C–H Activation

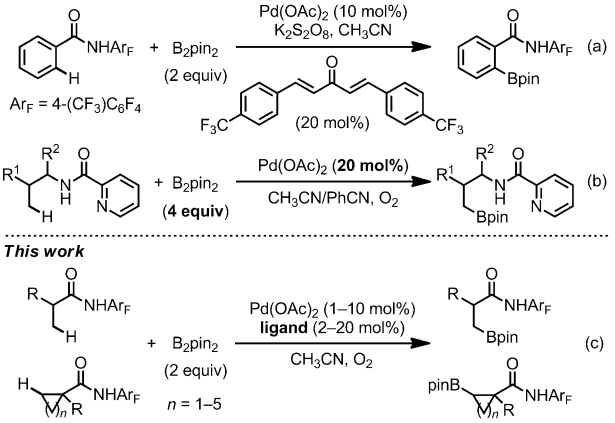
Deutsche Ausgabe: DOI: 10.1002/ange.201509996
Internationale Ausgabe: DOI: 10.1002/anie.201509996

Ligand-Promoted Borylation of C(sp^3)–H Bonds with Palladium(II) Catalysts

*Jian He, Heng Jiang, Ryosuke Takise, Ru-Yi Zhu, Gang Chen, Hui-Xiong Dai, T. G. Murali Dhar, Jun Shi, Hao Zhang, Peter T. W. Cheng, and Jin-Quan Yu**

Abstract: *A quinoline-based ligand effectively promotes the palladium-catalyzed borylation of C(sp^3)–H bonds. Primary β-C(sp^3)–H bonds in carboxylic acid derivatives as well as secondary C(sp^3)–H bonds in a variety of carbocyclic rings, including cyclopropanes, cyclobutanes, cyclopentanes, cyclohexanes, and cycloheptanes, can thus be borylated. This directed borylation method complements existing iridium(I)- and rhodium(I)-catalyzed C–H borylation reactions in terms of scope and operational conditions.*

The borylation of C–H bonds catalyzed by iridium,[1] rhodium,[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 into a variety of carbon–carbon and carbon–heteroatom bonds.[6] In contrast, the development of C–H borylation reactions with 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 reactions of arenes with Pd catalysts (Scheme 1 a).[9] Recently, Daugulis' bidentate directing group has been applied to the C(sp^3)–H borylation of amines with 20 mol % of a Pd catalyst (Scheme 1 b), but this method was limited to methyl C–H bonds.[10] Difficulties encountered in these efforts to develop a broadly useful C(sp^3)–H borylation reaction pointed to the need for a new ligand that can drastically promote C(sp^3)–H activation. Herein, we report an efficient Pd-catalyzed β-borylation of carboxylic acid derived amides with bis(pinacolato)diboron through ligand acceleration (Scheme 1 c). This C(sp^3)–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. The C(sp^3)–H borylation of this class of substrates has not been demonstrated using other catalytic systems.[1k–m,2d] Importantly, Pd^{II}-catalyzed C(sp^3)–H borylation proceeds through a reaction mechanism and redox processes that are fundamentally different to those of the Ir- and Rh-catalyzed C–H borylation reactions. Thus the successful development of an effective quinoline-based ligand paves the way for the development of further C–H borylation reactions using a new class of catalysts, which may emerge as an important and complementary approach to existing ones.



Scheme 1. Palladium-catalyzed directed C–H borylation.

We chose the Pd^{II}/Pd^0 catalytic cycle as a promising platform owing to our experience with this system in C–H cross-coupling,[8] as well as the precedents of Pd^{II}-catalyzed C–H borylation.[9] However, significant challenges have to be overcome for Pd^{II}-catalyzed C–H borylation. First, reductive elimination from a Pd–B species is 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} by transmetalation, resulting in deborylation or β-hydride elimination reactions. These potential hurdles could account for the low efficiency of previous methods[9a,10] for C(sp^3)–H borylation. For example, C(sp^3)–H borylation according to our highly optimized conditions initially developed for the *ortho* C–H borylation of benzamides resulted in low yields (see the Supporting Information). These early results suggested that it is crucial to identify a ligand that can drastically accelerate C–H activation under relatively mild conditions so that decomposition of the borylated products may be avoided. Our recently reported ligand-enabled Pd^{II}-catalyzed cross-coupling of C(sp^3)–H bonds with organosilicon coupling partners through a Pd^{II}/Pd^0 manifold[12] prompted us to focus on developing pyridine- or quinoline-

[*] J. He, H. Jiang, R. Takise, R.-Y. Zhu, Dr. G. Chen, Prof. Dr. H.-X. Dai, Prof. Dr. J.-Q. Yu
Department of Chemistry
The Scripps Research Institute (TSRI)
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: yu200@scripps.edu
Dr. T. G. M. Dhar
Discovery Chemistry, Bristol-Myers Squibb Company
Route 206 and Provinceline Road, Princeton, NJ 08543 (USA)
Dr. J. Shi, Dr. H. Zhang, Dr. P. T. W. Cheng
Discovery Chemistry, Bristol-Myers Squibb Company
311 Pennington Rocky Hill Road, Pennington, NJ 08534 (USA)

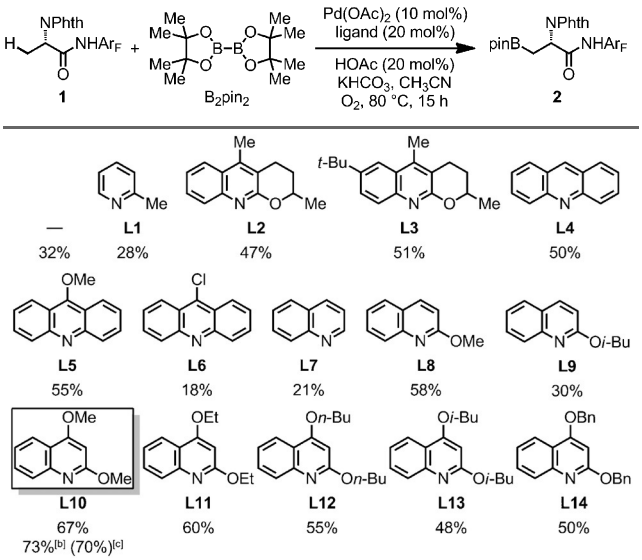
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509996.

based ligands that might promote C(sp^3)–H borylation reactions. Based on our previous method,[9a] we screened further palladium catalysts, bases, oxidants, and solvents using alanine-derived amide substrate **1**, which resulted in minor improvements (Table 1). The use of HOAc (20 mol%) helped prevent substrate decomposition,[13] and slightly improved the yield (see the Supporting Information). As 2-picoline (**L1**) is known to accelerate the C–H arylation of alanine-derived amide **1**,[13] we began our ligand screening with **L1**. Disappointingly, **L1** gave a slightly lower yield, which indicates that this ligand may not be compatible with the transmetalation or reductive-elimination step. Among several other pyridine ligands (see the Supporting Information), only 2,4,6-trimethoxypyridine improved the yield, namely to 45%. We then turned our attention to the electron-rich tricyclic quinoline ligands (**L2** and **L3**) that were previously used to promote C(sp^3)–H olefination by Pd^{II}/Pd^0 catalysis.[13] Encouragingly, the use of **L3** improved the yield to 51%. Whereas 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 ligand are beneficial. Guided by this observation, we systematically introduced alkyl and alkoxy groups onto the quinoline ring (see the Supporting Information). In spite of the poor reactivity resulting from the use of ligand **L7**, 2-methoxyquinoline (**L8**) provided the desired product in 58% yield. Replacing the methoxy group by a more hindered isobutoxy group (**L9**) drastically decreased the yield to 30%, revealing that the steric properties of ligands have a strong effect on the reaction. Gratifyingly, further increasing the electron density on the quinoline ligand improved the yield to 67% (**L10**). Various bulkier alkoxy groups at the 2- and 4-position of quinoline consistently led to a decrease in yield (**L11**–**L14**). To further improve the turnover of this reaction, we screened a number of ammonium salts that are known to prevent the aggregation of Pd^0 species.[14] The use of tetraethylammonium tetrafluoroborate ($TEABF_4$) increased the yield to 73%. To elucidate the role of the ligand and $TEABF_4$, we examined the influence of **L10** and additives on the rate profile (see the Supporting Information). The ligand increased the initial rate of the borylation reaction by a factor of five whereas $TEABF_4$ did not influence the rate. The substrates containing less electron-deficient amide auxiliaries gave much lower yields (see the Supporting Information), which is consistent with our previous observation that the acidity of aryl amides is important for the C(sp^3)–H activation. We have previously shown that the deprotonation of amides by inorganic bases promotes the activation of C(sp^3)–H bonds, leading to the formation of palladacycle intermediates.[13] Control experiments confirmed that O_2 is needed to render this reaction catalytic (see the Supporting Information). The requirement of O_2 for catalytic turnover is not consistent with a Pd^{II}/Pd^{IV} catalytic cycle. Instead, the proposed Pd^{II}/Pd^0 catalytic cycle is most likely operative. Importantly, this reaction also proceeded under air to give the desired product in 56% yield.

With the optimized reaction conditions in hand, we then subjected various carboxylic acid derived amides to the C(sp^3)–H borylation reaction conditions (Table 2). The borylation of substrates containing α-quaternary centers is efficient in general (**4a**–**4l**). Compound **3c**, an amide derivative of the drug gemfibrozil, was borylated to give **4c** in 70% yield. Aryl groups at the β- or γ-positions are well tolerated (**4e** and **4f**). It is worth mentioning that this borylation method is highly monoselective in the presence of two or three methyl groups, as the newly installed boron moiety is quite bulky and may also coordinate to the amide auxiliary,[9b,15] thus preventing a second β-C(sp^3)–H activation of the products (**4a**–**4f**). The monoselectivity observed with isobutyric and pivalic acid substrates is a distinct advantage over many β-C–H functionalization reactions where mixtures of the mono- and difunctionalization 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 the palladium catalyst, which gave the borylated products (**4d**–**4f**) in high yields. Importantly, the C(sp^3)–H borylation was carried out on a gram scale without any additives to provide **4a** in 67% yield (Scheme 2), which clearly indicates that Pd^{II}/L is the real catalyst and that the additives only provide minor improvement.

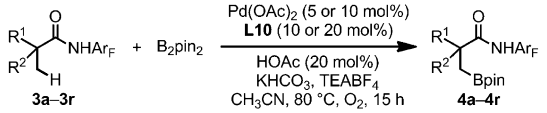
Whereas the methylene C–H borylation of an acyclic amide derived from 2-ethylbutanoic acid (**3t**) gave the borylated product in 25% yield (see the Supporting Information), a variety of cyclic amides were borylated in synthetically useful yields (Table 3). For example, a phthalimido group is tolerated under the reaction conditions (**6c** and **6g**).

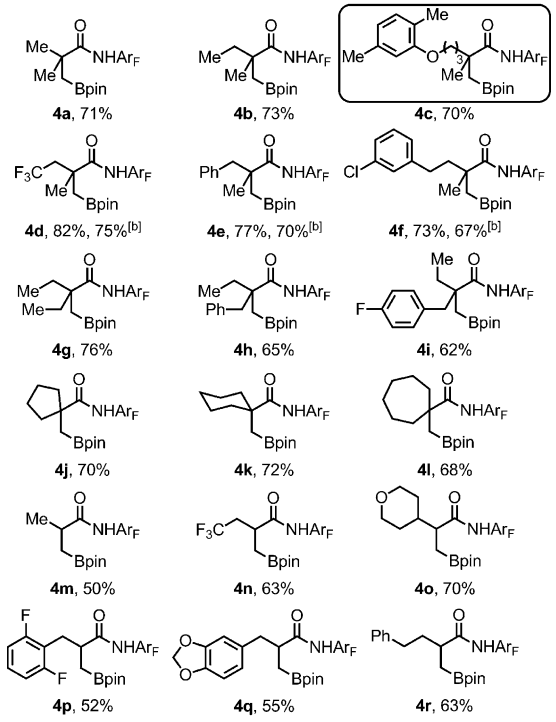
Table 1: Screening of ligands for the C(sp^3)–H borylation of alanine-derived amide **1**.[a]



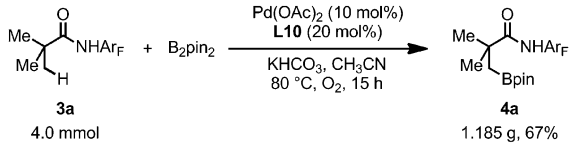
[a] Reaction conditions: substrate **1** (0.10 mmol), B_2pin_2 (2.0 equiv), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), HOAc (20 mol%), $KHCO_3$ (2.0 equiv), CH_3CN (1.5 mL), O_2, 80°C, 15 h. The yield was determined by ^1H NMR analysis of the crude product mixture using CH_2Br_2 as the internal standard. [b] $TEABF_4$ (50 mol%) was added. [c] Yield of isolated product.

Table 2: Substrate scope of the C(sp^3)–H borylation.[a]





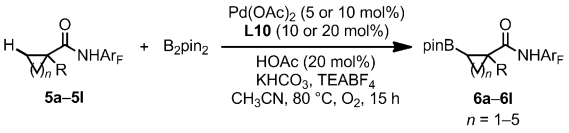
[a] Reaction conditions: **3a–3r** (0.10 mmol), B_2pin_2 (2.0 equiv), Pd(OAc)$_2$ (10 mol%), **L10** (20 mol%), HOAc (20 mol%), $TEABF_4$ (50 mol%), $KHCO_3$ (2.0 equiv), CH_3CN (1.5 mL), O_2, 80°C, 15 h. Yields of isolated products are given. [b] Pd(OAc)$_2$ (5 mol%) and **L10** (10 mol%) were used.

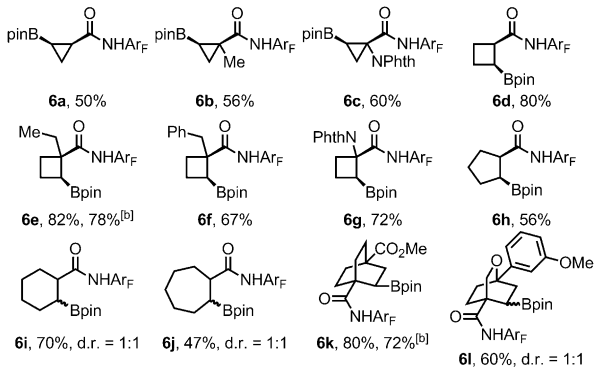


Scheme 2. Gram-scale C(sp^3)–H borylation.

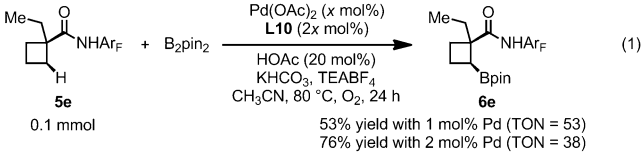
In contrast to the *cis* diastereomers obtained with cyclopropyl, cyclobutyl, and cyclopentyl substrates, the reactions of the cyclohexyl and cycloheptyl substrates **5i** and **5j** afforded mixtures of the *cis* and *trans* diastereomers in a 1:1 ratio (**6i** and **6j**). The equatorial directing group in cyclohexyl rings is known to enable both *cis* and *trans* cyclopalladation owing to the chair conformation. We also performed the borylation of the bicyclo[2.2.2]octanes **5k** and **5l** to rapidly diversify this class of three-dimensional drug scaffolds. Notably, Ir-catalyzed C(sp^3)–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** with 1–2 mol% of Pd(OAc)$_2$ [Eq. (1)]. This unprecedented low palladium loading speaks to the importance of ligand effects in C–H activation reactions.

Table 3: β-C(sp^3)–H borylation of cyclic carboxylic acid derivatives.[a]

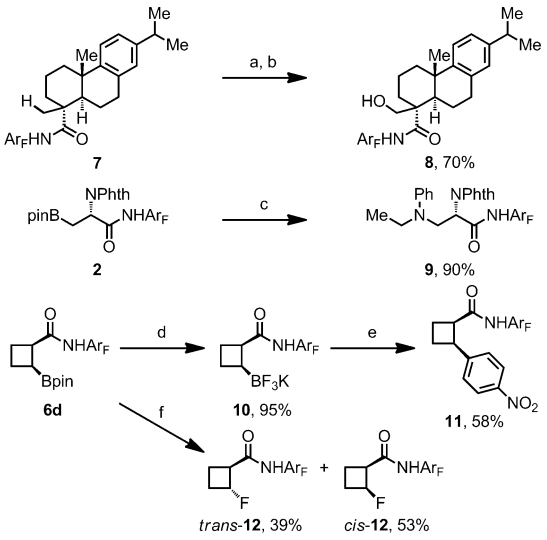




[a] Reaction conditions: **5a–5l** (0.10 mmol), B_2pin_2 (2.0 equiv), Pd(OAc)$_2$ (10 mol%), **L10** (20 mol%), HOAc (20 mol%), $TEABF_4$ (50 mol%), $KHCO_3$ (2.0 equiv), CH_3CN (1.5 mL), O_2, 80°C, 15 h. Yields of isolated products are given. [b] Pd(OAc)$_2$ (5 mol%) and **L10** (10 mol%) were used.



To illustrate the synthetic utility of this C(sp^3)–H borylation reaction (Scheme 3), we subjected substrate **7**, which is derived from dehydroabietic acid, to the borylation conditions. Treating the crude borylation product with hydrogen peroxide in THF afforded the desired hydroxylated product **8** in 70% yield over two steps. The borylated alanine **2** reacted with *N*-ethylaniline in the presence of Cu(OAc)$_2$ as the catalyst and Ag_2CO_3 as the oxidant to give the β-aminated product **9** in 90% yield.[17] Cyclobutylboronate ester **6c** was easily converted into the trifluoroborate salt **10** in 95% yield by using aqueous KHF_2 in acetonitrile. Under the Suzuki–Miyaura cross-coupling reaction conditions developed by Molander and co-workers,[18a] **10** was coupled with 1-chloro-4-nitrobenzene to give the arylated cyclobutane **11** in moderate yield. Whereas complete inversion of stereochemistry is generally observed for reactions with seemingly similar alkyl boron reagents that proceed by transmetalation,[15a,18] the transformation of **10** into **11** proceeded with retention, which is consistent with a transmetalation step that is directed by the amide auxiliary. The acidic amide is known to form an effectively coordinating amidate after deprotonation under basic conditions.[13] Finally, fluorination of the borylated



Scheme 3. Further transformations of the products obtained by C-(sp^3)–H borylation. a) B_2pin_2 (2.0 equiv), $Pd(OAc)_2$ (10 mol%), **L10** (20 mol%), HOAc (20 mol%), $TEABF_4$ (50 mol%), $KHCO_3$ (2.0 equiv), CH_3CN, O_2, 80°C, 15 h; b) H_2O_2, aqueous buffer (pH 7), THF, RT, 2 h; c) *N*-ethylaniline (1.5 equiv), $Cu(OAc)_2$ (10 mol%), Ag_2CO_3 (2.0 equiv), toluene, 100°C, 20 h; d) aq. KHF_2 (4.5 M, 5.1 equiv), CH_3CN, RT, 3 h; e) 1-chloro-4-nitrobenzene (1.0 equiv), **10** (1.2 equiv), $Pd(OAc)_2$ (10 mol%), SPhos (20 mol%), Cs_2CO_3 (3.0 equiv), cyclopentyl methyl ether (CPME)/H_2O (6.7:1), N_2, 95°C, 20 h; f) $AgNO_3$ (20 mol%), Selectfluor (3.0 equiv), TFA (4.0 equiv), DCM, H_2O, N_2, 50°C, 6 h.

product **6c** in the presence of $AgNO_3$ and Selectfluor[19] proceeded smoothly to yield two diastereomers, *trans*-**12** and *cis*-**12**, in 39% and 53% yield, respectively. The combination of C(sp^3)–H borylation with fluorination could find widespread application in drug discovery.

Our desire to improve this potentially powerful C(sp^3)–H borylation method prompted us to perform further kinetic studies on the dependence of the reaction on the concentration of the palladium catalyst and substrate **1** (see the Supporting Information). We found that the borylation reaction is first order with respect to Pd and zero order in the substrate. The observed intermolecular kinetic isotope effect (KIE) of **3b** and [D_6]-**3b** ($k_H/k_D = 3.3$) suggests that C–H cleavage is the rate-limiting step in this C(sp^3)–H borylation (see the Supporting Information). 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 the Supporting Information). Based on these mechanistic data, we propose the Pd^{II}/Pd^0 catalytic cycle shown in Figure 1.

In summary, we have developed a versatile palladium-catalyzed β-C(sp^3)–H borylation of a wide range of carboxylic acid derivatives using a quinoline-based ligand. The new method is compatible with methyl C(sp^3)–H bonds in both α-tertiary and α-quaternary carboxylic acids, as well as with methylene C(sp^3)–H bonds in a variety of cyclic carboxylic acids. The borylated products were converted into various organic synthons through carbon–carbon and carbon–heteroatom bond formation. Preliminary studies of the ligand

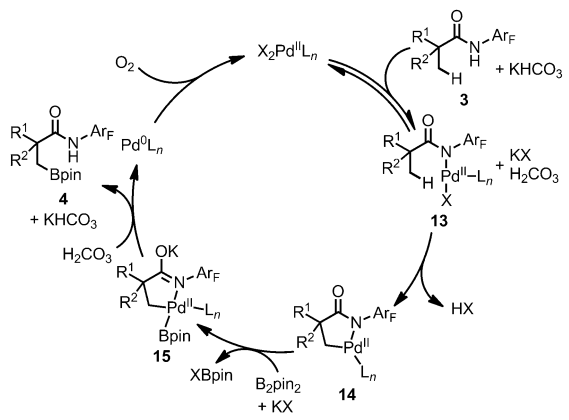


Figure 1. Plausible mechanism for C(sp^3)–H borylation.

structure–reactivity relationship indicate that electron-rich and sterically less hindered quinoline ligands are superior.

Acknowledgements

We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01GM084019) for financial support. We thank the NSF under the Science Across Virtual Institutes program as part of the CCI Center for Selective C–H Functionalization for funding a visiting student (R.T., CHE-1205646). We thank Prof. Donna G. Blackmond (The Scripps Research Institute) for insightful discussions.

Keywords: amino acids · borylation · C–H activation · palladium · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 785–789
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Received: October 26, 2015
Published online: November 27, 2015

