Gold(I)-Catalyzed Dehydrative Amination and Etherification of Allylic Alcohols

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry in the Graduate School of Duke University

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ABSTRACT

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Abstract

Allylic amines are important and fundamental building blocks due to their widespread occurrence in many natural products and the ability to further functionalize allylic amines by transformations on the double bond to generate a diverse range of compounds. Transition-metal catalyzed allylic substitution represents an attractive and efficient approach towards the synthesis of these allylic amines. However, limitations associated with the traditional methods developed for such allylic amination in terms of regiospecificity, atom economy and generality in these transformations, combined with the importance of allylic amination, prompted us to develop novel atom efficient and regiospecific methods for their synthesis.

A 1:1 mixture of AuCl[P(t-Bu)₂o-biphenyl] (5 mol %) and AgSbF₆ (5 mol %) catalyzed the intermolecular amination of underivatized allylic alcohols with 1-methyl-2-imidazolidinone and related nucleophiles. The first examples of intermolecular allylic amination was developed that in the case of γ-unsubstituted and γ-methyl-substituted allylic alcohols, occurred with high γ-regioselectivity and syn-stereoselectivity.

A 1:1 mixture of AuCl[P(t-Bu)₂o-biphenyl] (5 mol %) and AgSbF₆ (5 mol %) also served as a very efficient catalytic system for the intramolecular amination of allylic alcohols with alkylamines to form substituted pyrrolidine and piperidine derivatives. The protocol was effective for a range of secondary as well as primary alkylamines as nucleophiles with different substitutions on the alkyl chain tethering the nucleophile to the allylic alcohol. The method was also extended towards the total synthesis of the naturally occurring alkaloid (S)-(+-)coniine in two steps from the starting (R,Z)-8-(N-benzylamino)-3-octen-2-ol. In addition, gold(I)-catalyzed cyclization of (R,Z)-8-(N-benzylamino)-3-octen-2-ol (96% ee) led to isolation of (R,E)-1-benzyl-2-(1-
propenyl)piperidine in 99% yield and 96% ee that established the net syn-addition of the nucleophile with respect to the departing hydroxyl group.

A bis(gold) phosphine complex (S)-Au₂Cl₂(DTBM-MeOBIPHEP) (2.5 mol %) and AgClO₄ (5 mol %) catalyzed the intramolecular enantioselective dehydrative amination of allylic alcohols with carbamates to form the corresponding substituted pyrrolidines, piperidines, morpholines and piperazines in excellent yields and with up to 95% ee. This general and effective protocol tolerated a range of carbamates as well as sulfonamides as nucleophiles. Cyclization of chiral ε-amino allylic alcohols that possessed a stereogenic homoallylic or hydroxy-bound carbon atom occurred with an overriding catalyst control of asymmetric induction. In addition, stereochemical analysis of the cyclization of a chiral non-racemic secondary allylic alcohol established the net syn-displacement of the hydroxy group by the carbamate nucleophile.

Alongside allylic amination, a cationic gold(I)-N-heterocyclic carbene complex catalyzed the intermolecular etherification (alkoxylation) of allylic alcohols in a regiospecific and syn-stereoselective fashion. The transformation was highly efficient to utilize unactivated primary and secondary alcohols as nucleophiles with different allylic alcohols to undergo γ-regioselective etherification. Employment of a chiral nonracemic secondary allylic alcohol, trans-5-(benzyloxy)pent-3-en-2-ol (98% ee) showed a high level of chirality transfer on reaction with n-butanol to the corresponding allylic ether, (2-butoxypent-3-en-1-yloxy)methylbenzene (97% ee) and established the net syn-addition of the alcohol nucleophile with respect to the departing hydroxyl group of the allylic alcohol.
Dedicated to my husband, Dr. Pravas Deria, and my parents, Mr. Amitabha Mukhopadhyay and Mrs. Madhuchhanda Mukhopadhyay for their unwavering support.
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Chapter 1

Review on Transition Metal-Catalyzed Allylic Amination and Gold(I)-Catalyzed Dehydrative Functionalization of Allylic Alcohols
1.1 Allylic amination

Allylic amines are important and fundamental building blocks due to their prevalence in many natural products that display a wide range of biological activity (Figure 1.1). Therefore, considerable attention has been given over the years for developing new methods to synthesize allylic amines. In addition, allylic amines can be further functionalized by oxidation, reduction, or other transformations of the double bond to generate a range of compounds such as α- and β-amino acids, various alkaloids and carbohydrate derivatives. They also serve as highly useful substrates for different types of reactions such as ring-closing metathesis and asymmetric isomerization.

![Figure 1.1 Examples of biologically active natural products with allylic amine functionality](image)

Among the several methods developed to synthesize allylic amines, allylic substitution and the direct allylic amination of simple alkenes are most common. In the category of allylic substitution, transition metal-catalyzed allylic substitution represents an attractive route to the synthesis of allylic amines due to the regioselectivity, stereoselectivity, mild reaction conditions, high efficiency and atom economy.
1.2 Transition metal-catalyzed allylic amination

In 1965, Tsuji and coworkers first reported the allylic alkylation reaction with an electrophilic $\eta^3$-coordinated $\pi$-allyl palladium complex. After this report, initial attempts in this area led to the development of allylic substitutions catalytic in Pd(0) complexes. There have been numerous reports of palladium-catalyzed allylic substitution reactions since then involving allylic carbonates, esters, and acetates as electrophilic sources. The scope of nucleophiles in these substitutions has been mostly restricted to soft stabilized carbon nucleophiles derived from 1,3 dicarbonyl compounds, cyanoesters and malononitrilile, although heteroatom nucleophiles such as amines, amides and aryloxides have also been demonstrated. As an example, Bäckvall and coworkers reported the synthesis of 3-aryl-3-pyridylallylamines from dimethylamine and allylic acetates in the presence of catalytic palladium acetylacetonate and bis(diphenylphosphino)ethane (dppe) (eq 1.1). Palladium complexes in most cases tend to form the linear regioisomer by attack of the nucleophile to the less hindered carbon of the allylic electrophile. When the products of a reaction could consist of more than one constitutional isomer, and when one of the possible isomers is formed is excess over the other, the reaction is said to be a regioselective reaction and the corresponding isomers are called regioisomers.

Although a large number of the allylic substitution reactions are reported with palladium catalysts, other transition metals are also known to catalyze such transformations. Transition metal-complexes of ruthenium, rhodium and iridium are known to catalyze amination of allylic alcohol derivatives. In 1999, Mitsudo and coworkers reported a Ru-catalyzed allylic amination on cyclic allylic carbonates with primary and secondary alkylamines (eq 1.2). In the same year, Evans and coworkers demonstrated allylic substitution by an anionic arylamide nucleophile in presence of an
In 2001, Takeuchi demonstrated the Ir-catalyzed amination of allylic esters to give the branched allylic amine as the major product (eq 1.4). In addition to these transition metals, metal complexes of molybdenum, tungsten and iron are also known to catalyze allylic substitution reactions. Furthermore, allylic amination reactions catalyzed by nickel complexes are also known and in most cases, like palladium, they tend to give the linear regioisomer predominantly (eq 1.5).

1.2.1 Regioselectivity and mechanism of transition metal-catalyzed allylic substitution

The regioselectivity of palladium- and nickel-catalyzed allylic substitution leads to preferential formation of the less-substituted product. Conversely, in case of metals
like rhodium, iridium and ruthenium, the branched product is formed prefentially via nucleophilic attack at the more-substituted carbon of the metal bound π-allyl intermediate (eq 1.6). The mechanism of allylic substitution reactions is most often proposed to proceed through a metal bound π-allyl intermediate (III) as shown in Scheme 1.1. Initially, the low-valent metal complex such as palladium(0) or iridium(I) binds to the allylic alcohol derivative followed by ionization to form the η³-allylmetal intermediate, III and liberate the leaving group. This is followed by the attack of the nucleophile to the π-allyl intermediate. For soft nucleophiles, an outer-sphere attack generally occurs from the opposite face of the π-allyl complex to which the metal is bound. For hard nucleophiles, this addition is often inner-sphere where the nucleophile attacks from the same face of the metal-bound π-allyl complex. The electrophilic carbon of the η³-allylmetal intermediate where the nucleophilic addition occurs depends heavily on the nature of the metal and its coordination sphere; this ultimately determines the regioselective outcome of the reaction (IV or V).
Therefore, transition metal-catalyzed aminations of allylic acetates, esters, and carbonates have been extensively developed that shows a high level of regioselectivity. However, regiospecific allylic amination remain problematic. In a regioselective reaction, when only one of the regioisomer is formed depending on the nature of the substrate, then it is called a regiospecific reaction.

### 1.2.2 Asymmetric allylic amination

Many efforts directed towards the amination of allylic acetates, esters and carbonates have also been attempted in an asymmetric fashion.\(^{1b,2,6}\) In this regard, initial studies toward enantioselective allylic amination were mainly directed towards palladium catalysts with chiral ligands.\(^{2b}\) Symmetrical acyclic eletrophiles, such as derivatized 1,3-diphenylallyl alcohol, were most commonly used for asymmetric allylic amination.\(^{20}\) As an example, Faller and coworkers demostrated asymmetric allylic
amination of ethyl 1,3-diphenylallyl carbonate with benzylamine (eq 1.7) in presence of catalytic (π-allyl)palladium[(S)-L1] complex to afford the corresponding allylamine in 99% yield and 95% ee.\(^{21}\) Although palladium-catalyzed allylic substitutions usually favor the linear products, many chiral ligands have been reported by research groups of Trost and others that could achieve the formation of enantioenriched branched products.\(^2\) As an example, Dai and coworkers reported the palladium-catalyzed enantioselective amination of 1-phenylallyl acetate with benzylamine to form a 94:6 ratio of the branched to linear allylamine in 94% combined yield and 98% ee of the branched regioisomer (eq 1.8).\(^{22a}\)

\[
\text{Ph}^+\text{CO}_2\text{Et} + \text{PhCH}_2\text{NH}_2 \xrightarrow{[(\eta^3\text{-allyl})\text{Pd}((S)-\text{L1})\text{SbF}_6\text{(5 mol %)}]} \text{EtOAc, -25 °C, 24 h} \quad 99%, 95\% \text{ ee (R)}
\]

\[
\text{Ph}^-\text{CHOAc} + \text{PhCH}_2\text{NH}_2 \xrightarrow{[\text{Pd(C}_6\text{H}_5\text{Cl}_2\text{(2 mol %)}]} \text{CH}_2\text{Cl}_2, 0 °C, 7 h} \quad 94\% \text{ (branched:linear = 94:6), 98% ee (R)}
\]

Asymmetric allylic aminations have also been achieved in an intramolecular fashion. As an example, Trost and coworkers demonstrated enantioselective intramolecular amination of allylic acetate with 4-methoxybenzylamine in presence of catalytic [(\(\eta^3\)-allyl)PdCl\(_2\)] and chiral Trost ligand (R,R)-L2 to provide the corresponding 2-vinylpyrrolidinone in 92% yield and 81% ee (eq 1.9).\(^{22b}\)
Asymmetric allylic amination have been reported with transition metal complexes of Ir, Rh, Ru, and Mo to form the branched substitution product. As an example, iridium-catalyzed allylic substitution with cyclic secondary amines and other amine nucleophiles has been reported by Hartwig and coworkers. On treatment of cinnamyl methyl carbonate with morpholine in presence of catalytic [Ir(cod)Cl]_2 and the phosphoramidite ligand (R,R,R)-L3 provided the 4-(1-phenylallyl)morpholine in 92% yield and 97% ee (eq 1.10).

Therefore, transition metal-catalyzed asymmetric amination of allylic acetates, esters and carbonates has been one of the most well-established routes towards the synthesis of nonracemic chiral allylic amines. However, with the potential to reduce
synthetic routes and chemical waste, asymmetric aminations on underivatized allylic alcohols are more desirable. Despite the advances made, asymmetric allylic amination on underivatized allylic alcohols remain an unsolved challenge in catalysis.

1.3 Transition metal-catalyzed amination of underivatized allylic alcohols

There has been an ongoing interest in the catalytic amination of underivatized allylic alcohols as a route to synthesize allylic amines (Scheme 1.2). This is because the allylic alcohol derivatives such as allylic acetates, esters, and carbonates employed in the transition metal-catalyzed aminations are often synthesized from the free allylic alcohol. In addition, transition metal-catalyzed substitution of the allylic alcohol derivatives with the amine nucleophile also generates a stoichiometric amount of by-product. Therefore, an atom economical and environmentally benign approach of catalytic amination utilizing the underivatized allylic alcohol is highly attractive. However, due to the poor leaving ability of the hydroxyl group, transition-metal catalyzed amination of underivatized allylic alcohol is challenging.

Scheme 1.2

Initial attempts toward the catalytic amination of underivatized allylic alcohols either required harsh reaction conditions such as high temperature or involved in situ activation of the allylic alcohols with stoichiometric or sub-stoichiometric amounts of
Lewis acids such as Ti(Oi-Pr)$_4$, SnCl$_2$, BPh$_3$, BEt$_3$, BF$_3$Et$_2$O. As an example, in 1999, Yang and coworkers achieved the Pd-catalyzed intermolecular amination of allylic alcohols with anilines in presence of Ti(Oi-Pr)$_4$ (eq 1.11). A major drawback of this Lewis acid activation was the limitation in nucleophile scope as the more basic amines were rendered unreactive by coordination with the Lewis acid in the medium. Allylic substitutions of unactivated allylic alcohols were also previously reported by converting the alcohol into esters of inorganic acids such as As$_2$O$_3$, B$_2$O$_3$, CO$_2$, but these methods also lacked substrate generality. In 1996, Yamamoto and coworkers had reported a Pd(0)/phosphine catalyzed protocol for allylic amination in the presence of 1 atm of CO$_2$. As an example, amination of allylic alcohol with diethylamine in presence of catalytic tetrakis(triphenylphosphine)palladium under 1 atm CO$_2$ led to formation of N,N-diethylallylamine in 88% yield (eq 1.12). Allylic substitution reactions have also been reported involving other metal catalysts using in situ allylic alcohol activation. In 2007, Carreira and coworkers reported an Ir-catalyzed protocol employing sulfamic acid as an ammonia equivalent that also served as a Lewis acid activator of the allylic alcohol hydroxyl group. Reaction of the allylic alcohol with sulfamic acid in DMF as solvent was proposed to generate the reactive intermediate VI that subsequently forms the π-allyl intermediate in presence of iridium-catalyst to undergo nucleophilic addition by ammonia to give the allylamine isolated as its corresponding hydrochloride in 82% yield (eq 1.13).
In 2002, the first breakthrough in the catalytic amination of underivatized allylic alcohols was realized that did not require the employment of Lewis acidic cocatalyst.\(^{34}\) Ozawa and coworkers reported the allylic amination of different substituted allylic alcohols with aniline as the nucleophile in absence of any Lewis acid activation by utilizing catalytic (\(\pi\)-allyl)palladium(II)-complexes bearing an \(sp^2\)-hybridized phosphorus ligand (diphosphinidenecyclobutene). As an example, treatment of an \(E/Z\) mixture of crotol alcohol with aniline in presence of the cationic palladium(II) \(\pi\)-allyl complex provided the linear regioisomer of the allylamine as the major product in 85% yield after 6 h at room temperature (eq 1.14). Since then, there have been many reports employing Pd(0) as a catalyst to effect direct amination of allylic alcohols.\(^{35}\) Allylic substitution reactions have also been carried out in aqueous medium where the solvent is proposed to facilitate hydration of the hydroxyl group to form the \(\pi\)-allylpalladium
intermediate (eq 1.15). Although the reaction required no activators and allowed the use of amines as nucleophiles, equivalent amount of additives, such as Na$_2$CO$_3$, were required in certain cases. In addition, the palladium-catalyzed amination of either crotyl alcohol or 3-buten-2-ol with dibenzylamine led to the formation of a 2.4:1 mixture of linear to branched products, favoring the linear substitution product.

In addition to Pd(0) and Pd(II)-based catalysts for the intermolecular dehydrative amination of allylic alcohols, complexes of Pt(II), Bi(III), Mo(VI), and Au(III) have also been shown to catalyze allylic aminations. In 2008, le Floch and coworkers...
demonstrated that platinum(II)-catalysts containing ligands with large bite angles (DPP-Xantphos) effectively catalyze the amination of underivatized allylic alcohols with aryl and aliphatic amines to give the linear substituted allylic amine in high yield (eq 1.16).\textsuperscript{36c}

Later in 2009, a similar catalytic system was reported by Mashima and coworkers involving Pt(II)/Xantphos catalyst that expanded the scope of allylic amination to include different aliphatic and aromatic amines reacting with several substituted allylic alcohols (eq 1.17).\textsuperscript{36a}

\[
\text{Ph} \quad \text{OH} \quad + \quad \text{NH}_2 \quad \xrightarrow{\text{CH}_3\text{CN/toluene (1:1), 50 °C, 16 h}} \quad \text{Ph} \quad \text{OH} \quad + \quad \text{NH}_2 \quad \text{Ph} \quad (\text{eq 1.16})
\]

\[
\text{Me} \quad \text{OH} \quad + \quad \text{PhNH}_2 \quad \xrightarrow{\text{DMF, 80 °C, 24 h}} \quad \text{Me} \quad \text{OH} \quad + \quad \text{PhNH}_2 \quad \text{Ph} \quad (\text{eq 1.17})
\]

\[\text{[Pt(}{\eta}^3\text{-C}_3\text{H}_5\text{]}\text{L7]}\text{PF}_6 \quad (1 \text{ mol %})\]
\[\text{NH}_2\text{PF}_6 \quad (20 \text{ mol %})\]

In 2007, Shibasaki and coworkers reported the Bi(III)-catalyzed allylic substitution of underivatized allylic alcohols with electron-deficient nucleophiles such as sulfonamides and carbamates.\textsuperscript{23a} The reaction was performed in presence of catalytic amount of additive \text{KPF}_6 and a drying agent \text{CaSO}_4 (eq 1.18). Likewise, the Au(III)-catalyzed allylic amination of unactivated allylic alcohols was also reported in 2007 with sulfonamides and anilines as nucleophiles.\textsuperscript{38} The Au(III)-catalyzed reaction of 4-phenyl-3-buten-2-ol with \text{p-toluenesulfonamide} proceeded with the nucleophilic addition to the less-hindered carbon with formation of the more stable allylic amine (eq 1.19). In addition, mixtures of regioisomers were also observed with certain allylic alcohols. As an example, treatment of 2-octen-4-ol with \text{p-toluenesulfonamide} in presence of catalytic
AuCl₃ led to formation of a 1.9:1 mixture of regioisomers of the allylic amine (eq 1.20). Subsequently in 2009, a Mo(VI)-catalyzed direct allylic substitution in presence of catalytic ammonium hexafluorophosphate with amides, anilines and sulfonamides as nucleophiles was reported by Zhu and coworkers (eq 1.21).³⁷

![Chemical Reaction Equations]

Since the initial breakthrough by Ozawa and co-workers in 2002, there have been numerous reports in the literature that involve the direct substitution of the allylic alcohols in absence of any stoichiometric preactivation or the \textit{in situ} activation by stoichiometric or sub-stoichiometric amounts of activators. A number of these reactions also display a high degree of regioselectivity and can be carried out under mild conditions (room temperature). However, transition-metal catalyzed regiospecific amination of allylic alcohols still remains challenging. Thus an allylic amination that can be carried out on: i. variety of underivatized allylic alcohols; ii. with a battery of nucleophiles; iii. in a regiospecific as well as stereoselective fashion remains highly desirable.
1.3.1 Mechanism and stereoselectivity of catalytic amination involving underivatized allylic alcohols

The amination of underivatized allylic alcohols catalyzed by Pd(0)-, Pt(II)- and Ir(I)-complex is most often proposed to be similar to the allylic substitution reactions of derivatized allylic alcohols where it proceeds through the formation of the η³-allyl intermediate. le Floch and coworkers reported a comprehensive mechanistic study in 2006 on the direct amination of allylic alcohols with primary amines catalyzed by palladium(0) complexes in the absence of Lewis acid activation. Initial binding of the metal-complex in an η²-fashion (VII) with concomitant protonation of the hydroxyl group by the amine results in ionization to form the η³-allyl palladium intermediate (IX) (Scheme 1.3). Alternatively, Ozawa and coworkers have proposed a mechanism that invokes formation of a palladium-hydrido species as an intermediate in presence of strong π-acceptor ligands on palladium, which enables dehydration of the allylic alcohol to form the η³-allyl palladium intermediate. Intermediate IX then undergoes nucleophilic attack by the amine and dissociation of the allyl amine from the metal-complex to regenerate the active catalyst (XI). le Floch had shown that strong π-acceptor ligands on palladium favors the dissociation step, which is the rate-determining step in this case. There have been many reports on synthesis of allylic amines starting directly from the η³-allyl palladium intermediate (Scheme 1.3) that proves this catalytic cycle can be induced under experimental conditions.
Scheme 1.3

Stereospecific palladium and iridium-catalyzed amination of allylic alcohols have also been reported. Ozawa and coworkers have shown that an enantiomerically enriched 4-phenyl-3-buten-2-ol (98.5% ee) undergoes allylic amination with aniline to provide the corresponding allylic amine without any loss in optical purity (eq 1.20).

Allylic aminations catalyzed by other metal complexes such as Bi(III), Mo(VI), Au(III) have been proposed to proceed through a reaction mechanism that involve carbocationic intermediates. Shibasaki and coworkers demonstrated that when optically active allylic alcohol such as \((S,E)\)-1,3-diphenyl-2-propenol with >99% ee was subjected to the intermolecular amination with \(p\)-toluenesulfonamide in presence of catalytic
Bi(OTf)$_3$, a complete loss of chirality was observed to provide the racemic allylic amine 1 in 96% yield (eq 1.23). This complete loss of stereoselectivity could be due to formation of carbenium intermediates. Alternatively, the observed racemization could occur due to reversibility of the reaction. In fact, Shibasaki and coworkers observed that when racemic allylic amine 1 was subjected to the catalytic reaction conditions in presence of a different nucleophile, the transposed allylic amine 2 was isolated in 68% yield along with unreacted compound 1 (eq 1.24). Zhu and coworkers also observed the complete racemization of an optically enriched allylic alcohol, ($R,E$)-1,3-diphenyl-2-propenol (50% ee) on amination with $p$-toluenesulfonamide in presence of molybdenum(VI)-catalyst (eq 1.25). The observed racemization and additional mechanistic studies suggested a carbenium intermediate formation in the transition state of the molybdenum(VI)-catalyzed allylic amination.

Therefore, the transition-metal catalyzed amination of underivatized allylic alcohols is most often proposed to proceed via $\pi$-allyl metal complexed intermediates or
through carbocationic intermediates, thus making regiospecific amination challenging under these conditions.

1.3.2 Intramolecular catalytic amination of underivatized allylic alcohols

In addition to intermolecular allylic amination by direct substitution of allylic alcohols, intramolecular allylic substitutions have developed as an attractive route to generate aliphatic nitrogen heterocycles. Among these, palladium(II)-catalyzed cyclizations via N-alkylation of an allylic alcohol have been extensively studied\textsuperscript{40-41} and have been utilized in the synthesis of numerous N-heterocyclic natural products.\textsuperscript{41} The nucleophiles involved in this category are mostly carbamates and sulfonamides. In 1997, Hirai and co-workers reported construction of the piperidine ring in compound 4, as a single diastereomer, via a stereoselective bis(acetonitrile)palladium(II) chloride catalyzed cyclization of compound 3 (eq 1.26).\textsuperscript{41c} This was a key step in the total synthesis of the natural product (+)-prosopinine (5). Similar catalytic conditions were also employed in the total synthesis of the azasugar 1-deoxymannojirimycin (8, eq 1.27), where the nucleophile was a tert-butyl carbamate that underwent efficient stereoselective cyclization to form the vinyl piperidine 7 in a \textgreater 26:1 diastereomeric ratio.\textsuperscript{41d}
The mechanism ascribed to these intramolecular $N$-alkylations is via an initial aminopalladation of the allylic alcohol double bond. Uenishi and coworkers have more recently, in 2009, proposed a $\text{syn-azapalladation}, \text{syn-elimination}$ pathway to explain the stereochemical outcome of their catalytic allylic amination reaction (eq 1.28).\textsuperscript{41k} Stahl and coworkers have proposed that although $\text{syn-azapalladation}$ is favored under such reaction conditions, $\text{anti-azapalladation}$ can also take place under such conditions (Scheme 1.4).\textsuperscript{42} Thus, initial coordination of the Lewis acidic palladium(II)-catalyst to the alkene and the allylic alcohol leads to intermediate XII that is in equilibrium with the coordinated amine in intermediate XIII; this coordination of the palladium(II)-catalyst simultaneously to the double bond and the amine provides the chiral induction for the nucleophile to undergo a $\text{syn-addition}$. Intermediate XIV formed by $\text{syn-azapalladation}$ of XIII then undergoes $\text{syn-elimination}$ of Pd(Cl)OH to give the major product (trans-isomer). An $\text{anti-azapalladation}$ instead of a $\text{syn-azapalladation}$ at the initial step would lead to intermediate XVI, which then undergoes $\text{syn-elimination}$ of Pd(Cl)OH to lead to the minor isomer (cis-isomer). The cis-isomer is observed under certain reaction conditions depending on the nature of the substrate.
In addition to palladium(II)-catalyzed intramolecular N-alkylations employing underivatized allylic alcohols, Bi(III)$^{43}$- and Au(III)-catalyzed$^{44}$ protocols have also appeared in literature. In 2009, Kawai and coworkers have reported the Bi(OTf)$_3$ catalyzed intramolecular allylic amination of $o$-substituted 3-phenyl-2-propenols (eq 1.29)$^{43}$ Although the reaction showed a high level of regio- and stereoselectivity, it was restricted to the formation of arene-fused heterocycles. A Au(III)-catalyzed transformation was reported in the same year using aryl sulfonamides as nucleophiles to synthesize 1,2-dihydroquinolines from unactivated allylic alcohols (eq 1.30)$^{44}$ Mechanistically, these reactions are proposed to proceed via a true carbocation intermediate or Lewis-acid coordinated allyl carbenium type species.
Therefore, transition metal-catalyzed intramolecular amination of allylic alcohols have been well-developed as a route to obtain nitrogen heterocycles, but significant goals remain to be realized. Most of the palladium(II)-catalyzed allylic aminations require a high catalyst loading (15-30 mol%) to achieve high conversion at room temperature. The nucleophile scope for these reactions is limited to less basic sulfonamides and carbamates, as more basic alkylamines have not been employed as effective nucleophiles under palladium(II)-catalytic conditions. In addition, for transformations that involve a Lewis acid catalyzed pathway, although regioselective amination is achieved, stereospecific amination of underivatized allylic alcohols remains problematic.

1.3.3 Asymmetric catalytic amination of underivatized allylic alcohols

Transition metal-catalyzed asymmetric allylic amination of allylic esters, carbonates and phosphates represent one of the well-established routes to obtain the chiral nonracemic amines but obtaining similar amines via asymmetric allylic amination on underivatized allylic alcohols has been challenging. However, the scenario is rapidly changing as newer methods are being reported to achieve such catalytic transformations.
In 2007, Hartwig and coworkers reported an Ir(I)/triphenylborane catalyzed allylic amination of cinnamyl alcohols with aromatic amines with up to 94% ee. As an example, Ir(I)-catalyzed amination of cinnamyl alcohol with 2-methoxylaniline gave a 95:5 mixture of regioisomers that upon isolation gave 52% yield of the major branched regioisomer 9 in 94% ee (eq 1.31). Carreira and coworkers have shown an intermolecular dehydrative amination with sulfamic acid as both the nucleophile and the in situ activator of the allylic alcohol, but only one example of enantioselective allylic amination was demonstrated. Amination of 1-cyclohexylprop-2-enol with sulfamic acid in presence of catalytic [Ir(coe)$_2$Cl)$_2$ and (S)-L10 gave the corresponding allylic amine that was isolated as its hydrochloride in 70% yield and 70% ee (eq 1.32). Very recently, Carreira and coworkers reported the asymmetric synthesis of chiral secondary amines from racemic secondary allylic alcohols using sulfamic acid as the nucleophile in presence of the same Ir(I)/(S)-L10 catalytic system with up to 99% ee (eq 1.33).
Yamamoto and coworkers, in 2010, described the intramolecular allylic amination on free allylic alcohols with sulfonamides as nucleophiles catalyzed by Hg(OTf)$_2$/chiral binaphane (R)-L$_{11}$ complex.$^{48}$ The transformation showed a high enantioselectivity of up to 99% ee; however it was restricted to the synthesis of arene-fused nitrogen heterocycles and employed toxic mercury, albeit in a catalytic amount (1 mol%, eq 1.34). In 2011, Kitamura and coworkers reported the enantioselective dehydrative functionalizations of allylic alcohols employing a complex of CpRu(II) with the chiral bidentate sp$^2$-N containing ligand (S,S)-L$_{12}$. $^{49}$ The report described three examples using sulfonamides as nucleophiles to form pyrrolidine, arene-fused pyrrolidine and piperidine with up to 98% ee (eq 1.35). Very recently, in 2012, Kitamura...
and coworkers have utilized a catalytic system of CpRu(II)/(R)-L13 complex to synthesize different substituted pyrrolidine and piperidine hereocycles in an enantioselective fashion with carbamates and sulfonamides as nucleophiles with up to 98% ee. Therefore, with the growing interest in the synthesis of structurally diverse chiral nonracemic allylic amines employing underivatized allylic alcohols as nucleophiles, there remains a great deal of potential for improvement in terms of reaction scope, stereoselectivity and efficiency.
1.4 Gold(I)-catalyzed dehydrative functionalization of underivatized allylic alcohols

1.4.1 Importance of gold(I)-catalysis

Due to the reluctance of gold complexes to undergo redox transformations in a catalytic cycle, such as oxidative addition and reductive elimination, they were assumed less reactive as catalysts in comparison to other transition metals and therefore had been overlooked in the past. However, this redox-stability of gold has opened up new perspectives in catalysis and numerous reactions involving gold-catalysis have been emerging in increasing numbers over the past decade.

Within the family of gold(I)-complexes employed for the catalytic transformations, cationic metal complexes of type LAu+ where the cationic gold species is stabilized by suitable phosphine or carbene type ligands have emerged as very efficient catalysts for novel carbon-carbon and carbon-heteroatom bond formations (L = phosphine or carbene). These cationic LAu+ complexes are generally obtained as neutral halides LAuX (X = halide) and silver salts are commonly used to ionize LAuX to generate the LAu+ species in situ. In addition to the redox-stable nature of gold(I), the propensity of gold(I) to activate a carbon-carbon multiple bond due to its soft, carbophilic Lewis acidic nature, enables the formation of carbon-carbon and carbon-heteroatom bonds by attack of the nucleophile on the activated π-bond. Therefore, due to the π-acidic nature of gold being more pronounced than its oxophilic nature, gold-catalysis is less air- and moisture-sensitive and more tolerant to oxygen, alcohol and water than many other transition-metal catalysts or Lewis acids.

Furthermore, the ability of gold(I)-catalysts to be tolerant towards many functional groups increases its selectivity. In addition, although gold has a high affinity towards π-bonds, the advantage of a kinetically labile carbon-gold σ-bond towards acid
ensures facile protodeauration of the gold(I) σ-complex thus making it catalytically efficient. Due to all these inherent properties of gold, homogeneous gold-catalysis has gained tremendous impetus over the past decade and opened up new plethora of organic transformations that would otherwise be impossible.

1.4.2 Gold(I)-catalyzed functionalization of allylic alcohols

Gold(I)-complexes are capable of activating all C-C π-systems such as alkenes, alkynes, arenes, allenes, and dienes to render them susceptible to nucleophilic addition. Therefore, gold catalysts, in particular cationic Au(I) complexes, have emerged as very efficient catalysts for functionalization of C-C multiple bonds. Within the category of gold(I)-catalyzed activation of alkenes to develop novel regioselective and stereoselective catalytic methods, gold(I)-catalyzed functionalization of activated alkenes such as allylic alcohols that leads to dehydrative carbon-carbon and carbon-heteroatom bond formation represents a rapidly escalating new area of efficient catalytic transformations.

In 2009, Liu and coworkers demonstrated the synthesis of pyrroles via dehydrative amination of enynols followed by cycloisomerization in presence of catalytic Au(I)/Ag(I) complexes. As an example, treatment of enynol 11 with p-nitroaniline in presence of a catalytic 1:2 mixture (p-MeOC₆H₄)₃PAuCl and AgBF₄ led to formation of pyrrole 12 in 84% yield after 1 h (eq 1.37). However, it was determined that the initial step of dehydration amination of allylic alcohol was Ag-catalyzed when 3-phenyl-substituted enynols such as 11 were used as substrates. Therefore, treatment of treatment of 11 with p-nitroaniline in presence of only catalytic AgBF₄ led to formation of the allylic amine 13 in 90% yield after 4 h (eq 1.37).
In addition to gold(I)-catalyzed dehydrative amination, dehydrative alkylation and alkoxylation have also been reported with carbon and oxygen nucleophiles respectively. In 2009, Liu and coworkers described the cascade Friedel-Crafts/furan-alkyne cycloisomerization that lead to the formation of (Z)-aryl-enones in presence of gold(I)-catalysis. As an example, treatment of 11 and 2-methylfuran in presence of catalytic Ph3PAuNTf2 led to isolation of (Z)-aryl-enones 14 in 87% yield after 1 h (eq 1.38).

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In 2008, Aponick and coworkers reported a gold(I)-catalyzed intramolecular dehydrative alkoxylation of primary and secondary alcohols to form tetrahydropyrans and tetrahydrofurans in high yield and diastereoselectivity (eq 1.39). More recently, in 2011, Aponick and coworkers reported a stereospecific gold(I)-catalyzed intramolecular cyclizations of monoallylic diols to form substituted 2-vinyltetrahydropyrans. As an example, a 1:1 mixture of Ph3PAuCl and AgOTf catalyzed the intramolecular cyclization of monoallylic diol (R,Z)-17 to form the 2-vinyl substituted tetrahydropyran (R,E)-18 in 94% yield and 93% ee (eq 1.40). In addition to
formation of tetrahydrofurans and tetrahydropyrans, Aponick and coworkers also reported the synthesis of 2H-chromenes formed by the dehydrative *endo*-cyclization of o-(1-hydroxyallyl)-phenols (eq 1.41). In 2012, Bandini and coworkers have reported the synthesis of functionalized γ-vinylbutyro lactones by the intramolecular oxaallylic alkylation in presence of gold(I)-N-heterocyclic carbene complexes (eq 1.42).

Therefore, owing to the π-acidic nature of gold(I)-complexes and the robust nature of these catalysts under reaction conditions, much progress have been made in the past few years in the direct functionalization of allylic alcohols. Undoubtedly, there is an ongoing interest in this field and current efforts are directed towards the development of catalytic systems that would encompass a broader substrate and nucleophile scope with regio- and stereoselectivity.
1.4.3 Gold(I)-catalyzed asymmetric dehydrative functionalization of allylic alcohols

Concurrent to the research works in gold(I)-catalyzed dehydrative functionalization of underivatized allylic alcohols, accountable advances has been made in the fields of asymmetric dehydrative alkylations and alkoxylations catalyzed by chiral bisphosphine gold(I)-complexes. In 2009, Bandini and coworkers demonstrated the chiral bisphosphine gold(I)-catalyzed direct activation of allylic alcohols in an enantioselective intramolecular Friedel-Crafts alkylation of indoles to form 1-vinyl and 4-vinyltetrahydrocarbazoles. As an example, intramolecular dehydrative Friedel-Crafts alkylation of indolyl alcohol 23 in presence of catalytic [(S)-L14]Au2Cl2 and AgOTf led to isolation of the 1-vinyltetrahydrocarbazole in 84% yield and 90% ee (eq 1.43). In 2011, Bandini and coworkers also reported intramolecular dehydrative alkoxylation of underivatized allylic alcohols employing catalytic chiral bis(gold) phosphine complexes to form vinyl morpholines and vinyl-substituted seven-membered heterocycles (eq 1.44).

\[
\text{[(S)-L14]Au2Cl2 (10 mol %) + AgOTf (20 mol %) + toluene, 0 °C, 48 h \rightarrow 84%, 90% ee}
\]

(eq 1.43)

\[
\text{[(R)-L15]Au2Cl2 (2.5 mol %) + AgNTf2 (2.5 mol %) + toluene/CH2Cl2 (4:1), -10 °C, 4 h \rightarrow 92%, 92% ee}
\]

(eq 1.44)
Therefore, axially chiral bis(gold) phosphine complexes have been shown as efficient catalysts for the enantioselective dehydrative alklylation and alkoxylation of allylic alcohols. Application of these chiral bis(gold) phosphine complexes and other chiral gold-complexes will likely continue to emerge as new methodologies are developed.

1.5 Conclusions

Allylic amines and their derivatives are fundamental building blocks in the synthesis of natural products as well as compounds of pharmaceutical importance. Therefore, much progress has been made towards the development of novel methods to synthesize allylic amines, also in an enantioselective fashion. Transition metal-catalyzed aminations of allylic esters, carbonates and phosphates by different types of nitrogen-nucleophiles is a well-established protocol to synthesize these allylic amines. However, with the potential to condense synthetic sequences and reduce chemical waste, attention was given to new transition-metal catalyzed protocols that would enable direct functionalization of the allylic alcohols. Among other transition-metal catalysts, such as Pd(0), Pd(II), Pt(II), Mo(VI), Au(III), Bi(III), that have been shown to catalyze the direct functionalization of allylic alcohols, Au(I)-complexes have also emerged as efficient catalysts to facilitate such transformations in a regioselective and stereoselective fashion. In addition to dehydrative amination, cationic Au(I)-complexes have also been employed for catalytic alkylations and alkoxylations of underivatized allylic alcohols.

In this field of Au(I)-catalyzed direct functionalization of allylic alcohols, efforts made in the Widenhoefer lab were directed toward the heterofunctionalization of underivatized allylic alcohols with different \( N \)-nucleophiles. We have developed a Au(I)-catalyzed method for the allylic amination of unactivated allylic alcohols that in case of \( \gamma \)-unsubstituted or \( \gamma \)-methyl substituted allylic alcohols occur with a high \( \gamma \)-
regioselectivity and syn-stereoselectivity. This indicates toward a chemoselective π-activation of the allylic alcohol and nucleophilic attack preferentially at the γ-carbon of allylic alcohol (Chapter 2). We have shown that cationic Au(I)-complexes can catalyze the cyclisation of allylic alcohols with more basic nucleophiles like alkylamines that was unprecedented (Chapter 3). We were also able to demonstrate this intramolecular allylic amination in an asymmetric fashion with carbamates as nucleophiles utilizing chiral nonracemic bisphophine Au(I)-complexes as catalysts to give different nitrogen heterocycles in high yield and excellent enantioselectivity (Chapter 4). In addition to dehydrative amination, we have developed a new protocol for the regiospecific and stereospecific etherification of underivatized allylic alcohols employing Au(I)-N-heterocyclic carbene complexes (Chapter 5).
Chapter 2

Gold(I)-Catalyzed Amination of Allylic Alcohols with Cyclic Ureas and Related Nucleophiles

Portions of this chapter have been published: Mukherjee, P.; Widenhoefer, R. A. 

Gold(I) π-allylic alcohol complexes 16a and 16b were synthesized by Timothy J. Brown.
2.1 Background

Transition metal-catalyzed allylic substitution of allylic esters or carbonates represents one of the well-established routes towards the synthesis of allylic amines. With the ability to reduce chemical waste and make the transformation more atom-economical, there has been an ongoing interest in the synthesis of allylic amines through the direct catalytic amination of the underivatized allylic alcohols. Initial transformations in this area were realized with the in situ activation of the hydroxyl group by a Lewis acid. In 2002, Ozawa and coworkers reported the amination of allylic alcohols with anilines in presence of catalytic Pd(II) π-allyl complex without the need of a Lewis acidic cocatalyst. After this initial successful catalytic amination of allylic alcohols, different metal catalysts of Pd(0), Pt(II), Bi(III), Mo(VI), and Au(III) have been shown to catalyze intermolecular amination of underivatized allylic alcohols. While many of these reactions show very high regioselectivity and/or stereoselectivity, regiospecificity in such allylic amination still remains challenging because these reactions proceed either through a π-allyl intermediate or an allylic carbocation. Therefore, a regiospecific and stereoselective dehydrative amination of underivatized allylic alcohols is highly desirable.

In the area of gold-catalysis, cationic Au(I) complexes have emerged as efficient catalysts for the intermolecular and intramolecular hydroamination, which is the addition of an N—H bond across an unactivated C—C multiple bond such as alkenes, allenes and alkynes. Widenhoefer and other research groups have reported efficient Au(I)-catalyzed hydroamination reactions. In a recent report, Widenhoefer and coworkers demonstrated the intermolecular hydroamination of unactivated 1-alkenes with cyclic ureas catalyzed by gold(I) phosphine complexes (eq 2.1). The method was
also effective for the hydroamination of unactivated 1-alkenes with a distal functional group (eq 2.2).

\[
\text{MeN} \quad \text{NH} + \text{H}_2\text{C}==\text{CH}_3 \quad \overset{\text{AuCl}[\text{P(\text{t-Bu})_3(\text{o-biphenyl})]} \quad \text{(5 mol %)} \quad \text{AgSbF}_6 \quad \text{(5 mol %)} \quad \text{MeN} \quad \text{NH} + \text{H}_2\text{C}==\text{CH}(\text{CH}_2)_4\text{CO}_2\text{Et} \quad \text{dioxane, 100 °C, 62 h} \quad \text{97\%}
\]

(eq 2.1)

\[
\text{MeN} \quad \text{NH} + \text{H}_2\text{C}==\text{CH}(\text{CH}_2)_4\text{CO}_2\text{Et} \quad \overset{\text{AuCl}[\text{P(\text{t-Bu})_3(\text{o-biphenyl})]} \quad \text{(5 mol %)} \quad \text{AgSbF}_6 \quad \text{(5 mol %)} \quad \text{MeN} \quad \text{N} \quad \text{(CH}_3)_4\text{CO}_2\text{Et} \quad \text{dioxane, 100 °C, 40 h} \quad \text{90\%}
\]

(eq 2.2)

In an effort to further expand the scope of Au(I)-catalyzed intermolecular hydroamination to more functionalized alkenes, Widenhoefer and coworkers became interested to explore derivatized allylic alcohols such as allyloxytrimethylsilane as electrophiles in hydroamination reactions. Au(I)-catalyzed intermolecular reaction of allyloxytrimethylsilane with 1-methyl-2-imidazolidinone (1) provided the allylic amination product instead of the hydroamination adduct of 1 with the alkene of allyloxytrimethylsilane. Furthermore, intermolecular dehydrative amination of 1 with underivatized allylic alcohols was observed catalyzed by gold(I) phosphine complexes.

This chapter describes my contribution to the development of a gold(I)-catalyzed intermolecular amination of underivatized allylic alcohols with cyclic ureas and related nucleophiles that in the case of \(\gamma\)-unsubstituted and \(\gamma\)-methyl substituted allylic alcohols occurs with high \(\gamma\)-regioselectivity and syn-stereoselectivity.

2.2 Results and discussion

2.2.1 Scope of allylic amination with derivatized allylic substrates

In an initial experiment directed toward expanding the scope of gold(I)-catalyzed hydroamination with respect to alkenes, we investigated the reaction of 1-methyl-2-imidazolidinone (1) with allyloxytrimethylsilane under the optimized hydroamination
reaction conditions. Therefore, treatment of 1 with excess allyloxytrimethylsilane (15 equiv) in presence of a catalytic 1:1 mixture of AuCl[Pt-Bu](o-biphenyl)] [(2)AuCl] and AgSbF6 (5 mol %) in dioxane at 100 °C for 48 h led to the isolation of allylic amine 1-allyl-3-methyl-2-imidazolidinone (3) in 96% yield (Table 2.1, entry 1). This observation revealed the allylic substitution of allyloxytrimethylsilane by the nucleophile 1 and the loss of trimethylsilanol in presence of Au(I)-catalyst.

With this observation, we further probed the reaction scope with different allylic ethers. Although allyl benzyl ether and allyl phenyl ether proved to be good electrophiles under the reaction conditions to give the allylic amine 3 as the major product with minor hydroamination product (Table 2.1, entries 2-3), simple alkyl ether showed sluggish reactivity under these conditions (Table 2.1, entry 4). Furthermore, allylic acetate, a commonly used eletrophile in allyl substitution reactions, also underwent allylic amination to give 3 in a 69% yield (Table 2.1, entry 5). Subsequent optimization of reaction conditions also revealed that a 1-2 equivalents of allylic ether was sufficient to provide the allylic amine in a high yield at 60 °C after 24 h. As an example, reaction of 1 with diallyl ether under the optimized reaction conditions gave 3 in a 98% yield (Table 2.1, entry 6).
Table 2.1 Amination of allylic ethers (15 equiv) by cyclic urea 3 catalyzed by a mixture of (2)AuCl (5 mol %) and AgSbF₆ (5 mol %).

<table>
<thead>
<tr>
<th>entry</th>
<th>allylic ether</th>
<th>product</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>OMe</td>
<td>100</td>
<td>48</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>MeN</td>
<td>100</td>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>MeN</td>
<td>100</td>
<td>48</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>MeN</td>
<td>100</td>
<td>48</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>MeN</td>
<td>100</td>
<td>48</td>
<td>69</td>
</tr>
<tr>
<td>6c</td>
<td>OMe</td>
<td>MeN</td>
<td>60</td>
<td>24</td>
<td>98</td>
</tr>
</tbody>
</table>

a isolates yield of >95% purity. b Product ratios determined from 1H NMR analysis of the isolated material. c 2 equiv of diallyl ether used.

2.2.2 Gold(I)-catalyzed amination of allylic alcohol with different nucleophiles

The efficient allylic amination with allylic ethers suggested that underivatized allylic alcohols must also undergo gold(I)-catalyzed allylic amination. Indeed, when allylic alcohol (1 equiv) and cyclic urea 1 was subjected to catalytic amount of (2)AuCl (5 mol %) and AgSbF₆ (5 mol %), in 2 h allylic amine 3 was isolated in 99% yield (Table 2.2, entry 1). Therefore, we explored the scope of the amination of allylic alcohol with different nucleophiles. In addition to cyclic urea 1, 2-oxazolidinone and 2-imidazolidinone also underwent efficient gold(I)-catalyzed amination with allylic alcohol (Table 2.2, entries 2-3). Primary and secondary sulfonamides were also effective nucleophiles under these reaction conditions (Table 2.2, entries 4-6). Although 2-
pyrrolidinone, benzylcarbamate and $N$-methylbenzylamine underwent allylic amination, however they were less efficient than the above-mentioned nucleophiles (Table 2.2, entries 7-9).

**Table 2.2** Amination of allylic alcohol (2 equiv) as a function of nucleophile catalyzed by a mixture of (2)AuCl (5 mol %) and AgSbF$_6$ (5 mol %) in dioxane.

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile$^a$</th>
<th>major product</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X = O</td>
<td></td>
<td>100</td>
<td>2</td>
<td>99$^c$</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>48</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>60</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>TsNMeH</td>
<td>TsMeN</td>
<td>100</td>
<td>24</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>R = Ts</td>
<td>RHN$_2$</td>
<td>100</td>
<td>48</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>R = 4-MeOC$_6$H$_4$SO$_2$</td>
<td>RHN$_2$</td>
<td>100</td>
<td>24</td>
<td>100$^d$</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>80</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>CbzNH$_2$</td>
<td>CbzHN</td>
<td>100</td>
<td>72</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>BnNMeH</td>
<td>BnMeN</td>
<td>100</td>
<td>24</td>
<td>32</td>
</tr>
</tbody>
</table>

$^a$Ts = 4-toluenesulfonyl, Cbz = benzylxocarbonyl, Bn = benzyl. $^b$Isolated material of >95% purity. $^c$One equivalent of allyl alcohol employed. $^d$N,N-Diallyl-4-methoxybenzenesulphonamide was also isolated in 20% yield.

2.2.3 Gold(I)-catalyzed allylation of 1-methyl-2-imidazolidinone as a function of allylic alcohol

The rate, efficiency and selectivity demonstrated in the gold(I)-catalyzed amination of allylic alcohol and allylic ethers prompted us to explore the scope, regioselectivity and stereoselectivity of this reaction as a function of different allylic
alcohols. In a preliminary experiment to investigate the regiospecificity of allylic amination, the deuterium-labelled γ-unsubstituted allylic alcohol, 1,1-dideuterio-2-propenol was subjected to the catalytic 1:1 mixture of (2)AuCl (5 mol %) and AgSbF$_6$ (5 mol %) with 1 at 60 °C for 24 h, which led to the exclusive formation of 1-(3,3-dideuterio-2-propenyl)-3-methyl-2-imidazolidinone (3-γ,γ-d$_2$) (Table 2.3, entry 1). This result indicated the presence of a γ-selective pathway for the Au(I)-catalyzed amination of γ-unsubstituted allylic alcohols. Similarly, a number of γ-unsubstituted allylic alcohols substituted at the hydroxyl bound carbon atom underwent allylic amination with exclusive formation of the γ-substituted allylic amination products (Table 2.3, entries 2-5). For example, gold(I)-catalyzed amination of 3-buten-2-ol with 1 gave N-2-butenylurea 4 in >25:1 γ-regioselectivity (Table 2.3, entry 2). In addition, substrates with γ-methyl-substituted allylic alcohol also underwent γ-selective amination under Au(I)-catalysis. As an example, gold(I)-catalyzed allylic amination of trans-2-buten-1-ol with 1 led to the formation of N-(1-methyl-2-propenyl)urea 8 in >25:1 γ/α ratio, thus showing a γ-selective allylic amination pathway for the γ-methyl-substituted allylic alcohols as well (Table 2.3, entry 6). Likewise, reaction of 1 with 2-deuterio-3-penten-2-ol (10-1-d$_1$) catalyzed by (2)AuCl/AgSbF$_6$ formed only the allylic urea 11-γ-d$_1$ (Table 2.3, entry 8) and with 4-hexen-3-ol (13), N-(1-methyl-2-pentenyl)urea 14 was formed exclusively. Other allylic alcohols such as 2-cyclohexen-1-ol and 1,3-diphenyl-2-propenol also underwent allylic amination efficiently under the catalytic conditions (Table 2.3, entries 7 and 9).
Table 2.3 Allylation of 1 as a function of allylic alcohol catalyzed by a mixture of (2)AuCl (5 mol %) and AgSbF$_6$ (5 mol %) in dioxane (Nuc=N-methyl-2-imidazolidinone)

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>major product</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>$\gamma/\alpha$ ratio$^c$</th>
<th>E/Z ratio$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Allylic Alcohol 1" /></td>
<td><img src="image" alt="Allylic Alcohol 3" /></td>
<td>60</td>
<td>24</td>
<td>99</td>
<td>&gt;25:1</td>
<td>—</td>
</tr>
<tr>
<td>2$^a$</td>
<td>R = Me</td>
<td><img src="image" alt="Allylic Alcohol 4" /></td>
<td>60</td>
<td>24</td>
<td>91</td>
<td>&gt;25:1</td>
<td>2.4:1</td>
</tr>
<tr>
<td>3$^a$</td>
<td>R = Ph</td>
<td><img src="image" alt="Allylic Alcohol 5" /></td>
<td>60</td>
<td>24</td>
<td>94</td>
<td>&gt;25:1</td>
<td>6.7:1</td>
</tr>
<tr>
<td>4</td>
<td>R = Me</td>
<td><img src="image" alt="Allylic Alcohol 6a" /></td>
<td>60</td>
<td>24</td>
<td>100</td>
<td>&gt;25:1</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>R = -(CH$_2$)$_3$-</td>
<td><img src="image" alt="Allylic Alcohol 7" /></td>
<td>60</td>
<td>24</td>
<td>100</td>
<td>&gt;25:1</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Me-!CHOH</td>
<td><img src="image" alt="Allylic Alcohol 8" /></td>
<td>25</td>
<td>36</td>
<td>85</td>
<td>&gt;25:1</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Allylic Alcohol 9" /></td>
<td></td>
<td>100</td>
<td>48</td>
<td>97</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Allylic Alcohol 10-1-$d_1$" /></td>
<td><img src="image" alt="Allylic Alcohol 11-$\gamma$-$d_1$" /></td>
<td>60</td>
<td>24</td>
<td>100</td>
<td>&gt;25:1</td>
<td>3.7:1</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Allylic Alcohol 12" /></td>
<td></td>
<td>60</td>
<td>24</td>
<td>100</td>
<td>—</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Allylic Alcohol 13" /></td>
<td><img src="image" alt="Allylic Alcohol 14" /></td>
<td>60</td>
<td>24</td>
<td>100</td>
<td>&gt;25:1</td>
<td>4.3:1</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Allylic Alcohol 15" /></td>
<td></td>
<td>100</td>
<td>48</td>
<td>85</td>
<td>&lt;1:25</td>
<td>≥25:1</td>
</tr>
<tr>
<td>12$^a$</td>
<td><img src="image" alt="Allylic Alcohol 6a" /></td>
<td><img src="image" alt="Allylic Alcohol 6b" /> (minor product)</td>
<td>60</td>
<td>24</td>
<td>100</td>
<td>1:12</td>
<td>—</td>
</tr>
</tbody>
</table>

$^a$1 equiv allyl alcohol employed. $^b$Isolated material of >95% purity. $^c$Determined by $^1$H NMR analysis of the purified reaction mixture.
Unlike the selective $\gamma$-substitution of $\gamma$-unsubstituted and the $\gamma$-methyl-substituted allylic alcohols, gold(I)-catalyzed amination of cinnamyl alcohol with 1 led to the exclusive formation of $\alpha$-substitution product 5 (Table 2.3, entry 11). Similarly, allylic amination of 3-methyl-2-buten-1-ol with 1 under the (2)AuCl/AgSbF$_6$ catalytic conditions led to the formation of a 12:1 mixture of $\alpha$-substitution product 6a and $\gamma$-substitution product 6b in a quantitative yield (Table 2.3, entry 12).

2.2.4 Chirality transfer

The formation of $\gamma$-substitution product in the gold(I)-catalyzed amination of the $\gamma$-methyl-substituted allylic alcohols pointed towards the potential of a 1,3-chirality transfer in these gold(I)-catalyzed allylic aminations. Therefore, two enantiomerically enriched $\gamma$-methyl-substituted allylic alcohols with different alkyl substitutions at the allylic hydroxyl bound carbon were synthesized to evaluate the stereospecificity of gold(I)-catalyzed allylic amination with 1. Reaction of 1 with (R)-3-penten-2-ol [(R)-10] (92% ee) in presence of catalytic (2)AuCl/AgSbF$_6$ (5 mol %) at 60 °C for 24 h led to the isolation of a 4.2:1 mixture of (S,E)-11 with 86% ee and (R,Z)-11 with 91% ee in 99% combined yield (eq 2.3). Similarly, gold(I)-catalyzed allylic amination of (R)-4-hexen-3-ol [(R)-13] (96% ee) with 1 at 60 °C after 24 h led to isolation of a 4.3:1 mixture of (S,E)-14 with 91% ee and (R,Z)-14 with $\geq$95% ee in a quantitative yield (eq 2.4). Therefore, the stereochemical outcome of these reactions pointed toward a net syn-addition of the nucleophile with respect to the departing hydroxyl group.
2.2.5 Mechanism

The stereoselectivity of the gold(I)-catalyzed allylic amination of (R)-10 and (R)-13, with 1 that established the net syn-addition of the nucleophile with respect to the departing hydroxyl group is characteristic of a concerted $S_N2'$ substitution reaction.\(^{68}\) An $S_N2'$ substitution reaction is a concerted or stepwise bimolecular nucleophilic substitution with an overall allylic rearrangement. However, a mechanism for the gold(I)-catalyzed $\gamma$-amination of allylic alcohols via $\sigma$-activation of the hydroxyl group by gold(I) followed by a concerted or stepwise attack of the nucleophile at the $\gamma$-carbon seemed unlikely due to the low oxophilicity of gold(I). An alternative mechanism that involved $\pi$-activation of the allylic C=C bond followed by anti-addition of nucleophile and anti-elimination of water also accounts for the stereochemical outcome of the gold(I)-catalyzed allylic amination and is consistent with strong $\pi$-acidity of the cationic gold(I) complexes.\(^{55}\) Also noteworthy is that Maseras and coworkers have proposed the $\pi$-activation of allylic C=C bond in a gold(I)-catalyzed isomerization of allylic ethers with alcohols on the basis of DFT calculations.\(^{69}\) An important component in this gold(I)-catalyzed pathway was the formation of a six-membered chelate structure via hydrogen bonding between the nucleophile and the allylic hydroxy group that facilitates the nucleophilic addition and stabilizes the initially formed carbocationic intermediate.
We propose a mechanism for the conversion of (R)-10 to (S,E)-11 and (R,Z)-11 initiated by $\pi$-activation of the C=C bond of (R)-10 to form the gold(I) $\pi$-alkene complexes $si$-I and $re$-I respectively (Scheme 2.1, Nuc = N-methyl-2-imidazolidinone). Outersphere attack of the nucleophile to the alkene facilitated by an N—H⋯O hydrogen bond ($si$-II and $re$-II) leads to the formation of cyclic, hydrogen-bonded gold alkyl intermediates ($S,S,R$)-II and ($R,R,R$)-II, respectively. Anti-elimination of a hydrogen-bonded water molecule and the displacement of gold from ($S,S,R$)-II forms the major isomer ($S,E$)-11. A similar pathway involving anti-elimination from ($R,R,R$)-II leads to the other minor stereoisomer ($R,Z$)-11. Formation of ($S,E$)-11 in preference over ($R,Z$)-11 presumably due to the unfavorable steric interaction between the gold moiety and the C1 methyl in a cis orientation in the transition state leading to ($R,R,R$)-II that is absent in the transition state forming ($S,S,R$)-II.
2.2.6 Mechanism for the α-substitution products

The mechanism outlined for the γ-regioselective, syn-stereoselective pathway of the gold(I)-catalyzed allylic amination of (R)-10 does not account for the formation of the α-substitution products, as was observed in the case of allylic amination with cinnamyl alcohol and 3-methyl-2-buten-1-ol (Table 2.3, entries 11 and 12). The α-substitution products may form through a Lewis acid-catalyzed pathway involving allylic carbocation intermediates. However, other secondary pathways leading to the
formation of these products could also be possible. Indeed, we obtained evidence for
the formation of the α-substitution products through indirect reaction pathways.

In one experiment, the γ-substitution product (6b) that would arise from reaction
of 1 with 3-methyl-2-buten-1-ol was synthesized independently following a published
procedure and was subjected to the gold(I)-catalyzed allylic amination reaction
conditions. Therefore, an equimolar mixture of 1, 6b, cinnamyl alcohol, and water was
treated with a catalytic 1:1 mixture of (2)AuCl and AgSbF₆ at 60 °C in dioxane for 24 h.
Analysis of the purified reaction mixture by ¹H NMR spectroscopy revealed a ~2:1:1
mixture of unreacted 6b, cinnamyl urea 5, and the isomerized urea 6a that is the major
product under the allylic amination reaction of 1 with 3-methyl-2-buten-1-ol (eq 2.5).
Hence, this experiment demonstrates that the α-substitution product 6a can arise under
the gold(I)-catalyzed reaction conditions from isomerization of the γ-substitution
product.

In another set of experiments, an indirect pathway leading to the formation of α-
substitution products via the allylic transposition of 3-methyl-2-buten-1-ol was found.
When an equimolar mixture of 1 and 3-methyl-2-buten-1-ol was treated with a catalytic
1:1 mixture of (2)AuCl and AgSbF₆ at 60 °C in dioxane-­d₈, ¹H NMR analysis of the
reaction mixture at a low conversion (~17%) revealed the presence of 2-methyl-3-buten-
2-ol (~1%) and the γ-alkoxylation product 15 (~2%) along with the urea products 6a
(11%) and 6b (−3%) (eq 2.6). Monitoring this reaction with time revealed that 2-methyl-3-buten-2-ol and 15 persisted throughout the conversion of 3-methyl-2-buten-1-ol to 6a and 6b and was consumed at high conversion (−95%) (Figure 2.1). In addition, ¹H NMR analysis of the reaction of 1 with either 2-methyl-3-buten-2-ol or 15 revealed the exclusive formation of 6a at rates that were ≥6 times faster than the rate of reaction of 1 with 3-methyl-2-buten-1-ol under comparable reaction conditions.

Figure 2.1 Concentration versus time plot for the reaction of 1 (0.60 M) with 3-methyl-2-buten-1-ol (0.60 M; ◇) catalyzed by a 1:1 mixture of (2)AuCl and AgSbF₆ (5 mol %) in dioxane-d₈ at 60 °C to form 6a (△) and 6b (□).
Overall, the above observations revealed that in the case of 3-methyl-2-buten-1-ol and cinnamyl alcohol, formation of the α-substitution products can occur via secondary π-activation pathways. However, the formation of α-substitution products via Lewis acid catalyzed pathway that involves carbocationic intermediates cannot be ruled out.

2.2.7 Syntheses and isolation of gold(I) π-allylic alcohol complexes

The mechanism proposed for the gold(I)-catalyzed allylic amination is via the outer-sphere nucleophilic addition on the cationic gold(I) π-allylic alcohol complexes. Therefore, to learn more about the reactivity and structure of the cationic gold(I) π-allylic alcohol complexes, two monomeric, cationic, two-coordinate gold(I) π-allylic alcohol complex were synthesized (Figure 2.2).

![Figure 2.2 Synthesis of gold(I) π-allylic alcohol complexes.](image)

Treatment of a methylene chloride suspension of a 1:1 mixture of (2)AuCl and AgSbF₆ with 3-methyl-2-buten-1-ol for 6 h led to the isolation of [((2)Au(η²-Me₂C=CHCH₂OH)'][SbF₆]⁻ (16a) as an air- and thermally-stable white solid that was characterized by NMR, elemental analysis and X-ray crystallography (Figure 2.3). Slow diffusion of hexane into a methylene chloride solution of 3-methyl-2-buten-1-ol at 4 ºC gave colorless crystals of 16a suitable for X-ray analysis. The C=C bond of 3-methyl-2-
buten-1-ol is bound unsymmetrically to gold with a short Au–C1 and a long Au–C2 interaction ($\Delta d = 0.083 \text{ Å}$).

**Figure 2.3** ORTEP diagram of complex 16a $[(\text{2})\text{Au}(\eta^2-\text{Me}_2\text{C}=\text{CHCH}_2\text{OH})]^{+}$. Bond lengths: Au–C1 = 2.237 Å, Au–C2 = 2.320 Å. Bond angles: P–Au–C1: 169.7°, P–Au–C2: 147.9°.

In addition to 16a, gold(I) π-allylic alcohol complex $[(\text{2})\text{Au}(\eta^2-\text{H}_2\text{C}=\text{CHCH}_2\text{OH})]^{+}\text{SbF}_6^{-}$ (16b) was synthesized as a white solid in 99% yield following a similar procedure (Figure 2.2). Treatment of an equimolar mixture of 1 and 16b in a 6:1 solvent mixture of dioxane-$d_8$:CD$_2$Cl$_2$ at 60 °C showed formation of allylic amine 3 that indicated 16b as a catalytically active complex in the reaction. Additional experiments conducted with 16b such as treatment of a 1:1 mixture of 1 and 16b with a stoichiometric amount of triflic acid (HOTf) slowed down the rate of formation of the product 3. Similar observation was made on addition of an equivalent amount of 2,6-di-tert-butylpyridine to the 1:1 mixture of 1 and 16b where the rate of formation of 3 had
significantly dimished. Addition of an even stronger base than 2,6-di-tert-butylpyridine such as 1,8-diazabicycloundec-7-ene (DBU) completely stopped the allylic amination reaction and showed a sharpened $^1$H NMR spectrum of 1, 16b, and free allylic alcohol. Addition of an equivalent amount of HOTf to this reaction mixture immediately started formation of 3 owing to the consumption of DBU by HOTf.

2.2.8 Summary

To summarize, an efficient gold(I)-catalyzed amination of underivatized allylic alcohols with 1-methyl-2-imidazolidinone (1) and other related nucleophiles to give N-allylic ureas in high yields under mild reaction conditions was developed. In the cases of $\gamma$-unsubstituted and $\gamma$-methyl-substituted allylic alcohols, amination occurred with high $\gamma$-regioselectivity and syn-stereoselectivity. When 3-methyl-2-buten-1-ol or cinnamyl alcohol were used as electrophiles for allylic amination, gold(I)-catalyzed amination led to predominant formation of the $\alpha$-substitution product through indirect catalytic pathways or through a Lewis acid-catalyzed pathway involving carbocationic intermediates.

2.3 Experimental section

2.3.1 General methods

Catalytic reactions were performed in sealed heavy-walled pressure tubes under an atmosphere of dry nitrogen unless noted otherwise. Room temperature is 23 °C. NMR spectra were obtained on a Varian spectrometer operating at 400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR in CDCl$_3$ unless noted otherwise. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. Gas chromatography was performed on a Hewlett-Pakard 5890 gas chromatograph equipped with a 25 m polydimethylsiloxane capillary column. Chiral HPLC was performed on a Hewlett-Pakard chromatograph equipped
with a 0.46 cm X 25 cm Chiralpak AD-H column. Flash column chromatography was performed employing 200-400 mesh silica gel (EM). Thin layer chromatography (TLC) was performed on silica gel 60 F254. Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ).

Imidazolidin-2-one, oxazolidin-2-one, N-methylosylamide, p-methoxybenzenesulfonamide, pyrrolidin-2-one, tosylamide, benzyl carbamate, N-methylbenzylamine, allyl alcohol, crotyl alcohol, cinnamyl alcohol, 3-buten-2-ol, α-vinylbenzyl alcohol, 3-penten-2-ol, 1,3-diphenyl-2-propen-1-ol, 3-methyl-2-buten-1-ol, 2-methyl-3-buten-2-ol, 2-cyclohexen-1-ol, 1-vinyl cyclohexanol, acryloyl chloride, 4-hexen-3-ol, NaH, LiAlH₄, LiAlD₄, Pd/C (10 wt% loading, dry support), (+)-diisopropyltartrate, titanium(IV) isopropoxide, tert-butyl hydroperoxide solution (5.0-6.0 M in decane), 1,3-dicyclohexylcarbodiimide, dimethylaminopyridine, (R)-(+-α-methoxy-α-trifluoromethylphenylacetic acid, allyloxytrimethylsilane, diallyl ether, p-toluenesulfonyl chloride (Aldrich), 1-methylimidazolidin-2-one, anhydrous 1,4-dioxane (Acros) were used as received. Other ligands and silver salts were purchased from major suppliers and used as received. Gold complex \((2)\text{AuCl} [2 = P(t-Bu)_2-o-biphenyl]^{71}\) and \(3\)-methyl-2-butenyl-2-methyl-3-buten-2-yl ether (15)\(^{72}\) were prepared using published procedures.

### 2.3.2 Synthesis of deuterated allylic alcohols

**1,1-Dideuterio-2-propenol.**\(^{73}\) A solution of acryloyl chloride (1.6 g, 38 mmol) in ether (25 mL) was added dropwise to a stirred slurry of LiAlD₄ (5.6 g, 62 mmol) in ether (75 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 h, after which time it was cooled to 0 °C, opened to air, and treated sequentially with water (2 mL), 15% aqueous NaOH (2 mL), and water (2 mL). The resulting suspension was filtered through a plug of Celite and the precipitate was washed with ether. The filtrate
was concentrated using a rotary evaporator and the resulting oily residue was distilled (bp = 98-100 °C/760 torr) to give 1,1-dideuterio-2-propenol (1.3 g, 57%) as a colorless oil. Isotopic purity of 1,1-dideuterio-2-propenol was judged to be >95% on the basis of \(^1\)H and \(^{13}\)C NMR analysis. \(^1\)H NMR: \(\delta\) 5.87 (dd, \(J = 10.4, 17.2\) Hz, 1 H), 5.17 (dd, \(J = 2.0, 17.2\) Hz, 1 H), 5.03 (dd, \(J = 2.0, 10.4\) Hz, 1 H), 3.50 (br s, 1 H). \(^{13}\)C NMR: \(\delta\) 137.1, 114.9, 62.6 (quintet, \(J = 85.2\) Hz).

2-Deuterio-3-penten-2-ol. A solution of 3-penten-2-one (4.9 mL, 50 mmol) in ether (5 mL) was added dropwise to a stirred slurry of LiAlD\(_4\) (1.1 g, 25 mmol) in ether (50 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 4 h, opened to air, and treated sequentially with water (2 mL), 15% aqueous NaOH (2 mL), and water (2 mL). The resulting suspension was filtered through a plug of Celite and the precipitate was washed with ether. The filtrate was concentrated using a rotary evaporator to give 2-deuterio-3-buten-2-ol (2.7 g, 62%) as a colorless oil. The isotopic purity of the 2-deuterio-3-buten-2-ol was judged to be >95% on the basis of \(^1\)H and \(^{13}\)C NMR analysis. \(^1\)H NMR: \(\delta\) 5.51-5.42 (m, 1 H), 5.36 (d, \(J = 15.2\) Hz, 1 H), 3.11 (br s, 1 H), 1.52 (d, \(J = 6.0\) Hz, 3 H), 1.07 (s, 3 H). \(^{13}\)C NMR: \(\delta\) 135.3, 124.8, 67.7 (t, \(J = 88.8\) Hz), 22.9, 17.2.

2.3.3 Synthesis of allylated products

1-Allyl-3-methylimidazolidin-2-one (3). Allyl alcohol (21 mL, 0.30 mmol) was added to a suspension of (2)AuCl [\(2 = P(t\text{-Bu})_2\text{-biphenyl}; 7.9\) mg, 0.015 mmol], AgSbF\(_6\) (5.1 mg, 0.015 mmol) and 1-methylimidazolidin-2-one (1) (30 mg, 0.30 mmol) in 1,4-dioxane (0.5 mL) and the resulting mixture was stirred at 60 °C for 2 h. The resulting suspension was concentrated under vacuum and the residue was chromatographed (hexanes–EtOAc = 4:1 → 1:1) to give 3 (41.5 mg, 99%) as a colorless oil. TLC (hexanes–EtOAc = 1:1): \(R_f = 0.14\). \(^1\)H NMR: \(\delta\) 5.79–5.69 (m, 1 H), 5.20–5.13 (m, 2 H), 3.78 (td, \(J = 1.2, 6.4\) Hz, 2 H), 3.30–3.20 (m, 4 H), 2.78 (s, 3 H). \(^{13}\)C\(^{[1]}\)H NMR: \(\delta\) 161.4, 133.6, 117.4, 66.0, 40.8, 34.5, 30.8, 28.9, 23.1.
51.4. IR (neat, cm$^{-1}$): 2867, 1679, 1500, 1445, 1404, 1252, 1057, 994, 930, 760, 695, 657. Anal. calcd (found) for C$_7$H$_{12}$N$_2$O: H, 8.63 (8.60); C, 59.98 (59.84). HRMS calcd (found) for C$_7$H$_{12}$N$_2$O(M$^+$): 140.0950 (140.0947).

Remaining allylic ureas were synthesized employing procedures similar to that used to synthesize 3 unless noted otherwise. Reaction conditions are provided in Tables 2.1-2.3.

1-(1-(Benzyloxy)propan-2-yl)-3-methylimidazolidin-2-one. Colorless oil. TLC (hexanes–EtOAc = 1:1): $R_f = 0.15$. $^1$H NMR: δ 7.32-7.28 (m, 5 H), 4.54 (d, $J = 12$ Hz, 1 H), 4.45 (d, $J = 12$ Hz, 1 H), 4.23-4.18 (m, 1 H), 3.46 (dd, $J = 5.6$, 7 Hz, 2 H), 3.30-3.20 (m, 4 H), 2.76 (s, 3 H), 1.11 (d, $J = 1.6$, 7 Hz, 3 H).

1-Methyl-3-(1-phenoxypropan-2-yl)imidazolidin-2-one. Colorless oil. TLC (hexanes–EtOAc = 1:1): $R_f = 0.14$. $^1$H NMR: δ 7.24 (d, $J = 7.6$ Hz, 2 H), 6.91 (t, $J = 7.2$ Hz, 1 H), 6.87 (d, $J = 7.6$ Hz, 2 H), 4.34-4.26 (m, 1 H), 3.97 (d, $J = 5.6$ Hz, 2 H), 3.40-3.35 (m, 2 H), 3.28-3.19 (m, 2 H), 2.74 (s, 3 H), 1.25 (d, $J = 6.8$ Hz, 3 H).

3-Allyloxazolidin-2-one. Colorless pale yellow oil, 98%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.23$. $^1$H NMR: δ 5.81-5.71 (m, 1 H), 5.26-5.21 (m, 2 H), 4.32 (t, $J = 8$ Hz, 2 H), 3.85 (d, $J = 6.4$ Hz, 2 H), 3.51 (t, $J = 8.4$ Hz, 2 H). $^{13}$C{$^1$H} NMR: δ 158.2, 131.9, 118.6, 61.7, 46.9, 44.1.

1,3-Diallylimidazolidin-2-one. Pale yellow oil, 100%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.29$. $^1$H NMR: δ 5.80-5.70 (m, 2 H), 5.20-5.13 (m, 4 H), 3.79 (td, $J = 1.6$, 5.6 Hz, 4 H), 3.24 (s, 4 H). $^{13}$C{$^1$H} NMR: δ 160.7, 133.5, 117.4, 47.1, 42.3. IR (neat, cm$^{-1}$): 2867, 1682, 1644, 1491, 1444, 1415, 1342, 1252, 1101, 992, 926, 759, 698. HRMS calcd (found) for C$_9$H$_{14}$N$_2$O(M$^+$): 194.1419 (194.1418).

N-Allyl-N,4-dimethylbenzenesulfonamide. Colorless oil, 99%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.73$. $^1$H NMR: δ 7.64 (d, $J = 8.0$ Hz, 2 H), 7.29 (d, $J = 8.8$ Hz, 2 H), 7.08 (dd, 7 Hz, 1 H), 6.86 (d, $J = 8.8$ Hz, 1 H), 6.71 (dd, 7 Hz, 1 H).
5.72-5.62 (m, 1 H), 5.18-5.13 (m, 2 H), 3.59 (d, J = 6.4 Hz, 2 H), 2.62 (s, 3 H), 2.40 (s, 3 H).

$^{13}$C{\textsuperscript{1}H} NMR: δ 143.3, 134.3, 132.5, 129.6, 127.4, 119.1, 53.0, 34.1, 21.4.

**N- Allyl-4-methylbenzenesulfonylamine.** Colorless oil, 78%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.68$. $^1$H NMR: δ 7.76 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 5.77-5.67 (m, 1 H), 5.19-5.08 (m, 2 H), 4.52 (bs, 1 H), 3.58 (tt, J = 1.6, 6 Hz, 2 H), 2.43 (s, 3 H). $^{13}$C{\textsuperscript{1}H} NMR: δ 143.5, 136.9, 132.9, 129.7, 127.1, 117.7, 45.8, 21.5.

**Synthesis of N-allyl-4-methoxybenzenesulfonamide and N,N-diallyl-4-methoxybenzenesulfonamide.** Allyl alcohol (42 mL, 0.60 mmol) was added to a suspension of (2)AuCl $\mathcal{[2 = P(t-Bu)_2-o-biphenyl]}$; 7.9 mg, 0.015 mmol], AgSbF$_6$ (5.1 mg, 0.015 mmol) and p-methoxybenzenesulfonamide (56 mg, 0.30 mmol) in 1,4-dioxane (0.5 mL) and the resulting mixture was stirred at 100 ºC for 24 h. The resulting suspension was concentrated under vacuum and the residue was chromatographed (hexanes–EtOAc = 4:1 → 1:1) to give a 4:1 mixture of mono:diallylation products, N-allyl-4-methoxybenzenesulfonamide (54.5 mg, 80%, colorless oil) and N,N-diallyl-4-methoxybenzenesulfonamide (16.5 mg, 20%, colorless oil) separable by column chromatography.

For N-allyl-4-methoxybenzenesulfonamide: TLC (hexanes–EtOAc = 1:1): $R_f = 0.55$. $^1$H NMR: δ 7.78 (d, J = 8.8 Hz, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 5.69 (tdd, J = 5.6, 10.4, 17.2 Hz, 1 H), 5.16-5.04 (m, 2 H), 4.70 (t, J = 6.4 Hz, 1 H), 3.84 (s, 3 H), 3.54 (tt, J = 1.6, 6 Hz, 2 H). $^{13}$C{\textsuperscript{1}H} NMR: δ 162.9, 133.0, 131.4, 129.3, 117.6, 114.2, 55.6, 45.7.

For N,N-diallyl-4-methoxybenzenesulfonamide: TLC (hexanes–EtOAc = 1:1): $R_f = 0.73$. $^1$H NMR: δ 7.73 (d, J = 8.8 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 5.59 (tdd, J = 6.4, 10.0, 17.4 Hz, 2 H), 5.14-5.09 (m, 4 H), 3.85 (s, 3 H), 3.77 (d, J = 6 Hz, 4 H). $^{13}$C{\textsuperscript{1}H} NMR: δ 162.7, 132.6, 132.0, 129.2, 118.9, 114.2, 55.6, 49.2.
**1-Allylpyrrolidin-2-one.** Colorless oil, 42%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.11$. $^1$H NMR: $\delta$ 5.78-5.68 (m, 1 H), 5.21-5.15 (m, 2 H), 3.89 (d, $J = 6.4$ Hz, 2 H), 3.35 (t, $J = 6.8$ Hz, 2 H), 2.41 (t, $J = 7.6$ Hz, 2 H), 2.02 (quintet, $J = 7.2$ Hz, 2 H). $^{13}$C{$^1$H} NMR: $\delta$ 174.9, 134.6, 116.9, 71.7, 71.4, 31.4, 18.2.

**Benzyl allylcarbamate.** Colorless oil, 23%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.73$. $^1$H NMR: $\delta$ 7.37-7.31 (m, 5 H), 5.89-5.80 (m, 1 H), 5.22-5.12 (m, 2 H), 4.80 (bs, 1 H), 3.83 (t, $J = 5.2$ Hz, 2 H), 1.55 (s, 1 H). $^{13}$C{$^1$H} NMR: $\delta$ 156.3, 136.5, 134.4, 128.5, 128.1, 116.1, 66.8, 43.3.

**N-Benzyl-N-methylprop-2-en-1-amine.** Colorless oil, 32%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.42$. $^1$H NMR: $\delta$ 7.25-7.16 (m, 5 H), 5.89-5.79 (m, 1 H), 5.13 (dd, $J = 1.2, 16.8$ Hz, 1 H), 5.08 (dd, $J = 1.2, 10.4$ Hz, 1 H), 3.42 (s, 2 H), 2.96 (d, $J = 6.4$ Hz, 2 H), 2.12 (s, 3 H).

**1-(3,3-Dideuterio-2-propenyl)-3-methyl-imidazolidin-2-one (3-$\gamma$, $\gamma$-d$_2$).** Colorless oil, 99%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.14$. $^1$H NMR: $\delta$ 5.73 (s, 1 H), 3.77 (d, $J = 6.4$ Hz, 2 H), 3.29-3.20 (m, 4 H), 2.77 (s, 3 H). $^{13}$C{$^1$H} NMR: $\delta$ 161.3, 133.3, 117.0 (quintet, $J = 94.8$ Hz), 47.1, 45.0, 42.2, 31.3. HRMS calcd (found) for C$_7$H$_{10}$D$_2$N$_2$O (M$^+$): 142.1074 (142.1076).

**1-(2-Butenyl)-3-methylimidazolidin-2-one (4).** Pale yellow oil, 91%, 2.4:1 $E/Z$ mixture. TLC (hexanes–EtOAc = 1:1): $R_f = 0.17$. The $E$-configuration of the major diastereomer was established from the downfield shifts of the olefinic resonances in the $^{13}$C NMR spectrum and by analogy to remaining allylic ureas. $^1$H NMR: $\delta$ 5.68-5.54 (m, 1 H), 5.40-5.31 (m, 1 H), [3.81 (td, $J = 0.8, 7.2$ Hz), 3.69 (td, $J = 1.2, 6.8$ Hz), 2.4:1, 2 H], 3.26-3.16 (m, 4 H), 2.75 (s, 3 H), 1.65 (d, $J = 6.8$ Hz, 3 H). $^{13}$C{$^1$H} NMR [$E$ isomer]: $\delta$ 161.4, 128.9, 126.2, 46.4, 45.1, 42.1, 31.4, 17.6. $^{13}$C{$^1$H} NMR [$Z$ isomer]: $\delta$ 161.5, 127.9, 125.2, 45.1, 42.1, 40.6, 31.4, 12.8. IR (neat, cm$^{-1}$): 2919, 2858, 1683, 1499, 1444, 1404, 1357, 1245,
(E)-1-Cinnamyl-3-methylimidazolidin-2-one (5). Pale yellow oil, 85%. TLC (hexanes-EtOAc = 1:1): Rf = 0.12. 1H NMR: δ 7.37-7.29 (m, 4 H), 7.26-7.22 (m, 1 H), 6.53 (d, J = 15.6 Hz, 1 H), 6.15 (dt, J = 6.8, 15.6 Hz, 1 H), 3.96 (d, J = 6.8 Hz, 2 H), 3.29 (s, 4 H), 2.82 (s, 3 H). 13C{1H} NMR: δ 161.4, 136.6, 132.8, 128.5, 127.6, 126.4, 125.1, 46.7, 45.1, 42.3, 31.4. IR (neat, cm⁻¹): 2921, 1679, 1496, 1449, 1406, 1252, 1056, 967, 909, 729, 698, 645. Anal. calcd (found) for C₁₃H₁₄N₂O: H, 7.46 (7.47); C, 72.19 (72.10). HRMS calcd (found) for C₁₃H₁₆N₂O (M⁺): 216.1263 (216.1263).

(Z)-1-Cinnamyl-3-methylimidazolidin-2-one (5). Resonances corresponding to (Z)-5 were identified through analysis of a 6.7:1 mixture of (E)-5 and (Z)-5 and by comparison to the spectra of pure (E)-5. 1H NMR (partial spectra): δ 6.53 (d, J = 15.6 Hz, 1 H), 5.63 (td, J = 6.0, 11.6 Hz, 1 H), 3.96 (dd, J = 1.6, 6.8 Hz, 2 H), 3.26-3.17 (m, 4 H), 2.79 (s, 3 H). 13C{1H} NMR (partial spectra): δ 131.9, 128.8, 128.4, 128.2, 127.1, 125.6, 42.5, 42.4.

1-Methyl-3-(3-methylbut-2-enyl)imidazolidin-2-one (6a). Colorless oil, 100%. TLC (hexanes–EtOAc = 1:1): Rf = 0.19. 1H NMR (500 MHz): δ 5.11 (t, J = 7.2 Hz, 1 H), 3.74 (d, J = 7.2 Hz, 2 H), 3.25-3.17 (m, 4 H), 2.75 (s, 3 H), 1.69 (s, 3 H), 1.65 (s, 3 H). 13C{1H} NMR: δ 161.6, 136.2, 119.4, 45.2, 42.1, 41.9, 31.4, 25.7, 17.7. IR (neat, cm⁻¹): 2932, 1681, 1500, 1443, 1404, 1378, 1250, 1101, 1026, 849, 759, 650. Anal. calcd (found) for C₁₃H₁₆N₂O: H, 9.59 (9.58); C, 64.25 (64.10). HRMS calcd (found) for C₁₃H₁₆N₂O (M⁺): 168.1263 (168.1262).

1-Methyl-3-(2-methylbut-3-en-2-yl)imidazolidin-2-one (6b). An authentic sample of pure 6b was synthesized via the gold(I)-catalyzed intermolecular allene hydroamination. A suspension of 3-methyl-1,2-butadiene (35 mL, 0.36 mmol), 1 (36 mg,
0.36 mmol), (IPr)AuCl [IPr = (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine)] (11 mg, 0.018 mmol), and AgOTf (5 mg, 0.02 mmol) in dioxane (0.5 mL) was stirred at 23 °C for 18 h. The crude reaction mixture was chromatographed (hexanes–EtOAc = 4:1 → 1:1) to give 6b (55.8 mg, 92%) as a colorless oil. TLC (hexanes–EtOAc = 1:1): $R_f = 0.28$. $^1$H NMR: δ 6.03 (dd, $J = 10.8, 17.6$ Hz, 1 H), 5.09-5.02 (m, 2 H), 3.26-3.15 (m, 4 H), 2.72 (s, 3 H), 1.44 (s, 6 H). $^{13}$C($^1$H) NMR: δ 161.8, 143.3, 111.7, 56.4, 44.8, 41.8, 40.8, 31.3, 25.2. IR (neat, cm$^{-1}$): 2978, 2861, 1688, 1491, 1426, 1397, 1246, 1200, 1036, 920, 764, 737, 693. Anal. calcd (found) for C$_9$H$_{16}$N$_2$O: H, 9.59 (9.41); C, 64.25 (64.11). HRMS calcd (found) for C$_9$H$_{17}$N$_2$O(M$^+$): 169.1341 (169.1339).

1-(2-Cyclohexylideneethyl)-3-methylimidazolidin-2-one (7). Colorless oil, 100%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.23$. $^1$H NMR: δ 5.06 (t, $J = 7.2$ Hz, 1 H), 3.76 (d, $J = 7.6$ Hz, 2 H), 3.24-3.18 (m, 4 H), 2.75 (s, 3 H), 2.16 (t, $J = 5.6$ Hz, 2 H), 2.07 (t, $J = 5.2$ Hz, 2 H), 1.53-1.46 (m, 6 H). $^{13}$C($^1$H) NMR: δ 161.5, 144.4, 115.9, 45.1, 42.0, 40.9, 37.0, 31.4, 28.6, 28.5, 27.8, 26.7. IR (neat, cm$^{-1}$): 2926, 2853, 1686, 1497, 1442, 1403, 1249, 1049, 1003, 933, 851, 760, 652. Anal. calcd (found) for C$_{12}$H$_{20}$N$_2$O: H, 9.68 (9.37); C, 69.19 (68.98).

1-(But-3-en-2-yl)-3-methylimidazolidin-2-one (8). Pale yellow oil, 85%. TLC (hexanes-EtOAc = 1:1): $R_f = 0.18$. $^1$H NMR (500 MHz): δ 5.77-5.04 (m, 1 H), 5.16-5.12 (m, 2 H), 4.59-4.54 (m, 1 H), 3.28-3.18 (m, 4 H), 2.78 (s, 3 H), 1.21 (d, $J = 7.0$ Hz, 3 H). $^{13}$C($^1$H) NMR: δ 161.1, 138.0, 115.5, 49.2, 45.3, 37.7, 31.4, 15.9. IR (neat, cm$^{-1}$): 2871, 1679, 1497, 1440, 1403, 1279, 1251, 1046, 970, 925, 760, 706. Anal. calcd (found) for C$_8$H$_{14}$N$_2$O: H, 9.15 (9.21); C, 62.31 (62.36). HRMS calcd (found) for C$_8$H$_{14}$N$_2$O (M$^+$): 154.1106 (154.1103).

1-(Cyclohex-2-enyl)-3-methylimidazolidin-2-one (9). Pale yellow oil, 97%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.18$. $^1$H NMR: δ 5.83-5.78 (m, 1 H), 5.41-5.37 (m, 1 H), 5.08 (d, $J = 17.6$ Hz, 1 H), 4.59 (d, $J = 7.6$ Hz, 2 H), 3.24-3.18 (m, 4 H), 2.78 (s, 3 H), 1.21-1.14 (d, $J = 7.0$ Hz, 3 H). $^{13}$C($^1$H) NMR: δ 161.1, 138.0, 115.5, 49.2, 45.3, 37.7, 31.4, 15.9. IR (neat, cm$^{-1}$): 2871, 1679, 1497, 1440, 1403, 1279, 1251, 1046, 970, 925, 760, 706. Anal. calcd (found) for C$_8$H$_{14}$N$_2$O (M$^+$): 154.1106 (154.1103).
4.46-4.41 (m, 1 H), 3.20-3.17 (m, 4 H), 2.72 (s, 3 H), 2.01-1.94 (m, 2 H), 1.84-1.71 (m, 2 H), 1.69-1.61 (m, 1 H), 1.60-1.50 (m, 1 H). $^{13}$C$[^1]$H NMR: δ 161.3, 131.2, 128.1, 48.7, 45.4, 38.6, 31.5, 26.3, 24.6, 21.2. IR (neat, cm$^{-1}$): 2933, 2862, 1681, 1494, 1433, 1401, 1277, 1253, 1202, 1045, 965, 927, 760, 727, 710, 648. HRMS calcd (found) for C$_{10}$H$_{16}$N$_2$O (M$^+$): 180.1263 (180.1262).

1-Methyl-3-(3-penten-2-yl)imidazolidin-2-one (11). Pale yellow oil, 99%, E/Z = 4.2:1. TLC (hexanes–EtOAc = 1:1): $R_f$ = 0.19. $^1$H NMR: δ 5.63-5.54 (m, 1 H), 5.46-5.40 (m, 1 H), [4.84-4.77 (m), 4.51-4.45 (m), 4.2:1, 1 H], 3.27-3.17 (m, 4 H), 2.77 (s, 3 H), 1.68 (td, $J$ = 1.6, 6.4 Hz, 3 H), 1.19 (d, $J$ = 7.2 Hz, 3 H). $^{13}$C$[^1]$H NMR: δ 161.2, [130.7, 129.5 (4.2:1)], [126.9, 126.5 (1:4.2)], 126.6, 48.9, [45.5, 45.4 (1:4.2)], [37.8, 37.7 (1:4.2)], 31.5, [18.6, 17.8 (1:4.2)], [16.9, 13.3 (4.2:1)]. IR (neat, cm$^{-1}$): 2937, 1678, 1495, 1439, 1402, 1277, 1252, 1211, 1104, 1042, 1016, 969, 759. Anal. calcd (found) for C$_{13}$H$_{16}$N$_2$O: H, 9.59 (9.50); C, 64.25 (63.95). HRMS calcd (found) for C$_{9}$H$_{16}$N$_2$O(M$^+$): 168.1263 (168.1263).

1-(1-Methyl-3-deuterio-2-butenyl)-3-methyl-imidazolidin-2-one (11-$\gamma$-d$_1$). Pale yellow oil, 100%, E/Z = 3.7:1. TLC (hexanes–EtOAc = 1:1): $R_f$ = 0.19. $^1$H NMR: δ 5.40-5.32 (m, 1 H), [4.81-4.73 (m), 4.48-4.41 (m), 3.7:1, 1 H], 3.23-3.13 (m, 4 H), 2.72 (s, 3 H), 1.64 (d, $J$ = 8.8 Hz, 3 H), 1.13 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C$[^1]$H NMR: δ 161.1, [130.6, 129.4, 3.7:1], 126.2 (t, $J$ = 91.6 Hz), 48.8, 45.3, 44.7, 37.7, 37.6, 31.4, 18.6, 17.6, 16.8, 13.2. HRMS calcd (found) for C$_{9}$H$_{15}$DN$_2$O(M$^+$): 169.1325 (169.1323).

(E)-1-(1,3-Diphenylallyl)-3-methylimidazolidin-2-one (12). White solid (mp 102-104 °C), 100%. TLC (hexanes–EtOAc = 1:1): $R_f$ = 0.29. $^1$H NMR (500 MHz): δ 7.33 (d, $J$ = 7 Hz, 1 H), 7.27-7.15 (m, 9 H), 6.58 (d, $J$ = 16 Hz, 1 H), 6.39 (dd, $J$ = 6.5, 16 Hz, 1 H), 5.80 (d, $J$ = 6.5 Hz, 1 H), 3.29-3.14 (m, 4 H), 2.97-2.92 (m, 1 H), 2.74 (s, 3 H). $^{13}$C$[^1]$H NMR: δ 161.1, 139.2, 136.7, 133.0, 128.5, 127.9, 127.7, 127.5, 126.5, 126.3, 57.5, 45.2, 38.6, 31.4. IR (neat, cm$^{-1}$): 2881, 1678, 1503, 1434, 1404, 1276, 1245, 1208, 1060, 978, 787, 752, 700. Anal.
calcd (found) for C$_{19}$H$_{20}$N$_2$O: H, 6.89 (7.47); C, 78.05 (77.38). HRMS calcd (found) for C$_{19}$H$_{20}$N$_2$O (M$^+$): 292.1576 (292.1567).

1-(Hex-3-en-2-yl)-3-methylimidazolidin-2-one (14). Colorless oil, 100%, E/Z = 4.3:1. TLC (hexanes-EtOAc = 1:1): $R_f$ = 0.26. $^1$H NMR: δ 5.62-5.54 (m, 1 H), 5.46-5.26 (m, 1 H), [4.76 (m), 4.48 (m), 4.3:1, 2 H], 3.24-3.14 (m, 4 H), 2.74 (s, 3 H), 2.01 (q, $J$ = 7.6 Hz, 2 H), 1.16 (d, $J$ = 6.8 Hz, 3 H), 0.94 (t, $J$ = 7.6 Hz, 3 H). $^{13}$C($^1$H) NMR: δ 161.1, [134.4, 133.5, 1:4.3], [128.3, 127.9, 4.3:1], 48.7, [45.4, 45.3, 1:4.3], [37.7, 37.5, 1:4.3], 31.4, 25.3, 16.8, 13.5. IR (neat, cm$^{-1}$): 2964, 2872, 1686, 1494, 1435, 1401, 1276, 1252, 1209, 1045, 971, 923, 760, 730. HRMS calcd (found) for C$_{10}$H$_{18}$N$_2$O (M$^+$): 182.1419 (182.1426).

2.3.4 Synthesis and amination of enantiomerically enriched allylic alcohols

(R,E)-3-penten-2-ol [(R)-10]. (R)-10 was prepared in 27% yield and 92% ee by kinetic resolution of (±)-(E)-3-penten-2-ol employing a procedure reported by Sharpless.$^{80}$ The enantiopurity of (R)-10 was determined by HPLC analysis of the corresponding Mosher’s ester 3-penten-2-yl α-methoxy-α-trifluoromethylphenylacetate (17) and by comparison to the HPLC of 17 generated from racemic 10 (Figure 2.4).

Synthesis of (R,R)-17 and (R,S)-17. A suspension of 1,3-dicyclohexylcarbodiimide (170 mg, 0.81 mmol) and dimethylaminopyridine (7 mg, 0.06 mmol) in CH$_2$Cl$_2$ (2 mL) was added to a solution of (±)-10 (59 mL, 0.58 mmol) and (R)-(+) α-methoxy-α-trifluoromethylphenylacetic acid (0.14 g, 0.58 mmol) in CH$_2$Cl$_2$ (2 mL) at 0 ºC. The resulting mixture was warmed to room temperature and stirred overnight. The resulting suspension was filtered through a silica plug and the filtrate was concentrated and chromatographed (petroleum ether–ether = 4:1 → 1:1) to give a 1:1 mixture of (R,R)-17 and (R,S)-17 (156 mg, 89%) as a pale yellow oil. TLC (petroleum ether–ether = 4:1): $R_f$ = 0.64.
For (R,R)-17: $^1$H NMR (500 MHz): $\delta$ 7.53-7.51 (m, 2 H), 7.42-7.36 (m, 3 H), 5.88-5.81 (m, 1 H), 5.60-5.51 (m, 1 H), 5.46-5.41 (m, 1 H), 3.57 (s, 3 H), 1.71 (d, $J = 7$ Hz, 2 H), 1.40 (d, $J = 7$ Hz, 1 H).

For (R,S)-17: $^1$H NMR (500 MHz): $\delta$ 7.53-7.51 (m, 2 H), 7.42-7.36 (m, 3 H), 5.80-5.73 (m, 1 H), 5.60-5.51 (m, 1 H), 5.60-5.51 (m, 1 H), 3.55 (s, 3 H), 1.67 (d, $J = 6.5$ Hz, 2 H), 1.33 (d, $J = 6$ Hz, 1 H).

![HPLC traces](image)

**Figure 2.4** HPLC traces of a 1:1 mixture of (R,R)-17 and (R,S)-17 (left trace) and a 96:4 mixture of (R,R)-17 and (R,S)-17 (right trace). HPLC conditions: hexanes–isopropanol = 99.9:0.1 @ 0.5 mL/min.

(R,E)-4-Hexen-3-ol [(R)-13]. (R)-13 was prepared in 31% yield and 96% ee by kinetic resolution of (±)-(E)-4-hexen-3-ol employing a procedure reported by Sharpless.\(^8\) The enantiopurity of (R)-13 was determined by HPLC analysis of the corresponding Mosher’s ester 4-hexen-3-yl $\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetate (18) and by comparison to the HPLC of 18 generated from racemic 13 (Figure 2.5). Mosher’s ester 18 was synthesized employing a procedure similar to that used to synthesize 17. TLC (petroleum ether–ether = 4:1): $R_f = 0.71$. 

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For (R,R)-18: $^1$H NMR (500 MHz): $\delta$ 7.53-7.50 (m, 2 H), 7.40-7.37 (m, 3 H), 5.89-5.82 (m, 1 H), 5.49-5.44 (m, 1 H), 5.40-5.32 (m, 1 H), 3.55 (s, 3 H), 1.78-1.56 (m, 2 H), 1.73 (d, $J = 8$ Hz, 3 H), 0.82 (t, $J = 8$ Hz, 3 H).

For (R,S)-18: $^1$H NMR (500 MHz): $\delta$ 7.53-7.50 (m, 2 H), 7.40-7.37 (m, 3 H), 5.82-5.75 (m, 1 H), 5.40-5.31 (m, 1 H), 5.40-5.32 (m, 1 H), 3.56 (s, 3 H), 1.78-1.56 (m, 2 H), 1.69 (d, $J = 6.5$ Hz, 3 H), 0.92 (t, $J = 7.5$ Hz, 3 H).

![HPLC traces of a 1:1 mixture (left trace) and 98:2 mixture (right trace) of (R,R)-18 and (R,S)-18. HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.5 mL/min.](image)

Figure 2.5 HPLC traces of a 1:1 mixture (left trace) and 98:2 mixture (right trace) of (R,R)-18 and (R,S)-18. HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.5 mL/min.

Reaction of 1 with (R)-10. Gold(I)-catalyzed reaction of 1 with (R)-10 employing a procedure identical to that as used to synthesize racemic 11 led to isolation of a 4.2:1 mixture of (S,E)-11 and (R,Z)-11 in 99% combined yield (Scheme 2.2). The diastereomeric and enantiomeric purity of (S,E)-11 and (R,Z)-11 was determined by chiral HPLC analysis and by comparison to racemic samples of E-11 and Z-11 (Figures 2.6 and 2.7).
Figure 2.6 Chiral HPLC traces of racemic (E)-11 (left trace) and enantiomerically enriched (S,E)-11 (right trace). HPLC conditions: 99:1 hexanes-isopropanol @ 0.5 mL/min.

Figure 2.7 Chiral HPLC traces of (Z)-11 (left trace) and enantiomerically enriched (R,Z)-11 (right trace). HPLC conditions: 99:1 hexanes-isopropanol @ 0.5 mL/min.
Determination of absolute configuration of \((S,E)-11\) and \((R,Z)-11\). The absolute configuration of \((S,E)-11\) and \((R,Z)-11\) were determined by the following series of experiments. Reduction of a 4.2:1 mixture of \((S,E)-11\) (86% ee) and \((R,Z)-11\) (92% ee) (H\(_2\) over Pd/C) led to isolation of \((S)-1\)-methyl-3-(pentan-2-yl)imidazolidin-2-one \([(S)-19]\) in 83\% yield with 49\% ee (Scheme 2.2), which is very near the calculated value of 51\% ee for reduction of a 4.2:1 mixture of \((S,E)-11\) (86\% ee) and \((R,Z)-11\) (92\% ee), and therefore established that \((S,E)-11\) and \((R,Z)-11\) were of the opposite absolute configuration. An authentic sample of \((S)-19\) was synthesized independently by first converting \((R)-2\)-pentanol (95\% ee) to its corresponding tosylate \((R)-20\) in 84\% yield with 94\% ee, as determined by chiral HPLC analysis (Figure 2.9). \((R)-20\) was then reacted with the anion of \(1\) to give \((S)-19\) in 7\% yield with 94\% ee as determined by chiral HPLC analysis (Figure 2.10). Chiral HPLC analysis of \((S)-19\) (94\% ee) generated from \((R)-2\)-pentanol and \((S)-19\) (49\% ee) obtained via reduction of a 4.2:1 mixture of \((S,E)-11\) and \((R,Z)-11\) revealed that both samples were of the same absolute configuration and therefore established the absolute configuration of the \(N\)-allylic ureas formed in the gold(I)-catalyzed amination of \((R)-10\) with \(1\) as \((S,E)-11\) and \((R,Z)-11\) (Scheme 2.2).
Scheme 2.2

(S)-1-Methyl-3-(pentan-2-yl)imidazolidin-2-one [(S)-19] from 11. A 4.2:1 mixture of (S, E)-11 and (R, Z)-11 was reduced (H₂, Pd/C) using a published procedure to give (S)-19 in 83% yield and 49% ee as a colorless oil. TLC (hexanes–EtOAc = 1:1): Rf = 0.20. ¹H NMR: δ 3.95 (sextet, J = 6.4 Hz, 1 H), 3.27–3.13 (m, 4 H), 2.76 (s, 3 H), 1.48–1.21 (m, 4 H), 1.06 (d, J = 7.2 Hz, 3 H), 0.89 (t, J = 7.2 Hz, 3 H). ¹³C{¹H} NMR: δ 161.4, 47.4, 45.5, 37.0, 36.2, 31.5, 19.7, 17.8, 13.9. IR (neat, cm⁻¹): 2958, 2870, 1682, 1436, 1402, 1277, 1250, 1211, 1118, 1055, 920, 761, 731. HRMS calcd (found) for C₁₁H₂₀N₂O (M⁺): 170.1419 (170.1420). The enantiomeric excess of (S)-19 (49% ee) was determined by chiral HPLC analysis (Figure 2.8).
Figure 2.8 Chiral HPLC traces of racemic 19 (left trace) and (S)-19 (49% ee, right trace) obtained via reduction of a 4.2:1 mixture of (S,E)-11 (86% ee) and (R,Z)-11 (92% ee).

HPLC conditions: 98:2 hexanes-isopropanol @ 0.5 mL/min.

Independent synthesis of (S)-19. Reaction of (R)-2-pentanol with p-toluenesulfonyl chloride employing a published procedure gave (R)-pentan-2-yl-4-methylbenzenesulfonate [(R)-20] in 84% yield and 94% ee as a yellow oil. The enantiopurity of (R)-20 was determined by chiral HPLC analysis (Figure 2.9). 1-Methylimidazolidin-2-one (1; 30 mg, 0.3 mmol) in THF (1 mL) was added dropwise to a suspension of NaH (7 mg, 0.3 mmol) in THF (1 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was cooled to −78 °C, treated with a solution of (R)-20 (73 mg, 0.3 mmol) in THF (1 mL), and the resulting solution was stirred overnight at room temperature. The reaction mixture was treated with H₂O (0.5 mL) and extracted with ether. The combined ether extracts were dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 4:1 → 1:1) to give (S)-19 (5 mg, 7%, 94% ee) as a colorless oil. Enantiomeric purity of (S)-19 was determined by chiral HPLC analysis (Figure 2.10).
For (R)-20: $^1$H NMR: $\delta$ 7.75 (d, $J = 8.8$ Hz, 2 H), 7.29 (d, $J = 8.8$ Hz, 2 H), 4.58 (sextet, $J = 6.4$ Hz, 1 H), 2.40 (s, 3 H), 1.58-1.51 (m, 2 H), 1.46-1.38 (m, 2 H), 1.21 (d, $J = 6$ Hz, 3 H), 0.77 (t, $J = 7.2$ Hz, 3 H).

Figure 2.9 Chiral HPLC traces of racemic 20 (left trace) and (R)-20 (94% ee, right trace). HPLC conditions: 98:2 hexanes-isopropanol @ 0.5 mL/min.

Figure 2.10 Chiral HPLC traces of racemic 19 (left trace) and enantiomerically enriched (S)-19 (94% ee, right trace) generated from (R)-2-pentanol. HPLC conditions: 98:2 hexanes/isopropanol @ 0.5 mL/min.
Reaction of 1 with (R)-4-hexen-3-ol [(R)-13]. Reaction of 1 with (R)-13 catalyzed by a 1:1 mixture of (2)AuCl and AgOTf employing a procedure identical to that as used to synthesize racemic 1-methyl-3-(hex-3-en-2-yl)imidazolidin-2-one (14) led to isolation of a 4.3:1 mixture of (S,E)-14 and (R,Z)-14 in 100% combined yield. The diastereomeric and enantiomeric purity of (S,E)-14 and (R,Z)-14 was determined by chiral HPLC analysis and by comparison to racemic samples of E-14 and Z-14 (Figures 2.11 and 2.12). The absolute configuration of (S,E)-14 and (R,Z)-14 were assigned by analogy to (S,E)-11 and (R,Z)-11.

Figure 2.11 Chiral HPLC traces of racemic (E)-14 (left trace) and (S,E)-14 (right trace).

HPLC conditions: 99:1 hexanes-isopropanol @ 0.5 mL/min.
2.3.5 Kinetics experiments

Reaction of 1 with 3-methyl-2-buten-1-ol. A solution of 1 (0.60 M), 3-methyl-2-buten-1-ol (0.60 M), 1,3-dimethoxybenzene (1.0 mg; internal standard), and a catalytic 1:1 mixture of (2)AuCl and AgSbF$_6$ (5 mol %) in dioxane-$d_8$ was monitored periodically by $^1$H NMR spectroscopy at 60 °C. Analysis after 10 h revealed that 17% of 1 had been consumed to form 6a (11%), 6b (3%), 2-methyl-3-buten-2-ol (~1%), and 1,1-dimethyl-2-propenyl 3-methyl-2-butenyl ether (15; ~2%). Minor components 6b, 2-methyl-3-buten-2-ol, and 15 were identified by $^1$H NMR analysis and by comparison to authentic samples. The concentration of 3-methyl-2-buten-1-ol was determined by integrating the allylic methylene resonance at $\delta$ 3.97 (d, $J = 6.8$ Hz, 2 H). The concentration of 6a was determined by integrating the allylic methylene resonance at $\delta$ 3.74 (d, $J = 7.2$ Hz, 2 H). The concentrations of 6b, 2-methyl-3-buten-2-ol, and 15 were determined by integrating the internal olefinic proton of the respective compounds at $\delta$ 6.04 (dd, $J = 10.8, 17.6$ Hz, 1 H), 5.94 (dd, $J = 10.8, 17.4$ Hz, 1 H), and 5.82 (dd, $J = 10.8, 17.6$ Hz, 1 H). A plot of the relative concentrations of 3-methyl-2-buten-1-ol, 6a, and 6b versus time is depicted in
Figure 2.1. Under these conditions, 40% conversion was reached in 1440 min, 50% conversion in 1950 min and 75% conversion in 2880 min.

**Reaction of 1 with 3-methyl-2-buten-1-ol and water.** A solution of 1 (0.60 M), 3-methyl-2-buten-1-ol (0.60 M), water (0.60 M), and a catalytic 1:1 mixture of (2)AuCl and AgSbF$_6$ (5 mol %) in dioxane-$d_8$ was monitored periodically by $^1$H NMR spectroscopy at 60 °C. A plot of the relative concentrations of 3-methyl-2-buten-1-ol, 6a, and 6b versus time is depicted in Figure 2.13. Under these conditions, 25% conversion was reached in 530 min, 70% conversion in 1420 min and >95% conversion in 2840 min, which is ~1.5 times faster than in the absence of water.

![Concentration versus time plot](image)

**Figure 2.13** Concentration versus time plot for the reaction of 1 (0.60 M), 3-methyl-2-buten-1-ol (0.60 M; ◊) and water (0.60 M) catalyzed by a 1:1 mixture of (2)AuCl and AgSbF$_6$ (5 mol %) in dioxane-$d_8$ at 60 °C to form 6a (△) and 6b (□).
Reaction of 1 with 2-methyl-3-buten-2-ol. A solution of 1 (0.60 M), 2-methyl-3-buten-2-ol (0.60 M), and a catalytic 1:1 mixture of (2)AuCl and AgSbF$_6$ (5 mol %) in dioxane-$d_8$ was monitored periodically by $^1$H NMR spectroscopy at 60 °C. After 45 min, 25% of 1 had been consumed to form 6a as the exclusive product. After 165 min, 55% of 1 had been consumed to form 6a as the exclusive product, and after 20 h, 100% of 1 had been consumed to form 6a as the exclusive product.

Reaction of 1 with 15. A solution of 1 (0.60 M), 15 (0.60 M), and a catalytic 1:1 mixture of (2)AuCl and AgSbF$_6$ (5 mol %) in dioxane-$d_8$ was monitored periodically by $^1$H NMR spectroscopy at 60 °C. After 130 min, 13% of 1 had been consumed to form 6a as the exclusive product. After 265 min, 30% of 1 had been consumed to form 6a as the exclusive product, and after 24 h, 100% of 1 had been consumed to form 6a as the exclusive product.

Synthesis of 6a from 15. Ether 15 (92 mg, 0.60 mmol) was added to a suspension of (2)AuCl (7.9 mg, 0.015 mmol), AgSbF$_6$ (5.1 mg, 0.015 mmol) and 1 (30 mg, 0.30 mmol) in 1,4-dioxane (0.5 mL) and the resulting mixture was stirred at 60 °C for 24 h. The resulting suspension was concentrated under vacuum and the residue was chromatographed (hexanes–EtOAc = 4:1 → 1:1) to give 6a (50 mg, 98%) as a colorless oil.

Reaction of 3-methyl-2-buten-1-ol with catalytic 1:1 mixture of (2)AuCl and AgSbF$_6$. A solution of 3-methyl-2-buten-1-ol (0.60 M), and a catalytic 1:1 mixture of (2)AuCl and AgSbF$_6$ (5 mol %) in dioxane-$d_8$ was monitored periodically by $^1$H NMR spectroscopy at 60 °C. A plot of the relative concentrations of 3-methyl-2-buten-1-ol, 2-methyl-3-buten-2-ol, 15 and bis(3-methyl-2-butenyl)ether$^{73}$ versus time is depicted in Figure 2.14. Under these conditions, 20% conversion was reached in 1440 min to form a 3:1:1 mixture of 15, 2-methyl-3-buten-2-ol, and bis(3-methyl-2-butenyl)ether. 50%
conversion was reached in 5870 min to form a ~1:1 mixture of 15 and bis(3-methyl-2-buteny1)ether.

![Figure 2.14](image)

**Figure 2.14** Concentration versus time plot for the reaction of 3-methyl-2-butene-1-ol (0.60 M; ◇) catalyzed by a 1:1 mixture of (2)AuCl and AgSbF₆ (5 mol %) in dioxane-d₈ at 60 °C to form 2-methyl-3-buten-2-ol (△), 15 (□), and bis(3-methyl-2-buteny1)ether (○).

**Stability of 1-methyl-3-(2-methylbut-3-en-2-yl)imidazolidin-2-one (6b) under reaction conditions.** Cinnamyl alcohol (26 mL, 0.20 mmol) and water (3.6 mL, 0.20 mmol) were added to a suspension of (2)AuCl (7.9 mg, 0.015 mmol), AgSbF₆ (5.1 mg, 0.015 mmol), 1 (20 mg, 0.20 mmol) and 6b (34 mg, 0.20 mmol) in 1,4-dioxane (0.5 mL) and the resulting mixture was stirred at 60 °C for 24 h. The resulting suspension was concentrated under vacuum and the residue was chromatographed (hexanes–EtOAc = 4:1 → 1:1) to give 6a (9.4 mg, 28%), 6b (18.8 mg, 56%), and 5 (12.9 mg, 30%).
2.3.6 Syntheses of gold(I) π-allylic alcohol complexes

\{(\text{P}(\text{t-Bu})_{2}o\text{-biphenyl})\text{Au}(\eta^{2}\text{H}_{2}\text{C}=\text{CHCH}_{2}\text{OH})\}^{+} \text{SbF}_{6}^{-} (16a).\} A solution of (2)AuCl (60 mg, 0.113 mmol) and AgSbF_{6} (39 mg, 0.113 mmol) in CH_{2}Cl_{2} (2 mL) was stirred at room temperature for 5 min. Allyl alcohol (13.7 mg, 0.235 mmol) was added dropwise via syringe and the resulting suspension was stirred in a sealed flask at room temperature for 6 h. The resulting suspension was filtered and the filtrate concentrated to ~2 mL, diluted with hexanes (2 mL), and cooled at 4 °C for 24 h to form 16a (86 mg, 99%) as a white solid.

\^1H NMR (CD_{2}Cl_{2}): δ 7.89 (t, J = 8 Hz, 1 H), 7.68–7.52 (m, 5 H), 7.30–7.18 (m, 3 H), 6.24 (tdd, J = 2.5, 9, 16.5 Hz, 1 H, bound), 6.011 (tdd, J = 3.5, 9, 16.5 Hz, 1 H, free), 4.66 (dd, J = 1.5, 16.5 Hz, 1 H), 4.39 (br s, 2 H), 4.30 (dd, J = 1.5, 9 Hz, 1 H), 2.57 (br. s, 1 H), 1.41 (d, J = 16.5 Hz, 18 H).

\^13C\{^1H\} NMR (CD_{2}Cl_{2}): δ 148.7 (d, J = 13.5 Hz), 143.5 (d, J = 7.7 Hz), 138.9 (d, J = 10.6 Hz), 134.3, 133.7, 132.1, 129.9 (d, J = 13.5 Hz), 129.8, 128.4 (d, J = 7.7 Hz), 128.3, 124.8 (d, J = 47.1 Hz), 97.8, 62.9, 38.6 (d, J = 23.2 Hz), 30.8.

\(^{31}P\{^1H\}\) NMR (CD_{2}Cl_{2}): δ 64.7. Anal. calcd (found) for C_{23}H_{33}AuF_{6}OPSb: H, 4.21 (4.07); C, 35.00 (35.27).

\{(\text{P}(\text{t-Bu})_{2}o\text{-biphenyl})\text{Au}(\eta^{2}\text{Me}_{2}\text{C}=\text{CHCH}_{2}\text{OH})\}^{+} \text{SbF}_{6}^{-} (16b).\} Complex 16b was isolated in 96% yield as an off-white solid from reaction of 3-methyl-2-buten-1-ol with a mixture of (2)AuCl and AgSbF_{6} employing a procedure similar to that used to synthesize 16a. \(^1H\) NMR (CD_{2}Cl_{2}): δ 7.90 (t, J = 8 Hz, 1 H), 7.70–7.55 (m, 5 H), 7.30–7.18 (m, 3 H), 6.24 (ddd, J = 1, 9.5, 17 Hz, 1 H, bound), 5.87 (dd, J = 10, 17 Hz, 1 H, free), 4.69 (dd, J = 1.5, 9.5 Hz, 1 H), 4.46 (1.5, 9.5 Hz, 1 H), 2.40 (br s, 1 H), 2.09 (s, 3 H), 2.07 (br, 1 H), 1.41 (d, J = 16.5 Hz, 18 H).

\(^{13}C\{^1H\}\) NMR (CD_{2}Cl_{2}): δ 148.9 (d, J = 13.4 Hz), 143.7 (d, J = 6.7 Hz), 134.2, 133.8, 132.0, 130.1 (d, J = 14.4 Hz), 129.8, 128.4, 128.3 (d, J = 7.7 Hz), 124.3 (d, J = 48.1 Hz), 114.2, 59.2, 38.2 (d, J = 23.1 Hz), 30.9, 29.2, 22.5. \(^{31}P\{^1H\}\) NMR (CD_{2}Cl_{2}): δ 65.4. Anal. calcd (found) for C_{25}H_{37}AuF_{6}OPSb: H, 4.56 (4.59); C, 36.74 (36.80).
2.3.7 Reactions of gold(I) π-allylic alcohol complexes

Reaction of 16a with 1. 1-methyl-2-imidazolidinone (1.9 mg, 0.019 mmol) was added to an NMR tube that contained a 15% CD$_2$Cl$_2$ in dioxane-$d_8$ solution of 16a (15 mg, 0.019 mmol) at 60 °C. The tube was shaken, placed in the probe of an NMR spectrometer warmed at 60 °C and allowed to equilibrate for 10 minutes. After 10 minutes the $^1$H NMR spectrum showed resonances corresponding to the internal olefinic protons of bound ($\delta$ 5.90) and free ($\delta$ 5.81) allyl alcohol and 1-allyl-3-methylimidazolidin-2-one (3, $\delta$ 5.67). The reaction was observed out to one half-life ($t_{1/2} = 135$ min).

Reaction of 16a with 1 and HOTf. In a separate experiment, HOTf (0.3 mg, 0.002 mmol, 10 mol%) was added to an identical solution of 16a and 1, as above. Addition of a catalytic amount of HOTf was found to neither accelerate nor diminish the rate of reaction ($t_{1/2} = 135$ min). However, addition of one equivalent of HOTf (2.9 mg, 0.019 mmol) to an identical solution of 16a and 1-methyl-2-imidazolidinone significantly slowed the rate of reaction (29% conversion at 285 min).

Reaction of 16a with 1 and DBU. 1 (1.9 mg, 0.019 mmol) and DBU (2.9 mg, 0.019 mmol) were added to an NMR tube that contained a 15% CD$_2$Cl$_2$ in dioxane-$d_8$ solution of 16a (15 mg, 0.019 mmol) at 60 °C. The tube was shaken, placed in the probe of an NMR spectrometer warmed at 60 °C and allowed to equilibrate for 10 minutes. After 10 minutes the $^1$H NMR spectrum showed sharpened peaks corresponding to bound and free allylic alcohol and 1. No change was observed in the $^1$H NMR spectrum over the course of 2 h. Addition of HOTf (2.9 mg, 0.019 mmol) to this mixture resulted in immediate formation of allylic amination product 3.

In a separate experiment, DBU (2.0 mg, 0.013 mmol) was added to an NMR tube that contained a 15% CD$_2$Cl$_2$ in dioxane-$d_8$ solution of 16a (10 mg, 0.013 mmol) at 60 °C,
providing a $^1$H NMR spectrum identical to that obtained upon simultaneous addition of 1 and DBU to 16a.

**Reaction of 16a with 1 and LDA.** 1 (1.9 mg, 0.019 mmol) and LDA (2.1 mg, 0.019 mmol) were added to an NMR tube that contained a 15% CD$_2$Cl$_2$ in dioxane-$d_8$ solution of 16a (15 mg, 0.019 mmol) at 60 °C. The tube was shaken, placed in the probe of an NMR spectrometer warmed at 60 °C and allowed to equilibrate for 10 min. After 10 min, the $^1$H NMR spectrum showed resonances corresponding to the internal olefinic protons of bound ($\delta$ 5.94) and free ($\delta$ 5.87) allyl alcohol and 3 ($\delta$ 5.74) at ~ 1% conversion. No change was observed in the $^1$H NMR spectrum over the course of 2 h. All of the resonances were sharpened in a manner similar to that observed with the addition of DBU to a mixture of 1 and 16a.

In a separate experiment, the lithium salt of 1 (2.0 mg, 0.019 mmol, formed via addition of the urea to a THF/hexanes solution of LDA at -78 °C) was added to an NMR tube that contained a 15% CD$_2$Cl$_2$ in dioxane-$d_8$ solution of 16a (15 mg, 0.019 mmol) at 60 °C. The tube was shaken, placed in the probe of an NMR spectrometer warmed at 60 °C and allowed to equilibrate for 10 min. After 10 min, the $^1$H NMR spectrum showed resonances corresponding to the internal olefinic protons of bound ($\delta$ 6.01) and free ($\delta$ 5.89) allyl alcohol and 3 ($\delta$ 5.70) at ≤ 5% conversion. No change was observed in the $^1$H NMR spectrum over the course of 2 h. All of the resonances were broadened relative to that observed with the simultaneous addition of 1 and LDA to 16a.

**Reaction of 16a with 1 and 2,6-di-tert-butylypyridine.** 1 (1.9 mg, 0.019 mmol) and 2,6-di-tert-butylypyridine (3.6 mg, 0.019 mmol) were added to an NMR tube that contained a 15% CD$_2$Cl$_2$ in dioxane-$d_8$ solution of 16a (15 mg, 0.019 mmol) at 60 °C. The tube was shaken, placed in the probe of an NMR spectrometer warmed at 60 °C and allowed to equilibrate for 10 minutes. After 10 minutes, the $^1$H NMR spectrum showed
resonances corresponding to the internal olefinic protons of bound (δ 6.05) and free (δ 5.90) allyl alcohol and 3 (δ 5.74). The rate of allylic amination in the presence of 2,6-di-tert-butylpyridine (t₁/₂ = 480 min) was severely diminished relative to the reaction without added base.

**Reaction of 16b with 1.** 1 (1.9 mg, 0.019 mmol) was added to an NMR tube that contained a 15% CD₂Cl₂ in dioxane-d₈ solution of 16b (15 mg, 0.019 mmol) at 60 °C. The tube was shaken, placed in the probe of an NMR spectrometer warmed at 60 °C and allowed to equilibrate for 10 min. After 10 min. the ¹H NMR spectrum showed resonances corresponding to the internal olefinic protons of bound (δ 6.05) and free (δ 5.90) 3-methyl-2-buten-1-ol and 6a (δ 5.75). The tube was placed in an oil bath at 60 °C for 20 h. ¹H NMR analysis showed complete consumption of 16b and formation of 6a.

**X-ray crystal structure of 16b.** Colorless crystals of 16a were obtained by slow diffusion of hexanes through a CH₂Cl₂ solution of 16a at 4 °C. Diffraction data were obtained with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) on a Bruker Kappa Apex II diffractometer using the ω scan mode (Figure 2.2). Of the 5233 reflections, 4507 independent, observed reflections (I > 2σ (I)) were obtained with maximum h, k, l values of 9, 3, and 12, respectively. An absorption correction was applied (semi-emperical from equivalents). The solution method was SHELXS-97 (Sheldrick, 2008) and the refinement method was SHELXS-97 (Sheldrick, 2008). A table of crystal data and structure refinement is provided (Table 2.4).
2.3.8 Control experiments

1. **Gold/ligand only:** A suspension of 1 (30 mg, 0.30 mmol), allyl alcohol (0.26 g, 4.5 mmol), and (2)AuCl (16 mg, 0.03 mmol) in 1,4-dioxane (0.5 mL) in a sealed tube was stirred at 100 °C for 24 h, and then cooled to room temperature. GC, TLC, and $^1$H NMR analysis of the crude reaction mixture showed no detectable consumption of 1 and no
detectable formation of 3.

2. **Silver only:** A suspension of 1 (30 mg, 0.30 mmol), allyl alcohol (0.26 g, 4.5 mmol) and AgSbF$_6$ (10 mg, 0.03 mmol) in 1,4-dioxane (0.5 mL) in a sealed tube was stirred at 100 °C for 24 h and then cooled to room temperature. GC, TLC, and $^1$H NMR analysis of the crude reaction mixture showed no detectable consumption of 1 and no detectable formation of 3.

3. **Silver/ligand only:** A suspension of 1 (30 mg, 0.30 mmol), allyl alcohol (0.26 g, 4.5 mmol), AgSbF$_6$ (10 mg, 0.03 mmol) and P($t$-Bu)$_2$-o-biphenyl (9 mg, 0.03 mmol) in 1,4-dioxane (0.5 mL) in a pressure tube was stirred at 100 °C for 24 h and then cooled to room temperature. GC, TLC, and $^1$H NMR analysis of the crude reaction mixture showed no detectable consumption of 1 and no detectable formation of 3.

4. **HOTf only:** A suspension of 1-methyl-2-imidazolidione (30 mg, 0.30 mmol), allyl alcohol (0.262 g, 4.5 mmol) and HOTf (5 mg, 0.03 mmol) in 1,4-dioxane (0.5 mL) in a pressure tube was stirred at 100 °C for 24 h and then cooled to room temperature. GC, TLC, and $^1$H NMR analysis of the crude reaction mixture showed no detectable consumption of 1 and no detectable formation of 3.

5. **HOTf/ligand only:** A suspension of 1 (30 mg, 0.30 mmol), allyl alcohol (0.26 g, 4.5 mmol), HOTf (5 mg, 0.03 mmol) and 2 (9 mg, 0.03 mmol) in 1,4-dioxane (0.5 mL) in a pressure tube was stirred at 100 °C for 24 h and then cooled to room temperature. GC, TLC, and $^1$H NMR analysis of the crude reaction mixture showed no detectable consumption of 1 and no detectable formation of 3.
Chapter 3

Gold(I)-Catalyzed Intramolecular Amination of Allylic Alcohols with Alkylamines

Portions of this chapter have been published: Mukherjee, P.; Widenhoefer, R. A.

3.1 Background

Nitrogen containing heterocycles such as pyrrolidines and piperidines form an important class of compounds due to their prevalence in various natural products that exhibit varied and often potent pharmacological behavior. As a result, considerable attention has been given towards the synthesis of this class of compounds. Transition metal-catalyzed intramolecular amination of an underivatized allylic alcohol represents an attractive route towards the synthesis of these functionalized nitrogen heterocycles because of the ease of synthesis of the amine substrates, milder reaction conditions and atom economy since water is the only by-product. In addition, the 2-vinyl substitution on the heterocycle, generated by the allylic amination of an amine or carboxamide derivative on the allylic alcohol, provides a handle for further manipulation of the double bond to other functional groups.

![Figure 3.1](image)

**Figure 3.1** Examples of biologically important pyrrolidine and pyridine compounds.

Therefore, methods employing Au(III), Bi (III), and Pd (II) catalysts in combination with carbamates and sulfonamides as nucleophiles have been
demonstrated to undergo amination of underivatized allylic alcohols. Among these, palladium(II)-catalyzed cyclizations are mainly studied and have been utilized in the synthesis of numerous N-heterocyclic natural products.\textsuperscript{41} As an example, in 1997 Hirai and coworkers reported the synthesis of (-)-hydroxyseudamine where the piperidine core of the natural product was synthesized via a bis(acetonitrile)palladium(II) chloride mediated cyclization of compound 1 (eq 3.1).\textsuperscript{41f} However, a high catalyst loading (30 mol %) was required to enable efficient cyclization of 1. In general, most of the reported palladium(II)-catalyzed intramolecular allylic aminations require a high concentration of the palladium catalyst to ensure high efficiency (0.01 to 0.03 M) and always employ carbamates or sulfonamides as nucleophiles.

More recently, in 2009, Uenishi and coworkers demonstrated a Bi(OTf)\textsubscript{3} catalyzed intramolecular allylic amination with carbamates as nucleophile (eq 3.2).\textsuperscript{43} In the same year, Chan and coworkers reported a Au(III)-catalyzed protocol for the intramolecular allylic amination of underivatized allylic alcohols only with aryl sulfonamides as nucleophiles (eq 3.3).\textsuperscript{44} Overall, in contrast to the intermolecular allylic amination, which involves a subset of transformations that employ alkylamines as nucleophiles,
metal-catalyzed intramolecular amination of allylic alcohols with simple alkylamines has not been demonstrated.

![Equation 3.2]

We have developed an intermolecular amination of underivatized allylic alcohols with cyclic ureas and related nucleophiles catalyzed by a 1:1 mixture of (2)AuCl

\[ 2 = P(\text{-Bu})_2(o\text{-biphenyl}) \]

and AgSbF$_6$ (Chapter 2). Concurrent with our research efforts in allylic amination, Bandini and coworkers have developed a gold(I)-catalyzed intramolecular allylic arylation,\textsuperscript{64b} and Aponick and coworkers developed a gold(I)-catalyzed intramolecular allylic alkoxylation.\textsuperscript{65b} These reactions pointed towards the feasibility of an intramolecular allylic amination in presence of gold(I)-catalyst. Furthermore, Aponick and coworkers have demonstrated a gold(I)-catalyzed intramolecular amination of propargylic alcohols with secondary alkylamines that suggested alkylamines might be suitable nucleophiles under gold(I)-catalyzed conditions.\textsuperscript{65} Inspired by these reports, and guided by our experience with gold(I)-catalyzed intermolecular allylic amination, we targeted intramolecular cyclizations of underivatized allylic alcohols with simple alkylamines under gold(I)-catalysis. This chapter describes my contribution to the development of a first gold(I)-catalyzed intramolecular allylic amination with primary and secondary alkylamines as nucleophiles.
3.2 Results and discussion

3.2.1 Effect of nucleophile on the gold(I)-catalyzed intramolecular allylic amination

In an initial effort to develop the gold(I)-catalyzed protocol for intramolecular allylic amination, 6-(N-benzylamino)-5,5-diphenyl-2-hexenol (3a) was synthesized and subjected to the same catalytic conditions as employed for intermolecular allylic amination. In fact, the catalytic system proved to be highly efficient as treatment of 3a with a 1:1 mixture of (2)AuCl and AgSbF$_6$ (5 mol %) in dioxane at room temperature for 2 h led to formation of 2-vinyl pyrrolidine 4a isolated in 97% yield (Table 3.1, entry 1). In addition to N-benzylamine, other secondary alkylamines were also explored such as n-butylamine (3b) and a more sterically hindered tert-butylamine (3c). Both substrates, 3b and 3c underwent efficient cyclization in 2 h to form the corresponding 2-vinyl pyrrolidines 4b and 4c respectively in high yields (Table 3.1, entries 2-3). Gratifyingly, a primary alkylamine (3d) also underwent gold(I)-catalyzed intramolecular allylic amination, albeit in a longer reaction time of 48 h (Table 3.1, entry 4). Along with alkylamines, we also explored the scope of carbamates as nucleophiles in the intramolecular amination of allylic alcohols. On treatment of carbamate 3e with a catalytic 1:1 mixture of (2)AuCl and AgSbF$_6$ (5 mol %) in dioxane at room temperature for 72 h led to isolation of 4e in only 48% yield (Table 3.1, entry 5). Therefore, other silver salts in the the catalytic 1:1 mixture of (2)AuCl and silver salt were tested in order to investigate if there is any effect of different counterions of the precatalyst on the efficiency of the cyclization. Substitution of AgClO$_4$ for AgSbF$_6$ led to a marked improvement in the efficiency of cyclization of 3e and generated 4e in 97% isolated yield after 48 h (Table 3.1, entry 5).
Table 3.1 Effect of nucleophile on the gold(I)-catalyzed intramolecular amination of allylic alcohols 3.

<table>
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<th>entry</th>
<th>R</th>
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<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
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<td>Bn</td>
<td>3a</td>
<td>2</td>
<td>4a</td>
<td>97</td>
</tr>
<tr>
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<td>n-Bu</td>
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<td>2</td>
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<td>Cbz</td>
<td>3e</td>
<td>48</td>
<td>4e</td>
<td>97</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield in >95% purity.  <sup>b</sup>AgClO₄ used in place of AgSbF₆.

3.2.2 Substrate scope of intramolecular allylic amination

After the nucleophile scope, we next investigated the substrate scope in terms of the effect of ring size, substitutions on the backbone of the alkyl chain tethering the nucleophile to the allylic alcohol, substitution on the allylic hydroxyl bound carbon, and the alkene configuration on the efficiency and diastereoselectivity of gold(I)-catalyzed intramolecular allylic amination. Substrate 5a, with a cyclohexyl substitution on the alkyl chain tethering the nucleophile to the allylic alcohol, underwent efficient cyclization to form vinyl pyrrolidine 6a (Table 3.2, entry 1). In addition, a similar cyclohexyl-substituted allylic alcohol 5b that possessed an N-α-methylbenzylamine as nucleophile instead of N-benzylamine underwent gold(I)-catalyzed amination efficiently with a modest (2:1) diastereoselectivity (Table 3.2, entry 2). Although the gem-disubstitution on the alkyl chain tethering the allylic alcohol to the nucleophile facilitated intramolecular allylic amination, it was not essential. As an example, substrate 7a that possessed a C5 phenyl group underwent gold(I)-catalyzed cyclization
at 60 °C to form a 1.3:1 mixture of cis-8a and trans-8a in a 97% overall yield. cis-8a and trans-8a were separable by column chromatography (Table 3.2, entry 3). Similarly, substrate 7b with N-methylcyclohexyl amine as the nucleophile also underwent cyclization at 60 °C to form 8b in 99% yield as a 1.5:1 mixture of diastereomers (Table 3.2, entry 4). Finally, we looked into unsubstituted 6-(N-benzylamino)-2-hexenol (9; Z/E = 7.7:1) and it underwent efficient cyclization at 60 °C in 12 h to form 1-benzyl-2-vinylpyrrolidine (10) in 86% yield (Table 3.2, entry 5). On periodic analysis of the conversion of 9 to 10 by GC, it revealed that both the (Z)-isomer and the (E)-isomer of 9 cyclized at similar rates to form 10.

In addition to the formation of pyrrolidines, gold(I)-catalyzed intramolecular amination of allylic alcohols was also effective for the formation of piperidine derivatives. As an example, (Z)-6-(N-benzylamino)-2-heptenol (11) in presence of catalytic (2)AuCl and AgSbF₆ at 60 °C cyclized to form 1-benzyl-2-vinylpiperidine (12) in 91% isolated yield after 16 h (Table 3.2, entry 6). Likewise, gold(I)-catalyzed cyclization of (Z)-8-(N-benzylamino)-3-octen-2-ol (13), which possessed a methyl group on the allylic carbon bound to the hydroxyl, at 100 °C after 14 h formed 2-(1-propenyl)piperidine 14 in 99% yield with ≥ 50:1 diastereoselectivity (Table 3.2, entry 7). Gold(I)-catalyzed cyclization of the dithiane derivative 15 that possessed a stereogenic center α to the nucleophile benzylamine at 100 °C after 48 h provided cis-2,6-disubstituted piperidine 16 in 91% yield with 25:1 diastereoselectivity (Table 3.2, entry 8). Our particular interests in studying the cyclization of compound 15 under our developed gold(I)-catalyzed intramolecular amination was due to the fact that piperidine 16 and similar cis-2,6-disutituted piperidine analogs represent advanced intermediates in the synthesis of a range of naturally occurring piperidine alkaloids.86
Table 3.2 Substrate scope of the intramolecular amination of allylic alcohols catalyzed by a 1:1 mixture of (2)AuCl and AgSbF$_6$ in dioxane.

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<th>time (h)</th>
<th>heterocycle</th>
<th>yield (%)$^a$</th>
<th>dr$^b$</th>
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<td>6a</td>
<td>94</td>
<td>—</td>
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<tr>
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<td>5b [R = CH(Me)Ph]</td>
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<td>2</td>
<td>6b</td>
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<td>100</td>
<td>48</td>
<td>16</td>
<td>91</td>
<td>25:1</td>
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</table>

$^a$Isolated yield in >95% purity. $^b$Diastereomeric ratio determined by $^1$H NMR analysis of the crude reaction mixture.
3.2.3 Chirality transfer and synthesis of (S)-(+-)coniine

In order to evaluate the selectivity of 1,3-chirality transfer in the gold(I)-catalyzed intramolecular amination of allylic alcohols with secondary alkylamines, we synthesized enantiomerically and diastereomerically enriched \((R,Z)-8-(N\text{-benzylamino})-3\text{-octen}-2\text{-ol} \quad [(R,Z)-(13)]\) in 96% ee and 95% de. Treatment of \((R,Z)-13\) with a catalytic 1:1 mixture of \((2)\text{AuCl and AgSbF}_6\) at 100 °C after 14 h led to the formation of \((R,E)-14\) in 99% isolated yield as a single diastereomer \((\geq 50:1)\) (Scheme 3.1).

Scheme 3. 1

Piperidine \((R,E)-14\) was a precursor to the naturally occurring alkaloid \((S)-(+-)coniine\).\(^{41k,87}\) Therefore, a one-pot hydrogenation to cleave the benzyl group and reduce the exocyclic C=C bond using palladium on carbon \((\text{Pd/C, MeOH, HCOOH})\) followed by acidification with aqueous HCl gave \((S)-(+-)coniine hydrochloride in 90% isolated yield as a white solid. The absolute configuration of \((S)-(+-)coniine hydrochloride was established by measuring its optical rotation and comparing with known literature value \([\alpha]_D^{20} +6.9^\circ (c\ 0.1, \text{EtOH}); \text{ lit. } [\alpha]_D^{21} +7.1^\circ (c\ 1.0, \text{EtOH})\). This route to the synthesis of \((S)-(+-)coniine hydrochloride was also exploited to determine the enantiopurity and absolute configuration of \((R,E)-14\) generated by gold(I)-catalyzed intramolecular cyclization of \((R,Z)-13\). Therefore, treatment of \((S)-(+-)coniine hydrochloride with trifluoroacetic anhydride in presence of triethylamine formed \((S)-(+-)coniine\)
trifluoroacetamide in 85% yield and 96% ee determined by chiral phase GC analysis. Hence, all these results together revealed a complete transfer of chirality from (R,Z)-13 to (R,E)-14 and a net *syn*-addition of the nucleophile with respect to the departing hydroxyl group.

### 3.2.4 Mechanism

The net *syn*-addition of the nucleophile with respect to the departing hydroxyl group in the gold(I)-catalyzed conversion of (R,Z)-13 to (R,E)-14 is consistent with the mechanistic pathway in a concerted S$_{2'}$ substitution. However, such a pathway that invokes a σ-activation of the hydroxyl group by Au(I) is unlikely due to less oxophilicity and more pronounced π-acidity of Au(I). Therefore, nucleophilic addition to the π-bond activated by Au(I) followed by OH-elimination is more likely. Within this framework, two mechanistic pathways can lead to the formation of (R,E)-14 from (R,Z)-13: a *syn*-addition/*syn*-elimination or an *anti*-addition/*anti*-elimination. Although for Pd(II)-catalyzed allylic aminations and alkoxylations, a *syn*-addition/*syn*-elimination pathway is often proposed involving π-activation along with a hydroxyl group directed addition, strong tendency of cationic Au(I) complexes to form two-coordinate complexes instead of three rules out this possibility. Furthermore, Maseras and coworkers have shown computational evidence for an *anti*-addition/*anti*-elimination pathway in case of isomerization of allylic ethers in presence of alcohol. Therefore, in accordance with above, initial π-activation of the C=C bond of allylic alcohol by Au(I) leads to diastereomeric *si*-I and *re*-I complexes (Scheme 3.2). Outer-sphere attack by the pendant amine to the complexed C=C bond of *si*-I followed by a favorable hydrogen bonding with the hydroxyl group would lead to intermediate (R,S,R)-II. Proton transfer from the amine to the hydroxyl followed by *anti*-elimination of water and displacement of gold would lead to product (R,E)-14. In an analogous pathway for outer-sphere amine
addition on re-I and hydrogen bonding leads to intermediate (S,R,R)-II from where proton transfer, water elimination and gold displacement would lead to product (S,Z)-14. Now the unobserved latter pathway can be due to the unfavorable 1,3-diaxial interactions in the intermediate (S,R,R)-II between the methyl group and the methylene unit of the piperidine ring. This makes intermediate (S,R,R)-II much more unstable than the corresponding intermediate (R,S,R)-II that has a fully equatorial cis-decalin type configuration. This provides the rationale for the selective formation of (R,E)-14 as the only product.

Scheme 3.2

3.2.5 Summary

Therefore, in this methodology we have demonstrated a gold(I)-catalyzed intramolecular amination of underivatized allylic alcohols with primary and secondary
alkylamines. The reaction was effective for a variety of substitutions, alkene configuration and both pyrrolidines, and piperidines were synthesized efficiently. A selective chirality transfer was observed in the conversion of secondary nonracemic allylic alcohols and this observation demonstrated the net syn-addition of the nucleophile with respect to the departing hydroxyl group.

3.3 Experimental section

3.3.1 General methods

Catalytic reactions were performed in sealed tubes under an atmosphere of dry nitrogen unless noted otherwise. Room temperature is 23 °C. NMR spectra were obtained on at 500 MHz for 1H NMR and 126 MHz for 13C NMR in CDCl₃ unless noted otherwise. Gas chromatography was performed on a 25 m polydimethylsiloxane capillary column. Chiral HPLC was performed on a 0.46 cm × 25 cm Chiralpak AD-H column. Chiral GC was performed on a 20 m × 0.25 mm ChiralDEX GTA column. Flash column chromatography was performed employing 200-400 mesh silica gel. Thin layer chromatography (TLC) was performed on silica gel 60 F254. Diphenylacetonitrile, methyl trans-4-bromo-2-butenoate, imidazole, tert-butyldimethylsilyl chloride, benzylamine, cyclohexanecarbonitrile, butylamine, tert-butylamine, acetophenone, benzyl cyanide, tetrabutylammonium fluoride, cyclohexylamine, (R)-3-butyn-2-ol [[α]D₂ +45° (neat)], 3,4-dihydro-2H-pyran, sodium azide, samarium (II) iodide, benzyl chloroformate, NaH, DIBAL, LiAlH₄, and anhydrous 1,4-dioxane were used as received. Other ligands and silver salts were purchased from major suppliers and used as received. Gold complex (2)AuCl [2 = P(t-Bu)₂(6-biphenyl)]₇¹ trans-4-bromo-1-(2-tetrahydropyranloxy)-2-butene₉⁰ and 6-amino-1-(2-tetrahydropyranloxy)-2-hexene (24)₉¹ were prepared using published procedures. Dithiane intermediate 26 was synthesized employing the procedure developed by Hong and coworkers.₈⁶
3.3.2 Synthesis of γ- and δ-amino allylic alcohols

6-(N-Benzylamino)-5,5-diphenyl-2-hexenol (3a). A solution of diphenylacetonitrile (5.8 g, 30 mmol) in THF (24 mL) was added dropwise to a suspension of NaH (0.72 g, 30 mmol) in THF (18 mL) at 0 ºC, and the resulting suspension was stirred at 0 ºC for 1 h and then cooled to −78 ºC (Scheme 3.3). A solution of trans-methyl-4-bromocrotonate (4.2 mL, 36 mmol) in THF (12 mL) was added dropwise to the reaction mixture and the resulting suspension was warmed to room temperature overnight. The reaction mixture was treated with water (30 mL) and extracted with ether (3 × 30 mL). The combined ether extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 4:1) to give 5,5-diphenyl-5-cyanomethyl-2-pentenoate (17) as a white solid (7.78 g, 89%) (Scheme 3.3).

Scheme 3.3

DIBAL-H (5.3 mL, 30 mmol) was added over 15 min to a solution of 17 (2.91 g, 10 mmol) in CH₂Cl₂ (50 mL) at −78 ºC and the reaction mixture was stirred at −78 ºC for 1.5 h. Methanol (16 mL) and a saturated solution of Rochelle’s salt (30 mL) were added sequentially to the reaction mixture and the resulting slurry was stirred for 12 h. The
layers were separated, the aqueous fraction was extracted with CH$_2$Cl$_2$ (2 × 30 mL), and the combined organic extracts were washed with brine, dried (MgSO$_4$), concentrated, and chromatographed (hexanes–EtOAc = 20:1) to give 2,2-diphenyl-6-hydroxy-4-hexenal (18) as a colorless waxy solid (1.37 g, 52%).

A solution of 18 (1.4 g, 5.2 mmol), TBSCl (2.43 g, 16.1 mmol), and imidazole (1.80 g, 26.5 mmol) in CH$_2$Cl$_2$ (21 mL) was stirred at 0 ºC for 1.5 h. The resulting suspension was treated with saturated aqueous NH$_4$Cl and then extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), concentrated, and chromatographed (hexanes–EtOAc = 50:1) to give 2,2-diphenyl-6-(tert-butyldimethylsilyloxy)-4-hexenal (19) as colorless oil (1.96 g, 99%).

A solution of 19 (1.5 g, 3.9 mmol) and benzylamine (0.45 mL, 4.1 mmol) in methanol (25 mL) was stirred over activated 3Å molecular sieves at room temperature for 20 h. The reaction mixture was cooled to 0 ºC, treated with NaBH$_4$ (0.29 g, 7.9 mmol), and then warmed to room temperature over 6 h with stirring. Water (50 mL) and 1 M NaOH (5 mL) were added sequentially and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), and concentrated. The resulting oily residue was dissolved in THF (39 mL), cooled to 0 ºC, treated with TBAF (1 M solution in THF, 7.9 mL, 7.88 mmol), and the resulting solution was stirred for 1.5 h at 0 ºC. Aqueous NH$_4$Cl (6.9 M, 30 mL) was added to the resulting suspension, the layers were separated, and the organic fraction was extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), concentrated, and chromatographed (hexanes–EtOAc = 1:1) to give 3a (0.72 g, 51%, over 3 steps) as a yellow oil.
For 17: TLC (hexanes–EtOAc = 4:1): \( R_f = 0.25 \). \( ^1H \) NMR: \( \delta \) 7.33-7.22 (m, 10 H), 6.76 (td, \( J = 7.2, 15.6 \) Hz, 1 H), 6.90 (d, \( J = 15.6 \) Hz, 1 H), 3.62 (s, 3 H), 3.21 (d, \( J = 7.2 \) Hz, 2 H). \(^{13}C\)\(^1H\) NMR: \( \delta \) 165.8, 141.2, 138.9, 128.9, 128.2, 126.7, 125.7, 121.3, 51.5, 51.0, 42.1.

For 18: TLC (hexanes–EtOAc = 1:1): \( R_f = 0.5 \). \( ^1H \) NMR: \( \delta \) 9.79 (s, 1 H), 7.34 – 7.24 (m, 6 H), 7.17-7.15 (m, 4 H), 5.51 – 5.39 (m, 2 H), 3.83 (d, \( J = 4.4 \) Hz, 2 H), 3.05 (d, \( J = 5.6 \) Hz, 2 H), 1.82 (br s, 1 H). \(^{13}C\)\(^1H\) NMR: \( \delta \) 198.0, 139.1, 132.6, 128.6, 128.1, 126.9, 126.6, 63.1, 62.6, 36.7.

For 19: TLC (hexanes–EtOAc = 4:1): \( R_f = 0.72 \). \( ^1H \) NMR: \( \delta \) 9.80 (s, 1 H), 7.33 (t, \( J = 7.5 \) Hz, 3 H), 7.26 (t, \( J = 7.5 \) Hz, 2 H), 7.16 (d, \( J = 7 \) Hz, 3 H), 5.48 – 5.33 (m, 2 H), 3.95 (d, \( J = 4 \) Hz, 2 H), 3.05 (d, \( J = 6 \) Hz, 2 H), 0.80 (s, 9 H), 0.06 (s, 6 H).

For 3a: TLC (hexanes–EtOAc = 1:1): \( R_f = 0.2 \). \( ^1H \) NMR (400 MHz): \( \delta \) 7.22-7.05 (m, 15 H), 5.43 (td, \( J = 6, 16 \) Hz, 1 H), 5.10 (td, \( J = 7.2, 15.2 \) Hz, 1 H), 3.77 (d, \( J = 6 \) Hz, 2 H), 3.63 (s, 2 H), 3.09 (s, 2 H), 2.93 (d, \( J = 6.8 \) Hz, 2 H), 1.12 (br s, 2 H). \(^{13}C\)\(^1H\) NMR: \( \delta \) 146.6, 140.6, 132.2, 128.9, 128.1, 128.0, 127.9, 126.7, 126.0, 63.6, 55.0, 54.1, 50.2, 39.7. IR (neat, cm\(^{-1}\)): 3320, 3022, 2845, 1597, 1494, 1443, 1361, 1079, 1000, 972, 909, 752, 695, 627. Anal. calcd (found) for C\(_{25}\)H\(_{27}\)NO: H, 7.61 (7.66); C, 83.99 (84.01).

6-(N-Butylamino)-5,5-diphenyl-2-hexenol (3b) and 6-(N-tert-butylamino)-5,5-diphenyl-2-hexenol (3c) were synthesized employing procedures analogous to that used to synthesize 3a (Scheme 3.3).

For 3b: TLC (EtOAc): \( R_f = 0.25 \). \( ^1H \) NMR: \( \delta \) 7.32-7.29 (m, 4 H), 7.23-7.20 (m, 6 H), 5.63 (td, \( J = 6.5, 15 \) Hz, 1 H), 5.33 (td, \( J = 7.5, 15 \) Hz, 1 H), 3.98 (d, \( J = 6.5 \) Hz, 2 H), 3.21 (s, 2 H), 3.03 (d, \( J = 7 \) Hz, 2 H) 2.55 (t, \( J = 7.5 \) Hz, 2 H), 1.38 (quintet, \( J = 7 \) Hz, 2 H), 1.25 (sextet, \( J = 7.5 \) Hz, 2 H), 0.92 (br s, 2 H), 0.88 (t, \( J = 7.5 \) Hz). \(^{13}C\)\(^1H\) NMR: \( \delta \) 146.7, 132.2, 129.2, 128.0, 127.9, 125.9, 63.6, 56.0, 50.3, 50.1, 39.9, 31.9, 20.3, 13.9. IR (neat, cm\(^{-1}\)): 3314,
3055, 2926, 2857, 1579, 1097, 1001, 973, 754, 696, 626. Anal. calcd (found) for C$_{22}$H$_{29}$NO: H, 9.04 (9.10); C, 81.69 (81.60).

For 3c: TLC (hexanes–EtOAc = 1:1): $R_f$ = 0.13. $^1$H NMR: $\delta$ 7.28-7.10 (m, 10 H), 5.57 (td, $J$ = 6, 15.5 Hz, 1 H), 5.26 (td, $J$ = 7, 15.5 Hz, 1 H), 3.91 (d, $J$ = 6 Hz, 2 H), 3.13 (s, 2 H), 2.97 (d, $J$ = 7.5 Hz, 2 H), 0.95 (s, 9 H), 0.88 (br s, 2 H). $^{13}$C($^1$H) NMR: $\delta$ 147.1, 132.1, 129.3, 128.0, 127.8, 125.8, 63.7, 49.9, 48.5, 39.4, 29.1. IR (neat, cm$^{-1}$): 3397, 2963, 2867, 1738, 1597, 1495, 1443, 1360, 1234, 1102, 1045, 972, 910, 754, 697, 616. Anal. calcd (found) for C$_{22}$H$_{29}$NO: H, 9.04 (9.22); C, 81.69 (81.48).

(E)-Benzyl-(6-hydroxy-2,2-diphenylhex-4-en-1-yl)carbamate (3e). A solution of 17 (1.5 g, 5.0 mmol) in ether (15 mL) was added to a stirred suspension of LiAlH$_4$ (0.76 g, 20 mmol) in ether (35 mL) at 0 °C and the resulting suspension was warmed to room temperature and stirred for 3 h (Scheme 3.4). The reaction mixture was cooled to 0 °C and treated sequentially with water (1 mL), 15 % NaOH [(w/v), 1 mL] and water (1 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in ethanol/water (1:1, 16 mL), treated with solid NaHCO$_3$ (0.38 g, 4.5 mmol) and benzylchloroformate (0.51 mL, 3.6 mmol) and stirred at room temperature for 4 h. The resulting mixture was treated with water (30 mL) and then extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried (MgSO$_4$), concentrated, and chromatographed (hexanes–EtOAc = 1:1) to give 3e as a white waxy solid (0.68 g, 34%, over 2 steps). TLC (hexanes-EtOAc = 1:1): $R_f$ = 0.38. $E/Z = 24:1$. $^1$H NMR (400 MHz): $\delta$ 7.42-7.14 (m, 15 H), 5.59-5.52 (m, 1 H), 5.37-5.29 (m, 1 H), 5.01 (s, 2 H), 4.38 (s, 1 H), 3.95 (t, $J$ = 6 Hz, 4 H), 2.86 (d, $J$ = 6.8 Hz, 2 H), 1.86 (s, 1 H). $^{13}$C NMR (100 MHz): $\delta$ 156.3, 145.2, 136.2, 133.4, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 126.5, 66.8, 63.5, 50.1, 47.4. IR
6-Amino-5,5-diphenyl-2-hexen-1-ol (3d). Pure 3d was isolated from the deprotection of 3e employing a published procedure (Scheme 3.4). A solution of 3e (0.6 g, 1.5 mmol) and TBAF (1 M solution in THF, 2.2 mL, 2.2 mmol) in THF (15 mL) was refluxed for 2 h. The resulting solution was cooled to room temperature, treated with water (10 mL), and the resulting mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were dried (MgSO₄), concentrated, and chromatographed (CH₂Cl₂–methanol = 12:1) to give 3d (0.4 g, 67%) as a pale yellow oil. TLC (CH₂Cl₂–MeOH = 9:1): Rᵣ = 0.13. ¹H NMR (400 MHz): δ 7.26 (t, J = 7.5 Hz, 4 H), 7.18 (t, J = 8.5 Hz, 2 H), 7.14 (d, J = 8 Hz, 4 H), 5.59 (td, J = 6, 15 Hz, 1 H), 5.27 (td, J = 7, 15 Hz, 1 H), 3.92 (d, J = 6 Hz, 2 H), 3.28 (s, 2 H), 2.89 (d, J = 7 Hz, 2 H), 1.34 (br s, 3 H). ¹³C{¹H} NMR (100 MHz): δ 145.9, 132.6, 128.1, 128.0, 126.1, 63.2, 52.0, 48.4, 39.4. IR (neat, cm⁻¹): 3300, 3056, 2858, 1597, 1494, 1443, 1264, 1081, 1010, 973, 906, 727, 697, 645. Anal. calcd (found) for C₁₈H₂₁NO: H, 7.92 (7.77); C, 80.86 (79.45).

(E)-6-(N-Benzylamino)-5-cyclohexyl-2-hexenol (5a). Cyclohexanecarbonitrile (2.5 mL, 21 mmol) was added to a solution of LDA [generated in situ from n-BuLi (2.5 M solution in hexanes, 8.9 mL, 22.3 mmol) and diisopropylamine (3 mL, 21 mmol) in THF (51 mL)] at −78 °C (Scheme 3.5). The resulting solution was stirred for 1 h, treated with
trans-4-bromo-1-(2-tetrahydropyranloxy)-2-butene (5.3 g, 22.5 mmol), and then warmed to room temperature overnight with stirring. The resulting mixture was diluted with ether (50 mL), washed sequentially with water (2 × 50 mL) and brine (50 mL), dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 9:1) to give trans-5-cyano-5-cyclohexyl-1-(2-tetrahydropyranloxy)-2-pentene (20) as a pale yellow oil (5.05 g, 90%).

A solution of 20 (2.0 g, 7.6 mmol) in ether (25 mL) was added to a stirred suspension of LiAlH₄ (0.86 g, 23 mmol) in ether (30 mL) at 0 °C and the resulting suspension was warmed to room temperature and stirred for 3 h. The reaction mixture was cooled at 0 °C and treated sequentially with water (1.1 mL), 15 % NaOH [(w/v), 1.1 mL] and water (1.1 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in methanol (35 mL), treated with benzaldehyde (1.15 mL, 11.4 mmol), and the resulting solution was stirred over activated 3Å molecular sieves at room temperature for 6 h. The reaction mixture was cooled to 0 °C, treated with NaBH₄ (0.43 g, 11.4 mmol), and the resulting suspension was warmed to room temperature over 12 h with stirring. The resulting suspension was treated sequentially with water (60 mL) and 1M NaOH (6 mL) and extracted with CH₂Cl₂ (3 × 60 mL). The combined organic extracts
were washed with brine, dried (MgSO₄), and concentrated under vacuum. The resulting oily residue was dissolved in methanol (45 mL) and acidified through slow addition of concentrated aqueous HCl (37%, 7 mL) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum and the resulting oily residue was dissolved in CH₂Cl₂ and washed with saturated aqueous NaHCO₃. The aqueous washes were combined and extracted with CH₂Cl₂ and the combined organic extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 1:1) to give 4a as a yellow oil (1.1 g, 53%, over 4 steps).

For 20: TLC (hexanes–EtOAc = 4:1): Rᵣ = 0.44. ¹H NMR: δ 5.80-5.67 (m, 2 H), 4.61 (t, J = 3.5 Hz, 1 H), 4.21 (dd, J = 5.5, 13 Hz, 1 H), 3.97 (dd, J = 6, 13 Hz, 1 H), 3.86-3.82 (m, 1 H), 3.51-3.46 (m, 1 H), 2.26 (d, J = 6.5 Hz, 2 H), 1.93 (d, J = 13 Hz, 2 H), 1.83-1.49 (m, 12 H), 1.24-1.21 (m, 2 H). ¹³C{¹H} NMR: δ 131.4, 126.4, 123.0, 97.7, 66.9, 62.1, 42.9, 38.8, 35.1, 30.4, 25.2, 25.1, 22.7, 19.3. Anal. calcd (found) for C₁₆H₂₅NO: H, 9.57 (9.52); C, 72.96 (72.82).

For 5a: TLC (hexanes–EtOAc = 1:1): Rᵣ = 0.1. ¹H NMR: δ 7.31-7.28 (m, 4 H), 7.27-7.21 (m, 1 H), 5.60-5.58 (m, 2 H), 4.01 (d, J = 3.5 Hz, 2 H), 3.74 (s, 2 H), 2.37 (s, 2 H), 2.08 (d, J = 5 Hz, 2 H), 1.39-1.25 (m, 12 H). ¹³C{¹H} NMR: δ 140.9, 131.2, 129.4, 128.2, 128.1, 126.7, 63.7, 54.6, 36.7, 34.0, 26.3, 21.5. IR (neat, cm⁻¹): 3336, 2921, 2848, 1493, 1451, 1355, 1259, 1084, 1003, 973, 909, 847, 792, 733, 697. Anal. calcd (found) for C₁₈H₂₇NO: H, 9.95 (10.05); C, 79.07 (78.81).

(E)-6-[N-(1-Phenylethylamino)]-5-cyclohexyl-2-hexenol (5b). Compound 5b was synthesized employing a procedure analogous to that used to synthesize 5a (Scheme 3.5). TLC (CH₂Cl₂–MeOH = 16:1): Rᵣ = 0.10. ¹H NMR: δ 7.30-7.29 (m, 4 H), 7.22-7.20 (m, 1 H), 5.62-5.51 (m, 2 H), 4.01 (d, J = 5 Hz, 2 H), 3.63 (q, J = 6.5 Hz, 1 H), 2.29
(d, J = 11.5 Hz, 1 H), 2.17 (d, J = 12 Hz, 1 H), 2.07 (d, J = 6 Hz, 2 H), 1.30 (d, J = 6.5 Hz, 3 H), 1.36-1.19 (m, 12 H). $^{13}$C$^1$H NMR: δ 146.4, 131.1, 129.6, 128.2, 126.7, 126.6, 63.8, 59.0, 36.5, 34.1, 33.9, 26.3, 24.6, 21.5, 21.4. IR (neat, cm$^{-1}$): 3391, 2925, 2850, 1583, 1492, 1450, 1368, 1264, 1083, 974, 733, 700, 668. Anal. calcd (found) for C$_{19}$H$_{29}$NO: H, 10.17 (10.26); C, 79.39 (79.33).

(E)-6-(N-Benzylamino)-5-phenyl-2-hexenol (7a) (46%, over 4 steps) and (E)-6-(N-cyclohexylmethyl)-5-phenyl-2-hexenol (7b) (34%, over 4 steps) were synthesized from (E)-5-cyano-5-phenyl-1-(2-tetrahydropyran-2-yloxy)-2-pentene (21) employing procedures similar to that used to synthesize 5a. Compound 21 was synthesized employing a procedure similar to that used to synthesize 20 (Scheme 3.6).

Scheme 3. 6

For 21: TLC (hexanes–EtOAc = 4:1): $R_f$ = 0.29. $^1$H NMR: δ 7.36-7.28 (m, 5 H), 5.73-5.65 (m, 2 H), 4.57-4.55 (m, 1 H), 4.16 (d, J = 11.5 Hz, 1 H), 3.93 (d, J = 11.5 Hz, 1 H), 3.81 (t, J = 6.5 Hz, 2 H), 3.47-3.45 (m, 1 H), 2.65-2.56 (m, 2 H), 2.00-1.48 (m, 6 H). $^{13}$C$^1$H NMR: δ 135.1, 131.2, 128.9, 128.0, 127.2, 127.1, 120.2, 97.7, 66.8, 62.1, 38.4, 37.5, 30.4, 25.3, 19.3. Anal. calcd (found) for C$_{17}$H$_{21}$NO: H, 7.80 (7.74); C, 75.25 (75.09).

For 7a: TLC (EtOAc): $R_f$ = 0.1. $^1$H NMR: δ 7.30-7.25 (m, 4 H), 7.21-7.14 (m, 6 H), 5.59-5.48 (m, 2 H), 3.96 (d, J = 5 Hz, 2 H), 3.74 (d, J = 13.5 Hz, 1 H), 3.67 (d, J = 13.5 Hz, 1 H), 2.89-2.82 (m, 2 H), 2.80-2.75 (m, 1 H), 2.42-2.28 (m, 2 H), 1.32 (br s, 2 H). $^{13}$C$^1$H NMR
NMR: δ 143.0, 140.1, 130.8, 130.5, 128.5, 128.3, 127.9, 127.7, 126.8, 126.5, 63.4, 54.1, 53.7, 45.8, 37.2. IR (neat, cm⁻¹): 3306, 3025, 2916, 2847, 1600, 1494, 1451, 1366, 1078, 1001, 969, 753, 696. Anal. calcd (found) for C₁₉H₂₃NO: H, 8.24 (8.39); C, 81.10 (81.02).

For 7b: TLC (CH₂Cl₂-MeOH = 9:1): R_f = 0.2. ¹H NMR: δ 7.28 (t, J = 7.5 Hz, 2 H), 7.21-7.14 (m, 3 H), 5.61-5.50 (m, 2 H), 3.97 (d, J = 5.5 Hz, 2 H), 2.88-2.83 (m, 1 H), 2.82 (dd, J = 5.5, 11.5 Hz, 1 H), 2.73 (dd, J = 9, 11.5 Hz, 1 H), 2.41-2.28 (m, 4 H), 1.64-1.54 (m, 7 H), 1.37-1.25 (m, 1 H), 1.20-1.03 (m, 3 H), 0.8-0.71 (m, 2 H). ¹³C{¹H} NMR: δ 143.2, 130.9, 130.5, 128.6, 127.7, 126.6, 63.4, 56.5, 55.1, 45.7, 37.5, 37.4, 31.4, 31.3, 26.6, 26.0. IR (neat, cm⁻¹): 3315, 3026, 2918, 2847, 1493, 1447, 1365, 1087, 1009, 968, 758, 699. Anal. calcd (found) for C₁₉H₂₉NO: H, 10.17 (10.12); C, 79.39 (79.48).

(Z)-6-(N-Benzylzminio)-2-hexenol (9). A solution of 6-amino-1-(2-tetrahydropyranoxy)-2-hexene (22) (0.47 g, 2.4 mmol) and benzaldehyde (0.37 mL, 3.6 mmol) in methanol (13 mL) was stirred over activated 3Å molecular sieves at room temperature for 12 h (Scheme 3.7). The reaction mixture was cooled to 0 ºC, treated with NaBH₄ (0.14 g, 3.6 mmol), and the resulting suspension was warmed to room temperature over 12 h with stirring. The reaction mixture was treated sequentially with water (24 mL) and 1 M aqueous NaOH (2.5 mL), and the resulting mixture was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated under vacuum. The resulting residue was dissolved in methanol (14 mL) and acidified through slow addition of concentrated aqueous HCl (37%, 2.2 mL). The resulting mixture was stirred at room temperature for 2 h and then concentrated under vacuum. The resulting oily residue was dissolved in CH₂Cl₂ and washed with saturated aqueous NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ and the combined organic extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed (CH₂Cl₂-MeOH = 20:1) to give 9 (0.17 g, 25% over 3
steps, Z/E = 7.7:1) as a yellow oil. TLC (CH₂Cl₂–MeOH = 9:1): \( R_f = 0.12 \). ¹H NMR: \( \delta \) 7.35-7.24 (m, 5 H), [5.79-5.74 (m), 5.68-5.59 (m), 8:1, 1 H], [5.68-5.59 (m), 5.53-5.49 (m), 1:8, 1 H], [4.11 (d, \( J = 6.5 \) Hz), 4.05 (d, \( J = 5.0 \) Hz), 8:1, 2 H], [3.77 (s), 3.73 (s), 1:8, 2 H], [3.64 (t, \( J = 6.0 \) Hz), 3.44-3.43 (m), 8:1, 2 H], 2.61 (br s, 2 H), [2.24 (q, \( J = 7.0 \) Hz), 2.08 (q, \( J = 7.5 \) Hz), 8:1, 2 H], 1.62 (quintet, \( J = 7.0 \) Hz, 2 H). ¹³C{¹H} NMR: \( \delta \) 140.0, 132.2, 129.1, 128.3, 128.1, 126.9, 58.2, 53.9, 48.9, 29.2, 27.0. IR (neat, cm⁻¹): 3295, 3013, 2926, 2853, 1736, 1494, 1452, 1372, 1240, 1101, 1043, 1026, 732, 696, 601. Anal. calcd (found) for C₁₄H₁₉NO: H, 9.65 (9.69); C, 76.67 (76.64).

(Z)-6-(N-Benzylamino)-2-heptenol (11). Compound 11 was isolated in 59% yield over 3 steps from (Z)-7-amino-1-(2-tetrahydropyranyloxy)-2-heptene (23) employing a similar procedure used to synthesize 9 (Scheme 3.7). TLC (CH₂Cl₂–MeOH = 9:1): \( R_f = 0.12 \). ¹H NMR: \( \delta \) 7.32-7.21 (m, 5 H), 5.61-5.56 (m, 1 H), 4.12 (d, \( J = 6.5 \) Hz, 2 H), 3.74 (s, 2 H), 3.42 (d, \( J = 1.5 \) Hz, 2 H), 2.59 (t, \( J = 7.5 \) Hz, 2 H), 2.06 (q, \( J = 7.5 \) Hz, 2 H), 1.87 (br s, 2 H), 1.50 (m, 2 H), 1.37 (quintet, \( J = 7.5 \) Hz, 2 H). ¹³C{¹H} NMR: \( \delta \) 140.0, 132.2, 129.1, 128.3, 128.1, 126.9, 58.2, 53.9, 48.9, 29.2, 27.0. IR (neat, cm⁻¹): 3295, 3013, 2926, 2853, 1736, 1494, 1452, 1372, 1240, 1101, 1043, 1026, 732, 696, 601. Anal. calcd (found) for C₁₄H₁₉NO: H, 9.65 (9.69); C, 76.67 (76.64).

(Z)-8-(N-Benzylamino)-3-octen-2-ol (13). 8-Bromo-2-(2-tetrahydropyranyloxy)-3-octyne (24) was synthesized employing a procedure similar to that used to synthesize 6-bromo-1-(2-tetrahydropyranyloxy)-2-hexyne (Scheme 3.8). A solution of 24 (2.5 g,
8.57 mmol) and PTSA (0.08 g, 0.44 mmol) in methanol (25 mL) was stirred at room temperature for 2 h. The resulting mixture was treated with solid NaHCO₃ (0.14 g, 1.6 mmol), stirred for 5 min, and filtered. The filtrate was concentrated under vacuum and the resulting oily residue was dissolved in CH₂Cl₂ (35 mL) and cooled to 0 °C. Imidazole (2.97 g, 43.7 mmol) and TBSCl (4.0 g, 26.6 mmol) were added sequentially and the reaction mixture was stirred at 0 °C for 1.5 h. Saturated aqueous NH₄Cl was added and the mixture was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 50:1) to give the TBS-protected alcohol 25 (2.6 g, 95%) as a colorless oil.

Scheme 3. 8

A solution of 25 and sodium azide (0.66 g, 10.17 mmol) in DMSO (20 mL) was stirred at room temperature for 3 h, treated with water (30 mL), and extracted with tert-butyl methyl ether (3 × 40 mL). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated. The resulting oily residue was dissolved in degassed, hydrogen-sparged methanol (48 mL) and treated with Lindlar catalyst (0.48 g). The resulting suspension was stirred under H₂ (1 atm) at room temperature for 6 h. The resulting mixture was filtered through a pad of Celite and concentrated under vacuum. The resulting oily residue was dissolved in methanol (37 mL) and treated with benzaldehyde (1.24 mL, 12.2 mmol) and the resulting solution was stirred over activated
3Å molecular sieves at room temperature for 12 h. The reaction mixture was cooled to 0 °C and treated with NaBH₄ (0.46 g, 12.2 mmol) and the resulting suspension was warmed to room temperature over 12 h with stirring. The resulting suspension was treated sequentially with water (60 mL) and 1 M NaOH (6 mL) and then extracted with CH₂Cl₂ (3 × 60 mL). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated under vacuum. The resulting residue was dissolved in THF (80 mL), cooled to 0 °C, and treated with TBAF (1 M solution in THF, 16 mL, 16.3 mmol). The resulting mixture was stirred at 0 °C for 1 h, treated with aqueous NH₄Cl (6.9 M), and extracted with CH₂Cl₂ (3 × 80 mL). The combined organic extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 1:50) to give 13 (0.78 g, 41%, over 5 steps) as a pale yellow oil (Scheme 3.8).

**For 25:** TLC (hexanes–EtOAc = 4:1): Rf = 0.86. \(^1\)H NMR: δ 4.48 (ttq, J = 2.0, 6.5 Hz, 1 H), 3.40 (t, J = 7.0 Hz, 2 H), 2.21 (dt, J = 2.0, 7.0 Hz, 2 H), 1.95 (quintet, J = 7.0 Hz, 2 H), 1.62 (quintet, J = 7.5 Hz, 2 H), 1.35 (d, J = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H). \(^{13}\)C{\(^1\)H} NMR: δ 89.5, 82.5, 59.1, 33.2, 31.6, 26.9, 25.8, 25.6, 17.8, 14.1, –3.6, –4.6.

**For 13:** TLC (CH₂Cl₂–MeOH = 9:1): Rf = 0.24. \(^1\)H NMR: δ 7.33-7.21 (m, 5 H), 5.42-5.33 (m, 2 H), 4.58 (quintet, J = 6.5 Hz, 1 H), 3.75 (s, 2 H), 2.60 (t, J = 7.5 Hz, 2 H), 2.15-2.00 (m, 2 H), 1.82 (br s, 2 H), 1.49 (quintet, J = 7 Hz, 2 H), 1.38 (quintet, J = 7.5 Hz, 2 H), 1.20 (d, J = 6.5 Hz, 3 H). \(^{13}\)C{\(^1\)H} NMR: δ 140.2, 134.3, 130.5, 128.3, 128.1, 126.9, 63.5, 53.9, 48.9, 29.3, 27.1, 23.5. IR (neat, cm⁻¹): 3300, 2925, 2854, 1494, 1452, 1364, 1286, 1107, 1055, 923, 846, 732, 696, 600. Anal. calcd (found) for C₁₅H₂₃NO: H, 9.93 (10.04); C, 77.21 (77.16).

\((R,Z)\)-13. Compound \((R,Z)\)-13 was prepared from commercially available \((R)\)-3-butyn-2-ol using the same procedure as used to prepare 13. The enantiopurity of \((R,Z)\)-13 was determined by HPLC analysis of the corresponding trifluoroacetate ester and by
comparison to the HPLC of the trifluoroacetate ester generated from racemic 13 (Figure 3.2).

Figure 3.2 Chiral HPLC traces of racemic (Z)-13 trifluoroacetate ester (left trace) and enantiomerically enriched (R,Z)-13 trifluoroacetate ester (right trace).

(R,Z)-4-(2-(2-Benzylamino)propyl)-1,3-dithian-2-yl)but-2-en-1-ol (15). A solution of 26 (0.71 g, 1.8 mmol), imidazole (0.37 g, 5.5 mmol), and TBSCl (0.40 g, 2.64 mmol) in CH₂Cl₂ (7 mL) was stirred at 0 °C for 1.5 h (Scheme 3.9). The resulting suspension was treated with saturated aqueous NH₄Cl and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 9:1) to give 27 (0.85 g, 93%) as colorless oil.
A solution of 27 (0.85 g, 1.65 mmol) in DMF (4 mL) was added to a suspension of NaH (0.06 g, 2.47 mmol) in DMF (6 mL) and the resulting suspension was stirred at 0 ºC for 1 h, cooled to −78 ºC, and treated with benzyl bromide (0.49 mL, 4.12 mmol). The resulting mixture was warmed to room temperature and stirred for 18 h. The resulting suspension was treated with brine (10 mL) and extracted with ether (3 × 20 mL). The combined ether extracts were dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 60:1) to give 28 (0.91 g, 91%) as a pale yellow waxy solid (Scheme 3.9).

A suspension of 28 (0.91 g, 1.5 mmol), SmI₂ (0.1 M solution in THF, 90 mL, 9.0 mmol), water (0.5 mL, 27 mmol), and pyrrolidine (1.5 mL, 18 mmol) in THF (15 mL) was stirred at room temperature for 30 min. The reaction mixture was treated sequentially with aqueous Rochelle’s salt [10% (w/v), 50 mL] and aqueous K₂CO₃ [10% (w/v), 50 mL] and the resulting mixture was extracted with ether (3 × 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated under vacuum. The resulting oily residue was dissolved in THF (55 mL), cooled to 0 ºC, and treated with TBAF (1 M solution in THF, 2.3 mL, 2.3 mmol). The resulting mixture was stirred at 0 ºC for 1 h, treated with aqueous NH₄Cl (6.9 M), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO₄), concentrated, and
chromatographed (CH$_2$Cl$_2$–MeOH = 25:1) to give 15 (0.35 g, 69%, over 2 steps) as yellow oil.

For 27: TLC (hexanes–EtOAc = 2:1): $R_f = 0.59$. $^1$H NMR: $\delta$ 7.76 (d, $J = 8.5$ Hz, 2 H), 7.28 (d, $J = 8.0$ Hz, 2 H), 5.65-5.60 (m, 1 H), 5.53 (d, $J = 5$ Hz, 2 H), 5.43-5.38 (m, 1 H), 4.16-4.12 (m, 2 H), 3.52-3.46 (m, 1 H), 2.84-2.71 (m, 4 H), 2.40 (doublet of quintet, $J = 7.5$, 15.5 Hz, 2 H), 2.39 (s, 3 H), 2.20 (dd, $J = 8.5$, 15.5 Hz, 1 H), 2.03-1.83 (m, 2 H), 1.85 (dd, $J = 4$, 15.5 Hz, 1 H), 1.15 (d, $J = 6$ Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

For 28: TLC (hexanes–EtOAc = 4:1): $R_f = 0.31$. $^1$H NMR: $\delta$ 7.71 (d, $J = 8$ Hz, 2 H), 7.35 (d, $J = 6.5$ Hz, 2 H), 7.30-7.20 (m, 5 H), 5.61-5.56 (m, 1 H), 5.40-5.27 (m, 1 H), 4.57 (d, $J = 15.5$ Hz, 1 H), 4.18-4.08 (m, 4 H), 2.69-2.61 (m, 4 H), 2.46 (dq, $J = 7$, 15 Hz, 2 H), 2.40 (s, 3 H), 2.19 (dd, $J = 2.5$, 15 Hz, 1 H), 1.90-1.79 (m, 2 H), 1.78 (dd, $J = 8.5$, 15 Hz, 1 H), 1.11 (d, $J = 7$ Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 6 H). $^{13}$C{[H]} NMR: $\delta$ 143.1, 138.1, 137.9, 132.8, 129.6, 128.5, 128.4, 127.6, 127.3, 123.9, 60.0, 52.4, 52.1, 48.4, 44.9, 37.4, 26.1, 25.9, 24.6, 21.5, 21.0, 20.3, 14.2, -5.1.

For 15: TLC (CH$_2$Cl$_2$–MeOH = 9:1): $R_f = 0.32$. $^1$H NMR: $\delta$ 7.34-7.21 (m, 5 H), 5.79-5.74 (m, 1 H), 5.65-5.60 (m, 1 H), 4.10 (dd, $J = 7$, 13 Hz, 1 H), 4.03 (dd, $J = 6.5$, 13 Hz, 1 H), 3.86 (d, $J = 13$ Hz, 1 H), 3.68 (d, $J = 13$ Hz, 1 H), 3.08-3.04 (m, 1 H), 2.92 (br s, 2 H), 2.89-2.73 (m, 5 H), 2.63 (dd, $J = 7$, 15 Hz, 1 H), 2.21 (dd, $J = 7$, 15.5 Hz, 1 H), 1.95-1.91 (m, 2 H), 1.90 (dd, $J = 3.5$, 15.5 Hz, 1 H), 1.19 (d, $J = 6$ Hz, 3 H). $^{13}$C{[H]} NMR: $\delta$ 139.1, 132.0, 128.4, 127.7, 126.3, 58.1, 51.9, 50.8, 49.8, 45.2, 37.1, 26.3, 26.2, 24.8, 21.4. IR (neat, cm$^{-1}$): 3271, 3022, 2904, 1602, 1494, 1451, 1422, 1376, 1275, 1240, 1141, 1026, 906, 733, 697. Anal. calcd (found) for C$_{18}$H$_{27}$NOS$_2$: H, 8.06 (8.03); C, 64.05 (63.89).
3.3.3 Synthesis of 2-vinyl pyrrolidines and 2-vinyl piperidines

1-(N-Benzylamino)-4,4-diphenyl-2-vinylpyrrolidine (4a). A suspension of (2)AuCl \[2 = P(t-Bu)_2(o-biphenyl); 2.6 mg, 5 \times 10^{-3} \text{ mmol}] and AgSbF_6 (1.7 mg, 5 \times 10^{-3} \text{ mmol}) and 3a (36 mg, 0.10 mmol) in 1,4-dioxane (0.34 mL) in a sealed tube was stirred at room temperature for 2 h. The resulting suspension was concentrated under vacuum and the residue was chromatographed (hexanes–EtOAc = 40:1 → 10:1) to give 4a (33 mg, 97%) as a pale yellow oil. TLC (hexanes–EtOAc = 1:1): \( R_f = 0.86 \). \(^1\)H NMR (400 MHz): \( \delta \) 7.27-7.01 (m, 15 H), 5.76-5.767 (m, 1 H), 5.11 (d, \( J = 17.2 \) Hz, 1 H), 5.01 (d, \( J = 10 \) Hz, 1 H), 4.01 (d, \( J = 13.2 \) Hz, 1 H), 3.56 (d, \( J = 9.6 \) Hz, 1 H), 3.16-3.10 (m, 2 H), 2.83 (dd, \( J = 7.6, 13.2 \) Hz, 1 H), 2.75 (d, \( J = 10 \) Hz, 1 H), 2.32 (dd, \( J = 8, 13.2 \) Hz, 1 H). \(^{13}\)C\(^{1}\)H NMR (100 MHz): \( \delta \) 150.2, 148.4, 140.6, 139.9, 128.5, 128.2, 127.8, 127.4, 127.2, 126.7, 125.8, 125.5, 116.5, 68.0, 65.5, 57.6, 53.0, 46.5. IR (neat, cm\(^{-1}\)): 3024, 2920, 2787, 1597, 1492, 1444, 1369, 1243, 1166, 1126, 1027, 990, 918, 746, 694, 654. Anal. calcd (found) for C\(_{25}\)H\(_{25}\)N: H, 7.42 (7.39); C, 88.45 (88.37).

Remaining 2-vinyl pyrrolidines and 2-vinyl piperidines were synthesized employing procedures similar to that used to synthesize 4a. Reaction time and temperature for each heterocycle are provided in Tables 3.1 and 3.2.

1-(N-Butylamino)-4,4-diphenyl-2-vinylpyrrolidine (4b). Colorless oil, 96%. TLC (hexanes–EtOAc = 1:1): \( R_f = 0.84 \). \(^1\)H NMR: \( \delta \) 7.23-7.13 (m, 8 H), 7.11 (t, \( J = 7 \) Hz, 1 H), 7.05 (t, \( J = 7.5 \) Hz, 1 H), 5.61 (ddd, \( J = 8.5, 10, 17 \) Hz, 1 H), 5.04 (d, \( J = 17 \) Hz, 1 H), 5.01 (d, \( J = 10 \) Hz, 1 H), 3.81 (d, \( J = 9.5 \) Hz, 1 H), 2.94 (q, \( J = 8 \) Hz, 1 H), 2.80-2.65 (m, 3 H), 2.23 (dd, \( J = 8.5, 13 \) Hz, 1 H), 2.10-2.05 (m, 1 H), 1.49-1.38 (m, 2 H), 1.36-1.18 (m, 2 H), 0.84 (t, \( J = 7.5 \) Hz, 3 H). \(^{13}\)C\(^{1}\)H NMR: \( \delta \) 150.5, 148.5, 141.0, 128.2, 127.9, 127.4, 127.2, 125.8, 125.5, 116.0, 68.9, 66.2, 53.6, 53.0, 46.5, 31.0, 20.7, 14.0. IR (neat, cm\(^{-1}\)): 3057, 2928, 2789, 1597,
104, 1492, 1444, 1188, 1149, 1031, 991, 917, 760, 696, 654. Anal. calcd (found) for C_{22}H_{27}N: H, 8.91 (9.03); C, 86.51 (86.48).

1-(N-tert-Butylamino)-4,4-diphenyl-2-vinylpyrrolidine (4c). Yellow oil, 87%. TLC (hexanes–EtOAc = 1:1): R_f = 0.73. \(^1\)H NMR: \(\delta\) 7.42 (d, \(J = 7\) Hz, 2 H), 7.27-7.10 (m, 8 H), 5.39 (ddd, \(J = 8, 10, 17.5\) Hz, 1 H), 4.82 (d, \(J = 17\) Hz, 1 H), 4.59 (d, \(J = 10\) Hz, 1 H), 3.95 (dd, \(J = 1.5, 9\) Hz, 1 H), 3.68 (dt, 3, 10 Hz, 1 H), 3.05 (d, \(J = 9.5\) Hz, 1 H), 2.84 (dd, \(J = 10, 12.5\) Hz, 1 H), 2.32 (td, \(J = 1.5, 12.5\) Hz, 1 H), 1.10 (s, 9 H).

\(^1^3\)C\{\(^1\)H\} NMR: \(\delta\) 148.2, 147.8, 146.9, 128.2, 127.8, 127.7, 126.7, 125.8, 125.5, 111.2, 60.7, 58.2, 53.9, 52.4, 46.7, 27.2. IR (neat, cm\(^{-1}\)): 3058, 3022, 2967, 2868, 1597, 1493, 1446, 1416, 1313, 1229, 1204, 1126, 1029, 990, 906, 771, 750, 694, 654. Anal. calcd (found) for C_{22}H_{27}N: H, 8.91 (9.02); C, 86.51 (86.49).

4,4-Diphenyl-2-vinylpyrrolidine (4d). Dark yellow oil, 91%. TLC (CH\(_2\)Cl\(_2\)–MeOH = 9:1): R_f = 0.43. \(^1\)H NMR: \(\delta\) 7.34 (t, \(J = 8\) Hz, 2 H), 7.32-7.18 (m, 8 H), 5.88 (ddd, \(J = 7.5, 10, 17\) Hz, 1 H), 5.17 (d, \(J = 17.5\) Hz, 1 H), 5.04 (d, \(J = 9.5\) Hz, 1 H), 3.82-3.75 (m, 2 H), 3.50 (d, \(J = 11.5\) Hz, 1 H), 3.08 (br s, 1 H), 2.79 (dd, \(J = 7, 13.5\) Hz, 1 H), 2.29 (dd, \(J = 9, 12.5\) Hz, 1 H). \(^1^3\)C\{\(^1\)H\} NMR: \(\delta\) 147.1, 146.3, 146.0, 146.0, 128.4, 128.3, 126.9, 126.8, 126.2, 126.1, 114.9, 60.1, 57.5, 56.4, 44.9. IR (neat, cm\(^{-1}\)): 2921, 1596, 1493, 1446, 1264, 1032, 990, 906, 728, 697, 658, 581. Anal. calcd (found) for C_{18}H_{19}N: H, 7.68 (7.63); C, 86.70 (86.62).

Benzyl 4,4-diphenyl-2-vinylpyrrolidine-1-carboxylate (4e). White waxy solid, 97%. TLC (hexanes–EtOAc = 1:1): R_f = 0.82. \(^1\)H NMR (400 MHz) (1:1 ratio of rotamers): \(\delta\) 7.31-7.07 (m, 15 H), 5.75-5.63 (m, 1 H), 5.24-4.92 (m, 4 H), [4.68 (d, \(J = 11.6\) Hz), 4.54 (d, \(J = 11.3\) Hz), 1:1, 1 H], 4.14-4.00 (m, 1 H), 3.62 (dd, \(J = 7.3, 11.5\) Hz, 1 H), 2.77-2.73 (m, 1 H), 2.40-2.30 (m, 1 H). \(^1^3\)C\{\(^1\)H\} NMR (100 MHz) (1:1 ratio of rotamers): \(\delta\) 155.4, 154.6, 145.3, 144.7, 139.1, 138.4, 136.9, 136.7, 128.7, 128.6, 128.4, 128.2, 128.1, 127.9, 127.6, 127.4, 104
126.7, 126.5, 115.6, 115.0, 66.8, 59.4, 58.9, 56.1, 52.9, 52.6, 45.5, 44.5. Anal. calcd (found) for C\textsubscript{26}H\textsubscript{25}NO\textsubscript{2}: H, 6.57 (6.66); C, 81.43 (81.37).

1-(N-Benzylamino)-4-cyclohexyl-2-vinylpyrrolidine (6a). Pale yellow oil, 94%. TLC (hexanes–EtOAc = 1:1): \( R_f = 0.85 \). \(^1\)H NMR: \( \delta \) 7.30-7.19 (m, 5 H), 5.74 (ddd, \( J = 8.5, 10.5, 17.5 \) Hz, 1 H), 5.18 (dd, \( J = 2, 17 \) Hz, 1 H), 5.08 (dd, \( J = 2, 10 \) Hz, 1 H), 4.00 (d, \( J = 13.5 \) Hz, 1 H), 3.03 (d, \( J = 13.5 \) Hz, 1 H), 2.90 (q, \( J = 8.5 \) Hz, 1 H), 2.80 (d, \( J = 9 \) Hz, 1 H), 1.86 (d, \( J = 9 \) Hz, 1 H), 1.75 (dd, \( J = 7, 12.5 \) Hz, 1 H), 1.44 (dd, \( J = 9.5, 12.5 \) Hz, 1 H), 1.46-1.23 (m, 10 H). \(^{13}\)C\{\(^1\)H\} NMR: \( \delta \) 141.5, 140.0, 128.5, 128.0, 126.5, 116.0, 67.8, 57.9, 40.1, 39.1, 38.4, 26.0, 23.6, 23.5. IR (neat, cm\(^{-1}\)): 3027, 2922, 2850, 2783, 1493, 1449, 1422, 1368, 1307, 1259, 1180, 1133, 1069, 1028, 991, 917, 829, 735, 697. Anal. calcd (found) for C\textsubscript{18}H\textsubscript{25}N: H, 9.87 (9.82); C, 84.65 (84.56).

1-(N-1-phenylethylamino)-4-cyclohexyl-2-vinylpyrrolidine (6b). Yellow oil, 2:1 mixture of diastereomers, 99%. TLC (hexanes–EtOAc = 1:1): \( R_f = 0.81 \). \(^1\)H NMR: \( \delta \) 7.30 (d, \( J = 7 \) Hz, 1 H), 7.25-7.10 (m, 4 H), [5.74 (ddd, \( J = 8.5, 10, 18 \) Hz), 5.63 (ddd, \( J = 8.5, 10, 17.5 \) Hz), 2:1, 1 H], [5.04 (dd, \( J = 1.5, 17.5 \) Hz), 4.95 (dd, \( J = 1.5, 17.5 \) Hz), 2:1, 1 H], [5.00 (dd, \( J = 1.5, 10 \) Hz), 4.85 (dd, 5.00 (dd, \( J = 2, 10 \) Hz), 2:1, 2:1, 1 H), 3.75 (sextet, \( J = 7 \) Hz, 1 H), [3.25 (q, \( J = 7.5 \) Hz), 2.91 (q, \( J = 7.5 \) Hz), 1:2, 1 H], [2.68 (d, \( J = 9 \) Hz), 2.41 (d, \( J = 9 \) Hz), 2:1, 1 H], [2.19 (d, \( J = 8.5 \) Hz), 2.07 (d, \( J = 9.5 \) Hz), 1:2, 1 H], [1.69 (dd, \( J = 7.5, 12 \) Hz), 1.54 (dd, \( J = 7.5, 12.5 \) Hz), 1:2, 1 H], 1.38-1.18 (m, 10 H), [1.32 (d, \( J = 7.5 \) Hz), 1.21 (d, \( J = 7 \) Hz), 2:1, 2:1, 3 H], 1.12-1.03 (m, 1 H). \(^{13}\)C\{\(^1\)H\} NMR: \( \delta \) 145.2, 143.0, 141.9, 141.4, 128.2, 127.8, 127.7, 126.6, 126.2, 114.7, 114.5, 64.1, 63.7, 58.8, 56.5, 39.9, 39.7, 38.8, 38.6, 38.1, 37.6, 26.1, 26.0, 23.6, 23.5, 23.4, 21.4, 14.1. IR (neat, cm\(^{-1}\)): 3061, 2969, 2920, 2797, 1491, 1449, 1372, 1274, 1150, 1077, 992, 914, 762, 699. Anal. calcd (found) for C\textsubscript{18}H\textsubscript{25}N: H, 10.10 (10.17); C, 84.70 (84.63).
cis- And trans-1-(N-benzylamino)-4-phenyl-2-vinylpyrrolidine (cis-8a and trans-8a). A suspension of (2)AuCl (4.0 mg, 7.5 × 10⁻³ mmol), AgSbF₆ (2.6 mg, 7.5 × 10⁻³ mmol) and 7a (42 mg, 0.15 mmol) in 1,4-dioxane (0.51 mL) in a sealed tube was stirred at 60 °C for 8 h. The resulting suspension was concentrated under vacuum and the residue was chromatographed (hexanes–EtOAc = 40:1 → 10:1) to give a 1.3:1 mixture of cis-8a (21 mg, 54%) and trans-8a (16 mg, 41%) as pale yellow oils.

For cis-8a: TLC (hexanes–EtOAc = 9:1): R_f = 0.59. ¹H NMR: δ 7.26 (d, J = 7.5 Hz, 2 H), 7.23-7.15 (m, 6 H), 7.14 (t, J = 7.5 Hz, 1 H), 7.07 (tt, J = 1.5, 7 Hz, 1 H), 5.79 (ddd, J = 8.5, 10, 18 Hz, 1 H), 5.19 (dd, J = 2, 18 Hz, 1 H), 5.08 (dd, J = 2, 10 Hz, 1 H), 4.04 (d, J = 13 Hz, 1 H), 3.16 (dq, J = 4.5, 9 Hz, 1 H), 3.08 (br d, J = 13.5 Hz, 1 H), 2.98 (q, J = 8.5 Hz, 1 H), 2.97 (dd, J = 4, 9.5 Hz, 1 H), 2.55 (t, J = 9.5 Hz, 1 H), 2.37 (ddd, J = 6.5, 9.0, 13.0 Hz, 1 H), 1.70 (td, J = 9.0, 12.5 Hz, 1 H). ¹³C{¹H} NMR: δ 147.1, 140.7, 139.8, 128.5, 128.3, 128.1, 127.1, 126.6, 125.8, 116.7, 69.3, 60.8, 57.9, 42.3, 41.7. IR (neat, cm⁻¹): 3025, 2919, 2784, 1673, 1602, 1493, 1452, 1368, 1191, 1155, 1028, 990, 915, 838, 737, 696, 619. Anal. calcd (found) for C₁₉H₂₁N: H, 8.04 (7.95); C, 86.65 (86.52). The relative configuration of cis-8a was determined by combined 1D-¹H, 2D ¹H-¹H COSY, and 2D ¹H-¹H NOESY analysis (Figure 3.3-3.5). Key to determination of the cis arrangement of the exocyclic phenyl and vinyl groups of cis-8a was the presence of strong NOE cross peaks between H_e and H_i and between H_j and H_g (Figure 3.3). All other NOE data were consistent with this assignment.
Figure 3.3 $^1$H assignments (left structure) and all non-geminal NOE interactions identified from the $^1$H-$^1$H NOESY spectrum of cis-8a (right structure). Key NOE interactions involving H$_e$, H$_f$, and H$_g$ are indicated with bold type.

For trans-8a: TLC (hexanes–EtOAc = 9:1): $R_f = 0.45$. $^1$H NMR: $\delta$ 7.25-7.08 (m, 10 H), 5.79 (ddd, $J = 8, 10, 17$ Hz, 1 H), 5.19 (dd, $J = 1.5, 17$ Hz, 1 H), 5.10 (dd, $J = 1.5, 10$ Hz, 1 H), 4.00 (d, $J = 13$ Hz, 1 H), 3.33-3.26 (m, 1 H), 3.19 (t, $J = 7.5$ Hz, 1 H), 3.09-3.05 (m, 2 H), 2.16 (t, $J = 9.5$ Hz, 1 H), 2.12-2.03 (m, 2 H). $^{13}$C($^1$H) NMR: $\delta$ 144.5, 140.7, 139.2, 129.0, 128.3, 128.1, 127.3, 126.8, 126.1, 116.5, 68.5, 62.0, 58.0, 41.9, 39.9. IR (neat, cm$^{-1}$): 3025, 2919, 2784, 1673, 1602, 1493, 1452, 1368, 1191, 1155, 1028, 990, 915, 838, 737, 696, 619. Anal. calcd (found) for C$_{19}$H$_{21}$N: H, 8.04 (7.95); C, 86.65 (86.52).
Figure 3.4 $^1$H-$^1$H COSY spectrum of cis-8a. Proton assignments correspond to those depicted in Figure 3.3.
Figure 3.5 $^1$H-$^1$H NOESY spectrum of cis-8a. Proton assignments correspond to those depicted in Figure 3.3.
1-(N-2-Cyclohexylamino)-4-phenyl-2-vinylpyrrolidine (8b). Pale yellow oil, 1.5:1 mixture of diastereomers. TLC (hexanes–EtOAc = 1:1): \( R_f = 0.87 \). \(^1\)H NMR: \( \delta \) 7.34-7.15 (m, 5 H), 5.78-5.69 (m, 1 H), 5.15 (td, \( J = 2.5, 19 \) Hz, 1 H), 5.05 (td, \( J = 1.5, 10 \) Hz, 1 H), [3.47 (t, \( J = 7.5 \) Hz), 3.41-3.34 (m), 1:1.5], [3.22 (dq, \( J = 3.5, 8.5 \) Hz), 3.14 (dd, \( J = 4, 9.5 \) Hz), 1.5:1, 1 H], [2.94 (q, \( J = 8 \) Hz), 2.82 (q, \( J = 8 \) Hz), 1:1.5, 1 H], 2.56-2.46 (m, 1 H), 2.39-2.33 (m), 1:1.5, 1 H], 2.18-1.89 (m, 3 H), 1.68-1.60 (m, 4 H), 1.46-1.35 (m, 1 H), 1.26-1.09 (m, 3 H), 0.91-0.79 (m, 2 H). \(^{13}\)C\({}^1\)H NMR: \( \delta \) 147.7, 144.7, 141.4, 128.3, 127.4, 127.2, 126.0, 125.8, 115.9, 115.5, 70.2, 69.5, 62.7, 61.7, 61.4, 61.2, 42.5, 42.2, 41.9, 39.9, 37.0, 36.9, 32.2, 32.1, 31.7, 31.5, 26.9, 26.8, 26.2, 26.1, 26.0. IR (neat, cm\(^{-1}\)): 2921, 2850, 2786, 1683, 1492, 1448, 1264, 1078, 992, 918, 735, 699, 668. Anal. calcd (found) for C\(_{19}\)H\(_{27}\)N: H, 10.10 (9.98); C, 84.70 (84.64).

1-(N-Benzylamino)-2-vinylpyrrolidine (10).\(^{98}\) Yellow oil, 86%. TLC (hexanes–EtOAc = 1:1): \( R_f = 0.71 \). \(^1\)H NMR: \( \delta \) 7.33-7.20 (m, 5 H), 5.78 (ddd, \( J = 8.5, 10, 17 \) Hz, 1 H), 5.21 (dd, \( J = 1.5, 17 \) Hz, 1 H), 5.13 (dd, \( J = 1.5, 10 \) Hz, 1 H), 4.02 (d, \( J = 13 \) Hz, 1 H), 3.06 (d, \( J = 13 \) Hz, 1 H), 2.93 (dt, \( J = 2.5, 9 \) Hz, 1 H), 2.79 (q, \( J = 8.5 \) Hz, 1 H), 2.10 (q, \( J = 8.5 \) Hz, 1 H), 1.98-1.91 (m, 1 H), 1.80-1.60 (m, 3 H). \(^{13}\)C\({}^1\)H NMR: \( \delta \) 141.0, 139.5, 128.9, 128.1, 126.7, 116.5, 68.4, 58.0, 53.2, 31.5, 22.0.

1-(N-Benzylamino)-2-vinylpiperidine (12).\(^{98}\) Pale yellow oil, 91%. TLC (CH\(_2\)Cl\(_2\)-MeOH = 9:1): \( R_f = 0.59 \). \(^1\)H NMR: \( \delta \) 7.31-7.26 (m, 4 H), 7.22-7.19 (m, 1 H), 5.87 (ddd, \( J = 8.5, 10, 17 \) Hz, 1 H), 5.18 (dd, \( J = 2, 17 \) Hz, 1 H), 5.09 (dd, \( J = 2, 10 \) Hz, 1 H), 4.05 (d, \( J = 13.5 \) Hz, 1 H), 3.03 (d, \( J = 13.5 \) Hz, 1 H), 2.79 (td, \( J = 3, 11.5 \) Hz, 1 H), 2.66 (dt, \( J = 3, 11 \) Hz, 1 H), 1.86 (dt, \( J = 3, 11.5 \) Hz, 1 H), 1.71-1.60 (m, 2 H), 1.55-1.40 (m, 3 H), 1.28 (tq, \( J = 3.5, 12.5 \) Hz, 1 H). \(^{13}\)C\({}^1\)H NMR: \( \delta \) 142.6, 139.4, 129.0, 128.0, 126.5, 115.5, 66.6, 59.8, 52.1, 33.7, 25.8, 23.9. Anal. calcd (found) for C\(_{14}\)H\(_{19}\)N: H, 9.51 (9.21); C, 83.53 (83.29).
**(E)-1-Benzyl-2-(1-propenyl)piperidine (14).** Pale yellow oil, 99%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.57$. $^1$H NMR: $\delta$ 7.32-7.25 (m, 4 H), 7.21-7.18 (m, 1 H), 5.62-5.51 (m, 1 H), 5.46 (dd, $J = 8.5$, 15.5 Hz, 1 H), 4.07 (d, $J = 14$ Hz, 1 H), 3.00 (d, $J = 13.5$ Hz, 1 H), 2.77 (td, $J = 3$, 11.5 Hz, 1 H), 2.59 (dt, $J = 2$, 10 Hz, 1 H), 1.83 (dt, $J = 3$, 11.5 Hz, 1 H), 1.72-1.40 (m, 7 H), 1.68 (d, $J = 6.5$ Hz, 3 H), 1.25 (tq, $J = 4$, 12 Hz, 1 H). $^{13}$C($^1$H) NMR: $\delta$ 139.8, 135.2, 129.0, 127.9, 126.5, 126.4, 65.7, 59.7, 52.3, 33.9, 25.9, 24.1, 17.8.

**(8R,10R)-9-Benzyl-8-methyl-10-vinyl-1,5-dithia-9-azaspiro[5.5]undecane (16).** Tan oil, dr = 25:1, 91%. TLC (hexanes–EtOAc = 1:1): $R_f = 0.79$. $^1$H NMR: $\delta$ 7.33 (d, $J = 7.0$ Hz, 2 H), 7.25 (t, $J = 7.0$ Hz, 2 H), 7.16 (t, $J = 7.5$ Hz, 1 H), 5.73 (ddd, $J = 8.5$, 10.5, 17.5 Hz, 1 H), 5.18 (d, $J = 17.5$ Hz, 1 H), 5.01 (d, $J = 10.5$ Hz, 1 H), 4.00 (d, $J = 16$ Hz, 1 H), 3.63 (d, $J = 16$ Hz, 1 H), 3.44 (ddd, $J = 2.5$, 8.5 Hz, 11.0 Hz, 1 H), 2.97-2.87 (m, 2 H), 2.84-2.68 (m, 3 H), 2.26 (td, $J = 3$, 14 Hz, 1 H), 2.12 (td, $J = 2.5$, 13.5 Hz, 1 H), 2.03-1.90 (m, 2 H), 1.84 (d, $J = 11.5$, 14 Hz, 1 H), 1.71 (dd, $J = 11.5$, 14 Hz, 1 H), 0.96 (d, $J = 6.0$ Hz, 3 H). $^{13}$C($^1$H) NMR: $\delta$ 142.1, 141.8, 127.9, 127.8, 126.1, 116.3, 62.4, 54.9, 52.5, 48.1, 46.2, 44.5, 26.2, 25.9, 25.5, 21.9. IR (neat, cm$^{-1}$): 2932, 2904, 2815, 1492, 1451, 1422, 1379, 1340, 1307, 1185, 1093, 1068, 995, 916, 803, 727, 695, 608. Anal. calcd (found) for C$_{18}$H$_{25}$NS$_2$: H, 7.89 (7.86); C, 67.66 (67.60). The cis configuration of 16 was established from analysis of coupling constants in the $^1$H NMR spectrum (Figure 3.6); protons were assigned via 2D $^1$H-$^1$H COSY analysis (Figures 3.6 and 3.7). Particularly diagnostic was the pair of one-proton doublet of doublets at $\delta$ 1.84 ($J = 11.5$, 14 Hz) and 1.71 ($J = 11.5$, 14 Hz) assigned to H$_3_{ax}$ and H$_5_{ax}$, respectively that together established the cis-diequatorial arrangement of the exocyclic C2 vinyl group and C6 methyl group.
Figure 3.6 $^1$H assignments (left structure) and key coupling constants of protons $H_{3ax}$ and $H_{5ax}$ (right structure) of 16.
Figure 3.7 $^1$H-$^1$H COSY spectrum of 16. Proton assignments correspond to those depicted in Figure 3.6.
3.3.4 Synthesis of (S)-(+)‐coniine hydrochloride and determination of enantiopurity of (R,E)-14.

A solution of (R,E)-14 (55.4 mg, 0.26 mmol) in methanol (5 mL) was added to a suspension of Pd/C (0.20 g, 10 wt%) in methanol (5 mL). The resulting suspension was treated with formic acid (0.44 mL), refluxed for 20 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was neutralized with 15% aqueous NaOH and then acidified with 4 N HCl to pH ≈ 3. The resulting solution was concentrated under vacuum and extracted with chloroform (3 × 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated to give (S)-(+)‐coniine hydrochloride as a white solid (41 mg, 90%).[^41^] \([\alpha]_D = +6.9^\circ \) \((c = 0.1, \text{EtOH})\). \(^1\)H NMR: \(\delta 9.38 \text{ (br s, 1 H)}, 9.10 \text{ (br s, 1 H)}, 3.41 \text{ (d, } J = 12 \text{ Hz, 1 H)}, 2.90 \text{ (br s, 1 H)}, 2.82 - 2.75 \text{ (m, 1 H)}, 1.97 - 1.57 \text{ (m, 7 H)}, 1.47 - 1.34 \text{ (m, 3 H)}, 0.90 \text{ (t, } J = 7.5 \text{ Hz, 3 H})\). \(^13\)C \(^1\)H NMR: \(\delta 57.2, 44.7, 35.3, 28.2, 22.4, 22.2, 18.5, 13.7\). Anal. calcd (found) for C₈H₁₈ClN: H, 11.08 (10.92); C, 58.70 (58.81).

Trifluoroacetic anhydride (34 mL, 0.25 mmol) was added to a solution of (S)-(+)‐coniine hydrochloride (19 mg, 0.11 mmol) and triethylamine (13 mL, 0.91 mmol) in CH₂Cl₂ (1.7 mL) at 0 °C and the resulting suspension was warmed to room temperature and stirred for 2 h. Water (1 mL) was added and the reaction mixture was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic extracts were dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 20:1) to give (S)-(+)‐coniine trifluoroacetimide as a colorless oil (21.6 mg, 85%).[^100^] The enantiopurity of (S)-(+)‐coniine trifluoroacetimide was determined by GC analysis on chiral support and by comparison to the GC of (±)-coniine trifluoroacetimide (Figure 3.8). \(^1\)H NMR: 1.8:1 mixture of rotamers: \(\delta [4.67-4.64 \text{ (m), 4.02-3.96 \text{ (m), 1.8:1, 1 H)}, [4.35 \text{ (d, } J = 13 \text{ Hz), 3.74 \text{ (d, } J = 14 \text{ Hz), 1:1.8, 1 H)}, [3.13 \text{ (dt, } J = 2.5, 13 \text{ Hz), 2.80 (dt, } J = 2, 14 \text{ Hz), 1.8:1, 1 H)}, 1.73-1.60 \text{ (m, 6 H), 1.49-1.15 \text{ (m, 4 H), [0.90 (t, } J = 7.5 \text{ Hz), 0.89 (t, } J = 7.5 \text{ Hz), 1:1.8, 3 H)}\]. \(^13\)C
NMR: \[ \delta 155.9 \text{ (q, } J_{CF} = 34 \text{ Hz)}, 116.7 \text{ (q, } J_{CF} = 284 \text{ Hz)}, [53.5 \text{ (br s), 50.1, 1:1.8}, [40.9 \text{ (br s), 38.3, 1.8:1}, [32.1, 31.3, 1:1.8}, [28.5, 28.1, 1:1.8}, [26.1, 25.3, 1.8:1}, [19.2, 19.1, 1:1.8}, [18.7, 18.5, 1.8:1}, 13.9. \text{ Anal. calcd (found) for } C_{10}H_{16}F_{3}NO: H, 7.22 \text{ (7.12); C, 53.80 (53.68).}

Figure 3.8 Chiral GC traces of (±)-coniine trifluoroacetimide (left trace) and enantiomerically enriched (S)-(+) -coniine trifluoroacetate (right trace, 96% ee).

3.3.5 Control experiments

1. **Gold/ligand only:** A suspension of (2)AuCl \[2 = P(t-Bu)_2(o-biphenyl); 5.3 \text{ mg, 0.01 mmol}\] and 3a (36 mg, 0.10 mmol) in dioxane (0.34 mL) in a sealed tube was stirred at room temperature for 24 h. GC, TLC, and \(^1\)H NMR analysis of the crude reaction mixture showed no detectable consumption of 3a and no detectable formation of 4a.

2. **Silver only:** A suspension of 3a (36 mg, 0.10 mmol) and AgSbF\(_6\) (3.4 mg, 0.01
mmol) in dioxane (0.34 mL) in a sealed tube was stirred at room temperature for 24 h. 

\[ ^1H \text{NMR analysis of the crude reaction mixture showed } <10\% \text{ conversion to } 4a. \]

3. **HOTf only:** A suspension of HOTf (0.88 mL, 0.01 mmol) and 3a (36 mg, 0.10 mmol) in dioxane (0.34 mL) in a sealed tube was stirred at room temperature for 24 h. GC, TLC, and \[ ^1H \text{NMR analysis of the crude reaction mixture showed no detectable consumption of } 3a \text{ and no detectable formation of } 4a. \]
Chapter 4

Gold(I)-Catalyzed Enantioselective Intramolecular Dehydrative Amination of Allylic Alcohols with Carbamates

Portions of this chapter have been published: Mukherjee, P.; Widenhoefer, R. A.

4.1 Background

Transition metal-catalyzed enantioselective amination of allylic esters, carbonates and acetates represent an attractive route towards the synthesis of chiral, nonracemic allylic amines.\(^1\) Such an enantioselective transformation in an intramolecular fashion leads to the synthesis of chiral, nonracemic 2-vinyl substituted nitrogen heterocycles like pyrrolidines, piperdines, morpholines and piperazines that could be further functionalized to other substituted nitrogen heterocycles. These chiral, nonracemic nitrogen heterocycles have been extensively used as pharmaceutical agents and are part of numerous bioactive natural products (Figure 4.1).\(^{84-85,101}\) Therefore, new routes towards the synthesis of these compounds have been important.

![Figure 4.1 Examples of bioactive compounds containing morpholine, piperazine, pyrrolidine and piperidine scaffolds.](image)

With the potential to reduce chemical waste and condense synthetic routes, transition metal-catalyzed amination of underivatized allylic alcohols have gained importance over allylic esters and carbonates as electrophiles to synthesize
enantiomerically enriched allylic amines. There are many reports on the stereospecific amination of chiral secondary allylic alcohols as a route to obtain enantiomerically enriched allylic amines.\textsuperscript{34,41b,41k,43,102} As an example, Uenishi and coworkers demonstrated a Pd(II)-catalyzed stereospecific synthesis of 2,6-disubstituted piperidines from secondary allylic alcohols (eq 4.1).\textsuperscript{41k} However, although much has been demonstrated on stereospecific allylic amination, enantioselective amination of allylic alcohols still remain challenging and there are many limitations to current reported procedures.

\[
\text{H}_3\text{COOC} \quad \text{HO} \quad \text{NH} \quad \text{H}_2 \quad \text{PdCl}_2(\text{CH}_3\text{CN})_2 (30 \text{ mol } \% ) \quad \text{THF, RT, 6.5 h} \quad 81\% (88\% \text{ de})
\]

(eq 4.1)

Carreira and coworkers have reported an Ir(I)-catalyzed enantioselective amination of 1-cyclohexylprop-2-en-1-ol with sulfamic acid to form the allylic amine in 70\% ee (eq 4.2).\textsuperscript{33} However, only one example of enantioselective amination was documented. Hartwig and coworkers have developed an Ir(I)/BPh\textsubscript{3}-catalyzed enantioselective intermolecular amination of primary allylic alcohols with aromatic amines with up to 94\% ee.\textsuperscript{46} Although the catalytic transformation proceeded with good enantioselectivity, the substrate scope was limited to cinnamyl alcohols when catalytic amount of Lewis acid activator was used (eq 4.3).
In the area of enantioselective intramolecular allylic amination, in 2010, Yamamoto and coworkers have reported a Hg(II)-catalyzed amination on underivatized allylic alcohols with arylsulfonamides as nucleophiles (eq 4.4).\textsuperscript{48} Although high enantioselectivities of up to 99\% ee were realized with this system, the reaction employed toxic Hg(OTf)\textsubscript{2} as catalyst and was restricted only to the formation of arene-fused nitrogen heterocycles. More recently, in 2011, Kitamura and coworkers have reported a Ru(II)-catalyzed protocol for functionalization of allylic alcohols in an enantioselective fashion (eq 4.5).\textsuperscript{49} However, only three examples were reported with sulfonamides as nucleophiles with up to 97\% ee.
In response to these limitations, we sought to develop a general and efficient protocol for intramolecular enatioselective allylic amination. We have developed an intramolecular dehydrative amination of allylic alcohols with alkylamines catalyzed by achiral gold(I) phosphine complexes (Chapter 3). Encouraged by the efficiency and stereoselectivity of these transformations, and guided by previous work on enantioselective intramolecular allene hydroamination reported by Widenhoefer and as well as intramolecular alkoxylation of allylic alcohols reported by Bandini, we investigated the enantioselective amination of ε-benzylamino allylic alcohols employing axially chiral bis(gold) complexes as catalysts.

4.2 Results and discussion

4.2.1 Optimization and nucleophile scope

Since (E)-6-(N-benzylamino)-5,5-diphenyl-2-hexenol [(E)-1a] have undergone efficient allylic amination under achiral gold(I) phosphine complex catalyzed conditions, we initially targeted (E)-1a under axially chiral bisphosphine gold(I)-catalyzed reaction
conditions. However, optimization within this framework with different bisphosphines as ligands, silver salts, and solvents proved unsuccessful (Table 4.1). Treatment of (E)-1a with a catalytic 1:2 mixture of [(S)-2](AuCl)$_2$ and AgSbF$_6$ in dioxane at room temperature for 5 h led to quantitative conversion to 2-vinylpyrrolidine 3a, but with only 29% ee (Table 4.1, entry 5). When variations in the ligand bound to gold, counterion on the gold precatalyst, and use of different reaction solvent did not show any marked improvement on the enantioselectivity of the reaction, we then focused our attention on manipulation of the nucleophile as a means to amplify stereoinduction.

We first turned our attention to using carbamates as the nucleophile to observe its effect on the stereoinduction of the gold(I)-catalyzed enantioselective allylic amination. Optimization on (E)-benzyl (6-hydroxy-2,2-diphenylhex-4-en-1-yl)carbamate [(E)-1b] proved largely successful: treatment of a catalytic 1:2 mixture of [(S)-2](AuCl)$_2$ and different silver salts in dioxane or toluene as solvent at room temperature in 48 h gave moderate to high yield of 2-vinyl pyrrolidine 3b (30–99%) and the enantioselectivity improved from 48 to 79% ee (Table 4.2, entries 1-8) with AgClO$_4$ in dioxane providing the maximum enantioselectivity.
Table 4.1 Effect of ligand and reaction conditions on gold(I)-catalyzed enantioselective amination of (E)-1a (0.60 M)

<table>
<thead>
<tr>
<th>entry</th>
<th>P–P</th>
<th>solvent</th>
<th>X</th>
<th>convn (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-Binap</td>
<td>dioxane</td>
<td>SbF₆</td>
<td>90</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>ClO₄</td>
<td>91</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>OTf</td>
<td>100</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>OTs</td>
<td>100</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>SbF₆</td>
<td>100</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>PF₆</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>BF₄</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>toluene</td>
<td>SbF₆</td>
<td></td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>CH₂Cl₂</td>
<td>SbF₆</td>
<td></td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>MeOH</td>
<td>SbF₆</td>
<td></td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>SbF₆</td>
<td></td>
<td>90</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>pyridine</td>
<td>SbF₆</td>
<td></td>
<td>45</td>
<td>7</td>
</tr>
</tbody>
</table>

*a* Determined by ¹H NMR.  
*b* Determined by HPLC analysis on chiral support.  
*c* Isolated yield.
Table 4.2 Effect of ligand and reaction conditions on the gold(I)-catalyzed amination of (E)-1b (0.60 M)

<table>
<thead>
<tr>
<th>entry</th>
<th>P–P</th>
<th>solvent</th>
<th>X</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>OTf</td>
<td>25</td>
<td>72</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>NTf₂</td>
<td>25</td>
<td>48</td>
<td>52</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>BF₄⁻</td>
<td>25</td>
<td>72</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>(S)-2</td>
<td>toluene</td>
<td>OTs</td>
<td>25</td>
<td>72</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>(S)-2</td>
<td>toluene</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>72</td>
<td>99</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>(S)-2</td>
<td>toluene</td>
<td>PF₆⁻</td>
<td>25</td>
<td>72</td>
<td>88</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>(S)-2</td>
<td>toluene</td>
<td>SbF₅⁺</td>
<td>25</td>
<td>72</td>
<td>93</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>48</td>
<td>99</td>
<td>79</td>
</tr>
<tr>
<td>9</td>
<td>(R)-binap</td>
<td>dioxane</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>48</td>
<td>91</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>(S)-L5</td>
<td>dioxane</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>48</td>
<td>84</td>
<td>36</td>
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<td>dioxane</td>
<td>ClO₄⁻</td>
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<td>38</td>
</tr>
<tr>
<td>12</td>
<td>(R)-L7</td>
<td>dioxane</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>48</td>
<td>83</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>(S)-L8</td>
<td>dioxane</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>48</td>
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<td>29</td>
</tr>
<tr>
<td>14</td>
<td>(S)-2</td>
<td>CH₂Cl₂</td>
<td>OTf</td>
<td>25</td>
<td>72</td>
<td>93</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>(S)-2</td>
<td>MeOH</td>
<td>OTf</td>
<td>25</td>
<td>72</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>(S)-2</td>
<td>m-xylene</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>48</td>
<td>94</td>
<td>57</td>
</tr>
<tr>
<td>17</td>
<td>(S)-2</td>
<td>diglyme</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>48</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>18</td>
<td>(S)-2</td>
<td>toluene</td>
<td>ClO₄⁻</td>
<td>0</td>
<td>48</td>
<td>58&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60</td>
</tr>
<tr>
<td>19</td>
<td>(S)-2</td>
<td>toluene</td>
<td>ClO₄⁻</td>
<td>-20</td>
<td>48</td>
<td>61&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60</td>
</tr>
<tr>
<td>20</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>ClO₄⁻</td>
<td>80</td>
<td>2</td>
<td>89</td>
<td>63</td>
</tr>
<tr>
<td>21</td>
<td>(S)-2</td>
<td>dioxane</td>
<td>ClO₄⁻</td>
<td>25</td>
<td>24</td>
<td>40&lt;sup&gt;c&lt;/sup&gt;</td>
<td>75</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield. <sup>b</sup>Determined by HPLC analysis on chiral support. <sup>c</sup>[(E)-1b] = 0.30 M.
Effort towards further improvement in the enantioselectivity of the reaction by changing the nature of the ligand attached to gold to other bisphosphines did not improve the efficiency or the enantioselectivity of the reaction (Table 4.2, entries 9-13). A subsequent solvent screen of both polar as well as nonpolar solvents with respect to dioxane showed no improvement on enantioselectivity and therefore, dioxane was chosen for further studies (Table 4.2, entries 14-17). To observe any temperature effect on the stereoinduction, \((E)-1b\) was treated with a catalytic 1:2 mixture of \([((S)-2](AuCl)_2\) and \(AgClO_4\) in toluene at 0 °C and -20 °C respectively, however, the enantioselectivity dropped down to 60% from 68% at room temperature (Table 4.2, entries 5 and 18-19). Also a higher reaction temperature of 80 °C enhanced the reaction rate but did not show an improvement in the enantioselectivity (Table 4.2, entry 20). Finally, reducing the reaction concentration to half affected the reaction rate but did not exhibit any change in the reaction enantioselectivity (Table 4.2, entry 21). As a result, with the optimized reaction conditions for enantioselective allylic amination, we chose to investigate further the effect of other nitrogen nucleophiles on the stereoinduction. The absolute configuration of 3b was determined to be (S) by comparison to an HPLC trace of \((R)-3b\).\(^{103b}\)

Table 4.3 summarizes the effect of other carbamates and sulfonamide nucleophiles on the efficiency and stereoselectivity of the intramolecular dehydrative amination. Treatment of \(ter\)-butyloxy carbonyl- (Boc-) \([(E)-1c]\) and methoxycarbonyl-protected \(\varepsilon\)-aminoallylic alcohol \([(E)-1e]\) with a catalytic 1:2 mixture of \([(S)-2](AuCl)_2\) and \(AgClO_4\) in dioxane at room temperature after 48 h gave the corresponding 2-vinyl pyrrolidine in high yield (97-99%) and in comparable enantioselectivity with respect to benzyl carbamate as the nucleophile (Table 4.3, entries 1 and 3). With 2,2,2-trichloroethoxycarbonyl(Troc)-protected \(\varepsilon\)-aminoallylic alcohol \([(E)-1d]\), the reactivity of
the substrate was slower and therefore a catalytic 1:2 mixture of [(S)-2](AuCl)$_2$ and AgClO$_4$ in dioxane at 40 °C gave a 62% yield but with an improved enantioselectivity of 84% ee (Table 4.3, entry 2). Sulfonamide as nucleophile also underwent cyclization under the optimized reaction conditions to provide the 2-vinylpyrrolidine (S)-3f in 98% yield and 76% ee (Table 4.3, entry 4). Gratifyingly, fluorenlymethyloxycarbonyl(Fmoc)-protected ε-aminomallylic alcohol [(E)-1g] showed a marked amplification in stereoinduction as it underwent efficient gold(I)-catalyzed cyclization in dioxane at room temperature in 48 h to provide 2-vinyl pyrrolidine (S)-3g in 95% yield and with 91% ee (Table 4.3, entry 5).

**Table 4.3** Effect of the nucleophile on gold(I)-catalyzed intramolecular amination of allylic alcohols (E)-1 under optimized conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>R$^a$</th>
<th>X</th>
<th>pyrrolidine</th>
<th>yield (%)$^b$</th>
<th>ee (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc</td>
<td>ClO$_4$</td>
<td>3c</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td>2$^a$</td>
<td>Troc</td>
<td>ClO$_4$</td>
<td>3d</td>
<td>62</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>CO$_2$Me</td>
<td>ClO$_4$</td>
<td>3e</td>
<td>97</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Ts</td>
<td>ClO$_4$</td>
<td>3f</td>
<td>98</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>Fmoc</td>
<td>ClO$_4$</td>
<td>3g</td>
<td>95</td>
<td>91</td>
</tr>
</tbody>
</table>

$^a$Boc=tert-butyloxycarbonyl, Troc=2,2,2-trichloroethoxycarbonyl, Fmoc=fluorenlymethyloxycarbonyl. $^b$Isolated yield. $^c$Determined by HPLC analysis on chiral support. $^d$Reaction run at 40 °C.

### 4.2.2 Substrate scope of enantioselective intramolecular amination

With Fmoc-protected amine identified as the most effective nucleophile under the optimized gold(I)-catalyzed enantioselective intramolecular allylic amination, the scope of this reaction was evaluated as a function of alkene configuration, substitution and ring size (Table 4.4). The enantioselectivity of the intramolecular amination was
sensitive to the alkene configuration: (Z)-1g underwent efficient cyclization in 48 h to give 3g in 99% yield but with ≤5% ee (Table 4.4, entry 1). Therefore, scope of the reaction was further explored on substrates having trans alkene geometry. Substrates that had a gem-dialkyl substitution at the homoallylic position, such as dimethyl or cyclohexyl, cyclized efficiently with high enantioselectivity (90-94% ee, Table 4.4, entries 2-3). In addition, ε-amino allylic alcohol (8) without a gem-dialkyl substitution cyclized efficiently at room temperature in 48 h, albeit with a moderate enantioselectivity (62% ee) (Table 4.4, entry 4). The absolute configuration of 8 was assigned to be S through chemical correlation. The absolute configuration of the remaining heterocycles were assigned to be S by analogy.

Although ε-amino allylic alcohols having gem-dialkyl substitution at the homoallylic position cyclized with high enantioselectivity, homoallylic gem-disubstitution was not necessary for high enantioselectivity: gold(I)-catalyzed cyclization of 4, which possessed a single phenyl group at the homoallylic position, led to formation of pyrrolidine 5 in 87% yield as a 1:1 mixture of cis and trans diastereomers and both of them showed ≥90% ee (Table 4.4, entry 5). This is indicative of an overriding catalyst control of stereoinduction over the substrate. Likewise, compound 12 with an iso-propyl group at the homoallylic position instead of the phenyl group underwent cyclization with high stereoselectivity for both the diastereomers in 2-vinylpyrrolidine 13 (Table 4.4, entry 6). The gold-catalyzed enantioselective amination also tolerated gem-dialkyl substitutions at the allylic carbon bound to the hydroxyl group and led to the formation of vinylpyrrolidine with a tri-substituted alkene (15) and as a 1:1 mixture of diastereomers, both of which showed high enantioselectivity (88/90% ee) (Table 4.4, entry 7).
We next investigated the synthesis of six-membered nitrogen heterocycles and cyclization of a \( \phi \)-amino allylic alcohol 16, which possessed a \textit{gem}-dialkyl substitution on the alkyl chain tethering the nucleophile to the alcohol, underwent cyclization under gold-catalyzed condition to give 2-vinyl piperidine in 69% yield and a moderate 77% ee (Table 4.4, entry 8). We then considered the substitution of the homoallylic carbon with a heteroatom like oxygen or nitrogen that would lead to the synthesis of substituted morpholines and piperazines respectively. However, substitution of the homoallylic carbon by oxygen in the \( \phi \)-amino allylic alcohol 18 required a higher temperature (60 °C) to cyclize and gave 2-vinyl morpholine (19) in 92% yield with 57% ee (Table 4.4, entry 9). \textit{gem}-Dialkyl substitution on such a backbone \( \alpha \)- to the nucleophile made the cyclization rate even slower and degraded the enantioselectivity as well (Table 4.4, entry 10). Gratifyingly, substitution of the homoallylic carbon by a protected nitrogen group in the \( \phi \)-amino allylic alcohol proved highly efficient and showed a high improvement in enantioselectivity. Therefore, protecting groups on the nitrogen at the homoallylic position as well as the nitrogen nucleophile was varied to synthesize numerous differently protected 2-vinylpiperazines in high yields and enantioselectivities (Table 4.4, entries 11-13). As an example, gold(I)-catalyzed enantioselective intramolecular amination of an \( \phi \)-amino allylic alcohol 22 that possessed a Boc-protected amino group at the homoallylic position cyclized in 48 h at 50 °C to provide the 2-vinyl piperazine 23 in 86% yield and an excellent 94% ee (Table 4.4, entry 11).
Table 4.4 Substrate scope of the intramolecular amination (0.60 M) catalyzed by 1:2 mixture of [(S)-2](AuCl)$_2$ (2.5 mol%) and AgClO$_4$ (5 mol%) in dioxane at 25 °C for 48 h.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>heterocycle</th>
<th>yield (%)$^a$</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Z)-1g</td>
<td>3g</td>
<td>95</td>
<td>≤5</td>
</tr>
<tr>
<td>2</td>
<td>4 (R = Me)</td>
<td>5</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>6 [R = -{(CH$_2$)$_5$}]-</td>
<td>7</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>9</td>
<td>89</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>10 (R = Ph)</td>
<td>11</td>
<td>87$^c$</td>
<td>90/92</td>
</tr>
<tr>
<td>6</td>
<td>12 (R = i-Pr)</td>
<td>13</td>
<td>98$^c$</td>
<td>85/91</td>
</tr>
<tr>
<td>7</td>
<td>i-Pr 14</td>
<td>15</td>
<td>87$^c$</td>
<td>88/90</td>
</tr>
<tr>
<td>8</td>
<td>16 [R = -{(CH$_2$)$_5$}]-</td>
<td>17</td>
<td>69</td>
<td>77</td>
</tr>
<tr>
<td>9$^d$</td>
<td>18 (R = H)</td>
<td>19</td>
<td>92</td>
<td>57</td>
</tr>
<tr>
<td>10$^e$</td>
<td>20 [R = -{(CH$_2$)$_4$}]-</td>
<td>21</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>11$^e$</td>
<td>22 (R$^1$ = Fmoc, R$^2$ = Boc)</td>
<td>23</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>12$^e$</td>
<td>24 (R$^1$ = Fmoc, R$^2$ = Ts)</td>
<td>25</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>13$^e$</td>
<td>26 (R$^1$ = Boc, R$^2$ = Fmoc)</td>
<td>27</td>
<td>99</td>
<td>91</td>
</tr>
</tbody>
</table>

$^a$Isolated yield. $^b$Determined by HPLC analysis on chiral support. $^c$Diastereomeric ratio = ~1:1. $^d$Reaction run at 60 °C. $^e$Reaction run at 50 °C.
4.2.3 Enantioselective amination on a chiral secondary alcohol

In order to evaluate the effect of a chiral secondary allylic alcohol on the efficiency and stereoselectivity of this enantioselective gold(I)-catalyzed intramolecular dehydrative amination, ε-amino allylic alcohol 28 was synthesized and subjected to the optimized reaction conditions. Treatment of rac-28 with a catalytic 1:2 mixture of [(S)-2](AuCl)₂ and AgClO₄ in dioxane at room temperature after 48 h led to isolation of a 1:1 mixture of (E)-29 and (Z)-29 in 91% combined yield and 93% and 95% ee respectively (Scheme 4.1). Hydrogenation of this 1:1 mixture gave 2-propylpyrrolidine 30 in 92% yield and with 93% ee, which established that both (E)-29 and (Z)-29 possessed the same absolute configuration (S by analogy). In addition, conversion of rac-28 to 29 under gold(I)-catalyzed conditions was periodically monitored by HPLC and it revealed that both enantiomers of 28 reacted at similar rates ($k_S/k_R = 1.06$).

Enantiomerically enriched ε-amino allylic alcohol (R)-28 was synthesized and its cyclization catalyzed by [(S)-2](AuCl)₂/AgClO₄ led to isolation of a 40:1 mixture of (S,E)-29 with >99% ee and (R,Z)-29 with 12% ee in 93% combined yield (Scheme 4.2).
Similarly, cyclization of \((R)-28\) catalyzed by \([\textit{R}-2] \text{AuCl}_2/\text{AgClO}_4\) led to isolation of a 25:1 mixture of \((R,Z)-29\) with >99% ee and \((S,E)-29\) with 29% ee in 95% combined yield. Together, these results established that the asymmetric induction was solely determined by the catalyst configuration \((S\rightarrow S; R\rightarrow R)\) and the \(E/Z\) selectivity in the product is determined by the stereochemical relationship between the incipient \(N\)-bound stereocenter and the extant \(O\)-bound stereocenter \((S/R\rightarrow E; R/R\rightarrow Z)\). These results established the net \textit{syn}-addition of the carbamate nucleophile with respect to the departing hydroxyl group.

![Scheme 4.2](image)

**4.2.4 Mechanism**

The net \textit{syn} displacement of the hydroxy group by the carbamate nucleophile, which was also observed for the amination of allylic alcohols catalyzed by achiral monophosphine gold(I) complexes\(^{102b-c}\), is consistent with the mechanism involving \textit{anti}-addition of the nucleophile to the \(\text{C} = \text{C}\) bond activated by complexation with gold followed by \textit{anti}-elimination of the hydroxy group facilitated through an intramolecular \(\text{N} - \text{H} \cdots \text{O}\) hydrogen bonding (Scheme 4.3).\(^69\) Alternatively, the stereochemical outcome
of this reaction is also consistent with a net syn-substitution that involves a mechanism with \( \sigma \)-activation of the hydroxyl group followed by a concerted S_N2' displacement.\(^6\) Toste and coworkers have demonstrated that bis(gold) phosphine complexes are sufficiently Lewis acidic to activate the hydroxy group of an alcohol.\(^1\) However, our attempts to observe the cyclization of \((E)-1g\) in presence of catalytic amounts of triflic acid or BF_3•OEt_2 (10 mol %, 25 °C, 48 h) showed no detectable formation of product and hence ruled out the \( \sigma \)-activation pathway for this allylic amination. Therefore, outer-sphere addition of the carbamate to the complexed C=C bond leads to the cyclic, hydrogen-bonded gold-alkyl intermediate. Proton transfer from nucleophile to the hydroxy group followed by anti-elimination of water and displacement of gold would give 2-(1-propenyl)-pyrrolidine \((S,E)-29\).

![Scheme 4](image)

**Scheme 4. 3**

### 4.2.5 Summary

To summarize, a new protocol for the intramolecular enantioselective dehydrative amination of allylic alcohols catalyzed by bis(gold) phosphine complexes was developed. With carbamates used as nucleophiles, this procedure led to the formation of both five- and six-membered nitrogen heterocycles in high yields and with up to 95% ee. Cyclization of chiral \( \epsilon \)-amino allylic alcohols that possessed a stereogenic homoallylic or allylic hydroxy-bound carbon atom occurred with overriding catalyst
control of asymmetric induction. Finally, stereochemical analysis of the cyclization of enantiomerically enriched ε-amino allylic alcohol (R)-28, which possessed a secondary allylic alcohol moiety, established the net syn-displacement of the hydroxy group by the carbamate nucleophile.

4.3 Experimental section

4.3.1 General methods

Catalytic reactions were performed in sealed tubes under an atmosphere of dry nitrogen unless noted otherwise. NMR spectra were obtained on a 500 MHz for ¹H NMR and 126 MHz for ¹³C NMR in CDCl₃ unless noted otherwise. Gas chromatography was performed on a 25 m polydimethylsiloxane capillary column. HPLC to determine enantiomeric excesses was performed using a 0.46 cm × 25 cm Chiralpak AD-H column. Flash column chromatography was performed employing 200-400 mesh silica gel. Thin layer chromatography (TLC) was performed on silica gel 60 F254. Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). Unless noted otherwise, all reagents, ligands, and silver salts were purchased from major commercial suppliers and were used as received. Bis(gold chloride) precatalysts [P–P](AuCl)₂, substrates [(E)-1a] and [(E)-1b], and reagents 5,5-diphenyl-5-cyanomethyl-2-pentenoate, trans-(4-bromobut-2-en-1-yloxy)(tert-butyl)dimethylsilane, trans-6-bromo-2-hexen-1-ol, N-(cyanomethyl)-4-methylbenzenesulfonamide, were prepared using published procedures. (E)-4-Bromo-1-(2-tetrahydropyranyloxy)-2-butene (E/Z ≥25:1) was prepared from trans-methyl-4-bromocrotonate (E/Z ≥25:1) using published procedure. Pure methyl-4-bromocrotonate (E/Z ≥25:1) was obtained by purifying technical grade methyl-4-bromocrotonate via flash column chromatography.
4.3.2 Synthesis of $\varepsilon$- and $\phi$-amino allylic alcohols

$(E)$-Methyl-(6-hydroxy-2,2-diphenylhex-4-en-1-yl)carbamate [(E)-1e]. A solution of 5,5-diphenyl-5-cyanomethyl-2-pentenoate (1.5 g, 5.0 mmol) in ether (15 mL) was added to a stirred suspension of LiAlH$_4$ (0.76 g, 20 mmol) in ether (35 mL) at 0 °C and the resulting suspension was warmed to 25 °C and stirred for 3 h (Scheme 4.4). The reaction mixture was cooled to 0 °C and treated sequentially with water (1 mL), 15 % NaOH [(w/v), 1 mL] and water (1 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in THF (18 mL), cooled to 0 °C and treated with triethylamine (1 mL, 7.0 mmol) and methylchloroformate (0.33 mL, 4.2 mmol) and the resulting solution was stirred for 1 h. The resulting mixture was treated with water (30 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried (MgSO$_4$), concentrated, and chromatographed (hexanes–EtOAc = 1:1) to give $(E)$-1e as a white solid (0.94 g, 58%, over 2 steps). TLC (hexanes–EtOAc = 1:1): $R_f$ = 0.18. $E/Z = 24:1$. mp 78 - 82 °C. $^1$H NMR: $\delta$ 7.30 (t, $J = 7.5$ Hz, 4 H), 7.23 (t, $J = 7.5$ Hz, 2 H), 7.17 (d, $J = 8$ Hz, 4 H), 5.57 (td, $J = 6.5$, 15 Hz, 1 H), 5.34 (td, $J = 7$, 15 Hz, 1 H), 4.26 (br s, 1 H), 3.94 (s, 2 H), 3.93 (d, $J = 6.5$ Hz, 2 H), 3.62 (s, 3 H), 2.86 (d, $J = 7$ Hz, 2 H), 1.61 (br s, 1 H). $^{13}$C[1H] NMR: $\delta$ 157.0, 145.3, 133.3, 128.4, 128.0, 127.8, 126.6, 63.6, 52.2, 50.2, 47.4, 39.9. IR (neat, cm$^{-1}$): 3429, 2929, 1704, 1520, 1495, 1444, 1239, 1192, 1073, 1006, 975, 916, 756, 699. Anal. calcd (found) for C$_{20}$H$_{23}$NO$_3$: H, 7.12 (7.10); C, 73.82 (73.83).
Scheme 4.4

\((\text{E})\text{-}\text{tert-Butyl(6-hydroxy-2,2-diphenylhex-4-en-1-yl)carbamate}\) \([\text{(E)-}1\text{c}].\)

Compound \((\text{E})\text{-}1\text{c}\) was isolated as a white solid in 27\% yield employing a procedure analogous to that used to synthesize \((\text{E})\text{-}1\text{e}\) (Scheme 4.4). mp 88 - 91 °C. TLC (hexanes–EtOAc = 1:1): \(R_f = 0.4.\) \(^1\)H NMR: \(\delta\) 7.32-7.29 (m, 4 H), 7.22 (t, \(J = 7.5\) Hz, 2 H), 7.18 (d, \(J = 8\) Hz, 4 H), 5.59 (td, \(J = 6, 15.5\) Hz, 1 H), 5.32 (td, \(J = 7, 15.5\) Hz, 1 H), 4.13 (t, \(J = 7\) Hz, 1 H), 3.94 (d, \(J = 7\) Hz, 2 H), 3.88 (d, \(J = 6\) Hz, 2 H), 2.87 (d, \(J = 7\) Hz, 2 H), 1.69 (br s, 1 H), 1.39 (s, 9 H). \(^{13}\)C\(^{1}\)H NMR: \(\delta\) 155.8, 145.5, 133.3, 128.4, 128.3, 127.9, 126.5, 79.5, 63.6, 50.2, 46.9, 40.0, 28.4. IR (neat, cm\(^{-1}\)): 3436, 2976, 2929, 1704, 1495, 1444, 1391, 1363, 1220, 1162, 1069, 972, 864, 754, 697. Anal. calcd (found) for C\(_{23}\)H\(_{29}\)NO\(_3\): H, 7.95 (7.94); C, 75.17 (75.26).

\((\text{E})\text{-}\text{N-(6-hydroxy-2,2-diphenylhex-4-en-1-yl)-4-methylbenzenesulfonamide}\) \([\text{(E)-}1\text{f}].\)

A solution of diphenylacetonitrile (5.8 g, 30 mmol) in THF (24 mL) was added dropwise to a suspension of NaH (0.72 g, 30 mmol) in THF (18 mL) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h and then cooled to −78 °C (Scheme 4.5). A solution of \(\text{trans-(4-bromobut-2-en-1-yloxy)(tert-butyl)dimethylsiline}\) (9.55 g, 36 mmol) in THF (12 mL) was added dropwise to the reaction mixture and the resulting suspension was warmed to 25°C overnight. The reaction mixture was treated with water (30 mL) and extracted with ether (3 × 30 mL). The combined ether extracts were washed with brine, dried (MgSO\(_4\)), concentrated, and chromatographed (hexanes–
EtOAc = 9:1) to give trans-6-(tert-butyldimethylsilyloxy)-2,2-diphenylhex-4-enenitrile (31) as a brown oil (9.97 g, 88%).

Scheme 4.5

A solution of 31 (1.5 g, 4.0 mmol) in ether (15 mL) was added to a stirred suspension of LiAlH₄ (0.16 g, 4.4 mmol) in ether (15 mL) at 0 °C and the resulting suspension was warmed to 25 °C and stirred for 3 h (Scheme 4.5). The reaction mixture was cooled to 0 °C and treated sequentially with water (0.2 mL), 2 N NaCl (0.2 mL) and water (0.2 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in CH₂Cl₂ (15 mL), cooled to 0 °C and treated with triethylamine (0.6 mL, 4.4 mmol) and p-toluenesulfonylchloride (0.84 g, 4.4 mmol). The reaction mixture was warmed to room temperature overnight. The resulting mixture was treated with water (25 mL) and then extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried (MgSO₄), concentrated, filtered through a plug of silica gel with 4:1 hexanes-EtOAc and concentrated. The resulting oily residue was dissolved in THF (40 mL), cooled to 0 °C and treated with TBAF (1 M solution in THF, 6 mL, 6 mmol). The resulting solution was warmed to 25°C and stirred for 3 h. Water (25 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic
extracts were dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 1:1) to give (E)-1f (0.94 g, 56%, over 3 steps) as a white solid. mp 165 – 168 °C.

**For 31:** TLC (hexanes–EtOAc = 4:1): \(R_f = 0.7\). \(^1\)H NMR: \(\delta\) 7.40-7.34 (m, 8 H), 7.29 (tt, \(J = 2.5, 7\) Hz, 2 H), 5.73 (td, \(J = 5, 15\) Hz, 1 H), 5.57 (td, \(J = 7, 15\) Hz, 1 H), 4.10 (d, \(J = 5\) Hz, 2 H), 3.13 (d, \(J = 7\) Hz, 1 H), 0.84 (s, 9 H), 0.01 (s, 6 H). \(^{13}\)C\(^{1\text{H}}\) NMR: \(\delta\) 139.7, 135.2, 128.8, 127.8, 127.0, 123.1, 122.0, 63.1, 51.9, 42.4, 25.8, 18.3, -5.4. Anal. calcd (found) for C\(_{24}\)H\(_{31}\)NOSi: H, 8.28 (8.25); C, 76.34 (76.31).

**For (E)-1f:** TLC (hexanes–EtOAc = 1:1): \(R_f = 0.44\). \(^1\)H NMR: \(\delta\) 7.60 (d, \(J = 8\) Hz, 2 H), 7.29 (d, \(J = 8\) Hz, 2 H), 7.27-7.20 (m, 6 H), 7.05 (d, \(J = 7.5\) Hz, 4 H), 5.58 (td, \(J = 6, 15.5\) Hz, 1 H), 5.18 (td, \(J = 6.5, 15.5\) Hz, 1 H), 3.91 (t, \(J = 6\) Hz, 2 H), 3.83 (t, \(J = 7\) Hz, 1 H), 3.52 (d, \(J = 7\) Hz, 2 H), 2.92 (d, \(J = 6.5\) Hz, 2 H), 2.43 (s, 3 H), 2.43 (s, 3 H), 3.29 (t, \(J = 5\) Hz, 1 H). \(^{13}\)C\(^{1\text{H}}\) NMR: \(\delta\) 155.8, 145.5, 133.3, 128.4, 128.3, 127.9, 126.5, 79.5, 63.6, 50.2, 46.9, 40.0, 28.4. IR (neat, cm\(^{-1}\)): 3555, 2924, 1707, 1597, 1494, 1443, 1326, 1221, 1161, 1073, 976, 812, 754, 698, 668. Anal. calcd (found) for C\(_{25}\)H\(_{27}\)NO\(_3\)S: H, 6.46 (6.49); C, 71.23 (71.22).

**(E)-(9H-fluoren-9-yl)methyl(6-hydroxy-2,2-diphenylhex-4-en-1-yl)carbamate [(E)-1g]**. A solution of diphenylacetonitrile (1.32 g, 6.8 mmol) in THF (6 mL) was added dropwise to a suspension of NaH (0.27 g, 6.8 mmol) in THF (8 mL) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h and then cooled to −78 °C (Scheme 4.6). A solution of trans-4-bromo-1-(2-tetrahydropyranyl)-2-butene (E/Z ≥ 25:1) (2.9 g, 12.3 mmol) in THF (4 mL) was added dropwise to the reaction mixture and the resulting suspension was warmed to 25°C overnight. The reaction mixture was treated with water (7 mL) and extracted with ether (3 × 10 mL). The combined ether extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 4:1) to give (E)-2,2-diphenyl-6-(tetrahydro-2H-pyran-2-yloxy)hex-4-enenitrile (32) as a colorless oil (2.26 g, 95%, E/Z ≥ 25:1).
A solution of 32 (2.0 g, 5.7 mmol) in ether (21 mL) was added to a stirred suspension of LiAlH₄ (0.43 g, 11.5 mmol) in ether (21 mL) at 0 °C and the resulting suspension was warmed to 25°C and stirred for 3 h (Scheme 4.6). The reaction mixture was cooled to 0 °C and treated sequentially with water (0.5 mL), 15% NaOH [(w/v), 0.5 mL] and water (0.5 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in THF (28 mL), cooled to 0 °C and treated with triethylamine (2 mL, 14.3 mmol) and 9-fluorenylmethyl chloroformate (Fmoc-Cl) (1.77 g, 6.9 mmol). The reaction mixture was stirred at 0 °C for 3 h. The resulting mixture was treated with water (35 mL) and then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried (MgSO₄), concentrated, filtered through a plug of silica gel with 4:1 hexanes-EtOAc and concentrated. The resulting oily residue was dissolved in MeOH (30 mL), cooled to 0 °C and p-toluenesulfonic acid (0.09 g, 0.28 mmol) was added. The resulting solution was warmed to 25°C and stirred for 1.5 h. Aqueous NaHCO₃ (18.7 mM, 15 mL) and CH₂Cl₂ (30 mL) was added to the resulting solution, the layers were separated, and the aqueous fraction was re-extracted with CH₂Cl₂ (2 × 30 mL). The combined organic extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed.
(hexanes–EtOAc = 1:1) to give 1g (1.6 g, 58%, over 3 steps) as a white solid. mp 51 - 55 °C.

**For 32:** TLC (hexanes–EtOAc = 4:1): \( R_f = 0.36 \). \(^1\)H NMR: δ 7.39-7.26 (m, 10 H), 5.73 (td, \( J = 6 \), 15.5 Hz, 1 H), 5.62 (td, \( J = 7.5 \), 15.5 Hz, 1 H), 4.50 (t, \( J = 4 \) Hz, 1 H), 4.13 (dd, \( J = 6 \), 13 Hz, 1 H), 3.93 (dd, \( J = 6 \), 13 Hz, 1 H), 3.80 (dt, \( J = 5 \), 11 Hz, 1 H), 3.44 (dt, \( J = 5 \), 11 Hz, 1 H), 3.14 (d, \( J = 7.5 \) Hz, 2 H), 1.81-1.75 (m, 1 H), 1.67-1.62 (m, 1 H), 1.58-1.48 (m, 4H). \(^{13}\)C\(^{1}\)H NMR: δ 139.6, 139.5, 132.3, 128.8, 127.9, 127.8, 127.0, 126.9, 126.5, 97.4, 66.7, 62.2, 51.7, 42.5, 30.5, 25.3, 19.4. Anal. calcd (found) for C\(_{23}\)H\(_{25}\)NO\(_2\): H, 7.25 (7.23); C, 79.51 (79.47).

For \((E)-1g\): TLC (hexanes–EtOAc = 1:1): \( R_f = 0.36 \). \(^1\)H NMR (55 °C): δ 7.76 (d, \( J = 7.5 \) Hz, 2 H), 7.52 (d, \( J = 6.5 \) Hz, 2 H), 7.40 (t, \( J = 7 \) Hz, 2 H), 7.33-7.28 (m, 6 H), 7.24 (t, \( J = 7 \) Hz, 2 H), 7.18 (d, \( J = 7.5 \) Hz, 4 H), 5.54 (td, \( J = 6 \), 15 Hz, 1 H), 5.38-5.37 (m, 1 H), 4.38 (d, \( J = 7 \) Hz, 2 H), 4.31 (br s, 1 H), 4.18 (t, \( J = 7 \) Hz, 1 H), 3.92 (br s, 4 H), 2.84 (d, \( J = 7 \) Hz, 2 H), 1.29 (br s, 1 H). \(^{13}\)C\(^{1}\)H NMR: δ 156.4, 145.3, 143.9, 141.3, 133.4, 128.4, 127.9, 127.7, 127.1, 126.7, 125.0, 120.0, 66.7, 63.6, 50.6, 47.5, 47.3, 40.0. IR (neat, cm\(^{-1}\)): 3434, 2942, 1704, 1517, 1445, 1358, 1219, 1145, 1077, 1000, 973, 757, 740, 699. Anal. calcd (found) for C\(_{33}\)H\(_{31}\)NO\(_3\): H, 6.38 (6.39); C, 80.95 (80.91).

\((E)-2,2,2\)-trichloroethyl(6-hydroxy-2,2-diphenylhex-4-en-1-yl)carbamate \((E)-1d\). Compound \((E)-1d\) was isolated as a white solid in 63% yield employing a procedure analogous to that used to synthesize \((E)-1g\) (Scheme 4.6). mp 152 - 156 °C. TLC (hexanes–EtOAc = 1:1): \( R_f = 0.42 \). \(^1\)H NMR: δ 7.37-7.34 (m, 4 H), 7.28 (t, \( J = 8 \) Hz, 2 H), 7.21 (d, \( J = 8 \) Hz, 4 H), 5.61 (td, \( J = 6.5 \), 15 Hz, 1 H), 5.36 (td, \( J = 7 \), 15 Hz, 1 H), 4.72 (s, 2 H), 4.60 (t, \( J = 5.5 \) Hz, 1 H), 4.01 (d, \( J = 6.5 \) Hz, 2 H), 3.97 (br s, 2 H), 2.92 (d, \( J = 7 \) Hz, 2 H), 1.47 (br s, 1 H). \(^{13}\)C\(^{1}\)H NMR: δ 154.6, 145.0, 133.5, 128.4, 127.8, 127.7, 126.7, 95.5,
74.4, 63.5, 50.3, 47.7, 39.9. IR (neat, cm⁻¹): 3287, 2936, 1735, 1560, 1444, 1361, 1245, 1145, 1076, 814, 765, 704. Anal. calcd (found) for C₂₁H₂₂Cl₃NO₃: H, 5.01 (4.94); C, 56.97 (56.88).

(Z)-1g. Compound (Z)-1g was synthesized as a white solid in 66% yield from (Z)-2,2-diphenyl-6-(tetrahydro-2H-pyran-2-yloxy)hex-4-enenitrile (33) employing a procedure analogous to that used to synthesize (E)-1g (Scheme 4.7). Intermediate 33 was synthesized in 89% yield from diphenylacetonitrile and (Z)-4-bromo-1-(2-tetrahydropyranlyoxy)-2-butene (Z/E ≥25:1)¹⁰²c employing a procedure analogous to that used to synthesize (E)-2,2-diphenyl-6-(tetrahydro-2H-pyran-2-yloxy)hex-4-enenitrile (10).

Scheme 4.7

For 33: TLC (hexanes–EtOAc = 4:1): Rₖ = 0.41. ¹H NMR: δ 7.39-7.24 (m, 10 H), 5.74 (td, J = 7, 11 Hz, 1 H), 5.55 (td, J = 7, 11 Hz, 1 H), 4.59 (t, J = 3.5 Hz, 1 H), 4.19 (dd, J = 6, 13 Hz, 1 H), 4.01 (dd, J = 7, 13 Hz, 1 H), 3.85-3.81 (m, 1 H), 3.49 (td, J = 4, 10.5 Hz, 1 H), 3.20 (d, J = 7 Hz, 2 H), 1.82-1.74 (m, 1 H), 1.71-1.64 (m, 1 H), 1.58-1.48 (m, 4H). ¹³C{¹H} NMR: δ 139.4, 139.3, 130.5, 128.5, 127.7, 126.7, 125.7, 121.7, 97.5, 62.4, 61.8, 51.1, 37.4, 30.2, 25.0, 19.0. HRMS calcd (found) for C₂₃H₂₅NNaO₂: 370.1778 (370.1780).

For (Z)-1g: mp 48 - 52 °C. TLC (hexanes–EtOAc = 1:1): Rₖ = 0.39. ¹H NMR: δ 7.78 (d, J = 7 Hz, 2 H), 7.53 (d, J = 7 Hz, 2 H), 7.41 (t, J = 8 Hz, 2 H), 7.35-7.31 (m, 6 H), 5.81-5.74 (m, 1 H), 5.50 (d, J = 13 Hz, 1 H), 4.97 (d, J = 7 Hz, 1 H), 4.37-4.30 (m, 1 H), 3.69-3.62 (m, 1 H), 3.48-3.42 (m, 1 H), 3.18-3.12 (m, 1 H), 2.91-2.85 (m, 1 H), 2.05-2.00 (m, 2 H), 1.69-1.62 (m, 1 H), 1.50-1.44 (m, 4H). HRMS calcd (found) for C₂₅H₂₇NNa: 384.1626 (384.1627).
7.26 (t, J = 7.5 Hz, 2 H), 7.17 (d, J = 7.5 Hz, 4 H), 5.66 (td, J = 7.5, 10.5 Hz, 1 H), 5.23 (td, J = 7, 10.5 Hz, 1 H), 4.40-4.38 (m, 3 H), 4.19 (t, J = 6.5 Hz, 1 H), 3.97 (d, J = 6 Hz, 2 H), 3.92 (t, J = 6.5 Hz, 2 H), 2.86 (d, J = 7 Hz, 2 H), 2.04 (t, J = 5.5 Hz, 1 H).

13C{1H} NMR: δ 156.7, 145.3, 143.7, 141.2, 131.9, 128.3, 127.8, 127.6, 126.9, 126.8, 126.5, 124.8, 119.8, 66.7, 58.0, 50.6, 47.0, 33.6. IR (neat, cm⁻¹): 3429, 3015, 1705, 1495, 1477, 1215, 1146, 1102, 1032, 907, 738, 698, 666. Anal. calcd (found) for C₃₃H₃₁NO₃: H, 6.38 (6.33); C, 80.95 (80.95).

(E)-(9H-fluoren-9-yl)-methyl-(6-hydroxy-2,2-dimethylhex-4-en-1-yl)carbamate [(E)-4]. Isobutyronitrile (1.9 mL, 21 mmol) was added to a solution of LDA [generated in situ from n-BuLi (2.5 M solution in hexanes, 8.9 mL, 22.3 mmol) and diisopropylamine (3 mL, 21 mmol) in THF (51 mL)] at −78 ºC (Scheme 4.8). The resulting solution was stirred for 1 h, treated with trans-4-bromo-1-(2-tetrahydropyranoxy)-2-butene (5.3 g, 22.5 mmol), and then warmed to 25 ºC overnight with stirring. The resulting mixture was diluted with ether (50 mL), washed sequentially with water (2 × 50 mL) and brine (50 mL), dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 9:1) to give trans-2,2-dimethyl-6-((tetrahydro-2H-pyran-2-yl)oxy)hex-4-enenitrile (34) as a colorless oil (4.54 g, 97%). Compound 34 was converted to (E)-4 in 85% yield (over 3 steps) employing a procedure analogous to that used to convert 32 to (E)-1g.

For 34: TLC (hexanes–EtOAc = 4:1): Rf = 0.33. 1H NMR: δ 5.80-5.70 (m, 2 H), 4.63 (t, J = 4 Hz, 1 H), 4.23 (dd, J = 4.5, 12 Hz, 1 H), 4.00 (dd, J = 6, 12 Hz, 1 H), 3.89-3.84 (m, 1 H), 3.53-3.46 (m, 1 H), 2.80 (d, J = 8 Hz, 2 H), 1.86-1.80 (m, 1 H), 1.72 (tt, J = 3, 13 Hz, 1 H), 1.65-1.50 (m, 4H), 1.33 (s, 6 H). 13C{1H} NMR: δ 131.9, 126.8, 124.7, 98.0, 67.1, 62.3, 43.6, 32.3, 30.6, 26.3, 26.2, 25.4, 19.5. Anal. calcd (found) for C₁₃H₂₁NO₂: H, 9.48 (9.46); C, 69.92 (69.99).

For (E)-4: Colorless oil. TLC (hexanes–EtOAc = 1:1): Rf = 0.31. 1H NMR (55 ºC): δ 7.76 (d, J = 8 Hz, 2 H), 7.60 (d, J = 8 Hz, 2 H), 7.39 (t, J = 8 Hz, 2 H), 7.31 (t, J = 8 Hz, 2
H), 5.72-5.63 (m, 2 H), 4.77 (br s, 1 H), 4.45 (d, J = 6 Hz, 2 H), 4.23 (t, J = 7 Hz, 1 H), 4.09 (br s, 2 H), 3.02 (br s, 2 H), 1.96 (br s, 2 H), 1.54 (br s, 1 H), 0.88 (br s, 6 H). $^{13}$C{[H]} NMR: δ 156.7, 143.9, 141.3, 132.2, 128.5, 127.6, 126.9, 124.9, 119.9, 66.5, 63.5, 50.5, 47.3, 42.5, 34.9, 24.8. IR (neat, cm$^{-1}$): 3323, 3065, 2955, 1696, 1521, 1448, 1241, 1137, 1080, 999, 970, 907, 737, 645. Anal. calcd (found) for C$_{23}$H$_{27}$NO$_3$: H, 7.45 (7.37); C, 75.59 (75.47).

Scheme 4.8

(E)-9H-Fluoren-9-ylmethyl (1-(4-hydroxybut-2-en-1-yl)cyclohexyl)methyl carbamate [(E)-6]. Compound (E)-6 was synthesized as a colorless oil in 64% yield from (E)-1-(4-(tetrahydro-2H-pyran-2-yloxy)but-2-en-1-yl)cyclohexanecarbonitrile (35)$^{102c}$ (E/Z ≥ 25:1) employing a procedure similar to that used to synthesize (E)-1g (Scheme 4.8). TLC (hexanes–EtOAc = 1:1): $R_f = 0.36$. $^1$H NMR (60 °C): δ 7.79 (d, J = 8 Hz, 2 H), 7.62 (d, J = 7 Hz, 2 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.33 (t, J = 7.5 Hz, 2 H), 5.76-5.65 (m, 2 H), 4.74 (br s, 1 H), 4.48 (d, J = 6 Hz, 2 H), 4.25 (t, J = 7 Hz, 1 H), 4.10 (d, J = 4.5 Hz, 2 H), 3.13 (br s, 2 H), 2.06 (d, J = 6.5 Hz, 2 H), 1.61 (br s, 1 H), 1.49-1.23 (m, 10 H). $^{13}$C{[H]} NMR: δ 156.7, 143.9, 141.3, 132.1, 128.4, 127.6, 126.9, 124.9, 119.9, 66.4, 63.5, 47.5, 47.3, 38.6, 37.1, 33.3, 26.1, 21.3. IR (neat, cm$^{-1}$): 3326, 3064, 2919,2848, 1693, 1518, 1448, 1240, 1133, 1079, 996, 971, 757, 737, 620. Anal. calcd (found) for C$_{36}$H$_{35}$NO$_3$: H, 7.71 (7.70); C, 77.01 (76.93).
(E)-9H-fluoren-9-ylmethyl (6-hydroxyhex-4-en-1-yl)carbamate [E-(8)].

Dihydropyran (0.9 mL, 10.2 mmol) was added to a solution of (E)-6-bromo-2-hexen-1-ol (1.2 g, 6.8 mmol) and PPTS (0.17 g, 0.68 mmol) in CH₂Cl₂ (50 mL) and stirred at 25°C for 3 h (Scheme 4.9). The reaction mixture was treated with brine (40 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 4:1) to give (E)-2-(6-bromohex-2-en-1-yloxy)tetrahydro-2H-pyran (38) as a colorless oil (1.77 g, 99%, E/Z ≥ 25:1).

Scheme 4.9

A solution of 38 (1.6 g, 6.1 mmol) and sodium azide (0.49 g, 7.6 mmol) in DMSO (16 mL) was stirred at 25°C for 2.5 h, treated with water (25 mL), and extracted with tert-butyl methyl ether (3 × 30 mL). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated. The resulting oily residue was dissolved in ether (20 mL) and added to a stirred suspension of LiAlH₄ (0.23 g, 6.1 mmol) in ether (20 mL) at 0 °C and the resulting suspension was warmed to 25°C and stirred for 1.5 h (Scheme 4.9). The reaction mixture was cooled to 0 °C and treated sequentially with water (0.3 mL), 15 % NaOH [(w/v), 0.3 mL] and water (0.3 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in THF (30 mL), cooled to 0 °C and treated with triethylamine (2.1 mL, 15 mmol) and Fmoc-Cl (1.9 g, 7.2 mmol). The reaction mixture was stirred at 0 °C for 3 h. The resulting mixture was treated with water (35 mL) and
then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried (MgSO₄), concentrated, filtered through a plug of silica gel with 4:1 hexanes–EtOAc and concentrated. The resulting oily residue was dissolved in MeOH (40 mL), cooled to 0 °C and p-toluenesulfonic acid (0.06 g, 0.3 mmol) was added. The resulting solution was warmed to 25 °C and stirred for 1.5 h. Aqueous NaHCO₃ (20 mM, 15 mL) and CH₂Cl₂ (30 mL) was added to the resulting solution, the layers were separated, and the aqueous fraction was re-extracted with CH₂Cl₂ (2 × 30 mL). The combined organic extracts were washed with brine, dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 1:1) to give 38 (1.5 g, 74%, over 4 steps) as a white solid. mp 82–86 °C.

For 38: TLC (hexanes–EtOAc = 4:1): Rᶠ = 0.47. ¹H NMR: δ 5.66-5.56 (m, 2 H), 4.57 (br s, 1 H), 4.14 (dd, J = 5, 13 Hz, 1 H), 3.88 (dd, J = 6, 13 Hz, 1 H), 3.82 (t, J = 8.5 Hz, 1 H), 3.47-3.43 (m, 1 H), 3.36 (t, J = 6.5 Hz, 2 H), 2.16 (quartet, J = 6.5 Hz, 2 H), 1.90 (quintet, J = 7 Hz, 2 H), 1.81-1.76 (m, 1 H), 1.70-1.64 (m, 1H), 1.57-1.46 (m, 4 H). ¹³C[¹H] NMR: δ 131.7, 127.6, 97.7, 67.4, 62.0, 32.9, 31.7, 30.5, 30.4, 25.3, 19.4. HRMS calcd (found) for C₁₁H₁₉BrNaO₂ (MNa⁺): 285.0461 (285.0461).

For 8: TLC (hexanes–EtOAc = 1:1): Rᶠ = 0.20. ¹H NMR (55 °C): δ 7.76 (d, J = 7.5 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.39 (t, J = 8 Hz, 2 H), 7.31 (t, J = 8 Hz, 2 H), 5.70-5.63 (m, 2 H), 4.74 (br s, 1 H), 4.43 (d, J = 6.5 Hz, 2 H), 4.22 (t, J = 7 Hz, 1 H), 4.07 (br s, 2 H), 3.18 (br s, 2 H), 2.07 (br s, 2 H), 1.59 (br s, 2 H), 1.50 (br s, 1 H). ¹³C[¹H] NMR: δ 156.4, 143.9, 141.2, 131.6, 129.9, 127.6, 126.9, 124.9, 119.9, 66.4, 63.4, 47.2, 40.3, 29.2, 29.1. IR (neat, cm⁻¹): 3323, 2940, 1686, 1529, 1444, 1360, 1260, 1225, 1135, 1084, 1002, 967, 756, 736. Anal. calcd (found) for C₂₁H₂₃NO₅: H, 6.87 (6.94); C, 74.75 (74.65).

(E)-9H-fluoren-9-ylmethyl (6-hydroxy-2-phenylhex-4-en-1-yl)carbamate (10). Compound 10 was synthesized as a white solid in 68% yield from (E)-2-phenyl-6-(tetrahydro-2H-pyran-2-yloxy)hex-4-enenitrile (36)¹⁰²c (E/Z ≥ 25:1) employing a
procedure similar to that used to synthesize \((E)-1g\) (Scheme 4.8). mp 95 - 98 °C. TLC (hexanes–EtOAc = 1:1): \(R_f = 0.24\). \(^1\)H NMR (55 °C): \(\delta \) 7.76 (d, \(J = 8\) Hz, 2 H), 7.54 (d, \(J = 6\) Hz, 2 H), 7.39 (t, \(J = 7.5\) Hz, 2 H), 7.34-7.28 (m, 5 H), 7.15 (br s, 2 H), 5.66-5.59 (m, 2 H), 4.60 (br s, 1 H), 4.40 (br s, 2 H), 4.19 (t, \(J = 6\) Hz, 1 H), 4.01 (br s, 2 H), 3.58 (br s, 1 H), 3.26 (br s, 1 H), 2.86 (br s, 1 H), 2.39 (br s, 2 H), 1.30 (br s, 1 H).

\(^{13}\)C\Tag{\(^1\)H} NMR: \(\delta 156.3, 143.9, 141.9, 141.3, 131.4, 129.8, 128.7, 127.8, 127.6, 126.9, 126.8, 124.9, 119.9, 66.5, 63.4, 47.2, 45.9, 45.8, 36.3. IR (neat, cm\(^{-1}\)): 3337, 3026, 2922, 1697, 1525, 1448, 1360, 1245, 1222, 1141, 1084, 998, 969, 758, 739, 700. Anal. calcd (found) for \(C_{27}H_{27}NO_3\): H, 6.58 (6.58); C, 78.42 (78.39).

\((E)-9\)H-fluoren-9-ylmethyl (6-hydroxy-2-isopropylhex-4-en-1-yl)carbamate (12).

Compound 12 was synthesized as a white solid in 76% yield from \((E)-2\)-isopropyl-6-(tetrahydro-2H-pyran-2-yloxy)hex-4-enenitrile (37) employing a procedure similar to that used to synthesize \((E)-1g\) (Scheme 4.8). Compound 37 was synthesized from isovaleronitrile and \((E)-4\)-bromo-1-(2-tetrahydropyran-2-yloxy)-2-butene as a yellow oil in 77% yield employing a procedure similar to that used to synthesize 32 (Scheme 4.8).

For 37: TLC (hexanes–EtOAc = 4:1): \(R_f = 0.26\). \(^E/Z\geq 25:1\). \(^1\)H NMR: \(\delta 5.77-5.68\) (m, 2 H), 4.62 (dd, \(J = 4.5, 7.5\) Hz, 1 H), 4.21 (td, \(J = 6\), 12 Hz, 1 H), 3.96 (td, \(J = 5.5, 12\) Hz, 1 H), 3.88-3.83 (m, 1 H), 3.51-3.47 (m, 1 H), 2.48-2.44 (m, 1 H), 2.40-2.28 (m, 2 H), 1.91-1.80 (m, 2 H), 1.74-1.67 (m, 1 H), 1.60-1.50 (m, 4H), 1.05 (d, \(J = 7\) Hz, 6 H). \(^{13}\)C\Tag{\(^1\)H} NMR (1:1 ratio of diastereomers): \(\delta 130.4, [128.3, 128.1, 1:1], 120.6, [98.0, 97.9, 1:1], 67.1, [62.3, 62.2, 1:1], [39.2, 39.1, 1:1], [32.9, 32.8, 1:1], 30.6, [29.5, 29.4, 1:1], 25.4, 20.9, [19.5, 19.4, 1:1], 18.5. HRMS calcd (found) for \(C_{14}H_{25}NO_2\) (MH\(^+\)): 238.1802 (238.1803).

For 12: mp 48 - 52 °C. TLC (hexanes–EtOAc = 1:1): \(R_f = 0.34\). \(^1\)H NMR (60 °C): \(\delta 7.75 (d, J = 7.5\) Hz, 2 H), 7.60 (d, \(J = 7.5\) Hz, 2 H), 7.38 (t, \(J = 7.5\) Hz, 2 H), 7.30 (t, \(J = 7.5\) Hz, 2 H), 5.65 (br s, 2 H), 4.87 (br s, 1 H), 4.44 (br s, 2 H), 4.21 (t, \(J = 6.5\) Hz, 1 H), 4.05 (br s, 2 H), 3.17 (br s, 1 H), 3.13 (br s, 1 H), 2.13 (br s, 2 H), 1.94 (br s, 1 H), 1.71 (br s, 1 H), 1.71 (br s, 1 H), 1.71 (br s, 1 H).
1.43 (br s, 1 H), 0.90 (br s, 6 H). $^{13}$C($^1$H) NMR: δ 156.4, 143.8, 141.1, 130.9, 130.8, 127.5, 126.8, 124.8, 119.8, 66.3, 63.1, 47.1, 44.2, 41.8, 31.5, 28.2, 19.5, 18.8. IR (neat, cm$^{-1}$): 3338, 2949, 2871, 1689, 1535, 1447, 1260, 1148, 1019, 968, 732. Anal. calcd (found) for C$_{23}$H$_{29}$NO$_3$: H, 7.70 (7.63); C, 75.96 (75.92).

**rac-(E)-9H-fluoren-9-ylmethyl (1-(4-hydroxypent-2-en-1-ylcyclohexyl)methyl) carbamate (rac-28).** $n$-BuLi (2.5 M solution in hexanes, 8.3 mL, 20.8 mmol) was added dropwise to a stirred solution of (but-3-yn-2-yl)oxy)-tert-butyldimethylsilane (2.8 g, 15.4 mmol) in THF (30 mL) at –78 ºC (Scheme 4.10). The resulting solution was stirred at –78 ºC for 0.5 h, and paraformaldehyde (0.93 g, 30.8 mmol) was added slowly to the reaction. The reaction mixture was gradually warmed to 25°C over 2 h, treated with aqueous NH$_4$Cl (6.9 M) and extracted with ether (3 × 30 mL). The combined organic extracts were dried (MgSO$_4$), concentrated, and chromatographed (hexanes–EtOAc = 9:1) to give 4-((tert-butyldimethylsilyl)oxy)pent-2-yn-1-ol (39) as a colorless oil (3.04 g, 92%).

A solution of 39 (3.0 g, 14.1 mmol) in THF (40 mL) was added to a stirred suspension of LiAlH$_4$ (0.43 g, 11.5 mmol) in THF (40 mL) at 0 ºC and the resulting suspension was warmed to 25°C over 3 h. The reaction mixture was cooled to 0 ºC and treated sequentially with water (1 mL), aqueous NaCl (2 N, 1 mL) and water (1 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in CH$_2$Cl$_2$ (60 mL), cooled to 0 ºC and treated with triphenylphosphine (3.9 g, 14.9 mmol) and carbotetra bromide (5.7 g, 17.2 mmol). The reaction mixture was stirred at 0 ºC for 20 min, treated with saturated NaHCO$_3$ (35 mL) and then extracted with CH$_2$Cl$_2$ (2 × 30 mL). The combined organic extracts were dried (MgSO$_4$), concentrated, and chromatographed (hexanes–EtOAc = 9:1) to give (E)-(5-bromopent-3-en-2-yloxy) tert-butyldimethylsilane (40) as a yellow oil (3.2 g, 83%, over 2 steps).
Cyclohexanecarbonitrile (0.9 mL, 7.6 mmol) was added to a solution of LDA [generated in situ from n-BuLi (2.5 M solution in hexanes, 3.2 mL, 8.1 mmol) and diisopropylamine (1.1 mL, 7.6 mmol) in THF (18 mL)] at –78 ºC (Scheme 4.10). The resulting solution was stirred for 1 h, treated with trans-(5-bromopent-3-en-2-yloxy) tert-butyldimethylsilane (3.2 g, 11.4 mmol), and then warmed to 25 ºC overnight with stirring. The resulting mixture was diluted with ether (2 mL), washed sequentially with water (20 mL) and brine (20 mL), dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 9:1) to give trans-1-(4-tert-butyldimethylsilyloxy)but-2-en-1-yl)cyclohexanecarbonitrile (43) as a pale yellow oil (2.25 g, 97%).

A solution of 43 (1 g, 3.25 mmol) in THF (30 mL) at 0 ºC was treated with TBAF (1 M solution in THF, 4.9 mL, 4.9 mmol). The resulting mixture was stirred at 25 ºC for 2
h, treated with water (15 mL), and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (MgSO₄), and concentrated. The resulting oily residue was dissolved in ether (12.5 mL) and added to a stirred suspension of LiAlH₄ (0.19 g, 4.9 mmol) in ether (12.5 mL) at 0 °C and the resulting suspension was warmed to 25°C and stirred for 3 h (Scheme 4.10). The reaction mixture was cooled to 0 °C and treated with water (0.8 mL) and the resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in THF (16 mL), cooled to 0 °C and treated with triethylamine (0.7 mL, 4.9 mmol) and Fmoc-Cl (1 g, 3.9 mmol). The reaction mixture was stirred at 0 °C for 3 h. The resulting mixture was treated with water (20 mL) and then extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried (MgSO₄), concentrated, and chromatographed (hexanes–EtOAc = 1:1) to give (E)-9H-fluoren-9-ylmethyl (1-(4-hydroxypent-2-en-1-yl)cyclohexyl)methylcarbamate (rac-28) as a colorless waxy solid (0.72 g, 53%, over 3 steps).

For 39: TLC (hexanes–EtOAc = 4:1): Rₜ = 0.33. ¹H NMR: δ 4.54-4.50 (m, 1 H), 4.24 (d, J = 5 Hz, 2 H), 2.53 (br s, 1 H), 1.38 (d, J = 6.5 Hz, 3 H), 0.87 (s, 9 H), 0.09 (d, ²J_{SiH} = 6 Hz, 6 H). ¹³C{¹H} NMR: δ 87.9, 81.4, 59.0, 50.8, 25.7, 25.2, 4.7, - 4.7, - 5.0. HRMS calcd (found) for C₁₁H₂₂NaO₂Si(MNa⁺): 237.1281 (237.1282).

For 40: TLC (hexanes–EtOAc = 4:1): Rₜ = 0.79. E/Z ≥ 25:1. ¹H NMR: δ 5.86-5.73 (m, 2 H), 4.34-4.29 (m, 1 H), 3.94 (d, J = 7.5 Hz, 2 H), 1.20 (d, J = 6 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H). ¹³C{¹H} NMR: δ 139.7, 124.5, 68.1, 32.5, 25.8, 25.7, 24.1, - 4.6, - 4.8. Anal. calcd (found) for C₁₁H₂₃BrOSi: H, 8.30 (8.28); C, 47.30 (47.27).

For 43: TLC (hexanes–EtOAc = 9:1): Rₜ = 0.56. ¹H NMR: δ 5.67-5.57 (m, 2 H), 4.31-4.27 (m, 1 H), 2.22 (dd, J = 3, 7 Hz, 2 H), 1.91 (t, J = 9.5, 2 H), 1.72-1.55 (m, 8 H), 1.20 (d, J = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.04 (d, ²J_{SiH} = 3 Hz, 6 H). ¹³C{¹H} NMR: δ 139.9, 123.2,
121.7, 68.8, 42.8, 39.0, 35.3, 35.2, 25.8, 25.3, 24.5, 22.9, 18.2, - 4.7, - 4.9. HRMS calcd (found) for C_{18}H_{35}NOSi (MH^+): 308.2404 (308.2406).

For rac-28: TLC (hexanes–EtOAc = 1:1): R_f = 0.41. ¹H NMR (1:0.14 ratio of rotamers): δ 7.77 (d, J = 7.5 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.32 (t, J = 7.5 Hz, 2 H), 5.74-5.60 (m, 1 H), 5.53 (dd, J = 6.5, 15 Hz, 1 H), [4.79 (t, J = 6 Hz), 4.56 (br s), 1:0.14, 1 H], [4.50 (br s), 4.43 (d, J = 7 Hz, 2 H), 0.14:1, 2 H], [4.34-4.30 (m), 4.29-4.20 (m), 0.14:1, 2 H], [3.12 (dd, J = 7, 14 Hz), 2.91 (br s), 1:0.14, 1 H], [3.05 (dd, J = 7, 14 Hz), 2.91 (br s), 1:0.14, 1 H], [2.24 (d, J = 6.5 Hz), 2.02-1.99 (m), 0.14:1, 2 H], 1.99-1.89 (m, 2 H), [1.73-1.56 (m), 1.46-1.12 (m), 0.14:1, 8 H], [1.28 (d, J = 6.5 Hz), 1.24 (d, J = 6.5 Hz), 0.14:1, 3 H]. ¹³C{¹H} NMR: δ 156.6, 143.9, 141.3, 139.5, 137.3, 127.6, 127.0, 126.1, 124.9, 123.3, 119.9, 68.6, 66.4, 47.3, 38.7, 37.1, 35.3, 33.5, 33.2, 26.1, 23.3, 22.9, 21.3. IR (neat, cm⁻¹): 3333, 3065, 2921, 2850, 1697, 1518, 1448, 1365, 1242, 1132, 1057, 971, 757, 737. Anal. calcd (found) for C_{27}H_{33}NO_3: H, 7.93 (7.86); C, 77.29 (77.21).

(R)-28 (97% ee) was synthesized from (R)-3-butyn-2-ol (98% ee) in 49% yield employing a procedure analogous to that used to synthesize rac-28. HPLC (hexanes-isopropanol = 88:12, 1 mL/min, 25 °C): t_R (R) = 16.79 min, t_R (S) = 18.34 min (Figure 4.2).
Figure 4.2 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched (E)-9H-fluoren-9-ylmethyl (1-(4-hydroxypent-2-en-1-yl)cyclohexyl)methylcarbamate 28 (right trace). HPLC conditions: hexanes-isopropanol = 88:12, 1 mL/min.

(E)-9H-Fluoren-9-ylmethyl (6-hydroxy-2-isopropyl-6-methylhept-4-en-1-yl)carbamate (14). Compound 14 was synthesized as a pale yellow oil in 49% yield from (E)-6-(tert-butylidimethylsilyloxy)-2-isopropyl-6-methylhept-4-enenitrile (44) employing a procedure similar to that used to synthesize rac-28 (Scheme 4.10). Compound 44 was synthesized as a yellow oil in 61% yield from isovaleronitrile and (E)-(5-bromo-2-methylpent-3-en-2-yloxy) tert-butylidimethylsilane (42) employing a procedure similar to that used to synthesize 43. Compound 42 was synthesized as a colorless oil in 95% yield from 4-(tert-butylidimethylsilyloxy)-4-methylpent-2-yn-1-ol (41) employing a procedure similar to that used to synthesize 40 (Scheme 4.10). Compound 41 was synthesized as a pale yellow oil in 89% yield from (but-3-yn-2-yloxy)tert-butylidimethylsilane employing a procedure similar to that used to synthesize 39.
For 41: TLC (hexanes–EtOAc = 4:1): \( R_f = 0.28 \). \( ^1H \) NMR: \( \delta \) 4.25 (d, \( J = 5.5 \) Hz, 2 H), 2.22 (br s, 1 H), 1.44 (s, 6 H), 0.84 (s, 9 H), 0.14 (s, 6 H). \( ^{13}C\{^1H\} \) NMR: \( \delta \) 91.0, 80.5, 66.2, 50.9, 32.8, 25.6, 17.8, –2.9, –3.0. HRMS calcd (found) for C\(_{12}\)H\(_{24}\)LiOSi (MLi\(^+\)): 235.1699 (235.1704).

For 42: TLC (hexanes): \( R_f = 0.32 \). \( E/Z \geq 25:1 \). \( ^1H \) NMR: \( \delta \) 6.25–6.23 (m, 2 H), 4.38–4.37 (m, 2 H), 1.72 (s, 6 H), 1.30 (s, 9 H), 0.50 (s, 6 H). \( ^{13}C\{^1H\} \) NMR: \( \delta \) 143.9, 122.5, 72.5, 32.9, 30.2, 25.8, 25.7, –2.0. ESI-MS calcd (found) for C\(_{12}\)H\(_{25}\)BrNaOSi (MNa\(^+\)): 315.1 (315.1).

For 44: TLC (hexanes–EtOAc = 9:1): \( R_f = 0.43 \). \( ^1H \) NMR: \( \delta \) 5.68 (d, \( J = 15.5 \) Hz, 1 H), 5.61–5.53 (m, 1 H), 2.42 (td, \( J = 5.5, 8.5 \) Hz, 1 H), 2.36–2.29 (m, 1 H), 2.28–2.19 (m, 1 H), 1.84 (septet, \( J = 6.5 \) Hz, 1 H), 1.27 (s, 6 H), 1.05 (d, \( J = 6.5 \) Hz, 6 H), 0.86 (s, 9 H), 0.05 (s, 6 H). \( ^{13}C\{^1H\} \) NMR: \( \delta \) 142.9, 121.0, 119.3, 72.7, 39.4, 32.7, 30.5, 30.3, 29.4, 25.8, 20.9, 18.4, 18.0, –2.1. HRMS calcd (found) for C\(_{17}\)H\(_{33}\)NNaOSi (MNa\(^+\)): 318.2224 (318.2227).

For 14: TLC (hexanes–EtOAc = 1:1): \( R_f = 0.42 \). \( ^1H \) NMR (55 \(^\circ\) C): \( \delta \) 7.76 (d, \( J = 7.5 \) Hz, 1 H), 7.60 (d, \( J = 7.5 \) Hz, 2 H), 7.39 (t, \( J = 7.5 \) Hz, 2 H), 7.31 (t, \( J = 7.5 \) Hz, 2 H), 5.67–5.58 (m, 2 H), 4.67 (br s, 1 H), 4.43 (br s, 2 H), 4.22 (t, \( J = 6.5 \) Hz, 2 H), 3.21 (br s, 1 H), 3.12 (br s, 1 H), 2.12 (br s, 1 H), 1.98–1.91 (m, 1 H), 1.78–1.69 (m, 1 H), 1.50 (br s, 1 H), 1.43 (br s, 1 H), 1.31 (s, 6 H), 0.92 (d, \( J = 5 \) Hz, 6 H). \( ^{13}C\{^1H\} \) NMR: \( \delta \) 156.3, 143.9, 141.3, 139.7, 127.6, 125.7, 125.6, 124.9, 119.9, 70.4, 66.4, 47.3, 44.6, 42.1, 31.9, 29.8, 29.6, 28.6, 19.6, 19.1. IR (neat, cm\(^{-1}\)): 3328, 2919, 1692, 1543, 1521, 1448, 1239, 1135, 970, 757, 737, 620. Anal. calcd (found) for C\(_{26}\)H\(_{33}\)NO\(_3\): H, 8.16 (8.12); C, 76.62 (76.66).

\((E)-9H\)-fluoren-9-ylmethyl \((1-(5-hydroxypent-3-en-1-yl)cyclohexyl)methyl) carbamate (16). Compound 16 was synthesized as a colorless oil in 59% yield from \((E)-1-(5-(tetrahydro-2H-pyran-2-yloxy)pent-3-en-1-yl)cyclohexanecarbonitrile\) (45) employing a procedure similar to that used to synthesize rac-28 (Scheme 4.11).
Compound 45 was synthesized as a yellow oil in 67% yield from reaction of cyclohexanecarbonitrile and \((E)-2-(5\text{-bromopent-2-en-1-yloxy})\text{tetrahydro-2H-pyran}\) employing a procedure similar to that used to synthesize 35. \((E)-2-(5\text{-Bromopent-2-en-1-yloxy})\text{tetrahydro-2H-pyran} (E/Z \geq 25:1)\) was synthesized as a tan oil in 99% yield employing a procedure similar to that used to synthesize 38 (Scheme 4.11).

For 2-(5-Bromopent-2-en-1-yloxy)tetrahydro-2H-pyran: TLC (hexanes–EtOAc = 4:1): \(R_f = 0.49\). \(^1\text{H} \text{NMR: } \delta 5.66-5.63 \text{ (m, 2 H), 4.61-4.58} \text{ (m, 1 H), 4.15 (dd, } J = 3, 11.5 \text{ Hz, 1 H), 3.91 (dd, } J = 4, 11.5 \text{ Hz, 1 H), 3.85-3.79} \text{ (m, 1 H), 3.47-3.43} \text{ (m, 1 H), 3.35 (t, } J = 7.5 \text{ Hz, 2 H), 2.61-2.54} \text{ (m, 2 H), 1.80-1.73} \text{ (m, 1 H), 1.69-1.64} \text{ (m, 1 H), 1.55-1.46} \text{ (m, 4 H). } \(^{13}\text{C}\{^1\text{H}\} \text{NMR: } \delta 129.9, 129.2, 97.7, 67.1, 62.1, 35.4, 31.9, 30.4, 25.2, 19.3. \text{ HRMS calcd (found) for } \text{C}_{10}\text{H}_{17}\text{BrNaO}_2 \text{(MNa}^+) = 271.0304 \text{(271.0305).}

For 45: TLC (hexanes–EtOAc = 4:1): \(R_f = 0.48\). \(^1\text{H} \text{NMR: } \delta 5.63 \text{ (td, } J = 6.5, 15.5 \text{ Hz, 1 H), 5.55 (td, } J = 5.5, 15.5 \text{ Hz, 1 H), 4.53 (br s, 1 H), 4.10 (dd, } J = 5.5, 12.5 \text{ Hz, 1 H), 3.83 (dd, } J = 7.5, 12.5 \text{ Hz, 1 H), 3.79-3.75} \text{ (m, 1 H), 3.43-3.39} \text{ (m, 1 H), 2.20-2.15} \text{ (m, 2 H), 1.88 (d, } J = 13 \text{ Hz, 2 H), 1.77-1.70} \text{ (m, 1 H), 1.65-1.42} \text{ (m, 12 H), 1.17-1.08} \text{ (m, 3 H). } \(^{13}\text{C}\{^1\text{H}\)

HRMS calcd (found) for C\textsubscript{17}H\textsubscript{28}NO\textsubscript{2} (MH\textsuperscript{+}): 278.2115 (278.2113).

**For 16:** TLC (hexanes–EtOAc = 1:1): \( R_f = 0.37 \). \(^1\)H NMR (60 ºC): δ 7.75 (d, \( J = 7.5 \) Hz, 2 H), 7.60 (d, \( J = 7.5 \) Hz, 2 H), 7.38 (t, \( J = 7.5 \) Hz, 2 H), 7.30 (t, \( J = 7.5 \) Hz, 2 H), 5.68-5.61 (m, 2 H), 4.76 (br s, 1 H), 4.45 (d, \( J = 4.5 \) Hz, 2 H), 4.22 (d, \( J = 7 \) Hz, 1 H), 4.04 (d, \( J = 4.5 \) Hz, 2 H), 3.11 (br s, 2 H), 1.99 (br s, 2 H), 1.73 (br s, 1 H), 1.45-1.27 (m, 12 H). \(^{13}\)C\(^{1}\)H NMR: δ 156.6, 143.8, 141.1, 133.1, 128.8, 127.5, 126.9, 124.8, 119.8, 66.3, 63.4, 47.2, 47.1, 36.1, 34.4, 33.1, 26.0, 25.6, 21.2. IR (neat, cm\(^{-1}\)): 3323, 3064, 2920, 2848, 1696, 1522, 1447, 1335, 1240, 1146, 993, 967, 756, 737, 661. Anal. calcd (found) for C\textsubscript{27}H\textsubscript{33}NO\textsubscript{3}: H, 7.93 (7.91); C, 77.29 (77.20).

\( ^{(E)}\)-9\(^H\)-fluoren-9-ylmethyl 2-(4-hydroxybut-2-en-1-yloxy)ethylcarbamate (18).

A suspension of NaH (0.13 g, 3.3 mmol) in THF (4 mL) was added dropwise to a solution of ethanolamine (0.2 mL, 3.3 mmol) in THF (3 mL) at 0 ºC, and the resulting suspension was gradually heated to reflux for 1 h and then cooled to –78 ºC (Scheme 4.12). A solution of \( trans\)-4-bromo-1-(2-tetrahydropyranloxy)-2-butene \((E/Z \geq 25:1)\) (0.78 g, 3.3 mmol) in THF (2 mL) was added dropwise to the reaction mixture and the resulting suspension was warmed to room temperature overnight. The reaction mixture was treated with water (5 mL) and extracted with ether (3 × 10 mL). The combined ether extracts were dried (MgSO\textsubscript{4}), concentrated, and chromatographed (CH\textsubscript{2}Cl\textsubscript{2}–MeOH = 9:1) to give \( ^{(E)}\)-2-(4-tetrahydro-2\(^H\)-pyran-2-yloxybut-2-en-1-yloxy)ethanamine (46) as a yellow oil (0.45 g, 63%, \( E/Z \geq 25:1 \)).
Scheme 4. 12

(E)-9H-fluoren-9-ylmethyl 2-(4-hydroxybut-2-en-1-yloxy)ethylcarbamate (18) was synthesized as a white solid in 64% yield in 2 steps from 46 employing a procedure similar to that used to synthesize 6 (Scheme 4.12).

For 46: TLC (CH$_2$Cl$_2$-MeOH = 9:1): $R_f = 0.08$. $^1$H NMR: $\delta$ 5.83-5.80 (m, 2 H), 4.62 (t, $J = 3.5$ Hz, 1 H), 4.24 (dd, $J = 3.5$, 11.5 Hz, 1 H), 3.99 (br s, 2 H), 3.96 (dd, $J = 3$, 11.5 Hz, 1 H), 3.87-3.82 (m, 1 H), 3.51-3.47 (m, 1 H), 3.46 (t, $J = 5.5$ Hz, 2 H), 2.85 (br s, 2 H), 1.96 (br s, 2 H), 1.84-1.77 (m, 1 H), 1.71 (tt, $J = 3$, 13 Hz, 1 H), 1.61-1.49 (m, 4 H). $^{13}$C($^1$H) NMR: $\delta$ 129.5, 128.7, 97.9, 70.8, 70.3, 66.8, 62.1, 41.0, 30.4, 25.3, 12.3. HRMS calcd (found) for C$_{11}$H$_{22}$NO$_3$ (MH$^+$): 216.1594 (216.1595).

For 18: mp 68 - 72 °C. TLC (EtOAc): $R_f = 0.48$. $^1$H NMR (60 ºC): $\delta$ 7.75 (d, $J = 7.5$ Hz, 2 H), 7.59 (d, $J = 7.5$ Hz, 2 H), 7.38 (t, $J = 8$ Hz, 2 H), 7.30 (t, $J = 7.5$ Hz, 2 H), 5.87 (td, $J = 5$, 15.5 Hz, 1 H), 5.77 (td, $J = 5.5$, 15.5 Hz, 1 H), 5.19 (br s, 1 H), 4.43 (d, $J = 7$ Hz, 2 H), 4.22 (t, $J = 7$ Hz, 1 H), 4.13 (br s, 2 H), 3.97 (d, $J = 5.5$ Hz, 2 H), 3.48 (br s, 2 H), 3.36 (br s, 2 H), 1.96 (br s, 1 H). $^{13}$C($^1$H) NMR: $\delta$ 156.4, 143.8, 141.1, 132.6, 127.5, 126.9, 124.9, 119.8, 70.8, 68.8, 66.5, 62.4, 47.0, 40.8. IR (neat, cm$^{-1}$): 3321, 3064, 2859, 1697, 1529, 1448, 1356, 1247, 1094, 1004, 758, 739. Anal. calcd (found) for C$_{21}$H$_{33}$NO$_4$: H, 6.56 (6.54); C, 71.37 (71.35).
(E)-9H-fluoren-9-ylmethyl (1-(4-hydroxybut-2-en-1-yloxy)methyl)cyclopentyl carbamate (20). Compound 20 was synthesized as a white sticky solid in 72% yield from (E)-1-(4-tetrahydro-2H-pyran-2-yloxybut-2-en-1-yloxy)methyl)cyclopentanamine (47) employing a procedure similar to that used to synthesize 18 (Scheme 4.12). Compound 47 was synthesized from (1-aminocyclopentyl)methanol and trans-4-bromo-1-(2-tetrahydropyranyloxy)-2-butene as a yellow oil in 61% yield employing a procedure similar to that used to synthesize 46 (Scheme 4.12).

For 47: TLC (CH₂Cl₂–MeOH = 9:1): R_f = 0.10. ¹H NMR: δ 5.70-5.69 (m, 2 H), 4.51 (t, J = 3.5 Hz, 1 H), 4.12 (dd, J = 3, 11 Hz, 1 H), 3.89 (br s, 2 H), 3.85 (dd, J = 3, 11.5 Hz, 1 H), 3.73 (dt, J = 3.5, 11.5 Hz, 1 H), 3.39-3.35 (m, 1 H), 3.15 (s, 2 H), 1.72-1.28 (m, 16 H). ¹³C{¹H} NMR: δ 129.1, 128.6, 97.6, 78.6, 71.0, 66.7, 61.8, 61.2, 37.6, 30.3, 25.1, 24.1, 19.1.

For 20: TLC (hexanes–EtOAc = 1:1): R_f = 0.39. ¹H NMR (400 MHz): δ 7.76 (d, J = 7.2 Hz, 2 H), 7.60 (d, J = 7.2 Hz, 2 H), 7.40 (t, J = 7.2 Hz, 2 H), 7.31 (t, J = 7.2 Hz, 2 H), 5.88-5.81 (m, 1 H), 5.79-5.68 (m, 1 H), 4.97 (br s, 1 H), 4.34 (br s, 2 H), 4.22 (t, J = 6.4 Hz, 1 H), 4.11 (br s, 2 H), 3.99 (br s, 2 H), 3.51 (br s, 2 H), 1.91 (br s, 2 H), 1.75 (br s, 4 H), 1.61 (br s, 3 H).

(E)-tert-Butyl (2-(9H-fluoren-9-ylmethoxycarbonylaminoethyl)-4-hydroxybut-2-en-1-yl)carbamate (22). A suspension of NaH (0.35 g, 8.7 mmol) in THF (14 mL) was added dropwise to solution of N-Boc-ethylenediamine (1.4 g, 8.7 mmol) in THF (8 mL) at 0 °C, and the resulting suspension was warmed to 25 °C over 1 h and then cooled to –78 °C (Scheme 4.13). A solution of trans-4-bromo-1-(2-tetrahydropyranyloxy)-2-butene (E/Z ≥ 25:1) (2.5 g, 10.5 mmol) in THF (6 mL) was added dropwise to the reaction mixture and the resulting suspension was warmed to 25°C overnight. The reaction mixture was treated with water (10 mL) and extracted with ether (3 × 15 mL). The combined ether
extracts were dried (MgSO₄), concentrated, and chromatographed (CH₂Cl₂–MeOH = 9:1) to give (E)-tert-butyl (2-aminoethyl)(4-tetrahydro-2H-pyran-2-yloxybut-2-en-1-yl)carbamate (48) (dark yellow oil, 0.85 g, 31%, E/Z ≥ 25:1), and (E)-tert-butyl 2-(4-tetrahydro-2H-pyran-2-yloxybut-2-en-1-ylamino)ethyl carbamate (49) (pale yellow oil, 0.77 g, 28%, E/Z ≥ 25:1). Compound 22 was synthesized as a colorless waxy solid in 62% yield from 48 employing a procedure similar to that used to synthesize rac-6 (Scheme 4.13).

Scheme 4.13

For 48: TLC (CH₂Cl₂–MeOH = 9:1): Rₗ = 0.08. ¹H NMR: δ 5.72–5.63 (m, 2 H), 4.61 (t, J = 3.5 Hz, 1 H), 4.37 (br s, 2 H), 4.20 (dd, J = 4, 12 Hz, 1 H), 3.95 (dd, J = 5, 12 Hz, 1 H), 3.86–3.81 (m, 3 H), 3.52–3.46 (m, 1 H), 3.36–3.30 (m, 2 H), 3.03–2.87 (m, 2 H), 1.83–1.76 (m, 1 H), 1.73–1.68 (m, 1 H), 1.58–1.48 (m, 4 H), 1.43 (s, 9 H). ¹³C[¹H] NMR: δ 156.5, 129.2, 127.9, 97.9, 80.4, 66.8, 62.2, 49.7, 47.6, 40.2, 30.5, 28.4, 25.3, 19.4. HRMS calcd (found) for C₁₆H₃₃N₂O₄ (MH⁺): 315.2278 (315.2279).

For 22: TLC (hexanes–EtOAc = 1:2.5): Rₗ = 0.27. ¹H NMR (60 ºC): δ 7.74 (d, J = 7.5 Hz, 2 H), 7.58 (d, J = 7 Hz, 2 H), 7.37 (t, J = 7.5 Hz, 2 H), 7.28 (t, J = 7.5 Hz, 2 H), 5.76–5.72 (m, 1 H), 5.65 (td, J = 5.5, 15.5 Hz, 2 H), 5.30 (br s, 1 H), 4.41 (br s, 2 H), 4.19 (t, J = 6 Hz, 1 H), 4.08 (d, J = 4.5 Hz, 2 H), 3.81 (br s, 2 H), 3.31 (br s, 4 H), 2.26 (br s, 1 H), 1.46 (s, 9
H. $^{13}$C[$^1$H] NMR (60 ºC, 1:1 mixture of rotamers): δ 156.5, 155.8, 144.0, 141.3, 132.4, 127.6, 127.1, 127.0, 126.9, 124.9, 119.8, 80.1, 66.7, 62.6, 49.3, 47.4, 40.3, [28.4, 28.3]. IR (neat, cm$^{-1}$): 3334, 2971, 2855, 1677, 1521, 1477, 1411, 1365, 1208, 1165, 972, 887, 735. Anal. calcd (found) for C$_{26}$H$_{32}$N$_2$O$_5$: H, 7.13 (7.22); C, 69.01 (69.10).

(E)-9H-fluoren-9-ylmethyl 2-(N-(4-hydroxybut-2-en-1-yl)-4-methylphenylsulfonamidoethyl)carbamate (24). Compound 24 was synthesized as a white solid in 68% yield from (E)-N-cyanomethyl-4-methyl-N-(4-tetrahydro-2H-pyran-2-ylxybut-2-en-1-yl)benzenesulfonamide (50) employing a procedure similar to that used to synthesize (E)-1g (Scheme 4.14). Compound 50 was synthesized as a dark yellow oil in 95% yield from N-(cyanomethyl)-4-methylbenzenesulfonamide and trans-4-bromo-1-(2-tetrahydropranyloxy)-2-butene (E/Z ≥ 25:1) employing a procedure similar to that used to synthesize 46.

Scheme 4.14

For 50: TLC (CH$_2$Cl$_2$–MeOH = 9:1): $R_f$ = 0.42. $^1$H NMR: δ 7.71 (d, $J$ = 8.5 Hz, 2 H), 7.35 (d, $J$ = 8.5 Hz, 2 H), 5.87 (td, $J$ = 5, 15.5 Hz, 1 H), 5.66-5.58 (m, 1 H), 4.58 (t, $J$ = 4 Hz, 1 H), 4.20 (dd, $J$ = 4, 14.5 Hz, 1 H), 4.19 (s, 2 H), 3.98 (dd, $J$ = 5.5, 14.5 Hz, 1 H), 3.83-3.76 (m, 3 H), 3.50-3.45 (m, 1 H), 2.42 (s, 3 H), 1.84-1.76 (m, 1 H), 1.69 (tt, $J$ = 3, 12.5 Hz, 1 H), 1.59-1.48 (m, 4 H). $^{13}$C[$^1$H] NMR: δ 144.7, 134.3, 134.2, 130.1, 127.6, 123.9, 113.5, 98.3,
66.4, 62.3, 49.2, 34.5, 30.5, 25.4, 21.6, 19.4. Anal. calcd (found) for C₁₈H₂₄N₂O₄S: H, 6.64 (6.59); C, 59.32 (59.44).

For 24: mp 92 - 96 °C. TLC (hexanes–EtOAc = 1:2.5): R_f = 0.23. ¹H NMR (55 °C): δ 7.76 (d, J = 7.5 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 7.59 (d, J = 7.5 Hz, 2 H), 7.38 (t, J = 7.5 Hz, 2 H), 7.32-7.29 (m, 4 H), 5.77 (br s, 1 H), 5.62-5.58 (m, 1 H), 5.16 (br s, 1 H), 4.40 (br s, 2 H), 4.21 (t, J = 7 Hz, 1 H), 4.04 (d, J = 4.5 Hz, 2 H), 3.76 (br s, 2 H), 3.38 (br s, 2 H), 3.18 (br s, 2 H), 2.43 (s, 3 H), 2.16 (br s, 1 H). ¹³C{¹H} NMR: δ 156.7, 143.8, 143.7, 141.3, 135.6, 135.3, 129.8, 127.7, 127.2, 127.1, 126.2, 125.1, 119.9, 67.0, 62.7, 51.6, 47.1, 46.6, 40.4, 21.5. IR (neat, cm⁻¹): 3362, 2948, 1692, 1522, 1446, 1335, 1259, 1139, 974, 758, 731, 654. Anal. calcd (found) for C₂₈H₃₀N₂O₅S: H, 5.97 (5.97); C, 66.38 (66.42).

For 26: TLC (hexanes–EtOAc = 1:2.5): R_f = 0.23. ¹H NMR (55 °C): δ 7.76 (d, J = 7.5 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 7.59 (d, J = 7.5 Hz, 2 H), 7.38 (t, J = 7.5 Hz, 2 H), 7.32-7.29 (m, 4 H), 5.77 (br s, 1 H), 5.62-5.58 (m, 1 H), 5.16 (br s, 1 H), 4.40 (br s, 2 H), 4.21 (t, J = 7 Hz, 1 H), 4.04 (d, J = 4.5 Hz, 2 H), 3.76 (br s, 2 H), 3.38 (br s, 2 H), 3.18 (br s, 2 H), 2.43 (s, 3 H), 2.16 (br s, 1 H). ¹³C{¹H} NMR: δ 156.7, 143.8, 143.7, 141.3, 135.6, 135.3, 129.8, 127.7, 127.2, 127.1, 126.2, 125.1, 119.9, 67.0, 62.7, 51.6, 47.1, 46.6, 40.4, 21.5. IR (neat, cm⁻¹): 3362, 2948, 1692, 1522, 1446, 1335, 1259, 1139, 974, 758, 731, 654. Anal. calcd (found) for C₂₈H₃₀N₂O₅S: H, 5.97 (5.97); C, 66.38 (66.42).

(E)-9H-fluoren-9-ylmethyl (2-(tert-butoxycarbonylaminoethyl)-4-hydroxybut-2-en-1-yl)carbamate (26). Compound 26 was synthesized as a colorless waxy solid in 80% yield from 49 employing a procedure similar to that used to synthesize rac-28 (Scheme 4.13).

For 26: TLC (hexanes–EtOAc = 1:2.5): R_f = 0.30. ¹H NMR (60 °C): δ 7.76 (d, J = 8 Hz, 2 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.32 (t, J = 7.5 Hz, 2 H), 5.67 (br s, 1 H), 5.54 (br s, 1 H), 4.57 (br s, 3 H), 4.23 (t, J = 5.5 Hz, 1 H), 4.07 (br s, 2 H), 3.77 (br s, 2 H), 3.22 (br s, 4 H), 1.99 (br s, 1 H), 1.43 (s, 9 H). ¹³C{¹H} NMR (60 °C): δ 156.0, 144.2,
141.5, 132.8, 127.7, 127.2, 126.9, 124.8, 119.9, 79.6, 66.9, 62.8, 49.6, 47.7, 46.8, 39.4, 28.4. IR (neat, cm⁻¹): 3411, 2924, 1701, 1519, 1420, 1361, 1221, 1167, 1091, 972, 760, 741. Anal. calcd (found) for C₂₆H₃₂N₂O₅: H, 7.13 (7.16); C, 69.01 (69.03).

4.3.3 Synthesis of nitrogen heterocycles

1-(N-Benzylamino)-4,4-diphenyl-2-vinylpyrrolidine (3a).¹⁰²c A suspension of [(S)-2](AuCl)₂ (8.1 mg, 5.0 × 10⁻³ mmol), AgSbF₆ (3.4 mg, 1.0 × 10⁻² mmol) and (E)-1a (71 mg, 0.20 mmol) in dioxane (0.34 mL) in a sealed tube was stirred at 25 °C for 5 h. The resulting suspension was filtered through a silica plug with EtOAc, concentrated and conversion observed by ¹H NMR. HPLC (hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C): tᵣ(major) = 12.2 min, tᵣ(minor) = 12.9 min (Figure 4.3), 29% ee. TLC (hexanes–EtOAc = 1:1): Rₗ = 0.86. ¹H NMR (400 MHz): δ 7.27-7.01 (m, 15 H), 5.76-5.767 (m, 1 H), 5.11 (d, J = 17.2 Hz, 1 H), 5.01 (d, J = 10 Hz, 1 H), 4.01 (d, J = 13.2 Hz, 1 H), 3.56 (d, J = 9.6 Hz, 1 H), 3.16-3.10 (m, 2 H), 2.83 (dd, J = 7.6, 13.2 Hz, 1 H), 2.75 (d, J = 10 Hz, 1 H), 2.32 (dd, J = 8, 13.2 Hz, 1 H). ¹³C[¹H] NMR (100 MHz): δ 150.2, 148.4, 140.6, 139.9, 128.5, 128.2, 127.8, 127.4, 127.2, 126.7, 125.8, 125.5, 116.5, 68.0, 65.5, 57.6, 53.0, 46.5.
Figure 4.3 Chiral HPLC traces of racemic 3a (left trace) and enantiomerically enriched 3a (right trace). HPLC conditions: hexanes–isopropanol = 99.6:0.4, 0.4 mL/min, 25 °C.

Benzyl 4,4-diphenyl-2-vinylpyrrolidine-1-carboxylate [(S)-3b]. A suspension of [(S)-2](AuCl)₂ (8.1 mg, 5.0 × 10⁻³ mmol), AgClO₄ (2.1 mg, 1.0 × 10⁻² mmol) and (E)-1b (80 mg, 0.20 mmol) in dioxane (0.34 mL) in a sealed tube was stirred at 25 °C for 48 h. The resulting suspension was concentrated under vacuum and the residue was chromatographed (hexanes–EtOAc = 20:1 → 9:1) to give (S)-3b (76 mg, 99% yield, 79% ee) as a white waxy solid. HPLC (hexanes–isopropanol = 90:10, 0.5 mL/min, 25 C): tₛ(S) = 25.9 min, tₛ(R) = 29.9 min (Figure 4.4). The absolute configuration was established by comparison to the HPLC trace of (R)-3b. TLC (hexanes–EtOAc = 1:1): Rᵢ = 0.82. ¹H NMR (400 MHz) (1:1 ratio of rotamers): δ 7.31-7.07 (m, 15 H), 5.75-5.63 (m, 1 H), 5.24-4.92 (m, 4 H), [4.68 (d, J = 11.6 Hz), 4.54 (d, J = 11.3 Hz), 1:1, 1 H], 4.14-4.00 (m, 1 H), 3.62 (dd, J = 7.3, 11.5 Hz, 1 H), 2.77-2.73 (m, 1 H), 2.40-2.30 (m, 1 H). ¹³C¹H NMR (100 MHz) (1:1 ratio of rotamers): δ 155.4, 154.6, 145.3, 144.7, 139.1, 138.4, 136.9, 136.7, 128.7, 128.6, 128.4, 128.2, 128.1, 127.9, 127.6, 127.4, 126.7, 126.5, 115.6, 115.0, 66.8, 59.4, 58.9, 56.1, 52.9, 52.6, 45.5, 44.5. Anal. calcd (found) for C₂₆H₂₅NO₂: H, 6.59 (6.66); C, 81.42 (81.37).
Figure 4.4 Chiral HPLC traces of racemic 3b (left trace) and enantiomerically enriched (S)-3b (right trace). HPLC conditions: hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C.

All remaining enantioselective allylic amination reactions were performed employing procedures similar to that used to synthesize (S)-3b, unless noted otherwise. Reaction time and temperature are provided in Tables 4.3 and 4.4. Racemic heterocycles for HPLC analysis were prepared via cyclization of the appropriate substrate with a catalytic 1:1 mixture of AuCl[P(t-Bu)₂-o-biphenyl] and AgClO₄ employing a published procedure.¹⁰²c

**tert-Butyl 4,4-diphenyl-2-vinylpyrrolidine-1-carboxylate (3c).** White solid, 97% yield, 80% ee. mp 56 – 60 °C. HPLC (hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C): tᵣ(S) = 8.9 min, tᵣ(R) = 10.0 min (Figure 4.5). TLC (hexanes–EtOAc = 4:1): Rᵣ = 0.53. ¹H NMR (2:1 mixture of rotamers): δ 7.34-7.20 (m, 10 H), 5.87-5.73 (m, 1 H), 5.24-5.04 (m, 2 H), [4.76 (d, J = 12 Hz), 4.58 (d, J = 12 Hz), 2:1, 1 H], [4.16 (quartet, J = 7.5 Hz), 3.95 (quartet, J = 7.5 Hz), 1:2, 1 H], [3.68 (d, J = 11.5 Hz), 3.62 (d, J = 11.5 Hz), 1:2, 1 H], 2.87-
2.79 (m, 1 H), [2.48 (t, $J = 11.5$ Hz), 2.43 (t, $J = 11.5$ Hz), 2:1, 1 H], [1.54 (s), 1.45 (s), 1:2, 9 H]. $^{13}$C{$^1$H} NMR (2:1 mixture of rotamers): $\delta$ 155.1, 154.4, 145.5, 145.0, 139.6, 139.0, 128.5, 126.8, 126.6, 126.5, 126.4, 126.3, 114.9, 114.6, 79.6, 59.1, 58.9, 56.5, 55.5, 53.0, 52.6, 45.6, 44.8, 28.6, 28.3. Anal. calcd (found) for C$_{23}$H$_{27}$NO$_2$: H, 7.79 (7.87); C, 79.05 (79.06).

Figure 4.5 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 3c (right trace). HPLC conditions: hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C.

2,2,2-Trichloroethyl 4,4-diphenyl-2-vinylpyrrolidine-1-carboxylate (3d).$^{103a}$

Colorless waxy solid, 62% yield, 84% ee. HPLC (hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C): $t_R(S) = 12.4$ min, $t_R(R) = 13.6$ min (Figure 4.6). TLC (hexanes–EtOAc = 1:1): $R_f = 0.69$. $^1$H NMR (1:1 mixture of rotamers): $\delta$ 7.23-7.07 (m, 10 H), [5.73 (ddd, $J = 5$, 10.5, 14.5 Hz), 5.69 (ddd, $J = 4.5$, 10, 15 Hz), 1:1, 1 H], [5.19 (d, $J = 14.5$ Hz), 5.08 (d, $J = 15$ Hz), 1:1, 1 H], [5.13 (d, $J = 9.5$ Hz), 5.01 (d, $J = 10$ Hz), 1:1, 1 H], [4.92 (d, $J = 12$ Hz), 4.80 (d, $J = 12$ Hz), 1:1, 1 H], [4.72 (dd, $J = 2$, 11.5 Hz), 1:1, 1 H], [4.65 (dd, $J = 2$, 11.5 Hz), 1:1, 1 H], 4.53 (t, $J = 12$ Hz, 1 H), 4.15-4.09 (m, 1 H), [3.73 (d, $J = 11.5$ Hz), 3.65 (d, $J = 11.5$ Hz), 1:1, 1 H], [2.84 (dd, $J = 2$, 7 Hz), 2.81 (d, $J = 2$, 7 Hz), 1:1, 1 H], [2.41 (dd, $J = 9.5$, 12.5 Hz), 2.38 (d, $J = 10$, 13 Hz), 1:1, 1 H]. $^{13}$C{$^1$H} NMR (60 °C, 1:1 mixture of rotamers): $\delta$ 153.8,
152.6, 145.2, 144.5, 138.4, 137.8, 128.7, 128.6, 126.8, 126.7, 126.6, 126.5, 115.7, 95.8, 75.0, 
59.6, 59.5, 56.6, 56.4, 53.0, 45.6, 44.6. Anal. calcd (found) for C_{21}H_{20}Cl_{3}NO_{2}: H, 4.75 (4.84); 
C, 59.38 (59.43).

Figure 4.6 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 3d 
(right trace). HPLC conditions: hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C.

**Methyl 4,4-diphenyl-2-vinylpyrrolidin-1-carboxylate (3e).** Colorless oil, 
97% yield, 75% ee. HPLC (hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C): t_{R}(S) = 
13.4 min, t_{R}(R) = 14.8 min (Figure 4.7). TLC (hexanes–EtOAc = 1:1): R_{f} = 0.67. ^1H NMR 
(1:1 mixture of rotamers): δ 7.38–7.24 (m, 10 H), 5.89–5.79 (m, 1 H), [5.28 (d, J = 17 Hz), 
5.18 (d, J = 17 Hz), 1:1, 1 H], [5.17 (d, J = 10 Hz), 5.10 (d, J = 10 Hz), 1:1, 1 H], [4.81 (d, J = 
12 Hz), 4.63 (d, J = 11 Hz), 1:1, 1 H], [4.26 (quartet, J = 8 Hz), 4.13 (d, J = 8 Hz), 1:1, 1 H], 
[3.84 (s), 3.75 (s), 1:1, 3 H], 3.87–3.78 (m, 1 H), 2.94–2.91 (m, 1 H), 2.57–2.48 (m, 1 H).

^{13}C[^{1}H] NMR (1:1 mixture of rotamers): δ 156.0, 155.2, 145.4, 145.3, 144.9, 144.7, 139.1,
138.4, 128.6, 128.5, 126.7, 126.5, 126.4, 126.3, 115.6, 114.7, 59.4, 58.8, 56.1, 56.0, 52.8, 52.5, 52.3, 45.5, 44.5. Anal. calcd (found) for C\textsubscript{20}H\textsubscript{21}NO\textsubscript{2}: H, 6.89 (6.81); C, 78.15 (78.19).

Figure 4.7 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 3e (right trace). HPLC conditions: hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C.

4,4-Diphenyl-1-tosyl-2-vinylpyrrolidine (3f).\textsuperscript{103a} White waxy solid, 98% yield, 76% ee. HPLC (hexanes–isopropanol = 92:8, 0.5 mL/min, 25 °C): \( t_R(R) = 30.7 \text{ min} \), \( t_R(S) = 32.5 \text{ min} \) (Figure 4.8). TLC (hexanes–EtOAc = 1:1): \( R_f = 0.76 \). \( ^1\text{H} \) NMR: \( \delta = 7.55 \) (d, \( J = 8 \) Hz, 2 H), 7.17 (t, \( J = 8 \) Hz, 2 H), 7.13-7.05 (m, 10 H), 5.51 (ddd, \( J = 8.5, 10, 17.5 \) Hz, 1 H), 5.06 (d, \( J = 17.5 \) Hz, 1 H), 4.92 (d, \( J = 10 \) Hz, 1 H), 4.10 (d, \( J = 8.5 \) Hz, 1 H), 4.04-3.99 (m, 2 H), 2.71 (dd, \( J = 7.5, 12 \) Hz, 1 H), 2.37 (dd, \( J = 8, 12.5 \) Hz, 1 H), 2.32 (s, 3 H). \( ^{13}\text{C}\{^1\text{H}\} \) NMR: \( \delta \) 145.1, 144.5, 143.0, 138.6, 136.0, 129.4, 128.5, 127.2, 126.6, 126.5, 126.4, 126.3, 116.3, 61.9, 58.1, 52.5, 45.4, 21.4. IR (neat, cm\textsuperscript{-1}): 3024, 2921, 1596, 1494, 1446, 1337, 1156, 1116, 1030, 914, 750, 697, 661, 581. Anal. calcd (found) for C\textsubscript{25}H\textsubscript{23}NO\textsubscript{2}S: H, 6.24 (6.22); C, 74.41 (74.38).
Figure 4.8 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 3f (right trace). HPLC conditions: hexanes–isopropanol = 92:8, 0.5 mL/min, 25 °C.

(9H-Fluoren-9-yl)methyl 4,4-diphenyl-2-vinylpyrrolidine-1-carboxylate (3g).\textsuperscript{103b}

White solid, 95% yield, 91% ee. mp 51-53 °C. HPLC (hexanes–isopropanol = 90:10; 0.5 mL/min, 25 °C): $t_{R}(S) = 28.8$ min, $t_{R}(R) = 31.3$ min (Figure 4.9). TLC (hexanes–EtOAc = 1:1): $R_f = 0.79$. \textsuperscript{1}H NMR (1:1 mixture of rotamers): $\delta$ 7.82-7.18 (m, 18 H), [5.80 (ddd, $J = 7, 10, 17.5$ Hz), 5.71 (ddd, $J = 7, 10, 17$ Hz), 1:1, 1 H], [5.24 (d, $J = 17$ Hz), 4.97 (d, $J = 17$ Hz), 1:1, 1 H], 4.97 (d, $J = 12$ Hz, 0.5 H), 4.53-4.21 (m, 4 H), 4.07 (quartet, $J = 7.5$ Hz, 0.5 H), [3.77 (d, $J = 7.5$ Hz), 3.74 (d, $J = 7.5$ Hz), 1:1, 1 H], 2.88 (d, $J = 7$ Hz), 2.87 (d, $J = 6.5$ Hz), 1:1, 1 H], 2.51-2.41 (m, 1 H). \textsuperscript{13}C\textsuperscript{1}H NMR (60 °C, 1:1 mixture of rotamers): $\delta$ 155.4, 154.6, 145.5, 145.0, 144.3, 141.4, 139.0, 138.6, 128.7, 128.5, 127.6, 127.0, 126.8, 126.6, 126.5, 125.0, 119.9, 115.2, 114.9, 67.1, 59.2, 56.4, 53.0, 47.6, 45.7, 44.7. Anal. calcd (found) for C\textsubscript{33}H\textsubscript{29}NO\textsubscript{2}: H, 6.20 (6.21); C, 84.05 (84.08).
Figure 4.9 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 3g (right trace). HPLC conditions: hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C.

\((9H\text{-Fluoren-9-yl})\text{methyl}~4,4\text{-dimethyl-2-vinylpyrrolidine-1-carboxylate}~(5)\).

Colorless oil, 94% yield, 90% ee. HPLC (hexanes–isopropanol = 97:3, 0.5 mL/min, 25 °C): \(t_R(S) = 29.3\) min, \(t_R(R) = 31.4\) min (Figure 4.10). TLC (hexanes–EtOAc = 1:1): \(R_f = 0.79\). \(^1H\) NMR (1:1 mixture of rotamers): \(\delta\) 7.77 (d, \(J = 7\) Hz, 2 H), 7.61 (d, \(J = 7.5\) Hz, 2 H), 7.40 (t, \(J = 7\) Hz, 2 H), 7.31 (d, \(J = 7\) Hz, 2 H), [5.84-5.79 (m), 5.72-5.67 (m), 1:1, 1 H], [5.20 (d, \(J = 17\) Hz), 4.86 (d, \(J = 16\) Hz), 1:1, 1 H], [5.11 (d, \(J = 10\) Hz), 4.89 (d, \(J = 9\) Hz), 1:1, 1 H], 4.48-4.39 (m, 3 H), 4.26-4.16 (m, 1 H), [3.44 (d, \(J = 10\) Hz), 3.35 (d, \(J = 10.5\) Hz), 1:1, 1 H], [3.13 (d, \(J = 10.5\) Hz), 3.08 (d, \(J = 10.5\) Hz), 1:1, 1 H], 1.92-1.86 (m, 1 H), 1.57-1.50 (m, 1 H), [1.13 (s), 1.09 (s), 1:1, 3 H], [1.03 (s), 0.97 (s), 1:1, 3 H]. \(^13C\)\(^1H\) NMR (1:1 mixture of rotamers): \(\delta\) 155.7, 155.1, 144.4, 144.2, 144.1, 143.9, 141.3, 139.6, 139.1, 127.5, 126.9, 125.0, 119.9, 114.6, 114.0, 66.7, 60.0, 59.6, 59.5, 59.3, 47.4, 47.2, 46.3, 37.7, 37.1, 26.4, 26.3, 26.2. IR (neat, cm\(^{-1}\)): 2954, 2867, 1693, 1409, 1348, 1306, 1169, 1103, 983, 916, 757, 733, 620. Anal. calcd (found) for C\(_{23}\)H\(_{25}\)NO\(_2\): H, 7.25 (7.22); C, 79.51 (79.42).
Figure 4.10 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 5.

HPLC conditions: hexanes–isopropanol = 97:3, 0.5 mL/min, 25 °C.


Colorless oil, 95% yield, 94% ee. HPLC (hexanes–isopropanol = 98:2, 0.5 mL/min, 25 °C): $t_R(R) = 46.5$ min, $t_R(S) = 50.9$ min (Figure 4.11). TLC (hexanes–EtOAc = 1:1): $R_f = 0.72$. $^1$H NMR (60 ºC): $\delta$ 7.76 (d, $J = 7.5$ Hz, 2 H), 7.62 (d, $J = 7$ Hz, 2 H), 7.39 (t, $J = 7.5$ Hz, 2 H), 7.30 (d, $J = 7.5$ Hz, 2 H), 5.77 (br s, 1 H), 4.99 (br s, 2 H), 4.48 (d, $J = 5.5$ Hz, 2 H), 4.24 (br s, 2 H), 3.56 (br s, 1 H), 3.06 (d, $J = 11.5$ Hz, 1 H), 2.01 (dd, $J = 8$, 12.5 Hz, 1 H), 1.51-1.29 (m, 11 H). $^{13}$C($^1$H) NMR (60 ºC): $\delta$ 155.4, 144.5, 144.3, 141.5, 139.7, 127.5, 126.9, 125.0, 119.8, 113.9, 66.7, 58.9, 57.1, 47.7, 44.5, 41.5, 36.6, 35.2, 26.1, 23.7, 23.1. IR (neat, cm$^{-1}$): 2922, 2852, 1692, 1449, 1409, 1347, 1168, 1109, 983, 907, 756, 726, 645. Anal. calcd (found) for C$_{26}$H$_{29}$NO$_2$: H, 7.54 (7.49); C, 80.59 (80.52).
Figure 4.11 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 7 (right trace). HPLC conditions: hexanes–isopropanol = 98:2, 0.5 mL/min, 25 °C.

*(9H-Fluoren-9-yl)methyl 2-vinylpyrrolidine-1-carboxylate* (9). Colorless oil, 89% yield, 62% ee. HPLC (hexanes–isopropanol = 90:10, 1 mL/min, 25 °C): \( t_R(R) = 9.7 \) min, \( t_R(S) = 12.5 \) min (Figure 4.12). TLC (hexanes–EtOAc = 1:1): \( R_f = 0.63. \) \(^1\)H NMR (1:1 mixture of rotamers): \( \delta \) 7.77 (br s, 2 H), 7.62 (d, \( J = 7 \) Hz, 2 H), 7.40 (br s, 2 H), 7.31 (br d, \( J = 7 \) Hz, 2 H), 5.82-5.69 (m, 1 H), [5.12 (d, \( J = 17 \) Hz), 4.94 (d, \( J = 17 \) Hz), 1 H], [5.11 (d, \( J = 10 \) Hz), 5.00 (d, \( J = 10 \) Hz), 1 H], 4.51-4.21 (m, 4 H), 3.49 (br s, 2 H), 2.06-1.73 (m, 4 H). \(^{13}\)C\(^1\)H NMR (1:1 mixture of rotamers): \( \delta \) 155.2, 154.7, 144.3, 144.1, 141.3, 138.3, 137.9, 127.5, 126.9, 125.1, 119.8, 114.3, 114.1, 66.9, 59.4, 58.9, 47.4, 46.6, 46.3, 32.0, 31.1, 23.4, 22.4. IR (neat, cm\(^{-1}\)): 2947, 2874, 1692, 1448, 1407, 1342, 1267, 1241, 1178, 1089, 984, 911, 755, 735. Anal. calcd (found) for C\(_{21}\)H\(_{21}\)NO\(_2\): H, 6.63 (6.67); C, 78.97 (78.99).
Figure 4.12 HPLC traces of racemic (left trace) and enantiomerically enriched 9 (right trace). HPLC conditions: hexanes–isopropanol = 90:10, 1 mL/min, 25 °C.

(9H-Fluoren-9-yl)methyl 4-phenyl-2-vinylpyrrolidine-1-carboxylate (11).
Colorless oil, 87% yield, 1:1 mixture of diastereomers, 90/92% ee. HPLC (hexanes–isopropanol = 98:2, 0.5 mL/min, 25 °C): \[ t_R^{(R\text{-isomer A})} = 77.9 \text{ min}, \ t_R^{(S\text{-isomer A})} = 86.8 \text{ min}, \ t_R^{(R\text{-isomer B})} = 80.7 \text{ min}, \ t_R^{(S\text{-isomer B})} = 109.1 \text{ min} \] (Figure 4.13). TLC (hexanes–EtOAc = 1:1): \( R_f = 0.72 \). \(^1\)H NMR (60 °C, 1:1 mixture of diastereomers, 1:1 mixture of rotamers): \( \delta \) 7.76 (d, \( J = 7.5 \text{ Hz} \), 2 H), 7.63 (d, \( J = 7 \text{ Hz} \), 2 H), 7.40 (t, \( J = 7.5 \text{ Hz} \), 2 H), 7.35-7.29 (m, 4 H), 7.27-7.22 (m, 3 H), 5.85 (br s, 1 H), 5.12 (br s, 2 H), [4.52-4.48 (m), 4.35 (br s), 3 H], 4.25 (t, \( J = 6.5 \text{ Hz} \), 1 H), [4.10 (br s), 3.90-3.87 (m), 1 H], 3.52-3.47 (m, 1 H), [3.34 (t, \( J = 10.5 \text{ Hz} \), 3.30-3.23 (m), 1 H], [2.55 (quintet, \( J = 6 \text{ Hz} \), 2.24-2.18 (m), 1 H], [2.12 (dd, \( J = 5, 11.5 \text{ Hz} \), 1.89 (quartet, \( J = 12 \text{ Hz} \), 1 H). \(^{13}\)C\(^{1}\)H NMR (60 °C,1:1 mixture of diastereomers): \( \delta \) 154.8, 144.3, 141.5, 140.9, 140.3, 139.1, 138.1, 128.6, 127.5, 127.0, 126.9,
125.0, 119.8, 114.5, 67.0, 66.9, 60.3, 59.4, 53.1, 52.7, 47.6, 43.1, 40.6. IR (neat, cm⁻¹): 3027, 2944, 2873, 1693, 1448, 1407, 1343, 1192, 1105, 979, 915, 756, 736, 696. Anal. calcd (found) for C₂₇H₂₅NO₂: H, 6.37 (6.27); C, 82.00 (81.94).

Figure 4.13 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 11 (right trace). HPLC conditions: hexanes–isopropanol = 98:2, 0.5 mL/min, 25 °C.

(9H-Fluoren-9-yl)methyl 4-isopropyl-2-vinylpyrrolidine-1-carboxylate (13). Colorless oil, 98%, 1:1 mixture of diastereomers, 85/91% ee. HPLC (hexanes–isopropanol = 99.2:0.8, 0.5 mL/min, 25 °C): [tᵣ(R-isomer A) = 68.6 min, tᵣ(S-isomer A) = 94.7 min], [tᵣ(R-isomer B) = 70.7 min, tᵣ(S-isomer B) = 135.8 min] (Figure 4.14). TLC (hexanes–EtOAc = 4:1): Rₚ = 0.35. ¹H NMR (60 ºC, 1:1 mixture of diastereomers, 1:1 mixture of rotamers): δ 7.75 (d, J = 7.5 Hz, 2 H), 7.61 (d, J = 7.5 Hz, 2 H), 7.38 (t, J = 8 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 5.76 (br s, 1 H), 5.03 (br s, 2 H), 4.47 (br d, J = 6.5 Hz, 3 H), 4.23 (br s, 1 H), [3.82 (br s), 3.59 (t, J = 9 Hz), 1 H], [3.06 (br s), 2.93 (t, J = 10.5 Hz), 1 H], [2.28-2.23 (m), 1.96 (br s), 1 H], [1.83 (dd, J = 6, 12 Hz), 1.36 (q, J = 12 Hz), 1 H], 1.78-1.66 (m, 1 H), 1.54-1.47 (m, 1 H), 0.95-0.93 (m, 6 H). ¹³C[¹H] NMR (60 ºC, 1:1 mixture of diastereomers): δ 154.9 144.4, 141.5, 139.7, 138.5, 127.5, 126.9, 125.1, 119.8, 113.9, 66.9, 66.8, 60.5, 59.6, 51.5, 50.8, 47.6, 45.6, 43.1, 38.2, 36.5, 31.9, 31.7, 21.3, 20.9. IR (neat, cm⁻¹): 2957, 2870, 1692, 1449, 1410, 1344, 1186, 1105, 980, 908, 756, 725. Anal. calcd (found) for C₂₃H₂₇NO₂: H, 7.53 (7.56); C, 79.74 (79.79).
Figure 4.14 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 13.

HPLC conditions: hexanes–isopropanol = 99.2:0.8, 0.5 mL/min, 25 °C.

(9H-Fluoren-9-yl)methyl 4-isopropyl-2-(2-methylprop-1-en-1-yl)pyrrolidine-1-carboxylate (15). Colorless oil, 87%, 1:1 mixture of diastereomers, 88/90% ee. HPLC (hexanes–isopropanol = 99:1, 1 mL/min, 25 °C.): [t$_R$(R-isomer A) = 22.9 min, t$_R$(S-isomer A) = 36.5 min], [t$_R$(R-isomer B) = 24.1 min, t$_R$(S-isomer B) = 38.7 min] (Figure 4.15). TLC (hexanes–EtOAc = 4:1): $R_f = 0.49$. $^1$H NMR (60 ºC, 1:1 mixture of diastereomers): δ 7.75 (d, $J = 7.5$ Hz, 2 H), 7.61 (t, $J = 7.5$ Hz, 2 H), 7.38 (t, $J = 7.5$ Hz, 2 H), 7.30 (t, $J = 7.5$ Hz, 2 H), [5.20 (br s), 5.12 (br s), 1:1.2, 1 H], [4.61 (br s), 4.51-4.46 (m), 1:1.2, 1 H], 4.45-4.37 (m, 2 H), 4.23 (quartet, $J = 5.5$ Hz, 1 H), [3.82 (br s), 3.63 (t, $J = 9.5$ Hz, 1:1.2, 1 H), [3.05 (br s), 2.96 (t, $J = 11$ Hz), 1:1.2, 1 H], [2.27 (td, $J = 5.5$, 13.5 Hz), 2.07-1.99 (m), 1.2:1, 1 H], 1.76-1.68 (m, 2 H), 1.72 (s, 6 H), [1.60-1.45 (m), 1.32-1.23 (m), 1.2:1, 1 H], [0.96 (d, $J = 6.5$ Hz), 0.95 (d, $J = 7$ Hz), 1.2:1, 6 H]. $^{13}$C[$^1$H] NMR (60 ºC, 1:1 mixture of diastereomers): δ 154.9, 144.5, 141.5, 132.0, 127.6, 127.0, 126.9, 125.1, 119.8, 66.9, [56.5, 56.1], [51.5, 50.8], 47.7, [45.5, 44.2], 38.6, [32.1, 31.8], 25.6, [21.3, 21.2], [21.0, 20.9], 17.9. IR (neat, cm$^{-1}$): 2958, 2870,
Anal. calcd (found) for C_{26}H_{31}NO_2: H, 8.02 (8.04); C, 80.17 (80.20).

Figure 4.15 HPLC traces of racemic (left trace) and enantiomerically enriched 15 (right trace). HPLC conditions: hexanes–isopropanol = 99:1, 1 mL/min, 25 °C.

**Colorless waxy solid, 69% yield, 77% ee.** HPLC (hexanes–isopropanol = 99:1, 0.5 mL/min, 25 °C): t_R(S) = 50.9 min, t_R(R) = 54.2 min (Figure 4.16). TLC (hexanes–EtOAc = 1:1): R_f = 0.81. $^1$H NMR (2.5:1 mixture of rotamers): δ 7.76 (d, J = 8 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.39 (t, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 5.71 (ddd, J = 3.5, 11, 17.5 Hz, 1 H), 5.17 (d, J = 11 Hz, 1 H), 5.02 (d, J = 17.5 Hz, 1 H), 4.78 (br s, 1 H), [4.54 (br s), 4.49 (dd, J = 6, 10 Hz), 1:2.5, 2 H], [4.25 (t, J = 6 Hz), 4.03 (br s), 2.5:1, 1 H], [3.71 (s), 3.56 (br s), 2 H], 2.47 (br s, 1 H), 1.91-1.83 (m, 1 H), 1.54-1.15 (m, 12 H). $^{13}$C$^1$H NMR (55 °C, 1:1 mixture of rotamers): δ 156.0, 144.4, 144.3, 141.5, 136.6, 127.5, 127.0, 124.9, 119.9, 115.8, 67.1, 66.9, 52.6, 48.1, 47.7, 38.1, 32.9, 31.2, 31.0, 26.6, 24.0, 21.6, 21.5. IR (neat, cm$^{-1}$):
2921, 2847, 1690, 1448, 1420, 1246, 1218, 1143, 991, 914, 756, 735. Anal. calcd (found) for C$_2$H$_{31}$NO$_2$: H, 7.78 (7.72); C, 80.76 (80.77).

**Figure 4.16** HPLC traces of racemic (left trace) and enantiomerically enriched 17 (right trace). HPLC conditions: hexanes–isopropanol = 99:1, 0.5 mL/min, 25 °C.

(9H-Fluoren-9-yl)methyl 3-vinylmorpholine-4-carboxylate (19). Colorless sticky solid, 92% yield, 57% ee. HPLC (hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C.): 

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Figure 4.17. TLC (hexanes–EtOAc = 1:1): R$_f$ = 0.61.

$^1$H NMR (60 °C): δ 7.76 (d, J = 8 Hz, 2 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 5.90 (ddd, J = 5.5, 11, 17.5 Hz, 1 H), 5.23 (d, J = 11 Hz, 1 H), 5.13 (d, J = 17.5 Hz, 1 H), 4.54 (d, J = 6.5 Hz, 2 H), 4.39 (br s, 1 H), 4.24 (t, J = 6 Hz, 1 H), 3.88 (d, J = 12 Hz, 1 H), 3.83 (dd, J = 3.5, 11.5 Hz, 1 H), 3.72 (br d, J = 12.5 Hz, 1 H), 3.59 (dd, J = 3.5, 12 Hz, 1 H), 3.43 (dt, J = 2.5, 11.5 Hz, 1 H), 3.21 (dt, J = 4, 14 Hz, 1 H).

$^{13}$C($^1$H) NMR (60 °C): δ 155.4, 144.1, 141.5, 134.3, 127.7, 127.0, 124.9, 119.9, 117.4, 69.9, 67.2, 66.8, 53.5, 47.6, 40.1. IR (neat, cm$^{-1}$): 2960, 2852, 1693, 1448, 1414, 1291, 1259, 1223, 1099, 925, 858, 736, 620. Anal. calcd (found) for C$_{21}$H$_{31}$NO$_3$: H, 6.31 (6.23); C, 75.20 (75.03).

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Figure 4.17 HPLC traces of racemic (left trace) and enantiomerically enriched 19 (right trace). HPLC conditions: hexanes–isopropanol = 90:10, 0.5 mL/min, 25 °C.

(9H-fluoren-9-yl)methyl 7-vinyl-9-oxa-6-azaspiro[4.5]decane-6-carboxylate (21).

Colorless oil, 41% yield, 33% ee. HPLC (hexanes–isopropanol = 88:12, 1 mL/min, 25 °C.): $t_R(S) = 28.9$ min, $t_R(R) = 33.0$ min (Figure 4.18). TLC (hexanes–EtOAc = 1:1): $R_f = 0.69$. $^1$H NMR (400 MHz, 1:1 mixture of rotamers): $\delta$ 7.75 (d, $J = 7.2$ Hz, 2 H), 7.59 (d, $J = 7.6$ Hz, 2 H), 7.38 (t, $J = 7.6$ Hz, 2 H), 7.30 (t, $J = 7.6$ Hz, 2 H), [5.76 (br s), 5.69 (ddd, $J = 6.8$, 10, 17.2 Hz), 1:1, 1 H], [5.25 (d, $J = 17.2$ Hz), 5.14 (br s), 1:1, 1 H], [5.21 (d, $J = 10$ Hz), 4.99 (br s), 1:1, 1 H], 4.32 (br s, 2 H), 4.20 (t, $J = 6.8$ Hz, 1 H), 4.07-3.87 (m, 3 H), 3.49 (br s, 2 H), 1.92 (br s, 2 H), 1.73 (br s, 4 H), 1.57 (br s, 2 H).
Figure 4.18 HPLC traces of racemic (left trace) and enantiomerically enriched 21 (right trace). HPLC conditions: hexanes–isopropanol = 88:12, 1 mL/min, 25 °C.

1-(9H-Fluoren-9-yl)methyl 4-tert-butyl 2-vinylpiperazine-1,4-dicarboxylate (23).

White waxy solid, 86% yield, 94% ee. HPLC (hexanes–isopropanol = 99:1, 0.5 mL/min, 25 °C.): $t_R(S) = 138.5$ min, $t_R(R) = 145.2$ min (Figure 4.19). TLC (hexanes–EtOAc = 1:1): $R_f = 0.69$. $^1$H NMR (60 °C): $\delta$ 7.76 (d, $J = 7.5$ Hz, 2 H), 7.57 (d, $J = 7.5$ Hz, 2 H), 7.39 (t, $J = 7.5$ Hz, 2 H), 7.31 (t, $J = 7.5$ Hz, 2 H), 5.72 (ddd, $J = 5$, 10.5, 17.5 Hz, 1 H), 5.19 (d, $J = 10.5$ Hz, 1 H), 5.13 (d, $J = 17.5$ Hz, 1 H), 4.59 (br s, 1 H), 4.54 (d, $J = 6$ Hz, 2 H), 4.24 (t, $J = 6$ Hz, 1 H), 4.09 (d, $J = 12.5$ Hz, 1 H), 3.94 (br d, $J = 11$ Hz, 1 H), 3.80 (d, $J = 13.5$ Hz, 1 H), 3.08 (dt, $J = 3.5$, 12 Hz, 1 H), 3.00 (dd, $J = 4$, 13 Hz, 1 H), 2.80 (t, $J = 12$ Hz, 1 H), 1.47 (s, 9 H). $^{13}$C($^1$H) NMR (60 °C): $\delta$ 155.4, 154.7, 144.0, 141.5, 134.5, 127.7, 127.0, 124.9, 120.0, 117.3, 80.1, 67.3, 55.3, 47.6, 46.1, 43.5, 39.6, 28.4. IR (neat, cm$^{-1}$): 2973, 2927, 1687, 1415, 1309, 1251, 1218, 1165, 1095, 921, 756, 735. Anal. calcd (found) for C$_{26}$H$_{30}$N$_2$O$_4$: H, 6.96 (7.03); C, 71.87 (71.97).
Figure 4.19 HPLC traces of racemic (left trace) and enantiomerically enriched 23 (right trace). Minor peaks in the HPLC are traces of 27 (<5%) formed via cyclization of 26 present as an impurity in 22. Neither 27 nor 26 were detected in the NMR spectra of 23 or 27, respectively. HPLC conditions: hexanes–isopropanol = 99:1, 0.5 mL/min, 25 °C.

(9H-Fluoren-9-yl)methyl 4-tosyl-2-vinylpiperazine-1-carboxylate (25).

Colorless oil, 99% yield, 92% ee. HPLC (hexanes–isopropanol = 75:25, 1 mL/min, 30 °C):
t_R(S) = 24.2 min, t_R(R) = 32.2 min (Figure 4.20). TLC (hexanes–EtOAc = 1:1):  R_f = 0.58.

H NMR (60 °C):  δ 7.70 (d, J = 8 Hz, 2 H), 7.63 (d, J = 8.5 Hz, 2 H), 7.50 (d, J = 8 Hz, 2 H), 7.37-7.34 (m, 4 H), 7.26 (t, J = 7.5 Hz, 2 H), 5.80 (ddd, J = 5, 10.5, 17 Hz, 1 H), 5.25 (d, J = 10.5 Hz, 1 H), 5.18 (d, J = 17 Hz, 1 H), 4.59 (br s, 1 H), 4.51 (d, J = 6 Hz, 2 H), 4.18 (t, J = 6 Hz, 1 H), 3.83 (d, J = 12.5 Hz, 1 H), 3.73 (d, J = 11.5 Hz, 1 H), 3.61 (br d, J = 11.5 Hz, 1 H), 3.15 (dt, J = 3.5, 12 Hz, 1 H), 2.45 (s, 3 H), 2.38 (dt, J = 4.5, 11.5 Hz, 1 H), 2.20 (dt, J = 3.5, 13 Hz, 1 H).  C NMR (60 °C):  δ 154.9, 143.9, 143.7, 141.3, 133.2, 132.3, 129.7, 127.7, 127.6, 127.0, 124.8, 119.9, 118.5, 67.2, 52.0, 48.5, 47.3, 45.7, 38.9, 21.5. IR (neat, cm⁻¹): 2849, 176.
1696, 1449, 1350, 1302, 1223, 1164, 1106, 1085, 932, 814, 720. Anal. calcd (found) for C_{28}H_{28}N_{2}O_{4}: H, 5.78 (5.70); C, 68.83 (68.86).

Figure 4.20 HPLC traces of racemic (left trace) and enantiomerically enriched 25 (right trace). HPLC conditions: hexanes–isopropanol = 75:25, 1 mL/min, 30 °C.

4-(9H-Fluoren-9-yl)methyl 1-tert-butyl 2-vinylpiperazine-1,4-dicarboxylate (27). White waxy solid, 99% yield, 91% ee. HPLC (hexanes–isopropanol = 99:1, 0.5 mL/min, 25 °C): t_{R}(R) = 124.7 min, t_{R}(S) = 132.6 min (Figure 4.21). TLC (hexanes–EtOAc = 1:1): R_{f} = 0.76. \(^1\)H NMR (60 °C): δ 7.76 (d, J = 8 Hz, 2 H), 7.57 (d, J = 7.5 Hz, 2 H), 7.39 (t, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 5.65 (br s, 1 H), 5.17 (d, J = 10.5 Hz, 1 H), 5.13 (d, J = 17.5 Hz, 1 H), 4.62 (br s, 1 H), 4.54-4.48 (m, 2 H), 4.24 (t, J = 6.5 Hz, 1 H), 3.92 (br s, 2 H), 3.83 (br d, J = 13 Hz, 1 H), 3.08 (dd, J = 4, 13 Hz, 1 H), 3.03 (t, J = 11 Hz, 1 H), 2.90 (t, J = 12 Hz, 1 H), 1.48 (s, 9 H). \(^{13}\)C\(^{1}\)H NMR (60 °C, 1:1 mixture of rotamers): δ 155.3, 154.8, 144.0, 141.5, [134.7, 134.6], 127.7, 127.0, 124.8, 119.9, [117.1, 116.9], 80.2, 67.3, 53.0, [47.6, 47.5], 46.2, 43.5, 39.2, [28.4, 28.3]. IR (neat, cm\(^{-1}\)): 2974, 1686, 1449, 1400, 1249, 1220, 1164, 1099, 756, 725. Anal. calcd (found) for C_{26}H_{30}N_{2}O_{4}: H, 6.96 (6.93); C, 71.87 (71.76).
4.3.4 Gold(I)-catalyzed cyclization of chiral secondary alcohol

Gold(I)-catalyzed cyclization of rac-28. Treatment of rac-28 with a catalytic 1:2 mixture of [(S)-2](AuCl)$_2$ and AgClO$_4$ in dioxane at 25 °C for 48 h led to isolation of a 1.04:1 mixture of (E)-29 (93% ee) and (Z)-29 (95% ee) as a colorless oil in 91% combined yield. HPLC (hexanes–isopropanol = 98:2, 1 mL/min, 25 °C): [t$_R$(R,Z) = 17.3 min, t$_R$(S,Z) = 18.6 min, t$_R$(R,E) = 19.8 min, t$_R$(S,E) = 28.9 min] (Figure 4.22). TLC (hexanes–EtOAc = 4:1): $R_f = 0.38$. IR (neat, cm$^{-1}$): 2919, 2851, 1692, 1448, 1407, 1344, 1107, 959, 735. Anal. calcd (found) for C$_{27}$H$_{31}$NO$_2$: H, 7.78 (7.74); C, 80.76 (80.69).

For (E)-29: $^1$H NMR (−50 °C, 1:1 mixture of rotamers): δ [7.81 (d, $J = 10$ Hz), 7.79 (d, $J = 9$ Hz), 1:1, 2 H], [7.66 (d, $J = 8$ Hz), 7.64 (d, $J = 8$ Hz), 1:1, 2 H], 7.46-7.41 (m, 2 H), 7.38-7.32 (m, 2 H), [5.69 (qd, $J = 6.5$, 15.5 Hz), 5.40-5.37 (m), 1:1, 1 H], 5.33 (dd, $J = 6$, 15.5 Hz, 1 H), 4.47 (dd, $J = 6.5$, 10.5 Hz, 1 H), 4.39-4.20 (m, 3 H), [3.78 (br s), 3.42 (br s), 1:1, 1
H), [3.18 (br s, 3.03 (br s), 1:1, 1 H], [2.22 (br s), 1.78 (br s), 1:1, 1 H], [1.72 (d, J = 6.5 Hz), 1.63 (d, J = 5.5 Hz), 1:1, 3 H], 1.64-1.16 (m, 11 H). $^{13}$C[$^1$H] NMR (60 °C): δ 155.4, 144.5, 144.3, 141.4, 132.8, 127.5, 126.9, 125.3, 125.0, 119.8, 66.7, 58.3, 57.0, 47.7, 44.8, 41.3, 36.6, 35.1, 26.1, 23.8, 23.1, 17.4.

For (Z)-29: $^1$H NMR (–50 °C, 1:1 mixture of rotamers): δ [7.81 (d, J = 8 Hz), 7.79 (d, J = 7 Hz), 1:1, 2 H], [7.65 (d, J = 7 Hz), 7.59 (d, J = 7.5 Hz), 1:1, 2 H], 7.46-7.40 (m, 2 H), 7.38-7.31 (m, 2 H), [5.61 (qd, J = 7, 10.5 Hz), 5.47-5.42 (m), 1:1, 1 H], 5.39-5.30 (m, 1 H), [4.67 (quartet, J = 8 Hz), 4.60 (br s), 1 H], [4.45 (dd, J = 6.5, 10.5 Hz), 4.32 (br s), 1 H], 4.31 (br s, 1.5 H), 4.19 (t, J = 7 Hz, 0.5 H), [3.82 (br s), 3.54 (br s), 1:1, 1 H], [3.18 (d, J = 8 Hz), 3.05 (br s), 1:1, 1 H], [2.31 (br s), 1.86 (br s), 1:1, 1 H], 1.77 (d, J = 6.5 Hz, 3 H], 1.64-1.16 (m, 11 H). $^{13}$C[$^1$H] NMR (60 °C): δ 155.2, 144.5, 144.4, 141.5, 133.3, 127.5, 126.9, 125.3, 125.1, 119.9, 66.8, 57.0, 53.6, 47.7, 44.9, 41.3, 36.6, 35.0, 26.2, 23.8, 23.1, 12.8.

Figure 4.22 HPLC traces of a racemic 3.8:1 mixture of (E)-29 and (Z)-29 (left trace) and an enantiomerically enriched 1:1 mixture of (E)-29 (93% ee) and (Z)-29 (95% ee; right trace). HPLC conditions: hexanes-isopropanol = 98:2, 1 mL/min, 25 °C.
Kinetics of the gold(I)-catalyzed cyclization of rac-28. A suspension of [(S)-2](AuCl)₂ (8.1 mg, 5.0 × 10⁻³ mmol), AgClO₄ (2.1 mg, 1.0 × 10⁻² mmol), and rac-28 (84 mg, 0.20 mmol) in dioxane (0.34 mL) was stirred at 25 °C. Aliquots were removed periodically, filtered through a plug of silica gel with EtOAc, concentrated, and analyzed by HPLC. The response factors of rac-28, (E)-29, and (Z)-29 were determined by HPLC and NMR analysis of a stock sample of rac-28 and 29. Plots of ln{[(S)-28]ₜ/[(S)-28]₀} and ln{[(R)-28]ₜ/[(R)-28]₀} versus time were linear to >3 half lives with pseudo first-order rate constants of \( k_{\text{obs}} \) = 3.8 × 10⁻⁵ s⁻¹ for (S)-28 and \( k_{\text{obs}} \) = 3.5 × 10⁻⁵ s⁻¹ for (R)-28 (Figure 4.23).

![Figure 4.23](image_url)

Figure 4.23 Plots of ln{[(S)-28]ₜ/[(S)-28]₀} (□) and ln{[(R)-28]ₜ/[(R)-28]₀} (O) as a function of time for the reaction of rac-28 with a catalytic 1:2 mixture of [(S)-2](AuCl)₂ and AgClO₄ in dioxane at 25 °C, where \( k_{\text{obs}} \) [(S)-28] = 3.8 × 10⁻⁵ s⁻¹ and \( k_{\text{obs}} \) [(R)-28] = 3.5 × 10⁻⁵ s⁻¹.
Gold(I)-catalyzed cyclization of (R)-28. Treatment of (R)-28 (97% ee) with a catalytic mixture of [(S)-2](AuCl)₂ and AgClO₄ in dioxane at 25 °C for 48 h led to isolation of a 95.7:<0.2:1.9:2.4 mixture of (S,E)-29, (R,E)-29, (S,Z)-29, and (R,Z)-29 in 93% combined yield (Figure 4.24). Treatment of (R)-28 (97% ee) with a catalytic mixture of [(R)-2](AuCl)₂ and AgClO₄ led to isolation of a 3.8:2.1:<0.2:94.1 mixture of (S,E)-29, (R,E)-29, (S,Z)-29, and (R,Z)-29 in 95% combined yield (Figure 4.24). Note that in the former case, (S)-28 [(R)-28:(S)-28 = 98.5:1.5] represents the primary source of (S,Z)-29 and in the latter case, (S)-28 represents the primary source of (R,E)-29.

Figure 4.24 HPLC traces of a 95.7:<0.2:1.9:2.4 mixture of (S,E)-29, (R,E)-29, (S,Z)-29, and (R,Z)-29 isolated from cyclization of (R)-28 catalyzed by [(S)-2](AuCl)₂/AgClO₄ (left trace) and a 3.8:2.1:<0.2:94.1 mixture of (S,E)-29, (R,E)-29, (S,Z)-29, and (R,Z)-29 [(R)-2](AuCl)₂ isolated from cyclization of (R)-28 catalyzed by [(R)-2](AuCl)₂/AgClO₄ (right trace). HPLC conditions: hexanes-isopropanol = 98:2, 1 mL/min, 25 °C.
4.3.5 Stereochemical correlation studies

Determination of absolute configuration of 9. A sample of (S)-9 (62% ee) isolated from the cyclization of 8 catalyzed by a 1:2 mixture of [(S)-2](AuCl)2 and AgClO4 was converted to (S)-benzyl 2-vinylpyrrolidine-1-carboxylate [(S)-51] using a published procedure (Scheme 4.15).102c,108 An authentic sample of (S)-51 (89% ee) was synthesized in two steps from Z-L-prolinol employing published procedures.103a HPLC analysis [(hexanes–isopropanol = 95:5, 0.5 mL/min, 25 °C): tR(R) = 15.0 min, tR(S) = 16.3 min] established that both samples of (S)-51 possessed the same absolute configuration (Figure 4.25).

Scheme 4.15

For (S)-51:103a TLC (hexanes–EtOAc = 1:1): Rf = 0.71. 1H NMR: δ 7.77 (br s, 2 H), 7.34-7.22 (m, 5 H), 5.78-5.74 (m, 1 H), 5.14-4.97 (m, 4 H), 4.40 (br t, J = 7.2 Hz, 1 H), 3.48-3.44 (m, 2 H), 2.01-1.73 (m, 4 H). 13C[1H] NMR (1:1 mixture of rotamers): δ [154.9, 154.6], [138.4, 137.8], 136.9, [128.3, 128.1], [127.7, 127.6], [114.1, 113.9], 66.4, [59.3, 58.9], [46.5, 46.2], [31.8, 31.0], [23.3, 22.4]. Anal. calcd (found) for C14H17NO2: H, 7.41 (7.39); C, 72.70 (72.63).
Figure 4.25 HPLC traces of racemic (left trace) and enantiomerically enriched (S)-51 generated from (S)-9 (center trace, 62% ee) and an authentic sample of (S)-51 generated from Z-L-prolinol (89% ee) (right trace). HPLC conditions: hexanes–isopropanol = 95:5, 0.5 mL/min, 25 °C.

Correlation of (E)-29 and (Z)-29. A 1.04:1 mixture of (S,E)-29 (95% ee) and (S,Z)-29 (93% ee) was hydrogenated (H₂/Pd-C) using published procedure¹⁰²b to give 30 in 92% yield and 93% ee, indicating that the absolute configuration of both the diastereomers are same (S). rac-30 for HPLC analysis was prepared via hydrogenation (H₂/Pd-C) of a 3.84:1 mixture of (E)-29 and (Z)-29 obtained by the cyclization of rac-28 with a catalytic 1:1 mixture of AuCl[P(t-Bu)₂o-biphenyl] and AgClO₄ employing a published procedure.¹⁰²c

For 30: HPLC (hexanes-isopropanol = 98:2, 1 mL/min, 25 °C): tᵣ(R) = 17.1 min, tᵣ(S) = 19.2 min (Figure 4.26). TLC (hexanes–EtOAc = 1:1): Rₓ = 0.81. ¹H NMR (1:1 mixture of rotamers): δ 7.77 (d, J = 6.5 Hz, 2 H), 7.64-7.59 (m, 2 H), 7.39 (t, J = 7 Hz, 2 H),
7.31 (t, J = 7 Hz, 2 H), 4.62-4.22 (m, 3 H), 3.83-3.47 (m, 2 H), [2.93 (d, J = 11 Hz), 2.84 (d, J = 11.5 Hz), 1:1, 1 H], 2.02-1.85 (m, 2 H), 1.57-1.10 (m, 14 H), [0.93 (t, J = 7.5 Hz), 0.80 (t, J = 6.5 Hz), 1:1, 3 H]. $^{13}$C($^1$H) NMR (60 °C, 1:1 mixture of rotamers): δ 155.3, 144.4, 141.5, 127.5, 127.0, 124.9, 119.9, 66.5, 56.8, 47.8, [43.5, 41.3], 36.8, 34.9, [31.2, 29.8], 26.2, 23.9, 23.0, 18.7, 14.0. IR (neat, cm$^{-1}$): 2920, 2852, 1693, 1448, 1409, 1353, 1321, 1198, 1113, 1088, 971, 756, 735. Anal. calcd (found) for C$_{27}$H$_{33}$NO$_2$: H, 8.24 (8.17); C, 80.36 (80.31).

**Figure 4.26** HPLC traces of racemic (left trace) and enantiomerically enriched 30 (right trace). HPLC conditions: hexanes-isopropanol = 98:2, 1 mL/min, 25 °C.

(9H-Fluoren-9-yl)methyl 4-tosyl-2-vinylpiperazine-1-carboxylate (25).

Piperazine (R)-25 isolated from cyclization of 24 catalyzed by a 1:2 mixture of [(S)-2(AuCl)$_2$] and AgClO$_4$ was converted to 1,4-ditosyl-2-ethylpiperazine [(R)-52] in three steps using published procedures (Scheme 4.16).$^{102b, 108}$ Optical rotation of (R)-52 established the R-configuration [[α]$^D_{5}$ -7.5$^\circ$ (c 0.5, CHCl$_3$); lit. [α]$^D_{5}$ -6.2$^\circ$ (c 0.55, CHCl$_3$)].$^{109}$
Scheme 4. 16

For 52,^1^ 1H NMR: δ 7.61 (d, J = 8 Hz, 2 H), 7.54 (d, J = 8 Hz, 2 H), 7.31 (d, J = 8 Hz, 2 H), 7.21 (d, J = 8 Hz, 2 H), 3.87 (br s, 1 H), 3.75 (d, J = 13.5 Hz, 1 H), 3.58 (d, J = 11.5 Hz, 2 H), 3.20 (dt, J = 3, 13.5 Hz, 1 H), 2.44 (s, 3 H), 2.38 (s, 3 H), 2.27 (dd, J = 2.5, 12 Hz, 1 H), 2.20 (dd, J = 2, 12.5 Hz, 1 H), 1.74-1.68 (m, 1 H), 1.55-1.46 (m, 1 H), 0.82 (t, J = 7 Hz, 3 H). ^1^C{^1^H} NMR: δ 143.9, 143.4, 137.6, 132.3, 129.7, 129.6, 127.5, 126.9, 54.3, 47.6, 45.3, 39.9, 21.5, 21.4, 21.1, 10.6. HRMS calcd (found) for C_{20}H_{26}N_{2}NaO_{4}S_{2} (MNa\(^{+}\)): 445.1226 (445.1219).

4.3.6 Control experiments

1. **Gold/ligand only:** A suspension of [(S)-2](AuCl)\(_2\) (8.1 mg, 5.0 \times 10^{-3} mmol) and (E)-1g (98 mg, 0.20 mmol) in dioxane (0.34 mL) in a sealed tube was stirred at 25 °C for 48 h. TLC and ^1^H NMR analysis of the crude reaction mixture showed no detectable consumption of (E)-1g and no detectable formation of 3g.

2. **Silver only:** A suspension of AgClO\(_4\) (2.1 mg, 1.0 \times 10^{-2} mmol) and (E)-1g (98 mg, 0.20 mmol) in dioxane (0.34 mL) in a sealed tube was stirred at 25 °C for 48 h. TLC and ^1^H NMR analysis of the crude reaction mixture showed no detectable consumption of (E)-1g and no detectable formation of 3g.

3. **HOTf only:** A solution of HOTf (1.7 mL, 2.0 \times 10^{-2} mmol) and (E)-1g (98 mg, 0.20 mmol) in dioxane (0.34 mL) in a sealed tube was stirred at 25 °C for 48 h. TLC and ^1^H NMR analysis of the crude reaction mixture showed no detectable consumption of (E)-1g and no detectable formation of 3g.

4. **BF\(_3\)·Et\(_2\)O only:** A solution of BF\(_3\)·Et\(_2\)O (2.5 mL, 2.0 \times 10^{-2} mmol) and (E)-1g (98
mg, 0.20 mmol) in dioxane (0.34 mL) in a sealed tube was stirred at 25 °C for 48 h. TLC and ¹H NMR analysis of the crude reaction mixture showed no detectable consumption of (E)-1g and no detectable formation of 3g.
Chapter 5

Gold(I)-Catalyzed Intermolecular Regio- and Stereospecific Alkoxylation of Allylic Alcohols
5.1 Background

Alkyl allylic ethers are prevalent in many natural products and biologically active compounds, and are versatile substrates and building blocks in organic synthesis.\textsuperscript{110} As a result, considerable effort has been directed toward developing efficient and selective methods for the synthesis of allylic ethers.\textsuperscript{111} However, effective methods for their synthesis are limited; construction of the C–O bond via S\textsubscript{N}2 O-alkylation or O-allylation, as exemplified by the Williamson ether synthesis, is difficult due to the strong basicity of the alkoxide anion relative to its nucleophilicity.\textsuperscript{112} Therefore, displacement of alkyl halides by alkoxides is often prone to elimination reactions and hence loss of the stereogenic center.\textsuperscript{113}

Transition metal-catalyzed addition of an oxygen nucleophile to an (η\textsuperscript{3}-allyl)metal intermediate represents an attractive route towards the synthesis of alkyl allylic ethers with the potential to circumvent the problems associated with alkoxide basicity and to generate C–O bonds under mild conditions and with stereocontrol.\textsuperscript{2,7,114} As an example, Lee and coworkers demonstrated the Pd-catalyzed allylic etherification (alkoxylation) of allylic acetates with Zn(II) alkoxides at room temperature (eq 5.1). The procedure involved the use of sub-stoichiometric amounts of Zn(II)-alkoxide to promote the addition of aliphatic alcohols to a η\textsuperscript{3}-allylpalladium complex.\textsuperscript{115} Likewise, copper(I) alkoxides have also been used as nucleophiles for allylic alkoxylation, but the regioselectivity and scope of these transformations are limited and not fully resolved (eq 5.2).\textsuperscript{116} In addition to transition metal complexes of Pd and Rh, Ir-catalyzed allylic substitutions of allylic carbonates have been reported with lithium alkoxides as nucleophiles.\textsuperscript{117} Hartwig and coworkers have demonstrated the enantioselective intermolecular allylic alkoxylation of cinnamic esters with phenoxides to produce the branched allylic ether (eq 5.3).\textsuperscript{117a}
Allylic alkoxylation reactions that involve the in situ activation of the nucleophile, with reagents such as K$_3$PO$_4$ or triethylamine, instead of using metal alkoxides have also been reported.\textsuperscript{118} Hartwig and coworkers demonstrated the intermolecular addition of primary, secondary and tertiary alcohols to allylic acetates in the presence of excess alkali metal base K$_3$PO$_4$ (eq 5.4).\textsuperscript{118a} Trost and coworkers have reported the enantioselective allylic alkylation of alkyl borates with vinyl epoxides to form chiral nonracemic allylic ethers (eq 5.5).\textsuperscript{119} However, this transformation was restricted to primary alcohols as nucleophiles. Carreira and coworkers have reported an Ir-catalyzed method for the enantioselective synthesis of allylic ethers using silanoates as the hydroxide equivalent.\textsuperscript{120} However, the reaction required an extra step for the cleavage of the silyl enol ether.
Ongoing interest in the area of transition metal-catalyzed allylic alkoxylation has led to the use of unactivated alcohols as nucleophiles in the transition metal-catalyzed allylic alkoxylation. Pd\textsuperscript{121} and Ru-catalyzed\textsuperscript{122} reactions have been developed that allow the coupling of simple alcohols as the nucleophilic partners in the allylic alkoxylation reaction. As an example, Chan and coworkers developed a Pd-catalyzed asymmetric allylic alkoxylation with primary and secondary alcohols as nucleophiles involving a phosphinamidite thioether ligand on a ferrocene motif (eq 5.6).\textsuperscript{121b} However, this transformation was restructured to the use of 1,3-diphenylpropenyl acetate as the electrophilic partner.
Although a number of these transformations display high regio- and/or stereoselectivity, direct substitutions of unactivated allylic alcohols with neutral oxygen nucleophiles still remain scarce. Carreira and coworkers have recently reported an Ir-catalyzed direct enantioselective substitution of branched allylic alcohols to afford the branched allylic ethers (eq 5.7). However, the reaction scope was restricted to branched allylic alcohols, used \textit{m}-chlorobenzoic acid for \textit{in situ} activation of the underivatized allylic alcohol, and most of the substrates required prolonged reaction time.

\textbf{Transition metal-catalyzed intermolecular hydroalkoxylation of allenes with alcohols as a route to alkyl allylic ethers has also been reported.} Pd-catalyzed intermolecular hydroalkoxylation of allenes has been realized with alcohols to form alkyl allylic ethers (eq 5.8). However, the transformation required elevated reaction temperature and was effective only in the case of mono-substituted aryl allenes. Subsequently, Widenhoefer and coworkers reported a more general Au(I)-catalyzed protocol for the synthesis of alkyl allylic ethers with substituted allenes that was effective at room temperature (eq 5.9). This transformation leads to the formation of the less-substituted regioisomer by attack of the alcohol nucleophile at the less-substituted double bond of the allene.
Numerous routes toward the synthesis of alkyl allylic ethers have been realized, particularly the allylic substitutions of derivatized allylic alcohols. Although a significant number of these transformations display high levels of regio- and/or stereoselectivity, regiospecific allylic substitution remains problematic, presumably due to the intermediacy of π-allyl intermediates or allylic carbocations in these transformations. We have developed a gold(I)-catalyzed intermolecular amination of allylic alcohols with cyclic ureas and related nucleophiles (Chapter 2). This transformation displayed a high level of regiospecificity and syn-stereoselectivity for γ-unsusubstituted and γ-methyl-substituted allylic alcohols. Our continued interest in the area of gold(I)-catalyzed regiospecific allylic substitution led us to develop an intermolecular allylic alkoxylation by coupling an underivatized allylic alcohol with a second alcohol nucleophile in a highly γ-regiospecific and syn-stereospecific fashion employing gold(I) N-heterocyclic carbene complexes as catalysts. This chapter describes my contribution to the development of the gold(I)-catalyzed regio- and stereospecific alkoxylation of underivatized allylic alcohols. Further attempts towards an asymmetric version of this transformation are also discussed.
5.2 Results and discussion

5.2.1 Optimization

In an initial effort, 4-methylbenzyl alcohol and trans-2-buten-1-ol were subjected to the catalytic reaction conditions previously employed to good effect for the gold(I)-catalyzed intermolecular amination of allylic alcohols (Chapter 2). To our great excitement, treatment of 4-methylbenzyl alcohol and trans-2-buten-1-ol with a catalytic 1:1 mixture of AuCl[P(t-Bu)2(o-biphenyl)] [(2)AuCl] and AgSbF₆ in dioxane at room temperature after 48 h led to 53% conversion to form the γ-addition product 3 in preference over the α-addition product 4 in a 96:4 ratio (Scheme 5.1). Replacement of the silver salt to AgClO₄ led to a significant enhancement in rate, as the reaction reached almost quantitative conversion (98%) in 25 h at room temperature with a little lower 3:4 ratio (92:8, Scheme 5.1).

Scheme 5.1

The limits of the catalyst system employed to good effect for the synthesis of 3 proved unsuitable for the intermolecular alkoxylation of allylic alcohols possessing substitution at both the α and γ positions. As an example, treatment of trans-4-hexen-3-ol and 4-methylbenzylalcohol (4 equiv) with a catalytic 1:1 mixture of (2)AuCl and AgClO₄ in dioxane at room temperature for 24 h led to an 85% conversion to form the γ-addition product 5 and the α-addition product 6 in a 64:36 ratio (81% isolated yield, γ/α = 67:33, Table 5.1, entry 1). In an effort to improve the regioselectivity of this
transformation, the yield and regioselectivity of the transformation was screened as a function of supporting ligand, silver salt, and solvent. The gold(I)-catalyzed allylic alkoxylation was sensitive to the nature of the ligand, and the N-heterocyclic carbene (NHC) complex in (1)AuCl \[1 = 1,3\text{-bis}(2,6\text{-diisopropylphenyl}\text{imidazol-2-ylidine}] gave higher conversion (99\%) in 24 h and a better regioselectivity than did P(t-Bu)\(\alpha\)-biphenyl (75:25, Table 5.1, entries 2-4). Among the different solvents screened in presence of a catalytic mixture of (1)AuCl and AgClO\(_4\), methylene chloride showed reactivity and selectivity comparable to dioxane within a reaction time of 22 h (Table 5.1, entries 5-9). In addition, periodic GC analysis of the reaction of trans-4-hexen-3-ol and 4-methylbenzylalcohol (4 equiv) catalyzed by a 1:1 mixture of (1)AuCl and AgClO\(_4\) in methylene chloride at room temperature revealed formation of a 92:8 ratio of 5:6 after 4 h with 82\% conversion. After 5 h, 87\% conversion had been realized with a 5:6 ratio of 87:13 (Table 5.1, entry 10). This behavior was indicative of secondary reaction pathway that led to formation of the \(\alpha\)-substitution product 6. Chloroform proved to be a slightly less selective solvent than methylene chloride under analogous reaction conditions (Table 5.1, entry 11).
Table 5.1 Effect of ligand, counterion and reaction conditions on gold(I)-catalyzed intermolecular allylic alkoxylation of (E)-4-hexen-3-ol with 4-methylbenzyl alcohol.

<table>
<thead>
<tr>
<th>entry</th>
<th>L</th>
<th>solvent</th>
<th>X</th>
<th>time (h)</th>
<th>conv% (yield%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>5:6&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>dioxane</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>24</td>
<td>85 (81)</td>
<td>64:36 (67:33)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>dioxane</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>24</td>
<td>99 (90)</td>
<td>75:25 (75:25)</td>
</tr>
<tr>
<td>3</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>dioxane</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>24</td>
<td>100 (89)</td>
<td>55:45 (55:45)</td>
</tr>
<tr>
<td>4</td>
<td>P(t-Bu)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>dioxane</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>24</td>
<td>90 (-)</td>
<td>62:38 (-)</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>toluene</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>24</td>
<td>100 (-)</td>
<td>69:31 (-)</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>m-xylene</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>24</td>
<td>99 (-)</td>
<td>73:27 (-)</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>24</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>24</td>
<td>99 (-)</td>
<td>71:29 (-)</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>22</td>
<td>99 (-)</td>
<td>75:25 (-)</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>5</td>
<td>87 (-)</td>
<td>87:13 (-)</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>5</td>
<td>91 (-)</td>
<td>85:15 (-)</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>OTf</td>
<td>4</td>
<td>85 (-)</td>
<td>86:14 (-)</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>OTs</td>
<td>24</td>
<td>47 (-)</td>
<td>92:8 (-)</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>PF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>4</td>
<td>76 (-)</td>
<td>79:21 (-)</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4</td>
<td>82 (76)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>92:8 (&gt;95.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conversion determined by GC analysis (yield of isolated mixture of 5 and 6).<sup>b</sup>Ratio of 5:6 determined by GC analysis (ratio of isolated mixture of 5 and 6 determined by GC analysis).<sup>c</sup>Isolated yield of pure 5 with >95% purity.

Further evidence of an indirect reaction pathway for formation of the α-substitution product was obtained when different silver salts were screened in the gold(I)-catalyzed allylic alkoxylation reaction of trans-4-hexen-3-ol with 4-
methylbenzylalcohol (Table 5.1, entries 12-14). Although AgOTf, AgOTs, and AgPF$_6$ proved to be less effective counterions in comparison to AgClO$_4$ in this gold(I)-catalyzed allylic alkoxylation, periodic GC analysis of the reaction mixture employing AgOTs as the cocatalyst revealed 10% conversion after 4 h with >99:1 selectivity of the γ-substitution product 5. With increasing reaction time, the concentration of 6 increased gradually with increasing conversion and, after 24 h, 47% conversion was achieved to form a 92:8 ratio of regioisomers 5 and 6. Therefore, in a preparative-scale experiment, treatment of trans-4-hexen-3-ol and 4-methylbenzyl alcohol (4 equiv) with a catalytic 1:1 mixture of (1)AuCl and AgClO$_4$ in methylene chloride at room temperature after 4 h gave an 82% conversion with a 92:8 ratio of 5:6. Isolation of the crude reaction mixture provided the γ-regioisomer 5 in 76% yield in >95:5 γ/α ratio (Table 5.1, entry 15).

5.2.2 Scope of intermolecular allylic etherification

The scope of intermolecular alkoxylation of allylic alcohols was evaluated as a function of the substitution and C=C geometry of the allylic alcohol and the structure of the alcohol nucleophile (Table 5.2). In the case of γ-methyl substituted allylic alcohols and γ-unsubstituted allylic alcohols, gold(I)-catalyzed allylic alkoxylation occurred with predominant formation of the γ-addition product. As an example, gold(I)-catalyzed reaction of 4-methylbenzyl alcohol with trans-2-buten-1-ol gave a 94:6 mixture of regioisomers after 4 h at room temperature in 96% overall conversion, from which allylic ether 3 was isolated as a single regioisomer in 76% yield (Table 5.2, entry 1). Likewise, reaction of 4-methylbenzyl alcohol with 3-buten-2-ol catalyzed by a 1:1 mixture of (1)AuCl and AgClO$_4$ in methylene chloride at room temperature after 12 h gave an 89:11 ratio of γ/α regioisomers in 98% conversion from which 6 was isolated as a single regioisomer in 85% yield (Table 5.2, entry 2). Similarly, gold-catalyzed alkoxylation of γ-ethyl and γ-n-propyl allylic alcohols with 4-methylbenzyl alcohol led to selective
formation of the $\gamma$-substitution products (Table 5.2, entries 3-4). Benzyl alcohol proved to be a more effective nucleophile in $\gamma$-selective allylic alkoxylation, as reaction of benzyl alcohol with \textit{trans}-2-buten-1-ol or \textit{trans}-2-penten-1-ol gave the $\gamma$-substitution product exclusively in high isolated yields, 95% and 81% respectively (Table 5.2, entries 5-6). 2-Phenyl ethanol was also an effective nucleophile for the allylic alkoxylation of \textit{trans}-2-penten-1-ol to provide a 93:7 mixture of regioisomers, determined by GC analysis of the crude reaction mixture at 11 h for 88% conversion, from which (2-(pent-1-en-3-yl oxy)ethyl)benzene (11) was isolated in 87% yield (Table 5.2, entry 7). Gold(I)-catalyzed reaction of 3-penten-2-ol with 4-methylbenzyl alcohol progressed efficiently to give the allylic ether 12 in 100% conversion by 7 h at room temperature that was isolated in 96% yield (Table 5.2, entry 8).

Gold(I)-catalyzed allylic alkoxylation of a chiral racemic secondary alcohol, specifically the mono-benzyl protected \textit{trans}-2-pentene-1,4-diol, 13 with \textit{n}-butanol for 24 h at 40 °C gave an 84:16 mixture of $\gamma$/\textit{\alpha}-substitution products in the crude reaction mixture that upon purification gave 80% isolated yield of allylic ether 14 (Table 5.2, entry 9). Such 1,2-dioxygenated compounds are important synthetic precursors to different functionalized molecules and intermediates to natural products.\textsuperscript{127} Gold-catalyzed reaction of \textit{n}-butanol with the mono-benzoyl protected \textit{trans}-2-pentene-1,4-diol 16 was slower than was reaction with 13, providing 53% isolated yield of the allylic ether 17 as a single regioisomer (Table 5.2, entry 11). Methanol was also an effective nucleophile for the allylic alkoxylation and reaction of methanol with allylic alcohol 13 led to formation of an 84:16 mixture of $\gamma$/\textit{\alpha} regioisomers that upon isolation gave 15 in 77% yield after 7 h at 40 °C (Table 5.2, entry 10).

Gold(I)-catalyzed alkoxylation of underivatized allylic alcohols was largely insensitive to the configuration of the C=C bond of the allylic alcohol. As an example,
reaction of \( n \)-butanol with \((E)-18\) catalyzed by a 1:1 mixture of \((2)AuCl\) and \(AgClO_4\) in dioxane at 60 °C led to isolation of the \( \gamma \)-regioisomer 19 after 24 h in 52% yield (Table 5.2, entry 12). Likewise, reaction of \( n \)-butanol with \((Z)-18\) under identical reaction conditions gave 19 in 57% yield (Table 5.2, entry 13). The 1,1-disubstituted allylic alcohol, 2-methyl-3-penten-2-ol also underwent efficient gold-catalyzed allylic alkoxylation to give a 100% conversion of the allylic ether 20 as a single regioisomer (Table 5.2, entry 14). Isolation of the crude reaction mixture provided allylic ether 20 in 88% yield.

Notably, secondary alcohols also underwent gold(I)-catalyzed allylic alkoxylation. As an example, reaction of 1-phenyl-1-propanol with \( trans \)-2-penten-1-ol catalyzed by a 1:1 mixture of \((1)AuCl\) and \(AgClO_4\) in methylene chloride at room temperature for 18 h gave 75% conversion with a 92:8 \( \gamma/\alpha \) ratio. Purification of the crude reaction mixture gave 53% yield of the allylic ether 21 as a 2:1 mixture of diastereomers (Table 5.2, entry 15). In addition, cyclohexanol underwent gold(I)-catalyzed allylic alkoxylation with \( trans \)-2-penten-1-ol at 40 °C in 21 h to provide a 90:10 mixture of \( \gamma/\alpha \) regioisomers in 87% conversion that upon isolation gave allylic ether 22 in 76% yield (Table 5.2, entry 16).
Table 5.2 Intermolecular alkoxylation of allylic alcohols with alcohol nucleophiles (ROH, 4 equiv) catalyzed by a mixture of (1)AuCl (5 mol %) and AgClO₄ (5 mol %) in methylene chloride (0.6 M) at 23 ºC.

<table>
<thead>
<tr>
<th>entry</th>
<th>R of ROH</th>
<th>allylic alcohol</th>
<th>product</th>
<th>time (h)</th>
<th>conv.% (yield)</th>
<th>γ/α ratio</th>
<th>E/Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂⁻4-C₆H₄Me</td>
<td>Me—CH=CH—OH</td>
<td>3</td>
<td>4</td>
<td>96 (76)</td>
<td>94:6</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>CH₂⁻4-C₆H₄Me</td>
<td>Me—CH=CH—OH</td>
<td>4</td>
<td>12</td>
<td>98 (85)</td>
<td>89:11</td>
<td>5.3:1</td>
</tr>
<tr>
<td>3</td>
<td>CH₂⁻4-C₆H₄Me</td>
<td>Me—CH=CH—OH</td>
<td>7</td>
<td>9</td>
<td>95 (83)</td>
<td>92:8</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>CH₂⁻4-C₆H₄Me</td>
<td>Me—CH=CH—OH</td>
<td>8</td>
<td>18</td>
<td>82 (79)</td>
<td>92:8</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Ph</td>
<td>Me—CH=CH—OH</td>
<td>9</td>
<td>5</td>
<td>98 (95)</td>
<td>&gt;99:1</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Ph</td>
<td>Me—CH=CH—OH</td>
<td>10</td>
<td>14</td>
<td>83 (81)</td>
<td>&gt;99:1</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>CH₂CH₂Ph</td>
<td>Me—CH=CH—OH</td>
<td>11</td>
<td>11</td>
<td>88 (87)</td>
<td>93:7</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>CH₂⁻4-C₆H₄Me</td>
<td>Me—CH=CH—OH</td>
<td>12</td>
<td>7</td>
<td>100 (96)</td>
<td>—</td>
<td>9:1</td>
</tr>
<tr>
<td>9</td>
<td>n-Bu</td>
<td>Me—CH=CH—OH</td>
<td>13</td>
<td>24</td>
<td>ND (80)</td>
<td>84:16</td>
<td>8.3:1</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>Me—CH=CH—OH</td>
<td>14</td>
<td>7</td>
<td>ND (77)</td>
<td>84:16</td>
<td>10.3:1</td>
</tr>
<tr>
<td>11</td>
<td>n-Bu</td>
<td>Me—CH=CH—OH</td>
<td>15</td>
<td>24</td>
<td>ND (53)</td>
<td>94:6</td>
<td>13.4:1</td>
</tr>
</tbody>
</table>

*Conversion of crude reaction mixture determined by GC analysis (isolated yield γ-regioisomer in >95% purity). ND = not determined. Ratio determined by GC analysis of the crude reaction mixture. Determined by ¹H NMR analysis of the purified reaction mixture. Reaction temperature is 40 ºC. Reaction performed in neat n-BuOH (0.5 M) at 50 ºC.
5.2.3 Chirality transfer

This efficient $\gamma$-selective pathway for different $\gamma$-substituted allylic alcohols in the gold(I)-catalyzed allylic alkoxylation indicated a potential for 1,3-chirality transfer with $\gamma$-substituted chiral secondary allylic alcohol that would lead to the formation of nonracemic chiral allylic ethers. Therefore, two enantiomerically enriched allylic alcohols were synthesized and subjected to gold(I)-catalyzed allylic alkoxylation. In one experiment, gold(I)-catalyzed reaction of (R,E)-13 (98% ee) with $n$-butanol at 40 °C after 24 h led to formation of a 84:16 mixture of regioisomers 14 and 23 that upon isolation gave a 8:1 mixture of (R,E)-14 with 97% ee and (S,Z)-14 with 87% ee in 81% combined yield. In addition, allylic ether 23 was isolated as a 7.2:1 mixture of (R,E)-23 with 97% ee and (S,Z)-23 with 87% ee in 15% overall yield. The absolute configuration of (R,E)-14 and (S,Z)-14 were determined by HPLC correlation employing independent synthesis of

<table>
<thead>
<tr>
<th>entry</th>
<th>R of ROH</th>
<th>allylic alcohol</th>
<th>product</th>
<th>time (h)</th>
<th>convn.%</th>
<th>(yield%)</th>
<th>$\gamma/\alpha$ ratio$^b$</th>
<th>E/Z ratio$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12$^d$</td>
<td>n-Bu</td>
<td>BzO-(\text{--})OH</td>
<td>19</td>
<td>24</td>
<td>ND (52)</td>
<td>&gt;99:1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13$^d$</td>
<td>n-Bu</td>
<td>BzO-(\text{--})OH</td>
<td>19</td>
<td>24</td>
<td>ND (57)</td>
<td>&gt;99:1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>CH$_2$-4-C$_6$H$_4$Me</td>
<td>Me-(\text{--})OH</td>
<td>20</td>
<td>1</td>
<td>100 (88)</td>
<td>&gt;99:1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>CH(Ph)Et</td>
<td>Et-(\text{--})OH</td>
<td>21</td>
<td>18</td>
<td>75 (53$^a$)</td>
<td>92.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>16$^f$</td>
<td>Cy</td>
<td>Et-(\text{--})OH</td>
<td>22</td>
<td>21</td>
<td>87 (76)</td>
<td>90:10</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$^a$Conversion of crude reaction mixture determined by GC analysis (isolated yield of $\gamma$-regioisomer in >95% purity). ND = not determined. $^b$Ratio determined by GC analysis of the crude reaction mixture. $^c$Determined by $^1$H NMR analysis of the purified reaction mixture. $^d$(2)AuCl (5 mol %) used instead of (1)AuCl (5 mol %) and reaction performed in dioxane at 60 °C. $^e$Diastereomeric ratio = 2:4:1. $^f$Reaction temperature is 40 °C.
(R,E)-14 and (R,Z)-14 (Section 5.3.4). Similarly, the absolute configuration of (R,E)-23 and (S,Z)-23 were determined by HPLC correlation employing independent synthesis of (R,E)-23 and (R,Z)-23 (Section 5.3.4).

The stereochemical outcome of the allylic alkoxylation of (R,E)-13 with n-butanol established the net syn-addition of the nucleophile to the alkene π-face with respect to the departing hydroxyl group. In addition, the formation of the α-substitution product 23 through indirect reaction pathways, such as the gold(I)-catalyzed allylic alkoxylation of (R,E)-14 with n-butanol also occurs through a net syn-displacement of the leaving group by the nucleophile.

Scheme 5. 2

In a separate experiment, gold(I)-catalyzed reaction of (R,E)-16 with n-butanol at 50 °C under neat conditions after 24 h led to isolation of (R,E)-17 in 57% yield and >90% ee. The determination of enantiomeric purity was complicated due to coelution of the two enantiomers in the HPLC.
5.2.4 Acid-catalyzed allylic alkoxylation

The stereoselectivity in the gold(I)-catalyzed allylic alkoxylation of \((R)-13\) with \(n\)-butanol was consistent with the net \textit{syn}-addition of the nucleophile with respect to the departing hydroxyl group. This stereochemical outcome is characteristic of a concerted \(S_N2'\) substitution reaction\(^{68}\) involving the \(\sigma\)-activation of the hydroxyl group by gold(I) followed by the concerted or stepwise attack of the nucleophile at the \(\gamma\)-carbon followed by displacement of the hydroxyl group. Toste and coworkers have recently demonstrated that bis(gold) phosphine complexes are sufficiently Lewis acidic to acidify the hydroxyl group of an alcohol.\(^{104}\) For this reason, we explored the potential of Bronsted and Lewis acid catalyzed pathways for the allylic alkoxylation. However, in our attempt to observe the stereochemical outcome and the reactivity of the allylic alkoxylation in presence of Bronsted acid, such as triflic acid, revealed no transfer of chirality from the starting enantioenriched alcohol \((R)-13\) to the products. Treatment of \((R)-13\) with \(n\)-butanol in presence of catalytic triflic acid (5 mol \%) in methylene chloride at 40 °C after 24 h gave a 36:64 mixture of the \(\gamma\)- (14) and \(\alpha\)-substitution (23) products respectively, preferring the \(\alpha\)-substitution product (eq 5.11). Periodic analysis of this reaction by GC revealed formation of both the products from beginning: at an initial conversion of 29\% at 5 h, GC analysis of the reaction showed the presence of allylic ether 14 and 23 in a 40:60 ratio. Purification of the reaction mixture after 24 h led to isolation of a 5.8:1 mixture of \((E)-14\) with \(\leq 10\%\) ee and \((Z)-14\) with no ee in 22\% combined yield and also \((E)-23\) with 8\% ee in 40\% yield.
Furthermore, treatment of (R)-13 with n-butanol in presence of catalytic BF$_3$·OEt$_2$ (5 mol %) in methylene chloride at 40 ºC after 24 h gave a 31:69 mixture of the γ- (14) and α-substitution (23) products respectively, also preferring the α-substitution product (eq 5.12). Purification of the reaction mixture after 24 h led to isolation of a >50:1 mixture of (E)-14 with ≤14% ee and (Z)-14 with no ee in 22% combined yield. The E/Z ratio was determined from the HPLC analysis of the purified sample of allylic ether 14. In addition, the α-substitution product 23 was isolated in 26% yield with no ee as a single diastereomer.

All these results indicate that the allylic alkoxylation under acid-catalyzed conditions is non-regiospecific, less efficient and the loss of stereoselectivity is probably due to the formation of allylic carbocation intermediates.

5.2.5 Evaluation of primary and secondary reaction pathways

The changing γ/α ratio evidenced in the gold(I)-catalyzed allylic alkoxylation reaction with time pointed to the presence of primary and secondary reaction pathways.
To more firmly delineate this behavior, a number of additional experiments were performed. In one experiment, allylic ether 12 obtained from gold(I)-catalyzed allylic alkoxylation of trans-3-penten-2-ol and 4-methylbenzyl alcohol was subjected to the catalytic reaction conditions with a different nucleophile. Treatment of compound 12 with excess benzyl alcohol (4 equiv) in presence of a catalytic 1:1 mixture of (1)AuCl and AgClO₄ in methylene chloride after 24 h gave a 63% conversion to the allylic ether 24 formed by nucleophilic addition of benzyl alcohol to 12. Hence, this depicts that the α-substitution product formed later in the reaction can form through indirect reaction pathways such as gold(I)-catalyzed allylic substitution of the γ-product instead of direct gold(I)-catalyzed alkoxylation of allylic alcohol.

In a separate experiment, a 1:4 mixture of trans-4-hexen-3-ol and 4-methylbenzyl alcohol that contained a catalytic amount of (1)AuCl and AgClO₄ (5 mol%) in CD₂Cl₂ at room temperature was monitored periodically by ¹H NMR. ¹H NMR analysis of the reaction mixture at 40% conversion revealed only formation of the γ-alkoxylation product 5 (eq 5.14). Monitoring this reaction with time revealed that α-alkoxylation product 6 gradually starts forming later in the reaction and at 51% conversion, 6 was formed ~1% that accounts for a 97:3 γ/α ratio (Figure 5.1). In addition, ¹H NMR analysis of the reaction with prolonged time demonstrated that the secondary reaction pathway leading to the α-alkoxylation product 6 by gold(I)-catalyzed alkoxylation of γ-
alkoxylation product 5 with 4-methylbenzyl alcohol continued till a 50:50 mixture of γ/α alkoxylation product was reached.

![Reaction Equation](image)

**Figure 5.1** Concentration versus time plot for the reaction of trans-4-hexen-3-ol (0.60 M; ◇) with 4-methylbenzylalcohol (2.4 M) catalyzed by a 1:1 mixture of (1)AuCl and AgClO₄ (5 mol %) in CD₂Cl₂ at room temperature to form 5 (□) and 6 (△).

### 5.2.6 Mechanism

The stereoselectivity in the gold(I)-catalyzed allylic alkoxylation of (R)-13 with n-butanol was consistent with the net *syn*-addition of the nucleophile with respect to the
departing hydroxyl group. This stereochemical outcome is characteristic of a concerted
\(S_N2'\) substitution reaction\(^{68}\) involving the \(\sigma\)-activation of the hydroxyl group by gold(I).
However, loss of stereospecificity in the triflic acid or \(\text{BF}_3\cdot\text{OEt}_2\) catalyzed allylic
alkoxylation rule out a pathway involving \(\sigma\)-activation by gold. An alternative
mechanism in the gold(I)-catalyzed allylic alkoxylation would involve an initial \(\pi\)-
complexation of gold to the allylic C=C bond followed by an \emph{anti}-addition of the
nucleophile and \emph{anti}-elimination of the hydroxyl group, perhaps facilitated by an
intramolecular O–H⋯O hydrogen bond. This mechanism accounts for the
stereochemical outcome of the gold(I)-catalyzed allylic alkoxylation.\(^{55}\) Also noteworthy
is that Maseras and coworkers have proposed a \(\pi\)-activation of allylic C=C bond in a
gold(I)-catalyzed isomerization of allylic ethers with alcohols on the basis of DFT
calculations.\(^{69}\)

Therefore, an initial \(\pi\)-activation of C=C bond of \((R)-13\) forms the gold(I) \(\pi\)-alkene
complexes \(si-I\) and \(re-I\) (Scheme 5.3). Outersphere addition of the nucleophile to the
alkene \(\pi\)-face \emph{anti}- with respect to gold(I), also facilitated by an O–H⋯O hydrogen bond
as shown in \(si-II\) and \(re-II\), leads to the formation of cyclic, hydrogen-bonded gold alkyl
intermediates \((S,R,R)-II\) and \((R,S,R)-II\), respectively. \emph{Anti}-elimination of a hydrogen-
bonded water molecule and the displacement of gold from \((S,R,R)-II\) provides the allylic
ether \((R,E)-14\). A similar pathway from \((R,S,R)-II\) leads to the other minor stereoisomer
\((S,Z)-14\). Formation of \((R,E)-14\) in preference over \((S,Z)-14\) is possibly due to the
unfavorable steric interaction between the gold moiety and the C1 methyl in a \emph{cis}
orientation in the transition state leading to \((R,S,R)-II\) that is absent in the transition state
forming \((S,R,R)-II\).
The stereochemical outcome in the gold(I)-catalyzed allylic alkoxylation of (R,E)-14 and (S,Z)-14 with \(n\)-butanol to form the \(\alpha\)-addition products (R,E)-23 and (S,Z)-23 is also consistent with the net \(\text{syn}\)-addition of the nucleophile with respect to the departing alkoxy group. Therefore, a similar initial \(\pi\)-activation of the allylic ether 14 followed by a nucleophilic addition/O\(n\)-Bu elimination facilitated by an intramolecular hydrogen-bonding would lead to the allylic ethers (R,E)-23 and (S,Z)-23.
5.2.7 Enantioselective allylic alkoxylation

The high regiospecificity and stereoselectivity in the gold(I)-catalyzed allylic alkoxylation pointed towards the potential for an enantioselective dehydrative alkoxylation of underivatized allylic alcohols. Initial results in this transformation are summarized in Table 5.3. As a starting point, 4-methylbenzyl alcohol (4 equiv) and trans-2-buten-1-ol were subjected to the conditions optimized for the gold(I)-catalyzed enantioselective intramolecular amination of allylic alcohols with carbamates (Table 5.3, entry 1). Treatment of a 1:4 mixture of trans-2-buten-1-ol and 4-methylbenzyl alcohol with a catalytic 1:2 mixture of [(S)-25](AuCl)₂ and AgClO₄ for 44 h at room temperature led to the isolation of allylic ether 3 in 68% yield and 37% ee. Reactions with other nucleophiles such as benzyl alcohol and 2-phenyl ethanol with allylic alcohols such as trans-2-buten-1-ol and trans-2-penten-1-ol in presence of catalytic 1:2 mixture of [(S)-25](AuCl)₂ and AgClO₄ also gave the corresponding γ-regioisomer in moderate yield and a similar enantioselectivity as observed for 3 (Table 5.3, entries 2-3).

Therefore, manipulation of the reaction conditions was attempted. To evaluate the effect of nucleophile concentration, trans-2-penten-1-ol was subjected to gold(I)-catalyzed allylic alkoxylation with both 5 equivalent and 1 equivalent of 4-methylbenzyl alcohol under otherwise identical conditions employing a catalytic 1:2 mixture of [(S)-25](AuCl)₂ (2.5 mol %) and AgClO₄ (5 mol %) in dioxane at room temperature. Conditions of excess 4-methylbenzyl alcohol led to 78% conversion in 24 h with 70% isolated yield and 41% ee, while conditions of equimolar 4-methylbenzyl alcohol to trans-2-penten-1-ol led to only 25% conversion and 17% isolated yield after 48 h, however with 49% ee (Table 5.3, entries 4-5). Changing the chiral supporting ligand from (S)-di-tert-butylmethoxy biphep ligand, [(S)-25](AuCl)₂ to an (S)-di-tert-butylmethoxy segphos ligand, [(S)-26](AuCl)₂ showed an improved reaction rate to give
26% conversion and 23% isolated yield of allylic ether 7 in 24 h and an increase in enantioselectivity to 54% (Table 5.3, entry 6).

**Table 5.3** Enantioselective intermolecular allylic alkoxylation catalyzed by a 1:2 mixture of [(S)-25](AuCl)$_2$ (2.5 mol %) and AgClO$_4$ (5 mol %) in dioxane at 23 °C

<table>
<thead>
<tr>
<th>entry</th>
<th>R of ROH equiv (ROH) allylic alcohol</th>
<th>product</th>
<th>time (h)</th>
<th>convn% (yield%)$^a$</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$-4-C$_6$H$_4$Me 5 Me-(\equiv)OHOH</td>
<td>RO 3 Me</td>
<td>44</td>
<td>97 (68)</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Ph 5 Me-(\equiv)OHOH</td>
<td>RO 9 Et</td>
<td>24</td>
<td>72 (43)</td>
<td>32</td>
</tr>
<tr>
<td>3$^c$</td>
<td>CH$_2$CH$_2$Ph 4 Et-(\equiv)OHOH</td>
<td>RO 11 Et</td>
<td>24</td>
<td>84 (74)</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$-4-C$_6$H$_4$Me 5</td>
<td>RO 7</td>
<td>24</td>
<td>78 (70)</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$-4-C$_6$H$_4$Me 1</td>
<td>RO 7</td>
<td>48</td>
<td>25 (17)</td>
<td>49</td>
</tr>
<tr>
<td>6$^d$</td>
<td>CH$_2$-4-C$_6$H$_4$Me 1</td>
<td>RO 7</td>
<td>24</td>
<td>26 (23)</td>
<td>54</td>
</tr>
</tbody>
</table>

$^a$Conversion of crude reaction mixture determined by GC analysis (isolated yield of \(\gamma\)-regiosomer in >95% purity). $^b$Determined by HPLC analysis on chiral support. $^c$Methylene chloride used as solvent instead of dioxane. $^d$(S)-26[(AuCl)$_2$ used instead of [(S)-25](AuCl)$_2$.

5.2.8 Summary

In summary, we have developed the first \(\gamma\)-regioselective and syn-stereoselective intermolecular allylic alkoxylation that works for a wide range of allylic alcohols and alcohol nucleophiles in high yields and under mild conditions. With chiral nonracemic secondary alcohols, such as a monobenzyl protected trans-2-pentene-1,4-diol, gold(I)-
catalyzed allylic alkoxylation occurred with high regiospecificity in good yield (81%) and with excellent enantiospecificity (99% es). This effective 1,3-chirality transfer in the latter observation enabled to establish the net syn-addition of the nucleophile with respect to the departing hydroxyl group. Initial results on enantioselective allylic alkoxylation are encouraging and further attempts to develop this regiospecific allylic alkoxylation in an asymmetric fashion to be explored.

5.3 Experimental section

5.3.1 General methods

Catalytic reactions were performed in sealed tubes under an atmosphere of dry nitrogen unless noted otherwise. Room temperature is 23 °C. NMR spectra were obtained on a Varian spectrometer operating at 400 MHz for 1H NMR and 100 MHz for 13C NMR in CDCl₃ unless noted otherwise. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. Gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a 25 m polydimethylsiloxane capillary column. Chiral HPLC was performed on a Shimadzu chromatograph equipped with a 0.46 cm X 25 cm Chiralpak AD-H column or a Lux 5u Cellulose-1 column. Flash column chromatography was performed employing 200-400 mesh silica gel (EM). Thin layer chromatography (TLC) was performed on silica gel 60 F254.

Gold complexes (1)AuCl [1 = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine], (2)AuCl [2 = P(t-Bu)₂-o-biphenyl], trans-2-buten-1-ol, trans-2-penten-1-ol, trans-2-hexen-1-ol, 3-buten-2-ol, 3-penten-2-ol, 2-methyl-3-penten-2-ol, 4-methylbenzyl alcohol, benzyl alcohol, n-butanol, 1-phenyl-1-propanol, cyclohexanol, NaH, LiAlH₄, Lindlar catalyst, n-butyl bromide, benzyl bromide, tetrabutylammonium iodide, tetrabutylammonium fluoride (1 M solution in THF), benzoyl chloride, methylnitrogen bromide (3 M solution in THF), trans-ethyl crotonate, (R)-glycidyl benzyl ether, lithium acetylide
ethylendiamine complex, potassium tert-butoxide (Aldrich), anhydrous 1,4-dioxane (Acros) were used as received. Anhydrous methylene chloride was obtained from PureSolv multiple dispensing system. Other ligands and silver salts were purchased from major suppliers and used as received. 4-(tert-butyldimethylsilyloxy)pent-2-yn-1-ol\textsuperscript{128}, gold complexes [(S)-25](AuCl)\textsubscript{2} and [(S)-26](AuCl)\textsubscript{2},\textsuperscript{128} and trans-2-butene-1,4-diol\textsuperscript{129} were prepared using published procedures.

5.3.2 Synthesis of allylic alcohols

\textit{(E)}-5-(benzyloxy)pent-3-en-2-ol \textit{[(E)-13].} A solution of 4-(tert-butyldimethylsilyloxy)pent-2-yn-1-ol (3.0 g, 14 mmol) in THF (40 mL) was added to a stirred suspension of LiAlH\textsubscript{4} (0.79 g, 21 mmol) in THF (40 mL) at 0 °C and the resulting suspension was warmed to room temperature over 1 h. The reaction mixture was cooled to 0 °C and treated sequentially with water (1 mL), aqueous NaCl (2 N, 1 mL) and water (1 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in THF (25 mL) and added dropwise to a suspension of NaH (0.67 g, 28 mmol) in THF (35 mL) at room temperature, and the resulting suspension was stirred for 1 h (Scheme 5.4). Tetrabutylammonium iodide (0.26 g, 0.7 mmol) was added followed by dropwise addition of benzyl bromide (5 mL, 42 mmol) to the reaction mixture and the resulting suspension was stirred at room temperature overnight. The reaction mixture was treated with water (15 mL) and extracted with ether (3 × 20 mL). The combined ether extracts were washed with brine, dried (MgSO\textsubscript{4}), concentrated, filtered through a plug of silica gel with 4:1 hexanes–EtOAc and concentrated. The resulting oily residue was dissolved in THF (60 mL) and treated with TBAF (1 M solution in THF, 21 mL, 21 mmol). The resulting mixture was stirred at room temperature for 2 h, treated with water (60 mL), and extracted with EtOAc (3 × 40 mL). The combined organic extracts
were dried (MgSO\textsubscript{4}), concentrated, and chromatographed (hexanes–EtOAc = 2:1) to give trans-5-(benzyloxy)pent-3-en-2-ol [(E)-13] as a pale yellow oil (1.5 g, 56%, over 3 steps).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{Scheme 5. 4}};
\end{tikzpicture}
\end{center}

For (E)-13:\textsuperscript{130} TLC (hexanes–EtOAc = 1:1): \( R_f = 0.41 \). \textsuperscript{1}H NMR (500 MHz): \( \delta \) 7.39-7.27 (m, 5 H), 5.84-5.75 (m, 2 H), 4.53 (s, 2 H), 4.33 (quartet of doublet, \( J = 5.5, 6 \text{ Hz}, 1 \text{ H} \)), 4.02 (d, \( J = 4.5 \text{ Hz}, 2 \text{ H} \)), 1.87 (br s, 1 H), 1.28 (d, \( J = 6.5 \text{ Hz}, 3 \text{ H} \)). \textsuperscript{13}C\textsuperscript{1}H NMR (126 MHz): \( \delta \) 138.1, 137.1, 128.3, 127.7, 127.6, 126.1, 72.2, 70.1, 68.1, 23.1.

(E)-4-hydroxypent-2-en-1-yl benzoate [(E)-16]. A solution of 4-(tert-butyldimethylsilyloxy)pent-2-yn-1-ol (3.0 g, 14 mmol) in THF (40 mL) was added to a stirred suspension of LiAlH\textsubscript{4} (0.79 g, 21 mmol) in THF (40 mL) at 0 °C and the resulting suspension was warmed to room temperature over 1 h. The reaction mixture was cooled to 0 °C and treated sequentially with water (1 mL), aqueous NaCl (2 N, 1 mL) and water (1 mL). The resulting white suspension was filtered through a pad of Celite, washed with ether, and concentrated under vacuum. The resulting oily residue was dissolved in THF (60 mL) and treated with TBAF (1 M solution in THF, 21 mL, 21 mmol). The resulting mixture was stirred at room temperature for 2 h, treated with water (60 mL), and extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), and concentrated under vacuum. The resulting oily residue was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (20 mL), pyridine (7 mL) added and cooled to 0 °C (Scheme 5.5). Benzoyl chloride (0.54 mL, 4.7 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (8 mL) was added to the resulting solution at 0 °C over 2 h, and then warmed to room temperature overnight. The resulting mixture was washed sequentially with aqueous HCl (1 N, 2 × 25 mL),
saturated NaHCO$_3$ (25 mL), and brine (25 mL), dried (MgSO$_4$), concentrated, and chromatographed (hexanes–EtOAc = 2:1) to give trans-4-hydroxypent-2-en-1-yl benzoate [(E)-16] as a colorless oil (1.10 g, 38%, over 3 steps).

![Diagram](image)

**Scheme 5.5**

For (E)-16:$^{131}$ TLC (hexanes–EtOAc = 1:1): $R_f = 0.53$. $^1$H NMR: $\delta$ 8.06 (d, $J = 7.2$ Hz, 2 H), 7.56 (t, $J = 7.6$ Hz, 1 H), 7.44 (t, $J = 8$ Hz, 2 H), 5.96-5.85 (m, 2 H), 4.82 (d, $J = 3.6$ Hz, 2 H), 4.41-4.34 (m, 1 H), 1.67 (br s, 1 H), 1.31 (d, $J = 6.4$ Hz, 3 H). $^{13}$C[$^1$H] NMR (126 MHz): $\delta$ 166.3, 138.4, 133.0, 130.1, 129.6, 128.3, 123.7, 68.0, 64.7, 23.1.

[(E)-4-hydroxybut-2-en-1-yl] benzoate [(E)-18]. trans-4-hydroxybut-2-en-1-yl benzoate [(E)-18] was synthesized from trans-2-butene-1,4-diol as a colorless oil in 26% yield (over 2 steps) following a procedure similar to that used to synthesize 16 (Scheme 5.6). trans-2-butene-1,4-diol was synthesized from 2-butyn-1,4-diol following a literature procedure.$^{129}$

![Diagram](image)

**Scheme 5.6**

For (E)-18:$^{132}$ TLC (hexanes–EtOAc = 1:1): $R_f = 0.37$. $^1$H NMR: $\delta$ 8.05 (d, $J = 8.8$ Hz, 2 H), 7.56 (t, $J = 7.6$ Hz, 1 H), 7.44 (t, $J = 8$ Hz, 2 H), 6.02 (td, $J = 4.8$, 15.6 Hz, 1 H), 5.95 (td, $J = 6$, 15.6 Hz, 1 H), 4.84 (d, $J = 6$ Hz, 2 H), 4.21 (d, $J = 5.2$ Hz, 2 H), 1.60 (br s, 1 H). $^{13}$C[$^1$H] NMR (126 MHz): $\delta$ 166.3, 133.5, 133.0, 130.1, 129.6, 128.4, 125.1, 64.6, 62.7.
(Z)-4-hydroxybut-2-en-1-yl benzoate [(Z)-18]. cis-4-hydroxybut-2-en-1-yl benzoate [(Z)-18] was synthesized from cis-2-butene-1,4-diol as a colorless oil in 29% yield following a procedure similar to that used to synthesize (E)-18 (Scheme 5.7).

\[
\begin{align*}
\text{HO-} & \quad \text{OH} \\
\text{BzCl, CH}_2\text{Cl}_2, \text{pyridine, 0 °C, 2 h} & \quad \text{BzO} \\
\text{0 °C} \to \text{RT, 18h} & \quad \text{(Z)-18}
\end{align*}
\]

Scheme 5. 7

For (Z)-18: \textsuperscript{133} TLC (hexanes–EtOAc = 1:1): \( R_f = 0.43 \). \( ^1\text{H} \text{NMR: } \delta \) 8.03 (d, \( J = 6.8 \) Hz, 2 H), 7.56 (t, \( J = 7.6 \) Hz, 1 H), 7.43 (t, \( J = 8 \) Hz, 2 H), 5.91 (tt, \( J = 1.2, 6.8, 11.2 \) Hz, 1 H), 5.75 (ttd, \( J = 1.2, 7.2, 11.2 \) Hz, 1 H), 4.93 (d, \( J = 6.8 \) Hz, 2 H), 4.33 (d, \( J = 7.6 \) Hz, 2 H), 2.24 (br s, 1 H). \( ^{13}\text{C}[^1\text{H}] \text{NMR (126 MHz): } \delta \) 166.6, 133.5, 133.1, 130.0, 129.6, 128.4, 125.5, 60.6, 58.5.

(E)-2-methyl-3-penten-2-ol [(E)-27]. MeMgBr (3 M solution in THF, 15.6 mL, 46.7 mmol) was added dropwise to a stirred solution of trans-ethyl crotonate (2.6 mL, 21 mmol) in diethyl ether (20 mL) at 0 °C (Scheme 5.8). The resulting solution was stirred at 0 °C for 1 h, and gradually warmed to room temperature over 0.5 h, treated with aqueous HCl (2 M, 20 mL) and extracted with ether (3 × 30 mL). The combined organic extracts were dried (MgSO\(_4\)), concentrated, and chromatographed (pentane–ether = 4:1) to give trans-2-methyl-3-penten-2-ol [(E)-27] as a colorless oil (1.01 g, 48%).

\[
\begin{align*}
\text{Me} & \quad \text{OEt} \\
\text{0 °C} \to \text{RT, 1.5 h} & \quad \text{Me} \quad \text{Me} \\
\end{align*}
\]

Scheme 5. 8

For (E)-27: \textsuperscript{134} TLC (hexanes–EtOAc = 4:1): \( R_f = 0.26 \). \( ^1\text{H} \text{NMR: } \delta \) 5.68-5.57 (m, 2 H), 1.70 (br s, 1 H), 1.68-1.67 (m, 3 H), 1.29 (s, 6 H). \( ^{13}\text{C}[^1\text{H}] \text{NMR (126 MHz): } \delta \) 139.1, 121.8, 70.5, 29.7, 17.5.
5.3.3 Synthesis of allylic ethers

1-{(Hex-3-en-2-yloxy)methyl}-4-methylbenzene (5). A mixture of (1) AuCl [1 = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine; 9.3 mg, 0.015 mmol] and AgClO₄ (3.1 mg, 0.015 mmol) in methylene chloride (0.3 mL) was stirred at room temperature for 5 min. 4-Methylbenzyl alcohol (146.6 mg, 1.20 mmol) in methylene chloride (0.2 mL), and trans-4-hexen-3-ol (36 µL, 0.30 mmol) were added subsequently and the resulting mixture was stirred at room temperature for 4 h. Flash column chromatography of the crude reaction mixture (pentane–CH₂Cl₂ = 4:1 → 1:1) gave 5 (46.6 mg, 76%, E/Z = 9.1:1) as a colorless oil. The E-configuration of the major diastereomer was established from the coupling constants of the olefinic peaks in the ¹H NMR spectrum. TLC (hexanes–CH₂Cl₂ = 1:1): R₇ = 0.47. ¹H NMR: δ 7.23 (d, J = 8 Hz, 2 H), 7.14 (d, J = 7.6 Hz, 2 H), [5.66 (td, J = 6, 15.6 Hz), 5.55 (td, J = 7.6, 10.8 Hz), 9.1:1, 1 H], 5.38 (tdd, J = 1.6, 8, 15.6 Hz, 1 H), 4.51 (d, J = 12 Hz, 1 H), [4.33 (d, J = 12 Hz), 4.31 (d, J = 11.6 Hz), 9.1:1, 1 H], 3.87 (quartet of doublet, J = 6.4, 7 Hz, 1 H), 2.34 (s, 3 H), 2.08 (quartet of doublet, J = 7.6, 6.2 Hz, 2 H), [1.26 (d, J = 6.8 Hz), 1.24 (d, J = 6.8 Hz), 9.1:1, 3 H], [1.02 (t, J = 7.6 Hz), 0.98 (t, J = 7.6 Hz), 9.1:1, 3 H]. ¹³C{¹H} NMR: δ 136.9, 135.9, 134.7, 130.9, 129.0, 127.8, 75.5, 69.4, 25.2, 21.7, 21.1, 13.6. IR (neat, cm⁻¹): 2967, 2928, 2863, 1454, 1369, 1074, 969, 910, 799, 732, 475. HRMS calcd (found) for C₁₄H₁₉[(MH-H₂O)⁺]: 187.1481 (187.1178).

Remaining allylic ethers were synthesized employing procedures similar to that used to synthesize 5 unless noted otherwise. Reaction conditions are provided in Table 5.2.

1-{(But-3-en-2-yloxy)methyl}-4-methylbenzene (3). Colorless oil, 76%. TLC (CH₂Cl₂): R₇ = 0.74. ¹H NMR: δ 7.24 (d, J = 8 Hz, 2 H), 7.15 (d, J = 7.6 Hz, 2 H), 5.80 (ddd, J = 7.6, 10.4, 17.6 Hz, 1 H), 5.21 (d, J = 16 Hz, 1 H), 5.18 (d, J = 9.2 Hz, 1 H), 4.54 (d, J = 11.6 Hz, 1 H), 4.36 (d, J = 11.6 Hz, 1 H), 3.92 (quartet of doublet, J = 6.8, 6.8 Hz, 1 H),
2.35 (s, 3 H), 1.29 (d, J = 6.4 Hz, 3 H). $^{13}$C($^1$H) NMR: δ 140.3, 137.0, 135.7, 129.0, 127.8, 116.0, 75.9, 69.8, 21.4, 21.1. IR (neat, cm$^{-1}$): 2977, 2926, 2859, 1515, 1445, 1308, 1100, 992, 922, 799, 752, 481. PCI-MS calcd (found) for C$_{12}$H$_{17}$O (MH$^+$): 177.13 (177.10). HRMS calcd (found) for C$_{12}$H$_{15}$ [(MH-H$_2$O)$^+$]: 159.1169 (159.1164).

1-{(But-2-en-1-yloxy)methyl}-4-methylbenzene (4). Colorless oil, 85%, E/Z = 5.3:1. TLC (hexanes-CH$_2$Cl$_2$ = 1:1): $R_f = 0.38$. $^1$H NMR: δ 7.25 (d, J = 10 Hz, 2 H), 7.16 (d, J = 7.6 Hz, 2 H), 5.79-5.68 (m, 1 H), 5.67-5.59 (m, 1 H), [4.49 (s), 4.47 (s), 1:5.3, 2 H], [4.08 (td, J = 1.2, 6 Hz), 3.95 (td, J = 1.2, 6.4 Hz), 1:5.3, 2 H], 2.35 (s, 3 H), [1.73 (d, J = 6.4 Hz), 1.65 (d, J = 6 Hz), 5.3:1, 3 H]. $^{13}$C($^1$H) NMR: δ 137.1, 135.3, 129.5, [129.0, 127.9, 5.3:1], [127.8, 126.9, 5.3:1], 127.6, [71.9, 71.7, 1:5.3], [70.7, 65.2, 5.3:1], 21.1, 17.8. IR (neat, cm$^{-1}$): 3017, 2919, 2860, 1515, 1460, 1421, 1321, 1067, 992, 922, 801, 481. PCI-MS calcd (found) for C$_{12}$H$_{19}$O (MH$^+$): 177.13 (177.10). HRMS calcd (found) for C$_{12}$H$_{15}$ [(MH-H$_2$O)$^+$]: 159.1168 (159.1169).

1-Methyl-4-{(pent-1-en-3-yloxy)methyl}benzene (7). Colorless oil, 83%. TLC (pentane-CH$_2$Cl$_2$ = 1:1): $R_f = 0.51$. $^1$H NMR: δ 7.24 (d, J = 8 Hz, 2 H), 7.15 (d, J = 7.6 Hz, 2 H), 5.73 (ddd, J = 7.6, 10.4, 17.2 Hz, 1 H), 5.24 (d, J = 10 Hz, 1 H), 5.21 (d, J = 17.6 Hz, 1 H), 4.59 (d, J = 11.6 Hz, 1 H), 4.33 (d, J = 11.6 Hz, 1 H), 3.65 (td, J = 6.8, 7.2 Hz, 1 H), 2.35 (s, 3 H), 1.73-1.61 (m, 1 H), 1.59-1.49 (m, 1 H), 0.92 (t, J = 7.6 Hz, 3 H). $^{13}$C($^1$H) NMR: δ 139.0, 137.0, 135.8, 128.9, 127.8, 117.1, 81.7, 69.8, 28.3, 21.1, 9.8. IR (neat, cm$^{-1}$): 2964, 2930, 2860, 1515, 1460, 1421, 1321, 1067, 992, 922, 801, 481. PCI-MS calcd (found) for C$_{13}$H$_{19}$O (MH$^+$): 191.14 (191.20). HRMS calcd (found) for C$_{13}$H$_{17}$ [(MH-H$_2$O)$^+$]: 173.1325 (173.1320).

1-{(Hex-1-en-3-yloxy)methyl}-4-methylbenzene (8). Colorless oil, 79%. TLC (pentane-CH$_2$Cl$_2$ = 1:1): $R_f = 0.54$. $^1$H NMR: δ 7.23 (d, J = 7.6 Hz, 2 H), 7.15 (d, J = 8 Hz, 2 H), 5.74 (ddd, J = 7.6, 10.4, 16.8 Hz, 1 H), 5.22 (d, J = 10.4 Hz, 1 H), 5.20 (d, J = 16.8 Hz, 1
H), 4.56 (d, J = 12 Hz, 1 H), 4.31 (d, J = 11.6 Hz, 1 H), 3.72 (td, J = 7.2, 6 Hz, 1 H), 2.35 (s, 3 H), 1.68-1.59 (m, 1 H), 1.51-1.31 (m, 3 H), 0.89 (t, J = 7.2 Hz, 3 H). \textsuperscript{13}C{\textsuperscript{1}H} NMR: δ 139.3, 137.0, 135.8, 128.9, 127.8, 116.8, 80.1, 69.8, 37.7, 21.2, 18.6, 14.0. IR (neat, cm\textsuperscript{-1}): 2958, 2929, 2868, 1515, 1457, 1420, 1312, 1070, 991, 922, 800, 733, 480. PCI-MS calcd (found) for C\textsubscript{14}H\textsubscript{21}O (MH\textsuperscript{+}): 205.16 (205.20). HRMS calcd (found) for C\textsubscript{14}H\textsubscript{19}[(MH-H\textsubscript{2}O)\textsuperscript{+}]: 187.1481 (187.1476).

{(But-3-en-2-yloxy)methyl}benzene (9). Colorless oil, 95%. TLC (hexanes-CH\textsubscript{2}Cl\textsubscript{2} = 1:1): \textit{R}_{f} = 0.43. \textsuperscript{1}H NMR: δ 7.35-7.32 (m, 4 H), 7.32-7.28 (m, 1 H), 5.80 (ddd, J = 7.6, 10.4, 17.6 Hz, 1 H), 5.22 (d, J = 17.2 Hz, 1 H), 5.19 (d, J = 10 Hz, 1 H), 4.58 (d, J = 11.6 Hz, 1 H), 4.40 (d, J = 11.6 Hz, 1 H), 3.93 (quartet of doublet, J = 6.4, 7.2 Hz, 1 H), 1.30 (d, J = 6.4 Hz, 3 H). \textsuperscript{13}C{\textsuperscript{1}H} NMR: δ 140.2, 138.8, 128.3, 127.6, 127.4, 116.1, 76.2, 69.9, 21.4. IR (neat, cm\textsuperscript{-1}): 3065, 2976, 2860, 1496, 1452, 1369, 1269, 1073, 1026, 992, 921, 733, 695, 615. PCI-MS calcd (found) for C\textsubscript{11}H\textsubscript{15}O (MH\textsuperscript{+}): 163.11 (163.10). HRMS calcd (found) for C\textsubscript{11}H\textsubscript{13}[(MH-H\textsubscript{2}O)\textsuperscript{+}]: 145.1012 (145.1011).

{(Pent-1-en-3-yloxy)methyl}benzene (10). Colorless oil, 81%. TLC (hexanes-CH\textsubscript{2}Cl\textsubscript{2} = 1:1): \textit{R}_{f} = 0.44. \textsuperscript{1}H NMR: δ 7.40-7.34 (m, 4 H), 7.32-7.28 (m, 1 H), 5.80 (ddd, J = 7.6, 10.4, 17.2 Hz, 1 H), 5.24 (d, J = 10.8 Hz, 1 H), 5.21 (d, J = 17.2 Hz, 1 H), 4.61 (d, J = 12 Hz, 1 H), 4.37 (d, J = 12 Hz, 1 H), 3.66 (td, J = 6.4, 7.6 Hz, 1 H), 1.74-1.64 (m, 1 H), 1.60-1.49 (m, 1 H), 0.92 (t, J = 7.2 Hz, 3 H). \textsuperscript{13}C{\textsuperscript{1}H} NMR: δ 138.9, 138.8, 128.3, 127.7, 127.3, 117.2, 82.0, 70.0, 28.3, 9.8. IR (neat, cm\textsuperscript{-1}): 3030, 2965, 2932, 2860, 1454, 1387, 1321, 1091, 1062, 993, 923, 731, 695, 612. PCI-MS calcd (found) for C\textsubscript{12}H\textsubscript{17}O (MH\textsuperscript{+}): 177.13 (177.10). HRMS calcd (found) for C\textsubscript{12}H\textsubscript{15}[(MH-H\textsubscript{2}O)\textsuperscript{+}]: 159.1168 (159.1165).

{2-(Pent-1-en-3-yloxy)ethyl}benzene (11). Colorless oil, 87%. TLC (pentane-CH\textsubscript{2}Cl\textsubscript{2} = 1:1): \textit{R}_{f} = 0.53. \textsuperscript{1}H NMR: δ 7.31-7.27 (m, 2 H), 7.25-7.19 (m, 3 H), 5.67 (ddd, J = 8, 10.8, 17.2 Hz, 1 H), 5.16 (d, J = 10.4 Hz, 1 H), 5.16 (d, J = 17.6 Hz, 1 H), 3.72 (ddd, J =
6.4, 8, 9.2 Hz, 1 H), 3.56 (td, J = 6.8, 7.2 Hz, 1 H), 3.49 (ddd, J = 6.8, 8.4, 9.6 Hz, 1 H), 2.89 (ddd, J = 4.4, 6.4, 7.6 Hz, 2 H), 1.68-1.57 (m, 1 H), 1.55-1.45 (m, 1 H), 0.89 (t, J = 7.2 Hz, 3 H). $^{13}$C\{\textsuperscript{1}H\} NMR: δ 139.1, 139.0, 128.9, 128.2, 126.1, 116.7, 82.9, 69.4, 36.5, 28.2, 9.7. IR (neat, cm\(^{-1}\)): 3027, 2962, 2934, 2854, 1495, 1453, 1343, 1091, 1030, 992, 923, 969, 746, 697, 577. PCI-MS calcd (found) for C\textsubscript{13}H\textsubscript{19}O (MH\textsuperscript{+}): 191.14 (191.20). HRMS calcd (found) for C\textsubscript{13}H\textsubscript{17} [(MH-H\textsubscript{2}O)\textsuperscript{+}]: 173.1325 (173.1322).

1-Methyl-4-[(pent-3-en-2-yloxy)methyl]benzene (12). Colorless oil, 96%, E/Z = 9:1. TLC (pentane-CH\textsubscript{2}Cl\textsubscript{2} = 1:1): $R_f$ = 0.42. \textsuperscript{1}H NMR: δ 7.24 (d, J = 8 Hz, 2 H), 7.16 (d, J = 8 Hz, 2 H), 5.65 (quartet of doublet, $J = 6.4$, 15.4 Hz, 1 H), 5.43 (quartet of dd, $J = 1.6$, 8, 15.6 Hz, 1 H), [4.54 (d, $J = 11.6$ Hz), 4.53 (d, $J = 11.6$ Hz), 1:9, 1 H], 4.34 (d, $J = 12$ Hz, 1 H), 3.88 (quartet of doublet, $J = 6.4$, 7 Hz, 1 H), 2.36 (s, 3 H), [1.75 (dd, $J = 1.6$, 6.4 Hz), 1.65 (dd, $J = 2$, 6.8 Hz), 9:1, 3 H], [1.27 (d, $J = 6.4$ Hz), 1.26(d, $J = 6$ Hz), 9:1, 3 H]. $^{13}$C\{\textsuperscript{1}H\} NMR: δ 136.9, 135.9, 133.3, [128.9, 127.8, 9:1], [127.7, 126.3, 9:1], 127.6, [75.4, 69.5, 9:1], [69.4, 69.3, 1:9], 21.6, [21.3, 21.1, 1:9], 17.6. IR (neat, cm\(^{-1}\)): 2974, 2921, 2858, 1515, 1445, 1369, 1307, 1080, 1054, 1021, 967, 906, 799, 732, 476. PCI-MS calcd (found) for C\textsubscript{13}H\textsubscript{19}O (MH\textsuperscript{+}): 191.14 (191.20). HRMS calcd (found) for C\textsubscript{13}H\textsubscript{17} [(MH-H\textsubscript{2}O)\textsuperscript{+}]: 173.1325 (173.1322).

(2-Butoxypent-3-en-1-yloxy)methyl]benzene (14). Colorless oil, 80%, E/Z = 8.3:1. TLC (CH\textsubscript{2}Cl\textsubscript{2}): $R_f$ = 0.44. \textsuperscript{1}H NMR: δ 7.35-7.32 (m, 4 H), 7.30-7.27 (m, 1 H), 5.72 (quartet of doublet, $J = 6.4$, 15.6 Hz, 1 H), 5.43 (quartet of dd, $J = 1.6$, 7.8, 15.4 Hz, 1 H), [4.63 (d, $J = 12.8$ Hz), 4.62 (d, $J = 12.4$ Hz), 1:8.3, 1 H], [4.56 (d, $J = 12$ Hz), 4.55 (d, $J = 12.4$ Hz), 8.3:1, 1 H], 3.87 (ddd, $J = 4.8$, 7.2, 11.6 Hz, 1 H), 3.57-3.41 (m, 3 H), 3.35 (td, $J = 6.8$, 9.2 Hz, 1 H), [1.72 (dd, $J = 1.6$, 6.4 Hz), 1.69 (dd, $J = 1.6$, 6.8 Hz), 8.3:1, 3 H], 1.60-1.53 (m, 2 H), 1.42-1.33 (m, 2 H), 0.91 (t, $J = 7.2$ Hz, 3 H). $^{13}$C\{\textsuperscript{1}H\} NMR: δ 138.4, 129.3, 129.2, 128.3, [127.6, 126.5, 8.3:1], 127.4, 79.7, 73.3, 73.2, 68.4, [32.0, 31.9, 1:8.3], 19.3, 17.8, 13.9. IR (neat,
cm\(^{-1}\)): 2957, 2931, 2861, 1496, 1451, 1361, 1089, 1028, 966, 734, 696, 611. HRMS calcd (found) for C\(_{16}\)H\(_{24}\)NaO\(_2\) (MNa): 271.1669 (271.1664).

\((2\text{-Methoxypent-3-en-1-yloxy)methyl\}}\)benzene (15). Colorless oil, 77%, \(E/Z = 10.3:1\). TLC (CH\(_2\)Cl\(_2\)): \(R_f = 0.34\). \(^1\)H NMR: \(\delta\) 7.35-7.33 (m, 4 H), 7.32-7.27 (m, 1 H), 5.74 (quartet of doublet, \(J = 6.8, 15.2\) Hz, 1 H), 5.34 (quartet of dd, \(J = 1.6, 8, 15.4\) Hz, 1 H), [4.63 (d, \(J = 12.4\) Hz), 4.62 (d, \(J = 12.4\) Hz), 1:10.3, 1 H], [4.56 (d, \(J = 12\) Hz), 4.55 (d, \(J = 12.4\) Hz), 10.3:1, 1 H], 3.80-3.75 (m, 1 H), 3.54-3.41 (m, 2 H), [3.33 (s), 3.32 (s), 10.3:1, 3 H], [1.73 (dd, \(J = 1.6, 6.4\) Hz), 1.70 (dd, \(J = 1.6, 6.8\) Hz), 10.3:1, 3 H]. \(^{13}\)C\({}^1\)H NMR: \(\delta\) 138.3, 130.3, 128.3, 127.7, 127.6, 127.5, 81.4, 73.3, 73.0, 56.2, 17.8. IR (neat, cm\(^{-1}\)): 2858, 1496, 1451, 1362, 1266, 1196, 1089, 1029, 967, 908, 848, 728, 697. PCI-MS calcd (found) for C\(_{13}\)H\(_{19}\)O\(_2\) (MH\(^+\)):

2-Butoxybut-3-en-1-yl benzoate (17). Colorless oil, 53%, \(E/Z = 13.4:1\). TLC (CH\(_2\)Cl\(_2\)): \(R_f = 0.49\). \(^1\)H NMR (500 MHz): \(\delta\) 8.05 (d, \(J = 7.5\) Hz, 2 H), 7.56 (t, \(J = 8\) Hz, 1 H), 7.44 (t, \(J = 7.5\) Hz, 2 H), 5.79 (quartet of doublet, \(J = 6, 15.5\) Hz, 1 H), 5.42 (dd, \(J = 8, 15.5\) Hz, 1 H), [4.51-4.46 (m), 4.34-4.26 (m), 1:13.4, 2 H], 4.04-3.99 (m, 1 H), 3.58-3.53 (m, 1 H), 3.42-3.35 (m, 1 H), 1.74 (d, \(J = 6.5\) Hz, 3 H), 1.58-1.52 (m, 2 H), 1.40-1.33 (m, 2 H), 0.89 (t, \(J = 8\) Hz, 3 H). \(^{13}\)C\({}^1\)H NMR (126 MHz): \(\delta\) 166.4, 132.8, 130.3, 130.2, 129.6, 128.3, 128.2, 78.3, 68.6, 67.0, 31.8, 19.3, 17.8, 13.8. IR (neat, cm\(^{-1}\)): 2957, 2868, 1719, 1450, 1315, 1268, 1093, 1069, 1026, 967, 708. PCI-MS calcd (found) for C\(_{16}\)H\(_{23}\)O\(_3\) (MH\(^+\)):

2-Butoxybut-3-en-1-yl benzoate (19). Colorless oil, 57%. TLC (hexanes-EtOAc = 1:1): \(R_f = 0.84\). \(^1\)H NMR: \(\delta\) 8.05 (d, \(J = 8\) Hz, 2 H), 7.56 (t, \(J = 7.2\) Hz, 1 H), 7.44 (t, \(J = 8\) Hz, 2 H), 5.80 (ddd, \(J = 6.8, 10, 16.8\) Hz, 1 H), 5.38 (d, \(J = 16.8\) Hz, 1 H), 5.30 (d, \(J = 10.4\) Hz, 1 H), 4.38-4.28 (m, 2 H), 4.10-4.05 (m, 1 H), 3.58 (td, \(J = 6.4, 9.2\) Hz, 1 H), 3.41 (td, \(J = 6.4, 9.6\) Hz, 1 H), 1.60-1.53 (m, 2 H), 1.42-1.33 (m, 2 H), 0.89 (t, \(J = 7.2\) Hz, 3 H). \(^{13}\)C\({}^1\)H
NMR: δ 166.4, 135.3, 132.9, 129.1, 128.3, 118.5, 78.7, 69.0, 66.6, 31.8, 19.3, 13.8. IR (neat, cm⁻¹): 2957, 2868, 1719, 1451, 1314, 1267, 1095, 1069, 988, 930, 708, 687. PCI-MS calcd (found) for C₁₅H₂₁O₃ (MH⁺): 249.15 (249.15). HRMS calcd (found) for C₁₅H₂₀NaO₃ (MNa⁺): 271.1305 (271.1306).

1-Methyl-4-[[4-methylpent-3-en-2-yl]oxy)methyl]benzene (20). Colorless oil, 88%. TLC (hexanes-EtOAc = 4:1): Rᵣ = 0.68. ¹H NMR (500 MHz): δ 7.23 (d, J = 8 Hz, 2 H), 7.14 (d, J = 8 Hz, 2 H), 5.15 (td, J = 1.6, 8.8 Hz, 1 H), 4.51 (d, J = 11.5 Hz, 1 H), 4.32 (d, J = 11.5 Hz, 1 H), 4.21 (quartet of doublet, J = 6.5, 8.8 Hz, 1 H), 2.34 (s, 3 H), 1.77 (s, 3 H), 1.64 (s, 3 H), 1.23 (d, J = 6.5 Hz, 3 H). ¹³C{¹H} NMR (126 MHz): δ 136.9, 136.1, 134.7, 128.9, 127.7, 127.6, 70.8, 69.3, 25.8, 21.5, 21.1, 18.2. IR (neat, cm⁻¹): 2971, 2925, 2860, 1515, 1445, 1375, 1073, 1021, 841, 799, 750. HRMS calcd (found) for C₁₄H₂₀NaO (MNa⁺): 227.1406 (227.1406).

1-(Pent-1-en-3-yloxy)propyl]benzene (21). Colorless oil, 53%, dr = 2.4:1. TLC (pentane-CH₂Cl₂ = 1:1): Rᵣ = 0.76. ¹H NMR: δ 7.36-7.21 (m, 5 H), [5.66 (ddd, J = 8.4, 10.4, 17.6 Hz), 5.63 (ddd, J = 6.8, 10.4, 17.2 Hz), 1:2:4, 1 H], [5.19 (dd, J = 2, 10.4 Hz), 5.01 (d, J = 10.8 Hz), 1:2:4, 1 H], 5.05 (d, J = 17.6 Hz, 1 H), [4.28 (t, J = 6.4 Hz), 4.24 (t, J = 6.8 Hz), 2:4:1, 1 H], [3.71-3.66 (m), 3.42-3.37 (m), 2:4:1, 1 H], 1.86-1.34 (m, 4 H), [0.91 (t, J = 7.6 Hz), 0.85 (t, J = 7.2 Hz), 2:4:1, 3 H], [0.87 (t, J = 7.2 Hz), 0.81 (t, J = 7.6 Hz), 2:4:1, 3 H]. ¹³C{¹H} NMR: δ [143.5, 143.1, 2:4:1], [139.4, 139.3, 2:4:1], [128.1, 128.0, 1:2:4], [127.2, 127.0, 1:2:4], [126.9, 126.7, 1:2:4], 115.4, [80.8, 79.7, 2:4:1], [80.1, 79.3, 2:4:1], [31.3, 30.5, 1:2:4], [28.6, 27.2, 1:2:4], [10.4, 10.0, 1:2:4], [9.9, 9.3, 1:2:4]. IR (neat, cm⁻¹): 2963, 2932, 2874, 1452, 1379, 1071, 1051, 1010, 992, 921, 752, 735, 698, 539. PCI-MS calcd (found) for C₁₄H₂₁O (MH⁺): 205.16 (205.20). HRMS calcd (found) for C₁₄H₁₉ [(MH-H₂O)⁺]: 187.1481 (187.1479).

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(Pent-1-en-3-yloxy)cyclohexane (22). Colorless oil, 76%. TLC (pentane-CH$_2$Cl$_2$ = 1:1): $R_f = 0.52$. $^1$H NMR: $\delta$ 5.70 (ddd, $J = 7.2, 10, 17.2$ Hz, 1 H), 5.14 (d, $J = 17.6$ Hz, 1 H), 5.11 (d, $J = 10.8$ Hz, 1 H), 3.68 (td, $J = 7.2, 6$ Hz, 1 H), 3.29-3.24 (m, 1 H), 1.92-1.80 (m, 2 H), 1.76-1.70 (m, 2 H), 1.59-1.41 (m, 3 H), 1.34-1.16 (m, 5 H), 0.90 (t, $J = 7.2$ Hz, 3 H). $^{13}$C($^1$H) NMR: $\delta$ 140.3, 115.4, 79.6, 74.8, 33.6, 31.9, 28.8, 25.9, 24.5, 24.3, 10.1. IR (neat, cm$^{-1}$): 2924, 2854, 1261, 1120, 1022, 799, 667. PCI-MS calcd (found) for C$_{11}$H$_{21}$O (MH$^+$): 169.16 (169.15).

5.3.4 Synthesis and alkoxylation of enantiomerically enriched allylic alcohols

(R,E)-5-(benzyloxy)pent-3-en-2-ol [(R,E)-13]. (R,E)-13 was prepared in 63% yield (over 3 steps) and 98% ee (Figure 5.2) from (R)-4-(tert-butyldimethylsilyloxy)pent-2-yn-1-ol$^{28}$ following a procedure similar to that used to synthesize racemic (E)-13.

Figure 5.2 HPLC traces of racemic (E)-13 (left trace) and enantiomerically enriched (R,E)-13 (right trace). HPLC conditions: hexanes–isopropanol = 98:2 @ 0.4 mL/min,
Chiralpak AD-H column.

**Reaction of n-butanol with (R,E)-13.** Gold(I)-catalyzed reaction of n-butanol with (R,E)-13 employing a procedure identical to that as used to synthesize racemic 14 led to isolation of a 8:1 mixture of (R,E)-14 and (S,Z)-14 in 81% combined yield (Scheme 5.2). The diastereomeric and enantiomeric purity of (R,E)-14 and (S,Z)-14 was determined by chiral HPLC analysis and by comparison to racemic sample of 14 (Figure 5.3). In addition to γ-substitution product 14, the α-substitution product 23 was isolated as a 7.2:1 mixture of (R,E)-23 and (S,Z)-23 in 15% combined yield (Scheme 5.2). The diastereomeric and enantiomeric purity of (R,E)-23 and (S,Z)-23 was determined by chiral HPLC analysis and by comparison to racemic sample of 23 (Figures 5.4).

**For [(4-butoxypent-2-en-1-yl)oxy]methyl benzene (23):** Colorless oil, 15%, E/Z = 7.2:1. TLC (CH₂Cl₂): Rₚ = 0.34. ¹H NMR: δ 7.39-7.26 (m, 5 H), 5.75 (td, J = 5.6, 15.6 Hz, 1 H), 5.64 (dd, J = 7.2, 15.6 Hz, 1 H), 4.52 (s, 2 H), 4.03 (d, J = 5.6 Hz, 2 H), 3.85 (quartet of doublet, J = 6, 6.6 Hz, 1 H), 3.50-3.42 (m, 1 H), 3.31 (td, J = 6, 9.6 Hz, 1 H), 1.57-1.50 (m, 2 H), 1.39-1.33 (m, 2 H), [1.24 (d, J = 6.8 Hz), 1.21 (d, J = 6.4 Hz), 7.2:1, 3 H], [0.91 (t, J = 7.2 Hz), 0.90 (t, J = 7.6 Hz), 7.2:1, 3 H]. ¹³C{¹H} NMR: δ 138.2, 135.7, 128.4, 127.7, 127.6, 75.7, 72.1, 70.2, 68.1, 32.0, 21.4, 19.4, 13.9. IR (neat, cm⁻¹): 2959, 2931, 2870, 1453, 1371, 1269, 1090, 1025, 973, 741, 697, 598. HRMS calcd (found) for C₁₆H₂₄NaO₂ (MNa)⁺: 271.1669 (271.1662).
Figure 5.3 Chiral HPLC traces of racemic 8.3:1 mixture of (E)-14 and (Z)-14 (left trace), and enantiomerically enriched 8:1 (R,E)-14 and (S,Z)-14 (right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.2 mL/min, Lux 5u Cellulose-1 column.
Figure 5.4 Chiral HPLC traces of racemic 7.3:1 mixture of (E)-23 and (Z)-23 (left trace), and enantiomerically enriched mixture of 7.2:1 (R,E)-23 and (S,Z)-23 (right trace).

HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.3 mL/min, Chiralpak AD-H column.

**Determination of absolute configuration of (R,E)-14 and (S,Z)-14.** The absolute configuration of (R,E)-14 and (S,Z)-14 were determined by the following series of experiments. An authentic sample of (R)-28 was synthesized by opening of the epoxide ring of (R)-glycidyl benzyl ether by lithium acetylide ethylenediamine complex followed by isomerization of the alkyne in presence of potassium tert-butoxide (Scheme 5.9).\(^ {135}\) (R)-28 was then converted to (R,E)-14 by lithium aluminum hydride reduction of the alkyne followed by conversion of the free hydroxyl group to \(n\)-butoxy by treatment with \(n\)-butyl bromide after deprotonation of the hydroxyl by sodium hydride.\(^ {136}\) Chiral HPLC analysis of (R,E)-14 obtained from this route with >99% ee and that obtained from gold(I)-catalyzed etherification of (R,E)-13 (Scheme 5.2) revealed that they both have the
same absolute configuration (Figure 5.5). In a similar set of experiments, \((R)-28\) was converted to \((R,Z)-14\) by partial hydrogenation of the alkyne in presence of Lindlar catalyst followed by conversion of the free hydroxyl group to \(n\)-butoxy by treatment with \(n\)-butyl bromide after deprotonation of the hydroxyl by sodium hydride (Scheme 5.9).\(^{136}\) Chiral HPLC analysis of \((R,Z)-14\) with >99% ee obtained from this route and that obtained gold(I)-catalyzed etherification of \((R)-13\) (Scheme 5.2) revealed that they have opposite absolute configuration (Figure 5.5). Therefore, these experiments established that the absolute configuration of the allylic ethers formed in the gold(I)-catalyzed etherification of \((R)-13\) with \(n\)-butanol as \((R,E)-14\) and \((S,Z)-14\) (Scheme 5.2).

Scheme 5. 9

For \((R)-28:\)\(^{135}\) Yellow oil, 80%. TLC (hexanes–ether = 1:1): \(R_f = 0.31.\) \(^1H\) NMR: \(\delta\) 7.36-7.30 (m, 5 H), 4.61 (d, \(J = 4.8\) Hz, 2 H), 4.57-4.52 (m, 1 H), 3.62 (dd, \(J = 3.6, 9.6\) Hz, 1 H), 3.52 (dd, \(J = 8, 10\) Hz, 1 H), 2.42 (d, \(J = 4.4\) Hz, 1 H), 1.84 (d, \(J = 2.4\) Hz, 3 H). \(^{13}C\)\(^{\text{\(\delta\)}}\) NMR (126 MHz): \(\delta\) 137.6, 128.5, 127.8, 127.7, 82.1, 76.9, 73.9, 73.3, 61.8, 3.6.

For \((R,Z)-14:\) Colorless oil, 77% (over 2 steps). TLC (CH\(_2\)Cl\(_2\)): \(R_f = 0.38.\) \(^1H\) NMR: \(\delta\) 7.36-7.27 (m, 5 H), 5.71 (quartet of doublet, \(J = 6.8\), 11 Hz, 1 H), 5.32 (ddd, \(J = 1.6, 8.4, 10.8\) Hz, 1 H), 4.63 (d, \(J = 12.4\) Hz, 1 H), 4.56 (d, \(J = 12.4\) Hz, 1 H), 4.36-4.31 (m, 1 H), 3.57-3.48 (m, 2 H), 3.45-3.35 (m, 2 H), 1.69 (dd, \(J = 1.6, 6.8\) Hz, 3 H), 1.60-1.53 (m, 2 H),
1.42-1.33 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H). $^{13}$C$\text{[1H]}$ NMR: δ 138.5, 128.9, 128.4, 128.3, 127.6, 127.4, 74.2, 73.3, 72.9, 68.4, 32.0, 19.4, 13.9, 13.5. IR (neat, cm$^{-1}$): 3026, 2957, 2930, 2862, 1452, 1362, 1326, 1093, 1029, 910, 730, 696, 603. PCI-MS calcld (found) for C$_{16}$H$_{25}$O$_2$ (MH$^+$): 249.19 (249.20). HRMS calcld (found) for C$_{16}$H$_{24}$NaO$_2$ (MNa)$^+$: 271.1669 (271.1669).

Figure 5.5 Chiral HPLC traces of racemic 8.3:1 mixture of (E)-14 and (Z)-14 (left trace), enantiomerically enriched (R,E)-14 with >99% ee (center trace), and enantiomerically enriched (R,Z)-14 with >99% ee (right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.2 mL/min, Lux 5u Cellulose-1 column.

**Determination of absolute configuration of (R,E)-23 and (S,Z)-23.** The absolute configuration of (R,E)-23 and (S,Z)-23 were determined by the following series of experiments. An authentic sample of (R,E)-23 was synthesized by deprotonation of (R,E)-13 with sodium hydride followed by its alkylation with n-butyl bromide (eq 5.15).$^{13e}$ Chiral HPLC analysis of (R,E)-23 obtained from this route with 98% ee and that
obtained gold(I)-catalyzed etherification of (R)-13 (Scheme 5.2) revealed that they both have the same absolute configuration (Figure 5.6). In a similar set of experiments, (R,Z)-13 (98% ee) was converted to (R,Z)-23 by deprotonation of (R,Z)-13 with sodium hydride followed by its alkylation with n-butyl bromide (eq 5.16). Chiral HPLC analysis of (R,Z)-23 with >95% ee obtained from this route and that obtained from gold(I)-catalyzed etherification of (R)-13 (Scheme 5.2) revealed that they have opposite absolute configuration (Figure 5.6). Therefore, these experiments established that the absolute configuration of the α-substituted allylic ethers formed in the gold(I)-catalyzed etherification of (R)-13 with n-butanol as (R,E)-23 and (S,Z)-23 (Scheme 5.2).
Figure 5.6 Chiral HPLC traces of racemic 7.3:1 mixture of (E)-23 and (Z)-23 (left trace), enantiomerically enriched (R,E)-23 with 98% ee (center trace), and enantiomerically enriched (R,Z)-23 with >95% ee (right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.3 mL/min, Chiralpak AD-H column.

(R,E)-4-hydroxypent-2-en-1-yl benzoate [(R,E)-16]. (R,E)-16 was prepared in 31% yield (over 3 steps) and 97% ee (Figure 5.7) from (R)-4-(tert-butyldimethylsilyloxy)pent-2-yn-1-ol\textsuperscript{128} following a procedure similar to that used to synthesize racemic (E)-16.
Figure 5.7 HPLC traces of racemic (E)-16 (left trace) and enantiomerically enriched (R,E)-16 (right trace). HPLC conditions: hexanes–isopropanol = 90:10 @ 1.0 mL/min, Chiralpak AD-H column.

Reaction of $n$-butanol with (R,E)-16. Gold(I)-catalyzed reaction of $n$-butanol with (R,E)-16 employing a procedure identical to that as used to synthesize racemic 17 led to isolation of a 13.4:1 mixture of (R,E)-17 and (Z)-17 in 57% combined yield (eqn 5.10). The diastereomeric ratio of 17 was determined by $^1$H NMR analysis and the enantiomeric purity of (R,E)-17 was determined by chiral HPLC analysis and by comparison to racemic sample of 17 (Figure 5.8). The absolute configuration of (R,E)-17 was assigned by analogy to (R,E)-14.
Figure 5.8 Chiral HPLC traces of racemic (E)-17 (left trace), and enantiomerically enriched (R,E)-17 (right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.3 mL/min, Lux 5u Cellulose-1 column.

5.3.5 Acid-catalyzed alkoxylation of allylic alcohols

Reaction of \( n \)-butanol with \( (R,E) \)-13 in presence of catalytic TfOH. TfOH (1.3 µL, 0.015 mmol) was added to a solution of \( (R,E) \)-13 (57.7 mg, 0.30 mmol) and \( n \)-butanol (110 µL, 1.20 mmol) in methylene chloride (0.5 mL), and stirred at 40 °C. At 5 h, GC analysis of the reaction revealed formation of both \( \gamma \)- and \( \alpha \)-substitution products, 14 and 23 respectively in a 4:6 ratio with an overall 29% conversion. At 24 h, purification of the reaction mixture led to isolation of a 5.8:1 mixture of (E)-14 with ≤10% ee and (Z)-14 with no ee in 22% combined yield (Figure 5.9). In addition, allylic ether (E)-23 was isolated with ≤8% ee in 40% yield (Figure 5.10).
Figure 5.9 Chiral HPLC traces of racemic 8.3:1 mixture of (E)-14 and (Z)-14 (left trace), and 5.8:1 mixture of (R,E)-14 with ≤10% ee and (Z)-14 with no ee (right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.2 mL/min, Lux 5u Cellulose-1 column.

Figure 5.10 Chiral HPLC traces of racemic 7.3:1 mixture of (E)-23 and (Z)-23 (left
trace), and (E)-23 with ≤8% ee (right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.3 mL/min, Chiralpak AD-H column.

Reaction of n-butanol with (R,E)-13 in presence of catalytic BF$_3$OEt$_2$. BF$_3$OEt$_2$ (1.9 µL, 0.015 mmol) was added to a solution of (R,E)-13 (57.7 mg, 0.30 mmol) and n-butanol (110 µL, 1.20 mmol) in methylene chloride (0.5 mL), and stirred at 40 ºC. At 24 h, purification of the reaction mixture led to isolation of a >50:1 mixture of (E)-14 with ≤14% ee and (Z)-14 with no ee in 12% combined yield (Figure 5.11). In addition, allylic ether (E)-23 was isolated with no ee in 26% yield (Figure 5.12).

![Figure 5.11](image)

**Figure 5.11** Chiral HPLC traces of racemic 8.3:1 mixture of (E)-14 and (Z)-14 (left trace), and >50:1 mixture of (E)-14 with ≤14% ee and (Z)-14 with no ee (right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.2 mL/min, Lux 5u Cellulose-1 column.
Figure 5.12 Chiral HPLC traces of racemic 7.3:1 mixture of (E)-23 and (Z)-23 (left trace), and (E)-23 with no ee (right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.3 mL/min, Chiralpak AD-H column.

5.3.6 Kinetics experiment

Reaction of trans-4-hexen-3-ol with 4-methylbenzyl alcohol. A solution of trans-4-hexen-3-ol (0.60 M), 4-methylbenzyl alcohol (2.40 M), mesitylene (6.0 mg; internal standard), and a catalytic 1:1 mixture of (1)AuCl and AgClO$_4$ (5 mol %) in CD$_2$Cl$_2$ was monitored periodically by $^1$H NMR spectroscopy at room temperature. Analysis after 2 h revealed that 40% of trans-4-hexen-3-ol had been consumed to form 5 (40%) exclusively. The concentration of trans-4-hexen-3-ol was determined by integrating the alkene resonance at $\delta$ 5.66 (quartet of doublet, $J = 6.4, 15.2$ Hz, 1 H), and the concentration of 5 was determined by integrating the alkene resonance at $\delta$ 5.77 (td, $J = 6, 15.6$ Hz, 1 H). Monitoring this reaction with time revealed that $\alpha$-alkoxylation product 6 gradually starts forming later in the reaction. Analysis after 4 h revealed that
50% of trans-4-hexen-3-ol had been consumed to form 5 (49%), and 6 (~1%) (Figure 5.1). The concentration of 6 was determined by integrating the methyl resonance at δ 1.84 (dd, J = 1.6, 6.4 Hz, 3 H). ¹H NMR analysis of the reaction with prolonged time demonstrated that the secondary reaction pathway leading to the α-alkoxylation product 6 by gold(I)-catalyzed alkoxylation of γ-alkoxylation product 5 with 4-methylbenzylalcohol continued till a 50:50 mixture of γ/α alkoxylation product was reached. A plot of the relative concentrations of trans-4-hexen-3-ol, 5, and 6 versus time is depicted in Figure 5.1. Under these conditions, 40% conversion was reached in 2 h, 50% conversion in 4 h and 75% conversion in 8.2 h.

5.3.7 Enantioselective allylic alkoxylation

![Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 3 (37% ee, right trace).](image)

**Figure 5.13** Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 3 (37% ee, right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.4 mL/min, Lux 5u Cellulose-1 column.
Figure 5.14 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 9 (32% ee, right trace). HPLC conditions: 99:1 hexanes-isopropanol @ 0.4 mL/min, Lux 5u Cellulose-1 column.

Figure 5.152 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched
11 (26% ee, right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.3 mL/min, Lux 5u Cellulose-1 column.

Figure 5.16 Chiral HPLC traces of racemic (left trace) and enantiomerically enriched 7 (54% ee, right trace). HPLC conditions: 99.9:0.1 hexanes-isopropanol @ 0.4 mL/min, Lux 5u Cellulose-1 column.

5.3.8 Control experiments

1. **Silver only:** To a suspension of AgSbF₆ (5.1 mg, 0.015 mmol) in 1,4-dioxane (0.5 mL), benzyl alcohol (0.2 mL, 1.5 mmol) and trans-2-buten-1-ol (25 µL, 0.30 mmol) were added, and stirred at room temperature for 24 h. GC, TLC, and ¹H NMR analysis of the crude reaction mixture showed no detectable consumption of trans-2-buten-1-ol and no detectable formation of 9.

2. **Silver/ligand only:** To a suspension of AgSbF₆ (5.1 mg, 0.015 mmol) and P(t-Bu)₂-o-biphenyl (4.5 mg, 0.015 mmol) in 1,4-dioxane (0.5 mL), benzyl alcohol (0.2 mL, 1.5
mmol) and trans-2-buten-1-ol (25 µL, 0.30 mmol) were added, and stirred at room temperature for 24 h. GC, TLC, and \(^1\)H NMR analysis of the crude reaction mixture showed no detectable consumption of trans-2-buten-1-ol and no detectable formation of 9.

3. **HOTf with trans-2-penten-1-ol:** To a solution of 4-methylbenzyl alcohol (146.6 mg, 1.2 mmol) and trans-2-penten-1-ol (31 µL, 0.30 mmol) in methylene chloride (0.5 mL), TfOH (1.3 µL, 0.015 mmol) was added, and stirred at room temperature for 24 h. GC, TLC, and \(^1\)H NMR analysis of the crude reaction mixture showed no detectable consumption of trans-2-penten-1-ol and no detectable formation of 7.

4. **HOTf with trans-4-hexen-3-ol:** To a solution of 4-methylbenzyl alcohol (146.6 mg, 1.2 mmol) and trans-4-hexen-3-ol (36 µL, 0.30 mmol) in methylene chloride (0.5 mL), TfOH (1.3 µL, 0.015 mmol) was added, and stirred at 0 ºC. Periodic analysis of the reaction by GC showed formation of ~1:1 mixture of both products 5 and 6. As an example, at 40 min, GC analysis of the crude reaction mixture showed 1.5:1 mixture of allylic ethers 5 and 6 that accounted for 13% conversion.

Another set of reaction set up in an exact same way at room temperature after 4 h show a 1.3:1 ratio of 5 and 6 with an overall 99% conversion.
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