Nickel-Catalyzed Csp^2−Csp^3 Bond Formation via C−F Bond Activation
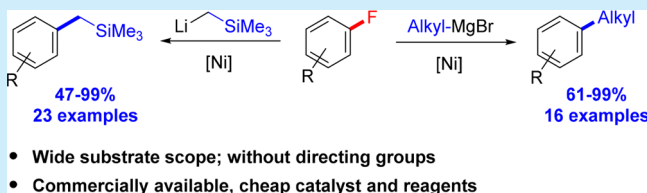
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S *Supporting Information*

ABSTRACT: A nickel-catalyzed cross coupling of aryl fluorides via C−F bond activation has been developed. The alkylation method allows selective replacement of aryl fluorides by alkyl groups and enables the synthesis of diverse and otherwise difficult to access scaffolds in good yields.
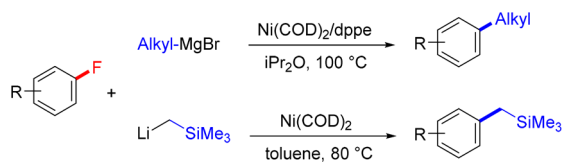
- Wide substrate scope; without directing groups
- Commercially available, cheap catalyst and reagents

In recent years, nickel-catalyzed cross-coupling reactions have received increasing attention as an alternative pathway for carbon−carbon bond construction due to the notable advantages of Ni catalysis in terms of economy and versatility. Being a relatively electropositive late-transition metal, nickel facilitates oxidative addition in cross-coupling reactions[1] and, therefore, enables cross-coupling reactions of electrophiles that are otherwise considerably less reactive under Pd catalysis. Thus, phenol derivatives,[2] aromatic nitriles,[3] and aryl fluorides[4] have been employed in nickel catalysis. Successful application of more inert bonds, such as C−F bonds, in cross-coupling reactions will allow functional group modification at a later stage for compounds containing additional functional moieties.[5] Fluorinated arenes have received great interest due to their roles in drug discovery and materials science.[6] Considering the intrinsic strength of the C−F bonds, the activation of unreactive Csp^2−F bonds for further chemical transformations has motivated researchers to attempt overcoming this challenge and develop methodologies for Csp^2−F bond activation. As a result, Csp^2−F bond activation has been achieved, and successful protocols have evolved for Kumada,[7] Suzuki,[8] Negishi,[9] Stille[10] and Sonogashira[11] coupling reactions. While many examples were described for Csp^2−Csp^2 and Csp^2−Csp bond formations, only a few reports on Csp^2−Csp^3 bond formation exist. The first example was reported by Kumada et al. in 1973[12] in which the desired cross-coupling product had been obtained in low yield due to the formation of side products arising from β-hydride elimination. Improvement has been achieved by changing the catalyst to Ni(dppp)Cl$_2$. However, β-hydride elimination was unavoidable.[13] Further progress was achieved by Nakamura et al. in 2012 with the introduction of a diphosphine POP ligand and use of in situ formed organozinc reagents.[9f] Other precedents of Csp^2−Csp^3 bond formation from aryl fluoride are rare, usually taking advantage of an *ortho*-directing electron-withdrawing group, leading to a narrow scope for the alkylation of aryl fluorides.[9a,14] The main challenge that

needs to be addressed in nickel-catalyzed C−F bond alkylations is suppression of the undesired β-hydride elimination. Herein, we report an efficient Ni-catalyzed alkylation of aryl fluorides which is suitable for a wide range of substrates, without the requirement of directing or activating groups. In addition to the coupling of aryl fluorides with Grignard reagents, the use of a Li nucleophile (LiCH$_2$SiMe$_3$) was also realized (Scheme 1).[15]

Regarding the choice of catalyst for the alkylation reaction, we started with the following considerations: (1) the bidentate structure of the ligand should stabilize the Ar−Ni^{II}−F complex formed; (2) COD (cyclooctadiene) introduced into the reaction mixture could help in stabilizing the regenerated Ni^0 until its next usage in a new catalytic cycle. As such, a catalytic system consisting of Ni(COD)$_2$ and readily available dppe was set as our starting point. The cross-coupling between commercially available **1a**, as aryl fluoride representative, and Grignard reagent **2a** was chosen as model reaction for the exploration of the optimal conditions. To our delight, the Ni(COD)$_2$/dppe combination proved to be effective, delivering the desired product in a high yield of 85% without the formation of β-hydride elimination side product (Table 1, entry 1). This result could be further improved to an excellent yield of 99% after increasing the reaction temperature to 100 °C (entry 2). However, when the reaction temperature was raised to 120 °C, the yield of the desired product **3a** decreased to 84% (entry 3). Further exploration of other ligands was also carried out. A control reaction, in which no added ligand was used, gave the product in a poor yield of 12% (entry 4), stressing the importance of an additional ligand in the reaction. Bidentate diphosphine ligands such as dcype and dppf provided good yields of 96% and 87% (entries 5 and 6). On the other hand, monodentate phosphine ligands PPh$_3$, PCy$_3$,

Scheme 1. Nickel-Catalyzed C−F Bond Alkylation

- Wide substrate scope
- Excellent yields (up to 99% yield)
- Without directing groups
- Cheap, commercially available catalyst and reagents

Table 1. Optimization of the Reaction Conditions[a]

entry	ligand	temp (°C)	solvent	yield[b] (%)
1	dppe	80	iPr$_2$O	85
2	dppe	100	iPr$_2$O	99
3	dppe	120	iPr$_2$O	84
4	−	100	iPr$_2$O	12
5	dcype	100	iPr$_2$O	96
6	dppf	100	iPr$_2$O	87
7[c]	PPh$_3$	100	iPr$_2$O	60[d]
8[c]	PCy$_3$	100	iPr$_2$O	33
9[c]	XPhos	100	iPr$_2$O	12
10	dppe	100	Et$_2$O	88
11	dppe	100	toluene	96

[a]Reaction conditions: 1a (0.25 mmol), 2a (0.5 mmol), Ni(COD)$_2$ (5 mol %), ligand (5 mol %), solvent (1 mL), 24 h. [b]Yield after purification. [c]10 mol % ligand was used. [d]Undesired homocoupling side product was formed as well.

and XPhos resulted in poor yields, with large amounts of unreacted starting material or unwanted homocoupling side product (entries 7−9). The bidentate diphosphine ligands provide sufficient rigidity compared to the monodentate phosphine ligands and could stabilize the Ar−Ni^{II}−F complex formed after oxidative addition.[16] The use of readily available and air-stable dppe is favorable since it provided the desired product in 99% yield. Next, different solvents were evaluated (entries 2, 10, and 11), and iPr$_2$O proved to be the solvent of choice (entry 2).

With the optimized reaction conditions in hand, the scope of the reaction with respect to the structure of both coupling partners was evaluated. Notably, a wide range of fluorinated substrates and different types of alkyl Grignard reagents could be applied in the reaction, providing the corresponding alkylated products 3a−p with excellent yields (Scheme 2). For example, the Csp^2−Csp^3 bond-forming reaction of aryl fluoride 1a was successful with different Grignard reagents 2a−i, leading to products 3a−i in up to 99% yield. In addition to the n-pentyl derivative 2a, Grignard reagents bearing short as well as long alkyl chain groups such as ethyl (2b) and n-dodecyl (2c) also performed well in this transformation. Notably, secondary, cyclic Grignard reagent 2d and branched alkyl derivative 2e were well tolerated, providing products 3d and 3e in 94% and 61% yields, respectively. Furthermore, the reaction was also successful with substrates 2f−h that bear an aromatic group at the terminal position, affording the coupling products 3f−h in excellent yields (93−99%). Our reaction

## Scheme 2. Substrate Scope of Ni-Catalyzed Csp2−Csp3 Bond Formation via Activation of Aryl Fluorides[a]
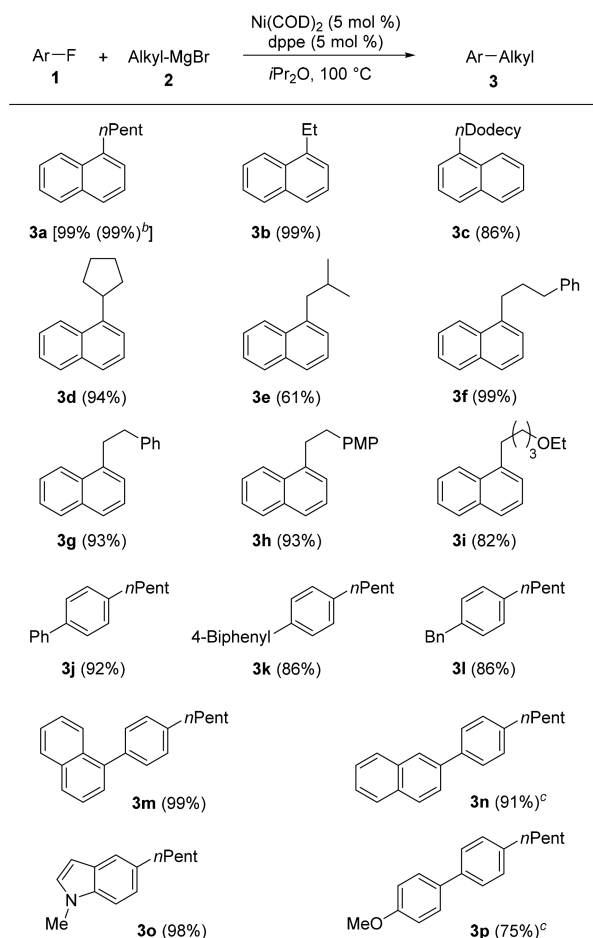
[a]Reaction conditions: 1a (0.25 mmol), 2a (0.5 mmol), Ni(COD)$_2$ (5 mol %), dppe (5 mol %), iPr$_2$O (1 mL), 100 °C, 24−60 h, yields after purification. [b]Reaction on 1 mmol scale, 72 h. [c]10 mol % of Ni(COD)$_2$/dppe.

Table 2. Optimization of the Reaction Conditions[a]

entry	Ni(COD)$_2$ (X mol %)	temp (°C)	solvent	yield[b] (%)
1	2.5	rt	toluene	43
2	2.5	50	toluene	75
3	2.5	80	toluene	99
4	2.5	60	THF	47
5	2.5	30	Et$_2$O	60
6	1	80	toluene	92
7	0.5	80	toluene	42
8	−	80	toluene	

[a]Reaction conditions: 1b (0.25 mmol), 4 (1.3 equiv), Ni(COD)$_2$ (X mol %), solvent (1.5 mL), 2 h. [b]Yield after purification.

conditions were also efficient when an ether functional group was present at the terminal position of the alkyl chain (3i, 82% yield). Next, the scope of the reaction with respect to the structure of the fluorinated coupling partner was evaluated. Substrates 1b−f, bearing various aryl substituents in the para-position of the fluorobenzene ring including phenyl (1b),

Scheme 3. Substrate Scope of the Aryl Fluoride Functionalization Reaction[a]
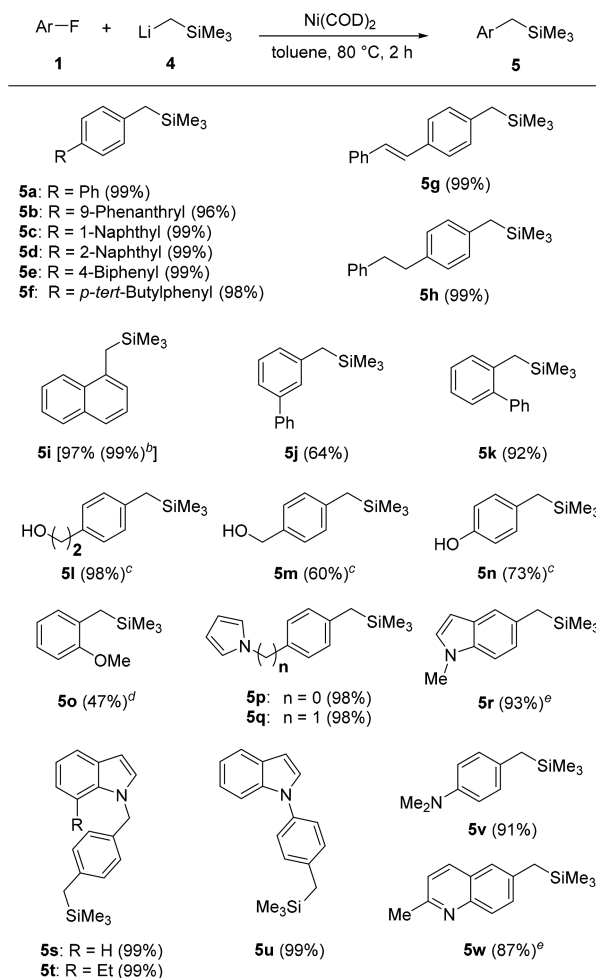
^{a}Reaction conditions: **1** (0.25 mmol), **4** (1.3 equiv), Ni(COD)$_2$ (2.5 mol %), toluene (1.5 mL), 2 h, yields after purification. ^{b}Reaction on 1 mmol scale, 2 h. ^{c}3 equiv of LiCH$_2$SiMe$_3$, 5 mol % of Ni(COD)$_2$, 16 h. ^{d}1.1 equiv of LiCH$_2$SiMe$_3$. ^{e}5 mol % of Ni(COD)$_2$, 16 h reaction time.

biphenyl (**1c**), benzyl (**1d**), and naphthyl (**1e**, and **1f**) led to full conversion of the starting materials and high yields (86–99%). Indole derivative **1g** underwent the reaction smoothly, providing the desired product **3o** with an excellent yield of 98%. For substrate **1h** that bears a methoxy functional group, the methoxy group successfully survived the reaction conditions furnishing the desired product **3p** in 75% yield.

Next, our attention was drawn to the commercially available nucleophile LiCH$_2$SiMe$_3$. We started the optimization study by reacting 4-biphenyl fluoride (**1b**) with LiCH$_2$SiMe$_3$ (**4**) in the presence of 2.5 mol % of Ni(COD)$_2$ in toluene at room temperature. Pleasingly, we obtained the corresponding ArCH$_2$SiMe$_3$ **5a** product in 43% yield (Table 2, entry 1). The yield could be considerably increased by raising the temperature to 80 °C (99%, entry 3). Lower yields were obtained when the reaction was carried out in THF (47%, entry 4) and diethyl ether (60%, entry 5). Reducing the catalyst loading to 1 mol % resulted in a slightly lower yield of 92% (entry 6), whereas a further decrease to 0.5 mol % led to a significantly lower yield of 42% (entry 7). Furthermore, in the

absence of the Ni catalyst, no conversion of the starting material was observed (entry 8).

This Csp^2–Csp^3 coupling reaction could be applied to a range of fluorinated substrates with generally excellent yields (Scheme 3). Various aryl substituents in the *para*-position of fluorobenzene led to full conversion of the starting materials and high yields (96–99%) for the desired products **5a–f**. The *trans*-stilbene substrate and its saturated derivative could be converted to **5g** and **5h** in quantitative yields. In addition, the 1-naphthyl derivative **5i** was obtained in 97% yield. Pleasingly, various alcohol derivatives were found to be good substrates for the coupling reaction, which produced good to high yields for the aromatic (**5n**), benzyllic (**5m**), and aliphatic (**5l**) derivatives. A series of nitrogen-containing compounds could also efficiently be subjected to the reaction conditions, yielding products **5p–w** with high to excellent yields (87–99%).

In summary, a direct method for the Csp^2–Csp^3 bond formation with aryl fluorides as electrophiles has been developed. By using a Ni(COD)$_2$/dppe catalytic system, the alkylation of aryl fluorides could be performed with various alkyl Grignard reagents with yields of up to 99%. The established methodology proved successful in avoiding the undesired β-hydride elimination and is appealing in terms of electrophile availability as no directing or activating groups are required. Moreover, the components of the catalytic system (Ni(COD)$_2$ and dppe) and the Grignard reagents are readily available. In addition, the use of LiCH$_2$SiMe$_3$ as nucleophile resulted in products that can be converted into more complex structures by taking advantage of the existing SiMe$_3$ group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02351.

> Detailed experimental procedures, spectral data for all compounds, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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