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Nickel-Catalyzed Stille Cross Coupling of C—O Electrophiles

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Supporting Information Placeholder

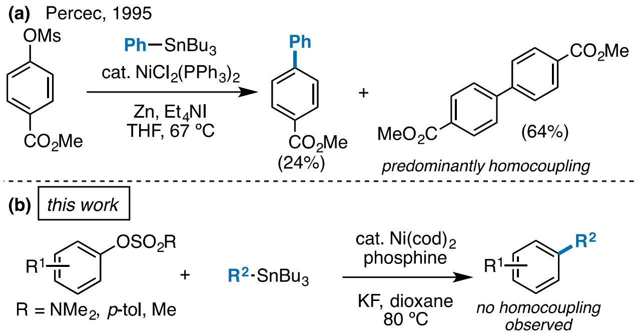
ABSTRACT: Aryl sulfamates, tosylates, and mesylates undergo efficient Ni-catalyzed cross coupling with diverse organostannanes in the presence of relatively unhindered alkylphosphine ligands and KF. The coupling is valuable for difficult bond constructions, such as aryl—heteroaryl, aryl—alkenyl, and aryl—alkynyl, using non-triflate phenol derivatives. A combination of experimental and computational studies implicate an unusual mechanism for transmetalation involving an 8-centered cyclic transition state. This reaction is inhibited by chloride sources due to slow transmetalation of organostannanes at a Ni(II)—chloride intermediate. These studies help to explain why prior efforts to achieve Ni-catalyzed Stille coupling of phenol derivatives were unsuccessful.

Keywords: *cross-coupling, DFT, nickel, phenol derivatives, transmetalation*

Phenol-derived electrophiles have numerous advantages over aryl halides as cross coupling partners including synthetic utility as directing groups as well as the low cost and high availability of phenols.[1] Highly activated phenol derivatives like aryl triflates are difficult to carry through multiple synthetic steps because of their tendency toward hydrolysis. However, recent developments in nickel catalysis have enabled less labile phenol derivatives such as sulfonates, sulfamates, carbamates, and esters to be used in Suzuki-Miyaura,[2] Negishi,[3] Kumada,[3a,4] and other cross couplings.[1] Despite these advances, the Ni-catalyzed Stille coupling of phenol derivatives has remained elusive since Percec's early report that homocoupling dominates in the reaction of aryl mesylates with $PhSnBu_3$ using $NiCl_2(PPh_3)_2$ as a precatalyst (Scheme 1a).[3a,5] The poor efficiency of cross coupling was attributed to slow transmetalation from tin to nickel.

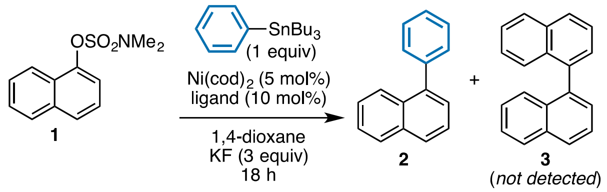
The palladium-catalyzed Stille coupling of aryl halides and triflates is a powerful C—C bond-forming strategy.[6] Although other methods—especially Suzuki-Miyaura couplings—are often preferred because of tin's toxicity, the Stille coupling remains important due to the stability and high functional group tolerance of organostannanes.[7,8] Nevertheless, when using more inert phenol-derived electrophiles, the Pd-catalyzed Stille reaction is limited to unhindered electron-deficient or -neutral aryl sulfonates and a small scope of organostannanes.[9] Because Ni is more reactive than Pd with C—O bonds,[1] we reasoned that Ni catalysis should enable more efficient and general Stille coupling of non-triflate phenol derivatives if the problem of slow transmetalation can be overcome. Here we report that Ni(0) catalyzes the cross coupling of diverse aryl sulfamates and sulfonates with aryl, heteroaryl, alkenyl, alkynyl, and allylstannanes (Scheme 1b). Moreover, we provide evidence for a novel transmetalation mechanism and an explanation for an inhibitory effect of chloride in this system.

Scheme 1. Ni-Catalyzed Stille Coupling of Phenol-Derived Electrophiles



We first examined the reaction between **1** and $PhSnBu_3$ in the presence of $Ni(cod)_2$, PCy_3, and KF in 1,4-dioxane (Table 1). Aryl sulfamates are synthetically valuable C—O electrophiles because they are also effective directing groups for *ortho* metalation.[10] The ligand PCy_3 was chosen on the basis of its efficacy in Ni-catalyzed Suzuki-Miyaura couplings of aryl sulfamates.[11] KF was added because fluoride is known to accelerate Pd-catalyzed Stille couplings.[6,12,13] Poor yield of **2** was observed after 18 h at 60 ºC (entry 1), but increasing the reaction temperature to 80 ºC improves the yield of **2** to 54% (entry 2). None of the homocoupled product **3** was detected. Interestingly, the addition of LiCl shuts down reactivity (entry 3) even though chloride salts are commonly included in Pd-catalyzed Stille couplings of aryl triflates.[6,14] Gratifyingly, nearly quantitative conversion to **2** was achieved with several less sterically hindered mono-, di-, and tri-alkylphosphines (entries 4–7). At least one alkyl substituent on the phosphine is needed for high conversion: the use of PPh_3 gives only moderate yield (entry 8). No reaction is observed in the absence of KF (entry 9).

Table 1. Optimization of the Ni-Catalyzed Stille Coupling



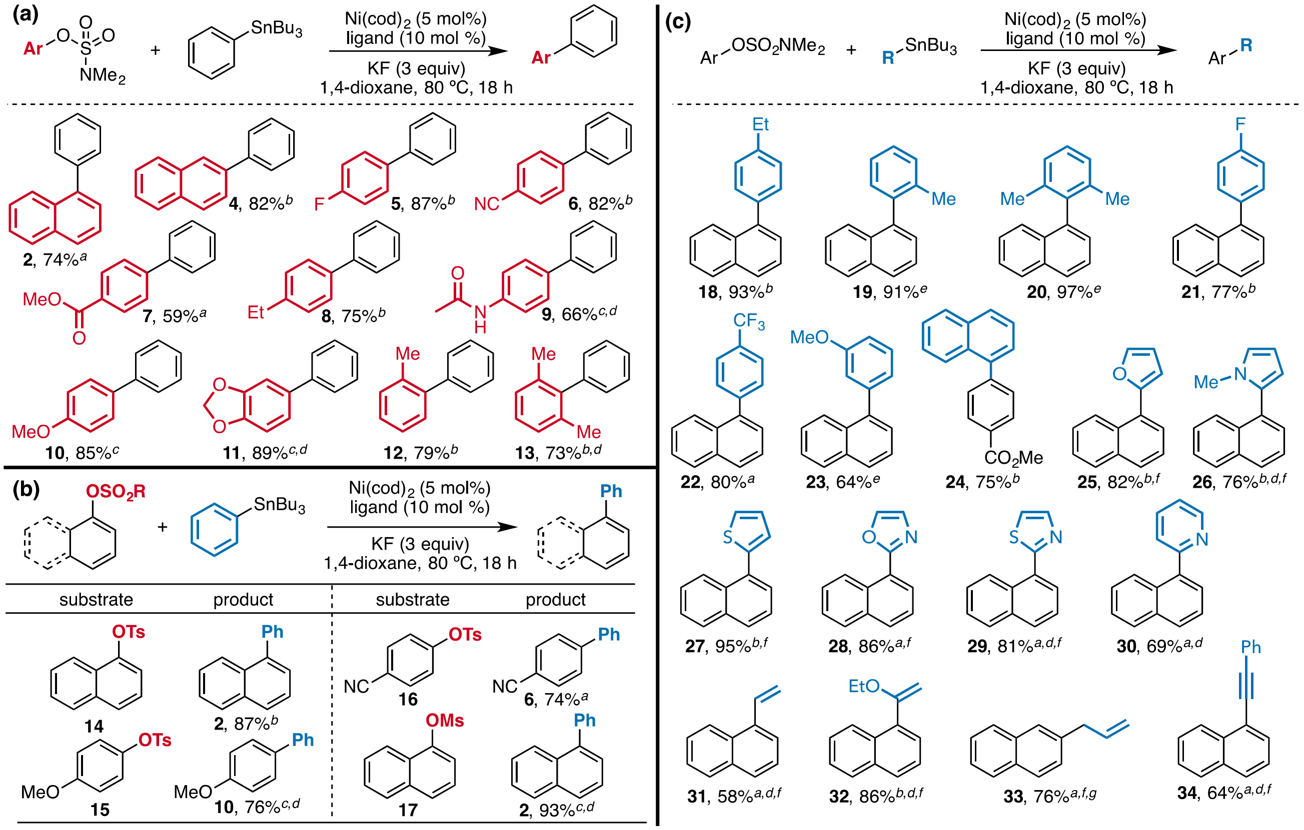
entry	ligand	temp. (ºC)	additive	**2** (%)[a]
1	PCy_3	60	--	27
2	PCy_3	80	--	60
3	PCy_3	80	LiCl (3 equiv)	n.d.
4	PBu_3	80	--	**88**
5	$PPhEt_2$	80	--	**≥99**
6	$PPhMe_2$	80	--	**96**
7	PPh_2Me	80	--	**≥99**
8	PPh_3	80	--	52
9[b]	$PPhEt_2$	80	--	n.d.

[a]GC yield calibrated against undecane as an internal standard. n.d. = not detected. Average of two runs. [b]Without KF.

With several optimal ligands in hand (PBu_3, $PPhEt_2$, $PPhMe_2$, PPh_2Me), the scope of aryl sulfamates was examined (Scheme 2a). Activated (**2**, **4**–**7**) and deactivated (**8**–**13**) aryl sulfamates undergo efficient cross coupling. Steric hindrance on the electrophile is well tolerated (**12**, **13**), as are fluorides,[15] nitriles,[16] esters,[1,2d,2e] amides,[17] and acetals[18] – functional groups that are also known to undergo activation by Ni(0) (**5**–**7**, **9**, **11**). In addition to aryl sulfamates, both activated (**14**, **16**) and deactivated (**15**) aryl tosylates, as well as naphthyl mesylate **17**, readily undergo the Ni-catalyzed Stille coupling (Scheme 2b).

Diverse organostannanes are effective coupling partners, including aryl tributylstannanes bearing electron-donating (**18**–**20**) and -withdrawing (**21**–**23**) substituents or containing fused aromatic rings (**24**) (Scheme 2c). This reaction is effective for constructing diverse C—C bonds that are largely inaccessible from non-triflate phenol derivatives by other cross coupling methods. For example, 2-(tributylstannyl) oxygen-, nitrogen-, and sulfur-containing five- and six-membered heteroaryl nucleophiles undergo efficient cross coupling (**25**–**30**). In contrast, the analogous Suzuki-Miyaura coupling of non-triflate phenol derivatives has not been demonstrated with most of the corresponding organoboron reagents.[19] Alkenyl stannanes (**31**, **32**) are readily coupled to afford products complementary to the Ni-catalyzed Heck reaction of non-triflate phenolic electrophiles,[20] a reaction that is limited to

Scheme 2. Scope of (a) Aryl Sulfamates, (b) Other Phenol Derivatives, and (c) Organostannanes.

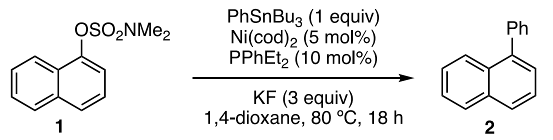


Ligand = [a]PPhMe$_2$, [b]PPhEt$_2$, [c]PBu$_3$. [d]With 10 mol% Ni(cod)$_2$ and 20 mol% ligand. [e]Ligand = PPh$_2$Me. [f]BHT added during isolation. [g]Product comprises ~9:1 ratio of **33** to the isomerized alkene 2-(1-propen-1-yl)naphthalene.

alkyl- or aryl-substituted alkenes and does not include enol ethers. The use of allyl- and alkynyltributyl stannanes permits allylation and alkynylation of phenol-derived electrophiles (**33**, **34**).[21,22]

As described above, during reaction optimization we found that 3 equiv of LiCl completely inhibits this Ni-catalyzed reaction (see Table 1 entry 3). Further exploration revealed that even a substoichiometric quantity of LiCl severely impairs catalysis (Table 2, compare entries 1 and 2). The inhibitory effect of LiCl is observed even when Li$^+$ is sequestered by a crown ether (entry 3), suggesting that inhibition is due to chloride rather than Li$^+$. The crown ether itself does not inhibit catalysis (entry 4). To further explore this phenomenon, additional chloride salts were evaluated as additives. Indeed, NBu$_4$Cl, KCl, and ZnCl$_2$ were all found to impair catalysis even at low loadings (10 mol%, entries 5–7).

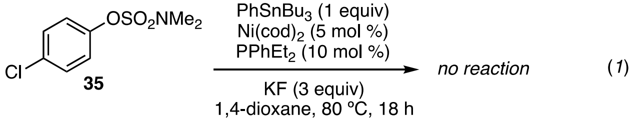
Table 2. Inhibition of catalysis by chloride sources.



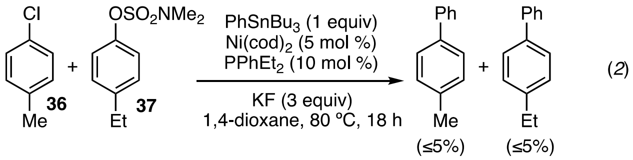
entry	additive(s)	**2** (%)[a]
1	none	≥99[b]
2	LiCl (10 mol%)	13[b]
3	LiCl (10 mol%) + 12-crown-4 (20 mol%)	13[b]
4	12-crown-4 (20 mol%)	≥99[b]
5	NBu$_4$Cl (10 mol%)	10[b]
6	KCl (10 mol%)	42[b]
7	ZnCl$_2$ (10 mol%)	n.d.

[a]GC yield calibrated against undecane as an internal standard. n.d. = not detected. [b]Average of two runs.

Consistent with catalyst inhibition by chloride sources, no reaction is observed using a chloro-substituted aryl sulfamate **35** (eq 1). An exogeneous aryl chloride **36** also inhibits the Ni-catalyzed Stille coupling of aryl sulfamate **37** (eq 2). Interestingly, cross coupling of the aryl chloride does not take place either, even though aryl chlorides are excellent coupling partners in other types of Ni-catalyzed



(1)



(2)

cross couplings.[23] We hypothesize that the Ni(II)—chloride species formed upon oxidative addition of an aryl chloride,[24] or by anion exchange between a Ni(II)—sulfamate and exogeneous Cl^-, is relatively inert toward transmetalation with $PhSnBu_3$.[25] Consequently, the catalyst is deactivated by aryl chlorides or chloride salts. This hypothesis could also help to explain why the use of $NiCl_2(PPh_3)$ leads to slow transmetalation with organostannanes, as described by Percec and coworkers.[3a]

To explore this hypothesis, DFT calculations were performed to compare possible mechanisms for transmetalation from tin to nickel using PMe_3 and $PhSnMe_3$ as computationally convenient models (Figure 1a).[26,27] We focused on transmetallation at Ni(II) because recent studies on related Suzuki-Miyaura couplings of aryl sulfamates support a Ni(0)/(II) catalytic cycle in which any Ni(I) species exist as unproductive off-cycle intermediates.[19a,28,29] Complex **38** represents the species resulting from oxidative addition of an aryl sulfamate at Ni(0).[30] In Mechanism A, **38** reacts directly with $PhSnMe_3$, and transmetalation proceeds through a 6-centered cyclic transition state (**TSA**). In Mechanism B, **38** is intercepted by a pentavalent tin fluoride species formed from the reaction of $PhSnMe_3$ with KF.[12b,h,i] Transmetalation takes place through a novel 8-centered transition state with K^+ acting as a bridge between fluoride and oxygen (**TSB**). Mechanism C represents a possible path in the presence of chloride salts: this mechanism proceeds through formation of Ni(II)–chloride complex **39C**, followed by transmetalation through a 4-centered cyclic transition state **TSC**. Finally, Mechanism D proceeds through formation of a Ni(II)–fluoride complex **39D** (by anion exchange using KF) and involves F····Sn bond-formation in the 4-centered transition state **TSD**.[31,32]

The calculations suggest that, in the absence of chloride, transmetalation proceeds through Mechanism B or D. Both mechanisms justify the requirement for KF in the catalytic conditions, and are characterized by relatively low free energies of activation (15.0 kcal/mol for **TSB** measured from **38**, and 20.4 kcal/mol for **TSD** measured from **39D**). In contrast, Mechanism A's barrier is much higher (27.8 kcal/mol for **TSA**). The relevance of Mechanism D depends on whether a Ni(II)–fluoride species (**39D**) forms rapidly under the reaction conditions. To explore this possibility, we turned to stoichiometric oxidative addition studies. Aryl sulfamate **42** reacts with $Ni(cod)_2$ and $PPhEt_2$ in 1,4-dioxane to give complex **43** (Figure 1B).[27b] When **43** is heated with KF in 1,4-dioxane for 1 h, no significant changes are observed by ^{31}P, ^{19}F, ^{1}H, or ^{13}C NMR, suggesting that sulfamate-for-fluoride anion exchange does not take place under these conditions.[33] As such, Mechanism D appears improbable, and Mechanism B is more likely to operate under the catalytic conditions.

Further support for the relevance of Mechanism B, involving a bridging K^+ during transmetalation, is provided by experimental evaluation of different counterions for fluoride (Table 3). Whereas **1** undergoes cross coupling in quantitative yield when KF is the fluoride source, LiF and NaF are completely ineffective for this transformation. The poor results with Li^+ and Na^+ counterions could also relate to worse solubility of these salts. However, even the

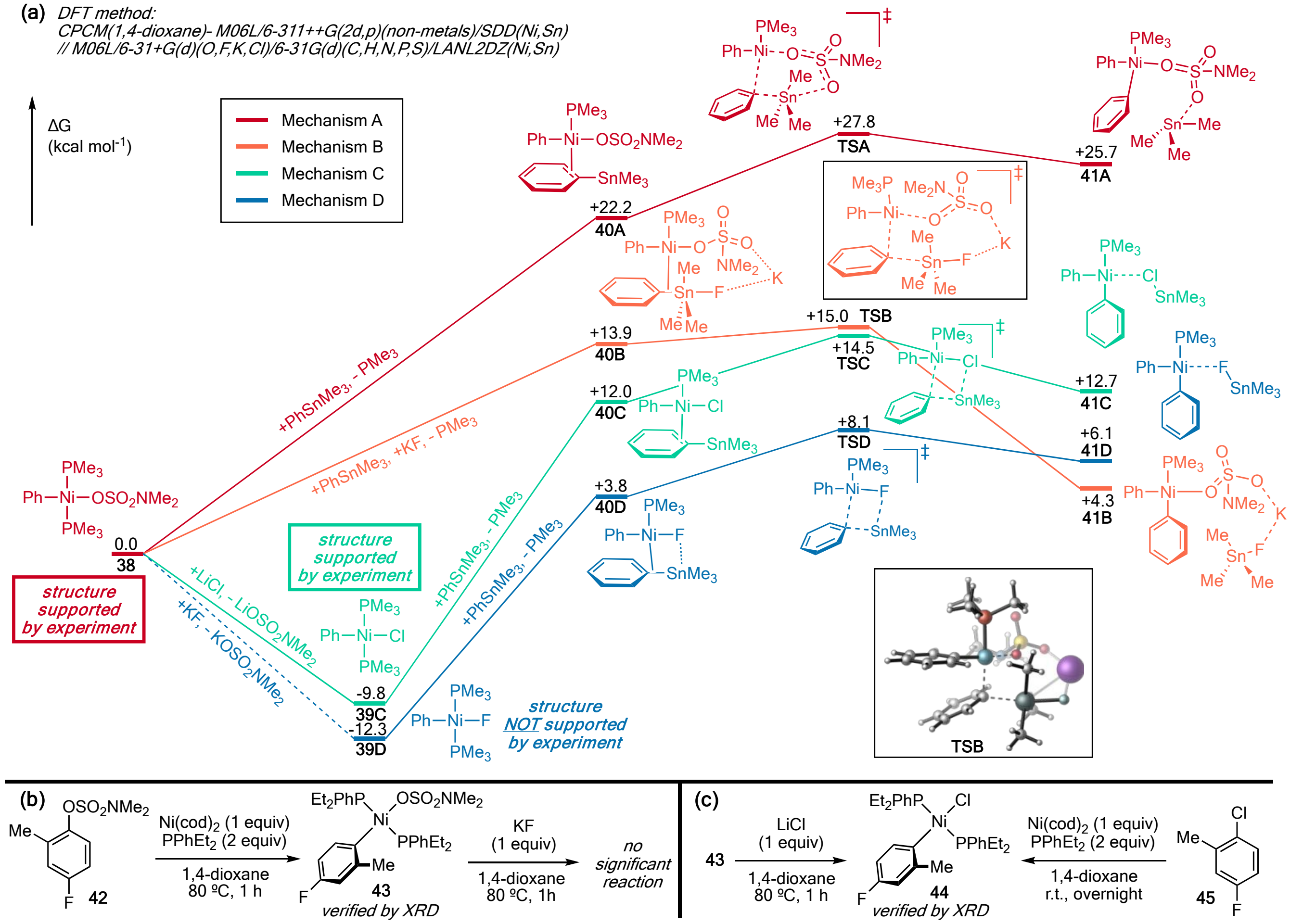
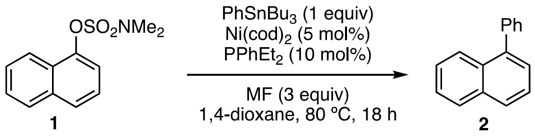


Figure 1. (a) Computational analysis of mechanistic possibilities for transmetalation. (b) Stoichiometric oxidative addition gives **43**, which does not react with KF. (c) Complex **43** reacts with LiCl.

highly soluble salt CsF gives considerably lower yields than KF, suggesting that Cs^+ may not be as effective as K^+ at forming a bridge during transmetalation.

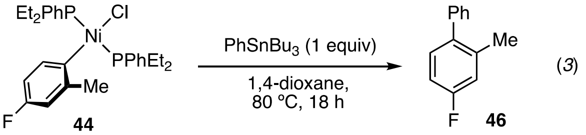
Table 3. Effect of fluoride source on cross coupling.



entry	M^+	**2** (%)[a]
1	K^+	≥99[b]
2	Li^+	n.d.
3	Na^+	n.d.
4	Cs^+	54[b]

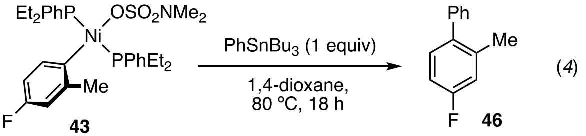
[a] GC yield calibrated against undecane as an internal standard. n.d. = not detected. [b] Average of two runs.

DFT predicts that transmetalation at a Ni(II)–chloride (Mechanism C) is considerably slower than transmetalation through either Mechanism B or D (ΔG‡ for **TSC** = 24.3 kcal/mol measured from **39C**). Accordingly, these calculations are consistent with inhibition by LiCl if a Ni(II)–chloride species forms rapidly under the reaction conditions. This possibility was also investigated through stoichiometric studies. In contrast to the observed lack of reactivity between **43** and KF, **43** is almost completely transformed into a new complex upon heating with LiCl in 1,4-dioxane for 1 h. The new complex is spectroscopically identical to the product formed upon reaction of aryl chloride **45** with $Ni(cod)_2/PPhEt_2$, corresponding to *trans* Ni(II)–chloride complex **44**. When complex **44** is heated with $PhSnBu_3$ and KF in 1,4-dioxane, only trace yield of the cross-coupled product **46** is observed (eq 3). In contrast, Ni(II)-sulfamate complex **43** provides ~42% yield of **46** under the same conditions using KF (eq 4). Notably, no cross coupling product is observed with either complex in the absence of KF. Taken together, these DFT and stoichiometric experimental studies support the hypothesis that the Ni-catalyzed Stille coupling is inhibited by chloride sources due to formation of a Ni(II)–chloride intermediate that is slow to undergo transmetalation with organostannanes.



44 **46**

without KF: n.d.
KF (3 equiv): ≤5%



43 **46**

without KF: n.d.
KF (3 equiv): 42%

In summary, this paper describes the first efficient Ni-catalyzed Stille cross-coupling of phenol-derived electrophiles. Avoidance of chloride sources and the use of KF and mono-, di-, or tri-alkylphosphines with moderate to low steric bulk are critical to achieving high yield of cross-coupled products. The cross coupling is characterized by a significantly expanded scope when compared to the Pd-catalyzed Stille coupling of aryl mesylates and tosylates.[9] This methodology is valuable for difficult bond constructions, such as aryl—heteroaryl, aryl—alkenyl, and aryl—alkynyl, using relatively inert phenol derivatives. Computational and experimental mechanistic studies suggest a novel 8-centered cyclic transmetalation transition state. In contrast to some Pd-catalyzed Stille couplings of aryl triflates, chloride sources have an inhibitory effect in this system due to the formation of Ni(II)–chloride intermediates that are slow to participate in transmetalation.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, characterization data, NMR spectra, crystallographic data, computational details, energies and Cartesian coordinates of minimum energy calculated structures (PDF)
X-ray crystallographic data for **43** and **44** (CIF)

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Notes
No competing financial interests have been declared.

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26. Calculations were performed at the CPCM(1,4-dioxane)–M06L/BS2//M06L/BS1 level, where BS1 = 6-31+G(d) for O, F, K, Cl, 6-31G(d) for C, H, N, P, S; and LANL2DZ for Ni, Sn; and BS2 = SDD for Ni, Sn; and 6-311++G(2d,p) for all other elements. Calculations performed using Gaussian09: (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; ; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; , J.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision C.1, Gaussian, Inc., Wallingford, CT, 2009. Images of optimized structures were generated with CYLview: (b) CYLview, 1.0b; Legault CY, Université de Sherbrooke, 2009 (http://www.cylview.org, accessed on 03/01/2019).

27. (a) The use of PMe_3 provides ~25% yield of **46** in the catalytic cross-coupling of substrate **42** with $PhSnBu_3$ (see SI). (b) Substrate **42** undergoes catalytic cross coupling with $PhSnBu_3$ in the presence of $Ni(cod)_2$, $PPhEt_2$, and KF to provide **46** in quantitative yield (see SI).

28. However, the involvement of odd-electron Ni species cannot be ruled out without a more in-depth mechanistic study.

29. Catalysis by Ni(I) was tentatively ruled out in a Ni-catalyzed Stille coupling of Ar—NMe_3^+ electrophiles (see ref 13).

30. Sulfamate can bind in a κ^1 or κ^2 fashion; based on experimental evidence its hapticity in an oxidative addition complex seems to depend on the size of the phosphine ligand. Compare complex **43** (κ^1 sulfamate with two $PPhEt_2$ ligands) to $ArNi(PCy_3)(\kappa^2\text{-}OSO_2NMe_2)$ in: Hooker, L. V.; Neufeldt, S. R. Ligation state of nickel during C—O bond activation with monodentate phosphines. *Tetrahedron* **2018**, *74*, 6717.

31. A 4-centered cyclic transition state involving Ni–fluoride has been proposed for the Ni-catalyzed Stille coupling of Ar—NMe_3^+ electrophiles (see ref 13).

32. 'Open' (non-cyclic) transmetalation transition states could not be located computationally. With palladium, these are considered most relevant in highly polar solvents in the absence of strongly coordinating anions, a scenario unlike the system currently under study.

33. Similarly, when **42** is stirred with $Ni(cod)_2$, $PPhEt_2$, and KF in 1,4-dioxane overnight, the only product observed by NMR is the nickel sulfamate complex **43** (there is no evidence for formation of a nickel fluoride species, see SI).

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