Cross-coupling of Amides with Alkylboranes via Nickel-catalyzed C–N Bond Cleavage

Xiangqian Liu, Chien-Chi Hsiao, Lin Guo, Magnus Rueping*

RWTH Aachen University, Institute of Organic Chemistry, Landoltweg 1, 52074 Aachen, Germany

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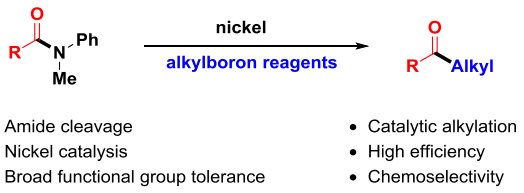
ABSTRACT: A protocol for the nickel-catalyzed alkylation of amides was established. The use of alkylboranes as nucleophilic partners allowed the use of mild reaction conditions and compatibility of various functional groups with respect to both coupling partners. The catalytic alkylation proceeded selectively at the amides in the presence of other functional groups as well as other carboxylic acid-derived moieties.

Over the past decades, transition-metal catalyzed cross-couplings have emerged as a powerful method for the selective construction of carbon-carbon and carbon-heteroatom bonds both in laboratory as well as on an industrial scale.[1] Although, the developed transformations have often involved catalysts based on palladium, good advances have been achieved also in nickel catalysis.[2] Nickel-catalyzed processes have gained popularity mainly due to the key features of nickel, such as facile oxidative addition[3] and ready access to multiple oxidation states,[4] which have facilitated the development of a broad range of innovative transformations.[2] As such, nickel was successfully applied in the activation of traditionally unreactive functional groups including phenol derivatives,[5] aromatic nitriles[6] or fluorides.[7] In our continuous efforts to investigate and disclose new reactivities based on nickel catalysis,[8] we aimed to employ amides, a typical stable functionality, as substrates in alkylation reactions.

Amides are key building blocks of proteins and common entities in natural and manufactured organic functional molecules.[9] In sharp contrast with their natural abundance, methodologies to functionalize the amide group are limited due to the resonance stability of the amide bond.[9-10] Nevertheless, the activation of amides[11-13] was reported by the groups of Garg (Ni)[12a-c, e,f,h,i,n,v] and Zou (Pd).[13b,c] In addition, the use of twisted amides to destabilize the C–N bond was introduced by Szostak group (Ni, Pd, Rh).[12-13] Many of the developed transformations focus on the establishment of C_{acyl}–C_{aryl} bonds, complementing the Weinreb amide chemistry[14] and allowing for the synthesis of aryl ketones. In addition, Garg and coworkers reported the nickel-catalyzed alkylation of Ts activated amides with alkylzinc reagents, however *N*-Ph, Me amides were not reactive under the developed conditions.[12i] Very recently, we discovered that by applying different reaction condition, aryl phenyl esters could be selectively converted into alkylated arenes or ketones.[8i] Hence, the development of general protocols for the synthesis of alkyl ketones from amides, is still highly desirable.

Due to their availability, broad functional group tolerance as well as environmental friendliness, alkylboron compounds are wildly used in the synthesis of complex natural products and the development of modern drugs and organic materials.[15-16]

Scheme 1. Nickel-catalyzed alkylation of amides with alkylboron reagents.

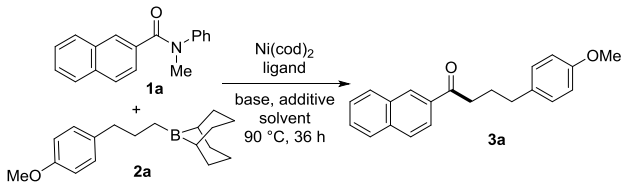


Among the alkylboron compounds commonly applied, *B*-alkyl-9-BBNs, which can be readily prepared *in situ* by hydroboration of the corresponding alkenes,[17] have shown high efficiency in couplings with a broad range of electrophilic reagents.[18-19] Inspired by these studies, we set forth to utilize *B*-alkyl-9-BBNs as nucleophilic partners in the nickel-catalyzed alkylation of amides. Although, catalytic acyl Suzuki-Miyaura reactions of acid halides,[20] anhydrides[20a] and activated esters[21,22] are known, the corresponding alkylation of amides has not been established.

Herein, we describe a versatile nickel-catalyzed alkylative Suzuki-Miyaura reaction of *N*-arylated amides via C–N bond cleavage, with high reactivity and broad functional group tolerance with respect to both coupling partners. To reach our goal, we initially investigated the reactivity of amide **1a** with *B*-alkyl-9-BBN **2a** under nickel catalysis (Table 1). Ligands are playing an essential role in the activation of inert bonds. Hence, initially the activity of various nickel complexes was examined in the presence of Cs_2CO_3 in iPr_2O at 90 °C. Monodentate and bidentate phosphine ligands proved to be inefficient in the transformation (Table 1, entries 1, 2). To our delight, when the *N*-heterocyclic carbene (NHC) ligand IPr·HCl [1,3-bis(2,6-diisopropylphe-nyl)imidazolium chloride] was tested, the desired cross-coupling product **3a** was isolated in moderate yield (Table 1, entry 4). Among the various *N*-Ph amides evaluated, *N*-Ph,Me amide proved to be the most reactive substrate (see Table S1 and S3 in the Supporting Information (SI)). Although the yield of ketone **3a** could be raised upon increasing the loading of $Ni(cod)_2$, the nickel to ligand ratio did not influence much the transformation (Table 1, entries 5, 6). A range of bases was examined and K_2CO_3

proved to be the most efficient for our alkylation process (Table 1, entries 7-12). Furthermore, as shown in Table 1, entries 13-15, the yield of ketone **3a** dropped remarkably when other solvents were used. In our previous work, a Lewis acid could facilitate the cleavage of C–O bonds.[8d] Thus, we questioned whether the C–N bond cleavage would proceed more smoothly in the presence of a Lewis acid. To our delight, after examining various Lewis acids (see Table S1 in the SI), we could isolate the corresponding ketone **3a** in 85% yield when the reaction was performed in the presence of 50 mol % LiCl (Table 1, entry 16). The yield dropped considerably when other Ni sources were employed (see Table S1, entries 27-29) and when the reaction time was shortened (Table 1, entry 17).

Table 1. Optimization of the reaction conditions.[a]



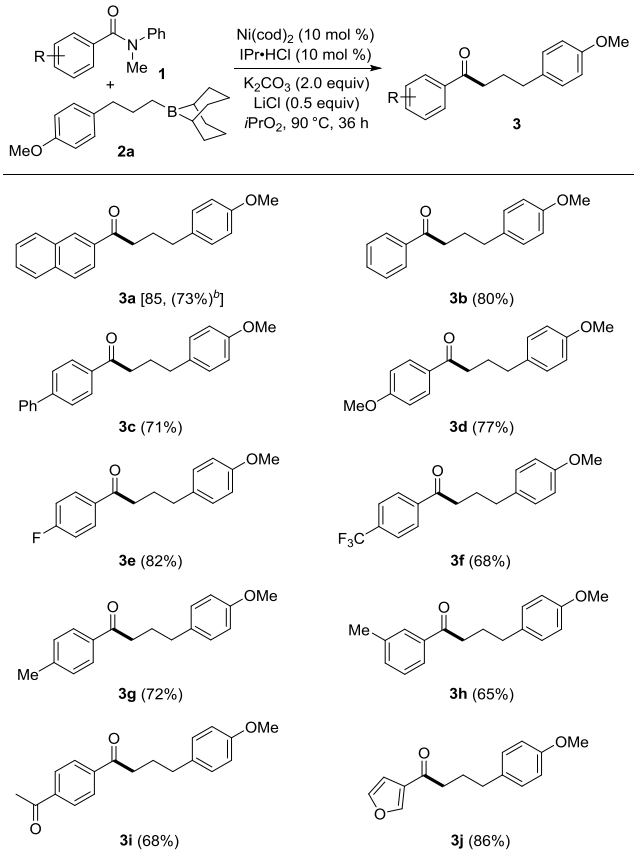
entry	ligand (mol %)	$Ni(cod)_2$ (mol %)	base	solvent	yield (%)[b]
1	PCy_3 (10)	5	Cs_2CO_3	iPr_2O	-
2	dcype (5)	5	Cs_2CO_3	iPr_2O	-
3	SIPr·HCl (10)	5	Cs_2CO_3	iPr_2O	28
4	IPr·HCl (10)	5	Cs_2CO_3	iPr_2O	48
5	IPr·HCl (20)	10	Cs_2CO_3	iPr_2O	60
6	IPr·HCl (10)	10	Cs_2CO_3	iPr_2O	61
7	IPr·HCl (10)	10	CsF	iPr_2O	23
8	IPr·HCl (10)	10	Li_2CO_3	iPr_2O	34
9	IPr·HCl (10)	10	Na_2CO_3	iPr_2O	44
10	IPr·HCl (10)	10	K_2CO_3	iPr_2O	72
11	IPr·HCl (10)	10	KO^tBu	iPr_2O	-
12	IPr·HCl (10)	10	K_3PO_4	iPr_2O	38
13	IPr·HCl (10)	10	K_2CO_3	toluene	56
14	IPr·HCl (10)	10	K_2CO_3	THF	43
15	IPr·HCl (10)	10	K_2CO_3	Et_2O	34
16[c]	IPr·HCl (10)	10	K_2CO_3	iPr_2O	85
17[c,d]	IPr·HCl (10)	10	K_2CO_3	iPr_2O	68

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), base (0.5 mmol), solvent (1.5 mL), sealed tube, 90 °C, 36 h. [b]Yield of the isolated product. [c]LiCl (0.125 mmol) was added. [d]18 h.

With the established reaction conditions in hand, we examined the scope and compatibility of the amide substrates (Scheme 2). Naphthyl, phenyl and biphenyl derivatives **1a-c** underwent the transformation smoothly, providing the corresponding products **3a-c** in high yields. Amide derivatives bearing electron-donating methoxy (**1d**) or electron-withdrawing F (**1e**) and CF_3 (**1f**) groups showed similar reactivity, indicating that the electronic nature of the substrate does not play an essential role in the cross-coupling reaction. The alkylation proceeded smoothly using also *para*- and *meta*-methyl substituted amides (**1g** and **1h**). The methyl ketone derivative **1i**, which was not tolerated in reaction with strong organometallic reagents, showed high efficiency in the transformation. Furyl amide **1j** was also compatible with the transformation, and the desired product **3j** was isolated in excellent yield. However, other heterocyclic derived substrates (e.g. pyridine and quinoline derived amides) were not compatible with our reaction conditions.

In order to show the scalability of our transformation, the reaction between **1a** and **2a** was performed on a 1 mmol scale and the corresponding product **3a** was isolated in 73% yield after 96 hours.

Scheme 2. Substrate scope of amides.[a]

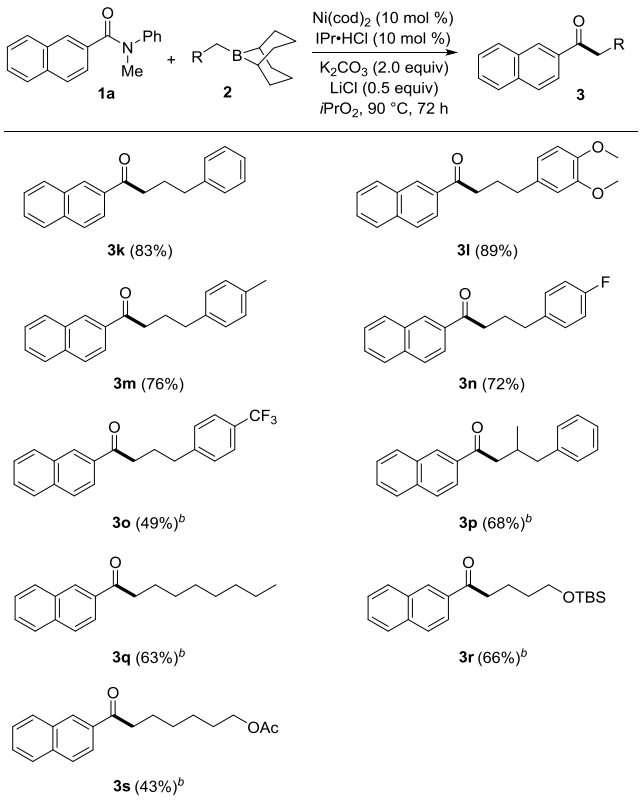


[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.5 mmol), $Ni(cod)_2$ (0.025 mmol), IPr·HCl (0.025 mmol), K_2CO_3 (0.5 mmol), LiCl (0.0125 mmol), iPr_2O (1.5 mL), sealed tube, 90 °C, 36 h. [b]Reaction on a 1 mmol scale, 96 h.

Furthermore, the generality of the alkylation was evaluated with respect to a variety of *B*-alkyl-9-BBNs. As shown in Scheme 3, a range of alkylborane reagents with various functional groups such as phenyl, *p*-methoxy phenyl, *p*-tolyl, *p*-fluoro phenyl, *p*-trifluoromethyl phenyl were suitable for the alkylation conditions providing the corresponding products **3k-o** in good to high yields. Branched and long linear aliphatic boranes were also compatible in the transformation, and the corresponding ketones **3p** and **3q** were obtained in good yields. In addition, a silyl ether and an ester derivative were also

tested under our conditions and yielded the desired products **3r** and **3s** with good efficiency.

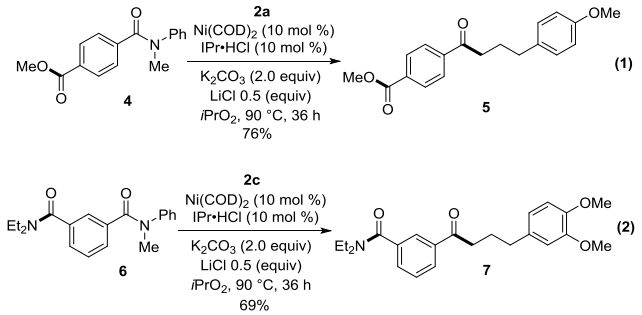
Scheme 3. Substrate scope of *B*-alkyl-9-BBNs.[a]



[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), $Ni(cod)_2$ (0.025 mmol), IPr·HCl (0.025 mmol), K_2CO_3 (0.5 mmol), LiCl (0.0125 mmol), *i*Pr_2O (1.5 mL), sealed tube, 90 °C, 72 h. [b]**2** (0.75 mmol) was used.

To demonstrate the utility of our protocol, two synthetic applications were performed (Scheme 4). Exposing amide derivative **4** to our coupling conditions we obtained ketone **5** with high efficiency without affecting the methyl ester group. When bisamide **6** was employed in the nickel-catalyzed alkylation, the *N*-alkyl, alkyl amide group survived and the corresponding product **7** was isolated in 69% yield. By applying the orthogonal reactivity between different carboxylic acid derived groups, the alkylation proceeded chemoselectively.

Scheme 4. Nickel-catalyzed chemoselective alkylation of carboxylic acid derivatives.



In summary, we have developed a versatile nickel-catalyzed alkylation of amides with alkylboranes as nucleophilic counterparts. The *N*-Ph,Me amides were cleaved under mild conditions and coupled with a range of functionalized alkylboranes with high efficiency. The catalytic alkylation proceeded selectively at the C–N bond of *N*-Ph,Me amides in the presence of ester and *N*-alkyl, alkyl amide groups. The good chemoselectivity exhibited by our protocol may not be achieved by applying the traditional ketone synthesis from amides in which typically strong organometallic reagents have to be used.

ASSOCIATED CONTENT

Supporting Information.
Detailed experimental procedures, spectral data for all compounds, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org."

AUTHOR INFORMATION

Corresponding Author

* magnus.rueping@rwth-aachen.de

Notes

The authors declare no competing financial interests.

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