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Cross-Coupling of Aryl/Alkenyl Ethers with Aryl Grignard Reagents through Nickel-Catalyzed C−O Activation

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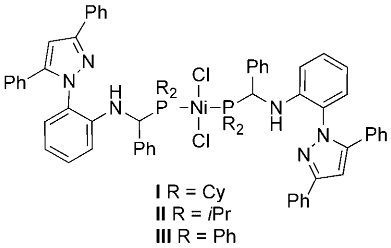
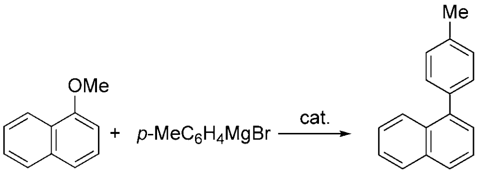
Cross-coupling reactions catalyzed by transition metals are versatile and powerful tools to construct new C−C bonds.[1,2] In a cross-coupling reaction, the electrophile species are predominantly organic halides and aryl/alkenyl triflates or sulfonates. The reactions that proceed through C−O activation of ethers and esters are very limited although these electrophilic substrates have drawn the attention of chemists even at the early stage of cross-coupling reactions.[3,4] The pioneering work on cross-coupling reactions with aryl/alkenyl methyl ethers as electrophiles was carried out by Wenkert et al. in 1979.[4a] However, this important discovery has been ignored for a long time. Recently, significant advances have been made in the cross-couplings of ethers, esters, carbamates, carbonates, and sulfamates catalyzed by transition metals and with Grignard reagents, organozinc reagents, and organoboron reagents as nucleophiles.[3,5–8] For example, Dankwardt has reported a reaction of aryl methyl ethers with aryl Grignard reagents using $[(Cy_3P)_2NiCl_2]$ or $[(PhPCy_2)NiCl_2]$ as a catalyst in 2004.[5c] In 2008, Shi and co-workers have reported the cross-coupling of aromatic or benzylic ethers with MeMgBr catalyzed by $[(Cy_3P)_2NiCl_2]$.[5d,e] Very recently, Shi and co-workers have reported a Kumada-type coupling of magnesium naphtholates as electrophiles.[9] Ackermann and Mulzer have also reported the C−OH bond functionalization of phenols through the activation of a C−O and a C−H bond catalyzed by ruthenium.[10] Although significant progress has been achieved, the substrate scope for these reactions is still limited and the development of more efficient catalytic systems is also desirable. In addition, alkenyl ethers are only seldom used as electrophiles. Some examples have been reported by Wenkert and et al., who carried out nickel-catalyzed cross-coupling between alkenyl ethers and Grignard reagents that resulted in relatively low yields of the products.[4] Related work is the nickel- or iron-catalyzed C−O bond cleavage of alkenyl carboxylates through reaction with organomagnesium, -zinc, or -boron reagents.[5f,6b,7d] Herein we report the efficient couplings of aryl and alkenyl ethers with aryl Grignard reagents catalyzed by nickel complexes.



Complexes **I**–**III** have been previously synthesized by our research group.[11] In preliminary studies of their catalytic properties, we investigated the reaction of 1-methoxynaphthalene with p-MeC_6H_4MgBr and found that complexes **I** and **II** catalyzed the reaction efficiently in THF at room temperature with 2.5 mol% of catalyst loading or in toluene at 120°C (bath temperature) with 1 mol% of catalyst loading (Table 1). At lower reaction temperature and in toluene the reaction did not reach completion (Table 1, entries 2, 3, and 8). The reaction catalyzed by complex **III** (2.5 mol%)

Table 1. Evaluation of the catalytic activity of complexes **I**–**III** in the reaction of 1-methoxynaphthalene with p-MeC_6H_4MgBr.[a]



	Cat. ([mol%])	Conditions	Yield [%][b]
1	**I** (2.5)	THF, 25°C, 24 h	91
2	**I** (2.5)	toluene, 25°C, 24 h	28
3	**I** (2.5)	toluene, 80°C, 24 h	81
4	**I** (2.5)	toluene, 120°C, 16 h	99
5	**I** (1.0)	toluene, 120°C, 16 h	95
6	**II** (2.5)	THF, 25°C, 24 h	96
7	**II** (2.5)	toluene, 120°C, 16 h	99
8	**II** (1.0)	toluene, 80°C, 24 h	69
9	**II** (1.0)	toluene, 120°C, 16 h	98
10	**III** (2.5)	THF, 25°C, 24 h	trace
11	**III** (2.5)	toluene, 120°C, 16 h	91

[a] The reactions were carried out using 1-methoxynaphthalene (0.5 mmol) and p-MeC_6H_4MgBr (0.75 mmol) in the presence of the catalyst under a nitrogen atmosphere. [b] Yield of isolated products.

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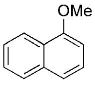
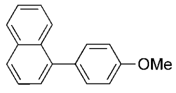
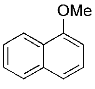
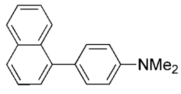
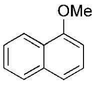
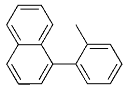
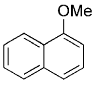
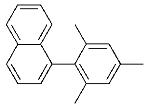
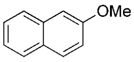
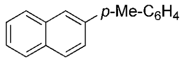
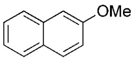
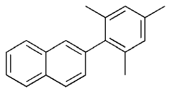
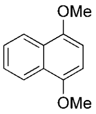
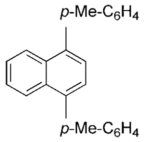
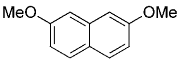
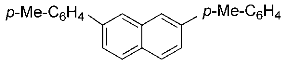
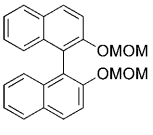
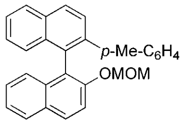
Table 2. Cross-coupling of aryl ethers with ArMgBr catalyzed by **I** or **II**.[a]

	Aryl ether	Product	Conditions	Cat. ([mol %])	Yield [%][b]
1			THF, 25 °C, 24 h	**II** (2.5)	94
2			THF, 25 °C, 24 h	**II** (2.5)	92
3			THF, 25 °C, 24 h	**II** (2.5)	85
4			toluene, 120 °C, 16 h	**II** (2.5)	89
5 6			THF, 25 °C, 24 h	**I** (2.5) **II** (2.5)	92 95
7			toluene, 120 °C, 16 h	**II** (2.5)	81
8 9			THF, reflux, 24 h	**II** (5)	84 91
10 11			THF, 25 °C, 24 h	**I** (5) **II** (5)	89 91
12 13			THF, reflux, 24 h	**I** (10) **II** (10)	81 82

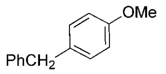
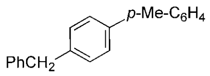
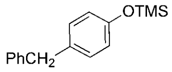
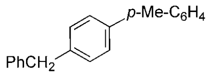
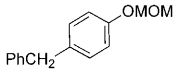
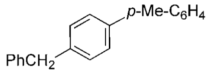
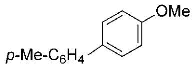
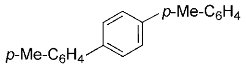
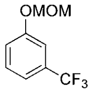
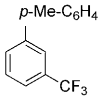
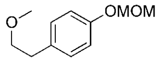
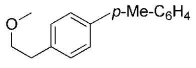
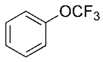
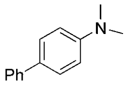
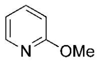
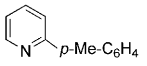
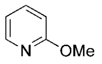
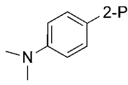
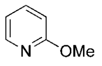
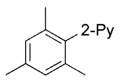
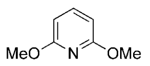
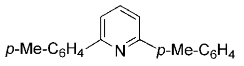
[a] The reactions were carried out using of aryl alkyl ethers (0.5 mmol) and the Grignard reagents (0.75 mmol) in the presence of complex **I** or **II** under nitrogen atmosphere; OMOM = Methoxymethoxy. [b] Yield of isolated products.

also proceeded well in toluene at 120 °C. However, the reaction in THF at room temperature formed the product only in trace amount. It was also found that in the catalyzed substitution reaction of 1-alkoxynaphthalene, MeO was a better leaving group compared with *n*BuO, *i*PrO, OMOM, and OTMS (see Table S1 in the Supporting Information).

The electron-rich Grignard reagents *p*-$MeOC_6H_4MgBr$ and *p*-$Me_2NC_6H_4MgBr$ reacted efficiently with 1-methoxynaphthalene in the presence of **II** (2.5 mol %) in THF at room temperature, thus giving the corresponding cross-coupling products in excellent yields (Table 2, entries 1 and 2). At such a temperature, the coupling product 1-(4-methoxyphenyl)naphthalene did not undergo further C−O cleavage. Reaction of *o*-MeC_6H_4MgBr with 1-methoxynaphthalene under the same reaction conditions resulted in a slightly lower yield of coupling product than that of *p*-MeC_6H_4MgBr (Table 1, entry 6 and Table 2, entry 3). The reaction between 2,4,6-$Me_3C_6H_2MgBr$ and 1-methoxynaphthalene under similar reaction conditions resulted in a very low yield of the products, owing to steric hindrance. However, a higher reaction temperature in toluene could drive the reaction to completion (Table 2, entry 4). The 2-methoxynaphthalene species has displayed a similar reactivity compared to 1-methoxynaphthalene: when treated with *p*-MeC_6H_4MgBr under catalysis by either **I** or **II,** led to excellent yields of the corresponding products (Table 2, entries 5 and 6). The reaction of 2-methoxynaphthalene with 2,4,6-$Me_3C_6H_2MgBr$ catalyzed by **II** in toluene at 120 °C also resulted in good yields of the corresponding product (Table 2, entry 7). Also, both **I** and **II** have efficiently catalyzed the reaction of 1,4-dimethoxynaphthalene or 2,7-dimethoxynaphthalene with *p*-MeC_6H_4MgBr, thus giving 1,4- or 2,7-di(*p*-tolyl)naphthalene in 84–91 % yields (Table 2, entries 8–10). It is noteworthy that the reaction of 1,4-dimethoxynaphthalene required reflux THF condition, whereas the reaction of 2,7-dimethoxynaphthalene proceeded at 25 °C in THF. Attempts to substitute one of the MeO groups on the dimethoxynaphthalenes by decreasing the amount of Grignard reagent were unsuccessful, because they led to the formation of a mixture of mono- and di-substituted products. In addition, it was also noted that **II** exhibited a higher catalytic activity than **I** in the reaction of dimethoxynaphthalenes. An interesting example is the reaction between 2,2′-bis(methoxymethoxy)-1,1′-binaphthyl and *p*-MeC_6H_4MgBr catalyzed by either **I** or **II** (Table 2, entries 12 and 13). Only one OMOM group was substituted, even when an excess of Grignard reagent was employed. The 2,2′-Bis(methoxy)-1,1′-binaphthyl species showed much lower reactivity compared with 2,2′-bis(methoxymethoxy)-1,1′-binaphthyl; the former gave the product in trace amount when treated with *p*-MeC_6H_4MgBr in the presence of **II**.

Substituted phenyl methyl ethers exhibited a lower reactivity than methoxynaphthalenes. Solvent optimization showed toluene to be superior to THF, dioxane, *n*Bu_2O, *i*Pr_2O, DME, and $CH_2(OEt)_2$ (see Table S2 in the Supporting Information). Experimental results have also shown that for the substituted phenyl ethers, each of OTMS, OMOM,

Table 3. Reaction of substituted phenyl ethers, 2-methoxypyridine, and 2,6-dimethoxypyridine with aryl Grignard reagents catalyzed by complex **I** or **II**.[a]

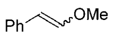
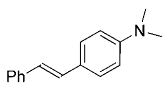
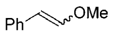
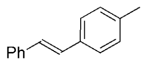
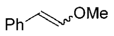
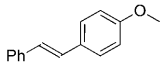
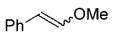
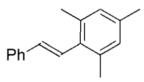
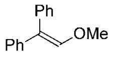
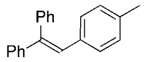
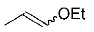
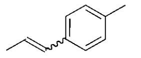
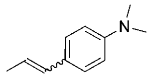
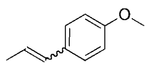
	Aryl ether	Product	Conditions	Cat. ([mol %])	Yield [%][b]
1			toluene, 120 °C, 16 h	**I** (5)	67
2			toluene, 120 °C, 16 h	**I** (5)	72
3			toluene, 120 °C, 16 h	**I** (5)	72
4				**II** (5)	74
5			toluene, 120 °C, 16 h	**II** (5)	68
6			toluene, 120 °C, 16 h	**I** (5)	71
7				**II** (5)	70
8			toluene, 120 °C, 16 h	**I** (5)	70
9				**II** (5)	75
10			toluene, 120 °C, 16 h	**I** (5)	83
11				**II** (5)	83
12			THF, 25 °C, 24 h	**II** (5)	91
13			THF, 25 °C, 24 h	**II** (5)	97
14			toluene, 90 °C, 16 h	**I** (5)	61
15				**II** (5)	63
16			THF, 25 °C, 24 h	**I** (10)	93
17				**II** (10)	95

[a] The reactions were carried out using aryl alkyl ethers (0.5 mmol) and the Grignard reagents (0.75 mmol) in the presence of complex **I** or **II** under nitrogen atmosphere; Py = pyridine, TMS = trimethylsilyl. [b] Yield of isolated products.

and OCF$_3$, was a better leaving group than OMe (Table 3, entries 1–9). The reaction of PhOCF$_3$ with *p*-Me$_2$NC$_6$H$_4$MgBr catalyzed by either **I** or **II** in toluene at 120 °C generated the cross-coupling products in 83 % yields (Table 3, entries 10 and 11). This result is quite different from that reported by Dankwardt, in which OCF$_3$ was indicated to be a poor leaving group.[5c] Reactions of other substituted phenyl ethers with *p*-MeC$_6$H$_4$MgBr under the same reaction conditions led to yields of 67–75 % of the corresponding products (Table 3, entries 1-9). 2-Methoxypyridine resulted to be a very reactive species in cross-coupling reactions: its reaction with *p*-Me$_2$NC$_6$H$_4$MgBr or *p*-MeC$_6$H$_4$MgBr in the presence of **II** produced corresponding coupling product in excellent yields. However, the reaction of 2-methoxypyridine with 2,4,6-Me$_3$C$_6$H$_2$MgBr was much more difficult. It required higher reaction temperature and gave coupling products in 61–63 % yields with both **I** or **II** as the catalyst. On the other hand, 2,6-dimethoxypyridine exhibited a high reactivity. It reacted with excess *p*-MeC$_6$H$_4$MgBr in the presence of **I** or **II** to form 2,6-di(*p*-tolyl)pyridine in 93 % and 95 % yields, respectively.

Alkenyl alkyl ethers also reacted smoothly with aryl Grignard reagents when **I** or **II** were used as the catalyst (Table 4). The bond cleavage of the C–O bond in the alkenyl was observed in each case. The reaction was carried out in THF at 50 °C or in toluene at 120 °C. For example, the reaction of PhCH=CHOMe with *p*-Me$_2$NC$_6$H$_4$MgBr catalyzed by **I** formed the coupling product with 93 % yield in toluene at 120 °C and with 91 % yield in THF at 50 °C (Table 4, entries 1 and 2). Complex **II** showed a slightly higher catalytic activity than **I**. However, the reaction of *p*-MeOC$_6$H$_4$MgBr with PhCH=CHOMe catalyzed by **II** gave a lower yield of the product compared with that of *p*-Me$_2$NC$_6$H$_4$MgBr. This may be a result of the coordination of the MeO group to the metal ion (e.g., Mg^{2+}), which would decrease the nucleophility of *p*-MeOC$_6$H$_4^-$. The sterically hindered species 2,4,6-Me$_3$C$_6$H$_2$MgBr showed low reactivity in the catalytic reaction. Its reaction with PhCH=CHOMe catalyzed by **II** in THF at 50 °C led to only 41 % yield (Table 4, entry 6). This result was improved by using more extreme reaction conditions. The same reactants in toluene at 120 °C afforded a 91 % yield of the coupling product (Table 4, entry 7). Ph$_2$C=CHOMe also reacted efficiently with *p*-MeC$_6$H$_4$MgBr in THF in the presence of **I** or **II**, thus giving the corresponding coupling products in 91 % and 95 % yields, respectively. MeCH=CHOEt showed good reactivity in the catalytic cross-coupling. Its reaction with *p*-MeC$_6$H$_4$MgBr or *p*-Me$_2$NC$_6$H$_4$MgBr in THF in the presence of **I** or **II** resulted in the formation of MeCH=CHAr (Ar = *p*-MeC$_6$H$_4$ or *p*-Me$_2$NC$_6$H$_4$) in excellent yields. We noted that the analogue reaction with *p*-MeOC$_6$H$_4$MgBr as nucleophile gave a lower yield compared with other nucleophiles. In addition, the reaction of PhCH=CHOMe resulted in the *E*-PhCH=CHAr product, while the reaction of MeCH=CHOEt always formed a mixture of the *Z*- and *E*-MeCH=CHAr products.

Table 4. Reaction of alkenyl methyl ethers with aryl Grignard reagents catalyzed by complex **I** or **II**.[a]

	Alkenyl ether	Product	Conditions	Cat. ([mol %])	Yield [%][b]
1			toluene, 120 °C, 12 h	**I** (5)	93
2			THF, 50 °C, 12 h	**I** (5)	91
3			THF, 50 °C, 12 h	**II** (5)	94
4			THF, 50 °C, 12 h	**II** (5)	92
5			THF, 50 °C, 12 h	**II** (5)	80
6			THF, 50 °C, 12 h	**II** (5)	41
7			toluene, 120 °C, 12 h	**II** (5)	91
8			THF, 50 °C, 12 h	**I** (5)	91
9				**II** (5)	95
10			THF, 50 °C, 12 h	**I** (5)	87
11				**II** (5)	90
12			THF, 50 °C, 12 h	**II** (5)	98[c]
13			THF, 50 °C, 12 h	**II** (5)	77

[a] The reactions were carried out using alkenyl alkyl ether (0.5 mmol) and the Grignard reagents (0.75 mmol) in the presence of complex **I** or **II** under nitrogen atmosphere. [b] Yield of isolated products unless otherwise stated. [c] A mixture of the cross-coupling product and $PhNMe_2$ was isolated by column chromatography and the yield was calculated based on the integral resulting from the ^1H NMR spectrum of the mixture.

In summary, we have shown the formation of a C−C bond through the cleavage of a sp^2 C−O bond in aryl/alkenyl ethers catalyzed by nickel and using aryl Grignard reagents as nucleophiles. In most cases, the nickel complex $[(iPr_2PR)NiCl_2]$ (**II**) displays a higher catalytic activity than $[(Cy_2PR)NiCl_2]$ (**I**) and both of them are much more active than $[(Ph_2PR)NiCl_2]$ (**III**). The reaction has a wide substrate scope and leads to the formation of the products in good to excellent yields. Further studies to activate the C−O bonds in substituted phenyl ethers more efficiently are under way.

Experimental Section

Representative procedure: A Schlenk tube was charged with a nickel complex (the amount needed), THF (2.0 mL), and aryl/alkenyl alkyl ethers (0.5 mmol). A solution of ArMgBr (0.75 mL, 1 M in THF, 0.75 mmol) was added dropwise at 25 °C under stirring. After stirring at this temperature for 24 h, the reaction mixture was quenched with water and extracted with diethyl ether (5 mL × 3). The combined organic phases were dried over $MgSO_4$, concentrated by rotary evaporation and purified by column chromatography on silica gel.

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Keywords: C−O activation · cross-coupling · Grignard reagents · homogeneous catalysis · nickel

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