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Efficient Enantioselective Additions of Terminal Alkynes and Aldehydes under Operationally Convenient Conditions

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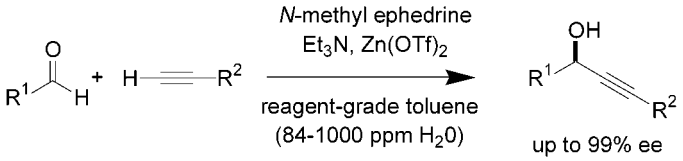
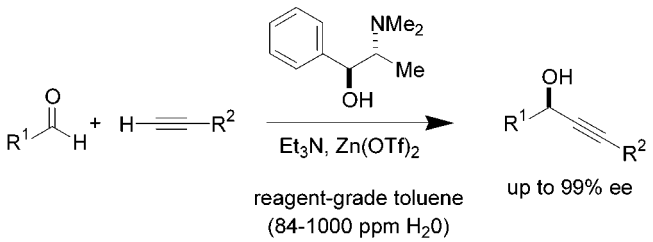
ABSTRACT



The enantioselective addition reaction of terminal acetylenes and aldehydes mediated by $Zn(OTf)_2$ and *N*-methyl ephedrine can be conducted with reagent grade solvent containing 84–1000 ppm H_2O. The products can be isolated in high yield and useful enantioselectivities (up to 99% ee).

The development of processes that are facile to carry out in the laboratory without recourse to inert atmosphere or rigorously dried and degassed solvent is an important goal in modern synthetic methodology. Such processes enjoy key advantages leading to considerable experimental simplification. Additionally, the cost structure of such processes is considerably more attractive in manufacturing. The identification of such processes can serve as a challenging goal that can lead to the discovery and development of new reaction chemistry. We have recently reported the enantioselective addition reactions of terminal acetylenes directly to aldehydes to furnish propargylic alcohols.[1] The process is convenient to carry out, requiring only amine base (Et_3N, Hunig's base), $Zn(OTf)_2$, and (+)- or (−)-*N*-methyl ephedrine in either stoichiometric or catalytic quantities. In preliminary experiments, we documented a single example wherein the addition reactions did not require the rigorous exclusion of oxygen or the use of meticulously dried solvents. Because of novel aspects and the potential use of such a

Scheme 1



(1) (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.

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process when compared against the typical organozinc additions,[2] we have embarked on a more extensive study of this reaction. We document herein a study of the reaction conducted with reagent grade toluene (84−1000 ppm H_2O) that provides adducts for a wide range of substrates in high yields and enantioselectivities (Table 1).[3] In general, given the absence of C═O addition processes involving putative organozinc reagents that can be carried out without recourse to conditions that rigorously exclude moisture and oxygen, the results we describe are unique and provide a benchmark for the further development of related chemical processes.

Each of the reactions that form the basis of this study was carried out in ACS reagent grade toluene whose water content was quantified using Karl Fischer titration. Although entirely unnecessary, the reaction vessel and stirbar were oven-dried prior to use, to properly control the amount of moisture in the system. As shown in Table 1, the addition reactions may be conducted on a wide range of substrates including aromatic and unsaturated aldehydes. Additionally, the structure of the terminal acetylene can be considerably varied leading to numerous adducts; thus, trimethyl silyl-, alkyl-, and aryl-acetylenes participate successfully in the reaction. The enantioselectivity as well as the yield of the adducts tabulated herein are comparable to those we have previously reported when the reaction had been conducted with rigorous exclusion of moisture and oxygen.

We hypothesize that the unique aspects of this system vis-á-vis the typical dialkyl and dialkynyl-zinc reagents stems from the fact that the process involves the intermediacy of a monoalkynylzinc species. As a result of the electron-deficient character of such a monosubstituted organozinc, the C−Zn bond is considerably kinetically less labile and thus seemingly compatible with limited amount of moisture and oxygen.

We have documented an extensive study of enantioselective addition reactions to aldehydes by terminal acetylenes utilizing reagent grade solvent (84−1000 ppm H_2O as measured by Karl Fischer titration) without recourse to inert atmosphere. This aspect of the reaction provides for a process that is convenient to execute. The identification of additional C−C bond forming reactions that lead to useful, optically active building blocks for asymmetric synthesis remains an important goal of our program. Mechanistic and preparative studies are underway and will be reported as results become available.

Acknowledgment. We thank the ETH for an internal research grant.

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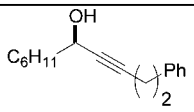
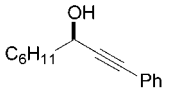
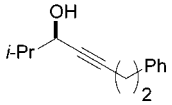
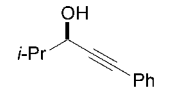
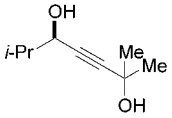
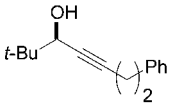
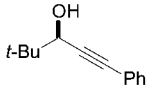
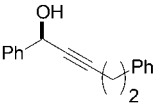
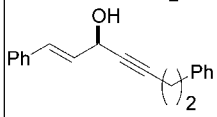
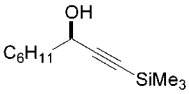
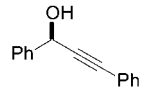
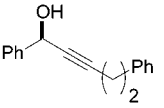
Table 1. Optically Active Propargylic Alcohols from Scheme 1[a]

Entry	Product	Yield	% ee	ppm H_2O
1		94%	97%	109
2		90%	97%	317
3		96%	89%	1000
4		88%	99%	120
5		96%	92%	208
6		92%	95%	208
7		85%	99%	109
8		95%	80%	109
10		67%	89%	109
11		80%	84%	104
12		90%	95%	84
13		82%	93%	208
14		67%	90%	109

[a] The addition reactions were conducted following the general protocol previously reported (see ref 1b), except that reagent grade toluene was used directly from a bottle and during the reaction setup and course no measures were taken to exclude ambient atmosphere. General procedure: 1.1 equiv of $Zn(OTf)_2$, 1.2 equiv of (+)-*N*-methyl ephedrine, and 1.2 equiv of Et_3N in toluene (0.3 M) at 23 °C. The enantiomeric excess was determined by HPLC as described previously. In all cases, the product chromatograms were compared against a known racemic mixture. Absolute configuration of the products was established by correlation with known compounds previously reported or through independent syntheses utilizing known methods.

(2) For reviews, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

(3) In all cases, product yields are reported for analytically pure material, that has been subjected to the usual battery of methods for characterization.