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Pinacol-Derived Chlorohydrosilane in Metal-Free Reductive Amination for the Preparation of Tertiary Alkylphenolmethyl Amines

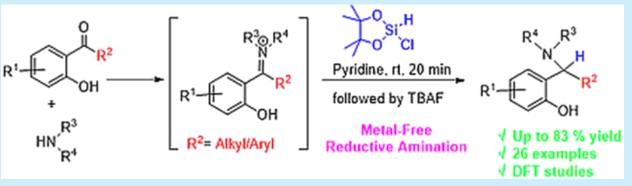
Benedicta Assoah,*,† Luis F. Veiros,‡ and Nuno R. Candeias*,†

†Faculty of Engineering and Natural Sciences, Tampere University, Korkeakoulunkatu 8, 33101 Tampere, Finland

‡Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Avenida Rovisco Pais No. 1, 1049-001 Lisboa, Portugal

Supporting Information

ABSTRACT: A new metal-free reductive amination protocol using a pinacol-derived chlorohydrosilane/pyridine system for the preparation of aminoalkylphenols is described. This method is selective toward iminiums derived from alkylphenol ketones under an in situ formation of a trialkoxyhydrosilane and activation with a Lewis base, as further indicated by computational studies. This method demonstrated high functional group tolerance affording an array of novel aminoalkylphenols in moderate to high yields with equimolar amounts of reactants and a wide substrate scope.



Amines are ubiquitous functionalities present in natural products, pharmaceuticals, agrochemicals, and synthetic materials.[1] Among the numerous methods available for the synthesis of amines, the one-pot reductive amination method[2−5] presents a versatile and preferable option considering efficiency and fast access to amines. Several reducing systems including metal hydrides[2] and catalytic hydrogenation methods[6] are employed for such transformations.[7] Nonetheless, poor selectivity and functional group tolerance (e.g., halogens and nitro groups) are some of the challenges associated with the hazardous reactivity of metal hydrides.[8] Catalytic hydrogenations also are often incompatible with compounds containing multiple bonds and reducible groups. They usually require harsh reaction conditions such as elevated temperatures and pressures. Reductive hydrosilylations present a milder, selective, good functional group tolerance and convenient alternative to these conventional methods, which have been widely explored in metal-catalyzed reduction systems for the reduction of imines,[9,10] iminiums,[11] and amides.[12−17]

Hydrosilanes require activation by either a Lewis acid[18] or a Lewis base[19] with a high affinity for silicon due to their typically weak hydride donating ability compared to other hydride sources. The metal-free catalytic hydrosilylation of amides[20,21] and reductive aminations with "frustrated Lewis pairs" of which $B(C_6F_5)_3$ has been established as a versatile catalyst[22,23] are some examples of hydrosilanes' activation by Lewis acids.

Hypervalency in silicon where its valence is expanded after complexation with a nucleophilic species leads to a higher hydride donating ability compared to its tetracoordinate counterpart,[24−26] and a variety of methods based on hydrosilane/Lewis acid combination have been explored for reductive amination.[3,27] On the other hand, reductive amination protocols which exploit activation of trichlorosilane as a reductant by various Lewis bases including DMF,[28] trialkylamines, acetonitrile, chiral *N*-formamide derivatives,[24] chiral sulfonamide, and *N*-picolinoylpyrrolidine derivatives, among others,[29] have been reported. Recently, HMPA and TMEDA have been shown to be suitable activators of highly reactive trichlorosilane in the reductive amination involving aldehydes and ketones with secondary amines.[30,31] Secondary and tertiary amines are achievable through hydrosilylation of C═N bonds using hypervalent hydrosilatrane.[32]

Tertiary diarylmethylamines (**I**) where one of the aryl substituents is a 2-phenol are typically prepared in good yields through Betti[33,34] or multicomponent Petasis borono-Mannich (PBM) reactions.[35,36] While these procedures are somewhat general for diarylmethyl moieties, tertiary alkylphenolmethyl amines (**II**) are more difficult to access this way, as less reactive alkyl aldehydes or alkyl boronic acids or esters are required. A few examples can nevertheless be found.[37−40]

In our previous work,[41] a novel 5-membered cyclic pinacol-derived chlorohydrosilane (PCS) was demonstrated to reduce salicylaldehydes catalyzed by a Lewis base (DMPU) in high yields and good chemo- and regioselectivity (Scheme 1). After reporting in the same work the ability of PCS to perform the reductive amination of a salicylaldehyde-derived iminium, we hypothesized that a similar transformation could be used in the reductive amination of iminiums derived from alkylphenol ketones and secondary amines. Herein, we report the first one-pot, metal- and protective-group-free reductive amination

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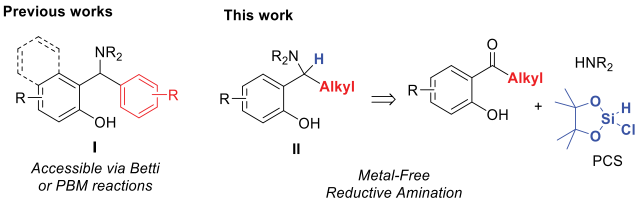
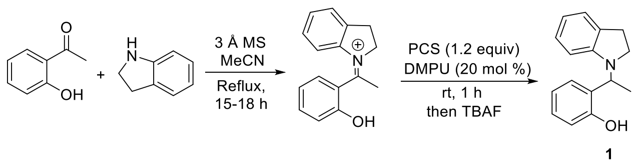
Scheme 1. Approaches to Alkylphenolmethyl Amines



method for preparation of tertiary alkylphenolmethyl amines. This reductive amination procedure is superior to the use of $NaCNBH_3$ since only equimolar amounts of amine are required and it is not susceptible to cyanide contamination. Moreover, the reduction of aromatic and unsaturated ketones by other borohydrides such as $Na(OAc)_3BH$ suffers from lack of reactivity.[4]

Optimization of the reaction conditions was initially examined with 2′-hydroxyacetophenone and indoline as substrates, affording the corresponding aminoalkylphenol **1**. Further screening of the reaction conditions regarding solvent, reaction times, and amounts of DMPU and indoline was performed (see the SI for complete screening). After identification of MeCN as the most promising solvent, we focused on the amount of Lewis base (Table 1). The desired

Table 1. Selected Entries in Optimization of Reductive Amination



entry[a]	deviation from reaction conditions	yield[b] (%)
1	none	61
2	without DMPU	42
3	1.2 equiv of indoline, without DMPU	63
4	2 equiv of indoline	84
5	2 equiv of indoline, without DMPU	80

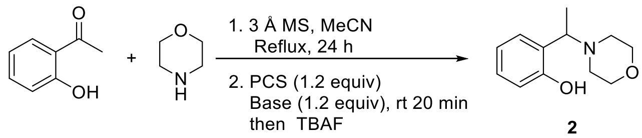
[a]Unless otherwise stated, condensation of 2′-hydroxyacetophenone (0.54 mmol) and indoline (0.54 mmol) in refluxing MeCN (1 mL). PCS (0.65 mmol) in MeCN (1 mL) is added over 5 min to the cooled mixture in the presence of DMPU (0.11 mmol) at rt. After 1 h, the mixture is treated with TBAF (1 M in THF, 0.75 mmol). [b]Isolated yields.

amine **1** was obtained in 61% yield with stoichiometric amounts of the ketone and indoline and 20 mol % of DMPU (entry 1). The absence of DMPU had a detrimental effect on the yield, which could be restored upon increasing the amount of indoline to 1.2 equiv (entries 2 and 3). Increasing the amount of indoline to 2 equiv provided the tertiary amine in up to 84% yield, regardless the presence of DMPU (entries 4 and 5).

In the subsequent studies, indoline was replaced by morpholine due to the easier purification of the product. Based on the above observations, we set out to investigate a Lewis base that would catalyze the reaction more effectively than DMPU, thus allowing us to keep an equimolar amount of secondary amine.

With equimolar amounts of amine and ketone, satisfactory yields of the product could only be obtained by increasing the amount of Lewis base. After various amounts of DMAP were screened (see the SI), 1.2 equiv of the base emerged the best result with 73% yield of the aminoalkylphenol (Table 2, entry 1). Screening other Lewis bases such as DBU and Hünig's base gave the aminoalkylphenol **2** in yields comparable to that using DMAP (Table 2, entries 2 and 3). Moderate yields were observed for triethylamine, collidine, and pyridine *N*-oxide (Table 2, entries 4–6). A rather low yield of **2** (45%, Table 2, entry 7) was observed with 1.2 equiv of DMPU. Gratifyingly, the desired product was obtained in 83% yield with pyridine (Table 2, entry 8), matching the previous result with an excess of the secondary amine (Table 1, entry 5). Without a base promoter, **2** was obtained in only 19% yield (Table 2, entry 9). The use of molecular sieves was vital for the reaction, as no reduced products were obtained in their absence.

Table 2. Lewis Base Screening



entry[a]	base	yield[b] (%)
1	DMAP	73
2	DIPEA	72
3	DBU	73
4	Et_3N	63
5	collidine	62
6	pyridine *N*-oxide	50
7	DMPU	45
8	pyridine	83[c]
9	none	19

[a]Condensation of 2′-hydroxyacetophenone (0.54 mmol) and morpholine (0.54 mmol) in refluxing MeCN (1 mL). PCS (0.65 mmol) in MeCN (1 mL) is added over 5 min to the cooled mixture in the presence of the Lewis base (0.65 mmol) at rt. After 20 min, the mixture is treated with TBAF (1 M in THF, 0.75 mmol). [b]Isolated yields. [c]No product detected without MS.

The substrate scope for different secondary amines with 2′-hydroxyacetophenone (Scheme 2) was examined. Tertiary amines **1–6** derived from cyclic and acyclic secondary amines were obtained in up to 83% yield, with the former proving superior. Next we expanded the substrate scope to various substituted 2′-hydroxyacetophenones, providing **7–15**. 5-Methyl-substituted 2′-hydroxyacetophenone-derived iminiums with either indoline or morpholine were readily reduced by PCS to the corresponding products **7** and **20**. This method demonstrated good functional group tolerance as halogens and nitro-substituted substrates susceptible to reductions allowed for the synthesis of their corresponding aminoalkylphenols (**8–14**, **21–25**) with morpholine, indoline, and tetrahydroquinoline. Reductions involving ethylaniline as substrate generally gave lower yields, but an optimized protocol employing 1.8 equiv of PCS afforded moderate yields of **22** and **23** (63 and 58%, respectively). The nitro- and methyl-substituted substrate gave a 63% yield of **14**, while that of the nitro and chloro derivative **13** gave a much lower yield of 27%. With the 4-methoxy-substituted 2′-hydroxyacetophenone, **11** was obtained in 60% yield. The alkylnaphtholmethyl amine **15** was also obtained in 50% yield with the standard reaction conditions. Further expansion of the substrate scope to

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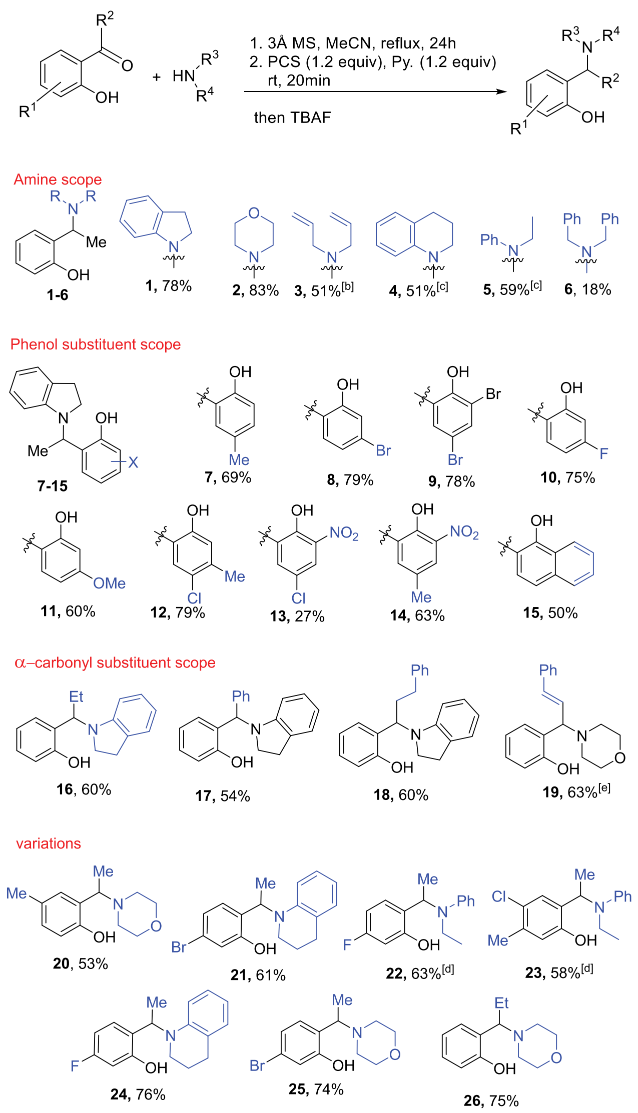
Scheme 2. PCS/Pyridine Reductive Amination Scope[a]



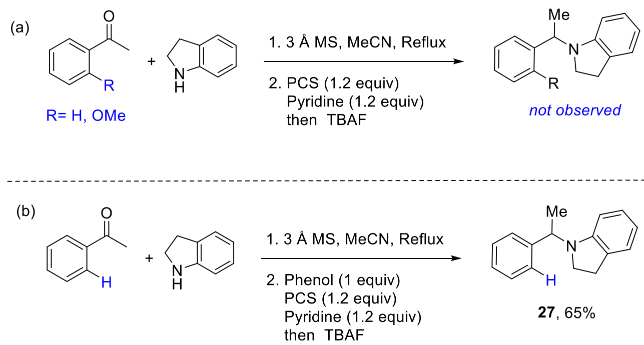
[a]All reactions performed on a 0.54 mmol scale of the hydroxy ketones. Isolated yields.; [b]30 h reflux. [c]Overnight reflux. [d]1.8 equiv of PCS. [e]10 h reflux.

different alkyl- and phenyl-substituted 2′-hydroxyphenones with indoline or morpholine allowed the formation of tertiary amines **16**–**18** and **26** in moderate yields (54–75%), while **19** from a morpholine-derived eniminium was obtained in 63%.

Under the optimized conditions, commercially available diphenylchlorosilane gave **1** in 66% yield after 2 h at rt, after iminium formation. The importance of the phenolic hydroxy group was verified by the absence of product on reduction of an acetophenone- or *o*-methoxyacetophenone-derived iminiums (Scheme 3a). Considering the phenolic OH's role in the reduction process, we also investigated the use of phenol additive for a more practical application of PCS as a reductant. Compound **27** was obtained in 65% yield suggesting a possible intermolecular hydride delivery process.

The reductive amination mechanism was studied via DFT[42] calculations using 2′-(hydroxy)acetophenone and dimethylamine as substrates (Figure 1). The starting point for the calculations is the trialkoxyhydrosilyliminium obtained from HCl loss from the initial hydrosilane.

Scheme 3. Importance of Phenolic Hydroxyl



The reduction proceeds through four steps. In the first step, from **A** to **B**, there is coordination of pyridine to the Si atom in the trialkoxyhydrosilyl iminium. The free energy barrier associated with this step is 2 kcal/mol, with respect to the pair of reactants (**A**), and the emergent Si–N bond in $\mathbf{TS_{AB}}$ is 3.30 Å, which gradually shortens to 2.07 Å, in **B**. The intermediate **B** is only 1 kcal/mol less stable than the separated reagents, and a rotation around the $Si-O_{phenol}$ bond produces **B′**, another conformer of similar stability. In the next step, there is hydride attack into the iminium C atom, from **B′** to **C**, through transition state $\mathbf{TS_{B'C}}$. This step has the highest energy barrier of the entire path, with $\mathbf{TS_{B'C}}$ being 16 kcal/mol less stable than intermediate **B′**.

Subsequently, **C′**, a conformer of **C**, suffers *N*-coordination to the Si atom, resulting in **D**. This occurs through transition state $\mathbf{TS_{C'D}}$ in a barrier less process. In the transition state $\mathbf{TS_{C'D}}$ the new Si–N bond is incipient with a distance of 3.54 Å, still 1.45 Å longer than its value in intermediate **D**. A prompt Si–N bond formation following the hydride attack indicates that those can be viewed as concerted.

Once the intermediate **D** is formed, the last step is liberation of pyridine to give species **E**. This step proceeds through the transition state $\mathbf{TS_{DE}}$ with an associated energy barrier of process of 12 kcal/mol. The distance of $Si-N_{pyridine}$ is elongated from 1.89 Å in **D** to 2.68 Å in the corresponding transition state, $\mathbf{TS_{DE}}$, indicating a well-advanced $Si-N_{pyridine}$ bond breaking. The overall reaction is thermodynamically favored with respect to the separated reactants with $\Delta G = -10$ kcal/mol.

DFT calculations were also performed for the DMPU-promoted mechanism, for comparison purposes (see the SI for details). Lower yields are obtained when DMPU is used as catalyst (Table 2) despite its function as an excellent Lewis base catalyst in the reduction of salicylaldehydes.[41] The reaction mechanism calculated for DMPU parallels the one obtained for pyridine with four consecutive steps. The major difference between the two reactions is the stability of the base–Si adducts in the pyridine and DMPU systems (intermediates **D** and **I**, respectively). The stability of **I**, 24 kcal/mol more stable than the separated reagents, makes DMPU loss the highest barrier step in the path ($\mathbf{TS_{IJ}}$: 26 kcal/mol).

Overall, the pyridine mechanism corresponds to a more facile reaction, the highest barrier being the hydride attack on $C_{C=N}$ ($\mathbf{TS_{B'C}}$, 17 kcal/mol relative to the separated reagents). These results indicate how strongly DMPU, an oxygen base, binds to the Si atom and consequently hampers the liberation of the base catalyst and release of the final product. Therefore, the more stable DMPU–Si adduct accounts for the observed

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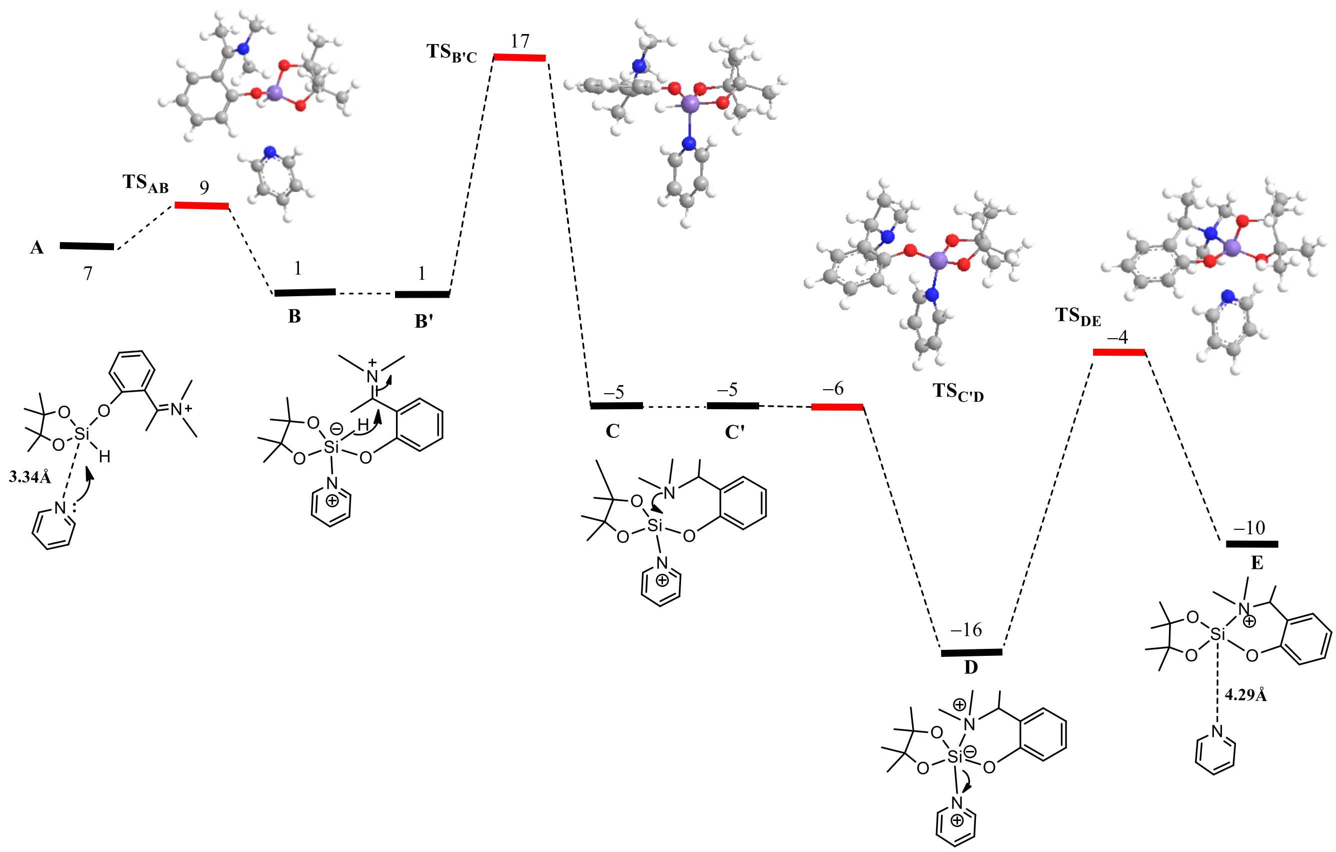

Figure 1. Free energy profile for the pyridine-catalyzed reductive amination. The free energy values (kcal/mol) are relative to the separated reagents: trialkoxyhydrosilyliminium plus pyridine.

lower yields compared to those of the pyridine system. The reductive amination mechanism without a Lewis base was also studied with DFT calculations (see the SI). The mechanism is concerted with simultaneous hydride transfer and N coordination to Si through a transition state with a significant energy barrier of 41 kcal/mol. The reaction is nevertheless exergonic with free energy balance of −15 kcal/mol. Comparison of the barriers calculated for the mechanism with and without Lewis base reveals the active role of that reactant as a promoter.

In summary, we have demonstrated the use of pinacol-derived chlorohydrosilane as an efficient reductant in a Lewis base promoted reductive amination. This protocol, based on the in situ formation of a trialkoxyhydrosilane with concomitant intramolecular hydride delivery, allowed the synthesis of an array of aminoalkylphenols in moderate to high yields while employing equimolar amounts of reactants. The scope of the method could be expanded by using phenol as an additive. The role and nature of the Lewis base were revealed by DFT calculations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00121.

Detailed experimental procedures, additional optimization data, computational data, characterization of compounds, and NMR spectra for all new procedures (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nuno.rafaelcandeias@tuni.fi.
*E-mail: benedicta.assoah@tuni.fi.

ORCID

Benedicta Assoah: 0000-0001-5877-2749
Luis F. Veiros: 0000-0001-5841-3519
Nuno R. Candeias: 0000-0003-2414-9064

Notes

The authors declare no competing financial interest.

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