ORGANIC
LETTERS

2005
Vol. 7, No. 12
2493–2495

Alkynes as Synthetic Equivalents to Stabilized Wittig Reagents: Intra- and Intermolecular Carbonyl Olefinations Catalyzed by Ag(I), BF$_3$, and HBF$_4$

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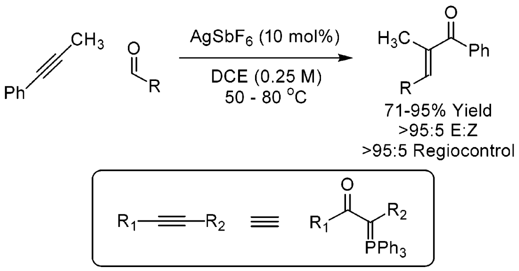
Received April 16, 2005

ABSTRACT



The first use of cationic silver ($AgSbF_4$) as a catalyst for intra- and intermolecular alkyne–carbonyl coupling to form conjugated enones is described, and a comparison to corresponding Brønsted acid (HBF_4) and Lewis acid (BF_3) catalyst systems is made. Notably, intermolecular coupling proceeds stereoselectively to afford the corresponding trisubstituted enones as single geometrical isomers. This transformation represents a completely atom economical alternative to the use of stabilized Wittig reagents in carbonyl olefination and may be viewed as a formal alkyne–carbonyl metathesis.

Despite tremendous advances in transition metal-catalyzed alkene–alkene, alkene–alkyne, and alkyne–alkyne metathesis,[1] related metal-catalyzed metatheses of carbonyl partners are far less developed.[2,3] The most broadly utilized method for carbonyl olefination is the Wittig reaction. However, many commonly employed variants of the Wittig reaction suffer due to the stoichiometric production of triphenylphosphine oxide. In view of this deficiency, we were inspired by reports of Brønsted and Lewis acid-catalyzed cyclizations of acetylenic ketones to afford conjugated enones: a formal alkyne–carbonyl metathesis.[4–6] In this account, we report the first late transition metal catalyst for formal alkyne–

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(1) For selected reviews, see: (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (b) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (e) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (f) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945. (g) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (h) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (i) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141.

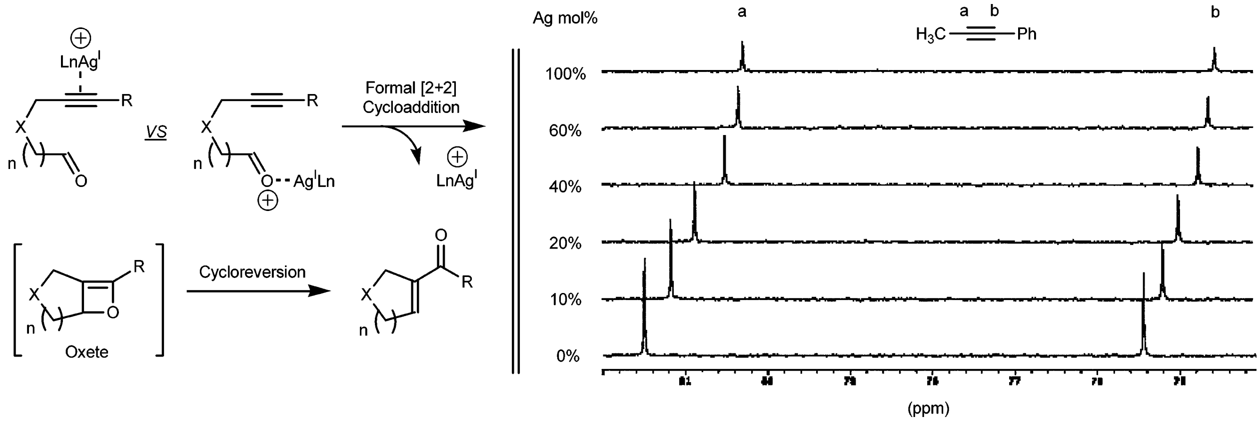
(2) For selected reviews encompassing carbonyl olefinations that are postulated to occur through the intermediacy of metal carbene complexes, see: (a) Nenajdenko, V. G.; Korotchenko, V. N.; Shastin, A. V.; Balenkova, E. S. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 1034. (b) Kuhn, F. E.; Santos, A. M. *Mini-Rev. Org. Chem.* **2004**, *1*, 55. (c) Breit, B. *Angew. Chem., Int. Ed.* **1998**, *37*, 453. (d) Ephritikhine, M. *Chem. Commun.* **1998**, 2549. (e) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.

(3) For selected examples of intramolecular alkylidene-mediated alkene–carbonyl metathesis, see: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800. (b) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 3800. (c) Nicalaou, K. C.; Posteema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.

(4) For examples of the catalytic cyclization of acetylenic ketones, see: (a) Harding, C. E.; Hanack, M. *Tetrahedron Lett.* **1971**, *12*, 1253. (b) Balf, R. J.; Rao, B.; Weiler, L. *Can. J. Chem.* **1971**, *49*, 3135. (c) Hanack, M.; Harding, C. E.; Derocque, J. *Chem. Ber.* **1972**, *105*, 421. (d) Lange, G. L.; Hall, T.-W. *J. Org. Chem.* **1974**, *39*, 3819. (e) Harding, C. E.; Stanford, G. R. *J. Org. Chem.* **1989**, *54*, 3054. (f) Harding, C. E.; King, S. L. *J. Org. Chem.* **1992**, *57*, 883. (g) Sisko, J.; Balog, A.; Curran, D. P. *J. Org. Chem.* **1992**, *57*, 4341. (h) Grunwell, J. R.; Wempe, M. F.; Mitchell, J.; Grunwell, J. R. *Tetrahedron Lett.* **1993**, *34*, 7163. (i) Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337. (j) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345. (k) Wempe, M. F.; Grunwell, J. R. *J. Org. Chem.* **1995**, *60*, 2714. (l) Wempe, M. F.; Grunwell, J. R. *Tetrahedron Lett.* **2000**, *41*, 6709.

10.1021/ol050838x CCC: $30.25 © 2005 American Chemical Society
Published on Web 05/11/2005

Scheme 1[a]



[a] Left: Alkyne−carbonyl metathesis via alkyne or aldehyde complexation-initiated oxete formation. Right: ^{13}C NMR spectroscopic analysis of an equimolar mixture of 1-phenyl propyne and isobutyraldehyde reveals a substantial upfield shift of the alkyne carbon signals upon addition of AgSbF$_6$, while signals corresponding to isobutyraldehyde exhibit negligible change.

carbonyl metathesis. Specifically, upon exposure to cationic Ag(I) salts, alkynes and aldehydes undergo intra- and intermolecular alkyne−carbonyl coupling to provide trisubstituted enones. Notably, in the case of intermolecular coupling, complete levels of regio- and stereocontrol are observed. Additionally, as part of a broad effort to develop the use of alkynes as atom economical alternatives to Wittig-type reagents, comparisons are made with related Brønsted acid (HBF$_4$)- and Lewis acid (BF$_3$•OEt$_2$)-catalyzed processes.

Brønsted and Lewis acid-catalyzed couplings of acetylenic carbonyl compounds are likely initiated through activation of the carbonyl partner by complexation of oxygen nonbonding electrons. While transannular ring closures of this type are unlikely to proceed through the intermediacy of *anti*-Bredt oxetes,[4k,l] simple nontransannular cyclizations may involve a mechanism involving stepwise oxete formation followed by cycloreversion to provide the conjugated enone. Such a mechanism is consistent with isotopic labeling studies on the acid-catalyzed rearrangement of 6-octyn-2-one in the presence of H$_2{}^{18}$O, which occurs without ^{18}O-incorporation.[4f] The independent preparation of oxetes, typically under photochemical conditions, and their authenticated cycloreversion lends additional support to this mechanism.[7]

An alternative catalytic mechanism potentially promoted through the use of a "carbophillic" Lewis acid involves alkyne complexation-initiated oxete formation (Scheme 1, right). Predicated on the basis of the well-established ability of silver(I) salts to form strong π-complexes with alkene and alkyne partners,[8,9] the intramolecular silver(I)-catalyzed metathesis of acetylenic aldehyde **3a** was explored. Gratifyingly, exposure of **3a** to substoichiometric quantities of AgSbF$_6$ (10 mol %) in dichloroethane at ambient temperature led to a nearly quantitative isolated yield of the trisubstituted enone **3b**. Withstanding changes in temperature, these conditions proved to be applicable across a diverse set of acetylenic aldehydes **1a**−**9a**, enabling formation of both five- and six-membered ring products. Additionally, as demonstrated by the cyclization of **10a**, acetylenic ketones in the form of 1,3-diones also participate in the reaction. In each case, Lewis (BF$_3$•OEt$_2$)- and Brønsted acid (HBF$_4$)-catalyzed reactions also were explored. For certain substrates, the silver(I) catalyst is more effective (**5a**, **6a**, **7a**, **9a**, **10a**), while in other cases (**1a**, **2a**) use of the Lewis or Brønsted acid catalyst is preferred (Table 1).

Intermolecular carbonyl metathesis of aliphatic and aromatic aldehydes (300 mol %) with 1-phenyl-1-propyne (100 mol %) affords enones **11b**−**14b**. Complete regioselection is observed. Additionally, the trisubstituted alkenes appear as single geometrical isomers. Under a range of related conditions, terminal alkynes such as phenylacetylene provide dramatically reduced yields of the analogous 1,2-disubsituted enone products (Table 2).

Addition of AgSbF$_6$ to an equimolar solution of 1-phenyl-1-propyne and isobutyraldehyde results in significant upfield

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(5) Intermolecular alkyne−aldehyde metathesis has been achieved using stoichiometric Lewis acid promoters: (a) Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 1613. (b) Hayashi, A.; Yamaguchi, M.; Hirama, M. *Synlett* **1995**, 195.

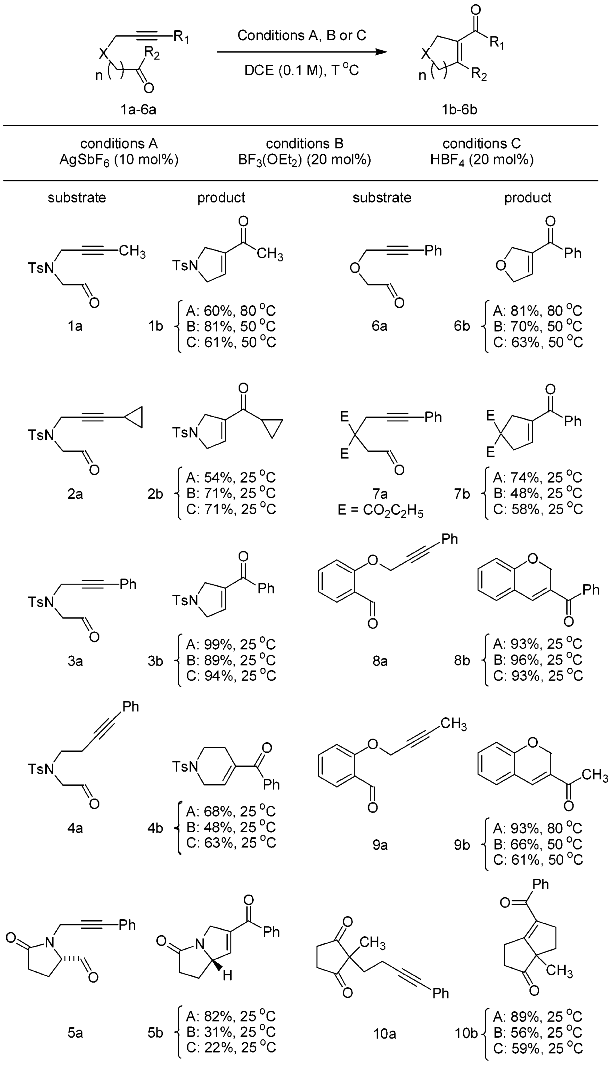
(6) A single example of catalytic intermolecular alkyne−aldehyde metathesis has been described. This Yb(OTf)$_3$-catalyzed process enables the formation of chalcones from aromatic alkynes: Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* **2003**, 552.

(7) For the isolation and cycloreversion of oxetes, see: (a) Friedrich, L. E.; Lam, P. Y.-S. *J. Org. Chem.* **1981**, *46*, 306. (b) Martino, P. C.; Shevlin, P. B. *J. Am. Chem. Soc.* **1980**, *102*, 5429. (c) Friedrich, L. E.; Bower, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6869. (d) Friedrich, L. E.; Schuster, G. B. *J. Am. Chem. Soc.* **1971**, *93*, 4602. (e) Middleton, W. J. *J. Org. Chem.* **1965**, *30*, 1307.

(8) For reviews encompassing Ag(I)−alkene complexes, see: (a) Bennett, M. A. *Chem. Rev.* **1962**, *62*, 611. (b) Quinn, H. W.; Tsai, J. H. *Adv. Inorg. Radiochem.* **1969**, *12*, 217. (c) Beverwijk, C. D. M.; Van der Kerk, G. J. M.; Leusink, A. J.; Noltes, J. G. *Organomet. Chem. Rev.* **1970**, *75*, 215. (d) Herberhold, M. In *Metal−π-Complexes*; Elsevier: Amsterdam, 1972; Vol. 2, pp 232−256.

(9) For selected examples of Ag(I)−alkyne complexes characterized by single-crystal X-ray diffraction analysis, see: (a) Ferrara, J. D.; Djebli, A.; Tessier-Youngs, C.; Youngs, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 647. (b) Gleiter, R.; Karcher, M.; Kratz, D.; Ziegler, M. L.; Nuber, B. *Chem. Ber.* **1990**, *123*, 1461. (c) Meier, H.; Dai, Y. *Tetrahedron Lett.* **1993**, *34*, 5277. (d) Nishinaga, T.; Kawamura, T.; Komatsu, K. *Chem. Commun.* **1998**, 2263. (e) Schulte, P.; Behrens, U. *J. Organomet. Chem.* **1998**, *563*, 235. (f) Chi, K.-M.; Lin, C.-T.; Peng, S.-M.; Lee, G.-H. *Organometallics* **1996**, *15*, 2660.

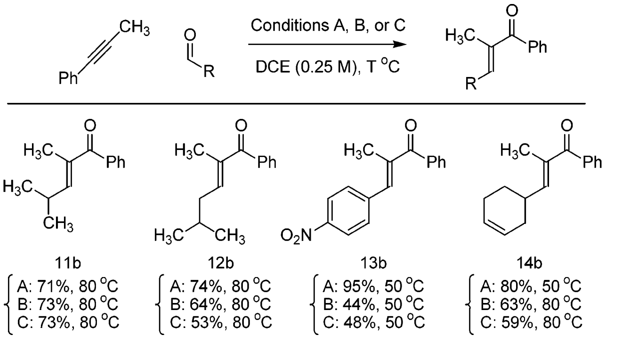
Table 1. Intramolecular Alkyne−Carbonyl Coupling Catalyzed by Ag(I)SbF_6, HBF_4, and BF_3•OEt_2[a]



substrate	product	A	B	C
1a	1b	60%, 80 °C	81%, 50 °C	61%, 50 °C
2a	2b	54%, 25 °C	71%, 25 °C	71%, 25 °C
3a	3b	99%, 25 °C	89%, 25 °C	94%, 25 °C
4a	4b	68%, 25 °C	48%, 25 °C	63%, 25 °C
5a	5b	82%, 25 °C	31%, 25 °C	22%, 25 °C
6a	6b	81%, 80 °C	70%, 50 °C	63%, 50 °C
7a (E = $CO_2C_2H_5$)	7b	74%, 25 °C	48%, 25 °C	58%, 25 °C
8a	8b	93%, 25 °C	96%, 25 °C	93%, 25 °C
9a	9b	93%, 80 °C	66%, 50 °C	61%, 50 °C
10a	10b	89%, 25 °C	56%, 25 °C	59%, 25 °C

[a] See Supporting Information for detailed experimental procedures.

Table 2. Intermolecular Alkyne−Carbonyl Coupling Catalyzed by Ag(I)SbF_6, HBF_4, and BF_3•OEt_2[a]



product	A	B	C
11b	71%, 80 °C	73%, 80 °C	73%, 80 °C
12b	74%, 80 °C	64%, 80 °C	53%, 80 °C
13b	95%, 50 °C	44%, 50 °C	48%, 50 °C
14b	80%, 50 °C	63%, 80 °C	59%, 80 °C

[a] See Supporting Information for detailed experimental procedures.

shifts of the alkyne signals in the ^{13}C NMR spectra. The aldehyde chemical shifts remain essentially unchanged. While these data suggest alkyne-initiated oxete formation, a Curtin−Hammett scenario in which coupling occurs through the intermediacy of small quantities of silver−aldehyde complex cannot be discounted. While it is possible that $AgSbF_6$ may react with residual moisture to produce Brønsted acids that may catalyze enone formation, the olefination proceeds readily in the presence of homogeneous and heterogeneous bases such as *i*-Pr_2NEt, 2,6-di-*tert*-butylpyridine, and K_2CO_3 (Scheme 1, left).

In summary, $AgSbF_6$ catalyzes intra- and intermolecular alkyne−carbonyl coupling to form conjugated enones. A comparison to corresponding Brønsted acid (HBF_4) and Lewis acid (BF_3) catalyst systems reveals that the $AgSbF_6$-catalyzed process is moderately more efficient in certain cases. Notably, intermolecular coupling proceeds stereoselectively to afford the corresponding trisubstituted enones as single geometrical isomers. This transformation represents a completely atom economical alternative to the use of stabilized Wittig reagents in carbonyl olefination and may be viewed as a formal alkyne−carbonyl metathesis. Future studies will focus on the development of improved second-generation catalyst systems.

Acknowledgment. Acknowledgment is made to the Research Corporation Cottrell Scholar Award (CS0927), the Alfred P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, the Robert A. Welch Foundation, Eli Lilly, and Merck for partial support of this research.

Supporting Information Available: Spectral data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

OL050838X