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Experimental and computational studies towards chemoselective C-F over C-Cl functionalisation: reversible oxidative addition is the key

Emily Jacobs[a] and Sinead T. Keaveney[a,*]

Abstract: Catalytic cross-coupling is a valuable tool for forming new carbon-carbon and carbon-heteroatom bonds, allowing access to a variety of structurally diverse compounds. However, for this methodology to reach its full potential, precise control over all competing cross coupling sites in poly-functionalised building blocks is required. Carbon-fluorine bonds are one of the most stable bonds in organic chemistry, with oxidative addition at C-F being much more difficult than at other C-halide bonds. As such, the development of methods to chemoselectively functionalise the C-F position in poly-halogenated arenes would be very challenging if selectivity was to be induced at the oxidative addition step. However, metal-halide complexes exhibit different trends in reactivity to the parent haloarenes, with metal-fluoride complexes known to be very reactive towards transmetalation. In this current work we sought to exploit the divergent reactivity of Ni-Cl and Ni-F intermediates to develop a chemoselective C-F functionalisation protocol, where selectivity is controlled by the transmetalation step. Our experimental studies highlight that such an approach is feasible, with a number of nickel catalysts shown to facilitate Hiyama cross coupling of 1-fluoronapthalene under base free conditions, while no cross coupling with 1-chloronapthalene occurred. Computational and experimental studies revealed the importance of reversible C-Cl oxidative addition for the development of selective C-F functionalisation, with ligand effects on the potential for reversibility also presented.

Introduction

Carbon – fluorine bond activation remains a key challenge in synthetic chemistry, with research in this field driven by the prevalence of commercially available fluoroarenes,[1], as well as the widespread industrial applications of fluorinated compounds in the pharmaceutical, materials chemistry and agrochemical sectors.[2] Catalytic cross coupling at the stable C-F bond is particularly attractive as it can permit derivatisation of poly- or per-fluorinated building blocks,[3] as well as providing a robust synthetic handle for late-stage diversification of complex molecules. Importantly, oxidative addition of C-F to a transition metal centre generates an active metal-F intermediate, which can also allow unique reactivity to be developed through the use of fluorinated substrates.[4]

While there have been substantial breakthroughs in fluoroarene cross coupling methodologies in recent years, the majority of procedures require nucleophillic organomagnesium[5] or organozinc[6] coupling partners, limiting applications to relatively robust substrates. In addition, elegant strategies to selectively functionalise C-F in the presence of C-H have been developed,[3a, 7] however catalytic procedures to selectively functionalise C-F in the presence of other C-halides are limited (Figure 1, top). Stoichiometric reactions of nickel complexes with activated pyrimidines marks the first demonstration of chemoselective C-F activation in the presence of C-Cl,[8] with use of a directing group also shown to be effective.[9] In addition, Ni-fluoride complexes have been shown to readily undergo transmetalation with boronic acids, while other Ni-halides do not.[4a] In this current work we sought to contribute to this emergent field through investigating a new approach to selective C-F functionalisation, where C-F over C-Cl selectivity could be induced at the transmetalation step (Figure 1, bottom).

In the proposed concept, selectivity is controlled by the divergent reactivity of the intermediate generated following oxidative addition: a metal-F intermediate can undergo direct and base-free transmetalation with organosilanses and boronic acids, whereas other metal-halides cannot.[4] Thus, base-free Hiyama or Suzuki cross coupling could allow chemoselective C-F functionalisation, in the presence of typically more active C-halide bonds, to be realised. This proposed selectivity is the opposite of what could be achieved if selectivity was controlled by the rate of C-halide oxidative addition to nickel.[10] Through combined experimental and computational investigations we demonstrate the feasibility of this approach, and uncover the key role that reversible oxidation addition will play in developing

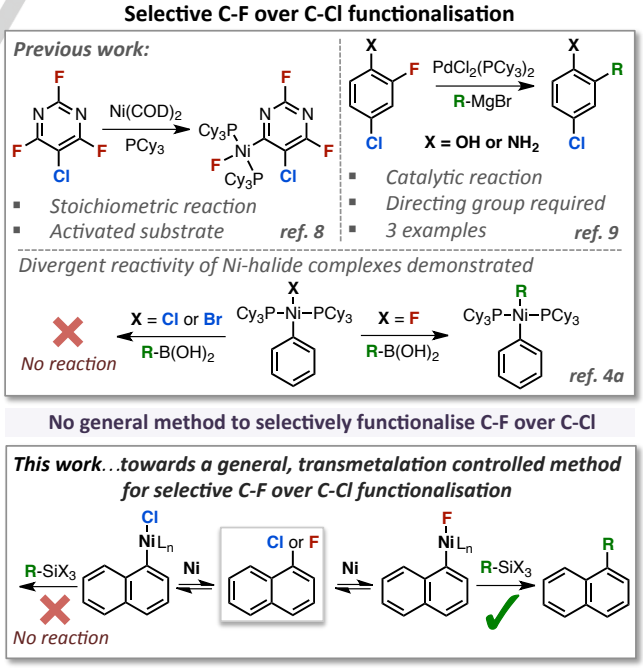

Figure 1: Top: previous work on selective C-F over C-Cl functionalisation, and studies on metal halide reactivity. Bottom: the concept explored in this work.

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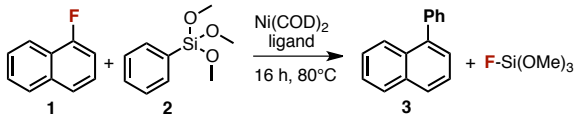
transmetalation-controlled selectivity. The insight presented in this current work lays the groundwork for designing chemoselective C-F functionalisation methodology in the future, as well as allowing the more rational design of ligands that could permit reversible oxidative addition.

Results and Discussion

Bimetallic C-F activation is often postulated in the Kumada or Negishi cross coupling of fluoroarenes, where the magnesium or zinc species are directly involved in the oxidation addition step.[11] This Lewis acid assisted activation accounts for the prevalence of Kumada and Negishi type C-F cross coupling approaches, with no reported examples of Hiyama cross coupling of unactivated fluoroarenes. As such, the first challenge is to develop a base-free Hiyama cross coupling protocol that can be applied to an unactivated fluoroarene. We chose the model reaction between 1-fluoronapthlene **1** and trimethoxyphenylsilane **2** (Scheme 1), with 1-fluoronapthalene **1** simply chosen to allow the homo- and cross coupling products to be differentiated.



Scheme 1: The model cross coupling reaction between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2**.

As oxidative addition at the inert C-F bond will be challenging, we initially chose to focus on the use of electron rich phosphine ligands, and the abundant metal nickel. A range of ligands were examined using a Ni:ligand ratio of 1:2, with poor sigma donating ligands, such as PPh_3, being ineffective (Tables 1 and S1). Surprisingly, use of the more electron rich and bulky biaryl phosphine ligands widely used for C-Cl activation,[12] such as SPhos, were also ineffective. While the electron rich PBu_3 ligand did not facilitate cross coupling, some product formation was observed for PCy_3 and $PCyp_3$ (where Cy = cyclohexyl and Cyp = cyclopentyl). This suggests that both increased sigma donating ability and steric bulk of the ligand favours cross coupling, with the latter likely due to promotion of the reductive elimination step. Interestingly, there appears to be a limit to which steric bulk promotes cross coupling, with no product formation observed when using P^tBu_3.

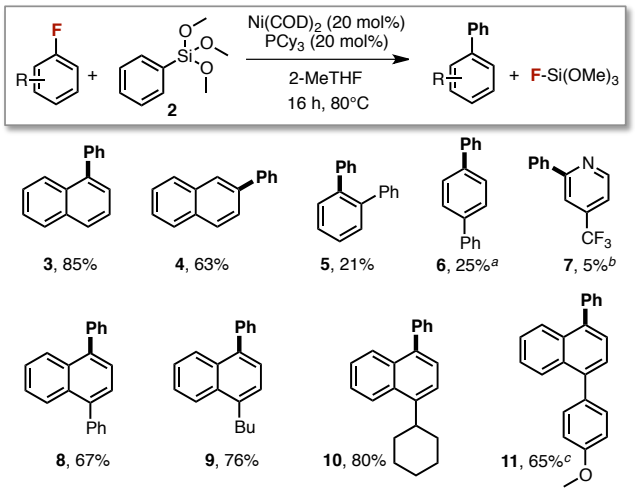
A variety of solvents were then considered, with 2-methyltetrahydrofuran (2-MeTHF) being most effective (Table S2). However, the reaction temperature was limited to 100 °C, with no product **3** formation observed at 80 °C (Table 1). While an additive free approach was desirable, we also tested a range of Lewis acid and base additives to probe their effect on this process. Despite broad screening, no increase in product formation was observed in any case (Table S3). The nickel to ligand ratio was found to impact cross coupling, with use of a 1:1 ratio allowing the reaction to proceed at 80 °C (Tables S4 and S5). Lastly, increasing the metal loading to 20 mol% raised the yield of **3** to 75%, with additional improvement offered by increasing the scale of the reaction. Ultimately, an excellent isolated yield of 85% was achieved (Table 1 and S6), with the remaining material being 1-methoxynapthalene which forms through *methoxy* group transfer, similar to that observed previously for activated fluoroarenes.[4c]

Table 1: Development of the reaction conditions to promote base free Hiyama cross coupling of 1-fluoronapthalene **1**. See Tables S1-6 for additional data.

Ligand	Temperature / °C	Solvent	Ni:ligand ratio	Ni loading	Yield **3** / %
-	100	Toluene	-	5 mol%	0
PPh_3	100	Toluene	1:2	5 mol%	0
SPhos	100	Toluene	1:2	5 mol%	0
PBu_3	100	Toluene	1:2	5 mol%	0
$PCyp_3$	100	Toluene	1:2	5 mol%	5
PCy_3	100	Toluene	1:2	5 mol%	5
P^tBu_3	100	Toluene	1:2	5 mol%	0
PCy_3	100	THF	1:2	5 mol%	2
PCy_3	100	2-MeTHF	1:2	5 mol%	10
PCy_3	130	2-MeTHF	1:2	5 mol%	4
PCy_3	80	2-MeTHF	1:2	5 mol%	trace
PCy_3	100	2-MeTHF	1:1	5 mol%	trace
PCy_3	80	2-MeTHF	1:1	5 mol%	10
PCy_3	80	2-MeTHF	1:1	10 mol%	32 (41[a])
PCy_3	80	2-MeTHF	1:1	20 mol%	75 (85[a])

Reaction conditions: 1-Fluoronapthalene **1** (13 µL, 0.1 mmol), trimethoxyphenylsilane **2** (37 µL, 0.2 mmol), $Ni(COD)_2$, ligand and solvent (0.3 mL) were added to a 4 mL pressure tube in an argon atmosphere glovebox. The tube was sealed, removed from the glovebox and heated for 16 hours. 4-Trifluoromethoxyanisole (15 µL, 0.1mmol) was added as the internal standard, and the crude reaction mixture was analysed using GC-MS, with the yield of product **3** determined using a calibration curve (see Figure S1). [a]Isolated yield, with the reaction performed on a larger scale (1 mmol of 1-fluoronapthalene **1**).

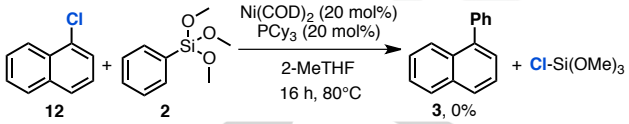
As this is the first example of Hiyama cross coupling of an unactivated fluoroarene, a small scope of substrates were considered, focusing on unactivated fluoroaromatic compounds (Scheme 2). We found that Hiyama cross coupling of 2-fluoronapthalene to give the product **4** proceeded well (63%), however some unreacted 2-fluoronapthalene, as well as 2-methoxynapthalene, was observed. Surprisingly, when using 2-fluorobiphenyl and 4-fluorobiphenyl lower yields of the cross-coupled products **5** (15%) and **6** (<5%) were observed, with mainly unreacted starting material remaining. The higher reactivity of 2-fluorobiphenyl compared to 4-fluorobiphenyl suggests that steric bulk promotes cross coupling.



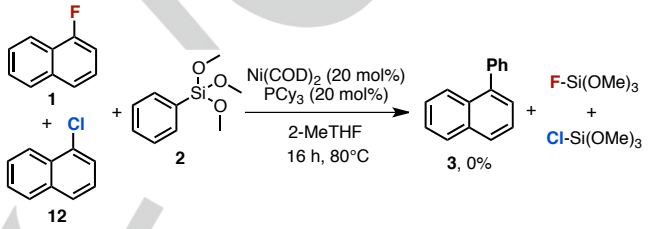
Scheme 2: Scope of the nickel catalysed, base free Hiyama cross coupling of fluoroaromatic compounds and trimethoxyphenylsilane **2**. *Reaction conditions: Fluoroarene (1 mmol), trimethoxyphenylsilane **2** (2 mmol), Ni(COD)$_2$ (0.2 mmol), PCy$_3$ (0.2 mmol) and solvent (3 mL). Isolated yields are reported, unless otherwise stated. [a]Reaction performed using PAd$_2$Bu (0.8 mmol), instead of PCy$_3$. [b]Yield determined by ^{19}F NMR, using 4-trifluoromethoxyanisole as internal standard. [c]Yield determined by ^{1}H NMR, using 4-trifluoromethoxyanisole as internal standard.*

As phenyl-based fluoroaromatic compounds will be considered in the chemoselectivity section of this manuscript, we sought to increase conversion of 4-fluorobiphenyl to the product **6** by using a different ligand. We found that the more bulky ligand di(1-adamantyl)-*n*-butylphosphine (PAd$_2$Bu) could effectively promote cross coupling, giving the product **6** in 25% isolated yield. The effectiveness of this more bulky ligand, relative to PCy$_3$, further suggests that increased steric bulk favours cross coupling, likely due to promotion of the reductive elimination step. Interestingly, when using an activated pyridine-based substrate low yields of the cross coupled product **7** was observed, with a significant amount of homo-coupling detected. Lastly, a number of substituted napthalenes were considered, with good yields of the products **8**-**11** observed, highlighting that electron-donating groups are tolerated.

With this protocol now in hand, we then moved onto the main focus of this work – studies towards the development of a selective C-F over C-Cl cross coupling protocol. The key proof of principle experiment, where 1-chloronapthalene **12** was used in place of 1-fluoronapthalene **1**, was performed. To our delight, we found that the product **3** did not form when 1-chloronapthalene **12** was used (Scheme 3), which is strong evidence of the divergent reactivity of the generated Ni-F and Ni-Cl intermediates. That is, the Ni-F intermediate will undergo direct transmetalation with the silane **2**, whereas the analogous Ni-Cl intermediate will be unreactive. While this is proof that the proposed transmetalation based selectivity approach is feasible, it is necessary for this selectivity to hold when both C-F and C-Cl groups are present. Unfortunately, in the competition experiment between 1-fluoronapthalene **1** and 1-chloronapthalene **12**, no product formation was observed (Scheme 4). Analysis of the crude reaction mixture by GC-MS indicated that only unreacted starting materials remained, with ^{19}F NMR spectroscopic analysis finding that >95% of 1-fluoronapthalene **1** was still present (relative to the internal standard 4-trifluoromethoxyanisole).



Scheme 3: The key control reaction with 1-chloronapthalene **12**, highlighting that cross coupling only occurs at C-F, not at C-Cl, under the developed conditions.



Scheme 4: The competition experiment between 1-fluoronapthalene **1** and 1-chloronapthalene **12**, where no cross coupling is observed.

To provide insight into the reaction mechanism, and to probe the origin of the observed reaction inhibition when both C-F and C-Cl are present, we turned to Density Functional Theory (DFT) calculations. All calculations were performed using Gaussian 16,[13] with geometry optimisations and frequency calculations performed using the ωB97X-D level of theory with the 6-31G (d) basis set for H, C, P, O, N, F and Cl, and the SDD basis set for Ni and Si. Single point energy calculations were performed using the M06L level of theory and the def2TZVP basis set, with the CPCM model used to incorporate the implicit solvent effects of THF (see the Supporting Information for more details, and testing of other computational methods). Our experimental data suggest that a less bulky NiPCy$_3$, not Ni(PCy$_3$)$_2$, based species is the active catalyst, thus a typical 3-centred oxidative addition transition state is likely.[14] Moreover, as no P-F formation was observed experimentally, ligand-assisted oxidative addition can be excluded,[15] and as no homo-coupling was observed, the formation of a Ni(I) species is unlikely.[10] Thus, in our DFT studies, 3-centered oxidative addition transition states were considered, which is consistent with that frequently reported for Ni catalysed oxidative addition of C(sp^2) electrophiles.[11b, 15-16]

Comparing the reaction profiles for Hiyama cross coupling at the C-F and C-Cl sites (Figure 2), it is clear that oxidative addition at C-Cl is favoured over C-F, as expected based on the reported rate constants for oxidative addition of different electrophiles to nickel.[10] Interestingly, two different transition states were located - one that involves explicit 2-MeTHF coordination, and one that does not. For the transition states that involve explicit 2-MeTHF coordination, the barriers for C-F and C-Cl oxidative addition were 28.4 and 8.0 kcal mol^{-1}, respectively. When considering the transition states that do not

involve 2-MeTHF coordination, the barrier for C-Cl oxidative addition is unchanged (8.2 kcal mol^{-1}), however there is a significant decrease in the barrier for C-F oxidative addition (23.8 kcal mol^{-1}). The differences in the Gibbs free energy for oxidative addition when considering the two transition states suggest that direct solvent coordination does not affect C-Cl oxidative addition, yet disfavours oxidative addition at C-F. As such, use of non-coordinating solvents may be a useful tool to help promote selective C-F activation.

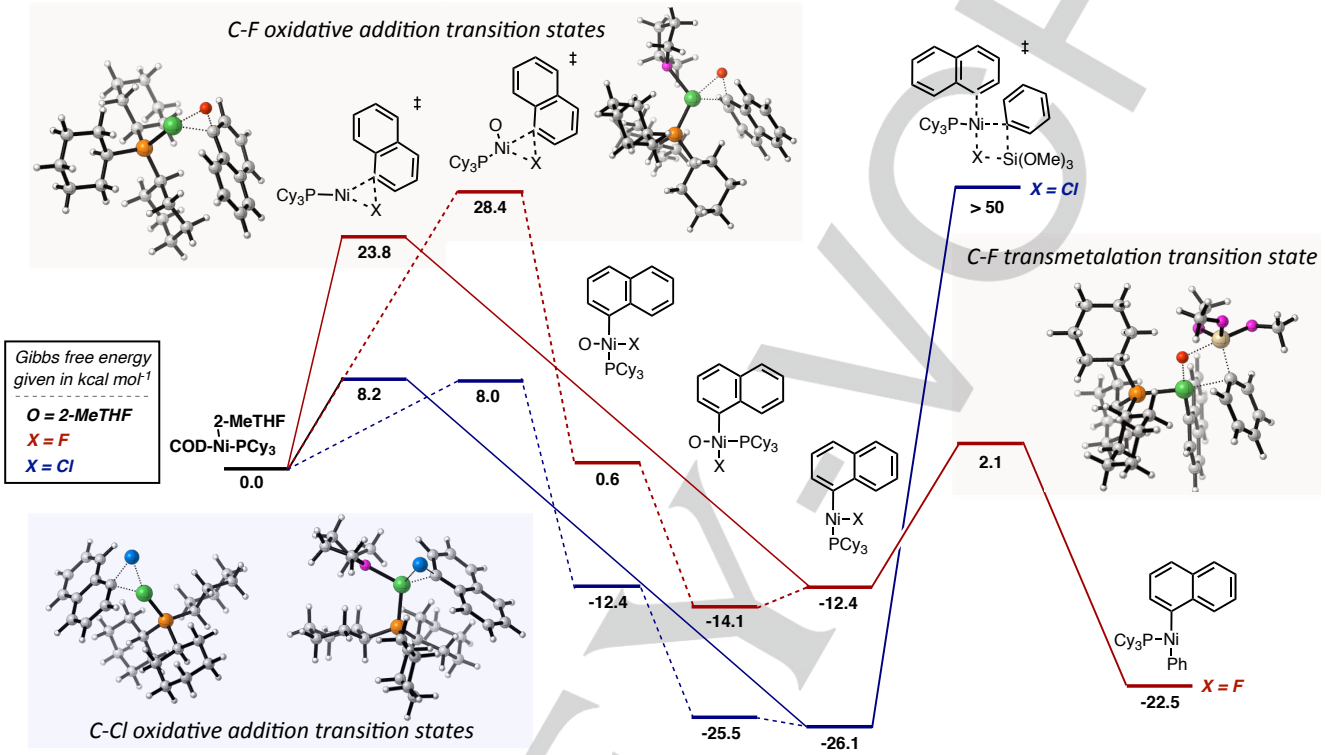


Figure 2: The calculated reaction profiles for the Hiyama cross coupling reaction between trimethoxyphenylsilane **2** and either 1-fluoronapthalene **1** (red) or 1-chloronapthalene **12** (blue), focusing on the key oxidative addition and transmetalation steps. CPCM (THF) M06L/def2TZVP//ωB97X-D/6-31G(d)+SDD, Gibbs free energy given in kcal mol^{-1}.

Following oxidative addition, a number of different intermediates could form. For the intermediates that feature direct 2-MeTHF coordination, the lowest energy species for both Ni-F and Ni-Cl have the naphthalene and halide moieties *trans* to each other. Prior to transmetalation the 2-MeTHF molecule will likely dissociate to form the three coordinate naphthalene-Ni-halide species.

A significant difference between the 1-fluoronapthalene **1** and 1- chloronapthalene **12** reaction pathways was observed at the transmetalation step; while a low energy transition state could be located for the Ni-F analogue, no low energy transition state could be located for direct transmetalation with the Ni-Cl intermediate. This is in agreement with previous computational[17] and experimental[4a] studies on direct transmetalation at metal-halide intermediates, and suggests that the barrier for direct transmetalation at the generated Ni-Cl intermediate is very high. This computational data further supports the conclusion from our experimental work – that base free Hiyama cross coupling cannot occur for 1- chloronapthalene **12** due to the challenging transmetalation step.

The reaction profiles also provide key insights into the origin of the experimentally observed reaction inhibition when both C-Cl and C-F are present. While the only productive cross coupling pathway begins with oxidative addition at C-F, the competing oxidative addition at C-Cl will lead to the very stable Ni-Cl intermediate (-26.1 kcal mol^{-1}). Under the developed reaction conditions, it is likely that formation of the Ni-Cl intermediate is irreversible, thus the nickel catalyst gets trapped as the Ni-Cl intermediate, inhibiting cross coupling. As such, to achieve chemoselective cross coupling at C-F, oxidative addition at C-Cl needs to be reversible. To examine how to promote reversible oxidative addition at C-Cl, a series of ligands were investigated (Figure 3). This is particularly important as there is a growing interest in harnessing reversible oxidative addition to develop unique reactivity,[18] thus further insight into ligand effects on reversibility is needed. In addition, there is precedent for reversible oxidative addition at Ni allowing the higher energy reaction pathway to be followed, leading to selective product formation.[18e] As such, achieving selective C-F over C-Cl functionalisation is feasible if the C-Cl oxidation addition step is reversible.

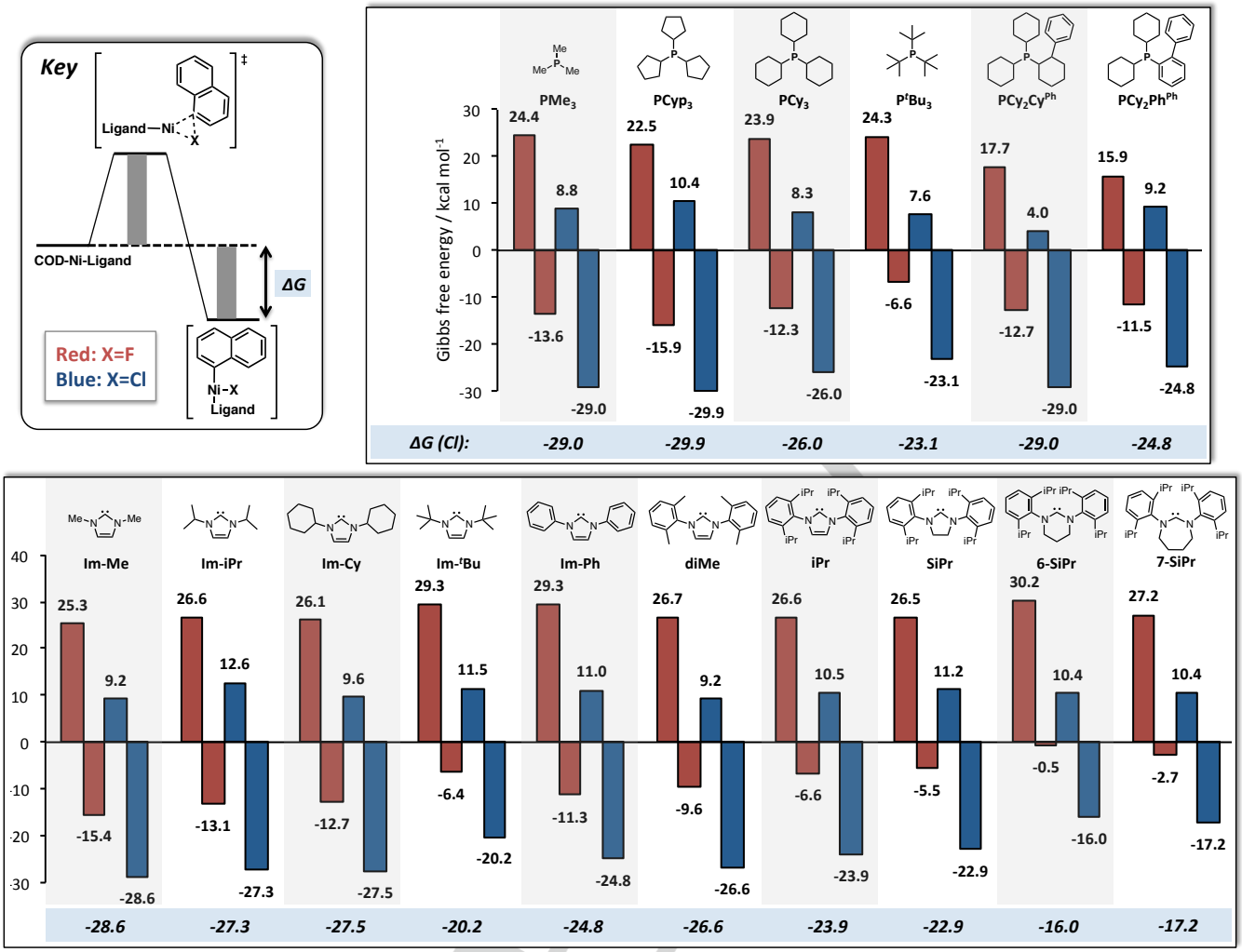


Figure 3: Assessment of the ability of a range of Ni-ligand species to promote oxidative additive at either 1-fluoronapthalene **1** (red) or 1-chloronapthalene **12** (blue), with a focus on the potential for reversible C-Cl oxidative addition. CPCM (THF) M06L/def2TZVP//ωB97X-D/6-31G(d)+SDD, Gibbs free energy given in kcal mol^{-1}.

In this section, the focus was on understanding how the ligand affects the relative barriers for oxidative addition at C-F and C-Cl, as well as the stability of the generated Ni-Cl intermediate. Of particular importance was the potential for reversible C-Cl oxidative addition, which can be assessed by comparing the energy difference between the Ni-Cl intermediate and the resting state of the catalyst (ΔG(Cl), see Figure 3 '*Key*'). A negative value indicates that the Ni-Cl intermediate is more stable than the catalyst ground state. As such, as this value becomes less negative (and ideally, positive), the potential for reversible oxidative addition increases. It should be noted that the true nature of the catalyst resting state would play a key role in determining whether oxidative addition is reversible. For example, when using multiple equivalents of ligand a more stable Ni complex may form, which would make reversible oxidative addition more likely as ΔG(Cl) will be less negative. However, for consistency, in all calculations the resting state of the catalyst was the ligand-Ni-COD species, and the oxidation addition transition states did not involve explicit 2-MeTHF coordination.

To begin with, the ligands PMe_3, $PCyp_3$, PCy_3 and P^tBu_3 were examined (Figure 3). These ligands were chosen as they have comparable sigma donating abilities, yet highly varied steric bulk. Interestingly, it was found that, in general, the barrier for oxidative addition at C-Cl decreases with increasing steric bulk, with the best ligand being P^tBu_3. In contrast, less bulky ligands were generally favoured for C-F oxidative addition, with $PCyp_3$ being most effective. In terms of Ni-halide intermediate stability, as the steric bulk on the ligand increases, both the Ni-F and Ni-Cl intermediates become less stable. This is important, as it indicates that the potential for reversible oxidative addition increases with greater steric bulk on the ligand. This effect can be clearly seen when comparing the difference in energy between the ground state catalyst and the Ni-Cl intermediate (ΔG(Cl)): the PMe_3 and $PCyp_3$ ligands have the most negative ΔG(Cl) (-29.0 and -29.9 kcal mol^{-1}, respectively), and the P^tBu_3 ligand has the least negative ΔG(Cl) of -23.1 kcal mol^{-1}. As such,

in this series the P^{t}Bu$_3$ ligand is most likely to facilitate selective cross coupling at C-F over C-Cl.

In the initial development of our base-free Hiyama cross coupling reaction we found that use of Ni(COD)$_2$ with P^{t}Bu$_3$ was ineffective at promoting cross coupling (Table 1), which is consistent with the ineffectiveness of bulky phosphines in nickel catalysis observed previously.[19] However, considering the potential of this ligand to promote reversible oxidative addition at C-Cl, we re-visited the use of P^{t}Bu$_3$. Unfortunately, even after a thorough investigation of different reaction conditions when using Ni-P^{t}Bu$_3$ or Pd-P^{t}Bu$_3$ based catalysts, no cross coupling between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2** was ever observed (Tables S7, S8, S9 and S10). These results highlight a key challenge we have encountered: fluoroarene cross coupling does not proceed when the ligand is too bulky, however reversible C-Cl oxidative addition requires a bulky ligand. These contradicting requirements make the development of the desired chemoselective C-F over C-Cl functionalisation protocol very difficult.

Despite this challenge, we examined a more diverse range of ligands using DFT, to probe their potential for promoting chemoselective C-F cross coupling. Considering the widespread use of biarylphosphine-type ligands for chloroarene cross coupling reactions,[12] we next examined PCy$_3$ and PCy$_2$Ph derivatives with an *ortho* phenyl substituent (PCy$_2$Cy^{Ph} and PCy$_2$Ph^{Ph}, respectively). We were particularly interested in examining how potential interactions between the phenyl substituent and the Ni centre affect the oxidative addition transition states and Ni-halide intermediate stability. It was found that there was a significant decrease in the barrier for both C-F and C-Cl oxidative addition when using PCy$_2$Cy^{Ph} and PCy$_2$Ph^{Ph}, relative to PCy$_3$ (Figure 3). This is likely due to favourable Ph-Ni interactions, as can be seen in both the C-F and C-Cl oxidative addition transition states (see Figure 4 for the PCy$_2$Ph^{Ph} analogues). However, the Ni-halide intermediates had similar stability to the PCy$_3$ analogues, with ΔG(Cl) ranging between -24.8 to -29.0 kcal mol^{-1} for this series. As such, PCy$_2$Cy^{Ph} and PCy$_2$Ph^{Ph} are unlikely to be able to promote selective C-F functionalisation, in the presence of C-Cl.

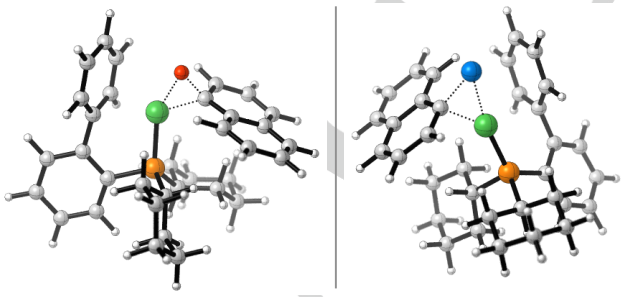


Figure 4: The calculated transition states for oxidative addition of either 1-fluoronapthalene **1** (left) or 1-chloronapthalene **12** (right) to Ni-PCy$_2$Ph^{Ph}.

Considering that use of an electron-rich ligand is likely key to achieving C-F functionalisation, we next examined a range of *N*-heterocyclic carbene ligands, as variation of the *N*-substituent allows fine-tuning of steric bulk. To begin with, simple alkyl substituted carbenes were considered (Im-Me, Im-^{i}Pr, Im-Cy and Im-^{t}Bu, Figure 3). As expected based on the phosphine series, it was found that, in general, bulkier substituents on the carbene ligand destabilised the Ni-halide intermediates, with the Im-^{t}Bu ligand having the least negative ΔG(Cl) of -20.2 kcal mol^{-1}. However, experimental tests using Im-^{t}Bu found that this ligand was unable to promote cross coupling between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2**, with only 0-5% yield of the product **3** observed under the conditions examined (Table S11).

We next moved to aryl substituted *N*-heterocyclic carbene ligands, as these can allow increased steric bulk around the Ni centre to be introduced. In our computational analyses of the phenyl-substituted *N*-heterocyclic carbene series Im-Ph, diMe and iPr (Figure 3), it was surprising to see that the inclusion of *ortho* substituents on the phenyl ring had little effect on the potential for reversibility, with all ligands having ΔG(Cl) within -23.9 to -26.6 kcal mol^{-1}. The data for the iPr and SiPr ligands were also very similar, suggesting that saturation of the backbone of the imidazolium ring has little effect on the energy of the oxidative addition transition states, or the Ni-halide intermediates.

As steric bulk around the Ni centre will likely increase the potential for C-Cl reversibility, the ring expanded carbenes 6-SiPr and 7-SiPr were considered next. It was found that there was a significant difference in ΔG(Cl) between SiPr and 6-SiPr (-22.9 and -16.0 kcal mol^{-1}, respectively), due to destabilisation of the Ni-Cl intermediate when moving from SiPr to 6-SiPr. Interestingly, there were only minor changes in ΔG(Cl) when moving from 6-SiPr to the ring expanded 7-SiPr analogue, likely due to the buckling of the 7-membered ring to reduce steric congestion around the NCN centre.

Overall, based on the computational data for the aryl substituted *N*-heterocyclic carbene ligands, the 6-SiPr ligand has the greatest potential for promoting chemoselective C-F over C-Cl cross coupling. As such, the 6-SiPr ligand was synthesised, along with the iPr and SiPr ligands for comparison (see Supporting Information for details). We also examined the commonly used IMes ligand as an additional comparison. We first performed a series of optimisation reactions to refine the developed reaction conditions so that cross coupling between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2** would occur (Table S11). We found that while iPr and SiPr could promote cross coupling between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2** in good yields (62% and 58%, respectively, see Table S11), no product **3** formation occurred when both 1-fluoronapthalene **1** and 1-chloronapthalene **12** were present in the reaction mixture (Table S12). In contrast, the IMes ligand was ineffective at promoting cross coupling between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2**, with <5% conversion to the product **3** observed (Table S11). This difference in activity between the iPr and iMes ligands suggests that the *ortho* isopropyl groups on the ligand are important for promoting fluoroarene cross coupling.

Experimental studies on the key 6-SiPr ligand found that this species was also ineffective at promoting cross coupling between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2** (<1% product **3** formed). As such, the ability of the 6-SiPr ligand

to facilitate chemoselective C-F over C-Cl functionalisation was unable to be properly investigated. This parallels our results from the P^{t}Bu$_3$ ligand – while ligand bulk increases the potential for reversible oxidative addition at C-Cl, ligands that are too bulky are not able to facilitate nickel catalysed cross coupling between 1-fluoronapthalene **1** and the silane **2** (Figure 5).

As an additional investigation into chemoselective C-F functionalisation, the ligands PCy$_2$^{t}Bu and PAd$_2$Bu were examined experimentally (Figure 5). These asymmetric phosphine ligands were chosen as they are more sterically congested than PCy$_3$, however less crowded than P*t*Bu$_3$, and therefore might lie in the 'sweet-spot' of steric congestion to allow both C-F cross coupling and C-Cl reversibility to occur. Through analysis of a range of reaction conditions it was found that both PCy$_2$^{t}Bu and PAd$_2$Bu promote cross coupling between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2** in high yields (85% and 92%, respectively, see Table S7), highlighting that these bulky phosphine ligands are excellent at promoting fluoroarene cross coupling. For the bulky ligand PCy$_2$^{t}Bu it was found that toluene was a more effective solvent than 2-MeTHF – for example, when using a Ni to ligand ratio of 1:4, use of toluene led to 85% of the product **3**, whereas use of 2-MeTHF only gave 54% of the product **3** (Table S7). This data supports the conclusions from our DFT analyses – that use of non-coordinating solvents may increase fluoroarene cross coupling through decreasing the barrier for oxidative addition. We next performed competition experiments between 1-fluoronapthalene **1** and 1-chloronapthalene **12** using the ligands PCy$_2$^{t}Bu and PAd$_2$Bu. For all of the conditions examined, cross coupling was inhibited when 1-chloronapthalene **12** was added to the reaction mixture, with only unreacted starting materials present in the mixture (Table S10). As it has been previously demonstrated that excess ligand can help promote reversible oxidative addition,[18f] nickel to ligand ratios of 1:2, 1:4 and 1:8 were also examined. However, in all cases no formation of the cross coupling product **3** was observed when 1-chloronapthalene **12** was present (Figure 5).

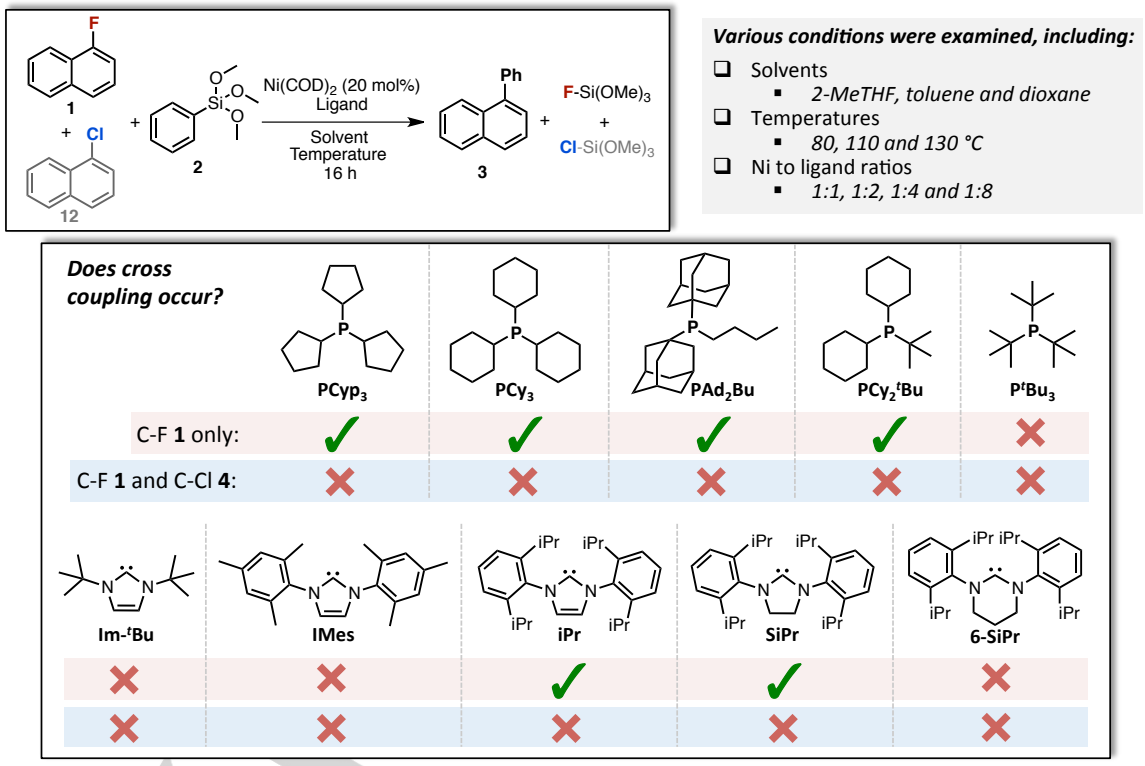


Figure 5: Summary of the results of the experimental investigations into the base-free Hiyama cross coupling reaction between 1-fluoronapthalene **1** and trimethoxyphenylsilane **2** when different ligands are used. See the Supporting Information for further details, and the specific reaction conditions examined.

Lastly, a number of fluoroarenes that feature a competing cross coupling site were considered (Figure 6, compounds **14**-**20**). In this section we used reaction conditions identified as being most promising for promoting chemoselective C-F functionalisation (see Tables S7-S12), focusing on the ligands PCy$_2$^{t}Bu, PAd$_2$Bu and iPr. Initially, the control compound 4-fluorobiphenyl **13** was tested to confirm that C-F cross coupling can occur under these reaction conditions, as the majority of compounds **14**-**20** are phenyl-based (not napthyl). Under the three sets of reaction conditions examined (Figure 6) the desired product **6** formed in relatively low yields (10-35%, see Table S13). Despite these lower yields, this data confirms that fluoroarene cross coupling can occur with compound **13** under the reaction conditions considered, and thus the competition experiments with compounds **14**-**20** are valid.

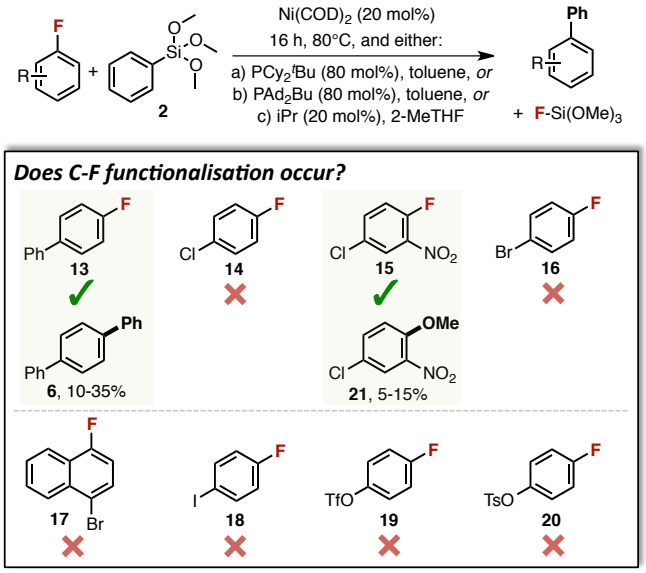


Figure 6: Competition experiments using fluoroarenes that feature an additional site for cross coupling. Ts = p-toluenesulfonyl, and Tf = trifluoromethanesulfonyl. See Table S13 for additional data.

To begin with, compounds **14** and **15** were considered, as they both feature a competing C-Cl site. No cross coupling was observed for 1-chloro-4-fluorobenzene **14**, with GC-MS analysis of the crude reaction mixture indicating that mainly unreacted starting material was present, as well as a small amount (<5%) of 4,4'-difluoro-1,1'-biphenyl, which would arise from homo-coupling at the C-Cl site. Pleasingly, for 4-chloro-1-fluoro-2-nitrobenzene **15** chemoselective C-F functionalisation was observed, however the *methoxy* based product **21** formed. While this highlights that selective functionalisation at C-F is possible, the desired cross coupling pathway leading to *phenyl* group incorporation did not occur. In addition, the *nitro* substituent on compound **15** is likely activating the C-F bond, which would bias C-F functionalisation.

Compounds **16**-**20** performed similar to 1-chloro-4-fluorobenzene **14**, with no fluoroarene cross coupling observed. The main species present in the crude reaction mixtures were unreacted starting materials, however homo-coupling was observed in varying amounts for compounds **15**-**19** (5-50%, see Table S13). Interesting, no 4,4'-difluoro-1,1'-biphenyl was observed for compound **20**, suggesting that homo-coupling does not occur as readily at the C-OTs bond (where Ts = *p*-toluenesulfonyl).

Conclusions

In summary, we have developed the first example of base free Hiyama cross coupling of unactivated fluoroarenes. This is important as it highlights that efficient, mono-metallic C-F activation can be achieved under relatively mild conditions using nickel catalysis, with a number of phosphine and carbene ligands shown to be effective. In general, bulky and electron rich ligands are required, however there is a limit to the steric bulk tolerated, with the bulky P^{t}Bu$_3$ and 6-SiPr ligands unable to promote cross coupling. The mechanistic insight we have provided into mono-metallic C-F activation lays the groundwork for developing effective Suzuki and Hiyama fluoroarene cross coupling methodology. Many of the current C-F functionalisation protocols involve bimetallic C-F activation through the use of nucleophillic organomagnesium or organozinc cross coupling partners. As such, greater functional group tolerance may be achieved through the use of milder boronic acid or silane reagents.

We have also demonstrated that the divergent reactivity of Ni-Cl and Ni-F intermediates could permit selective, transmetalation controlled C-F functionalisation, with chloroarene cross coupling ineffective under the developed base-free conditions. However, reversible oxidative addition at the C-Cl position is needed for chemoselective C-F functionalisation to be realised. Detailed computational and experimental studies provided valuable insight into ligand effects on the barriers for oxidative addition and the stability of the generated Ni-halide intermediates. In general, the Ni-halide intermediates become less stable when the ligand gets more bulky, with the 6-SiPr, 7-SiPr, Im-^{t}Bu and P^{t}Bu$_3$ ligands found to be the most promising candidates for promoting reversible C-Cl oxidative addition. A key challenge we encountered is that fluoroarene cross coupling does not proceed when the ligand is too bulky, however destabilisation of the Ni-Cl intermediate requires a very bulky ligand. These contradicting requirements make the development of the desired chemoselective C-F over C-Cl functionalisation protocol challenging. In future work, alternative approaches to destabilising the Ni-Cl intermediate will be explored, such as the design of new ligands or the use of destabilising additives.

Experimental Section

See the Supporting Information for all experimental details, additional catalytic data and control experiments.

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Keywords: chemoselectivity • DFT • C-F activation • reversibility • mechanism

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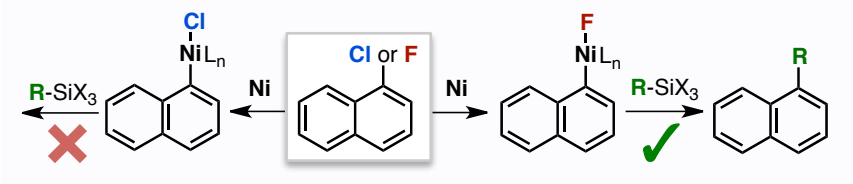

Base-free Hiyama cross coupling of unactivated fluoroarenes was developed, demonstrating that efficient, mono-metallic C-F activation can be achieved using nickel catalysis. Experimental and computational investigations into the potential for selective C-F cross coupling in the presence of more active C-halides were performed, highlighting that transmetalation-controlled C-F selectivity may be possible if reversible oxidative addition can be achieved.

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