Alkylation

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Nickel-Catalyzed Alkoxy–Alkyl Interconversion with Alkylborane Reagents through C–O Bond Activation of Aryl and Enol Ethers

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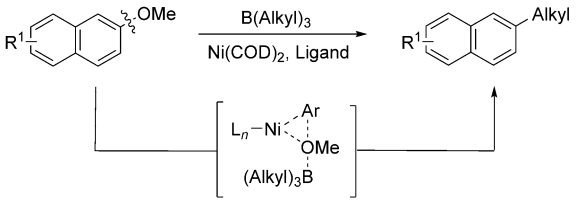
Abstract: *A nickel-catalyzed alkylation of polycyclic aromatic methyl ethers as well as methyl enol ethers with B-alkyl 9-BBN and trialkylborane reagents that involves the cleavage of stable C(sp^2)–OMe bonds is described. The transformation has a wide substrate scope and good chemoselectivity profile while proceeding under mild reaction conditions; it provides a versatile way to form C(sp^2)–C(sp^3) bonds that does not suffer from β-hydride elimination. Furthermore, a selective and sequential alkylation process by cleavage of inert C–O bonds is presented to demonstrate the advantage of this method.*

In recent years, C_{Ar}–O electrophiles have emerged as powerful alternatives to the commonly used aryl halide coupling partners mainly owing to the environmentally benign nature, natural abundance, and ready availability of phenols and derivatives thereof.[1] Compared with aryl tosylates, esters, carbamates, and sulfonates, aryl ethers, and in particular aryl methyl ethers, are the simplest derivatives in the phenol series. Nevertheless, they have only been scarcely used as substrates in metal-catalyzed cross-coupling reactions. The key challenges are associated with the high activation energy required for C–OMe bond scission and the low propensity of methoxy residues to act as leaving groups.[1i] Since Wenkert and co-workers reported the first Ni-catalyzed alkylation reaction of aryl methyl ethers with aromatic Grignard reagents,[2] the scope of metal-catalyzed cross-couplings of aryl ethers has been expanded considerably, and now includes a wide range of nucleophilic coupling partners. Whereas various nucleophiles were successfully applied for the arylation,[3] amination,[4] borylation,[5] alkynylation,[6] and reductive deoxygenation[7] of methoxyarenes, an efficient and general method for replacing the alkoxy with an alkyl group is still missing.

Shi, Chatani, and our group have independently developed methods for the metal-catalyzed alkylation of alkoxyarenes with alkylmagnesium,[8] alkyllithium,[9] and alkylaluminum reagents.[10] However, these methods have serious restrictions in terms of the alkyl group that can be introduced. In general, none of these approaches features a high tolerance to functional groups, and good yields were obtained only for methylation, where no competing β-hydride elimination can take place. The high reactivity of the organometallic nucleophiles enables the use of substrates bearing less reactive functional groups whereas it is not compatible with derivatives containing carbonyl (esters/ketones), silyl, or amino groups.

Therefore, the disclosure of new methods within this field is still a highly desirable goal. With these considerations in mind, we began to search for a more general catalytic system and nucleophiles that can be used for the efficient alkylation of aromatic ethers. Owing to their environmentally friendly nature, operational simplicity, and superior functional group tolerance, alkylboranes are widely used in the synthesis of natural products and bioactive molecules.[11,12] Hence, the use of alkylboranes as coupling partners in cross-coupling reactions with C(sp^2)–O electrophiles, in particular methoxynaphthalene derivatives, seemed advantageous. In addition, the limitations associated with undesired side reactions, including the often observed β-hydride elimination, might be overcome. Furthermore, alkylboranes can act as Lewis acids, and coordination to the alkoxy group should have a positive effect on the oxidative addition of the naphthyl ether C–O bond (Scheme 1).



Scheme 1. Considerations for the alkylation of naphthyl ethers by C–OMe bond activation.

Herein, we describe the development of a new method for the direct nickel-catalyzed alkylation[13] of naphthyl ethers and related polyaromatic systems with alkylboranes, which exhibits high reactivity and wide substrate scope. In addition, the transformation is applicable to a range of methyl enol ethers, providing access to alkylated vinylarenes.

We began our investigations by examining the reactivity of 2-methoxynaphthalene (**1a**) with *B*-alkyl 9-BBN **2a** in the presence of $Ni(COD)_2$ (10 mol%) and IPr·HCl (20 mol%) in diisopropyl ether (Table 1). As expected, the nature of the

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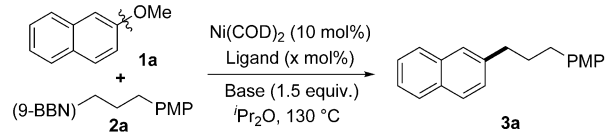
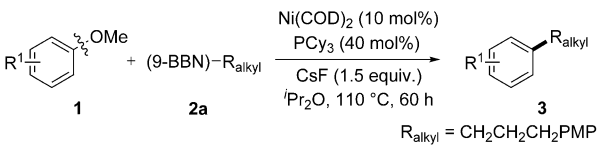
Table 1: Optimization of the nickel-catalyzed alkylation of 2-methoxynaphthalene.[a]

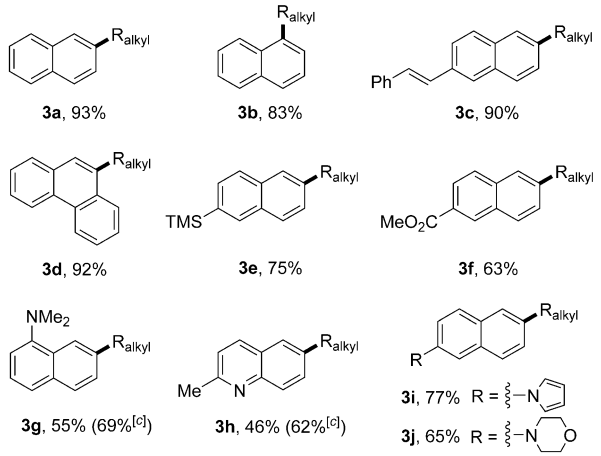


Entry	Base	Ligand (*x* mol%)	Time [h]	Yield [%][b]
1	Cs_2CO_3	IPr·HCl (20)	12	2
2	K_3PO_4	IPr·HCl (20)	12	0
3	Na_2CO_3	IPr·HCl (20)	12	trace
4	CsCl	IPr·HCl (20)	12	5
5	CsF	IPr·HCl (20)	12	18
6	CsF	PPh_3 (20)	12	0
7	CsF	dcype (10)	12	0
8	CsF	PCy_3 (20)	12	28
9	CsF	PCy_3 (20)	36	53
10	CsF	PCy_3 (20)	60	61
11	CsF	PCy_3 (20)	84	56
12	CsF	PCy_3 (40)	60	91
13[c]	**CsF**	**PCy_3 (40)**	**60**	**95 (93)**[d]
14[e]	CsF	PCy_3 (40)	60	31
15[f]	CsF	PCy_3 (40)	60	0
16	CsF	–	60	0

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.32 mmol, 1.6 equiv), $Ni(COD)_2$ (10 mol%), ligand (*x* mol%), base (1.5 equiv), $^iPr_2O$ (0.2 M), 130 °C. [b] Yields determined by NMR analysis using 1,3,5-$(OMe)_3C_6H_3$ as the internal standard. [c] 110 °C. [d] Yield of isolated product. [e] 100 °C. [f] Without $Ni(cod)_2$. 9-BBN = 9-borabicyclo[3.3.1]nonane, COD = cyclooctadiene, dcype = 1,2-bis(dicyclohexylphosphino)ethane, IPr·HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, PMP = *para*-methoxyphenyl.

Table 2: Substrate scope for polycyclic aromatic methyl ethers.[a,b]





[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.32 mmol, 1.6 equiv), $Ni(COD)_2$ (10 mol%), PCy_3 (40 mol%), CsF (1.5 equiv) in $^iPr_2O$ (0.2 M) at 110 °C for 60 h. [b] Yields of isolated products are given. [c] $Ni(COD)_2$ (20 mol%), PCy_3 (80 mol%).

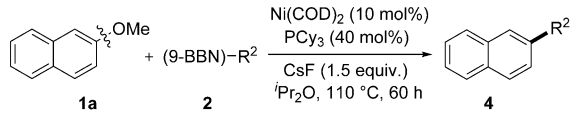
base played a critical role for the success of the reaction.[14] As shown in entries 1–5, the alkylated product **3a** was obtained in 18% yield when cesium fluoride was employed as the base whereas the use of other bases could not improve the yield further. Furthermore, the ligand plays a crucial role in the C–O bond-cleaving reaction. Therefore, the replacement of IPr·HCl by PCy_3 under otherwise identical reaction conditions significantly improved the yield (entry 8), whereas the use of other phosphine and N-heterocyclic carbene ligands was unsatisfactory (entries 6 and 7).[15] Pleasingly, extending the reaction time led to better results (entries 9–11). Interestingly, the ratio of $Ni(cod)_2$ and PCy_3 ligand had a dramatic effect on the reactivity, and **3a** was obtained in 91% yield when the ratio was changed from 1:2 to 1:4 (entry 10 vs. 12).[3b,16] Furthermore, a slight decrease in temperature enabled the isolation of **3a** in 93% yield (entry 13). The yield of the reaction decreased dramatically when the reaction was performed at 100 °C (entry 14). Furthermore, control experiments revealed that the reaction did not occur in the absence of nickel catalyst or ligand (entries 15 and 16).

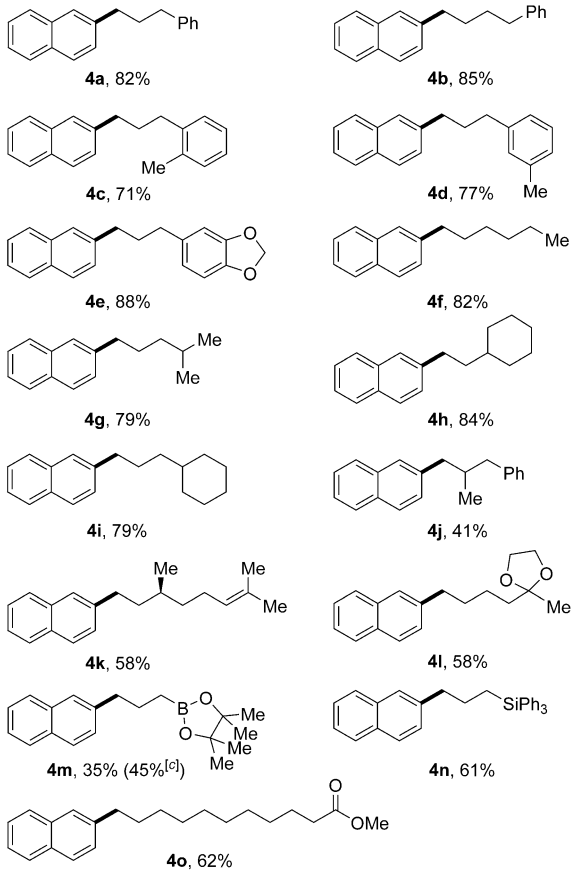
Encouraged by our initial results, we next focused on the preparative scope and generality of our nickel-catalyzed alkylation reaction. As shown in Table 2, a range of polycyclic aromatic methyl ethers **1a–j** with different substitution patterns could be easily converted into the desired products **3a–j** by employing *B*-alkyl 9-BBN **2a** as the coupling partner.

Notably, the chemoselectivity profile of this method was nicely illustrated by the fact that functional groups such as silyl, ester, and amine groups (**1e–g**) were tolerated under the present conditions. It was further demonstrated that nitrogen-containing heterocycles, including quinoline (**1h**), pyrrole (**1i**), and morpholine (**1j**), did not interfere with the $C(sp^2)$–$C(sp^3)$ bond formation, giving the desired products in good yields. Phenyl methyl ethers were also tested under the optimized conditions; however, only traces of the alkylated products were formed probably owing to their higher aromaticity and slightly lower propensity to undergo C–O bond cleavage.[17]

We subsequently turned our attention to the preparative scope of our reaction with respect to various *B*-alkyl 9-BBN nucleophiles **2a–o** in combination with 2-methoxynaphthalene (**1a**) as the coupling partner. As shown in Table 3, two *B*-alkyl 9-BBN derivatives bearing short and long phenyl-substituted alkyl chains underwent this reaction in excellent yields (**4a**, **4b**). The use of methyl-substituted alkylboranes smoothly provided the corresponding cross-coupling products (**4c**, **4d**), whereas the use of a benzodioxole-substituted alkylborane gave **4e** in 88% yield. Aliphatic substituents (**4f–i**) are also perfectly suitable for the alkylation, which further enhances the utility and applicability of this method. With 2-methyl-substituted *B*-alkyl 9-BBN **2j** as the coupling partner, the yield was only moderate, probably owing to steric hindrance. Furthermore, the chemoselectivity profile of this method was illustrated by the fact that substrates with olefin (**2k**), dioxolane (**2l**), boronic ester (**2m**), silyl (**2n**), and ester groups (**2o**) all afforded the corresponding products in good to high yields.

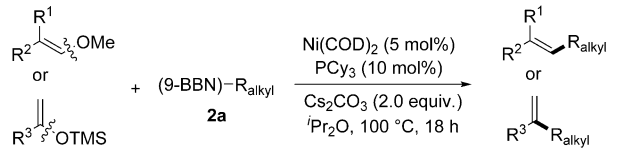
Table 3: Substrate scope for *B*-alkyl 9-BBN derivatives.[a,b]

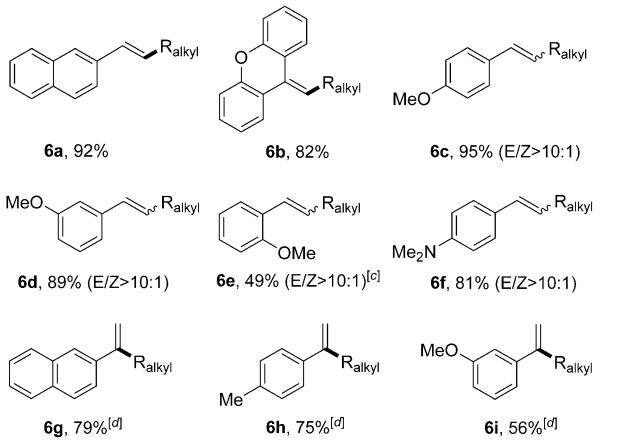




[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.32 mmol, 1.6 equiv), $Ni(COD)_2$ (10 mol%), PCy_3 (40 mol%), CsF (1.5 equiv) in $^iPr_2O$ (0.2 M) at 110 °C for 60 h. [b] Yields of isolated products are given. [c] $Ni(COD)_2$ (20 mol%), PCy_3 (80 mol%).

Table 4: Substrate scope for enol ethers.[a,b]





[a] Reaction conditions: **5** (0.25 mmol), **2a** (0.5 mmol), $Ni(COD)_2$ (5 mol%), PCy_3 (10 mol%), Cs_2CO_3 (2.0 equiv) in $^iPr_2O$ (1.5 mL) at 100 °C for 18 h. [b] Yields of isolated products are given. [c] 48 h. [d] **5** (0.25 mmol), **2a** (0.5 mmol), $Ni(COD)_2$, (10 mol%), PCy_3 (20 mol%), Cs_2CO_3 (2.0 equiv) in $^iPr_2O$ (1.5 mL) at 70 °C for 18 h.

Subsequently, our attention was drawn to enol ethers[16a] as potential substrates for the alkylation process. With (*E*)-2-(2-methoxyvinyl)naphthalene (**5a**) and *B*-alkyl 9-BBN **2a** as the coupling partner, we searched for suitable reaction conditions (see the Supporting Information, Table S9). With the optimized reaction conditions in hand, the scope with respect to enol ethers was investigated (Table 4). Not only extended aromatic substrates, but also simple aryl alkenes were suitable for this transformation (**6a–f**). It should be noted that when a 1:1 *E*/*Z* mixture of a substrate was exposed to the reaction conditions, the desired product was isolated with high stereoselectivity ($E/Z > 10{:}1$) as isomerization takes place under the reaction conditions.[16a] Furthermore, the alkylation protocol could be extended to alkenyl silyl ethers with slightly modified coupling conditions (**6g–i**).

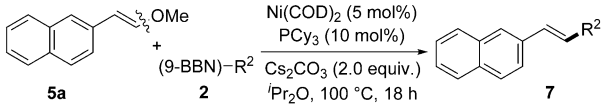
Next, we examined the preparative scope and generality of our cross-coupling reaction with various *B*-alkyl 9-BBN derivatives. As shown in Table 5, a broad range of *B*-alkyl 9-BBN reagents bearing different substituents reacted with high efficiency. Different aromatic and aliphatic groups were compatible with our coupling reaction, and the corresponding products **7a–h** were obtained in high yields. The Suzuki–Miyaura alkylation was also suitable for sensitive functional groups that are usually not compatible with organometallic reagents, such as ester, amide, acetal, and boronic ester moieties, providing products **7i–m** in very high yields.

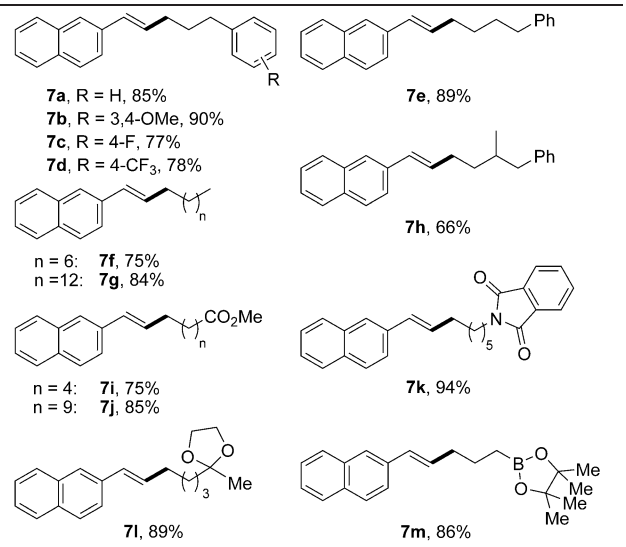
We then decided to examine the reactivity of other alkylboron species. Although *B*-alkyl 9-BBNs are the most efficient and commonly used Suzuki-type alkylating reagents, the use of commercially available alkylating reagents such as trialkylboranes could simplify the transformation. Gratifyingly, we observed that polycyclic aromatic methyl ethers bearing various functional groups could be cross-coupled with triethylborane **8** in good yields (Table 6).

Overall, we believe that the results shown in Tables 2–6 nicely illustrate the good reactivity and applicability of our method for using *B*-alkyl 9-BBN and trialkylborane reagents as coupling partners. This approach is attractive owing to its substrate scope and chemoselectivity profile as aryl methyl ethers and methyl enol ethers bearing various functional groups can be used in an alkylative cross-coupling for the first time.

To demonstrate the usefulness of our method, a selective and sequential C–O bond activation process was attempted (Scheme 2). For this purpose, the pivalate group in compound **10** was first alkylated in a cross-coupling reaction developed in our group[18] that involves the use of an N-heterocyclic carbene ligand and cesium carbonate and left the methoxy group intact. Subsequently, the stable C–OMe bond could be

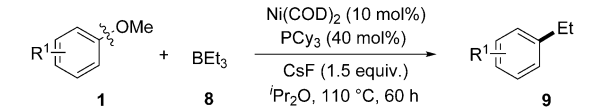
Table 5: Substrate scope for *B*-alkyl 9-BBNs.[a]

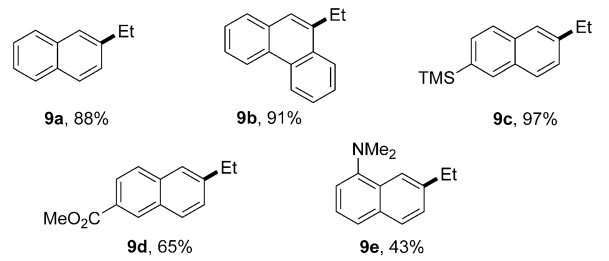




[a] Reaction conditions: **5a** (0.25 mmol), **2** (0.5 mmol), $Ni(COD)_2$ (5 mol%), PCy_3 (10 mol%), Cs_2CO_3 (2.0 equiv) in $^iPr_2O$ (1.5 mL) at 100°C for 18 h.

Table 6: Substrate scope for the reaction of aromatic methyl ethers with triethylborane as the coupling partner.[a,b]

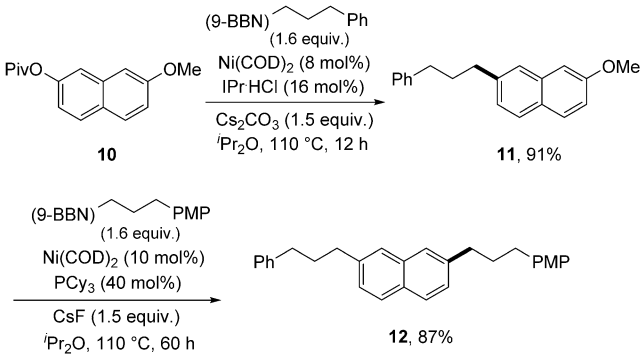




[a] Reaction conditions: **1** (0.20 mmol), **8** (0.40 mmol, 2 equiv), 1.0 M in hexanes), $Ni(COD)_2$ (10 mol%), PCy_3 (40 mol%), CsF (1.5 equiv) in $^iPr_2O$ (0.2 M) at 110°C for 60 h. [b] Yields of isolated products are given.

activated and functionalized with *B*-alkyl 9-BBN with the $Ni(cod)_2/PCy_3$ catalyst system to furnish **12**. The reactivity differences between naphthyl carboxylates and naphthyl methyl ethers for C–O bond cleavage are crucial for efficient sequential C–O bond activation and the functionalization of aromatic frameworks.

In conclusion, we have developed the first alkylation reaction of polycyclic aromatic methyl ethers, which is based on the use of alkylboron reagents as coupling partners and involves the cleavage of highly inert C–OMe bonds. This reaction shows broad functional group tolerance, providing



Scheme 2. Sequential alkylation of two different inert C–O bonds.

a practical and versatile way to form various $C(sp^2)–C(sp^3)$ bonds that does not suffer from β-hydride elimination. This enables the synthesis of various products in high yields. Diverse synthetically readily accessible and naturally occurring methoxy arenes were efficiently transformed into a variety of alkyl-substituted molecules. As such, this process will be of interest for the replacement of methoxy groups, for example, after their use as directing groups in Friedel–Crafts reactions, *ortho* lithiations, or metal-catalyzed C–H functionalizations. In retrosynthesis planning, methoxy groups can thus be considered as directing groups and, at the same time, as placeholders for alkyl groups. Furthermore, this method is applicable to a range of methyl enol ethers, providing access to valuable alkyl vinylarenes.

Acknowledgements

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Keywords: alkylation · alkylboron reagents · aromatic methyl ethers · C–O activation · nickel catalysis

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Communications

Alkylation

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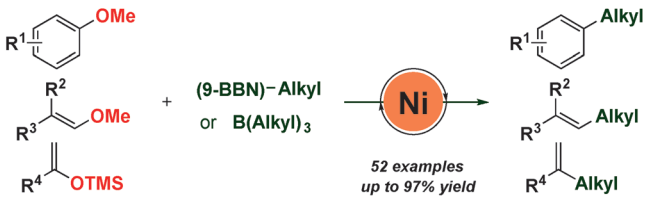
Nickel-Catalyzed Alkoxy–Alkyl Interconversion with Alkylborane Reagents through C–O Bond Activation of Aryl and Enol Ethers



No side reactions: A nickel-catalyzed Suzuki-type alkylation of aryl methyl ethers and methyl enol ethers with *B*-alkyl 9-BBN and trialkylborane reagents has been developed, which involves the cleavage of highly inert C(sp^2)–OMe bonds. This transformation provides a versatile way to build C(sp^2)–C(sp^3) bonds that does not suffer from β-hydride elimination.

