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The Discovery of Novel Reactivity in the Development of C−C Bond-Forming Reactions: In Situ Generation of Zinc Acetylides with Zn^{II}/R_3N

D. E. FRANTZ, R. FÄSSLER,
C. S. TOMOOKA, AND E. M. CARREIRA*
Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, Zürich, Switzerland

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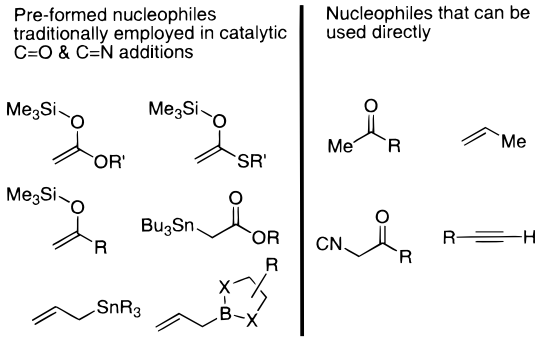
ABSTRACT

There have been great strides in expanding the scope, application, and versatility of known reaction types (i.e., Mukaiyama aldol). It is interesting to speculate that limitations in the number of such known basic reaction types constitute the greatest barrier in the development of practical processes. The catalytic generation of transition-metal metalloenolates and alkynilides under conditions compatible with electrophilic reaction partners provides fresh avenues for the development of new efficient asymmetric processes leading to C−C bond formation.

Introduction

The addition reactions of nucleophiles and aldehydes, ketones, or C═N electrophiles are important processes in organic synthesis.[1] Such addition reactions are intrinsically efficient in the production of useful building blocks, as a new stereogenic center and a new carbon−carbon bond are established in a single operation. The most commonly employed catalytic, asymmetric carbonyl and imine addition reactions generally rely on a tried-and-tested set of nucleophilic reactants such as enolsilanes (i.e., aldol additions[2] and hetero-Diels−Alder cycloadditions[3]), allylstannanes, -silanes, or -boranes (allylation),[4] and dialkylzinc reagents.[5] These processes have proven remarkably effective and enjoy a broad range of applications in the context of complex molecule construction. Several aspects of these processes, however, can detract from their utility and efficiency.[6] First, in most of the processes the prescribed starting nucleophile, such as enol silanes, is not commercially available, and thus preparative applications of these reactions necessitate their synthesis as a separate step (Chart 1). Moreover, such nucleophiles are often not amenable to prolonged storage and must be utilized shortly after preparation. Second, those nucleophilic reagents that may be purchased either are pyrophoric (Me_2Zn) or include organoelement moieties (Sn) with adverse effects on the environment. Third, because the ultimate end products of a synthesis route rarely incorporate silyl, stannyl, or boryl groups, these can be superfluous. Because these groups must subsequently be removed and disposed of, processes in which they are involved are inherently lacking in atom economy.[7]

Chart 1



An increasingly important objective in our investigations in the area of asymmetric synthesis is the discovery and development of novel processes that utilize readily available nucleophilic starting materials that do not require prior preparation and exclude superfluous functionality. Such boundary conditions necessarily impose strict limits on the types of nucleophilic reactants that can be considered, namely, ketones, esters, alkenes, and alkynes (Chart 1). Moreover, the imposition of the boundary conditions outlined above on the starting materials restricts the reaction types that can be recruited in the development of novel processes; in this respect, reliance on traditional, commonly employed Lewis acid activation strategies may no longer suffice.

In this Account, we present some of the recent work that has been reported from our laboratories involving the identification of novel mechanistic constructs for the subsequent development of practical, asymmetric C−C bond-forming reactions. Our work on the nucleophilic activation of enol silanes by chiral bis-phosphine×e1·CuF complexes for catalytic, enantioselective aldol addition reactions led us to search for other latent nucleophiles amenable to activation toward C═O and C═N additions. This has resulted in the discovery of a novel process for

Doug E. Frantz was born in Kettering, OH (USA), in 1971. He obtained his B.S. degree from Stephen F. Austin State University in Nacogdoches, TX (1994). He received his Ph.D. from Texas A&M University under the direction of Daniel A. Singleton (1998). He subsequently carried out postdoctoral research at ETH-Zürich under the direction of Erick M. Carreira, and he is currently a research scientist at Merck Research Laboratories in Rahway, NJ.

Roger Fässler was born in Zürich, Switzerland, in 1968. He completed his apprenticeship at Givaudan-Roure Research Laboratories in Dübendorf, Switzerland, in 1987, where he remained employed until 1990. He subsequently earned a matura in 1993, following which he arrived at ETH-Zürich where he obtained his diploma in chemistry in 1999 under the direction of Armido Studer. He is currently a graduate student at the ETH-Zürich under the direction of Erick M. Carreira.

Craig S. Tomooka was born in Downey, CA (USA), in 1974. He received his B.S. degree from the University of California, Irvine, in 1996 under the direction of Harold W. Moore. He is currently a California Institute of Technology graduate student working under the direction of Erick M. Carreira at ETH-Zürich.

Erick M. Carreira was born in Havana, Cuba, in 1963. He received his B.S. degree from the University of Illinois at Urbana−Champaign working with Scott Denmark and his Ph.D. from Harvard University (1990) working under the direction of David A. Evans. After postdoctoral research at the California Institute of Technology with Peter Dervan, he joined the faculty at California Institute of Technology as an assistant professor (1992). He was promoted to associate professor in 1996, and subsequently to professor (1998). He is currently at the ETH-Zürich.

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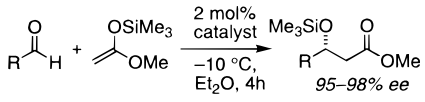
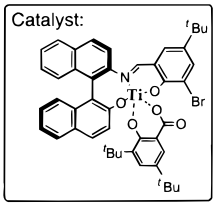
the catalytic generation of zinc acetylides under mild conditions. Although the chemistry has only been studied recently, we provide ample evidence that attests to the versatility and utility of this method in catalytic and asymmetric synthesis.

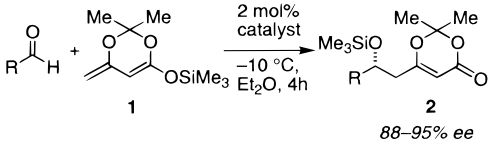
Background

In 1994, we reported a catalytic, enantioselective aldol addition reaction that affords acetate aldol and acetoacetate adducts in high yield and enantioselectivity (eqs 1 and 2).[8,9] The salient features of this process remain (1) low catalyst loads (0.2−5 mol %), (2) high enantioselectivity (up to 99.8% ee), (3) broad substrate tolerance (aliphatic, aromatic, unsaturated aldehydes), (4) ease of execution (0 °C, Et_2O, 2−6 h), and (5) availability of catalyst (two steps).



R = aliphatic, aromatic, functionalized (1)

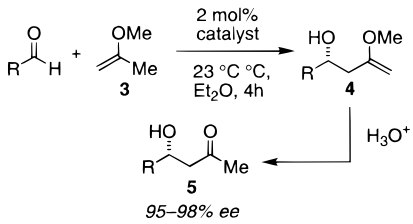




(2)

These addition reactions, along with those that have been reported by other laboratories,[2] followed the mechanistic construct, or reactivity mode, discovered, studied, and espoused by Mukaiyama in 1974.[10] The mechanistic fundamental at the core of this reaction process is the activation of the electrophilic reacting partner, most commonly the aldehyde, ketone, or imine, through its coordination to a Lewis acidic transition-metal complex.[11] The fact that the reaction involves Si atom transfer in proceeding from the starting *O*-silyl enolate to the *O*-silyl ether product allowed for its subsequent evolution and ultimate development into a myriad of catalytic asymmetric versions. The mechanistic studies and models that have been proposed by a number of researchers underscore the electrophilic activation aspect of the reaction and generally exclude interaction between enolsilane and the activated electrophilic species.[9b,12] Indeed, these reactions are often characterized as proceeding through open, extended transition states.[13]

In the context of our work on the identification and development of novel Lewis acid catalysts for the Mukiayama aldol addition reaction, we documented the catalytic, enantioselective reaction of 2-methoxypropene (**3**) in aldehyde addition reactions (eq 3).[14] In this process,

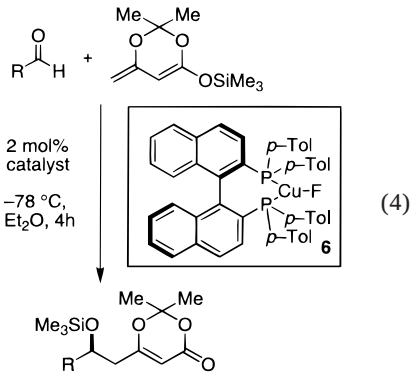


(3)

we noted that the 2-methoxypropene functioned as an enolate equivalent, which following workup could provide access to the acetone **5**, hydroxyacetone, or acetate aldol adducts. In the development of this process, we became keenly aware that the ability to use the commercially available 2-methoxypropene as the nucleophilic partner imparted a critical advantage to the process: in particular, in contrast to enolsilane nucleophiles ubiquitously employed in Mukaiyama aldol addition reactions, methoxypropene required no prior preparation in the laboratory. This aspect seemed to us particularly attractive and took special significance in our subsequent focus on the development and discovery of practical processes for catalytic C═O and C═N addition reactions. However, despite the appeal of such ready processes utilizing commercially available nucleophiles, our ability to further identify new reactivity paradigms and subsequently implement these in new processes for C−C bond formation was limited by the lack of other reactive nucleophiles for aldehyde addition reactions that met the boundary conditions we had set for ourselves. This prompted us to search for new mechanistic/reactivity modes for the development of novel, efficient C−C bond-forming reactions.

Identification of Novel Mechanistic Options

As discussed above, the majority of approaches to the asymmetric catalytic aldol addition reaction reported to date involve the use of chiral Lewis acids that activate the aldehyde component toward addition by enol silanes.[2,15,16] In contrast, the development and study of catalytic processes that recursively generate metalloenolates which participate in asymmetric addition to aldehydes has been limited.[17,18] This concept, however, has recently begun to receive increasing attention, as it offers unique opportunities for the development of catalytic C−C bond-forming reactions lacking precedence. The processes that have been reported to proceed through putative enolate−metal complexes can be categorized according to the method by which the reactive metalloenolate is produced: (1) deprotonation of a C−H acid and (2) desilylative metalation of an enol silane. Examples of the former processes have been documented with C−H acids with $pK_a < 20$.[18,19] These include the classic addition reaction of Hayashi and Ito involving isonitrileacetate esters in the presence of chiral Au·bisphosphine complexes[18b] and, more recently, the nitroalkane and ketone addition reactions mediated by Ln·binaphthoxide catalysts.[19] The catalytic generation of functional metalloenolate intermediates from enol silanes enjoys less precedence; however, several recent examples have been reported in the context of catalytic asymmetric synthesis.[20,21]



(4)

We have documented a new reaction process for the aldol addition reaction of enolsilanes and aldehydes utilizing bisphosphine·CuF (**6**), bisphosphine·CuF_2, or bisphosphine·Cu(O^tBu) as catalyst (eq 4).[21] Importantly, we have suggested that the reaction process appears to proceed through a mechanistic construct involving catalytic generation of a chiral metal dienolate initiated by the reaction of the enol silane with the transition metal fluoride or *tert*-butoxide complex.[22] The active complex is generated readily in situ under a variety of conditions upon mixing (*S*)-Tol-BINAP[23] with either Cu(OTf) or Cu-$(OTf)_2$, and $(Bu_4N)Ph_3SiF_2$ (TBAT) or Cu(O^tBu). For a range of aldehydes, the adducts are isolated in useful yields and up to 95% ee utilizing typically as little as 2 mol % catalyst. Moreover, the reaction may be conducted on a preparative multigram scale utilizing as little as 0.5 mol % catalyst without deleterious effects on the product enantiomeric excess or yields.[24] In a series of mechanistic studies, we have accumulated data that are consistent with the reaction proceeding through a metalloenolate intermediate. This work, along with the reactions reported recently by Shibasaki, contrasts with the majority of processes that have been reported to date and provides a conceptual and practical alternative to the well-established Lewis acid-promoted stereoselective aldol reactions.

Our work involving 2-methoxypropene as a useful, readily available nucleophile for aldehyde addition reactions coupled with the subsequent study of aldol addition reactions involving nucleophilic activation of enol silanes led us subsequently to search for new transformations that would constitute a hybrid of these two processes incorporating readily available nucleophiles amenable to activation in situ. As discussed above, these boundary conditions limit the selection of potential nucleophiles to most common functional group classes including nitroalkanes, ketones, alkenes, and alkynes. The in situ generation of nucleophilic enolates derived from ketones and nitro alkanes for catalytic, enantioselective aldehyde addition reactions has been documented in a series of elegant, pioneering studies by Shibasaki. The use of alkenes as reactants in ene-like addition reactions to aldehydes has been the subject of extensive studies by Mikami and Nakai,[25] and more recently by Evans,[26] both involving Lewis acid activation of the aldehyde. In contrast, the use of terminal alkynes directly in C═O and C═N addition reactions had little precedence and constitutes the area upon which we chose to focus our efforts.

Terminal Acetylenes in C═X Addition Reactions

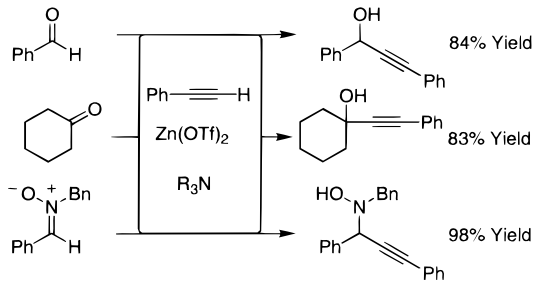
The use of metalated terminal alkynes as nucleophiles for C−C bond formation is well appreciated.[27] Metalated acetylenes participate in Pd^0-catalyzed C(sp)−C(sp) and C(sp)−C(sp^2) couplings, a transformation at the core of modern synthesis.[28] The carbanionic acetylides derived from alkali or alkaline earth metals are known to undergo additions to a wide range of electrophiles (such as aldehydes, imines, epoxides, acid chlorides) to furnish adducts of great synthetic versatility.[29] The reactive alkynilides that are generally utilized, however, are commonly prepared from a terminal alkyne and strong bases such as carbanions (BuLi,[30] EtMgBr,[31] Me_2Zn[32]), metalated amides (KHMDS, LDA, Et_2NLi), alkoxides (potassium *tert*-butoxide), and hydroxides (KOH, CsOH).[33] Because the electrophiles used in combination with metalated terminal alkynes are incompatible with the strong bases that have been traditionally utilized in the generation of the corresponding acetylide, in general, alkyne deprotonation must be necessarily carried out as a separate step. We surmised that the ability to carry out nucleophilic additions of terminal alkynes to C═O or C═N without the use of such pyrophoric, stoichiometric bases would lead to great simplification of the processes. The successful implementation of such a concept, however, demanded that we identify a mild process for the in situ generation of metal acetylides that would participate in reactions involving nucleophilic addition to C═O and C═N electrophiles.

Our initial exploration into this area looked to the known chemistry of Cu(I) or Ag(I) salts and acetylenes in the presence of amine bases. It is generally accepted that complexation of terminal acetylenes with Cu(I) or Ag(I) yields π-complexes. These complexes labilize the terminal C(sp)−H so that even weakly basic amines can effect deprotonation with concomitant generation of the corresponding metal alkynilide.[34] Although the use of such copper acetylides in Pd-mediated coupling reactions is well precedented (for example, Sonogashira, Eglington, Glaser, and Cadiot−Chodkiewicz coupling reactions), the ability of copper acetylides generated under such conditions to participate in additions to aldehydes as a general method has not been documented.[35] Following an expanded screening of metal salts, we observed that Zn-$(OTf)_2$ in combination with tertiary amine bases leads to the generation of the corresponding zinc acetylide. Importantly, unlike acetylides derived from Cu(I) or Ag(I), zinc acetylides were observed to add to aldehydes, ketones, and nitrones (Scheme 1).

A number of spectroscopic observations (^1H and ^{13}C NMR along with IR) are consistent with the hypothesis we have posited that, in the presence of $Zn(OTf)_2$ and amine bases, a zinc alkynilide is formed in situ in analogy to the known chemistry of terminal alkynes with Cu(I) or Ag(I) salts (eq 5). For example, in ^{13}C NMR spectroscopic

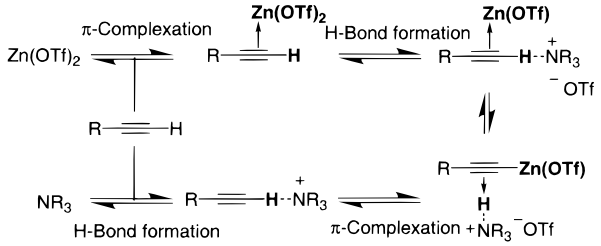
$$RC{\equiv}C{-}H \xrightarrow[R_3N]{Zn(OTf)_2} \begin{matrix} RC{\equiv}C{-}Zn{-}X \\ + \\ Et_3N{\bullet}HOTf \end{matrix} \quad (5)$$

Scheme 1



studies, we have witnessed that treatment of 4-phenyl-1-butyne with $^{i}Pr_2NEt$ and $Zn(OTf)_2$ at 23 °C leads to large, characteristic shifts of the resonances corresponding to the sp-hybridized carbons.[36] Particularly compelling evidence for the in situ formation of a zinc acetylide was found through a series of experiments involving infrared spectroscopy. Thus, we have observed that, for a broad range of acetylenes, treatment with base (Et_3N, $^{i}Pr_2NEt$, *N*-methylmorpholine, 1,2,2,6,6-pentamethylpiperidine) and $Zn(OTf)_2$ leads to complete disappearance of the C−H stretch (3275 cm^{-1}) within 2−5 min. We have also demonstrated that the metalation process is reversible. Thus, following the observed disappearance of the acetylene C−H resonance, when the same mixture was treated with triflic acid, resurgence of the IR signal corresponding to the C−H stretch of the terminal acetylene was observed. Collectively these experiments are consistent with the mechanistic scheme we have proposed as a working model wherein a zinc acetylide is generated in situ. It is interesting to speculate that the formation of the zinc acetylide may proceed through a hydrogen-bonded σ-complex which undergoes tautomerization to the hydrogen-bonded π-complex (Scheme 2). In this regard, ample

Scheme 2

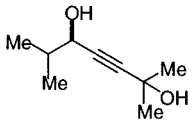
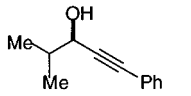
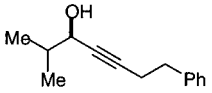
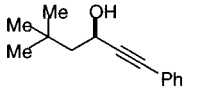
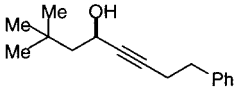
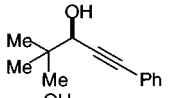
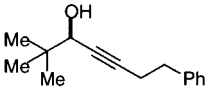
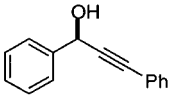
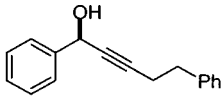
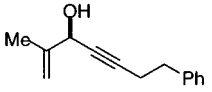
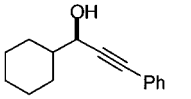
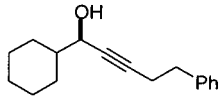
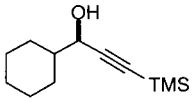
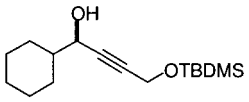
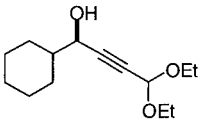
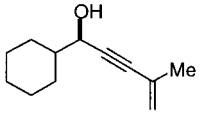
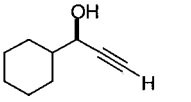


precedence may be found for such hydrogen-bonded structures involving acetylenes as H-bond acceptors and H-bond donors.[37]

Asymmetric Addition of Zinc Acetylides to Aldehydes

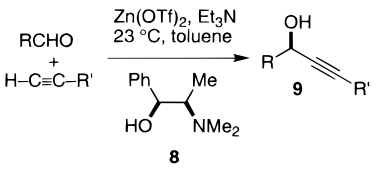
Having identified a mild, new method that allows the in situ catalytic generation of reactive zinc acetylides, we proceeded to examine whether such a process could be successfully employed in practical and useful asymmetric additions to C═O and C═N electrophiles. We first focused on enantioselective additions of terminal acetylenes to aldehydes to furnish propargylic alcohols. The methodologies which have been devised for the asymmetric

Table 1. Enantioselective Aldehyde Additions

Entry	Propargyl Alcohol	Yield	ee
1		97%	98%
2		95%	90%
3		90%	99%
4		90%	97%
5		72%	99%
6		99%	94%
7		84%	99%
8		53%	94%
9		52%	96%
10		35%	92%
11		99%	96%
12		98%	99%
13		93%	98%
14		83%	98%
15		90%	98%
16		94%	98%
17		70%	98%

synthesis of optically active propargylic alcohols involve either nucleophilic addition of metalated acetylenes to aldehydes or ynone reduction.[38−42] Catalytic, enantioselective ynone reduction methods have been reported by Noyori and Corey employing chiral ruthenium complexes and oxazaborolidines as catalysts, respectively. The second general approach is exemplified by the oxazaborolidine-catalyzed enantioselective addition of alkynylboranes to aldehydes.[43] The latter method can have an intrinsic synthetic advantage over ynone reduction methods.[44] This can be appreciated when it is considered that in the latter reaction a new C−C bond is formed with concomitant generation of a stereogenic center in a single transformation, whereas in the former process the C−C bond and the stereogenic center are formed separately.

We have observed that aldehyde addition reactions can be conducted in the presence of optically active amino alcohols to give adducts enantioselectively. Of those ligands screened, *N*-methylephedrine (≈$3/g) has proven most effective.[45] Thus, in the presence of $Zn(OTf)_2$, amine base, and (+)-*N*-methylephedrine (**8**) terminal acetylenes are observed to undergo additions to aldehydes, furnishing adducts **9** in up to 99% ee in good yields (eq 6, Table 1).[46] As can be appreciated from the examples shown, the Zn-



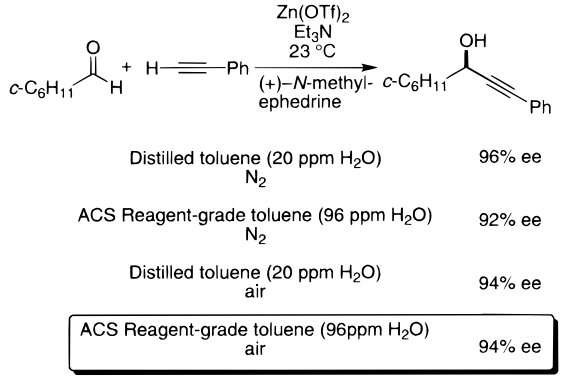
(6)

(II)-mediated reaction displays much tolerance toward functionality in both the starting aldehyde and alkyne. Importantly, following completion of the reaction, simple aqueous extraction allows the separation of (+)-*N*-methylephedrine ligand from the desired adducts and subsequent recovery for reuse.

We have investigated the effect of various experimental parameters, such as substrate concentration, solvent, solvent quality, and the presence of air, on the product selectivity and yield. Over the 10-fold range of aldehyde concentrations (0.1−1.0 M) that we have investigated, the optical purity of the adducts remains unchanged. Interestingly, the use of CH_2Cl_2 instead of toluene results in only small decreases (2%) in enantioselectivity; however, the use of THF leads to diminution of the optical purity of the adducts by 10−15%. Additional experiments have revealed that the enantioselective aldehyde reaction is tolerant of moisture and oxygen, allowing the additions to be conducted with reagent grade solvent (≈300 ppm H_2O) under an atmosphere of air (Scheme 3). The fact that the reaction does not need to be conducted under inert atmosphere is a feature that sharply contrasts the reaction conditions typically prescribed in enantioselective organozinc additions to aldehydes. The pyrophoric nature of the organozinc reagents (i.e., Me_2Zn, Et_2Zn) utilized in such additions precludes exposure to oxygen or moisture.[47]

We anticipate that additional studies should provide important insight into the structure of the reactive species

Scheme 3

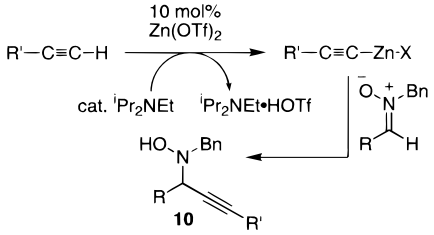


and pertinent intermediates that will lead to the development into a catalytic process.[48] The fact that reactive metal acetylide complexes can be generated under mild conditions and that these participate in enantioselective additions in the presence of inexpensive ligands offers new opportunities for the development of other useful asymmetric processes, such as epoxide opening, conjugate additions, and imine additions.

Catalytic Acetylide Additions to *N*-Benzyl Nitrones

Addition reactions of carbanions to C═N electrophiles can be an efficient, practical route to optically active propargylic amines and their derivatives. In an effort to investigate new electrophile classes for C═N bond additions, we have examined nitrones. There are some unique aspects of nitrones and their adducts that have captivated our attention: (1) nitrones are trivially prepared (RCHO + RNHOH); (2) nitrones are typically crystalline materials which are stable and easily purified; and (3) the propargylic hydroxylamine adducts provide entry to a large number of useful, versatile synthetic building blocks, including amines, amino ketones, amino acids, and isoxazolines.[49] Moreover, in comparison to aldehydes and aldimines, the use of nitrones as electrophiles in catalytic C−C bond-forming processes has not been extensively investigated.[50]

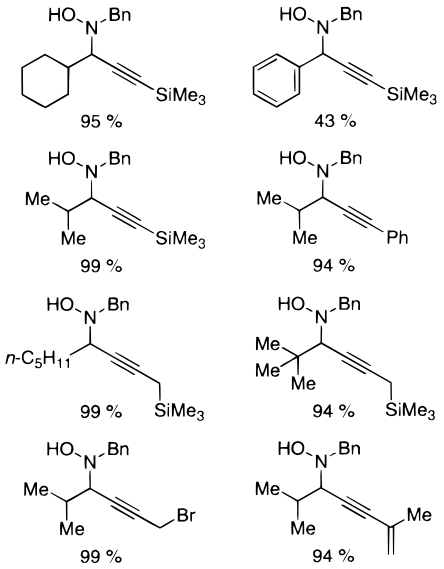
We have observed that the combination of $Zn(OTf)_2$ and a tertiary amine base allows for the rapid addition of terminal acetylenes to *N*-benzyl nitrones at room temperature. Upon further study and optimization of the



(7)

reaction conditions, we realized that the reaction proceeds quite well with catalytic amounts of $Zn(OTf)_2$ and amine base to afford *N*-hydroxylamine adducts **10** in preparatively useful yields (up to 99%) (eq 7 and Chart 2).[51] As

Chart 2



shown in Chart 2 and Figure 1, the addition reactions are quite general for a broad range of nitrones and terminal acetylenes.

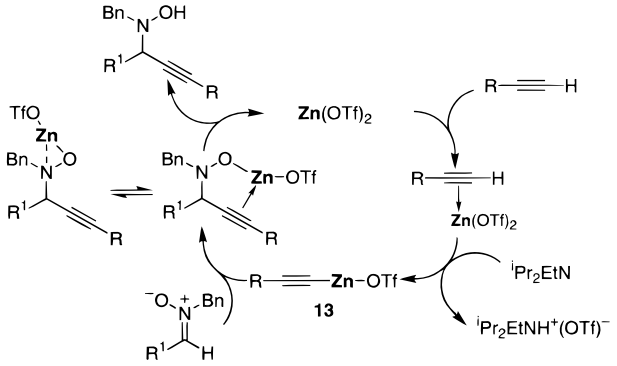
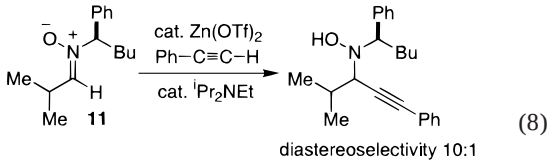


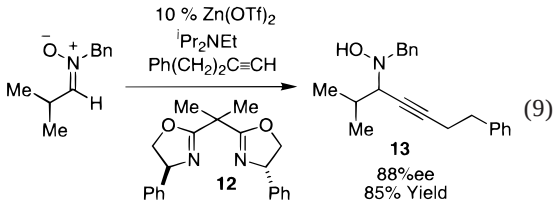
FIGURE 1. Working model for the catalytic additions of terminal acetylenes to nitrones.

The potential of this methodology in asymmetric catalytic synthesis is exemplified by experiments which suggest that the process can be diastereoselective or enantioselective through the use of a chiral auxiliary on the nitrone or a chiral ligand with Zn(II). Thus, for example, the addition of $^{i}Pr_3SiC{\equiv}C{-}H$ to nitrone **11**, prepared from isobutyraldehyde and (±)-4-phenyl-4-(*N*-hydroxylamino)butane, afforded adducts as an 88:12 mixture of diastereomers (eq 8).[52] In a complementary fashion, the addition of 4-phenylbutyne to *C*-isopropyl *N*-benzyl nitrone in the presence of catalytic amounts of $Zn(OTf)_2$ and chiral bisoxazoline **12** as a ligand for Zn(II) furnished adduct **13** in 88% ee and 85% yield (eq 9).

Although much work remains to be carried out to delineate the mechanistic details of the catalytic process, in Figure 1 we illustrate our working model. In analogy to the Ag(I) and Cu(I) chemistry we hypothesize that Zn(II) forms a π-complex with the terminal acetylene, thereby acidifying the terminal C(sp)−H bond. The amine base subsequently participates in a proton abstraction to deliver the corresponding zinc acetylide **13**. Following



(8)



(9)

addition of the metalated alkynilide, the adduct undergoes protonation by either the trialkylammonium hydrotriflate or the starting terminal acetylene to provide Zn(II).

Conclusion

We have discussed our developments in the field of asymmetric C═O and C═N addition reactions. Our initial studies involving metal-mediated activation of enol silanes to generate catalytic aldol addition reaction involving metalloenolate intermediates led to the indentification of a little-used mechanistic construct for C═O and C═N additions, namely activation of the nucleophilic component. In developing this conceptual framework further, we have identified a novel reaction chemistry of acetylenes that allows for the in situ generation of the corresponding carbanion under mild conditions. The addition reactions to aldehydes in the presence of *N*-methylephedrine were shown to be highly enantioselective and efficient. More importantly, exploratory work has revealed that the carbanionic zinc acetylide generated in situ possesses unusual, remarkable tolerance to moisture and oxygen, providing a practical and efficient method for the preparation of optically active propargylic alcohols. We have also discussed the catalytic additions to nitrones which provide useful products in the form of propargylic hydroxylamines.

Organic chemists have displayed great ingenuity in the preparation of novel reagents that expand the scope, application, and versatility of known reaction types (i.e., the Mukaiyama aldol reaction). However, it is interesting to speculate that it is the limitations in the number of such known chemical reaction types that constitute the greatest barrier in the development of truly practical reaction processes. The catalytic generation of reactive transition-metal metalloenolates and alkynilides from the corresponding terminal alkyne under conditions that are compatible with electrophilic reaction partners provides fresh avenues for the development of new, efficient asymmetric processes leading to C−C bond formation.

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