Mesoionic N-heterocyclic olefin catalysed reductive functionalization of CO$_2$ for consecutive N-methylation of amines

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A mesoionic N-heterocyclic olefin (mNHO) was introduced as a metal-free catalyst for the reductive functionalization of CO$_2$ leading to consecutive double N-methylation of primary amines in the presence of 9-borabicyclo[3.3.1]nonane (9-BBN). A wide range of secondary amines and primary amines were successfully methylated under mild conditions. The catalyst sustained over six successive cycles of N-methylation of secondary amines without compromising its activity, which encouraged us to check its efficacy towards double N-methylation of primary amines. Moreover, this method was utilized for the synthesis of two commercially available drug molecules. A detailed mechanistic cycle was proposed by performing a series of control reactions along with the successful characterisation of active catalytic intermediates either by single-crystal X-ray study or by NMR spectroscopic studies in association with DFT calculations.

Introduction

Carbon dioxide (CO$_2$), the major nontoxic and increasingly abundant greenhouse gas, has potential to be one of the most useful reagents as a sustainable C1 building block with an enormous industrial prospect for the synthesis of value-added fine chemicals. In recent years, the catalytic activation of CO$_2$ to form new C-O, C-N, and C-C bonds has become more useful in synthetic chemistry through the reductive functionalization pathway. Towards reductive functionalization of CO$_2$, N-methylation for the construction of new C-N bonds in the presence of a hydride source such as borohydride or hydrosilanes is considered to be one of the promising and efficient routes. In particular, N-methylation of amines can give rise to products which are broadly used in the synthesis of medicines, dyes, agrochemicals, perfumes and drugs. Traditionally, N-methylanilines are synthesized using stoichiometric amounts of toxic reagents such as formaldehyde, methyl iodide, dimethyl sulphate etc. Thus, the use of CO$_2$ as a methylaing reagent under a reductive atmosphere is an attractive alternative to produce N-methyl amines through direct functionalization of amines. In the last decade, several metal catalysts and a few metal-free catalysts were reported for this catalytic transformation in the presence of hydrosilanes as a reducing agent and all of these studies were carried out at an elevated temperature. However, these methods have very limited potential towards consecutive N-methylation involving primary amines. In contrast to N-methylation of secondary amines, double N-methylation of primary amines has been considered challenging due to their much lower reactivity. Moreover, borohydrides as reducing agents were less studied than hydrosilanes for the reductive functionalization of CO$_2$ leading to N-methylation.

In this context, metal-free nucleophiles such as proazaphosphatrane super bases and carbodicarbenes have displayed moderate reactivity towards N-methylation using CO$_2$ which works only at a high temperature (100 °C) in the presence of BBN. A closer look at the mechanism described earlier reveals that it passes through the following key steps: (I) formation of boron formate, (II) formyl group transfer and (III) the reduction of the formyl group to the methyl group. Among these steps, steps II and III can be achieved only at high temperature. However, these authors recently introduced a super nucleophilic mesoionic N-heterocyclic olefin (mNHO) as a catalyst (Scheme 1a).

It may be recalled that N-heterocyclic olefins (NHOs), alkylidene derivatives of N-heterocyclic carbene (NHC) and carbodicarbenes (NHOs), have been emerging as metal-free catalysts for various organic transformations including CO$_2$ activation, polymerization, and hydroamination reactions. Besides these NHOs, Hansmann and co-workers recently introduced a super nucleophilic mesoionic N-heterocyclic olefin (mNHO) containing a polarised exocyclic double bond. The Tolman electronic parameter (TEP) of the Tolman electronic parameter (TEP) of 1 (2023 cm$^{-1}$) suggests that mNHO 1 has the strongest donor property...
a) Donor ability of carbenes, NHOs and mNHO:

![Scheme 1](image)

b) This work: mNHO as the catalyst for mono and double N-methylation:

![Scheme 2](image)

Results and discussion

The present investigation was started by optimizing the N-methylation of amines using CO₂ in the presence of a catalytic amount of mNHO (1), diphenylamine (2a) as a model substrate and borane as a reducing agent (see the ESI; Table S1†). To our delight, after several trial runs, it was observed that the mNHO works as an efficient catalyst for the N-methylation of secondary amines under mild conditions. Furthermore, such an optimization study unravelled that 9-BBN is the best hydride source delivering the highest isolated yield of 95% using 5 mol% mNHO (1) under 1 atmospheric pressure of CO₂ at 40 °C. Having the optimal catalytic conditions in hand, the scope of the reaction was further evaluated for the N-methylation of various secondary amines with 9-BBN as a hydride donor and mNHO (1) as a catalyst under 1 atm pressure of CO₂ (Scheme 2).

The secondary amines containing N-alkyl or N-aryl groups displayed an excellent activity towards N-methylation in the presence of catalyst 1. Diphenylamine derivatives (2) afforded the corresponding methylated products (3a–3h) in good to excellent isolated yields (73–95%). The diphenylamines containing electron donating groups have been found to be highly reactive under the optimized reaction conditions providing very good yields (79–86%) of N-methyl amines 3b–3f (Scheme 2). The bromo and chloro-substituted diphenylamines underwent N-methylation with 73% (3g) and 76% (3h) yields, respectively (Scheme 2). This catalytic protocol was also applied for the N-methylation of an N-heterocyclic amine, affording the N-methylated product 3i in a good yield (73%, Scheme 2). The substituted N-methylamines resulted in the formation of the N,N-dimethyl aniline derivatives 3j–3o in moderate to excellent isolated yields (55–80%) under the same reaction protocol (Scheme 2).

The 6e reduction of CO₂ leading to mono-N-methylated products in excellent yields made us curious if the same catalyst can be used for double N-methylation by performing consecutive 12e reduction. To succeed with such an objective, we argued in favor of a catalyst which would be highly sustainable under the reaction conditions to carry out the further methylation
The para position of primary aryl amines donating substituents. The electron donating substituents at focused on a variety of primary amines containing electron leading to the dimethylaniline derivatives 5b.

Scheme 3 Longevity of the catalyst. Reaction conditions: amines (0.2 mmol), CO2 (1 atm), 9-BBN (0.8 mmol), and dry THF (0.5 mL). A bar diagram showing yield (average yield of two experiments) versus number of catalytic cycles, emphasizing that the catalyst remains equally efficient over six successive catalytic cycles.

affording the N,N-dimethylaniline derivatives 5g–5i in moderate to very good yields (52–78%, Scheme 4). The ortho substituted aniline derivatives 4j–4m also exhibited moderate to very good reactivity and afforded the N,N-dimethylaniline derivatives 5j–5m (59–77%, Scheme 4). The 1-naphthylamine 4n showed good reactivity and was converted to N,N-dimethyl-1-naphthylamine 5n in 73% yield (Scheme 4). Aliphatic primary amines 4o–4p also responded well to our optimized protocol by delivering moderate to good yields (47–69%). The compound 4q containing both the ‘NH2’ group and ‘NH-Ph’ group in the same molecule was successfully methylated to form 5q resulting in 61% yield to achieve consecutive triple N-methylation counting to a total of 18e reduction process (Scheme 4). We have tried selective N-monomethylation of primary amines by lowering the amount of 9-BBN and altering the reaction conditions; however, these attempts were not successful (see the ESI, Scheme S19†).

Furthermore, the current catalytic protocol was applied to synthesize two commercially available drug molecules such as angustureine28,29 (7), an anti-malarial drug (Scheme 5a), and pempidine30 (9), a ganglion-blocking drug (Scheme 5b), with...
84% and 72% yields, respectively. Although compound 9 was synthesized earlier by reductive functionalization of CO₂, this is the first report of the synthesis of 7 using CO₂ as a reagent. These examples highlight the synthetic applicability of the current method.

Next, to delve into the mechanistic details of such a catalytic N-methylation process, a series of control reactions were carried out. At first, a stoichiometric reaction between mNHO 1 and 9-BBN in a 1 : 1 ratio was performed in toluene (Fig. 1a). After the completion of the reaction, an off-white solid was isolated from the reaction mixture. The 11B NMR spectrum of this off-white solid in C₆D₆ revealed a singlet at δ = 11.2 ppm (see the ESI; Fig. S3†), which is indicative of the formation of a mNHO–9BBN adduct (10). In another control reaction between mNHO and CO₂, the formation of the mNHO–CO₂ adduct was revealed. However, in our reaction protocol, we first mixed mNHO and 9-BBN (excess) and a mNHO–9BBN adduct (10) was formed. This observation discards the possibility of the involvement of the mNHO–CO₂ adduct in the reaction considering the sequence of addition of reagents. Furthermore, mNHO–9-BBN (10) was successfully crystallized from toluene under an argon atmosphere at −25 °C with 62% yield (Fig. 1a). The X-ray structure (Fig. 1b) revealed the C1–B1 bond length (1.689(4) Å) in 10 was slightly elongated compared to that observed for the tNHC–9-BBN adduct (1.636(2) Å). The C1–C2 bond length (1.483(4) Å) of 10 was longer than that of mNHO 1 (1.432(2) Å), which indicates that the π-electron cloud of mNHO has moved towards the boron center and increased the B–H hydride donor ability. To understand the reactivity of 10, a reaction between 10 and CO₂ was performed at room temperature for 30 min in THF (Fig. 1c). After completion of the reaction, the solvent was dried and a white solid product was obtained. 1H NMR (δ = 8.67 ppm) and 13C NMR spectroscopy (δ = 166.27 ppm) studies suggest the formation of the mNHO–boron formate intermediate 11 (see the ESI; Fig. S4 and S5†). To further investigate the
reaction mechanism, a series of control reactions were performed (Scheme 6). At first, the isolated 10 was used as a catalyst in the double N-methylation of substrate 4a which afforded the corresponding N,N-dimethylated product 5a in a very good yield (85%) under the optimized conditions (Scheme 6a) and it compares very well with the catalytic outcome (88% yield, see Scheme 4) using free mNHO 1. This experiment suggests that mNHO–9-BBN adduct 10 is a catalytically active intermediate for this N,N-dimethylation reaction. Next, in a screw cap NMR tube, 4-iodo aniline (4a) and 9-BBN were taken in a 1 : 1 ratio in the presence of 5 mol% 1 in C6D6 at room temperature (Scheme 6b) and the reaction was monitored by 1H NMR spectroscopy. During this reaction, a gas was evolved, which was identified as dihydrogen from the 1H NMR spectroscopy peak at δ = 4.47 ppm and further confirmed by GC–MS analysis (see the ESI; Fig. S7 and S8‡). After completion of this reaction (12 h), 1H and 13C NMR spectroscopy of the reaction mixture confirmed the formation of an N-borylated compound 12 (see the ESI; Fig. S9 and S10‡). Similar to that for 4-iodo aniline, we also observed the dehydrogenative B–N coupling product 12a for the aniline substrate (see the ESI; Fig. S11 and S12‡). Such an N-borylation of amines with hydrogen liberation has been reported earlier.

Furthermore, when 12 was treated with 7 equiv. of 9-BBN and 5 mol% of 1 under 1 atm pressure of CO2 at 40 °C, it afforded 4-iodo N,N-dimethyl aniline 5a in 86% yield, which confirms that the reaction proceeds through the intermediacy of 12 (Scheme 6c). It has been reported earlier that the N-methylation of amines proceeds in a stepwise manner through the N-formylation of amines.16,27 To check this, we performed the reduction of formanilide 13, using 2.5 equiv. of 9-BBN in the presence of catalyst 1 (Scheme 6d). The formation of N-methyl aniline in 76% yield suggests that the N-methylation reaction proceeds via N-formylation. A control reaction between formanilide 13 and 9-BBN in the absence of the mNHO catalyst did not produce N-methyl aniline which indicates the involvement of the catalyst during this step. We performed a stoichiometric reaction between mNHO–boron formate 11 and 12 in a 1 : 1 ratio which afforded 4-iodo N-formylamine 13a with 79% yield (Scheme 6e), characterized by 1H and 13C{1H} NMR spectroscopy (see the ESI, Fig. S18 and S19‡). Formation of 13a suggests that the N-methylation reaction proceeds through N-formylation.

A full reaction path was mapped with the help of DFT calculations using the M06-2X/6-311+G(d)-SMD(THF)//B3LYP/6-31G(d) level of theory (for full energy profile diagrams, see the ESI, Fig. S95 and S96‡). Based on the calculated reaction energetics and the experimental support, a plausible reaction mechanism was sketched for N,N-dimethylation of primary amines in Scheme 7. At first, mNHO 1 reacts with 9-BBN to form mNHO–9-BBN adduct 10, which was crystallographically and NMR spectroscopically characterized. In this step, the B–H bond of the borane gets activated through coordination of a strong nucleophile mNHO. In the next step, the activated B–H bond inserts a CO2 molecule forming the intermediate 11 through TS1 (Fig. 2a) which is 8.9 kcal mol⁻¹ (ΔDG‡) lower in energy than that of the catalyst free conditions. Compound 11 was characterized by NMR spectroscopic studies. Simultaneously, the amine is activated by reaction with 9-BBN forming the N-borylated compound 12 with the liberation of hydrogen gas. In the subsequent step, the formyl group was transferred to the intermediate 11 to N-borylated amine 12 leading to the formation of formanilide 13 and (9-BBN)2O as a byproduct, which was characterized by NMR spectroscopy (see the ESI; Fig. S24 and S25‡). The theoretical study reveals that the transition state TS2, corresponding to the formyl transfer, is energetically less favorable than that of the uncatalyzed one without the assistance of the mNHO catalyst (ΔDG‡ = −22.0 kcal mol⁻¹). However, with the help of a series of control reactions (see
Scheme 6e, also see the ESI; Schemes S11–S13†, we indeed found that the involvement of the mNHO catalyst is compulsory for the formyl transfer from mNHO–9-BBN formate 11 to the N-borylamine 12 species. This is in consonance with the fact that the formation of 9-BBN formate is not favorable in the absence of mNHO (indicated from the difference in the transition barrier corresponding to TS1 for catalyzed and uncatalysed reactions). After the formation of N-formylated product 13 as the reaction intermediate, it undergoes further reduction to intermediate 14 involving TS3f. Computational study suggests that this step does not require the involvement of a catalyst. Next, 14 undergoes further reduction with the mNHO–9-BBN adduct through TS4 (Fig. 2b) which is 23.5 kcal mol$^{-1}$ lower than that of the catalyst free conditions. This step afforded the final $N,N$-dimethyl aniline along with the formation of (9-BBN)$_2$O as a byproduct. For double $N$-methylation, the mechanistic steps discussed above may repeat to deliver the final $N,N$-dimethylated product.

Conclusions

In the present work, mNHO has been introduced as the catalyst for $N,N$-dimethylation and $N$-methylation of primary and secondary amines, under mild conditions, using CO$_2$ as the C1 source and 9-BBN as the hydride source. Moreover, this newly developed methodology was successfully extended towards the preparation of two commercially available drug molecules. This result demonstrates that mNHO can be used as an efficient catalyst for the consecutive 12e reduction process leading to double $N$-methylation. A series of control reactions and theoretical calculations were performed to understand the underlying mechanistic pathway through the isolation and characterization of various reaction intermediates either by single-crystal X-ray study or by NMR spectroscopy along with the realization of different transition states. Further application for functionalization of CO$_2$ using mNHO as a metal-free catalyst is currently ongoing in our laboratory.

Data availability

All experimental procedures, characterization details, copies of NMR spectra for all compounds, and computational data related to this article have been uploaded as part of the ESI. Crystallographic data for 10 have been deposited at the CCDC under 2065467 and can be obtained from https://www.ccdc.cam.ac.uk/structures/.

Author contributions

SKM and SM conceived the idea of this work. SM carried out all synthetic and catalytic experiments as well as DFT calculations. AD contributed to X-ray structure determination. SKM supervised the overall work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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