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Direct Catalytic Reductive N-Alkylation of Amines with Carboxylic Acids: Chemoselective Enamine Formation and further Functionalizations

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KEYWORDS: chemoselective N-alkylation, carboxylic acids, enamine, hydrosilylation, functionalization

ABSTRACT. Direct reductive N-alkylation of secondary amines with carboxylic acids using molybdenum hexacarbonyl (5 mol%) as catalyst and diethoxymethylsilane as reducing agent generate enamines in a straightforward fashion in high yields. The formed enamines are without the need for isolation or purification further reacted with trimethylsilyl cyanide in the same reaction flask to yield α-amino nitriles in good yields.

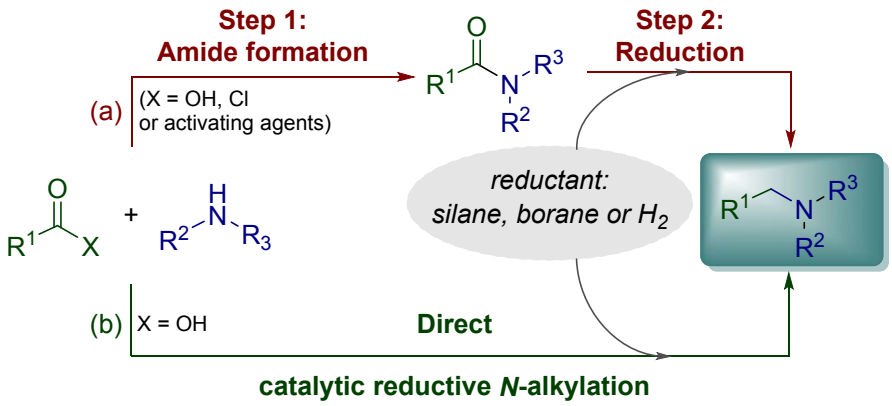
In the optimized reaction conditions equimolar amounts of carboxylic acid and amine are reacted under neat conditions, and a catalytic amount of trifluoroethanol (0.1 mol%) is added along with TMSCN for the cyanation step. The reductive N-alkylation reaction is demonstrated to be highly chemoselective, tolerating a multitude of different functional groups present in the starting carboxylic acids and amines. The reaction is scalable and the generated α-amino nitriles are converted to other useful compounds, e.g. α-amino acids or amino-tetrazoles. In addition, the intermediate enamines are further transformed into triazolines, sulfonylformamidines, pyrimidinediones and TMS-propargylamines, respectively, in high yields under mild reaction conditions. Benzoic acids react with secondary amines under similar conditions to give tertiary amines in high yields, and using this methodology, the biologically active compound Piribedil was isolated in 80% yield in a direct one-pot reaction set-up.

INTRODUCTION

Substituted amines are important functional groups present in numerous biologically active organic compounds such as amino acids, nucleotides and alkaloids. Substituted

amines play an important role in chemistry and biology, frequently being used as versatile building blocks for organic and biological systems, agrochemicals and pharmaceuticals.[1] Therefore, methods that enable efficient synthesis of substituted amines have been pursued intensively. Among the different methodologies available, catalytic reduction protocols of imines and amides constitute fundamental routes for their preparation.[2] However, an inherent drawback of such synthetic protocols is the need of proper starting materials, where the latter frequently needs to be prepared and isolated prior to the reduction step (Scheme 1, a).[3]

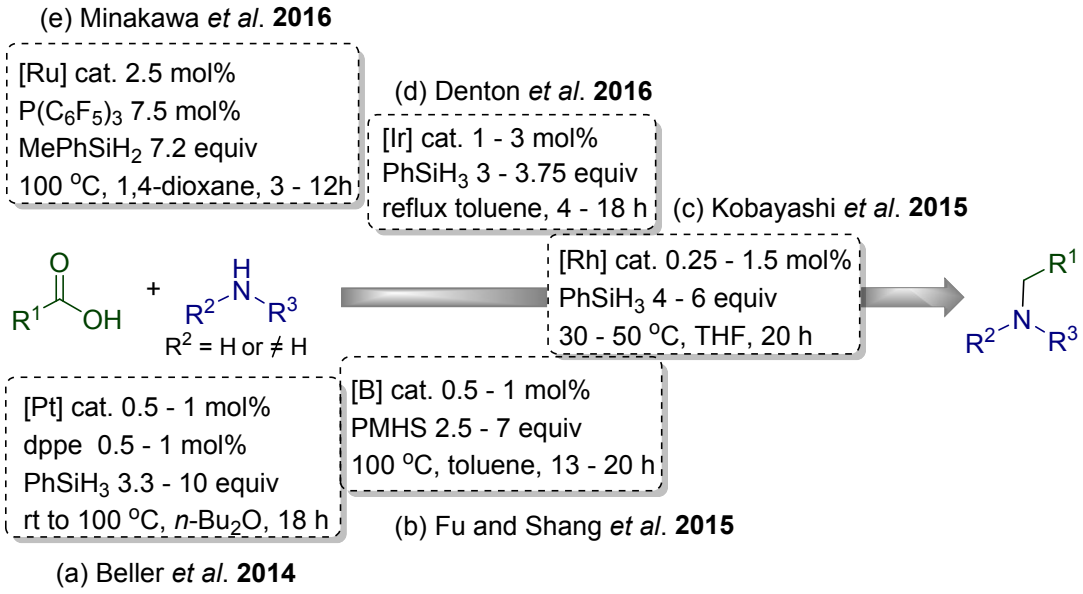
Direct reductive amination of carbonyl compounds represent a well-established and practical approach for the formation of substituted amines. In this sense, mainly aldehydes or ketones are reacted with amines in the presence of a reducing agent to afford the desired products.[4]



Scheme 1. Methods for reductive N-alkylation of amines: (a) Two-step amide formation and subsequent reduction using silane, borane or H_2 as reductant. (b) Direct catalytic reductive protocol using carboxylic agents as alkylating reagents with silane, borane or H_2 as reductant.

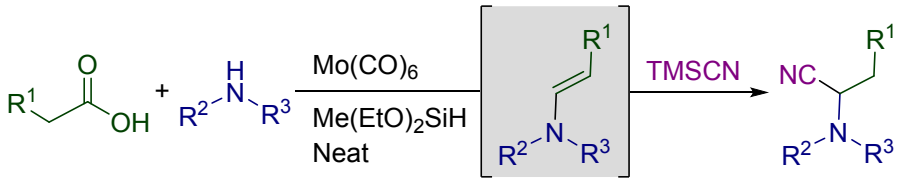
In contrast, the use of such a strategy starting from carboxylic acids is significantly less studied due to the lower reactivity of the acids and the intermediate amides. Nevertheless, direct reductive alkylation of amines with carboxylic acids offer several advantages. Carboxylic acids are frequently rather stable, non-toxic, and readily available with large structural variation, which make such compounds most suitable as N-alkylating agents for the formation of substituted amines (Scheme 1, b).[5]

A limited number of methodologies have been presented for the catalytic N-alkylation of amines with carboxylic acids in the presence of silanes (Scheme 2). The first protocol reported was by Beller's group in 2014, where a [Platinum/dppe] complex was used to obtain a broad scope of N-alkylamines in high yields (Scheme 2, a).[6] A year later, Fu, Shang and co-workers reported on a catalytic boron-acid system employing polymethylhydrosiloxane (PMHS) as hydride source, and they obtained more than twenty N-alkylamines in excellent yields (Scheme 2, b).[7] After these pioneering works, different methodologies have been published by the groups of Kobayashi, Denton and Minakawa for the same transformation using rhodium-,[8] iridium-,[9] and ruthenium-based[10] catalysts, respectively (Scheme 2, c, d and e).



Scheme 2. Catalytic N-alkylation of amines with carboxylic acids under hydrosilylation conditions.

In spite of the recent breakthroughs and the progress made in this field over the last years, there are, to the best of our knowledge, no reports on the selective N-alkylation of amines with carboxylic acids leading to enamines. Carboxylic acids possessing α-hydrogens are particular interesting since partial reduction of the intermediate amide can lead to the corresponding enamines. Enamines are reactive intermediates present in a number of organic transformations and can thus serve as suitable synthetic handles for a number of further elaborations. Herein we describe an un-precedented, mild and chemoselective catalytic protocol for the reductive N-alkylation of amines using carboxylic acids under hydrosilylation conditions, which allows for the formation of enamines and the subsequent functionalization of these into α-amino nitriles (Scheme 3).



Scheme 3. This work: $Mo(CO)_6$ catalyzed selective N-alkylation of amines with carboxylic acids under hydrosilylation conditions.

RESULTS AND DISCUSSION

We have previously developed a highly chemoselective protocol for the reduction of amides based on catalytic amounts of $Mo(CO)_6$ and TMDS (1,1,3,3-tetramethyldisiloxane) as terminal reductant.[11] Depending on the reaction conditions used, we were able to selectively convert amides to either amines or aldehydes, via an intermediate silylhemiaminal. Performing the reduction on carboxamides bearing α-hydrogens opened a direct route for the formation of enamines, which were subsequently further functionalized.[12,13] This methodology was successfully applied in the chemoselective reductive functionalization of amides into bi-functional compounds such as α-amino nitriles, an essential class of compounds with interesting

pharmacological and biological properties.[13,14] The ready availability of carboxylic acids and amines prompted us to examine a similar process, where the direct amidation followed by reductive functionalization would yield highly functionalized compounds from simple starting materials using a one-pot setup. We started by investigating different reaction parameters such as testing various silanes, temperatures and solvents for the reaction between phenylacetic acid (**1a**) and pyrrolidine (**2a**). The reductive vinylation of **2a** in the presence of 5 mol% of $Mo(CO)_6$ and $Me(EtO)_2SiH$ as hydride source, gave the corresponding enamine **3a'** in 89% ^1H NMR yield. To our delight, performing the reaction under neat conditions and with stoichiometric amounts of the reagents allowed for full conversion to the enamine in less than 3 hours, hence demonstrating high efficiency and excellent atom economy (For more details on the optimization procedure and results, see the Supporting Information).

Enamines are frequently used as reactive intermediates in many organic transformation. Addition of trimethylsilyl cyanide (TMSCN, 2 equiv) and catalytic amounts of 2,2,2-trifluoroethanol (TFE) after the initial formation of **3a'** gratifyingly resulted in the formation of the corresponding α-amino nitrile **3a** in 90% in less than 1

hour (for more information, see the Supporting Information). Attempts to obtain **3a** by addition of TMSCN from the beginning of the reaction sequence did not result in the desired product and we only observed the formation of the corresponding amide.

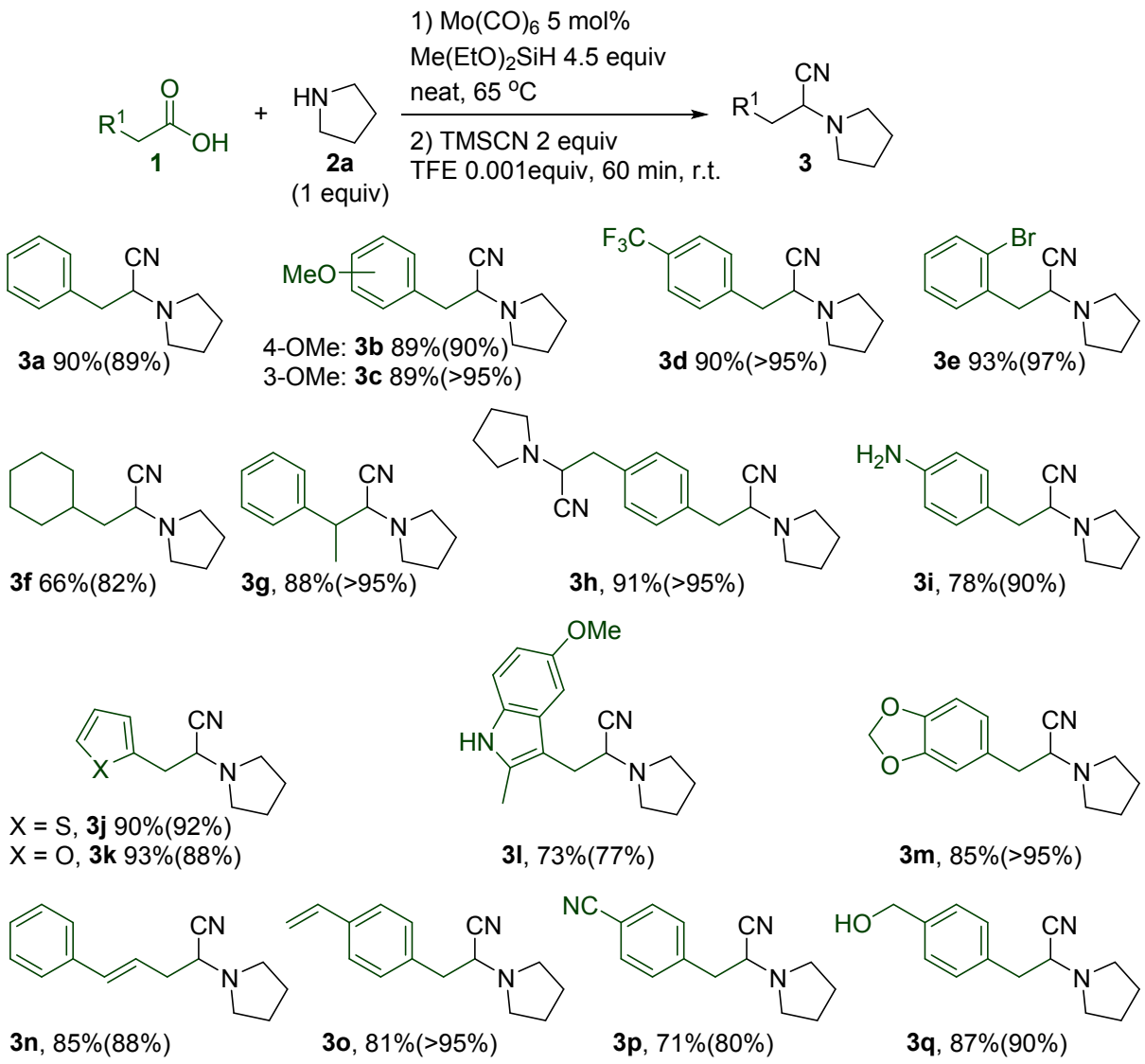
With the above conditions in hand, the scope of the catalytic reductive alkylation of amines into enamines followed by subsequent functionalization into α-amino nitriles in a one-pot reaction setup was studied in detail. As shown in Scheme 4, a variety of aryl- and alkyl-acetic acids were successfully used for the vinylation of pyrrolidine generating the corresponding enamines, which thereafter were further functionalized into the final products.

Phenyl acetic acids carrying electron-donating or electron-withdrawing substituents gave the desired α-amino nitriles **3b**, **3c**, **3d** and **3e**, respectively in high yields (Scheme 4). The direct formation of α-amino nitrile **3e** without dehalogenation allows for further functionalizations into even more complex structures. When 2-cyclohexylacetic acid was used as alkylating agent, a good ^{1}H NMR yield was observed in the initial formation of the corresponding enamine, however, **3f** was only isolated in moderate yield. High yield was achieved for double alkylation using 1,4-phenylenediacetic acid, giving in

quantitative yield of the corresponding di-cyanation product **3h**. Next, we turned out our attention to carboxylic acids containing different functional groups. Amino group (**3i**) and heterocycles (**3j, 3k** and **3l**) were well tolerated giving the corresponding enamines and subsequent α-amino nitrile in moderate to high yields. In the case of *trans*-styrylacetic acid (**1n**), the conjugated intermediate enamine was quantitatively formed allowing for the formation of **3n** in high yield. This catalytic methodology also tolerated acetals, terminal olefins and cyano groups and α-amino nitriles **3m**, **3o** and **3p**, respectively, were obtained in high yields. To our delight, the hydroxyl moiety (**3q**) was not silylated under the reaction conditions, which demonstrates the high level of chemoselectivity of this protocol. When this catalytic protocol was applied on linear aliphatic acids and phenylacetic acids containing nitro and aldehydes groups, respectively, no or small amounts of the corresponding enamines were detected by ^{1}H NMR analysis.

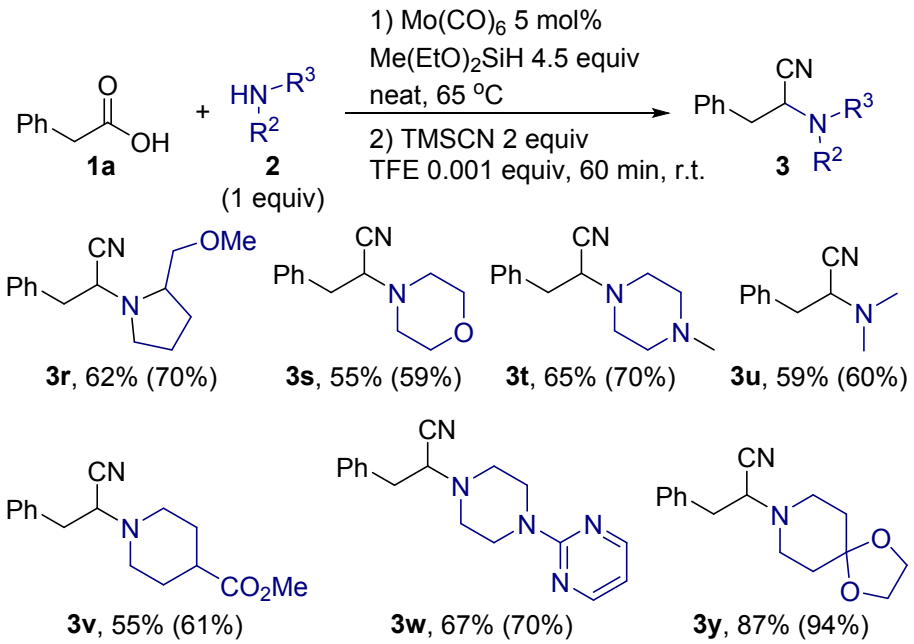
Next, we focused on the alkylation of different amines (Scheme 5). Moderate basic amines such as morpholine afforded the enamine and the subsequent α-amino nitrile **3s** in good yield. N-methyl amines are of special interest because of their role in the regulation of several biological processes.[15] In this respect, N-methyl piperazine and

dimethyl amine were successfully vinylated with phenyl acetic acid to the corresponding enamines, and subsequently reacted with TMSCN to afford α-amino nitriles **3t** and **3u**, respectively, in good isolated yields. Interestingly, no reduction of the ester moiety on the piperidinyl carboxylate derivative was observed although the enamine (**3v'**) was only formed in 61% ^{1}H NMR yield. When the amine containing an acetal moiety was used, high yield was obtained for α-amino nitrile **3y**.



Scheme 4. N-alkylation of **2a** with various carboxylic acids[a].

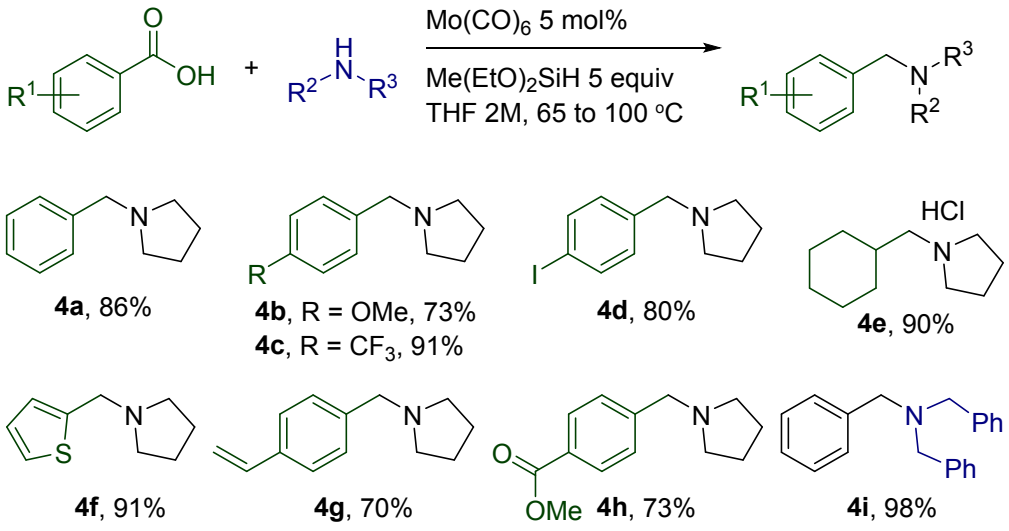
[a] Isolated yields. In parenthesis ^{1}H NMR yields for the corresponding enamine using 1,3,5-trimethoxybenzene as internal standard. Step 1: $Mo(CO)_6$ (0.05 mmol), carboxylic acid (1.00 mmol), pyrrolidine **2a** (1.01 mmol), $Me(EtO)_2SiH$ (4.50 equiv). For information about temperature and time for each substrate, see Table S3 in Supporting Information. Step 2: TMSCN (2.00 equiv), TFE (100 μL), r.t., 60 min.



Scheme 5. N-alkylation of different amines with **1a**[a].

[a] Isolated yields. In parenthesis ^{1}H NMR yields for the corresponding enamine using 1,3,5-trimethoxybenzene as internal standard. Step 1: $Mo(CO)_6$ (0.05 mmol), **1a** (1.00 mmol), amine (1.01 mmol), $Me(EtO)_2SiH$ (4.50 equiv). For information about temperature and time for each substrate, see Table S3 in the Supporting Information. Step 2: TMSCN (2.00 equiv), TFE (100 μL), r.t., 60 min.

Anilines and primary aliphatic amines were poor substrates in this protocol, where N-methyl anilines typically gave less than 20% ^{1}H NMR yield of the desired enamine (not shown).



Scheme 6. N-alkylation of amines with benzoic acids[a].

[a] Isolated yields. $Mo(CO)_6$ (0.05 mmol), carboxylic acid (1.00 mmol), starting amine (2.00 mmol), $Me(EtO)_2SiH$ (5 equiv), THF (0.5 mL), 65 °C (2h) and then 100 °C (2h).

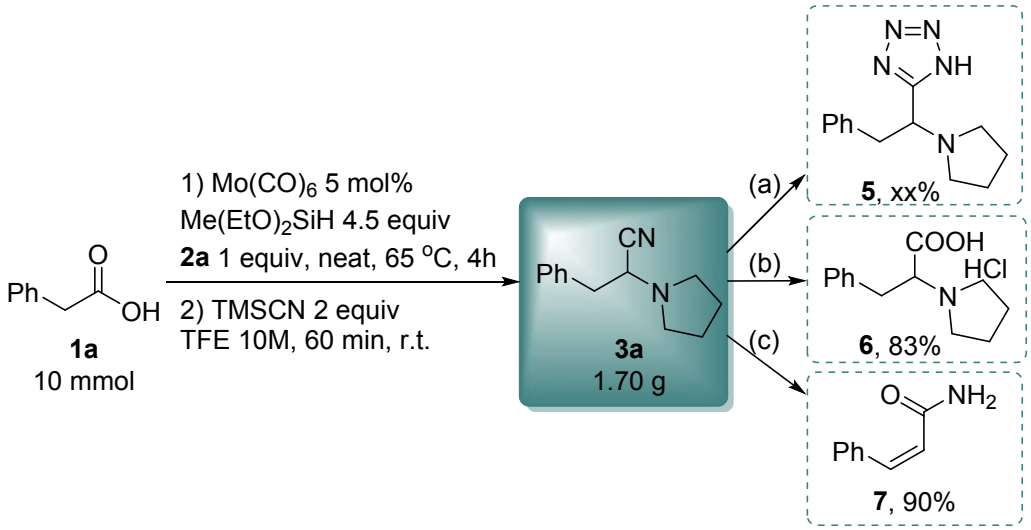
We thereafter investigated the use of benzoic acids as alkylating agents. In these cases, tetrahydrofuran (THF) as reaction media and two equivalents of the starting amine were required for a successful reaction outcome. Under these conditions, we studied a series of different benzoic acids, and the corresponding amines were isolated in good to high yields (Scheme 6). The methodology is applicable for both electron-rich and electron-poor benzoic acids. Methoxy-, trifluoromethyl- and iodobenzoic acids, aliphatic and heteroaryl-carboxylic acids were all well tolerated affording **4b**, **4c**, **4d**, **4e** and **4f**, respectively, in good yields. Furthermore, functional groups such as olefins (**4g**) and esters (**4h**) remained untouched under the reaction conditions, which highlight the level of chemoselectivity of this methodology (Scheme 6).

Some limitations using benzoic acids as alkylating agents were found when the reactions were carried out with acids containing alkyne, nitro and ketone functionalities.

In these cases we observed no formation of the alkylated amines (for more information, see the Supporting Information).

APPLICATIONS

α-Amino nitriles are valuable bi-functional compounds due to their widespread use in chemistry and biology. One mode of reactivity of these compounds is via functional group interconversion of the nitrile group in which the original carbon atom connectivity is preserved. Furthermore, a highly relevant aspect in academia and industry is the ability to scale up catalytic protocols. With these aspects in mind, we performed the direct α-amino nitrile formation on a preparative scale followed by further functionalization of the nitrile group (Scheme 7). The α-amino nitrile formation was efficiently performed on a 10 mmol scale yielding 1.70 g of **3a**, which subsequently was transformed into tetrazole **5**, α-amino acid **6** and the carbon extended primary amide **7**, in high yields.

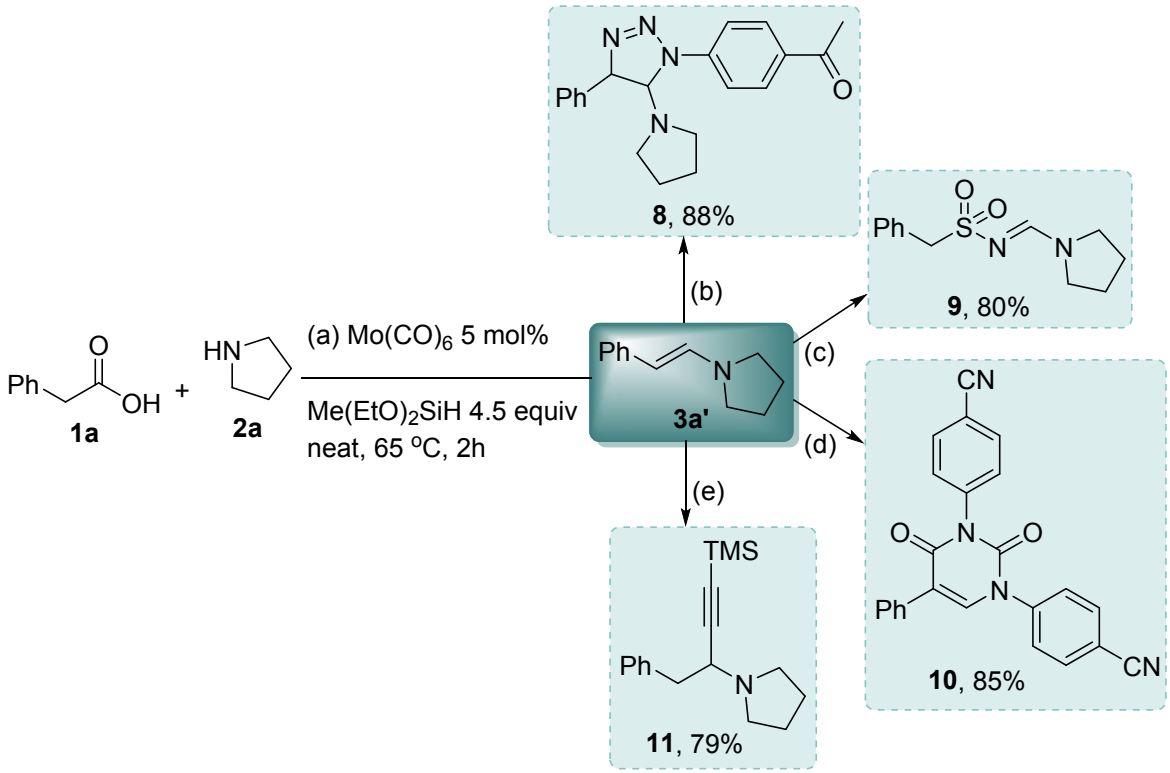


Scheme 7. Preparative scale and derivatization of **3a**.[a]

[a] Isolated yields. Step 1: $Mo(CO)_6$ (0.5 mmol), **1a** (10.0 mmol), **2a** (10.1 mmol), $Me(EtO)_2SiH$ (45.0 equiv), 65 °C, 4h. Step 2: TMSCN (20.0 equiv), TFE (1.0 mL), r.t., 60 min. (a) $TMSN_3$ (10.0 equiv), Bu_3SnO (0.6 equiv), toluene, 70 °C, 2 d; (b) HCl (37% wt), reflux, 24 h; (c) H_2O_2 (2.0 equiv), K_2CO_3 (1.2 equiv), DMSO, 40 °C, 4h.

To further demonstrate the applicability of this methodology we used standard reaction protocols for the functionalization the enamine **3a'**, which was converted into triazoline **8**, sulfonylformamidine **9**, pyrimidinedione **10** and the TMS-propargylamine **11**, respectively, in high yields under mild reaction conditions (Scheme 8). In the latter

case, compound **11** was generated using trimethylsilyl-acetylene without the need of a copper source. [16]

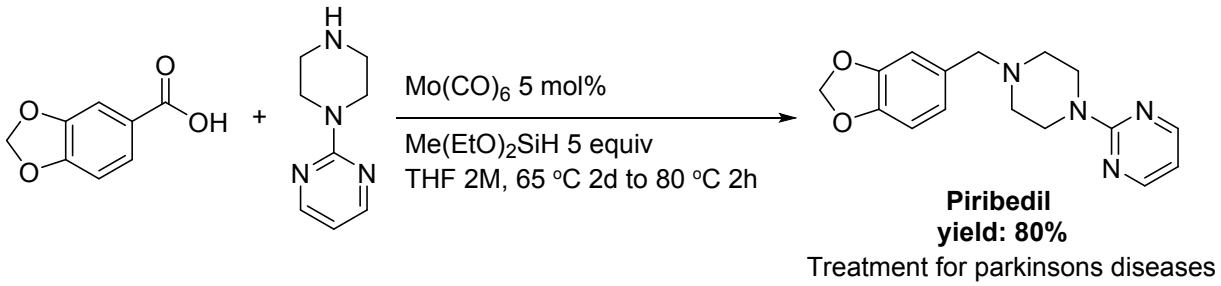


Scheme 8. Further functionalization of **3a'**.[a]

[a] Isolated yields. (a) $Mo(CO)_6$ (0.05 mmol), **1a** (1.00 mmol), **2a** (1.01 mmol), $Me(EtO)_2SiH$ (4.50 equiv), 65 °C, 3h. (b) 1-(4-azidophenyl)ethan-1-one (1.50 mmol), TFE (100 μL), 40 °C, 2h (c) phenylmethanesulfonyl azide (1.50 mmol), TFE (100 μL), r.t., 40 min. (d) 4-cyanophenylisocyanate (2.00 mmol), TFE (100 μL), 65 °C, 2 h. (e) ethynyltrimethylsilane (2.00 mmol), TFE (100 μL), 65 °C, 2 h.

In addition we targeted the pharmaceutical active compound Piribedil, a dopamine D2 agonist used in the treatment of Parkinson disease and for circulatory disorders.[17] The

use of the molybdenum-based catalytic protocol allowed a facile alkylation of N-pyrimidylpiperazine with piperonylic acid, and Piribedil was isolated in 80% yield (Scheme 9).



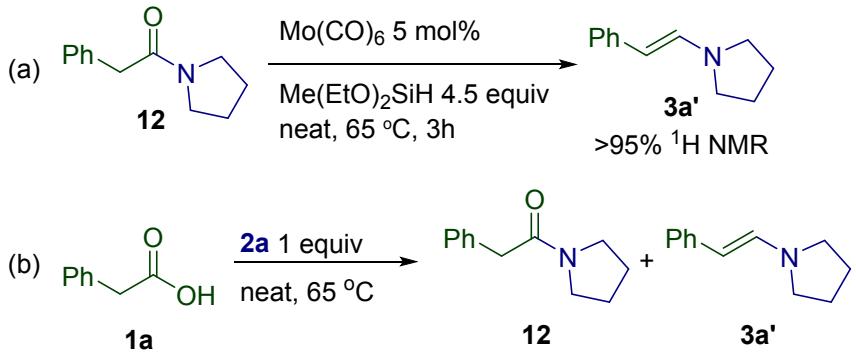
Scheme 9. One pot synthesis of Piribedil.

REACTION PATHWAYS

With respect to the reaction mechanism, two main pathways have been proposed for the alkylation of amines with carboxylic acids. Conventional reductive amination of aldehydes, generated by reduction of the corresponding acid,[18] or a direct condensation reaction promoted by the hydrosilane to generate the subsequent carboxamide intermediate followed by in situ reduction.[7b,19]

In order to obtain more information about the reaction mechanism, several control experiments were conducted. Since amide formation was detected during the optimization of reaction conditions and the evaluation of the scope of this protocol, initial formation of a carboxamide intermediate followed by a subsequent reduction of the amide appears to be a plausible reaction pathway. Indeed, the reaction of 2-phenyl-1-pyrrolidinylethan-1-one **12**, under same reaction conditions generated the enamine intermediate quantitatively (Scheme 10, a). When the reaction between **1a** and pyrrolidine (**2a**) was carried out only in presence of $Me(EtO)_2SiH$ at 65 °C, we observed full conversion to amide **12** in 90 minutes. Moreover, using the same reaction setup without adding the silane, but with a catalytic amount of $Mo(CO)_6$ present, resulted in full recovery of the starting materials after heating the reaction mixture at 65 °C for 90 minutes (Scheme 10, b). Additionally, we investigated if $Mo(CO)_6$ had any effect on the reaction rate in the amidation step. We set up a series of experiments using phenylacetic acid (**1a**) and pyrrolidine (**2a**) as model substrates for the reactions, sampled aliquots at different time points and analyzed these by ^1H NMR. Figure 1 displays the kinetic profiles for two different reaction setups, one using the standard

conditions, and in the second no catalyst was added. Both reactions were performed with the same initial concentrations of **1a** and **2a**. The results clearly demonstrate that $Mo(CO)_6$ increase the rate of amide formation in comparison to the catalyst-free reaction, and most interestingly, first upon full conversion of amine and acid to amide, the enamine starts to form. Hence, the molybdenum catalyst plays a dual role in 1) increasing the rate of amide formation and 2) being essential in the enamine generating process.



(b.1) $Me(EtO)_2SiH$ 4.5 equiv, 90 min	>95%	-
(b.2) $Mo(CO)_6$, 90 min	-	-

Scheme 10. Mechanistic experiments.[a]

[a] ^1H NMR yields using 1,3,5-trimethoxybenzene as internal standard (a) $Mo(CO)_6$ (0.05 mmol), **12** (0.50 mmol), $Me(EtO)_2SiH$ (4.5 equiv), 65 °C, 3h. (b) **1a** (1.0 mmol), **2a** (1.01 mmol), (b.1) $Me(EtO)_2SiH$ (4.5 equiv), 65 °C, 90 min. (b.2) $Mo(CO)_6$ (0.05 mmol), 65 °C, 90 min.

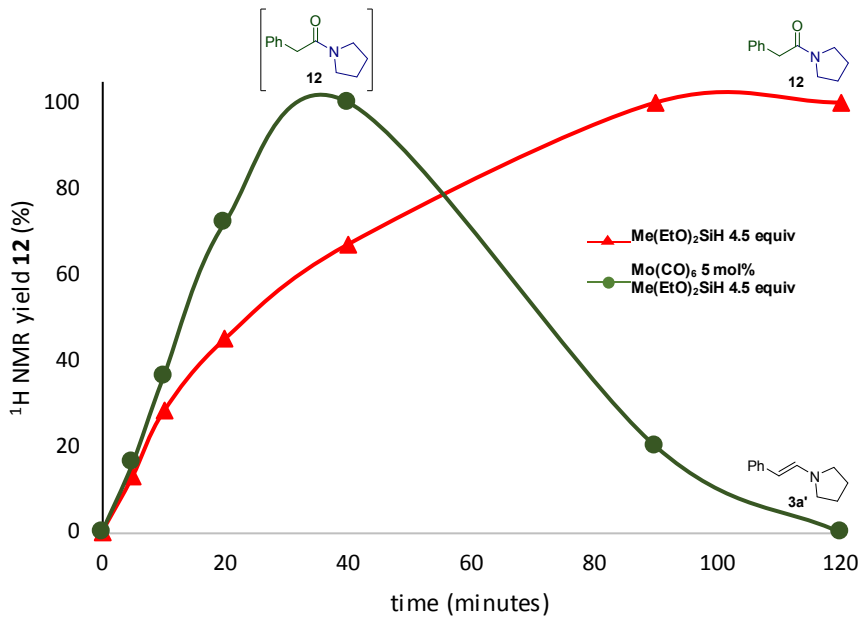
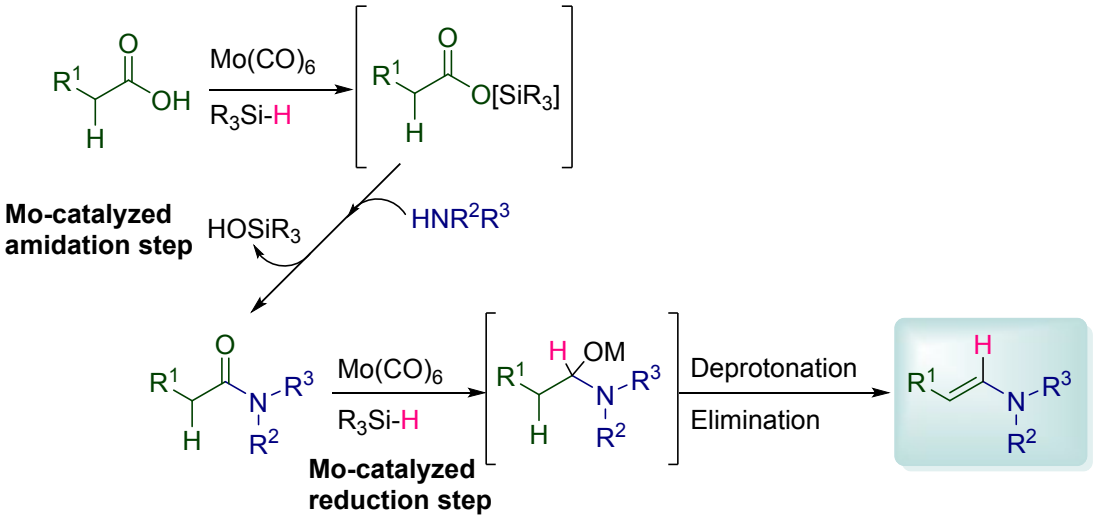


Figure 1. Kinetics profile using standard conditions and under absence of $Mo(CO)_6$.[a]

[a] ^{1}H NMR yields using 1,3,5-trimethoxybenzene as internal standard. $Mo(CO)_6$ (0.05 mmol), **1a** (1 mmol), **2a** (1.01 mmol), $Mo(CO)_6$ (0.05 mmol), $Me(EtO)_2SiH$ (4.5 equiv), 65 °C, 90 min.

On the basis of the above-mentioned results and previous mechanistic investigations on the $Mo(CO)_6$-catalyzed amide reduction by Pannell and co-workers,[20] a plausible reaction mechanism is depicted in Scheme 11. The initial direct condensation reaction to generate the carboxamide intermediate is likely to proceed via formation of a silyl-ester in a reaction between the carboxylic acid and the Mo-silane system. The silyl-ester act as an acylating agent reacting with the amine nucleophile to generate the amide. A

possible Lewis-acid activation of the silyl-ester by the Mo-catalyst is expected and can explain the increased reaction rate in this step. The reduction step where the enamine is generated requires a hydride-attack, catalyzed by the Mo-silane system, on the C=O bond of the amide to generate an intermediate silylhemiaminal which collapse into the enamine via a deprotonation-elimination step. As presented in Figure 1, the enamine **3a´** starts to form first upon completion of the amide generating step. A possible explanation for this behavior could be an inhibition of the Mo-catalyst by coordination of free amine to the metal center. Hence, at low amine concentration, the Mo-silane system becomes active and facilitate the formation of the enamine.



Scheme 11. A plausible reaction mechanism for the amidation-enamine formation reaction.

SUMMARY

In conclusion, we have developed a general and straightforward molybdenum-catalyzed reductive N-alkylation of amines with a variety of carboxylic acids in the presence of diethoxymethylsilane as reducing agent, which generate tertiary amines or enamines. The generated enamines were efficiently *in situ* trapped with various reagents to generate a variety of more complex organic compounds, e.g. α-amino nitriles, heterocycles and propargylamines. This green alkylation protocol, which avoid the isolation of synthetic intermediates, allows for a direct route to structurally diverse organic compounds from simple starting material, in a straightforward fashion. This catalytic protocol display an excellent level of chemoselectivity and it can furthermore be run on a preparative scale. The synthetic utility of this methodology on the formation of complex biologically active compounds was demonstrated in the preparation of the drug molecule, Piribedil.

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ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Text, tables, and figures giving experimental procedures and characterization data (PDF)

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