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Nucleophilic Activation of Alkenyl and Aryl Boronates by a Chiral $Cu^{I}F$ Complex: Catalytic Enantioselective Alkenylation and Arylation of Aldehydes

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Abstract: A new method for the catalytic enantioselective alkenylation and arylation of aldehydes involves the activation of alkenyl and aryl boronates by a catalytic amount of the $Cu^{I}F$–DTBM-segphos complex through transmetalation, generating novel alkenyl and aryl copper species. These reagents act as the actual nucleophile. A range of aldehydes can be converted into optically active secondary allyl alcohols or diaryl methanols with excellent enantioselectivity. The appropriate choice of additives, depending on the substrate, is critical to ensure high yields of products. These additives possibly modulate the catalyst turnover step from copper alkoxide intermediates generated by the addition of organocopper reagents to aldehydes.

Keywords: alkenylation · arylation · asymmetric catalysis · boron · copper

Introduction

Enantiomerically enriched allylic alcohols and diaryl methanols are versatile chiral building blocks in organic synthesis. Kinetic resolution by the Sharpless epoxidation[1] and enantioselective addition of alkenyl zinc reagents to carbonyl compounds[2] are the two main catalytic methods for the synthesis of enantiomerically enriched allylic alcohols. Even those synthetically useful methodologies have drawbacks. Although the Sharpless kinetic resolution reliably produces high enantioselectivity from a wide range of substrates, catalyst turnover is not necessarily high, and the maximum chemical yield is intrinsically 50%. On the other hand, catalytic enantioselective alkenylation of carbonyl compounds constructs allylic asymmetric carbon atoms through carbon–carbon bond formation. Alkenyl zinc reagents are almost always used as a nucleophile in this type of reaction owing to their modest reactivity, which can be enhanced by an asymmetric catalyst. There are two main methods for the preparation of alkenyl zinc reagents. Oppolzer and Radinov reported that alkenyl zinc can be generated through transmetalation of alkenyl boron and dialkyl zinc species.[2a] After the generation of alkenyl boron intermediates by hydroboration of terminal alkynes, a stoichiometric amount of dialkyl zinc is added at −78 °C. The alkenyl zinc solution formed was used directly in the presence of the Noyori 3-*exo*-dimethylaminoisoborneol (DAIB) catalyst in the enantioselective alkenylation of aldehydes by Oppolzer and Radinov. This method for the generation of alkenyl zinc reagents was utilized in catalytic enantioselective alkenylations developed by the groups of Bräse,[2c] Chan,[2d] Yang,[2e] and Walsh.[2f] Another method was developed by Wipf and Ribe[2b] and involved the hydrozirconation of terminal alkynes with the Schwartz reagent[3] followed by transmetalation with zinc by the addition of dimethylzinc.[4] Wipf and Ribe utilized this alkenyl zinc species in a catalytic enantioselective alkenylation of aldehydes.[2b] Recently, the latter method was extended to a catalytic enantioselective alkenylation of ketones by Walsh and Li.[2g,h] In this reaction, further transmetalation from alkenylzinc to alkenyltitanium requires a stoichiometric amount of $Ti(OiPr)_4$. Therefore, existing methods for catalytic enantioselective alkenylation require stoichiometric amounts of at least two metals (B and Zn; Zr and Zn; Zr, Zn, and Ti).[5] The sensitivity of organozinc reagents to air and water is an additional concern in terms of user-friendliness.

With regard to the synthesis of enantiomerically enriched diaryl methanols, the catalytic enantioselective reduction of diaryl ketones[6] and the catalytic enantioselective arylation

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of aldehydes[7] have been studied. In the former reaction, two aryl substituents on a prochiral carbonyl carbon atom need to be differentiated by an asymmetric catalyst. This type of differentiation is only possible for substrates with two aryl groups of significantly different electronic character. On the other hand, the difficulty of the latter reaction derives from the fact that reactions between aldehydes and diphenylzinc proceed spontaneously without activation of the catalyst. Fu and co-workers reported the first example in this category in which a chiral azaferrocene ligand allows the formation of products with moderate enantioselectivity.[7a] Much higher enantioselectivity was demonstrated by Pu and Huang, who used a binol-derived catalyst (20 mol%) pretreated with Et_2Zn (40 mol%) under dilute conditions.[7b] Bolm et al. efficiently suppressed the uncatalyzed background reaction of Ph_2Zn by decreasing its concentration by taking advantage of the ligand exchange between Ph_2Zn and unreactive Et_2Zn.[7d] Moreover, the Bolm group developed an excellent catalytic enantioselective arylation reaction by using a combination of aryl boronic acids and Et_2Zn in the presence of a polyether modifier.[7e] Because a wide variety of aryl boronic acids is commercially available, this reaction significantly expanded the nucleophile scope of catalytic enantioselective aldehyde arylation. Although enantioselectivity remains to be improved, chiral Rh-catalyzed asymmetric addition of aryl boron reagents to aldehydes has also been investigated.[8]

Recently, we reported a completely new approach for the synthesis of enantiomerically enriched allylic alcohols and diaryl methanols by using a chiral $Cu^{I}F$ catalyst and alkenyl methoxysilanes or dimethoxydiphenylsilane as nucleophiles (Scheme 1).[9] In this reaction, excellent enantioselectivity was observed for a range of aldehydes, including aromatic, α,β-unsaturated, and aliphatic aldehydes. Mechanistically, this reaction proceeds through an active alkenyl copper nucleophile, generated by transmetalation of copper and silicon.[10] A bulky chiral ligand, DTBM-segphos, facilitated this transmetalation. This reaction is the first example of the catalytic enantioselective intermolecular addition of stable alkenyl silanes and aryl silanes to carbonyl groups. Because a variety of alkenyl silanes can be synthesized readily through olefin metathesis[11] or hydrosilylation[12] and because alkenyl silanes and phenylsilanes are generally stable and easy to handle, this new method is a user-friendly catalytic enantioselective synthesis of allylic alcohols and diaryl methanols. Herein, we describe a valuable extension of this chemistry: catalytic enantioselective alkenylation and arylation of aldehydes with alkenyl and aryl boronates as nucleophiles (Scheme 1).

Abstract in Japanese:
キラル１価フッ化銅触媒を用いて、アルケニルホウ素やアリールホウ素を求核剤とするアルデヒドに対する触媒的不斉アルケニル化反応およびアリール化反応を開発した。合成的に有用な収率と反応性を発現するために、TBATやTBAT-BF_3・OEt_2、$PhBF_3K$といった基質に応じた添加剤が有効であった。芳香族アルデヒドやα-分枝脂肪族アルデヒドから、90% eeを超える極めて高いエナンチオ選択性で生成物が得られた。

Results and Discussion

A previously optimized method for the preparation of catalysts for enantioselective alkenylsilylation[9] involves reduction of $CuF_2{\cdot}2H_2O$ in situ to Cu with chiral phosphine DTBM-segphos (2 equiv). When we applied this method to the reaction between benzaldehyde (**1a**) and vinylboronic acid pinacol ester (**2a**) in the presence of the catalyst (10 mol%), product **3aa** was obtained in 67% yield with 90% *ee* in 24 h (Table 1, entry 1).[13] The enantiomeric excess of the product was similar to that obtained with vinyltrimethoxysilane as a nucleophile.[9] This result suggests that the actual nucleophile in both reactions is the same vinylcopper species. To improve the chemical yield, the effects of Lewis base additives were investigated. In our previous catalytic enantioselective allylboration of ketones, we found that the addition of a catalytic amount of $La(O\mathit{i}Pr)_3$ dramatically improved catalyst activity.[14] Similarly, in our previous catalytic enantioselective alkenylsilylation of aldehydes with an internal alkenyl silane, significantly higher reactivity was observed in the presence of a catalytic amount of tetrabutylammonium difluorotriphenylsilicate (TBAT).[9] Rate acceleration by Lewis base additives was attributed to facilitation of the rate-determining catalyst turnover step (see below). In the case of the reaction between **1a** and **2a**, improved reactivity was observed in the presence of TBAT (15 mol%). The product was obtained in an improved 90% yield with 90% *ee* in 30 min (Table 1, entry 2).[15] The catalyst loading

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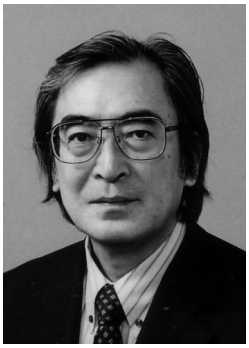

Masakatsu Shibasaki *was born in 1947 in Saitama, Japan, and received his PhD from the Univ. of Tokyo in 1974 with Prof. S. Yamada. After postdoctoral studies with Prof. E. J. Corey at Harvard Univ., he returned to Japan in 1977 and joined Tokyo Univ. as an Associate Prof. In 1983 he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at Hokkaido Univ., before returning to the Univ. of Tokyo as a Prof. in 1991. His research interests entail asymmetric catalysis, including asymmetric Heck reactions and reactions promoted by asymmetric bifunctional complexes, as well as the medicinal chemistry of biologically significant compounds.*

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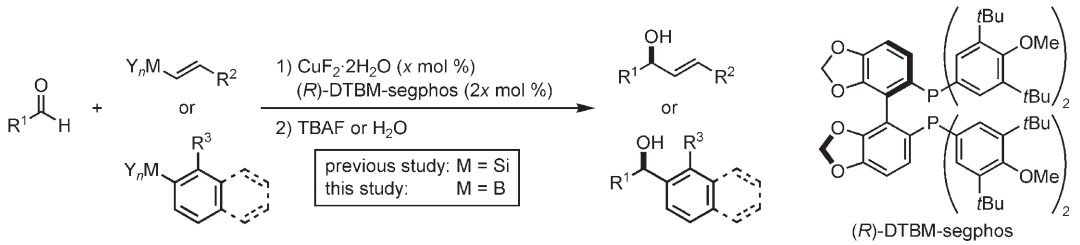
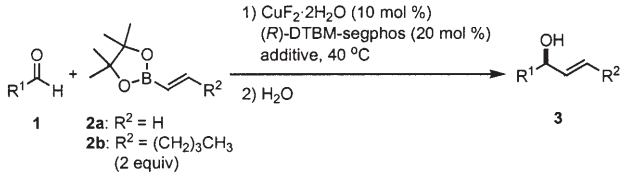
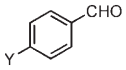
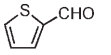
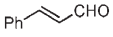
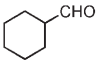
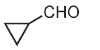
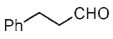


Scheme 1. Catalytic enantioselective alkenylation and arylation with a chiral CuF complex. TBAT = tetrabutylammonium difluorotriphenylsilicate.

Table 1. Catalytic enantioselective alkenylation of aldehydes.



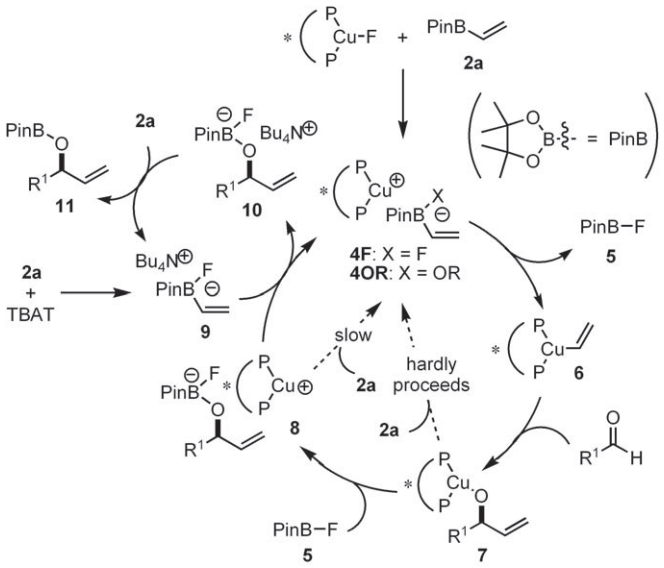
Entry		Substrate	Boronate	Additive [mol%]	t [h]	Yield [%][a]	ee [%][b]
1[c]		**1a**: Y = H	**2a**	none	24	67	90
2[c]		**1a**	**2a**	TBAT (15)	0.5	90	90
3[d,e]		**1a**	**2a**	TBAT (3)	30	93	95
4[c]		**1b**: Y = CH_3	**2a**	TBAT (15)	1	99	93
5[c]		**1c**: Y = Cl	**2a**	TBAT (15)	1	99	93
6[d]		**1d**	**2a**	TBAT (15)	6	95	96
7[d]		**1e**	**2a**	TBAT (15)	6	98	90
8[c]		**1a**	**2b**	TBAT (15)	8	88	88
9[d]		**1b**	**2b**	TBAT (15)	1	90	91
10[d]		**1f**	**2a**	TBAT (15)	12	42	98
11[d]		**1f**	**2a**	TBAT (30) + $BF_3{\cdot}OEt_2$ (30)	14	94	98
12[d]		**1g**	**2b**	TBAT (30) + $BF_3{\cdot}OEt_2$ (30)	8	87	92
13[d]		**1h**	**2a**	TBAT (30) + $BF_3{\cdot}OEt_2$ (30)	14	5	–
14[c]		**1i**	**2a**	TBAT (15)	90	0	–

[a] Yield of isolated product. [b] Determined by chiral HPLC. [c] Solvent = DMF. [d] Solvent = toluene. [e] Catalyst: 2 mol%, 1-mmol scale.

was decreased to 2 mol%, and the product was obtained with a slightly improved enantioselectivity (Table 1, entry 3). Under the conditions that involved 10 mol% of catalyst, products from non-enolizable aldehydes were obtained in excellent yield and enantioselectivity (Table 1, entries 4–7). In several entries, reactions in toluene led to slightly higher chemical yield and enantioselectivity than those performed in *N*,*N*-dimethylformamide (DMF). The same conditions were also applicable to reactions of an alkyl-substituted alkenyl boronate (Table 1, entries 8 and 9).

Although a detailed study of the role of TBAT is required in future, a working mechanistic hypothesis based on previous studies of our catalytic alkenylsilylation[9] and CuF-catalyzed enantioselective allylation reaction[16] is proposed in (Scheme 2). The active nucleophile—vinyl copper **6**—should be generated from CuF and **2a** via fluoroborate **4F** through transmetalation. The fact that the enantioselectivity was almost constant, even when using structurally different vinylation reagents (vinylsilane or vinylboronate), supported the idea that a vinyl copper species is the actual nucleophile. After enantioselective addition of the vinyl copper to an aldehyde, copper alkoxide **7** is generated. The catalyst turnover step from **7** to **4** should be rate-determining in the overall catalytic cycle.[17] Direct conversion of **7** into **4OR** by alkoxide ligand transfer from Cu to B should be very slow. Indeed, CuO*t*Bu[18]–DTBM-segphos (10 mol%) failed to promote the vinylation reaction detectably, even after heating at 40 °C for 24 h. Therefore, catalyst turnover might begin in the event that **7** is trapped by electrophilic fluoroboronate **5**, which is generated in the initial vinylcopper formation step (from **4F** to **6**), to give fluoroborate **8**. In the absence of TBAT (Table 1, entry 1), regeneration of the catalytically active **4** occurs when **8** transfers its fluoride or alkoxide ligand to **2a** (dashed arrow from **8** to **4** in Scheme 2). On the basis of the results of Table 1, entry 1, however, this step is not efficient. When TBAT is present as an additive (Table 1, entry 2), fluoroboronate **9** is believed to be produced in the reaction mixture by the reaction of TBAT with **2a**. In this case, catalyst turnover (from **8** to **4**) can take place through a facile cation exchange between **8** and **9**. Thus, the rate-determining catalyst turnover step is facilitated.[19]

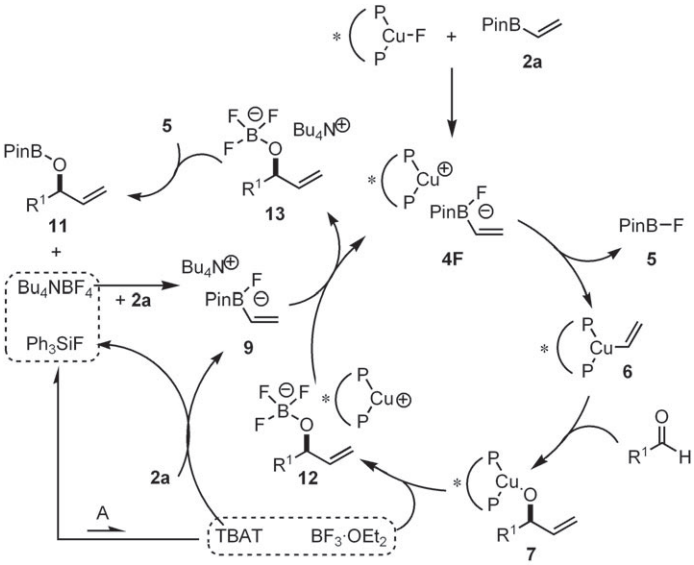
Further intensive additive screening was necessary when this reaction was applied to aliphatic aldehydes (e.g. **1f**).



Scheme 2. Proposed catalytic cycle for the reaction in the presence of TBAT. Pin = pinacol.

Under the optimized conditions described above and in the presence of TBAT (15 mol%), the vinylation product **3fa** was obtained in only 42% yield, albeit with 98% *ee* (Table 1, entry 10). Aldehyde trimers (diastereomeric mixtures) derived from homo-aldol condensation constituted a major by-product (35%). This side reaction pathway could be promoted by the intermediate copper alkoxide **7** working as a Brönsted base. To facilitate the rapid trapping of **7**, more acidic additives were screened. In the presence of TBAT (30 mol%) and $BF_3{\cdot}OEt_2$ (30 mol%), trimer formation was almost completely suppressed, and the desired product was obtained in 94% yield (Table 1, entry 11). The enantiomeric excess of the product remained excellent (98% *ee*). In contrast, a reaction with $BF_3{\cdot}OEt_2$ as the sole additive did not produce any desired product, and the trimers were obtained in 15% yield. The TBAT–$BF_3{\cdot}OEt_2$ additive combination was also effective for cyclopropanecarboxaldehyde (**1g**; Table 1, entry 12). Although TBAT–$BF_3{\cdot}OEt_2$ successfully suppressed the homo-aldol reaction in the case of α-branched alkyl-substituted aldehydes, reactions of linear aliphatic aldehydes are still difficult, and many by-products derived from the homo-aldol reaction were produced without giving the desired vinylation product (Table 1, entry 13). No reaction proceeded when acetophenone was used as substrate (Table 1, entry 14).

To gain some insight into the origin of the significant combination additive effect, the following experiments were conducted. First, the generation of Bu_4NBF_4 ($\delta = -150.2$ ppm) and Ph_3SiF ($\delta = -169.7$ ppm) was observed by ^{19}F NMR spectroscopy when TBAT and $BF_3{\cdot}OEt_2$ were mixed in toluene. On the basis of this observation, catalytic enantioselective vinylations between **1f** and **2a** were performed in the presence of either Bu_4NBF_4 or Ph_3SiF (15 mol%). Surprisingly, neither reaction produced the vinylation product **3fa** efficiently. Only homo-aldol trimer formation occurred in the presence of Bu_4NBF_4, and **3fa** was obtained in only 15% yield in the presence of Ph_3SiF. On the other hand, **3fa** was obtained in 50% yield in the presence of both Bu_4NBF_4 and Ph_3SiF. These results clearly demonstrate that both Bu_4NBF_4 and Ph_3SiF (or TBAT and $BF_3{\cdot}OEt_2$) are essential for effective suppression of the homo-aldol reaction. The beneficial effect of the combination additive can be explained as shown in Scheme 3. A very



Scheme 3. Proposed catalytic cycle for the reaction in the presence of TBAT–$BF_3{\cdot}OEt_2$.

small amount of BF_3 should exist in equilibrium (step A in Scheme 3) in the presence of TBAT and $BF_3{\cdot}OEt_2$.[20] Highly electrophilic BF_3 can trap the intermediate copper alkoxide **7** very quickly, before **7** deprotonates the aldehyde to generate borate **12**. Cation exchange between **12** and **9** completes the catalytic cycle, giving **4F** and **13**. BF_3 should be regenerated from **13** and **5** as follows: ligand exchange between **13** and **5** produces **11** and Bu_4NBF_4. The Bu_4NBF_4 formed reacts with Ph_3SiF, generated by the reaction of TBAT and **2a**, to give BF_3 through step A.

Having established a catalytic enantioselective alkenyl boration, we next extended the reaction conditions to the catalytic enantioselective arylation of aldehydes. When the optimized conditions (10 mol% CuF–DTBM-segphos and 15 mol% TBAT in DMF at 60°C) were applied to the reaction of *p*-chlorobenzaldehyde (**1c**) and phenylboronic acid pinacol ester, the product **14ca** was obtained in only trace amounts after 90 h. A change in solvent from DMF to toluene improved the reactivity slightly: **14ca** was obtained in 27% yield. Lewis base additives other than TBAT were also screened; however, the maximum yield was still only 31% (92% *ee* with $PhBF_3K$ as additive). Thus, we next optimized nucleophile structure. Although **14ca** was not produced at all when using phenylboronic acid or triphenylboroxin as nucleophiles, phenylboronic acid ethylene glycol ester (**15a**)

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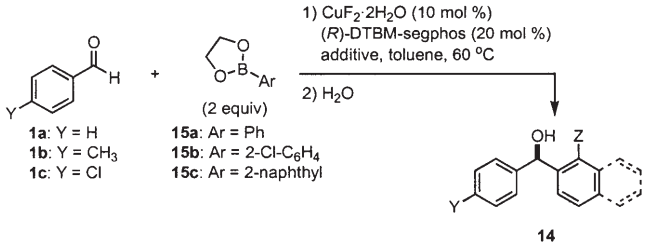
Table 2. Catalytic enantioselective arylation of aldehydes.



Entry	Substrate	Nucleophile	Additive (mol %)	t [h]	Yield [%][a]	*ee* (%)[b]
1	**1c**	**15a**	TBAT (15)	32	90	90
2	**1c**	**15a**	$PhBF_3K$ (15)	25	96	90
3	**1b**	**15a**	$PhBF_3K$ (15)	28	89	92
4	**1a**	**15b**	$PhBF_3K$ (15)	52	70	90
5	**1a**	**15c**	$PhBF_3K$ (15)	52	79	83

[a] Yield of isolated product. [b] Determined by chiral HPLC.

afforded product **14ca** in 90% yield with 90% *ee* in the presence of TBAT (15 mol%; Table 2, entry 1). The yield was further improved to 96% in the presence of $PhBF_3K$ (Table 2, entry 2) with no change in enantioselectivity. Similarly, excellent enantioselectivity was attained by using *p*-tolualdehyde (**1b**) as substrate (Table 2, entry 3). Other nucleophiles such as **15b** and **15c** were used successfully (Table 2, entries 4 and 5). As similar reaction rates were observed in the presence of either additive TBAT or $PhBF_3K$, the two can be considered to accelerate the catalytic cycle through a similar mechanism (Scheme 2). We propose that steric crowding around boron dramatically influences reactivity (compare the reactivities of phenylboronic acid pinacol ester and **15a**) because the trapping rate of the intermediate copper alkoxide should be significantly faster when using sterically less hindered boron.

Conclusions

A catalytic enantioselective alkenylation and arylation of aldehydes was developed with stable and readily available alkenyl and aryl boronates as nucleophiles. The $Cu^{I}F$–DTBM-segphos complex, prepared in situ under reductive conditions from $Cu^{II}F_2$ and DTBM-segphos (2 equiv), was used as an asymmetric catalyst. The catalyst loading was decreased to 2 mol% under optimized conditions; however, 10 mol% of catalyst was normally used. The appropriate choice of additives significantly improved the product yield. In alkenylation reactions, TBAT or the TBAT–$BF_3{\cdot}OEt_2$ combination was effective in reactions with aromatic or aliphatic aldehydes, respectively. In arylation reactions, $PhBF_3K$ gave the best results. These additives did not change the enantioselectivity, suggesting that the additives work in the catalytic cycle after the enantioselectivity is determined. We propose that the additives facilitate the catalyst turnover step from the intermediate copper alkoxide. Specifically, the TBAT–$BF_3{\cdot}OEt_2$ combination efficiently suppresses the undesired homo-aldol reaction of substrate aliphatic aldehydes by rapidly trapping the copper alkoxide. This process has several advantages over catalytic enantioselective alkenylation and arylation reactions with zinc reagents: 1) a wide variety of stable alkenyl and aryl boronates are commercially available (this is a distinct advantage, even over the previously reported reaction using organosilanes[9]); 2) overall, less metal is required by the reaction. The remaining limitations of this reaction are its inapplicability to linear aliphatic aldehydes, and its unreactivity toward simple ketones.[21] Furthermore, catalyst loading needs to be minimized further. Efforts to expand the scope of this reaction are currently ongoing.

Experimental Section

General

DTBM-segphos was provided by the Takasago International Cooperation. All the compounds synthesized in this paper are known compounds.[9,22]

Syntheses

Typical procedure for preparation of alkenyl boronic acid pinacol ester:[23] A solution of 1-hexyne (5 mL, 43.5 mmol) and pinacolborane (6.6 mL, 45.7 mmol) in CH_2Cl_2 (21.8 mL) was added to $[HZrCp_2Cl]$ (1.12 g, 4.35 mmol) in an ice bath, and the resulting solution was stirred at room temperature for 15 h. Water was added, and the products were extracted with Et_2O. After evaporation of the organic solvent, pure **2b** was obtained in 72% yield after purification by SiO_2 column chromatography (Et_2O/hexane 5:95).

Typical procedure for preparation of arylboronic acid ethylene glycol ester: Anhydrous ethylene glycol (1.11 mL, 20 mmol) was added to a solution of phenylboronic acid (2.55 g, 20 mmol) in Et_2O (16.8 mL). The mixture was stirred for 12 h at room temperature, and then extracted with hexane (20 mL). Evaporation of the solvent gave **14** in 95% yield. This compound was used for the catalytic enantioselective reaction without further purification.

Typical procedure (**3fa**): A suspension of $CuF_2{\cdot}2H_2O$ (1.5 mg, 0.011 mmol) and (*R*)-DTBM-segphos (25.5 mg, 0.021 mmol) in MeOH (1 mL) was heated at reflux for 2 h with vigorous stirring. During this period, the poorly soluble $Cu^{II}F_2$ dissolved to give a colorless to pale-purple solution. The solvent was evaporated, and the residue was azeotropically dried (twice) by coevaporation with toluene. The complex was dried under vacuum for 2 h, and TBAT (17.4 mg, 0.032 mmol) and toluene (0.25 mL) were then added. $BF_3{\cdot}OEt_2$ (4 μL, 0.032 mmol), **1f** (13.5 μL, 0.105 mmol), and **2a** (37 μL, 0.21 mmol) were added to the solution at room temperature, and the mixture was stirred at 40 °C for 14 h. H_2O was added, and the products were extracted with EtOAc. The combined organic layer was washed with a saturated solution of NaCl and dried over Na_2SO_4. Filtration, evaporation of the solvent, and purification by SiO_2 column chromatography gave **3fa** (94%, 98% *ee* based on chiral HPLC analysis).[9]

Typical procedure for catalytic enantioselective phenylation of aldehydes (**14c**): $PhBF_3K$ (3 mg, 0.016 mmol), toluene (0.25 mL), **15** (29 μL, 0.21 mmol), and **1c** (14.8 mg, 0.11 mmol) were added to the CuF–DTBM-segphos complex prepared as described above (Cu: 0.011 mmol), and the mixture was warmed to 60 °C. The mixture was stirred for 25 h, and H_2O was added. Workup and purification as described above afforded **14c** (96%). The enantiomeric excess was determined by chiral HPLC analysis as described in reference [9].

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