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Selective Reduction

Lewis Base Catalyzed Intramolecular Reduction of Salicylaldehydes by Pinacol-Derived Chlorohydrosilane

Benedicta Assoah,*[a] João R. Vale,[a,b] Elina Kalenius,[c] Luis F. Veiros,[d] and Nuno R. Candeias*[a]

Abstract: A newly developed stable chlorohydrosilane derived from pinacol is herein described. This was successfully used in the reduction of salicylaldehydes in reasonable to excellent yields (51–97 %). The ability of the hydrosilane to react as a reducing agent is increased upon the in situ formation of a trialkoxyhydrosilane and activation with a Lewis base, as further indicated by density functional theory studies. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was identified to be a suitable catalyst for this metal-free reduction, promoting the regio- and chemoselective reduction of aldehydes in *ortho*-position to phenols, despite the presence of vicinal ketones. The performance of pinacol-derived chlorohydrosilane in the reduction of salicylaldehydes was further observed to be superior to that of well-established commercially available chlorohydrosilanes.

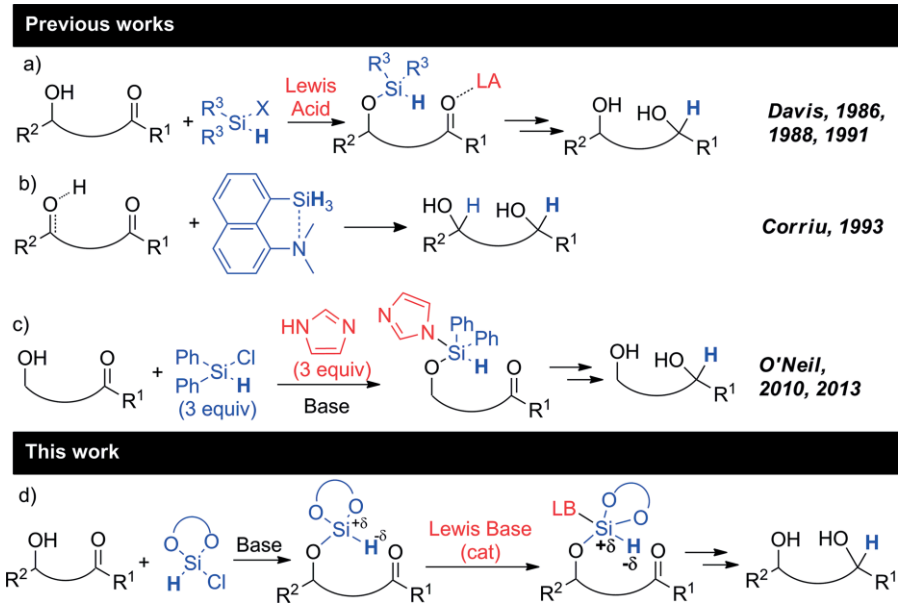
Introduction

The reduction of carbon-heteroatom unsaturated organic compounds remains one of the most essential transformations in synthetic organic chemistry for both academic and industrial applications. An array of catalytic protocols such as hydrogenation reactions, electron transfer and hydride transfer reductions have been explored extensively with carbon-heteroatom multiple bond reductions.[1]

In recent years, catalytic hydrosilylation has made significant progress and is being used as a major tool in the reduction of organic substrates, serving as a convenient alternative to the use of hydrogenation and metal hydrides.[2] Since the electronic and steric properties of hydrosilanes can be tuned by interaction with unreactive functional groups in the substrate or with external chemical agents, these reagents have found their way in the reduction toolbox of synthetic chemists, as they can be used to perform a large variety of chemoselective reductions under mild conditions.[3] Specifically, their reducing properties towards carbonyl can be controlled by the silicon substituents along with catalysts[2a,4] such as Lewis acids,[5] Lewis bases[6] or transition metal complexes.[7] Despite the notable progresses made in transition metal catalyzed hydrosilylations,[3c,8] the metal-free version of such reductions has received tremendous importance in recent research endeavors;[3a] as they benefit from the absence of costly and often toxic metal catalysts and the need to remove any metal impurities particularly relevant for pharmaceutical products.[9]

Mild reductions of carbonyl groups to the corresponding alcohol functionality by metal-free hydrosilylation methods have been largely accomplished through use of acid and bases as catalysts.[2a,6b] Despite the rather low Si–H bond energy of hydrosilanes when compared with C–H bond, employing hydrosilanes in metal-free carbonyl reduction requires either carbonyl activation by complexation with Brønsted or Lewis acids or activation of the hydrosilane, in which $B(C_6F_5)_3$ has been extensively explored.[10] Both alcohols or hydrocarbons[5,11] can be obtained, depending on the reaction conditions and the hydrosilane used. One of the approaches explored in the activation of hydrosilanes has been the expansion of tetrahedral silicon to a pentavalent anion intermediate upon complexation with nucleophilic species.[12] Silicon valence expansion leads to a redistribution of the electronic density, polarizing the covalent bonds around silicon, decreasing silicon electron density and increasing the electron density of the silicon substituents. Overall, these results in a higher hydride donating ability of the pentavalent complex when compared with its tetracoordinate counterpart.[13] Mitsuo and co-workers reported an in situ formation of pentacoordinate bis(diolato)hydridosilicates from trichlorosilane and catechol or 2,2′-dihydroxybiphenyl for the reduction of carbonyl compounds. However, pentacoordinate hydridosilicates from aliphatic diols such as 1,2-ethanediol and pinacol proved to be less effective as reducing agents.[14] Cs_2CO_3[3a,15] TBAF,[16] *t*BuOK,[17] CsF, and KF[6a] have been re-

[a] *Laboratory of Chemistry and Bioengineering, Tampere University of Technology, Korkeakoulunkatu 8, 33101 Tampere, Finland*
E-mail: benedicta.assoah@tut.fi
nuno.rafaelcandeias@tut.fi
http://www.tut.fi/syn
[b] *Instituto de Investigação do Medicamento (iMed.ULisboa), Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal*
[c] *University of Jyväskylä, Department of Chemistry, Nanoscience Center, Jyväskylä, Finland*
[d] *Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais No. 1, 1049-001 Lisboa, Portugal*
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800544.



Scheme 1. Intramolecular hydrosilylation of hydroxy carbonyl compounds.

ported as active catalysts or activators in the chemoselective hydrosilylation of aldehydes and ketones, while being tolerant to other functional groups. Hypervalent Cl_3SiH-DMF silicate was described by Kobayashi et al. to be an effective reducing agent in the reduction of aldehydes, imines and in the reductive amination of aldehydes.[18]

The intramolecular hydrosilylation of carbonyl compounds has been explored as a way to achieve stereoselective reductions due to more constrained cyclic transition states (Scheme 1). Davis and co-workers achieved moderate to excellent stereoselectivities on the intramolecular hydrosilylation of β-hydroxyketones using Lewis acid catalysis (Scheme 1a),[19] while intramolecular hydrosilylation of β-hydroxyesters was better accomplished with catalytic amounts of fluoride.[20] Pentacoordinate hydrosilanes, activated by an internal N–Si bond have been successfully used in the same kind of transformation (Scheme 1b).[21] More recently, O'Neil and co-workers[6b,6c] reported a cooperative Lewis base-mediated intramolecular carbonyl hydrosilylation of β-hydroxyketones (Scheme 1c). The hydrosilyl ether formed upon reaction of the hydroxyl group with diphenylchlorosilane, in presence of a tertiary base, could undergo an intramolecular hydride delivery promoted by imidazole. However, the system was not rendered catalytic and the use of superstoichiometric amounts of imidazole and diphenylchlorosilane were required.

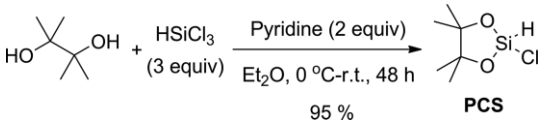
Considering that the hydride character of hydrosilanes is highly dependent on the silicon substituents, we envisioned that alkoxy derived hydrosilanes would be highly reactive under certain constrains (Scheme 1d). The hydride character would be further increased by constraining the silicon atom within a ring, as known that 4- and five-membered silacycles have higher Lewis acid character than their acyclic counterparts, due to strain release.[22] Cyclic structures derived from silicon could have their Lewis acid character further increased upon complexation with a Lewis base, as a pentavalent silicon complex would form.[23] Such an event would activate a Lewis basic site such as oxygen of a carbonyl, and simultaneously decrease the Si–H bond strength.

In order to verify these assumptions a novel chlorohydrosilane was prepared and its reactivity tested in the Lewis base catalyzed hydrosilylation of salicylaldehyde derivatives, which we used in several instances in multicomponent Petasis borono-Mannich reaction.[24] Notably, despite the widely available methods for reduction of salicylaldehyde,[25] as far as our knowledge goes its Lewis base-catalyzed hydrosilylation has never been reported.

Results and Discussion

Our initial attempts on the preparation of five-membered chlorohydrosilane derived from ethylene glycol with $HSiCl_3$ in presence of different amines resulted in complex mixtures due to disproportionation and formation of silicon-amine adducts.[26] Questioning the putative high reactivity of the five-membered chlorohydrosilane formed under such conditions, the ethylene glycol was replaced by pinacol aiming at increasing the stability of the chlorohydrosilane. Gladly, treatment of pinacol with an excess amount of trichlorosilane and pyridine in diethyl ether under inert atmosphere yielded the desired pinacol-derived chlorohydrosilane (PCS) in nearly quantitative yield after filtration and solvent removal (Scheme 2). Just as many chlorosilanes, PCS is an air and moisture sensitive clear colorless liquid that can be stored for at least 6 months at –20 °C under inert atmosphere without any change in reactivity.

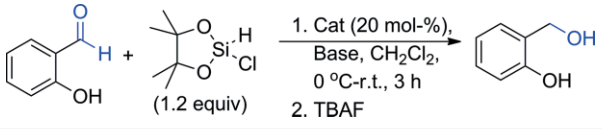
The ability of PCS to serve as a reducing agent was tested in the hydrosilylation of salicylaldehyde in dichloromethane (Table 1), for which the corresponding salicyl alcohol was obtained in 24 % yield after 72 h in dichloromethane in absence of base (entry 1). Gratifyingly, the same alcohol was obtained



Scheme 2. Preparation of pinacol-derived chlorohydrosilane (PCS).

in 70 % after 3 h when using triethylamine as a hydrochloric acid sequester (entry 2). When diminishing the amount of base to 20 mol-%, reduction was rather incomplete as judged by TLC, and the product was formed in only 29 %, indicating the dual role of the amine as a catalyst and HCl sequester (entry 3). Screening of other bases prone for HCl sequestering and Lewis base catalysis, such as pyridine and Hünig's base, led to product formation in lower yields (entries 4 and 5). Use of DMF as reaction solvent, in absence of any additive, resulted in salicyl alcohol formation in 68 % likely due to the Lewis base character of DMF.[27] Although the promoter role of triethylamine was notoriously visible, a more effective Lewis base was searched to be used in combination with the amine HCl sequester. Moderate yields were observed when using PPh_3, pyridine *N*-oxide and HMPA, for which presence of triethylamine had a negligible effect (entries 7–9). Gladly, when using 20 mol-% of DMPU, an environmentally benign substitute to HMPA,[28] the desired product was obtained in excellent 94 % yield after 3 h (entry 10), for which the presence of triethylamine showed a negligible effect other than HCl trapping.

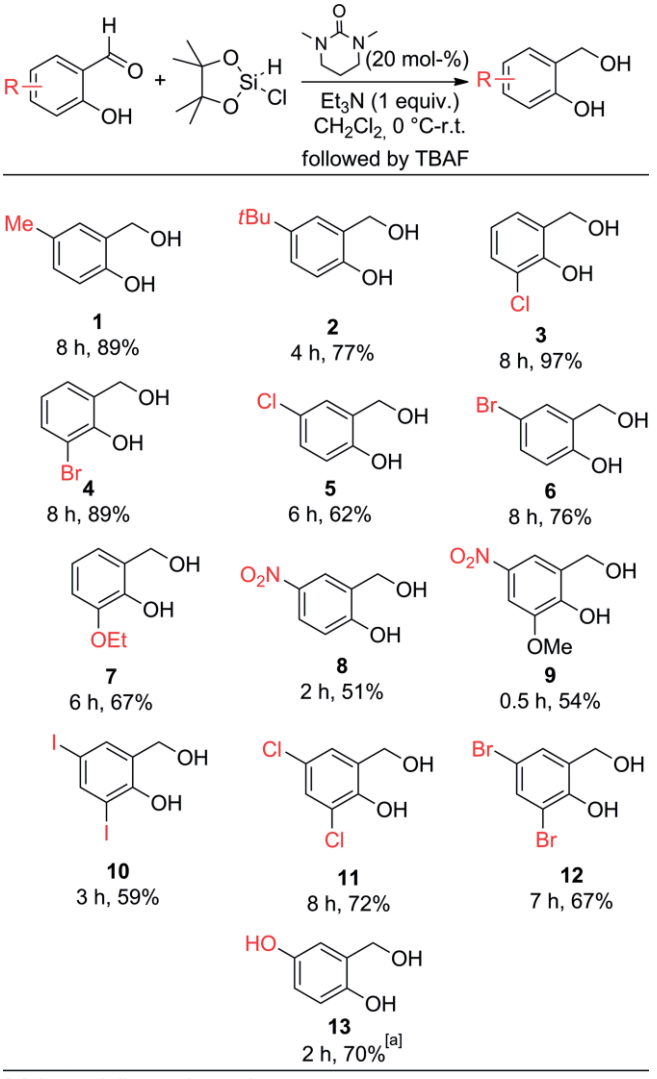
Table 1. Lewis base-catalyzed reduction of salicylaldehyde with PCS.



Entry[a]	Base [equiv.]	Cat.	Yield [%][b]
1	–	–	24[c]
2	Et_3N (1.2)	–	70
3	–	Et_3N	29
4	DIPEA (1.2)	–	51
5	pyridine (1.2)	–	58
6	DMF[d]	–	68
7	Et_3N (1.0)	PPh_3	58 (57)[e]
8	Et_3N (1.0)	pyridine *N*-oxide	70 (56)[e]
9	Et_3N (1.0)	HMPA	64 (64)[e]
10	Et_3N (1.0)	DMPU	94 (97)[e]

[a] PCS (0.65 mmol) in DCM (1 mL) was added over 5 min to a mixture of salicylaldehyde (0.54 mmol), base and catalyst in DCM (1.5 mL) at 0 °C. After 20 min, mixture was left reacting at room temperature for 3 h and then treated with TBAF (1 M in THF, 0.75 mmol). [b] Isolated yield. [c] Reaction conducted for 72 h. [d] DMF used as solvent. [e] Reaction yield in absence of TEA in parenthesis.

After optimization of the reaction conditions, the reduction of different substituted salicylaldehydes was performed (Scheme 3). Reaction times varied between 0.5 h and 8 h, affording the desired salicyl alcohols in reasonable to excellent yields (51–97 %). 5-Alkyl-substituted salicylaldehydes were promptly reduced to afford **1** and **2** after desilylation with TBAF. Despite the presence of nitro and halogen substituents susceptible to reduction, the salicylaldehydes efficiently undergo reduction of the carbonyl group. 3-Halogen substituted salicylaldehydes were generally reduced more efficiently affording **3** and **4** in excellent yields, while 5-halogen derivatives were obtained in slightly lower yields as for **5** and **6**. 5-Nitrosalicylaldehydes could be efficiently reduced in less than 2 h, affording **8** and **9** in up to 54 % yield. Notably, despite the vicinity of ether groups to the hydroxyl substituent of salicylaldehyde, no reduction of 3-alkoxy substituents was observed, as only the corresponding salicyl alcohols **7** and **9** were obtained. The procedure was further expanded to the reduction of 3,5-dihalogens resulting in formation of **10**–**12** in up to 72 % yield. As a continuation of our work on preparation of hydroquinone from quinic acid,[29] we also performed the reduction of readily available formyl-hydroquinone.[30] The reduced product **13** was obtained in 70 % yield by changing the solvent from dichloromethane to acetonitrile without increasing the amount of PCS.

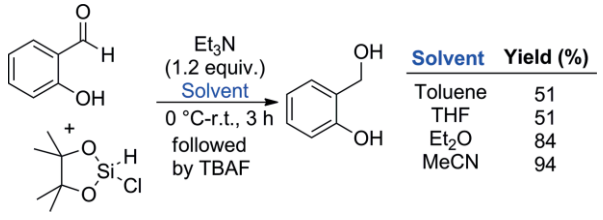


[a] Acetonitrile used as solvent.

Scheme 3. Scope of Lewis base-promoted reduction of salicylaldehydes with PCS.

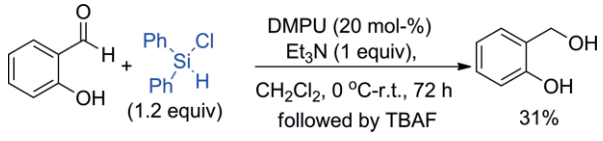
Considering the observed dual role of triethylamine in the reduction of salicylaldehyde, as the use of 1.2 equiv. allowed formation of the desired product in 70 % yield (Table 1, entry 2), we have optimized the reaction conditions as this could ren-

der a more practical use of PCS as reducing agent. Gratefully, salicyl alcohol could be obtained in 94 % isolated yield in acetonitrile after 3 h and further treatment with TBAF (Scheme 4). Nevertheless, a superior catalytic role of DMPU was observed, as the use of 20 mol-% in DCM led to formation of salicyl alcohol in 97 % yield in the absence of any HCl sequester (Table 1, entry 10).



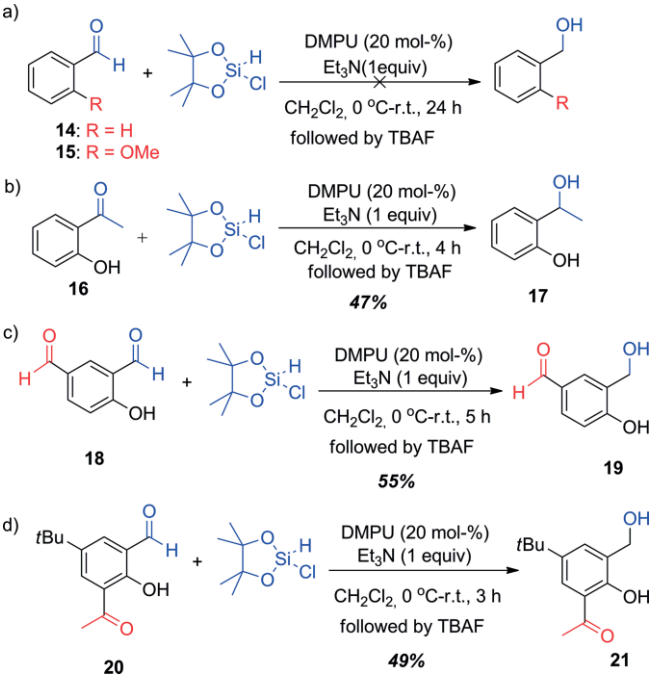
Scheme 4. Optimization for dual use of Et_3N in reduction of salicylaldehyde with PCS.

In order to attest the superiority of PCS for salicylaldehyde reduction, commercially available chlorohydrosilanes were tested using the optimized procedures. When using diphenylchlorosilane with dichloromethane as solvent and DMPU as catalyst in presence of stoichiometric amount of triethylamine, salicylic alcohol was obtained in only 31 % yield after 72 h (Scheme 5). Chlorodimethylsilane and chlorodiisopropylsilane failed in providing the reduced product under the same conditions.



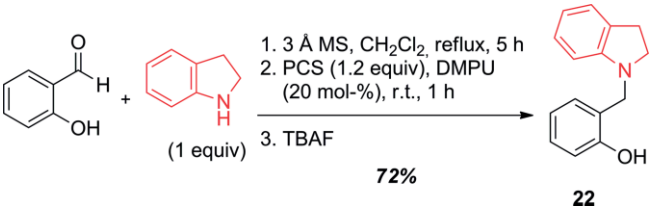
Scheme 5. Reduction of salicylaldehyde with diphenylchlorosilane.

The several attempts to reduce benzaldehyde with PCS using the optimized protocol proved futile, even when increasing the reaction time to 24 h or the reaction temperature. The lack of reactivity of benzaldehyde towards PCS indicate the required formation of a trialkoxyhydrosilane as well as the intramolecular reduction process. Furthermore, the reduction of *O*-methyl salicylaldehyde **15** was not accomplished with the reaction conditions as only starting material was visible after 24 h (Scheme 6a). Despite the rather high reactivity of PCS, its ability to reduce aryl ketones is notoriously low, as confirmed by formation of **17** in only 47 % yield after 4 h (Scheme 6b). With such information in hand, we also examined the chemo- and regioselectivity of the reduction process (Scheme 6c and d). Gratifyingly, our system allowed the regioselective reduction of 5-formyl salicylaldehyde **18**, resulting in exclusive reduction of the aldehyde group in the *ortho*-phenol position in 55 % yield. In order to test the chemoselectivity of the system, **20** was synthesized and submitted to the same reduction conditions. Despite the previously observed reduction of the ketone in **16**, the chemoselective reduction of the aldehyde functionality of **20** was observed, rendering product **21** exclusively in 49 % yield after 3 h.



Scheme 6. Regioselective and chemoselective DMPU-catalyzed reduction of salicylaldehydes with PCS.

In order to expand the suitability of this system to the reduction of carbon-heteroatom unsaturated bonds, PCS was tested as a reducing agent in the reductive amination of a salicylaldehyde-derived iminium (Scheme 7). After condensation of salicylaldehyde and indoline for 6 h in refluxing dichloromethane, the in situ formed iminium was reduced by PCS, affording the corresponding tertiary amine **22** in 72 % yield. Delightfully, despite the high propensity of PCS towards hydrolysis, the use of molecular sieves was enough to trap the water formed in the condensation process. Optimization of this process and its expansion to other amines is under way and will be reported in due course.



Scheme 7. DMPU-catalyzed reductive amination of salicylaldehyde-derived iminium with PCS.

The mechanism of aldehyde reduction with PCS was studied by means of DFT calculations[31] using salicylaldehyde as substrate. The calculations starting point is the trialkoxyhydrosilane that results from HCl loss from the initial hydrosilane, and the free energy profile obtained is depicted in Figure 1.

In the first step of the mechanism, from **A** to **B**, there is coordination of the base, DMPU, to the Si-atom in the trialkoxyhydrosilane. In the corresponding transition state, $\mathbf{TS_{AB}}$, the new Si–O bond is only incipient with a distance of 2.56 Å, still 0.58 Å longer than its final value, in **B**. This is a very facile step

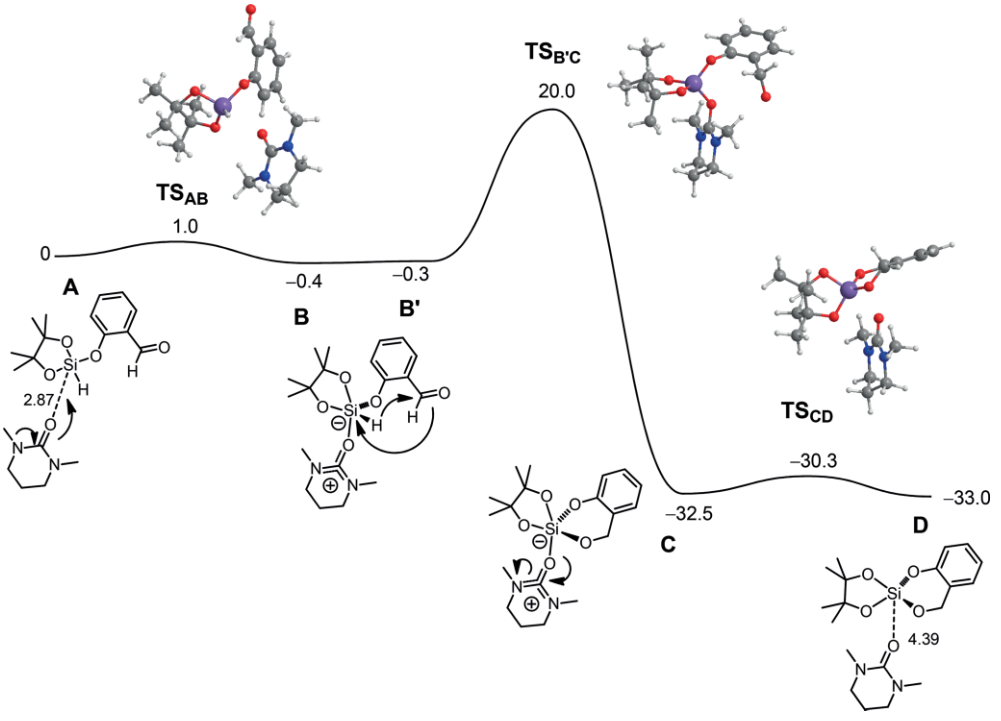


Figure 1. Free energy profile for the reduction of salicylaldehyde with PCS catalyzed by DMPU. Free energy values [kcal/mol] relative to the pair of reactants, DMPU plus the trialkoxyhydrosilane (**A**). Distances in Å.

with a negligible barrier of only 1.0 kcal/mol and the resulting intermediate (**B**) is only 0.4 kcal/mol more stable than the reagents. From **B**, there is rotation around the Si–O_{phenol} bond that leads to another conformer, **B′**. In the following step, from **B′** to **C**, there is hydride attack into the carbonyl C-atom and coordination of the corresponding O-atom to silicon. In the transition state, **TS$_{B'C}$**, formation of the new C–H bond is practically accomplished with a bond length only 0.03 Å longer than the one existing in **C**, while the Si–O bond is only beginning to form with a distance of 4.09 Å, indicating a non-synchronous process in which C–H bond formation precedes the C–O counterpart. The barrier associated with this step is the highest of all path, **TS$_{B'C}$** being 20.0 kcal/mol less stable than the reactants, but the process is clearly exergonic with ΔG = –32.2 kcal/mol. In the last step of the mechanism, there is liberation of the catalyst, DMPU, and formation of the final product, salicyl alcohol. In the corresponding transition state, **TS$_{CD}$**, the process of Si–O_{DMPU} bond breaking is well advanced, with distance of 2.37 Å, already 0.55 Å longer than the one present in intermediate **C**. This is a fairly easy step with a barrier of only 2.2 kcal/mol, and overall the reaction is thermodynamically favorable, with a free energy balance of ΔG = –33.0 kcal/mol.

The mechanism of salicylaldehyde reduction in the absence of catalyst was also investigated by DFT calculations, for comparison purposes. The free energy profile obtained is represented in Figure 2.

The reaction starts with coordination of the carbonyl O-atom to silicon, from **E** to **F**. From **F**, there is hydride transfer from silicon to the $C_{C=O}$-atom, through transition state **TS$_{FG}$**. In the transition state the process of Si–H bond breaking and C–H bond formation is halfway through with distances of 1.61 and

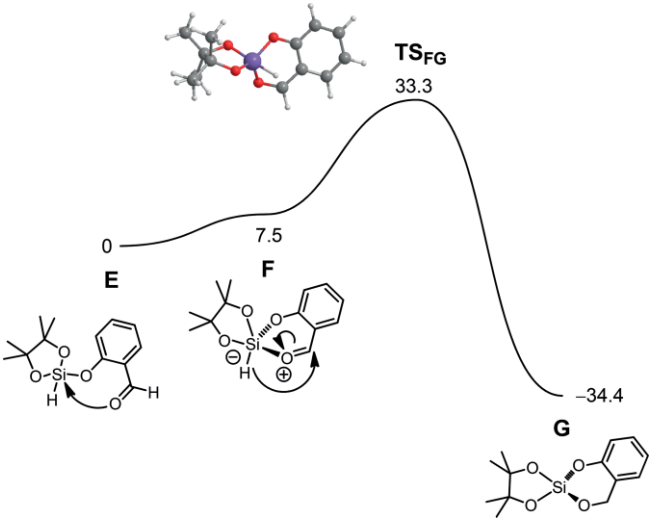


Figure 2. Free energy profile for the reduction of salicylaldehyde with PCS in the absence of catalyst. Free energy values [kcal/mol] relative to the trialkoxyhydrosilane (**E**).

1.87 Å, respectively. Significantly, the reaction has an associated barrier of 33.3 kcal/mol, and the overall process is very favorable with ΔG = –34.4 kcal/mol. The comparison of the two mechanism shows the role of DMPU as catalyst, lowering 12.9 kcal/mol the total barrier of the reaction.

Conclusions

Herein we report the easy preparation of a novel chlorohydrosilane derived from pinacol that can be easily isolated by simple

filtration to remove the pyridinium chloride salt. Its Lewis base promoted and metal-free reduction of salicylaldehydes enables the preparation of several substituted salicyl alcohols in reasonable to excellent yields. Despite the high reactivity of the developed system, we demonstrated its ability to perform the desired reductions in a regio- and chemoselective manner due to the in situ formation of a trialkoxyhydrosilane followed by intramolecular hydride delivery promoted by a Lewis base. From screening of several Lewis bases, DMPU was identified as the best base in promoting the intramolecular hydride delivery, and its catalytic role was further verified by DFT calculations. Nevertheless, a more practical procedure using small excess of common triethylamine is also reported. The potential use of pinacol-derived chlorohydrosilane has been preliminarily demonstrated through its ability to perform the reductive amination of a salicylaldehyde-derived iminium.

Experimental Section

All syntheses were carried out in oven-dried glassware under inert atmosphere. Dichloromethane was dried by distillation under argon with calcium hydride. Triethylamine, pyridine and DMF were purified and dried before use. Reactions were monitored through thin-layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F254). Visualization of the developed plates was performed under UV lights at 254 nm and by staining with cerium ammonium molybdate. Flash column chromatography was performed on silica gel 60 (40–63 μm) as stationary phase. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz in a 300 MHz Varian Mercury spectrometer, using $CDCl_3$ as solvent. ^{29}Si NMR was recorded at 99 MHz in a Jeol ECZR 500. Chemical shifts (δ) are reported in ppm referenced to the $CDCl_3$ residual peak (δ = 7.26 ppm) or TMS peak (δ = 0.00 ppm) for ^{1}H NMR, to $CDCl_3$ (δ = 77.16 ppm) for ^{13}C NMR and to TMS for ^{29}Si NMR (δ = 0.00 ppm). The following abbreviations were used to describe peak splitting patterns: s = singlet, d = doublet, t = triplet, m = multiplet. Coupling constants, *J*, were reported in Hertz [Hz]. High-resolution mass spectra were recorded on a Waters ESI-TOF MS spectrometer or on ABSciex QSTAR Elite ESI-Q-TOF.

Synthesis of the Pinacol-Derived Chlorohydrosilane (PCS): A solution of trichlorosilane (22.3 g, 166 mmol) in diethyl ether (150 mL) in a round-bottomed flask fitted with a dropping funnel under argon was cooled to 0 °C in an ice bath. A mixture of pinacol (6.5 g, 55 mmol) and pyridine (9 mL, 111 mmol) in diethyl ether (100 mL) was transferred to the dropping funnel via a syringe and added slowly to the reaction mixture for about an hour. After complete addition, the mixture was warmed up to room temperature and stirred for 48 h. The pyridinium chloride salt was then filtered out and the solvents evaporated under reduced pressure affording PCS in 95 % yield (9.8 g, 54.5 mmol), that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.45 (s, 12 H, CH_3) 5.69 (s, 1 H, SiH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 84.6 ppm. ^{29}Si NMR (99 MHz, $CDCl_3$, 25 °C, TMS): δ = –37.5 (d, J_{Si-H} = 354 Hz) ppm. HR-MS (ESI$^+$): calculated for $C_6H_{15}O_3Si^+$ [M – Cl + H_2O]$^+$ 163.0785, found 163.0786. For [$C_6H_{13}O^+$] calculated 101.0961, found 101.0961.

General Procedure for DMPU-Catalyzed Hydrosilylation of Salicylaldehyde: DMPU (14 mg, 0.11 mmol) followed by triethylamine (66 mg, 0.54 mmol) were added to a stirred solution of salicylaldehyde (0.54 mmol) in dichloromethane (1.5 mL) at 0 °C. A solution of PCS (0.65 mmol) in dichloromethane (1 mL) was added dropwise via syringe pump to the reaction mixture over 5 min and the resulting solution stirred at this temperature for 20 min and then warmed to room temperature. After consumption of salicylaldehyde, as judged by TLC, the reaction was treated with a solution of TBAF in 1 M THF (0.75 mL, 0.75 mmol) and stirred for 30 min. The mixture was then quenched with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried with $MgSO_4$, filtered out and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography. NMR spectra of compounds **1**–**2**, **4**–**9**, **11**–**13**, **17**, **19** and **22** are consistent with previously reported.[32]

3: Yield 97 % (83 mg, 0.52 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.45 (br. s., 1 H; CH_2OH) 4.79 (s, 2 H, $ArCH_2$) 6.71 (br. s., 1 H; ArOH) 6.82 (t, *J* = 8.2 Hz, 1 H; ArH) 7.09 (d, *J* = 8.2 Hz, 1 H; ArH) 7.28 (dd, *J* = 6.4, 1.8 Hz, 1 H; ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.7, 120.4, 120.8, 127.0, 127.4, 128.8, 150.2 ppm. MS (ESI) *m/z* calculated for $C_7H_7ClO_2Na^+$ [M + Na]$^+$ 181.0027, found 181.0034.

10: Yield 59 % (119 mg, 0.32 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.28–2.56 (br.s., 1 H; CH_2OH) 4.76 (s, 2 H, $ArCH_2$) 7.27–7.33 (br.s., 1 H; ArOH) 7.36–7.41 (m, 1 H, ArH) 7.91 (d, *J* = 1.8 Hz, 1 H; ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = ppm, 63.1, 82.5, 86.9, 127.7, 136.8, 145.3, 154.2 ppm. MS (ESI) *m/z* calculated for $C_7H_6I_2O_2^+$ [M]$^+$ 376.8452, found 376.8455.

Preparation of 3-Acetyl-5-(*tert*-butyl)salicylaldehyde (20) and Reduction by PCS: 4-*tert*-Butyl-2,6-diformylphenol (300 mg, 1.45 mmol, 1 equiv.) was dissolved in 5 mL of dry DCM in a round-bottomed flask under Argon. Triethylamine (252 μL, 1.81 mmol, 1.25 equiv.) and DMAP were added (18 mg, 0.15 mmol, 0.1 equiv.). Then, *tert*-butyldimethylsilyl chloride (264 mg, 1.75 mmol, 1.2 equiv.) was added. The solution was stirred at room temperature for three hours. The reaction was quenched with 5 mL of saturated aqueous NH_4Cl solution and the layers separated. The organic phase was collected and the aqueous phase extracted with DCM (2 × 5 mL). The organic phases were combined, dried with $MgSO_4$, filtered, and the solvent evaporated under vacuum. Purification by flash chromatography (Hex/DCM, 1:1) gave **20a** in 75 % yield (349 mg, 1.09 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = ppm 0.17 [s, 6 H, $Si(CH_3)_2$] 1.09 (s, 9 H, *t*Bu) 1.34 (s, 9 H, *t*Bu) 8.10 (s, 2 H, ArH) 10.35 (s, 2 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = ppm –4.4, 18.6, 25.8, 31.2, 34.8, 128.8, 131.8, 145.9, 158.9, 189.0 ppm.

20a: (376 mg, 1.17 mmol, 1 equiv.) was dissolved in 13 mL of dry THF in a round-bottomed flask under argon. The solution was cooled to –78 °C and MeLi (1.17 mL of 1.6 M solution, 1.17 mmol, 1 equiv.) was added dropwise. After addition, the solution was warmed to room temperature for 10 min. The reaction was quenched with 15 mL of saturated aqueous NH_4Cl solution and the layers separated. The organic phase was collected and the aqueous phase extracted with Et_2O (2 × 15 mL). The organic phases were combined, dried with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. Purification by flash chromatography (Hex/DCM, 4:1) gave **20b** in 61 % yield (241 mg, 0.72 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = –0.01 (s, 3 H, $SiCH_3$) 0.07 (s, 3 H, $SiCH_3$) 0.92 (s, 9 H, *t*Bu) 1.33 (s, 9 H, *t*Bu) 1.41 (d, *J* = 6.4 Hz, 3 H; CH_3CH) 5.23 (q, *J* = 6.1 Hz, 1 H; CHOTBDMS) 7.40 (d, *J* = 2.3 Hz, 1 H; ArH) 7.90 (d, *J* = 2.3 Hz, 1 H; ArH) 9.89 (s, 1 H, CHO) 11.08 (s, 1 H, ArOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –4.8, 18.4, 25.3, 26.0, 31.4, 34.4, 65.0, 128.1, 131.7, 135.0, 142.6, 155.6, 197.1 ppm.

20b: (201 mg, 0.6 mmol, 1 equiv.) was dissolved in 5 mL of THF. The solution was cooled to 0 °C and TBAF (1.2 mL of 1 M solution,

1.2 mmol, 2 equiv.) was added. The reaction was then warmed to room temperature for 30 min. The solution was diluted with 15 mL of Et_2O and washed with saturated $NaHCO_3$ aqueous solution (3 × 15 mL). The organic layer was collected, dried with $MgSO_4$, filtered and the solvent evaporated to give **20c** as a colorless oil in quantitative yield (0.6 mmol, 137 mg), which was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.33 (s, 9 H, *t*Bu) 1.55 (d, J = 6.4 Hz, 3 H; CH_3CH) 5.17 (q, J = 6.8 Hz, 1 H; CHOH) 7.44 (d, J = 2.9 Hz, 1 H; ArH) 7.69 (d, J = 2.3 Hz, 1 H; ArH) 9.90 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 31.4, 34.4, 66.3, 120.0, 128.8, 131.4, 133.3, 142.9, 156.7, 197.2 ppm.

20c: Was dissolved in 24 mL of dry DCM in a round-bottomed flask under Argon. $NaHCO_3$ (126 mg, 1.5 mmol, 2.5 equiv.) was added and the solution cooled to 0 °C. Dess–Martin periodinane (306 mg, 0.72 mmol, 1.2 equiv.) was added and the reaction warmed to room temperature for 30 min. The reaction was then quenched with 2 % $Na_2S_2O_3$ aqueous solution (25 mL) and the layers were separated. The organic phase was collected and the aqueous phase extracted with DCM (2 × 25 mL). The organic phases were combined and the solvent dried with $MgSO_4$, filtered and the solvents evaporated. Purification by flash chromatography (DCM) gave 3-acetyl-5-(*tert*-butyl)salicylaldehyde **20** in 50 % yield (66 mg, 0.30 mmol) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.34 (s, 9 H, *t*Bu) 2.69 (s, 3 H, CH_3CO) 7.90–8.13 (m, 2 H, ArH) 10.44 (s, 1 H, CHO) 12.66 (s, 1 H, ArOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 31.3, 34.4, 121.4, 124.1, 132.8, 133.9, 142.0, 162.4, 190.2, 203.9 ppm. MS (ESI^+) *m/z* calculated for $C_{13}H_{17}O_3^+$ $[M + H]^+$ 221.1172, found 221.1161.

21: 49 % yield (20 mg), following general procedure, starting from 0.182 mmol (40 mg) of **20**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.32 (s, 12 H, *t*Bu) 2.51–2.56 (br.s., 1 H, CH_2OH) 2.66 (s, 3 H, CH_3) 4.74 (s, 2 H, $ArCH_2$) 7.56 (d, J = 2.3 Hz, 1 H; ArH) 7.64 (d, J = 2.3 Hz, 1 H; ArH) 12.57 (s, 1 H, ArOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8, 34.2, 61.8, 110.0, 118.8, 125.8, 129.2, 133.2, 141.4, 158.4, 204.97 ppm. MS (ESI) *m/z* calculated for $C_{13}H_{19}O_3^+$ $[M + H]^+$ 223.1329, found 223.1329.

Reductive Amination of Salicylaldehyde and Indoline-Derived Iminium: A mixture of salicylaldehyde (0.54 mmol), indoline (64.4 mg, 0.54 mmol) and molecular sieves (3 Å, 255 mg) in dichloromethane (1 mL) was refluxed for 5 h under argon. The mixture was then cooled to room temp. and DMPU (0.11 mmol, 14 mg) added in one portion followed by dropwise addition of a solution of PCS (0.65 mmol) in dichloromethane (1 mL) via a syringe pump over 5 min. The resulting mixture was stirred for 1 h, treated with a solution of TBAF in 1 M THF (0.75 mL, 0.75 mmol) and stirred for additional 10 min. The mixture was quenched with saturated NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered out and solvent removed under reduced pressure. The crude product obtained was purified by flash column chromatography to afford **22** in 72 % yield (87 mg, 0.39 mmol), with similar spectral characterization as described previously.[32l]

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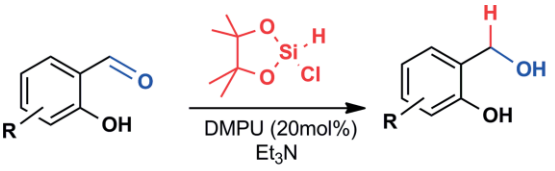

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