# Nickel-mediated trifluoromethylation of phenol derivatives via C−O bond activation

**Wei-Qiang Hu,[1] Shen Pan,[1] Xiu-Hua Xu,[1] David A. Vicic,[3] Feng-Ling Qing[1,2]***

[1]Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

[2]College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

[3]Department of Chemistry, Lehigh University, 6 E. Packer Avenue, Bethlehem, Pennsylvania 18015, United States

*Correspondence to: flq@mail.sioc.ac.cn

**Abstract:**

The increasing pharmaceutical importance of trifluoromethylarenes has stimulated the development of more efficient trifluoromethylation reaction. Tremendous efforts have focused on copper- and palladium-mediated/catalyzed trifluoromethylation of aryl halides. In contrast, no general method exists for the conversion of widely available inert electrophiles, such as phenol derivatives, into the corresponding trifluoromethylated arenes. We report herein a practical nickel-mediated trifluoromethylation of phenol derivatives with readily available trimethyl(trifluoromethyl)silane. The strategy relies on $PMe_3$-promoted oxidative addition and transmetalation, and $CCl_3CN$-induced reductive elimination. The broad utility of this transformation has been demonstrated through the direct incorporation of $CF_3$ to aromatic and heteroaromatic systems including bio-relevant compounds.

**One Sentence Summary:**

The transformation of abundant yet inert phenol derivatives to valuable trifluoromethylarenes was achieved for the first time.

**Main Text:**

Over the past few decades, transition metal-mediated/catalyzed cross-coupling reactions have emerged as one of the most significant and powerful methodologies for carbon−carbon and carbon−heteroatom bond formation in organic and medicinal chemistry, as exemplified by the 2010 Nobel Prize in chemistry *(1-3)*. Normally, aryl halides are used as the electrophilic coupling partners due to their relatively high reactivity. Recently, intensive efforts have focused on the use of more abundant, yet more inert, electrophiles in place of aryl halides. Among such derivatives, oxygen-based electrophiles such as phenols have garnered considerable attention because of the abundance of phenols in nature and the ease of which their structures and electronics can be tuned. To date, a variety of nucleophiles, including organoboron, organozinc, organolithium, hydride, amine, and carbon nucleophiles have been employed in the coupling reactions with phenol-derived electrophiles *(4-8)*. However, the generation of valuable trifluoromethylated and fluoroalkylated arenes from phenol electrophiles is unknown.

Trifluoromethylarenes are important structural motifs in pharmaceuticals and agrochemicals due to the enhancement of metabolic stability, lipophilicity, and bioavailability upon the introduction of the trifluoromethyl group ($CF_3$-) *(9)*. For instance, four trifluoromethylarene-containing drugs were approved by FDA in 2018 (Figure 1A) *(10)*. Transition-metal assisted trifluoromethylation reactions have become the most important approaches to trifluoromethylarenes *(11)*. Notably, new breakthroughs have rapidly emerged for synthesis of trifluoromethylarenes in the last decade, including copper-, palladium-, or silver-mediated/catalyzed trifluoromethylation of aryl iodides (*12*), aryl chlorides (*13*), aryl bromides (*14*), aromatic C−H bonds *(15, 16)*, arylboronic acids *(17, 18)*, aryldiazonium salts *(19-21)*, diaryliodonium salts *(22)*, and aryl thianthrenium salts *(23)* (Figure 1B). Despite these impressive achievements, the cross-coupling of abundant phenol-based electrophiles with trifluoromethylating reagents has not yet been reported and remains a formidable challenge in synthetic chemistry.

Nickel is an earth-abundant metal that has been extensively used in cross-coupling reactions, and can mediate chemical bond forming reactions that are difficult with palladium or copper *(4-8, 24)*. However, nickel-promoted trifluoromethylation reactions are less developed, in sharp contrast to the well-documented copper-, palladium-, and silver-assisted variations (Figure 1B) (*11-23*). Only very recently have nickel-mediated *(25)* and -catalyzed *(26)* C−H trifluoromethylation of arenes using $Ni^{IV}$-$CF_3$ complexes as $CF_3$ radical sources been reported. If a nickel-mediated trifluoromethylation of phenol derivatives could be achieved, the reaction would provide not only the first examples of $C_{aryl}$−O bond trifluoromethylation, but also a general and practical nickel-promoted trifluoromethylation cross-coupling protocol that would significantly impact the discovery fields (Figure 1C).

We imagined that a $C_{aryl}$−O bond trifluoromethylation of phenolic substrates would involve the eventual generation of (aryl)$Ni^{II}(CF_3)$ intermediates. Such (aryl)$Ni^{II}(CF_3)$ complexes supported by ligands (**II,** Figure 1C**)** are known to be stable and isolable. In 2008, Vicic originally reported that a variety of (dippe)Ni(aryl)($CF_3$) complexes (**II**) were prepared from the transmetalation of (dippe)Ni(aryl)(Br) complexes with $TMSCF_3$ (*27*). However, the reductive elimination of Ar−$CF_3$ from (dippe)Ni(aryl)($CF_3$) has been shown to be unfeasible (*27-30*). Later, Sanford and co-workers prepared the high valent $ArNi^{IV}CF_3$ and $ArNi^{III}CF_3$ complexes supported by tris(pyrazolyl)borate *(31, 32)*, and demonstrated that the high valent $ArNiCF_3$ complexes underwent reductive elimination for the formation of $ArCF_3$ (*31-34*). Notably, in some high valent $ArNiCF_3$ complexes, $CF_3$ only served as a ligand and the reductive elimination did not yield $ArCF_3$ *(35, 36)*. Based on the above considerations, the transmetalation of (aryl)$ArNi^{II}$(OR) complex (**I**) (Figure 1C**)** for the formation of (aryl)$Ni^{II}(CF_3)$ derivatives (**II**), followed by the reductive elimination of aryl-$CF_3$ would be the key reactions required for the successful nickel-mediated trifluoromethylation of phenol derivatives.

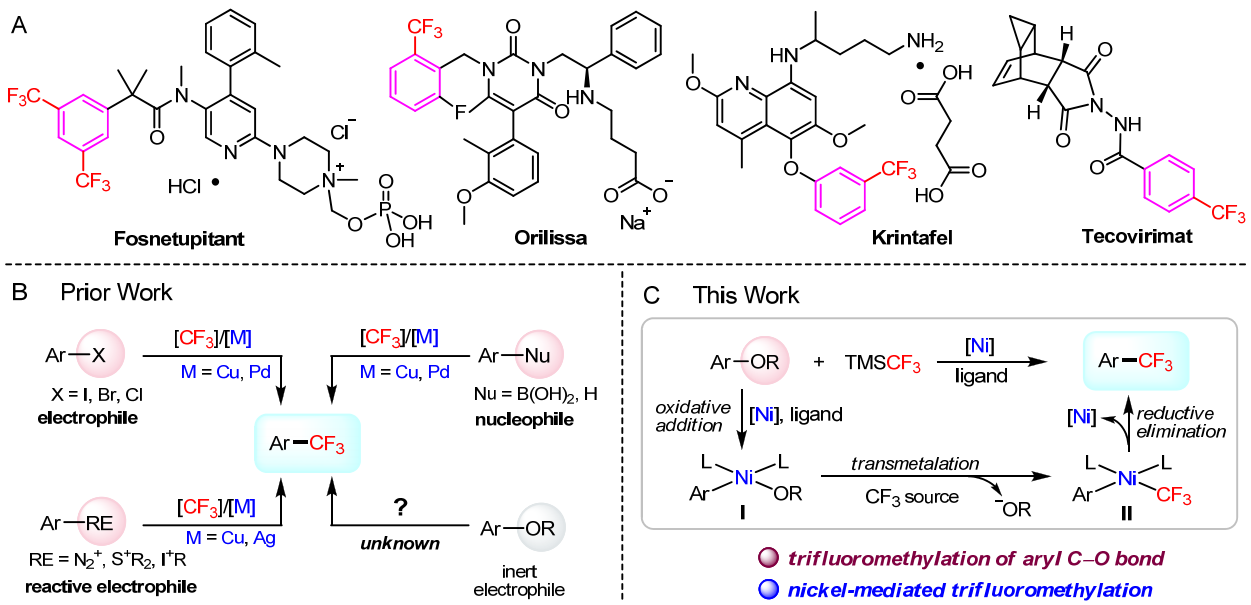


**Fig. 1. Transition-metal promoted cross-coupling trifluoromethylation of aromatic compounds**. (**A**) Four trifluoromethylarene-containing drugs approved by FDA in 2018. (**B**) Cu-, Pd-, and Ag-assisted trifluoromethylation of aromatic substrates. (**C**) Ni-mediated trifluoromethylation of inert phenol derivatives.

We began our investigations by demonstrating that (dcype)Ni(2-Np)(OPiv) (**2**) could be derived from the activation of model substrate 2-NpOPiv (**1a**) with (dcype)Ni(COD) in toluene at 90 °C (*37*). Subsequently, we investigated the transmetalation of **2** with $TMSCF_3$ (Figure 2A). Compared to the previous known transmetalation of Ni−Br complexes with $CF_3$ sources (*27*), the transmetalation of aryl pivalates proved more challenging. The desired (dcype)Ni(2-Np)($CF_3$) (**3**) was formed only in 18% yield along with two byproducts (dcype)Ni($CF_3$)(OPiv) (**4**) in 4% yield and (dcype)Ni($CF_3$)$_2$ (**5**) in 3% yield from the reaction of **2** with 3.0 equiv. of $TMSCF_3$ in the presence of 1.2 equiv. of CsF in toluene (Figure 2A, entry 1). The GC-MS analysis of the reaction mixture indicated that **2** was mainly converted into naphthalene. The structures of trifluoromethyl nickel complexes **3** and **5** were confirmed by X-ray crystallography, whereas complex **4** was assigned by comparison of the NMR data with reported data (*38*). In the light of previous transmetalation mechanistic studies (*39-42*), the transmetalation of **2** with $TMSCF_3$ and MF (for M = Cs and Ag) probably proceeds through four-membered transition states **int-I** and **int-II** to afford complexes **3** and **4**, respectively. We envisioned that the cation effect might change the ratio of complexes **3** to **4**/**5**. Indeed, a notable cation effect of MF was observed. The

selectivity for the formation of **3** was significantly improved when $NBu_4F$ was used as the activator (Figure 2A, entry 3). Moreover, the yield of **3** could be increased by employing the less sterically hindered $NMe_4F$ instead of $NBu_4F$ (Figure 2A, entry 4).

To further improve the yield of the targeted (aryl)Ni($CF_3$) intermediate, we explored ligand effects. We attempted to synthesize complex **int-III** (Figure 2B) supported by $PMe_3$ instead of dcype through the reaction of **1a** with $Ni(COD)_2$ and $PMe_3$. However, this reaction failed to give **int-III**. Interestingly, **Int-III** was formed in nearly quantitative yield through ligand exchange of complex **2** with $PMe_3$ and the resulting reaction mixture could be used directly for transmetalation (Figure 2B) to give **3** in yields that were much higher than in the absence of any added $PMe_3$. Reaction of **Int-III** generated *in situ* with 3.0 equiv. of $TMSCF_3$ in the presence of 1.2 equiv. of $NMe_4F$ gave complex **3** in 98% yield (Figure 2B, entry 1), and the expected complex **int-IV** was not detected by $^{19}F$ or $^{31}P$ NMR spectroscopy. To our delight, the reaction of **2** with 1.2 equiv. of $TMSCF_3$ and 4.0 equiv. of $PMe_3$ without added $NMe_4F$ proceeded efficiently to afford **3** in 97% yield (Figure 2B, entry 3). Normally, the use of fluoride as the activator is required for the transmetalation with $TMSCF_3$. Conversion of **2** to **3** represents a rare example of a "fluoride-free" transmetalation with $TMSCF_3$.

Encouraged by the $PMe_3$-promoted highly efficient transmetalation of complex **2** with $TMSCF_3$ under mild reaction conditions, we next explored the direct conversion of substrate **1a** to **3**. Treatment of **1a** with 1.2 equiv of (dcype)Ni(COD) and 1.2 equiv of $TMSCF_3$ in the presence of 0.2 equiv of $PMe_3$ in toluene at 40 °C for 24 h afforded **3** in 95% yield (Figure 2C). Here, the nickel-mediated $C_{aryl}$–O bond activation occurred at a lower temperature than that in the absence of added $PMe_3$. This result shows that $PMe_3$ not only catalyzes the transmetalation reaction but also accelerates the oxidative addition of the aryl pivalate. The oxidative addition of **1a** with (dcype)Ni(COD), ligand exchange of **2** with $PMe_3$, transmetalation of **int-III** with $TMSCF_3$, and ligand exchange of **int-IV** with dcype were involved for the $PMe_3$-catalyzed direct transformation of **1a** to **3** (Figure 2C). Overall, the unique $PMe_3$-catalyzed direct preparation of $ArNi^{II}CF_3$ complex from ArOPiv features several advantages: 1) simple substrates and reagents; 2) mild reaction conditions; 3) excellent yield; and 4) superb chemoselectivity.

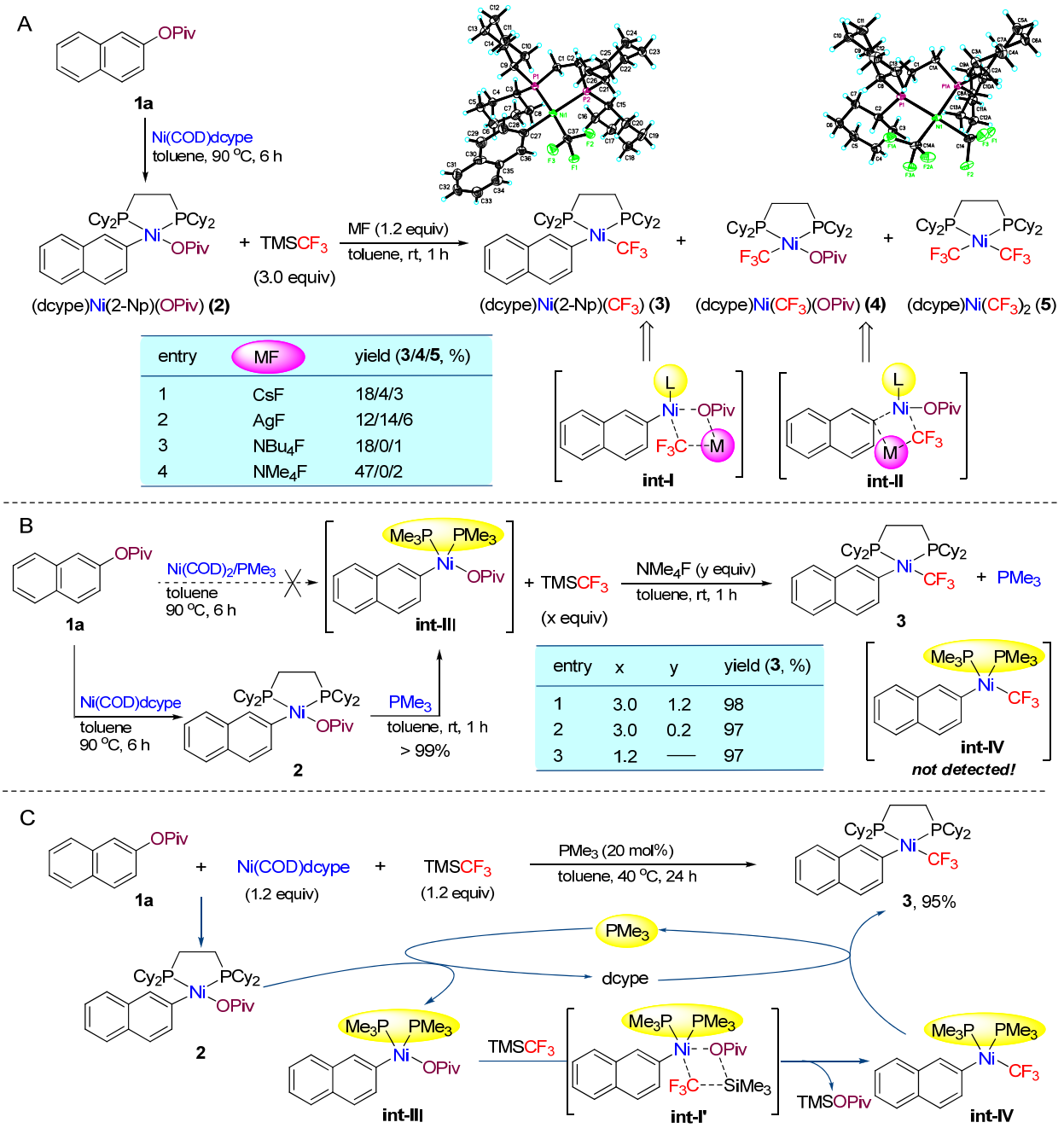


**Fig. 2. Transmetalation of ArNiOPiv with $TMSCF_3$.** (**A**) Preliminary investigations of transmetalation. (**B**) $PMe_3$-promoted transmetalation of **2** with $TMSCF_3$. (**C**) $PMe_3$-catalyzed direct conversion of **1a** to **3**. Piv, pivaloyl; COD, 1,5-cyclooctadiene; dcype, 1,2-bis(dicyclohexylphosphino)ethane; TMS, trimethylsilyl; Cy, cyclohexyl; Np, naphthyl; Me, methyl; Bu, butyl.

We next turned our attention to the reductive elimination of trifluoromethylated arene from (dcype)Ni(2-Np)($CF_3$) (**3**). Prior studies from Sanford *(31, 32, 35)* indicated that high valent $ArNi^{IV}CF_3$ and $ArNi^{III}CF_3$ complexes underwent facile Ar−$CF_3$ bond-forming reductive elimination. On the basis of these results, we probed the oxidatively-induced reductive elimination of **3** (Figure 3A). Sanford's studies have revealed that *S*-(trifluoromethyl)-dibenzothiophenium triflate (TDTT) and phenyliodine diacetate (PIDA) could enable the oxidation of $ArNi^{II}CF_3$ complexes to $ArNi^{IV}CF_3$ complexes. However, treatment of **3** with TDTT or PIDA in MeCN/THF afforded the reductive elimination product **6a** in trace yields (Figure 3A). Screening of different oxidants revealed that 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) promoted the reductive elimination efficiently, affording **6a** in 70% yield (Figure 3A). Considering the operational simplicity, we further examined other oxidants with toluene as the medium, which was used as the solvent for oxidative addition and transmetalation. To our delight, the electrophilic halogenating reagents *(43)*, such as *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), and *N*-fluorobenzenesulfonimide (NFSI) afforded **6a** in moderate yields. The unusual and mild electrophilic chlorinating reagent, $CCl_3CN$, was optimal for furnishing **6a** in 86% yield (Figure 3A). To the best of our knowledge, the unique property of $CCl_3CN$ for oxidizing Ni complexes has never been reported *(44)*. Thus, we carefully studied this $CCl_3CN$-induced reductive elimination of **3**. Besides the formation of the trifluoromethylarene **6a**, the reaction also delivered (dcype)$NiCl_2$ (**7**) in 93% yield. The structure of **7** was confirmed by X-ray crystallography (Figure 3B). The ESI-MS analysis of the reaction mixture indicated that a high valent $[(dcype)Ni^{IV}(2\text{-Np})(CF_3)(Cl)]^+$ (**int-III**) was generated (see Supporting Information). Furthermore, when the reaction was performed in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the TEMPO-$CF_3$ was formed (Figure 3C). This result demonstrated that $CF_3$ radical was generated in the reaction mixture, which was consistent with the previous reports that high valent $Ni^{III}CF_3$ and $Ni^{IV}CF_3$ complexes were prone to release $CF_3$ radical *(25, 26, 45)*. On the basis of the above experimental results, we hypothesized that $CCl_3CN$ served as a mild and effective oxidant for converting $ArNi^{II}CF_3$ to high valent $ArNiCF_3$ species, which subsequently underwent reductive elimination to afford 2-Np$CF_3$. To our surprise, the reaction of **3** and $CCl_3CN$ in the presence of 2,6-di-*tert*-butyl-4-methyphenol (BHT) afforded the desired **6a** and the unexpected chlorodifluoromethylated product **8** (Figure 3C). We assumed that product **8** was

formed through Ni difluorocarbene intermediates *(46, 47)*. Finally, we were pleased to find that the formation of compound **8** was inhibited when $NBu_4Cl$ was added to the reaction mixture. Furthermore, the yield of **6a** was improved from 86% to 93% in the presence of $NBu_4Cl$ (Figure 3C). Notably, this $CCl_3CN$-induced reductive elimination was also applicable to other $ArNi^{II}CF_3$ complexes (dppe)Ni(Ph)($CF_3$) (**9**) and (dtbpy)Ni(Ph)($CF_3$) (**10**), delivering the desired $PhCF_3$ in good yields (Figure 3D).

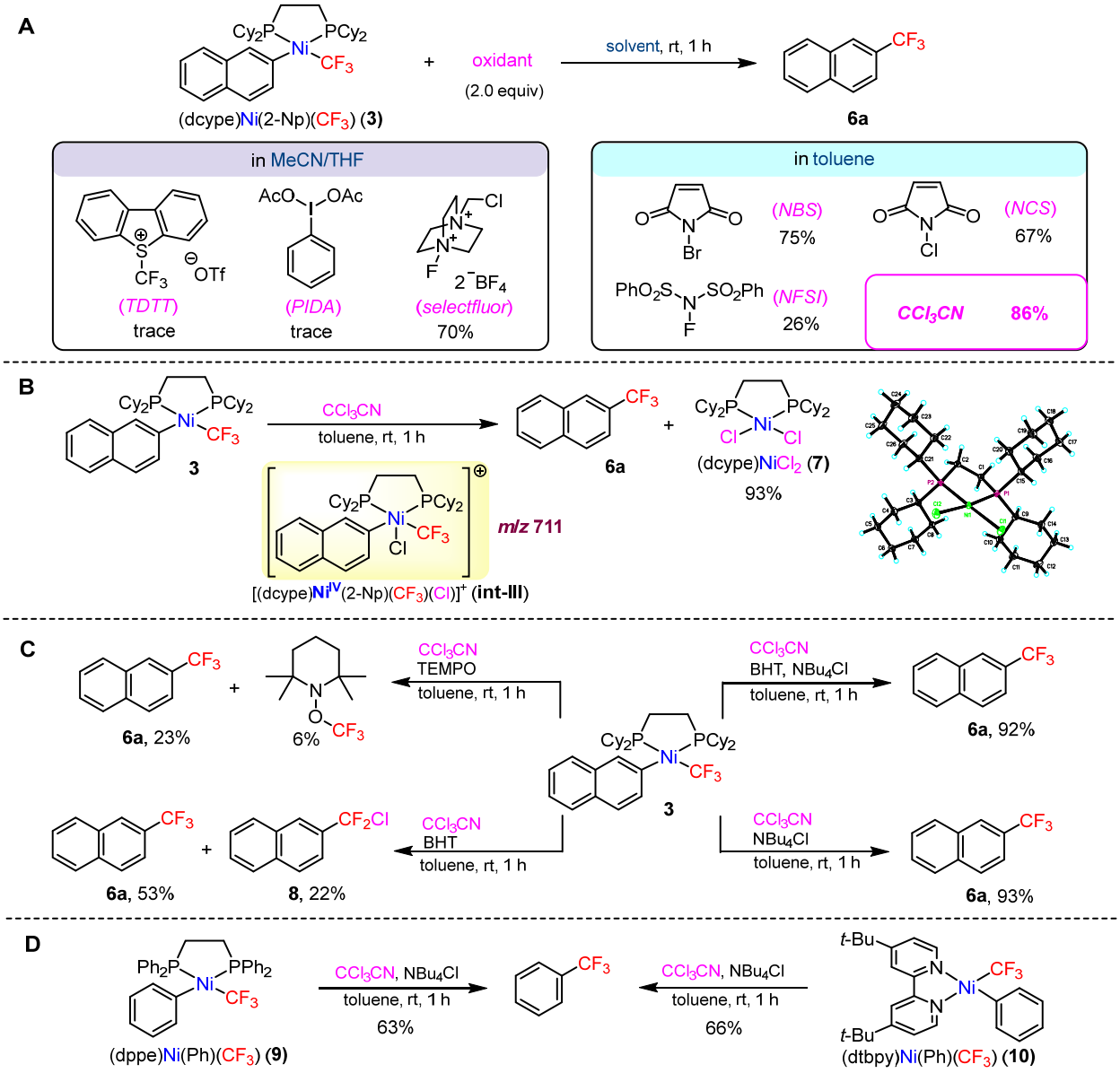


**Fig. 3. Oxidatively-induced reductive elimination.** (**A**) Screening of oxidants. (**B**) Trapping of the reaction intermediate. (**C**) Reductive elimination in the presence of TEMPO or BHT. (**D**) Reductive elimination of other $ArNi^{II}CF_3$ complexes. Ac, acetyl; THF, tetrahydrofuran; Ph,

phenyl; TEMPO, 2,2,6,6-tetramethylpiperidin-1-yl; BHT, 2,6-di-*tert*-butyl-4-methyphenol; dppe, 1,2-bis(diphenylphosphino)ethane; dtbpy, 4,4'-di-*tert*-butyl-2,2'-bipyridine; *t*-Bu, *tert*-butyl.

Having established the stepwise trifluoromethylation processes of 2-NpOPiv (**1a**), we then examined the one-pot conversion of 2-NpOPiv (**1a**) to 2-Np$CF_3$ (**6a**). Fortunately, treatment of **1a** with (dcype)Ni(COD), $TMSCF_3$, and $PMe_3$ in toluene at 40 ºC for 24 h followed by addition of $CCl_3CN$ and $NBu_4Cl$ at room temperature for 1h afforded **6a** in 93% isolated yield. This protocol was successfully extended to various aryl pivalates (Figure 4A). A variety of naphthyl pivalates (**1a**-**j**) possessing a diverse set of substitution patterns was efficiently transformed into the trifluoromethylated products. Both electron-donating and electron-withdrawing substitutions including alkyl (**1b**), alkoxy (**1c**,**d**), nitrile (**1e**), ketone (**1f**), and ester (**1g-i**) were well tolerated. Furthermore, heteroaromatic substrates such as quinoline (**1k**), indole (**1l**), benzofuran (**1m**), dibenzo[*b*,*d*]furan (**1n**), benzo[*b*]thiophene (**1o**), and dibenzo[*b*,*d*]thiophene (**1p**) were all compatible with this reaction. Normally, non-π-extended phenol derivatives are challenge substrates in C−O bond functionalization reactions *(6,7)*. We were pleased to find that a wide variety of simple phenyl pivalates (**1q-ab**) were competent substrates, providing the desired products in good yields. Likewise, aryl pivalates containing nitrile (**1w**), ketone (**1s**,**x**,**y**), and ester (**1z**) could be coupled with similar ease. Notably, *meta*- and *ortho*-substituted substrates (**1u**,**ab**) also furnished the desired products in moderate yields. Finally, the compatibility of this trifluoromethylation protocol with bio-relevant molecules was also examined. The trifluoromethylation of protected tyrosine (**1ac**), estrone (**1ad**), bisphenol FL (**1af**), alpinetin (**1ah**), and formonoetin (**1ai**) proceeded smoothly to deliver the corresponding products in moderate yields. Camptothecin (**1ae**), amiodarone (**1ag**), and fenofibrate (**1af**) analogues were readily converted to the trifluoromethylated products. These results clearly demonstrated the potential utility of the current protocol in late-stage functionalizations in medicinal or agrochemical research.

This nickel-promoted one-pot trifluoromethylation strategy was further extended to other phenol derivatives. For instance, treatment of a series of aryl esters under the standard reaction conditions afforded the desired product **6a** in moderate to good yields (Figure 4B). Notably, after the slight modification of reaction conditions, aryl cyanide **11** and aryl thioester **12** were also

converted to **6a** in moderate yields respectively (Figure 4C), which indicated the potential application of this protocol in trifluoromethylating other types of inert aryl electrophiles.

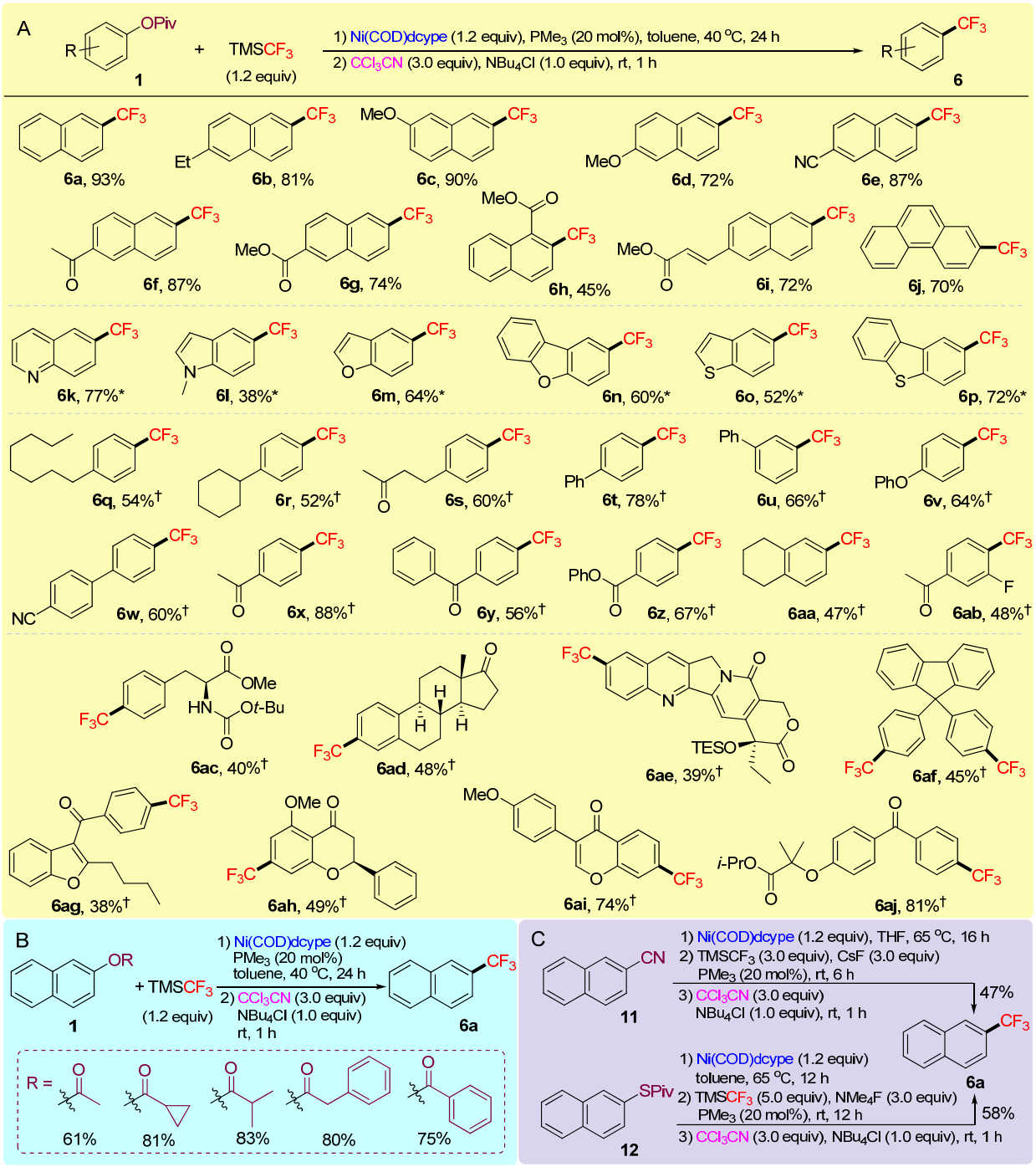


**Fig. 4. Nickel-promoted trifluoromethylation of inert aryl electrophiles.** (**A**) Trifluoromethylation of aryl pivalates. Reaction conditions: aryl pivalate (0.2 mmol), $TMSCF_3$ (0.24 mmol), Ni(COD)dcype (0.24 mmol), and $PMe_3$ (0.04 mmol) in toluene (2.0 mL) were

stirred at 40 °C for 24 h, then $CCl_3CN$ (0.6 mmol) and $NBu_4Cl$ (0.2 mmol) were added and stirred at room temperature (rt) for 1 h. *Oxidative addition and transmetalation at 60 °C, 24 h. †Oxidative addition and transmetalation at 60 °C, 36 h. (**B**) Trifluoromethylation of other aryl esters. (**C**) Trifluoromethylation of aryl cyanide and aryl thioester. Isolated yields are reported for all reactions. Et, ethyl; TES, triethylsilyl; *i*-Pr, *iso*-propyl.

**References and Notes:**


1. R. F. Heck, Acylation, methylation, and carboxyalkylation of olefins by group VIII metal derivatives. *J. Am. Chem. Soc*. **90**, 5518–5526 (1968).
2. E.-I. Negishi, A. O. King, N. Okukado, Selective carbon-carbon bond formation via transition metal catalysis. 3. A highly selective synthesis of unsymmetrical biaryls and diarylmethanes by the nickel- or palladium-catalyzed reaction of aryl- and benzylzinc derivatives with aryl halides. *J. Org. Chem*. **42**, 1821–1823 (1977).
3. N. Miyaura, K. Yamada, A. Suzuki, A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Lett.* **20**, 3437–3440 (1979).
4. D.-G. Yu, B.-J. Li, Z.-J. Shi, Exploration of new C−O electrophiles in cross-coupling Reactions. *Acc. Chem. Res.* **43**, 1486–1495 (2010).
5. B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, Nickel-catalyzed cross-couplings involving carbon-oxygen bonds. *Chem. Rev.* **111**, 1346–1416 (2011).
6. J. Cornella, C. Zarate, R. Martin, Metal-catalyzed activation of ethers via C−O bond cleavage: a new strategy for molecular diversity. *Chem. Soc. Rev.* **43**, 8081–8097 (2014).
7. M. Tobisu, N. Chatani, Cross-couplings using aryl ethers via C−O bond activation enabled by nickel catalysts. *Acc. Chem. Res.* **48**, 1717–1726 (2015).
8. Zeng, H.; Qiu, Z.; Domínguez-Huerta, A.; Hearne, Z.; Chen, Z.; Li, C.-J. An adventure in sustainable cross-coupling of phenols and derivatives via carbon-oxygen bond cleavage. *ACS Catal.* **7**, 510–519 (2017).
9. S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **37**, 320–330 (2008).
10. A. Mullard, 2018 FDA drug approvals. *Nat. Rev. Drug Discov.* **18**, 85–89 (2019).
11. O. A. Tomashenko, V. V. Grushin, Aromatic trifluoromethylation with metal complexes. *Chem. Rev.* **111**, 4475–4521 (2011).
12. M. Oishi, H. Kondo, H. Amii, Aromatic trifluoromethylation catalytic in copper. *Chem. Commun.* **2009**, 1909–1911 (2009).
13. E. J. Cho, T. D. Senecal, T. kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, The palladium-catalyzed trifluoromethylation of aryl chlorides. *Science* **328**, 1679–1681 (2010).

14. C. Le, T. Q. Chen, Tao. Liang, P. Zhang, D. W. C. MacMillan, A radical approach to the copper oxidative addition problem: Trifluoromethylation of bromoarenes. *Science* **360**, 1010–1014 (2018).

15. X.-S. Wang, L. Truesdale, J.-Q. Yu, Pd(II)-catalyzed ortho-trifluoromethylation of arenes using TFA as a promoter. *J. Am. Chem. Soc.* **132**, 3648–3649 (2010).

16. L. Chu, F.-L. Qing, Copper-catalyzed direct C−H oxidative trifluoromethylation of heteroarenes. *J. Am. Chem. Soc*. **134**, 1298–1304 (2012).

17. L. Chu, F.-L. Qing, Copper-mediated oxidative trifluoromethylation of boronic acids. *Org. Lett*. **12**, 5060–5063 (2010).

18. T. D. Senecal, A. T. Parsons, S. L. Buchwald, Room temperature aryl trifluoromethylation via copper-mediated oxidative cross-coupling. *J. Org. Chem*. **76**, 1174–1176 (2011).

19. G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooβen, Sandmeyer trifluoromethylation of arenediazonium tetrafluoroborates. *Angew. Chem. Int. Ed*. **52**, 7972–7975 (2013).

20. J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu, Y. Fu, Copper-promoted Sandmeyer trifluoromethylation reaction. *J. Am. Chem. Soc*. **135**, 8436–8439 (2013).

21. X. Wang, Y. Xu, F.-Y. Mo, G.-J. Ji, D. Qiu, J.-J. Feng, Y.-X. Ye, S.-N. Zhang, Y. Zhang, J.-B. Wang, Silver-mediated trifluoromethylation of aryldiazonium salts: conversion of amino group into trifluoromethyl group. *J. Am. Chem. Soc*. **135**, 10330–10333 (2013).

22. J.-Y. Yang, X.-H. Xu, F.-L. Qing, Copper-mediated trifluoromethylation of diaryliodonium salts with $TMSCF_3$ at room temperature. *J. Fluorine Chem*. **180**, 175–180 (2015).

23. F. Ye, F. Berger, H. Jia, J. Ford, A. Wortman, J. Börgel, C. Genicot, T. Ritter, Aryl sulfonium salts for site-selective late-stage trifluoromethylation. *Angew. Chem. Int. Ed*. **58**, 14615–14619 (2019).

24. S. Z. Tasker, E. A. Standley, T. F. Jamison, Recent advances in homogeneous nickel catalysis. *Nature* **509**, 299–309 (2014).

25. F. D'Accriscio, P. Borja, N. Saffon-Merceron, M. Fustier-Boutignon, N. Mézailles, N. Nebra, C−H bond trifluoromethylation of arenes enabled by a robust, high-valent nickel(IV) complex. *Angew. Chem. Int. Ed*. **56**, 12898–12902 (2017).

26. E. A. Meucci, S. N. Nguyen, N. M. Camasso, E. Chong, A. Ariafard, A. J. Canty, M. S. Sanford, Nickel(IV)-catalyzed C−H trifluoromethylation of (hetero)arenes. *J. Am. Chem. Soc*. **141**, 12872–12879 (2019).

27. G. G. Dubinina, W. W. Brennessel, J. L. Miller, D. A. Vicic, Exploring trifluoromethylation reactions at nickel: a structural and reactivity study. *Organometallics* **27**, 3933–3938 (2008).

28. B. Vabre, P. Petiot, R. Declercq, D. Zargarian, Fluoro and trifluoromethyl derivatives of POCOP-type pincer complexes of nickel: preparation and reactivities in $SN_2$ fluorination and direct benzylation of unactivated arenes. *Organometallics* **33**, 5173–5184 (2014).

29. J. Jover, F. M. Miloserdov, J. Benet-Buchholz, V. V. Grushin, F. Maseras, On the feasibility of nickel-catalyzed trifluoromethylation of aryl halides. *Organometallics* **33**, 6531–6543 (2014).

30. J. Hao, B. Vabre, D. Zargarian, POCOP-ligated nickel siloxide complexes: syntheses, characterization, and r eactivities. *Organometallics* **33**, 6568–6576 (2014).

31. J. R. Bour, N. M. Camasso, M. S. Sanford, Oxidation of Ni(II) to Ni(IV) with aryl electrophiles enables Ni-mediated aryl–$CF_3$ coupling. *J. Am. Chem. Soc*. **137**, 8034–8037 (2015).

32. J. R. Bour, N. M. Camasso, E. A. Meucci, J. W. Kampf, A. J. Canty, M. S. Sanford, Carbon-carbon bond-forming reductive elimination from isolated nickel(III) complexes. *J. Am. Chem. Soc*. **138**, 16105–16111 (2016).

33. M. Rovira, S. Roldán-Gómez, V. Martin-Diaconescu, C. J. Whiteoak, A. Company, J. M. Luis, X. Ribas, Trifluoromethylation of a well-defined square-planar aryl-$Ni^{II}$ complex involving $Ni^{III}/CF_3$ and $Ni^{IV}$-$CF_3$ intermediate species. *Chem. Eur. J*. **23**, 11662–11668 (2017).

34. E. A. Meucci, N. M. Camasso, M. S. Sanford, An organometalllic $Ni^{IV}$ complex that participates in competing transmetalation and C($sp^2$)−O bond-forming reductive elimination reactions. *Organometallics* **36**, 247–250 (2017).

35. N. M. Camasso, M. S. Sanford, Design, synthesis, and carbon-heteroatom coupling reactions of organometallic nickel(IV) complexes. *Science* **347**, 1218–1220 (2015).

36. W. Zhou, S. Zheng, J. W. Schultz, N. P. Rath, L. M. Mirica, Aromatic cyanoalkylation through double C−H activation mediated by Ni(III). *J. Am. Chem. Soc*. **138**, 5777–5780 (2016).

37. R. J. Somerville, L. V. A. Hale, E. Gómez-Bengoa, J. Burés, R. Martin, Intermediacy of Ni−Ni species in $sp^2$ C−O bond cleavage of aryl esters: relevance in catalytic C−Si bond formation. *J. Am. Chem. Soc*. **140**, 8771–8780 (2018).

38. A. Maleckis, M. S. Sanford, Synthesis of fluoroalkyl palladium and nickel complexes via decarbonylation of acylmetal species. *Organometallics* **33**, 3831–3839 (2014).

39. Z. Li, S.-L. Zhang, Y. Fu, Q.-X. Guo, L. Liu, Mechanism of Ni-catalyzed selective C−O bond activation in cross-coupling of aryl esters. *J. Am. Chem. Soc*. **131**, 8815–8823 (2009).

40. H. Xu, K. Muto, J. Yamaguchi, C. Zhao, K. Itami, D. G. Musaev, Key mechanistic features of Ni-Catalyzed C−H/C−O biaryl coupling of azoles and naphthalen-2-yl pivalates. *J. Am. Chem. Soc*. **136**, 14834–14844 (2014).

41. X. Liu, C.-C. Hsiao, I. Kalvet, M. Leiendecker, L. Guo, F. Schoenebeck, M. Rueping, Lewis acid assisted nickel-catalyzed cross-coupling of aryl methyl ethers by C−O bond-cleaving alkylation: prevention of undesired β-hydride elimination. *Angew. Chem. Int. Ed*. **55**, 6093–6098 (2016).

42. M. C. Schwarzer, R. Konno, T. Hojo, A. Ohtsuki, K. Nakamura, A. Yasutome, H. Takahashi, T. Shimasaki, M. Tobisu, N. Chatani, S. Mori, Combined theoretical and experimental studies of nickel-catalyzed cross-coupling of methoxyarenes with arylboronic esters via C−O bond cleavage. *J. Am. Chem. Soc*. **139**, 10347–10358 (2017).

43. G. E. Martinez, C. Ocampo, Y. J. Park, A. R. Fout, Accessing pincer bis(carbene) Ni(IV) complexes from Ni(II) via halogen and halogen surrogates. *J. Am. Chem. Soc*. **138**, 4290–4293 (2016).

44. N. G. Connelly, W. E. Geiger, Chemical redox agents for organometallic chemistry. *Chem. Rev*. **96**, 877–910 (1996).

45. C.-P. Zhang, H. Wang, A. Klein, C. Biewer, K. Stirnat, Y. Yamaguchi, L. Xu, V. Gomez-Benitez, D. A. Vicic, A five-coordinate nickel(II) fluoroalkyl complex as a precursor to a spectroscopically detectable Ni(III) species. *J. Am. Chem. Soc*. **135**, 8141–8144 (2013).

46. G. M. Lee, I. Korobkov, R. T. Baker, $d^8$ Nickel and palladium difluorocarbenes derived from trifluoromethyl POCOP-type pincer complexes. *J. Organomet. Chem*. **847**, 270–277 (2017).

47. X.-P. Fu, X.-S. Xue, X.-Y. Zhang, Y.-L. Xiao, S. Zhang, Y.-L. Guo, X. Leng, K. N. Houk, X. Zhang, Controllable catalytic difluorocarbene transfer enables access to diversified fluoroalkylated arenes. *Nat. Chem.* **11**, 948–956 (2019).

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**Supplementary Materials:**

Materials and Methods

Supplementary Text

Figs S1-S18

Tables S1-S8

Spectral Data

References (*48-51*)