

Cite this: *Chem. Sci.*, 2016, 7, 1076

Nickel-catalyzed trifluoromethylthiolation of Csp²–O bonds†

Alexander B. Dürr,‡ Guoyin Yin,‡ Indrek Kalvet, François Napoly and Franziska Schoenebeck*

While nickel catalysts have previously been shown to activate even the least reactive Csp²–O bonds, *i.e.* aryl ethers, in the context of C–C bond formation, little is known about the reactivity limits and molecular requirements for the introduction of valuable functional groups under homogeneous nickel catalysis. We identified that due to the high reactivity of Ni-catalysts, they are also prone to react with existing or installed functional groups, which ultimately causes catalyst deactivation. The scope of the Ni-catalyzed coupling protocol will therefore be dictated by the reactivity of the functional groups towards the catalyst. Herein, we showed that the application of computational tools allowed the identification of matching functional groups in terms of suitable leaving groups and tolerated functional groups. This allowed for the development of the first efficient protocol to trifluoromethylthiolate Csp²–O bonds, giving the mild and operationally simple C–SCF₃ coupling of a range of aryl, vinyl triflates and nonaflates. The novel methodology was also applied to biologically active and pharmaceutical relevant targets, showcasing its robustness and wide applicability.

Received 6th September 2015

Accepted 30th October 2015

DOI: 10.1039/c5sc03359d

www.rsc.org/chemicalscience

Introduction

Owing to nickel's non-precious nature and its higher reactivity in the first elementary step of cross coupling cycles, *i.e.* the oxidative addition, the field of homogeneous Ni-catalysis has long been considered promising, yet also challenging.¹ This is because difficulties have frequently been encountered in taming nickel's reactive nature to achieve desired selectivities and scope.² In spite of that, in recent years there has been impressive progress in the activation of the least reactive bonds, such as aromatic ethers or aryl fluorides.³ However, these milestones typically featured the conversion of C–OMe (or C–F⁴) to inert C–C or C–H bonds.^{5,6}

By contrast, less is known about the reactivity limits and molecular requirements for the installation of *potentially reactive functional groups*. We therefore envisioned that a computationally assisted development⁷ of an unprecedented Ni-catalyzed protocol for C-heteroatom bond formation presents an ideal challenge to (i) identify the general reactivity requirements for efficient Ni-catalysis and (ii) demonstrate the viability of applying computational tools to assess substrate scope.

RWTH Aachen University, Institute of Organic Chemistry, Landoltweg 1, 52074 Aachen, Germany. E-mail: franziska.schoenebeck@rwth-Aachen.de

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, ReactIR studies, computational information and Cartesian coordinates of calculated species as well as full ref. 17 are given. See DOI: 10.1039/c5sc03359d

‡ These authors contributed equally. The authors declare no competing financial interests.

As a suitable test case, we focused on the nickel-catalyzed trifluoromethylthiolation of Csp²–O bonds.⁸

The SCF₃ group makes molecules more lipophilic, increasing their membrane permeability and bioavailability.⁹ These properties are of considerable interest in a pharmaceutical and agrochemical context. Consequently, numerous efforts have been undertaken to synthesize aryltrifluoromethyl sulfides.^{10,11} In particular the direct catalytic introduction of SCF₃ is an attractive approach. While aryl halides¹² or boronic acids¹³ have successfully been converted to C–SCF₃ *via* metal catalyzed cross-coupling strategies or oxidative protocols,¹⁴ to date, there is no report of a direct and catalytic trifluoromethylthiolation of Csp²–O bonds.

Results and discussion

Given the widespread abundance of phenols, the trifluoromethylthiolation of phenol derivatives would be highly attractive for synthetic diversity. In this context, the scope could in principle range from more activated derivatives (*e.g.* aryl triflates) to the least reactive derivatives, *i.e.* aryl ethers which are present in biomass feedstocks (such as lignin¹⁵).⁶ However, while Ni-catalysis has recently been successfully utilized to activate aromatic ethers,³ we hypothesized that there might be a fundamental reactivity conflict in introducing SCF₃; the created SCF₃-product would be expected to be inherently more reactive towards oxidative addition¹⁶ which may impede further transformation.



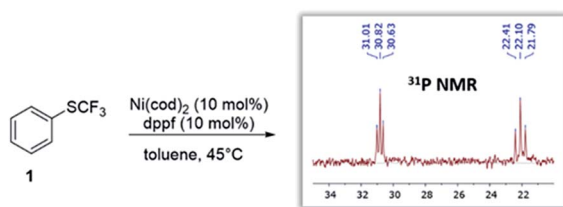


Fig. 1 Reaction of catalyst [(dppf)Ni(cod)] with the desired product (ArSCF₃) leads to catalyst deactivation.

To test this, we subjected Ni(cod)₂/dppf to PhSCF₃ **1** (see Fig. 1). We recently showed that this system triggers the mild trifluoromethylthiolation of aryl chlorides, proceeding *via* Ni⁽⁰⁾/Ni^(II) catalysis with [(dppf)Ni(cod)] formed as the active catalyst.^{12e} In accordance with our hypothesis, the reaction of the [Ni⁽⁰⁾] catalyst with PhSCF₃ is indeed seen, even under mild reaction conditions (45 °C), as judged by ³¹P-NMR spectroscopic analysis. A complete disappearance of the characteristic ³¹P-NMR singlet signal of [(dppf)Ni⁽⁰⁾(cod)] (33.8 ppm)^{12e} occurred, and the formation of a new species was seen that appears as two triplets at 30.8 ppm (with *J* = 23.0 Hz) and at 22.1 ppm (with *J* = 37.6 Hz) by ³¹P-NMR spectroscopic analysis (see Fig. 1). While our efforts to structurally characterize the latter by X-ray crystallography have so far been unsuccessful, the formed species clearly constitutes a catalyst deactivation product. The subjecting of this species as a catalyst (or also stoichiometrically) in the trifluoromethylthiolation of aryl chlorides did not yield ArSCF₃. This indicates that oxidative addition by a [Ni⁽⁰⁾] catalyst to the product is facile and eventually leads to catalytically inactive species. To achieve productive catalysis and high overall conversion, it is therefore of utmost importance to avoid this deactivation process.

Our computational assessment¹⁷ of the oxidative addition of [(dppf)Ni(cod)] to Ph-SCF₃ **1** suggests an activation free energy barrier of $\Delta G^\ddagger = 19.2$ kcal mol⁻¹, and it uses the M06L method with a CPCM solvation model to account for toluene and the mixed 6-311++G(d,p) and LANL2DZ (for Ni, Fe) basis set.^{17,18}

This value now sets the bar for the possible reaction scope. The 'to-be-transformed' bond must show a barrier *lower* than 19.2 kcal mol⁻¹ to avoid catalyst loss *via* an unproductive reaction with the product (ArSCF₃).

Identification of suitable leaving groups – computational assessment & experimental tests

We subsequently undertook computational studies to identify matching leaving groups 'OR' (Fig. 2) that would show the desired greater reactivity than the Csp²-SCF₃ bond. For the cleavage of the C–O bonds, mechanistic support for Ni⁽⁰⁾/Ni^(II)^{5i,6} and also Ni^(I)-catalysis¹⁹ has previously been reported. However, on the basis of our previous mechanistic study^{12e} and the observation that (dppf)Ni^(I)Cl is ineffective as a catalyst in C–SCF₃ bond formation,^{12e,20} as a first approximation, we calculated the activation barrier of oxidative addition using [(dppf)Ni⁽⁰⁾(cod)] to a range of phenol derivatives (Ph–OR), with R = alkyl (ether), R'C=O (pivalate), SO₂R'' (sulfonic esters). Fig. 2

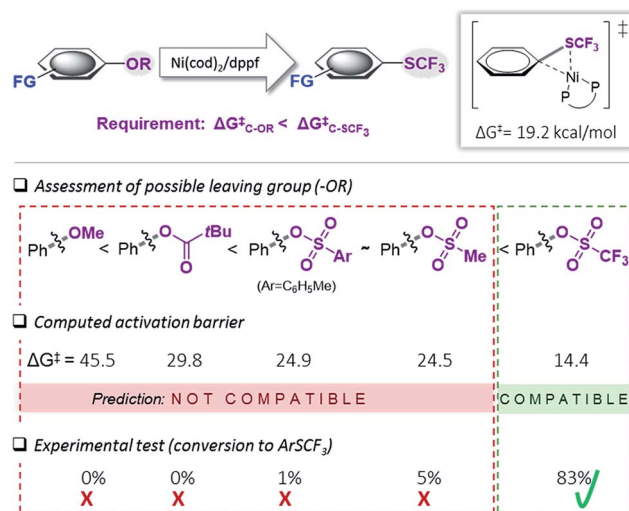


Fig. 2 Calculated free energy barrier (ΔG^\ddagger) for the oxidative addition of [(dppf)Ni⁽⁰⁾(cod)] to various Ph–OR and the testing of the prediction. Free energies in kcal mol⁻¹, calculated at CPCM (toluene) M06L/6-311++G(d,p) with LANL2DZ (for Ni, Fe).¹⁷

presents the results. This computational assessment suggests that in the context of C–O to C–SCF₃ conversion, the inherently high reactivity of C–SCF₃ only allows for triflate precursors as suitable starting materials. Alternative C–O leaving groups that have previously been employed in the Ni-catalyzed construction of inert C–C bonds, such as aryl ethers (OMe), mesylates (OMs), tosylates (OTs) or pivalates (OPiv)^{3,6} are predicted to be incompatible with Ni⁽⁰⁾-catalyzed trifluoromethylthiolation, as they would generally be less reactive than Ar–SCF₃, hence favoring catalyst deactivation *via* reaction with the product.²¹

To experimentally test this computationally predicted trend, we subjected Ni(cod)₂/dppf along with the easily accessible SCF₃-source (Me₄N)SCF₃ to Ar–OR derivatives (in toluene at 45 °C), ranging from the predicted low (aryl ether) to high (aryl triflate) reactivity (Fig. 2). In accordance with expectations, at best, a low conversion was seen for phenyl mesylates (5%), tosylates (1%) or pivalates (0%). In stark contrast, phenyl triflate showed excellent conversion to PhSCF₃ (83%).

We additionally followed the conversion ArOTf → ArSCF₃ with ReactIR®. This analysis showed that the transformation was rapid, being essentially complete in 1.5 h with only little increase in conversion over the subsequent hours (see ESI, Fig. S1†). We also analyzed the reactions of those substrates that showed little conversion (≤5%), *i.e.* AROMs and AROTf, by ³¹P-NMR spectroscopic analyses. We observed that essentially all of the [Ni⁽⁰⁾] catalyst had transformed to the catalytically inactive species described in Fig. 1 within 3 h reaction time. This clearly highlights that while [Ni⁽⁰⁾] is in fact capable of reacting with Ph–OMs or –OTs, the catalyst is rapidly consumed as soon as some of the more reactive PhSCF₃ molecules are generated. This corroborates with the strict requirement of suitably matching functionality and tailored reactivity progression from a “more” to “less reactive” functionality.



Computational assessment of functional group tolerance

We subsequently set out to test for the generality of the identified Ni-catalyzed trifluoromethylthiolation of activated C–O bonds and computationally assess the functional group (FG) tolerance (see Fig. 3). As we determined a barrier of $\Delta G^\ddagger = 14.4$ kcal mol⁻¹ for the oxidative addition of [(dppf)Ni⁽⁰⁾(cod)] to Ph–OTf, all additional functional groups (FG) in the substrates will only be compatible if the reactivity of the C–FG bond is lower than that of Ph–OTf.

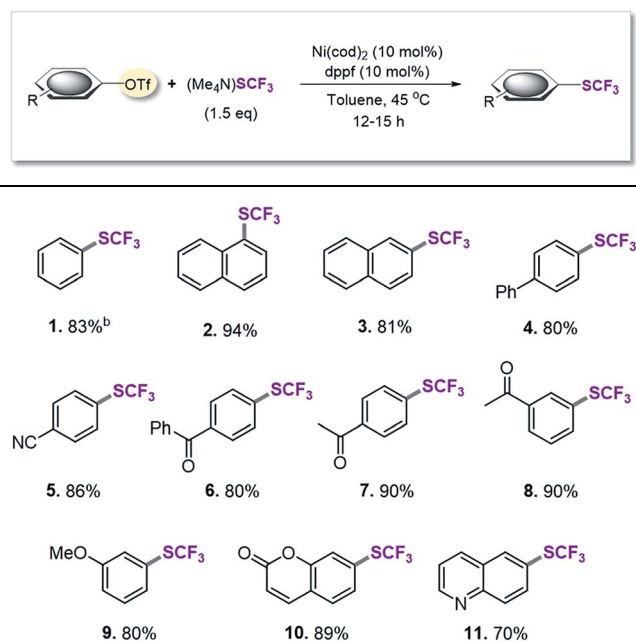
The computational results depicted in Fig. 3 suggest a tolerance of the protocol to ketone functional groups, C–C or benzylic C–O bonds. In all cases, the requirement of $\Delta G^\ddagger_{\text{C-FG}} > 14.4$ kcal mol⁻¹ is fulfilled. Even aromatic C–CN bonds that were previously shown to be reactive under Ni-catalysis conditions²² are predicted to be compatible.

SCF₃-coupling of aryl triflates

On the basis of this computationally guided substrate scope, we subjected a range of aryl triflates to standard catalysis conditions. Table 1 presents the results. A number of aryl- and heteroaryl triflates were coupled in good to excellent yields. The transformation was compatible with ketone (6, 7 and 8, Table 1), ether (9) and cyano (5) functional groups. Two heterocyclic examples (10, 11) were also trifluoromethylthiolated in good yields (see Table 1).

We next searched for bioactive molecules of greater complexity that would fulfil our reactivity requirements and show compatibility with the computationally predicted scope. Estrone (an estrogenic hormone), 6-hydroxy flavanone (a plant secondary metabolite used *inter alia* as an antioxidant) and δ -tocopherol (vitamin E) show an excellent functional group match, containing predominantly ketone and benzylic C–O bonds that are predicted to be less reactive than C–OTf and C–SCF₃. Trifluoromethylthiolation was successfully accomplished

Table 1 Ni(0)-catalyzed trifluoromethylthiolation of Ar–OTf^a



^a Ni(cod)₂ (11.0 mg, 0.04 mmol), dppf (22.2 mg, 0.04 mmol), aryl triflate (0.4 mmol), (Me₄N)SCF₃ (104 mg, 0.6 mmol), toluene (2 mL), under inert atmosphere, isolated yield. ^b Yield determined by ¹⁹F-NMR analysis using PhCF₃ as the internal standard.

in 62–96% yield, highlighting the potential of this method for pharmaceutical applications (see Scheme 1).

SCF₃-coupling of vinyl triflates

Vinyl SCF₃-compounds are also of significance, finding applications as herbicides for example.²³ However, the current methodological repertoire to access these compounds relies predominantly on indirect strategies²⁴ or requiring stoichiometric amounts of metal.^{13b,25} The direct construction of C_{vinyl}–

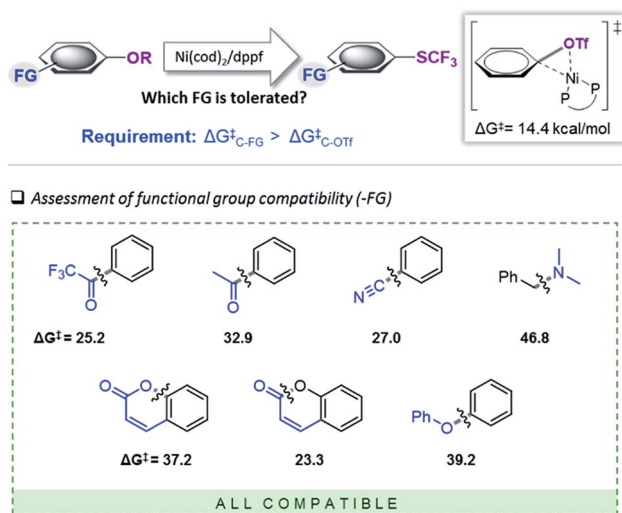
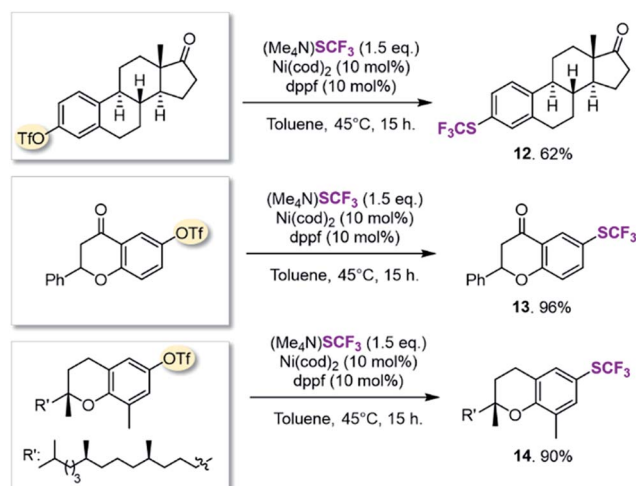


Fig. 3 Computational scoping. Activation free energies (in kcal mol⁻¹) calculated at CPCM (toluene) M06L/6-311++G(d,p) & LANL2DZ (for Ni, Fe)²⁷ for the addition of [(dppf)Ni(cod)].



Scheme 1 Synthesis of bioactive molecules.



SCF₃ in a catalytic manner would be a highly attractive approach. It has been accomplished *via* the Cu-catalyzed trifluoromethylthiolation of vinyl boronic acids with electrophilic SCF₃-sources.^{13c-e} In a nucleophilic context, the catalytic installation of C_{vinyl}-SCF₃ is limited to vinyl iodides and requires harsh reaction conditions (110 °C).²⁶

A mild Ni-catalyzed conversion of readily accessible C_{vinyl}-OR derivatives to C_{vinyl}-SCF₃ would thus substantially widen the synthetic repertoire.

Our calculation of the barrier for the oxidative addition of [Ni⁰] to C_{vinyl}-SCF₃ indicated $\Delta G^\ddagger = 18.8 \text{ kcal mol}^{-1}$. This barrier constitutes the upper limit for the reactivity of a potential leaving group (OR). C_{vinyl}-OPiv and C_{vinyl}-OMs show higher or similarly high barriers for oxidative addition ($\Delta G^\ddagger = 22.1$ and $17.7 \text{ kcal mol}^{-1}$) and are hence ruled out. C_{vinyl}-OTf on the other hand is predicted to be highly reactive ($\Delta G^\ddagger = 5.2 \text{ kcal mol}^{-1}$) and should hence be a compatible match.

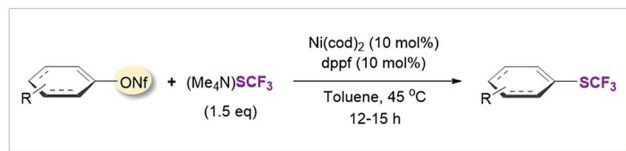
After applying standard catalysis conditions,²⁷ we successfully transformed a number of vinyl triflates to the corresponding trifluoromethylthiolated counterparts (see Table 2).

The protocol proved to be compatible with a heterocyclic moiety (20, Table 2), a benzyl protecting group (17), and was successful for fully aliphatic (15) as well as conjugated (18, 19) vinyl triflate derivatives. Compound 19 (Table 2) was afforded in a slightly lower yield (44%). However, upon closer inspection, it became clear that this was related to the inherent instability of the vinyl triflate starting material.

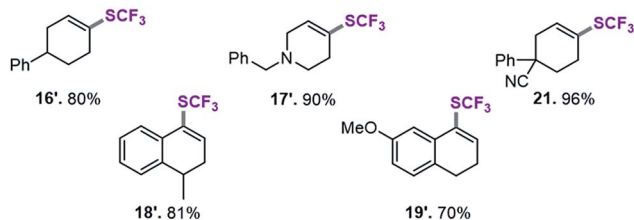
Assessment of aryl and vinyl nonaflates

We therefore shifted our attention to potentially more stable analogues and considered nonaflates.²⁸ Both, aryl and vinyl nonaflates are computationally predicted to be compatible with Ni-catalyzed trifluoromethylthiolation, showing similarly low or even lower barriers for oxidative addition by [Ni⁰] than the

Table 3 Ni(0)-catalyzed trifluoromethylthiolation of vinyl and aryl nonaflates^{a,b}



Vinyl Nonaflates

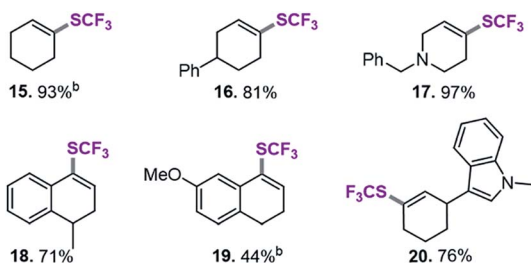
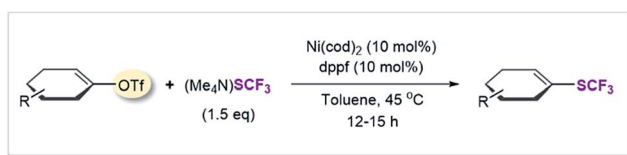


Aryl Nonaflates



^a Conditions for the coupling of vinyl nonaflates: Ni(cod)₂ (5.5 mg, 0.02 mmol), dppf (11.1 mg, 0.02 mmol), vinyl nonaflate (0.2 mmol), (Me₄N)SCF₃ (52 mg, 0.3 mmol), PhCN (20.6 mg, 0.2 mmol),²⁷ toluene (1 mL), under inert atmosphere, isolated yield. ^b Conditions for the coupling of aryl nonaflates Ni(cod)₂ (11.0 mg, 0.04 mmol), dppf (22.2 mg, 0.04 mmol), aryl nonaflate (0.4 mmol), (Me₄N)SCF₃ (104 mg, 0.6 mmol), toluene (2 mL), under inert atmosphere, isolated yield. ^c Reaction performed with MeCN (16.4 mg, 0.4 mmol). ^d Yield determined by ¹⁹F-NMR analysis using PhCF₃ as the internal standard.

Table 2 Ni(0)-catalyzed trifluoromethylthiolation of vinyl-OTf^a



^a Ni(cod)₂ (5.5 mg, 0.02 mmol), dppf (11.1 mg, 0.02 mmol), vinyl triflate (0.2 mmol), (Me₄N)SCF₃ (52 mg, 0.3 mmol), PhCN (20.6 mg, 0.2 mmol),²⁷ toluene (1 mL), under inert atmosphere, isolated yield. ^b Yield determined by ¹⁹F-NMR analysis using PhCF₃ as the internal standard.

corresponding triflates ($\Delta G^\ddagger = 4.8$ for addition to C_{vinyl}-ONf and $\Delta G^\ddagger = 10.6 \text{ kcal mol}^{-1}$ for addition to Ph-ONf). In accordance with these computational predictions, excellent conversions to aryl- and C_{vinyl}-SCF₃ were observed (see Table 3). Particularly notable is the synthesis of 19' (Table 3) which was now high-yielding (as opposed to its preparation in Table 2), reflecting the greater robustness of vinyl nonaflates over vinyl triflates.²⁹

Conclusions

The inherently high reactivities of Ni-catalysts may be fundamentally at conflict with introducing a wide range of functional groups, as shown here for the introduction of the pharmaceutically and agrochemically valuable SCF₃ group. We identified that the reaction of the Ni-catalyst with the desired product, ArSCF₃, triggers undesirable catalyst deactivation reactions that ultimately inhibit catalysis. The overall substrate scope is therefore dictated by the reactivity of the desired functionality towards the catalyst (here: C-SCF₃). The application of computational tools allowed for the identification of matching



functional groups in terms of suitable leaving groups and tolerated functional groups. As a result, the first Ni-catalyzed C–SCF₃ coupling of aryl and vinyl C–O bonds has been developed. Given the highly reactive nature of C–SCF₃, only those C–OR derivatives of even greater reactivity, *i.e.* triflates and nonaflates, allow for efficient C–SCF₃ coupling. The protocol is mild, general and operationally simple.

Given that computational methods, software and hardware have evolved to a level, at which calculations can nowadays frequently be done faster than experiments,³⁰ we anticipate that the herein applied approach will find applications in the development of, but not limited to, homogeneous Ni-catalysis.

Acknowledgements

We thank the MIWF NRW and the RWTH Aachen University for financial support. The authors gratefully acknowledge the computing time granted on the RWTH Bull Cluster in Aachen (grant number JARA0091).

Notes and references

- For reviews, see: (a) Y. Tamaru, in *Modern Organonickel Chemistry*, Wiley-VCH, Weinheim, 2005; (b) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417; (c) F.-S. Han, *Chem. Soc. Rev.*, 2013, **42**, 5270; (d) J. Montgomery, *Organonickel Chemistry*, in *Organometallics in Synthesis: Fourth Manual*, ed. B. H. Lipshutz, Wiley, Hoboken, N.J., 2013, pp. 319–428.
- C. C. J. Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062.
- For an overview, see: S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299.
- Examples of Ni-catalyzed C–F activation, see: (a) T. Braun, S. P. Foxon, R. N. Perutz and P. H. Walton, *Angew. Chem., Int. Ed.*, 1999, **38**, 3326; (b) L. Ackermann, R. Born, J. H. Spatz and D. Meyer, *Angew. Chem., Int. Ed.*, 2005, **44**, 7216; (c) S. A. Johnson, C. W. Huff, F. Ferheen Mustafa and M. Saliba, *J. Am. Chem. Soc.*, 2008, **130**, 17278; (d) M. Tobisu, T. Xu, T. Shimasaki and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 19505.
- For examples, see: (a) J. W. Dankwardt, *Angew. Chem., Int. Ed.*, 2004, **43**, 2428; (b) M. Tobisu, T. Shimasaki and N. Chatani, *Angew. Chem., Int. Ed.*, 2008, **47**, 4866; (c) B.-T. Guan, S.-K. Xiang, T. Wu, Z.-P. Sun, B.-Q. Wang, K.-Q. Zhao and Z.-J. Shi, *Chem. Commun.*, 2008, 1437; (d) P. Alvarez-Bercedo and R. Martin, *J. Am. Chem. Soc.*, 2010, **132**, 17352; (e) A. G. Sergeev and J. F. Hartwig, *Science*, 2011, **332**, 439; (f) M. Tobisu, K. Yamakawa, T. Shimasaki and N. Chatani, *Chem. Commun.*, 2011, **47**, 2946; (g) A. G. Sergeev, J. D. Webb and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 20226; (h) A. R. Ehle, Q. Zhou and M. P. Watson, *Org. Lett.*, 2012, **14**, 1202; (i) K. Muto, J. Yamaguchi, A. Lei and K. Itami, *J. Am. Chem. Soc.*, 2013, **135**, 16384; (j) Y. Hoshimoto, H. J. Yabuki, R. Kumar, H. Suzuki, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2014, **136**, 16752.
- For recent reviews on Ni-catalyzed C–O bond cleavages, see: (a) B. Su, Z.-C. Cao and Z.-J. Shi, *Acc. Chem. Res.*, 2015, **48**, 886; (b) J. Cornella, C. Zarate and R. Martin, *Chem. Soc. Rev.*, 2014, **43**, 8081; (c) T. Mesganaw and N. K. Garg, *Org. Process Res. Dev.*, 2013, **17**, 29; (d) J. Yamaguchi, K. Muto and K. Itami, *Eur. J. Org. Chem.*, 2013, 19; (e) A. Correa, J. Cornella and R. Martin, *Angew. Chem., Int. Ed.*, 2013, **52**, 1878; (f) B.-J. Li, D.-G. Yu, C.-L. Sun and Z.-J. Shi, *Chem.–Eur. J.*, 2011, **17**, 1728; (g) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346; (h) D.-G. Yu, B.-J. Li and Z.-J. Shi, *Acc. Chem. Res.*, 2010, **43**, 1486.
- For recent reviews on combining experiment and computation, see: (a) K. J. Bonney and F. Schoenebeck, *Chem. Soc. Rev.*, 2014, **43**, 6609; (b) A. S.-K. Tsang, I. A. Sanhueza and F. Schoenebeck, *Chem.–Eur. J.*, 2014, **20**, 16432; (c) G.-J. Cheng, X. Zhang, L. W. Chung, L. Xu and Y.-D. Wu, *J. Am. Chem. Soc.*, 2015, **137**, 1706.
- For examples of our activities to introduce fluorine containing groups, see: (a) P. Anstaett and F. Schoenebeck, *Chem.–Eur. J.*, 2011, **17**, 12340; (b) I. A. Sanhueza, M. C. Nielsen, M. Ottiger and F. Schoenebeck, *Helv. Chim. Acta*, 2012, **95**, 2231; (c) I. A. Sanhueza, K. J. Bonney, M. C. Nielsen and F. Schoenebeck, *J. Org. Chem.*, 2013, **78**, 7749; (d) M. C. Nielsen, K. J. Bonney and F. Schoenebeck, *Angew. Chem., Int. Ed.*, 2014, **53**, 5903; (e) M. Aufiero, T. Sperger, A. S.-K. Tsang and F. Schoenebeck, *Angew. Chem., Int. Ed.*, 2015, **54**, 10322.
- (a) A. Leo, P. Y. C. Jow, C. Silipo and C. Hansch, *J. Med. Chem.*, 1975, **18**, 865; (b) C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
- For non-catalytic or indirect synthetic methods to generate ArSCF₃ from aryl sulfides or disulfides with trifluoromethylation reagents, see: (a) V. N. Boiko, G. M. Shchupak and L. M. Yagupolskii, *Journal of Organic Chemistry of the USSR*, 1977, **13**, 972; (b) C. Wakselman and M. Tordeux, *Chem. Commun.*, 1984, 793; (c) T. Umemoto and S. Ishihara, *Tetrahedron Lett.*, 1990, **31**, 3579; (d) C. Wakselman, M. Tordeux, J. L. Clavel and B. R. Langlois, *Chem. Commun.*, 1991, 993; (e) N. Roques, *J. Fluorine Chem.*, 2001, **107**, 311; (f) G. Blond, T. Billard and B. R. Langlois, *Tetrahedron Lett.*, 2001, **42**, 2473; (g) C. Pooput, M. Medebielle and W. R. Dolbier, *Org. Lett.*, 2004, **6**, 301; (h) F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.*, 2005, **105**, 827. For syntheses in which ‘SCF₃’ functions as nucleophile or electrophile, see: (i) T. Billard and B. R. Langlois, *Tetrahedron Lett.*, 1996, **37**, 6865; (j) D. J. Adams, A. Goddard, J. H. Clark and D. J. Macquarrie, *Chem. Commun.*, 2000, 987; (k) D. J. Adams and J. H. Clark, *J. Org. Chem.*, 2000, **65**, 1456; (l) I. Kieltsch, P. Eisenberger and A. Togni, *Angew. Chem., Int. Ed.*, 2007, **46**, 754; (m) S. Capone, I. Kieltsch, O. Flögel, G. Lelais, A. Togni and D. Seebach, *Helv. Chim. Acta*, 2008, **91**, 2035; (n) K. Stanek, R. Koller and A. Togni, *J. Org. Chem.*, 2008, **73**, 7678; (o) B. Manteau, S. Pazenok, J.-P. Vors and F. R. Leroux, *J. Fluorine Chem.*, 2010, **131**, 140; (p) F. Baert, J. Colomb and T. Billard, *Angew. Chem., Int. Ed.*, 2012, **51**, 10382.



- 11 For recent reviews, see: (a) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors and F. R. Leroux, *Beilstein J. Org. Chem.*, 2013, **9**, 2476; (b) P. Chen and G. Liu, *Synthesis*, 2013, **45**, 2919; (c) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (d) F. Toulgoat, S. Alazet and T. Billard, *Eur. J. Org. Chem.*, 2014, 2415.
- 12 (a) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 7312; (b) C.-P. Zhang and D. A. Vacic, *J. Am. Chem. Soc.*, 2012, **134**, 183; (c) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan and K.-W. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1548; (d) J. Xu, X. Mu, P. Chen, J. Ye and G. Liu, *Org. Lett.*, 2014, **16**, 3942; (e) G. Yin, I. Kalvet, U. Englert and F. Schoenebeck, *J. Am. Chem. Soc.*, 2015, **137**, 4164; (f) G. Yin, I. Kalvet and F. Schoenebeck, *Angew. Chem., Int. Ed.*, 2015, **54**, 6809.
- 13 (a) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2012, **51**, 2492; (b) C.-P. Zhang and D. A. Vacic, *Chem.-Asian J.*, 2012, **7**, 1756; (c) X. Shao, X. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 3457; (d) R. Pluta, P. Nikolaienko and M. Rueping, *Angew. Chem., Int. Ed.*, 2014, **53**, 1650; (e) Q. Glenadel, S. Alazet, A. Tlili and T. Billard, *Chem.-Eur. J.*, 2015, **21**, 14694.
- 14 For examples of metal-catalyzed C–H trifluoromethylthiolation of arenes, see: (a) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237; (b) C. Xu and Q. Shen, *Org. Lett.*, 2014, **16**, 2046.
- 15 J. Zakzeski, P. C. A. Bruijninx, A. L. Jongerius and B. M. Weckhuysen, *Chem. Rev.*, 2010, **110**, 3552.
- 16 For precedence of aryl sulfide cleavage under Ni-catalysis, see: (a) S. Kanemura, A. Kondoh, H. Yorimitsu and K. Oshima, *Synthesis*, 2008, 2659; (b) K. Lee, C. M. Counciller and J. P. Stambuli, *Org. Lett.*, 2009, **11**, 1457; (c) L. Melzig, A. Metzger and P. Knochel, *Chem.-Eur. J.*, 2011, **17**, 2948; (d) N. Barbero and R. Martin, *Org. Lett.*, 2012, **14**, 796.
- 17 *Gaussian 09, Revision D.01*, M. J. Frisch, *et al.*, [see ESI† for full reference], The geometries were optimized in the gas-phase at B3LYP/6-31G(d) with LANL2DZ (for Ni, Fe).
- 18 For appropriateness of method, see: (a) T. Sperger, I. A. Sanhueza, I. Kalvet and F. Schoenebeck, *Chem. Rev.*, 2015, **115**, 9532; (b) M. T. Haynes, P. Liu, R. D. Baxter, A. J. Nett, K. N. Houk and J. Montgomery, *J. Am. Chem. Soc.*, 2014, **136**, 17495; (c) T. Mesganaw, A. L. Silberstein, S. D. Ramgren, N. Fine Nathel, X. Hong, P. Liu and N. K. Garg, *Chem. Sci.*, 2011, **2**, 1766; (d) See also: ref. 12e.
- 19 For mechanistic support of Ni⁽⁰⁾ as catalyst in C–O cleavage, see: J. Cornella, E. Gomez-Bengoa and R. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 1997.
- 20 Using 10 mol% of [(dppf)Ni⁽⁰⁾(Cl)] complex as catalyst for the trifluoromethylthiolation of PhOTf with (Me₄N)(SCF₃) at 45 °C for 12 h in toluene, no reaction was seen.
- 21 We did not consider the influence of other substituents or alternative mechanisms on this trend. It is likely, that specialized substrates with electronic bias may also allow for selected examples of these functional groups to be converted. The goal of this assessment was to identify compatible functionality that would allow for widest possible scope in the context of [Ni(0)] catalysis.
- 22 (a) J. J. Garcia, N. M. Brunkan and W. D. Jones, *J. Am. Chem. Soc.*, 2002, **124**, 9547; (b) D.-G. Yu, M. Yu, B.-T. Guan, B.-J. Li, Y. Zheng, Z.-H. Wu and Z.-J. Shi, *Org. Lett.*, 2009, **11**, 3374; (c) J.-S. Zhang, T. Chen, J. Yang and L.-B. Han, *Chem. Commun.*, 2015, **51**, 7540.
- 23 S. Scheiblich, T. Maier and H. Baltruschat, PCT Int. Appl., CODEN: PIXXD2, WO 01/36410A1, 2001, 41 pp.
- 24 For a review, see: A. Y. Sizov, A. N. Kovregin and A. F. Ermolov, *Russ. Chem. Rev.*, 2003, **72**, 357.
- 25 Y. Huang, J. Ding, C. Wu, H. Zheng and Z. Weng, *J. Org. Chem.*, 2015, **80**, 2912.
- 26 M. Rueping, N. Tolstoluzhsky and P. Nikolaienko, *Chem.-Eur. J.*, 2013, **19**, 14043.
- 27 PhCN was also added. For the beneficial effect of nitrile, see: ref. 12e.
- 28 J. Högermeier and H.-U. Reissig, *Adv. Synth. Catal.*, 2009, **351**, 2747.
- 29 For examples of the superiority of nonaflates: (a) S. Bräse and A. de Meijere, *Angew. Chem., Int. Ed.*, 1995, **34**, 2545; (b) K. Voigt, P. von Zezschwitz, K. Rosauer, A. Lansky, A. Adams, O. Reiser and A. de Meijere, *Eur. J. Org. Chem.*, 1998, 152; (c) A. E. Jensen, W. Dohle and P. Knochel, *Tetrahedron*, 2000, **56**, 4197; (d) G. Dunet and P. Knochel, *Synlett*, 2006, 407.
- 30 The total time necessary for optimization, frequency and energy calculation of the oxidative addition TSs was on average 11.5 h (using 6 cores and 10GB memory on a MPI-S node of the RWTH Bull cluster).

