ASYMMETRIC ALKYNE ADDITION TO ALDEHYDES AND KETONES

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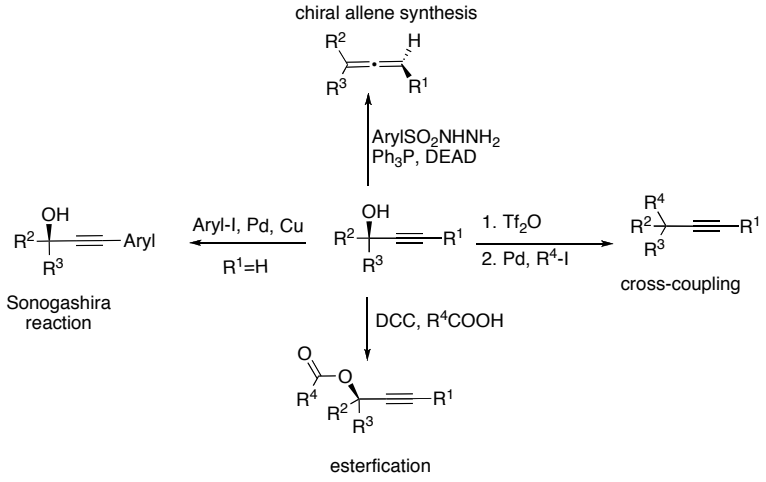
INTRODUCTION

Chiral propargylic alcohols are important compounds, as this structural motif is often found in pharmaceutical compounds as well as natural products and can also serve as versatile synthetic intermediates.[1] Although there are many methods available for the preparation of these compounds (e.g. asymmetric reduction of ynones[2]), the addition of an alkyne to an aldehyde or ketone is attractive because of the creation of a stereodefined alcohol with concomitant C-C bond formation. Additionally, the preparation of tertiary propargylic alcohols cannot be accomplished by reduction. The synthetic usefulness of enantiopure propargylic alcohols is apparent through the diverse reactions that allow for further functionalization (Scheme 1). From the initial reports utilizing alkynyllithium reagents to the recent modifications employing alkynylzinc reagents, the substrate scope has expanded significantly using both aromatic and aliphatic aldehydes as well as pro-chiral ketones.[3]

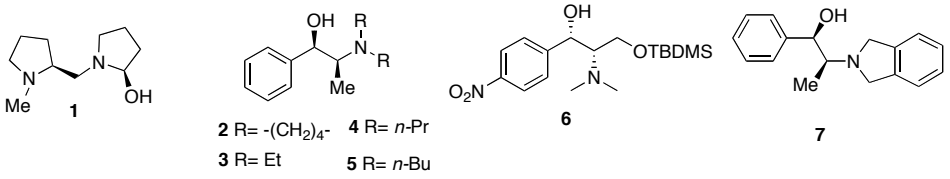
Scheme 1. Transformations of Propargylic Alcohols



The first asymmetric addition of an alkyne to a carbonyl group was reported by Mukaiyama in 1979.[4] The addition of an alkynyllithium reagent to benzaldehyde in the presence of a chiral bis-pyrrolidine ligand **1** (Chart 1) afforded the propargylic alcohol with modest enantioselectivity. Although the scope of the reaction was relatively limited, good selectivity could be obtained (er 85:15). These early reports were limited by the narrow substrate scope and the need for superstoichiometric amount of chiral ligand (4.0 equiv). These drawbacks stimulated a great deal of research that has provided major

improvements in substrate scope, nucleophile scope, ligand design, and selectivity over the last three decades.[3]

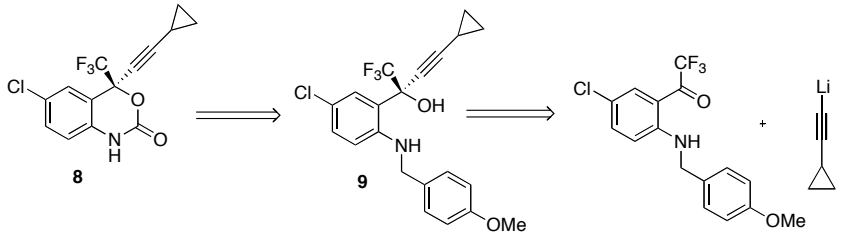
Chart 1. **Chiral Amino Alcohol Ligands For Alkyne Addition**



LITHIUM AND BORON ACETYLIDES

Following the initial reports, the addition of alkynes into carbonyl compounds was further studied to expand the scope of the aldehyde, ketone, and alkyne substrates. As part of the process development for Efavirenz, **8**, a pharmaceutical target for the treatment of HIV,[5] the Merck Research Laboratories devised a route involving carbamate formation from the stereodefined tertiary propargylic alcohol (Scheme 2). This alcohol, in turn, was envisaged to arise from the addition of a metalated alkyne to a trifluoromethyl ketone.

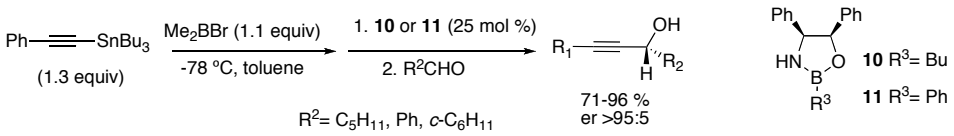
Scheme 2. Retrosynthetic Analysis of Pharmaceutical Target Efavirenz



On the basis of the previous reports of alkyne additions into aldehydes, an investigation of chiral ligands was undertaken.[5] By performing a ligand survey that incorporated chiral amino alcohols **2**-**5**, the ideal ligand was found to be ephedrine derivative **2** (2.0 equiv) which afforded the desired tertiary alcohol in high enantioselectivity (98:2 er).[5]

Despite the high selectivity of the asymmetric alkyne addition, the use of superstoichiometric amounts of **2** makes other conditions to the desired compound more appealing. Corey and co-workers described the first reaction that employed a chiral ligand in substoichiometric amounts to direct the asymmetric alkyne addition into carbonyl compounds utilizing alkynyl boranes.[6] The nucleophilic alkynyl borane was generated in situ via transmetalation of the alkynylstannanes with bromodimethylborane. The alkynyl borane underwent smooth addition into aldehydes in the presence of oxazaborolidine ligands **10** and **11** (25 mol %) in high yields and selectivity (Scheme 3).

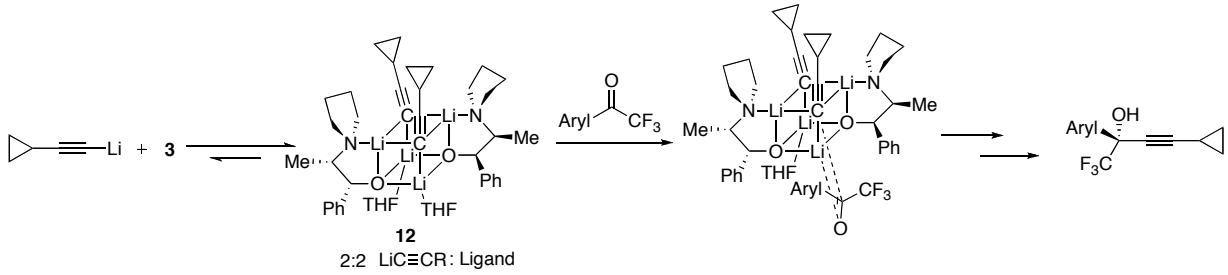
Scheme 3. Reaction of Alkynylstannanes with Oxazaborolidine Ligands



Mechanistic Studies With Lithium Acetylides

Mechanistic studies on the reactions of lithium acetylides have provided important insights. The mechanism of lithium acetylide addition to trifluoromethyl ketones, demonstrated in the synthesis of **8**, was investigated using ^{13}C and ^{6}Li NMR, X-ray crystallography, as well as MNDO semi-empirical computations.[7] It was determined that the lithium acetylide forms multiple aggregates with the chiral ligand that are dependent on temperature and stoichiometry. NMR spectroscopy and X-ray analysis confirmed that the aggregate that produces the highest selectivity, **12** (Scheme 4) exists in an aggregation structure of 2:2 (ligand/RLi). A stereochemical model proposed that **12** could lead to the preferential attack of the carbonyl at one of two faces. Steric interactions between the aromatic ring and the chiral ligand are the controlling element for the observed selectivity (Scheme 4).

Scheme 4. **Proposed Intermediates of Lithium Acetylide Addition**



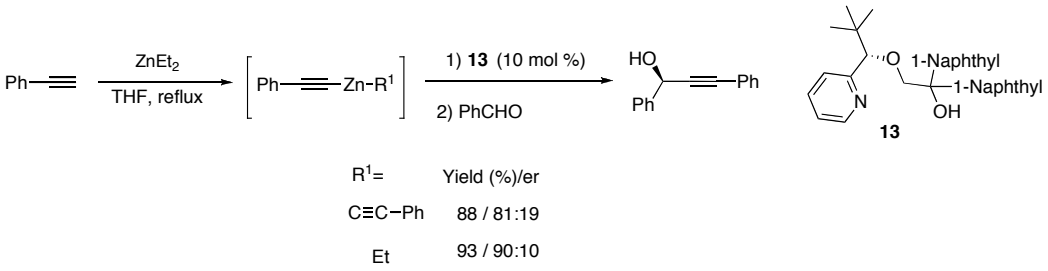
ZINC ACETYLIDE ADDITION INTO CARBONYL COMPOUNDS

Despite many advances, the use of lithium and boron acetylide addition to carbonyl compounds is still limited. Pioneering studies by Soai and Noyori on the asymmetric addition of dialkylzinc to carbonyl compounds suggested that the analogous addition of alkynylzinc reagents should be feasible.[8] The seminal report that utilized dialkynylzinc reagents in the asymmetric addition to carbonyl compounds employed ephedrine derivative ent-**5** to obtain high yields (36-99 %) and modest selectivities (er ~60:40) for the corresponding alcohol.[9] The limited enantioselectivity of the reaction of dialkynylzinc reagents to aldehydes led to the development of more effective ligands and alkynylzinc nucleophiles.

To probe the effect of the organozinc nucleophile, alkynylzinc(II) intermediates were investigated. In 1994, the in situ preparation of alkynylzinc species prior to the addition to carbonyl compounds was developed.[10] Ethyl(alkynyl)zinc was found to be more reactive in comparison to bis(alkynyl)zinc and could be prepared in situ by adding an equimolar ratio of the terminal alkyne with

diethylzinc (Scheme 5). However, competing alkyl addition from the Et_2Zn proved problematic. Improvement in the rate of formation of the alkyl(alkynyl)zinc intermediate should circumvent these problems and provide higher yields of the desired propargylic alcohols (vide infra).

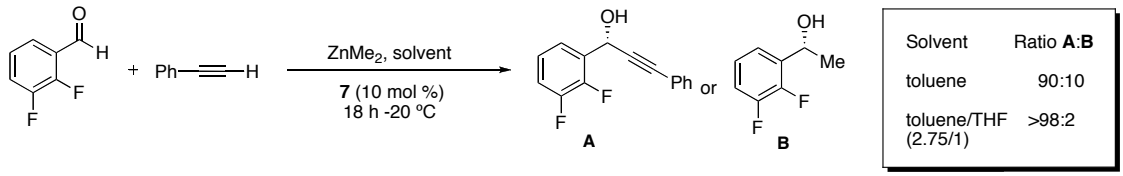
Scheme 5. Reactivity of Alkynylzinc Intermediates



Diorganozinc Reagents

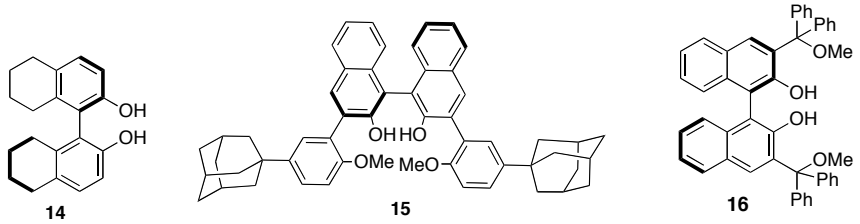
Because the addition of alkynylzinc to carbonyl compounds using chiral alcohol ligands yielded only modest selectivity for a small substrate scope, there remains an unmet need for a more efficient and general catalytic system. Chiral amino alcohols **2** and **7** catalyze the asymmetric addition of aliphatic and aromatic alkynylzinc reagents to aromatic aldehydes.[11] Addition of the alkyl residue (from the dialkylzinc reagent) to the carbonyl group was suppressed by using a mixture of toluene and THF (< 2 % alkylation product) (Scheme 6). Alternatively, it was later discovered that the use of a different chiral ligand and reaction conditions could eliminate the possibility of alkyl addition.

Scheme 6. **Solvent Suppression of Alkyl Addition**



In addition to amino alcohols, other chiral directing groups have been employed for asymmetric acetylide additions. BINOL derivatives are efficient ligands for the asymmetric alkyne addition to carbonyl compounds (Chart 2).[12] In situ generation of a Ti(O*i*-Pr)$_4$/BINOL complex and alkynylzinc species affords the desired propargylic alcohols in good yields and enantioselectivities. It was observed that only a substoichiometric amount of Ti(O*i*-Pr)$_4$ is needed (50 mol %) if the alkynylzinc species is formed prior to the addition of Ti-BINOL complex.[13] The alkynylzinc species formed by this method suppresses competing side reactions and leads to an increase in yield and enantiomeric purity.

Chart 2. BINOL Derived Chiral Ligands

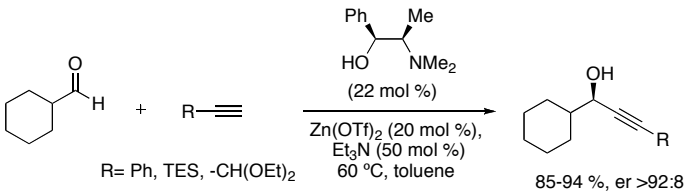


With the emergence of the Ti-BINOL catalyst system, the effect of substituents about the BINOL core was examined. Different 3,3'-substitued BINOL ligands for the asymmetric addition of alkynes to carbonyl compounds were investigated.[14] With 3,3'-substituted BINOL **15** (10 mol %), the addition of phenylacetylene to aromatic aldehydes could be carried out without the need for $Ti(O\textit{i}\text{-}Pr)_4$ to obtain the propargylic alcohols in moderate yields and high selectivity.[13b] A structural activity relationship study was performed on BINOL derivative **16** to determine the role of the 3,3'-substituted BINOL ligands. The coordinating ability as well as the steric bulk of the 3,3'- position is essential for reactivity. Inversion of the –OH and -OMe positions affords limited reactivity while removal of the bulky gem-diphenyl groups led to diminished enantioselectivity. Although the substrate scope has been expanded by using diorganozinc reagents, additions into aliphatic aldehydes employed a different zinc(II) precursor.

Alkyne Additions Utilizing Zn(II) Triflate

Carreira and co-workers pioneered an alternative strategy to carry out the addition by in situ generation of the zinc reagent using $Zn(OTf)_2$.[15] With the use of a stoichiometric amount of (+)-*N*-methylephedrine, aliphatic aldehydes underwent nucleophilic attack by alkynes to yield the corresponding propargylic alcohol in high yields and selectivities. Although the reaction must be performed using stoichiometric amounts of chiral ligand, the reaction can be performed open to the atmosphere with only modest decrease in enantiopurity. Subsequent development led to a catalytic process in both zinc and ligand. This protocol can be used with many aldehydes and is considered to be the ideal conditions for additions to aliphatic aldehydes. (Scheme 7).[15b]

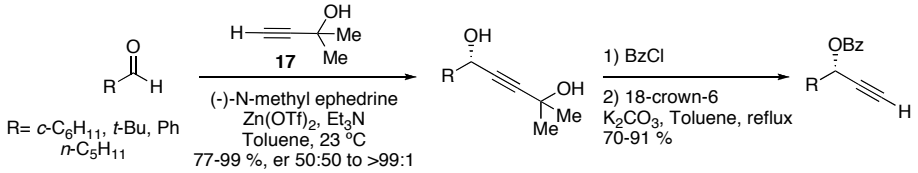
Scheme 7. Catalytic Alkyne Addition to Aldehydes Using $Zn(OTf)_2$



Under similar conditions, the addition of acetylene to aldehydes with stoichiometric amounts of $Zn(OTf)_2$ and (+)-*N*-methylephedrine, affords the propargylic alcohol in high selectivity.[16] The major

drawbacks of this reaction are the long reaction times and modest yields. This problem can be overcome by the use of an acetylene equivalent 2-methyl-3-butyn-2-ol, **17** (Scheme 8).[17] The chiral propargylic alcohol formed from **17** undergoes a thermal fragmentation of acetone to furnish the terminal alkyne in high yields (70-91 %) and selectivity (er: 7:1 to 99:1). Although alkynylzinc addition to aldehydes has been expanded significantly over the last three decades the preparation of tertiary propargylic alcohols by this method has received little attention.[18]

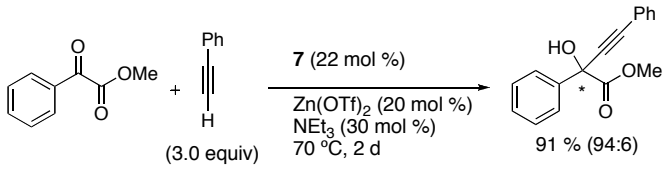
Scheme 8. **Addition of 2-Methyl-3-butyn-2-ol to Aldehydes**



Preparation of Tertiary Propargylic Alcohols

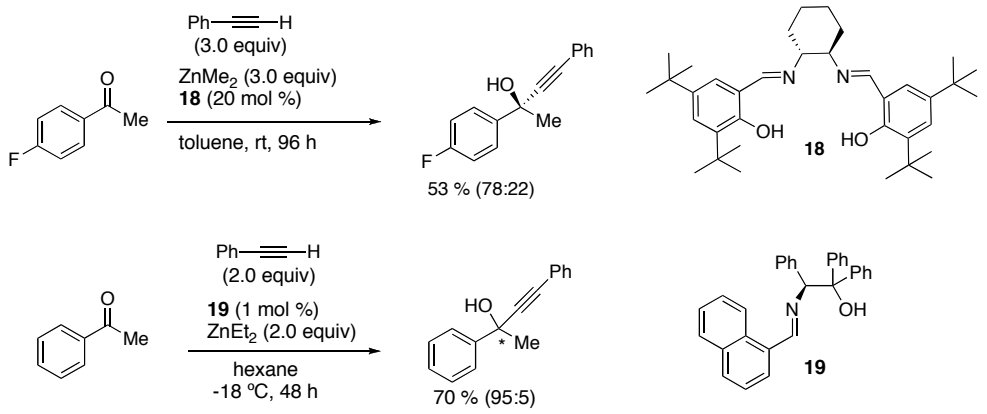
Apart from the synthetic studies on Efavirenz,[5] only a few reports involving asymmetric additions of alkynes to ketones are known.[19] Jiang and coworkers reported that α-keto esters undergo nucleophilic addition of zinc acetylides (generated in situ from alkyne, triethylamine, and $Zn(OTf)_2$) in the presence of **7** to generate the chiral tertiary alcohol in high yield and selectivity (Scheme 9).[20] The reactions could be performed in the absence of solvent; however, the alkyne needed to be used in superstoichiometric amounts (3 equiv).

Scheme 9. Alkyne Addition to α-Ketoesters



The asymmetric alkynylzinc addition to unactivated ketones has been reported using a bifunctional chiral salen ligand **18**[21] as well as a chiral Schiff base ligand, **19**.[22] The former process is limited due to the lower yields and enantioselectivities of the desired chiral tertiary alcohol. However, the use of a substoichiometric amount of **19** significantly improved the yields and enantiomeric composition of the tertiary alcohols (Scheme 10). Despite the improved conditions the reaction can only be applied to aromatic ketones.

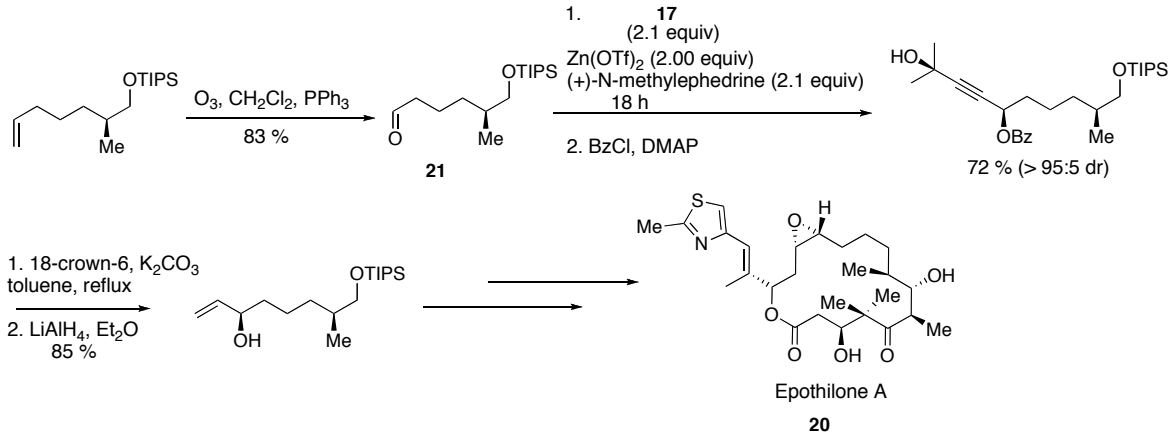
Scheme 10. Alkyne Addition to Unactivated Ketones



APPLICATIONS IN SYNTHESIS

Aside from the aforementioned Efavirenz synthesis, the asymmetric addition of alkynes to carbonyl compounds has been used to synthesize a variety of targets. The asymmetric alkyne addition to aldehydes was utilized in the synthesis of Epothilone A **20**, a natural product isolated from myxobacterium that exhibits biological activity similar to taxol.[23] Construction of the macrocycle was affected by the addition **17**, to aldehyde **21** to afford the propargylic alcohol in high yield and diastereoselectivity (Scheme 11).[24] The secondary alcohol was protected and upon thermal fragmentation and reduction the allylic alcohol was prepared in high yield. This fragment was then applied to the total synthesis of Epothilone A in 21 steps.

Scheme 11. Synthesis of Epothilone A



CONCLUSIONS

Chiral propargylic alcohols are useful intermediates in synthetic organic chemistry.[25,26] Whereas the asymmetric reduction of ynones is an attractive method for the preparation of these intermediates, asymmetric alkyne addition to carbonyl compounds offers an alternative method of carbon-carbon bond formation with concomitant formation of a chiral alcohols as well as the possibility of generating chiral

tertiary alcohols. Methods employing chiral amino alcohols and BINOL derivatives with a zinc(II) precursor have tremendously expanded the scope and optimized the yields of the process since the first reported case by Mukaiyama. Unactivated ketones remain a challenging substrate class and general reaction conditions need to be developed to provide high yields and enantioselectivities for tertiary propargylic alcohols.

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