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DIC−Borane-Catalyzed Selective Methylation of Primary Amines with CO_2 Using Boranes as Reducing Agents

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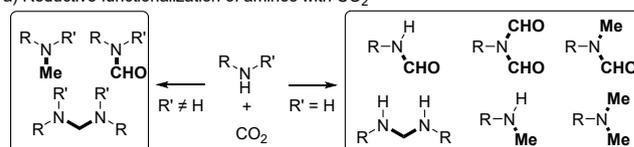**The selective reductive *N*-methylation and *N,N*-dimethylation of primary amines using CO_2 are some of the most significant challenges faced by organic chemists. Herein, we report the highly selective *N,N'*-diisopropylcarbodiimide-catalyzed methylation of primary amines using 1 atm CO_2 under metal-free conditions. The borane–piperazine and borane–trimethylamine complexes were used as reducing agents for the *N*-methylation and *N,N*-dimethylation of various aromatic primary amines, respectively, in the presence of CO_2. Mechanistic studies suggest that the selectivity of methylation is controlled by the steric effects of amines and boranes.**

In recent times, the reductive functionalization of carbon dioxide with amines has become one of the most attractive protocols for CO_2 transformation because it can be used to generate various value-added amine derivatives.[1] Controlling the reactivity and selectivity of such reactions is the most challenging goal. The selective reductive coupling of secondary amines with CO_2 has been well developed because of the low selectivity of CO_2 reduction.[2] In contrast, the reductive coupling of primary amines with CO_2 has been rarely reported owing to the multi-reactive sites of primary amines and multi-oxidative states of CO_2, which leads to a complex mixture of various functionalized amines such as mono-formylated amines,[3] bis-formylated amines,[4] aminals,[2d, 5] mono-methylated amines,[6] and dimethylated amines[2c, 7] (Scheme 1a). The reductive methylation of amines provides a straightforward and sustainable method for the synthesis of *N*-methylamines or *N,N*-dimethylamines, which are commonly found moieties in drugs, natural products, and dyes.[8] Thus, the development of synthetic strategies that produce *N*-methylamines and *N,N*-dimethylamines by the selective reductive coupling of primary amines using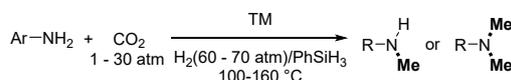 CO_2 is highly desirable. However, to achieve this objective, certain challenges need to be overcome: 1. The catalyst should be able to distinguish between the reactivities of primary amines and *N*-methylamines with CO_2. 2. The reducing ability of the reducing agents should be controlled such that they do not further reduce the methylated products.

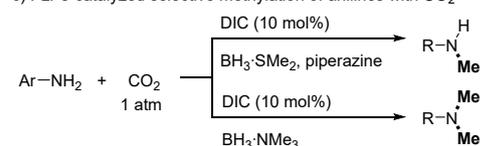**Scheme 1.** Reductive functionalization of amines with CO_2.

Breakthroughs in the selective *N*-methylation and *N,N*-dimethylation of primary amines using CO_2 have rarely been reported. For instance, Cantat *et. al.* carried out the selective methylation of amines using the $IPrZnCl_2$ complex and by controlling the reaction time (Scheme 1b).[6a] Beller and Shi used a homogenous Ru catalyst and a heterogeneous $CuAlO_x$[6d] catalyst for the selective mono- and di-methylation reactions, respectively, by tuning the pressure of the CO_2/H_2 mixture and by controlling the reaction time.[6b,c] Although these reactions achieve the desired selectivity, they require transition metal catalysts and harsh reaction conditions (high pressure and temperature). Moreover, these reactions have a narrow

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† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

substrate scope and poor selectivity, which hampers the wide application of this synthetically useful transformation.

To develop a sustainable, economical, and easy-to-handle procedure for CO_2 transformation, our group has investigated cheap and readily available organocatalysts for CO_2 activation under mild conditions.[9] Thus, 2-amino-6-picoline—borane[9b] and 2-aminothiazole—borane[9c] catalytic systems were developed for the reductive methylation of amines with CO_2. In our previous study, we found that different borane-amine complexes exhibit different selectivities for the production of formylated or methylated amines. These results motivated us to extend this unique reactivity and reductive ability to the selective reduction of CO_2 using primary amines. Herein, we report for the first time that non-metal catalytic systems realize the selective monomethylation and dimethylation of primary amines using 1 atm CO_2 in the presence of different borane complexes. A catalytic amount of *N,N'*-diisopropylcarbodiimide (**DIC**) was used in these reactions. Monomethylated amines were obtained in the presence of borane—piperazine complexes, and dimethylated amines were obtained in the presence of borane—trimethylamine complexes (Scheme 1c).

Based on the frustrated Lewis pair (FLP) catalysts developed in our previously study, various heteroaromatic amines were selected for the reductive functionalization of CO_2 with aniline in the presence of the BH_3·piperazine complex, which was generated in situ from BH_3·SMe_2 and piperazine **B1** in toluene at 95 °C (Table 1). Interestingly, the mono-methylated product **3a** was selectively obtained in low yields using 2-aminopyridine (**I**) or 2-aminothiazole (**III**) as the catalyst (entries 1 and 3). The use of 6-amino-2-picoline (**II**) significantly enhanced the conversion and improved the yield of **3a** to 51% with excellent selectivity (entry 2). Furthermore, **DIC**[10] was used as a catalyst to efficiently produce **3a** in 86% yield with high selectivity (entry 4). We propose that the hydroboration of **DIC** with borane is much faster than the dehydrogenation of heteroamines (**I**, **II**, and **III**) with borane, generating an FLP catalyst in situ to accelerate the reaction. However, the same type of catalyst, *N,N'*-dicylohexylcarbodiimide (**DCC**), dramatically decreased the yield of **3a** to 21% (entry 5). Next, the use of various boranes was investigated for the reductive methylation reactions. The borane—trimethylamine complex, an efficient reducing agent for CO_2 reduction, resulted in the good conversion of aniline but with low selectivity, affording a mixture of formanilide (**2a**), **3a**, *N*-methyl-formanilide (**4a**), and *N,N*-dimethylaniline (**5a**) (entry 6). The use of pinacolborane (HBpin) as a reducing agent promoted the reaction, affording **3a** in 11% yield, along with **5a** in 1% yield (entry 7). Because the borane-amine complexes could be generated in situ from BH_3·SMe_2 and amines, several amines were screened with BH_3·SMe_2 (entries 8–10). For instance, a mixture of products was obtained in the presence of *N,N,N',N'*-tetramethylethylenediamine (**B2**) (entry 8). Intriguingly, the use of 1-methylpiperazine (**B3**) or 1,4-dimethylpiperazine (**B4**) as bases resulted in different selectivities. Mono-functionalized anilines **2a** and **3a** were obtained with **B3** (entry 9), whereas di-functionalized anilines **4a** and **5a** were obtained with **B4** (entry 10). The solvent screening results revealed that only aromatic and ether solvents promoted the reaction, while other solvents such as glyme, 1,2-dichloroethane (DCE), *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) completely thwarted the reaction. The use of 1,4-dioxane yielded **3a** in 56% yield with high selectivity (entry 11); however, the use of THF afforded **2a** as the sole product in 35% yield (entry 12). These results indicate that the solvents might affect the reducibility of the borane complexes. Control experiments revealed that both **DIC** and **B1** were crucial for this reaction (entries 13 and 14). In addition, **DIC** exhibited a much higher efficiency for reductive dimethylation, affording 5a in 95% yield using only 4 equiv. of BH_3·NMe_3 under 1 atm CO_2 in glyme at 100 °C for 6 h (entry 15). However, when the same reaction was catalyzed by 6-amino-2-picoline, excess boranes (6 equiv. BH_3·NMe_3) and a longer reaction time (24 h) were required.[9b]

Table 1. Optimization of reductive methylation of aniline with CO_2.[a]

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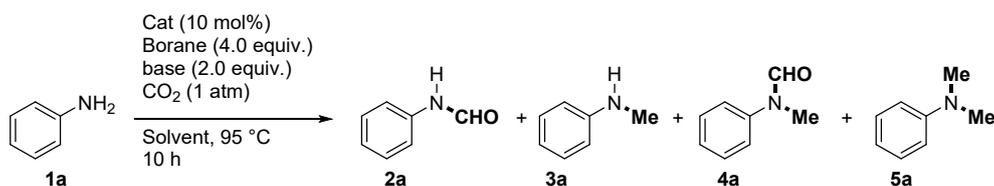
| Entry	Catalyst	Borane	Base	Solvent	Yield of **2a**/%	Yield of **3a**/%	Yield of **4a**/%	Yield of **5a**/%
1	**I**	$BH_3 \cdot SMe_2$	**B1**	Toluene	-	9	-	-
2	**II**	$BH_3 \cdot SMe_2$	**B1**	Toluene	-	51	-	-
3	**III**	$BH_3 \cdot SMe_2$	**B1**	Toluene	-	4	-	-
4	**DIC**	$BH_3 \cdot SMe_2$	**B1**	Toluene	-	86	-	-
5	**DCC**	$BH_3 \cdot SMe_2$	**B1**	Toluene	-	21	-	-
6	**DIC**	$BH_3 \cdot NMe_3$	-	Toluene	28	6	23	31
7	**DIC**	HBpin	-	Toluene	-	11	-	1
8	**DIC**	$BH_3 \cdot SMe_2$	**B2**	Toluene	16	17	21	39
9	**DIC**	$BH_3 \cdot SMe_2$	**B3**	Toluene	14	32	-	-
10	**DIC**	$BH_3 \cdot SMe_2$	**B4**	Toluene	-	-	11	42
11	**DIC**	$BH_3 \cdot SMe_2$	**B1**	1,4-Dioxane	-	56	-	-
12	**DIC**	$BH_3 \cdot SMe_2$	**B1**	THF	35	-	-	-
13	**DIC**	$BH_3 \cdot SMe_2$	-	Toluene	-	-	-	-
14	-	$BH_3 \cdot SMe_2$	**B1**	Toluene	-	-	-	-
15[b]	**DIC**	$BH_3 \cdot NMe_3$	-	Glyme	-	-	-	95
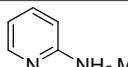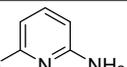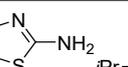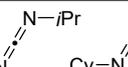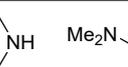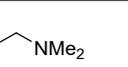
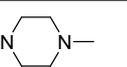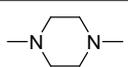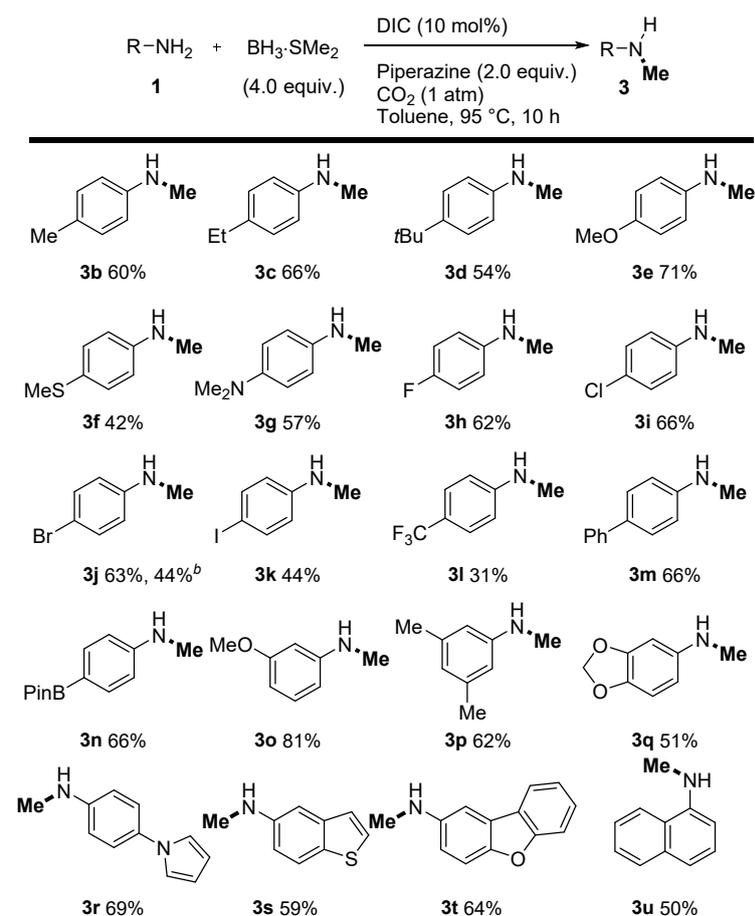**I** **II** **III** **DIC** **DCC** **B1** **B2** **B3** **B4**

[a] Reaction conditions: The reaction was carried out on a 0.3 mmol scale in 0.4 mL of solvent in a closed 20 mL Schlenk tube for 6 h; the yield was determined by GC with tridecane as the internal standard. HBpin = pinacolborane [b] in 0.2 ml solvent at 100 °C for 6 h.

With the optimized monomethylation conditions in hand, we explored the scope of various amines in this reaction (Table 2). The reactions displayed significant selectivity, in that only mono-methylated anilines were produced. Anilines bearing alkyl groups at the *para* (**3b**, **3c**, and **3d**) and *meta* (**3p**) positions were reacted with CO_2 to afford monomethylated amines in modest to good yields. Functional groups such as methoxyl (**3e** and **3o**), thiomethyl (**3f**), *N,N*-dimethylamino (**3g**), and methylenedioxy (**3q**) were well tolerated. Anilines bearing halide groups and pinacol boronate ester (Bpin) groups, which are frequently used for diverse latent coupling transformations, reacted with CO_2 to afford mono-methylated products in moderate-to-good yields (**3h**-**3k**, **3n**). In addition, the mono-methylation of 4-bromoaniline could be scale up to 5 mmol scale to produce **3j** in 44% yield. Heterocycles such as pyrrole (**3r**), benzothiazole (**3s**), and dibenzofuran (**3t**) also participated in the reaction, affording the corresponding products in good yields. Moreover, 1-naphthylamine was reacted with CO_2 to afford **3u** in 50% yield. However, aliphatic amines did not react with CO_2 under these conditions.

Table 2. Monomethylation of amines with CO_2.[a]

$$R-NH_2 \ + \ BH_3 \cdot SMe_2 \xrightarrow[\substack{\text{Piperazine (2.0 equiv.)} \\ CO_2 \text{ (1 atm)} \\ \text{Toluene, 95 °C, 10 h}}]{\text{DIC (10 mol%)}} R-N\substack{H \\ \text{Me}}$$

1 (4.0 equiv.) **3**

3b 60% **3c** 66% **3d** 54% **3e** 71%

3f 42% **3g** 57% **3h** 62% **3i** 66%

3j 63%, 44%[b] **3k** 44% **3l** 31% **3m** 66%

3n 66% **3o** 81% **3p** 62% **3q** 51%

3r 69% **3s** 59% **3t** 64% **3u** 50%

[a] Reaction conditions: The reaction was carried out on a 0.3 mmol scale in Toluene with a CO_2 balloon. [b] in 5 mmol scale for 72 h.
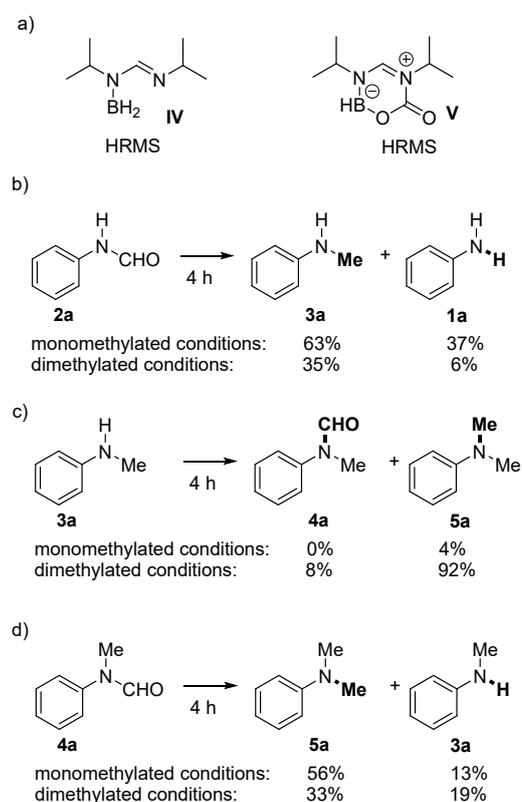
Subsequently, we evaluated the DIC-catalyzed dimethylation of anilines with CO_2 in the presence of the borane−trimethylamine complex (Table 3). The dimethylation reactions of electron-rich and electron-deficient anilines proceeded efficiently, affording the desired dimethylated products in good to excellent yields (**5b–5u**). A wide range of functional groups, such as methoxy (**5e**), thiomethyl (**5f**), halides (**5h–5k, 5z, 5aa**), nitro (**5v**), cyano (**5w**), ester (**5x**), free alcohol (**5y**), and Bpin (**5n**), were well tolerated. In most cases, only dimethylated products were obtained with high selectivity. Notably, the scale-up reaction of 4-bormoaniline afforded **5j** in 64% yield. An excess amount of borane trimethylamine complex is required in the case of anilines bearing Lewis basic functional groups because of the chelating character of Lewis acidic borane. The steric hindrance of anilines did not affect the reaction efficiency because *meta*-bromoaniline and *ortho*-bromoaniline reacted smoothly to afford the *N,N*-dimethylanilines **5z** and **5aa** in 80% and 81% yields, respectively. Furthermore, heteroarenes reacted efficiently with CO_2 to yield products **5r–5t** and **5ab–5ae**). The present DIC–borane catalytic system was further used for the post-modification of Imiquimod, which shows efficacy against tumors, affording the demethylated product **5ad** in 63% yield.[11] 7-Amino-4-methylcoumarin reacted with CO_2 to afford **5ae**, which could potentially be used as an organic donor-acceptor molecule with antibacterial activity.[12] The reaction of various aliphatic amines also afforded the corresponding products **5af–5ai** in good yields.

Table 3. Dimethylation of amines with CO_2.[a]
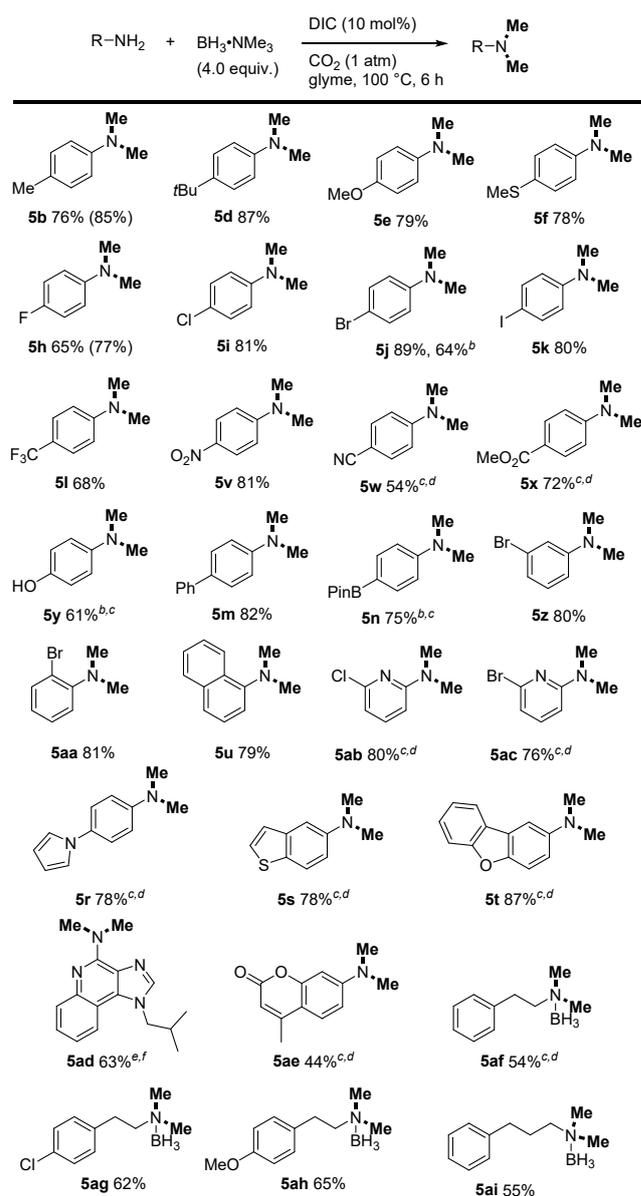
^{a} Reaction conditions: The reaction was carried out on a 0.3 mmol scale in glyme with a CO_2 balloon. NMR yield is shown in parenthesis. ^{b} in 5 mmol scale for 72 h. ^{c} 12 h. ^{d} 6 equiv. of BH₃·NMe₃. ^{e} 8 equiv. of BH₃·NMe₃. ^{f} 24 h.

To gain insight into the reaction mechanism, a series of control and mechanistic experiments were performed (Scheme 2). First, intermediates **IV** and **V** were detected by HRMS for the reactions of **DIC** with the borane−trimethylamine/borane−piperazine complexes and CO_2, respectively (Scheme 2a). Based on our previous work on intramolecular FLPs catalysts for CO_2 activation, we assumed that **IV** and **V** were the key intermediates for CO_2 activation. Furthermore, to identify the reaction intermediates, the reactions of **2a** were performed under both reaction conditions. The desired product *N*-methylaniline **3a** was obtained along with aniline **1a** [13] under both reaction conditions (Scheme 2b).

Notably, the reductive conversion of **2a** is more efficient under mono-methylation conditions. A similar reactivity was also observed in the reaction of **4a** (Scheme 2d). These results reveal that the formation of formanilide **2a** might be the rate-determining step under the mono-methylation conditions because of the fast reduction of **2a**. Most importantly, the reaction of **3a** only produced **5a** in 4% yield under the mono-methylation conditions (Scheme 2c), indicating that the sterically encumbered *N*-methylanilines and borane−piperazine complex hindered the reductive coupling reaction of **3a** with CO_2. Therefore, we conclude that the steric effects of the anilines and the borane−piperazine complex is the major reason for the selective mono-methylation of primary amines. But we also cannot exclude the possibility of solvent effect on the selectivity. By comparing the dimethylation results shown in Scheme 3b–d, the reductive coupling of **3a** with CO_2 efficiently afforded **5a** in 92% yield (Scheme 2c), while the reduction of **2a** and **4a** was much slower, indicating that formanilides **2a** and **4a** might not be the intermediates for the dimethylation reaction.

a)

b)

2a → **3a** + **1a**

	3a	1a
monomethylated conditions:	63%	37%
dimethylated conditions:	35%	6%

c)

3a → **4a** + **5a**

	4a	5a
monomethylated conditions:	0%	4%
dimethylated conditions:	8%	92%

d)

4a → **5a** + **3a**

	5a	3a
monomethylated conditions:	56%	13%
dimethylated conditions:	33%	19%

Scheme 2. Control experiments.

On the basis of the aforementioned mechanistic studies, we postulated a plausible reaction mechanism (Scheme 3). First, **DIC** reacts with borane *via* hydroboration to generate an active species **IV**, which acts as an intramolecular FLP to capture CO_2 to form the zwitterionic intermediate **V**. Meanwhile, aminoborane compound **VI,** which is generated from **1a** and borane through dehydrogenation, reacts with **V** to afford carbamoyl borate **VII** and releases the FLP catalyst **IV** to close the catalytic cycle. In the presence of the borane-piperazine complex, the reduction of **VII** affords formanilide **2a**; this

reduction reaction is the rate-determining step. **2a** could be quickly converted to mono-methylated amines **3a** and aniline. The monomethylated product could not react further with CO_2 because of the bulky borane−piperazine complex and **3a**. Under dimethylated conditions, we proposed that the borane-trimethylamine complex reduces **VII** to form formamide acetal-type intermediate **VIII**, which could also be reduced to **3a** and **1a**. **3a** was further reacted with CO_2 to afford dimethylated product **5a** in the presence of **IV** and the borane−trimethylamine complex.
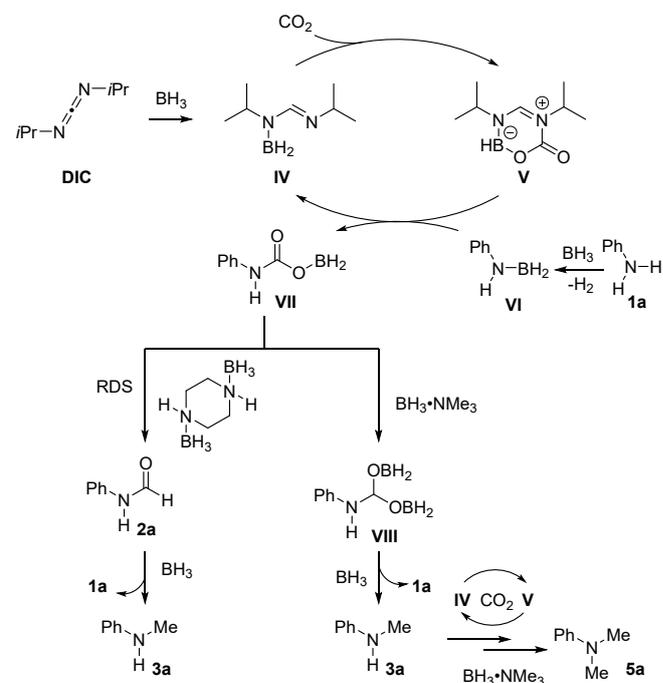
Scheme 3. Proposed mechanism for the *N*-methylation and *N,N*-dimethylation reaction.

Conclusions

In conclusion, the highly selective methylation of primary amines was achieved in the presence of the DIC−BH_3·piperazine and DIC−BH_3·NMe_3 catalytic systems. Diversely functionalized anilines were mono-methylated and di-methylated in good yields and high selectivity. Mechanistic studies indicate that the selectivity of the reaction is mainly controlled by the sterically demanding structures of anilines and borane complexes. The further expansion of the substrate scope of the present catalytic systems and mechanistic studies are currently ongoing.

Author Contributions

H.Z. carried out the reactions and analysed the data. Y.Z. did preliminary experiments. K. G. designed and supervised the project. K. G. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

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