C–H Activation

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Phenyltrimethylammonium Salts as Methylation Reagents in the Nickel-Catalyzed Methylation of C–H Bonds

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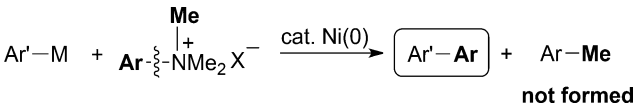
Abstract: *Methylation of $C(sp^2)$–H bonds was achieved through the Ni^{II}-catalyzed reaction of benzamides with phenyltrimethylammonium bromide or iodide as the source of the methyl group. The reaction has a broad scope and shows high functional-group compatibility. The reaction is also applicable to the methylation of $C(sp^3)$–H bonds in aliphatic amides.*

The transition-metal-catalyzed cross-coupling reaction has emerged as one of the most reliable and versatile C–C bond-forming methods in organic synthesis.[1] Aryltrimethylammonium salts were recently found to be applicable as an electrophilic coupling partner in place of the extensively used aryl halides or their pseudohalides in various catalytic cross-coupling reactions as arylation reagents, especially in Ni-catalyzed cross-coupling reactions (Scheme 1). Wenkert and co-workers have reported Ni-catalyzed Kumada–Tamao

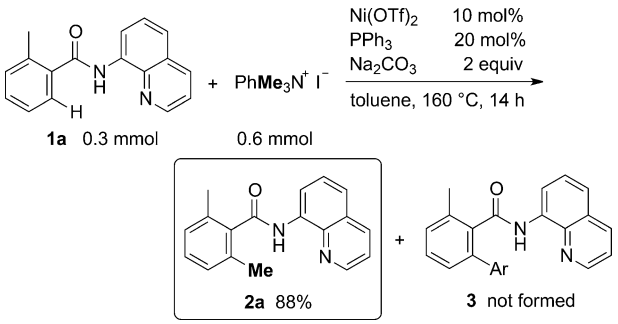


Scheme 1. Cross-coupling reactions with aryltrimethylammonium salts.

coupling with aryltrimethylammoinium iodide.[2] Later, Ni-catalyzed Suzuki–Miyaura coupling,[3] Negishi coupling,[4] amination,[5] and borylation[6] with aryltrimethylammonium salts were reported. Quite recently, aryltrimethylammonium triflates have been used as C–H arylation reagents in the Pd-catalyzed arylation of azoles.[7] Benzyltrimethylammonium salts have also been used as benzylating reagents in cross-coupling reactions.[6,8] However, the use of ammonium salts as methylation reagents in cross-coupling reactions has never been reported (Scheme 1).[9] We report herein the Ni-catalyzed methylation of C–H bonds in aromatic amides with phenyltrimethylammonium salts, which function as methylation reagents.

The transition-metal-catalyzed functionalization of C–H bonds to other chemical bonds has great significance in synthetic chemistry because of its high efficiency.[10] A wide variety of direct functionalizations of C–H bonds, including arylation, alkylation, amination, hydroxylation, halogenation, thionylation, borylation, and silylation, has been reported to date. However, examples of the methylation of C–H bonds still remain rare compared to other extensively studied types of C–C bond formation, such as arylation, alkylation, and allylation reactions, although methylation is fundamental in medicinal chemistry; the biological and physical properties of a drug can be greatly affected by the addition of just one methyl group to a lead compound.[11] In 1984, Tremont reported the Pd^{II}-mediated reaction of acetanilides with MeI, which results in methylation at the *ortho* position.[12] A catalytic version using MeI as the methylation reagent was subsequently reported by several groups.[13,14] Organometallic reagents, such as Me_4Sn,[15] $MeB(OH)_2$,[16] MeMgCl,[17] Me_3Al,[18] Me_2Zn,[19] peroxides,[20] and others,[21] can also be used in the methylation of C–H bonds. The development of a methylating reagent that is easy to use and is not sensitive to air continues to be a significant challenge. The present reaction involves the first reported use of aryltrimethylammonium salts in catalytic transformations of C–H bonds.[22]

Reaction of the aromatic amide **1a** with 2 equivalents of $PhMe_3N^+I^-$ (mp 227 °C (subl.)) in the presence of $Ni(OTf)_2$ and PPh_3 in toluene at 160 °C for 14 h gave the methylation product **2a** in 88% yield of isolated product (97% NMR yield; Scheme 2). No arylation product (**3**) was detected. When the reaction was carried out in the absence of PPh_3, **2a** was obtained in 37% NMR yield. The reaction was significantly affected by the nature of the base used: $NaHCO_3$ gave 92% NMR yield, Li_2CO_3 0%, K_2CO_3 40%, NaO*t*Bu 0%, and no base 0%. When the reaction was carried out at 140 °C, **2a** was obtained in 88% NMR yield, along with recovered 9% **1a**. It was found that $PhMe_3N^+Br^-$ showed comparable reactivity; using $PhMe_3N^+Br^-$ gave **2a** in 90% yield of isolated product, along with a small amount of recovered **1a**. No reaction occurred when $PhMe_3N^+PF_6^-$ was used. Curiously, tetramethylammonium iodide also showed no reactivity.



Scheme 2. Phenyltrimethylammonium iodide as the C–H methylation reagent in the Ni-catalyzed reaction of aromatic amides.

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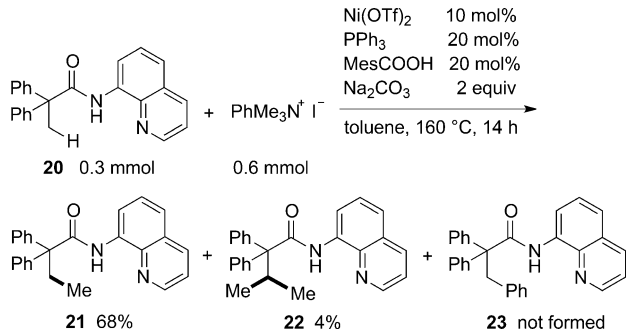
The scope of this methylation reaction with respect to the amides was investigated (Table 1). The reaction shows a broad substrate scope and high functional-group tolerance. A wide variety of functional groups, such as methoxy, benzyloxy, siloxy, acetoxy, fluoride, chloride, iodide, ketone, and trifluoromethyl groups, were tolerated. In the case of *meta*-substituted aromatic amides, the less hindered C–H bond was methylated exclusively.

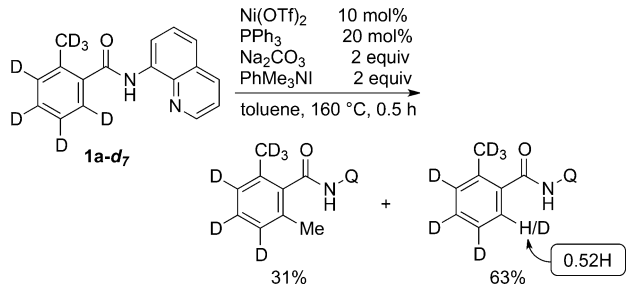
The present system was applicable to the methylation of $C(sp^3)$–H bonds (Scheme 3). The addition of MesCOOH resulted in an increased product yield. The reaction of **20** gave the methylation product **21** in 68% yield of isolated product, along with 4% dimethyl isomer **22** and 14% recovered **20**. The phenylation product **23** was not formed.



Scheme 3. Phenyltrimethylammonium iodide as the C–H methylation reagent in the Ni-catalyzed reaction of aliphatic amide **20**.

The deuterated amide **1a-d_7** was reacted with $PhMe_3NI$ for 0.5 h under otherwise standard reaction conditions (Scheme 4). As observed in the case of C–H alkylation and arylation reactions,[14,23,24] a significant amount of H/D exchange occurred at the *ortho* position (52% H) in the recovered amide, even after 0.5 h. This result indicates that cleavage of the C–H bonds is fast and reversible and thus unlikely to be the rate-determining step in the reaction.

The reaction is not completely inhibited by the addition of the radical trapping reagent TEMPO. When 1 equivalent of TEMPO was used, **2a** was produced in 53% yield along with 19% recovered **1a**. Even when 3 equivalents of TEMPO were used, **2a** was obtained in 16% yield along with 31% recovered **1a**. In both cases, the methyl TEMPO ether was not detected and an as yet unidentified product was formed in small amounts. The results suggest that an intermediate free-



Scheme 4. H/D exchange when using **1a-d_7**.

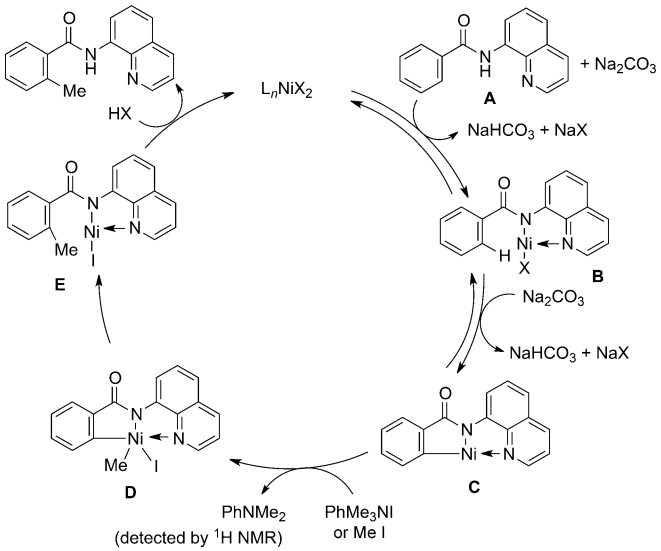
Table 1: Ni-catalyzed methylation of C–H bonds with phenyltrimethylammonium iodide.[a]

Amide	Product[b]
R = OMe (**1b**)	**2b** 78%[c,d]
OCH_2Ph (**1c**)	**2c** 72%[c]
$OSiMe_2{}^tBu$ (**1d**)	**2d** 88%
Me (**1e**)	**2e** 93%
Ph (**1f**)	**2f** 89%
Cl (**1g**)	**2g** 67%[c]
I (**1h**)	**2h** 62%[c,d]
$C(O)CH_3$ (**1i**)	**2i** 85%
CF_3 (**1j**)	**2j** 88%
4	**5** 78%
6	**7** 84%
8	**9** 72%
10	**11** 79%
12	**13** 88%
14	**15** 87%
16	**17** 69%[c,e]
18	**19** 84%

[a] Reaction conditions: amide (0.3 mmol), $PhMe_3NI$ (0.6 mmol), $Ni(OTf)_2$ (0.03 mmol), PPh_3 (0.06 mmol), Na_2CO_3 (0.6 mmol) in toluene (1 mL) at 160 °C for 14 h. [b] Yield of isolated product. [c] Isolated by GPC after column chromatography. [d] At 140 °C. [e] For 24 h.

radical species does not appear to be involved in this methylation system.

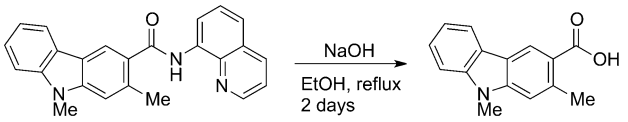
A proposed mechanism involving a Ni^{II}/Ni^{IV} catalytic cycle is shown in Scheme 5, which is essentially the same as that proposed for C–H alkylation and arylation reactions.[14,23,24] The coordination of the N(sp^2) atom to the Ni^{II} complex followed by ligand exchange on the N(sp^3) atom gives complex **B**. Cleavage of the *ortho* C–H bonds gives the nickelacycle **C**, and this step is accelerated by Na_2CO_3. Oxidative addition of $PhMe_3NI$, followed by reductive elimination to give **E**, which undergoes protonation, results in the formation of the methylation product with regeneration of the Ni^{II} species.



Scheme 5. Proposed mechanism.

The most curious issue is why phenylation does not take place in this system, since aryltrimthylammonium salts are known to serve as arylation reagents in various cross-coupling reactions with the aid of a Ni catalyst.[2–6] Our experimental results indicate that phenylation did not take place under the reaction conditions when using the Ni^{II} complex as the catalyst precursor, and the reported fact that phenyltrimethylammonium salts function as phenylation reagents in various cross-coupling reactions when using Ni^0 complexes suggest that Ni^0 is not a key catalytic species in the present methylation reaction. The Ph–N bond in $PhMe_3N^+I^-$ does not undergoes oxidative addition to the Ni^{II} center in complex **C**, probably because the Ni^{II} species is not sufficiently nucleophilic to participate in the oxidative addition compared to Ni^0. Instead, a Me–N bond undergoes oxidative addition through an S_N2-type mechanism. Alternatively, oxidative addition of MeI, which may be generated by the thermal decomposition of $PhMe_3N^+I^-$, cannot be excluded as a possibility.[25]

The 8-aminoquiloline moiety in **19** was easily removed by hydrolysis under basic conditions to give the corresponding carboxylic acid **24** in 88% yield of isolated product (Scheme 6).



Scheme 6. Hydrolysis of the methylation product.

In summary, we report the development of a highly efficient process for the methylation of C–H bonds using phenyltrimethlammonium bromide or iodide as the methylation reagent. A combination of a Ni^{II} catalyst and an 8-aminoquinoline directing group facilitates the reaction. The reaction displays a broad substrate scope and high functional-group tolerance.

Experimental Section

2-methyl-*N*-(8-quinolyl)benzamide (**1a**, 78.7 mg, 0.3 mmol), $PhMe_3NI$ (158 mg, 0.6 mmol), $Ni(OTf)_2$ (10.7 mg, 0.03 mmol), PPh_3 (15.7 mg, 0.06 mmol), Na_2CO_3 (63.6 mg, 0.6 mmol) and toluene (1 mL) were added to an oven-dried 5 mL screw-capped vial in a glove box. The mixture was stirred for 14 h at 160 °C followed by cooling. The resulting mixture was filtered through a celite pad and the filtrate concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 20:1) to afford the desired methylated product **2a** (73.1 mg, 88%) as a white solid.

Acknowledgements

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