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Nickel-Catalyzed Cross-Coupling of Anisoles with Alkyl Grignard Reagents via C−O Bond Cleavage

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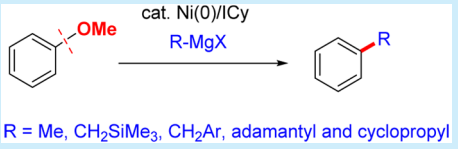
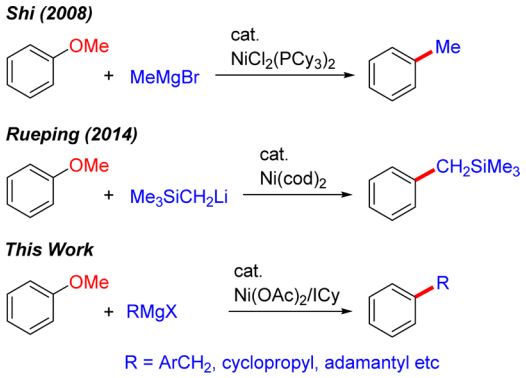
Supporting Information

ABSTRACT: Nickel-catalyzed cross-coupling of methoxyarenes with alkyl Grignard reagents, which involves the cleavage of the C(aryl)−OMe bond, has been developed. The use of 1,3-dicyclohexylimidazol-2-ylidene as a ligand allows the introduction of a variety of alkyl groups, including Me, Me_3SiCH_2, $ArCH_2$, adamantyl, and cyclopropyl. The method can also be used for the alkylative elaboration of complex molecules bearing a C(aryl)−OMe bond.



Since the pioneering works of Kumada and Tamao,[1] and Corriu and Masse,[2] the nickel-catalyzed cross-coupling of aryl halides with Grignard reagents has continued to attract considerable interest as a powerful method for the construction of carbon−carbon bonds.[3] Despite the moisture/air sensitivity and modest functional group tolerance of Grignard reagents compared with the corresponding boron and zinc reagents, the Kumada−Tamao−Corriu (KTC) reaction remains a highly valued synthetic transformation. The popularity of this method can be attributed in part to the availability of a large number of inexpensive and nontoxic magnesium reagents, as evidenced by the many examples reported in the literature of the industrial application of this reaction.[4] In addition to the practical advantages of this reaction, the high nucleophilicity of Grignard reagents can be used to allow the cross-coupling of unconventional coupling partners that would otherwise be too inert to react.[5−9] Among the unconventional groups reacted in this way, we were particularly intrigued by an early study reported by Wenkert describing the nickel-catalyzed KTC-type cross-coupling of methoxyarenes with ArMgX,[10] which involved the activation of an inert C(aryl)−OMe bond.[11] Over the past decade, the scope of the nickel-catalyzed cross-coupling of methoxyarenes has expanded considerably to a wide range of nucleophiles, including organoboron,[12] organozinc,[13] organolithium,[14] hydride,[15] amine,[16] and boron[17] nucleophiles. However, the scope of this reaction still remains limited compared with that of the corresponding cross-coupling reaction using aryl halides. In particular, the carbon nucleophiles that can be coupled with methoxyarenes have been primarily restricted to $C(sp^2)$-based nucleophiles. We recently reported the first alkynylation of methoxyarenes, which allowed the introduction of a C(sp) center.[18] With respect to their alkylation,[19] methoxyarenes can only undergo cross-coupling with two specific $C(sp^3)$ nucleophiles (Scheme 1). The first of these cross-coupling reactions is methylation using MeMgX,[20] and the second involves the introduction of a trimethylsilylmethyl group using Me_3SiCH_2Li.[14a,21,22] Herein, we report that the 1,3-dicyclohexylimidazol-2-ylidene (ICy) ligand can be used to significantly expand the scope of the alkylMgX reagents used in the nickel-catalyzed KTC-type cross-coupling of anisole derivatives. Notably, the use of the ICy ligand allowed the introduction of arylmethyl, adamantyl, and cyclopropyl groups via the cleavage of an Ar−OMe bond.

Scheme 1. Ni-Catalyzed Alkylation of Anisoles via the Activation of the C−OMe Bond



Since Dankwardt's seminal report on the KTC-type cross-coupling of anisoles with ArMgX,[10c] PCy_3 has been used as one of the most effective ligands for cross-coupling reactions involving the activation of the C(aryl)−O bonds in anisoles.[11] We previously reported that NHC ligands could be used to achieve the nickel-catalyzed cross-coupling of methoxyarenes with nucleophiles that were otherwise unreactive when PCy_3 was used as the ligand.[12c,15f,16,18] These findings prompted us to investigate whether a series of NHC ligands could be used to promote the KTC-type cross-coupling of methoxyarenes with a wider range of Grignard reagents. We initially examined the effect of the ligand on the reaction of the anisole derivative **1** with Me_3SiCH_2MgCl (**2a**) using $Ni(OAc)_2$ as the catalyst precursor (Table 1). As expected, the use of PCy_3 did not give any of the desired alkylated product **1a** (entry 1). In contrast,

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Table 1. Ni-Catalyzed Cross-Coupling of 1 with 2a: the Effect of the Ligand[a]

entry	ligand	GC yield of **1a** (%)
1	PCy_3	0
2	IMes·HCl (R = 2,4,6-$Me_3C_6H_2$)	0
3	IPr·HCl (R = 2,6-$^iPr_2C_6H_3$)	0
4	IMe·HCl (R = Me)	4
5	I^{i}Pr·HCl (R = ^{i}Pr)	29
6	ICy·HCl (R = cyclohexyl)	62
7	I^{t}Bu·HCl (R = ^{t}Bu)	0

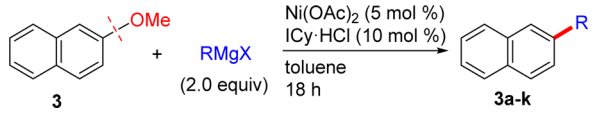
[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.50 mmol), $Ni(OAc)_2$ (0.0125 mmol), and ligand (0.025 mmol) in toluene (1.0 mL) at room temperature for 18 h.

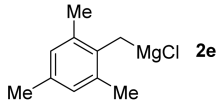
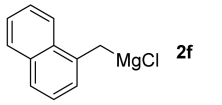
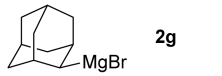
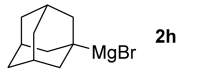
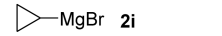
the addition of an *N*-alkyl-substituted NHC to the reaction led to the formation of **1a** with ICy being identified as the optimal NHC ligand in terms of the yield (entry 6). It should be noted that removing THF used during the preparation of Me_3SiCH_2MgCl and running the reaction in toluene alone is important for obtaining high conversion (see Supporting Information for details).

Having identified ICy as the optimal ligand, we proceeded to examine the scope of the Grignard reagents in the nickel-catalyzed cross-coupling of methoxyarene **3** (Table 2). Given that the alkyl Grignard reagents bearing a β-hydrogen, such as $^nC_5H_{11}MgBr$ (**2j**, entry 10) and ^{i}PrMgBr (**2k**, entry 11), afforded the undesired reduction product (i.e., naphthalene)[23] instead of the alkylation product, we focused specifically on Grignard reagents with no β-hydrogens. ^{t}BuCH$_2$MgBr (**2b**) behaved in a similar manner to **2a** and efficiently underwent the cross-coupling at room temperature to provide **3b** (entry 2). This result demonstrated that the presence of an α-silyl group in the Grignard reagent, as in **2a**, was not critical to the success of this alkylation process. The methylation (entry 3) and benzylation (entry 4) reactions also proceeded smoothly using the Ni/ICy system, albeit at a higher reaction temperature of 100 °C. Sterically hindered (entry 5) and π-extended ArCH$_2$ (entry 6) groups were also amenable to this reaction, allowing the synthesis of various diarylmethane derivatives from readily available methoxyarenes. Two adamantyl-Grignard reagents, **2g** and **2h**, were found to be suitable nucleophiles for the nickel-catalyzed cross-coupling of **3**, even though they both have β-hydrogen atoms. These arylations successfully occurred at both the secondary (entry 7) and tertiary (entry 8) carbon atoms of the adamantyl group, most likely because the undesired β-hydrogen elimination would be forbidden by Bredt's rule.[24] These results therefore represent the first reported examples of the cross-coupling reactions of methoxyarenes with secondary and tertiary alkyl groups. It is noteworthy that cyclopropyl-MgBr (**2i**, entry 9) was also coupled with **3** under these nickel-catalyzed conditions to form 2-cyclopropylnaphthalene (**3i**), along with a ring opened product **3i′** (**3i**:**3i′** = 9:1).

As shown in Scheme 2, the Ni/ICy catalyst catalyzed the KTC-type cross-coupling of a wide variety of methoxyarenes. Notably, these reaction conditions could be applied to ethoxy and isopropoxy groups as well as methoxy groups. Consistent with the previous cross-couplings of methoxyarenes,[11] a C(naphthyl)−O bond is more reactive than a C(phenyl)−O bond, allowing the regioselective alkylation of 2-phenoxynaphthalene to form **3a**. Functional groups, including amines **8**, acetals **12**, and amides **13**, were well tolerated. One useful feature of this KTC-type cross-coupling of methoxyarenes is its compatibility with a free hydroxyl group in the substrate by simply increasing the number of equivalents of the Grignard reagents to 3 equiv, as exemplified by the reactions of **9**, **10**, and **11**. This protocol was also found to be robust enough for the alkylation of the methoxy group at sterically congested positions, such as those found in compounds **7** and **14**. Moreover, several heteroaryl ethers, including pyridine **16**, quinoline **17**, carbazole **18**, and indole **19**, were successfully alkylated under these conditions via the loss of their methoxy groups. This alkylation method was also applicable to alkenyl ether substrates. For example, a cis-substituted homoallylic alcohol was synthesized by the cross-coupling of 2,3-dihydrofuran **21**. It is noteworthy that this alkylation can be performed on the gram scale using 1 mol % of the catalyst (eq 1).[25]

Table 2. Ni/ICy-Catalyzed Alkylation of Aryl Methyl Ethers: Scope of the Grignard Reagents[a]



entry	Grignard reagent	temperature (°C)	yield (%)[b]
1	Me_3SiCH_2MgCl (**2a**)	rt	92
2	^{t}BuCH$_2$MgBr (**2b**)	rt	>99
3	CH_3MgBr (**2c**)	100	96[c]
4	$PhCH_2MgBr$ (**2d**)	100	96
5	 **2e**	100	87
6	 **2f**	100	88
7	 **2g**	100	87
8	 **2h**	100	74
9[d]	 **2i**	80	84 (9:1)[e]
10[d]	$^nC_5H_{11}MgBr$ (**2j**)	140	0 (6)[g]
11[f]	^{i}PrMgBr (**2k**)	100	0 (70)[g]

[a]Reaction conditions: **3** (0.25 mmol), Grignard reagent (0.50 mmol), $Ni(OAc)_2$ (0.0125 mmol), and ICy·HCl (0.025 mmol) in toluene (1.0 mL) for 18 h. [b]Isolated yield of the alkylated product unless otherwise noted. [c]The yield was determined by GC due to the volatility of the product. [d]The reaction was run using $Ni(OAc)_2$ (0.025 mmol) and ICy·HCl (0.050 mmol). [e]The yield was determined by NMR analysis. The product was formed as a 9:1 mixture of 2-cyclopropylnaphthalene (**3i**) and (*E*)-2-(prop-1-en-1-yl)naphthalene (**3i′**). [f]$Ni(OAc)_2$ (0.050 mmol) and ICy·HCl (0.050 mmol) were used. [g]GC yield of naphthalene.

We also examined alkylation of 1,2-dimethoxybenzene (**22**) (Table 3). When **2a** (entries 1 and 2) or **2b** (entries 3 and 4) was used as the alkylating reagent in the Ni/ICy-catalyzed reaction of **22**, the monoalkylated product was produced selectively with the second methoxy group in the product remaining intact, even when a large excess (4.0 equiv) of the

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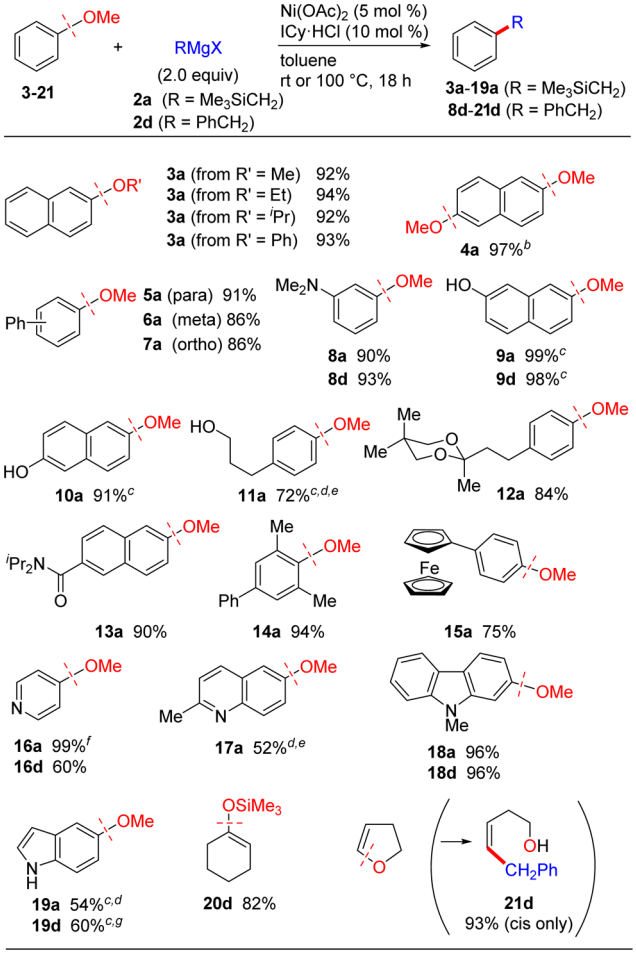
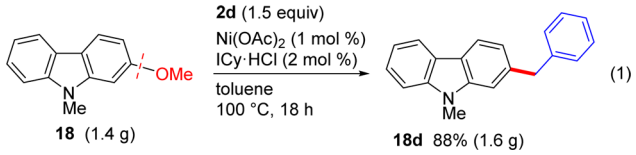
Scheme 2. Ni/ICy-Catalyzed Alkylation of Aryl Ethers[a]



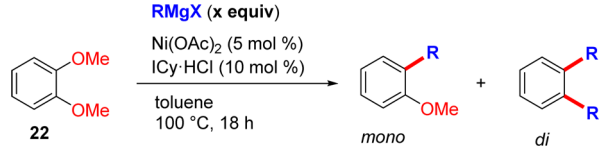
[a]Reaction conditions: aryl ether (0.25 mmol), Grignard reagent (0.50 mmol), $Ni(OAc)_2$ (0.0125 mmol), and ICy·HCl (0.025 mmol) in toluene (1.0 mL) for 18 h. The yields shown are the isolated yield. [b]Grignard reagent (1.0 mmol) was used. [c]Grignard reagent (0.75 mmol) was used. [d]$Ni(OAc)_2$ (0.025 mmol) and ICy·HCl (0.050 mmol) were used. [e]Run at 80 °C. [f]The yield was determined by GC because of the volatility of the product. [g]$Ni(OAc)_2$ (0.0075 mmol) and ICy·HCl (0.015 mmol) were used.



Grignard reagent was used. In contrast, the use of **2d** as an alkylating agent allowed a high level of control over the mono/di alkylation depending on the amount of the Grignard reagent used (entries 5 and 6). These results can be rationalized by a simple steric effect with the Me_3SiCH_2 and $^tBuCH_2$ (Charton ν value: 1.34)[26] groups being large enough to block a second alkylation at their ortho position. In contrast, the $PhCH_2$ group (Charton ν value: 0.70) would be too small to block the second alkylation.

The power and utility of this alkylation method was further demonstrated by its application to complex methoxyarene substrates (Scheme 3). For example, the structural elaboration of complex alkaloid dextromethorphan **23**, which is a marketed antitussive agent, was readily accomplished using our nickel-catalyzed KTC-type cross-coupling. Furthermore, the alkylation of estradiol proceeded smoothly using the corresponding methyl ether **24** while leaving the aliphatic alcohol moiety intact.

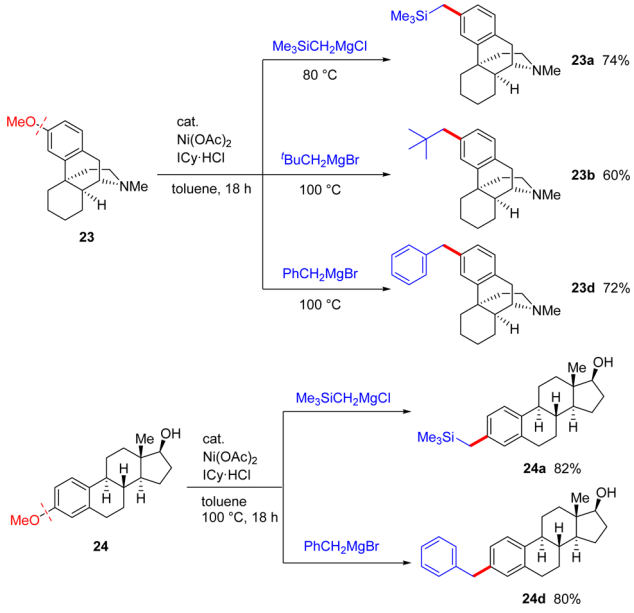
Table 3. Alkylation of 1,2-Dimethoxybenzene



entry	RMgX	x	Charton parameter of R	yields (%) mono	yields (%) di
1	Me_3SiCH_2MgCl	1.5	---	91[a]	0
2	Me_3SiCH_2MgCl	4.0	---	89[a]	0
3	$^tBuCH_2MgBr$	1.5	1.34	97[a]	0
4	$^tBuCH_2MgBr$	4.0	1.34	82[a]	0
5	$PhCH_2MgBr$	1.5	0.70	76	trace
6	$PhCH_2MgBr$	4.0	0.70	trace	63

[a]The yield was determined by GC because of the volatility of the product.

Scheme 3. Alkylative Elaboration of Complex Anisole Derivatives



In summary, we have shown that a Ni/ICy system can be used to promote the KTC-type alkylative cross-coupling of methoxyarenes with a range of alkyl Grignard reagents. This new protocol allows, for the first time, the introduction of $ArCH_2$, adamantyl, and cyclopropyl groups to methoxyarenes via the cleavage of their C(aryl)−O bonds. Considering the widespread availability and robust nature of compounds bearing a methoxy group, this new alkylation method could be used for the late stage elaboration of complex aryl ethers.

■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures and characterization of products (PDF)

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Notes

The authors declare no competing financial interest.

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(23) The reduction product is most likely to be generated through undesired β-hydrogen elimination of the alkylnickel intermediate rather than the nickel methoxide intermediate (see ref 15f) based on a labeling experiment. See the Supporting Information for details.

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(25) Additional notes regarding the scope and limitations: (a) Benzyl methyl ether was unreactive under these conditions. (b) Acetal and amide functionalities reacted when the reaction was performed at 100 °C.

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