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Enantioselective Alkylation of Aldehydes Using Functionalized Alkylboron Reagents Catalyzed by a Chiral Titanium Complex

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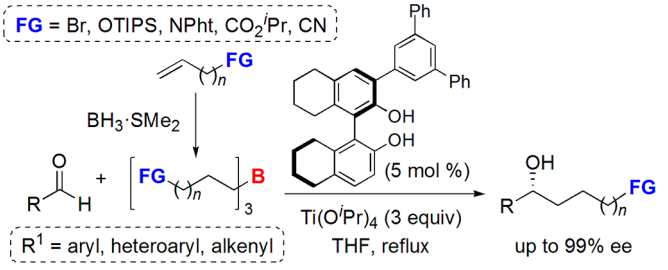
ABSTRACT



A practical method is developed for the synthesis of enantioenriched functionalized secondary alcohols through catalytic enantioselective alkylation of aldehydes. Functionalized alkylboron reagents, $[FG-(CH_2)_n]_3B$ (FG = Br, TIPSO, PhtN, $CO_2{}^iPr$, and CN) prepared from terminal olefin precursors by hydroboration, undergo enantioselective addition to aldehydes in the presence of a catalytic amount (5 mol %) of 3-(3,5-diphenylphenyl)-H_8-BINOL and excess titanium tetraisopropoxide to afford the corresponding functionalized alcohols in high enantioselectivities up to 99% ee.

A variety of methods have been developed for the catalytic enantioselective alkylation of aldehydes[1] ever since the seminal report of a chiral amino alcohol catalyzed reaction with dialkylzinc reagents by Noyori and co-workers.[2] However, the scope of alkyl groups that can be introduced is relatively limited. The situation is in good contrast to a wide range of aryl groups that can be introduced by a relevant catalytic enantioselective arylation reaction.[3] In particular, very few methods have been developed for the enantioselective addition of functionalized alkyl groups that would provide an efficient entry into chiral polyfunctional alcohols,[4,5] despite recent significant advances in the chemistry of the functionalized organometallic reagents.[6] Taking advantage of the easy access by the hydroboration of alkene precursors and high functional group tolerance, an alkylboron reagent would serve as one of the optimal reagents for the alkylation of aldehydes (Scheme 1). Indeed, Knochel and co-workers have reported a highly enantioselective method for aldehyde alkylation using alkylboron reagents.[5] In this method, functionalized

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(5) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229–8243.

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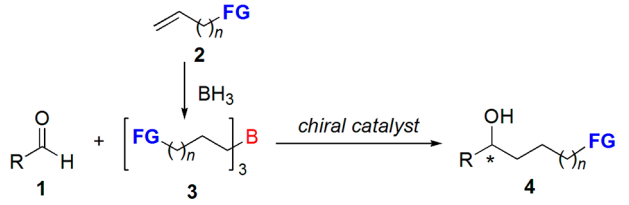
alkylboranes [FG−$(CH_2)_n$]BEt_2, prepared by hydroboration of the corresponding terminal alkenes with Et_2BH, was converted to dialkylzinc reagents [FG−$(CH_2)_n]_2Zn$ by a B/Zn exchange reaction with Et_2Zn and used in the presence of a chiral *bis*-triflylamide titanium complex for the enantioselective synthesis of polyfunctional secondary alcohols. Although the reaction exhibited high functional group tolerance and excellent selectivity at an 8 mol % catalyst loading, the use of pyrophoric neat Et_2Zn in large excess and its removal before use in the alkylation reaction make this protocol practically less attractive.

Scheme 1. Enantioselective Synthesis of Functionalized Secondary Alcohols from Terminal Alkenes and Aldehydes

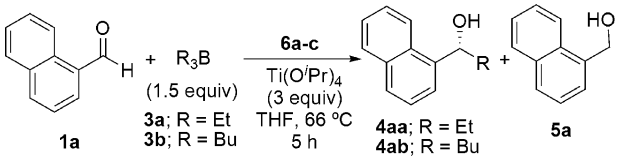


Recently, we have reported an enantioselective alkylation of aldehydes using Et_3B via direct boron to titanium transmetalation through the catalysis of a chiral titanium complex derived from 3-(3,5-diphenylphenyl)-H_8-BINOL (DPP-H_8-BINOL **6a**).[7] In the present study, we examined the application of the catalyst system to the enantioselective synthesis of polyfunctional chiral secondary alcohols using functionalized trialkylboranes **3** prepared from terminal alkenes **2**.[8]

Treatment of 1-naphthaldehyde (**1a**) with Et_3B (**3a**) (1.5 equiv) in the presence of (*R*)-DPP-H_8-BINOL **6a** (2 mol %) and $Ti(O^iPr)_4$ (3 equiv) in refluxing THF afforded the corresponding ethylation product **4aa** in 83% yield and in 96% ee (Scheme 2, entry 1).[7] Under these conditions, the reaction of **1a** with Bu_3B (**3b**) resulted in the major formation of the reduction product **5a** (49%) (entry 2). Butyl adduct **4ab** was obtained as a minor product, while maintaining high enantioselectivity. When 5 mol % of **6a** was employed, the yield of **4ab** was improved to 57% with retardation of the competing reduction (entry 3). (*R*)-DPP-BINOL **6c** (5 mol %) exhibited a slightly better result with respect to the yield of **4ab** but with lower enantioselectivity (entry 4). (*R*)-H_8-BINOL **6b** afforded the major reduction product even at 20 mol % loading (entry 5).

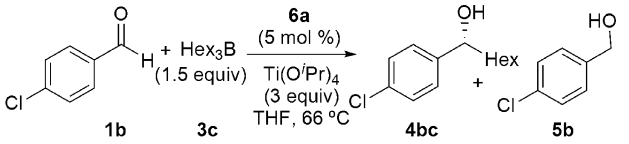
The undesirable reduction of aldehydes could proceed through dehydroboration[9] by alkylboranes **3** and/or

Scheme 2. Optimization of Reaction Conditions



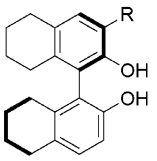
entry	R_3B	BINOLs **6** (mol %)	**3**	yield	ee (%)	**5a** (%)
1[7,a]	**2a**	**6a** (2)	**4aa**	83	96	6
2[7]	**2b**	**6a** (2)	**4ab**	28	92	49
3	**2b**	**6a** (5)	**4ab**	57	94	24
4	**2b**	**6c** (5)	**4ab**	64	90	26
5	**2b**	**6b** (20)	**4ab**	11	*b*	55

[a] The reaction was carried out for 2 h. [b] Ee was not determined.

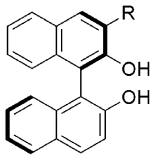


entry	conditions	**4bc** yield (%)	**4bc** ee (%)	**5b** (%)
6	without slow addition, 5 h	52	96	33
7	slow addition for 2 h and then 1 h	60	95	12
8	slow addition for 4 h and then 1 h	70	95	17
9[c]	slow addition for 4 h and then 1 h	21	96	30

[c] $HexBCy_2$ (1.5 equiv) was used.



6a; R = 3,5-diphenylphenyl
6b; R = H



6c; R = 3,5-diphenylphenyl

through Meerwein−Ponndorf−Verley-type reduction[10] by titanium tetraisopropoxide. We speculated that an alkyltitanium [$RTi(O^iPr)_3$] is an active species for alkylation of aldehydes. Its generation might be a rate-determining step by unfavorable transmetalation of the alkylboranes with titanium tetraisopropoxide, requiring THF refluxing conditions. According to this mechanistic proposition, the substrate aldehyde would be reduced by the coexisting alkylboranes and/or titanium tetraisopropoxide during the slow generation of the alkyltitanium reagents. To circumvent the problem, the reaction of *p*-chlorobenzaldehyde (**1b**) with Hex_3B (**2c**) was carried out under similar conditions of entry 3 by slowly adding the aldehyde. In accord with our expectation, the slow addition of **1b** improved the yield of corresponding product **3bc** to 60% and 70% after 2 and 4 h, respectively (entries 7 and 8 vs entry 6). In our recent study on enantioselective alkenylation of aldehydes by using alk-1-enyl dicyclohexylboranes (RCH=CHBCy_2), addition of the alkenyl groups took place selectively without the

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(8) For nonenantioselective carbonyl addition of alkylboron reagents catalyzed by a nickel complex, see: (a) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2005**, *7*, 4689–4691. (b) Hirano, K.; Yorimitsu, H.; Oshima, K. *Adv. Synth. Catal.* **2006**, *348*, 1543–1546. See, also: (c) Takahashi, G.; Shirakawa, E.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2005**, 1459–1460.

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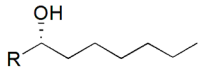
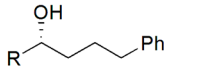
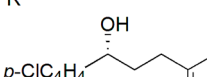
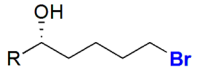
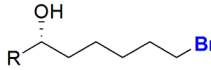
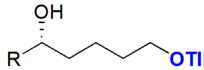
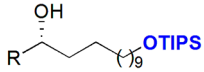
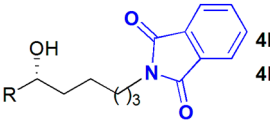
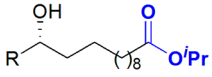
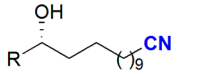
(10) Mahrwald, R.; Schick, H. *Synthesis* **1990**, 592–595.

(11) Shono, T.; Harada, T. *Org. Lett.* **2010**, *12*, 5270–5273.

Table 1. Catalytic Enantioselective Alkylation of Aldehydes Using Alkylboron Reagents[a]

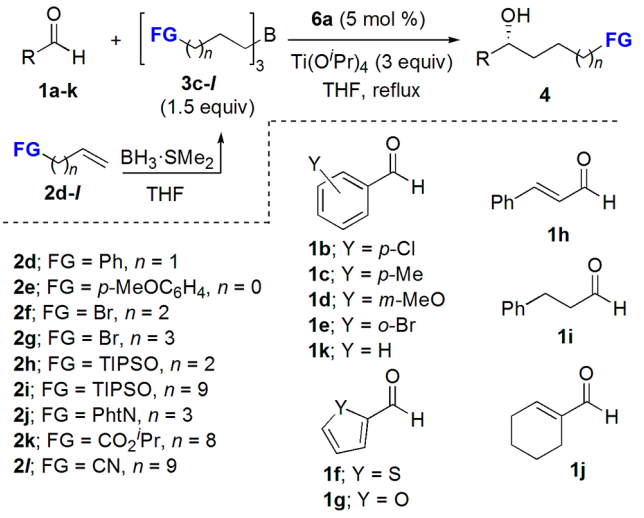
entry	product **4**	yield (%)[b]	ee (%)[c]
1	 **4ac**; R = 1-Naphthyl	64	94
2	**4bc**; R = *p*-ClC_6H_4-	70	96[d]
3	**4cc**; R = *p*-MeC_6H_4-	64	90
4	**4dc**; R = *m*-$MeOC_6H_4$-	64	96
5	**4ec**; R = *o*-BrC_6H_4-	35	66
6	**4fc**; R = 2-Thienyl-	68	94
7	**4gc**; R = 2-Furyl-	53	91
8	**4hc**; R = PhCH=CH-	61	91
9	**4ic**; R = $PhCH_2CH_2$-	28	72[d]
10	 **4bd**; R = *p*-ClC_4H_4-	72	99
11	 **4jd**; R = 1-*c*-Hexenyl-	73	96
12	**4be**	48	96
13	 **4bf**; R = *p*-ClC_4H_4-	68	91
14	**4kf**; R = Ph	71	93
15	 **4bg**; R = *p*-ClC_4H_4-	55	94
16	**4fg**; R = 2-Thienyl-	54	94
17	 **4bh**; R = *p*-ClC_4H_4-	70	93
18	**4eh**; R = *o*-BrC_4H_4-	44	64
19	 **4ai**; R = 1-Naphthyl-	70	94
20	**4bi**; R = *p*-ClC_4H_4-	70	93
21	 **4bj** R = *p*-ClC_4H_4-	74	96
22	**4hj**; R = PhCH=CH-	66	89
23	 **4bk**; R = *p*-ClC_4H_4-	76	98
24	**4fk**; R = 2-Thienyl-	53	97
25	 **4b*l***; R = *p*-ClC_4H_4-	74	93
26	**4f*l***; R = 2-Thienyl-	74	96

[a] Reactions were carried out by adding aldehydes **1** (0.5 mmol) in THF (0.7 mL) slowly for 4 h to a solution of boron reagents **3** (1.5 M) (1.5 equiv), **6a** (5 mol %), and $Ti(O^iPr)_4$ (3 equiv) in THF at 66 °C. The reaction mixture was refluxed further for 1 h. [b] Isolated yield. [c] Determined by a chiral phase LC analysis. [d] The absolute configuration was determined to be *R*. See Supporting Information for details.

participation of the cyclohexyl group.[11] Based on this observation, hexylation of **2b** was examined by using $HexBCy_2$ (1.5 equiv) as a boron reagent (entry 9). Although hexyl adduct **3bc** was obtained as a sole alkylation product, the reaction was sluggish and the reduction pathway predominated (entry 9).

Under the slow addition conditions (Scheme 2, entry 8), the scope of the catalytic enantioselective alkylation was studied first for a range of aldehydes **1a**–**i** by using Hex_3B

Scheme 3. Catalytic Enantioselective Alkylation of Aldehydes by Using Alkylboron Reagents



(**3c**) (Scheme 3). The reaction of *para* and *meta* substituted benzaldehyde derivatives (**1b**–**d**) as well as 1-naphthaldehyde **1a** afforded the corresponding products **4** in good yields and in high selectivities (90–96% ee) (Table 1, entries 1–4). On the other hand, moderate enantioselectivity was observed for *ortho* substituted derivative **1e** (entry 5). The reaction exhibited high enantioselectivity (91–94% ee) also for heteroaromatic aldehydes **1f**,**g** and α,β-unsaturated aldehyde **1h** (entries 6–8). Aliphatic aldehyde **1j** was considerably less reactive, affording the corresponding product **4ic** in low yield with an inferior selectivity (72% ee).

To clarify the scope for alkylboron reagents **3**, reactions were carried out with those prepared from terminal alkenes **2** by hydroboration with $BH_3 \cdot SMe_2$. Boron reagents **3**, prepared from aryl substituted olefins **2d**,**e** and ω-bromo-1-alkenes **2f**,**g**, underwent enantioselective addition to aromatic, heteroaromatic, and α,β-unsaturated aldehydes to give the corresponding alkylation products **4** in high enantioselectivity (91–99%). Functionalized alkylboron reagents prepared from TIPS protected olefinic alcohols **2h**,**i** and the phthalimide derivative (**2j**) of pent-4-enylamine also underwent enantioselective addition to aromatic aldehydes to furnish the corresponding monoprotected diols and amino alcohols, respectively, in 89–96% ee, with the exception of the reaction of *o*-bromo derivative **1f** (entries 17–22). Alkylboron reagents bearing isopropyl ester and cyano groups, derived from terminal functionalized alkenes **2k**,***l***, could be used successfully in the present reaction (entries 23–26). The corresponding functionalized secondary alcohols were obtained in good yields and high enantioselectivities (93–97% ee).

Recently, we have reported an alternative method for enantioselective addition of functionalized alkyl groups to

(12) Kinoshita, Y.; Kanehira, S.; Hayashi, Y.; Harada, T. *Chem.—Eur. J.* **2013**, *19*, 3311–3314.

aldehydes by using alkylzinc bromide reagents [FG−$(CH_2)_n$−ZnBr·LiCl] in the presence of the DPP-H_8-BINOL-derived titanium catalyst.[12] Notably, the two methods can be employed in the preparation of enantiomerically enriched functionalized alcohols in a complementary manner. Thus, for example, starting from ω-bromo-1-alkene **2f**,**g**, the enantioselective addition of terminal alkenyl groups can be achieved *via* the corresponding alkylzinc bromide reagents (CH_2=CH$(CH_2)_n$ZnBr; n = 2, 3) while, on the other hand, the application of the present method realizes the enantioselective addition of ω-bromoalkyl groups (entries 13−16).

In summary, we have developed a practical method for the enantioselective synthesis of functionalized secondary alcohols starting from readily available terminal alkenes and aldehydes via alkylboron reagents. The reaction can be carried out at a low catalyst loading (5 mol %) and is applicable to a variety of functionalized alkenes, including those containing a bromine atom, a protected alcohol and amine, an ester, and a nitrile.

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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.

The authors declare no competing financial interest.