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Cu-Catalyzed Enantioselective Boron Addition to *N*-Heteroaryl-Substituted Alkenes

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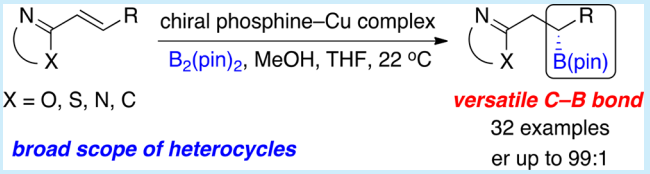
Supporting Information

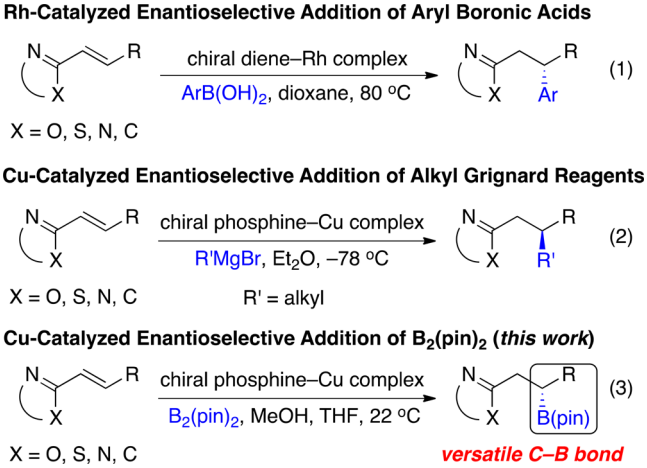
ABSTRACT: Catalytic enantioselective Cu–B(pin) (pin = pinacolato) addition to *N*-heteroaryl-substituted alkenes followed by protonation promoted by phosphine–Cu complexes is presented. The resulting alkylboron products that contain a *N*-heteroaryl moiety are afforded in up to 97% yield and 99:1 enantiomeric ratio. The highly versatile C–B(pin) bond can be converted to a range of useful functional groups, delivering a variety of enantiomerically enriched building blocks that are otherwise difficult to access. The utility of this method is further demonstrated by application to a fragment synthesis of biologically active molecule U-75302. Preliminary mechanistic studies revealed that the adjacent N atom of the heterocycles plays a unique role in high reactivity and enantioselectivity.



Functionalized *N*-containing aromatic heterocycles are prevalent motifs in biologically active pharmaceutical molecules (88%).[1] Furthermore, approximately half of the pharmaceutical ingredients bear stereogenic centers.[1] It is crucial to produce any chiral pharmaceutical molecule as a single enantiomer, since the two enantiomers of a chiral drug can exhibit different biological activity. Catalytic enantioselective formation of a versatile C–B bond represents one of the most important strategies for construction of chiral molecules, as the C–B bond can be easily transformed into C–C, C–O, C–N, and C–halogen bonds.[2] Catalytic enantioselective boron addition to alkenes represents a powerful method for creating new stereogenic C–B bonds from easily accessible alkenes.[3] In this context, the catalytic enantioselective addition of a boron nucleophile to conjugated heteroaryl alkenes constitutes an attractive strategy to generate valuable chiral heterocyclic aromatic compounds. Although there are few reports on transition-metal-catalyzed enantioselective addition of carbon nucleophiles to *β*-substituted alkenyl *N*-heteroarenes,[4] enantioselective addition of a boron nucleophile remains unprecedented.[5]

In 1998, a pioneering work of Ni-catalyzed addition of Grignard reagents to alkenylpyridines was reported, although the reaction provided low enantioselectivity.[4a] It was not until 2010 that a highly enantioselective Rh-catalyzed addition of arylboronic acids to *β*-substituted alkenyl *N*-heteroarenes was disclosed (Scheme 1, eq 1).[4b] In 2016, the first Cu-catalyzed enantioselective addition of alkyl Grignard reagents was revealed (Scheme 1, eq 2).[4e] The paucity of methodologies for catalytic enantioselective nucleophilic addition to *N*-heteroaryl alkenes was attributed to the relatively weak activation from the *N*-heteroaromatic moiety. Furthermore, coordination of the heteroatoms to the metal center might negatively impact the reactivity and enantioselectivity. We

Scheme 1. Catalytic Enantioselective Nucleophilic Addition to *N*-Heteroaryl Alkenes



decided to explore the addition of a boron group to alkenyl heteroaromatic compounds. We reasoned that a proper choice of ligand might solve challenges to the reactivity and enantioselectivity. Herein, we described an unprecedented protocol of phosphine–Cu-catalyzed enantioselective boron addition to *N*-heteroaryl alkenes, affording versatile alkylboron products that can be further converted to a variety of useful heterocycle-containing chiral building blocks in high efficiency and enantioselectivity (Scheme 1, eq 3).

We began our studies by investigating ligand optimization. Reaction of alkenylpyridine **1a** with $B_2(pin)_2$ and MeOH in the

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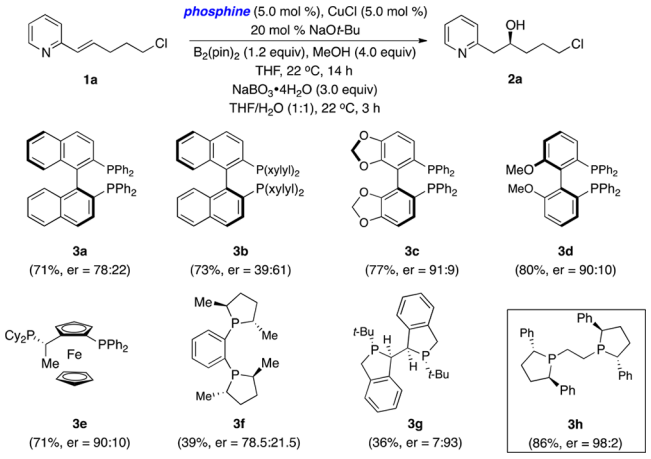
presence of a BINAP−Cu complex followed by oxidative workup with $NaBO_3·4H_2O$ afforded alcohol **2a** in 71% yield and 78:22 er (**3a**) (Scheme 2). The initial alkylboron product

Scheme 2. Ligand Screen[a]

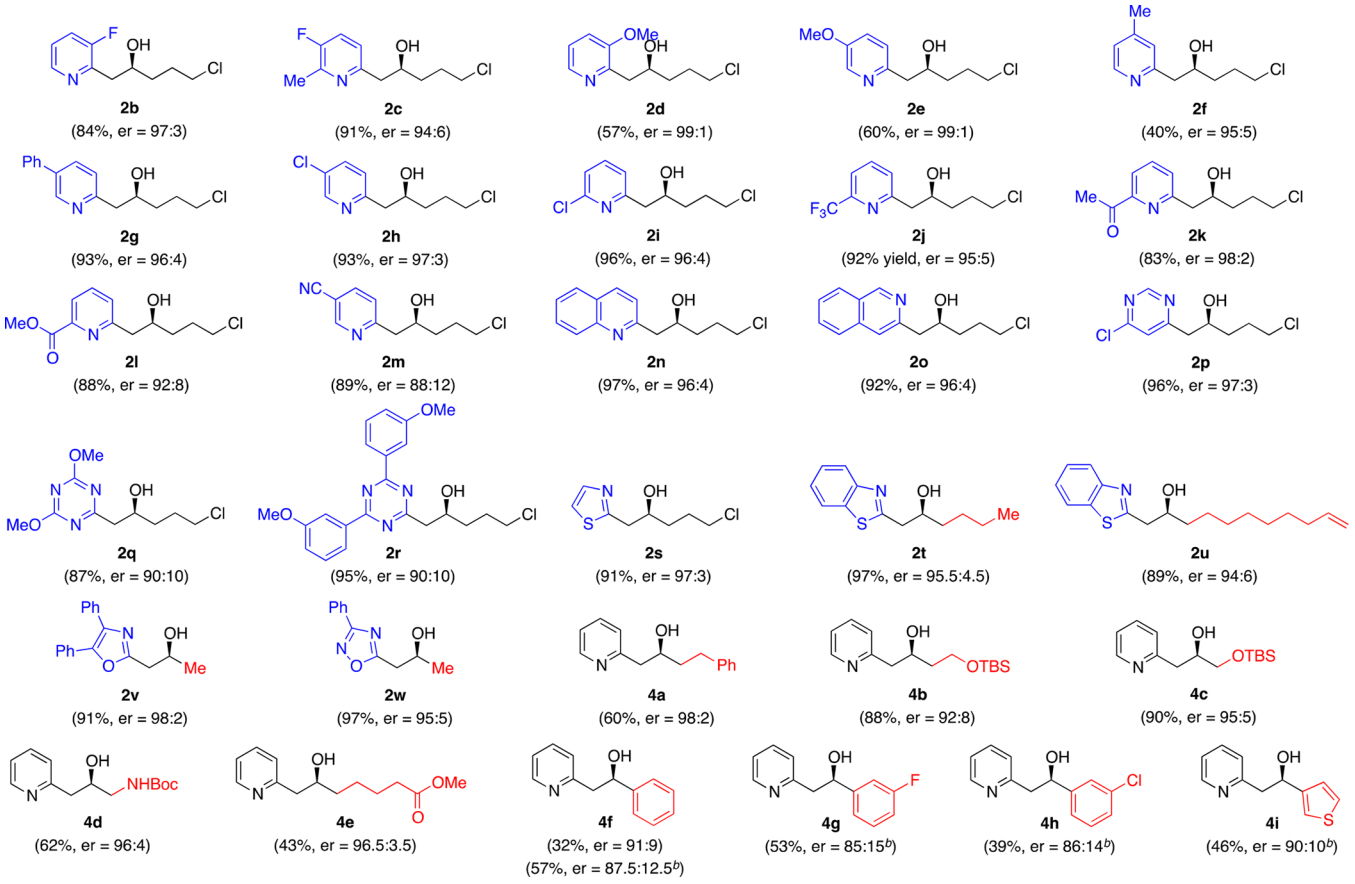


[a]The reactions were performed under a N_2 atmosphere. Yields correspond to isolated and purified products; er was determined by HPLC analysis. See the Supporting Information (SI) for details.

was not stable during silica gel column chromatography purification due to chelation of the Lewis basic pyridine to boron. Cu complexes of bisphosphines with smaller dihedral angles promoted the reaction in 77−80% yield and 90:10−91:9 er (**3c−d**). Modification of the substituents on phosphorus to 3,5-dimethylphenyl did not lead to any improvement in enantioselectivity (**3b**). Transformation of **1a** promoted by a Cu complex generated from **3e** delivered **2a** in 71% yield and 90:10 er. Reactions with bisphosphines that have stereogenic centers on phosphorus provided a 36−39% yield with a 78.5:21.5−93:7 er (**3f−g**). Finally, a Cu complex derived from (*R,R*)-Ph-BPE **3h** provided the desired product in 86% yield and 98:2 er.

With the optimal conditions in hand, we investigated the substrate scope (Scheme 3). Alkenes substituted with pyridines containing electron-donating and -withdrawing groups are suitable substrates (**2b−m**), although reactions of pyridyl alkenes with electron-donating groups resulted in lower efficiency (**2d−f**). It is worth mentioning that ketone, carboxylic acid ester, and cyano groups are well tolerated (**2k−m**). Alkenes with a wide range of *N*-heteroaryl groups can be used in the reaction. Reactions of alkenes substituted with quinoline and isoquinoline delivered desired products in 92−97% yield and 96:4 er (**2n−o**). Transformations of pyrimidine- and triazine-substituted alkenes provided alcohols in 87−96% yield and 90:10−97:3 er (**2p−r**). Products bearing thiazole **2s**, benzothiazole **2t−u**, oxazole **2v**, and 1,3,4-oxadiazole **2w** were generated in 89−97% yield and 94:6−97:3 er. Alkenylpyridines substituted with functionalized alkyl groups at the β-position afforded desired products in 43−90% yield and 92:8−98:2 er (**2t−w**, **4a−4e**). A terminal alkene remained untouched under

Scheme 3. Substrate Scope[a]



[a]Same conditions and analytical methods as in Scheme 2; see the SI for details. [b]7.5 mol % **3g** was used.

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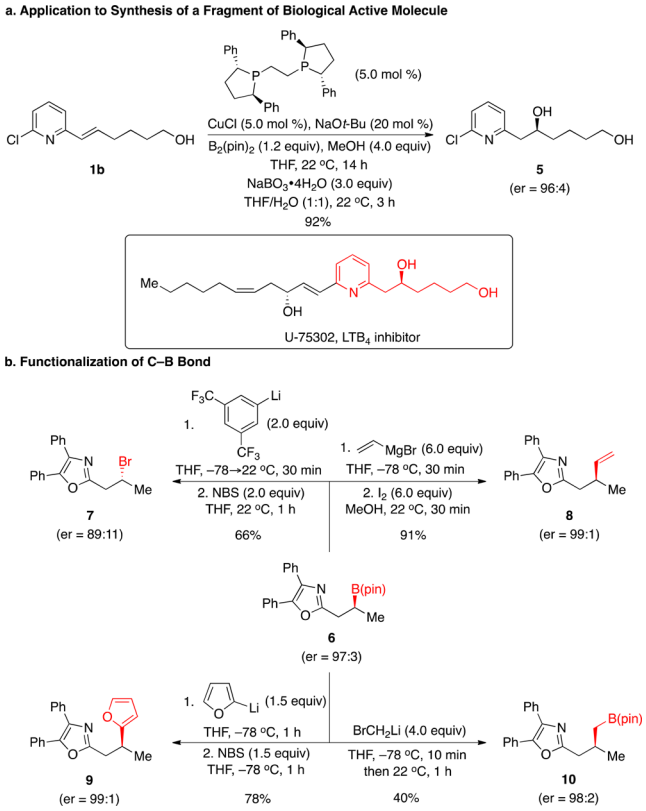
reaction conditions (**2u**). Reactions of styrylpyridines in the presence of the (*R*,*R*)-Ph-BPE−Cu complex provide lower efficiency and enantioselectivity (**4f**). Reinvestigation of other ligands revealed that a Cu complex formed from **3g** led to higher efficiency in spite of slightly lower enantioselectivity (**4f**−**i**). No regioisomers were observed in these cases, indicating the N-heteroaryl can stabilize the C−Cu bond better in the Cu−B(pin) addition process.

The utility of this method is demonstrated by a fragment synthesis of an LTB_4 inhibitor U-75302.[6] Reaction of alkenylpyridine **1b** bearing an unprotected hydroxyl group promoted by the (*R*,*R*)-Ph-BPE−Cu complex followed by oxidative workup afforded alcohol **5** in 92% yield and 96:4 er (Scheme 4a). Compound **5** may serve as a precursor for

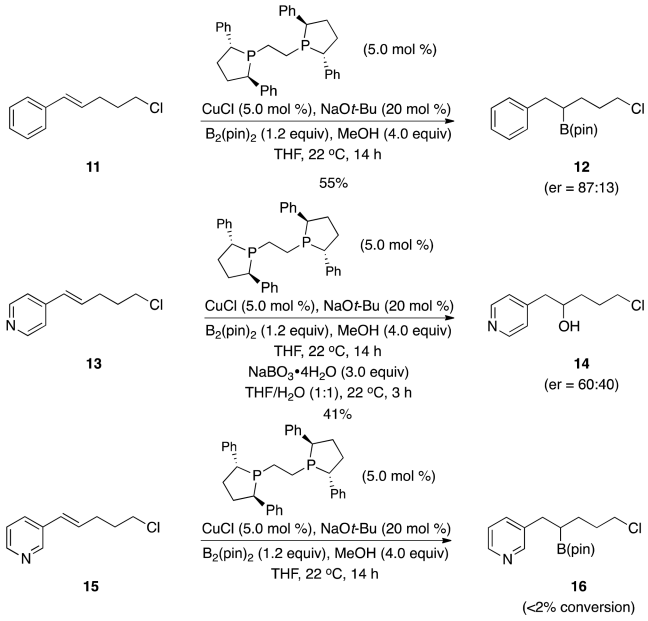
Scheme 4. Functionalization and Applications



synthesis of LTB_4 inhibitor U-75302. In addition, the boron addition products can be transformed into a wide range of enantioenriched building blocks that contain *N*-heterocycles. The C−B(pin) bond was converted to a C−Br bond according to the conditions developed by Aggarwal and co-workers, albeit with lower stereospecificity.[7] Zweifel olefination of heterocycle-containing alkylboron **6** led to **8** in 91% yield and 99:1 er, a formal enantioselective alkenyl addition product that was otherwise difficult to access.[8] Arylation of alkylboron **6** in the presence of 2-furyllithium followed by treatment of NBS provided **9** in 78% yield and 99:1 er.[9] Homologation of the C−B(pin) bond in **6** resulted in alkylboron **10** in 98:2 er albeit in 40% yield.[10]

To investigate the influence of the heterocycles on the reactivity and enantioselectivity, we performed the reactions in Scheme 5. Transformation of phenyl-substituted alkene **11** under the optimal conditions for the pyridyl-substituted analog resulted in incomplete conversion of substrate and afforded

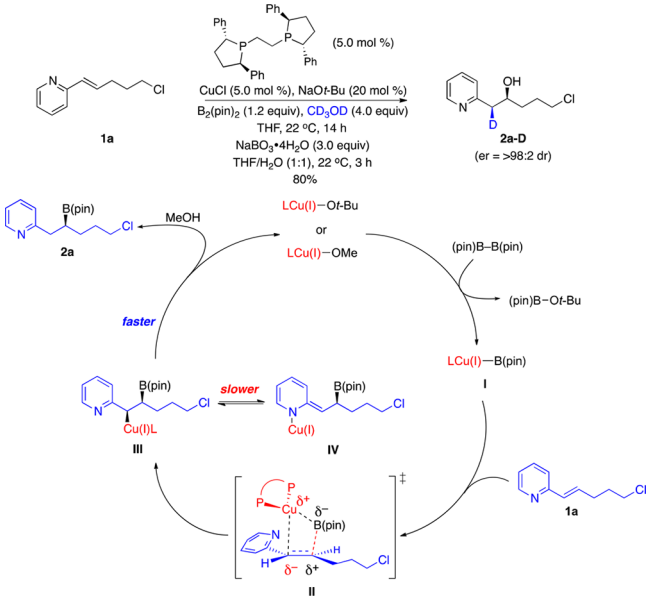
Scheme 5. Investigations on the Function of N-Heterocycles



hydroboration product **12** in lower yield (55% vs 86%) and lower enantioselectivity (87:13 er vs 98:2 er). Furthermore, 4-alkenylpyridine **13** was transformed in 41% yield and 60:40 er and 3-alkenylpyridine **15** did not undergo any reaction. All these results indicate that the heterocycles have significant impacts on both reactivity and enantioselectivity. It is plausible that the N atom might coordinate to the Lewis acidic metal center, enhancing the electrophilicity of the β-carbon of heteroaryl alkenes (**II**, Scheme 6) and leading to a better-organized transition state for higher enantioselectivity.

To further explore the nature of the organocopper intermediate and protonation process, we conducted the reaction with d_4-methanol. As indicated in Scheme 6, a single diastereomer **2a-D** was generated, illustrating that the possible isomerization of the C−Cu bond that has been proposed

Scheme 6. Proposed Catalytic Cycle



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previously is slower than the protonation process.[4g−i] The proposed catalytic cycle is shown in Scheme 6. Cu−B(pin) species generated from reaction of Cu−alkoxide with $B_2(pin)_2$ underwent *syn*-addition to the *N*-heteroaryl alkene **1a** to provide an organocopper intermediate **III** through transition state **II**, which reacted with methanol to deliver **2a** and regenerated the Cu−alkoxide. The organocopper intermediate **III** was afforded in high diastereoselectivity.

In summary, we have developed an operationally simple and chemoselective Cu-catalyzed boron enantioselective addition to a wide range of *N*-heteroaryl alkenes, affording alkylboron compounds that can be functionalized to a variety of useful *N*-heterocycle-containing chiral building blocks with high efficiency and enantioselectivity. The utility of the method is further demonstrated by a fragment synthesis of LTB_4 inhibitor U-75302. Further mechanistic studies and development of new reactions with *N*-heteroaryl alkenes are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03327.

Experimental procedures, spectroscopic data, and NMR spectra of all products (PDF)

Accession Codes

CCDC 1574301 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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