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Communication

Ketone Reduction

1-Hydrosilatrane: A Locomotive for Efficient Ketone Reductions

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Abstract: An efficient method for the reduction of ketones with 1-hydrosilatrane is described. In the presence of a Lewis base activator, the resulting secondary alcohols are rapidly formed in good to excellent yields (20 examples, 71–99 % yields). The relative bulkiness of 1-hydrosilatrane also enables the diastereoselective reduction of (–)-menthone to (+)-neomenthol, and the use of a chiral alkoxide activator can lead to the enantioselective reduction of prochiral ketones.

Introduction

The reduction of carbonyl groups is one of the most significant and well-studied chemical transformations, which provides access to a plethora of products from simple starting materials.[1] The development of chiral reducing agents has further given access to asymmetric products from prochiral ketones,[1a] including the crucially important, optically pure secondary alcohols.[2]

Organosilicon hydrides, simply referred to as silanes, can act as hydride sources in such reduction reactions. Unlike borohydrides and aluminohydrides, however, silanes are typically weak hydride donors and thus do not react with weak electrophiles such as ketones and aldehydes unless the electrophilicity of the carbonyl group is enhanced.[3] This activation can be achieved by adding a Lewis acid, which can coordinate to the carbonyl oxygen atom;[4] alternatively, the Lewis acid can activate the silicon–hydrogen bond, making the hydride much more nucleophilic.[5] In a related approach, the silicon atom itself can be made more Lewis acidic by adding a Lewis base with a high affinity for silicon, such as a fluoride,[6] or by adding an oxide anion.[7] The latter approach results in a Lewis acidic, hypervalent, pentacoordinate hydrosilanide anion, which can form a complex with the carbonyl-oxygen atom and then donate its hydride to the electrophilic carbon center. The increased hydride-donating ability of hypervalent silicon is well-known[8] and has been studied and exploited in an array of chemical transformations.[9]

Currently, polymethylhydrosiloxane (PMHS) is the most commonly used silane for carbonyl reductions due to its low toxicity, relatively high stability, and low cost.[10] Mechanistic studies have suggested that it forms the volatile and dangerous $MeSiH_3$ in situ as the active reducing species.[7e] A similar disproportionation is known to occur with $(EtO)_3SiH$, which forms the extremely pyrophoric SiH_4.[11] These unwanted attributes could create complications for large-scale industrial applications.

Silatranes are caged structures in which the nitrogen atom donates its lone pair of electrons to the silicon atom, forming a pentacoordinate silicon.[12] Since their discovery in the 1960s,[13] silatranes have been extensively studied for myriad uses.[14] 1-Hydrosilatrane (Figure 1) is a promising reducing agent due to its pre-activated pentacoordinate silicon atom and relatively high stability with respect to other silanes.[15] It is air- and moisture-stable, easy to handle, and cheaply synthesized from boratrane.[15b]

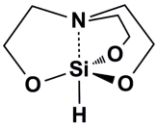

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Figure 1. 1-Hydrosilatrane.

Although 1-arylsilatranes are known to be toxic,[16] to have been commercialized as zooicides,[17] and even to be portrayed as poison in movies,[18] 1-hydrosilatrane has a much better safety profile; the hydride derivative possesses an intraperitoneal (IP) LD_{50} value of 100 mg/kg while the dangerous aryl-substituted version has an IP LD_{50} value of 0.33 mg/kg.[19] Interestingly, 1-alkyl and 1-alkoxysilatranes (with IP LD_{50} values of 3000 and 2100 mg/kg, respectively) are non-toxic[16] and do have pharmacological properties[20] and beneficial effects when fed to livestock.[21]

The application of 1-hydrosilatrane (**1**) as a reducing agent was published in 1976 by Eaborn et al., who reported the reduction of both acetone and 4-hydroxybenzaldehyde without an activator.[22] This work was narrow in scope and, furthermore, irreproducible in our hands. However, we were inspired and proceeded to develop a method for the reduction of aldehydes by using **1** in the presence of a Lewis base activator.[23] Herein, we discuss the activation of 1-hydrosilatrane (**1**) with a Lewis base to reduce ketones in an operationally simple manner, as well as the scope and stereoselectivity of the reaction.

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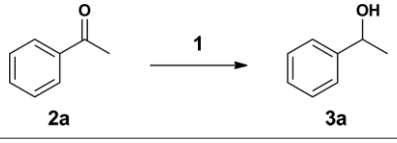
Results and Discussion

Acetophenone (**2a**) was reduced in *N*,*N*-dimethylformamide (DMF) at room temperature within 70 min by using 1.1 equiv. of 1-hydrosilatrane in the presence of 1 equiv. of potassium *tert*-butoxide, giving 94 % conversion to 1-phenylethanol (**3a**; Table 1, Entry 1). A brief survey of solvents (Table 1, Entries 2–4) suggested that the more polar the solvent, the greater the yield; this is likely due to the fact that **1** is more soluble in polar solvents.

Table 1. Optimization of the reduction reaction.



Entry	Activator ([equiv.])	**1** [equiv.]	Solvent	Time [min]	Yield [%]
1	*t*BuOK (1)	1.1	DMF	40	94
2	*t*BuOK (1)	1.1	DCM	40	81
3	*t*BuOK (1)	1.1	MeCN	40	74
4	*t*BuOK (1)	1.1	THF	40	15
5	NaOH (1)	1.5	DMF	70	22
6	K_2CO_3 (1)	1.5	DMF	70	0
7	NEt_3 (1)	1.5	DMF	70	0
8	*t*BuOK (0.5)	1.1	DMF	70	20
9[a]	*t*BuOK (0.5)	1.1	DMF	2880	99+

[a] The ketone reduced in this reaction was 2-methoxyacetophenone (**2b**).

Substitution of sodium hydroxide for *tert*-butoxide (Table 1, Entry 5) induced the reduction of acetophenone (**2a**), but with low conversion. The use of a large excess of sodium hydroxide under the optimized conditions gave higher yields – up to 86 % when the entirety of a crushed pellet was added (Entry 12, Section 4 of the Supporting Information) – but still was not as effective as potassium *tert*-butoxide. Milder Lewis bases (Table 1, Entries 6 and 7) gave no conversion, which indicates the need for a stronger base to activate **1**. Lowering the amount of *tert*-butoxide to 0.5 equiv. gave lower yields (Table 1, Entry 8). However, when 2-methoxyacetophenone (**2b**) was treated with **1** and 0.5 equiv. of *tert*-butoxide for 48 h, the yield of alcohol **3b** was greater than 99 %, demonstrating that the activator can act catalytically (Table 1, Entry 9).

The scope of this reaction is broad, as can be seen in Figure 2: ketones bearing electron-donating groups such as methoxy, allyloxy, or phenyl groups (**2b–f**), inductively electron-withdrawing groups such as halides (**2g** and **h**), or strong electron-withdrawing groups such as a nitro group (**2i**), can be reduced in good to excellent yields. Potentially reactive nitro (**3i**) and allyl (**3e**) substituents were tolerated well by the system; a trial reaction with a single α,β-unsaturated carbonyl group (chalcone) unfortunately yielded an inseparable mixture of products. Substitution at the α position is also accepted (**2j–l**), even when the substituent is an arene (**2m–p**). The system is not limited to phenylketones, as can be seen from the reduction of cyclohexanone (**2q**), heptanone (**2r**), and octanone (**2s**). The isolated yields for the aliphatic alcohols may be lower due to their increased water solubility and hence lower recovery during work-up.

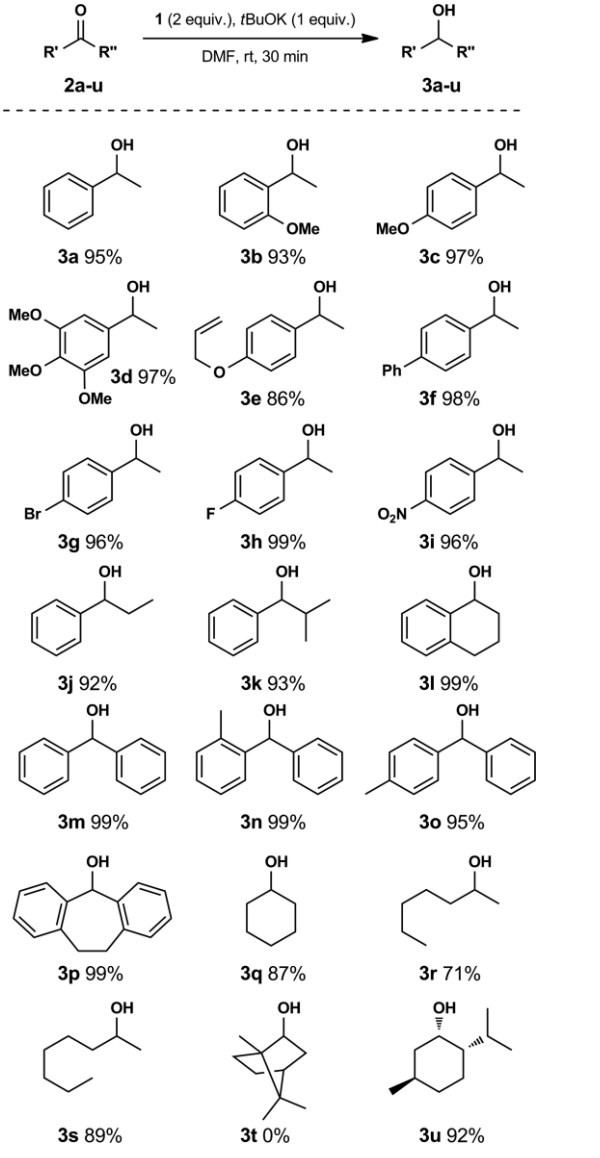


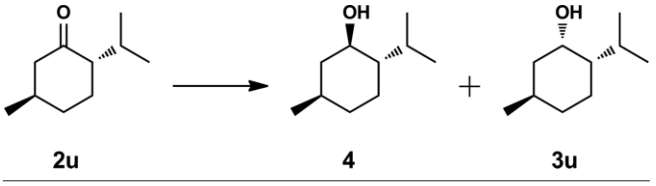
Figure 2. Scope of the reduction of ketones with 1-hydrosilatrane (**1**).

The system appears to be limited by steric effects, as indicated by the inability of 1-hydrosilatrane to reduce the sterically hindered carbonyl group in camphor (**2t**). However, the bulk of silatrane served useful in the reduction of (–)-menthone (**2u**), which proved to be diastereoselective: the product is almost exclusively (+)-neomenthol (**3u**).

Reagents with such high selectivity for a single diastereomer in the reduction of (–)-menthone (**2u**) are scarce, and of those, few favor the thermodynamically less stable (+)-neomenthol (**3u**; Table 2). Commonly used, commercially available L-selectride (Table 2, Entry 3) provides (+)-neomenthol but also forms a significant amount of the undesired side product (+)-*iso*-neomenthol. Unlike reductions using certain bulky reducing agents in which the diastereoselectivity is solvent dependent,[24] we do not see a significant difference in our selectivity when the solvent is changed from polar DMF (Table 2, Entry 9) to nonpolar toluene (Table 2, Entry 10). This is likely due to the bulk of 1-hydrosilatrane (**1**), which can only approach (–)-menthone (**2u**)

from the less sterically hindered face in an equatorial attack (Figure 3) regardless of the choice of solvent.

Table 2. Stereoselectivity in the reduction of (–)-menthone.



Entry	Reducing agent	4/3u	Ref.
1	$NaBH_4$	35:65	[26]
2	$LiB(C_2H_5)_3H$	10:90	[26]
3	L-selectride	0:85[a]	[26]
4	$LiAlH_4$	72:28	[27]
5	$Al(iPrO)(iBu)_2H$	1:99	[24]
6	PMHS[b]/TBAF[c]/PCy_3	40:60	[28]
7	Pt/C•H_2	19:81	[29]
8	$B(C_6H_5)_3/H_2$	100:0	[30]
9	1-hydrosilatrane (**1**)/*t*BuOK[e]	3:97	
10	1-hydrosilatrane (**1**)/*t*BuOK[f]	1:99	

[a] 15 % Formation of *iso*-neomenthol due to racemization. [b] Polymethylhydrosiloxane. [c] Tetra-*n*-butylammonium fluoride. [d] Tricyclohexylphosphine. [e] DMF as solvent. [f] Toluene as solvent.

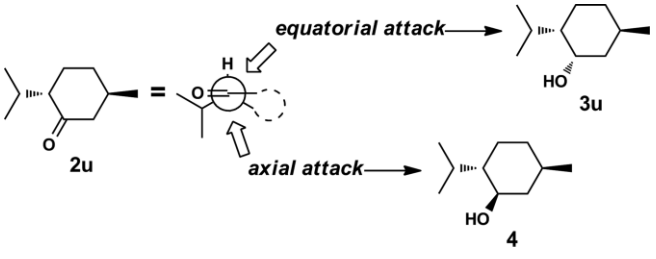


Figure 3. Steric hindrance on (–)-menthone.

This stereoselectivity of the reduction of **2u**, as well as the inability to reduce camphor (**2t**), suggests that a close proximity is required between hydride donor **1** and the carbonyl group. The increased solubility of **1** in the presence of an activator and the inherent need of an activator for a reduction to occur enable us to propose a mechanism (Figure 4). The Lewis base activator coordinates with the silicon, breaking the dative bond between silicon and nitrogen, maintaining the silicon as pentacoordinate.[25] The silicon then forms a hexacoordinate complex with the carbonyl-oxygen atom, at which point the hydride is transferred to the electrophilic carbon center to reform the pentacoordinate silicon.[7c,9a] This continues to collapse by elimination of the Lewis base activator to form the alkoxysilatrane. Support for this arises from the observation that when acetophenone is reduced in the presence of *tert*-butoxide as activator, 1-(phenylethoxy)silatrane can be detected by GC–MS and ^{1}H NMR spectroscopy after neutral work-up.[31]

The observation of intact alkoxysilatrane before work-up suggests that the mechanism is different to that of PMHS or $(EtO)_3SiH$ activated by a Lewis base, in which highly unstable hydrosilanes such as $MeSiH_3$ and SiH_4 are formed in situ to act as reducing agents.[7e] Avoiding such volatile and reactive intermediates renders hydrosilatrane **1** a both safer and more

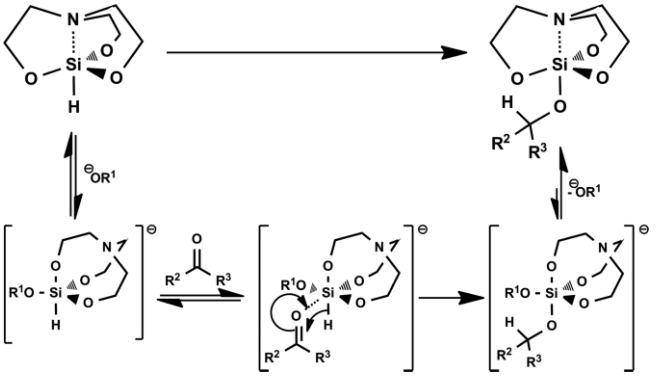


Figure 4. Proposed mechanism.

operationally friendly reducing reagent than PMHS and other alkoxyhydrosilanes.

Prior to work-up, smaller amounts of *tert*-butoxysilatrane are also present. The fact that the reaction can be run with catalytic amounts of *tert*-butoxide supports this mechanism, and the prominence of 1-(phenylethoxy)silatrane as the main silatrane product formed (prior to work-up) implies that little of the phenylethoxide is released during the reaction and is therefore available to act as the Lewis base activator. We speculate that the preferential release of one alkoxide over another is sterically motivated, though more experimental work is required before this can be stated with certainty.

Due to the steric constraints of the system, it was speculated that a chiral activator could induce enantioselectivity in the reduction of prochiral ketones. As the alkoxide product largely remains attached to the silatrane, interference of this substrate as a less selective activator is minimized.[7a] (1*S*,2*R*)-(+)-1,2-diphenyl-2-amino-1-ethanol (**5**) was deprotonated with sodium hydride in situ and used as an activator for **1** in the reduction of 2-methylbenzophenone (**2n**); this gave a respectable enantiomeric ratio of 87:13 (Figure 5). We are encouraged by this isolated result, and work on further development of this asymmetric version of the reaction is already underway. It is worth noting that a chiral ligand could be utilized catalytically, so long as it is preferentially released during the last step of the proposed mechanism.

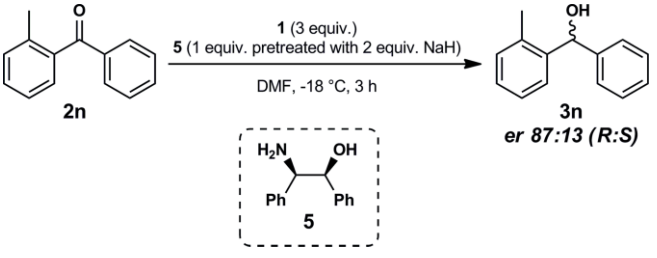


Figure 5. Enantioselectivity in the reduction of prochiral ketone **2n**.

Conclusion

The reduction of a broad range of ketones with 1-hydrosilatrane (**1**) in excellent yields is reported. High diastereoselectivity of the reduction of (–)-menthone (**2u**) to (+)-neomenthol (**3u**) was

observed, which is consistent with a bulky reducing intermediate. A mechanism in agreement with our observations was proposed. Unlike with PMHS and $(EtO)_3SiH$, volatile and extremely hazardous-active hydrosilane species are not formed, therefore making **1** a much safer alternative for large-scale reactions. Enantioselectivity was observed for the reduction of prochiral ketone **2n** with **1** and a chiral activator. Further research is underway to improve the enantioselectivity as well as to explore the reduction of other significant functional groups.

Experimental Section

General Procedure: To a 25 mL round-bottomed flask containing 5 mL of *N*,*N*-dimethylformamide were added 1-hydrosilatrane (0.263 g, 2.0 mmol) and ketone (1.0 mmol). The resulting solution was stirred for 1 min, after which 1 M *t*BuOK in THF (1.0 mmol, 1.0 mL) was added. The reaction mixture was allowed to stir for 30 min. The reaction was quenched with 25 mL of 3 M HCl and extracted with 30 mL of ethyl acetate. The organic layer was washed with brine (3 ×50 mL) and dried with anhydrous sodium sulfate. After filtration, the solvent was removed under vacuum to yield the product. No further steps were taken for purification.

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Keywords: Silanes · Reduction · Metal free · Diastereoselectivity · Enantioselectivity

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[31] For spectra of the crude intermediates, see the Supporting Information.

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