

## Aryl Mesylates in Metal Catalyzed Homocoupling and Cross-Coupling Reactions. 2. Suzuki-Type Nickel-Catalyzed Cross-Coupling of Aryl Arenesulfonates and Aryl Mesylates with Arylboronic Acids

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The Ni(0)-catalyzed Suzuki-type cross-coupling reaction of various aryl sulfonates including mesylate with arylboronic acids in the presence of  $K_3PO_4$  is reported. The Ni(0) catalyst is generated *in situ* from  $NiCl_2(dppf)$  and Zn. This novel reaction, which yields unsymmetrical biaryls in good yields under mild conditions, is highly regiospecific and tolerates various functional groups. The influence of the effects of the substituent of the aromatic substrates, the nature of the leaving group, solvent, and type of catalyst, and base on the reaction yield are discussed. The reactivity of various Ni(0) catalysts was compared to that of the less reactive Pd(0) catalysts.

### Introduction

The palladium-catalyzed cross-coupling reaction of organoboron compounds (arylboronic acid and its esters) with aromatic organic electrophiles (i.e., halides<sup>1a-f</sup> and triflates<sup>1g-i,k</sup>) in the presence of a base is known as the "Suzuki reaction" and represents an important method for the formation of aromatic carbon-carbon bonds.<sup>1,2</sup> High yields have been obtained with many substrates containing a wide range of functional groups on either coupling partner.<sup>1</sup> The reaction is regiospecific and stereospecific and is not sensitive toward steric hindrance.<sup>1a,b,j</sup> These factors make the Suzuki reaction particularly attractive and versatile.

The most reactive and therefore often used aryl halides in Suzuki reaction are aryl bromides and iodides.<sup>1a-f</sup> Aryl chlorides do not participate in this cross-coupling except when used in conjunction with electron-deficient groups.<sup>2d,3</sup> The use of aryl triflates has been recently demonstrated in the Suzuki reaction.<sup>1g-i,k</sup>

Triflates are base sensitive and thermally labile. Therefore, mild reaction conditions have been developed for the cross-coupling reaction of arylboronic acids with triflates. These include the selection of more efficient catalysts such as  $PdCl_2(dppf)$ ,<sup>1h,k</sup> the utilization of weak nonaqueous basic conditions such as powdered  $K_3PO_4$  suspended in polar solvents (THF, dioxane),<sup>1h,j,k</sup> and the addition of alkali metal halide to promote the cross-coupling and/or to prevent the premature catalyst

decomposition.<sup>1g,k</sup> One of the challenges in the Suzuki-type cross-coupling is to extend this reaction from electron-rich aryl triflates to less reactive aryl sulfonates and aryl chlorides, which show poor reactivity toward oxidative addition in the catalytic cycle. A recent approach to this problem involves the activation of aryl triflates by complexation of electron-withdrawing  $Cr(CO)_3$  to the arene moiety.<sup>4</sup>

Alternative sulfonate leaving groups besides triflate have not been reported to be active in Suzuki-type reactions.<sup>2a-c,e</sup> Aryl mesylates, benzenesulfonates, and tosylates are much less expensive than triflates and are unreactive toward palladium catalysts.

We have recently reported that aryl sulfonates including mesylate undergo homocoupling in high yield in the presence of Ni(0) catalysts generated *in situ*.<sup>5</sup> Therefore, aryl mesylates undergo oxidative addition to Ni(0) complexes. Since the Suzuki-type cross-coupling reaction also involves oxidative addition, followed by transmetalation and reductive elimination, the unprecedented cross-coupling reaction of aryl mesylates with arylboronic acids was investigated. Herein, we report the use of the mesylate leaving group in a novel nickel-catalyzed Suzuki-type cross-coupling reaction.

### Results and Discussion

**Palladium-Catalyzed Cross-Coupling.** A series of experiments was performed in order to determine the feasibility of using alternative sulfonate leaving groups besides triflate in the Pd(0)-catalyzed cross-coupling reaction of aryl sulfonates with phenylboronic acid (Table 1). The cross-coupling reaction of various aryl sulfonates and phenylboronic acid was mediated in toluene by the Pd(0) catalyst  $[Pd(PPh_3)_4]$  in the presence of LiCl and 2 M  $Na_2CO_3$ . These reaction conditions are typical for the Suzuki reaction<sup>1a-e</sup> and were slightly modified by comparison to those used for the cross-coupling of aryl bromide with phenylboronic acid.<sup>1a</sup> Under these conditions, from various *p*-carbomethoxyphenyl sulfonates, only the triflate leaving group produced high yield

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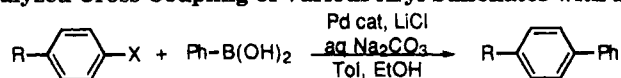
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Table 1. Pd(0)-Catalyzed Cross-Coupling of Various Aryl Sulfonates with Phenylboronic Acid<sup>a</sup>

entry	R	X	catalyst	yield <sup>b</sup> (%)
1	CH <sub>3</sub> O <sub>2</sub> C	CF <sub>3</sub> SO <sub>2</sub> O	Pd(PPh <sub>3</sub> ) <sub>4</sub>	>99
2	CH <sub>3</sub> O <sub>2</sub> C	<i>p</i> -FPhSO <sub>2</sub> O	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0
3	CH <sub>3</sub> O <sub>2</sub> C	CH <sub>3</sub> SO <sub>2</sub> O	Pd(PPh <sub>3</sub> ) <sub>4</sub>	0
4	CH <sub>3</sub> O <sub>2</sub> C	CH <sub>3</sub> SO <sub>2</sub> O	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	0
5	CH <sub>3</sub> O <sub>2</sub> C	CH <sub>3</sub> SO <sub>2</sub> O	Pd(OAc) <sub>2</sub> + 2 equiv of PPh <sub>3</sub> <sup>c</sup>	0
6	CH <sub>3</sub> O <sub>2</sub> C	CH <sub>3</sub> SO <sub>2</sub> O	Pd(OAc) <sub>2</sub> + 1.1 equiv of dppp <sup>c</sup>	traces
7	CH <sub>3</sub> O <sub>2</sub> C	CH <sub>3</sub> SO <sub>2</sub> O	PdCl <sub>2</sub> (dppf)	25 <sup>d</sup>
8	CH <sub>3</sub> O <sub>2</sub> C	CH <sub>3</sub> SO <sub>2</sub> O	PdCl <sub>2</sub> (dppf)	5 <sup>d,e</sup>
9	CH <sub>3</sub> O <sub>2</sub> C	CH <sub>3</sub> SO <sub>2</sub> O	PdCl <sub>2</sub> (dppf) + 1 equiv of PPh <sub>3</sub> <sup>c</sup>	traces
10	CH <sub>3</sub> CO	<i>p</i> -FPhSO <sub>2</sub> O	PdCl <sub>2</sub> (dppf)	21 <sup>d</sup>
11	CH <sub>3</sub> CO	CH <sub>3</sub> SO <sub>2</sub> O	PdCl <sub>2</sub> (dppf)	0 <sup>d</sup>
12	CH <sub>3</sub> CO	CH <sub>3</sub> SO <sub>2</sub> O	Pd(OAc) <sub>2</sub> + 1.1 equiv of dppp <sup>c</sup>	17 <sup>f</sup>

<sup>a</sup> Reactions were run with 5 mol % Pd catalyst, 3 equiv of LiCl, and 2.6 equiv of aqueous Na<sub>2</sub>CO<sub>3</sub> in a mixture of Tol + EtOH at 90 °C under N<sub>2</sub> for 12 h, unless otherwise noted. <sup>b</sup> Actual yields determined by GC measurements were based on percent conversion of the starting substrate. <sup>c</sup> Equivalents relative to Pd catalyst. <sup>d</sup> Catalyst decomposed in the early stage of the reaction. <sup>e</sup> Reaction run in the absence of LiCl. <sup>f</sup> Trace amount of acetophenone was detected by GC.

(>99%) (entry 1). *p*-Fluorobenzenesulfonate and methanesulfonate did not undergo the cross-coupling reaction (entries 2 and 3). Only unreacted starting substrates were isolated from these experiments.

Several other Pd catalysts were investigated (entries 4–7). PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and Pd(OAc)<sub>2</sub> gave no cross-coupled product (entries 4–6). Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) [PdCl<sub>2</sub>(dppf)], an effective catalyst for Suzuki<sup>1h,k</sup> and for other cross-coupling reactions<sup>6</sup> was found to catalyze the reaction. However, the yield was low (25%) (entry 7), and early catalyst decomposition was observed. Therefore, in order to prevent premature catalyst decomposition, this reaction was performed with the addition of 1 equiv of PPh<sub>3</sub> (per equiv of Pd). Although this resulted in a substantial enhancement of the stability of the catalyst, the additional PPh<sub>3</sub> totally suppressed the cross-coupling reaction (entry 9). Similarly, the stabilization of the catalyst via the addition of dppf did not improve the yield. LiCl, which was reported to be necessary in the reaction of triflates with boronic acids,<sup>15</sup> was found to be essential for the Pd-catalyzed reaction. In the absence of LiCl, much faster catalyst decomposition occurred, resulting in a very low reaction yield (entry 8).

The effect of various Pd catalysts on *p*-acetyl-substituted aryl sulfonates was studied (entries 10–12). The *p*-fluorobenzenesulfonate leaving group gave 21% yield when using PdCl<sub>2</sub>(dppf) (entry 10). In contrast, methanesulfonate was quite inert under the same conditions (entry 11). However, when the catalyst was changed to Pd(OAc)<sub>2</sub> in the presence of 1,3-bis(diphenylphosphino)propane (dppp), a 17% yield of cross-coupled product was obtained (entry 12). No further improvement in yield was obtained by employing various reaction conditions. Phosphine-free ligandless Pd catalysts such as tris(dibenzylideneacetone)dipalladium [Pd<sub>2</sub>(dba)<sub>3</sub>] are known to be efficient catalysts for the Stille cross-coupling reaction.<sup>7a</sup> Similarly, Pd<sub>2</sub>(dba)<sub>3</sub>·C<sub>6</sub>H<sub>6</sub> has been reported to be the most efficient catalyst for the Suzuki coupling.<sup>1f</sup> However, aryl mesylates did not participate in the cross-coupling reaction in the presence of the ligandless

catalyst [Pd<sub>2</sub>(dba)<sub>3</sub>] under conventional conditions. Similar results were obtained with the utilization of bulky monodentate ligands<sup>7b,c</sup> [P(Cy)<sub>3</sub>, AsPh<sub>3</sub>, and P(*o*-toly)] and bidentate ligands [1,2-bis(diphenylphosphino)ethane (dppe) and dppp],<sup>7d</sup> which have accelerated the oxidative addition in other Pd-catalyzed cross-coupling reactions and with the use of anhydrous basic conditions (K<sub>3</sub>PO<sub>4</sub> in dioxane).<sup>1h,j,k</sup>

The mechanistic sequence of reactions for the transition metal-catalyzed cross-coupling reactions involves sequential oxidative addition, transmetalation, and reductive elimination.<sup>8</sup> The reductive elimination step is expected to be identical regardless of whether an aryl triflate or aryl mesylate is involved. In the reaction of aryl halides with arylboronic acids, a ligand exchange reaction between the halide and an OH<sup>-</sup> ion was proposed to take place prior to the transmetalation step.<sup>2a,9</sup> If a similar ligand exchange reaction takes place between the sulfonate group and an OH<sup>-</sup> ion, the transmetalation step would be identical for both aryl triflates and aryl mesylates. Therefore, the transmetalation and reductive elimination steps are not expected to account for the difference in reactivity. If a ligand exchange reaction takes place in the case of aryl sulfonates between the sulfonate group and an OH<sup>-</sup> ion prior to transmetalation, the physical properties of the sulfonate are expected to influence the rate of this reaction. However, if the oxidative addition product of aryl mesylate to Pd(0) has ionic character,<sup>10</sup> i.e., [ArPd(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup>[OMs]<sup>-</sup>, the difference between triflate and mesylate groups may not have a significant impact on the reaction rate of this step. In addition, the difference in leaving group reactivity is expected to influence the rate of oxidative addition.<sup>11</sup>

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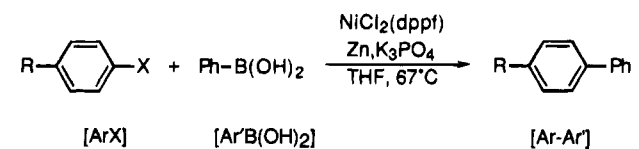
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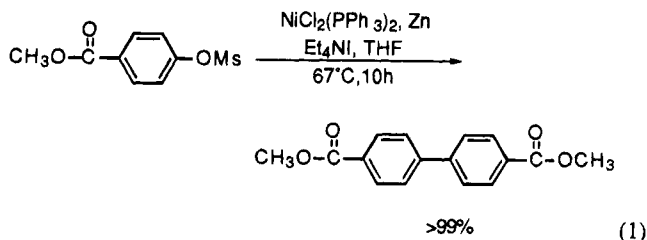
**Table 2.** Ni(0)-Catalyzed Cross-Coupling of Various Aryl Sulfonates with Phenylboronic Acid<sup>a</sup>

entry	R	X	GC yield (%)		
			Ar-Ar'	Ar-H	Ar-Ar
1	CH <sub>3</sub> O <sub>2</sub> C	CF <sub>3</sub> SO <sub>2</sub> O	80	19	1
2	CH <sub>3</sub> O <sub>2</sub> C	<i>p</i> -FPhSO <sub>2</sub> O	42	traces	0 <sup>b</sup>
3	CH <sub>3</sub> O <sub>2</sub> C	<i>p</i> -CH <sub>3</sub> PhSO <sub>2</sub> O	40	traces	traces <sup>b</sup>
4	CH <sub>3</sub> O <sub>2</sub> C	PhSO <sub>2</sub> O	37	0	0 <sup>b</sup>
5	CH <sub>3</sub> O <sub>2</sub> C	CH <sub>3</sub> SO <sub>2</sub> O	48	traces	0 <sup>b</sup>
6	CH <sub>3</sub> CO	CH <sub>3</sub> SO <sub>2</sub> O	51	traces	traces <sup>b</sup>
7	CH <sub>3</sub>	CH <sub>3</sub> SO <sub>2</sub> O	33 <sup>b</sup>		
8	CH <sub>3</sub> O	CH <sub>3</sub> SO <sub>2</sub> O	39 <sup>b</sup>		

<sup>a</sup> Reactions were run with 10 mol % NiCl<sub>2</sub>(dppf), 1.7 equiv of Zn, and 3 equiv of K<sub>3</sub>PO<sub>4</sub> in THF at 67 °C under N<sub>2</sub> for 24 h. <sup>b</sup> The remaining material isolated was unreacted starting substrate.

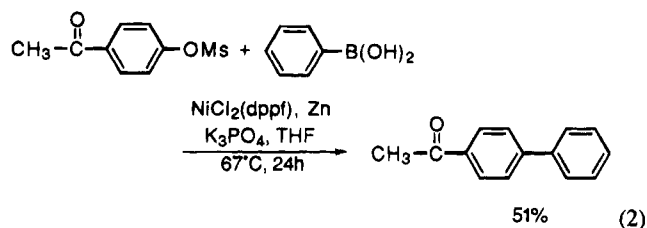
Therefore, it is possible that the low yields obtained in the preceding reaction are the result of a slow rate of oxidative addition of aryl mesylates to the *in situ*-generated Pd(0) species. In order to accelerate the rate of oxidative addition by making the Pd catalyst more nucleophilic, various kinds of palladium catalysts were employed. Among them, PdCl<sub>2</sub>(dppf) was found to be the most reactive, although the obtained yield was not satisfactory to be useful. These results indicate that the low yields obtained in Pd(0)-catalyzed cross-coupling reactions of aryl mesylates with phenylboronic acid may be due to an inherent low reactivity of aryl mesylates toward Pd(0) species in the oxidative addition step.

**Nickel-Catalyzed Cross-Coupling.** Although aryl mesylates and arenesulfonates have a low reactivity toward Pd(0) species, they undergo oxidative addition to Ni(0) complexes.<sup>5</sup> Ni(0) is a stronger nucleophile than Pd(0). The Ni(II) species resulting from the oxidative addition can undergo a further high-yield reaction in the presence of Zn with additional aryl mesylate to give symmetrical homocoupled biaryls (eq 1). Therefore,



Ni(0) is sufficiently nucleophilic to undergo oxidative addition with aryl mesylates, and the resulting Ni(II) species can participate in further reactions with organic electrophiles. Consequently, the utility of Ni(0) catalysts in the cross-coupling reaction of aryl mesylates with phenylboronic acid was investigated.

It was found that a Ni(0) species incorporating the 1,1'-bis(diphenylphosphino)ferrocene (dppf) ligand is an effective catalyst for the cross-coupling reaction (Table 2). Thus, moderate yields with high selectivity were obtained using 10 mol % NiCl<sub>2</sub>(dppf) in the presence of 1.7 equiv of Zn and 3.0 equiv of K<sub>3</sub>PO<sub>4</sub> in THF at 67 °C (eq 2). Only trace amounts (<1%) of homocoupled product was detected. Thus slight changes in the reaction conditions



(most significantly, the substitution of dppf for PPh<sub>3</sub> and the addition of phenylboronic acid and K<sub>3</sub>PO<sub>4</sub>) virtually closed the reaction pathway which leads to the homocoupled product. This result is very important because *this is the first example in which a Ni catalyst is used in a Suzuki reaction*. The substitution of Ni catalysts for Pd catalysts represents significant cost savings. In addition, the substitution of the mesylate leaving group for triflate is also an improvement on the basis of both ease of synthesis and cost.

The dppf ligand has been shown to be an excellent ligand in other cross-coupling reactions.<sup>6</sup> The high selectivity and moderate reactivity are due to the electronic and steric features of the dppf ligand. Dppf ligand is known to increase the nucleophilicity of the transition metal (Ni or Pd) and to facilitate the reductive elimination of the diorganometal complex (R-M-R'), leading to carbon-carbon bond formation.<sup>6</sup> The effect of dppf ligand in Pd(0)-catalyzed cross-coupling of aryl mesylates with phenylboronic acid was also observed, although the yield was relatively low (*vide supra*). NiCl<sub>2</sub>(dppf)-catalyzed cross-coupling of unactivated electrophiles with Grignard reagents,<sup>12</sup> and with diorganozinc reagents<sup>13</sup> were reported.

In the conventional Suzuki reaction, benzene or toluene were used as the solvent, and an aqueous Na<sub>2</sub>CO<sub>3</sub> solution accelerated the rate of transmetalation step of the catalytic cycle.<sup>1a-e</sup> In contrast to other cross-coupling reactions such as Grignard, organotin, and organozinc reactions, the base is essential in the Suzuki reaction. Although extensive studies have been made on the effect of various kinds of base, aqueous systems containing inorganic bases such as Na<sub>2</sub>CO<sub>3</sub> have been proved to be the most effective.<sup>2a</sup> However, the aqueous systems cannot be employed in the Ni(0)-catalyzed coupling reaction, since protic sources such as water deactivate the nickel catalyst and also generate substantial amounts of reduction side product.<sup>14</sup>

Recently, it was reported that a nonaqueous system consisting of powdered K<sub>3</sub>PO<sub>4</sub> suspended in dioxane accelerates the coupling reaction of aryl triflate with organoboron compounds.<sup>1h,j,k</sup> THF has been found to be an efficient solvent in reference to the rate and selectivity of the Ni(0)-catalyzed homocoupling reaction.<sup>5</sup> Therefore, THF was employed as solvent and K<sub>3</sub>PO<sub>4</sub> as base for the initial studies of Ni(0)-catalyzed cross-coupling of various aryl sulfonates including mesylate with phenylboronic acid. The results are summarized in Table 2.

A series of the nickel-catalyzed cross-coupling reactions was carried out with various *p*-carbomethoxyphenyl sulfonates in order to evaluate the relative effectiveness of several sulfonate leaving groups (entries 1-5). Of the sulfonates examined, the triflate group is the most

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**Table 3. Effect of Various Reaction Conditions on the NiCl<sub>2</sub>(dppf)-Catalyzed Cross-Coupling of Methyl 4-[(methylsulfonyl)oxy]benzoate [ArOSO<sub>2</sub>CH<sub>3</sub>] with Phenylboronic Acid [Ar'B(OH)<sub>2</sub>]<sup>a</sup>**

entry	solvent	temp (°C)	base (equiv)	halide (equiv)	GC yield (%)		
					Ar-Ar'	Ar-H	Ar-Ar
1	THF	67	K <sub>3</sub> PO <sub>4</sub> (1.5)	none	41	traces	0
2	THF	67	K <sub>3</sub> PO <sub>4</sub> (3.0)	none	48	traces	0
3 <sup>b</sup>	THF	67	K <sub>3</sub> PO <sub>4</sub> (3.0)	none	37		
4 <sup>c</sup>	THF	67	K <sub>3</sub> PO <sub>4</sub> (3.0)	none	16		
5 <sup>d</sup>	THF	67	K <sub>3</sub> PO <sub>4</sub> (3.0)	none	36		
6	THF	67	K <sub>3</sub> PO <sub>4</sub> (3.0)	Et <sub>4</sub> Ni (1.0)	46	traces	0
7	THF	67	K <sub>3</sub> PO <sub>4</sub> (3.0)	KBr (2.0)	46	<1	traces
8	THF	67	Na <sub>2</sub> CO <sub>3</sub> (2.0)	none	30	13	0
9 <sup>e</sup>	THF	67	K <sub>3</sub> PO <sub>4</sub> (3.0)	none	0	0	0
10 <sup>f</sup>	THF	67	K <sub>3</sub> PO <sub>4</sub> (3.0)	none	54	4	3
11	dioxane	95	K <sub>3</sub> PO <sub>4</sub> (1.5)	none	36	2	0
12	dioxane	95	K <sub>3</sub> PO <sub>4</sub> (1.5)	LiCl (3.0)	27	3	0
13 <sup>g</sup>	dioxane	95	K <sub>3</sub> PO <sub>4</sub> (1.5)	none	18	5	0
14 <sup>h</sup>	dioxane	95	K <sub>3</sub> PO <sub>4</sub> (3.0)	none	67	4	1
15	dioxane	70	K <sub>3</sub> PO <sub>4</sub> (3.0)	none	48	<1	traces

<sup>a</sup> Reactions were run with 10 mol % NiCl<sub>2</sub>(dppf), 1.7 equiv of Zn, and a base as indicated in THF or dioxane under N<sub>2</sub> for 24 h, unless otherwise noted. <sup>b</sup> NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was used instead of NiCl<sub>2</sub>(dppf). <sup>c</sup> NiCl<sub>2</sub>(dppe) was used instead of NiCl<sub>2</sub>(dppf). <sup>d</sup> NiCl<sub>2</sub>(dppp) was used instead of NiCl<sub>2</sub>(dppf). <sup>e</sup> Reaction run in the absence of Zn. <sup>f</sup> Reaction run with 30 mol % NiCl<sub>2</sub>(dppf). <sup>g</sup> Reaction run with 3 equiv of Zn. <sup>h</sup> Also produced methyl 4-hydroxybenzoate (8%).

reactive.<sup>15</sup> The highest yield (80%) was obtained with the triflate leaving group (entry 1). However, substantial amounts of reduction side products were observed (19%). The use of four other less reactive sulfonate leaving groups, *p*-fluorobenzenesulfonate, *p*-toluenesulfonate, benzenesulfonate, and methanesulfonate, resulted in moderate yields (37–48%) (entries 2–5). It is noteworthy that these four sulfonates, including mesylate, which are apparently much less reactive than triflate, gave cross-coupled products highly selectively with only trace amounts (<1%) of side reaction products. Most of the isolated materials were unreacted starting substrates. In comparison with Pd(0)-catalyzed Suzuki reaction of aryl mesylate with phenylboronic acid (Table 1, entry 7), the Ni(0)-mediated cross-coupling reaction gave much higher yields of cross-coupled product (Table 2, entry 5).

The effect of various substituents on the cross-coupling reaction, when using the mesylate leaving group, was studied (entry 5–8). Higher yields were obtained when using electron-withdrawing *p*-acetyl- and *p*-carbomethoxyphenyl mesylates, which are substantially more reactive than both the electron-donating *p*-methyl- and *p*-methoxyphenyl mesylates.

In order to further improve the yield of Ni(0)-catalyzed cross-coupling of methyl 4-[(methylsulfonyl)oxy]benzoate with phenylboronic acid, various reaction conditions were employed (Table 3). The effect of the amount of base, K<sub>3</sub>PO<sub>4</sub>, was studied in both THF and dioxane (entries 1, 2, 11, 14, and 15). At 67 °C in THF, a doubling of the amount of K<sub>3</sub>PO<sub>4</sub> resulted in a slightly increased yield (cf. entries 1 and 2). In contrast, at 95 °C in dioxane, the effect of the amount of K<sub>3</sub>PO<sub>4</sub> was more pronounced (entry 11 vs 14). A substantially increased yield (67%) was obtained with 3.0 equiv of K<sub>3</sub>PO<sub>4</sub> at 95 °C, although side reactions such as reduction (4%) and O–S bond cleavage (8%) occurred (entry 14). However, when the reaction was performed at 70 °C in the presence of 3.0 equiv of K<sub>3</sub>PO<sub>4</sub>, the yield decreased (48%) (cf. entries 14 and 15). These results can be rationalized as follows. The reaction step involving base may occur partly through a heterogeneous mechanism because of the low solubility of K<sub>3</sub>PO<sub>4</sub> in THF or dioxane. As a result, relatively large

amounts of K<sub>3</sub>PO<sub>4</sub> are necessary to accelerate the transmetalation step of the catalytic cycle. The yield increased as the relative amount of K<sub>3</sub>PO<sub>4</sub> increased (entry 1 vs 2 and 11 vs 14). Therefore, an additive effect of K<sub>3</sub>PO<sub>4</sub> was evident for this coupling reaction. However, this additive effect was less significant when using THF at low temperature (67 °C) (entry 1 vs 2). In contrast, when using dioxane at an elevated temperature (95 °C), the K<sub>3</sub>PO<sub>4</sub> additive effect became dramatic due to the enhanced solubility of K<sub>3</sub>PO<sub>4</sub>, with a significant increase in yield (entry 11 vs 14). When the reaction temperature was lowered to 70 °C, the yield also decreased. This could be due to the decreased solubility of K<sub>3</sub>PO<sub>4</sub> and/or decreased reactivity of mesylate (entry 14 vs 15).

The addition of Et<sub>4</sub>Ni as a halide source, which was reported to enhance the reaction rate of nickel-catalyzed homocoupling of aryl mesylates,<sup>5</sup> resulted in no change in yield (entry 6). The use of other halide sources (KBr and LiCl) was not effective (entries 7 and 12). The use of Na<sub>2</sub>CO<sub>3</sub> instead of K<sub>3</sub>PO<sub>4</sub> resulted in a decrease in yield, probably due to the lower solubility of Na<sub>2</sub>CO<sub>3</sub> (entry 8).

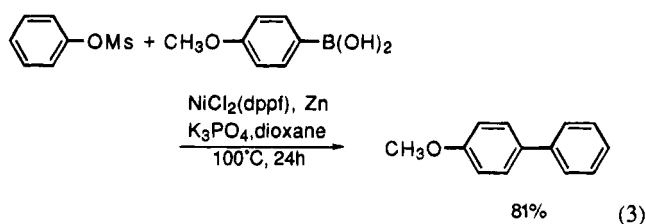
In the absence of Zn, no cross-coupled product was obtained (entry 9). In the Ni(0)-catalyzed homocoupling reaction, a reducing agent such as Zn is essential for the *in situ* generation of the reactive Ni(0) species from Ni(II). In contrast, in the Pd(0)-catalyzed reaction, added base and/or solvent are sufficient to reduce the Pd(II) *in situ* to generate Pd(0). No zinc additive effect was observed for the Ni(0)-catalyzed cross-coupling reaction. Increased amounts of Zn actually resulted in a lower yield (entry 11 vs 13).

In addition to NiCl<sub>2</sub>(dppf), other nickel catalysts such as NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, NiCl<sub>2</sub>(dppe), and NiCl<sub>2</sub>(dppp) were employed in the cross-coupling reaction (entries 2–5). The highest yields were obtained with NiCl<sub>2</sub>(dppf). This is due to the unique electronic and steric features of the dppf ligand (*vide supra*) (entry 2). The nickel catalyst containing the monodentate PPh<sub>3</sub> ligand was less effective (entry 3). NiCl<sub>2</sub>(dppe) and NiCl<sub>2</sub>(dppp) appeared to generate a Ni(0) bidentate ligand complex that was too stable, resulting in low yields (entries 4 and 5). The superiority of bulky dppf ligand over other ligands may be due to an enhanced rate of oxidative addition by formation of a more coordinatively unsaturated nickel

species and/or by electron-rich ferrocene moieties. When the amount of  $\text{NiCl}_2(\text{dppf})$  catalyst was increased, a slight increase in yield was obtained (entry 10). No significant additive effect on the amount of  $\text{Ni}(0)$  catalyst was observed.

In regard to the solvent, the coupling proceeded very selectively in THF, resulting exclusively in cross-coupled product in moderate yield (48%) with trace amounts of side reaction products (entry 2). When the reaction was carried out in dioxane at a higher temperature (95 °C), a good yield (67%) of the desired cross-coupled product was obtained (entry 14). In addition to the cross-coupled biaryl product, reduction product (4%) and O–S bond cleavage product (8%) were also detected. The latter is probably due to the increased solubility of  $\text{K}_3\text{PO}_4$  in dioxane at an elevated temperature (*vide supra*). The reactivity of the catalyst increased with an increase in temperature. However, the selectivity to the cross-coupled product decreased.

In summary, the highest yield (67%) in the cross-coupling reaction of methyl 4-[(methylsulfonyl)oxy]benzoate with phenylboronic acid was obtained using 0.10 equiv of  $\text{NiCl}_2(\text{dppf})$ , 3 equiv of  $\text{K}_3\text{PO}_4$ , and 1.7 equiv of Zn in dioxane at 95 °C. The same reaction conditions with a slight increase in temperature to 100 °C were utilized in the cross-coupling reaction of phenyl mesylate with (4-methoxyphenyl)boronic acid to give an 81% yield of 4-methoxybiphenyl (eq 3). There were only trace



amounts (<1%) of reduction side product and 18% of the unreacted mesylate. The reaction time is not optimized.

In our previous paper,<sup>5</sup> it was demonstrated that activated aryl mesylates undergo oxidative addition to  $\text{Ni}(0)$  complexes, resulting in almost quantitative consumption of the starting substrates even though side reactions such as reduction and transarylation occurred. From the control experiments, all the side reactions were found to occur after the oxidative addition step of the  $\text{Ni}(0)$ -catalyzed homocoupling cycle.

On the other hand, in the present study of  $\text{Ni}(0)$ -catalyzed cross-coupling reactions of aryl sulfonates (except aryl triflates) with arylboronic acids, incomplete reactions were often detected, and most of the materials isolated were unreacted starting substrates. This suggests that oxidative addition of aryl sulfonates including mesylate to  $\text{Ni}(0)$  complexes under cross-coupling conditions is relatively slow compared to the one under homocoupling conditions. In no case have we observed early formation of black colloidal nickel under  $\text{Ni}(0)$ -catalyzed cross-coupling conditions.

The reason for this incomplete reaction is not clear at present. One possible explanation is that the nickel catalyst forms some type of complex with the polar boronic acid moiety that inhibits the oxidative addition of the aryl mesylate, thus preventing the cross-coupling reaction. This poisoning of the nickel catalyst by boronic acid would be expected to result in incomplete reaction and recovery of starting substrates without the formation

of significant amounts of side reaction product. Another possibility is the poisoning of the  $\text{Ni}(0)$  catalyst by the oxidative addition of a carbon–boron bond of arylboronic acid to  $\text{Ni}(0)$  catalyst. Oxidative addition of arylboronic acid to  $\text{Pd}(0)$  to give  $[\text{ArPdB}(\text{OH})_2]$  was recently reported in a Heck-type reaction.<sup>16</sup> This poisoning of the  $\text{Ni}(0)$  catalyst by boronic acid would be expected to have a more significant effect on reaction yields with less reactive substrates (compare Table 2, entries 1 and 5). Complete consumption of aryl triflate occurs with 80% yield cross-coupled product and 20% yield side reaction products (Table 2, entry 1), while with the less reactive aryl mesylate incomplete reaction is obtained (48% yield cross-coupled product and only trace amounts of side reaction product) (Table 2, entry 5).

**Reaction Mechanism.** The general mechanism of a transition metal ( $\text{Ni}$  or  $\text{Pd}$ )-catalyzed cross-coupling reaction between organoelectrophiles and organometallic reagents involves sequential oxidative addition, transmetalation, and reductive elimination.<sup>8</sup>

The transmetalation step has been considered as the rate-determining step among these three steps in the  $\text{Pd}$ -catalyzed Suzuki reaction of aryl halides with arylboronic acids.<sup>2a–c</sup> This is due to the low nucleophilic nature of arylboronic acid. Recent studies using electrospray ionization mass spectrometry (ESI-MS) to detect transient catalytic intermediates in  $\text{Pd}(0)$ -catalyzed cross-coupling of arylboronic acids with bromopyridines also confirmed the presence of oxidative addition and transmetalation steps in the catalytic cycle.<sup>17</sup>

Since a base is essential to increase the rate of the transmetalation step,<sup>1</sup> the base is expected to enhance the nucleophilic (or anionic) nature of arylboronic acid by the formation of an arylboronate,<sup>2a–c</sup> and/or to undergo a ligand exchange reaction with halide prior to the transmetalation step,<sup>9</sup> resulting in an  $[\text{ArPdL}_2\text{OH}]$  species (when the base is the hydroxide ion). However, this species was not observed as a catalytic intermediate by ESI-MS studies (*vide supra*).<sup>17</sup>

Although the detailed mechanism is not clear at present, the mechanism for nickel-catalyzed cross-coupling of aryl mesylates with arylboronic acids may be similar to that for palladium-catalyzed cross-coupling of aryl halides with arylboronic acids, suggested by Suzuki.<sup>2a,9</sup> The most plausible mechanism is outlined in Scheme 1.

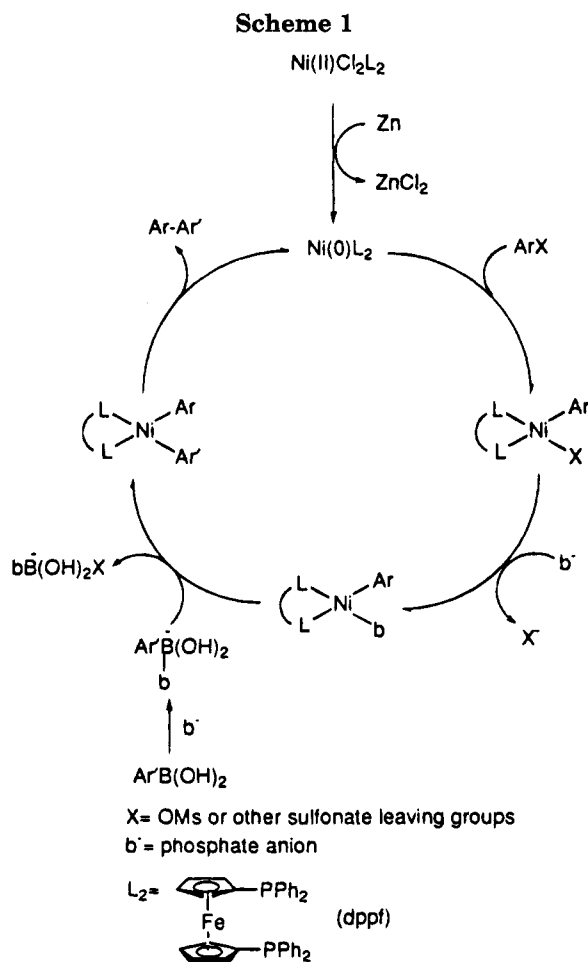
The first step of the mechanism involves the reduction of  $\text{Ni}(\text{II})$  to  $\text{Ni}(0)$  by Zn. This is followed by the oxidative addition of  $\text{ArX}$  ( $\text{X}$  = mesylate or other sulfonate leaving groups) to the  $\text{Ni}(0)$  species. This  $\text{Ni}(\text{II})$  species may have an ionic structure,<sup>10</sup> i.e.,  $[\text{ArNiL}_2]^+[\text{OMs}]^-$ . A similar  $\text{Pd}(\text{II})$  complex  $[\text{ArPdL}_n]^+[\text{OTf}]^-$  has been proposed to result from the oxidative addition of  $\text{ArOTf}$  to  $\text{Pd}(0)$  in the presence of  $\text{PPh}_3$ .<sup>10b</sup>

If the mesylate anion is weakly coordinating, like the triflate anion,<sup>18</sup> the phosphate anion may exchange with the mesylate ion in the oxidative addition product to generate a more reactive intermediate oxo–nickel complex. This nickel complex then undergoes the subsequent transmetalation reaction, resulting in diaryl nickel(II) species. This step is followed by reductive elimination to generate the cross-coupled product and regenerate the catalyst.

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### Conclusions

Aryl arenesulfonates and aryl mesylate participate in Ni(0)-catalyzed Suzuki-type cross-coupling reactions with arylboronic acid in THF or dioxane, forming functional unsymmetrical biaryls in good yields (up to 81%). This reaction is significant for several reasons. First, the substitution of a Ni catalyst for Pd catalysts represents significant cost savings. Second, functional aryl mesylates are readily obtainable from substituted phenols, hydroquinones, and bisphenols and are much less expensive than the corresponding triflates. Third, aryl mesylates are less susceptible to hydrolysis, when compared to aryl triflates on treatment with a base which is essential in Suzuki cross-coupling. The reaction conditions need to be refined in order to improve the reaction yield. Thus, the results reported here demonstrate the potential applicability of arenesulfonates and -mesylate leaving groups in metal-catalyzed cross-coupling reactions.

### Experimental Section

**General Methods.** General experimental information is identical to that previously reported.<sup>5</sup> All cross-coupling reactions were carried out under nitrogen using oven-dried

(110 °C) glassware. Unless otherwise noted, all reagents were purchased from commercial sources (Aldrich or Lancaster) and used without further purification. Pyridine was dried over CaH<sub>2</sub> and distilled. THF, dioxane, and toluene were distilled from sodium benzophenone ketyl. Zinc dust (325 mesh) was stirred in acetic acid, washed with water, and dried in vacuo at 120 °C. Pd(PPh<sub>3</sub>)<sub>4</sub>,<sup>19</sup> PdCl<sub>2</sub>(dppf),<sup>6a</sup> NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>,<sup>20</sup> NiCl<sub>2</sub>(dppf),<sup>21</sup> NiCl<sub>2</sub>(dpe),<sup>22</sup> and NiCl<sub>2</sub>(dppp)<sup>23</sup> were prepared according to literature procedures. Aryl sulfonates were prepared from the corresponding phenol as reported previously.<sup>5</sup> Phenylboronic acid [white crystals; mp 218 °C (EtOH) (lit.<sup>24</sup> mp 217–220 °C)] and (4-methoxyphenyl)boronic acid [white crystals; mp 206 °C (EtOH) (lit.<sup>24</sup> mp 207 °C)] were prepared according to literature procedures.<sup>24</sup>

**General Procedure for Palladium-Catalyzed Cross-Coupling.** Arylboronic acid (0.55 mmol) in ethanol (1 mL) was added via a syringe to a mixture of aryl sulfonate (0.5 mmol), LiCl (1.5 mmol), 2 M Na<sub>2</sub>CO<sub>3</sub> (0.65 mL), toluene (4 mL), and the palladium catalyst (0.025 mmol). The mixture was stirred at 90 °C under N<sub>2</sub> for 12 h. The percent conversion of the starting aryl sulfonate was determined by GC, using diphenyl ether as an internal standard. The GC yields are summarized in Table 1.

**General Procedure for Nickel-Catalyzed Cross-Coupling.** In a typical reaction a 125 mL Schlenk tube was charged with aryl sulfonate (0.5 mmol), arylboronic acid (0.55 mmol), NiCl<sub>2</sub>(dppf) (0.05 mmol), Zn powder (0.86 mmol), K<sub>3</sub>PO<sub>4</sub> (1.5 mmol), and a magnetic stirring bar. After the tube was sealed with a rubber septum, the contents were dried at 25 °C under reduced pressure (1 × 10<sup>-3</sup> mmHg) for 3 h. Then the tube was filled with N<sub>2</sub>, followed by three evacuation-filling cycles. Freshly distilled THF (1.0 mL) was added via a syringe through the rubber septum. The reaction mixture was stirred at 67 °C for 24 h. The mixture was cooled to 25 °C, filtered, diluted with CHCl<sub>3</sub> (10 mL), washed with H<sub>2</sub>O (10 mL), and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo*, and the residue was purified by column chromatography (SiO<sub>2</sub>; hexanes/ethyl acetate) and recrystallized from CHCl<sub>3</sub>/hexanes. The percent conversion of the starting aryl sulfonate was determined by GC measurements using diphenyl ether as an internal standard. The GC yields are summarized in Tables 2 and 3.

**Biaryls.** 4-Carbomethoxybiphenyl: white crystals; mp 116–117 °C (benzene) (lit.<sup>25</sup> mp 117.5 °C). 4-Acetylbiphenyl: white needles; mp 119–120 °C (ethanol) (lit.<sup>26</sup> mp 121 °C). 4-Methylbiphenyl: white crystals; mp 47–48 °C (hexanes) (lit.<sup>27</sup> mp 47.5 °C). 4-Methoxybiphenyl: white crystals; mp 87–88 °C (benzene) (lit.<sup>27</sup> mp 89–90 °C).

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