**Catalytic Asymmetric Alkyne Addition to Aldehydes and Applications of Propargylic Alcohols in Synthesis**

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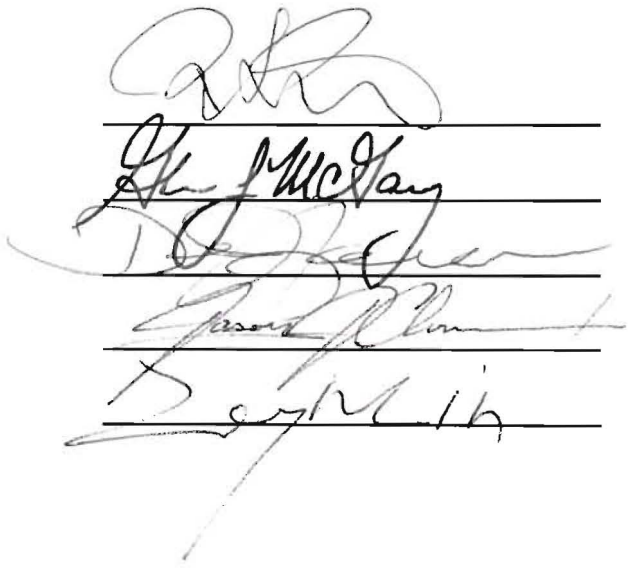

# Abstract


**Catalytic Asymmetric Alkyne Addition to Aldehydes and Applications of Propargylic Alcohols in Synthesis**

A toolbox of catalytic systems for the asymmetric alkynylzinc addition to aldehydes has been constructed to provide high enantioselectivities for a diverse range of alkynes. A new $H_8$BINOL-based bifunctional catalytic system for the highly enantioselective addition of alkyl propiolates to aliphatic aldehydes was developed to address a remaining limitation in asymmetric alkyne additions. This system was also found to be highly enantioselective for additions to aromatic and α,β-unsaturated aldehydes. With effective methods to access a variety of optically active propargylic alcohols, the utility of propargylic alcohol based enynes in the diastereoselective intramolecular Pauson-Khand Reaction was demonstrated. High diastereoselectivities could be obtained (up to ≥ 99:1), with the diastereoselectivity of the cycloaddition being influenced by the size of the alkyne substituent.

From this foundation a flexible strategy for the asymmetric synthesis of the 5,5,7- and 5,5,8-polycyclic ring systems common in a variety of natural products was developed. Key to this strategy was the development of a highly enantioselective BINOL-$ZnEt_2$-$Ti(O^iPr)_4$-$Cy_2NH$ catalytic system for the addition of 1,3-diynes to enals, a chemoselective and diastereoselective Pauson-Khand-type reaction of dienediyne substrates, and enyne metathesis to form the 7- and 8-membered ring systems. These polycyclic ring systems contain an embedded 1,3-diene that has been shown to be a suitable reaction partner for a highly stereoselective [4+2] cycloaddition reaction to furnish the 5,5,7,6-ring system as a single stereoisomer.

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# Chapter 1. Introduction to Asymmetric Catalysis and Catalytic Asymmetric Alkynylzinc Additions to Aldehydes

## 1.1 Introduction

Asymmetric synthesis is an integral part of modern organic chemistry. This is due largely to nature's inherent value of stereochemistry. Amino acids, the fundamental building blocks of proteins, are chiral and as a result the proteins and enzymes that are key actors in biological processes are chiral entities. Due to the innate chirality of biological targets, it is no surprise that the enantiomers of drug molecules can differ significantly in biological activity, pharmacokinetics, and toxicity.[1] This makes methods to access asymmetric molecules highly valuable for medicinal chemists and pharmaceutical companies. Attesting to the importance of stereochemistry to the medicinal world, two-thirds of prescription drugs are chiral.[2] The pharmaceutical industry has moved away from racemic drugs to the synthesis and evaluation of single enantiomer drugs, such that by 2001 almost no racemate drugs were marketed.[3] In large part, this biological demand for asymmetric methodologies has driven the development of asymmetric synthesis. Despite significant advances, there is still much ground to be gained for asymmetric synthesis both in reaction scope and practical utility. As a result, a large portion of the chirality contained in marketed drugs is still derived from the pool of naturally available chiral building blocks.[3] Beyond medicine, asymmetric synthesis is also relevant for other applications, including agricultural chemicals, flavors, fragrances, and materials.[2] Additionally, the continual discovery of biologically and chemically

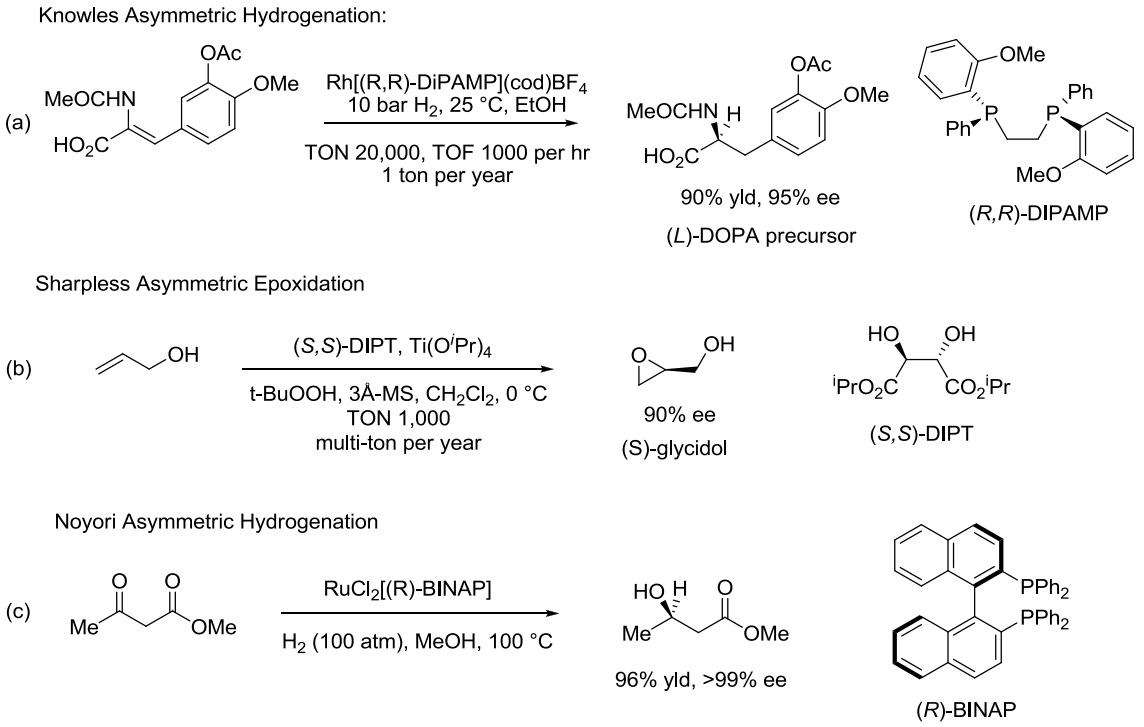
interesting natural products possessing multiple sights of chirality has motivated the investigation of new methods for asymmetric synthesis.

Asymmetric catalysis has become an increasingly important field within asymmetric synthesis. Asymmetric catalysis can broadly be defined as the use of substoichiometric amounts of "enantioenriched catalysts to transform prochiral and racemic substances into valuable enantioenriched synthetic building blocks."[4] The awarding of the 2001 Nobel Prize in Chemistry to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless, pioneers in the field of asymmetric catalysis, emphasizes the importance of asymmetric catalysis to the scientific community. As shown in Scheme 1.1 Knowles developed a highly efficient asymmetric hydrogenation of α-acylamidoacrylic acids. Highlighting the importance of asymmetric catalysis for the synthesis of pharmaceuticals, this method was applied to the synthesis of (*L*)-3,4-dihydroxyphenylalanine (*L*-DOPA), an anti-Parkinson's drug.[5c] Sharpless's asymmetric epoxidation[6] and Noyori's asymmetric hydrogenation[7] (Scheme 1.1) have become widely utilized mainstays in organic synthesis and demonstrate the importance of asymmetric catalysis to the synthetic community.

The field of asymmetric catalysis offers many advantages for asymmetric synthesis over other strategies.[2] Methodologies such as the use of chiral auxiliaries require stoichiometric amounts of chiral reagents, and resolution of racemic mixtures of enantiomers yields a maximum of 50% of the desired enantiomer. In contrast asymmetric catalysis employs substoichiometric amounts of chiral catalysts that are regenerated, and possesses the potential of achieving yields reaching 100%. This increased efficiency mimics in the laboratory what nature has perfected in enzyme

catalysis. Despite significant advances in asymmetric catalysis, we are still far from achieving the effectiveness of enzymes.

**Scheme 1.1.** Widely Useful Catalytic Asymmetric Reactions.




An ideal catalytic system should be efficient in several ways. First chemical yield and stereoselectivity should be maximized with the minimal use of all reagents and waste. Trost has termed one measure of this efficiency "atom economy," in which the molecular weight of the desired products is divided by the sum of the molecular weights of *all* the substances produced in the stoichiometric equation.[8] For a reaction to possess high atom economy it must proceed with high levels of selectivity, including chemoselectivity, regioselectivity, and stereoselectivity, and without significant amounts of byproducts. Secondly, cost and availability of the reagents must also be considered if a method is to be practical. This discourages the use of chiral catalysts accessed by

multi-step reaction pathways. Thirdly, scalability of the catalyzed process is important if it is to be useful in a variety of contexts. Especially important for industry is the turnover number (TON), or the number of catalytic cycles each catalyst molecule is capable of performing, and turnover frequency (TOF), or the amount of time it takes for each catalyst molecule to complete the catalytic cycle.[4] These factors are important because of the costs associated with running large scale chemical reactors. Use of a chiral catalyst capable of high TON and TOF significantly reduces the catalyst loadings and reaction times and decreases the cost of the process. These criteria have been best accomplished in reductive and oxidative reactions as exemplified in Scheme 1.1. The use of Knowles' asymmetric hydrogenation produces 1 ton per year of the (*L*)-DOPA precursor, and Sharpless's asymmetric epoxidation produces multiple tons per year of (S)-glycidol, a useful chiral building block.[4] The development of catalytic asymmetric carbon-carbon bond forming reactions has not yet reached this level of effectiveness.

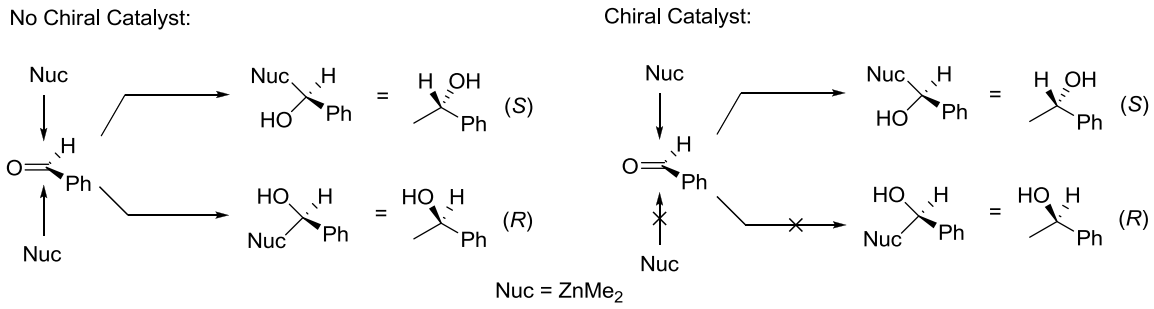
## 1.2 General Principles of Asymmetric Catalysis

### *a. Ligand Accelerated Catalysis*

Catalyzed asymmetric reactions generally involve a prochiral substrate that in the presence of another reagent is transformed into a chiral molecule. If the reaction proceeds in the absence of a chiral reagent a mixture of enantiomers would be produced. For example, in the addition of $ZnMe_2$ to benzaldehyde, the nucleophilic methyl species could add to the top or bottom face of the prochiral electrophile, generating a 50/50 mixture of the (*R*) and (*S*) enantiomers (Scheme 1.2). In contrast, in the presence of a chiral catalyst the reaction could proceed with attack primarily on one of the prochiral

faces of the aldehyde. This causes the product to be formed as an excess of one enantiomer.

**Scheme 1.2.** Racemic and Asymmetric Reaction Pathways of $ZnMe_2$ Addition to Benzaldehyde.

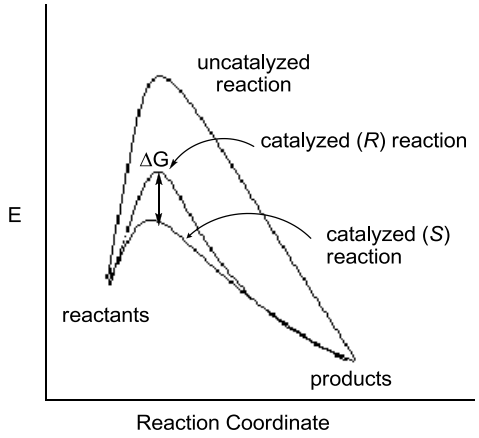



Ideally the two achiral reagents would not react with each other in the absence of the chiral catalyst. The addition of a chiral catalyst then allows the reaction to proceed in a chiral environment. This scenario is termed ligand accelerated catalysis,[9] and is advantageous because the racemic background reaction is eliminated and does not erode the enantioselectivity of the process. In a simplified understanding, the preference for nucleophilic attack on one prochiral face of the aldehyde can be accounted for by two possible diastereomeric reaction pathways created by the presence of the chiral catalyst. One pathway leads to attack on the top or *si* face of the aldehyde as shown in Scheme 1.2 to form the (*S*)-enantiomer, and the other leads to attack on the bottom or *re* face of the aldehyde as shown in Scheme 1.2 to form the (*R*)-enantiomer.

If the difference in energy between the two diastereomeric pathways is large enough, high enantiomeric excess can be achieved. Based on the equation $\Delta G = -RT\ln K$ (K = enantiomeric ratio), an energy difference of 2.7 kcal/mol provides an enantiomeric ratio of ~99:1 at room temperature. This difference in energy could be the result of

significant stabilization of the (S)-pathway or significant destabilization of the (*R*)-pathway by the chiral catalyst. Figure 1.1 shows a reaction coordinate of an ideal ligand accelerated catalytic system. Here the energy of the uncatalyzed reaction is too high to produce the product. The catalyzed pathway lowers the energy of the reaction so that it is now possible. Furthermore, it lowers the energy of the (*S*)-reaction pathway in comparison to the (*R*)-reaction pathway to a great enough extent that only this pathway is preferred.

**Figure 1.1.** Uncatalyzed and Asymmetric Catalyzed Reaction Coordinate.

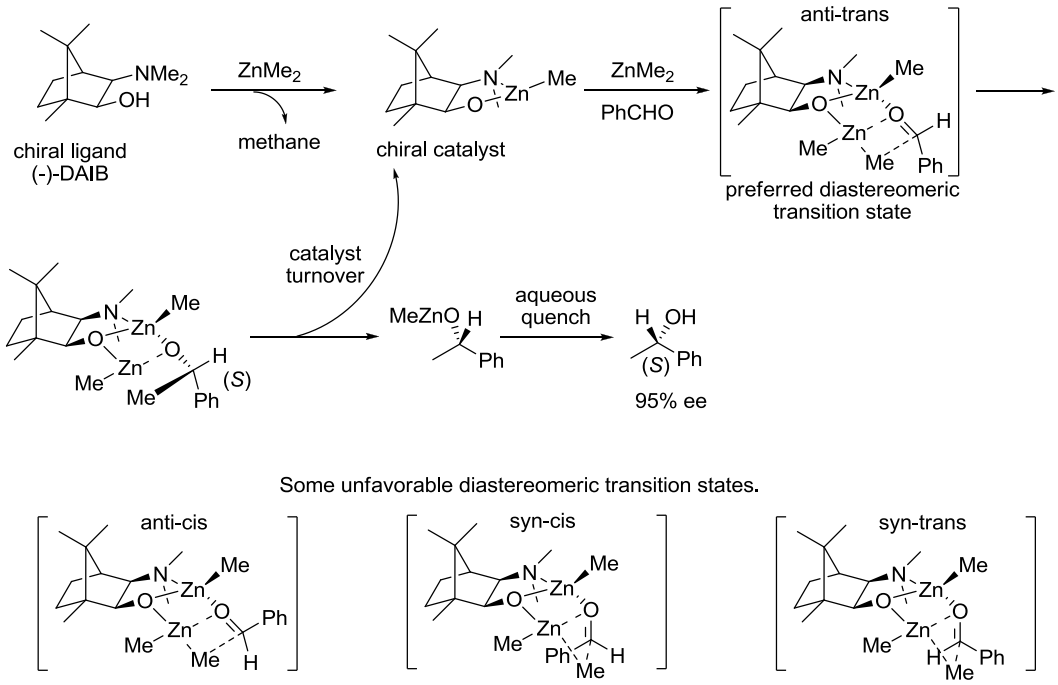



The use of (-)-3-exo-dimethylaminoisobornenol, (-)-DAIB, as a chiral ligand for the asymmetric addition of $ZnMe_2$ to benzaldehyde can serve to illustrate the principle of ligand accelerated catalysis.[4,10] As the activation energy barrier of the uncatalyzed reaction is too high, no reaction is observed between $ZnMe_2$ and benzaldehyde at room temperature. As shown in Scheme 1.3, addition of the chiral ligand (-)-DAIB leads to deprotonation of its hydroxyl group in the presence of $ZnMe_2$ to form the active catalyst species, a β–amino zinc alkoxide. This catalyst coordinates $ZnMe_2$ and benzaldehyde and activates them for the reaction. While multiple diastereomeric transition states are

available, energetically only two are viable. The aldehyde coordinates in an *anti*-trans fashion with respect to the chiral ligand, and the attack is on the *si* face of benzaldehyde. This diastereomeric transition state is sufficiently lower in energy than alternative transition states, and thus the corresponding (*S*)-alcohol is formed in 95% ee.

This example highlights the fact that there are often multiple reaction pathways available for an asymmetric catalytic process, and that a reaction can not always be sufficiently understood using a two-state model. This is not problematic as long as only one pathway is predominate, or as long as the lowest energy pathways lead to the same enantiomer of the final product.

**Scheme 1.3.** (-)-DAIB Catalyzed Addition of $ZnMe_2$ to Benzaldehyde.

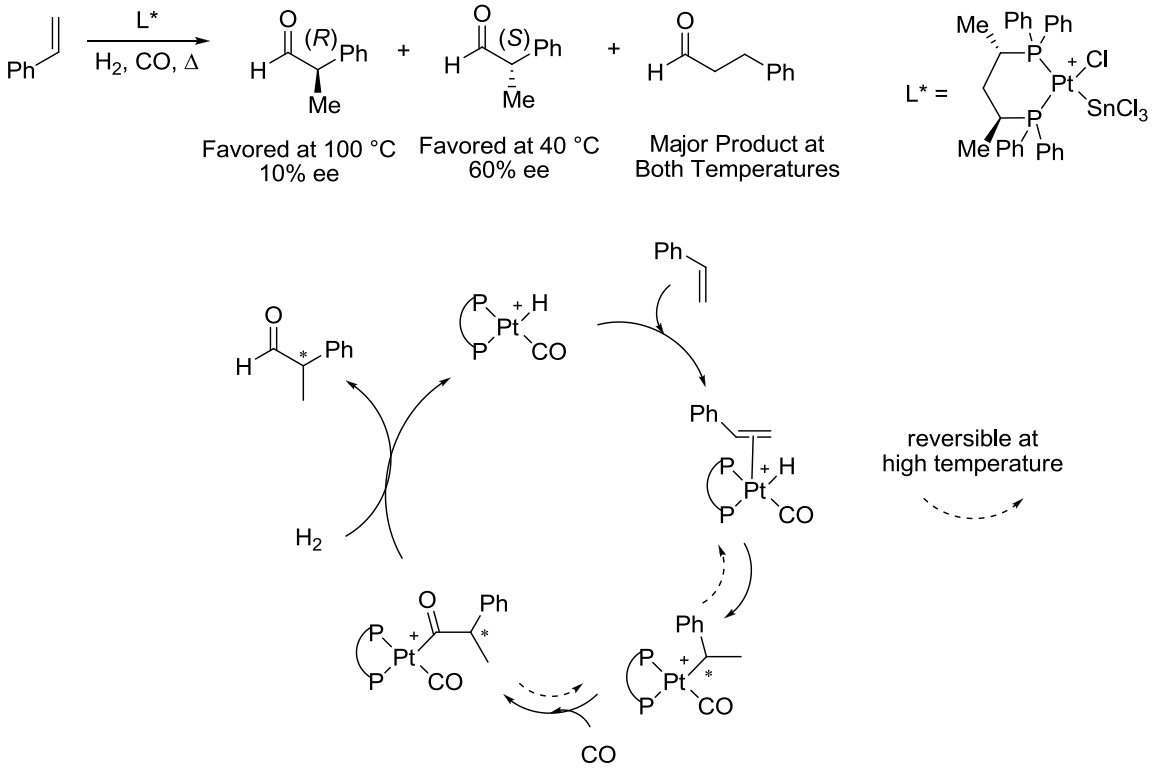



*b. Temperature, Solvent, and Additive Effects*

Many factors of the catalytic system impact the enantioselectivity of the reaction. Among these are temperature and solvent effects. Often lowering the reaction

temperature corresponds to an increase in enantioselectivity due to the relationship $\Delta G = -RT\ln K$. However, this is not always the case because as the temperature changes different reaction pathways can become available and the rate-determining step can change. This means that in practice, asymmetric-catalyzed reactions should be screened over a range of temperatures. If the enantioselectivity does not follow a linear relationship with the inverse of the temperature, this suggests that different reaction pathways become important at different temperatures for determining the stereoselectivity of the process.

**Scheme 1.4.** Temperature Effect on Enantioselectivity in Platinum Catalyzed Hydroformylation.



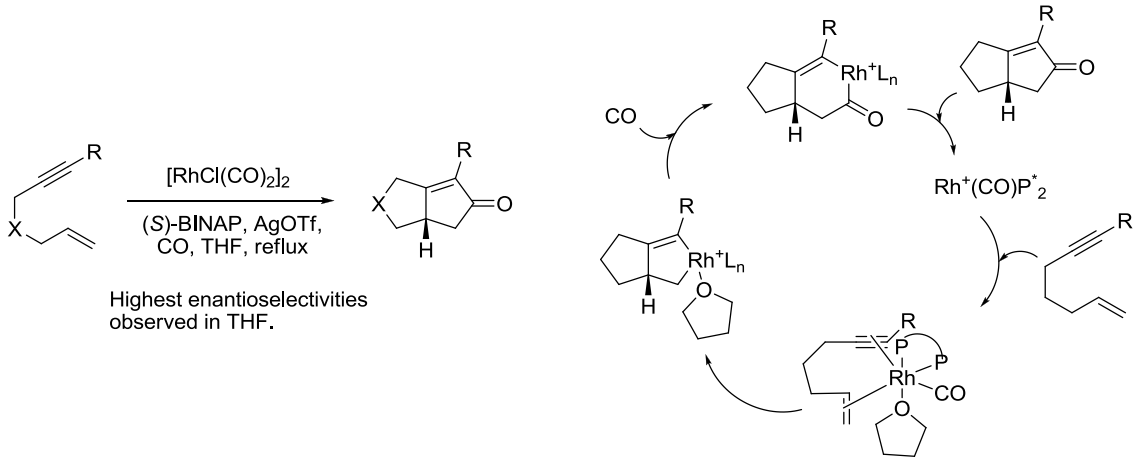

An example of this can be seen in the platinum catalyzed hydroformylation of styrene shown in Scheme 1.4.[11] At lower temperatures (40 °C) the (*S*)-enantiomer

predominated, with the stereodiscriminating step occurring during platinum hydride addition to styrene to form the platinum alkyl intermediate. At higher temperatures (100 °C) this step becomes reversible as does platinum acyl formation, and platinum acyl hydrogenolysis becomes rate determining. As the (R)-enantiomer undergoes this step more quickly, it is favored at higher temperatures.

The choice of solvent can also significantly impact the enantioselectivity of the reaction. The solvent polarity is important to ensure the solubility of all the reaction components, especially the chiral catalyst, and the polarity can affect the stability of the competing diastereomeric reaction pathways. The coordinating ability of the solvent should also be considered. Strongly coordinating solvents such as THF are capable of altering metal catalysts significantly, and can result in greatly enhanced or diminished enantioselectivity or shut down the reaction altogether. For example, in the asymmetric PK-type reaction of achiral enynes, the use of THF was required for high enantioselectivity (Scheme 1.5).[12] In this case it was proposed that coordination of the solvent to Rh encourages the formation of octahedral geometry at the metal center which is thought to be more favorable for stereodiscrimination during the oxidative addition step. Finally concentration effects can also be observed. Higher concentrations, besides generating less waste, are usually optimal for efficiency of the reaction, unless undesired reactions start to become competitive at these concentrations. Concentration can affect enantioselectivity as well, though this effect is not usually pronounced.[13] At lower concentrations the reaction mixture is less saturated with the catalyst and the background reaction could become competitive. Again the practical implication is that it is best to

screen a number of solvents and concentrations during the optimization of an asymmetric catalytic system.

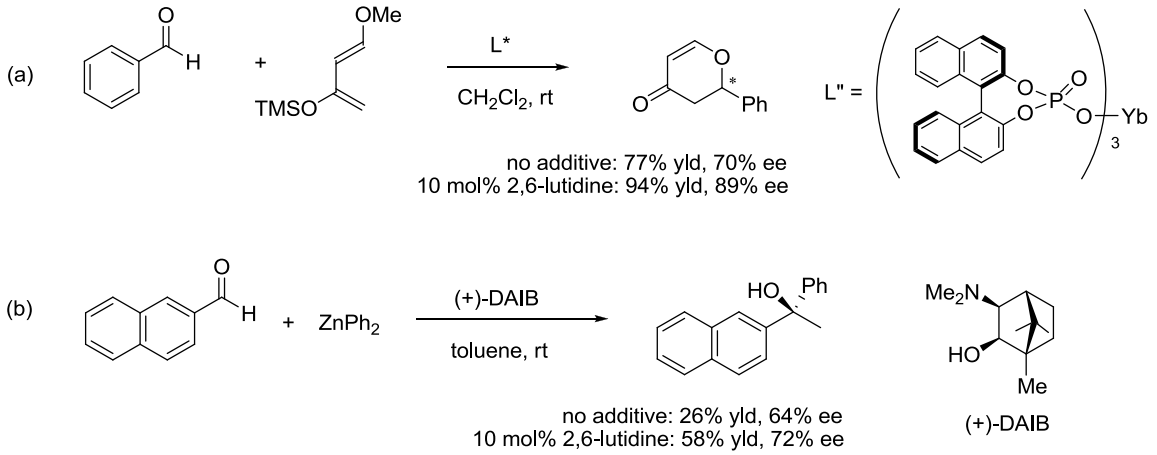
**Scheme 1.5.** Solvent Effect on Enantioselectivity in Rhodium Catalyzed Pauson Khand-Type Cyclization.




Additives have often been shown to affect the enantioselectivity of the reaction.[14] These additives are usually Lewis bases and can function in a variety of ways. Among these are: promoting the dissociation of inactive catalyst aggregates, aiding in the removal of the product from the catalyst to increase the TOF, coordination to metal centers resulting in a change of metal geometry or electronic character, and poisoning less enantioselective but more active catalysts.[14] In any given instance a combination of these effects may be operative. The use of achiral additives is especially appealing as a large number of additives can be quickly screened, and may significantly improve a moderately successful catalyst system. A variety of additives have proven effective including amines, pyridines, pyridine N-oxides, alcohols, phosphines, phosphine oxides, and halides. For example, in the $Yb^{III}$-phosphate catalyzed asymmetric hetero Diels-Alder reaction addition of 10 mol % 2,6-lutidine caused an increase in ee from 70% to

89%, as shown in Scheme 1.6a.[15] In this case the amine was thought to be responsible for dissociating catalyst aggregates and thereby increasing the solubility of the catalyst. Simple alcohols such as methanol have also been used successfully. In the asymmetric addition of diphenylzinc to ketones reported by Fu and Dosa, addition of 1.5 equiv of methanol increased the enantioselectivity from 64 to 72% ee, along with doubling the yield (Scheme 1.6b). Here it was postulated that the addition of methanol altered the nature of the zinc catalyst species. These examples highlight the potential benefit of screening achiral additives to improve the enantioselectivity of a reaction.

**Scheme 1.6.** Beneficial Effect of Achiral Additives in Asymmetric Catalysis.

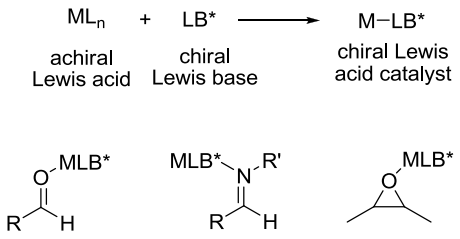



*c. Lewis Acid Catalysis*

Chiral catalysts can function in a variety of ways. The most common mechanism however is through Lewis acid catalysis. In these instances a Lewis acidic species is combined with a chiral Lewis basic ligand to generate a chiral Lewis acid catalyst (Figure 1.2). It is preferable for the resulting catalytic species to be more active than the free Lewis acid. In this way the reaction is promoted only in the chiral environment. It is possible, however, for the free Lewis acid to be more catalytically active. This is termed

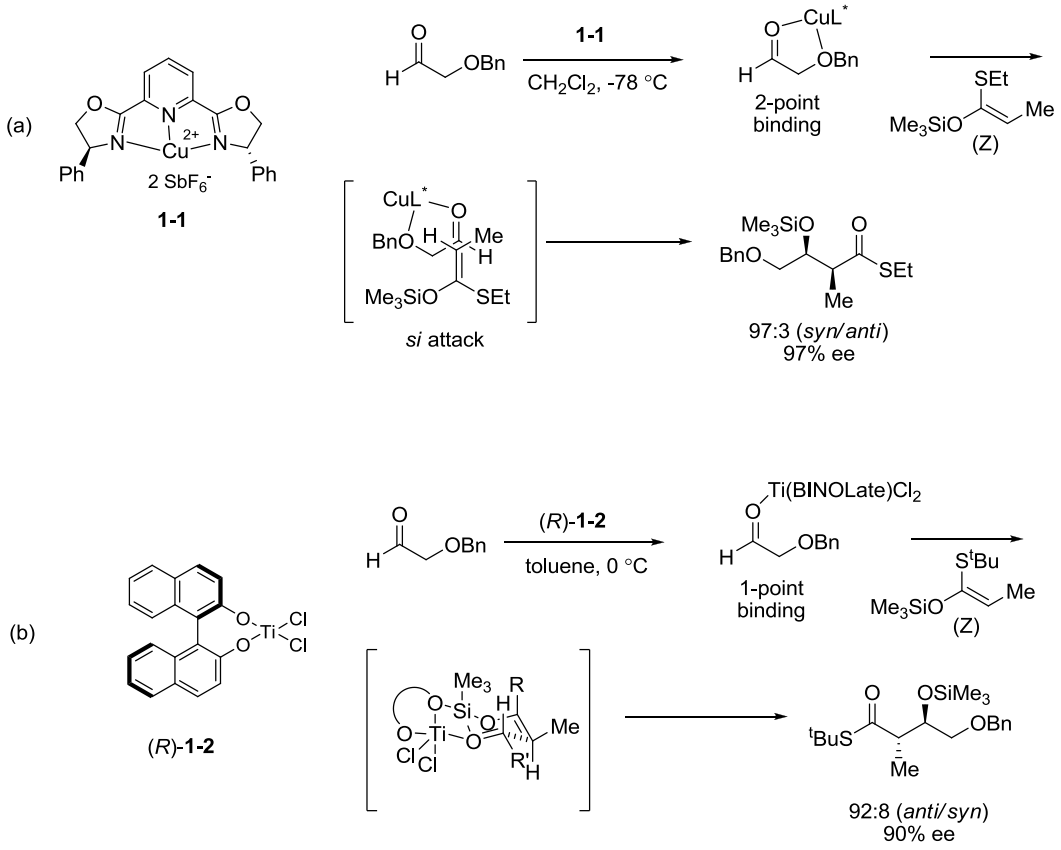
ligand decelerated catalysis, and in these instances an excess of the chiral ligand must be employed to ensure a minimal amount of the free achiral metal species is present. The common use of chiral Lewis acid catalysis is due to the large number of Lewis basic functional groups. For example, carbonyl compounds, epoxides, and imines are common substrates in which chiral Lewis acidic catalysis has been highly successful. For these substrates, coordination of the Lewis acid serves to lower the energy of the lowest unoccupied molecular orbital (LUMO), activating the electrophile toward nucleophilic addition.

**Figure 1.2.** Formation of Chiral Lewis Acid and Common Substrates.




Coordination of the Lewis acid catalyst may occur through one-point or multiple-point binding with the substrate depending on the nature of the substrate and chiral catalyst.[4] Several general factors can be associated with these modes of coordination. Two-point binding can be advantageous because it greatly restricts the possible orientations of the activated substrate in the catalytic pocket. However, useful substrates are limited to those containing other chelating groups in the molecule. In contrast, in one point binding rotation around the Lewis acid-substrate bond is possible, and thus increased substrate orientations are more likely. When this mode can be employed successfully it represents a much more general catalyst system.

**Scheme 1.7.** Mukaiyama Aldol Catalyzed by One-Point and Two-Point Binding Catalytic Systems.



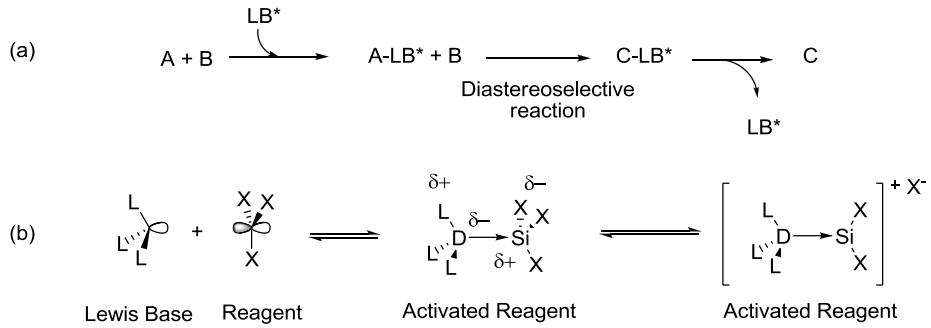

An example[4] of one- and two-point binding is illustrated in the Mukaiyama aldol reaction catalyzed by the Cu-PhPyBox catalyst[16] and the (BINOLate)$TiCl_2$ catalyst (Scheme 1.7).[17] The Cu-PhPyBox catalyst is thought to proceed via two-point binding since a second chelating group in the electrophile is necessary for high enantioselectivities to be obtained. For these substrates the nucleophile was observed to attack the *si* face of the aldehyde. In contrast, the (BINOLate)$TiCl_2$ catalyst likely functions through a one-point binding mechanism since it is also effective for nonchelating substrates. In this example, the different modes of binding can serve to promote different outcomes for the reaction. Due to an open transition state and the two-

point binding of the substrate in the Cu-PhPyBox catalyzed reaction, the diastereoselectivity of the resulting β–hyroxy ketone is *syn* when either the (E) or (Z)-silyl ketene acetal is used (Scheme 1.7a). In contrast, the one-point binding of the (BINOLate)$TiCl_2$ catalyst makes possible a closed transition state in which the silyl ketene acetal could be coordinated by one of the BINOLate oxygens (Scheme 1.7b). In this instance the diastereoselectivity is determined by the geometry of the silyl ketene acetal.

*d. Lewis Base Catalysis*

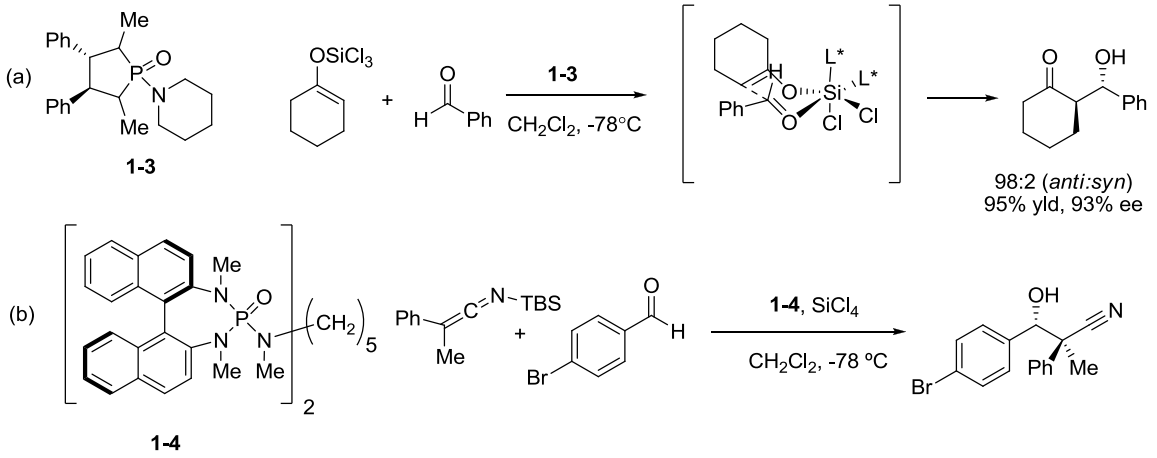
Lewis base catalysis (also referred to as nucleophilic catalysis) is also a prominent mode of asymmetric induction, especially in reaction systems in which Lewis acidic catalysis is not possible. In this scenario, that catalyst typically functions by a covalent or noncovalent interaction with a Lewis base accepting substrate involved in the reaction. This yields an activated chiral substrate which then undergoes a diastereoselective reaction to yield the optically active product and regenerate the catalyst (Figure 1.3a). For Lewis base catalysis to be viable it must be an instance of ligand-accelerated catalysis or the racemic background reaction will predominate.

**Figure 1.3.** Lewis Base Catalysis.



An example of this is Denmark's use of chiral phosphoramide catalysts in the Mukaiyama aldol reaction.[18] The principle of Lewis base catalysis in this system is illustrated in Figure 1.3b. Here a silicon-containing reagent is the Lewis base acceptor. The neutral donor can coordinate with the Lewis acidic silicon contained in the substrate. Due to silicon's polarizable Si-X bonds an excess of electron density is built up on the more electronegative X groups. This causes the silicon to possess a greater degree of positive character, and can even proceed to the point that one of the negatively charged ligands dissociates leaving a cationic silicon center.

**Scheme 1.8.** Lewis Base Catalyzed Mukaiyama Aldol Reaction by Chiral Phosphoramide Ligands.



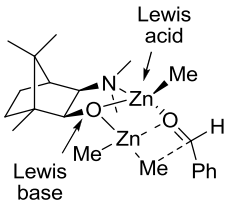

Early work by Denmark's group focused on the use of silicon containing substrates such as trichlorosilyl enolates.[18b] An example of this is shown in Scheme 1.8a. Here the chiral Lewis basic ligand coordinates with the silicon of the enol trichlorosilane. This coordination builds up excess negative charge on the atoms bound to silicon, making the silicon more Lewis acidic such that it binds and activates the aldehyde towards addition in the chiral environment. Later work utilized this principle with the use of

stoichiometric $SiCl_4$, allowing a wider range of substrates useful for this catalytic system (Scheme 1.8b).[18c] Although an external Lewis acid is employed, this is still considered a case of Lewis base catalysis, because the amount of the chiral Lewis base employed is catalytic, and the stoichiometric achiral Lewis acid is unable to catalyze the reaction on its own.

*e. Bifunctional Catalysis*

Lewis acid and Lewis base activation can be combined into a single catalyst structure, resulting in a bifunctional catalyst. This type of catalyst benefits from a more sophisticated activation of the substrates in which the catalyst brings together and activates both reaction partners in a chiral environment. Bifunctional catalysts can be separated into two classes.[4] Interdependent bifunctional catalysts contain two catalytic sites that are electronically coupled to each other. Independent bifunctional catalysts possess catalytic sites that are electronically independent.

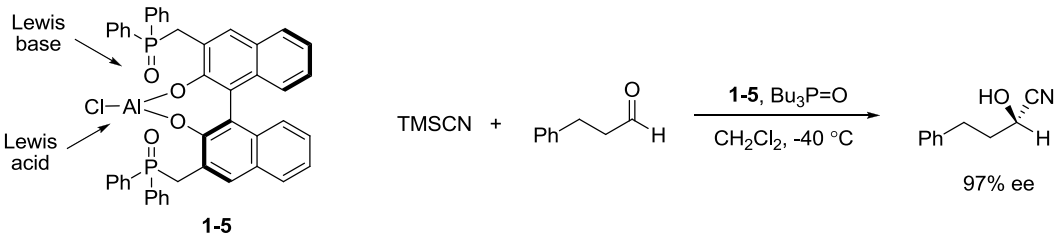
**Figure 1.4.** Interdependent Bifunctional Catalyst.




For example, the chiral catalyst derived from DAIB and $ZnMe_2$ represents an interdependent bifunctional catalyst (Figure 1.4). The Lewis acidic Zn metal serves to activate the aldehyde, while the neighboring Lewis basic oxygen atom activates the $ZnMe_2$ for addition. The catalytic sites are interdependent because they are coordinated with one another and altering the Lewis basic sight will also alter the Lewis acidic zinc metal. While this interdependence makes it difficult to fine-tune one catalytic site

without affecting the other, the connectivity of the active sites can lead to a highly ordered transition state.

**Scheme 1.9.** Independent Bifunctional Catalyst for Cyanosilylation of Aldehydes.



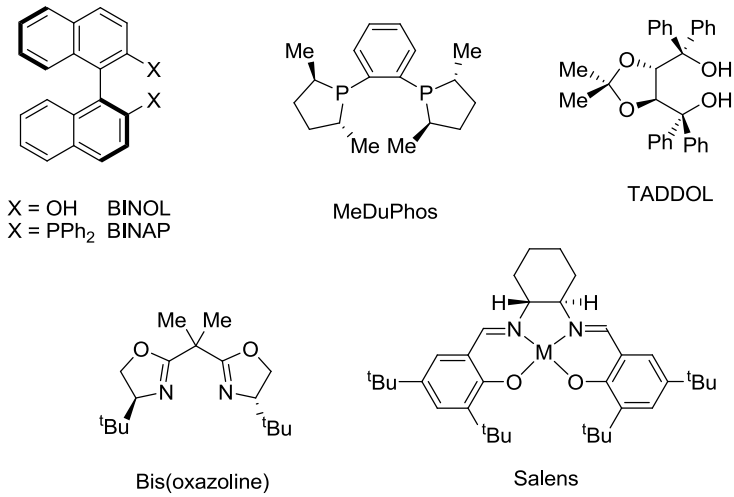

In contrast an independent bifunctional catalyst possesses two catalytic sites separated by intervening atoms in the catalyst structure. This allows one catalytic site to be tuned while holding the other constant. However, the distance of the catalytic sites from one another presents the possibility of a less ordered transition state due to the more flexible catalyst structure. In these systems it is important that the two catalytic sites do not quench each other and deactivate the catalyst. An example of an independent Lewis acid-Lewis base bifunctional catalyst is seen in Scheme 1.9 for the cyanosilylation of aldehydes.[19] In bifunctional catalyst **1-5** the aluminum metal center serves as the Lewis acid to activate the aldehyde and the distal phosphine oxides serve as the Lewis base to activate the cyanide nucleophile. Here an advantage of the independent catalytic sites was utilized, as several phosphine oxides derivatives were screened to identify the optimal linker distance and structural characteristics.

*f. Catalyst Structure*

In all of these modes of asymmetric induction, the stereocontrol of the reaction is most often the result of steric bias imposed by the chiral catalyst. In other words, coordination of the chiral catalyst may preferentially shield one of the prochiral faces of

the substrate. Due to this means of transmitting stereocontrol it has been reasoned and often observed that chiral ligands possessing a $C_2$-symmetric axis are more enantioselective than non $C_2$-symmetric ligands. This has be accounted for by the fewer metal-ligand adducts and diastereomeric transition states possible for the more symmetric ligands in comparison to less symmetric ones.[20,21] As evidence of this, of the "privileged ligands" described by Yoon and Jacobson in 2003, a significant number are characterized by $C_2$-symmetry (Figure 1.5).[22] These ligand classes have been termed "privileged" because they have shown utility in asymmetric catalysis over a range of reactions.

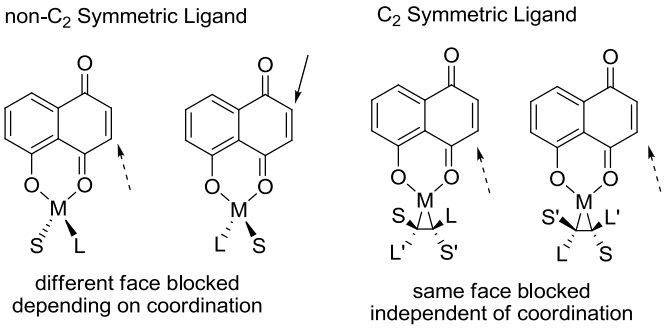
**Figure 1.5.** $C_2$-Symmetric "Privileged" Ligands.



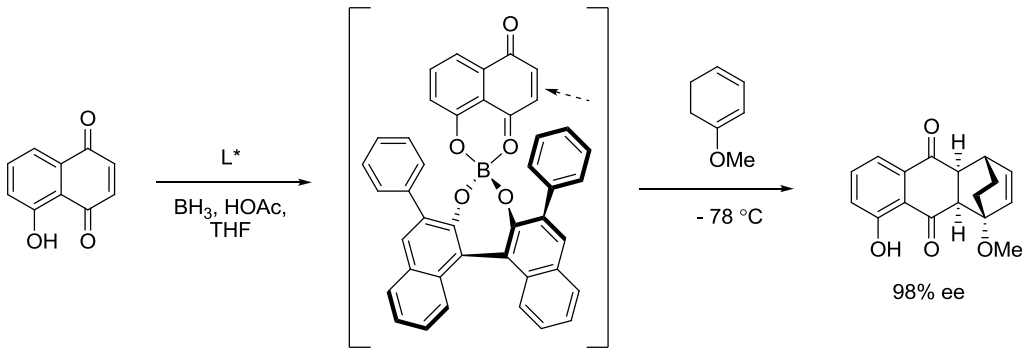

An example of the advantage of $C_2$-symmetry was exemplified by Kelly's rational design of a $C_2$-symmetric ligand for the Diels Alder reaction of peri-hydroxyquinones (Scheme 1.10).[23] During efforts to develop a chiral catalyst to activate the dieneophile and block one of its faces, Kelly and co-workers realized that a non-$C_2$-symmetric catalyst possessing a large blocking ligand in combination with a smaller ligand could bind to the substrate in multiple modes (Figure 1.6). These different modes of binding would block opposite faces of the dienophile. In contrast, a bidentate ligand possessing

$C_2$-symmetry has fewer binding modes and should block the same face regardless its approach to the dienophile. This strategy was successfully employed in the Diels-Alder reaction shown in Scheme 1.10. Using a functionalized BINOL ligand bearing phenyl substituents at the 3,3'-positions, the Diels Alder product was formed in 98% ee. When the blocking phenyl groups were replaced with sterically smaller methyl groups the enantioselectivity was reduced to 70%.

**Figure 1.6.** Advantages of $C_2$-Symmetric Ligand.



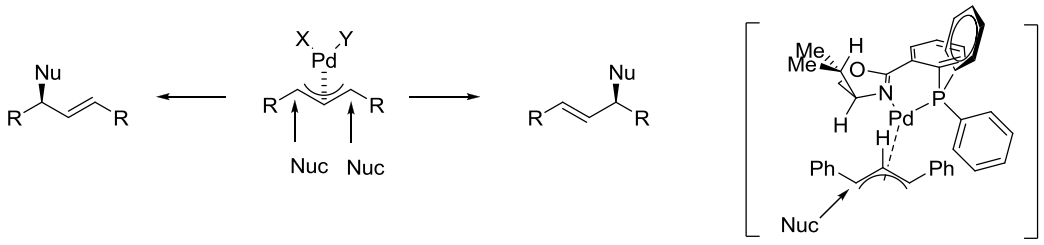

**Scheme 1.10.** $C_2$-Symmetric Catalyst for Asymmetric Diels Alder Reaction.




However, as Pflatz and Drury have pointed out, "Although the concept of $C_2$ symmetry has been very successful, there is no fundamental reason why $C_2$-symmetric ligands should necessarily be superior to their nonsymmetrical counterparts."[21] A good example of this case was demonstrated by the use of the phosphinooxazoline (PHOX) ligands for asymmetric allylation reactions of symmetrical allyl complexes.[21] In these

reactions, the enantiocontrol is determined by the regioselectivity of the nucleophilic attack (Figure 1.7). This example points out that electronic biasing by the ligand can also be an important means of stereocontrol. In this scenario a $C_2$-symmetric ligand will be unable to provide any electronic bias to direct which position is attacked. However, an unsymmetrical ligand containing different coordinating groups on the metal could electronically differentiate the two possible positions of attack, constituting a better chiral catalyst for this reaction. This was demonstrated by use of the PHOX ligands for the asymmetric alkylation of symmetrical allylic acetates with dimethyl sodiomalonate in which the steric and electronic properties of the chiral catalyst are responsible for the enantiocontrol of the reaction. The binding mode of the π-allyl system to the metal is governed by the steric bias of the ligand. Once coordinated the allyl species is most reactive *trans* to the phosphorus ligand due to the electronic bias imparted by the chiral catalyst, leading to good regiocontrol and thus enantioselectivity (Figure 1.7). It can be concluded that different types of ligands can be optimal depending on the mechanism of the reaction.

**Figure 1.7.** Potential Advantages of Non-$C_2$-Symmetric Catalysts.




*g. Summary*

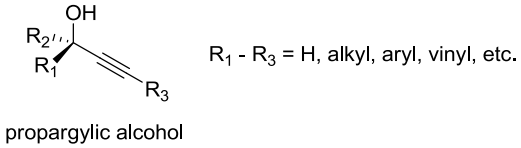
Despite these basic concepts, in actual practice designing a successful chiral catalyst is extremely complex. A host of factors can contribute to the stereocontrol

imposed by the chiral catalyst and cause a large number of diastereomeric pathways to be available. This makes *a priori* design of a ligand for a given reaction difficult. Due to the complexities of catalytic systems, Walsh has accurately stated that, "the era of rationally designed catalysts may be in the distant future."[24] Still, Walsh maintains that chance of success is higher when the ligand design takes into account the principles of asymmetric catalysis and the potential mechanism of the reaction to be catalyzed.[4] From this rational starting point however, there is no substitute for an empirically and theoretically driven cycle of catalyst design, screening, optimization, and modification.

### 1.3 Asymmetric Alkynylzinc Additions to Aldehydes

A specialized field within asymmetric catalysis is the asymmetric synthesis of propargylic alcohols. The structure of the propargylic alcohol is defined by an alkyne containing an adjacent alcohol as shown in Figure 1.8. Propargylic alcohols possess chirality at the propargylic carbon when $R_1 \neq R_2$. They are secondary alcohols when $R_1$ or $R_2$ = hydrogen and tertiary alcohols when $R_1$ and $R_2 \neq$ hydrogen. Significant attention has been directed towards these substrates due to their promising utility as chiral building blocks for the synthesis of more complex molecules.

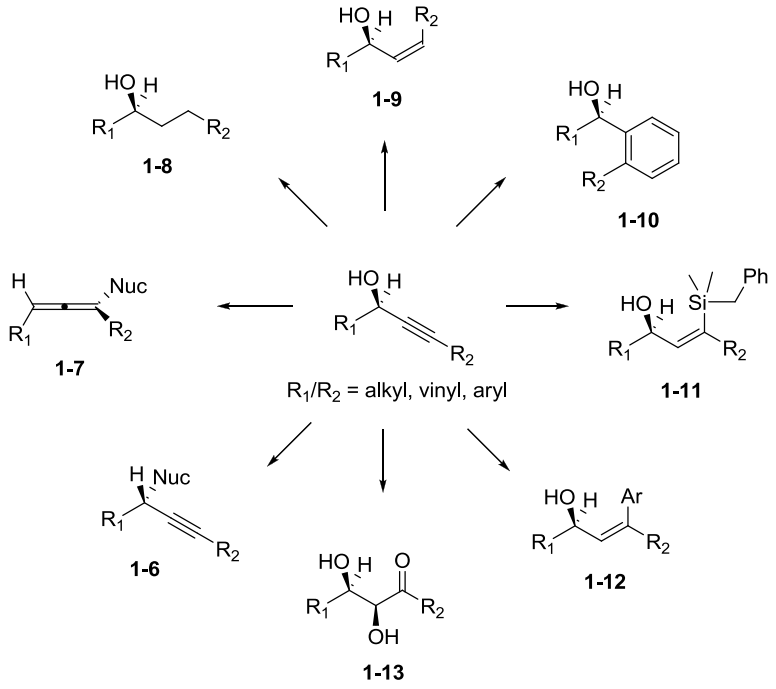
**Figure 1.8.** Propargylic Alcohols



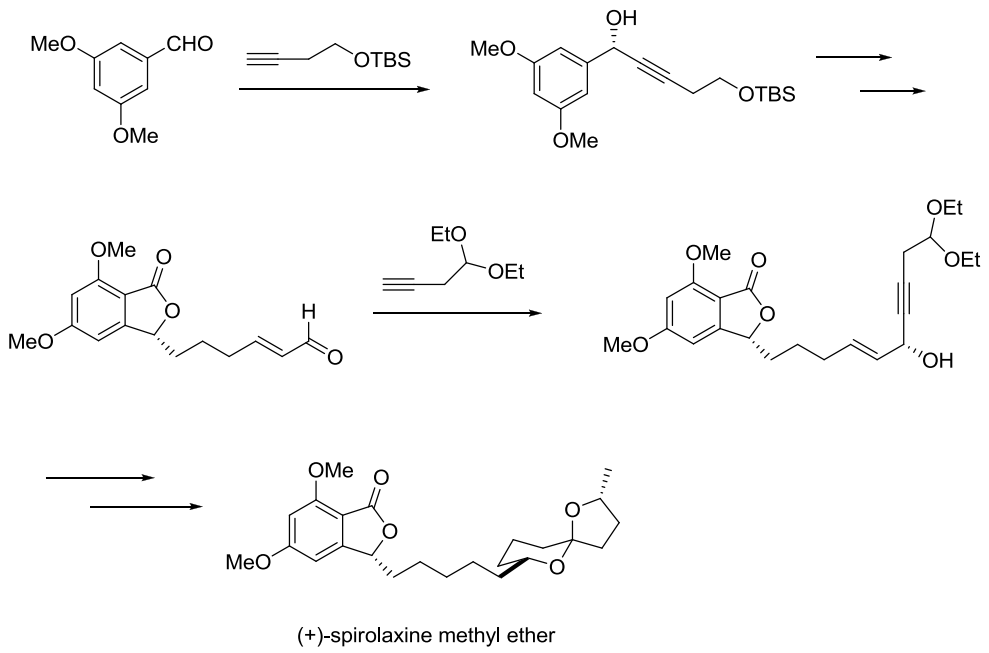
*a. Utility of Propargylic Alcohols*

As shown in Figure 1.9 propargylic alcohols are versatile substrates for a variety of further transformations due to the chemistry of the alcohol and the alkyne functionalities.[25] For example, the propargylic position can be modified by $S_N2$ displacement of the activated alcohol to yield **1-6**. Alternatively $S_N2$' displacement can provide access to the optically active allenes, **1-7**. The chemistry of the triple bond can also be utilized, by reducing it completely to alkane **1-8**, or selectively to alkene **1-9**. Alternatively the triple bond could be left in tact and used in a metal catalyzed [2+2+2] cycloaddition to access benzylic alcohol **1-10**.[26] As developed by Trost and coworkers, metal catalyzed hydrosilylation can afford vinyl silane **1-11** with good regioselectivity.[27] These vinyl silanes can be used in palladium catalyzed cross coupling reactions to afford trisubstituted olefin **1-12**, or oxidatively transformed into hydroxy ketones **1-13**.[28]

**Figure 1.9.** Synthetic Transformations of Propargylic Alcohols.



**Scheme 1.11.** Use of Propargylic Alcohol Intermediates in the Synthesis of (+)-Spirolaxine Methyl Ether.



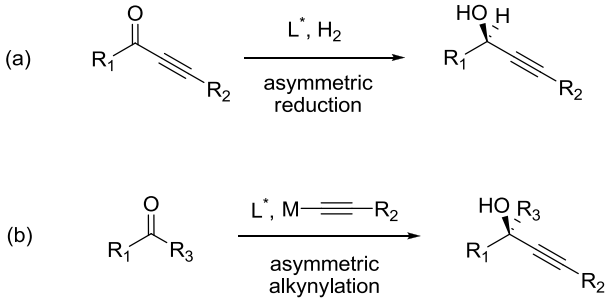

Due to the variety of transformations accessible to these substrates, propargylic alcohols have often been employed in the synthesis of complex molecules.[29] A noteworthy example has been demonstrated in the synthesis of (+)-spirolaxine methyl ether as shown in Scheme 1.11.[30] Here Trost and coworkers introduced the concept of using acetylenes as ketone surrogates. Ketones have held a central position in organic synthesis due to their ability to act as an electrophile at the carbonyl or as a nucleophile through enolate formation. Trost argues that in analogous manner acetylenes possess this bifunctional reactivity, acting as nucleophiles via deprotonation of the alkyne hydrogen or as electrophiles through activation of the $\pi$ system with metal reagents. Acetylenes can be good substitutes for ketones because they are inert to many of the reaction conditions that affect ketones, as well as opening new possibilities for synthetic transformations.[30] Demonstrating the effectiveness of this strategy, (+)-spirolaxine

methyl ether was accessed using two key asymmetric additions of alkynes to aldehydes to form the corresponding propargylic alcohols in route to the final product.

*b. Synthesis of Optically Active Propargylic Alcohols*

Optically active propargylic alcohols have most commonly been accessed through two routes—asymmetric ynone reduction and asymmetric metal-catalyzed alkyne additions to carbonyls.[25] Although either method is viable, the asymmetric alkyne addition strategy possesses several inherent advantages. First, ynone reduction is hampered by the necessity to prepare the alkynyl ketone, an intermediate often observed to be unstable. Beyond the difficulties associated with these substrates, the requirement to form the ynone is less efficient, as at least two synthetic steps are required to reach the desired optically active propargylic alcohol. Secondly, ynone reduction can never be extended to access tertiary propargylic alcohols due to the addition of hydrogen. Asymmetric alkyne addition is a preferable strategy because it addresses both of the drawbacks associated with ynone reduction. It is a much more efficient process as the carbon-carbon bond and new stereocenter are formed in one step. Furthermore, asymmetric alkyne additions to ketones can provide tertiary propargylic alcohols.

**Figure 1.10.** Methods to Access Optically Active Propargylic Alcohols.



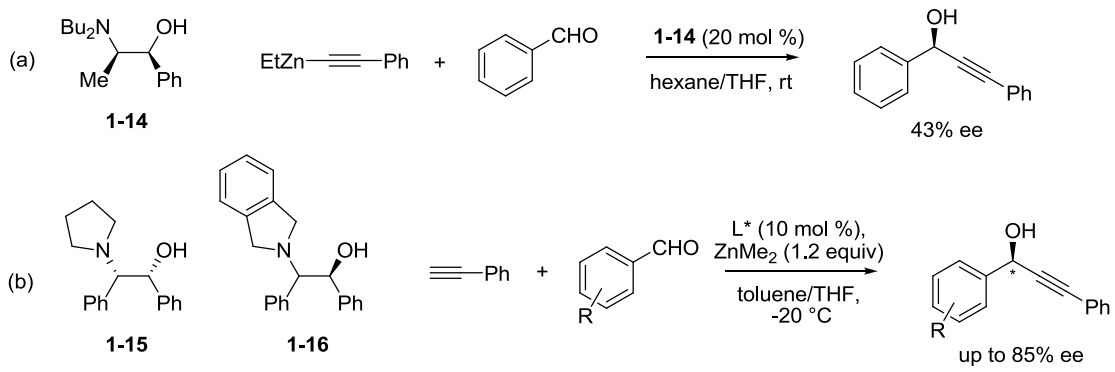
For metal catalyzed asymmetric alkyne additions to carbonyls, the use of zinc to form the corresponding zinc acetylides has been most widely studied.[29] This is due to the many advantages associated with alkynylzinc reagents. First, as a matter of practicality, zinc acetylenes can be conveniently prepared *in situ*, as demonstrated through the reaction of terminal alkynes with dialkylzincs. In many catalytic systems the alkynylzinc can be formed under mild reaction conditions, thus tolerating other sensitive functional groups present on the alkyne. Secondly, and importantly for asymmetric induction, alkynylzinc reagents exhibit a relatively slow background addition to carbonyl compounds in the absence of a catalyst.[25] This minimizes the racemic background reaction that can erode enantioselectivity. Finally, zinc acetylides exhibit a wide range of functional group tolerance, and are unreactive toward esters, amides, nitro groups, and nitriles. All of these features make alkynylzinc reagents attractive nucleophiles for asymmetric catalysis.

Soai and coworkers reported the first catalytic enantioselective alkynylzinc addition to aldehydes in 1990, testing a variety of amino alcohol ligands.[31] As shown in Scheme 1.12a, using 20 mol % of amino alcohol ligand **1-14** in combination with $ZnEt_2$ catalyzed the addition of phenylacetylene to benzaldehyde in 43% ee. In this method the alkynylzinc nucleophile was preformed by heating the alkyne with $ZnEt_2$. While high enantioselectivities were not obtained, this report demonstrated the viability of catalytic asymmetric alkynylzinc additions to aldehydes.

In 1999, Li and coworkers demonstrated that modifications of the amino alcohol framework could create a much more enantioselective catalyst (Scheme 1.12b).[32] Replacement of the methyl group with an additional phenyl group, and the use of cyclic

amines as shown in ligands **1-15** and **1-16** led to catalysts capable of affecting phenylacetylene addition to aromatic aldehydes in up to 85% ee. Here $ZnMe_2$ was used to form the alkynylzinc, and it was found that the alkynylzinc could be formed at low temperatures in the presence of the amino alcohol ligand.

**Scheme 1.12.** Early Amino Alcohol Catalyzed Alkynylzinc Additions to Aldehydes.

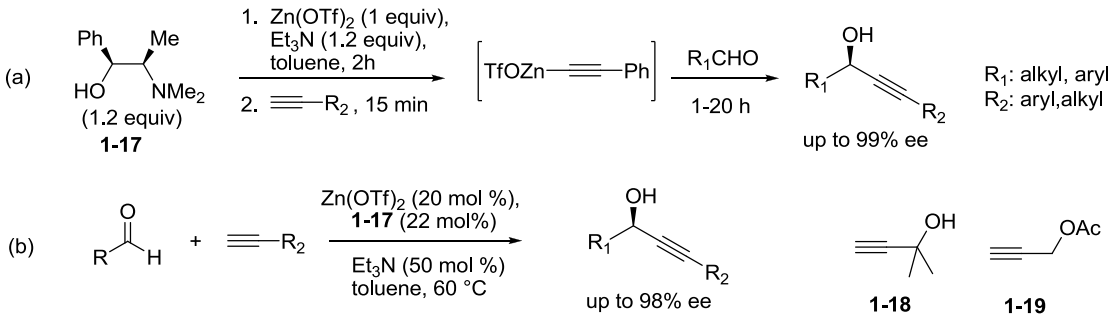



A breakthrough in asymmetric alkynylzinc additions to aldehydes was discovered by Carreira and coworkers in 2000 as for the first time enantioselectivities above 90% were obtained for a broad range of substrates.[33] Instead of using dialkylzinc reagents, $Zn(OTf)_2$ and $Et_3N$ were employed to form the alkynylzinc nucleophile. In the presence of N-methylephedrine (**1-17**) the desired propargylic alcohols could be formed with excellent enantioselectivity (Scheme 1.13a). This method was also shown to be effective with functional alkynes such as **1-18**[33d] and **1-19**.[33e] It was later found that the reaction could be carried out using catalytic amounts of $Zn(OTf)_2$ and **1-17** by heating the reaction to 60 °C (Scheme 1.13b).[33f]

Beyond being the first highly enantioselective report for the addition of alkynes to aldehydes, this catalytic system possessed several advantages. Importantly all of the reaction components were commercially available and relatively inexpensive. This was

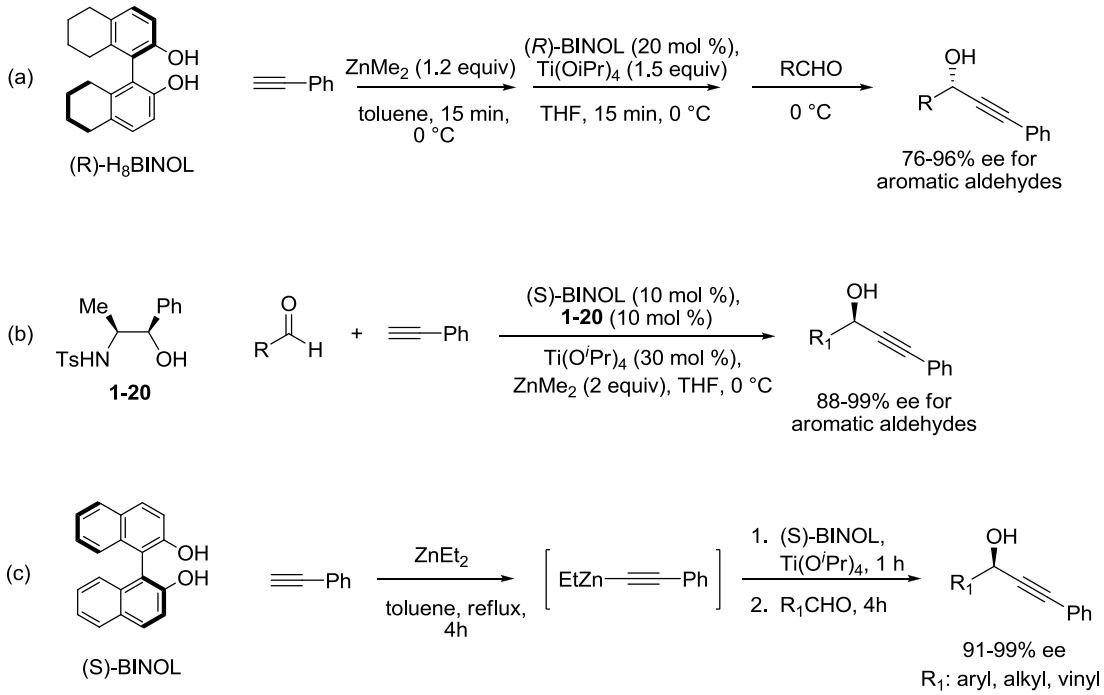
especially important since in its early development stoichiometric amounts of the chiral ligand were required. Secondly, it was shown to be effective for a variety of alkynes, tolerating aryl, alkyl, and functional alkyl substituents. Finally, this catalytic system was extremely robust, and was demonstrated to tolerate water and air. One limitation of the system was reduced yields for addition to aromatic aldehydes because of competitive Cannizaro reactions. Additionally, for linear aliphatic aldehydes competitive aldol condensation was found to occur under the basic reaction conditions.

**Scheme 1.13.** N-Methylephedrine/$Zn(OTf)_2$ Catalyzed Asymmetric Alkyne Addition to Aldehydes.




Highly enantioselective systems utilizing optically active 1,1'-bi-2-napthol (BINOL) were discovered by Pu[34] and Chan[35] in 2002. Chan's system utilized $ZnMe_2$ and $Ti(O^iPr)_4$ in combination with (*R*)-BINOL or the partially hydrogenated derivative (*R*)-$H_8$BINOL for the addition of phenylacetylene to aromatic aldehydes in high enantioselectivity (Scheme 1.14a). Aliphatic aldehydes produced lower enantioselectivities. In this system the reaction was performed at 0 °C and in many cases $H_8$BINOL provided higher enantioselectivities than BINOL. It was later found that the addition of sulfonamide **1-20** as a co-catalyst resulted in increased enantioselectivities (Scheme 1.14b).

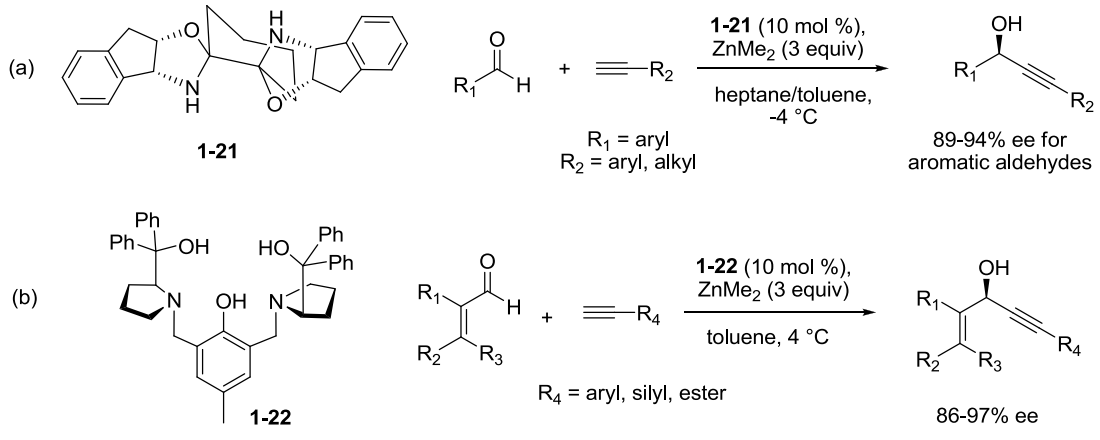
**Scheme 1.14.** BINOL/$ZnR_2$/$Ti(O^iPr)_4$ Catalyzed Asymmetric Alkyne Addition to Aldehydes.




Pu's BINOL system utilized $ZnEt_2$ to form the alkynylzinc (Scheme 1.14c). This required reflux of phenylacetylene with $ZnEt_2$ in toluene. Addition of (*S*)-BINOL and $Ti(O^iPr)_4$ forms the active catalyst, and addition of aromatic, aliphatic, or α,β-unsaturated aldehydes yielded the corresponding propargylic alcohols in high enantiomeric excess.[34] Under these conditions (triisopropylsilyl)acetylene was also found to add to benzaldehyde in 92% ee. High enantioselectivities could be achieved with 20 mol % of (*S*)-BINOL and 50 mol % of $Ti(O^iPr)_4$ for aromatic aldehydes, and aliphatic and α,β-unsaturated aldehydes required 40 mol % of (*S*)-BINOL and 100 mol % of $Ti(O^iPr)_4$ for high ees. This catalytic system was noteworthy due to its large substrate scope in the aldehyde, and the commercial availability of all the reaction components.

From these successes a large number of catalytic systems for the addition of alkynylzincs to aldehydes have been developed.[25,29] Among these, most notable are bisoxazolidine ligand **1-21**[36] and Trost's ProPhenol catalyst **1-22**.[37] The bisoxazolidine ligand was shown to be effective for the addition of a variety of aryl and alkyl alkynes to aromatic aldehydes. This reaction system was exceptionally simple, as all the reagents could be combined together in one step, and only the ligand (10 mol %) and $ZnMe_2$ were necessary for high enantioselectivity. However, this system provided poorer enantioselectivities for aliphatic aldehydes. Trost's ProPhenol catalyst system was also efficient, requiring only 10 mol % of the ligand $ZnMe_2$ (3 equiv), and was shown to be particularly effective for the addition of a range of alkynes to α,β-unsaturated aldehydes. Since its development, the ProPhenol catalyzed asymmetric alkyne addition has been successfully utilized by Trost and coworkers in the synthesis of several natural products.[37]

**Scheme 1.15.** Bisoxazolidine and ProPhenol Catalyzed Asymmetric Alkyne Addition to Aldehydes.



*c. Summary*

The last decade has witnessed the design of many highly effective catalytic systems for asymmetric alkynylzinc additions to aldehydes. However, there is still much room for improvement, as no catalytic system is highly effective for every type of alkyne and aldehyde substrate. Interestingly, the majority of the catalytic systems reported in the literature have been shown to be effective for alkynylzinc additions to aromatic aldehydes, and these systems often provide inferior results for aliphatic aldehydes.

Of the available methods, most significant for their high enantioselectivities and practical utility are Carreira's N-methylephedrine system, Pu's BINOL-based catalytic systems, and Trost's ProPhenol catalyst. Carreira's N-methylephedrine method was the first highly enantioselective catalytic system, and demonstrates remarkable substrate tolerance in regards to the alkyne. However, it is somewhat limited in its use for aromatic and linear aliphatic aldehydes, as significantly decreased yields are observed due to competitive side reactions. Conversely, Pu's BINOL system, while demonstrated to be effective for a smaller range of alkynes, has a large substrate scope in regard to the aldehyde and has been demonstrated to provide excellent enantioselectivities for aromatic, aliphatic, linear aliphatic, and $\alpha,\beta$-unsaturated aldehydes. Trost's ProPhenol catalytic system has proven to be highly effective for the addition of diverse alkynes to $\alpha,\beta$-unsaturated aldehydes, but has not been demonstrated to be as effective for other aldehydes.

Importantly, these catalytic systems are readily accessible to the synthetic community, as all the reagents are commercially available. Accordingly, these methods have often been employed in the literature, but with varying degrees of success for more

complex substrates, often times failing to yield good reactivity and selectivity.[38] The continuing utility of optically active propargylic alcohols in organic synthesis will continue to drive research in this area such that more sensitive and complex alkyne and aldehyde coupling partners will one day become fully compatible with this methodology.

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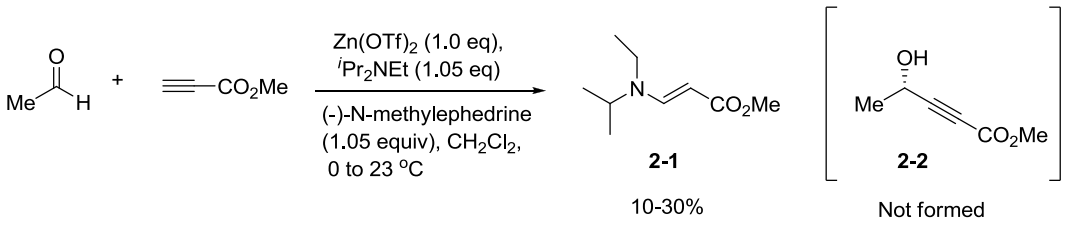
# Chapter 2. Catalytic Asymmetric Addition of Alkyl Propiolates to Aldehydes Catalyzed by Bifunctional $H_8$BINOLs

## 2.1. Introduction

Despite the significant advances in asymmetric alkynylzinc addition to aldehydes in the early 2000s several challenges remained. One of these challenges was revealed in 2004 when Koide and coworkers attempted to apply Carriera's N-methylephedrine system to the addition of methyl propiolate to acetaldehyde, finding that they were unable to obtain the desired product.[1] Instead of the expected γ-hydroxy-α,β-acetylenic ester **2-2**, Koide and coworkers isolated compound **2-1**, the result of a conjugate addition of the amine base to methyl propiolate followed by loss of an isopropyl group (Scheme 2.1). This finding highlighted that the Michael acceptor reactivity possessed by alkynoates renders these alkynes incompatible with catalytic systems employing stoichiometric amounts of amine bases.

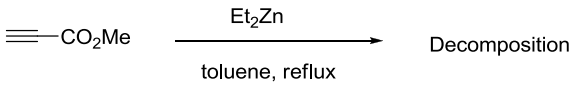
**Scheme 2.1.** Application of N-methylephedrine/$Zn(OTf)_2$ System to Alkyl Propiolates.




Similarly our group was also unsuccessful in attempts to extend our BINOL-based methodology to alkynoates. Under elevated temperatures methyl propiolate decomposed, failing to generate the alkynylzinc nucleophile (Scheme 2.2). This finding drew further attention to the sensitivity of alkynoates, and demonstrated that this increased sensitivity makes these substrates incompatible with catalytic systems

employing relatively harsh reaction conditions for formation of the alkynylzinc nucleophile. The incompatibility of alkynoates with the available methods of asymmetric alkynylzinc addition was a glaring limitation to the field, especially given the utility of γ-hydroxy-α,β-acetylenic esters in the literature.

**Scheme 2.2.** Application of BINOL/$ZnEt_2$ System to Alkyl Propiolates.



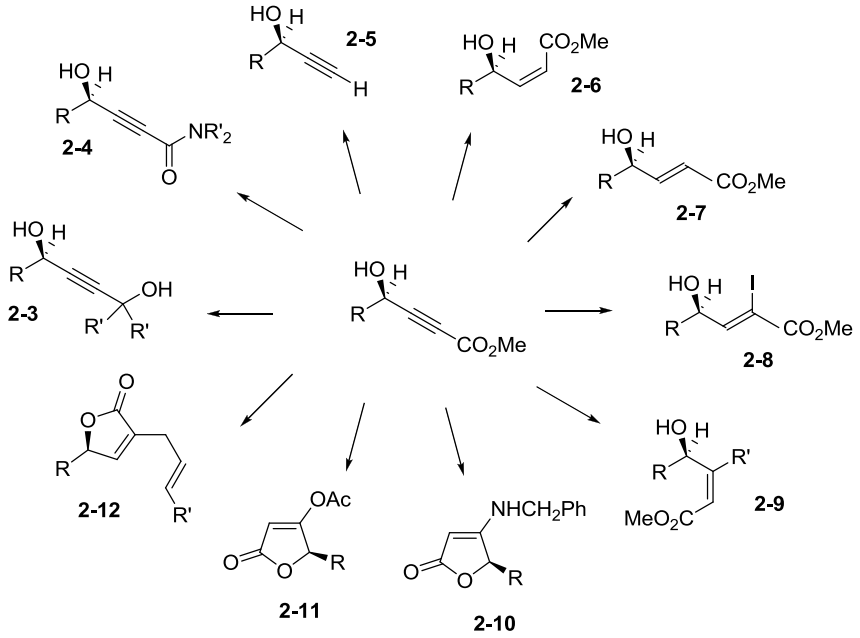

This chapter will discuss the utility of γ-hydroxy-α,β-acetylenic esters in organic synthesis, methods to access the optically active compounds, and the development of catalytic systems for asymmetric alkyl propiolate addition to aldehydes. The development of a new catalytic system for alkyl propiolate addition to address shortcomings in substrate scope will be reported.

*a. Utility of γ-hydroxy-α,β-acetylenic esters*

Interest in the asymmetric synthesis of γ-hydroxy-α,β-acetylenic esters has been stimulated by their significant utility as synthetic intermediates. In particular this class of compounds possesses three adjacent, chemically distinct functional groups capable of further transformation (Figure 2.1).[2] The combination of these functional groups opens up a wide range of reactivity for this type of propargylic alcohol. For example, the ester can be transformed into the alcohol (**2-3**) or amide (**2-4**), or removed via saponification followed by decarboxylation to yield the terminal acetylene (**2-5**).[3] The alkyne can be selectively reduced to the *cis* alkene (**2-6**) in the presence of hydrogen and Lindlar's catalyst,[4] or the *trans* alkene (**2-7**) with $NaBH_4$ in methanol or Red-Al in THF at low temperatures.[5] Quenching the Red-Al reduction at low temperatures with $I_2$ yields the

corresponding vinyl iodide **2-8**, which was shown to be capable of further transformation in the Stille and Sonogoshira couplings.[5]

**Figure 2.1.** Possible Transformations of Optically Active γ-Hydroxy-α,β-Acetylenic Esters.[2]

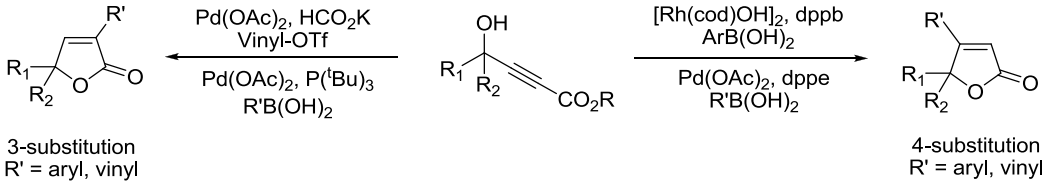



Due to conjugation with the ester, the alkyne can act as a Michael acceptor (**2-9**). Additionally, the proximity of the alcohol to the ester allows for the formation of cyclic structures upon reduction of the triple bond. Our laboratory has shown that γ-hydroxy-α,β-acetylenic esters can undergo conjugate addition with benzylamine, followed by intramolecular cyclization of the alcohol with the ester to form chiral 4-amino-2(5*H*)-furanone products (**2-10**).[6] Additional functionality can also be introduced by metal catalyzed reactions. γ-Hydroxy-α,β-acetylenic esters have been shown to undergo regiospecific hydration in the presence of Zeise's dimer, $[PtCl_2(C_2H_4)]_2$, providing access

optically active tetronic acids (**2-11**).[7] A ruthenium-catalyzed Alder-ene reaction can provide access to butenolides with substituents at the α carbon.[8]

Substituted 2(5H)-furanones can be accessed from γ-tertiary-hydroxy-α,β-acetylenic esters by rhodium and palladium catalyzed hydrovinylation and hydroarylation of the alkyne followed by cyclization (Scheme 2.3).[9] Interestingly, Arcadi found that the $Pd(OAc)_2$ catalyzed reaction with vinyl triflates yielded the 3-substituted-2(5H)-furanones,[9a] while the $[Rh(cod)OH]_2$ catalyzed reaction with arylboronic acids afforded the 4-substituted-2(5H)-furanones.[9b] Oh independently reported a similar $Pd(OAc)_2$-catalyzed reaction in which the regioselectivity was governed by the phosphine ligand employed. Use of 1,2-bis(diphenylphosphino)ethane (dppe) favored substitution at the 4-position, while use of tri(*tert*-butyl)phosphine yielded 3-substituted products.[9c]

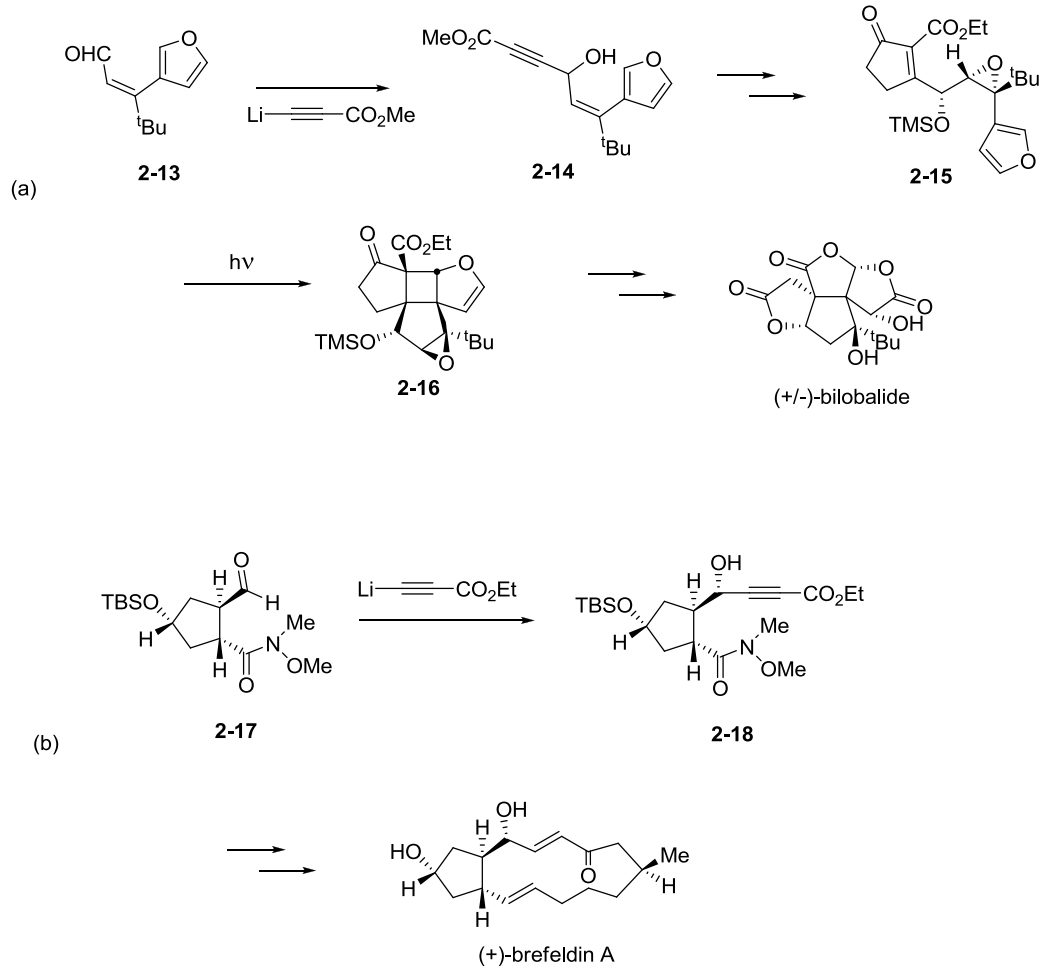
**Scheme 2.3.** Regioselective Synthesis of 2(5H)-Furanones.




Due to this wide range of reactivity, γ-hydroxy-α,β-acetylenic esters have often been utilized in the synthesis of natural products.[10] In Crimmins' synthesis of (±)-bilobalide, addition of methyl propiolate to aldehyde **2-13** formed racemic γ-hydroxy-α,β-acetylenic ester intermediate **2-14**, which was used to access photocyclization precursor **2-15 (**Scheme 2.4). Stereoselective [2+2] cycloaddition of this substrate led to the key tetracyclic core.[10a] While Crimmins' synthesis was racemic, asymmetric methods to access optically active **2-14** would have allowed for the enantioselective synthesis of

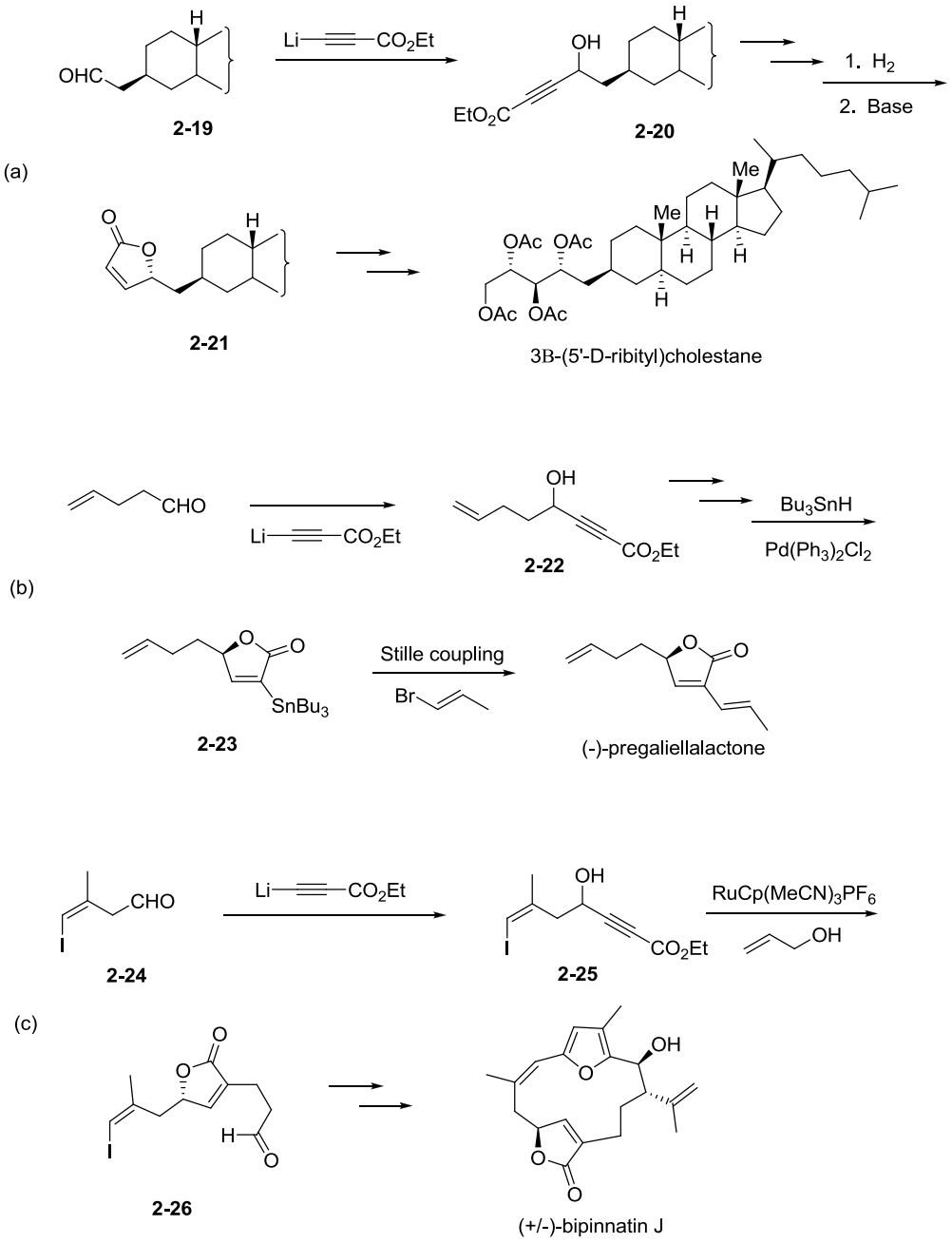
bilobalide. In contrast, optically active γ-hydroxy-α,β-acetylenic esters have been frequently used in total synthesis by means of diastereoselective additions to chiral aldehydes.[11] Trost and coworkers employed this strategy in the synthesis of (+)-brefeldin A.[11b] Addition of lithiated ethyl propiolate to aldehyde **2-17** afforded propargylic alcohol **2-18** in 6:1 dr. This intermediate was further elaborated to the natural product, utilizing the ester of the alkynoate to form the macrolactone.

**Scheme 2.4.** Synthesis of (±)-Bilobalide and (+)-Brefeldin A Utilizing γ-Hydroxy-α,β-acetylenic Ester Intermediates.



γ-Hydroxy-α,β-acetylenic esters have also been commonly used in total synthesis as precursors for the formation of butenolide rings, a ubiquitous structural feature in natural products. Simple butenolides can be accessed from γ-hydroxy-α,β-acetylenic esters through reduction of the double bond and lactonization, as exemplified in the synthesis of 3β-(5'-D-ribityl)cholestane (Scheme 2.5a).[12a] In this report the alkyne was reduced to the *cis* alkene by use of Lindlar catalyst in the presence of $H_2$ and lactone **2-21** was formed under basic conditions. Functionalized butenolides derived from γ-hydroxy-α,β-acetylenic esters are also commonly utilized and have been accessed by hydrometallation/cyclization reactions or the ruthenium-catalyzed Alder-ene reaction. For example, in the synthesis of (-)-pregaliellalactone, addition of ethyl propiolate to 4-pentenal led to propargylic alcohol **2-22** (Scheme 2.5b). After installation of the chiral center by oxidation to the ynone and then asymmetric reduction, palladium-catalyzed hydrostannylation and cyclization, followed by Stille cross coupling of stannyl butenolide **2-23** with 1-bromo-1-propene afforded the substituted butenolide (-)-pregaliellalactone.[12b] Trauner's synthesis (±)-bipinnatin J demonstrates the Alder-ene strategy to access substituted butenolides.[12c] Propargylic alcohol **2-25** was accessed by the addition of lithiated ethyl propiolate to aldehyde **2-24**. The ruthenium catalyzed Alder-ene reaction with allyl alcohol provided substituted butenolide **2-26** as a key intermediate in route to (±)-bipinnatin J.

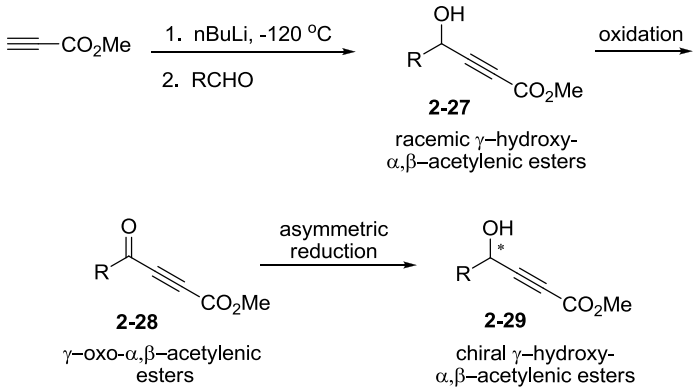
**Scheme 2.5.** Use of γ-Hydroxy-α,β-acetylenic Ester Intermediates for Butenolide Construction in Total Synthesis.



*b. Synthesis of Optically Active γ-hydroxy-α,β-acetylenic esters*

The versatile utility of chiral γ-hydroxy-α,β-acetylenic esters and their common application in the synthesis of complex molecules emphasized the need for an efficient enantioselective preparation of these compounds. However, due to the described limitations in asymmetric alkyne addition to aldehydes, until recently, chiral γ-hydroxy-α,β-acetylenic esters could only be accessed by diastereoselective additions of metalated alkyl propiolates to chiral aldehydes and epoxides or by asymmetric ynone reduction. For the achiral aldehydes utilized in the total syntheses shown in Scheme 2.5b-c, asymmetric ketone reduction was the only alternative.

**Scheme 2.6.** Preparation of Chiral γ-Hydroxy-α,β-acetylenic Esters by Ynone Reduction.

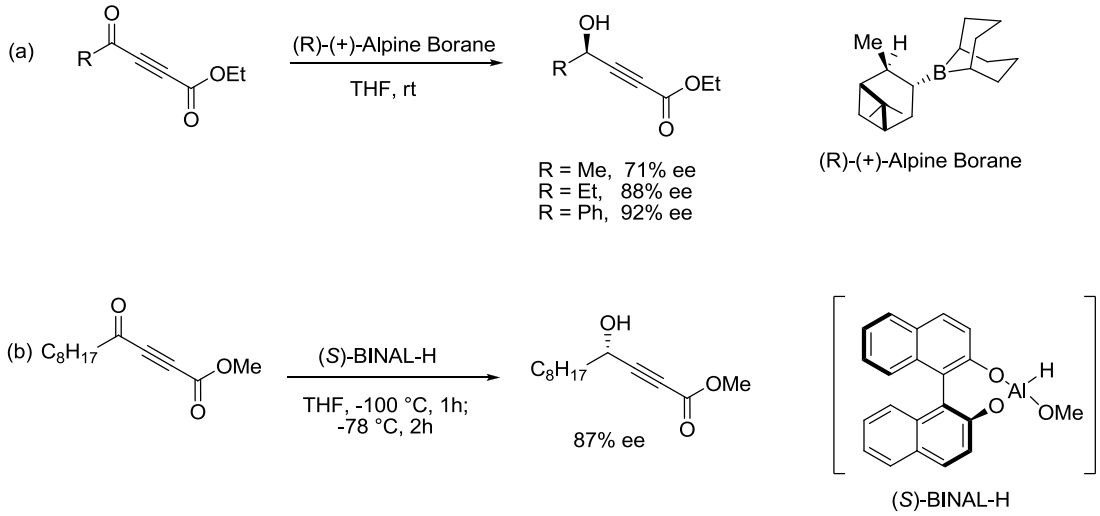



In this strategy the racemic γ-hydroxy-α,β-acetylenic ester is first prepared, most commonly by Midland's method via treatment of the alkynoate with $^{n}$BuLi at low temperatures and subsequent addition of the aldehyde (Scheme 2.6).[13] In this method the temperature and stoichiometry must be carefully controlled to prevent addition of the base to the aldehyde as well as to ester of the alkynoate. Accordingly, it was later found that sterically bulky bases such as lithium hexamethyldisilazide (LHMDS) are better for

alkyl propiolates.[14] After oxidation of the alcohol to afford ynone **2-28**, the three step sequence culminates in asymmetric reduction to afford chiral alcohol **2-29**.

The asymmetric reduction of γ-oxo-α,β,-acetylenic esters to yield chiral γ-hydroxy-α,β-acetylenic esters was first reported by Midland in 1980 (Scheme 2.7a).[15] Using Alpine-Borane γ-oxo-α,β,-acetylenic esters could be reduced at room temperature to yield the corresponding alcohols in moderate to high enantioselectivity, with higher enantioselectivity being afforded for larger substituents adjacent to the ketone. This strategy can provide either enantiomer of the desired alcohol by the correct choice of the asymmetric reducing agent, and is effective for alkyl, aryl, and vinyl ketones. Later in 1984, Noyori and coworkers found that lithium aluminum hydride ($LiAlH_4$) premixed with BINOL to form BINAL-H can enantioselectively reduce γ-oxo-α,β,-acetylenic esters to the corresponding chiral alcohol (Scheme 2.7b).[16] However, this method requires large excess of the BINAL-H reagent (3 equiv) and low reaction temperatures (-100 to -78 °C).

**Scheme 2.7.** Asymmetric Reductions of γ-Oxo-α,β,-acetylenic Esters.

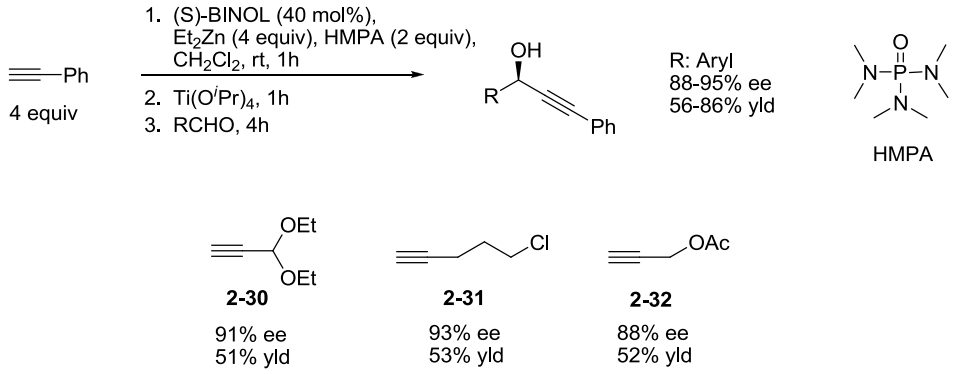


When considering these methods to access optically active γ-hydroxy-α,β-acetylenic esters several shortcomings are apparent. Diastereoselective additions of metalated propiolates are limited to chiral substrates, as well as being restricted to the stereocontrol induced by the electrophile. Although ynone reduction can provide access to chiral γ-hydroxy-α,β-acetylenic esters from achiral aldehydes, this strategy is limited by its inherent inefficiency and its inability to be extended to the formation of quaternary stereocenters (see Chapter 1 for discussion). If asymmetric alkyne additions could be achieved employing alkynoates, these limitations could be overcome, providing a much more efficient process in which the carbon-carbon bond and the stereocenter could be formed in one step.

The first breakthrough was foreshadowed by our lab in 2004 when Ge Gao discovered that the addition of hexamethylphosphoramide (HMPA) to a solution of phenylacetylene and $ZnEt_2$ facilitated the formation of the alkynylzinc nucleophile at room temperature in 1 h, alleviating the need for refluxing in toluene solution.[17] In this scenario it is thought that HMPA acts as a Lewis base to coordinate $ZnEt_2$ and activate it toward deprotonation of the alkyne. In the presence of 40 mol % BINOL and 100 mol % $Ti(O^iPr)_4$ alkynylzincs generated in this manner demonstrated highly enantioselective addition to a range of aromatic aldehydes (88-95% ee) and an α,β-unsaturated aldehyde, trans-cinnamaldehyde, in 92% ee (Scheme 2.8). Interestingly, the addition of HMPA slightly reduced the enantioselectivity from the original BINOL catalytic system. For example, using 20 mol % BINOL and 50 mol % $Ti(O^iPr)_4$ in the addition of phenylacetylene to benzaldehyde at room temperature resulted in 96% ee when the alkynylzinc was formed by refluxing in toluene solution.[18] When the same conditions

were applied with the addition of HMPA to form the alkynylzinc, the product was formed in 83% ee.[17] For aromatic aldehydes this slight erosion of enantioselectivity was overcome by increasing the amounts of BINOL to 40 mol % and $Ti(O^iPr)_4$ to 100 mol %, resulting in 93% ee for the addition of phenylacetylene to benzaldehyde.

**Scheme 2.8.** Enantioselective Addition of Alkynes to Aromatic Aldehydes in the Presence of $ZnEt_2$, HMPA, (*S*)-BINOL, and $Ti(O^iPr)_4$.

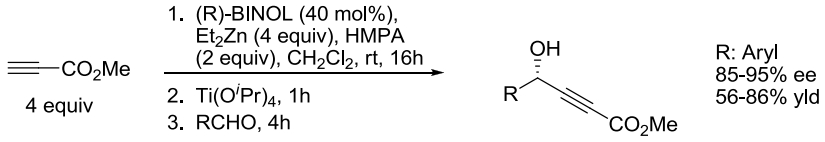



The use of HMPA to facilitate alkynylzinc formation was a substantial improvement for two reasons. First, it simplified the reaction procedure allowing the entire reaction to be conducted at room temperature. Secondly, and more importantly, the milder reaction conditions made possible the use of functional alkynes, such as alkynes **2-30**, **2-31**, and **2-32**. These alkynes were also demonstrated to undergo addition to benzaldehyde in high enantioselectivities in the presence of the BINOL catalyst system, although in reduced yields. These findings suggested that the more sensitive alkynoates might be compatible with this catalytic system.

Initial application of the reaction conditions shown in Scheme 2.8 for the addition of methyl propiolate to benzaldehyde afforded the product in low yield. However, upon prolonged treatment of methyl propiolate with $ZnEt_2$ and HMPA for 16 h the product

could be obtained in good yield and high enantioselectivity (69% yield, 91% ee).[19] This demonstrated that the formation of the alkynylzinc was slower in the case of methyl propiolate as compared to phenylacetylene. By allowing long enough time for the formation of the alkynylzinc good yields could be obtained. Application of the reaction conditions shown in Scheme 2.9 resulted in high enantioselectivities for the addition of methyl propiolate to a range of aromatic aldehydes (85-95%) and 91% ee for trans-cinnamaldehyde. This represented the first highly enantioselective addition of an alkynoate to aromatic and α,β-unsaturated aldehydes.

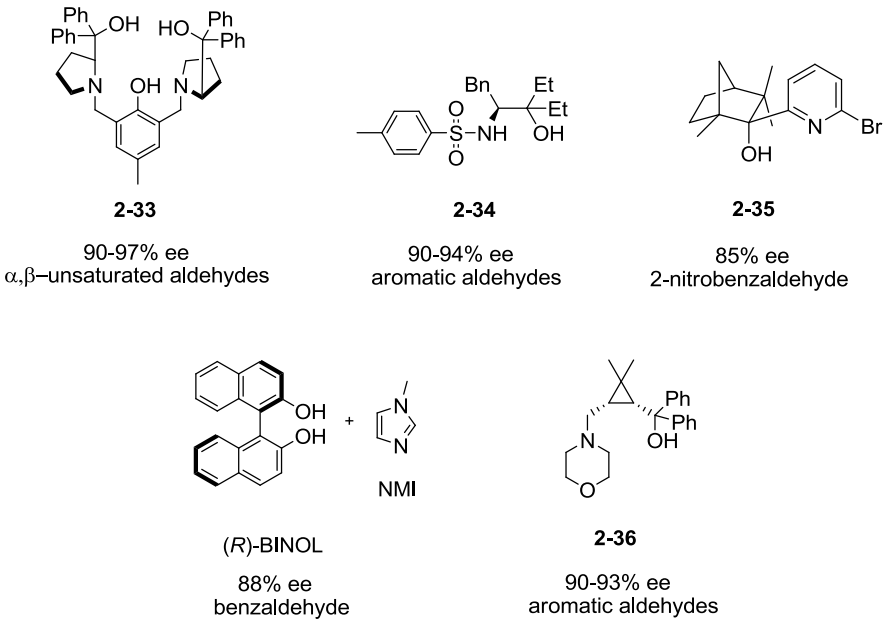
**Scheme 2.9.** First Highly Enantioselective Addition of Methyl Propiolate to Aromatic Aldehydes.




Following our lab's initial report in 2006, several other catalytic systems for the addition of alkynoates to aldehydes quickly followed. Later that year Trost and coworkers revealed that the proline based ProPhenol (Figure 2.2) catalyst in combination with $ZnMe_2$ was particularly effective for the addition of methyl propiolate to α,β-unsaturated aldehydes, catalyzing the reaction in 90-97% ee for four substrates.[20] The reaction was conducted in toluene at 4 °C for 20-48 h, using 10 mol % of **2-33** and 3 equiv of $ZnMe_2$ and methyl propiolate. This catalytic system was later successfully employed in the addition of methyl propiolate to an α,β-unsaturated dialdehyde as a key step in the synthesis of adociacetylene B.[21] The addition of alkynoates was found to be

less effective for the addition to aromatic aldehydes. The addition of ethyl propiolate to 2-methoxybenzaldehyde under identical conditions resulted in only 82% ee.[20]

**Figure 2.2**. Chiral Ligands for the Enantioselective Addition of Alkynoates to Aldehydes.




The following year in 2007 Wang introduced an alternative system for the addition of methyl propiolate to aromatic aldehydes employing β-sulfonamide ligand **2-34**.[22] In this system the Lewis basic oxygen present in the sulfonamide group was able to activate $ZnEt_2$ for the formation of the alkynylzinc, although the addition of 1 equiv 1,2-dimethoxyethane (DME) additive was necessary to achieve good yields. The alkynylzinc was formed with 30 mol % of ligand **2-34** in combination with 3 equiv methyl propiolate, 3 equiv $ZnEt_2$, and 1 equiv DME in toluene for 7 h at room temperature. Addition of 30 mol % $Ti(O^iPr)_4$ for 0.5 h, followed by addition of the aldehyde resulted in 90-94% ee for aromatic aldehydes. The system was less effective for α,β-unsaturated aldehydes, resulting in 85% ee for trans-cinnamaldehyde and 82% ee for crotonaldehyde. Jacobi

von Wangelin also reported an effective catalyst for aromatic aldehydes in 2007, utilizing 20 mol % of hydroxy-pyridine catalyst **2-35** in combination with $ZnMe_2$ to catalyze the addition of ethyl propiolate to 2-nitrobenzaldehyde in 85% ee.[23]

An important improvement of our group's HMPA system was also discovered in 2007 by You and coworkers.[24] They found that N-methylimidazole (NMI) could replace HMPA as a Lewis base. This was an important improvement because while 2 equiv of HMPA, a toxic substance, was employed in our system, only 5 mol % of NMI was required for You's catalytic system. Reducing the amount of the additive allowed for the reduction of the amount of BINOL necessary. Whereas 40 mol % BINOL was used with HMPA, it was found that only 10 mol % BINOL was required for the highly enantioselective addition of various alkynes to aromatic aldehydes. The use of NMI as the Lewis base was also demonstrated to be effective with an alkynoate. In this system 2.1 equiv of methyl propiolate was combined with 2 equiv $ZnEt_2$, 10 mol % BINOL, and 5 mol % NMI in $CH_2Cl_2$ for 24 h. $Ti(O^iPr)_4$ (25 mol %) was then added and stirred for 1 h, followed by addition of the benzaldehyde for 12 h resulting in the product in 68% yield and 88% ee. These findings demonstrated that catalytic amounts of amine bases are compatible with alkynoates and can be effective Lewis bases for activation of $ZnEt_2$.

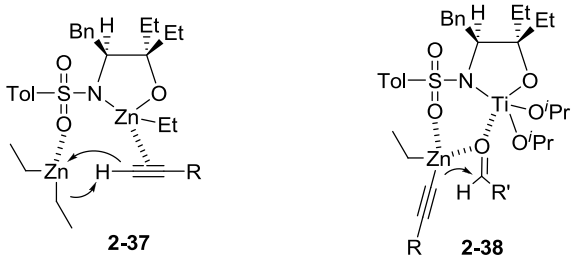
In 2009, chiral cyclopropane amino alcohol **2-36** in combination with $ZnMe_2$ was found to catalyze the addition of methyl propiolate to aromatic aldehydes in 90-93% ee. Here methyl propiolate was first stirred with $ZnMe_2$ for 1.5 h in toluene at room temperature. This solution was added to amino alcohol ligand **2-36** at 0 °C and stirred for 30 min, followed by addition of the aldehyde maintaining the temperature at 0 °C for a

reaction time of 24 h. Notably this system did not require the use of $Ti(O^iPr)_4$ for high enantioselectivity.

Inspection of the existing methodology for alkynoate addition to aldehydes reveals several important features of the dialkylzinc-based systems. First, a Lewis basic functionality is necessary for the formation of the alkynylzinc nucleophile. The use of an appropriate Lewis base is especially important for alkynoates given their increased sensitivity to harsh reaction conditions. The Lewis base can either be added externally, such as HMPA or NMI, or be incorporated into the chiral ligand, such as the nitrogen atoms in ProPhenol ligand **2-33** and amino alcohols **2-35** and **2-36**, and the sulfonyl oxygen atoms in β-sulfonamide ligand **2-34**. In addition to the Lewis base required for formation of the nucleophile, a Lewis acidic center is critical for stereocontrol. These exist as chiral alcohols and amines that form a chiral Lewis acid upon coordination with zinc and/or titanium, thereby activating the electrophile in a chiral environment.

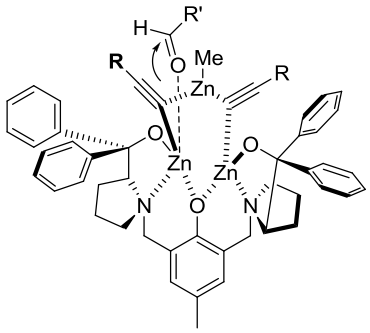
Considering these general requirements, the catalytic systems reported for alkynoate additions to aldehydes can be separated into two classes. The first represents chiral Lewis acid catalysts with external Lewis bases such as the BINOL based systems. The second class represents bifunctional catalysts, in which the Lewis basic and Lewis acidic functionalities are incorporated into a single catalyst structure, as typified by Trost's ProPhenol catalyst, Wang's β-sulfonamide ligand, and amino alcohols **2-35** and **2-36**.

**Figure 2.3.** Proposed Catalytic Intermediates for β-Sulfonamide Ligand **2-34**.




Wang and Trost have proposed catalytic cycles that highlight the potential advantages of bifunctional catalysts. Wang's β-sulfonamide ligand **2-34** nicely illustrates the synergistic interactions of the Lewis acidic and Lewis basic sites in a bifunctional catalyst (Figure 2.3). Intermediate **2-37** depicts formation of the alkynylzinc intermediate. Here $ZnEt_2$ is coordinated by the Lewis basic sulfonamide oxygen, activating it toward deprotonation of the alkyne. Simultaneously the zinc metal center serves as a Lewis acid to help labilize the alkyne's terminal hydrogen. This intramolecular cooperation serves to activate both reaction partners as well as bringing them together, catalyzing the formation of the alkynylzinc in a highly efficient manner. A similar cooperativity is proposed for addition of the alkyne to the aldehyde. Simultaneous activation of the alkynylzinc intermediate by the Lewis base and activation of the aldehyde by the titanium based Lewis acid in a compact chiral environment leads to formation of the chiral γ-hydroxy-α,β-acetylenic ester in high enantioselectivity. Likewise, Trost's ProPhenol ligand acts as a bifunctional catalyst. Trost and coworkers proposed the intermediate shown in Figure 2.4, in which both reaction partners are simultaneously activated in the chiral pocket.

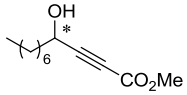
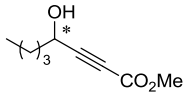
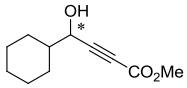
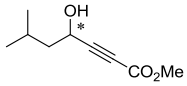
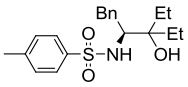
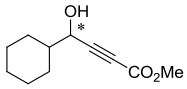
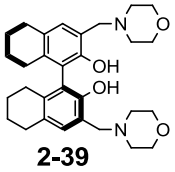
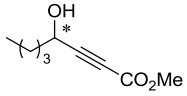
**Figure 2.4.** Proposed Catalytic Intermediate for ProPhenol Ligand **2-33**.




Close examination of the methodology for the addition of alkynoates to aldehydes reveals an important gap in the substrate scope. The BINOL based systems, β-sulfonamide ligand **2-34**, and amino alcohol ligands **2-35** and **2-36** are effective for aromatic aldehydes, and Trost's ProPhenol ligand **2-33** was successfully applied to α,β-unsaturated aldehydes. A successful catalytic system for the addition of alkynoates to aliphatic aldehydes has not been demonstrated. Application of the above systems to aliphatic aldehydes has been limited and largely produced unsatisfactory results. Use of the BINOL/HMPA system could only catalyze the addition of methyl propiolate to aliphatic aldehydes in 81-89% ee for four substrates (Table 2.1).[25] β-sulfonamide ligand **2-34** could catalyze the addition of methyl propiolate to cyclohexanecarboxaldehyde in only 79% ee.[22] In 2006 our lab explored the use of amino alcohol $H_8$BINOL-based ligand **2-39** , but was only able to obtain 70% ee for the addition of methyl propiolate to valeraldehyde.[26] It was not until 2008 that the first report of an alkynoate addition to an aliphatic aldehyde in greater than 90% ee was reported in the total synthesis of (-)-ushikulide A. Using Trost's ProPhenol catalyst the addition of methyl propiolate to isovaleraldehyde was carried out it 88% yield and 95% ee.[27] However, high enantioselectivities were demonstrated for only one substrate, and a reaction time of 60 h

at 5 °C was necessary to provide good results. As a whole, these findings demonstrate the significant challenge for additions of alkynoates to aliphatic aldehydes.

**Table 2.1.** Alkynoate Additions to Aliphatic Aldehydes.

| entry | ligand | aldehyde | product | yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | (*S*)-BINOL | octyl aldehyde |  | 72 | 81 |
| 2 | (*S*)-BINOL | valeraldehyde |  | 76 | 89 |
| 3 | (*S*)-BINOL | cyclohexane-carboxaldehyde |  | 60 | 81 |
| 4 | (*S*)-BINOL | isovaleraldehdye |  | 73 | 83 |
| 5 |  | cyclohexane-carboxaldehyde |  | 80 | 79 |
| 6 |  **2-39** | valeraldehyde |  | - | 70 |

## 2.2. Highly Enantioselective Alkyl Propiolate Addition to Aldehydes

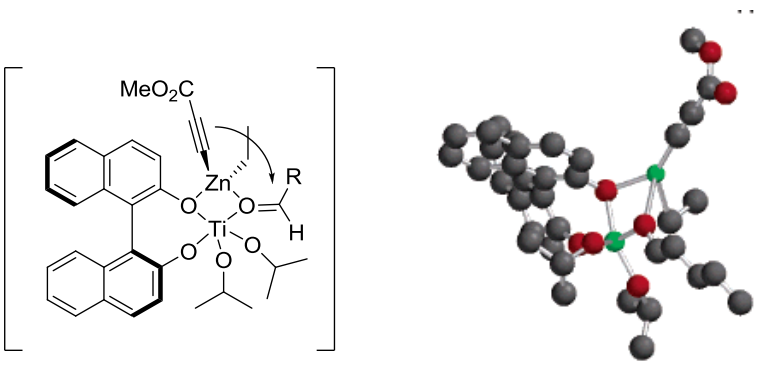
*a. Chiral Ligand Strategy and Design*

Given these limited and unsatisfactory results, and the prevalence and utility of chiral γ-hydroxy-α,β-acetylenic esters derived from aliphatic aldehydes in the literature, we sought to address this challenge—the highly enantioselective addition of alkynoates to aliphatic aldehydes. Toward this goal we first stepped back to consider our strategy. Given the moderate success of BINOL for the addition of methyl propiolate to aliphatic aldehydes we thought that high enantioselectivities could likely be attained by modification of the BINOL scaffold. To determine what modifications might be

beneficial we examined the tentative intermediate suggested for the BINOL/$ZnEt_2$/$Ti(O^iPr)_4$ catalytic system.[25] The intermediate shown in Figure 2.5 was based on a molecular modeling structure established with the PC Spartan-Semiempirical PM3 program.

In this intermediate the ethyl group of the ethylalkynylzinc is proposed to be back in order to avoid interaction of its α sp3 carbon with the 3-H of the (S)-BINOL ligand. The less sterically demanding linear alkyne occupies the forward position. The positioning of the zinc substituents in turn affects the orientation of the aldehyde. Resultantly the larger R group of the aldehyde is oriented up to avoid interaction with the ethyl group on the zinc. This positioning also minimizes its interactions with the isoproxy groups on titanium, which are oriented to reduce their interaction with the aromatic rings of (*S*)-BINOL. In this scenario the alkynyl group attacks the *si* face of the aldehyde forming the observed (*R*)-product.

**Figure 2.5.** Proposed Intermediate for BINOL/$ZnEt_2$/$Ti(O^iPr)_4$ Catalyzed Alkynoate Addition to Aldehydes.[25]

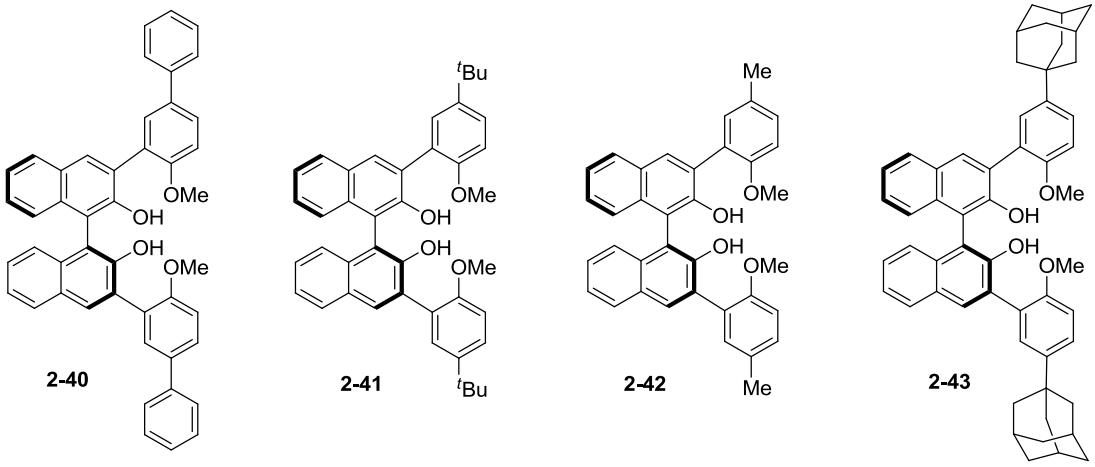



From this understanding several key elements for stereocontrol can be proposed. First is the coordination of the zinc by the chiral ligand. This coordination is significant

because it constrains the orientation of the zinc substituents through steric interactions with the chiral ligand. Second is the coordination of the titanium by the chiral ligand and establishment of a preferred orientation for the isopropoxy groups. The positioning of the zinc substituents and isopropoxy groups in turn are important for orienting the aldehyde, which is brought into the chiral environment through coordination with the oxophilic titanium. From this understanding it is reasonable to propose that an increase in the steric bulkiness of the ligand at the 3,3' positions could rigidify the orientation of the zinc substituents and the isopropoxy groups which are responsible for controlling the orientation of the aldehyde. In BINOL, the 3,3' hydrogen atoms are suggested to be partially responsible for the steric orientation. Replacement of the hydrogen atoms with larger groups could enhance the steric bias the ligand imposes, effectively extending the chirality of the ligand forward and providing additional steric restraints to position the aldehyde.

If the bulky groups incorporated at the 3,3' position contain Lewis basic heteroatoms capable of coordination with zinc and titanium, this would give rise to a bifunctional catalyst containing distinct sites to coordinate and synergistically activate the electrophilic and nucleophilic reaction partners. This could create an even more defined catalytic pocket, though not necessarily in cooperation with the proposed effects in the BINOL system. Additional sites of coordination and the extended chirality of the ligand could override or change the effects of the zinc and titanium substituents. However, as long as the new controlling elements of the ligand form an improved conformation for the catalytic pocket the chiral induction could be improved.

**Figure 2.6** Bifunctional 3,3'-Dianisyl-BINOL Ligands for Asymmetric Phenylacetylene Addition to Aromatic Aldehydes.




This idea has been successfully implemented in a number of cases. Our laboratory in particular has set a precedent for the success of 3,3'-bifunctional BINOL-based ligands for alkyne additions to aldehydes. The choice of the substituents has been shown to be important for good enantiocontrol.[28] For the addition of phenylacetylene to aromatic aldehydes ligands **2-40** to **2-43** have been shown to be effective (Figure 2.6). Interestingly, in this series of ligands neither electron-donating nor electron-withdrawing substituents on the anisyl substituents promoted high enantioselectivity. Instead it seems that a steric effect was important, as ligands containing bulky groups in the *para* position provided the best enantioselectivities. This can be seen by comparing ligand **2-42** containing a *para* methyl group and ligand **2-41** containing a *para* $^{t}$Bu group. For the addition of phenylacetylene to 3-chlorobenzaldehyde in the presence of 10 mol % of the ligand and 25 mol % $Ti(O^{i}Pr)_4$, ligand **2-42** afforded 56% ee while ligand **2-41** provided a much higher ee of 84%. The very bulky adamantyl containing ligand **2-43** was found

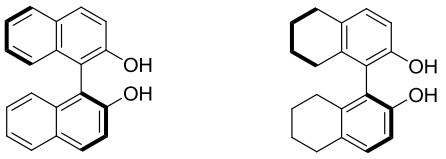
to be a highly effective ligand, catalyzing phenylacetylene addition to various aromatic aldehydes in 80-94% ee.[29]

In view of the precedent for the successful use of 3,3'-substituents in asymmetric alkyne additions we chose to design a new class of 3,3'-substituted BINOL-based bifunctional ligands to address the challenging addition of alkynoates to aliphatic aldehydes. In this strategy the incorporation of the Lewis basic sites to form bifunctional ligands was envisioned to play a dual role. First, the Lewis base would take the place of HMPA for the formation of the alkynylzinc at room temperature. Secondly, we also hoped that it would provide an increase in enantioselectivity through synergistic interactions with the Lewis acidic sites in the chiral catalytic pocket. Oxygen and nitrogen heteroatoms are the most common Lewis basic sites in bifunctional ligands utilizing zinc. As the incorporation of nitrogen atoms into ligand **2-39** failed to promote high enantioselectivity for methyl propioloate addition to valeraldehyde (Table 1), we chose to use oxygen atoms as the Lewis base through the incorporation of anisyl groups into the BINOL scaffold like in ligands **2-40** through **2-43**. Since these ligands were effective for phenylacetylene addition to aromatic aldehydes, we hypothesized that alteration of this class of ligands would provide a good starting point in our search for an effective catalyst for the addition of alkynoates to aliphatic aldehydes. As one of the major drawbacks of bifunctional catalysts is the lengthy synthetic sequences required to access the ligands, we were also interested in efficient routes to ligands of this type.

We chose to alter this class of ligands through the use of the partially hydrogenated BINOL, $H_8$BINOL (Figure 2.7). The use of $H_8$BINOL was motivated by recent reports in which the use of $H_8$BINOL and its derivatives often demonstrate

improved enantioselectivities over the parent BINOL-based compounds.[30] As these improvements in enantioselectivity were observed over a wide range of metal catalyzed asymmetric transformations, it was reasonable to assume that this might also hold true in our case. The enhanced stereocontrol of $H_8$BINOL based ligands has been attributed to the steric and electronic changes caused by the partial hydrogenation of the BINOL framework. Reduction of the rear naphthyl $sp^2$ carbon atoms to tetrahedral $sp^3$ carbon atoms increases the steric bulkiness of the $H_8$BINOL ligand. This increased steric interaction causes an increased dihedral angle in $H_8$BINOL (94.3°) as compared to BINOL (72.3°).[30] This increase in dihedral angle, and the resulting increase in rigidity of the $H_8$BINOL-based derivatives can often lead to increased chiral induction.

**Figure 2.7.** (*S*)-BINOL and (*S*)-$H_8$BINOL.

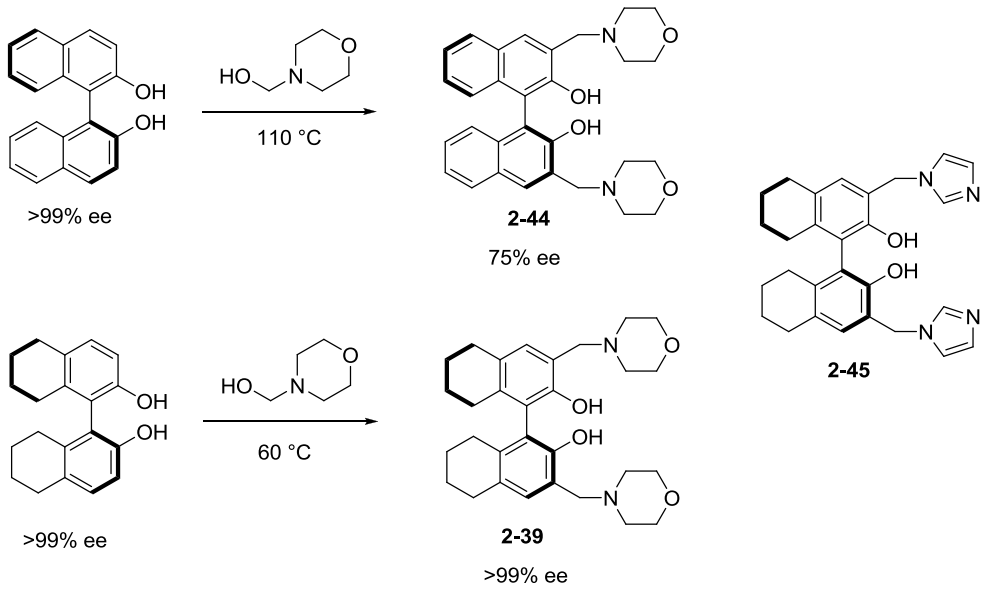



(*S*)-BINOL (*S*)-$H_8$BINOL

A change in electronics is also caused by the partial reduction of BINOL, with $H_8$BINOL becoming more electron rich relative to BINOL. When the phenolic oxygen atoms of a BINOL-based ligand are deprotonated under basic reaction conditions the negative charge can be delocalized over the fully conjugated napthyl rings. In $H_8$BINOL this delocalizing effect is reduced by the presence of only one aromatic ring, and this ring is substituted with electron donating alkyl groups. This results in an increased basicity of the phenolic oxygens in $H_8$BINOL as compared to BINOL. This subtle change in the

electronic nature of the ligand can also alter the properties of the catalytic system, and may also be responsible for increased chiral induction in some instances.

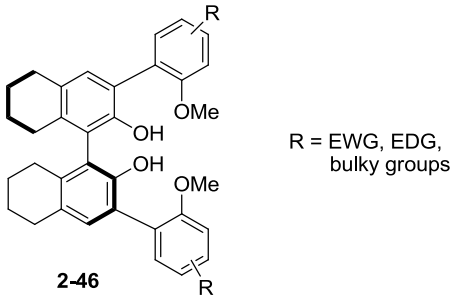
**Scheme 2.10.** Functionalization of BINOL and $H_8$BINOL at 3,3'-Positions.




This change in electronics is also useful for the incorporation of substituents at the 3,3' positions of $H_8$BINOL. The increased reactivity of $H_8$BINOL for 3,3'-derivatization has been illustrated by our group in the synthesis of BINOL-Amine **2-44** and $H_8$BINOL-Amine ligand **2-39**.[26,31] As shown in Scheme 2.10, in the Mannich-type reaction of BINOL and morpholinomethanol, a temperature of 110 °C was necessary for formation of the product, and the high reaction temperatures resulted in partial racemization of the ligand (75% ee).[31a] Recrystallization was required to obtain the enantiomerically pure product. In contrast, the reaction of $H_8$BINOL and morpholinomethanol occurred much more readily, requiring heating to only 60 °C and providing the product in 98% yield without racemization as **2-39** was isolated in 99% ee.[31b,d] It should also be noted that in cases where higher temperatures are necessary, such as in the formation of $H_8$BINOL-

Amine **2-45**, the increased steric bulk of $H_8$BINOL and its derivatives make it more resistant to racemization. No racemization was observed in the formation of this ligand, even though it was heated at 135 °C for 8 h.[31e] These characteristics make $H_8$BINOL an exceptional scaffold for the rapid construction of bifunctional ligands.

**Figure 2.8.** Design of Bifunctional 3,3'-Dianisyl-$H_8$BINOL Ligands.

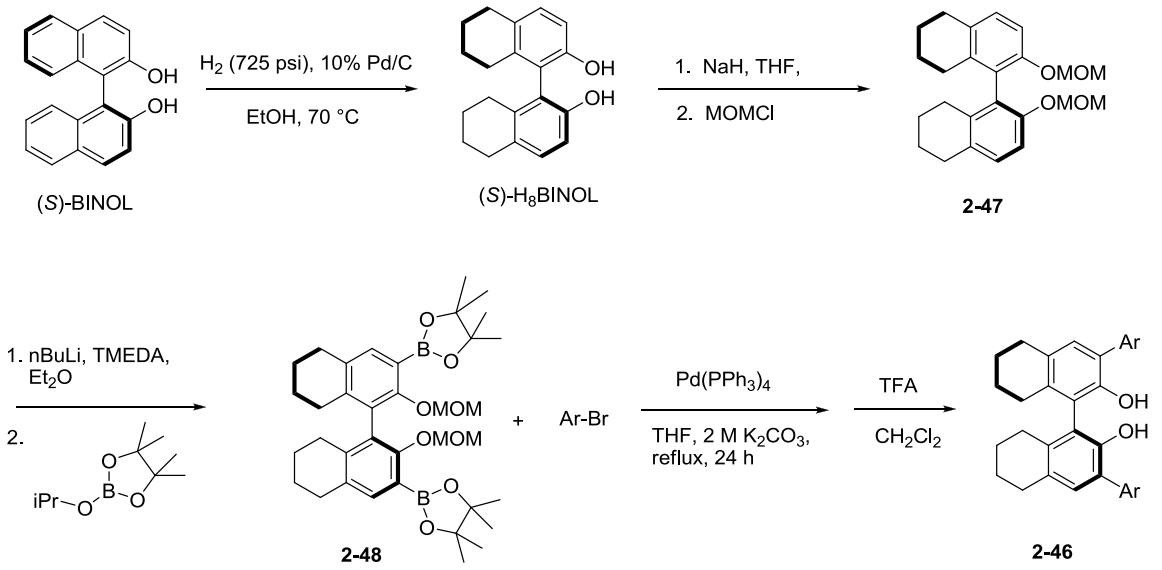



**2-46**

Given the precedence for 3,3'-dianisyl-BINOL bifunctional ligands in asymmetric alkynylations, examples of enhanced chiral induction in $H_8$BINOL based ligands, and the ease of derivatization of $H_8$BINOL at the 3,3' positions, we designed 3,3'-dianisyl-$H_8$BINOL ligands with the general structure of **2-46**. This design allowed us to test electronic and steric effects through variation of the substituents on the anisyl rings. Employing the reaction sequence as shown in Scheme 2.11 allowed efficient access to a variety of 3,3'-dianisyl-$H_8$BINOL ligands. (S)-$H_8$BINOL was first prepared from (S)-BINOL via high pressure hydrogenation (725 psi $H_2$) in the presence of 5% Pd/C under elevated temperatures (60 °C) according to a literature procedure.[32] Alternatively, $H_8$BINOL is commercially available. The $H_8$BINOL hydroxyl groups were protected via treatment with sodium hydride in THF followed by addition of chloromethyl methyl ether (MOMCl) to afford **2-47**. Ortho-lithiation with nBuLi and TMEDA, followed by quenching with the 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded the

$H_8$BINOL boronic ester coupling partner, **2-48**, ideal for the rapid synthesis of a variety of 3,3'-dianisyl-$H_8$BINOL derivatives. Reaction of **2-48** with a variety of aryl bromides under typical Suzuki reaction conditions utilizing $Pd(PPh_3)_4$, followed by deprotection of the MOM protecting groups with trifluoroacetic acid afforded a small class of 3,3'-dianisyl-$H_8$BINOL bifunctional ligands.

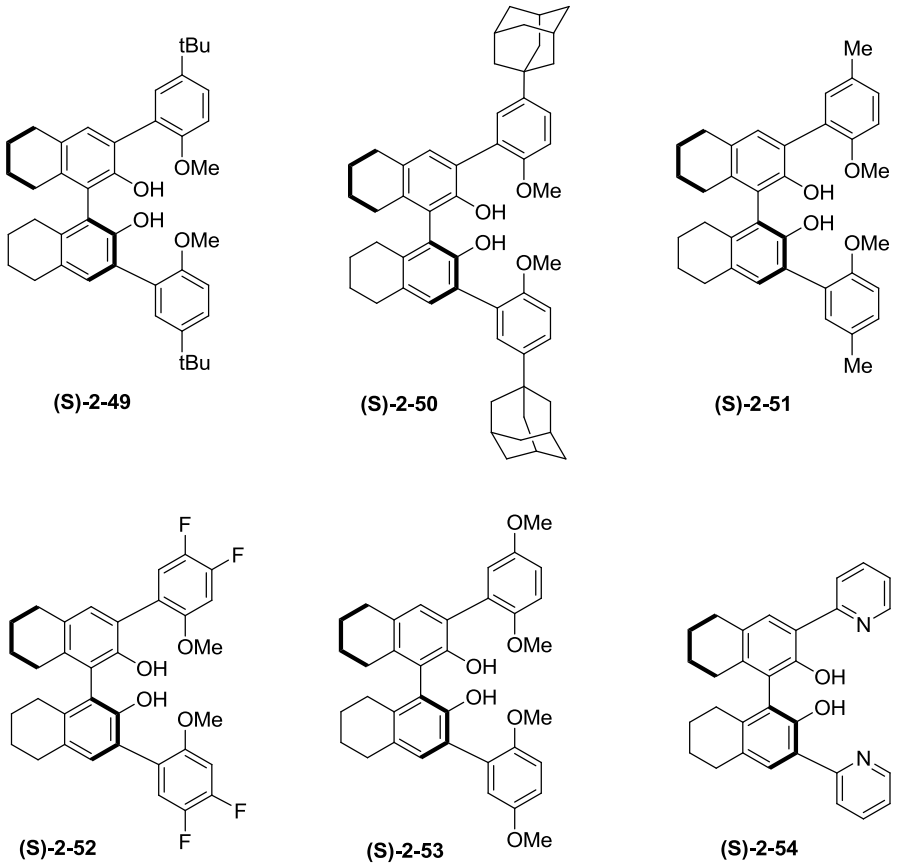
**Scheme 2.11.** Synthesis of Bifunctional 3,3'-Dianisyl-$H_8$BINOL Ligands.




As seen in Figure 2.9 we chose a variety of aryl bromides to test electronic and steric factors. Ligand **2-53** possesses an electron-donating methoxy group in the *para* position of the anisyl ring. In contrast ligand **2-52** contains electron-withdrawing fluorine substituents on the anisyl rings. Ligands **2-49** to **2-51** contain moderately electron-donating alkyl groups in the *para* position of the anisyl ring. Furthermore these alkyl groups are of varying size, from a small methyl group in ligand **2-49**, to a larger $^t$Bu group in ligand **2-50**, and the very sterically bulky adamantyl group in ligand **2-51**. Finally, the structurally different and more basic pyridine functionality was incorporated

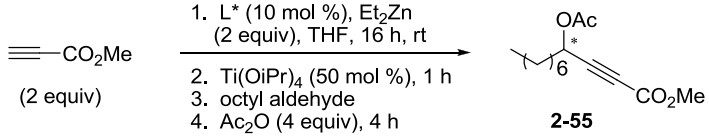
into ligand **2-54** to test whether the anisyl methoxy functionality was optimum for this catalytic system.

**Figure 2.9.** Bifunctional 3,3'-Dianisyl-$H_8$BINOL Ligands.




With these ligands in hand we tested them for the addition of methyl propiolate to a linear aliphatic aldehyde, octyl aldehyde (Scheme 2.12). We first stirred 2 equiv of methyl propiolate and $ZnEt_2$ in the presence of 10 mol % of the chiral ligand in THF at room temperature for 16 h. Following the formation of the alkynylzinc nucleophile, 50 mol % of $Ti(O^iPr)_4$ was added and the reaction mixture was stirred for 1 h. Octyl aldehyde was then added. After consumption of the aldehyde the reaction was quenched with acetic anhydride (4 equiv) for ease of purification and HPLC analysis to yield acetate **2-55**.

**Scheme 2.12.** Reaction Conditions for Ligand Screening of Methyl Propiolate Addition to Octyl Aldehyde.




The use of ligands **2-49** – **2-54** revealed that the Lewis basic anisyl methoxy group plays a significant role in the stereocontrol and efficiency of the reaction. As shown in Table 2.2, use of ligand **2-52** (entry 4) demonstrated that electron-withdrawing substituents on the anisyl ring were detrimental in terms of enantioselectivity (70% ee) and chemical yield (34%). In contrast, the electron-donating groups at the *para* position of the anisyl rings in **2-53** (entry 5) substantially improved the yield (52%) and enantioselectivity (86% ee). Ligands with moderately electron-donating alkyl groups in the *para* position proved optimal, as ligands **2-49** – **2-51** (entries 1-3) all catalyzed the reaction with enantioselectivities of 90% and 91% and in better yields (59-70%).

This ligand screening demonstrated that the electronic character of the 3,3' Lewis basic anisyl substituents is important for achieving good enantiocontrol. At the same time, it established that the steric bulk at the *para* position of the anisyl ring does not play a key role in chiral induction in this catalytic system, as the use of ligands **2-49** – **2-51** all resulted in similar enantioselectivities. The use of the pyridine containing ligand **2-54** confirmed that the use of the anisyl functionality as the Lewis basic site is preferred, as the pyridine containing ligand catalyzed the reaction in much lower enantioselectivity (34% ee, entry 6).

**Table 2.2.** Ligand Screen for Addition of Methyl Propiolate to Octyl Aldehyde.

| entry | ligand | yield (%) | ee (%) |
|---|---|---|---|
| 1 | **2-49** | 70 | 91 |
| 2 | **2-50** | 63 | 90 |
| 3 | **2-51** | 59 | 90 |
| 4 | **2-52** | 34 | 70 |
| 5 | **2-53** | 52 | 86 |
| 6 | **2-54** | 48 | 34 |

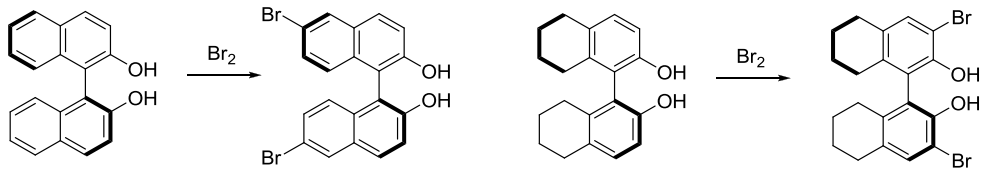
(a) $ZnEt_2$/methyl propiolate/$L^*$/$Ti(O^iPr)_4$/aldehyde= 2:2:0.1:0.5:1.

From this screening we choose ligand **2-49** containing $^t$Bu groups at the *para* position of the anisyl ring, as it was most effective in terms of chemical yield and enantioselectivity. With a promising catalytic system identified, we pursued a more efficient synthesis of chiral ligand **2-49**. While using $H_8$BINOL boronic ester intermediate **2-48** was ideal for creating a library of ligands it wasn't the most efficient route in terms of overall yield from our chiral starting material $H_8$BINOL. Thus we switched the boronic ester coupling partner for the Suzuki reaction to the anisyl derivative and the aryl bromide to $H_8$BINOL.

Easy access to 3,3'-dibromo-$H_8$BINOL was possible because electrophilic aromatic substitution reactions of $H_8$BINOL are known to occur exclusively at the 3,3' positions. This is not the case for BINOL. For example, treatment of $H_8$BINOL with $Br_2$ results in addition of bromine to the 3,3' positions,[33] while treatment of BINOL with $Br_2$ was found to yield bromination first at the 6,6' positions.[34] Incorporation of bromine at

the 3,3' postions of BINOL requires a longer synthetic sequence—protection of the hydroxyl groups and then ortho-lithiation followed by treatment with $Br_2$.[35]

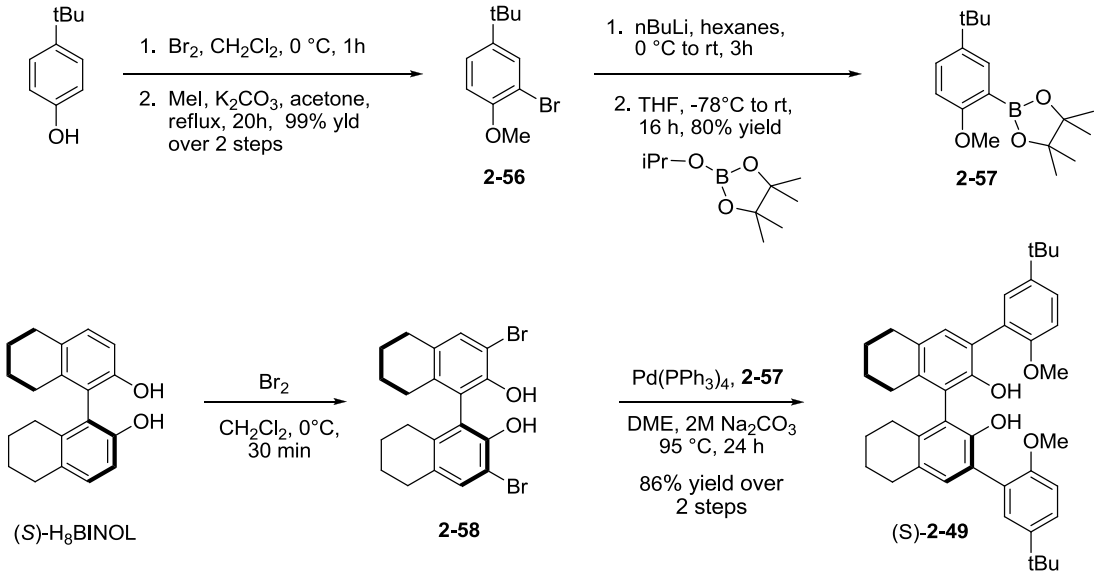
**Scheme 2.13.** Regioselective Bromination of BINOL and $H_8$BINOL.




The anisyl boronic ester intermediate was prepared as shown in Scheme 2.14. Commercially available 4-*tert*-butylphenol was first treated with bromine in $CH_2Cl_2$ at 0 °C for 1 h. After quenching with sodium sulfite and extraction, the brominated phenol was treated with MeI and $K_2CO_3$ in refluxing acetone for 20 h to yield 2-bromo-4-$^t$butyl-1-methoxybenzene, **2-56**, in 99% yield over 2 steps. Treatment of **2-56**, with $^n$BuLi in hexanes over 3 h furnished the aryl nucleophile via lithium-halogen exchange, and quenching with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded the anisyl boronic ester coupling partner **2-57** in 80% yield.

The aryl bromide for the Suzuki coupling was readily prepared by treatment of $H_8$BINOL with bromine at 0 °C for 30 min to yield 3,3'-dibromo-$H_8$BINOL. At this point we were curious to see if we could streamline the synthesis by performing the Suzuki coupling without protecting $H_8$BINOL's hydroxyl groups. A survey of the literature revealed this was possible.[36] Heating 3,3'-dibromo-$H_8$BINOL and boronic ester **2-57** (2 equiv) at 95 °C in the presence of 10 mol % $Pd(PPh_3)_4$ in DME and 2M $Na_2CO_3$ for 24 h afforded (*S*)-**2-49** in 86% yield over 2 steps from $H_8$BINOL on a 2 g scale. The ee of (*S*)-**2-49** was determined to be 98% by HPLC analysis (Chiralcel OD column).

**Scheme 2.14.** Improved Synthesis of **2-49**.




*b. Enantioselective Addition of Alkyl Propiolates to Aliphatic Aldehydes*

With an efficient synthesis of our ligand we turned to optimizing the reaction conditions as displayed in Table 2.3. We first conducted a solvent screen using 2 equiv methyl propiolate and $ZnEt_2$, 10 mol % of (*S*)-**2-49**, and 50 mol % $Ti(O^iPr)_4$. As compared to THF (91% ee, entry 1), use of less coordinating solvents such as $CH_2Cl_2$, $Et_2O$, and toluene all diminished the enantioselectivity (entries 2-4). In support of this trend, the coordinating solvent 1,4-dioxane provided an ee value closer to that found in THF (87% ee), though in decreased yield. Of all solvents, $Et_2O$ provided the best reactivity (73% yld) but the poorest selectivity (37% ee). Having identified THF as the optimal solvent we next screened the amount of $Ti(O^iPr)_4$ necessary for high enantioselectivity. Interestingly, the use of 0 and 10 mol % $Ti(O^iPr)_4$ resulted in no enantioselectivity (entries 6-7). Increasing the amount of $Ti(O^iPr)_4$ to 25 mol % improved the enantioselectivity to 76% ee (entry 8). Further increase to 100 mol %

**Table 2.3.** Optimization of Reaction Conditions for Methyl Propiolate Addition to Octyl Aldehyde Catalyzed by (*S*)-**2-49**.[a]

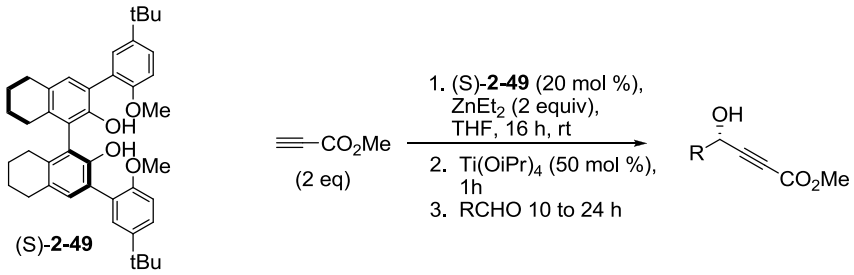
| entry | (S)-**49** mol % | solvent (aldehyde conc M) | $Ti(O^iPr)_4$ (mol %) | yield (%) | ee (%)[f] |
|---|---|---|---|---|---|
| 1 | 10% | THF (0.1 M) | 50% | 70 | 91 |
| 2 | 10% | $CH_2Cl_2$ (0.1 M) | 50% | 51 | 78 |
| 3 | 10% | $Et_2O$ (0.1 M) | 50% | 73 | 37 |
| 4 | 10% | Toluene (0.1 M) | 50% | 44 | 69 |
| 5 | 10% | 1,4-dioxane (0.1 M) | 50% | 49 | 87 |
| 6 | 10% | THF (0.1 M) | 0% | 28 | 0 |
| 7 | 10% | THF (0.1 M) | 10% | 27 | 0 |
| 8 | 10% | THF (0.1 M) | 25% | 51 | 76 |
| 9 | 10% | THF (0.1 M) | 100% | 47 | 91 |
| 10[b] | 10% | THF (0.2 M) | 50% | 65 | 90 |
| 11[c] | 10% | THF (0.05) | 50% | 40 | 90 |
| 12[d] | 10% | THF (0.1M) | 50% | 48 | 90 |
| **13[e]** | **20%** | **THF (0.1 M)** | **50%** | **84** | **95** |

(a) Unless otherwise indicated, the following conditions were employed: 0.025 mmol (*S*)-**2-49** (10 mol %), 2.5 mL solvent, 0.5 mmol $ZnEt_2$ (2 equiv), and 0.5 mmol methyl propiolate (2 equiv) were combined and stirred for 16 h at rt. Then 0.125 mmol $Ti(O^iPr)_4$ (0.5 equiv, 50 mol %) was added, and the mixture was stirred for 1 h, followed by the addition of 0.25 mmol octyl aldehyde (1 equiv). After consumption of the aldehyde the reaction was quenched with 1.0 mmol acetic anhydride (4 equiv) for ease of purification and HPLC analysis. (b) 1.25 mL THF. (c) 5 mL THF. (d) $Ti(O^iPr)_4$ was added in the first step. (e) 0.5 mmol octyl aldehyde was used; 0.1 mmol (*S*)-**2-49** (0.2 equiv, 20 mol %) was used. The equivalents of the other reagents remained the same, i.e., their quantities were doubled. (f) Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column).

$Ti(O^iPr)_4$ restored the high enantioselectivity (91% ee), but diminished the yield (entry 9). Thus 50 mol % $Ti(O^iPr)_4$ was determined to be optimal. Dilution and concentration had no effect on enantioselectivity, and dilution significantly decreased the yield (entries 10-11). Addition of $Ti(O^iPr)_4$ in the first step also decreased the yield though the enantioselectivity could be maintained (entry 12). Finally, doubling the amount of the chiral ligand (*S*)-**2-49** to 20 mol % improved the yield (84%) and enantioselectivity (95% ee) as shown in entry 13.

The resulting general procedure for the optimized reaction as shown in entry 13 of Table 2.3 and Scheme 2.15 is as follows. Under nitrogen, (*S*)-**2-49** (61.9 mg, 0.1 mmol, 20 mol %) was dissolved in THF (5 mL) in a 10 mL flame-dried flask. $ZnEt_2$ (103 μL, 1 mmol, 2 equiv) and methyl propiolate (89 μL, 1 mmol, 2 equiv) were added sequentially and the mixture was stirred for 16 h at room temperature, yielding a light yellow solution. $Ti(O^iPr)_4$ (74 μL, 0.25 mmol, 50 mol %) was then added and the mixture was stirred for 1 h. To the resulting dark orange solution, an aldehyde was added and the reaction was monitored by TLC or $^1H$ NMR. Upon consumption of the aldehyde, the reaction was quenched with ammonium chloride (saturated aqueous). The reaction mixture was extracted three times with $CH_2Cl_2$ and the organic layer was dried with sodium sulfate and concentrated. The resultant oil was purified by flash chromatography on silica gel. First eluting with 2:1 $CH_2Cl_2$:hexanes cleanly separates the ligand from the product, providing an efficient means of recovering the ligand. After removal of the ligand, the column was eluted with hexanes/ethylacetate (10-30% ethyl acetate) to give the desired product. The ee was determined by HPLC analysis (Chiracel OD or AD-H column).

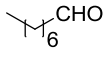
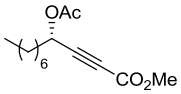
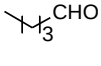
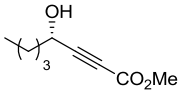
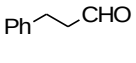
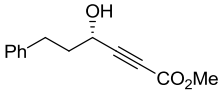
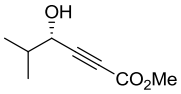
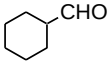
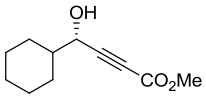
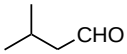
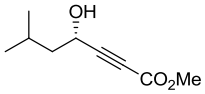
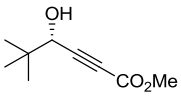
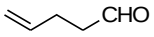
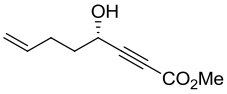
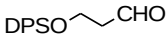
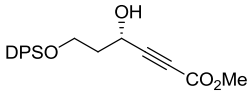
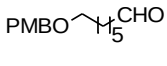
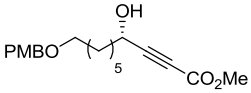
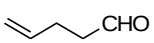
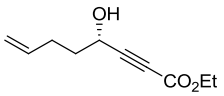
**Scheme 2.15.** Addition of Methyl Propiolate to Aliphatic Aldehydes Catalyzed by (*S*)-**2-49**.




These conditions were applied to a range of aliphatic aldehydes as shown in Table 2.4. In general, good yields and excellent enantioselectivities were obtained for linear aliphatic aldehydes (entries 1-3), α-branched aldehydes (entry 4), cyclohexanecarboxaldehyde (entry 5), and β-branched aldehydes (entry 6). A limitation of the catalytic system was found with a very bulky aldehyde, trimethylacetaldehyde, as the product could be generated in only 30% yield under the normal reaction conditions. This demonstrates that the steric bulkiness of the $^{t}$Bu group presents a problem for this catalytic system in terms of reactivity, though high enantioselectivity (94% ee) was still obtained (entry 7). Higher loadings of the ligand and other reagents using 4 equiv of methyl propiolate and $ZnEt_2$ with 40 mol % of the ligand and 100 mol % $Ti(O^{i}Pr)_4$ provided the product in an improved yield of 55% and 97% ee (entry 7). Importantly, functional aldehydes were also compatible with this methodology. The use of an enal, 4-pentenal (entry 8), provided high enantioselectivities comparable to the unfunctionalized linear aliphatic aldehydes used in entries 1-3. Aldehydes containing alcohols protected with TBS and PMB groups were also tolerated (entries 9-10). Finally this system is not limited to methyl propiolate. Ethyl propiolate gives similar results for the addition to 4-

pentenal (entry 11). The absolute configuration of the product in entry 11 of Table 2.4 was determined to be *S* by comparing its optical rotation with that in the literature.[12a] By analogy all other products were assigned to be *S*.

**Table 2.4.** Addition of Methyl Propiolate to Aliphatic Aldehydes Catalyzed by (S)-**2-49**.[a]

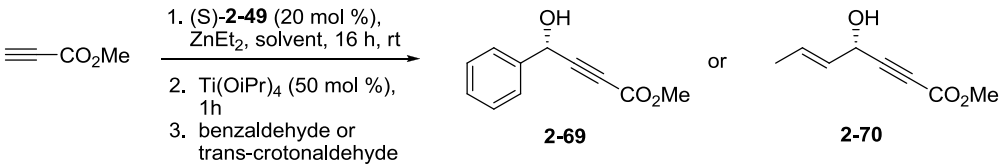
| entry | aldehyde | product | | yield (%) | ee (%)[b] |
|---|---|---|---|---|---|
| 1 |  |  | **2-55** | 84 | 95 |
| 2 |  |  | **2-59** | 84 | 94 |
| 3 |  |  | **2-60** | 83 | 93 |
| 4 |  |  | **2-61** | 67 | 89[c] |
| 5 |  |  | **2-62** | 84 | 95 |
| 6 |  |  | **2-63** | 71 | 90 |
| 7 |  |  | **2-64** | 30<br>55 | 94<br>97[d] |
| 8 |  |  | **2-65** | 63 | 95 |
| 9[e] |  |  | **2-66** | 60 | 90 |
| 10 |  |  | **2-67** | 56 | 92 |
| 11 |  |  | **2-68** | 60 | 95 |

(a) $ZnEt_2$/methyl propiolate/(S)-**2-49**/$Ti(O^iPr)_4$/aldehyde = 2:2:0.2:0.5:1. (b) Determined by HPLC analysis on Chiralcel OD or AD-H column. (c) Determined by $^1H$ NMR of mandelate acetate. (d) $ZnEt_2$/methyl propiolate/(S)-**2-49**/$Ti(O^iPr)_4$/aldehyde = 4:4:0.4:1:1. (e) 100 mol % $Ti(O^iPr)_4$.

*c. Enantioselective Addition of Alkyl Propiolates to Aromatic and α,β-Unsaturated Aldehydes*

These findings represented the first report of a highly enantioselective catalytic system for the addition of alkynoates to a wide range of aliphatic aldehydes. While we were pleased to discover a catalytic system that provided a solution for the existing gap in the substrate scope—the addition of alkynoates to aliphatic aldehydes—we also wanted to determine whether our ligand was general for the addition of alkynoates to all types of aldehydes. This would be the ideal catalytic system because it would require only a single ligand for any alkynoate addition one wished to perform. Thus we explored the use of ligand (*S*)-**2-49** for the addition of methyl propiolate to an aromatic aldehyde, benzaldehyde, and an α,β-unsaturated aldehyde, *trans*-crotonaldehyde.

**Scheme 2.16.** Addition of Methyl Propiolate to Benzaldehyde and *trans*-Crotonaldehyde Catalyzed by (*S*)-**2-49**.




**2-69** **2-70**

We began by testing our standard conditions for the addition of methyl propiolate to benzaldehyde (Scheme 2.16), but found that we were unable to form the desired product in THF (Table 2.5, entry 1). A solvent screen revealed that the product could be formed in low yields in other solvents such as $CH_2Cl_2$ or $Et_2O$, though with good enantioselectivity (entries 2-3). Increasing the catalyst loading to 30 mol % was able to increase the yields and enantioselectivities (entries 4-6). As was observed for aliphatic aldehydes, $Et_2O$ proved to be the best solvent in terms of reactivity, though poorest in

terms of enantioselectivity. Higher loadings of the other reagents (3 equiv of methyl propiolate and $ZnEt_2$) were able to increase the yield to 91%, but was accompanied by a slight drop in enantioselectivity (entry 7). Finally, it was found that use of a mixed solvent system was able to maintain the good reactivity present in $Et_2O$ and provide a modest improvement in enantioselectivity. Using 20 mol % of (*S*)-**2-49**, 2 equiv of methyl propiolate and $ZnEt_2$, in a $Et_2O$/THF (4/1) mixed solvent system afforded the product in 64% yield and 91% ee.

**Table 2.5.** Addition of Methyl Propiolate to Benzaldehyde Catalyzed by (S)-**2-49**.[a]

| entry | solvent | (*S*)-**2-49** (mol %) | yield (%) | ee (%)[d] |
|---|---|---|---|---|
| 1 | THF | 20 | -- | -- |
| 2 | $CH_2Cl_2$ | 20 | 30 | 91 |
| 3 | $Et_2O$ | 20 | 56 | 88 |
| 4 | $CH_2Cl_2$ | 30 | 49 | 93 |
| 5 | Toluene | 30 | 34 | 92 |
| 6 | $Et_2O$ | 30 | 65 | 91 |
| 7[b] | $Et_2O$ | 30 | 91 | 88 |
| **8[c]** | **$Et_2O$/THF** | **20** | **64** | **91** |

(a) $ZnEt_2$/methyl propiolate/$Ti(O^iPr)_4$/aldehyde = 2:2:0.5:1. (b) 3 equiv $ZnEt_2$/methyl propiolate. (c) $Et_2O$/THF (4/1). (d) Determined by HPLC analysis on Chiralcel OD column.

We next turned to an α,β-unsaturated aldehyde, trans-crotonaldehyde, and encountered similar results. Using 3 equiv of methyl propiolate and $ZnEt_2$ in the presence of 20 mol % of (*S*)-**2-49** in THF formed the product in high enantioselectivity (95% ee) but low yield (25%) as shown in entry 1 of Table 2.6. Use of 1,4-dioxane resulted in even higher enantioselectivity (97% ee) though still in low yield (26%, entry

2). Switching to non-coordinating solvents such as $CH_2Cl_2$, $Et_2O$, and toluene increased the yields substantially without too greatly sacrificing the enantioselectivity (entries 3-5). Since $Et_2O$ was the best solvent in terms of reactivity and 1,4-dioxane the best in terms of selectivity we again tested a mixed solvent system (entry 6). Using a 4/1 ratio of $Et_2O$/ 1,4-dioxane afforded the product in 85% yield and 95% ee, and in a shortened reaction time of 4 h after addition of the aldehyde. We were also interested in screening the amount of $Ti(O^iPr)_4$ necessary for high enantioselectivity. In contrast to the results found with aliphatic aldehydes, some enantioselectivity could be obtained in the absence of $Ti(O^iPr)_4$ (entry 7), although in low yield, and good enantioselectivity could be obtained with only 10 mol % $Ti(O^iPr)_4$ (entry 8). However, these reactions were much slower than those with 20 mol % of $Ti(O^iPr)_4$ or higher, requiring 24 h to consume the aldehyde as observed by TLC. Increasing the amount of $Ti(O^iPr)_4$ to 20 mol % and above caused small increases in enantioselectivity (entries 9-11), and the use of 50 mol % $Ti(O^iPr)_4$ was determined to be optimal.

The use of the mixed solvent systems for benzaldehyde and trans-crotonaldehyde demonstrated that we could use one solvent to promote reactivity ($Et_2O$) and one solvent to facilitate enantioselectivity—in this system a coordinating solvent such as THF or 1,4-dioxane. As we consistently observed higher enantioselectivities in coordinating solvents, this suggested that coordination of the solvent with the zinc species present in the catalytic system was beneficial for selectivity. This prompted us to investigate how much of the coordinating solvent was necessary to maintain high enantiocontrol. To test this we chose the addition of methyl propiolate to trans-crotonaldehyde since this allowed

a significant variance in ee values from 95% ee in the $Et_2O$/1,4-dioxane (4/1) mixed solvent system to 87% ee in $Et_2O$.

**Table 2.6.** Addition of Methyl Propiolate to trans-Crotonaldehyde Catalyzed by (S)-**2-49**.[a]

| entry | solvent | % (*S*)-**1** | $Ti(O^iPr)_4$ (mol %) | yield (%) | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | THF | 20 | 50 | 25 | 95 |
| 2 | 1,4-dioxane | 20 | 50 | 26 | 97 |
| 3 | $CH_2Cl_2$ | 20 | 50 | 70 | 91 |
| 4 | Toluene | 20 | 50 | 62 | 89 |
| 5 | $Et_2O$ | 20 | 50 | 80 | 87 |
| **6[b]** | **$Et_2O$/1,4-dioxane** | **20** | **50** | **90** | **95** |
| 7[b] | $Et_2O$/1,4-dioxane | 20 | 0 | 16 | 28 |
| 8[b] | $Et_2O$/1,4-dioxane | 20 | 10 | 73 | 87 |
| 9[b] | $Et_2O$/1,4-dioxane | 20 | 20 | 87 | 93 |
| 10[b] | $Et_2O$/1,4-dioxane | 20 | 40 | 90 | 94 |
| 11[b] | $Et_2O$/1,4-dioxane | 20 | 60 | 90 | 95 |
| 12[b] | $Et_2O$/1,4-dioxane | 20 | 80 | 86 | 95 |

(a) $ZnEt_2$/methyl propiolate/aldehyde = 3:3:1. (b) $Et_2O$/1,4-dioxane (4/1). (c) Determined by HPLC analysis on Chiralcel OD column.

**Table 2.7.** Variation of $Et_2O$/1,4-Dioxane Solvent Ratio for the Addition of Methyl Methyl Propiolate to trans-Crotonaldehyde Catalyzed by (S)-**2-49**.[a]

| entry | $Et_2O$/1,4-dioxane (equiv)[b] | yield (%) | ee (%) |
|---|---|---|---|
| 1 | 3/1 (9.7 equiv) | 89 | 95 |
| 2 | 4/1 (7.8 equiv) | 85 | 95 |
| 3 | 5/1 (6.6 equiv) | 87 | 95 |
| 4 | 10/1 (3.6 equiv) | 91 | 94 |
| 5 | 2.7 equiv | 84 | 92 |
| 6 | 2 equiv | 86 | 90 |
| 7 | 1.3 equiv | 86 | 89 |
| 8 | 0.7 equiv | 86 | 88 |

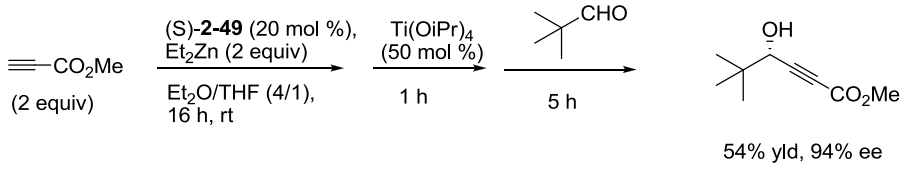
(a) $ZnEt_2$/methyl propiolate/$Ti(O^iPr)_4$/aldehyde = 3:3:0.5:1. (b) Equivalents of 1,4-dioxane relative to $ZnEt_2$.

To examine the amount of 1,4-dioxane necessary for high enantioselectivity we followed our optimized procedure for the addition of methyl propiolate to α,β-unsaturated aldehydes, 3 equiv methyl propiolate and $ZnEt_2$ with 20 mol % **2-49**. We then varied the ratio of $Et_2O$ and 1,4-dioxane, calculating how many equivalents of 1,4-dixoane were present relative to $ZnEt_2$. The amount of 1,4-dioxane relative to zinc was screened from ~10 equiv to less than 1 equiv. As shown in Table 2.6 an enantioselectivity of 95% was maintained in the range of 9.7 to 6.6 equiv of the coordinating solvent (entries 1-3), and was still high (94% ee) in the presence of 3.6 equiv of 1,4-dioxane. Beyond this point, the enantioselectivity began to decrease steadily as the equivalents of 1,4-dioxane were reduced (entries 5-7). When less than one equivalent of 1,4-dioxane was used, no beneficial effect on selectivity was observed as

the enantioselectivity was similar to that found when using $Et_2O$ alone (entry 8). From this screening it appears that ≥3.5 equiv of the coordinating solvent relative to zinc are necessary for high enantioselectivity.

With the success of the mixed solvent system for aromatic and α,β-unsaturated aldehydes, we wondered if the mixed solvent system could be used to address the decreased reactivity for sterically hindered aliphatic aldehydes such as trimethylacetaldehyde. As shown in Scheme 2.17, use of a 4/1 mixed solvent system of $Et_2O$/THF (THF was previously found to be a better solvent than 1,4-dioxane for aliphatic aldehydes) with 2 equiv methyl propiolate and $ZnEt_2$ in the presence of 20 mol % (*S*)-**2-49** provided the product in 54% yield and 94% ee. Previously, using the same conditions in THF had afforded the product in 30% yield and 94% ee, and increased loadings of all reagents had afforded 55% yield and 97% ee (see Table 2.4, entry 7). This demonstrated that the use of the mixed solvent system was able to substantially improve reactivity for aliphatic aldehydes without compromising enantioselectivity.

**Scheme 2.17.** Addition of Methyl Propiolate to Trimethylacetaldehyde Catalyzed by (S)-**2-49** in Mixed Solvent System.

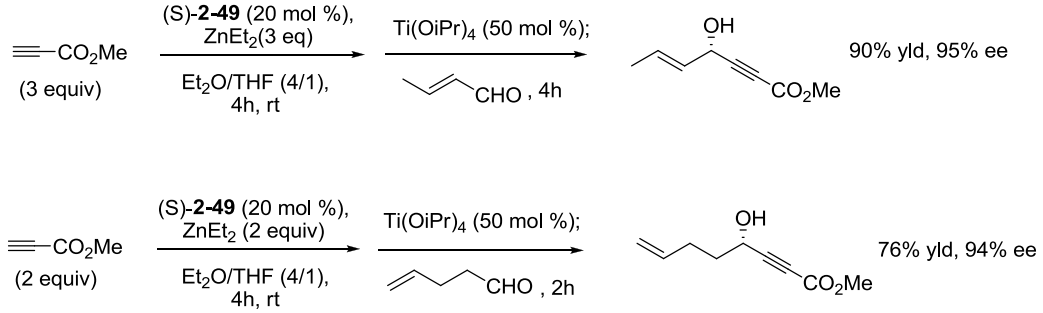



54% yld, 94% ee

With the increased reactivity afforded by the mixed solvent system we next investigated the amount of time necessary to form the alkynylzinc, hypothesizing that 16 h was no longer necessary for high yields. We also suspected this possibility because the formation of the alkynylzinc is accompanied by a color change from a clear solution to a

light amber color. In the mixed solvent system this color change occurred much more quickly, within 3 to 4 h. Testing 2, 3, and 4 h reaction times for the first step in the addition of methyl propiolate to trans-crotonaldehyde resulted in yields of 83%, 87%, and 90% respectively, as compared with 90% yield when the first step was allowed to proceed for 16 h. This confirmed our hypothesis that the alkynylzinc nucleophile was able to form much more quickly in the presence of $Et_2O$, and that the mixed solvent system could improve the efficiency of the reaction procedure by shortening the reaction time. We were also able to simplify the procedure further by finding that a mixing time of 1 h after the addition of $Ti(O^iPr)_4$ was not necessary for high enantioselectivity. Mixing times of 30 min, 15 min, and immediate addition of the aldehyde following the addition of $Ti(O^iPr)_4$ did not reduce the enantioselectivity or yield. This indicates that the chiral catalyst forms very quickly upon the addition of $Ti(O^iPr)_4$. Application of these modified conditions for the addition of methyl propiolate to an aliphatic aldehdye, 4-pentenal, were also successful, providing the product in 76% yield and 94% ee within 2 h after addition of the aldehyde. These optimized reaction conditions (Scheme 2.18) represented a large improvement in the simplicity and efficiency of this method.

**Scheme 2.18.** Optimized Reaction Conditions for Addition of Methyl Propiolate to α,β-Unsaturated and Aliphatic Aldehydes Catalyzed by (*S*)-**2-49**.



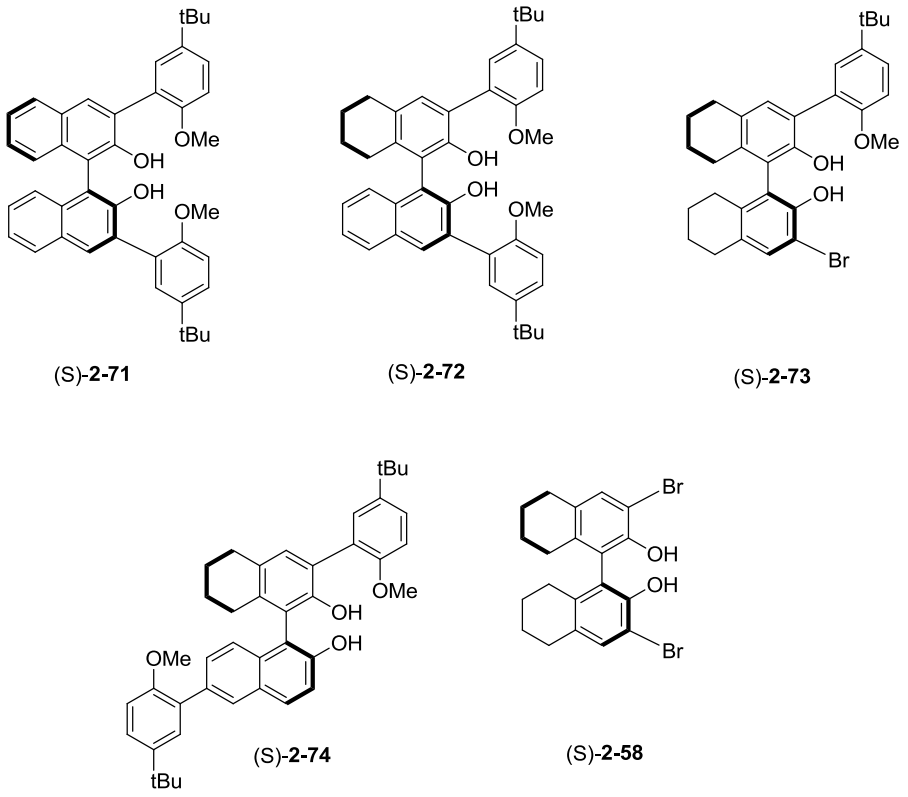
The high enantioselectivities obtained (greater than 90% ee) with 20 mol % (*S*)-**2-49** for the addition of methyl propiolate to aliphatic, aromatic, and α,β-unsaturated aldehydes makes this catalytic system the most general and effective method thus far reported for alkynoate additions to aldehydes. Most importantly, (*S*)-**2-49** is the only reported catalyst shown to be effective for the addition of alkynoates to a wide range of aliphatic aldehydes, including functional aliphatic aldehydes. The addition of ethyl propiolate to aliphatic aldehydes is similar with this catalytic system. Finally, this catalytic system has gone through several iterations of optimization such that it has become highly practical and user friendly. The entire procedure can be performed at room temperature in 8 h or less for aliphatic and α,β-unsaturated aldehydes, and the ligand can be easily recovered and recycled.

*d. Possible Models of Enantiocontrol*

With the discovery of an effective catalytic system for the addition of alkynoates to a variety of aldehydes we were interested in gaining insight into what features of the ligand where important for reactivity and enantiocontrol. Several questions came to mind. First, was the use of $H_8$BINOL beneficial for enantioselectivity as we had hypothesized? We had demonstrated that the use of $H_8$BINOL greatly simplified the preparation of this class of ligands, but was it also responsible for the high enantioselectivity? How would the use of BINOL or $H_4$BINOL-based derivatives impact the enantioselectivity, and would the loss of C2 symmetry in the $H_4$BINOL-based derivatives be detrimental to stereoselectivity? Secondly, we knew that the 3,3'-anisyl groups were necessary for reactivity, as no product is generated when methyl propiolate, $ZnEt_2$, and BINOL are combined with an aldehyde in the absence of a Lewis basic

additive. We also knew from our original ligand screening that the electronic character of the anisyl methoxy greatly impacted enantioselectivity, as ligand **2-52** containing anisyl groups with electron withdrawing substituents displayed substantially reduced enantioselectivity. This suggested that coordination of the anisyl methoxy to zinc or titanium was involved in enantiocontrol. However, where both of the anisyl groups required for high enantioselectivities? Could one of the anisyl moieties be substituted with another group or removed entirely?

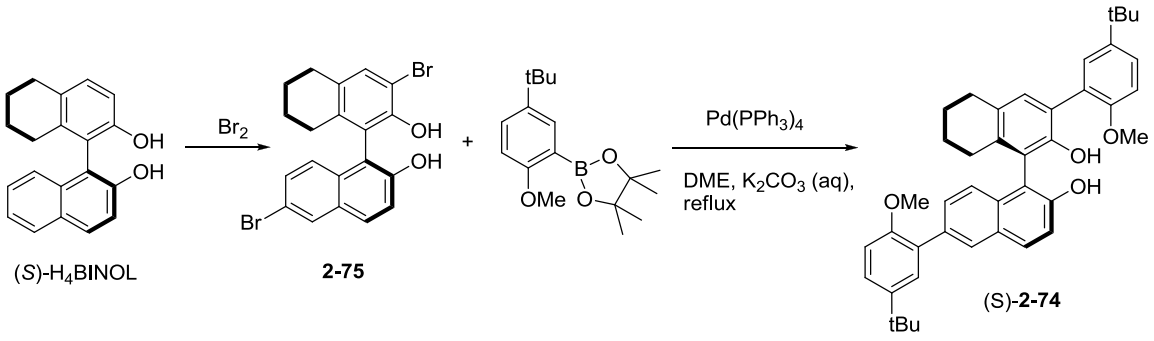
**Figure 2.10.** BINOL, $H_4$BINOL, and $H_8$BINOL Derivatives Synthesized.




Some interesting insights into these questions were made possible by the synthesis of ligands **2-71** to **2-74** by Yue Yang (Figure 2.10). In order to probe the effect of the $H_8$BINOL backbone, BINOL based **2-71** and $H_4$BINOL based **2-72** were synthesized in a manner analogous to that shown in Scheme 2.11. The $H_4$BINOL based

ligand **2-72** also provided a means to test the effect of loss of $C_2$ symmetry in the chiral ligand. The effects of the 3,3'-anisyl groups was probed by replacement of one of the anisyl groups with a bromine atom in ligand **2-73**. This compound was simply the monocoupling product of the Suzuki reaction to access **2-49** shown in Scheme 2.13. $H_4$BINOL derivative **2-74** with a hydrogen atom at the 3' position was also synthesized. Furthermore this ligand contained an anisyl group at the 6' position. Ligand **2-74** was synthesized from the Suzuki coupling of 3,6'-dibromide **2-75** which arose from the treatment of $H_4$BINOL with bromine as shown in Scheme 2.19.

**Scheme 2.19.** Synthesis of Ligand **2-74**.




These ligands were then tested by Yang Yue for the addition of methyl propiolate to valeraldehyde, using 20 mol % of the chiral ligand and 50 mol % of $Ti(O^iPr)_4$ in THF as shown in Scheme 2.20. The results are shown in Table 2.7, and provide insight into the important structural characteristics of $H_8$BINOL ligand **2-49**. The use of BINOL based ligand **2-71** resulted in a 10% decrease in ee (85% ee, entry 2), demonstrating that the $H_8$BINOL backbone was beneficial for high enantioselectivity as we had hypothesized. The use of the $H_4$BINOL derivative **2-72** resulted in even lower enantioselectivity (77% ee, entry 3) than the $H_8$BINOL and BINOL derivatives, demonstrating that $C_2$ symmetry in the chiral ligand is important for good enantiocontrol.

Testing monoanisyl $H_8$BINOL-based ligand **2-73** resulted in 89% ee (entry 4). $H_4$BINOL derivative **2-74** gave low and surprisingly opposite enantioselectivity (-50% ee, entry 5).

**Scheme 2.20.** Addition of Methyl Propiolate to Valeraldehyde in the Presence of Various Chiral Ligands.

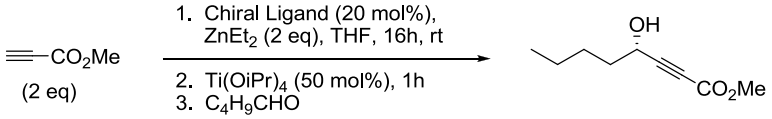



**Table 2.8.** Comparison of BINOL, $H_4$BINOL, and $H_8$BINOL Chiral Ligands for the Addition of Methyl Propiolate to Valeraldehyde.[a]

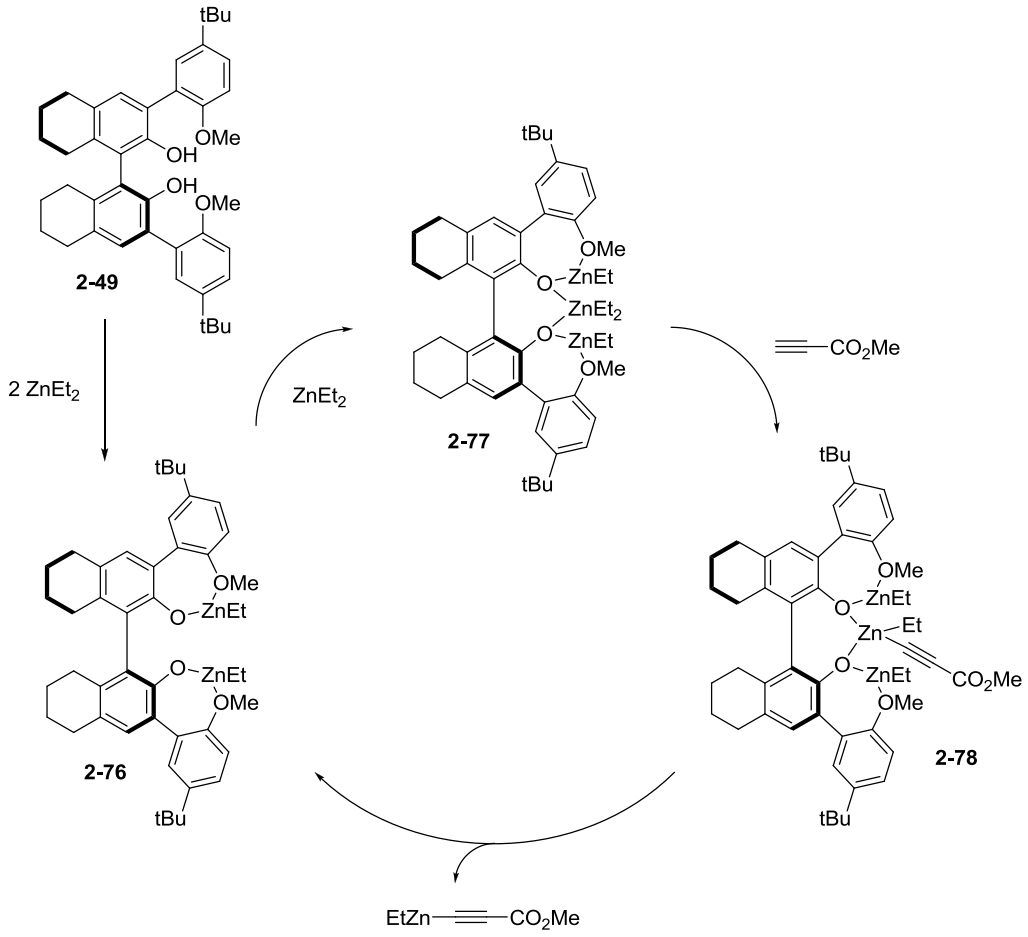
| entry | ligand | yield (%) | ee (%) |
|---|---|---|---|
| 1 | (*S*)-**2-49** | 84 | 95 |
| 2 | (*S*)-**2-71** | 62 | 85 |
| 3 | (*S*)-**2-72** | 94 | 77 |
| 4 | (*S*)-**2-73** | 83 | 89 |
| 5 | (*S*)-**2-74** | 45 | -50 |
| 6 | (*S*)-**2-58** | 0 | - |

(a) $ZnEt_2$/methyl propiolate/Ti($O^iPr$)$_4$/aldehyde = 2:2:0.5:1.

The results of entries 4 and 5 suggest that the bromine atom at the 3 position in ligand **2-73** could be important for enantiocontrol, because replacement of this group with a hydrogen atom in ligand **2-74** resulted in the formation of the opposite enantiomer. Thus, while both anisyl groups are not essential for enantioselectivity, the steric environment created by substituents at the 3,3' positions does appear important for good enantiocontrol. This is supported by the fact that there is a correlation between the

reduced enantioselectivity and the decreased size of the bromine atom in ligand **2-73** compared with the anisyl group in ligand **2-49**. The use of 3,3'-dibromo-$H_8$BINOL, **2-58**, was not able to generate the product (entry 6). As Lewis basic coordination to zinc has been shown to catalyze the formation of the alkynylzinc nucleophile, this demonstrates that the bromine atom is likely functioning in a steric role and not involved in coordination of the zinc metal center.

**Figure 2.11.** Possible Catalytic Cycle for the Formation of the Alkynylzinc Nucleophile.



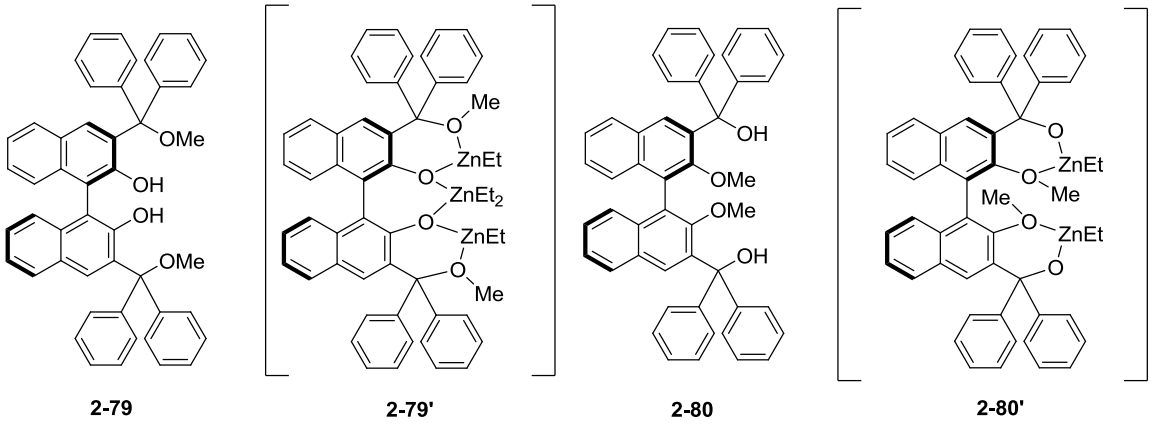

While the exact mechanism is unknown, on the basis of these findings and our group's previous studies in asymmetric alkyne additions to aldehydes the following tentative mechanism for $H_8$BINOL ligand **2-49** can be proposed. First, the

alkynylethylzinc nucleophile can be formed as shown in Figure 2.11. Reaction of **2-49** with 2 equivs of $ZnEt_2$ results in deprotonation of the hydroxyl groups. The zinc metal centers likely coordinate with the anisyl methoxy groups as shown in intermediate **2-76**. This coordination is important for formation of the alkynylzinc species, as no product is observed in the absence of a Lewis base. In intermediate **2-76** the more basic central $H_8$BINOL oxygen atoms can coordinate another equiv of $ZnEt_2$ to generate intermediate **2-77**. The coordination of the first 2 equiv of zinc by the anisyl methoxy groups allows more electron density to be present in the central oxygen atoms, such that the newly coordinated $ZnEt_2$ is activated for the deprotonation of methyl propiolate to yield intermediate **2-78**. The catalytic cycle is completed by dissociation of the alkynylzinc.

This hypothesis is supported by the finding that the yield is drastically reduced (34%) when the anisyl ring is electron deficient, as in ligand **2-52** containing electron withdrawing fluorine atoms. In this ligand less electron density is available to the coordinated $ZnEt_2$ to aid in deprotonation of the alkyne in intermediate **2-77**. That coordination of $ZnEt_2$ with the central $H_8$BINOL oxygen atoms is responsible for the formation of the alkynylzinc is supported by our group's previous studies with chiral ligands **2-79** and **2-80** (Figure 2.12). While **2-79** could facilitate formation of the alkynylzinc **2-80** could not. This indicates that coordination of the central BINOL oxygen atoms with $ZnEt_2$ as shown in intermediate **2-79'** could be important for formation of the alkynylzinc. In intermediate **2-80'** the BINOL oxygen atoms would be sterically and electronically less favorable for coordination of another equiv of $ZnEt_2$. The increased yield for the $H_8$BINOL derivative as compared with the BINOL based derivative (84% vs 62%) also supports this hypothesis. Due to the partial reduction of the

naphthyl ring the oxygen atoms of $H_8$BINOL are more basic than those in BINOL, providing extra electron density for the coordination of $ZnEt_2$ to promote deprotonation of the alkynoate.

**Figure 2.12**. Ligands **2-79** and **2-80** and Possible Intermediates Upon Deprotonation with $ZnEt_2$.

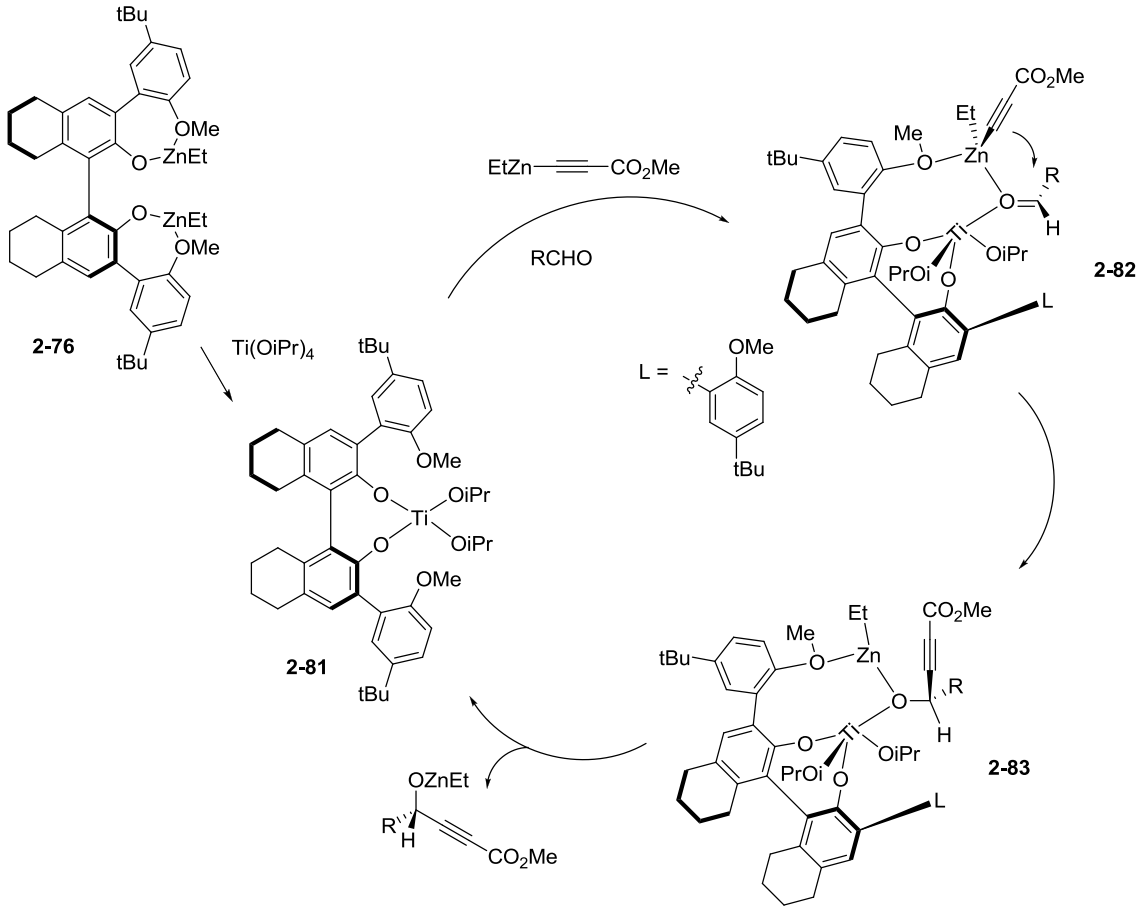



**2-79** **2-79'** **2-80** **2-80'**

After the alkynylzinc nucleophile is formed, $Ti(O^iPr)_4$ is added, and a second catalytic cycle can be proposed as shown in Figure 2.13. Reaction of intermediate **2-76** with $Ti(O^iPr)_4$ can generate **2-81**. Coordination of the anisyl methoxy group with the previously generated alkynylzinc, and coordination of the aldehyde with the titanium and zinc metal centers can form proposed intermediate **2-82**. Coordination of the alkynylzinc by the anisyl methoxy groups is supported by the significant impact of the electronics of the anisyl ring on the enantioselectivity.

From this coordination the alkynylzinc is proposed to be oriented with the longer alkynyl group up, away from the anisyl ring and $H_8$BINOL backbone. In this intermediate the Ti(IV) center can exist in a five-coordinate square pyramidal geometry and is responsible for binding the aldehyde in the chiral catalytic pocket. The other anisyl ring serves as a bulky group to direct the orientation of the bound aldehyde, such

**Figure 2.13.** Proposed Catalytic Cycle for the Enantioselective Addition of the Alkynylzinc Nucleophile to an Aldehyde.




that the larger R group is pointed away from the substituent at the 3 position to minimize steric interaction. From this proposed intermediate the alkyne attacks the *re* face of the aldehyde to give the observed (*S*)-product. This hypothesis is supported by the reduced but still good enantioselectivity found when the 3 position is substituted with a sterically smaller bromine atom (ligand **2-73**), and the greatly decreased and reversed enantioselectivity observed with the 3 position is substituted with a hydrogen atom (ligand **2-74**). In the latter case the removal of steric bulk at the 3 position could cause the aldehyde to reorient such that it is attacked from the opposite face. Though the exact

mechanism for stereocontrol is unknown, we believe this proposal is consistent with the experimental data and provides a reasonable model to help us understand the process.

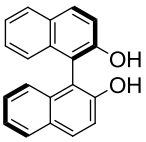
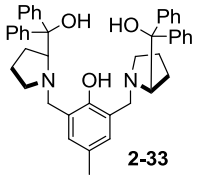
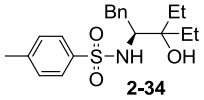
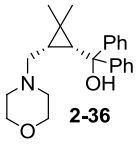
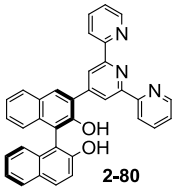
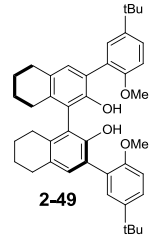
*d. Summary*

In summary, we have developed a novel and highly effective catalytic system utilizing (*S*)-**2-49** in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ for the addition of alkynoates to aliphatic aldehydes. Table 2.9 compares the catalytic system utilizing (*S*)-**2-49** with the existing methods for asymmetric alkynoates additions to aldehydes, including the more recently developed BINOL terpyridine ligand **2-80** shown to be effective for alkynoate additions to aromatic aldehydes.[37] As can be seen from Table 2.9, ligand (*S*)-**2-49** represents the first catalytic system reported to be effective for the addition of alkynoates to a large range of aliphatic aldehydes in high enantioselectivities. Additionally, this system is also effective for aromatic and α,β-unsaturated aldehydes, making this the most general and effective catalytic system for the addition of alkynoates to aldehydes. This system has been optimized such that it is user friendly and the chiral ligand can be easily recovered. The design of this system highlights the potential advantages for enantiocontrol of $H_8$BINOL derivatives over BINOL-based ligands, and the advantages of the use of a bifunctional catalyst system to improve enantiocontrol for difficult substrates.

In addition, an efficient synthesis of bifunctional (*S*)-**2-49** has been developed, providing access to the ligand in 86% yield over 2 steps from $H_8$BINOL. This synthetic scheme takes advantage of the different reactivity of $H_8$BINOL in comparison with BINOL, and demonstrates that these ligands can be accessed much more readily than their BINOL-based counterparts. The easy preparation of this class of ligands makes

their use by the synthetic community more practical. Finally, through the synthesis of derivatives of (*S*)-**2-49**, we gained an understanding of the important structural features for enantiocontrol and were able to propose a tentative catalytic cycle. This may aid in the design of future chiral ligands for asymmetric alkyne additions to aldehydes.

**Table 2.9.** Catalytic Systems for Alkynoate Additions to Aldehydes.

| chiral ligand | mol % | $ZnR_2$ (equiv) | $Ti(O^iPr)_4$ (mol %) | Rxn. Temp | Aliphatic Aldehydes | Aromatic Aldehydes | α,β-Unsat. Aldehydes |
|---|---|---|---|---|---|---|---|
|  | 40 | $ZnEt_2$ (4 eq) | 100 | rt | 4<br>81-89% ee | 15<br>85-95% ee | 2<br>90-92% ee |
|  **2-33** | 10 | $ZnMe_2$ (3 eq) | -- | 4 °C | 1<br>95% ee | 1<br>82% ee | 4<br>90-97% ee |
|  **2-34** | 30 | $ZnEt_2$ (3 eq) | 30 | rt | 1<br>79% ee | 10<br>90-94% ee | 2<br>82-85% ee |
|  **2-36** | 20 | $ZnMe_2$ (3 eq) | -- | 0 °C | -- | 10<br>90-93% ee | -- |
|  **2-80** | 20 | $ZnEt_2$ (4 eq) | 50 | rt | 1<br>47% ee | 12<br>87-98% ee | -- |
|  **2-49** | 20 | $ZnEt_2$ (2 eq) | 50 | rt | 10<br>89-95% ee | 1<br>91% ee | 1<br>95% ee |

**2.3. Experimental and Characterization.**

*a. General Data and Instruments*

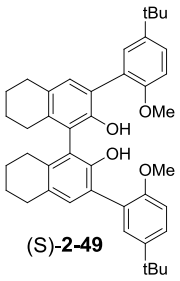
All $^{1}H$ and $^{13}C$ NMR spectra were obtained using a Varian 300 MHz spectrometer. HPLC analyses were carried out with a Waters 600 Pump and Waters 996 Photodiode Array Detector using a Chiralcel OD or Chiralpak AD-H column. Optical rotation values were measured with the Jasco Digital Polarimeter P-2000.

All reactions were carried out under nitrogen unless otherwise noted. All chemicals were purchased from Sigma Aldrich Chemical Co. or Alfa Aesar with the exception of the diethylzinc (95%) and $Pd(PPh_3)_4$ which were purchased from Strem Chemicals, Inc. Toluene, THF, and 1,4-dioxane were distilled over sodium and benzophenone under nitrogen atmosphere. Methylene chloride and diethyl ether were dried by passing through activated alumina columns under nitrogen. Solvents were stored over 4 Å molecular sieves. Methyl propiolate was distilled under reduced pressure from 4 Å molecular sieves prior to use. All aldehydes were passed through a plug of alumina and distilled from 4 Å molecular sieves prior to use. 3-(*tert*-butyldiphenylsilyloxy)propanal[38] and 7-(4-methoxybenzyloxy)heptanal[39] were kindly provided by Martin Herold and Cėline Griot, members of Dr. Marshall's lab, and were prepared according to literature procedures. High resolution mass spectra were obtained from the University of California, Riverside (UCR) Mass Spectrometry Facility.

*b. Preparation and Characterization of Ligands (S)-**2-49** – (S)-**2-54***

Ligands (S)-**2-49 –** (S)-**2-54** were initially prepared in analogy to the corresponding previously reported BINOL ligands,[40] as displayed in reaction Scheme 2.11. The ligands were dried from THF prior to use in catalysis.

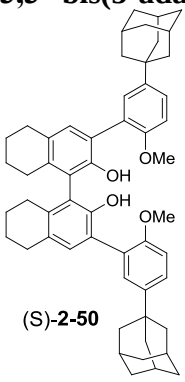
**3,3'-bis(5-*tert*-butyl-2-methoxyphenyl)-5,5'6,6',7,7',8,8'-octahydro-1,1'-binapthyl-2-2'-diol, 2-49:**



(S)-**2-49**

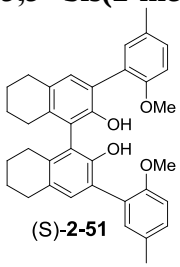
98% ee determined by HPLC analysis: OD column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 18.71 min $t_{minor}$ = 22.98 min. $[\alpha]_D$ = -7.01 (c = 1.14, THF). $^1$H NMR (75 MHz, $CDCl_3$) $\delta$ 1.34 (s, 18H), 1.77 (bs, 8H), 2.27-2.35 (m, 2H), 2.50-2.58 (m, 2H), 2.84 (bs, 4H), 3.81 (s, 6H), 5.85 (s, 2H), 6.91 (d, 2H, J = 8.7 Hz), 7.05 (s, 2H), 7.35 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 2.4 Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 23.16, 23.21, 27.17, 29.39, 31.53, 34.21, 56.00, 110.68, 124.01, 124.01, 125.35, 126.96, 129.35, 129.51, 131.33, 136.50, 144.18, 148.65, 153.54. HRMS ($MH^+$) for $C_{42}H_{51}O_4$ Calcd: 619.3782 Found: 619.3792.

**3,3'-bis(5-adamantyl-2-methoxyphenyl)-5,5'6,6',7,7',8,8'-octahydro-1,1'-binapthyl-2-2'-diol, 2-50:**



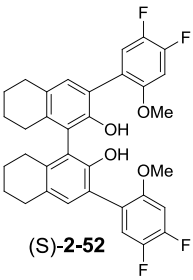
(S)-**2-50**

$[\alpha]_D$ = -4.19 (c = 1.09, THF). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.78 (bs, 20H), 1.94 (bs, 12H), 2.10 (bs, 6H), 2.28-2.35 (m, 2H), 2.50-2.59 (m, 2H), 2.85 (bs, 4H), 3.82 (s, 6H), 5.88 (s, 2H), 6.94 (d, 2H, J = 9 Hz), 7.06 (s, 2H), 7.32 (d, 2H, J = 8.4 Hz), 7.42 (d, 2H, J = 2.4 Hz) $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 23.13, 23.18, 27.12, 28.90, 29.36, 35.64, 36.71, 43.28, 55.91, 110.64, 124.02, 124.14, 124.81, 126.95, 129.11, 129.26, 131.28, 136.40, 144.47, 148.58, 153.48. HRMS ($MH^+$) for $C_{54}H_{63}O_4$ Calcd: 775.4721 Found: 775.4735.

**3,3'-bis(2-methoxy-5-methylphenyl)-5,5'6,6',7,7',8,8'-octahydro-1,1'-binapthyl-2-2'-diol, 2-51:** 

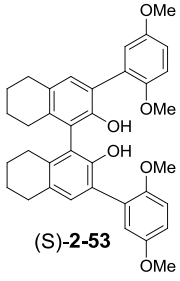
(S)-**2-51**

$[\alpha]_D$ = -6.63 (c = 0.31, THF). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.74-1.76 (m, 8H) 2.24-2.30 (m, 2H), 2.34 (s, 6H), 2.47-2.55 (m, 2H), 2.82 (bs, 4H), 3.80 (s, 6H), 5.79 (s, 2H), 6.89 (d, 2H, J = 8.4 Hz), 7.04 (s, 2H), 7.13 (d, 2H, J = 8.4 Hz), 7.21 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.52, 23.13, 23.20, 27.11, 29.34, 56.11, 111.20, 123.67, 123.71, 127.49, 129.04, 129.43, 130.81, 131.30, 132.79, 136.53, 148.62, 153.76. HRMS ($MH^+$) for $C_{36}H_{39}O_4$ Calcd: 535.2843 Found: 535.2852.

**3,3'-bis(4,5-difluoro-2-methoxyphenyl)-5,5'6,6',7,7',8,8'-octahydro-1,1'-binapthyl-2-2'-diol, 2-52:** 

(S)-**2-52**

$[\alpha]_D$ = -7.77 (c = 1.31, THF). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.76 (bs, 8H), 2.23-2.31 (m, 2H), 2.40-2.47 (m, 2H), 2.81 (bs, 4H), 3.79 (s, 6H), 5.31 (s, 2H), 6.81 (dd, 2H, J = 6.9, 12.5 Hz), 7.02 (s, 2H), 7.22 (dd, 2H, J = 9.2, 11.0 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 22.96, 23.01, 27.12, 29.21, 56.68, 101.20 (d, $^2J_{CF}$ = 20.9 Hz), 119.85 (d, $^2J_{CF}$ = 20.9 Hz), 121.61, 122.18, 123.47, 129.93, 131.75, 137.16, 144.59 (dd, $J_{CF}$ = 240.0, 12.4, Hz), 148.50, 149.68 (dd, $J_{CF}$ = 246.8, 13.5 Hz), 152.23 (d, $^3J_{CF}$ = 6.2 Hz). HRMS ($MH^+$) for $C_{34}H_{31}O_4F_4$ Calcd: 579.2153 Found: 579.2159.

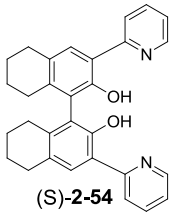
**3,3'-bis(2,5-dimethoxyphenyl)-5,5'6,6',7,7',8,8'-octahydro-1,1'-binapthyl-2-2'-diol, 2-53:** 

(S)-**2-53**

$[\alpha]_D$ = -0.33 (c = 0.96, THF). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.77 (bs, 8H), 2.25-2.33 (m, 2H), 2.48-2.56 (m, 2H), 2.83 (bs, 4H), 3.78 (s, 6H), 3.82 (s, 6H), 5.92 (s, 2H), 6.86-6.95 (m, 4H), 7.00 (d, 2H, J = 2.7 Hz), 7.08 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.41, 23.48, 27.45,

29.65, 56.03, 57.10, 113.05, 114.00, 117.73, 123.87, 124.45, 129.16, 129.84, 131.53, 137.10, 148.91, 150.26, 154.56. HRMS ($MH^+$) for $C_{36}H_{39}O_6$ Calcd: 567.2741 Found: 567.2750.

**3,3'-di(pyridin-2-yl)-5,5'6,6',7,7',8,8'-octahydro-1,1'-binapthyl-2-2'-diol, 2-54:**



(S)-**2-54**

$[\alpha]_D$ = 90.53 (c = 1.36, THF). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.71-1.80 (m, 8H), 2.27-2.33 (m, 2H), 2.51-2.59 (m, 2H), 2.85 (bs, 4H), 5.92 (s, 2H), 7.12-7.16 (m, 2H), 7.58 (s, 2H), 7.78 (t, 2H, J = 8.4 Hz), 7.94 (d, 2H J = 8.4 Hz), 8.37 (d, 2H, J = 4.8 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.11, 23.20, 27.25, 29.55, 116.32, 118.77, 120.65, 125.63, 125.91, 127.14, 137.34, 139.63, 145.42, 154.66, 158.31. HRMS ($MH^+$) for $C_{30}H_{29}N_2O_4$ Calcd: 449.2224 Found: 449.2225.

*c. Improved Ligand Preparation for (S)-**2-49***

**Preparation of (*S*)-3,3'-dibromo-$H_8$BINOL, 2-58.** [41]

The reaction was carried out with a slight modification to the published procedure. $H_8$BINOL (2 g, 6.79 mmol) was dissolved in $CH_2Cl_2$ (75 mL) and cooled to 0 °C. Bromine (0.73 mL, 14.3 mmol) was added in one portion, and after 30 minutes the reaction mixture was quenched with 75 mL sodium sulfite (saturated, aqueous). The organic layer was separated and the aqueous layer was extracted twice with $CH_2Cl_2$ (30 mL). The resultant organic layers were dried and concentrated, and purified by flash chromatography on silica gel (10% EtOAc/hexanes) to yield **2-58** as a white solid in 92% yield (2.83 g). $^1$H NMR (300 MHz, $CDCl_3$): δ 1.54-1.75 (m, 8H), 2.08-2.19 (m, 2H), 2.23-2.38 (m, 2H), 2.72-2.76 (m, 4H), 5.09 (s, 2H), 7.28 (s, 2H).

**Preparation of 2-bromo-4-*tert*-butyl-1-methoxybenzene, 2-56:** [42]

The procedure was performed in accordance with previous reports. 4-*tert*-butylphenol (10 g, 0.07 mol) was dissolved in $CH_2Cl_2$ (200 mL) and cooled to 0 °C. Bromine (3.4 mL, 0.07 mol) was added in one portion. After 1 hour the reaction was quenched with 150 mL sodium sulfite (saturated, aqueous). The organic layer was separated and the aqueous layer was extracted two times with $CH_2Cl_2$ (75 mL). The organic layer were dried and concentrated. The resultant oil was dissolved in acetone (200 mL). $K_2CO_3$ (23 g, 0.17 mol), and MeI (8.7 mL, 0.14 mol) were added, and the mixture was refluxed at 65 °C for 20 h. The reaction mixture was cooled and extracted three times with $CH_2Cl_2$ (200 ml x 1; 100 mL x 2). The organic layer was dried and concentrated to yield **2-56** as an oil in 99% yield over the two steps (16.1 g). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.29 (s, 9H), 3.88 (s, 3H), 6.84 (d, 1H, J = 8.7 Hz), 7.29 (d, 1H, J = 2.4 Hz), 7.54 (d, 1H, J = 2.4 Hz).

**Preparation of 2-(5-*tert*-butyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 2-57:**

2-Bromo-4-*tert*-butyl-1-methoxybenzene (8 g, 33.0 mmol) was dissolved in hexanes and cooled to 0 °C. $^n$BuLi (1.45M, 22.7 mL, 33.0 mmol) was added and the reaction mixture was allowed to warm to room temperature over 3 h, during which a white precipitate formed. The reaction mixture was cooled to -78 °C and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (13.4 mL, 65.8 mmol) in 30 mL of THF was added via cannula transfer. The reaction was allowed to warm to room temperature and stirred for 16 h. The generated salts were removed by filtration through a Buchner funnel, rinsing with $CH_2Cl_2$. The collected organic layer was concentrated and purified by flash chromatography over a short silica gel column (10% EtOAc/hexanes), yielding

**2-57** as an off-white solid in 80% yield (7.7 g). (Extended time on the column results in partial hydrolysis to the boronic acid.) $^{1}$H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 1.38 (s, 12H), 3.83 (s, 3H), 6.82 (d, 1H, J = 8.7 Hz), 7.43 (dd, 1H, J = 2.7, 8.7 Hz), 7.69-7.71 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.77, 31.50, 33.95, 55.92, 88.25, 110.13, 129.20, 133.14, 142.26, 162.03.

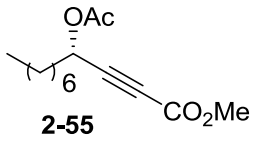
**Preparation of (S)-3,3'-bis(5-*tert*-butyl-2-methoxyphenyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-diol, (*S*)-2-49:** Under nitrogen atmosphere (*S*)-3,3'-dibromo-$H_8$BINOL (**2-58**) (2 g, 4.4 mmol), 2-(5-*tert*-butyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2-57**) (3.85 g, 13.3 mmol, 3 eq.), and $Pd(PPh_3)_4$ (512 mg, 0.4 mmol, 10 mol %) were placed in a 2-neck flask fitted with a reflux condenser fitted with a vacuum adaptor. Degassed dimethoxyethane (25 mL) and 2M $Na_2CO_3$ (20 mL) were transferred into the flask via cannula transfer. To ensure the removal of oxygen, the reaction vessel was freeze pumped (-78 °C) and refilled with nitrogen three times. The reaction mixture was then heated at 95 °C for 24 h. After cooled to room temperature, the mixture was extracted with $CH_2Cl_2$ (3 x 40 mL). The combined organic layers were washed with 2M HCl (3 x 40 mL), dried, and concentrated. Silica gel chromatography (8% EtOAc/hexanes) afforded (*S*)-**2-49** as a white solid in 94% yield (2.57 g). Prior to use in catalysis (S)-**2-49** was dissolved in $CH_2Cl_2$ and stirred with 2 equivalents of trifluoroacetic acid for 1 h to remove any metal impurities. After flash chromatography over silica gel the ligand was dried by dissolving in THF and pumping under vacuum prior to use in catalysis. (See above for characterization data.)

*d. Preparation of Racemic γ-Hydroxy-α,β-acetylenic Esters for HPLC Analysis*[43]

Methyl propiolate (44.5 μL, 0.5 mmol) was dissolved in $CH_2Cl_2$. $ZnEt_2$ (51.5μL, 0.5 mmol) and NMI (2μL, 0.025 mmol) were added and the mixture was stirred for 4 h. An aldehyde (0.25 mmol) was added, and the reaction mixture was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), extracted with $CH_2Cl_2$ (3 x 10 mL), dried, and concentrated. The racemic alcohols were purified by flash chromatography over silica gel (10-20% EtOAc/hexanes).

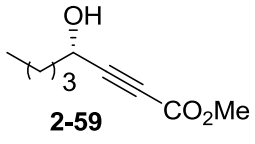
*e. Preparation and Characterization of Optically Active γ-hydroxy-α,β-acetylenic esters*

Under nitrogen atmosphere, (*S*)-**2-49** (61.9 mg, 0.1 mmol, 20 mol %) was dissolved in THF (5 mL) in a 10 mL flame dried flask. $ZnEt_2$ (103 μL, 1 mmol, 2 equiv) and methyl propiolate (89 μL, 1 mmol, 2 equiv) were added sequentially and the mixture was stirred for 16 hours at room temperature, yielding a light yellow solution. $Ti(O^iPr)_4$ (74 μL, 0.25 mmol, 50 mol %) was then added and the reaction mixture was stirred for 1 h. To the resulting dark orange solution, an aldehyde was added and the reaction was monitored by TLC or crude NMR. Upon consumption of the aldehyde, the reaction was quenched with saturated aqueous ammonium choride (5 mL). The reaction mixture was extracted three times with $CH_2Cl_2$ and the organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash chromatography on silica gel. First eluting with 2:1 $CH_2Cl_2$:hexanes cleanly separates the ligand from the product. After removal of the ligand, the column was eluted with hexanes/ethylacetate (10-20% ethyl acetate) to give the product as an oil in 55-84% yield and 89-97% ee.



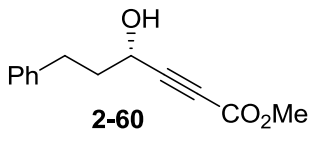
**2-55**

**(*S*)-Methyl 4-acetoxyundec-2-ynoate, 2-55:** Reaction time: 9h. 84% yield. 95% ee determined by HPLC analysis: AD-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 56.07 min $t_{minor}$ = 51.73 min. $[\alpha]_D$ = -75.71 (c = 1.05, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.86 (t, 3H, J = 6.9 Hz), 1.28 (bs, 8H), 1.41-1.46 (m, 2H), 1.77-1.85 (m, 2H), 2.10 (s, 3H), 3.78 (s, 3H), 5.43 (t, 1H, J = 6.8 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.99, 20.72, 22.52, 24.76, 28.90, 28.94, 31.62, 33.81, 52.74, 63.04, 76.37, 84.57, 153.38, 169.61. HRMS ($MH^+$) for $C_{14}H_{23}O_4$ Calcd: 255.1591 Found: 255.1591.



**2-59**

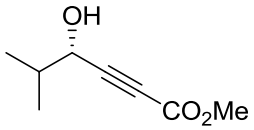
**(*S*)-Methyl 4-hydroxyoct-2-ynoate, 2-59:** Reaction time: 10h. 84% yield. 94% ee determined by HPLC analysis: OD column, 98:2 hexanes:$^{i}$PrOH, flow rate = 0.5 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 16.44 min $t_{minor}$ = 14.97 min. $[\alpha]_D$ = -4.30 (c = 1.01, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (t, 3H, J = 7.2 Hz), 1.32-1.39 (m, 4H), 1.73-1.79 (m, 2H), 1.94-1.96 (m, 1H), 3.79 (s, 3H), 4.5 (t, 1H, J = 6.2 Hz). This data corresponds to the known compound.[44]



**2-60**

**(*S*)-Methyl 4-hydroxy-6-phenylhex-2-ynoate, 2-60:** Reaction time: 10h. 83% yield. 93% ee determined by HPLC analysis: OD column, 95:5 hexanes:$^{i}$PrOH, flow rate = 0.5 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 27.74 min $t_{minor}$ = 30.56 min. $[\alpha]_D$ = 53.98 (c = 1.12, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.93

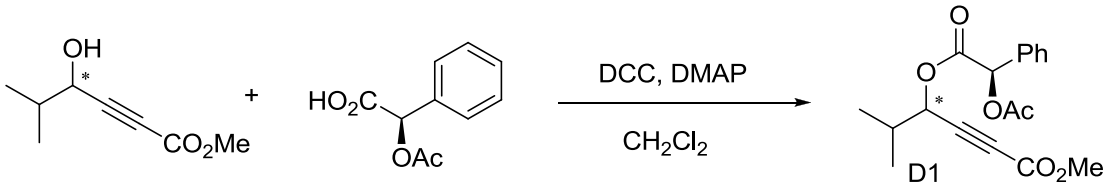
(d, 1H, J = 5.7 Hz), 2.09 (q, 2H, J = 6.3 Hz), 2.82 (t, 2H, J = 7.7 Hz), 3.80 (s, 3H), 4.48 (q, 1H, J = 6.3 Hz), 7.20-7.33 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 30.99, 38.09, 52.82, 61.03, 76.30, 88.18, 126.08, 128.42, 140.52, 153.90. HRMS ($MH^+$) for $C_{13}H_{15}O_3$ Calcd: 219.1016 Found: 219.1022.



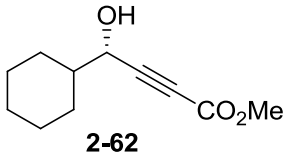

**2-61**

**(*S*)-Methyl 4-hydroxy-5-methylhex-2-ynoate, 2-61:** Reaction time: 9h. 67% yield. 89% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D$ = 2.44 (c = 0.42, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.03 (dd, 6H, J = 4.4, 6.8 Hz), 1.96 (octet, 2H), 3.79 (s, 3H), 4.29 (t, 1H, J = 5.9 Hz). This data corresponds to the known compound.[45]

*Preparation of the mandelic acetate derivative of **2-61** for the NMR analysis:*

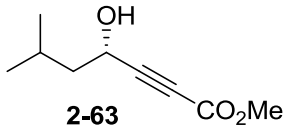



The γ-hydroxy-α,β-acetylenic ester (20 mg), DCC (2 equiv), DMAP (2 equiv), and (R)-O-acetylmandelic acid (2 equiv) were dissolved in $CH_2Cl_2$ (5 mL). The reaction was monitored by TLC. After consumption of the starting material (30 min to 1 hour), the crude mixture was passed through a short silica gel column eluted with 30% EtOAc/hexanes. The ee determination was based on the proton signal at δ~5.9 ppm in the $^1$H NMR spectrum.



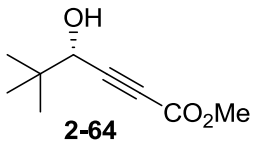
**2-62**

**(*S*)-Methyl 4-cyclohexyl-4-hydroxybut-2-ynoate, 2-63:** Reaction time: 9h. 84% yield. 95% ee determined by HPLC analysis: AD-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 73.66 min $t_{minor}$ = 78.68 min. $[\alpha]_D$ = 5.04 (c = 1.01, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.06-1.33 (m, 6H), 1.57-1.70 (m, 2H), 1.76-1.88 (m, 4H), 3.78 (s, 3H), 4.28 (t, 1H, J = 6.2 Hz). This data corresponds to the known compound.[8]



**2-63**

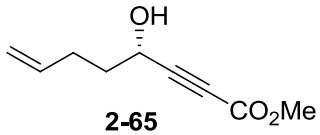
**(*S*)-Methyl 4-hydroxy-6-methylhept-2-ynoate, 2-64:** Reaction time: 16h. 71% yield. 90% ee determined by HPLC analysis: OD column, 90:10 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 6.83 min $t_{minor}$ = 6.30 min. $[\alpha]_D$ = -13.55 (c = 0.82, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (d, 3H, J = 2.4 Hz), 0.96 (d, 3H, J = 2.4 Hz), 1.57-1.73 (m, 2H), 1.76-1.91 (m, 2H), 3.78 (s, 3H), 4.54 (q, 1H, J = 6 Hz). This data corresponds to the known compound.[8]



**2-64**

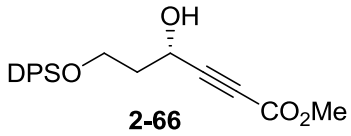
**(*S*)-Methyl 4-hydroxy-5,5-dimethylhex-2-ynoate, 2-62:** Reaction time: 24h. 55% yield. 97% ee determined by HPLC analysis: AD-H column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 17.80 min $t_{minor}$ = 19.65 min. $[\alpha]_D$ = -5.48 (c = 0.54, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.03 (s, 9H), 1.93-1.95 (m, 1 H), 3.78 (s, 3H), 4.14 (d, 1H, J = 6.3 Hz). $^{13}$C NMR $\delta$ (75 MHz,

$CDCl_3$) 25.19, 36.03, 52.78, 70.94, 76.58, 87.29, 153.81. HRMS ($MH^+$) for $C_9H_{15}O_3$ Calcd: 171.1016 Found: 171.1016.



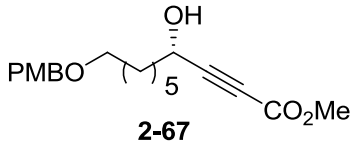
**2-65**

**(*S*)-Methyl 4-hydroxyoct-7-en-2-ynoate, 2-65:** Reaction time: 10h. 63% yield. 95% ee determined by HPLC analysis: OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 14.88 min $t_{minor}$ = 12.84 min. $[\alpha]_D$ = 9.99 (c = 1.06, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.84-1.91 (m, 2H), 1.97 (bs, 1H), 2.26 (q, 2H, J = 7.8 Hz), 3.79 (s, 3H), 4.53 (q, 1H, J = 5.7 Hz), 5.01-5.12 (m, 2H), 5.75-5.88 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 29.04, 35.71, 52.84, 61.38, 76.32, 87.97, 115.81, 136.92, 153.82. HRMS ($MH^+$) for $C_9H_{13}O_3$ Calcd: 169.0859 Found: 169.0863.



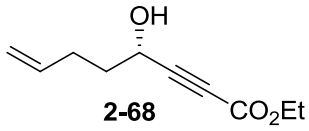
**2-66**

**(*S*)-Methyl 6-(*tert*-butyldiphenylsilyloxy)-4-hydroxyhex-2-ynoate, 2-66:** Reaction time: 24h. 60% yield. 90% ee determined by HPLC analysis: AD-H column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 14.24 min $t_{minor}$ = 12.57 min. $[\alpha]_D$ = -1.67 (c = 1.15, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.05 (s, 9H), 1.87-1.97 (m, 1H), 2.05-2.17 (m, 1H), 3.52 (d, 1H, J = 6 Hz), 3.80 (s, 3H), 3.85 (q, 1H, J = 5.4 Hz), 4.02-4.09 (m, 1H), 4.80-4.86 (m, 1H), 7.38-7.48 (m, 6H), 7.65-7.70 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.99, 26.72, 37.59, 52.77, 61.40, 61.50, 76.39, 87.64, 127.83, 129.92, 132.53, 135.52. HRMS ($MNa^+$) for $C_{23}H_{28}O_4NaSi$ Calcd: 419.1649 Found: 419.1649.




**2-67**

**(*S*)-Methyl 4-hydroxy-10-(4-methoxybenzyloxy)dec-2-ynoate, 2-67:** Reaction time: 24h. 56% yield. 92% ee determined by HPLC analysis: OD column, 90:10 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 19.14 min $t_{minor}$ = 12.99 min. $[\alpha]_D$ = -0.91 (c = 0.84, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.33-1.49 (m, 6H), 1.57-1.62 (m, 2H), 1.72-1.77 (m, 2H), 1.92 (d, 1H, J = 5.7 Hz), 3.43 (t, 2H, J = 6.5 Hz), 3.78 (s, 3H), 3.80 (s, 3H), 4.43 (s, 2H), 4.49 (q, 1H, J = 6.3 Hz), 6.88 (d, 2H, J = 7.8 Hz), 7.26 (d, 2H, J = 8.4 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 24.79, 25.95, 28.88, 29.52, 36.69, 52.77, 55.21, 61.91, 69.93, 72.45, 76.09, 88.30, 113.68, 129.24, 130.57, 153.79, 159.02. HRMS ($MNa^+$) for $C_{19}H_{26}O_5Na$ Calcd: 357.1672 Found: 357.1672.




**2-68**

**(*S*)-Ethyl 4-hydroxyoct-7-en-2-ynoate, 2-68:** Reaction time: 10h. 60% yield. 95% ee determined by HPLC analysis: OD column, 98:20 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 18.47 min $t_{minor}$ = 16.27 min. $[\alpha]_D$ = 13.57 (c = 1.04, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.32 (t, 3H, J = 7.1 Hz), 1.84-1.95 (m, 3H), 2.26 (q, 2H, J= 7.5 Hz), 4.25 (q, 2H, J = 7.2 Hz), 4.52 (q, 1H, J = 6.3 Hz), 5.03 (d, 1H, J = 10.2 Hz), 5.09 (d, 1H, J= 17.1 Hz), 5.75-5.86 (m, 1H). This data corresponds to the known compound.[46] By comparison to the reported optical rotation, the compound's absolute configuration is assigned to be (S).[11] All other compounds are assigned by analogy.

*f. Optimized Procedure for Alkynoate Additions to Aldehydes*

Under nitrogen atmosphere in a 10 mL flame dried flask, (*S*)-**2-49** (61.9 mg, 0.1 mmol, 20 mol %) was dissolved in the $Et_2O$/THF (4/1, 5 mL) mixed solvent system for aromatic and aliphatic aldehydes and the $Et_2O$/1,4-dioxane (4/1, 5 mL) mixed solvent system for α,β–unsaturated aldehydes. For aliphatic and aromatic aldehydes $ZnEt_2$ (103 μL, 1 mmol, 2 equiv) and methyl propiolate (89 μL, 1 mmol, 2 equiv) were added sequentially and the mixture was stirred for 4 hours at room temperature, yielding an amber solution. For α,β-unsaturated aldehydes 3 equiv $ZnEt_2$ (155 μL, 1.5 mmol) and methyl propiolate (134 μL, 1.5 mmol) were used. $Ti(O^iPr)_4$ (74 μL, 0.25 mmol, 50 mol %) was then added, followed by the addition of an aldehyde and the reaction was monitored by TLC or crude NMR. Aliphatic and α,β–unsaturated aldehydes were consumed within 2-4 h, and aromatic aldehydes were consumed within 16 h. Upon consumption of the aldehyde, the reaction was quenched with saturated aqueous ammonium choride (5 mL). The reaction mixture was extracted three times with $CH_2Cl_2$ and the organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash chromatography on silica gel. First eluting with 2:1 $CH_2Cl_2$:hexanes cleanly separates the ligand from the product. After removal of the ligand, the column was eluted with hexanes/ethylacetate (10-20% ethyl acetate) to give the product.

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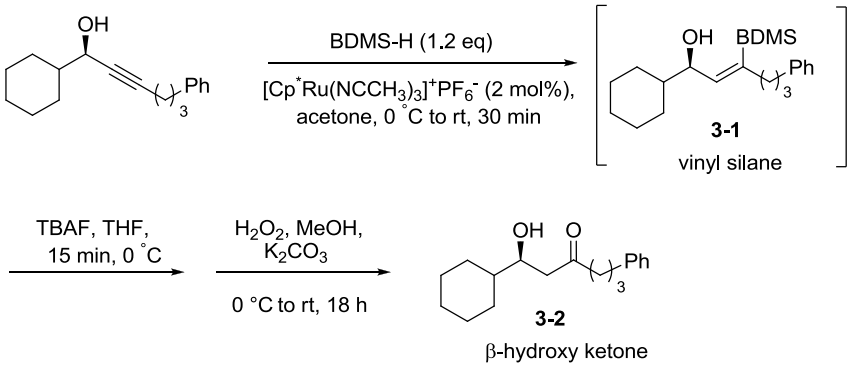
# Chapter 3. Synthesis of Optically Active Propargylic Alcohol-Based Enynes for the Intramolecular Pauson-Khand Reaction

## 3.1. Introduction

As discussed in Chapter 1 optically active propargylic alcohols are of great utility in synthetic organic chemistry. These compounds can be subjected to a variety of further transformations and thus have been used frequently in the synthesis of complex molecules.[1] To further extend the application of this class of molecules, our laboratory and others have studied transformations of enantioenriched propargylic alcohols for the synthesis of useful classes of chiral organic compounds. For example, Trost and coworkers have demonstrated the regioselective ruthenium-catalyzed *trans*-hydrosilylation of propargylic alcohols with benzyldimethylsilane (BDMS-H) to access useful vinyl silanes.[2] The vinyl silane intermediates were shown to undergo oxidative cleavage to afford β-hydroxy ketones (Scheme 3.1), providing an alternative to asymmetric aldol reactions.

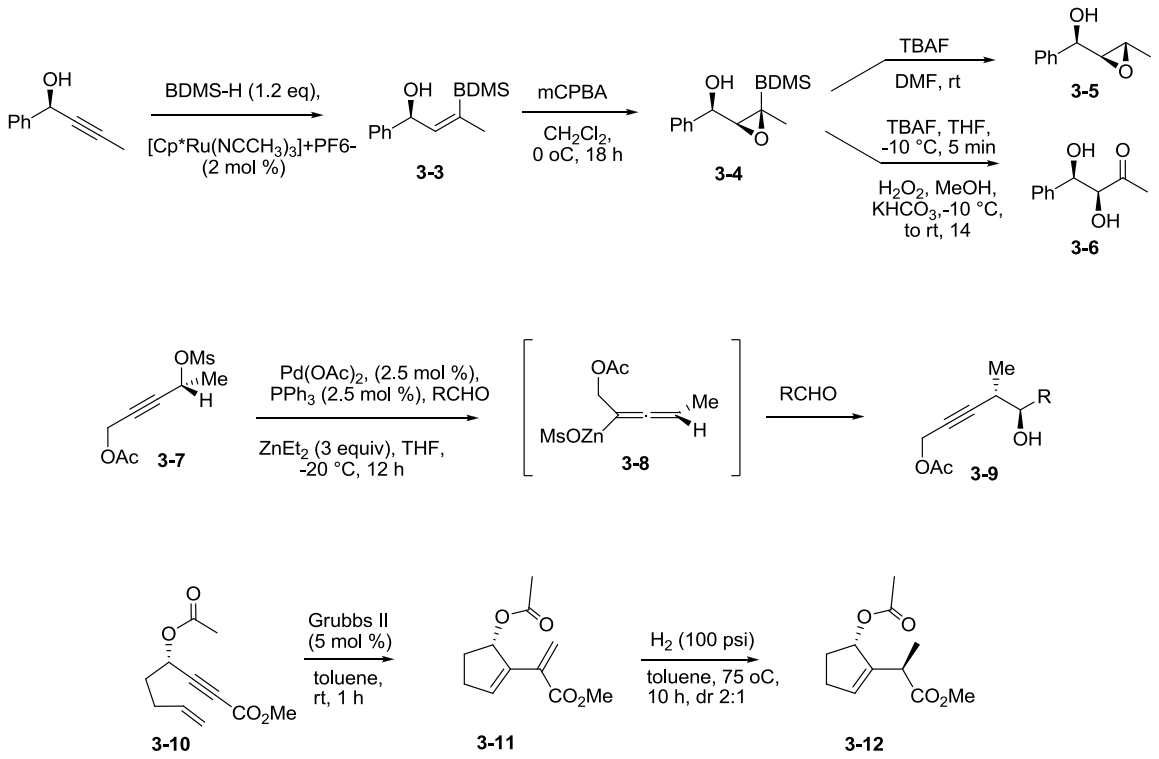
**Scheme 3.1.** Transformation of Optically Active Propargylic Alcohols to β-Hydroxy Ketone.



Diastereoselective transformations of optically active propargylic alcohols are of particular interest. Not only is the functionality present in the propargylic alcohol utilized for the formation of structures of increased molecular complexity, but the chiral information is also transferred, controlling the creation of new stereocenters. Trost's vinyl silane methodology demonstrates this type of reaction. Epoxidation of optically active vinyl silane **3-3** with mCPBA affords the corresponding epoxide **3-4** in high diastereoselectivity (>20:1), with the configuration of the new epoxide being controlled by the chiral alcohol. Protodesilylation of this intermediate yields syn-epoxy alcohol **3-5** and oxidation yields dihydroxyketone **3-6**. Marshall and coworkers have also elegantly demonstrated the utility of propargylic alcohols in the diastereoselective synthesis of homopropargylic alcohol adducts.[3] Treatment of enantioenriched propargylic mesylate **3-7** with $Pd(OAc)_2$ and $PPh_3$ followed by transmetallation with $ZnEt_2$ or other metals yields chiral allenylmetal reagents. Addition to aldehydes provides the corresponding *anti* homopropargylic alcohols **3-9** with good diastereoselectivity (> 98:2).

Our group has explored the diastereoselective transformations of γ-hydroxy-α,β-acetylenic esters utilizing a tandem Grubbs II-catalyzed ring closing metathesis (RCM)/hydrogenation reaction to provide access to optically active cycloalkenes. Acetate protected γ-hydroxy-α,β-acetylenic ester **3-10** first undergoes a Grubbs II-catalyzed RCM to afford cyclic diene **3-11**, followed by a highly chemoselective hydrogenation reaction to afford **3-12** in moderate diastereoselectivity (2:1).[4] It is our goal to further expand the usefulness of optically active propargylic alcohols in diastereoselective transformations, targeting the development of highly diastereoselective reactions.

**Scheme 3.2.** Diastereoselective Transformations of Enantioenriched Propargylic Alcohols.




Toward this goal the most efficient means of accessing the optically active propargylic alcohol precursors must first be established. The versatility of propargylic alcohol intermediates has stimulated extensive investigations into the synthesis of these molecules through the asymmetric addition of alkynes to carbonyl compounds. Consequently, a large number of catalytic systems have been reported for this transformation (see Chapter 1). Our group has also developed a variety of zinc-based catalytic systems for the addition of alkynes to aromatic, aliphatic, and α,β-unsaturated aldehydes.

This chapter will discuss and compare our laboratory's previously reported BINOL-based methods for asymmetric alkyne additions to aldehydes, as well as

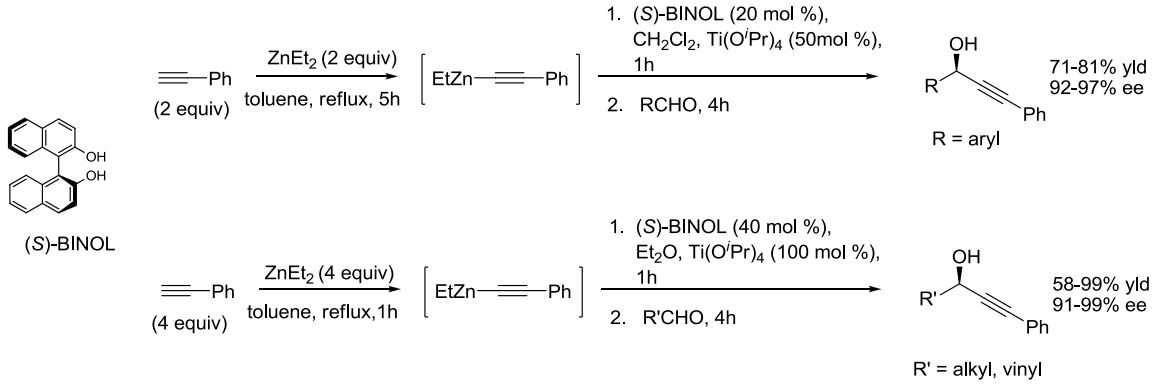
reporting extensions of the newly developed catalytic system for alkyl propiolate addition discussed in Chapter 2 for more general applications in asymmetric alkyne addition. A direct comparison of the most effective and useful systems for the addition of various alkyne classes to aliphatic aldehydes will be discussed, and the discovery of a new catalytic system to address a remaining challenge in the alkyne substrate scope will be reported. From these studies a toolbox of catalytic systems for the asymmetric addition of diverse classes of alkynes to aldehydes will be established. With the most effective methods to access a variety of optically active propargylic alcohols determined, the utility of these products in diastereoselective transformations will be extended to the intramolecular Pauson-Khand Reaction.

*a. BINOL-Based Catalytic Systems*

In 2002 our group's initial work in this field demonstrated that BINOL in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ could catalyze the reaction of phenylacetylene with aromatic aldehydes in high enantiomeric excess. This reaction was performed in three steps. The alkynylzinc nucleophile was first formed by reflux of the alkyne (2 equiv) with $ZnEt_2$ (2 equiv) in toluene to generate an alkynylethylzinc species. Elevated temperatures were necessary to generate the propargylic alcohol as the major product, otherwise ethyl addition to the aldehyde predominated due to the excess $ZnEt_2$ in the reaction mixture. The active catalyst was then formed through the addition of BINOL (20 mol %) and $Ti(O^iPr)_4$ (50 mol %) and a second solvent to enhance the enantioselectivity. $CH_2Cl_2$ was found to be the optimal solvent in the second step to promote high enantioselectivities. Finally, the aldehyde was added to the reaction mixture containing the preformed alkynylzinc nucleophile and chiral catalyst. As shown

in Scheme 3.3, these conditions were applied to a range of aromatic aldehydes to form the corresponding propargylic alcohols in good yields (71-81%) and excellent enantioselectivities (92-97% ee).[5]

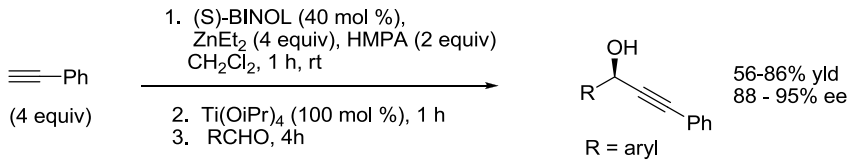
**Scheme 3.3.** Enantioselective Addition of Phenylacetylene to Aldehydes Catalyzed by BINOL/$ZnEt_2$/$Ti(O^iPr)_4$.




When the conditions found to be effective for aromatic aldehydes were applied for the addition of phenylacetylene to nonyl aldehyde, an aliphatic aldehyde, only 75% ee could be obtained, demonstrating that aliphatic aldehydes are more challenging substrates for the BINOL system. Good enantioselectivities could be obtained, however, upon modification of the reaction conditions. Increasing the amount of BINOL (40 mol %), $Ti(O^iPr)_4$ (100 mol %), $ZnEt_2$ (4 equiv), and phenylacetylene (4 equiv), as well as changing the solvent in the second step from $CH_2Cl_2$ to $Et_2O$ provided the product in 91% ee.[6] When these conditions were applied to a variety of aliphatic aldehydes good yields (58-99%) and enantioselectivities (91-97%) were obtained. Furthermore, excellent results were obtained employing these conditions for $\alpha,\beta$-unsaturated aldehydes, forming the products in yields of 89-96% and enantioselectivities of 94-99% for four substrates.

Due to the limitations associated with forming the alkynylzinc under elevated temperatures, methods to form the alkynylzinc under milder conditions were explored. In 2006, inspired by a report that terminal alkynes react rapidly with $ZnEt_2$ in polar aprotic solvents such as DMF, DMSO, and HMPA,[7] our laboratory investigated the use of these solvents as additives to facilitate the formation of the alkynylzinc nucleophile at room temperature. Using between 1 to 4 equiv of these additives allowed the formation of the propargylic alcohol as the major product, with HMPA providing the best results. Mixing HMPA (2 equiv) with $ZnEt_2$ (4 equiv), phenylacetylene (4 equiv), and BINOL (40 mol %) for 1 h formed the alkynylzinc at room temperature. Addition of $Ti(O^iPr)_4$ (100 mol %) and stirring for 1 h, followed by addition of the aldehyde resulted in good yields (56-86%) and high enantioselectivities (88-95% ee) for a range of aromatic aldehydes as shown in Scheme 3.4. The discovery that a Lewis basic additive could facilitate the formation of the alkynylzinc at room temperature was a significant improvement to the BINOL catalytic system, improving ease of operation and opening the catalytic system to the use of more sensitive alkyne substrates (see Chapter 2). However, higher loadings of BINOL were required to produce high enantioselectivities for aromatic aldehydes comparable to those obtained with the original system. This suggests that the presence of HMPA interferes to some degree with the enantiocontrol of the chiral catalyst.

**Scheme 3.4.** Enantioselective Addition of Phenylacetylene to Aromatic Aldehydes Catalyzed by BINOL/$ZnEt_2$/$Ti(O^iPr)_4$ with HMPA Additive.

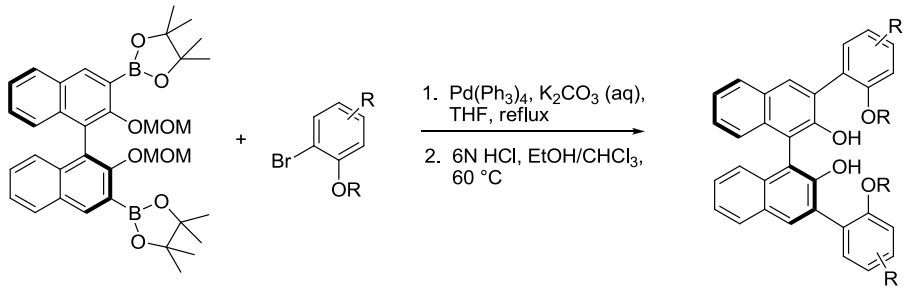


In addition to the BINOL catalytic systems our group has also explored the use of functionalized BINOL ligands for asymmetric alkynylation reactions. These ligands were designed to improve the BINOL system through the addition of additional functionality at the 3,3' positions of BINOL and $H_8$BINOL. In this way the catalytic pocket could be extended and modified, with the goal of forming the alkynylzinc at room temperature without additives and achieving high enantioselectivity without the use of $Ti(O^iPr)_4$. The functionalized ligands developed by our laboratory can be divided into four classes: 3,3'-bisanisyl-substituted BINOLs, 3,3'-bis(diphenylmethoxy)methyl-substituted BINOLs, BINOL-salens, and 3,3'-$H_8$BINOL-Amines.[8]

*b. 3,3'-Bisanisyl-Substituted-BINOL Catalytic Systems*

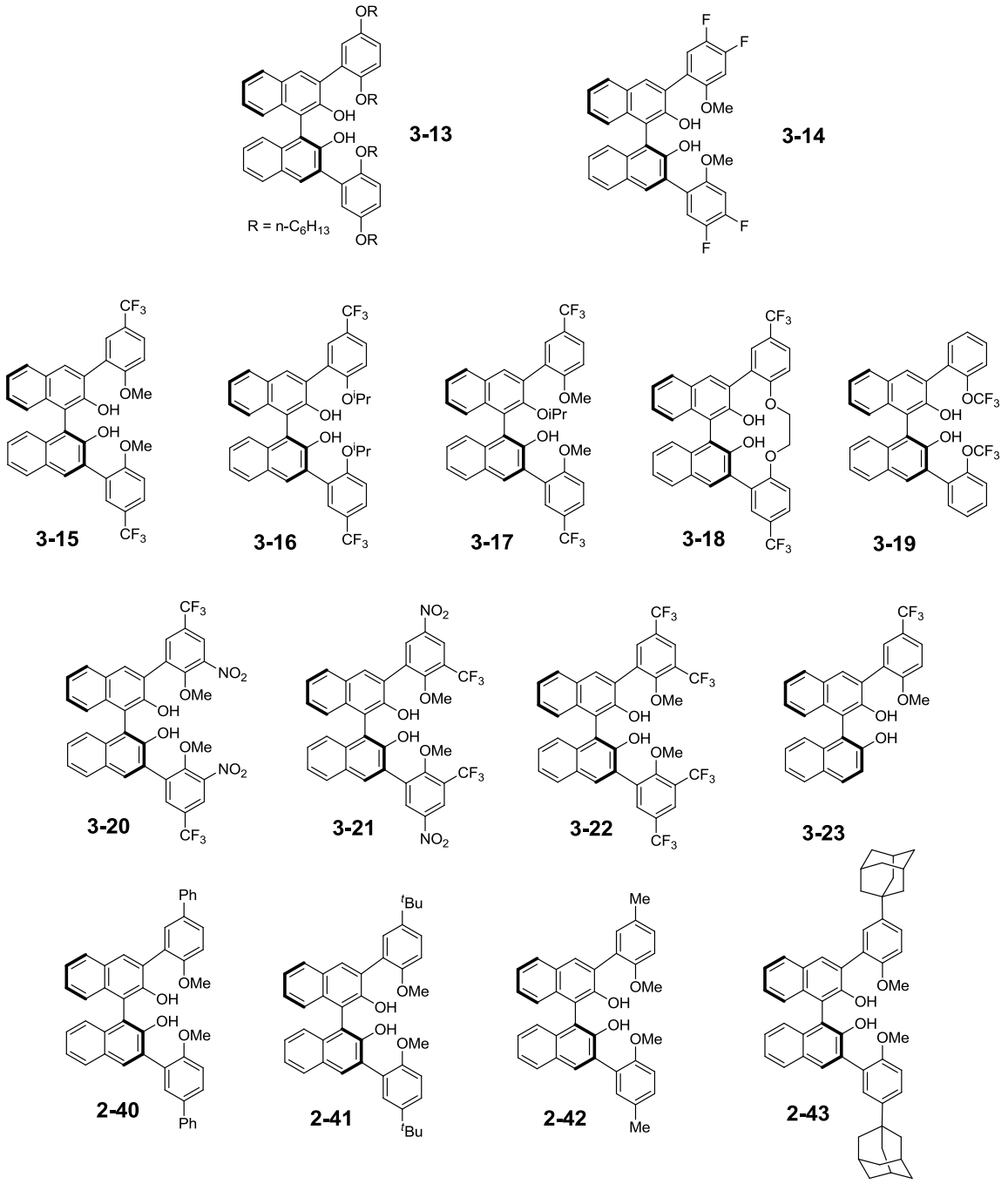
In the late 1990s our laboratory successfully utilized 3,3'-bisanisyl-substituted-BINOLs for asymmetric catalysis employing $ZnR_2$ reagents. For example, ligand **3-13** was found to catalyze $ZnEt_2$ addition to aromatic, aliphatic, and α,β-unsaturated aldehydes in high enantioselectivities.[9] Likewise, ligand **3-14** bearing electron withdrawing groups on the anisyl rings was found to be highly effective for diphenylzinc additions to aromatic aldehydes.[10] In 2002, in an attempt to extend the success of this class of ligands to alkynylzinc additions to aldehydes, derivatives **3-15** to **3-23** and **2-40** (Figure 3.3) were synthesized via a Suzuki coupling according to the general method shown in Scheme 3.5.[9,10] These ligands were then tested for the addition of phenylacetylene to benzaldehyde.[11]

**Scheme 3.5.** Preparation of 3,3'-Bisanisyl-Substituted BINOL Ligands.




Use of ligand **3-14** to **3-23** containing electron withdrawing substituents and ligand **3-13** containing electron donating substituents proved to be unsuccessful, producing low enantioselectivities (0-67% ee). However, use of ligand **2-40** (20 mol %), containing phenyl groups in the *para* position of the anisyl ring, produced a promising result of 80% ee. Since the electronic withdrawing groups of ligand **3-14** to **3-23** did not provide good enantioselectivities, it was suspected that a steric effect and not an electronic effect was responsible for the improved stereocontrol. This hypothesis was supported through the synthesis of ligand **2-41** containing the sterically bulky $^{t}$Bu groups. Use of ligand **2-41** (10 mol %) to catalyze the reaction of phenylacetylene with benzaldehyde afforded the product in higher enantioselectivity, 85% ee, even though a smaller amount of the chiral ligand was used. This steric effect was rather surprising because the site of the steric bulk was located at a remote site on the chiral ligand. Further evidence of this effect was obtained through the synthesis of ligand **2-42**, containing smaller methyl groups at the *para* position of the anisyl ring. Testing this ligand for the addition of phenylacetylene to a few aromatic aldehydes consistently resulted in lower enantioselectivities in comparison with the bulkier ligand **2-41**.

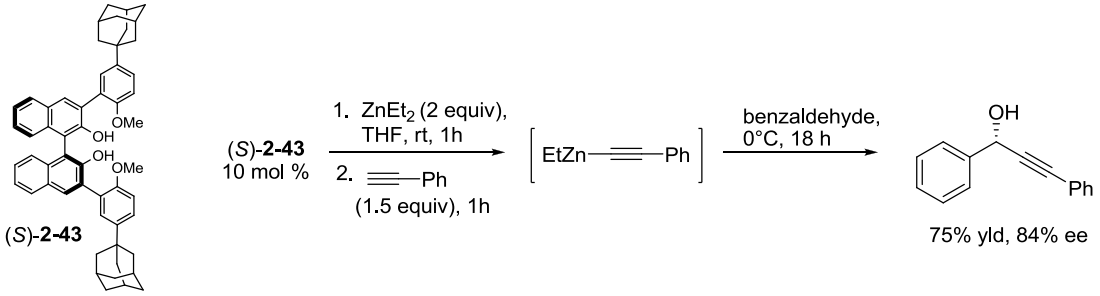
**Figure 3.1.** 3,3'-Bisanisyl-substituted-BINOLs for Alkynylzinc Additions to Aldehydes.




In addition to discovering this curious steric effect it was also found that the anisole methoxy groups of ligand **2-41** could facilitate the formation the alkynylzinc

nucleophile at room temperature by reaction of the alkyne, $ZnEt_2$, and ligand in THF for 12 h. This was the first time our group had demonstrated the ability to form the alkynylzinc at room temperature. This characteristic would become a feature of the functionalized BINOL ligands containing heteroatoms in the substituents at the 3,3' positions.

**Scheme 3.6.** 3,3'-Bisanisyl-Substituted-BINOL Catalyzed Asymmetric Phenylacetylene Additions to Aromatic Aldehydes.



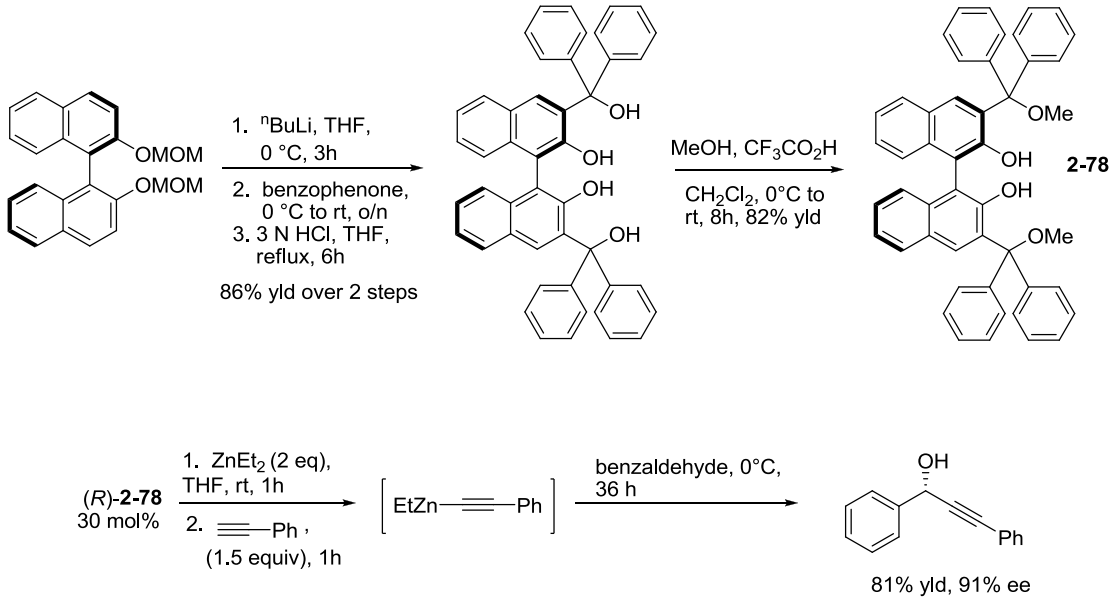

Since increased steric bulk improved enantioselectivity, ligand **2-43** bearing even bulkier adamantyl groups was prepared to improve the catalyst structure further.[12] When this ligand was tested for the asymmetric alkyne addition it was found that high enantioselectivities could be obtained without $Ti(O^iPr)_4$. It was also found that the alkynylzinc could be formed at room temperature in the presence of the ligand. Using **2-43** (10 mol %), $ZnEt_2$ (2 equiv), and phenylacetylene (1.5 equiv) for the addition to benzaldehyde afforded the corresponding propargylic alcohol in 75% yield and 84% ee when the aldehyde was added at 0°C, as shown in Scheme 3.6. These conditions were applied to a range of aromatic aldehydes, providing modest to good yields (45-75%) and good enantioselectivities (80-94% ee). Although the results were not quite as good as the

original BINOL system, the discovery of a highly enantioselective BINOL catalyst that did not require $Ti(O^iPr)_4$ was a considerable conceptual advance.

*c. 3,3'-Bis(diphenylmethoxy)methyl-Substituted-BINOL Catalytic Systems*

As increased steric bulkiness in the bifunctional BINOL-based ligands was found to be beneficial, attempts to improve the catalytic system further centered on moving the steric bulk closer to the catalytic pocket. In 2007 with this goal in mind 3,3'-bis(diphenylmethoxy)methyl-substituted BINOL **2-78**, synthesized according to Scheme 3.3,[13] was tested for the asymmetric addition of phenylacetylene to benzaldehyde.[14]

**Scheme 3.7.** Synthesis of 3,3'-Bis(diphenylmethoxy)methyl-Substituted BINOL Ligand and Use in Asymmetric Alkyne Addition.



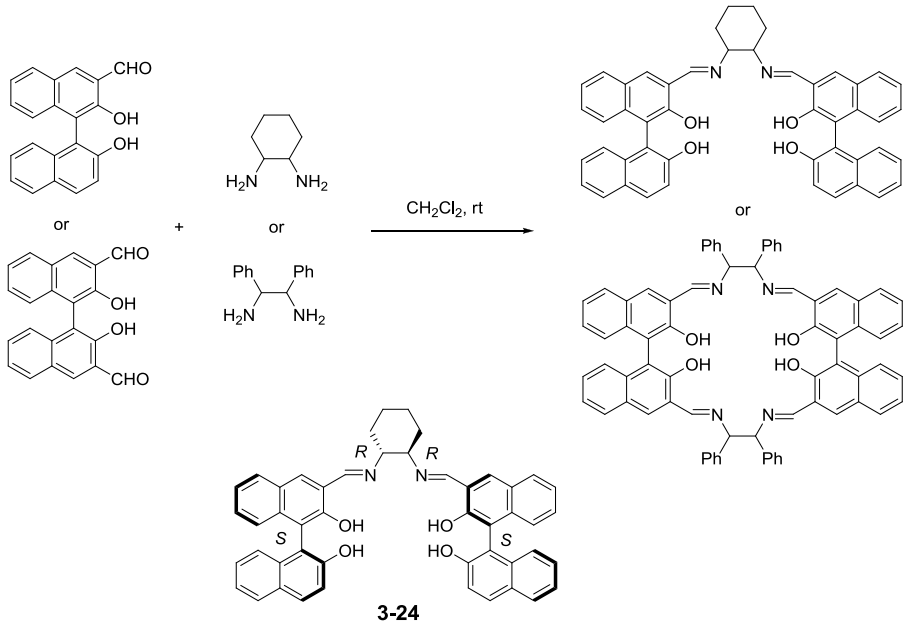

Similarly to the 3,3'-bisanisyl-substituted-BINOLs, the alkynylzinc nucleophile could be formed at room temperature by premixing $ZnEt_2$ and the alkyne in the presence of the ligand. Using 30 mol % of the ligand, 2 equiv $ZnEt_2$, and 1.5 equiv phenylacetylene in THF at 0 °C, as shown in Scheme 3.7, was able to afford the

propargylic alcohol in 81% yield and 91% ee. This class of ligands was also effective without $Ti(O^iPr)_4$. Application of this catalytic system to a range of aromatic aldehydes provided consistently better results in comparison with ligand **2-43**, affording the chiral propargylic alcohols in yields of 67-81% and enantioselectivities of 86-94%.[15] In particular, ligand **2-78** substantially reduced ethyl addition side products as compared with bisanisyl ligand **2-43.** The fact that the bis(diphenylmethoxy)methyl-substituted BINOL and the 3,3'-bisanisyl-substituted BINOL catalytic systems give the opposite enantiomers of the product when the chirality of the BINOL backbone is the same demonstrates that the mechanism of enantiocontrol for these two classes of ligands is very different.

*d. BINOL-Salen Catalytic Systems*

During this time the use of BINOL-Salen ligands were also being investigated by our group for the asymmetric addition of alkynes to aldehydes. This class of ligands was originally reported by Katsuki for asymmetric epoxidation reactions[16] and later further developed by Kozlowski for a range of asymmetric catalytic applications.[17] These compounds can be synthesized as shown in Scheme 3.8 through the condensation of a BINOL aldehyde with chiral diamines. Monoaldehydes afford acyclic structures, with dialdehydes affording cyclic compounds. As these ligands were effective in a range of asymmetric transformations, in 2004 our group tested several BINOL-Salen ligands for asymmetric alkyne additions, identifying monocyclic **3-24** as a promising catalyst.[18]

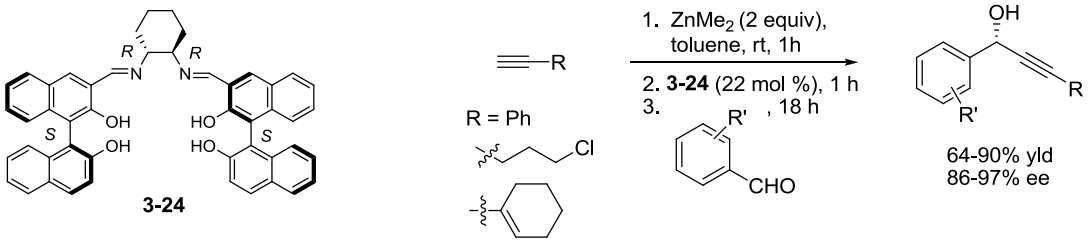
**Scheme 3.8.** Synthesis of BINOL-Salen Ligands.




**3-24**

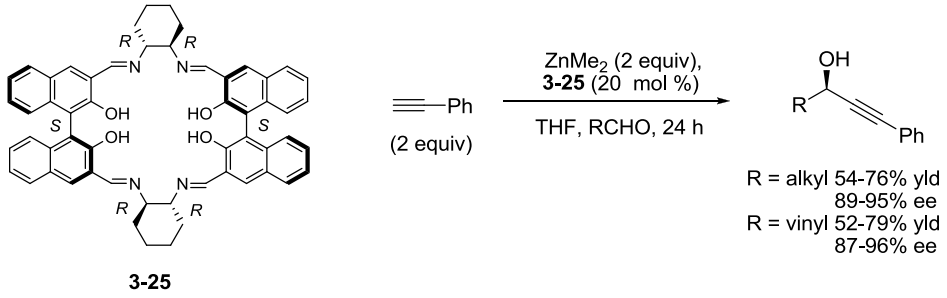
Use of 15 mol % of **3-24**, 2.1 equiv phenylacetylene, and 2.0 equiv $ZnEt_2$ promoted the formation of the alkynylzinc at room temperature and addition to benzaldehyde provided the product in 79% ee. Increasing the loading of the chiral ligand to 22 mol % and switching to $ZnMe_2$, resulting in substantially increased enantioselectivity (92% ee). As shown in Scheme 3.9 these conditions were found to be highly effective for the addition of a variety of alkynes to aromatic aldehydes providing the propargylic alcohols in 86-97% ee. Addition to an α,β-unsaturated aldehyde was also shown to proceed with high enantioselectivity (94% ee). Although the enantioselectivities provided using BINOL-Salen **3-24** were not quite as high as those using the original BINOL system, the reaction procedure was simplified by avoiding heating steps and the use of $Ti(O^iPr)_4$.

**Scheme 3.9.** BINOL-SalenCatalyzed Asymmetric Phenylacetylene Additions to Aromatic Aldehydes.




Application of acyclic ligand **3-24** for the addition of phenylacetylene to an aliphatic aldehyde, octyl aldehyde, resulted in only 61% ee, again demonstrating that aliphatic aldehydes tend to be challenging substrates for BINOL based asymmetric alkynylations. In 2007, use of macrocylic BINOL-Salen **3-25** was found to provide improved enantiocontrol for additions to aliphatic aldehydes.[19] Interestingly, the absolute configurations of the products using macrocyclic ligand **3-25** were the opposite of those using acyclic ligand **3-24**. Using 20 mol % of **3-25** in combination with $ZnMe_2$ (2 equiv) in THF was found to catalyze the addition of phenylacetylene (2 equiv) to a variety of aliphatic aldehydes in 89-95% ee as shown in Scheme 3.10. α,β-Unsaturated aldehydes

**Scheme 3.10.** BINOL-Salen Catalyzed Asymmetric Phenylacetylene Additions to Aliphatic and α,β-Unsaturated Aldehydes.



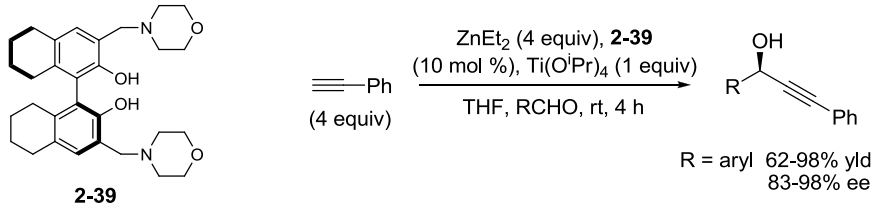
afforded good results as well (87-96% ee). Ligand **3-25** was also effective for an aromatic aldehyde, benzaldehyde (81% ee), though the selectivity was not as high as with acyclic BINOL-Salen **3-24** (92% ee). BINOL-Salen macrocycle **3-25** represents the only catalytic system reported by our group that has been demonstrated to be effective for alkyne additions to aliphatic aldehydes without the use of $Ti(O^iPr)_4$. Furthermore this system represents an improvement in the simplicity of the catalytic procedure, as all the reagents can be combined in one step without preforming the alkynylzinc or active catalyst.

*e. $H_8$BINOL-Amine Catalytic System*

During these investigations, in 2006 our group discovered a highly efficient one-step method for the synthesis of $H_8$BINOL-amine ligands (see Chapter 2). When tested for the addition of phenylacetylene (4 equiv) to benzaldehyde in the presence of 10 mol % ligand, 4 equiv of $ZnEt_2$, and 100 mol % $Ti(O^iPr)_4$, ligand **2-39** catalyzed the reaction in 93% yield and 83% ee. Like the BINOL-Salen **3-25** all the reagents could be combined at the same time and the alkynylzinc was formed at room temperature. Increasing the amount of the chiral catalyst to 20 and 40 mol % did not enhance the enantioselectivity of the reaction. When applied to a variety of aromatic aldehydes, as shown in Scheme 3.11, it was found that while the catalytic system produced good enantioselectivities for *meta*- and *para*-substituted aromatic aldehydes (83-91% ee), it was highly effective for *ortho*-substituted aldehydes (89-98% ee). Ligand **2-39** was not effective for aliphatic aldehydes, with the addition of phenylacetylene to octyl aldehyde resulting in only 67% ee. The major advantage associated with ligand **2-39** is the highly

efficient preparation of the ligand, and the high enantioselectivities afforded for *ortho*-substituted aryl aldehydes.

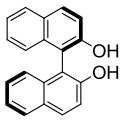
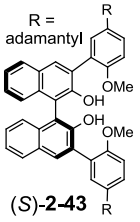
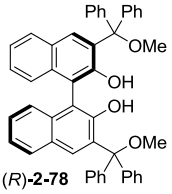
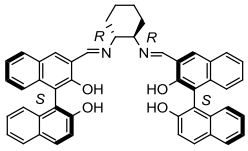
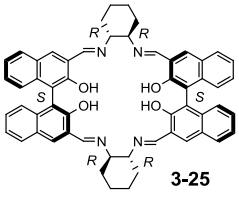
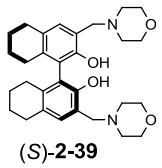
**Scheme 3.11.** 3,3'-Bimorpholinomethyl $H_8$BINOL Catalyzed Asymmetric Phenylacetylene Additions to Aromatic Aldehydes.




*e. Comparison of Catalytic Systems*

Comparison of these methods reveals the advantages among the various catalytic systems as displayed in Table 3.1. First, as a matter of practicality, the accessibility of the chiral ligand should be considered. All of the functionalized BINOL ligands except BINOL-Am ligand **2-39** require four synthetic steps from commercially available starting materials. This makes the BINOL methods by far the most attractive to the broader synthetic community because all the reagents are commercially available. Secondly, the ease of operation is important. The original BINOL method requires formation of the alkynylzinc by reflux in toluene whereas the other catalytic systems offer the advantage of performing the reaction at room temperature. Thirdly, the alkyne substrate scope determines which catalytic system should be used in a particular instance. The elevated reaction temperatures of the original BINOL system are known to limit the types of alkynes that can be used. In contrast, the use of external Lewis basic additives such as HMPA, or internal Lewis basic sites in the functionalized BINOLs allow the alkynylzinc to be formed at room temperature and opens the methodology to a broader range of

**Table 3.1.** Comparison of BINOL-Based Methods for Asymmetric Alkyne Additions to Aldehydes.

| chiral ligand | steps to make ligand | mol (%) | $ZnR_2$ (equiv) | rxn temp. | $Ti(O^iPr)_4$ (mol %) | aldehyde: ee |
|---|---|---|---|---|---|---|
|  | 0 | 20 | $ZnEt_2$ (2 equiv) | 1st step: reflux<br>2nd step: rt<br>3rd step: rt | 50 | Aromatic: 92-98% ee<br>Aliphatic: 91-97% ee<br>α,β-Unsaturated: 96-99% ee |
| | | 40 | $ZnEt_2$ (4 equiv) | | 100 | |
| (S)-BINOL + HMPA | 0 | 40 | $ZnEt_2$ (4 equiv) | 1st step:rt<br>2nd step: rt<br>3rd step:rt | 100 | Aromatic: 88-95% ee<br>α,β-Unsaturated: 92% ee |
|  (*S*)-**2-43** | 4 | 10 | $ZnEt_2$ (2 equiv) | 1st step: rt<br>2nd step: rt<br>3rd step: 0 °C | -- | Aromatic: 80-92% ee |
|  (*R*)-**2-78** | 4 | 30 | $ZnEt_2$ (2 equiv) | 1st step: rt<br>2nd step: rt<br>3rd step: 0 °C | -- | Aromatic: 86-94% ee |
|  **3-24** | 4 | 22 | $ZnMe_2$ (2 equiv) | 1st step: rt<br>2nd step: rt<br>3rd step: rt | -- | Aromatic: 86-97% ee<br>Aliphatic: 61% ee<br>α,β-Unsaturated: 94% ee |
|  **3-25** | 4 | 20 | $ZnMe_2$ (2 equiv) | 1 step: rt | -- | Aromatic: 81% ee<br>Aliphatic: 91-93% ee<br>α,β-Unsaturated: 87-96% ee |
|  (*S*)-**2-39** | 1 | 10 | $ZnEt_2$ (4 equiv) | 1 step: rt | 100 | Aromatic: 83-98% ee<br>Aliphatic: 67% ee |

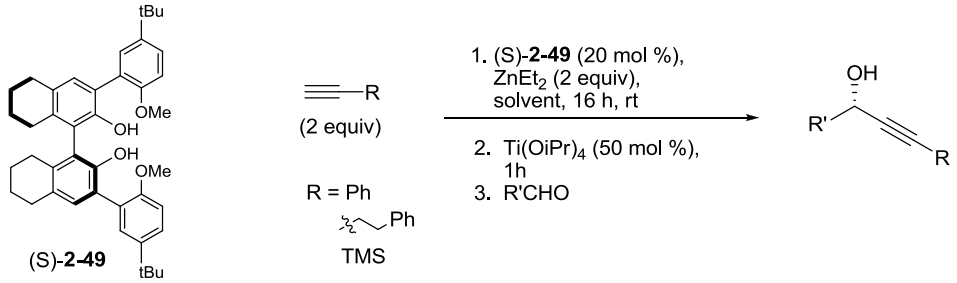
alkyne substrates. Fourthly, the functionalized BINOL ligands have been shown to open the possibility of promoting high enantioselectivity in the absence of $Ti(O^iPr)_4$ which is necessary for enantioselectivity in the unfunctionalized BINOL systems. The elimination of an additional metal necessary for enantiocontrol represents an improvement of the catalytic system. Lastly, the substrate scope of the aldehyde is significant. The methods described are largely centered on aromatic aldehydes, while aliphatic aldehydes have been demonstrated to be more challenging substrates. Only the original BINOL system and the macrocyclic BINOL-Salen ligands have been shown to provide enantioselectivities ≥90% for aliphatic aldehydes.

### 3.2. Asymmetric Alkyne Additions to Aliphatic Aldehydes

*a. Extension of (S)-**2-49** Catalytic System to Addition of Diverse Alkynes to Aldehydes*

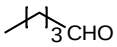
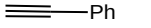
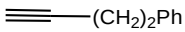
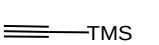
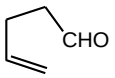
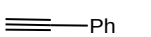
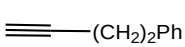
We wanted to investigate our newly developed catalytic system employing **2-49** for the addition of a variety of alkynes to aldehydes. This system was highly effective for alkyl propiolates and we wondered if it could also be successful in the addition of other alkynes. We examined a range of alkynes, testing an aryl alkyne (phenylacetylene), an alkyl alkyne (4-phenyl-1-butyne), and a silyl alkyne (trimethylsilylacetylene). For these

**Scheme 3.12.** Addition of Various Alkynes to Aliphatic and Aromatic Aldehydes Catalyzed by (*S*)-**2-49.**



reactions 20 mol % of ligand **2-49**, 2 equiv $ZnEt_2$ and alkyne, and 50 mol % $Ti(O^iPr)_4$ was employed, as shown in Scheme 3.12. For additions to aliphatic aldehydes THF was used as a solvent, and in the addition to aromatic aldehydes a $Et_2O$/THF (4:1) mixed solvent system was used.

**Table 3.2.** The Reaction of Various Alkynes with Aliphatic and Aromatic Aldehydes Catalyzed by (*S*)-**2-49**.[a]

| entry | aldehyde | alkyne | yield (%) | ee (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 88 | 81 |
| 2 | |  | 78 | 84 |
| 3 | |  | 65 | 91 |
| 4 |  |  | 97 | 81 |
| 5 | |  | 67 | 81 |
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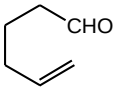
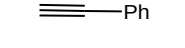
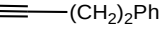
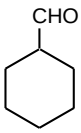
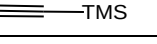
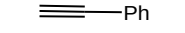
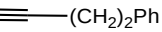
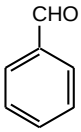
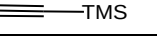
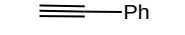
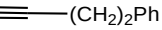
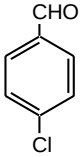
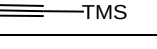
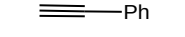
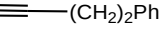
| 7 |  |  | 84 | 87 |
| 8 | |  | 74 | 81 |
| 9 | |  | 68 | 91 |
| 10 |  |  | 94 | 80 |
| 11 | |  | 83 | 77 |
| 12 | |  | 81 | 88 |
| 13 |  |  | 91 | 83 |
| 14 | |  | 61 | 89 |
| 15 | |  | 50 | 95 |
| 16 |  |  | 87 | 84 |
| 17 | |  | 72 | 80 |
| 18 | |  | 68 | 94 |

a. (*S*)-**2-49**:$ZnEt_2$:$Ti(O^iPr)_4$:alkyne:aldehyde = 0.2:2:0.5:2:1. THF was used as the solvent for the addition to the aliphatic aldehydes, and a $Et_2O$/THF (4:1) mixed solvent was used for the addition to the aromatic aldehydes. b. The ee of the products was determined by using the $^1H$ NMR spectra of their esters prepared with (*R*)-PhCH(OAc)$CO_2H$, or by HPLC-Chiralcel OD column or Chiralpak AD-H column.

These reactions were performed by Yang Yue, and the results are shown in Table 3.2.[20] Yang found that under these conditions ligand **2-49** catalyzed the reaction of phenylacetylene with a variety of aldehydes in 81 – 87% ee and the reaction of 4-phenyl-1-butyne with 77 – 89% ee. Interestingly ligand **2-49** performs equally well for aliphatic and aromatic substrates for these alkynes. Trimethylsilylacetylene proved to be a better substrate, affording enantioselectivities of 88 – 95%. These results demonstrate that **2-49** is generally useful for the asymmetric addition of a range of alkynes to aldehydes. However, it is most effective for alkyl propiolates and cannot provide high enantioselectivities (≥90% ee) for all alkyne substrates.

*b. Comparison of Methods*

In light of these and previous findings, we wanted to examine our available catalytic systems and determine what system was best for the addition of a variety of alkynes with aliphatic aldehydes. We limited our comparison to aliphatic aldehydes for a couple of reasons. First, aliphatic aldehydes have traditionally been the most challenging substrates for our catalytic systems. By targeting aliphatic aldehydes we could determine the limits of our methodology. Secondly and more importantly, aliphatic aldehydes often possess additional functional groups such as protected alcohols or sites of unsaturation. This functionality opens a larger range of possibilities for further transformations of the chiral propargylic alcohols. Accordingly, it is propargylic alcohols derived from additions to aliphatic aldehydes that are most commonly employed in total synthesis.

In the comparison of methods for the addition of diverse alkynes to aliphatic aldehydes we considered four factors. These factors were motivated by our desire for our methodology to be accessible to the broader synthetic community. First, can the catalytic

system provide good yields and enantioselectivities (ideally ≥90% ee) for the addition of a particular alkyne to aliphatic aldehydes? Secondly, are all the components of the catalytic system commercially available? A system where the chiral ligand is commercially available is preferable to a system where it has to be synthesized. Where the chiral ligand has to be prepared, the synthetic route should be short and the loadings of the chiral reagent should be minimized for its use to be practical. Thirdly, what is the cost associated with the method? Are large quantities of the reagents required, and are the reagents required more or less expensive compared with alternative methods? Fourthly, which system is better in terms of safety and ease of operation? Avoiding the use of toxic substances is desirable, and circumventing heating or cooling steps in the reaction leads to a more user friendly synthetic procedure.

From these considerations we limited our comparison to three catalytic systems. The first was our group's original BINOL/$ZnEt_2$/$Ti(O^iPr)_4$ catalytic system in which the alkynylzinc nucleophile is first preformed by reflux of the alkyne with $ZnEt_2$ in toluene (Method I). The second system is the BINOL/$ZnEt_2$/$Ti(O^iPr)_4$ catalytic system in which the alkynylzinc nucleophile is formed through the addition of an external Lewis base, such as HMPA as discovered by our laboratory, or N-methylimidzaole (NMI) as discovered by You and coworkers[21] (Method II and III). The direct comparison of the original BINOL system with the BINOL systems employing Lewis basic additives would allow us to determine whether the external Lewis base was detrimental to enantiocontrol. The final system is bifunctional $H_8$BINOL ligand **2-49** (Method IV), as this ligand is the only catalyst demonstrated to be effective for the addition of alkynoates to aliphatic aldehydes, and can be accessed in 2 steps from commercially available $H_8$BINOL.

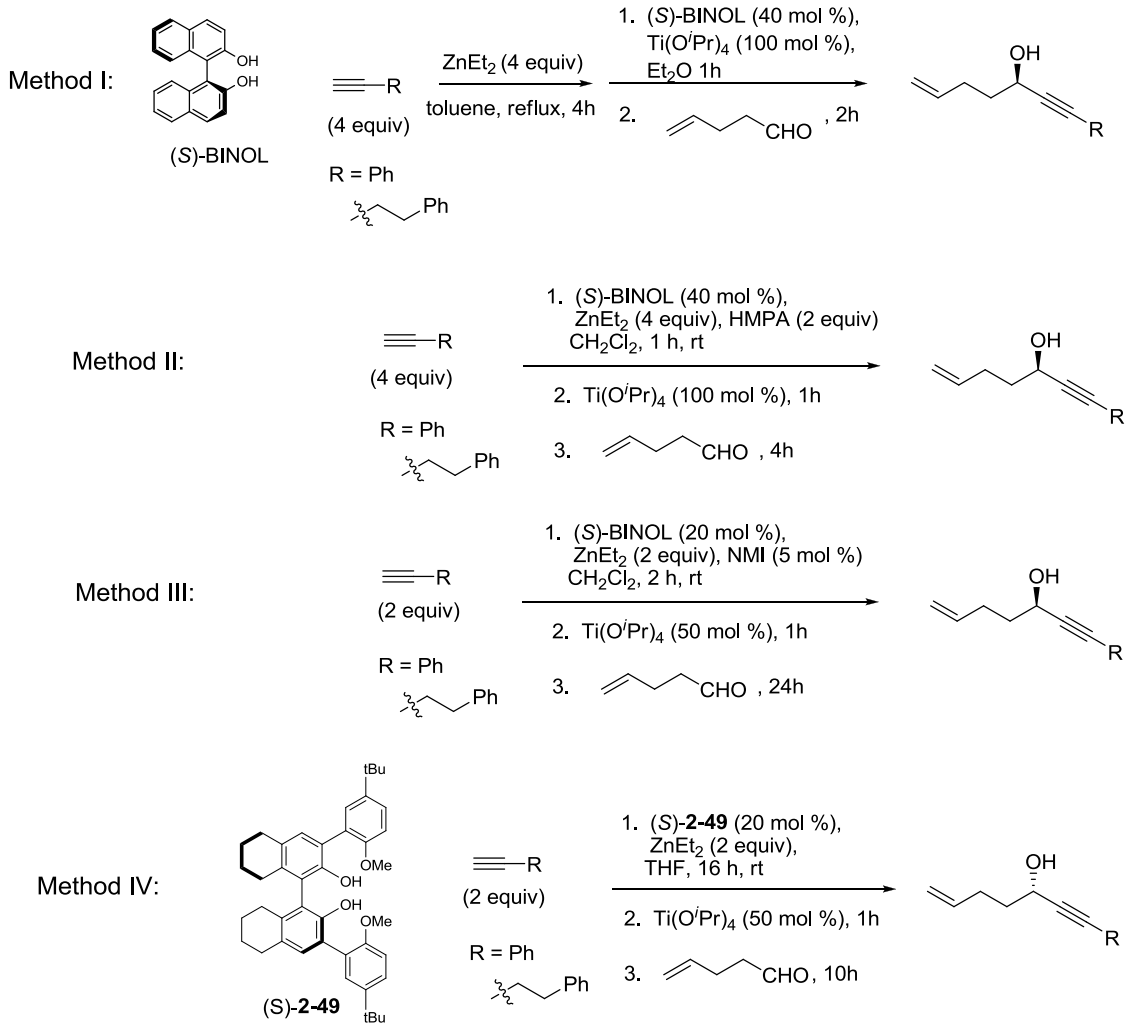
Limitation to these three systems was due to the fact that the other catalytic systems required the preparation of the chiral ligand through multi-step reaction pathways or were ineffective for additions to aliphatic aldehydes. Of these ligands only the macrocyclic BINOL-Salen was shown to be effective for the addition of alkynes to aliphatic aldehydes. The longer synthetic sequences required to access this ligand, without improved enantioselectivities over BINOL, makes this system less practical.

With these systems identified, we set out to test the addition of a variety of alkynes to aliphatic aldehydes. We first started with an aromatic substituted alkyne, phenylacetylene, and an alkyl substituted alkyne, 4-phenyl-1-butyne. For this screening we chose a functional linear aliphatic aldehyde, 4-pentenal. We employed the optimized reaction conditions for each catalytic system as shown in Scheme 3.13. Method I forms the alkynylzinc under elevated temperatures. The alkyne (2 mmol, 4 equiv) was first treated with $ZnEt_2$ (2 mmol, 4 equiv) in refluxing toluene (1 mL) for 4 h, during which time grey precipitates formed. To the reaction mixture was added $Et_2O$ (8 mL), (*S*)-BINOL (0.2 mmol, 40 mol %), and $Ti(O^iPr)_4$ (0.5 mmol, 1 equiv). After 1 h an aldehyde (0.5 mmol) was added.

Method II utilizes the Lewis basic additive HMPA. The alkyne (2 mmol, 4 equiv), $ZnEt_2$ (2 mmol, 4 equiv), (*S*)-BINOL (0.2 mmol, 40 mol %), and HMPA (2 equiv) were first combined in $CH_2Cl_2$ (6 mL), and stirred for 1 h. To the solution was added $Ti(O^iPr)_4$ (0.5 mmol, 1 equiv), and after stirring 1 h an aldehyde (0.5 mmol) was added. Method III replaces the Lewis basic additive HMPA with NMI and also reduces the loadings of the other reagents, as reported by You and coworkers. Here the alkyne (1 mmol, 2 equiv), $ZnEt_2$ (1 mmol, 2 equiv), (*S*)-BINOL (0.1 mmol, 20 mol %), and NMI (5

mol %) were combined in $CH_2Cl_2$ (6 mL), and stirred for 2 h. To the solution was added $Ti(O^iPr)_4$ (0.25 mmol, 50 mol %), and after stirring 1 h an aldehyde (0.5 mmol) was added.

**Scheme 3.13.** Methods I – IV for Asymmetric Alkyne Additions to Aliphatic Aldehydes.



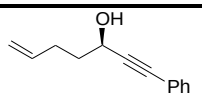
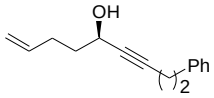
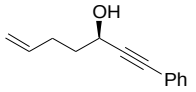
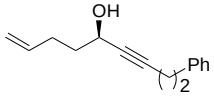
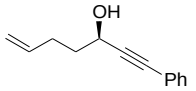
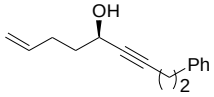
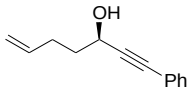
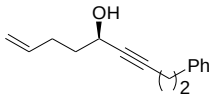
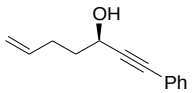
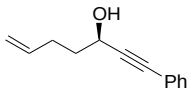
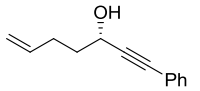
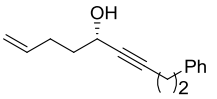

Method IV employs bifunctional ligand (*S*)-**2-49**. The ligand (0.1 mmol, 20 mol %) was first combined with the alkyne (1 mmol, 2 equiv) and $ZnEt_2$ (1 mmol, 2 equiv) in THF (5 mL) and stirred for 16 h. Subsequently $Ti(O^iPr)_4$ (0.25 mmol, 50 mol %) was

added. The reaction mixture was stirred for 1 h followed by the addition of an aldehyde (0.5 mmol).

The results are summarized in Table 3.3. When our original BINOL-catalyzed procedure involving heating the alkyne with $ZnEt_2$ in refluxing toluene was used (Method I), excellent enantioselectivities and yields were obtained for the addition of the aryl alkyne (95% ee) and the alkyl alkyne (94% ee) to 4-pentenal (entries 1 and 2). Recently, the partially hydrogenated BINOL, $H_8$BINOL, has also been studied in asymmetric catalysis and has often been found to lead to increased enantioselectivity over BINOL in asymmetric processes.[22] In an analogous system reported by Chan, it was found that $H_8$BINOL provided slightly increased enantioselectivity in the addition of phenylacetylene to aromatic aldehydes.[23] We were interested to see whether $H_8$BINOL could also improve the enantioselectivity under our reaction conditions. Replacing BINOL with $H_8$BINOL, however, slightly decreased the enantioselectivities for both phenylacetylene and 4-phenyl-1-butyne to 91% ee (entries 3 and 4).

The use of Lewis basic additives was tested next. When HMPA was used as the additive to allow the reaction to be conducted at room temperature the enantioselectivity was diminished in both cases (entries 5 and 6), yielding 81% ee for the addition of the aryl and alkyl alkynes. This demonstrates that the presence of HMPA as a Lewis basic additive, although facilitating formation of the alkynylzinc nucleophile erodes the enantiocontrol of the asymmetric process. When HMPA was replaced with NMI, and the quantity of the chiral ligand was reduced to 20 mol % as reported by You and co-workers, the enantioselectivity dropped further, decreasing to 68% ee for the aryl alkyne and 69% ee for the alkyl alkyne. Doubling the amounts of all the reagents allowed

**Table 3.3.** Asymmetric Aryl and Alkyl Alkyne Addition to 4-Pentenal.

| entry | alkyne | ligand | mol % ligand | additive | product | yield (%) | ee (%)[g] |
|---|---|---|---|---|---|---|---|
| 1[a] |  | (*S*)-BINOL | 40 | - |  | 88 | 94 |
| 2[a] |  | (*S*)-BINOL | 40 | - |  | 95 | 95 |
| 3[a] |  | (*S*)-$H_8$BINOL | 40 | - |  | 87 | 91 |
| 4[a] |  | (*S*)-$H_8$BINOL | 40 | - |  | 66 | 91 |
| 5[b] |  | (*S*)-BINOL | 40 | HMPA |  | 92 | 81 |
| 6[b] |  | (*S*)-BINOL | 40 | HMPA |  | 28 | 82 |
| 7[c] |  | (*S*)-BINOL | 20 | NMI |  | 32 | 68 |
| 8[c] |  | (*S*)-BINOL | 20 | NMI |  | 26 | 69 |
| 9[d] |  | (*S*)-BINOL | 40 | NMI |  | 25 | 84 |
| 10[d,e] |  | (*S*)-BINOL | 40 | NMI |  | 74 | 90 |
| 9[f] |  | (*S*)-**2-49** | 20 | - |  | 97 | 81 |
| 10[f] |  | (*S*)-**2-49** | 20 | - |  | 67 | 81 |

(a) Method I: An alkyne (2 mmol, 4 equiv) and $ZnEt_2$ (2 mmol, 4 equiv) were heated at reflux in toluene (1 mL) for 4 h. $Et_2O$ (8 mL), ligand (0.2 mmol, 40 mol %), and $Ti(OiPr)_4$ (0.5 mmol, 1 equiv) were added. After 1 h 4-pentenal was added (0.5 mmol). (b) Method II: BINOL (0.2 mmol, 40 mol %), HMPA (1 mmol, 2 equiv), alkyne (2 mmol, 4 equiv), and $ZnEt_2$ (2 mmol, 4 equiv) were stirred in $CH_2Cl_2$ (6 mL) for 1 h at rt. $Ti(OiPr)_4$ (0.5 mmol, 1 equiv) was added and after 1 h followed by the addition of 4-pentenal (0.5 mmol). (c) Method III: BINOL (0.1 mmol, 20 mol %), NMI (0.025 mmol, 0.05 equiv), alkyne (1 mmol, 2 equiv), and $ZnEt_2$ (1 mmol, 2 equiv) were stirred in $CH_2Cl_2$ (6 mL) for 2 h at rt. $Ti(OiPr)_4$ (0.25 mmol, 50 mol %) was added and after 1h followed by the addition of 4-pentenal (0.5 mmol). (d) Method III was followed with the quantities of all reagents doubled, excluding NMI. (e) The alkynylzinc was allowed to form over 20 h at rt. (f) Method IV: (*S*)-**2-49** (0.1 mmol, 20 mol %), alkyne (1 mmol, 2 equiv), and $ZnEt_2$ (1 mmol, 2 equiv) were stirred in THF (5 mL) for 16 h at rt. $Ti(OiPr)_4$ (0.125 mmol, 50 mol %) was added and stirred for 1h, followed by the addition of 4-pentenal (0.5 mmol). (g) Determined by HPLC analysis with Chiralcel OD or Chiralpak AD-H column.

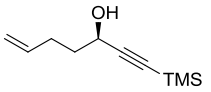
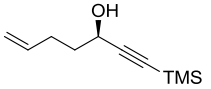
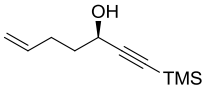
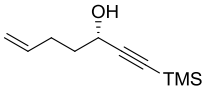
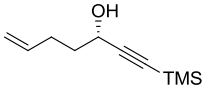
for a direct comparison of NMI with HMPA as a Lewis base additive. For the addition of phenylacetylene to 4-pentenal 25% yield and 84% ee was obtained under these conditions (entry 9). The greatly diminished yields are probably due to the fact that 5 mol % of NMI is used in comparison with 2 equiv of HMPA. When the alkynylzinc was allowed to form over 20 h, both the yield and enantioselectivity were improved substantially (74% yld, 90% ee, entry 10). The interesting increase in enantioselectivity likely indicates that the enantiocontrol of the reaction is improved in the presence of the alkynylethylzinc species in contrast to when unreacted $ZnEt_2$ is present. As shown previously, the addition of the aryl and alkyl alkyne to 5-hexenal in the presence of 20 mol % (*S*)-**2-49** afforded enantioselectivities of 81% ee for both substrates.

From this study, it became apparent that the original BINOL based system (Method I) was superior for the addition of aryl and alkyl alkynes to aliphatic aldehydes, as this was the only catalytic system that could afford enantioselectivities >90%. While the addition of Lewis basic additives simplified the reaction procedure by allowing the entire reaction to be conducted at room temperature, the presence of the Lewis base had a detrimental effect on enantioselectivity in the addition to aliphatic aldehydes. Use of the bifunctional ligand found to be effective in the addition of alkynoates to aliphatic aldehydes did not provide an improvement.

While the simple aryl and alkyl alkynes employed above are compatible with the elevated temperatures necessary to form the alkynylzinc, more sensitive substrates are not. This excludes the use of our original BINOL system in these instances, and necessitates the use of additives or bifunctional catalysts so that the reaction can be conducted under milder conditions. For example, alkynoates such as methyl propiolate

decompose under refluxing conditions in toluene in the presence of $ZnEt_2$. As discussed in Chapter 2, for these substrates bifunctional ligand (*S*)-**2-49** was found to be superior for additions to aliphatic aldehydes, as the use of Lewis basic additives could not achieve high enantioselectivities (≥90% ee). We also wanted to examine the addition of functional trialkylsilyl acetylenes to aliphatic aldehydes.

**Table 3.4.** Asymmetric Trimethylsilylacetylene Addition to 4-Pentenal.

| entry | alkyne | ligand | mol % ligand | additive | product | yield (%) | ee (%)[e] |
|---|---|---|---|---|---|---|---|
| 1[a] | ≡—TMS | (*S*)-BINOL | 40 | - |  | 37 | 84 |
| 2[b] | ≡—TMS | (*S*)-BINOL | 40 | HMPA |  | 89 | 80 |
| 3[c] | ≡—TMS | (*S*)-BINOL | 40 | NMI |  | 31 | 75 |
| 4[d] | ≡—TMS | (*S*)-**2-49** | 20 | - |  | 68 | 88 |
| 5[e] | ≡—TMS | (*S*)-**2-49** | 20 | - |  | 90 | 88 |

(a) Method I, Table 3.3. (b) Method II, Table 3.3. (c) Method III, Footnote d,e Table 3.3. (d) Method IV, Table 3.3. (e) Method IV, Table 3.3 was followed except that the alkynylzinc was first formed in $Et_2O$ (1 mL). After 16 h, THF (5 mL) was added and the other reagents were added as normal.

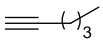
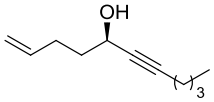
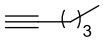
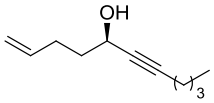
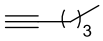
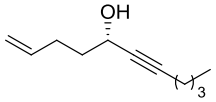
We tested our original BINOL system (Method I), the HMPA/BINOL system (Method II), and bifunctional ligand (*S*)-**2-49** (Method IV) for the addition of trimethylsilylacetylene to 4-pentenal using our standard reaction conditions. We also tested the use of NMI as a Lewis base under the improved reaction conditions (doubling the amounts of reagents and 20 h for formation of the alkynylzinc). The results are summarized in Table 3.4. As shown in entry 1 the original BINOL system affords the product in 84% ee and reduced yield (37%). The use of HMPA allows for the alkynylzinc to be formed at room temperature and increases the yield dramatically to

89%, with a slight decrease in the enantioselectivity (80%, entry 2). Use of NMI is less active in formation of the alkynylzinc intermediate, even with the extended reaction time, resulting in 31% yield and 75% ee (entry 3). The ethyl addition product is also observed in this instance. Use of (*S*)-**2-49** with THF as a solvent resulted in high enantioselectivity (88% ee) and 66% yield. The yield could be improved substantially without loss of enantioselectivity by first forming the alkynylzinc in $Et_2O$ (1 mL), and then adding THF (5 mL) in the second step. These findings demonstrate that the catalytic system utilizing (*S*)-**2-49** is superior when using trimethylsilylacetylene.

*c. Addition of Linear Alkyl Alkynes with Linear Aliphatic Aldehydes*

During these investigations we uncovered a new challenge for asymmetric alkyne additions to aldehydes—the addition of linear alkynes to linear aliphatic aldehydes. As shown in Table 3.5, our catalytic systems were unable to provide high enantioselective for the addition of 1-hexyne to valeraldehyde. Using NMI as a Lewis basic additive afforded the product in low yield (36%) and enantioselectivity (64%, entry 2). Testing ligand **2-49** for this reaction increased the yield, but lowered the enantioselectivity (56%, entry 3). Only the original BINOL system was able to provide good yield (76%) and enantioselectivity (83% ee, entry 1), although this enantioselectivity is considerably lower than that afforded by another alkyl alkyne, 4-phenyl-1-butyne (95% ee, Table 3.3, entry 2). The lower enantioselectivities observed for the linear alkyne could be due to the smaller steric bias of the linear alkyne in the catalytic pocket.

**Table 3.5.** Asymmetric Trimethylsilylacetylene Addition to 4-Pentenal.

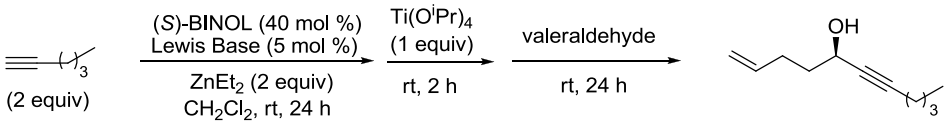
| entry | zlkyne | ligand | mol % Ligand | Additive | Product | Yield (%) | ee (%)[e] |
|---|---|---|---|---|---|---|---|
| 1[a] |  | (*S*)-BINOL | 40 | - |  | 76 | 83 |
| 2[b] |  | (*S*)-BINOL | 40 | NMI |  | 36 | 64 |
| 3[c] |  | **2-49** | 20 | - |  | 63 | 56 |

(a) Method I, Table 3.3. (b) Method III, Footnote d,e Table 3.3. (d) Method IV, Table 3.3.

The difficulty in the addition of linear alkynes to linear aliphatic aldehydes is also apparent in the literature, as no highly enantioselective catalytic system has been reported for these substrates. Those reports involving the asymmetric addition of linear alkynes to linear aldehydes all employ stoichiometric amounts of chiral amino alcohol ligands.[24] To address this gap in the substrate scope of our alkyne addition methodology we set out to improve the enantioselectivity of this reaction by searching for a better Lewis basic additive. From our comparison of the original BINOL system and the BINOL systems using HMPA and NMI, we knew that the Lewis base employed could substantially affect the enantioselectivity of the reaction. So far we had only observed a negative effect in the reduction of enantioselectivity. For phenylacetylene additions to aliphatic aldehydes NMI had proven to be a better Lewis basic additive than HMPA. This was likely because a much smaller amount of the additive was employed, thus minimizing its interference in the enantiocontrol of the reaction. However, for linear alkyne substrates this interference was still significant as the enantioselectivity was decreased by nearly 20%. We wondered if a superior Lewis basic additive could be found that better minimized the

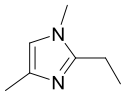
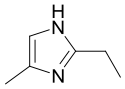
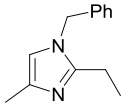
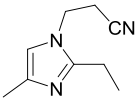
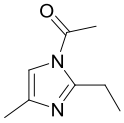
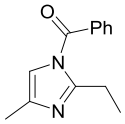
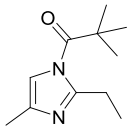
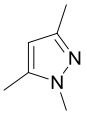
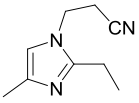
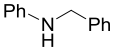
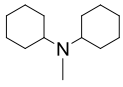
detrimental effect of the Lewis base on enantioselectivity. Furthermore, it was possible that the right Lewis base could enhance the enantioselectivity of the reaction, as additives have often been employed in asymmetric catalysis to improve selectivity (see Chapter 1).

**Scheme 3.14.** Addition of 1-Hexyne to Valeraldehyde Catalyzed by BINOL/$ZnEt_2$/$Ti(O^iPr)_4$ in the Presence of Lewis Base Additives.




With this goal, we first set out to modify the structure of NMI in attempt to improve the enantioselectivity of the reaction. These reactions were performed by Yuhao Du using the conditions shown in Scheme 3.14, and the results are displayed in Table 3.6.[25] Du first modified NMI through the addition of alkyl groups on the heterocyclic ring, increasing the basicity and steric bulk of the additive. While this improved the yield it did not improve the enantioselectivity (entry 2). Varying the substituent on nitrogen proved to be important as shown in entries 3-10. Removal of the N-methyl group decreased the yield without affecting the enantioselectivity. Changing to a benzyl substituent improved the enantioselectivity to 70% (entry 4). Use of an ethyl cyanide substituent increased the selectivity further to 76% ee (entry 5), though the yield was low. The yield could be improved using $Et_2O$ as the solvent, while maintaining the enantioselectivity (entry 15). Electron withdrawing substituents on the imidazole nitrogen did not improve the enantioselectivity further, but were generally better than unmodified NMI (entries 8-10). Use of other N-heterocycles such as a pyrazine and pyrazole did not provide better enantioselectivities (entries 11-12).

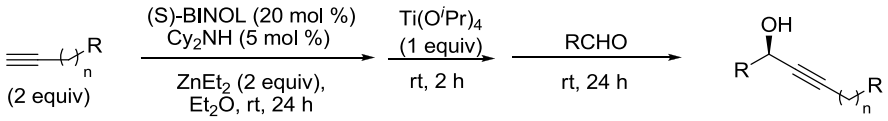
**Table 3.6.** Addition of 1-Hexyne to Valeraldehyde in the Presence of Lewis Bases.

| entry | base | (mol %) | solvent | yield (%) | ee (%)[a] |
|---|---|---|---|---|---|
| 1 | NMI | 5 | $CH_2Cl_2$ | 36 | 64 |
| 2 |  | 5 | $CH_2Cl_2$ | 92 | 62 |
| 3 |  | 5 | $CH_2Cl_2$ | 25 | 66 |
| 4 |  | 5 | $CH_2Cl_2$ | 44 | 70 |
| 5 |  | 5 | $CH_2Cl_2$ | 34 | 76 |
| 6 | | 10 | $CH_2Cl_2$ | 52 | 70 |
| 7 | | 2.5 | $CH_2Cl_2$ | 30 | 75 |
| 8 |  | 5 | $CH_2Cl_2$ | 49 | 71 |
| 9 |  | 5 | $CH_2Cl_2$ | 56 | 72 |
| 10 |  | 5 | $CH_2Cl_2$ | 49 | 61 |
| 11 |  | 5 | $CH_2Cl_2$ | 50 | 72 |
| 12 |  | 5 | $CH_2Cl_2$ | 75 | 60 |
| 13 |  | 5 | THF | 95 | 55 |
| 14 | | 5 | Toluene | 56 | 56 |
| 15 | | 5 | $Et_2O$ | 83 | 77 |
| 16 | $CH_3NH(CH_2)_3NH_2$ | 5 | $Et_2O$ | 91 | 64 |
| 17 | $^{i}$PrNH | 5 | $Et_2O$ | 40 | 79 |
| 18 |  | 5 | $Et_2O$ | 76 | 77 |
| **19** | **$Cy_2NH$** | **5** | **$Et_2O$** | **59** | **84** |
| 20 | $Et_3N$ | 5 | $Et_2O$ | 56 | 74 |
| 21 |  | 5 | $Et_2O$ | 51 | 78 |
| 22 | $N(n\text{-}C_4H_9)_4Br$ | 5 | $Et_2O$ | 44 | 77 |

[a] Determined by using the $^1$H NMR spectra of their esters prepared with (*R*)-PhCH(OAc)$CO_2$H.

As these results were still unsatisfactory primary, secondary and tertiary amines were screened as additives. A primary amine was found to greatly improve the yield but not the enantioselectivity (entry 16). Secondary amines served to enhance the enantioselectivity, with increased steric bulk providing better selectivity (entries 17-19). In particular dicyclohexylamine ($Cy_2NH$) was able to catalyze the reaction in 84% ee. Use of tertiary amines lowered the enantioselectivity to <80%, though these enantioselectivities were better than those achieved with a primary amine (entries 20-21). Finally a quaternary amine salt was also found to catalyze the reaction in 77% ee (entry 22).

**Scheme 3.15.** Addition of Linear Alkynes to Linear Aliphatic Aldehydes.

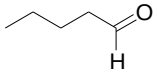
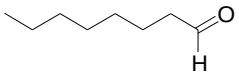
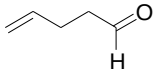
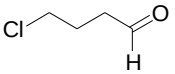
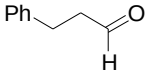



From this screening, Du identified $Cy_2NH$ as a superior Lewis base additive for the addition of linear alkynes to linear aliphatic aldehydes. The reaction conditions were further optimized, with the reaction conditions shown in Scheme 3.15 found to be optimal. As shown in Table 3.7 when these conditions were applied to a range of linear alkynes and linear aldehydes good yields (57-77%) and enantioselectivities (77-89%) were obtained over a range of alkyne and aldehyde substrates.

Du's findings represented the first catalytic system reported to be effective for linear aliphatic alkynes and linear aliphatic aldehydes. Interestingly, the presence of the Lewis basic additive $Cy_2NH$ slightly improves the enantioselectivity of the reaction. For example, direct comparison of the original BINOL system with the catalytic system utilizing $Cy_2NH$ (5 mol %) as an additive in the addition of 1-hexyne to 4-pentenal

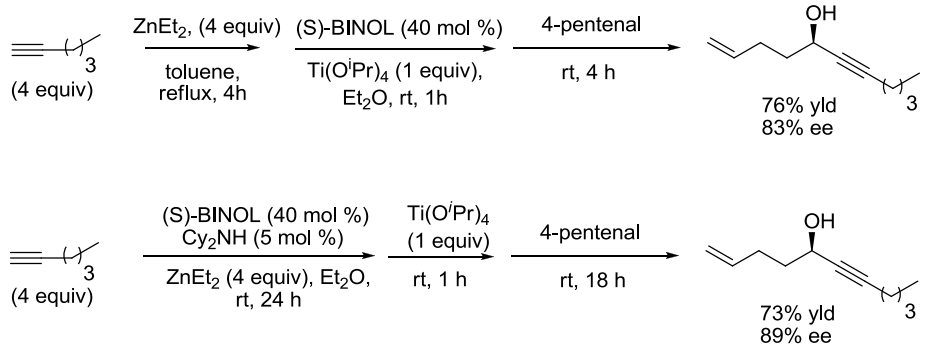
improves the enantioselectivity of the reaction from 83% ee to 89% ee as shown in Scheme 3.16. This is the first time we have observed the Lewis basic additive to be beneficial for the enantiocontrol of an asymmetric alkyne addition using the BINOL/$ZnEt_2$/$Ti(O^iPr)_4$ catalytic system.

**Table 3.7.** Reactions of Linear Alkynes with Linear Aldehydes in the Presence of (*S*)-BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/$Cy_2NH$.

| entry | alkyne | aldehyde | yield (%) | ee (%)[a] |
|---|---|---|---|---|
| 1 | n-$C_4H_9$— |  | 73 | 81 |
| 2 | n-$C_6H_{13}$— | | 61 | 87 |
| 3 | Cl | | 77 | 88 |
| 4 | n-$C_4H_9$— |  | 76 | 85 |
| 5 | n-$C_6H_{13}$— | | 67 | 85 |
| 6 | Cl | | 70 | 89 |
| 7 | n-$C_4H_9$— |  | 63 | 87 |
| 8 | n-$C_6H_{13}$— | | 59 | 83 |
| 9 | Cl | | 60 | 88 |
| 10 | n-$C_6H_{13}$— |  | 57 | 77 |
| 11 | Cl | | 61 | 83 |
| 12 | n-$C_4H_9$— |  | 71 | 83 |
| 13 | n-$C_6H_{13}$— | | 74 | 84 |
| 14 | Cl | | 65 | 89 |

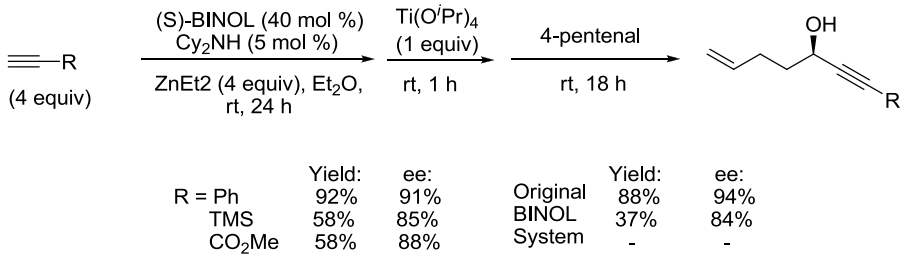
[a] Determined by using the $^1H$ NMR spectra of their esters prepared with (*R*)-PhCH(OAc)$CO_2H$.

**Scheme 3.16.** Effect of $Cy_2NH$ on BINOL/$ZnEt_2$/$Ti(O^iPr)_4$ Catalyzed Asymmetric Addition of Linear Alkyl Alkyne.



Encouraged by this discovery we also tested the use of $Cy_2NH$ for the addition of other types of alkynes including phenylacetylene, trimethylsilylacetylene, and methyl propiolate to aliphatic aldehydes. In these cases however, $Cy_2NH$ was unable to improve the enantioselectivity of the reaction over the original BINOL system. As shown in Scheme 3.17, lower or similar enantioselectivities were obtained, although the enantioselectivities were still good. Thus, while $Cy_2NH$ does not appear to interfere too greatly with the enantiocontrol of the reaction for these substrates, it does not enhance it as it does for linear alkyl alkynes.

**Scheme 3.17.** Addition of Various Alkynes to 4-Pentenal Catalyzed by BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/$Cy_2NH$.

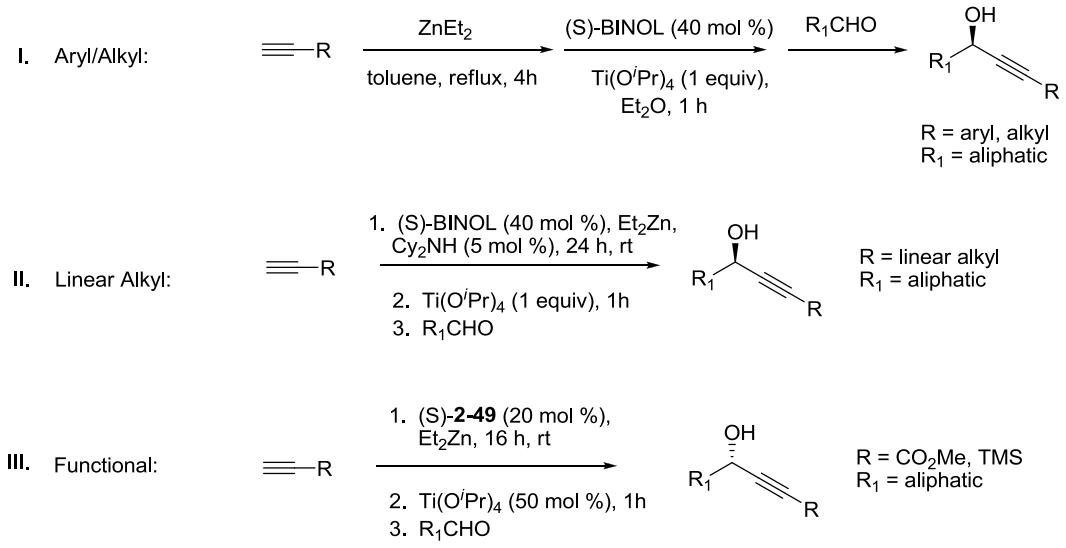



| | Yield: | ee: | | Yield: | ee: |
|---|---|---|---|---|---|
| R = Ph | 92% | 91% | Original | 88% | 94% |
| TMS | 58% | 85% | BINOL | 37% | 84% |
| $CO_2Me$ | 58% | 88% | System | - | - |

*d. Toolbox of Catalytic Methods and Use for Asymmetric Alkyne Addition*

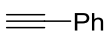
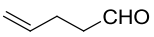
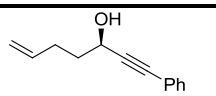
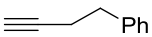
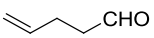
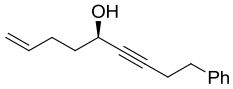
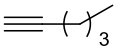
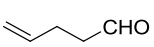
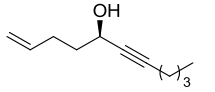
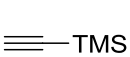
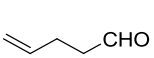
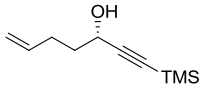
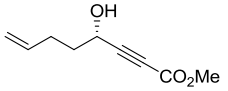
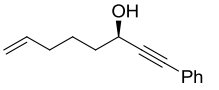
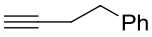
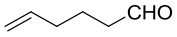
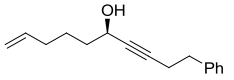
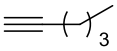
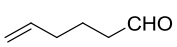
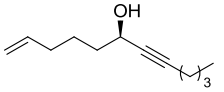
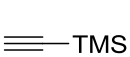
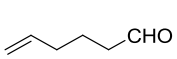
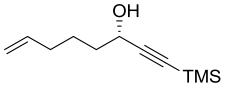
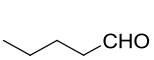
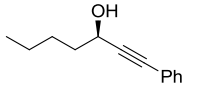
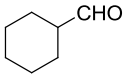
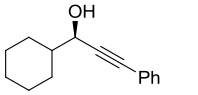
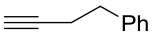
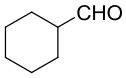
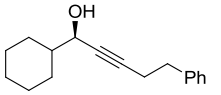
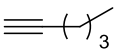
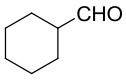
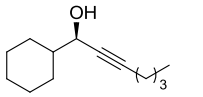
From this comparison of methods we are able to construct a highly effective toolbox of methods for the addition of structurally diverse alkynes to aliphatic aldehydes as shown in Figure 3.2. For simple aryl and alkyl alkynes, the original BINOL catalytic system in which the alkynylzinc is formed by reflux in toluene is optimal as it provides the highest enantioselectivities. For functional alkynes such as alkyl propiolates and trimethylsilylacetylene, ligand (*S*)-**2-49** is superior for additions to aliphatic aldehydes. Finally, for linear alkyl alkynes, the use of $Cy_2NH$ as a Lewis basic additive provides the

**Figure 3.2.** Optimal Methods for Additions of Various Alkynes to Aliphatic Aldehydes.




best enantioselectivities. The simplicity and effectiveness of these methods, especially the BINOL systems in which all the reagents are commercially available, make these viable methods for use by the synthetic community. Application of these methods for addition of various alkynes to 4-pentenal, 5-hexenal, valeraldehyde, and cyclohexanecarboxaldehyde provided efficient access to a range of propargylic alcohol-based enynes and enyne precursors in good yields and enantioselectivities as shown in Table 3.8.

**Table 3.8.** Preparation of Propargylic Alcohol Enyne Precusors.[a]

| entry | alkyne | aldehyde | method | product | | yld | ee[b] |
|---|---|---|---|---|---|---|---|
| 1 |  |  | I |  | **3-26** | 88 | 94 |
| 2 |  |  | I |  | **3-27** | 95 | 95 |
| 3 |  |  | II |  | **3-28** | 73 | 89 |
| 4 |  |  | III |  | **3-29** | 90 | 88 |
| 5 |  |  | III |  | **3-30** | 63 | 95 |
| 6 |  |  | I |  | **3-31** | 87 | 93 |
| 7 |  |  | I |  | **3-32** | 83 | 90 |
| 8 |  |  | II |  | **3-33** | 83 | 83 |
| 9 |  |  | III |  | **3-34** | 91 | 91 |
| 10 |  |  | I |  | **3-35** | 89 | 95 |
| 11 |  |  | I |  | **3-36** | 88 | 96 |
| 12 |  |  | I |  | **3-37** | 94 | 84 |
| 13 |  |  | II |  | **3-38** | 84 | 81 |
| 14 |  |  | III |  | **3-39** | 88 | 88 |

(a) Methods from Figure 3.1. See experimental section for full procedural details. (b) Determined by HPLC analysis with Chiralcel OD or Chiralpak AD-H column or by using the $^1$H NMR spectra of their esters prepared with (*R*)-PhCH(OAc)$CO_2$H.

### 3.3. Diastereoselective Intramolecular Pauson-Khand Reaction

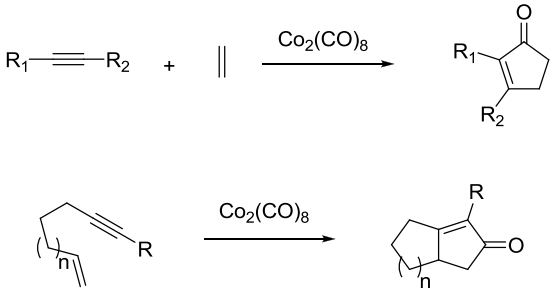
With effective methods established for the addition of diverse alkynes with aliphatic aldehydes, we now had ready access to a wide range of optically active propargylic alcohols. We next turned to utilizing these substrates in diastereoselective transformations. Since we had used 4-pentenal during the exploration of the optimum catalytic systems, we had synthesized a range of optically active enynes. We thought that the Pauson-Khand reaction was an attractive application for these types of substrates.

*a. Pauson-Khand Reaction*

The Pauson-Khand (PK) reaction is a powerful tool for the construction of cyclopentenone rings.[26] Discovered first as an intermolecular reaction in the early 1970s,[27] the PK reaction is a formal [2 + 2 + 1] cycloaddition of an alkyne, alkene, and carbon monoxide. A decade later, Schore and coworkers pioneered the intramolecular reaction,[28] opening access to multi-cyclic ring structures through this methodology. The intramolecular version of the Pauson-Khand reaction has proven to be an efficient means of greatly increasing a molecule's structural complexity in one step.

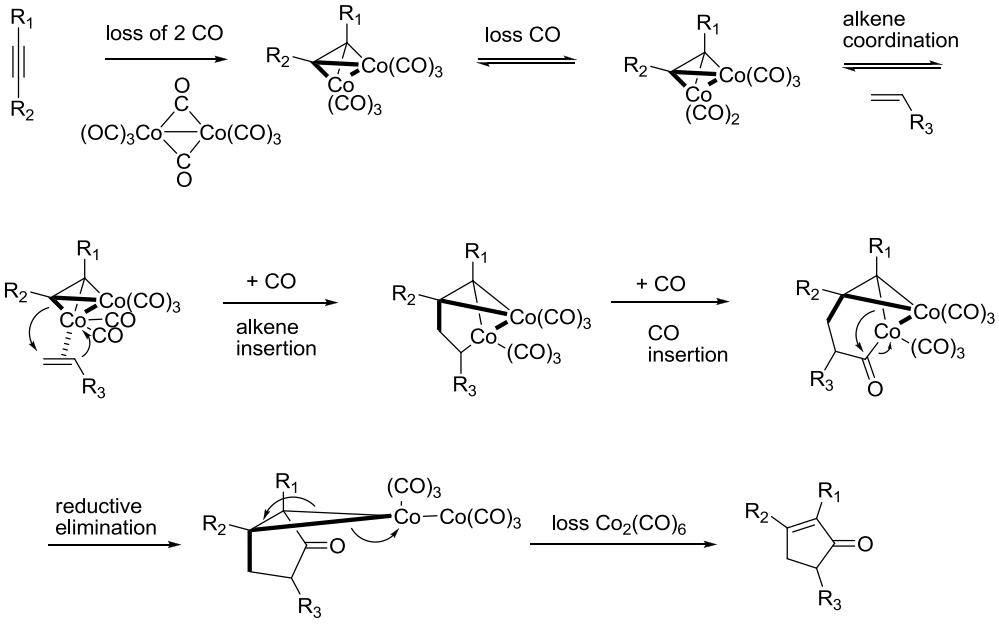
As originally developed by Pauson and Khand, the classical PKR is performed in two steps. The cobalt-alkyne complex is first formed at room temperature through mixing of the alkyne with a stoichiometric amount of $Co_2(CO)_8$. The cyclization is then affected at elevated temperatures, usually in refluxing toluene. The high reaction temperatures often resulted in limited substrate scope and reduced yields. Due to recent advances in the reaction scope and improvements in yields through the discovery of an array of promoters, the PK reaction has been increasingly utilized in the synthesis of complex multi-cyclic molecules.[26]

**Figure 3.3**. Intermolecular and Intramolecular Pauson-Khand Reaction.




In an attempt to better understand and improve the reaction, a mechanism for the PKR has been proposed as shown in Figure 3.4.[26] The first step involves complexation of the alkyne with $Co_2(CO)_8$, liberating two molecules of carbon monoxide. From this intermediate an equivalent of carbon monoxide can reversibly dissociate, providing an open coordination site for the alkene's π electrons. Upon coordination with the metal, the

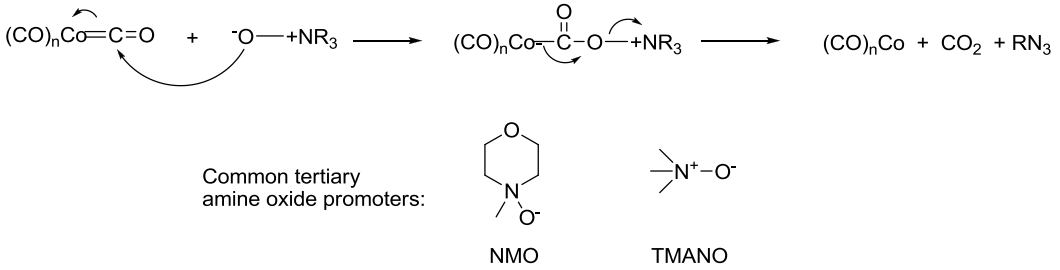
**Figure 3.4.** Proposed Mechanism for the Pauson-Khand Reaction.




alkene can then insert into the alkyne-cobalt bond to form the resulting cobaltacycle. In the intermolecular reaction, this carbon-carbon bond forming step occurs at the less

sterically hindered end of the alkyne ($R_1 > R_2$), providing regioselectivity with respect to the alkyne. Regioselectivity arising from the alkene is difficult to predict. Next, carbon monoxide insertion into the cobaltacycle occurs, followed by reductive elimination to form a carbon-carbon bond. Decomplexation of dicobalthexacarbonyl results in the desired cyclopentenone. This mechanism has been generally accepted, although no intermediates have been successfully detected other than the cobalt-hexacarbonylalkyne complex.

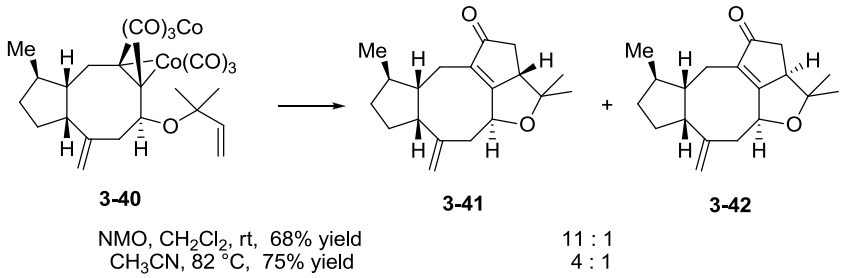
**Figure 3.5.** Tertiary Amine Oxide Promoters for the PKR.




In this mechanism, the rate limiting step was thought to be the initial dissociation of carbon monoxide to open a coordination site for the alkene. Therefore, the use of promoters to facilitate carbon monoxide dissociation have been intensively investigated. For this purpose, the use of tertiary amine N-oxides were discovered simultaneously by Schreiber[29] and Jeong,[30] and have proven to be one of the most popular and effective promoters of the PK reaction. As shown in Figure 3.5, the amine N-oxides are thought to accelerate the reaction by oxidizing one of the carbon monoxide ligands in the interemediate cobalt-enyne complex, releasing carbon dioxide and opening a coordination site for the alkene on one of the cobalt atoms. The amine oxides most commonly used are N-methylmorpholine-N-oxide (NMO), introduced by Schreiber, and trimethylamine N-oxide (TMANO), introduced by Jeong.

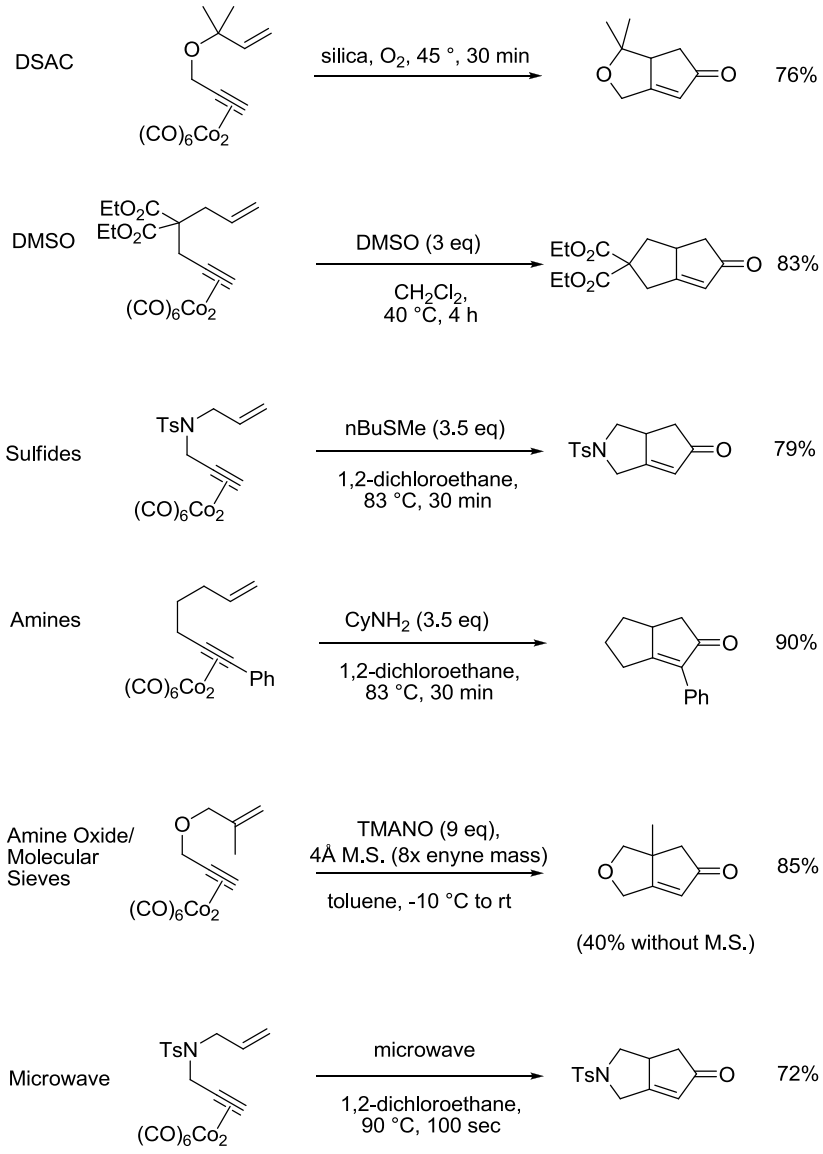
The use of amine oxides has made it possible to perform the PK reaction at room temperature or below, where traditionally elevated temperatures were required. These milder reaction conditions have greatly expanded the synthetic utility of the PKR. Furthermore, lowering the reaction temperature has also been shown to improve the diastereoselectivity of the reaction. As reported by Schreiber and shown in Scheme 3.18 the use of NMO at room temperature to promote the PK reaction of **3-40** improved the diastereoselectivity of the resulting cycloaddition product.[29]

**Scheme 3.18**. Improved Diastereoselectivity Employing NMO as a Promoter for the PKR.




A variety of other promoters have also been explored to accelerate the PK reaction. The first of these to be successful was the use of dry state absorption conditions (DSAC) using silica as reported by Smit and Caple in 1986 (Scheme 3.19). Interestingly, the presence of oxygen was necessary to promote high yields.[31] These conditions allowed a significant reduction in reaction temperature and time and were found to be useful for a variety of substrates containing allyl ethers. It was hypothesized that absorption of the metal onto the silica facilitates ligand exchange, and that hydrogen bonding of the ether oxygen to the solid surface serves to force the hydrophobic portions of the molecule together to promote the reaction.

**Scheme 3.19.** Promoters of the Pauson-Khand Reaction.




The use of sulfur containing compounds has also shown promise as promoters of the PK reaction. Use of 3 equiv of dimethyl sulfoxide (DMSO) was shown to promote the PK reaction with similar results as the amine oxides, though elevated temperatures in $CH_2Cl_2$ and benzene are necessary (Scheme 3.19).[32] Sulfides have also been successfully employed, with less sterically hindered sulfides more efficiently accelerating the reaction. Use of 3.5 equiv of n-butyl methyl sulfide in dichloroethane at elevated temperatures

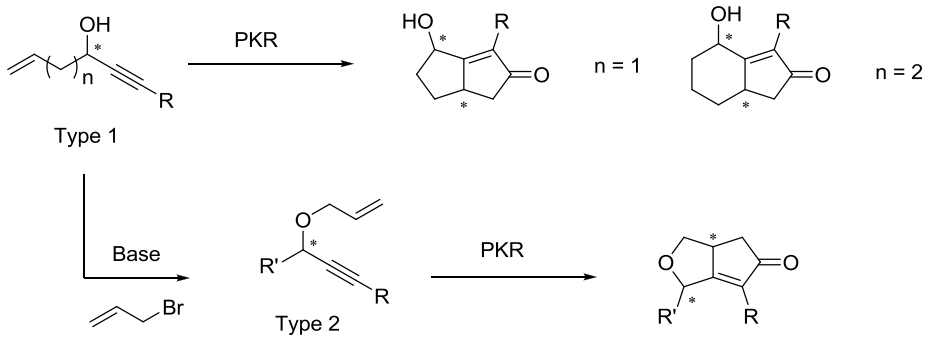
proved to be highly effective for cyclizations of substrates bearing a nitrogen tether.[33] The sulfoxides and sulfides are thought to accelerate the PK reaction through a coordinating effect on the metal displacing one of the CO ligands. More recently, thioureas have been reported to accelerate the Pauson-Khand reaction, with tetramethylthiourea (TMTU) being found to be a particularly effective promoter.[34]

In a similar fashion, amines have been shown to enhance the PK reaction.[35] Use of 3.5 equiv of cyclohexylamine at elevated temperatures has been shown to greatly increase the reaction rate and yields of a variety of enyne substrates. The use of powdered molecular sieves (8 x mass of enyne substrate) has been reported by Pérez-Castells to dramatically improve yields in the TMANO amine oxide promoted PK reaction for difficult substrates such as substituted olefins.[36] The molecular sieves are thought to promote the reaction by retaining CO molecules. In contrast to the addition of promoters, microwave heating is also an effective means of promoting the PK reaction, and has been shown to decrease reaction times to as little as 100 sec.[37]

*b. Intramolecular Pauson-Khand Reaction of Propargylic Alcohol Based Enynes*

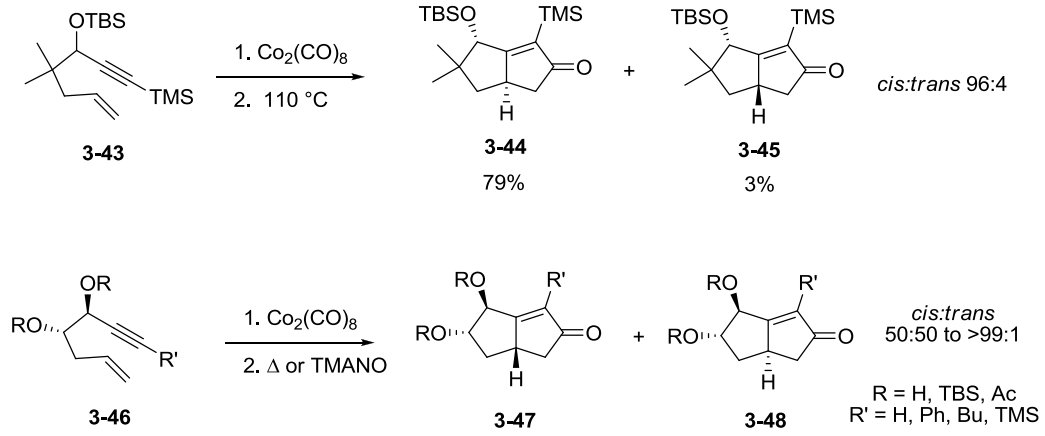
Our asymmetric alkyne addition methodology provided efficient entry into a wide range of optically active enyne precursors similar to the achiral enynes shown in Scheme 3.19. From our method the alkene could be incorporated into the portion of the molecule derived from the aldehyde (Figure 3.6, Type 1) or through derivatization of the alcohol with allyl bromide, the alkene could be incorporated as the allyl ether (Figure 3.6, Type 2). If the propargylic stereocenter was able to efficiently influence the creation of the new chiral center in the intramolecular PK reaction, this methodology could provide efficient access to an array of optically active 5,5- and 6,5-fused bicycles.

**Figure 3.6**. Chiral Enyne Precursors and Diastereoselective Pauson-Khand Reaction.




Evidence for the success of this strategy has been suggested in the literature. Numerous examples of achiral and racemic propargylic alcohol-based enynes and propargyl allyl ethers have been shown to be effective for the intramolecular PK reaction.[38] Furthermore, highly diastereoselective intramolecular PK reactions have also been reported in many instances. For example, as shown in Scheme 3.20 Magnus has reported the intramolecular PK of racemic propargylic alcohol **3-43**, forming diastereomer **3-44** as the major product and demonstrating that high diastereoselectivity can be achieved in the intramolecular PK reaction.[38a] Enantiomerically enriched propargylic alcohols have also often been used successfully.[39] A particularly relevant example was reported by Mukai and Hanaoka. Optically active diol enynes **3-46**, in which the chiral centers were derived from dimethyl L-tartrate through a lengthy reaction pathway, were shown to undergo the intramolecular PK with some substrates demonstrating excellent diastereoselectivity (Scheme 3.21).[39j] In this example and others involving optically active enynes, additional chiral centers were often present to contribute to the stereocontrol of the reaction and to aid in isolation of the resulting optically active diastereomers.

**Scheme 3.20.** Diastereoselective Intramolecular Pauson-Khand Reaction of Propargylic Alcohol Based Enynes.

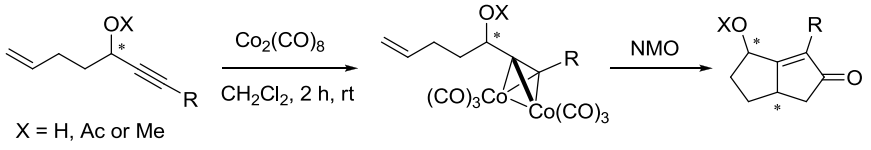



With a wide range of optically active enynes accessible in one or two steps from our asymmetric alkyne addition method and a promising diastereoselective transformation, we set out to explore the intramolecular PK reaction to generate various bicyclic enones. We chose to begin by employing the amine N-oxide promoters since they have proven to be the most effective and popular promoters of the PK reaction, and because they have been demonstrated to improve the diastereoselectivity of the intramolecular cyclization in comparison to thermal reaction conditions.[29] In most cases, we used NMO since this compound is much less expensive and the tertiary amine oxides are used in large excess (Sigma Aldrich, NMO: $2.29/gram, TMANO: $19.68/gram).

We first investigated the intramolecular PK reaction of the propargylic alcohol-based enynes prepared from the asymmetric alkyne addition to 4-pentenal to generate 5,5-fused bicyclic products (Scheme 3.21). The enynes were first treated with $Co_2(CO)_8$ (1.2 equiv) in methylene chloride at room temperature for 2 h to form the cobalt-alkyne complex, followed by the addition of NMO (10 equivalents). The results are summarized

in Table 3.9. Disappointingly, use of the unprotected propargylic alcohol **3-29** was not able to produce the desired product (entry 1). Suspecting that the hydroxyl group may be problematic, we next prepared the acetate-protected enynes through treatment of the alcohols with acetic anhydride in the presence of DMAP. The protected enynes were effective substrates for the PK reaction. As shown in entries 2-4 of Table 3.9, the PK cycloaddition products were obtained from various propargylic acetates. Aryl, alkyl, and linear alkyl substituents on the terminal alkyne all underwent the reaction in good yields (81-94%) and with excellent diastereoselectivity (93:7 to 95:5).

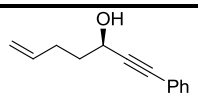
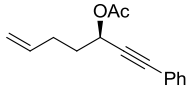
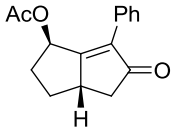
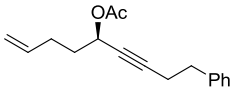
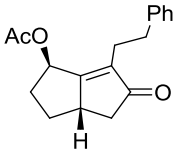
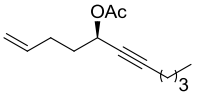
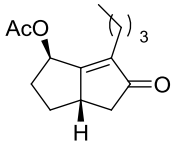
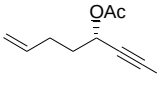
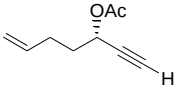
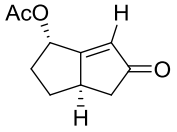
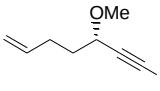
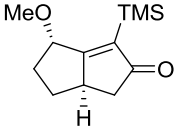
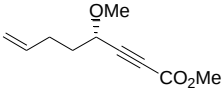
**Scheme 3.21.** Intramolecular PK Reaction of the Enynes Derived from the Asymmetric Alkyne Addition to 4-Pentenal.




When enyne **3-52** containing a terminal trimethylsilyl (TMS) group was used the desired PK reaction product was not obtained (entry 5a). As the TMS group was problematic it was removed by treatment with $K_2CO_3$ in MeOH to yield enyne **3-53**. The terminal alkyne substrate was then tested in the PK reaction leading to the cycloaddition product in good yield (83%) but with significantly reduced diastereoselectivity (75:25, entry 6). As use of the terminal alkyne did not prove to be an effective solution, we returned to the TMS containing enyne substrate.

Since the TMS group was incompatible with the amine oxide conditions, we turned to thermal reaction conditions, heating the preformed cobalt-enyne complex in acetonitrile at 72-75 °C (Method B, Table 3.9). Disappointingly, these conditions led

**Table 3.9.** Results for the Intramolecular PK Reaction to Form the 5,5-Fused Bicyclic Products.

| entry | enyne | | ee | method[a] | product | | yield[b] | dr[c] |
|---|---|---|---|---|---|---|---|---|
| 1 |  | **3-26** | 94 | A | - | | - | - |
| 2 |  | **3-49** | 94 | A |  | **3-56** | 94 | 95:5 |
| 3 |  | **3-50** | 95 | A |  | **3-57** | 81 | 93:7 |
| 4 |  | **3-51** | 89 | A |  | **3-58** | 85 | 95:5 |
| 5 |  | **3-52** | 88 | A<br>B | -<br>- | | -<br>- | -<br>- |
| 6 |  | **3-53** | 88 | A |  | **3-59** | 83 | 75:25 |
| 7 |  | **3-54** | 88 | B |  | **3-60** | 69 | >99:1 |
| 8 |  | **3-55** | 95 | A, B | - | | - | - |

**3-43**

[a]*Method A*: An enyne (0.25 mmol) and $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) were combined in $CH_2Cl_2$ (12.5 mL, 0.02 M) and stirred for 2 h. NMO (293 mg, 2.5 mmol, 10 equiv) was added and the reaction stirred for 3-5 h. *Method B*: An enyne (0.25 mmol) and $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) were combined in $CH_2Cl_2$ (10 mL, 0.025 M) and stirred for 2 h. $CH_2Cl_2$ was removed under vacuum and MeCN (10 mL, 0.025 M) was added. The reaction was heated at 72-75 °C for 24h. [b]Combined yield of diastereomers. [c]Diastereomers observed by $^1$H NMR and dr quantified by HPLC analysis (Chiralpak AD-H column).

largely to decomposition of the starting material and the desired product could not be isolated (entry 5b). In order to minimize the competing decomposition we replaced the acetyl protecting group with the more stable methyl group. Use of this substrate under

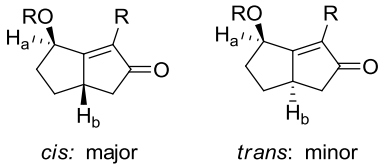
thermal reaction conditions led to the formation of the biscyclopentenoid product in good yield (69%) and with excellent diastereoselectivity (>99:1, entry 7). The enyne prepared from methyl propiolate addition to 4-pentenal also proved to be a difficult substrate. Both Method A and B were ineffective for enyne **3-55**, and no conditions were found that could promote the PK reaction of this substrate (entry 8). Electron deficient alkynes have been historically challenging for the PK reaction.[40]

The diastereoselectivities in Table 3.9 were determined by HPLC analysis with Chiralpak AD-H column. In order to determine the enantiomeric purity of the cycloaddition product we prepared the racemic version of the enyne in entry 2 and found that the enantiomers of **3-56** could be resolved by using HPLC Chiralpak AD-H column. This analysis showed that the enantiomeric purity of the starting enyne in entry 2 was maintained in the product (94% ee). We also found that the diastereoselectivity for the racemic enyne in the PK reaction was the same as that observed for the enantiomerically enriched one. Thus, the intermolecular interaction of the chiral enyne had no effect on the intramolecular cyclization.

The major diastereomer for each substrate shown in Table 3.9 could be easily separated by column chromatography, allowing the isolation of a single stereoisomer for these reactions. The products were determined to be the *cis*-bicyclic compounds (Figure 3.7) by correlation with the known chemical shifts of the related compounds.[41] The NMR signal of $H_a$ was observed to have a more upfield chemical shift in the *cis* isomer than that in the *trans* isomer. All of the products in Table 3.9 manifested this diagnostic chemical shift pattern. For example, for the product in entry 2, $H_a$ in the major *cis* diastereomer resonated at 5.7 ppm while $H_a$ in the minor *trans* diastereomer resonated at

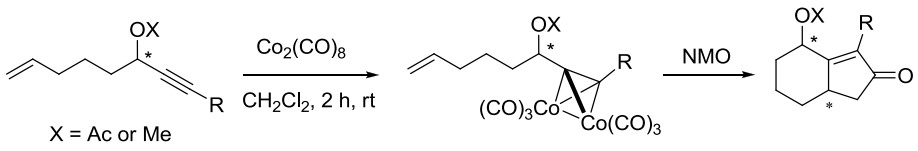
6.4 ppm. The assignment of the stereochemistry in these products is in accord with the well-documented literature precedent for this type of PK transformation.[39j, 42]

**Figure 3.7.** The c*is*- and *trans*-Isomers of the 5.5.-Fused Bicyclic Products.




We also studied the intramolecular PK reaction of the chiral propargylic alcohol-based enynes prepared from the asymmetric alkyne addition to 5-hexenal to generate 6,5-fused bicyclic products (Scheme 3.22). The results are summarized in Table 3.10. Surprisingly, when the acetate of the propargylic alcohol-based enyne was used, only a very small amount of the cycloaddition product was obtained (entry 1). Furthermore, significant amounts of decomposition were observed. As the corresponding 5,5-bicyclic product was easily formed under these reaction conditions we suspected that a competition existed between decomposition of the propargylic acetate and the desired cycloaddition. Since the 5,5-bicyclic products could be formed, cyclization to form the 5-membered ring is likely faster than cyclization to form the 6-membered ring, thus resulting in a different outcome of the reaction.

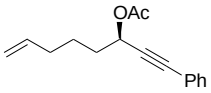
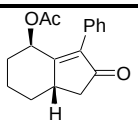
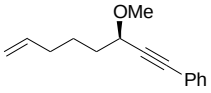
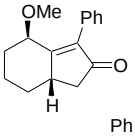
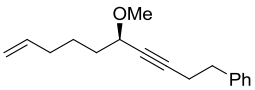
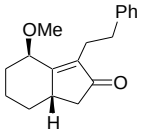
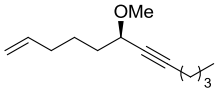
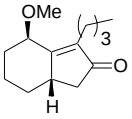
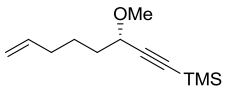
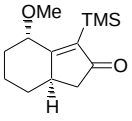
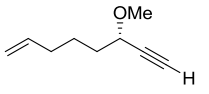
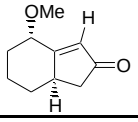
**Scheme 3.22.** Intramolecular PK Reaction of the Enynes Derived from the Asymmetric Alkyne Addition to 5-Hexenal.



As we had found that use of a methyl protecting group slowed down the decomposition of the TMS proparygylic alcohol based enyne and allowed the desired cyclization to occur, we again replaced the acetyl protecting group with a more stable methyl group. Pleasingly, these substrates proved to be effective for the PK reaction. Under the normal reaction conditions (Method A) the cyclization proceeded smoothly to give the desired 6,5-bicyclic products in good yield (77-93%) and with excellent diastereoselectivity (92:8 to 95:5 entry 2-4). These results are similar to the diastereoselectivity and chemical yield obtained with the 5,5-bicyclic products. Thus while formation of the 6-membered ring is slower than formation of the 5-membered ring, when the substrate is stable under the reaction conditions the cycloaddition to form the 6,5-bicycle proceeds with similar levels of efficiency and diastereocontrol.

The enyne prepared from trimethylsilylacetylene again proved to be a challenging substrate. Applying the thermal reaction conditions (Method B) yielded the desired cycloaddition product with high diastereoselectivity (94:6) but in low yield (47%, entry 5). As the amine oxide conditions where incompatible with the trimethylsilyl group, we turned to a variety of other promoters shown to be effective for the intramolecular PKR. Use of n-butyl methyl sulfide (15.15 equiv) to promote the cycloaddition in 1,4-dioxane under an elevated reaction temperature of 100 $^{o}$C (Method C)[43] gave an increased yield (56%), and maintained the same high diastereoselectivity (entry 6). When tetramethylthiourea (TMTU, 4 equiv) was used as the promoter under refluxing toluene (Method D),[44] the product was obtained in better yield (81%), but with a reduction in diastereoselectivity (87:13 entry 7).

**Table 3.10.** Results for the Intramolecular PK Reactions to Form the 6,5-Fused Bicyclic Products.

| entry | enyne | | ee | method[a] | product | | yield[b] | dr[c] |
|---|---|---|---|---|---|---|---|---|
| 1 |  | **3-61** | 93 | A |  | **3-67** | Very low | - |
| 2 |  | **3-62** | 93 | A |  | **3-68** | 93 | 92:8 |
| 3 |  | **3-63** | 90 | A |  | **3-69** | 77 | 93:7 |
| 4 |  | **3-64** | 83 | A |  | **3-70** | 79 | 95:5 |
| 5 | | | | B | | | 47 | 94:6 |
| 6 |  | **3-65** | 91 | C |  | **3-71** | 56 | 94:6 |
| 7 | | | | D | | | 81 | 87:13 |
| 8 |  | **3-66** | 91 | A |  | **3-72** | 61 | 84:16 |

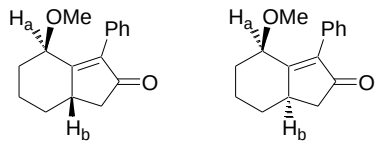
[a]*Method A, B*: See Table 3. *Method C*: An enyne (0.25 mmol) and $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) were combined in $CH_2Cl_2$ (5 mL, 0.05 M) and stirred for 2 h. $CH_2Cl_2$ was removed under vacuum and 1,4-dioxane (5 mL, 0.05 M) and n-butyl methyl sulfide (465 μL, 3.79 mmol, 15.15 equiv) were added. The reaction was heated at 100 °C for 16 h. *Method D*: An enyne (0.25 mmol) and $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) were combined in toluene (5 mL, 0.05 M) and stirred for 2 h. TMTU (132 mg, 1 mmol, 4 equiv) was added and the reaction was heated at 112 °C for 16h. [b]Combined yield of diastereomers. [c]Diastereomers observed by $^1$H NMR and dr quantified by HPLC analysis (Chiralpak AD-H or Chiralcel OD column).

We also tested terminal enyne **3-66**. Similar to our previous observation, the substrate bearing the terminal alkyne underwent the PK reaction in the presence of NMO with much lower diastereoselectivity than the other substrates (84:16, entry 8). Therefore the stereochemistry of the cycloaddition is sensitive to the size of the substituent on the alkyne, with larger substituents providing increased diastereocontrol. Since the smaller

hydrogen atom consistently results in lower diastereoselectivity larger substituents on the alkyne are desirable to achieve high diastereoselectivity.

In accord with literature precedence,[42] the *cis*-structure was assigned to the major diastereomer of the 6,5-fused bicyclic products (Figure 3.6). This assignment is supported by the NOESY spectra of **3-68** in entry 2 of Table 3.10. Both the major and minor diastereomers of **3-68** were isolated. The NOESY spectrum of the minor diastereomer indicates an NOE effect between $H_a$ and $H_b$ (Figure 3.8) which is absent in the major diastereomer. Thus, the minor diastereomer is the *trans* isomer and the major diastereomer is the *cis* isomer. The enantiomeric purity of the propargylic alcohol starting material was found to be maintained in the 6,5-fused bicyclic product by analyzing the racemic and chiral product of **3-68** with HPLC-Chiralpak AD-H column.

**Figure 3.8**. The c*is*-and *trans*-Isomers of the 6,5-Fused Bicyclic Products.

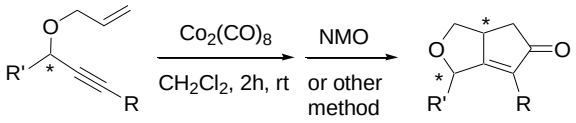



*cis:* major *trans:* minor

We next examined the PK reaction of the chiral enynes derived from the propargyl allyl ethers to generate fused 5,5-bicycles containing an oxygen heteroatom (Scheme 3.23). The results are summarized in Table 3.11. As we observed previously, NMO proved to be an effective promoter except in the case of the trimethysilyl containing enyne. We first tested enyne **3-73**, prepared from a linear aldehyde, finding that the diastereoselectivity was slightly lower than expected (87:13, entry 1). Hypothesizing that the size of the propargylic substituent was important for high diastereoselectivity we prepared enyne **3-74** containing the bulkier cyclohexyl group at

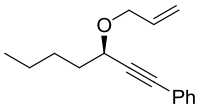
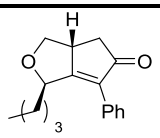
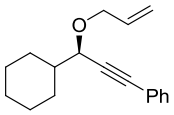
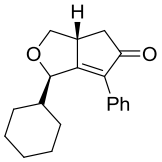
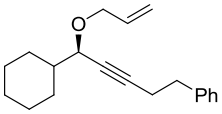
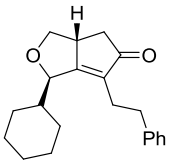
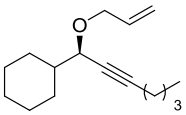
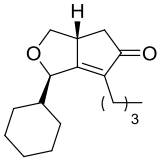
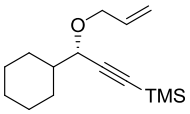
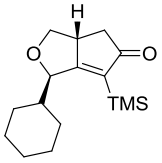
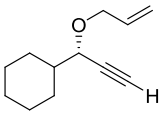
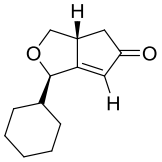
the propargylic position. As we hoped, use of this substrate resulted in greatly enhanced diastereoselectivity (>99:1, entry 2), demonstrating that steric bulk at the propargylic position was beneficial for high selectivity. Testing other enynes prepared from the addition of alkyl alkynes to cyclohexanecarboxaldehyde resulted in consistently high diastereoselectivity, with only one diastereomer observed in the cycloaddition product (entries 3 and 4).

**Scheme 3.23.** Intramolecular PK Reaction of Chiral Propargylic Allylic Ethers.




For enyne **3-77** prepared from trimethylsilylacetylene, three methods were tested to promote the cycloaddition. As shown in entries 5 – 7, all three methods gave high diastereoselectivity. Using NMO as the promoter (Method A, entry 5) and heating in acetonitrile (Method B, entry 6) provided the product in low yield. Use of TMANO as the promoter in the presence of air and molecular sieves[45] (Method E, entry 7) was able to improve the yield up to 50%. As expected hydrogen substituted alkyne **3-78** gave much lower diastereoselectivity (65:35, entry 8) than those bearing an alkyl, aryl or trimethylsilyl substituent. Thus for the enynes derived from propargyl allyl ethers, the sizes of the alkyne substituent and the propargylic substituent control the diastereoselectivity. The enantiomeric purity of the propargylic alcohol was found to be maintained in the cycloaddition product by analyzing product **3-80** in entry 2 and the corresponding racemate with HPLC-Chiralcel OD column.

**Table 3.11.** Results for the Intramolecular PK Reactions of Chiral Propargylic Allylic Ethers.

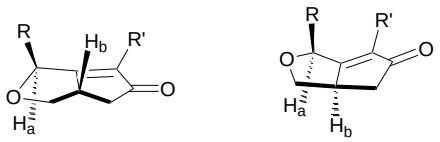
| entry | enyne | | ee | method[a] | product | | yield[b] | dr[c] |
|---|---|---|---|---|---|---|---|---|
| 1 |  | **3-73** | 95 | A |  | **3-79** | 82 | 87:13 |
| 2 |  | **3-74** | 96 | A |  | **3-80** | 83 | >99:1 |
| 3 |  | **3-75** | 84 | A |  | **3-81** | 66 | >99:1 |
| 4 |  | **3-76** | 81 | A |  | **3-82** | 64 | >99:1 |
| 5 | | | | A | | | 33 | >99:1 |
| 6 |  | **3-77** | 88 | B |  | **3-83** | 31 | >99:1 |
| 7 | | | | E | | | 50 | >99:1 |
| 8 |  | **3-78** | 88 | A |  | **3-84** | 55 | 65:35 |

[a]*Method A, B*: See Table 3. *Method E:* An enyne (0.2 mmol, 1 equiv), $Co_2(CO)_8$ (78.7 mg, 0.23 mmol, 1.15 equiv), and 4-Å MS (8 wt. equiv) were combined in $CH_2Cl_2$ (5 mL, 0.04 M) and stirred for 2 h. The reaction mixture was cooled to -20 °C and TMANO (120.2 mg, 1.6 mmol, 8 equiv) was added over 10 min. After bubbling the reaction mixture with compressed air (passed through a drying filter) for 20 minutes the reaction was warmed to rt and stirred 16h. [b]Combined yield of diastereomers. [c]Diastereomers observed by $^1$H NMR and dr quantified by chiral HPLC analysis (Chiralpak AD-H and Chiralcel OD column).

As in the previous cyclizations, the *cis* diastereomer is expected to be the major product.[46] Analyses of the major and minor diastereomers of product **3-79** in entry 1 by NOESY spectroscopy support this structural assignment. A NOE effect is observed between $H_a$ and $H_b$ in the minor diastereomer but not in the major diastereomer (Figure

3.9). Therefore, the minor diastereomer is assigned to be the *trans* isomer and the major diastereomer the *cis* isomer. Notably, formation of the related *trans* isomer as the major product was recently reported via a PK-type reaction in the presence of a $PdCl_2$-thiourea catalyst.[44] This method, in combination with our work, should provide access to all four possible stereoisomers of the products with high optical purity.

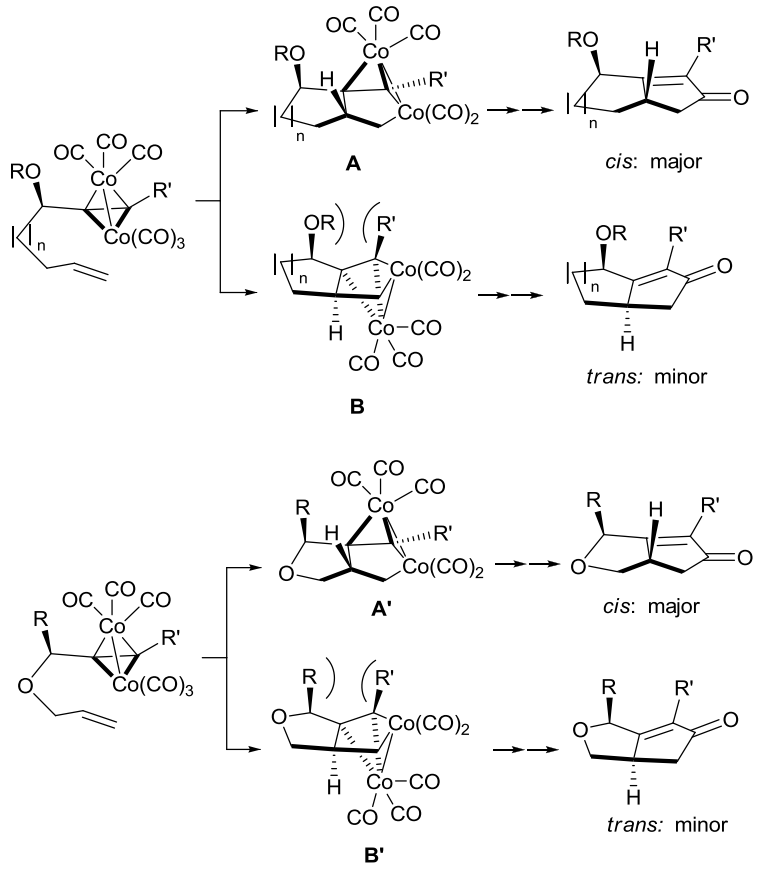
**Figure 3.9.** The *cis* and *trans* Isomers of the 5,5-Fused Bicyclic Products from the Propargyl Allyl Ethers.




*cis:* major *trans:* minor

Magnus[38a] and others[39j,42j] have proposed a mechanistic explanation for the formation of the *cis*-isomer in the intramolecular PKR of enynes analogous to those we have studied. According to the proposed mechanism, the stereo discriminating step occurs during the formation of the cobalt-metallacycles (Figure 3.8). It was suggested that only two metallacycles **A** and **B** could be possible due to the preference for the formation of the *cis*-fused bicyclic systems. As shown in Figure 3.8, the formation of metallacycle **B** is less favorable because of 1,3-pseudoaxial steric interactions between the OR and R' groups. These interactions are not present in metallacycle **A**, causing this intermediate to be favored and leading to the *cis*-fused product as the major diastereomer. This mechanistic explanation can be extended to the PKR of the propargyl allyl ethers as shown in the more favorable intermediate metallacycle **A'** and the less favorable metallacycle **B'**.

**Figure 3.10.** Proposed Mechanism for the Diastereoselective Intramolecular PKR.




*c. Summary*

In summary, we have compiled a highly effective toolbox of catalytic methods for the addition of structurally diverse alkynes bearing aryl, alkyl, linear alkyl, silyl, and ester substituents to aliphatic aldehydes. During the construction of this toolbox, we uncovered the challenging addition of linear alkyl alkynes to linear aliphatic aldehydes and discovered that $Cy_2NH$ was the optimal Lewis basic additive for these substrates with the BINOL/$ZnEt_2$/Ti($O^iPr$)$_4$ catalyst system. This toolbox of methods emphasizes the remarkable substrate scope compatible with the BINOL catalytic systems.

We have also demonstrated that the use of the catalytic asymmetric alkyne addition methodology developed in our laboratory can provide rapid access to a variety of chiral

propargylic alcohol-based enyne precursors with high enantiomeric purity for the PK reaction. Protection of the propargylic alcohols with either an acetyl or a methyl group allows for the resulting enynes to undergo an intramolecular PK reaction to form the corresponding optically active 5,5- or 5,6-fused bicyclic products with high diastereoselectivity. In the major product, the propargylic substituent and the bridge head hydrogen are *cis* with respect to each other on the fused bicyclic rings. The high enantiomeric purity of the propargylic alcohols is maintained in the PK cycloaddition products. The chiral propargyl allyl ethers are also found to undergo highly diastereoselective PK cycloaddition with retention of enantiomeric purity. Thus, the chiral information in these enyne precursors is efficiently transferred to the fused bicyclic products. These findings expand the utility of chiral propargylic alcohols as precursors for diastereoselective transformation.

**3.4. Experimental and Characterization.**

*a. General Data and Instruments*

All $^{1}H$ and $^{13}C$ NMR spectra were obtained using a Varian 300 MHz or 500 MHz spectrometer. HPLC analyses were carried out with a Waters 600 Pump and Waters 996 Photodiode Array Detector using a Chiralcel OD, Chiralcel OB-H or Chiralpak AD-H column. Optical rotation values were measured with the Jasco Digital Polarimeter P-2000.

All reactions were carried out under nitrogen unless otherwise noted. All chemicals were purchased from Sigma Aldrich Chemical Co. or Alfa Aesar with the exception of the Diethylzinc (95%) which was purchased from Strem Chemicals, Inc. Dicobalt octacarbonyl was purchased from Alfa Aesar and stored at 0 °C under inert atmosphere. 4-methylmorpholine N-oxide was purchased from Sigma Aldrich and used as received. Toluene, THF, and 1,4-dioxane were distilled over sodium and benzophenone under nitrogen atmosphere. Methylene chloride and diethyl ether were dried by passing through activated alumina columns under nitrogen. Solvents were stored over 4 Å molecular sieves. All alkynes and aldehydes were passed through a plug of alumina and distilled from 4 Å molecular sieves prior to use and stored under nitrogen atmosphere. High resolution mass spectra were obtained from the University of California, Riverside (UCR) Mass Spectrometry Facility and the University of Illinois (at Urbana-Champaign) Mass Spectrometry Laboratory. The samples were analyzed by ESI and the $[MH^{+}]$ was observed.

*b. General Asymmetric Alkyne Addition Procedures*

*Method I: Aryl and Alkyl Alkynes*

Under nitrogen, toluene (1 mL), alkyne (phenylacetylene or 4-phenyl-1-butyne, 2 mmol, 4 equiv), and $ZnEt_2$ (205 μL, 2 mmol, 4 equiv) were combined in a 25 mL flame dried flask. The flask was mounted with a flame dried reflux condenser fitted with a stopcock vacuum/nitrogen adaptor. The reaction mixture was then heated at reflux (oil bath 120-130 °C) for 4 h during which a gray precipitates formed. After cooled to rt, (*S*)-BINOL (>99% ee, 57.2 mg, 0.2 mmol, 40 mol %), $Et_2O$ (8 mL), and $Ti(O^iPr)_4$ (150 μL, 0.5 mmol, 1 equiv) were added and the resulting dark orange solution was stirred for 1 h. An aldehyde (0.5 mmol) was then added. After consumption of the aldehyde (typically 2 h, monitored by TLC or crude $^1H$ NMR) the reaction was quenched with saturated aqueous ammonium chloride (5 mL). The reaction mixture was extracted three times with $CH_2Cl_2$ and the organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel, eluted with hexanes/ethyl acetate (0-15% ethyl acetate) to give the product in 83-95% yield and 85-96% ee.

*Method II: Linear Alkyl Alkynes*

Under nitrogen, (*S*)-BINOL (57.2 mg, 0.2 mmol, 40 mol %), dicyclohexylamine (5 μL, 0.025 mmol, 0.05 equiv), 1-hexyne (230 μL, 2 mmol, 4 equiv), and $ZnEt_2$ (205 μL, 2 mmol, 4 equiv) were combined in $Et_2O$ (6 mL) in a 10 mL flame-dried flask and stirred at room temperature for 24 h. $Ti(O^iPr)_4$ (150 μL, 0.5 mmol, 1 equiv) was then added and the reaction mixture was stirred for 2 h. To the resulting dark orange solution, an aldehyde was added and the reaction was monitored by TLC or crude NMR. Upon

consumption of the aldehdye (approximately 18 h), the reaction was quenched with saturated aqueous ammonium chloride (5 mL). The reaction mixture was extracted three times with $CH_2Cl_2$ and the organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography eluted with hexanes/ethyl acetate (0-10% ethyl acetate) to give the product as an oil in 73-83% yield and 81-89% ee.

*Method III: Trialkylsilyl Alkynes (See Chapter 2 for Alkyl Propiolates)*

Under nitrogen atmosphere, (*S*)-**2-49** (61.9 mg, 0.1 mmol, 20 mol %) was dissolved in $Et_2O$ (1 mL) in a 10 mL flame dried flask. $ZnEt_2$ (103 μL, 1 mmol, 2 equiv) and trimethylsilylacetylene (141 μL, 1 mmol, 2 equiv) were added sequentially and the mixture was stirred for 16 hours at room temperature, yielding a light tan solid. After venting the reaction flask (build-up of ethane gas), the solid was dissolved in THF (5 mL). $Ti(O^iPr)_4$ (74 μL, 0.25 mmol, 50 mol %) was then added and the reaction mixture was stirred for 1 h. To the resulting dark orange solution, an aldehyde was added and the reaction was monitored by TLC or crude NMR. Upon consumption of the aldehdye (typically 2 hours), the reaction was quenched with saturated aqueous ammonium choride (5 mL). The reaction mixture was extracted three times with $CH_2Cl_2$ and the organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash chromatography on silica gel. First eluting with 2:1 $CH_2Cl_2$:hexanes cleanly separates the ligand from the product. After removal of the ligand, the column was eluted with hexanes/ethyl acetate (5-10% ethyl acetate) to give the product as an oil in 79-90% yield and 88-91% ee.

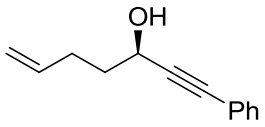
*c. Preparation of Racemic Propargylic Alcohols for HPLC Analysis*

Under nitrogen atmosphere in 10 mL flame dried flask, an alkyne (2 mmol, 2 equiv) in THF (5 mL) was cooled to -78 °C. nBuLi (2 mmol, 2equiv) was added and the mixture was stirred for 30 minutes. An aldehyde was then added. After 30 minutes the reaction was quenched with saturated aqueous ammonium choride (5 mL). The reaction mixture was extracted three times with $CH_2Cl_2$ and the organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate (0-15% ethyl acetate).

*d. Preparation of Mandelic Ester Derivatives for Determination of ee*

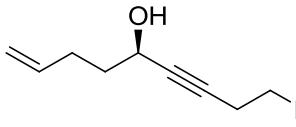
The propargylic alcohol (20 mg), DCC (2 equiv), DMAP (2 equiv), and (*R*)-O-acetylmandelic acid (2 equiv) were dissolved in $CH_2Cl_2$ (5 mL). The reaction was monitored by TLC. After consumption of the starting material (30 min to 1 h), the crude mixture was passed through a short silica gel column eluted with 30% EtOAc/hexanes. The ee determination was based on the integration of the proton signals at δ~5.9 ppm in the $^1$H NMR spectrum.

*e. Characterization of Optically Active Propargylic Alcohols*

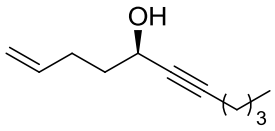



**(R)-1-phenylhept-6-en-1-yn-3-ol, 3-26.** 88% yield. 94% ee determined by HPLC analysis: Chiralcel OD column, 90:10 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: $t_{major}$ = 8.5, $t_{minor}$ = 22.7. $[\alpha]_D^{25}$ = -3.5 (c = 1.19, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.32 (m, 3H), 5.86 (m, 1H), 5.09

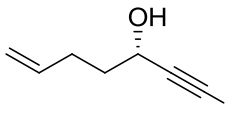
(m, 2H), 4.64 (q, 1H, J = 6.0 Hz), 2.32 (q, 2H, J = 6 Hz), 1.92 (m, 3H). These data are consistent with those reported.[4]



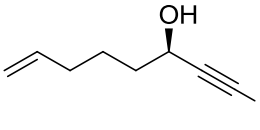

**(R)-9-phenylnon-1-en-6-yn-5-ol, 3-27.** 95% yield. 95% ee determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 65.8, $t_{minor}$ = 61.7. $[\alpha]_D^{25}$ = -4.8 (c = 0.87, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.25 (m, 5H), 5.82 (m, 1H), 5.02 (m, 2H), 4.36 (m, 1H), 2.83 (t, 2H, J = 9.0 Hz), 2.52 (td, 2H, J = 9.0, 3.0 Hz), 2.18 (q, 2H, J = 9.0 Hz), 1.75 (m, 2H), 1.67 (d, 1H, J = 9.0 Hz). These data are consistent with those reported.[4]



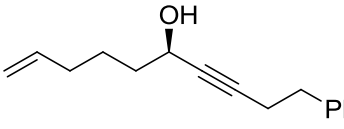

**(R)-undec-1-en-6-yn-5-ol, 3-28.** 73% yield. 89% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = -9.0 (c = 0.76, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.84 (m, 1H), 5.03 (m, 2H), 4.38 (m, 1H), 2.22 (m, 4H), 1.75 (m, 3H), 1.45 (m, 4H), 0.91 (t, 3H, J = 6.0 Hz). These data are consistent with those reported.[25]



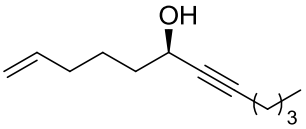

**(S)-1-(trimethylsilyl)hept-6-en-1-yn-3-ol, 3-29.** 90% yield. 88% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = 10.3 (c = 1.21, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.84 (m, 1H), 5.04 (m, 2H), 4.39 (q, 1H, J = 9.0 Hz), 2.24 (q, 2H, J = 6.0 Hz), 1.80 (m, 3H), 0.17 (s, 9H). These data are consistent with those reported.[4]



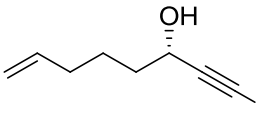

**(R)-1-phenyloct-7-en-1-yn-3-ol, 3-31.** 87% yield. 93% ee determined by HPLC analysis: Chiralcel OD column, 90:10 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 7.6, $t_{minor}$ = 24.4. $[\alpha]_D^{25}$ = -7.0 (c = 0.35, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.43 (m, 2H), 7.31 (m, 3H), 5.84 (m, 1H), 5.00 (m, 2H), 4.61 (q, 1H, J = 6.0 Hz), 2.14 (q, 2H, J = 6.0 Hz), 1.82 (m, 3H), 1.64 (m, 2H). These data are consistent with those reported.[4]



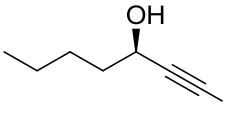

**(R)-1-phenyldec-9-en-3-yn-5-ol, 3-32.** 83% yield. 90% ee determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 62.6, $t_{minor}$ = 58.4. $[\alpha]_D^{25}$ = 2.7 (c =1.17, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.26 (m, 5H), 5.80 (m, 1H), 5.00 (m, 2H), 4.44 (q, 1H, J = 6.0 Hz), 2.82 (t, 2H, J = 9.0 Hz), 2.51 (td, 2H, J = 9.0, 3.0 Hz), 2.08 (q, 2H, J = 6.0 Hz), 1.66 (m, 3H), 1.51 (m, 2H). These data are consistent with those reported.[4]



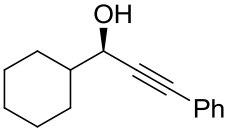

**(R)-dodec-1-en-7-yn-6-ol, 3-33.** 83% yield. 83% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = 6.4 (c = 0.79, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.81 (m, 1H), 5.00 (m, 2H), 4.36 (q, 1H, J = 6.0 Hz), 2.21 (td, 2H, J = 6.0, 3.0 Hz), 2.10 (q, 2H, J = 6.0 Hz), 1.71-1.64 (m, 3H), 1.57-1.38 (m, 6H), 0.91 (t, 3H, J = 6.0 Hz). These data are consistent with those reported.[25]



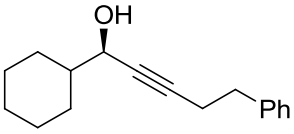

**(S)-1-(trimethylsilyl)oct-7-en-1-yn-3-ol, 3-34.** 91% yield. 91% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = -1.3 (c = 1.19, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.81 (m, 1H), 4.99 (m, 2H), 4.37 (q, 1H, J = 6.0 Hz), 2.10 (q, 2H, J = 6.0 Hz), 1.71 (m, 3H), 1.58 (m, 2H), 0.17 (s, 9H). These data are consistent with those reported.[4]



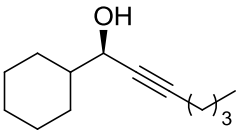

**(R)-1-phenylhept-1-yn-3-ol, 3-35.** 89% yield. 95% ee determined by HPLC analysis: Chiralcel OD column, 90:10 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 7.0, $t_{minor}$ = 17.8. $[\alpha]_D^{25}$ = -1.4 (c = 1.50, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.44 (m, 2H), 7.29 (m, 3H), 4.60 (q, 1H, J = 6.0 Hz), 2.02 (bs, 1H), 1.81 (m, 2H), 1.50 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H, J = 6.0 Hz). These data are consistent with those reported.[4]



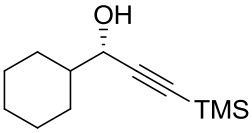

**(R)-1-cyclohexyl-3-phenylprop-2-yn-1-ol, 3-36.** 88% yield. 96% ee determined by HPLC analysis: Chiralcel OD column, 90:10 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 7.1, $t_{minor}$ = 14.6. $[\alpha]_D^{25}$ = -10.8 (c = 0.64, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.44 (m, 2H), 7.31 (m, 3H), 4.38 (t, 1H, J = 6.0 Hz), 1.88 (m, 2H), 1.80 (m, 3H), 1.70 (m, 2H), 1.23 (m, 5H). These data are consistent with those reported.[4]




**(R)-1-cyclohexyl-5-phenylpent-2-yn-1-ol, 3-37.** 94% yield. 84% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = -0.7 (c = 1.07, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 4.10 (m, 1H), 2.83 (t, 2H, J = 9.0 Hz), 2.53 (td, 2H, J = 9.0, 3.0 Hz), 1.71 (m, 4H), 1.60 (d, 1H, J = 3.0 Hz), 1.46 (m, 1H), 1.13 (m, 6H). These data are consistent with those reported.[4]




**(R)-1-cyclohexylhept-2-yn-1-ol, 3-38.** 84% yield. 81% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = -5.8 (c = 0.79, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 4.13 (m, 1H), 2.22 (t, 2H, J = 6.0 Hz), 1.83 (m, 4H), 1.63 (d, 1H, J = 6.0 Hz), 1.40 (m, 5H), 1.18 (m, 6H), 0.91 (t, 3H, J = 6.0 Hz). These data are consistent with those reported.[47]




**(S)-1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-ol, 3-39.** 88% yield. 88% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = 6.0 (c = 1.15, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 4.13 (t, 1H, J = 6.0 Hz), 1.82 (m, 4H), 1.70 (d, 1H, J = 6.0 Hz), 1.53 (m, 1H), 1.15 (m, 6H), 0.17 (s, 9H). These data are consistent with those reported.[4]

*f. General Procedures for Protection and Derivation of Optically Active Propargylic Alcohols*

*i. Acetate Protection of Propargylic Alcohols*

Under nitrogen in a 10 mL flame-dried flask, a propargylic alcohol (~0.4 mmol, 1 equiv), DMAP (0.1 equiv), and acetic anhydride (2 equiv) were combined in $CH_2Cl_2$ (5 mL). After consumption of the starting material (30 min), the reaction mixture was directly loaded onto a short silica gel column and purified by flash chromatography eluted with hexanes/ethyl acetate (0-5% ethyl acetate) to yield the product in 97-99% yield.

*ii. Methyl Protection of Propargylic Alcohols*

*Method a:*

Under nitrogen in a 10 mL flask, a propargylic alcohol (0.4 mmol) and methyl iodide (75 μL, 1.2 mmol, 3 equiv) were dissolved in DMSO (4 mL). KOH pellets (45 mg, 0.8 mmol, 2 equiv) were ground up and added to the flask. After 1.5 hours the reaction mixture was directly loaded onto a short silica gel column and purified by flash chromatography eluted with hexanes/ethyl acetate (0-5% ethyl acetate) to yield the product in 83-87% yield.

*Method b:*[48]

Due to the incompatibility of the TMS group with the strongly basic conditions of Method a, Method b was employed for all substrates containing the TMS group. Under nitrogen in a 10 mL flask, a propargylic alcohol (0.4 mmol) was dissolved in THF (2 mL) and cooled to -78 °C. $^{n}$BuLi (0.4 mmol, 1 equiv) was added and the mixture was stirred for 10 min. Methyl iodide (200 μL, 3.2 mmol, 8 equiv) was then added. The reaction

flask was warmed to -40 °C and DMSO (57 μL, 0.8 mmol, 2 equiv) was added resulting in white precipitates. The reaction flask was allowed to warm to room temperature over night. Upon consumption of the starting material, the reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL), extracted three times with $CH_2Cl_2$, dried with sodium sulfate, and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (0-5% ethyl acetate) to give the product in 90-98% yield.

*iii. Allyl Protection of Propargylic Alcohols*

*Method a:*

Under nitrogen, in a 10 mL flask, a propargylic alcohol (0.4 mmol) and allyl bromide (104 μL, 1.2 mmol, 3 equiv) were dissolved in DMSO (4 mL). KOH pellets (45 mg, 0.8 mmol, 2 equiv) were ground up and added to the flask. After 1.5 h the reaction mixture was directly loaded onto a short silica gel column and purified by flash chromatography eluted with hexanes/ethyl acetate (0-5% ethyl acetate) to yield the product in 57-73% yield.

*Method b:*[48]

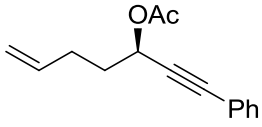
Due to the incompatibility of the TMS group with the strongly basic conditions of Method a, Method b was employed for substrates containing the TMS group. Under nitrogen in a 10 mL flask, a propargylic alcohol (0.4 mmol) was dissolved in THF (2 mL) and cooled to -78 °C. $^{n}$BuLi (0.4 mmol, 1 equiv) was added and the mixture was stirred for 10 min. Allyl bromide (277 μL, 3.2 mmol, 8 equiv) was then added. The reaction flask was warmed to -40 °C and DMSO (57 μL, 0.8 mmol, 2 equiv) was added resulting in white precipitates. The reaction flask was allowed to warm to room temperature over

night. Upon consumption of the starting material, the reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL), extracted three times with $CH_2Cl_2$, dried with sodium sulfate, and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (0-5% ethyl acetate) to give the product in 73% yield.

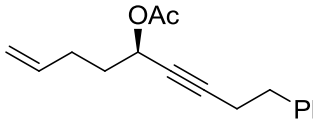
*iv. Removal of Acetylene TMS Group*

The TMS group was removed under basic conditions. **3-52** and **3-66** were prepared from **3-53** and **3-65** respectively. The TMS propargylic alcohol precursor (0.4 mmol) was dissolved in MeOH (8 mL) and $K_2CO_3$ (1.2 mmol, 3 equiv) was added. The reaction mixture was stirred for 2 h and then purified by a short silica gel column eluted with hexanes/ethyl acetate (0-10% ethyl acetate) to give the product in 80-94% yield. *Note: Due to the volatility of **3-66** the rotovap water bath was kept below 25* °C *during concentration of the product.*

*g. Characterization of Enyne Precursors for the PK Reaction*

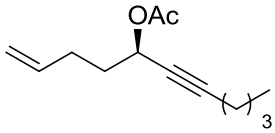



**(R)-1-phenylhept-6-en-1-yn-3-yl acetate, 3-49.** 99% yield. $[\alpha]_D^{25}$ = 115.0 (c = 0.42, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.31 (m, 3H), 5.85 (m, 1H), 5.62 (t, 1H, J = 6.0 Hz), 5.06 (m, 2H), 2.28 (q, 2H, J = 9.0 Hz), 2.12 (s, 3H), 1.96 (m, 2H).

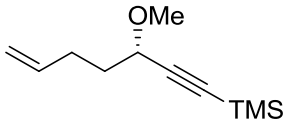



**(R)-9-phenylnon-1-en-6-yn-5-yl acetate, 3-50.** 97% yield. $[\alpha]_D^{25}$ = 74.8 (c = 1.01, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.79 (m,

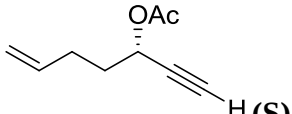
1H), 5.34 (tt, 1H, J = 6.0, 3.0 Hz), 5.01(m, 2H), 2.82 (t, 2H, J = 9.0 Hz), 2.51 (td, 2H, J = 9.0, 3.0 Hz), 2.12 (q, 2H, J = 6.0 Hz), 2.07 (s, 3H), 1.80 (m, 2H).



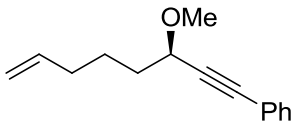

**(R)-undec-1-en-6-yn-5-yl acetate, 3-51.** 98% yield. $[\alpha]_D^{25}$ = 84.8 (c = 0.76, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.36 (tt, 1H, J = 6.0, 3.0 Hz), 5.03 (m, 2H), 2.21 (m, 4H), 2.07 (s, 3H), 1.83 (m, 2H), 1.43 (m, 4H), 0.90 (t, 3H, J = 6.0 Hz).




**(S)-(3-methoxyhept-6-en-1-ynyl)trimethylsilane, 3-53.** 96% yield. $[\alpha]_D^{25}$ = -46.0 (c = 1.01, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.02 (m, 2H), 3.94 (t, 1H, J = 6.0 Hz), 3.40 (s, 3H), 2.21 (q, 2H, J = 6.0 Hz), 1.78 (m, 2H), 0.18 (s, 9H).

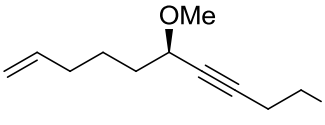



**(S)-hept-6-en-1-yn-3-yl acetate, 3-52.** 85% yield over 2 steps. $[\alpha]_D^{25}$ = -68.9 (c = 1.07, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.36 (td, 1H, J = 6.0, 3.0 Hz), 5.04 (m, 2H), 2.47 (d, 1H, J = 3.0 Hz), 2.22 (q, 2H, J = 9.0 Hz), 2.09 (s, 3H), 1.88 (m, 2H).

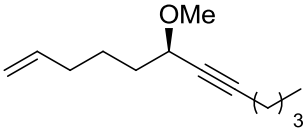



**(R)-(3-methoxyoct-7-en-1-ynyl)benzene, 3-62.** 83% yield. $[\alpha]_D^{25}$ = 61.0 (c = 1.49, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.29 (m,

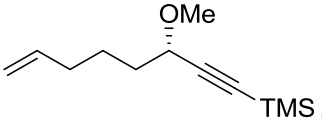
3H), 5.83 (m, 1H), 5.01 (m, 2H), 4.18 (t, 1H, J = 6.0 Hz), 3.47 (s, 3H), 2.12 (q, 2H, J = 6.0 Hz), 1.82 (m, 2H), 1.64 (m, 2H).



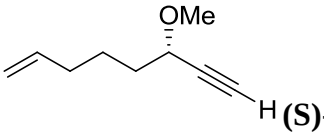

**(R)-(5-methoxydec-9-en-3-ynyl)benzene, 3-63.** 87% yield. $[\alpha]_D^{25}$ = 40.6 (c = 0.95, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.80 (m, 1H), 4.99 (m, 2H), 3.90 (t, 1H, J = 6.0 Hz), 3.33 (s, 3H), 2.84 (t, 2H, J = 9.0 Hz), 2.53 (td, 2H, J = 9.0, 3.0 Hz), 2.06 (q, 2H, J = 6.0 Hz), 1.66 (m, 2H), 1.51 (q, 2H, J = 9.0 Hz).




**(R)-6-methoxydodec-1-en-7-yne, 3-64.** 84% yield. $[\alpha]_D^{25}$ = 51.0 (c = 1.27, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 4.99 (m, 2H), 3.92 (tt, 1H, J = 6.0, 3.0 Hz), 3.38 (s, 3H), 2.23 (td, 2H, J = 6.0, 3.0 Hz), 2.08 (q, 2H, J = 6.0 Hz), 1.68 (m, 2H), 1.47 (m, 6H), 0.91 (t, 3H, J = 6.0 Hz).

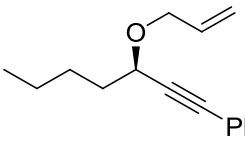



**(S)-(3-methoxyoct-7-en-1-ynyl)trimethylsilane, 3-65.** 98% yield. $[\alpha]_D^{25}$ = -56.4 (c = 1.02, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.00 (m, 2H), 3.93 (t, 1H, J = 6.0 Hz), 3.39 (s, 3H), 2.08 (q, 2H, J = 6.0 Hz), 1.70 (m, 2H), 1.55 (m, 2H), 0.17 (s, 9H).

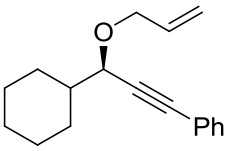



**(S)-oct-7-en-1-yn-3-yl acetate, 3-66.** 80% yield. *Note: Due to volatility of product water bath is not heated above 25°C during rotary evaporation.*

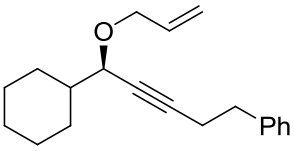
$[\alpha]_D^{25}$ = -14.9 (c = 1.02, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.00 (m, 2H), 3.94 (td, 1H, J = 6.0, 2.0 Hz), 3.41 (s, 3H), 2.44 (dd, 1H, J = 3.0, 0.6 Hz), 2.09 (q, 2H, J = 6.0 Hz), 1.73 (m, 2H), 1.57 (m, 2H).



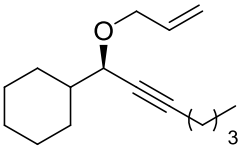

**(R)-(3-(allyloxy)hept-1-ynyl)benzene, 3-73.** 73% yield. $[\alpha]_D^{25}$ = 112.4 (c = 1.18, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.31(m, 3H), 5.97 (m, 1H), 5.28 (m, 2H), 4.32 (m, 2H), 4.04 (m, 1H), 1.83 (m, 2H), 1.51 (m, 2H), 1.38 (m, 2H), 0.94 (t, 3H, J = 6.0 Hz).



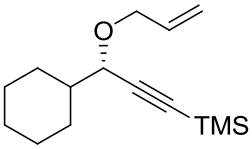

**(R)-(3-(allyloxy)-3-cyclohexylprop-1-ynyl)benzene, 3-74.** 69% yield. $[\alpha]_D^{25}$ = 93.9 (c = 1.10, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.31 (m, 3H), 6.96 (m, 1H), 5.28 (m, 2H), 4.33 (m, 1H), 4.08 (d, 1H, J = 6.0 Hz), 4.03 (m, 1H), 1.94 (m, 2H), 1.71 (m, 4H), 1.21 (m, 5H).



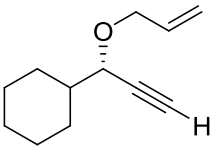

**(R)-(5-(allyloxy)-5-cyclohexylpent-3-ynyl)benzene, 3-75.** 73% yield. $[\alpha]_D^{25}$ = 37.1 (c = 1.00, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.90 (m, 1H), 5.21 (m, 2H), 4.17 (m, 1H), 3.85 (m, 2H), 2.84 (t, 2H, J = 6.0 Hz), 2.54 (t, 2H, J = 6.0 Hz), 1.77 (m, 5H), 1.14 (m, 6H).



**(R)-(1-(allyloxy)hept-2-ynyl)cyclohexane, 3-76.** 57% yield. $[\alpha]_D^{25}$ = 58.8 (c = 0.87, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.24 (m, 2H), 4.24 (m, 1H), 3.93 (m, 1H), 3.83 (dt, 1 H, J = 6.0, 3.0 Hz), 2.23 (td, 2H, J = 6.0, 3.0Hz), 1.84 (m, 2H), 1.68 (m, 3H), 1.48 (m, 5H), 1.19 (m, 5H), 0.91 (t, 3H, J = 6.0 Hz).



**(S)-(3-(allyloxy)-3-cyclohexylprop-1-ynyl)trimethylsilane, 3-77.** 73% yield. $[\alpha]_D^{25}$ = -65.6 (c = 0.92, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.24 (m, 2H), 4.25 (m, 1H), 3.94 (m, 1H), 3.84 (d, 1H, J= 6.0 Hz), 1.85 (m, 2H), 1.74 (m, 1H,), 1.60 (m, 2H), 1.17 (m, 6H), 0.18 (s, 9H).



**(S)-(1-(allyloxy)prop-2-ynyl)cyclohexane, 3-78.** 94% yield. $[\alpha]_D^{25}$ = -60.7 (c = 0.67, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.26 (m, 2H), 4.27 (m, 1H), 3.96 (m, 1H), 3.86 (dd, 1H, J = 6.0, 3.0 Hz), 2.42 (d, 1H, J = 3.0 Hz), 1.87 (m, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.18 (m, 5H).

*h. General Procedures for the Intramolecular PK Reaction*

*Method A*

Under nitrogen in a 25 mL flame-dried flask, an enyne substrate (0.25 mmol, 1 equiv) was dissolved in $CH_2Cl_2$ (12.5 mL, 0.02 M). $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 2 h, during which formation of the cobalt-complexed en-yne was observed by TLC analysis. To the dark amber colored

solution was added *N*-methylmorpholine *N*-oxide (293 mg, 2.5 mmol, 10 equiv). The reaction was monitored by TLC. After the consumption of the cobalt-complexed en-yne (3 - 5 h), the cobalt blue solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (10-40% ethyl acetate) yielded a mixture of diastereomers. Both diastereomers were observable by $^1$H NMR spectroscopy, and the diastereomeric ratio was determined by HPLC equipped with a Chiralcel OD or Chiralpak AD-H column. The major diastereomer was separated by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (10-40% ethyl acetate).

*Method B*

Under nitrogen in a 25 mL flame-dried flask, an enyne substrate (0.25 mmol, 1 equiv) was dissolved in $CH_2Cl_2$ (10 mL, 0.025 M). $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) was added and the flask was fitted with a stopcock vacuum/nitrogen adaptor. After 2 h, the solvent was removed under vacuum, and the resulting amber colored oil was redissolved in acetonitrile (10 mL, 0.025 M). The flask was connected with a flame-dried reflux condenser fitted with a stopcock vacuum/nitrogen adaptor and the reaction mixture was heated at 72 - 75 °C for 24 h. The dark colored solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (0-30% ethyl acetate) yielded the product (in some cases as a mixture of diastereomers). The diastereomers were observable by $^1$H NMR, and the diastereomeric ratio was determined by HPLC equipped wih a Chiralcel OD or Chiralpak AD-H column. The major diastereomer was separated by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (0-30% ethyl acetate).

*Method C*

Under nitrogen in a 25 mL flame-dried flask, an en-yne substrate (0.25 mmol, 1 equiv) was dissolved in $CH_2Cl_2$ (5 mL, 0.05 M). $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) was added and the flask was fitted with a stopcock vacuum/nitrogen adaptor. After 2 h, the solvent was removed under vacuum, and the resulting amber colored oil was redissolved in 1,4-dioxane (5 mL, 0.05 M). n-Butyl methyl sulfide (465 μL, 3.79 mmol, 15.15 equiv) was then added. The flask was connected with a flame-dried reflux condenser fitted with a stopcock vacuum/nitrogen adaptor and the reaction mixture was heated at 100 °C for 16 h. The dark colored solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (0-30% ethyl acetate) yielded the product (P10) as a mixture of diastereomers. The diastereomers were observable by $^1$H NMR, and the diastereomeric ratio was determined by HPLC equipped with a Chiralcel OD column. The major diastereomer was separated by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (0-30% ethyl acetate).

*Method D*

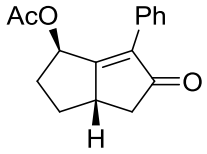
Under nitrogen in a 25 mL flame-dried flask, an en-yne substrate (0.25 mmol, 1 equiv) was dissolved in toluene (5 mL, 0.05 M). $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 2 h. To the resulting dark amber colored solution was added tetramethylthiourea (132 mg, 1 mmol, 4 equiv). The flask was connected with a flame-dried reflux condenser fitted with a stopcock vacuum/nitrogen adaptor and the reaction mixture was heated at 112 °C for 16 h. The dark colored solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (0-30% ethyl acetate) yielded the product (**P10**) as a mixture of

diastereomers. The diastereomers were observable by $^1$H NMR, and the diastereomeric ratio was determined by HPLC equipped with a Chiralcel OD column. The major diastereomer was separated by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (0-30% ethyl acetate).

*Method E*

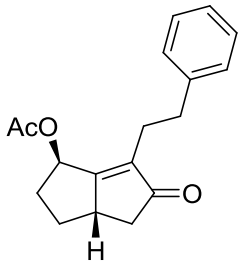
Under nitrogen in a 25 mL flame-dried flask, an en-yne substrate (0.2 mmol, 1 equiv) was dissolved in $CH_2Cl_2$ (5 mL, 0.04 M) containing activated 4-Å molecular sieves (8 wt. equiv). $Co_2(CO)_8$ (78.7 mg, 0.23 mmol, 1.15 equiv) was added and the reaction mixture was stirred for 2 h, during which formation of the cobalt-complexed en-yne was observed by TLC analysis. The reaction mixture was cooled to -20 °C and trimethylamine N-oxide (120.2 mg, 1.6 mmol, 8 equiv) was added in 4 equal portions over 10 min. The reaction mixture was then bubbled with compressed air (passed through a drying filter) for 20 min. The flask was then allowed to remain open to air, covering with a drying tube. The cooling bath was removed and the reaction was allowed to warm to room temperature and stirred for 15 h. The cobalt blue solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (10-40% ethyl acetate) yielded the product as a single diastereomer.

*i. Characterization of PK Cycloaddition Products*

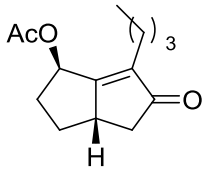



**(1R,3aS)-5-oxo-6-phenyl-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate, 3-56.** 94% yield. 95:5 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:$^i$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ =

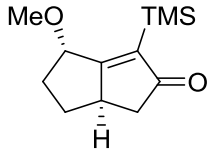
56.3, 60.1 $t_{minor}$ = 77.1. 94% ee determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 56.3 $t_{minor}$ = 60.1. $[\alpha]_D^{25}$ = -89.1 (c = 0.89, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50 (m, 2H), 7.37 (m, 3H), 5.65 (m, 1H), 3.22 (m, 1H), 2.90 (dd, 1H, J = 18.0, 6.6 Hz), 2.65 (p, 1H, J = 7.2 Hz), 2.31 (m, 2H), 2.17 (s, 3H), 1.94 (m, 1H), 1.17 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 208.5, 175.7, 170.0, 138.3, 130.5, 128.8, 128.5, 128.0, 70.8, 43.1, 41.9, 35.1, 29.2, 21.2. HRMS ($MH^+$) for $C_{16}H_{17}O_3$ Calcd: 257.1183 Found: 257.1179.



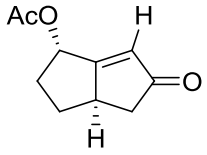

**(1R,3aS)-5-oxo-6-phenethyl-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate , 3-57.** 81% yield. 93:7 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 235 nm, retention time: $t_{major}$ = 39.7, 43.0, $t_{minor}$ = 56.2. 94% ee determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 235 nm, retention time: $t_{major}$ = 39.7 $t_{minor}$ = 43.0. $[\alpha]_D^{25}$ = -84.5 (c = 1.00, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.17m, 5H), 5.17 (m, 1H), 2.94 (m, 1H), 2.85-2.75 (m, 1H), 2.66 (m, 4H), 2.11 (m, 3H), 2.01 (s, 3H), 1.82 (m, 1H), 0.95-0.82 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 210.6, 176.1, 170.1, 141.3, 138.1, 128.7, 128.2, 125.9, 68.6, 42.3, 40.8, 33.7, 33.2, 28.9, 25.8, 21.0. HRMS ($MH^+$) for $C_{18}H_{21}O_3$ Calcd: 285.1496 Found: 285.1493.



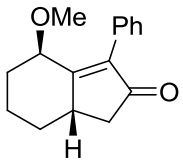

**(1R,3aS)-6-butyl-5-oxo-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate , 3-58.** 85% yield. 95:5 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 7.6 $t_{minor}$ = 9.6. $[\alpha]_D^{25}$ = -91.9 (c = 1.14, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.74 (m, 1H), 3.02 (m, 1H), 2.69 (dd, 1H, J = 18.0, 6.0 Hz), 2.52 (p, 1H, J = 6 Hz), 2.24 (m, 3H), 2.07 (s, 3H), 2.06 (dd, 1H, J = 18.0, 3.0 Hz), 1.94 (m, 1H), 1.33 (m, 4H), 1.06 (p, 1H, J = 9.0 Hz), 0.88 (t, 3H, J = 6 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 210.7, 174.9, 170.2, 139.9, 68.8, 42.1, 41.3, 34.1, 30.3, 29.2, 23.6, 22.5, 21.0, 13.8. HRMS ($MH^+$) for $C_{14}H_{21}O_3$ Calcd: 237.1491 Found: 237.1485.



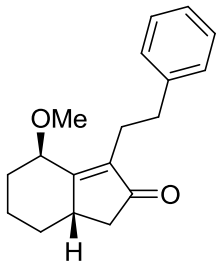

**(4S,6aR)-4-methoxy-3-(trimethylsilyl)-4,5,6,6a-tetrahydropentalen-2(1H)-one , 3-60.** 69% yield. >99:1 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 235 nm, retention time: $t_{major}$ = 19.3. $[\alpha]_D^{25}$ = 138.4 (c = 1.07, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.41 (m, 1H), 3.33 (s, 3H), 3.08 (m, 1H), 2.64 (dd, 1H, J = 18.0, 9.0 Hz), 2.24 (m, 2H), 2.03 (dd, 1H, J = 18.0, 3.0 Hz), 1.94 (m, 1H), 1.08 (m, 1H), 0.23 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 215.0, 192.0, 139.0, 76.4, 56.2, 43.9, 43.7, 32.8, 28.1, -1.1. HRMS ($MH^+$) for $C_{12}H_{21}O_2Si$ Calcd: 225.1311 Found: 225.1308.



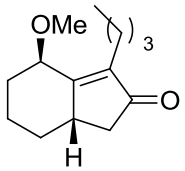

**(1S,3aR)-5-oxo-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate (P5, , 3-59.** 83% yield. 75:25 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:*i*PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 24.7, $t_{minor}$ = 29.3. $[\alpha]_D^{25}$ = 94.8 (c = 0.67, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.13 (m, 1H), 5.67-5.63 (m, 1H), 3.12 (m, 1H), 2.69 (dd, 1H, J = 18.0, 6.0 Hz), 2.50 (p, 1H, J = 7.2 Hz), 2.31-2.22 (m, 1H), 2.11 (dd, 1H, J = 18.0, 3.0 Hz), 2.07 (s, 3H), 2.05-1.95 (m, 1H), 1.21-1.10 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 210.6, 182.8, 170.3, 128.5, 69.5, 43.6, 42.6, 33.1, 28.9, 20.9. HRMS ($MH^+$) for $C_{10}H_{13}O_3$ Calcd: 181.0865. Found: 181.0873.




**(4R,7aS)-4-methoxy-3-phenyl-5,6,7,7a-tetrahydro-1H-inden-2(4H)-one, 3-68.** 93% yield. 92:8 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:*i*PrOH, flow rate = 0.3 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 43.9, 45.8, $t_{minor}$ = 56.8. 93% ee determined by HPLC analysis: Chiralcel OB-H column, 98:2 hexanes:*i*PrOH, flow rate = 2 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 17.10 $t_{minor}$ = 12.78. $[\alpha]_D^{25}$ = -96.6 (c = 0.69, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38 (m, 3H), 7.24 (m, 2H), 4.43 (t, 1H, J = 3.0 Hz), 3.19 (s, 3H), 3.10-3.04 (m, 1H), 2.74 (dd, 1H, J = 18.0, 6 Hz), 2.23 (m, 2H), 2.12 (dd, 1H, J = 18.0, 3.0 Hz), 1.92 (m, 1H), 1.57 (m, 2H), 1.18 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 206.9, 174.2, 139.6, 130.8, 129.0, 128.3, 127.9, 72.9, 56.1, 41.7, 36.1, 35.6, 31.9, 19.7. HRMS ($MH^+$) for $C_{16}H_{19}O_2$ Calcd: 243.1385. Found: 243.1285.

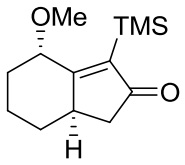



**(4R,7aS)-4-methoxy-3-phenethyl-5,6,7,7a-tetrahydro-1H-inden-2(4H)-one, 3-69.** 77% yield. 93:7 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:*i*PrOH, flow rate = 0.3 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 37.5, 38.5, $t_{minor}$ = 44.5. $[\alpha]_D^{25}$ = -58.3 (c = 0.86, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.16 (m, 5H), 3.99 (t, 1H, J = 3.0 Hz), 3.09 (s, 3H), 2.62 (m, 6H), 2.05 (m, 1H), 1.93 (dd, 1H, J = 18.0, 3 Hz), 1.85 (m, 1H), 1.72 (m, 1H), 1.41 (m, 1H), 0.85 (m, 1H), 0.70 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 208.9, 173.2, 141.2, 138.5, 128.7, 128.3, 126.0, 72.6, 55.9, 41.5, 36.2, 35.3, 34.0, 31.6, 25.0, 19.6. HRMS ($MH^+$) for $C_{18}H_{23}O_2$ Calcd: 271.1698. Found: 271.1688.

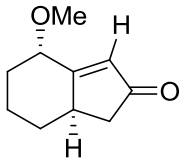



**(4R,7aS)-3-butyl-4-methoxy-5,6,7,7a-tetrahydro-1H-inden-2(4H)-one , 3-70.** 79% yield. 95:5 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:*i*PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 5.7, 6.1, $t_{minor}$ = 6.8. $[\alpha]_D^{25}$ = -118.0 (c =1.335, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.36 (t, 1H, J = 3 Hz), 3.24 (s, 3H), 2.86 (m, 1H), 2.56 (dd, 1H, J = 18.0, 6.3 Hz), 2.20 (m, 4H), 1.94 (dd, 1H, J = 18.0, 3 Hz), 1.84 (1H), 1.58 (m, 1H), 1.37 (m, 5H), 1.01 (m, 1H), 0.90 (t, 3H, J = 7.2 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 209.1, 172.2, 140.3, 72.8, 56.1, 41.5, 36.0, 35.5,

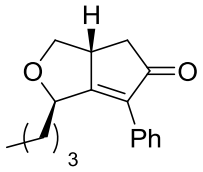
32.3, 31.1, 22.7, 22.5, 19.8, 13.9. HRMS ($MH^+$) for $C_{14}H_{23}O_2$ Calcd: 223.1698. Found: 223.1694.



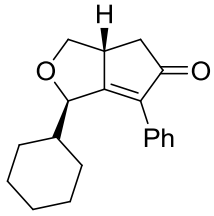

**(4S,7aR)-4-methoxy-3-(trimethylsilyl)-5,6,7,7a-tetrahydro-1H-inden-2(4H)-one, 3-71.** 47% yield. 94:6 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:*i*PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 5.5, $t_{minor}$ = 7.1. $[\alpha]_D^{25}$ = 100.8 (c =0.70, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.48 (t, 1H, J = 3Hz), 3.26 (s, 3H), 2.97 (m, 1H), 2.53 (dd, 1H, J = 18.0, 6.9 Hz), 2.17 (m, 2H), 1.92 (dd, 1H, J = 18.0, 2.4 Hz), 1.85 (m, 1H), 1.49 (m, 2H), 1.09 (m, 1H), 0.24 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 213.2, 188.4, 139.7, 74.5, 56.0, 42.6, 39.1, 36.1, 32.7, 19.5, -0.1. HRMS ($MH^+$) for $C_{13}H_{23}O_2Si$ Calcd: 239.1467. Found: 239.1468.




**(4S,7aR)-4-methoxy-5,6,7,7a-tetrahydro-1H-inden-2(4H)-one, 3-72.** 61% yield. 84:16 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:*i*PrOH, flow rate = 1.0 mL/min, $\lambda$ = 235 nm, retention time: $t_{major}$ = 11.2, $t_{minor}$ = 15.6. $[\alpha]_D^{25}$ = 76.9 (c =0.37, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.99 (m, 1H), 4.23 (bs, 1H), 3.25 (s, 3H), 2.95 (m, 1H), 2.61 (dd, 1H, J = 18.0, 6.0 Hz), 2.20 (m, 1H), 2.16 (m, 1H), 2.00 (dd, 1H, J = 18.0, 1.8 Hz), 1.83 (m, 1H), 1.55 (m, 2H), 1.10 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 208.9, 181.2, 129.2, 75.0, 56.3, 42.2, 37.7, 35.2, 32.6, 19.6. HRMS ($MH^+$) for $C_{10}H_{15}O_2$ Calcd: 167.1072. Found: 167.1074.

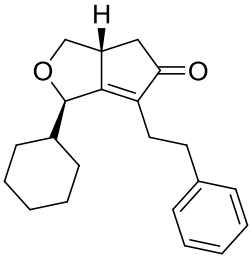


**(1R,3aR)-1-butyl-6-phenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 3-79.** 82% yield. 87:13 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:*i*PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 14.5, 15.3, $t_{minor}$ = 19.7. $[\alpha]_D^{25}$ = 165.1 (c =1.28, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.42 (m, 5H), 4.81 (m, 1H), 4.39 (t, 1H, J = 6.0 Hz), 3.32 (m, 2H), 2.82 (dd, 1H, J = 18.0, 6.0 Hz), 2.30 (dd, 1H, J = 18.0, 3.0 Hz), 1.82 (m, 2H), 1.42 (m, 4H), 0.90 (t, 3H, J = 7.2 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 207.4, 179.9, 135.0, 130.9, 128.5, 128.4, 128.2, 76.3, 71.2, 42.7, 39.7, 34.9, 27.5, 22.5, 13.9. HRMS ($MH^+$) for $C_{17}H_{21}O_2$ Calcd: 257.1542. Found: 257.1535.

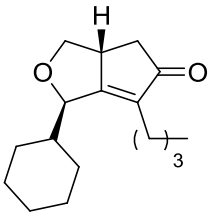


**(1R,3aR)-1-cyclohexyl-6-phenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 3-80.** 83% yield. >99:1 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:*i*PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 17.00. 96% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 17.0, $t_{minor}$ = 14.2. $[\alpha]_D^{25}$ = 247.0 (c =2.18, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40 (m, 5H), 4.72 (d, 1H, J = 3.0 Hz), 4.38 (t, 1H, J = 6.0 Hz), 3.36-3.25 (m, 2H), 2.80 (dd, 1H, J = 18.0, 6.0 Hz), 2.28 (dd, 1H, J = 18.0, 3.0 Hz), 1.72-1.56 (m, 6H), 1.25-1.17 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 207.3, 179.6, 135.9, 131.2, 128.4, 128.2, 80.7, 71.2,

43.4, 43.1, 39.5, 29.4, 28.0, 26.2, 26.0. HRMS ($MH^+$) for $C_{19}H_{23}O_2$ Calcd: 283.1698. Found: 283.1699.

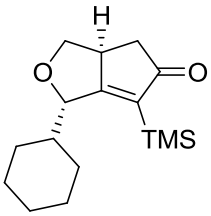


**(1R,3aR)-1-cyclohexyl-6-phenethyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 3-81.** 66% yield. >99:1 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:*i*PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 11.3. $[\alpha]_D^{25}$ = 144.3 (c =0.6, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.20 (m, 5H), 4.21 (t, 1H, J = 6.0 Hz), 3.91 (d, 1H, J = 6.0 Hz), 3.01 (m, 2H), 2.80 (m, 2H), 2.56 (m, 3H), 2.05 (dd, 1H, J = 18.0, 3 Hz), 1.68 (m, 5H), 1.46 (m, 1H), 1.23 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 209.2, 179.1, 141.2, 136.5, 128.5, 128.4, 126.2, 80.2, 71.4, 43.0, 42.6, 39.1, 33.4, 29.2, 26.2, 26.1, 25.9. HRMS ($MH^+$) for $C_{21}H_{27}O_2$ Calcd: 311.2011. Found: 311.2005.

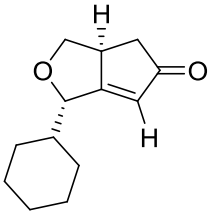


**(1R,3aR)-6-butyl-1-cyclohexyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 3-82.** 64% yield. >99:1 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 7.2. $[\alpha]_D^{25}$ = 71.18 (c =1.16, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.43 (d, 1H, J = 6.0 Hz), 4.29 (t, 1H, J = 6.0 Hz), 3.17 (m, 2H), 2.62 (dd, 1H, J = 18.0, 6.0 Hz), 2.20 (m, 2H), 2.06 (dd, 1H, J = 18.0, 2.7 Hz), 1.69 (m, 6H), 1.26 (m, 9H), 0.90 (t, 3H, J = 6.9 Hz). $^{13}$C

NMR (75 MHz, $CDCl_3$) δ 209.2, 177.7, 137.7, 80.3, 71.4, 42.9, 42.7, 38.9, 29.8, 29.1, 28.7, 26.1, 26.0, 25.9, 24.2, 22.7, 13.8. HRMS ($MH^+$) for $C_{17}H_{27}O_2$ Calcd: 263.2011. Found: 263.2007.




**(1S,3aS)-1-cyclohexyl-6-(trimethylsilyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 3-83.** 50% yield. >99:1 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: $t_{major}$ = 6.2. $[\alpha]_D^{25}$ = -152.9 (c =0.95, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 4.48 (d, 1H, J = 3.0 Hz), 4.29 (t, 1H, J = 6.9 Hz), 3.21 (m, 2H), 2.56 (dd, 1H, J = 18.0, 6 Hz), 2.05 (dd, 1H, J = 18.0, 3.6 Hz), 1.77 (m, 2H), 1.65 (m, 4H), 1.23 (m, 5H), 0.21 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 213.3, 192.6, 136.3, 80.8, 71.0, 46.3, 42.8, 40.6, 30.0, 27.4, 26.5, 26.1, 26.0, -1.1. HRMS ($MH^+$) for $C_{16}H_{27}O_2Si$ Calcd: 279.1780. Found: 279.1778.




**(1S,3aS)-1-cyclohexyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 3-84.** 55% yield. 65:35 dr determined by HPLC analysis of the minor enantiomers since the peaks of these diastereomers are fully resolved: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: $t_{major}$ =15.4, $t_{minor}$ =14.1. $[\alpha]_D^{25}$ = -151.2 (c = 0.62, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.99 (s, 1H), 4.36

(d, 1H, J = 9.0 Hz), 4.31 (t, 1H, J = 6.0 Hz), 3.26 (m, 2H), 2.60 (dd, 1H, J = 18.0, 6 Hz), 2.11 (dd, 1H, J = 18.0, 3.0 Hz), 1.74 (m, 6H), 1.12 (m, 5H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 209.1, 186.6, 125.3, 81.3, 71.3, 45.7, 41.7, 39.5, 29.1, 28.5, 26.2, 25.8. HRMS ($MH^+$) for $C_{13}H_{19}O_2$ Calcd: 207.1385. Found: 207.1377.

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improve the enantioselectivity for the addition of phenylacetylene to aromatic aldehydes.

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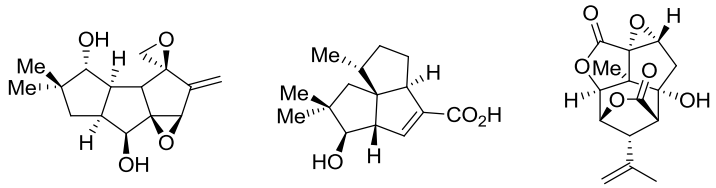
# Chapter 4. From Highly Enantioselective 1,3-Diyne Addition to Aldehydes to Facile Asymmetric Synthesis of Polycyclic Compounds

## 4.1 Introduction

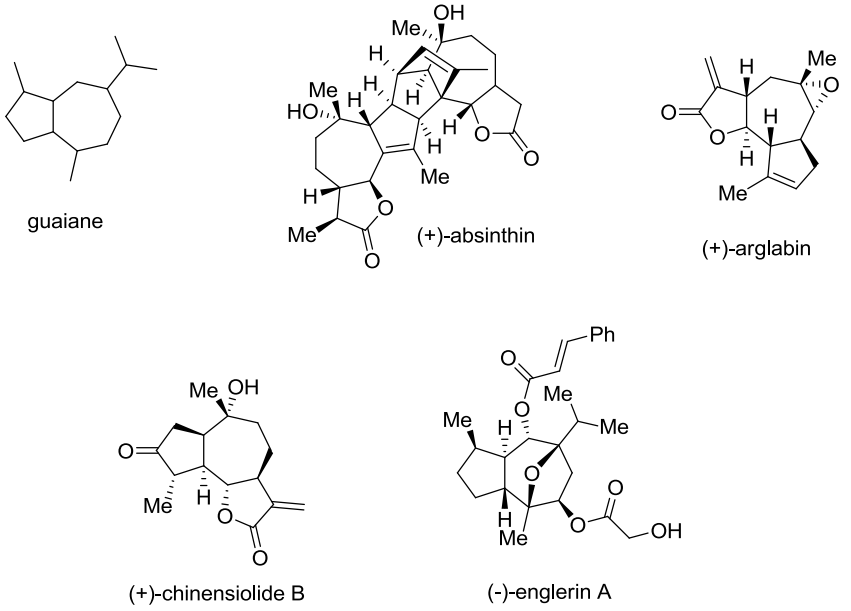
During our investigations of the intramolecular Pauson-Khand reaction of enynes derived from propargylic alcohols we were impressed by the utility of the cyclization for the rapid construction of the 5,5- and 5,6-bicyclic motif that is often encountered in a variety of polycyclic natural products. Among these, the triquinane sesquiterpenes represent a large class of 5-membered polycyclic natural products. This family is characterized by the linear ring pattern exemplified by coriolin and the angular ring pattern displayed by pentalenic acid.[1] The 5,6-biyclic structure is also commonly encountered as demonstrated by the picrotoxane family.[2] We had gained valuable experience through our investigations of the diastereoselective intramolecular PK reaction from optically active enynes accessed by our asymmetric alkyne addition methodology. Through this study, optically active bicyclic compounds could be rapidly assembled as a single diastereomer in three steps from acyclic starting materials. We were interested in investigating the potential of this pathway for the creation of less explored polycyclic systems found in natural products.

**Figure 4.1.** Examples of Natural Products Containing the 5,5- and 5,6-Bicyclic Motif.



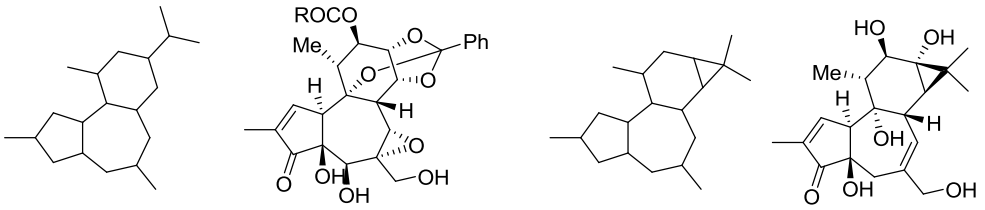
Polycyclic systems containing medium sized rings are also frequent structural motifs in nature. Among these polycyclic systems fused 5,7- and 5,8-rings comprise the structural core of a variety of natural products, as well as commonly being embedded in more complex polycyclic ring structures. For example the fused 5,7-ring system of the perhydroazulene skeleton is the common structural feature of the large guaiane family of sesquiterpenes.[3] Due to their wide and promising biological activity,[3] members of the guaiane family have been frequent targets of total synthesis. These include the biologically active dimeric guaianolide (+)-absinthin,[4] (+)-arglabin, an inhibitor of farnesyl transferase and subsequently the RAS proto-oncogene,[5] (+)-chinensiolide B, shown to be active against liver and lung cancer cells lines,[6] and most recently exemplified by several elegant syntheses of englerin A, a selective and highly potent inhibitor of renal cancer cell lines.[7]

**Figure 4.2.** Biologically Active Members of the Guaiane Family.



Daphnane diterpenes[8] possessing a 5,7,6-fused ring system, and the structurally related tiglianes[9] possessing a 5,7,6,3-ring system also make up important families of natural products with an extensive range of biological activity. The daphanes include gnididin, gniditrin, and gnidicin which possess antileukemic activity,[8c] and the tiglianes are best exemplified by phorbol,[9a] a potent tumor promoter useful in studies of the mechanism of carcinogenesis. Other derivatives of the phorbol structure have been shown to have anti-tumor and anti-HIV activity.[9a]

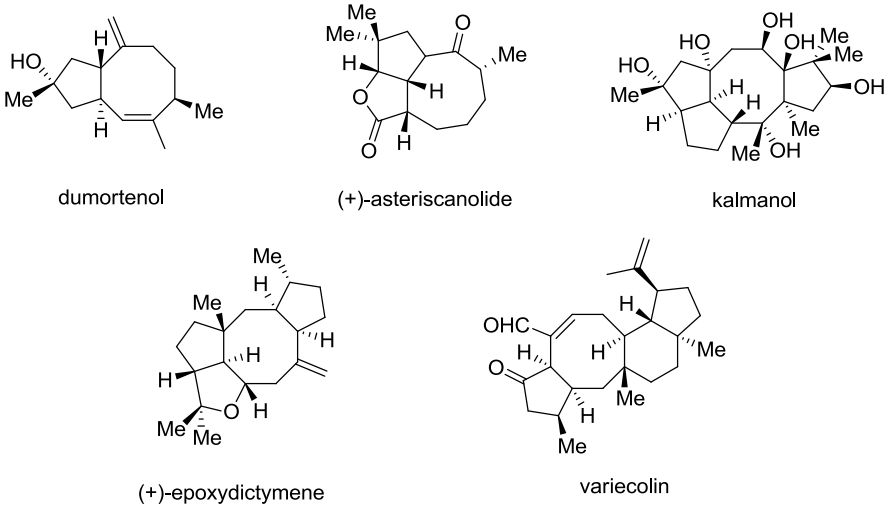
**Figure 4.3**. Daphnane and Tigliane Ring Systems and Biologically Active Derivatives.




Additionally, interesting and biologically active natural products containing the fused 5,8-ring system are also common (Figure 4.4).[10] These are exemplified by dumorenol and its derivatives,[11] (+)-asteriscanolide,[12] kalmanol,[13] (+)-epoxydictymene,[14] and variecolin, a potent immunosuppressant.[15] Interestingly, the 5,5,8-ring system is a common structural feature among several of these natural products.

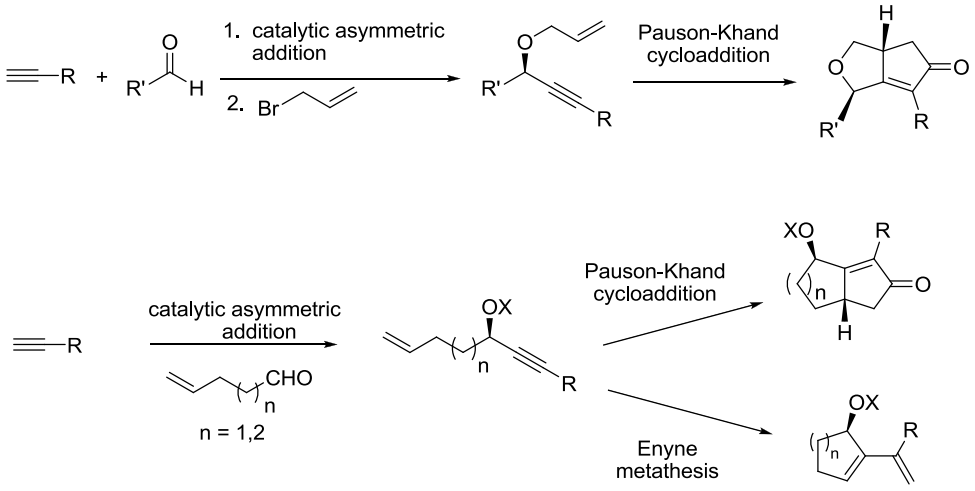
Given the wide array of biologically active natural products containing fused 5,7- and 5,8-ring systems and the more complex 5,7,6- and 5,5,8-polycyclic ring systems, a flexible route to enantioselectively access these types of structures from acyclic precursors would be attractive. In addition to our study of the intramolecular Pauson-Khand (PK) reaction of enynes derived from propargylic alcohols,[16] we had also recently

**Figure 4.4.** Polycyclic Systems Containing 5,8-Fused Ring Systems.




studied the enyne metathesis of propargylic alcohol based enynes to provide access to optically active diene containing 5- or 6-membered rings (Scheme 4.1).[17] With these studies in mind we began to consider routes from acyclic precursors to access optically active polycyclic systems containing medium sized fused rings.

**Scheme 4.1**. Pauson-Khand Reaction and Enyne Metathesis of Optically Active Propargylic Alcohol Based Enynes.

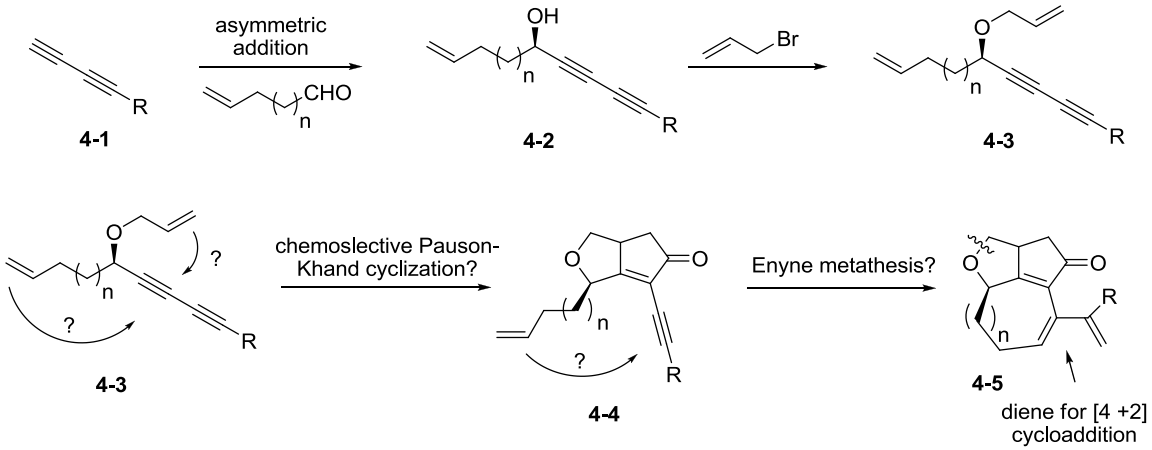


Ideally, we hoped to design a strategy that would allow access to the core 5,7- and 5,8-ring systems present in a variety of natural products, while retaining the flexibility to pursue more complex ring structures such as the 5,7,6-ring system of the daphnanes and tiglianes or the 5,5,8-ring system present in compounds like epoxydictymene. While the intramolecular PK reaction from simple enynes provides efficient access to 5,5- and 5,6-bicyclic systems, it has met with limited success in the formation of medium sized ring systems,[18] often requiring embedded aromatic rings in the enyne to facilitate the reaction.[19] More importantly, the resulting bicyclic products would lack the functionality to quickly establish more complex polycyclic structures. In contrast enyne metathesis has been a valuable method to access medium sized 7- and 8-membered rings.[20] As entropy loss is a significant challenge for the formation of 8-membered rings, rings present in the enyne precursor are known to be beneficial for promoting the reaction.[20a]

In order to develop a facile acyclic precursor route to the optically active polycyclic systems containing medium sized fused rings, we proposed the synthetic route shown in Scheme 4.2. We would first target the preparation of optically active dienediynes **4-3** by the asymmetric addition of 1,3-diyne **4-1** to enals followed by treatment of the resulting enediynol **4-2** with allyl bromide. These substrates could potentially undergo a chemoselective PK reaction to give the 5,5-bicyclic compounds **4-4** and retain unreacted functional groups for the subsequent enyne metathesis to generate the medium sized rings to form the 5,5,7- and 5,5,8-tricyclic products **4-5**. If one of the ether bonds in the hydrofuran ring of **4-5** could be cleaved, it would furnish the 5,7- and 5,8-carbocycles. Furthermore, these polycyclic substrates would contain an embedded 1,3-diene which could participate in the Diels-Alder cycloadditions to form the 5,7,6-carbocycles present

in the daphnanes and tiglianes. The array of synthetic options available from this route prompted us to explore the viability of this pathway.

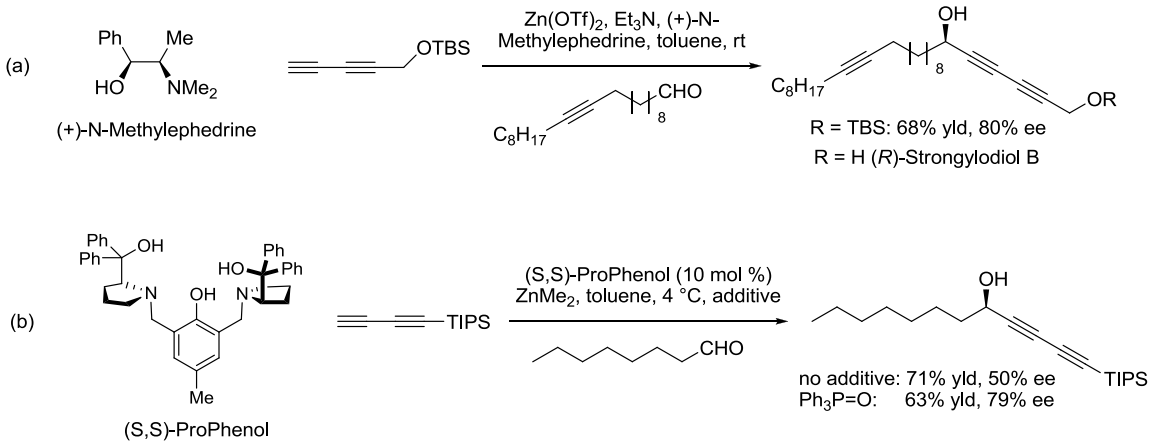
**Scheme 4.2**. Chiral Dienediynes as Acyclic Precursors to Polycyclic Compounds.




Key to the success of this strategy was the enantioselective 1,3-diyne addition to enals to generate the optically active acyclic dienediyne precursors. Although a large number of catalytic systems have been reported for the highly enantioselective catalytic addition of alkynes to aldehydes,[21] enantioselective additions of 1,3-diynes have proved to be more challenging. In 2003, Carreira and coworkers were able to access the biologically active strongylodiols from the addition of a 1,3-diyne to aliphatic aldehydes.[22] While good enantioselectivities could be obtained (80-82% ee), 4 equivalents of the chiral ligand and slow addition of the aldehyde with a syringe pump were required for good enantiocontrol.

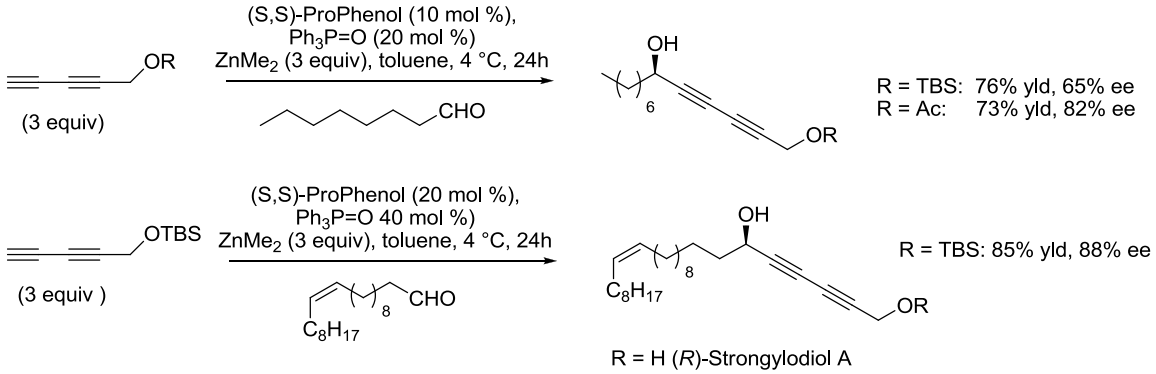
Recently, Trost and coworkers have demonstrated an enantioselective ProPhenol catalyzed addition of 1,3-diynes to aldehydes.[23] While the ProPhenol catalyst has been highly successful in a variety of alkyne additions to aldehydes,[24] initial application of

**Scheme 4.3**. Enantioselective Additions of 1,3-Diynes.




their catalytic system for the addition of buta-1,3-diynyltriisopropylsilane to octyl aldehyde resulted in only moderate enantioselectivity (50% ee, Scheme 4.3). It was found however, that the enantioselectivity could be improved up to 79% ee in the presence of triphenylphosphine oxide (TPPO) as an additive. In this manner high enantioselectivities were achieved for the addition of buta-1,3-diynyltriisopropylsilane to benzaldehyde (87% ee) and a range of *trans* α,β-unsaturated aldehydes (84-97% ee) utilizing 10 mol % of the (*S*,S)-ProPhenol ligand. Other aliphatic aldehydes also proved to be challenging in the addition of buta-1,3-diynyltriisopropylsilane, resulting in enantioselectivities ranging from 67-83%. However, this method was successfully extended to several other 1,3-diyne nucleophiles including acetate and *tert*-butyldimethylsilyl (TBS) protected penta-2,4-diyn-1-ol (Scheme 4.4). For these substrates the acetate protected 1,3-diyne was found to provide significantly higher enantioselectivity (82% vs. 65% ee). When this substrate was applied to the synthesis of (*R*)-strongylodiol A, the enanantioselective diyne addition could be performed in 85% yield and 88% ee by doubling the catalyst loading (Scheme 4.4).

**Scheme 4.4**. Protecting Group Effect on (*S*,*S*)-ProPhenol Catalyzed Enantioselective 1,3-Diyne Addition to Octyl Aldehyde and Synthesis of (*R*)-Strongylodiol A.




These reports demonstrate the challenges associated with 1,3-diyne nucleophiles in comparison with simple alkynes. We were curious to see if our BINOL-$ZnEt_2$-$Ti(O^iPr)_4$ catalytic system developed for the addition of alkynes to aldehydes,[25] would prove effective for 1,3-diynes. In particular we hoped it would be highly enantioselective for the linear aliphatic aldehydes necessary to synthesize the dienediyne precursors for the PK cyclization. If this substrates could be accessed in high optical purity we could then explore the chemoselective and diastereoselective PK cyclization, followed by enyne metathesis to access polycyclic rings systems containing the 5,5,7- and 5,5,8-membered ring core. Finally, use of the conjugated diene in tricycle **4-5** could be tested for the Diels-Alder reaction to yield 5,5,7,6-polycyclic compounds. This chapter will discuss a successful story toward these goals.

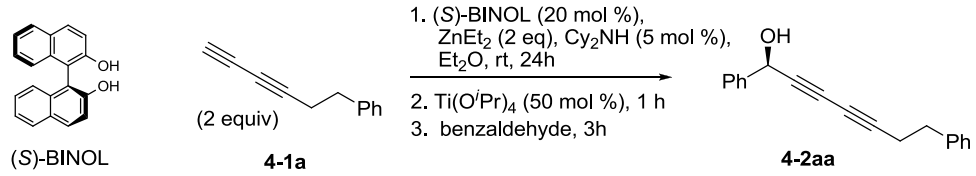
### 4.2. Enantioselective 1,3-Diyne Addition to Aldehydes

With the opportunity to explore 1,3-diyne additions to aldehydes, we wanted to develop a highly enantioselective catalytic system for diverse 1,3-diynes nucleophiles containing alkyl, aryl, and silyl substituents. As Trost and coworkers had demonstrated a

highly effective system for additions to α,β-unsaturated aldehydes, we hoped to discover a catalytic system general for a wide range of aromatic and aliphatic aldehydes. To address these challenges we turned to our methodology for the asymmetric alkynylation of aldehydes.

In 2002, we[25a] and Chan[26] found that 1,1'-bi-2-napthol (BINOL) in combination with $Ti(O^iPr)_4$ and $ZnR_2$ was a highly enantioselective catalytic system for the reaction of alkynes with aromatic aldehydes to generate optically active propargylic alcohols. We later expanded this system to aliphatic and α,β-unsaturated aldehydes.[25b] Since this method required heating the terminal alkyne with $ZnEt_2$ in toluene at reflux in order to prepare the alkynylzinc nucleophile it was not applicable for sensitive alkynes. To circumvent the elevated temperatures required to form the alkynylzinc, we discovered that the addition of hexamethylphosphoramide (HMPA) allowed the reaction to be performed entirely at room temperature, as the Lewis basic additive HMPA accelerates the reaction of $ZnEt_2$ with terminal alkynes.[27] Later You and coworkers revealed that N-methylimidazole (NMI) is a more efficient Lewis basic additive than HMPA.[28] Recently, we have further reported that the use of biscyclohexylamine ($Cy_2NH$) in comparison to other Lewis bases significantly improves the asymmetric addition of linear alkyl alkynes to linear aldehydes.[29] Since 1,3-diynes possess an extended linear steric environment as result of the additional triple bond we chose to began our investigations with $Cy_2NH$ as the Lewis basic additive. For these initial experiments we identified hexa-3,4-diynylbenzene, **4-1a**, as an easily accessible and robust 1,3-diyne.

**Scheme 4.5**. (*S*)-BINOL Catalyzed Hexa-3,4-Diynylbenzene Addition to Benzaldehyde.




Application of the previously developed reaction conditions utilizing 2 equiv of $ZnEt_2$ and diyne **4-1a**, 5 mol % $Cy_2NH$, 20 mol % (*S*)-BINOL, and 50 mol % $Ti(O^iPr)_4$ for the addition to benzaldehyde as shown in Scheme 4.5 resulted in excellent yield (98%) and enantioselectivity (95% ee). Given previous reports involving the enantioselective additions of 1,3-diynes, we found it remarkable that the unmodified method developed for simple alkynes was highly effective for 1,3-diynes. In order to better understand the catalytic system, we probed different parts of the reaction system including the solvent and ratio of $Ti(O^iPr)_4$ to BINOL as shown in Table 4.1. A solvent screen revealed that while THF, a coordinating solvent, resulted in a decreased enantioselectivity (68%, entry 2), $CH_2Cl_2$ and toluene and retained high enantioselectivity but in diminished yield. Having identified $Et_2O$ as the optimal solvent we next screened the amount of $Ti(O^iPr)_4$ necessary for high enantioselectivity. Increasing and decreasing the amount of $Ti(O^iPr)_4$ slightly lowered the enantioselectivity (entries 5,6), indicating that a 2.5:1 ratio of $Ti(O^iPr)_4$:BINOL is optimal for this catalytic system. We also probed the efficiency of the first step of the reaction by investigating the amount of time in the first step needed for the formation of the diynylzinc. Decreasing the time of the first step to 16 h maintained the high yield and enantioselectivity (entry 7). Further decreasing the time to 8 h resulted in a slight reduction of the yield and ee (entry 8). Finally, we tested the limits of the chiral catalyst necessary for high enantiocontrol. Reduced loadings of

**Table 4.1.** Optimization of Conditions for the Reaction of Hexa-3,4-Diynylbenzene with Benzaldehyde Catalyzed by (*S*)-BINOL/$ZnEt_2$/$Cy_2NH$/$Ti(O^iPr)_4$.[a]

| entry | BINOL mol % | diyne/$ZnEt_2$ (equiv.) | solvent | time 1st step | $Ti(O^iPr)_4$ (mol %) | yield (%) | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | 20 | 2 | $Et_2O$ | 24 h | 50 | 98 | 95 |
| 2 | 20 | 2 | THF | 24 h | 50 | 41 | 68 |
| 3 | 20 | 2 | $CH_2Cl_2$ | 24 h | 50 | 77 | 94 |
| 4 | 20 | 2 | Toluene | 24 h | 50 | 51 | 96 |
| 5 | 20 | 2 | $Et_2O$ | 24 h | 100 | 94 | 93 |
| 6 | 20 | 2 | $Et_2O$ | 16 h | 25 | 91 | 86 |
| 7 | 20 | 2 | $Et_2O$ | 16 h | 50 | 97 | 94 |
| 8 | 20 | 2 | $Et_2O$ | 8 h | 50 | 85 | 91 |
| 9 | 10 | 2 | $Et_2O$ | 16 h | 25 | 96 | 94 |
| 10 | 5 | 2 | $Et_2O$ | 16 h | 12.5 | 98 | 78 |
| **11**[b] | **10** | **2** | **$Et_2O$** | **16 h** | **25** | **95** | **94** |

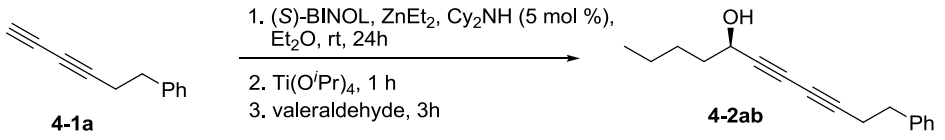
(a) Unless otherwise indicated, the following conditions were employed: A diyne was dissolved in solvent (3 mL). (*S*)-BINOL, $Cy_2NH$ (5 mol %), and $ZnEt_2$ were added the reaction stirred for 24, 16, or 8 h. $Ti(O^iPr)_4$ was then added and stirred for 1h. Benzaldehyde (0.25 mmol) was added and stirred for 3 h. (b) $Ti(O^iPr)_4$ and the aldehyde were added in the same step. (c) Enantiomeric excess was determined by HPLC analysis (Chiralpack AD-H column).

BINOL (10 mol %) and $Ti(O^iPr)_4$ (25 mol) still catalyzed the reaction in high enantioselectivity (entry 9). Further reduction to 5 mol % BINOL resulted in substantially diminished ee. To simplify the reaction procedure, we tested the addition of $Ti(O^iPr)_4$ followed by benzaldehyde in the same step (entry 11), finding that this did not

diminish the yield or ee. This indicates that the chiral catalyst forms very quickly following the addition of $Ti(O^iPr)_4$.

With an effective system for 1,3-diyne additions to aromatic aldehydes we next investigated the addition of hexa-3,4-diynylbenzene to a linear aliphatic aldehyde, valeraldehyde, as shown in Scheme 4.6. Using the conditions found to be optimal for aromatic aldehydes resulted in good yield (96%), but only moderate enantioselectivity (66% ee, entry 1, Table 4.2). This was not disheartening, as aliphatic aldehydes typically require higher loadings of BINOL to achieve high enantioselectivities. Doubling the amount of BINOL (20 mol %) and $Ti(O^iPr)_4$ (50 mol %) improved the enantioselectivity to 82% ee (entry 2). Screening THF, $CH_2Cl_2$, and toluene confirmed that $Et_2O$ was the optimal solvent (entries 3-5). Toluene provided the highest enantioselectivity (84% ee) but only a moderate yield (55%, entry 5). Lowering the temperature did not prove to be beneficial, as addition of the aldehyde at 0 °C diminished the ee (59%, entry 6). A surprising result was uncovered when the equivalents of the 1,3-diyne and $ZnEt_2$ were decreased, as this significantly decreased the enantioselectivity (50% ee, entry 7).

**Scheme 4.6.** (*S*)-BINOL Catalyzed Hexa-3,4-diynylbenzene Addition to Valeraldehyde.




In order to improve the enantioselectivity further, the use of 30 mol % and 40 mol % BINOL was tested. Use of 30 mol % BINOL in combination with 2 equiv of the 1,3-diyne and $ZnEt_2$ resulted in a decrease in ee (69%, entry 8). Increasing to 3 equiv of

**Table 4.2.** Optimization of Conditions for the Reaction of Hexa-3,4-Diynylbenzene with Valeraldehyde Catalyzed by (*S*)-BINOL/$ZnEt_2$/$Cy_2NH$/$Ti(O^iPr)_4$.[a]

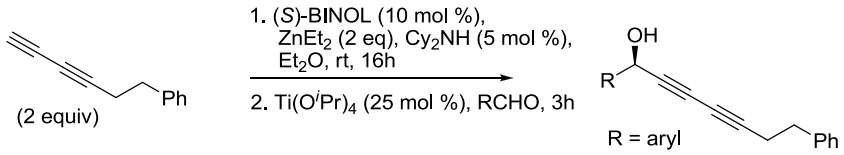
| entry | BINOL mol % | diyne/$ZnEt_2$ (equiv.) | solvent | time 1st step | $Ti(O^iPr)_4$ (mol %) | yield (%) | ee (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | 10 | 2 | $Et_2O$ | 16 h | 25 | 96 | 66 |
| 2 | 20 | 2 | $Et_2O$ | 24 h | 50 | 97 | 82 |
| 3 | 20 | 2 | THF | 24 h | 50 | 58 | 60 |
| 4 | 20 | 2 | $CH_2Cl_2$ | 24 h | 50 | 95 | 62 |
| 5 | 20 | 2 | Toluene | 24 h | 50 | 55 | 84 |
| 6[b] | 20 | 2 | $Et_2O$ | 16 h | 50 | 64 | 59 |
| 7 | 20 | 1.5 | $Et_2O$ | 16 h | 50 | 62 | 50 |
| 8 | 30 | 2 | $Et_2O$ | 16 h | 75 | 83 | 69 |
| 9 | 30 | 3 | $Et_2O$ | 16 h | 75 | 95 | 85 |
| 10 | 40 | 2 | $Et_2O$ | 16 h | 50 | 88 | 60 |
| 11 | 40 | 2 | $Et_2O$ | 16 h | 100 | 82 | 69 |
| 12 | 40 | 3 | $Et_2O$ | 16 h | 100 | 91 | 92 |
| **13[c]** | **40** | **3** | **$Et_2O$** | **16 h** | **100** | **92** | **92** |

(a) Unless otherwise indicated, the following conditions were employed: A diyne was dissolved in solvent (3 mL). (*S*)-BINOL, $Cy_2NH$ (5 mol %), and $ZnEt_2$ were added the reaction stirred for 24 or 16 h. $Ti(O^iPr)_4$ was then added and stirred for 1h. Valeraldehyde (0.25 mmol) was added and stirred for 3 h. (b) Aldehyde added at 0 °C and the reaction was maintained at this temperature until quenched. (c) $Ti(O^iPr)_4$ and the aldehyde were added in the same step. (d) Enantiomeric excess was determined by HPLC analysis (Chiralcel OD column).

the diyne and $ZnEt_2$ restored the enantioselectivity (85%, entry 9). Use of 40 mol % BINOL and 100 mol % $Ti(O^iPr)_4$ further improved the enantioselectivity to 92% (entry

12). When the aldehyde was added immediately followed the addition of $Ti(O^iPr)_4$ the high yield and ee were maintained (entry 13).

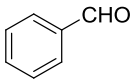
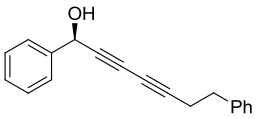
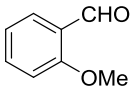
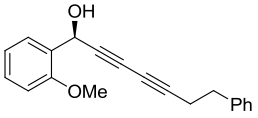
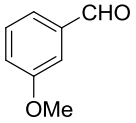
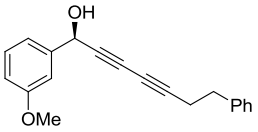
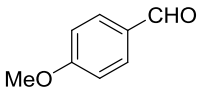
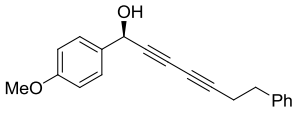
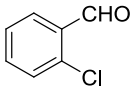
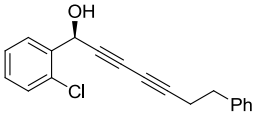
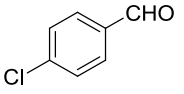
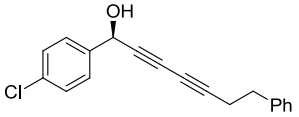
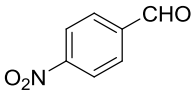
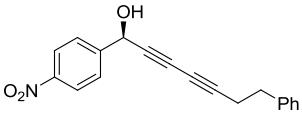
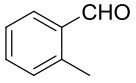
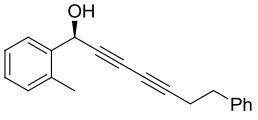
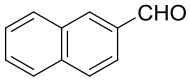
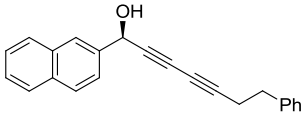
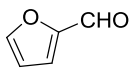
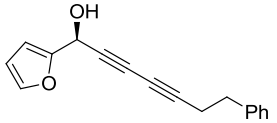
**Scheme 4.7.** (*S*)-BINOL Catalyzed Hexa-3,4-diynylbenzene Addition to Aromatic Aldehydes.




With effective systems for the addition of hexa-3,4-diynylbenzene to benzaldehyde and valeraldehyde we turned to probing the generality of this method for a variety of aromatic and aliphatic aldehydes (Tables 4.3 and 4.4). Employing the optimized conditions for benzaldehyde (Table 4.1, entry11), the catalytic system was found to be highly enantioselective for a wide range of aromatic aldehydes (Table 4.3), including aldehydes bearing electron-donating (entries 2-4) and electron-withdrawing (entries 5-7) substituents. The method was also successful with *ortho*-, *meta*-, and *para*-substituted benzaldehydes. However it was found that in some cases the *ortho*-substituted benzaldehyde substrates required increasing the loading of BINOL to 20 mol % to achieve high enantioselectivity (entries 5 and 8). 2-Naphthaldehyde and 2-furaldehyde also furnished the optically active propargylic alcohols in good yield and enantioselectivity (entries 9 and 10).

Application of the optimized conditions for valeraldehyde (entry 13, Table 4.2) also proved to be highly enantioselective for a range of substrates, furnishing the propargylic alcohols in 87-92% ee (Table 4.4). Simple linear aliphatic aldehydes (entries

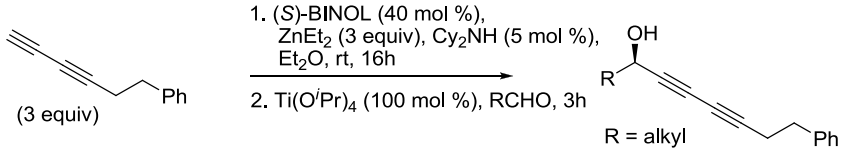
**Table 4.3.** Addition of Hexa-3,4-diynylbenzene to Aromatic Aldehydes Catalyzed by (*S*)-BINOL/$ZnEt_2$/$Cy_2NH$/$Ti(O^iPr)_4$.[a]

| entry | aldehyde | product | | yield (%) | ee (%)[c] |
|---|---|---|---|---|---|
| 1 |  |  | **4-2aa** | 95 | 94 |
| 2 |  |  | **4-2ac** | 81 | 91 |
| 3 |  |  | **4-2ad** | 96 | 90 |
| 4 |  |  | **4-2ae** | 94 | 94 |
| 5 |  |  | **4-2af** | 92<br>92 | 79<br>89[b] |
| 6 |  |  | **4-2ag** | 94 | 92 |
| 7 |  |  | **4-2ah** | 56 | 90 |
| 8 |  |  | **4-2ai** | 98<br>98 | 74<br>92[b] |
| 9 |  |  | **4-2aj** | 98 | 93 |
| 10 |  |  | **4-2ak** | 89 | 85 |

(a) Diyne/$ZnEt_2$/$Cy_2NH$/(*S*)-BINOL/$Ti(O^iPr)_4$/aldehyde = 2:2:0.05:0.1:0.25:1. (b) Diyne/$ZnEt_2$/$Cy_2NH$/(*S*)-BINOL/$Ti(O^iPr)_4$/aldehyde = 2:2:0.05:0.2:0.50:1. (c) Determined by HPLC analysis (Chiralcel OD, OB-H, or Chiralpak AD-H column).

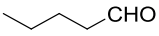
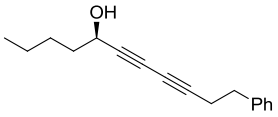
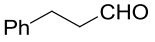
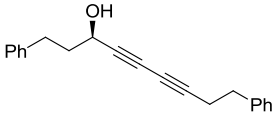
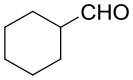
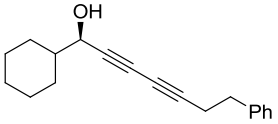
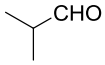
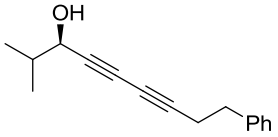
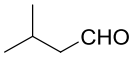
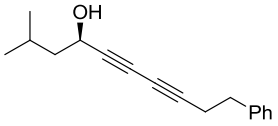
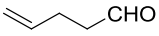
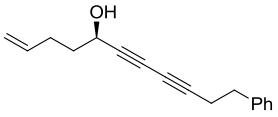
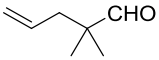
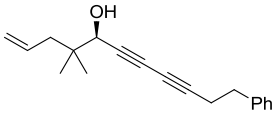
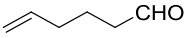
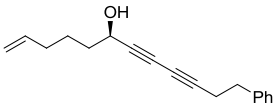
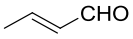
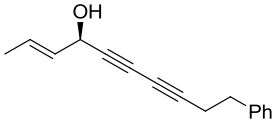
1 and 2), α-branched aldehydes (entry 3 and 4), and β-branched aldehydes (entry 5) were all tolerated and furnished high yields and enantioselectivities. Importantly, a variety of enals were compatible with the catalytic system, providing the corresponding enediynes in good yields (80-86%) and 89-92% ee (entries 6-8). Finally, an α,β-unsaturated aldehyde, trans-crotonaldehyde, was also found to be well-suited for this catalytic system (92% ee, entry 9).

**Scheme 4.8.** (*S*)-BINOL Catalyzed Hexa-3,4-diynylbenzene Addition to Aliphatic Aldehydes.



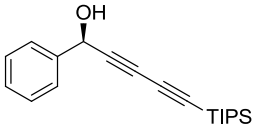
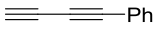
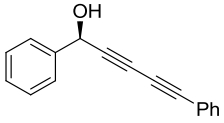
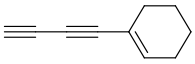
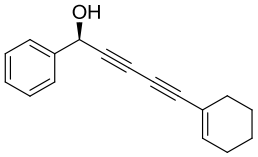
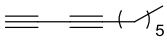
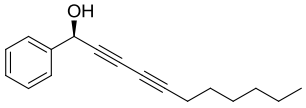
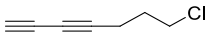
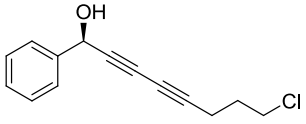
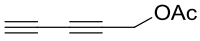
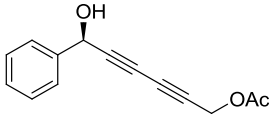
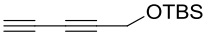
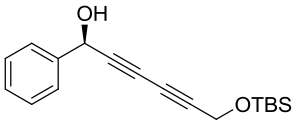
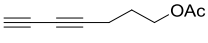
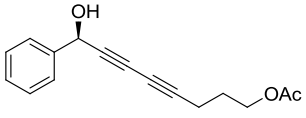
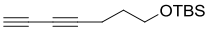
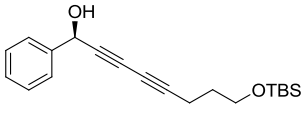

Having established the substrate scope in regards to the aldehyde, we next turned to exploring the compatibility of a range of 1,3-diynes with our catalytic system. To this end we prepared a variety of 1,3-diynes containing simple and functionalized alkyl substituents, as well as a silyl-substituted, aryl-substituted, and vinyl-substituted 1,3-diyne. With these substrates in hand we began by testing the enantioselective addition of various 1,3-diynes to benzaldehyde. The results summarized in Table 4.5 demonstrate that the catalytic system is tolerant of a wide range of terminal functionalities exhibiting a range of steric and electronic properties. Excellent yields and high enantioselectivities were obtained for 1,3-diynes containing the triisopropylsilyl (TIPS) ( 91% ee, entry 1), phenyl (88%, entry 2), and cyclohexenyl (90% ee, entry 3) substituents. A variety of alkyl substituents were also explored, revealing that 1,3-diynes containing linear alkyl groups (94% ee, entry 4), halogen containing alkyl groups (91% ee, entry 5), and

**Table 4.4.** Addition of Hexa-3,4-Diynylbenzene to Aliphatic Aldehydes Catalyzed by (*S*)-BINOL/$ZnEt_2$/$Cy_2NH$/$Ti(O^iPr)_4$.[a]

| entry | aldehyde | product | | yield (%) | ee (%)[b] |
|---|---|---|---|---|---|
| 1 |  |  | **4-2ab** | 92 | 92 |
| 2 |  |  | **4-2al** | 93 | 88 |
| 3 |  |  | **4-2am** | 91 | 91 |
| 4 |  |  | **4-2an** | 95 | 90 |
| 5 |  |  | **4-2ao** | 90 | 87 |
| 6 |  |  | **4-2ap** | 80 | 92 |
| 7 |  |  | **4-2aq** | 82 | 89 |
| 8 |  |  | **4-2ar** | 86 | 90 |
| 9 |  |  | **4-2as** | 99 | 92 |

(a) Diyne/$ZnEt_2$/$Cy_2NH$/(*S*)-BINOL/$Ti(O^iPr)_4$/aldehyde = 3:3:0.05:0.4:1:1. (b) Determined by HPLC analysis (Chiralcel OD, OB-H, or Chiralpak AD-H column).

**Table 4.5.** Addition of Diynes to Benzaldehyde Catalyzed by (*S*)-BINOL/$ZnEt_2$/ $Cy_2NH$/$Ti(O^iPr)_4$.[a]

| entry | diyne | product | yield (%) | ee (%)[b] |
|---|---|---|---|---|
| 1 |  **1b** |  **4-2ba** | 98 | 91 |
| 2 |  **1c** |  **4-2ca** | 98 | 88 |
| 3 |  **1d** |  **4-2da** | 99 | 90 |
| 4 |  **1e** |  **4-2ea** | 87 | 94 |
| 5 |  **1f** |  **4-2fa** | 95 | 91 |
| 6 |  **1g** |  **4-2ga** | 87 | 83 |
| 7 |  **1h** |  **4-2ha** | 95 | 94 |
| 8 |  **1i** |  **4-2ia** | 78 | 86 |
| 9 |  **1j** |  **4-2ja** | 97 | 92 |

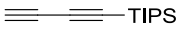
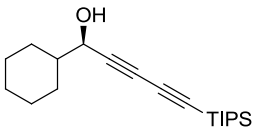
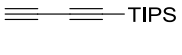
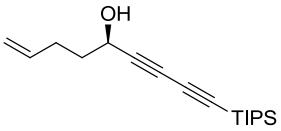
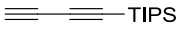
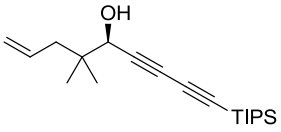
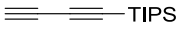
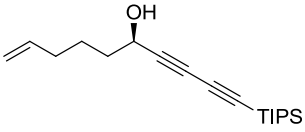
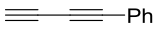
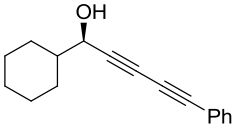
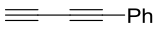
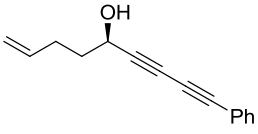
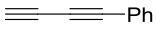
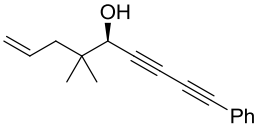
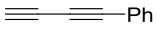
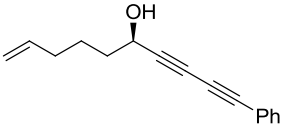
(a) Diyne/$ZnEt_2$/$Cy_2NH$/(*S*)-BINOL/$Ti(O^iPr)_4$/aldehyde = 2:2:0.05:0.1:0.25:1. (b) Determined by HPLC analysis (Chiralcel OD, OB-H, or Chiralpak AD-H column).

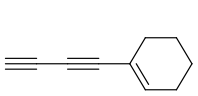
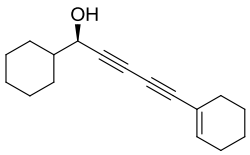
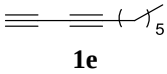
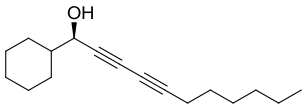
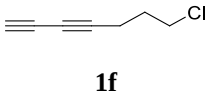
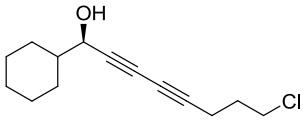
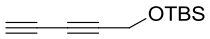
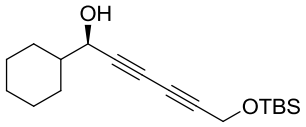
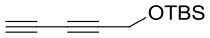
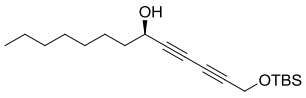
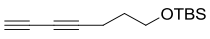
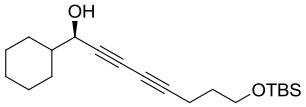
protected alcohols (83-94% ee, entries 6-9) were all appropriate nucleophiles for the addition to benzaldehyde. Interestingly our catalytic system proved to be more effective for 1,3-diynes bearing *tert*-butyldimethylsilyl (TBS) protected alcohols in comparison to the acetate protecting group (entries 7 and 9 vs. entries 6 and 8). This provides a complementary method to the ProPhenol system developed by Trost and coworkers, as their catalytic system was found to be more effective for 1,3-diynes bearing the acetate protecting group.

In light of this success we expanded our methodology to the addition of a variety 1,3-diynes with aliphatic aldehydes. As shown in Table 4.6, silyl (89% ee, entry 1), aryl (92% ee, entry 5), and vinyl (90% ee, entry 9) containing diynes are all suitable nucleophiles for the addition to cyclohexanecarboxaldehyde providing high yields and enantioselectivities. Interestingly, 1,3-diynes containing linear alkyl substituents were found to be slightly more challenging in comparison to other substrates for additions to aliphatic aldehydes providing enantioselectivities of 85-86% (entries 10 and 11). Functional 1,3-diynes containing silyl-protected alcohols were also suitable donors, and were found to provide high enantioselectivities (88-92% ee) for cyclic and linear aliphatic aldehydes (entries 12-14). Having already established that alkyl substituted diynes were effective for additions to enals, we also focused on the addition of silyl and aryl-substituted diynes to aliphatic aldehydes containing terminal alkenes. The desired enediynes could be accessed in good yields and high enantioselectivities, with the addition of buta-1,3-diynyltriisopropylsilane (**4-1b**) affording enantioselectivities of 88-95% (entries 2-4), and the addition of buta-1,3-diynylbenzene (**4-1c**) resulting in 89-91% ee. These findings represent the first catalytic system demonstrated to provide high

enantioselectivities for the addition of a range of 1,3-diynes to a variety of aliphatic and aromatic aldehydes.

**Table 4.6.** Addition of Diynes to Aliphatic Aldehydes Catalyzed by (*S*)-BINOL/$ZnEt_2$/$Cy_2NH$/$Ti(O^iPr)_4$.[a]

| entry | diyne | product | | yield (%) | ee (%)[b] |
|---|---|---|---|---|---|
| 1 |  **1b** |  | **4-2bm** | 99 | 89 |
| 2 |  **1b** |  | **4-2bp** | 94 | 95 |
| 3 |  **1b** |  | **4-2bq** | 98 | 88 |
| 4 |  **1b** |  | **4-2br** | 87 | 91 |
| 5 |  **1c** |  | **4-2cm** | 98 | 92 |
| 6 |  **1c** |  | **4-2cp** | 97 | 90 |
| 7 |  **1c** |  | **4-2cq** | 97 | 89 |
| 8 |  **1c** |  | **4-2cr** | 73 | 91 |

| | | | | | |
|---|---|---|---|---|---|
| 9 |  **1d** |  | **4-2dm** | 99 | 90 |
| 10 |  **1e** |  | **4-2em** | 97 | 86 |
| 11 |  **1f** |  | **4-2fm** | 98 | 85 |
| 12 |  **1h** |  | **4-2hm** | 98 | 91 |
| 13 |  **1h** |  | **4-2ht** | 89 | 88 |
| 14 |  **1j** |  | **4-2jm** | 99 | 92 |

(a) Diyne/$ZnEt_2$/$Cy_2NH$/(*S*)-BINOL/$Ti(O^iPr)_4$/aldehyde = 3:3:0.05:0.4:1:1. (b) Determined by HPLC analysis (Chiralcel OD, OB-H, or Chiralpak AD-H column).

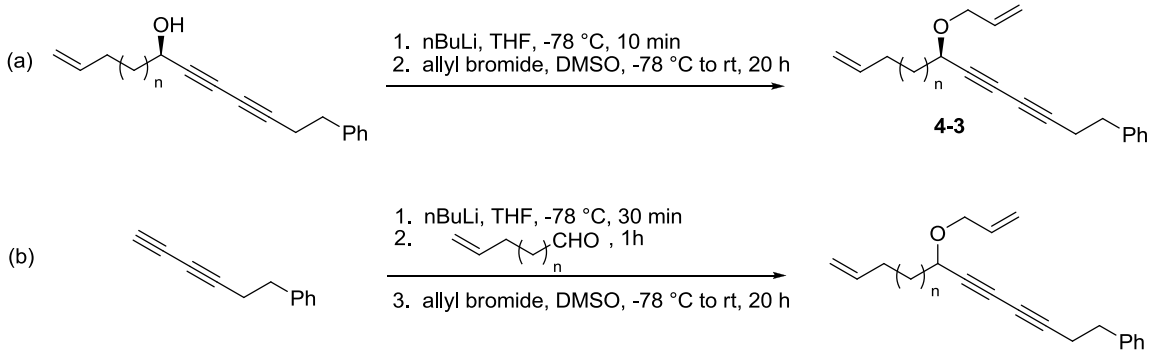
### 4.3. Construction of Optically Active Polycycles from Dienediyne Precursors

*a. Diastereoselective Pauson-Khand Reaction of Optically Active Dienediynes.*

Having established an effective catalytic system to access optically active enediynes we prepared to explore the reactivity of dienediynes **4-3** in the PK reaction. As shown in Scheme 4.9a, deprotonation of the propargylic alcohol at low temperatures with $^n$BuLi followed by derivatization with allyl bromide afforded the optically active substrates in high yields. Alternatively, the racemic dienediynes could be easily prepared

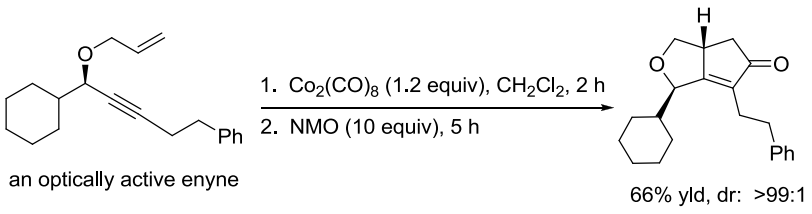
in the one pot method shown in Scheme 4.9b, and these substrates were used to screen conditions for the PK reaction.

**Scheme 4.9.** Preparation of Optically Active and Racemic Dienediynes.



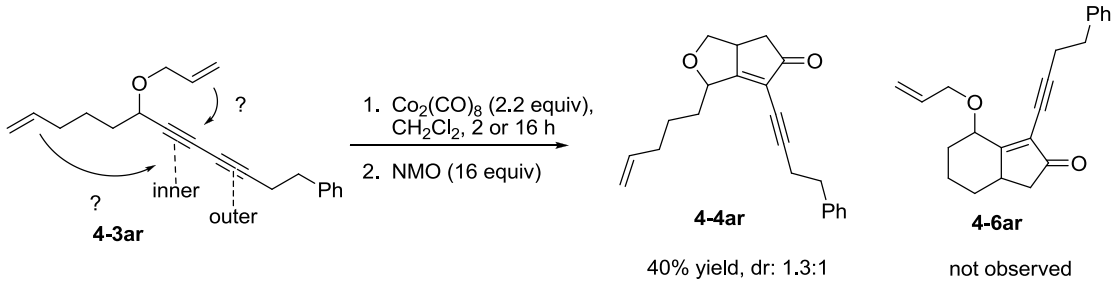

The intramolecular PK reaction of enynes in the presence of stoichiometric $Co_2(CO)_8$ has been extensively studied. Over the years, many highly diastereoselective cyclizations of this type have been reported.[30] As shown in Scheme 4.10 and discussed in Chapter 3, optically active propargylic alcohol-based enynes can undergo the highly diastereoselective PK cycloaddition in the presence of $Co_2(CO)_8$ and N-methylmorpholine oxide (NMO).[16] We began by applying the reaction conditions in Scheme 4.10 to the PK cycloaddition of the dienediynes.

**Scheme 4.10.** The Highly Diastereoselective PK Reaction of the Propargylic Alcohol-Based Enyne.



Because dienediynes such as **4-3ar** in Scheme 4.11 contained multiple reactive sites, we were conscious of several challenges unique to these substrates. First, would the cobalt be able to coordinate the desired alkyne of the 1,3-diyne effectively enough to promote the cyclization? It is expected that initial coordination of the outer alkyne would be sterically more favorable which could hinder coordination of a second equivalent of cobalt to the internal alkyne. Secondly, two alkenes were present in the substrate, raising the question of chemoselectivity. There was some precedent that allyloxy double bond should be favored,[31] but would this pathway predominate to a great enough extent to yield one cycloaddition product?

**Scheme 4.11.** Potential Chemoselectivity Challenge for PK Reaction of Dienediynes.

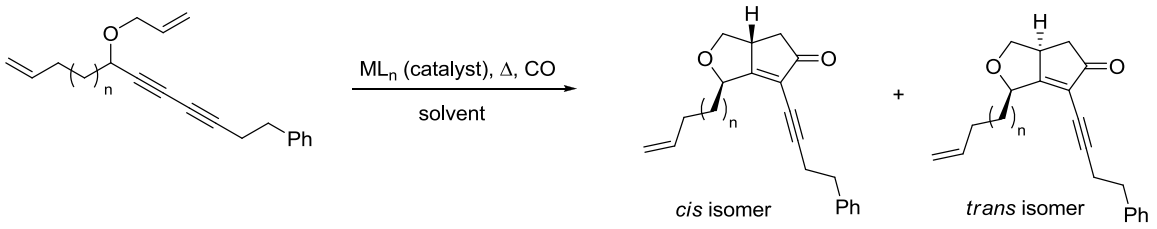



We conducted the reaction of **4-3ar** in the presence of 2.2 equiv of $Co_2(CO)_8$ and 16 equiv of NMO at room temperature (Scheme 4.11). This however only led to the formation of very small amounts of the cycloaddition products. Realizing that a longer time might be required for the complexation of the cobalt to both alkynes of **4-3ar**, we extended the first step reaction time from 2 h to 16 h. Upon treatment with NMO, the 5,5-cycloaddition product **4-4ar** was generated in moderate yield (~40%) without the formation of **4-6ar**. This reveals that the allyl ether reaction pathway was favored exclusively and good chemoselectivity could be achieved with these substrates.

However, unlike the high diastereoselectivity we observed for the PK cycloaddition of the propargylic alcohol-based enyne as shown in Scheme 4.10, the PK cycloaddition of **4-3ar** proceeded with little diastereoselectivity (1.3:1). Attempts to improve the yield and diastereoselectivity of the $Co_2(CO)_8$ mediated reaction by applying the various reaction conditions and promoters we found to be effective for the propargylic based alcohol enynes were unsuccessful.[16] Thermal reaction conditions employing reflux in acetonitrile or toluene, and the use of common promoters such as *n*-butyl methyl sulfide in dichloroethane at 83 °C[32] and tetramethylthiourea (TMTU) under reflux in toluene[33] all failed to produce more than trace amounts of the desired cycloaddition product.

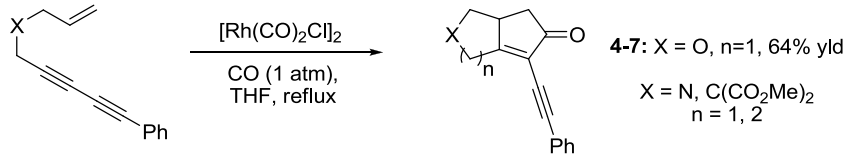
Having been unsuccessful employing stoichiometric amounts of $Co_2(CO)_8$, we began to suspect that the metal-*catalyzed* Pauson-Khand-type reaction could be more suitable for diyne substrates (Scheme 4.12). In recent years a variety of transition metals including Ti,[34] Zr,[35] Ni,[36] Mo,[37] Ru,[38] Rh,[39] Ir,[40] and Pd[41] have been utilized for the catalytic Pauson-Khand-type reaction in the presence of a CO source.[42] We chose to test several of the more widely applied and commercially available catalytic systems. It was found that the $[Cp_2Ti(CO)_2]$[34] and $PdCl_2$-thiourea[41] catalytic systems led to the opposite diastereomers of the cycloaddition product, but the yields were very low (10-25%). As expected for enyne substrates,[41] the $[Cp_2Ti(CO)_2]$ catalyzed reaction yielded *cis*-**4-4ar** in 10:1 dr and the $PdCl_2$-thiourea catalyzed reaction yielded *trans*-**4-4ar** in 8:1 dr. Using the $[Ir(cod)Cl_2]$-BINAP[40] catalytic system failed to generate the cycloaddition product.

**Scheme 4.12.** Transition Metal Catalyzed PK-Type Reaction of Dienediynes.




At this time we uncovered a report by Zhang and coworkers in which $[Rh(CO)_2Cl]_2$ was shown to catalyze the efficient PK cycloaddition of the structurally analogous enediynes under 1 atm CO in refluxing THF. In this work enediyne **4-7** was found to undergo the $[Rh(CO)_2Cl]_2$ catalyzed PK-type reaction in 64% yield as shown in Scheme 4.13).[43] These reaction conditions were also successfully applied by Zhang and coworkers to a variety of 1,3-diynes containing nitrogen and dimethylmalonate tethers, producing the corresponding 5,5-fused bicycles and a 5,6-fused ring system in 53-83% yield.

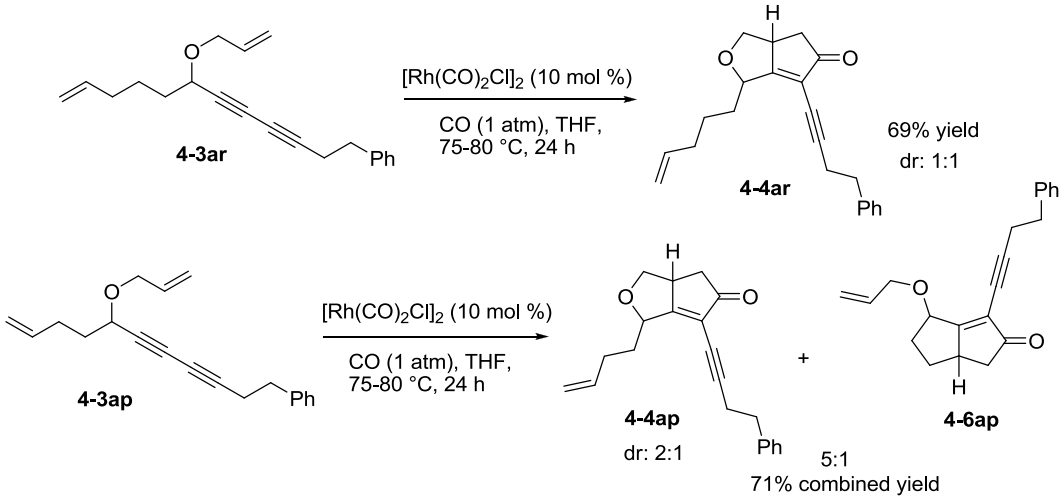
**Scheme 4.13**. $[Rh(CO)_2Cl]_2$ Catalyzed PK-type Reaction of Enediynes.




Applying the $[Rh(CO)_2Cl]_2$ (10 mol %) catalytic system to dienediyne **4-3ar** proved successful, forming cycloaddition product **4-4ar** chemoselectively in 69% yield (Scheme 4.14). However, no diastereoselectivity was observed with dr = 1:1. Application of this method to dienediyne **4-3ap** also proceeded in good yield (71%), but without exclusive chemoselectivity as a 5:1 ratio of cycloaddition product **4-4ap**:**4-6ap** was observed (Scheme 4.14). This was likely due to the faster formation of the 5,5-ring system in comparison with the 5,6-ring system. Therefore, for enediyne **4-3ap**

competitive cyclization pathways are present, although the pathway involving the allyl ether is still favored. Promisingly, for this substrate a degree of diastereoselection was observed (2:1 dr).

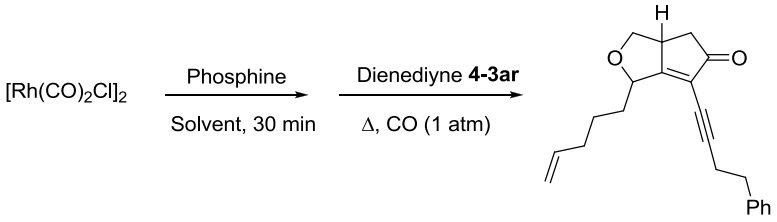
**Scheme 4.14**. $[Rh(CO)_2Cl]_2$ Catalyzed PK-type Reaction of Dienediynes.




In order to improve the diastereoselectivity of the Rh-catalyzed PK cycloaddition of the dienediynes, we tested the addition of phosphine ligands to tune the catalytic properties of the Rh complex.[39c,44] We hypothesized that coordination of phosphine ligands to the rhodium metal could modify the catalyst structure by creating a more restricted steric environment that might induce diastereoselection. The results are summarized in Table 4.7. Our initial attempts to employ simple monodentate and bidentate phosphines in combination with $[Rh(CO)_2Cl]_2$ to catalyze the reaction of **4-3ar** under 1 atm CO in refluxing THF as shown in Scheme 4.15 were found to deactivate the catalyst and yield no product (Table 4.7, entry 1). Elevated temperatures in refluxing toluene restored the reactivity although the yields were reduced (entries 2-4). Bidenate 1,3-bis(diphenylphosphino)propane (dppp) promoted increasing diastereoselectivity (up to 4:1 dr) as its equivalents relative to the rhodium metal center were increased.

However, this improvement was accompanied by an unacceptable drop in chemical yield. In contrast, use of monodenate $PPh_3$ failed to induce diastereoselectivity (entry 3). Bidentate 1,2-bis(diphenylphosphino)benzene provided a 3:1 dr, but in only 36% yield (entry 4).

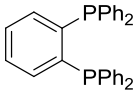
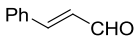
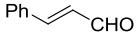
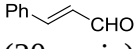
**Scheme 4.15.** Rh-Phosphine Catalyzed PK-Type Reaction of Dienediyne **4-3ar**.




Unable to achieve satisfactory yields we prepared and isolated $[RhCl(CO)dppp]_2$ from the reaction of $[Rh(cod)Cl]_2$ with dppp and CO,[45] in hopes that the isolated catalyst would provide better chemical yield. This was the case as the yield was improved to 71%, but disappointingly all diastereoselection was lost (entry 5a). The diastereoselectivity could be restored to 4:1 by the addition of dppp (10%) but this again reduced the yield (entry 5b). We next turned to the use of the cationic rhodium-BINAP catalyst system reported by Jeong,[39b] hoping that the cationic metal center would be beneficial for diastereoselectivity. While reasonable yields could be obtained with this method (54-67%), diastereoselectivities of only 2:1 were observed (entries 6 and 7).

In 2002, an interesting report by Shibata and coworkers disclosed a $[Rh(cod)Cl]_2$-phosphine catalytic system employing aldehydes as the solvent and CO source, alleviating the need for the use of toxic carbon monoxide gas.[46] Attracted by the advantages of this method we tested the reaction of dienediyne **4-3ar** with *trans*-cinnamaldehyde as the CO source (Scheme 4.16). Although use of dppp as the

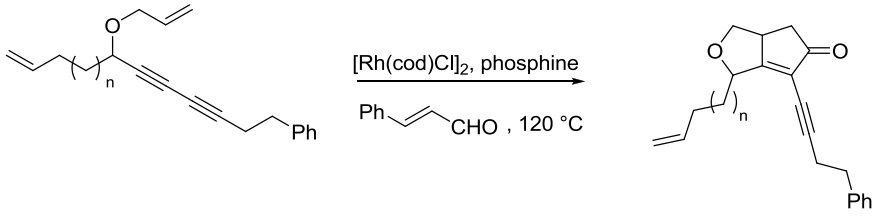
**Table 4.7.** Pauson-Khand Type Cyclization of Dienediynes **4-3ar** and **4-3ap**.[a]

| entry | metal (mol %) | phosphine (mol %) | additive (mol %) | solvent (reflux) | yield (%) | dr[b] |
|---|---|---|---|---|---|---|
| 1 | $[RhCl(CO)_2]_2$ (10) | a. $PPh_3$ (40)<br>b. $P^tBu_3$ (40)<br>c. dppp (40) | - | THF | - | - |
| 2 | $[RhCl(CO)_2]_2$ (10) | a. dppp (12)<br>b. dppp (20)<br>c. dppp (30) | - | toluene | a. 54<br>b. 33<br>c. 27 | a. 2:1<br>b. 4:1<br>c. 4:1 |
| 3 | $[RhCl(CO)_2]_2$ (10) | $PPh_3$ (40) | - | toluene | 33 | 1:1 |
| 4 | $[RhCl(CO)_2]_2$ (10) |  (22) | - | toluene | 36 | 3:1 |
| 5 | $[RhCl(CO)dppp]_2$ (10) | a. –<br>b. dppp (10) | - | toluene | a. 71<br>b. 28 | a. 1:1<br>b. 4:1 |
| 6[c] | $[RhCl(CO)_2]_2$ (6) | BINAP (18) | AgOTf (24) | THF | 67 | 2:1 |
| 7[c] | $[RhCl(CO)_2]_2$ (6) | tol-BINAP (18) | AgOTf (24) | THF | 54 | 2:1 |
| 8[d] | $[Rh(cod)Cl]_2$ (10) | dppp (20) |  (20 equiv) | -- | 60 | 1:1 |
| 9[d] | $[Rh(cod)Cl]_2$ (10) | BINAP (20) |  (20 equiv) | -- | 84 | 2:1 |
| 10[d,e] | $[Rh(cod)Cl]_2$ (10) | BINAP (20) |  (20 equiv) | -- | 64 | 2:1 |

(a)Unless otherwise indicated, the following conditions were employed: A metal and phosphine were combined in solvent (0.03 M relative to dienediyne) and stirred for 30 min. Dienediyne **4-3ar** was then added, the mixture was bubbled with CO gas for 2 min, and the reaction was heated at reflux under CO (1 atm, balloon) for 18 h. (b) Determined by integration of $^1H$ NMR spectra. (c) $[RhCl(CO)_2]_2$ and phosphine were combined in THF (0.03 M relative to dienediyne) and stirred for 10 min. AgOTf was added and stirred for 30 min. Dienediyne **4-3ar** was then added, the mixture was bubbled with CO gas for 2 min, and the reaction was heated at reflux under CO (1 atm, balloon) for 18 h. (c) $[Rh(cod)Cl]_2$, phosphine, and dienediyne **4-3ar** were combined in cinnamaldehyde and heated at 120 °C under nitrogen for 5 h. (e) Dienediyne **4-3ap** was used.

phosphine ligand did not provide any diastereoselectivity (entry 8), use of BINAP afforded the product in 84% yield and 2:1 dr (entry 9). Applying this method to dienediyne **4-3ap** yielded **4-4ap** with complete chemoselectivity in 64% yield and 2:1 dr (entry 10).

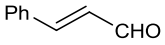
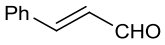
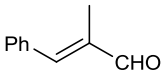
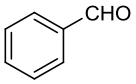
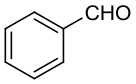
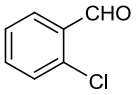
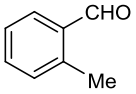
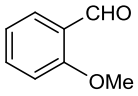
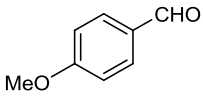
**Scheme 4.16**. $[Rh(cod)Cl]_2$ Catalyzed PK-Type Reaction with Aldehydes as a CO Source.




Encouraged by this result we tested the influence of the aldehyde CO source on the diastereoselectivity. In their initial paper Shibata and coworkers had revealed that benzaldehyde and 2-hexenal could also be competent CO donors.[46] If the aldehyde was associated in some way with the stereodetermining step an appropriate aldehyde could potentially fine-tune the catalytic center and enhance the diastereoselectivity. Furthermore, Shibata had demonstrated that the reaction could proceed at lower temperatures, though in reduced yields and longer reaction times. We also tested varied reaction temperatures in hopes of improving the diastereoselectivity.

Employing dienediyne **4-3ap** we screened a variety of aromatic aldehydes and reaction temperatures using 10 mol % $[Rh(cod)Cl]_2$, 20 mol % *rac*-BINAP, and 20 equiv of the aldehyde. As shown in Table 4.8 the product could still be generated when the reaction temperature was lowered to 80 °C with cinnamaldehyde as the CO source, although this did not improve the diastereoselectivity (entries 1 and 2). Switching to the

**Table 4.8.** Screening of Aldehyde CO Source for PK-Type Cyclization of Dienediynes.[a]

| entry | aldehyde | temperature | rxn time | yield (%) | dr[b] |
|---|---|---|---|---|---|
| 1 |  | 120 | 5h | 64 | 2:1 |
| 2 |  | 80 | 16h | 69 | 2:1 |
| 3 |  | 100 | 14h | 46 | 3:1 |
| 4 |  | 120 | 5h | 49 | 2:1 |
| **5** |  | **80** | **16h** | **60** | **4:1** |
| 6 |  | 100 | 16h | 65 | 2:1 |
| 7 |  | 100 | 16h | 37 | 3:1 |
| 8 |  | 100<br>80 | 16h | 47<br>38 | 3:1<br>4:1 |
| 9 |  | 80 | 16h | 32 | 4:1 |

Dienyne/[Rh(cod)Cl]$_2$/rac-BINAP/aldehyde = 1:0.10:0.20:20. Dienediyne **4-3ap** was used. (b)Determined by integration of $^1$H NMR spectra.

more sterically bulky α-methyl-*trans*-cinnamaldehyde supported our hypothesis that the aldehyde could impact the diastereoselectivity, improving the dr to 3:1 (entry 3). Lowering the temperature to 80 °C for this aldehyde resulted in only minimal amounts of

the desired product. Use of benzaldehyde as the CO donor did not improve the diastereoselectivity at high reaction temperatures (entry 4). However, lowering the reaction temperature to 80 °C provided a promising result, affording the product in 60% yield and 4:1 dr (entry 5). A variety of *ortho*-substituted aromatic aldehydes containing electron donating and withdrawing groups were then screened but did further enhance the diastereoselectivity (entries 6-9). From this small screening it appears that electron withdrawing substituents on the aromatic ring promote higher reactivity at the cost of diastereoselectivity, with electron donating substituents having the opposite effect. There was little difference in yield and diastereoselectivity between *ortho*- and *para*-anisaldehyde (entries 8 and 9). In all the experiments of Table 4.8, the product **4-6ap** was not observed. Thus, this catalytic system is highly chemoselective.

Since the conditions of entry 5 in Table 4.8 have provided the desired PK-cycloaddition product of the dienediyne **4-3ap** with practically useful yield and diastereoselectivity, we applied this catalyst system to the reaction of a variety of optically active dienediynes. The dienediynes were combined with 15 mol % $[Rh(cod)Cl]_2$, 30 mol % *rac*-BINAP, and 20 equiv benzaldehyde, heating at 80 °C. The results are summarized in Table 4.9. As shown in entries 1 – 6, the optically active dienediynes with alkyl, aryl and triisopropylsilyl substituents on the alkyne underwent the catalytic PK-cycloaddition to give the 5,5-fused bicyclic product with 48 – 78% yields and 3:1 – 4:1 dr. Importantly, the diastereomers could be separated by column chromatography, providing access to optically active and densely functionalized bicycles as a single diastereomer. We further found that when the steric bulkiness adjacent to the chiral center of the substrates increases, the diastereoselctivity of the catalytic PK-

cyclcoaddition was greatly enhanced. As shown in entries 7 – 9, excellent diastereoselectivity up to >20:1 was achieved with 51 – 71% yield. This great enhancement in selectivity can be attributed to the much larger steric bias provided by the geminal methyl groups. Analysis of the racemic and optically active product in entry 2 by chiral HPLC (Chiralpak AD-H column), confirmed that the cyclization proceeded without loss of optical purity. These results represent the first diastereoselective PK-type reaction of 1,3-diyne substrates.

**Scheme 4.17.** $[Rh(cod)Cl]_2$-BINAP catalyzed PK-Type Reaction of Various Dienediynes with Benzaldehyde as the CO Source.

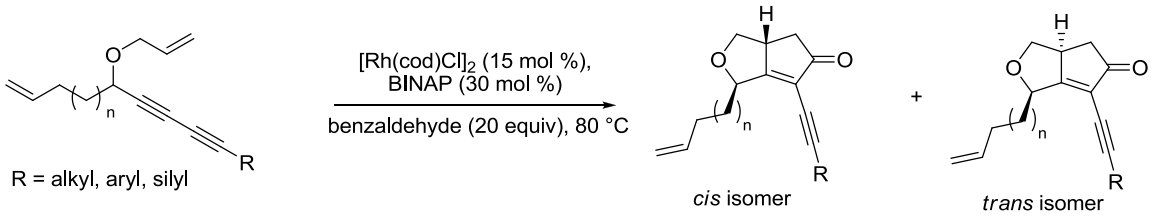
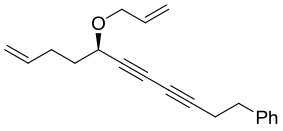
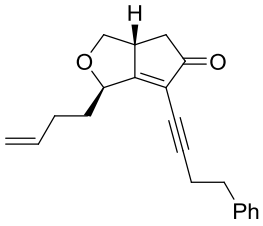
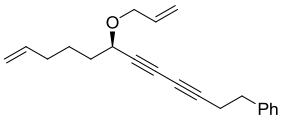
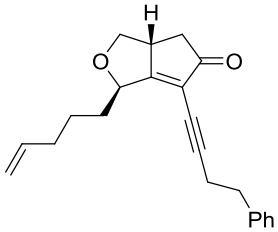
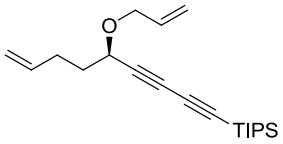
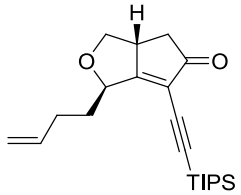
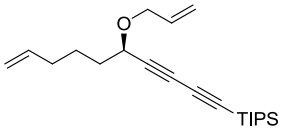
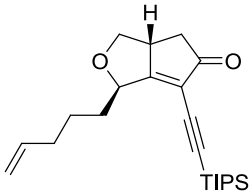
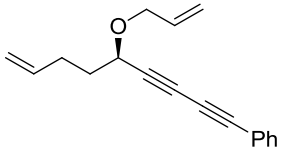
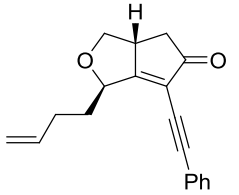
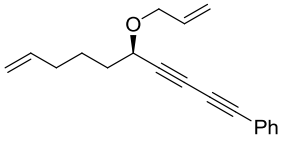
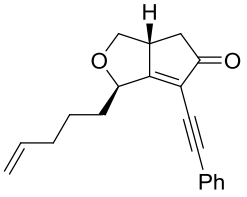
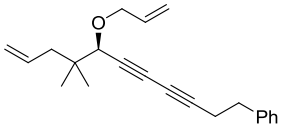
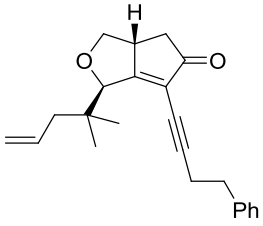
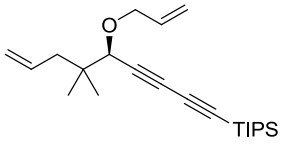
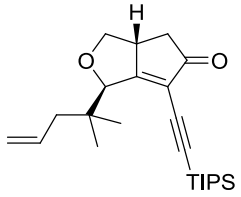
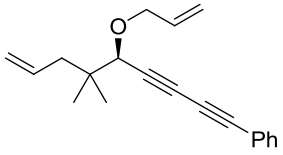
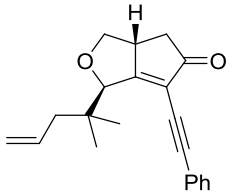



**Table 4.9.** $[Rh(cod)Cl]_2$-BINAP catalyzed PK-Type Cyclization of Dienediynes.[a]

| entry | dienediyne (ee) | rxn time | product | | yield (%) | dr [b] |
|---|---|---|---|---|---|---|
| 1 |  **4-3ap** (92% ee) | 16h |  | **4-4ap** | 62 | 4:1 |
| 2 |  **4-3ar** (90% ee) | 20h |  | **4-4ar** | 73 | 4:1 |

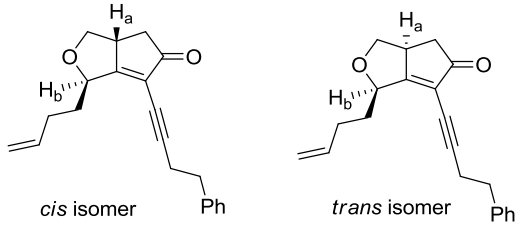
| | | | | | | |
|---|---|---|---|---|---|---|
| 3 |  **4-3bp** (95% ee) | 16h |  | **4-4bp** | 76 | 4:1 |
| 4 |  **4-3br** (91% ee) | 16h |  | **4-4br** | 60 | 3:1 |
| 5 |  **4-3cp** (90% ee) | 10h |  | **4-4cp** | 57 | 3:1 |
| 6 |  **4-3cr** (91% ee) | 16h |  | **4-4cr** | 48 | 4:1 |
| 7 |  **4-3aq** (89% ee) | 36h |  | **4-4aq** | 51 | 17:1 |
| 8 |  **4-3bq** (88% ee) | 60h |  | **4-4bq** | 68 | >20:1[c] |
| 9 |  **4-3cq** (89% ee) | 18h |  | **4-4cq** | 71 | 18:1 |

(a) Dienyne/$[Rh(cod)Cl]_2$/rac-BINAP/benzaldehyde = 1:0.15:0.30:20. (b) Ratio of *cis*:*trans* isomer. Determined by integration of $^1H$ NMR spectra. (c) Only 1 diastereomer was observed.

The *cis* and *trans* stereoisomers of the PK-cycloaddition of the dienediynes were determined on the basis of the correlation with the known chemical shifts of the

analogous cycloaddition products derived from enynes.[16] For these substrates the *cis* isomer has been observed to have a more upfield chemical shift in relation to the *trans* isomer. For example, for product **4-4ap**, $H_b$ resonates at $\delta$ 4.66 in the *cis* isomer (major), while in the *trans* isomer (minor) $H_b$ resonates at $\delta$ 4.79; that is the *cis* isomer gives a more upfield $H_b$ signal than the *trans* isomer. All of the products in Table 4.9 manifested this diagnostic chemical shift pattern. Analyses of the major and minor diastereomers of **4-4ap** by NOESY spectroscopy support this structural assignment. A NOE effect was observed between $H_a$ and $H_b$ in the minor diastereomer but not in the major diastereomer. Therefore, the minor diastereomer is determined to be the *trans* isomer and the major one to be the *cis* isomer.

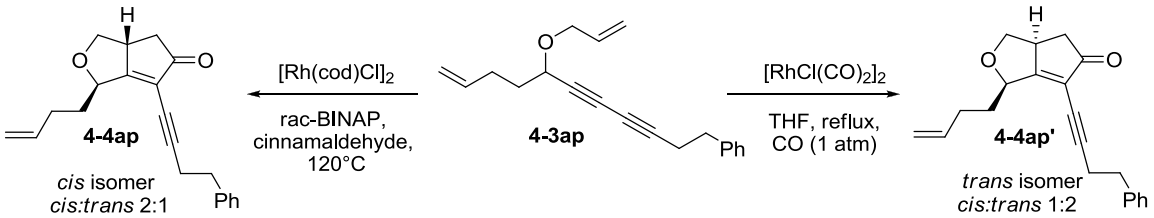
**Figure 4.5.** The *cis* and *trans* Isomers of the PK-Type Cycloaddition of Dienediynes.




*b. Diastereocontrol of Rhodium-Catalyzed PK-Type Cyclization*

During our study of the Rh-catalyzed PK-type cyclization of dienediynes we encountered an interesting reversal of diastereoselectivity using substrate **4-3ap** when the reaction was catalyzed by a Rh-phosphine catalyst as opposed to use of the phosphine free $[RhCl(CO)_2]_2$ catalyst. As shown in Scheme 4.18, the reaction of **4-3ap** in the presence of $[Rh(cod)Cl]_2$ and *rac*-BINAP yields *cis* **4-4ap** as the major diastereomer, while the reaction of **4-3ap** in the presence of $[RhCl(CO)_2]_2$ yields *trans* **4-4ap'** as the major stereoisomer.

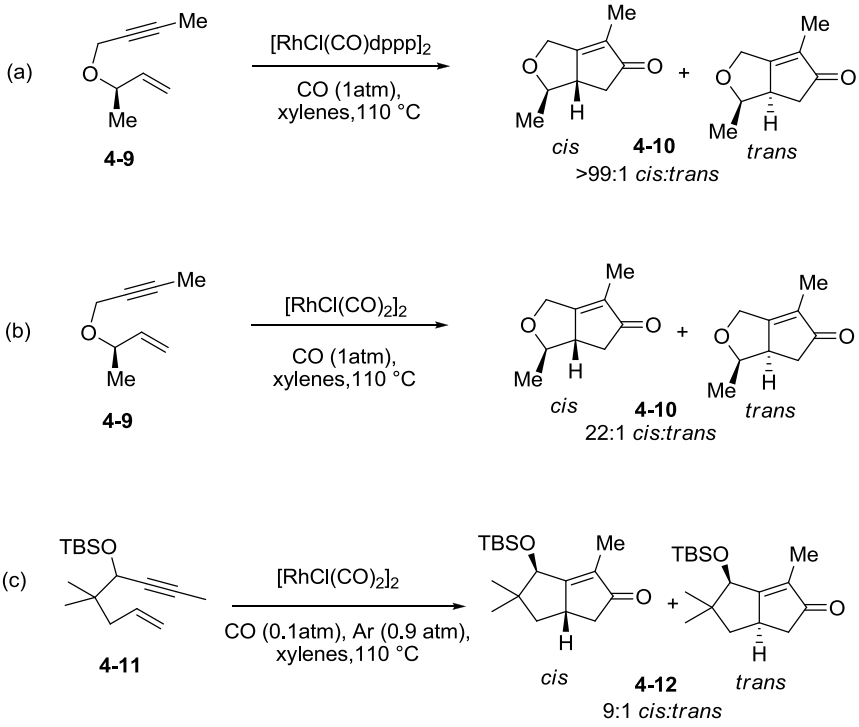
**Scheme 4.18**. Reversal of Diastereoselectivity By Employing Phosphine Ligand in the Rh Catalyzed PK-Type Cyclization.




Intrigued by this result we considered the mechanism of the Rh catalyzed PK-type cyclization. While there have been no reports of the diastereoselective Rh-catalyzed PK-type cyclization of enediynes, there have been a handful of reports of diastereoselective Rh-catalyzed cylizations involving enynes.[38d,47] The most thorough investigations have been directed toward enynes bearing the chiral center at the allylic rather than the propargylic position. Evans and coworkers first demonstrated that the reaction could be highly diastereoselective in their report of a tandem Rh-catalyzed allylic alkylation-PK annulation.[47a] They later examined the diastereoselectivity of the reaction in more detail.[47b] As shown in Scheme 4.19a, excellent diastereoselectivity can be obtained from substrates bearing a chiral center at the allylic position. Interestingly, the use of a Rh-phosphine catalyst results in higher diastereoselectivities for this substrate than a phosphine free catalyst system (Scheme 4.19b). In constrast to our observations with dienediyne **4-3ap**, for enyne **4-9** the same *cis* cycloadduct **4-10** was observed as the major product in both cases. In a report of the Rh-catalyzed cycloaddition of an enyne containing a propargylic substituent, substrate **4-11** possess sterically bulky geminal methyl groups at the propargylic positions underwent the PK-type reaction in the presence of the phosphine free $[RhCl(CO)_2]_2$ catalyst to form cycloadduct **4-12** in 9:1

diastereoselectivity. In this example the *cis* diastereomer was isolated as the major product (Scheme 4.19c).[38d] This report was also in contrast to our observation that dienediyne **4-3ap** formed the *trans* diastereomer when subjected to the $[RhCl(CO)_2]_2$ catalytic system.

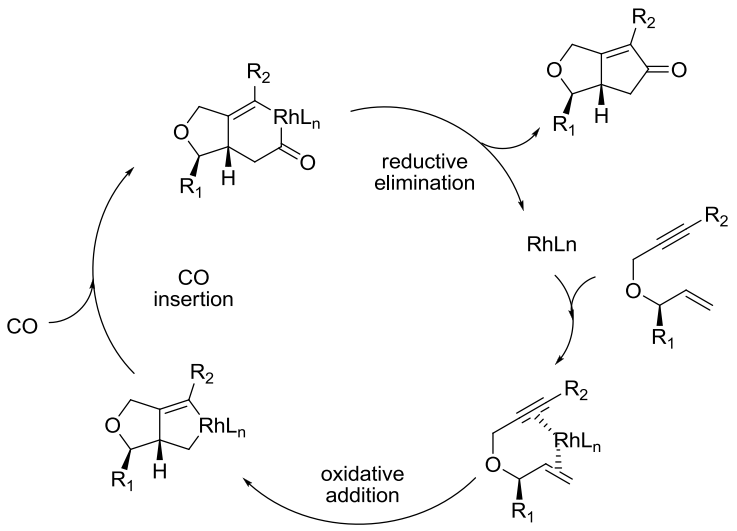
**Scheme 4.19.** Examples of Diastereoselective Rh-Catalyzed PK-Type Reactions of Enynes.




To rationalize the observed *cis* diastereoselectivity of the Rh-phosphine catalyzed reaction, Evans and coworkers initially proposed the mechanistic hypothesis shown in Scheme 4.20.[47a] They later analyzed the phosphine free $[RhCl(CO)_2]_2$ reaction on a computational level.[47b] The catalytic cycle is accepted to occur through formation of the Rh-enyne π complex, oxidative addition, CO insertion in the Rh-carbon bond, and finally reductive elimination to yield the bicycle. The key diastereoselection step involves the

facial selectivity of the rhodium metal center with respect to the enyne. For this coordination it is reasonable to assume that the Rh metal prefers complexation with the face of the enyne opposite the larger substituent $R_1$. The subsequent oxidative addition step from this intermediate sets the stereochemistry of the cycloadduct. The major product in Scheme 4.19c from the enyne containing the propargylic substituent can be accounted for by invoking the same mechanistic rational.

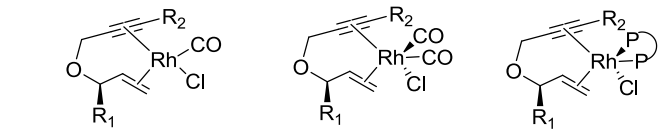
**Scheme 4.20.** Proposed Mechanism for Diastereoselective Rh-Catalyzed PK-Type Reaction of Enynes.




The degree of diastereoselectivity in this transformation was found to be affected by the ligands on the Rh metal. An explanation for this effect was proposed through Evans and Baik's computational study of the phosphine free $[RhCl(CO)_2]_2$ catalytic system. They found that both four- and five-coordinate Rh metal complexes are viable catalysts in the reaction pathway (Figure 4.6). Examining these two Rh species revealed that the five-coordinate Rh metal catalyst leads to much higher diastereoselectivity. This was due to the much larger energy difference in the two diastereomeric transition states

of the oxidative addition for the five-coordinate Rh species. Based on this mechanistic insight, the diastereoselectivity of the reaction was found to be greatly increased by forcing the five-coordinate Rh complex through the introduction of dppp as a bidentate phosphine ligand.

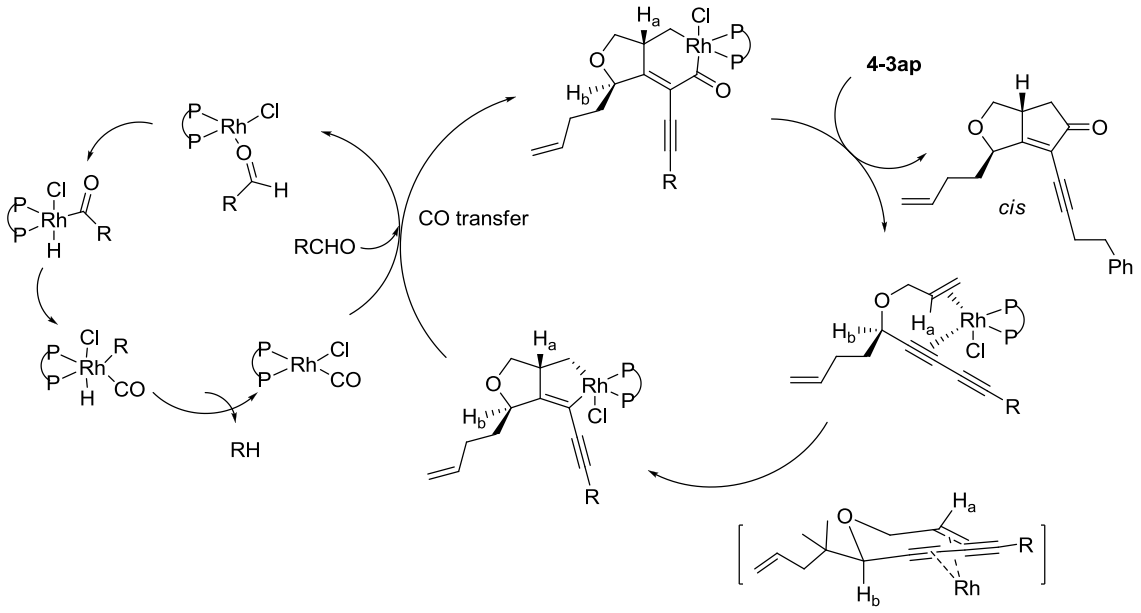
**Figure 4.6.** Four- and Five-Coordinate Rhodium Metal Complexes.




On the basis of these studies we considered the the cyclization of dienediyne **4-3ap** in an attempt to understand why the major diastereomer was different in the presence and absence of a phosphine ligand. The mechanism for the $[Rh(cod)Cl]_2$-rac-BINAP catalyzed reaction employing aldehydes as a CO source consists of two catalytic cycles as proposed by Shibata and coworkers.[38] As shown in Scheme 4.21, the first catalytic cycle involves the established decarbonlyation pathway. Based on a series of studies, Shibata and coworkers propose that the CO is transferred directly from the decarbonylation cycle without the generation of free CO gas. The second catalytic cycle involves rhodium coordination of the enyne and subsequent cyclization. In this mechanism the diastereoselectivity should be goverened by the facial selectivity of the rhodium metal center upon coordination with the dienediyne. In accord with the rational invoked for the enyne substrates, the Rh-phosphine metal complex should prefer to coordinate the face of the enyne opposite to the more sterically bulky alkyl chain at the propargylic position. A chair transition state can be proposed for the subsequent cyclization, in which the more favorable orientation places the bulky alkyl group at the

equitorial position. This produces the rhodium metallacycle in which the alkyl group and $H_a$ are on the same face of the bicycle and results in the *cis* isomer of the product shown in Scheme 4.21.

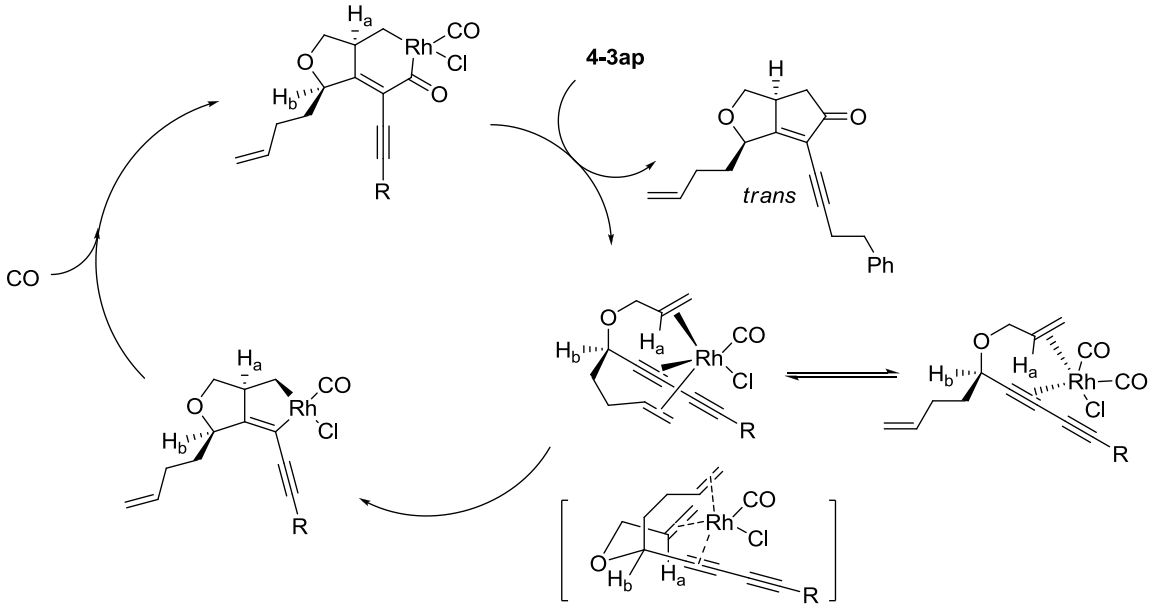
**Scheme 4.21.** Proposed Catalytic Cycle For $[RhCl(CO)_2]_2$-Phosphine Catalyzed PK-Type Reaction of Dienediyne **4-3ap** with Aldehydes as a CO Source.[38]




In the absence of a phosphine ligand the rhodium metal for the $[RhCl(CO)_2]_2$ catalytic system, the active catalyst exists as an equilibrium of the four- and five-coordinate complexes shown in Scheme 4.22. This presents the possibility that the rhodium metal center could be coordinated by functional groups present in the substrate. In this instance it is possible that the alkene in dienediyne **4-3ap** is in close enough proximity to coordinate with the rhodium metal center. As shown in the possible chair transition state, positioning the alkyl group in the axial position could allow for an interaction of the alkene with the Rh metal. This would cause the Rh metal center to chose the same face of the enyne as the coordinating group, placing the coordinating

alkene and $H_a$ on the opposite face of the newly formed metallacycle and forming the *trans* diastereomer (Scheme 4.22).

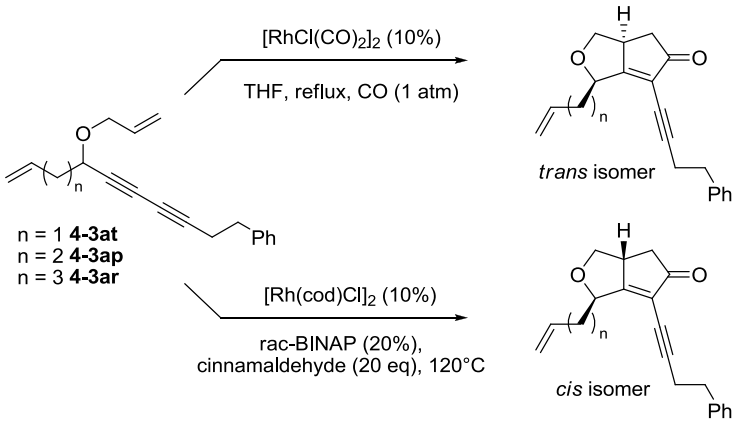
**Scheme 4.22.** Proposed Catalytic Cycle for $[RhCl(CO)_2]_2$ Catalyzed PK-Type Reaction of Dienediyne **4-3apr** in the Absence of Phosphine Ligands.




If this mechanistic hypothesis was correct, it opened the possibility of accessing either diastereomer of the cycloaddition product for substrates possessing a suitable coordinating group. In order to investigate our hypothesis we tested the cyclization of dienediyne **4-3at** bearing an olefin one carbon closer to the propargylic position (Scheme 4.23). We had previously observed that the cyclization of dienediyne **4-3ar** bearing the olefin one carbon further away from the propargylic position provided no diastereoselectivity in the $[Rh(CO)_2Cl]_2$ catalyzed reaction. Presumably for this substrate the alkene was too far away to effectively coordinate with the rhodium metal center and provide diastereoselectivity. If coordination of the alkene was responsible for the observed diastereoselectivity, moving the alkene one carbon closer in dienediyne **4-**

**3at** should improve the substrate controlled diastereoselectivity in the $[Rh(CO)_2Cl]_2$ catalyzed reaction. This improvement was observed, as dienediyne **4-3at** (Scheme 4.23, n=1) underwent the PK cyclization yielding the *trans* isomer as the major product in 65% yield and 3:1 dr. Testing dienediyne **4-3at** in the Rh-phosphine catalyzed system provided the *cis* diastereomer as the major product in 2:1 dr.

**Scheme 4.23.** Rhodium Catalyzed PK-Type Reaction of Dienediynes in the Presence and Absence of Phosphine Ligands.

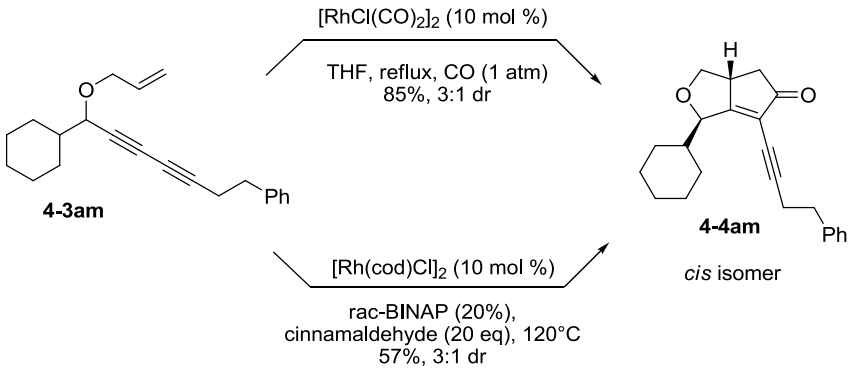



| Product | yield | *cis:trans*(dr) |
|---|---|---|
| n = 1 **4-4at'** | 65% | 1:3 |
| n = 2 **4-4ap'** | 71% | 1:2 |
| n = 3 **4-4ar'** | 68% | 1:1 |

| Product | yield | *cis:trans*(dr) |
|---|---|---|
| n = 1 **4-4at** | 77% | 2:1 |
| n = 2 **4-4ap** | 64% | 2:1 |
| n = 3 **4-4ar** | 84% | 2:1 |

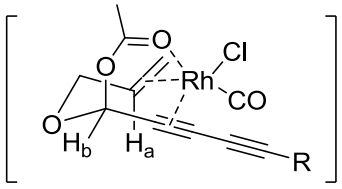
To further test our hypothesis we prepared enediyne **4-3am**. This substrate containing the bulkly cyclohexyl ring and no coordinating groups should provide the same diastereomer with both methods, with the rhodium favoring coordination of the face opposite the cyclohexyl ring. As shown in Scheme 4.24, this result was observed, with the *cis* diastereomer being formed through both methods. Interestingly the phosphine ligand was not shown to have a beneficial effect on the diastereoselectivity of the reaction as both methods yielded a 3:1 diastereoselectivity.

**Scheme 4.24.** Rhodium Catalyzed PK-Type Reaction of Enediyne **4-3am** in the Presence and Absence of Phosphine Ligands.




To further test the role of the coordinating group enediyne **4-3au** containing a potentially strongly coordinating acetate group and enediyne **4-3av** containing the poorer coordinating methyl group were synthesized. As a good coordinating group in close proximity we expected that the acetate would lead to enhanced diastereocontrol (Figure 4.7). As shown in Scheme 4.25, applying the phosphine free Rh catalyst revealed that the

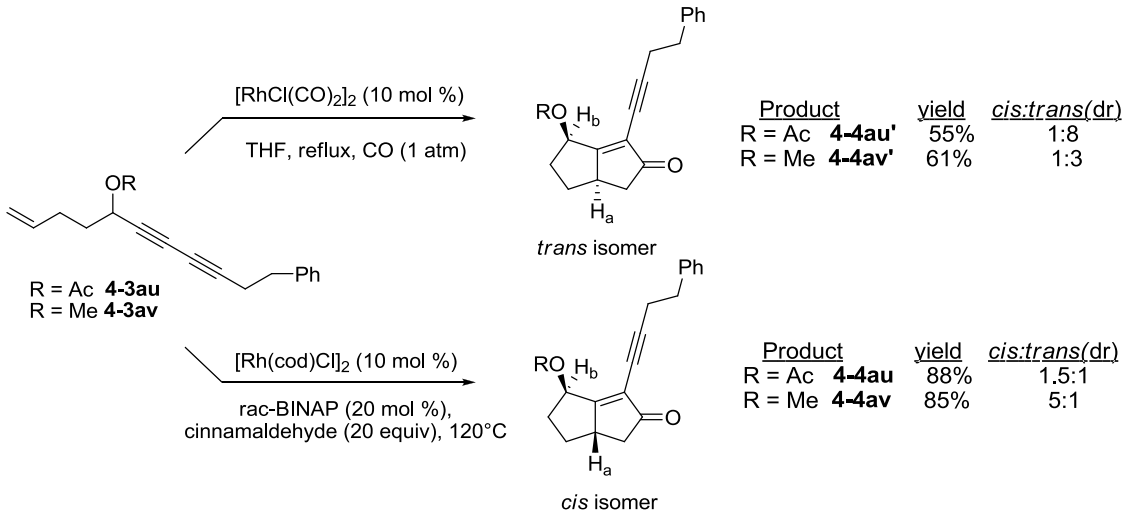
**Figure 4.7.** Proposed Directing Effect of Acetate Via Coordination to Rhodium Metal Center.




acetate functionality could provide a high level of substrate control, forming the *trans* diastereomer as the major product in 8:1 selectivity. This assignment was based on the well known chemical shift for this class of 5,5-fused bicycles in which the NMR signal of $H_b$ is known to have a more downfield chemical shift in the *trans* isomer relative to the *cis* isomer.[48] Use of the phosphine-free conditions with methoxy containing enediyne **4-**

**3av** also formed the *trans* diastereomer as the major product, but with lower selectivity (3:1 dr). This was in line with our hypothesis, as the more poorly coordinating methoxy group provided the product in lower diastereoselectivity.

**Scheme 4.25.** Rhodium Catalyzed PK-Type Reaction of Enediynes in the Presence and Absence of Phosphine Ligands.




| Product | yield | *cis:trans*(dr) |
|---|---|---|
| R = Ac **4-4au'** | 55% | 1:8 |
| R = Me **4-4av'** | 61% | 1:3 |

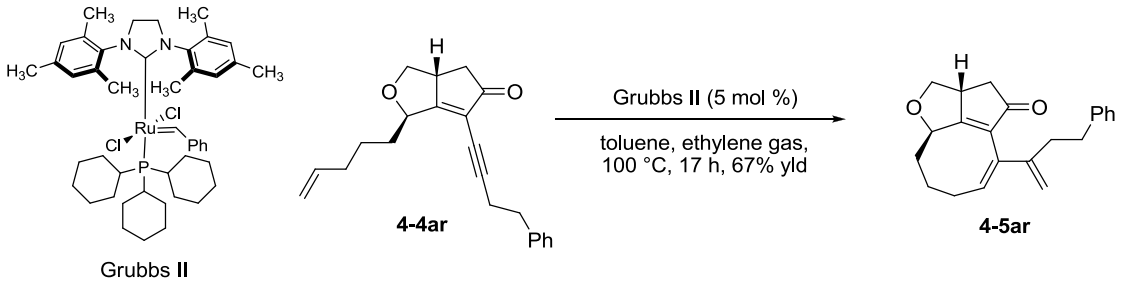
| Product | yield | *cis:trans*(dr) |
|---|---|---|
| R = Ac **4-4au** | 88% | 1.5:1 |
| R = Me **4-4av** | 85% | 5:1 |

As expected, application of the $[Rh(cod)Cl]_2$-BINAP catalytic system utilizing *trans*-cinnamaldehyde as the CO source reversed the diastereoselectivity. For acetate protected **4-3au** low diastereoselectivity (1.5:1) was observed, suggesting that the acetate may still be able to coordinate with the Rh metal center to some degree. Interestingly, in this catalytic system use of methoxy protected **4-3av** produced good levels of diastereocontrol (5:1). These complimentary methods allow access to either diastereomer with good levels of control for this class of enediynes. Thus, the desired *cis* or *trans* cycloadduct can be selected based on the protecting group and cyclization method utilized.

*c. Ring-Closing Metathesis to Construct the 5,5,7- and 5,5,8-Tricyclic Compounds*

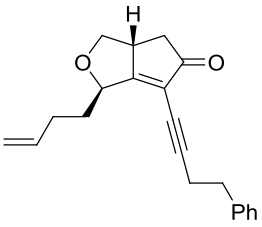
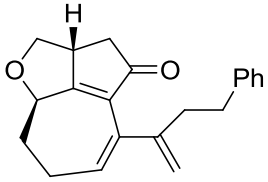
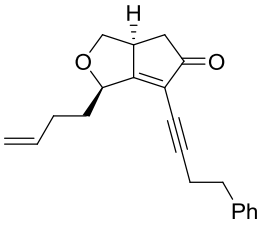
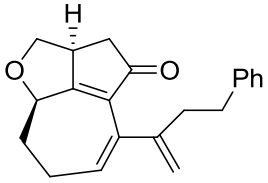
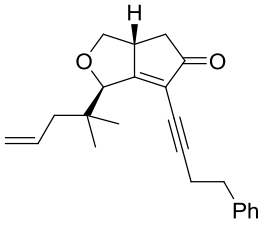
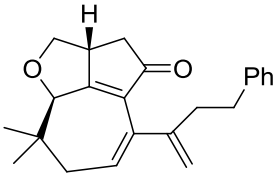
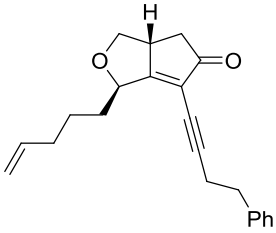
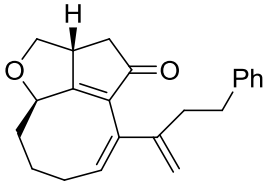
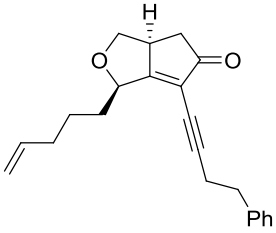
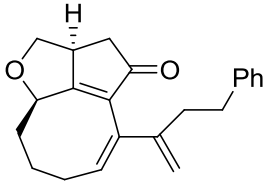
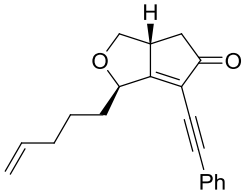
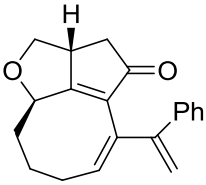
Having established an effective route to access optically active bicycles containing functional groups for further transformations we turned out attention to construction of the desired 5,5,7- and 5,5,8-containing polycyclic core via enyne metathesis. We began by testing the Grubbs II catalyst with bicycle **4-4ar** in hopes of forming the corresponding 5,5,8-ring system. However, the reaction did not proceed under ambient or elevated temperatures (refluxing $CH_2Cl_2$ and toluene), returning only the starting material. As ethylene gas has been demonstrated to promote enyne metathesis for difficult substrates,[49] we conducted the enyne metathesis of **4-4ar** in the presence of ethylene gas (1 atm). Since no reaction was observed at room temperature we tested the reaction in a sealed tube, first bubbling the solution with ethylene gas for 2 minutes. Promisingly, employing 5 mol % of Grubbs II catalyst in $CH_2Cl_2$ at 45 °C provided partial conversion to the desired 8-membered ring. Heating to 100 °C in toluene in a sealed tube fully consumed the starting material, providing the product (**4-5ar**) in 67% yield (Scheme 4.26).

**Scheme 4.26.** Grubbs II Catalyzed Enyne Metathesis in the Presence of Ethylene Gas.




We applied these reaction conditions to both diastereomers of enynes **4-4ap** and **4-4ar** (Table 4.10). For more difficult substrates it was found that adding a second

**Table 4.10.** Enyne Metathesis to Access Optically Active Polycyclic 7- and 8-Membered Ring Systems.[a]

| entry | enyne | | Grubbs II (mol %) | rxn time | product | yield (%) |
|---|---|---|---|---|---|---|
| 1[b,c] |  | **4-4ap** | 15 | 24h |  **4-5ap** | 63 |
| 2 |  | **4-4ap'** | 5 | 17h |  **4-5ap'** | 73 |
| 3[c] |  | **4-4aq** | 20 | 24h |  **4-5aq** | 51 |
| 4 |  | **4-4ar** | 5 | 17h |  **4-5ar** | 67 |
| 5[c] |  | **4-4ar'** | 10 | 24h |  **4-5ar'** | 68 |
| 6[c] |  | **4-4cr** | 10 | 24h |  **4-5cr** | 73 |

(a) Enyne/Grubbs II/toluene/$\Delta$ = 1:0.05-0.20:0.025M:100°C (b) $CH_2Cl_2$, 45°C. (c) Grubbs II added in 2 portions. 2nd portion added after 12h. See experimental section for details.

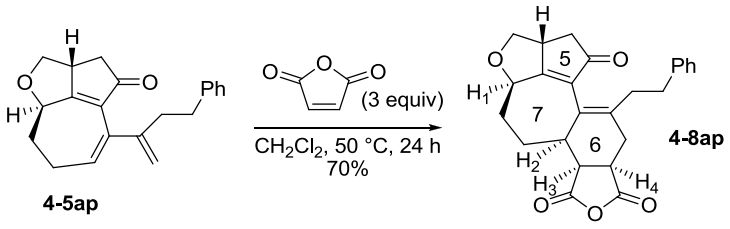
portion of the Grubbs II catalyst after 12h could significantly improve the yield. In this way both diastereomers of the 5,5,7- and 5,5,8-ring systems could be accessed in good yields. For formation of the 5,5,7-ring system it was observed that the *trans* enyne diastereomer **4-4ap'** underwent the enyne metathesis reaction more smoothly (entry 2). While the *cis* diastereomer was not stable at higher temperatures it could be accessed in good yield at reduced temperatures (45 °C) in $CH_2Cl_2$ by adding the catalyst in two portions. Enyne metathesis of the **4-4aq** did not react in $CH_2Cl_2$ at 45 °C, but this substrate was found to be moderately stable under the elevated reaction temperatures in toluene providing the product in 51% yield with the addition of two portions of the catalyst (entry 3). For formation of the 5,5,8- rings system the *trans* enyne diastereomer **4-4ar'** proved to be the more challenging substrate (entries 5 vs. 4), requiring a longer reaction time and addition of the Grubbs II catalyst in two portions. An aryl substituted enyne was also found to be a suitable substrate for enyne bond reorganization, providing the product in 73% yield (entry 6). The analogous TIPS substituted enyne **4-4br** failed to yield the desired 5,5,8- ring system.

*d. Highly Diastereoselective Diels-Alder Reaction to Construct a Fused 5,5,7,6-Polycyclic Compound*

A important feature of using enyne metathesis to access the optically active 5,5,7- and 5,5,8-polycyclic ring systems is that this method furnishes a conjugated diene functionality that can be exploited for the formation of more complex polycyclic systems. In particular, we hoped to use the newly formed diene to access the 5,7,6-ring system present in the daphnane and tigliane ring systems via a Diels-Alder cycloaddition. To test this idea we tested the [4+2] cycloaddition of **4-5ap** with maleic anhydride. The

reaction proceeded at 50 °C in a sealed tube cleanly furnishing the cycloaddition product as a single diastereomer in 70% yield and setting three new stereocenters. (Scheme 4.27).

**Scheme 4.27.** [4 + 2] Cycloaddition of Diene **4-5ap** with Maleic Anhydride.




The stereochemistry of **4-8ap** was determined by NOESY and COESY 2D $^1$H NMR analyses. We observed NOE effects between $H_2$ and $H_3$ and between $H_3$ and $H_4$ which is consistent with the expected *endo* cycloaddition between maleic anhydride and a conjugated diene. The $^1$H NMR signal of $H_3$ is observed at $\delta$ 3.26 (dd, $J_{H3\text{-}H4}$ = 9.75 Hz and $J_{H2\text{-}H3}$ = 5.25 Hz) and the coupling constants support the *syn* configuration of the three protons $H_{2\text{-}4}$ generated from the *endo* cycloadditon. A NOE effect between $H_1$ and $H_2$ was also observed. This indicates that the dienophile maleic anhydride approaches the diene unit of **4-5ap** from the top face in an *endo* fashion to generate the product **4-8ap** in which the four bridge-head hydrogens $H_{1\text{-}4}$ are all on the same side as shown. The structural assignment for **4-8ap** is supported by a single crystal X-ray analysis of this compound as shown in Figure 4.8.

One hypothesis for the preferred top face attack of the dienophile on **4-5ap** is that this approach avoids the steric repulsion between the carbonyl oxygen of maleic anhydride and the axial hydrogen atom $H_1$ in the *endo* pathway as shown in the proposed transition state Figure 4.9. That is, the chiral center established from the catalytic

asymmetric diyne addition to aldehydes should have directed this asymmetric Diels-Alder reaction. Thus, the polycyclic compound **4-8ap** with 5 stereocenters has been constructed from the corresponding acyclic dienediyne in three steps with high diastereoselectivity. The multiple functional groups in **4-8ap** should allow further structural elaboration of this compound.

**Figure 4.8**. The X-Ray Structure of **4-8ap**.

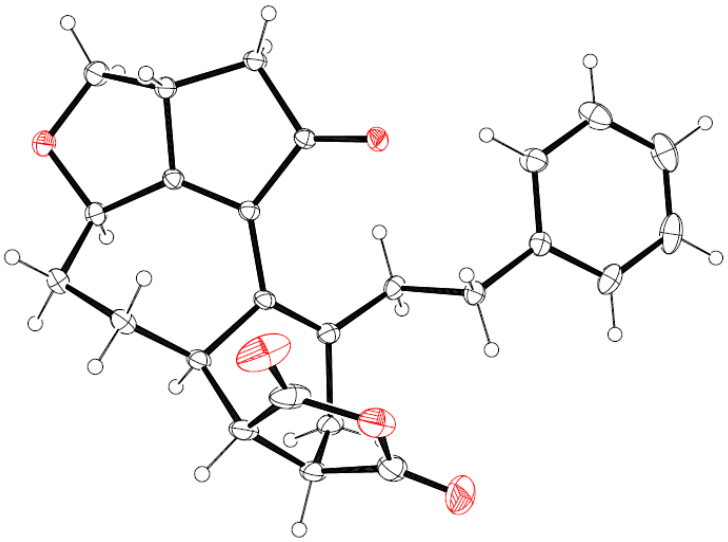
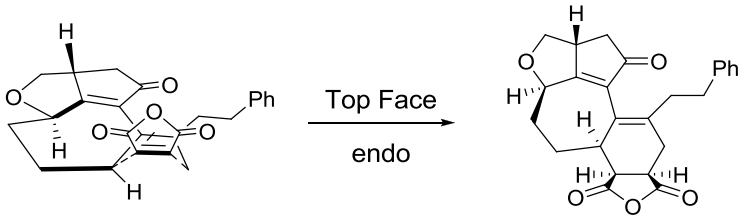


**Figure 4.9.** Proposed *Endo* Top Face Attack.




*e. Summary*

In conclusion we have demonstrated a flexible strategy for the construction of polycyclic ring systems containing the 5,7- and 5,8-membered ring core common in a variety of natural products. Key to this strategy was the development of a highly

enantioselective BINOL-$ZnEt_2$-$Ti(O^iPr)_4$-$Cy_2NH$ catalytic system for the addition of 1,3-diynes to enals, a chemoselective and diastereoselective PK-type reaction of dienediyne substrates, and enyne metathesis to form the 7- and 8-membered ring systems. Notably, these polycyclic ring systems contain an embedded diene that can allow the formation of additional ring structures through cycloaddition reactions.

The BINOL-$ZnEt_2$-$Ti(O^iPr)_4$ utilizing $Cy_2NH$ as a Lewis basic additive was shown to possess a large substrate scope, providing excellent yields and high enantioselectivities for a range of 1,3-diynes bearing alkyl, aryl, and silyl substituents with a variety of aromatic and aliphatic aldehydes. It was found that functional 1,3-diynes penta-2,4-diyn-1-ol (**4-1h**) and hepta-4,6-diyn-1-ol (**4-1j**) bearing the TBS protecting group were more effective the those bearing an acetate protecting group.

The $[Rh(cod)Cl]_2$-BINAP catalytic system utilizing aldehydes as the CO source[38] was found to promote the chemoselective and diastereoselective cyclization of dienediyne substrates. Excellent diastereoselectivities could be achieved in substrates possessing significant steric bulk close to the propargylic center. A complimentary method to access the opposite diastereomer of the cycloaddition products was also explored, in which substrates bearing coordinating groups were observed to coordinate to the metal center in the absence of phosphine ligands. This coordination was able to direct the facial selectivity of the metal with the enyne.

Finally, enyne metathesis utilizing Grubbs II catalyst in the presence of ethylene gas was found to be an effective method for formation of 5,5,7- and 5,5,8-polycyclic ring systems for alkynes containing alkyl and aryl substituents. The resulting diene has been shown to be a suitable reaction partner for a highly stereoselective [4+2] cycloaddition

reaction to furnish the 5,5,7,6-ring system. The Diels-Alder reaction was determined to undergo *endo* top face attack on the diene, with the chiral center established in the asymmetric diyne addition directing the stereocontrol of the reaction. This strategy provides a flexible route for the synthesis of a variety of polycyclic ring systems in high optical purity.

## 4.4. Experimental and Characterization

*a. General Data and Instruments*

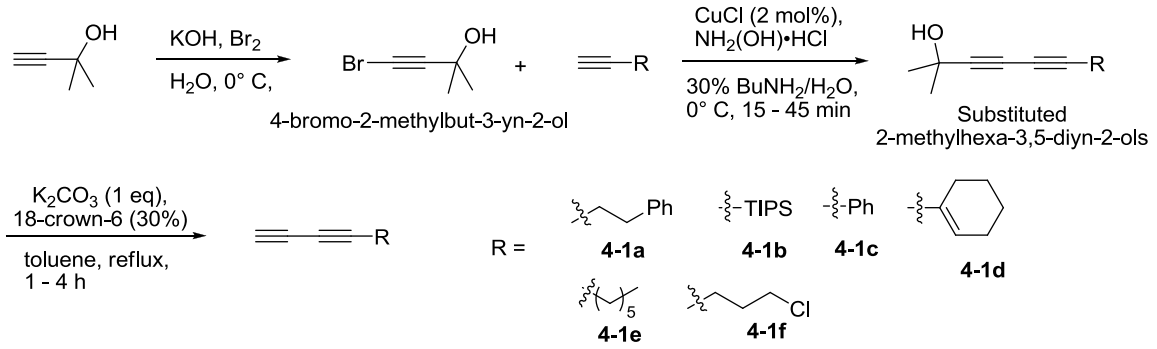
All $^{1}H$ and $^{13}C$ NMR spectra were obtained using a Varian 300 MHz or 500 MHz spectrometer. HPLC analyses were carried out with a Waters 600 Pump and Waters 996 Photodiode Array Detector using a Chiralcel OD, Chiralcel OB-H or Chiralpak AD-H column. Optical rotation values were measured with the Jasco Digital Polarimeter P-2000. High resolution mass spectra were obtained from the University of California, Riverside (UCR) Mass Spectrometry Facility and the University of Illinois (at Urbana-Champaign) Mass Spectrometry Laboratory. The samples were analyzed by ESI and the $[MH^+]$ or $[MNa^+]$ was observed.

All commercial chemicals were used as received unless otherwise noted. $Cy_2NH$ was distilled prior to use. $ZnEt_2$ (95%), $[Rh(cod)Cl]_2$, and $[Rh(CO)_2Cl]_2$ was purchased from Strem Chemicals, Inc. All reactions were carried out under a dry nitrogen atmosphere unless otherwise noted. Toluene, THF, and 1,4-dioxane were distilled over sodium and benzophenone under nitrogen atmosphere. Methylene chloride and diethyl ether were dried by passing through activated alumina columns under nitrogen. Solvents were stored over 4 Å molecular sieves. All aldehydes were passed through a plug of alumina and distilled from 4 Å molecular sieves prior to use and stored under nitrogen atmosphere. All 1,3-diynes were passed through a plug of alumina and then stored at -15°C in $Et_2O$ solution. Prior to use they were concentrated.

*b. Preparation of 1,3-Diynes*

All 1,3-diynes were prepared by literature procedures or slight modification thereof.[50]

*i. Preparation of Diynes **4-1a** – **4-1f***



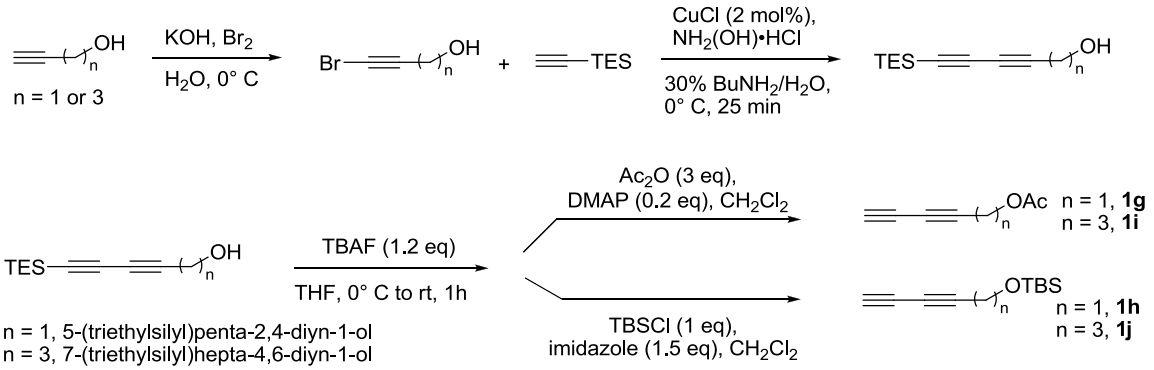

4-Bromo-2-methylbut-3-yn-2-ol was first prepared. Under ambient atmosphere KOH (60 g, 1.1 mol, 5.2 equiv) was dissolved in $H_2O$ (400 mL) and cooled to 0 °C. $Br_2$ (8 mL, 0.15 mol, 0.75 equiv) was then added dropwise via syringe to the stirred solution. After 15 min, 2-methyl-3-butyn-2-ol (20 mL, 0.20 mol, 1 equiv) was added dropwise via addition funnel. After stirring for 30 min, the reaction was warmed to rt and extracted with $Et_2O$ (5 x 100 mL). The organic phase was dried with magnesium sulfate, filtered, concentrated, and purified by column chromatography (90:10 hexanes:EtOAc) on silica gel to afford 4-bromo-2-methyl-3-but-3-yn-2-ol in 70-80% yield.

The Cadiot-Chodkiewicz cross coupling was performed as follows: CuCl (63 mg, 0.64 mmol, 2 mol %) was added to a solution of degassed 30% $BuNH_2/H_2O$ (89 mL). The blue color was quenched by the addition of a spatula's tip of $NH_2(OH)$•HCl. An alkyne (35 mmol, 1 equiv) was added and the reaction mixture was cooled to 0 °C, often becoming a yellow cloudy solution. 4-Bromo-2-methyl-3-but-3-yn-2-ol (6.0 g, 36.75 mmol, 1.05 equiv) was added in $Et_2O$ (5 mL). An additional portion of $Et_2O$ (5 mL) was used to rinse the vial and added to the reaction mixture. Every few minutes a spatula's tip of $NH_2(OH)$•HCl was added to the reaction mixture, or when a green color was

observed in the solution. After completion of the reaction as determined by TLC the aqueous mixture was warmed to rt and extracted with $Et_2O$ (3 x 75 mL). The organic phase was dried with magnesium sulfate, filtered, concentrated, and purified by column chromatography (hexanes:EtOAc) on silica gel to afford the terminally substituted 2-methylhexa-3,5-diyn-2-ols in 65-87% yield.

The fragmentation reaction was adapted from Carreira's method[50c] and performed as follows: $K_2CO_3$ (3.52 g, 25.5 mmol, 1 equiv) and 18-crown-6 (2.02 g, 7.6 mmol, 0.3 equiv) were combined in a Schlenk flask fitted with a reflux condenser and vacuum/nitrogen adapter. The flask was placed under $N_2$ atmosphere. A terminally substituted 2-methylhexa-3,5-diyn-2-ol (25.5 mmol, 1 equiv) was dissolved in toluene (77 mL, 0.33 M) under nitrogen atmosphere and transferred via cannula to the reaction flask. The reaction mixture was heated at reflux until the reaction was determined to be complete by TLC (1-4 h). *Note: Care should be taken with the aryl, cyclohexenyl, and TIPS substrates not to allow the reaction to continue for longer than 1 to 1.5 h as significant decomposition of the product occurs.* The solution was cooled to room temperature, extracted with EtOAc (4 x 75 mL), dried with magnesium sulfate and concentrated. The crude oil was purified by column chromatography on silica gel eluting with hexanes to yield the terminal 1,3-diynes in 55-85% yield. The 1,3-diynes were passed through a short plug of alumina and then stored in $Et_2O$ solution in the laboratory freezer. Prior to use they were concentrated. *Note: The concentrated aryl containing substrate should not be placed under high vacuum as this causes rapid formation of polymerized products.*

*ii. Preparation of the Diynes* ***4-1g*** *–* ***4-1j***




Acetate and TBS protected 1,3-diyn-ols were prepared according to Marino's method.[50b] The brominated alkyn-ols were prepared and the Cadiot-Chodkiewicz coupling were performed in analogy to the previously described procedures. A representative procedure for removal of the TES group and protection of the alcohol is described below:

7-(Triethylsilyl)hepta-4,6-diyn-1-ol (30 mmol, 1 equiv) was dissolved in THF (75 mL) and cooled to 0 °C. TBAF (36 mL, 36 mmol, 1M in THF) was added and the reaction was allowed to warm to rt over 1 h. The reaction was quenched with aqueous $NH_4Cl$ (saturated), extracted with $CH_2Cl_2$ (3 x 25 mL), dried with sodium sulfate, filtered, and concentrated. The crude product was then redissolved in $CH_2Cl_2$ (50 mL) and split into 2 portions.

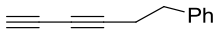
Acetate protection: $Ac_2O$ (2.8 mL, 30 mmol, 2 equiv) and DMAP (367 mg, 3.0 mmol, 0.2 equiv) were added and the solution was stirred until the reaction was judged to be complete by TLC (~1h). Aqueous $NH_4Cl$ (saturated) was added and the reaction was extracted with $CH_2Cl_2$ (3 x 20 mL), dried with sodium sulfate, filtered, and concentrated.

The product was purified by column chromatography on silica gel to yield the product in 77% yield over 2 steps.

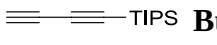
TBS protection: TBSCl (2.26 g, 15 mmol, 1 equiv) and imidazole (1.53 g, 22.5 mmol, 1.5 equiv) were added and the solution was stirred until the reaction was judged to be complete by TLC (~30 min). Aqueous $NH_4Cl$ (saturated) was added and the reaction was extracted with $CH_2Cl_2$ (3 x 20 mL), dried with sodium sulfate, filtered, and concentrated. The product was purified by column chromatography to yield the product in 70% yield over 2 steps.

These 1,3-diynes were passed through a short plug of alumina and stored in $Et_2O$ solution in the laboratory freezer. Prior to use they were concentrated.

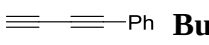
*c. Characterization of 1,3-Diynes*



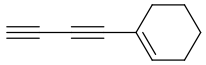

**Hexa-3,5-diynylbenzene, 4-1a.** $^1$H NMR (300 MHz, CDCl3) δ 7.27 (m, 5H), 2.86 (t, 2H, J = 7.5 Hz), 2.56 (t, 2H, J = 7.5 Hz), 1.98 (s, 1H). This data is in accord with that reported.[51]



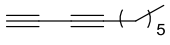

**Buta-1,3-diynyltriisopropylsilane, 4-1b.** $^1$H NMR (300 MHz, CDCl3) δ 2.07 (s, 1H), 1.09 (s, 21H). This data is in accord with that reported.[50a]

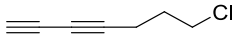


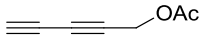

**Buta-1,3-diynylbenzene, 4-1c.** $^1$H NMR (300 MHz, CDCl3) δ 7.52 (m, 2H), 7.35 (m, 3H), 2.48 (s, 1H). This data is in accord with that reported.[52]

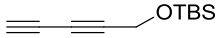


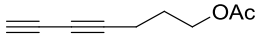
**1-(Buta-1,3-diynyl)cyclohex-1-ene, 4-1d.** $^1$H NMR (300 MHz, CDCl3) δ 6.32 (m, 1H), 2.37 (s, 1H), 2.12 (m, 4H), 1.61 (m, 4H). This data is in accord with that reported.[50a]

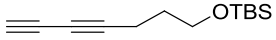
 **Deca-1,3-diyne, 4-1e.** $^{1}$H NMR (300 MHz, CDCl3) δ 2.26 (t, 2H, J = 7.0 Hz), 1.95 (s, 1H), 1.34 (m, 6H), 0.89 (t, 3H, J = 6.6 Hz), 1.54 (p, 2H, J = 6.6 Hz). This data is in accord with that reported.[51]

 **7-Chlorohepta-1,3-diyne, 4-1f.** $^{1}$H NMR (300 MHz, CDCl3) δ 3.65 (t, 2H, J = 6.0 Hz), 2.48 (m, 2H), 2.00 (m, 2H), 1.98 (s, 1H). This data is in accord with that reported.[51]

 **Penta-2,4-diynyl acetate, 4-1g.** $^{1}$H NMR (300 MHz, CDCl3) δ 4.72 (s, 2H), 2.20 (s, 1H), 2.11 (s, 3H). This data is in accord with that reported.[50a]

 **tert-Butyldimethyl(penta-2,4-diynyloxy)silane, 4-1h.** $^{1}$H NMR (300 MHz, CDCl3) δ 4.36 (s, 2H), 2.15 (s, 1H), 0.91 (s, 9H), 0.12 (s, 6H). This data is in accord with that reported.[53]

 **Hepta-4,6-diynyl acetate, 4-1i.** $^{1}$H NMR (300 MHz, CDCl3) δ 4.15 (t, 2H, J =6.3 Hz), 2.37 (m, 2H), 2.05 (s, 3H), 1.98 (s, 1H), 1.87 (p, 2H, J = 6.6 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.7, 76.6, 68.0, 65.2, 64.9, 62.6, 26.9, 20.6, 15.7. HRMS (EI) for $C_9H_{10}O_2$ Calcd: 150.06808. Found: 150.06720.

 **tert-Butyl(hepta-4,6-diynyloxy)dimethylsilane, 4-1j.** $^{1}$H NMR (300 MHz, $CDCl_3$) δ 3.68 (t, 2H, J =6.o Hz), 2.36 (t, 2H, J = 6.3 Hz), 1.95 (s, 1H), 1.73 (p, 2H, J = 6.0 Hz), 0.89 (s, 9H), 0.05 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 78.1, 68.4, 64.7, 64.4, 61.2, 31.0, 25.9, 18.3, 15.5, -5.4. HRMS (EI, M-$CH_3$) for $C_{13}H_{22}OSi$ Calcd: 207.12053. Found: 207.12104.

*d. 1,3-Diyne Addition to Aldehydes*

*i. Enantioselective 1,3-Diyne Addition to Aromatic Aldehydes*

Under nitrogen a 1,3-diyne (0.5 mmol, 2 equiv) was weighed into a tared flask and dissolved in $Et_2O$ (3 mL). (*S*)-BINOL (>99% ee, 7.2 mg, 0.025 mmol, 10 mol %), $Cy_2NH$ (2.5 μL, 0.0125 mmol, 5 mol %), $ZnEt_2$ (51.3 μL, 0.5 mmol, 2 equiv) were added, and the reaction mixture was stirred for 16 h. $Ti(O^iPr)_4$ (18.5 μL, 0.0625 mmol, 25 mol %) and then an aldehyde (0.25 mmol, 1 equiv) were added and the solution was stirred for 3 h during which time the aldehyde was judged to be consumed by TLC. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and extracted three times with $CH_2Cl_2$. The organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel, eluted with hexanes/ethylacetate (0-15% ethyl acetate) to give the product in 56-99% yield and 83-94% ee.

*ii. Enantioselective 1,3-Diyne Addition to Aliphatic and α,β-Unsaturated Aldehydes*

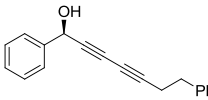
Under nitrogen a 1,3-diyne (0.75 mmol, 3 equiv) was weighed into a tared flask and dissolved in $Et_2O$ (3 mL). (*S*)-BINOL (>99% ee, 28.6 mg, 0.1 mmol, 40 mol %), $Cy_2NH$ (2.5 μL, 0.0125 mmol, 5 mol %), $ZnEt_2$ (76.9 μL, 0.75 mmol, 3 equiv) were added, and the reaction mixture was stirred for 16 h. $Ti(O^iPr)_4$ (74 μL, 0.25 mmol, 100 mol %) and then an aldehyde (0.25 mmol, 1 equiv) were added and the solution was stirred for 3 h during which time the aldehyde was judged to be consumed by TLC. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and extracted three times with $CH_2Cl_2$. The organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica

gel, eluted with hexanes/ethylacetate (0-15% ethyl acetate) to give the product in 77-99% yield and 85-95% ee. *Note: This reaction was found to be successfully scaled up with the use of 2 mmol of the aldehyde.*

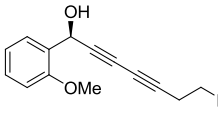
*iii. Racemic 1,3-Diyne Addition to Aldehydes*

A 1,3-diyne (0.3 mmol, 1.5 equiv) was weighed into a tared flask and placed under nitrogen atmosphere. The diyne was dissolved in THF (3 mL), and cooled to -78 °C. nBuLi (2.5M, 0.12 mL) was added and the reaction mixture stirred for 30 min. An aldehyde was then added. After 1 h the reaction was quenched with saturated aqueous ammonium chloride (5 mL), and extracted three times with $CH_2Cl_2$. The organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel.

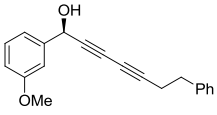
*e. Characterization 1,3-Diyne Addition Products*



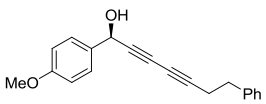

**(R)-1,7-diphenylhepta-2,4-diyn-1-ol, 4-2aa.** 95% yield. 94% ee determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 21.1 $t_{minor}$ = 18.4. $[\alpha]_D^{25}$ = -5.2 (c = 0.48 $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.54 (d, 2H, J = 5.0 Hz), 7.37 (m, 5H), 7.25 (m, 2H), 5.51 (d, 1H, J = 5.0 Hz), 2.88 (t, 2H, J = 7.5 Hz), 2.62 (t, 2H, J = 7.5 Hz), 2.38 (d 1H, J = 5.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 139.9, 139.7, 128.6, 128.5, 128.4, 128.3, 126.6, 126.5, 81.5, 75.1, 71.6, 65.0, 64.9, 34.3, 21.5. HRMS ($MNa^+$) for $C_{19}H_{16}O$ Calcd: 283.1099. Found: 283.1104.



**(S)-1-(2-methoxyphenyl)-7-phenylhepta-2,4-diyn-1-ol, 4-2ac.** 81% yield. 91% ee determined by HPLC analysis: Chiralcel OD column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 58.6 $t_{minor}$ = 40.2. $[\alpha]_D^{25}$ = -12.0 (c = 2.35, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.47 (d, 1H, J = 12.0 Hz), 7.29 (m, 4H), 7.22 (m, 3H), 6.95 (m, 2H), 5.69 (d, 1H, J = 9.0 Hz), 3.90 (s, 3H), 3.01 (d, 1H, J= 9.0), 2.85 (t, 2H, J = 7.5), 2.58 (t, 2H, J = 7.5). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 156.6, 139.9, 129.8, 128.4, 128.3, 128.0, 127.9, 126.4, 120.85, 110.9, 80.9, 75.0, 70.7, 65.3, 61.7, 55.6, 34.4, 21.4. HRMS ($MNa^+$) for $C_{20}H_{18}O_2$ Calcd: 313.1204. Found: 313.1206.

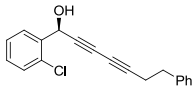


**(R)-1-(3-methoxyphenyl)-7-phenylhepta-2,4-diyn-1-ol, 4-2ad.** 96% yield. 90% ee determined by HPLC analysis: Chiralcel OD column, 90:10 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 44.5 $t_{minor}$ = 22.3. $[\alpha]_D^{25}$ = 5.5 (c = 0.59, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.33 (m, 3H), 7.25 (m, 3H), 7.10 (m, 2H), 6.90 (m, 1H), 5.48 (d, 1H, J = 5.0 Hz), 3.84 (s, 3H), 2.88 (t, 3H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.5 Hz), 2.54 (d, 1H, J = 5.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 159.8, 141.4, 140.0, 129.8, 128.5, 128.4, 126.6, 118.9, 114.3, 112.0, 81.6, 71.6, 65.2, 64.9, 55.3, 34.4, 21.5. HRMS ($MNa^+$) for $C_{20}H_{18}O_2$ Calcd: 313.1204. Found: 313.1201.

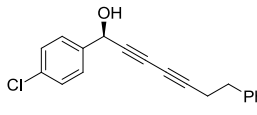


**(R)-1-(4-methoxyphenyl)-7-phenylhepta-2,4-diyn-1-ol, 4-2ae.** 94% yield. 94% ee determined by HPLC analysis: Chiralcel OD column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 47.5 $t_{minor}$ =

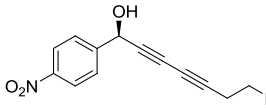
40.9. $[\alpha]_D^{25}$ = -0.9 (c = 0.80, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.44 (d, 2H, J= 10.0 Hz), 7.33 (t, 2H, J = 7.5 Hz), 7.24 (m, 3H), 6.91 (d, 2H, J = 10.0 Hz), 5.44 (s, 1H), 3.82 (s, 3H), 2.87 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.5 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 159.6, 139.9, 132.1, 128.3, 128.0, 126.4, 113.5, 77.4, 71.3, 64.5, 55.2, 34.3, 21.4. HRMS ($MNa^+$) for $C_{20}H_{18}O_2$ Calcd: 313.1204. Found: 313.1204.



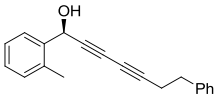

**(S)-1-(2-chlorophenyl)-7-phenylhepta-2,4-diyn-1-ol, 4-2af.** 92% yield 89% ee determined by HPLC analysis: Chiralcel OB-H column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: $t_{major}$ = 72.0 $t_{minor}$ = 63.4. $[\alpha]_D^{25}$ = -60.2 (c = 0.76, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, 1H, J = 7.5, 3.0 Hz), 7.30 (m, 8H), 5.86 (d, 1H, J = 5.0 Hz), 2.87 (t, 2H, J = 7.5 Hz), 2.67 (d, 1H, J = 5.0 Hz), 2.60 (t, 2H, J = 7.5 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 139.8, 137.0, 132.5, 129.8, 129.7, 128.4, 128.3, 127.2, 126.5, 81.6, 74.0, 65.0, 62.2, 34.3, 21.4. HRMS ($MNa^+$) for $C_{19}H_{15}OCl$ Calcd: 317.0709. Found: 317.0706.



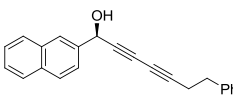

**(R)-1-(4-chlorophenyl)-7-phenylhepta-2,4-diyn-1-ol, 4-2ag.** 94% yield. 92% ee determined by HPLC analysis: Chiralcel OB-H column, 95:5 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: $t_{major}$ = 41.6 $t_{minor}$ = 32.3. $[\alpha]_D^{25}$ = 1.7 (c = 0.28, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.33 (m, 4H), 7.23 (m, 3H), 5.48 (d, 1H, J = 5.0 Hz), 2.86 (t, 2H, J = 7.5 Hz), 2.60 (t, 2H, J = 7.5 Hz), 2.18 (d, 1H, J = 5.0 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 139.8, 138.2, 134.3, 130.8, 129.0, 128.7, 128.5, 128.3, 128.0, 126.5, 81.9, 74.6, 71.8, 64.9, 64.2, 34.3, 21.4. HRMS ($MNa^+$) for $C_{19}H_{15}OCl$ Calcd: 317.0709. Found: 317.0722.



**(R)-1-(4-nitrophenyl)-7-phenylhepta-2,4-diyn-1-ol, 4-2ah.** 56% yield. 90% ee determined by HPLC analysis: Chiralcel OD, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 54.0 $t_{minor}$ = 70.8. $[\alpha]_D^{25}$ = 7.1 (c = 1.54, $CHCl_3$) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.24 (d, 2H, J = 8.5 Hz), 7.70 (d, 2H, J = 8.5 Hz), 7.32 (m, 2H), 7.26 (m, 1H), 7.22 (m, 2H), 5.61 (s, 1H), 2.87 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.5 Hz), 2.51 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 147.8, 146.4, 139.7, 128.5, 128.3, 127.3, 126.6, 123.8, 82.6, 73.6, 72.6, 64.6, 63.9, 34.2, 21.4. HRMS ($MNa^+$) for $C_{19}H_{15}NO_3$ Calcd: 328.0950. Found: 328.0956.

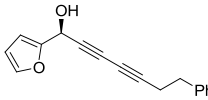


**(S)-7-phenyl-1-o-tolylhepta-2,4-diyn-1-ol, 4-2ai.** 98% yield. 92% ee determined by HPLC analysis: Chiralcel OB-H column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 225 nm, retention time: $t_{major}$ = 40.6 $t_{minor}$ = 33.1. $[\alpha]_D^{25}$ = -31.9 (c = 0.45, $CHCl_3$) $\delta$ 7.64 (m, 1H), 7.29 (m, 8H), 5.64 (d, 1H, J = 5.0 Hz), 2.88 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.5 Hz), 2.45 (s, 3H), 2.39 (d, 1H, J = 5.0 Hz). $^1$H NMR (300 MHz, $CDCl_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 140.2, 137.9, 136.2, 131.0, 128.8, 128.6, 126.8, 81.7, 75.3, 71.7, 65.5, 63.0, 34.7, 21.8, 19.2. HRMS ($MNa^+$) for $C_{20}H_{18}O$ Calcd: 297.1255. Found: 297.1256.

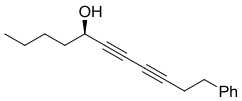


**(R)-1-(naphthalen-2-yl)-7-phenylhepta-2,4-diyn-1-ol, 4-2aj.** 98% yield. 93% ee determined by HPLC analysis: Chiralcel OD column, 90:10 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 240 nm, retention time: $t_{major}$ = 36.0 $t_{minor}$ = 30.5. $[\alpha]_D^{25}$ = -13.2 (c = 0.38, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.96 (s, 1H), 7.88

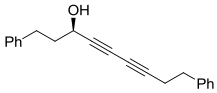
(m, 3H), 7.63 (m, 1H), 7.54 (m, 2H), 7.35 (m, 2H), 7.25 (m, 3H), 5.67 (d, 1H, J = 5.0 Hz), 2.89 (t, 2H, J = 7.5 Hz), 2.63 (t, 2H, J = 7.5 Hz), 2.62 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 139.8, 137.0, 133.2, 133.0, 128.6, 128.4, 128.3, 128.2, 127.6, 126.5, 126.4, 126.3, 125.5, 124.4, 81.7, 75.1, 71.8, 65.1, 65.0, 34.3, 21.4. HRMS ($MNa^+$) for $C_{23}H_{18}O$ Calcd: 333.1255. Found: 333.1279.



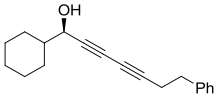

**(S)-1-(furan-2-yl)-7-phenylhepta-2,4-diyn-1-ol, 4-2ak.** 89% yield. 85% ee determined by HPLC analysis: Chiralcel OB-H column, 95:5 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 230 nm, retention time: $t_{major}$ = 44.7 $t_{minor}$ = 54.0. $[\alpha]_D^{25}$ = 3.2 (c = 1.36, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.33 (t, 2H, J = 7.5 Hz), 7.25 (m, 3H), 6.47 (d, 1H, J = 3.5 Hz), 6.37 (m, 1H), 5.51 (s, 1H), 2.89 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.5 Hz), 2.47 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 152.1, 143.2, 139.9, 128.5, 128.4, 126.6, 110.5, 108.2, 81.7, 72.6, 70.9, 65.0, 58.5, 34.4, 21.5. HRMS ($MNa^+$) for $C_{17}H_{14}O_2$ Calcd: 273.0891. Found: 273.0892.



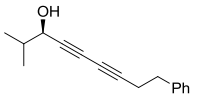

**(R)-11-phenylundeca-6,8-diyn-5-ol, 4-2ab.** 92% yield. 92% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 215 nm, retention time: $t_{major}$ = 23.1 $t_{minor}$ = 27.4. $[\alpha]_D^{25}$ = -2.5 (c = 0.96, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 7.32 (t, 2H, J = 7.5 Hz), 7.23 (m, 3H), 4.41 (t, 1H, J = 6.5 Hz), 2.86 (t, 2H, J = 7.5 Hz), 2.59 (t, 2H, J = 7.5 Hz), 2.59 (s, 1H), 1.72 (m, 2H), 1.45 (m, 2H), 1.36 (m, 2H), 0.93 (t, 3H, J = 7.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 139.9, 128.4, 128.3, 126.4, 80.6, 76.8, 69.7, 65.1, 62.8, 37.3, 34.4, 27.1, 22.3, 21.4, 13.9. HRMS ($MNa^+$) for $C_{17}H_{20}O$ Calcd: 263.1412. Found: 263.1414.




**(R)-1,9-diphenylnona-4,6-diyn-3-ol, 4-2al.** 93% yield. 88% ee determined by HPLC analysis: Chiralpak AD-H column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 38.3 $t_{minor}$ = 46.0. $[\alpha]_D^{25}$ = -76.0 (c = 0.51, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 7.24 (m, 4H), 7.26 (m, 6H), 4.42 (t, 1H, J = 6.5 Hz), 2.89 (t, 2H, J = 7.5 Hz), 2.82 (t, 2H, J = 6.5 Hz), 2.62 (t, 2H, J = 7.5 Hz), 2.06 (m, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 140.9, 139.9, 128.43, 128.40, 128.3, 126.4, 126.0, 80.8, 76.5, 70.2, 65.1, 62.0, 38.9, 34.4, 31.2, 21.4. HRMS ($MNa^+$) for $C_{21}H_{20}O$ Calcd: 311.1412. Found: 311.1409.

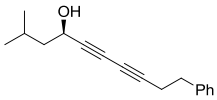



**(R)-1-cyclohexyl-7-phenylhepta-2,4-diyn-1-ol, 4-2am.** 91% yield. 91% ee determined by HPLC analysis: Chiralcel OB-H column, 99:1 hexanes:$^{i}$PrOH, flow rate = 0.5 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 32.8 $t_{minor}$ = 37.6. $[\alpha]_D^{25}$ = -13.3 (c = 0.50, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.28 (m, 5H), 4.20 (d, 1H, J = 6.0 Hz), 2.86 (t, 2H, J = 7.5 Hz), 2.58 (t, 2H, J = 7.5 Hz), 1.82 (m, 3H), 1.69 (m, 1H), 1.57 (m, 1H), 1.19 (m, 6 H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 139.9, 128.4, 128.3, 126.4, 80.3, 76.1, 70.5, 67.5, 65.1, 44.1, 34.4, 28.5, 28.0, 26.2, 25.76, 25.75, 21.4. HRMS ($MNa^+$) for $C_{19}H_{22}O$ Calcd: 289.1568. Found: 289.1568.

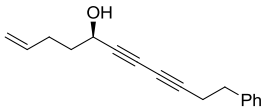



**(R)-2-methyl-9-phenylnona-4,6-diyn-3-ol, 4-2an.** 95% yield 90% ee determined by HPLC analysis: Chiralcel OB-H column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 19.2 $t_{minor}$ = 22.2. $[\alpha]_D^{25}$ = -6.7 (c = 0.51, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.32 (m, 2H), 7.23 (m, 3H), 4.22 (d, 1H, J = 5.7

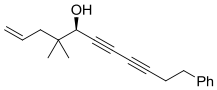
Hz), 2.85 (t, 2H, J = 7.5 Hz), 2.58 (t, 2H, J = 7.5 Hz), 2.06 (s, 1H), 1.90 (m, 1H), 1.01 (t, 6H, J = 6.3 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 139.9, 128.4, 128.3, 126.4, 80.2, 75.8, 70.4, 68.2, 65.1, 34.5, 34.4, 21.4, 18.0, 17.4. HRMS ($MNa^+$) for $C_{16}H_{18}O$ Calcd: 249.1255. Found: 249.1256.



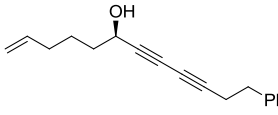

**(R)-2-methyl-10-phenyldeca-5,7-diyn-4-ol, 4-2ao.** 90% yield. 87% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 0.3 mL/min, λ = 215 nm, retention time: $t_{major}$ = 57.1 $t_{minor}$ = 66.6. $[\alpha]_D^{25}$ = 4.0 (c = 0.94, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 7.32 (t, 2H, J = 7.5 Hz), 7.24 (m, 3H), 4.45 (t, 1H, J = 7.3 Hz), 2.86 (t, 2H, J = 7.5 Hz), 2.59 (t, 2H, J = 7.5 Hz), 2.09 (s, 1H), 1.85 (m, 1H), 1.66 (m, 1H), 1.58 (m, 1H), 0.95 (dd, 6 H, J = 8.5, 6.5 Hz) . $^{13}$C NMR (125 MHz, $CDCl_3$) δ 139.9, 128.4, 128.3, 126.4, 80.6, 77.0, 69.7, 65.1, 61.3, 46.5, 34.4, 24.6, 22.4, 21.4 . HRMS ($MNa^+$) for $C_{17}H_{20}O$ Calcd: 263.1412. Found: 263.1414.



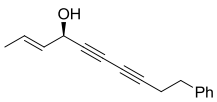

**(R)-11-phenylundeca-1-en-6,8-diyn-5-ol, 4-2ap.** 80% yield. 92% ee determined by HPLC analysis: Chiralpak OD column, 98:2 hexanes:$^i$PrOH, flow rate = 0.3 mL/min, λ = 215 nm, retention time: $t_{major}$ = 71.2 $t_{minor}$ = 79.9. $[\alpha]_D^{25}$ = -17.8 (c = 1.79, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.27 (m, 5H), 5.82 (m, 1H), 5.06 (m, 2H), 4.44 (t, 1H, J = 6.6 Hz), 2.86 (t, 2H, J = 7.5 Hz), 2.58 (t, 2H, J = 7.5 Hz), 2.40 (q, 2H, J = 7.2 Hz), 2.04 (s, 1H), 1.82 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 139.9, 137.3, 128.5, 126.5, 115.5, 80.7, 76.5, 70.0, 65.0, 62.2, 36.5, 34.4, 29.2, 21.4. HRMS ($MNa^+$) for $C_{17}H_{18}O$ Calcd: 261.1255. Found: 261.1257.




**(R)-4,4-dimethyl-11-phenylundeca-1-en-6,8-diyn-5-ol, 4-2aq.** 82% yield. 89% ee determined by HPLC analysis: Chiralpack AD-H column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 16.7 $t_{minor}$ = 18.9. $[\alpha]_D^{25}$ = -19.6 (c = 0.52, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.33 (m, 2H), 7.24 (m, 3H), 5.86 (m, 1H), 5.12 (m, 2H), 4.14 (s, 1H), 2.87 (t, 2H, J = 7.5 Hz), 2.59 (t, 2H, J = 7.5 Hz), 2.16 (m, 2H), 1.99 (s, 1H), 1.00 (d, 6H, J = 2.7 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 139.9, 134.6, 128.4, 128.3, 126.4, 117.9, 80.2, 75.6, 71.0, 70.5, 65.2, 42.7, 39.1, 34.4, 22.6, 22.5, 21.4. HRMS ($MNa^+$) for $C_{19}H_{22}O$ Calcd: 289.1568. Found: 289.1566.

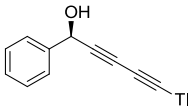



**(R)-12-phenyldodeca-1-en-7,9-diyn-6-ol, 4-2ar.** 86% yield. 90% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 24.9 $t_{minor}$ = 31.3. $[\alpha]_D^{25}$ = -6.9 (c = 0.52, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.27 (m, 5H), 5.80 (m, 1H), 5.02 (m, 2H), 4.42 (t, 1H, J = 6.6 Hz), 2.86 (t, 2H, J = 7.5 Hz), 2.58 (t, 2H, J = 7.5 Hz), 2.10 (m, 3H), 1.74 (m, 2H), 1.57 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 139.9, 138.2, 128.4, 128.3, 126.4, 114.9, 80.6, 76.5, 69.8, 65.0, 62.6, 36.9, 34.4, 33.2, 24.2, 21.4. HRMS ($MNa^+$) for $C_{18}H_{22}O$ Calcd: 275.1412. Found: 275.1410.

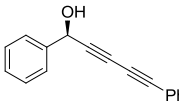



**(R,E)-10-phenyldeca-2-en-5,7-diyn-4-ol, 4-2as.** 99% yield. 92% ee determined by HPLC analysis: Chiralcel OB-H column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 25.1 $t_{minor}$ = 21.3. $[\alpha]_D^{25}$ = -71.9 (c = **0.52**, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 7.32 (m, 2H), 7.23 (m, 3H), 5.91 (m, 1H),

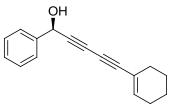
5.61 (m, 1H), 4.86 (t, 1H, J = 5.5 Hz), 2.86 (t, 2H, J = 7.5 Hz), 2.59 (t, 2H, J = 7.5 Hz), 1.95 (d, 1H, J = 5.5 Hz), 1.74 (d, 3H, J = 6.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 139.9, 129.6, 129.4, 128.5, 128.4, 126.5, 81.2, 75.0, 70.8, 65.1, 63.3, 34.4, 21.5, 17.5. HRMS ($MNa^+$) for $C_{16}H_{16}O$ Calcd: 247.1099. Found: 247.1091.



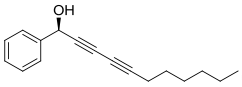

**(R)-1-phenyl-5-(triisopropylsilyl)penta-2,4-diyn-1-ol, 4-2ba.** 98% yield. 91% ee determined by HPLC analysis of desilylated diyne (TIPS group removed via treatment with TBAF): Chiralpak AD-H column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: $t_{major}$ = 30.6 $t_{minor}$ = 25.6. $[\alpha]_D^{25}$ = -7.9 (c = 0.75, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.53 (m, 2H), 7.39 (m, 3H), 5.54 (d, 1H, J = 6.0 Hz), 2.19 (d, 1H, J = 6.0 Hz), 1.09 (s, 21H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 139.5, 128.73, 128.67, 126.6, 88.7, 85.9, 75.6, 71.9, 65.0, 18.5, 11.2. This data is in accord with that reported.[1a]



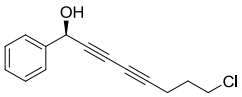

**(R)-1,5-diphenylpenta-2,4-diyn-1-ol, 4-2ca.** 98% yield. 88% ee determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: $t_{major}$ = 19.1 $t_{minor}$ = 17.6. $[\alpha]_D^{25}$ = -13.8 (c = 0.59, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.57 (m, 2H), 7.51 (m, 2H), 7.37 (m, 6H), 5.60 (d, 1H, J = 6.0 Hz), 2.60 (d, 1H, J = 6.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 139.9, 132.6, 129.4, 128.74, 128.67, 128.4, 126.7, 121.3, 81.6, 79.4, 73.1, 71.3, 65.1. This data is in accord with that reported.[54]



**(R)-5-cyclohexenyl-1-phenylpenta-2,4-diyn-1-ol, 4-2da.** 99% yield. 90% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 25.5 $t_{minor}$ = 23.2. $[\alpha]_D^{25}$ = -8.2 (c = 0.41, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.53 (m, 2H), 7.38 (m, 3H), 6.30 (m, 1H), 5.56 (d, 1H, J = 6.0 Hz), 2.18 (d, 1H, J = 6.0 Hz), 2.11 (m, 4H), 1.59 (m, 4H). $^{13}$C NMR (1255 MHz, $CDCl_3$) $\delta$ 139.8, 139.3, 128.6, 128.5, 126.2, 119.4, 81.5, 80.5, 71.5, 70.6, 65.1, 28.4, 25.8, 22.0, 21.2. HRMS ($MNa^+$) for $C_{17}H_{16}O$ Calcd: 259.1099. Found: 259.1101.

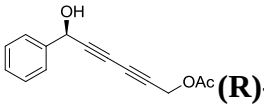


**(R)-1-phenylundeca-2,4-diyn-1-ol, 4-2ea.** 87% yield. 94% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 30.5 $t_{minor}$ = 20.8. $[\alpha]_D^{25}$ = -4.8 (c = 0.49, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.52 (m, 2h), 7.36 (m, 3H), 5.51 (d, 1H, J = 6.0 Hz), 2.29 (t, 2H, J = 6.0 Hz), 2.17 (d, 1H, J = 6.0 Hz), 1.53 (m, 2H), 1.40 (m, 2H), 1.28 (m, 4H), 0.89 (t, 3H, J = 6.6 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 139.9, 128.6, 128.5, 126.6, 82.7, 74.7, 71.2, 64.9, 64.2, 31.2, 28.5, 28.0, 22.5, 19.3, 14.0. HRMS ($MNa^+$) for $C_{17}H_{20}O$ Calcd: 263.1412. Found: 263.1411.

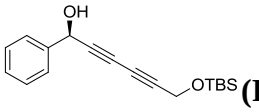


**(R)-8-chloro-1-phenylocta-2,4-diyn-1-ol, 4-2fa.** 95% yield. 91% ee determined by analyzing the $^1$H NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = -2.8 (c = 0.96, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 7.52 (m, 2H), 7.37 (m, 3H), 5.49 (s, 1H), 3.64 (t, 2H, J = 6.5 Hz), 2.55 (bs, 1H), 2.51 (t, 2H, J = 6.5 Hz), 1.99 (t, 2H, J = 6.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 139.7, 128.6, 128.5, 126.6, 80.3, 75.3, 71.3,

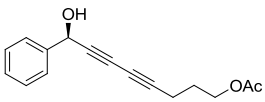
65.3, 64.9, 43.3, 30.7, 16.7. HRMS ($MNa^+$) for $C_{14}H_{13}ClO$ Calcd: 225.0533. Found: 225.0533.




**(R)-6-hydroxy-6-phenylhexa-2,4-diynyl acetate, 4-2ga.** 87% yield 83% ee determined by HPLC analysis: Chiralcel OD column, 95:5 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 221 nm, retention time: $t_{major}$ = 53.6 $t_{minor}$ = 45.5. $[\alpha]_D^{25}$ = -2.2 (c = 1.49, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) 7.52 (m, 2H), 7.37 (m, 3H), 5.49 (d, 1H, J = 6.0 Hz), 4.47 (s, 2H), 2.44 (d, 1H, J = 6.0 Hz), 2.10 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.1, 139.3, 128.8, 126.6, 79.0, 74.1, 70.4, 70.3, 64.9, 52.3, 20.6. HRMS ($MNa^+$) for $C_{14}H_{12}O_3$ Calcd: 251.0684. Found: 251.0689.

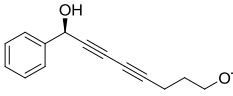



**(R)-6-(tert-butyldimethylsilyloxy)-1-phenylhexa-2,4-diyn-1-ol, 4-2ha.** 95% yield. 94% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 218 nm, retention time: $t_{major}$ = 28.1 $t_{minor}$ = 20.9. $[\alpha]_D^{25}$ = -3.2 (c = 0.31 $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 7.51 (m, 2H), 7.38 (m, 3H), 5.51 (d, 1H, J = 5.0 Hz), 4.39 (s, 2H), 2.51 (d, 1H, J = 5.0 Hz), 0.90 (s, 9H), 0.13 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 139.5, 128.7, 128.6, 126.6, 79.0, 78.1, 70.8, 68.8, 64.9, 52.0, 25.71, 18.2, -5.2. HRMS ($MNa^+$) for $C_{18}H_{24}O_2Si$ Calcd: 323.1443. Found: 323.1447.

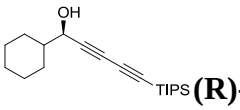



**(R)-8-hydroxy-8-phenylocta-4,6-diynyl acetate, 4-2ia.** 78% yield. 86% ee determined by HPLC analysis: Chiralpak OD column, 95:5 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 215 nm, retention time: $t_{major}$ = 51.7 $t_{minor}$ = 39.1. $[\alpha]_D^{25}$ = -2.7 (c =

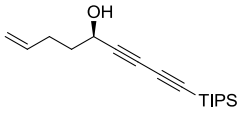
0.33, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) 7.51 (m, 2H), 7.36 (m, 3H), 5.49 (d, 1H, J = 6.0 Hz), 4.14 (t, 2H, J = 6.0 Hz), 2.53 (d, 1H, J = 6.0 Hz), 2.40 (t, 2H, J = 7.0 Hz), 2.05 (s, 3H), 1.86 (p, 2H, J = 7.0 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 171.1, 139.8, 128.6, 128.5, 126.6, 80.7, 75.3, 71.3, 65.1, 64.9, 62.9, 27.2, 20.9, 16.3. HRMS ($MNa^+$) for $C_{16}H_{16}O_3$ Calcd: 279.0997. Found: 279.0995.



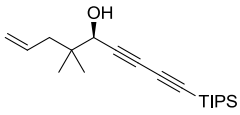

**(R)-8-(tert-butyldimethylsilyloxy)-1-phenylocta-2,4-diyn-1-ol, 4-2ja.** 97% yield 92% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: $t_{major}$ = 25.8 $t_{minor}$ = 17.1. $[\alpha]_D^{25}$ = -1.6 (c = 0.75, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) 7.52 (m, 2H), 7.36 (m, 3H), 5.50 (d, 1H, J = 6.5 Hz), 3.68 (t, 2H, J = 7.5 Hz), 2.39 (t, 2H, J = 7.0 Hz), 2.35 (d, 1H, J = 6.5 Hz), 1.74 (p, 2H, J = 6.0 Hz), 0.90 (s, 9H), 0.07 (s, 6H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 139.9, 128.7, 128.5, 126.6, 82.2, 74.7, 71.7, 65.0, 64.4, 61.3, 31.1, 25.9, 18.3, 15.8, -5.4. HRMS ($MNa^+$) for $C_{20}H_{28}O_2Si$ Calcd: 351.1756. Found: 351.1763.



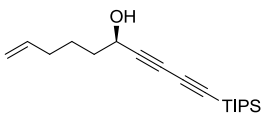

**(R)-1-cyclohexyl-5-(triisopropylsilyl)penta-2,4-diyn-1-ol, 4-2bm.** 99% yield. 89% ee determined by HPLC analysis of desilylated diyne (TIPS group removed via treatment with TBAF): Chiralpak AD-H column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 240 nm, retention time: $t_{major}$ = 18.2 $t_{minor}$ = 16.6. $[\alpha]_D^{25}$ = -11.8 (c = 0.76, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) 4.21 (t, 1H, J = 6.0 Hz), 1.95 (d, 1H, J = 6.0 Hz), 1.86 (m, 2H), 1.78 (m, 2H), 1.68 (m, 1H), 1.58 (m, 1H), 1.20 (m, 5H), 1.08 (s, 21H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 88.9, 84.4, 76.6, 70.9, 67.6, 44.1, 28.4 28.2, 26.2, 25.8, 18.5, 11.2. . This data is in agreement with that reported.[1a]




**(R)-1-(triisopropylsilyl)nona-8-en-1,3-diyn-5-ol, 4-2bp.** 94% yield. 95% ee determined by HPLC analysis of desilylated diyne (TIPS group removed via treatment with TBAF): Chiralcel OB-H column, 98:2 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 33.9 $t_{minor}$ = 29.7. $[\alpha]_D^{25}$ = -24.6 (c = 0.49, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.83 (m, 1H), 5.05 (m, 2H), 4.46 (t, 1H, J = 6.5 Hz), 2.25 (m, 2H), 1.83 (m, 3H), 1.08 (s, 21H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 137.3, 115.6, 88.7, 85.0, 70.5, 62.3, 36.4, 29.2, 18.5, 11.2. HRMS ($MNa^+$) for $C_{18}H_{30}OSi$ Calcd: 313.1964. Found: 313.1964.

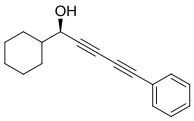



**(R)-6,6-dimethyl-1-(triisopropylsilyl)nona-8-en-1,3-diyn-5-ol, 4-2bq.** 98% yield. 88% ee determined by HPLC analysis of desilylated diyne (TIPS group removed via treatment with TBAF): Chiralcel OB-H column, 98:2 hexanes:$^{i}$PrOH, flow rate = 0.3 mL/min, $\lambda$ = 230 nm, retention time: $t_{major}$ = 21.8 $t_{minor}$ = 23.5. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.83 (m, 1H), 5.10 (m, 2H), 4.20 (s, 1H), 2.18 (m, 1H), 2.10 (m, 1H), 1.88 (s, 1H), 1.08 (m, 21H), 0.99 (d, 6H, J = 5.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 134.5, 118.0, 88.9, 84.4, 76.1, 71.5, 70.7, 42.7, 39.2, 22.7, 22.6, 18.5, 11.2. The $^1$H data is in agreement with that reported.[50a]

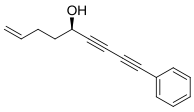



**(R)-1-(triisopropylsilyl)deca-9-en-1,3-diyn-5-ol, 4-2br.** 87% yield. 91% ee determined by HPLC analysis of desilylated diyne (TIPS group removed via treatment with TBAF): Chiralpak AD-H column, 98:2 hexanes:$^{i}$PrOH, flow rate = 1.0

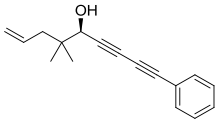
mL/min, λ = 254 nm, retention time: $t_{major}$ = 16.8 $t_{minor}$ = 18.7. $[\alpha]_D^{25}$ = -8.4 (c = 0.32, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 5.79 (m, 1H), 5.00 (m, 2H), 4.44 (t, 1H, J = 6.5 Hz), 2.10 (m, 2H), 1.94 (s, 1H), 1.74 (m, 2H), 1.57 (m, 2H), 1.08 (s, 21H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.2, 115.0, 88.8, 84.9, 77.3, 70.2, 62.7, 36.8, 33.2, 24.2, 18.5, 11.2. HRMS ($MNa^+$) for $C_{19}H_{32}OSi$ Calcd: 327.2120. Found: 327.2119.



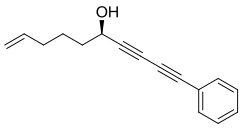

**(R)-1-cyclohexyl-5-phenylpenta-2,4-diyn-1-ol, 4-2cm.** 98% yield. 92% ee determined by HPLC analysis: Chiralcel OD column, 95:5 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: $t_{major}$ = 22.6 $t_{minor}$ = 29.5. $[\alpha]_D^{25}$ = -17.2 (c = 0.21, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 7.49 (m, 2H), 7.33 (m, 3H), 4.30 (t, 1H, J = 5.0 Hz), 2.04 (d, 1H, J = 5.0 Hz), 1.89 (m, 2H), 1.80 (m, 2H), 1.64 (m, 2H), 1.20 (m, 5H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 132.5, 129.2, 128.4, 121.4, 82.6, 78.3, 73.3, 70.24, 67.8, 44.1, 28.5, 28.1, 26.2, 25.80, 25.77. HRMS ($MNa^+$) for $C_{17}H_{18}O$ Calcd: 261.1255. Found: 261.1260.



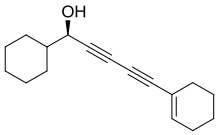

**(R)-1-phenylnona-8-en-1,3-diyn-5-ol, 4-2cp.** 97% yield. 90% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:$^i$PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: $t_{major}$ = 57.5 $t_{minor}$ = 70.3. $[\alpha]_D^{25}$ = -36.1 (c = 0.43, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$). δ 7.49 (m, 2H), 7.33 (m, 3H), 5.85 (m, 1H), 5.07 (m, 2H), 4.55 (t, 1H, J = 6.6 Hz), 2.28 (m, 3H), 1.88 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 133.3, 132.5, 129.3, 128.4, 121.4, 115.6, 83.0, 78.7, 73.2, 69.8, 62.4, 36.5, 29.3. HRMS ($MNa^+$) for $C_{15}H_{14}O$ Calcd: 233.0942. Found: 233.0941.



**(R)-6,6-dimethyl-1-phenylnona-8-en-1,3-diyn-5-ol, 4-2cq.** 97% yield. 89% ee determined by HPLC analysis: Chiralcel OD column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 14.6 $t_{minor}$ = 24.3. $[\alpha]_D^{25}$ = -32.1 (c = 0.20, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.50 (m, 2H), 7.34 (m, 3H), 5.86 (m, 1H), 5.12 (m, 2H), 4.23 (s, 1H), 2.22 (m, 1H), 2.14 (m, 1H), 2.00 (s, 1H), 1.03 (d, 6H, J = 4.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 134.6, 132.5, 129.2, 128.4, 121.4, 118.1, 82.1, 78.2, 73.3, 70.8, 42.7, 39.2, 22.7, 22.6. HRMS ($MNa^+$) for $C_{17}H_{18}O$ Calcd: 261.1255. Found: 261.1253.

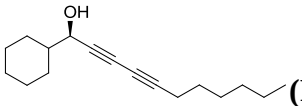


**(R)-1-phenyldeca-9-en-1,3-diyn-5-ol, 4-2cr.** 73% yield. 91% ee determined by HPLC analysis: Chiralcel OD column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 23.9 $t_{minor}$ = 33.1. $[\alpha]_D^{25}$ = -9.1 (c = 0.15, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$7.49 (m, 2H), 7.33 (m, 3H), 5.85 (m, 1H), 5.07 (m, 2H), 4.55 (t, 1H, J = 6.5 Hz), 2.13 (m, 3H), 1.78 (m, 2H), 1.61 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 138.2, 132.5, 129.3, 128.4, 121.4, 115.0, 88.2, 78.6, 73.2, 69.6, 62.8, 36.9, 33.2, 24.2. HRMS ($MNa^+$) for $C_{16}H_{16}O$ Calcd: 247.1099. Found: 247.1098.

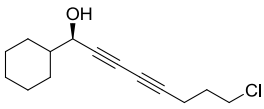


**(R)-5-cyclohexenyl-1-cyclohexylpenta-2,4-diyn-1-ol, 4-2dm.** 99% yield. 90% ee determined by HPLC analysis: Chiralcel OD column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 17.2 $t_{minor}$ = 15.4. $[\alpha]_D^{25}$ = -8.0

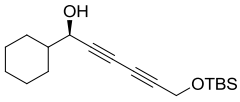
(c = 0.28, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) 6.27 (m, 1H), 4.24 (t, 1H, J = 5.5 Hz), 2.11 (m, 4H), 1.94 (d, 1H, J = 5.5 Hz), 1.84 (m, 2H), 1.76 (m, 2H), 1.63 (m, 6H), 1.15 (m, 5H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 139.0, 119.5, 81.5, 80.4, 70.7, 70.5, 67.8, 44.1, 28.5, 28.0, 26.2, 25.80, 25.77, 22.0, 21.2. HRMS ($MNa^+$) for $C_{17}H_{22}O$ Calcd: 265.1560. Found: 265.1568.



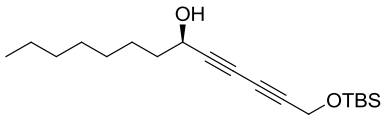

**(R)-1-cyclohexylundeca-2,4-diyn-1-ol, 4-2em.** 97% yield. 86% ee determined by analyzing the $^1H$ NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = -7.2 (c = 1.41, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) 4.19 (d, 1H, J = 6.0 Hz), 2.27 (t, 2H, J = 7.0 Hz), 1.83 (m, 3H), 1.76 (m, 2H), 1.66 (m, 1H), 1.53 (m, 2H), 1.38 (m, 2H), 1.27 (m, 6H), 1.13 (m, 3H), 0.88 (t, 3H, J = 7.5 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 81.5, 75.6, 70.6, 67.6, 64.4, 44.1, 31.2, 28.5, 28.1, 28.0, 26.2, 25.80, 25.77, 22.5, 19.3, 14.0. HRMS ($MNa^+$) for $C_{17}H_{26}O$ Calcd: 269.1881. Found: 269.1883.



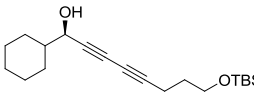

**(R)-8-chloro-1-cyclohexylocta-2,4-diyn-1-ol, 4-2fm.** 98% yield 85% ee determined by analyzing the $^1H$ NMR spectrum of the (R)-mandalate ester derivative. $[\alpha]_D^{25}$ = -10.3 (c = 0.60, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) 4.19 (t, 1H, J = 5.0 Hz), 3.64 (t, 2H, J = 6.3 Hz), 2.49 (t, 2H, J = 6.6 Hz) 1.99 (p, 2H, J = 6.6 Hz), 1.81 (m, 5H), 1.68 (m, 1H), 1.58 (m, 1H), 1.20 (m, 5H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 79.1, 76.2, 70.3, 67.5, 65.4, 44.1, 43.4, 30.8, 28.5, 28.0, 26.2, 25.8, 25.7, 16.7. HRMS ($MNa^+$) for $C_{14}H_{19}ClO$ Calcd: 261.1022. Found: 261.1029.




**(R)-6-(tert-butyldimethylsilyloxy)-1-cyclohexylhexa-2,4-diyn-1-ol, 4-2hm.** 98% yield. 91% ee determined by HPLC analysis of desilylated alcohol (TBS group removed via treatment with TBAF): Chiralcel OB-H column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 20.5 $t_{minor}$ = 26.2. $[\alpha]_D^{25}$ = -7.4 (c = 1.44, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 4.39 (s, 2H), 4.23 (d, 1H, J = 5.5 Hz), 1.85 (m, 2H), 1.78 (m, 2H), 1.69 (m, 1H), 1.59 (m, 1H), 1.20 (m, 5H), 0.91 (s, 9H), 0.13 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 79.1, 77.8, 69.8, 68.9, 67.5, 52.0, 44.0, 28.5, 28.0, 26.2, 25.8, 25.7, 18.2, -5.3. HRMS ($MNa^+$) for $C_{18}H_{30}O_2Si$ Calcd: 329.1913. Found: 329.1921.




**(R)-1-(tert-butyldimethylsilyloxy)trideca-2,4-diyn-6-ol, 4-2ht.** 89% yield. 88% ee determined by HPLC analysis of desilylated alcohol (TBS group removed via treatment with TBAF): Chiralcel OB-H column, 95:5 hexanes:$^{i}$PrOH, flow rate = 1.0 mL/min, $\lambda$ = 254 nm, retention time: $t_{major}$ = 13.2 $t_{minor}$ = 15.6. $[\alpha]_D^{25}$ = -5.4 (c = 3.53, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 4.43 (q, 1H, J = 6.5 Hz), 4.38 (s, 2H), 1.76 (d, 1H, J = 5.5. Hz), 1.72 (m, 2H), 1.41 (m, 2H), 1.29 (m, 8H), 0.91 (s, 9H), 0.88 (t, 3H, J = 7.0 Hz), 0.12 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 79.9, 78.1, 69.1, 68.9, 62.8, 52.0, 37.5, 31.7, 29.1, 25.7, 25.0, 22.6, 18.2, 14.0, -5.2.




**(R)-8-(tert-butyldimethylsilyloxy)-1-cyclohexylocta-2,4-diyn-1-ol, 4-2jm.** 99% yield. 92% ee determined by HPLC analysis of desilylated alcohol (TBS group removed via treatment with TBAF): Chiralcel OB-H column, 95:5 hexanes:$^{i}$PrOH,

flow rate = 1.0 mL/min, $\lambda$ = 240 nm, retention time: $t_{major}$ = 16.6 $t_{minor}$ = 26.9. $[\alpha]_D^{25}$ = -7.1 (c = 3.53, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) 4.19 (t, 1H, J = 6.0 Hz), 3.68 (t, 2H, J = 6.0 Hz), 2.38 (t, 2H, J = 7.0 Hz), 1.84 (m, 2H), 1.73 (m, 6H), 1.57 (m, 1H), 1.16 (m, 5H), 0.89 (s, 1H), 0.05 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 81.0, 70.6, 67.5, 64.6, 61.3, 44.1, 31.1, 28.5, 28.0, 26.2, 25.9, 25.80, 25.77, 18.3, 15.7, -5.4. HRMS ($MNa^+$) for $C_{20}H_{34}O_2Si$ Calcd: 357.2226. Found: 357.2221.

*f. Preparation of Dienediynes*

*i. Optically Active Dienediynes*

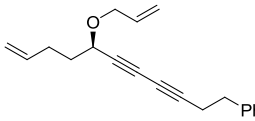
Under nitrogen a propargylic alcohol (1.5 mmol, 1 equiv) was dissolved in THF (7.5 mL) and cooled to -78 °C. $^n$BuLi (1.5 mmol, 1 equiv) was added and the mixture was stirred for 10 min. Allyl bromide (1.04 mL, 12 mmol, 8 equiv) was then added, followed by the addition of DMSO (0.21 mL, 3.0 mmol, 2 equiv). The reaction flask was allowed to warm to room temperature over night. Upon consumption of the starting material, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL), extracted three times with $CH_2Cl_2$, dried with sodium sulfate, and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel eluted with hexanes/ethylacetate (0-5% ethyl acetate) to give the product in 82-93% yield.

*ii. Racemic Dienediynes*

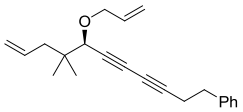
A 1,3-diyne (1.5 equiv) was weighed into a tared flask and placed under nitrogen atmosphere. The diyne was dissolved in THF (0.2 M), and cooled to -78 °C. nBuLi (1.4 equiv) was added and the reaction mixture stirred for 30 min. An aldehyde was then added. After 1 h allyl bromide (8 equiv) and DMSO (2 equiv) were added and the

reaction solution was allowed to warm to room temperature over night. The reaction was quenched with saturated aqueous ammonium chloride, and extracted three times with $CH_2Cl_2$. The organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel to afford the product in 65-85% yield.

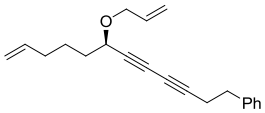
*g. Characterization of Dienediynes*



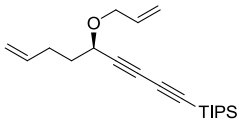
**(R)-(7-(allyloxy)undeca-10-en-3,5-diynyl)benzene, 4-3ap.** 82% yield. $[\alpha]_D^{25}$ = 66.7 (c = 0.69, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.26 (m, 3H), 5.94 (m, 1H), 5.84 (m, 1H), 5.30 (m, 2H), 5.07 (m, 2H), 4.29 (m, 1H), 4.17 (t, 1H, J = 6.5 Hz), 3.98 (m, 1H), 2.89 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.5 Hz), 2.27 (q, 2H, J = 7.0 Hz), 1.88 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.5, 134.3, 128.5, 128.4, 126.5, 117.6, 115.4, 80.1, 75.2, 70.8, 69.9, 68.5, 65.3, 34.8, 34.4, 29.4, 21.5.



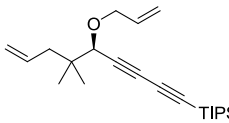
**(R)-(7-(allyloxy)-8,8-dimethylundeca-10-en-3,5-diynyl)benzene, 4-3aq.** 91% yield. $[\alpha]_D^{25}$ = 72.2 (c = 0.90, $CHCl_3$). $^1$H NMR (30 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.84 (m, 2h), 5.25 (m, 2H), 5.05 (m, 2H), 4.27 (m, 1H), 3.89 (m, 1H), 3.78 (s, 1H), 2.87 (t, 2H, J = 7.5 Hz), 2.58 (t, 2H, J = 7.5 Hz), 2.13 (m, 2H), 0.97 (d, 6H, J = 7.5 Hz). $^{13}$C NMR (7 MHz, $CDCl_3$) δ 140.0, 134.6, 134.4, 128.5, 128.3, 126.5, 117.6, 117.1, 79.4, 76.6, 74.4, 71.5, 70.2, 65.4, 43.0, 38.7, 34.5, 23.2, 22.9, 21.5.



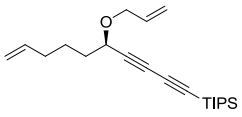

**(R)-(7-(allyloxy)dodeca-11-en-3,5-diynyl)benzene, 4-3ar.** 83% yield. $[\alpha]_D^{25}$ = 88.1(c = 0.80, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.26 (m, 3H), 5.94 (m, 1H), 5.84 (m, 1H), 5.30 (m, 2H), 5.04 (m, 2H), 4.29 (m, 1H), 4.16 (t, 1H, 6.5 Hz), 3.90 (m, 1H), 2.89 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.5 Hz), 2.12 (q, 2H, J = 6.5 Hz), 1.78 (m, 2H), 1.61 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 139.9, 138.2, 134.1, 128.4, 128.3, 126.4, 117.4, 114.7, 79.9, 75.3, 70.5, 69.2, 68.9, 65.2, 34.9, 34.4, 33.3, 24.3, 21.4.



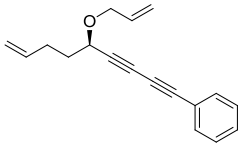

**(R)-(5-(allyloxy)nona-8-en-1,3-diynyl)triisopropylsilane, 4-3bp.** 93% yield. $[\alpha]_D^{25}$ = 63.6 (c = 0.79, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.80 (m, 1H), 5.25 (m, 2H), 5.03 (m, 2H), 4.27 (m, 1H), 4.15 (t, 1H, J = 6.5 Hz), 3.95 (m , 2H), 2.23 (q, 2H, J = 6.5 Hz), 1.85 (m, 2H), 1.09 (m, 21H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.4, 134.1, 117.6, 115.3, 89.0, 84.1, 75.8, 71.0, 70.0, 68.4, 34.6, 29.3, 18.5, 11.2.



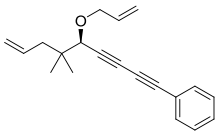

**(R)-(5-(allyloxy)-6,6-dimethylnona-8-en-1,3-diynyl)-tiisopropylsilane, 4-3bq.** 92% yield. $[\alpha]_D^{25}$ = 78.3 (c = 1.70, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 5.90 (m,1H), 5.79 (m, 1H), 5.25 (m, 2H), 5.05 (m, 2H), 4.30 (m, 1H), 3.90 (m, 1H), 3.80 (s, 1H), 2.15 (m, 2H), 1.09 (s, 21H), 0.99 (d, 6H, J = 11.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 134.6, 134.3, 117.7, 117.2, 89.2, 83.4, 76.8, 75.1, 71.9, 70.4, 43.0, 38.9, 23.2, 22.9, 18.5, 11.3.



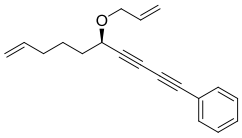

**(R)-(5-(allyloxy)deca-9-en-1,3-diynyl)triisopropylsilane, 4-3br.** 86% yield. $[\alpha]_D^{25}$ = 60.0 (c = 1.27, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.79 (m, 1H), 5.26 (m, 2H), 4.99 (m, 2H), 4.26 (m, 1H), 4.13 (t, 1H, J = 6.5 Hz), 3.95 (m, 1H), 2.08 (q, 2H, J = 6.5 Hz), 1.75 (m, 2H), 1.57 (m, 2H), 1.09 (s, 21H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.2, 134.1, 117.5, 114.8, 89.0, 83.9, 76.0, 70.9, 69.9, 68.9, 34.9, 33.3, 24.4, 18.5, 11.2.



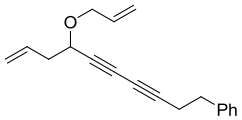

**(R)-(5-(allyloxy)nona-8-en-1,3-diynyl)benzene, 4-3cp.** 83% yield. $[\alpha]_D^{25}$ = 68.4 (c = 0.98, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.34 (m, 3H), 5.93 (m, 1H), 5.83 (m, 1H), 5.28 (m, 2H), 5.05 (m, 2H), 4.30 (m, 1H), 4.24 (t, 1H, J = 6.5 Hz), 4.00 (m, 1H), 4.28 (q, 2H, J = 6.5 Hz), 1.89 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.4, 134.1, 132.5, 129.2, 128.4, 121.4, 117.6, 115.4, 81.8, 78.0, 73.4, 70.4, 69.9, 68.6, 34.6, 29.3.



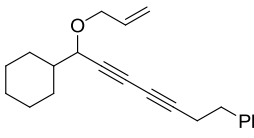

**(R)-(5-(allyloxy)-6,6-dimethylnona-8-en-1,3-diynyl)benzene, 4-3cq.** 93% yield. $[\alpha]_D^{25}$ = 85.3 (c = 1.57, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.35 (m, 3H), 5.94 (m, 1H), 5.84 (m, 1H), 5.30 (m, 2H), 5.10 (m, 2H), 4.34 (m, 1H), 3.96 (m, 1H), 3.91 (s, 1H), 2.21 (m, 2H), 1.06 (d, 6H, J = 12.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 134.5, 134.3, 132.5, 129.1, 128.4, 121.5, 117.7, 117.2, 81.1, 77.4, 76.9, 73.6, 71.2, 70.3, 43.0, 38.8, 23.2, 22.9.



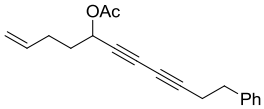
**(R)-(5-(allyloxy)deca-9-en-1,3-diynyl)benzene, 4-3cr.** 88% yield. $[\alpha]_D^{25}$ = 111.1 (c = 0.85, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.33 (m, 3H), 5.88 (m, 2H), 5.28 (m, 2H), 5.02 (m, 2H), 4.30 (m, 1H), 4.23 (t, 1H, J = 6.3 Hz), 4.00 (m, 1H), 2.11 (q, 2H, J = 6.0 Hz), 1.81 (m, 2h), 1.62 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 138.3, 134.1, 132.5, 129.2, 128.4, 121.5, 117.6, 114.9, 82.0, 77.9, 73.4, 70.3, 69.9, 69.1, 35.0, 33.3, 24.4.



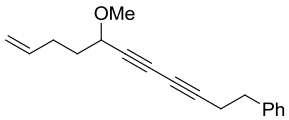
**(7-(allyloxy)deca-9-en-3,5-diynyl)benzene, 4-3at.** 93% yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.24 (m, 2H), 5.90 (m, 2H), 5.29 (m, 2H), 5.17 (m, 2H), 4.28 (m, 1H), 4.18 (t, 1H, J = 6.5 Hz), 3.99 (m, 1H), 2.88 (t, 2H, J = 7.5 Hz), 2.60 (t, 2H, J = 7.5 Hz), 2.52 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 139.9, 134.0, 133.1, 128.4, 128.3, 126.4, 118.0, 117.6, 80.2, 74.7, 70.9, 69.7, 68.6, 65.1, 39.9, 34.4, 21.5.



**(7-(allyloxy)-7-cyclohexylhepta-3,5-diynyl)benzene, 4-3am.** 93% yield. $^1$H NMR (500 MHz, CDCl3) δ 7.34 (m, 2H), 7.25 (m, 3H), 5.92 (m, 1H), 5.27 (m, 2H), 4.28 (m, 1H), 3.95 (m, 1H), 3.93 (d, 1H, J = 6.0 Hz), 2.88 (t, 2H, J = 7.5 Hz), 2.60 (t, 2H, J = 7.5 Hz), 1.88 (m, 2H), 1.78 (m, 2H), 1.68 (m, 2H), 1.20 (m, 5H). $^{13}$C NMR (125 MHz, CDCl3) δ 140.0, 134.3, 128.4, 128.3, 126.4, 117.3, 79.6, 74.8, 74.0, 71.1, 69.9, 65.3, 42.7, 34.5, 28.9, 28.4, 26.3, 25.9, 25.8, 21.4.




**11-phenylundeca-1-en-6,8-diyn-5-yl acetate, 4-3au.** 93% yield. $^{1}$H NMR (500 MHz, CDCl3) δ 7.31 (m, 2H), 7.22 (m, 3H), 5.79 (m, 1H), 5.40 (t, 1H, J = 6.5 Hz), 5.04 (m, 2H), 2.85 (t, 2H, J = 7.5 Hz), 2.58 (t, 2H, J = 7.5 Hz), 2.21 (q, 2H, J = 6.5 Hz), 2.08 (s, 3H), 1.87 (m, 2H). $^{13}$C NMR (125 MHz, CDCl3) δ 169.7, 139.9, 136.7, 128.5, 128.3, 126.5, 115.7, 80.9, 72.9, 70.4, 65.0, 63.7, 34.3, 33.7, 29.1, 21.4, 20.9.




**(7-methoxyundeca-10-en-3,5-diynyl)benzene, 4-3av.** 93% yield. $^{1}$H NMR (500 MHz, CDCl3) δ 7.33 (m, 2H), 7.24 (m, 3H), 5.81 (m, 1H), 5.04 (m, 2H), 4.01 (t, 1 H, J = 6.5 Hz), 3.41 (s, 3H), 2.87 (t, 2H, J = 7.5 Hz), 2.59 (t, 2H, J = 7.5 Hz), 2.21 (q, 2H, J = 6.5 Hz), 1.82 (m, 2H). $^{13}$C NMR (125 MHz, CDCl3) δ 140.0, 137.4, 128.5, 128.3, 126.5, 115.3, 80.0, 75.0, 70.9, 70.8, 65.2, 56.7, 34.6, 34.5, 29.3, 21.5.

*h. Rhodium Catalyzed Pauson-Khand Type Cyclization*

*$Rh(cod)Cl]_2$-BINAP Catalyzed PK-Type Cyclization of Dienediynes Utilizing Benzaldehyde as the CO Source.*

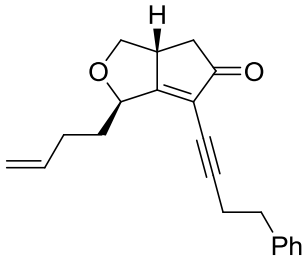
Under nitrogen, a dienediyne (0.25 mmol) was weighed into a tared flask. $[Rh(cod)Cl]_2$ (18.5 mg, 0.038 mmol, 0.15 equiv), rac-BINAP (46.7 mg, 0.075 mmol, 0.30 equiv), and benzaldehyde (0.51 mL, 5 mmol, 20 equiv) were added and the flask was fitted with a reflux condenser fit with a vacuum/nitrogen adapter. The reaction was heated under at 80 °C for the time indicated in Table 4.9 until the reaction was determined to be complete by TLC or crude $^{1}$H NMR. The reaction mixture was cooled

to room temperature and directly purified by column chromatography. Benzaldehyde was eluted with 95:5 hexanes:EtOAc, and the product was eluted with 90:10 to 80:20 hexanes:EtOAc depending on the substrate to yield the *cis* diastereomer as the major product in 48-73% yld and 3:1 to >20:1 dr.

*$[RhCl(CO)_2]_2$ Catalyzed PK-Type Cyclization of Dienediynes and Enediynes With CO.*

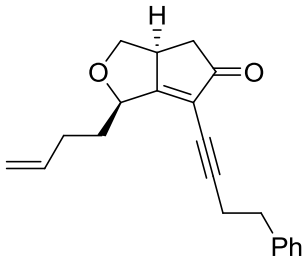
Under nitrogen, a dienediyne or enediyne (0.20 mmol) was weighed into a tared Schlenk flask and dissolved in THF (4 mL, 0.05 M). $[RhCl(CO)_2]_2$ (7.8 mg, 0.02 mmol, 0.10 equiv), was added and the flask was fitted with a reflux condenser fit with a septum. The solution was bubbled with CO gas for 2 minutes and then placed under CO atmosphere (balloon). The reaction was heated at 75-80 °C for 24 h. The reaction mixture was cooled to room temperature and the CO was released cautiously in the hood. The reaction solution was concentrated and the crude product was purified by column chromatography, eluting with hexanes:EtOAc to yield the *trans* diastereomer as the major product when sufficient coordinating groups were present in the substrate.

*i. Characterization of PK-Type Cycloadducts*

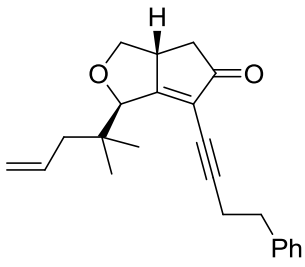



**(1R,3aR)-1-(but-3-enyl)-6-(4-phenylbut-1-ynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4ap.** 62% yield. 4:1 dr. 16h rxn time. $[\alpha]_D^{25}$ = 116.5 (c = 1.46, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29, (m, 2H), 7.22 (m, 2H), 5.83, (m, 1H), 5.04 (m, 2H), 4.64 (t, 1H, J = 6.5 Hz), 4.30 (t, 1H, J = 6.0 Hz), 3.22 (m, 2H),

2.89 (m, 2H), 2.71 (m, 3H), 2.18 (m, 3H), 1.78 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.3, 185.6, 140.1, 137.4, 128.3, 128.3, 126.3, 121.0, 115.2, 99.5, 76.1, 71.3, 70.6, 43.2, 39.0, 34.6, 33.2, 29.2, 21.7. HRMS ($MH^+$) for $C_{21}H_{22}O_2$ Calcd: 307.1698. Found: 307.1692.

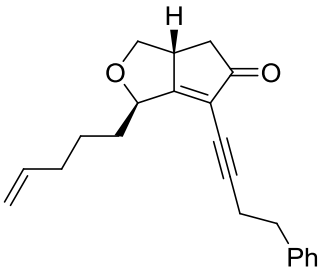



**(1R,3aS)-1-(but-3-enyl)-6-(4-phenylbut-1-ynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4ap'.** $[\alpha]_D^{25}$ = 1.14 (c = 0.32, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.22 (m, 3H), 5.80 (m, 1H), 5.04 (m, 2H), 4.79 (dd, 1H, J = 8.5, 3.0 Hz), 4.25 (t, 1H, J = 7.0 Hz), 3.31 (m, 2H), 2.89 (t, 2H, J = 7.5 Hz), 2.71 (m, 3H), 2.16 (m, 4H), 1.70 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.7, 184.5, 140.2, 137.7, 128.4, 128.4, 126.4, 120.4, 115.3, 99.8, 75.8, 70.6, 70.3, 44.7, 38.9, 34.7, 30.9, 29.8, 21.8. HRMS ($MH^+$) for $C_{21}H_{22}O_2$ Calcd: 307.1698. Found: 307.1693.

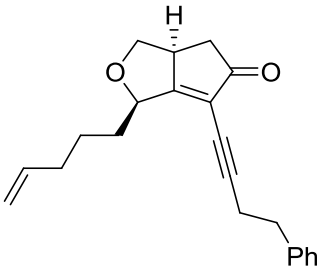



**(1R,3aR)-1-(2-methylpent-4-en-2-yl)-6-(4-phenylbut-1-ynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4aq.** 51% yield. 17:1 dr. 36h rxn time. $[\alpha]_D^{25}$ = 231.77 (c = 0.90, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.22 (m, 3H), 5.83, (m, 1H), 5.07 (m, 2H), 4.38 (s, 1H), 4.32 (m, 1H), 3.22 (m, 2H), 2.86 (m, 2H), 2.71 (m, 3H), 2.21 (m, 1H), 2.13 (m 1H), 1.99 (m, 1H), 0.93 (s, 3H), 0.90 (s, 3H).

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.7, 184.3, 140.2, 134.4, 128.4, 128.4, 126.3, 123.3, 117.8, 99.9, 84.2, 71.8, 71.2, 44.2, 43.2, 39.4, 39.0, 34.6, 23.4, 23.3, 21.8. HRMS ($MH^+$) for $C_{23}H_{26}O_2$ Calcd: 335.2011. Found: 335.2011.

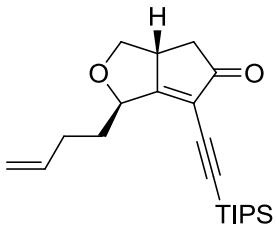



**(1R,3aR)-1-(pent-4-enyl)-6-(4-phenylbut-1-ynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4ar.** 73% yield. 4:1 dr. 20h rxn time. $[\alpha]_D^{25}$ = 0.3 (c = 1.36, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.22 (m, 3H), 5.78 (m, 1H), 5.00 (m, 2H), 4.63 (t, 1H, J = 6.5 Hz), 4.30 (t, 1H, J = 6.0 Hz), 3.23 (m, 2H), 2.88 (m, 2H), 2.71 (m, 3H), 2.16 (dd, 1H, J = 18.0, 3.0 Hz), 2.09 (q, 2H, J = 6.5 Hz), 1.70 (m, 2H), 1.52 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.4, 185.8, 140.2, 138.1, 128.4, 126.3, 120.9, 114.9, 99.5, 76.6, 71.3, 70.7, 43.3, 39.0, 34.7, 33.6, 33.4, 24.3, 21.8. HRMS ($MH^+$) for $C_{22}H_{24}O_2$ Calcd: 321.1855. Found: 321.1849.

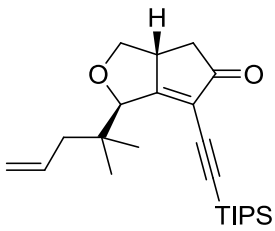



**(1R,3aS)-1-(pent-4-enyl)-6-(4-phenylbut-1-ynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4ar'.** $[\alpha]_D^{25}$ = 1.9 (c = 0.22, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.23 (m, 3H), 5.79 (m, 1H), 5.00 (m, 2H), 4.79 (dd, 1H, J = 8.0, 3.0 Hz), 4.25 (t, 1H, J = 7.0 Hz), 3.30 (m, 2H), 2.90 (m, 2H), 2.70 (m, 3H), 2.19 (dd, 1H, J = 17.5, 3.0 Hz), 2.06 (m, 3H), 1.64 (m, 1H), 1.54 (m, 2H). $^{13}$C NMR

(125 MHz, $CDCl_3$) δ 205.7, 184.7, 140.2, 138.4, 128.4, 128.4, 126.4, 120.4, 114.8, 99.7, 76.5, 70.7, 70.4, 44.7, 38.9, 34.7, 33.5, 31.2, 24.9, 21.9. HRMS ($MH^+$) for $C_{22}H_{24}O_2$ Calcd: 321.1855. Found: 321.1846.

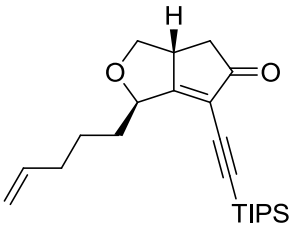



**(1R,3aR)-1-(but-3-enyl)-6-((triisopropylsilyl)ethynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4bp.** 76% yield. 4:1 dr. 16h rxn time. $[\alpha]_D^{25}$ = 177.2 (c = 2.80, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.02 (m, 2H), 4.74 (t, 1H, J = 6.5 Hz), 4.33 (m, 1H), 3.28 (m, 2H), 2.72 (m, 1H), 2.25 (m, 2H), 2.18 (m, 1H), 1.87 (q, 2H, 7.5 Hz), 1.09 (s, 21H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 204.2, 187.1, 137.2, 121.1, 115.4, 101.9, 95.6, 76.4, 71.4, 43.4, 39.3, 33.4, 29.5, 18.6, 11.1. HRMS ($MH^+$) for $C_{22}H_{35}O_2Si$ Calcd: 359.2406. Found: 359.2406.

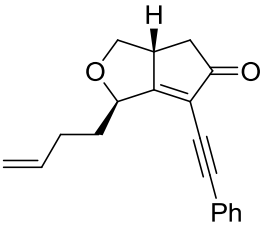



**1R,3aR)-1-(2-methylpent-4-en-2-yl)-6-((triisopropylsilyl)ethynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4bq.** 68% yield. >20 :1 dr (only 1 diastereomer observed). 60h rxn time. $[\alpha]_D^{25}$ = 118.0 (c = 1.79, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.06 (m, 2H), 4.47 (s, 1H), 4.34 (m, 1H), 3.26 (m, 2H), 2.70 (m, 1H), 2.27 (m, 1H), 2.15 (dd, 1H, J = 18.0 Hz, 2.5 Hz), 2.04 (m, 1H), 1.09 (s, 21H), 1.03 (s, 3H), 0.96 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$)

δ 204.7, 184.7, 134.3, 123.5, 117.9, 102.4, 96.8, 84.3, 71.2, 44.3, 43.4, 39.6, 39.2, 23.6, 23.5, 18.6, 11.1. HRMS ($MH^+$) for $C_{24}H_{38}O_2Si$ Calcd: 387.2719. Found: 387.2716.

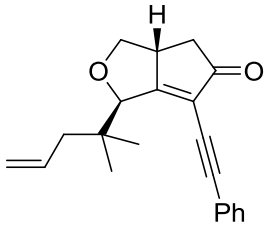



**(1R,3aR)-1-(pent-4-enyl)-6-((triisopropylsilyl)ethynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4br.** 60% yield. 3:1 dr. 16h rxn time. $[\alpha]_D^{25}$ = 177.2 (c = 2.00, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1H), 4.98 (m, 2H), 4.72 (t, 1H, J = 6.0 Hz), 4.32 (m, 1H), 3.26 (m, 2H), 2.71 (m, 1H), 2.18 (dd, 1H, J = 18.0, 2.7 Hz), 2.09 (q, 2H, J = 7.2 Hz), 1.79 (m, 2H), 1.60 (m, 2H), 1.09 (s, 21H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 204.3, 187.3, 138.0, 121.1, 115.1, 101.8, 95.7, 77.0, 71.4, 43.4, 39.3, 33.7, 33.6, 24.7, 18.6, 11.1. HRMS ($MH^+$) for $C_{23}H_{37}O_2Si$ Calcd: 373.2563. Found: 373.2560.

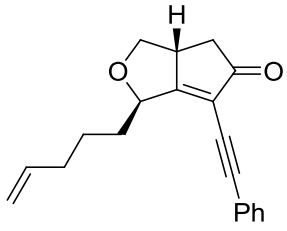



**(1R,3aR)-1-(but-3-enyl)-6-(phenylethynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-onel, 4-4cp.** 57% yield. 3:1 dr. 10h rxn time. $[\alpha]_D^{25}$ = 221.8 (c = 0.32, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.34 (m, 3H), 5.88 (m, 1H), 5.07 (m, 2H), 4.82 (t, 1H, J = 6.5 Hz), 4.36 (t, 1H, J = 7.5 Hz), 3.36 (m, 1H), 3.30 (m, 1H), 2.78 (dd, 1H, J = 18.0, 6.0 Hz), 2.32 (m, 2H), 2.25 (dd, 1H, J = 17.5, 3.5 Hz), 1.93 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 204.7, 186.4, 137.3, 131.8, 129.0, 128.3,

122.2, 120.8, 115.5, 98.6, 78.6, 76.4, 71.4, 43.6, 39.2, 33.5, 29.3. HRMS ($MH^+$) for $C_{19}H_{19}O_2$ Calcd: 279.1385. Found: 279.1385.

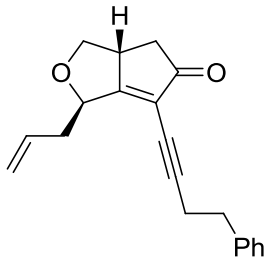



**(1R,3aR)-1-(2-methylpent-4-en-2-yl)-6-(phenylethynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4cq.** 71% yield. 18:1 dr. 18h rxn time. $[\alpha]_D^{25}$ = 186.2 (c = 1.45, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.33 (m, 3H), 5.89 (m, 3H), 5.10 (m, 2H), 4.54 (s, 1H), 4.38 (t, 1H, J = 6.5 Hz), 3.33 (m, 1H), 3.28 (m, 1H), 2.77 (dd, 1H, J = 23.0, 6.0 Hz), 2.31 (m, 1H), 2.21 (m, 1H), 2.11 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.0, 185.1, 134.3, 131.8, 129.0, 128.3, 123.0, 122.3, 118.0, 98.9, 84.5, 79.8, 71.2, 44.6, 43.4, 39.6, 39.2, 23.6, 23.5. HRMS ($MH^+$) for $C_{21}H_{22}O_2$ Calcd: 307.1698. Found: 307.1700.

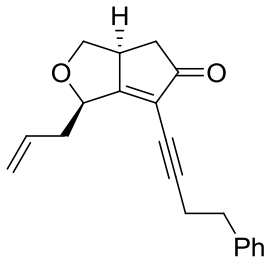



**(1R,3aR)-1-(pent-4-enyl)-6-(phenylethynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4cr.** 48% yield. 4:1 dr. 16h rxn time. $[\alpha]_D^{25}$ = 235.4 (c = 1.26, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.33 (m, 3H), 5.80 (m, 1H), 5.01 (m, 2H), 4.81 (t, 1H, J = 6.5 Hz), 4.36 (t, 1H, J = 7.5 Hz), 3.34 (m, 1H), 3.30 (m, 1H), 2.78 (dd, 1H, J = 17.5, 6.5 Hz), 2.25 (dd, 1H, J = 19.5, 3.5 Hz), 2.15 (q, 2H, J = 7.5 Hz), 1.85 (m, 2H), 1.66 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 204.7, 186.6, 138.0,

131.8, 129.0, 128.3, 122.2, 120.7, 115.1, 98.5, 78.6, 76.9, 71.4, 43.6, 39.2, 33.7, 33.4, 24.5. HRMS ($MH^+$) for $C_{20}H_{21}O_2$ Calcd: 293.1542. Found: 293.1541.

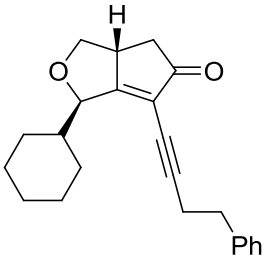



**1-allyl-6-(4-phenylbut-1-ynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4at.** Racemic product-relative stereochemistry shown. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.24 (m, 3H), 5.80 (m, 1H), 5.13 (m, 2H), 4.70 (t, 1H, J = 6.0 Hz), 4.32 (m, 1H), 3.24 (m, 2H), 2.89 (t, 2H, J = 7.5 Hz), 2.72 (m, 3H), 2.50 (m, 1H), 2.42 (m, 1H), 2.17 (dd, 1H, J = 17.5, 2.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.4, 185.2, 140.2, 132.7, 128.4, 128.4, 126.4, 121.1, 118.4, 99.8, 76.3, 71.7, 71.5, 70.6, 43.4, 39.1, 38.2, 34.7, 21.8. HRMS ($MH^+$) for $C_{20}H_{21}O_2$ Calcd: 293.1542. Found: 293.1534.

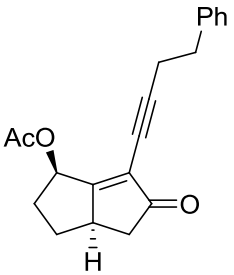



**1-allyl-6-(4-phenylbut-1-ynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4at'.** 94% yield. 95% dr. Racemic product-relative stereochemistry shown. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.21 (m, 3H), 5.81 (m, 1H), 5.13 (m, 2H), 4.86 (m, 1H), 4.25 (m, 1H), 3.32 (m, 2H), 2.90 (t, 2H, J = 7.5 Hz), 2.76 (m, 3H), 2.70 (m, 1H), 2.41 (m, 1H), 2.19 (dd, 1H, J = 18.5, 3.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.6, 183.7, 140.1, 133.6, 128.4, 128.4, 126.4, 120.7, 118.1, 100.0,

75.9, 70.8, 70.7, 44.6, 38.9, 36.0, 34.6, 21.8. HRMS ($MH^+$) for $C_{20}H_{21}O_2$ Calcd: 293.1542. Found: 293.1534.

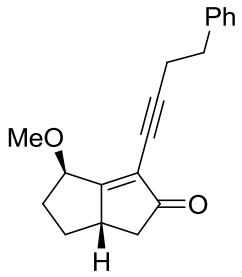



**1-cyclohexyl-6-(4-phenylbut-1-ynyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one, 4-4am.** Racemic product-relative stereochemistry shown. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.24 (m, 3H), 4.43 (d, 1H, J = 6.0 Hz), 4.30 (m, 1H), 3.22 (m, 2H), 2.89 (m, 2H), 2.71 (m, 3H), 2.15 (m, 1H), 1.73 (m, 5H), 1.22 (m, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.7, 185.2, 140.2, 128.4, 126.4, 122.1, 99.3, 81.4, 71.3, 71.2, 43.7, 42.9, 38.9, 34.7, 29.7, 29.1, 28.8, 26.2, 25.9, 21.8. HRMS ($MH^+$) for $C_{23}H_{27}O_2$ Calcd: 335.2011. Found: 335.2014.




**(1R,3aR)-5-oxo-6-(4-phenylbut-1-ynyl)-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate, 4-4au.** $[\alpha]_D^{25}$ = 19.4 (c = 0.20, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.21 (m, 3H), 6.09 (d, 1H, J = 9.0 Hz), 2.96 (m ,1H), 2.88 (t, 2H, J = 7.5 Hz), 2.73 (dd, 1H, J = 18.5, 6.5 Hz), 2.67 (m, 2H), 2.40 (m, 1H), 2.20 (m, 1H), 2.16 (m, 1H), 2.02 (s, 3H), 1.98 (m, 1H), 1.45 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 206.0, 184.0, 170.1, 140.3, 128.4, 128.3, 126.3, 122.5, 99.3, 70.6, 70.1, 42.8,

42.0, 34.9, 33.2, 29.8, 22.0, 20.3. HRMS ($MH^+$) for $C_{20}H_{20}O_3$ Calcd: 309.1491. Found: 309.1487.




**4-methoxy-3-(4-phenylbut-1-ynyl)-4,5,6,6a-tetrahydropentalen-2(1H)-one, 4-4av.** Racemic product-relative stereochemistry shown. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.23 (m, 3H), 4.36 (m, 1H), 3.28 (s, 3H), 3.09, m, 1H), 2.89 (m, 2H), 2.76 (m, 3H), 2.36 (m, 1H), 2.22 (m, 1H), 2.12 (dd, 1H, J = 18.5, 2.5 Hz), 1.91 (m, 1H), 1.03 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 207.5, 184.4, 140.2, 128.4, 128.4, 126.4, 124.1, 98.1, 75.9, 71.5, 57.6, 42.0, 41.1, 34.7, 33.5, 28.7, 21.7. HRMS ($MH^+$) for $C_{19}H_{20}O_2$ Calcd: 281.1542. Found: 281.1540.

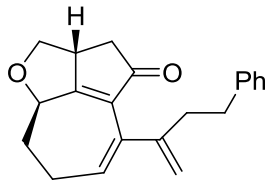
*j. Grubbs II Catalyzed Enyne Metathesis*

Under nitrogen, an enyne (0.1 mmol, 1 equiv) was weighed into a flame-dried tared vial and dissolved in toluene or $CH_2Cl_2$ (4 mL, 0.025M). Grubbs II catalyst (see table below) was added and the vial was fit with a rubber septum. Ethylene gas was bubbled through the reaction solution for 2 min (venting with a needle through the septum). The septum was replaced with a screw cap and the vial was tightly sealed (wrapping the cap with parafilm and electrical tape). The vial was heated at the temperature and for the amount of time shown below. When indicated the reaction was heated for 12 h and allowed to cool to room temperature. Under nitrogen a second portion of Grubbs II catalyst was added, the solution was bubbled with ethylene gas for 1.5 min, and the tube was resealed and heated for an additional 12 h. Following completion of the reaction the

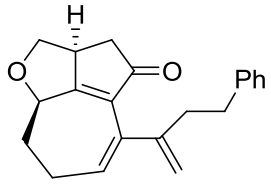
crude reaction mixture was directly purified by column chromatography (75:25 hexanes:EtOAc) to yield the product in 51-73% yield. Care was taken with the sensitive diene products.

| entry | eyne | Grubbs II 1st Step (mol %) | sovent/tmp | rx tme | Grubbs II 2nd Step (mol %) | rn tme |
|---|---|---|---|---|---|---|
| 1 | **4ap** | 10 | $CH_2Cl_2$/45 °C | 12 h | 5 | 12 h |
| 2 | **4ap'** | 5 | Tolune/100 °C | 17 h | - | - |
| 3 | **4aq** | 10 | Tolune/100 °C | 10 h | 10 | 12 h |
| 4 | **4ar** | 5 | Tolune/100 °C | 17 h | - | - |
| 5 | **4ar'** | 5 | Tolune/100 °C | 12 h | 5 | 12 h |
| 6 | **4cr** | 5 | Tolune/100 °C | 12 h | 5 | 12 h |

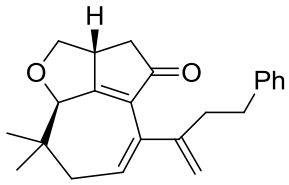
k. *Characterization of Enyne Metathesis Products*



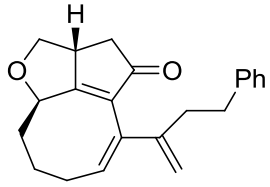

**(2aR,8aR)-5-(4-phenylbut-1-en-2-yl)-2a,3,8,8a-tetrahydro-2H-azuleno[8,1-bc]furan-4(7H)-one, 4-5ap.** 62% yield. $[\alpha]_D^{25}$ = 125.1 (c = 0.63, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.17 (m, 3H), 6.29 (t, 1H, J = 6.5 Hz), 4.99 (s, 2H), 4.47 (m, 1H), 4.35 (t, 1H, J = 8.5 Hz), 3.41 (m, 2H), 2.77 (m, 2H), 2.68 (m, 2H), 2.51 (m, 1H), 2.41 (m, 1H), 2.32 (m, 1H), 2.25 (m, 2H), 2.05 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.0, 190.0, 146.9, 142.0, 137.4, 134.3, 131.3, 128.4, 128.3, 125.8, 113.6, 77.5, 74.2, 43.7, 42.5, 41.4, 36.6, 34.8, 26.6. HRMS ($MH^+$) for $C_{21}H_{22}O_2$ Calcd: 307.1698. Found: 307.1696.



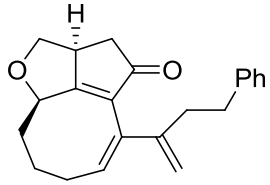
**(2aS,8aR)-5-(4-phenylbut-1-en-2-yl)-2a,3,8,8a-tetrahydro-2H-azuleno[8,1-bc]furan-4(7H)-one, 4-5ap'.** 73% yield. $[\alpha]_D^{25}$ = -52.8 (c = 1.16, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.17 (m, 3H), 6.01 (t, 1H, J = 6.0 Hz), 4.94 (d, 2H, J = 16.0 Hz), 4.74 (t, 1H, J = 5.5 Hz), 4.30 (t, 1H, J = 8.0 Hz), 3.42 (m, 1H), 3.36 (m, 1H), 2.75 (m, 2H), 2.70 (m, 1H), 2.48 (m, 2H), 2.30 (m, 1H), 2.21 (m, 1H), 2.15 (m, 1H), 2.05 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.7, 181.1, 148.5, 142.2, 134.1, 133.5, 132.5, 128.4, 128.2, 125.7, 112.2, 75.0, 70.9, 42.7, 39.8, 36.6, 34.7, 32.7, 24.9. HRMS ($MH^+$) for $C_{21}H_{22}O_2$ Calcd: 307.1698. Found: 307.1699.



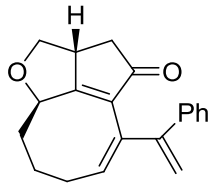
**(2aR,8aR)-8,8-dimethyl-5-(4-phenylbut-1-en-2-yl)-2a,3,8,8a-tetrahydro-2H-azuleno[8,1-bc]furan-4(7H)-one, 4-5aq.** 52% yield. $[\alpha]_D^{25}$ = -39.8 (c = 0.52, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.19 (m, 3H), 5.10 (d, 1H, J = 1.0 Hz), 4.89 (d, 1H, J = 1.0 Hz), 4.72 (t, 1H, J = 8.5 Hz), 3.82 (m, 1H), 3.45 (m, 1H), 2.75 (m, 1H), 2.61 (m, 2H), 2.49 (m, 2H), 2.23 (m, 1H), 1.76 (m, 1H), 1.50 (m, 1H), 1.17 (d, 6H, J = 9.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.2, 158.9, 149.7, 147.9, 142.0, 128.4, 128.3, 128.2, 126.6, 125.8, 125.7, 116.0, 112.4, 77.9, 45.8, 41.3, 37.4, 36.9, 36.0, 34.8, 33.5, 28.1, 26.5. HRMS ($MH^+$) for $C_{23}H_{26}O_2$ Calcd: 335.2011. Found: 335.2010.



**4-5ar.** 67% yield. $[\alpha]_D^{25}$ = 103.0 (c = 1.44, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.16 (m, 3H), 6.11 (t, 1H, J = 7.5 Hz), 4.95 (d, 2H, J = 32.5 Hz), 4.39 (t, 1H, J = 5.5 Hz), 4.11 (m, 1H0, 3.29 (m, 2H), 2.78 (dd, 1H, J = 17.5, 6.0 Hz), 2.69 (m, 2H), 2.48 (m, 2H), 2.39 (m, 1H), 2.29 (dd, 1H, J = 17.5, 2.5 Hz), 2.02 (m, 2H), 1.39 (m, 1H), 1.17 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 206.8, 181.8, 146.2, 142.0, 134.0, 133.5, 132.8, 128.3, 128.3, 125.8, 113.6, 78.2, 71.5, 41.9, 40.7, 36.8, 34.9, 30.1, 28.4, 23.3. HRMS ($MH^+$) for $C_{22}H_{24}O_2$ Calcd: 321.1855. Found: 321.1845.



**4-5ar'.** 62% yield. $[\alpha]_D^{25}$ = -74.3 (c = 0.22, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.20 (m, 3H), 5.95 (t, 1H, J = 8.0 Hz), 4.96 (d, 2H, J = 41.5 Hz), 4.74 (d, 1H, J = 7.0 Hz), 4.36 (m, 1H), 3.44 (m, 2H), 2.81 (t, 2H, J = 8.0 Hz), 2.76 (dd, 1H, J = 18.5, 6.0 Hz), 2.51 (m, 2H), 2.25 (m, 2H), 2.03 (m, 2H), 1.90 (m, 2H), 1.67 (m, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 207.4, 177.3, 142.2, 135.5, 133.5, 129.5, 129.4, 128.4, 128.3, 125.8, 113.1, 75.7, 71.4, 42.0, 40.8, 36.2, 34.9, 26.8, 26.2. HRMS ($MH^+$) for $C_{22}H_{24}O_2$ Calcd: 321.1855. Found: 321.1853.

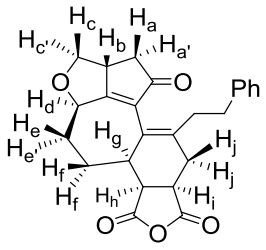


**4-5cr.** 62% yield. $[\alpha]_D^{25}$ = 184.5 (c = 0.88, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.23 (m, 2H), 7.16 (m, 3H), 6.20 (t, 1H, J = 8.5 Hz), 5.26 (s, 1H), 4.32 (t, 1H, J

= 7.5 Hz), 4.23 (m, 1H), 3.24 (m, 1H), 3.12 (m, 1H), 2.58 (dd, 1H, J = 17.0, 6.0 Hz), 2.52 (m, 1H), 2.06 (m, 2H), 1.83 (dd, 1H, J = 17.5, 3.5 Hz), 1.47 (m, 1H), 1.24 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 206.1, 180.9, 148.4, 140.9, 136.0, 134.2, 133.5, 127.8, 127.5, 114.6, 78.8, 71.2, 42.1, 40.5, 29.8, 28.6, 23.3. HRMS ($MH^+$) for $C_{20}H_{20}O_2$ Calcd: 293.1542. Found: 293.1542.

*l. Diels-Alder Cycloaddition Procedure and Characterization*

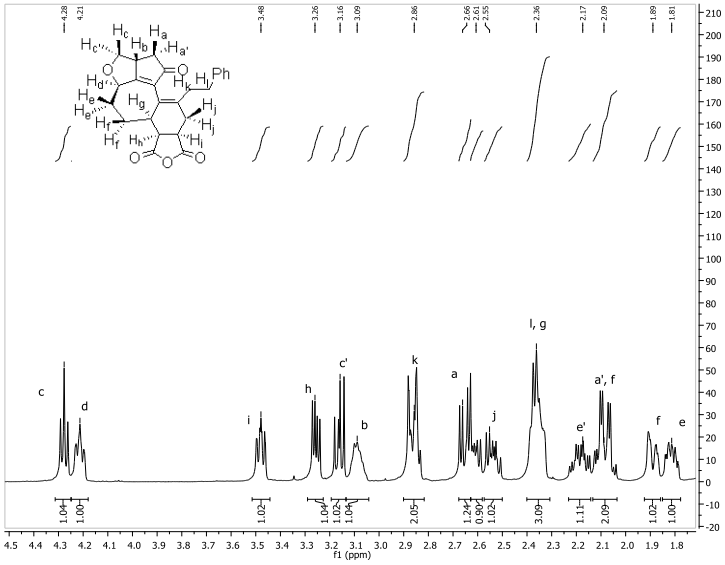
Under nitrogen cyclic diene **4-5ap** (53 mg, 0.173 mmol, 1 equiv) was weighed into a flame-dried tared vial and dissolved in $CH_2Cl_2$ (3.5 mL, 0.05M). Maleic anhydride (51 mg, 0.52 mmol, 3 equiv) was added and the vial was tightly sealed (wrapping the cap with parafilm and electrical tape). The vial was heated at 50 C for 24 h during which time the starting material was consumed. After cooling to room temperature the crude reaction mixture was directly purified by column chromatography (40:60 hexanes:EtOAc) to yield the product as a white solid in 70% yield as a single stereoisomer. $[\alpha]_D^{25}$ = 11.4 (c = 0.35, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.19 (m, 2H), 7.14 (m, 1H), 7.05 (m, 2H), 4.28 (t, 1H, J = 7.5 Hz), 4.21 (m, 1H), 3.48 (m, 1H), 3.26 (dd, 1H, J = 9.75, 5.25 Hz), 3.16 (dd, 1H, J = 11.0, 8.0 Hz), 3.09 (m, 1H), 2.86 (m, 2H), 2.66 (dd, 1H, J = 16.0, 6.0 Hz), 2.61 (m, 1H), 2.55 (m, 1H), 2.36 (m, 3H), 2.17 (m, 1H), 2.08 (m, 2H), 1.89 (m, 1H), 1.81 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 204.0, 184.8, 173.6, 171.4, 141.6, 140.8, 130.0, 128.5, 128.2, 126.9, 125.8, 74.6, 72.6, 46.9, 43.2, 42.7, 40.8, 38.1, 37.9, 33.8, 30.0, 29.1, 27.4. IR 3059, 3025, 2926, 2855, 1844, 1771, 1705, 1673, 1618, 1602, 1495, 1452, 1441. HRMS ($MH^+$) for $C_{25}H_{24}O_5$ Calcd: 405.1702. Found: 405.1700.




Cyloaddition product **5-8ap** was characterized by NOESY and COESY 2D NMR correlations. The proton resonances were assigned starting from the two protons resonating ~4 ppm. The protons adjacent to the oxygen should represent this chemical shift. The resonance at 4.21 ppm was assigned to $H_d$ based on the observed COSY interactions of this proton with the upfield signals at 2.17 and 1.81 ppm which should belong $H_e$ and $H_{e'}$. We tentatively assigned the proton at 2.17 ppm as $H_{e'}$ based on an observed NOE between $H_d$ and this proton. Tracing the COSY and NOESY interactions of $H_e$ and $H_{e'}$ allowed for the assignment of protons $H_f$. The signal at 4.28 displayed a significant COSY interaction with the proton at 3.16 ppm, identifying these two signals at $H_c$ and $H_{c'}$. A small observed NOE effect between $H_d$ and the resonance at 3.16 ppm allowed for this signal to be assigned to $H_{c'}$. With $H_c$,/$H_{c'}$ assigned, the COSY interactions with these protons observed at 3.09 allows the assignment of $H_b$. The interaction of $H_b$ with signals at 2.66 ppm and 2.08 ppm allows for the assignment of $H_a$ and $H_{a'}$ where $H_{a'}$ is assigned based on a NOESY interaction with $H_{c'}$. In support of this assignment $H_b$ and $H_a$ also display a NOE interaction.

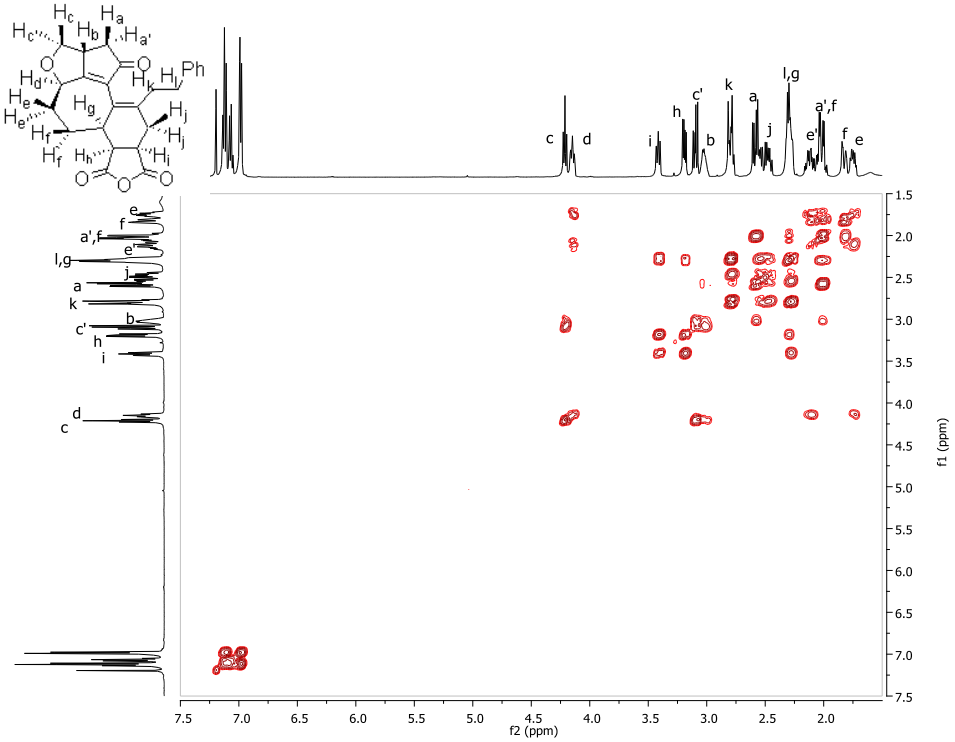
With the 5,5-bicyclic ring assigned we turned to the side of the molecule close to the phenyl ring. NOE effects were observed between the phenyl hydrogen atoms and the protons at 2.86 ppm (2H), 2.61 pmm (1H), 2.55 ppm (1H), and 2.36 ppm (3H). The allylic protons should be further downfield. The chemical shift and integration allow for

the assignment of $H_k$ to the signal at 2.86 ppm, and $H_j$ to the resonances at 2.61 ppm and 2.55 ppm. The signal at 2.36 ppm corresponds to $H_l$ and the presence of an additional proton not yet identified.

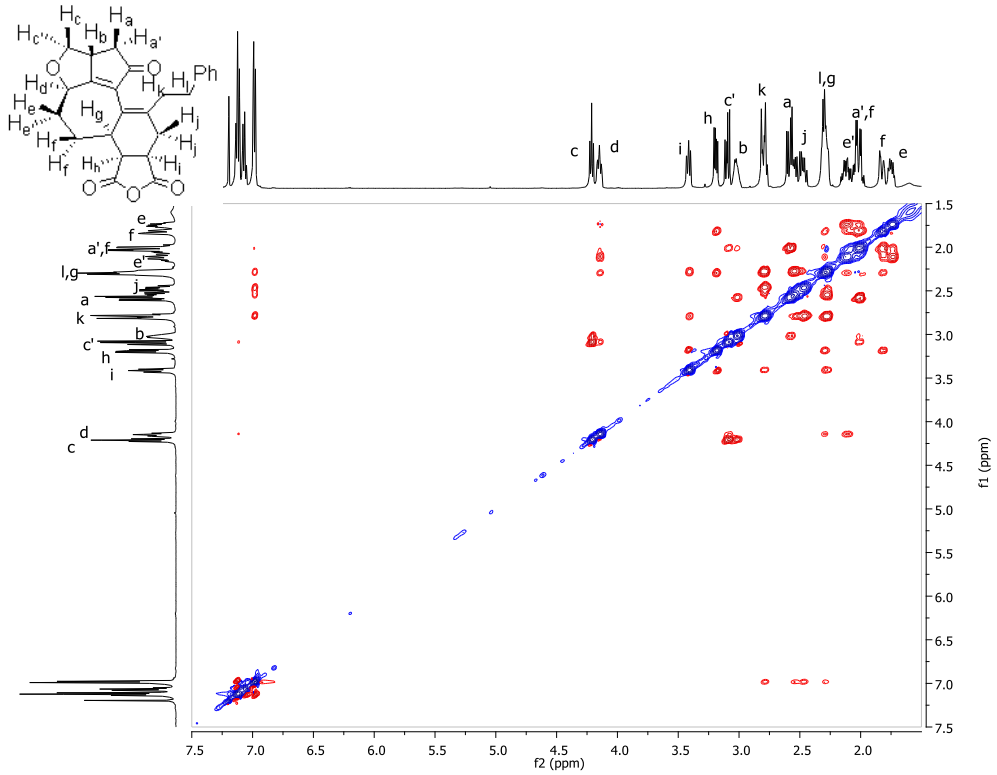


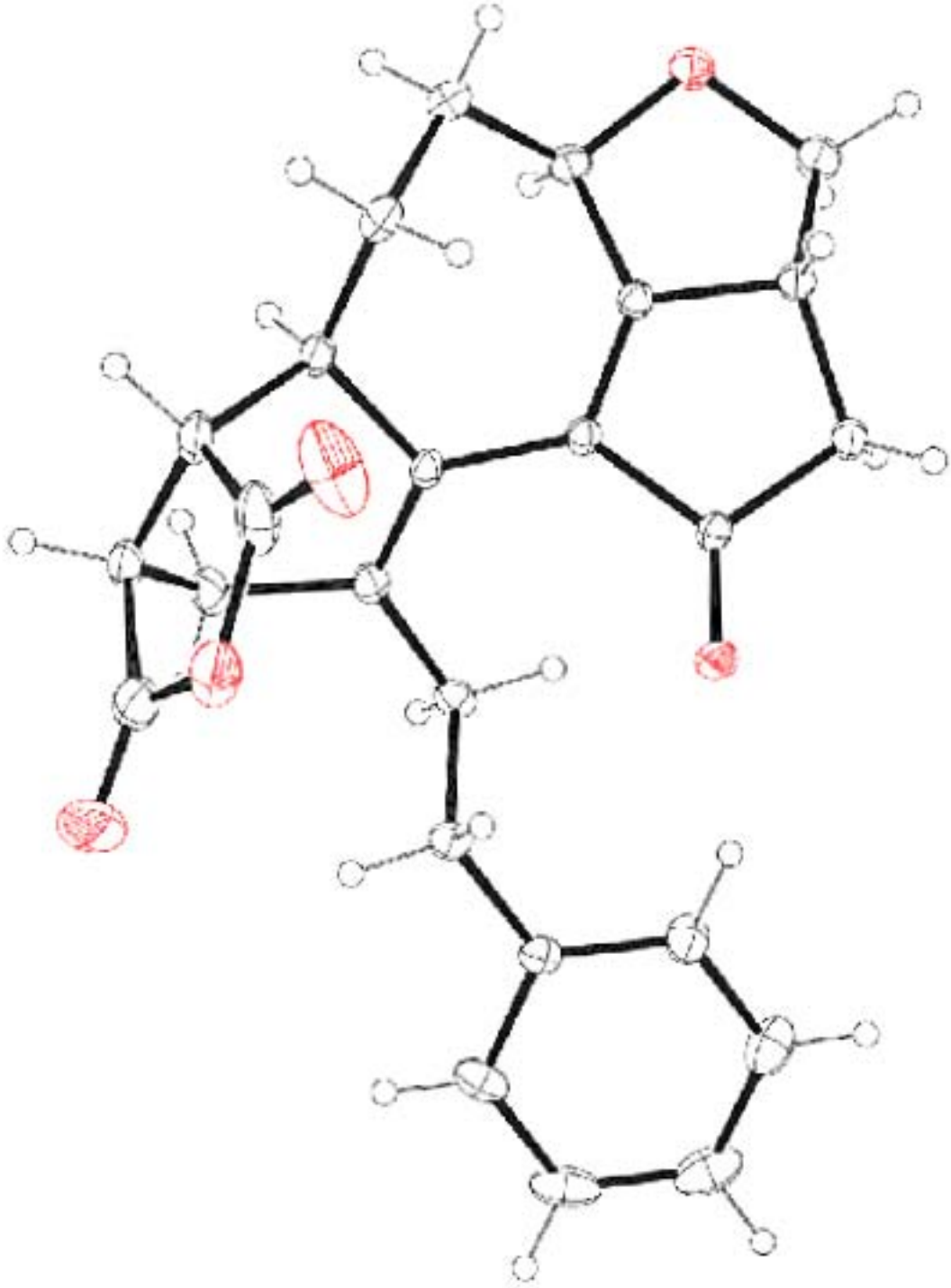

With these assignments made only $H_g$, $H_h$, and $H_i$ and the resonances at 3.48 ppm and 3.26 ppm and the additional proton at 2.36 ppm remained to be assigned. $H_g$ was assigned to the resonance at 2.36 ppm based on the COSY and NOESY interaction observed with $H_f$. $H_h$ was assigned to the proton at 3.26 ppm based on the strong NOE interaction of this proton with $H_f$, allowing $H_i$ to be assigned to the resonance at 3.48. This assignment was supported by the strong COSY interactions between $H_f$ and $H_i$. Having assigned these protons the relative stereochemistry of $H_g$, $H_h$, and $H_i$ was determined to be *syn*, based on the strong NOE interactions these protons displayed with each of the others. A tentative assignment of the absolute stereochemistry was made possible based on a key interaction between $H_d$ and $H_g$. Since $H_d$ is known to be in the down orientation from the asymmetric diyne addition $H_g$ can also be assigned to be down. This assignment was confirmed by single crystal X-ray analysis.

COSY spectra of **5-8ap**




NOESY spectra of **5-8ap**





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# Chapter 5. Other Attempted Research Projects

## 5.1 Organocatalysis Using $H_8$BINOL Based Ligands

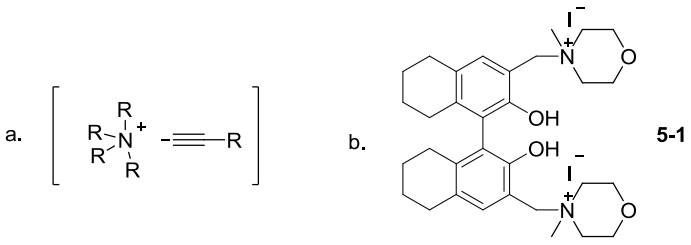
Asymmetric organocatalysis represents the next hurdle in the synthesis of propargylic alcohols. Organocatalysis has been defined as, "the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom."[1] However, organocatalysis also traditionally includes phase-transfer reaction conditions, in which a metal ion may be present through association with a base. No advances have been made in asymmetric organocatalysis of propargylic alcohols. However, there have been several methods reported for the catalytic deprotonation of terminal alkynes with alkali hydroxides for additions to carbonyl compounds that could provide the basis for asymmetric counterparts.

In 1996 Babler showed that potassium *tert*-butoxide in DMSO catalytically promoted the addition of alkynes to ketones.[2] Similarly, in 1999 Knochel reported that 10-30 mol% of $CsOH•H_2O$ activated terminal alkynes for addition to aldehydes and ketones.[3] The reaction was typically performed in THF, or in a 1:1 mixture of THF and DMSO for less acidic alkynes. In contrast to Babler and Knochel's alkali bases, Saito and coworkers demonstrated the utility of catalytic amounts of triton B as an organic base in alkyne addition to ketones and aldehydes in 2003.[4] Only DMSO was a suitable solvent. Notably Saito proposed the formation of an ammonium acetylide intermediate, and suggested the use of a chiral quaternary ammonium salt to induce stereocontrol.

In 2005, Weil and Schreiner utilizing phase-transfer conditions generated an ammonium base in situ from TBABr and NaOH.[5] Transferring the hydroxide base from the water to the fluorobenzene organic phase dramatically increased its basicity, and

allowed the deprotonation of terminal alkynes without DMSO as a solvent. Weil and Schreiner also proposed coordination between the phase-transfer catalyst and the resulting carbanion, and stated its implications for stereocontrol. The successful application of this concept has not yet been reported.

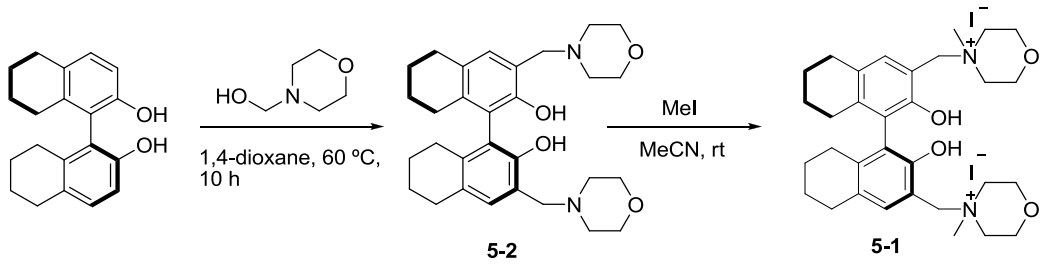
**Figure 5.1**. Ion pair intermediate complex proposed by Saito and Proposed Quaternary Amine.




We envisioned applying our $H_8$-BINOL derivatives in organocatalysis. Given Saito's proposal of a complex between a positively charged quaternary amine base and the resulting acetylide anion we designed ligand **5-1**. We hoped that this ligand, in the presence of $CsOH•H_2O$, demonstrated by Knochel to activate terminal alkynes, would be capable of the asymmetric organocatalysis of propargylic alcohols.

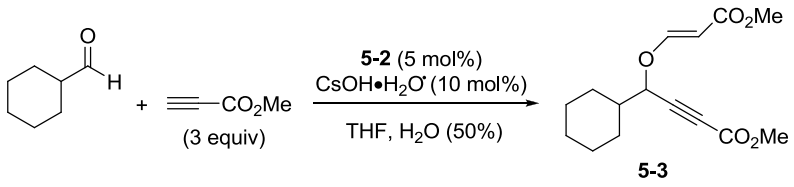
The preparation of **5-1** is shown in Scheme 5.1. Ligand **5-2** was first prepared by the reported method.[6] The quaternary amine base was then formed by stirring with MeI (10 equiv) at rt in DMSO for 4 days. While refluxing in MeCN consumed the starting material more rapidly the elevated reaction temperatures resulted in increased impurities in the reaction mixture and it was more difficult to purify **5-1**.

**Scheme 5.1.** Synthesis of Quaternary Amine Salt **5-1**.




With ligand **5-1** in hand efforts were made toward the asymmetric organocatalysis of propargylic alcohols. We began by mixing 5 mol % of ligand **5-1** with 10 mol % $CsOH\bullet H_2O$ in THF for 45 min. Methyl propiolate was added, and after 15 minutes the aldehyde was added. Though the expected propargylic alcohol was not obtained, enol ether propargylic alcohol **5-3** was isolated in 65% yield (Scheme 5.2), though as the racemic product. Importantly, a small amount of water was found to be necessary for the reaction to proceed efficiently. This small amount of water was present initially in the alkyne reagent, but switching to a new bottle of methyl propiolate prevented the reaction from being repeated cleanly. We then determined that 50 mol % of $H_2O$ was necessary for the reaction to proceed efficiently.

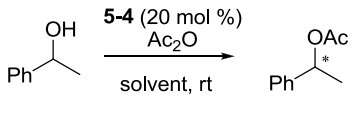
**Scheme 5.2**. Synthesis of Propargylic Enol Ether.

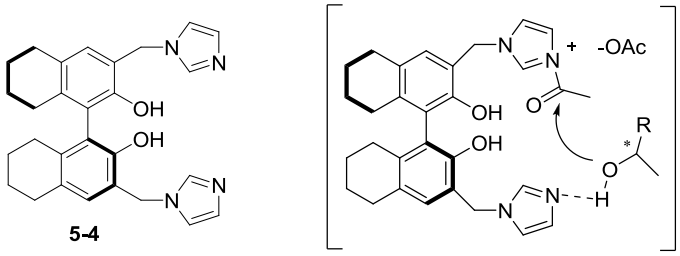



Similar reactivity has been demonstrated by Tejador with amine bases,[7] however amine containing ligand **5-2** was not able to catalyze the transformation. It was also possible that iodide performed the catalysis. Thus we investigated each component of the system to see which components were necessary for catalytic activity. To this end we

tested the following reaction systems: the use of only ligand **5-2**; NaI and $CsOH•H_2O$; TBAI and $CsOH•H_2O$; and TBAI alone. The tested conditions tested were as follows: a. **5-1** (5 mol %), THF, $H_2O$ (50 mol %). b. NaI (10 mol %), $CsOH•H_2O$ (10 mol %), THF, $H_2O$ (50 mol %) c. TBAI (10 mol %), $CsOH•H_2O$ (10 mol %), THF, $H_2O$ (50 mol %) d. TBAI (10 mol %), THF, $H_2O$ (50 mol%). None of these conditions successfully catalyzed the reaction, suggesting that ligand **5-2** and not just one of its components is necessary to the catalysis. This presents promising opportunities for controlling enantioselectivity.

**Scheme 5.3.** Kinetic Resolution of Secondary Alcohols.

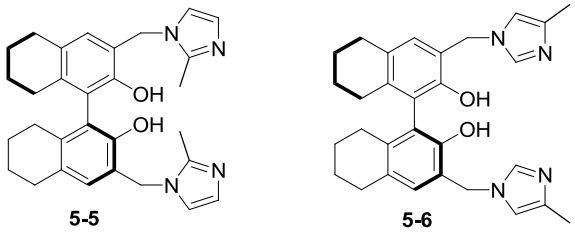



A more investigated area of asymmetric organocatalysis is the kinetic resolution of alcohols. Scott Miller has done a significant amount of work in this area, demonstrating that peptides containing imidazole functional units are highly effective acylation catalysts.[8] We had synthesized imidazole containing ligand **5-4** to catalyze the asymmetric addition of methyl propiolate to aldehydes in the absence of $Ti(O^iPr)_4$, but found that it produced only the racemic product. Given the imidazole moieties we tested ligand **5-4** in the kinetic resolution of secondary alcohols. This reaction was conducted by mixing 20 mol % of ligand **5-4** with 1-phenylethanol and 50 mol % $Ac_2O$ in a solvent. While no enantioselectivity was observed in $CH_2Cl_2$, THF, and $Et_2O$ and small

enantioselectivity of 19% ee was obtained in toluene. Increasing to 80 mol% of the ligand improved the enantioselectivity up to 33%. Use of acetyl chloride as the acylating agent resulted in the racemic product. Switching to hexanes increased the ee to 29%, though the ligand is poorly soluble in this solvent, and the reaction proceeded very slowly over 3-4 days. A proposed transition state is shown in Scheme 5.3.

**Figure 5.2.** Imidazole Containing $H_8$BINOL Ligands.

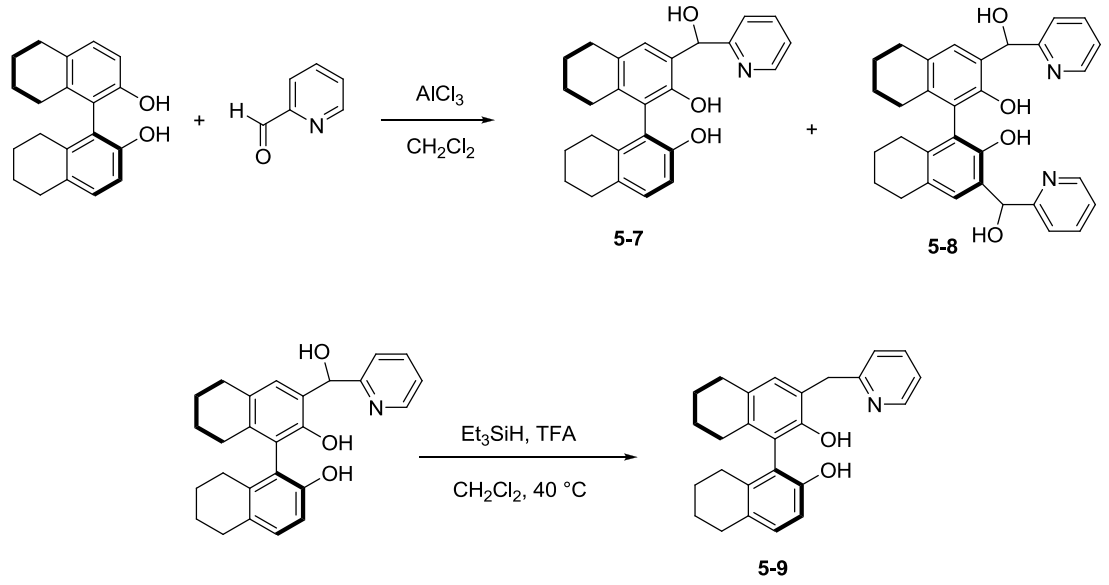



In attempts to improve the enantioselectivity ligands **5-5** and **5-6** (Figure 5.2) were prepared according to normal methods (heating the imidazole methanol in the presence of $H_8$BINOL and 1,4-dioxane at 135 °C).[9] While these ligands also catalyzed the acylation of 1-phenylethanol they did not improve the enantioselectivity. Ligand **5-5** resulted in only the racemic product suggesting the positioning of the methyl group disturbed the catalytic pocket. Ligand **5-6** provided similar results to **5-4**.

In considering amine containing ligands we also pursued the synthesis of ligand **5-7** and **5-8** via the $AlCl_3$ promoted reaction of $H_8$BINOL with 2-pyridinecarboxaldehyde.[10] First premixing $AlCl_3$ (2 equiv) and $H_8$BINOL in $CH_2Cl_2$ followed by the addition of 2-pyridinecarboxaldehyde (8 equiv) after 30 minutes and stirring overnight resulted in a mixture of the mono-substituted **5-7** and di-substituted **5-8** products observed in a combined yield of 67%. Multiple diastereomers were observed with respect to the newly formed alcohol, and could not be cleanly separated by column

chromatography. Attempts to remove the benzylic hydroxyl group by hydrogenation under Pd catalysis were not successful. Treatment of mono-substituted **5-7** of $Et_3SiH$ (1.1 equiv) and TFA (10 equiv) in $CH_2Cl_2$ with heating at 40 °C overnight resulted in partial conversion to give product **5-8** in 24% yield. Given the inability to fully purify these ligands they were not tested for organocatalytic reactions, but the interesting method for the formation of bifunctional $H_8$BINOL based ligands could be useful with improvements.

**Scheme 5.4.** Synthesis of $H_8$BINOL Pryidinemethanols.

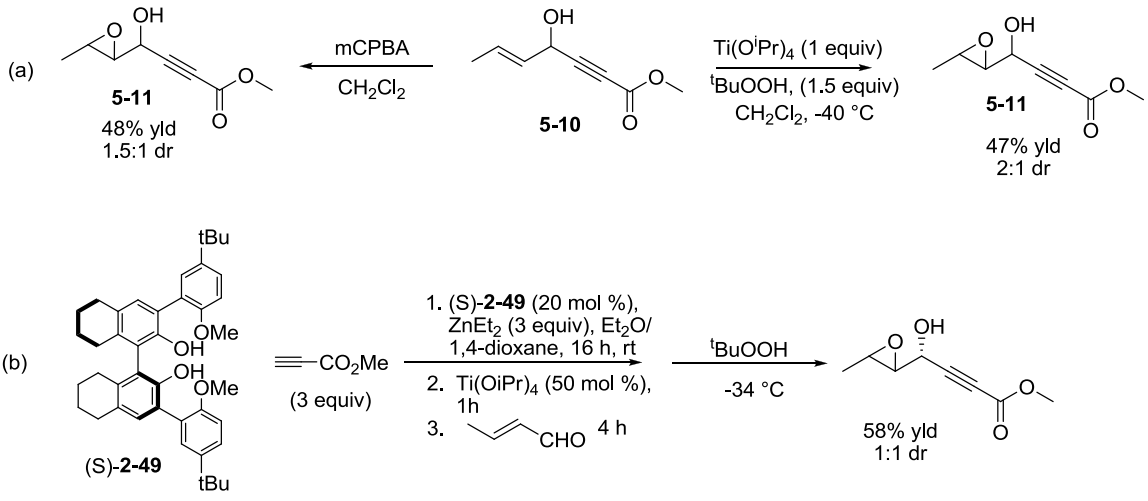



## 5.2. Applications of γ-Hydroxy-α,β-Acetylenic Esters

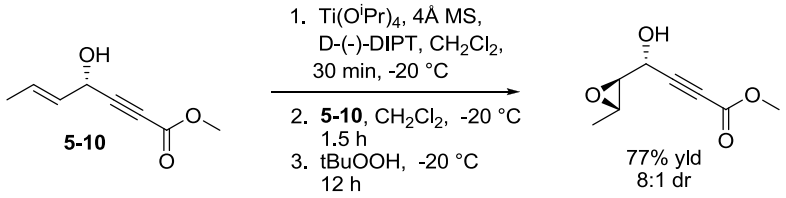
Given our successful development of a catalytic system for the addition of alkyl propiolates to a range of aldehydes (see Chapter 2), we were interested in applications of the resulting γ-hydroxy-α,β-acetylenic esters. We were particularly interested in tandem alkynylation/epoxidation reactions as a route to synthesize sugars and sugar derivatives. We began by testing the epoxidation of **5-10** to determine the inherent diastereocontrol of

the reaction. Epoxidation with mCPBA or $Ti(O^iPr)_4$ and $^tBuOOH$ (Scheme 5.5a) resulted in little diastereocontrol and moderate yields of 40-50%. It was also found that epoxidation of **5-10** with $Ti(O^iPr)_4$ and $^tBuOOH$ in the presence of chiral ligand (*S*)-**2-49** found to be effective for addition of alkyl propiolates to aldehydes resulted in a lower dr of 1.2:1. This revealed that ligand **2-49** was not good for controlling the epoxidation, and that the tandem alkynylation/epoxidation reaction was not likely to be highly diastereoselective for formation of the epoxide. Performing the tandem alkylation/epoxidation in one pot led to the product in 58% yield in a 1:1 ratio of diastereomers (Scheme 5.5b). Since the tandem reaction and substrate controlled epoxidation were not effective, the epoxidation was conducted using Sharpless asymmetric epoxidation as shown in Scheme 5.6. Use of D-(-)-DIPT produced the syn epoxide in 77% yield and 8:1 dr.

**Scheme 5.5.** Epoxidation of γ-Hydroxy-α,β-Acetylenic Ester.



**Scheme 5.6.** Sharpless Asymmetric Epoxidation of γ-Hydroxy-α,β-Acetylenic Esters.



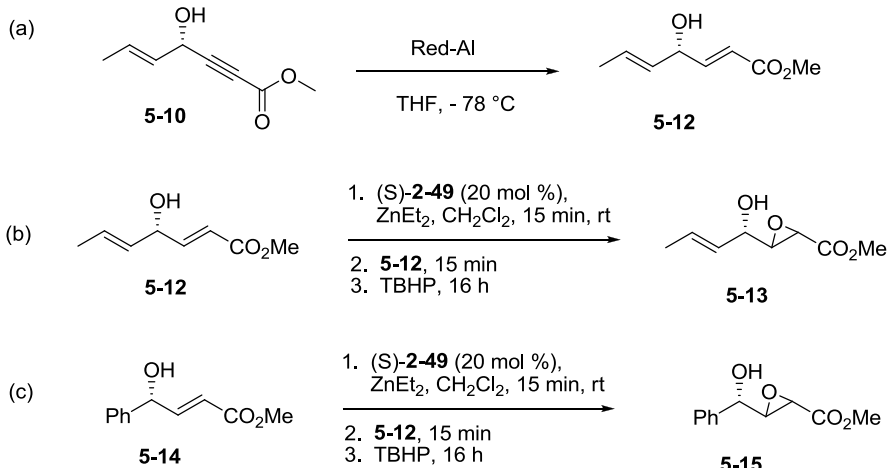

Koide and coworkers have reported the *trans* reduction of γ-hydroxy-α,β-acetylenic esters.[11] We successfully applied this reduction to propargylic alcohol **5-10**, using Red-Al at -78 °C to synthesize diene **5-12**. We were also able to perform this reaction with a variety of aryl and alkyl substituents at the propargylic position. We also found that the reduction could be performed in one pot with the asymmetric alkyne addition by cooling the reaction to -78 °C after formation of the γ-hydroxy-α,β-acetylenic esters and adding Red-Al slowly.

When compound **5-12** was epoxidized under nucleophilic epoxidation conditions in the presence of (*S*)-**2-49** a diastereoselectivity of 9:1 and yield of 51% was observed in $CH_2Cl_2$. Testing other solvents revealed lower yields and drs: $Et_2O$-27% yld, 5:1 dr, THF-42% yld, 6:1 dr, toluene, 20% yld, 7:1 dr. Use of (*R*)-**2-49** did not reverse the diastereoselectivity of the product and led to a similar dr. When the epoxidation was carried out in the absence of the chiral ligand the dr decreased slightly to 7:1.

Use of BINOL as the chiral ligand resulted in a dr of 4:1 for (*S*)-BINOL and 6:1 for (*R*)-BINOL, though both yields were very low (~15%). Use of (D)-(-)-DIPT did not form the desired product. Switching the allylic alcohol substituent to a phenyl group increased the dr to 15:1 producing **5-15** in a yield of 55% (Scheme 5.7c), but this diastereoselectivity could also not be reverse by using to (*R*)-**2-49**. Epoxidation of **5-14**

in the absence of the chiral ligand decreased the dr to 9:1. We also tested various reaction conditions for the nucleophilic opening of epoxide **5-13**. Testing the use of $NaN_3$ in DMF at 65 °C, $NaN_3$ and $NH_4Cl$ in EtOH under reflux, and $NaN_3$, $BF_3$-$OEt_2$ in $CH_2Cl_2$ at rt all failed to produce the desired product.

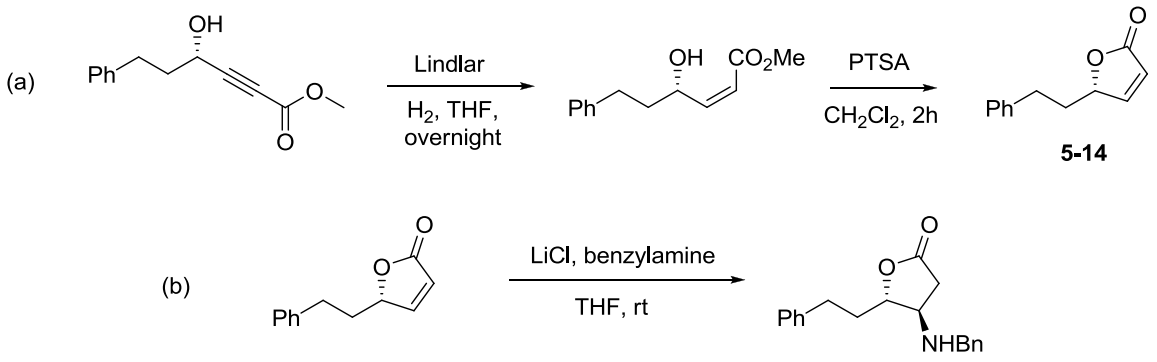
**Scheme 5.7.** Red-Al Reduction of γ-Hydroxy-α,β-Acetylenic Esters and Nucleophilic Epoxidation.




Butenolides can be readily prepared from γ-hydroxy-α,β-acetylenic esters via reduction of the alkyne in the presence of Lindlar's catalyst and $H_2$ followed by the addition of PTSA to assist the cyclization. As shown in Scheme 5.8, butenolides were obtained in this manner with yields of 70-80%. It was found that the Pd catalyst should be filtered away from the newly formed allylic alcohol prior to the addition of PTSA for the reaction to proceed smoothly. Additions of benzylamine to butenolide **5-14**, resulted in the formation of a single diastereomer, but the yield was low and the starting material was not consumed (~20% yld). Heating did not improve the reaction, but resulted in the formation of side products. The use of water as the solvent dramatically increased the rate

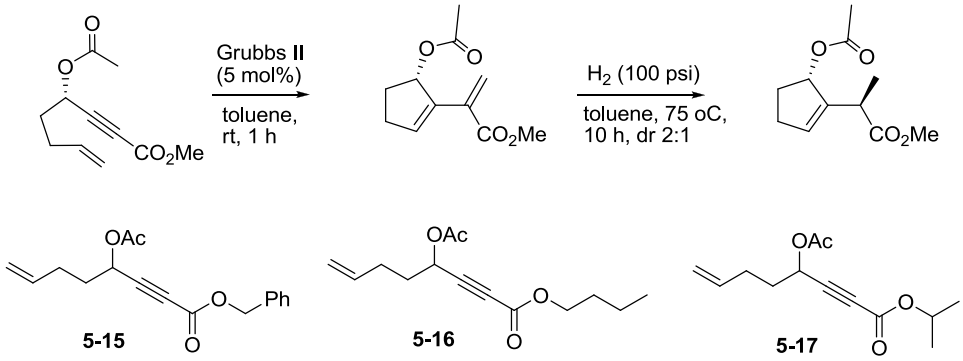
of the reaction, but the butenolide ring had limited stability under these reaction conditions and a variety of ring opened products were observed.

**Scheme 5.8.** Access to Butenolides and Conjugate Amine Addition.



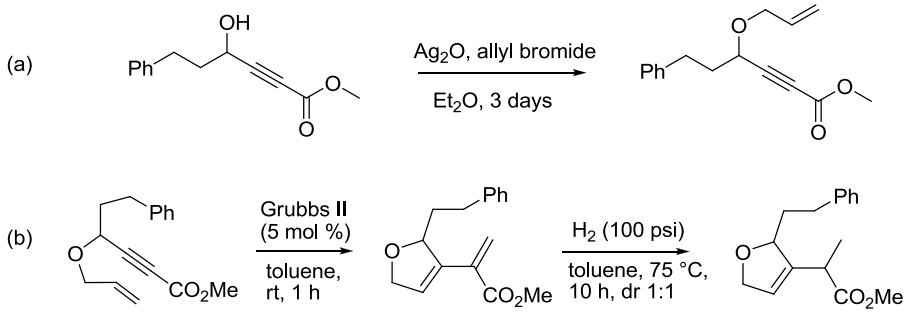

In 2009 our group has explored the diastereoselective transformations of γ-hydroxy-α,β-acetylenic esters utilizing a tandem Grubbs II-catalyzed ring closing metathesis (RCM)/hydrogenation reaction to provide access to optically active cycloalkenes. Acetate protected γ-hydroxy-α,β-acetylenic ester first underwent a Grubbs II catalyzed RCM to afford cyclic dienes followed by a highly chemoselective hydrogenation reaction to afford the product in moderate diastereoselectivity of 2:1 (Scheme 5.9).[12] In an attempt to further improve the dr we synthesized a variety of derivatives containing bulkier ester substituents. Thus substrates **5-15** to **5-17** were prepared and subjected to the reaction conditions shown in Scheme 5.9. However, no improvement in dr was observed, with each substrate undergoing the reaction in a dr of ~2:1.

**Scheme 5.9.** Tandem Ring Closing Metathesis/Hydrogenation Reaction.




We also attempted the tandem reaction using propargylic alcohol **5-18**. It was found that this substrate was sensitive to basic conditions for protection of the alcohol with allyl bromide and underwent decomposition when using nBuLi at low temperatures. However $Ag_2O$ was able to provide the product in 60% yield as shown in Scheme 5.10a. When **5-18** was subjected to the RCM/$H_2$ the reduced product was formed in very low yield and no dr although it appeared that the initial enyne ring closing metathesis proceeded smoothly by TLC.

**Scheme 5.10.** Tandem Ring Closing Metathesis/Hydrogenation Reaction of Allyl Ether.



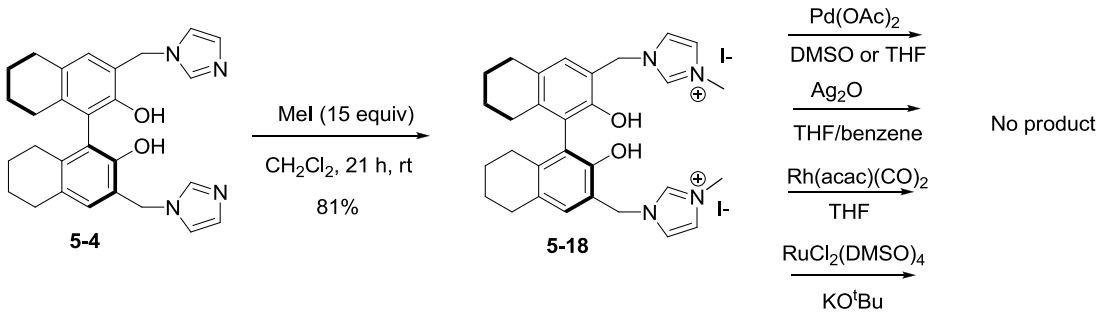

## 4.3. Chiral N-Heterocyclic Carbene $H_8$BINOL Ligands

N-Heterocyclic carbenes (NHCs) have become a popular ligand for organometallic reactions.[13] We thought that imidazole ligand **5-4** may be a good starting point for the synthesis of chiral $H_8$BINOL based NHC ligands. The methyl imidazole

salt **5-18** was first formed and isolated by stirring **5-4** with MeI (15 equiv) in $CH_2Cl_2$ for 21 h (Scheme 5.11). We also explored the formation of polymers from polymers from **5-4** by reaction with 1,4-di-iodobutane and 1,6-di-iodohexane at room temperature and elevated temperatures, but these reactions did not provide the desired product.

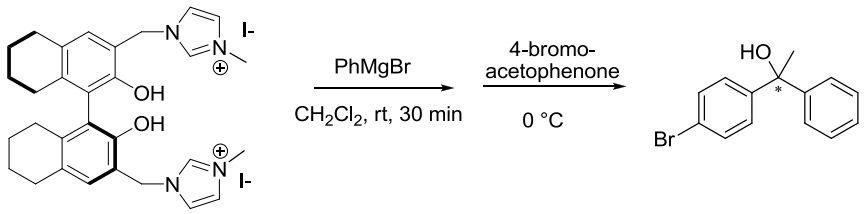
Attempts to form an NHC-metal complex by stirring **5-18** with $Pd(OAc)_2$ in DMSO or THF; by reaction with $Ag_2O$ in THF/benzene; by reaction with $Rh(acac)(CO)_2$ in THF; and by reaction with $RuCl_2(DMSO)_4$ and $KO^tBu$ were all unsuccessful and led to unidentifiable mixtures (Scheme 5.11).

**Scheme 5.11.** Attempts at NHC-Metal Complexes.



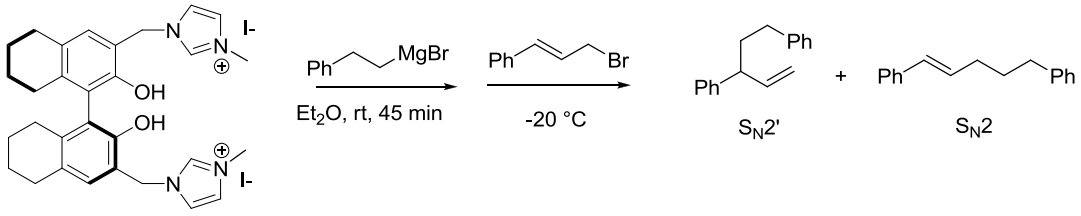

We also tested the use of an *in situ* prepared NHC-metal complex for the addition of Grignard reagents to ketones as shown in Scheme 5.12. Reaction of 20 mol % **5-18** with 2 equiv PhMgBr and then addition of 4-bromo-acetophenone led to the tertiary alcohol in 86% yield and 19% ee. The rate of the reaction was rapid, as the ketone was consumed within 3-4 h. Further increasing to 50 mol % and 1 equiv of ligand **5-18** increased the ee to 24% and 39% respectively. The product was not formed when $ZnPh_2$ was used instead of PhMgBr.

**Scheme 5.12.** Addition of Phenyl Grignard to Ketone Catalyzed by **5-18**.




An asymmetric allylation reaction was also tested as shown in Scheme 5.13. For this reaction the desired product from the result of the $S_N2$' was not formed as the major product. Instead $S_N2$ substitution predominated. Only THF allowed for the desired $S_N2$' product to be formed in reasonable amounts ($S_N2$':$S_N2$ 1:2, 74% combined yield), but the product could not be separated by HPLC and possessed a very small optical rotation value (-1.83, $CHCl_3$).

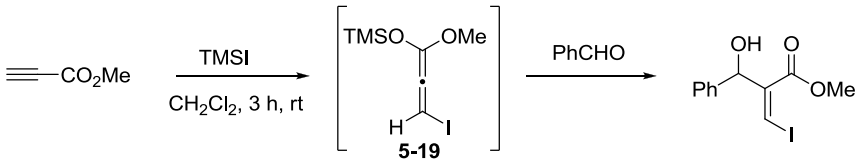
**Scheme 5.13**. Attempted Asymmetric Allylation Reaction.




## 4.4. Miscellaneous Asymmetric Metal Catalyzed Reactions

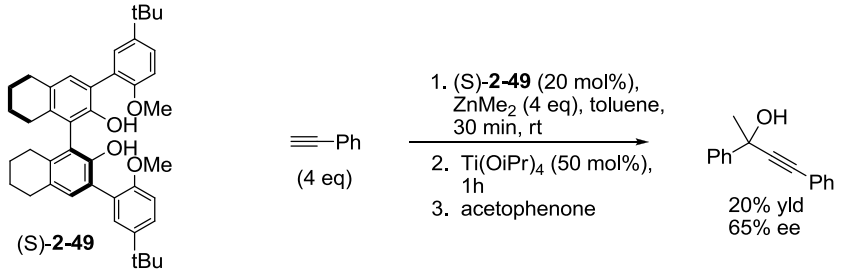
We attempted a Baylis-Hillman type reaction of methyl propiolate with aldehydes by first forming allene **5-19** via treatment of methyl propiolate with TMSI in $CH_2Cl_2$ at room temperature for 3 h. This allene was found to add to benzaldehyde in 30% yield. Attempts at an enantioselective version using ligand (*S*)-**2-49**, quaternary amine $H_8$BINOL salts **5-1** and **5-18**, and $H_8$BINOL-Amine ligand **2-39** did not improve the yield or provide any enantioselectivity. The use of tartaric acid in the presence of amine bases to catalyze the reaction did not result in the formation of the product.

**Scheme 5.14.** Baylis-Hillman Type Reaction of Methyl Propiolate, TMSI, and Benzaldehyde.




We were interested in testing the use of ligand **2-49** for additions to ketones. No conditions were found that could catalyze the addition of methyl propiolate to ketones. Addition of the more reactive phenylacetylene to acetophenone under the optimized reaction conditions reported in Chapter 2 also did not produce the product. However, replacing $ZnEt_2$ with $ZnMe_2$ and using toluene as the solvent produced the product in low yield (20%) and with 65% ee. The low yield could not be improved despite the use of 4 equiv of phenylacetylene and $ZnMe_2$. Attempted additions to α-keto-esters failed to produce the product.

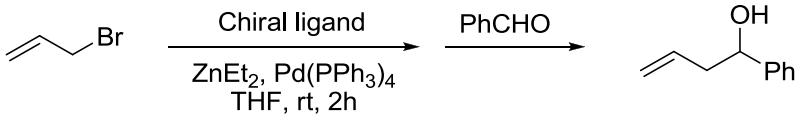
**Scheme 5.15.** Attempted Alkyne Addition to Ketones.




We tested the addition of allyl bromide to benzaldehyde using $ZnEt_2$ and $Pd(PPh_3)_4$ as shown in Scheme 5.16. The racemic reaction proceeded in good yield (78%) by mixing 1.2 equiv allyl bromide with $ZnEt_2$ (1.2 equiv) and $Pd(PPh_3)_4$ (5 mol %) in THF for 2 h at rt followed by addition of benzaldehyde. However, use of $H_8$BINOL-Amine ligand **2-39** with and without $Ti(O^iPr)_4$ and quaternary amine $H_8$BINOL salt **5-18**

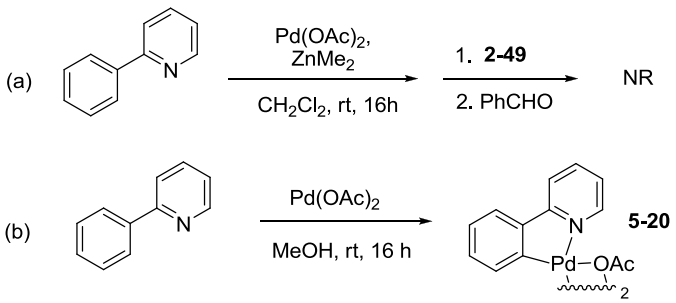
were unable to produce any enantioselectivity. Use of polymer bound triphenylphosphine failed to yield the product. Testing formation of the allylzinc species by metals other than $Pd(PPh_3)_4$ (Pd/C, $Ni(COD)_2$, $Pd_2dba_3$, and CuI) all failed to produce the product. Attempts to form the allylzinc in the absence of $Pd(PPh_3)_4$ by reflux in toluene with $ZnEt_2$ or by mixing with $ZnEt_2$ and Li(acac) in NMP also could not form the product.

**Scheme 5.16.** Attempted Asymmetric Allyl Addition to Aldehydes.




We attempted to form an arylzinc nucleophile via C-H of phenylpyridine. Mixing $Pd(OAc)_2$ (0.2 equiv), $ZnMe_2$ (2 equiv), phenylpyridine (2 equiv), in $CH_2Cl_2$ at rt for 16 h, followed by addition of $H_8$BINOL-Amine ligand **2-39** and then benzaldehyde did not form the aryl addition product and the aldehyde remained unreacted (Scheme 5.17a).

**Scheme 5.17.** Attempts at C-H Activation and Addition to Aldehydes.




Realizing that the acetic acid produced by Pd C-H insertion into the aryl bond would consume the $ZnMe_2$ we next formed the Pd-aryl species **5-20** by reaction of phenylpyridine with $Pd(OAc)_2$ (0.7 equiv) in MeOH at rt for 16 h (Scheme 5.17b), resulting in **5-20** in 75% yield. However, reaction of **5-20** with $ZnEt_2$ or $ZnMe_2$,

followed by addition of $H_8$BINOL-Amine ligand **2-39** and then benzaldehyde at -78 °C did not result in the desired product, nor did warming to rt. It was noticed that the solution turned a dark black upon the addition of $ZnR_2$ to **5-20** at rt or as the reaction temperature warmed above -20 °C, and it was assumed that this intermediate decomposed under these conditions.

## 4.5. Experimental

*Synthesis of Quaternary Amine **5-1**.*

Ligand **5-2** (0.54 g, 1.1 mmol) was combined with methyl iodide (0.68 mL, 11.0 mmol) in acetonitrile (6 mL), and stirred for 4 days at room temperature. The acetonitrile was removed under reduced pressure yielding a yellow solid. The product was isolate by mixed solvent crystallization in methanol and ether, yielding a pale yellow solid (0.33 g). 40% yield. $^1$H NMR (300 MHz DMSO) δ 1.59-1.62 (m, 8H), 1.98-2.07 (m, 4H), 2.70 (s, 4H), 3.05 (s, 6H), 3.34-3.50 (m, 8H), 3.98 (s, 8H), 4.47-4.51 (d, J=12, 2H), 4.63-4.67 (d, J=9, 2H), 7.16 (s, 2H), 8.28 (s, 2H).

*General Procedure for Synthesis of Propargylic Enol Ether.*

**(S)-5-2** (20 mg, 0.026 mmol, 5 mol%) was stirred in THF with CsOH•$H_2O$ (8.5 mg, 0.0515 mmol, 0.1 eq) for 45 minutes. Methyl propiolate (137 μL, 1.54 mmol, 3 eq) was added and the mixture was stirred for an additional 15 minutes. $H_2O$ (4.6 μL, 0.25 mmol, .5 eq) and cyclohexanecarboxaldehyde (62 μL, 0.52 mmol) were then added in sequence. The aldehyde was added dropwise over 15 minutes. The mixture was allowed to react for 24 hours, until determined to be complete by $^1$H-NMR. The organic layer was extracted with $CH_2Cl_2$ (3 x 15 mL) and purified via flash chromatography eluting with 0-15% hexanes/ethyl acetate. 93 mg of the product was isolated as a clear oil. 65% yield. $^1$H-NMR (300 MHz, $CDCl_3$) δ 1.17-1.20 (m, 5 H), 1.75-1.82 (m, 6H), 3.69 (s, 3H), 3.78 (s, 3H), 4.40-4.42 (d, J=6, 1H), 5.33-5.37 (d, J=12, 1H), 7.51-7.55 (d, J=12, 1H).

*General Procedure for Kinetic Resolution of Secondary Alcohols Using Ligand* ***5-3***.

Ligand **5-3** (20 mol% ) was first dissolved in a solvent. The secondary alcohol (1 equiv) and $Ac_2O$ (0.5 equiv) were added and the reaction was allowed to stir over several days. The progress of the reaction was monitored by $^1H$ NMR to quantify the conversion of the starting material into the product. The reaction was noted to proceed slowly. After 2 days the reaction was quenched with ammonium sulfate (saturated aqueous), extracted with $CH_2Cl_2$, and the product was purified by column chromatography. The enantioselectivity was then determined by HPLC using a Chiralcel OD-H column.

*Synthesis of* ***5-7*** *and* ***5-8***.

To a suspension of $AlCl_3$ (2 equiv) in $CH_2Cl_2$ was added $H_8$BINOL (1 equiv). After stirring for 30 minutes 2-pyridinecarboxaldehyde (8 equiv) was added and the reaction was stirred overnight. The reaction was then quenched with ammonium chloride, extracted with $CH_2Cl_2$ and purified by column chromatography. The mono-substituted and di-substituted products were observed, along with multiple diastereomers at the newly formed alcohol, which could not be cleanly separated by column chromatography.

*General Procedure for Red-Al Reduction of* $\gamma$*-Hydroxy-*$\alpha,\beta$*-Acetylenic Esters*.

In a flame dried pear flask a γ-hydroxy-α,β-acetylenic ester (0.25 mmol) was dissolved in THF (0.2 M). In a round botoom flask a solution of Red-Al (2 equiv) in THF (1 mL) was cooled to -78 °, and the propargylic alcohol was added to this flask via cannula transfer. After 20 min the reaction was judged to be complete by TLC and quenched with 0.1 M HCl (13 mL). After extraction the product was purified by column chromatography.

*General Procedure for Epoxidation of αβ-Unsaturated Esters by (S)-**2-49**.*

In a flame dried round bottom flask (*S*)-**2-49** (20 mol %) was dissolved in $CH_2Cl_2$ and $ZnEt_2$ (1 equiv) was added. After 15 min the allylic alcohol was added in $CH_2Cl_2$ and stirred for 30 min. TBHP (3 equiv) was then added at rt and the reaction was stirred overnight. After consumption of the starting material the product was quenched with ammonium chloride (saturated aqueous) and $Na_2SO_3$ (saturated aqueous). After extraction and filtration through a small plug of silica in a sinter funnel, the product was purified by column chromatography.

*Formation of Butenolides from γ-Hydroxy-α,β-Acetylenic Esters.*

The starting γ-hydroxy-α,β-acetylenic ester was first dissolved in THF (0.4 M) and Lindlar's catalysts was added (15 wt %). The solution was bubbled with $H_2$ for 5 min, and then the reaction was allowed to proceed overnight under an atmosphere of $H_2$. After consumption of the starting material the solid Pd catalyst was removed by filtration through a short plug of silica. The solvent was removed and the crude product was redissolved in $CH_2Cl_2$. PTSA (10 mol %) was added and the reaction stirred for 2 hours. The reaction mixture was then directly loaded onto a column and purified.

*General Procedure for Aryl Grignard Addition to Ketones Catalyzed by (S)-**5-18**.*

Ligand **5-18** (20 mol %) was first dissolved in $CH_2Cl_2$. PhMgBr (2 equiv) were added and the reaction was stirred for 30 min. After cooling to 0 C 4-bromo-acetophenone was added and the reaction was followed by TLC. After consumption of the ketone (3 h), the reaction was quenched with ammonium sulfate (saturated aqueous) and the product was purified by column chromatography.

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# Chapter 6. Conclusions and Outlook

The utility of optically active propargylic alcohols in organic synthesis has driven the development of methods for asymmetric alkyne additions to carbonyl compounds. While a decade ago the synthetic chemist had to rely on the asymmetric reductions of ynones to access optically active propargylic alcohols, there are now an abundance of catalytic systems for asymmetric alkyne additions to aldehydes. In this research, our laboratory and others have made remarkable progress such that we now have highly enantioselective methods for the addition of various alkynes to aromatic, aliphatic, and $\alpha,\beta$-unsaturated aldehydes.

As a part of these efforts we have provided new methods for the first catalytic highly enantioselective addition of alkyl propiolates to aliphatic aldehydes (Chapter 2), the first catalytic enantioselective addition of linear alkyl alkynes to linear aliphatic aldehydes (Chapter 3), and the most complete and effective method to date for the catalytic highly enantioselective addition of diverse 1,3-diynes to aromatic and aliphatic aldehydes (Chapter 4). From these studies and earlier work in our laboratory we have developed a toolbox of catalytic systems to provide highly enantioselective methods for the addition of the most common classes of simple alkynes to aliphatic aldehydes (Chapter 3). Additionally, in the development of the asymmetric addition of 1,3-diynes to aromatic and aliphatic aldehydes, we demonstrated that a variety of alkyl, aryl, silyl, and vinyl diyne substituents are compatible with the catalyst system.

The substrate scope available to our methods (with respect to both the alkyne and aldehyde) and the high enantioselectivities that can be achieved provide a

significant contribution to the synthetic chemist's repertoire for the creation of optically active propargylic alcohols. All of the catalyst systems in our toolbox (and for the 1,3-diyne addition) are accessible to the synthetic community, as all the chiral ligands and reagents are commercially available with the exception of ligand (*S*)-**2-49**, which can be accessed in 86% yield over 2 steps starting from $H_8$BINOL. The easy preparation of this class of ligands makes its use by the synthetic community possible.

As research in asymmetric alkyne additions to carbonyl compounds moves forward several challenges must be addressed. Most importantly is the extension of the existing catalytic systems to more complex alkyne and aldehyde reaction partners. The types of alkynes and aldehydes that are useful to the synthetic chemist may not be good substrates for existing catalysts. Methods need to be developed that can tolerate chirality present in the alkyne and aldehyde and still provide high levels of enantiocontrol regardless of the influence of the substrate. Furthermore, methods need to be extended more successfully for alkyne additions to ketones. Where the current systems are lacking, better catalysts must be developed to provide solutions to these problems. It will not be until we can meet these challenges that catalytic asymmetric alkyne additions will begin to mature as a powerful methodology for the installation of hydroxyl-bearing stereogenic centers. The continued usefulness of propargylic alcohols in synthesis will continue to drive research in this area.

The discovery of new applications for optically active propargylic alcohols increases the utility of this class of compounds for the synthetic chemist. To this end, we have shown that asymmetric alkyne addition to enals provides rapid access to a

variety of chiral propargylic alcohol-based enyne substrates for the Pauson-Khand reaction providing access to biscyclopentenones (Chapter 3). Protection of the propargylic alcohols with either an acetyl or a methyl group allows for the resulting enynes to undergo an intramolecular PK reaction to form the corresponding optically active 5,5- or 5,6-fused bicyclic products with high diastereoselectivity. Importantly the high enantiomeric purity of the propargylic alcohols was found to be maintained in the PK cycloaddition products. Chiral propargyl allyl ethers also undergo the highly diastereoselective PK cycloaddition with retention of enantiomeric purity. Not only does this method provide cyclic compounds of increased molecular complexity from acyclic precursors, but the chiral information is efficiently transferred to the creation of the new stereogenic center in the biscyclopentenone products. These findings provide an efficient asymmetric construction of cyclic systems from optically active propargylic alcohol enynes.

We have shown the potential of this approach in the design of a flexible strategy for the construction of polycyclic ring systems containing the 5,7- and 5,8-membered ring core common in a variety of natural products (Chapter 4). Key to this strategy was the development a chemoselective and diastereoselective PK-type reaction of dienediyne substrates to form the 5,5-ring system, coupled with enyne metathesis to form the 7- and 8-membered ring systems. Notably, these polycyclic ring systems contain an embedded diene that allows the formation of additional ring structures through cycloaddition reactions. To this end the diene has been utilized in a Diels-Alder cycloaddition reaction to furnish the 5,5,7,6-ring system as a single stereoisomer. The flexibility present in this strategy for the asymmetric construction

of a variety of 5,5,7-, 5,5,8,- and 5,5,7,6-polycyclic ring systems makes this method a significant contribution for the synthesis of optically active polycyclic compounds.

Furthermore, we have also developed the first diastereoselective Pauson-Khand cyclization of diyne-containing substrates (Chapter 4). Using a $[Rh(cod)Cl]_2$-BINAP catalytic system utilizing aldehydes as the CO source it was found that excellent diastereoselectivities could be achieved in substrates possessing significant steric bulk close to the propargylic center, generating the *cis* stereoisomer as the major product. Importantly, a complimentary method to access the opposite *trans* diastereomer of the cycloaddition products has also been discovered. It was found that substrates bearing groups capable of coordination to the Rh metal center could reverse the diastereoselectivity. A simple mechanistic understanding has been proposed for this observation, which is also able to successfully account for the diastereoselectivities observed in other Rh-catalyzed PK-type reactions in the literature.

Our studies on applications of optically active propargylic alcohols in synthesis have shown that novel, highly useful transformations exist for the use of this class of compounds in addition to the utility already demonstrated in the literature. In particular the presence of the alkyne functional group opens a new array of reactivity for propargylic alcohols that is not available to other optically active alcohols. The usefulness of propargylic alcohols in organic synthesis remains a ripe area to be explored and utilized in the synthesis of complex molecules.