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$B(C_6F_5)_3$-Catalyzed C−H Alkylation of *N*-Alkylamines Using Silicon Enolates without External Oxidant

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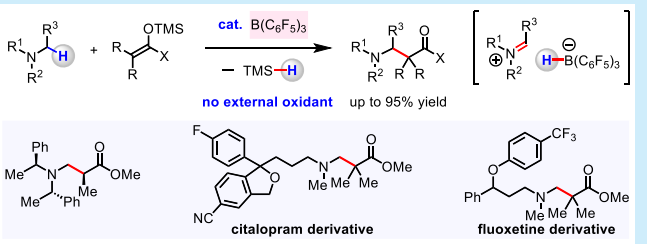
Supporting Information

ABSTRACT: An efficient method for the coupling of *N*-alkylamines with silicon enolates to generate *β*-amino carbonyl compounds is disclosed. These reactions proceed by activation of *α*-amino C−H bonds by $B(C_6F_5)_3$, which likely generates a "frustrated" acid/base complex in the presence of large *N*-alkylamines. The transformation requires no external oxidant and releases hydrosilane as a byproduct. The utility of this method is demonstrated in the late-stage functionalization of bioactive molecules such as citalopram, atomoxetine, and fluoxetine.



Enolate nucleophiles are commonly employed in addition reactions to C═N bonds (i.e., Mannich-type processes), since this process reliably generates several classes of important *β*-amino carbonyl molecules.[1−5] In these reactions, imine or iminium ion intermediates are either prepared in situ or in a separate operation through condensation of an amine and a carbonyl compound, *α*-fragmentation of iminium ion precursors, or oxidation of tertiary amines.[1−5] The latter method (i.e., oxidative Mannich-type reactions; see Figure 1A) employs organometallic catalysts (e.g., Ru, Rh, Cu, V complexes) and stoichiometric oxidants (e.g., *t*-BuOOH, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, O_2) to convert *N*-alkylamines (**I**) to their corresponding iminium ions, which then react with various enolate equivalents (**II**).[2,3] Such a process, while notable, requires external oxidants, and the scope of amines is largely confined to tetrahydroisoquinoline and *N*,*N*-dimethylaniline derivatives.[2,3]

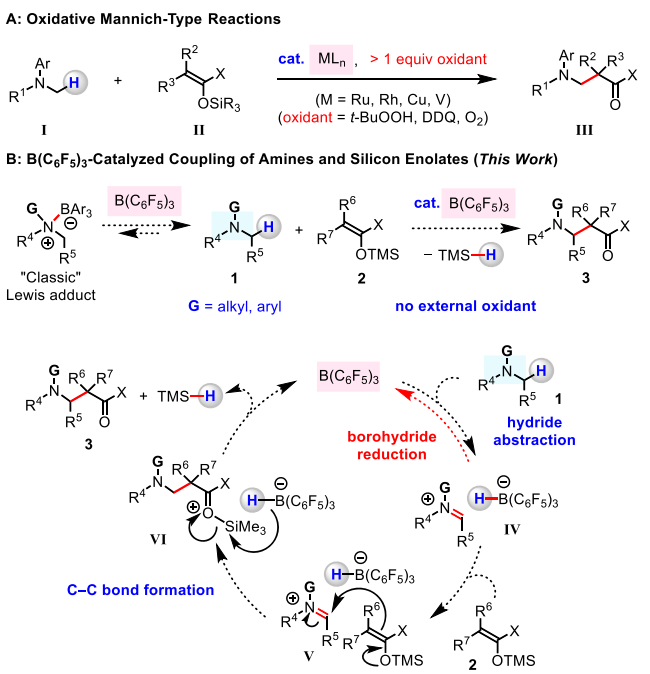


Figure 1. Coupling of *N*-alkylamines and silicon enolates.

We surmised that an attractive alternative to the oxidative Mannich-type reaction would entail rupture of an *α*-amino C−H bond of an *N*-alkylamine (**1**) by a boron-based Lewis acid (Figure 1B). Hydride abstraction from an *N*-alkylamine by organoborane compounds to furnish an iminium ion (**IV**) has been previously investigated.[6−12] An important advantage of this approach is that an array of *N*-alkylamines (including those that lack the fused *N*-aryl groups) can be converted to **IV** without the use of an external oxidant.[6−10] Reaction of **IV** with an enol equivalent (**2**) would forge a C−C bond (**V**), subsequently releasing the *β*-amino carbonyl product **3**, the Lewis acid catalyst, and a hydrosilane as an environmentally benign byproduct (**VI**). Here, we disclose the results of our studies regarding the realization of the above catalytic cycle.

To initiate our investigations, we needed an appropriate combination of acid catalyst and amine substrate that is capable of undergoing hydride transfer, as opposed to forming a stable acid/base adduct. Accordingly, we considered pairing the strongly Lewis acidic $B(C_6F_5)_3$ with a hindered amine (Scheme 1). We first probed the ability of $B(C_6F_5)_3$ to convert a *N*,*N*-dimethylaniline to its derived iminium ion, which could then be trapped by a silyl ketene acetal (Scheme 1). Treatment of *N*,*N*-dimethylaniline (**1a**) and 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (**2a**) with 20 mol % $B(C_6F_5)_3$ afforded **3a** in 31% yield (DCE, 22 °C). We reasoned that

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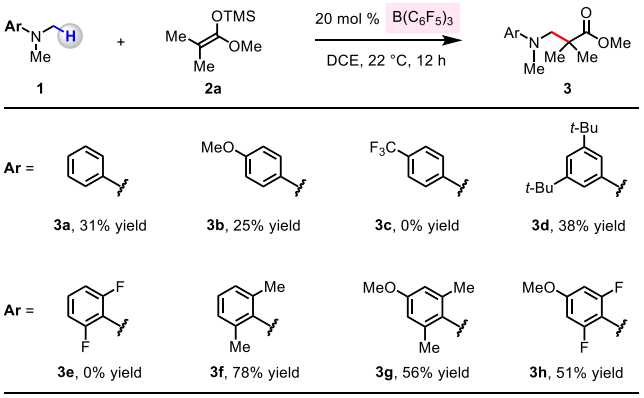
Scheme 1. Evaluation of *N*-Aryl Substituents[a,b]



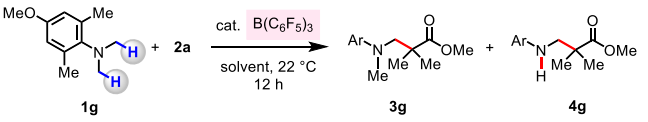
[a]Conditions: *N*,*N*-dimethylaniline (0.1 mmol), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (0.2 mmol), $B(C_6F_5)_3$ (20 mol %), dichloroethane (0.25 mL), under N_2, 22 °C, 12 h. [b]Yields were determined by ^1H NMR analysis of unpurified product mixtures with mesitylene as the internal standard. See the Supporting Information for details.

electron-donating *N*-aryl substituents might improve the efficiency of $B(C_6F_5)_3$-catalyzed hydride abstraction by enhancing the hydride donor ability of the α-amino C−H bond and by stabilizing the resultant iminium ion intermediate. In the event, the reaction with electron-donating *para*-methoxy-substituted **1b** afforded **3b** in 25% yield. None of the desired product was observed with electron-deficient *para*-trifluoromethylphenyl-substituted **1c**. With 3,5-di-*tert*-butyl-substituted **1d**, the C−C bond forming product **3d** was obtained in 38% yield.

To evaluate the effect of using more-hindered amines, we tested a range of *ortho*-disubstituted anilines. Whereas 2,6-difluoro-*N*,*N*-dimethylaniline (**1e**) gave none of the Mannich-type product, reaction of the larger and more electron-rich *N*,*N*-2,6-tetramethylaniline (**1f**) resulted in the formation of **3f** in 78% yield, which marks a considerable improvement in efficiency. Encouraged by this finding, we studied the reaction with 4-methoxy-*N*,*N*-2,6-tetramethylaniline (**1g**), which gave **3g** in 56% yield; the *N*-aryl substituent in **3g** was removed under oxidative conditions.[13] By using the less-hindered and more-electron-deficient 2,6-difluoro-4-methoxyphenyl-substituted **1h**, we were able to obtain **3h** in 51% yield.

With the aim to further increase efficiency, we set out to identify the optimal conditions with the transformation that affords **3g**, serving as the representative process (Table 1). There were no products formed without any $B(C_6F_5)_3$ present (Table 1, entry 2). In some instances (Table 1, entries 1 and 3−9), secondary amine **4g** was also obtained, probably through the cleavage of the N−Me bond, because of the reaction of in-situ-generated iminium ion with water. Among the *N*,*N*-dimethylanilines evaluated, only in the cases of *ortho*-dimethyl-substituted **1f** and **1g** were the latter type of byproducts formed. At lower catalyst loading (10 mol %), loss of the methyl unit was minimized and **3g** was formed more selectively in 71% yield (Table 1, entry 3). Next, we examined the effect of using ethereal solvents to investigate if these more polar solvents could facilitate the Mannich reaction, which involves ionic intermediates. In diethyl ether, and with 10 mol % catalyst loading, **3g** was formed in 83% yield, but with 5.0 mol % catalyst, there was a considerable diminution in efficiency (22% yield; see Table 1, entries 4 and 5). With THF

Table 1. Evaluation of Various Reaction Parameters[a,b]



entry	Lewis acid	catalyst loading (%)	solvent	Yield (%) 3g	4g
1	$B(C_6F_5)_3$	20	DCE	56	35
2	none	0	DCE	0	0
3	$B(C_6F_5)_3$	10	DCE	71	22
4	$B(C_6F_5)_3$	10	Et_2O	83	17
5	$B(C_6F_5)_3$	5.0	Et_2O	22	<5
6	$B(C_6F_5)_3$	10	THF	38	<5
7	$B(C_6F_5)_3$	10	toluene	75	21
8	$B(C_6F_5)_3$	10	benzene	81	16
9	$B(C_6F_5)_3$	5.0	benzene	>95	<5
10	$BF_3{\cdot}OEt_2$	10	benzene	0	0
11	BPh_3	10	benzene	0	0

[a]Conditions: 4-methoxy-*N*,*N*,2,6-tetramethylaniline (0.1 mmol), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (0.2 mmol), Lewis acid, solvent (0.25 mL), under N_2, 22 °C, 12 h. [b]Yields were determined by ^1H NMR analysis of unpurified product mixtures with mesitylene as the internal standard. See the Supporting Information for details.

as the solvent, **3g** was obtained in 38% yield (Table 1, entry 6). Use of less-polar aromatic hydrocarbons such as benzene and toluene as the solvent and with 10 mol % $B(C_6F_5)_3$ led to the formation of **3g** in 81% and 75% yield, respectively (Table 1, entries 7 and 8). With benzene and 5.0 mol % $B(C_6F_5)_3$ loading, **3g** was obtained with high selectivity (<5% of **4g**) and in >95% yield (Table 1, entry 9). Use of less-hindered $BF_3{\cdot}OEt_2$ or less-acidic BPh_3 proved to be ineffective (Table 1, entries 10 and 11), providing support for the hypothesis that acidic $B(C_6F_5)_3$, along with sterically demanding and electron-rich *N*-alkylamines, represent the most effective catalyst/substrate combination.

A significant assortment of *N*,*N*-dialkylanilines may be used (Scheme 2). Reaction of *N*,*N*-dimethyl-substituted **1g** afforded **3g** in 80% yield after purification (5.0 mol % $B(C_6F_5)_3$). With *N*-benzyl and *N*-cyclopropylmethyl-substituted substrates, **3i** and **3j** were isolated in 64% and 56% yield, respectively; thus, in these instances, α-amino methylene C−H bonds remained intact. α-Amino C−H bond of *N*-arylpyrrolidine **1k** could be converted to a C−C bond by the use of 10 mol % $B(C_6F_5)_3$, affording **3k** in 90% yield. 1-(4-Methoxy-2,6-dimethylphenyl)-pyrrolidin-3-ol (**1l**), possessing an unprotected hydroxyl group, furnished the desired products in their *O*-silylated forms **3l** (31% yield, 4.0:1 *trans*:*cis*) and **3m** (23% yield, >20:1 *trans*:*cis*).[14] Reaction with α-methyl-substituted pyrrolidine delivered **3n** in 70% yield and *trans*:*cis* of 7.0:1. When *N*-arylpiperidine **1o** was used, **3o** was isolated in 38% yield with the reaction being performed at 50 °C. A series of trialkyl-substituted amines that lack the fused *N*-aryl group were coupled efficiently with ((1-methoxyprop-1-en-1-yl)oxy)-trimethylsilane (**2b**), leading to the formation of **5a**−**5d** (88%−95% yield). Reaction of methyl (*S*)-3-(bis((*S*)-1-phenylethyl)amino)-2-methylpropanoate with **2b** delivered **5d** as a 1.6:1 mixture of diastereomers, which were separable through silica gel chromatography, allowing us to produce the β-amino esters in enantiomerically pure form (see the Supporting Information for details).

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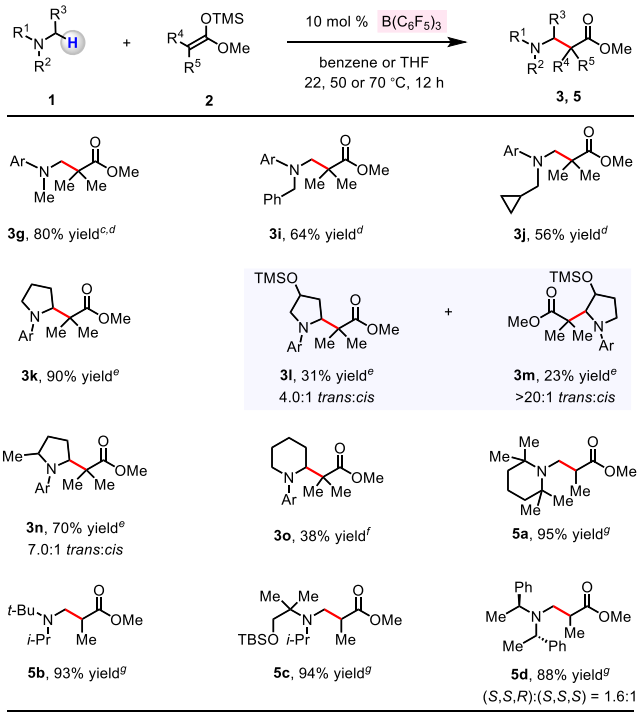
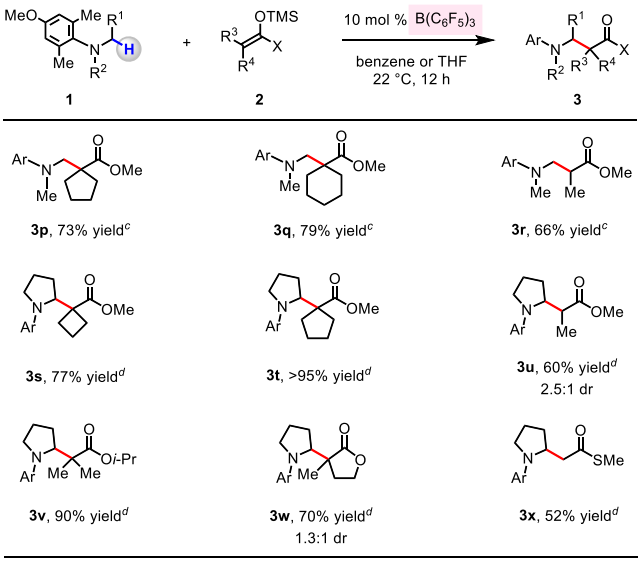
Scheme 2. Evaluation of Different *N*-Alkylamines[a,b]



[a]Conditions: *N*,*N*-dialkylaniline (0.2 mmol), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (0.4 mmol), $B(C_6F_5)_3$ (10 mol %), solvent (0.5 mL), under N_2, 22 °C, 12 h. [b]Yield of purified products. [c]$B(C_6F_5)_3$ (5.0 mol %) was used. [d]Benzene was used. [e]THF was used. [f]Benzene was used and reaction was performed at 50 °C. [g]Benzene was used and reaction was performed at 70 °C. See the Supporting Information for details.

Next, we explored the range of silicon enolates (Scheme 3). Cyclopentyl- and cyclohexyl-substituted variants reacted with **1g** to give **3p** and **3q** in 73% and 79% yield, respectively. The less sterically demanding ketene acetal (**2b**) afforded **3r** in 66% yield. A broader range of ketene acetals proved to be applicable to reactions with *N*-arylpyrrolidine. α-Cycloalkylesters and methyl propionate could thus be installed, furnishing the corresponding 2-substituted pyrrolidine products **3s**−**3u** in 60% to >95% yield. Nucleophilic partners derived from isopropyl isobutyrate and 3-methyldihydrofuran-2(3*H*)-one were found to be compatible, as indicated by efficient synthesis of **3v** (90% yield) and **3w** (70% yield, 1.3:1 dr). In addition to silyl ketene acetals, trimethyl((1-(methylthio)vinyl)oxy)silane could be used, as the transformation affording β-amino thioester **3x** illustrates (52% yield).

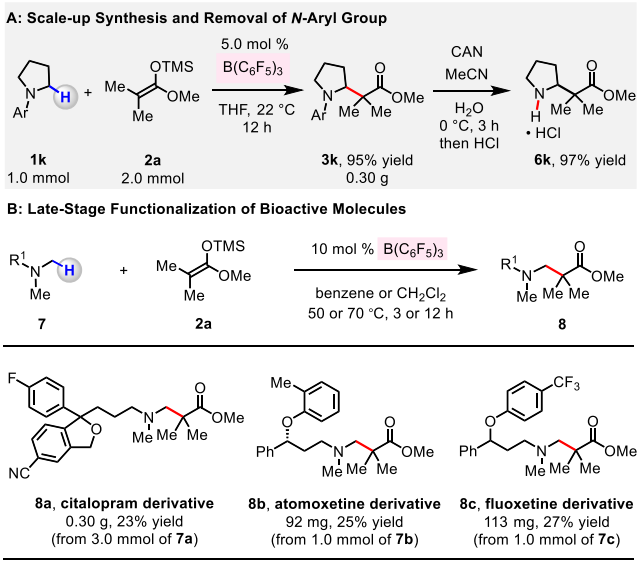
Scheme 3. Evaluation of Various Silicon Enolates[a,b]



[a]Conditions: *N*,*N*-dialkylaniline (0.2 mmol), silicon enolate (0.4 mmol), $B(C_6F_5)_3$ (10 mol %), solvent (0.5 mL), under N_2, 22 °C, 12 h. [b]Yield of purified products. [c]Benzene was used. [d]THF was used. See the Supporting Information for details.

The catalytic protocol is scalable, as highlighted by the 1.0 mmol synthesis of **3k**, which was obtained in 95% yield by the use of 5.0 mol % $B(C_6F_5)_3$ (Scheme 4A). The 4-methoxy-2,6-dimethylphenyl group of **3k** could be readily removed under oxidative conditions to deliver **6k** in 97% yield.[13] This method is applicable in the late-stage functionalization of bioactive molecules containing an *N*-alkylamine moiety such as citalopram (antidepressant), atomoxetine (treatment for ADHD), and fluoxetine (antidepressant) (Scheme 4B). *N*-Methyl C−H bonds of these drug compounds were selectively converted to C−C bonds to afford a useful amount of β-amino carbonyl compounds **8a** (23% yield, 0.30 g), **8b** (25% yield, 92 mg), and **8c** (27% yield, 113 mg).

Scheme 4. Scale-Up Synthesis and Late-Stage Functionalization of Bioactive Molecules



[a]See the Supporting Information for details.

In summary, we have developed a catalytic method for a $B(C_6F_5)_3$-catalyzed C−C bond forming process that provides access to an assortment of β-amino carbonyl compounds. Acyclic as well as cyclic amines may be used as pro-electrophiles. On the basis of our mechanistic hypotheses, it should be possible to develop an enantioselective version of this C−C bond-forming reaction through design of a chiral Lewis acid catalyst,[15] and also to expand the scope of nucleophiles. Investigations along these lines are currently underway.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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