Biaryl Synthesis

Nickel-Catalyzed Cross-Coupling of Aryl Grignard Reagents with Aromatic Alkyl Ethers: An Efficient Synthesis of Unsymmetrical Biaryls**

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Transition-metal-catalyzed cross-coupling reactions play a major role in the formation of C–C bonds. As a result, the cross-coupling of aryl halides (and pseudohalides) with organometallic reagents have become a steadfast method in organic synthesis.[1] This methodology has been used to prepare biaryl compounds, which are prevalent in both natural products and drug compounds.[2] In the more challenging cross-coupling reactions unreactive substrates, such as aryl nitriles,[3] aryl fluorides,[4] and aryl carbamates[5] are coupled with an organometallic reagent and generally require nickel catalysis. Wenkert et al. reported the $[NiCl_2(PPh_3)_2]$-mediated cross-coupling of anisoles with aromatic Grignard reagents.[6] The scope of this process is rather limited, and the only substrates that provide the desired biaryl products in synthetically useful yields are the more reactive 1- and 2-methoxynaphthalene derivatives. In this communication, we report a general, high-yielding nickel-catalyzed cross-coupling of nonactivated aromatic ethers with aryl Grignard reagents.

Our initial attempts in cross-coupling an anisole derivative with *p*-TolMgBr utilized a nickel catalyst prepared in situ from $[Ni(acac)_2]$ (acac = acetylacetonyl) and various phosphane ligands in THF. Unfortunately, the reaction did not proceed to completion under any of the conditions tested (Table 1). From these studies, it was found that PCy_3 (Cy = cyclohexyl), an electron-rich ligand, was the best phosphane ligand with $[Ni(acac)_2]$. The reaction utilizing $[Ni(acac)_2]$/PCy_3 in a nonpolar solvent system (e.g. $(EtO)_2CH_2$) per-

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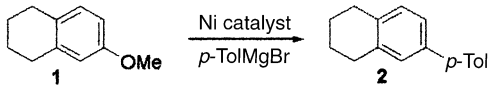
Table 1: Ni-catalyzed cross-coupling in THF: Ligand optimization.[a]



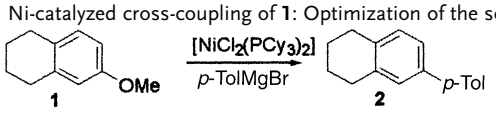
Entry	Nickel cat.	Recovd. **1** [%]	Yield **2** [%]
1	$[NiCl_2(PMe_3)_2]$	82	2
2	$[NiCl_2(PEt_3)_2]$	74	15
3	$[Ni(acac)_2]/2\,Cy_3P$	33	64
4	$[Ni(acac)_2]/2\,iPr_3P$	44	55
5	$[Ni(acac)_2]/2\,iBu_3P$	66	26
6	$[Ni(acac)_2]/2\,tBu_2MeP$	51	37
7	$[Ni(acac)_2]/2\,PhCy_2P$	46	51
8	$[Ni(acac)_2]/2\,tBu_3P$	78	4

[a] Reactions were carried out with 5 mol% nickel catalyst in THF at 60°C for 15 h and 3.0 equiv Grignard reagent. Yields were determined by GC with tridecane as an internal standard.

formed poorly. This may be a result of the lack of solubility of the nickel precatalyst. The application of a nonpolar solvent media (vide supra) was imperative for this cross-coupling to proceed in high yields.

A major improvement was attained when the cross-coupling reaction was performed with 5 mol% $[NiCl_2(PCy_3)_2]$[7] in THF (Table 2, entry 1). In addition, it

Table 2: Ni-catalyzed cross-coupling of **1**: Optimization of the solvent.[a]



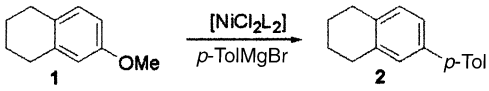
Entry	Solv.	*t* [h]	Recovd. **1** [%]	Conv. **2** [%]
1	THF	15	25	64
2[b]	THF	15	23	73
3	toluene	15	9	76
4	iPr_2O	15	0	93
5	$(Et_2O)_2CH_2$	6	10	82
6	*t*AmOMe	6	8	65
7	nBu_2O	6	0	87

[a] Reaction temperature was 60°C. The conversions were determined by GC analysis with tridecane as an internal standard. [b] 10 mol% PCy_3 was added.

was found that the yield of biaryl was higher when an additional 10 mol% PCy_3 was also added to the reaction mixture (Table 2, entry 2). The choice of solvent played a major role in the efficiency of the reaction. It was determined that nonpolar solvent media was preferred. As illustrated in Table 2, the nonpolar ethers such as $(EtO)_2CH_2$, Bu_2O, iPr_2O, and *t*AmOMe (*t*Am = $CEtMe_2$) afforded the highest yields. In addition, toluene can be utilized as a solvent, and in some cases it was the preferred solvent system (Table 2, entry 3). Presumably, when nonpolar media is used, MgBr(OMe), which may poison the desired catalytic cycle, is removed by precipitation. This may account for the inability of the reaction to reach complete conversion in a more polar solvent such as THF. Furthermore, no reaction transpires when dimethoxyethane or diglyme is used as the reaction solvent.

After several phosphane ligands had been surveyed, it became clear that the yield of the reaction was dependent on the cone angle of the ligand (Table 3).[8] Ligands such as PMe_3 with a small cone angle and sterically larger phosphanes such

Table 3: Ni-catalyzed cross-coupling of **1**: Optimization of the phosphane.[a]



Entry	L	Recovd. **1** [%]	Conv. **2** [%]
1	PMe_3	33	33
2	PEt_3	75	7
3	$PiBu_3$	32	42
4	$PiPr_3$	<1	82
5	PCy_3	0	93
6	$PhPCy_2$	<1	92
7	Ph_2PCy	7	81
8	Ph_3P	74	15

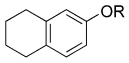
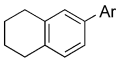
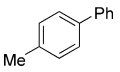
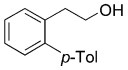
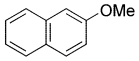
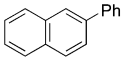
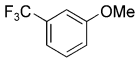
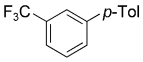
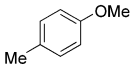
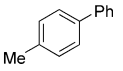
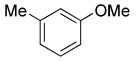
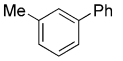
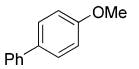
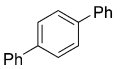
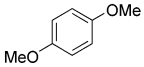
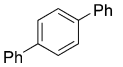
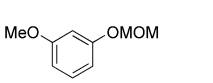
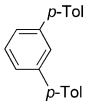
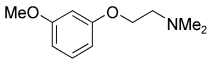
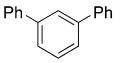
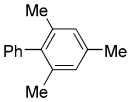
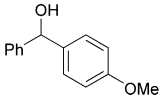
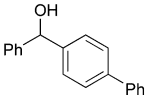
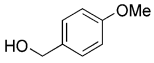
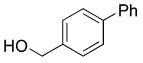
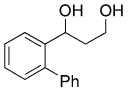
[a] Reactions were carried out at 60°C in iPr_2O for 15 h with 5 mol% nickel catalyst. Conversions were determined by GC analysis with tridecane as an internal standard.

as tBu_2PMe performed poorly in this cross-coupling. However, it was found that ligands with intermediate cone angles provided the highest conversion to the desired biaryl **2**. Among the best phosphane ligands surveyed were iPr_3P, Cy_3P, and $PhCy_2P$ (Table 3, entries 4–6). The ligands that are better σ donors were found to be more active, and complete conversion was possible at lower temperatures (PCy_3 and $PhPCy_2$). Even Ph_2PCy was a competent ligand if the reaction was performed at >80°C for 15 h. In stark contrast, application of Wenkert's catalyst system using $[NiCl_2(PPh_3)_2]$ in iPr_2O resulted in low conversions (Table 3, entry 8).

While 5 mol% of the nickel catalyst was preferred, the nickel catalyst loading could be reduced to 2.5 mol%, provided an additional 5 mol% PCy_3 was present. In most cases 3.0 equiv Grignard reagent was generally utilized; however, in some examples the amount of Grignard could be reduced to 1.5 equiv, provided that the $[NiCl_2(PCy_3)_2]$ complex was used. It was interesting to note the biaryl cross-coupling could be achieved under microwave conditions (Table 4, entry 2), which significantly reduces the reaction time.[9]

At this point it was interesting to explore whether the Ni-catalyzed C–O activation process was applicable to other ether leaving groups besides the methoxy group in anisole systems. As can be seen in Table 4 (entries 4–11) a large number of ether leaving groups are compatible with this chemistry including ethyl, methoxyethyl, *N*,*N*-dimethylaminoethyl, methoxymethyl (MOM), and hydroxyethyl ethers. Interestingly, even the sterically hindered trimethylsilyl (TMS) ether (Table 4, entries 7, 10) afforded good yields of the desired biaryl adduct. Currently, aryl triflates are well established as cross-coupling partners in biaryl synthesis; however, these compounds are known to lack long-term stability.[10] On the other hand, the corresponding trimethylsilyl ethers, which are readily prepared from the correspond-

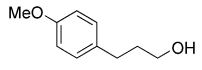
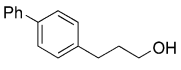
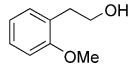
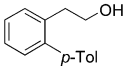
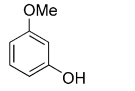
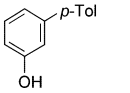
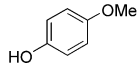
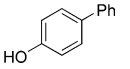
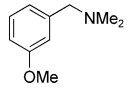
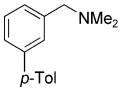
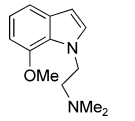
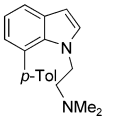
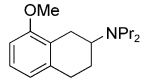
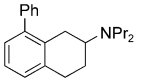
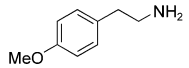
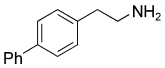
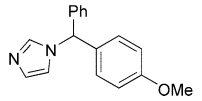
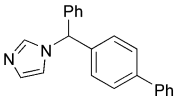
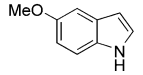
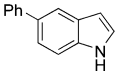
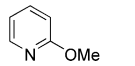
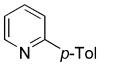
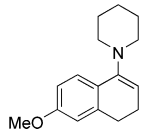
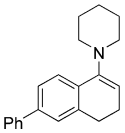
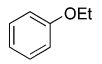
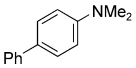
Table 4: Synthesis of biaryl compounds by Ni-catalyzed cross-coupling of aromatic alkyl ethers with organomagnesium reagents.[a]

Entry	Arom. ether	Product	Solvent	*T* [°C]	Cat.	Conv. [%]
						
1	R = Me	Ar = *p*-Tol	$(EtO)_2CH_2$	100	[c]	94
2[b]	R = Me	Ar = *p*-Tol	$(EtO)_2CH_2$	105	[c]	72
3	R = Me	Ar = *m*-Tol	*t*BuOMe	65	[c]	89
4	R = $(CH_2)_2OMe$	Ar = *p*-Tol	$(EtO)_2CH_2$	100	[c]	77
5	R = $(CH_2)_2NMe_2$	Ar = *p*-Tol	$(EtO)_2CH_2$	95	[c]	99
6	R = MOM	Ar = *p*-Tol	*t*AmOMe	80	[c]	92
7	R = TMS	Ar = *p*-Tol	*t*AmOMe	60	[c]	70
						
8	R = Et		$(EtO)_2CH_2$	90	[c]	73
9	R = CH_2CH_2OH		$(EtO)_2CH_2$	80	[c]	67
10	R = TMS		$(EtO)_2CH_2$	90	[c]	72
11	R = CF_3		iPr_2O	80	[d]	30
12			PhMe	60	[c]	62
13			*t*AmOMe, Et_2O	23	[e]	89
14			*t*AmOMe, Et_2O	23	[e]	91
15			PhMe	60	[c]	61
16			$(EtO)_2CH_2$, Et_2O *t*AmOMe, Et_2O	35 23	[c] [e]	93 92
17			*t*AmOMe, Et_2O	23–65	[c]	78
18			*t*AmOMe, Et_2O	80	[e]	86
19			*t*AmOMe, Et_2O	80	[e]	95
20			iPr_2O	80	[c]	87
21			*t*AmOMe, Et_2O	80	[c]	88
22			*t*AmOMe	60–100	[c]	80
23			*t*AmOMe	80	[c]	75
24			*t*AmOMe, Et_2O	80	[e]	61
25			*t*AmOMe	80	[c]	85
26			*t*AmOMe, Et_2O	80	[c]	51

ing phenol, are much more stable than the triflates and are excellent substrates in this nickel-catalyzed cross-coupling. In addition, the trifluoromethyloxy group also provided the *p*-phenyltoluene under the nickel-catalyzed conditions; however, it was found to be a poor leaving group under a variety of conditions (Table 4, entry 11). Interestingly, a cyclic ether (Table 4, entry 12) performed well in the arylation reaction, yielding a biaryl compound with an *ortho*-hydroxyethyl group. In general, the yields for the hydrocarbon biaryl adducts (Table 4, entries 1–23) are superior to those containing any functionality (vide supra). Furthermore, diarylation of the bisether substrates provides *m*-terphenyl and *p*-terphenyl in high yields (Table 4, entries 19–21). The nickel-catalyzed cross-coupling reaction can tolerate steric hindrance in either the aromatic ether or the Grignard reagent. For example, 2-methoxybiphenyl cross-couples with *p*-tolylMgBr (Table 4, entry 22). Upon heating from 60 °C to 100 °C, with an additional 15 h at 100 °C under these conditions the terphenyl derivative was realized in 80 % conversion. Reaction of a sterically hindered Grignard such as mesitylmagnesium bromide with phenetole (ethyl phenyl ether), under the standard nickel-catalyzed conditions, supplied phenylmesitylene in high yield (Table 4, entry 23).

Kumada–Corriu cross-coupling reactions are known for their poor tolerance of functional groups. However, the present reaction performs well with many functional groups present on the aryl ether such as alcohols, phenols, amines, enamines and N-heterocycles. The cross-coupling yields of these functionalized substrates range from 54–85 % (Table 4, entries 24–39). The aryl ether substrates containing benzylic alcohol moieties (Table 4, entries 24–26) or even those substituted with an *ortho*-positioned hydroxyethyl side chain afforded the desired biaryl compounds in high yield (Table 4, entries 28). Interestingly, the *meta*- and *para*-methoxyphenols undergo efficient coupling to give the corresponding phenylphenols (Table 4, entries 29 and 30). This was remarkable considering that the magnesium phenoxide, formed from the phenol derivative and PhMgBr, is very electron-rich, and the rate of oxidative addition should be significantly reduced. We were gratified that amines and N-heterocycles performed so well in the cross-coupling, considering the requirement for the nonpolar nature of the solvent. To

Table 4: (Continued)

Entry	Arom. ether	Product	Solvent	*T* [°C]	Cat.	Conv. [%]
27			*t*AmOMe, Et_2O	80	[e]	77
28			$(EtO)_2CH_2$, Et_2O	80	[c]	63
29			*t*AmOMe	90	[f]	78 (75)
30			*t*AmOMe	80	[e]	63
31			PhMe	60	[c]	(73)
32			*t*AmOMe	80	[c]	55
33			*t*AmOMe, Et_2O	80	[e]	81
34			*t*AmOMe, Et_2O	23	[e]	82
35			*t*AmOMe, Et_2O	80	[e]	(74)
36			*t*AmOMe, Et_2O	23	[e]	67 (54)
37			THF	23	[g]	73
38			$(EtO)_2CH_2$	80	[c]	58
39			$(EtO)_2CH_2$	70	[c]	77

[a] Conversions were determined by GC methods with tridecane as an internal standard. Yields of isolated products are given in parentheses. Reactions were run for 15 h unless otherwise specified. An additional equivalent of Grignard reagent was added with substrates containing acidic functionality. [b] Reaction was performed under microwave conditions (30 min, 105 °C) using the Emrys Creator from Personal Chemistry. [c] $[NiCl_2(PCy_3)_2]/2\,PCy_3$. [d] $[NiCl_2(Ph_2PCy)_2]/2\,Ph_2PCy$. [e] $[NiCl_2(PhPCy_2)_2]$. [f] $[NiCl_2(PhPCy_2)_2]/2\,PhPCy_2$. [g] $[NiCl_2(PMe_3)_2]$.

this end, the anisole with a potentially labile benzylic amine functionality undergoes efficient cross-coupling in toluene (Table 4, entry 31). The protected 7-methoxyindole derivative smoothly reacts with *p*-TolMgBr under nickel catalysis to afford the desired biaryl (Table 4, entry 32). Interestingly, the analogous unprotected 7-methoxyindole does not react under these conditions. Combination of the 8-methoxytetrahydronaphthalenyl amine derivative and PhMgBr under the Ni-catalyzed conditions furnishes the desired biarylamine (Table 4, entry 33), which was reported to possess 5-HT_{1A} activity.[11] The reaction of 4-methoxyphenethylamine (Table 4, entry 34) and PhMgBr in the presence of $[NiCl_2(PhPCy_2)_2]$ provides the 4-phenylphenethylamine. It was interesting to note that the primary amine was tolerated during this cross-coupling event. Many N-heterocycles were compatible with the reaction conditions. The imidazole derivative participated in the nickel-catalyzed cross-coupling to afford bifonazole, which is a drug known for its antifungal activity (Table 4, entry 35).[12] Heterocycles, such as 5-methoxyindole and 2-methoxypyridine, when combined with PhMgBr, furnished the desired arylation products in good yield (Table 4, entries 36 and 37). The combination of the enamine derived from 6-methoxy-1-tetralone and PhMgBr with $[NiCl_2(PCy_3)_2]/PCy_3$ provided the biaryl derivative; thus a reactive ketone could be protected as an enamine during the course of the coupling reaction (Table 4, entry 38). Application of an organomagnesium reagent containing a functional group was illustrated by the cross-coupling of *N*,*N*-dimethylaminophenylmagnesium bromide with phenetole under the standard nickel-catalyzed conditions with phenetole (Table 4, entry 39).

In summary, we have demonstrated the synthetic utility of the Kumada–Corriu-type cross-coupling of various anisole and other aromatic ether derivatives with aryl Grignard reagents.[13] The reaction has a very broad scope with respect to the anisole derivative and affords the desired biaryl compounds in high yield. Paramount to this cross-coupling procedure was the application of a nickel(II) phosphane complex (PCy_3 or $PhPCy_2$) in a nonpolar solvent. The reaction will support functionality such as alcohols, the hydroxy groups of phenols, amines, enamines, and *N*-heterocycles in the aromatic ether substrate. Due to the ubiquitous nature of the aryl ether group in pharmaceutically active molecules, this new biaryl synthesis should find wide applicability in medicinal chemistry.

Experimental Section

Representative procedure: 6-(4-methylphenyl)-1,2,3,4-tetrahydronaphthalene (Table 4, entry 5): In a reaction flask were placed

$[NiCl_2(PCy_3)_2]$ (69.0 mg, 0.0999 mmol), PCy_3 (57.8 mg, 0.206 mmol), tridecane (328 mg, 1.778 mmol, as an internal standard), and *N*,*N*-dimethyl-*N*-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethyl]amine (409 mg, 1.867 mmol). The solvent in the *p*-TolMgBr reagent (1M in ether, 6.0 mmol) was removed under reduced pressure and replaced with diethoxymethane (6.0 mL). This solution was then added to the above catalyst mixture under a nitrogen atmosphere at room temperature. The resulting solution was stirred for several minutes at room temperature and then warmed to 95°C for 15 h. A sample was withdrawn and quenched by adding it to 1M aqueous sodium citrate, which was then extracted with ethyl acetate. GC analysis of the organic phase showed the presence of 6-(4-methylphenyl)-1,2,3,4-tetrahydronaphthalene (1.85 mmol, 99% conversion), bitoluene (0.65 mmol), and *p*-methylphenol (0.58 mmol) in the reaction mixture. In general, the optimal conditions for each substrate had to be determined by experimentation. The temperature for the cross-coupling was found to range from room temperature to 100°C depending on the steric nature of the anisole. In general, the most effective catalyst system was either $[NiCl_2(PCy_3)_2]$, $[NiCl_2(PCy_3)_2]$/$2\,PCy_3$, or $[NiCl_2(PhPCy_2)_2]$. The most useful solvents were found to be *t*AmOMe, $(EtO)_2CH_2$, PhMe, and *t*BuOMe. The choice of solvent was found to depend on the temperature of the reaction and the solubility of the Grignard reagent in the selected solvent. In general, the Grignard reagents were found to be most soluble in PhMe; however, this was not usually the best solvent for the cross-coupling procedure. In some cases it was best to use a mixture of PhMe and one of the ether solvents listed above. The most general and effective conditions were the use of 5 mol% $[NiCl_2(PhPCy_2)_2]$ in *t*AmOMe at a temperature determined primarly by the steric hindrance of the anisole. The reactions were over after 15 h reaction time (at 80°C); however, in some cases the reaction can reach completion in as little as 3 h. Activated anisole compounds (2-methoxypyridine, 1- and 2-methoxynaphthalene) could be coupled using a variety of nickel complexes such as $[NiCl_2(PMe_3)_2]$ or $[Ni(acac)_2]$/neopentylphosphite in THF.

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Keywords: anisole · biaryls · C—C coupling · nickel · phosphane ligands

[1] For general references, see: E.-i. Negishi, F. Liu in *Metal-Catalyzed Cross-Coupling Reactions*, *Vol. 1* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 1–48; b) V. Farina in *Comprehensive Organometallic Chemistry II*, *Vol. 3.4* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, L. S. Hegedus), Pergamon, Oxford, **1995**, pp. 161–240; c) R. J. P. Corriu, J. P. Masse, *Chem. Commun.* **1972**, 144; d) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374; e) For a review on nickel-catalyzed cross-coupling of Grignard reagents and aryl halides, see: M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669.

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[13] Several organomagnesium derivatives were screened to delineate their scope in the cross-coupling. It was found that only aryl Grignard reagents participate in the reaction; alkyl and alkenyl Grignard reagents return only the starting anisole derivative under a variety of conditions.

