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Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aldehydes: An Efficient Route to Enantiomerically Enriched α-Alkoxyorganoboronate Esters

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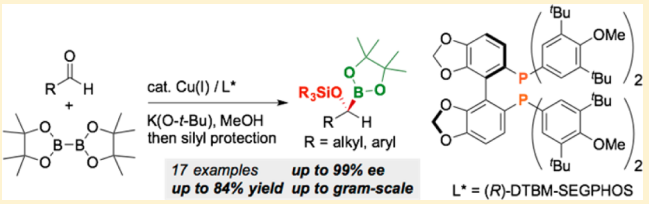
Supporting Information

ABSTRACT: The first catalytic enantioselective nucleophilic borylation of a C═O double bond has been achieved. A series of aldehydes reacted with a diboron reagent in the presence of a copper(I)/DTBM-SEGPHOS complex catalyst using MeOH as a proton source to give the corresponding optically active α-alkoxyorganoboronate esters with excellent enantioselectivities. Furthermore, the products could be readily converted to the corresponding functionalized chiral alcohol derivatives through stereospecific C−C bond forming reactions involving the stereogenic C−B bond.

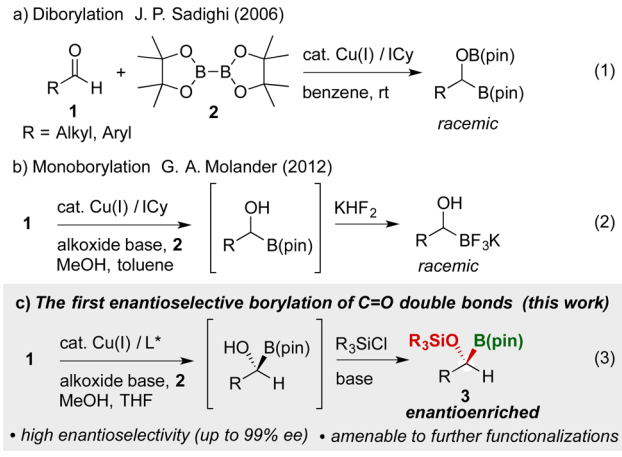


INTRODUCTION

Enantioenriched organoboronate esters are a particularly important class of chiral compounds that have attracted considerable interest from researchers working in a variety of different fields because of their broad range of synthetic and medicinal applications.[1] Significant research efforts have recently been focused on the development of catalytic enantioselective strategies for the construction of stereogenic C−B bonds.[2] In particular, copper(I)-catalyzed enantioselective borylation reactions with diboron reagents have emerged as efficient methods for the synthesis of chiral organoboronate with high enantioselectivity.[3−5] Despite this recent progress in borylation chemistry, there have been no reports in the literature pertaining to the catalytic enantioselective borylation of carbon−oxygen double bonds.[6,7] The development of a novel transformation of this type would allow for the direct synthesis of chiral α-alkoxyorganoboronate esters, which could be used as chiral building blocks in organic synthesis and medicinal chemistry.[8] Molander and Wisniewski[9] reported the successful development of a stereospecific cross-coupling reaction between chiral potassium α-(benzyloxy)alkyltrifluoroborates and aryl halides. It is noteworthy, however, that this pioneering work required the synthesis of an enantiomerically enriched α-alkoxyorganotrifluoroborate through multiple synthetic transformations as well as the addition of a stoichiometric amount of a chiral auxiliary.[10] Thus, the development of a new method for the catalytic enantioselective addition of boron nucleophiles to carbonyl compounds to give chiral α-alkoxyorganoboronate esters is therefore highly beneficial.[9,11−13]

The first of these pioneering studies toward the catalytic borylation of aldehydes was reported by Sadighi et al.[12] in 2006, where an *N*-heterocyclic carbine(NHC)/copper(I) complex was found to catalyze the diboration of both aliphatic and aromatic aldehydes (Scheme 1a). More recently, Molander et al.[9] developed a process for the copper(I)-catalyzed monoborylation of aldehydes using methanol as a proton source (Scheme 1b). Despite the considerable progress made by these researchers, their works have not yet been extended to the development of enantioselective processes via the introduction of a chiral ligand. Herein, we report the development of the first catalytic enantioselective borylation of aldehydes with a diboron compound to afford the corresponding chiral α-alkoxyorganoboronate esters using a copper(I)/DTBM-SEGPHOS complex catalyst (Scheme 1c). This new reaction exhibited excellent enantioselectivities and a broad substrate

Scheme 1. Catalytic Borylation of Aldehydes



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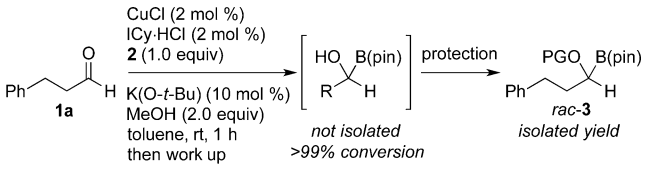
scope, and the products could be converted to the corresponding enantiomerically enriched secondary alcohol derivatives through stereospecific C−C bond forming reactions.

RESULTS AND DISCUSSION

Our initial efforts in this study were focused on the development of a suitable method for the purification and isolation of α-hydroxyalkylboronate esters, which are generally unstable to purification by column chromatography over silica gel. Although the borylated products can be isolated by converting them to the corresponding organotrifluoroborates, it can be difficult to determine the ee values of these products by HPLC analysis.[9] With this in mind, it would be a critical requirement of any newly developed enantioselective process to incorporate an isolation procedure that would allow for HPLC analysis of the resulting products. We have attempted various etherifications of the hydroxy group in the product resulting from the borylation of aliphatic aldehyde **1a** in the presence of a copper(I)/ICy complex catalytic system, but yields were poor (Table 1, entries 1−3, <33% yields).[14] Other protection strategies, including the esterification and carbamylation, under various conditions were investigated, but resulted in low isolated yields (Table 1, entries 4−7, <22% yields). Pleasingly, however, the desired product could be obtained in sufficiently good yield (Table 1, entry 8, 64% yield) when a standard silyl protection protocol was used to protect the hydroxyl group of the crude product. $BnMe_2Si-$ and Ph_2MeSi- as well as Me_3Si- groups can also be used without significant difference in the yields and the product stability. We used several silyl groups suitable for HPLC analysis.[15]

Table 1. Investigation of the Protecting Group for Isolating the Aldehyde Borylation Product

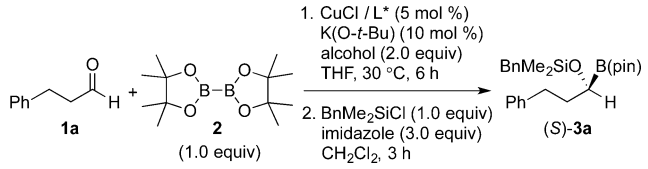


entry	PG	reaction conditions	yield (%)[a]
1	Bn−	BnBr, NaH, THF	26 (34)
2	Bn−	benzyloxypyridinium salt, MgO	33 (38)
3	Me−	Me_3OBF_4, CH_2Cl_2	28 (35)
4	PhCO−	PhCOOH, EDC, DMAP	22 (55)
5	PhCO−	$(PhCO)_2O$, DMAP, CH_2Cl_2	20 (48)
6	PhCO−	PhCOCl, pyridine, DMAP	17 (43)
7	Me_2NCO-	Me_2NCOCl, pyridine, CH_2Cl_2	− (53)
8	Me_3Si-	Me_3SiCl, imidazole, CH_2Cl_2	64 (70)

[a]The NMR yields of *rac*-**3** are shown in parentheses.

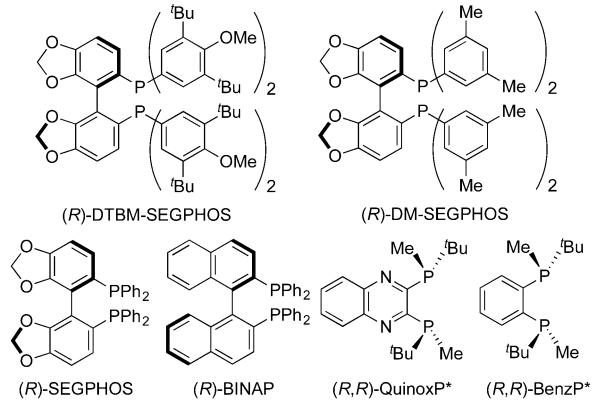
With an optimized procedure in hand, we proceeded to investigate the enantioselective borylation process using chiral bisphosphine ligands (Table 2). The reaction of aliphatic aldehyde **1a** with bis(pinacolato)diboron (**2**) (1.0 equiv) in the presence of CuCl/(*R*)-DTBM-SEGPHOS (5 mol %), K(O-*t*-Bu) (10 mol %), and MeOH (2.0 equiv), which was used as a proton source, in THF at 30 °C (Table 2) afforded the desired product (*S*)-**3a** in good yield (72%) with excellent enantioselectivity (96% ee) via the silyl protection of the crude α-hydroxyalkylboronate (Table 2, entry 1). The use of the less sterically encumbered SEGPHOS type ligands led to a significant decrease in the enantioselectivity of the reaction

Table 2. Optimization of the Reaction Conditions for the Copper(I)-Catalyzed Enantioselective Borylation of Aliphatic Aldehyde 1a[a]



entry	chiral ligand	alcohol	yield (%)[b]	ee (%)[c]
1	(*R*)-DTBM-SEGPHOS	MeOH	72(70)	96
2	(*R*)-DM-SEGPHOS	MeOH	71	32
3	(*R*)-SEGPHOS	MeOH	74	24
4	(*R*)-BINAP	MeOH	66	69
5	(*R,R*)-QuinoxP*	MeOH	61	69
6	(*R,R*)-BenzP*	MeOH	68	60
7[d]	(*R*)-DTBM-SEGPHOS	*i*-PrOH	28	53
8[e]	(*R*)-DTBM-SEGPHOS	none	34	22
9[f]	(*R*)-DTBM-SEGPHOS	MeOH	65(59)	96

[a]Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.5 mmol), and K(O-*t*-Bu) (0.05 mmol) in THF (1.0 mL). [b]NMR yields. Isolated yields are shown in parentheses. [c]The ee values for **3a** were determined by HPLC analysis. [d]The reaction time was 15 h. [e]The reaction time was 24 h. [f]The reaction was carried out with 1 mol % copper(I) catalyst and the reaction time was 24 h.



(Table 2, entries 2 and 3). The use of chiral phosphine ligands such as (*R*)-BINAP, (*R,R*)-QuinoxP*, and (*R,R*)-BenzP* also gave poor results (Table 2, entries 4−6). The nature of the proton source was also determined to be important to the reactivity and enantioselectivity observed during the transformation (Table 2, entries 7 and 8). For example, the use of *i*-PrOH instead of MeOH resulted in a low yield (28%) and enantioselectivity (53% ee) (Table 2, entry 7). Furthermore, when the reaction was conducted without MeOH, the reaction was not completed after longer reaction time (24 h) to afford a lower yield (34%) of the product with a lower enantioselectivity (22% ee) (Table 2, entry 8). This enantioselective borylation also proceeded with 1 mol % copper(I) catalyst and showed high enantioselectivity (96% ee), while longer reaction time was required for the completion of the reaction (Table 2, entry 9).

Next, we proceeded to investigate the scope of enantioselective borylation using various aldehydes (Table 3). The reaction of simple aliphatic aldehydes proceeded well to give the desired products in sufficient yields with high enantioselectivities (Table 3, entries 1−5). Pleasingly, the products of the reactions involving α-branched aliphatic aldehydes could be

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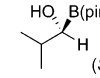
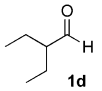
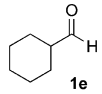
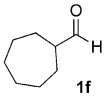
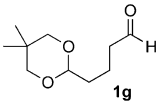
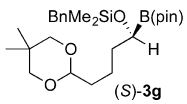
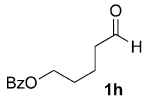
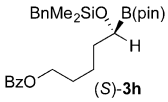
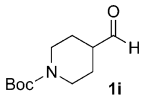
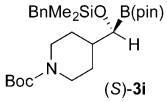
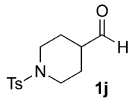
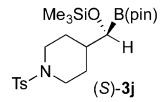
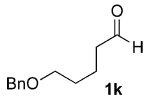
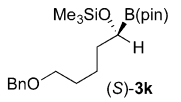
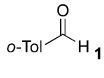
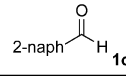
Table 3. Substrate Scope of the Enantioselective Borylation of Aliphatic and Aromatic Aldehydes[a]

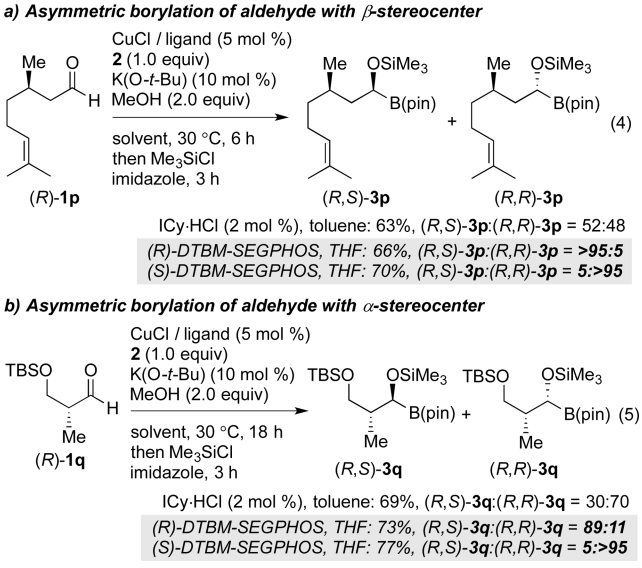
entry	substrate	product	yield (%)[b]	ee (%)[c]
1[d]	 **1b**	 (*S*)-**3b**	51	96
2[d,e]	 **1c**	 (*S*)-**3c**	77	96
3[d,e]	 **1d**	 (*S*)-**3d**	82	92
4[d]	 **1e**	 (*S*)-**3e**	61	95
5[d]	 **1f**	 (*S*)-**3f**	84	95
6	 **1g**	 (*S*)-**3g**	66	85
7	 **1h**	 (*S*)-**3h**	69	90
8	 **1i**	 (*S*)-**3i**	81	95
9	 **1j**	 (*S*)-**3j**	52	91
10	 **1k**	 (*S*)-**3k**	69	95
11	 **1l**	 (*S*)-**3l**	trace	–
12	 **1m**	 (*S*)-**3m**	34	90
13	 **1n**	 (*S*)-**3n**	66	65
14[f]	 **1o**	 (*S*)-**3o**	22(71)	99

[a]Conditions: CuCl (0.025 mmol), (*R*)-DTBM-SEGPHOS (0.025 mmol), **1** (0.5 mmol), **2** (0.5 mmol), MeOH (1.0 mmol), and K(O-*t*-Bu) (0.05 mmol) in THF (1.0 mL). [b]Isolated yield. [c]Ee values for **3** were determined by HPLC analysis. [d]Ee values were determined after stereospecific derivatization. [e]Isolated yield without silyl protection. [f]Isolated yield by converting into the corresponding potassium α-hydroxyalkyltrifluoroborate using KHF_2 is shown in parentheses.

isolated by flash column chromatography in good yields without the need for the protection of the alcohol moiety (Table 3, entries 2 and 3). It is noteworthy that this reaction exhibited good functional group compatibility, with aliphatic aldehydes bearing acetal, ester, Boc-protected amine, sulfonamide and benzyl ether groups reacting smoothly to give the corresponding chiral boronates with high enantioselectivities (Table 3, entries 6–10). Unfortunately, however, pivalaldehyde did not react under the current conditions (Table 3, entry 11). Several aromatic aldehydes were also investigated (Table 3, entries 12–14).[16] Benzaldehyde proceeded through the reaction with high enantioselectivity (90% ee) to give the desired product, albeit in a low isolated yield (i.e., 66% yield by NMR, 34% isolated yield) because of the poor stability of the product toward purification by column chromatography over silica gel (Table 3, entry 12). The application of the optimized conditions to the more sterically hindered 2-methylbenzaldehyde led to an improved chemical yield (66%), but the enantioselectivity was decreased (65% ee) (Table 2, entry 13). 2-Naphtaldehyde was also reacted with high enantioselectivity (99% ee), but resulted in a low isolated yield (22%) (Table 3, entry 14). Pleasingly, we found that the product derived from 2-naphtaldehyde could be isolated in good yield by converting the corresponding potassium α-hydroxylalkyltrifluoroborate using KHF_2 (71%).[9]

We also tested the asymmetric borylation of chiral aldehyde substrates to ensure the extent of substrate versus catalyst control (Scheme 2). While reaction of (*R*)-citronellal [(*R*)-**1p**]

Scheme 2. Catalyst-Controlled Asymmetric Borylation of Chiral Aldehyde Substrates



led to diastereomeric mixtures (d.r. 52:48) using the ICy/CuCl achiral catalyst, when the ligand (*R*)- and (*S*)-DTBM-SEGPHOS was used, excellent diastereoselectivities (d.r. > 95:5 and d.r. 5:>95, respectively) were observed, indicating complete catalyst control (Scheme 2a, eq 4). Furthermore, employing ICy as the ligand for the borylation of α-chiral aldehyde (*R*)-**1q** resulted in a moderate diastereomeric ratio (d.r. 30:70) while using the ligand (*R*)- and (*S*)-DTBM-SEGPHOS provided high catalyst-controlled stereoselectivities (d.r. 89:11 and >95:5, respectively) (Scheme 2b, eq 5).

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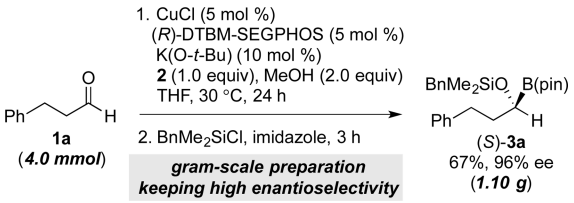
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

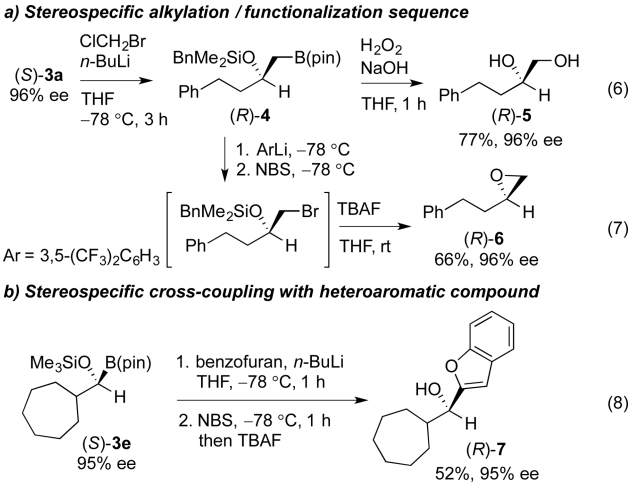
To demonstrate utility of this protocol, we investigated the gram-scale synthesis of α-alkoxyorganoboronate esters (Scheme 3). The borylation of **1a** was carried out on 4.0 mmol scale, affording the product (*S*)-**3a** in good yield with excellent enantioselectivity (67%, 96% ee).

Scheme 3. Gram-Scale Synthesis of Enantioenriched Chiral α-Alkoxyorganoboronate Esters



Enantioenriched α-alkoxyorganoboronate esters could potentially be used as building blocks in organic synthesis for the preparation of various functionalized chiral compounds. With this in mind, we conducted a preliminary investigation of the stereospecific C−C bond forming reactions of the chiral boronate products using homologation methods (Scheme 4).

Scheme 4. Stereospecific C−C Bond Forming Reactions of Chiral α-Alkoxyorganoboronate Esters



The borylation product (*S*)-**3a** was subjected to a one-carbon homologation process where it was treated with a halomethyllithium reagent followed by H_2O_2 oxidation to provide the desired alkylated diol product in a completely stereospecific manner (Scheme 4a, eq 6).[17] Furthermore, the chiral epoxide (*R*)-**6** was successfully obtained using the same homologation strategy followed by a bromination/deprotection sequence (Scheme 4a, eq 7).[18] Aggarwal et al.[19] recently reported the enantiospecific coupling of optically active alkylboronates with aryllithium compounds, and this novel method was applied to the chiral boronate synthesized in the current study (Scheme 4b, eq 8). The cross-coupling of (*S*)-**3e** with benzofuran proceeded and the subsequent deprotection of the silyl group afforded the arylated product (*R*)-**7** with excellent stereospecificity.

We have proposed a possible reaction mechanism for the current copper(I)-catalyzed borylation of aldehydes, which is shown in Figure 1.[20] The reaction of CuCl with the ligand and K(O-*t*-Bu) would result in the formation of copper(I) alkoxide

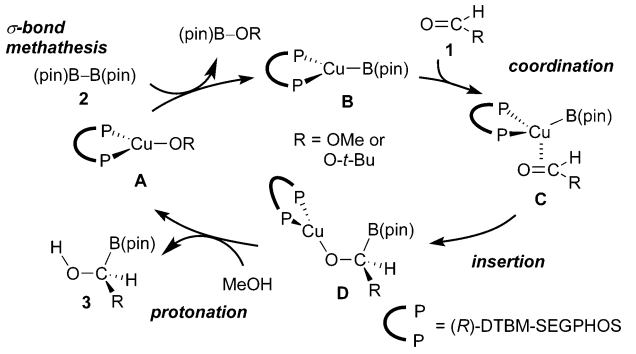


Figure 1. Proposed reaction mechanism for copper(I)-catalyzed enantioselective borylation of aldehydes.

A, which would initially react with diboron **2** to afford the boryl copper(I) intermediate **B**. The coordination of the aldehyde **1** to intermediate **B** would result in the formation of the π-complex **C**, which would undergo an insertion reaction to give the borylated copper(I) alkoxide **D**. The protonation of **D** would proceed in the presence of methanol to give the borylation product **3** as well as regenerating the copper(I) alkoxide **A**. Preliminary DFT studies with B3PW91/cc-pVDZ[21] showed that the reaction of SEGPHOS/Cu$B(O_2C_2H_4)$ with formaldehyde proceeds with a low activation barrier of +6.8 kcal/mol ($\Delta G^{\ddagger}$) to produce LCu−OCH_2−$B(O_2C_2H_4)$ product. The reaction path to LCu−CH_2O−$B(O_2C_2H_4)$ was found to be unfavorable.

CONCLUSION

In summary, we have developed, for the first time, enantioselective nucleophilic borylation of aldehydes using a copper(I)/DTBM-SEGPHOS chiral complex catalyst to afford chiral α-alkoxyorganoboronate esters with excellent enantioselectivities. The newly synthesized chiral α-alkoxyorganoboronate esters could be transformed to functionalized chiral alcohol derivatives using stereospecific C−C bond forming reactions. Recently, copper(I)-catalyzed enantioselective 1,2-silyl additions to C=O and C=N double bonds using a silylboron reagent have been reported.[22] We believe that these studies as well as the present our work on the catalytic enantioselective 1,2-metal addition of carbonyl compounds will provide attractive umpolung pathways for the synthesis of useful enantioenriched functionalized alcohols. Further studies directed toward the elucidation of the reaction mechanism[20] and the development of methodologies for the enantioselective borylation of other carbonyl compounds such as ketones as well as imines are currently underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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