

# NiCl<sub>2</sub>(dppe)-Catalyzed Cross-Coupling of Aryl Mesylates, Arenesulfonates, and Halides with Arylboronic Acids

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An investigation of the NiCl<sub>2</sub>(dppe)-, NiCl<sub>2</sub>(dppb)-, NiCl<sub>2</sub>(dppf)-, NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>-, and NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>catalyzed cross-coupling of the previously unreported aryl mesylates, and of aryl arenesulfonates, chlorides, bromides, and iodides containing electron-withdrawing and electron-donating substituents with anyl boronic acids, in the absence of a reducing agent, is reported. NiCl<sub>2</sub>(dppe) was the only catalyst that exhibited high and solvent-independent activity in the two solvents investigated, toluene and dioxane. NiCl<sub>2</sub>(dppe) with an excess of dppe, NiCl<sub>2</sub>(dppe)/dppe, was reactive in the cross-coupling of electron-poor aryl mesylates, tosylates, chlorides, bromides, and iodides. This catalyst was also efficient in the cross-coupling of aryl bromides and iodides containing electrondonating substituents. Most surprisingly, the replacement of the excess dppe from NiCl<sub>2</sub>(dppe)/ dppe with excess PPh<sub>3</sub> generated NiCl<sub>2</sub>(dppe)/PPh<sub>3</sub>, which was found to be reactive for the crosscoupling of both electron-rich and electron-poor aryl mesylates and chlorides. Therefore, the solventindependent reactivity of NiCl<sub>2</sub>(dppe) provides an inexpensive and general nickel catalyst for the cross-coupling of aryl mesylates, tosylates, chlorides, bromides, and iodides with aryl boronic acids.

## Introduction

Palladium-catalyzed Suzuki-type cross-coupling is one of the most powerful methods to form carbon-carbon bonds<sup>1–3</sup> originally, mostly from aryl bromides, iodides, and triflates.<sup>4</sup> Developments from different laboratories<sup>5-9</sup> have provided methods to activate palladium toward the less expensive and reactive aryl chlorides. However, the high cost of palladium<sup>10</sup> and the ligands required to activate it<sup>11</sup> limits its use at least in the large-scale synthesis of inexpensive compounds. Although vinyl

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tosylates have been shown to be active in cross-coupling reactions,<sup>12-14</sup> aryl mesylates and tosylates are not sufficiently reactive<sup>15</sup> for conventional Suzuki reaction conditions. Recently, the cross-coupling of alkyl tosylates with alkyl 9-BBN boranes<sup>16</sup> and a Pd-catalyzed crosscoupling of aryl tosylates with aryl boronic acids were reported.17

Ni(0)-catalyzed homocoupling of aryl mesylates<sup>18</sup> and the Ni(0)-catalyzed cross-coupling of aryl boronic acids with aryl mesylates and other sulfonates<sup>15</sup> were reported in 1995 from our laboratory. NiCl<sub>2</sub>(dppf)/Zn/K<sub>3</sub>PO<sub>4</sub>/dioxane was found to be the most suitable catalytic system for this Suzuki-type cross-coupling. Zinc was used to generate Ni(0) species in situ. Other groups have expanded the scope of the Ni(0)-catalyzed cross-coupling reaction. For example, exchanging *n*-BuLi for Zn as reducing agent allowed the cross-coupling of aryl chloride<sup>19,20</sup> and aryl mesylates<sup>21</sup> with aryl boronic acids. Subsequently, the cross-coupling of aryl chlorides with

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aryl boronic acids in dioxane/water with use of the catalytic system NiCl<sub>2</sub>(dppe)/TPPTS/Zn/K<sub>3</sub>PO<sub>4</sub><sup>22</sup> and by generating Ni(0) from Ni(II) on charcoal with *n*-BuLi/PPh<sub>3</sub>/dioxane<sup>23</sup> have been demonstrated. Additional phosphine-free systems such as NiCl<sub>2</sub>/bpy or NiCl<sub>2</sub>/NEt<sub>3</sub>/Na<sub>3</sub>PO<sub>4</sub> have also been elaborated.<sup>24</sup>

An important advance on the nickel-catalyzed reaction was generated when aryl chlorides have been shown to cross-couple without the need of an external reducing agent.<sup>25</sup> By adapting our original reaction conditions,<sup>15</sup> it was demonstrated that NiCl<sub>2</sub>(dppf)/dioxane as well as NiX<sub>2</sub> together with other solvents and ligands have efficiently catalyzed this cross-coupling reaction. Soon after, electron-deficient aryl chlorides have been shown to undergo the Suzuki cross-coupling in the presence of NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/PPh<sub>3</sub>/K<sub>3</sub>PO<sub>4</sub>/toluene at 80 °C.<sup>26</sup> While this work was in progress, the cross-couplings of aryl tosylates with NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>/PCy<sub>3</sub>/K<sub>3</sub>PO<sub>4</sub>/dioxane<sup>27</sup> and of aryl bromides with the ligandless system NiCl<sub>2</sub>·6H<sub>2</sub>O/K<sub>3</sub>PO<sub>4</sub>/ dioxane<sup>28</sup> have been reported. These two catalysts are active at 130 °C. A catalytic cycle related to Pd(0)catalyzed cross-coupling has been suggested for the Ni-(II)-catalyzed reaction (Scheme S1, Supporting Information).<sup>26</sup> In the first step of this cycle self-coupling of aryl boronic acid reduces Ni(II) to Ni(0) via a Pd(II)-related mechanism.29

An inspection of the previous reports on the Nicatalyzed cross-coupling reaction showed that different results were generated by minor changes of the experimental conditions. For example, it was reported<sup>24</sup> that in the cross-coupling of aryl chlorides NiCl<sub>2</sub>(dppe) was not active in anisole while NiCl<sub>2</sub>(dppf) was efficient both in anisole and dioxane. Toluene was found to be the best solvent when the cross-coupling of aryl chlorides was catalyzed by NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>,<sup>25</sup> while dioxane was the most suitable solvent when the crosscoupling of aryl tosylates was catalyzed by NiCl<sub>2</sub>(PCv<sub>3</sub>)<sub>2</sub>.<sup>26</sup> (Table S1, Supporting Information). Surprisingly, NiCl<sub>2</sub> complexes with ligands such as dppb, dppp, and dppe were reported to be less efficient than NiCl<sub>2</sub>(dppf) and  $NiCl_2(PPh_3)_2$  both in the presence<sup>18,20</sup> and in the absence of a reducing agent.<sup>24</sup> This is unexpected since dppb, dppe, and dppp are more electron rich than PPh<sub>3</sub>.

Aryl mesylates are much less expensive and more stable than aryl triflates. Therefore, their entry into the Ni(II)-catalyzed cross-coupling would provide a desirable method for the creation of carbon–carbon bonds starting from phenols. A single example of Ni(II)-catalyzed crosscoupling of an aryl mesylate without the use of an

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TABLE 1. Influence of Leaving Group, Catalyst,Ligand, and Solvent on the Ni(II)-CatalyzedCross-Coupling Reaction

MeO <sub>2</sub> C-X+	
K <sub>3</sub> PO <sub>4</sub> , 5 %catalyst/ligand	
solvent, 80 °C, 14 h	

				solvent ar	nd conv (%)
entry	Х	catalyst	ligand/%	dioxane	PhMe
1	Cl	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	PCy <sub>3</sub> /10	>95	>95
2	Cl	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	PPh <sub>3</sub> /10	19	95
3	Cl	NiCl <sub>2</sub> (dppe)	dppe/5	91	>95, 92 <sup>a</sup>
4	Cl	NiCl <sub>2</sub> (dppb)	dppb/5	80	10
5	Cl	NiCl <sub>2</sub> (dppf)	dppf/5	>95	87
6	OMs	$NiCl_2(PCy_3)_2$	PCy <sub>3</sub> /10	>95	22
7	OMs	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	PPh <sub>3</sub> /10	18	88
8	OMs	NiCl <sub>2</sub> (dppe)	dppe/5	>95	77, 70 <sup>a</sup>
9	OMs	NiCl <sub>2</sub> (dppb)	dppb/5	70	50
10	OMs	NiCl <sub>2</sub> (dppf)	dppf/5	57	12
11	OTs	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	PCy <sub>3</sub> /10	95	52
12	OTs	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	PPh <sub>3</sub> /10	24	75
13	OTs	NiCl <sub>2</sub> (dppe)	dppe/5	82	87
14	OTs	NiCl <sub>2</sub> (dppb)	dppb/5	traces	50
15	OTs	NiCl <sub>2</sub> (dppf)	dppf/5	20	20
<sup>a</sup> Rea dppe.	actions	carried out with	1 mol % of	catalyst and	d 1 mol % of

external reducing agent pre-dates this report.<sup>20</sup> Here we report our investigations on the influence of a diversity of leaving groups (mesylates, tosylates, chlorides, bromides and iodides), catalysts [NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>, NiCl<sub>2</sub>(dppe), NiCl<sub>2</sub>(dppf), and NiCl<sub>2</sub>(dppb)], excess ligands (PPh<sub>3</sub>, PCy<sub>3</sub>, dppe, dppf, and dppb), and two solvents (toluene and dioxane) on the Ni(II)-catalyzed crosscoupling of aryl derivatives containing electron-withdrawing and electron-donating substituents, in the absence of a reducing agent.

## **Results and Discussion**

Five catalysts, NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>, NiCl<sub>2</sub>(dppe), NiCl<sub>2</sub>(dppf), and NiCl<sub>2</sub>(dppb), were investigated (Table 1). Each catalyst was tested in both dioxane and toluene. Three leaving groups (X = -OMs, -OTs, and -Cl) were first compared for activity. 4-Substituted methyl benzoate was selected as a model substrate. Cross-coupling reactions were performed at 80 °C for 14 h with 5 mol % catalyst.

Effect of Catalyst. In view of the previous results reported for cross-couplings catalyzed by NiCl<sub>2</sub>(dppe) in the presence<sup>18,20</sup> and absence<sup>24</sup> of a reducing agent, it was surprising to find that NiCl<sub>2</sub>(dppe) was the most reactive catalyst for electron-poor aryl mesylates and chlorides in both dioxane and toluene, when 1 equiv of dppe was added per equivalent of catalyst (Table 1, entries 3, 8, and 13). Previously, NiCl<sub>2</sub>(dppe) was reported to be reactive for cross-coupling reactions carried out in the presence of zinc as reducing agent and the additional ligand TPPTS.<sup>21</sup> NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> are also efficient in these cross-coupling reactions. However, their reactivity is very sensitive to the nature of solvent (Table 1). NiCl<sub>2</sub>(dppf) was reactive in the cross-coupling of aryl chlorides carried out in dioxane and toluene (Table 1, entry 5). However, NiCl<sub>2</sub>(dppf) was less reactive for the cross-coupling of aryl mesylates and tosylates when no reducing agent was added. NiCl<sub>2</sub>(dppb) was the least general catalyst, giving good yields only for the crosscoupling of aryl mesylates and chlorides in dioxane (Table 1, entries 4 and 9).

Effect of the Leaving Group. Aryl chlorides produced high conversions with nearly all catalysts. NiCl<sub>2</sub>- $(PCy_3)_2$  and  $NiCl_2(dppe)$  were active in both dioxane and in toluene with aryl chlorides, while NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, NiCl<sub>2</sub>-(dppb), and NiCl<sub>2</sub>(dppf) showed solvent-dependent activity. The reactivity of aryl mesylates is dependent on the choice of both catalyst and solvent. Aryl tosylates generate modest conversions in reactions catalyzed by NiCl<sub>2</sub>-(dppe) and  $NiCl_2(PPh_3)_2$  and high conversions in reactions catalyzed by NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> above 80 °C.

**Effect of Solvent.** Except for the case of NiCl<sub>2</sub>(dppe) the nature of the solvent had a strong influence on the cross-coupling reaction. NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> was very efficient for the cross-coupling of aryl chlorides in both dioxane and toluene. However, the cross-coupling of aryl sulfonates in dioxane produced higher conversions when  $NiCl_2(PCy_3)_2$  was used as catalyst. Regardless of the nature of the leaving group, toluene produced the highest conversions in the NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>-catalyzed reactions (Table 1).

**Optimization of the Cross-Coupling for Electron-**Deficient Aryl Mesylates and Chlorides. The absence of additional ligand decreased the reactivity of all catalysts. However, most of their reactivity was restored when half of the original amount of ligand was added (Table S2, compare entries 4-6 with 7-9). When less and electron-rich ligand was used, a significant amount of self-coupling product of the aryl mesylate or chloride was observed (Table S2, entries 1 and 2).

Catalyst concentrations as low as 1 mol % were sufficient for the efficient cross-coupling of electrondeficient aryl chlorides (Table 1, entry 3 and footnote a). However, in the cross-coupling of electron-poor aryl mesylates a lower catalyst concentration decreased the conversion (Table 1, entry 8 and footnote a). In addition, although the NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> system could be used to crosscouple aryl chlorides at 60 °C, aryl mesylates were not reactive at this temperature (Table S2, Supporting Information, entries 1 and 2). However, the NiCl<sub>2</sub>(dppe) system could be used for the cross-coupling of both activated aryl mesylates and chlorides at 60 °C (Table S2, Supporting Information, entry 3). Neither NiCl<sub>2</sub>-(PPh<sub>3</sub>)<sub>2</sub>, nor NiCl<sub>2</sub>(dppe) were efficient in the crosscoupling of aryl chlorides and aryl mesylates at 40 °C (Table S2, Supporting Information, entries 4-6).

**Electronic Influence of the Aryl Mesylate Sub**strate. A selected series of aryl mesylates containing various substituents was studied in cross-coupling reactions catalyzed with NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, NiCl<sub>2</sub>(PCy)<sub>3</sub>, and NiCl<sub>2</sub>-(dppe). High yields were obtained when either cyano or acetyl groups were present in the para position of the aryl mesylate (Table 2, entries 1-5). Methyl-4-phenylbenzoate was obtained in 88% and 98% yields with NiCl<sub>2</sub>-(PPh<sub>3</sub>)<sub>2</sub> and NiCl<sub>2</sub>(dppe), respectively (Table 2, entries 6-8). However, electron-neutral and electron-rich aryl mesylates did not provide preparative yields in the NiCl<sub>2</sub>-(PPh<sub>3</sub>)<sub>2</sub>- and NiCl<sub>2</sub>(dppe)-catalyzed reactions (Table 3, entries 10-12 and 16). As expected, the more electronrich ligand, NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> in dioxane, was very efficient (Table 2, entries 9 and 13–15) in these reactions.

TABLE 2. Influence of the Substrate Substituent on the Ni(II)-Catalyzed Cross-Coupling of Aryl Mesylates



entry	R	catalyst	ligand/%	solvent	yield (%) <sup>a</sup>
1	CN	NiCl <sub>2</sub> (dppe)	dppe/5	PhMe	92 (>99)
2	CN	NiCl <sub>2</sub> (dppe)	dppe/5	dioxane	88 (>99)
3	Ac	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	PPh <sub>3</sub> /10	PhMe	84
4	Ac	NiCl <sub>2</sub> (dppe)	dppe/5	dioxane	- (50)
5	Ac	$NiCl_2(PCy_3)_2$	PCy <sub>3</sub> /10	dioxane	72 (80)
6	CO <sub>2</sub> Me	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	PPh <sub>3</sub> /10	PhMe	96 (>99)
7	CO <sub>2</sub> Me	NiCl <sub>2</sub> (dppe)	dppe/5	PhMe	96 (>99)
8	CO <sub>2</sub> Me	NiCl <sub>2</sub> (dppe)	dppe/5	dioxane	90 (>99)
9	OMe	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	PCy <sub>3</sub> /10	dioxane	89 (>99)
10	OMe	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	PPĥ <sub>3</sub> /10	PhMe	63 (67)
11	1-nph <sup>b</sup>	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	PPh <sub>3</sub> /10	PhMe	63 (68)
12	1-npf <sup>b</sup>	NiCl <sub>2</sub> (dppe)	dppe/5	dioxane	55 (76)
13	1-npf <sup>b</sup>	$NiCl_2(PCy_3)_2$	PCy <sub>3</sub> /10	dioxane	95 (>99)
14	NHÂc	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	PCy <sub>3</sub> /10	dioxane	76 (>99)
15	OBn	NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub>	PCy <sub>3</sub> /10	dioxane	73 (>99)
16	OBn	NiCl <sub>2</sub> (dppe)	dppe/5	dioxane	28 (40)

<sup>a</sup> Isolated yields; <sup>1</sup>H NMR determined conversions are in parentheses. <sup>b</sup> 1-Naphthyl.

TABLE 3. Optimization of the NiCl<sub>2</sub>(dppe)/dppe **Catalytic System for Electron-Rich Aryl Mesylates and** Chlorides

		$\langle \rangle$	-B(OH) <sub>2</sub> + X-	-{	le	
	K <sub>3</sub> P	O <sub>4</sub> , NiCl <sub>2</sub> (d <b>)</b> solvent, 80 <sup>0</sup>	ope)/dppe ℃, 14 h	MeO-		>
entry	Х	solvent	Ni(II) (%)	dppe (%)	<i>T</i> (°C)	yield (%)
1	Cl	PhMe	5	2.5	80	10
2	Cl	PhMe	5	7.5	80	66
3	Cl	PhMe	5	5	100	63
4	Cl	PhMe	5	7.5	100	84
5	OMs	PhMe	5	5	100	25
6	OMs	PhMe	5	10	100	<10
7	OMs	PhMe	5	75	100	28 40 <sup>a</sup>

100

5

31

5 <sup>a</sup> Conversion determined by <sup>1</sup>H NMR spectroscopy.

OMs dioxane

8

**Optimization of NiCl<sub>2</sub>(dppe) Catalyst for the Cross-Coupling.** The influence of temperature, nature of catalyst, catalyst, and excess ligand concentrations on the cross-coupling reaction of 4-chloroanisole and 4-methoxy-phenyl mesylate with phenyl boronic acid were investigated (Table 3). At elevated temperature with a higher ligand concentration only 4-chloroanisole reacted in good yields. Methoxy-substituted aryl mesylates did not couple more efficiently even with increased ligand concentration and temperature.

**Cross-Coupling with Ni(II) Catalysts Containing** Mixed Ligands. The cross-coupling reaction catalyzed by NiCl<sub>2</sub>(dppe) was most efficient when an excess of ligand that provided two additional phosphorus atoms per Ni(II) was used. In previous examples, the excess ligand used was identical with the ligand bound to the Ni(II) species. A series of experiments in which the NiCl<sub>2</sub>-(dppe) catalyst was stabilized by an excess of a monodentate ligand such as PPh3 was also performed. Unexpectedly, the experiments reported in Table 4 demonstrate

TABLE 4. Effect of Excess Monodentate PPh<sub>3</sub> as Additional Ligand to NiCl<sub>2</sub>(dppe)-Catalyzed Cross-Coupling Reactions



				cat.	PPh₂	conv (	%) <i>a</i>
entry	R	Х	solvent	(%)	(%)	biphenyl <sup>b</sup>	biaryl
1	<i>p</i> -OMe	OMs	PhMe	5	10	nd <sup>c</sup>	80
2	<i>p</i> -OMe	Cl	PhMe	5	10	nd	78
3	<i>p</i> -OMe	OMs	PhMe	5	10	nd	$30^d$
4	<i>p</i> -OMe	Cl	PhMe	5	10	nd	$71^d$
5	<i>p</i> -OMe	OMs	PhMe	5	5	nd	75
6	<i>p</i> -OMe	Cl	PhMe	5	5	nd	74
7	<i>p</i> -OMe	OMs	PhMe	$5^e$	10	nd	54
8	<i>p</i> -OMe	Cl	PhMe <sup>f</sup>	$5^g$	5	nd	89
9	<i>p</i> -OMe	OMs	PhMe <sup>f</sup>	$5^g$	5	nd	57
10	o-OMe	OMs	PhMe	5	10	nd	75
11	1-naphthyl	OMs	PhMe	5	10	nd	86
12	3,5-OMe	OMs	PhMe	5	10	<5	99 (89)
13	<i>p</i> -OMe	OMs	PhMe	3	6	nd	58
14	<i>p</i> -OMe	OMs	PhMe	1	2	<3	56
15	<i>p</i> -CO <sub>2</sub> Me	Cl	PhMe	5	10	<6	82
16	<i>p</i> -CO <sub>2</sub> Me	Cl	dioxane	5	10	<6	82
17	<i>p</i> -CO <sub>2</sub> Me	OMs	PhMe	5	10	4	90 (86)
18	o-CO <sub>2</sub> Me	OMs	PhMe	5	10	nd	96 (89)
19	<i>m</i> -CO <sub>2</sub> Me	OMs	PhMe	5	10	nd	85 (76)
20	<i>p</i> -CO <sub>2</sub> Me	Cl	dioxane	1	2	2	73
21	<i>p</i> -CO <sub>2</sub> Me	OMs	PhMe	1	2	3	82
22	<i>p</i> -CO <sub>2</sub> Me	OMs	dioxane	1	2	3	78
23	<i>p</i> -CO <sub>2</sub> Me	OMs	PhMe	0.5	1	<3	86 (77)
24	<i>p</i> -CO <sub>2</sub> Me	OMs	dioxane <sup>h</sup>	5	10	nd	16
25	p-CO₂Me	OMs	$dioxane^h$	5	20	5	63

 $^a$  Isolated yields are in parentheses.  $^b$  Not determined.  $^c$  Biphenyl from the self-coupling of ArB(OH)<sub>2</sub>.  $^d$  Reaction temperature 60 °C.  $^e$  NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as catalyst.  $^f$  PCy<sub>3</sub> as ligand.  $^g$  dppe as excess ligand.  $^h$  As received A.C.S. reagent grade dioxane used as solvent.

that the most general catalyst for the cross-coupling of aryl mesylates and chlorides containing electron-donating substituents in para, meta, and ortho positions to the leaving group was NiCl<sub>2</sub>(dppe)/PPh<sub>3</sub>. Replacing PPh<sub>3</sub> with the more electron-rich PCy<sub>3</sub> reduced the reactivity of the catalyst (compare entries 1 and 7 in Table 4). This is an unexpected result. In addition, the catalyst concentration could be reduced to 1 mol % for aryl chlorides and mesylates containing electron-donating substituents and to 0.5 mol % for electron-withdrawing derivatives. With a 20 mol % excess of PPh<sub>3</sub> the cross-coupling reaction was efficient in as received A.C.S. reagent grade dioxane (Table 4, entries 24 and 25). The small amount of biphenyl generated by the self-coupling of phenyl boronic acid is proportional to the amount of catalyst used and does not interfere with the separation of the pure crosscoupled product by recrystallization or column chromatography. Without any attempt to optimize the reaction conditions, these experiments have demonstrated that NiCl<sub>2</sub>(dppe)/PPh<sub>3</sub> is the most general nickel-based catalytic system for the cross-coupling of aryl mesylates and aryl chlorides.

**Cross-Coupling of Aryl Bromides and Iodides.** The capability of the  $NiCl_2(dppe)$  catalyst for the crosscoupling of aryl bromides and iodides was also investigated (Table 5). Ni(II)-catalyzed cross-couplings of aryl bromides and iodides were previously reported only with

 TABLE 5. Aryl Bromides and Iodides in the

 Nickel-Catalyzed Cross-Coupling

			B(OH) <sub>2</sub>	+ x-{=						
	$\xrightarrow{\text{K}_3\text{PO}_4, \text{ NiCl}_2(\text{dppe})/\text{dppe}}_{\text{solvent, 80 °C, 14 h}} R  R$									
entry	Х	R	solvent	Ni (%)	dppe (%)	yield (%)				
1	Br	CO <sub>2</sub> Me	PhMe	5	5	85, 71 <sup>a</sup>				
2	Br	CO <sub>2</sub> Me	dioxane	5	5	83				
3	Br	CO <sub>2</sub> Me	PhMe	5	10	73				
4	Br	CO <sub>2</sub> Me	PhMe	1	1	88				
5	Br	CO <sub>2</sub> Me	dioxane	1	1	66				
6	Ι	CO <sub>2</sub> Me	PhMe	5	5	82				
7	Ι	CO <sub>2</sub> Me	PhMe	5	10	73				
8	Ι	OMe	PhMe	5	5	83, 72 <sup>a</sup>				
9	Ι	OMe	PhMe	1	1	27, $50^{b}$				
10	Ι	OMe	PhMe	1	2	52, 77 <sup>c</sup>				
11	Ι	OMe	dioxane	5	5	75				
12	Br	OMe	PhMe	5	5	73				
13	Br	OMe	PhMe	5	10	66				
<sup>a</sup> NiC emper	Cl <sub>2</sub> (PF ature	Ph <sub>3</sub> ) <sub>2</sub> with , 100 °C. <sup>c</sup>	10 mol % Reaction t	of PPh <sub>3</sub> ime, 22 h	was used.	<sup>b</sup> Reaction				

NiCl<sub>2</sub>(NEt<sub>3</sub>)<sub>2</sub> and NiCl<sub>2</sub>(bpy) catalysts.<sup>30</sup> Both aryl bromides and iodides containing electron-withdrawing and electron-donating substituents were efficiently crosscoupled in high conversions with use of NiCl<sub>2</sub>(dppe) catalyst. Side products derived from the reduction or homocoupling of the aryl halides were not detected at all or were observed only in trace amounts. The NiCl<sub>2</sub>(dppe) system exhibited higher reactivity than NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (Table 5, entries 1 and 8). Catalyst concentrations could be reduced to 1 mol % when methyl-4-bromobenzoate was used (Table 5, entries 4 and 5). Iodoanisole was an effective cross-coupling partner under standard reaction conditions. Furthermore, a larger excess of ligand and an extended reaction time allowed the cross-coupling of iodoanisole with phenyl boronic acid when only 1 mol % of NiCl<sub>2</sub>(dppe) was used.

Synthesis of Multifunctional Biphenyls. These nickel-catalyzed cross-coupling reaction conditions have been employed in the preparation of several precursors required for the synthesis of novel  $AB_2$  and  $AB_3$  self-assembling dendritic building blocks.<sup>31</sup> Replacing the previously used  $AB_2$  and  $AB_3$  benzyl ether building blocks with the corresponding biphenyl methyl ethers will expand the dimensions, the 3-dimensional structures, and the functions generated from the previous library of supramolecular dendrimers.<sup>32</sup> The very good isolated yields obtained in the synthesis of the multifunctional

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		E	3(OH) <sub>2</sub> + X-	$R^3$ $R^2$	K <sub>3</sub> PO <sub>4</sub> , catalyst/ligan solvent, 80 °C, 14 h	$d \rightarrow R^2 \xrightarrow{R^3}_{R^1}$		
entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	catalyst	ligand (%)	solvent	yield (%) <sup>a</sup>
1	Н	OMe	Н	Cl	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	PPh <sub>3</sub>	PhMe	79
2	OMe	Н	OMe	Cl	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	$PPh_3$	PhMe	74
3	OMe	Н	OMe	Cl	NiCl <sub>2</sub> (dppe)	$PPh_3$	PhMe	86
4	OMe	OMe	Н	Br	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	$PPh_3$	PhMe	75 (88), 85 <sup>b</sup>
5	OMe	OMe	Н	Br	NiCl <sub>2</sub> (dppe)	dppe	PhMe	78 (97)
6	OMe	OMe	Н	Br	NiCl <sub>2</sub> (dppe)	dppe	dioxane	81 (93)
~	OMe	OMe	OMe	Br	NiCl <sub>2</sub> (dppe)	dppe	PhMe	96

biphenyls reported in Table 6 demonstrate the synthetic utility of the  $NiCl_2(dppe)$  catalytic system.

## Conclusions

The NiCl<sub>2</sub>(dppe)-, NiCl<sub>2</sub>(dppb)-, NiCl<sub>2</sub>(dppf)-, NiCl<sub>2</sub>-(PCy<sub>3</sub>)<sub>2</sub>-, and NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>-catalyzed Suzuki-type crosscoupling of aryl mesylates, tosylates, chlorides, bromides, and iodides containing electron-withdrawing and electrondonating substituents, in the absence of a reducing agent, was investigated. Contrary to previous publications<sup>18,20,24</sup> reporting that NiCl<sub>2</sub>(dppe) was unreactive in the absence of a reducing agent, we have discovered that NiCl<sub>2</sub>(dppe) in the presence of an excess of dppe, NiCl<sub>2</sub>(dppe)/dppe, is the most general nickel catalyst for the cross-coupling of aryl mesylates, tosylates, chlorides, bromides, and iodides containing electron-withdrawing substituents and of aryl bromides and iodides containing electron-donating substituents, in both dioxane and toluene. NiCl<sub>2</sub>(dppe) containing an excess of PPh<sub>3</sub>, (NiCl<sub>2</sub>(dppe)/PPh<sub>3</sub>), is a general catalyst for the cross-coupling of aryl mesylates and chlorides containing both electron-donating and electron-withdrawing substituents. In the two solvents investigated, dioxane and toluene, all other nickel catalysts exhibited solvent-dependent reactivity.

## **Experimental Section**

**Materials and General Methods.** Materials and general methods are available in the Supporting Information.

General Procedure for the Synthesis of Aryl Mesylates. A modified literature procedure was used.<sup>12</sup> A flamedried round-bottom flask equipped with a magnetic stir bar was charged with hydroquinone monobenzyl ether (25 mmol, 5.0 g), 25 mL of CH<sub>2</sub>Cl<sub>2</sub>, and 5 mL of pyridine. The homogeneous mixture was cooled in an ice water bath and methane sulfonyl chloride was added dropwise (1.2 equiv, 3.4 g, 2.3 mL, 30 mmol). After TLC or <sup>1</sup>H NMR spectroscopy analysis showed total consumption of the starting material, the reaction was quenched with H<sub>2</sub>O (40 mL). The phases were separated and the aqueous layer was extracted with  $CH_2Cl_2$  (3  $\times$  20 mL). The combined organic extracts were washed successively with 15% HCl ( $2 \times 20$  mL), H<sub>2</sub>O ( $2 \times 25$  mL), and saturated aqueous NaCl solution ( $2 \times 20$  mL). After drying over MgSO<sub>4</sub>, the crude product was recrystallized from hexane/toluene/EtOAc (2:1: 1) to afford the aryl mesylate (5.87 g, 85%).

**4-(Methanesulfonyl)oxy Benzyloxybenzene.** White rhomboids (toluene), mp 129–131 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.43–7.34 (m, 5H), 7.21 (d, J= 8.8 Hz, 2H), 6.99 (d, J= 8.8 Hz, 2H), 5.06 (s, 2H), 3.10 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  158.0, 143.2, 136.8, 129.0, 128.5, 127.8, 123.38, 116.2, 70.8,

37.4.  $R_f$  (3:1 hexanes/EtOAc) 0.25. HRMS (M + Na) calcd 305.0510, found 305.0505.

General Procedure for the Cross-Coupling Experiments. To a 25-mL Schlenk tube equipped with a magnetic stir bar were added 2 mmol of aryl halide or mesylate,<sup>34</sup> 0.290 g of phenyl boronic acid (2.4 mmol, 1.2 equiv), 0.10 mmol of Nickel catalyst, 6 mmol (1.391 g) of K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O, and phosphine to give 4 equiv of P for every Ni. The reaction vessel was equipped with a glass stopper and sealed. The Schlenk tube was evacuated and backfilled through the sidearm with Ar several times before being allowed to sit under Ar for at least 30 min. Solvent (10 mL) was added under Ar and the sidearm was closed. The reaction was heated to 80 °C (oil bath temperature) for 14 h. At the end of this time period, the reaction was quenched by opening to air and the addition of 15 mL of Et<sub>2</sub>O or DCM. The solids were filtered off and washed. The resultant solution was dried with  $\mathrm{MgSO}_4$  and filtered. The solution was concentrated under reduced pressure to give the crude biaryl. Purification via column chromotography gave the title compounds.

**4'-Phenylacetophenone.** White plates, mp 117–119 °C (lit.<sup>5b</sup> 120–121 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.03 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz), 7.63 (d, J = 7.9 Hz, 2H), 7.46 (dd, J = 7.5, 7.0 Hz, 2H), 7.40 (tt, J = 7.3, 1.3 Hz, 1H), 2.64 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  198.0, 146.2, 140.3, 136.3, 129.3, 129.3, 128.6, 127.6, 127.6, 26.9.  $R_f$  (3:1 hexanes/ EtOAc) 0.40.

**4'-Phenylacetanilide.** White needles, mp 168–170 °C (lit.<sup>35</sup> 168–170 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (br s, 1H), 7.57–7.52 (m, 6H), 7.42 (dd, J = 7.3, 7.5 Hz, 2H) 7.32 (t, J = 7.3 Hz, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  169.0, 140.8, 137.6, 129.1, 127.9, 127.1, 120.7, 24.8.  $R_f$  (3:1 hexanes/EtOAc) 0.06.

**4'-Methyl-4-Methoxybiphenyl.** White plates, mp 106–107 °C (lit.<sup>36</sup> 109 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  138.4, 136., 134.2, 129.8, 128.3, 126.9, 114.6, 55.7, 21.3.  $R_f$  (3:1 hexanes/EtOAc) 0.66.

**4-Cyanobiphenyl.** White powder, mp 84–86 °C (lit.<sup>5c</sup> 86– 87 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 7.5 Hz, 2H), 7.46 (dd, J = 7.6, 7.5 Hz, 2H), 7.43 (tt, J = 7.5, 2.1 Hz). <sup>13</sup>C NMR

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(125 MHz, CDCl<sub>3</sub>)  $\delta$  139.6, 132.9, 129.5, 129.0, 128.1, 127.6, 119.2.  $R_f$  (3:1 hexanes/EtOAc) 0.47.

**4'-Methyl-3,4-Dimethoxybiphenyl.** White plates (EtOH), mp 63–65 °C (lit.<sup>37</sup> 62–64 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ 7.45 (d, J = 8.1 Hz, 2H), 7.23 (dd, J = 8.8, 8.6 Hz, 2H), 7.12 (dd, J = 8.3, 2.2 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 2.38 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  149.6, 148.9, 138.6, 136.9, 134.7, 129.8, 127.1, 119.57, 112.0, 110.9, 56.4, 56.3, 21.4.  $R_f$  (3:1 hexanes/EtOAc) 0.39.

**3,4-Dimethoxybiphenyl.** White needles (EtOH), mp 68– 70 °C (lit.<sup>38</sup> 70.5 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.57 (d, J = 7.9 Hz, 2H), 7.42 (dd, J = 7.9, 7.7 Hz, 2H), 7.32 (tt, J =7.3, 1.3, 1H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 7.13 (d, J = 2.3Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  149.6, 149.1, 141.5, 134.07, 129.1, 127.2, 127.2, 119.8, 112.0, 111.0, 56.4, 56.3.  $R_f$  (3:1 hexanes/EtOAc) 0.39.

**4-Methoxybiphenyl.** White powder (EtOH), mp 85–87 °C (lit.<sup>5a</sup> 83–84 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 (d, J=7.3 Hz, 2H), 7.58 (d, J= 8.8 Hz, 2H), 7.45 (dd, J= 7.8, 7.8 Hz, 2H), 7.34 (dd, J= 7.3, 1.3 Hz), 7.02 (d, J= 8.6 Hz, 2H), 3.88 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  159.5, 141.2, 134.1, 129.0, 128.5, 128.0, 127.0, 114.6, 55.7.  $R_f$ (3:1 hexanes/EtOAc) 0.67.

**4'-Methyl-3,5-Dimethoxybiphenyl.** White needles (hexane), mp 55–56 °C (lit.<sup>39</sup> 57.3–57.5 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.50 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 6.75 (d, J = 2.2 Hz, 2H), 6.48 (t, J = 2.2 Hz, 1H), 3.86 (s, 6H), 2.41 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  161.4, 143.8, 138.7, 137.7, 129.7, 127.3, 105.6, 99.4, 55.7, 21.4.  $R_f$  (3:1 hexanes/ EtOAc) 0.60.

**4-Benzyloxybiphenyl.** White rhomboids, mp 131–133 °C (lit.<sup>40</sup> 136 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.54 (d, J = 7.2 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.45 (2H, J = 7.3 Hz), 7.42–7.28 (m, 6H), 7.04 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H). <sup>13</sup>C NMR

(125 MHz, CDCl<sub>3</sub>)  $\delta$  158.8, 137.4, 129.1, 129.0, 128.5, 128.3, 128.1, 127.8, 127.1, 127.0, 115.5.  $R_f$ (3:1 hexanes/EtOAc) 0.66.

**Biphenyl-4-Carboxylic Acid Methyl Ester.** White crystals, mp 114–115 °C (lit.<sup>41</sup> 117–118 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.10 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.47 (dd, J = 7.5, 7.2 Hz, 2H), 7.38 (tt, J = 7.4, 1.5 Hz, 1H), 3.94 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  167.3, 146.0, 140.4, 130.4, 129.3, 129.3, 128.5, 127.6, 127.4, 52.4.  $R_f$  (3:1 hexanes/EtOAc) 0.64.

**3**',**4**',**5**'-**Trimethoxy-4-methylbiphenyl**. Hexane, mp 65 °C. Purity (HPLC) 99+ %. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  2.41 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 6.78 (s, 2H), 7.25 (d, 2H, J = 8.0 Hz), 7.46 (d, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C)  $\delta$ 153.7, 138.7, 137.8, 137.4, 137.3, 129.7, 127.2, 104.7, 61.2, 21.3. Anal. Calcd for C<sub>16</sub>H<sub>18</sub>O<sub>3</sub>: C, 74.39; H, 7.02. Found: C, 74.16; H, 7.08.

**1-Phenylnaphthalene.** Colorless viscous liquid.<sup>42</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.96 (m, 2H), 7.93 (d, J = 8.2 Hz, 1H), 7.56 (m, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  141.1, 140.6, 134.2, 132.01, 130.4, 128.6, 128.0, 127.6, 127.5, 127.3, 126.4, 126.4, 126.1, 125.7.  $R_f$  (5:1 hexanes/EtOAc) 0.53.

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**Supporting Information Available:** Materials and general methods, a scheme showing the catalytic cycle proposed for the Ni(II)-catalyzed Suzuki-type reaction, three tables of experimental results, NMR spectra of 4-(methanesulfonyl)oxy benzyloxybenzene and 3',4',5'-trimethoxy-4-methylbiphenyl, and additional supporting references. This material is available free of charge via the Internet at http://pubs.acs.org.

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