

Catalytic in Situ Generation of Zn(II)-Alkynilides under Mild Conditions: A Novel C=N Addition Process Utilizing Terminal Acetylenes

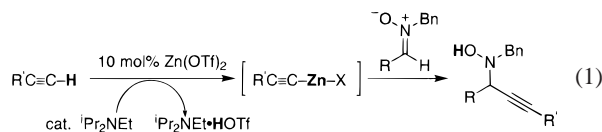
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The discovery and study of new stoichiometric and catalytic reactions that lead to C–C bond formation by additions to C=O or C=N are of fundamental importance in the continuing development of efficient processes for chemical synthesis. Metalated terminal alkynes are an ideal class of versatile nucleophiles that add to a wide range of electrophiles, affording adducts of great synthetic versatility.^{1,2} The alkynilides typically employed in such processes are commonly prepared from an acetylene and organolithium (i.e., BuLi)³ or organomagnesium bases (i.e., EtMgBr).⁴ Because the aldehydes and imines used are incompatible with such basic and nucleophilic reagents, alkyne deprotonation must necessarily be carried out as a separate step.⁵ The ability to carry out nucleophilic additions of alkynes to C=O or C=N without the use of such strong, pyrophoric, stoichiometric bases would lead to great simplification of the processes.⁶ Of greater importance, the catalytic generation of reactive transition-metal alkynilides from the corresponding terminal alkyne in situ under conditions that are compatible with electrophilic reaction partners would provide fresh avenues for the development of new, efficient asymmetric processes leading to C–C bond-formation.

In this contribution, we document our observations involving the addition of terminal alkynes to nitrones in the presence of both catalytic transition-metal and base, 10 mol % Zn(OTf)₂ in combination with 25 mol % ⁱPr₂NEt (eq 1), under mild conditions (23 °C). The reaction is observed to work well with *N*-benzyl nitrones and a broad range of terminal acetylenes including enynes, trimethylsilyl acetylene, propargyl trimethylsilane, as well as propargyl bromide.



When compared to other hydrocarbons, the C–H bond of a terminal acetylene is unique in its kinetic and thermodynamic

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(6) (a) For the addition of terminal acetylenes to ketones mediated by 10–20 mol % KO^tBu in DMSO, see: Babler, J. H.; Liptak, V. P.; Phan, N. J. *Org. Chem.* **1996**, *61*, 416. (b) During the preparation of this manuscript, an important, novel process was reported for the addition of terminal acetylenes to aliphatic aldehydes and ketones utilizing 10 mol % CsOH in DMSO, see: Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463.

acidity.¹ In this regard, the deprotonation of 1-alkynes with RLi, RMgBr, or LiNⁱPr₂ is rapid and quantitative; additionally, alkali metal alkoxides and hydroxides are sufficiently basic to effect deprotonation.⁶ The complexation of alkynes with metals, such as Cu(I) and Ag(I), yields π -complexes with further labilization of the terminal C–H such that even weakly basic amines can effect deprotonation with concomitant generation of the corresponding Cu or Ag alkynilide.⁷ Such phenomena have long been appreciated to provide ready access to copper acetylides that can subsequently participate in C–C bond forming processes such as the Castro–Stephens, Eglinton, Cadiot–Chodkiewicz, and Sonogashira coupling reactions.⁸ An interesting dichotomy in the reactivity of metal acetylides exists: transition-metal alkynilides which can be trivially generated under mild, catalytic conditions (RC≡C–H + Cu(I) + Et₃N, 23 °C), in general, fail to participate in nucleophilic C=O or C=N addition reactions. In contrast, alkali and alkaline earth metal acetylides, typically prepared with stoichiometric BuLi or EtMgBr, readily participate in such processes. Recently, we have been studying catalytic C–C bond-forming processes that proceed by activation of nucleophiles as opposed to the more commonly employed strategy of electrophilic activation.⁹ In this context, we have been interested in developing methods that lead to the generation of metal alkynilides directly from terminal acetylenes under conditions that parallel those involving Ag(I) or Cu(I) in simplicity and mildness (Et₃N, 23 °C) but that can subsequently be utilized in catalytic nucleophilic C=O and C=N addition reactions.

In our preliminary investigations, we have chosen to examine the feasibility of carrying out catalytic acetylide additions to nitrones to give propargyl hydroxylamines. In contrast to other C=N electrophiles such as aldimines, there are some unique aspects of nitrones and their adducts that have captivated our attention: (1) nitrone preparation is trivial; (2) nitrones are typically crystalline materials which are stable and easily purified; (3) the propargyl hydroxylamine adducts provide entry to a large number of useful, versatile synthetic building blocks including amines, amino ketones, amino acids, and isoxazolines, as documented in the literature.¹⁰ 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.¹¹

Treatment of several terminal alkynes with Cu(I) salts (CuX; X = Cl, Br, I, OTf) and various tertiary amine bases afforded quantitative formation of the Cu-acetylides, as expected. However,

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
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(9) For recent mechanistic investigations in aldol addition reactions involving nucleophilic activation, see: (a) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124. (b) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.

(10) (a) Dagoneau, C.; Denis, J.-N.; Vallée, Y. *Synlett* **1999**, 602. (b) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 5627. (c) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1759. (d) Merino, P.; Anoro, S.; Castillo, E.; Merchan, F.; Tejero, T. *Tetrahedron: Asymmetry* **1996**, *7*, 18887.

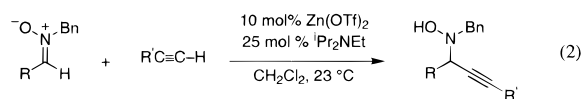
(11) For a recent report of the addition of silyl ketene acetals to nitrones, see: (a) Ohtake, H.; Imada, Y.; Murahashi, S. I. *J. Org. Chem.* **1999**, *64*, 3790. For highly diastereoselective additions to chiral ketimines, see: (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) Liu, G.; Cogan, D.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (d) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (e) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.

Table 1. Alkyne Additions to Nitrones

Entry	Nitrone	Alkyne	Time	Yield
1	<i>c</i> -C ₆ H ₁₁	Me ₃ SiC≡C-H	12h	95%
2	Ph	Me ₃ SiC≡C-H	24h	43%
3	C ₃ H ₁₁	Me ₃ SiC≡C-H	12h	62%
4		Me ₃ SiCH ₂ C≡C-H	12h	90%
5	^t Bu	Me ₃ SiCH ₂ C≡C-H	12h	67%
6	Me ₂ CH	Me ₃ SiC≡C-H	12h	99%
7		BuC≡C-H	3h	95%
8		Ph(CH ₂) ₂ C≡C-H	3h	96%
9		TBSOCH ₂ C≡C-H	6h	85%
10		PhC≡C-H	1h	94%
11		^t BuC≡C-H	1h	93%
12		BrCH ₂ C≡C-H	3h	68%
13			3h	85%

all attempts to induce these to add to nitrones were unsuccessful.¹² Similar lack of reactivity was observed with metal salts such as Mg(OTf)₂, Mn(OTf)₂, ZnCl₂, or ZnI₂. Marginal success was accomplished utilizing Sn(OTf)₂, in accordance with the work of Yamaguchi with aldehydes, where a large excess of Sn(II), alkyne, and amine base (3–5 equiv each) were required for addition.¹³ In subsequent investigations, we were pleased to observe that the use of Zn(OTf)₂ and ^tPr₂NEt leads to product formation.

When a solution of a terminal acetylene and nitrone (0.25 M in CH₂Cl₂)¹⁴ is treated with 10 mol % of Zn(OTf)₂ and 25 mol % Hünig's base at 23 °C, propargyl *N*-hydroxylamine adducts are isolated in 1–24 h in preparatively useful yields (up to 99%) (eq 2 and Table 1). A survey of amine bases (Et₃N, Bu₃N, ^tPr₂-



NH, C₅H₅N, and piperidine) revealed that the optimal yield of the propargyl hydroxylamine adducts was obtained with Hünig's base. The process possesses remarkably wide substrate scope for both starting nitrone and alkyne. In general, nitrones derived from aliphatic aldehydes are more reactive than the corresponding aromatic counterparts, as has been observed in prior studies involving stoichiometric additions.¹⁵

The additions we describe are simple to conduct in the laboratory with the Zn(OTf)₂, Hünig's base, and CH₂Cl₂ used as received from commercial sources. The fact that a wide range of

(12) Under harsh conditions, in the presence of CuI, dppe, K₂CO₃, and H₂O in DMF at 80 °C, the addition of acetylenes to nitrones has been reported to give alkynyl imines in a reaction that may proceed through the initial formation of a dipolar cycloadduct. The acetylenes and nitrone substrates examined in the study were primarily derived from aromatic aldehydes and aryl alkynes, see: Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

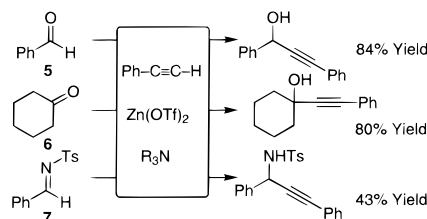
(13) Yamaguchi, M.; Hayashi, A.; Minami, T. *J. Org. Chem.* **1991**, *56*, 4091.

(14) We have also observed that the addition reaction can be conducted in acetonitrile solvent.

(15) Denis, J.-N.; Tchertchian, S.; Tomassini, A.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 5503.

(16) Similar large downfield shifts for the acetylenic carbons of alkynyl alkyzincs has been reported, see: Koning, A. J.; Van Rijn, P. E.; Boersma, J.; Van Der Kerk, G. J. M. *J. Organomet. Chem.* **1979**, *174*, 129.

(17) For a leading reference to enantioselective additions of stoichiometric Zn-acetylides to aldehydes and ketones utilizing chiral amino alcohol-based ligands, see: Tan, L. S.; Cheng, C. Y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711

Scheme 1

alkynes can be utilized offers access to products possessing great versatility for subsequent synthetic elaboration. The process contrasts the existing more conventional methods for nucleophilic additions which require generation of the alkynilide by treatment with strong bases. In this regard, the direct addition of propargyl bromide (entry 11) would not be possible utilizing such protocols (RLi, RMgBr, or MOH).

The mechanistic details of the process we have described are currently under scrutiny in order to determine the nature of the reactive species involved. On the basis of a number of experimental observations, our current hypothesis is that a zinc alkynilide is formed *in situ* in analogy to the known chemistry of terminal alkynes and Cu(I) or Ag(I) salts in the presence of amine bases. In support of this postulate, in ¹³C NMR spectroscopic studies, we have witnessed that treatment of 4-phenyl-1-butyne with ^tPr₂NEt and Zn(OTf)₂ at 23 °C leads to large, characteristic shifts of the resonances corresponding to the sp-hybridized carbons.¹⁶ The fact that we have not observed reactions in the presence of other Lewis acids argues against a Lewis-acid accelerated dipolar cycloaddition or a Prins-like reaction.

Additional studies suggest that the process is not limited to nitrones, with aldehydes **5**, ketones **6**, and *N*-tosyl aldimines **7** serving as electrophiles to give propargyl alcohols and amines (Scheme 1). Moreover, the potential of this reaction is further illustrated by preliminary 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).¹⁷ Thus, the addition of ^tPr₃SiC≡CH to the chiral nitrone derived from 4-phenyl-4-hydroxylaminobutane and isobutyraldehyde affords the corresponding adducts in 88:12 diastereoselectivity. Moreover, when the addition of phenyl acetylene to *C*-cyclohexyl *N*-benzyl nitrone (see nitrone in entry 1, Table 1) was carried out in the presence of (+)-*N*-methyl-pseudoephedrine the adduct was isolated in 60% ee and 88% yield.

In summary, we have reported a novel Zn(II)-catalyzed process for the addition of terminal acetylenes to *N*-benzyl nitrones that obviates prior stoichiometric generation of the alkynilide. The reaction process affords propargyl hydroxylamine adducts in good yields under mild conditions in CH₂Cl₂ at 23 °C, with the reagents and solvents conveniently utilized as received from commercial sources. The addition reaction is observed to work well with a broad range of terminal acetylenes including functionalized acetylenes (TBSOCH₂C≡CH, trimethylsilyl acetylene, propargyl trimethylsilane, and propargyl bromide). In our working model, we postulate that the process proceeds through the intermediacy of a Zn(II)-alkynilide. The catalytic generation of a transition-metal acetylde that is reactive toward C=O and C=N electrophiles under mild conditions is novel and provides avenues for the subsequent further development of efficient asymmetric, catalytic C–C bond-formation.

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Supporting Information Available: Experimental details and characterization for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.