



Andrews, Keith Gordon and Summers, Declan and Donnelly, Liam and Denton, Ross Matthew (2015) Catalytic reductive N-alkylation of amines using carboxylic acids. *Chemical Communications* . ISSN 1364-548X (In Press)

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Catalytic Reductive *N*-Alkylation of Amines using Carboxylic Acids

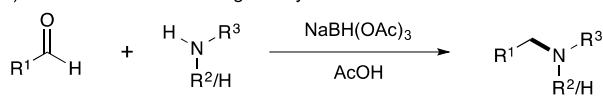
Keith G. Andrews, Declan M. Summers, Liam J. Donnelly and Ross M. Denton*

We report a catalytic reductive alkylation reaction of primary or secondary amines with carboxylic acids. The two-phase process involves silane mediated direct amidation followed by catalytic reduction.

Reductive amination between aldehydes and amines (Scheme 1A) constitutes one of the most versatile methods for carbon-nitrogen bond construction and underpins the synthesis of natural products, active pharmaceutical ingredients, agrochemicals and advanced materials.^{1,2} Despite its importance and prevalence there are several disadvantages associated with the conventional process, including the handling of unstable aldehydes (mostly accessed *via* stoichiometric oxidation) and selectivity for monoalkylated products.

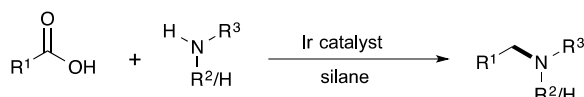
Replacing aldehydes with carboxylic acids, which are far easier to store and handle (Scheme 1B), would open up a powerful complementary approach to reductive *N*-alkylation with high synthetic utility. However, such reductive amination from the higher oxidation level remains underexplored.^{3,4}

(A) Reductive amination using aldehydes and amines



(B) This work:

Catalytic reductive *N*-alkylation using carboxylic acids and amines

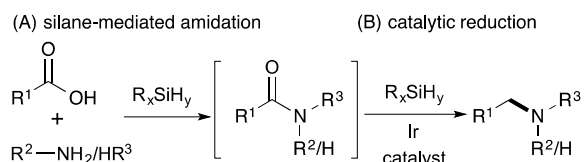


Scheme 1. a) Classical reductive amination reaction. b) This work: catalytic reductive alkylation using carboxylic acids.

Indeed, until recently, the only reported reductive amination of higher carboxylic acids was the interesting but non-preparative system investigated by Cole-Hamilton and co-workers.^{3g} Very recent work by the group of Beller describes the platinum-catalysed reductive *N*-alkylation of amines with carboxylic acids⁵ while a metal-free borane-catalysed protocol was disclosed by Fu and Shang.⁶ A further report from Beller documents a ruthenium-catalysed process, which exploits hydrogen as a terminal reductant.⁷ Despite these recent breakthroughs, the development of a highly practical method – the former two reports require Schlenk apparatus; the latter high pressures in an autoclave – remains a significant challenge.

Herein we describe an alternative protocol for catalytic *N*-alkylation (Scheme 2) that exploits the dual reactivity of phenylsilane in a two phase process consisting of direct amidation⁸ followed by catalytic amide reduction.⁹

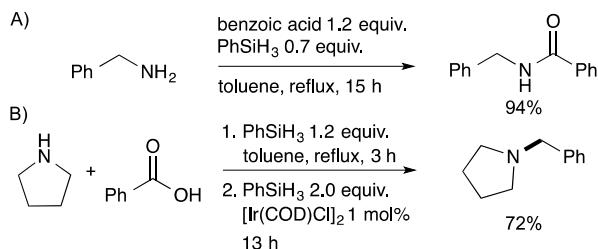
N-alkylation exploiting dual silane reactivity



Scheme 2. Catalytic *N*-alkylation of amines based upon silane dual reactivity.

The strategic separation of the carbon-nitrogen bond formation from the reduction is key to our process and prevents unwanted reduction of the carboxylic acid and the generation of alcohol by-products.¹⁰ The result is a practical, robust method, which can be carried out in conventional glassware under standard conditions with favourable loadings of silane and carboxylic acid.

We began by examining the amidation phase of the reductive alkylation procedure. The phenylsilane-mediated amidation of Ruan and co-workers⁸ was unsuitable in its original form due to the high silane loading (3 equivalents of PhSiH₃) and use of DMF as solvent. We therefore developed an alternative procedure in toluene in which the silane loading was significantly reduced (Scheme 3A).¹¹



Scheme 3. a) Direct amidation reaction. b) Proof of concept of a one-pot two-step reductive alkylation reaction from carboxylic acids.

This procedure constitutes a synthetically useful amidation system in its own right and full details, including mechanistic studies, will be reported in due course. We next tested the one-pot *N*-alkylation reaction (Scheme 3B). Gratifyingly the addition of 1 mol% [Ir(COD)Cl]₂ and an additional 2.0 equivalents of phenylsilane gave the amine product in 72% isolated yield. The reduction conditions represent a modification of Brookhart and Cheng's powerful iridium-catalysed secondary amide reduction methodology; the original procedure did not report the reduction of tertiary amides and utilised the more expensive and volatile diethylsilane.¹²

With proof-of-concept established we carried out additional optimisation of the amidation and reduction phases¹¹ to give a set of general conditions. The scope of the improved process was then examined with a range of carboxylic acids and amines (Table 1). Our standard protocol for the alkylation of secondary amines involved carrying out reactions in round bottom flasks fitted with a reflux condenser under a nitrogen or argon atmosphere in toluene. In most cases anhydrous solvent was used, however, the reaction could also be carried out in Winchester grade toluene and open to air with only minor losses.¹¹ In each case 1.5 equivalents of the carboxylic acid and a total of 3.0 equivalents of phenylsilane were used, which compares favourably with existing methods.^{5,6}

Good to very good isolated yields were obtained for a range of aliphatic and aromatic carboxylic acids (Table 1), including electron poor aryl groups (entries 4-5). Both cyclic and acyclic amines are effective substrates (e.g. entries 1-4 and 5-6); 5- and 6-membered rings are tolerated (e.g. entries 7-8), including somewhat deactivated amines such as morpholine and piperazines (e.g. entries 3, 8). More hindered aliphatic carboxylic acids with α -substitution were tolerated (entries 10-11). Sterically hindered amines, however, led to lower conversions (entries 12-13); these lower conversions are amidation limited.

Pyridines are tolerated, and the pyridine-containing tertiary amine **3e** was isolated in 79% yield (entry 5). To demonstrate the general practicability of the reaction, product **3e** was also prepared on gram-scale (5.0 mmol, 1.4 g product) with an identical isolated yield of 79%. In this case, 0.55 of the 1.50 equivalents of carboxylic acid used were reclaimed during the work-up.

Table 1. Reductive alkylation of secondary amines.

		$ \begin{array}{c} \text{R}^1-\text{C}(=\text{O})\text{OH} \\ \text{1.5 equiv.} \\ \text{1} \end{array} + \begin{array}{c} \text{H} \\ \\ \text{R}^2-\text{N}-\text{R}^3 \\ \text{2} \end{array} \xrightarrow[\text{[Ir(COD)Cl]}_2 \text{ 1 mol\% reflux, 3 h}]{\begin{array}{c} \text{1. PhSiH}_3 \text{ 1.0 equiv.} \\ \text{toluene, reflux, 15 h} \\ \text{2. PhSiH}_3 \text{ 2.0 equiv.} \end{array}} \begin{array}{c} \text{R}^1-\text{CH}_2-\text{N}(\text{R}^2)(\text{R}^3) \\ \text{3} \end{array} $		
Entry	Tertiary amine product	Isolated yield (%)		
1	3a	78 ^b		
2	3b X = CH ₂	80 ^b		
3	3c X = NMe	56 ^b		
4	3d	76 ^b		
5	3e	79 ^{b,c}		
6	3f	67		
7	3g	83		
8	3h	72		
9	3i R = H	56 ^b		
10	3j R = CH ₃	89 ^b		
11	3k	78 ^b		
12	3l R = ⁱ Pr	15		
13	3m R = Et	29 ^b		
14	3n	60 ^{b,d}		
15	3o	40 ^e		
16	3p	54 ^{b,f}		

^aAll reactions were carried out in 0.6 mL toluene on a 0.5 mmol scale with respect to starting amine and purified by acid/base work-up. ^bFurther purified via flash column chromatography. ^cReaction also performed on 5.0 mmol scale. ^dMass balance includes ~30% enamine. ^ereaction performed using 1.0 equiv. cinnamic acid, result is conversion by ¹H-NMR; ~16% alkene material remains. ^fcarboxylic acid 1.5 mmol used.

This potentially valuable recovery of the carboxylic acid component is not possible in reaction manifolds in which over-reduction of the *in situ* generated aldehyde is a competing process.¹⁰

Problematic substrates include those whose derived iminium ion can rearrange. For example, use of a phenylacetic acid (entry 14) resulted in ~30% of the conjugated enamine of product **3n**.¹³ Nevertheless, a reasonable isolated yield of 60% of the desired amine **3n** was achieved. Likewise, cinnamic acids (e.g. entry 15) were susceptible to some alkene reduction, and only 40% conversion to the desired amine **3o** was observed by ¹H-NMR. In this case, both the enamine and allylic amine products were observed. Attempts to reduce the remaining alkenes with extended reaction times and increased silane loadings proved unsuccessful, suggesting reduction occurred primarily during reduction of the amide/iminium species. In agreement with the scope of Brookhart and Cheng,^{12a} nitriles, nitro groups and esters (not shown) led to mixtures of reduced products, although all three groups are tolerated in the initial amidation step. Methylaniline underwent alkylation to give **3p** in moderate yield (entry 16); increasing the equivalents of (recoverable) carboxylic acid improves the initial conversion to amide for less basic amines. Further tolerated functional groups include ethers and aryl halides.

When secondary amide *N*-benzylbenzamide was included as an additive in the standard reaction (not shown), only 40% of the desired tertiary amine **3a** was observed, but 90% of the secondary amide remained unreacted, indicating that modest yields of tertiary amines can be obtained in the presence of secondary amides.

We next examined reductive alkylation reactions of primary amines to afford secondary amines, a more challenging transformation due to the decreased Lewis-basicity of the intermediate secondary amide.

In preliminary experiments using the above developed conditions with phenylsilane as reductant, the amide was obtained as the major product.¹¹ Therefore, in combination with the phenylsilane-mediated amidation reaction, we employed the protocol developed by Brookhart,^{12a} with an increased iridium but reduced silane loading (Table 2). A particular strength of this new procedure is the 1:1 stoichiometry of the carboxylic acid and amine. While the reaction affords good yields after 2 h amidation with 0.75 equivalents of phenylsilane (entry 1, 77%), a longer amidation phase (16 h) and increased phenylsilane loadings (1.0 equivalent) can give slightly improved yields.

Dibenzylamines with differentially substituted aryl groups are obtained in good yields (entries 1-3) and primary aliphatic acids are also particularly good substrates (entries 4-5). More sterically hindered carboxylic acids are also efficient in the amination process (entries 6-7). Also of note is the tolerance of a range of protecting groups, namely TBS ethers (entry 7), aryl methyl ethers (e.g. entry 4), *N*-Boc, *O*-Bn and *N*-Bn (entry 8), and acetals (entry 9).

Deactivated (entries 6-7) and more hindered (entry 5) amines are both tolerated, but, as before, anilines require a modified procedure to give good yields (entry 10). In this case, the initial amidation step benefits from two (or three) equivalents of carboxylic acid, which do not hinder the reduction process and can be recovered unmodified at the end of the reaction. As before, nitro groups and esters are not well-tolerated due to competing reduction processes.^{12a}

Table 2. Reductive alkylation of primary amines

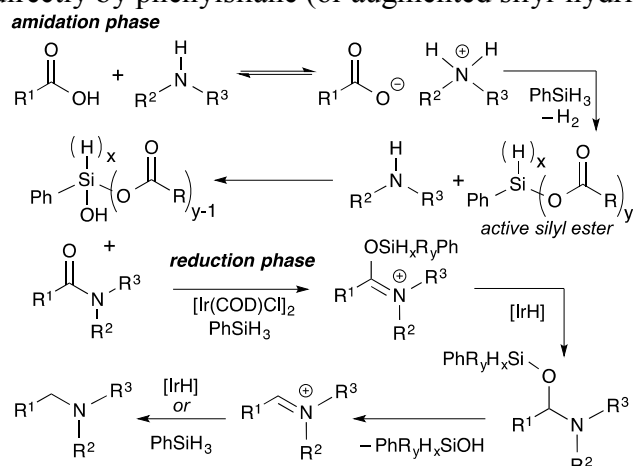
Entry	Secondary amine product	Isolated yield (%)
1 5a		77
2 5b		79 ^b
3 5c		66 ^{b,c}
4 5d		77 ^b
5 5e		81 ^b
6 5f		60 ^{b,c,d}
7 5g		86 ^{b,c}
8 5h		62 ^b
9 5i		66 ^{b,c}
10 5j		63 ^{b,c,e}
11 5k		35 ^{b,c}
12 5l		48 ^{b,c,f}

^aStandard conditions: 0.5 mmol acid and amine in 0.6 mL toluene. ^bAmidation reaction time length, 16 h.

^cPhSiH₃ 1.0 equiv. used in amidation step. ^d1.2 equiv. carboxylic acid used. ^e2.0 equivalents carboxylic acid in amidation step. ^fPhSiH₃ 1.5 equiv. in amidation step.

While nitriles participate in the amidation reaction without issue, they are reduced in presence of iridium and only modest yields are obtained (entry 11). Aryl halides are tolerated (entries 2, 3, 12). Phenols may become silylated during the amidation process; however, the phenol-containing amine product is recoverable after work-up (entry 12).

Our current mechanistic hypothesis involves the initial base-catalysed dehydrogenative formation of silyl ester intermediates,¹⁴ which act as acylating agents in the presence of the amine nucleophile.¹⁵ The ability of phenylsilane (PhSiH_3) to form multiply-substituted silicon centres allows substoichiometric silane loadings in the amidation step. The reduction phase requires activation of the Lewis-basic amide, probably by *O*-silylation from a species of type $\text{R}_3\text{Si}[\text{Ir}]\text{-H}$. The reduction of the activated species may be performed by Ir-H species as proposed by Brookhart and co-workers,^{12a} or in the case of the iminium ion, directly by phenylsilane (or augmented silyl-hydride containing species).



Scheme 7. Proposed general mechanism for reductive alkylation of secondary amines.

In conclusion we have established a robust, direct reductive N-alkylation reaction of amines with carboxylic acids. Notably, the reaction is more practical than existing methodologies,⁵⁻⁷ amenable to a typical flask/condenser set-up instead of Schlenk/autoclave conditions, and has been demonstrated at gram scale (5.0 mmol).

Conceptually, the *N*-alkylation protocol differs from previous reports as it operates in a distinct amidation/reduction manifold. Separating C-N bond formation and reduction avoids the requirement for sacrificial carboxylic acid and large excesses of silane, allowing unused carboxylic acid to be reclaimed upon work-up. This strategic approach is important as many compatible catalytic silane-mediated amide reduction methods are known,⁹ and the opportunity to develop the procedure with cheaper catalysts and hydrosilanes has not escaped our attention.

Finally, the catalytic formation and high reactivity of the silyl ester species generated in the amidation step represents an underexplored and potentially useful method of carboxyl activation.

We are grateful to Dr. Mick Cooper, Graham Coxhill, Shazad Aslam and Kevin Butler for analytical support.

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Alcohols have been produced as unwanted by-products in the Beller protocol (ref. 5). Carboxylic acid reduction is also possible in the Fu protocol (ref 6).

For details refer to the Supporting Information.

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