A Simple, Mild, Catalytic, Enantioselective Addition of Terminal Acetylenes to Aldehydes

Neel K. Anand and Erick M. Carreira*

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

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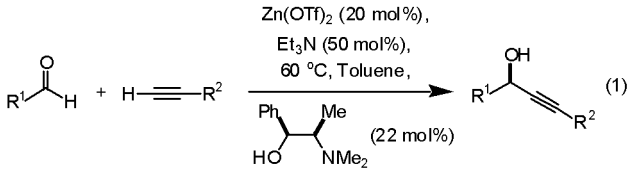
The enantioselective addition of terminal acetylenes to aldehydes[1] or ketones[2] affords direct access to optically active propargyl alcohols which are useful, versatile building blocks that enjoy wide application in chemical synthesis. The existing methods for carrying out these enantioselective addition reactions require the use of stoichiometric quantities of metalated acetylenes, which have taken the form of boryl acetylides or, more recently, in situ generated Zn(II) alkynilides.[1−3] In our continuing interest in the development of mild, practical methods for asymmetric C−C bond-formation,[1e] we have investigated the in situ C−H activation of terminal acetylenes to give nucleophilic carbanions that participate in catalytic, enantioselective additions to aldehydes. Herein, we report the enantioselective addition of terminal acetylenes to aldehydes, which is catalytic in both metal and chiral ligand. This is the first time that Zn−carbanions have been added enantioselectively to aldehydes using *truly catalytic* amounts of metal; previously, stoichiometric R_2Zn has always been employed.[3] The propargylic adducts are isolated in useful yields and excellent selectivities. Additionally, we document the first example of an alkynilide addition to an aldehyde that can be conducted solvent-free with 1.0 equiv of aldehyde and 1.05 equiv of alkyne.[4] As such, this volumetrically efficient[5] process exemplifies ideal atom economy,[6] not only because the two reactants comprise the product but also since it obviates the use of solvent.



To date, the processes that have been reported for the enantioselective additions of a wide range of nonstabilized carbanions to carbonyls prescribe stoichiometric amounts of an organometal (RM, M = Zn, Ti, Mg, Li) or organometalloid (Si, B, Sn) nucleophile.[3,7] Importantly, those processes which are noted as catalytic, are catalytic in metal *only with respect to* the active, chiral complex that serves to activate the nucleophilic or electrophilic reaction partners.[8] With the exception of methods proceeding via enolates reported by Shibasaki and Trost,[9] to the best of our knowledge, a method to enantioselectively add in situ generated carbanions to aldehydes which is truly catalytic in metal is unprecedented.

We recently documented the enantioselective addition of Zn-alkynilides to aldehydes using stoichiometric quantities of commercially available $Zn(OTf)_2$, (+)- or (−)-*N*-methylephedrine and Et_3N.[1c−g] In analogy to the additions of R_2Zn in the presence of chiral catalysts,[3f] the products were obtained in high enantioselectivities, however, by contrast, the addition reactions of in situ generated Zn-alkynilides were not catalytic. Even after numerous investigations involving the use of additives and various ligands, as well as variation of solvent, the reaction proved recalcitrant to catalysis. We speculated that the lack of turnover was a consequence of a kinetic barrier inhibiting protonation of the first-formed Zn-alkoxide.

We subsequently determined that catalysis could be attained by conducting the reaction at 60 °C (Table 1).[10] The catalytic process displays wide substrate scope and is compatible with functionality on both the alkyne and the aldehyde. At the current level of development the addition works ideally with α-substituted aldehydes,[11] while unbranched unsubstituted aliphatic aldehydes deliver products in high enantioselectivites and useful yields (entries 5 and 16).[12] With α,α-disubstituted aldehydes, the reaction worked most efficiently when a 20 mol %:10 mol % ratio of $Zn(OTf)_2$:(+)-*N*-methylephedrine was employed (entries 6 and 7).[13] In general, although the use of 20 mol % $Zn(OTf)_2$ [14] reliably affords adducts in the selectivities and yields noted,[15] we found that the ligand could be reduced to as little as 5 mol % with retention of high enantioselectivity.[16] The robust nature of the process is underscored when it is noted that, even when the reaction was conducted at 100 °C, propargyl alcohol adduct was produced in high % ee (entries 12 and 14). We have also observed that the catalytic addition reaction is tolerant of moisture and air. For example, when 4-phenyl-1-butyne was added to cyclohexane carboxaldehyde under an atmosphere of air using freshly opened bottle of ACS reagent-grade toluene (103 ppm H_2O content by Karl Fischer titration) the chiral propargyl alcohol was formed

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(3) For enantioselective procedures which are catalytic with respect to the chiral ligand, see: (a) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937. (b) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251. (c) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151. (d) Ishizaki, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1901. (e) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichelle, L.; Reider, P. J. *Synthesis* **1999**, 1453. (f) For an excellent recent review, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

(4) Very recently, a system for the enantioselective alkylation of aldehydes using 3.4−10 mol % of chiral ligand and 2.2−5 equiv of Et_2Zn without additional solvent has been reported: Sato, I.; Saito, T.; Soai, K. *J. Chem. Soc., Chem. Commun.* **2000**, 2471

(5) Jacobsen, E. N.; Finney, N. S. *Chem. Biol.* **1994**, *1*, 85.

(6) Trost, B. M. *Science* **1991**, *254*, 1471.

(7) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363.

(8) The Alder ene reaction of olefins and aldehydes, if considered to proceed via an ionic rather than pericyclic mechanism, may constitute one exception, see: (a) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(9) (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (b) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (c) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (d) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.

(10) Racemic addition could also be achieved at this temperature using catalytic quantities of $Zn(OTf)_2$ in the absence of the chiral ligand by conducting the reaction in acetonitrile.

(11) We have investigated a variety of conditions to add alkynes to aromatic aldehydes and have found that the yields are considerably reduced due to Canizzaro reaction.

(12) The remaining aldehyde was consumed in aldol self-condensation.

(13) Reactivity dependence on the relative stoichiometry of aldehyde, zinc species, and ligand in related systems has been reported: Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.

(14) With certain substrates 10 mol % $Zn(OTf)_2$ suffices.

(15) We have also conducted the addition reaction on 50 mmol scale to give the adduct of entry 2 in 94% yield and 96% ee.

(16) When 4-phenyl-1-butyne was added to cyclohexane−carboxaldehyde using 20 mol % of $Zn(OTf)_2$ and 5 mol % of ligand, the chiral propargyl alcohol was formed in 79% yield and 91% ee (cf. Table 1, entry 2).

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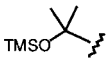
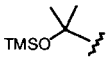
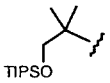
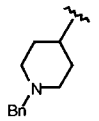
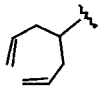
Table 1. Catalytic, Enantioselective Addition of Alkynes to Aldehydes[a]

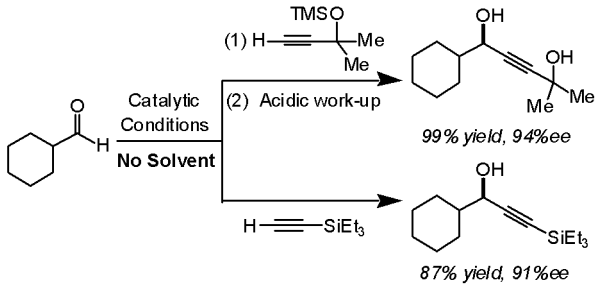
Entry	R^1CHO	R^2CCH	Time	Yield	ee[b,c]
1	*c*-C_6H_{11}	Bn_2NCH_2	2h	91%	97%
2		$Ph(CH_2)_2$	4h	89%	94%
3		Ph	5h[d]	94%	86%
4	*i*–Pr		5h	77%[i]	98%
5	*n*-C_7H_{15}	$Ph(CH_2)_2$	20h[g]	45%	92%
6	*t*-Bu		24h[h]	77%	93%
7		$TBSOCH_2$	5h[h]	81%	93%
8	*c*-C_6H_{11}		9h	88%	94%
9		*n*-C_4H_9	6h[e]	81%	93%
10			4h	80%[i]	99%
11		Et_3Si	7h	85%	96%
12		Bn_2NCH_2	5h[f]	80%	95%
13	*c*-C_6H_{11}	$TBSOCH_2$	5h	88%	90%
14		Bn_2NCH_2	5h[f]	81%	94%
15		$Ph(CH_2)_2$	6h	80%	93%
16	*n*-C_7H_{15}	Bn_2NCH_2	24h[g]	55%	91%

[a] 20 mol % $Zn(OTf)_2$, 22 mol % (+)-*N*-methylephedrine, 50 mol % Et_3N, 1.2 equiv alkyne, and 1.0 equiv (0.5 mmol) aldehyde in toluene (1 M) at 60 °C. [b] For entries 4, 7−11, 13, and 15 the adducts were converted to their 3,5-dinitrobenzoate esters and then analyzed by HPLC using Chiralcel column; for all other entries the ee was determined directly by Chiralcel HPLC analysis. [c] Absolute configuration of the products was established by correlation with known compounds or by analogy. [d] Stirred at 23 °C. [e] Stirred at 50 °C. [f] Stirred at 100 °C. [g] Aldehyde was added dropwise to the reaction mixture over 2.5 h. [h] 10 mol % (+)-*N*-methylephedrine was used. [i] Yield and ee shown for the desilylated product.

in 79% yield and 92% ee (cf. Table 1, entry 2). All of these results demonstrate that the system is highly versatile and amenable to fine-tuning of conditions for optimization of selectivity for a given substrate.

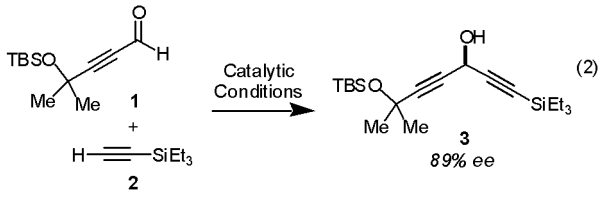
To maximize the practicality and efficiency of the catalytic reaction, we subsequently embarked on a study aimed at examining whether alkyne addition could be conducted in the absence of solvent. In this respect, excellent yields and enantioselectivities were achieved in a reaction mixture consisting of 1.0 equiv of aldehyde and 1.05 equiv of alkyne along with catalytic quantities of Zn(II), amine, and ligand (Scheme 1). A number of observations which attest to the advantages of the solvent-free system

Scheme 1



are worth noting: first, unlike the reaction in toluene, the solvent-free reaction did not require the prescribed 2 h mixing period (Zn, ligand, and amine) to form the active complex, therefore reducing the overall time required for the reaction, and second, aqueous workup could be obviated, as direct transfer of the contents of the reaction vessel onto a column of silica yielded, after the chromatographic purification, analytically pure chiral propargyl alcohol adduct.

Finally, using the catalytic addition reaction it is possible to access optically active dialkynyl methanols (eq 2). Thus, in preliminary results the addition of alkyne **2** to alkynal **1** furnished alcohol **3** in 89% ee. Such alcohols in which the ends of the alkynes are differentiated provide ideal building blocks that can be extensively synthetically elaborated, not only for use in traditional total synthesis but also for materials application.[17]



In conclusion, we have described the first process in which terminal alkynes undergo addition to aldehydes in up to 99% ee using truly catalytic quantities of metal and ligand. The procedure is practical, facile, and utilizes reactants that require no prior preparation; moreover, the Zn(II) salt and both enantiomers of the chiral ligand are commercially available. The conditions tolerate air and moisture and are very versatile; thus, while the general procedure described works well for a variety of substrates, the range of reaction conditions that can be employed is sufficiently broad to allow the relative amounts of Zn(II) and ligand to be varied. The flexibility of the method is especially highlighted by the fact that the addition can be conducted at temperatures as high as 100 °C to afford products in excellent yields and %ee. We have also demonstrated the first example of a solvent-free alkynilide addition reaction that furnishes chiral propargyl alcohols as useful building blocks with excellent enantioselectivity. As such the process epitomizes the concept of atom economy. Further studies are underway and will be reported in due course.

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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.

JA016378U

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