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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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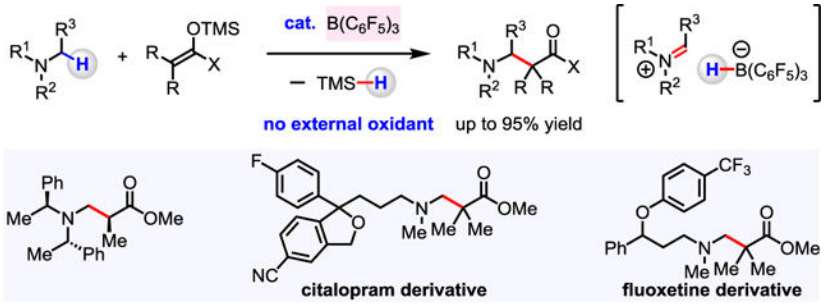
Abstract

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 by-product. The utility of this method is demonstrated in the late-stage functionalization of bioactive molecules such as citalopram, atomoxetine, and fluoxetine.

Graphical Abstract



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: 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]

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

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]

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 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 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 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 (entry 2).

In some instances (entries 1 and 3–9), secondary amine **4g** was also obtained, probably through the cleavage of the N–Me bond due to 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 (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, entries 4–5). With THF as the solvent, **3g** was obtained in 38% yield (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 (entries 7–8). 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 (entry 9). Use of less hindered BF_3•OEt_2 or less acidic BPh_3 proved to be ineffective (entries 10–11), 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).

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).

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).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements.

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References

(1). For reviews on various types of Mannich-type reactions, see:(a)Kobayashi S.; Ishitani H Catalytic Enantioselective Addition to Imines. Chem. Rev. 1999, 99, 1069–1094. [PubMed: 11749440] (b)Córdova A The Direct Catalytic Asymmetric Mannich Reaction. Acc. Chem. Res. 2004, 37, 102–112. [PubMed: 14967057] (c)Sodeoka M; Hamashima Y Development of Catalytic Enantioselective Reactions via Palladium Enolates as Key Intermediates. Bull. Chem. Soc. Jpn. 2005, 78, 941–956.(d)Wenzel AG; Jacobsen EN in Enantioselective Synthesis of beta-Amino Acids, Juaristi E, Soloshonok V, Eds.; Wiley-VCH: New York, 2005; Chapter 4.(e)Shibasaki M; Matsunaga S Metal/linked-BINOL complexes: Applications in direct catalytic asymmetric Mannich-type reactions. J. Organomet. Chem. 2006, 691, 2089–2100.(f)Ting A; Schaus SE Organocatalytic Asymmetric Mannich Reactions: New Methodology, Catalyst Design, and Synthetic Applications. Eur. J. Org. Chem. 2007, 2007, 5797–5815.(g)Verkade JMM; Hemert L. J. C.v..; Quaedflieg PJLM.; Rutjes FPJT Organocatalysed asymmetric Mannich Reaction. Chem. Soc. Rev. 2008, 37, 29–41. [PubMed: 18197331] (h)Weiner B; Szymański W; Janssen DB; Minnaard AJ; Feringa BL Recent advances in the catalytic asymmetric synthesis of β-amino acids. Chem. Soc. Rev. 2010, 39, 1656–1691. [PubMed: 20419214] (i)Karimi B; Enders D; Jafari E Recent Advances in Metal-Catalyzed Asymmetric Mannich Reactions. Synthesis 2013, 45, 2769–2812.(j)Shirakawa S; Maruoka K Recent Developments in Asymmetric Phase-Transfer Reactions. Angew. Chem., Int. Ed. 2013, 52, 4312–4348.

(2). For selected examples of oxidative Mannich-type reactions, see:(a)Catino AJ; Nichols JM; Nettles BJ; Doyle MP The Oxidative Mannich Reaction Catalyzed by Dirhodium Caprolactamate. J. Am. Chem. Soc. 2006, 128, 5648–5649. [PubMed: 16637627] (b)Sureshkumar D; Sud A; Klussmann M Aerobic Oxidative Coupling of Tertiary Amines with Silyl Enolates and Ketene Acetals. Synlett 2009, 2009, 1558–1561.(c)Chu L; Zhang X; Qing F-L CuBr-Catalyzed Oxidative

Difluoromethylation of Tertiary Amines with Difluoroenol Silyl Ethers. Org. Lett. 2009, 11, 2197–2200. [PubMed: 19378964] (d)Sud A; Sureshkumar D; Klussmann M Oxidative coupling of amines and ketones by combined vanadium- and organocatalysis. Chem. Commun. 2009, 3169–3171.(e)Rueping M; Vila C; Koenigs RM; Poscharny K; Fabry DC Dual catalysis: combining photoredox and Lewis base catalysis for direct Mannich reactions. Chem. Commun. 2011, 47, 2360–2362.(f)Boess E; Sureshkumar D; Sud A; Wirtz C; Farès C; Klussmann M Mechanistic Studies on a Cu-Catalyzed Aerobic Oxidative Coupling Reaction with N-Phenyl Tetrahydroisoquinoline: Structure of Intermediates and the Role of Methanol As a Solvent. J. Am. Chem. Soc. 2011, 133, 8106–8109. [PubMed: 21561084] (g)Boess E; Schmitz C; Klussmann M A Comparative Mechanistic Study of Cu-Catalyzed Oxidative Coupling Reactions with N-Phenyltetrahydroisoquinoline. J. Am. Chem. Soc. 2012, 134, 5317–5325. [PubMed: 22338603] (h)Ratnikov MO; Doyle MP Mechanistic Investigation of Oxidative Mannich Reaction with tert-Butyl Hydroperoxide. The Role of Transition Metal Salt. J. Am. Chem. Soc. 2013, 135, 1549–1557. [PubMed: 23298175]

(3). For reviews of amine functionalization by catalytic oxidation of α-amino C–H bonds, see: (a)Murahashi S; Zhang D. Ruthenium catalyzed biomimetic oxidation in organic synthesis inspired by cytochrome P-450. Chem. Soc. Rev. 2008, 37, 1490–1501. [PubMed: 18648675] (b)Li C-J Cross-Dehydrogenative Coupling (CDC): Exploring C–C Bond Formations beyond Functional Group Transformations. Acc. Chem. Res. 2009, 42, 335–344. [PubMed: 19220064] (c)Girard SA; Knauber T; Li C-J The Cross-Dehydrogenative Coupling of Csp3–H Bonds: A Versatile Strategy for C–C Bond Formations. Angew. Chem., Int. Ed. 2014, 53, 74–100.

(4). For recent advances of oxidant-free Mannich-type reactions through α-amino C–H functionalization, see:(a)Chen W.; Seidel D The Redox-Mannich Reaction. Org. Lett. 2014, 16, 3158–3161. [PubMed: 24857691] (b)Ma L; Seidel D Intramolecular Redox-Mannich Reactions: Facile Access to the Tetrahydroprotoberberine Core. Chem. Eur. J. 2015, 21, 12908–12913. [PubMed: 26220197] (c)Chen W; Seidel D Redox-Annulation of Cyclic Amines and β-Ketoaldehydes. Org. Lett. 2016, 18, 1024–1027. [PubMed: 26895555]

(5). (a)Chan JZ; Yao W; Hastings BT; Lok CK; Wasa M Direct Mannich-Type Reactions Promoted by Frustrated Lewis Acid/Bronsted Base Catalysts. Angew. Chem., Int. Ed. 2016, 55, 13877–13881. (b)Shang M; Cao M; Wang Q; Wasa M Enantioselective Direct Mannich-Type Reaction Catalyzed by Frustrated Lewis Acid/Brønsted Base Complexes. Angew. Chem., Int. Ed. 2017, 56, 13338–13341.

(6). For reviews of frustrated Lewis pair chemistry, see:(a)Rokob TA.; Pápai I. Hydrogen Activation by Frustrated Lewis Pairs: Insights from Computational Studies. Top. Curr. Chem. 2013, 334, 157–211. [PubMed: 23138687] (b)Ashley AE; O'Hare D Top. Curr. Chem. 2013, 334, 191–218. [PubMed: 23114497] (c)Feng X; Du H Metal-free asymmetric hydrogenation and hydrosilylation catalyzed by frustrated Lewis pairs. Tetrahedron Lett. 2014, 55, 6959–6964.(d)Stephan DW; Erker G Frustrated Lewis Pair Chemistry: Development and Perspectives. Angew. Chem., Int. Ed. 2015, 54, 6400–6441.(e)Stephan DW Frustrated Lewis Pairs. J. Am. Chem. Soc. 2015, 137, 10018–10032. [PubMed: 26214241] (f)Oestreich M; Hermeke J; Mohr J A unified survey of Si–H and H–H bond activation catalysed by electron-deficient boranes. Chem. Soc. Rev. 2015, 44, 2202–2220. [PubMed: 25679769] (g)Stephan DW The broadening reach of frustrated Lewis pair chemistry. Science 2016, 354, aaf7229.

(7). For organoborane-mediated hydride abstraction from N-alkylamines, see:(a)Millot N.; Santini CC.; Fenet B.; Basset JM. Formation and Characterization of Zwitterionic Stereoisomers from the Reaction of B(C6F5)3 and NEt2Ph: (E)- and (Z)- [EtPhN+=CHCH2–B–(C6F5)3]. Eur. J. Inorg. Chem. 2002, 3328–3335.(b)Focante F; Mercandelli P; Sironi A; Resconi L Complexes of tris(pentafluorophenyl)boron with nitrogen-containing compounds: Synthesis, reactivity and metallocene activation. Coord. Chem. Rev. 2006, 250, 170–188.(c)Farrell JM; Heiden ZM; Stephan DW Metal-Free Transfer Hydrogenation Catalysis by B(C6F5)3. Organometallics 2011, 30, 4497–4500.(d)Schwendemann S; Fröhlich R; Kehr G; Erker G Intramolecular frustrated N/B lewis pairs by enamine hydroboration. Chem. Sci. 2011, 2, 1842–1849.(e)Chen J; Chen EX-Y Reactivity of Amine/E(C6F5)3 (E = B, Al) Lewis Pairs toward Linear and Cyclic Acrylic Monomers: Hydrogenation vs. Polymerization. Molecules 2015, 20, 9575–9590. [PubMed: 26016548] (f)Chen G-Q; Kehr G; Daniliuc CG; Bursch M; Grimme S; Erker G Intermolecular Redox-Neutral Amine C–H Functionalization Induced by the Strong Boron Lewis Acid

B(C6F5)3 in the Frustrated Lewis Pair Regime. Chem. Eur. J. 2017, 23, 4723–4729. [PubMed: 28164392]

(8). For B(C6F5)3-catalyzed dehydrogenation of N-heterocycles, see:(a)Maier AFG.; Tussing S.; Schneider T.; Flörke U.; Qu A-W.; Grimme S.; Paradies J. Frustrated Lewis Pair Catalyzed Dehydrogenative Oxidation of Indolines and Other Heterocycles. Angew. Chem., Int. Ed. 2016, 55, 12219–12223.(b)Kojima M; Kanai M Tris(pentafluorophenyl)borane-catalyzed Acceptorless Dehydrogenation of N-Heterocycles. Angew. Chem., Int. Ed. 2016, 55, 12224–12227.

(9). For organoborane-catalyzed allylic C–H abstraction, see:(a)Chatterjee I.; Oestreich M. B(C6F5)3-Catalyzed Transfer Hydrogenation of Imines and Related Heteroarenes Using Cyclohexa-1,4-dienes as a Dihydrogen Source. Angew. Chem., Int. Ed. 2015, 54, 1965–1968.(b)Chatterjee I; Qu Z-W; Grimme S; Oestreich MB(C6F5)3¬-Catalyzed Transfer of Dihydrogen from One Unsaturated Hydrocarbon to Another. Angew. Chem., Int. Ed. 2015, 54, 12158–12162.(c)Keess S; Oestreich M Cyclohexa-1,4-dienes in transition-metal-free ionic transfer processes. Chem. Sci. 2017, 8, 4688–4695. [PubMed: 28936336]

(10). Shang M; Chan JZ; Cao M; Chang Y; Wang Q; Cook B; Torker S; Wasa M C–H Functionalization of Amines via Alkene-Derived Nucleophiles through Cooperative Action of Chiral and Achiral Lewis Acid Catalysts: Applications in Enantioselective Synthesis. J. Am. Chem. Soc. 2018, 140, 10593–10601. [PubMed: 30045617]

(11). For reviews regarding α-amino C–H functionalization, see:(a)Campos KR. Direct sp3 C–H bond activation adjacent to nitrogen in heterocycles. Chem. Soc. Rev. 2007, 36, 1069–1084. [PubMed: 17576475] (b)Davies HML; Manning JR Catalytic C–H functionalization by metal carbenoid and nitrenoid insertion. Nature 2008, 451, 417–424. [PubMed: 18216847] (c)Chiral Amine Synthesis: Methods, Developments and Applications; Nugent TC., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2010.(d)Mitchell EA; Peschiulli A; Lefevre N; Meerpoel L; Maes BUW Direct α-functionalization of saturated cyclic amines. Chem. Eur. J. 2012, 18, 10092–10142. [PubMed: 22829434] (e)Girard SA; Knauber T; Li C-J The cross-dehydrogenative coupling of Csp3–H bonds: A versatile strategy for C–C bond formations. Angew. Chem., Int. Ed. 2014, 53, 74–100.(f)Haibach MC; Seidel D C–H Bond functionalization through intramolecular hydride transfer. Angew. Chem., Int. Ed. 2014, 53, 5010–5036.

(12). For representative examples of α-amino C–H bond functionalization, see:(a)Davies HML; Hansen T; Hopper DW; Panaro SA Highly Regio-, Diastereo-, and Enantioselective C–H Insertions of Methyl Aryldiazoacetates into Cyclic N-Boc-Protected Amines. Asymmetric Synthesis of Novel C2-Symmetric Amines and threo-Methylphenidate. J. Am. Chem. Soc. 1999, 121, 6509–6510.(b)Li Z; Li C-J CuBr-Catalyzed Efficient Alkynylation of sp3 C–H Bonds Adjacent to a Nitrogen Atom. J. Am. Chem. Soc, 2004, 126, 11810–11811. [PubMed: 15382913] (c)DiRocco DA; Rovis T Catalytic Asymmetric α-Acylation of Tertiary Amines Mediated by a Dual Catalysis Mode: N-Heterocyclic Carbene and Photoredox Catalysis. J. Am. Chem. Soc. 2012, 134, 8094–8097. [PubMed: 22548244] (d)Cordier CJ; Lundgren RJ; Fu GC Enantioconvergent Cross-Coupling of Racemic Alkylmetal Reagents with Unactivated Secondary Alkyl Electrophiles: Catalytic Asymmetric Negishi α-Alkylations of N-Boc-pyrrolidine. J. Am. Chem. Soc. 2013, 135, 10946–10949. [PubMed: 23869442] (e)Bergonzini G; Schindler CS; Wallentin C-J; Jacobsen EN; Stephenson CRJ Photoredox activation and anion binding catalysis in the dual catalytic enantioselective synthesis of β-amino esters. Chem. Sci. 2014, 5, 112–116. (f)Espelt LR; McPherson IS; Wiensch EM; Yoon TP Enantioselective conjugate additions of α-amino radicals via cooperative photoredox and Lewis acid catalysis. J. Am. Chem. Soc. 2015, 137, 2452–2455. [PubMed: 25668687] (g)Osverger TJ; Rogness DC; Kohrt JT; Stepan AF; White MC Oxidative diversification of amino acids and peptides by small-molecule iron catalysis. Nature 2016, 537, 214–219. [PubMed: 27479323] (h)Le C; Liang Y; Evans RW; Li X; MacMillan DWC Selective sp3 C–H alkylation via polarity-match-based cross-coupling. Nature 2017, 547, 79–83. [PubMed: 28636596] (i)Jain P; Verma P; Xia G; Yu J-Q Enantioselective amine α-functionalization via palladium-catalysed C–H arylation of thioamides. Nat. Chem. 2017, 9, 140–144. [PubMed: 28282045] (j)Chen W; Ma L; Paul A; Seidel D Direct α-C–H bond functionalization of unprotected cyclic amines. Nat. Chem. 2018, 10, 165–169. [PubMed: 29359746] (k)McManus JB; Onuska NPR; Nicewicz DA Generation and alkylation of α-carbamyl radicals via organic photoredox catalysis. J. Am. Chem. Soc. 2018, 140, 9056–9060. [PubMed: 29986129] (l)Ye J; Kalvet I; Schoenebeck F; Rovis T Direct α-alkylation of primary

aliphatic amines enabled by CO2 and electrostatics. Nat. Chem. 2018, 10, 1037–1041. [PubMed: 30061617]

(13). Jurberg ID; Peng B; Wöstefeld E; Wasserloos M; Maulide N Intramolecular Redox-Triggered C–H Functionalization. Angew. Chem., Int. Ed. 2012, 51, 1950–1953.

(14). After isolation by silica gel column chromatography, 3l and 3m were treated with an aqueous solution of 4 N HCl and characterized as their corresponding non-silylated compounds. See the Supporting Information for details.

(15). Süsse L; Hermeke J; Oestreich M The Asymmetric Piers Hydrosilylation. J. Am. Chem. Soc. 2016, 138, 6940–6943. [PubMed: 27212565]

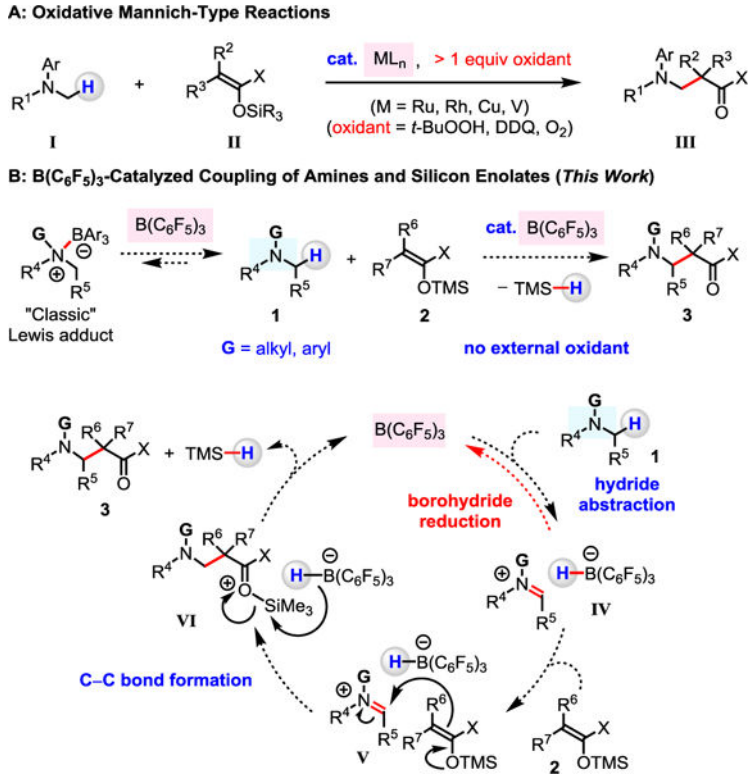
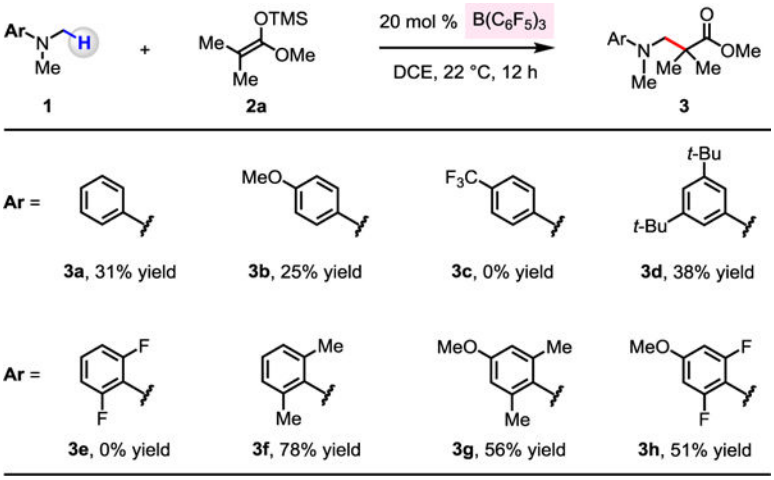


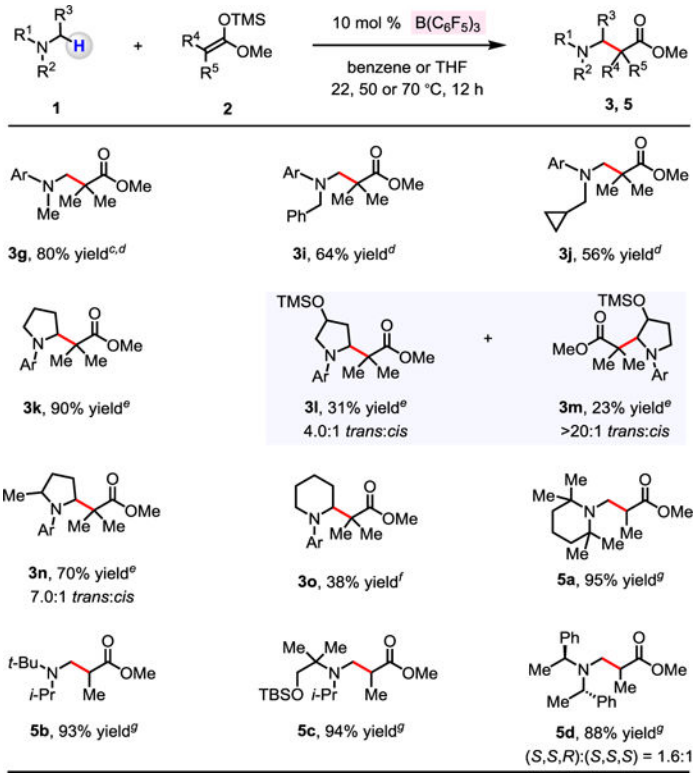
Figure 1.
Coupling of *N*-Alkylamines and Silicon Enolates



Scheme 1.

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

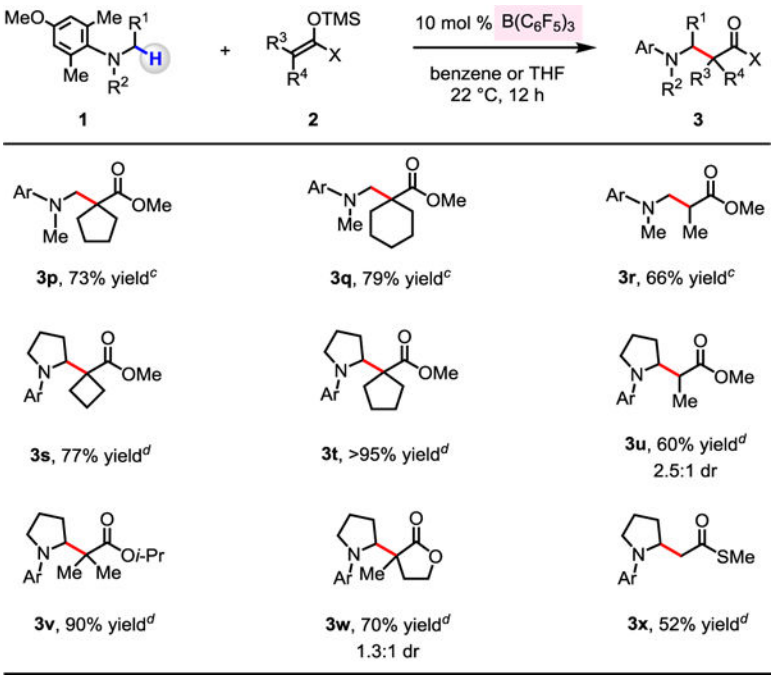
[a] Conditions: *N,N*-dimethylaniline (0.1 mmol), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (0.2 mmol), $B(C_6F_5)_3$ (20 mol %), dichloroethane (0.25 mL), under N_2, 22 °C, 12 h. [b] Yields were determined by ^1H NMR analysis of unpurified product mixtures with mesitylene as the internal standard.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



Scheme 2.

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

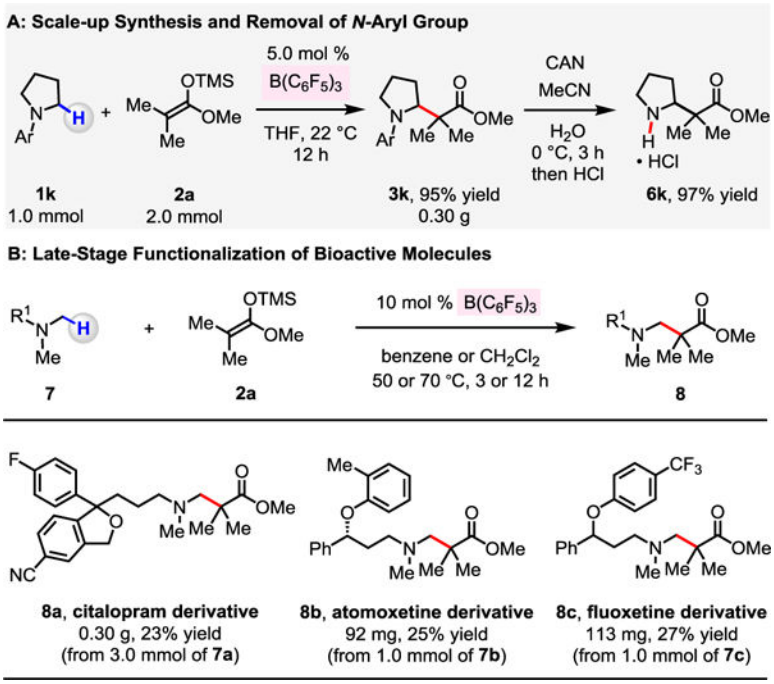
[a] Conditions: *N,N*-dialkylaniline (0.2 mmol), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (0.4 mmol), $B(C_6F_5)_3$, solvent (0.5 mL), under N_2, 22 °C, 12 h. [b] Yield of purified products. [c] $B(C_6F_5)_3$ (5.0 mol %) was used. [d] Benzene (0.5 mL) was used. [e] THF (0.5 mL) was used. [f] $B(C_6F_5)_3$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



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, under N_2, 22 °C, 12 h. [b] Yield of purified products. [c] Benzene (0.5 mL) was used. [d] THF (0.5 mL) was used. See the Supporting Information for details.



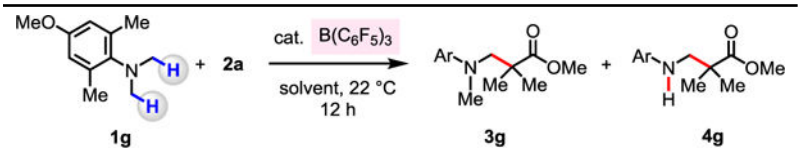
Scheme 4.

Scale-Up Synthesis and Late-Stage Functionalization of Bioactive Molecules

[a] See the Supporting Information for details.

Table 1.

Evaluation of Various Reaction Parameters [a,b]



1g 3g 4g

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•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.