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Pd(II)-Catalyzed Enantioselective C−H Activation of Cyclopropanes

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Supporting Information

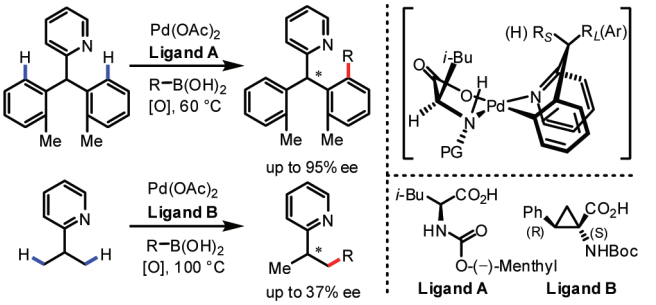
ABSTRACT: Systematic ligand development has led to the identification of novel mono-*N*-protected amino acid ligands for Pd(II)-catalyzed enantioselective C−H activation of cyclopropanes. A diverse range of organoboron reagents can be used as coupling partners, and the reaction proceeds under mild conditions. These results provide a new retrosynthetic disconnection for the construction of enantioenriched *cis*-substituted cyclopropanecarboxylic acids.

Recently, Pd-catalyzed asymmetric C−H activation reactions using a chiral auxiliary[1] or chiral ligand have been demonstrated.[2−6] Spectroscopic and crystallographic investigations have provided valuable insights into the process by which [Pd(II)−mono-*N*-protected amino acid] catalysts asymmetrically cleave prochiral C−H bonds.[2] Nevertheless, achieving high levels of enantioselectivity in these reactions remains a significant challenge, largely because of the paucity of suitable ligand scaffolds capable of effecting stereoinduction during C−H cleavage. In our previous work, high enantioselectivity was obtained in the desymmetrization of prochiral aryl C−H bonds (up to 95% ee; Scheme 1), and promising initial results were also found in asymmetric alkyl C−H activation (up to 37% ee) by using [Pd(II)−mono-*N*-protected amino acid] catalysts.[2a]

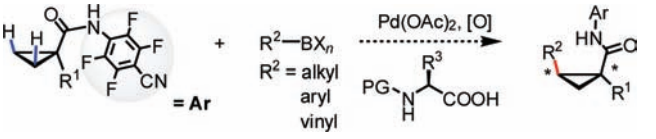
Encouraged by these precedents, we sought to develop enantioselective C−H activation reactions of cyclopropanes.[7] Because of the prominence of enantiopure cyclopropanes in natural products and pharmaceuticals, a diverse collection of transition metal-mediated transformations have been developed for their synthesis.[8] Herein we report a complementary method that constitutes the first example of enantioselective cyclopropyl C−H activation/organoboron cross-coupling (Scheme 2).[9,10] A diverse collection of aryl-, alkyl-, and vinylboron coupling partners are compatible with these reaction conditions. Systematic ligand tuning has led to the development of a protocol that gives high levels of stereoinduction under mild conditions. This reaction provides a versatile route for the synthesis of *cis*-substituted chiral cyclopropanecarboxylates.

On the basis of our recent success in utilizing acidic *N*-arylamides as weakly coordinating directing groups for a diverse range of alkyl and aryl C−H functionalization reactions,[11,12] we first sought to establish a robust reaction to cross-couple **1**, the amide derivative of 1-methylcyclopropanecarboxylic acid, with phenylboronic acid pinacol ester (Ph−BPin) in the absence of a chiral ligand. Extensive screening revealed that a 2:1 mixture of mono- and diarylated products (**1a**) could be obtained in 91% yield at 100 °C. Gratifyingly, aryl-, alkyl-, and vinylboron reagents were all suitable coupling partners (Table 1). Importantly, this is the first example of Pd(II)-catalyzed cross-coupling of alkyl

Scheme 1. Desymmetrization of Prochiral C−H Bonds



Scheme 2. Asymmetric Cyclopropane C−H Activation



C−H bonds with vinylboron reagents (**1c** and **1d**). The use of boronic acid pinacol esters (BPin) and $NaHCO_3$ were crucial for arylation and vinylation, while potassium trifluoroborate salts (BF_3K) and Li_2CO_3 were optimal for alkylation. The presence of 40 mol % dimethyl sulfoxide (DMSO) was found to promote arylation and vinylation (**1a**−**d**),[13] while the addition of *N*,*N*-dimethylformamide (DMF) as a cosolvent was beneficial for alkylation (**1e**−**h**). *Importantly, even when the temperature was lowered to 40 °C, substrate* ***1*** *could still be arylated without a major decline in yield (78%, mono:di =2.7:1).*

With the mild cross-coupling protocol at 40 °C in hand, we proceeded to examine systematically mono-*N*-protected amino acid ligands in an effort to develop an enantioselective protocol (Table 2). We initially focused on screening mono-*N*-protected L-leucine and found that carbamate groups gave superior ee and mono selectivity compared with amide groups. The mono selectivity also improved proportionally with the ee [for complete ligand screening data, see the Supporting Information (SI)]. On the basis of this observation, we further optimized the conditions using Fmoc-Leu-OH as the ligand and discovered that loadings of 5 mol % catalyst and 10 mol % ligand at 40 °C gave the highest ee (50%). The ee dropped to 12% when the temperature was raised to 70 °C. Increasing the catalyst loading to 10 mol % gave an improved yield (60%) but decreased the ee (40%); importantly, adding the catalyst and ligand in two batches gave high

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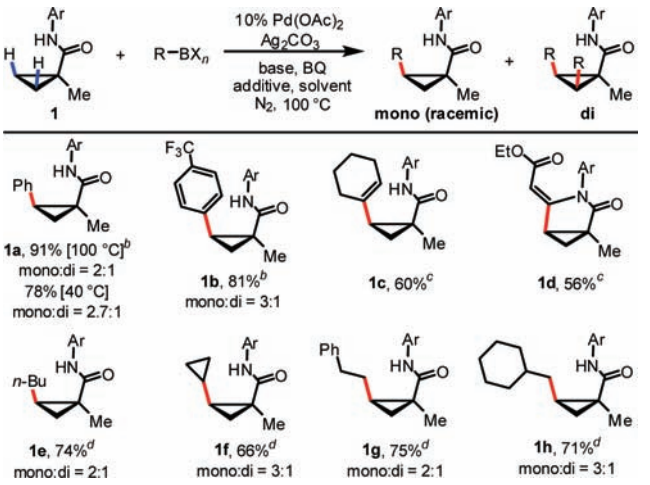
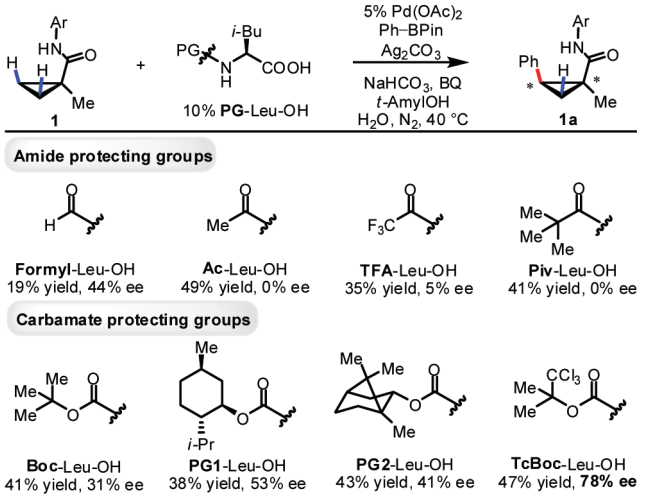
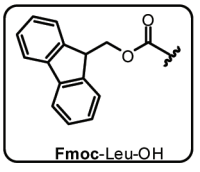
Table 1. Racemic Cross-Coupling of Cyclopropyl C−H Bonds with Organoboron Reagents[a]



[a] The mono:di ratio was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard. [b] Conditions: 0.1 mmol of substrate, 10 mol % $Pd(OAc)_2$, 2.0 equiv of Ar−BPin, 1.5 equiv of Ag_2CO_3, 3.0 equiv of $NaHCO_3$, 0.5 equiv of BQ, 5 equiv of H_2O, 40 mol % DMSO, 0.5 mL of *t*-Amyl-OH, 100 °C, N_2, 12 h. [c] Conditions: 0.1 mmol of substrate, 10 mol % $Pd(OAc)_2$, 1.2 equiv of vinyl−BPin, 1.5 equiv of Ag_2CO_3, 3.0 equiv of $NaHCO_3$, 0.5 equiv of BQ, 40 mol % DMSO, 0.5 mL of THF, 100 °C, N_2, 6 h. [d] Conditions: 0.1 mmol of substrate, 10 mol % $Pd(OAc)_2$, 2.0 equiv of alkyl−BF_3K, 1.5 equiv of Ag_2CO_3, 3.0 equiv of Li_2CO_3, 0.5 equiv of BQ, 0.1 mL of DMF, 0.5 mL of THF, 100 °C, N_2, 12 h.

Table 2. Screening of Ligand Protecting Groups[a,b]

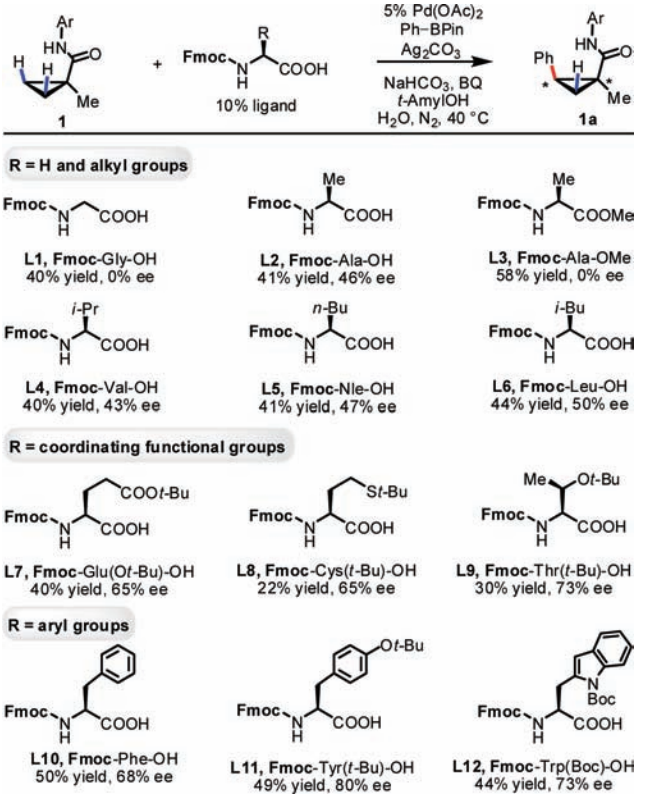




Pd loading	Temperature (°C)	yield (%)	ee (%)
10 mol%	100	72	4
10 mol%	40	60	40
5 mol%	40	44	**50**
5 mol% x 2	40	**74**	**48**
5 mol%	70	58	12

[a] Conditions (unless otherwise specified): 0.1 mmol of substrate, 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 1.0 equiv of Ph−BPin, 1.0 equiv of Ag_2CO_3, 3.0 equiv of $NaHCO_3$, 0.5 equiv of BQ, 5 equiv of H_2O, 0.5 mL of *t*-Amyl-OH, 40 °C, N_2, 12 h. [b] The yields were determined by ^{1}H NMR analysis of the crude products using CH_2Br_2 as an internal standard. Stereochemical assignment is tentative.

Table 3. Screening of Amino Acid Side Chains[a,b]



[a] The conditions are identical to those given in Table 2. [b] The yields were determined by ^{1}H NMR analysis of the crude products using CH_2Br_2 as an internal standard. Stereochemical assignments are tentative.

yield (74%) while maintaining the ee (48%). The addition of DMSO improved the yield but led to erosion of the ee, presumably because DMSO is capable of competing with the ligand for coordination to Pd. The presence of H_2O enhanced the yield (likely by promoting transmetalation)[7] without reducing the ee. Of the various carbamate protecting groups that were tested, 2,2,2-trichloro-*tert*-butyloxycarbonyl (TcBoc) afforded the best ee (78%) and yield (47%).

We subsequently investigated the effect of the amino acid backbone. Although TcBoc-Leu-OH gave the highest ee, we instead focused on Fmoc-protected amino acids because of their commercial availability (Table 3). As expected, achiral Fmoc-Gly-OH (**L1**) gave a racemic mixture of products. The carboxylic acid moiety was found to be essential for stereoinduction, as Fmoc-alanine methyl ester (**L3**) gave no ee. Fmoc-protected amino acids containing hydrophobic alkyl chains (**L2** and **L4**−**L6**) gave ee values between 43 and 50%. Intriguingly, coordinating functional groups on the side chain, such as an ester (**L7**), thioether (**L8**), or ether (**L9**), gave improved ee of 65−73%; however, the conversion dropped to <40% in each case. We then screened amino acids with aryl side chains (**L10** and **L11**). To our delight, Fmoc-Phe-OH and its derivatives gave improved ee values of 68% and above, with Fmoc-Tyr(*t*-Bu)-OH (**L11**) giving 80% ee and 49% product yield. Fmoc-Trp(Boc)-OH (**L12**) also gave 73% ee. These combined findings signaled to us that having an aryl group on the amino acid side chain is crucial for obtaining high ee.

Having established that both the TcBoc protecting group and phenylalanine backbone are beneficial for enantioselectivity, we

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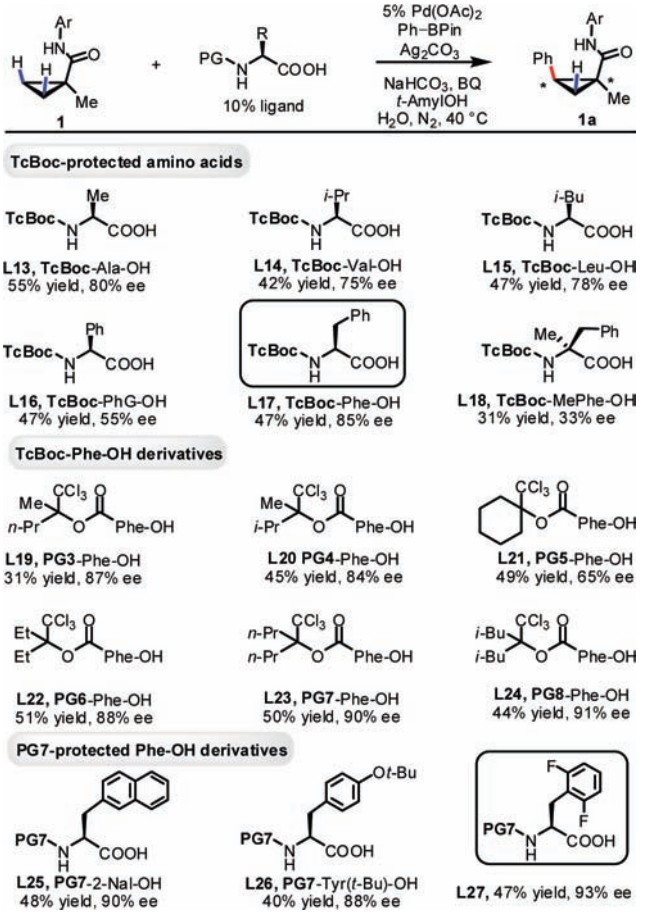
Table 4. Systematic Tuning of the Amino Acid Ligand[a,b]

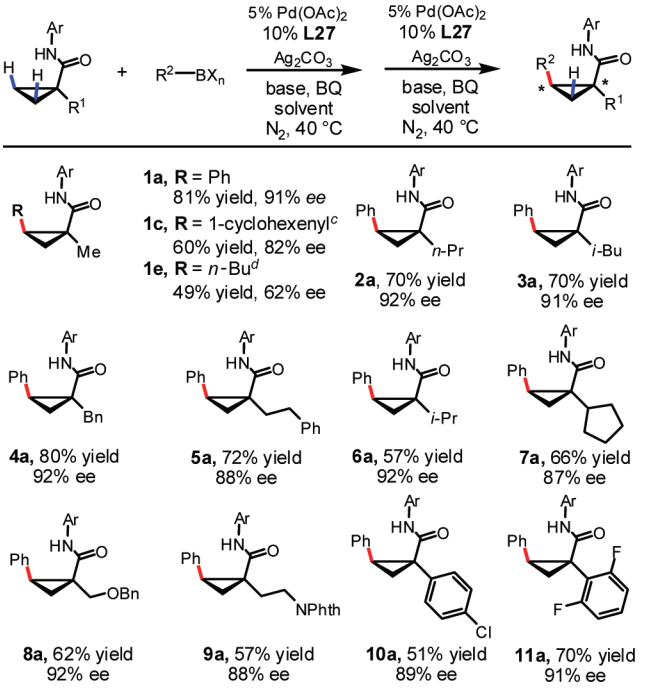


[a] The conditions are identical to those given in Table 2. [b] The yields were determined by ^{1}H NMR analysis of the crude products using CH_2Br_2 as an internal standard. Stereochemical assignment is tentative.

synthesized a series of TcBoc-protected amino acids (**L13**–**L18**). We confirmed that TcBoc-Phe-OH (**L17**) gave better ee (85%) than those with alkyl side chains (**L13**–**L15**) (Table 4). TcBoc-PhG-OH (**L16**) and TcBoc-MePhe-OH (**L18**), both of which possess an aryl group, however, gave significantly lower ee. Further optimization of the protecting group on phenylalanine was carried out. While retaining the CCl_3 moiety present in TcBoc, we varied the two alkyl groups and found that **L23** and **L24** improved the ee to 90 and 91%, respectively. Subsequently, the newly designed protecting group (**PG7**) in **L23** was installed on commercially available phenylalanine derivatives (**L25**–**L27**). Substitution on the phenyl ring was found to have a modest effect on the enantioselectivity, with **L27** improving the ee to 93%. To investigate in more detail whether the CCl_3 moiety of the TcBoc group has a dominant effect on the enantioselectivity, we extensively screened a variety of sterically hindered protecting groups with phenylalanine (see the SI); however, only 48–62% ee was obtained. The CCl_3 moiety presumably serves not only as a sterically bulky group but also tunes the electronic properties of the nitrogen atom through its electron-withdrawing character.

With the optimized reaction conditions in hand, we performed enantioselective C–H/organoboron cross-coupling of cyclopropane **1** with Ph–BPin, 1-cyclohexenyl–BPin and *n*-butyl–BF_3K (Table 5). The reagents (excluding the substrate) were added in

Table 5. Asymmetric Cyclopropane C–H Functionalization[a,b]



[a] Conditions: (first batch) 0.1 mmol of substrate, 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 1.0 equiv of Ph–BPin, 0.75 equiv of Ag_2CO_3, 2.0 equiv of $NaHCO_3$, 0.25 equiv of BQ, 3 equiv of H_2O, 0.5 mL of *t*-Amyl-OH, 40 °C, N_2, 6 h; (second batch) 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 0.5 equiv of Ph–BPin, 0.75 equiv of Ag_2CO_3, 1.0 equiv of $NaHCO_3$, 0.25 equiv of BQ, 1 equiv of H_2O, 0.2 mL of *t*-Amyl-OH, 40 °C, N_2, 6 h. [b] Isolated yields are given. Stereochemical assignments are tentative. [c] Conditions: (first batch) 0.1 mmol of substrate, 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 0.5 equiv of vinyl–BPin, 0.75 equiv of Ag_2CO_3, 2.0 equiv of $NaHCO_3$, 0.25 equiv of BQ, 0.5 mL of THF, 50 °C, N_2, 6 h; (second batch) 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 0.5 equiv of vinyl–BPin, 0.75 equiv of Ag_2CO_3, 1.0 equiv of $NaHCO_3$, 0.25 equiv of BQ, 0.2 mL of THF, 50 °C, N_2, 6 h. [d] Conditions: (first batch) 0.1 mmol of substrate, 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 1.0 equiv of *n*-Bu–BF_3K, 0.75 equiv of Ag_2CO_3, 1.5 equiv of Li_2CO_3, 0.25 equiv of BQ, 3 equiv of H_2O, 0.5 mL of THF, 70 °C, N_2, 6 h; (second batch) 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 0.5 equiv of *n*-Bu–BF_3K, 0.75 equiv of Ag_2CO_3, 0.75 equiv of Li_2CO_3, 0.25 equiv of BQ, 0.2 mL of THF, 70 °C, N_2, 6 h.

two batches, using 5 mol % catalyst and 10 mol % ligand (**L27**) in each batch to give the optimal yield and ee. The addition of the reactants in a single batch resulted in inferior and inconsistent results. The apparent dependence of the ee's on the catalyst concentration remains to be investigated. Phenylated product **1a** was obtained in 81% yield and 91% ee. The cross-coupling of 1-cyclohexenyl- and *n*-butylboron reagents required elevated temperatures of 50 and 70 °C to obtain appreciable product formation, which decreased the ee values to 82 and 62%, respectively. Primary alkyl, isopropyl, and cyclopentyl groups at the α-position of the cyclopropane were tolerated, giving good ee values (**2a**–**7a**). β-Benzyl ethers (**8a**) and γ-phthalimide-protected amines (**9a**) were compatible, as was α-substitution with an aryl group (**10a** and **11a**). Substitution of the aryl ring with electron-withdrawing halide groups suppressed competitive *ortho*-C(aryl)–H functionalization. The chiral cyclopropane products could also undergo further C–H coupling reactions to give

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cis-1,2,3-substituted cyclopropanes under the same conditions in the absence of ligands, albeit in low yields (20−38%). Unfortunately, substrates containing an α-hydrogen atom or α-heteroatoms gave poor yields and ee's at 40 °C. Detailed mechanistic studies through spectroscopic and crystallographic analyses as well as further optimization of the ligand and the reaction conditions are underway to solve these problems.[14]

In summary, the first example of enantioselective C−H activation of cyclopropanes has been achieved through systematic tuning of the mono-*N*-protected amino acid ligand and reaction conditions. Enantioselective C−H/R−BX_n cross-coupling with aryl-, vinyl-, and alkylboron reagents provides a new disconnection for the synthesis of *cis*-substituted chiral cyclopropanecarboxylic acids. Studies to expand the substrate scope and extend this methodology to other prochiral methyl and methylene C−H bonds are ongoing in our laboratory.

■ ASSOCIATED CONTENT

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

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■ REFERENCES

(1) (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (b) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (c) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(2) (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (b) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460.

(3) For recent examples of asymmetric Pd(0)-catalyzed intramolecular C−H functionalization reactions using chiral phosphine or carbene ligands, see: (a) Albicker, M. R.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 9139. (b) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7261. (c) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (d) Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, *47*, 11483.

(4) For an example of Ru-catalyzed atropselective alkylation, see: Kakiuchi, F.; Le Gendre, P.; Yamada, A.; Ohtaki, H.; Murai, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2647.

(5) For examples of C−H activation followed by enantioselective addition to olefins, see: (a) Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett.* **1999**, *28*, 55. (b) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192.

(6) For enantioselective carbenoid and nitrenoid insertion reactions, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 9253. (c) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220. (d) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825.

(7) For stoichiometric metalation of cyclopropyl C−H bonds, see: (a) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 7272. (b) Ruhland, K.; Herdtweck, E. *Adv. Synth. Catal.* **2005**, *347*, 398. (c) Eaton, P. E.; Daniels, R. G.; Casucci, D.; Cunkle, G. T.; Engel, P. *J. Org. Chem.* **1987**, *52*, 2100.

(8) For reviews of asymmetric cyclopropanation, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. (d) Denmark, S. E.; Beutner, G. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 85 ff.

(9) For reviews of *B*-alkyl Suzuki−Miyaura cross-coupling, see: (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (b) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013. (c) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240.

(10) For pioneering examples of asymmetric alkyl−alkyl Suzuki−Miyaura cross-coupling reactions, see: (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694. (b) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027. (c) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908.

(11) (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (b) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275. (c) Wasa, M.; Yu, J.-Q. *Tetrahedron* **2010**, *66*, 4811. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (e) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (f) Wasa, M.; Chan, K. S. L; Yu, J.-Q. *Chem. Lett.* **2011**, *40*, 1004.

(12) For recent reviews of Pd-catalyzed alkyl C−H activation, see: (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605.

(13) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348.

(14) The reaction can be scaled up to 0.3 mmol of substrate without a major decline in ee or yield (**1a**, 71% yield, 86% ee), provided that vigorous stirring is maintained throughout the course of the reaction. For details on scalability, see the SI.