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Copper-Catalyzed Regio- and Enantioselective Aminoboration of Unactivated Terminal Alkenes

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Dedication ((optional))

Abstract: A CuCl/(*R*,*R*)-PTBP-BDPP-catalyzed regioselective and enantioselective aminoboration of simple and unactivated terminal alkenes with bis(pinacolato)diboron (pinB–Bpin) and hydroxylamines has been developed. The amino group and boryl group are incorporated at the internal position and terminal position, respectively, and the corresponding chiral β -borylalkylamines are obtained with good to high enantiomeric ratios. The asymmetric copper catalysis allows for rapid and concise transformation of readily available olefinic feedstock-like materials into functionalized chiral alkylamines of high potential in medicinal and pharmaceutical chemistry.

Catalytic asymmetric reactions of simple and abundant aliphatic terminal alkenes have been longstanding research subjects in chemistry.^[1] synthetic organic Among them, the enantioselective difunctionalization in a fully intermolecular manner has particularly received significant attention because abundant olefinic feedstock-like materials can be readily transformed into highly functionalized chiral molecules, which are invaluable building blocks in the synthesis of complex natural products and biologically active compounds. The most reliable and well-known process is the Os-catalyzed dihydroxylation originally developed by Sharpless.^[2] More recently, the asymmetric diboration with chiral Pt and Rh catalysts has been developed by Morken^[3] and Nishiyama,^[4] in which the incorporated boryl group can participate in various post functionalization reactions in stereospecific and siteselective manners.^[5] The former research group also reported the asymmetric organocatalytic diboration.^[6] On the other hand, the unsymmetrical difunctionalization is much more challenging because not only enantioselectivity but also regioselectivity should be catalytically controlled. In 1995, Negishi developed the Zr-catalyzed asymmetric carboalumination (ZACA) of simple terminal alkenes with high regioselectivity as well as enantioselectivity. The formed chiral alkylaluminum intermediates underwent subsequent oxygenation and Pdcatalyzed cross-coupling reaction, giving the corresponding difunctionalized chiral molecules.^[7] However, there still remains a large demand for further development of enantioselective and regioselective difunctionalization catalysis with more versatile functional group incorporation. Herein, we report a CuCl/(R,R)-

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PTBP-BDPP-catalyzed regioand enantioselective aminoboration^[8] of unactivated terminal alkenes with bis(pinacolato)diboron (pinB-Bpin) and hydroxylamines.^[9] The asymmetric copper catalysis guides the amino group and boryl group to the internal position and terminal position, respectively, and the corresponding chiral β-borylalkylamines are obtained with good to high enantiomeric ratios. The boron moiety can be a useful synthetic handle for further manipulations, thus providing versatile chiral alkylamines, of great value in medicinal and pharmaceutical applications, from the simple and abundant terminal alkenes.

Our optimization studies commenced with vinylcyclohexane (1a), pinB–Bpin, and O-benzoyl-*N*,*N*-dibenzylhydroxylamine (2a) as model substrates. Given our recent findings^[8] and literature information,^[10] the plausible catalytic cycle includes 1) σ -bond metathesis of L*CuOfBu with pinB–Bpin, forming the active boryl copper species L*Cu-Bpin, 2) insertion of 1a into the Cu-B bond of L*Cu-Bpin, 3) stereoretentive C–N bond formation with the hydroxylamine 2a, and 4) regeneration of starting copper alkoxide L*CuOfBu by salt metathesis with MOfBu (Scheme 1). Both the regioselectivity and enantioselectivity can be determined in the insertion step, and the optimization of electronic and steric nature of ancillary ligand is thus a key to success.



Scheme 1. Working hypothesis of regio- and enantioselective coppercatalyzed aminoboration of vinylcyclohexane (**1a**) with pinB–Bpin and and *O*benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**). Bz = benzoyl, Bn = benzyl, L* = chiral ligand.

After extensive screening of chiral bisphosphine ligands on the basis of reported Cu-catalyzed borylation with diboron reagents,^[11] we pleasingly found that a combination of CuCl catalyst, (*R*,*R*)-PTBP-BDPP ligand, and NaO*t*Bu base promoted regio- and enantioselective aminoboration of **1a** to form the terminally borylated β -borylalkylamine **3aa** in 76% yield with 24:1 COMMUNICATION

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regioisomeric ratio (r.r.) and 96:4 enantiomeric ratio (e.r.) (Scheme 2; 0.25 mmol scale). The reaction could also be scaled up to 1 mmol with the maintenance of regio- and enantioselectivity. The formed aminoborated product **3aa** was easily oxidized with aq. H_2O_2 into the corresponding chiral aminoalcohol **3aa-O** without erosion of enantiomeric ratio. Notably, the *tert*-butyl group at the *para*-position in the benzene ring of (*R*,*R*)-PTBP-BDPP was critical for the high regioselectivity and enantioselectivity; analogous (*S*,*S*)-BDPP, (*S*,*S*)-XyI-BDPP, and (*S*,*S*)-PMP-BDPP resulted in lower regioisomeric ratio (6.7:1–9:1) and enantiomeric ratio (17:83–10:90). Such a remote steric hindrance is particularly important for the terminal borylation selectivity because the bisphosphine-ligated copper moiety should be located at the more sterically hindered internal position (Scheme 1).^[12,13]



Scheme 2. Optimal conditions for CuCl/(R,R)-PTBP-BDPP-catalyzed regioand enantioselective aminoboration of vinylcyclohexane (**1a**) and performance of other BDPP-type ligands. Isolated yields are given for the reaction with (R,R)-PTBP-BDPP. The e.r. refers to the enantiomeric ratio of major regioisomer.

With conditions in Scheme 2, we first investigated the scope of hydroxylamines 2 with 1a. The representative products are shown in Scheme 3. Except for 3aa, all aminoborated compounds 3 were less stable for column chromatographic purification, and thus the isolation and determination of regioisomeric and enantiomeric ratios were performed after the oxidation^[14] into NaBO₃-mediated the corresponding aminoalcohols 3-O. Other acyclic amines including N,N-N-benzyl-N-methylamine, diethvlamine. N-hexvl-Npentenvlamine underwent the reaction to form the corresponding chiral aminoalcohols 3ab-O, 3ac-O, and 3ad-O with high regioselectivity (11.5:1-13:1 r.r.) and enantioselectivity (95:5-The CuCl/(R,R)-PTBP-BDPP catalyst was also 96:4 e.r.) with cyclic amines; piperidine, morpholine, compatible thiomorpholine, and azepane-containing aminoalcohols 3ae-O-3ah-O were obtained with 8:1->25:1 r.r. and 95:5-96:4 e.r. As mentioned above, whereas the enantioselectivity was uniformly high, the regioselectivity was somewhat dependent on the steric and electronic nature of hydroxylamine.^[15]



Scheme 3. Copper-catalyzed regio- and enantioselective aminoboration of vinylcyclohexane (1a) with bis(pinacolato)diboron and various hydroxylamines 2. Conditions: CuCl (0.025 mmol), (*R*,*R*)-PTBP-BDPP (0.025 mmol), 1a (0.75 mmol for 3aa–3ac, 1.25 mmol for 3ad–3ah), pinB–Bpin (0.38 mmol), 2 (0.25 mmol), NaO/Bu (0.38 mmol), THF (1.5 mL), RT, 4 h, N₂, then NaBO₃•OH₂ (2.5 mmol), THF/H₂O (1:1), RT, overnight, open flask. Isolated yields based on 2 are given. ¹H NMR yield in the Bpin form is in parentheses. Regioisomeric ratio (r.r.) and enantiomeric ratio (e.r.) were determined by ¹H NMR and HPLC analysis on a chiral stationary phase, respectively. [a] Combined isolated yield of 3-O and regioisomeric 3'-O.

We next tested several aliphatic terminal alkenes 1 for the regio- and enantioselective aminoboration with 2a (Table 1). Almost products could be isolated in the Bpin form by purification with column chromatography, but determination of enantiomeric ratio was conducted after the oxidation with aq. H₂O₂ because of better stability and reproducibility of the corresponding aminoalcohols for HPLC analysis. In addition to vinylcyclohexane (1a), allylically substituted vinylcyclopentane (1b) and 1,1-diphenyl-2-propene (1c) provided the high regioselectivity (>25:1 r.r.) while the former gave better enantioselectivity (94:6 e.r. for 3ba-O vs 80:20 e.r. for 3ca-O; entries 1 and 2). Allylbenzene derivatives 1d-1f were also viable substrates, and high regioselectivity (13:1-24:1 r.r.) and acceptable enantioselectivity (80:20-95:5 e.r.) were observed (entries 3-5). The homoallylbenzene 1g resulted in somewhat lower regio- and enantioselectivity (5.3:1 r.r. and 77:23 e.r.; entry 6), but the introduction of additional substituent at the homoallylic position increased the values of both r.r. and e.r. (6.7:1 r.r. and 91:9 e.r. for 3ha-O, 8.1:1 r.r. and 83:17 e.r. for 3ia-O; entries 7 and 8). The simplest 1-octene (1j) could also be converted to the corresponding chiral aminoborated product with synthetically useful level of 5.3:1 r.r. and 82:18 e.r. (entry 9). Moreover, the asymmetric Cu catalysis was tolerated with silyl ether (1k), ester (1l), and imide (1m) groups to furnish the functionality-enriched chiral alkylamines with 6.7:1-10:1 r.r. and 83:17-89:11 e.r. (3ka-O-3ma-O; entries 10-12).

Table 1. Copper-catalyzed regio- and enantioselective aminoboration of various simple terminal alkenes **1** with bis(pinacolato)diboron and O-benzoyl-N,N-dibenzylhydroxylamine (**2a**).^[a]

R 🦄 + 1	pinB-Bpin BzO-NBn ₂ 2a CuCl (10 mo (<i>R,R</i>)-PTBP- Na THF,	1%) BDPP (10 mol%) NBn₂ ⊡ OtBu R RT, 4 h R 3	aq. H ₂ O ₂ aq. NaOH THF/EtOH RT, 30 min 3-0
Entry	1	3 , Yield [%], r.r. ^[b]	3-O , Yield [%], e.r. ^[c]
1		3ba , 62 (74), >25:1	3ba-O , 44, 96:4
2	Ph Ph 1c	3ca , 35 (42), >25:1	3ca-O , 31, 80:20
3	Ph 1d	3da , (57), 24:1	3da-O , 36, 80:20
4	MeO 1e	3ea , 60 (76), 24:1	3ea-O , 51, 95:5
5	1f	3fa , 63 (80), 13:1	3fa-O , 43, 81:19
6	Ph 1g	3ga , 55, 5.3:1	3ga-O , 38, 77:23
7 ^[d]	Ph Ph 1h	3ha , 65, 6.7:1	3ha-O , 48, 91:9
8	ـــــــــــــــــــــــــــــــــــــ	3ia , 41 (57), 8.1:1	3ia-O , 30, 83:17
9	C ₆ H ₁₃ 1j	3ja , 67, 5.3:1	3ja-O , 40, 82:18
10	TBSO 1k	3ka , 64, 6.7:1	3ka-O , 54, 83:17
11	PivO	3la , 75, 9:1	3la-O , 56, 83:17
12 ^[e]	PhthN	3ma , 45, 10:1	3ma-O , 31, 89:11

[a] Conditions: CuCl (0.025 mmol), (*R*,*R*)-PTBP-BDPP (0.025 mmol), **1** (1.0 mmol), pinB–Bpin (0.38 mmol), **2a** (0.25 mmol), NaOfBu (0.38 mmol), THF (1.5 mL), RT, 4 h, N₂, then aq. H₂O₂ (30%, 0.5 mL, 5 mmol), aq. NaOH (3 M, 0.5 mL, 1.5 mmol), THF/EtOH (1.0/0.50 mL), RT, open flask, 30 min. [b] Combined isolated yields of **3** and regioisomeric **3'** are given. ¹H NMR yields are in parentheses. Regioisomeric ratio (r.r.) was determined by ¹H NMR. [c] Isolated yields of **3-O** based on **2a** are given. Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral stationary phase. [d] Under LiOfBumodified conditions: **1h** (0.25 mmol), pinB–Bpin (0.38 mmol), **2a** (0.38 mmol), LiOfBu (0.75 mmol). [e] Oxidation was performed with NaBO₃•OH₂ (2.5 mmol) in THF/H₂O (1:1) at RT, overnight. PhtNN = phthalimidyl, TBS = *tert*-butylciarbonyl.

Based on the rich chemistry of Bpin moiety, the obtained aminoborated product **3aa** can be readily derivatized into several functionalized chiral alkylamines (Scheme 4). The treatment with MeO-NHLi followed by Boc protection afforded the corresponding optically active 1,2-diamine **4** with orthogonal protecting groups.^[16] The conversion of **3aa** into the internal ammonium trifluoroborate salt **5**^[17] was also possible by using a KF/tartaric acid protocol, which was originally developed by Lloyd-Jones.^[18] Notably, in this case, **5** was purified by simple filtration without any column chromatography. Additionally, onecarbon homologation and successive Suzuki-Miyaura crosscoupling furnished the arylated product **7** in an acceptable overall yield. During the aforementioned transformations, the enantiomeric ratio remained well.^[19]

To get insight into the mechanism proposed in Scheme 1, we finally monitored the reaction mixture by ${}^{31}P{}^{1}H{}$ and ${}^{11}B{}$ NMR (Scheme 5). Initial simple mixing of (*R*,*R*)-PTBP-BDPP and CuOtBu in [D₈]THF at room temperature gave almost no significant change in ${}^{31}P{}^{1}H{}$ NMR, probably because of tetrameric structure of CuOtBu.^[20] However, upon treatment

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with pinB–Bpin (δ 30.6 ppm in ¹¹B NMR), the original ³¹P{¹H} signal of (R,R)-PTBP-BDPP (δ –6.8 ppm) was shifted to δ –4.8 ppm. Concurrently, one new signal corresponding to pinB-OtBu appeared at δ 21.2 ppm in ^{11}B NMR. $^{[21]}$ Theses spectra changes suggest the formation of (R,R)-PTBP-BDPP-ligated Cu-Bpin species, although the corresponding ¹¹B signal was not detected, same as reported analogous phosphine-supported borylcopper complexes.^[22] Additionally, pinB-Bpin seems to accelerate the coordination of (R.R)-PTBP-BDPP to Cu center by promoting the dissociation of aggregated CuOtBu or formation of Cu-Bpin species. Subsequent addition of vinylcyclohexane (1a) form a new but small signal at δ 34.0 ppm in ¹¹B NMR, which is assigned to be an alkene-inserted β -boryl alkylcopper complex.^[10a] However, any additional changes were not observed even after 40 min at room temperature. On the other hand, in the presence of NaOtBu an amount of β-boryl alkylcopper complex was increased to be over that of the starting pinB-Bpin after 1 h at room temperature, thus suggesting NaOtBu can accelerate the alkene insertion into the borylcopper species as well as play roles in the CuOtBu generation and regeneration steps.^[23] Finally, we observed the formation of aminoborated product **3aa** (δ 35.0 ppm in ¹¹B NMR, also confirmed by ¹H NMR) and complete consumption of pinB-Bpin by addition of O-benzoyl-N,N-dibenzylhydroxylamine (2a). On the basis of the above findings, it is stated that the alkene insertion step can be rate-limiting and greatly promoted by external alkoxide base. Additionally, the following C-N forming process is relatively facile and strongly drives the process to the product formation.

In conclusion, we have developed a CuCl/(R,R)-PTBP-BDPP-catalyzed regioselective and enantioselective aminoboration of simple terminal alkenes. The asymmetric catalysis can convert the readily available and abundant olefinic feedstock-like materials to chiral functionalized alkylamines of great values in medicinal and pharmaceutical chemistry. Additionally, preliminary mechanistic studies suggest the ratelimiting alkene insertion to phosphine-ligated borylcoppers and additional roles of alkoxide bases in the insertion step. Further improvement of regio- and enantioselectivity, expansion of substrate scope, and application to complex molecule synthesis are ongoing in our laboratory.



Scheme 4. Derivatization of optically active aminoborated product 3aa. Boc = tert-butoxycarbonyl, RuPhos = dicyclohexylphosphino-2',6'diisopropoxybiphenyl.

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Scheme 5. NMR studies.

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Remote control: A copper-catalyzed regioselective and enantioselective aminoboration of unactivated terminal alkenes with bis(pinacolato)diboron and hydroxylamines has been developed to deliver the terminally borylated chiral β -borylalkylamines in good yields. The key to achieve the high regio- and enantioselectivity is the use of (*R*,*R*)-PTBP-BDPP ligand of remote steric hindrance with the para *tert*-butyl group. The asymmetric copper catalysis can readily transform the abundant olefinic feedstock-like materials into functional chiral alkylamines of great interest in medicinal and pharmaceutical applications.

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