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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

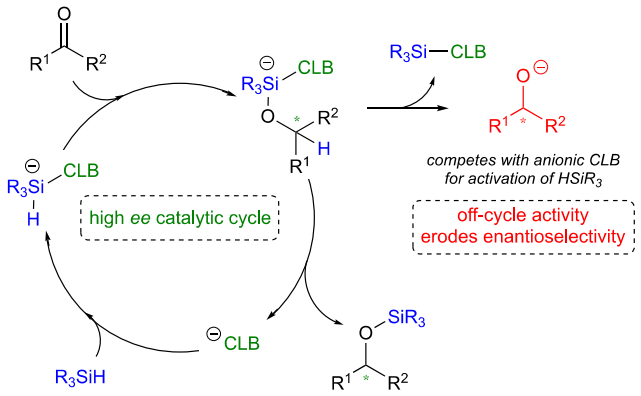


Fig. 1. Enantioselective reduction of ketones using hydrosilanes with a chiral Lewis base (CLB) catalyst and the competing pathway.

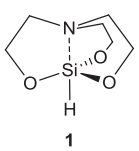
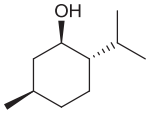
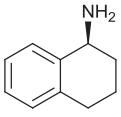
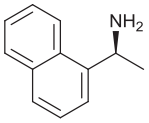
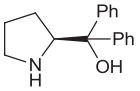
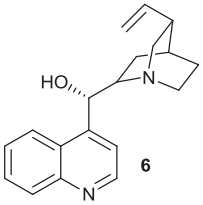
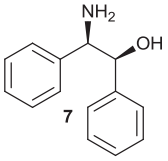
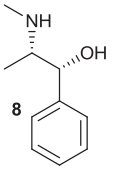


Fig. 2. 1-Hydrosilatrane.

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.