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

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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 could be used as coupling partners, and the reaction was found to proceed 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 have been demonstrated through the use of a chiral auxiliary[1] or chiral ligand.[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 due to the paucity of suitable ligand scaffolds capable of effecting stereoinduction during C–H cleavage. In our previous work, high *ee* was obtained in the desymmetrization of prochiral aryl C–H bonds (up to 95%, 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] Owing to the prominence of enantiopure cyclopropanes in natural products and pharmaceuticals, a diverse collection of transition metal–mediated transformation have been developed for their synthesis.[8] Herein, we report a complementary method, which constitutes the first example of the enantioselective cyclopropyl C–H activation/organoboron cross-coupling (Scheme 2).[9,10] A diverse collection of aryl-, alkyl-, and vinylboron coupling partners were 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 cyclopropane carboxylates.

Based on 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 the amide derivative of 1-methylcyclopropanecarboxylic acid (**1**) 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 di-arylated 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,

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this is the first example of Pd(II)-catalyzed cross-coupling of alkyl C–H bonds with vinyl boron 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$_3$K) and Li$_2$CO$_3$ were optimal for alkylation. The presence of 40 mol% of DMSO was found to promote arylation and vinylation (**1a**–**1d**),[13] while the addition of 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 monoselectivity, compared with amide groups. The monoselectivity was also improved proportionally with the *ee* (for complete ligand screening data, see SI). Based on this observation, we further optimized conditions using Fmoc-Leu-OH as the ligand and discovered that 5 mol% catalyst and 10 mol% ligand loadings at 40 °C gave the highest *ee* (50%). The *ee* dropped to 12% when temperature was raised to 70 °C. Increasing the catalyst loading to 10 mol% gave improved yield (60%) but decreased the *ee* (40%); importantly, adding the catalyst and ligand in two batches gave high 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$_2$O enhanced the yield (likely by promoting transmetallation)[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 due to 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**, **L4**–**L6**) gave *ee* values between 43 and 50%. Intriguingly, coordinating functional groups on the side chain such as an ester (**L7**), thioether (**L8**), and ether (**L9**) gave improved *ee*, between 65 and 73%; however, the conversion dropped to below 40% in each case. We then screened amino acids with aryl side chains (**L10**, **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 an aryl group on the amino acid side chain was crucial for obtaining high *ee*.

Having established that both the TcBoc protecting group and phenylalanine backbone were beneficial for enantioselectivity, we 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 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$_3$K (Table 5). The reactants (excluding the substrate) were added in 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 ees on the concentration of catalysts remains to be investigated. Phenylated product **1a** was obtained in 81% yield and 91% *ee*. The cross-coupling of 1-cyclohexenyl- and *n*-butyl-boron 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, *iso*-propyl, 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**, **11a**). Substitution of the aryl ring with electron-withdrawing halide groups suppressed competitive *ortho*-C(aryl)–H functionalization. The chiral cycloproprane products could also undergo further C–H coupling reactions to give *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* 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 was 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 to extend this methodology to other prochiral methyl and methylene C–H bonds are ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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 Supporting Information.
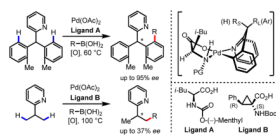
Scheme 1.
Desymmetrization of Prochiral C–H Bonds
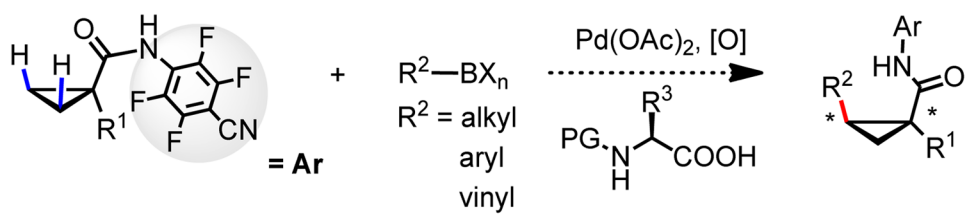
Scheme 2.
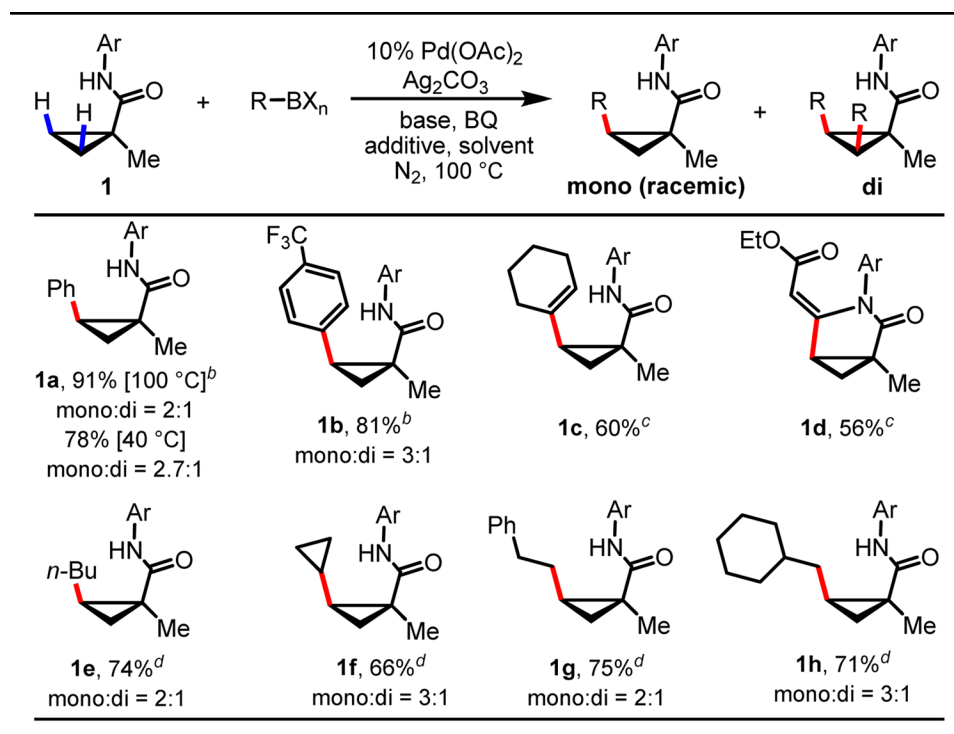Asymmetric Cyclopropane C–H Activation

Table 1

Racemic Cross-Coupling of Cyclopropyl C–H Bonds with Organoboron Reagents[a]

1a, 91% [100 °C][b]
mono:di = 2:1
78% [40 °C]
mono:di = 2.7:1

1b, 81%[b]
mono:di = 3:1

1c, 60%[c]

1d, 56%[c]

1e, 74%[d]
mono:di = 2:1

1f, 66%[d]
mono:di = 3:1

1g, 75%[d]
mono:di = 2:1

1h, 71%[d]
mono:di = 3:1

[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$_2$CO$_3$, 3.0 equiv of NaHCO$_3$, 0.5 equiv of BQ, 5 equiv of H$_2$O, 40 mol% DMSO, 0.5 mL of t-AmylOH, 100 °C, N$_2$, 12 h.

[c]0.1 mmol of substrate, 10 mol% Pd(OAc)$_2$, 1.2 equiv of vinyl–BPin, 1.5 equiv of Ag$_2$CO$_3$, 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]0.1 mmol of substrate, 10 mol% Pd(OAc)$_2$, 2.0 equiv of alkyl–BF$_3$K, 1.5 equiv of Ag$_2$CO$_3$, 3.0 equiv of Li$_2$CO$_3$, 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]
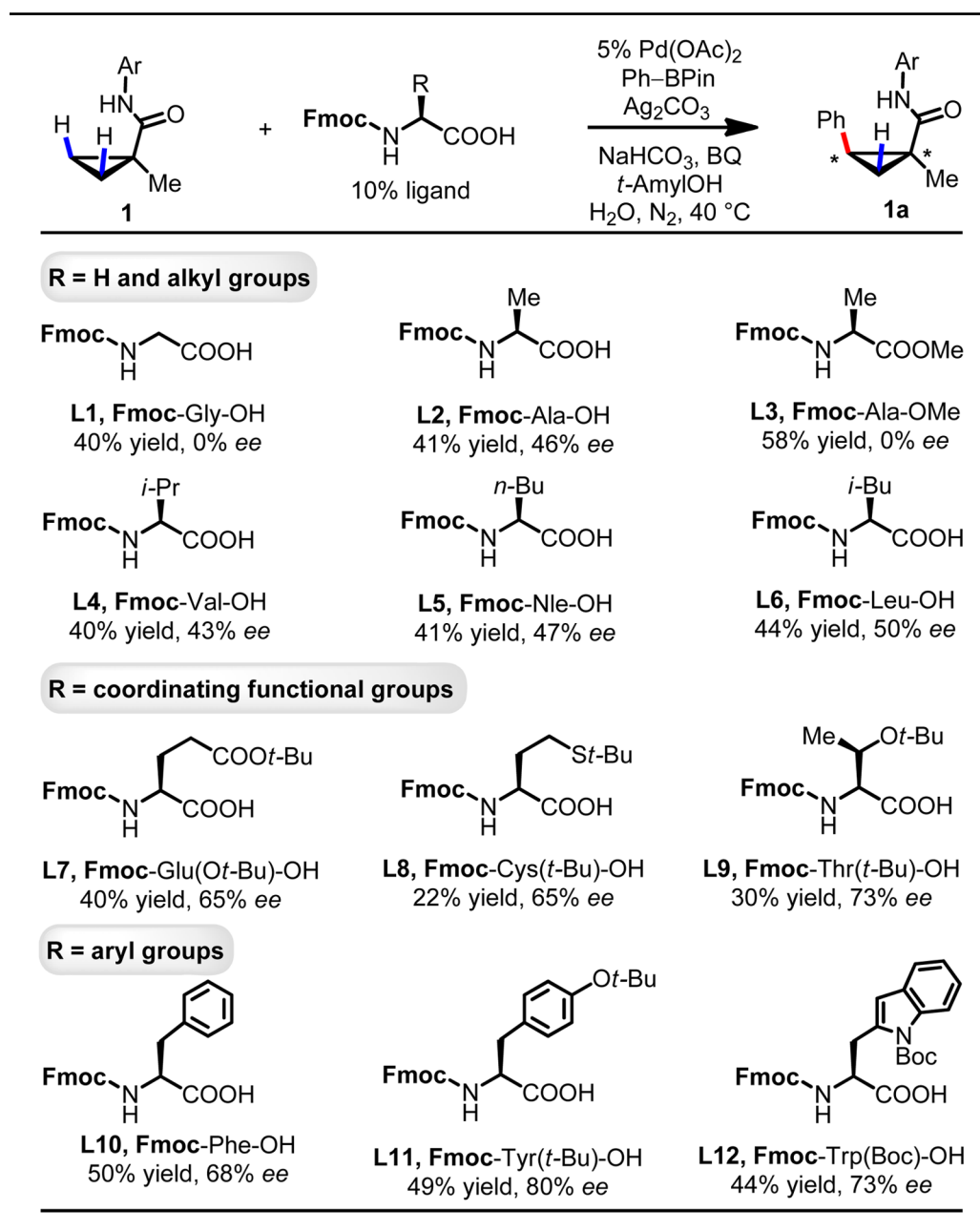

Amide protecting groups

Formyl-Leu-OH
19% yield, 44% *ee*

Ac-Leu-OH
49% yield, 0% *ee*

TFA-Leu-OH
35% yield, 5% *ee*

Piv-Leu-OH
41% yield, 0% *ee*

Carbamate protecting groups

Boc-Leu-OH
41% yield, 31% *ee*

PG1-Leu-OH
38% yield, 53% *ee*

PG2-Leu-OH
43% yield, 41% *ee*

TcBoc-Leu-OH
47% yield, **78% ee**

| 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

Fmoc-Leu-OH

[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$_2$CO$_3$, 3.0 equiv of NaHCO$_3$, 0.5 equiv of BQ, 5 equiv of H$_2$O, 0.5 mL of *t*-AmylOH, 40 °C, N$_2$, 12 h.

[b]The yield was determined by ^{1}H NMR analysis of the crude product using CH$_2$Br$_2$ as an internal standard. Stereochemical assignment is tentative.

Table 3

Screening of the Amino Acid Side Chains[a,b]

R = H and alkyl groups

L1, Fmoc-Gly-OH
40% yield, 0% *ee*

L2, Fmoc-Ala-OH
41% yield, 46% *ee*

L3, Fmoc-Ala-OMe
58% yield, 0% *ee*

L4, Fmoc-Val-OH
40% yield, 43% *ee*

L5, Fmoc-Nle-OH
41% yield, 47% *ee*

L6, Fmoc-Leu-OH
44% yield, 50% *ee*

R = coordinating functional groups

L7, Fmoc-Glu(O*t*-Bu)-OH
40% yield, 65% *ee*

L8, Fmoc-Cys(*t*-Bu)-OH
22% yield, 65% *ee*

L9, Fmoc-Thr(*t*-Bu)-OH
30% yield, 73% *ee*

R = aryl groups

L10, Fmoc-Phe-OH
50% yield, 68% *ee*

L11, Fmoc-Tyr(*t*-Bu)-OH
49% yield, 80% *ee*

L12, Fmoc-Trp(Boc)-OH
44% yield, 73% *ee*

[a]The conditions are identical to Table 2.

[b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard. Stereochemical assignment is tentative.
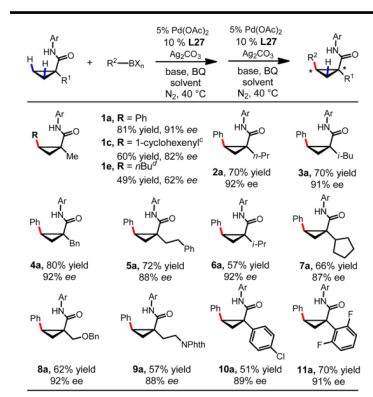
Table 4

Systematic Tuning of the Amino Acid Ligands*a,b*
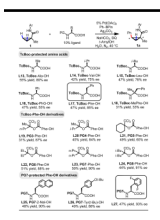
*a*The conditions are identical to Table 2.

*b*The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard. Stereochemical assignment is tentative.

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$_2$CO$_3$, 2.0 equiv of NaHCO$_3$, 0.25 equiv of BQ, 3 equiv of H$_2$O, 0.5 mL of t-AmylOH, 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$_2$CO$_3$, 1.0 equiv of NaHCO$_3$, 0.25 equiv of BQ, 1 equiv of H$_2$O, 0.2 mL of t-AmylOH, 40 °C, N$_2$, 6 h.

[b] Isolated yield. Stereochemical assignment is 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$_2$CO$_3$, 2.0 equiv of NaHCO$_3$, 0.25 equiv of BQ, 0.5 mL of THF, 50 °C, N$_2$, 6 h. (Second batch) 5mol% Pd(OAc)$_2$, 10 mol% ligand, 0.5 equiv of vinyl–BPin, 0.75 equiv of Ag$_2$CO$_3$, 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$_3$K, 0.75 equiv of Ag$_2$CO$_3$, 1.5 equiv of Li$_2$CO$_3$, 0.25 equiv of BQ, 3 equiv of H$_2$O, 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$_3$K, 0.75 equiv of Ag$_2$CO$_3$, 0.75 equiv of Li$_2$CO$_3$, 0.25 equiv of BQ, 0.2 mL of THF, 70 °C, N$_2$, 6 h.