C(sp^2)–C(sp^3) Coupling

International Edition: DOI: 10.1002/anie.201510497
German Edition: DOI: 10.1002/ange.201510497

Lewis Acid Assisted Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers by C–O Bond-Cleaving Alkylation: Prevention of Undesired β-Hydride Elimination

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Dedicated to Professor Dieter Enders on the occasion of his 70th birthday

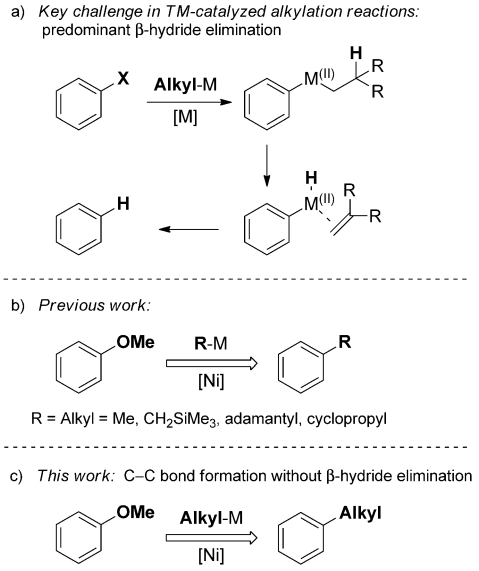
Abstract: *In the presence of trialkylaluminum reagents, diverse aryl methyl ethers can be transformed into valuable products by C–O bond-cleaving alkylation, for the first time without the limiting β-hydride elimination. This new nickel-catalyzed dealkoxylative alkylation method enables powerful orthogonal synthetic strategies for the transformation of a variety of naturally occurring and easily accessible anisole derivatives. The directing and/or activating properties of aromatic methoxy groups are utilized first, before they are replaced by alkyl chains in a subsequent coupling process.*

Transition-metal-catalyzed carbon–carbon and carbon–heteroatom cross-coupling reactions play an important role in modern organic chemistry and are widely used in the synthesis of organic materials, natural products, and therapeutics.[1] Typically, organic halides or activated phenol derivatives such as triflates are used as the electrophiles and can be coupled with a variety of organic or organometallic nucleophiles, both on the laboratory and industrial scale.[1d–h] Owing to their natural availability, lower toxicity, and reduced cost, unactivated phenol derivatives have emerged in the last few years to further complement organic halides as cross-coupling partners.[2] In particular, the use of simple, stable, inexpensive, and in many cases naturally available anisole derivatives is not only economically attractive but also an environmentally friendly alternative to existing methods.

Aromatic methoxy groups activate aromatic systems for Friedel–Crafts reactions,[3] *ortho* metalations,[4] and electrophilic aromatic substitutions.[3a,5] Furthermore, the C(sp^2)–OMe bond is often considered to be inert towards harsh reaction conditions and most cross-coupling catalysts.[6] In combination with new cross-coupling reactions targeting the C(sp^2)–OMe bond, these properties could enable synthetic strategies where the methoxy group could first serve as a directing and/or activating group before it is replaced by a new functional group. Whereas nickel-catalyzed cross-couplings[7] of anisole derivatives were already pioneered in the late 1970s by Wenkert et al.,[8] aryl ether cross-couplings are limited to arylation,[9] methylation,[10] alkynylation,[11] amination,[12] *ipso* borylation,[13] and reduction where the methoxy group is exchanged with a hydrogen atom.[14] Furthermore, we recently reported a functionalization strategy that enables the transformation of anisole derivatives into diverse products by C–O bond cleavage in a two-step process.[15]

However, the introduction of alkyl groups as nucleophiles by nickel catalysis may suffer from competing β-hydride elimination (Scheme 1 a). Thus far, this has limited the scope to transformations where this side reaction is either not possible or highly unfavorable. These examples include methylation[10,16,17] and the replacement of methoxy groups with an adamantyl or a cyclopropyl group[17b] (Scheme 1 b).

The unwanted β-hydride elimination, the high activation barrier of the oxidative-addition step,[18] and the poor leaving-group properties of methoxy groups render the use of aryl



Scheme 1. Catalytic C–C bond formation after activation of unreactive C–O bonds.

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201510497.

methyl ethers as electrophiles in cross-coupling reactions highly challenging. Reaction conditions, which can facilitate the energetically demanding cleavage, promote simultaneously the competing β-hydride elimination, so that the direct introduction of a long-chain alkyl group was previously not possible. We were thus very interested in developing the first dealkoxylative alkylation reaction (Scheme 1c). The use of easily accessible anisole derivatives allows orthogonal synthetic strategies that initially use the directing and/or activating properties of aromatic methoxy groups, before they are replaced by an alkyl chain bearing β-hydrogen atoms.

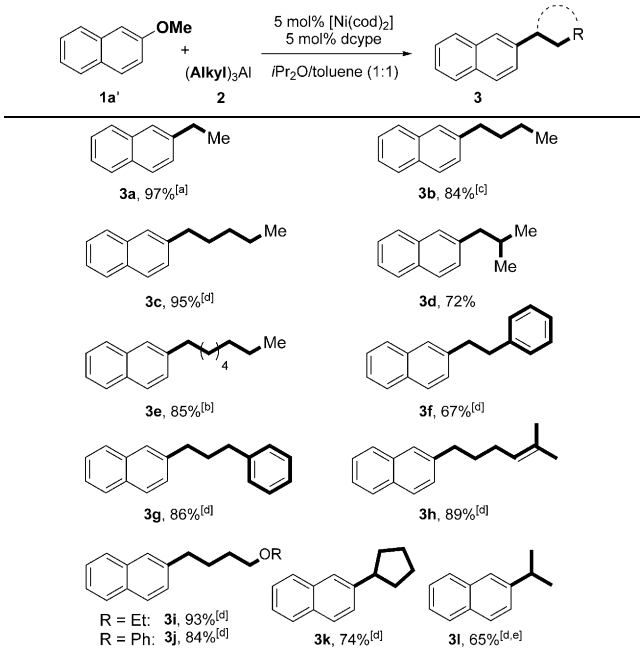
Our studies began with examining the activation of the C–O bond. We envisioned that Lewis acids might be able to lower the activation energy of C(sp^2)–OMe bond cleavage through polarization/activation.[19] Aluminum reagents, for example, benefit from their strong Lewis acidity and high oxophilicity,[20,21] and the transmetalation step could be energetically favored by the formation of stable dialkylaluminum methoxide. Although no dealkoxylative C–C bond formation was observed in the nickel-catalyzed hydrogenolysis of aryl methyl ethers[14b] in the presence of $AlMe_3$, the development of a first dealkoxylative alkylation appeared feasible based on our earlier experiences.

With these considerations in mind, we chose to study the reaction between 2-methoxynaphthalene and triethylaluminum to investigate C–O bond cleavage in the presence of various nickel catalysts in iPr_2O. Whereas the combination of $[Ni(cod)_2]$ and PCy_3 has previously proven to be key for C–O bond activation, no product was formed in our reaction (see the Supporting Information, Table S1, entry 1). Moreover, other monodentate ligands were not successful either. On the other hand, the bidentate dcype ligand[22] led to full conversion into the desired product under the applied conditions. Further studies resulted in the optimized reaction conditions, which entailed the use of a solvent mixture of iPr_2O/toluene (1:1) at 100 °C (Table S1). In situ generated triethylaluminum[21] gave rise to a slightly lower yield (Table S1, entry 22). Control experiments further showed that no conversion was achieved without the addition of a nickel catalyst (Table S1). Moreover, other nucleophiles, including Li, Mg, or Zn organometallic reagents, did not provide comparable reactivities. Both C–O bond activation by Lewis acidic trialkylaluminum and the dcype ligand appear to be critical for the desired alkylation process.

With the optimized reaction conditions in hand, the scope of the alkylation was investigated. A series of short- and long-chain trialkylaluminum nucleophiles with phenyl, alkenyl, and ether moieties as well as a cyclopentyl derivative were employed in this reaction after being prepared in situ from easily accessible lithium and Grignard reagents (Table 1). The corresponding products **3a**–**k** were obtained in good yields. The reaction with the *i*Pr reagent led to a 1:1.15 mixture of 2-isopropyl- and 2-propylnaphthalene in 65% yield (see the Supporting Information).

Subsequently, a large variety of aryl methyl ethers were subjected to the nickel-catalyzed reaction and coupled with different aluminum reagents (Table 2). 1,4-Dimethoxynaphthalene, for example, gave rise to the doubly functionalized product **4b** in good yield. Biphenyl substrates also led to

Table 1: Substrate scope of the aryl ether alkylation.

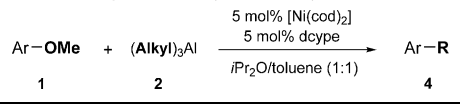


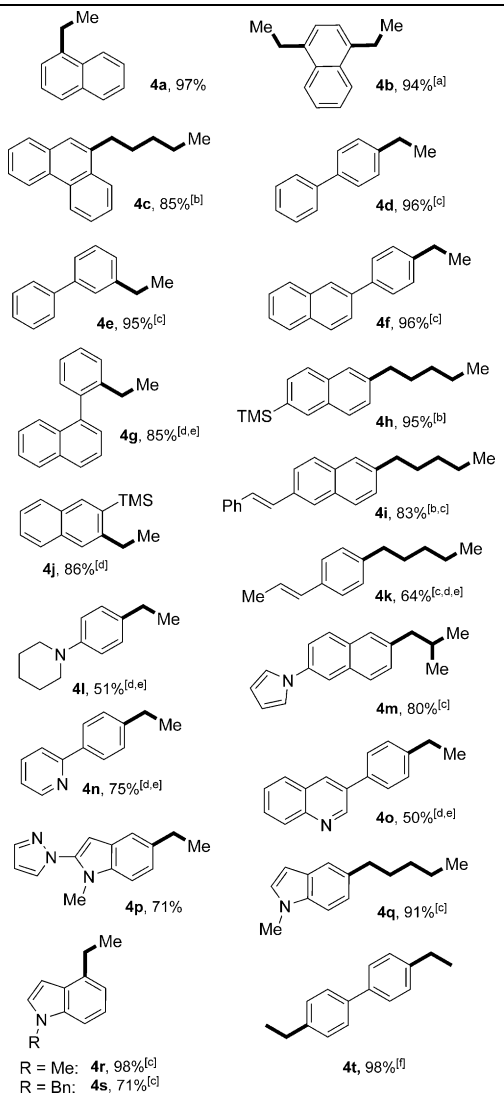
Reaction conditions: **1a'** (0.25 mmol), **2** (0.5 mmol), $[Ni(cod)_2]$ (0.0125 mmol), dcype (0.0125 mmol), iPr_2O/toluene (1:1, 1.5 mL), sealed reaction tube, 100 °C, 72 h. [a] 12 h. [b] 120 °C, 72 h. [c] R_3Al was prepared in situ from $AlCl_3$ and the corresponding lithium reagent. [d] R_3Al was prepared in situ from $AlCl_3$ and the corresponding Grignard reagent. [e] A mixture of 2-isopropyl- and 2-propylnaphthalene was formed. dcype = 1,2-bis(dicyclohexylphosphino)ethane.

excellent yields of the corresponding products at slightly elevated temperatures (**4d**–**g**). Furthermore, substrates with a bulky trimethylsilyl (TMS) moiety are also suitable for the reaction (**4h**, **4j**) even when this group is in direct vicinity to the OMe group. *ortho*-Arylated anisole was also converted in good yield (**4g**) as well as substrates with a conjugated double bond (**4i**, **4k**), including naturally available anethole. The amino-substituted aryl methyl ether **1l** and a series of heterocyclic pyrrole, pyrazole, pyridine, or quinoline substrates (**1m**–**p**) were also suitable for the alkylation reaction. Different indole derivatives were directly coupled in the C4 as well as in the C5 position (**4p**–**s**). Anisole **1t** (Ar = 4-F-1,1′-biphenyl) was bis-alkylated in good yield to product **4t**. Anisole derivatives with cyano, ester, and amide groups, however, are not compatible with the reaction conditions.

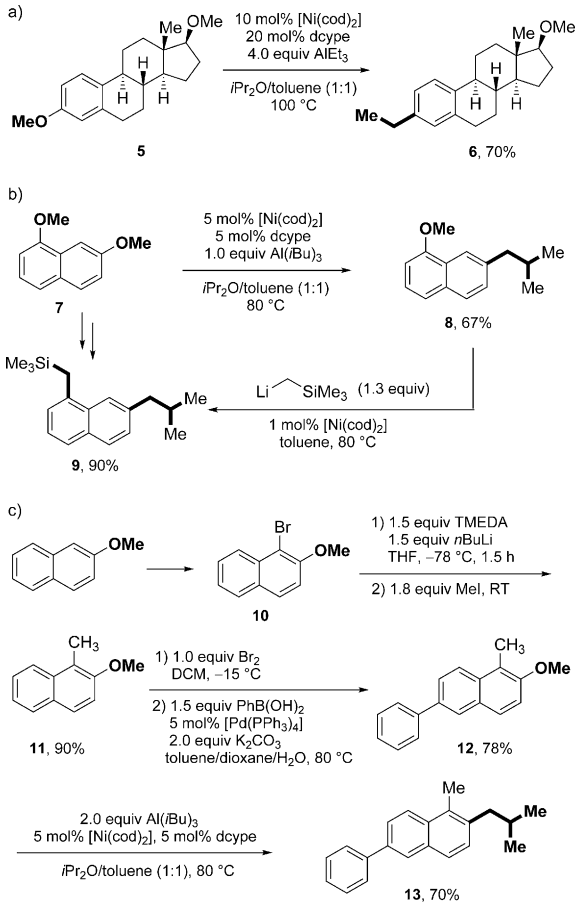
To demonstrate the different synthetic applications of the developed method, we synthesized three products that would not be as readily accessible without this method (Scheme 2). Owing to the broad variety of natural and pharmacologically or agrochemically relevant anisole derivatives, the developed dealkoxylative alkylation method might be used for the late-stage modification of various compounds. As an example, we submitted dimethoxy-β-estradiol (**5**) to our nickel-catalyzed reaction conditions and isolated the corresponding alkylation product **6** in 70% yield (Scheme 2a). Furthermore, we were able to show that the two methoxy groups in 1,7-dimethoxynaphthalene (**7**) can be functionalized selectively.

Table 2: Substrate scope of the aryl ether alkylation.





Reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), $[Ni(cod)_2]$ (0.0125 mmol), dcype (0.0125 mmol), iPr_2O/toluene (1:1, 1.5 mL), sealed reaction tube, 100 °C, 12 h. [a] With 1.0 mmol of $AlEt_3$. [b] R_3Al was generated in situ from the Grignard reagents and $AlCl_3$. [c] 120 °C, 72 h. [d] 140 °C, 72 h. [e] $[Ni(cod)_2]$ (0.025 mmol), dcype (0.025 mmol). [f] Starting from **1t** (Ar = 4-F-1,1′-biphenyl); $AlEt_3$ (0.75 mmol). 120 °C, 72 h.



Scheme 2. The developed alkylation method enables the facile synthesis of products that are otherwise difficult to access.

With bulky triisobutylaluminum, alkylation first took place selectively at the C7 position. Subsequently, the C1 position could be functionalized with $LiCH_2SiMe_3$ for further transformations (Scheme 2b). The developed method also enabled us to approach an orthogonal synthetic strategy that would first temporarily make use of the directing and/or activating characteristics of the methoxy group and then enable its further functionalization (Scheme 2c). Therefore, 2-methoxynaphthalene was first selectively brominated in the C1 position. Subsequent lithiation followed by reaction with methyl iodide furnished 1-methyl-2-methoxynaphthalene (**11**), which was then selectively brominated in the C5 position.

Then, the C5 position was arylated in a Pd-catalyzed Suzuki–Miyaura reaction; subsequently, our nickel-catalyzed reaction led to methoxy cleavage and alkylation. This reaction sequence is an example of an orthogonal synthetic strategy, which further enhances the possibilities for the synthesis of diverse novel alkyl-functionalized products.

To confirm the significant coordination between the aryl methyl ethers and trialkylaluminum, we studied our reaction system by ^{27}Al and ^{1}H NMR spectroscopy (Figures S1–S6). A significant shift of the ^{27}Al resonance of $AlEt_3$ from 158 to 181 ppm was observed in the presence of 2-methoxynaphthalene. At the same time, the ^{1}H methoxy resonance was shifted from 3.40 to 3.49 ppm. Furthermore, the ^{1}H signals of $AlEt_3$ were shifted in the presence of 2-methoxynaphthalene (CH_2: from 0.29 to 0.16 ppm, CH_3; from 1.09 to 1.30 ppm).

Furthermore, we conducted computational studies using the CPCM (Et_2O) M06L/def2-TZVP// ωB97X-D/6-31G(d) (SDD for Ni) method to gain greater insight.[23] Our calculations (summarized in Figure 1) revealed that oxidative addition to the aryl ether C–O bond strongly benefits from the coordination of the Lewis acid ($\Delta G^{\ddagger}_{OA} = 18.6$ kcal mol^{-1}).[24] In contrast, a prohibitively high activation free

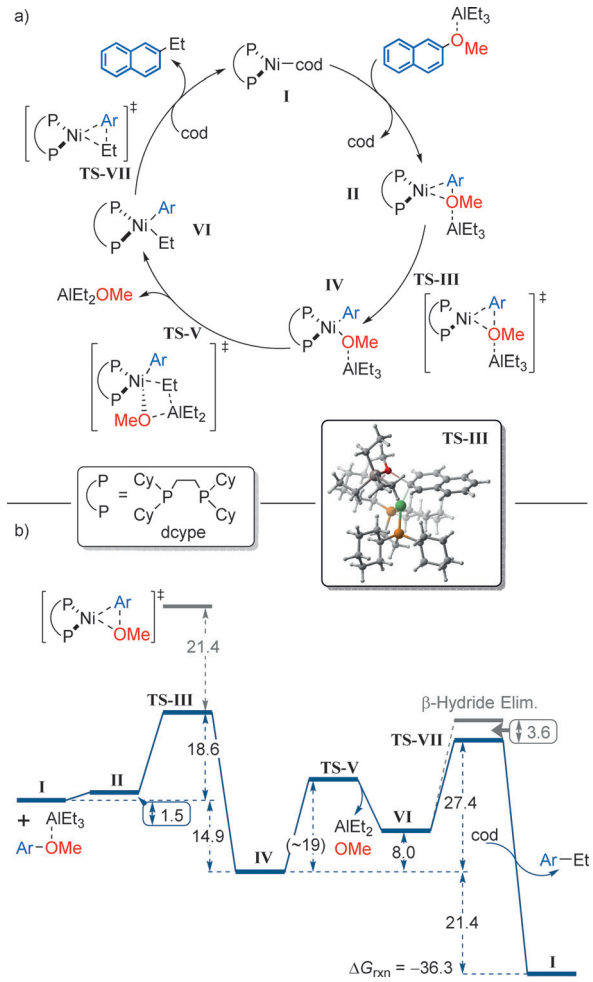


Figure 1. a) Proposed catalytic cycle for the [(dcype)Ni(cod)] catalyzed alkylation of 2-methoxynaphthalene with $AlEt_3$. b) Calculated reaction pathway (Gibbs energy in kcal mol^{-1}) at the CPCM (Et_2O) M06L/def2-TZVP//ωB97X-D/6-31G(d) (SDD for Ni) level of theory.

energy barrier of 40.0 kcal mol^{-1} was calculated in the absence of the Lewis acid. Furthermore, our calculations suggest that the coordination of $AlEt_3$ to the OMe group strongly favors the formation of Ni^{II} complex **IV**. Thereafter, transmetalation from the Ni^{II} intermediate was calculated to be relatively facile, with a barrier of $\Delta G^{\ddagger}_{TM} \approx 19$ kcal mol^{-1},[25] which is then followed by an irreversible reductive elimination from **VI** ($\Delta G^{\ddagger}_{RE} = 27.4$ kcal mol^{-1}). The competing β-hydride elimination was predicted to have an activation barrier that is 3.6 kcal mol^{-1} higher than that of the reductive elimination to form Naph–Et[26] and is therefore disfavored. This is likely due to the prerequisite of initial dissociation of one phosphine arm to create a free coordination site for the β-hydride elimination. Owing to the generally very high activation barrier of Ni^0-catalyzed oxidative addition to aryl ethers in the absence of Lewis acids, alternative mechanistic proposals, for example via Ni^I intermediates, have been suggested.[27] However, our calculations suggest that $AlEt_3$ has a dramatic influence on the reaction, essentially leading to a drop in the activation barrier by 20 kcal mol^{-1}.

To support our calculated reaction profile experimentally, we analyzed the reaction of a [Ni^{II}(X)(Ar)] complex with $AlEt_3$.[28] Successful transmetalation should result in a [Ni^{II}-(Et)(Ar)] complex, which eventually forms Ar–Et. Our studies indeed led to quantitative formation of Ar–Et, underlining the presence of a competent Ni^{II} intermediate (see the Supporting Information).

In conclusion, the newly developed Lewis acid assisted nickel-catalyzed cross-coupling reaction constitutes the first broadly applicable method for the alkylation of anisole derivatives under C–OMe bond cleavage. This was achieved as a result of the effective interplay of various factors: the Lewis acidic trialkylaluminums facilitate the oxidative addition by activating the C–OMe bond, the formation of stable dialkylaluminum methoxide favors an efficient transmetalation step, and the nickel catalyst with a bidentate dcype ligand undergoes the catalytic cycle for the tested substrates efficiently, suppressing the competing β-hydride elimination and affording the desired products with high yields. Naturally occurring and synthetically easily accessible structurally diverse anisole derivatives can thus be efficiently transformed into a variety of alkyl-substituted molecules. Building on our newly developed Lewis acid assisted cross-coupling reaction, we further demonstrated diversity-oriented, anisole-based strategies for the synthesis of a variety of novel products. The development of further C–O bond-cleaving cross-coupling reactions is an ongoing effort in our laboratories.

Acknowledgments

X.L. and L.G. were supported by the China Scholarship Council, C.-C.H. was supported by a DAAD fellowship, and M.L. was supported by a Kekulé fellowship (Fonds der Chemischen Industrie) and the Studienstiftung des deutschen Volkes. We gratefully acknowledge the computing time granted on the RWTH Bull Cluster in Aachen (JARA0091).

Keywords: C–O bond activation · C–C cross-coupling · cross-coupling · nickel · trialkylaluminum

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6093–6098
Angew. Chem. **2016**, *128*, 6198–6203

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Received: November 12, 2015
Revised: January 4, 2016
Published online: April 8, 2016

