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Metal-Catalyzed Dealkoxylative C$_{aryl}$–C$_{sp^3}$ Cross-Coupling—Replacement of Aromatic Methoxy Groups of Aryl Ethers by Employing a Functionalized Nucleophile**

*Matthias Leiendecker, Chien-Chi Hsiao, Lin Guo, Nurtalya Alandini, and Magnus Rueping**

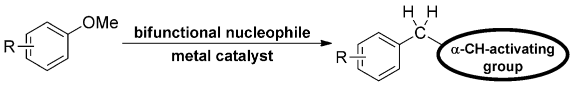
***Abstract:** The direct replacement of aromatic methoxy groups with activated carbon nucleophiles would give rise to novel synthetic pathways for targeted and diversity-oriented syntheses. We demonstrate here that this transformation can be achieved in a one-step reaction involving a bifunctional organolithium nucleophile in combination with a C_{Ar}–OMe bond-cleaving nickel catalyst. The resulting products are stable, α-CH active, and suitable for various further modifications.*

The ability to activate aromatic systems while being inert towards common cross-coupling catalysts is a key feature of methoxy groups.[1] Synthetic applications include the optimization of activity and regioselectivity in electrophilic aromatic substitutions such as Friedel–Crafts-type reactions,[2] *ortho*-metalation,[3] and transition-metal-catalyzed cross-coupling reactions.[4]

During our attempts to synthesize gephyrotoxin, we realized that the option to replace an aromatic methoxy group with a functional carbon moiety in the 5-methoxy-tetrahydroquinoline framework could lead to a tremendous shortcut in one of the rationalized synthetic pathways.[5] Since a method as such did not exist, but would be a powerful and generally useful synthetic tool, we decided to study C_{Ar}–O bond-cleavage reactions. Wenkert et al. reported in 1979 a nickel-catalyzed reaction of anisoles with aromatic Grignard reagents that afforded biaryls.[6] The initially limited scope was expanded in 2004 by Dankwardt, who found a significant improvement in the reactivity with PCy_3 ligands (Cy = cyclohexyl).[7] Furthermore, Shi and co-workers reported a one-step methylation procedure through the use of methylmagnesium bromide.[8] However, a general alkylation method is not known due to the dominating β-H elimination side reaction.[9,10]

More recently, the reductive cleavage of aromatic methoxy groups with hydride donors in the presence of a Ni catalyst gained attention.[11] These are important advancements given the high stability of the C_{Ar}–O bond, the availability of diverse natural anisoles, and the ecological and economic advantages over aromatic halides as cross-coupling electrophiles.[12] However, methoxy-group-replacing C_{Ar}–C_{sp^3} bond-forming reactions are so far limited to methylations.

The ability to substitute the methoxy group with an activated carbon atom (Scheme 1) would open a pathway to novel and simple synthetic strategies. One could, for example, design syntheses where the methoxy group first acts as a directing and/or an activating group and is subsequently replaced by a functional moiety. This concept could be beneficial for targeted as well as diversity-oriented syntheses and could ideally be applied to a wide range of substrates.



Scheme 1. Concept of the methoxy-group-replacing aryl functionalization.

With the aim of transforming this concept into a synthetic method we searched for potential catalysts and nucleophiles. The latter could consist of a bifunctional CH_2 moiety, for example organometallic species, necessary for the replacement of the methoxy group, and a direct or indirect α-C-activating group. Thus, we decided to target $ArCH_2SiMe_3$ products since they are stable and offer various options for subsequent transformations (Scheme 2) and are at the same time inert towards common cross-coupling catalysts.[13–20]

With these considerations in mind we began to evaluate MCH_2SiMe_3 nucleophiles in the presence of readily available nickel catalysts. Grignard reagents of the $XMgCH_2SiMe_3$ type showed reduced reactivity because of the trimethylsilane (TMS) functionality. Organolithium reagents had so far not been successfully applied in methoxy-group-replacing coupling reactions because of their high reactivity and fast decomposition under the coupling conditions.[21] However, $LiCH_2SiMe_3$ proved to be a good nucleophile under the reaction conditions.

To our delight the reaction of $LiCH_2SiMe_3$ with 2-methoxynaphthalene in the presence of $[NiCl_2(PCy_3)_2]$ in toluene at 80 °C yielded 93 % of the corresponding product **3a** (Table 1, entry 1). The yield could even be increased to 99 % when the catalytic complex was formed in situ from $[Ni(cod)_2]$ (cod = 1,5-cyclooctadiene) and PCy_3 (Table 1, entry 2). Furthermore, the same result could be achieved with only

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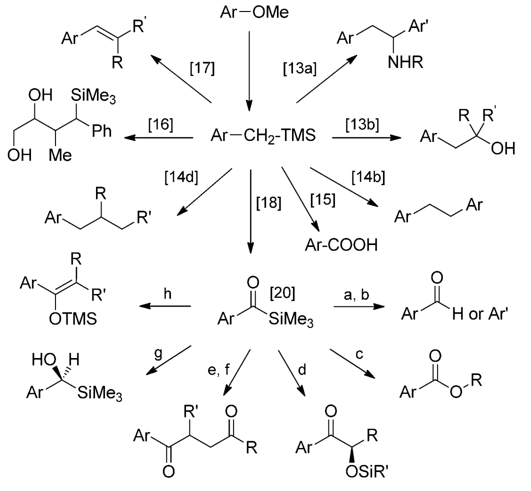
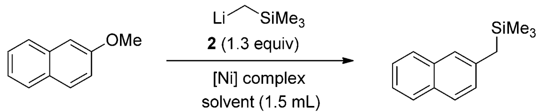


Scheme 2. Use of $ArCH_2SiMe_3$ products in further transformations.

Table 1: Optimization of the reaction conditions.



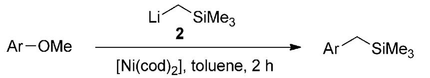
1a (0.25 mmol)

3a

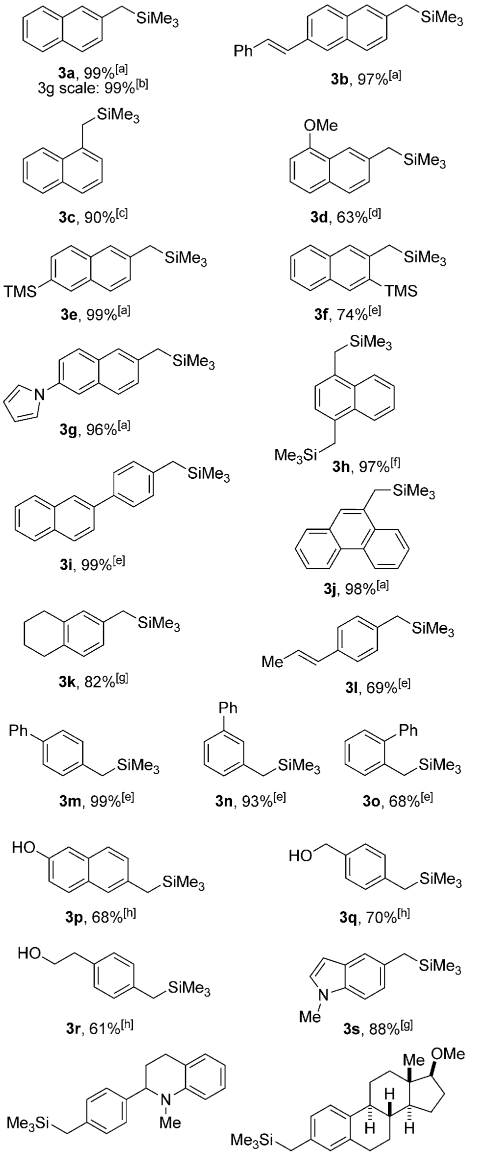
Entry	[Ni(cod)$_2$] [mol%]	PCy$_3$ [mol%]	Solvent	*T* [°C]	*t* [h]	Yield [%][a]
1[b]	–	–	toluene	80	2	93
2	2.5	5	toluene	80	2	99
3	2.5	5	THF	60	2	84
4	2.5	5	Et$_2$O	30	2	99
5	2.5	5	toluene	50	2	99
6	2.5	5	toluene	RT	2	97
7	1	2	toluene	80	2	99
8	–	–	toluene	80	2	–
9	–	5	toluene	80	2	–
10	2.5	–	toluene	80	1.5	99
11	1	–	toluene	50	1.5	99
12	1	-	toluene	RT	1.5	97

[a] Yield of isolated products. [b] 5 mol% [NiCl$_2$(PCy$_3$)$_2$] was used.

Table 2: Substrate scope of the dealkoxylative aryl functionalization. In general, the reaction was performed with 0.25 mmol ArOMe and 1.3 equiv $LiCH_2SiMe_3$ in 1.5 mL toluene; yields are of isolated products.



1a-u **3a-u**



3a, 99%[a]
3g scale: 99%[b]
3b, 97%[a]
3c, 90%[c]
3d, 63%[d]
3e, 99%[a]
3f, 74%[e]
3g, 96%[a]
3h, 97%[f]
3i, 99%[e]
3j, 98%[a]
3k, 82%[g]
3l, 69%[e]
3m, 99%[e]
3n, 93%[e]
3o, 68%[e]
3p, 68%[h]
3q, 70%[h]
3r, 61%[h]
3s, 88%[g]
3t, 84%[i]
3u, 87%[j]

[a] 1 mol% [Ni(cod)$_2$], 50°C. [b] 0.3 mol% [Ni(cod)$_2$], Scale-up experiment with 15 mmol 2-methoxynaphthaline in 60 mL toluene, 80°C, 14 h. [c] 1 mol% [Ni(cod)$_2$], 80°C. [d] 0.7 equiv $LiCH_2SiMe_3$, 2.5 mol% [Ni(cod)$_2$], 80°C. [e] 2.5 mol% [Ni(cod)$_2$], 80°C. [f] 2.5 mol% [Ni(cod)$_2$], 80°C, 2.6 equiv $LiCH_2SiMe_3$. [g] 5 mol% [Ni(cod)$_2$], 80°C. [h] 10 mol% [Ni(cod)$_2$], 80°C, 3.3 equiv $LiCH_2SiMe_3$. [i] 5 mol% [Ni(cod)$_2$], 80°C, 14 h. [j] 10 mol% [Ni(cod)$_2$], 80°C.

1 mol% of catalyst (Table 1, entry 7). The use of 2.5 mol% catalyst at reduced temperatures of 50°C or room temperature led to yields of 99% and 97%, respectively (Table 1, entries 5 and 6). The use of diethyl ether as the solvent led to similar yields (Table 1, entry 4), whereas reactions in THF did not lead to full conversion (Table 1, entry 3). Control experiments (Table 1, entries 8–10) showed that omission of the PCy_3 ligand did not change the reaction outcome. This is surprising since phosphine ligands played a major role in previous C_{Ar}–O bond-cleavage studies and contributed actively to the proposed mechanisms.[6–11,22,23]

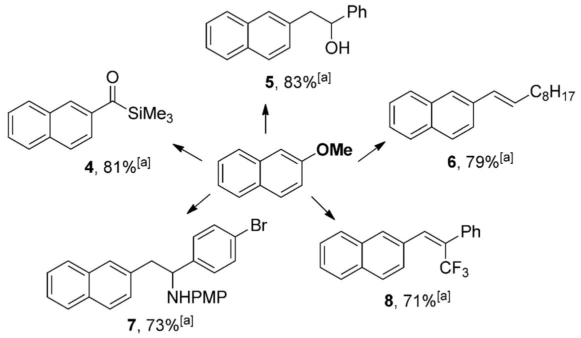
Intensive mechanistic studies by Martin et al. indicate a Ni^I species instead of the typical Ni^0/Ni^{II} couple in the catalytic cycle of the anisole reduction.[22] However, it has been shown that the use of $LiCH_2SiMe_3$ in Co-catalyzed processes can lead to formation of an active complex.[24] A classic catalytic cycle involving oxidative addition, transmetalation, and reductive elimination can be assumed for our transformation; however, exact mechanistic investigations including DFT studies need to be carried out. Reaction optimization with 1 mol% [Ni(cod)$_2$] but without PCy_3 as a ligand led to yields of 99% at 50°C and 97% at room temperature (Table 1, entries 11 and 12). The preliminary studies suggested that higher temperatures are required for other substrates. Thus, we decided to investigate the scope with the following conditions: 0.25 mmol of the anisol derivative, 1 mol% [Ni(cod)$_2$], and 1.3 equiv of LiCH$_2$SiMe$_3$ in 1.5 mL toluene for 2 h at 50 °C.

A broad range of substrates could be applied in this new nickel-catalyzed dealkoxylative functionalization and the corresponding products were obtained in good yields (Table 2). Methoxynaphthalenes (**1a–h**) showed high reactivity and could be transformed into the products in excellent yields. Substrates containing two aromatic methoxy groups could be substituted twice (**1h**) or selectively in one position (**1d**), if an excess of 1,7-dimethoxynaphthalene was used. Phenanthrene (**1j**), tetrahydronaphthaline (**1k**), and biphenyl-methoxy substrates (**1m–o**) are also suitable for the transformation. In addition, substrates containing free aromatic, benzylic, or aliphatic alcohols (**1p–r**) as well as double bonds (**1b**, **1l**) were converted into the corresponding products. It was further demonstrated that the nitrogen-containing pyrrole (**1g**), indole (**1s**), and tetrahydroquinoline (**1t**) are suitable for replacement of the methoxy functional group. A high yield (87%) was obtained for a direct modification of dimethoxy-β-estradiol (**1u**) as an example of a more complex natural product. This example shows that aromatic methoxy groups can be selectively modified in the presence of aliphatic ones. In a scale-up experiment with only 0.3 mol% of catalyst, 15 mmol of 2-methoxynaphthalene were transformed into 3.18 g (99%) of the corresponding product (**3a**).

The resulting stable ArCH$_2$SiMe$_3$ products can readily be transformed into various products by Peterson olefination,[17] a fluoride-mediated mechanism,[13] photocatalysis,[14] gold catalysis,[15] or to the corresponding acyl silane by oxidation (Scheme 2).[18,19] Whereas a silicon-mediated α-anion stabilization at the CH$_2$ group is utilized for the deprotonation/addition/elimination sequence in the Peterson olefination reaction, the silicon atom can also be useful for fluoride-mediated reactions (with TBAF and TBAT) that lead to an active anion. In this case, the generation of trimethylsilyl fluoride allows the CH$_2$ group to act as a nucleophile, which led to the formation of saturated products.

To demonstrate the utility of our reaction, we converted the ArCH$_2$SiMe$_3$ substrates[13b,18,25] into the corresponding products **4–7**[13,17-19,26] thereby also developing a new method for the preparation of 1-aryl-1-trifluoromethyl-2-aryl alkenes such as **8** (Scheme 3). Other important substrate classes that are directly accessible from our substrates include olefins,[17] various alcohols[13b] and amines[13a] in the β-position to the aryl group, diols,[16] and aromatic carboxylic acids[15] (Scheme 2). The oxidation to acyl silanes extends the scope and allows the synthesis of further alcohols, aldehydes, ketones, esters, and acetals as well as other diverse structural elements.[18–20]

In summary, a new method has been introduced which allows direct replacement of aromatic methoxy groups with bifunctional nucleophiles. Synthetically, this can be achieved in a one-step nickel-catalyzed reaction of aryl ethers, whereby the products are obtained in good yields under mild reaction conditions. The products formed are stable, α-C active, and suitable for various further modifications. To demonstrate the utility of the developed method, several Ar-OMe ethers were directly transformed into diverse valuable synthetic building blocks in good yields.



Scheme 3. Transformation of the Ar-OMe group to form valuable products. PMP = *p*-methoxyphenyl. [a] Overall yield (Ar-OMe→product).

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[26] See the Supporting Information for more details.

Aryl Ether Cross-Coupling

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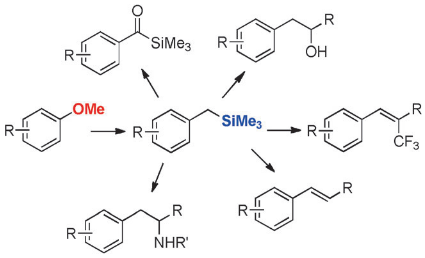
Metal-Catalyzed Dealkoxylative C_{aryl}–C_{sp^3} Cross-Coupling—Replacement of Aromatic Methoxy Groups of Aryl Ethers by Employing a Functionalized Nucleophile



The direct replacement of aromatic methoxy groups with activated carbon nucleophiles would give rise to novel synthetic pathways for targeted and diversity-oriented syntheses. The use of a bifunctional nucleophile in a nickel-catalyzed cross-coupling reaction has resulted in diverse aryl methyl ethers being transformed into α-carbon-activated products.