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Palladium and Nickel Catalyzed Suzuki Cross-Coupling with Alkyl Fluorides

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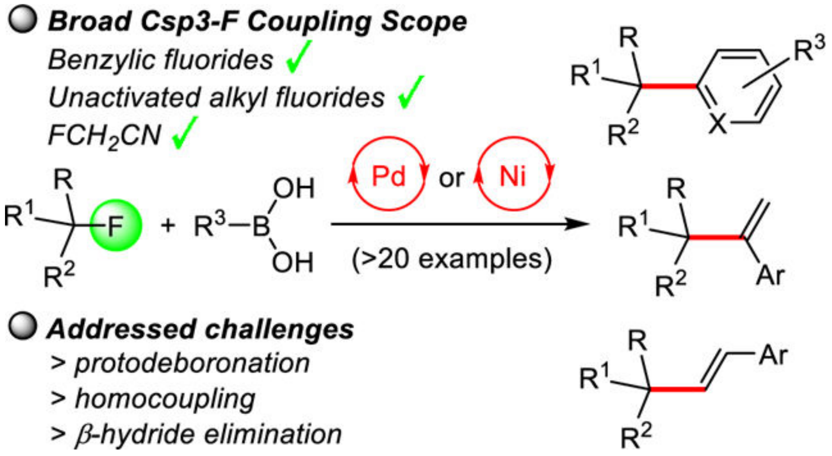
Abstract

Suzuki cross-coupling of benzylic and unactivated aliphatic fluorides with aryl- and alkenylboronic acids has been achieved via mechanistically distinct Pd and Ni catalyzed pathways that outperform competing protodeboronation, β-hydride elimination and homocoupling processes. The utility is demonstrated with more than twenty examples including heterocyclic structures, 1,1-disubstituted and *trans*-1,2-disubstituted alkenes, and by the incorporation of acetonitrile into functionalized (hetero)arenes.

Graphical Abstract



Keywords

Suzuki cross-coupling; alkyl fluorides; boronic acids; C-F bond functionalization; carbon-carbon bond formation

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Author Contributions
The manuscript was written through contributions from all authors. All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT
Supporting Information. Experimental details, synthetic procedures, NMR spectra and X-ray crystallographic analysis The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

The increasing demand for fluorinated compounds has nurtured the introduction of numerous methods that selectively manipulate common functional groups to incorporate fluorine.[1] The widespread success of organofluorines entails multifaceted consequences; it provides new synthetic opportunities but also gives rise to environmental concerns. The chemical stability and resistance to metabolic degradation of the C-F bond result in accumulation of potentially toxic pollutants that can ultimately migrate into the food chain. Several groups have started to address this problem with the introduction of hydrodefluorination reactions that convert C-F into C-H bonds.[2–5] Alternatively, the steady growth of a large pool of commercially available or easily prepared fluorinated building blocks sets the stage for new synthetic developments that in stark contrast to traditional methods target the C-F bond moiety for selective functionalization.

To date, chemoselective organofluorine functionalization has remained challenging and often requires harsh reaction conditions to overcome the low reactivity and high bond dissociation energy (>100 kcal/mol) of the C_{sp3}-F bond. Significant progress has been reported with substitution, elimination and cross-coupling reactions using aryl or alkenyl fluorides.[6] Despite emerging reports on carbon-heteroatom bond formation[7–11] and carbon-carbon bond construction[12–17] the development of methods that exploit aliphatic substrates still lacks behind C_{sp2}-F bond functionalization capabilities and is often limited to allylic, propargylic or benzylic fluorides.[18–23] In particular when highly reactive Lewis acids are required for the carbon-fluorine activation step, the synthetic utility is severely compromised due to low functional group tolerance and competing elimination or rearrangement pathways that result in unsatisfactory yields.

Our laboratory has become increasingly interested in organofluorine chemistry[24–36] and we have encountered synthetically useful C-F bond scission pathways over the years.[16,37] This encouraged us to investigate if alkyl fluorides can be applied in Suzuki cross-couplings despite the well-known challenges that aliphatic substrate pose. Transition metal catalyzed C-C bond formation with alkyl halides via cross-coupling pathways has proven complicated, in part because of competing β-hydride elimination or other side reactions. Alkyl fluorides have remained particularly difficult substrates. Kumada-Corriu reactions with Grignard reagents have been reported while broadly useful Suzuki coupling protocols remain elusive.[38–51] We now demonstrate C_{sp2}-C_{sp3} bond construction based on catalytic Suzuki cross-coupling of both benzylic and unactivated aliphatic fluorides with arylboronic or vinylboronic acids (Scheme 1). This is accomplished based on mechanistically distinct palladium and nickel catalysis to overcome competing protodeboronation, β-hydride elimination and homocoupling processes. The cross-coupling is generally high-yielding, utilizes commercially available catalysts, inexpensive LiI to generate LiF which serves as a thermodynamic sink to enable C-F bond activation, and exhibits high functional group compatibility.

At the onset of this study, we examined the palladium catalyzed cross-coupling of 4-nitrobenzyl fluoride, **1**, and phenylboronic acid, **2** (Table 1 and SI). We envisaged that the use of a thermodynamic sink to compensate for the endothermic cleavage of the C_{sp3}-F bond might allow transition metal catalyzed C_{sp2}-C_{sp3} bond formation with aryl- and vinylboronic acids. We selected LiI as the most promising Lewis acid for this task because of the high fluoride affinity of lithium and the expectation that the presence of lithium salts would not interfere with the transition metal catalysis.

After some initial screening of solvent, base and temperature using palladium acetate and tri-*tert*-butylphosphine as ligand, we were able to isolate 1-benzyl-4-nitrobenzene, **3**, in encouraging 60% yield (entries 1–8 in Table 1). Microwave irradiation proved to accelerate the reaction but did not give superior yields compared to conventional heating (compare entries 2 and 3). Further reaction analysis revealed formation of substantial amounts of biphenyl and 1,2-bis(4-nitrophenyl)ethane, **4**, which was unequivocally identified by X-ray analysis. To suppress the homocoupling process, which could result from dynamic exchange between intermediate alkyl(aryl)Pd(II) complexes, we continued with optimizing the catalyst structure using cesium carbonate as base and toluene as solvent at 100 °C. The testing of several mono- and bidentate phosphines under these conditions showed that the desired C_{sp2}-C_{sp3} cross-coupling product **3** is formed in 95% yield when tri(*o*-tolyl)phosphine is used as ligand (entries 9–18). It is noteworthy that we obtained **3** in 97% yield when the reaction was conducted at 1.25 mmol under otherwise identical conditions.

We then examined the reaction scope and found that high yields are obtained with benzylic fluorides and also with readily available fluoroacetonitrile, providing access to unsymmetrically substituted 1,1’-di(hetero)arylalkanes and practical means to introduce an acetonitrile group into an aromatic ring via Suzuki coupling (Scheme 2). We first screened a variety of arylboronic acids and benzylic fluorides which gave the desired products **3** and **5-12** exhibiting several functional groups that are not tolerated under standard Kumada-Corriu reaction conditions as well as heterocyclic structures in 86–96% yield. The reaction with sterically demanding fluoroadamantane still gave **13** in 41% yield. The same protocol allows coupling of fluoroacetonitrile and we isolated **14** and **15** from the reactions with (3-(ethoxycarbonyl)-5-nitrophenyl)boronic acid and 2-pyridylboronic acid, respectively, in 83–91% yield. Alternatively, vinylboronic acids can be used as well and the *trans*-1,2- and 1,1-disubstituted alkenes **16**-**18** were produced in 81–89% yield.

Unfortunately, the reaction with fluorocyclohexane, **19**, and 4-methoxycarbonylphenyl boronic acid, **20**, was low-yielding which we attributed to competing protodeboronation and uncontrolled HF elimination, a major challenge when electrophiles susceptible to β-hydride elimination are used in late transition metal catalysis. To mitigate these complications and to further expand the realm of C_{sp2}-C_{sp3} cross-coupling to unactivated alkyl fluorides we resorted to nickel catalysis in order to facilitate the oxidative addition step with these challenging substrates and to reduce the rate of undesirable β-hydride elimination.[52] We systematically investigated Ni salts, base additives, solvents, N- and P-donating ligands comprising a wide range of electronic and steric properties, pincer ligands that presumably block a vacant coordination site which is a prerequisite for β-hydride elimination as well as prefabricated complexes (Scheme 3 and SI).

While several combinations gave the desired cross-coupling product **21** from **18** and the arylboronic acid **20** superior results were obtained with 5 mol% of $Ni(cod)_2$ and 4,4’-di-tert-butyl-2,2’-dipyridyl, **L8**, in the presence of LiI and cesium carbonate in toluene. We were thus able to prepare **21** in 71% yield, and we successfully employed other primary and secondary alkyl fluorides exhibiting β-hydrogen atoms in this protocol, producing **22**-**26** in 63–74% yield. Under the optimized conditions, formation of by-products due to β-hydride elimination and protodemetalation is generally suppressed to only 10–20% and less than 10%, respectively, while traces of homocoupling products are observed. However, secondary benzylic fluorides remain challenging and **27** was obtained in only 24% yield. A decrease in yields was observed when $Ni(cod)_2$ was replaced by $NiCl_2$, $NiBr_2$, NiI_2 or $Ni(ClO_4)_2$ and when K_2CO_3, K_3PO_4 or KO*t*-Bu were used as base. The reaction did not occur in dioxane, DMF, IPA and *t*-BuOH.

Several features of the transition metal catalyzed Suzuki cross-coupling chemistry merit additional discussion. Both benzylic and unactivated alkyl monofluorides containing β-hydrogens can be used which transforms the accessible chemical space of the notoriously inert C_{sp3}-F bond and introduces aliphatic fluorides to synthetic transformations generally associated with chlorides, bromides and iodides. In addition, common functionalities including aryl fluoride bonds, ester, nitro and nitrile groups are tolerated which further extends the application scope and utility. For example, the fluorinated arenes **7**, **11** and **24** were produced in 69–97% yield, demonstrating successful C_{sp3}-F bond activation while C_{sp2}-F bonds are left intact. Formation of the desired cross-coupling products was not observed in the absence of a transition metal catalyst or when LiI was replaced by MgI_2 under otherwise identical reaction conditions.[53] The Pd and Ni catalyzed Suzuki couplings with benzylic and unactivated alkyl fluorides, respectively, appear to occur via mechanistically distinct pathways. The addition of the radical scavenger TEMPO into the standard palladium catalysis protocol did not affect the reaction outcome. In fact, we obtained **3** from phenylboronic acid and 4-nitrobenzyl fluoride in 94–96% yields when we added one or five equivalents of TEMPO which is in agreement with a nonradical two-electron transfer mechanism (Scheme 4).

By contrast, the Ni catalyzed Suzuki reaction with fluorocyclohexane did not give the cross-coupling product **22** in the presence of TEMPO which indicates the involvement of a single-electron transfer process and radical intermediates although a reaction shutdown due to catalyst poisoning cannot be excluded. We were able to corroborate the predominance of a radical pathway during Ni catalysis using 6-fluorohex-1-ene, **28**, as cyclizable probe in our standard protocol developed for unactivated alkyl fluorides. GC-MS and NMR spectroscopy analysis of the radical clock reaction experiment with **28** revealed that the 5-exo-trig cyclization product **29** was formed in 68% yield while the acyclic cross-coupling product **30** was obtained in only 10% yield. We note, however, that migratory insertion of an organonickel intermediate would provide the same outcome.

In conclusion, we have achieved Suzuki cross-coupling with benzylic and unactivated aliphatic fluorides using arylboronic or vinylboronic acids. The palladium and nickel catalyzed methods utilize commercially available metal complexes, ligands and inexpensive LiI producing LiF which serves as a thermodynamic sink to facilitate C-F bond activation with a variety of monofluoroalkyl compounds under conditions that are compatible with the catalytic carbon-carbon bond formation steps. Mechanistically distinct pathways that effectively control competing protodeboronation, β-hydride elimination and homocoupling processes thus enable generally high-yielding cross-coupling chemistry with high functional group compatibility. The utility is demonstrated with more than twenty examples including heterocyclic structures, 1,1-disubstituted and *trans*-1,2-disubstituted alkenes, and by the incorporation of the synthetically versatile acetonitrile group into functionalized (hetero)arenes. This study thus significantly extends C-F bond functionalization chemistry to challenging aliphatic substrates that now can be used for the synthesis of multifunctional compounds by late-transition metal catalysis.

General Procedure

To a reaction vial containing a Teflon-coated magnetic stirring bar were sequentially added $Pd(OAc)_2$ (15 mg, 0.065 mmol, 5 mol%), $P(o\text{-tolyl})_3$ (39 mg, 0.129 mmol, 10 mol%), 1-(fluoromethyl)-4-nitrobenzene (200 mg, 1.29 mmol), phenylboronic acid (314 mg, 2.58 mmol), LiI (259 mg, 1.94 mmol) and Cs_2CO_3 (840 mg, 2.58 mmol) followed by 10 mL of toluene under inert atmosphere. The vial was sealed, wrapped with aluminum foil, and stirred at 100 °C in an oil bath for 18 hours. After full conversion was achieved based on TLC analysis, the solvent was removed and the crude product was purified by flash column chromatography on silica gel using 19:1 hexanes/ethyl acetate as the mobile phase. 1-Benzyl-4-nitrobenzene, **3**, was obtained as a colorless oil in 97% yield (266 mg, 1.25 mmol). $R_f = 0.5$ (hexanes/EtOAc, 4:1); ^{1}H NMR (400 MHz, chloroform-*d*) $\delta = 8.13$ (d, $J = 8.4$ Hz, 2H), 7.36 – 7.28 (m, 4H), 7.24 (m, 1H), 7.17 (d, $J = 6.8$ Hz, 2H), 4.07 (s, 2H); ^{13}C NMR (100 MHz, chloroform-*d*) $\delta = 149.0$, 146.7, 139.3, 129.8, 129.1, 128.9, 126.9, 123.9, 41.9; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{13}H_{12}NO_2$ 214.0863, found 214.0866.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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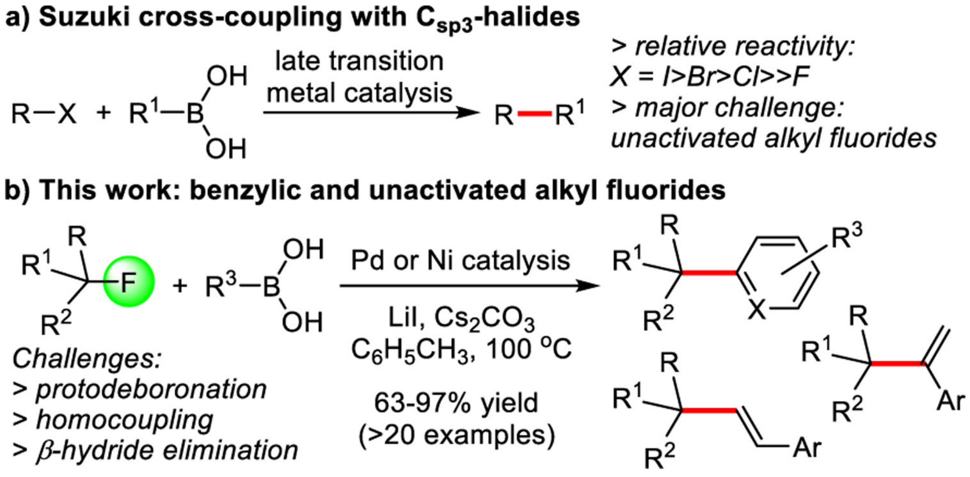
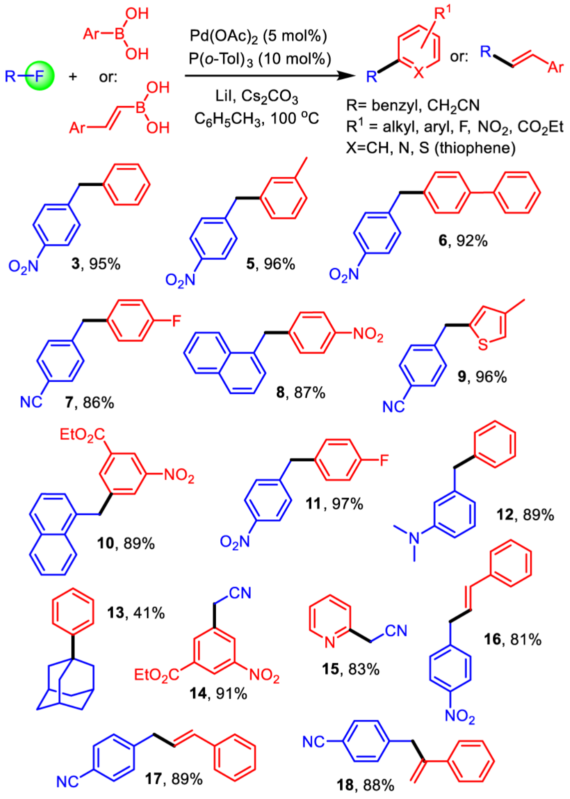
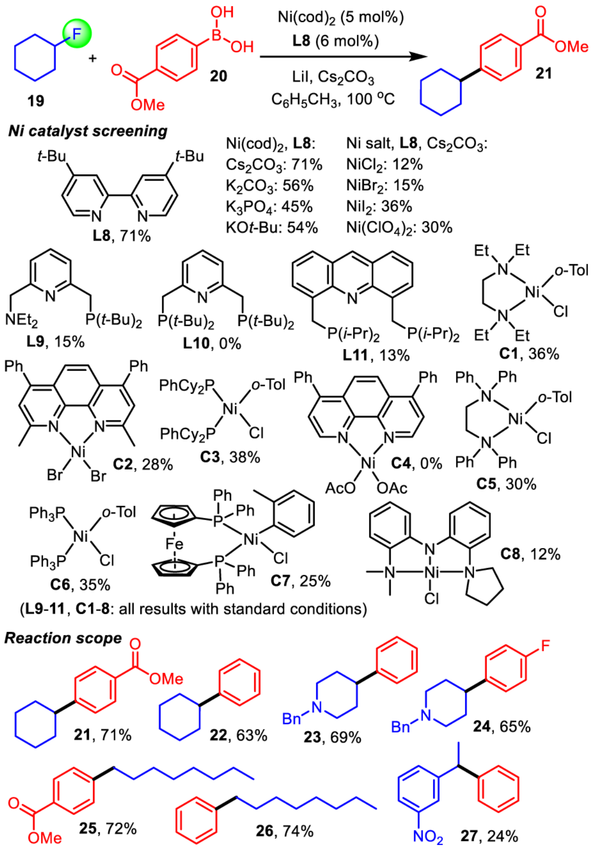


Scheme 1. Scope and challenges of transition metal catalyzed Suzuki cross-coupling chemistry.



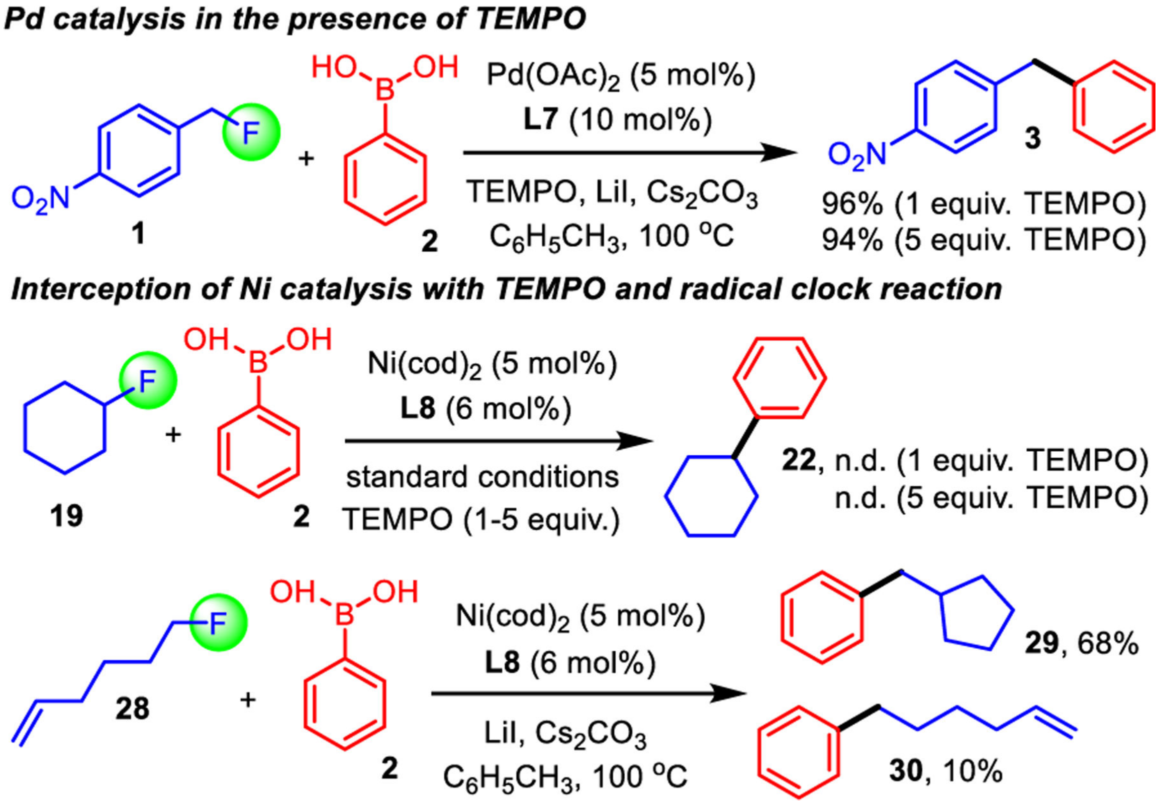
Scheme 2. Reaction scope of the Suzuki cross-coupling with benzylic fluorides and fluoroacetonitrile.

$Pd(OAc)_2$ (5 mol%), P(o-tolyl)$_3$ (10 mol%), fluoroacetonitrile or benzylic fluoride (0.2 mmol), boronic acid (0.4 mmol), LiI (0.3 mmol) and Cs_2CO_3 (0.4 mmol) in 2 mL of dry toluene under inert atmosphere at 100 °C for 18 hours. All reported yields are for isolated products. See SI for details.



Scheme 3. Development of nickel catalyzed Suzuki cross-coupling with unactivated alkyl fluorides.

Ni(cod)$_2$ (5 mol%), **L8** (6 mol%), alkyl fluoride (0.2 mmol), boronic acid (0.4 mmol), LiI (0.3 mmol) and Cs$_2$CO$_3$ (0.4 mmol) in 2 mL of dry toluene under inert atmosphere at 100 °C for 48 hours. All reported yields are for isolated products. See SI for more details.

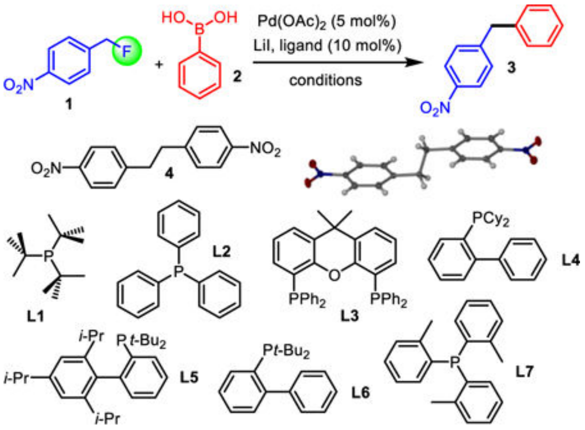


Scheme 4. Radical trapping experiments with TEMPO and clock reaction analysis with fluoride 28.

See SI for details. n.d. = not detected.

Table 1.

Development of palladium catalyzed Suzuki cross-coupling with activated fluorides.



Entry	Ligand	Base	Time (h)	Temp. (°C)	Yield (%)
1	L1	K_2CO_3	24	25	0
2	L1	K_2CO_3	18	80	33
3	L1	K_2CO_3	2	90	29[a]
4	L1	K_3PO_4	18	80	33
5	L1	K_3PO_4	18	100	40
6	L1	Cs_2CO_3	18	70	43
7	L1	Cs_2CO_3	18	100	60[b]
8	L1	Cs_2CO_3	18	100	54[c]
9	L2	Cs_2CO_3	36	100	68
10	L2	K_2CO_3	18	100	28
11	L2	K_3PO_4	18	100	42
12	L3	Cs_2CO_3	18	100	54
13	L4	Cs_2CO_3	18	100	57
14	L5	Cs_2CO_3	18	100	29
15	L6	Cs_2CO_3	18	100	51
16	L7	Cs_2CO_3	18	100	92
17	L7	Cs_2CO_3	18	100	95[d]
18	L7	Cs_2CO_3	18	100	91[e]

Conditions: **1** (0.2 mmol), **2** (0.6 mmol), LiI (0.3 mmol), Pd(OAc)$_2$ (5 mol%), ligand (10 mol%) in 2.0 mL toluene.

[a] Microwave reaction.

[b] 28% of **4** isolated.

[c] *m*-xylene used as solvent.

[d] 0.4 mmol of **2**.

[e] 0.3 mmol of **2**. All reported yields are for isolated product **3**.