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Nickel-Catalyzed Alkylative Cross-Coupling of Anisoles with Grignard Reagents via C–O Bond Activation

Mamoru Tobisu,*[,†,‡] Tsuyoshi Takahira,[‡] Toshifumi Morioka,[‡] and Naoto Chatani*[,‡]

[‡]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan
[†]Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

Supporting Information

ABSTRACT: We report nickel-catalyzed cross-coupling of methoxyarenes with alkylmagnesium halides, in which a methoxy group is eliminated. A wide range of alkyl groups, including those bearing β-hydrogens, can be introduced directly at the ipso position of anisole derivatives. We demonstrate that the robustness of a methoxy group allows this alkylation protocol to be used to synthesize elaborate molecules by combining it with traditional cross-coupling reactions or oxidative transformation. The success of this method is dependent on the use of alkylmagnesium iodides, but not chlorides or bromides, which highlights the importance of the halide used in developing catalytic reactions using Grignard reagents.

Since being discovered in 1900,[1] the Grignard reagents, generally described as RMgX, have been perhaps the most widely used organometallic reagents in organic synthesis.[2−4] The reactivity of Grignard reagents is affected by many factors, including the Lewis basicity and steric properties of the solvent[2−4] as well as external metal salt additives.[5,6] The nature of the halogen atom in a Grignard reagent can also affect properties such as aggregation state[7] or basicity[8] of the reagent. However, the choice of halide is predominantly determined by its reactivity in the halogen-magnesium exchange reaction (R–I > R–Br > R–Cl),[4] and the impact of the halide on the reactivity of Grignard reagents remains underappreciated for most reactions using them.[9−11] Here, we report nickel-catalyzed cross-coupling of anisole derivatives with Grignard reagents, with reactivity being largely dependent on the halogen atom in the Grignard reagent being used.

The use of methoxyarenes in cross-coupling reactions as alternatives to aryl halides has gained considerable attention because it will allow more economical and ecological chemical processes.[12−16] Although significant progress has been made over the past decade, in particular with a nickel catalyst, the diversity of compatible coupling partners remains limited compared with classical cross-coupling reactions using aryl halides. With regard to carbon–carbon bond-forming processes, although methods for arylation[17−21] and alkynylation[22] are available, there are no reports on alkylation reactions of anisole derivatives via C(aryl)–O bond cleavage, except for those using alkylating reagents without β-hydrogens such as methylation or benzylation[23−26] and those using anisoles having a directing group[27−29] (Figure 1). In this work, we describe the first cross-coupling of anisole derivatives with β-hydrogen containing alkylmagnesium halides.

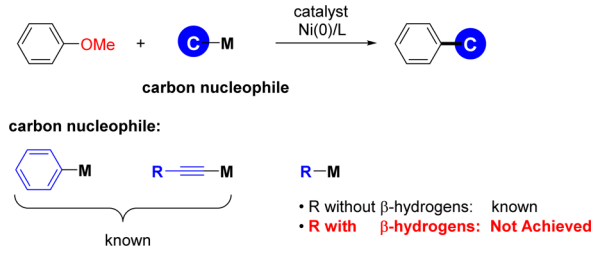

Figure 1. Nickel-catalyzed cross-coupling of anisoles: scope and limitations of carbon nucleophiles.

We initially investigated a nickel(0)-catalyzed reaction of 2-methoxynaphthalene (**1**) with *n*-C_5H_{11}MgBr (**2a-Br**). The Grignard reagents used in this study were purchased or prepared as diethyl ether (Et_2O) solutions. The cross-coupling reaction was conducted in toluene after removing excess Et_2O prior to heat for safety reasons. Initial ligand screening revealed that neither tricyclohexylphosphine (PCy_3) nor 1,3-dicyclohexylimidazol-2-ylidene (ICy), which are reported to be the most effective ligands for C(aryl)–O bond activation,[15,16] efficiently formed the desired cross-coupling product **1a** with most of **1** being recovered (entries 1 and 2 in Table 1a). Because naphthalene (11%) was formed in the case of PCy_3, we hypothesized that β-hydrogen elimination from a putative alkylnickel intermediate may inhibit efficient catalysis. To suppress this potential side reaction pathway, a series of bidentate ligands were examined,[30] although no bidentate ligands have been reported to promote the activation of a C(aryl)–OMe bond. Interestingly, the alkylated product **1a** was produced at 41% yield with 48% of the starting compound **1** being recovered when 1,2-bis(dicyclohexylphosphino)ethane (dcype)[31] was used. To further increase the yield of **1a**, various other parameters were investigated using a dcype ligand (see Supporting Information for details of optimization studies). To our surprise, the halogen atom in the Grignard reagent **2a** was revealed to exert a tremendous impact on this alkylative cross-coupling. While the yield of **1a** was low to modest with **2a-Cl** and **2a-Br**, the use of the Grignard reagent prepared from *n*-C_5H_{11}I, i.e., **2a-I**, led to the formation of **1a** in 97% yield without an accompanying reduced product **3** (entries 1–3 in Table 1b). The

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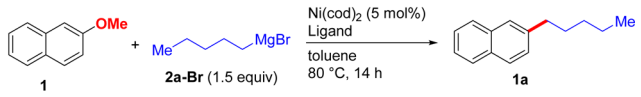
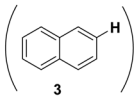
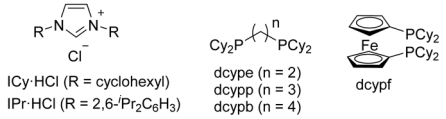
Table 1. Optimization of Nickel-Catalyzed Alkylation of 2-Methoxynaphthalene (1)[a]

a Effect of ligands

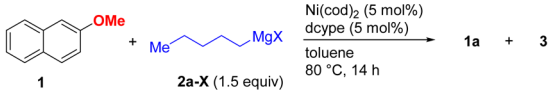


entry	ligand (x mol%)	GC yield (%) 1a	3	1
1	PCy_3 (10)	2	11	84
2	ICy·HCl (10)	0	0	99
3	IPr·HCl (10)	0	1	97
4	dcype (5)	41	6	48
5	dcypp (5)	22	3	77
6	dcypb (5)	8	12	74
7	dcypf (5)	0	2	94





b Effect of the halide in the Grignard reagent



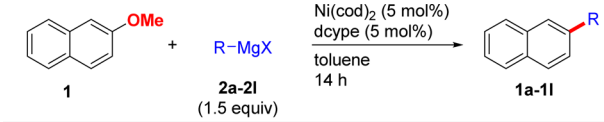
entry	X in $^nC_5H_{11}MgX$	GC yield (%) 1a	3	1
1	Br	41	6	48
2	Cl	21	8	65
3	I	97	0	0
4[b]	Br	99	0	0
5[b]	Cl	99	0	0

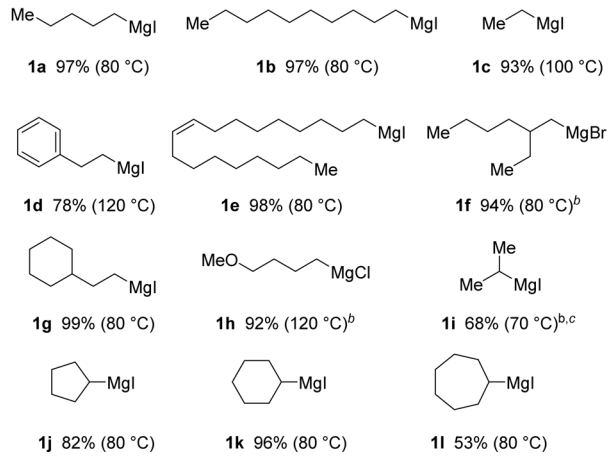
[a]Reaction conditions: **1** (0.25 mmol), **2a-X** (0.38 mmol), $Ni(cod)_2$ (0.013 mmol), and ligand (0.025 mmol for monodentate ligands; 0.013 mmol for bidentate ligands) in toluene (1.0 mL) at 80 °C for 14 h; yield refers to yield determined by GC. [b]MgI_2 (0.38 mmol) was added.

cross-coupling with **2a-Cl** and **2a-Br** proceeds quantitatively when 1.5 equiv of MgI_2 is added (entries 4 and 5). The addition of LiI also improved the yield but was less effective than MgI_2 (see Supporting Information for details). An accelerating effect of MgX_2 has been observed in other cross-coupling reactions.[32−35]

Under these optimized conditions, the scope of Grignard reagents was investigated (Scheme 1). This method was able to introduce a wide range of β-hydrogen containing alkyl groups to **1** efficiently. Grignard reagents derived from simple linear alkyl halides such as **2a−c** are excellent coupling partners to form the corresponding alkylated products, irrespective of chain length. A phenethyl group, which is highly prone to β-hydrogen elimination, underwent cross-coupling with **1** successfully to provide **1d**. Grignard reagents containing a *cis*-alkene **2e**, a β-branched alkyl **2f**, a γ-branched alkyl **2g**, and a methoxy group **2h** were compatible for this cross-coupling, which allows structural modification of methoxy groups with elaborate alkyl groups. Notably, this Ni/dcype system was also able to couple several secondary alkylmagnesium iodides. Isopropylmagnesium iodide (**2i**) underwent the cross-coupling with **1** to generate 2-isopropylnapthalene along with 2-propylnaphthalene (iso/normal = 92:8, 68% combined yield). Five to seven cycloalkyl groups can readily be introduced by using the corresponding Grignard reagents to generate **1j−1l**. PhMgBr can also be

Scheme 1. Scope of Grignard Reagents[a]





[a]Reaction conditions: **1** (0.25 mmol), Grignard reagent (0.38 mmol), $Ni(cod)_2$ (0.013 mmol), and dcype (0.013 mmol) in toluene (1.0 mL) for 14 h; yield refers to isolated yield. [b]MgI_2 (0.38 mmol) was added. [c]The product was obtained as a 92:8 mixture of iso and normal isomers.

coupled with **1** even in the absence of MgI_2 under Ni/dcype-catalyzed conditions (64%).

Nickel/dcype-catalyzed alkylative cross-coupling of various aryl ethers were investigated next (Scheme 2). A methoxy group on an array of aromatic rings such as naphthalene and phenanthrene can be substituted by an alkyl group under these conditions to form the corresponding products **4a−7a**. The cross-coupling can proceed even in the presence of protic functionalities including OH and NH groups simply by increasing the amount of the Grignard reagent to 2.5 equiv, as exemplified in the production of **9a−11a**, **24a**, and **25a**. A phenoxy group can serve as a better leaving group than a methoxy group to form **12b**. This reactivity was successfully applied to an alkylative ring-opening reaction of dibenzofuran (**13**) for the synthesis of a 2,2′-disubstituted biphenyl derivative. This alkylation protocol was further extended to enol ether substrates such as **14−16**.

Consistent with previously reported nickel-catalyzed cross-coupling reactions of methoxyarenes with other nucleophiles,[15,16] substrates without fused aromatic rings were much less reactive. For example, simple anisole (**17**) did not generate the alkylated product at all under the standard conditions. However, the cross-coupling of less reactive methoxyarenes becomes viable by adding an extra equivalent of MgI_2 (Scheme 2b). Under these modified conditions, anisole derivatives **17−21** can be alkylated successfully. Substrates containing heteroaromatic moieties such as indoles and pyridines (**10**, **11**, **22−24**) could also undergo this alkylative cross-coupling. This method can successfully be used for the alkylation of methoxy groups included in alkaloidal and steroidal scaffolds as in **11**, **24**, and **25**. These results demonstrate that the lipophilicity of bioactive compounds can easily be modified by our method through the introduction of various alkyl groups, which is essential for regulating drug properties such as bioavailability and metabolic

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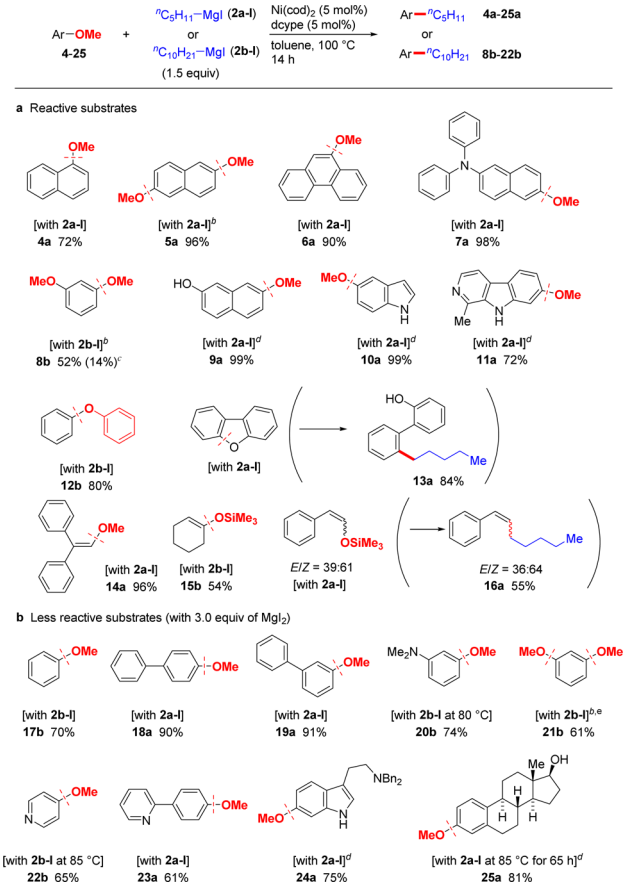
Scheme 2. Scope of Aryl Ethers[a]



[a]Reaction conditions: **1** (0.25 mmol), Grignard reagent (0.38 mmol), Ni(cod)$_2$ (0.013 mmol), and dcype (0.013 mmol) in toluene (1.0 mL) at 100 °C for 14 h; yield refers to isolated yield. [b]Grignard reagent (0.75 mmol), Ni(cod)$_2$ (0.025 mmol), and dcype (0.025 mmol) were added. [c]Yield of a dialkylated product **21b**. [d]Grignard reagent (0.63 mmol) was added. [e]MgI$_2$ (1.5 mmol) was added.

stability. The current limitation of this catalytic alkylation reaction is its sensitivity to steric effects (1-methoxy-2-methylbenzene is completely unreactive even in the presence of MgI$_2$.)

To demonstrate the scalability of this method, alkylation of **26** was conducted on a 1.1 g scale (Figure 2a). Although we routinely used Ni(cod)$_2$ for our exploratory studies, air-stable Ni(acac)$_2$ (acac = acetylacetonate) served as a useful precatalyst to provide the alkylated product **26a** in good yield.

Combination of this methoxy alkylation method with other synthetic transformations enables rapid access to more elaborate aromatic compounds. For example, one of the straightforward methods for the preparation of triphenylene derivatives involves Suzuki–Miyaura arylation of diboromide **27**, followed by oxidative cyclization[36] (Figure 2b). The latter transformation often requires methoxy-substituted substrates to facilitate the oxidative process, which in turn has limited the range of the triphenylene derivatives accessible by this sequence. Our method allows for substitution of the methoxy groups in **29** with a diverse range of alkyl groups, which will be useful to control the physical properties of π-conjugated molecules, including solubility and aggregation behaviors.

Although the mechanistic details of this alkylative cross-coupling largely remain to be elucidated, several preliminary

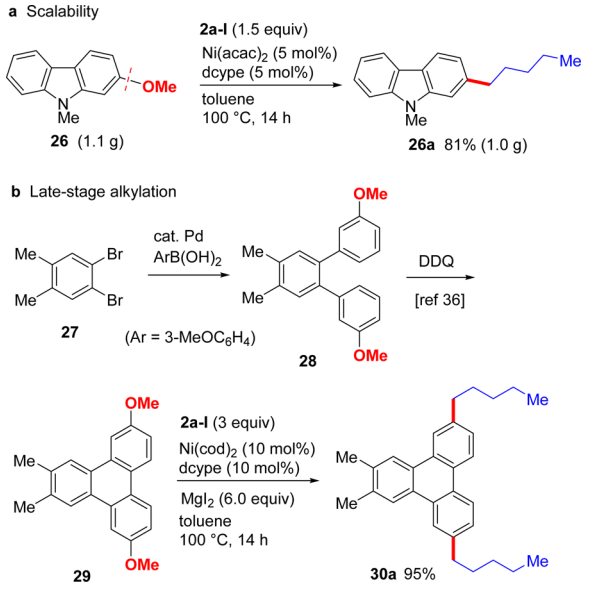


Figure 2. Scalability and synthetic application.

experiments provided us some insights. One possible mechanism for C–O bond cleavage in this reaction is oxidative addition to Ni(dcype), which can be facilitated by the coordination of the ether oxygen atom to Lewis acid MgI$_2$. However, this mechanism is unlikely based on the following observation. A mixture of Ni(cod)$_2$ (1 equiv), dcype (1 equiv), MgI$_2$ (2 equiv), and **1** (2 equiv) in toluene-d_8 was heated to 80 °C. Monitoring the mixture by ^{31}P NMR over 14 h revealed that C–O bond cleavage did not occur under these conditions, and **1** was recovered quantitatively (see Supporting Information). These results indicate that the presence of Grignard reagents is essential for the cleavage of C(aryl)–OMe bond. On the basis of theoretical studies on a related arylation reaction,[37] anionic nickelate(0) species generated by the reaction of Ni(dcype) with RMgI,[38−40] rather than neutral Ni(dcype), is presumably responsible for the C–O bond cleavage process.

It is well established that the constitution of Grignard reagents in solution is complex, and in a simplified sense, RMgX is in equilibrium with R$_2$Mg and MgX$_2$ (Schlenk equilibrium).[2,3] This raises the possibility that R$_2$Mg might serve as the true alkylating reagent in Ni/dcype-catalyzed cross-coupling. However, cross-coupling of **1** with Et$_2$Mg under our standard catalytic conditions resulted in a lower yield of **1c** (16%), suggesting that RMgX serves as the major alkylating reagent in our catalytic reaction. The use of RMgI, not RMgCl or RMgBr, is the key to achieve this alkylative cross-coupling of methoxyarenes. The reactivity difference between halides (I > Br > Cl) cannot be attributable to the different ratios of RMgX/R$_2$Mg since the cross-coupling reactions were conducted with an excess amount of a Grignard reagent and the Schlenk equilibrium should be much faster than the cross-coupling reaction. For the same reason, the role of an extra amount of MgI$_2$ in the reactions of less reactive substrates (Table 1b) should not be able to drive the Schlenk equilibrium from R$_2$Mg to RMgI. Consistent with this consideration, addition of MgCl$_2$ or MgBr$_2$ in cross-coupling using RMgCl or RMgBr, respectively, did not improve the yield of the products.

In summary, we have developed the first general method for the alkylation of anisole derivatives via C–O bond activation.[41] Although significant progress has been made in the cross-coupling using alkylmetal reagents,[42] this method allows for the

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introduction of a variety of β-hydrogen-containing alkyl groups directly to the ipso position of methoxyarenes. Given the prevalence of methoxyarene substructure in biologically active compounds or π-conjugated materials, this method should serve as a useful protocol for their derivatization. The markedly higher reactivity of RMgI than RMgCl or RMgBr in this alkylative cross-coupling calls for special attention to the effect of the specific halide used when developing catalytic reactions using Grignard reagents. A theoretical study on the mechanism of this cross-coupling and further expansion of the scope of the nucleophiles in methoxy cross-coupling reactions are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03253.

Detailed experimental procedures and characterization of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*tobisu@chem.eng.osaka-u.ac.jp

*chatani@chem.eng.osaka-u.ac.jp

Notes

The authors declare no competing financial interest.

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