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Enantioselective Rh- or Ir-Catalyzed Directed C(sp^3)–H Borylation with Phosphoramidite Chiral Ligands

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In honor of the late Professor Yoshihiko Ito

Enantioselective heteroatom-directed C(sp^3)–H borylation reactions of 2-aminopyridines and 2-alkylpyridines with Rh- and Ir catalytic systems using commercially available chiral monophosphine ligands, respectively, were developed. This methodology provides an innovative example of a homogenous catalytic system for C(sp^3)–H borylation, and allows the direct synthesis of optically active alkylboronates with moderate level of enantioselectivity.

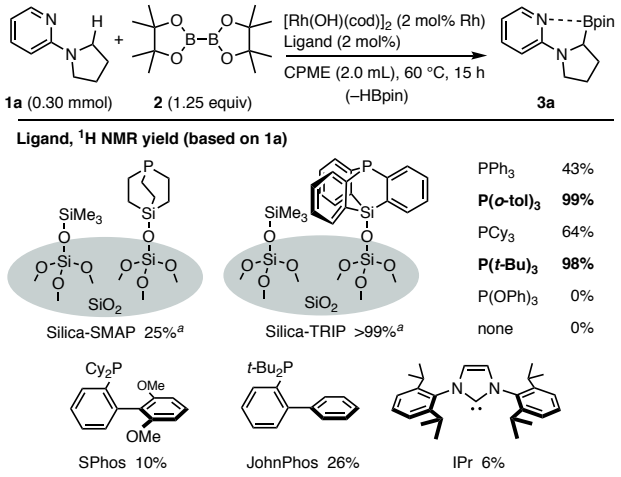
Keywords: C–H Activation, Borylation, Asymmetric Catalysis

The synthesis of highly functionalized molecules via the direct and selective transformation of C–H bonds is a highly attractive strategy and a fundamental frontier in organic synthesis. C–H bond activation strategies in transition metal catalysis have become one of the most expedient and powerful tools in molecular diversification.[1,2] While there has been a significant progress in the direct transformation of C(sp^2)–H bonds, the functionalization of the C(sp^3)–H bonds remains challenging due to both the absence of π-orbitals that can interact with a transition metal and the sterically demanding geometrical nature of C(sp^3)–H bonds compared to planar C(sp^2)–H bonds. Moreover, enantioselective C(sp^3)–H functionalization contributing to an efficient access to optically active molecules is underdeveloped.[3]

Recently, our group reported the heteroatom-directed borylation of C(sp^3)–H bonds with heterogeneous Rh- and Ir-catalyst systems based on silica-supported bridgehead monophosphines, Silica-SMAP and Silica-TRIP.[4–6] This strategy allowed site-selective borylation of the *N*-adjacent or unactivated C(sp^3)–H bonds located γ to *N* or *O* atoms in the directing groups due to the proximity effects by the heteroatom-to-metal coordination. We next turned our attention to develop their enantioselective versions to give optically active alkylboronates.[7] Along this line, however, the structural modification of the silica-supported caged phosphines aiming to the asymmetric reactions would be challenging. On the basis of our knowledge that the controlled mono-P-ligation toward metals is crucial,[8] we thought to use appropriate *soluble* ligands to realize the heteroatom-directed C(sp^3)–H borylation.[9] This protocol can open a synthetic opportunity to explore and extend the borylation reactions under homogeneous catalysis.[10]

Herein, we report the Rh- or Ir-catalyzed site-selective C(sp^3)–H borylation of 2-aminopyridines and 2-alkylpyridines providing an innovative example of a homogenous catalytic system. The use of a readily available chiral phosphoramidite as a ligand allows the direct synthesis of optically active alkylboronates with moderate level of enantioselectivity.

Initially, to investigate the possibility of catalytic borylation using homogeneous ligands, our studies commenced by using 2-(pyrrolidine-1-yl)pyridine (**1a**) as the substrate towards Rh-catalyzed *N*-adjacent C(sp^3)–H borylation using bis(pinacolato)diboron (**2**, 1.25 equiv) (Scheme 1). The reaction was conducted in CPME at 60 °C over 15 h in the presence of [Rh(OH)(cod)]$_2$ (2 mol% Rh) as a metal source with the utilization of a series of achiral monodentate phosphine ligands having different steric and electronic natures.



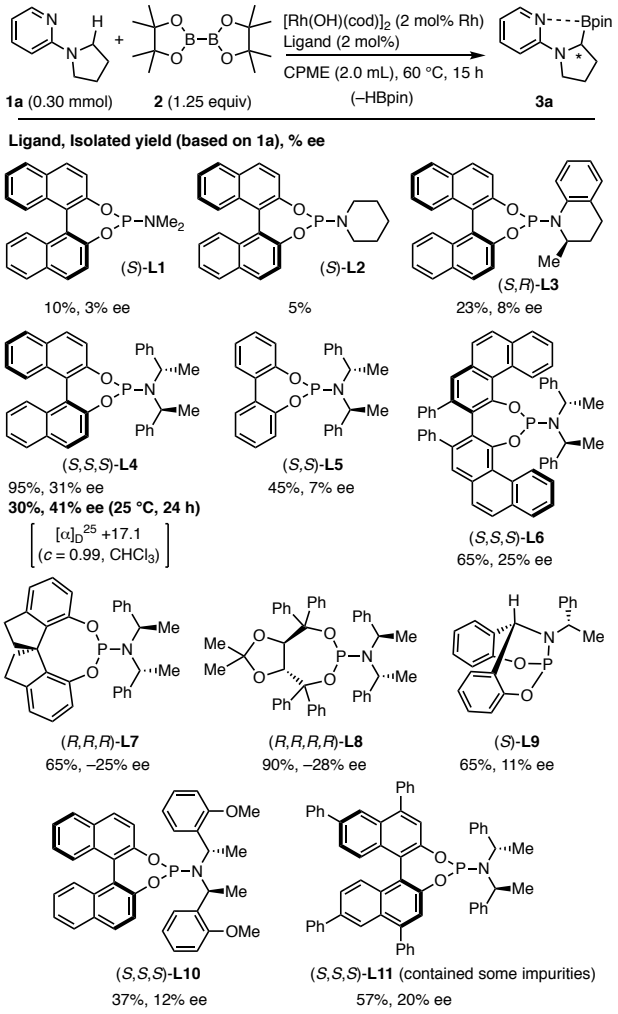
[a][Rh(OH)(cod)]$_2$ (0.5 mol% Rh), ligand (0.5 mol% P), CPME (1.5 mL).

Scheme 1. Rh-catalyzed *N*-adjacent C(sp^3)–H borylation using homogeneous and heterogeneous achiral ligands.

Several commonly used homogeneous monophosphine ligands delivered the *N*-adjacent C(sp^3)–H borylation product **3a** at considerable yields despite their lower reactivity as compared to the heterogeneous Silica-TRIP system[4a] with the exception of P(*o*-tol)$_3$ and P(*t*-Bu)$_3$ that gave the product in almost quantitative yield.[11] The steric demand of such bulky ligands would assist formation of catalytically active mono-P-ligated metal species. However, Buchwald ligands, possessing bulky electron-rich dialkylbiaryl phosphines, such as SPhos and JohnPhos exhibited limited performance (<26%). A bulky *N*-heterocyclic carbene ligand IPr was also ineffective (6%).

Nonetheless, these initial results suggested that catalytic borylation reactions using homogeneous phosphine ligands parallel to the heterogeneous system could be realized.

Inspired by these findings, we turned our attention to the possibility of asymmetric catalytic C(sp^3)–H borylation using homogeneous chiral monodentate ligands (2 mol% Rh, Rh/P 1:1; Scheme 2). We began our ligand screening with BINOL-derived phosphoramidites as they offer elements of variability at the amine-nitrogen site as well as at the chiral atropisomeric ligand backbone.[12]



Scheme 2. Ligand Effects in the Rh-catalyzed *N*-adjacent C(sp^3)–H bond borylation of **1a**.

(*S*)-**L1** and (*S*)-**L2** bearing *N*-dimethyl and *N*-pentamethylene moieties, respectively, gave **3a** in low yields with (*S*)-**L1** exhibiting a low enantioselection at only 3%. The incorporation of an amine moiety having a stereogenic center led to an increase in both yield and enantioselectivity. The use of (*S*,*R*)-**L3** bearing a chiral tetrahydroquinoline derivative improved the reaction yield but exhibited poor enantioselectivity (23% yield, 8% ee). To our delight, (*S*,*S*,*S*)-**L4** showed promising reactivity giving the product at 95% yield with a moderate enantioselectivity of 31% in favour of the (+)-isomer. The enantioselectivity with (*S*,*S*,*S*)-**L4** was then increased to 41% ee by conducting the reaction at 25 °C over 24 h, with a consequential decrease in the yield of **3a** to 30%.

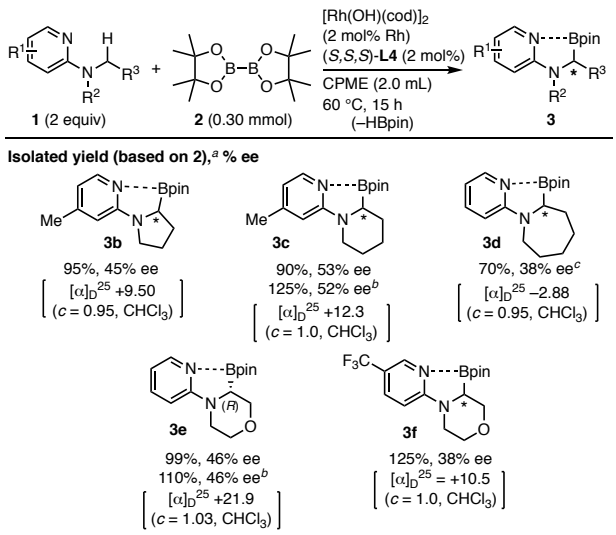
Other P-backbones of the phosphoramidite ligands bearing the bis[(*S*)-1-phenylethyl]amine moiety were also investigated. An achiral biphenyl-based ligand (*S*,*S*)-**L5** resulted in the loss of both reactivity and enantioselectivity (45% yield, 7% ee). The use of chiral P-backbones bearing VAPOL- [(*S*,*S*,*S*)-**L6**], spirobiindanyl- [(*R*,*R*,*R*)-**L7**] or TADDOL [(*R*,*R*,*R*,*R*)-**L8**] proved ineffective in the improvement of the enantioinduction while keeping the good to excellent reactivity (65–90% yields, –28 to 25% ees). A chiral phosphoramidite (*S*)-**L9** based on a bicyclic bridgehead structure showed some reactivity towards the borylation reaction,[13] but its asymmetric induction proved to be inferior to (*S*,*S*,*S*)-**L4** (11% ee *vs*. 31% ee).

Introducing substituents at the (*S*,*S*,*S*)-**L4** scaffold did not lead to any enhanced effect on both the reactivity and enantioselectivity. Specifically, (*S*,*S*,*S*)-**L10** bearing MeO-substituents on the phenyl ring of the bis[(*S*)-1-phenylethyl]amine moiety at *ortho* position was less effective (37% yield, 12% ee). Introducing Ph-substituents in both the 4,4'- and 6,6'-positions on the BINOL moiety, (*S*,*S*,*S*)-**L11** resulted in the erosion of both reactivity and enantioselectivity (57% yield, 20% ee). Thus, both the reactivity and enantioselectivity of the present borylation protocol using chiral monodentate phosphoramidites is highly sensitive to their ligand structures.

While the results showed only the moderate enantioinduction in product **3a**, this method provides the first example of a homogenous system utilizing a known, simple, and readily available monophosphine ligand enabling the direct activation and the subsequent borylation of *N*-adjacent C(sp^3)–H bond.[14] From this exemplary reactivity using (*S*,*S*,*S*)-**L4**, we then investigated the compatibility of this transformation with several 2-aminopyridines (2 mol% Rh, 60 °C in CPME, 2 equiv of **1**, yields based on **2**). The results are summarized in Scheme 3.

The reaction of 4-methyl-2-(pyrrolidin-1-yl)pyridine proceeded smoothly to give the corresponding α-amino boronate **3b** in an improved enantioselectivity in favour of the (+)-isomer as compared to the parent substrate **3a** (45% ee *vs* 31% ee). Its piperidine analogue was also borylated, affording (+)-**3c** in 53% ee. The seven-membered azepane derivative was likewise tolerable with slightly decreased enantioselectivity [38% ee for (–)-**3d**, 4.5:1 conformer ratio based on ^{11}B NMR]. The borylation of morpholine derivatives to give **3e** and **3f** occurred at the position adjacent to the morpholine *N* atom at excellent reactivity and modest enantioselectivity (46 and 38% ees, respectively). Larger-scale reactions (7 mmol for **2**) proceeded efficiently to give **3c** or **3e** in high yields without loss of the enantioselectivity. Despite the moderate level of enantioselectivity observed for the borylation products, product (+)-**3e** was further purified by a semi-preparative chiral HPLC system (>99% ee) and the absolute configuration was unambiguously determined to be *R* by vibrational circular dichroism (VCD) measurement.[15] While

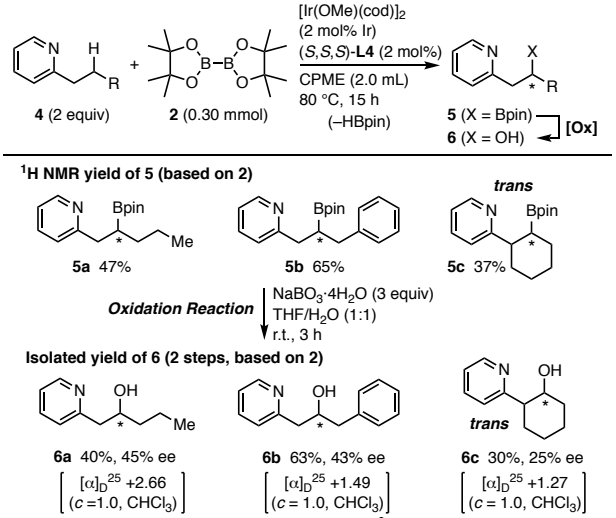
the absolute configuration of the other borylated products were not directly determined, probable correlation can be inferred from the observed optical rotation values (Scheme 3).



[a]Yields in excess of 100% indicate that the HBpin formed during the catalytic turnover also served as a borylation agent (theoretical maximum yield is 200%). [b]7 mmol scale reaction for **2** (10 mL of CPME). [c]The 4.5:1 conformer ratio based on ^{11}B NMR.

Scheme 3. Asymmetric C(sp^3)–H Borylation of **1**.

This protocol using (*S*,*S*,*S*)-**L4** was extended to the Ir-catalyzed asymmetric C(sp^3)–H borylation of 2-alkylpyridines **4** (2 mol% Ir, 80 °C in CPME, 2 equiv of **4**, yields based on **2**; Scheme 4). The enantioselectivity was evaluated by converting the borylation products **5** to the corresponding alcohols **6** with a borylation/oxidation sequence. The C–H asymmetric borylation proceeded not only in linear alkyl substrates (**5a** and **5b**) but also in cyclic alkyl moiety (**5c**) with moderate enantioselectivity (25–45% ees).[16]



Scheme 4. Asymmetric C(sp^3)–H Borylation of **4** followed by Oxidation.

In light of the ligand effects identified in the present borylation reactions, we hypothesize the formation of C(sp^3)–M–P metallacycles as the possible active species responsible for the observed reactivity. As exemplified by the results with ligands (*S*)-**L1** to (*S*,*S*,*S*)-**L4** shown in Scheme 2, the yields of the borylation product **3a** increased when the phosphoramidite ligands have available β-hydrogens with respect to the *N*-atom on the amine moiety to form putative five-membered metallacycles. This reactivity based on the formation of an iridacycle upon the deprotonation of one of the methyl groups in bis[(*S*)-1-phenylethyl]amine moiety of (*S*,*S*,*S*)-**L4** was also reported in the case of Ir-catalyzed enantioselective allylic substitution reactions.[17,18]

In summary, we have developed homogeneous catalytic systems leading to the activation and subsequent site-selective borylation of C(sp^3)–H bonds in 2-aminopyridines and 2-alkylpyridines. The use of simple and readily available chiral monophosphine ligand (*S*,*S*,*S*)-**L4** allowed asymmetric C(sp^3)–H borylation, giving enantioenriched alkylboronates. Consequently, efforts to improve the enantioselectivity of these transformations by looking into different considerations like the development of new ligand platforms and the modification of the ligand structure are underway in our laboratory.

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Supporting Information

Experimental procedures, spectral and analytical data. This material is available on http://dx.doi.org/10.1246/############.

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