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1-Hydrosilatrane: a locomotive for efficient ketone reductions

Sami E. Varjosaari,[a] Vladislav Skrypai,[a] Paolo Suating,[a] Joseph J. M. Hurley,[a] Thomas M. Gilbert,[a] and Marc J. Adler*[a]

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

The reduction of carbonyl groups is one of the most significant and well-studied chemical transformations, providing access to a plethora of products from simple starting materials.[1] The development of chiral reducing agents has further given access to asymmetric products,[1a] including the crucially important optically pure secondary alcohols, from prochiral ketones.[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 carbon center is enhanced.[3] Such activation can be achieved by adding a Lewis acid, which can coordinate with the carbonyl oxygen;[4] alternatively, the Lewis acid can activate the silicon hydride bond, making the hydride much more nucleophilic.[5] In a related approach, the silicon itself can be made more Lewis acidic by adding a Lewis base whose affinity for silicon is high, such as a fluoride,[6] or an oxide anion:[7] this results in a Lewis acidic hypervalent pentacoordinate hydrosilanide anion, which can form a complex with the carbonyl oxygen 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 reduction 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, forming a pentacoordinate silicon.[12] Since their discovery in the 1960s,[13] they 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]

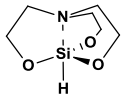

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Figure 1. 1-Hydrosilatrane.

Although 1-arylsilatranes are known to be toxic,[16] having been commercialized as zooicides[17] and even being portrayed as poison in movies,[18] 1-hydrosilatrane has a much better safety profile: the hydride derivative possesses an intraperitoneal (IP) LD_{50} of 100 mg/kg while the dangerous aryl-substituted version has an IP LD50 of 0.33 mg/kg.[19] Interestingly, 1-alkyl and 1-alkoxysilatranes (with IP LD_{50}s of 3000 and 2100 mg/kg, respectively) are non-toxic[16a] and actually 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. We were inspired, however, and proceeded to develop a method for the reduction of aldehydes 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 scope and stereoselectivity of the reaction.

Acetophenone (**2a**) was reduced in *N*,*N*-dimethylformamide (DMF) at room temperature within 70 minutes using 1.1 equivalents of 1-hydrosilatrane in the presence of 1 equivalent 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 of alcohol from ketone: this is likely due to the fact that **1** is more soluble in polar solvents.

Substitution of sodium hydroxide for *tert*-butoxide (Table 1, Entry 5) induced reduction of acetophenone (**2a**), but with low conversion. Excess amounts of sodium hydroxide in optimized conditions gave higher yields, but these still were not as good as with *tert*-butoxide (see Supporting Information). Milder Lewis bases (Table 1, Entries 6-7) gave no conversion, indicating the need of a stronger base to activate **1**. Lowering the amount of *tert*-butoxide to 0.5 equivalents gave lower yields (Table 1, Entry 8). However, when 2-methoxyacetophenone (**2b**) was treated with 1 and 0.5 equivalents 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).

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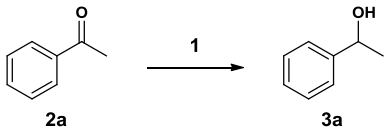

Table 1. Optimization of reaction.

Entry	Activator (eq)	Equivalents of **1**	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	TEA (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).

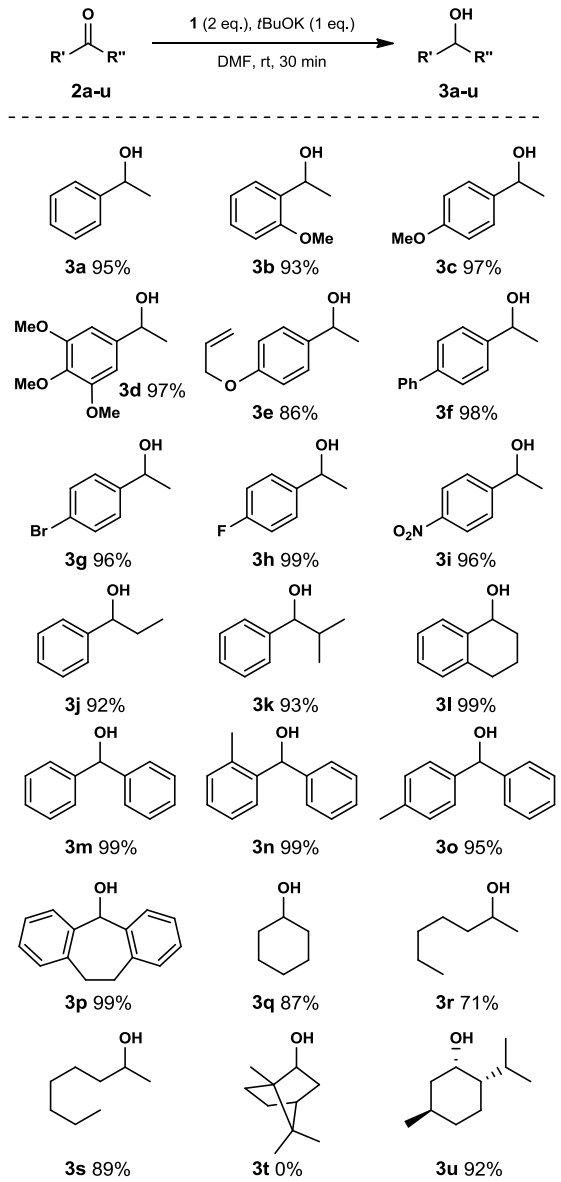

Figure 2. Scope of the reduction of ketones with 1-hydrosilatrane (**1**)

The scope of this reaction is broad, as seen in Figure 2: ketones bearing electron donating groups such as methoxy, allyloxy, and phenyl (**2b-f**), inductively electron withdrawing groups such as halides as in (**2g-h**), and strong electron withdrawing groups such as a nitro group (**2i**) can be reduced in good to excellent yield. Potentially reactive nitro (**3i**) and allyl (**3e**) substituents were tolerated well by the system; a trial reaction with a single *α*,*β*-unsaturated carbonyl (chalcone) unfortunately yielded an inseparable mixture of products. Substitution at the *α* position is also acceptable (**2j-l**), even when the substituent is an arene (**2m-p**). The system is not limited to phenylketones, as can be seen with 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.

The system appears to be limited by steric effects, as can be seen by the inability of 1-hydrosilatrane to reduce the sterically hindered carbonyl in camphor (**2t)**. However, the bulk of silatrane served useful in the reduction (-)-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 (+)-isoneomenthol. Unlike reductions using certain bulky reducing agents where the diastereoselectivity is solvent dependent,[24] we do not see a significant difference in our selectivity when the solvent is changed from a polar solvent, DMF (Table 2, Entry 9), to a nonpolar solvent such as toluene (Table 2, Entry 10). This is likely due to the bulk of the 1-hydrosilatrane **1**, which can only approach (-)-menthone (**2u**) from the less sterically hindered face in an equatorial attack (Figure 3) regardless of choice of solvent**.**

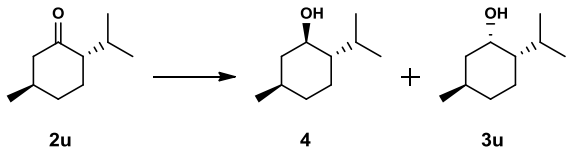

Table 2. Stereoselectivity in the reduction of (-)-menthone

entry	reducing agent	**4**:**3u**	reference
1	$NaBH_4$	35:65	27
2	$LiB(C_2H_5)_3H$	10:90	27
3	L-selectride	0:85[a]	27
4	$LiAlH_4$	72:28	28
5	Al(*i*PrO)(*i*Bu)$_2$H	1:99	24
6	PMHS/TBAF/Pcy	40:60	29
7	Pt/C.H_2	19:81	30
8	$B(C_6H_5)_3/H_2$	100:0	31
9	1-Hydrosilatrane/^{t}BuOK [b]	3:97	
10	1-Hydrosilatrane/^{t}BuOK [c]	1:99	

[a] 15% formation of iso-neomenthol due to racemization. [b] DMF as solvent. [c] Toluene as solvent.

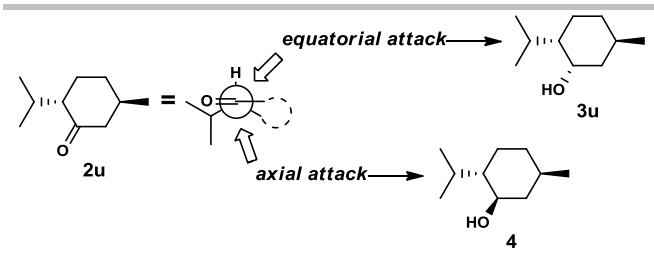

Figure 3. Steric hindrance on (-)-menthone.

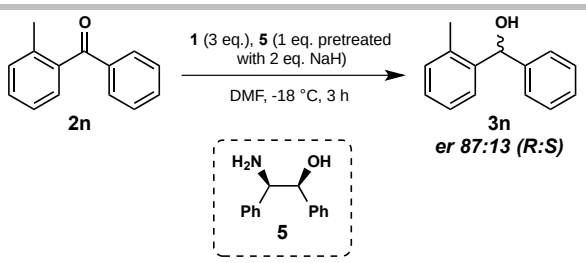

Figure 5. Enantioselectivity in the reduction of prochiral ketone **2n**.

This stereoselectivity of the reduction of **2u**, as well as the inability to do so with camphor, suggests that close proximity is required between the hydride donor, **1**, and the carbonyl. The increased solubility of **1** in the presence of an activator and the inherent need of an activator for a reduction to occur allows 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, at which point the hydride is transferred to the electrophilic carbon center to reform the pentacoordinate silicon.[7c, 26] This goes on 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 activator, 1-(phenylethoxy)silatrane can be seen on the GCMS trace and in the ^{1}H NMR spectrum after neutral workup.[32]

The observation of intact alkoxysilatrane before workup 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 a both safer and more operationally friendly reducing reagent than PMHS and other alkoxyhydrosilanes.

Following reaction but prior to workup, smaller amounts of *tert*-butoxysilatrane are also seen. 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 workup) implies that little of the phenylethoxide is released during reaction and is therefore available to act as the Lewis base activator. We speculate that the preferencial release of one alkoxide over another is sterically motivated, though more experimental work is required before this could be stated with certainty.

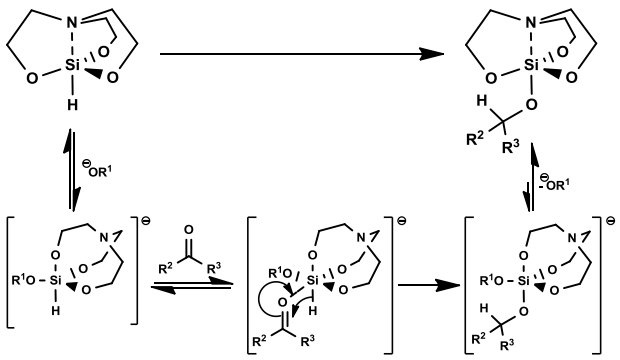

Figure 4. Proposed mechanism.

Due to the steric constraints of the system, it was speculated that a chiral activator could give enantioselectivity with prochiral ketones. As the alkoxide product largely remains attached to the silatrane, interference of this substrate as a less selective activator is minimized.[7a] (*1S*,*2R*)-(+)-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.

This communication reports the reduction of a broad range of ketones with 1-hydrosilatrane (**1)** in excellent yields. High diastereoselectivity of the reduction of (-)-menthone (**2u**) to (+)-neomenthol (**3u**) was observed, consistent with a bulky reducing intermediate. A mechanism consistent with our observations was proposed. Unlike PMHS and $(EtO)_3SiH$, volatile and extremely hazardous active hydrosilane species are not formed, therefore making 1-hydrosilatrane 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 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 *N*,*N*-dimethylformamide, was added 1-hydrosilatrane (0.263 g, 2.0 mmol), and ketone (1.0 mmol). The resulting solution was stirred for 1 minute, after which 1 M *t*-BuOK in THF (1.0 mmol, 1.0 mL) was added. Reaction mixture was allowed to stir for 30 min. Reaction was quenched with 25 mL 3 M HCl, and extracted with 30 mL ethyl acetate. Organic layer was washed with brine (50 mL x 3), and dried with anhydrous sodium sulphate. After filtration, the solvent was removed under vacuum to yield product. No further steps were taken for purification.

Acknowledgements

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Keywords: silanes • reduction • metal-free • diastereoselectivity • enantioselectivity

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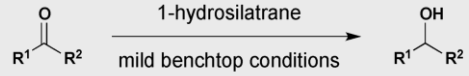
[32] For spectra of the crude intermediates, see Supporting Information

Entry for the Table of Contents (Please choose one layout)

KEY WORDS: Ketone Reduction

COMMUNICATION



20 examples: up to 99% yield, 99:1 dr, 87:13 er

The next 'trane out of 'tone 1-Hydrosilatrane is shown to be an effective, cheap, safe, and easy-to-use hydride source for the efficient reduction of a variety of ketones. Examples of both diastereoselectivity and enantioselectivity in the reaction are also demonstrated.

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