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

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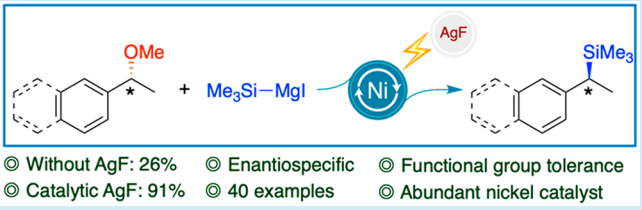
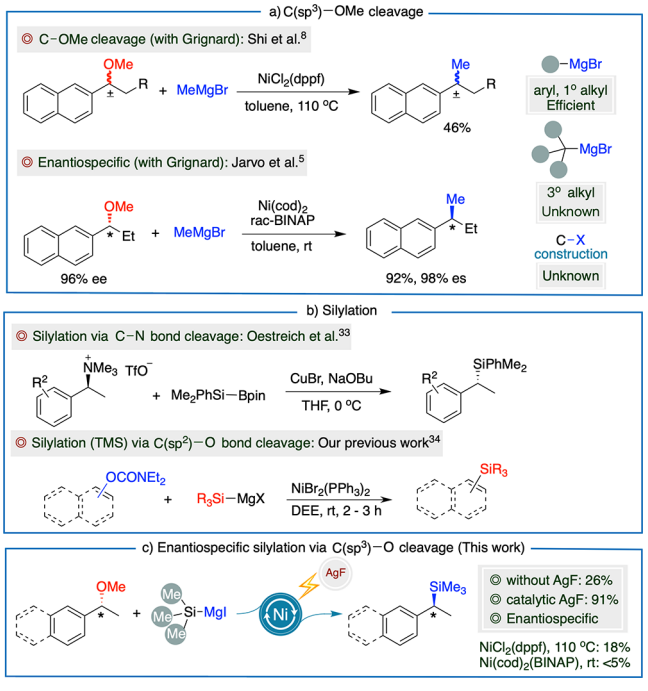
ABSTRACT: Benzylic stereocenters are found in bioactive and drug molecules, as enantiopure benzylic alcohols have been used to build such a stereogenic center, but are limited to the construction of a C−C bond. Silylation of alkyl alcohols has the potential to build bioactive molecules and building blocks; 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(sp^3)−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(sp^3)−O bond cleavage] in cross-coupling reactions mostly rely on the conversion of alcohols into corresponding esters[10−12] 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 η^3-benzylnickel complexes,[17,24−30] which is favored by the molecules having extended conjugation and lower Dewar's energy (aromaticity).[31−33]

Scheme 1. Cross-Coupling Reactions via C−O Bond Cleavage



Despite the success of Grignard reagents (unhindered) as a coupling partner in C(sp^3)−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 disciplines[34−36] 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).[37−44] Recently, for the first time, we introduced an economical Me_3SiMgI (directly synthesized from TMSI) in cross-coupling reactions [C(sp^2)−OCb bond cleavage] for the synthesis of $ArSiMe_3$,[45] a useful organosilane for further synthetic transformations (Scheme 1b).

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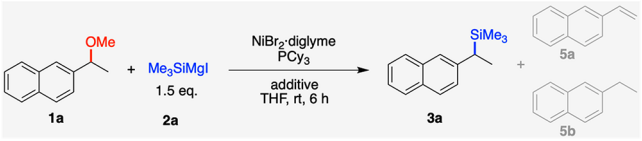
In accordance with our interest in nickel-mediated cross-coupling reactions,[45,46] we were further interested in capitalizing on the application of Me_3SiMgI in enantiospecific cross-coupling reactions via C(sp^3)−O bond cleavage. We were optimistic that the methodology developed by Shi,[17] Jarvo,[11,18−21] and others[10,47,48] (Scheme 1a) could be borrowed for the use of Me_3SiMgI as the coupling partner; however, these literature protocols were not amenable to Me_3SiMgI, and traces of the cross-coupled product were observed (Scheme 1c), highlighting the limitation of these literature strategies. The commonly employed silylating agent $PhMe_2SiBpin$[13,49] also failed to furnish the desired product. As a result, we developed an AgF-assisted nickel catalysis that results in the complete conversion of benzylic methyl ethers. The methodology was also extended to enantiospecific silylation.

We commenced our study with 2-(1-methoxyethyl)-naphthalene **1a** and Me_3SiMgI **2a** [prepared from TMSI and Mg (stored at room temperature)]. When benzyl methyl ether **1a** was subjected to the previous methods,[17,18] a minimal amount of cross-coupled product **3a** was observed (Table 1, entries 1 and 2). Subsequently, a library of nickel catalysts and ligands were screened, and the selected entries are listed in Table 1. Both $NiBr_2$·glyme and $NiBr_2$·diglyme were equally effective, affording the cross-coupled product **3a** in 21% and 22% yields, respectively, with traces (<5%) of eliminated and reduced byproducts **5a** and **5b** (entries 3 and 4, respectively). While $NiCl_2$·diglyme afforded product **3a** in 12% yield (entry 6), $Ni(cod)_2$ completely shut down the reaction (discussed below). The use of a bidentate phosphine ligand (dcype) 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, affoded 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 Et_2O or toluene had a detrimental effect on the yield (entries 16 and 17). No reaction was observed when NiF_2 was employed in place of $NiBr_2$·diglyme (entry 18). Decreasing the amount of Me_3SiMgI also decreased the yield (entry 19). Employing stoichiometric $NiBr_2$·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 % $NiBr_2$·diglyme/PCy_3 without a significant compromise in the yield (entry 14).

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from above	additive (equiv)	1a, 5b (%)[b]	3a (%)[b]
1[c]	$Ni(cod)_2$/*rac*-BINAP	–	97, 4	<5
2[d]	$NiCl_2$/dppf, 110 °C	–	62, 20	18
3	$NiBr_2$·glyme	–	71, 5	21
4	none	–	70, 5	22, 21[e]
5	$Ni(cod)_2$	–	95, <5	<5
6	$NiCl_2$·diglyme	–	82, 0	12
7	dcype	–	74, 5	20
8	none	AgF (2.0)	28, <5	66
9	none	AgBr (2.0)	50, 19	24
10	none	LiF (2.0)	55, 10	36
11	none	CsF (2.0)	57, 8	34
12	none	$MgBr_2$	78, 14	6
13	0 °C	AgF (2.0)	ND, <5	96
14	0 °C	AgF (0.5)	<5, <5	91, 88[f]
15	0 °C	AgF (0.2)	20, 7	70
16	Et_2O, 0 °C	AgF (0.5)	79, <5	31
17	toluene, 0 °C	AgF (0.5)	38, <5	66
18	NiF_2, 0 °C	–	96, <5	<5
19	1.0 equiv of **2a**, 0 °C	AgF (0.5)	36, <5	62
20	1 equiv of $NiBr_2$·PCy_3, 0 °C	–	ND, 52	44
21[g]	0 °C	AgF (0.5)	73, <5	25

[a]Reaction conditions: 0.20 mmol of **1a**, 0.30 mmol of Me_3SiMgI·TMEDA **2a** (0.35 M in toluene), 20 mol % $NiBr_2$·diglyme, 20 mol % PCy_3, additive, and 0.15 M THF. [b]GC yield. [c]With 5 mol % $Ni(cod)_2$, 10 mol % *rac*-BINAP, and toluene for 24 h. [d]With 2 mol % $NiCl_2$/dppf and 2 mol % dppf for 12 h. [e]After 20 h. [f]isolated yield and repeated ∼10 times throughout the project. [g]**1a** was added after the addition of all other reagents.

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 sterically bulkier $PhMe_2SiMgBr$ and $Ph_2MeSiMgBr$ also afforded the corresponding products **3ga** and **3gb** in good yields.[50] A broad range of functional groups were well tolerated, which provides an opportunity for further derivatization of the cross-coupled products. Aryl ethers [C(sp^2)−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**), CF_3 (**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;[51] 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)[31−33,52−57] may have a profound impact on the outcome of the reactivity. For example, the empirical

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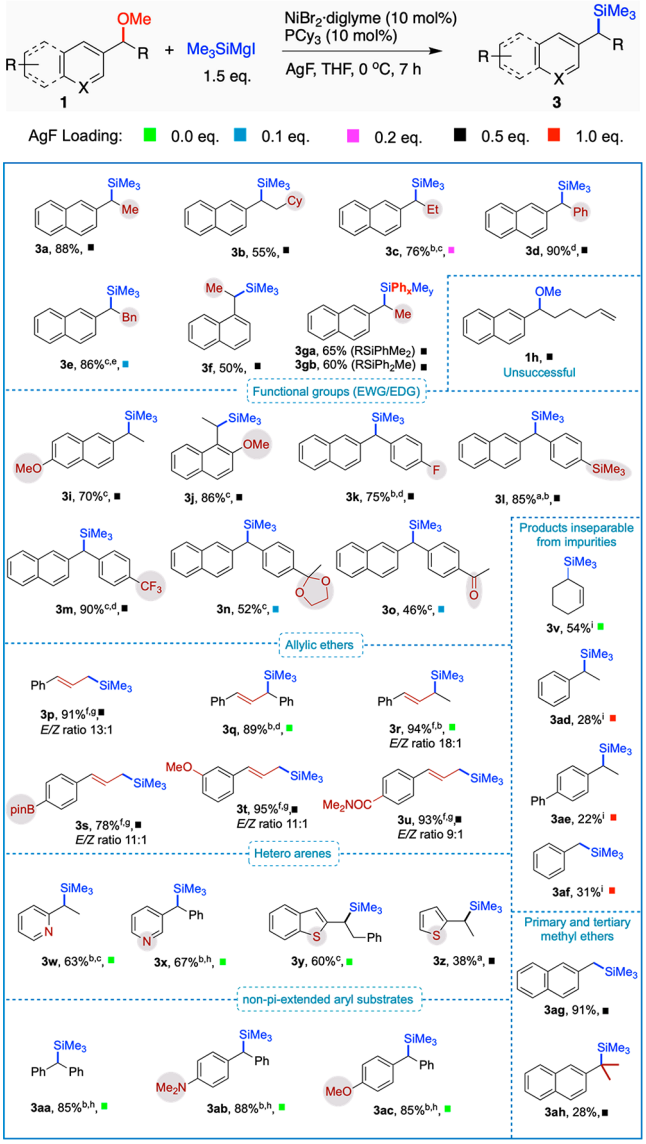
Table 2. Scope of Substrates[a]

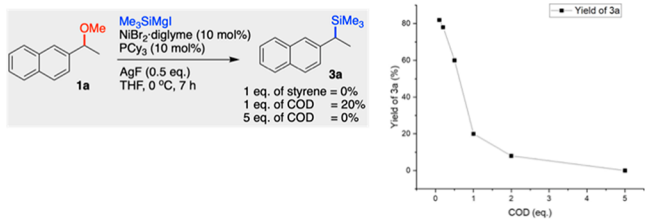


[a]Reaction conditions: 0.2 mmol of **1a**, 0.3 mmol of Me_3SiMgI·TMEDA **2a** (0.35 M in toluene), $NiBr_2$·diglyme (10 mol %), PCy_3 (10 mol %), AgF, and THF (0.15 M). [b]Toluene instead of THF. [c]With 20 mol % $NiBr_2$·diglyme and PCy_3. [d]With 15 mol % $NiBr_2$·diglyme and PCy_3. [e]Toluene:THF (4:1). [f]With 5 mol % $NiBr_2$·diglyme and PCy_3. [g]With 0.24 mmol of **2a**. [h]MOE (methoxyethyl) protection instead of methyl, $MgBr_2$ (1.0 equiv), DPEphos (20 mol %), and $NiBr_2$·diglyme (20 mol %). [i]NMR yield.

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 methoxyethyl (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 methoxyethyl (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.

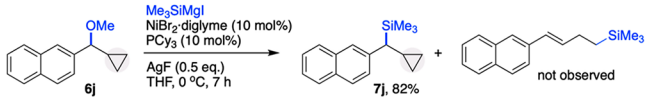
Unfortunately, alkene **1h** did not yield the cross-coupled product. Although alkenes are known to promote nickel-mediated cross-coupling reactions,[58,59] it has been reported that 1,5-cyclohexadiene (COD) may form an off-cycle nickel species that is ineffective in C–O bond cleavage.[60] Similarly, 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).

Scheme 2. Alkenes Inhibit the Reaction



As expected, the strategy was successfully extended to enantiospecific silylation of enantiopure alcohols via a two-electron pathway (instead of SET[3]) to afford the cross-coupled product with inversion of stereochemistry.[20] 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. Benzothiophene afforded 70% es; however, the enantiopurity of the corresponding methyl ether was only 35%.[61] The absolute stereochemistry of product **7** was identified via Fleming–Tamao oxidation [**5d** (Table 3)].

Scheme 3. Radical Clock Experiment



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

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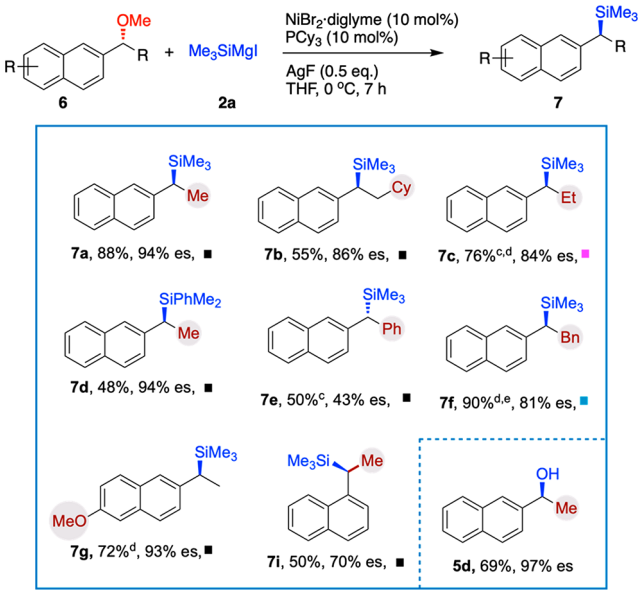
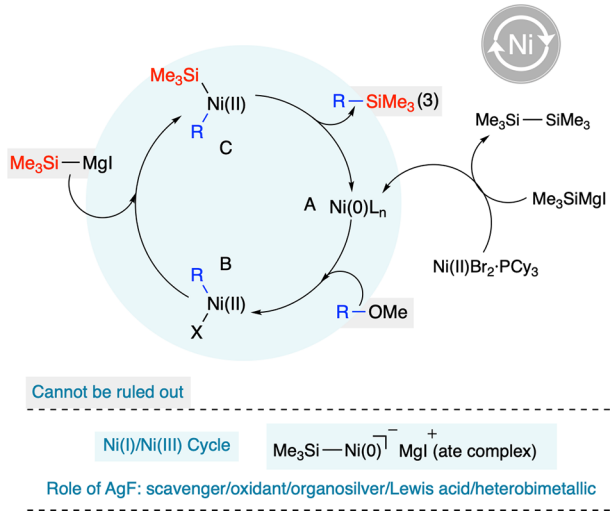
Table 3. Enantiospecific Silylation[a,b]



[a]With 0.2 mmol of **6**, 0.3 mmol of **2a**, Me_3SiMgI (0.35 M in toluene), $NiBr_2$·diglyme (10 mol %), PCy_3 (10 mol %), AgF (0.5 equiv), and THF (0.15 M). [b]GC yield. [c]Toluene instead of THF. [d]With 20 mol % $NiBr_2$.diglyme and PCy_3. [e]Toluene:THF (4:1).

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)

Scheme 4. Mechanistic Hypothesis



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_3SiMgI, 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_3SiMgI;[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_3SiMgI 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 organosilver 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 $PhMe_2SiMgBr$ and $Ph_2MeSiMgBr$ 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04316.

Additional observations and data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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