Aryl Mesylates in Metal Catalyzed Homo- and Cross-Coupling Reactions. 4. Scope and Limitations of Aryl Mesylates in Nickel Catalyzed Cross-Coupling Reactions

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This paper describes the synthetic utility of aryl mesylates derived from phenols in various transition metal-catalyzed cross-coupling reactions. The Ni(0)-catalyzed cross-couplings of aryl mesylates with organometallic carbanion synthons (organotin, -magnesium, and -zinc compounds) are described. It is demonstrated that Stille-type coupling reaction based on organotin compounds results in low yields due to the sluggish transmetalation step of the reaction cycle. Good to high yields of cross-coupled products are obtained by using more reactive organomagnesium and -zinc compounds as coupling partners. The Ni(0)-catalyzed cyanation of aryl mesylates is also described. Various aryl mesylates are converted to aryl nitriles in high yields by reaction with KCN in the presence of Ni(0) catalyst in DMF. In addition, the Ni(0)-catalyzed aromatic nucleophilic substitution reaction of aryl mesylates with the heteroatom-nucleophile, benzenethiolate anion, is also presented.

Introduction

Until recently, aryl mesylates were considered unreactive in transition-metal-mediated coupling and cross-coupling reactions. It was recently reported that arylmesylates participate in several synthetically important reactions.[1] These reactions include a Ni(0)-catalyzed homocoupling reaction for the synthesis of symmetrical biaryls,[1a,b] "Suzuki" type cross-coupling reactions with aryl boronic acids,[1c] and the synthesis of poly(*p*-phenylenes) via the polymerization of aryl bismesylates.[1d] These reactions provide convenient (i.e. two step) and inexpensive (relative to triflate methodology) methods to effect carbon–carbon bond formation at phenolic carbon–oxygen bonds. The unexpected synthetic utility of aryl mesylates in these reactions provided evidence that aryl mesylates can oxidatively add to Ni(0) and that the product of this oxidative addition can be transformed into useful products. Consequently, aryl mesylates may participate in other important cross-coupling reactions. In order to determine this, we undertook an investigation of the reactivity of aryl mesylates in nickel-catalyzed cross-coupling reactions with various organometallic carbanion synthons (i.e., organotin, -zinc, and -magnesium compounds), a cyanide anion, and a heteroatom-nucleophile (benzenethiolate anion). The purpose of this paper is to provide a broad survey of the reactivity of aryl mesylates in these important cross-coupling reactions, with the intention that this may spur the further development of this methodology.

The transition metal (palladium or nickel)-catalyzed cross-coupling reaction of an organic electrophile with an organometallic reagent is a versatile method for carbon–carbon bond formation.[2] Aromatic electrophiles such as aryl halides (mostly aryl bromides and iodides) and aryl triflates couple efficiently with various organometallic reagents (organotin,[3] -zinc,[4] -boron,[5] and -magnesium[6] compounds) as coupling partners or undergo addition reactions to alkene[7] and alkynes[8] under mild conditions. The participation of aryl triflates in these cross-coupling reactions is especially important in organic synthesis since this provides an efficient two-step method for the conversion of the phenolic carbon–oxygen bond to a carbon–carbon bond, which is often useful when appropriate halides are unavailable. Since aryl triflates are readily prepared from phenols[9] and they undergo facile oxidative addition to transition metals,[10a] the scope of the application of these compounds in transition metal-catalyzed reactions has broadened enormously.[10]

The classic methods for the introduction of the nitrile group into an aromatic ring are the Sandmeyer reaction[11a–c] and the cyanation of aromatic halides with

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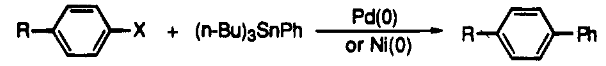
CuCN.[11d] More recently general methods for the cyanation of aryl halides involving Pd(0)-[12] or Ni(0)-catalysts[13] have been developed. Pd-catalysts have been utilized for the cyanation of aryl iodides and bromides[12a–e] and activated aryl chlorides.[12f] Ni-catalysts have been utilized for the cyanation of aryl iodides, aryl bromides, unactivated aryl chlorides,[13a–c] and heteroaryl bromides and chlorides.[13d] Tetracyanocobaltate has also been used for the cyanation reaction of several aryl halides.[14] In addition, aryl triflates have been cyanated in reactions utilizing Pd-[12a,15a] or Ni-catalysts.[15] The participation of aryl triflates in the metal-catalyzed cyanation reaction is of particular importance since it provides the shortest synthetic route for the conversion of an aromatic hydroxy group to a cyano group.

The typical method for the formation of aromatic carbon–heteroatom bonds is via S_NAr or $S_{RN}1$ displacement of a halogen.[16] Since aryl halides usually exhibit low reactivity toward nucleophiles, the S_NAr process requires activation of the aryl halide with electron-withdrawing groups. Recently transition metal catalysts were utilized to mediate the nucleophilic substitution reaction of aryl halides with heteroatoms such as sulfur[17,18] and phosphorus.[19] These reactions usually proceed regiospecifically under mild conditions.

In regard to sulfur containing nucleophiles, Ni(0)-catalyzed thiation of aryl halides (mostly bromides and iodides) with thiol,[17a] thiourea,[17b] and thiolate anion[17c] have been described. Pd(0)-catalyzed thiation of aryl halides with thioamide[18a] and thiolate anion[18b–d] was also reported. Recently, it was reported that chloroanilines (and their derivatives) react efficiently in NMP at high temperatures (up to 190 °C) with arenethiolate anions to give the corresponding aryl sulfides in the absence of transition metal catalysis.[20]

Table 1. Pd(0)- and Ni(0)-Catalyzed Cross-Coupling Reactions of Various Aryl Sulfonates with (Tri-*n*-butylphenyl)stannane[a]



entry	R	X	catalyst	yield[b] (%)
1	CH_3CO	CH_3SO_2O	$Pd(OAc)_2$ + 1.1 equiv dppp[c]	0
2	CH_3CO	CH_3SO_2O	$PdCl_2(dppf)$ + 2.0 equiv dppf[c]	13
3	CH_3O_2C	CH_3SO_2O	$NiCl_2(PPh_3)_2$	24[d]
4	CH_3O_2C	CH_3SO_2O	$NiCl_2(dppf)$	23[e]

[a] Pd(0)-catalyzed reactions were run with 5 mol % Pd catalyst, 3 equiv of LiCl, and 1.2 equiv of $PhSn(n\text{-}Bu)_3$ in DMF at 110 °C under N_2 for 24 h. Ni(0)-catalyzed reactions were run with 10 mol % Ni catalyst, 1.7 equiv of Zn, 1.5 equiv of Et_4NI, and 1.1 equiv of $PhSn(n\text{-}Bu)_3$ in THF at 67 °C under N_2 for 24 h. [b] Yields relative to aryl mesylate were determined by GC using diphenyl ether as an internal standard. [c] Equivalents relative to Pd catalyst. [d] Also produced 4,4′-dicarbomethoxybiphenyl (64%). [e] Also produced 4,4′-dicarbomethoxybiphenyl (45%).

Ni(0)-catalyzed nucleophilic displacement of aryl halides with phosphorus compounds was reported.[19a] Aryl triflate was also reported to undergo Pd(0)-catalyzed nucleophilic substitution reaction with phosphorus nucleophile,[19b] thereby providing a method for the conversion of phenols into phosphines. However, a synthetic procedure for the conversion of a phenolic oxygen to a sulfur atom has not been reported.

In summary, triflates participate, with high yields, in a number of important cross-coupling reactions. However, the high price of triflating agents (e.g., triflic anhydride) is a hindrance to the more extensive exploitation of the reactivity of this type of substrate. Therefore, the development of alternative leaving groups with similar reactivity is an important goal. The mesylate group was recently demonstrated to be a suitable alternative in several reactions.[1] We herein report that aryl mesylates participate in a number of important Ni(0)-catalyzed cross-coupling reactions resulting in good to high yields of products. Because a variety of substituted phenols are readily available and inexpensive, the use of the mesylate leaving group in Ni(0)-catalyzed cross-coupling reactions provides a very convenient and general method for the conversion of the phenolic carbon–oxygen bond to a carbon–carbon bond or to a carbon–heteroatom bond.

Results and Discussion

Ni(0)-Catalyzed Cross-Coupling of Aryl Mesylates with (Tri-*n*-butylphenyl) stannane. Table 1 summarizes a few selected results on the Pd(0)- and Ni(0)-catalyzed cross-coupling of various aryl sulfonates in-

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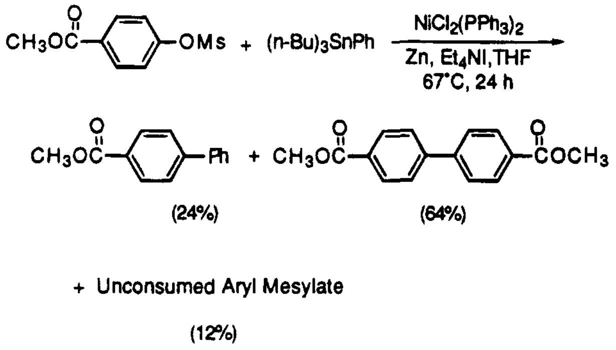
cluding mesylate with (tri-*n*-butylphenyl)stannane. A series of palladium-catalyzed reactions with electron-withdrawing *p*-acetyl and *p*-methoxycarbonyl substituted sulfonates was performed to examine the applicability of the well known "Stille coupling" methodology (i.e., palladium-catalyzed reaction of aryl triflate with organostannane) to the use of less reactive aryl mesylate as substrate. Previously, the cross-coupling of 4-acetylphenyl *p*-fluorobenzenesulfonate with tri-*n*-butylphenylstannane, catalyzed by Pd(OAc)$_2$ in the presence of dppp ligand in DMF, was reported to give a 85% yield of 4-acetylbiphenyl.[21] However, under the same conditions, only unreacted starting substrate was isolated with the mesylate (entry 1, in Table 1). In contrast, PdCl$_2$(dppf) was found to catalyze the reaction, although the yield was low (13%, entry 2 in Table 1). No further improvement in yield was obtained by employing various conditions. It is likely that the low yields obtained in Pd(0)-catalyzed Stille reaction of aryl mesylates are due to an inherent low reactivity of aryl mesylates toward palladium catalysts.

Since aryl mesylates have a high reactivity toward Ni(0) species,[1] cross-coupling of *p*-(methoxycarbonyl)phenyl mesylate with (tri-*n*-butylphenyl)stannane in the presence of a nickel catalyst (NiCl$_2$(PPh$_3$)$_2$ or NiCl$_2$(dppf)) was attempted (entries 3 and 4 in Table 1). In both cases, relatively low yields (23–24%) of cross-coupled product, as well as a fairly large amount of homo-coupled side product (45–64%), were obtained (eq 1).

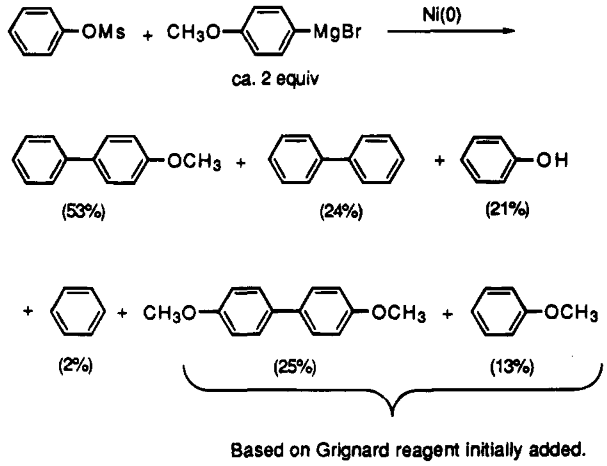


(1)

This large amount of side product may be rationalized by the poor reactivity of organostannane toward the ArNi(II)L$_2$X species (L = PPh$_3$ or THF) resulting from the oxidative addition of aryl mesylate to Ni(0) (i.e., sluggish transmetalation step of the reaction cycle), which retard the reaction leading to the cross-coupled product. On the other hand, the Ni(II) species can be further reduced by zinc to give Ni(I) species. Another mesylate can oxidatively add to this species to give a diaryl Ni(III) complex which undergoes rapid reductive elimination, resulting in the formation of the homocoupled product. In general, the transmetalation has been considered as the rate-determining step in the catalytic cycle of Pd(0)-catalyzed Stille reaction.[22] Various efforts to enhance the reactivity of the tin compound toward transmetalation resulted only in low yields.

Ni(0)-Catalyzed Cross-Coupling of Aryl Mesylates with Organomagnesium and -Zinc Compounds. The utility of organomagnesium and -zinc compounds as coupling partners with aryl mesylates in nickel(0)-catalyzed reactions was investigated. These compounds are more reactive than organostannanes toward organic electrophiles due to the partial covalent bond character of the C–Sn bond. Therefore, the slow transmetalation step (*vide supra*) was avoided. Zinc reagents were prepared *in situ* by transmetalation of the corresponding Grignard reagents with zinc chloride. For our feasibility study, we selected aryl mesylates containing no sensitive functional groups toward Grignard or zinc reagents. Table 2 lists the range of the substrates and organometallics studied.

All experiments were performed by using a catalytic system consisting of 0.1 equiv of NiCl$_2$(dppf) and 1.0 equiv of Zn. Cross-coupled products were obtained in moderate yields (Table II). When the nickel catalyst was changed to NiCl$_2$(PPh$_3$)$_2$ even in the presence of excess PPh$_3$, early catalyst decomposition was observed. Zn was not essential for the reduction of Ni(II) to Ni(0) in the presence of Grignard and zinc reagents. However, the amount of homocoupled side products derived from the Grignard and zinc reagents increased in the absence of Zn (*vide infra*). The aryl mesylate was completely consumed in most reactions involving organomagnesium compounds. In contrast, significant amounts of aryl mesylate remained in the reactions of organozinc compounds (Table 2, entries 3 and 6). Variable amounts of the two homocoupled side products, derived from aryl mesylate and Grignard reagent (or zinc reagent) were also produced (eq 2). Reduction of the aryl mesylate and Grignard reagent also occurred during the cross-coupling process. In addition, the highly reactive Grignard reagent also effected the cleavage of the sulfur–oxygen bond in aryl mesylate. The use of lower amounts of Grignard reagent produces lower yields of cross-coupling product and more homocoupling of the aryl mesylate.



(2)

It is noteworthy that Grignard reagents, being more reactive than the corresponding zinc reagents, gave higher yields of cross-coupled product (c.f. entry 2 vs entry 3, and entry 5 vs entry 6 in Table 2). The coupling reaction was inhibited by the presence of a substituent group in the ortho-position of the mesylate (c.f. entry 5 vs 7 in Table 2).

Ni(0)-Catalyzed Cyanation of Aryl Mesylates. The general procedure used for the preparation of aryl nitriles utilized the Ni(0)-catalyzed cross-coupling reaction of aryl mesylates derived from the corresponding phenols with KCN (eq 3).

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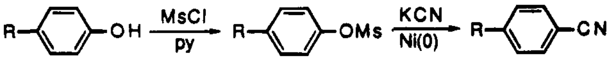
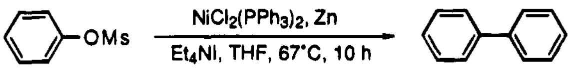


R= H, CH$_3$CO, CH$_3$O$_2$C, CN, CH$_3$ (3)

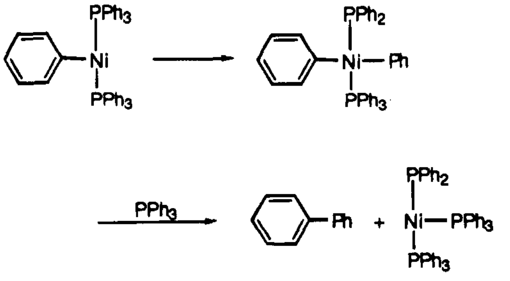
The method used to generate the Ni(0) catalyst *in situ* was first employed for the cyanation of aryl halides.[13] The Ni(0) catalyst was prepared *in situ* from NiCl$_2$(PPh$_3$)$_2$ or NiCl$_2$(dppf) with added phosphine ligand (i.e., PPh$_3$ or dppf) usually present. Excess Zn powder was used as a reducing agent. In some reactions, Et$_4$NI was added as an iodide ion source. However, it is not required when a sufficient quantity of added phosphine ligand is present (*vide infra*). The iodide ion has been reported to facilitate the electron transfer between Ni and Zn in the reduction step.[23ab] Cyanide ions poison the nickel catalyst when their concentration is too high.[13] One approach to maintaining a low concentration of cyanide ion is to use a cyanide ion source which has low solubility in the reaction solvent.[13c] Thus, a series of cyanation experiments was performed with phenyl mesylate using KCN as cyanide ion source in THF, CH$_3$CN, or DMF at 60 °C (Table 3).

When the Ni(0) catalyst was generated from NiCl$_2$(PPh$_3$)$_2$ in THF with no added PPh$_3$, the cross-coupled product (benzonitrile) was obtained in 21% yield (Table 3, entry 1). A side reaction product (biphenyl) was formed in 11% yield. The balance of phenyl mesylate (68%) remained unreacted. There are several reactions which could generate biphenyl. Perhaps, the most likely one, is the homocoupling reaction of phenyl mesylate to give biphenyl. This reaction has been shown to proceed in 91% yield in THF (eq 4).[1a]



91% (4)

Another possible source of biphenyl is the coupling of phenyl mesylate with a phenyl group from PPh$_3$ (eq 5).[1a] When the reaction was performed in a dipolar aprotic solvent such as CH$_3$CN under identical conditions as entry 1 in Table 3, the same amount of benzonitrile was formed (21%) and a greatly reduced amount of biphenyl (0.09%) was obtained (Table 3, entry 2). The addition of 0.2 equiv of PPh$_3$ to the reaction mixture in THF resulted in a slightly increased benzonitrile yield (25%) and in a greatly reduced amount of biphenyl (1.1%, Table 3, entry 3).



(5)

Table 2. Ni(0)-Catalyzed Cross-Coupling Reaction of Aryl Mesylates with Organomagnesium and -Zinc Compounds[a]

entry	ArOMs	RMX	product	yield[b] (%)
1	PhOMs	p-CH$_3$PhMgBr	p-CH$_3$PhPh	46
2	PhOMs	p-CH$_3$OPhMgBr	p-CH$_3$OPhPh	53
3	PhOMs	p-CH$_3$OPhZnCl	p-CH$_3$OPhPh	31[c]
4	PhOMs	n-BuMgBr	n-BuPh	31
5	p-CH$_3$PhOMs	CH$_3$MgI	p-CH$_3$PhCH$_3$	83[d]
6	p-CH$_3$PhOMs	CH$_3$ZnCl	p-CH$_3$PhCH$_3$	73[e]
7	o-CH$_3$PhOMs	CH$_3$MgI	o-CH$_3$PhCH$_3$	66
8	p-CH$_3$OPhOMs	CH$_3$MgI	p-CH$_3$OPhCH$_3$	54
9	p-CH$_3$OPhOMs	PhMgBr	p-CH$_3$OPhPh	60

[a] Reactions were run with 10 mol % NiCl$_2$(dppf), 1.0 equiv of Zn, and 1.8–2.0 equiv of RMX in THF at rt under N$_2$ for 10 h. [b] Yields relative to aryl mesylate were determined by GC using diphenyl ether as an internal standard. Complete consumption ($\geq$99%) of aryl mesylate occurred unless otherwise noted. [c] 56% PhOMs, [d] 5% p-CH$_3$PhOMs, and [e] 11% p-CH$_3$PhOMs, respectively, remained after reaction.

When the same reaction conditions were utilized using CH$_3$CN as solvent, the yield was slightly reduced (17%), but the amount of biphenyl formed (0.01%) was greatly reduced (Table 3, entry 4). The detection of biphenyl in the reaction mixture was not surprising given that THF had previously been shown to be an excellent solvent for the homocoupling reaction.[1a] Therefore, in order to reduce the amount of homocoupled side product, dipolar aprotic solvents such as CH$_3$CN or DMF were utilized as solvent for most of the cyanation reactions of the present study (*vide infra*).

A virtually identical yield to that obtained using Et$_4$NI, could be obtained in its absence in CH$_3$CN by increasing the amount of PPh$_3$ (cf. Table 3, entries 3 and 5). These results indicate that an identical yield of cyanation product could be obtained in the absence of Et$_4$NI by increasing the amount of PPh$_3$ appropriately. The same trend was also observed previously for the Ni(0)-catalyzed homocoupling reaction of aryl mesylates.[1a]

In CH$_3$CN, a catalytic species generated from NiCl$_2$(dppf) and dppf produced higher yields (e.g. 34%, Table 3, entry 6) although more biphenyl (5.6%) was obtained. An almost identical yield (32%) was obtained in the absence of Et$_4$NI when extra dppf was added (c.f., Table 3, entries 6 and 7). In contrast a 28% yield was obtained with the NiCl$_2$(PPh$_3$)$_2$ catalytic system with only 0.09% biphenyl formation (Table 3, entry 5). An increased conversion to benzonitrile (55%) was obtained using 0.30 equiv of NiCl$_2$(PPh$_3$)$_2$ with only trace amounts of biphenyl (0.05%) detected (Table III, entry 8).

The highest yields were obtained when DMF was used as the reaction solvent. When the cyanation was performed using 0.1 equiv of NiCl$_2$(PPh$_3$)$_2$ in DMF at 60 °C, an increased amount of benzonitrile was obtained, significantly without the formation of the homocoupled side product (60%, Table 3, entry 9). When the same reaction conditions were utilized at a higher temperature of 80 °C, a higher yield of benzonitrile with a trace amount of homocoupled side product was obtained (80%, Table 3, entry 10). Recently the Pd(PPh$_3$)$_4$-catalyzed high yield reaction of aryl bromides with Zn(CN)$_2$, which is less soluble than KCN in DMF, was reported.[12e] However, a very low yield (3%, Table 3, entry 11) was obtained using Zn(CN)$_2$ as the cyanide source. Interestingly, the addition of 1 equiv of NaBr as a halide source with a

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[23] (a) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80. (b) Zembayashi, M.; Tamao, K.; Yoshida, J.; Kumada, M. *Tetrahedron Lett.* **1977**, 4089. (c) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460. (d) Colon, I.; Kelsey, D. R. *J. Org. Chem.* **1986**, *51*, 2627. (e) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547. (f) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319. (g) Amatore, C.; Jutand, A. *Organometallics* **1988**, *7*, 2203.

Table 3. Nickel (0) Catalyzed Cyanation of Phenyl Mesylate[a]

$$\text{Ph-OMs} + \text{KCN} \xrightarrow[\text{-KOMs}]{\text{Ni(0)}} \text{Ph-CN} + \text{Ph-Ph}$$

entry	nickel catalyst (equiv)[b]	PPh_3 (equiv)[b]	Zn (equiv)[b]	Et_4NI (equiv)[b]	KCN (equiv)[b]	solvent	reaction time (h)	GC yield[c] (%)	
								PhCN	Ph_2
1	$NiCl_2(PPh_3)_2$ (0.10)	–	1.7	1.5	1.1	THF	12	21	11
2	$NiCl_2(PPh_3)_2$ (0.10)	–	1.7	1.5	1.1	CH_3CN	12	21	0.09
3	$NiCl_2(PPh_3)_2$ (0.10)	0.2	1.7	1.5	1.1	THF	12	25	1.1
4	$NiCl_2(PPh_3)_2$ (0.10)	0.2	1.7	1.5	1.1	CH_3CN	12	17	0.01
5	$NiCl_2(PPh_3)_2$ (0.10)	0.8	0.6	–	1.1	CH_3CN	24	28	0.09
6	$NiCl_2$(dppf) (0.10)	0.1[d]	0.3	0.3	1.5	CH_3CN	12	34	5.6
7	$NiCl_2$(dppf) (0.10)	0.4[d]	0.6	–	1.5	CH_3CN	12	32	4.7
8	$NiCl_2(PPh_3)_2$ (0.10)	0.6	0.6	0.6	1.5	CH_3CN	12	55	0.05
9	$NiCl_2(PPh_3)_2$ (0.10)	0.2	1.0	–	1.5	DMF	12	60	–
10[e]	$NiCl_2(PPh_3)_2$ (0.10)	0.2	1.0	–	1.5	DMF	12	80[f]	0.1
11[e]	$NiCl_2(PPh_3)_2$ (0.10)	0.2	1.0	–	1.0[g]	DMF	12	3[h]	0.4
12[i,j]	$NiCl_2(PPh_3)_2$ (0.10)	0.2	1.0	–	1.0[g]	DMF	12	46[k]	11

[a] All reactions were performed at 60 °C unless otherwise noted. [b] Equivalents relative to phenyl mesylate. [c] Yields relative to phenyl mesylate were determined by GC using diphenyl ether as an internal standard. Incomplete reaction of phenyl mesylate occurred unless otherwise noted. [d] Dppf was used as added ligand instead of PPh_3. [e] The reaction was carried out at 80 °C. [f] 1% PhOMs and 4% PhH were present after the reaction. [g] $Zn(CN)_2$ was used instead of KCN. [h] <1% PhOMs was present after the reaction. [i] The reaction was carried out at 100 °C. [j] 1.0 equiv of NaBr was added. [k] 7% PhOMs was present after the reaction.

Table 4. Nickel(0)-Catalyzed Cyanation of Various Aryl Mesylates[a]

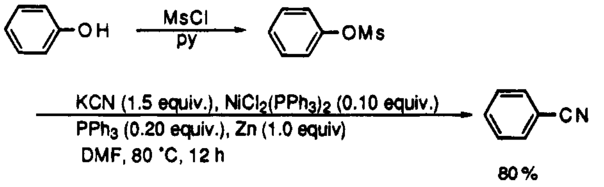
$$\text{R-Ph-OMs} + \text{KCN} \xrightarrow[\text{-KOMs}]{\text{Ni(0)}} \text{R-Ph-CN} + \text{R-Ph-Ph-R} + \text{R-Ph-H}$$

entry	R	GC yield[b] (%)		
		RPhCN	RPhPhR	RPhH
1	*p*-CH_3CO	93	–	7
2	*p*-CH_3O_2C	84	1	15
3	*o*-CH_3O_2C	59	–	4[c]
4	*p*-CN	81	–	19
5	*p*-CH_3	77	–	23
6	*p*-CH_3O	82	–	18

[a] All reactions were performed in DMF at 80 °C for 12 h. Molar ratio of ArOMs/$NiCl_2(PPh_3)_2$/PPh_3/Zn/KCN was 1.0/0.10/0.20/1.0/1.5. [b] Yields relative to aryl mesylate were determined by GC using diphenyl ether as an internal standard. [c] The remaining material isolated was unreacted starting material (37%).

concurrent increase in temperature to 100 °C promoted the cyanation resulting in a much higher yield of 46%, although a significant amount of biphenyl (11%) was obtained (Table 3, entry 12).

In summary, the highest yield in the cyanation reaction of phenyl mesylate was obtained in the reaction with KCN (1.5 equiv) in DMF at 80 °C in the presence of $NiCl_2(PPh_3)_2$ (0.10 equiv), PPh_3 (0.20 equiv) and Zn (1.0 equiv) (eq 6).



(6)

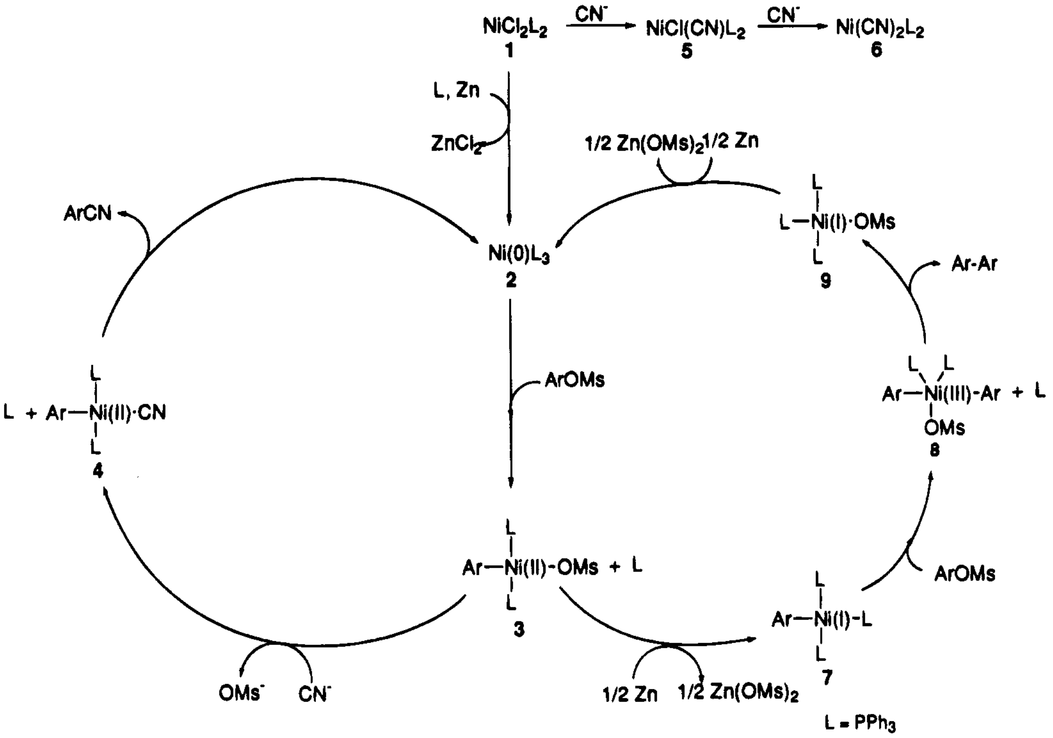
Previous Ni-catalyzed cyanation procedures have often involved tedious procedures such as the pretreatment of Ni(II) with Zn followed by successive addition of substrate and cyanide or the slow addition of cyanide into the mixture of catalyst and substrate. These procedures have been employed in order to efficiently generate the active Ni(0) catalysts and to prevent it from being poisoned by the cyanide ion.[13b,c] However, these precautions were unnecessary in the present cyanation reaction. Therefore, this method is an experimentally convenient procedure.

Using these reaction conditions, the influence of substituents on the cyanation reaction was investigated. The results are presented in Table 4. Increased yields, relative to phenyl mesylate, were obtained when the para substituent was an electron-withdrawing group (i.e., acetyl, carbomethoxy or cyano, entries 1–2 and 4 in Table 4). When the para-substituent was the electron-donating *p*-methyl group, a reduced yield was obtained (Table 4, entry 5). However, slightly increased yield (relative to phenyl mesylate) was obtained when the substituent was a methoxy group (82%, entry 6 in Table 4). The position of the substituent also affected the cyanation yield. Lower yields were obtained with an ortho-substituted substrate in comparison to a para-substituted substrate (Table 4, entry 2 versus entry 3). The highest yield was achieved with 4-acetylphenyl mesylate (93%, entry 1 in Table 4).

In all cases except for entry 3, complete consumption of the starting substrates was observed and a reduction side reaction occurred. This side reaction occurs after the oxidative addition step of the Ni(0) catalytic cycle (*vide infra*). Therefore, this indicates that premature catalyst inactivation by cyanide ions does not occur to an appreciable extent in DMF using the reported reaction conditions. Otherwise an incomplete reaction with the recovery of unreacted starting substrates, as occurred in THF and CH_3CN, would be expected.

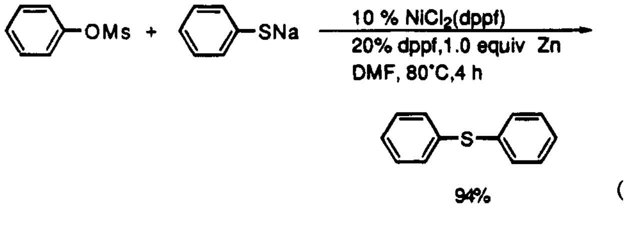
The major side reaction product formed in THF and CH_3CN was the homocoupled biaryl (*vide supra*). However, when the reaction was performed in DMF at 80 °C, a substantial amount of reduction side product was formed. In this case, the homocoupled side reaction product was formed in 0–1% yield (Table 4, entries 1–6). These results can be rationalized as follows. When THF or CH_3CN was used homocoupling can compete with the desired cyanation, because of the relatively low concentration of cyanide. In contrast, when DMF was used, the initial oxidative addition product was less stable and could easily be reduced by adventitious proton sources.

Scheme 1. Plausible Mechanism of Ni(0)-Catalyzed Cyanation of Aryl Mesylate



Mechanistic considerations have been discussed for the Ni(0)-catalyzed homocoupling[23] and for the cyanation of aromatic halides.[13c] A similar mechanism for the Ni(0)-catalyzed cyanation of aryl mesylate is shown in Scheme 1 as a working model for discussion. The success of the cyanation reaction is dependent on the CN^- ion being present at the proper concentration. If the concentration of CN^- is too high, the reaction of $NiCl_2(PPh_3)_2$, **1**, with CN^- to form $NiCl(CN)(PPh_3)_2$, **5**, and $Ni(CN)_2(PPh_3)_2$, **6**, becomes deleterious. These products cannot be reduced by Zn to Ni(0).[13c] However, since **5** and **6** can function as CN^- sources, it is possible that $Ni(0)(PPh_3)_3$ may be regenerated from these species by a series of steps involving conversion to $NiCl_m(OMs)_{m-2}(PPh_3)_2$ followed by reduction with Zn in the presence of PPh_3. This sequence of reactions depends upon the presence of the active Ni-catalytic species. Thus, the complete reaction of **1** with CN^- terminates the catalytic cycle. In addition, CN^- promotes the decomposition of **2**.[13a] Alternatively, if the CN^- concentration is too low, homocoupling may be favored as **3** may be reduced by Zn to give **7** before **3** can react with CN^- to produce **4**.

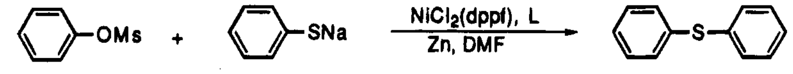
Ni(0)-Catalyzed Cross-Coupling of Aryl Mesylates with Sodium Benzenethiolate. The reaction of phenyl mesylate with sodium benzenethiolate in the presence of a Ni(0) catalyst generated from $NiCl_2$(dppf) gave high yields of diphenyl sulfide (eq 7).



(7)

The reaction products are summarized in Table 5. The side products are benzene and biphenyl. The highest yield of cross-coupled product (94%) was obtained when 20% dppf was added to the reaction solution containing $NiCl_2$(dppf) (Table 5, entry 5). Lower yields of cross-coupled product were obtained when lower amounts of dppf were added. One function of the dppf is to stabilize the catalyst against premature decomposition. Catalyst decomposition occurred within 2.5 h at 60 °C when no dppf was added (Table 5, entry 1). Diphenyl sulfide was formed in 74.5% yield. Substantial amounts of side products (10.4% benzene and 3.7% biphenyl) and unreacted phenyl mesylate (11.6%) were also detected. An improved yield of diphenyl sulfide (77%) and complete consumption of phenyl mesylate were obtained by increasing the reaction temperature to 80 °C and adding 5% dppf to the reaction solution (Table 5, entry 2). An increased amount of benzene (21%) was also obtained and a reduced amount of biphenyl (2%) were obtained. The yield of diphenyl sulfide improved to 83% by adding 10% dppf (Table 5, entry 3). The amount of the side product formation (16% benzene, 1% biphenyl) was reduced. The addition of 20% dppf resulted in a further improvement in the yield of diphenyl sulfide (87%) with a further reduction in the amount of side product formation (11% benzene, 2% biphenyl, entry 4 in Table 5). A higher yield of diphenyl sulfide (94%) and lower yields of side product formation (3.9% benzene, 0.2% biphenyl) were obtained by quenching the reaction after 4 h (Table 5, entry 5). A small amount of phenyl mesylate (1.9%) remained unreacted. A lowering of the reaction temperature to 60 °C resulted in 88% yield of Ph_2S after 21.5 h and in greatly reduced side reaction product formation (1.5% benzene and 0.09% biphenyl, entry 6 in Table 5). However, 9.6% unreacted phenyl mesylate remained. The addition of 20% PPh_3 resulted in the formation of 83% diphenyl sulfide, 15% benzene, and 2% biphenyl (Table 5, entry 7). The generation of the Ni(0) catalyst from $NiCl_2(PPh_3)_2$ in the presence of an additional 20% PPh_3 resulted in premature catalyst decomposition and only 34% conversion to Ph_2S (Table 5, entry 8).

Table 5. Ni(0)-Catalyzed Cross-Coupling of Phenyl Mesylate with Sodium Benzenethiolate[a]

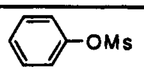
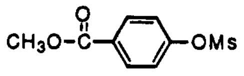
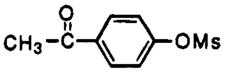
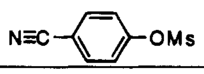


entry	added ligand	amount of ligand (mol %)	temp (°C)	time (h)	yield[b] (%)			
					PhSPh	PhH	Ph_2	PhOMs
1	–	0	60	2.5[d]	74.5	10.4	3.7	11.6
2	dppf	5	80	12	77	21	2	
3	dppf	10	80	12	83	16	1	
4	dppf	20	80	6	87	11	2	
5	dppf	20	80	4	94	3.9	0.2	1.9
6	dppf	20	60	21.5	88	1.5	0.09	9.6
7	PPh_3	20	80	12	83	15	2	
8[c]	PPh_3	20	80	2.5[d]	34	5	5	36

[a] Reactions were run with 1.0 mmol of PhOMs, 1.2 mmol of PhSNa, 0.10 mmol of $NiCl_2$(dppf), and 1.0 mmol of Zn in 1.0 mL of DMF under an inert atmosphere. [b] Yield determined by GC using Ph_2O as an internal standard. [c] $NiCl_2(PPh_3)_2$ substituted for $NiCl_2$(dppf). [d] Rapid catalyst decomposition.

Table 6. Ni(0)-Catalyzed Cross-Coupling of Substituted Aryl Mesylates with Sodium Benzenethiolate[a]

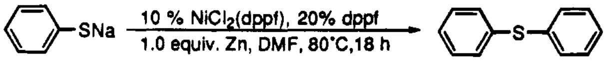
$$\text{ArOMs} + \text{PhSNa} \xrightarrow[\text{1.0 equiv. Zn, DMF}]{\text{10 \% NiCl}_2\text{(dppf), 20\% dppf}} \text{Ar–S–Ph}$$

entry	ArOMs	time (h)	yield[b] (%)		
			ArSPh	PhSPh	ArH
1		4.0	94		3.9
2		1.8	29 (16)	30	11
3		3.0	(32)		
4		1.8	20 (10)	36	18

[a] Reactions were run with 1.0 mmol of ArOMs, 1.2 mmol of PhSNa, 0.10 mmol of $NiCl_2$(dppf), 0.20 mmol of dppf, and 1.0 mmol of Zn in 1.0 mL of DMF under an inert atmosphere at 80 °C. [b] Yield determined by GC using Ph_2O as an internal standard, isolated yield in parentheses.

The Ni(0)-catalyzed cross-coupling reaction of para-substituted aryl mesylates with sodium benzenethiolate resulted in the low yield formation of unsymmetrical diaryl sulfides (Table 6). The aryl mesylate which gave the highest yield of cross-coupled product was 4-acetylphenyl methanesulfonate (32% isolated). Lower yields were obtained with methyl 4-(methylsulfonyloxy)benzoate (29%) and 4-cyanophenyl methansulfonate (20%). The major side reaction products were Ph_2S and the reduced aryl mesylate, i.e., ArH.

Diphenyl sulfide was formed in trace amounts (0.7%) when sodium benzenethiolate was reacted with the nickel catalyst in the absence of aryl mesylate (eq 8). This low yield indicates that the reaction of PhSNa with the Ni catalyst was not the source of the Ph_2S side product.



0.7% (8)

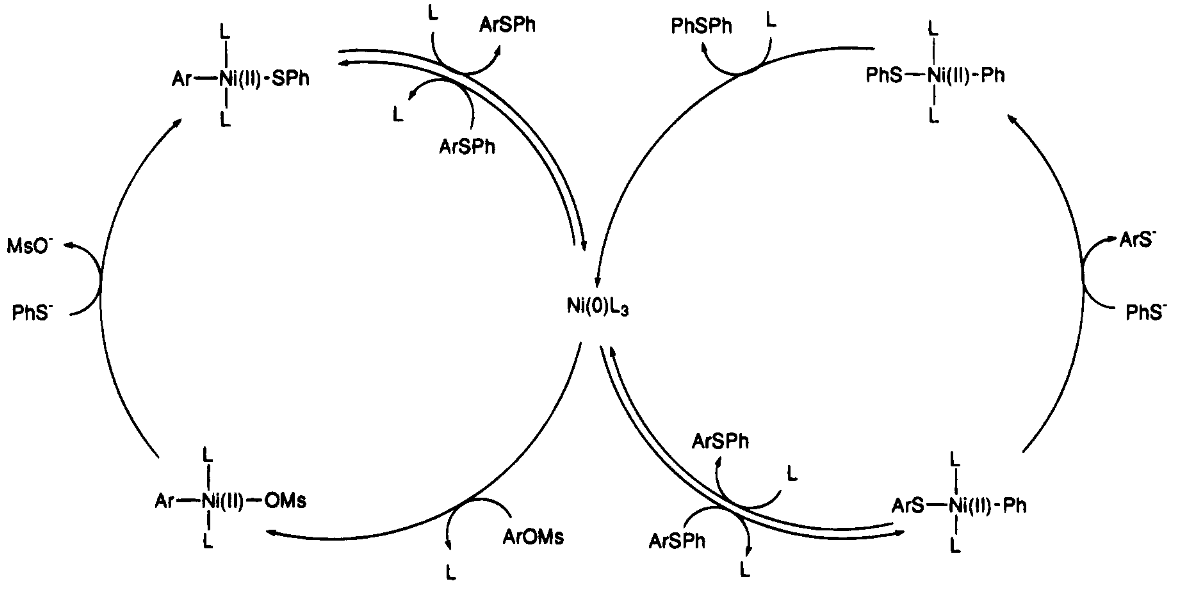
The low yield of cross-coupled product may be the result of the ability of the initially formed cross-coupled product to oxidatively add to the Ni(0) catalyst. In some cases this oxidative addition can lead to the formation of side products. A possible sequence of reactions leading to the formation of Ph_2S is shown in Scheme 2. This sequence is analogous to one suggested in the reaction of aryl halides with aromatic thiols.[17a] This sequence begins with the oxidative addition of aryl mesylate to a Ni(0) species to form $ArNi(OMs)L_2$. A ligand exchange reaction gives $ArNi(SPh)L_2$. Reductive elimination of ArSPh from this species gives the cross-coupled product and regenerates a Ni(0) species. ArSPh can participate in reactions which lead to side product formation. This is because ArSPh can oxidatively add to Ni(0). This can occur by cleavage of the aryl–sulfur bond or the phenyl–sulfur bond. Cleavage of the aryl–sulfur bond regenerates $ArNi(SPh)L_2$. Reductive elimination from this species results in no change in the product distribution. However, cleavage of the phenyl–sulfur bond gives $PhNi(SAr)L_2$. The ArS^- group can exchange with a PhS^- group to give $PhNi(SPh)L_2$. Reductive elimination gives Ph_2S and the Ni(0) species.

Reactivity of Aryl Mesylates in Ni(0)-Catalyzed Heck-Type Olefination. Various efforts to develop Heck-type olefination of aryl mesylate based on the use of Ni(0)-phosphine complexes did not produce coupled product. In all experiments, only unreacted starting substrates were recovered. It is likely that vinyl compounds coordinate to the Ni(0) species so strongly that the catalyst becomes inactive toward oxidative addition of the aryl mesylates.

Conclusions

The experiments reported here demonstrate that under nickel catalysis, aryl mesylates can be cross-coupled with various organometallic carbanion synthons (organotin, -magnesium, and zinc compounds), cyanide anion, and benzenethiolate anion. Catalyst systems consisting of $NiCl_2(PPh_3)_2$ or $NiCl_2$(dppf) in the presence of Zn were proven to be efficient for various transformations of aryl mesylates. Although Stille-type coupling reactions based on organotin compound result in low yields, good to high yields of cross-coupled products are obtained by using generally more reactive organomagnesium and -zinc compounds as coupling partners. The Ni(0)-catalyzed aromatic nucleophilic substitution reactions of aryl mesylates with cyanide anion provides a convenient method for the conversion of phenolic oxygen into a nitrile. In addition, the reaction of phenyl mesylate with the benzenethiolate anion provides the first example of the two step conversion of a phenol to a diarylsulfide. Since the

Scheme 2 Possible Mechanism of Diaryl Sulfide Formation



product of this reaction can undergo oxidative addition to Ni(0), yields of cross-coupled sulfides were low. In summary, aryl mesylates participate in a number of Ni(0)-catalyzed coupling reactions. Some of these reactions (i.e. homocoupling, "Suzuki" type cross-coupling, and cyanation) occur with product yields high enough to be synthetically useful. While other reactions are not yet synthetically useful, the results reported demonstrate that they do participate in these reactions. Therefore these reactions may become synthetically useful upon further refinement of the reaction conditions.

Experimental Section

General Methods. General experimental information is identical to that previously reported.[1a] All Ni(0)-mediated reactions were carried out under argon in oven-dried (110 °C) glassware using standard Schlenk line techniques.[24] Yields were determined by GC (10% SP-2100 column, diphenyl ether as an internal standard).

Except when otherwise noted, all materials were obtained from commercial suppliers and used without further purification. KCN was dried at 110 °C under reduced pressure (1×10^{-3} mmHg) for 24 h prior to use. Pyridine was dried over CaH_2 and distilled. CH_3CN and DMF were dried with CaH_2. THF was distilled from sodium–benzophenone ketyl. Zinc dust (325 mesh) was stirred in acetic acid, washed with water, and dried *in vacuo* at 120 °C. Unless otherwise noted, all compounds synthesized in the present paper were purified until their 200 MHz ^{1}H-NMR spectra corresponded to the expected structure, and the purity was established by comparison with published mp or found to be higher than 99.5% by GC or HPLC.

$PdCl_2$(dppf),[25] $NiCl_2(PPh_3)_2$,[26] $NiCl_2$(dppf),[27] and tri-*n*-butylphenylstannane[28] were prepared according to literature procedures.

Grignard Reagents. Methyl magnesium iodide (3.0 M solution in Et_2O) was obtained from Aldrich. Other Grignard reagents were prepared by the reaction of magnesium turnings with the corresponding halides in THF.

Zinc Reagents. Zinc reagents were prepared *in situ* by mixing anhydrous zinc chloride (1.1 equiv) with the corresponding Grignard reagents (1.0 equiv) in THF at 0–25 °C for 0.5 h. After the reaction was complete, the mixture was transferred via cannula through a small pad of Celite in sintered glass funnel directly into a Schlenk tube containing a mixture of aryl mesylate, $NiCl_2$(dppf), and Zn (*vide infra*).

Aryl Sulfonates. The preparations of 4-acetylphenyl *p*-fluorobenzenesulfonate, 4-acetylphenyl methanesulfonate, methyl 4-(methylsulfonyloxy)benzoate, methyl 2-(methylsulfonyloxy)benzoate, phenyl methanesulfonate, 4-cyanophenyl methanesulfonate, 4-tolyl methanesulfonate, and 4-methoxyphenyl methanesulfonate were reported previously.[1a]

2-Tolylmethanesulfonate was prepared by the reaction of methanesulfonyl chloride with *o*-cresol in pyridine[29] (85%): colorless oil, purified by column chromatography (SiO_2, hexanes/Et_2O = 10/1) and vacuum distilled; bp 105–107 °C/0.005 mmHg; ^{1}H NMR δ 7.27–7.18 (m, 4H), 3.12 (s, 3H), 2.33 (s, 3H).

General Procedure for Pd(0)-Catalyzed Cross-Coupling of Aryl Sulfonates with (Tri-*n*-butylphenyl)stannane. A 25 mL three-neck flask equipped with a reflux condenser, nitrogen inlet, and rubber septum was charged with aryl sulfonate (0.5 mmol), LiCl (1.5 mmol), and DMF (2 mL). The flask was flushed with nitrogen, and the palladium catalyst (0.025 mmol) was added. After 10 min of stirring, (tri-*n*-butylphenyl)stannane was added. The mixture was stirred at 110 °C under N_2 for 24 h. The actual yields based on percent conversion of the starting aryl sulfonate were determined by GC measurements using diphenyl ether as an internal standard. The GC yields are summarized in Table 1.

General Procedure for Ni(0)-Catalyzed Cross-Coupling of Aryl Sulfonates with (Tri-*n*-butylphenyl)stannane. All reactions were carried out under nitrogen using oven-dried (110 °C) glassware. In a typical reaction a 125 mL Schlenk tube was charged with aryl sulfonate (0.5 mmol), (tri-*n*-butylphenyl)stannane (0.55 mmol), $NiCl_2(PPh_3)_2$ (0.05 mmol), Zn powder (0.86 mmol), Et_4NI (0.75 mmol), and a magnetic stirring bar. After sealing the tube with a rubber septum, the contents were placed under N_2 by three evacuation-filling cycles. Freshly distilled THF (1.0 mL) was added via a syringe through the rubber septum. The reaction mixture was heated to the reflux temperature and stirred at this temperature for 24 h. Then it was cooled to 25 °C, filtered, diluted with water, extracted with $CHCl_3$, and dried ($MgSO_4$). The yields based

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on percent conversion of the starting aryl sulfonate were determined by GC measurements using diphenyl ether as an internal standard. The GC yields are summarized in Table 1.

Biaryls. 4-(Carbomethoxy)biphenyl: white crystals; mp 116–117 °C (benzene) (lit.[30] 117.5 °C).

4-Acetylbiphenyl: white needles; mp 119–120 °C (ethanol) (lit.[31] 121 °C).

General Procedure for Ni(0)-Catalyzed Cross-Coupling of Aryl Mesylates with Grignard and Zinc Reagents. In a typical reaction a 125 mL Schlenk tube was charged with aryl mesylate (0.5 mmol), NiCl$_2$(dppf) (0.05 mmol), Zn powder (0.5 mmol) and a magnetic stirring bar. After sealing the tube with a rubber septum, the contents were dried at 25 °C under reduced pressure (1×10^{-3} mmHg) for 3 h. The tube was filled with N$_2$ followed by three evacuation-filling cycles. Freshly distilled THF (0.5 mL) was added via syringe through the rubber septum. The mixture was stirred at room temperature for 10 min. During this time the color of the mixture gradually became deep red-brown. Grignard reagent (0.9–1.0 mmol in THF) was added to the reaction mixture via syringe through the rubber septum. The mixture was stirred at room temperature for 10 h, filtered, diluted with water, extracted with CHCl$_3$, and dried (MgSO$_4$) and the solvent removed *in vacuo*. The corresponding cross-coupled product was purified by column chromatography (SiO$_2$, hexanes/ethyl acetate). The yields based on percent conversion of the starting aryl mesylate were determined by GC measurements using diphenyl ether as an internal standard. The GC yields are summarized in Table 2.

Cross-Coupled Products. Butylbenzene, *o*-xylene, *p*-xylene, and 4-methylanisole were identified by coinjection with authentic samples (Aldrich) using GC. 4-Methylbiphenyl: white crystals; mp 47–48 °C (hexanes) (lit.[31] 47.5 °C). 4-Methoxybiphenyl: white crystals; mp 87–88 °C (benzene) (lit.[32] 89–90 °C).

General Procedure for Ni(0)-Catalyzed Cyanation of Aryl Mesylates. In a typical reaction, a 125 mL Schlenk tube was charged with aryl mesylate (1.0 mmol), NiCl$_2$(PPh$_3$)$_2$ (0.1 mmol), PPh$_3$ (0.2 mmol), Zn powder (1.0 mmol), KCN (1.5 mmol), and a magnetic stirring bar. After sealing the tube with a rubber septum, the content was dried at 25 °C under reduced pressure (1×10^{-3} mmHg) for 1 h. Then it was placed under an Ar atmosphere, and freshly distilled DMF (0.60 mL) was added via a syringe through the rubber septum. The mixture was stirred at room temperature for 5 min, and during this time the color of the mixture gradually changed from green into deep red brown. The reaction mixture was stirred at 80 °C for 12 h. After cooling to 25 °C, CHCl$_3$ (20 mL) and 10% aqueous HCl (20 mL) were added. After stirring for 20 min the CHCl$_3$ layer was separated, washed with H$_2$O, and dried (MgSO$_4$) and the solvent evaporated *in vacuo*. The corresponding aryl nitrile was purified by column chromatography (silica gel, hexanes/ethyl acetate). The actual yields based on percent conversion of the starting aryl mesylate were determined by GC measurements using diphenyl ether as an internal standard. The GC yields are summarized in Tables 3 and 4.

Aryl Nitriles. Benzonitrile was identified by comparison with an authentic sample using GC.

***p*-Acetylbenzonitrile**: white crystals; mp 56–58 °C (hexanes) (lit.[12a] 56.5–57 °C); ^{1}H NMR (CDCl$_3$) δ 8.05 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 2.65 (s, 3H).

Methyl *p*-cyanobenzoate: white crystals; mp 67–68 °C (hexanes) (lit.[12a] 67–68 °C); ^{1}H NMR (CDCl$_3$) δ 8.14 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 3.96 (s, 3H).

Methyl *o*-cyanobenzoate: white crystals; mp 48–49 °C (hexanes) (lit.[12a] 48.5–49 °C); ^{1}H NMR (CDCl$_3$) δ 8.10–8.18 (m, 1H), 7.65–7.80 (m, 3H), 4.00 (s, 3H).

1,4-Dicyanobenzene: white crystals; mp 224 °C (hexanes) (lit.[12a] 221–222 °C); ^{1}H NMR (CDCl$_3$) δ 7.80 (s, 4H).

***p*-Cyanotoluene**: white crystals; mp 27 °C (hexanes) (lit.[12a] 25.5–27.5 °C); ^{1}H NMR (CDCl$_3$) δ 7.73 (d, J = 7.7 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H), 2.41 (s, 3H).

***p*-Methoxybenzonitrile**: white crystals; mp 57–58 °C (benzene) (lit.[12a] 56–56.5 °C); ^{1}H NMR (CDCl$_3$) δ 7.67 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 3.91 (s, 3H).

General Procedure for Ni(0)-Catalyzed Cross-Coupling of Aryl Mesylates with Sodium Benzenethiolate. Diphenyl Sulfide.[17c] All reactions were carried out under argon using oven-dried (110 °C) glassware. In a typical reaction a 125 mL Schlenk tube was charged with phenyl mesylate (1.0 mmol), sodium benzenethiolate (1.2 mmol), NiCl$_2$(dppf) (0.10 mmol), dppf (0.20 mmol) Zn powder (1.0 mmol), and a magnetic stirring bar. The tube was sealed with a rubber septum and placed under an Ar atmosphere. DMF (1.0 mL) was added via a syringe through the rubber septum. The solution immediately turned red. The reaction mixture was stirred at 80 °C for 3 h. After the reaction mixture cooled to room temperature, diphenyl ether and CH$_2$Cl$_2$ (3 mL) were added. The mixture was washed with 10% HCl(aq) (3×3 mL) and H$_2$O (2×3 mL), filtered, and dried (MgSO$_4$). The yield was then determined by GC. Diphenyl sulfide was identified by its ^{1}H NMR spectra and by its GC retention time when coinjected with an authentic sample. Isolated yields were determined by a modified procedure in which Ph$_2$O was not added, and the CH$_2$Cl$_2$ was evaporated *in vacuo*. The corresponding diaryl sulfide was obtained after column chromatography (silica gel, hexanes/ethyl acetate).

4-(Phenylthio)acetophenone[33] (32%): ^{1}H NMR δ 7.82 (d, J = 8.5 Hz, 2H), 7.49 (m, 2H), 7.39 (m, 3H), 7.21 (d, J = 8.5 Hz, 2H), 2.55 (s, 3H).

Methyl 4-(phenylthio)benzoate (16%): ^{1}H NMR δ 7.82 (d, J = 8.4 Hz, 2H), 7.40 (m, 2H), 7.31 (m, 3H), 7.13 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H).

4-(Phenylthio)benzonitrile[17c] (10%): ^{1}H NMR δ 7.68–7.25 (m, 7H), 7.08 (d, J = 8.4 Hz, 2H).

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