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Direct Addition of TMS-acetylene to Aldimines Catalyzed by a Simple, Commercially Available Ir(I) Complex

Christian Fischer and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH-Hönggerberg,
CH-8093 Zürich, Switzerland

carreira@org.chem.ethz.ch

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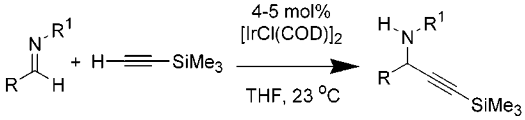
ABSTRACT



A new, convenient procedure for the addition reaction of trimethylsilylacetylene to imines is described. Simply treating a solution of aldimine and trimethylsilyl acetylene with catalytic [IrCl(COD)]$_2$ furnishes the adduct in preparatively useful yields. Interestingly, the reaction may be conducted in the absence of solvent.

Propargylic amines, like the corresponding propargylic alcohols, can serve as important building blocks for organic synthesis.[1,2] However, while propargylic alcohols can be prepared through a variety of transformations,[3−5] in general, reliable methods that provide access to propargylic amines are far fewer.[6−9] Carbanion addition to *N*-alkyl aldimines typically prescribe the use of Lewis acidic additives (i.e., $BF_3{\cdot}OEt_2$) as a means of activating the aldimine substrate. By contrast, reactions of *N*-acyl, *N*-sulfonyl, or *N*-aryl aldimines proceed without necessary additional activation. In either case, to date, imine addition reactions typically require the use of stoichiometric quantities of alkali, alkaline earth, or transition metal carbanions, or alternatively organoboranes, -silanes, or -stannanes. Herein, we report a novel process that is considerably simplified over previously documented $C{=}N$ addition reactions, proceeding at room temperature and requiring only *N*-alkyl or *N*-aryl aldimines,

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(4) Catalytic methods: (a) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938. (b) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(5) For the addition of lithium and magnesium acetylides to trifluoromethyl aryl ketones, see: (a) Tan, L.; Chen, C.-Y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 711. (b) For a recent report on the addition of aromatic aldehydes with alkynylzinc reagents generated in situ from terminal acetylenes and dimethylzinc, see: Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1999**, 1453. (c) For a recent study of chelation-controlled stannylacetylene additions to aldehydes, see: Evans, D. A.; Halstead, D. P.; Allison, B. D. *Tetrahedron Lett.* **1999**, *40*, 4461.

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(7) For Cu-mediated addition of terminal acetylenes to *N*-alkyl imines at elavated temperatures, see: Rohm and Haas Co. U.S. Patent 2,665,311, 1950.

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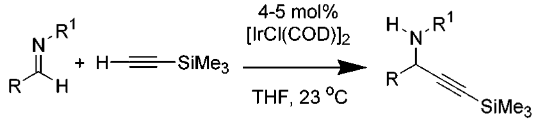
trimethylsilylacetylene, and catalytic amounts (4−5 mol %) of $[IrCl(COD)]_2$ (Scheme 1). Importantly, it is worth noting that the Ir(I) catalyst is a commercially available, air-stable, and easily handled complex; moreover, the additions can be carried out in the absence of solvent, providing for a highly atom-economical process.

Scheme 1

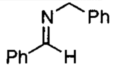
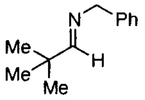
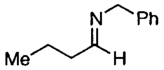
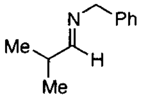
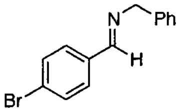
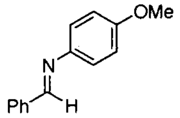


We have been interested in the development of practical C−C bond-forming reactions involving Zn-acetylides wherein the combination of amine and Zn(II) synergistically effect the in situ generation of reactive alkynilides.[10] In principle, the use of the amine is superfluous, as the transformation involves net atom-transfer of the acetylene proton to the product heteroatom. Consequently, we sought to identify a metal complex that would insert into the terminal acetylene C−H to serve formally as the repository of the proton and alkynilide fragments and, importantly, subsequently possesses suitable reactivity to undergo addition to imines.[11]

Late transition-metal σ-bound alkynilides enjoy a rich, diverse coordination and reaction chemistry.[12,13] Typically, these species serve as precursors to metal vinylidenes or allenylidenes that participate in oligomerization[14,15] or ring-closing metathesis.[16] However, such alkynilides have not been used in nucleophilic addition reactions with C═X electrophiles of use for fine chemicals synthesis.[12]

An initial screening of transition-metal complexes known to form metal acetylides led us to identify $[IrCl(COD)]_2$ as unique in its extraordinary ability to catalyze the addition of trimethylsilylacetylene to aldimines at room temperature. As shown in Scheme 1 and Table 1 (entries 1−5), *N*-benzyl aldimines derived from aromatic as well as aliphatic aldehydes participate in the Ir-catalyzed addition reaction. With the latter class of substrates, it should be noted that unbranched (entry 3), along with branched (entries 2 and 4), aldimines work well. As shown in entry 6, an aldimine prepared from *p*-methoxyaniline is also a substrate. The use of such imines has recently received attention, because *N*-aryl protecting groups are readily oxidatively cleaved.[17] We have, nonetheless, focused on the use of *N*-benzyl-derived aldimines, as the resultant protected amines are more convenient intermediates for synthesis.

Table 1. Addition Reaction of $Me_3SiC≡C−H$ to Aldimines[a]

entry	substrate	yield
1		76 %
2		84 %
3		69 %
4		65 %[b]
5		54 %
6		85 %

[a] In a typical reaction, 1.5 equiv of $Me_3SiC≡CH$ and aldimine are sequentially added to 5 mol % of $[IrCl(COD)]_2$ in THF at 23 °C and stirred for 24 h. [b] Reaction time is 36 h, and 2.0 equiv of acetylene was used.

The efficiency and practicality of the process is demonstrated by a series of addition reactions, which we have carried out under solvent-free conditions (Scheme 2). Thus, when a suspension of the Ir(I) complex in neat *N*-benzyl aldimine is treated with trimethylsilylacetylene, adducts are formed cleanly in preparatively useful yields (69−85%).

We have made a few observations in the course of the preliminary study that are worth noting as they suggest further avenues to pursue. First, at elevated temperatures (60 °C) the yield drops significantly (48% for the benzaldehyde derived *N*-benzylimine). When the reaction components are heated to 120 °C, no adduct was observed and the imine

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(10) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245. (b) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (c) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. (d) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233. (e) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964. (f) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611. (g) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

(11) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.

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(13) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, 2534. In this work, Ishii has reported the Ir-catalyzed synthesis of imines by the coupling of aldehydes, amines, and alkynes. It should be noted that at the end of this manuscript the authors describe a "failed" reaction in which a byproduct is isolated in an unspecified yield that corresponds to the adduct of acetylene plus aldimine. Although it is not the focus of the study, this process may be related to the one that we independently describe herein.

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(15) Ohmura, T.; Yorozuya, S.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2000**, *19*, 365.

(16) (a) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 1315. (b) Picquet, M.; Touchard, D.; Bruneau, C.; Dixneuf, P. H. *New. J. Chem.* **1999**, *23*, 141. (c) Saoud, M.; Romerosa, A.; Peruzzini, M. *Organometallics* **2000**, *19*, 4005.

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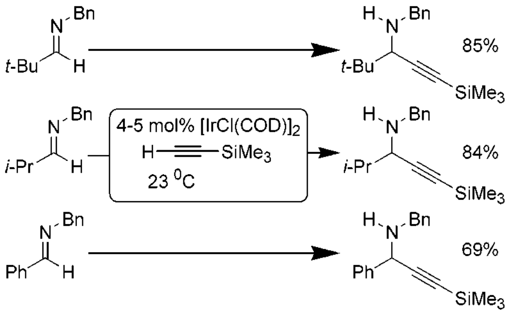
Scheme 2



can be recovered unchanged. These observations are consistent with the known oligomerization chemistry of acetylenes in the presence of Ir(I) at elevated temperatures.[18,19] Second, the use of *N*-*p*-methoxyphenyl-derived aldimine leads to enhanced rates. Third, to date only silylacetylenes, as exemplified by trimethylsilylacetylene, participate in the addition reaction. Although this may at first consideration seem limiting, the use of silylacetylenes in the reaction provides wide leeway in the subsequent functionalization of the adducts. In this respect, numerous mild methods may be employed for the desilylation of silylacetylenes to furnish terminal acetylenes that are themselves substrates for subsequent elaboration, such as alkylation, carboxylation, Zn-catalyzed aldehyde additions, and Cu- and Pd-mediated processes.[20] Thus, the use of silylacetylene, itself an item of commerce, furnishes useful propargylamine adducts that are the synthetic equivalent of C_2H_2 addition reactions to aldimines. Finally, the addition reactions can be conducted in the presence of added phosphines with a range of effects. Thus, for example, while in the presence of triphenylphosphine no product formation is observed after 2 days under otherwise identical conditions to that reported above, the presence of tri-*tert*-butylphosphine leads to rate acceleration. Such ligand-dependent phenomena will certainly be useful in the subsequent identification and study of asymmetric processes.

We have documented a novel process involving the direct addition of TMS-acetylene to aldimines which is convenient and remarkably simple. The propargylic amines are formed at room temperature, with the addition reaction requiring catalytic [IrCl(COD)]$_2$, itself a commercially available, stable, and easily handled complex. Additionally it can be carried out in the absence of solvent, providing for a highly atom-economical process. In the broadest context, the observations we have described provide new opportunities for the development of synthetically useful transition-metal mediated C−C bond-forming reactions involving activation of simple hydrocarbons at room temperature to provide access to versatile building blocks for chemical synthesis.

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

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[18] At 0 °C the reaction does not proceed; however upon warming the same reaction mixture to room temperature, product formation can be observed.

[19] See for example: Takeuchi, R.; Tanaka, S.; Nakaya, Y. *Tetrahedron Lett.* **2001**, *42*, 2991.

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