Methylation of arenes *via* Ni-catalyzed aryl C–O/F activation†

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Aryl C–O and C–F can be transformed into C–Me *via* Ni-catalyzed coupling with MeMgBr under mild conditions.

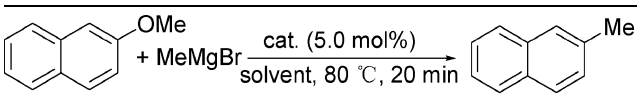
An alkoxy arene is a common structural unit in various natural products, biologically active compounds and organic functional materials.[1] Direct functionalization of alkoxy arenes offers a new pathway to readily broaden the diversity of functional molecules, and could thus be utilized to construct libraries for the discovery of new features. However, the activation of aryl C–OR (R = alkyl) bonds is a challenging task for organic chemists due to their relatively high bond energy and the selectivity issues arising from the two different types of C–O bonds (aromatic C–O and alkyl C–O). Compared with the wide utilization of aryl halides in coupling chemistry,[2] studies on alkoxy arenes are rare. Kakiuchi and co-workers reported the functionalization of methoxy arenes catalyzed by Ru(0) species, assisted by a carbonyl group as a directing group.[3] Direct arylation of C–OMe has recently been reported with a large excess of aryl Grignard reagents.[4] However, no efficient method to methylate anisole and its derivatives was reported.[5] Herein, we report a practical methylation of aryl C–O/F *via* Ni(0)-catalysis.

Traditionally, formation of aryl–Me took place by transition metal catalyzed coupling reactions from aryl halides.[6] Starting from aryl C–OMe, methylation could perform through the sequential reactions of deprotection, triflation and coupling.[7] We initiated this project by studying the direct transformation of the methoxy group to the methyl group, starting from 2-methoxynaphthalene and methyl Grignard reagent. Various conditions were screened (Table 1). $NiCl_2$ and $NiCl_2(PPh_3)_2$ gave very low yields for this reaction in toluene (entries 1 and 5). Gratifyingly, the efficiency can be improved by varying ligands, solvent, and reaction temperature. PCy_3 was the best ligand to support different Ni(II) catalysts. Catalyst loading could be decreased to 2.0 mol% (entry 4). Diethyl ether also served as a good solvent under reflux (entry 18). However, relatively polar solvents, such as dioxane and THF, dramatically diminished the efficiency.

Different substrates were further investigated (Table 2). With different alkoxy groups, the methylation took place smoothly (entries 1–5, Table 2). However, steric hindrance slightly decreased the efficiency of the reaction. MOM and TMS protected 2-naphthol could also be transformed into the methylated products in good yields (entries 6 and 7, Table 2). Interestingly, when phenyl 2-naphthyl ether was applied as the substrate, the methylation only occurred on the naphthyl scaffold, with phenol as a by-product. It indicated that different sp^2 C–O bonds of hetero diaryl ethers could be differentiated in the reaction, which offered the chance to control the chemo- and regioselectivity of the methylation. However, only 2-naphthol was isolated as the main product from 2-naphthyl acetate, arising from the high reactivity of Grignard reagents toward the addition to esters. In addition, free naphthol is not a suitable substrate for this transformation.

Furthermore, the coupling of 2-naphthol derivatives was performed very well to afford the desired products in excellent

Table 1 Methylation of **1a** under different conditions[a]



1a **2** **3a**

Entry	Cat.	L (mol%)	Solvent	Yield (%)
1	$NiCl_2$		Toluene	Trace
2	$NiCl_2$	PCy_3 (10.0)	Toluene	22
3[b]	$NiCl_2(PCy_3)_2$		Toluene	96 (92)
4[c]	$NiCl_2(PCy_3)_2$		Toluene	93
5	$NiCl_2(PPh_3)_2$		Toluene	4
6	$NiCl_2$	PPh_3 (10.0)	Toluene	0
7	$NiBr_2$		Toluene	Trace
8	$NiBr_2$	PCy_3 (10.0)	Toluene	60
9	$Ni(acac)_2$		Toluene	10
10	$Ni(acac)_2$	PCy_3 (10.0)	Toluene	90
11	$NiCl_2$(dppe)		Toluene	4
12	$NiCl_2$(dppf)		Toluene	7
13	$PdCl_2$	PCy_3 (20.0)	Toluene	Trace
14	$CoCl_2$	PCy_3 (20.0)	Toluene	Trace
15	$FeCl_2$	PCy_3 (20.0)	Toluene	Trace
16	$NiCl_2(PCy_3)_2$		Dioxane	49
17[d]	$NiCl_2(PCy_3)_2$		THF	62
18[d]	$NiCl_2(PCy_3)_2$		Et_2O	90

[a] 1.2 Equiv. of Grignard reagent were used and GC yields were determined with the use of *n*-dodecane as an internal standard if without further note. [b] Isolated yield reported in the parentheses. [c] 2.0 mol% of $NiCl_2(PCy_3)_2$ was used as the catalyst. [d] The reaction was carried out under reflux for 1 h.

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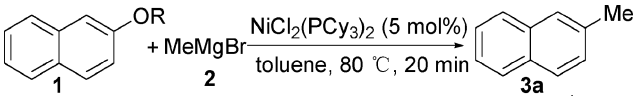
Table 2 Methylation of different alkoxy naphthalenes **1**[a]



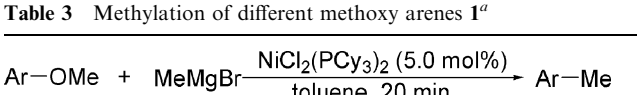
Entry	1	R	3a (%)[b]
1	**1a**	Me	92
2	**1b**	Et	92
3	**1c**	Bu^n	96
4	**1d**	Bu^i	91
5	**1e**	Bu^t	88
6	**1f**	MOM	69
7	**1g**	TMS	95
8	**1h**	Ph	95
9[c]	**1i**	OAc	<5
10[c]	**1j**	H	<5

[a] All the reactions were carried out on the scale of 0.5 mmol of **1**, 0.6 mmol of **2**, 5.0 mol% $NiCl_2(PCy_3)_2$ in 4 mL of toluene. [b] Isolated yields if without further note. [c] GC yields with the use of *n*-dodecane as an internal standard.

efficiency, no matter whether the ether was located at 1- or 2-positions (entries 1 and 2, Table 3). Alkenyl and aryl groups did not affect this transformation (entries 3–5, Table 3). When derivatives of anisole were submitted to this transformation, the temperature of the reaction needed to be increased to 110 °C to facilitate the reaction. MeMgBr reacted with anisole to afford toluene in a good conversion without observation of any by-products by GC spectroscopy (entry 7, Table 3). It was noteworthy that steric effects in the aromatic ring did not play a critical role (*cf.* entries 8 and 9, Table 3).

Highly reactive C–Br could not be tolerated. Such functionality was transformed into a methyl group along with C–OMe in an excess amount of MeMgBr (entry 1, Table 4). Different dialkyl ethers located at both the 2- and 6-positions on the same naphthalene could not be functionalized stepwise according to their steric effects (entries 2–5, Table 4). Instead, these substituted naphthalenes could be dimethylated in one

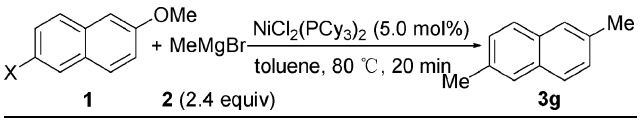
Table 3 Methylation of different methoxy arenes **1**[a]



Entry	1	Ar	3 (%)[b]
1[c]	**1a**	2-Naphthyl	**3a** (93)
2[c]	**1k**	1-Naphthyl	**3b** (92)
3[c]	**1l**	6-Phenyl-2-naphthyl	**3c** (98)
4[c]	**1m**	(*E*)-6-Styryl-2-naphthyl	**3d** (94)
5[d]	**1n**	(*E*)-4-Styrylphenyl	**3e** (93)
6[d,e]	**1o**	4-Phenylphenyl	**3f** (92)
7[d,f]	**1p**	Phenyl	(62)
8[d,f]	**1q**	4-Tolyl	(74)
9[d,f]	**1r**	2-Tolyl	(71)

[a] All the reactions were carried out on the scale of 0.5 mmol of **1**, 0.75 mmol of **2**, and 5.0 mol% of $Ni(PCy_3)_2Cl_2$. [b] Isolated yields if without further note. [c] The reaction was carried out at 80 °C. [d] The reaction was carried out at 110 °C. [e] *tert*-Butyl phenyl ether was used as a substrate. [f] The reaction was carried out in mesitylene and the yield was determined by GC with the use of *n*-dodecane as an internal standard.

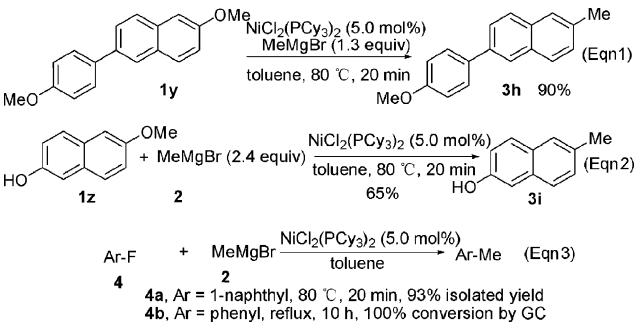
Table 4 Methylation of different dialkoxy naphthalenes **1**



Entry	1	2	3	4	5	6
1	**1s**	**1t**	**1u**	**1v**	**1w**	**1x**
X =	Br	OMe	OBu^n	OPr^i	OBu^t	OPh
3g (%)	91	99	99	97	97	96

step with an excess amount of MeMgBr. Serving as protecting groups for 2,6-naphthalenediol, methyl and phenyl could not be discriminated under these coupling conditions either (entry 6, Table 4).

To further clarify the reactivity of different methoxy groups under the same conditions, we tested the methylation of dimethoxy ether **1y**. We found that monomethylation took place in 90% isolated yield in the presence of 1.3 equiv. of MeMgBr, with a small amount of dimethylated product as the by-product [eqn (1)]. It indicated that the different methoxy groups in the same molecule could be well differentiated. Moreover, it is noteworthy that a free hydroxy group is compatible under these conditions, and did not affect the methylation of the methoxy group with an excess amount of MeMgBr, and the hydroxy group could be further transformed into other functionalities [eqn (2)]. Finally, methylation of the C–F bond also took place under these conditions although C–F is very stable.[8] Simple aryl fluorides **4a** and **4b** were tested and the desired methylated products were obtained in excellent conversions under these conditions [eqn (3)].



In summary, we have developed a practical way to construct aryl C–Me bonds by methylating aromatic C–OR (R = alkyl, aryl) and C–F *via* Ni(0) catalysis under mild conditions. Further study to apply this transformation is under way.

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