Communication

Pd(II)-Catalyzed Enantioselective C(sp3)–H Borylation

Jian He, Qian Shao, Qingfeng Wu, and Jin-Quan Yu

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 17 Feb 2017

Pd(II)-Catalyzed Enantioselective $C(sp^3)$–H Borylation

Jian He, Qian Shao,† Qingfeng Wu,† and Jin-Quan Yu*

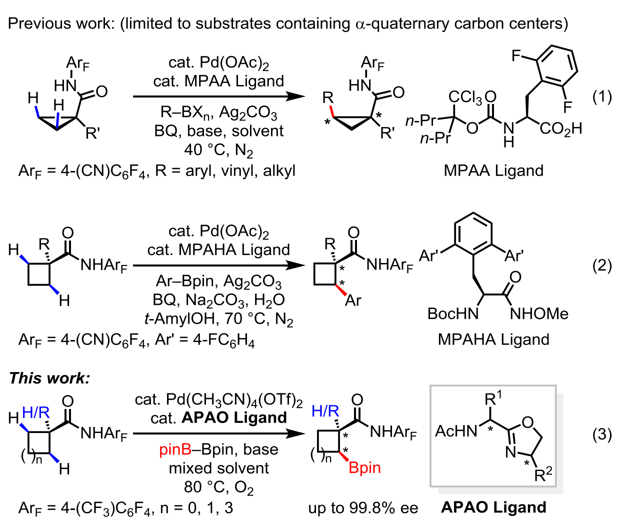
Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037

ABSTRACT: Pd(II)-catalyzed enantioselective borylation of $C(sp^3)$–H bonds has been realized for the first time using chiral acetyl-protected aminomethyl oxazoline ligands. This reaction is compatible with carbocyclic amides containing *α*-tertiary as well as *α*-quaternary carbon centers. The chiral *β*-borylated amides are useful synthons for the synthesis of chiral *β*-hydroxylated, *β*-fluorinated, and *β*-arylated carboxylic acids.

Differentiation of prochiral C–H bonds through metal insertion has recently emerged as a promising approach in asymmetric catalysis.[1,2] A number of Pd(0)-catalyzed enantioselective intramolecular $C(sp^3)$–H arylation and alkylation reactions have been realized by the use of chiral *N*-heterocyclic carbene[3] or phosphine ligands.[4,5] The feasibility of Pd(II)-catalyzed enantioselective intermolecular $C(sp^3)$–H activation was initially demonstrated using mono-*N*-protected amino acid (MPAA) ligands.[6] Major advances have been recently made by using a weakly coordinating monodentate substrate and a chiral bidentate ligand. The design of chiral bidentate acetyl-protected aminoethyl quinoline (APAQ) and mono-*N*-protected aminomethyl oxazoline (MPAO) ligands for asymmetric induction have led to the development of enantioselective intermolecular arylation of methylene $C(sp^3)$–H bonds and *gem*-dimethyl $C(sp^3)$–H bonds, respectively.[7,8]

The development of these enantioselective $C(sp^3)$–H activation reactions involving Pd(II)/Pd(IV) redox catalysis calls into question whether enantioselective $C(sp^3)$–H activation reactions with nucleophiles through Pd(II)/Pd(0) redox catalysis are compatible with the APAQ and MPAO ligands. Although both catalytic reactions proceed through the same asymmetric C–H insertion intermediates, the transmetalation and reductive elimination steps in Pd(II)/Pd(0) catalytic cycles may require

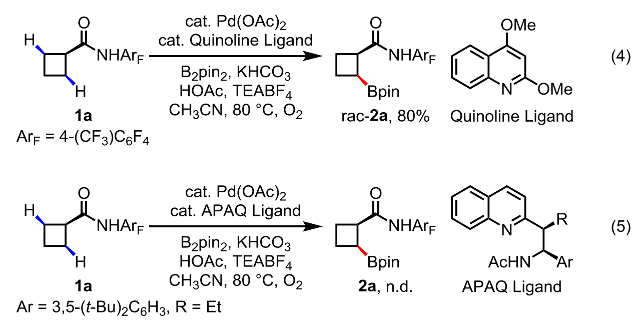
Scheme 1. Enantioselective $C(sp^3)$–H Activation via Pd(II)/Pd(0) Catalysis



different ligand scaffolds. Enantioselective $C(sp^3)$–H cross-coupling reactions via Pd(II)/Pd(0) catalysis have been developed using MPAA and mono-*N*-protected *α*-amino-*O*-methylhydroxamic acid (MPAHA) ligands, albeit with significant limitations (Scheme 1, eqs 1 and 2).[6,9] Notably, enantioselective $C(sp^3)$–H borylation has not been developed to date.[10–12] Herein, we report the first example of Pd(II)-catalyzed enantioselective *β*-borylation of carboxylic acid-derived amides with bis(pinacolato)diboron using acetyl-protected aminomethyl oxazoline (APAO) ligands (Scheme 1, eq 3). A range of cyclic amides, including cyclopropanes, cyclobutanes, and cyclohexanes, can be successfully borylated with high levels of enantioselectivity. This reaction is compatible with amide substrates containing *α*-tertiary as well as *α*-quaternary carbon centers. Notably, O_2 is used as the sole oxidant for this Pd(II)/Pd(0) catalysis.

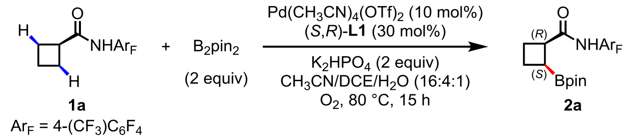
We have previously developed $C(sp^3)$–H borylation promoted by a monodentate quinoline ligand (Scheme 2, eq 4).[12f] Since the recently developed chiral APAQ ligands for enantioselective *β*-C–H arylation also contain a quinoline moiety,[7] we initiated our investigation on the borylation of **1a** using this type of ligands (Scheme 2, eq 5). Although these bidentate quinoline ligands are known to promote $C(sp^3)$–H cleavage of amide substrates, they failed to provide any desired borylated products under our previously established conditions. It appears that this ligand scaffold is not compatible with the transmetalation or the $C(sp^3)$–B reductive elimination step.

Scheme 2. Palladium-Catalyzed $C(sp^3)$–H Borylation using Quinoline-Based Ligands

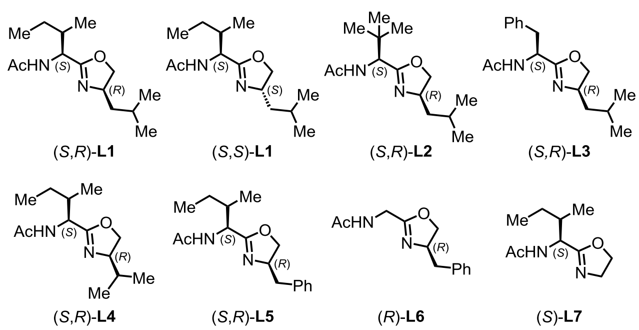


Considering the previously observed significant steric effect of ligands on $C(sp^3)$–H borylation,[12f] we replaced the quinoline motif with a variety of heterocycles. We found acetyl-protected aminomethyl oxazolines as the only effective ligands for this unprecedented enantioselective $C(sp^3)$–H borylation reaction. The enantioenriched borylated product **2a** was obtained in 82% ^1H NMR yield and 95.6% ee when reacting **1a** with bis(pinacolato)diboron in the presence of $Pd(CH_3CN)_4(OTf)_2$ (10 mol%), bidentate oxazoline ligand (*S*,*R*)-**L1** (30 mol%), and K_2HPO_4 in the mixed solvent ($CH_3CN/DCE/H_2O$) at 80 °C under O_2 atmosphere for 15 h (Table 1, entry 1). Control experiments revealed that the palladium catalyst and base were crucial for the $C(sp^3)$–H borylation to proceed (entries 2 and 3). Low reaction

Table 1. Effect of Reaction Parameters in Pd(II)-Catalyzed Enantioselective C(sp^3)–H Borylation of Cyclic Amide 1a[a,b]



entry	variation from standard conditions	ee (%)	yield (%)
1	none	95.6	82
2	no $Pd(CH_3CN)_4(OTf)_2$	–	n.d.
3	no K_2HPO_4	–	n.d.
4	no (*S*,*R*)-**L1**	0	21
5	(*S*,*R*)-**L1** (20 mol%)	93.4	85
6	(*S*,*S*)-**L1**, instead of (*S*,*R*)-**L1**	50.4	24
7	(*S*,*R*)-**L2**, instead of (*S*,*R*)-**L1**	95.0	82
8	(*S*,*R*)-**L3**, instead of (*S*,*R*)-**L1**	93.6	72
9	(*S*,*R*)-**L4**, instead of (*S*,*R*)-**L1**	92.6	71
10	(*S*,*R*)-**L5**, instead of (*S*,*R*)-**L1**	92.2	76
11	(*R*)-**L6**, instead of (*S*,*R*)-**L1**	51.0	13
12	(*S*)-**L7**, instead of (*S*,*R*)-**L1**	78.8	57
13[c]	$Pd(CH_3CN)_4(OTf)_2$ (5 mol%)	89.0	67
14	$Pd(OAc)_2$, instead of $Pd(CH_3CN)_4(OTf)_2$	78.4	63
15	$KHCO_3$, instead of K_2HPO_4	89.4	58
16	CH_3CN only	93.4	64
17	DCE only	72.4	19
18	CH_3CN/DCE (4:1)	95.6	65
19	60 °C, instead of 80 °C	95.4	38
20	under air (capped vial)	94.8	61



[a]Reaction conditions: substrate **1a**, B_2pin_2 (2.0 equiv), $Pd(CH_3CN)_4(OTf)_2$ (10 mol%), APAO ligand (30 mol%), K_2HPO_4 (2.0 equiv), $CH_3CN/DCE/H_2O$ (16:4:1), O_2, 80 °C, 15 h. [b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase. [c](*S*,*R*)-**L1** (15 mol%) was used.

conversion was observed in the absence of ligands (entry 4). Decreasing the loading of (*S*,*R*)-**L1** to 20 mol% slightly increased the yield of **2a**, but the ee dropped to 93.4% (entry 5). The use of (*S*,*S*)-**L1**, the other diastereomer of the optimal ligand, drastically decreased yield and ee to 24% and 50.4%, respectively (entry 6). Changing the substituents on both the side chain and the oxazoline moiety of (*S*,*R*)-APAO ligands did not have significant impact on reactivity and enantioselectivity (entries 7–10). However, the chiral oxazoline ligands lacking a stereocenter on either the side chain or the oxazoline moiety gave poor enantioselectivity (entries 11 and 12), which speaks to the importance of both chiral centers on the APAO ligand backbones for asymmetric induction. The observed significant impact of both chiral centers on the enantioselectivity can be explained by the potential structures of the C–H insertion intermediates shown in Figure 1. When (*S*,*R*)-oxazoline ligands are employed in C(sp^3)–H borylation, the substituents on both chiral centers of the ligand backbone exert a synergistic effect in asymmetric induction through the steric repulsion with the cyclobutane ring, favoring five-membered palladacycle **Intermediate A** over **Intermediate B**. Reducing the amount of $Pd(CH_3CN)_4(OTf)_2$ to 5 mol% gave **2a** in 67% yield and 89.0% ee (entry 13). The fine tuning of palladium sources, bases, and solvents was also essential for achieving high levels of enantioselectivity in this C(sp^3)–H borylation (entries 14–18). A similar ee value was obtained when conducting the reaction at 60 °C, but the yield was significantly lower (entry 19). The reaction could also be carried out in air, affording the desired product in 61% yield and 94.8% ee (entry 20).

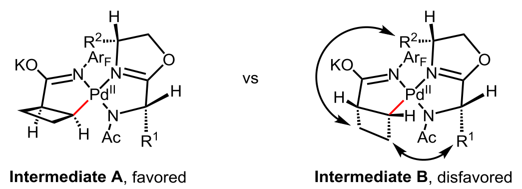
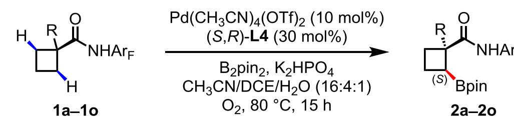
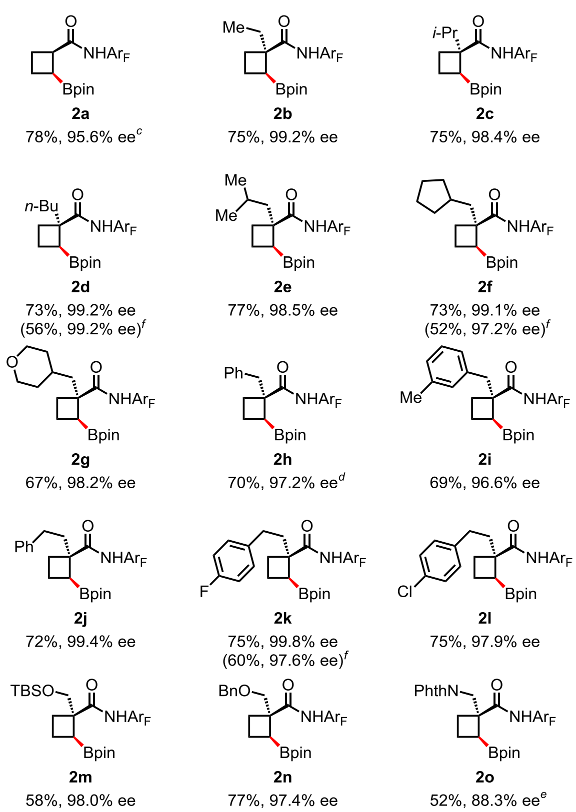


Figure 1. The proposed asymmetric induction model in enantioselective C(sp^3)–H borylation of cyclobutanes.

With the optimal reaction conditions in hand, we then evaluated the scope of cyclobutanecarboxylic acid-derived amides towards

Table 2. Substrate Scope for Enantioselective C(sp^3)–H Borylation of Cyclobutanecarboxylic Amides[a,b]



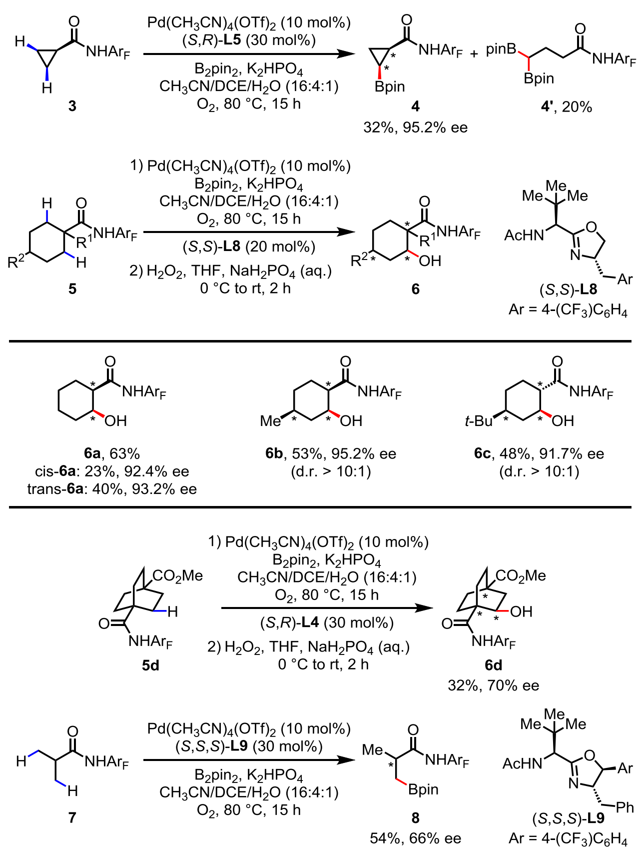


[a]Reaction conditions: substrate **1a–1o**, B_2pin_2 (2.0 equiv), $Pd(CH_3CN)_4(OTf)_2$ (10 mol%), (*S*,*R*)-**L4** (30 mol%), K_2HPO_4 (2.0 equiv), $CH_3CN/DCE/H_2O$ (16:4:1), O_2, 80 °C, 15 h. [b]Isolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase. [c](*S*,*R*)-**L1** (30 mol%) was used. [d](*S*,*R*)-**L5** (30 mol%) was used. [e]CH_3CN/DCE (4:1) was used as the mixed solvent. [f]$Pd(CH_3CN)_4(OTf)_2$ (5 mol%) and (*S*,*R*)-**L4** (15 mol%) were used.

enantioselective $C(sp^3)$–H borylation (Table 2). While (*S*,*R*)-**L1** was superior in the borylation of amide substrate **1a** bearing an *α*-hydrogen atom, (*S*,*R*)-**L4** containing an isopropyl group on the oxazoline moiety gave better enantioselectivity for substrates containing *α*-quaternary carbon centers in general. Simple *α*-alkyl substituted amides could be borylated in good yields with excellent levels of enantioselectivity, ranging from 98.4% to 99.2% ee (**2b**–**2f**). A variety of aromatic rings at the *β*- or *γ*-positions of the exocyclic alkyl side chain were well tolerated (**2h**–**2i**). $C(sp^2)$–H borylation was not detected in the functionalization of these substrates. (*S*,*R*)-**L5** gave the highest enantioselectivity in the borylation of amide **1h** containing a simple benzyl group at the *α*-position. Substrates with potentially coordinating heteroatoms such as oxygen (**1g**, **1m**, and **1n**) and nitrogen (**1o**) on the *α*-substituents were also compatible with this enantioselective $C(sp^3)$–H borylation. Even though water had to be excluded from the solvent mixture to prevent hydrolysis of the phthalimido group, $C(sp^3)$–H borylation of *β*-amino acid substrate **1o** still provided the desired product **2o** in a moderate yield. The absolute configuration of the borylated compounds was confirmed by X-ray crystallographic analysis after an oxidation sequence (see Supporting Information). To probe the efficiency of this catalytic system, we also carried out the enantioselective $C(sp^3)$–H borylation in the presence of 5 mol% of $Pd(CH_3CN)_4(OTf)_2$ and 15 mol% of (*S*,*R*)-**L4**, which provided the desired products (**2d**, **2f**, and **2k**) in 52–60% yield and 97.2–99.2% ee.

Under similar reaction conditions using (*S*,*R*)-**L5** as the optimal ligand, cyclopropanecarboxylic amide **3** was borylated in 32% yield and 95.2% ee, while an unexpected diborylated product **4** was also obtained in 20% isolated yield. $Pd(CH_3CN)_4(OTf)_2$ was found to promote the side product formation, but the detailed reaction mechanism remains to be exploited. In the borylation of cyclohexane and *gem*-dimethyl substrates (**5a**–**5c** and **7**), (*S*,*S*)-APAO ligands were substantially more effective than their (*S*,*R*)-

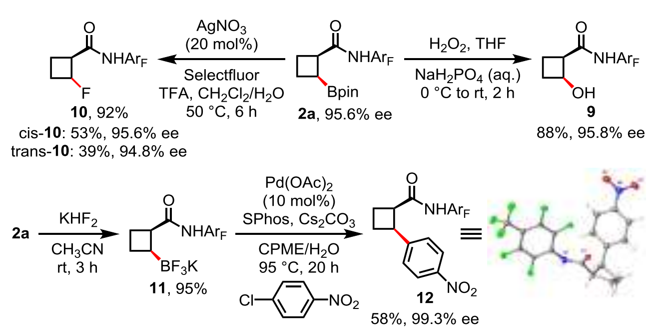
Scheme 3. Enantioselective $C(sp^3)$–H Borylation of Other Cyclic and Acyclic Amides



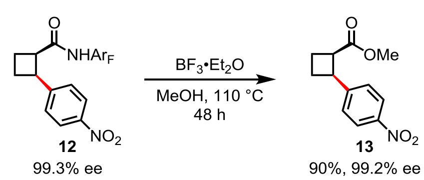
diastereomers, which is consistent with the ligand effect in the enantioselective $C(sp^3)$–H arylation of amide **7** with aryl iodides.[8] The use of (*S*,*S*)-**L8** (20 mol%) to activate cyclohexanecarboxylic amide **5a** gave the chiral borylated product as a cis- and trans-mixture which was then oxidized to provide *cis*-**6a** and *trans*-**6a** in 92.4% and 93.2% ee, respectively. The borylation/oxidation ofboth cis- and trans-4-substituted cyclohexane substrates furnished the desired products (**6b** and **6c**) with high levels of diastereoselectivity (d.r. > 10:1) and enantioselectivity (95.2% and 91.7% ee, respectively). The reaction conditions was also applied to the asymmetric $C(sp^3)$–H functionalization of the bicyclo[2.2.2]octane (**5d**), giving the enantioenriched hydroxylated product (**6d**) in 70% ee. With the aid of (*S*,*S*,*S*)-**L9**, desymmetrization of the isopropyl group in isobutyric acid derivative **7** afforded **8** in moderate yield (54%) and enantioselectivity (66% ee).

To further demonstrate the synthetic utility of this enantioselective $C(sp^3)$–H borylation reaction,[13] we subjected the chiral cyclobutylboronate ester **2a** to various reaction conditions, constructing a range of *β*-chiral centers containing carbon–heteroatom or carbon–carbon bonds (Scheme 4). After reacting **2a** with hydrogen peroxide in THF and NaH_2PO_4 aqueous solution, the desired *β*-hydroxylated product **9** could be obtained in 88% yield and 95.8% ee. The combination of $AgNO_3$ and Selectfluor in CH_2Cl_2/H_2O (1:1) converted **2a** into chiral *β*-fluorinated cyclobutanecarboxylic acid derivatives (cis-**10** and trans-**10**) in a total yield of 92% through a radical pathway.[14] High ee values were maintained in both diastereomers. Treatment of the borylated product **2a** with KHF_2 in acetonitrile led to the formation of trifluoroborate salt **11** in 95% yield after recrystallization. The Suzuki-Miyaura cross-coupling between 1-chloro-4-nitrobenzene and **11** provided the *β*-arylated product **12** in 99.3% ee with retention of stereochemistry.[15] The absolute configuration of **12** was also confirmed by X-ray crystallographic analysis. Removal of the amide auxiliary by $BF_3 \cdot Et_2O$ in methanol gave the corresponding ester **13** in 90% yield without loss of enantiomeric purity (Scheme 5).[16]

Scheme 4. Synthetic Applications of Enantioselective $C(sp^3)$–H Borylation



Scheme 5. Removal of the Amide Auxiliary



In summary, we have developed enantioselective $C(sp^3)$–H borylation of weakly coordinating carboxylic amides via a Pd(II)/Pd(0) catalytic cycle. Pivotal to the success of this asymmetric catalysis was the use of chiral bidentate APAO ligands. This reaction is compatible with carbocyclic substrates containing *α*-tertiary as well as *α*-quaternary carbon centers. The borylated products can be converted into various chiral *β*-hydroxylated, *β*-

fluorinated, and β-arylated carboxylic acids. Development of more effective chiral bidentate ligands to enable highly enantioselective borylation of *gem*-dimethyl C(sp^3)–H bonds is currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

AURHOR INFORMATION

Corresponding Author

*yu200@scripps.edu

Author Contributions

[†]Q.S. and Q.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01GM084019) for financial support.

REFERENCES

(1) (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (e) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (f) Pedroni, J.; Cramer, N. *Chem. Commun.* **2015**, *51*, 17647. (g) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635. (h) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *ASAP*, DOI: 10.1021/acs.chemrev.6b00622.

(2) (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (b) Gao, D.-W.; Shi, Y.-C.; Gu, Q.; Zhao, Z.-L.; You, S.-L. *J. Am. Chem. Soc.* **2013**, *135*, 86. (c) Yan, S.-B.; Zhang, S.; Duan, W.-L. *Org. Lett.* **2015**, *17*, 2458. (d) Wang, H.; Tong, H.-R.; He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2016**, *55*, 15387.

(3) (a) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (b) Katayev, D.; Nakanishi, M.; Buergi, T.; Kündig, E. P. *Chem. Sci.* **2012**, *3*, 1422. (c) Larionov, E.; Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Chem. Sci.* **2013**, *4*, 1995. (d) Katayev, D.; Larionov, E.; Nakanishi, M.; Besnard, C.; Kündig, E. P. *Chem. - Eur. J.* **2014**, *20*, 15021.

(4) (a) Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, *47*, 11483. (b) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2238. (c) Martin, N.; Pierre, C.; Davi, M.; Jazzar, R.; Baudoin, O. *Chem. - Eur. J.* **2012**, *18*, 4480.

(5) (a) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842. (b) Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 9064. (c) Pedroni, J.; Saget, T.; Donets, P. A.; Cramer, N. *Chem. Sci.* **2015**, *6*, 5164. (d) Pedroni, J. Cramer, N. *Angew. Chem., Int. Ed.* **2015**, *54*, 11826.

(6) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598.

(7) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. *Science* **2016**, *353*, 1023.

(8) Wu, Q.-F.; Shen, P.-X.; He, J.; Wang, X.-B.; Zhang, F.; Shao, Q.; Zhu, R.-Y.; Mapelli, C.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *Science* **2017**, *355*, 499.

(9) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138.

(10) (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (b) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E. Jr.; Smith, M. R. III. *Science* **2002**, *295*, 305.

(11) For representative examples of transition-metal-catalyzed non-directed C(sp^3)–H borylation, see: (a) Chen, H.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391. (b) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (c) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168. (d) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 13684. (e) Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 12422. (f) Palmer, W. N.; Obligacion, J. V.; Pappas, I.; Chirik, P. J. *J. Am. Chem. Soc.* **2016**, *138*, 766.

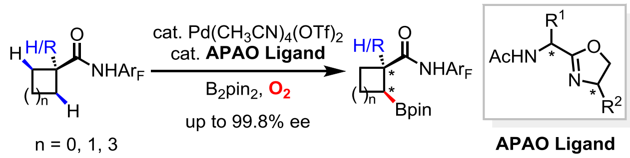
(12) For representative examples of transition-metal-catalyzed directed C(sp^3)–H borylation, see: (a) Kawamorita, S.; Miyazaki, T.; Iwai, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 12924. (b) Kawamorita, S.; Murakami, R.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2013**, *135*, 2947. (c) Cho, S. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 8157. (d) Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3899. (e) Miyamura, S.; Araki, M.; Suzuki, T.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 846. (f) He, J.; Jiang, H.; Takise, R.; Zhu, R.-Y.; Chen, G.; Dai, H.-X.; Dhar, T. G. M.; Shi, J.; Zhang, H.; Cheng, P. T. W.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 785. (g) Larsen, M. A.; Cho, S. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 762.

(13) (a) Hall, D. G., Ed. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, Germany, 2005. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (e) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (f) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602. (g) Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2014**, *505*, 386. (h) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433. (i) Fang, L.; Yan, L.; Haeffner, F.; Morken, J. P. *J. Am. Chem. Soc.* **2016**, *138*, 2508.

(14) (a) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. *J. Am. Chem. Soc.* **2014**, *136*, 16439. (b) Ramírez, J.; Fernández, E. *Tetrahedron Lett.* **2007**, *48*, 3841.

(15) (a) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (b) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-Y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108. (c) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894. (d) Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738. (e) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 14027.

(16) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216.



First example of enantioselective C–H borylation
Pd(II)/Pd(0) catalysis using O_2 as the sole oxidant