Acetylenes in Catalysis: Enantioselective Additions to Carbonyl Groups and Imines and Applications Beyond

Pier Giorgio Cozzi,*[a] Robert Hilgraf,[b] and Nicole Zimmermann[c]

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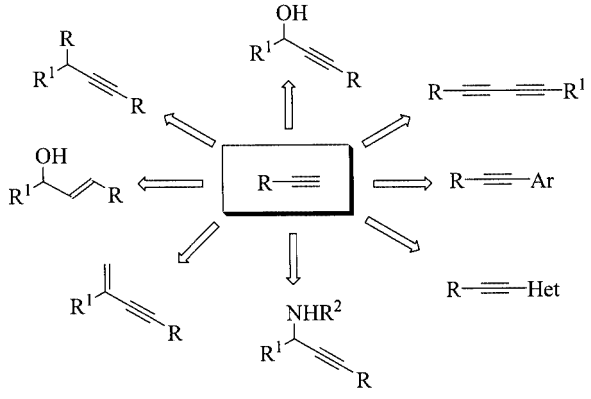
Acetylenes represent a class of versatile building blocks, which are widely used in organic synthesis. Over the past years, a considerable number of publications have appeared that focus on the enantioselective addition of acetylenes to carbonyls and imines. In addition, novel applications for acetylenes have emerged in the literature. We herein present an overview of recent results in these areas.

Introduction

Chiral propargylic alcohols have been used as key intermediates in the syntheses of complex organic molecules.[1] The most efficient route for their synthesis utilizes the enantioselective addition of acetylenes to carbonyl compounds. In this review we would like to give a concise and up to date overview of different catalytic methodologies described in recent years. Novel methods for the synthesis of propargylamines will also be discussed. In addition, new applications of acetylenes will be presented, showing that acetylenic intermediates are indeed versatile, useful and adapted to perform a variety of synthetic transformations.

Acetylenes as Nucleophiles

The addition of nucleophiles to carbonyl substrates or imines is an important and established process in organic synthesis.[2] New stereogenic centers and C−C bonds are formed in a single step. However, in the case of the stereoselective catalytic version of this reaction, only a limited set of nucleophiles such as enolsilanes, allylstannanes, -silanes or -boranes, and alkylzinc reagents can be used.[3] These nucleophiles have been extensively applied in total synthesis or in the preparation of useful intermediates. But they have clear disadvantages in that they are often not commercially available, difficult to prepare, and exhibit severe environmental and safety problems. In order to overcome these limitations and problems, novel strategies need to be explored in which more convenient nucleophiles such as ketones, esters or alkynes are used. In recent years alkynes have emerged as promising nucleophiles for selective and mild C−C bond forming reactions (Scheme 1).[4]



Scheme 1

Metalated acetylenes are used in Pd^0-catalyzed coupling reactions (Sonogashira coupling and its variants)[5] and also in the addition of electrophiles such as aldehydes, imines,

[a] Dipartimento di Chimica "G. Ciamician",
Via Selmi 2, 40126 Bologna, Italy
Fax: (internat.) +39-051-2099456
E-mail: piergiorgio.cozzi@ciam.unibo.it
[b] Celgene,
4550 Towne Centre Court, San Diego, CA 92121, USA
Fax: (internat.) +1-858-795-4719
E-mail: rhilgraf@celgene.com
[c] Vertex Pharmaceuticals Inc.,
11010 Torreyana Road, San Diego, CA 92121, USA
Fax: (internat.) +1-858-404-6726
E-mail: nicole_zimmermann@sd.vrtx.com

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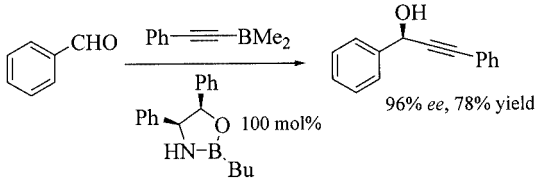
epoxides and acyl chlorides. One advantage of alkynes as nucleophiles is their easy metalation: A large variety of strong bases such as alkyl derivatives (BuLi,[6] EtMgBr,[7] Me_2Zn[7]), metalated amides [$KN(TMS)_2$, $NaN(TMS)_2$, LDA, Et_2NLi] or alkoxides (tBuOK)[8] achieve metalation of acetylenes. Even hydroxides (KOH or CsOH)[9] can be used. On the other hand, deprotonation can take place with weakly basic amines in the presence of Cu^I or Ag^I salts.[10] These late transition metals increase the acidity of the C(sp)−H atom by formation of a π-complex. Due to the ease of formation of the active species from alkynes, the practical use of these nucleophiles has attracted much attention over the past years.

The use of strong bases for the generation of the active alkyne nucleophiles is incompatible with electrophiles such as ketones or aldehydes, and clearly does not allow their in situ formation. Therefore, in most cases the alkyne deprotonation needs to be performed in a separate step. In addition, the reactivity of the alkynide needs to be moderate in order to allow stereocontrol by a chiral promoter. In the course of this article two different solutions for these problems will be discussed. As dialkylzinc reagents do not react with aldehydes or ketones in the absence of activators such as amino alcohols, dialkylzinc reagents can function as bases to catalyze the addition of alkynes to carbonyls. Alternatively, metals able to enhance the acidity of the C(sp)−H atom can be employed in the presence of tertiary amines.

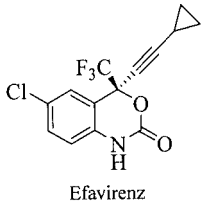
Enantioselective Addition of Acetylenes to Aldehydes and Ketones Mediated by Chiral Ligands

One of the early examples for the enantioselective addition of alkynes to aldehydes with a chiral ligand system was reported by Corey and Cimprich. They showed that the addition of alkynylboranes to aldehydes at low temperature in the presence of stoichiometric amounts of the proline-derived oxazaborolidine afforded propargylic alcohols with up to 96% *ee* (Scheme 2).[11]



Scheme 2

This reaction could also be carried out with substoichiometric amounts of chiral ligand. Another example is the addition of lithium trimethylsilylacetylide to substituted cyclohexanones in the presence of (2*S*,2′*S*)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-methy]pyrrolidine as chiral ligand.[12] Enantiomeric excesses of up to 82% were obtained using stoichiometric amounts of the ligand. The total synthesis of the potent nonnucleosidal HIV reverse transcriptase inhibitor Efavirenz has attracted considerable interest over the last years (Figure 1). In the course of the search for a large scale synthesis, scientists from Merck reported the addition of lithium cyclopropylacetylide to a suitable precursor in the presence of chiral ligands.[13] Ad-



Efavirenz

Figure 1. HIV inhibitor Efavirenz

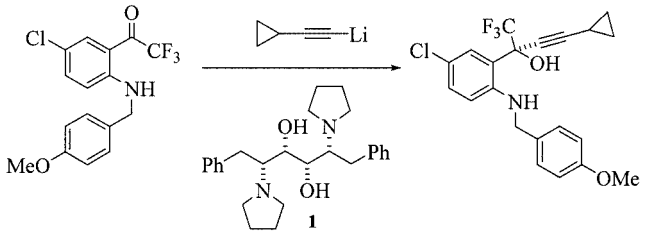
Pier Giorgio Cozzi was born in Legnano (Milan) in 1963. He studied chemistry at the University of Milan, under the guidance of Professor Cesare Gennari in 1989. After spending four years as a researcher in Lausanne (Switzerland) with Professor Carlo Floriani, he was appointed as a Lecturer (in 1994) and then Associate Professor (in 2000) at the University of Bologna. The development of new, enantioselective catalytic reactions, the design of new chiral ligands, and the formation of quaternary stereocenters using new synthetic methodologies are his main interests. Professor Pier Giorgio Cozzi has been a visiting professor at the Universities of Aachen (Germany), Neuchâtel (Switzerland), Ottawa (Canada), Basel (Switzerland), Aarhus (Denmark), and he is a member of two European Networks in the Sixth Framework Program; the European LigBank, and IBA$_2$C projects.

Robert Hilgraf was born in Hannover (Germany) in 1970. He studied chemistry at the universities of Hamburg and Leicester. After his diploma thesis with Prof. Wittko Francke, he began his Ph.D. work with Prof. Andreas Pfaltz at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany) in November 1997. He obtained his Ph.D. degree in November 2000 at the University of Basel (Switzerland) and subsequently moved on to the Scripps Research Institute in La Jolla (USA) as a postdoctoral research associate with Prof. K. Barry Sharpless. Since December 2002 he works as a medicinal chemist at Celgene in San Diego (USA). He has received numerous fellowships including a Kekulé Fellowship for his graduate research, and postdoctoral fellowships from the DAAD, the Novartis Foundation and the Swiss National Science Foundation (SNF).

Nicole Zimmermann was born in Hildesheim (Germany) in 1972. She studied chemistry at the universities of Hamburg and Leicester. After her diploma thesis with Prof. Wittko Francke, she did her Ph.D. thesis under the guidance of Prof. Andreas Pfaltz at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany) and at the University of Basel (Switzerland) from November 1997 to January 2001. After postdoctoral studies with Prof. Peter G. Schultz at the Scripps Research Institute in La Jolla (USA), she joined Vertex Pharmaceuticals in San Diego (USA) in August 2002. She has been awarded a Kekulé Fellowship for her graduate studies and a Feodor-Lynen Fellowship of the Alexander-von-Humboldt Foundation for her postdoctoral research.

ditional careful investigations of the reactive intermediate responsible for the chiral induction were carried out in collaboration with Collum using detailed ^{6}Li NMR studies.[14] Tan described an improved method by the formation of a chiral zincate that resulted in a practical and effective asymmetric alkynylation of a precursor for the synthesis of Efavirenz.[15]

Another synthetic approach towards a precursor of Efavirenz was described by Jiang who employed a stoichiometric amount of the chiral C_2 symmetric diol **1** in the presence of lithium acetylides (Scheme 3).[16] The outcome of the reaction proved to be quite sensitive to the substitution pattern of the acetylides.

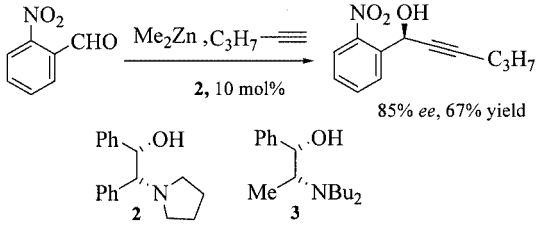


Scheme 3

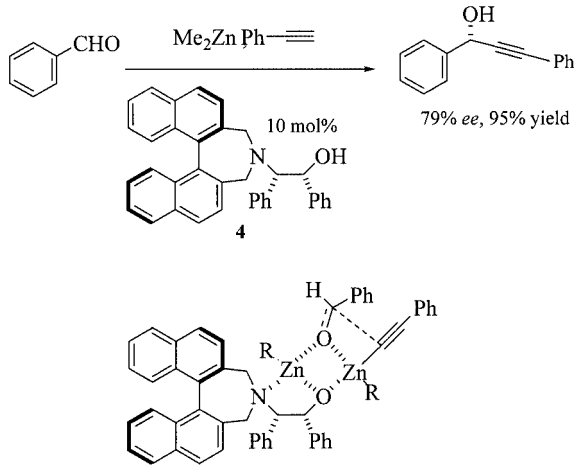
Dialkylzinc-Mediated Enantioselective Additions of Acetylenes to Aldehydes

The use of chiral amino alcohols as ligands for the enantioselective addition of dialkylzinc reagents to aldehydes has been extensively explored in recent years. Starting from the seminal contributions of Noyori,[17] hundreds of chiral amino alcohols have been synthesized and tested in one privileged reaction: the addition of Et_2Zn to aldehydes. The first enantioselective addition of alkynylzinc reagents to benzaldehyde was reported by Soai and afforded moderate enantiomeric excesses.[18] The use of chiral amino alcohols in the asymmetric addition of alkynes has also been reported in the literature. Li and co-workers described the application of amino alcohols **2** and **3** and their derivatives to catalyze the reaction of terminal alkynes with aromatic aldehydes (Scheme 4). Enantiomeric excesses of up to 85% were obtained.[19] In addition, pyridine alcohol ligands have been found to effectively promote the addition of alkynylzinc reagents to aldehydes.[20]

Chan et al. used binaphthylamino alcohol **4**, which can be prepared in a few steps from commercially available BI-



Scheme 4



Scheme 5

NOL for a similar addition reaction (Scheme 5).[21] This method afforded good enantiocontrol for aromatic aldehydes, whereas aliphatic aldehydes resulted in lower *ee*'s. Crucial for the success of this reaction was the choice of the otherwise rarely used Me_2Zn as the promoting agent. Whereas other alkylzinc reagents react with aldehydes in the presence of amino alcohols, the less reactive Me_2Zn does not add to the aldehyde but only forms the active zinc complex and deprotonates the phenylacetylene.[22] The proposed transition state for the reaction consists of a bimetallic species that is also common for other reactions of dialkylzinc with aldehydes (Scheme 5).

Another highly reactive class of ligands for the addition of Ph_2Zn to aldehydes is the group of chiral ferrocenyl ligands. Bolm reported a high enantiocontrol for the addition of Ph_2Zn to aldehydes using a mixed zinc reagent.[23] Theoretical studies provided more information about the proposed transition state and the equilibrium of different catalytic species in solution.[24] Most recently, the use of chiral ferrocenyl ligands could be extended to the addition of phenylacetylene to aldehydes. Ligands **5**–**7** (Figure 2) afforded good enantiomeric excesses with a variety of different aldehydes. Since the ferrocenyl oxazolines do not promote the addition of Et_2Zn to aldehydes, the reactive system can be prepared by adding the ligands directly to a mixture containing phenylacetylene and Et_2Zn.[25]

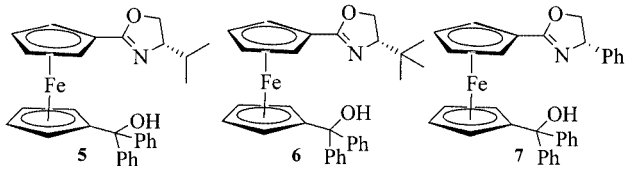


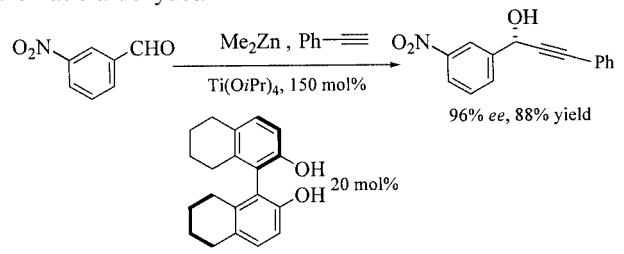
Figure 2. Chiral ferrocenyl oxazoline ligands

Oxazolidine ligands were also reported to promote the addition of alkynylzinc to aldehydes. Although the enantiomeric excesses obtained were only moderate, addition of alkynes other than phenylacetylene was described.[26] Quite interesting results, both in terms of yield and enantioselectivity, were obtained by Pu with a BINOL-salen ligand that

catalyzes the addition of aryl and alkylalkynes to aromatic aldehydes at room temperature with high enantioselectivities (86−97% *ee*).[27]

Titanium-Mediated Enantioselective Addition of Acetylenes to Aldehydes

Chiral titanium alkoxide complexes are readily prepared and are useful for a variety of enantioselective transformations. Especially, BINOL and its derivatives have emerged as privileged chiral ligands in this area.[28] Titanium BINOL complexes are usually prepared in situ and are obtained as a mixture of different species in equilibrium. Ding and coworkers reported a highly enantioselective addition of Et_2Zn to aldehydes catalyzed by a combination of BINOL and a chelating dinitrogen ligand.[29] In the absence of the dinitrogen ligand no enantiocontrol was observed. However, Chan reported an asymmetric alkynylation in the presence of Ti(O*i*Pr)$_4$ as additive and with BINOL and H_8-BINOL as ligands without addition of a dinitrogen ligand (Scheme 6). Enantiomeric excesses of up to 96% were obtained, and the procedure could be applied to aliphatic and aromatic aldehydes.[30]



Scheme 6

The active complex was prepared by stirring the BINOL derivatives with Ti(O*i*Pr)$_4$, and addition of the resulting solution to the mixture of phenylacetylenes and Me_2Zn. The role of Ti(O*i*Pr)$_4$ is to produce the active catalyst and to facilitate the transmetalation. Recent studies on the mechanism of the addition of alkylzinc reagents in the presence of Ti(O*i*Pr)$_4$ suggest that the role of Ti(O*i*Pr)$_4$ is to receive an alkyl group from the zinc reagent and to bind the chiral titanium catalyst in a preset form (Figure 3).[31]

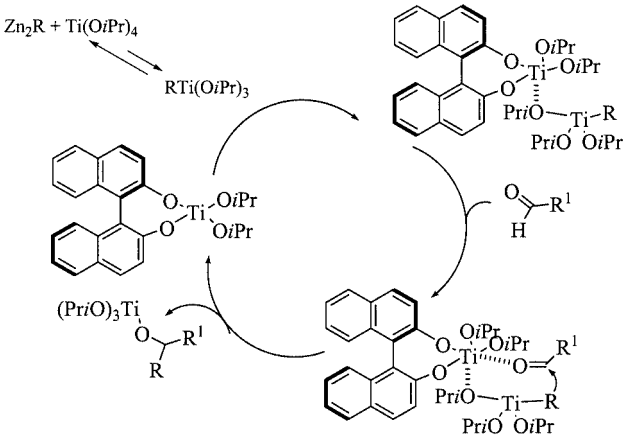


Figure 3. Proposed catalytic cycle

In all cases, a bimetallic catalyst with two titanium atoms seems to be necessary in order to achieve stereoselectivity. However, this hypothesis needs to be proven by detailed kinetic studies.

In a series of papers Pu and co-workers described an analogous BINOL/Ti(O*i*Pr)$_4$ system to that of Chan and investigated in detail the procedure for the preparation of the reactive zinc alkylides.[32] In contrast to Chan's procedure, Pu obtained zinc alkylides by heating a mixture of Et_2Zn and phenylacetylene in toluene under reflux. Based on theoretical calculations, the equilibrium between Me_2Zn and phenylacetylene is completely shifted towards the reagents. In addition, some detailed NMR spectroscopic studies of the reaction mixture of alkylzinc reagents and substituted acetylenes revealed that the formation of the supposed active species is only obtained to some extent, and that its ratio is determined by the presence of coordinating species such as solvent or ligands.[33] Pu defined optimized protocols for the addition of phenylacetylene to aromatic and aliphatic aldehydes yielding high enantiomeric excesses of up to 98%. For the addition of phenylacetylene to aliphatic aldehydes it was necessary to use Et_2O as a solvent and to use up to 40 mol % of BINOL ligand (relative to aldehyde). In addition, a fourfold excess of the mixture of phenylacetylene and Et_2Zn was used (relative to aldehyde). Pu also prepared a small library of different substituted BINOLs and found remarkable remote effects of the substituents on the outcome of the alkynylation reaction.[34]

In a further optimization Pu found that the active catalyst could also be prepared at room temperature by stirring phenylacetylene and Et_2Zn in the presence of chiral ligand **8**. The authors suggest that a zinc complex is formed by the reaction of Et_2Zn and ligand **8**, which catalyzes the formation of the alkynylzinc reagent from phenyl acetylene and Et_2Zn (Figure 4).

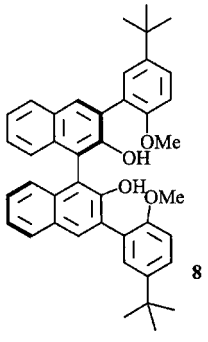


Figure 4. Pu's ligand

Independently, Chan et al. were able to improve their previous results by utilizing the concept of "asymmetric activation". Mikami first introduced this idea for the enantioselective carbonyl-ene reaction.[35] He reported the in situ preparation of self-assembled titanium catalysts from Ti(O*i*Pr)$_4$ and several chiral ligand components that resulted in enhanced reaction rates and enantioselectivities. Chan successfully applied this concept for the titanium-cat-

alyzed alkynylation reaction by combining BINOL with different types of chiral ligands (Figure 5).[36]

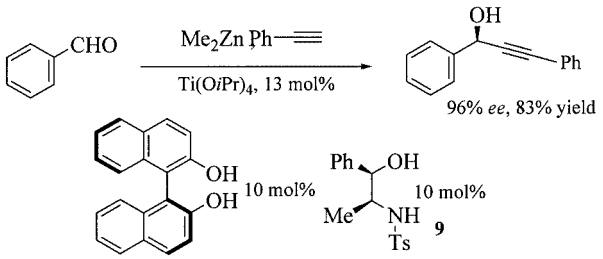
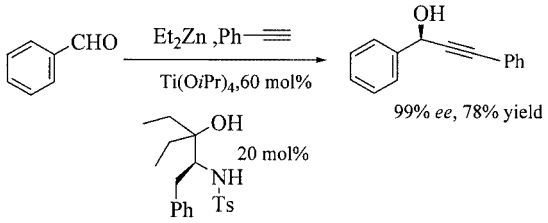


Figure 5. Self-assembled titanium catalyst

The combination of BINOL with chiral sulfonamides increased the catalytic activity and the enantioselectivity of the alkynylation of aldehydes using $Ti(OiPr)_4$ as catalyst precursor. With sulfonamide **9** (10 mol %) and BINOL (10 mol %), remarkably high enantioselectivities of 92−99% *ee* could be achieved for aromatic aldehydes. By using this methodology, a complex mixture of several titanium catalysts is formed in solution, and the addition of an additive modifies the equilibrium between the different species to form a selective and highly active catalyst. This concept is still based on intuition and "trial and error" but can be efficiently combined with high throughput technologies. As another additive, Chan identified phenols to be the additive of choice for self-assembled titanium catalysts from BINOL/$Ti(OiPr)_4$.[37] With phenols as additives, higher enantiomeric excesses were obtained for most cases with aliphatic and aromatic aldehydes. Other derivatives of BINOL have been used as well: a family of optically pure 7,7′-disubstituted-2,2′-dihydroxy-1,1′-dinaphthyls was tested in the catalytic addition of phenylacetylene to aromatic aldehydes, and afforded good yields and high enantioselectivities.[38]

Both sulfonamides and phenols possess acidic groups that can react with titanium isopropoxide. In particular, titanium sulfonamide complexes are used as Lewis acids in the transfer of alkylzinc reagents to aldehydes.[39] Walsh described the structural characterization of titanium bis(sulfonamide) complexes and their properties in enantioselective catalytic reactions.[40] It is noteworthy that although the NH group of the sulfonamides are believed to be acidic enough, no reaction occurs between $Ti(OiPr)_4$ and bis-sulfonamide even after prolonged reaction times. Diethylzinc acts as the deprotonating agent and allows the formation of the titanium complexes. Although the procedure described in the literature indicates that mixing of the sulfonamide with $Ti(OiPr)_4$ is the crucial step, the formation of the catalytic active species occurs only when Et_2Zn is added to the reaction mixture.[41] Recently, Wang reported a highly enantioselective addition of phenylacetylene to aromatic aldehydes catalyzed by *N*-sulfonated amino alcohols, which are easily prepared in a few steps from L-phenylalanine (Scheme 7).[42]. Enantiomeric excesses between 90−99% were achieved for this reaction, which is specific for aromatic aldehydes.

An interesting detail is the fact that the reaction procedure is simple relative to previous procedures. The reactive alkynylzinc reagent can easily be prepared in situ by mixing phenylacetylene, ligand, $Ti(OiPr)_4$ and Et_2Zn at room temperature.

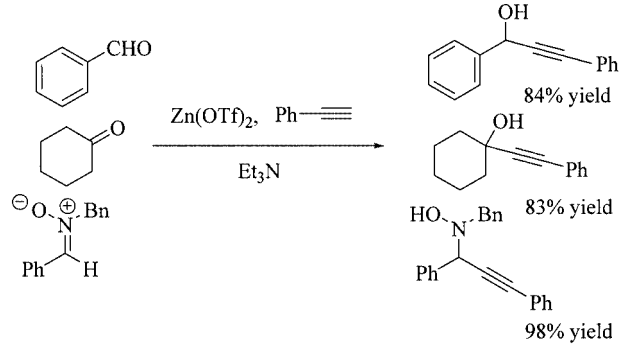


Scheme 7

Other emerging chiral ligands for this reaction are L−proline and its derivatives, and chiral Schiff bases. Boc-L-proline was recently reported as a chiral ligand for the addition of phenylacetylene to aromatic aldehydes in the presence of $Ti(OiPr)_4$. The reaction was conducted at room temperature in the presence of Et_2Zn. The authors suggest the formation of a chelated titanium complex.[43] Chiral Schiff bases in the presence of $Ti(OiPr)_4$ also promote the addition of phenylacetylene to benzaldehyde affording promising enantioselectivities.[44] Cinchona alkaloids were found to be able to promote the addition of various alkynes in the presence of more than stoichiometric amount of $Ti(OiPr)_4$.[45] Although the ligand needs to be used in large quantities, alkaloids are inexpensive additives and can be recovered by practical acid-base extraction.

Direct Formation of Zinc Acetylides, Enantioselective Addition of Acetylenes Catalyzed by $Zn(OTf)_2$

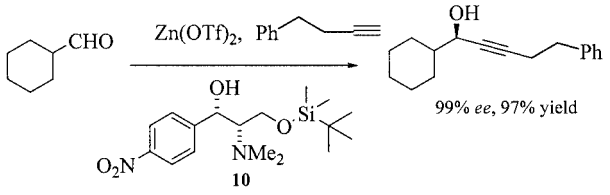
The preparation of reactive metal acetylides (B, Al, Ce, V and Mn) is normally realized by transmetalation of Li, Na or Mg acetylides. Yamaguchi found the first evidence that metal acetylides could also be formed by the proper selection of a metal salt in combination with an appropriate amine.[46] $Sn(OTf)_2$ in the presence of 1,6-bis(dimethylamino)naphthalene or DBU formed the reactive acetylide in CH_2Cl_2, which afforded good isolated yields in the addition to aldehydes and ketones. Carreira found that $Zn(OTf)_2$ in combination with an amine led to the formation of the corresponding zinc acetylides, which could be successfully added to carbonyl compounds and nitrones (Scheme 8).[47]



Scheme 8

Evidence for the in situ formation of zinc acetylides was obtained by spectroscopic IR studies, and the formation appears to be reversible.

Other Lewis acids such as GaI_3,[48] $ZnCl_2$ [49] and $InBr_3$ [50] are also able to promote the alkynylation of carbonyl compounds in the presence of amines. Carreira was able to extend his findings to develop an enantioselective methodology that uses inexpensive ephedrine as a chiral ligand.[51] This method gave excellent yields and enantioselectivities (up to 97% *ee*) with various substituted aliphatic aldehydes, whereas aromatic aldehydes gave lower yields due to side reactions such as Cannizzaro reactions. It is worth mentioning that this method worked without the exclusion of air and with commercial grade solvents (δ = 300 ppm of water). A further improvement reported by the same author was the use of ephedrine in catalytic amounts. To overcome the problem of low turnover in the catalytic cycle, the reaction needed to be performed at higher temperature (60 °C) and in the presence of another base like Et_3N.[52] This mild procedure was applied in the total synthesis of several natural products. The enantioselective synthesis of (*R*)-strongylodiols A and B,[53] musclide B[54] and leuscandrolide A[55] was accomplished with the enantioselective addition of acetylene mediated by ephedrines in the key steps. Jiang described the use of different amino alcohols such as (1*S*,2*S*)-2-dimethylamino-1-(*p*-nitrophenyl)-3-(*tert*-butyldimethylsilyloxy)propan-1-ol (**10**, see Scheme 9).[56]



Scheme 9

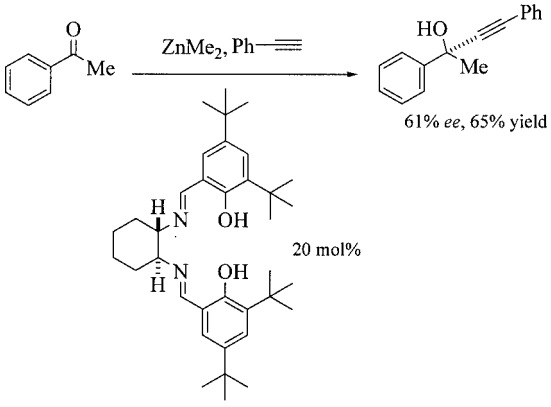
This ligand was used in stoichiometric amounts and afforded excellent enantiomeric excesses of up to 99% with aliphatic aldehydes and could also be applied for aromatic aldehydes, giving slightly inferior yields. In another publication, Jiang described the use of $Zn(ODf)_2$ obtained from difluoromethanesulfonic acid as a different zinc Lewis acid. Although the acidity of difluoromethanesulfonic acid is lower than that of triflic acid, the corresponding zinc salt allows the preparation of zinc alkynides from the enantioselective addition to aldehydes, in good yields and enantiomeric excesses.[56]

Enantioselective Addition of Acetylenes to Ketones

Since ketones are less reactive electrophiles than aldehydes, they still represent a challenging class of substrates for modern organic synthesis. While hundreds of efficient methodologies have been reported for the enantioselective addition of nucleophiles to aldehydes, the formation of quaternary stereocenters is still scarcely developed.[58] In recent years few novel methods were introduced, most of them based on the double activation concept.[59]

So far only three different approaches have been successfully applied for the enantioselective addition of acetylene to ketones.[60] Jiang used their above-mentioned catalyst systems for the addition of zinc acetylides to α-keto esters derivatives. He reported that ligand **10** could be used to catalyze the enantioselective addition of zinc alkynylide to α-keto esters.[61] Similar results were obtained with (−)-*N*-methylephedrine as the chiral ligand. In this case (−)-*N*-methylephedrine was used in 22 mol % and, as reported previously, higher temperatures (70 °C) were critical to ensure high turnover numbers. Base and $Zn(OTf)_2$ were used in catalytic amounts. Hindered aliphatic as well as aromatic α-keto esters could be used to give tertiary α-hydroxy-β-ynyl esters in excellent enantiomeric excesses of up to 94%.

The first general method that allowed the enantioselective addition of acetylenes to ketones was introduced by Cozzi and is based on the Salen framework (Scheme 10).[62]



Scheme 10

Salen has peculiar properties and metal salen complexes are able to act in a cooperative manner.[63] Salen-metal complexes can behave as bifunctional Lewis acid/Lewis base catalysts (Figure 6).[64]

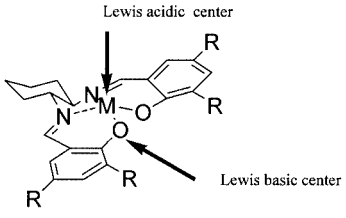
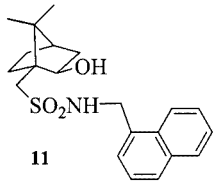


Figure 6. Bifunctional Salen-metal complexes

The oxygen atoms of salen metal complexes can coordinate to reactive organometallic fragments.[65] Our group recently discovered a highly diastereo- and enantioselective salen-promoted addition of phenylacetylene to chiral ketones. Even functionalized aliphatic ketones seem to be well tolerated substrates for salen-mediated reactions.[66]

A third method reported by Chan is based on the concept to increase the reactivity of ketones by employing a strong Lewis acid. Since copper(II) triflate in combination with bis-oxazolines is well established in the addition of nu-

cleophiles to ketones,[67] Chan examined $Cu(OTf)_2$ with different ligands in the addition of phenylacetylene to aromatic ketones. He found that ligand **11** introduced by Yus[68] was very efficient in the addition of phenylacetylene to aromatic ketones with enantioselectivities of up to 97% *ee* (Figure 7).[69]



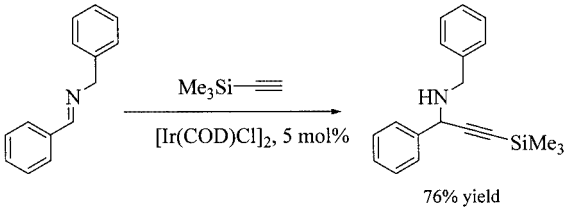
11

Figure 7. Yus' sulfonamide ligand

Recently we have found that BINOL could be used in the enantioselective addition of acetylenes to ketones and that the results obtained are quite promising in terms of yields and enantiomeric excesses.[70]

Enantioselective Alkynylation of Imines and Enamines

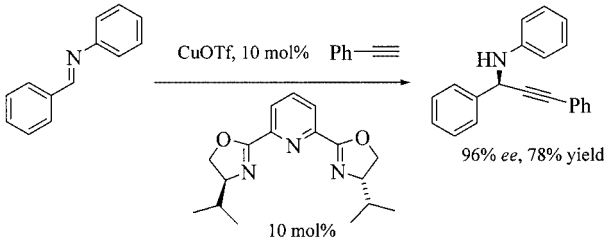
Propargylamines are important synthetic intermediates for the preparation of various nitrogen-containing compounds such as allylamines, pyrroles, β-lactams, and pyrrolides.[71] Methods for the 1,2-addition of alkynes to imines by a direct nucleophilic addition have barely been developed due to the poor electrophilicity of the azomethine carbon. Lewis acid activators, such as TMSOTf, BF_3 or TMSCl have been introduced in order to activate the imino moiety. Jiang reported the addition of alkynes to chiral imines using TMSCl in the presence of $ZnCl_2/Et_3N$ with moderate diastereoselection.[48] Acid chlorides can also be used as activators in the addition of copper acetylides to imines giving access to an efficient and general three-component coupling method to prepare propargylamines.[72] An interesting iridium-mediated addition of alkynes to imines was described by Carreira (Scheme 11).[73] The reaction is performed with a mixture of aldimine and trimethylsilyl acetylene in the presence of $[IrCl(COD)]_2$.



Scheme 11

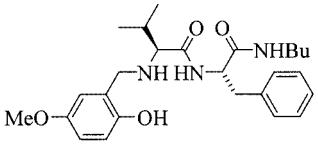
Based on the observation that ruthenium complexes can activate acetylenes, Li developed the first enantioselective addition of acetylenes to imines (Scheme 12).[74]

In another publication, Li described an efficient three-component reaction between aldehydes, alkynes and amines catalyzed by gold in water. Although the reaction is not enantioselective, the conditions used are environmentally



Scheme 12

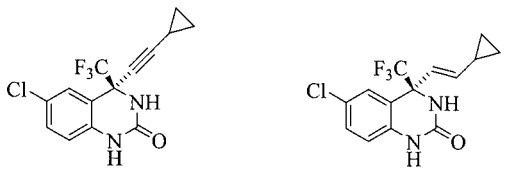
benign, and the possibility to form an organometallic gold complex in water is interesting.[75] Snapper and Hoveyda reported an enantioselective addition of alkynylzinc reagents to a variety of *o*-anisidyl imines promoted by the chiral ligand **12** in the presence of $Zr(OiPr)_4 \cdot iPrOH$ (Figure 8).[76] Consistent with reports from Kobayashi[77] on the use of $Zr(OiPr)_4 \cdot iPrOH$ as a Lewis acid, the chelating structure of the imine plays a major role. The reaction is promoted by a mixed zinc reagent obtained upon the addition of [(trimethylsilyl)methyl]zinc.[78] The use of the mixed reagent was necessary to avoid the formation of amines derived from the addition of a methyl group, a side reaction that takes place in the presence of Me_2Zn and terminal alkynes.



12

Figure 8. Ligand for Zr-catalyzed alkynylzinc additions to imines

Knochel reported a Cu-Quinap-catalyzed addition of alkynes to enamines that afforded enantioenriched alkynylamines.[79] The synthesis of a key intermediate for the preparation of Efavirenz was recently reported by Jiang using the addition of zinc acetylides to reactive ketoimines in the presence of a chiral amino alcohol under mild conditions.[80] This method is a substantial advance in the area as the enantioselective addition takes place without the use of harsh reaction conditions, expensive reagents or low reaction temperatures. Second generation HIV nonnucleoside reverse transcriptase inhibitors **13** and **14** were prepared by a direct alkynylation of cyclic *N*-acyl ketimines mediated by $Zn(OTf)_2$ and Et_3N in the presence of chiral amino alcohols (Figure 9).[81] Whereas the use of ephedrine as chiral amino alcohol resulted in poor enantioselectivities, chloramphenicol bases, readily obtained from commercial sources, af-



13 **14**

Figure 9. Second generation HIV inhibitors

forded up to 99% *ee*. This reaction was also amenable for scale-up as it was run on a hundred gram scale yielding the product in 96% yield and 99% *ee*.

Catalytic Reactions Mediated by Organometallic Complexes on Propargylic Alcohols

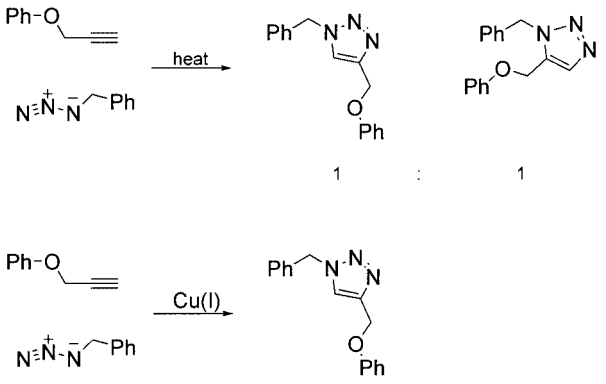
In general, propargylic alcohols can be considered as surrogates for aldols provided that a chemo- and regioselective insertion of a carbonyl group into the alkyne carbon atom β to the alcohol can be achieved. Available methods for the synthesis of optically active secondary or tertiary propargylic alcohols as discussed previously make this strategy an interesting opportunity for the selective introduction of aldol fragments into a synthetic strategy. Trost developed a ruthenium-catalyzed hydrosilylation that allows the regioselective functionalization of propargylic alcohols.[81] The reaction is performed in the presence of catalytic amounts of $[Cp^*Ru(NCCH_3)_3]^+ PF_6^-$ (Scheme 13). Benzyldimethylsilane was used as the hydrosilylating agent and allows a variety of subsequent reactions. Oxidative removal of the silane group was carried out in a one-pot procedure with hydrogen peroxide and tetrabutylammonium fluoride.

This method could be applied to the diastereoselective addition of acetylene to chiral aldehydes affording the chelation controlled or Felkin−Anh products. Yoshida and Ihara used propargylic carbonate, readily obtained from propargylic alcohols, in a novel palladium-catalyzed cascade reaction.[82] The propargylic carbonate reacts with phenols to give a phenoxy-substituted cyclic carbonate under CO_2 evolution. The versatile alkyne functionality makes transition metal-catalyzed propargyl etherification an attractive method for the formation of sp^3 C−O bonds.[83]

Acetylenes in Click Chemistry

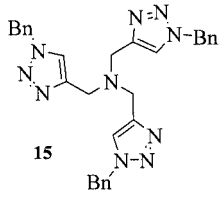
Click chemistry is a modular approach that uses only the most practical and reliable chemical transformations. Huisgen's 1,3-dipolar cycloaddition reaction between alkynes and azides is one of the prototype reactions in click chemistry and is considered as "cream of the crop" by Sharpless.[84] The reaction is highly chemoselective affording only the desired 1,2,3-triazole even in the presence of a large variety of other functional groups. In addition, the reaction is high yielding and can be carried out in water (Scheme 14).

Azides and alkynes are among the least reactive functional groups and normally require prolonged heating to



Scheme 14

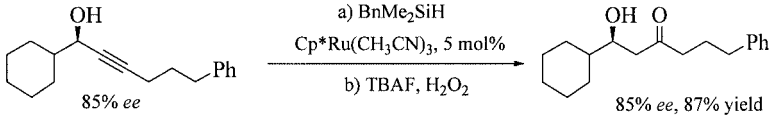
form the cycloaddition product. Two different approaches were developed by Sharpless that can dramatically accelerate the rate of the cycloaddition reaction. By using the catalytic site of Acetylcholine esterase (AChE) as the "reaction vessel", the cycloaddition took place at room temperature and a femtomolar inhibitor of the enzyme was identified in situ.[85] Tornøe and Sharpless independently reported a copper(I)-catalyzed version of the [3+2] addition in which the 1,4-regioisomer is exclusively formed and which also allows the rapid synthesis of compound libraries.[86] Since copper(I) has a high tendency to disproportionate, the reaction needs to be carried out either in the presence of a reducing agent such as ascorbic acid or in the presence of a suitable ligand that can stabilize the copper(I) oxidation state in water and under air. Such a ligand **15** was developed by utilizing the click chemistry approach: a number of different ligands were synthesized via [3+2] addition between acetylenes and azides and screened for the ability to stabilize Cu^I (Figure 10).[87]



15

Figure 10. Copper(I) stabilizing ligand

Ligand **15** was successfully applied for a new bioconjugation strategy, which benefited from the exceptionally high orthogonality and robustness of the cycloaddition reaction that can even be carried out in living organisms. Applications range from virus,[88] cell,[89] and protein labeling,[90] in vivo activity based protein profiling[91] to DNA labeling.[92]



Scheme 13

Conclusion and Outlook

In summary, acetylenes have gained increasingly more recognition as a promising class of compounds both in the area of asymmetric catalysis as well as in other applications. Numerous novel metal catalysts and chiral ligands have been developed for the enantioselective addition of acetylenes to aldehydes, ketones and imines over the past years. New catalyst systems have been identified that allow the use of milder and environmentally more friendly reaction conditions. Further optimizations have resulted in higher enantioselectivities and improved tolerance for other functional groups present. However, several of those methods still have limitations, e.g. specific orders for the addition of reagents, restricted substrate scope and the absence of ligands with a broader range of application. In addition to the use of acetylenes in enantioselective reactions, they have proven to be key intermediates in a broad spectrum of applications. Propargylic alcohols can be considered as surrogates for aldols. Click chemistry is a powerful tool in biomedical research, ranging from combinatorial chemistry for lead discovery, to bioconjugation strategies for proteomics and DNA research. After the completion of the review, a number of papers appeared in the 2004 literature which are relevant to these topics.[93−107]

Acknowledgments

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