Nickel-Mediated Enantiospecific Silylation via Benzylic C–OMe Bond Cleavage

Venkadesh Balakrishnan,† Vetrivelan Murugesan,† Bincy Chindan, and Ramesh Rasappan*

ABSTRACT: Benzylic stereocenters are found in bioactive and drug molecules, as enantiopure benzylic alcohols have been used to build such a stereogenic center, but are limited to the construction of a C–C bond. Silylation of alkyl alcohols has the potential to build bioactive molecules and building blocks; however, the development of such a process is challenging and unknown. Herein, we describe an unprecedented AgF-assisted nickel catalysis in the enantiospecific silylation of benzylic ethers.

Cross-coupling reactions that forge C–X (X = C, B, N, O, Si, etc.) bonds are of central importance in synthetic organic chemistry.1–8 The use of enantiopure benzylic alcohol as an electrophilic coupling partner [via C(sp3)–O bond cleavage] is highly attractive because the benzylic stereocenters exist in numerous bioactive and drug molecules, including Cinacalcet, Naproxen, and Methallenestril (Scheme 1).9 Methods exploiting benzylic alcohols [via C(sp3)–O bond cleavage] in cross-coupling reactions mostly rely on the conversion of alcohols into corresponding esters10–12 or ethers.3,13–15 Among them, methyl ethers are highly attractive largely because of the stability, atom economy, and a commonly encountered protecting group in organic synthesis.16 The group of Shi employed MeMgBr to successfully cross-couple benzylic methyl ethers;17 recently, Jarvo and co-workers improved the methodology to incorporate enantiopure methyl ethers in cross-coupling reactions (Scheme 1a).3,11,18–23 The success of this methodology stems from the formation of η3-benzylnickel complexes,17,24–30 which is favored by the molecules having extended conjugation and lower Dewar’s energy (aromaticity).31–33 Despite the success of Grignard reagents (unhindered) as a coupling partner in C(sp3)–OMe bond cleavage, the cross-coupling reactions of ethers remain essentially limited to C–C bond-forming reactions. On the contrary, organosilicons (C–Si bond) have widespread applications across various disciplines34–36 and are versatile intermediates in organic synthesis.37–41 Consequently, considerable effort in cross-coupling reactions has been spent to contribute to the synthesis of organosilanes, including silylation via C–N bond cleavage (Scheme 1b).42–44 Recently, for the first time, we introduced an economical Me3SiMgI (directly synthesized from TMSI) in cross-coupling reactions [C(sp2)–OCb bond cleavage] for the synthesis of ArSiMe3,45 a useful organosilane for further synthetic transformations (Scheme 1b).

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In accordance with our interest in nickel-mediated cross-coupling reactions, we were further interested in capitalizing on the application of Me₃SiMgI in enantiospecific cross-coupling reactions via C(sp³)–O bond cleavage. We were optimistic that the methodology developed by Shi, Jarvo, and others could be borrowed for the use of Me₃SiMgI as the coupling partner; however, these literature protocols were not amenable to Me₃SiMgI, and traces of the cross-coupled product were observed (Scheme 1a), highlighting the limitation of these literature strategies. The commonly employed silylating agent PhMe₂SiBpin, which did not afford product 3a in 12% yield (entry 6), Ni(cod)₂ completely shut down the reaction (discussed below). The use of a bidentate phosphine ligand (dppe) had no impact on the yield (entry 7). This led us to screen a list of additives, and the results are listed in Table 1 (entries 8–12). A remarkable improvement in the yield to 66% was observed with AgF (2 equiv) being as an additive (entry 8). The other additives, including AgBr, LiF, and CsF, afforded product 3a in yields of only 24%, 36%, and 34%, respectively, with a significant amount of byproducts 5a and 5b. Pleasingly, the yield soared to 96% when the temperature was decreased to 0 °C (entry 13), possibly slowing the degradation of nickel to black. The use of less polar Et₂O or toluene had a detrimental effect on the yield (entries 16 and 17). No reaction was observed when NiF₂ was employed in place of NiBr₂-diglyme (entry 18). Decreasing the amount of Me₃SiMgI also decreased the yield (entry 19). Employing stoichiometric NiBr₂-diglyme afforded 3a in 44% yield and 5b in 52% yield (entry 20) with complete consumption of 1a. Further tuning of the reaction condition revealed that the reaction could be carried out with 0.5 equiv of AgF and 10 mol % NiBr₂-diglyme/PCy₃ without a significant compromise in the yield (entry 14).

With the optimized conditions in hand, we moved further to expand the scope of the substrates. Methyl ethers 1 with various α-substituents, including alkyl and aryl groups, were well tolerated; the cyclohexyl (1b), ethyl (1c), phenyl (1d), and benzyl (1e) derivatives afforded the corresponding cross-coupled products in very good yields (Table 2). The 1-naphthyl derivative afforded product 3f in 50% isolated yield, and the use of stericly bulkier PhMe₂SiMgBr and Ph₂MeSiMgBr also afforded the corresponding products 3ga and 3gb in good yields. A broad range of functional groups were well tolerated, which provides an opportunity for further derivatization of the cross-coupled products. Aryl ethers [C(sp³)–O] (1i, 1j, 1t, and 1ac) were intact under the optimized condition, and the chemoselective cross-coupled products (3i, 3j, 3t, and 3ac) were isolated in 70%, 86%, 95%, and 85% yields, respectively. The sensitive ketal group was stable and afforded coupled product 3n in 52% yield; partial decomposition of 3n may be at play. Substrates bearing fluoride (1k), CF₃ (1m), TMS (1l), amine (1ab), and amide (1u) groups were also compatible and afforded the cross-coupled products in very good yields. Interestingly, boronic ester 1s afforded cross-coupled product 3s in 78% yield, although it can provide trialkyl borane with organometallic reagents. Ketone derivative 1o also afforded coupled product 3o in 46% yield along with traces of an undesired alcohol byproduct. Allylic ethers were subsequently investigated; as expected, the reactions were efficient, affording the synthetically versatile allylsilanes 3p–u in excellent yields and E/Z ratios.

Given the importance of heteroarenes in pharmaceuticals and agrochemicals, we subjected pyridine, benzothiophene, and thiophene derivatives to cross-coupling reactions and obtained cross-coupled products 3w–z in good yields. It is worth noting that the allyl ethers (1q and 1r), pyridines (1w and 1x), and benzothiophene 1y do not require AgF, and it is expected that substrates with varying Dewar’s resonance energy (aromaticity) may have a profound impact on the outcome of the reactivity. For example, the empirical

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Table 1. Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>deviation from above</th>
<th>additive (equiv)</th>
<th>1a (%)</th>
<th>3a (%)</th>
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<tr>
<td>1a</td>
<td>0</td>
<td>Ni(cod)₂/rac-BINAP</td>
<td>97, 4</td>
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<td>2a</td>
<td>0</td>
<td>NiCl₂/dppf, 110 °C</td>
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<td>18</td>
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<tr>
<td>3a</td>
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<td>NiBr₂/diglyme</td>
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<td>21</td>
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<tr>
<td>4a</td>
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<td>none</td>
<td>70, 5</td>
<td>22, 21</td>
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<tr>
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<td>0</td>
<td>Ni(cod)₂</td>
<td>95, 5</td>
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<td>36</td>
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<td>11a</td>
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<td>CaF (2.0)</td>
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<td>12a</td>
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<td>MgBr₂</td>
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<td>6</td>
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<tr>
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<td>96</td>
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<td>14a</td>
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<td>70</td>
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<tr>
<td>16a</td>
<td>Br₂O, 0 °C</td>
<td>AgF (0.5)</td>
<td>79, &lt;5</td>
<td>31</td>
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<tr>
<td>17a</td>
<td>toluene, 0 °C</td>
<td>AgF (0.5)</td>
<td>38, &lt;5</td>
<td>66</td>
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<tr>
<td>18a</td>
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<td>AgF (0.5)</td>
<td>36, &lt;5</td>
<td>62</td>
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<td>19a</td>
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<td>ND, 52</td>
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<td>1 equiv of NiBr₂/PCy₃, 0 °C</td>
<td>AgF (0.5)</td>
<td>73, &lt;5</td>
<td>25</td>
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*Reaction conditions: 0.20 mmol of 1a, 0.30 mmol of Me₃SiMgI, TMEDA 2a (0.35 M in toluene), 20 mol % NiBr₂-diglyme, 20 mol % PCy₃, and 0.15 M THF. A GC yield. *With 5 mol % Ni(cod)₂, 10 mol % rac-BINAP, and toluene for 24 h. With 2 mol % NiCl₂/dppf and 2 mol % dppe for 12 h. After 20 h. *Isolated yield and repeated ~10 times throughout the project. a1a was added after the addition of all other reagents.
resonance energy for benzothiophene (π-rich) 1y is lower than that of naphthalene (80.3 kcal/mol vs 69.8 kcal/mol), and the π-deficient pyridines 3w and 3x have a higher normalized resonance energy per π-electron (β = 0.058) than naphthalene (β = 0.055). Additional coordination from pyridine’s nitrogen may be at play; however, thiophene 3y (β = 0.032) does require AgF. The simple phenyl derivatives 1ad−af underwent cross-coupling reactions with moderate conversion; however, the products were inseparable from the impurities due to the lower boiling point and apolar nature of the products. Phenyl derivatives 1aa−ac (benzene, β = 0.065) require a methoxymethyl (MOE) directing group to facilitate the oxidative addition and to deliver products 3aa−ac in very good yields. Primary methyl ether 1ag gave 91% silylated product 3ag; however, sterically hindered tertiary methyl ether 1ah gave only 28% of cross-coupled product 3ah. In general, most of the heteroarenes and methoxymethyl (MOE)-protected alcohols do not require AgF. Although few allylic substrates afforded excellent conversion in the absence of AgF, some of them still require AgF to improve the conversion.

Unfortunately, alkene 1h did not yield the cross-coupled product. Although alkenes are known to promote nickel-mediated cross-coupling reactions, it has been reported that 1,5-cyclohexadiene (COD) may form an off-cycle nickel species that is ineffective in C–O bond cleavage. Similarly, we also observed the inactivity of Ni(cod)2 (Table 1, entry 5); however, employing 0.1 equiv of COD in the standard reaction still afforded 82% of cross-coupled product 3a. We determined that the inactivity of Ni(cod)2 is due to the unavailability of COD to stabilize the Ni(0) species. With 1 equiv of styrene, the reaction was completely shut down. The formation of volatile silylated byproducts from 1h, styrene, and COD is responsible for the poor conversion. A gradual increase in the amount of COD gradually decreased the yield of 3a (Scheme 2).

As expected, the strategy was successfully extended to enantiospecific silylation of enantiopure alcohols via a two-electron pathway (instead of SET) to afford the cross-coupled product with inversion of stereocchemistry. Under the optimized condition from Table 1, we obtained silylated product 7a with 94% es (Scheme 3). A change in the additive, solvent, or temperature was detrimental to the enantiospecificity. In addition, the scope of the substrates was extended, and the results are summarized in Table 3. Most of the methyl ethers 6 afforded very good enantiospecificity, although a few substrates gave moderate enantiospecificity. Benzothoniophene afforded 70% es; however, the enantiopurity of the corresponding methyl ether was only 35%. The absolute stereochemistry of product 7 was identified via Fleming–Tamao oxidation [5d (Table 3)].

We carried out a radical clock experiment with substrate 6j to identify the loss of enantiospecificity via the formation of a radical intermediate; however, the reaction afforded cross-coupled product 7j in 82% isolated yield, so thus, the homolytic cleavage of the C–OMe bond is unlikely. The possibility of reversible oxidative addition was also examined, and the unreacted/recovered methyl ether 6a did not lose

<table>
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<th>Table 2. Scope of Substrates</th>
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"Reaction conditions: 0.2 mmol of 1a, 0.3 mmol of Me3SiMgCl·TMEDA 2a (0.35 M in toluene), NiBr2·diglyme (10 mol %), PCy3 (10 mol %), AgF, and THF (0.15 M). Toluene instead of THF.

β-Tolueno:THF (4:1). With 5 mol % NiBr2-diglyme and PCy3. With 20 mol % NiBr2-diglyme and PCy3. With 0.24 mmol of 2a. MOE (methoxymethyl) protection instead of methyl, MgBr2 (1.0 equiv), DPEphos (20 mol %), and NiBr2-diglyme (20 mol %). "NMR yield.
enantiopurity (see page 67 of the Supporting Information). In addition, employing KOEt or NaOEt in the standard reaction did not intercept the intermediate nickel complex (Scheme 4) to deliver the corresponding -OEt-substituted product of 6a. These experiments exclude the reversibility of oxidative addition, and a double inversion might be responsible for the loss of enantiospecificity.\(^21\)

Although a detailed mechanistic study is in progress, we propose a mechanism based on the earlier findings.\(^45,60\) Upon mixing NiBr\(_2\) and Me\(_3\)SiMgI, we expect the formation of Ni(0) species; however, the Ni(I) species and the Ni(I)/Ni(III) catalytic cycle cannot be ruled out without further studies. The formed Ni(0) species may form a reversible or irreversible ate complex with Me\(_3\)SiMgI,\(^13\) a further study is in progress to identify the nature of the resting state. Oxidative addition of Ni(0) complex A to the methyl ether leads to intermediate Ni(II) complex B. Subsequent transmetalation with Me\(_3\)SiMgI generates intermediate complex C, which delivers cross-coupled product 3 via reductive elimination. The catalytic role of AgF is being studied in our laboratory, it can act as an oxidant or halide scavenger. The in situ formation of organosilover or bimetallic (M-Ag) complexes cannot be ruled out without further study. They could also act as a Lewis acid.

In summary, we developed nickel-mediated silylation via C(sp\(^3\))−O bond cleavage for the first time. The methodology is compatible with a variety of functional groups, including ketone, acetal, amide, amine, boronic ester, and aryl ether groups. Heteroarenes and simple arenes are also found to be compatible. Sterically bulkier PhMe\(_2\)SiMgBr and Ph\(_2\)MeSiMgBr also afforded the cross-coupled products. Alkenes inhibit the reaction by the formation unwanted byproducts. A radical clock experiment showed that there is no radical intermediate present in the reaction. The methodology was also extended to enantiospecific silylation. The identification of the role of AgF, the actual intermediates, and the mechanistic pathway is currently being pursued in our laboratory.
(36) Apeloig, Y. The chemistry of organic silicon compounds; Wiley, 1989; p 1700.
(43) Greenhalgh, M. Iron-catalyzed hydroisilylation of alkynes and alkynes; Springer International Publishing: Cham, Switzerland, 2016; pp 33–83.


The moderate yield can be attributed to the use of THF instead of toluene during the preparation of PhMe₂SiMgBr.


George, P. Critique of the resonance energy concept with particular reference to nitrogen heterocycles, especially porphyrins. Chem. Rev. 1975, 75, 85–111.


Synthesis of enantiopure cinnamic and pyridyl ethers was not successful.