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Fundamental Studies and Development of Nickel-Catalyzed Trifluoromethylthiolation of Aryl Chlorides: Active Catalytic Species and Key Roles of Ligand and Traceless MeCN Additive Revealed

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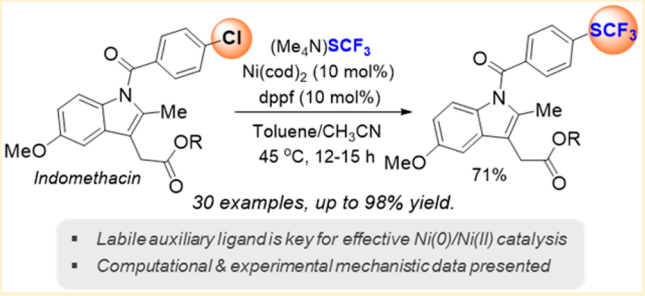
Supporting Information

ABSTRACT: A catalytic protocol to convert aryl and heteroaryl chlorides to the corresponding trifluoromethyl sulfides is reported herein. It relies on a relatively inexpensive $Ni(cod)_2$/dppf (cod = 1,5-cyclooctadiene; dppf = 1,1′-bis(diphenylphosphino)ferrocene) catalyst system and the readily accessible coupling reagent $(Me_4N)SCF_3$. Our computational and experimental mechanistic data are consistent with a $Ni^{(0)}/Ni^{(II)}$ cycle and inconsistent with $Ni^{(I)}$ as the reactive species. The relevant intermediates were prepared, characterized by X-ray crystallography, and tested for their catalytic competence. This revealed that a monomeric tricoordinate $Ni^{(I)}$ complex is favored for dppf and Cl whose role was unambiguously assigned as being an off-cycle catalyst deactivation product. Only bidentate ligands with wide bite angles (e.g., dppf) are effective. These bulky ligands render the catalyst resting state as [(P−P)Ni(cod)]. The latter is more reactive than $Ni(P-P)_2$, which was found to be the resting state for ligands with smaller bite angles and suffers from an initial high-energy dissociation of one ligand prior to oxidative addition, rendering the system unreactive. The key to effective catalysis is hence the presence of a labile auxiliary ligand in the catalyst resting state. For more challenging substrates, high conversions were achieved via the employment of MeCN as a traceless additive. Mechanistic data suggest that its beneficial role lies in decreasing the energetic span, therefore accelerating product formation. Finally, the methodology has been applied to synthetic targets of pharmaceutical relevance.



INTRODUCTION

Catalysis is an integral and indispensable discipline in modern academic and industrial chemistry. Specifically, metal-based processes have enabled numerous processes and revolutionized the synthetic repertoire.[1] Nowadays there is increasing academic and industrial interest in more sustainable alternatives to those transformations typically achieved by precious metals. In this context, nickel is an attractive alternative to palladium, not only because of its greater abundance and lower cost but also its ability to react with bonds that generally would be inert toward palladium or copper.[2,3] However, despite promising reactivity precedent, the field of Ni catalysis has generally progressed more slowly over the past decades compared to Pd-based methodology.[4] This has been ascribed to the challenges in steering Ni-based processes toward desired reactivities, as summarized by Colacot and Snieckus:[4]

"...Thus, nickel remained the brutish older brother to palladium, able to affect the coupling of a wider range of halide partners for which palladium failed. However, repeatedly over the coming years, palladium would usurp nickel because its reactivity could be modulated through the use of ligands whilst still retaining its improved selectivity..."

Undoubtedly, modulation of the steric and electronic properties of electron-donating ligands, particularly phosphines, has had a tremendous impact in organometallic catalysis.[5] However, for nickel there is little understanding of precise ligand effects on the elemental catalytic steps. Moreover, an additional crucial challenge is nickel's propensity to exist in and interchange readily between various oxidation states.[2d,6] In this context, several reports have implicated $Ni^{(I)}$ species as intermediates,[7,8] either via $Ni^{(I)}/Ni^{(III)}$ catalysis or by in situ generation through comproportionation or electron transfer events. Another possibility is the side reaction of key catalytic $Ni^{(II)}$ intermediates to give $Ni^{(I)}$ with concomitant formation of biaryl (see Figure 1).[2d,9]

Modulation of the ligand sphere at Ni centers therefore not only may impact the reactivities and selectivities of the elementary catalytic steps but also likely influences the favored oxidation state. For the development of general and efficient Ni-catalyzed processes, there is hence a greater need to carefully balance these competing effects. Gaining fundamental understanding of these phenomena is therefore of utmost importance.

Specific Case Study. A representative case for the divergent developments of Ni- and Pd-based catalysis is the metal-catalyzed C−S bond formation of aryl chlorides. While there are numerous precedents for Pd-based chemistry,[10] the

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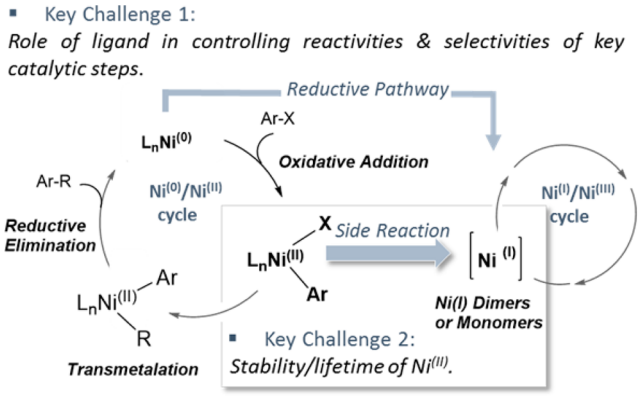

Figure 1. Possible $Ni^{(0)}/Ni^{(II)}$ or $Ni^{(I)}/Ni^{(III)}$ catalytic cycles and key challenges for the development of Ni catalysis.

coupling of aryl chlorides to give the corresponding aryl sulfides via Ni catalysis is essentially undeveloped.[11] This might be due to the ability of Ni catalysts to cleave aromatic C−S bonds,[12] which highlights a possible additional challenge for reaction development.

As part of our ongoing mechanistic and methodological program in organometallic chemistry[13] and also with respect to the generation of fluorine-containing compounds,[14] we chose the challenge of $C-SCF_3$ bond formation as a platform for fundamental studies of the effects of ligands and additives on the key catalytic steps in Ni catalysis. The overall aim was to develop the first trifluoromethylthiolation of aryl chlorides (Figure 2).

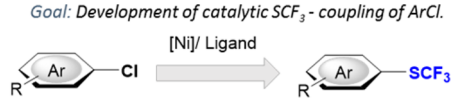

Figure 2. Chosen challenge for fundamental studies of Ni catalysis.

Because of the high lipophilicity of the SCF_3 moiety, which influences membrane permeability and bioavailability, aryl trifluoromethyl sulfides ($ArSCF_3$) are important compounds in pharmaceutical and agrochemical research,[15] and there is considerable interest in the development of straightforward and general methods to introduce SCF_3 groups into molecules.[16] The direct cross-coupling of abundant and stable aryl halide precursors would be highly attractive in this context. However, the current repertoire of metal-catalyzed coupling methodologies is limited to coupling of aryl bromides and iodides, which has been accomplished via Pd, Ni, and Cu catalysis.[17] To date there is no general and catalytic method available to convert aryl chlorides to $ArSCF_3$.[18,19] However, in view of the lower expense and greater availability of aryl chlorides compared with aryl bromides and iodides, the coupling of C−Cl would be inherently more attractive.

We herein describe the development of a mild and efficient protocol for the conversion of aryl and heteroaryl chlorides to the corresponding trifluoromethyl sulfides catalyzed by Ni-$(cod)_2$/dppf (cod = 1,5-cyclooctadiene; dppf = 1,1′-bis-(diphenylphosphino)ferrocene). Mechanistic (experimental and computational) studies of the favored reaction pathways, insights into the crucial roles of the ligand and additive, and applications to drug molecules are presented.

RESULTS AND DISCUSSION

While no protocol exists for coupling of aryl chlorides to give $ArSCF_3$, Zhang and Vicic[17b] described an elegant Ni$(cod)_2$/bipyridine-catalyzed coupling protocol of aryl iodides and bromides to give $ArSCF_3$. This method proved to be ineffective for the coupling of ArCl however. We hypothesized that $Ni^{(0)}$ catalysts in conjunction with N ligands (e.g., bipyridine) may be unreactive with aryl chlorides because these systems frequently react via electron transfer processes involving radical intermediates.[7c−e,8a,f] By contrast, we envisaged that the use of phosphine ligands might create a much more reactive catalysis system that may proceed via $Ni^{(0)}/Ni^{(II)}$ catalysis (see Figure 1 and later discussion).

Identification of an Effective Catalytic System. We initially subjected 1-chloro-4-methoxybenzene **1** and the readily accessible reagent $(Me_4N)SCF_3$[20] to various test reactions, in which we explored the effect of the ligand, precatalyst, solvent, and temperature. To our delight, conversion of ArCl **1** to $ArSCF_3$ was seen when Ni$(cod)_2$ was employed as the precatalyst in conjunction with a wide-bite-angle ligand (xantphos, dppf, or binap) in toluene.[21] In stark contrast, ligands with smaller bite angles (e.g., dppe) or monodentate ligands were completely ineffective (see Figure 3). Additional information can be found in Table S1 in the Supporting Information.

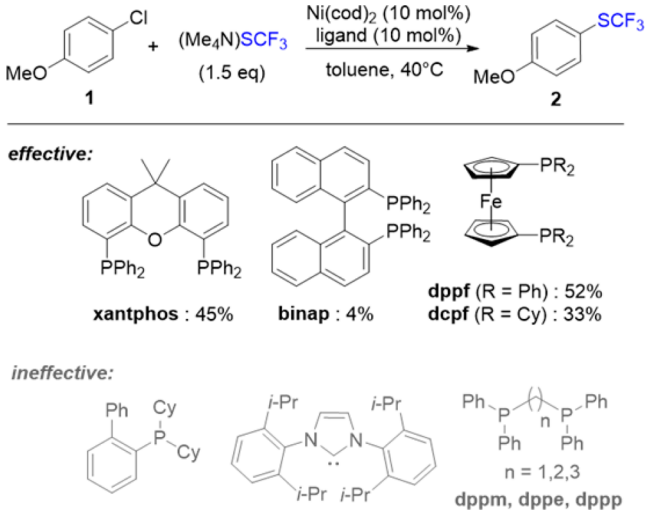

Figure 3. Effect of the ligand on the Ni-catalyzed SCF_3 coupling of ArCl. Yields of $ArSCF_3$ are given. See Table S1 in the Supporting Information for additional data.

While no detailed mechanistic information on Ni-catalyzed C−S bond formations is available, the ineffectiveness of monodentate ligands parallels observations previously made in Pd-based C−S coupling reactions. It has been assumed that monodentate ligands may be displaced from the Pd center by nucleophilic RS^- anions.[10d] While this hypothesis would in principle account for the different conversions with mono- and bidentate ligands, it does not account for the fact that only wide-bite-angle ligands are effective under our Ni-catalyzed coupling conditions. Wide-bite-angle ligands are generally more labile and susceptible to displacement by nucleophiles than ligands with smaller bite angles.[22] To gain more insight, we embarked on detailed mechanistic studies.

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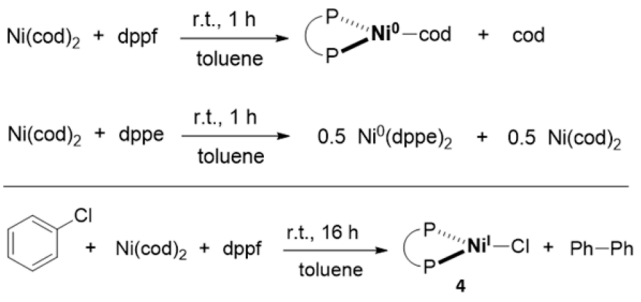
Elucidation of the Favored Reaction Pathway: $Ni^{(0)}$ or $Ni^{(I)}$ and Coordination Sphere of the Active Ni Species?

We subsequently undertook comparative mechanistic studies with the ligands dppf (which had given high conversion in our initial assessments in Figure 3) and 1,2-bis-(diphenylphosphino)ethane (dppe) as a small-bite-angle representative that had not given conversion (see Figure 3). When we added dppf to $Ni(cod)_2$ in a 1:1 metal to ligand ratio in toluene, we observed the exclusive formation of [(dppf)Ni-(cod)] as judged by ^1H and ^{31}P NMR analyses and X-ray crystallography (see Figure 4). By contrast, for dppe the



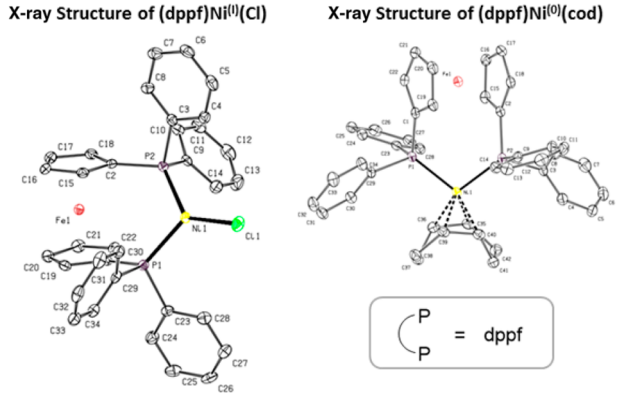


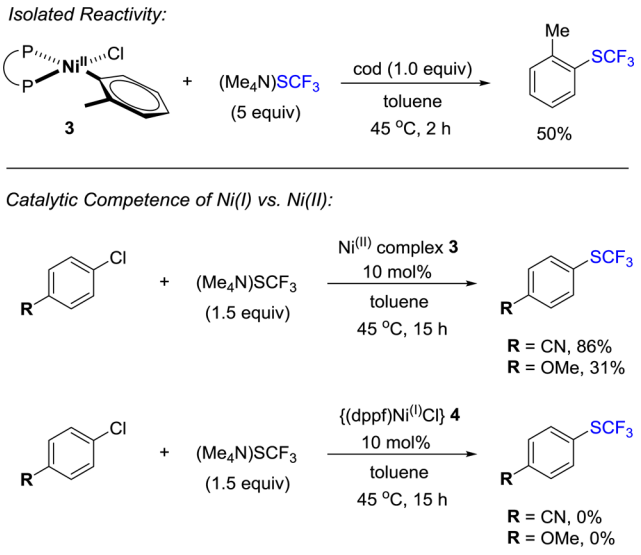
Figure 4. Different $Ni^{(0)}$ species formed with dppf and dppe and X-ray structures of [(dppf)$Ni^{(I)}$(Cl)] (**4**) and [(dppf)$Ni^{(0)}$(cod)] .

analogous experiment gave rise to the cod-free complex [$(dppe)_2Ni^{(0)}$]. Examination of the actual $Ni(cod)_2$/dppf-catalyzed SCF_3 coupling of **1** (as shown in Figure 3) revealed that [(dppf)Ni(cod)] was also the resting state of the catalytic reaction. These observations highlight the different propensities of the ligands to bind to $Ni^{(0)}$ and to displace the auxiliary cod ligand. Because of the greater steric demand of dppf, the favored state involves a single dppf ligand in the Ni sphere with additional stabilization by the relatively small cod ligand. For the smaller dppe, two ligands can readily be accommodated in the coordination sphere. This has a significant impact on the activity of the catalyst, as we will show later.

Having elucidated the favored resting state of the $Ni(cod)_2$/dppf catalytic system, we subsequently explored the likely mechanism by which the catalysis proceeds. While a pathway involving the $Ni^{(0)}$ and $Ni^{(II)}$ oxidation states constitutes one mechanistic possibility, several previous reports have proposed $Ni^{(I)}$ as an active catalytic species (Figure 1),[7,8] most recently by Martin and co-workers for the cleavage of aromatic C−O bonds.[7h] To investigate this, we embarked on the preparation of the key [(dppf)$Ni^{(II)}$(Cl)(Ar)] and $Ni^{(I)}$ complexes to test for their catalytic competence. The choice of "Ar" significantly impacts the stability of the $Ni^{(II)}$ complex, which may be converted to $Ni^{(I)}$ with concomitant formation of biaryl. For Ar = 2-MePh, the stable $Ni^{(II)}$ complex **3** was reported by Buchwald and co-workers.[23] By contrast, for Ar = Ph, upon oxidative addition of $Ni(cod)_2$/dppf to PhCl we isolated a $Ni^{(I)}$ monomer and Ph−Ph. The novel complex [(dppf)$Ni^{(I)}$(Cl)] (**4**) was fully characterized by X-ray crystallography (Figure 4). While three-coordinate transition-metal complexes are generally considered to be rare,[24b] there have been previous encounters of monomeric $Ni^{(I)}$ complexes.[24,25]

We subsequently tested for the ability of $Ni^{(II)}$ complex **3** to (i) produce $ArSCF_3$ under stoichiometric conditions and (ii) act as a precatalyst in the Ni-catalyzed trifluoromethylthiolation of aryl chlorides. Scheme 1 presents the results. $Ni^{(II)}$ complex **3**

Scheme 1. Test of the Catalytic Competence of $Ni^{(I)}$ versus $Ni^{(II)}$ [26]



indeed proved to be both a competent intermediate and precatalyst, supporting that $Ni^{(0)}/Ni^{(II)}$ catalysis is operative. In contrast, the $Ni^{(I)}$ complex **4** proved catalytically inactive (see Scheme 1 bottom).[27] These results strongly indicate that the SCF_3 coupling proceeds via $Ni^{(0)}/Ni^{(II)}$ catalysis.

Origin of the Ligand Effect: A Computational Study.

To understand why wide-bite-angle ligands are privileged in the Ni-catalyzed trifluoromethylthiolation of aryl chlorides, we undertook computational studies[28] of the oxidative addition and reductive elimination steps for the $Ni^{(0)}/Ni^{(II)}$ coupling cycle.[29] We compared the reaction profiles for the wide-bite-angle (=effective) ligand dppf versus the smaller-bite-angle (=ineffective) ligand dppe. Our calculations employed the B3LYP functional and the mixed basis set 6-31G(d) and LANL2DZ (for Ni, Fe) for geometry optimizations. Energies were obtained via single-point CPCM calculations (with toluene as solvent) at the M06L/6-311++G(d,p) (with LANL2DZ for Ni, Fe) level.[30] The results are given in Figures 5 and 6. For the effective $Ni(cod)_2$/dppf catalysis system, we calculated the oxidative addition of [(dppf)$Ni^{(0)}$(cod)] to chlorobenzene with concomitant loss of a cod ligand (see Figure 5). The activation free energy barrier ($\Delta G^{\ddagger}$) for this step was calculated to be 24.4 kcal/mol, and this process was predicted to be roughly thermoneutral overall. The reductive elimination of $PhSCF_3$ from [(dppf)$Ni^{(II)}$(SCF_3)(Ph)] was calculated to be slightly more facile, proceeding with $\Delta G^{\ddagger}$ = 16.4 kcal/mol. The recoordination of the auxiliary cod ligand is

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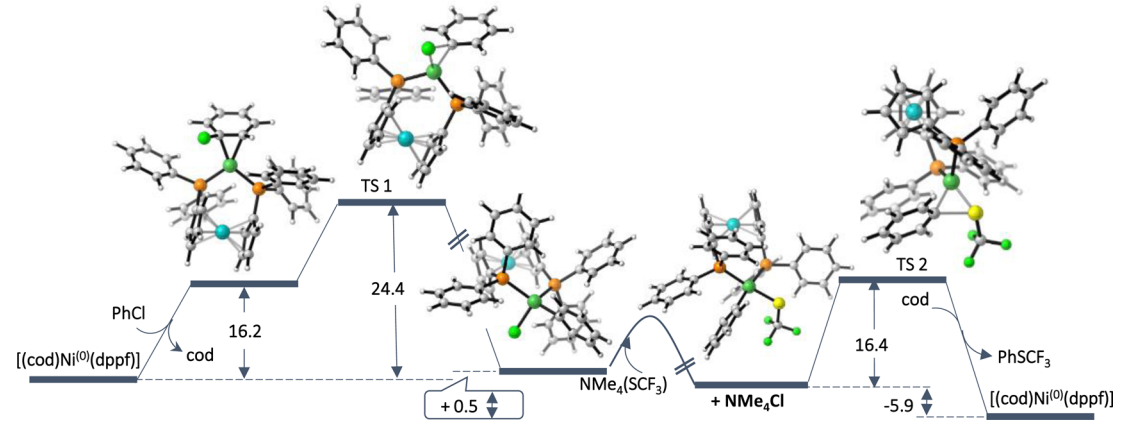

Figure 5. Free energy barriers for the oxidative addition and reductive elimination of the SCF_3 coupling of PhCl employing the (effective) dppf ligand, calculated at the CPCM (toluene) M06L/6-311++G(d,p)//B3LYP/6-31G(d) [with LANL2DZ for Ni, Fe] level.

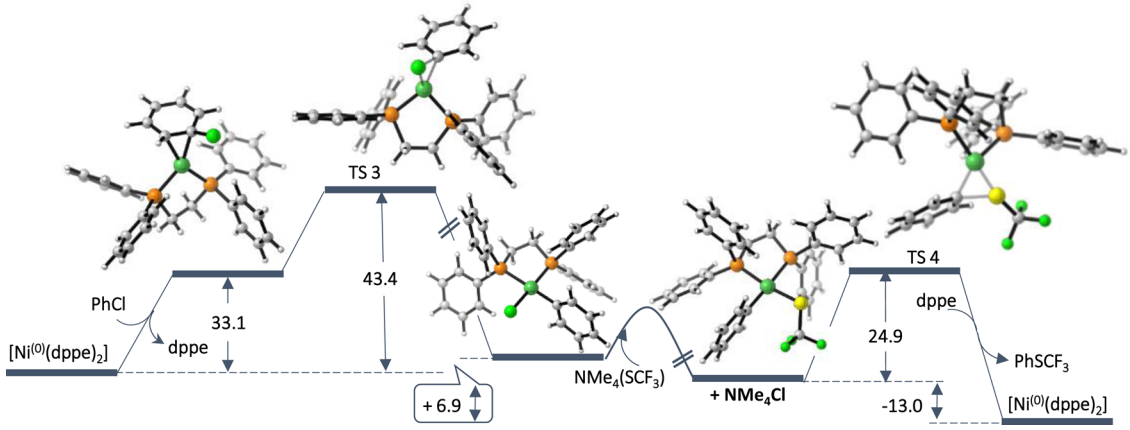

Figure 6. Free energy barriers for the oxidative addition and reductive elimination of the SCF_3 coupling of PhCl employing the (ineffective) dppe ligand, calculated at the CPCM (toluene) M06L/6-311++G(d,p)//B3LYP/6-31G(d) [with LANL2DZ for Ni] level.

crucial to stabilize the otherwise highly reactive $[(dppf)Ni^{(0)}]$ species.

Performing the analogous calculations for $[(dppe)_2Ni^{(0)}]$ gave significantly larger activation free energy barriers for oxidative addition to PhCl and reductive elimination of $PhSCF_3$ (see Figure 6). These findings are in line with the experimental observations. No conversion to $ArSCF_3$ was seen under $Ni(cod)_2$/dppe conditions. The larger barrier in the oxidative addition step ($\Delta G^{\ddagger}$ = 43.4 kcal/mol) is primarily due to the energy penalty associated with the dissociation of one dppe ligand from $[(dppe)_2Ni^{(0)}]$ (ΔG_{rxn} = 33.1 kcal/mol). In the case of dppf, a weaker-binding cod ligand needs to be displaced from $[(dppf)Ni^{(0)}(cod)]$ to enable the subsequent oxidative addition.

Although phosphine ligands with smaller bite angles generally render the metal center more nucleophilic (and hence more reactive toward oxidative addition), the large ligand dissociation energy associated with dppe outweighs this. On the other hand, the observation of a ca. 7 kcal/mol higher barrier for reductive elimination in the case of dppe is in accord with commonly accepted bite-angle trends, i.e., wide-bite-angle ligands generally lead to more facile reductive elimination. These findings highlight the importance of the presence of a weakly binding auxiliary ligand (e.g., cod) in the catalyst. They further explain several previous reactivity observations of $L_2Ni^{(0)}$ complexes (with L = bidentate ligand) being ineffective catalysts.[31]

Exploration of Scope. Encouraged by these mechanistic insights, we continued our developments with dppf as the ligand and explored the scope of the $Ni(cod)_2$/dppf catalytic system.

Employing mild reaction conditions (45 °C) in toluene allowed the coupling of electron-rich and electron-deficient aryl chlorides with $(Me_4N)SCF_3$, yielding the corresponding $ArSCF_3$ compounds in good to excellent yields (see Table 1). The bicyclic aromatic substrate 1-chloronaphthalene (entry 13) also gave its trifluoromethylthiolated counterpart in high yield. Dichloroarenes (entries 14 and 15) gave predominantly the bis(SCF_3) products under these conditions in mixtures with the monofunctionalized arenes.

For heterocyclic arenes, which play an important role in medicinal and agrochemical research, trifluoromethylthiolation was successfully accomplished for a number of examples (see Table 2). Quinoxaline, thiophene, and acridine derivatives afforded the corresponding trifluoromethyl sulfides in good to excellent yields. Notably, benzyl- and *tert*-butoxycarbonyl (Boc)-protected indoles were well-tolerated under these conditions.

While the protocol allowed the successful SCF_3 coupling of a number of aryl chlorides, some substrates gave rise to higher conversions than others under these conditions. Intrigued by these observations and with a view to increasing the substrate scope, we subsequently undertook additional mechanistic studies.

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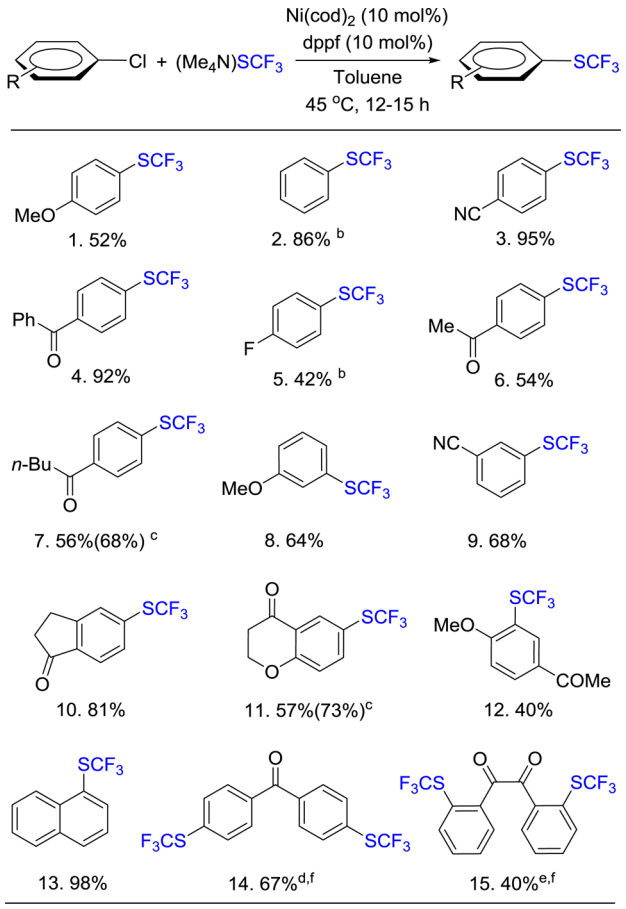
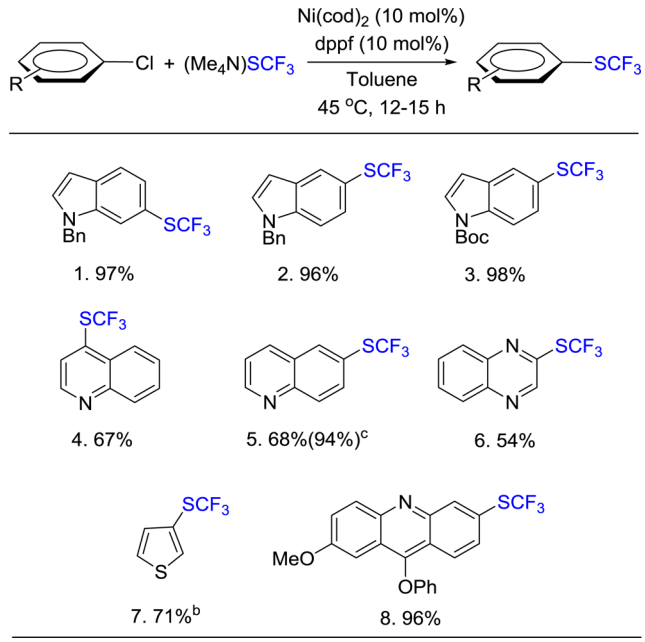
Table 1. Scope of the $Ni^{(0)}$-Catalyzed SCF_3 Coupling of ArCl[a]



[a]Conditions: $Ni(cod)_2$ (11.1 mg, 0.04 mmol), dppf (22.2 mg, 0.04 mmol), ArCl (0.4 mmol), $(Me_4N)SCF_3$ (0.6 mmol, 102 mg), toluene (2 mL). Isolated yields are shown. [b]The yield was determined by ^{19}F NMR analysis against $PhCF_3$. [c]The datum in parentheses corresponds to the yield of the reaction with 15 mol % $Ni(cod)_2$ and 15 mol % dppf. [d]A 7% yield of the monosubstituted product was also observed by GC–MS. [e]A 20% yield of the monosubstituted product was also obtained. [f]Ni/dppf (0.08 mmol) and $(Me_4N)SCF_3$ (1.2 mmol) were used.

Increase in Substrate Scope and Application to Synthetic Targets of Pharmaceutical Relevance: Beneficial Effect of MeCN Additive. Our above computational and resting-state analyses highlighted that ligand binding was a critical reactivity-controlling factor. As the mixture of $Ni(cod)_2$ and dppf (1:1 ratio) produced [(dppf)Ni(cod)] along with 1 equiv of free cod ligand (see Figure 4), we were concerned that the additional equivalent of cod may impede the SCF_3-coupling reactivity. To gain deeper insight, we monitored the Ni-catalyzed trifluoromethylthiolation of *p*-methoxyaryl chloride **1** over time (see Figure 7), comparing the effectiveness of [(dppf)Ni(cod)] (yellow) with $Ni(cod)_2$/dppf (red). Indeed, the excess equivalent of cod that is present under conditions in which [(dppf)Ni(cod)] is generated in situ significantly affects the reaction rate and overall efficiency. While this suggests that the isolated [(dppf)Ni(cod)] catalyst should be used to achieve high conversions of more challenging aryl chlorides, a protocol in which the catalyst is generated in situ from commercially available components would still pose advantages in terms of operational simplicity. Thus, with the objective to potentially generate a more reactive catalyst system in situ, we subsequently studied the effect of additives. The key requirement for the additive is that it should bind less strongly to $Ni^{(0)}$ than cod, therefore furnishing a more reactive catalyst.

Table 2. Scope of the $Ni^{(0)}$-Catalyzed Trifluoromethylthiolation of Heteroaryl Chlorides[a]



[a]Conditions: $Ni(cod)_2$ (11.1 mg, 0.04 mmol), dppf (22.2 mg, 0.04 mmol), ArCl (0.4 mmol), $(Me_4N)SCF_3$ (0.6 mmol, 102 mg), toluene (2 mL). Isolated yields are shown. [b]The yield was determined by ^{19}F NMR analysis against $PhCF_3$. [c]The datum in parentheses corresponds to the yield of the reaction with 15 mol % $Ni(cod)_2$ and 15 mol % dppf.

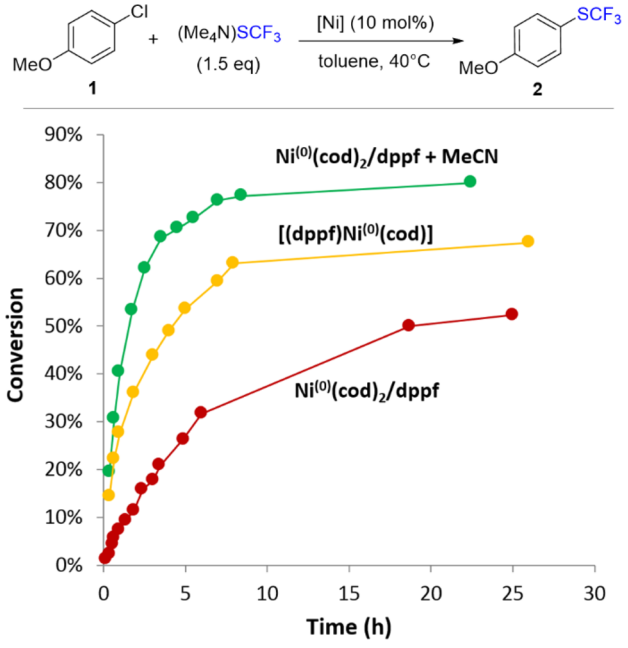


Figure 7. Time courses for the conversion of **1** to **2** using (i) the standard $Ni(cod)_2$/(dppf) system (red), which forms [(dppf)-$Ni^{(0)}$(cod)] + cod in situ; (ii) [(dppf)$Ni^{(0)}$(cod)] (yellow); and (iii) $Ni(cod)_2$/(dppf) in the presence of MeCN (1.0 equiv relative to **1**) (green).

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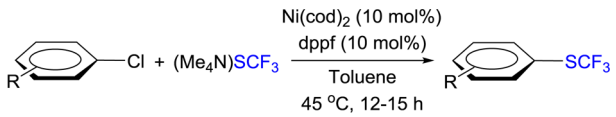
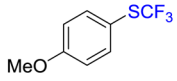
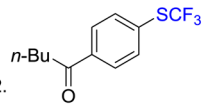
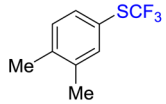
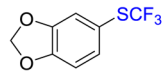
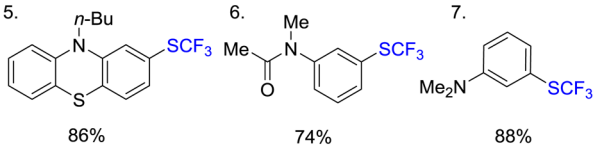
It has previously been established that $Ni^{(0)}$ can bind nitrile compounds in an η^2 fashion to the cyano group.[3e,32] Such $Ni^{(0)}$ complexes in turn were also shown to be robust and efficient (pre)catalysts.[9b,32b] However, in terms of synthetic applicability of the protocol as well as atom economy and minimization of waste, the stoichiometric addition of an aromatic nitrile is not very desirable. We therefore explored the effect of acetonitrile, which could simply be used as a traceless additive (i.e., a cosolvent). Pleasingly, excellent conversion with substrate **1** (see Figure 7) and an overall higher reaction rate than with the isolated or in situ-generated [(dppf)Ni(cod)] catalyst were seen. We subsequently subjected a number of challenging aryl chloride substrates to $Ni(cod)_2$/dppf catalysis conditions in the presence of MeCN. Table 3 shows the results. Addition of

Table 3. Effect of MeCN Additive on the $Ni^{(0)}$-Catalyzed SCF_3 Coupling of ArCl[a]



		Additive-free[a]	With MeCN[a,b]
1.		52%	76%
2.		56%	81%
3.		trace	50%
4.		trace	61%

Additional examples with MeCN[a,b]

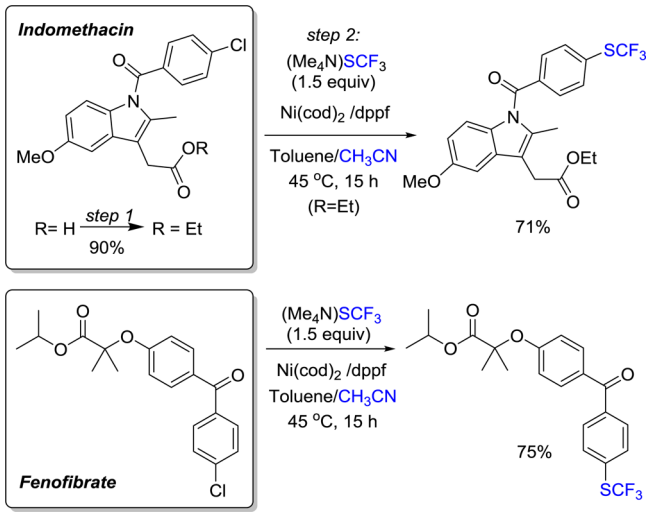


[a]Conditions: $Ni(cod)_2$ (11.1 mg, 0.04 mmol), dppf (22.2 mg, 0.04 mmol), aryl chloride (0.4 mmol), $(Me_4N)SCF_3$ (0.6 mmol, 102 mg), toluene (2 mL). Isolated yields are shown. [b]CH_3CN (20 μL) was added.

MeCN proved to be advantageous in a number of cases (entries 1−4), with increases of up to 61% in the observed yield. Moreover, the trifluoromethylthiolation of heterocyclic and functionalized aromatic chlorides was achieved in good yields (entries 5−7), showing compatibility with amide (entry 6) and amine (entry 7) functional groups.

As a stern test of our newly developed methodology and the advantageous acetonitrile effect, we also investigated the trifluoromethylthiolation of a few drug molecules that contain aromatic C−Cl sites. In this context, we first O-protected the anti-inflammatory drug indomethacin (Scheme 2) and subjected the product to our improved trifluoromethylthiolation protocol. The corresponding SCF_3-substituted product was isolated in a pleasing 71% yield. Moreover, we also succeeded in the trifluoromethylthiolation of fenofibrate, a drug against cardiovascular disease, highlighting the scope and applicability of this methodology in a pharmaceutical context.

Scheme 2. Application of the $Ni(cod)_2$/dppf/MeCN SCF_3-Coupling Protocol to Pharmaceutically Relevant Molecules



Effect of MeCN: Mechanistic Insights Gained with Computation and Experiment. To gain deeper insight into the accelerating effect of MeCN, we initially assessed whether nitrile additives other than MeCN would be similarly active. Thus, we studied the SCF_3 coupling of 1,2-dimethyl-4-chlorobenzene (**5**) under $Ni(cod)_2$/dppf catalysis in toluene and added a variety of nitriles that differed in their steric and/or electronic properties (see Table 4). While all of the additives explored had a beneficial effect on the reaction compared with the additive-free conditions (entry 1), the electron-rich nitriles led to higher conversions (e.g., compare entries 5, 10, and 12 with entries 7 and 8). It has previously been suggested that the reactivity enhancement observed in the presence of a nitrile could potentially be due to binding of the nitrile in the oxidative addition step.[8b] While this would be consistent with the greater effectiveness of the electron-rich (and potentially more donating) nitriles, this theory appears to be inconsistent with the lack of steric influence in the activity of the nitrile additives (see entries 9 and 10). In line with this, all of our attempts to computationally locate transition states that had both dppf and MeCN bound led to dissociation of MeCN in all of the cases examined.

Thus, the effect of nitrile additives, particularly when employed in excess, may lie in the displacement of cod ligands from a $Ni^{(0)}$ precursor and generation of a more reactive nitrile-bound (pre)catalyst.[33] This assumption would be consistent with the observation that the $Ni(cod)_2$/dppf reaction in the presence of nitrile was no longer impaired by the excess equivalent of cod (compare the red and green lines in Figure 7).[34]

To examine this further, we studied the extent of cod displacement from $[(dppf)Ni^{(0)}(cod)]$ in the presence of MeCN (by ^{31}P and ^{1}H NMR; see Figure S3 in the Supporting Information). Addition of 10 equiv of MeCN to 1 equiv of $[(dppf)Ni^{(0)}(cod)]$ in C_6D_6 showed an increase in the amount of free cod ligand by 10% shortly after addition. The fact that complete displacement of the cod ligand by MeCN was not

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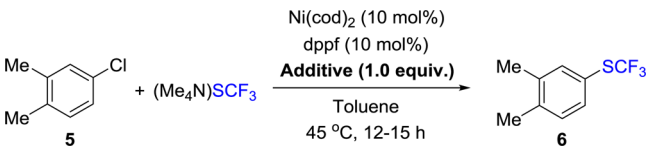
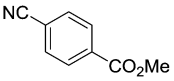
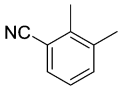
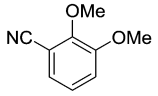
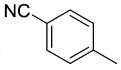
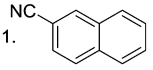
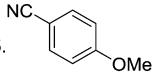
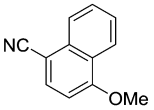
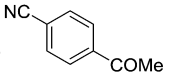
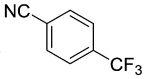
Table 4. Examination of the Effect of Different Nitrile Additives on the Conversion of 5 to $ArSCF_3$ 6[a]



	Additive	Yield of 6		Additive	Yield of 6
1.	none	trace	8.		43%
2.		57% (50%)	9.		77%
3.		70%	10.		72%
4.		66%	11.		42%
5.		72%	12.		81% (72%)
6.		6%			
7.		26%			

[a]Conditions: $Ni(cod)_2$ (11.1 mg, 0.04 mmol), dppf (22.2 mg, 0.04 mmol), ArCl (0.4 mmol), R−CN (0.4 mmol), $(Me_4N)SCF_3$ (0.6 mmol, 102 mg), toluene (2 mL). Conversions were determined by calibrated GC−MS. Yields obtained from isolation are given in parentheses.

obtained suggests that the MeCN is more weakly coordinating than cod (as required for efficient catalysis), indicating that different $Ni^{(0)}$ species may in fact be reversibly equilibrated in the reaction mixture, i.e. [(dppf)$Ni^{(0)}$(cod)] with [(dppf)-$Ni^{(0)}$(MeCN)]. The weaker coordinating ability of MeCN implies that MeCN is also more readily dissociated from [$Ni^{(0)}$] prior to oxidative addition, rendering the [$Ni^{(0)}$] catalysis system more reactive. In line with this, our calculations of the oxidative addition of [(dppf)$Ni^{(0)}$(MeCN)] to PhCl predict a 9 kcal/mol lower activation free energy barrier than for [(dppf)$Ni^{(0)}$(cod)] at the CPCM (toluene) M06L/def2-TZVP level of theory. (While this reactivity difference appears to be substantial, it may likely be overestimated.[35])

However, the *catalytic turnover* and hence the reaction progress depend on both the driving forces (i.e., the reaction free energies, ΔG_{rxn}) and activation barriers ($\Delta G^{\ddagger}$) of the individual catalysis steps. Overall, the free energy difference between the lowest and highest point of the reaction path dictates the catalytic efficiency and reaction speed. This energy difference has been coined as the "energetic span (δG°_{max})".[36,37] The more reactive nature of [(dppf)$Ni^{(0)}$(MeCN)] means in essence that the energy of [$Ni^{(0)}$] is raised, which overall lowers the energetic span and hence leads to higher turnover frequencies (see Figure 8 for a qualitative drawing).

CONCLUSIONS

We have developed a mild and efficient Ni-catalyzed protocol for the functionalization of aryl- and heteroaryl chlorides to give the corresponding trifluoromethyl sulfides ($ArSCF_3$). Several electronically varied arenes, including quinoxaline, thiophene, acridine, and indole derivatives as well as the pharmaceutically relevant drugs indomethacin and fenofibrate, were converted to their SCF_3 counterparts in high yields. The method constitutes a significant step forward within the field of catalytic trifluoromethylthiolations of arenes (and Ni-catalyzed C−SR bond formation more generally), as it substantially broadens the current substrate scope while employing a relatively inexpensive catalyst system. Extensive mechanistic studies were performed to gain insight into the favored reaction mechanism and ligand and additive effects. While the catalysis was found to be consistent with a $Ni^{(0)}/Ni^{(II)}$ cycle, the corresponding $Ni^{(I)}$ complex proved to be catalytically incompetent and instead constitutes a product of catalyst deactivation. The employed phosphine ligand strongly influences the overall catalytic activity via control of the ligand sphere in the resting state. The small-bite-angle ligand dppe was found to form [$Ni^{(0)}(dppe)_2$] as the resting state, while the effective wide-bite-angle ligand dppf forms [(dppf)$Ni^{(0)}$(cod)]. Computational studies revealed that the initial ligand dissociation step to give "$Ni^{(0)}$L" is the key difference in catalytic performance. The dissociation of one dppe from [$Ni^{(0)}(dppe)_2$] is associated with a much greater energy penalty than the loss of cod from [(dppf)$Ni^{(0)}$(cod)], rendering the latter a much more reactive system. Further studies showed that the addition of MeCN as traceless additive to $Ni^{(0)}(cod)_2$/dppf leads to increased catalytic activity and hence greater substrate scope. Computational and experimental data suggest that the

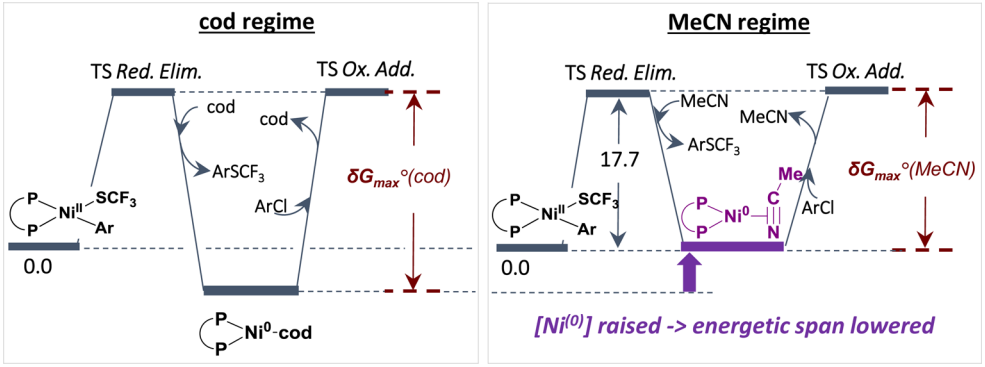


Figure 8. Schematic representation of the energetic span δG°_{max} and turnover for the catalysis by (left) [(dppf)Ni(cod] and (right) [(dppf)Ni(MeCN)].

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the beneficial effect of MeCN is due to the in situ formation of a more reactive [(dppf)Ni$^{(0)}$(MeCN)] catalyst that undergoes more facile oxidative addition, allowing also the coupling of electron-rich ArCl substrates. In addition, this leads to a decreased energetic span of the catalytic cycle and hence gives rise to higher turnover numbers. As the key reactivity findings herein are independent of the actual coupling partner, we anticipate that these results will be broadly applicable to the development of general Ni$^{(0)}$-catalyzed carbon−carbon and carbon−heteroatom bond formation reactions, including those traditionally enabled by precious Pd$^{(0)}$ catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures, spectroscopic data, computational information, Cartesian coordinates of calculated species, and complete ref 28 (as SI ref 4). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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