Synthetic Methods

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Boron-Catalyzed N-Alkylation of Amines using Carboxylic Acids**

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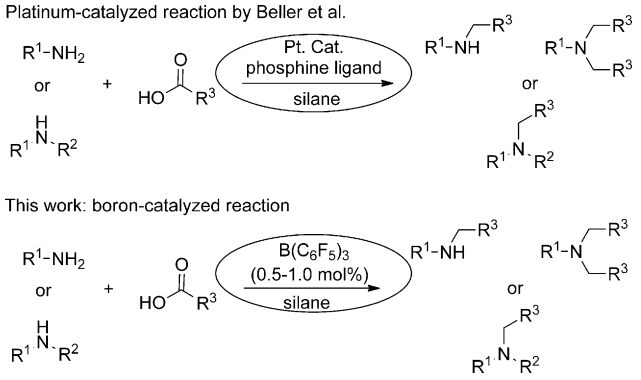
Abstract: *A boron-based catalyst was found to catalyze the straightforward alkylation of amines with readily available carboxylic acids in the presence of silane as the reducing agent. Various types of primary and secondary amines can be smoothly alkylated with good selectivity and good functional-group compatibility. This metal-free amine alkylation was successfully applied to the synthesis of three commercial medicinal compounds, Butenafine, Cinacalcet. and Piribedil, in a one-pot manner without using any metal catalysts.*

Alkylation of amines is an important process, in both laboratory synthesis and the chemical industry.[1] Alkylated amine structures appear widely in pharmaceuticals, agrochemicals, and materials.[2] Traditional methods of alkylating an amine include noncatalytic reactions using hazardous alkyl halides for substitutions,[3] or using air-sensitive aldehydes for reductive aminations.[4] Compared with traditional methods, a general catalytic method for the alkylation of amines utilizing carboxylic acid is more appealing because of the step economy and easy availability of the carboxylic acids. Recently, direct catalytic alkylation of amines using carboxylic acids was achieved by Beller et al. and they utilized a platinum/diphosphine-based catalyst (Scheme 1).[5] With our interest in sustainable catalysis using abundant main group elements, we proposed that a boron-based catalyst, which has utility in amide condensations[6] and amide reductions with a silane,[7a] might also serve as a suitable catalyst for this process. Herein we show that a boron-based catalyst, $B(C_6F_5)_3$, which can form a frustrated Lewis pair (FLP),[8,9] can catalyze the straightforward N-alkylation of amines using carboxylic acids in the presence of a silane reducing agent with good selectivity and good functional-group compatibility (Scheme 1). The boron catalyst enables efficient reductive carbon–nitrogen bond formation in preference to the undesired reduction of the carboxylic acid. The required loading of the boron catalyst is only 1 mol% and can be used for a wide scope of substrates, thus generating products in good yield. A turnover number up to 700 was achieved. The work presented herein provides a new metal-free method of synthesizing alkylated amines using carboxylic acids, and it also demonstrates a new example of reductive carbon–nitrogen bond formation through FLP catalysis.



Scheme 1. Catalytic N-alkylation of amines using carboxylic acids.

Because formic acid is an ideal C1 source derived from biomass,[10] and methylated amine structures appear widely in pharmaceuticals,[11] our research started with the methylation of *N*-methylaniline with formic acid,[10a,12] as demonstrated in Table 1. The optimal reaction conditions, discovered after systematic optimization, are listed in entry 1 of Table 1. Phenylsilane (0.8 mmol) was added by a gas-tight syringe to a mixture of *N*-methylaniline (0.2 mmol), formic acid (0.46 mmol), and tris(perfluorophenyl)borane (1.0 mol%, 0.002 mmol) in dibutyl ether. After heating the mixture at 100 °C for 8 hours, *N*,*N*-dimethylaniline (**2a**) was obtained quantitatively. No amide byproduct (**3a**) was detected. Parameters which control this reaction are also given in Table 1. A control experiment showed that $B(C_6F_5)_3$ is essential for this reaction; without the catalyst, only the amide byproduct can be detected (entry 2). Other boron catalysts, such as trifluoroborane (entry 3) and a boronic ester (entry 7), are not effective catalysts. Boronic acids, which were previously reported to be effective for amide condensations[6] and amide reductions,[7a] are totally ineffective for this one-pot amine alkylation reaction (entries 5 and 6). Other boron catalysts and metal Lewis acid catalysts (see the Supporting Information) failed in serving as an efficient catalyst, thus suggesting that the tris(perfluorophenyl)borane does not only act simply as a Lewis acid catalyst. The unique catalytic activity of tris(perfluorophenyl)borane may be attributed to its ability to form an FLP with carbonyl groups to activate the silane[13] and thus induce reductive C–N bond formation. Although Et_3SiH failed to serve as a reducing agent for this reaction (entry 8), PMHS (polymethylhydrosiloxane), Et_2SiH_2, and Ph_2SiH_2 all served as reducing agents (entries 9–11). The lower reactivity of the tertiary silane, compared with that of the secondary silane, may be ascribed to the steric effect. It should be noted that PMHS is a cheap,

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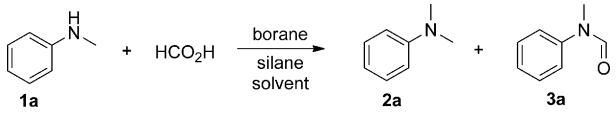
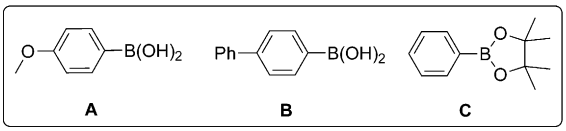
Table 1: Catalytic N-methylation of *N*-methylaniline using formic acid.[a]

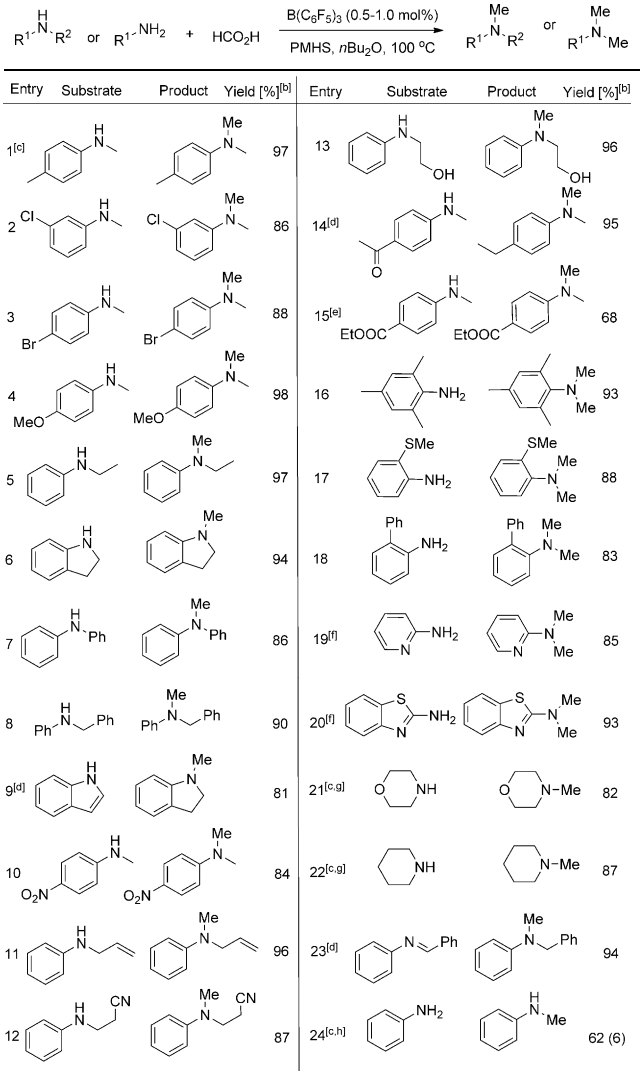




Entry	Catalyst	Silane	Solvent	Yield [%][b]	
				2a	**3a**
1	$B(C_6F_5)_3$	$PhSiH_3$	nBu_2O	99	–
2	none	PMHS	nBu_2O	0	45
3[c]	$BF_3\ OEt_2$	$PhSiH_3$	nBu_2O	5	3
4[c,d]	Et_3B	$PhSiH_3$	nBu_2O	49	2
5[c]	**A**	$PhSiH_3$	nBu_2O	1	5
6[c]	**B**	$PhSiH_3$	nBu_2O	1	10
7[c]	**C**	$PhSiH_3$	nBu_2O	<1	5
8	$B(C_6F_5)_3$	Et_3SiH	nBu_2O	6	61
9	$B(C_6F_5)_3$	PMHS	nBu_2O	98	–
10	$B(C_6F_5)_3$	Et_2SiH_2	nBu_2O	97	–
11	$B(C_6F_5)_3$	Ph_2SiH_2	nBu_2O	92	–
12	$B(C_6F_5)_3$	PMHS	1,4-dioxane	96	–
13	$B(C_6F_5)_3$	PMHS	toluene	95	–
14	$B(C_6F_5)_3$	PMHS	mesitylene	90	2
15	$B(C_6F_5)_3$	PMHS	DMF	5	51
16	$B(C_6F_5)_3$	PMHS	acetonitrile	2	61
17[e]	$B(C_6F_5)_3$	PMHS	nBu_2O	92	4
18[f]	$B(C_6F_5)_3$	PMHS	nBu_2O	72	26

[a] Reaction conditions: *N*-methylaniline (0.2 mmol), silane (4.0 equiv), catalyst (1.0 mol%), HCO_2H (2.3 equiv), solvent (1.0 mL), 100°C, 8 h. [b] Determined by GC analysis of the reaction mixture after quenching with aqueous NaOH solution. *n*-Dodecane was used as an internal standard. [c] Catalyst (5.0 mol%). [d] Et_3B in a THF solution (1.0 mol L^{-1}). [e] $B(C_6F_5)_3$ (0.5 mol%). [f] $B(C_6F_5)_3$ (0.1 mol%). PMHS = polymethylhydrosiloxane.

Table 2: N-methylation of various amines with formic acid.[a]



[a] Reaction conditions for secondary amines: substrate (0.2 mmol), PMHS (4.0 equiv), $B(C_6F_5)_3$ (0.5 mol%), HCO_2H (2.3 equiv), nBu_2O (1.0 mL), 100°C, 8–10 h. For primary amines: substrate (0.2 mmol), PMHS (8.0 equiv), $B(C_6F_5)_3$ (1.0 mol%), HCO_2H (4.0 equiv), nBu_2O (2.0 mL), 100°C, 8–15 h. [b] Yield of isolated product. [c] Determined by GC analysis using *n*-dodecane as an internal standard instead of isolation. [d] PMHS (5.0 equiv). [e] PMHS (3.5 equiv), 8 h. [f] $PhSiH_3$ (8.0 equiv). [g] 120°C, 18 h. [h] PMHS (3.0 equiv), HCO_2H (1.3 equiv), 1,4-dioxane (1.0 mL), 110°C, 3 h; the yield of the dimethylation product is given within parentheses.

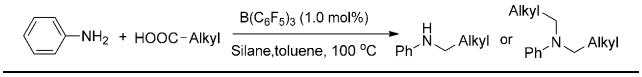
stable, and environmentally friendly hydrosilane, which is more suitable to serve as a reducing agent for large-scale production.[14] A study of the solvent effect revealed that ethers and arenes are suitable solvents (entries 12–14), but polar solvents such as DMF (entry 15) and acetonitrile (entry 16) are unsuitable. It is notable that the catalyst loading can be lowered to 0.5 mol% and still lead to 92% of the desired product. Further lowering the loading to 0.1 mol% gave the product in 72% yield.

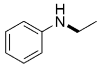
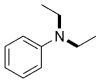
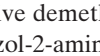
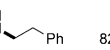
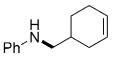
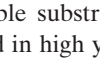
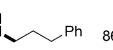
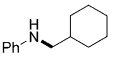
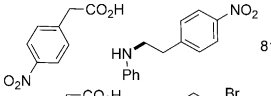
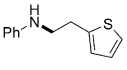
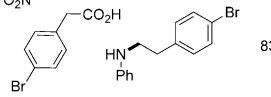
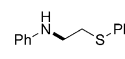
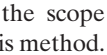
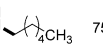
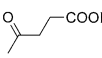
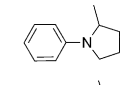
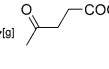
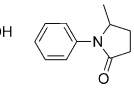
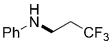
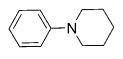
With the optimal reaction conditions in hand, we investigated the scope of this reaction using formic acid and various amine coupling partners (Table 2). Various *N*-methylanilines can be successfully methylated in excellent yield (entries 1–4 and 10). The electronic effect on the phenyl ring has no significant effect on the reaction outcome (entries 4 and 10). *N*-ethyl and *N*-benzylaniline can also be successfully methylated with formic acid in excellent yield (entries 5 and 8). Indoline also gives the N-methylated product in high yield (entry 6). Besides N-alkylated aniline, methylation of diphenylamine also took place smoothly (entry 7). Indole gives 1-methylindoline as the major product, in which the double bond is hydrogenated during the reaction. This reaction also has good functional-group compatibility; an aryl chloride (entry 2), aryl bromide (entry 3), ether (entry 4), and thioether (entry 17) are all well tolerated. It is surprising to find that even a nitro group (entry 10) and cyano group (entry 12) are well tolerated without any undesired reduction. A terminal alkene structure, which is sensitive to transition-metal catalysis, also remained intact (entry 11). Although there are reports that the combination of silane and a borane catalyst can directly reduce alcohols to alkanes,[15a,b] in our reaction, an alcohol is tolerated (entry 13). The ketone functionality cannot be tolerated, and instead a high yield of the deoxygenated product was obtained (entry 14). Esters can

be partially tolerated by reducing the amount the silane used (entry 15). The reaction is not limited to secondary amines as it also works well for primary amines. The reaction of aniline can selectively give the dimethylated products (entries 16–18). Steric bulk on the *ortho* position of the aniline is well tolerated (entry 16). Basic-nitrogen-containing heteroaromatic amines are important structural motifs in pharmaceuticals, and their alkylation using alkyl halides always causes undesired side reactions.[16] Our method can also be applied to the alkylation of nitrogen-containing heteroaromatic amines as demonstrated the selective demethylation of by pyridin-2-amine and benzo[*d*]thiazol-2-amine in excellent yields (entries 19 and 20). Not only aromatic amines but also aliphatic amines are suitable substrates, for piperidine and morpholine are methylated in high yield (entries 21 and 22). An interesting domino reductive alkylation of an imine was observed wherein the imine can be reduced in situ and alkylated in one pot (entry 23). For a primary amine, the degree of methylation can be controlled by tuning the stoichiometry of the reagent (entry 24).

After evaluating the scope with respect to amine coupling partners, we also studied the scope of carboxylic acids to explore the generality of this method. Table 3 summarizes the results to demonstrate the scope with respect to the carboxylic acid coupling partner. For acetic acid, both monoethylation and diethylation can be selectively achieved by adjusting the stoichiometry of the reagent (see the Supporting Information for details). It was found that when carboxylic acids with longer chains were used, monoalkylation products were the major products. For alkylation of aniline with 2-phenylacetic acid or 3-phenylpropanoic acid, mono-N-alkylation products were obtained in good yield, and no dialkylation was observed. It is interesting that the nitro group on the carboxylic acid is also compatible. Aryl bromides remain intact in this metal-free process and make additional functionalization by cross-coupling reactions possible. Hexanoic acid gives the mono-*N*-hexyl-substituted aniline in good yield (entry 7). Importantly, using 2,2,2-trifluoroacetic acid and 3,3,3-trifluoropropanoic acid gives the trifluoromethyl-containing aniline product in moderate yields (entries 8 and 9). These trifluoromethyl-containing anilines are useful building blocks in the pharmaceutical industry. When biomass-derived lactic acid was used, the N-propyl-substituted product was obtained, thus demonstrating that a hydrodeoxygenation process also took place to remove the α-OH group, and making lactic acid a suitable C3 source for propylation (entry 10). Using acrylic acid also gives the N-propyl-substituted product (entry 11). Tertiary carboxylic acids, such as cyclohexanecarboxylic acid and cyclohex-3-ene-1-carboxylic acid, also gave the monoalkylated products in good yields without detection of any dialkylation. It should be noted for cyclohex-3-ene-1-carboxylic acid that the cyclohexene moiety remains intact. Sulfur-containing carboxylic acids are amenable substrates (entries 14 and 15). We also tried to apply biomass-derived levulinic acid to this transformation, and it was found that phenylpyrrolidinone and phenylpyrrolidine can be selectively obtained in high yields by tuning the stoichiometry of the silane agent. When 5-bromopentanoic acid was used, sequential reductive C–N formation and S_N2 substitution took place to deliver 1-phenylpiperidine (entry 18). It should be noted that the undesired reduction of the carboxylic acid to form either the alcohol or alkane was detected.[15c]

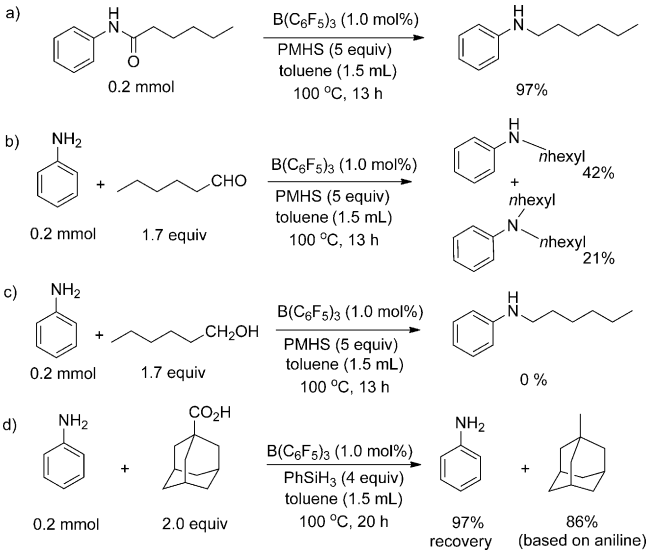
Table 3: N-Alkylation with various carboxylic acids.[a]



Entry	Substrate	Product	Yield [%][b]	Entry	Substrate	Product	Yield [%][b]
1[c]	CH_3CO_2H		81	10[e]			76
2[d]	CH_3CO_2H		87	11[f]			78
3[c]			82	12			65
4[c]			86	13			71
5			81	14			63
6			83	15			62
7			75	16			86
8	CF_3CO_2H		68	17[g]			91
9	$CF_3CH_2CO_2H$		57	18			75

[a] Reaction conditions: aniline (0.2 mmol), $B(C_6F_5)_3$ (1.0 mol%), PMHS (5.0 equiv), acids (1.7 equiv), toluene (1.5 mL), 100 °C, 13 h. [b] Yield of isolated product. [c] Determined by GC analysis using *n*-dodecane as an internal standard instead of isolation. [d] CH_3CO_2H (5.0 equiv), PMHS (7.0 equiv). [e] 2-Hydroxypropanoic acid (2.0 equiv), $PhSiH_3$ (4.0 equiv), 20 h. [f] PMHS (6.0 equiv). [g] PMHS (2.5 equiv).

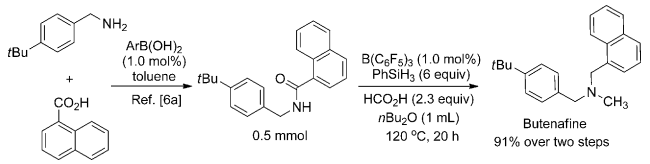
Several control experiments were conducted to obtain information about the reaction mechanism (Scheme 2). First, *N*-hexylbenzamide was tested under the same reaction conditions, and it generated the amine product quantitatively.[7b,c] When hexanal was used instead of hexanoic acid, a mixture of mono- and dialkylation products was obtained in low yields. When hexan-1-ol was used, no alkylation product was obtained at all. It should be noted that when a carboxylic acid with a bulky group adjacent to the carbonyl group were tested, no C–N bond-formation product was obtained. Instead, only the reduced alkane product was obtained. It should also be noted that according to the report by Gevorgyan et al., reduction of carboxylic acid under B-$(C_6F_5)_3$/silane conditions does not proceed via an aldehyde intermediate.[15c] These observations suggest the possibility that the reaction proceeds through an amide intermediate, and reducing the carboxylic acid to the aldehyde with subsequent reductive amination is unlikely because of the different selectivity observed. The unique catalytic activity of



Scheme 2. Control experiments: a) reduction of *N*-hexylbenzamide. b) Reductive amination of hexanal. c) Using hexan-1-ol. d) Using adamantane-1-carboxylic acid.

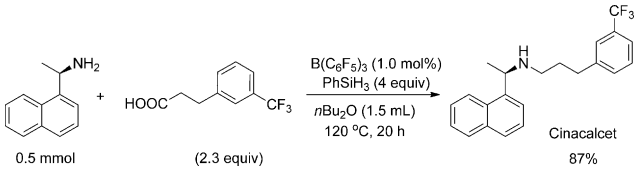
tris(perfluorophenyl)borane and the selective reductive C–N bond formation in preference to reduction of the carboxylic acid suggests an FLP mechanism in which the boron and carbonyl of the substrate form a FLP to activate the silane[13b–d,17] and catalyze the reductive formation of the C–N bond.[18]

Considering the toxicity and cost of transition-metal catalysts, the pharmaceutical industry desires synthetic routes which avoid utilizing expensive and toxic transition metals. We successfully applied this boron-catalyzed method to the preparation of three commercialized drug molecules. The three routes all solely rely on the boron-based catalyst, and no metal was needed. As depicted in Scheme 3, Butenafine, an antimycotic agent, can be prepared in two

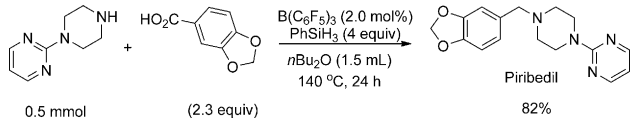


Scheme 3. Two-step, metal-free synthesis of Butenafine.

steps from commercially available starting materials.[19] First, by using a boronic-acid catalyzed amide condensation, followed by $B(C_6F_5)_3$-catalyzed reduction of amide and direct reductive N-methylation with formic acid, gave the drug molecule in 91% yield. Scheme 4 shows a facile preparation of Cinacalcet,[5,20] a drug for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and hypocalcemia. Scheme 5 demonstrates the new preparation method for Piribedil,[21] a piperazine dopamine agonist used in the treatment of Parkinson's disease, in one step. Avoiding the use of transition metals and expensive ligands makes these three sustainable routes



Scheme 4. One-pot, metal-free synthesis of Cinacalcet.



Scheme 5. One-pot, metal-free synthesis of Piribedil.

appealing from both an economic and environmental point of view.

In conclusion, we have found that a boron-based catalyst can catalyze straightforward alkylation of amines with carboxylic acids in the presence of silane as a reducing agent. Both primary and secondary amines can be smoothly alkylated with good selectivity and good functional-group compatibility. The application of this method was demonstrated by the one-pot, metal-free syntheses of three drug molecules, namely, Butenafine, Cinacalcet, and Piribedil.

Keywords: alkylation · amines · boron · frustrated Lewis pair · synthetic methods

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