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Enantioselective metal-free reduction of ketones by a user-friendly silane with a reusable chiral additive

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ABSTRACT

1-Hydrosilatrane, a safe and easy-to-handle reducing reagent that can be inexpensively accessed, has been shown to reduce prochiral ketones asymmetrically in the presence of chiral 1,2-aminoalcohols with *ees* ranging from 8% to 86%. The best result was achieved using ephedrine as the source of chirality, which is readily commercially available. The additive can be recovered through extraction and reused without any erosion of enantioselectivity.

Introduction

The asymmetric reduction of ketones represents one of the most efficient methods to synthesize chiral alcohols, which are of significant importance in the pharmaceutical, agrochemical, and flavor industries [1]. Many efficient methods have been developed for this transformation with transition metal and main group reagents, both catalytically and stoichiometrically [2]. Transition metal catalysts have been used in asymmetric hydrogenation and hydride transfer reactions with great success, but tend to be expensive, unstable under ambient conditions, and/or can contaminate products by metal-leaching, frequently making these methods difficult to apply on preparative scales [3,4a]. Furthermore, the chiral ligands required for such reactions are often expensive and difficult to access. Organocatalysts have emerged as alternatives to transition metal catalysts without these key drawbacks [4]. Some of the most notable organocatalytic systems include the CBS method using chiral boranes [1c,5] and chiral Lewis acids with Hantzsch esters [6].

In contrast to boranes, hydrosilanes have been relatively underdeveloped for the chiral reduction of ketones. Hydrosilanes are popular reducing agents as they can be inexpensive, chemically stable, and easy-to-handle hydride sources [7]. The most successful applications of hydrosilanes to the asymmetric reduction of prochiral ketones, however, involve the use of highly reactive silanes such as trialkoxy- or trichlorosilanes, which are difficult to work with due to their rapid degradative reaction with atmospheric water. Generally, hydrosilanes require an exogenous activator or catalyst to effect reduction, and it is through this additive that stereochemical information is usually communicated [8]. Chiral hydrosilanes can be used for moderate enantioselectivity, but can be difficult to synthesize and are required in stoichiometric amounts [9].

The first organocatalyzed asymmetric reduction of ketones was achieved by Hosomi and co-workers, using chiral lithium diolates and aminoalcoholates to activate trimethoxysilanes, forming secondary alcohols in good yields and enantioselectivity [10]. Since then, several other groups have used chiral anionic Lewis bases to activate alkoxysilanes with varying degrees of success [11]; the highest enantioselectivities were achieved with an axially chiral binaphthol derivative [11b]. Even greater enantioselectivity has been achieved using the more reactive trichlorosilane with neutral chiral Lewis base activators [12].

Polymethylhydrosiloxane (PMHS) is a popular silane due to its stability, low cost, and ease of handling [13]. Although PMHS has shown potential in processes for the asymmetric hydrosilylation of ketones, the most effective methods require metal catalysts [14]. Furthermore, the active silane species in the presence of Lewis bases has been suggested to be the more pyrophoric methylsilane, complicating the use of Lewis bases as organocatalysts in large scale hydrosilylations [15].

In order to observe high enantioselectivity in any asymmetric catalytic reaction one must have effective catalyst turnover. The particular issue with the asymmetric reduction of ketones with hydrosilanes using chiral Lewis base catalysts is that the product

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alkoxide can compete with the chiral activator and as a result erode enantioselectivity; this is further compounded with alkoxysilanes, where the alkoxide ligands of the silane could also be released during the reaction and offer competing, enantioambivalent pathways [11b]. High enantioselectivity can be achieved when the silane remains bound to the product alkoxide and the chiral Lewis base catalyst can turn over efficiently (Fig. 1). Catalytic systems are useful for minimizing both waste and cost, as chiral sources can be expensive and difficult to recapture and recycle. Yet the technical difficulty in controlling such reactions – coupled with the impracticality of using highly reactive silanes – has prevented significant advancement in the field of metal-free asymmetric reduction using hydrosilanes.

1-Hydrosilatrane **1** (Fig. 2), a caged alkoxysilane, has been shown to be an effective reducing agent for ketones in the presence of a Lewis base additive [16]. As a white crystalline solid, 1-hydrosilatrane **1** is safe and much easier to handle than reactive silicon hydride sources, yet it is also a more active atom-transfer reagent than typical robust hydrosilanes such as trialkylsilanes [17]. In the course of our study regarding the reduction of ketones with achiral additives we observed evidence of diastereoselectivity, which made us believe that using a chiral Lewis base could result in an enantioselective version of this reaction. We also saw tentative signs of the silatrane moiety preferring to remain attached to the alkoxide product [18], potentially indicating the feasibility of running this reaction with catalytic amounts of the chiral Lewis base.

Results and discussion

Activator screening

This study commenced with a screening of stoichiometric amounts of several chiral Lewis base activators (Table 1). All activators were deprotonated in situ with sodium hydride and then cooled prior to the addition of acetophenone and 1-hydrosilatrane. Enantioselectivity was determined by chiral GCMS, and the stereochemistry of the major product was determined by comparison to

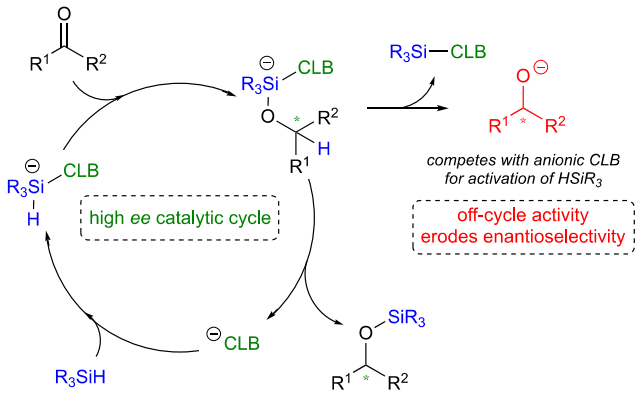


Fig. 1. Enantioselective reduction of ketones using hydrosilanes with a chiral Lewis base (CLB) catalyst and the competing pathway.

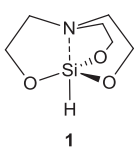
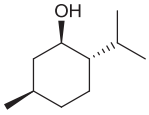
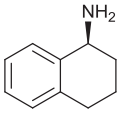
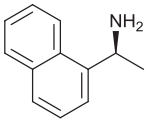
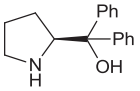
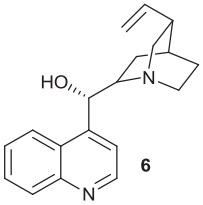
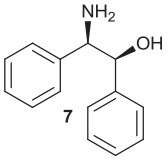
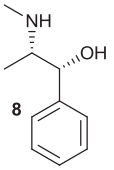


Fig. 2. 1-Hydrosilatrane.

Table 1
Screening of activators.[a]

Entry	Activator[b]	Conversion (%)	*ee* (%)[c]
1	 **2**	50	0
2[d]	 **3**	28	0
3	 **4**	86	0
4	 **5**	10	0
5[d]	 **6**	>99	44
6	 **7**	99	70
7	 **8**	85	64[e]

[a] Reaction conditions: acetophenone (0.1 mmol), deprotonated activator (0.11 mmol), 1-hydrosilatrane (0.2–0.3 mmol), dry THF (3 mL), −30 °C, 6 h.
[b] Deprotonated in situ with NaH (2 equiv.) with respect to the activator.
[c] ee determined by GCMS; the (R) enantiomer was the major product except where noted.
[d] Reaction ran at −10 °C.
[e] The (S) enantiomer was the major product.

previously reported data in the literature. Mono-anionic activators (**2**–**4**) gave much lower enantioselectivity (Table 1, entries 1–3) than the ones with two deprotonated heteroatoms (**6**, **7**, **8**) (Table 1, entries 5–7). (1*S*,2*R*)-1,2-Diphenylethanolamine **7** gave the highest enantioselectivity, followed by (1*R*,2*S*)-(−)-ephedrine **8** and cinchonine **6**. We were particularly pleased with the viability of **8** as a source of chirality as it is a readily available and low-cost reagent; additionally, various stereoisomers are also commercially available for further investigation. Somewhat surprisingly, (*R*)-(+)-diphenylprolinol **5** gave no enantioselectivity and very poor conversion (Table 1, entry 4), possibly because the oxygen is too sterically hindered for effective activation of the silatrane.

We decided to push forward with optimization using compound **7**, which was identified as the best activator in this initial screening.

Solvent screening

Solvent screening (Table 2) demonstrated THF as the best solvent for this reaction, giving high conversion and good enantioselectivity (Table 2, entry 1). 2-MeTHF was a suitable alternative, but due to its relatively high freezing point, the temperature could not be lowered below 0 °C (Table 2, entry 2). Mixing 2-Me-THF with benzene allowed for a slightly lower reaction temperature but did not significantly improve the enantioselectivity (Table 2, entry 3). Hexane, diethyl ether and *m*-xylene gave poor conversion and enantioselectivity (Table 2, entries 5, 6, 9, respectively), most likely due to the poor dissolution of 1-hydrosilatrane.

Temperature optimization

The temperature dependence of enantioselectivity was tested (Fig. 3) and a correlation between the decreased temperature and increased enantioselectivity was observed down to −30 °C; below this temperature no benefit was seen with respect to the enantioselectivity and the rate of reaction was impractically slow.

Activator loading

We next examined the impact of additive loading on enantioselectivity. Gratifyingly, asymmetric induction was observed using catalytic amounts of **7** [19], however the *ee*s in these cases were modest and the conversions were unacceptably low (Table 3, entries 1–2). The conversions and enantiomeric ratio were significantly lower compared to a stoichiometric amount of the activator (Table 3, entry 3). Increasing the loading of activator **7** from 1 equivalent to 2 equivalents increased the enantioselectivity (Table 3, entry 3 vs. 4), however the 6% increase in *ee* was much less prominent than expected. Coincidentally the same increase (6%) was observed when doubling the amount (1 equivalent to 2 equivalents) of activator **8** (Table 3, entry 5 vs 6). Increasing the activator loading of **8** to 8 equivalents gave the highest *ee* of 86% (Table 3, entry 7). This large excess of **8** is not ideal as a general method, though with activator recycling could be useful. As activator **7** gave better conversion and higher enantioselectivity at lower equivalents, the optimal conditions were set at 2 equivalents of activator **7** in THF, at −30 °C for 6 h.

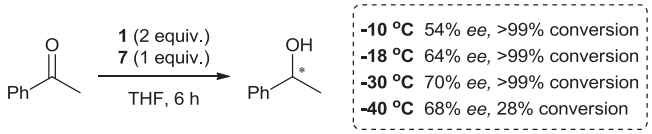
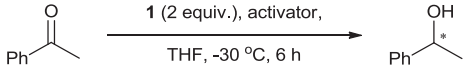


Fig. 3. Effect of temperature on the enantioselectivity.

Table 3
Activator loading-to-enantioselectivity relationship.

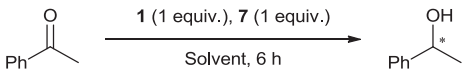


Entry	Activator (equiv.)[a]	Conversion (%)	*ee* (%)[b]
1	**7** (0.08)	14	22
2	**7** (0.6)	34	40
3	**7** (1.0)	99	70
4	**7** (2.0)	>99	76
5	**8** (1.0)	85	64[c]
6	**8** (2.0)	>99	70[c]
7	**8** (8.0)	>99	86[c]

[a] Deprotonated in situ with NaH (2 equiv.) with respect to the activator.
[b] *ee* determined by GCMS; the (R) enantiomer was the major product except where noted.
[c] The (S) enantiomer was the major product.

As discussed in the introduction, the development of a truly catalytic metal-free hydrosilane reduction requires significant molecular engineering, and while this may certainly be an attainable goal it is worthwhile to consider practical solutions. Two ways to mitigate the negative impact of using stoichiometric (or superstoichiometric) amounts of the additive are a) to use an inexpensive, readily available source of chirality and b) have the ability to easily recover and reuse the additive. Catalyst **8** (and its stereoisomers) can satisfy a) with a cost of less than $10/g [20]; and to address b) we demonstrated that catalyst **7** can be recovered during work up with a simple acid-base wash and reused on the same scale with no loss in enantioselectivity (Fig. 4a). Note that this reaction was run in benzene to assist in activator recovery, however this was shown to be unnecessary. Catalyst **7** was extracted from the combined waste of multiple reactions run in THF and reused in a larger scale (1.0 mmol) reaction (Fig. 4b). In this scaled-up reaction the product was obtained with 67% *ee* in an 86% isolated yield, and catalyst **7** was again recovered (98%). We believe these features indicate the practicality of this method for generating important chiral building blocks.

Table 2
Solvent optimization.



Entry	Solvent	T (°C)	Conversion (%)	*ee* (%)[a]
1	THF	−30	>99	70
2	2-MeTHF	0	98	62
3	C_6H_6/2-MeTHF (2:1)	−10	98	60
4	C_6H_6	5 to 25[b]	99	56
5	hexane	−96 to 25[b]	20	54
6	Et_2O	−30	14	52
7	toluene	−95 to 25[b]	>99	50
8	DMF	−8	90	42
9	m-xylene	−30	21	24
10	MeCN	−10	35	10

[a] *ee* determined by GCMS; the (R) enantiomer was the major product in all cases.
[b] Reaction mixture frozen with N_2(l) (−196 °C) prior to the addition of 1-hydrosilatrane, and allowed to warm to 25 °C.

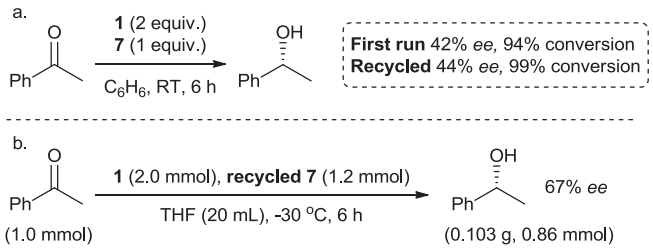
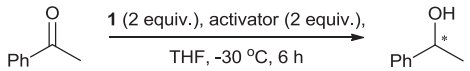
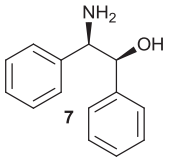
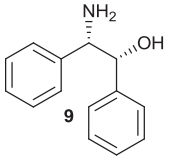
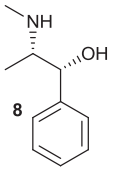
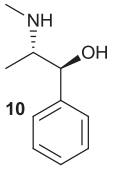


Fig. 4. (a) Demonstration of the direct reusability of activator **7**, and (b) larger scale reaction with recycled **7**.

Table 4
Effect of activator stereochemistry on enantioselectivity in reduction of acetophenone with hydrosilatrane.



Entry	Activator[a]	*ee* (%)[b]	Stereochemistry of the major product
1	 **7**	76	*R*
2	 **9**	78	*S*
3	 **8**	70	*S*
4	 **10**	52	*R*

[a] Deprotonated in situ with NaH (2 equiv.) with respect to the activator.
[b] *ee* determined by GCMS; conversion in all cases was >99%.

Effect of activator stereochemistry

The reduction was then tested to see how different stereoisomers of the examined activators affected the enantioselectivity (Table 4). Exchanging activator **7** for its enantiomer **9** gave full inversion and no loss in enantioselectivity (Table 4, entries 1 vs. 2) as expected. In contrast, exchanging activator **8** with its epimer **10** (in which the C-O stereocenter is inverted) resulted in a decrease of the enantioselectivity (Table 4, entries 3 vs. 4). Interestingly, the sense of enantioselectivity was inverted when using **10** compared to **8**, demonstrating that the oxygen stereocenter dictates the absolute stereochemistry of the product in this instance.

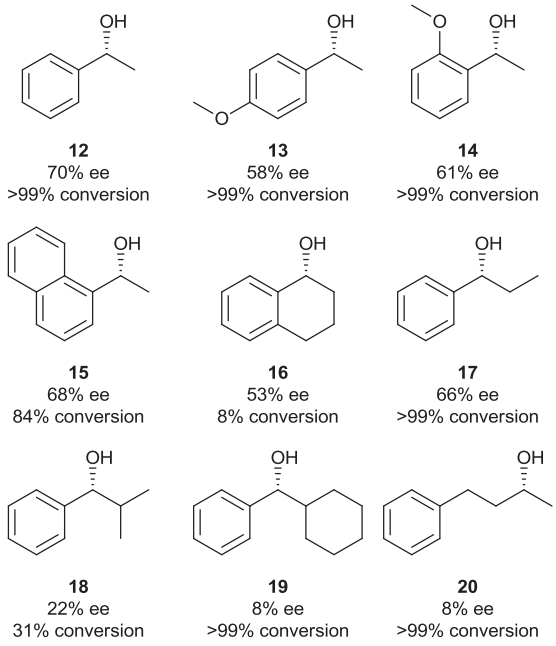


Fig. 5. Scope of select prochiral ketones. Reaction conditions: 1-hydrosilatrane **1** (2 equiv.), activator **7** (1 equiv.), dry THF (3 mL), −30 °C, 6 h. *ee* and conversion determined by GCMS; the enantiomer shown was the major product.

Reaction scope

Further studies involved reducing a small range of ketones to investigate the scope and limitations of the asymmetric reduction using 1-hydrosilatrane and activator **7** (Fig. 5). Increasing the electron density of the aromatic ring (**12** vs. **13**, **14, 16**) decreased the enantioselectivity, whilst substituting phenyl with naphthyl (**12** vs. **15**) had no significant effect (though conversion was not as efficient in the latter). Results of the reduction of α-substituted acetophenone derivatives were mixed. Cyclic α-substitution significantly decreased conversion (**12** vs. **16**). A methyl group at the α position resulted in only a small decrease in selectivity (**12** vs **17**), but a second methyl group, dramatically reduced the enantioselectivity to 22% *ee* (**12** vs **18**), whilst substituting it with a cyclohexyl group (**19**) further reduced the enantioselectivity to 8% *ee*. The reaction conditions were not effective to form aliphatic alcohol **20** from the dialkyl prochiral ketone precursor.

Conclusion

In summary, we have developed a method for the asymmetric reduction of prochiral ketones using chiral Lewis bases as activators and 1-hydrosilatrane as the hydride source. The enantioselectivity is good in several cases, with *ee*s up to 86%. While stoichiometric (or more) amounts of the chiral activator are required for useful outcomes, the reused activator remains just as effective as in its initial use. The studied reaction demonstrates both utility in its current state and promise for future studies that are able to expand on the number of chiral Lewis base activators examined.

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A. Supplementary data

Supplementary data (The ESI contains general information and procedures, characterization of products, yields, chiral GCMS data, and NMR spectra.) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.06.032.

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[18] See the ESI of our previous work, Ref. [16].

[19] For more information on our attempts to make the system catalytic, see the ESI.

[20] The cost of (1*R*,2*S*)-ephedrine on the Sigma Aldrich website (USA) was $960 USD/100g as of December 2017.