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Very Important Publication

Simple Metal-Free Direct Reductive Amination Using Hydrosilatrane to Form Secondary and Tertiary Amines

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Abstract: This work describes the use of cheap, safe, and easy-to-handle hydrosilatrane as the reductant in direct reductive amination reactions. This efficient method enables a facile, metal-free access to secondary and tertiary amines from a wide range of aldehydes and ketones, with the synthesis of tertiary amines requiring no additives at all. This reaction demonstrates excellent functional group tolerance, chemoselectivity, and scalability.

Keywords: direct reductive amination; green chemistry; 1-hydrosilatrane; metal-free conditions; solvent-free reaction

Introduction

Due to the ubiquity of amines in important biologically active molecules in nature, and in a wide range of applications from pharmaceuticals to fine chemicals, effective syntheses are of paramount importance.[1]

Although various methods are known,[2] direct reductive amination (DRA) is considered the most practical method for the synthesis of amines, and therefore is the most widely used.[3] DRA involves a reaction between an amine and an aldehyde, or ketone, to form an imine or iminium ion *in situ*, which is then converted by a reducing agent to the corresponding amine.[4] While several methods exist for the formation of secondary amines,[3] there are few studies on direct reductive aminations that form tertiary amines due to the steric influence on enamine/iminium ion formation at equilibrium.[5] Additionally, DRA using secondary arylamines to form aromatic tertiary amines has been described as challenging,[6] and only a handful of procedures are known.[5,7]

For DRA, choosing a chemoselective reducing agent is crucial: the reductant must be able to reduce the imine or iminium ion but not the parent carbonyl compound (or other functionalities present).[8] For example, catalytic hydrogenation with metal catalysts is effective on a large scale but tends not to tolerate unsaturated substituents on the reactants.[9]

The most commonly used reducing agents for DRA are $NaBH_3CN$[4] and $NaBH(OAc)_3$[10] due to their wide availability, simplicity of use, chemoselectivity, and mild reaction condition requirements. However, $NaBH_3CN$ is toxic, forms toxic by-products during work-up, and tends to require large excesses of amine, whilst $NaBH(OAc)_3$ is not compatible with most aromatic ketones, or with aromatic secondary amines.[1b,10,11] Other borohydride derivatives overcome these issues but require more complex purification techniques.[3a,12]

Organosilanes have been reported as efficient alternatives to borohydrides for DRA, as they require simpler purification methods due to their good solubility in organic solvents.[12] PMHS has been the silane of choice due to its non-toxicity, low price, and inertness in the absence of an activator.[13] However, PMHS and other organosilanes require activating catalysts for reduction to occur.[11a,14] These catalysts all have their drawbacks. For example, trifluoroacetic acid cannot be used with acid-labile functionalities,[15]

Bu_2SnCl_2, $SnCl_2$, and $BiCl_3$ are toxic,[5,16] and $InCl_3$ is expensive and a known teratogen.[17]

1-Hydrosilatrane **1** (Figure 1, also called silatrane) has largely been overlooked as a reducing agent since it was first synthesized by Frye et al. in 1961.[18] Silatrane has a cage structure with a lone pair of electrons

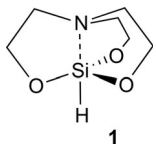

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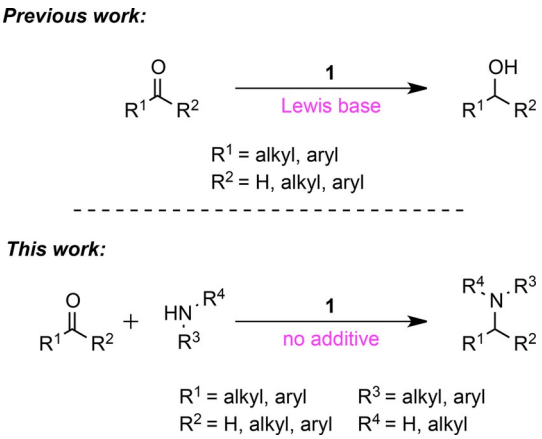
Figure 1. 1-Hydrosilatrane

on nitrogen oriented towards the silicon, rendering it effectively pentacoordinate. This has the potential to make silatrane a good reducing agent because the increase in electron density at the hypervalent silicon center should make the hydride more hydridic.[19] Furthermore, the hypervalent silicon should be more Lewis acidic and therefore more likely to further coordinate reducible Lewis base functionalities such as carbonyls.[20] Silatrane is easy and inexpensive to synthesize, and is an air- and moisture-stable solid making it trouble-free to handle.[21]

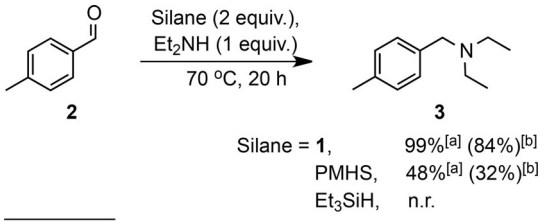
Our previous work has shown that **1** is good reducing agent for aldehydes[22] and ketones[23] in the presence of a Lewis base (Scheme 1), but does not readily reduce nitro, vinyl or aryl halide functional groups. To the best of our knowledge **1** has not previously been considered as a reducing agent for direct reductive aminations. We describe here our successes in accomplishing this.



Scheme 1. 1-Hydrosilatrane as a reducing agent.

Results and Discussion

After optimization,[24] DRA was conducted by combining **1**, aldehyde **2**, and secondary amine in a vial, which was heated at 70 °C overnight to give corresponding amine **3** product in high yields. As can be seen in Scheme 2, exchanging PMHS for **1** under neat conditions gave a much lower yield of product, while no reaction was observed when triethylsilane was used as the reductant.



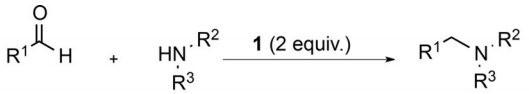
[a] Yields determined by GC-MS.
[b] Isolated yields.

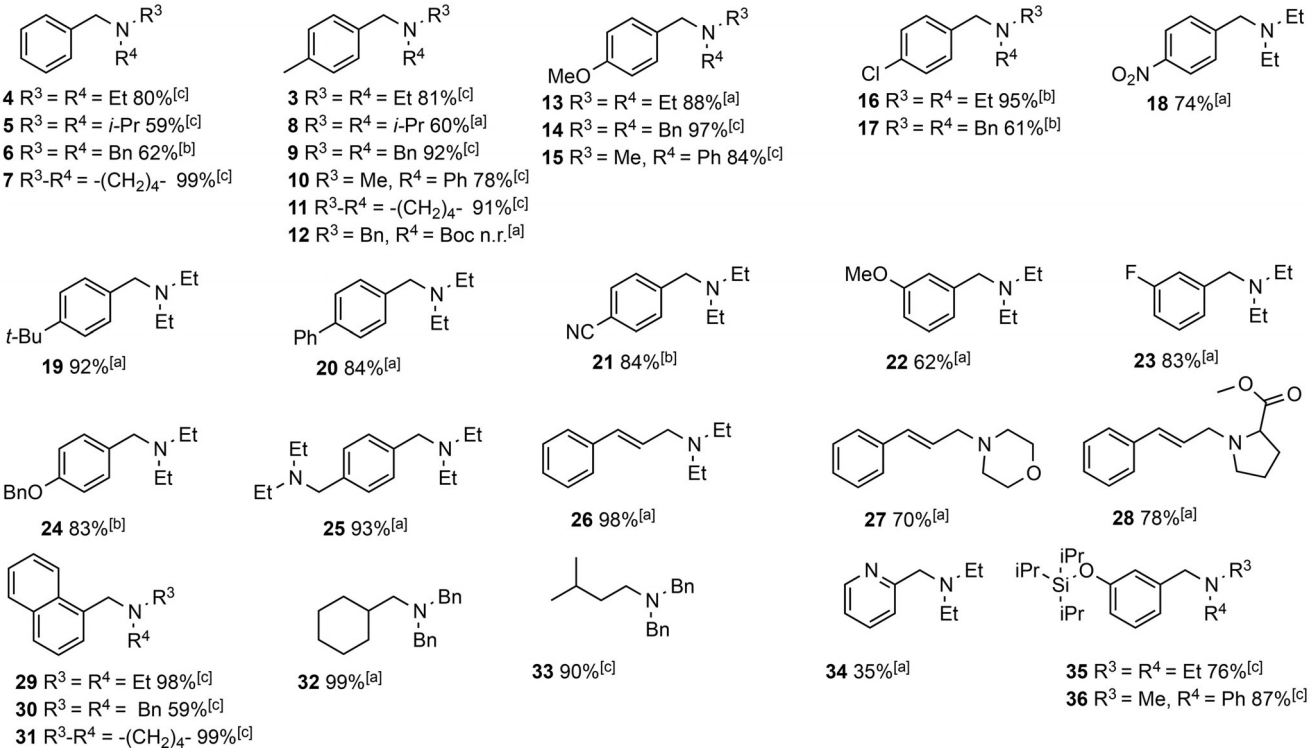
Scheme 2. Comparative effectiveness of different silanes using the optimized method.

Table 1 demonstrates the broad applicability of this method for the reaction of secondary amines with aldehydes to form tertiary amines. Benzaldehyde reacted with secondary amines to give products **4**–**7**. A clear pattern is seen relating the steric bulk of the amine and the resulting isolated yield (compare **4** and **3** to **5** and **8**, for example): this discrepancy is not related to the reaction itself, but rather due to the method of purification (acid extraction) as inspection by GC-MS prior to work-up indicated quantitative conversion. The reaction works well with both electron-rich (**3**, **9**–**11**, **13**–**15**, **19**–**20**, **22**, **24**) and electron-poor (**16**–**18**, **21**, **23**) aromatic aldehydes. Both aldehyde forms of teraphthdialdehyde were readily aminated to give bis-tertiary amine **25**.

The α,β-unsaturated cinnamaldehyde gave high yields of the tertiary amines **26**–**28** with no reduction of the double bond observed. DRA of 1-naphthaldehyde gave high yields of **29** and **31** with diethylamine and pyrrolidine, respectively; the relatively low isolated yield of **30** (using dibenzylamine) was due to the low solubility of the product complicating work-up. The reaction is not limited to aromatic aldehydes, as the aliphatic cyclohexylcarboxaldehyde and isovaleraldehyde produced **32** and **33** in excellent yields. Picolinaldehyde formed **34** but the isolation was difficult due to enhanced solubility of the product in water. Very good functional group tolerance is observed, as reducible groups such as nitro (**18**), cyano (**21**), olefin (**26**–**28**), and ester (**28**) along with common protecting groups such as benzyl (**24**) and triisopropylsilyl (**35** and **36**) remain unaffected. With respect to the amines, high yields are obtained with acyclic and cyclic aliphatic secondary amines, as well as the far less nucleophilic aromatic amines. However, the reaction was not successful with N-Boc protected amine

Table 1. Scope of aldehydes and secondary amines for DRA to form tertiary amines.[d]





[a] $CHCl_3$ as solvent, 60 °C, 2 equivalents of amine.
[b] MeCN as solvent, 70 °C, 1.2 equivalents of aldehyde.
[c] No solvent, 70 °C, 2 equivalents of aldehyde.
[d] Isolated yields, reaction ran overnight, monitored by GC until completion.

12, as it does not form the required iminium ion under our conditions.

We further desired to extend this method to the formation of secondary amines, however, under neat conditions propylamine with *para*-tolualdehyde only gave the corresponding imine in quantitative yield with no observed reduction.[24] We postulated that protonation of the imine would allow its reduction by **1**. Using acetic acid as the solvent, reductive amination of a series of aldehydes was observed at room temperature within 1 hour (Table 2). The reaction works well with both electron-rich (**38**–**42**) and electron-poor (**44**) aldehydes, as well as α,β-unsaturated aldehydes (**45**) and aliphatic aldehydes (**46**). O-Protected amino acids can be used as an amine source as well, as no reduction of the ester is observed (**43**). Both aliphatic and aromatic amines give excellent yields.

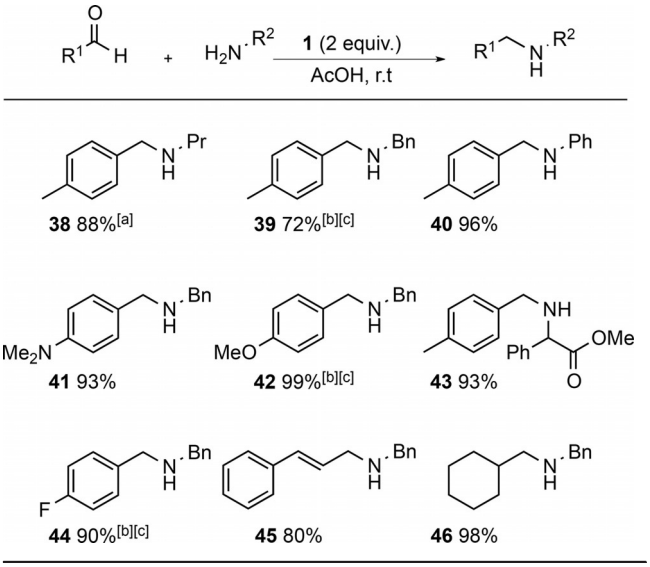
Having explored the scope of tertiary and secondary amine synthesis *via* aldehydes, we decided to further study the possibility of reductive aminations with ketones. Formation of the enamine was observed when the reactions were attempted neat, but was avoided when small amounts of solvent were used, suggesting the importance of having silatrane available in solution as the iminium is formed. Overall, DRA involving a range of ketones and amines was observed (Table 3).

Dimethylamine, pyrrolidine and morpholine reacted with acetophenone to form the corresponding tertiary amines **48**, **49** and **50**. In contrast, diethylamine did not react with acetophenone (**47**) or with the more active nitroacetophenone (**52**).This seemed to be due to the inability of diethylamine to form the required iminium ion.

Potentially reducible nitro **51** and allyloxy **53** groups remained intact indicating some functional group tolerance. The steric effect of the bulkier isopropyl group in the reaction forming **54** did not seem to have a great negative effect on the yield. Both cyclic (**55**) and acyclic (**56**) aliphatic ketones gave good yields.

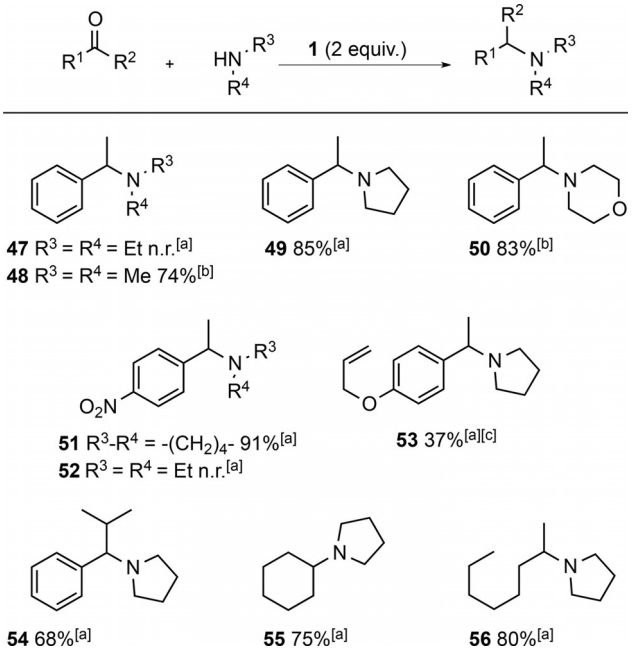
Primary amines also reacted with ketones, albeit much more slowly than with the aldehydes, requiring

Table 2. Scope of aldehydes and primary amines for DRA to form secondary amines[d]



[a] In the absence of acetic acid, the corresponding imine was isolated in quantitative yield.
[b] Reactions ran at 70 °C.
[c] Reaction ran overnight.
[d] Isolated yields, reaction time 1 h unless otherwise stated.

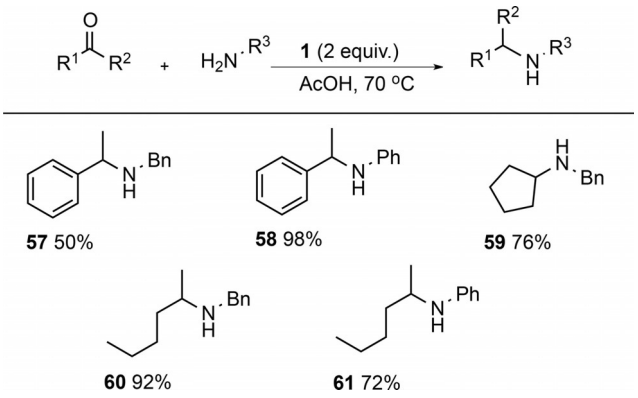
Table 3. Scope of ketones and secondary amines for DRA to form tertiary amines.[d]



[a] $CHCl_3$ as solvent, 60 °C, 2 equivalents of amine.
[b] MeCN as solvent, 70 °C, 1.2 equivalents of aldehyde.
[c] Unable to fully purify product.
[d] Isolated yields, reaction ran overnight, monitored by GC until completion.

higher temperatures and longer reaction times (Table 4). Acetophenone reacted with benzylamine to give **57** in modest yield whilst aniline gave a much higher yield of **58**. Both cyclic and acyclic aliphatic ketones reacted well with both benzylic (**59**, **60**) and aromatic amines (**61**).

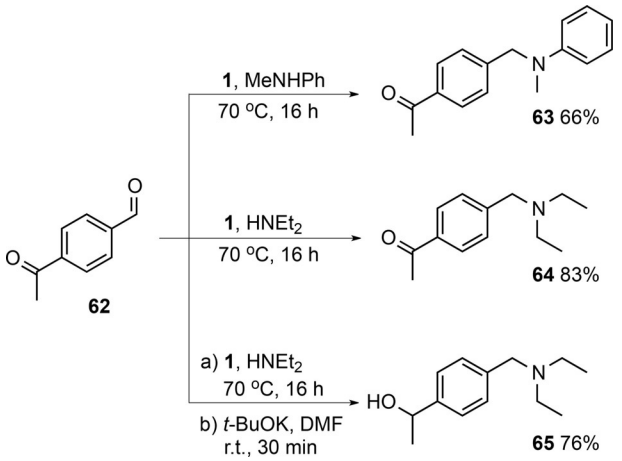
Table 4. Scope of ketones and primary amines for DRA to form secondary amines[a]



[a] Isolated yields, reaction ran overnight, monitored by GC until completion.

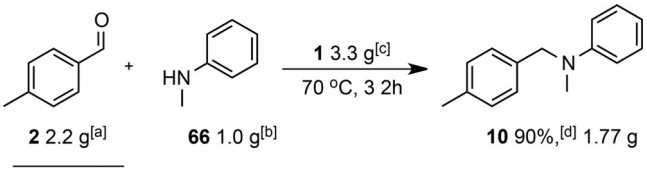
DRAs of ketones and aldehydes with ammonium salts were unsuccesful mainly due to overalkylation. Similar obstacles have been recently noted in the literature.[25]

To study the chemoselectivity of the DRAs we ran several competition reactions with 4-acetylbenzaldehyde **62** (Scheme 3). Under neat conditions, the aldehyde is reduced preferentially over the ketone by both *N*-methylaniline to form **63** and diethylamine to form **64** with good and very good isolated yields. Amino alcohol **65** was formed in one pot through reduction of *in situ* generated **64** by **1**.



Scheme 3. Chemoselectivity of DRA with 1-hydrosilatrane.

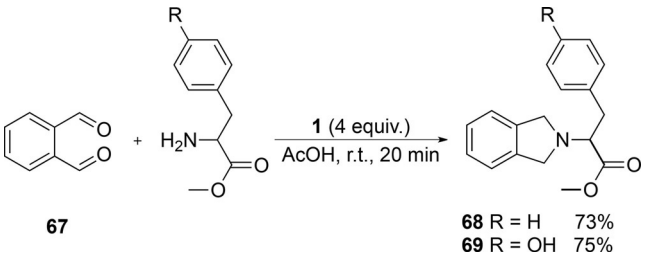
To test the utility and safety of this reaction, we performed the reaction on a multigram scale to produce **10**, as demonstrated in Scheme 4. It must be noted that PMHS and other alkoxysilanes would not be suitable for a scaled up reaction as volatile and pyrophoric active species are potentially formed during the reaction.[26] Although a stoichiometric amount of 1-hydrosilatrane is required, it is inexpensive to synthesize[24] and upon aqueous work-up silatrane is hydrolyzed into silicon dioxide and triethanolamine, which are environmentally benign and potentially recyclable waste products.



[a] 18.6 mmol (2 equiv.).
[b] 9.3 mmol (1 equiv.).
[c] 18.6 mmol (2 equiv.).
[d] Isolated yield.

Scheme 4. Gram-scale reaction using 1-hydrosilatrane under solvent-free conditions.

Many significant pharmaceutically relevant compounds are alkaloids, and for this reason the synthesis of amines is of great practical interest in this field. To highlight this application, we applied our described method for reductive amination using **1** in the synthesis of two 2-substituted isoindoline derivatives of α-amino acids. (Scheme 5) Compounds **68** and **69** are selective COX-2 and COX-1 inhibitors, respectively, of which **68** has been singled out for further study as an anti-inflammatory agent.[27] Both compounds have also shown moderate antiproliferative activity towards HeLa cells.[28] To form the isoindoline structure, one aldehyde of an *ortho*-dialdehyde arene would have to undergo intermolecular reductive amination, whereupon the other aldehyde function would have to undergo intramolecular reductive amination. Phthaldialdehyde **67** reacted with the two corresponding amino acid methyl esters to give the isoindoline products **68** and **69** in one step, in very good yield. (Scheme 5)



Scheme 5. Synthesis of biologically active compounds of interest. Isolated yields reported.

Mechanistically, the data preliminarily suggest that iminium ion formation is required for the reaction to proceed. The *in situ*-generated condensation products of secondary amines and aldehydes are readily reduced by **1**, whilst primary amines and aldehydes form imines without reduction. However, in the presence of acetic acid, the imine can be protonated to the iminium ion, and reduction occurs to the amine. Based on our current understanding of **1** as a reducing reagent (i.e., that it requires a nucleophilic activator to transfer the hydride),[22,23] a Lewis base formed *in situ* may act as the activator. Alternatively, iminiums are significantly more electrophilic than either aldehydes or ketones,[29] so **1** may be able to reduce such reactive compounds in the absence of an activator. Further mechanistic studies are currently ongoing.

Conclusions

We have demonstrated **1** as an efficient reducing agent in the direct reductive amination of aldehydes and ketones to form secondary and tertiary amines. This is a reasonably green procedure, as tertiary amines form readily without any solvent, catalyst, or other additives, and secondary amines form when environmentally friendly acetic acid is used as a solvent. Both alkyl- and arylamines give high yields. The scope is broad with good functional group tolerance and chemoselectivity. The method is extremely simple, as no inert atmosphere or exclusion of water is necessary, with the added benefit of **1** being a stable, cheap, easy to handle, and versatile reducing agent.

Experimental Section

General Considerations

All chemicals were obtained from commercial sources and used without further purification. Column chromatography was performed using silica gel from Macherey–Nagel (60M, 0.04–0.063 mm). ^{1}H NMR, and ^{13}C NMR were recorded on either 300 or 500 MHz Bruker Avance III spectrometer. Chemical shifts are reported in ppm with the solvent resonance as internal standard (^{1}H NMR $CDCl_3$ $\delta = 7.28$, ^{13}C NMR $CDCl_3$ $\delta = 77.01$). IR spectra were acquired using an ATI Mattson FT-IR spectrophotometer on neat samples. Melting points were obtained using a Mel-temp capillary heating apparatus. MS data were obtained with a Shimadzu GCMS QC2010S spectrometer at 275 °C.

General Procedure for Synthesis of Tertiary Amines from Aldehydes

In a 5-dram vial containing 1-hydrosilatrane (2 mmol) were added aldehyde (1.5 mmol) and secondary amine (1 mmol). The vial was sealed and heated at 70 °C overnight. The resulting residue was dissolved in dichloromethane and extracted with 1 M HCl three times. The aqueous extract was neutralized with 4 M NaOH and extracted with dichloromethane three times. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under low pressure. The resulting residue was analyzed with no further purification unless otherwise stated. See the Supporting Information for characterization details.

General Procedure for Synthesis of Secondary Amines from Aldehydes

To a 5-dram vial containing aldehyde (1 mmol), primary amine (1.2 mmol) and acetic acid (1 mL) was added 1-hydrosilatrane (2 mmol). The reaction mixture was stirred using a magnetic stir bar for 1.5 h after which the reaction was neutralized using 1 M NaOH and extracted using dichloromethane three times. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under low pressure. The resulting residue was analyzed with no further purification unless otherwise stated. See the Supporting Information for characterization details.

General Procedure for Synthesis of Tertiary Amines from Ketones

In a 5-dram vial containing 1-hydrosilatrane (2 mmol) were added ketone (1 mmol), secondary amine (1.2 mmol) and 0.2 mL solvent. The vial was sealed and heated at 70 °C overnight. The resulting residue was dissolved in dichloromethane and extracted with 1 M HCl three times. The aqueous extract was neutralized with 4 M NaOH and extracted with dichloromethane three times. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under low pressure. The resulting residue was analyzed with no further purification unless otherwise stated. See the Supporting Information for characterization details.

General Procedure for Synthesis of Secondary Amines from Ketones

To a 5-dram vial containing ketone (1 mmol), primary amine (1.2 mmol) and acetic acid (1 mL) was added 1-hydrosilatrane (2 mmol). The reaction mixture was stirred using a magnetic stir bar for 2 h after which the reaction was neutralized using 1 M NaOH and extracted using dichloromethane three times. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under low pressure. The resulting residue was analyzed with no further purification unless otherwise stated. See the Supporting Information for characterization details.

General Procedure for Synthesis of Isoindoles

To a 5-dram vial containing amino acid methyl ester hydrochloride (1 mmol), phthalaldehyde (1 mmol) and 1 mL of acetic acid was added 1-hydrosilatrane (2 mmol). The resulting mixture was stirred at room temperature for 2 h, and quenched with 1 M NaOH. The resulting mixture was extracted three times with dichloromethane, the combined organic layers were dried over anhydrous sodium sulfate and concentrated under low pressure. The residue was than purified using column chromatography with hexane/ethyl acetate (4/1) to give the isoindole derivative. See the Supporting Information for characterization details.

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