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Enantioselective Addition of 2-Methyl-3-butyn-2-ol to Aldehydes: Preparation of 3-Hydroxy-1-butynes

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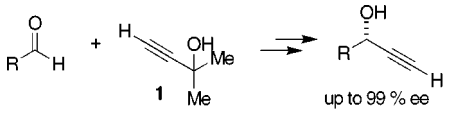
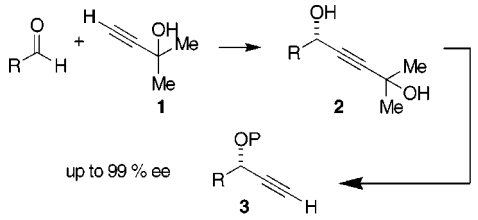
ABSTRACT



We report the first example of enantioselective aldehyde additions of 2-methyl-3-butyn-2-ol, a commodity bulk chemical that is readily available. Following a facile fragmentation reaction, the addition reactions provide access to optically active terminal acetylenes as useful building blocks for asymmetric synthesis.

Optically active propargylic alcohols constitute important building blocks for asymmetric synthesis, as they are used in diverse areas, including the synthesis of natural products, pharmaceuticals, and macromolecules.[1] Of the various propargylic alcohols that can be envisioned as versatile starting materials, those derived from the addition of ethyne, or its equivalent, to aldehydes would be optimal, because subsequent derivatization of the terminal alkyne (alkylation, acylation, or Sonogashira coupling) would afford access to a broad range of optically active, secondary propargylic alcohols.[2] In this Letter we report a convenient procedure for the preparation of such chiral 3-hydroxy-1-alkynes involving the unprecedented enantioselective additions of the inexpensive commodity chemical 2-methyl-3-butyn-2-ol **1** and aldehydes in the presence of $Zn(OTf)_2$, Et_3N, and (*R*)- or (*S*)-*N*-methylephedrine. The isolated adducts readily undergo subsequent thermal fragmentation to furnish the desired propargylic alcohols **3** in excellent yields and up to 99% ee (Scheme 1).

Scheme 1



We have been interested in the development of novel enantioselective C−C bond-forming reactions that utilize readily available starting materials.[3,4] In this regard, we have recently documented the enantioselective addition reaction of terminal acetylenes directly to aldehydes in the presence of $Zn(OTf)_2$, Et_3N, and (*R*)- or (*S*)- *N*-methylephedrine to furnish propargylic alcohols in preparatively useful yields and up to 99% ee. In subsequent investigations, we observed

(1) For some recent examples, see: (a) Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467. (b) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131. (c) Tan, L.; Chen, C.-Y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711. (d) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.

(2) *The Chemistry of Triple Bonded Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; Parts 1 and 2.

(3) (a) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (b) Carreira, E. M.; Singer, R. A. *Drug Discovery Today* **1996**, *1*, 145.

(4) (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.; Tomooka, C. S.; Fässler, R.; Carreira E. M. *Accs. Chem. Res.* **2000**, *33*, 373.

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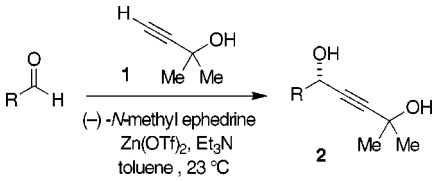
that ethyne could be utilized in the enantioselective aldehyde additions when the reactions are conducted with saturated solutions of acetylene in a pressurized, sealed vessel at 23 °C.[5] However, despite the novelty and the inherent atom efficiency of this process, two critical features, namely, the observed long-reaction times and the handling of pressurized reaction vessels, rendered the process somewhat unwieldy at the current level of development. We thus embarked on a study aimed at identifying inexpensive practical equivalents of acetylene that could be safely handled in the laboratory and readily employed in these aldehyde additions. In this regard, 2-methyl-3-butyn-2-ol (**1**) seemed attractive as a potential acetylene equivalent in the addition reactions for two key reasons: (1) as a commodity chemical, 2-methyl-3-butyn-2-ol can be purchased at $3/kg and (2) *C*-alkylated derivatives had been previously shown to undergo fragmentation reactions thermally to furnish acetone and the corresponding terminal alkyne.[6,7]

At the outset, it was unclear whether an alkyne such as 2-methyl-3-butyn-2-ol, possessing a free alcohol, would be suitable in the nucleophilic addition reactions which we have postulated to proceed via alkynyl zinc intermediates. Nevertheless, trial experiments quickly revealed that **1** readily participates in aldehyde additions, furnishing optically active propargylic alcohols in high enantioselectivities (up to 99% ee) and in excellent yields (Scheme 2, Table 1).

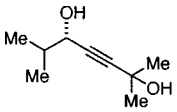
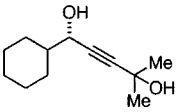
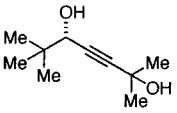
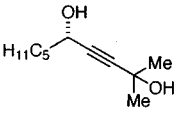
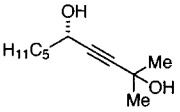
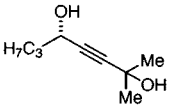
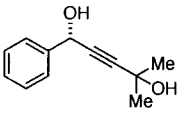
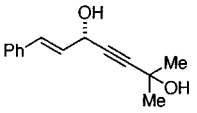
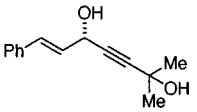
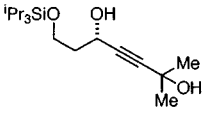
Scheme 2



A number of important observations were made in the context of these studies that lead to significant improvements over the addition reactions we initially reported.[4] The addition reactions utilizing **1**, in general, proceeded at rates that are faster than those observed with other terminal alkynes we have previously documented. Moreover, the reactions involving 2-methyl-3-butyn-2-ol (**1**) display wider scope, providing adducts for a broader range of functionalized aromatic and aliphatic aldehydes. Given these unanticipated benefits, we undertook a careful study of the reaction conditions aimed at process optimization. In this regard, we have observed that the stoichiometry of the ligand, $Zn(OTf)_2$, and amine base can be varied substantially, leading to an increase in the yields and enantioselectivities for a number of adducts (cf. entry 4 versus 5 and 8 versus 9). For example, although hexanal affords product in 51% ee when 1.1 equivof Et_3N, 1.1 equiv of $Zn(OTf)_2$, and 1.2 equiv of *N*-methylephedrine are employed (see Table 1, entry 4), doubling the amount of these components furnishes product in 98% ee (entry 5). Thus, product yields and enantioselectivities can be optimized by convenient alteration of the stoichiometry.

We anticipate certain applications of this methodology wherein it maybe desirable to isolate protected alcohol adducts from the reaction mixture. In this regard, we

Table 1. Enantioselective Addition Reactions of **1**[a]

entry	R	adduct		yield	% ee
1	*iso*-Pr		**2 a**	97%	98%
2	*c*-C_6H_{11}		**2 b**	89%	99%
3	*tert*-Bu		**2 c**	82%	98%
4	*n*-C_5H_{11}		**2 d**	81%	51%
5	*n*-C_5H_{11}		**2 d**	81%[b,c]	98%
6	*n*-C_3H_7		**2 e**	77%[b,c]	99%
7	Ph		**2 f**	96%[d]	98%
8	*t*-PhCH=CH		**2 g**	47%	75%
9	*t*-PhCH=CH		**2 g**	99%[d]	88%
10	$^iPr_3SiO(CH_2)_2$		**2 h**	82%[b,c]	97%

[a] Unless noted the reactions are conducted at 23 °C, at 0.37 M [alkyne] utilizing 1.2 equiv of *N*-methylephedrine, 1.1 equiv of $Zn(OTf)_2$, and 1.1 equiv of Et_3N. [b] Reactions conducted with 2.1 equiv of *N*-methylephedrine and 2.0 equiv of $Zn(OTf)_2$. [c] A 0.4 M solution of the aldehyde was added over 4 h. [d] Reactions conducted with 3.1 equiv of *N*-methylephedrine and 3.0 equiv of Zn(OTf).

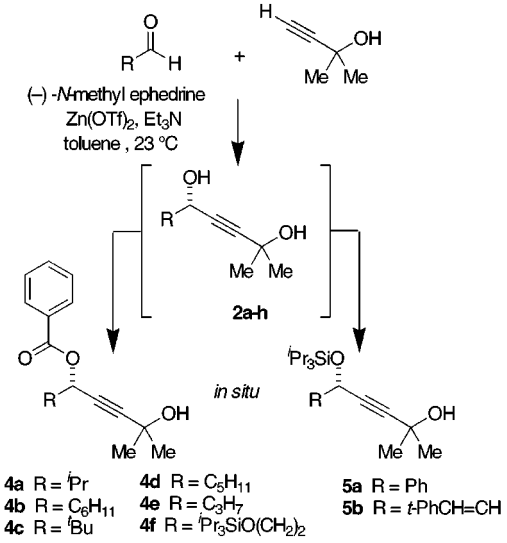
(5) Carreira, E. M.; Sasaki, H. Unpublished results.

(6) For catalytic, enantioselective additions of borylacetylides, see: (a) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151. For the asymmetric addition of preformed bisalkynylzinc reagents to aryl ketones, see ref 1c.

(7) For the preparation of propargylic alcohols by ynone reduction, see: (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.

examined whether protected alkyne/aldehyde adducts could be easily accessed (Scheme 3, Table 2). It is important to

Scheme 3



note that this approach proved particularly useful for addition reactions affording low molecular weight, volatile products. The adducts resulting from chemoselective benzoylation of the secondary alcohol in **2** could be isolated from a two-step, one-pot sequence. Thus, following complete consumption of the starting aldehyde in the alkyne addition reaction, the reaction mixture was treated directly with benzoyl chloride (Scheme 3, **2a**−**e**,**h** → **4a**−**f**) to afford **4a**−**f** in useful yields. The corresponding silyl-protected adducts were most effectively accessed by treatment of the unpurified alkyne adducts isolated from the addition reaction with $^{i}Pr_3$-SiOTf/2,6-lutidine.

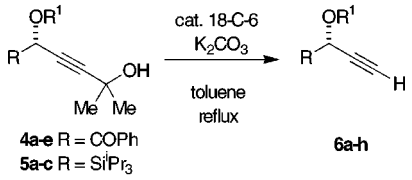
The C−C cleavage reaction of adducts **4a**−**f** and **5a**−**b** to acetone and the corresponding terminal acetylene can provide useful chiral 3-hydroxy-1-butynes. In this regard, in the presence of 20−40 mol % of 18-C-6 and K_2CO_3 in refluxing toluene, we observed fragmentation to furnish optically active, terminal propargylic alkynes **6a**−**h** (Scheme

Table 2. Preparation of Protected Adducts

entry	R	product	% ee[e]	yield
1	*iso*-Pr	**4a**	98%	91%[a]
2	*c*-C_6H_{11}	**4b**	99%	81%[a]
3	*tert*-Bu	**4c**	98%	76%[a]
4	*n*-C_5H_{11}	**4d**	98%	78%[b]
5	C_3H_7	**4e**	99%	77%[b]
6	Ph	**5a**	98%	96%[b]
7	*t*-PhCH=CH	**5b**	88%	92%[b]
8	$^{i}Pr_3SiO(CH_2)_2$	**4f**	97%	81%[b]

[a] Overall yield for two steps: addition and in situ protection. [b] Overall yield for two steps: addition and a subsequent protection following workup of the addition reaction.

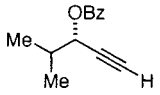
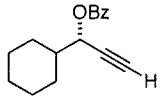
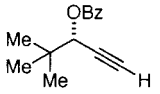
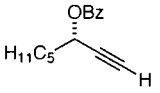
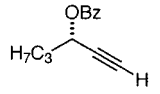
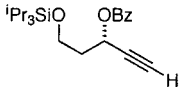
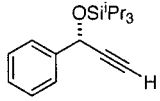
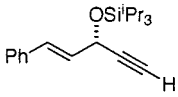
Scheme 4



4, Table 3).[8] Although for certain aliphatic substrates the cleavage reaction can be conducted on the unprotected adducts, in general, the yields were greatly improved when the protected substrates were utilized. In this regard, for most cases, the use of the benzoate-protected secondary alcohol provides adduct in excellent yields (entries 1−6). However, the cleavage reaction of the aromatic adducts is optimal with the use of the bulky triisopropylsilyl ether (entries 7, 8).

In summary, we report the first examples of enantioselective alkyne additions that utilize 2-methyl-3-butyn-2-ol. Following a facile fragmentation reaction, the latter

Table 3. Fragmentation Reactions of **4** or **5**

entry	product		yield
1		**6 a**	91%
2		**6 b**	90%
3		**6 c**	86%
4		**6 d**	91%
5		**6 e**	89%
6		**6 f**	88%
7		**6 g**	83%
8		**6 h**	70%

[a] Reactions were conducted at 0.4 M in substrate with 1 equiv of K_2CO_3 and 20−40 mol % of 18-C-6 in refluxing toluene.

addition reactions provide access to optically active terminal acetylenes as useful building blocks for asymmetric synthesis. In addition to practical aspects, the results we document illustrate the versatility of the process involving in situ activation of terminal acetylenes by $Zn(OTf)_2$, which is tolerant of functionalized alkynes such as 2-methyl-3-butyn-2-ol, incorporating a free alcohol.

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Supporting Information Available: Full characterization and experimental procedures for the adducts of 2-methyl-3-butyn-2-ol (Table 1), the protected derivatives (Table 2), and the fragmentation products (Table 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Although there is precedence for the cleavage of acetone/alkyne adducts thermally (≈200 °C), these examples are in general devoid of competing functionality in the substrate. The majority of acetone cleavage reactions have been performed on conjugated alkynes, see for example: (a) Inouye, M.; Hyodo, Y.; Nakazumi, H. *J. Org. Chem.* **1999**, *64*, 2704. (b) Swindell, C. S.; Fan, W. *J. Org. Chem.* **1996**, *61*, 1109.