Asymmetric Reduction

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Remote Chiral Induction in the Organocatalytic Hydrosilylation of Aromatic Ketones and Ketimines**

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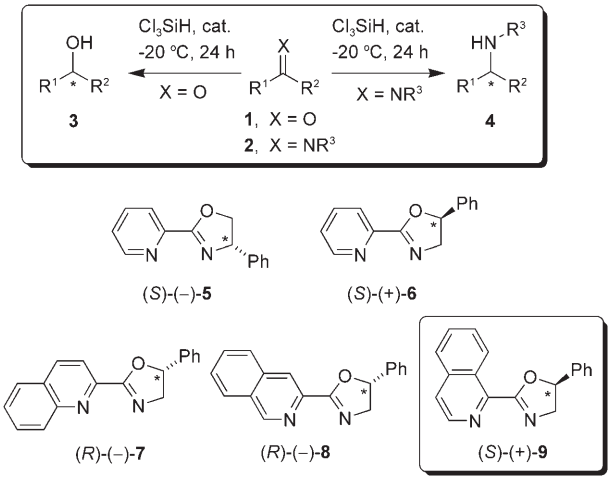
Dedicated to Professor Henri Kagan on the occasion of his 75th birthday

Asymmetric hydrogenation, hydroboration, and hydrosilylation are the most frequently used catalytic methods for the reduction of prochiral ketones **1** and imines **2** (Scheme 1).[1]



Scheme 1. Catalytic reduction of ketones and ketimines; for R^1–R^3, see Tables 1 and 2.

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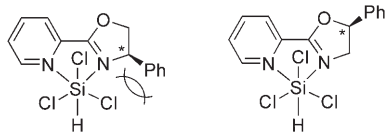
Although asymmetric hydrogenation remains favored by industry in general, it is not free of problems, namely, those associated with metal leaching, high pressure, and the cost of the catalyst and its regeneration. Stoichiometric borane reduction, catalyzed by chiral oxazaborolidine, avoids most of these problems and offers high levels of enantioselection,[1] but its cost is prohibitive for large-scale industrial application. The recently developed reduction of imines, which uses the Hantsch dihydropyridine as a stoichiometric reducing agent and a chiral Brønsted acid as an organocatalyst,[2] is also tainted by the cost implications. Transition-metal-catalyzed hydrosilylation[1,3,4] on the other hand relies on much cheaper silanes as reducing agents but shares the problem of metal leaching with hydrogenation. Furthermore, the current methods usually perform well with either ketones or imines, but rarely with both classes.[4] The alternative metal-free methods[2,5] are rare and considerably less effective;[6] nevertheless, a promising development has recently been reported,[7] which relies on Cl_3SiH, an inexpensive and easy-to-handle reducing agent.[8] Herein, we report an organocatalytic hydrosilylation applicable to both ketones and ketimines.

As part of our program focusing on the activation of organosilicon reagents by Lewis bases,[9] we examined 2-pyridyloxazolines of type **5**, derived from (*S*)-phenylglycinol, as potential organocatalysts in the hydrosilylation of aromatic ketones with Cl_3SiH (Scheme 1, **1**→**3**). Initial attempts to reduce acetophenone (**1a**) in the presence of **5** (20 mol%, $CHCl_3$, −20°C, 24 h) resulted in a rather low conversion into alcohol **3a** (Table 1, entry 1). By contrast, the isomeric oxazoline **6**, obtained from (*S*)-mandelic acid, proved much more reactive and furnished **3a** in 78% *ee* (entry 2).[10] Reduction of a series of aromatic ketones **1b–e**, catalyzed by **6**, proceeded in a similar fashion, with 70–80% *ee* (entries 3–6). On the other hand, reduction of the non-aromatic ketone **1f** resulted in the formation of a racemic product (entry 7). Other solvents, such as toluene, diethyl ether, and THF, proved inferior.

The lower reactivity of **5** relative to **6** can be conjectured to originate from an increase in the steric radius of the extra-coordinate silicon moiety by coordination to the ligand. Thus, the coordination of Cl_3SiH to **5** is impaired by the adjacent phenyl group (Scheme 2, **A**), whereas this adverse effect is absent in chelate **B**, derived from **6**.[11]



Scheme 2. Coordination of Cl_3SiH to (2-pyridyl)oxazolines.

To improve the efficacy of the catalyst and to shed more light on the mechanism, related oxazolines were prepared with the quinoline **7** or isoquinoline **8** and **9** fragments in place of the pyridine moiety (Scheme 1). No reduction was observed with **7** ($CHCl_3$, −20°C; Table 1, entry 8), presumably because of the steric constraints imposed by the quinoline moiety, thus mirroring the behavior of **5**. The 3-isoquinoline catalyst **8** was approximately as efficient as the parent (pyridyl)oxazoline **6** (entry 9; compare with entry 2). A real improvement over a range of substrates (**1a–e, g, h**) was attained with the 1-isoquinolyl catalyst **9** (entries 10–16), which allowed the catalyst loading to be lowered to 10 mol% and provided by far the best enantioselectivities in the metal-free hydrosilylation of ketones to date (≤94% *ee*).

Importantly, catalyst **9** was also found to exhibit high efficiency in the reduction of *N*-aryl imines **2a–f** (Table 2). Therefore, it can be regarded as the first organocatalyst that

Table 1: Reduction of ketones (**1**→**3**) with trichlorosilane catalyzed by **5–9**.[a]

Entry	Catalyst (mol%)	Ketone	R^1, R^2	Yield [%]	*ee* [%][b,c]
1	(*S*)-**5** (20)	**1a**	Ph, Me	29[d]	66[g]
2	(*S*)-**6** (20)	**1a**	Ph, Me	85[d]	78
3	(*S*)-**6** (20)	**1b**	2-MeO-C_6H_4, Me	100[d]	77
4	(*S*)-**6** (20)	**1c**	2-F-C_6H_4, Me	30[d]	70
5	(*S*)-**6** (20)	**1d**	4-Me-C_6H_4, Me	100[d]	80
6	(*S*)-**6** (20)	**1e**	Ph, Et	91[d]	80
7	(*S*)-**6** (20)	**1f**	*c*-C_6H_{11}, Me	67[d,e]	0
8	(*R*)-**7** (20)	**1a**	Ph, Me	0	–
9	(*R*)-**8** (20)	**1a**	Ph, Me	41[e,f]	73[g]
10	(*S*)-**9** (10)	**1a**	Ph, Me	85[f]	84
11	(*S*)-**9** (10)	**1b**	2-MeO-C_6H_4, Me	50[f]	87
12	(*S*)-**9** (10)	**1c**	2-F-C_6H_4, Me	35[f]	70
13	(*S*)-**9** (10)	**1d**	4-Me-C_6H_4, Me	90[f]	85
14	(*S*)-**9** (10)	**1e**	Ph, Et	55[f]	86
15	(*S*)-**9** (10)	**1g**	2-naphth, Me	93[f]	94
16	(*S*)-**9** (10)	**1h**	6-Me-2-naphth, Me	93[f]	92

[a] The reactions were carried out on a 0.4-mmol scale with Cl_3SiH (2.1 equiv) in $CHCl_3$ in the presence of the catalyst at −20°C for 24 h. [b] Determined by chiral GC or HPLC. [c] All products **3** were *R* configured (unless stated otherwise), as revealed by comparison of their optical rotation with the literature data. [d] Conversion determined by GC of the reaction mixture after a standard work up. [e] The reaction was carried out in CH_2Cl_2. [f] Yield of the isolated product (shown to be pure by ^1H NMR spectroscopic analysis). [g] The product was *S* configured. naphth = napthyl.

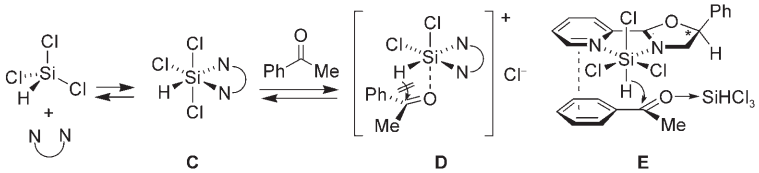
Table 2: Reduction of ketimines (**2–4**) with trichlorosilane catalyzed by **9**.[a]

Entry	Imine	R^1, R^2, R^3	Yield [%][b]	*ee* [%][c,d]
1	**2a**	Ph, Me, Ph	65	87
2	**2b**	Ph, Me, PMP[e]	60	85
3	**2c**	2-naphth, Me, Ph	67	87 (98[f])
4	**2d**	2-naphth, Me, PMP[e]	67	86
5	**2e**	4-MeO-C_6H_4, Me, PMP[e]	51	87
6	**2f**	4-CF_3-C_6H_4, Me, PMP[e]	65	87

[a] The reactions were carried out on a 0.4-mmol scale with $HSiCl_3$ (2.0 equiv) in $CHCl_3$ in the presence of catalyst **9** (20 mol%) at −20°C for 24 h. [b] Yield of the isolated product (product shown to be pure by ^1H NMR spectroscopic analysis). [c] Amines **4** were *R* configured, as revealed by comparison of their optical rotation and their HPLC retention times with the literature data. [d] Enantiomeric excess was determined by HPLC. [e] PMP = *p*-methoxyphenyl. [f] After a single recrystallization from methanol.

allows reduction of both ketones and ketimines with a practically useful enantioselectivity.

To rationalize the high selectivity of catalysts **6**, **8**, and **9**, the following issues have to be taken into account: 1) Table 1 reveals that the order of reactivity of the ketones displays a good correlation with their Brønsted basicity[12] (pK_{HB}): 2-MeO-C_6H_4COMe (1.34) > PhCOMe (1.11) > 2-F-C_6H_4COMe (0.90). If we accept that this trend can be extrapolated to Lewis basicity, the results would suggest that the carbonyl oxygen atom is coordinated to the weakly Lewis acidic Cl_3SiH in the transition state.[13] 2) Trichlorosilane does not reduce carbonyl or heterocarbonyl compounds unless activated by Lewis bases through the formation of extra-coordinate silicon species, such as **C**, in the case of bidentate activators (Scheme 3).[7] Coordination of the carbonyl group



Scheme 3. Mechanism of hydrosilylation.

(**D**) might be presumed (upon replacement of a chloride atom at the silicon center) but can be regarded as unproductive, since the corresponding four-membered transition state (TS) for the reduction is unlikely.[13,14] 3) A linear relationship between the enantiopurity of catalyst **6** and the product was observed for the reduction of acetophenone (**1a**→**3a**), thus suggesting that only one molecule of the catalyst is actively involved in the enantiodifferentiating event. 4) The role of the substituent on the oxazoline rings in **6**, **8**, and **9** can be attributed to the shielding of one of the faces of the catalyst by the Ph group.[15]

Accordingly, the following mechanistic picture can be drawn: the *N*,*N*-chelation of Cl_3SiH by the catalyst creates an activated hydrosilylating species, while another molecule of Cl_3SiH is likely to activate the ketone by coordination to the oxygen atom in the *E* fashion.[16] The ketone–Cl_3SiH complex will then approach the catalyst–Cl_3SiH complex from the less-hindered side (as dictated by the remote chiral center in the catalyst). Transition state **E**, which accommodates all these effects, is consistent with the experimentally observed *si*-facial selectivity of the reaction and with the features discussed herein. It can also be hypothesized that **E** will be stabilized by arene–arene interactions between the heteroaromatic systems of the catalyst and the substrate.[17]

The potential role of the latter π–π interactions in shaping the TS[17] was assessed by a computational analysis of the pyridine–acetophenone model complex (Figure 1).[18] The successive scans, according to the steering angle (θ), the distance between the planes (r_1), and the parallel displacement of the two molecules (r), were carried out (each scan starting at the geometry of interaction energy minimum of the previous scan). The lowest interaction energy found by the potential-energy surface scans was at $-6.3\ kcal\,mol^{-1}$. The

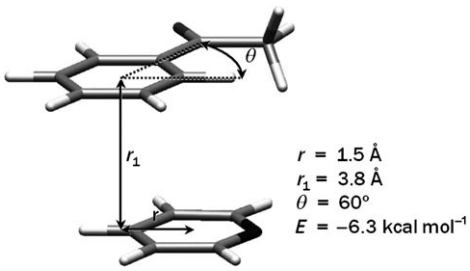


Figure 1. Arene–arene interactions of acetophenone (**1a**) with pyridine as the model TS **E**.

magnitude of this interaction lends credence to the proposed involvement of π stacking in the transition state **E**.

A similar mechanism can be envisaged for the reduction of imines. However, the coordination of Cl_3SiH to the nitrogen atom is unlikely, as this would create a very crowded environment. Hence, the R^3 group of imine **2** can be assumed to fill the space that the $SiHCl_3$ group fills in **E**. Experimental data support this hypothesis: Note that the electron-rich ketones react faster than their electron-poor counterparts (Table 1, entries 3 versus 4 and 11 versus 12), which is consistent with the carbonyl basicity (see below) and, therefore, its propensity to coordinate the Lewis acidic Cl_3SiH. By contrast, imines exhibit the opposite trend (Table 2, entries 5 versus 6).

In conclusion, we have developed a new, practical, metal-free protocol for the enantioselective reduction of aromatic ketones (≤94% *ee*) and ketimines (≤87% *ee*). The reaction is characterized by an unusual, long-ranging chiral induction. The enantiodifferentiation is presumed to be aided by aromatic interactions between the catalyst and the substrate.

Experimental Section

General procedure for the asymmetric reduction of ketones **1** and ketimines **2** with trichlorosilane: Trichlorosilane (86 μL, 0.84 mmol, 2.1 equiv) was slowly added dropwise to a solution of the catalyst (11.0 mg, 0.04 mmol or 21.9 mg, 0.08 mmol) and the corresponding ketone or imine (0.40 mmol, 1.0 equiv) in $CHCl_3$ (2 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 24 h, after which time saturated aqueous $NaHCO_3$ (1 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$. Concentration in vacuo followed by flash chromatography on silica gel (2 × 15 cm) with petroleum ether/ethyl acetate (20:1) or CH_2Cl_2 as the eluent afforded alcohols **3a**–**3h** or amines **4a**–**4f**.

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