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C−F Activation for $C(sp^2)$−$C(sp^3)$ Cross-Coupling by a Secondary Phosphine Oxide (SPO)-Nickel Complex

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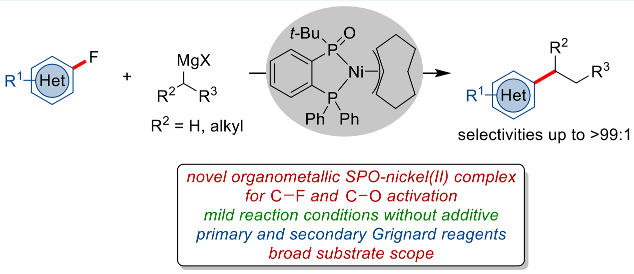
ABSTRACT: A secondary phosphine oxide (SPO)-nickel catalyst allowed the activation of otherwise inert C−F bonds of unactivated arenes in terms of challenging couplings with primary and secondary alkyl Grignard reagents. The C−F activation is characterized by mild reaction conditions and high levels of branched selectivity. Electron-rich and electron-deficient arenes were suitable electrophiles for this transformation. In addition, this strategy also proved suitable to heterocycles and for the activation of C−O bonds under slightly modified conditions.



The formation of carbon−carbon bonds via metal-catalyzed cross-couplings has been recognized as a powerful tool for molecular synthesis.[1] While classical cross-coupling reactions focused on traditional electrophiles, such as aryl iodides, triflates, and bromides, the activation of inert C−F bonds is significantly more challenging.[2] The use of fluorine labeled compounds in absorption distribution metabolism and excretion (ADME) studies render aryl fluorides especially useful for early stage as well as late stage modifications.[3] While $C(sp^2)$−F bonds are otherwise inert with a bond dissociation energy of ∼126 kcal/mol,[4] the use of specific nickel catalyst enabled cross-couplings with these challenging electrophiles.[5] Unfortunately, only a few reports on selective $C(sp^2)$−$C(sp^3)$ bond formations are known and are mostly restricted to alkyl electrophiles with the aid of sterically congested ligands.[6] Much less attention has been focused on related reactions with branched nucleophiles,[7] due to competing β-hydride eliminations favored for hemilabile ligands[8] as well as highly nucleophilic transition metals.[9] In a seminal report, Kumada reported one coupling between an aryl fluoride and a secondary Grignard which was accompanied by an undesired isomerization (Figure 1a).[10] Since then, only selected examples were disclosed,[11] including a major recent advance by Cornella by highly branch-selective alkylations of aryl fluorides.[8a] The key to success was a dialkyl substitution pattern on an air-sensitive dppe ligand backbone combined with an additional base (Scheme 1b). Even though this approach enabled the alkylation at the α-position of some *N*-containing heterocycles, a general method toward branched and linear alkylating reagents, by efficient nickel catalysis, continues to be in high demand.[12] Within our program on nickel catalysis[13] with secondary phosphine oxide (SPO)[14] preligands,[15] we have now devised a generally applicable strategy for the nickel-catalyzed C−F alkylation of unactivated aryl fluorides with primary and secondary alkylmagnesium reagents. Notable

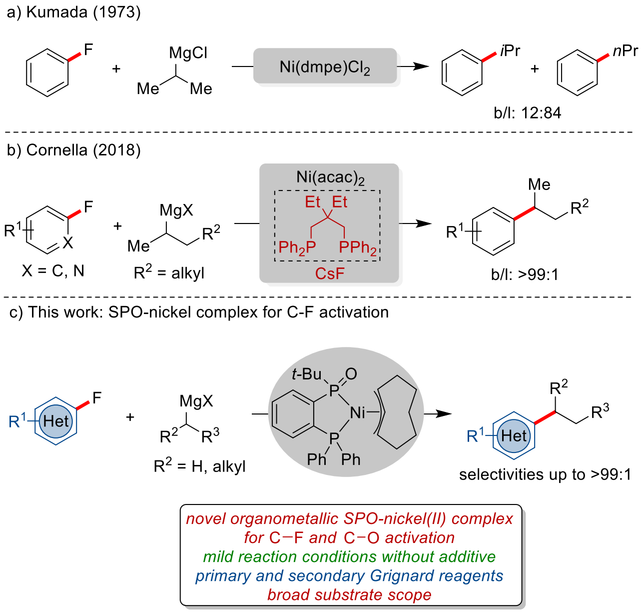


Figure 1. Nickel catalyzed C−F alkylations.

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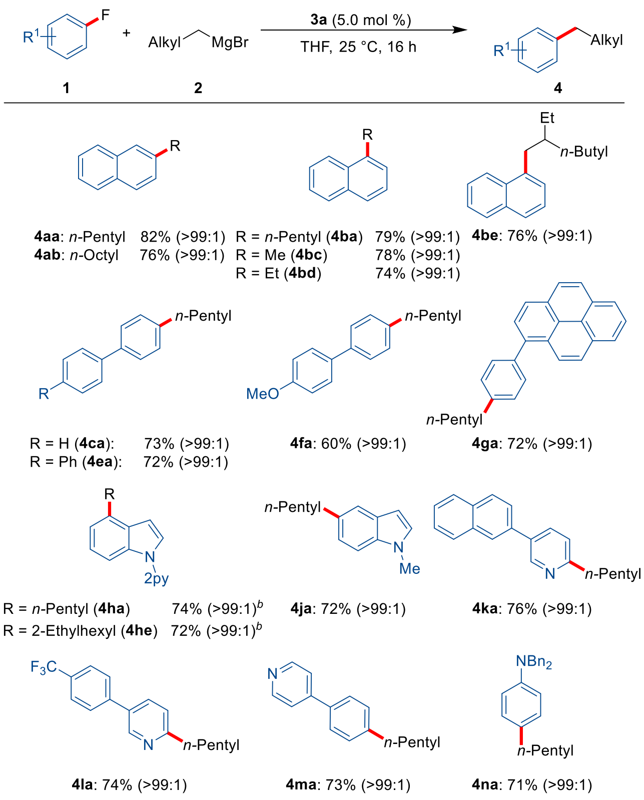
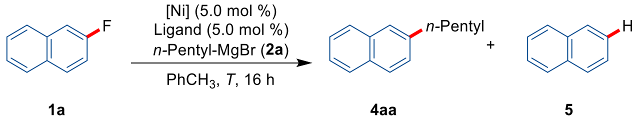
Scheme 1. Scope of the Linear-Selective Alkylation by SPO-Nickel C−F Activation[a]



[a]Linear/branched selectivities in parentheses. [b]Byproduct observed.

Table 1. SPO-Nickel Catalyzed Alkylation with Linear Grignard Reagents[a]



entry	[Ni]	ligand	*T*/°C	**4aa**/**5** [%][b]
1	$Ni(acac)_2$	–	100	18/20
2	$Ni(acac)_2$	dppe	100	<10
3	$Ni(cod)_2$	dppe	100	89/6
4	$Ni(cod)_2$	dppe	25	–[c]
5	$Ni(cod)_2$	$(Ph)_2P(O)H$	100	63/24
6	$Ni(cod)_2$	**L1**	100	70/20
7	**3a**		100	75/15
8			25	82/2[c,d]

[a]General reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), [Ni] (5.0 mol %), Ligand (5.0 mol %), $PhCH_3$ (0.50 mL), *T*, 16 h, isolated yield. [b]Ratio of **4aa**/**5** determined by ^1H NMR spectroscopy. [c]THF as solvent. [d]0.25 N.

features of our findings include (1) the use of Earth-abundant nickel catalysis for synthetically meaningful C−F activations, (2) a novel SPO-nickel complex which was fully characterized by X-ray diffraction analysis, (3) exceedingly mild reaction conditions, and (4) outstanding selectivities with secondary alkylating reagents (Figure 1c).

We commenced our studies by testing a variety of nickel precursors and ligands for the envisioned C−F alkylation of **1a** (Table 1 and Table S1 in the Supporting Information).

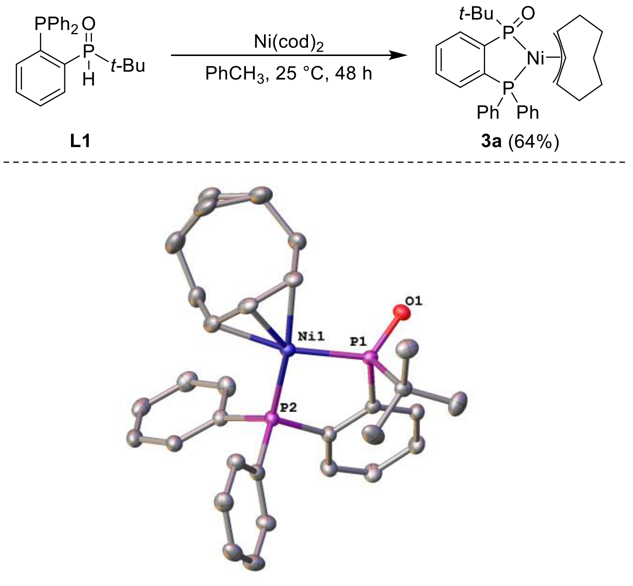
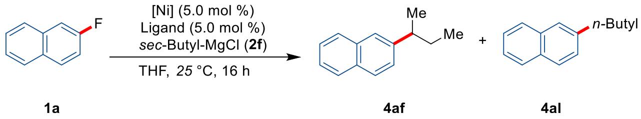


Figure 2. Synthesis and molecular structure of complex **3a**. Thermal ellipsoids are drawn at the 50% probability level and carbon bound H atoms are omitted for clarity.

Table 2. SPO-Nickel Catalyzed Alkylation with Branched Grignard Reagents[a]



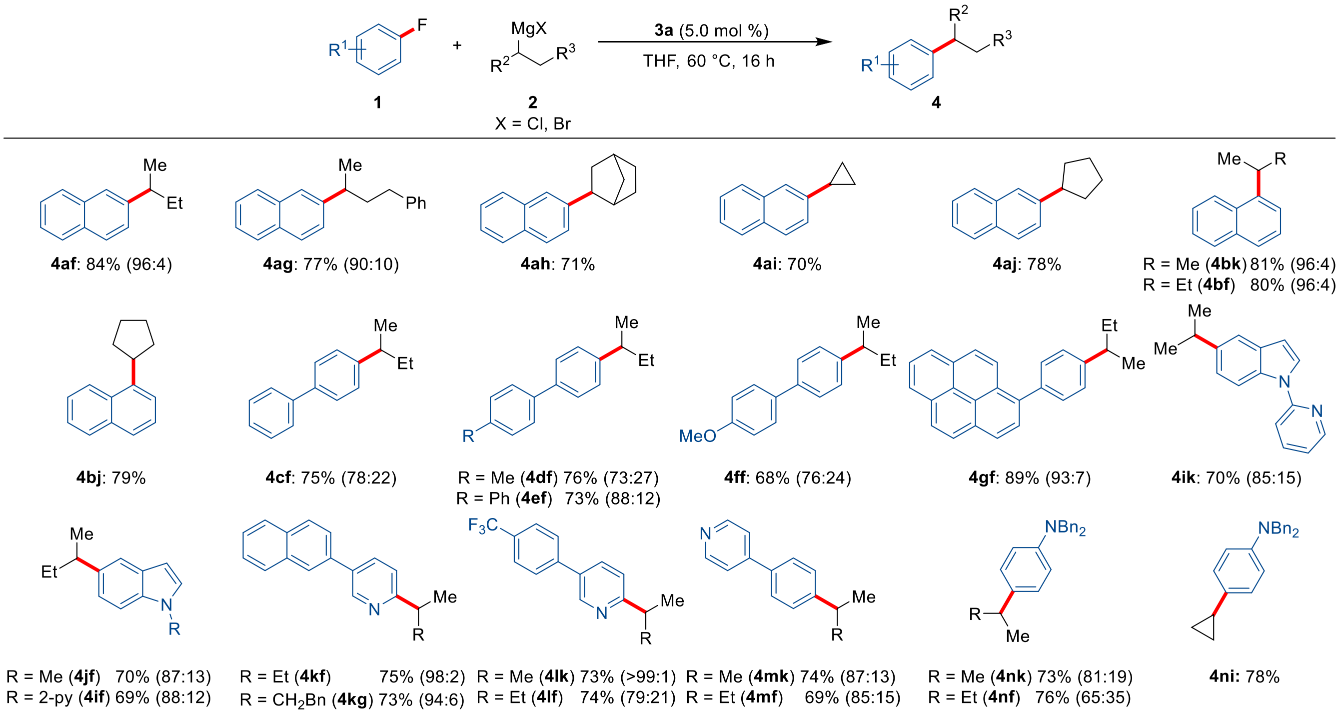
entry	[Ni]	ligand	**4af** [%]	b/l [%][b]
1	$Ni(cod)_2$	dppe	–	–
2	$Ni(acac)_2$	dppe	–	–
3	**3a**		57[c]	93/7
4			56[d]	93/7
5			60	92/8
6			84[e,f]	96/4
7			77[e–g]	95/5

[a]General reaction conditions: **1a** (0.25 mmol), **2f** (0.50 mmol), [Ni] (5.0 mol %), Ligand (5.0 mol %), solvent (0.50 mL), 25 °C, 16 h, isolated yield. [b]Ratio of **4af**/**4al** determined by ^1H NMR spectroscopy. [c]$PhCH_3$ as solvent. [d]2-MeTHF as solvent. [e]60 °C. [f]0.50 mmol scale. [g]30 min.

While $Ni(acac)_2$ showed minor reactivity without ligand, the addition of the commonly used phosphine ligand dppe facilitated the transformation only with a nickel(0) precatalyst (entries 1−3). Notable, nickel(0) precatalyst combined with dppe failed to give any conversion at ambient temperature (entry 4). Hence, we next studied air- and moisture-stable SPO preligands, resulting in a moderate yield and selectivity (entry 5). In contrast, the bidentate SPO ligand **L1** yielded product **4aa** in 70% yield and reduced the formation of the undesired dehalogenation product **5** (entry 6). Subsequent treatment of $Ni(cod)_2$ with **L1** resulted in the formation of complex **3a**, which was isolated and crystallographically characterized (Figure 2).

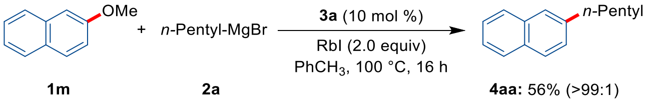
To our delight complex **3a** was found to be catalytically active, yielding the desired product **4aa** in an increased yield and improved selectivity (entry 7). It is assumed that the SPO-phosphine nickel(II) precatalyst and the Grignard reagent

Scheme 2. Scope of the Branched-Selective Alkylation by SPO-Nickel Catalysis[a]



[a]Branched/linear selectivities in parentheses.

Scheme 3. C−O Alkylation by SPO-Nickel Catalysis[a]



[a]Linear/branched selectivities in parentheses.

form a nickel/magnesium bimetallic catalytic species that carries out push−pull cooperative activation of the aryl fluoride.[5i,m,16] Lowering the reaction temperature and changing the solvent to THF improves the yield and suppresses the formation of **5** (entry 8). Subsequently, we explored the catalyst's versatility, with respect to the viable structures of fluoroarenes **1** and alkyl nucleophiles **2**. Notably, a wide range of fluoroarenes **1** and alkylmagnesium bromides **2** were converted in an efficient manner to provide the corresponding products **4** in excellent yield (Scheme 1). The $C(sp^2)-C(sp^3)$ bond formation of arylfluoride **1a** was successful performed with different alkylmagnesium reagents, delivering the corresponding products **4aa**−**4ba** in up to 82% yield. The tether had no major influence (**2b**−**2d**). In addition, also the branched reagent **2e** delivered **4be** selectively without isomerization. The variation with respect to fluoroarene **1** was not limited to naphthalene derivatives. Indeed, also structural motifs such as phenyl (**4ca**), biphenyl (**4ea**), and pyrene (**4ga**) were efficiently transferred. To our delight, the C−O bond successfully survived under the reaction conditions (**4fa**), without interference, indicating notable innate chemoselectivity. Finally *N*-protected indoles (**4ha**, **4he**, and **4ja**) show high catalytic performance yielding otherwise difficult to synthesize motifs that were studied in C−H transformations.[17] In addition, pyridines (**1k**−**m**) are tolerated by the SPO-nickel regime, showing no deactivation of catalyst **3a** by potentially coordination, generating (**4ka**−**4ma**) in good yield without commonly obtained Ziegler alkylation at the more acidic α-position to the heteroatom.[18] Finally, also an electron-rich *N*-protected aniline derivative was converted successfully yielding **4na** in good yield and selectivity.

Based on the outstanding selectivity within the linear alkylation, we became interested in the considerably more challenging alkylation with secondary alkylmagnesium halides. We initiated our studies here again with **1a** as the model substrate and *sec*-butylmagnesium chloride (**2f**) as the alkylation reagent (Table 2 and Table S4 in the Supporting Information). Communally used nickel precursors with established phosphine ligand failed to facilitate the envisioned transformation (entries 1−2). In contrast, the well-defined catalyst **3a** proved to be suitable, yielding desired product **4af** in moderate yield and selectivity (entry 3). Further optimization showed that biomass-derived 2-MeTHF is also suitable for this transformation (entry 4).[19] A slightly increased temperature is needed for a higher conversion and better selectivity (entry 6). The high reactivity of catalyst **3a** toward unactivated C−F bonds was further reflected by a high TOF, yielding **4af** in 77% yield after only 0.5 h (entry 7).

Under the optimized reaction conditions, various acyclic secondary Grignard reagents, such as *s*-BuMgCl (**4af**), (4-phenylbutan-2-yl)magnesium bromide (**4ag**), and *i*-PrMgCl (**4bk**), were successfully converted by the SPO-nickel catalyst **3a** (Scheme 2). All secondary alkylating reagents delivered the coupling product with excellent selectivities and good yields. Furthermore, cyclic secondary Grignard reagents, such as a bulky bicycle- (**4ah**), cyclpropyl- (**4ai**), and cyclopentyl (**4aj**−**4bj**) -magnesium halide, were also suitable coupling partners with excellent yields and high levels of selectivity without observable ring opening.[20] The use of *para*-substituted arenes did not influence the reaction (**4cf**−**4ef**), and indeed C−O bonds stay intact during the course of the reaction (**4ff**). In addition, pyrene fluorophores proved to be compatible within the SPO-nickel catalysis regime (**4gf**). Biologically relevant heterocyclic motifs, such as indole, are well tolerated (**4ik**, **4jf**, and **4if**). Pyridine motifs were selectively converted with *s*-BuMgCl (**4kf-mf**), (4-phenylbutan-2-yl)magnesium bromide (**4kg**), and *i*-PrMgCl (**4lk** and **4mk**). Finally, also an electron-rich *N*-protected aniline derivative is converted successfully with acyclic coupling reagents yielding the *para* alkylated products **4nk** and **4nf** in good yield and moderate selectivity, whereas a cyclic nucleophile generated the product with excellent selectivity (**4ni**). Importantly, no substitution in the α-position to the heteroatom was observed, highlighting the selectivity of the SPO-nickel regime.

In consideration of the activity of the SPO-nickel catalyst **3a** to C−F bonds, we became intrigued regarding the selectivity toward other inert bonds. Indeed, we could achieve the activation of 2-naphthyl methyl ether with **3a** under slightly altered reaction conditions,[21] notably without any isomerized product being formed for the linear-selective alkylation and moderate selectivity for the branched-selective alkylation (Scheme 3).[22]

In conclusion, we have developed a well-defined novel SPO-phosphine nickel catalyst, for the activation of otherwise inert C−F bonds. The cross-coupling with the air-stable nickel(II) enabled primary and secondary alkylations with high levels of selectivity. A wealth of electron-rich and electron-deficient arenes proved suitable electrophiles for this transformation under mild reaction conditions. Finally, the SPO-nickel catalyst **3a** proved valid for C(sp^2)−OMe alkylations, prompting future methodological developments.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02609.

Detailed experimental procedures, compound characterization data, X-ray crystallography data, and NMR spectra (PDF)

Accession Codes

CCDC 1991589 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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