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Catalytic Enantioselective Synthesis of Secondary Allylic Alcohols from Terminal Alkynes and Aldehydes via 1-Alkenylboron Reagents

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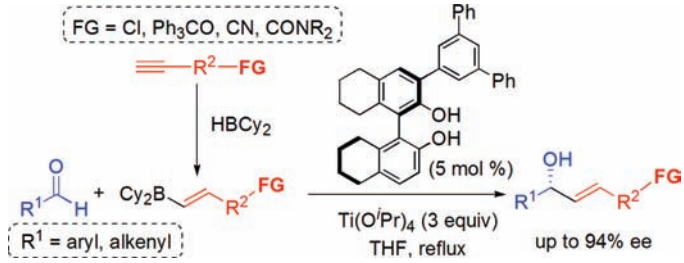
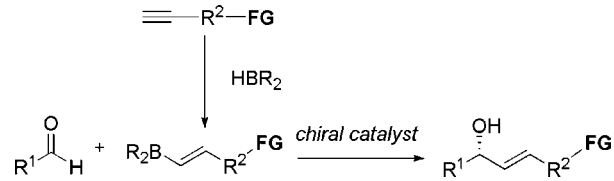
ABSTRACT



A practical one-pot method has been developed for preparing enantioenriched secondary allylic alcohols starting from terminal alkynes and aldehydes. Hydroboration of terminal alkynes with dicyclohexylborane and subsequent reaction of the resulting alkenylboron reagents with aldehydes in the presence of a catalytic amount (5 mol %) of 3-(3,5-diphenylphenyl)-H_8-BINOL and excess titanium tetraisopropoxide afforded the corresponding allylic alcohols in high enantioselectivities up to 94% ee.

Enantiomerically enriched chiral secondary allylic alcohols are important synthetic precursors. They are also found in numerous naturally occurring and biologically active compounds. Much attention has been focused on their catalytic enantioselective synthesis.[1−3] Of several approaches, the one based on alkyne hydroboration and subsequent catalytic enantioselective alkenylation of aldehydes with the resulting 1-alkenylboron reagents is particularly attractive in view of a wide availability of alkynes and aldehydes as well as potential functional-group tolerance (Scheme 1). In 1992,

Scheme 1. Enantioselective Synthesis of Secondary Allylic Alcohols from Terminal Alkynes and Aldehydes



Oppolzer and Radinov developed an enantioselective alkenylation of aldehydes catalyzed by chiral amino alcohol DAIB (3-*exo*-(dimethylamino)isoborneol), in which alkenylboron reagents are used after converting to alkenylzinc

(1) For kinetic resolution by the Sharpless epoxidation, see: (a) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, A. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; p 231.

(2) For early reports on enantioselective alkenylation of aldehydes, see: (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645–5648. (b) von dem Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719–5730.

(3) For the Nozaki−Hiyama−Kishi Coupling, see: (a) Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387–15393. (b) Hargadena, G. C.; Guirya, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407–2424.

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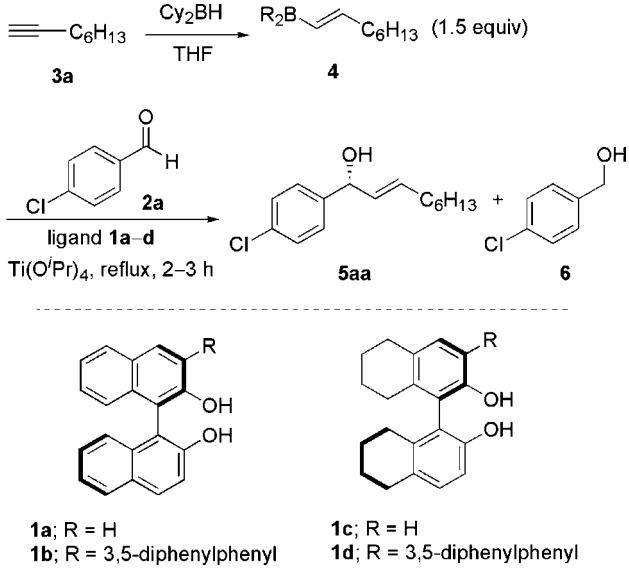
species through transmetalation with Me_2Zn or Et_2Zn.[4] Following this report, several efficient catalytic systems have been developed for the enantioselective alkenylation of aldehydes via boron/zinc transmetalation of the alkenylboron reagents.[5,6] Despite these advances, the requirement of the relatively expensive and pyrophoric dialkylzinc reagents in transmetalation makes this approach less attractive in practical applications.[7] Recently, Shibasaki and Kanai reported a new approach, without involving the boron/zinc transmetalation, using 1-alkenylboronic acid esters by the catalysis of a chiral Cu(I)F complex.[8] However, the boron reagents need to be prepared beforehand and are not appropriate for a one-pot synthesis starting from alkynes and aldehydes.

A recent report from our laboratory revealed that triethylborane can be used in the enantioselective alkylation of aldehyde.[9] In the presence of DPP-H_8-BINOL (**1d**) (2 mol %) and titanium tetraisopropoxide (3 equiv), triethylborane reacts with aromatic and unsaturated aldehydes to give ethylation products with high enantioselectivities. It occurred to us that, with a similar catalyst system, 1-alkenylboron reagents could be employed in the enantioselective alkenylation without using the dialkylzinc reagents. We now report a practical one-pot method for the catalytic enantioselective synthesis of secondary allylic alcohols starting from terminal alkynes and aldehydes via 1-alkenylboron reagents.

Hydroboration of 1-octyne (**3a**) with dicyclohexylborane in THF gave *trans*-1-octenylborane **4** regioselectively (Scheme 2).[10] Upon heating **4** (1.5 equiv) with *p*-chlorobenzaldehyde

Scheme 2. Catalytic Enantioselective Synthesis of Alcohol **5aa**



(**2a**) in THF under reflux for 3 h, dehydroboration[11] of **4** took place preferentially to give reduction product **6** in 41% yield with minor formation of alkenylation product *rac*-**5aa** (Table 1, entry 1). When the reaction of **2a** and **4** was carried out in the presence of titanium tetraisopropoxide (3 equiv), alkenylation became a major process, affording *rac*-**5aa** in 51% yield (entry 2). Under these conditions, enantioselective formation of (*R*)-**5aa** was observed by the addition of 5 mol % of BINOL derivatives **1a**−**d** (entries 3−6). Thus, for example, upon heating **2a** and **4** (1.5 equiv) in the presence of (*R*)-**1a** (5 mol %) and titanium tetraisopropoxide (3 equiv) in THF under reflux, (*R*)-**5aa** was obtained in 75% ee and in 71% yield. Of these ligands, the best result was obtained with (*R*)-DPP-H_8-BINOL (**1d**), which provided (*R*)-**5aa** in 89% ee and in 62% yield (entry 6). The yield and the enantioselectivity were improved by the increase of the amount of the alkenylboron reagent **4** (2 equiv) (entry 7). For the reaction employing **4** (1.5 equiv), decreasing the

Table 1. Catalytic Enantioselective Synthesis of Alcohol **5aa**[a]

	ligand	$Ti(O^iPr)_4$	**5aa**		**6**
entry	(mol %)	(equiv)	yield (%)	ee (%)	yield (%)
1	–	–	17	–	41
2	–	3	51	–	22
3	**1a** (5)	3	71	75	27
4	**1b** (5)	3	56	82	27
5	**1c** (5)	3	59	71	26
6	**1d** (5)	3	62	89	23
7[b]	**1d** (5)	3	72	91	25
8	**1d** (5)	1.5	42	86	20
9	**1d** (5)	4.5	61	89	22
10[c]	**1d** (5)	3	8	0	37
11	**1d** (2)	3	67	86	22

[a] Unless otherwise noted, reactions were carried out with *trans*-(oct-1-ennyl)BCy_2 **4a** (1.5 equiv) in refluxing THF for 2−3 h. [b] 2 equiv of **4a** was employed. [c] The reaction was carried out at room temperature for 7 h.

(4) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170–173.

(5) (a) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257–1258. (b) Dahmen, S. D.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119–4122. (c) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225–12231. (d) Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677–10683. (e) Ji, J.-X.; Qiu, L.-Q.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589–1590. (f) Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13608–13609. (g) Jeon, S.-J.; Chen, Y. K.; Walsh, P. J. *Org. Lett.* **2005**, *7*, 1729–1732. (h) Sprout, C. M.; Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 7408–7417. (i) Richmond, M. L.; Sprout, C. M.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 8835–8840. (j) Lauterwasser, F.; Gall, J.; Höfener, S.; Bräse, S. *Adv. Synth. Catal.* **2006**, *348*, 2068–2074. (k) Wu, H.-L.; Wu, P.-Y.; Uang, B.-J. *J. Org. Chem.* **2007**, *72*, 5935–5937. (l) Kerrigan, M. H.; Jeon, S.-J.; Chen, Y. K.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8434–8445. (n) Kim, H. Y.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 402–412.

(6) For a relevant approach based on hydrozirconylation of alkynes, see; (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197–5200. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454–6455.

(7) Catalytic enantioselective reductive coupling of alkynes and aldehydes is a promising alternative: (a) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442–3443. (b) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718–719. (c) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568–9569. (d) Yang, Y.; Zhu, S.-F.; Zhou, C.-Y.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2008**, *130*, 14052–14053. For review; see; (e) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34–46.

(8) Tomita, D.; Kanai, M.; Shibasaki, M. *Chem. Asian J.* **2006**, *1*−*2*, 161–166.

(9) Ukon, T.; Harada, T. *Eur. J. Org. Chem.* **2008**, 4405–4407.

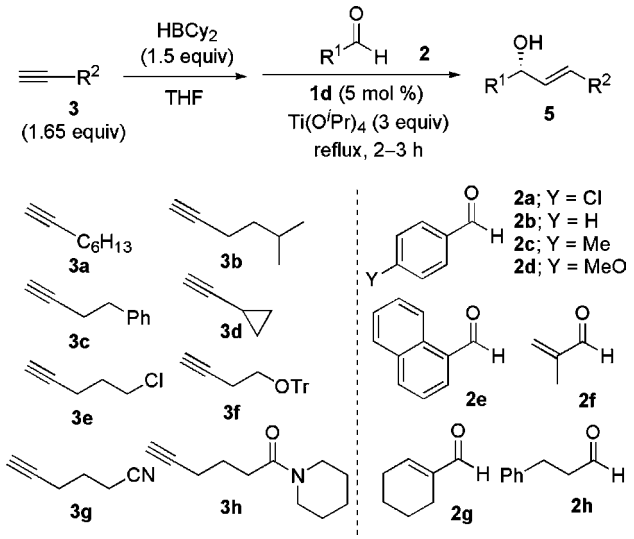
(10) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. *J. Org. Chem.* **1977**, *42*, 1392–1398.

(11) Midland, M. M.; Petre, J. E.; Zderic, S. A.; Kazubski, A. *J. Am. Chem. Soc.* **1982**, *104*, 528–531.

amount of titanium tetraisopropoxide to 1.5 equiv resulted in a decrease of the product yield and enantioselectivity (entry 8), while 4.5 equiv of titanium tetraisopropoxide did not afford better results (entry 9). At room temperature, the reaction was sluggish, giving *rac*-**5aa** in low yield and **6** as a major product (entry 10). At a 2 mol % catalyst loading, the yield of (*R*)-**5aa** was comparable, while the enantioselectivity was decreased to 86% ee (entry 11).

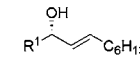
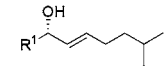
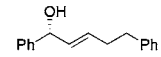
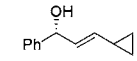
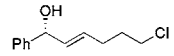
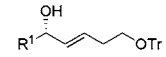
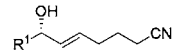
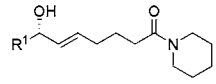
Under the conditions employing ligand **1d** (5 mol %) with titanium tetraisopropoxide (3 equiv) in refluxing THF, the scope of the present catalytic enantioselective synthesis of secondary allylic alcohols was examined for a variety of aldehydes **2a**−**h** and alkynes **3a**−**h** (Scheme 3). Hydroboration of alkyne **3a** with dicyclohexylborane followed by the reactions of the resulting alkenylboron reagent with aromatic aldehydes **2a**−**e** afforded 1-aryl-non-2-en-1-ols **5** in 60−72% yields with high enantioselectivities (90−94% ee) (Table 2, entries 1−6). The alkenylboron reagent also underwent enantioselective addition to α,β-unsaturated aldehydes **2f**,**g** to give divinyl carbinol **5fa** (93% ee) and **5ga** (91% ee) (entries 7 and 8). Lower, still acceptable, enantioselectivity was obtained in the reaction of aliphatic aldehyde **2h** (entry 9).

Scheme 3. Catalytic Enantioselective Synthesis of Secondary Allylic Alcohols **5** from Aldehydes **2** and Alkynes **3**



The scope of the reaction was then examined by varying the structure of the alkynes. High enantioselectivities (90−94% ee) were obtained for branched alkyne **3b** and phenyl-substituted alkyne **3c** in the reaction of aromatic aldehydes **2a**,**b** (entries 10−12), while the reaction of cyclopropylethyne (**3d**) and **2b** resulted in lower enantioselectivity (entry 13). The present reaction conditions are compatible with a range of functionalized alkynes, including those containing a chlorine atom, a protected alcohol, a nitrile, and an amide. Thus, alkenylboron reagents derived from 5-chloro-pent-1-yne (**3e**) and 4-trityloxy-but-1-yne (**3f**) underwent addition to **2a**,**b** in high enantioselectivities (87−91% ee) (entries 14−16). It should be noted that hexynenitrile **3g** and hexynamide **3h** were also successfully employed in the enantioselective alkenylation despite the potential reactivity of a cyano and amide functional groups (entries 17−20). The corresponding functionalized allylic alcohols were obtained also in high enantioselectivities (87−94% ee). To our knowledge, these reactions are the first examples of enantioselective alkenylation starting from alkynenitriles and alkynamides.

Table 2. Catalytic Enantioselective Synthesis of Secondary Allylic Alcohols **5** from Aldehydes **2** and Alkynes **3**[a]

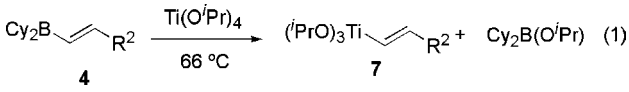
entry	allylic alcohol	yield (%)	ee (%)[b]
1	 **5aa**; R^1 = *p*-ClC_6H_4	62	89
2[c]	**5aa**	72	91
3	**5ba**; R^1 = Ph	60	90
4	**5ca**; R^1 = *p*-MeC_6H_4	60	90
5[c]	**5da**; R^1 = *p*-$MeOC_6H_4$	68	90
6	**5ea**; R^1 = 1-naphthyl	62	94
7	**5fa**; R^1 = CH_2=C(Me)	46	93
8	**5ga**; R^1 = 1-*c*-hexenyl	59	91
9	**5ha**; R^1 = $PhCH_2CH_2$	43	82
10	 **5ab**; R^1 = *p*-ClC_6H_4	62	90
11	**5bb**; R^1 = Ph	66	92
12	 **5bc**	67	94
13	 **5bd**	61	78
14	 **5be**	66	90
15	 **5af**; R^1 = *p*-ClC_6H_4	63	87
16	**5bf**; R^1 = Ph	70	91
17[c]	 **5bg**; R^1 = Ph	74	93
18[c]	**5cg**; R^1 = *p*-MeC_6H_4	63	91
19[c]	 **5ah**; R^1 = *p*-ClC_6H_4	64	87
20[c]	**5bh**; R^1 = Ph	64	94

[a] Unless otherwise noted, reactions were carried out by refluxing a THF solution of an alkenylboron reagent (1.5 equiv), prepared from alkyne **3** (1.65 equiv) and Cy_2BH (1.5 equiv), aldehyde **2**, ligand **1d** (5 mol %), and titanium tetraisopropoxide (3 equiv) for 2−3 h. [b] Determined by chiral stationary phase HPLC or capillary GC analysis. [c] The reaction was carried out with an alkenylboron reagent prepared from alkyne **3** (2.2 equiv) and Cy_2BH (2 equiv).

We speculate that alkenylboron reagent **4** undergoes boron/titanium transmetalation with titanium tetraisopropoxide selectively on the alkenyl group to produce alkenyltitanium **7** as an active intermediate (eq 1).[12,13] The low-yield formation of racemic product (*rac*-**5aa**) in the reaction at

(12) Alternatively, **7** would form an aggregate with concurrently produced $Cy_2B(O^iPr)$ and participate in the catalytic reaction. For a relevant aggregation with $ArAl(O^iPr)_2$, see: Wu, K.-H.; Gau, H-.M. *J. Am. Chem. Soc.* **2006**, *128*, 14808–14809.

room temperature (Table 1, entry 10) suggests that the boron/titanium transmetalation would be very slow at the low temperature and require THF reflux conditions to proceed. The result of a control experiment in the absence of ligand (Table 1, entry 2) implies that alkenyltitanium **7** would undergo facile addition in refluxing THF to give *rac*-**5** without the catalysis. The high enantioselectivities observed in the present reactions even at a relatively low catalyst loading could be rationalized not only by superior activity of the catalyst[14] but also by a relatively low concentration of alkenyltitanium **7** due to the slow rate of the transmetalation step.



4 **7**

In summary, we have developed a practical method for the highly enantioselective synthesis of secondary allylic alcohols starting from readily available 1-alkynes and aldehydes via 1-alkenylboron reagents. The reaction can be carried out by a one-pot operation without employing dialkylzinc reagents at a low catalyst loading (5 mol %). The reaction is applicable to a variety of functionalized alkynes, including those containing a chlorine atom, a protected alcohol, a nitrile, and an amide.

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Supporting Information Available: Experimental procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For mechanistic aspects of BINOLate-Ti catalysis, see: Baisells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336–10348.

(14) (a) Harada, T.; Kanda, K. *Org. Lett.* **2006**, *8*, 3817–3819. (b) Harada, T.; Ukon, T. *Tetrahedron: Asymmetry* **2007**, *18*, 2499–2502. (c) Muramatsu, Y.; Harada, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1088–1090. (d) Muramatsu, Y.; Harada, T. *Chem.—Eur. J.* **2008**, *14*, 10560–10563. (e) Muramatsu, Y.; Kanehira, S.; Tanigawa, M.; Miyawaki, Y.; Harada, T. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 19–32.