

Zn-Alkynylide Additions to Acyl
Iminiums

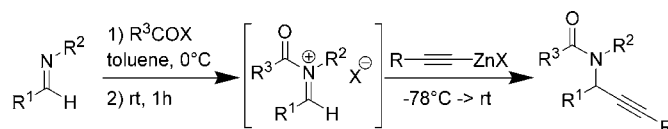
Christian Fischer and Erick M. Carreira*

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

carreira@org.chem.ethz.ch

Received March 7, 2004

ABSTRACT



A new addition reaction of zinc-alkynylides to *N*-acyl and *N*-phosphinoyl iminiums is reported. These can be prepared in situ from imines with acid halides in the presence of a Zn-acetylide. The reaction is general with regard to imine, alkyne, and acid halides, allowing access to a large number of differentially protected propargylic amines.

Propargylic amines, like the corresponding propargylic alcohols, can serve as high-value added intermediates and building blocks for organic synthesis.^{1,2} However, while propargylic alcohols can be conveniently prepared using a variety of synthetic transformations,^{3–5} in general, methods that provide reliable and convenient access to propargylic amines are far fewer.^{6–8} Recently, we⁹ and others¹⁰ have reported the addition reaction of terminal alkynes to imines catalytic in transition metal. Our continuing interest in the chemistry of zinc-alkynylides¹¹ prepared directly from

terminal alkynes and zinc salts with trialkylamine bases have led us to the discovery that imines activated in situ with a range of acid halides serve as reactive electrophiles toward addition by zinc-alkynylides.

There have been numerous reports on the addition reaction of 1-alkynes and imines proceeding via Zn-acetylides, generated from terminal acetylenes under the novel conditions we reported (Zn(OTf)₂, R₃N, 23 °C). In general, these

(1) (a) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410.

(2) For selected examples of the use of optically active propargylic alcohols in synthesis, see: (a) Trost, B. M.; Hipskind, P. A.; Chung, J. Y. L.; Chan, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1502. (b) Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1992**, *57*, 1242. (c) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 6457. (d) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(3) Stoichiometric reductions: (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211. (b) Yamaguchi, S.; Mosher, H. S.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254. (c) Nishizawa, M.; Yamada, M.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 247. (d) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16.

(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.

(6) For addition of alkynylides to imines, see: (a) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970. (b) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051. (c) Brasseur, D.; Marek, I.; Normant, J.-F. *Tetrahedron* **1996**, *52*, 7235. (d) Sato, Y.; Nishimata, T.; Mori, M. *Heterocycles* **1997**, *44*, 443. (e) Cossy, J.; Poitevin, C.; Pardo, D. G.; Peglion, J.-L.; Dessinges, A. *Synlett* **1998**, *3*, 251. (f) Courtois, G.; Desre, V.; Miginiac, L. *J. Organomet. Chem.* **1998**, *570*, 279. (g) Florio, S.; Troisi, L.; Capriati, V.; Suppa, G. *Eur. J. Org. Chem.* **2000**, *65*, 3793. (h) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122.

(7) For Cu-mediated addition of acetylene gas to *N*-alkyl imines at elevated temperatures, see: Rohm + Haas Co. U.S. Patent 2 665 311, 1950.

(8) For representative additions of other carbanions to imines, see: (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138. (d) Knudsen, K.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (e) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984.

(9) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319.

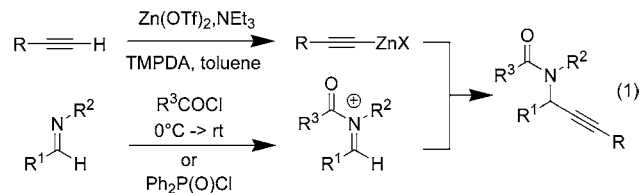
(10) (a) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268. (b) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (c) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473. (d) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (e) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (f) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797. (g) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

reports tend to include a rather limited number of imine and alkyne substrates, most typically aromatic aldimines and phenyl acetylene.¹² Moreover, examples involving additions to acyl iminiums to give amide products are, to date, wholly unprecedented.

Mechanistic observations suggest that the species generated under the conditions we have described give rise to organozinc reagents that are unique, displaying quite different characteristics relative to the more traditional dialkyl or dialkynylzinc reagents previously documented. We have been interested in exploring the reactivity and behavior of these systems with a wide range of electrophiles. Prospecting studies in our group revealed that zinc-alkynylides prepared from terminal alkynes, Zn(OTf)₂, and triethylamine do not undergo addition to simple unactivated imines under a variety of conditions. However, in the presence of Lewis acid promoters such as BF₃·OEt₂, imine additions could be observed, albeit long reaction times (days) were necessary, and, depending on the imine, extensive decomposition of the aldimine was observed.

In further investigations, we noted that the reaction of imines with acyl halides leads to the formation of a putative acyl iminium, which undergoes additions by zinc-alkynylides in good yields over 1 h (eq 1).¹³ In the experiment, when a solution of the imine and acid chloride (toluene, 0 °C) was added to a solution of Zn-acetylide (terminal acetylene, Zn(OTf)₂, Et₃N, and *N,N,N',N'*-tetramethylpropylene diamine, TMPDA¹⁴) rapid formation of propargyl amide was observed (eq 1, Table 1).

The addition reaction displays broad scope (Table 1): imines derived from aromatic and aliphatic aldehydes furnish adducts in good yields. Aldimines with protecting groups such as *N*-allyl, *N*-benzyl, or *N*-(*p*-methoxy-phenyl) react with zinc-alkynylides derived from phenylacetylene, silylacetylenes (entries 1 and 2), alkyl-substituted alkynes such as 4-phenylbutyne (entry 8), bulky 2,2-dimethylbutyne (entry



5), and propargyl trimethylsilane (entry 6). Isoquinoline (entry 12) can be utilized in the addition reaction.

As indicated in Table 1, a number of acyl halides were examined as activating agents from which acetyl chloride, acetyl bromide, benzoyl chloride, and trichloroacetyl chloride were particularly useful. The product propargyl amides were obtained in high yields for any combination of the three components in the reaction.

We proceeded to address the question of whether other activating agents could be employed for the activation of imines, allowing access to differentially protected propargylic amines. A protecting group that is often used in imine addition reactions is the diphenylphosphinoyl moiety.¹⁵ This masking group has an important advantage, as it is conveniently cleaved from the product amides with Brønsted acids.¹⁶ Because phosphinoyl chlorides are more tame as

Table 1. Zinc-Alkynylide Additions to *N*-Acyl Iminiums^a

entry	R ¹	R ²	R ³ COX	RCCH	yield (%)
1	Ph	PMP	AcBr	TMS-C≡C-H	70
2	2-Furyl	PMP	AcBr	Ph-C≡C-H	73
3	Ph	Allyl	BzCl	Ph-C≡C-H	83
4	Ph	Allyl	AcCl	Ph-C≡C-H	82
5	Ph	Allyl	BzCl	<i>t</i> Bu-C≡C-H	79
6	Ph	Allyl	BzCl	TMS-CH ₂ -C≡C-H	77
7	Ph	Allyl	BzCl	TES-C≡C-H	70
8	Ph	Allyl	AcCl	Ph-CH ₂ -CH ₂ -C≡C-H	80
9	4-(MeO)-Ph	Allyl	BzCl	Ph-C≡C-H	80
10	Ph	<i>n</i> Bu	CCl ₃ COCl	Ph-C≡C-H	84
11	<i>t</i> Bu	Allyl	CCl ₃ COCl	Ph-C≡C-H	83
12			BzCl	Ph-C≡C-H	83 ^b
13			BzCl	Ph-C≡C-H	86 ^b

^a In a typical reaction, Zn(OTf)₂ (0.6 mmol), NEt₃ (0.66 mmol), TMPDA (0.66 mmol), and alkyne (0.66 mmol) along with imine (0.5 mmol) and the acyl halide (0.5 mmol) were used. Yields refer to isolated yields after chromatography. TMPDA = *N,N,N',N'*-tetramethyl propane diamine. PMP = *p*-methoxy phenyl. For details, see Supporting Information

(11) (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) Boyall, D.; Lopez, F.; Sasaki, H.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233. (d) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964. (e) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017. (f) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (g) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605. (h) Diez, R. S.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, *58*, 8341. (i) Fässler, R.; Frantz, D. E.; Ötiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054. (j) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813.

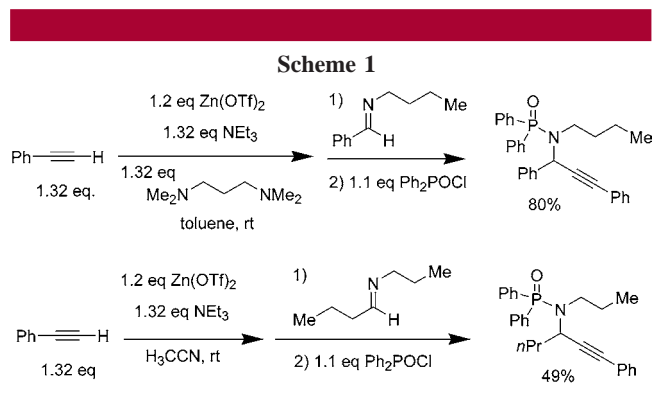
(12) (a) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, *44*, 6767. (b) Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216.

(13) Use of acylating reagents to facilitate nucleophilic additions to imines is most commonly employed in additions to heteroaromatic compounds such as quinolines. For selected examples, see: (a) Mori, S.; Iwakura, H.; Takechi, S. *Tetrahedron Lett.* **1988**, *29*, 5391. (b) Shair, M. D.; Yoon, T.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem.* **1994**, *106*, 2578. (c) Elbaum, D.; Porco, J. A., Jr.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 211. (d) Brana, M. F.; Moran, M.; De Vega, M. J. P.; Pita-Romero, I. *J. Org. Chem.* **1996**, *61*, 1369. (e) Nicolaou, K. C.; Gross, J. L.; Kerr, M. A. *J. Heterocycl. Chem.* **1996**, *33*, 735. (f) Unno, R.; Michishita, H.; Inagaki, H.; Baba, Y.; Jomori, T.; Nishikawa, T.; Isobe, M. *Chem. Pharm. Bull.* **1997**, *45*, 125. (g) Magnus, P.; Eisenbeis, S. A.; Fairhurst, R. A.; Iliadis, T.; Magnus, N. A.; Parry, D. *J. Am. Chem. Soc.* **1997**, *119*, 5591. (h) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Sadar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.

(14) We have found that the addition of TMPDA leads to a homogeneous solution of the acetylide in toluene and overall faster, cleaner reactions.

reagents than their carboxylic acid chloride counterparts, we examined the possibility of conducting the reaction using a simplified reaction protocol, wherein imine activation (imine + phosphinoyl halide) and acetylene metalation (acetylene + Zn(II) + amine base) are effected in one reaction vessel. Successful implementation of this protocol would require differential reactivity, or chemoselective reaction, of the phosphinoyl chloride and the Zn-acetylide versus imine.

In the experiment, we observed that both aromatic and aliphatic aldimines react with zinc-alkynylides directly in the presence of diphenylphosphinic chloride to give the corresponding diphenylphosphinic acid-derived propargyl amides (Scheme 1). Given the fact that in control experiments Zn-



acetylides were shown to be unreactive toward imines in the

(15) For selected recent examples, see: (a) Yamamoto, Y.; Kubota, Y.; Honda, Y.; Fukui, H.; Asao, N.; Nemoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 3161. (b) Cantrill, A. A.; Hall, L. D.; Jarvis, A. N.; Osborn, H. M. I.; Raphy, J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1996**, 2631. (c) Gaul, C.; Schaerer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66*, 3059. (d) Pinho, P.; Andersson, P. G. *Tetrahedron* **2001**, *57*, 1615. (e) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (f) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692. (g) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712.

(16) For a recent example, see: Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761.

absence of acid chloride activator, the results strongly suggest that imine preferentially reacts with the phosphinoyl chloride to give an activated phosphinoyl iminium that then undergoes addition by the acetylide.

In an effort to provide some detailed insight into the reaction process involving activation by carboxylic acid halides, we have carried out some ^1H NMR spectroscopic experiments. When a solution of benzyl-benzylidene-amine is treated with benzoyl chloride in toluene- d_8 at room temperature, formation of a precipitate is observed, which we believe to be the *N*-acyl iminium salt. The monitoring of the reaction by ^1H NMR allowed us to determine that the imine is quantitatively consumed upon addition of the acyl halide within 1 h as determined by the disappearance of the singlet at δ 4.52 ppm, corresponding to the benzylic protons. When the carboxylic acid halide is added directly to a solution of zinc-alkynylide and imine, no propargylic amide is formed and decomposition ensues. We surmise that the alkynylide adds to the acid chloride to afford the corresponding ynone that then subsequently participates in a number of further reactions.

We have documented a new process for the synthesis of fully differentially protected propargylic amines via a zinc-alkynylide addition to *N*-acyl iminiums prepared in situ from aldimines and acid halides. Additionally, we have shown the feasibility of direct activation by phosphinic chlorides and alkynylation of an acyl imine without recourse to activation. The development of asymmetric and catalytic zinc-alkynylide addition reactions to *N*-acyl imines and iminiums is ongoing and will be reported in due course.

Acknowledgment. We are grateful for the support of this research by Sumika, Ltd., Japan.

Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL049578U