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Ligand-Promoted Borylation of C(sp³)–H Bonds with Pd(II) Catalysts

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Abstract

A quinoline-based ligand is identified to effectively promote Pd-catalyzed borylation of C(sp³)–H bonds. Primary β-C(sp³)–H bonds in carboxylic acid derivatives as well as secondary C(sp³)–H bonds in a variety of carbocyclic rings including cyclopropanes, cyclobutanes, cyclopentanes, cyclohexanes, and cycloheptanes are borylated. This directed borylation method complements existing Ir(I) and Rh(I)-catalyzed C–H borylation reactions in terms of scope and operational conditions.

Keywords

amino acids; borylation; C–H activation; palladium; synthetic methods

C–H borylation catalyzed by Ir,^[1] Rh,^[2] and other metals^[3–5] is an important research topic in the field of C–H activation, as the newly formed carbon–boron bonds can be converted to a variety of carbon–carbon and carbon–heteroatom bonds.^[6] In contrast, development of C–H borylation reactions using Pd catalysts has met with limited success.^[7] Building on the Pd(II)-catalyzed cross-coupling of C–H bonds with organoboron reagents,^[8] we and others developed rare examples of directed *ortho*-borylation of arenes with Pd catalysts (eq 1).^[9] Recently, C(sp³)–H borylation of amines using the Daugulis' bidentate directing group has also been reported using 20 mol% Pd catalysts (eq 2), albeit limited to methyl C–H bonds.^[10] Difficulties encountered in these efforts to develop a broadly useful C(sp³)–H borylation reaction pointed to the need for a new ligand that can drastically promote C(sp³)–H activation. Herein we report an efficient Pd-catalyzed β-borylation of carboxylic acid-derived amides with bis(pinacolato)diboron through ligand acceleration (eq 3). This C(sp³)–H borylation reaction is compatible with α-methyl C–H bonds as well as methylene C–H bonds in a wide range of cyclic amide substrates, including cyclopropanes, cyclobutanes, cyclopentanes, cyclohexanes, and cycloheptanes. C(sp³)–H borylation of this class of substrates has not been demonstrated using other catalytic systems.^[1k,1l,1m,2d] Importantly, Pd(II)-catalyzed C(sp³)–H borylation proceeds through a fundamentally different reaction mechanism and redox chemistry from the Ir- and Rh-catalyzed C–H borylation reactions. Thus, the successful development of an effective quinoline-based ligand paves the way for further development of C–H borylation chemistry using a new class of catalysts, which may emerge as an important and complementary approach to existing ones.

We choose the Pd(II)/Pd(0) catalytic cycle as a promising platform due to our experience with this system in the C–H cross-coupling,^[8] as well as the precedents of Pd(II)-catalyzed C–H borylation.^[9] However, significant challenges exist for Pd(II)-catalyzed C–H borylation. First, the reductive elimination step involving Pd–B species are known to be inefficient in the absence of a suitable ligand as shown in the palladium-catalyzed borylation of aryl halides.^[11] A second potentially problematic issue is that the borylated products could also react with Pd(II) via transmetalation, resulting in deborylation or β-hydride

elimination reactions. These potential hurdles could account for the low efficiency of previous conditions^[9a,10] for C(sp³)-H borylation. For example, C(sp³)-H borylation using our highly optimized conditions initially developed for *ortho*-C-H borylation of benzamides resulted in low yields (see Supporting Information [SI]). These earlier results suggest that it is crucial to identify a ligand that can drastically accelerate C-H activation under relatively mild conditions so that the decomposition of borylated products may be avoided. Our recent finding of ligand-enabled Pd(II)-catalyzed cross-coupling of C(sp³)-H bonds with organosilicon coupling partners through a Pd(II)/Pd(0) manifold^[12] prompted us to focus on developing pyridine or quinoline-based ligands that might promote C(sp³)-H borylation reactions. Based on our previous protocol,^[9a] we further screened palladium catalysts, bases, oxidants, and solvents using alanine-derived amide substrate **1**, which resulted in minor improvement (Table 1). 20 mol% HOAc helped prevent the substrate decomposition,^[13] and slightly improved the yield (see SI). Since 2-picoline (**L1**) was known to accelerate C-H arylation of alanine-derived amide **1**,^[13] we began our ligand screening with **L1**. Disappointingly, **L1** gave slightly lower yield which indicates this ligand may not be compatible with the transmetalation or reductive elimination step. Among several other pyridine ligands (see SI), only 2,4,6-trimethoxypyridine improved the yield to 45%. We then switched our attention to the electron-rich tricyclic quinoline ligands (**L2**, **L3**) that were previously used to promote C(sp³)-H olefination in Pd(II)/Pd(0) catalysis.^[13] Encouragingly, the use of **L3** improved the yield to 51%. While simple acridine (**L4**) gave a similar result to **L3**, installation of a methoxy group at the 9-position of acridine increased the yield to 55% (**L5**). Replacement of **L5** with electron-deficient 9-chloroacridine (**L6**) drastically decreased the yield to 18%, suggesting that electron-rich substituents on the ligands are beneficial. Guided by this observation, we introduced alkyl and alkoxy groups onto quinoline rings systematically (see SI). In spite of the poor reactivity from ligand **L7**, 2-methoxyquinoline (**L8**) provided the desired product in 58% yield. Replacing the methoxy group by the more hindered isobutoxy group drastically decreased the yield to 30% revealing strong steric effect from ligands (**L9**). Gratifyingly, further increasing the electron density of quinoline ligands improved the yield to 67% (**L10**). Various bulkier alkoxy groups at 2,4-positions of quinoline consistently led to a decrease in yields (**L11-L14**). To further improve the turnover of this reaction, we screened a number of ammonium salts that are known to prevent aggregation of Pd(0) species.^[14] The use of tetraethylammonium tetrafluoroborate (TEABF₄) increased the yield to 73%. To elucidate the role of ligand and TEABF₄, we examined the influence of **L10** and additives on the rate profile (see SI). The ligand increased the initial rate of the borylation reaction by 5-fold while TEABF₄ did not influence the rate. The less electron-withdrawing auxiliaries gave much lower yields (see SI), which is consistent with our previous observation that the acidity of arylamides is important for the C(sp³)-H activation. We have previously shown that deprotonation of amides by inorganic bases promotes the activation of C(sp³)-H bonds, leading to the formation of palladacycle intermediates.^[13] Control experiments confirm that O₂ is needed to render this reaction catalytic (see SI). The requirement of O₂ for catalytic turnovers is not consistent with a Pd(II)/Pd(IV) catalytic cycle. Instead, the proposed Pd(II)/Pd(0) catalysis is most likely operative. Importantly, this reaction also proceeds under air to give 56% yield.

Having identified the optimal reaction conditions, we then evaluated the scope of the carboxylic acid-derived amides towards C(sp³)-H borylation (Table 2). The borylation reactions of substrates containing α -quaternary centers are efficient in general (**4a–4l**). The amide **3c** of the parent drug gemfibrozil is borylated to give **4c** in 70% yield. Aryl groups at the β - or γ -positions are well tolerated (**4e**, **4f**). It is worth mentioning that this borylation protocol is highly mono-selective in the presence of two or three methyl groups, as the newly installed boron species are quite bulky and may also coordinate to the amide auxiliary,^[9b,15] thus preventing a second β -C(sp³)-H cleavage of the products (**4a–4f**). The observed mono-selectivity with isobutyric and pivalic acid substrates is a distinct advantage over many β -C-H functionalization reactions where a mixture of mono- and di-functionalization products are obtained.^[16] Amides possessing α -protons are compatible with the reaction conditions as well (**4m–4r**). We also performed the borylation reactions using 5 mol% of palladium catalysts, giving the borylated products (**4d–4f**) in high yields. Importantly, a gram-scale C(sp³)-H borylation was carried out without using any additives to provide **4a** in 67% yield (Scheme 2), which clearly indicates that Pd(II)/L is the real catalyst and the additives only provide minor improvement.

While the methylene C-H borylation of an acyclic amide derived from 2-ethylbutanoic acid (**3t**) gives the borylated product in 25% yield (see SI), a variety of cyclic amides are borylated in synthetically useful yields (Table 3). Of note is that a phthalimido group is tolerated under the reaction conditions (**6c**, **6g**). In contrast with *cis*-diastereomers obtained with cyclopropyl, cyclobutyl and cyclopentyl substrates, the reactions of cyclohexyl and cycloheptyl substrates **5i** and **5j** afford a mixture of *cis*- and *trans*-diastereomers in a 1:1 ratio (**6i**, **6j**). The equatorial directing group in cyclohexyl rings is known to accommodate both *cis*- and *trans*-cyclopalladation due to the chair conformation. We have also performed the borylation of bicyclo[2.2.2]octane substrates **5k** and **5l** to rapidly diversify this class of three-dimensional drug scaffolds. Notably, Ir-catalyzed C(sp³)-H borylation of carbocyclic systems has only been demonstrated with cyclopropylamine^[1m] and 2-cyclohexylpyridine substrates.^[1k] To further demonstrate the efficiency of this ligand-promoted borylation reaction, we conducted the reaction of cyclobutyl substrate **5e** by the use of 1–2 mol% of Pd(OAc)₂ (eq 4). This unprecedented low palladium loading speaks to the importance of ligand effect in C-H activation reactions.

(4)

To illustrate the synthetic utility of this C(sp³)-H borylation reaction (Scheme 3), we subjected substrate **7** derived from dehydroabietic acid to the borylation conditions. Treating the crude borylation product subsequently with hydrogen peroxide in THF affords the desired hydroxylated product **8** in 70% yield over two steps. The borylated alanine **2** reacts with *N*-ethylaniline in the presence of Cu(OAc)₂ as catalyst and Ag₂CO₃ as oxidant to give

the β -aminated product **9** in 90% yield.^[17] The cyclobutylboronate ester **6c** is easily converted to the trifluoroborate salt **10** using KHF_2 (aq) in acetonitrile in 95% yield. Under Suzuki-Miyaura cross-coupling reaction conditions developed by Molander and co-workers,^[18b] **10** is coupled with 1-chloro-4-nitrobenzene to give the arylated cyclobutane **11** in a moderate yield. Contrary to the complete inversion in stereochemistry via transmetalation with seemingly similar alkyl borons,^[15a,18] retention is observed in the transformation from **10** to **11**. The observed retention of stereochemistry is consistent with a transmetalation step directed by the amide auxiliary. The acidic amide is known to form an effectively coordinating amidate following the deprotonation under basic conditions.^[13] Fluorination reaction of the borylated product **6c** in the presence of AgNO_3 and Selectfluor^[19] proceeds smoothly to yield two diastereomers, **12-trans** and **12-cis** in 39% and 53% yields respectively. The combination of $\text{C}(\text{sp}^3)\text{-H}$ borylation and fluorination could find widespread application in drug discovery.

Our desire to improve this potentially powerful $\text{C}(\text{sp}^3)\text{-H}$ borylation method prompted us to perform further kinetic studies on the concentration dependences of the palladium catalyst and substrate **1** (see SI). We found that the borylation reaction is first order in $[\text{Pd}]$ and zero order in substrate. The observed intermolecular KIE of **3b** and **3b-*d*₆** ($k_{\text{H}}/k_{\text{D}} = 3.3$) suggests that C–H cleavage is the rate-limiting step in this $\text{C}(\text{sp}^3)\text{-H}$ borylation reaction (see SI). To further investigate the reaction mechanism, we carried out a stoichiometric reaction of the palladacycle intermediate with B_2pin_2 and obtained the desired borylated product in 59% yield (see SI). Based on these mechanistic data, we propose the following Pd(II)/Pd(0) catalytic cycle (Figure 1).

In summary, we have developed a versatile Pd-catalyzed $\beta\text{-C}(\text{sp}^3)\text{-H}$ borylation of a wide range of carboxylic acid derivatives using a quinoline-based ligand. The new method is compatible with methyl $\text{C}(\text{sp}^3)\text{-H}$ bonds in both α -tertiary and α -quaternary carboxylic acids, as well as methylene $\text{C}(\text{sp}^3)\text{-H}$ bonds in a variety of cyclic carboxylic acids. The borylated products are converted into various organic synthons through carbon–carbon and carbon–heteroatom bond formation. Preliminary ligand structure/reactivity relationship also indicates superiority of electron-rich and sterically less hindered quinoline ligands.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Plausible mechanism of C(sp³)-H borylation.

This work

Scheme 1.
Palladium-catalyzed directed C–H borylation

Scheme 2.
Gram-scale C(sp³)-H borylation

Scheme 3.

Applications of C(sp³)–H borylation. a) B₂pin₂ (2.0 equiv), Pd(OAc)₂ (10 mol%), **L10** (20 mol%), HOAc (20 mol%), TEABF₄ (50 mol%), KHCO₃ (2.0 equiv), CH₃CN, O₂, 80 °C, 15 h. b) H₂O₂, aqueous buffer (pH = 7), THF, rt, 2 h. c) *N*-ethylaniline (1.5 equiv), Cu(OAc)₂ (10 mol%), Ag₂CO₃ (2.0 equiv), toluene, 100 °C, 20 h. d) KHF₂ (aq) (4.5 M, 5.1 equiv), CH₃CN, rt, 3 h. e) 1-chloro-4-nitrobenzene (1.0 equiv), **10** (1.2 equiv), Pd(OAc)₂ (10 mol%), SPhos (20 mol%), Cs₂CO₃ (3.0 equiv), CPME/H₂O (6.7/1), N₂, 95 °C, 20 h. f) AgNO₃ (20 mol%), Selectfluor (3.0 equiv), TFA (4.0 equiv), DCM, H₂O, N₂, 50 °C, 6 h.

Table 1

Screening of ligands for C(sp³)-H borylation of alanine-derived amide **1**.^[a,b]

—	32%
28%
47%
51%
50%
55%
18%
21%
58%
30%
67%
60%
55%
48%
50%
73% ^[c] (70%) ^[d]	

^[a] Reaction conditions: substrate **1** (0.10 mmol), B₂pin₂ (2.0 equiv), Pd(OAc)₂ (10 mol%), ligand (20 mol%), HOAc (20 mol%), KHCO₃ (2.0 equiv), CH₃CN (1.5 mL), O₂, 80 °C, 15 h.

^[b] The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

^[c] TEABF₄ (50 mol%) was added.

^[d] Isolated yields.

Table 2

Substrate scope for C(sp³)-H borylation.^[a,b]

^[a] Reaction conditions: substrate **3a–3r** (0.10 mmol), B₂pin₂ (2.0 equiv), Pd(OAc)₂ (10 mol%), **L10** (20 mol%), HOAc (20 mol%), TEABF₄ (50 mol%), KHCO₃ (2.0 equiv), CH₃CN (1.5 mL), O₂, 80 °C, 15 h.

^[b] Yields of isolated products.

$[c]$ Pd(OAc)₂ (5 mol%) and **L10** (10 mol%) were used.

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Table 3

 β -C(sp³)-H borylation of cyclic carboxylic acid derivatives.^[a,b]

^[a] Reaction conditions: substrate **5a–5l** (0.10 mmol), B₂pin₂ (2.0 equiv), Pd(OAc)₂ (10 mol%), **L10** (20 mol%), HOAc (20 mol%), TEABF₄ (50 mol%), KHCO₃ (2.0 equiv), CH₃CN (1.5 mL), O₂, 80 °C, 15 h.

^[b] Yields of isolated products.

^[c] Pd(OAc)₂ (5 mol%) and **L10** (10 mol%) were used.