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Nickel-catalyzed Cross-coupling of Anisole Derivatives with Trimethylaluminum through the Cleavage of Carbon–Oxygen Bonds

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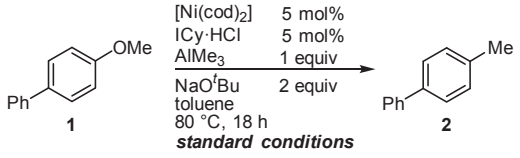
Nickel-catalyzed cross-coupling of methoxyarenes with trimethylaluminum is described. The use of 1,3-dicyclohexylimidazol-2-ylidene as a ligand and NaO^{t}Bu as a base promotes the methylation of anisole derivatives via the cleavage of normally unreactive aryl carbon–oxygen bonds.

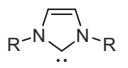
Methoxyarene is a common structural motif found in natural and unnatural organic molecules. It is therefore important to develop catalytic methods that can elaborate anisole derivatives. Although the synthetic methods for the conversion of anisole derivatives are dominated by the functionalization of aromatic C–H bonds, catalytic substitution of a methoxy group in anisole derivatives has recently attracted much attention as a new tool for organic synthesis.[1,2] Despite the advances made in the last decade, the diversity of the nucleophile used for methoxy substitution still remains limited because of the inertness of C(aryl)–O bonds in anisole derivatives compared with those in aryl sulfonates and carboxylates. To date, the nucleophiles that can be used for the substitution of methoxyarenes include Grignard,[3–5] organolithium,[6] organoboron,[7] organozinc,[8] hydride,[9] amine,[10] and boron[11] reagents. It has been reported that the scope of aryl ether substrates strongly depends on the nature of the nucleophile, probably because it influences the mechanism of the key C–O bond cleavage process, as indicated by several theoretical studies.[9d,12] Therefore, systematic exploration of the various nucleophiles used in nickel-catalyzed cross-coupling of aryl ethers is of fundamental importance to understand the nickel-mediated activation of inert C–O bonds. We report herein the first cross-coupling of anisole derivatives with an organoaluminum reagent: methylation using trimethylaluminum ($AlMe_3$).[13]

We first examined the nickel-catalyzed methylation of 4-methoxybiphenyl (**1**) with $AlMe_3$ (Table 1). After screening various conditions, it was found that the reaction of **1** (0.25 mmol) with $AlMe_3$ (0.25 mmol, 1.8 M solution in toluene) in the presence of $[Ni(cod)_2]$ (5 mol %) and ICy·HCl (5 mol %, ICy: 1,3-dicyclohexylimidazol-2-ylidene) in toluene at 80 °C for 18 h gave 4-methylbiphenyl (**2**) in 97% yield according to GC analysis (Entry 1). The methylation did not proceed in the absence of a nickel catalyst, which excludes a pathway via the S_NAr mechanism (Entry 2).[14] Replacing the ICy ligand with PCy_3[2] (Entry 4) or other NHCs (Entries 5–7) led to a substantial decrease in the yield of **2**, highlighting the prominent ability of ICy to activate C–OMe bonds.[4b,5,7c] Methylation occurred much less efficiently when $[Ni(acac)_2]$ or $Ni(OAc)_2$ was used as the catalyst precursor instead of $[Ni(cod)_2]$ (Entries 8 and 9). Air-stable DABCO·2$AlMe_3$[15] (Entry 10) and $AlEt_3$ (data not shown) did not provide the corresponding cross-coupling product under these conditions. Although the yield of **2** decreased to 48% when 0.33 equiv of $AlMe_3$ was used (Entry 11), the use of $Al(OEt)Me_2$ (1.66 M in toluene solution) in place of $AlMe_3$ afforded **2** in 93% yield (Entry 12). The amount of base added is critical, as evidenced by the fact that no methylated product **2** was formed when the amount of NaO^{t}Bu was decreased to 10 mol % (Entry 12).

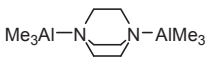
Table 1. Optimization of reaction conditions[a]



Entry	Variation from standard conditions	GC yields/%	
		2	**1**
1	none	97	0
2	without $[Ni(cod)_2]$, ICy·HCl	0	85
3	without ICy·HCl	3	56
4	PCy_3 instead of ICy·HCl	5	60
5	IPr·HCl instead of ICy·HCl	39	43
6	IMes·HCl instead of ICy·HCl	14	15
7	I^{t}Bu·HCl instead of ICy·HCl	6	50
8	$[Ni(acac)_2]$ instead of $[Ni(cod)_2]$	10	68
9	$Ni(OAc)_2$ instead of $[Ni(cod)_2]$	8	65
10	DABCO·2$AlMe_3$ instead of $AlMe_3$	23	66
11	$AlMe_3$ 0.33 equiv instead of 1.0 equiv	48	32
12	$Al(OEt)Me_2$ instead of $AlMe_3$	93	0
13	NaO^{t}Bu (10 mol %) instead of 2 equiv	0	88
14[b]	**ICy·HBF$_4$ instead of ICy·HCl**	**>99 (99)**	**0**



ICy (R = cyclohexyl)
IPr (R = 2,6-^{i}Pr$_2$C$_6$H$_3$)
IMes (R = 2,4,6-Me$_3$C$_6$H$_2$)
I^{t}Bu (R = ^{t}Bu)

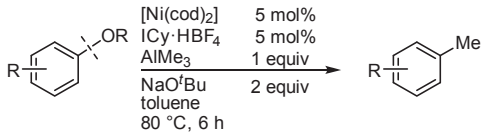


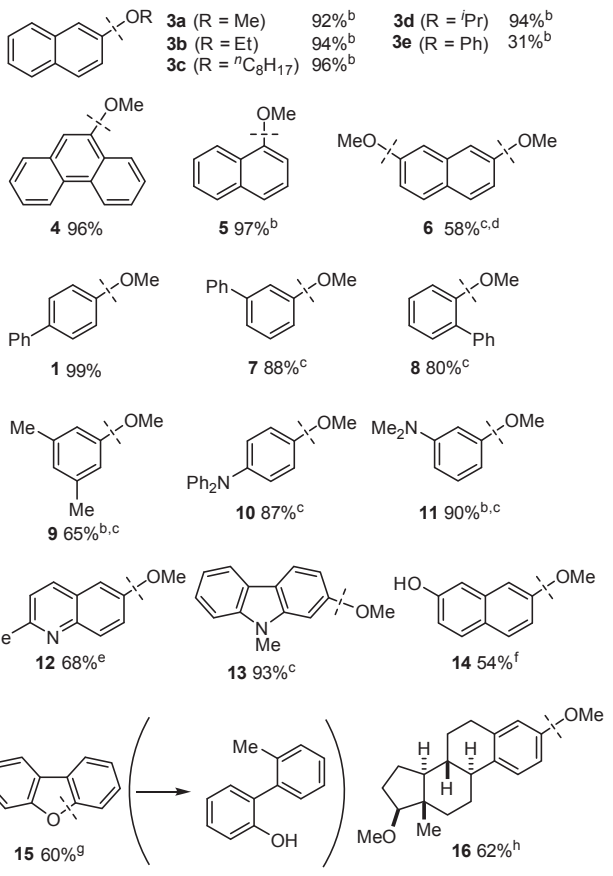
DABCO·2$AlMe_3$

[a]Reaction conditions: **1** (0.25 mmol), $AlMe_3$ (0.25 mmol), $[Ni(cod)_2]$ (0.013 mmol), ligand (0.013 mmol), NaO^{t}Bu (0.50 mmol) in toluene (1.0 mL) for 6 h at 80 °C. [b]The reaction was performed for 6 h instead of 18 h, and the yield in parentheses is the isolated yield.

Having optimized the reaction conditions, we explored the scope of this nickel-catalyzed cross-coupling of aryl methyl ethers with $AlMe_3$ (Table 2). The effect of the alkoxy group on the methylation reaction was then examined. Primary alkoxy groups, including EtO and the longer ^{n}C$_8$H$_{17}$O groups, were efficiently methylated under these conditions, as exemplified by the reactions of **3b** and **3c**. Notably, the bulkier ^{i}PrO group also underwent this methylation efficiently (**3d**), whereas the PhO

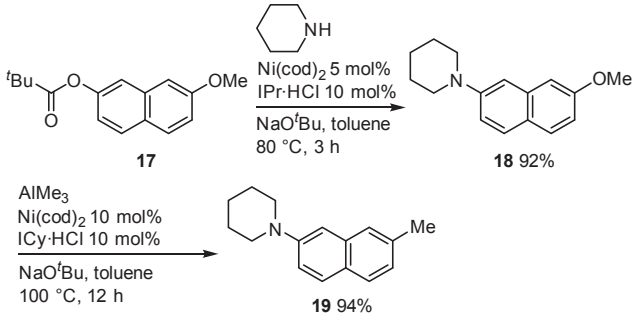
Table 2. Substrate scope[a]





[a]Reaction conditions: aryl ether (0.25 mmol), $AlMe_3$ (0.25 mmol), $[Ni(cod)_2]$ (0.013 mmol), ICy·HBF_4 (0.013 mmol), NaO^{t}Bu (0.50 mmol) in toluene (1.0 mL) at 80 °C for 6 h. [b]Yield was determined by GC analysis because of the volatility of the product. [c]$[Ni(cod)_2]$ (0.025 mmol), ICy·HBF_4 (0.025 mmol) at 100 °C for 6 h. [d]A monomethylated product was also obtained as an inseparable mixture with the unreacted starting material. NMR yields for the monomethylated product and the recovered **6** were 17% and 14%, respectively. [e]$[Ni(cod)_2]$ (0.025 mmol), ICy·HBF_4 (0.025 mmol) at 80 °C for 6 h. [f]$AlMe_3$ (0.50 mmol), $[Ni(cod)_2]$ (0.025 mmol), ICy·HBF_4 (0.025 mmol), NaO^{t}Bu (0.75 mmol) at 120 °C for 6 h. [g]$[Ni(cod)_2]$ (0.025 mmol), ICy·HBF_4 (0.025 mmol) at 80 °C for 18 h. [h]$[Ni(cod)_2]$ (0.038 mmol), ICy·HBF_4 (0.038 mmol) at 80 °C for 18 h.

group was less reactive under the current conditions (**3e**). Benzyl methyl ethers, such as 4-(methoxymethyl)-1,1′-biphenyl, did not form the corresponding methylated product, but a reduced product (4-methyl-1,1′-biphenyl) was obtained instead (ca. 60%). Alkoxy groups on polyaromatic scaffolds such as phenanthrene **4** and naphthalene **5** successfully underwent nickel-catalyzed cross-coupling under the same reaction conditions to provide the corresponding methylated arenes. This reaction also exhibited a high level of tolerance toward substrates bearing a bulky ortho substituent, such as **8**, as well



Scheme 1. Sequential functionalization of two different inert C–O bonds.

as substrates bearing a free hydroxy group, like **14**. Less reactive electron-rich anisoles also underwent cross-coupling to provide the corresponding methylated products **9–11**. Heteroarenes, e.g., electron-deficient quinolone **12** and electron-rich carbazole **13**, were also good substrates. This methylation method was also applicable to dibenzofuran **15**, the reaction of which led to a ring-opened product. The methylation of relatively complex substrates was also possible, allowing synthesis of a methylated analogue of a natural product derivative **16**.

The difference in reactivity between aryl methyl ethers and aryl carboxylates in nickel-catalyzed C–O bond functionalization allows rapid sequential functionalization of aromatic frameworks (Scheme 1). The pivalate group in **17** could be aminated through our previously reported cross-coupling reaction using an IPr ligand without affecting the methoxy group.[16] The methoxy group in **18** was subsequently methylated using the current reaction to furnish **19**.

In conclusion, we developed a nickel-catalyzed methylation of anisole derivatives using $AlMe_3$ that proceeds through the cleavage of C–O bonds. This reaction represents the first cross-coupling of aryl ethers with an organoaluminum reagent. Given the profound effects of a methyl group in drug discovery processes,[17] expanding the repertoire of methylation methods by our development reported here will benefit synthetic chemists. Additional studies to further expand the scope of nickel-catalyzed C–O bond functionalization are ongoing in our laboratory.

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Supporting Information is available electronically on J-STAGE.

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