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Diastereoselective Synthesis of *syn*-1,3-Diols by Titanium-Mediated Reductive Coupling of Propargylic Alcohols

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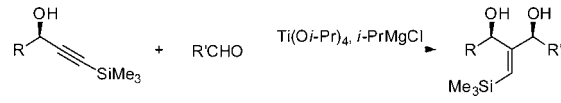
ABSTRACT



A titanium-mediated, hydroxy-directed reductive coupling reaction of propargylic alcohols and aldehydes/ketones is described. Excellent diastereoselectivity and synthetically useful yields have been obtained for a range of substrates. This transformation has enabled a highly convergent three-component approach to *syn*-1,3-diols using (trimethylsilyl)acetylene as a C1 linchpin.

Homochiral 1,3-diols are ubiquitous in natural products of polyketide origin. The synthesis of these structural motifs normally relies on stereoselctive C−H or C−C bond formation of β-hydroxycarbonyl compounds or C−O bond formation of homoallylic alcohols (Figure 1).[1] These β-hydroxycarbonyl compounds and homoallylic alcohols are in turn prepared by stereoselective aldol or allylation reactions. Theoretically, a 1,3-diol can be more convergently prepared by sequential couplings of a 1,1-bismetallic C1 linchpin or its functional equivalent with two aldehydes. We envisioned terminal acetylenes to be such functional equivalents of 1,1-bismetallic reagents. A synthetic sequence consisting of a stereoselective alkynylation of the first aldehyde followed by a diastereoselective reductive coupling of the propargylic alcohol intermediate with a second aldehyde would lead to formation of a 1,3-diol. The enantio- and diastereoselective alkynylations of aldehydes have been well documented, and the alkyne-aldehyde reductive couplings by a number of transition metal based systems are also known.[2,3] While

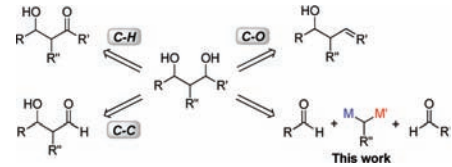


Figure 1. Synthesis of 1,3-diols.

(1) For a recent review: Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557–588.

(2) For the enantio- and diastereoselective alkynylations of aldehydes: (a) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151–3152. (b) Tan, L.; Chen, C. Y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711–713. (c) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807. (d) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688. (e) Xu, M. H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555–4557. (f) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8–9. (g) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095–4105. (h) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739–749. (i) Guillarme, G.; Ple, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355–2403. (j) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983.

(3) For some reviews: (a) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835–2886. (b) Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753–775. (c) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834. (d) Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759–784. (e) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908. (f) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269–1279. (g) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441–4449. (h) Montgomery, J.; Sormune, G. J. *Top. Curr. Chem.* **2007**, *279*, 1–23. (i) Iida, H.; Krische, M. J. *Top. Curr. Chem.* **2007**, *279*, 77–104. (j) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063–1072. (k) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34–46.

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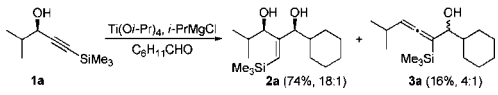
enantioselective variants of these reductive couplings have been reported for limited sets of substrates,[3] very few examples exist for diastereoselective alkyne-aldehyde reductive couplings. One such precedent was from the lab of Micalizio, which reported that ene-1,5-diols could be prepared by the reductive coupling of homopropargylic alcohols and aldehydes with moderate diastereoselectivity.[4] Herein we report the first highly diastereoselecitve hydroxy-directed alkyne-aldehyde reductive coupling of propargylic alcohols and aldehydes to *syn*-1,3-diols by Ti(O*i*-Pr)$_4$/*i*-PrMgCl.[5]

We chose the propargylic alcohols derived from (trimethylsilyl)acetylene for the investigation because the trimethylsilyl group had been reported to direct the titanium-mediated reductive coupling with aldehydes to occur at the acetylene carbon distal to the silyl group.[6] In addition, the silyl group can later be removed by protodesilylation or used as a handle for additional transformations. An initial concern was that β-elimination of the hydroxy group might compete with the desired reductive coupling process because derivatives of propargylic alcohols have been known to undergo β-elimination under titanium-mediated reductive coupling conditions to give rise to allenyltitanium species.[7] However, we speculated that the elimination reaction pathway could be suppressed by initial formation of an alkoxide, which had been shown to be compatible with the titanium-mediated reductive coupling conditions.[8,9] In addition, advantage could be taken of the propargylic alkoxide for hydroxy-directed reductive coupling to achieve diastereocontrol.[10] To validate these hypotheses, we used propargylic alcohol **1a**, prepared from (trimethylsilyl)acetylene and isobutyraldehyde, as the test substrate. We were gratified to find that the desired coupling did occur between **1a** and cyclohexanecarboxaldehyde under the reductive conditions mediated by Ti(O*i*-Pr)$_4$/*i*-PrMgCl, and diastereoselective (dr = 18:1) formation of the *syn*-1,3-diol **2a** was unambiguously confirmed by X-ray crystallographic analysis (Scheme 1). A major side

Scheme 1. Reductive Coupling of **1a**

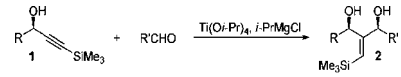


product was identified to be **3a**, arising from regioisomeric coupling of the titanocyclopropene intermediate with cyclohexanecarboxaldehyde.

Experiments were carried out to optimize the reaction conditions. Formation of **3a** was minimized by conducting the reaction at −40 to −50 °C (see Supporting Information). Whereas Ti(O*i*-Pr)$_4$ and ClTi(O*i*-Pr)$_3$ gave similar results for the reductive coupling, replacement of *i*-PrMgCl with *i*-PrMgCl·LiCl or *c*-C_5H_9MgCl gave inferior yields and diastereoselectivities. Similar results were obtained when the reaction was carried out with toluene or THF as the solvent.

We probed the scope of the reaction using a range of propargylic alcohols and aldehydes. Most of these substrates showed excellent diastereoselectivity and synthetically useful yields (Table 1). Notable exceptions are aromatic and α,β-unsaturated aldehydes. For example, reductive coupling of **1a** with benzaldehyde gave less than satisfactory yield as a result of the competing pinnacol reaction (entry 5),[11] and cinnamaldehyde gave only a trace amount of the coupling product (not shown). A remedy to these inefficient reductive couplings with aromatic and α,β-unsaturated aldehydes was to prepare the propargylic alcohols from these aldehydes instead. Good diastereoselectivity and synthetically useful yields were obtained from these propargylic alcohols (entries 11 and 12). The reactions could be carried out at a scale of 10 mmol of the propargylic alcohols with similar results (entries 1 and 6). Enantiomeric purity of the propargylic alcohol was maintained under the reductive coupling condi-

Table 1. Reductive Coupling of Propargylic Alcohols and Aldehydes



entry[a]	**1**	R	R′	**2**	yield (%)[b] (*syn*/*anti*)
1	**1a**	*i*-Pr	Cy	**2a**	74 (18:1)
2	**1a**		*i*-Pr	**2b**	58 (18:1)
3	**1a**		Et	**2c**	58 (18:1)
4	**1a**		*t*-Bu	**2d**	trace
5	**1a**		Ph	**2e**	47 (7:1)
6	**1b**[c]	$PhCH_2CH_2$	Cy	**2f**[c]	60 (>20:1)
7	**1c**	*n*-Pr	Cy	**2g**	78 (20:1)
8	**1c**		*i*-Pr	**2h**	57 (>20:1)
9	**1d**	Et	Cy	**2i**	71 (>20:1)
10	**1d**		Et	**2j**	58 (>20:1)
11	**1e**	Ph	Cy	**2k**	77 (4:1)
12	**1f**	PhCHCH	Cy	**2l**	43 (10:1)
13	**1g**	Cy	Cy	**2m**	74 (11:1)
14	**1h**	*t*-Bu	Cy	**2n**	trace

[a] Reaction conditions: 1.0 equiv of the propargylic alcohol, 1.6 equiv of Ti(O*i*-Pr)$_4$ in diethyl ether, and 3.2 equiv of *i*-PrMgCl, −40 °C, 4 h; then 3.5 equiv of the aldehyde, −78 to −40 °C, 18 h. [b] Isolated yield. [c] >94% ee, determined by HPLC analysis with a CHIRALCEL IB column.

(4) (a) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694–3695. (b) Bahadoor, A. B.; Micalizio, G. C. *Org. Lett.* **2006**, *8*, 1181–1184.

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(6) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203–3206.

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(8) See ref 3a,b and Urabe, H.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7329–7332.

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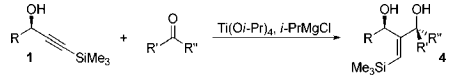
(10) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(11) (a) Muramatsu, Y.; Harada, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1088–1090. (b) Matiushenkov, E. A.; Sokolov, N. A.; Kulinkovich, O. G. *Synlett* **2004**, 77–80.

tions (entry 6). The steric requirements of the *tert*-butyl groups have been attributed to the low reactivities of entries 4 and 14.

The reductive coupling of propargylic alcohols was not limited to aldehydes. While only a limited set of ketones have been tested (Table 2), synthetically useful diastereo-

Table 2. Reductive Coupling of Propargylic Alcohols and Ketones

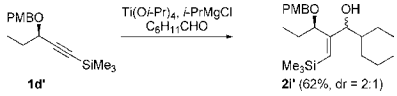


entry	1	R	R′	R″	2	yield (%)
1	**1c**	*n*-Pr	-$(CH_2)_5$-		**4a**	66
2	**1c**		Ph	Me	**4b**	17 (>20:1)
3	**1d**	Et	*n*-Bu	Me	**4c**	62 (11:1)
4	**1d**		Et	Me	**4d**	56 (2:1)
5	**1a**	*i*-Pr	vinyl	Me	**4e**	26 (4:1)

selectivity and yields were obtained for nonaromatic ketones (entries 1 and 3). The stereochemistry of the major products was assigned by analogy to that of the coupling products with aldehydes. Interestingly, only the 1,2-addition product (**4e**) was obtained when methyl vinyl ketone was used as the substrate (entry 5).

To verify that the reductive coupling is indeed directed by the propargylic hydroxy group, the PMB-protected propargylic alcohol **1d′** and cyclohexanecarboxaldehyde were subjected to the same titanium-mediated reductive coupling conditions (Scheme 2).[12] Although the coupling reaction did

Scheme 2. Reductive Coupling of **1d′**

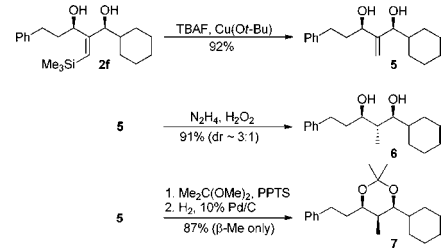


occur in 62% yield, the diastereoselectivity (dr = 2:1) of the reaction was mostly lost, indicating the pivotal role of the hydroxy group in the stereoselectivity of the reaction. However, a better understanding of the directing effect of the hydroxy group in the titanium-mediated reductive coupling still awaits further mechanistic studies.

The synthetic utility of these *syn*-1,3-diols was deomonstrated by the stereoselective conversion of **2f** to both the *anti*,*anti*- and *syn*,*syn*-stereotriads **6** and **7** (Scheme 3). First,

(12) A single example of titanium-mediated reductive coupling of a THP-protected secondary propargylic alcohol and propionaldehyde had been reported, but with no indication of diastereoselectivity of the reaction: Yamashita, K.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 7275–7278.

Scheme 3. Reduction of *syn*-1,3-Diol **2f**



the vinylsilane **2f** was protodesilylated by TBAF-Cu(O*t*-Bu) to give diol **5**.[13] Reduction of **5** by the in situ prepared diimide gave the *anti*,*anti*-stereotriad **6** with moderate diastereoselectivity (dr ~3:1). On the other hand, masking the diol **5** as an acetonide prior to catalytic hydrogenation by H_2 and 10% Pd/C allowed its diastereoselective reduction to generate the *syn*,*syn*-stereotriad **7** exclusively. Thus, titanium-mediated reductive coupling of propargylic alcohols and aldehydes followed by protodesilylation and diastereoselective reduction provides a convergent and highly efficient entry to both the *anti*,*anti*- and *syn*,*syn*-stereotriads, which are important structural motifs common to natural products of polyketide origin.

In summary, a titanium-mediated, hydroxy-directed reductive coupling of propargylic alcohols and aldehydes/ketones has been developed. Excellent diastereoselectivity and synthetically useful yields were obtained with a range of substrates. This reaction enabled a highly convergent three-component approach to *syn*-1,3-diols using (trimethylsilyl)-acetylene as a C1 linchpin and with other reagents of low costs.[14] These diols could be conveniently transformed into valuable building blocks for target-oriented synthesis. Applications of this approach in target-oriented synthesis are in progress and the results will be reported in due course.

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For an interesting comparison of the true costs of the reductive coupling by the stoichiometric Ti(O*i*-Pr)$_4$/*i*-PrMgCl system and the substoichiometric Ni-, Rh-, Ir-, and Ru-based systems, see ref 11 of Chen, M. Z.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 4982–4985.