965 (s), 2925 (m), 2873 (s), 2253 (m), 1597 (m), 1508 (m), 1455 (m), 1376 (s), 1313 (m), 1273 (s), 1166 (s), 1125 (s), 1085 (s), 1047 (s), 954 (m), 892 (m), 862 (s), 826 (s), 784 (s), 754 (s), 717 (m), 651 (m)

MS: (EI, 70 eV)

253.1 (5.8), 158.0 (13.3), 157.0 (100.0), 155.0 (5.8), 130.1 (6.5), 129.0 (54.7), 128.0 (17.8), 127.0 (13.9)

HRMS: calcd for $C_{17}H_{19}NO$: 253.1467, found 253.1467

TLC: R_f 0.10 (CH_2Cl_2/hexanes, 6/1)[UV (254 nm)]

SFC: (2*S*,3*R*)-**60gi**, t_R 12.1 min (4.7%); (2*R*,3*S*)-**60gi**, t_R 14.2min (54.7%); (2*R/S*, 3*R/S*)-**60gi**, t_R 18.9 min (40.6%) (Chiralpak AS, 150 bar, 40 °C, 4% MeOH in CO_2, 2.5 mL/min, 220 nm)

Opt. Rot.: $[\alpha]_D^{24}$ 58.9 (c = 0.52)

Analysis: $C_{18}H_{19}NO$ (253.34)

Calcd:	C, 80.60;	H, 7.56;	N, 5.53%
Found:	C, 80.87;	H, 7.43;	N, 5.66%

Data for (2*S*,3*S*)-**60gi**:

mp: 128-133 °C

^{1}H-NMR: (500 MHz, $CDCl_3$)

7.87-7.84 (m, 4 H, HC(5,12,10,7)), 7.61 (dd, *J* = 8.6, 1.4, 1 H, HC(13)), 7.52-7.50 (m, 2 H, HC(8,9)), 4.89 (s, 1 H, HC(3)), 2.46 (br s, 1 H, OH), 2.29 (qq, *J* = 6.8, 6.8, 1 H, HC(15)), 1.24 (d, *J* = 6.8, 3 H, H_3C(16, 16')), 1.05 (d, *J* = 6.6, 3 H, H_3C(16, 16')), 1.04 (s, 3 H, H_3C(14))

^{13}C-NMR: (126 MHz, $CDCl_3$)

136.9 (C(4)), 133.6(C(6)), 132.9 (C(7)), 128.3 (C(12, 10, 7)), 128.3 (C(12, 10, 7)), 127.8 (C(12, 10, 7)), 127.1 (C(5)), 126.59 (C(9, 8)), 126.5 (C(9, 8)), 125.1(C(13)), 122.85 (C(1)), 75.5 (C(3)), 48.1 (C(2)), 31.6 (C(15)), 19.3 (C(16, 16')), 16.7 (C(16, 16')), 15.8 (C(14))

IR: (KBr Pellet)

3549 (s), 2965 (s), 2935 (m), 2904 (m), 2878 (m), 2240 (m), 1505 (m), 1463 (m), 1395 (m), 1376 (s), 1306 (m), 1270 (s), 1166 (m), 1124 (m), 1057 (s), 898 (s), 869 (s), 832 (s), 775 (m), 761 (s)

MS: (EI, 70 eV)

253.1 (2.4), 158.0 (13.1), 157.0 (100.0), 155.0 (9.2), 129.0 (77.7), 128.0 (32.3), 127.0 (25.9), 77.0 (8.5), 75.0 (12.9), 73.0 (10.9)

HRMS: calcd for $C_{17}H_{19}NO$: 253.1467, found 253.1468

TLC: R_f 0.07 (CH_2Cl_2/hexanes, 6/1) [UV (254 nm)]

SFC: (2*R*/*S*,3*R*/*S*)-**60gi**, t_R 6.53 min (59.3%); (2*S*,3*S*)-**60gi**, t_R 7.09 min (39.4%); (2*R*,3*R*)-**60gi**, t_R 8.0 min (1.3%) (Chiralpak AD, 125 bar, 40 °C, 8% MeOH in CO_2, 3.0 mL/min, 220 nm)

Opt. Rot.: $[\alpha]_D^{24}$ 51.8 (c =0.52, $CHCl_3$)

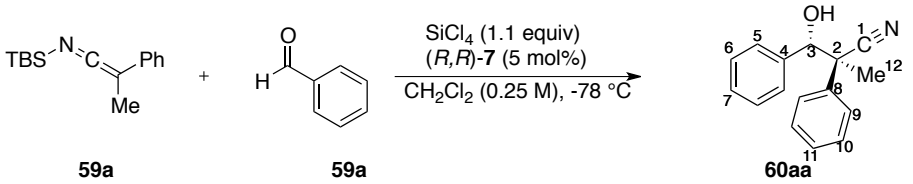
Analysis: $C_{18}H_{19}NO$ (253.34)

Calcd:	C, 80.60;	H, 7.56;	N, 5.53%
Found:	C, 80.87;	H, 7.43;	N, 5.66%

7.4.1.3 Survey of Aromatic Aldehydes in the Aldol Addition of Silyl Ketene Imine.

Note: 1H NMR and SFC data for the initial screen of aromatic aldehydes on 0.5 mmol scale are reported here, descriptive runs (1.0 mmol) and full characterization of these products was performed by Mr. Mathew Burk (see, reference 69).

Preparation of (2*R*,3*S*)-3-Hydroxy-2-methyl-2,3-diphenylpropanenitrile (60aa) (Table 2, entry 1)



59a **59a** **60aa**

Following general procedure 2, 51 μL (0.5 mmol) of benzaldehyde was combined with 21 mg (0.025 mmol, 0.05 equiv) of bis-phosphoramide (*R,R*)- **7**, 63 μL (0.55 mmol, 1.1 equiv) of silicon tetrachloride and 147 mg of silyl ketene imine **13a** (0.6 mmol, 1.2 equiv) to yield, after purification by silica gel chromatography (hexanes/EtOAc, 4/1), 97 mg (67%) of β-hydroxy nitrile **60aa** as a white solid.

Data for **14aa:**

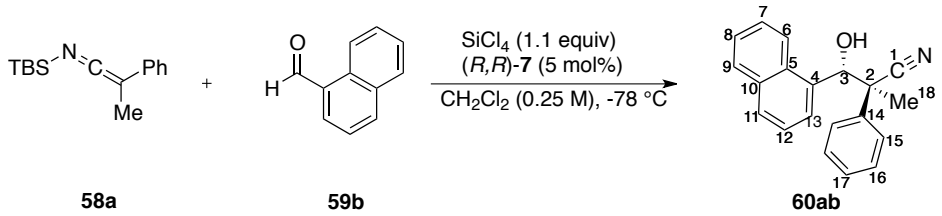
^{1}H-NMR: (500 MHz, $CDCl_3$)

7.49 (dt, *J* = 8.3, 1.7, 2 H, HC(10)), 7.43-7.37 (m, 3 H, HC(10,11)), 7.37-7.30 (m, 5 H, HC(5,6,7)), 4.87 (s, 1 H, HC(3)), 2.24 (br. s, 1 H, OH), 1.61 (s, 3 H, H_3C(12))

TLC: R_f 0.17 (hexanes/EtOAc, 4/1)[UV (254 nm)]

SFC: (2*R*,3*S*)-**60aa,** t_R 3.37 min (96.2 %); (2*S*,3*S*)-**60aa,** t_R 4.87 min (3.8 %) (Chiralpak AS, 125 psi, 40 ºC, 13.0% MeOH in CO_2, 3.0 mL/min, 220 nm

Preparation of (2*R*,3*S*)-3-Hydroxy-2-methyl-3-(1-naphthyl)-2-phenylpropanenitrile (60ab) (Table 2, entry 2)



Following general procedure 2, 68 μL (0.5 mmol) of 1-napthaldehyde was combined with 21 mg (0.025 mmol, 0.05 equiv) of bis-phosphoramide ((*R,R*)-**7**), 63 μL (0.55 mmol, 1.1 equiv) of silicon tetrachloride and 147 mg of silyl ketene imine **58a** (0.6 mmol, 1.2 equiv) to yield, after purification by silica gel chromatography (hexanes/EtOAc, 4/1), 97 mg (67%) of β-hydroxy nitrile **60ab** as a white solid.

Data for **60ab:**

^{1} H-NMR: (500 MHz, $CDCl_3$)

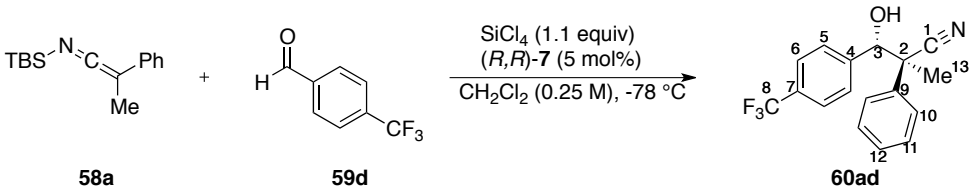
8.04-8.00 (m, 1 H, HC(17)), 7.95-7.91 (m, 1 H, HC(11)), 7.90-7.87 (m, 2 H, HC(6,9)), 7.63-7.57 (m, 3 H, HC(16,7,8)), 7.50-7.45 (m, 2 H, HC(12,13)), 7.45-7.40 (m,2 H, HC(15)), 7.40-7.35 (m,1 H, HC(7,8)), 5.86 (s, 1H, HC(3)), 2.31 (br. s, 1H, OH), 1.55 (s, 3H, H3C(18))

TLC: R_f 0.26 (hexanes/EtOAc, 4/1)[UV (254 nm)]

SFC: (2*R*,3*S*)-**60ab,** t_R 8.57 min (98.7%); (2*R*,3*S*)-**60ab,** t_R 12.62 min (1.3%) (Chiralpak AS, 115 psi,

40 ºC, 9% MeOH in CO_2, 3.5 mL/min, 220 nm)

Preparation of (2*R*,3*S*)-3-hydroxy-2-methyl-2-phenyl-3-(4-trifluoromethylphenyl)propanenitrile (60ad) (Table 2, entry 4)



Following general procedure 2, 68 μL (0.5 mmol) of 4-trifluoromethylbenzaldehyde was combined with 21 mg (0.025 mmol, 0.05 equiv) of bis-phosphoramide (*R,R*)-**7**, 63 μL (0.55 mmol, 1.1 equiv) of silicon tetrachloride and 147 mg of silyl ketene imine **58a** (0.6 mmol, 1.2 equiv) to yield, after purification by silica gel chromatography (hexanes/EtOAc, 4/1), 124 mg (82%) of β-hydroxy nitrile **60ad** as a white solid.

Data for **60ad:**

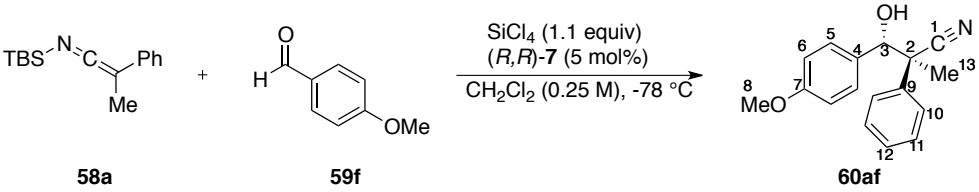
^{1}H-NMR: (500 MHz, $CDCl_3$)

7.60-7.56 (m, 2 H, HC(6)), 7.47-7.37 (m, 7 H, HC(5,10,11,12)), 4.95 (s, 1 H, HC(3)), 1.62 (s, 3 H, H3C(13)).

TLC: R_f 0.25 (hexanes/EtOAc, 4/1)[UV (254 nm)]

SFC: (2*R*,3*S*)-**60ad**, t_R 5.46 min (98.5 %); (2*S*,3*S*)-**60ad**, t_R 6.63 min (1.5 %) (Chiralpak AD, 125 psi, 40 ºC, 4.5% MeOH in CO_2, 3.2 mL/min, 220 nm)

Preparation of (2*R*,3*S*)-3-Hydroxy-3-(4-methoxyphenyl)-2-methyl-2-phenylpropanenitrile (60af) (Table 2, entry 6)



Following general procedure 2, 61 μL (0.5 mmol) of 4-methoxybenzaldehyde was combined with 21 mg (0.025 mmol, 0.05 equiv) of bis-phosphoramide (*R,R*)-**7**, 63 μL (0.55 mmol, 1.1 equiv) of silicon tetrachloride and 147 mg of silyl ketene imine **58a** (0.6 mmol, 1.2 equiv) to yield, after purification by silica gel chromatography (hexanes/EtOAc, 4/1), 122 mg (92%) of β-hydroxy nitrile **60af** as a white solid.

Data for **60af:**

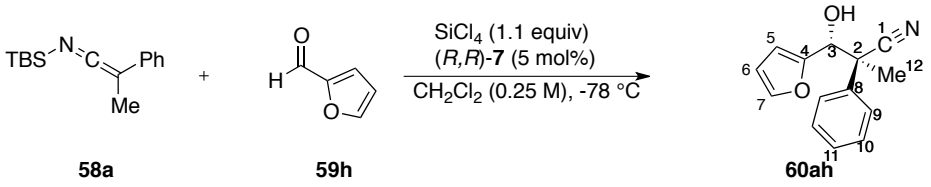
^{1}H-NMR: (500 MHz, $CDCl_3$)

7.49-7.45 (m, 2 H, HC(10)), 7.43-7.34 (m, 3 H, HC(11,12)), 7.24-7.20 (m, 2 H, HC(5)), 6.87-6.83 (m, 2 H, 2 H, HC(6)), 4.81 (s, 1 H, HC(3)), 3.81 (s, 3 H, H3C(8)), 2.38 (br s, 1 H, OH), 1.58 (s, 3 H, H3C(13))

TLC: R_f 0.15 (hexanes/EtOAc, 4/1)[UV (254 nm)]

SFC: (2*R*,3*S*)-**60af,** t_R 15.15 min (95.4%); (2*S*,3*S*)-**60af,** t_R 19.71 min (4.6%) (Chiralpak OD, 150 psi, 40 ºC, 6.0% MeOH in CO_2, 2.2 mL/min, 220 nm

Preparation of (2*R*,3*S*)-3-(2-Furyl)-3-hydroxy-2-methyl-2-phenylpropanenitrile (60ah) (Table 2, entry 8)



58a **59h** **60ah**

Following general procedure 2, 42 μL (0.5 mmol) of 2-furfualdehyde was combined with 21 mg (0.025 mmol, 0.05 equiv) of bis-phosphoramide ((*R,R*)-**11**), 63 μL (0.55 mmol, 1.1 equiv) of silicon tetrachloride and 147 mg of silyl ketene imine **58a** (0.6 mmol, 1.2 equiv) to yield, after

purification by silica gel chromatography (hexanes/EtOAc, 4/1), 88 mg (77%) of β-hydroxy nitrile **60ah** as a yellow oil.

Data for **60ah**:

^{1}H-NMR: (500 MHz, $CDCl_3$)

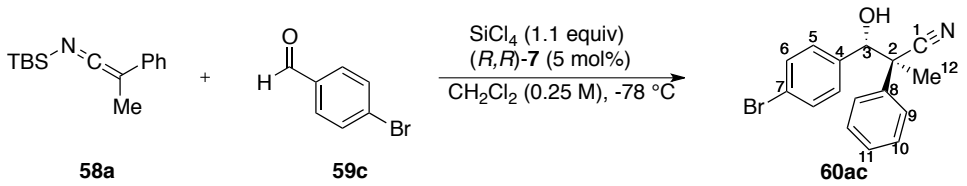
7.47-7.44 (m, 2 H, HC(9)), 7.41-7.32 (m, 2 H, HC(7,10,11)), 6.41 (d, *J* = 3.4, 1 H, HC(5)), 6.37 (dd, *J* = 1.8, 3.3, HC(6)), 4.89 (s, 1 H, HC(3)), 2.74 (br s, 1 H, OH), 1.64 (s, 3 H,H3C(12))

TLC: R_f 0.14 (hexanes/EtOAc, 4/1)[UV (254 nm)]

SFC: (2*R*,3*S*)**60ah,** t_R 2.97 min (95.6 %); (2*S*,3*S*)-**60ah,** t_R 3.31 min (4.4 %) (Chiralpak AD, 125 psi, 40 ºC, 10% MeOH in CO_2, 3.15 mL/min, 220 nm)

7.4.1.4 Preparation of an Aldol Derivative for X-ray Analysis.

Preparation of (2*R*,3*S*)-3-Hydroxy-2-methyl-2-phenyl-3-(4-bromophenyl)propanenitrile (60ac) (Table 2, entry 3)



Following General Procedure 2, 185 mg of 4-bromobenzaldhyde (1.0 mmol) was combined with 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv), and 0.95 mL of a 1.25 M solution of silyl ketene imine **58a** in CH_2Cl_2 (1.2 mmol, 1.2 equiv) to yield after column chromatography (SiO_2 (30 g), 3 cm diam., hexanes/EtOAc, 4/1) 303 mg of a white solid, which was recrystallized from hot benzene (ca. 0.5 mL) and pentanes (ca. 1 - 0.5 mL) to yield 294 mg (93%) of **60ac** as white needles.

Data for **60ac**:

mp: 109-110 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.45-7.37 (m, 7 H, HC(6, 9, 10, 11)), 7.13 (d, J = 8.5, 2 H, HC(5)), 4.84 (s, 1 H, HC(3)), 2.44 (s, 1 H, OH), 1.60 (s, 3 H, HC(12))

^{13}C NMR: (125 MHz, $CDCl_3$)

137.04 (C(4, 8)), 136.77 (C(4, 8)), 131.31 (C(9, 10, 6)), 129.35 (C(6)), 129.09 (C(9, 10, 6)), 128.72 (C(11)), 126.87 (C(9, 10, 6)), 123.06 (C(7)), 121.74 (C(1)), 79.26 (C(3)), 49.48 (C(2)), 22.31 (C(12)).

IR: (neat)

3430 (s), 3054 (w), 3023 (s), 2992 (m), 2945 (m), 2894 (m), 2242 (m), 1490 (s), 1446 (s), 1404 (s), 1302 (m), 1238 (m), 1199 (m), 1073 (s), 1046 (s), 1010 (s), 827 (s), 737(s), 696 (s)

MS: (ESI)

466.2 (24), 449.0 (18), 431.1 (41), 429.1 (37), 411.3 (18), 340.0 (100), 338.0 (92), 334.1 (22), 298.0 (56), 133.1 (48), 130.2 (45)

HRMS: Calcd for $C_{16}H_{14}BrNONa$, 338.0155, found: 338.0163

TLC: R_f 0.16 (hexanes/EtOAc, 4/1)[UV (254 nm)

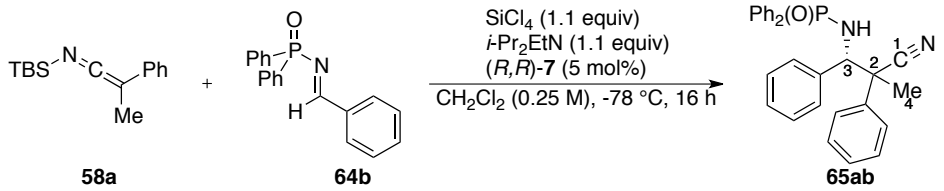
Opt. Rot.: $[\alpha]_D^{24}$ +16.0 (c = 0.46, $CHCl_3$)

SFC: (2*S*,3*R*)-**60ac**, t_R 8.68 min (1.0%); (2*R/S*,3*R/S*)-**60ac**, t_R 10.1 min (0.6%); (2*R/S*,3*R/S*)-**60ac**, t_R 11.2 min (0.5%); (2*R*,3*S*)-**60ac**, t_R 13.6 min (97.9%) (Chiralpak OB, 125 bar, 40 °C, 5% MeOH in CO_2, 2.5 mL/min, 220 nm)

Analysis: $C_{16}H_{14}BrNO$ (316.19)

Calcd:	C, 60.78;	H, 4.46;	N, 4.43%
Found:	C, 60.95;	H, 4.35;	N, 4.33%

7.4.1.5 Survey of Protected Aromatic Imines in the Mannich Reaction of Silyl Ketene Imine. Preparation of *N*-((1*S*)-2-cyano-1,2-diphenylpropyl)-*P*,*P*-diphenylphosphinic amide (65ab) [TWW-X-30]



Following General Procedure 2, 92 mg of (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide (**64b**, 0.25 mmol) was combined with 10 mg of (*R,R*)-**5** (0.0125 mmol, 0.05 equiv), 32 µL of $SiCl_4$ (0.275 mmol, 1.1 equiv), 43 mL of *i*-Pr_2EtN (0.25 mmol, 1.0 equiv), and 0.30 mL of a 1.0 M solution of silyl ketene imine **58a** in CH_2Cl_2 (0.30 mmol, 1.2 equiv) at -70 °C for 16 h to yield after column chromatography (SiO_2 (30 g), 2 cm diam., hexanes/EtOAc (3/1-2/1 gradient)) 87 mg (67%) of **65ab** as a white solid. The diastereomeric ratio was determined to be 70:30 by 1H NMR integration. The data reported below is for the inseparable mixture, and the minor diastereomer peaks are indicated whenever possible.

Data for **65ab**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.80 (dd, *J* = 12.9, 7.6 Hz, 2H), 7.62 – 7.52 (m, 3H), 7.50 – 7.20 (m, 15H), 7.18 – 7.00 (m, 10H), 6.77 (d, *J* = 7.3 Hz, 2H), 4.57 – 4.41 (m, 0.4 H, minor diastereomer) 4.36 (t, *J* = 11.3 Hz, 1H), 3.85 (t, *J* = 11.0 Hz, 1H), 3.44 (dd, *J* = 10.8, 7.5, 0.4 H,

minor diastereomer), 2.17 (s, 1.2 H, minor diastereomer), 2.12 (s, 3H), 1.68 (s, 1.4 H).

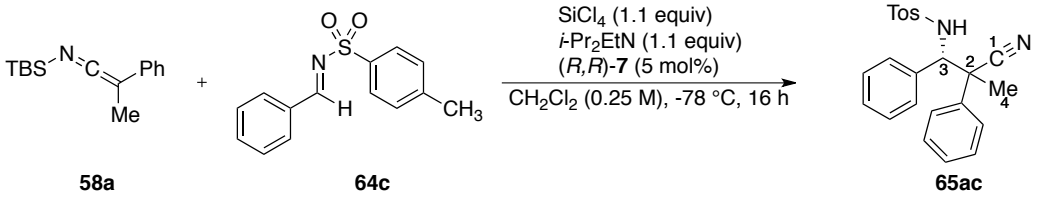
^{31}P NMR: (200 MHz, $CDCl_3$)

25.05 (s), 24.37 (s, minor diastereomer)

TLC: R_f 0.23 (hexanes/EtOAc, 2/1) [UV (254 nm), CAM]

SFC: t_{R1} 14.3 min (36.3%); t_{R2} 18.5 min (37.1%); t_{R3} 22.2 min (12.1%, minor diastereomer); t_{R4} 24.7 min (14.5%, minor diastereomer) (Chiralpak AD, 125 bar, 40 °C, 5% MeOH in CO_2, 3.5 mL/min, 220 nm)

Preparation of *N*-((1*S*)-2-cyano-1,2-diphenylpropyl)-4-methylbenzenesulfonamide (65ac) [TWW-X-30]



58a **64c** **65ac**

Following General Procedure 2, 64 mg of (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (**64c**, 0.25 mmol) was combined with 10 mg of (*R,R*)-**7** (0.0125 mmol, 0.05 equiv), 32 μL of $SiCl_4$ (0.275 mmol, 1.1 equiv), 43 mL of *i*-Pr_2EtN (0.25 mmol, 1.0 equiv), and 0.3 mL of a 1.0 M solution of silyl ketene imine **58a** in CH_2Cl_2 (0.3 mmol, 1.2 equiv) at -25 °C for 24 h to yield after column chromatography (SiO_2 (30 g), 2 cm diam., hexanes/EtOAc (6/1 – 5/1 gradient)) 45 mg (97%) of **65ac** as a white solid. The diastereomeric ratio was determined to be 70:30 by 1H NMR integration. The data reported below is for the inseparable mixture.

Data for **65ac**:

^{1}H NMR: (500 MHz, $CDCl_3$)

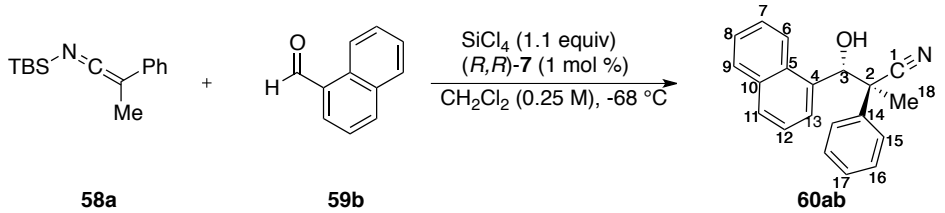
7.25 (d, J = 8.4 Hz, 1H), 7.10 – 6.94 (m, 5H), 6.84 (d, J = 7.4 Hz, 1H), 6.81 (t, J = 6.4 Hz, 3H), 6.74 (t, J = 7.7 Hz, 1H), 6.45 (d, J = 7.4 Hz, 1H), 5.12 (d, J = 10.4 Hz, 1H), 4.65 (d, J = 8.6 Hz, 1H), 4.46 (d, J = 8.5 Hz, 1H), 4.33 (d, J = 10.5 Hz, 1H), 2.14 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.87 (s, 3H).

TLC: R_f 0.2 (hexanes/EtOAc, 5/1) [UV (254 nm), CAM]

SFC: t_{R1} 2.8 min (21.3%); t_{R2} 3.1 min (21.5%); t_{R3} 3.7 min (28.6%); t_{R4} 4.9 min (28.7%) (Chiralpak OJ, 125 bar, 40 °C, 8% MeOH in CO_2, 2.8 mL/min, 220 nm)

7.4.1.6. In Situ IR Kinetic Studies on Lewis Base Catalyzed Aldol Additions.

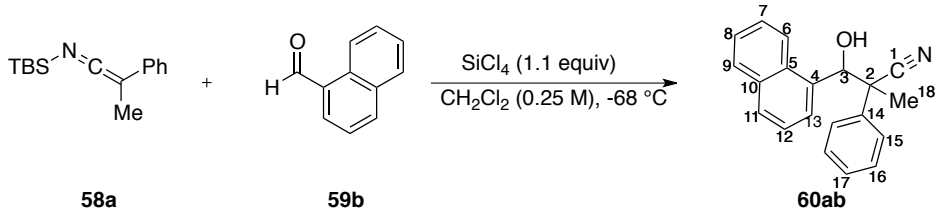
General Procedure 3. React IR monitoring of the Catalyzed Rate for the Addition of SKI 58a to 1-Naphthaldehyde [TWW-VII-13].



An oven-dried, three necked reactor containing a stir bar and temperature probe was attached to the 10 mm DiComp React-IR probe and purged with argon for 15 minutes. The reactor was charged 9.3 mg of (*R,R*)-**7** (0.01 mmol, 0.01 eqiuv) and 4.6 mL of anhydrous dichloromethane. The solution was stirred, cooled to -68 °C (internal) and a background scan was obtained (4 scans / 4 cm^{-1} resolution / 1 gain / 1200-1800 cm^{-1} spectral window). Next, 128 µl of $SiCl_4$ (0.275 mmol, 1.1 equiv) and 0.4 mL of a 2.5 M solution of 1-naphthaldehyde in CH_2Cl_2 (0.5 mmol, 1.0 equiv) was added and the reaction sequence was initiated using the

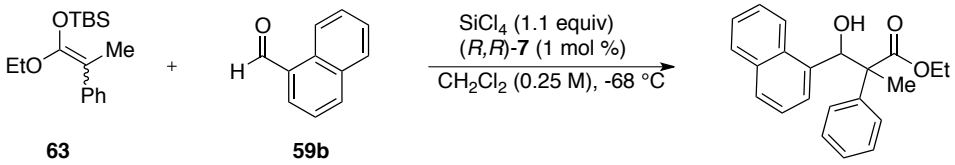
React-IR software (4 scans / 10 sec interval / 4 cm^{-1} resolution / 1 gain /1200-1800 cm^{-1} spectral window). Four scans of the aldehyde were acquired and then 0.58 mL (0.3 mmol, 1.2 equiv) of a 2.06 M solution of **58a** was added via syringe in a single portion. The reaction progress was monitored by disappearance of the aldehyde band at 1702 cm^{-1} for 30 min at -68 °C and then quenched and worked-up using same procedure as listed above (general procedure 2). After verification of the product **60ab** by ^1H NMR the crude material was discarded. Raw data is reported for reaction time (min), spectrum number, and aldehyde absorbance in Table 17.

Monitoring of the Background Rate for the Addition of SKI 58a to 1-Naphthaldehyde [TWW-VII-20].



Following General Procedure 3, 0.4 mL of a 2.5 M solution of 1-naphthaldehyde (1.0 mmol) was combined with 126 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv), 0.58 mL of a 2.06 M solution of silyl ketene imine **58a** and 4.6 mL of CH_2Cl_2 (0.25 M) in a React-IR cell and the reaction progress was monitored for 30 min at -68 °C. The reaction mixture was quenched and worked-up using same procedure as listed above (general procedure 2). After verification of the product **60ab** by ^1H NMR the crude material was discarded. The raw data is reported for reaction time (min), spectrum number, and aldehyde absorbance in Table 17.

Monitoring of the Catalyzed Rate for the Addition of SKA 58a to 1-Naphthaldehyde [TWW-VII-15].



Following General Procedure 3, 0.4 mL of a 2.5 M solution of 1-naphthaldehyde (1.0 mmol) was combined with 9 mg of (*R,R*)-**7** (0.01 mmol, 0.01 eqiuv), 126 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv), 0.58 mL of a 2.06 M solution of silyl ketene acetal **63** and 4.6 mL of CH_2Cl_2 (0.25 M) in a React-IR cell and the reaction progress was monitored for 30 min at -68 °C. The reaction mixture was quenched and worked-up using same procedure as listed above (general procedure 2). After verification of the product by ^{1}H NMR the crude material was discarded. The raw data is reported for reaction time (min), spectrum number, and aldehyde absorbance in Table 17

Table 17. React-IR Data

TWWVII20			TWWVII13			TWWVII15		
Time (min)	Spectra	Abs.	Time (min)	Spectra	Abs.	Time (min)	Spectra	Abs.
0.0	1	0.105	0.0	1	0.089	0.0	1	0.113
0.2	2	0.105	0.2	2	0.091	0.2	2	0.108
0.3	3	0.108	0.3	3	0.094	0.3	3	0.111
0.5	4	0.102	0.5	4	0.090	0.5	4	0.106
0.7	5	0.090	0.7	5	0.051	0.7	5	0.109
0.8	6	0.082	0.8	6	0.022	0.8	6	0.101
1.0	7	0.074	1.0	7	0.007	1.0	7	0.102
1.2	8	0.069	1.2	8	0.004	1.2	8	0.098
1.3	9	0.069	1.3	9	0.001	1.3	9	0.100
1.5	10	0.059	1.5	10	-0.001	1.5	10	0.098
1.7	11	0.067	1.7	11	-0.002	1.7	11	0.098
1.8	12	0.060	1.8	12	-0.006	1.8	12	0.095
2.0	13	0.056	2.0	13	-0.003	2.0	13	0.096
2.2	14	0.056	2.2	14	-0.007	2.2	14	0.092
2.3	15	0.051	2.3	15	-0.007	2.3	15	0.091
2.5	16	0.058	2.5	16	-0.007	2.5	16	0.097
2.7	17	0.059	2.7	17	-0.001	2.7	17	0.102
2.8	18	0.048	2.8	18	-0.010	2.8	18	0.101

Table 17 (cont.)

3.0	19	0.056	3.0	19	-0.008	3.0	19	0.100
3.2	20	0.050	3.2	20	-0.012	3.2	20	0.088
3.3	21	0.048	3.3	21	-0.008	3.3	21	0.094
3.5	22	0.048	3.5	22	-0.007	3.5	22	0.096
3.7	23	0.047	3.7	23	-0.009	3.7	23	0.094
3.8	24	0.052	3.8	24	-0.008	3.8	24	0.092
4.0	25	0.047	4.0	25	-0.011	4.0	25	0.094
4.2	26	0.047	4.2	26	-0.011	4.2	26	0.097
4.3	27	0.045	4.3	27	-0.013	4.3	27	0.086
4.5	28	0.045	4.5	28	-0.009	4.5	28	0.088
4.7	29	0.043	4.7	29	-0.012	4.7	29	0.090
4.8	30	0.038	4.8	30	-0.014	4.8	30	0.088
5.0	31	0.040	5.0	31	-0.015	5.0	31	0.093
5.2	32	0.041	5.2	32	-0.012	5.2	32	0.087
5.3	33	0.039	5.3	33	-0.009	5.3	33	0.089
5.5	34	0.045	5.5	34	-0.010	5.5	34	0.090
5.7	35	0.043	5.7	35	-0.009	5.7	35	0.090
5.8	36	0.043	5.8	36	-0.011	5.8	36	0.088
6.0	37	0.041	6.0	37	-0.010	6.0	37	0.089
6.2	38	0.042	6.2	38	-0.014	6.2	38	0.092
6.3	39	0.037	6.3	39	-0.011	6.3	39	0.082
6.5	40	0.040	6.5	40	-0.013	6.5	40	0.094
6.7	41	0.039	6.7	41	-0.012	6.7	41	0.087
6.8	42	0.035	6.8	42	-0.009	6.8	42	0.085
7.0	43	0.030	7.0	43	-0.012	7.0	43	0.087
7.2	44	0.034	7.2	44	-0.009	7.2	44	0.085
7.3	45	0.032	7.3	45	-0.010	7.3	45	0.093
7.5	46	0.031	7.5	46	-0.011	7.5	46	0.085
7.7	47	0.033	7.7	47	-0.009	7.7	47	0.088
7.8	48	0.032	7.8	48	-0.008	7.8	48	0.088
8.0	49	0.031	8.0	49	-0.015	8.0	49	0.091
8.2	50	0.031	8.2	50	-0.008	8.2	50	0.087
8.3	51	0.034	8.3	51	-0.010	8.3	51	0.084
8.5	52	0.030	8.5	52	-0.010	8.5	52	0.083
8.7	53	0.030	8.7	53	-0.012	8.7	53	0.087
8.8	54	0.031	8.8	54	-0.013	8.8	54	0.088
9.0	55	0.033	9.0	55	-0.012	9.0	55	0.095
9.2	56	0.030	9.2	56	-0.010	9.2	56	0.084
9.3	57	0.023	9.3	57	-0.011	9.3	57	0.083
9.5	58	0.031	9.5	58	-0.011	9.5	58	0.085
9.7	59	0.029	9.7	59	-0.007	9.7	59	0.088
9.8	60	0.032	9.8	60	-0.005	9.8	60	0.093
10.0	61	0.031	10.0	61	-0.007	10.0	61	0.085
10.2	62	0.027	10.2	62	-0.008	10.2	62	0.082
10.3	63	0.029	10.3	63	-0.013	10.3	63	0.083
10.5	64	0.024	10.5	64	-0.013	10.5	64	0.092
10.7	65	0.028	10.7	65	-0.012	10.7	65	0.088

Table 17 (cont.)

10.8	66	0.026	10.8	66	-0.009	10.8	66	0.084
11.0	67	0.025	11.0	67	-0.010	11.0	67	0.087
11.2	68	0.030	11.2	68	-0.012	11.2	68	0.094
11.3	69	0.023	11.3	69	-0.010	11.3	69	0.077
11.5	70	0.031	11.5	70	-0.008	11.5	70	0.078
11.7	71	0.029	11.7	71	-0.010	11.7	71	0.084
11.8	72	0.026	11.8	72	-0.012	11.8	72	0.091
12.0	73	0.029	12.0	73	-0.012	12.0	73	0.084
12.2	74	0.026	12.2	74	-0.008	12.2	74	0.085
12.3	75	0.027	12.3	75	-0.006	12.3	75	0.088
12.5	76	0.023	12.5	76	-0.010	12.5	76	0.083
12.7	77	0.024	12.7	77	-0.008	12.7	77	0.080
12.8	78	0.026	12.8	78	-0.009	12.8	78	0.083
13.0	79	0.022	13.0	79	-0.012	13.0	79	0.086
13.2	80	0.026	13.2	80	-0.013	13.2	80	0.086
13.3	81	0.026	13.3	81	-0.013	13.3	81	0.088
13.5	82	0.025	13.5	82	-0.010	13.5	82	0.081
13.7	83	0.020	13.7	83	-0.007	13.7	83	0.081
13.8	84	0.025	13.8	84	-0.011	13.8	84	0.085
14.0	85	0.021	14.0	85	-0.008	14.0	85	0.080
14.2	86	0.021	14.2	86	-0.010	14.2	86	0.081
14.3	87	0.021	14.3	87	-0.010	14.3	87	0.083
14.5	88	0.023	14.5	88	-0.005	14.5	88	0.083
14.7	89	0.026	14.7	89	-0.012	14.7	89	0.083
14.8	90	0.025	14.8	90	-0.010	14.8	90	0.082
15.0	91	0.022	15.0	91	-0.009	15.0	91	0.086
15.2	92	0.028	15.2	92	-0.009	15.2	92	0.082
15.3	93	0.022	15.3	93	-0.007	15.3	93	0.090
15.5	94	0.019	15.5	94	-0.008	15.5	94	0.086
15.7	95	0.021	15.7	95	-0.011	15.7	95	0.083
15.8	96	0.021	15.8	96	-0.009	15.8	96	0.079
16.0	97	0.022	16.0	97	-0.011	16.0	97	0.083
16.2	98	0.020	16.2	98	-0.011	16.2	98	0.080
16.3	99	0.024	16.3	99	-0.009	16.3	99	0.083
16.5	100	0.022	16.5	100	-0.006	16.5	100	0.083
16.7	101	0.020	16.7	101	-0.009	16.7	101	0.078
16.8	102	0.020	16.8	102	-0.009	16.8	102	0.081
17.0	103	0.023	17.0	103	-0.009	17.0	103	0.080
17.2	104	0.022	17.2	104	-0.008	17.2	104	0.085
17.3	105	0.024	17.3	105	-0.010	17.3	105	0.079
17.5	106	0.020	17.5	106	-0.008	17.5	106	0.086
17.7	107	0.021	17.7	107	-0.009	17.7	107	0.087
17.8	108	0.020	17.8	108	-0.011	17.8	108	0.079
18.0	109	0.018	18.0	109	-0.008	18.0	109	0.080
18.2	110	0.017	18.2	110	-0.006	18.2	110	0.084
18.3	111	0.022	18.3	111	-0.011	18.3	111	0.086
18.5	112	0.020	18.5	112	-0.009	18.5	112	0.085

Table 17 (cont.)

18.7	113	0.020	18.7	113	-0.007	18.7	113	0.083
18.8	114	0.019	18.8	114	-0.007	18.8	114	0.083
19.0	115	0.020	19.0	115	-0.008	19.0	115	0.087
19.2	116	0.019	19.2	116	-0.008	19.2	116	0.084
19.3	117	0.019	19.3	117	-0.007	19.3	117	0.081
19.5	118	0.018	19.5	118	-0.007	19.5	118	0.084
19.7	119	0.017	19.7	119	-0.009	19.7	119	0.078
19.8	120	0.022	19.8	120	-0.008	19.8	120	0.077
20.0	121	0.021	20.0	121	-0.012	20.0	121	0.087
20.2	122	0.021	20.2	122	-0.007	20.2	122	0.088
20.3	123	0.018	20.3	123	-0.011	20.3	123	0.087
20.5	124	0.020	20.5	124	-0.009	20.5	124	0.087
20.7	125	0.020	20.7	125	-0.005	20.7	125	0.079
20.8	126	0.022	20.8	126	-0.010	20.8	126	0.078
21.0	127	0.018	21.0	127	-0.008	21.0	127	0.081
21.2	128	0.018	21.2	128	-0.009	21.2	128	0.077
21.3	129	0.020	21.3	129	-0.014	21.3	129	0.084
21.5	130	0.013	21.5	130	-0.012	21.5	130	0.084
21.7	131	0.016	21.7	131	-0.008	21.7	131	0.085
21.8	132	0.018	21.8	132	-0.004	21.8	132	0.087
22.0	133	0.021	22.0	133	-0.009	22.0	133	0.084
22.2	134	0.019	22.2	134	-0.006	22.2	134	0.084
22.3	135	0.021	22.3	135	-0.008	22.3	135	0.083
22.5	136	0.013	22.5	136	-0.010	22.5	136	0.084
22.7	137	0.015	22.7	137	-0.009	22.7	137	0.082
22.8	138	0.023	22.8	138	-0.013	22.8	138	0.082
23.0	139	0.016	23.0	139	-0.011	23.0	139	0.085
23.2	140	0.018	23.2	140	-0.009	23.2	140	0.085
23.3	141	0.018	23.3	141	-0.007	23.3	141	0.087
23.5	142	0.017	23.5	142	-0.008	23.5	142	0.079
23.7	143	0.017	23.7	143	-0.009	23.7	143	0.083
23.8	144	0.016	23.8	144	-0.009	23.8	144	0.091
24.0	145	0.018	24.0	145	-0.010	24.0	145	0.081
24.2	146	0.018	24.2	146	-0.009	24.2	146	0.080
24.3	147	0.018	24.3	147	-0.005	24.3	147	0.082
24.5	148	0.018	24.5	148	-0.010	24.5	148	0.081
24.7	149	0.015	24.7	149	-0.006	24.7	149	0.086
24.8	150	0.015	24.8	150	-0.009	24.8	150	0.078
25.0	151	0.015	25.0	151	-0.013	25.0	151	0.090
25.2	152	0.019	25.2	152	-0.008	25.2	152	0.091
25.3	153	0.020	25.3	153	-0.010	25.3	153	0.087
25.5	154	0.016	25.5	154	-0.007	25.5	154	0.089
25.7	155	0.016	25.7	155	-0.011	25.7	155	0.083
25.8	156	0.013	25.8	156	-0.009	25.8	156	0.084
26.0	157	0.018	26.0	157	-0.009	26.0	157	0.082
26.2	158	0.014	26.2	158	-0.010	26.2	158	0.083
26.3	159	0.016	26.3	159	-0.007	26.3	159	0.086

Table 17 (cont.)

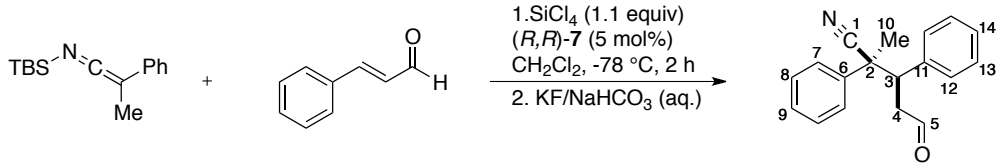
26.5	160	0.014	26.5	160	-0.009	26.5	160	0.087
26.7	161	0.014	26.7	161	-0.006	26.7	161	0.081
26.8	162	0.012	26.8	162	-0.009	26.8	162	0.080
27.0	163	0.017	27.0	163	-0.012	27.0	163	0.077
27.2	164	0.015	27.2	164	-0.008	27.2	164	0.081
27.3	165	0.019	27.3	165	-0.008	27.3	165	0.085
27.5	166	0.018	27.5	166	-0.011	27.5	166	0.085
27.7	167	0.015	27.7	167	-0.011	27.7	167	0.084
27.8	168	0.017	27.8	168	-0.010	27.8	168	0.092
28.0	169	0.009	28.0	169	-0.013	28.0	169	0.080
28.2	170	0.016	28.2	170	-0.012	28.2	170	0.078
28.3	171	0.015	28.3	171	-0.009	28.3	171	0.081
28.5	172	0.017	28.5	172	-0.007	28.5	172	0.083
28.7	173	0.016	28.7	173	-0.009	28.7	173	0.084
28.8	174	0.016	28.8	174	-0.012	28.8	174	0.078
29.0	175	0.016	29.0	175	-0.007	29.0	175	0.083
29.2	176	0.016	29.2	176	-0.008	29.2	176	0.084
29.3	177	0.015	29.3	177	-0.008	29.3	177	0.091
29.5	178	0.015	29.5	178	-0.011	29.5	178	0.087
29.7	179	0.013	29.7	179	-0.008	29.7	179	0.084
29.8	180	0.016	29.8	180	-0.009	29.8	180	0.078
30.0	181	0.014	30.0	181	-0.012	30.0	181	0.085
30.2	182	0.007	30.2	182	-0.016	30.2	182	0.085
30.3	183	0.013	30.3	183	-0.013	30.3	183	0.082
30.5	184	0.015	30.5	184	-0.009	30.5	184	0.084
30.7	185	0.013	30.7	185	-0.007	30.7	185	0.087
30.8	186	0.013	30.8	186	-0.009	30.8	186	0.087

7.4.2 Enantioselective Michael Additions of Silyl Ketene Imine.

7.4.2.1 Addition of a Silyl Ketene Imine to α,β-Unsaturated Carbonyl Compounds.

General Procedure 4. Conjugate Addition of 58a to α,β-Unsaturated Electrophiles.

Preparation of (*2S,3R*)-2-Methyl-5-oxo-2,3-diphenylpentanenitrile (62aa) (Table 6, Entry 1)



58a **61a** (*2S,3R*)-**62aa**

To a flame-dried 10-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 μL of cinnamaldehyde (1.00 mmol) and 5.0 mL anhydrous CH_2Cl_2 (0.2 M in enal). The solution was stirred, cooled to -78 °C (internal) with a dry ice/acetone bath and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were added via syringe to the reaction vessel. The resulting yellow solution was stirred for 5 min at -78 °C and then 0.87 mL of a 1.38 M solution of **58a** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 was added dropwise via syringe over 3 min. The yellow reaction mixture was allowed to stir for an additional 2 h at -78 °C and was then quenched by transferring the cold solution to a 50-mL Erlenmeyer flask containing a stirred, sat. aq. solution of $NaHCO_3$ (10 mL) and KF (10 mL). The biphasic mixture was stirred vigorously for 1 h at rt and then filtered through a pad of packed Celite (ca 7 g) in a 60-mL, in a coarse, glass-sintered Büchner funnel. The filter cake was washed with 10 mL of CH_2Cl_2 and 10 mL of H_2O and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the organic extracts were combined, washed with brine (1 x 25 mL), and dried over $MgSO_4$ (ca 3 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a viscous, yellow oil. The crude residue was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (9:1, 200 mL to 8:1, 320 mL)) to afford 183 mg of **7** (70%) as a clear, colorless solid after concentration and drying *in vacuo* for 4 h (23 °C, 0.3 mm Hg). The overall yield of the reaction was determined to be 84% after isolation of later, mixed column fractions, which gave 34 mg of a clear, colorless oil determined to be the minor diastereomer of 1,4-addition, contaminated with 10% of 1,2-addition product by ^{1}H NMR analysis. The ratio of constitutional isomers (i.e. 1,4:1,2) and the diastereomeric ratio were determined to be 92:8 and 82:18, respectively, by ^{1}H NMR analysis of

the crude product.

Data for **62aa**:

mp: 116-117 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.35 (s, 1 H, HC(5)), 7.57 (d, *J* = 7.9 Hz, 2 H, HC(Aryl)), 7.45 (dd, *J* = 15.1, 7.7 Hz, 4 H, HC(Aryl)), 7.35 (dt, *J* = 24.9, 7.2 Hz, 4 H, HC(Aryl)), 3.63 (dd, *J* = 10.8, 3.5 Hz, 1 H, HC(3)), 3.17 (dd, *J* = 17.7, 10.8 Hz, 1 H, H_2C(4)), 2.58 (dd, *J* = 17.6, 3.5 Hz, 1 H, H_2C(4)), 1.48 (s, 3 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

199.0 (C(5)), 139.2 (C(Aryl)), 137.8 (C(Aryl)), 129.1 (C(Aryl)), 128.9 (C(Aryl)), 128.7 (C(Aryl)), 128.3 (C(Aryl)), 128.1 (C(Aryl)), 125.8 (C(Aryl)) 121.7 (C(1)), 49.0 (C(3)), 47.2 (C(2)), 45.7 (C(4)), 26.4 (C(10))

IR: ($CHCl_3$)

3061 (m), 3000 (m), 2896 (m), 2842 (m), 2739 (m), 2234 (m), 1721 (s), 1600 (m), 1494 (s), 1445 (s), 1416 (m), 1386 (m), 1365 (m), 1340 (m), 1295 (m), 1080 (m), 1022 (m), 923 (m), 791 (m), 703 (s)

MS: (ESI)

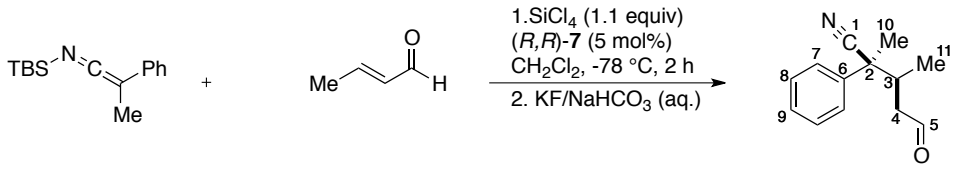
286.1 (58.6) 256.8 (68.9) 254.9 (56.8) 227.0 (48.3) 216.9 (100.0) 206.9 (46.5) 198.9 (41.3) 91.0 (17.2) 81.0 (50.0)

HRMS: calcd for $C_{18}H_{19}NONa^{+}$: 286.1208, found: 286.1198

TLC: R_f 0.16 (hexane/EtOAc, 7:1) [silica gel, CAM]

SFC: See **alc-62aa**, section 7.4.2.3

Preparation of (*2R,3S*)-2,3-Dimethyl-5-oxo-2-phenylpentanenitrile (72) (Table 6, entry 2)



58a **69** (*2S,3R*)-**72**

Following General Procedure 4, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 82 µL (1.0 mmol) of (*E*)-crotonaldehyde, and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.83 mL of a 1.46 M solution of **58a** (1.2 mmol, 1.2 equiv) to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (10:1, 220 mL to 9:1, 300 mL)) and drying *in vacuo* (23°C, 0.3 mmHg, 4 h) 122 mg of **72** (61%) as a clear, colorless oil. The overall yield of the reaction was determined to be 74% after isolation of an additional 26 mg of material from later, mixed column fractions. The ratio of constitutional isomers (*i.e.* 1,4:1,2) and the diastereomeric ratio were determined to be 92:8 and 84:16, respectively, by ^{1}H NMR analysis of the crude product.

Data for **72**:

^{1}H NMR: (500 MHz, $CDCl_3$)

9.54 (d, *J* = 1.2 Hz, 1 H, HC(5)), 7.46 – 7.37 (m, 4 H, HC(Aryl)), 7.35 – 7.31 (m, 1 H, HC(Aryl)), 2.64 (dqd, *J* = 9.8, 6.7, 3.1 Hz, 1 H, HC(3)), 2.43 (ddd, *J* = 17.9, 9.9, 1.7 Hz, 1 H, H_2C(4)), 2.33 (dd, *J* = 17.9, 3.1 Hz, 1 H, H_2C(4)), 1.73 (s, 3 H, H_3C(10)), 1.22 (d, *J* = 6.6 Hz, 3 H, H_3C(11)).

^{13}C NMR: (125 MHz, $CDCl_3$)

199.9 (C(5)), 139.5 (C(6)), 129.1 (C(7,8)), 128.2 (C(9)), 125.7 (C(7,8)), 121.5 (C(1)), 47.5 (C(4)), 47.1 (C(2)), 37.1 (C(3)), 25.4 (C(10)), 16.1 C(11)

IR: ($CHCl_3$)

3062 (m), 3030 (m), 2985 (m), 2941 (m), 2885 (m), 2833 (m), 2236 (w), 1724 (s), 1601 (w), 1495 (s), 1447 (s), 1387 (m), 1293 (m), 1080 (w), 1034 (m), 765 (s), 710 (s), 703 (s)

MS: (ESI)

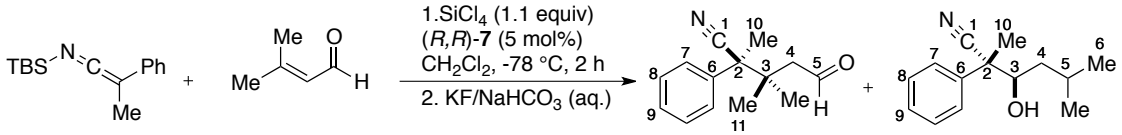
224.1 (35.5), 213.1 (75.0), 201.2 (19.9), 181.1 (100.0), 101.1 (15.3), 81.0 (12.9)

HRMS: calcd for $C_{13}H_{15}NONa^{+}$: 224.1051, found: 224.1060

TLC: R_f 0.14 (hexane/EtOAc, 8:1) [silica gel, CAM]

SFC: See **alc-72**, section 7.4.2.3

Preparation of (*S*)-2,3,3-Trimethyl-5-oxo-2-phenylpentanenitrile (73a) (Table 6, entry 3)



Following General Procedure 4, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 97 µL (1.0 mmol) of 3,3-dimethylpropenal (**70**), and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.87 mL of a 1.38 M solution of **1** (1.2 mmol, 1.2 equiv) to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (9:1, 200 mL to 8:1, 270 mL to 7:1, 320 mL)) and drying *in vacuo* (23°C, 0.3 mmHg, 4 h) 81 mg of **73a** (38%) as a clear, colorless oil. The overall yield of the reaction was determined to be 78% after isolation of 86 mg of **73b** (from later column fractions) as a clear, colorless oil. The diasteromeric ratio of **73b** was determined to be 92:8 by ^{1}H NMR analysis of the chromatographically homogeneous material. The ratio of constitutional isomers (*i.e.* 1,4:1,2) was determined to be 48:52 by ^{1}H NMR analysis of the crude product.

Data for **73a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

9.69 (t, *J* = 2.8 Hz, 1 H, HC(5)), 7.43 (dd, *J* = 5.3, 3.2 Hz, 2 H, HC(7)), 7.41 – 7.32 (m, 3 H, HC(Aryl)), 2.44 (dd, *J* = 14.6, 2.6 Hz, 1 H, $H_2C(4)$), 2.39 (dd, *J* = 14.6, 2.7 Hz, 1 H, $H_2C(4)$), 1.78 (s, 3 H, $H_3C(10)$), 1.25 (s, 3 H, $H_3C(11)$), 1.21 (s, 3 H, $H_3C(11)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

201.4 (C(5)), 136.3 (C(6)), 128.2 (C(9)), 128.2 (C(7,8)), 128.0 (C(7,8)), 122.9 (C(1)), 50.7 (C(4)), 50.6 (C(2)), 39.7 (C(3)), 23.3 (C(11)), 22.7 (C(11)), 20.6 (C(10))

IR: ($CHCl_3$)

3504 (s), 3056 (w), 3032 (w), 2978 (m), 2950 (m), 1496 (m), 1457 (m), 1411 (m), 1393 (m), 1366 (m), 1330 (w), 1283 (w), 1258 (m), 1181 (m), 1090 (s), 1048 (s), 909 (w), 758 (s), 727 (m), 703 (s)

MS: (ESI)

254.1 (100.0), 238.1 (30.7), 230.2 (30.1), 217.2 (16.5), 216.1 (76.3), 99.1 (13.0)

HRMS: calcd for $C_{14}H_{18}NO^{+}$: 216.1388, found: 216.1389

TLC: R_f 0.14 (hexane/EtOAc, 8:1) [silica gel, CAM]

SFC: See **alc-73a**, section 7.4.2.3

Data for **73b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.52 (d, *J* = 7.4 Hz, 2 H), 7.41 (t, *J* = 7.7 Hz, 2 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 5.34 (d, *J* = 9.1 Hz, 1 H), 4.52 (dd, *J* = 9.1, 4.1 Hz, 1H), 1.82 (s, 1 H, OH), 1.79 (s, 3 H),

1.66 (s, 3 H), 1.65 (s, 3 H)

^{13}C NMR: (125 MHz, $CDCl_3$)

140.0 (C(5)), 137.6 (C(7)), 128.8 (C(9)), 128.1 (C(10)), 126.6 (C(8)), 121.9 (C(4)), 121.8 (C(1)), 73.9 (C(3)), 48.9 (C(2)), 25.9 (C(6)), 22.7 (C(6')), 18.7 (C(11))

IR: ($CHCl_3$)

3459 (s), 3062 (m), 3029 (m), 2986 (s), 2937 (s), 2915 (s), 2239 (m), 1675 (m), 1601 (m), 1497 (s), 1446 (s), 1378 (s), 1266 (w), 1109 (w), 1065 (w), 1025 (s), 914 (m), 764 (m), 731 (m), 698 (s)

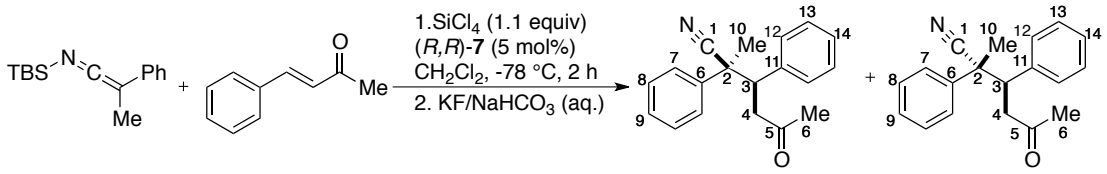
MS: (ESI)

238.1 (54.4), 199.1 (19.5), 198.1 (100.0), 181.1 (11.2), 171.1 (50.8),

HRMS: calcd for $C_{14}H_{17}NONa^+$: 238.1208, found: 238.1208

TLC: R_f 0.07 (hexane/EtOAc, 8:1) [silica gel, CAM]

Preparation of (*2S,3R*)-2-Methyl-5-oxo-2,3-diphenylhexanenitrile (74a) (Table 6, entry 4)



Following General Procedure 4, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 146 mg (1.0 mmol) of *(E)*-4-phenyl-3-butene-2-one, and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.83 mL of a 1.46 M solution of **58a** (1.2 mmol, 1.2 equiv) to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (10:1, 220 mL to 9:1, 300 mL to 7:1, 160 mL)) and drying *in vacuo* (23°C, 0.3 mmHg, 4 h) 118 mg of **74a** (43%) as white needles. The overall yield of the reaction was determined to be 80% after isolation of 103 mg of **74b**

(from later column fractions) as white needles. The ratio of constitutional isomers (*i.e.* 1,4:1,2) and the diastereomeric ratio were determined to be >99:1 and 54:46, respectively, by ^{1}H NMR analysis of the crude product.

Data for **74a**:

mp: 135-136 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.57 (d, J = 8.1 Hz, 2 H, HC(Aryl)), 7.50 – 7.40 (m, 4 H, (HC(Aryl)), 7.40 – 7.33 (m, 3 H, HC(Aryl)), 7.30 (t, J = 7.2 Hz, 1 H, HC(Aryl)), 3.64 (dd, J = 10.7, 3.2 Hz, 1 H, HC(3)), 3.19 (dd, J = 17.2, 10.7 Hz, 1 H, $H_2C(4)$), 2.49 (dd, J = 17.2, 3.2 Hz, 1 H, $H_2C(4)$), 1.87 (s, 3 H, $H_3C(13)$), 1.43 (s, 3 H, $H_3C(11)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

205.5 (C(5)), 139.6 (C(7, 12)), 138.5 (C(7, 12)), 129.1 (C(Aryl)), 129.0 (C(Aryl)), 128.6 (C(Aryl)), 128.2 (C(Aryl)), 127.9 (C(Aryl)) 125.9 (C(Aryl)) 122.1 (C(1)), 49.7 (C(3)), 47.2 (C(2)), 45.6 (C(4)), 30.7 (C(6)), 26.9 (C(11))

IR: (KBr)

3062 (m), 3028 (m), 3007 (m), 2936 (w), 2900 (w), 2234 (w), 1719 (s), 1600 (w), 1497 (m), 1446 (m), 1416 (m), 1368 (s), 1258 (w), 1169 (m), 1080 (w), 1021 (m), 923 (m), 766 (s), 702 (s)

MS: (ESI)

300.2 (100.0), 278.2 (98.8), 260.2 (55.0), 233.2 (36.6), 220.1 (81.1), 147.1 (14.8)

HRMS: calcd for $C_{19}H_{20}NO^{+}$: 278.1545, found: 278.1538

TLC: R_f 0.14 (Hexane/EtOAc, 8:1) [silica gel, $KMnO_4$]

SFC: (*2S,3S*)-**74a**, t_R 5.47 min (45.8%); (*2R,3R*)-**74a**, t_R 6.1 min (54.2%), (Chiralpak AD,

125 bar, 2.5% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Data for **74b**:

mp: 69-70 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.25 – 7.21 (m, 3 H, HC(Aryl)), 7.19 – 7.15 (m, 2 H, HC(Aryl)), 7.13 – 7.08 (m, 3 H, HC(Aryl)), 6.93 (dd, *J* = 7.3, 2.0 Hz, 2 H, HC(Aryl)), 3.67 (dd, *J* = 9.4, 4.5 Hz, 1 H, HC(3)), 3.18 (dd, *J* = 17.1, 9.4 Hz, 1 H, $H_2C(4)$), 3.09 (dd, *J* = 17.1, 4.5 Hz, 1 H, $H_2C(4)$), 2.05 (s, 3 H, $H_3C(6)$), 1.80 (s, 3 H, $H_3C(11)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

205.7 (C(5)), 138.3 (C(7, 12)), 138.1 (C(7, 12)), 128.9 (C(Aryl)), 128.3 (C(Aryl)), 127.9 (C(Aryl)), 127.8 (C(Aryl)), 127.4 (C(Aryl)), 126.4 (C(Aryl)), 122.7 (C(1)), 50.0 (C(3)), 46.9 (C(2)), 45.5 (C(4)), 30.8 (C(6)), 25.4 (C(11))

IR: (KBr)

3064 (m), 3027 (m), 2985 (m), 2950 (m), 2239 (m), 1955 (w), 1882 (w), 1716 (s), 1601 (m), 1494 (s), 1447 (s), 1357 (s), 1295 (s), 1217 (s), 1159 (s), 1084 (m), 1026 (m), 783 (s), 751 (s), 712 (s), 696 (s)

MS: (ESI)

300.2 (100.0), 278.2 (83.4), 260.2 (50.8), 233.1 (26.0), 220.1 (75.6), 147.1 (13.6), 129.1 (10.0)

HRMS: calcd for $C_{19}H_{20}NO^+$: 278.1545, found: 278.1543

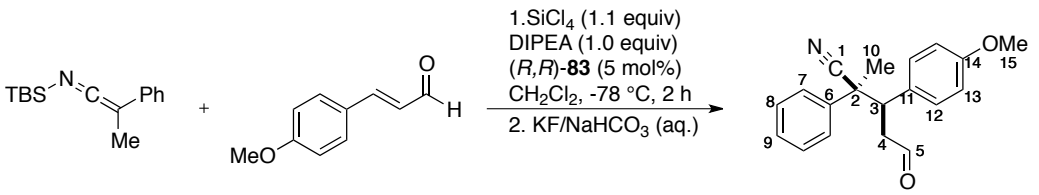
TLC: R_f 0.09 (Hexane/EtOAc, 8:1) [silica gel, $KMnO_4$]

SFC: (*2S,3R*)-**74b**, t_R 5.8 min (79.3%); (*2R,3S*)-**74b**, t_R 6.3 min (20.7%), (Chiralpak AD, 125 bar, 2.5% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

7.4.2.2 Addition of a Silyl Ketene Imine to α,β-Unsaturated Aromatic Aldehydes.

General Procedure 5. Conjugate Addition of SKI 58a to α,β-Unsaturated Aldehydes

Preparation of (*2S,3R*)-3-(4-Methoxyphenyl)-2-methyl-5-oxo-2-phenylpentanenitrile (62ab) (Table 8, entry 2)



To a flame-dried 10-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 35 mg of (*R,R*)-**83** (0.05 mmol, 0.05 equiv), 162 mg of (*E*)-3-(4-methoxyphenyl)propenaldehyde (1.00 mmol) and 5.0 mL anhydrous CH_2Cl_2 (0.2 M in enal). The solution was stirred, cooled to -78 °C with a dry ice/acetone bath and then 175 μL of *N,N*-diisopropylethylamine (1.0 mmol, 1.0 equiv) followed by 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were added via syringe. The resulting, yellow solution was stirred for 5 min at -78 °C (internal) and then 0.77 mL of a 1.56 M solution of **58a** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 was added dropwise via syringe over 3 min. The yellow reaction mixture was allowed to stir for an additional 2 h at -78 °C and was then quenched by transferring the cold solution to a 50-mL Erlenmeyer flask containing a stirred, sat. aq. solution of $NaHCO_3$ (10 mL) and KF (10 mL). The biphasic mixture was stirred vigorously for 1 h at rt and was then filtered through a pad of packed Celite (ca 7 g) in a 60-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with 10 mL CH_2Cl_2 and 10 mL H_2O and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the organic layers were combined, washed with brine (1 x 25 mL), and dried over $MgSO_4$ (ca 3 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm

Hg) to give a viscous, yellow oil. The crude residue was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (7:1, 320 mL to 6:1, 280 mL)) to afford 210 mg of **62ab** (72%) as a clear, colorless oil after concentration and drying *in vacuo* for 4 h (23 °C, 0.3 mm Hg). The overall yield of the reaction was determined to be 79% after isolation of later, mixed column fractions, which gave 23 mg of a clear, colorless oil determined to be the minor diastereomer of 1,4-addition, contaminated with 2% of 1,2-addition product by ^{1}H NMR analysis. The ratio of constitutional isomers (i.e. 1,4:1,2) and the diastereomeric ratio were determined to be 92:8 and 91:9, respectively, by ^{1}H NMR analysis of the crude product.

Data for **62ab**:

^{1}H NMR: (500 MHz, $CDCl_3$)

9.34 (d, *J* = 1.1 Hz, 1 H, HC(5)), 7.56 – 7.53 (m, 2 H, HC(Aryl)), 7.43 (dd, *J* = 10.4, 4.9 Hz, 2 H, HC(Aryl)), 7.36 (d, *J* = 8.8 Hz, 3 H, HC(12) and HC(Aryl), 6.90 (d, *J* = 8.8 Hz, 2 H, HC(13)), 3.80 (s, 3 H, H_3C(15)), 3.57 (dd, *J* = 11.0, 3.7 Hz, 1 H, HC(3)), 3.10 (ddd, *J* = 17.4, 11.0, 2.0 Hz, 1 H, H_2C(4)), 2.53 (ddd, *J* = 17.4, 3.6, 0.6 Hz, 1 H, H_2C(4)), 1.48 (s, 3 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

199.2 (C(5)), 159.3 (C(14)), 139.3 (C(Aryl)), 130.0 (C(Aryl)), 129.6 (C(Aryl)), 129.1 (C(Aryl)), 128.2 (C(Aryl)), 125.7 (C(Aryl)), 121.8 (C(1)), 114.0 (C(13)), 55.2 (C(15)), 48.4 (C(3)), 47.5 (C(2)), 45.7 (C(4)), 26.3 (C(10))

IR: ($CHCl_3$)

3062 (m), 3019 (s), 2907 (m), 2937 (m), 2837 (s), 2730 (m), 2236 (m), 1724 (s), 1611 (s), 1514 (s), 1446 (m), 1380 (m), 1293 (s), 1252 (s), 1182 (s), 1118 (m), 1080 (m), 1035 (s), 835 (s), 756 (s)

MS: (ESI)

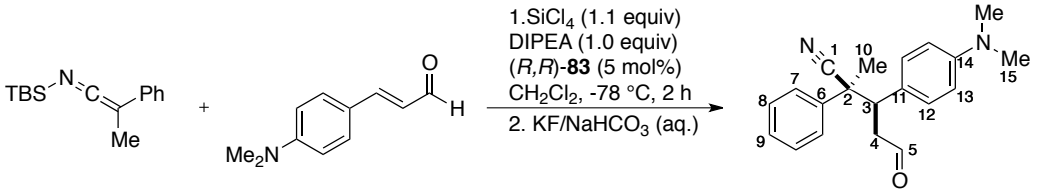
394.4 (50.8), 349.2 (29.6), 348.2 (100.0), 316.1 (14.2)

HRMS: calcd for $C_{19}H_{19}NO_2Na^+$: 316.1313, found: 316.1312

TLC: R_f 0.11 (hexane/EtOAc, 6:1) [silica gel, CAM]

SFC: See **alc-62ab**, section 7.4.2.3

Preparation of (*2S,3R*)-3-(4-(Dimethylamino)phenyl)-2-methyl-5-oxo-2-phenylpentane nitrile (62ac) (Table 8, entry 3)



58a **61c** **(*2S,3R*)-62ac**

Following General Procedure 5, 35 mg of (*R,R*)-**83** (0.05 mmol, 0.05 equiv), 175 mg (1.0 mmol) of (*E*)-3-(4-dimethylaminophenyl)propenal, 175 µL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.85 mL of a 1.42 M solution of **58a** (1.2 mmol, 1.2 equiv) to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (6:1, 350 mL to 5:1, 300 mL)) and drying *in vacuo* (23°C, 0.3 mmHg, 4 h) 150 mg of **62ac** (49%) as a clear, colorless oil. The overall yield of the reaction was determined to be 94% after isolation of an additional 138 mg of material from later, mixed column fractions. The ratio of constitutional isomers (*i.e.* 1,4:1,2) and the diastereomeric ratio were determined to be >98:2 and 68:32, respectively, by ^{1}H NMR analysis of the crude product.

Data for **62ac**:

^{1}H NMR: (500 MHz, $CDCl_3$)

9.34 (dd, *J* = 1.9, 0.9 Hz, 1 H, HC(5)), 7.55 (d, *J* = 7.3 Hz, 2 H, HC(7)), 7.42 (t, *J* = 7.6 Hz, 2 H, HC(8)), 7.35 (t, *J* = 6.8 Hz, 1 H, HC(9)), 7.29 (d, *J* = 8.7 Hz, 2 H, HC(12)), 6.71 (d, *J* = 8.8 Hz, 2 H, HC(13)), 3.51 (dd, *J* = 11.1, 3.8 Hz, 1 H, HC(3)), 3.09 (ddd, *J* = 17.2, 11.1, 2.2 Hz, 1 H, H_2C(3)), 2.96 (s, 6H, H_3C(15)), 2.49 (ddd, *J* = 17.2, 3.7, 0.9 Hz, 1 H, H_2C(4)), 1.49 (s, 3 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

199.8 (C(5)), 150.2 (C(14)), 139.6 (C(6)), 129.7 (C(12)), 129.1 (C(Aryl)), 128.1 (C(Aryl)), 125.8 (C(6)), 124.8 (C(Aryl)), 122.0 (C(1)), 112.3 (C(13)), 48.6 (C(3)), 47.7 (C(2)), 45.7 (C(4)), 40.4 (C(15)), 26.4 (C(10))

IR: ($CHCl_3$)

3035 (w), 2988 (m), 2938 (m), 2892 (m), 2810 (m), 2730 (w), 2236 (w), 1724 (s), 1614 (s), 1524 (s), 1493 (m), 1446 (m), 1355 (s), 1227 (m), 1195 (m), 1167 (m), 1079 (m), 1062 (s), 947 (m), 912 (s), 821 (s), 733 (s), 700 (s)

MS: (ESI)

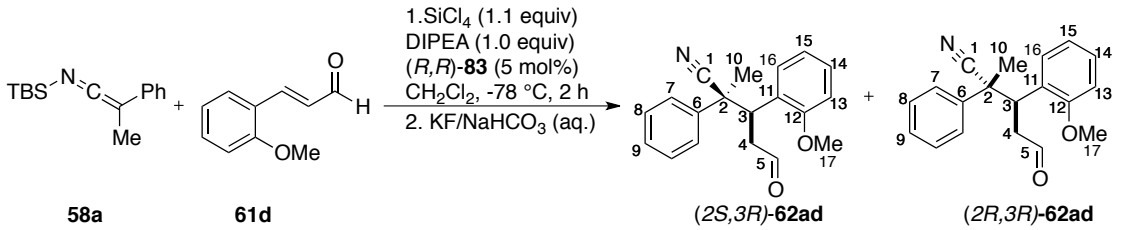
340.2 (26.6), 339.2 (100.0), 325.2 (10.0), 307.2 (37.3)

HRMS: calcd for $C_{20}H_{23}N_2O^+$: 307.1810, found: 307.1801

TLC: R_f 0.17 (hexane/EtOAc, 4:1) [silica gel, $KMnO_4$]

SFC: See **alc-62ac**, section 7.4.2.3

Preparation of (*2S,3R*)-3-(4-Methoxyphenyl)-2-methyl-5-oxo-2-phenylpentanenitrile (62ad) (Table 8, entry 4)



Following general procedure 5, 35 mg of (*R,R*)-**83** (0.05 mmol, 0.05 equiv), 162 mg (1.0 mmol) of (*E*)-3-(2-methoxyphenyl)propenal (**61d**), 175 µL of *N,N*-Diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.77 mL of a 1.56 M solution of **58a** (1.2 mmol, 1.2 equiv) to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (8:1, 270 mL to 7:1, 480 mL)) and drying *in vacuo* (23°C, 0.3 mmHg, 4 h) 153 mg of (2*S*,3*R*)-**62ad** (52%) as a clear, colorless oil. The overall yield of the reaction was determined to be 83% after isolation of an additional 28 mg of material from, mixed column fractions and 61 mg of clean minor diastereomer (2*R*,3*R*)-**62ad**. The ratio of constitutional isomers (*i.e.* 1,4:1,2) and the diastereomeric ratio were determined to be 95:5 and 68:32, respectively, by ^{1}H NMR analysis of the crude product.

Data for (2*S*,*3R*)-**62ad** (Major Diastereomer):

^{1}H NMR: (500 MHz, $CDCl_3$)

9.27 (s, 1 H, HC(5)), 7.61 (d, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 7.39 – 7.33 (m, 1 H), 7.33 – 7.28 (m, 1 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 4.45 (s, 1H), 3.91 (s, 3 H), 3.17 – 2.97 (m, 1 H), 2.50 (dd, *J* = 17.2, 4.1 Hz, 1 H), 1.49 (s, 3 H)

^{13}C NMR: (125 MHz, $CDCl_3$)

199.6 (C(5)), 157.7 (C(12)), 139.8 (C(6)), 129.1 (C(Aryl)), 128.9 (C(Aryl)), 128.1

(C(Aryl)), 127.7 (C(Aryl)), 126.3 (C(Aryl)), 125.8 (C(Aryl)), 121.7 (C(1)), 121.1 (C(15)), 110.7 (C(13)), 55.6 (C(17)), 48.0 (C(3)), 45.5 (C(4)), 38.9 (C(2)), 25.3 (C(10))

IR: ($CHCl_3$)

3064 (m), 3035 (m), 2988 (m), 2941 (s), 2839 (m), 2728 (m), 2253 (m), 1724 (s), 1600 (s), 1493 (s), 1445 (s), 1414 (m), 1380 (m), 1293 (s), 1244 (s), 1172 (m), 1118 (s), 1079 (m), 1028 (s), 912 (s), 757 (s), 734 (s),

MS: (ESI)

294.2 (15.9), 276.1 (40.2), 250.1 (30.7), 249.1 (100.0), 177.1 (36.6), 163.1 (10.6)

HRMS: calcd for $C_{19}H_{20}NO_2^+$: 294.1494, found: 294.1492

TLC: R_f 0.18 (hexane/EtOAc, 6:1) [silica gel, CAM]

SFC: See (2*S*,3*R*)-**alc-62ad**, section 7.4.2.3

Data for (2*S*,3*R*)-**62ad** (Minor Diastereomer):

^{1}H NMR: (500 MHz, $CDCl_3$)

9.50 (t, J = 1.8 Hz, 1 H, HC(5)), 7.24 (app s, 5 H, HC(7, 8, 9)), 7.15 (td, J = 7.9, 1.6 Hz, 1 H, HC(16)), 7.07 (dd, J = 7.6, 1.2 Hz, 1 H, HC(15)), 6.84 (t, J = 7.5 Hz, 1 H, HC(14)), 6.67 (d, J = 8.3 Hz, 1 H, HC(13)), 4.42 – 4.37 (m, 1 H, HC3)), 3.59 (s, 3 H, H_3C(17)), 3.07 – 2.99 (m, 2 H, H_2C(4)), 1.83 (s, 3 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

200.0 (C(5)), 157.1 (C(12)), 137.7 (C(6)), 128.7 (C(Aryl)), 128.5 (C(Aryl)), 127.8 (C(Aryl)), 127.7 (C(Aryl)), 126.7 (C(Aryl)), 125.9 (C(Aryl)), 122.9 (C(1)), 120.3 (C(15)), 110.3 (C(13)), 55.1 (C(17)), 46.5 (C(3)), 45.4 (C(4)), 39.9 (C(2)), 24.7 (C(10))

IR: ($CHCl_3$)

3063 (w), 3033 (m), 2992 (m), 2941 (m), 2838 (m), 2729 (w), 2253 (w), 2235 (w), 1725 (s), 1600 (m), 1493 (s), 1463 (s), 1447 (m), 1382 (m), 1293 (m), 1248 (s), 1118 (m), 1029 (s), 912 (s), 755 (s), 733 (s), 699 (s),

MS: (ESI)

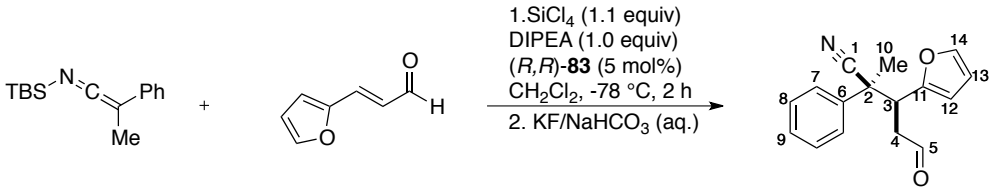
294.2 (26.0), 276.2 (83.4), 250.1 (35.5), 249.1 (100.0), 177.1 (31.3), 145.1 (14.2)

HRMS: calcd for $C_{19}H_{20}NO_2^+$: 294.1484, found: 294.1489

TLC: R_f 0.12 (hexane/EtOAc, 8:1) [silica gel, CAM]

SFC: See (2*R*,*3R*)-**alc-62ad**, section 7.4.2.3

Preparation of (*2S,3S*)-3-(Furan-2-yl)-2-methyl-5-oxo-2-phenylpentanenitrile (62ae) (Table 8, entry 5)



58a **61e** (*2S,3S*)-**62ae**

Following General Procedure 5, 35 mg of (*R,R*)-**83** (0.05 mmol, 0.05 equiv), 122 mg (1.0 mmol) of (*E*)-3-(2-furyl)propenal (**61e**), 175 µL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.85 mL of a 1.42 M solution of **58a** (1.2 mmol, 1.2 equiv) to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (8:1, 270 mL to 7:1, 320 mL to 6:1, 280 mL)) and drying *in vacuo* (23°C, 0.3 mmHg, 4 h) 140 mg of **62ae** (55%) as a clear, colorless oil. The overall yield of the reaction was determined to be 78% after isolation of an additional 57 mg of material from later, mixed column fractions. The ratio of constitutional isomers (*i.e.* 1,4:1,2) and the

diastereomeric ratio were determined to be 92:8 and 81:19, respectively, by ^{1}H NMR analysis of the crude product.

Data for **62ae**:

^{1}H NMR: (500 MHz, $CDCl_3$)

9.46 (s, 1 H, HC(5)), 7.51 (d, J = 8.5 Hz, 2 H, HC(7)), 7.47 – 7.39 (m, 3 H, HC(Aryl)), 7.39 – 7.32 (m, 1 H, HC(Aryl)), 6.37 (dd, J = 3.1, 1.8 Hz, 1 H, HC(13)), 6.33 (d, J = 3.2 Hz, 1 H, HC(Aryl)), 3.81 (dd, J = 11.2, 3.2 Hz, 1 H, HC(3)), 3.14 (ddd, J = 17.7, 11.2, 1.4 Hz, 1 H, H_2C(4)), 2.50 (dd, J = 17.8, 3.3 Hz, 1 H, H_2C(4)), 1.58 (s, 3 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

198.5 (C(5)), 151.7 (C(11)), 142.3 (C(14)), 138.7 (C(6)), 129.2 (C(Aryl)), 128.4 (C(Aryl)), 125.7 (C(Aryl)), 121.3 (C(1)), 110.6 (C(13)), 108.6 (C(12)), 47.2 (C(2)), 44.3 (C(4)), 42.6 (C(3)), 26.0 (C(10)).

IR: ($CHCl_3$)

3118 (w), 3063 (w), 3030 (w), 2990 (m), 2940 (m), 2901 (w), 2834 (m), 2733 (w), 2239 (w), 1725 (s), 1600 (m), 1495 (s), 1447 (s), 1385 (m), 1270 (m), 1150 (m), 1079 (m), 1014 (s), 914 (m), 737 (s)

MS: (ESI)

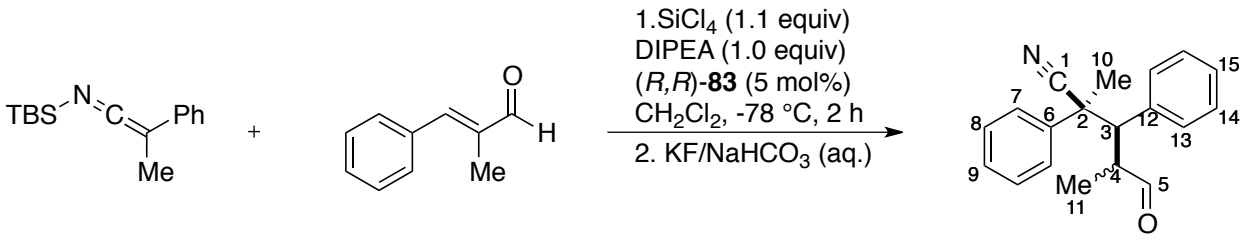
254.1 (18.3), 236.1 (28.9), 211.1 (12.4), 210.1 (66.8), 175.1 (15.3), 174.1 (100.0), 137.1 (36.1)

HRMS: calcd for $C_{16}H_{16}NO_2^+$: 254.1181, found: 254.1171

TLC: R_f 0.13 (hexane/EtOAc, 7:1) [silica gel, CAM]

SFC: See (2*R*,*3R*)-**alc-62ae**, section 7.4.2.3

Preparation of (*2S,3R*)-2,4-Dimethyl-5-oxo-2,3-diphenylpentanenitrile (62af) (Table 8, entry 6)



58a **61f** **(*2S,3R*)-62af**

Following General Procedure 5, 35 mg of (*R,R*)-**83** (0.05 mmol, 0.05 equiv), 140 µL (1.0 mmol) of (*E*)-α-methylcinnamaldehyde (**61f**), 175 µL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.52 mL of a 2.27 M solution of **58a** (1.2 mmol, 1.2 equiv) to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (15:1, 160 mL to 12:1, 260 mL to 10:1, 220 mL to 9:1, 200 mL)) and drying *in vacuo* (23°C, 0.3 mmHg, 4 h) 108 mg of **62af** (55%) as white needles. The overall yield of the reaction was determined to be 78% after isolation of an additional 130 mg of material from later, mixed column fractions. The ratio of constitutional isomers (*i.e.* 1,4:1,2) and the diastereomeric ratio were determined to be 93:7 and 81:10:4:2, respectively, by ^{1}H NMR analysis of the crude product.

Data for **62af**:

^{1}H NMR: (500 MHz, $CDCl_3$)

9.57 (d, *J* = 2.5 Hz, 1 H, HC(5)), 7.62 (d, *J* = 7.4 Hz, 2 H, HC(Aryl)), 7.45 (t, *J* = 7.8 Hz, 4 H, HC(Aryl)), 7.40 – 7.32 (m, 4 H, HC(Aryl)), 3.35 (d, *J* = 7.7 Hz, 1 H, HC(3)), 3.02 (ddq, *J* = 7.2, 2.4 Hz, 1 H, H_3C(4)), 1.41 (s, 3H, HC(10)), 0.76 (d, *J* = 7.0 Hz, 3 H, H_3C(11))

^{13}C NMR: (125 MHz, $CDCl_3$)

201.9 (C(5)), 140.5 (C(Aryl)), 137.6 (C(Aryl)), 129.4 (C(Aryl)), 129.2 (C(Aryl)), 129.0 (C(Aryl)), 128.2 (C(Aryl)), 125.7 (C(Aryl)), 122.4 (C(1)), 56.8 (C(3)), 49.5 (C(4)), 46.0 (C(2)), 29.2 (C(10)), 14.2 (C(11))

IR: ($CHCl_3$)

3063 (m), 3031 (m), 2988 (m), 2936 (m), 2876 (w), 2825 (w), 2254 (w), 1720 (s), 1600 (m), 1494 (m), 1453 (s), 1379 (w), 1083 (w), 912 (s), 788 (w), 761 (m), 733 (s), 701 (s)

MS: (ESI)

300.1 (100.0), 295.2 (41.4), 276.1 (14.7), 260.1 (13.0), 233.1 (47.9), 131.1 (16.5), 130.1 (33.7)

HRMS: calcd for $C_{16}H_{16}NONa^+$: 300.1364, found: 300.1354

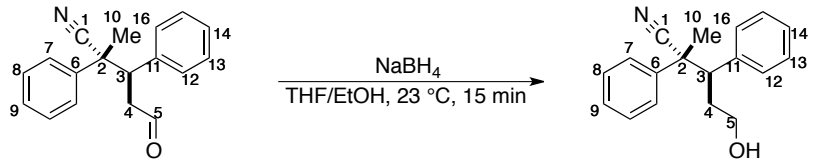
TLC: R_f 0.18 (hexane/EtOAc, 9:1) [silica gel, CAM]

SFC: See **alc-62af**, section 7.4.2.3

7.4.2.3 Sodium Borohydride Reduction of Aldehydes for SFC Analysis.

General Procedure 6: Sodium Borohydride Reduction of Aldehydes for CSP-SFC Analysis

Preparation of (*2S,3R*)-5-Hydroxy-2-methyl-2,3-diphenylpentanenitrile (alc-62aa) (Table 8, Entry 1):



62aa **alc-62aa**

To an oven-dried 25-mL, single-necked flask fitted with a magnetic stir bar, nitrogen inlet and a septum were added 98 mg of **7** (0.37 mmol), and 3.7 mL of 1:1

tetrahydrofuran/ethanol (0.1 M). The solution was stirred at room temperature and 15 mg of sodium borohydride (0.40 mmol, 1.1 equiv) were added in a single portion. The resulting heterogeneous solution was stirred for 15 min at room temperature and then was acidified to pH 3 by the addition of a few drops of 1 M HCl (aq.) Next, 10 mL of H_2O and 10 mL of EtOAc were added and the solution was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aqueous layer was extracted with EtOAc (2 x 20mL) and the organic extracts were combined, washed with $NaHCO_3$ (aq.) (1 x 20 mL) and brine (1 x 20 mL), and dried over Na_2SO_4 (ca 2 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a clear, colorless oil. The crude residue was purified by column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 2:1) to afford 98 mg of **alc-62aa** (99%) as a clear, colorless oil after concentration and drying *in vacuo* for 2 h (23 °C, 0.3 mm Hg).

Data for **alc-62aa**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.59 – 7.53 (m, 2 H, HC(Aryl)), 7.46 – 7.30 (m, 8 H, HC(Aryl)), 3.51 – 3.31 (m, 1 H, $H_2C(5)$), 3.18 (dd, J = 12.1, 3.1 Hz, 2 H, HC(3)), 3.22 – 3.11 (m, 2 H, $H_2C(5)$), 2.18 – 2.00 (m, 1 H, $H_2C(4)$), 1.83 – 1.66 (m, 1 H, $H_2C(4)$), 1.44 (s, 3 H, $H_3C(10)$), 1.01 (s, 1 H, OH)

^{13}C NMR: (125 MHz, $CDCl_3$)

140.2 (C(Aryl)), 138.2 (C(Aryl)), 129.1 (C(Aryl)), 128.9 (C(Aryl)), 128.6 (C(Aryl)), 127.8 (C(Aryl)), 125.8 (C(Aryl)), 122.3 (C(1)), 60.1 (C(5)), 51.5 (C(3)), 47.3 (C(5)), 33.8 (C(4)), 26.9 (C(10))

IR: ($CHCl_3$)

3435 (m), 3062 (m), 3030 (m), 2987 (m), 2940 (m), 2882 (m), 2238 (w), 1601 (m),

1495 (s), 1447 (s), 1380 (m), 1078 (m), 1035 (s), 911 (s), 783 (s)

MS: (ESI)

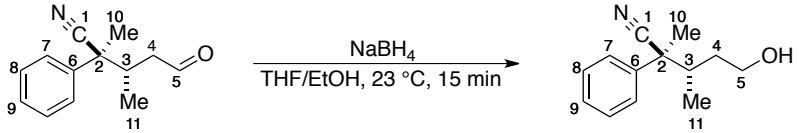
266.2 (100.0), 248.1 (20.1), 222.1 (17.1), 221.1 (86.3), 143.1 (25.4), 105.1 (17.7), 91.1 (11.2)

HRMS: calcd for $C_{18}H_{20}NO^+$: 266.1545, found: 266.1538

TLC: R_f 0.18 (hexane/EtOAc, 2:1) [silica gel, $KMnO_4$]

SFC: (*2R,3S*)-**alc-62aa**, t_R 3.9 min (72.5%); (*2S,3R*)-**alc-62aa**, t_R 4.5 min (27.5%), (Chiralpak AD, 125 bar, 8% MeOH in CO_2, 3.0 mL/min, 220 nm, 40 °C

Preparation of (*2S,3S*)-5-Hydroxy-2,3-dimethyl-2-phenylpentanenitrile (alc-72) (Table 8, Entry 2)



Following General Procedure 6, 122 mg of **72** (0.6 mmol) was combined with 25 mg of $NaBH_4$ (1.1 equiv, 0.66 mmol) and 6.6 mL of THF/EtOH 1:1 (0.1 M) to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 3:1) and drying *in vacuo* (23°C, 0.3 mm Hg, 2 h) 100 mg of **alc-72** (82%) as a clear, colorless oil.

Data for **alc-72**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.43 (d, *J* = 7.6 Hz, 2 H, CH(7)), 7.38 (t, *J* = 7.6 Hz, 2 H, HC(8)), 7.30 (t, *J* = 7.2 Hz, 1 H, HC(9)), 3.66 – 3.56 (m, 1 H, $H_2C(5)$), 3.55 – 3.44 (m, 1 H, $H_2C(5)$), 2.25 – 2.10 (m, 1 H, HC(3)), 1.69 (s, 3 H, $H_3C(10)$), 1.54 (dt, *J* = 13.7, 6.9 Hz, 1 H, $H_2C(4)$), 1.38 – 1.27 (m, 2 H, $H_2C(4)$ and OH), 1.15 (d, *J* = 6.7 Hz, 3 H, $H_3C(11)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

140.5 (C(6)), 129.1 (C(7,8)), 127.9 (C(7,8)), 126.1 (C(9)), 122.6 (C(1)), 60.6 (C(5)), 47.8 (C(2)), 39.3 (C(3)), 35.6 (C(4)), 25.6 (C(10)), 14.9 (C(11))

IR: ($CHCl_3$)

3435 (s), 3062 (m), 3027 (m), 2979 (s), 2942 (s), 2236 (m), 1601 (w), 1495 (s), 1447 (s), 1386 (m), 1221 (m), 1063 (s), 1023 (m), 761 (s), 700 (s)

MS: (ESI)

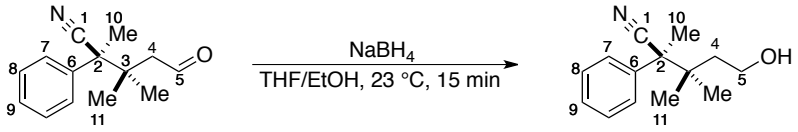
226.1 (47.3), 204.2 (79.2), 187.0 (21.8), 186.1 (32.5), 179.0 (30.1), 159.1 (100.0), 117.1 (28.9), 102.1 (18.9)

HRMS: calcd for $C_{13}H_{18}NO^+$: 204.1388, found: 204.1385

TLC: R_f 0.11 (hexane/EtOAc, 3:1) [silica gel, $KMnO_4$]

SFC: (*2R,3R*)-**alc-72**, t_R 5.4 min (49.1%); (*2S,3S*)-**alc-72**, t_R 6.1 min (50.9%), (Chiralpak OB, 125 bar, 1% MeOH in CO_2, 2.25 mL/min, 210 nm, 40 °C)

Preparation of (*S*)-5-Hydroxy-2,3,3-trimethyl-2-phenylpentanenitrile (alc-73) (Table 8, Entry 3)



73 **alc-73**

Following General Procedure 6, 76 mg of **73** (0.35 mmol) was combined with 15 mg of $NaBH_4$ (1.1 equiv, 0.38 mmol) and 3.5 mL of THF/EtOH 1:1 (0.1 M) to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 2:1) and drying *in vacuo* (23°C, 0.3 mm Hg, 2 h) 75 mg of **alc-73** (99%) as a clear, colorless oil.

Data for **alc-73**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.43 (d, J = 7.3 Hz, 2 H, HC(7)), 7.39 – 7.29 (m, 3 H, HC(8, 9)), 3.67 (t, J = 7.4 Hz, 2 H, $H_2C(5)$), 1.78 (s, 3 H, $H_3C(10)$), 1.74 – 1.60 (m, 2 H, $H_2C(4)$), 1.46 (s, 1 H, OH), 1.04 (s, 6 H, $H_3C(11)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

137.1 (C(6)), 128.2 (C(7, 8)), 127.8 (C(7, 8)), 127.7 (C(9)), 123.7 (C(1)), 59.5 (C(5)), 51.0 (C(2)), 39.6 (C(4)), 39.0 (C(3)), 22.7 (C(11)), 22.5 (C(11)), 20.8 (C(10))

IR: ($CHCl_3$)

3436 (s), 3090 (m), 3062 (m), 2974 (s), 2234 (s), 1600 (s), 1495 (s), 1446 (s), 1396 (s), 1380 (s), 1162 (m), 1093 (s), 1077 (s), 1045 (s), 1008 (s), 972 (m), 912 (s), 732 (s)

MS: (ESI)

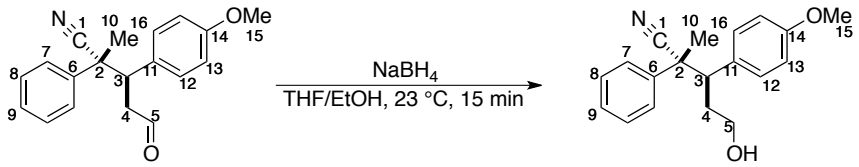
241.1 (12.4), 240.1 (71.0), 218.2 (100.0), 201.1 (13.6), 200.1 (82.8), 173.1 (30.1), 144.1 (11.2), 131.1 (20.7)

HRMS: calcd for $C_{14}H_{20}NO^{+}$: 218.1545, found: 218.1542

TLC: R_f 0.12 (hexane/EtOAc, 2:1) [silica gel, $KMnO_4$]

SFC: (*2S*)-**alc-73**, t_R 2.4 min (54.8%); (*2R*)-**alc-73**, t_R 3.5 min (45.2%), (Chiralpak AD, 125 bar, 10% MeOH in CO_2, 3.2 mL/min, 206 nm, 40 °C)

Preparation of (*2S,3R*)-5-Hydroxy-3-(4-methoxyphenyl)-2-methyl-2-phenylpentane nitrile (alc-62ab) (Table 8, Entry 2)



62ab **alc-62ab**

Following General Procedure 6, 130 mg of **62ab** (0.44 mmol) was combined with 18 mg of $NaBH_4$ (1.1 equiv, 0.48 mmol) and 4.4 mL of THF/EtOH 1:1 (0.1 M) to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 2:1) and drying *in vacuo* (23°C, 0.3 mm Hg, 2h) 128 mg of **alc-62ab** (99%) as a clear, colorless oil.

Data for **alc-62ab**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.52 (d, *J* = 7.4 Hz, 2 H, HC(7)), 7.41 (t, *J* = 7.7 Hz, 2 H, HC(Aryl)), 7.35-7.29 (m, 3 H, HC(Aryl)), 6.90 (d, *J* = 8.8 Hz, 2 H, HC(13)), 3.82 (s, 3 H, H_3C(15)), 3.43 – 3.36 (m, 1 H, H_2C(5)), 3.20 – 3.15 (m, 1 H, H_2C(5)), 3.13 (dd, *J* = 12.2, 3.0 Hz, 1 H, HC(3)), 2.11 – 1.97 (m, 1 H, H_2C(4)), 1.76 – 1.63 (m, 1 H, H_2C(4)), 1.43 (s, 3 H, H_3C(10)), 1.16 (s, 1 H, OH)

^{13}C NMR: (125 MHz, $CDCl_3$)

159.1 (C(15)), 140.3 (C(6)), 130.1 (C(Aryl)), 128.9 (C(Aryl)), 127.8 (C(Aryl)), 125.9 (C(Aryl)), 122.4 (C(1)), 114.0 (C(13)), 60.2 (C(5)), 55.2 (C(15)), 50.8 (C(4)), 47.8 (C(2)), 33.8 (C(4)), 26.9 (C(10))

IR: ($CHCl_3$)

3467 (m), 3062 (w), 3036 (w), 2990 (m), 2938 (m), 2837 (w), 2250 (w), 1611 (m), 1513 (s), 1445 (m), 1306 (m), 1250 (s), 1181 (s), 1077 (m), 1035 (s), 910 (s), 834

(s), 733 (s), 699 (w)

MS: (ESI)

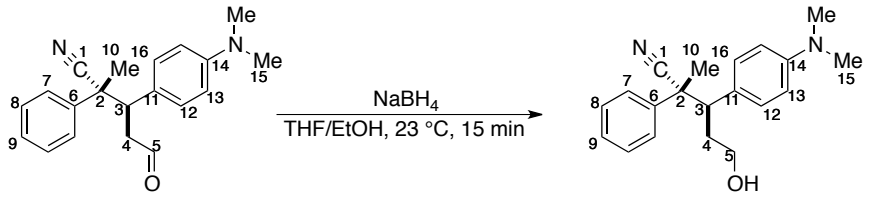
318.2 (17.2), 313.2 (17.8), 297.2 (21.3), 296.2 (100.0), 251.2 (7.1), 165.1 (10.6), 121.1 (7.7)

HRMS: calcd for $C_{19}H_{22}NO_2^+$: 296.1651, found: 296.1657

TLC: R_f 0.16 (hexane/EtOAc, 2:1) [silica gel, CAM]

SFC: (*2S,3R*)-**alc-62ab**, t_R 2.9 min (72.5%); (*2R,3S*)-**alc-62ab**, t_R 3.8 min (27.5%), (Chiralpak AD, 125 bar, 12.5% MeOH in CO_2, 3.0 mL/min, 220 nm, 40 °C)

Preparation of (*2S,3R*)-3-(4-(Dimethylamino)phenyl)-5-hydroxy-2-methyl-2-phenylpentane nitrile (alc-62ac) (Table 8, Entry 3)



62ac **alc-62ac**

Following General Procedure 6, 123 mg of **62ac** (0.40 mmol) was combined with 17 mg of $NaBH_4$ (1.1 equiv, 0.44 mmol) and 4.4 mL of THF/EtOH 1:1 (0.10 M) to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 2:1) and drying *in vacuo* (23°C, 0.3 mm Hg, 2 h) 121 mg of **alc-62ac** (98%) as a clear, colorless oil.

Data for **alc-62ac**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.53 (d, J = 7.5 Hz, 1 H, HC(7)), 7.40 (t, J = 7.7 Hz, 1 H, HC(Aryl)), 7.32 (t, J = 7.3 Hz, 1 H, HC(Aryl)), 7.26 (d, J = 7.9 Hz, 1 H, HC(12)), 6.72 (d, J = 8.8 Hz, 1 H, HC(13)), 3.43 – 3.31 (m, 1 H, $H_2C(5)$), 3.18 (dd, J = 14.0, 8.8 Hz, 1 H, $H_2C(5)$),

3.05 (dd, J = 12.2, 2.9 Hz, 1 H, HC(3)), 2.96 (s, 6 H, H_3C(15)), 2.03 (tt, J = 13.4, 4.8 Hz, 1 H, H_2C(4)), 1.74 – 1.61 (m, 1 H, H_2C(4)), 1.44 (s, 1 H, H_3C(10)), 1.27 (s, 1 H, OH)

^{13}C NMR: (125 MHz, $CDCl_3$)

150.0 (C(14)), 140.5 (C(6)), 129.7 (C(Aryl)), 128.8 (C(Aryl)), 127.6 (C(Aryl)), 125.8 (C(Aryl)), 125.5 (C(Aryl)), 122.6 ((C(1)), 112.4 (C(13)), 60.4 (C(5)), 50.8 (C(3)), 47.9 (C(2)), 40.4 (C(15)), 33.7 (C(4)), 26.9 (C(10))

IR: ($CHCl_3$)

3414 (m), 3035 (m), 2986 (m), 2940 (s), 2885 (s), 2804 (m), 2238 (m), 1614 (s), 1523 (s), 1493 (m), 1446 (s), 1352 (s), 1227 (m), 1166 (s), 1132 (m), 1041 (s), 948 (m), 911 (s), 820 (s), 763 (s), 733 (s), 699 (s)

MS: (ESI)

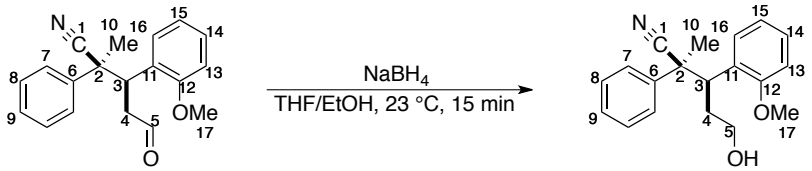
310.2 (25.4), 309.2 (100.0)

HRMS: calcd for $C_{20}H_{25}N_2O^+$: 309.1967, found: 309.1974

TLC: R_f 0.11 (hexane/EtOAc, 2:1) [silica gel, $KMnO_4$]

SFC: (*2S,3R*)-**alc-62ac**, t_R 3.5 min (59.4%); (*2R,3S*)-**alc-62ac**, t_R 5.7 min (40.6%), (Chiralpak AD, 125 bar, 12.5% MeOH in CO_2, 3.0 mL/min, 220 nm, 40 °C

Preparation of (*2S,3S*)-5-Hydroxy-3-(2-methoxyphenyl)-2-methyl-2-phenylpentanenitrile ((2*S*,3*S*)-alc-26a) (Table 8, Entry 4)



(2*S*,3*S*)-62ad (2*S*,3*S*)-alc-62ad

Following general procedure 6, 96 mg of (2*S*,3*S*)-**62ad** (0.33 mmol) was combined with 14 mg of $NaBH_4$ (1.1 equiv, 0.36 mmol) and 3.6 mL of THF/EtOH 1:1 (0.10 M) to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 2:1) and drying *in vacuo* (23°C, 0.3 mm Hg, 2h) 96 mg of (2*S*,3*S*)-**alc-26a** (99%) as a clear, colorless oil.

Data for (2*S*,3*S*)-**alc-26a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.65 (d, *J* = 7.6 Hz, 1 H, HC(16)), 7.59 (d, *J* = 7.5 Hz, 2 H, HC(7)), 7.42 (t, *J* = 7.7 Hz, 2 H, HC(8)), 7.36 – 7.22 (m, 2 H, HC(Aryl)), 7.06 (t, *J* = 7.5 Hz, 1 H, HC(14)), 6.94 (d, *J* = 8.2 Hz, 1 H, HC(13)), 4.02 (dd, *J* = 12.4, 3.1 Hz, 1 H, HC(3)), 3.86 (s, 3 H, H_3C(17)), 3.33 (ddd, *J* = 10.6, 6.7, 4.0 Hz, 1 H, H_2C(5)), 3.21 – 3.10 (m, 1 H, H_2C(5)), 2.03 (ddd, *J* = 13.1, 9.8, 4.8 Hz, 1 H, H_2C(4)), 1.83 – 1.64 (m, 1 H, H_2C(4)), 1.43 (s, 3 H, H_3C(10)), 1.27 (s, 1 H, OH)

^{13}C NMR: (125 MHz, $CDCl_3$)

158.1 (C(12)), 140.8 (C(6)), 128.8 (C(Aryl)), 128.4 (C(Aryl)), 127.7 (C(Aryl)), 127.6 (C(Aryl)), 126.8 (C(Aryl)), 125.9 (C(Aryl)), 122.4 (C(1)), 121.2 (C(15)), 110.5 (C(13)), 60.4 (C(5)), 55.7 (C(17)), 48.1 (C(2)), 40.3 (C(3)), 33.8 (C(4)), 25.9 (C(10))

IR: ($CHCl_3$)

3467 (m), 3063 (w), 3035 (m), 2940 (s), 2883 (m), 2839 (m), 2247 (w), 1600 (m), 1493 (s), 1463 (s), 1445 (s), 1379 (w), 1291 (m), 1243 (s), 1029 (s), 1445 (s), 1379 (w), 1291 (m), 1243 (s), 1029 (s), 911 (s), 759 (s), 733 (s)

MS: (ESI)

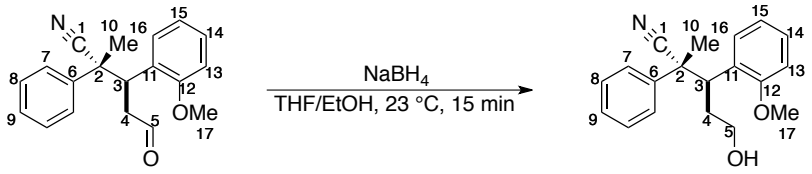
318.2 (10.6), 297.2 (22.4), 296.2 (100.0), 278.2 (10.7), 251.2 (10.5)

HRMS: calcd for $C_{19}H_{22}NO_2^+$: 296.1651, found: 296.1644

TLC: R_f 0.20 (hexane/EtOAc, 2:1) [silica gel, CAM]

SFC: (*2R,3R*)-**alc-62ad**, t_R 9.1 min (14.3%); (*2S,3S*)-**alc-62ad**, t_R 11.6 min (85.6%), (Chiralpak OD, 125 bar, 5.0% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

(*2R,3S*)-5-Hydroxy-3-(2-methoxyphenyl)-2-methyl-2-phenylpentanenitrile ((2*R*,3*S*)-alc-26b) (Table 8, Entry 4)



Following General Procedure 6, 96 mg of (2*R*,3*S*)-**62ad** (0.33 mmol) was combined with 14 mg of $NaBH_4$ (1.1 equiv, 0.36 mmol) and 3.6 mL of 1:1 THF:EtOH (0.10 M) to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 2:1) and drying *in vacuo* (23°C, 0.3 mm Hg, 2 h) 96 mg of (2*R*,3*S*)-**alc-26b** (99%) as a clear, colorless oil.

Data for (2*R*,3*S*)-**alc-26b** (minor diastereomer):

^{1}H NMR: (500 MHz, $CDCl_3$)

7.29 - 7.20 (m, 3 H, HC(Aryl)), 7.19 - 7.13 (m, 3 H, HC(Aryl)), 7.09 (t, *J* = 7.1 Hz, 1 H, HC(15)), 6.85 (t, *J* = 7.3 Hz, 1 H, HC(14)), 6.63 (d, *J* = 8.3 Hz, 1 H, HC(13)), 3.96 (d, *J* = 11.8 Hz, 1 H, HC(3)), 3.57 (s, 3 H, H_3C(17)), 3.56 - 3.34 (m, 1 H, H_2C(5)), 3.27 (td, *J* = 10.2, 5.2 Hz, 1 H, H_2C(5)), 2.45 - 2.24 (m, 1 H, H_2C(4)), 2.12 - 1.95 (m, 1 H, H_2C(4)), 1.86 (s, 3 H, H_3C(10)), 1.62 (s, 1 H, OH)

^{13}C NMR: (125 MHz, $CDCl_3$)

157.2 (C(12)), 138.9 (C(6)), 128.1 (C(Aryl)), 127.7 (C(Aryl)), 127.6 (C(Aryl)),

127.3 (C(Aryl)), 126.8 (C(Aryl)), 126.4 (C(Aryl)), 123.3 (C(15)), 120.5 (C(1)), 110.3 (C(13)), 60.6 (C(17)), 55.3 (C(5)), 46.8 (C(2)), 40.9 (C(3)), 34.0 (C(4)), 25.8 (C(10))

IR: ($CHCl_3$)

3437 (m), 3063 (m), 3033 (m), 2956 (s), 2838 (m), 2236 (w), 1600 (m), 1493 (s), 1463 (s), 1447 (m), 1291 (m), 1245 (s), 1116 (m), 1029 (s), 911 (m), 755 (s), 733 (s)

MS: (ESI)

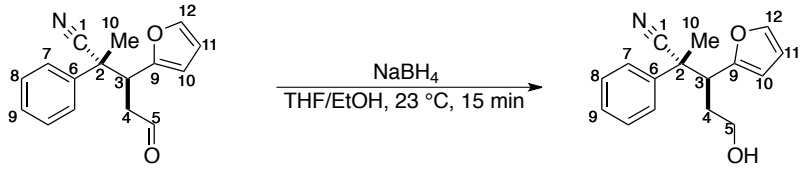
318.2 (27.8), 297.2 (20.1), 296.2 (100.0), 278.2 (61.5), 251.2 (24.8), 250.1 (12.4)

HRMS: calcd for $C_{19}H_{22}NO_2^+$: 296.1651, found: 296.1647

TLC: R_f 0.13 (hexane/EtOAc, 2:1) [silica gel, CAM]

SFC: (*2R,3R*)-**alc-62ad**, t_R 12.7 min (26.8%); (*2R,3S*)-**alc-62ad**, t_R 16.3 min (73.2%), (Chiralpak OD, 125 bar, 5.0% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Preparation of (*2S,3S*)-3-(Furan-2-yl)-5-hydroxy-2-methyl-2-phenylpentanenitrile (alc-62ae) (Table 8, Entry 5)



62ae **alc-62ae**

Following general procedure 6, 60 mg of **62ae** (0.25 mmol) was combined with 10 mg of $NaBH_4$ (1.1 equiv, 0.26 mmol) and 2.5 mL of THF/EtOH 1:1 (0.10 M) to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 2:1) and drying *in vacuo* (23°C, 0.3 mm Hg, 2 h) 61 mg of **alc-62ae** (99%) as a clear, colorless oil.

Data for **alc-62ae**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.49 (d, *J* = 7.4 Hz, 2 H, HC(7)), 7.44 – 7.37 (m, 3 H, HC(Aryl)), 7.33 (t, *J* = 7.3 Hz, 1 H, HC(Aryl)), 6.37 (dd, *J* = 3.1, 1.9 Hz, 1 H, HC(13)), 6.32 (d, *J* = 3.2 Hz, 1 H, HC(12)), 3.55 – 3.45 (m, 1 H, $H_2C(5)$), 3.40 (dd, *J* = 12.2, 3.0 Hz, 1 H, HC(3)), 3.26 (dq, *J* = 15.2, 5.1 Hz, 1 H, $H_2C(5)$), 2.05 (tt, *J* = 13.4, 4.3 Hz, 1 H, $H_2C(4)$), 1.76 – 1.61 (m, 1 H, $H_2C(4)$), 1.54 (s, 3 H, $H_3C(10)$), 1.24 (s, 1 H, OH).

^{13}C NMR: (125 MHz, $CDCl_3$)

152.6 (C(11)), 142.1 (C(14)), 139.6 (C(6)), 128.9 (C(7, 8)), 128.0 (C(9)), 125.7 (C(7, 8)), 122.0 (C(1)), 110.4 (C(13)), 108.5 (C(12)), 60.0 (C(5)), 47.5 (C(3)), 45.2 (C(2)), 33.1 (C(4)), 26.3 (C(10))

IR: ($CHCl_3$)

3451 (s), 3116 (w), 3063 (w), 3030 (w), 2988 (m), 2940 (m), 2883 (m), 2241 (m), 1600 (w), 1495 (s), 1447 (s), 1380 (m), 1239 (m), 1149 (m), 1078 (m), 1040 (s), 1011 (s), 912 (s), 811 (w), 734 (s)

MS: (ESI)

279.1 (20.1), 278.1 (100.0), 275.1 (33.1), 262.1 (47.9), 256.1 (52.0), 229.1 (7.6), 211.1 (28.4), 125.1 (27.8)

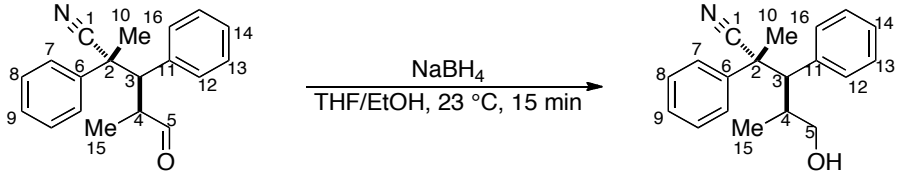
HRMS: calcd for $C_{16}H_{18}NO_2^+$: 256.1338, found: 256.1326

TLC: R_f 0.17 (hexane:EtOAc, 2:1) [silica gel, CAM]

SFC: (*2S,3S*)-**alc-62ae**, t_R 8.7 min (79.0%); (*2R,3R*)-**alc-62ae**, t_R 9.4 min (21.0%), (Chiralpak AD, 125 bar, 4.0% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Preparation of (*2S,3R*)-5-Hydroxy-2,4-dimethyl-2,3-diphenylpentanenitrile (alc-62af)

(Table 8, Entry 6)



28 **alc-28**

Following General Procedure 6, 105 mg of **62af** (0.38 mmol) was combined with 16 mg of $NaBH_4$ (1.1 equiv, 0.42 mmol) and 3.8 mL of THF/EtOH 1:1 (0.10 M) to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, 2/1 hexanes/EtOAc) and drying *in vacuo* (23°C, 0.3 mm Hg, 2 h) 102 mg of **alc-62af** (96%) as a clear, colorless oil.

Data for **alc-62af**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.60 (d, J = 7.8 Hz, 2 H, HC(Aryl)), 7.45 – 7.36 (m, 5 H, HC(Aryl)), 7.32 (t, J = 7.4 Hz, 3 H, HC(Aryl)), 3.55 (dd, J = 10.7, 3.1 Hz, 1 H, H_2C(5)), 3.25 – 3.16 (m, 1 H, H_2C(5) and HC(3)), 2.32 – 2.22 (m, 1 H, HC(4)), 1.29 (s, 4 H, H_3C(10) and OH), 0.71 (d, J = 6.9 Hz, 3 H, H_3C(11))

^{13}C NMR: (125 MHz, $CDCl_3$)

142.0 (C(6, 12)), 139.6 (C(6, 12)), 128.9 (C(Aryl)), 128.7 (C(Aryl)), 127.5 (C(Aryl)), 127.5 (C(Aryl)), 125.5 (C(Aryl)), 123.0 (C(1)), 66.0 (C(5)), 56.3 (C(3)), 45.8 (C(2)), 39.2 (C(4)), 30.4 (C(10)), 17.3 (C(11))

IR: ($CHCl_3$)

3436 (m), 3062 (m), 3030 (w), 2966 (m), 2936 (m), 2237 (w), 1600 (m), 1494 (s), 1454 (s), 1378 (m), 1082 (m), 1034 (s), 983 (m), 911 (s), 762 (m), 732 (s), 702 (s)

MS: (ESI)

303.2 (11.8), 302.2 (52.6), 286.2 (15.3), 281.2 (18.9), 280.2 (100.0), 235.2 (17.7), 130.1 (6.5)

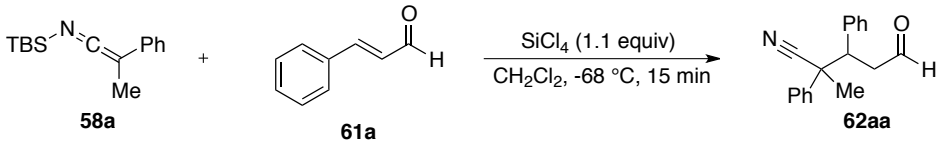
HRMS: calcd for $C_{19}H_{22}NO^+$: 280.1701, found: 280.1693

TLC: R_f 0.17 (hexane:EtOAc, 3:1) [silica gel, CAM]

SFC: (*2R,3S*)-**alc-62af**, t_R 10.1 min (30.6%); (*2S,3R*)-**alc-62af**, t_R 11.6 min (69.4%), (Chiralpak AD, 125 bar, 2.5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

7.4.2.4. In Situ IR Kinetic Studies on Lewis Base Catalyzed Michael Additions.

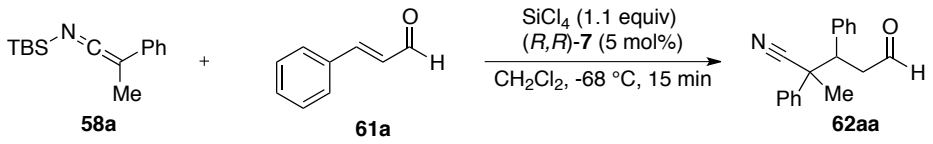
General Procedure 7. React IR monitoring of the Background Rate for the Conjugate Addition of SKI 58a to Cinnamaldehyde [TWW-VII-78].



An oven-dried, three necked reactor containing a stir bar and temperature probe was attached to the 10 mm DiComp React-IR probe and purged with argon for 15 minutes. The reactor was charged with 4.5 mL of anhydrous dichloromethane, cooled to -68 °C (internal) and a background scan was obtained (4 scans / 4 cm^{-1} resolution / 1 gain / 1000-1800 cm^{-1} spectral window). Next, 128 µl of $SiCl_4$ (0.275 mmol, 1.1 equiv) and 125 µL cinnamaldehyde (1.0 mmol, 1.0 equiv) was added and the reaction sequence was initiated using the React-IR software (4 scans / 10 sec interval / 4 cm^{-1} resolution / 1 gain /1200-1800 cm^{-1} spectral window). Four scans of the aldehyde were acquired and then 0.55 mL (0.3 mmol, 1.2 equiv) of a 2.18 M solution of **58a** was added via syringe in a single portion. The reaction progress was monitored by disappearance of the aldehyde band at 1678 cm^{-1} for 15 min at -68 °C and then quenched and worked-up using same procedure as listed above (general procedure 5). After verification of

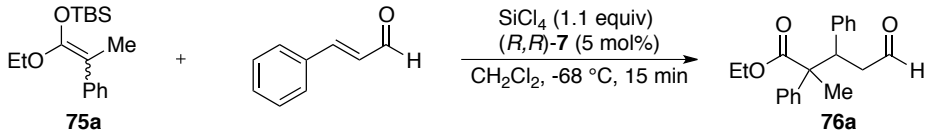
product **62aa** by ^{1}H NMR the crude material was discarded. Raw data is reported for reaction time (min) and aldehyde absorbance in Table 18.

Monitoring of the Catalyzed Rate for the Conjugate Addition of SKI 58a to Cinnamaldehyde [TWW-VIII-52].



Following General Procedure 7, 31.5 μL of cinnamaldehyde (1.0 mmol) was combined with 10.5 mg of (*R,R*)-**7** (0.05 mmol, 0.05 eqiuv), 31.5 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv), 0.27 mL of a 1.13 M solution of silyl ketene imine **58a** and 1.25 mL of CH_2Cl_2 in a React-IR cell and the reaction progress was monitored for 15 min at -68 °C. The reaction mixture was quenched and worked-up using same procedure as listed above (general procedure 5). After verification of the product by ^{1}H NMR the crude material was discarded. The raw data is reported for reaction time (min), spectrum number, and aldehyde absorbance in Table 18.

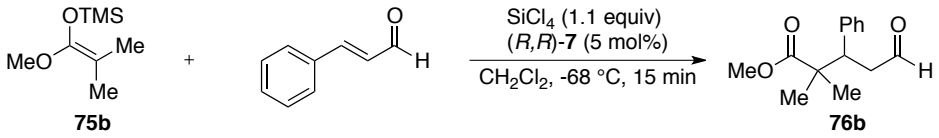
Monitoring of the Catalyzed Rate for the Conjugate Addition of SKA 75a to Cinnamaldehyde [TWW-VII-97].



Following General Procedure 7, 0.125 mL of a 2.0 M solution of cinnamaldehyde (0.25 mmol) was combined with 10.5 mg of (*R,R*)-**7** (0.05 mmol, 0.05 eqiuv), 31.5 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv), 0.125 mL of a 2.4 M solution of silyl ketene acetal **75a** and 1.25 mL of CH_2Cl_2 in a React-IR cell and the reaction progress was monitored for 15 min at -68 °C. The

reaction mixture was quenched and worked-up using same procedure as listed above (general procedure 5). After verification of product **76a** by ^{1}H NMR the crude material was discarded. The raw data is reported for reaction time (min), spectrum number, and aldehyde absorbance in Table 18.

Monitoring of the Catalyzed Rate for the Conjugate Addition of SKA 75b to Cinnamaldehyde [TWW-VII-90].



Following General Procedure 7, 0.12 mL of a 1.98 M solution of cinnamaldehyde (0.25 mmol) was combined with 10.5 mg of (*R,R*)-**7** (0.05 mmol, 0.05 eqiuv), 31.5 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv), 0.23 mL of a 1.31 M solution of silyl ketene acetal **75b** and 1.25 mL of CH_2Cl_2 in a React-IR cell and the reaction progress was monitored for 15 min at -68 °C. The reaction mixture was quenched and worked-up using same procedure as listed above (general procedure 5). After verification of product **76b** by ^{1}H NMR the crude material was discarded. The raw data is reported for reaction time (min), spectrum number, and aldehyde absorbance in Table 18.

Table 18. React-IR Data for Conjugate Addition of Silyl Ketene Imine and Acetal

TWW-VII-78		TWW-VIII-52		TWW-VII-97		TWW-VII-90	
Time (min)	Abs.	Time (min)	Abs.	Time (min)	Abs.	Time (Min)	Abs.
0.0	0.220	0.0	0.151	0.0	0.148	0.0	0.140
0.2	0.218	0.2	0.155	0.2	0.151	0.2	0.140
0.3	0.218	0.3	0.150	0.4	0.151	0.3	0.142
0.5	0.219	0.5	0.153	0.5	0.152	0.5	0.140
0.7	0.097	0.7	0.153	0.7	0.153	0.7	0.140
1.0	0.123	0.8	0.153	0.8	0.151	0.8	0.142
1.2	0.124	1.0	0.022	1.0	0.154	1.0	0.140
1.3	0.122	1.2	0.011	1.2	0.152	1.2	0.141

Table 18 (cont.)

1.5	0.120	1.3	0.009	1.4	0.153	1.3	0.139
1.7	0.122	1.5	0.009	1.5	0.152	1.5	0.140
1.8	0.123	1.7	0.009	1.7	0.156	1.7	0.141
2.0	0.121	1.8	0.011	1.8	0.154	1.8	0.139
2.2	0.122	2.0	0.010	2.0	0.154	2.0	0.009
2.3	0.121	2.2	0.011	2.2	0.156	2.2	0.007
2.5	0.121	2.3	0.011	2.3	0.161	2.3	0.005
2.7	0.122	2.5	0.010	2.5	0.159	2.5	0.006
2.8	0.122	2.7	0.010	2.7	0.157	2.7	0.004
3.0	0.118	2.8	0.012	2.8	0.160	2.8	0.005
3.2	0.120	3.0	0.008	3.0	0.158	3.0	0.002
3.3	0.119	3.2	0.011	3.2	0.157	3.2	0.003
3.5	0.123	3.3	0.012	3.3	0.157	3.3	0.003
3.7	0.117	3.5	0.011	3.5	0.157	3.5	0.004
3.8	0.120	3.7	0.011	3.7	0.158	3.7	0.002
4.0	0.116	3.8	0.011	3.8	0.158	3.8	0.005
4.2	0.124	4.0	0.011	4.0	0.156	4.0	0.005
4.3	0.118	4.2	0.011	4.2	0.158	4.2	0.006
4.5	0.117	4.3	0.010	4.3	0.156	4.3	0.004
4.7	0.119	4.5	0.011	4.5	0.156	4.5	0.003
4.8	0.115	4.7	0.008	4.7	0.155	4.7	0.005
5.0	0.120	4.8	0.010	4.8	0.156	4.8	0.002
5.2	0.120	5.0	0.012	5.0	0.156	5.0	0.003
5.3	0.117	5.2	0.011	5.2	0.155	5.2	0.003
5.5	0.117	5.3	0.014	5.3	0.155	5.3	0.004
5.7	0.120	5.5	0.010	5.5	0.152	5.5	0.005
5.8	0.117	5.7	0.011	5.7	0.156	5.7	0.005
6.0	0.120	5.8	0.012	5.8	0.156	5.8	0.003
6.2	0.117	6.0	0.012	6.0	0.153	6.0	0.004
6.3	0.119	6.2	0.010	6.2	0.154	6.2	0.004
6.5	0.120	6.3	0.010	6.3	0.154	6.3	0.006
6.7	0.115	6.5	0.009	6.5	0.153	6.5	0.002
6.8	0.116	6.7	0.010	6.7	0.155	6.7	0.003
7.0	0.116	6.8	0.011	6.8	0.155	6.8	0.002
7.2	0.119	7.0	0.012	7.0	0.154	7.0	0.001
7.3	0.118	7.2	0.010	7.2	0.151	7.2	0.004
7.5	0.118	7.3	0.012	7.4	0.150	7.3	0.005
7.7	0.119	7.5	0.009	7.5	0.152	7.5	0.002
7.8	0.119	7.7	0.010	7.7	0.152	7.7	0.003
8.0	0.119	7.8	0.011	7.8	0.150	7.8	0.002
8.2	0.117	8.0	0.011	8.0	0.148	8.0	0.004
8.3	0.118	8.2	0.010	8.2	0.151	8.2	0.006
8.5	0.115	8.3	0.010	8.3	0.153	8.3	0.006
8.7	0.116	8.5	0.010	8.5	0.150	8.5	0.003
8.8	0.116	8.7	0.009	8.7	0.149	8.7	0.002
9.0	0.116	8.8	0.009	8.8	0.149	8.8	0.005
9.2	0.117	9.0	0.009	9.0	0.148	9.0	0.001

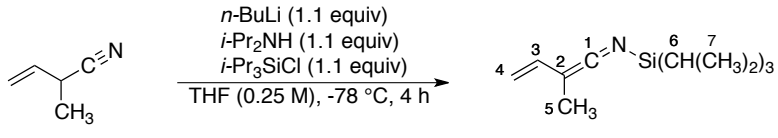
Table 18 (cont.)

9.3	0.117	9.2	0.010	9.2	0.148	9.2	0.004
9.5	0.118	9.3	0.012	9.3	0.148	9.3	0.005
9.7	0.118	9.5	0.011	9.5	0.147	9.5	0.005
9.8	0.114	9.7	0.011	9.7	0.148	9.7	0.007
10.0	0.118	9.8	0.010	9.8	0.148	9.8	0.006
10.2	0.117	10.0	0.010	10.0	0.149	10.0	0.003
10.3	0.116	10.2	0.012	10.2	0.148	10.2	0.004
10.5	0.117	10.3	0.012	10.3	0.147	10.3	0.003
10.7	0.118	10.5	0.009	10.5	0.147	10.5	0.004
10.8	0.112	10.7	0.010	10.7	0.147	10.7	0.001
11.0	0.118	10.8	0.010	10.8	0.147	10.8	0.005
11.2	0.117	11.0	0.011	11.0	0.148	11.0	0.004
11.3	0.116	11.2	0.008	11.2	0.147	11.2	0.004
11.5	0.116	11.3	0.009	11.3	0.145	11.3	0.003
11.7	0.117	11.5	0.011	11.5	0.146	11.5	0.003
11.8	0.112	11.7	0.011	11.7	0.146	11.7	0.002
12.0	0.117	11.8	0.011	11.8	0.146	11.8	0.004
12.2	0.118	12.0	0.012	12.0	0.147	12.0	0.005
12.3	0.118	12.2	0.010	12.2	0.144	12.2	0.005
12.5	0.116	12.3	0.009	12.3	0.144	12.3	0.005
12.7	0.117	12.5	0.012	12.5	0.143	12.5	0.004
12.8	0.116	12.7	0.012	12.7	0.145	12.7	0.003
13.0	0.118	12.8	0.011	12.8	0.142	12.8	0.004
13.2	0.114	13.0	0.010	13.0	0.142	13.0	0.004
13.3	0.118	13.2	0.009	13.2	0.144	13.2	0.005
13.5	0.117	13.3	0.010	13.3	0.142	13.3	0.002
13.7	0.119	13.5	0.008	13.5	0.142	13.5	0.003
13.8	0.118	13.7	0.010	13.7	0.143	13.7	0.003
14.0	0.118	13.8	0.013	13.9	0.144	13.8	0.003
14.2	0.114	14.0	0.011	14.0	0.144	14.0	0.003

7.4.3 Vinylogous Aldol Addition of *N*-Silyl Vinylketene Imine.

7.4.3.1 Preparation of an *N*-Silyl Vinylketene Imine.

Preparation of 1,1,1-triisopropyl-N-(2-methylbuta-1,3-dien-1-ylidene)silanamine (102)



To a flame-dried, 50-mL, single-necked, Schlenk flask fitted with a magnetic stir bar,

argon inlet and septum was added 1.60 mL of diisopropylamine (11.4 mmol, 1.05 equiv) and 18.0 mL of anhydrous THF (0.64 M). The solution was cooled to -78 °C (internal) with a dry ice/acetone bath and then 4.85 mL of *n*-BuLi (11.4 mmol, 1.05 equiv) was added over several minutes. The resulting yellow solution of LDA (0.5 M) was stirred at -78 °C for 15 min and then 2.45 mL (11.4 mmol, 1.05 equiv) of TIPSCl was added dropwise via syringe over 3 min. The reaction components were stirred for 5 min and then a solution of 0.88 g of 2-methyl-3-butenenitrile (10.9 mmol) in 22.0 mL of THF (0.5 M), pre-cooled to -78 °C (Acetone/CO_2), was added dropwise via cannula over 30 min to the LDA/TIPSCl. The resulting bright yellow homogeneous solution was stirred for 4 h at -78 °C and then the bath was removed and the solution stirred for 15 min. During this time the reaction color darkens from yellow to orange. The solvent was removed under high vacuum (0.5 mm Hg) at 0 °C (ice bath) and the resulting red residue (ca. 1 mL) was taken up in 15 mL of anhydrous pentanes and stirred vigorously under argon. The resulting yellow heterogeneous solution with white precipitate was filtered via cannula into a flame-dried, weighed 50-mL, round-bottomed flask. The Schlenk flask was further washed with 15 mL of anhydrous pentanes and the filtrated added via cannula filtration to the round bottom flask. The clear, orange filtrate was concentrated under vacuum (0.5 mm Hg) and then was stirred under high vacuum (0.2 mm Hg) for 30 min at ambient temperature to afford 2.40 g (94%) of **102** as an orange liquid. The crude mixture was transferred via pipette to a shortpath distillation apparatus and distilled under vacuum to afford 1.8 g (70%) of **102** as a clear, yellow liquid. The purity was judged by ^{1}H NMR to be >93% silyl ketene imine and was used in subsequent reactions without further purification.

Data for **102**:

bp: 58 – 60 °C at 400 mtorr

^{1}H NMR: (500 MHz, C_6D_6)

6.63 (dd, *J* = 16.5, 10.8 Hz, 1 H, HC(3)), 4.75 (s, 1 H, $H_2C(4)$), 4.73 (dd, *J* = 7.4, 1.3 Hz, 1 H, $H_2C(4)$), 1.76 (s, 3 H, $H_3C(5)$), 1.0 – 0.98 (m, 21 H, $H_2C(6)$ and $H_3C(7)$).

^{13}C NMR: (125 MHz, C_6D_6)

185.9 (C(1)), 133.9 (C(3)), 102.2 (C(4)), 48.0 (C(2)), 17.8 (C(7)), 12.0 (C(5)), 10.6 (C(6))

IR: (NaCl plates, neat)

3090 (m), 2944 (s), 2867 (m), 2727 (w), 2274 (s), 1833 (w), 1721 (w), 1601 (s), 1464 (s), 1384 (m), 1371 (m), 1347 (s), 1286 (w), 1251 (s), 1071 (m), 1016 (m), 995 (s), 976 (s), 919 (m), 882 (w).

MS: (70 eV, EI)

237.2 (29.3), 226.1 (22.2), 210.1 (100.0), 183.1 (15.4), 156.1 (42.3), 128.1 (33.1), 115.1 (27.2), 112.1 (17.1), 100.0 (46.1), 87.1 (20.9), 86.0 (21.0), 84.0 (20.9), 73.1 (22.2), 59.1 (31.4)

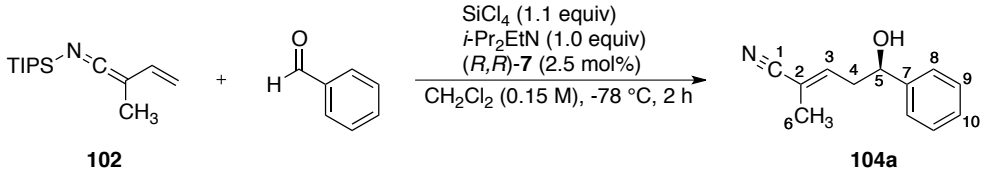
HRMS: calcd for $C_{14}H_{27}NSi$: 237.1913, found: 237.1921

7.4.3.2 Addition of *N*-Silyl Vinylketene Imine to Aromatic Aldehydes.

General Procedure 8. Vinylogous Addition of *N*-Silyl Vinylketene Imine 102 to Aromatic Aldehydes.

Preparation of (*E,R*)-5-hydroxy-2-methyl-5-phenylpent-2-enenitrile (104a)

(Table 9, entry 1)



102 **104a**

To a flame-dried, 10-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 μL of benzaldehyde (1.00 mmol) and 5.75 mL anhydrous CH_2Cl_2 (0.17 M in aldehyde). The solution was stirred, cooled to -78 °C (internal) with a dry ice/acetone bath and then 35 μL of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were added via syringe to the reaction vessel. The resulting solution was stirred for 5 min at -78 °C and then 0.95 mL of a 1.22 M solution of silyl ketene imine **102** (1.15 mmol, 1.15 equiv) in dichloromethane was added dropwise via syringe over 10 min. The yellow reaction mixture was allowed to stir for an additional 2 h at -78 °C before 0.60 mL of a 3:1:1 mixture of Et_3N/CH_2Cl_2/MeOH was added via syringe. The quenched solution was stirred for 3 min at -78 °C and then was transferred to a 50-mL Erlenmeyer flask containing a stirred, sat. aq. solution of $NaHCO_3$ (10 mL) and KF (10 mL). The biphasic mixture was stirred vigorously for 2 h at rt and then was filtered through a pad of packed Celite (ca. 7 g) in a 60-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with 10 mL of CH_2Cl_2 and 10 mL of H_2O and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aquaeos layer was extracted with CH_2Cl_2 (2 x 25 mL) and the resulting organic extracts were combined, washed with brine (1 x 25 mL), and dried over Na_2SO_4 (ca. 3 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil. The crude residue was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (5:1 to 3:1) to afford 183 mg of **104a** (97%) as a clear, colorless oil after drying *in*

vacuo for 1 h. Further purification by Kugelrohr distillation (165 – 179 °C, 0.40 mm Hg) produced 182 mg of analytically pure **104a** (97%) as a clear, colorless oil. The *gamma/alpha* ratio was determined to be 99:1 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **104a**:

bp: 160 – 165 °C (0.40 mm Hg, kugelrohr)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.40 – 7.27 (m, 5 H, HC(Aryl)), 6.39 (app t, J = 7.4, 1 H, HC(3)), 4.82 – 4.74 (m, 1 H, HC(5)), 2.60 (ddd, J = 21.7, 14.8, 7.0 Hz, 2 H, H_2C(4)), 2.32 (br s, 1 H, OH), 1.77 (s, 3 H, H_3C(6))

^{13}C NMR: (125 MHz, $CDCl_3$)

143.9 (C(3)), 143.1 (C(7)), 128.6 (C(9)), 128.0 (C(10)), 125.6 (C(8)), 120.4 (C(1)), 111.3 (C(2)), 72.8 (C(5)), 38.0 (C(4)), 15.0 (C(6))

IR: (neat)

3436 (s), 2886 (m), 1386 (s), 905 (s), 3087 (m), 2218 (s), 1309 (m), 764 (s), 3063 (m), 1640 (m), 1199 (m), 701 (s), 3031 (m), 1494 (s), 1080 (m), 2926 (m), 1454 (s), 1049 (s)

MS: (ESI)

211.1 (10.0), 210.1 (100.0, M + Na), 196.9 (4.0), 138.9 (4.1), 81.0 (5.4)

HRMS: calcd for $C_{12}H_{13}NONa^{+}$: 210.0889, found: 210.0895

TLC: 0.11 (hexane/EtOAc, 5:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +36.2 (c = 2.0, $CHCl_3$)

SFC: (*E,5R*)-**104a**, t_R 8.5 min (93.4%); (*E,5S*)-**104a**, t_R 9.3 min (6.6%), (Chiralpak OD, 200 bar, 5% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

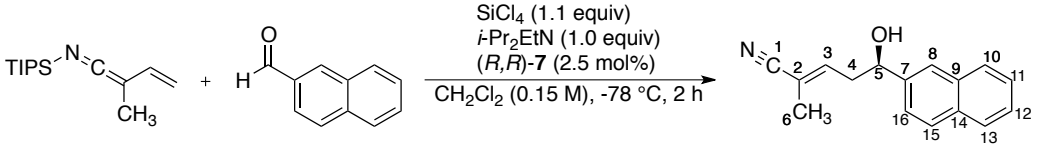
Analysis: $C_{12}H_{13}NO$ (187.100)

Calcd: C, 76.98; H, 7.00; N, 7.48%

Found: C, 77.23; H, 6.90; N, 7.11%

Preparation of (*E,R*)-5-hydroxy-2-methyl-5-(naphthalen-2-yl)pent-2-enenitrile (104b)

(Table 8, entry 2)



Following General Procedure 8, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 141 mg of 2-naphthaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.92 mL of a 1.24 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (5:1 to 4:1)) and drying *in vacuo* (Abderhalden, 40 °C, 0.3 mm Hg) 229 mg of **104b** (97%) as a white solid. The *gamma/alpha* ratio was determined to be 99:1 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **104b**:

mp: 81 – 82 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.84 (t, J = 7.9 Hz, 3 H, HC(10,13,15)), 7.76 (s, 1 H, HC(8)), 7.55 – 7.48 (m, 2 H, HC(11,12)), 7.44 (dd, J = 8.5, 1.5 Hz, 1 H, HC(16)), 6.41 (t, J = 7.4 Hz, 1 H, HC(3)), 4.92 (t, J = 6.3 Hz, 1 H, HC(5)), 2.79 – 2.55 (m, 2 H, H_2C(4)), 2.33 (s, 1 H, OH), 1.77 (s, 3H, H_3C(6))

^{13}C NMR: (125 MHz, $CDCl_3$)

143.8 (C(3)), 140.4 (C(7)), 133.1 (C(9,14)), 133.1 (C(9,14)), 128.6 (C(10,13,15)), 127.9 (C(10,13,15)), 127.7 (C(10,13,15)), 126.4 (C(11,12)), 126.2 (C(11,12), 124.5 (C(8)), 123.4 (C(16)), 120.2 (C(1)), 111.3 (C(2)), 72.9 (C(5)), 37.9 (C(4)), 15.0 (C(6))

IR: (KBr Pellet)

3435 (s), 3056 (s), 3016 (s), 2961 (m), 2925 (m), 2218 (s), 1637 (m), 1601 (m), 1508 (m), 1441 (m), 1382 (m), 1274 (m), 1216 (s), 1122 (m), 1050 (s), 900 (m)

MS: (ESI)

260.1 (100.0, M+Na), 239.1 (35.5), 213.1 (57.4), 197.1 (14.7), 181.1 (43.1)

HRMS: calcd for $C_{16}H_{15}NONa^+$: 260.1051, found: 260.1054

TLC: 0.90 (hexane/EtOAc, 4:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +34.9 (c = 2.33, $CHCl_3$)

SFC: (E,5*S*)-**104b**, t_R 5.9 min (7.1%); (*E*,5*R*)-**104b**, t_R 7.3 min (92.9%), (Chiralpak OD, 200 bar, 15% MeOH in CO_2, 3.0 mL/min, 220 nm, 40 °C)

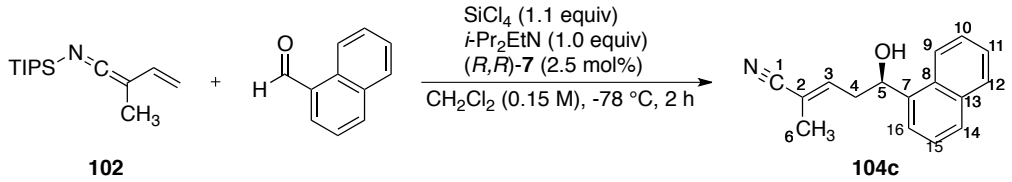
Analysis: $C_{16}H_{15}NO$ (237.296)

Calcd: C, 80.98; H, 6.37; N, 5.90%

Found: C, 80.66; H, 6.40; N, 5.94%

Preparation of (*E,R*)-5-hydroxy-2-methyl-5-(naphthalen-1-yl)pent-2-enenitrile (104c)

(Table 9, entry 3)



102 **104c**

Following General Procedure 8, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 136 µL of 1-naphtaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.92 mL of a 1.24 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (5:1 to 4:1)) 219 mg of gamma product **104c** (97%) contaminated with 4% of the alpha addition-product. Analytically pure material was obtained after a 2nd SiO_2 gel column (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (6:1 to 5:1)) and Kugelrohr distillation (215 – 225 °C, 0.40 mm Hg) to yield 202 mg of **104c** as a colorless, yellow oil (87%). The *gamma/alpha* ratio was determined to be 97:5 and the *E/Z* ratio determined to be 87:13 by ^{1}H NMR (500 MHz) analysis of the crude product. The *E/Z* isomers could not be separated by column chromatograph or distillation.

Data for **104c**:

bp: 190 – 200 °C (0.42 mm Hg, kugelrohr)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.99 (d, *J* = 8.1 Hz, 1 H, HC(9)), 7.89 (d, *J* = 9.4 Hz, 1 H, HC(12)), 7.80 (d, *J* = 8.2 Hz, 1 H, HC(14)), 7.61 (d, *J* = 7.1 Hz, 1 H, HC(16)), 7.58 – 7.44 (m, 3 H, HC(10,11,15)), 6.48 (td, *J* = 7.3, 1.3 Hz, 1 H, HC(3)), 5.94 – 5.19 (m, 1 H, HC(5)),

2.83 – 2.63 (m, 2 H, $H_2C(4)$), 2.58 (s, 1 H, OH), 1.70 (s, 3 H, $H_3C(6)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

144.3 (C(3)), 138.5 (C(7)), 133.7 (C(8,13)),= 129.8 (C(8,14)), 129.0 (C(12)), 128.4 (C(14)), 126.3 (C(10,11,15)), 125.7 (C(10,11,15)), 125.3 (C(10,11,15), 122.9 (C(16)), 122.4 (C(9)), 120.3 (C(1)), 111.1 (C(2)), 69.5 (C(5)), 36.9 (C(4)), 14.9 (C(6))

IR: (neat)

3436 (s), 3051 (m), 2955 (m), 2925 (m), 2218 (s), 1639 (m), 1597 (m), 1511 (m), 1434 (s), 1394 (m), 1355 (m), 1327 (m), 1261 (m), 1230 (m), 1168 (m), 1064 (s), 1035 (s), 1018 (s), 995 (m), 904 (s), 802 (s), 780 (s)

MS: (ESI)

260.1 (100.0), 239.1 (11.8), 220.1 (9.4), 213.1 (15.3), 181.1 (16.9)

HRMS: calcd for $C_{16}H_{15}NONa^+$: 260.1051, found: 260.1051

TLC: 0.14 (hexane/EtOAc, 4:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +9.8 (c = 1.74, CH_3Cl)

SFC: (*Z,5R*)-**104c**, t_R 14.3 min (6.9%); (*E,5S*)-**104c**, t_R 16.7 min (37.5%); (*Z,5S*)-**104c**, t_R 19.3 min (0.4%); (*E,5R*)-**104c**, t_R 22.3 min (55.2%); (Chiralpak OD, 200 bar, 5-15% MeOH (gradient over 20 min and then isocratic) in CO_2, 2.5 mL/min, 220 nm, 40 °C)

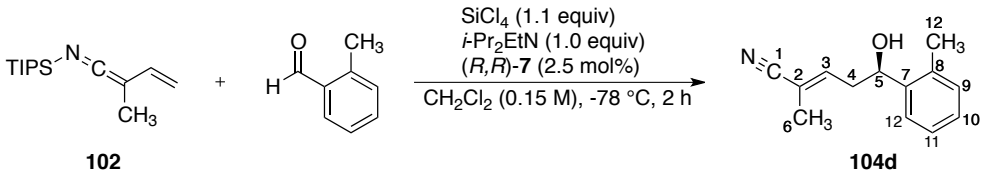
Analysis: $C_{13}H_{15}NO_2$ (217.263)

Calcd: C, 71.87; H, 6.96; N, 6.45%

Found: C, 71.87; H, 6.99; N, 6.51%

Preparation of (*E,R)*-5-hydroxy-2-methyl-5-(o-tolyl)pent-2-enenitrile (104d)

(Table 9 entry 4)



Following General Procedure 8, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 116 µL of 2-methylbenzaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.93 mL of a 1.23 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (5:1 to 4:1)) and and drying *in vacuo* gave 202 mg of **104d** (91%) as a yellow oil. Further purification by Kugelrohr distillation (175 – 180 °C, 0.40 mm Hg) produced 175 mg of analytically pure **104d** (87%) as a clear, colorless oil. The *gamma/alpha* ratio was determined to be 96:4 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **104d**:

bp: 175 – 180 °C (0.4 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.46 (d, *J* = 7.5 Hz, 1 H, HC(12)), 7.25 (t, *J* = 7.2 Hz, 1 H, HC(10)), 7.20 (td, *J* = 7.4, 1.4 Hz, 1 H, HC(11)), 7.15 (d, *J* = 7.4 Hz, 1 H, HC(9)), 6.45 (td, *J* = 7.4, 1.4 Hz, 1 H, HC(3)), 5.10 – 5.02 (m, 1 H, HC(5)), 2.62 – 2.50 (m, 2 H, HC(4)), 2.32 (s, 3 H, H_3C(13)), 1.79 (s, 3 H, H_3C(6))

^{13}C NMR: (125 MHz, $CDCl_3$)

144.4 (C(3)), 141.2 (C(7)), 134.1 (C(8)), 130.5 (C(9)), 127.7 (C(11)), 126.5 (C(10)), 125.0 (C(12)), 120.4 (C(1)), 111.2 (C(2)), 69.1 (C(5)), 36.7 (C(4)), 18.9 (C(12)), 15.0 (C(6))

IR: (neat)

3435 (s), 3025 (m), 2954 (m), 2927 (s), 2218 (s), 1639 (m), 1488 (s), 1461 (s), 1440 (s), 1384 (s), 1310 (m), 1286 (m), 1220 (m), 1085 (m), 1044 (s), 904 (s), 760 (s)

MS: (ESI)

224.1 (100.0, M + Na), 213.1 (30.1), 197.1 (7.1),184.1 (9.4), 181.1 (13.0), 138.9 (5.9), 81.0 (5.5)

HRMS: calcd for $C_{13}H_{15}NONa^{+}$: 224.1046, found: 224.1053

TLC: 0.14 (hexane/EtOAc, 4:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +71.9 (c = 2.03, EtOH)

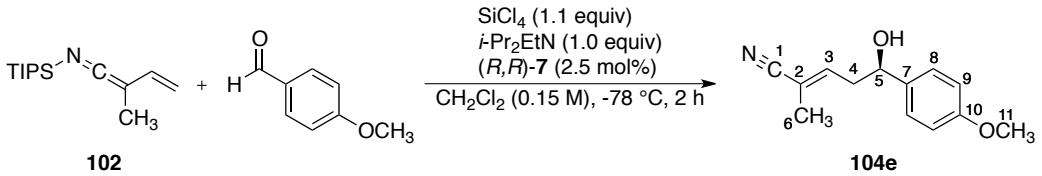
SFC: (E,5*S*)-**104d**, t_R 3.6 min (7.8%); (*E*,5*R*)-**104d**, t_R 4.0 min (92.2%), (Chiralpak OD, 200 bar, 5% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Analysis: $C_{13}H_{15}NO$ (201.264)

Calcd: C, 77.58; H, 7.51; N, 6.96%

Found: C, 77.76; H, 7.46; N, 7.04%

Preparation of (*E,R*)-5-hydroxy-5-(4-methoxyphenyl)-2-methylpent-2-enenitrile (104e) (Table 9, entry 5)



102 **104e**

Following General Procedure 8, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 122 μL of 4-methoxybenzaldehyde (1.0 mmol), 35 μL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.95 mL of a 1.21 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (4:1 to 3:1)) and drying *in vacuo* gave 204 mg of **104e** (93%) as a yellow oil. Further purification by Kugelrohr distillation (185 – 190 °C, 0.40 mm Hg) produced 203 mg of analytically pure **104e** (93%) as a clear, yellow oil. The *gamma/alpha* ratio was determined to be 99:1 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **104e**:

bp: 185 – 190 °C (0.4 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.24 (d, *J* = 8.7 Hz, 2 H, HC(8)), 6.88 (d, *J* = 8.7 Hz, 2 H, HC(9)), 6.36 (tq, *J* = 7.4, 1.5 Hz, 1 H, HC(3)), 4.73 (app t, *J* = 6.5 Hz, 1 H), 3.80 (s, 3 H, H_3C(11)), 2.68 – 2.48 (m, 2 H, H_2C(4)), 2.18 (s, 1 H, OH), 1.78 (d, *J* = 1.3 Hz, 3 H, H_3C(6))

^{13}C NMR: (125 MHz, $CDCl_3$)

159.3 (C(10)), 144.0 (C(3)), 135.2 (C(7)), 126.9 (C(8)), 120.4 (C(1)), 114.0 (C(9)), 111.1 (C(2)), 72.5 (C(5)), 55.3 (C(11)), 37.9 (C(4)), 15.0 (C(6))

IR: (neat)

3436 (s), 3001 (m), 2956 (m), 2837 (m), 2218 (s), 1612 (s), 1585 (m), 1513 (s), 1463 (m), 1442 (m), 1386 (m), 1303 (s), 1248 (s), 1176 (s), 1034 (s), 911 (m)

MS: (ESI)

240.1 (100.0), 239.1 (45.5), 219.1 (25.4), 213.1 (62.7), 200.1 (24.8), 240.1 (100.0),

239.1 (45.5), 219.1 (25.4), 213.1 (62.7), 200.1 (24.8)

HRMS: calcd for $C_{13}H_{15}NO_2Na^+$: 240.1000, found: 240.0997

TLC: 0.18 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +29.2 (c = 2.26, CH_3Cl)

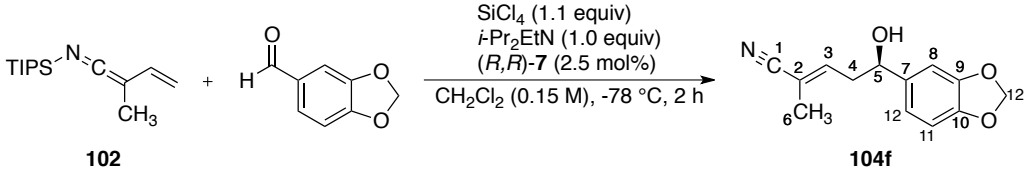
SFC: (E,5*R*)-**104e**, t_R 10.9 min (97.0%); (*E*,5*S*)-**104e**, t_R 12.4 min (3.0%), (Chiralpak OB, 200 bar, 5 – 10% MeOH gradient over 20 min in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{13}H_{15}NO_3$ (231.263); Average over six runs

Calcd: C, 71.87; H, 6.96; N, 6.45%

Found: C, 71.54; H, 6.75; N, 6.27%

Preparation of (*E,R*)-5-(benzo[d][1,3]dioxol-5-yl)-5-hydroxy-2-methylpent-2-enenitrile (105f) (Table 9, entry 6)



102 **104f**

Following General Procedure 8, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 150 mg of piperonal (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.95 mL of a 1.21 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (4:1 to 3:1)) and and drying *in vacuo* gave 217 mg of **104f** (94%) as a yellow oil. Further purification by Kugelrohr distillation (180 – 190 °C, 0.40 mm Hg) produced 212 mg of analytically pure **104f** (92%) as a clear, colorless oil. The *gamma/alpha* ratio was determined to be 99:1 and the *E/Z* ratio determined to be 97:3 by ^1H

NMR (500 MHz) analysis of the crude product.

Data for **104f**:

bp: 180 – 190 °C (0.4 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

6.83 (d, J = 0.8 Hz, 1 H, HC(8)), 6.80 – 6.74 (m, 2 H, HC(11,12)), 6.36 (tq, J = 7.4, 1.5 Hz, 1 H, HC(3)), 5.96 (s, 2 H, H_2C(13)), 4.69 (dd, J = 7.2, 5.8 Hz, 1 H, HC(5)), 2.66 – 2.47 (m, 2 H, H_2C(4)), 2.09 (br s, 1 H, OH), 1.81 (s, 3 H, H_3C(6)).

^{13}C NMR: (125 MHz, $CDCl_3$)

147.9 (C(9)), 147.3 (C(10)), 143.8 (C(3)), 137.1 (C(7)), 120.4 (C(1)), 119.1 (C(12)), 111.2 (C(2)), 108.2 (C(11)), 106.0 (C(8)), 101.1 (C(13)), 72.7 (C(5)), 37.9 (C(4)), 15.1 (C(6))

IR: (neat)

3436 (s), 3073 (w), 2926 (m), 2958 (m), 2896 (s), 2780 (w), 2218 (s), 1638 (w), 1503 (s), 1487 (s), 1443 (s), 1385 (m), 1326 (m), 1326 (m), 1244 (s), 1123 (w), 1097 (m), 1038 (s), 932 (s).

MS: (ESI)

254.1 (100.0, M+Na), 239.1 (71.0), 219.1 (38.4), 213.1 (91.1), 206.9 (26.0), 198.9 (37.8), 181.1 (81.0), 138.9 (14.2), 127.0 (11.8), 81.0 (26.0).

HRMS: calcd for $C_{13}H_{13}NO_3Na^+$: 254.0793, found: 254.0794

TLC: 0.19 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +11.8 (c = 2.04, $CHCl_3$)

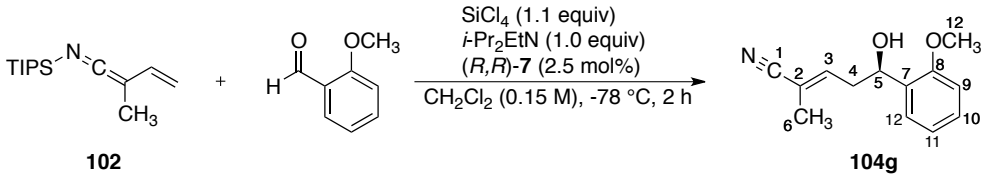
SFC: (E,5*S*)-**104f**, t_R 13.2 min (7.1%); (*E*,5*R*)-**104f**, t_R 14.0 min (92.9%), (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{13}H_{15}NO_3$ (231.247); Average over four runs and carbon is low by 0.41%

Calcd: C, 67.52; H, 5.67; N, 6.06%

Found: C, 67.11; H, 5.54; N, 6.07%

Preparation of (*E,R*)-5-hydroxy-5-(2-methoxyphenyl)-2-methylpent-2-enenitrile (104g) (Table 9, entry 7)



102 **104g**

Following General Procedure 8, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 136 mg of 2-methoxybenzaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.93 mL of a 1.23 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (4:1 to 3:1)) 210 mg of gamma product **104g** (97%) contaminated with 1% of the alpha addition-product. Analytically pure material was obtained after a 2nd SiO_2 gel column (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (6:1 to 4:1)) and kugelrohr distillation (190 – 200 °C, 0.42 mm Hg) to yield 200 mg of **104g** as a clear, colorless oil (92%). The *gamma/alpha* ratio was determined to be 97:3 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **104g**:

bp: 190 – 200 °C (0.42 mm Hg, kugelrohr)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.33 – 7.24 (m, 3 H, HC(12,10)), 6.98 (t, *J* = 7.5 Hz, 1 H, HC(11)), 6.90 (d, *J* = 8.2 Hz, 1 H, HC(9)), 6.46 (td, *J* = 7.4, 1.2 Hz, 1 H, HC(3)), 5.00 (app q, *J* = 6.2 Hz, 1 H, HC(5)), 3.87 (s, 3 H, $H_3C(13)$), 2.66 (t, *J* = 6.9 Hz, 2 H, $H_2C(4)$), 2.58 (d, *J* = 5.9 Hz, 1 H, OH), 1.80 (s, 3 H, $H_3C(6)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

156.1 (C(8)), 144.7 (C(3)), 130.8 (C(7)), 128.8 (C(10)), 126.5 (C(12)), 120.9 (C(11)), 120.5 (C(1)), 110.6 (C(2)), 110.4 (C(9)), 69.2 (C(5)), 55.2 (C(13)), 36.3 (C(4)), 14.9 (C(6))

IR: (neat)

3436 (s), 3037 (m), 3004 (m), 2939 (s), 2838 (m), 2218 (s), 1638 (s), 1601 (m), 1588 (s), 1490 (s), 1463 (s), 1439 (s), 1386 (m), 1287 (s), 1240 (s), 1463 (s), 1439 (s), 1386 (m), 1287 (s) 1240 (s), 1177 (s), 1161 (s), 1115 (s), 1086 (m), 1048 (s), 906 (m), 756 (s)

MS: (ESI)

240.1 (100.0, M+Na), 213.1 (7.0), 200.1 (11.8) 173.1 (6.0)

HRMS: calcd for $C_{13}H_{15}NO_2Na^+$: 240.1000, found: 240.1001

TLC: 0.3 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +41.8 (c = 2.14, EtOH)

SFC: (E,5*S*)-**104g**, t_R 4.8 min (5.5%); (*E*,5*R*)-**104g**, t_R 5.3 min (94.5%), (Chiralpak OD, 200 bar, 7.5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

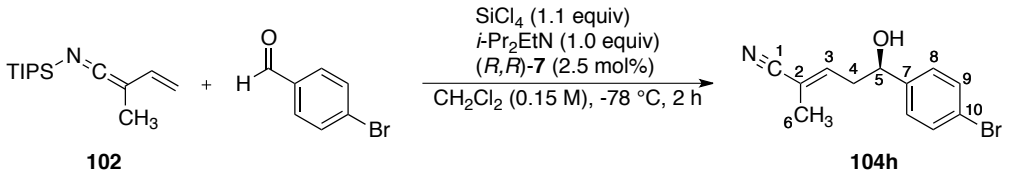
Analysis: $C_{13}H_{15}NO_2$ (217.263)

Calcd: C, 71.87; H, 6.96; N, 6.45%

Found: C, 71.87; H, 6.99; N, 6.51%

Preparation of (E,*R*)-5-(4-bromophenyl)-5-hydroxy-2-methylpent-2-enenitrile (104h)

(Table 9, entry 8)



102 **104h**

Following General Procedure 8, 21 mg of (*R,R*)-**6** (0.025 mmol, 0.025 equiv), 185 mg of 4-bromobenzaldehyde (1.0 mmol), 35 μL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.93 mL of a 1.23 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (5:1 to 3:1)) and and drying *in vacuo* (Abderhalden, 40 °C, 0.3 mm Hg) 252 mg of **104h** (95%) as yellow needles. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **104h**:

mp: 56 – 57 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.50 (d, *J* = 8.3 Hz, 2 H, HC(9)), 7.22 (d, *J* = 8.4 Hz, 2 H, HC(8)), 6.38 (app td, *J* = 7.4, 1.0 Hz, 1 H, HC(3)), 4.78 (app t, *J* = 7.7 Hz, 1 H, HC(5)), 2.67 – 2.50 (m, 2 H, H_2C(4)), 2.11 (s, 1 H, OH), 1.79 (s, 3 H, H_3C(6))

^{13}C NMR: (125 MHz, $CDCl_3$)

143.4 (C(3)), 142.1 (C(5)), 131.8 (C(9)), 127.3 (C(8)), 121.8 (C(10)), 120.2 (C(1)), 111.7 (C(2)), 72.2 (C(5)), 37.9 (C(4)), 15.0 (C(6))

IR: ($CHCl_3$)

3447 (s), 3018 (s), 2925 (m), 2894 (m), 2220 (s), 1638 (m), 1592 (m), 1404 (m), 1216 (s), 1070 (s), 1010 (s)

MS: (ESI)

290.0 (49.0), 288.0 (49.0, M + Na), 256.8 (21.8), 250.2 (26.6), 239.1 (47.3), 221.2 (17.7), 213.1 (100.0), 197.1 (24.8), 181.1 (53.8), 81.0 (14.2)

HRMS: calcd for $C_{12}H_{12}NOBrNa^+$: 287.9995, found: 288.0005

TLC: 0.08 (hexane/EtOAc, 4:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +27.3 (c = 2.28, $CHCl_3$)

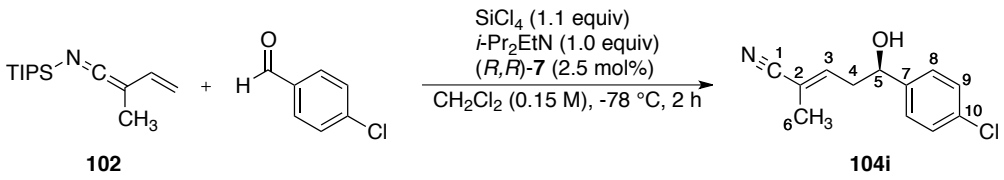
SFC: (E,5*S*)-**104h**, t_R 5.3 min (7.3%); (*E*,5*R*)-**104h**, t_R 5.7 min (92.7%), (Chiralpak OD, 200 bar, 10% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Analysis: $C_{12}H_{12}NOBr$ (266.134)

Calcd: C, 54.16; H, 4.54; N, 5.26%

Found: C, 54.15; H, 4.24; N, 5.27%

Preparation of (*R,E*)-5-(4-chlorophenyl)-5-hydroxy-2-methylpent-2-enenitrile (104i) (Table 9, entry 9)



102 **104i**

Following General Procedure 8, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 140 mg of 4-chlorobenzaldehyde (1.0 mmol), 35 μL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.93 mL of a 1.23 M solution of **102**

(1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (3:1 to 2:1)) and and drying *in vacuo* (Abderhalden, 40 °C, 0.3 mm Hg) 202 mg of **104i** (91%) as yellow needles. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **104i**:

mp: 52 – 53 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.33 (d, *J* = 8.5 Hz, 2 H, HC(9)), 7.26 (d, *J* = 8.5 Hz, 2 H, HC(8)), 6.37 (app td, *J* = 7.4, 1.5 Hz, 1 H, HC(3)), 4.78 (dd, *J* = 7.1, 5.6 Hz, 1 H, HC(5)), 2.66 – 2.47 (m, 2 H, H_2C(4)), 2.28 (br s, 1 H, OH), 1.78 (s, 3 H, H_3C(6))

^{13}C NMR: (125 MHz, $CDCl_3$)

143.4 (C(3)), 141.6 (C(7)), 133.7 (C(10)), 128.8 (C(9)), 127.0 (C(8)), 120.2 (C(1)), 111.6 (C(2)), 72.1 (C(5)), 38.0 (C(4)), 15.0 (C(6))

IR: (neat)

3467 (s), 3058 (m), 2950 (m), 2922 (s), 2882 (s), 2223 (s), 1639 (s), 1487 (s), 1387 (s), 1332 (m), 1308 (m), 1286 (m), 1262 (s), 1230 (s), 1184 (s), 1088 (s), 1011 (s), 911 (s), 869 (s), 839 (s), 801 (s)

MS: (EI, 70 meV)

222.1 (1.0), 203.0 (1.4), 143.0 (30.4), 141.0 (100.0), 139.0 (11.4), 113.0 (19.5), 81.1 (12.3), 77.1 (58.1), 75.0 (7.6), 51.0 (11.2)

HRMS: calcd for $C_{12}H_{13}NOCl^+$: 222.0680, found: 222.0705

TLC: 023 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +31.5 (c = 2.16, $CHCl_3$)

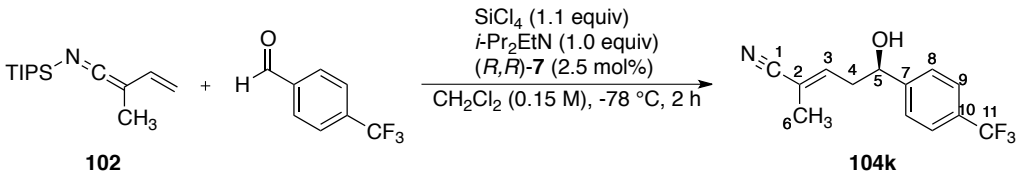
SFC: (E,5*S*)-**104i**, t_R 7.9 min (8.6%); (*E*,5*R*)-**104i**, t_R 8.5 min (91.4%), (Chiralpak OD, 200 bar, 5-15% MeOH gradient over 20 min in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{12}H_{12}NOCl$ (221.682)

Calcd: C, 65.02; H, 5.46; N, 6.32%

Found: C, 65.04; H, 5.42 N, 6.13%

Preparation of (*E,R*)-5-hydroxy-2-methyl-5-(4-(trifluoromethyl)phenyl)pent-2-enenitrile (104k) (Table 9, entry 10)



102 **104k**

Following General Procedure 8, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 136 μL of 4-trifluoromethylbenzaldehyde (1.0 mmol), 35 μL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.93 mL of a 1.23 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (3:1 to 2:1)) and and drying *in vacuo* (Abderhalden, 23 °C, 0.3 mm Hg) 237 mg of **104k** (93%) as yellow needles. The *gamma/alpha* ratio was determined to be 92:8 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **104k**:

mp: 37 – 38 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.64 (d, *J* = 8.2 Hz, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H), 6.40 (ddq, *J* = 7.5, 7.5 1.5 Hz, 1 H), 4.94 – 4.87 (m, 1 H), 2.70 – 2.53 (m, 2 H), 2.06 (d, *J* = 3.2 Hz, 1 H), 1.80 (s, *J* = 1.5 Hz, 3 H)

^{13}C NMR: (125 MHz, $CDCl_3$)

147.1 (s, (C(7)), 143.2 (s, C(1)), 130.2 (q, *J* = 32.4 Hz, (C(10)), 125.9 (s, (C(8)), 125.6 (q, *J* = 3.7 Hz, (C9)), 123.9 (q, *J* = 272.1 Hz, (C11)), 120.2 (s, C(1)), 111.8 (s, C(3)), 72.2 (s, C(5)), 38.0 (s, C(4)), 15.0 (s, (C(6))

IR: (neat)

3468 (s), 3063 (m), 2936 (m), 2886 (m), 2228 (s), 1619 (s), 1414 (s), 1322 (s), 1234 (s), 1120 (s), 1066 (s), 1016 (s), 903 (s), 854 (s), 739 (m)

MS: (EI, 70 meV)

256.1 (3.9), 236.1 (8.8), 175.0 (100.0), 173.0 (18.3), 147.0 (11.3), 145.0 (21.4), 127.0 (85.1), 81.1 (77.1), 77.1 (10.1), 53.1 (13.2)

HRMS: calcd for $C_{13}H_{13}NOF_3^+$: 256.0944, found: 256.0953

TLC: 0.24 (hexane/EtOAc, x:x) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +20.5 (c = 2.51, $CHCl_3$)

SFC: (E,5*S*)-**104k**, t_R 5.5 min (22.8%); (*E*,5*S*)-**104k**, t_R 6.1 min (77.2%), (Chiralpak OD, 200 bar, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{13}H_{13}NOF_3$ (255.235)

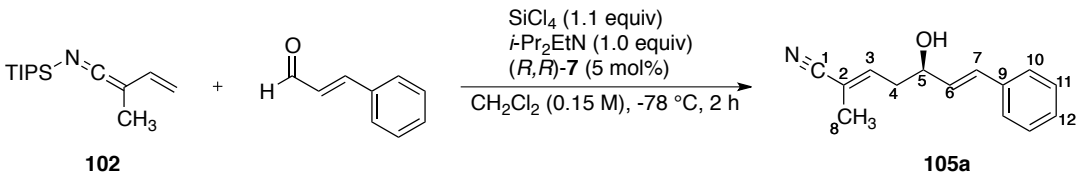
Calcd: C, 61.17; H, 4.74; N, 5.16%

Found: C, 61.16; H, 4.49; N, 5.15%

7.4.3.3 Addition of *N*-Silyl Vinylketene Imine to Olefinic Aldehydes.

Preparation of (2*E*,6*E*,*R*)-5-hydroxy-2-methyl-7-phenylhepta-2,6-dienenitrile (105a)

(Table 10, entry 1)



102 **105a**

Following General Procedure 8, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 µL of cinnamaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.90 mL of a 1.28 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (3:1 to 2:1)) 180 mg of **105a** (84%) as a yellow oil. Further purification by Kugelrohr distillation (190 – 200 °C, 0.40 mm Hg) produced 179 mg of pure **105a** (84%) as a yellow oil. The *gamma/alpha*, 1,2-/1,4-addition and E/Z ratios were determined to be 99:1, 90:10 and 99:1, respectively, by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **105a**:

bp: 190 – 200 °C (0.4 mm Hg, kugelrohr)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.39 – 7.32 (m, 4 H, HC(10,11)), 7.28 (dt, *J* = 4.6, 1.8 Hz, 1 H, HC(12)), 6.62 (d, *J* = 15.9 Hz, 1 H, HC(7)), 6.47 (tq, *J* = 7.4, 1.5 Hz, 1 H, HC(3)), 6.20 (dd, *J* = 15.9, 6.8 Hz, 1 H, HC(6)), 4.43 (app q, *J* = 6.6 Hz, 1 H, HC(5)), 2.62 – 2.42 (m, 2 H, H_2C(4)), 1.91 (d, *J* = 1.3 Hz, 3 H, H_3C(8)), 1.71 (br s, 1 H, OH)

^{13}C NMR: (125 MHz, $CDCl_3$)

143.7 (C(3)), 136.0 (C(9)), 131.4 (C(7)), 130.4 (C(6)), 128.6 (C(11)), 128.0 (C(12)), 126.5 (C(10)), 120.4 (C(1)), 111.2 (C(2)), 71.4 (C(5)), 36.2 (C(4)), 15.2 (C(8))

IR: (neat)

3418 (s), 3082 (w), 3027 (m), 2926 (m), 2218 (s), 1640 (w), 1599 (w), 1494 (m), 1449 (m), 1386 (m), 1311 (m), 1157 (w), 1104 (m), 1070 (m), 1034 (s), 969 (s), 901 (m), 750 (s)

MS: (ESI)

236.1 (35.5, M+Na), 227.0 (57.9), 218.9 (34.3), 216.9 (100.0), 208.9 (26.6), 206.9 (41.4), 198.9 (37.8), 159.0 (12.4), 138.9 (13.0), 91.0 (14.7), 81.0 (26.6).

HRMS: calcd for $C_{14}H_{15}NONa^+$: 236.1051, found: 236.1044

TLC: 0.24 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +2.6 (c = 1.7, $CHCl_3$)

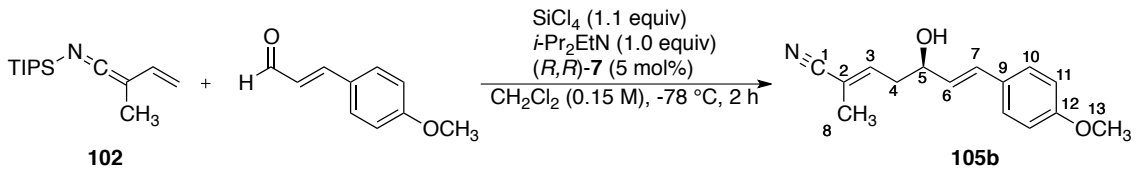
SFC: (2*E*,6*E*,*R*)-**105a**, t_R 6.1 min (92.4%); (2*E*,6*E*,*S*)-**105a**, t_R 9.5 min (7.6%), (Chiralpak OD, 200 bar, 10% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{14}H_{15}NO$ (213.275)

Calcd: C, 78.84; H, 7.09; N, 6.57%

Found: C, 78.57; H, 6.65; N, 6.39%

Preparation of (2*E*,6*E*,*R*)-5-hydroxy-7-(4-methoxyphenyl)-2-methylhepta-2,6-dienenitrile (105b) (Table 10, entry 2)



102 **105b**

Following General Procedure 8, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 162 mg of 4-methoxycinnamaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.90 mL of a 1.28 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (3:1 to 2:1)) and drying *in vacuo* (Abderhalden, 55 °C, 0.4 mm Hg) 191 mg of **105b** (79%) as yellow needles. The *gamma/alpha*, 1,2-/1,4-addition and E/Z ratios were determined to be 99:1, 90:10 and 99:1, respectively, by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **105b**:

mp: 84 – 85 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.30 (d, *J* = 8.6 Hz, 2 H, HC(11)), 6.86 (d, *J* = 8.7 Hz, 2 H, HC(10)), 6.54 (d, *J* = 15.8 Hz, 1 H, HC(7)), 6.45 (td, *J* = 7.4, 1.5 Hz, 1 H, HC(3)), 6.04 (dd, *J* = 15.8, 7.0 Hz, 1 H, HC(6)), 4.37 (q, *J* = 6.4 Hz, 1 H, HC(5)), 3.81 (s, 3 H, H_3C(13)), 2.56 – 2.41 (m, 2 H, H_2C(4)), 2.01, (s, 1 H, OH) 1.88 (d, *J* = 1.2 Hz, 3 H, H_3C(8))

^{13}C NMR: (125 MHz, $CDCl_3$)

159.5 (C(12)), 143.9 (C(3)), 131.0 (C(7)), 128.7 (C(9)), 128.2 (C(6)), 127.7 (C(10)), 120.4 (C(1)), 114.0 (C(11)) 111.2 (C(2)), 71.6 (C(5)), 55.3 (C(13)), 36.3 (C(4)), 15.2 (C(8))

IR: ($CHCl_3$)

3457 (s), 3018 (s), 2959 (m), 2934 (m), 2838 (m), 2219 (m), 1648 (w), 1607 (s), 1577 (w), 1513 (m), 1464 (m), 1442 (m), 1421 (m), 1382 (s), 1303 (m), 1250 (s), 1216 (s), 1175 (s), 1100 (s), 1034 (s), 968 (s), 902 (m), 851 (m), 817 (m)

MS: (ESI)

266.1 (100.0), 256.8 (7.1), 227.0 (8.8), 216.9 (15.9), 206.9 (5.9)

HRMS: calcd for $C_{15}H_{17}NO_2Na^+$: 266.1157, found: 266.1160

TLC: 0.18 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24} - 2.0$ (c = 1.8, $CHCl_3$)

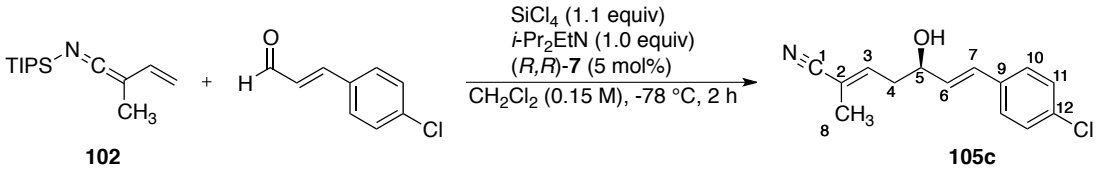
SFC: (2*E*,6*E*,*R*)-**105b**, t_R 7.1 min (92.7%); (2*E*,6*E*,3*S*)-**105b**, t_R 8.2 min (7.3%), (Chiralpak OD, 200 bar, 10% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{15}H_{17}NO_2$ (243.301)

Calcd: C, 74.05; H, 7.04; N, 5.76%

Found: C, 73.90; H, 6.99; N, 5.79%

Preparation of (2*E*,6*E*,*R*)-7-(4-chlorophenyl)-5-hydroxy-2-methylhepta-2,6-dienenitrile (105c) (Table10, entry 3)



Following General Procedure 8, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 167 mg of 4-chlorocinnamaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.90 mL of a 1.28 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (3:1 to 2:1)) and drying *in vacuo* (Abderhalden, 55 °C, 0.4 mm Hg) 196 mg of **105c** (79%) as yellow needles. The

gamma/alpha, 1,2-/1,4-addition and E/Z ratios were determined to be 99:1, 90:10 and 99:1, respectively, by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **105c**:

mp: 87 – 88 °C

^{1}H NMR: (500 MHz, $CDCl_3$) 7.29 (s, 4 H, HC(10,11)), 6.56 (d, *J* = 15.9 Hz, 1 H, HC(7)), 6.44 (td, *J* = 7.4, 1.5 Hz, 1 H, HC(3)), 6.16 (dd, *J* = 15.9, 6.6 Hz, 1 H, HC(6)), 4.40 (q, *J* = 6.4 Hz, 1 H, $H_2C(5)$), 2.56 – 2.40 (m, 2 H, $H_2C(4)$), 2.14 (br s, 1 H, OH), 1.88 (s, 3 H, $H_3C(8)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

143.9 (C(3)), 134.8 (C(9)), 133.9 (C(12)), 131.4 (C(6)), 130.3 (C(7)), 129.0 (C(10)), 127.9 (C(11)), 120.6 (C(1)), 111.6 (C(2)), 71.4 (C(5)), 36.4 (C(4)), 15.4 (C(8))

IR: ($CHCl_3$)

3460 (s), 3018 (s), 2959 (s), 2921 (m), 2865 (m), 2222 (s), 1642 (m), 1491 (s), 1416 (m), 1398 (m), 1329 (s), 1304 (m), 1216 (s), 1091 (s), 969 (s), 890 (m), 750 (m)

MS: (ESI)

266.1 (100.0), 256.8 (7.1), 227.0 (8.8), 216.9 (15.9), 206.9 (5.9)

HRMS: calcd for $C_{14}H_{14}NOClNa^{+}$: 270.0662, found: 270.0662

TLC: 0.20 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +0.30 (c = 1.9, $CHCl_3$)

SFC: (2*E*,6*E*,*R*)-**105c**, t_R 6.5 min (91.3%); (2*E*,6*E*,3*S*)-**105c**, t_R 7.7 min (8.7%), (Chiralpak OD, 200 bar, 10% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

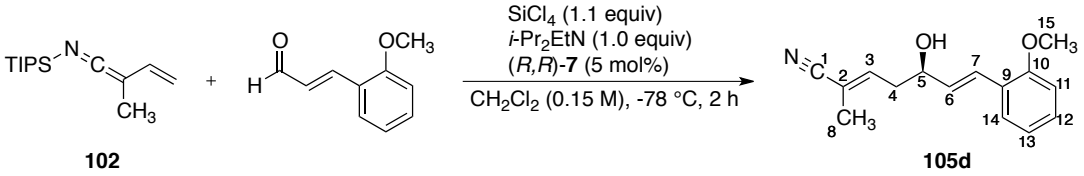
Analysis: $C_{14}H_{14}NOCl$ (247.720)

Calcd: C, 67.88; H, 5.70; N, 5.69%

Found: C, 67.80; H, 5.73; N, 5.69%

Preparation of (2*E*,6*E*,*R*)-5-hydroxy-2-methyl-7-phenylhepta-2,6-dienenitrile (105d)

(Table 10, entry 4)



Following General Procedure 8, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 162 mg of 2-methoxycinnamaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.90 mL of a 1.28 M solution of **102** (1.15 mmol, 1.15 equiv) in CH_2Cl_2 to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (3:1 to 2:1)) 195 mg of **105d** (80%) as a yellow oil. Further purification by Kugelrohr distillation (200 – 210 °C, 0.35 mm Hg) produced 193 mg of analytically pure **105d** (79%) as a yellow oil. The *gamma/alpha*, 1,2-/1,4-addition and *E/Z* ratios were determined to be 99:1, 90:10 and 94:6, respectively, by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **105d**:

bp: 200 – 210 °C (0.35 mm Hg, kugelrohr)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.40 (dd, J = 7.6, 1.5 Hz, 1 H, HC(14)), 7.29 – 7.22 (m, 1 H, HC(12)), 6.97 – 6.86 (m, 3 H, HC(11,14) and HC(7)), 6.48 (td, J = 7.4, 1.4 Hz, 1 H, HC(3)), 6.21 (dd, J

= 16.0, 7.0 Hz, 1 H, HC(6)), 4.48 – 4.38 (m, 1 H, HC(5)), 3.86 (s, 3 H, H_3C(15)), 2.60 – 2.45 (m, 2 H, H_2C(4)), 1.90 (d, *J* = 0.6 Hz, 3 H, H_3C(8)), 1.75 (d, *J* = 3.4 Hz, 1 H, OH)

^{13}C NMR: (125 MHz, $CDCl_3$)

156.8 (C(10)), 143.9 (C(3)), 131.1 (C(6)), 129.1 (C(12)), 127.0 (C(14)), 126.5 (C(7)), 124.9 (C(9)), 120.7 (C(13)), 120.4 (C(1)), 111.2 (C(2)), 110.9 (C(11)), 72.0 (C(5)), 55.4 (C(15)), 36.2 (C(4)), 15.2 (C(8))

IR: (neat)

3418 (s), 3003 (m), 2938 (s), 2218 (s), 1644 (m), 1598 (s), 1580 (m), 1488 (s), 1463 (s), 1455 (s), 1436 (m), 1385 (m), 1292 (m), 1028 (s), 976 (s), 901 (w), 754 (s)

MS: (ESI)

266.1 (100.0, M+Na), 226.1 (5.5)

HRMS: calcd for $C_{15}H_{17}NO_2Na^+$: 266.1157, found: 266.1158

TLC: 0.23 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +5.8 (c = 1.8, $CHCl_3$)

SFC: (2*Z*,6*E*,*R*)-**105d**, t_R 7.8 min (2.8%); (2*E*,6*E*,3*R*)-**105d**, t_R 11.8 min (89.4%), (2*Z*,6*E*,*S*)-**105d**, t_R 12.8 min (2.5%); (2*E*,6*E*,3*S*)-**105d**, t_R 19.1 min (5.3%), (Chiralpak OD, 200 bar, 10% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

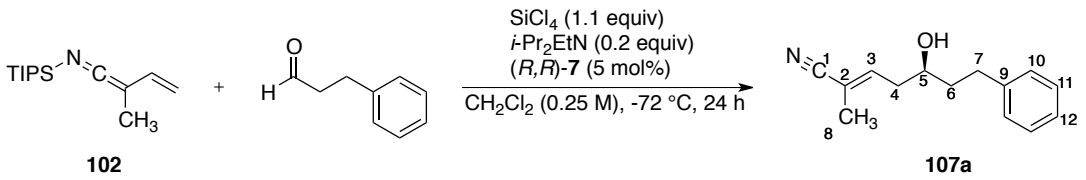
Analysis: $C_{15}H_{17}NO_2$ (243.301)

Calcd: C, 74.05; H, 7.04; N, 5.76%

Found: C, 73.85; H, 6.88; N, 5.75%

7.4.3.4 Addition of *N*-Silyl Vinylketene Imine to Aliphatic Aldehydes.

General Procedure 9. Vinylogous Aldol Addition of *N*-Silyl Vinylketene Imine 102 to Aliphatic Aldehydes. Preparation of (*E,S*)-5-hydroxy-2-methyldec-2-enenitrile (107a) (Table 11, entry 1)



102 **107a**

To a flame-dried, 10-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 132 μL of hydrocinnamaldehyde (1.00 mmol) and 3.15 mL anhydrous CH_2Cl_2 (0.32 M in aldehyde). The solution was stirred, cooled to -72 °C (internal) with a cyrostat bath and then 35 μL of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were added via syringe to the reaction vessel. The resulting solution was stirred for 5 min at -78 °C and then 0.85 mL of a 1.54 M solution of silyl ketene imine **102** (1.30 mmol, 1.30 equiv) in dichloromethane was added dropwise via syringe over 10 min. The yellow reaction mixture was allowed to stir for an additional 24 h at -72 °C before 0.60 mL of a 3:1:1 mixture of Et_3N/CH_2Cl_2/MeOH was added via syringe. The quenched solution was stirred for 3 min at -72 °C and then was transferred to a 50-mL Erlenmeyer flask containing a stirred, sat. aq. solution of $NaHCO_3$ (10 mL) and KF (10 mL). The biphasic mixture was stirred vigorously for 2 h at rt and then was filtered through a pad of packed Celite (ca. 7 g) in a 60-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with 10 mL of CH_2Cl_2 and 10 mL of H_2O and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aquaeos layer was extracted with CH_2Cl_2 (2 x 25 mL) and the resulting organic extracts were

combined, washed with brine (1 x 25 mL), and dried over Na_2SO_4 (ca. 3 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil. The crude residue was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (5:1 to 3:1) to afford 145 mg of **107a** (67%) as a clear, yellow oil after drying *in vacuo* for 1 h. Further purification by Kugelrohr distillation (179 – 180 °C, 0.45 mm Hg) produced 140 mg of analytically pure **107a** (65%) as a clear, colorless liquid. The *gamma/alpha* ratio was determined to be 99:1 and the *E/Z* ratio determined to be 96:4 by ^{1}H NMR (500 MHz) analysis of the crude product.

General procedure 9 was repeated at -55 °C for 24 h to give a crude residue which was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (5:1 to 3:1) to afford 176 mg of **107a** (82%) as a clear, slight yellow liquid after drying *in vacuo* for 3 h. The *gamma/alpha* ratio was determined to be 99:1 and the *E/Z* ratio determined to be 96:4 by ^{1}H NMR (500 MHz) analysis of the crude product. The spectroscopic data for each run was consistent and only the SFC data has been tabulated below (see, Data for **107a** run at -55 °C).

Data for **107a** (run at -72 °C):

bp: 170 – 180 °C (0.45 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.30 (t, J = 7.6 Hz, 2 H, HC(11)), 7.21 (dd, J = 11.0, 7.8 Hz, 3 H, HC(10,12)), 6.43 (tq, J = 7.6, 1.5 Hz, 1 H, HC(3)), 3.76 (app p, J = 6.1 Hz, 1 H, HC(5)), 2.80 (ddd, J = 14.8, 7.6 Hz, 1 H, H_2C(4)), 2.69 (ddd, J = 13.8, 8.0 Hz, 1 H, H_2C(4')), 2.36 (app t, J = 6.8 Hz, 2 H, H_2C(7)), 1.88 (d, J = 0.8 Hz, 3 H, H_3C(8)), 1.85 – 1.75 (m, 2 H, H_2C(6) and OH)

^{13}C NMR: (125 MHz, $CDCl_3$)

144.4 (C(3)), 141.3 (C(9)), 128.5 (C(11)), 128.3 (C(10)), 126.0 (C(12)), 120.4 (C(1)), 111.1 (C(2)), 69.8 (C(5)), 38.7 (C(6)), 36.5 (C(7)), 31.9 (C(4)), 15.1 (C(8))

IR: (neat)

3436 (s), 3061 (w), 3026 (m), 2927 (s), 2861 (m), 2218 (s), 1639 (m), 1603 (m), 1495 (m), 1454 (s), 1396 (m), 1316 (w), 1153 (w), 1051 (s), 1029 (m), 904 (m), 748 (m), 700 (s)

MS: (ESI)

238.1 (100.0, M+Na), 198.1 (6.2), 139.0 (5.0), 81.0 (4.5)

HRMS: calcd for $C_{14}H_{17}NONa^{+}$: 238.1208, found: 238.1207

TLC: 0.26 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –8.4 (c = 2.24, $CHCl_3$)

SFC: (E,5*S*)-**107a**, t_{R1} 4.7 min (95.1%); (*E,5R*)-**107a**; t_{R2} 5.8 min (4.9%), (Chiralpak OD, 200 bar, 10% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{14}H_{17}NO$ (215.291);

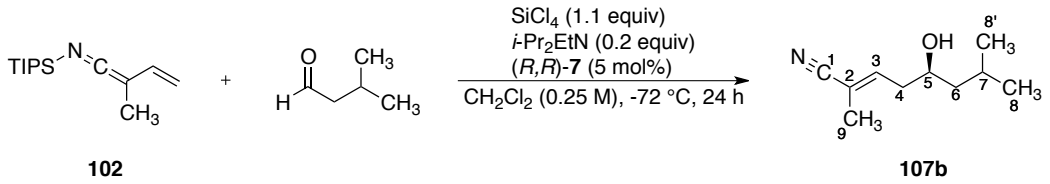
Calcd: C, 78.10; H, 7.96; N, 6.51%

Found: C, 78.26; H, 7.82; N, 6.79%

Data for **107a** (run at -55 °C):

SFC: (E,5*S*)-**107a**, t_{R1} 4.8 min (94.9%); (*E,5R*)-**107a**; t_{R2} 5.8 min (5.1%), (Chiralpak OD, 200 bar, 10% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Preparation of (*S,E*)-5-hydroxy-2,7-dimethyloct-2-enenitrile (107b) (Table 10, entry 2)



102 **107b**

Following General Procedure 9, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 107 µL of isovaleraldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 1.35 mL of a 1.00 M solution of **102** (1.35 mmol, 1.35 equiv) in 2.65 mL CH_2Cl_2 (0.25 M) to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (7:1 to 5:1)) and and drying *in vacuo* gave 100 mg of **107b** (60%) as a clear, colorless liquid. Further purification by Kugelrohr distillation (150 – 160 °C, 3.5 mm Hg) produced 95 mg of analytically pure **107b** (57%) as a clear, colorless liquid. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

General procedure 9 was repeated at -55 °C for 24 h to give a crude residue which was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (7:1 to 5:1) to afford 143 mg of **107b** (86%) as a clear, colorless liquid after Kugelrohr distillation (145 – 155, 3.5 mm Hg). The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product. The spectroscopic data for each run was consistent and characterization data reported below is for run at-72 °C. See DNB-derivative **DNB107b** for er determination by SFC analysis for run at -55 °C.

Data for **107b** (run at -72 °C):

bp: 160 – 170 °C (3.5 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

6.45 (td, *J* = 7.5, 1.5 Hz, 1 H, HC(3)), 3.81 (ddt, *J* = 9.1, 7.1, 4.6 Hz, 1 H, HC(5)), 2.38 – 2.23 (m, 2 H, $H_2C(4)$), 1.88 (s, 3 H, $H_3C(9)$), 1.81 – 1.67 (m, 1 H, $H_2C(7)$ and OH)), 1.42 (ddd, *J* = 14.2, 9.1, 5.4 Hz, 1 H, $H_2C(6)$), 1.22 (ddd, *J* = 14.2, 9.1, 5.4 Hz, 1 H, $H_2C(6')$), 0.92 (dd, *J* = 9.6, 6.6 Hz, 6 H, $H_3C(8)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

144.7 (C(3)), 120.5 (C(1)), 111.0 (C(2)), 68.6 (C(5)), 46.3 (C(6)), 36.8 (C(4)), 24.6 (C(7)), 23.3 (C(8)), 21.9 (C(8)), 15.1 (C(9))

IR: (neat)

3443 (s), 2956 (s), 2870 (s), 2219 (s), 1640 (m), 1469 (m), 1385 (m), 1368 (m), 1230 (w), 1171 (w), 1137 (m), 1065 (m), 1028 (m), 994 (m), 903 (m)

MS: (ESI)

190.1 (100.0, M+Na), 168.1 (15.3), 139.1 (5.9), 89.1 (6.0)

HRMS: calcd for $C_{10}H_{17}NONa^+$: 190.1208, found:190.1213

calcd for $C_{10}H_{18}NO^+$: 168.1388, found: 168.1389

TLC: 0.31 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –0.5 (c = 2.11, $CHCl_3$)

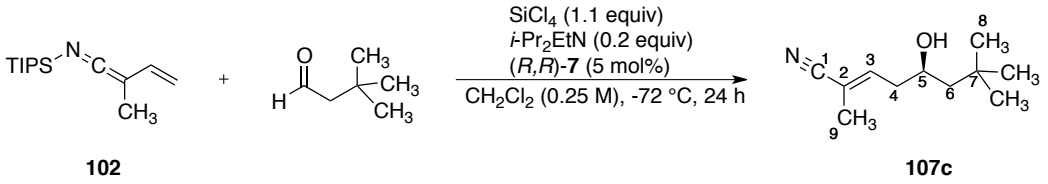
SFC: See 3,5-dinitrobenzoyl derivative **DNB107b**, section 7.4.3.5

Analysis: $C_{11}H_{19}NO$ (181.274);

Calcd: C, 72.88 H, 10.56; N, 7.73%

Found: C, 73.25; H, 10.50; N, 8.11%

Preparation of (*R,E*)-5-hydroxy-2,7,7-trimethyloct-2-enenitrile (107c) (Table 11, entry 3)



102 **107c**

Following General Procedure 9, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 126 µL of 3,3-dimethylbutryaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 1.28 mL of a 1.05 M solution of **102** (1.35 mmol, 1.35 equiv) in 2.6 mL CH_2Cl_2 (0.25 M) to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (7:1 to 5:1)) and and drying *in vacuo* gave 149 mg of **107c** (82%) as a clear, colorless liquid. Further purification by Kugelrohr distillation (150 – 160 °C, 0.83 mm Hg) produced 148 mg of analytically pure **107c** (82%) as a clear, colorless liquid. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **107c**:

bp: 150 – 160 °C (0.83 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

6.44 (tq, *J* = 7.5, 1.5 Hz, 1 H, HC(3)), 3.90 – 3.86 (m, 1 H, HC(5)), 2.38 – 2.24 (m, 2 H), 1.88 (d, *J* = 1.5 Hz, 3 H, $H_3C(9)$) 1.56 (s, 1 H, OH), 1.41 (dd, *J* = 14.6, 8.4 Hz, 1 H, $H_2C(6)$), 1.33 (dd, *J* = 14.6, 2.5 Hz, 1 H, $H_2C(6')$), 0.96 (s, 9 H, $H_3C(8)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

144.6 (C(3)), 120.5 (C(1)), 111.1 (C(2)), 68.3 (C(5)), 50.8 (C(6)), 38.3 (C(4)), 30.3 (C(7)), 30.0 (C(8)), 15.2 (C(9))

IR: (neat)

3447 (s), 2953 (s), 2869 (s), 2219 (s), 1639 (w), 1475 (m), 1393 (m), 1364 (s), 1330 (w), 1248 (m), 1156 (w), 1062 (m), 1010 (m), 901 (m), 847 (m), 730 (m)

MS: (ESI)

204.1 (100.0, M+Na), 198.9 (7.1), 182.2 (17.7), 138.9 (6.5), 81.1 (5.1)

HRMS: calcd for $C_{11}H_{19}NONa^{+}$: 204.1364, found: 204.1367

calcd for $C_{11}H_{20}NO^{+}$: 182.1545, found: 182.1545

TLC: 0.37 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –3.2 (c = 2.24, $CHCl_3$)

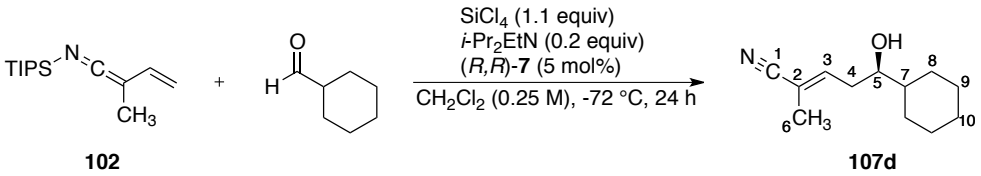
SFC: See 3,5-dinitrobenzoyl derivative **DNB107c**, section 7.4.3.5

Analysis: $C_{11}H_{19}NO$ (181.274);

Calcd: C, 72.88 H, 10.56; N, 7.73%

Found: C, 73.25; H, 10.50; N, 8.11%

Preparation of (*R,E*)-5-cyclohexyl-5-hydroxy-2-methylpent-2-enenitrile (107d) (Table 11, entry 4)



102 **107d**

Following General Procedure 9, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 121 µL of cyclohexanecarboxaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 1.28 mL of a 1.05 M solution of **102** (1.35 mmol, 1.35 equiv) in 2.6 mL CH_2Cl_2 (0.25 M) to yield after column

chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (7:1 to 5:1)) and and drying *in vacuo* (Abderhalden, 23 °C, 0.5 mm Hg) gave 121 mg of **107d** (63%) as clear, colorless needles. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **107d**:

mp: 40 – 41 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

6.47 (td, *J* = 7.5, 1.5 Hz, 1 H, HC(3)), 3.46 (ddd, *J* = 8.2, 5.8, 4.2 Hz, 1 H, HC(5)), 2.42 – 2.22 (m, 2 H, $H_2C(4)$), 1.88 (s, 3 H, $H_3C(6)$), 1.85 – 1.73 (m, 3 H, HC(7) and $H_2C(8_{eq})$), 1.72 – 1.60 (m, 3 H, OH and $H_2C(9_{eq})$) 1.39 – 0.94 (m, 6 H, $H_2C(8_{ax}, 9_{ax}, 10)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

145.5 (C(3)), 120.5 (C(1)), 110.6 (C(2)), 74.8 (C(5)), 43.4 (C(7)), 33.3 (C(4)), 29.1 (C(8,9)), 27.8 (C(8,9)), 26.3 (C(8,9)), 26.1 (C(8,9)), 25.9 (C(10)), 15.1 (C(6))

IR: ($CHCl_3$)

3443 (s), 2925 (s), 2853 (s), 2218 (s), 1639 (s), 1450 (s), 1385 (m), 1314 (m), 1271 (m), 1226 (w), 1185 (w), 1085 (m), 1059 (m), 1037 (s), 993 (m), 960 (w), 892 (m), 840 (w)

MS: (ESI)

216.1 (100.0, M+Na), 194.1 (4.4), 139.2 (5.0), 81.1 (4.6)

HRMS: calcd for $C_{12}H_{19}NONa^+$: 216.1364, found: 216.1364

calcd for $C_{12}H_{20}NO^+$: 194.1545, found: 182.1545

TLC: 0.13 (hexane/EtOAc, 5:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +24.5 (c = 2.04, $CHCl_3$)

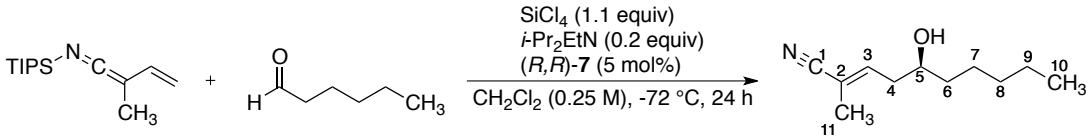
SFC: See 3,5-dinitrobenzoyl derivative **DNB107d**, section 7.4.3.5

Analysis: $C_{12}H_{19}NO$ (193.285);

Calcd: C, 74.57 H, 9.91; N, 7.25%

Found: C, 74.48; H, 10.03; N, 7.34%

Preparation of (*E,S*)-5-hydroxy-2-methyldec-2-enenitrile (107e) (Table 11, entry 5)



102 **107e**

Following General Procedure 9, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 123 µL of 1-hexanal (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.65 mL of a 2.02 M solution of **102** (1.30 mmol, 1.30 equiv) in 3.35 mL CH_2Cl_2 (0.25 M) to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (6:1 to 5:1)) and and drying *in vacuo* gave 137 mg of **107e** (75%) as a clear, colorless liquid. Further purification by Kugelrohr distillation (150 – 160 °C, 0.74 mm Hg) produced 136 mg of analytically pure **107e** (75%) as a clear, colorless liquid. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

General procedure 9 was repeated at -55 °C for 24 h to give a crude residue which was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (7:1 to 4:1) to afford 147 mg of **107e** (81%) as a clear, colorless liquid after drying *in vacuo* for 3 h. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by

^{1}H NMR (500 MHz) analysis of the crude product. The spectroscopic data for each run was consistent and characterization data reported below is for -72 °C run. See DNB-derivative **DNB107e** for er determination by SFC analysis for run at -55 °C.

Data for **107e** (run at -72 °C):

bp: 150 – 160 °C (0.74 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

6.45 (td, J = 7.5, 1.5 Hz, 1 H, HC(6)), 3.78 – 3.64 (m, 1 H, HC(5)), 2.40 – 2.23 (m, 1 H, H_2(4)), 1.88 (s, 3 H, H_3C(11)), 1.79 (s, 1 H, OH), 1.50 – 1.39 (m, 3 H, H_2C(6,7)), 1.35 – 1.21 (m, 5 H, H_2C(7',8,9)), 0.88 (t, J = 6.9 Hz, 3 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

144.8 (C(3)), 120.5 (C(1)), 110.9 (C(2)), 70.5 (C(5)), 37.2 (C(6)), 36.2 (C(4)), 31.6 (C(8)), 25.2 (C(7)), 22.5 (C(9)), 15.1 (C(11)), 14.0 (C(10))

IR: (neat)

3443 (s), 2955 (s), 2930 (s), 2859 (s), 2218 (s), 1639 (m), 1458 (m), 1380 (m), 1341 (m), 1235 (m), 1125 (m), 1037 (m), 900 (m), 726 (m)

MS: (ESI)

204.1 (100.0, M+Na), 182.1 (6.0)

HRMS: calcd for $C_{11}H_{19}NONa^+$: 204.1364, found: 204.1364

TLC: 0.34 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +7.9 (c = 2.25, $CHCl_3$)

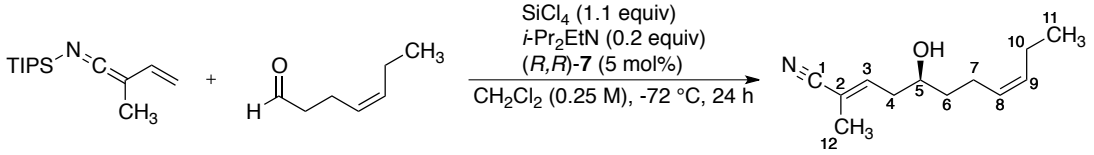
SFC: See 3,5-dinitrobenzoyl derivative **DNB107e**, section 7.4.3.5

Analysis: $C_{11}H_{19}NO$ (181.275);

Calcd: C, 72.88; H, 10.56; N, 7.73%

Found: C, 72.81; H, 10.36; N, 7.94%

Preparation of (S,2E,8Z)-5-hydroxy-2-methylundeca-2,8-dienenitrile (107f) (Table 11, entry 8)



102 **107f**

Following General Procedure 9, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 132 µL of 4-cis-heptenal (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 1.35 mL of a 1.00 M solution of **102** (1.35 mmol, 1.35 equiv) in 2.65 mL CH_2Cl_2 (0.25 M) to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (7:1 to 5:1)) and drying *in vacuo* gave 107 mg of **107f** (55%) as a clear, yellow liquid. Further purification by Kugelrohr distillation (150 – 160 °C, 0.9 mm Hg) produced 107 mg of analytically pure **107f** (55%) as a clear, colorless liquid. Isomeric impurity that was present in the cis-4-heptenal (93% from Aldrich) could not be physically separated by chromatography or distillation, but could be separated by CSP-SFC analysis (see, DNB derivative **DNB107f**, section 7.4.3.5). The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^1H NMR (500 MHz) analysis of the crude product.

General procedure 9 was repeated at -55 °C for 24 h to give a crude residue which was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient

(7:1 to 5:1) to afford 165 mg of **107f** (86%) as a clear, yellow liquid after drying *in vacuo* for 3 h. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product. The spectroscopic data for each run was consistent and characterization data reported below is for -72 °C run. See DNB-derivative **DNB107f** for er determination by SFC analysis for run at -55 °C.

Data for **107f** (run at -72 °C):

bp: 150 – 160 °C (0.95 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

6.44 (td, *J* = 7.5, 1.5 Hz, 1 H, HC(3)), 5.45 – 5.38 (m, 1 H, HC(9)), 5.35 – 5.28 (m, 1 H, HC(8)), 3.74 (app p, *J* = 6.3 Hz, 1 H, HC(5)) 2.39 – 2.27 (m, 2 H, $H_2C(4)$), 2.22 – 2.08 (m, 2 H, $H_2C(7)$), 2.08 – 1.99 (m, 2 H, $H_2C(10)$), 1.88 (d, *J* = 0.9 Hz, 3 H, $H_3C(12)$), 1.82 (s, 1 H, OH), 1.53 (dd, *J* = 14.2, 6.9 Hz, 2 H, $H_2C(6)$), 0.96 (t, *J* = 7.5 Hz, 3 H, $H_3C(11)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

144.6 (C(3)), 132.8 (C(9)), 127.8 (C(8)), 120.4 (C(1)), 111.0 (C(2)), 70.3 (C(5)), 36.9 (C(6)), 36.3 (C(4)), 23.4 (C(7)), 20.5 (C(10)), 15.1 (C(12)), 14.3 (C(11))

IR: (neat)

3438 (s), 3005 (s), 2962 (s), 2931 (s), 2873 (s), 2219 (s), 1640 (m), 1455 (s), 1410 (s), 1306 (m), 1240 (w), 1123 (m), 1067 (s), 976 (m), 901 (m), 796 (w), 723 (m)

MS: (ESI)

217.1 (15.1), 216.1 (100.0, M+Na), 139.1 (4.5)

HRMS: calcd for $C_{12}H_{19}NONa^{+}$: 216.1364, found: 216.1364

TLC: 0.13 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +7.9 (c = 2.25, $CHCl_3$)

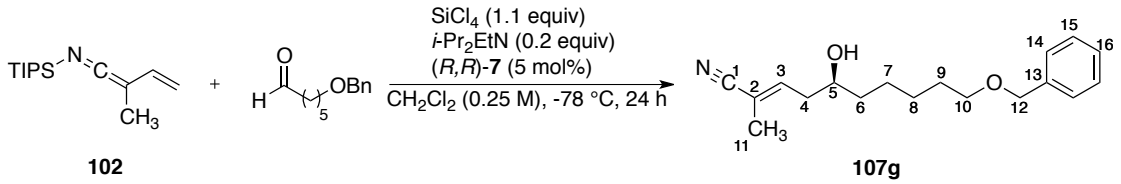
SFC: See 3,5-dinitrobenzoyl derivative **DNB107f**, section 7.4.3.5

Analysis: $C_{11}H_{19}NO$ (181.274);

Calcd: C, 74.56 H, 9.91; N, 7.25%

Found: C, 74.46; H, 9.95; N, 7.35%

Preparation of (*S,E*)-10-(benzyloxy)-5-hydroxy-2-methyldec-2-enenitrile (107g) (Table 11, entry 7)



Following General Procedure 9, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 206 mg of 6-(benzyloxy)hexanal (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.85 mL of a 1.54 M solution of **102** (1.30 mmol, 1.30 equiv) in 3.15 mL CH_2Cl_2 (0.25 M) to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (4:1 to 3:1)) and and drying *in vacuo* gave 213 mg of **107g** (74%) as a clear, yellow liquid. Further purification by Kugelrohr distillation (170 – 180 °C, 0.450 mm Hg) produced 213 mg of analytically pure **107g** (74%) as a clear, colorless liquid. The *gamma/alpha* ratio was determined to be 96:4 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **107g**:

bp: 215 – 225 °C (0.45 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.37 – 7.31 (m, 4 H, HC(14,15), 7.30 – 7.27 (m, 1 H, HC(16)), 6.44 (td, J = 7.5, 1.3 Hz, 1 H, HC(3)), 4.50 (s, 1 H, $H_2C(12)$), 3.76 – 3.63 (m, 1 H, HC(5)), 3.47 (t, J = 6.5 Hz, 1 H, $H_2C(10)$), 1.87 (s, 1 H, $H_3C(11)$), 1.82 (s, 1 H, OH), 1.63 (app p, J = 6.8 Hz, 1 H, $H_2C(6)$), 1.53 – 1.28 (m, 2 H, $H_2(7,8,9)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

144.7 (C(3)), 138.5 (C(13)), 128.3 (C(15)), 127.6 (C(14)), 127.5 (C(16)), 120.4 (C(1)), 110.9 (C(2)), 72.9 (C(12)), 70.4 (C(5)), 70.2 (C(10)), 37.1 (C(9)), 36.3 (C(4)), 29.6 (C(6)), 26.1 (C(8)), 25.3 (C(7)), 15.1 (C(11))

IR: (neat)

3434 (s), 3031 (m), 2934 (s), 2218 (s), 1639 (w), 1496 (w), 1455 (m), 1436 (m), 1362 (m), 1205 (w), 1098 (s), 1029 (s), 903 (w), 737 (s), 700 (s)

MS: (ESI)

310.2 (100.0, M+Na), 288.2 (5.5), 91.1 (5.7).

HRMS: calcd for $C_{18}H_{25}NO_2Na^+$: 310.1783, found: 310.1784

calcd for $C_{18}H_{26}NO_2^+$: 288.1964, found: 288.1964

TLC: 0.2 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +4.0 (c = 2.52, $CHCl_3$)

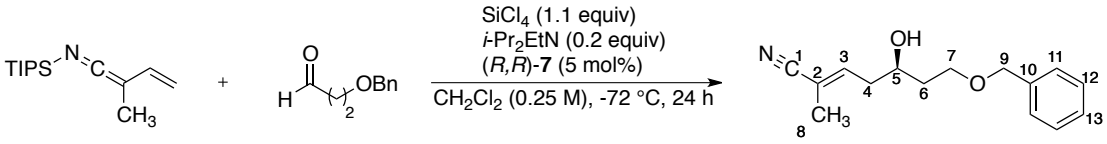
SFC: (E,5*R*)-**107g**, t_{R1} 6.1min (9.7%); (*E*,3*S*)-**107g**; t_{R2} 6.6 min (90.3%), (Chiralpak AD, 200 bar, 10% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Analysis: $C_{18}H_{25}NO_2$ (287.397);

Calcd: C, 78.10; H, 7.96; N, 6.51%

Found: C, 78.26; H, 7.82; N, 6.79%

Preparation of (*E,R*)-7-(benzyloxy)-5-hydroxy-2-methylhept-2-enenitrile (107h) (Table 11, entry 8)



Following General Procedure 9, 42 mg of (*R,R*)-**7** (0.05 mmol, 0.05 equiv), 107 µL of 3-benzyloxypropionaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 equiv, 0.2 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 1.33 mL of a 1.02 M solution of **102** (1.35 mmol, 1.35 equiv) in 2.7 mL CH_2Cl_2 (0.25 M) at -72 °C (cyrostat) for 24 h to yield after column chromatography (30 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (7:1 to 5:1)) and and drying *in vacuo* gave 137 mg of **107h** (56%) as a clear, colorless liquid. Further purification by Kugelrohr distillation (190 – 200 °C, 0.38 mm Hg) produced 133 mg of analytically pure **107h** (54%) as a clear, colorless liquid. The *gamma/alpha* ratio was determined to be 98:2 and the *E/Z* ratio determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

General procedure 9 was repeated at -55 °C for 24 h to give a crude residue which was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (5:1 to 2:1) to afford 191 mg of **107h** (78%) as a clear, slight yellow liquid after drying *in vacuo* for 3 h. The *gamma/alpha* ratio was determined to be 99:1 and the *E/Z* ratio determined to be 96:4 by ^{1}H NMR (500 MHz) analysis of the crude product. The spectroscopic data for each run was consistent and only the SFC data has been tabulated below (see, data for **107h** run at -55 °C).

Data for **107h** (run at -72 °C):

bp: 190 – 200 °C (0.38 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.39 – 7.26 (m, 5 H, HC(11,12,13)), 6.45 (td, *J* = 7.4, 1.5 Hz, 1 H, HC(3)), 4.52 (s, 2H, $H_2C(9)$), 3.98 – 3.91 (m, 1 H, HC(5)), 3.72 (dt, *J* = 9.6, 4.9 Hz, 1 H, $H_2C(7)$), 3.65 (td, *J* = 9.0, 3.8 Hz, 1 H, $H_2C(7')$), 3.25 (br s, 1 H, OH), 2.40 – 2.27 (m, 2 H, $H_2C(4)$), 1.86 (d, *J* = 1.0 Hz, 3 H, $H_3C(8)$), 1.84 – 1.67 (m, 2 H, $H_2C(6)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

144.5 (C(3)), 137.5 (C(10)), 128.5 (C(12)), 127.9 (C(13)), 127.7 (C(11)), 120.5 (C(1)), 110.8 (C(2)), 73.4 (C(9)), 70.3 (C(5)), 68.9 (C(7)), 36.2 (C(4)), 35.9 (C(6)), 15.1 (C(8))

IR: (neat)

3470 (s), 3031 (m), 2921 (s), 2865 (s), 2217 (s), 1640 (w), 1495 (m), 1454 (s), 1365 (m), 1315 (w), 1207 (m), 1096 (s), 1027 (m), 909 (m), 740 (m), 699 (s)

MS: (ESI)

190.1 (100.0, M+Na), 168.1 (15.3), 139.1 (5.9), 89.1 (6.0)

HRMS: calcd for $C_{15}H_{19}NO_2Na^+$: 268.1313, found: 268.1312

calcd for $C_{15}H_{20}NO_2^+$: 246.1494, found: 246.1496

TLC: 0.18 (hexane/EtOAc, 2:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +7.6 (c = 2.16, $CHCl_3$)

SFC: (E,5*S*)-**107h**, t_{R1} 8.8 min (24.0%); (*E*,5*R*)-**107h**; t_{R2} 9.4 min (76.0%), (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.10 mL/min, 220 nm, 40 °C)

Analysis: $C_{15}H_{19}NO_2$ (245.317);

Calcd: C, 73.44 H, 7.81; N, 5.71%

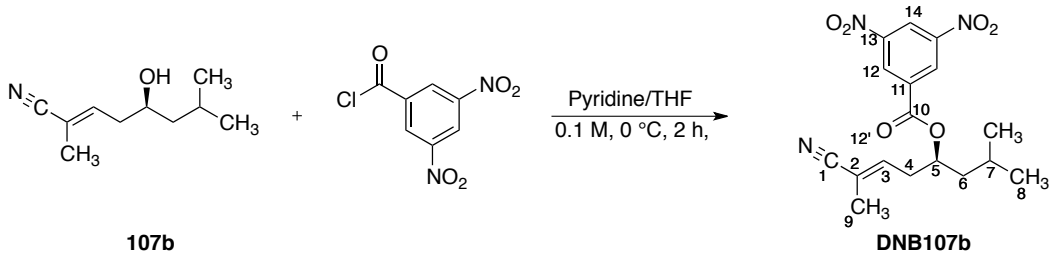
Found: C, 73.36; H, 7.98; N, 5.87%

Data for **107h**(run at -55 °C):

SFC: (E,5*S*)-**107h**, t_{R1} 8.8 min (22.5%); (*E*,5*R*)-**107h**; t_{R2} 9.4 min (77.5%), (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.10 mL/min, 220 nm, 40 °C)

7.4.3.5 Derivatization of Aliphatic Products for SFC Analysis.

General Procedure 10, preparation of (*S*,*E*)-7-cyano-2-methyloct-6-en-4-yl 3,5-dinitrobenzoate (DNB-107b) (Table 11 entry 2)



107b **DNB107b**

To a flame-dried, 25-mL, single-necked round-bottomed flask fitted with a magnetic stir bar and argon inlet were added 25 mg of nitrile **107b** (0.15 mmol) and 2 mL of a 1:1 mixture of pyridine/THF (0.1 M in nitrile). The resulting homogeneous solution was stirred and cooled to 0 °C (ice bath) and then 69 mg of 3,5-dinitrobenzoylchloride (0.30 mmol, 2.0 equiv) was charged into the flask in one portion. The resulting heterogeneous reaction mixture was allowed to stir for 15 min at 0 °C and then warmed to ambient temperature and stirred for an additional 2 h. The reaction mixture was quenched by the addition of 5 mL H_2O followed by 10 mL of EtOAc. The quenched solution was transferred to a 60-mL separtory funnel where the organic layer was isolated. The aqueous layer was extracted with EtOAc (2 x 15 mL) and the resulting organic layers were combined, washed successively with 1 M aq. HCl (2 x 10 mL) and brine (2 x 10 mL) and then dried over $MgSO_4$ (ca. 0.75 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow solid. The crude residue was purified by silica gel

plug filtration (15 g SiO_2, ∅ 20 mm column, 350 mL of hexanes/EtOAc (6:1)) and drying *in vacuo* 52 mg of **DNB107b** (96%) as a white amorphous solid.

The general procedure 10 was repeated with 26.1 mg of **107b** (0.15 mmol) obtained from a vinylogous aldol reaction run at -55 °C. The resulting crude residue was purified by silica gel plug filtration (15 g SiO_2, ∅ 20 mm column, 350 mL of hexanes/EtOAc (6:1)) and drying *in vacuo* to give 53 mg of **DNB107b** (98%) as a white amorphous solid. The spectroscopic data for each run was consistent and only the SFC data for the -55 °C run has been tabulated (see, data for **DNB107b** run at –55 °C).

Data for **DNB107b** (–72 °C run):

mp: 104 – 105 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.24 (t, J = 2.1 Hz, 1 H, HC(9)), 9.12 (d, J = 2.1 Hz, 2 H, HC(12)), 6.37 (td, J = 7.5, 1.5 Hz, 1 H, HC(3)), 5.39 (td, J = 10.2, 5.9 Hz, 1 H, HC(5)), 2.71 – 2.56 (m, 2 H, H_2C(4)), 1.92 (d, J = 1.1 Hz, 3 H, H_3C(9)), 1.82 (ddd, J = 14.3, 9.1, 5.5 Hz, 1 H, H_2C(6)), 1.72 – 1.62 (m, 1 H, HC(7)), 1.49 (ddd, J = 14.0, 8.5, 4.3 Hz, 1 H, H_2C(6')), 0.97 (dd, J = 8.4, 6.6 Hz, 6 H, H_3C(8))

^{13}C NMR: (125 MHz, $CDCl_3$)

162.0 (C(10)), 148.7 (C(13)), 141.7 (C(3)), 133.6 (C(11)), 129.3 (C(12)), 122.6 (C(14)), 119.8 (C(1)), 112.6 (C(2)), 74.0 (C(5)), 42.8 (C(6)). 33.6 (C(4)), 24.8 (C(7)), 23.0 (C(8)), 22.0 (C(8)), 15.2 (C(9))

IR: (neat)

3109 (m), 2964 (s), 2874 (m), 2218 (s), 1715 (s), 1632 (m), 1548 (m), 1463 (m), 1422 (m), 1371 (m), 1346 (m), 1290 (s), 1216 (w), 1175 (m), 1073 (s), 915 (s)

MS: (ESI)

384.1 (100.0, M+Na)

HRMS: calcd for $C_{17}H_{19}N_3O_6Na^+$: 384.1172, found: 384.1175

TLC: 0.15 (hexane/EtOAc, 2:1) [UV and CAM]

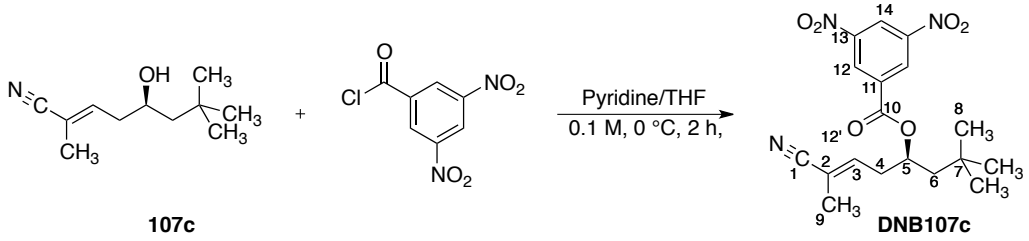
Opt. Rot.: $[\alpha]_D^{24}$ +1.7 (c = 2.08, $CHCl_3$)

SFC: (E,5*S*)-**DNB107b**, t_R 8.4 min (98.4%); (*E*,3*R*)-**DNB107b**; t_R 10.0 min (1.6%), (Chiralpak OD, 200 bar, 5-10% MeOH gradient over 20 min in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Data for **DNB107b** (–55 °C run):

SFC: (E,5*S*)-**DNB107b**, t_{R1} 8.4 min (97.7%); (*E*,5*R*)-**DNB107b**; t_R 10.0 min (2.3%), (Chiralpak OD, 200 bar, 5-10% MeOH gradient over 20 min in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Preparation of (*E,R*)-7-cyano-2,2-dimethyloct-6-en-4-yl 3,5-dinitrobenzoate (DNB107c) (Table 11, entry 3)



107c **DNB107c**

Following General Procedure 10, 42 mg (0.23 mmol) of (*E,R*)-5-hydroxy-2,7,7-trimethyloct-2-enenitrile (**107c**) and 107 mg (0.45 mmol, 2.0 equiv) of 3,5-dinitrobenzoylchloride were combined in 2.3 mL of 1:1 THF/Pyridine (0.1 M) at 0 °C for 2 h to yield after silica gel plug filtration (15 g SiO_2, ∅ 20 mm column, 350 mL of hexanes/EtOAc (6:1)) and drying *in vacuo* 87 mg of **DNB107c** (99%) as a white amorphous solid.

Data for **DNB107c**:

mp: 119 – 120 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.24 (t, *J* = 2.1 Hz, 1 H, HC(14)), 9.12 (d, *J* = 2.1 Hz, 2 H, HC(12)), 6.36 (td, *J* = 7.5, 1.5 Hz, 1 H, HC(3)), 5.50 – 5.35 (m, 1 H, HC(5)), 2.70 – 2.52 (m, 2 H, $H_2C(4)$), 1.93 – 1.85 (m, 4 H, $H_2C(6)$ and $H_3C(9)$), 1.52 (dd, *J* = 15.1, 2.1 Hz, 1 H, $H_2C(6')$), 0.95 (s, 9 H, $H_3C(8)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

162.0 (C(10)), 148.8 (C(13)), 141.5 (C(3)), 133.6 (C(11)), 129.3 (C(12)), 122.6 (C(14)), 119.8 (C(1)), 112.7 (C(5)), 73.3 (C(6)), 47.1 (C(4)), 34.9 (C(4)), 30.3 (C(1)), 29.7 (C(8)), 15.2 (C(9))

IR: (neat)

3111 (m), 3021 (m), 2954 (s), 2219 (s), 1719 (s), 1629 (m), 1546 (s), 1459 (m), 1417 (w), 1344 (s), 1277 (m), 1216 (s), 1167 (s), 1074 (m), 1043 (m), 957 (w), 918 (m)

MS: (ESI)

398.1 (100.0, M+Na), 393.2 (14.7)

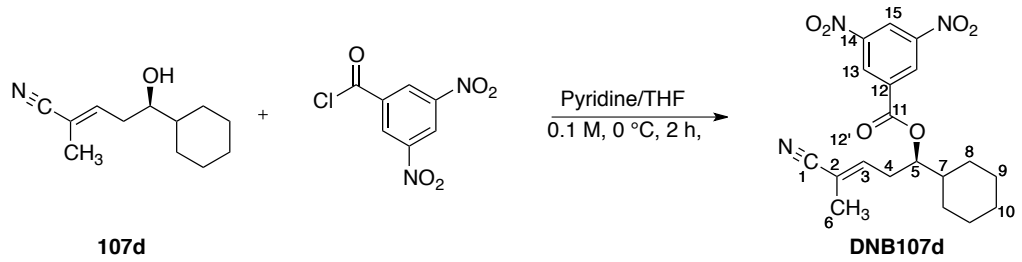
HRMS: calcd for $C_{18}H_{21}N_3O_6Na^+$: 398.1328, found: 398.1329

TLC: 0.16 (hexane/EtOAc, 7:1) [UV and CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –8.8 (c = 2.01, $CHCl_3$)

SFC: (E,5*R*)-**DNB107c**, t_R 4.5 min (96.4%); (*E*,3*S*)-**DNB107c**; t_R 6.2 min (3.6%), (Chiralpak OD, 200 bar, 7.5% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Preparation of (*E,R*)-7-cyano-2,2-dimethyloct-6-en-4-yl 3,5-dinitrobenzoate (DNB107d) (Table 11, entry 4)



Following General Procedure 10, 28.6 mg (0.15 mmol) of (*E,R*)-4-cyano-1-cyclohexylpent-3-en-1-yl 3,5-dinitrobenzoate (**107d**) and 68 mg (0.30 mmol, 2.0 equiv) of 3,5-dinitrobenzoylchloride were combined in 1.5 mL of 1:1 THF/Pyridine (0.1 M) at 0 °C for 2 h to yield after silica gel plug filtration (15 g SiO_2, ∅ 20 mm column, 350 mL of hexanes/EtOAc (6:1)) and drying *in vacuo* 55 mg of **DNB107d** (98%) as a white amorphous solid.

Data for **DNB107d**:

mp: 90 – 91 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.24 (t, *J* = 2.1 Hz, 1 H, HC(15)), 9.11 (d, *J* = 2.1 Hz, 2 H, HC(13)), 6.36 (td, *J* = 7.5, 1.5, 1 H, HC(3)), 5.16 (dt, *J* = 7.5, 5.6 Hz, 1 H, HC(5)), 2.74 – 2.57 (m, 2 H, H_2C(4)), 1.90 (d, *J* = 1.2 Hz, 3 H, H_3C(6)), 1.85 – 1.66 (m, 5 H, HC(7) and H_2C(8)), 1.37 – 1.01 (m, 5 H, H_2C(9,10))

^{13}C NMR: (125 MHz, $CDCl_3$)

162.0 (C(11)), 148.7 (C(14)), 142.3 (C(3)), 133.6 (C(12)), 129.3 (C(13)), 122.6 (C(15)), 119.9 (C(1)), 112.3 (C(2)), 79.2 (C(5)), 41.1 (C(7)), 30.5 (C(4)), 30.0 (C(8,9)), 28.3 (C(8,9)), 26.0 (C(8,9)), 25.8 (C(8,9)), 25.7 (C(10)), 15.1 (C(6))

IR: (neat)

3104 (m), 3020 (w), 2930 (s), 2855 (s), 2219 (m), 1730 (m), 1629 (s), 1547 (s), 1450 (m), 1345 (s), 1278 (s), 1167 (s), 1076 (m), 993 (s), 921 (m), 891 (m), 825 (m)

MS: (ESI)

410.1 (100.0, M+Na)

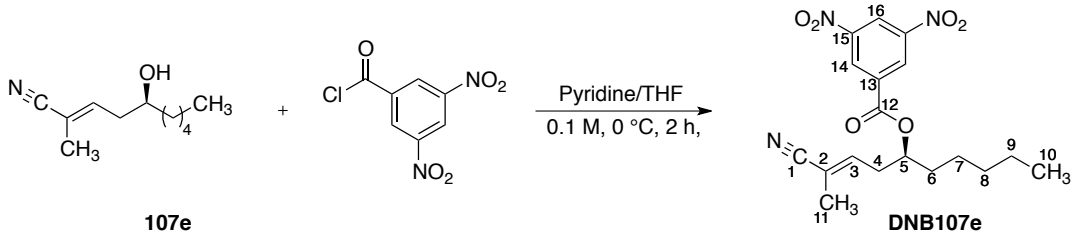
HRMS: calcd for $C_{19}H_{21}N_3O_6Na^+$: 410.1328, found: 410.1331

TLC: 0.17 (hexane/EtOAc, x:x) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +19.1 (c = 1.86, EtOH)

SFC: (E,5*S*)-**DNB107d**, t_{R1} 2.9 min (1.5%); (*E*,3*R*)-**DNB107d**; t_{R2} 4.6 min (98.5%), (Chiralpak AD, 200 bar, 15% MeOH in CO_2, 3.0 mL/min, 220 nm, 40 °C)

Preparation of *(E,S)*-2-cyanodec-2-en-5-yl 3,5-dinitrobenzoate (DNB-107e) (Table 11, entry 5)



107e **DNB107e**

Following General Procedure 10, 41 mg (0.23 mmol) of (*E,R*)-5-hydroxy-2,7,7-trimethyloct-2-enenitrile (**107e**) and 104 mg (0.45 mmol, 2.0 equiv) of 3,5-dinitrobenzoylchloride were combined in 2.3 mL of 1:1 THF/Pyridine (0.1 M) at 0 °C for 2 h to yield after silica gel plug filitration (15 g SiO_2, ∅ 20 mm column, 350 mL of hexanes/EtOAc (6:1)) and drying *in vacuo* 84 mg of **DNB107e** (97%) as a white amorphorus solid.

General procedure 10 was repeated with 36 mg **107e** (0.15 mmol) obtained from a -55 °C

run. The resulting crude residue was purified by silica gel plug filtration (15 g SiO_2, ∅ 20 mm column, 350 mL of hexanes/EtOAc (6:1)) and drying *in vacuo* to give 72 mg of **DNB107e** (97%) as a white amorphorus solid. The spectroscopic data for each run was consistent and only the SFC data for the -55 °C run has been tabulated (see, data for **DNB107e** run at -55 °C).

Data for **DNB107e** (–72 °C run):

mp: 61 – 62 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.26 (t, *J* = 2.1 Hz, 1 H, HC(16)), 9.13 (d, *J* = 2.1 Hz, 2 H, HC(14)), 6.36 (td, *J* = 7.5, 1.5 Hz, 1 H, HC(3)), 5.33 – 5.24 (m, 1 H, HC(5)), 2.73 – 2.57 (m, 2 H, $H_2C(4)$), 1.93 (d, *J* = 0.8 Hz, 3 H, $H_3C(11)$), 1.91 – 1.66 (m, 2 H, $H_2C(6)$), 1.61 – 1.17 (m, 6 H, $H_2C(7,8,9)$), 0.89 (t, *J* = 7.0 Hz, 3 H, $H_3C(10)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

162.0 (C(12)), 148.7 (C(15)), 141.7 (C(3)), 133.6 (C(13)), 129.3 (C(14)), 122.6 (C(16)), 119.8 (C(1)), 112.5 (C(2)), 75.6 (C(5)), 33.8 (C(6)), 33.0 (C(4)), 31.4 (C(8)), 25.0 (C(7)), 22.4 (C(9)), 15.2 (C(11)), 13.9 (C(10))

IR: (neat)

3103 (m), 3020 (m), 2930 (s), 2830 (m), 2219 (m), 1729 (s), 1629 (m), 1545 (s), 1459 (m), 1345 (s), 1275 (s), 1168 (s), 1075 (m), 921 (m)

MS: (ESI)

398.1 (100.0, M+Na)

HRMS: calcd for $C_{18}H_{21}N_3O_6Na^+$: 398.1330, found: 398.1328

TLC: 0.16 (hexane/EtOAc, 7:1) [UV and CAM]

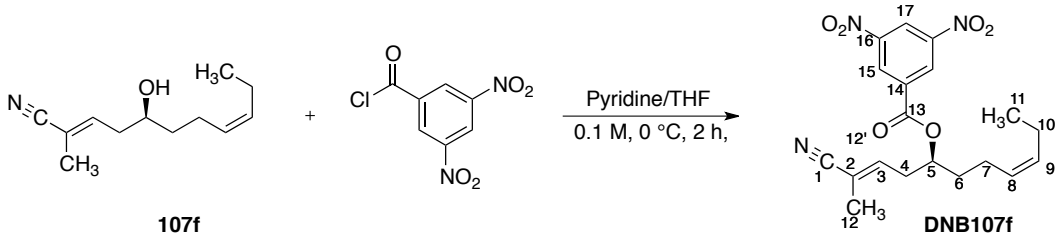
Opt. Rot.: $[\alpha]_D^{24}$ +8.9 (c = 2.06, $CHCl_3$)

SFC: (E,5*S*)-**DNB107e**, t_R 8.6 min (91.9%); (*E*,5*R*)-**DNB107e**; t_R 10.2 min (8.1%), (Chiralpak OD, 200 bar, 5-20% MeOH gradient over 20 min in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Data for **DNB107e** (–55 °C run):

SFC: (E,5*S*)-**DNB107e**, t_{R1} 8.6 min (90.0%); (*E*,5*R*)-**DNB107e**; t_{R2} 10.2 min (10.0%), (Chiralpak OD, 200 bar, 5-20% MeOH gradient over 20 min in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Preparation of (2*E*,8*Z*,*S*)-2-cyanoundeca-2,8-dien-5-yl 3,5-dinitrobenzoate (DNB107f) (Table 11, entry 6)



Following General Procedure 10, 18 mg (0.09 mmol) of (2*E*,8*Z*,*S*)-5-hydroxy-2-methylundeca-2,8-dienenitrile (**107f**) and 43 mg (0.18 mmol, 2.0 equiv) of 3,5-dinitrobenzoylchloride were combined in 1.5 mL of 1:1 THF/Pyridine (0.1 M) at 0 °C for 2 h to yield after silica gel plug filtration (15 g SiO_2, ∅ 20 mm column, 350 mL of hexanes/EtOAc (6:1)) and drying *in vacuo* 34 mg of **DNB107f** (98%) as a yellow oil.

General procedure 10 was repeated with 29 mg **107e** (0.15 mmol) obtained from a -55 °C run. The resulting crude residue was purified by silica gel plug filtration (15 g SiO_2, ∅ 20 mm column, 350 mL of hexanes/EtOAc (6:1)) and drying *in vacuo* to give 57 mg of **DNB107e** (99%) as a yellow oil. The spectroscopic data for each run was consistent and only the SFC data for the -55 °C run has been tabulated below (see, data for **DNB107f** run at -55 °C).

Data for **DNB107f** (–72 °C run):

^{1}H NMR: (500 MHz, $CDCl_3$)

9.26 (t, *J* = 2.0 Hz, 1 H, HC(17)), 9.14 (d, *J* = 2.1 Hz, 2 H, HC(15)), 6.37 (td, *J* = 7.5, 1.4 Hz, 1 H, HC(3)), 5.47 – 5.40 (m, 1 H, HC(9)), 5.37 – 5.25 (m, 2 H, HC(8) and HC(5)), 2.78 – 2.56 (m, 3 H, $H_2C(4)$), 2.18 (q, *J* = 7.3 Hz, 2 H, $H_2C(6)$), 2.04 – 1.88 (m, 6 H, $H_2C(7,10)$ and $H_3C(12)$), 1.79 (ddd, *J* = 22.0, 7.8, 4.8 Hz, 1 H, $H_2C(7)$), 0.94 (dd, *J* = 9.3, 5.8 Hz, 3 H, $H_3C(11)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

162.0 (C(13)), 148.8 (C(16)), 141.5 (C(3)), 133.6 (C(14)), 133.4 (C(9)), 129.3 (C(15)), 126.6 (C(8)), 122.6 (C(17)), 119.8 (C(1)), 112.7 (C(2)), 75.2 (C(5)), 33.7 (C(6)), 33.0 (C(4)), 23.0 (C(7)), 20.6 (C(10)), 15.2 (C(12)), 14.2 (C(11))

IR: (neat)

3104 (m), 3008 (m), 2963 (s), 2932 (s), 2219 (m), 1731 (s), 1630 (m), 1590 (w), 1548 (s), 1462 (m), 1345 (s), 1276 (s), 1168 (s), 1076 (s), 1035 (s), 921 (m), 883 (m)

MS: (ESI)

410.1 (100.0, M+Na), 405.2 (8.9), 388.2 (6.2)

HRMS: calcd for $C_{19}H_{21}N_3O_6Na^+$: 410.1328, found: 410.1332

calcd for $C_{19}H_{22}N_3O_6$: 388.1509, found: 388.1509

TLC: 0.15 (hexane/EtOAc, 2:1) [UV and CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +3.5 (c = 1.96, $CHCl_3$)

SFC: (2*E*,8*Z*,5*S*)-**DNB107f**, t_R 9.3 min (88.0%); (2*E*,8*Z*,5*S*)-**DNB107f**; t_R 11.7 min (12.0%); (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C)

Isomeric impurity at 13.6 min, integrates for 6.6% of total area (not reflected in above percentages).

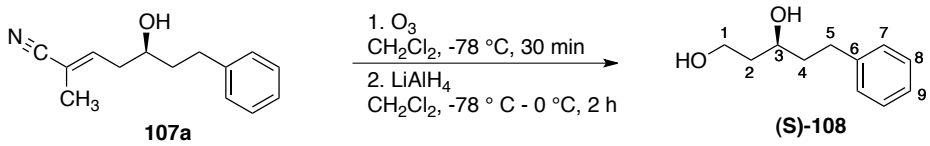
Data for **DNB107f** (–55 °C run):

SFC: (2*E*,8*Z*,5*S*)-**DNB107f**, t_R 9.3 min (87.2%); (2*E*,8*Z*,5*S*)-**DNB107f**; t_R 11.7 min (12.8%); (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C) Isomeric impurity at 13.6 min, integrates for 6.7% of total area (not reflected in above percentages).

7.4.3.6 Determination of the Absolute Configuration of the Nitrile Products.

General Procedure 11. Ozonolysis of α,β-Unsaturated Nitriles.

Preparation of (*S*)-5-phenylpentane-1,3-diol (108).



To a flame-dried 25 mL 2-neck round-bottomed flask was added 54 mg of nitrile **107a** (0.25 mmol) and 5.0 mL of CH_2Cl_2 (0.05 M). The solution was cooled to -78 °C (CO_2/Acetone) and then a mixture of O_3/O_2 gas was bubbled into the flask through a gas dispersion tube for 20 min; a deep blue color persisted in the flask after 5 min. The solution was sparged with Argon to remove excess ozone and then a solution 0.85 mL of a 1.20 M solution of $LiAl_4$ (1.0 mmol, 4.0 eqiuv) in THF was added via syringe. The resulting colorless solution was stirred for 20 min at -78 °C and then warmed to rt and stirred for an additional 40 min. The mixture was then was slowly transferred to a 50-mL Erlenmeyer flask containing 10 mL of a stirred, sat. aq. solution of Rochelle's salt. The biphasic mixture was stirred vigorously for 1 h at rt and was then transferred to a 60 mL separatory funnel, where the organic layer was isolated. The aq. layer was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic extracts were washed with Brine, dried over

$NaSO_4$, and concentrated in vacuo. The resulting organic residue was purified by column chromatography (15 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (1:1 to 1:2), CAM) to yield 31 mg of (*S*)-**108** as a clear, colorless oil. The spectroscopic data for (*S*)-**108** was consistent with previously reported literature values.[27b,102]

Data for **108**:

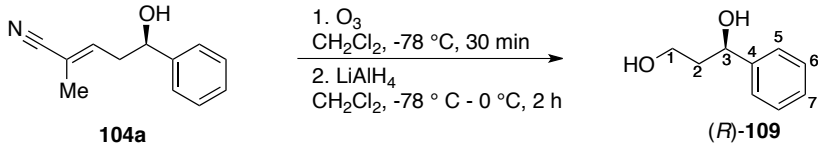
^{1}H NMR: (500 MHz, $CDCl_3$)

7.31 – 7.25 (m, 2 H, HC(Aryl)), 7.23 – 7.18 (m, 3 H, HC(Aryl)), 3.90 (app dt, *J* = 8.1, 4.3 Hz, 2 H, $H_2C(1)$), 3.83 (app dt, *J* = 11.3, 5.7 Hz, 1 H, HC(3), 2.86 – 2.74 (m, 1 H, $H_2C(5)$), 2.69 (ddd, *J* = 13.8, 9.4, 6.8 Hz, 1 H, HC(5)), 2.53 (s, 1 H, OH), 2.32 (s, 1 H, OH), 1.89 – 1.70 (m, 4 H, $H_2C(2,4)$)

TLC: R_f 0.29 (hexane/EtOAc, 1:2) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –10.0 (c = 1.05, EtOH); lit. $[\alpha]_D^{24}$ –7.21 (c = 1.52, EtOH) for (*3S*)-**108**[27b,102]

Preparation of (*R*)-1-phenylpropane-1,3-diol (108)



104a (*R*)-**109**

Following general procedure 11, a solution of 60 mg nitrile **104a** (0.32 mmol) in 6.4 mL CH_2Cl_2 (0.05 M) was treated with a mixture of ozone in oxygen followed by reduction with 1.1. mL of a 1.2 M solution of $LiAl_4$ in THF (1.28 mmol, 4.0 equiv) to yield, after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, 16 x 150 mm fractions, hexanes/EtOAc gradient (1:1 to 1:2), CAM) 34 mg (70%) of (*R*)-**109** as a clear, colorless oil. The spectroscopic data for (*R*)-**109** was consistent with previously reported literature values.[27b,102]

Data for **109**:

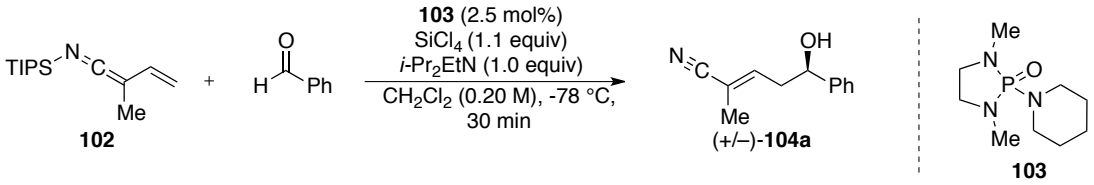
^{1}H NMR: (500 MHz, $CDCl_3$)

7.37 (m, 4 H, HC(5,6), 7.28 (td, *J* = 5.9, 2.6 Hz, 1 H, HC(7)), 4.97 (dd, *J* = 8.4, 3.8 Hz, 1 H, HC(3)), 3.91 – 3.81 (m, 2 H, $H_2C(1)$), 2.83 (br s, 1 H, OH), 2.37 (br s, 1 H, OH), 2.09 – 1.98 (m, 1 H, $H_2C(2)$), 1.97 – 1.89 (m, 1 H, $H_2C(2)$)

TLC: R_f 0.28 (hexane/EtOAc, 1:2) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +58.8 (c = 1.2, $CHCl_3$); lit. $[\alpha]_D^{24}$ –63 (c = 0.98, $CHCl_3$) for (*3S*)-**109**[27b,102]

7.4.3.7 In Situ IR Kinetic Studies on the Vinylogous Addition of *N*-Silyl Vinylketene Imine. React IR monitoring of the Catalyzed Rate for the Vinylogous Addition of SKI 102 to Benzaldehyde [TWW-X-46].



An oven-dried, three necked reactor containing a stir bar and temperature probe was attached to the 10 mm DiComp React-IR probe and purged with argon for 15 minutes. The reactor was charged with 5 mg of Lewis base catalyst **103**, 43 µL of *i*-PrEtN (0.25 eqiuv, 1.0 equiv) and 1.5 mL of anhydrous dichloromethane. The mixture was stirred and cooled to -68 °C (internal) and a background scan was obtained (256 scans / 8 cm^{-1} resolution / 1 gain / 1000-2000 cm^{-1} spectral window). Next, 32 µl of $SiCl_4$ (0.275 mmol, 1.1 equiv) and 25 µL benzaldehyde (1.0 mmol, 1.0 equiv) was added and the reaction sequence was initiated using the React-IR software (16 scans / 15 sec interval / 8 cm^{-1} resolution / 1 gain /1000-2000 cm^{-1} spectral window). Nine scans of the aldehyde were acquired and then 0.6 mL (0.3 mmol, 1.2 equiv) of a 0.5 M solution of SKI **102** was added via syringe in a single portion. The reaction progress was monitored by disappearance of the aldehyde band at 1702 cm^{-1} for 15 min at -68 °C and then

quenched and worked-up using same procedure as listed above (general procedure 4). The crude product was determined to have a 95:5 E/Z ratio and 98:2 γ/α-addition ratio by ^{1}H NMR integration. After verification of the product by ^{1}H NMR the crude material was discarded. Raw data is reported for reaction time, spectral number and aldehyde absorbance in Table 19.

Table 19. React IR Data for Vinylogous Addition of SKI **102** to Benzaldehyde

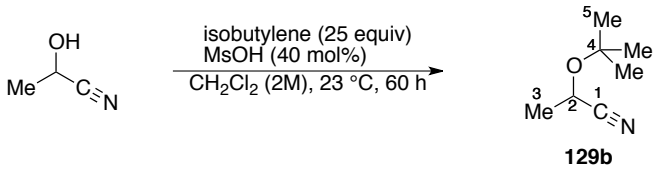
TWW-X-46			
Rxn time (sec)	Rxn time (min)	Spectra	Abs
0.0	0.0	1	0.054
15.9	0.3	2	0.052
31.0	0.5	3	0.054
46.1	0.8	4	0.053
60.1	1.0	5	0.052
75.2	1.3	6	0.052
90.2	1.5	7	0.053
105.3	1.8	8	0.053
135.3	2.3	9	0.053
150.4	2.5	10	0.036
165.4	2.8	11	0.012
180.5	3.0	12	0.003
195.5	3.3	13	0.002
210.5	3.5	14	0.001
225.6	3.8	15	0.002
240.6	4.0	16	0.001
255.7	4.3	17	0.002
270.8	4.5	18	0.003
285.9	4.8	19	0.002
300.9	5.0	20	0.001
316.0	5.3	21	0.002
330.0	5.5	22	0.003
345.1	5.8	23	0.002
360.1	6.0	24	0.002
375.2	6.3	25	0.002
390.2	6.5	26	0.002
405.3	6.8	27	0.002
420.3	7.0	28	0.003
435.4	7.3	29	0.003
450.5	7.5	30	0.003
465.6	7.8	31	0.002
480.7	8.0	32	0.003

7.4.4 Aldol and Cross-Benzoin Reactions of *N*-Silyl Oxyketene Imine.

7.4.4.1 *t*-Butyl Protection of Cyanohydrins.

General Procedure 12. *tert*-Butyl Protection of Cyanohydrin with Isobutylene.

Preparation of 2-(*tert*-Butoxy)propanenitrile (129b) (Table 12, Entry 1).



129b

To a 250-mL Parr shaker bottle with a Teflon screw cap and O-ring was added 105 g (1.87 mol, 22 equiv) of liquefied isobutylene (condensed at -78 °C using a two-neck 500-mL flask and a dry-ice condenser) and 20 mL of CH_2Cl_2. The mixture was cooled to 0 °C (ice bath) and 5.88 g (82.7 mmol) of acetaldehyde cyanohydrin as a solution in 20.6 mL CH_2Cl_2 (4.0 M) was added via cannula. The shaker bottle was capped and inverted several times to achieve a clear, colorless homogenous solution and then was cooled to -78 °C (dry ice/acetone bath) and 2 mL (30.3 mmol, 0.4 equiv) of methanesulfonic acid was slowly added over 2 min via syringe. The shaker bottle was then tightly sealed with the screw cap, connected to a Parr shaker and shook for 60 h at 23 °C. The resulting clear, yellow solution was removed from the Parr shaker, re-cooled to -78 °C, and the pressure was carefully released in a well-ventilated hood. The cold reaction mixture was quenched by transferring it to a 1-L beaker containing a pre-cooled (0 °C, ice bath), stirred solution of 150 mL satd aq. $NaHCO_{3\ (aq)}$. The shaker bottle was rinsed with diethyl ether (2 x 50 mL) and the washes were added to the beaker. The quenched mixture was stirred for 1 h at 0 °C and then was warmed to ambient temperature and stirred for an additional 3 h. The resultant biphasic mixture was poured into a 1-L separatory funnel and the organic layer was isolated. The aqueous layer was extracted with diethyl ether (2 x 100 mL) and then the organic extracts were combined, washed with brine (3 x 75 mL), and dried over $MgSO_4$ (ca 7.5 g). The

solution was filtered and the volatiles were removed by distillation at ambient pressure (bp 35-40 °C) to give 9.5 g of a clear yellow liquid. The crude mixture was purified by vacuum distillation over dried K_2CO_3 (0.75 g) to afford 5.2 g (50%) of **129b** as a clear, colorless liquid.

Data for **129b**:

bp: 50 - 52 °C (43 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

4.29 (q, *J* = 6.8 Hz, 1 H, HC(2)), 1.47 (d, *J* = 6.8 Hz, 3 H, H_3C(3)), 1.25 (s, 9 H, H_3C(5))

^{13}C NMR: (125 MHz, $CDCl_3$)

121.36 (C(1)), 76.28 (C(4)), 56.43 (C(2)) , 27.42 (C(5)), 21.73 (C(3))

IR: (KBr Pellet)

2980 (s), 2940 (m), 2876 (w), 1474 (m), 1445 (m), 1394 (m), 1370 (s), 1337 (m), 1304 (w), 1260 (m), 1239 (m), 1192 (s), 1118 (s), 1103 (s), 1063 (s), 1026 (w), 967 (s), 921 (w), 849 (m), 810 (w), 745 (w)

MS: (EI, 70 meV)

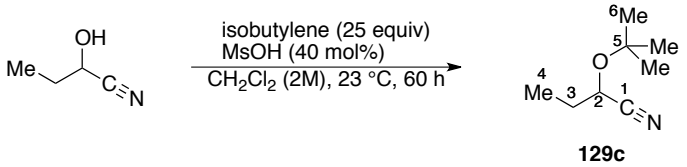
127.1 (2.1), 112.1 (41.5, $M^+ - CH_3$), 102.1 (7.9), 59.1 (100.0), 57.1 (87.1), 54.1 (9.2)

Analysis: $C_8H_{15}NO$ (141.211)

Calcd: C, 66.10; H, 10.30; N, 11.01%

Found: C, 65.86; H, 10.25; N, 10.96%

Preparation of 2-(*tert*-Butoxy)butanenitrile (129c) (Table, 12, entry 2)



129c

Following General Procedure 12, 6.38 g (75.0 mmol) of propionaldehyde cyanohydrin was combined with a 85.0 g of isobutylene (20.2 equiv, 1.51 mol) and 2.0 mL of methanesulfonic acid (0.4 equiv, 30.3 mmol) in a Parr shaker bottle to afford 6.0 g of **129c** (57%) as a clear, colorless liquid after vacuum distillation from K_2CO_3.

Data for **129c**:

bp: 66 - 69 °C (15 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

4.10 (t, J = 6.7 Hz, 1 H, HC(2)), 1.85 – 1.71 (m, 2 H, $H_2C(3)$), 1.27 (s, 9 H, $H_3C(6)$), 1.03 (t, J = 7.4 Hz, 3 H, $H_3C(4)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

120.9 (C(1)), 76.2 (C(5)), 62.0 (C(2)), 28.5 (C(3)), 27.5 (C(6)), 9.3 (C(4))

IR: (KBr Pellet)

2977 (s), 2940 (s), 2881 (m), 1465 (m), 1394 (m), 1370 (s), 1344 (w), 1263 (m), 1237 (m), 1191 (s), 1112 (s), 1092 (s), 1075 (s), 1007 (s), 943 (s), 925 (w), 877 (m), 731 (w)

MS: (EI, 70 meV)

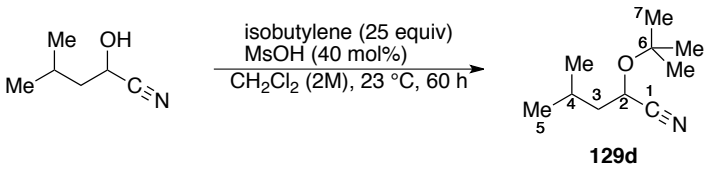
126.1 (33.7, $M^+ - CH_3$), 68.1 (25.7), 59.1 (100.0), 57.2 (69.3)

Analysis: $C_8H_{15}NO$ (141.211)

Calcd: C, 68.04; H, 10.71; N, 9.92%

Found: C, 68.09; H, 10.79; N, 9.71%

Preparation of 2-(*tert*-Butoxy)-4-methylpentanenitrile (129d) (Table 12, entry 4)



129d

Following General Procedure 12, 8.27 g (73.1 mmol) of isovaleraldehyde cyanohydrin was combined with 85.0 g of isobutylene (20.7 equiv, 1.51 mol) and 2.0 mL of methanesulfonic acid (0.40 equiv, 30.3 mmol) in a Parr shaker bottle to afford, after vacuum distillation, 6.92 g of **129d** (56% yield, >96% purity by ^{1}H-NMR) as a clear, light yellow liquid. Analytically pure material was obtained after a vacuum to distillation over K_2CO_3 to afford 6.48 g of **129d** (52%) as a clear, colorless liquid.

Data for **129d:**

bp: 63 - 65 °C (8.6 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

4.19 (dd, J = 8.1, 6.3 Hz, 1 H, HC(2)), 1.88 – 1.76 (m, 1 H, HC(4)), 1.72 – 1.56 (m, 2 H, H_2C(3)), 1.27 (s, 3 H, H_3C(7)), 0.94 (d, J = 6.7 Hz, 3 H, H_3C(5)), 0.92 (d, J = 6.6 Hz, 3 H, H_3C(5))

^{13}C NMR: (125 MHz, $CDCl_3$)

121.20 (C(1)), 76.18 (C(6)), 59.33 (C(2)), 43.91 (C(3)), 27.58 (C(7)), 24.03 (C(4)), 22.51 (C(5)), 22.01 (C(5))

IR: (KBr Pellet)

2962 (s), 2874 (s), 1469 (m), 1393 (m), 1370 (s), 1260 (m), 1238 (m), 1191 (s), 1128 (m), 1078 (s), 1023 (m), 1003 (w), 961 (w), 906 (w), 884 (w), 834 (w), 738 (w)

MS: (EI, 70 meV)

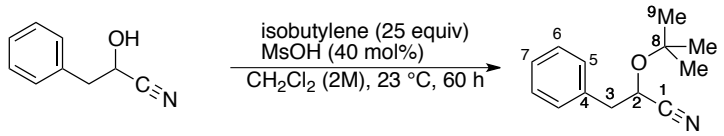
154.1 (38.7), 96.1 (35.6), 69.1 (12.9), 59.1 (100.0), 57.1 (91.4), 54.1 (25.2)

Analysis: $C_{10}H_{19}NO$ (169.26)

Calcd: C, 70.96; H, 11.31; N, 8.28%

Found: C, 70.74; H, 11.42; N, 8.12%

Preparation of 2-(*tert*-Butoxy)-3-phenylpropanenitrile (129e) (Table 12, entry 5)



129e

Following General Procedure 12, 8.82 g (60.0 mmol) of phenylacetaldehyde cyanohydrin was combined with a 80.3 g of isobutylene (24.0 equiv, 1.44 mol) and 1.5 mL of methanesulfonic acid (0.39 equiv, 23.1 mmol) in a Parr shaker bottle to afford 7.4 g of **129e** (60%) as a clear, colorless liquid after vacuum distillation from K_2CO_3.

Data for **129e**:

bp: 73 - 75 °C (0.75 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.34 – 7.22 (m, 5 H, HC(5, 6, 7)), 4.26 (dd, J = 7.9, 6.1 Hz, 1 H, HC(2)), 3.05 (dd, J = 13.6, 6.1 Hz, 1 H, H_2C(3)), 3.00 (dd, J = 13.6, 7.9 Hz, 1 H, H_2C(3)), 1.13 (s, 9 H, H_3C(9))

^{13}C NMR: (125 MHz, $CDCl_3$)

135.18 (C(4)), 129.72 (C(5)), 128.39 (C(6)), 127.29 (C(7)), 120.47 (C(1)), 76.53 (C(8)), 62.27 (C(2)), 41.51 (C(3)), 27.29 (C(9))

IR: (KBr Pellet)

3085 (w), 3065 (w), 3032 (w), 2977 (s), 2935 (m), 2872 (w), 1674 (w), 1605 (w), 1497 (m), 1455 (m), 1394 (m), 1370 (s), 1341 (w), 1260 (m), 1238 (m), 1186 (s), 1081 (s), 1027 (m), 940 (m), 833 (w), 750 (s), 699 (s)

MS: (EI, 70 meV)

203.2 (31.4), 147.1 (31.9), 131.1 (11.2), 130.1 (76.9), 103.1 (20.5), 92.1 (44.9), 91.1 (82.0), 77.1 (20.1), 65.1 (12.4), 57.2 (100.0), 51.0 (11.2)

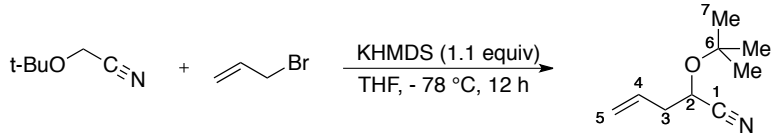
HRMS: calcd for $C_{13}H_{17}ON$: 203.1310, found: 203.1310

Analysis: $C_{13}H_{17}NO$ (203.28)

Calcd: C, 76.81; H, 8.43; N, 6.89%

Found: C, 76.84; H, 8.65; N, 6.90%

Preparation of 2-(*tert*-Butoxy)pent-4-enenitrile (129f) by alkylation of 129a.



129f

To a flame-dried, 50-mL, single-necked, Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum was added 5.48 g of KHMDS (27.5 mmol, 1.1 equiv) and 27.5 mL of anhydrous THF (1.0 M in KHMDS). The solution was stirred at rt until a homogeneous solution resulted and then was cooled to -78 °C (internal) with a dry ice/acetone bath. The reaction mixture was stirred at -78 °C for 5 min and then a solution of 2.83 g 2-(*tert*-butoxy)acetonitrile (25.0 mmol) in 12.5 mL of anhydrous THF (2.0 M in nitrile) was added dropwise via cannula over 15 minutes. The resulting bright-yellow reaction mixture was stirred for 5 min at -78 °C and then a solution of 2.4 mL allyl bromide (27.5 mmol, 1.1 equiv) in 12.5 mL of anhydrous THF

(2.0 M in allyl bromide) was added via cannula over 15 min. The addition afforded a dark red solution that was allowed to stir for 1 h at -78 °C and was then warmed to ambient temperature and stirred for an additional 12 h prior to being quenched by the addition of 50 mL of sat. aq. NH_4Cl solution. The quenched solution was transferred to a 250-mL separatory funnel where the organic layer was isolated. The aqueous layer was extracted with Et_2O (3 x 75 mL) and the resulting organic layers were combined, washed successively with 1 M HCl (1 x 50 mL), and brine (2 x 50 mL) and then dried over $MgSO_4$ (ca. 5 g). The solution was filtered and concentrated *in vacuo* (40 °C, 450 mm Hg) to give a yellow liquid. The crude residue was purified by column chromatography (110 g SiO_2 gel, ∅ 50 mm column, pentanes/Et_2O gradient (30:1, 620 mL to 25:1, 780 mL)) to afford 1.5 g of **129f** (39%) as a clear, yellow oil. Further purification by Kugelrohr distillation (105-110 °C, 12.5 mm Hg) produced 1.31 g of analytically pure **129f** (34%) as a clear, colorless liquid.

Data for **129f**:

^{1}H NMR: (500 MHz, $CDCl_3$)

5.80 (ddt, J = 17.2, 10.1, 7.1 Hz, 1 H, HC(4)), 5.21 (app t, J = 11.9 Hz, 2 H, H_2C(9)), 4.19 (app t, J = 6.8 Hz, 1 H, HC(2)), 2.57 – 2.43 (m, 2 H, H_2C(3)), 1.27 (s, 9 H, H_3C(7))

^{13}C NMR: (125 MHz, $CDCl_3$)

131.3 (C(4)), 120.4 (C(1)), 119.7 (C(5)), 76.5 (C(6)), 60.9 (C(2)), 39.4 (C(3)), 27.5 (C(7))

IR: (neat)

3083 (w), 2979 (s), 2938 (s), 2876 (w), 1644 (w), 1474 (m), 1433 (w), 1394 (m), 1370 (s), 1260 (m), 1239 (m), 1189 (s), 1126 (w), 1079 (s), 1024 (s), 994 (m), 923

(s), 870 (w)

MS: (EI, 70 eV)

138.1 (10.6), 80.0 (30.4), 59.1 (36.9), 57.1 (100.0), 53.1 (16.6)

Analysis: $C_{13}H_{17}NO$ (203.28)

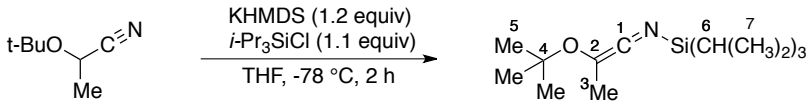
Calcd: C, 70.55; H, 9.87; N, 9.14%

Found: C, 70.72; H, 10.06; N, 9.28%

7.4.4.2 Synthesis of *N*-Silyl Oxyketene Imines.

General Procedure 13. Preparation of α-*tert*-Butoxy *N*-Silyl Ketene Imines.

Preparation of *N*-(2-*tert*-Butoxyprop-1-enylidene)-1,1,1-triisopropylsilanamine (130b) (Table 13, entry 1)



129b **130b**

To a flame-dried, 50-mL, single-necked, Schlenk flask fitted with a magnetic stir bar, argon inlet and septum was added 1.40 g of KHMDS (7.0 mmol, 1.2 equiv) and 7.0 mL of anhydrous THF (1.0 M in KHMDS). The solution was stirred at rt until a homogeneous solution resulted and then was cooled to -78 °C (internal) with a dry ice/acetone bath. The reaction mixture was stirred at -78 °C for 5 min and then a solution of 0.75 g *tert*-butoxy nitrile **129b** (5.86 mmol) and 1.4 mL (5.03 mmol, 1.1 equiv) TIPSCl in 7.9 mL of anhydrous THF (~0.5 M solution in nitrile) was added dropwise via cannula over 10 min. The resulting bright-yellow reaction mixture was stirred for 2 h at -78 °C and then was allowed to warm to 0 °C and was stirred for 5 min during which time the color changed from yellow to orange. The reaction mixture was concentrated under high vacuum (0.5 mm Hg) and the resulting thick, orange gel

(ca. 3 mL) was taken up in 20 mL of anhydrous hexanes (20 mL) and was stirred vigorously under argon. The heterogeneous solution was opened to air and filtered through a pad of packed Celite (ca. 5 g) using a 30-mL, glass-sintered Buchner funnel and then was collected into a flame-dried, weighed 50-mL, round-bottomed flask. The filter cake and Schlenk flask were further washed with 15 mL of anhydrous hexanes. The clear, orange filtrate was concentrated under vacuum (0.5 mm Hg) and then was stirred under high vacuum (0.2 mm Hg) for 12 h at ambient temperature to afford 1.56 g (94%) of **130b** as an orange liquid, which was used in subsequent reactions without further purification.

Data for **130b**:

^{1}H NMR: (500 MHz, C_6D_6)

1.96 (s, 3 H, $H_3C(3)$), 1.26 (s, 9 H, $H_3C(5)$), 1.12 – 1.05 (m, 21 H, HC(6) and $H_3C(7)$)

^{13}C NMR: (125 MHz, C_6D_6)

209.3 (C(1)), 86.3 (C(2)), 78.9 (C(4)), 28.8 (C(3)), 18.3 (C(6)), 18.0 (C(5)), 12.0 (C(7)).

IR: (NaCl plates, neat)

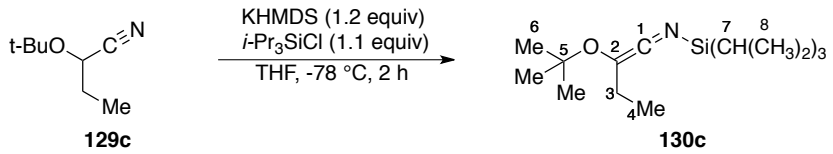
2945 (s), 2868 (s), 2037 (s), 1464 (s), 1384 (m), 1357 (m), 1257 (w), 1166 (s), 1071 (w), 996 (m), 919 (w), 883 (s), 815 (w), 732 (m), 671 (s)

MS: (70 eV, EI)

283.2 (5.4), 184.1 (47.0), 158.1 (13.9), 157.1 (100.0), 115.1 (53.4), 87.1 (27.6), 73.0 (28.7), 59.0 (41.4), 57.0 (30.6)

HRMS: calcd for $C_{16}H_{33}ONSi$: 283.2332, found: 283.2330

Preparation of *N*-(2-(*tert*-Butoxy)but-1-en-1-ylidene)-1,1,1-triisopropylsilanamine (130c) (Table 13, entry 2)



Following General Procedure 13, KHMDS (1.1 g, 5.5 mmol, 1.2 equiv) in 5.5 mL THF and a solution of *tert*-butoxy nitrile **129c** (0.65 g, 4.6 mmol, 1.0 equiv), TIPSCl (1.1 mL, 5.0 mmol, 1.1 equiv) in 7.2 mL THF were combined to afford 1.28 g (94%) of **130c** as an orange liquid, which was used without further purification.

Data for **130c**:

^{1}H NMR: (500 MHz, C_6D_6)

2.34 (q, J = 7.4, 2 H, $H_2C(3)$), 1.29 (s, 9 H, $H_3C(6)$, 1.14-1.12 (m, 6 H, $H_3C(4)$ and HC(7)), 1.11 – 1.09 (m, 18 H, $H_3C(8)$)

^{13}C NMR: (125 MHz, C_6D_6)

208.97 (C(1)), 92.79 (C(1)), 78.76 (C(1)), 28.87 (C(1)), 25.55 (C(1)), 18.01 (C(1)), 12.15 (C(1)), 11.97 (C(1)),

IR: (NaCl plates, neat)

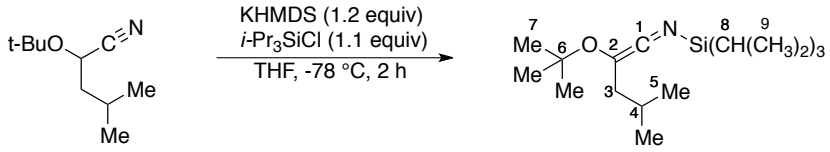
2945 (s), 2867 (s), 2033 (s), 1659 (w), 1463 (s), 1385 (s), 1362 (s), 1310 (m), 1256 (m), 1165 (s), 1060 (m), 996 (m), 919 (w), 882 (s), 839 (w), 807 (w), 736 (m), 682 (s)

MS: (EI, 70 eV)

297.2 (28.1), 240.2 (25.1), 184.1 (65.3), 115.1 (35.9), 73.1 (20.9)

HRMS: calcd for $C_{17}H_{35}ONSi$: 297.2488, found: 297.2486

Preparation of *N*-(2-*tert*-Butoxy-4-methylpent-1-enylidene)-1,1,1-triisopropylsilanamine (130d) (Table 13, entry 3)



Following General Procedure 13, KHMDS (0.97g, 4.87 mmol, 1.2 equiv) in 4.8 mL THF and a solution of *tert*-butoxy nitrile **129d** (0.68 g, 4.06 mmol), TIPSCl (0.96 mL, 4.46 mmol, 1.1 equiv) in 6.2 mL THF were combined to afford 1.23 g (93%) of **130d** as a yellow liquid, which was used without further purification.

Data for **130d**:

^{1}H NMR: (500 MHz, C_6D_6)

2.19 (d, J = 7.0, 2 H, $H_2C(3)$), 2.05-1.97 (m, J = 6.6, 13.2, 1 H, HC(4)), 1.28 (s, 9 H, $H_3C(7)$), 1.14 – 1.07 (m, 21 H, HC(8) and $H_3C(9)$), 1.05 (d, J = 6.6, 6 H, $H_3C(5)$).

^{13}C NMR: (125 MHz, C_6D_6)

208.8 (C(1)), 89.8 (C(2)), 78.9 (C(6)), 42.3 (C(3)), 28.9 (C(7)), 26.7 (C(4)), 23.0 (C(5)), 18.0 (C(9)), 12.1 (C(8))

IR: (neat)

2948 (s), 2868 (s), 2036 (s), 1656 (w), 1464 (m), 1387 (m), 1362 (m), 1279 (w), 1256 (w), 1166 (m), 1072 (w), 1016 (w), 995 (w), 921 (w), 883 (s), 824 (w), 734 (m), 683 (s)

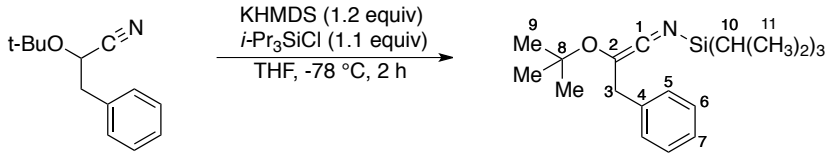
MS: (70 eV, EI)

325.2 (6.3), 300.2 (10.7), 258.1 (10.5), 242.1 (47.9), 215.1 (19.3), 242.1 (47.9), 215.1 (19.3), 200.1 (11.1), 184.1 (39.8), 157.1 (96.4), 115.1 (23.9), 103.1 (16.0),

85.1 (26.3), 73.0 (16.3), 59.0 (24.9), 57.0 (100.0)

HRMS: calcd for $C_{19}H_{39}ONSi$: 325.2801, found: 325.2799

Preparation of *N*-(2-*tert*-Butoxy-3-phenylprop-1-enylidene)-1,1,1-triisopropylsilanamine (130e) (Table 1, entry 4)



129e **130e**

Following General Procedure 13, KHMDS (0.96 g, 4.82 mmol, 1.2 equiv) in 4.8 mL THF and a solution of *tert*-butoxy nitrile **129e** (0.82 g, 4.01 mmol), TIPSCl (0.94 mL, 4.41 mmol, 1.1 equiv) in 6.3 mL THF were combined to afford 1.33 g (93%) of **130e** as a yellow liquid, which was used without further purification.

Data for **130e**:

^{1}H NMR: (500 MHz, C_6D_6)

7.32 (d, J = 7.5, 2 H, HC(5, 6)), 7.18 – 7.14 (m, 2 H, HC(5, 6), 7.06 (t, J = 7.4, 1 H, HC(7)), 3.59 (s, 2 H, H_2C(3)), 1.29 (s, 9 H, H_3C(9)), 1.03 – 0.99 (m, J = 1.8, 21 H, HC(10) and H_3C(11))

^{13}C NMR: (125 MHz, C_6D_6)

206.3 (C(1)), 139.6 (C(4)), 129.6 (C(5)), 128.4 (C(6)), 126.4 (C(7)), 91.7 (C(2)), 79.2 (C(8)), 39.16 (C(3)), 28.9 (C(4)), 18.0 (C(11)), 12.0 (C(10)).

IR: (NaCl plates, neat)

3028 (w), 2945 (s), 2867 (s), 2039 (s), 1659 (w), 1463 (s), 1385 (s), 1362 (s), 1258 (m), 1140 (s), 1072 (w), 1016 (w), 996 (m), 920 (w), 883 (s), 826 (w), 735 (m), 699

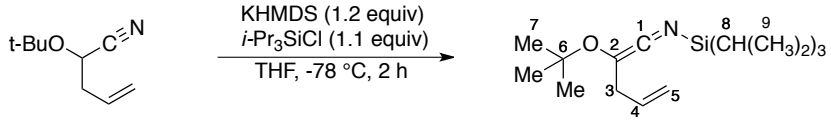
(s), 684 (s)

MS: (EI, 70 eV)

359.2 (13.2), 302.2 (19.2), 184.1 (80.1), 157.1 (100.0), 115.1 (28.1), 91.0 (44.3), 57.0 (29.3)

HRMS: calcd for $C_{22}H_{37}ONSi$: 359.2644, found: 359.2644

Preparation of *N*-(2-(*tert*-butoxy)penta-1,4-dien-1-ylidene)-1,1,1-triisopropylsilanamine (130f) (Table 1, entry 5)



129f **130f**

Following General Procedure 13, KHMDS (0.86 g, 4.3 mmol, 1.2 equiv) in 4.3 mL THF and a solution of *tert*-butoxy nitrile **129f** (0.55 g, 3.6 mmol), TIPSCl (0.85 mL, 4.0 mmol, 1.1 equiv) in 3.6 mL THF were combined to afford 1.08 g (97%) of **130f** as a dark orange liquid, which was used without further purification.

Data for **130f**:

^{1}H NMR: (500 MHz, C_6D_6)

5.12 – 4.87 (m, 1 H, HC(4)), 4.15 (d, J = 17.0 Hz, 1 H, $H_2C(5)$), 4.03 (d, J = 10.0 Hz, 1 H, $H_2C(5)$), 2.03 (dd, J = 6.7, 1.1 Hz, 2 H, $H_2C(3)$), 0.26 (s, 9 H, $H_3C(7)$), 0.16 – 0.04 (m, 21 H, HC(8) and $H_3C(9)$).

^{13}C NMR: (125 MHz, C_6D_6)

206.8 (C(1)), 135.7 (C(4)), 116.1 (C(5)), 89.6 (C(2)), 79.0 (C(6)), 37.4 (C(3)), 28.8 (C(7)), 18.0 (C(9)), 12.1 (C(8)).

IR: (neat)

3078 (w), 2945 (s), 2868 (s), 2037 (s), 1640 (w), 1464 (s), 1416 (m), 1362 (s), 1276 (m), 1256 (m), 1157 (s), 1071 (m), 1016 (m), 993 (s), 910 (s), 882 (s), 831 (w), 735 (w), 682 (s)

MS: (70 eV, EI)

309.2 (9.2), 252.2 (9.9), 184.2 (61.1), 157.2 (100.0), 115.1 (48.7), 87.1 (29.0), 73.1 (32.1), 59.1 (44.4)

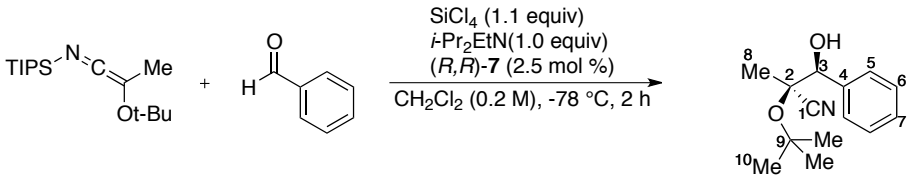
HRMS: calcd for $C_{18}H_{35}ONSi$: 309.2497, found: 309.2488

7.4.4.3 Glycolate Aldol Additions of *N*-Silyl Oxyketene Imines.

General Procedure 14. Addition of *N*-Silyl Oxyketene Imines to Aromatic Aldehydes.

(2*R*,3*S*)-2-(*tert*-Butoxy)-3-hydroxy-2-methyl-3-phenylpropanenitrile (132ba)

(Table 14, entry 1)



130b **131a** **132ba**

To a flame-dried, 10-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 μL of benzaldehyde (1.00 mmol) and 5.0 mL anhydrous CH_2Cl_2 (0.2 M in aldehyde). The solution was stirred, cooled to -78 °C (internal) with a dry ice/acetone bath and then 175 μL of *N,N*-diisopropylethylamine (1.00 mmol, 1.0 equiv) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were added via syringe to the reaction vessel. The resulting solution was stirred for 5 min at -78 °C and then 0.84 mL of a 1.43 M solution of silyl ketene imine **130b** (1.2 mmol, 1.2 equiv) in dichloromethane was added dropwise via syringe over 3 min. The yellow reaction mixture was

allowed to stir for an additional 2 h at -78 °C before 0.65 mL of a 2:1:1 mixture of $Et_3N/CH_2Cl_2/MeOH$ was added via syringe. The quenched solution was stirred for 5 min at -78 °C and then was transferred to a 50-mL Erlenmeyer flask containing a stirred, sat. aq. solution of $NaHCO_3$ (10 mL) and KF (10 mL). The biphasic mixture was stirred vigorously for 1 h at rt and then was filtered through a pad of packed Celite (ca. 7 g) in a 60-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with 10 mL of CH_2Cl_2 and 10 mL of H_2O and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aquaeos layer was extracted with CH_2Cl_2 (2 x 20 mL) and the resulting organic extracts were combined, washed with brine (1 x 25 mL), and dried over $MgSO_4$ (ca. 3 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil. The crude residue was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (11:1, 120 mL to 9:1, 300 mL)) to afford 195 mg of **132ba** (84%) as a viscous, yellow oil after drying *in vacuo* for 12 h (Abderhalden, 40 °C, 0.3 mm Hg). The diastereomeric ratio was determined to be 96:4 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **132ba**:

mp: 63-65 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.50 (d, J = 7.7 Hz, 2 H, HC(5)), 7.41 – 7.33 (m, 3 H, HC(6, 7)), 4.57 (s, 1 H, HC(3)), 3.33 (s, 1 H, OH), 1.50 (s, 3 H, H_3C(8)), 1.46 (s, 9 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

136.2 (C(4)), 128.8 (C(7)), 128.2 (C(5, 6)), 128.0 (C(5, 6)), 120.3 (C(1), 80.2 (C(3)), 79.0 (C(2)), 74.7 (C(9)), 29.9 (C(10)), 24.0 (C(8))

IR: (KBr Pellet)

3505 (s), 3070 (m), 2985 (s), 2936 (m), 2886 (s), 1497 (m), 1455 (s), 1368 (s), 1318 (s), 1225 (s), 1198 (s), 1125 (s), 1089 (s), 1060 (s), 1028 (m), 972 (s), 871 (m), 818 (m), 772 (m), 740 (s)

MS: (ESI)

256.1 (63.9, M + Na^+), 240.1 (18.3), 207.1 (8.3), 152.1 (13.6), 151.1 (100.0), 133.0 (97.6), 105.1 (50.3)

HRMS: calcd for $C_{14}H_{19}NO_2Na^+$: 256.1308, found: 256.1310

TLC: 0.15 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –12.7 (c = 2.13, EtOH)

SFC: see 3,5-DNB-derivative **DNB132ba**

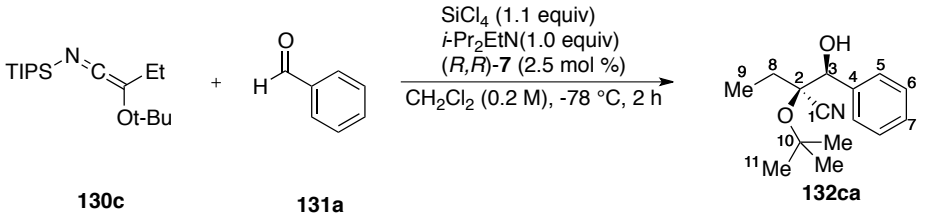
Analysis: $C_{14}H_{19}NO_2$ (233.306)

Calcd: C, 72.07; H, 8.21; N, 6.00%

Found: C, 71.94; H, 8.37; N, 6.05%

(*2R,3S*)-2-Ethyl-2-(*tert*-butoxy)-3-hydroxy-3-phenylpropanenitrile (132ca)

(Table 14, entry 2)



Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 µL of benzaldehyde (1.0 mmol), 175 µL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.78 mL of a 1.54 M solution of **130c** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm

column, hexanes/EtOAc gradient (12:1, 260 mL to 10:1, 220 mL)) and kugelrohr distillation (120-125 °C, 0.33 mm Hg) 226 mg of **132ca** (92%) as a clear, colorless oil. The diastereomeric ratio was determined to be 98.5:1.5 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **132ca**:

bp: 120-125 °C (0.33 mm Hg , kugelrohr)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.50 (d, J = 7.5 Hz, 2 H, HC(5)), 7.44 – 7.31 (m, 3 H, HC(6, 7)), 4.76 (d, J = 3.8 Hz, 1 H, HC(3)), 3.08 (d, J = 3.7 Hz, 1 H, OH), 2.02 (dq, J = 15.0, 7.5 Hz, 1 H, H_2C(8)), 1.67 (dq, J = 14.7, 7.4 Hz, 1 H, H_2C(8)), 1.45 (s, 9 H, H_3C(9)), 1.06 (t, J = 7.4 Hz, 3 H, H_3C(11))

^{13}C NMR: (125 MHz, $CDCl_3$)

136.8 (C(4)), 128.6 (C(7)), 128.0 (C(5, 6)), 127.9 (C(5, 6)), 120.0 (C(1)), 78.8 (C(2)), 77.7 (C(10)), 76.1 (C(3)), 29.6 (C(11)), 29.4 (C(8)), 8.1 (C(9))

IR: (neat)

3477 (s), 3064 (m), 3033 (m), 2979 (s), 2940 (s), 2882 (m), 1495 (m), 1455 (s), 1394 (s), 1368 (s), 1329 (w), 1285 (m), 1252 (m), 1236 (m), 1184 (s), 1149 (s), 1119 (m), 1086 (s), 1056 (s), 1028 (s), 1002 (m), 948 (m), 890 (m), 867 (w), 735 (s)

MS: (ESI)

270.1 (58.5), 254.1 (20.1), 165.1 (81.1), 148.1 (12.4), 147.1 (100.0), 119.1 (18.9), 91.1 (34.9)

HRMS: calcd for $C_{15}H_{21}NO_2Na^{+}$: 270.1465, found: 270.1471

TLC: 0.19 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –13.2 (c = 1.84, EtOH)

SFC: (2*S*,3*R*)-**132ca**, t_R 6.2 min (0.6%); (2*R*,3*S*)-**132ca**, t_R 8.6 min (99.4%), (Chiralpak OD, 125 bar, 2% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

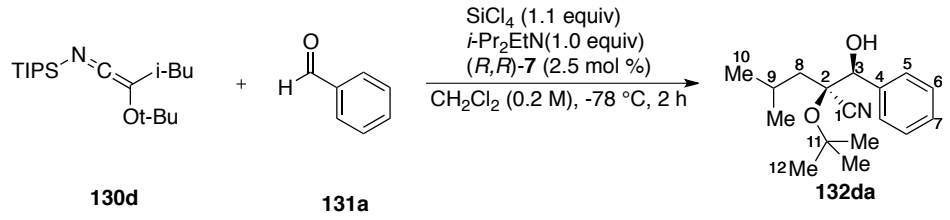
Analysis: $C_{15}H_{21}NO_2$ (247.333)

Calcd: C, 72.84; H, 8.56; N, 5.66%

Found: C, 72.74; H, 8.79; N, 5.77%

(2*R*,3*S*)-2-(*tert*-Butoxy)-3-hydroxy-2-(2-methylpropane)-3-phenylpropanenitrile (132da)

(Table 14, entry 3)



Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 µL of benzaldehyde (1.0 mmol), 175 µL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.82 mL of a 1.47 M solution of **130d** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (12:1, 260 mL to 10:1, 220 mL)) and drying *in vacuo* (Abderhalden, 34 °C, 0.3 mm Hg) 253 mg of **132da** (92%) as a white needles. The diastereomeric ratio was determined to be 98:2 by ^{1}H NMR (500 MHz) analysis of the crude product. Analytically pure material was obtained after recrystallization from hot EtOAc (ca. 0.25 mL) and hexanes (ca. 1.5 mL).

Data for **132da**:

mp: 85-86 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.50 (d, J = 8.0 Hz, 2 H, HC(5)), 7.41 – 7.30 (m, 3 H, HC(6, 7)), 4.80 (d, J = 4.1 Hz, 1 H, HC(3)), 3.08 (d, J = 4.6 Hz, 1 H, OH), 1.97 – 1.82 (m, 2 H, HC(9) and $H_2C(8)$), 1.58 (dd, J = 14.1, 5.1 Hz, 1 H $H_2C(8)$), 1.45 (s, 9H, $H_3C(12)$), 1.01 (d, J = 6.4 Hz, 3 H, $H_3C(10)$), 0.99 (d, J = 6.5 Hz, 3 H, $H_3C(10)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

137.2 (C(4)), 128.6 (C(7)), 128.1 (C(5, 6)), 127.9 (C(5, 6)), 120.4 (C(1)), 78.9 (C(2)), 77.0 (C(11)), 76.9 (C(3)), 44.8 (C(8)), 29.6 (C(12)), 24.6 (C(9, 10)), 24.2 (C(9, 10)), 23.9 (C(9, 10))

IR: (KBr Pellet)

3470 (s), 3036 (w), 3064 (w), 2981 (s), 2963 (s), 2868 (s), 1498 (w), 1473 (m), 1453 (m), 1406 (m), 1367 (s), 1285 (m), 1271 (m), 1187 (m), 1138 (m), 1084 (s), 1057 (s), 1029 (m), 1003 (w), 954 (w), 897 (m), 860 (m), 748 (m), 699 (s)

MS: (ESI)

298.1 (65.6, M + Na^+), 288.0 (56.2), 272.1 (22.5), 263.1 (18.9), 231.0 (11.8), 194.1 (14.7), 193.1 (100.0), 175.1 (45.5), 158.0 (26.6), 119.0 (31.9), 91.0 (52.6)

HRMS: calcd for $C_{17}H_{25}NO_2Na^+$: 298.1788, found: 298.1783

TLC: 0.22 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –3.8 (c = 1.6, EtOH)

SFC: (2*S*,3*R*)-**132da**, t_R 6.6 min (0.4%); (2*R*,3*S*)-**132da**, t_R 7.5 min (99.6%), (Chiralpak OD, 125 bar, 2% MeOH in CO_2, 2.5 mL/min, 210 nm, 40 °C)

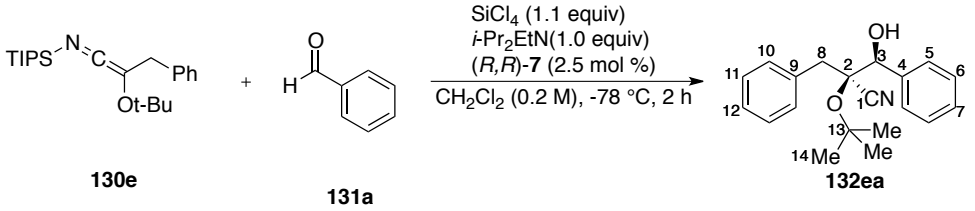
Analysis: $C_{17}H_{25}NO_2$ (275.385)

Calcd: C, 74.14; H, 9.15; N, 5.09%

Found: C, 74.39; H, 9.41; N, 5.34%

(2*R*,3*S*)-2-Benzyl-2-(*tert*-butoxy)-3-hydroxy-3-phenylpropanenitrile (132ea)

(Table 14, entry 4)



Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 µL of benzaldehyde (1.0 mmol), 175 µL of *N,N*-diisopropylethylamine (1.0 mmol, 1.0 equiv) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.90 mL of a 1.33 M solution of **130e** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (9:1, 300 mL to 8:1, 270 mL)) and drying *in vacuo* (Abderhalden, 23 °C, 0.3 mm Hg) 286 mg of **132ea** (93%) as a clear, colorless oil. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **132ea**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.40 (d, J = 7.6 Hz, 4 H, HC(5, 10)), 7.38 – 7.28 (m, 6H, HC(6, 7, 11, 12)), 4.74 (d, J = 6.5 Hz, 1H, HC(3)), 3.31 (d, J = 13.5 Hz, 1H, H_2C(8)), 2.98 – 2.94 (m, 2H, H_2C(8) and OH), 1.28 (s, 9H, H_3C(14))

^{13}C NMR: (125 MHz, $CDCl_3$)

137.6 (C(4)), 134.4 (C(9)), 131.0 (C(5, 6, 10, 11)), 128.4 (C(7, 12)), 128.3 (C(5, 6, 10, 11)), 128.1 (C(5, 6, 10, 11)), 127.7 (C(5, 6, 10, 11), 127.4 (C(7, 12)), 119.7 (C(1)), 79.0 (C(2)), 76.2 (C(3)), 42.7 (C(8)), 29.3 (C(14))

IR: ($CHCl_3$)

3467 (s), 3088 (w), 3064 (w), 3033 (s), 2937 (s), 2978 (s), 2937 (w), 1496 (s), 1454 (s), 1394 (s), 1368 (m), 1234 (m), 1176 (s), 1084 (s), 1052 (s), 1028 (s), 938 (w), 910 (s), 832 (w), 760 (m)

MS: (ESI)

332.1 (21.4, M + Na^+), 322.0 (47.6), 316.1 (13.1), 310.1 (11.3), 284.2 (10.7), 227.1 (33.3) 221.2 (20.2), 210.1 (18.4), 209.1 (100.0), 131.0 (28.5)

HRMS: calcd for $C_{20}H_{23}NO_2Na^+$: 332.1621, found: 332.1627

TLC: 0.15 (hexane/EtOAc, 8:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –32.0 (c = 2.28, $CHCl_3$)

SFC: (2*S*,3*R*)-**132ea**, t_R 5.9 min (0.2%); (2*R*,3*S*)-**132ea**, t_R 8.9 min (99.8%), (Chiralpak OD, 125 bar, 6% MeOH in CO_2, 2.7 mL/min, 220 nm, 40 °C)

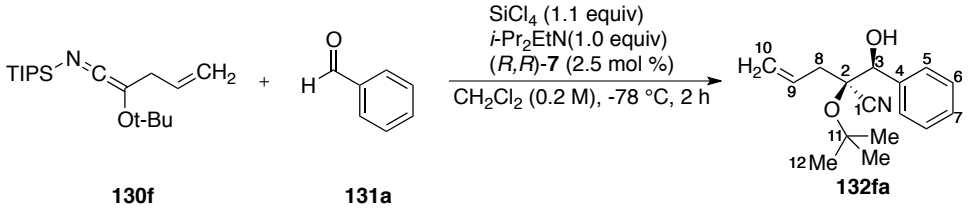
Analysis: $C_{20}H_{23}NO_2$ (309.402)

Calcd: C, 77.64; H, 7.49; N, 4.53%

Found: C, 77.38; H, 7.41; N, 4.69%

(2*R*,3*S*)-2-(*tert*-Butoxy)-3-hydroxy-2-(prop-2-ene)-3-phenylpropanenitrile (132fa)

(Table 14, entry 5)



Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 μL of benzaldehyde (1.0 mmol), 175 μL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130

µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.96 mL of a 1.35 M solution of **130f** (1.3 mmol, 1.3 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (10:1, 300 mL to 9:1, 200 mL)) and drying *in vacuo* (Abderhalden, 40 °C, 0.3 mm Hg) 224 mg of **132fa** (90%) as yellow needles. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **132fa**:

mp: 42-43 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.51 (d, *J* = 8.0 Hz, 2 H, HC(5)), 7.42 – 7.30 (m, 3 H, HC(6, 7)), 5.91 – 5.87 (m, 1 H, HC(9)), 5.26 (dd, *J* = 29.8, 13.7 Hz, 2 H, H_2C(10)), 4.73 (s, 1 H, HC(3)), 3.10 (s, 1 H, OH), 2.80 (dd, *J* = 14.9, 6.4 Hz, 1 H, H_2C(8)), 2.44 (dd, *J* = 14.9, 7.6 Hz, 1 H, H_2C(8)), 1.45 (s, 9 H, H_3C(12).

^{13}C NMR: (125 MHz, $CDCl_3$)

136.7 (C(4)), 130.8 (C(9)), 128.7 (C(7)), 128.1 (C(5, 6)), 128.0 (C(5, 6)), 120.4 (C(10)), 119.5 (C(1)), 79.2 (C(2)), 76.6 (C(11)), 76.5 (C(3)), 40.7 (C(8)), 29.6 (C(12))

IR: (KBr Pellet)

3439 (s), 3085 (m), 3063 (m), 3028 (m), 2985 (s), 2929 (m), 1643 (m), 1496 (m), 1455 (s), 1431 (m), 1394 (s), 1340 (m), 1258 (s), 1179 (s), 1148 (s), 1088 (s), 1028 (s), 1052 (s), 996 (s), 919 (s), 846 (m), 782 (m), 705 (s)

MS: (ESI)

305.2 (18.3), 283.1 (21.1), 282.1 (100.0, M + Na^+), 242.3 (8.3), 131.1 (5.4), 85.1

(4.7)

HRMS: calcd for $C_{16}H_{21}NO_2Na^+$: 282.1465, found: 282.1468

TLC: 0.19 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ – 3.9 (c = 2.1, EtOH)

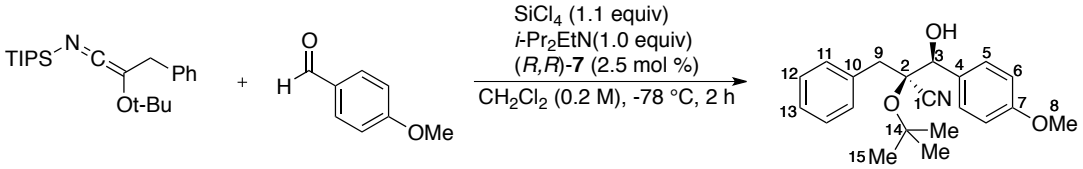
SFC: (2*R*,3*S*)-**132fa**, t_R 10.5 min (99.9%); (2*S*,3*R*)-**132fa**, t_R 11.9 min (0.1%), (Chiralpak OD, 125 bar, 2% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{16}H_{21}NO_2$ (259.343)

Calcd: C, 74.10; H, 8.16; N, 5.40%

Found: C, 74.09; H, 8.41; N, 5.57%

Preparation of (2*R*,3*S*)-2-Benzyl-2-*tert*-butoxy-3-hydroxy-3-(4-methoxyphenyl)propane-nitrile (132eb) (Table 15, entry 1)



130e **131b** **132eb**

Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 122 μL of 4-methoxybenzaldehyde (1.0 mmol), 175 μL of *N,N*-diisopropylethylamine (1.0 mmol, 1.0 equiv) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.91 mL of a 1.43 M solution of **130e** (1.3 mmol, 1.3 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (8:1, 270 mL to 6:1, 210 mL)) and drying *in vacuo* (Abderhalden, 40 °C, 0.3 mm Hg) 314 mg of **132eb** (93%) as a yellow oil. The diastereomeric ratio was determined to be 98:2 by ^{1}H NMR (500 MHz) analysis of the crude product

Data for **132eb:**

^{1}H NMR: (500 MHz, $CDCl_3$)

7.39 (d, *J* = 8.2, 1 H, HC(5)), 7.37 – 7.27 (m, 5 H, HC(11, 12, 13)), 6.88 (d, *J* = 8.2 1 H, HC(6)), 4.69 (d, *J* = 6.5, 1 H, HC(3)), 3.81 (s, 3 H, H_3C(8)), 3.27 (d, *J* = 13.4, 1 H, H_2C(9)), 3.08 – 2.85 (m, 2 H, H_2C(9) and OH), 1.29 (s, 9 H, H_3C(15))

^{13}C NMR: (125 MHz, $CDCl_3$)

159.6 (C(7)), 134.5 (C(10)), 131.0 (C(11)), 129.7 (C(4)), 129.3 (C(12)), 128.2 (C(5)), 127.3 (C(13)), 119.8 (C(1)), 113.1 (C(6)), 79.0 (C(2)), 77.2 (C(14)), 75.9 (C(3)), 55.2 (C(8)), 42.6 (C(9)), 29.4 (C(15))

IR: (neat)

3469 (s), 3066 (m), 3018 (s), 2979 (s), 2838 (m), 1612 (s), 1585 (m), 1514 (s), 1497 (m), 1455 (m), 1442 (m), 1394 (m), 1369 (m), 1304 (m), 1248 (s), 1219 (s), 1081 (s), 1033 (s), 941 (w), 908 (w), 883 (m), 745 (s), 702 (s), 680 (s)

MS: (ESI)

362.1 (100.0, M + Na^+), 357.2 (20.8), 340.2 (14.3), 266.1 (11.9), 240.1 (18.4), 239.1 (82.7), 211.1 (30.3), 180.1 (9.5), 149.1 (11.9), 91.0 (8.3)

HRMS: calcd for $C_{21}H_{25}NO_3Na^+$: 362.1727, found: 362.1738

TLC: 0.09 (hexane/EtOAc, 8:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ – 35.6 (c = 2.07, $CHCl_3$)

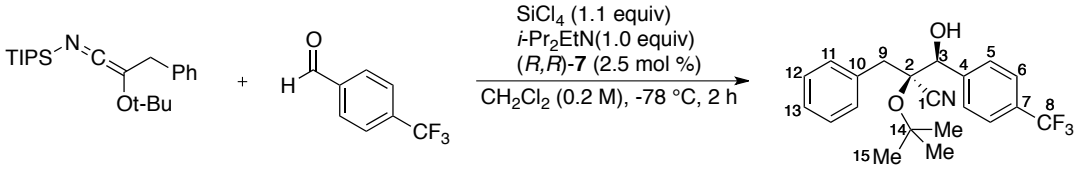
SFC: (2*R*,3*S*)-**132eb**, t_R 11.9 min (99.8%); (2*S*,3*R*)-**132eb**, t_R 13.8 min (0.2%), (Chiralpak OD, 125 bar, 4.5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{21}H_{25}NO_3$ (339.428)

Calcd: C, 74.31; H, 7.42; N, 4.23%

Found: C, 74.34; H, 7.61; N, 4.23%

Preparation of (2*R*,3*S*)-2-Benzyl-2-*tert*-butoxy-3-hydroxy-3-(4-(trifluoromethyl)phenyl) propanenitrile (132ec) (Table 15, entry 2)



Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 137 µL of 4-(trifluoromethyl)benzaldehyde (1.0 mmol), 175 µL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.90 mL of a 1.33 M solution of **130e** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (9:1, 200 mL to 8:1, 200 mL)) and drying *in vacuo* (Abderhalden, 60 °C, 0.3 mm Hg) 351 mg of **132ec** (93%) as a white solid. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **132ec**:

mp: 80 – 81 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.61 (d, *J* = 8.2, 2 H, HC(6)), 7.51 (d, *J* = 8.1, 2 H, HC(5)), 7.40 – 7.32 (m, 5 H, HC(11, 12, 13)), 4.78 (d, *J* = 7.3, 1 H, HC(3)), 3.32 (d, *J* = 13.5, 1 H, H_2C(9)), 3.10 (d, *J* = 6.9, 1 H, OH), 2.95 (d, *J* = 13.5, 1 H, H_2C(9)), 1.29 (s, 9H, H_3C(15))

^{13}C NMR: (125 MHz, $CDCl_3$)

141.6 (C(4)), 134.0 (C(10)), 131.0 (C(11)), 130.5 (q, J = 32.3, (C(7)), 128.5 (C(5,

12)), 128.4 (C5, 12), 127.6 (C(13)), 125.1 (q, J = 272, C(8)), 124.6 (q, J = 3.7, C(6)), 119.4 (C(1)), 79.4 (C(2)), 76.9 (C(14)), 75.5 (C(3)), 42.5 (C(9)), 29.4 (C(15))

IR: (KBr Pellet)

3477 (s), 3066 (w), 3033 (w), 2982 (s), 2936 (m), 2907 (m) 1620 (m), 1497 (m), 1456 (m), 1421 (m), 1396 (s), 1325 (s), 1253 (m), 1168 (s), 1130 (s), 1068 (s), 1018 (s), 960 (w), 929 (w), 907 (w), 845 (s), 826 (m), 791 (m), 704 (s)

MS: (ESI)

400.1 (29.2, M + Na^+), 390.0 (8.9), 300.2 (8.3), 295.1 (39.3), 278.1 (17.8), 277.1 (100.0), 249.1 (7.1), 222.1 (10.7), 181.1 (9.5), 149.1 (23.2), 106.1 (5.9)

HRMS: calcd for $C_{21}H_{22}NO_2F_3Na^+$: 400.1495, found: 400.1509

TLC: 0.11 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –37.5 (c = 2.13, $CHCl_3$)

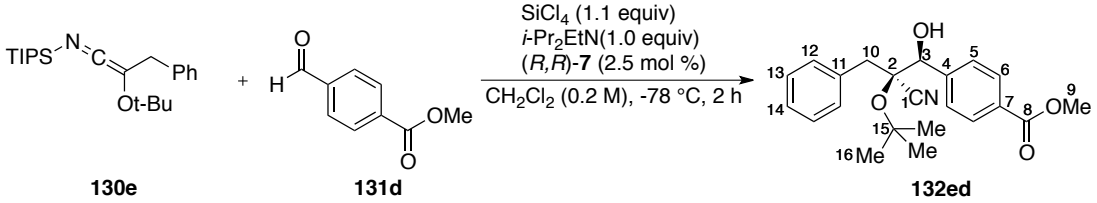
SFC: (2*R,*3*S*)-**132ec**, t_R 9.6 min (99.5%); (2*S,*3*R*)-**132ec**, t_R 11.6 min (0.5%), (Chiralpak AD, 125 bar, 2% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{21}H_{22}F_3NO_2$ (377.400)

Calcd: C, 66.83; H, 5.88; N, 3.71%

Found: C, 66.70; H, 5.86; N, 3.89%

(2*R*,3*S*)-2-Benzyl-3-(4-methoxycarbonylphenyl)-2-*tert*-butoxy-3-hydroxypropanenitrile (132ed) (Table 15, entry 3)



Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 164 mg of methyl 4-formylbenzoate (1.0 mmol), 175 μL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.90 mL of a 1.33 M solution of **130e** (1.3 mmol, 1.3 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc (6:1)) and drying *in vacuo* (Abderhalden, 40 °C, 0.3 mm Hg) 335 mg of **132ed** (91%) as a white solid. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **132ed**:

mp: 50–52 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

8.01 (d, *J* = 8.3 Hz, 2 H, HC(6)), 7.47 (d, *J* = 8.2 Hz, 2 H, HC(5)), 7.39 (d, *J* = 6.9 Hz, 2 H, HC(12)), 7.36 – 7.31 (m, 3 H, HC(13, 14)), 4.78 (d, *J* = 7.3 Hz, 1 H, HC(3)), 3.91 (s, 3 H, H_3C(9)), 3.32 (d, *J* = 13.4 Hz, 1 H, H_2C(10)), 3.19 (d, *J* = 5.1 Hz, 1 H, OH), 2.94 (d, *J* = 13.4 Hz, 1 H, H_2C(10)), 1.27 (s, 9 H, H_3C(16))

^{13}C NMR: (125 MHz, $CDCl_3$)

166.8 (C(8)), 142.8 (C(4)), 134.1 (C(11)), 131.0 (C(12)), 130.1 (C(7)), 129.0 (C(5), 128.3 (C(6, 13)), 128.2 (C(6, 13)), 127.5 (C(14)), 119.5 (C(1)), 79.2 (C(2)), 76.8 (C(15)), 75.7 (C(3)), 52.1 (C(9)), 42.6 (C(10)), 29.3 (C(16))

IR: (KBr Pellet)

3476 (s), 3064 (w), 3032 (w), 2979 (s), 1725 (s), 1612 (m), 1497 (m), 1437 (m), 1416 (m), 1394 (m), 1369 (m), 1279 (s), 1177 (s), 1085 (s), 1019 (s), 965 (w), 941 (w), 910 (w), 857 (w), 811 (w), 769 (m), 743 (m), 702 (s)

MS: (ESI)

390.1 (100.0, M + Na^+), 385.2 (22.6), 368.2 (10.1), 285.1 (72.0), 267.1 (91.1), 258.6 (20.2), 235.1 (14.9), 180.1 (14.3), 149.1 (79.7), 131.0 (14.8)

HRMS: calcd for $C_{22}H_{25}NO_4Na^+$: 390.1676, found: 390.1685

TLC: 0.04 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –55.0 (c = 1.12, $CHCl_3$)

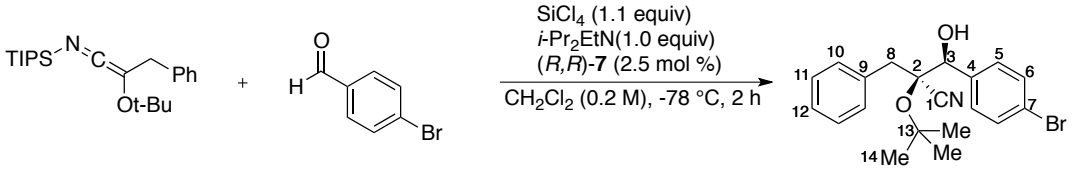
SFC: (2*R*,3*S*)-**132ed**, t_R 12.2 min (98.6%); (2*S*,3*R*)-**132ed**, t_R 17.7 min (1.4%), (Chiralpak AD, 130 bar, 4% MeOH in CO_2, 2.7 mL/min, 220 nm, 40 °C)

Analysis: $C_{22}H_{25}NO_4$ (367.438)

Calcd: C, 71.91; H, 6.86; N, 3.81%

Found: C, 72.06; H, 6.85; N, 4.00%

Preparation of (2*R*,3*S*)-2-Benzyl-3-(4-bromophenyl)-2-*tert*-butoxy-3-hydroxypropanenitrile (132ee) (Table 15, entry 4)



Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 185 mg of 4-bromobenzaldehyde (1.0 mmol), 175 µL of *N,N*-diisopropylethylamine (1.0 mmol, 1.0 equiv) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.90 mL of a 1.34 M solution of **130e** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (9:1, 300 mL to 8:1, 200 mL)) and drying *in vacuo* (Abderhalden, 40 °C, 0.3 mm Hg) 368 mg of **132ee** (95%) as a clear, colorless amorphous solid. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude

product.

Data for **132ee**:

mp: 77–78 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.48 (d, *J* = 8.5, 1 H, HC(6)), 7.40 – 7.30 (m, 5 H, HC(10, 11, 12)), 7.26 (d, *J* = 8.5, 1 H, HC(5)), 4.68 (s, 1 H, HC(3)), 3.29 (d, *J* = 13.5, 1 H, $H_2C(8)$), 3.00 (s, 1 H, OH), 2.94 (d, *J* = 13.5, 1 H, $H_2C(8)$), 1.29 (s, 9 H, $H_3C(14)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

136.7 (C(4)), 134.1 (C(9)), 131.0 (C(6, 10), 130.9 (C(6, 10), 129.8 (C(5, 11)), 128.3 (C(5, 11)), 127.5 (C(12)), 122.6 (C(7)), 119.5 (C(1)), 79.2 (C(2)), 76.9 (C(13)), 75.5 (C(3)), 42.5 (C(8)), 29.4 (C(14))

IR: (KBr Pellet)

3489 (s), 3064 (w), 3031 (w), 2975 (s) 2870 (w), 1591 (m), 1488 (m), 1454 (m), 1393 (m), 1368 (m), 1252 (m), 1174 (s), 1090 (s), 1053 (s), 1012 (s), 905 (w), 822 (m), 787 (m), 759 (m), 743 (w), 702 (s), 685 (m), 604 (m),

MS: (ESI)

412.0 (60.4), 307.0 (34.1), 289.0 (99.0), 287.0 (100.0), 222.2 (16.1), 149.1 (73.6), 131.0 (32.9)

HRMS: calcd for $C_{20}H_{22}NO_2BrNa^+$: 410.0726, found: 410.0726

TLC: 0.10 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –49.4 (c = 2.16, $CHCl_3$)

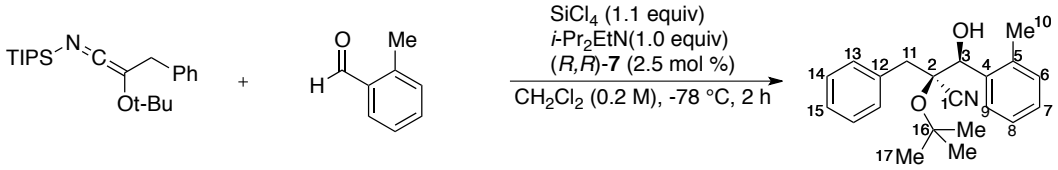
SFC: (2*R*,3*S*)-**132ee**, t_R 5.0 min (99.9%); (2*S*,3*R*)-**132ee**, t_R 6.3 min (0.1%), (Chiralpak AD, 125 bar, 8% MeOH in CO_2, 2.8 mL/min, 220 nm, 40 °C)

Analysis: $C_{20}H_{22}BrNO_2$ (388.298)

Calcd: C, 61.86; H, 5.71; N, 3.61%

Found: C, 61.78; H, 5.65; N, 3.66%

Preparation of (2*R*,3*S*)-2-Benzyl-2-*tert*-butoxy-3-hydroxy-3-(2-tolyl)propanenitrile (132ef) (Table 15, entry 5)



130e **131f** **132ef**

Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 115 µL of 2-tolualdehyde (1.0 mmol), 175 µL of *N,N*-diisopropylethylamine (1.0 mmol, 1.0 equiv) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.92 mL of a 1.31 M solution of **130e** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (10:1, 220 mL to 9:1, 300 mL)) and drying *in vacuo* (Abderhalden, 55 °C, 0.3 mm Hg) 300 mg of **132ef** (93%) as white needles. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **132ef**:

mp: 112-114 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.55 (d, *J* = 7.4, 1 H, HC(9)), 7.48 (d, *J* = 7.3, 2 H, HC(6) and HC(aryl)), 7.39 – 7.32 (m, 3 H, HC(aryl)), 7.28 – 7.17 (m, 2 H, HC(aryl)), 7.09 (d, *J* = 7.1, 1 H, HC(7)), 4.95 (d, *J* = 9.4, 1 H, (HC(3)), 3.38 (d, *J* = 13.1, 1 H, $H_2C(11)$), 3.31 (d, *J* = 13.1, 1 H, $H_2C(11)$), 3.12 (d, *J* = 9.4, 1 H, OH), 1.96 (s, 3 H, $H_3C(10)$), 1.41 (s, 9 H,

$H_3C(15)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

136.8 (C(4)), 136.3 (C(9)), 134.1 (C(12)), 130.9 (C(13)), 130.4 (C(aryl)), 128.5 (C(14)), 128.2 (C(aryl)), 127.6 (C(aryl)), 127.5 (C(aryl)), 125.4 (C(aryl)), 119.3 (C(1)), 79.4 (C(2)), 76.4 (C(16)), 70.3 (C(3)), 43.8 (C(11)), 29.7 (C(17)), 19.3 (C(10))

IR: (KBr Pellet)

3504 (s), 3056 (w), 3032 (w), 2978 (m), 2950 (m), 1496 (m), 1457 (m), 1411 (m), 1393 (m), 1366 (m), 1330 (w), 1283 (w), 1258 (m), 1181 (m), 1090 (s), 1048 (s), 909 (w), 758 (s), 727 (m), 703 (s)

MS: (ESI)

347.2 (17.1), 346.2 (69.8), 330.2 (11.2), 241.1, (11.8) 224.1 (19.5) 223.1 (100.0), 149.1 (40.2), 131.0 (43.2)

HRMS: calcd for $C_{21}H_{25}NO_2Na^+$: 346.1777, found: 346.1779

TLC: 0.16 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –7.9 (c = 1.98, $CHCl_3$)

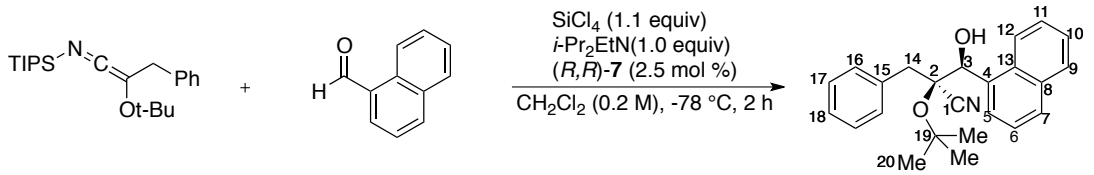
SFC: (2*R*,3*S*)-**132ef**, t_R 12.2 min (98.9%); (2*S*,3*R*)-**132ef**, t_R 14.5 min (1.1%), (Chiralpak OD, 125 bar, 2% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{21}H_{25}NO_2$ (323.429)

Calcd: C, 77.98; H, 7.79; N, 4.33%

Found: C, 78.15; H, 7.98; N, 4.48%

Preparation of (2*R*,3*S*)-2-Benzyl-2-*tert*-butoxy-3-hydroxy-3-(naphthalen-1-yl)propane nitrile (132eg) (Table 15, entry 6)



130e **131g** **132eg**

Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 136 µL of 1-naphthaldehyde (1.0 mmol), 175 µL of *N,N*-diisopropylethylamine (1.0 mmol, 1.0 equiv) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.92 mL of a 1.31 M solution of **130e** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (10:1, 220 mL to 9:1, 300 mL)) and drying *in vacuo* (Abderhalden, 55 °C, 0.3 mm Hg) 319 mg of **130eg** (89%) as a yellow solid. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **130eg**:

mp: 113–115 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.86 – 7.81 (m, 3 H, HC(7, 9, 12)), 7.59 (d, *J* = 8.6, 1 H, HC(aryl)), 7.53 (t, *J* = 7.7, 1 H, HC(aryl)), 7.48 (d, *J* = 7.0, 2 H, HC(aryl)), 7.45 – 7.31 (m, 5 H, HC(aryl)), 5.59 (d, *J* = 7.7, 1 H, HC(3)), 3.34 (d, *J* = 13.3, 1 H, H_2C(14)), 3.28 (d, *J* = 13.3, 1 H, H_2C(14)), 3.22 (d, *J* = 7.4, 1 H, OH), 1.34 (s, 9 H, H_3C(20)).

^{13}C NMR: (125 MHz, $CDCl_3$)

134.3 (C(13)), 134.2 (C(15)), 133.5 (C(4)), 131.6 (C(8)), 131.0 (C(16), 129.2 (C(aryl)), 128.7 (C(17)), 128.5 (C(aryl)), 127.6 (C(aryl)), 126.2 (C(aryl)), 125.9 (C(aryl)), 125.4 (C(aryl)), 124.7 (C(aryl)), 123.4 (C(aryl)), 119.3 (C(1)), 79.5

(C(2)), 76.9 (C(19)), 71.1 (C(3)), 44.1 (C(14)), 29.6 (C(20))

IR: (KBr Pellet)

3498 (s), 3061 (m), 3028 (m), 2980 (s), 2929 (m), 1513 (m), 1497 (m), 1455 (m), 1417 (m), 1394 (m), 1368 (s), 1271 (m), 1251 (m), 1172 (m), 1092 (s), 1063 (s), 1000 (m), 934 (w), 902 (w), 803 (w), 788 (s), 772 (s), 751 (m), 703 (s), 660 (w)

MS: (ESI)

383.2 (27.3), 382.1 (89.8), 377.2 (36.9), 360.2 (10.1), 277.1 (14.2), 260.1 (25.0), 259.1 (100.0), 149.1 (13.7), 131.0 (14.8), 91.0 (17.8)

HRMS: calcd for $C_{24}H_{25}NO_2Na^+$: 382.1777, found: 382.1775

TLC: 0.13 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +45.9 (c = 2.08, $CHCl_3$)

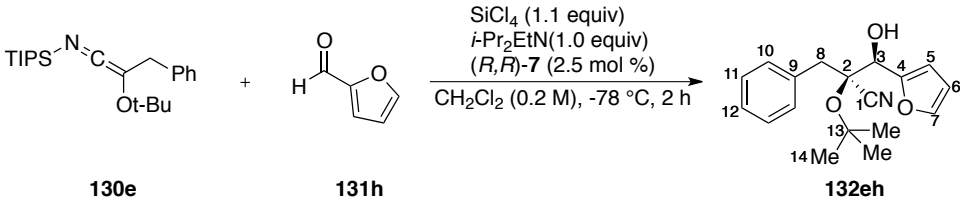
SFC: (2*S*,3*R*)-**130eg**, t_R 13.7 min (6.5%); (2*R*,3*S*)-**130eg**, t_R 17.7 min (93.5%), (Chiralpak OD, 125 bar, 8% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{24}H_{25}NO_2$ (359.461)

Calcd: C, 80.19; H, 7.01; N, 3.90%

Found: C, 80.32; H, 7.02; N, 3.88%

Preparation of (2*R*,3*S*)-2-Benzyl-2-*tert*-butoxy-3-(furan-2-yl)-3-hydroxypropanenitrile (130eh) (Table 15, entry 7)



130e **131h** **132eh**

Following General Procedure 14, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 83 μL of 2-

furaldehyde (1.0 mmol), 175 μL of *N,N*-diisopropylethylamine (1.0 mmol, 1.0 equiv) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.9 mL of a 1.33 M solution of **130e** (1.2 mmol, 1.2 equiv) in CH_2Cl_2 to yield after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (9:1, 300 mL to 8:1, 270 mL)) and drying *in vacuo* (Abderhalden, 40 °C, 0.3 mm Hg) 286 mg of **132eh** (93%) as a viscous yellow oil. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **132eh**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.46 – 7.38 (m, 3 H, HC(7) and HC(aryl)), 7.38 – 7.28 (m, 3 H, HC(aryl)), 6.44 (d, *J* = 3.3, 1 H, HC(5)), 6.40 (dd, *J* = 3.3, 1.8, 1 H, HC(6)), 4.75 (d, *J* = 7.3, 1 H, HC(3)), 3.34 (d, *J* = 13.5, 1 H, $H_2C(8)$), 3.10 (d, *J* = 13.5, 1 H, $H_2C(8)$), 2.98 (d, *J* = 7.7, 1 H, OH), 1.33 (s, 9 H, $H_3C(14)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

151.1 (C(4)), 142.2 (C(7)), 134.1 (C(9)), 131.1 (C(10)), 128.3 (C(11)), 127.5 (C(12)), 119.4 (C(1)), 110.5 (C(5)), 109.0 (C(6)), 79.2 (C(2)), 76.3 (C(13)), 71.1 (C(3)), 42.5 (C(8)), 29.3 (C(14))

IR: (NaCl plates, neat)

3459 (s), 3064 (w), 3032 (m), 2979 (s), 2937 (m), 1498 (m), 1455 (s), 1393 (m), 1368 (s), 1255 (m), 1235 (m), 1177 (s), 1149 (s), 1086 (s), 1011 (s), 935 (m), 909 (m), 885 (w), 814 (w), 787 (m), 743 (s), 701 (s)

MS: (ESI)

323.1 (25.4), 322.1 (100.0), 306.2 (10.6), 222.1 (8.9), 199.1 (11.8), 149.2 (21.3),

131.0 (23.1)

HRMS: calcd for $C_{18}H_{21}NO_3Na$: 322.1413, found: 322.1426

TLC: 0.13 (hexane/EtOAc, 8:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ –45.4 (c = 1.98, $CHCl_3$)

SFC: (2*R*,3*S*)-**132eh**, t_R 18.4 min (99.6%); (2*S*,3*R*)-**132eh**, t_R 20.6 min (0.4%), (Chiralpak OD, 125 bar, 1% MeOH in CO_2, 3 mL/min, 220 nm, 40 °C)

Analysis: $C_{18}H_{21}NO_3$ (299.364)

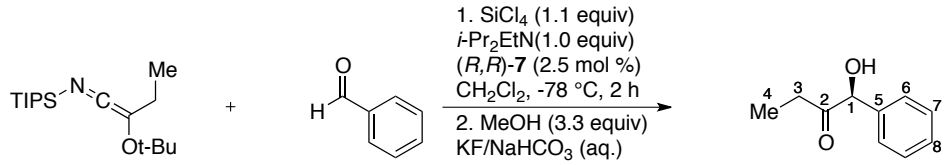
Calcd: C, 72.22; H, 7.07; N, 4.68%

Found: C, 72.27; H, 7.10; N, 4.59%

7.4.4.4 Cross-Benzoin Reactions of *N*-Silyl Oxyketene Imines.

General Procedure 15. Cross-Benzoin Reaction of *N*-Silyl Oxyketene Imines with Aromatic Aldehydes.

Preparation of (*S*)-1-hydroxy-1-phenylbutan-2-one (134ca) (Table 16, entry 1)



130c **131a** **134ca**

To a flame-dried, 10-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 μL of benzaldehyde (1.00 mmol) and 5.0 mL of anhydrous CH_2Cl_2 (0.2 M in aldehyde). The solution was stirred, cooled to -78 °C (internal) with a dry ice/acetone bath and then 35 μL of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were added via syringe to the reaction vessel. The resulting solution was stirred for 5 min at -78 °C

and then 0.75 mL of a 1.73 M solution of silyl ketene imine **130c** (1.4 mmol, 1.4 equiv) in CH_2Cl_2 was added dropwise via syringe over 3 min. The yellow reaction mixture was allowed to stir for an additional 2 h at -78 °C before 135 μL of CH_3OH was added via syringe. The quenched solution was stirred 30 min at -78 °C and then was warmed to 0 °C and was stirred for 1.5 h prior to being transferred to a 50-mL Erlenmeyer flask containing a stirred, sat. aq. solution of $NaHCO_3$ (10 mL) and KF (10 mL). The biphasic mixture was stirred vigorously for 2 h at rt and then filtered through a pad of packed Celite (ca. 7 g) in a 60-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with 10 mL of CH_2Cl_2 and 10 mL of H_2O and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the resulting organic layers were combined, washed with brine (1 x 25 mL), and dried over Na_2SO_4 (ca. 3 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil. The crude material was purified by column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (10:1, 220 mL to 8:1, 360 mL)) and kugelrohr distillation to afford 129 mg of **134ca** (79%) as a white solid.

Data for **134ca**:

mp: 39–40 °C

bp: 105–115 °C (0.95 mm Hg , kugelrohr)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.40 – 7.28 (m, 5 H, HC(6, 7, 8)), 5.09 (s, 1 H, HC(1)), 4.38 (s, 1 H, OH), 2.46 – 2.25 (m, 2 H, H_2C(3)), 1.00 (t, J = 7.3 Hz, 3 H, H_3C(4))

^{13}C NMR: (125 MHz, $CDCl_3$)

210.1 (C(2)), 138.3 (C(5)), 128.9 (C(7)), 128.6 (C(8)), 127.3 (C(6)), 79.4 (C(1)),

31.1 (C(2)), 7.6 (C(4))

IR: (neat)

3403 (s), 3085 (w), 3063 (m), 3028 (m), 2970 (s), 2935 (m), 2840 (m), 1719 (s), 1492 (s), 1452 (s), 1409 (s), 1343 (s), 1286 (s), 1218 (s), 1133 (s), 1095 (s), 1073 (s), 1019 (s), 978 (s), 859 (s), 755 (s), 700 (s), 677 (s), 624 (s)

MS: (ESI)

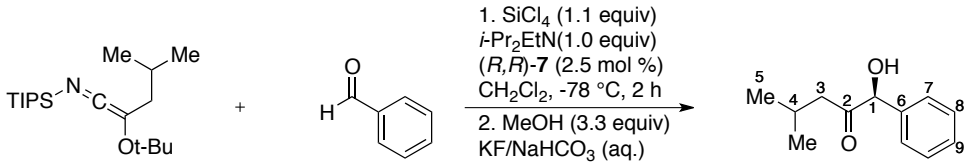
192.1 (2.1), 107.1 (100.0), 85.1 (14.8), 79.1 (29.6), 57.1 (19.0)

TLC: 0.16 (hexane/EtOAc, 7:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +389.8 (c = 2.06, $CHCl_3$)

SFC: (*R*)-**134ca**, t_R 2.5 min (1.0%); (*S*)-**134ca**, t_R 3.2 min (99.0%), (Chiralpak OB, 125 bar, 2.5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Preparation of (*S*)-1-Hydroxy-4-methyl-1-phenylpentan-2-one (134da) (Table 16, entry 2)



130d **131a** **134da**

Following General Procedure 15, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 µl of benzaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.92 mL of a 1.53 M solution of **130d** (1.4 mmol, 1.4 equiv) in CH_2Cl_2 and 135 µL of CH_3OH (3.3 equiv, 3.3 mmol) to yield, after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (12:1, 260 mL to 10:1, 220 mL)) and drying *in vacuo* (1 h at 0.5 mm Hg and 23 °C) 157 mg of **134da** (82%) as a yellow oil.

Data for **134da**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.43 – 7.28 (m, 5 H, HC(7, 8, 9)), 5.04 (s, 1 H, HC(1)), 4.40 (s, 1 H, OH), 2.27 (dd, J = 16.2, 6.7 Hz, 1 H, $H_2C(3)$), 2.17 (dd, J = 16.3, 7.0 Hz, 1 H, $H_2C(3)$), 2.09 (tq, J = 13.2, 6.7 Hz, 1 H, HC(4)), 0.87 (d, J = 6.6 Hz, 3 H, $H_3C(5)$), 0.73 (d, J = 6.6 Hz, 3 H, $H_3C(5)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

209.1 (C(2)), 137.9 (C(6)), 128.9 (C(7, 8)), 128.6 (C(9)), 127.5 (C(7, 8)), 80.0 (C(1)), 46.6 (C(3)), 24.6 (C(4)), 22.5 (C(5)), 22.2 (C(5))

IR: (KBr Pellet)

3459 (m), 3064 (w), 3031 (w), 2959 (s), 2932 (m), 2872 (m), 1713 (s), 1494 (m), 1467 (m), 1454 (m), 1387 (m), 1367 (m), 1293 (w), 1192 (m), 1170 (w), 1150 (w), 1092 (m), 1070 (m), 1036 (s), 952 (w), 925 (w), 760 (m), 700 (s)

MS: (ESI)

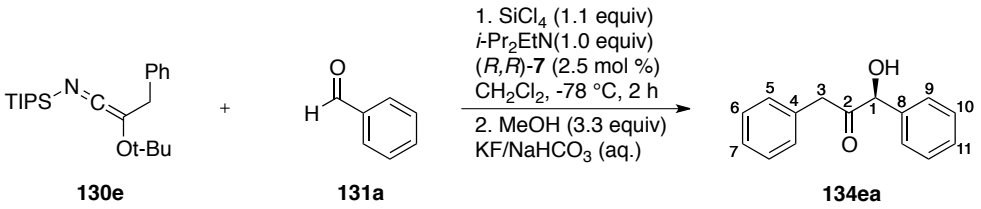
192.1 (2.1), 107.1 (100.0), 85.1 (14.8), 79.1 (29.6), 57.1 (19.0)

TLC: 0.20 (hexane/EtOAc, 7:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +317.8 (c = 1.84, $CHCl_3$)

SFC: (*R*)-**134da**, t_R 1.7 min (1.2%); (*S*)-**134da**, t_R 2.0 min (98.8%), (Chiralpak OB, 150 bar, 2.5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Preparation of (*S*)-1-Hydroxy-1,3-diphenylpropan-2-one (134ea) (Table 16, entry 3)



130e **131a** **134ea**

Following General Procedure 15, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 102 µL of benzaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.84 mL of a 1.66 M solution of **130e** (1.4 mmol, 1.4 equiv) in CH_2Cl_2 and 135 µL of CH_3OH (3.3 equiv, 3.3 mmol) to yield, after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, CH_2Cl_2/Et_2O, 40:1) and recrystallization from hot toluene (ca. 5 mL), 190 mg of **134ea** (84%) as fine, white needles.

Data for **134ea**:

mp: 128–129 °C (toluene)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.44 – 7.37 (m, 3 H, HC(6, 7, 10, 11)), 7.33 (d, *J* = 7.3 Hz, 2 H, HC(5, 9)), 7.31 – 7.23 (m, 3 H, HC(6, 7, 10, 11)), 7.02 (d, *J* = 7.2 Hz, 2 H, HC(5, 9)), 5.21 (s, 1 H, HC(1)), 4.27 (s, 1 H, OH), 3.66 (s, 2 H, H_2C(3))

^{13}C NMR: (125 MHz, $CDCl_3$)

206.9 (C(2)), 137.5 (C(8)), 132.8 (C(4)), 129.3 (C(5, 6, 9, 10)), 129.1 (C(5, 6, 9, 10)), 128.9 (C(7, 11)), 128.7 (C(5, 6, 9, 10)), 127.7 (C(5, 6, 9, 10)), 127.2 (C(7, 11)), 79.2 (C(1)), 44.6 (C(3))

IR: (KBr Pellet)

3425 (s), 3375 (s), 3063 (w), 3028 (w), 2886 (w), 1712 (s), 1652 (m), 1556 (m), 1539 (m), 1496 (m), 1450 (m), 1418 (m), 1329 (m), 1276 (m), 1230 (w), 1152 (w),

1127 (w), 1078 (m), 1042 (s), 1021 (m), 886 (w), 762 (m), 751 (m), 695 (s)

MS: (ESI)

249.1 (100.0, M + Na^+), 234.1 (10.1), 233.1 (60.9), 210.1 (8.8), 209.1 (69.2), 181.1 (8.3), 131.0 (18.3)

HRMS: calcd for $C_{15}H_{14}O_2Na^+$: 249.0886, found: 249.0884

TLC: 0.12 (hexane/EtOAc, 7:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +331.1° (c = 1.98, $CHCl_3$)

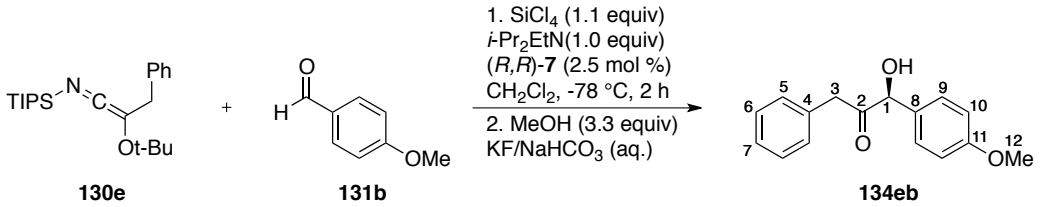
SFC: (*S*)-**134ea**, t_R 4.5 min (99.95%); (*R*)-**134ea**, t_R 5.3 min (0.05%), (Chiralpak AD, 125 bar, 10% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{15}H_{21}NO_2$ (259.343)

Calcd: C, 79.62; H, 6.24;

Found: C, 79.34; H, 6.20;

Preparation of (*S*)-1-Hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-2-one (134eb) (Table 16, entry 4)



130e **131b** **134eb**

Following General Procedure 15, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 122 µL of 4-methoxybenzaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.84 mL of a 1.66 M solution of **130e** (1.4 mmol, 1.4 equiv) in CH_2Cl_2 and 135 µL of CH_3OH (3.3 equiv, 3.3 mmol) to yield, after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, CH_2Cl_2/Et_2O, 40:1) and

recrystallization from hot toluene (ca. 5 mL), 192 mg of **134eb** (75%) as fine, white needles.

Data for **134eb**:

mp: 135–136 °C (toluene)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.32 – 7.25 (m, 3 H, HC(6, 7)), 7.23 (d, *J* = 8.6 Hz, 2 H, HC(9)), 7.03 (d, *J* = 6.6 Hz, 2 H, HC(5)), 6.94 (d, *J* = 8.7 Hz, 2 H, HC(10)), 5.16 (s, 1H, HC(1)), 4.22 (s, 1H, OH), 3.84 (s, 3 H, H_3C(12)), 3.67 (d, *J* = 15.8 Hz, 1 H, H_2C(8)), 3.63 (d, *J* = 15.7 Hz, 1 H, H_2C(8))

^{13}C NMR: (125 MHz, $CDCl_3$)

207.2 (C(2)), 160.0 (C(11)), 133.0 (C(4, 8)), 129.6 (C(4, 8)), 129.3 (C(5, 6, 9)), 129.0 (C(5, 6, 9)), 128.6 (C(5, 6, 9)), 127.2 (C(7)), 114.4 (C(10)), 78.6 (C(1)), 55.3 (C(12)), 44.5 (C(8))

IR: (KBr Pellet)

3430 (s), 3390 (s), 3063 (w), 3009 (w), 2960 (w), 2893 (w), 2838 (w), 1706 (s), 1605 (m), 1508 (m), 1464 (m), 1423 (w), 1375 (w), 1322 (w), 1255 (s), 1234 (m), 1173 (s), 1048 (s), 1030 (s), 822 (s), 761 (m), 700 (s)

MS: (ESI)

280.1 (21.3), 279.1 (100.0), 263.1 (32.5), 240.1 (15.9), 239.1 (82.8), 212.1 (10.0), 211.1 (49.1), 91.0 (11.8)

HRMS: calcd for $C_{16}H_{16}O_3Na^+$: 279.0992, found: 279.0993

TLC: 0.07 (hexane/EtOAc, 7:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +326.2 (c = 1.98, $CHCl_3$)

SFC: (*S*)-**9eb**, t_R 5.5 min (99.6%); (*R*)-**9eb**, t_R 6.5 min (0.4%), (Chiralpak AD, 150 bar,

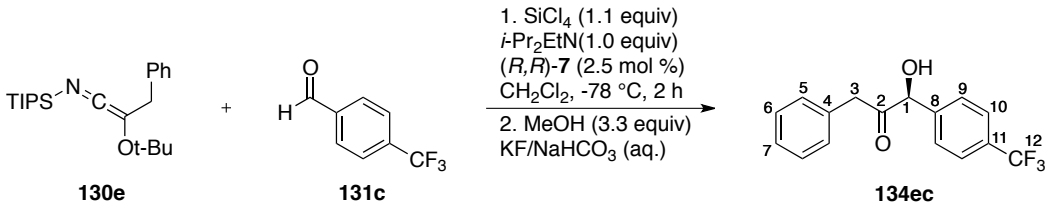
10% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{16}H_{16}O_3$ (256.109)

Calcd: C, 74.98; H, 6.29%

Found: C, 74.71; H, 6.22%

Preparation of (*S*)-1-Hydroxy-3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-2-one (9ec) (Table 16, entry 5)



Following General Procedure 15, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 137 µl of 4-(trifluoromethyl)benzaldehyde (1.0 mmol), 35 µL of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv) and 130 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.91 mL of a 1.55 M solution of **130e** (1.4 mmol, 1.4 equiv) in CH_2Cl_2 and 135 µL of CH_3OH (3.3 equiv, 3.3 mmol) to yield, after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, CH_2Cl_2/Et_2O, 40:1) and recrystallization from hot toluene (ca. 5 mL), 227 mg of **134ec** (77%) as fine, white needles.

Data for **134ec**:

mp: 139–140 °C (toluene)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.66 (d, *J* = 8.1 Hz, 2 H, HC(10)), 7.44 (d, *J* = 8.0 Hz, 2 H, HC(9)), 7.34 – 7.21 (m, 3 H, HC(6, 7)), 7.01 (d, *J* = 7.2 Hz, 2 H, HC(5)), 5.26 (s, 1 H, HC(1)), 4.33 (s, 1 H, OH), 3.67 (s, 2 H, H_2C(3))

^{13}C NMR: (125 MHz, $CDCl_3$)

206.1 (C(2)), 141.4 (C(8)), 132.4 (C(4)), 131.1 (q, J = 32.6 Hz, HC(11)), 129.3 (C(5, 6, 9)), 128.8 (C(5, 6, 9)), 128.0 (C(5, 6, 9)), 127.4 (C(7)), 126.0 (q, J = 3.7 Hz, HC(10)), 123.8 (q, J = 272.3 Hz, C(12)), 78.6 (C(1)), 44.7 (C(3))

IR: (KBr Pellet)

3426 (s), 3070 (w), 3030 (w), 2964 (w), 2902 (m), 1710 (s), 1616 (m), 1603 (w), 1496 (s), 1455 (m), 1419 (s), 1333 (s), 1233 (m), 1158 (s), 1101 (s), 1071 (s), 1042 (s), 1016 (s), 959 (w), 830 (s), 758 (s), 704 (s), 686 (m), 610 (s)

MS: (ESI)

317.0 (100.0), 301.1 (29.6), 277.0 (40.4), 275.1 (50.0), 235.1 (11.3), 227.1 (14.8), 213.1 (7.7)

HRMS: calcd for $C_{16}H_{13}O_2F_3Na^+$: 317.0760, found: 317.0757

TLC: 0.10 (hexane/EtOAc, 7:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +234.0 (c = 2.22, $CHCl_3$)

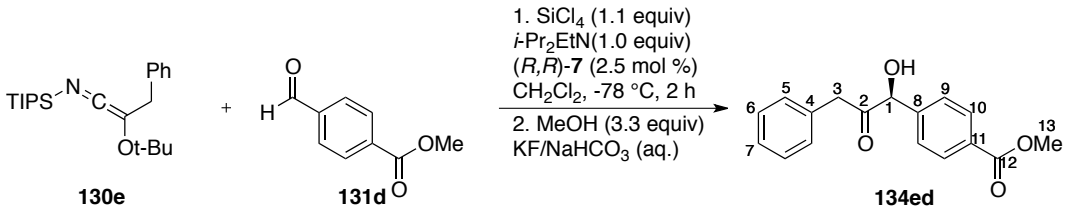
SFC: (*S*)-**134ec**, t_R 3.8 min (99.6%); (*R*)-**134ec**, t_R 4,3 min (0.4%), (Chiralpak AD, 125 bar, 7% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Analysis: $C_{16}H_{13}O_2F_3$ (294.268)

Calcd: C, 65.30; H, 4.45%

Found: C, 65.32; H, 4.64%

Preparation of Methyl (*S*)-4-(1-Hydroxy-2-oxo-3-phenylpropyl)benzoate (9ed) (Table 16, entry 6)



Following General Procedure 15, 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv), 164 mg of methyl 4-formylbenzoate (1.0 mmol), 35 μL of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv) and 130 μL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.85 mL of a 1.65 M solution of **130e** (1.4 mmol, 1.4 equiv) in CH_2Cl_2 and 135 μL of CH_3OH (3.3 equiv, 3.3 mmol) to yield, after column chromatography (25 g SiO_2 gel, ∅ 20 mm column, CH_2Cl_2/Et_2O, 35:1) and recrystallization from hot toluene, 222 mg of **134ed** (78%) as fine, white needles.

Data for **134ed**:

mp: 123–124 °C (toluene)

^{1}H NMR: (500 MHz, $CDCl_3$)

8.07 (d, *J* = 8.2 Hz, 2 H, HC(10)), 7.40 (d, *J* = 8.2 Hz, 2 H, HC(9)), 7.33 – 7.20 (m, 3 H, HC(6, 7)), 7.00 (d, *J* = 6.8 Hz, 2 H, HC(5)), 5.25 (s, 1 H, HC(1)), 4.32 (s, 1 H, OH), 3.94 (s, 3 H, H_3C(13)), 3.65 (s, 2 H, H_2C(3))

^{13}C NMR: (125 MHz, $CDCl_3$)

206.2 (C(2)), 166.5 (C(12)), 142.4 (C(8)), 132.4 (C(4, 11)), 130.6 (C(4, 11)), 130.2 (C(5, 6, 9, 10)), 129.3 (C(5, 6, 9, 10)), 128.7 (C(5, 6, 9, 10)), 127.6 (C(5, 6, 9, 10)), 127.3 (C(7)), 78.8 (C(1)), 52.2 (C(13)), 44.6 (C(3))

IR: (KBr Pellet)

3426 (s), 3029 (m), 2992 (m), 2951 (m), 2885 (m), 1718 (s), 1606 (m), 1498 (m),

1455 (s), 1441 (s), 1492 (m), 1375 (m), 1309 (m), 1278 (s), 1193 (s), 1153 (m), 1128 (s), 1112 (s), 1100 (s), 1048 (s), 1017 (s), 964 (w), 927 (w), 847 (m), 770 (s)

MS: (ESI)

308.1 (18.9), 307.1 (91.7), 302.1 (22.4), 285.1 (44.9), 268.1 (23.2), 267.1 (100.0), 239.1 (7.7), 235.0 (8.3), 131.0 (6.6)

HRMS: calcd for $C_{17}H_{16}O_4Na^+$: 307.0941, found: 307.0942

TLC: 0.06 (hexane/EtOAc, 7:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +259.9 (c = 2.26, $CHCl_3$)

SFC: (*S*)-**134ed**, t_R 5.9 min (99.6%); (*R*)-**134ed**, t_R 6.8 min (0.4%), (Chiralpak OB, 125 bar, 10% MeOH in CO_2, 2.7 mL/min, 220 nm, 40 °C)

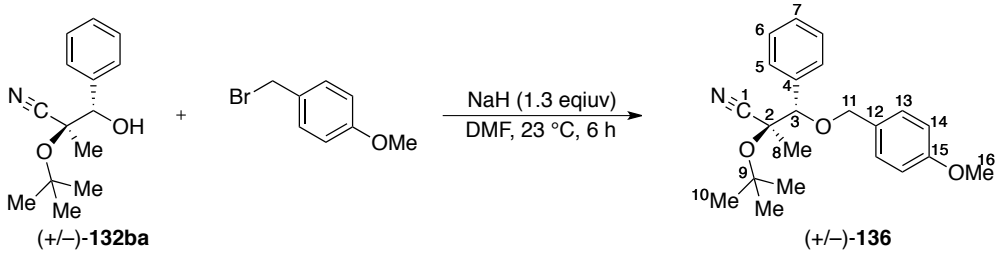
Analysis: $C_{17}H_{16}O_4$ (284.306)

Calcd: C, 71.82; H, 5.67%

Found: C, 72.10; H, 5.64%

7.4.4.5 Transformations of Glycolate Aldol Products.

Protection of Nitrile (+/–)-6ba with 4-Methoxybenzyl bromide. Preparation of (+/–)-2-(*tert*-Butoxy)-3-((4-methoxybenzyl)oxy)-2-methyl-3-phenyl Propanenitrile (136) (Scheme 54b)



To a flame-dried, 50-mL, three-necked, round-bottomed flask fitted with a magnetic stir bar, argon inlet, temperature probe and a septum were added 419 mg of nitrile **132ba** (1.80

mmol) and 7.2 mL of anhydrous dimethylformamide (0.25 M in nitrile). The clear, colorless solution was stirred, cooled to 0 °C (internal) with an ice bath, and then 56 mg of sodium hydride (2.34 mmol, 1.3 equiv) was charged into the flask portionwise over 2 min. The resulting orange, heterogeneous mixture was stirred for 25 min at 0 °C and then 0.32 mL of 4-methoxybenzyl bromide (2.16 mmol, 1.2 equiv) was added dropwise via syringe over 1 min. The orange reaction mixture was allowed to stir for 30 min at 0 °C and was then warmed to ambient temperature and stirred for an additional 5 h before being quenched by the addition of 25 mL of H_2O and 10 mL of EtOAc. The quenched solution was transferred to a 60-mL separtory where the organic layer was isolated. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the resulting organic layers were combined, washed successively with 1 M HCl (1 x 50 mL), and brine (2 x 50 mL) and then dried over $MgSO_4$ (ca. 3 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a viscous, yellow oil. The crude residue was purified by column chromatography (30 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (20:1, 210 mL to 18:1, 380 mL)) to afford 568 mg of **136** (90%) as a clear, yellow oil. Further purification by Kugelrohr distillation (120-125 °C, 0.25 mm Hg) produced 562 mg of analytically pure **136** (89%) as a clear, colorless oil. The diastereomeric ratio was determined to be 95:5 by ^{1}H NMR (500 MHz) analysis of the crude product.

This reaction has been repeated on a larger scale (7 mmol), obtained 2.4 g (95%) of **136** after column chromatography and kugelrohr distillation. Similar purity observed by ^{1}H-NMR.

Data for **136**:

bp: 120-125 °C (0.25 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.45 – 7.40 (m, 2 H, HC(5)), 7.40 – 7.33 (m, 3 H, HC(6, 7)), 7.30 (d, J = 8.5 Hz, 2

H, HC(13)), 6.89 (d, J = 8.6 Hz, 2 H, HC(14)), 4.58 (d, J = 11.3 Hz, 1 H, $H_2C(11)$), 4.50 (s, 1 H, HC(3)), 4.39 (d, J = 11.3 Hz, 1 H, $H_2C(11)$), 3.82 (s, 3 H, $H_3C(16)$), 1.42 (s, 3 H, $H_3C(8)$), 1.34 (s, 9 H, $H_3C(10)$

^{13}C NMR: (125 MHz, $CDCl_3$)

159.2 (C(15)), 135.5 (C(4)), 129.6 (C(aryl)), 129.5 (C(aryl)), 128.9 (C(12)), 128.3 (C(aryl)), 127.7 (C(aryl)), 122.2 (C(1)), 113.7 (C(14)), 84.2 (C(3)), 77.8 (C(2)), 72.8 (C(9)), 71.3 (C(11)), 55.2 (C(16)), 29.7 (C(10)), 23.0 (C(8))

IR: (KBr Pellet)

3063 (m), 3033 (m), 2978 (s), 2937 (s), 2872 (m), 2837 (m), 1613 (s), 1586 (m), 1514 (s), 1454 (m), 1393 (m), 1369 (s), 1302 (m), 1249 (s), 1174 (s), 1150 (s), 1118 (s), 1069 (s), 1034 (s), 985 (m), 823 (m), 744 (m), 700 (s)

MS: (ESI)

377.2 (21.3), 376.2 (100.0), 369.2 (14.2), 293.1 (21.3), 121.1 (18.3)

HRMS: (ESI)

calcd for $C_{22}H_{27}NO_3Na^+$: 376.1889, found: 376.1879

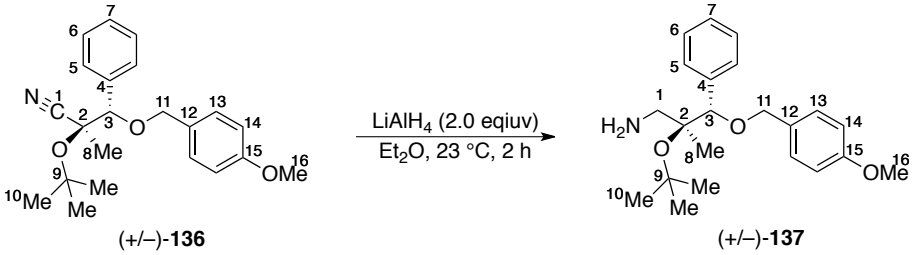
TLC: 0.15 (hexane/EtOAc, 17.5:1) [CAM]

Analysis: $C_{22}H_{27}NO_3$ (353.454)

Calcd: C, 74.76; H, 7.70; N, 3.96%

Found: C, 74.65; H, 7.97; N, 4.02%

Reduction of PMB-protected nitrile 136 with lithium aluminum hydride. Preparation of (+/-)-2-(*tert*-Butoxy)-3-((4-methoxybenzyl)oxy)-2-methyl-3-phenylpropan-1-amine (137) (Scheme 54a).



(+/–)-**136** (+/–)-**137**

To a flame-dried, 15-mL, single-necked, round-bottomed flask fitted with a magnetic stir bar, reflux condensor, argon inlet, and a septum were added 78 mg of $LiAlH_4$ (2.0 mmol, 2.0 equiv) and 0.75 mL of anhydrous Et_2O (2.6 M). The grey, heterogeneous mixture was stirred at room temperature and then a solution of 360 mg of **136** (1.0 mmol) in 1.0 mL of anhydrous Et_2O was added dropwise via cannula to the $LiAlH_4$ solution at a rate such that a gentle reflux was maintained. Upon completion of the addition, the flask containing **136** was rinsed with Et_2O (1 x 0.5 mL) and added to the round-bottomed flask. The reaction mixture was stirred for 1h 15 min at rt and was then quenched by the careful, dropwise addition of 80 µL of H_2O followed by 80 µL of 15% aq. NaOH and finally 240 µL of H_2O. The resulting thick, heterogeneous mixture was diluted with 4 mL of Et_2O, stirred vigorously for 1 h, and then was filtered through a pad of packed Celite (ca. 3 g) in a 30-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with Et_2O (3 x 10 mL) and then the filtrate was transferred to a 125-mL Erlenmeyer flask and dried over $NaSO_4$ (ca. 3 g) with stirring. The solution was filtered, concentrated *in vacuo* (40 °C, 30 mm Hg) and then purified by Kugelrohr distillation (165-170 °C, 0.20 mm Hg) to afford 343 mg of **137** (96%) as a clear, colorless oil. The diastereomeric ratio was determined to be 95:5 by ^1H NMR (500 MHz) analysis of the crude product.

Data for **137**:

bp: 165-170 °C (0.20 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.39 (d, *J* = 7.5 Hz, 2 H, HC(5)), 7.33 (t, *J* = 7.3 Hz, 2 H, HC(6)), 7.31 – 7.25 (m, 1 H, HC(7)), 7.22 (d, *J* = 8.1 Hz, 2 H, HC(13)), 6.89 (d, *J* = 8.2 Hz, 2 H, HC(14)), 4.51 (d, *J* = 11.6 Hz, 1 H, $H_2C(11)$), 4.28 (s, 1 H, HC(3)), 4.14 (d, *J* = 11.6 Hz, 1 H, $H_2C(11)$), 2.98 (d, *J* = 13.8 Hz, 1 H, $H_2C(1)$), 2.69 (d, *J* = 13.8 Hz, 1 H, $H_2C(1)$), 1.10 (s, 1 H, 2H, NH_2), 1.08 (s, 3 H, $H_3C(8)$), 1.05 (s, 9 H, $H_3C(10)$)

^{13}C NMR: (125 MHz, $CDCl_3$)

159.2 (C(15)), 139.0 (C(4)), 130.4 (C(12)), 129.6 (C(aryl)), 129.3 (C(aryl)), 127.0 (C(aryl)), 126.9 (C(aryl)), 113.8 (C(14)), 80.2 (C(2)), 80.1 (C(3)), 74.5 (C(9)), 70.2 (C(11)), 55.2 (C(16)), 48.6 (C(1)), 31.1 (C(10)), 18.5 (C(8))

IR: (KBr Pellet)

3387 (w), 3061 (m), 3031 (m), 2974 (s), 2869 (s), 2836 (m), 1612 (s), 1585 (m), 1513 (s), 1585 (s), 1465 (s), 1453 (s), 1389 (s), 1302 (s), 1248 (s), 1172 (s), 1091 (s), 1064 (s), 1036 (s), 969 (m), 824 (s), 789 (m), 741 (s), 702 (s)

MS: (ESI)

358.2 (16.6), 303.2 (27.2), 302.2 (100.0), 121.1 (48.5)

HRMS: (ESI)

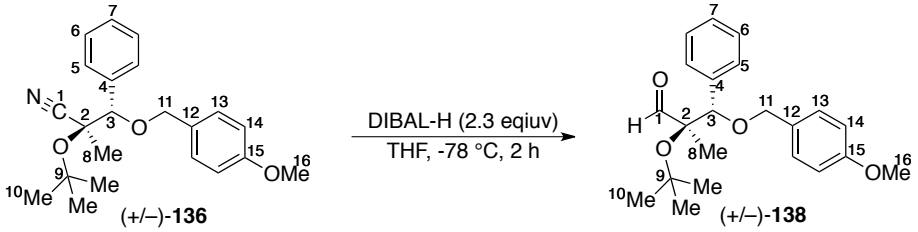
calcd for $C_{22}H_{32}NO_3^+$: 358.2377, found: 358.2386

Analysis: $C_{22}H_{32}NO_3$ (357.486)

Calcd: C, 74.16; H, 8.81; N, 3.87%

Found: C, 73.91; H, 8.74; N, 3.92%

Reduction of PMB-Protected Nitrile 136 with Diisobutylaluminum Hydride. Preparation of (+/-)-2-(*tert*-butoxy)-3-((4-methoxybenzyl)oxy)-2-methyl-3-phenylpropanal (138) (Scheme 54b).



To a flame-dried, 10-mL, Schlenk flask fitted with a magnetic stir bar, argon inlet, and a septum were added 408 mg of **136** (1.15 mmol) and 0.75 mL of anhydrous THF (1.5 M). The solution was stirred, cooled to -78 °C with a dry ice/acetone bath and then 2.3 mL of a 1.0 M solution of DIBAL-H (2.30 mmol, 2.0 equiv) in hexanes was added dropwise via syringe over 2 min. The resulting solution was stirred for 1 h at -78 °C and then allowed to warm to 0 °C and stirred for 1 h 15 min. The reaction mixture was then re-cooled to -78 °C and quenched by the addition of 3.0 mL EtOAc dropwise via syringe over 3 min. The quenched solution was allowed to warm by removal of the dry ice/acetone bath, stirred for 15 min and then was transferred to a stirred aq. sat. solution of Rochelle's salt. The biphasic mixture was vigorously stirred for 2 h at rt and then filtered through a pad of packed Celite (ca. 7 g) in a 60-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with 20 mL of EtOAc and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aqueous layer was extracted with EtOAc (3 x 25 mL) and the resulting organic layers were combined, washed successively with 1 M aq. HCl (1 x 30 mL) and brine (3 x 30 mL), and then were dried over $MgSO_4$ (ca. 3 g). The dried extracts were filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil. The crude residue was purified by Kugelrohr distillation (165-170 °C, 0.18 mm Hg) to afford 344 mg of **138** (84%) as a clear, colorless oil. The diastereomeric ratio

was determined to be 95:5 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **138**:

bp: 165-170 °C (0.18 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

9.47 (s, 1 H, HC(1)), 7.44 – 7.29 (m, 5 H, HC(5, 6, 7)), 7.14 (d, *J* = 8.3 Hz, 2 H, HC(13)), 6.86 (d, *J* = 8.6 Hz, 2 H, HC(14)), 4.50 (d, *J* = 11.7 Hz, 1 H, H_2C(11)), 4.47 (s, 1 H, HC(3)), 4.15 (d, *J* = 11.7 Hz, 1 H, H_2C(11)), 3.81 (s, 3 H, H_3C(16)), 1.19 (s, 3 H, H_3C(8)), 1.09 (s, 9 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

203.9 (C(1)), 159.2 (C(15)), 136.4 (C(4)), 129.7 (C(12)), 128.6 (C(aryl)), 127.7 (C(aryl)), 127.4 (C(aryl)), 113.7 (C(aryl)), 82.4 (C(2)), 81.0 (C(3)), 75.9 (C(9)), 70.3 (C(11)), 55.2 (C(16)), 30.9 (C(10)), 14.9 (C(8))

IR: (KBr Pellet)

3063 (w), 3032 (w), 2976 (m), 2871 (m), 2836 (m), 1739 (s), 1612 (m), 1465 (m), 1454 (m), 1391 (m), 1366 (m), 1302 (m), 1249 (s), 1174 (s), 1153 (m), 1134 (m), 1092 (s), 1066 (s), 1035 (s), 977 (w), 848 (w), 820 (m), 751 (m), 720 (s)

MS: (ESI)

380.2 (23.6), 379.2 (100.0), 374.2 (74.5), 363.2 (56.2), 326.2 (14.2), 241.1 (11.8), 195.1 (13.6), 177.1 (10.6)

HRMS: (ESI)

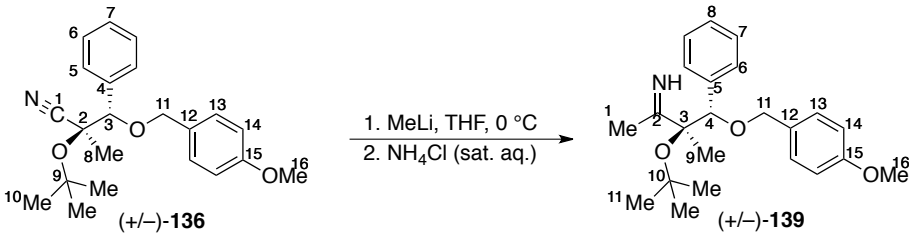
calcd for $C_{22}H_{28}O_4Na^{+}$: 379.1880, found: 379.1875

Analysis: $C_{22}H_{28}O_4$ (356.45)

Calcd: C, 74.13; H, 7.92%

Found: C, 74.27; H, 7.85%

Formation of Methyl Imines by the Addition of Methyllithium to PMB-Protected Nitrile. 136. Preparation of (+/-)-3-(*tert*-butoxy)-4-((4-methoxybenzyl)oxy)-3-methyl-4-phenylbutan-2-imine (139) (Scheme 55a).



To a flame-dried, 10-mL, Schlenk flask fitted with a magnetic stir bar, argon inlet, and a septum were added 379 mg of **136** (1.07 mmol) and 2.7 mL of anhydrous THF (0.4 M). The solution was stirred, cooled to 0 °C with a ice bath and then 1.75 mL of a 1.53 M solution of methyl lithium (2.67 mmol, 2.5 equiv) in Et_2O was added dropwise via syringe over 2 min. The resulting, bright-yellow solution was stirred for 2.5 h at 0 °C and then quenched by the careful addition of 2.0 mL of H_2O. The quenched reaction mixture was warmed to rt and was allowed to stir for 10 min prior to being transferred to a 125-mL separatory funnel solution which contained 60 mL of sat. aq. NH_4Cl solution. The biphasic mixture was vigorously shaken and then the organic layer was isolated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The resulting organic layers were combined, washed with brine (2 x 30 mL), and dried over $MgSO_4$ (ca. 3 g). The dried extracts were filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil, which was purified by Kugelrohr distillation (185-190 °C, 0.40 mm Hg) to afford 395 mg (96%) of **139** as clear, colorless oil. NMR spectra were obtained in $CDCl_3$ that had been

filtered through basic alumina to avoid hydrolysis of the imine to the ketone. The diastereomeric ratio was determined to be 95:5 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **139**:

bp: 165-170 °C (0.18 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

9.58 (br s, 1 H, NH), 7.42 (dd, *J* = 8.1, 1.2 Hz, 2 H, HC(6)), 7.38 – 7.28 (m, 3 H, HC(7, 8)), 7.17 (d, *J* = 8.7 Hz, 2 H, HC(14)), 6.86 (d, *J* = 8.7 Hz, 2 H, HC(15)), 4.40 (d, *J* = 11.1 Hz, 1 H, $H_2C(12)$), 4.24 (s, 1 H, HC(4)), 4.13 (d, *J* = 11.1 Hz, 1 H, $H_2C(12)$), 3.80 (s, 3 H, $H_3C(17)$), 2.11 (s, 3 H, $H_3C(1)$), 1.29 (s, 3 H, $H_3C(9)$), 1.07 (s, 9 H, $H_3C(11)$).

^{13}C NMR: (125 MHz, $CDCl_3$)

185.7 (C(2)), 159.1 (C(16)), 137.6 (C(5)), 130.0 (C(13)), 129.4 (C(aryl)), 129.4 (C(aryl)), 128.8 (C(aryl)), 127.3 (C(aryl)), 127.1 (C(aryl)), 113.6 (C(15)), 81.1 (C(3)), 77.2 (C(10)), 75.3 (C(12)), 71.0 (C(4))

IR: (KBr Pellet)

3227 (w), 3062 (w), 3032 (w), 2974 (s), 2917 (s), 2836 (s), 1614 (s), 1613 (s), 1586 (m), 1514 (s), 1493 (w), 1466 (m), 1453 (m), 1391 (m), 1366 (s), 1326 (m), 1302 (m), 1249 (s), 1173 (s), 1158 (s), 1124 (s), 1094 (s), 1066 (s), 1035 (s)

MS: (ESI)

370.3 (23.6), 264.2 (11.8), 209.2 (21.9), 208.1 (100.0), 191.1 (32.5), 176.1 (12.4), 121.1 (73.9)

HRMS: (ESI)

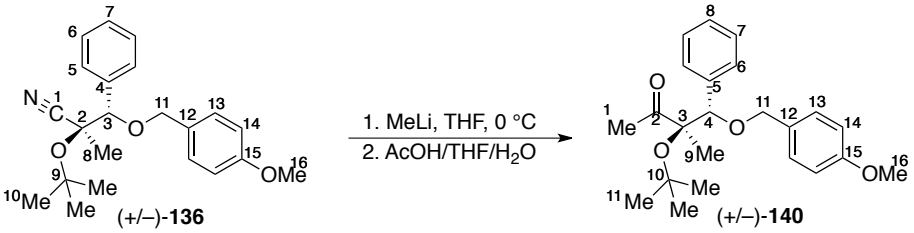
calcd for $C_{23}H_{32}NO_3^+$: 370.5076, found: 370.2381

Analysis: $C_{23}H_{31}NO_3$ (369.497)

Calcd: C, 74.76; H, 8.46; N, 3.79%

Found: C, 74.81; H, 8.68; N, 3.71%

Formation of Methyl Ketones by the Addition of Methyllithium to PMB-Protected Nitrile 136. Preparation of (+/-)-3-(*tert*-Butoxy)-4-((4-methoxybenzyl)oxy)-3-methyl-4-phenylbutan-2-one (140) (Scheme 55b).



To a flame-dried, 10-mL, Schlenk flask fitted with a magnetic stir bar, argon inlet, and a septum were added 377 mg of **136** (1.07 mmol) and 2.7 mL of anhydrous THF (0.4 M). The solution was stirred, cooled to 0 °C with a ice bath and then 1.75 mL of a 1.53 M solution of methyl lithium (2.67 mmol, 2.5 equiv) in Et_2O was added dropwise via syringe over 2 min. The resulting, bright yellow-solution was stirred for 2.5 h at 0 °C and then quenched by the careful addition of 0.75 mL of H_2O. The quenched reaction mixture was warmed to rt and allowed to stir for 5 min prior to being transferred to a 50-mL Erlenmeyer flask containing 20 mL of a stirred 4:1:1 mixture of AcOH/THF/H_2O. The biphasic mixture was vigorously stirred at rt for 5 h and was then diluted with 10 mL of EtOAc and transferred to a 125-mL separatory funnel which contained 50 mL of aq. 2 M NaOH solution. Thenorganic layer was removed and the aqueous layer was extracted with EtOAc (2 x 25 mL). The resulting organic extracts were combined, washed successively with sat. aq. $NaHCO_3$ (2 x 40 mL) and brine (2 x 40 mL) solution, and then were dried over $MgSO_4$ (ca. 3 g). The dried extracts were filtered and concentrated *in vacuo*

(40 °C, 30 mm Hg) to give a viscous, yellow oil. The crude residue was purified by column chromatography (20 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc, 12.5:1) to afford 363 mg of **140** (96%) as a clear, slight, yellow oil. Further purification by Kugelrohr distillation (170-175 °C, 0.33 mm Hg) gave 360 mg of analytically pure **140** (92%) as a clear, colorless oil. The diastereomeric ratio was determined to be 95:5 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **140**:

bp: 170-175 °C (0.33 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.43 (d, J = 7.0 Hz, 2 H, HC(6)), 7.39 – 7.31 (m, 3 H, HC(7, 8)), 7.14 (d, J = 8.6 Hz, 2 H, HC(14)), 6.86 (d, J = 8.6 Hz, 2 H, HC(15)), 4.55 (s, 1 H, HC(4)), 4.50 (d, J = 11.6 Hz, 1 H, H_2C(12)), 4.14 (d, J = 11.6 Hz, 1 H, H_2C(12)), 3.80 (s, 3 H, H_3C(17)), 2.11 (s, 3 H, H_3C(1)), 1.16 (s, 3 H, H_3C(9)), 1.07 (s, 9 H, H_3C(11))

^{13}C NMR: (125 MHz, $CDCl_3$)

212.0 (C(2)), 159.2 (C(16)), 136.9 (C(5)), 129.6 (C(14)), 129.5 (C(13)), 128.6 (C(6,7)), 127.5 (C(8)), 127.3 (C(6,7)), 113.6 (C(15)), 83.8 (C(3)), 83.2 (C(4)), 75.6 (C(10)), 70.3 (C(12)), 55.2 (C(17)), 30.4 (C(11)), 24.0 (C(1)), 16.3 (C(9))

IR: (KBr Pellet)

3062 (m), 2974 (s), 2836 (m), 1719 (s), 1612 (s), 1585 (m), 1514 (s), 1494 (m), 1454 (m), 1391 (s), 1365 (s), 1302 (m), 1249 (s), 1174 (s), 1134 (s), 1094 (s), 1065 (s), 1035 (s), 985 (m), 955 (m), 820 (s), 757 (m), 741 (s), 706 (s)

MS: (ESI)

409.2 (49.7), 393.3 (97.6), 388.3 (63.3), 377.3 (15.4), 241.2 (8.3), 122.1 (15.9),

121.1 (100.0)

HRMS: (ESI)

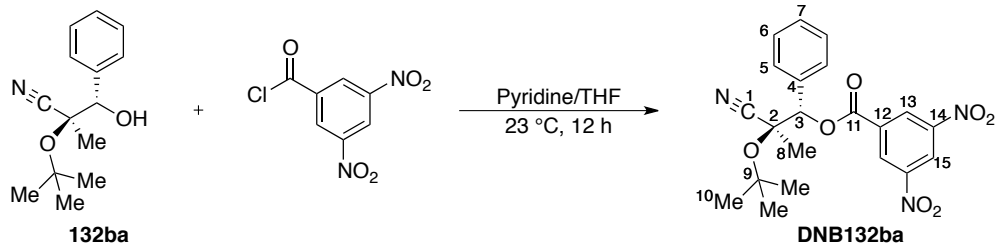
calcd for $C_{23}H_{30}O_4Na^+$: 393.2036, found: 393.2043

Analysis: $C_{22}H_{28}O_4$ (369.497)

Calcd: C, 74.56; H, 8.16%

Found: C, 74.52; H, 8.29%

Derivatization of Nitrile 6ba with 3,5-Dinitrobenzoyl Chloride for CSP-SFC Analysis. Preparation of (1*S*,2*R*)-2-(*tert*-Butoxy)-2-cyano-1-phenylpropyl 3,5-Dinitrobenzoate (DNB132ba).



132ba **DNB132ba**

To a flame-dried, 25-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 46 mg of nitrile (–)-**132ba** (0.20 mmol) and 2 mL of a 1:1 mixture of pyridine/THF (0.1 M in nitrile). The resulting homogeneous solution was stirred at ambient temperature and then 113 mg of 3,5-dinitrobenzoyl chloride (0.5 mmol, 2.5 equiv) was charged into the flask as portions over 2 min. The resulting yellow, heterogeneous reaction mixture was allowed to stir for 12 h at ambient temperature and then quenched by the addition of 5 mL H_2O followed by 15 mL of EtOAc. The quenched solution was transferred to a 60-mL separtory funnel where the organic layer was isolated. The aqueous layer was extracted with EtOAc (2 x 15 mL) and the resulting organic layers were combined, washed successively with 1 M aq. HCl (2 x 10 mL), satd aq. $NaHCO_3$ (2 x 10 mL) solution and brine (2 x 10 mL) and then dried over

$MgSO_4$ (ca. 1 g). The solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil. The crude residue was purified by column chromatography (20 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (12:1, 260 mL to 10:1, 110 mL)) to afford 83 mg of **DNB132ba** (96%) as a white foam after drying *in vacuo* for 3 h (23 °C, 0.7 mm Hg).

Data for **DNB132ba**:

mp: 100-101 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.27 – 9.23 (m, 3 H, HC(13, 15)), 7.56 (dd, *J* = 6.3, 2.6 Hz, 2 H, HC(5)), 7.45 – 7.37 (m, 3 H, HC(6, 7)), 6.09 (s, 1 H, HC(1)), 1.56 (s, 3 H, H_3C(3)), 1.40 (s, 9 H, H_3C(10))

^{13}C NMR: (125 MHz, $CDCl_3$)

161.0 (C(11)), 148.8 (C(14)), 133.3 (C(4,12)), 133.2 (C(4,12)), 129.7 (C(Aryl)), 129.4 (C(aryl)), 128.5 (C(aryl)), 128.1 (C(aryl)), 122.7 (C(15)), 119.9 (C(8)), 81.6 (C(1)), 78.8 (C(2)), 72.4 (C(9)), 29.7 (C(10)), 24.8 (C(3))

IR: (KBr Pellet)

3102 (m), 2981 (m), 2256 (w), 1743 (s), 1629 (s), 1456 (m), 1394 (w), 1369 (m), 1345 (m), 1270 (s), 1162 (s), 1120 (m), 1077 (m), 1002 (m), 912 (m), 731 (s), 703

MS: (ESI)

451.1 (23.6), 450.1 (100.0), 445.2 (24.2), 413.1 (8.3), 338.3 (11.8), 181.1 (17.7)

HRMS: (ESI)

calcd for $C_{21}H_{21}N_3O_7Na^+$: 450.1272 , found: 450.1262

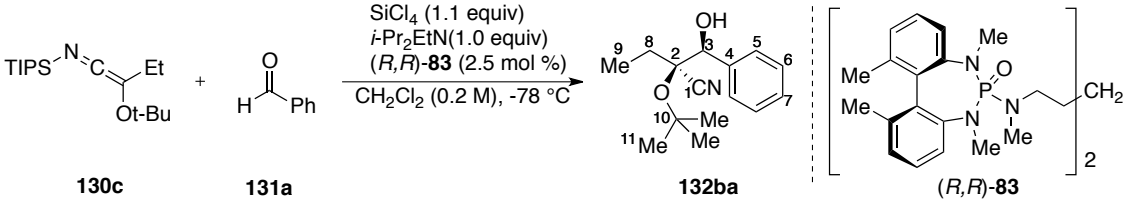
TLC: 0.18 (hexane/EtOAc, 9:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ -86.4 (c = 1.97, $CHCl_3$)

SFC: (1*S*,2*R*)-**DNB132ba**, t_R 9.8 min (99.4%); (1*R*,2*S*)-**DNB132ba**, t_R 10.6 min (0.6%), (Chiralpak OD, 125 bar, 5% MeOH in CO_2, 2.4 mL/min, 220 nm, 40 °C)

7.4.4.6 In Situ IR Kinetic Analysis for the Addition of *N*-Silyl Oxyketene Imine.

React-IR monitoring for addition of *N*-Silyl *tert*-ButoxyKetene Imine 130c with benzaldehyde catalyzed by bisphosphoramide (*R,R*)-83 [TWW-XI-51]

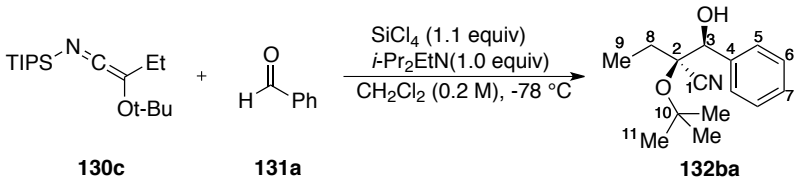


130c **131a** **132ba** (*R,R*)-**83**

An oven-dried, three necked reactor containing a stir bar and temperature probe was attached to the 10 mm DiComp React-IR probe and purged with argon for 15 minutes. The reactor was then charged with 8.8 mg of (*R,R*)-**83** (0.0125 mmol, 0.025 equiv), 3.0 mL of anhydrous dichloromethane (0.16 M) and 96 μL of diisopropylethyl amine (0.55 mmol, 1.1 mmol) . The solution was stirred, cooled to -78 °C and then a background scan of the mixture was obtained (256 scans / 16 cm^{-1} resolution / 1 gain / 1000-2000 cm^{-1} spectral window). Next, 63 μl of $SiCl_4$ (0.55 mmol, 1.1 equiv) and 51 mL (0.5 mmol, 1.0 equiv) of freshly distilled benzaldehyde was added and the reaction sequence was initiated using the React-IR software (16 scans / 30 sec interval / 16 cm^{-1} resolution / 1 gain /1000-2000 cm^{-1} spectral window). Five scans of the aldehyde were acquired and then 0.6 mL (0.6 mmol, 1.2 equiv) of a 1.02 M solution of **130c** was added via syringe in a single portion. The reaction progress was monitored by disappearance of the aldehyde band at 1702 cm^{-1} for 1 hour at -78 °C and then quenched and worked-up using same procedure as listed above (general procedure 3). The crude material was purified by column chromatography (20 g SiO_2 gel, ∅ 20 mm column, Pentane/*tert*-butylmethyl

ether, 7:1) to afford 118 mg of **132ca** as a clear-yellow liquid. The diastereomeric ratio was determined to be 98.5:1.5 by ^{1}H NMR (500 MHz) analysis of the crude product. The enantiomeric ratio was determined to be 99:1 by CSP-SFC analysis. The ^{1}H-NMR and LC data was consistent with data obtained from previous runs. Raw data is reported for reaction time (min), spectrum number and aldehyde absorbance in Table 20.

React-IR monitoring of the background reaction rate for the addition *N*-Silyl *tert*-Butoxy Ketene Imine 130c to benzaldehyde.



130c **131a** **132ba**

An oven-dried, three necked reactor containing a stir bar and temperature probe was attached to the 10 mm DiComp React-IR probe and purged with argon for 15 minutes. The reactor was then charged with 48 μL of diisopropylethyl amine (0.275 mmol, 1.1 mmol) and 1.5 mL of anhydrous dichloromethane (0.16 M). The solution was stirred, cooled to -78 °C and then a background scan of the mixture was obtained (256 scans / 16 cm^{-1} resolution / 1 gain / 1000-2000 cm^{-1} spectral window). Next, 33 μl of $SiCl_4$ (0.275 mmol, 1.1 equiv) and 25 μL (0.5 mmol, 1.0 equiv) of freshly distilled benzaldehyde was added and the reaction sequence was initiated using the React-IR software (16 scans / 30 sec interval / 16 cm^{-1} resolution / 1 gain /1000-2000 cm^{-1} spectral window). Five scans of the aldehyde were acquired and then 0.3 mL (0.3 mmol, 1.2 equiv) of a 1.02 M solution of **130c** was added via syringe in a single portion. The reaction progress was monitored by disappearance of the aldehyde band at 1702 cm^{-1} for 3 hour at -78 °C and then quenched and worked-up using same procedure as listed above (general procedure 3).

The crude material showed only minor amounts of the desired product by ^{1}H NMR. Raw data is reported for reaction time (min), spectrum number and aldehyde absorbance in Table 20.

Table 20. React-IR Data for Catalyzed and Background Rates for *N*-Silyl Oxyketene Imines.

TWW-XI-51			TWW-XI-49		
Rxn time (min)	Spectra	Abs	Rxn time (min)	Spectra	Abs
0.0	1	0.037	0.0	1	0.049
0.5	2	0.038	0.5	2	0.048
1.0	3	0.037	1.0	3	0.047
1.5	4	0.037	1.5	4	0.048
2.0	5	0.036	2.0	5	0.047
2.5	6	0.013	2.5	6	0.040
3.0	7	0.006	3.0	7	0.040
3.5	8	0.003	3.5	8	0.039
4.0	9	0.002	4.0	9	0.039
4.5	10	0.001	4.5	10	0.039
5.0	11	0.001	5.0	11	0.039
5.5	12	0.001	5.5	12	0.039
6.0	13	0.000	6.0	13	0.038
6.5	14	0.001	6.5	14	0.038
7.0	15	0.000	7.0	15	0.038
7.5	16	0.000	7.5	16	0.038
8.0	17	0.000	8.0	17	0.039
8.5	18	0.000	8.5	18	0.038
9.0	19	0.000	9.0	19	0.037
9.5	20	0.001	9.5	20	0.038
10.0	21	0.000	10.0	21	0.039
10.5	22	-0.001	10.5	22	0.037
11.0	23	0.000	11.0	23	0.038
11.5	24	-0.001	11.5	24	0.038
12.0	25	0.000	12.0	25	0.039
12.5	26	0.000	12.5	26	0.040
13.0	27	-0.001	13.0	27	0.039
13.5	28	0.001	13.5	28	0.039
14.0	29	0.000	14.0	29	0.040
14.5	30	0.000	14.5	30	0.040
15.0	31	0.000	15.0	31	0.040
15.5	32	0.000	15.5	32	0.040
16.0	33	-0.001	16.0	33	0.039
16.5	34	0.000	16.5	34	0.040
17.0	35	0.000	17.0	35	0.041
17.5	36	0.000	17.5	36	0.040

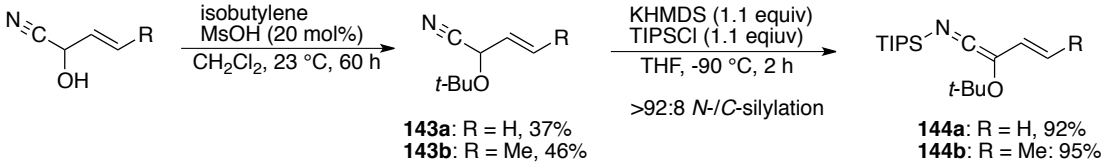
Table 20 (cont.)

18.0	37	0.000	18.0	37	0.042
18.5	38	0.000	18.5	38	0.040
19.0	39	0.000	19.0	39	0.040
19.5	40	0.000	19.5	40	0.041
20.0	41	0.000	20.0	41	0.042
21.0	42	0.000	20.5	42	0.041
21.5	43	0.000	21.0	43	0.040
22.0	44	0.000	21.5	44	0.041
22.5	45	-0.001	22.0	45	0.040
23.0	46	0.001	22.5	46	0.040
23.5	47	-0.001	23.0	47	0.041
24.0	48	-0.002	23.5	48	0.041
24.5	49	-0.004	24.0	49	0.040
25.0	50	-0.003	24.5	50	0.040
25.5	51	-0.002	25.0	51	0.041
26.0	52	-0.003	25.5	52	0.040
26.5	53	-0.003	26.0	53	0.041
27.0	54	-0.003	26.5	54	0.040
27.5	55	-0.003	27.0	55	0.041
28.0	56	-0.001	27.5	56	0.041
28.5	57	-0.002	28.0	57	0.042
29.0	58	-0.002	28.5	58	0.039
29.5	59	-0.002	29.0	59	0.040
30.0	60	-0.002	29.5	60	0.040
30.5	61	-0.001	30.0	61	0.040
31.0	62	-0.002	30.5	62	0.040
31.5	63	-0.001	31.0	63	0.040
32.0	64	-0.001	31.5	64	0.040
32.5	65	-0.002	32.0	65	0.038

Appendix A: Lewis Base Catalyzed Vinylogous Additions of N-Silyl Oxyketene Imines – Application to Homoenolate Equivalents

A.1 Proof of Principle Experiments. To examine the ability of *N*-silyl oxyketene imines to serve as homoenolate equivalents, *t*-butyl protected cyanohydrins (**143a-b**) derived from acrolein and crotonaldehyde were prepared and reacted with potassium hexamethyldisilazane and triisopropylsilyl chloride (Scheme 56). Initially, the same experimental conditions that were developed and described in Chapter 6 for the preparation of *N*-silyl oxyketene imines were employed. However, as compared to cyanohydrins derived from aliphatic aldehydes, the olefinic substrates proved to be a more sensitive class of protected cyanohydrins, requiring reduced reaction temperatures (-90 °C) to obtain ketene imines (**144a-b**) in similar yields and purities. In addition, these unsaturated nucleophiles tended to be more prone to side reactions such as hydrolysis or polymerization and greater care in the handling and storage of these reagents was required.

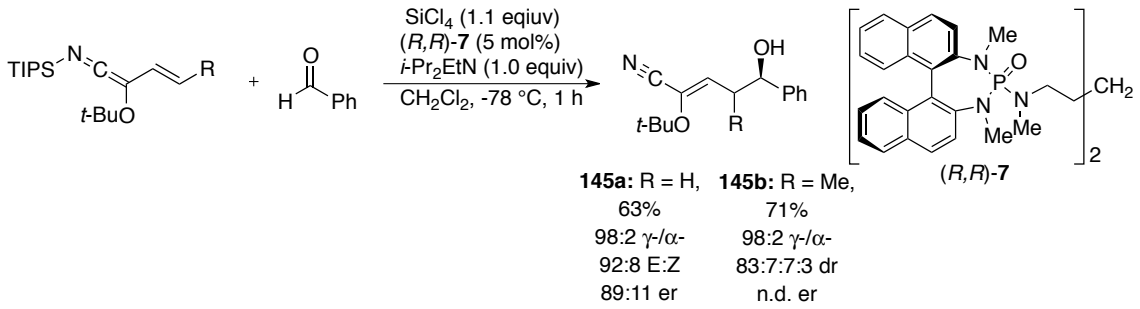
Scheme 56



Achieving homoenolate-type reactivity, with this new class of vinylogous *N*-silyl oxyketene imine, requires selective γ-addition of the nucleophile to the carbonyl group of an aldehyde. To assess the site selectivity in the addition reaction, nucleophiles **144a-b** were reacted with benzaldehyde in the presence of stoichiometric silicon tetrachloride and 5 mol % of Lewis base catalyst (*R,R*)-**1** (Scheme 57). High γ-site selectivity was observed for the addition of both vinylogous *N*-silyl oxy ketene imines and the products were isolated in moderate to good yields.

The acrolein-derived nucleophile **144a** yielded selectively the (*E*)-*t*-butyl protected enol nitrile **145a** in 92:8 *E*/*Z* ratio and 89:11 er. However, a more complex mixture of diastereomers was observed in the addition of the crotonaldehyde derived ketene imine **144b** to benzaldehyde, resulting in the isolation of *t*-butyl protected enol nitrile **145b** as a combination of both *E/Z* and *syn/anti* isomers. Unfortunately the enantiomeric ratio and identity of the major product in **145b** could not be determined due to difficulties in the separation of these isomers by either physical (*e.g.* column chromatography) or analytical (*e.g*. HPLC or SFC) means.

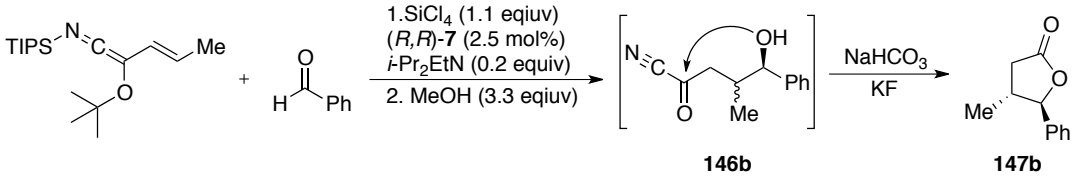
Scheme 57



To simplify the product mixtures from the homoenolate addition and allow for determination of the enantiomeric composition for the protected enol nitrile **145b**, studies aimed at the *in-situ* deprotection and cyclization of the γ-addition product were conducted. In chapter six, the capacity for *N*-silyl oxyketene imines, derived from aliphatic aldehydes, to serve as acyl anion equivalents was revealed by *in-situ* deprotection and retro-cyanation of the direct product of the aldol addition, a trichlorosilyl ether. A similar process was envisioned for vinylogous *N*-silyl ketene imines additions, wherein hydrolysis of the trichlorosilyl ether could be used for deprotection of the *t*-butyl protected enol nitrile **145**, yielding an acyl cyanide compound (**146**) after tautomerization (Scheme 58). The expected product of the reaction following basic workup

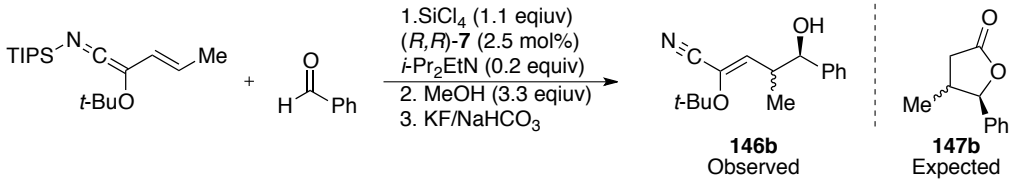
is the γ-butyrolactone **147b**, which results from intramolecular attack of the hydroxyl group and release of cyanide.

Scheme 58



To test this hypothesis crotonaldehyde derived *N*-silyl oxyketene imine **146b** was reacted with benzaldehyde and the reaction was quenched with methanol (Scheme 59). Surprisingly, the γ-addition product was cleanly isolated from the reaction mixture in similar yield and selectivity as was previously observed. The *t*-butyl protected enol ether **146b** was astonishingly resilient to deprotection, for example subjecting the isolated product to neat formic acid resulted in formylation of the free secondary alcohol, but left the *t*-butyl group intact. This observed difference in reactivity between *t*-butyl ethers and *t*-butyl enol ethers towards acidic deprotection can be attributed to the difference in basicity expected for the lone pair of oxygen hybridized in an sp^2 versus an sp^3 orbital. Although stronger acids would be able to overcome the high pK_b of *t*-butyl protected enol ethers, an alternative protecting group that would allow for a milder, in-situ deprotection was sought.

Scheme 59

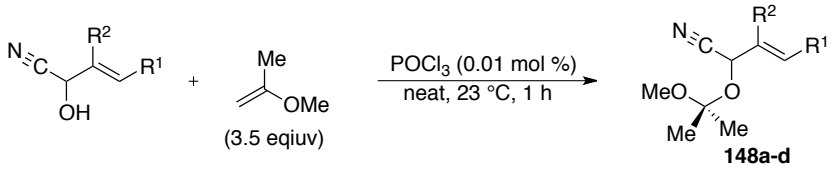


A.2 Development of a 2nd Generation Protecting Group Strategy. In evaluating protecting groups for the preparation of *N*-silyl oxyketene imines, a number of different criteria

can be considered such as: (1) sterically encumbered groups that allow for silylation at the less encumbered *N*-terminus, (2) installation under acidic conditions due to the sensitivity of cyanohydrins to basic media, (3) stability to alkyllithium and amide bases, and (4) high yielding, robust and scalable procedures for the preparation and removal of the protecting group. Studies in Chapter six on the synthesis *N*-silyl oxyketene imines established the *t*-butyl ether as a protecting group that embodied these features and allowed for the selective synthesis of the ketene imine structure. The goal of the current study was to identify a protecting group that retained the crucial elements of the *t*-butyl protecting group, but also allowed for milder acidic deprotection. For this reason, protection of the cyanohydrins with 2-methoxypropene to give methoxy isopropyl ethers (MIP-OR) was chosen.

The MIP protecting group is advantageous because it retains much of the steric bulk of the *t*-butyl group, is stable to strongly basic conditions, and is extremely labile under even mildly acidic conditions. Furthermore, the preparation of MIP protected cyanohydrins is well precedented and accomplished by simply mixing the cyanohydrin with neat 2-methoxypropene and a sub-stoichiometric amount of acid catalyst.[103] Following this method a number of different MIP protected unsaturated cyanohydrins (**148a-d**) were prepared in high yield (Table 21).

Table 21. Synthesis of MIP Protected Cyanohydrins Derived from α,β-Unsaturated Aldehydes

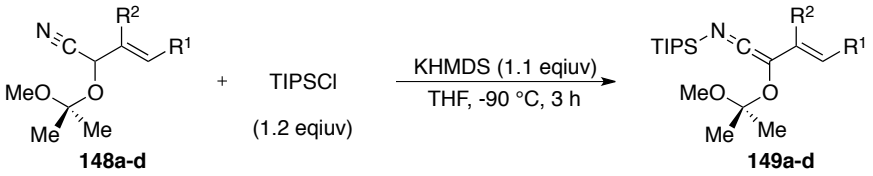


entry	R^1	R^2	Product	Yield (%)[b]
1	H	H	**148a**	90
2	Me	H	**148b**	86
3	Et	H	**148c**	89
4	H	Me	**148d**	82

[a] Reactions employed 4.0 equiv of 2-methoxypropene and 0.02 mol% of phosphorus oxychloride for 1 h at 23 °C. [b] Yield of distilled products.

A.3 Synthesis of MIP Protected *N*-Silyl Oxyketene Imines. The reaction of cyanohydrins with 2-methoxypropene provided a robust and reliable route to MIP protected cyanohydrins, which presented significant advantages over the previously employed *t*-butyl protection in terms of yield and operation. However, it was unclear if the MIP protecting group would allow for the selective synthesis of *N*-silyl oxyketene imine isomer over the more thermodynamically favored *C*-silylated product. To study the product ratios for this reaction, the MIP protected cyanohydrins **148a-d** were reacted with KHMDS and TIPSCl under the conditions previously optimized for *t*-butyl protected cyanohydrins. Pleasingly, the MIP protected cyanohydrins yielded the *N*-silyl ketene imines **149a-d** with selectivities and yields identical to those obtained with *t*-butyl protected cyanohydrins (Table 22).

Table 22. Synthesis of N-Silyl Oxyketene Imines from MIP-Protected Cyanohydrins



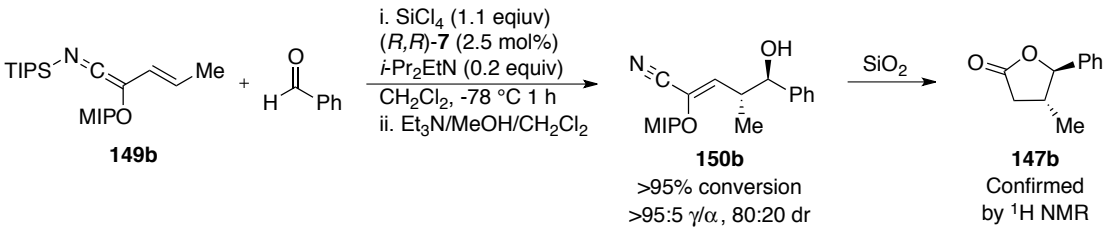
entry	R^1	R^2	Product	Yield (%)[b]
1	H	H	**149a**	90
2	Me	H	**149b**	86
3	Et	H	**149c**	89
4	H	Me	**149d**	82

[a] Reactions employed 1.1 equiv of KHMDS, 1.2 equiv of TIPSCl in THF (0.2 M) at -90 °C for 2 h. [b] Yield reported for crude products after 12 h under high vacuum.

A.4 Development of Lewis Base Catalyzed Homoenolate Additions. With a reliable method for the preparation of MIP protected *N*-silyl oxyketene imines identified, focused shifted towards developing Lewis base catalyzed homoenolate additions of these vinylogous ketene imines. Initial studies examined the addition to SKI **148b** to benzaldehyde under standard reaction conditions and using a basic quench method to allow for isolation of the MIP protected enol nitrile (Scheme 60). Analysis of the crude reaction by ^{1}H NMR showed clean conversion to

nitrile **150b** with high selectivity for γ–addition and in moderate diastereoselectivity. Interestingly, attempts to purify the MIP protected enol nitrile **150b** by column chromatography resulted in isolation of the desired γ-lactone **147b**, demonstrating the sensitivity of the MIP protecting group to acidic media. The serendipitous discovery of γ-lactone **147b** provided a proof principle for the ability of silyl ketene imines to act as homoenolate equivalents and the next goal was to determine a one-pot procedure for obtaining these homoaldol lactone products in good yields.

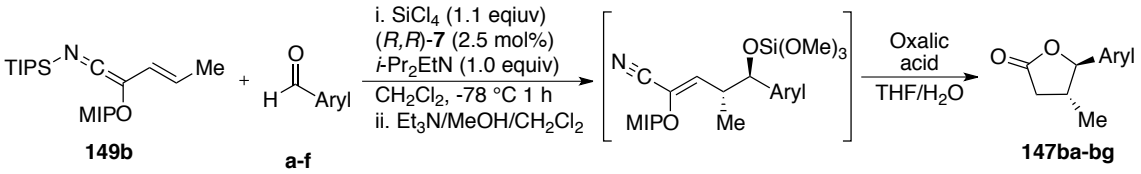
Scheme 60



A.5 Aldehyde Survey in Lewis Base Catalyzed Homoenolate Additions. Given the lability of the MIP protected enol nitrile to acidic conditions, we envisioned that a mild acidic workup would allow for the isolation of the lactone products directly. To test this hypothesis crotonaldehyde derived ketene imine **149b** was reacted with benzaldehyde in the presence of $SiCl_4$ and (*R,R*)-7, quenched with a 3:1 solution of Et_3N and MeOH at low temperature and then poured into an acidic aqueous solution of oxalic acid in THF. Gratifyingly, this modified workup procedure resulted in the isolation of γ-lactone **147b** in good yield, moderate diastereoselectivity and high enantioselectivity (Table 23, entry 2). On the basis of this promising result other aromatic aldehydes were examined to establish the generality of the homoenolate addition with respect to the aldehyde structure. Various electron-rich, electron-poor and hindered aromatic aldehydes were investigated and overall the γ-lactone products were isolated in good yield,

moderate diastereoselectivity and good enantioselectivity (Table 23). Electron-neutral aromatic aldehydes such as benzaldehyde and 2-naphthaldehyde underwent addition in high yields and good enantioselectivities (Table 23, entries 1-2). Electron-rich aromatic aldehydes exhibited the highest enantiomeric ratios, for example the addition of SKI **149b** to 4-methoxybenzaldehyde gave lactone **147bd** in 97:3 er (Table 23, entry 4). Alternatively, electron poor aromatic aldehydes reacted with attenuated enantioselectivities, consistent with a competitive achiral background (Table 23, entry 9-10). The addition of SKI **149b** to the sterically hindered aldehyde, 1-naphthaldehyde occurred with slightly reduced enantioselectivity; however, slightly less hindered aromatic aldehydes such as 2-methyl benzaldehyde yielded γ-lactone **147bf** with an improved enantiomeric ratio of 94:6.

Table 23. Aromatic Aldehyde Survey in the Addition of *N*-Silyl Oxyketene Imine **149b**[a]



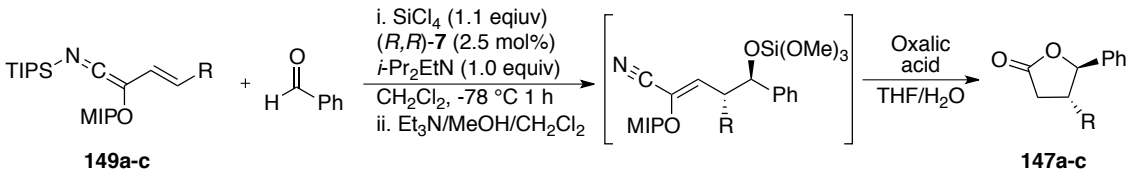
Entry	Aryl	Product	Yield %[b]	dr[c]	er[d]
1	C_6H_5 (**a**)	**147ba**	98	4:1	96:4
2	2-naphthyl (**b**)	**147bb**	98	4:1	92.5:7.5
3	4-$CF_3C_6H_4$ (**c**)	**147bc**	80	4:1	82:18
4	4-BrC_6H_4 (**d**)	**147bd**	93	4:1	98.9:1.1
5	4-$CH_3OC_6H_4$ (**e**)	**147be**	78	4:1	96.5:3.5
6	2-$CH_3C_6H_4$ (**f**)	**147bf**	76	4:1	93:7
7	1-napthyl (**g**)	**147bg**	67	4:1	87.5:12.5

[a]Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of silyl ketene imine, 1.0 equiv of *i*-Pr_2EtN, 0.05 equiv of (*R*,*R*)-**7** at 0.20 M in CH_2Cl_2 at –78 °C for 2h. [b]Yield of chromatographically homogeneous material. [d]Determined by ^1H NMR Analysis on the crude mixture. [d]Determined by CSP-SFC for the major *anti* product.

A.6 Nucleophile Survey in Lewis Base Catalyzed Homoenolate Additions. The first survey of nucleophile structure examined the unsubstituted silyl oxyketene imine **149a** derived from acrolein. In this case, the γ-lactone **147ac** was isolated in moderate yield and with reduced

enantiomeric ratio as compared to additions with mono-substituted ketene imine **149b** (Table 24, compare entries 1 and 2). The diminished enantioselectivities observed for this addition could be resulting from a competitive background reaction for this less-hindered and more reactive nucleophile. Not surprisingly, the ethyl substituted ketene imine **149c** underwent addition to benzaldehyde to give lactone **147ca** in similar diastereo- and enantioselectivity as was observed for the methyl substituted ketene imine **149b** (Table 24, entry 3).

Table 24. Survey of *N*-Silyl Oxyketene Imines in the Addition to Benzaldehyde[a]



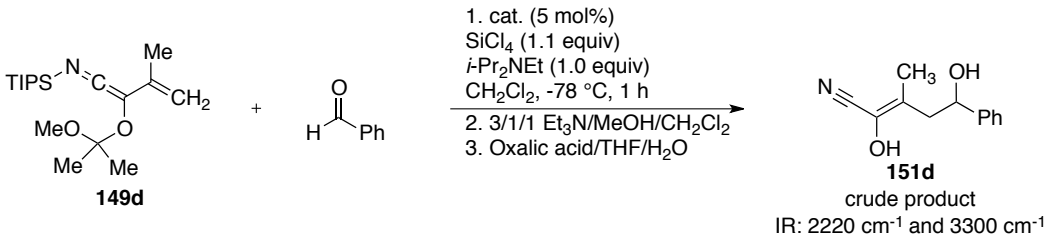
Entry	R^1	Product	Yield %[b]	dr[c]	er[d,e]
1	H	**147a**	50	n/a	88:12
2	Me	**147b**	98	4:1	96:4
3	Et	**147c**	85	4:1	93:7

[a]Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of silyl ketene imine, 1.0 equiv of *i*-Pr_2EtN, 0.05 equiv of (*R*,*R*)-**7** at 0.20 M in CH_2Cl_2 at –78 °C for 2h. [b]Yield of chromatographically homogeneous material. [d]Determined by ^1H NMR Analysis on the crude mixture. [d]Determined by CSP-SFC for the major *anti* product where applicable. [e]The *R* absolute configuration assigned by comparison of the optical rotation for **147a** to literature values, all others by analogy.[104]

Continuing to explore the scope in the homoenolate addition with respect to the nucleophile structure MIP protected silyl ketene imine **147d** derived from a α–substituted aldehyde was examined. This nucleophiles underwent a highly site selective γ-addition with benzaldehyde, but did not undergo cyclization to the desired lactone. Instead the unprotected enol nitrile **151** was isolated from the crude reaction mixtures (Scheme 61). Spectroscopic support for this surprising product was corroborated by IR studies that showed the characteristic nitrile and alcohol stretch. The reluctance of enol nitrile **151** to undergo tautomerization and subsequent cyclization to the lactone could result from the additional ground state stabilization

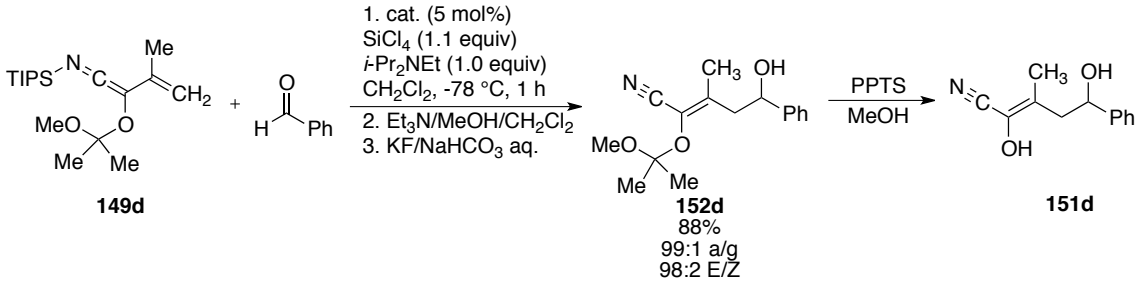
energy, imparted by tetra-substituted double bond. The enol nitrile **151d** was not stable to column chromatography and only resulted in isolation of minor amounts of the desired γ-lactone.

Scheme 61



To gain further support for the formation of enol nitrile **151d**, the homoenolate addition with benzaldehyde was rerun and quenched under basic conditions resulting in the formation of the MIP protected nitrile product **152d**. Purification of the crude reaction mixture with SiO_2 gel deactivated with Et_3N allowed for the isolation of clean material in 88% yield and with only minor amounts of acidic deprotection (<2% by ^1H NMR). Subsequent treatment of the protected nitrile **152d** with catalytic amounts of PPTS in MeOH yielded the same enol nitrile intermediate **151d** as had been previously observed, and provided additional support for this unusually stable compound (Scheme 62).

Scheme 62

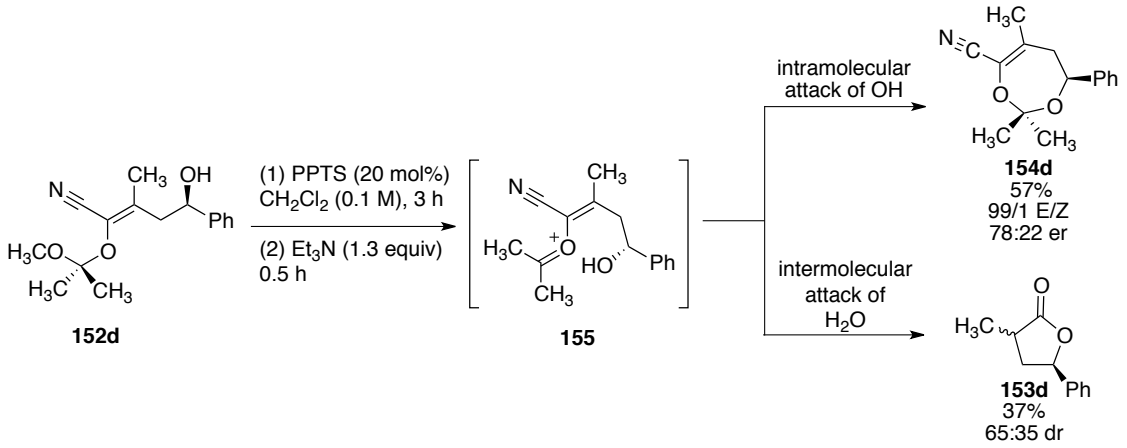


Clearly the unprotected enol nitrile **151d** was stable under mildly acidic conditions and not prone to undergo tautomerization/lactonization. As a final attempt to achieve cyclization of

this substrate class we envisioned that treatment of the unprotected enol nitrile with strong base would trigger retrocyantion and subsequent lactonization. To test this hypothesis the MIP protected enol nitrile **152d** was treated with 20 mol% of PPTS in dichloromethane for 3 h and then quenched with excess Et_3N. Examination of the ^1H NMR for the crude reaction mixture showed a 60:40 mixture of the desired lactone **153d** and a new unknown product that had clearly retained the *gem*-dimethyl substituents of the MIP protecting group (Scheme 63). Separation of the desired lactone and unknown product by column chromatography allowed for characterization and assignment of the pure samples. Interestingly, the spectroscopic data collected for the unknown intermediate all supported formation of the cyclic ketal **154d**, resulting from intramolecular cyclization of the hydroxyl group onto the oxocarbenium intermediate **155**. Formation of this interesting cyclic ketal product can be rationalized by realizing that the acidic deprotection conditions employed in this case were fairly anhydrous, allowing for an intramolecular ketal exchange. Adventitious water present in the media (from the PPTS or solvent) would have resulted in formation of the fully deprotected enol nitrile **151d**, which would explain the isolation of lactone products upon treatment with Et_3N. These observation suggest that it would be possible to achieve the desired γ-lactone by deprotection of the MIP protected nitrile followed by basic work-up; however, the conditions would require addition of at least 1 equiv of H_2O to avoid competitive cyclic ketal formation in the acidic deprotection step. Unfortunately, analysis of the enantiomeric ratio for the cyclic ketal product by SFC revealed a moderate enantioselectivity for the addition of *N*-silyl ketene imine **149d** to benzaldehyde. Furthermore, the low diastereoselectivity observed for the γ-lactone **153d**, suggests that in situ protonation of the enol nitrile is not very selective. For these reasons, further

investigation into developing a direct procedure for obtaining the γ-lactone from this product class was terminated.

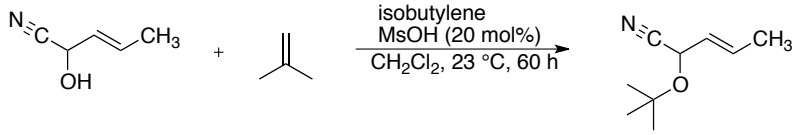
Scheme 63



A.7 Conclusions and Outlook. In conclusion, the Lewis base catalyzed homoenolate addition of *N*-silyl oxyketene imine derived from α,β-unsaturated aldehydes has been described. Key to the development of this method was utilization of 2-methoxypropene for the protection of the unsaturated cyanohydrins. This more labile protecting group allowed for the facile deprotection of the protected enol nitrile products resulting from selective γ-addition of the silyl ketene imines to aromatic aldehydes. The major limitations to this method were the poor diastereoselectivity observed for substituted ketene imines, the reduced enantiomeric ratio observed with electron-poor aromatic aldehydes and the lack of generality to structural variations in the *N*-silyl oxyketene imines. Future work should focus on other classes of protecting groups to allow for higher diastereoselectivity in the addition step.

A.8 Experimental Procedures

General Procedure 13. *tert*-Butyl Protection of Cyanohydrin with Isobutylene. Preparation of (*E*)-2-(*tert*-butoxy)pent-3-enenitrile (143b) (Scheme 56)



To a 250-mL Parr shaker bottle with a Teflon screw cap and O-ring was added 100 g (1.8 mol, 22 equiv) of liquefied isobutylene (condensed at -78 °C using a two-neck 500-mL flask and a dry-ice condenser) and 20 mL of CH_2Cl_2. The mixture was cooled to 0 °C (ice bath) and 7.97 g (82.11 mmol) of crotonaldehyde cyanohydrin as a solution in 20.6 mL CH_2Cl_2 (4.0 M) was added via cannula. The shaker bottle was capped and inverted several times to achieve a clear, colorless homogenous solution and then was cooled to -78 °C (dry ice/acetone bath) and 0.5 mL (8.2 mmol, 0.1 equiv) of methanesulfonic acid was slowly added over 2 min via syringe. The shaker bottle was then tightly sealed with the screw cap, connected to a Parr shaker and shook for 60 h at 23 °C. The resulting clear, yellow solution was removed from the Parr shaker, re-cooled to -78 °C, and the pressure was carefully released in a well-ventilated hood. The cold reaction mixture was quenched by transferring it to a 1-L beaker containing a pre-cooled (0 °C, ice bath), stirred solution of 150 mL satd aq. $NaHCO_{3\ (aq)}$. The shaker bottle was rinsed with diethyl ether (2 x 50 mL) and the washes were added to the beaker. The quenched mixture was stirred for 1 h at 0 °C and then was warmed to ambient temperature and stirred for an additional 3 h. The resultant biphasic mixture was poured into a 1-L separatory funnel and the organic layer was isolated. The aqueous layer was extracted with diethyl ether (2 x 100 mL) and then the organic extracts were combined, washed with brine (3 x 75 mL), and dried over $MgSO_4$ (ca 7.5 g). The solution was filtered and the volatiles were removed by distillation at ambient pressure

(bp 30 –45 °C) to give 8.1 g of a clear yellow liquid. The crude mixture was purified by vacuum distillation over dried K_2CO_3 (0.75 g) to afford 4.1 g (32%) of **xx** as a clear, colorless liquid.

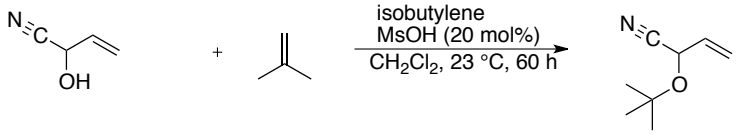
Data for **143b**:

bp: 70 - 72 °C (10 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

6.03 (dqd, *J* = 14.6, 6.6, 1.3 Hz, 1H), 5.50 (dddd, *J* = 7.2, 5.1, 3.3, 1.6 Hz, 1H), 4.71 (d, *J* = 5.6 Hz, 1H), 1.76 (dt, *J* = 6.6, 1.4 Hz, 3H), 1.30 (s, 9H)

Preparation of 2-(*tert*-Butoxy)butanenitrile (143a) (Scheme 56)



x (22 equiv) x

Following General Procedure 13, 2.34 g (28.0 mmol) of acrolein cyanohydrin was combined with a 42 g of isobutylene (28 equiv, 749 mol) and 0.46 mL of methanesulfonic acid (0.4 equiv, 30.3 mmol) in a Parr shaker bottle to afford 1.4 g of **3c** (36%) as a clear, colorless liquid after vacuum distillation from K_2CO_3.

Data for **143a**:

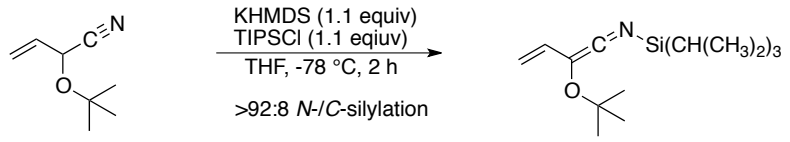
bp: 50 - 55 °C (15 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

5.84 (ddd, *J* = 17.0, 10.2, 4.8 Hz, 1H), 5.61 (dd, *J* = 17.0, 1.6 Hz, 1H), 5.39 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.78 (dt, *J* = 4.8, 1.6 Hz, 1H), 1.32 (s, 9H)

General Procedure 14. Preparation of α-*tert*-Butoxy *N*-Silyl Ketene Imines.

Preparation of *N*-(2-(*tert*-butoxy)buta-1,3-dien-1-ylidene)-1,1,1-triisopropylsilanamine (144a) (Scheme 56)



143a **144a**

To a flame-dried, 50-mL, single-necked, Schlenk flask fitted with a magnetic stir bar, argon inlet and septum was added 576 mg of KHMDS (7.0 mmol, 1.2 equiv) and 3.0 mL of anhydrous THF (1.0 M in KHMDS). The solution was stirred at rt until a homogeneous solution resulted and then was cooled to -90 °C (internal) with a liq. N_2/pentane bath. The reaction mixture was stirred at -78 °C for 5 min and then a solution of 0.34 g *tert*-butoxy nitrile **143a** (5.86 mmol) and 0.56 mL (5.03 mmol, 1.1 equiv) TIPSCl in 3.0 mL of anhydrous THF (~0.5 M solution in nitrile) was added dropwise via cannula over 10 min. The resulting bright-yellow reaction mixture was stirred for 2 h at -90 °C and then was allowed to warm to 0 °C and was stirred for 5 min during which time the color changed from yellow to orange. The reaction mixture was concentrated under high vacuum (0.5 mm Hg) and the resulting thick, orange gel (ca. 3 mL) was taken up in 20 mL of anhydrous hexanes (20 mL) and was stirred vigorously under argon. The heterogeneous solution was opened to air and filtered through a pad of packed Celite (ca. 5 g) using a 30-mL, glass-sintered Buchner funnel and then was collected into a flame-dried, weighed 50-mL, round-bottomed flask. The filter cake and Schlenk flask were further washed with 15 mL of anhydrous hexanes. The clear, orange filtrate was concentrated under vacuum (0.5 mm Hg) and then was stirred under high vacuum (0.2 mm Hg) for 12 h at

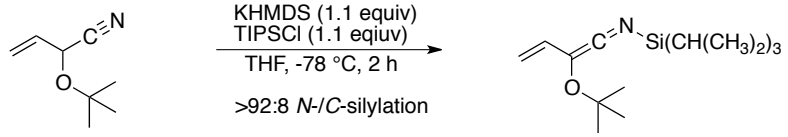
ambient temperature to afford 651 mg (92%) of **144a** as an orange liquid, which was used in subsequent reactions without further purification.

Data for **144a**:

^{1}H NMR: (500 MHz, C_6D_6)

6.44 (dd, J = 16.4, 10.7 Hz, 1H), 5.27 (dd, J = 16.9, 2.1 Hz, 1H), 4.82 (dd, J = 10.7, 1.7 Hz, 1H), 1.34 (s, 9H), 1.00 (d, J = 4.5 Hz, 21H)

Preparation of (*E*)-*N*-(2-(*tert*-butoxy)penta-1,3-dien-1-ylidene)-1,1,1-triisopropylsilanamine (144b) (Scheme 56)



143a **144a**

Following General Procedure 14, KHMDS (0.58 g, 2.9 mmol, 1.1 equiv) in 6.0 mL THF and a solution of *tert*-butoxy nitrile **143b** (0.4 g, 2.6 mmol, 1.0 equiv), TIPSCl (0.63 mL, 2.9 mmol, 1.1 equiv) in 5.0 mL THF were combined to afford 1.28 g (94%) of **144b** as an orange liquid, which was used without further purification.

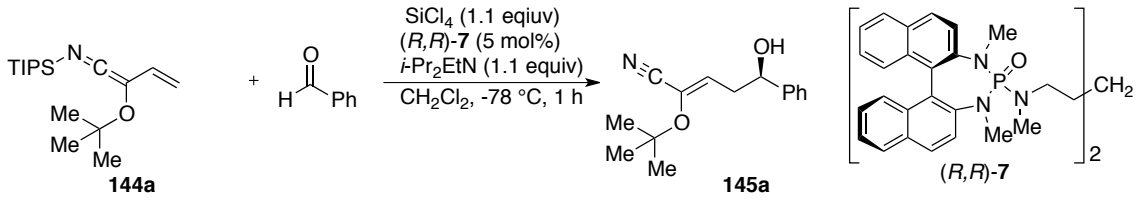
Data for **144b**:

^{1}H NMR: (500 MHz, C_6D_6)

6.10 (ddd, J = 14.9, 3.0, 1.4 Hz, 1H), 5.60 (dq, J = 14.9, 6.7 Hz, 1H), 1.83 (dd, J = 6.7, 1.5 Hz, 3H), 1.35 (s, 9H), 1.04 (dd, J = 7.0, 3.8 Hz, 21H)

General Procedure 15. Homoenolate Addition of *N*-Silyl *tert*-Butoxy Ketene Imines with Benzaldehyde

Preparation of (*R*,*Z*)-2-(*tert*-butoxy)-5-hydroxy-5-phenylpent-2-enenitrile (145a) (Scheme 57)



To a flame-dried, 10-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 10.5 mg of (*R,R*)-**7** (0.0125 mmol, 0.025 equiv), 31 μL of benzaldehyde (0.3 mmol) and 1.5 mL anhydrous CH_2Cl_2 (0.2 M in aldehyde). The solution was stirred, cooled to -78 °C (internal) with a dry ice/acetone bath and then 52 μL of *N,N*-diisopropylethylamine (0.33 mmol, 1.1 equiv) and 37 μL of $SiCl_4$ (0.33 mmol, 1.1 equiv) were added via syringe to the reaction vessel. The resulting solution was stirred for 5 min at -78 °C and then 0.24 mL of a 1.9 M solution of silyl ketene imine **144a** (0.45 mmol, 1.5 equiv) in dichloromethane was added dropwise via syringe over 3 min. The yellow reaction mixture was allowed to stir for an additional 2 h at -78 °C before 0.4 mL of a 2:1:1 mixture of Et_3N/CH_2Cl_2/MeOH was added via syringe. The quenched solution was stirred for 5 min at -78 °C and then was transferred to a 50-mL Erlenmeyer flask containing a stirred, sat. aq. solution of $NaHCO_3$ (10 mL) and KF (10 mL). The biphasic mixture was stirred vigorously for 1 h at rt and then was filtered through a pad of packed Celite (ca. 7 g) in a 60-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with 10 mL of CH_2Cl_2 and 10 mL of H_2O and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the resulting organic extracts

were combined, washed with brine (1 x 25 mL), and dried over $MgSO_4$ (ca. 1 g). we solution was filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil. The crude residue was purified by column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (6:1 to 4:1)) to afford 46 mg of **145a** (63%) as a yellow oil. The E/Z ratio and γ/α were determined to be 92:8 and 98:2, respectively by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **145a**:

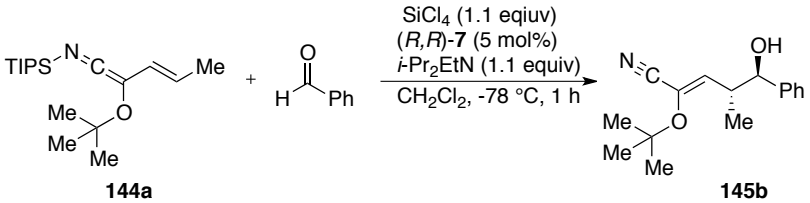
^{1}H NMR: (500 MHz, $CDCl_3$)

7.40 – 7.28 (m, 6H), 5.86 (t, J = 7.4 Hz, 1H), 4.82 – 4.71 (m, 1H), 2.73 – 2.61 (m, 2H), 2.01 (s, 1H), 1.37 (s, 10H)

TLC: 0. 2 (hexane/EtOAc, 4:1) [CAM]

SFC: (*R*)-**145a**, t_R 6.2 min (88.8%); (*S*)-**145a**, t_R 8.6 min (11.2%), (Chiralpak OD, 175 bar, 5% MeOH in CO_2, 3.0 mL/min, 210 nm, 40 °C

Preparation of (4*R*,5*R*,*Z*)-2-(*tert*-butoxy)-5-hydroxy-4-methyl-5-phenylpent-2-enenitrile (145b) (Scheme 57)



Following General Procedure 15, 10.5 mg of (*R,R*)-**7** (0.0125 mmol, 0.025 equiv), 31 µL of benzaldehyde (1.0 mmol), 52 µL of *N,N*-diisopropylethylamine (1.0 equiv, 1.0 mmol) and 37 µL of $SiCl_4$ (1.1 mmol, 1.1 equiv) were combined with 0.85 mL of a 0.46 M solution of **144a** (1.2 mmol, 1.2 equiv) in 1.5 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel,

∅ 20 mm column, hexanes/EtOAc gradient (6:1 to 4:1)) 55 mg of **145b** (71%) as a clear, colorless oil. The diastereomeric ratio was determined to be 83:7:7:3 mixture by ^{1}H NMR (500 MHz) analysis of the crude product. The diastereomers could not be distinguished between E/Z and *syn/anti* within this product mixture. SFC conditions could not be obtained because the diastereomers could not be separated by column chromatography.

Data for **145b**:

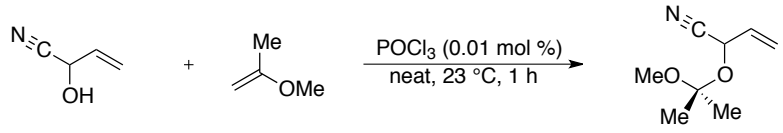
^{1}H NMR: (500 MHz, $CDCl_3$)

7.39 – 7.25 (m, 6H), 5.78 (d, J = 9.9 Hz, 1H), 4.52 (dd, J = 6.7, 2.9 Hz, 1H), 3.08 (m, 1H), 2.01 (d, J = 3.0 Hz, 1H, OH), 1.34 (s, 9H), 0.93 (d, J = 6.9 Hz, 3H)

TLC: 0.22 (hexane/EtOAc, 4:1) [CAM]

General Procedure 16. Methoxy Isopropyl (MIP) Ether Protection of Cyanohydrin with 2-Methoxy Propene.

Preparation of 2-((2-methoxypropan-2-yl)oxy)but-3-enenitrile (148a) (Table 21, entry 1)



148a

To a flame-dried 25 mL round-bottomed flask was added 1.35 g of acrolein cyanohydrin (16.3 mmol) and 6 mL of 2-methoxypropene (2.6 M). The solution was stirred under argon at room temperature and then 2 μL of phosphorus oxychloride was added via syringe. The solution was stirred for 1 h at room temperature and then quenched by adding 25 μL of Et_3N and transferred to a 60 mL separatory funnel. Next, 20 mL of diethyl ether was added to the separatory funnel and the organic layer was washed with H_2O (2 x 20 mL) and $NaHCO_3$ sat'd aq. solution (1 x 20 mL) and then dried over $MgSO_4$. The solution was filtered and concentrated

(400 mm Hg, 23 °C) to give a clear, colorless liquid. Purification of the crude material by vacuum distillation gave 2.1 g (84%) of clean **148a** as a clear, colorless liquid.

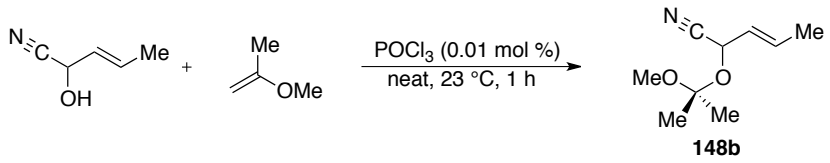
Data for **148a**:

bp: 55 - 57 °C (5.5 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

5.86 (ddd, *J* = 17.0, 10.2, 5.3 Hz, 1H), 5.61 (dd, *J* = 16.9, 1.3 Hz, 1H), 5.41 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.98 (dt, *J* = 5.3, 1.4 Hz, 1H), 3.25 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H)

Preparation of (*E*)-2-((2-methoxypropan-2-yl)oxy)pent-3-enenitrile (148b) (Table 21, entry 2)



148b

Following General Procedure 16, 3.78 g (39.0 mmol) of crotonaldehyde cyanohydrin was combined with a 14 mL of 2-methoxoypropene (2.75M) and 5 μL of phosphorus oxychloride (0.05 mmol, 0.001 equiv) to afford 6.0 g of **148b** (92%) as a clear, colorless liquid after vacuum distillation.

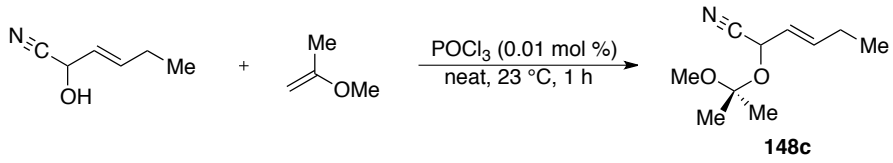
Data for **148b**:

bp: 41 - 42 °C (0.5 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

6.03 (dqd, *J* = 14.5, 6.6, 1.2 Hz, 1H), 5.53 (ddq, *J* = 15.4, 5.9, 1.6 Hz, 1H), 4.97 – 4.84 (m, 1H), 3.24 (s, 3H), 1.75 (d, *J* = 6.3 Hz 3H), 1.48 (s, 3H), 1.37 (s, 3H)

Preparation of (*E*)-2-((2-methoxypropan-2-yl)oxy)hex-3-enenitrile (148c) (Table 21, entry 3)



148c

Following General Procedure 16, 2.74 g (24.7 mmol) of (*E*)-2-pentenal cyanohydrin was combined with a 9.0 mL of 2-methoxoypropene (2.75M) and 10 µL of phosphorus oxychloride (0.05 mmol, 0.001 equiv) to afford 3.5 g of **148c** (76%) as a clear, colorless liquid after vacuum distillation.

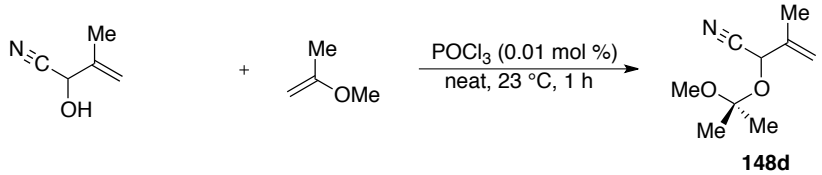
Data for **148c**:

bp: 65 - 68 °C (2.8 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

6.14 – 6.00 (m, 1H), 5.49 (dd, *J* = 15.4, 6.1 Hz, 1H), 4.92 (d, *J* = 6.1 Hz, 1H), 3.24 (s, 3H), 2.22 – 2.05 (m, 2H), 1.48 (s, 3H), 1.38 (s, 3H), 1.03 (t, *J* = 7.4 Hz, 3H)

Preparation of 2-((2-methoxypropan-2-yl)oxy)-3-methylbut-3-enenitrile (148d) (Table 21, entry 2)



148d

Following General Procedure 16, 2.64 g (27.2 mmol) of methacrolein cyanohydrin was combined with a 10 mL of 2-methoxoypropene (2.75M) and 10 µL of phosphorus oxychloride (0.05 mmol, 0.001 equiv) to afford 3.7 g of **148d** (82%) as a clear, colorless liquid after vacuum distillation.

Data for **148d**:

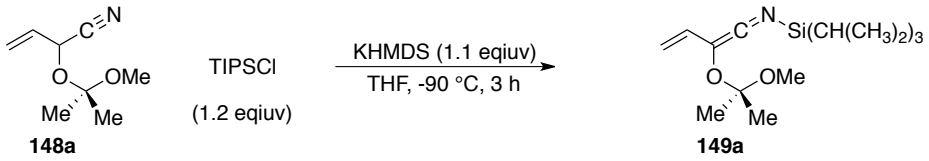
bp: 50 - 52 °C (0.9 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

5.25 (s, 1H), 5.08 (s, 1H), 4.85 (s, 1H), 3.24 (s, 3H), 1.89 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H)

Preparation of MIP Protected *N*-Silyl Oxyketene Imines.

Preparation of 1,1,1-triisopropyl-N-(2-((2-methoxypropan-2-yl)oxy)buta-1,3-dien-1-ylidene)silanamine (149a) (Table 22, entry 1)



148a **149a**

Following General Procedure 14, KHMDS (0.455 g, 2.3 mmol, 1.1 equiv) in 4.6 mL THF and a solution nitrile **148a** (0.32 g, 2.1 mmol, 1.0 equiv), TIPSCl (0.48 mL, 2.3 mmol, 1.1 equiv) in 4 mL THF were combined at -90 °C to afford 0.59 g (92%) of **149a** as an red liquid, which was used without further purification.

Data for **149a**:

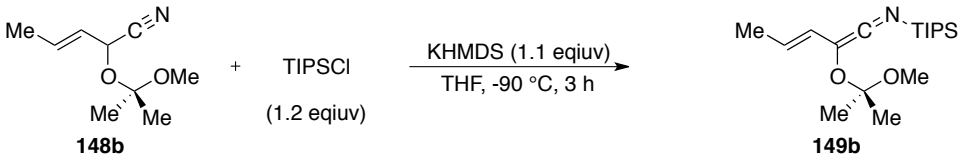
^{1}H NMR: (500 MHz, C_6D_6)

6.42 (dd, J = 16.6, 10.8 Hz, 1H), 5.21 (dd, J = 16.6, 1.9 Hz, 1H), 4.80 (dd, J = 10.8, 1.9 Hz, 1H), 3.18 (s, 3H), 1.48 (s, 6H), 1.05 – 1.00 (m, 21H)

IR: (neat)

2944 (s), 2893 (s), 2867 (s), 2045 (s), 1689 (w), 1599 (s), 1463 (s), 1380 (s), 1371 (s), 1329 (s), 1269 (s), 1238 (s), 1210 (s), 1181 (s), 1139 (s), 1069 (s), 1024 (s), 1023 (s), 996 (m), 969 (m), 882 (s)

Preparation of (E)-1,1,1-triisopropyl-N-(2-((2-methoxypropan-2-yl)oxy)penta-1,3-dien-1-ylidene)silanamine (149b) (Table 22, entry 2)



Following General Procedure 14, KHMDS (0.71 g, 3.6 mmol, 1.1 equiv) in 3.5 mL THF and a solution nitrile **148b** (0.55 g, 3.25 mmol, 1.0 equiv), TIPSCl (0.76 mL, 3.6 mmol, 1.1 equiv) in 3 mL THF were combined at -90 °C to afford 1.0 g (99%) of **149b** as an red liquid, which was used without further purification. The E/Z ratio was determined to be 92:8 by ^{1}H NMR integration of the crude reaction mixture

Data for **149b**:

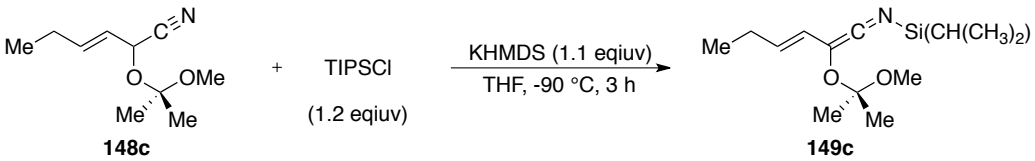
^{1}H NMR: (500 MHz, C_6D_6)

6.08 (dq, J = 14.9, 1.5 Hz, 1H), 5.63– 5.48 (m, 1H), 3.20 (s, 3H), 1.84 (dd, J = 6.7, 1.5 Hz, 3H), 1.48 (s, 6H), 1.10 – 1.00 (m, 21H).

IR: (neat)

2991 (m), 2945 (s), 2892 (s), 2868 (s), 2039 (s), 1638 (m), 1463 (s), 1381 (s), 1371 (s), 1257 (s), 1209 (s), 1182 (s), 1141 (s), 1069 (s), 1016 (w), 995 (s), 958 (m), 943 (m), 884 (s)

Preparation of (*E*)-1,1,1-triisopropyl-N-(2-((2-methoxypropan-2-yl)oxy)hexa-1,3-dien-1-ylidene)silanamine (149c) (Table 22, entry 3)



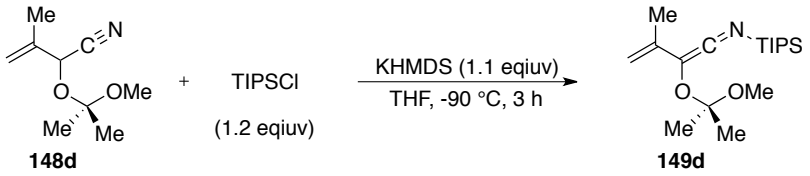
Following General Procedure 14, KHMDS (0.49 g, 2.5 mmol, 1.1 equiv) in 5.0 mL THF and a solution nitrile **148c** (0.41 g, 2.25 mmol, 1.0 equiv), TIPSCl (0.52 mL, 2.5 mmol, 1.1 equiv) in 4.5 mL THF were combined at -90 °C to afford 0.74 g (97%) of **149c** as a red liquid, which was used without further purification. The *E/Z* ratio was determined to be 95:5 by ^{1}H NMR integration of the crude reaction mixture

Data for **149c**:

^{1}H NMR: (500 MHz, C_6D_6)

6.09 (ddd, *J* = 15.0, 1.7, 1.0 Hz, 1H), 5.63 (dt, *J* = 14.9, 6.8 Hz, 1H), 3.21 (s, 3H), 2.29 – 2.12 (m, 2H), 1.50 (s, 6H), 1.12 – 0.99 (m, 24H)

Preparation of (E)-1,1,1-triisopropyl-N-(2-((2-methoxypropan-2-yl)oxy)penta-1,3-dien-1-ylidene)silanamine (149d) (Table 22, entry 4)



Following General Procedure 14, KHMDS (0.52 g, 2.6 mmol, 1.1 equiv) in 5.0 mL THF and a solution nitrile **148d** (0.40 g, 2.36 mmol, 1.0 equiv), TIPSCl (0.55 mL, 2.6 mmol, 1.1 equiv) in 4.5 mL THF were combined at -90 °C to afford 0.71 g (93%) of **149d** as a red liquid, which was used without further purification.

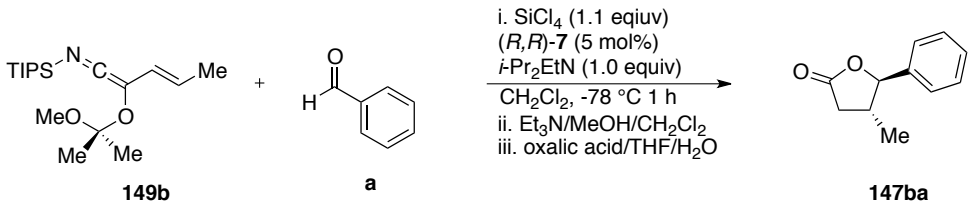
Data for **149d**:

^{1}H NMR: (500 MHz, C_6D_6)

5.11 (s, 1H), 4.66 (s, 1H), 3.20 (s, 3H), 1.88 (s, 3H), 1.49 (s, 6H), 1.09 – 1.01 (m, 22H)

General Procedure 17. Homoenolate Addition of *N*-Silyl *tert*-Butoxy Ketene Imines with Benzaldehyde for the Synthesis of γ-Lactones.

Preparation of (4*R*,5*R*)-4-methyl-5-phenyldihydrofuran-2(3*H*)-one (147ba) (Table 23, entry 1)



To a flame-dried, 10-mL, single-necked Schlenk flask fitted with a magnetic stir bar, argon inlet and a septum were added 16 mg of (*R,R*)-**7** (0.025 mmol, 0.05 equiv), 41 μL of benzaldehyde (0.4 mmol) and 2.0 mL anhydrous CH_2Cl_2 (0.2 M in aldehyde). The solution was stirred, cooled to -78 °C (internal) with a dry ice/acetone bath and then 70 μL of *N,N*-diisopropylethylamine (0.4 mmol, 1.0 equiv) and 50 μL of $SiCl_4$ (0.44 mmol, 1.1 equiv) were added via syringe to the reaction vessel. The resulting solution was stirred for 5 min at -78 °C and then 0.28 mL of a 1.69 M solution of silyl ketene imine **149b** (0.48 mmol, 1.2 equiv) in dichloromethane was added dropwise via syringe over 3 min. The yellow reaction mixture was allowed to stir for an additional 2 h at -78 °C before 0.4 mL of a 3:1:1 mixture of Et_3N/CH_2Cl_2/MeOH was added via syringe. The quenched solution was stirred for 5 min at -78 °C and then was transferred to a 50-mL Erlenmeyer flask containing a stirred solution of 1.0 g oxalic acid in 20 mL of 1:1 THF/H_2O. The biphasic mixture was stirred vigorously for 2 h at rt and then was filtered through a pad of packed Celite (ca. 7 g) in a 60-mL, coarse, glass-sintered Büchner funnel. The filter cake was washed with 15 mL of EtOAc and 10 mL of H_2O and then the filtrate was transferred to a 125-mL separatory funnel where the organic layer was isolated. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the resulting organic extracts were

combined, washed with $NaHCO_3$ sat'd aq. solution (1 x 20 mL) and brine (1 x 20 mL). The solution was dried over $MgSO_4$ (ca. 1 g), filtered and concentrated *in vacuo* (40 °C, 30 mm Hg) to give a yellow oil. The crude residue was purified by column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (7:1)) to afford 63 mg of **147ba** (89%) as a yellow oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **147ba**:

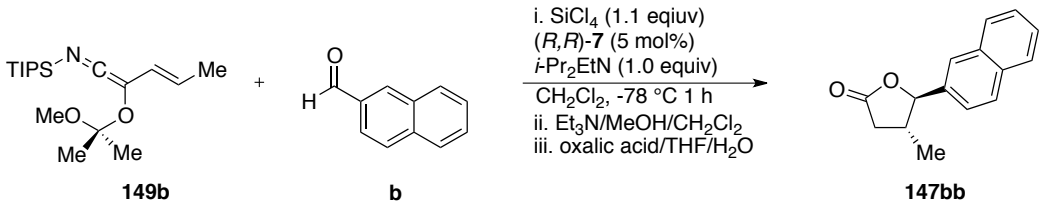
^{1}H NMR: (500 MHz, $CDCl_3$)

7.43 – 7.31 (m, 5H), 4.94 (d, J = 8.4 Hz, 1H), 2.79 (dd, J = 17.1, 7.8 Hz, 1H), 2.54 – 2.43 (m, 1H), 2.34 (dd, J = 17.1, 10.5 Hz, 1H), 1.19 (d, J = 6.6 Hz, 3H)

TLC: 0.11 (hexane/EtOAc, 7:1) [CAM]

HPLC: (4*R,5S*)-**147ba**, t_R 22.7 min (5.5%); (4*R,5R*)-**147ba**, t_R 27.9 min (94.5%), (Chiralpak Walk-O, 1 10% IPA in hexanes, 1.0 mL/min, 220 nm)

Preparation of (4R,5R)-4-methyl-5-(naphthalen-2-yl)dihydrofuran-2(3H)-one (147bb) (Table 23, entry 2)



Following General Procedure 17, 8.5 mg of (*R,R*)-**7** (0.01 mmol, 0.05 equiv), 31 mg of 2-naphthaldehyde (0.2 mmol), 34 μL of *N,N*-diisopropylethylamine (0.20 mmol, 1.0 equiv) and 0.22 mL of $SiCl_4$ (0.22 mmol, 1.1 equiv, 1.0 M solution in CH_2Cl_2) were combined with 0.8 mL of a 0.3 M solution of **149b** (1.2 mmol, 1.2 equiv) in 1.0 mL of CH_2Cl_2 to yield after column

chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (5:1 to 4:1)) 44 mg of **147bb** (99%) as a clear, colorless oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **147bb**:

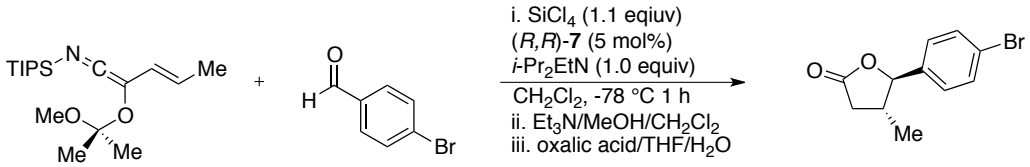
^{1}H NMR: (500 MHz, $CDCl_3$)

7.89 (d, *J* = 8.5 Hz, 1H), 7.86 (dd, *J* = 5.0, 2.5 Hz, 2H), 7.80 (s, 1H), 7.52 (p, *J* = 4.9 Hz, 2H), 7.44 (dd, *J* = 8.5, 1.8 Hz, 1H), 5.12 (d, *J* = 8.3 Hz, 1H), 2.84 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.65 – 2.53 (m, 1H), 2.39 (dd, *J* = 17.2, 10.3 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H)

TLC: 0.19 (hexane/EtOAc, 3:1) [CAM]

SFC: (4*R,5S*)-**147bb**, t_R 8.4 min (7.7%); (4*R,5R*)-**147bb**, t_R 9.9 min (92.3%), (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Preparation of (4R,5R)-5-(4-bromophenyl)-4-methyldihydrofuran-2(3H)-one (149bc) (Table 23, entry 3)



Following General Procedure 17, 8.5 mg of (*R,R*)-**7** (0.01 mmol, 0.05 equiv), 37 mg of 4-bromobenzaldehyde (0.2 mmol), 34 μL of *N,N*-diisopropylethylamine (0.20 mmol, 1.0 equiv) and 0.22 mL of $SiCl_4$ (0.22 mmol, 1.1 equiv, 1.0 M solution in CH_2Cl_2) were combined with 0.8 mL of a 0.3 M solution of **149b** (1.2 mmol, 1.2 equiv) in 1.0 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (4:1 to 3:1)) 42 mg

of **149bc** (82%) as a clear, colorless oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **149bc**:

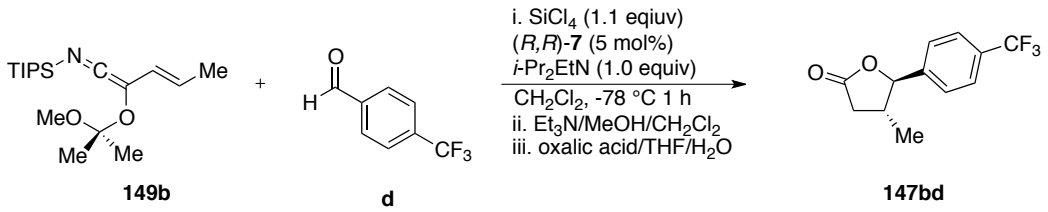
^{1}H NMR: (500 MHz, $CDCl_3$)

7.53 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 4.89 (d, *J* = 8.3 Hz, 1H), 2.78 (dd, *J* = 16.7, 7.4 Hz, 1H), 2.50 – 2.39 (m, 1H), 2.34 (dd, *J* = 16.8, 10.6 Hz, 1H), 1.19 (d, *J* = 6.4 Hz, 4H)

TLC: 0.15 (hexane/EtOAc, 3:1) [CAM]

SFC: (4*R,5S*)-**149bc**, t_R 7.8 min (10.6%); (4*R,5R*)-**149bc**, t_R 9.8 min (89.4%), (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Preparation of (4R,5R)-4-methyl-5-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (147bd) (Table 23, entry 4)



Following General Procedure 17, 8.5 mg of (*R,R*)-**7** (0.01 mmol, 0.05 equiv), 27 μL of 4-trifluromethylbenzaldehyde (0.2 mmol), 34 μL of *N,N*-diisopropylethylamine (0.2 mmol, 1.0 equiv) and 0.22 mL of a 1.0 M solution of $SiCl_4$ in CH_2Cl_2 (0.22 mmol, 1.1 equiv) were combined with 0.8 mL of a 0.30 M solution of **149b** (1.2 mmol, 1.2 equiv) in 1.0 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (4:1 to 3:1)) 39 mg of **147bd** (79%) as a clear, colorless oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **147bd**:

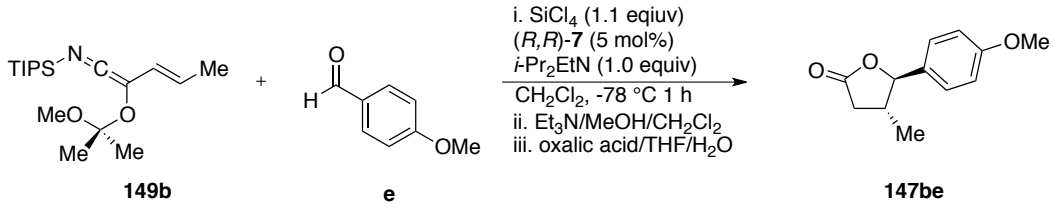
^{1}H NMR: (500 MHz, $CDCl_3$)

7.67 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 5.00 (d, J = 8.2 Hz, 1H), 2.81 (dd, J = 16.7, 7.4 Hz, 1H), 2.50 – 2.40 (m, 1H), 2.37 (dd, J = 16.7, 10.4 Hz, 1H), 1.23 (d, J = 6.5 Hz, 3H)

TLC: 0.14 (hexane/EtOAc, 2:1) [CAM]

SFC: (4*R*,5*S*)-**147bd**, t_R 2.5 min (17.5%); (4*R,5R*)-**147bd**, t_R 2.9 min (82.5%), (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Preparation of (4R,5R)-5-(4-methoxyphenyl)-4-methyldihydrofuran-2(3H)-one (147be) (Table 23, entry 5)



Following General Procedure 17, 8.5 mg of (*R,R*)-**7** (0.01 mmol, 0.05 equiv), 24 µL of 4-methoxybenzaldehyde (0.2 mmol), 34 µL of *N,N*-diisopropylethylamine (0.2 mmol, 1.0 equiv) and 25 µL of $SiCl_4$ (0.22 mmol, 1.1 equiv) were combined with 1.3 mL of a 0.20 M solution of **149b** (1.2 mmol, 1.2 equiv) in 1.0 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (4:1 to 3:1)) 40 mg of **147be** (99%) as a clear, colorless oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **147be**:

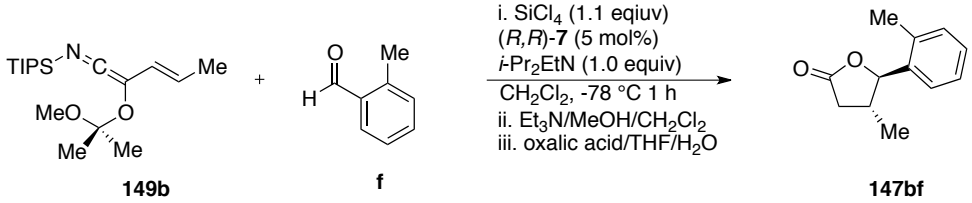
^{1}H NMR: (500 MHz, $CDCl_3$)

7.27 (d, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.89 (d, *J* = 8.6 Hz, 1H), 3.82 (s, 3H), 2.79 (dd, *J* = 17.0, 7.7 Hz, 1H), 2.56 – 2.41 (m, 1H), 2.34 (dd, *J* = 17.0, 10.8 Hz, 1H), 1.16 (d, *J* = 6.6 Hz, 3H)

TLC: 0.2 (hexane/EtOAc, 3:1) [CAM]

SFC: (4*R,5S*)-**147be**, t_R 5.2 min (3.5%); (4*R,5R*)-**147be**, t_R 6.8 min (96.5%), (Chiralpak AD, 200 bar, 5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Preparation of (4R,5R)-4-methyl-5-(o-tolyl)dihydrofuran-2(3H)-one (147bf) (Table 23, entry 6)



Following General Procedure 17, 8.5 mg of (*R,R*)-**7** (0.01 mmol, 0.05 equiv), 23 μL of 2-methylbenzaldehyde (0.2 mmol), 34 μL of *N,N*-diisopropylethylamine (0.2 mmol, 1.0 equiv) and 0.22 mL of a 1.0 M solution of $SiCl_4$ in CH_2Cl_2 (0.22 mmol, 1.1 equiv) were combined with 0.8 mL of a 0.30 M solution of **149b** (1.2 mmol, 1.2 equiv) in 1.0 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (6:1 to 5:1)) 29 mg of **147bf** (76%) as a clear, colorless oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **147bf**:

^{1}H NMR: (500 MHz, $CDCl_3$)

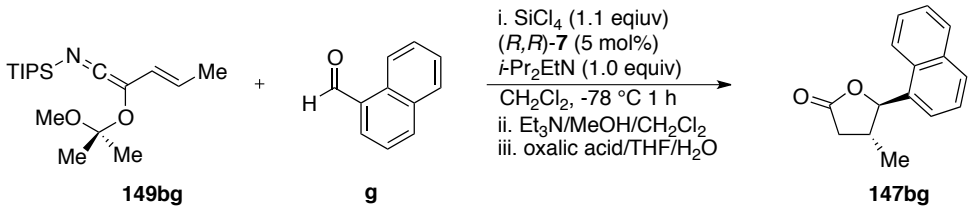
7.33 – 7.17 (m, 4H), 5.27 (d, *J* = 6.8 Hz, 1H), 2.80 (dd, *J* = 17.2, 7.9 Hz, 1H),

2.64 – 2.51 (m, 1H), 2.37 (s, 3H), 2.32 (dd, J = 17.2, 8.3 Hz, 1H), 1.23 (d, J = 6.7 Hz, 1H)

TLC: 0.16 (hexane/EtOAc, 3:1) [CAM]

SFC: (4*R*,5*R*)-**147bf**, t_R 4.4 min (92.7%); (4*R,5S*)-**147bf**, t_R 4.8 min (7.3%), (Chiralpak OD, 200 bar, 4% MeOH in CO_2, 2.1 mL/min, 220 nm, 40 °C)

Preparation of (4R,5R)-4-methyl-5-(naphthalen-1-yl)dihydrofuran-2(3H)-one (147bg) (Table 23, entry 7)



Following General Procedure 17, 8.5 mg of (*R,R*)-**7** (0.01 mmol, 0.05 equiv), 27 µL of 1-naphthaldehyde (0.2 mmol), 34 µL of *N,N*-diisopropylethylamine (0.2 mmol, 1.0 equiv) and 25 µL of $SiCl_4$ (0.22 mmol, 1.1 equiv) were combined with 1.3 mL of a 0.20 M solution of **149bg** (1.2 mmol, 1.2 equiv) in 1.0 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (5:1 to 4:1)) 29 mg of **147bg** (76%) as a clear, colorless oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **147bg**:

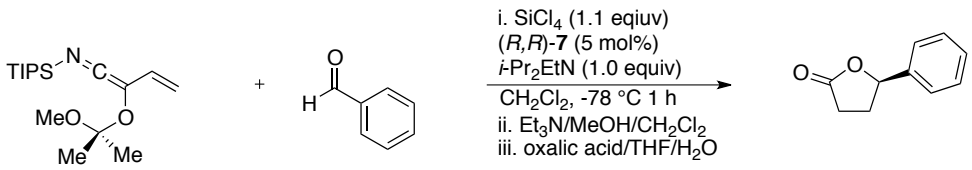
^{1}H NMR: (500 MHz, $CDCl_3$)

7.95 – 7.82 (m, 3H), 7.61 – 7.45 (m, 4H), 5.81 (d, J = 5.2 Hz, 1H), 2.89 – 2.70 (m, 2H), 2.35 (dd, J = 16.7, 5.9 Hz, 1H), 1.37 (d, J = 6.7 Hz, 3H)

TLC: 0.27 (hexane/EtOAc, 4:1) [CAM]

SFC: (4*R,5S*)-**147bg**, t_R 4.2 min (12.5%); (4*R,5R*)-**147bg**, t_R 7.4 min (87.5%), (Chiralpak OD, 200 bar, 15% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C)

Preparation of (*R*)-5-phenyldihydrofuran-2(3H)-one (147a) (Table 24, entry 1)



149a **147a**

Following General Procedure 17, 13 mg of (*R,R*)-**7** (0.16 mmol, 0.05 equiv), 33 µL of benzaldehyde (0.32 mmol), 56 µL of *N,N*-diisopropylethylamine (0.32 mmol, 1.1 equiv) and 40 µL of $SiCl_4$ (0.35 mmol, 1.1 equiv) were combined with 1.9 mL of a 0.2 M solution of **149a** (1.2 mmol, 1.2 equiv) in 1.6 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (6:1 to 4:1)) 25 mg of **147a** (48%) as a clear, colorless oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis of the crude product.

Data for **147a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

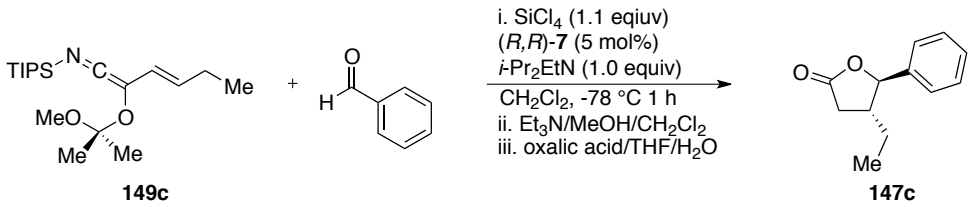
7.43 – 7.31 (m, 5H), 5.57 – 5.47 (m, 1H), 2.72 – 2.62 (m, 3H), 2.27 – 2.14 (m, 1H)

TLC: 0.22 (hexane/EtOAc, 3:1) [CAM]

Opt. Rot.: $[\alpha]_D^{24}$ +23 (c = 4.3, $CHCl_3$), literature reports $[\alpha]_D^{24}$ –32 (c = 4.3, $CHCl_3$) for (*S*)[104]

HPLC: (*S*)-**147a**, t_R 22.6 min (11.7%); (*R*)-**147a**, t_R 26.2 min (88.3%), (Chiralpak Walk-O, 10% IPA in hexanes, 1.1 mL/min, 220 nm

Preparation of (4*R*,5*R*)-4-ethyl-5-phenyldihydrofuran-2(3H)-one (Table 24, entry 3)



Following General Procedure 17, 16 mg of (*R,R*)-**7** (0.02 mmol, 0.05 equiv), 41 μL of benzaldehyde (0.4 mmol), 70 μL of *N,N*-diisopropylethylamine (0.4 mmol, 1.0 equiv) and 50 μL of $SiCl_4$ (0.44 mmol, 1.1 equiv) were combined with 0.34 mL of a 1.43 M solution of **149c** (1.2 mmol, 1.2 equiv) in 2.0 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (7:1 to 5:1)) 64 mg of **147c** (85%) as a clear, colorless oil. The diastereomeric ratio was determined to be 80:20 by ^{1}H NMR (500 MHz) analysis.

Data for **147c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.43 – 7.30 (m, 5H), 5.03 (d, J = 7.5 Hz, 1H), 2.79 (q, J = 11.7 Hz, 1H), 2.36 (dt, J = 21.3, 9.5 Hz, 2H), 1.74 – 1.63 (m, 1H), 1.52 – 1.41 (m, 1H), 0.94 (t, J = 7.4 Hz, 3H)

TLC: 0.17 (hexane/EtOAc, 6:1) [CAM]

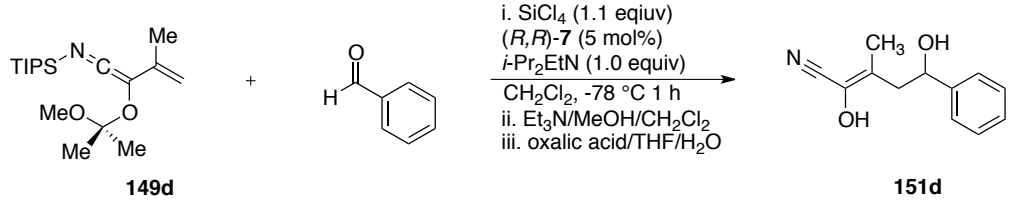
HPLC: (4*R,5S*)-**147c**, t_R 26.4 min (7.3%); (4*R*,5*R*)-**147c**, t_R 31.7 min (92.7%), (Chiralpak Walk-O, 10% MeOH in hexanes, 0.75 mL/min, 254 nm)

Homoenolate Addition of α-Methyl Derived *N*-Silyl Oxyketene Imine 149d.

Evidence for the Formation of Enol Nitrile 151d Under Acidic Quench Conditions (Scheme 61).

Following General Procedure 17, 16 mg of (*R,R*)-**7** (0.02 mmol, 0.05 equiv), 41 μL of benzaldehyde (0.4 mmol), 70 μL of *N,N*-diisopropylethylamine (0.4 mmol, 1.0 equiv) and 50 μL

of $SiCl_4$ (0.44 mmol, 1.1 equiv) were combined with 0.31 mL of a 1.53 M solution of **149d** (1.2 mmol, 1.2 equiv) in 2.0 mL of CH_2Cl_2 to yield a crude yellow oil after concentration. Analysis of the oil by ^{1}H NMR and IR suggested formation of enol nitrile **151d** (data reported below).



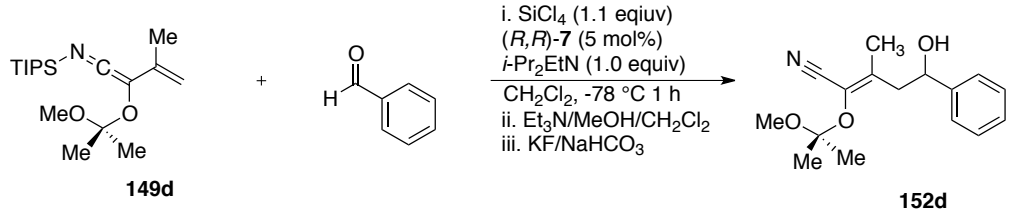
Data for **151d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.40 – 7.22 (m, 5H), 4.97 (dd, J = 8.3, 2.6 Hz, 1H), 2.70 (dd, J = 14.2, 8.4 Hz, 1H), 2.43 (dd, J = 14.2, 2.7 Hz, 1H), 1.73 (s, 3H).

IR: 3390 (s), 3033 (s), 2943 (s), 2866 (s), 2221 (m), 1760 (s), 1645 (s), 1462 (s), 1383 (m), 1332 (m), 1286 (m), 1250 (s), 1197 (s), 1159 (s), 1045 (s), 999 (m), 910 (s), 883 (s), 819 (s).

Preparation of (Z)-5-hydroxy-2-((2-methoxypropan-2-yl)oxy)-3-methyl-5-phenylpent-2-enenitrile (152d) Under Basic Conditions (Scheme 62).



Following General Procedure 14, 16 mg of (*R,R*)-**7** (0.02 mmol, 0.05 equiv), 41 µL of benzaldehyde (0.4 mmol), 70 µL of *N,N*-diisopropylethylamine (0.4 mmol, 1.0 equiv) and 50 µL of $SiCl_4$ (0.44 mmol, 1.1 equiv) were combined with 0.36 mL of a 1.44 M solution of **149d** (1.2 mmol, 1.2 equiv) in 2.0 mL of CH_2Cl_2 to yield after column chromatography (15 g SiO_2 gel

deactivated with Et_3N, ∅ 20 mm column, hexanes/EtOAc/EtN_3 (4:1:0.02)) 93 mg of **152d** (85%) as a clear, colorless oil. The α:γ ratio was determined to be 99:1 by ^1H NMR (500 MHz) analysis of the crude product.

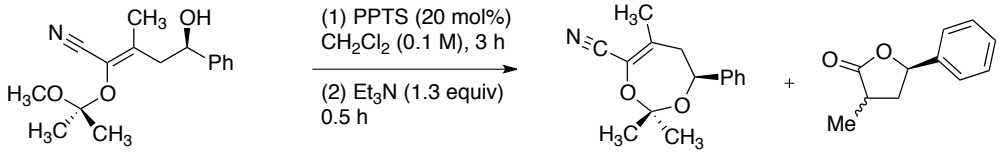
Data for **152d**:

^1H NMR: (500 MHz, $CDCl_3$)

7.39 – 7.34 (m, 3H), 7.32 – 7.28 (m, 1H), 4.90 (dt, *J* = 8.5, 4.2 Hz, 1H), 3.38 (s, 3H), 2.78 (dd, *J* = 13.5, 8.8 Hz, 1H), 2.51 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.25 (d, *J* = 3.6 Hz, 1H), 1.99 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H)

TLC: 0.1 (hexane/EtOAc/Et_3N, 4:1:0.02) [CAM]

Preparation of (S)-2,2,5-trimethyl-7-phenyl-6,7-dihydro-1,3-dioxepine-4-carbonitrile (154d) (Scheme 63)



152d **154d** **153d**

To a flame-dried 10 mL round-bottomed flask was added 105 mg of MIP protected enol nitrile **152d** (0.40 mmol) and 1.9 mL of CH_2Cl_2 (0.2 M). The solution was stirred under argon at room temperature and then 24 mg of pyridinium *p*-toluene sulfate (0.10 mmol, 0.25 equiv) was added in one portion. The solution was stirred for 2 h at room temperature and then quenched by adding 74 μL of Et_3N (0.53 mmol, 1.4 equiv). The quenched solution was stirred for 15 min at rt and then 5 mL of H_2O was added and the mixture was transferred to a 60 mL separatory funnel. Next, 10 mL of dichloromethane was added to the separatory funnel and the organic layer was isolated. The organic layer was extracted with CH_2Cl_2 (2 x 10 mL) and then combined and dried

over $MgSO_4$. The solution was filtered and concentrated (200 mm Hg, 23 °C) to give a clear, colorless liquid. The residue was purified by column chromatography (15 g SiO_2 gel, ∅ 20 mm column, hexanes/EtOAc gradient (9:1 to 6:1)) to yield 47 mg of **154d** (57%) as a clear, colorless oil. Also, isolated 22 mg of γ-lactone **153d** (37%) in 65:35 dr from later column fractions.

Data for **154d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.38 – 7.27 (m, 5H), 5.38 (dd, J = 11.5, 3.5 Hz, 1H), 2.72 (dd, J = 18.6, 3.1 Hz, 1H), 2.53 (dd, J = 18.6, 11.5 Hz, 1H), 1.97 (s, 3H), 1.58 (s, 4H), 1.49 (s, 3H)

TLC: 0.1 (hexane/EtOAc/Et_3N, 4:1:0.02) [CAM]

SFC: (*S*)-**154d**, t_R 3.25 min (17.8%); (*R*)-**154d**, t_R 3.65 min (82.2%), (Chiralpak OB, 200 bar, 2.5% MeOH in CO_2, 1.8 mL/min, 220 nm, 40 °C)

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