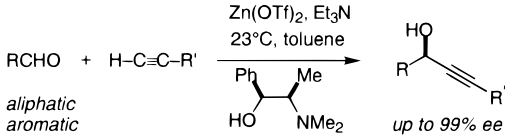
Facile Enantioselective Synthesis of Propargylic Alcohols by Direct Addition of Terminal Alkynes to Aldehydes

Doug E. Frantz, Roger Fässler, and Erick M. Carreira*

Laboratorium für Organische Chemie
ETH-Zürich, Universitätstrasse 16
CH-8092 Zürich, Switzerland

Received October 28, 1999

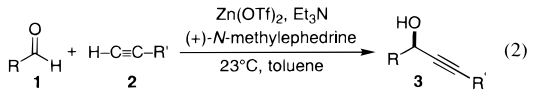
Chiral secondary propargylic alcohols are versatile, useful building blocks for asymmetric synthesis. Their utility is amply demonstrated in numerous elegant syntheses that have employed such carbinols as key starting materials.[1] The methods which have been devised for the asymmetric synthesis of optically active propargylic alcohols involve either nucleophilic addition of metalated acetylenes to aldehydes or ynone reduction.[2−6] Although some of the various catalysts and reagents for these processes are currently commercially available, the known methods require the preparation of one of the starting substrates, because neither ynones nor metalated terminal alkynes (stannyl, boryl or zinc) are widely accessible from commercial sources. We have been interested in the development of practical, synthetic processes for C−C bond formation, employing readily available substrates that do not require prior preparation.[7] In this contribution, we report a facile synthesis of optically active propargylic alcohols in up to 99% ee under mild conditions (23 °C) by direct coupling of aldehydes with a wide range of terminal alkynes in the presence of *N*-methylephedrine as a chiral additive (eq 1).



(1)

Two general approaches to the preparation of optically active propargylic alcohols have been reported starting from either ynones or aldehydes. It is worth noting that aldehyde addition methods can have a strategic synthetic advantage over ynone reduction methods.[8] This results from the inherent efficiency of a reaction that forms a new C−C bond with concomitant creation of a stereogenic center in a single transformation versus a reaction in which the C−C bond and the stereogenic center are formed separately. In this regard, in the addition of alkynes to aldehydes, maximum efficiency would result from the use of terminal acetylenes *directly* without a separate preparative metalation step.[9]

In preliminary studies, we observed that in the presence of Zn(OTf)$_2$ and an amine base at 23 °C terminal acetylenes undergo addition to aldehydes in good yields. A key feature of our mechanistic hypothesis for this novel addition reaction is the in situ generation of a zinc alkynylide, in analogy to the known



(2)

Table 1. Enantioselective Additions of RC≡CH to Aldehydes[a]

Entry	Aldehyde	Alkyne	Time	Yield	ee[b,c]
1	*c*-C_6H_{11}	Ph	1h	99%	96%
2		$Ph(CH_2)_2$	4h	98%	99%[d]
3	*iso*–Pr	$Ph(CH_2)_2$	2h	90%	99%
4		Ph	2h	95%	90%
5	PhCH=CH	$Ph(CH_2)_2$	20h	39%	80%
6	*tert*-Bu	$Ph(CH_2)_2$	2h	84%	99%
7		Ph	2h	99%	94%
8	Ph	$Ph(CH_2)_2$	20h	52%	96%
9		Ph	20h	53%	94%
10	*c*-C_6H_{11}	Me_3Si	2h	93%	98%
11	Me_3CCH_2	$Ph(CH_2)_2$	2h	72%	99%
12		Ph	2h	90%	97%
13	*c*-C_6H_{11}	Me_3SiCH_2	4h	84%	98%
14		TBDMSOCH$_2$	5h	83%	98%
15			8h	90%	98%
16			3h	94%	98%
17	*iso*–Pr		4h	97%	98%

[a] The addition reaction was conducted using 1.1 equiv Zn(OTf)$_2$, 1.2 equiv (+)-*N*-methylephedrine, and 1.2 equiv Et$_3$N in toluene (0.3 M) at 23 °C. [b] Absolute configuration of the products was established by correlation with known compounds or by analogy.[2e,3b,4] [c] When (−)-*N*-methylephedrine was used as the ligand, the opposite enantiomer was isolated in comparable yield and ee.

(1) For selected examples of the use of optically active propargylic alcohols in synthesis, see: (a) Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1992**, *57*, 1242. (b) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 6457. (c) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(2) Stoichiometric ketone 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) Mishizawa, M.; Yamada, M.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 247. (d) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. (e) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021.

(3) Catalytic ketone reductions: (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. (c) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214.

(4) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.

(5) For the asymmetric 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 the enantioselective addition of zinc acetylides (generated from the corresponding lithium acetylides) to aldehydes, see: Niwa, S.; Soai, K. *J. Chem Soc., Perkin Trans. 1* **1990**, 937. Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547.

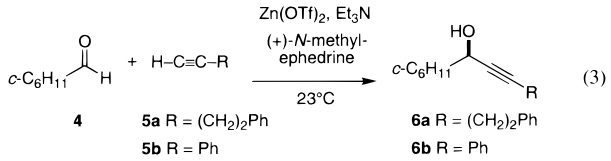
(6) For other methods see: (a) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymmetry* **1991**, *2*, 635. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (c) Singer, R. A.; Shepard, M. S.; Carreira E. M. *Tetrahedron* **1998**, *54*, 7025.

(7) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (b) Ledford, B. E.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 8125. (c) Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363.

(8) (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis;* Wiley: New York, 1989. (b) Hendrickson, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 5439.

(9) In recent work, we have described that acetylenes participate in catalytic additions to nitrones in good yields, and we presented spectroscopic evidence for the in situ generation of zinc acetylides based on ^{13}C NMR data: Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.

10.1021/ja993838z CCC: $19.00 © 2000 American Chemical Society
Published on Web 02/09/2000



(3)

4 **5a** R = $(CH_2)_2Ph$; **5b** R = Ph **6a** R = $(CH_2)_2Ph$; **6b** R = Ph

Table 2. Effect of Concentration and Solvent on ee **4** + **5a**, eq 3

[*c*-C_6H_{11}CHO][a] (M)	ee (%)
0.1	99
0.33	99
1.0	99

Solvent	ee (%)
Toluene[b]	99
CH_2Cl_2[b]	97
THF[b]	81

[a] Reactions in toluene. [b] All solvents were distilled and passed through a column of activated neutral alumina under argon. Water content: <20 ppm (Karl Fischer titration).

reaction of Cu(I) salts and amine bases with terminal acetylenes.[10] On the basis of this hypothesis and our interest in developing an enantioselective version of this mild method for the synthesis of chiral propargylic alcohols, we examined the use of inexpensive, commercially available chiral additives as putative ligands for Zn(II). We were delighted to find that the addition reactions could be conducted in the presence of optically active amino alcohols to give optically active adducts. Of those additives screened, *N*-methylephedrine (~$3/g) has proven most effective. Thus, treatment of a solution of an aldehyde and alkyne in toluene with 1.1 equiv $Zn(OTf)_2$, 1.2 equiv each of Et_3N and (+)-*N*-methylephedrine in toluene at 23 °C in 2−20 h furnishes adducts in up to 99% ee in good yields (eq 2, Table 1).[11] Importantly, after the reaction is complete, the (+)-*N*-methylephedrine can be easily separated from the adducts by simple aqueous extraction (acid wash). It could be subsequently recovered following extraction of the alkaline aqueous layer. For each of the propargylic adducts, analysis by HPLC permitted the enantiomeric purity of the products to be determined.

A preliminary study of the reaction was conducted with the aim of determining its sensitivity to substrate concentration, solvent, solvent quality, and the presence of air. As a test case for concentration and solvent effects, the stereoselectivity in the addition of cyclohexane carboxaldehyde **4** and 1-phenyl-4-butyne **5a** in the presence of (+)-*N*-methylephedrine, $Zn(OTf)_2$, and Et_3N was examined (eq 3). Over the range of aldehyde concentrations that we have investigated (0.1−1.0 M), the optical purity of the adducts **6a** remains unchanged (99% ee). The use of CH_2Cl_2 instead of toluene resulted in only a small decrease (2%) in enantioselectivity whereas in THF the optical purity of the adduct **6a** is diminished albeit only to 81% ee (see Table 2). It is rather interesting that the optical purity of the adduct remains high in THF since in the well-studied addition of dialkylzinc reagents to aldehydes the product enantioselectivity is adversely affected in this solvent.

(10) The analogy to Cu chemistry has its limitations, however, as Cu-alkynylides do not normally undergo nucleophilic additions to aldehydes.

(11) We have observed that unbranched *n*-aliphatic aldehydes give products in slightly lower % ee's, albeit in modest yields. For example, the addition of phenylacetylene to hexanal furnishes the corresponding adduct in 88% ee and 50% yield. The remaining aldehyde is consumed in the formation of self-condensation aldol products, as determined by mass balance. As seen in Table 2, aldehydes with either α- or *β*- substitution participate as excellent substrates in the addition reaction.

(12) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994, Chapter 5.

Table 3. Effect of Moisture and O_2 on ee **4** + **5b**, eq 3

Conditions (4 + 5b)	Yield (%)	ee (%)
Dried/distilled toluene[a]; N_2 atmosphere	99	96
Freshly opened bottle of ACS reagent-grade toluene[b]; N_2 atmosphere	90	92
Dried/distilled toluene[a]; air	92	94
Freshly opened bottle of ACS reagent-grade toluene[b]; air	92	94

[a] Water content: <20 ppm (Karl Fischer titration). [b] Water content: 96 ppm (Karl Fischer titration); oxygen content: ≤320 ppm at 23 °C.

In a second set of experiments, the sensitivity of product enantiopurity was tested as a function of the source of the toluene solvent and the nature of the reaction atmosphere during the setup and throughout the course of the process. When a reaction using **4** and **5b** was allowed to proceed in ACS reagent-grade toluene out of a freshly opened bottle (~280 ppm H_2O by Karl Fischer) only a slight diminution in enantioselectivity for product **6b** was noted (eq 3, 92 versus 96% ee). Interestingly, when the reaction was setup and allowed to proceed without inert N_2 atmosphere (i.e., conducted in air, 3000−6000 ppm H_2O, ≤320 ppm O_2) adduct **6b** was isolated in 94% ee and in equally good yield (see Table 3). The fact that the reaction may be conducted in air sharply contrasts the reaction conditions required in enantioselective organozinc additions to aldehydes. The pyrophoric nature of the organozinc reagents (i.e., Me_2Zn, Et_2Zn) utilized in such additions preclude exposure to oxygen or moisture.[12,13]

We have described a novel, practical method for the synthesis of optically active secondary propargylic alcohols from terminal alkynes and aldehydes. The salient features of the reaction process include: (1) both starting reactants are readily available, (2) terminal alkynes are used without requiring a separate preparative refunctionalization/activation step, (3) the *N*-methylephedrine chiral additive can be purchased in either enantiomeric form as an inexpensive commodity, and (4) the reaction procedure is easy to execute. We have demonstrated that the process possesses wide scope for both aldehydes and alkynes and, importantly, that the procedure is remarkably insensitive to the more capricious reaction variables such as solvent, concentration, and reaction atmosphere. 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.

Acknowledgment. We thank the ETH, Kontaktgruppe für Forschungsfragen (KGF), and Hoffmann-La Roche for their generous support.

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.

JA993838Z

(13) In preliminary studies we have observed that the process displays positive nonlinear behavior. Thus, when 4-phenyl-1-butyne was added to cyclohexanecarboxaldehyde in the presence of *N*-methylephedrine (20% ee), the resulting propargylic alcohol was isolated in 39% ee.