

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

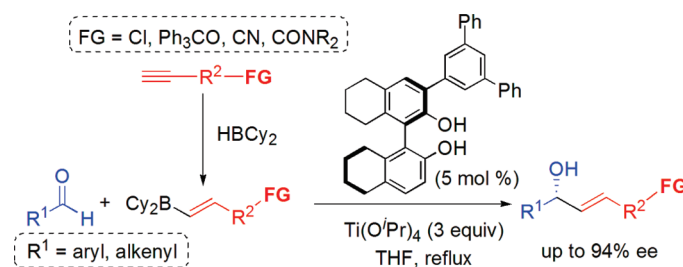
Takashi Shono and Toshiro Harada*

Department of Chemistry and Materials Technology, Kyoto Institute of Technology,
Matsugasaki, Sakyo-ku, Kyoto, Japan, 606-8585

harada@chem.kit.ac.jp

Received September 26, 2010

ABSTRACT

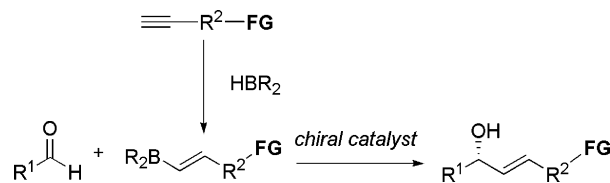


A practical one-pot method has been developed for preparing enantioenriched secondary allylic alcohols starting from terminal alkynes and aldehydes. Hydroboration of terminal alkynes with dicyclohexylborane and subsequent reaction of the resulting alkenylboron reagents with aldehydes in the presence of a catalytic amount (5 mol %) of 3-(3,5-diphenylphenyl)-H₈-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.

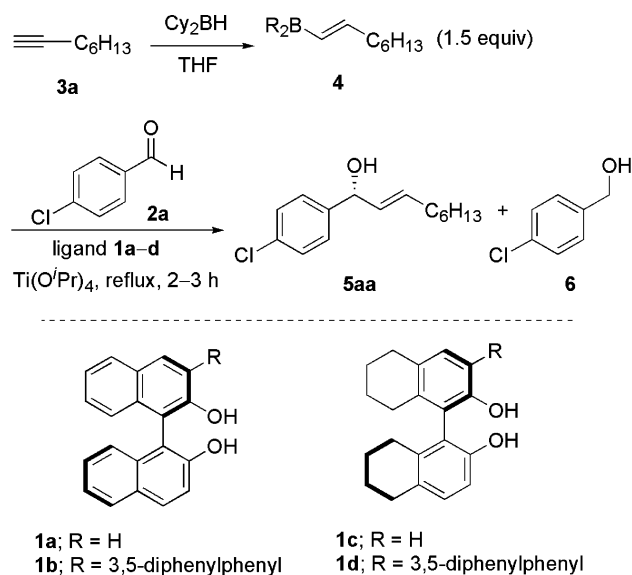
(3) For the Nozaki–Hiyama–Kishi Coupling, see: (a) Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387–15393. (b) Hargadena, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407–2424.

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 $\text{Cu}(\text{I})\text{F}$ 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 tetrakisopropoxide (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, dehydroboration¹¹ 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

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

entry	ligand (mol %)	Ti(O ⁱ Pr) ₄ (equiv)	5aa yield (%)	5aa ee (%)	6 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-en-1-yl)BCy₂ **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.

out in the presence of titanium tetrakisopropoxide (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 tetrakisopropoxide (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

(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.

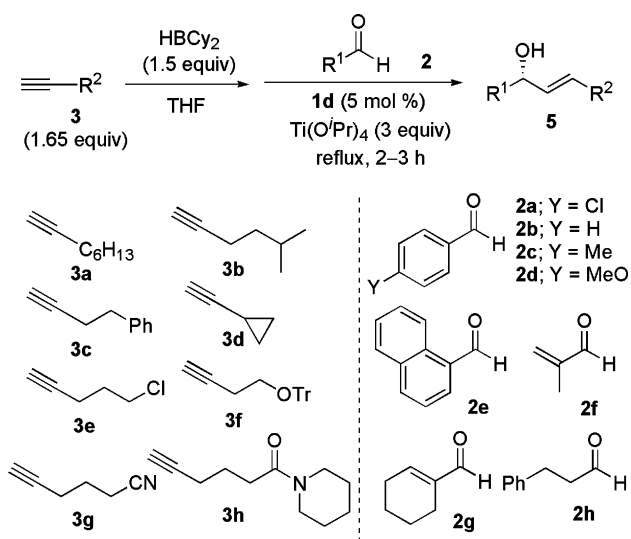
(10) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. *J. Org. Chem.* **1977**, 42, 1392–1398.

(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). Hydrobo-

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



ration 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).

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

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 = <i>p</i> -ClC ₆ H ₄	62 89
2 ^c		5aa	72 91
3		5ba ; R ¹ = Ph	60 90
4		5ca ; R ¹ = <i>p</i> -MeC ₆ H ₄	60 90
5 ^c		5da ; R ¹ = <i>p</i> -MeOC ₆ H 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 ₂ CH ₂	43 82
10		5ab ; R ¹ = <i>p</i> -ClC ₆ H 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 = <i>p</i> -ClC ₆ H ₄	63 87
16		5bf ; R ¹ = Ph	70 91
17 ^c		5bg ; R ¹ = Ph	74 93
18 ^c		5cg ; R ¹ = <i>p</i> -MeC ₆ H ₄	63 91
19 ^c		5ah ; R ¹ = <i>p</i> -ClC ₆ H ₄	64 87
20 ^c		5bh ; R ¹ = Ph	64 94

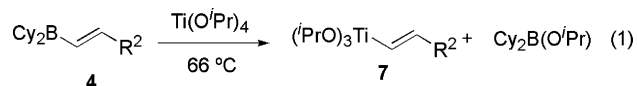
^a Unless otherwise noted, reactions were carried out by refluxing a THF solution of an alkenylboron reagent (1.5 equiv), prepared from alkyne **3** (1.65 equiv) and Cy₂BH (1.5 equiv), aldehyde **2**, ligand **1d** (5 mol %), and titanium tetraisopropoxide (3 equiv) for 2–3 h. ^b Determined by chiral 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 Cy₂BH (2 equiv).

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.

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 Cy₂B(OiPr) and participate in the catalytic reaction. For a relevant aggregation with ArAl(OiPr)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 catalyst¹⁴ but also by a relatively low concentration of alkenyltitanium **7** due to the slow rate of the transmetalation step.



In summary, we have developed a practical method for the highly enantioselective synthesis of secondary allylic

(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.

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.

Acknowledgment. This work was supported by KAKENHI (20550095) and by Kyoto Institute of Technology Research Fund.

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

OL1023213

(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.