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Asymmetric Reduction of Imines with Trichlorosilane, Catalyzed by Sigamide, an Amino Acid-Derived Formamide: Scope and Limitations†

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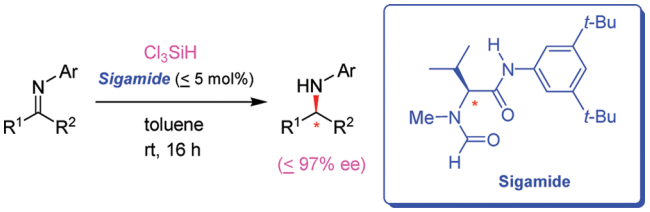

Enantioselective reduction of ketimines **6**−**10** with trichlorosilane can be catalyzed by the *N*-methyl valine-derived Lewis-basic formamide (*S*)-**23** (Sigamide) with high enantioselectivity (≤97% ee) and low catalyst loading (1−5 mol %) at room temperature in toluene. The reaction is efficient with ketimines derived from aromatic amines (aniline and anisidine) and aromatic, heteroaromatic, conjugated, and even nonaromatic ketones **1**−**5**, in which the steric difference between the alkyl groups R^1 and R^2 is sufficient. Simple nitrogen heteroaromatics (**8a**,**b**,**d**) exhibit low enantioselectivities due to the competing coordination of the reagent but increased steric hindrance in the vicinity of the nitrogen (**8c**,**e**) results in a considerable improvement. Cyclic imines **32d-d** exhibited low to modest enantioselectivities.

Introduction

Enantioselective reduction of imines with trichlorosilane, catalyzed by chiral, metal-free Lewis bases,[1] is gradually gaining ground as a reliable protocol for obtaining chiral amines of high enantiomeric purity (Scheme 1). This new organocatalytic methodology has the promise to successfully compete with the traditional metal-catalyzed reductions,[2−6] such as hydrogenation,[3,6] that are generally tainted by metal leaching, high pressure, and cost implications. In view of its simplicity and reliability, this approach may even become an

† Dedicated to Prof. Josef Michl on the occasion of his 70th birthday.

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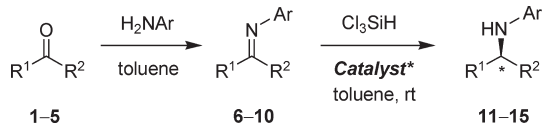
SCHEME 1. Preparation of Selected Ketimines and Their Asymmetric Reduction[a]



[a]For R[1], R[2], and Ar, see Table 1.

attractive alternative to the existing enzymatic methods for amine production,[7] and can complement another organocatalytic protocol, based on the biomimetic reduction with Hantzsch ester.[8]

In the past few years, we have developed a series of Lewis-basic organocatalysts for the reduction of imines with Cl_3SiH.[9,10] Those, based on the scaffold derived from *N*-methyl valine (Chart 1) proved to be most promising. A detailed investigation of the structure−activity relationship of the catalysts, using a set of model imines **6**, has led to the following conclusions:[9b] (1) Valine's isopropyl group, as in **16**, represents an optimum in terms of enantioselectivity (≤95% ee). The cyclohexyl analogue, derived from cyclohexyl glycine, exhibited almost identical selectivities, whereas other catalysts with *t*-Bu, $PhCH_2$, Ph, and Me in place of the original *i*-Pr proved less enantioselective.[9b,11] (2) The *N*-methyl group is crucial as the corresponding NH derivative exhibited low enantioselectivity (≤35% ee).[9b] (3) The formamide function at the *N*-terminus of valine is another key factor; the corresponding acetamide, trifluoroacetamide, carbamate, and urea derivatives reacted sluggishly and gave racemic products.[9b] (4) The carboxyl terminus of the parent valine needs to be converted into an amide with a primary aromatic amine.[9] Amides derived from secondary aromatic amines (e.g., MeNHPh), as well as their nonaromatic congeners (e.g., that derived from $BuNH_2$), proved inferior.[9b] (5) Anilide **16**, our first catalyst, exhibited good enantioselectivities (≤90% ee); introduction of alkyl groups into the anilide moiety, as in **17** (Kenamide) and **18**, had a small but noticeable effect (≤92% ee).[9b,c,h] Sigamide (**23**), with two *tert*-butyl groups, was identified as an optimum (≤95% ee at rt with 1−5 mol % loading).[9c] Other substituents, such as 3,5-dimethoxy (**19**) and 3,5-di(trifluoromethyl) (**20**), had a minor negative effect on the enantioselectivity.[9b] By appending a fluorous tag (**21**)[9c] or by anchoring the catalyst to a resin (**22**),[9e] nanoparticle,[9f] soluble polymer,[9i] or a dendron,[9j] we have simplified the isolation of the product with little effect on the reaction efficiency.

Several other groups have participated in the development of this methodology (Chart 2).[12−14] Thus, Matsumura was actually the first to demonstrate a promising enantioselectivity in the reduction of **6a** with the proline-derived formamide **24** as catalyst (≤68% ee).[12a] More recently, Sun[13] showed that expansion of the five-membered ring of the proline moiety as in the six-membered pipecolinic derivative **25**, or in its piperazidine analogue **26**, and further elaboration of the carboxylic terminus of the parent amino acid, had a beneficial effect on the enantioselectivity, which could now be increased up to 95% ee (at 0 °C with 10 mol % catalyst loading).[10d,13b,c] On the other hand, the proline-derived

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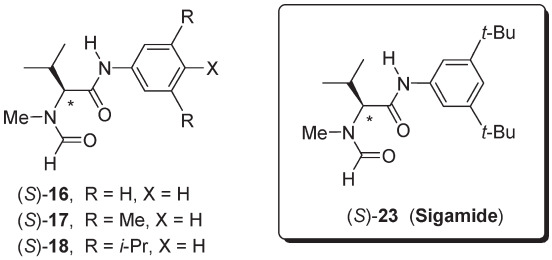
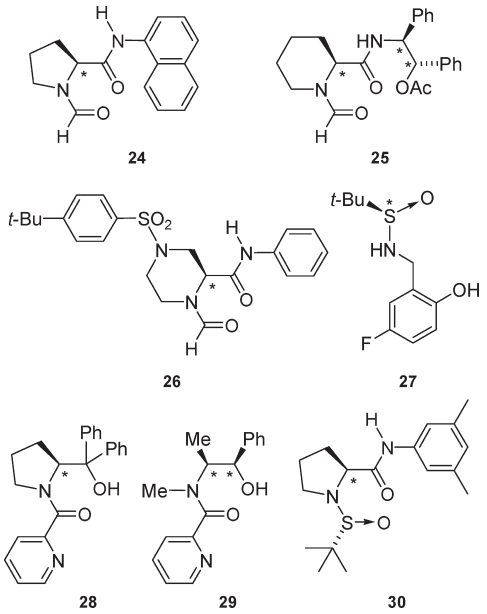
CHART 1. Catalysts for the Asymmetric Reduction of Imines



(*S*)-**16**, R = H, X = H
(*S*)-**17**, R = Me, X = H
(*S*)-**18**, R = *i*-Pr, X = H
(*S*)-**19**, R = OMe, X = H
(*S*)-**20**, R = CF_3, X = H
(*S*)-**21**, R = Me, X = $O(CH_2)_2C_6F_{13}$
(*S*)-**22**, R = Me, X = $O(CH_2)$-Polymer

CHART 2. Other Catalysts for the Asymmetric Reduction of Imines



dimer analogous to **24**, expected to offer an extensive chelation of the reagent, did not provide any particular advantage (≤77% ee).[13d,15] An interesting catalyst with a novel design, featuring a sulfinamide group as the chiral element (**27**), was also successful (≤92% ee at −20 °C with 20 mol % catalyst loading).[13e] On the other hand, replacement of the formamide moiety in the original proline scaffold by the α-picolinic amide, in conjunction with the introduction of a hindered tertiary hydroxyl in place of the amide function of proline (**28**), did not lead to any improvement (≤75% ee).[12b] Nevertheless, the latter design presented one interesting structural feature to be further elaborated, namely the α-picolinic amide moiety and the hydroxy group. Being apparently inspired by this new turn, Zhang has recently developed the α-picolinic amide **29**, in which he employed ephedrine as the chiral scaffold.[14] The latter catalyst exhibited high enantioselectivities (≤93% at −10 °C with 20 mol % catalyst loading) and seems to have the promise to work even with those substrates with which other catalysts were either inefficient or failed. Sulfinamide **30**, introduced by Sun, represents the most recent addition to this family; here, he replaced the Lewis-basic formyl group of the proline-derived catalyst **24** by the *t*-BuSO moiety, which resulted in the enhanced enantioselectivities (≤97% ee at 0 °C with 10 mol % catalyst loading).[13f] An analogous bissulfinamide, which apparently coordinates to trichlorosilane in a bidentate fashion, exhibited comparable enantioselectivities (≤96% ee at −20 °C with 10 mol % catalyst loading).[13g]

Herein, we present an orchestration of our earlier work,[9] using Sigamide (**23**), our champion catalyst, which is now commercially available. The substrate portfolio, originally limited mainly to the imines derived from acetophenone and its congeners,[9,12−14] is substantially expanded to the heterocyclic and aliphatic realm; tolerance of a variety of functional groups and substitution patterns is also demonstrated.

Results and Discussion

In our previous studies,[9] we have identified the *N*-methyl valine-derived formamide **23** (Sigamide) as the organocatalyst of choice for the reduction of aromatic ketimines **6a−e** (Scheme 1 and Table 1). High levels of enantioselectivities were attained (91−94% ee), typically with 5 mol % catalyst loading (Table 1, entries 3−8). In fact, the loading can be reduced to 1 mol % without any loss of enantioselectivity (entry 5)[9c] but further lowering turned out to lead to unreliable results, as the uncatalyzed background reaction (vide infra) began to compete. Sigamide **23** exhibited slightly higher enantioselectivities than its dimethyl analogue Kenamide **17** (Table 1, compare entries 1 and 2 with 3); therefore, Sigamide was used as the sole catalyst in the present study. Toluene was identified previously by us as an optimal solvent, with slightly higher enantioselectivities than those attained with the less environmentally friendly $CHCl_3$ or CH_2Cl_2.[9a−d,16] Therefore, we felt no need to explore other solvents again. Sufficiently high enantioselectivities have been found for the reductions run at room temperature, with only a marginal improvement at 0 or −20 °C or lower (at the expense of the reaction rate);[9] hence, ambient temperature (15−20 °C) was maintained for all reductions throughout this study.

Synthesis of Ketimines 6−10. The preparation of ketimines **6−8** (Scheme 1) from the corresponding methylketones **1−3** and aniline or anisidine, using Dean−Stark conditions in the presence of *p*-TsOH as catalyst or using molecular sieves to remove water, was mostly uneventful and afforded the required imines in good isolated yields (no optimization was attempted): **6a** (68%),[3k,6] **6b** (66%),[17] **6c** (53%),[9c] **6d** (68%),[9b,c,10b] **6e** (60%),[9b,c,10b] **6f** (87%), **6g** (64%),[4c,9b] **6h** (71%),[9e] **7a** (55%), **7b** (22%), **7c** (31%), **7d** (38%),[9c] **8a** (95%), **8b** (96%), **8c** (∼57%), **8d** (95%), **8e** (73%), **8f** (56%), **8g** (41%), **8h** (78%), **8i** (74%), **8j** (74%), **8k** (72%), 8*l* (74%), **8m** (31%), **8n** (57%), and **8o** (40%). Other sterically undemanding arylalkyl ketones were also readily converted into the corresponding imines **9a** (48%), **9b** (16%), **9c** (40%), 9d (38%), **9e** (72%), **9f** (27%), **9g** (58%), **34c** (69%),[3p] and **34d** (70%)[4c] under the same conditions. However, the

(15) The heptacoordinate silicon, portrayed in the proposed transition state by Sun,[13d] seems unlikely.

(16) Other solvents, such as MeCN, THF, and ether, proved inferior,[9a−d] while the Lewis-basic DMF, DMSO, or HMPA could not be used as these would interfere with the catalyst coordination of the silicon. Protic solvents would decompose the reagent, so that they were also excluded.

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TABLE 1. Reduction of Ketimines 6−10 with Trichlorosilane to Give Amines 11−15, Catalyzed by the *N*-Methyl Valine-Derived Formamides (*S*)-17 and (*S*)-23[a]

entry	catalyst (mol %)	imine **6−10**	R^1	R^2	Ar	amine **11−15**	yield (%)[b]	**11−15**[c] % ee[d]
1	**17** (10)	**6a**	Ph	Me	Ph	**11a**	81	92[e]
2	**17** (10)	**6b**	Ph	Me	4-MeO-C_6H_4	**11b**	85	91[e]
3	**23** (5)	**6b**	Ph	Me	4-MeO-C_6H_4	**11b**	95	94[f]
4	**23** (2.5)	**6b**	Ph	Me	4-MeO-C_6H_4	**11b**	92	94[f]
5	**23** (1)	**6b**	Ph	Me	4-MeO-C_6H_4	**11b**	92	93[f]
6	**23** (5)	**6c**	Ph	Me	3,5-$Me_2C_6H_3$	**11c**	89	92[f]
7	**23** (5)	**6d**	4-$CF_3C_6H_4$	Me	4-MeO-C_6H_4	**11d**	92	92[f]
8	**23** (5)	**6e**	4-$MeOC_6H_4$	Me	4-MeO-C_6H_4	**11e**	91	91[f]
9	**23** (5)	**6f**	3-(*t*-Bu)Me_2SiO-C_6H_4	Me	4-MeO-C_6H_4	**11f**	72	93
10	**17** (10)	**6g**	2-MeC_6H_4	Me	Ph	**11g**	90	92[e]
11	**23** (5)	**6h**	2-naphthyl	Me	4-MeO-C_6H_4	**11h**	93	92[f]
12	**23** (5)	**7a**	(*E*)-PhCH=CH	Me	4-MeO-C_6H_4	**12a**	94	81[f]
13	**23** (5)	**7b**	(*E*)-PhCH=C(Me)	Me	4-MeO-C_6H_4	**12b**	62	84
14	**23** (5)	**7c**	*c*-hexyl	Me	4-MeO-C_6H_4	**12c**	86	85[f]
15	**23** (5)	**7d**	*i*-Pr	Me	4-MeO-C_6H_4	**12d**	83	62[f]
16	**23** (5)	**7e**	*t*-Bu	Me	4-MeO-C_6H_4	**12e**	63 [92[g]]	39 [38[g]]
17	**23** (5)	**8a**	2-pyridyl	Me	4-MeO-C_6H_4	**13a**	72	7
18	**23** (5)	**8b**	4-pyridyl	Me	4-MeO-C_6H_4	**13b**	85	21
19	**23** (5)	**8c**	2,6-(i-Pr)$_2$-4-pyridyl	Me	4-MeO-C_6H_4	**13c**	∼68[i]	78
20	**23** (5)	**8d**	2-thiazolyl	Me	4-MeO-C_6H_4	**13d**	83	13
21	**23** (5)	**8e**	5-(*i*-Pr)-2-thiazolyl	Me	4-MeO-C_6H_4	**13e**	71	34
22	**23** (5)	**8f**	1-Me-2-indolyl	Me	4-MeO-C_6H_4	**13f**	77	91
23	**23** (5)	**8g**	thiophen-2-yl	Me	4-MeO-C_6H_4	**13g**	77	89
24	**23** (5)	**8h**	2-furyl	Me	4-MeO-C_6H_4	**13h**	62 [57[h]]	56 [62[h]]
25	**23** (5)	**8i**	5-Me-2-furyl	Me	4-MeO-C_6H_4	**13i**	86	45
26	**23** (5)	**8j**	5-(Me_3Si)-2-furyl	Me	4-MeO-C_6H_4	**13j**	62	63
27	**23** (5)	**8k**	5-(EtO_2C)-2-furyl	Me	4-MeO-C_6H_4	**13k**	62	70
28	**23** (5)	**8l**	2-benzofuryl	Me	4-MeO-C_6H_4	**13*l***	79	70
29	**23** (5)	**8m**	3-furyl	Me	4-MeO-C_6H_4	**13m**	60	77
30	**23** (5)	**8n**	3-benzofuryl	Me	4-MeO-C_6H_4	**13n**	84	65
31	**23** (5)	**8o**	2,5-Me_2-3-furyl	Me	4-MeO-C_6H_4	**13o**	90	91
32	**23** (5)	**9a**	Ph	Et	4-MeO-C_6H_4	**14a**	81	92
33	**23** (5)	**9b**	Ph	$(CH_2)_3CH=CH_2$	4-MeO-C_6H_4	**14b**	64	84
34	**23** (5)	**9c**	3-Cl-C_6H_4	$(CH_2)_3CH=CH_2$	4-MeO-C_6H_4	**14c**	62	82
35	**23** (5)	**9d**	3-MeO-C_6H_4	$(CH_2)_3CH=CH_2$	4-MeO-C_6H_4	**14d**	98	90
36	**23** (5)	**9e**	3-MeO-C_6H_4	$(CH_2)_2CH=CH_2$	4-MeO-C_6H_4	**14e**	99	95
37	**23** (5)	**9f**	Ph	$(CH_2)_2$Ph	4-MeO-C_6H_4	**14f**	95	95
38	**23** (5)	**9g**	3-(*t*-Bu)Me_2SiO-C_6H_4	$(CH_2)_2$(3,4,5-MeO-C_6H_2)	4-MeO-C_6H_4	**14g**	69	96
39	**23** (5)	**9h**	Ph	*i*-Pr	4-MeO-C_6H_4	**14h**	98	97
40	**23** (5)	**9i**	Ph	*c*-Pr	4-MeO-C_6H_4	**14i**	87	95
41	**23** (5)	**9j**	Ph	*c*-Bu	4-MeO-C_6H_4	**14j**	75	94
42	**23** (5)	**9k**	Ph	*c*-hexyl	4-MeO-C_6H_4	**14k**	83	76
43	**23** (5)	**9l**	Ph	*t*-Bu	4-MeO-C_6H_4	**14*l***	18 [46[g]]	10 [10[g]]
44	**23** (5)	**9m**	2-furyl	*i*-Pr	4-MeO-C_6H_4	**14m**	∼75[i]	85
45	**23** (5)	**9n**	4-MeO-C_6H_4	4-CF_3-C_6H_4	4-MeO-C_6H_4	**14n**	79	6
46	**23** (5)	**10a**	Ph	CH_2Cl	4-MeO-C_6H_4	**15a**	98[j]	96[k,l]
47	**23** (5)	**10b**	4-Cl-C_6H_4	CH_2Cl	4-MeO-C_6H_4	**15b**	87[j]	91[k,l]
48	**23** (5)	**10c**	4-F-C_6H_4	CH_2Cl	4-MeO-C_6H_4	**15c**	92[j]	94[k,l]
49	**23** (5)	**10d**	2-Cl-C_6H_4	CH_2Cl	4-MeO-C_6H_4	**15d**	54[j,m]	96[k,l]
50	**23** (5)	**10e**	2-Cl-C_6H_4	CH_2Cl	4-Cl-C_6H_4	**15e**	87[j,m]	95[k,l]
51	**23** (5)	**10f**	2-Cl-C_6H_4	CH_2Cl	4−F-C_6H_4	**15f**	86[j,m]	95[k,l]
52	**23** (5)	**10g**	4-MeO-C_6H_4	CH_2Cl	4-MeO-C_6H_4	**15g**	86[j,m]	91[k,l]
53	**23** (5)	**10h**	3-MeO-C_6H_4	CH_2Cl	4-MeO-C_6H_4	**15h**	84[j,m]	92[k,l]
54	**23** (5)	**10i**	2-naphthyl	CH_2Cl	4-MeO-C_6H_4	**15i**	92[j,m]	91[k,l]
55	**23** (5)	**10j**	Ph	CH_2CN	Ph	**15j**	97[n]	87[o,p]
56	**23** (5)	**10k**	Ph	CH_2CN	4-MeO-C_6H_4	**15k**	75[n]	87[p]
57	**23** (5)	**10l**	Ph	CH_2CO_2Et	4-MeO-C_6H_4	**15*l***	98[n]	89[p,q]
58	**23** (5)	**10m**	4-F-C_6H_4	CH_2CO_2Et	4-MeO-C_6H_4	**15m**	95[n]	90[p]
59	**23** (5)	**10n**	4-MeO-C_6H_4	CH_2CO_2Et	4-MeO-C_6H_4	**15n**	80[n]	88[p]
60	**17** (10)	**10o**	Ph	CO_2Me	Ph	**15o**	69[h]	59[e,l]
61	**23** (5)	**10p**	Ph	$(CH_2)_2CO_2Me$	4-MeO-C_6H_4	**15p**	38[r]	88
62	**23** (5)	**32a**	na	na	na	**33a**	69	25[s]
63	**23** (5)	**32b**	na	na	na	**33b**	91	46[s]
64	**23** (5)	**32c**	na	na	na	**33c**	89	0
65	**23** (5)	**32d**	na	na	na	**33d**	83	10

[a]The reaction was carried out at 0.2 mmol scale with 2.0 equiv of Cl_3SiH at 18 °C for 16 h in toluene unless stated otherwise. [b]Isolated yield. [c]The absolute configuration of the amines was established by comparison of their optical rotation (measured in $CHCl_3$) with the literature data (see the Experimental Section) and/or by comparison of their HPLC behavior with that of authentic samples.[9] Amines **11a**,**b**,**d**,**e**,**h** and **15k**,***l*** were (*S*)-configured; the configuration of the remaining amines is assumed to be (*S*) in analogy with the rest of the series and our previous experiments. [d]Determined by chiral HPLC. [e]References 9a and 9b. [f]Reference 9c. [g]In the presence of AcOH (1 equiv). [h]The reaction was carried out at −20 °C for 24 h. [i]Estimated yield (NMR) as the starting imine could not be isolated as a pure compound. [j]The reaction was carried out for 24 h. [k]See ref 9d for preliminary results. [l]The product was (*R*)-configured; however, note the change in the preference of the substituents in the Cahn−Ingold−Prelog system. [m]The imine was generated in situ and reduced without isolation. [n]The reaction was carried out for 48 h in the presence of acetic acid (1 equiv). [o]A single crystallization from hexane afforded **15j** of 99.9% ee. [p]Reference 9g. [q]A single crystallization from hexane afforded **15*l*** of 99.8% ee. [r]2-Methoxy-1-(4′-methoxyphenyl)-5-phenyl-1*H*-pyrrole was isolated as the major byproduct (27%), arising by a ring-closure of **15p**. [s]For the absolute configuration, see the text and ref 24.

sterically more hindered ketones, such as phenylisopropyl ketone, proved less reactive, so that imine **9h** was obtained in only 29% yield and **9m** in ~10% yield (not isolated as a pure compound). Therefore, $TiCl_4$ was employed instead of p-TsOH[18] for ketones with *c*-Pr, *c*-Bu, *c*-Hex, *t*-Bu, and two aryl groups to obtain the sterically more congested imines **7e** (75%), **9i** (52%), **9j** (63%), **9k** (53%), **9*l*** (68%), and **9n** (69%). The α-chloro imines **10a** (68%),[9d] **10b** (66%),[9d] and **10c** (46%)[9d] were prepared either by using the standard *p*-TsOH/Dean−Stark method or the molecular sieves. However, their electron-rich or sterically congested counterparts **10d**−**i** proved rather unstable and difficult to prepare in a pure state; therefore, they were generated in situ (with an excess of the ketone[19]) prior to the reduction and were not isolated. The remaining imines **10j**,[9g] **10k**,[9g] **10*l***,[9g] 10m,[9g] and **10n**[9g] were obtained in their tautomeric enamine forms **31j** (62%),[9g] **31k** (51%),[9g] **31*l*** (66%),[9g] **31m** (72%),[9g] and **31n** (72%)[9g] (Scheme 2) by the reaction of anisidine or aniline with the corresponding ketonitriles in acetic acid[9g,20] or from ketoesters in ethanol.[21] Imines **10o** (87%)[9b,12a] and 10p (60%) were prepared from the corresponding ketones by using the Dean−Stark method. Interestingly, attempted synthesis or in situ generation of the imines derived from α-methoxyacetophenone and α-phthalimidoacetophenone (and anisidine) failed.

In most cases, anisidine, rather than aniline, was employed in the imine synthesis. While the reactivity of these two types of imines hardly differs,[9] the *p*-methoxyphenyl group has the advantage that it can be oxidatively removed from the resulting amine to produce a primary amine,[9d] which renders the whole protocol more versatile.

The configuration at the imine double bond was predominantly (*E*) (7:1−10:1), as revealed by ^{1}H NMR spectroscopy for **6**−**8** and **9a**−**g**; for the chloroimines **10a**−**i** the same predominant configuration needs to be denoted as (*Z*) due to the change in substituent preference in the Cahn−Ingold−Prelog system. Mixtures of (*E*/*Z*) isomers were isolated when the R^2 group was bulky, in particular for **9h**−**m** (5:2−5:3), whereas **9n** was a ~3:2 mixture; for details, see the Experimental Section. Imines **10j**−**n** preferentially exist in their enamine form **31j**−**n** (Scheme 2). The β-enamino esters **31*l***−**n** were obtained as pure (*Z*) isomers, which are apparently more stable owing to an intramolecular hydrogen bonding between the N−H and the ester carbonyl group. By contrast, the β-enamino nitriles **31j**,**k** readily equilibrate to a mixture of (*Z*/*E*) isomers, e.g., in $CDCl_3$ solutions.[9g] The isomerization is facilitated by a trace of Brønsted acids and apparently occurs via the imine tautomer **10j**−**n**, which is assumed to be the actual species reduced by trichlorosilane (vide infra).[9g]

Reduction of Ketimines 6−10. The reduction of ketimines (Scheme 1 and Table 1) was carried out under our standard conditions,[9] i.e., with 2 equiv of Cl_3SiH (this excess could be considerably lowered for larger-scale operations) in toluene (an optimized solvent) at room temperature (15−20 °C) overnight (a compromise to attain both good reaction rates and enantioselectivities), mostly with Sigamide (**23**) as catalyst at 5 mol % loading (although 1 mol % was also shown to be equally effective[9c]) under an argon atmosphere. In some cases, acetic acid (≤1 equiv) was added to the reaction mixture (vide infra).

Imines **6a**−**h**, derived from acetophenone and its congeners, afforded the corresponding amines **11a**−**h** in high yields and >90% ee (entries 1−11). Sigamide (**23**) was found to be a slightly more efficient catalyst than Kenamide (**17**) (compare entries 2 and 3). Electronic properties of the imine had no effect on the reduction, as documented by the extreme examples of the electron-poor and electron-rich imines **6d** and **6e** (Table 1, entries 7 and 8). Similarly, an increased steric hindrance, exercised by an ortho substituent (**6g**), proved to be of no consequence (entry 10).

Distance separation between the aromatic nucleus and the imine moiety, as in the conjugated cinnamyl derivatives **7a** and **7b**, had a minor negative effect on the enantioselectivity (81/84% ee; entries 12 and 13); a noticeable deceleration of the reaction, reflected in the lower isolated yield, was observed for the more sterically hindered methyl homologue **7b**.

A complete removal of the conjugated π-system, as in the cyclohexyl analogue **7c**, also resulted in a minor decrease in enantioselectivity (to 85% ee, entry 14) as compared to the phenyl analogue **6b** (94% ee, entry 3). However, it is pertinent to note that this decrease was found to be more substantial when the less bulky catalyst **16** was employed (37% ee at rt and 59% ee at −20 °C),[9b] demonstrating the superiority of Sigamide (**23**). With the less sterically hindered isopropyl derivative **7d**, the enantioselectivity dropped to 62% ee (entry 15). On the other hand, the sterically much more congested *tert*-butyl derivative **7e** reacted sluggishly and the enantioselectivity was found to decrease further (entry 16).

Introduction of a heteroatom into the aromatic system of model compounds is always an ultimate goal in view of the role that heterocyclic compounds play in the pharmaceutical industry. Therefore, the set of the imines to be investigated was extended to representative examples of the heteroaromatic realm. The pyridyl derivatives **8a**,**b** were reduced cleanly but the products turned out to be almost racemic (entries 17 and 18). In another study, we have shown that the pyridine nitrogen is capable of coordinating the silicon of Cl_3SiH;[10c] hence, the lack of enantioselection in the case of **8a**,**b** can be attributed to this type of coordination, which is nonchiral and can compete with the coordination to the chiral catalyst. The same effect can account for the very low enantioselectivity observed for the thiazole derivative **8d** (entry 20). To reduce or eliminate the undesired coordination, a steric bulk was built around the nitrogen of the substrate, as in the 2,6-diisopropylpyridine derivative **8c**. This strategy proved to have a positive impact, as the enantioselectivity in the latter case was increased to 78% ee (entry 19). Introduction of just one isopropyl group, as in **8e**, was less effective (34% ee, entry 21). In contrast to the pyridine-derived imines, the *N*-methyl-2-indolyl derivative **8f** with a noncoordinating nitrogen atom again exhibited high enantioselectivity (91% ee; entry 22).

Sulfur as a heteroatom is apparently free of negative effects, as shown by the thiophen-2-yl derivative **8g**, where the enantioselectivity (89% ee, entry 23) was close to that

(18) For the method, see: Sulmon, P.; De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Synthesis* **1985**, 192.

(19) The excess of the ketone does not interfere with the imine reduction, as ketones do not undergo reduction with Cl_3SiH and this type of catalyst.[9d]

(20) This procedure was a further modification of the original protocol: Rao, V. V. R.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 1* **2002**, *1232*.

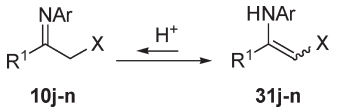
(21) Dai, Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, *7*, 5343.

observed for the acetophenone-derived imines (entry 3). Furan- and benzofuran-derived imines **8h**−**n** were found to be reduced with the efficiency laying between that of the sulfur and nitrogen heterocycles (45−77% ee, entries 24−30); the 3-furyl derivative **8m** exhibited a significantly higher level of asymmetric induction (77% ee, entry 29) than its 2-furyl isomer **8h** (56% and 62% ee at rt and at −20 °C, respectively, entry 24). Again, increasing the steric bulk had a positive effect, as documented by the dimethyl derivative **8o** (91% ee, entry 31).

The imines investigated so far were all derived from acetophenone and its congeners, i.e., from aryl/heteroaryl methyl ketones. Naturally, it was of interest to vary the original methyl group, as in **9**. The ethyl analogue **9a** turned out to behave in the same way as its methyl counterpart (92% ee, entry 32; compare with entry 3). Further extension of the alkyl chain (with a terminal double bond, a possible site for further elaboration), as in **9b**−**e**, had only a marginal effect on the enantioselectivity (84−95% ee, entries 33−36). Derivatives **9f**,**g** with an aromatic system at the terminus of the alkyl chain exhibited one of the highest enantioselectivities (95−96% ee, entries 37 and 38). Branching in the R^2 group, as in the isopropyl, cyclopropyl, and cyclobutyl derivatives **9h**−**j**, had a positive effect (94−97% ee, entries 39−41). For the bulkier cyclohexyl derivative **9k**, where the two six-membered rings differ in their electronic nature (Ph vs. *c*-Hex), a minor decrease in enantioselectivity was observed (76% ee, entry 42). On the other hand, reduction of the highly congested *tert*-butyl derivative **9*l*** proved very sluggish and gave an almost racemic product (entry 43). Good enantioselectivity was restored for the furyl isopropyl analogue **9m** (85% ee, entry 44). Finally, the case of the Ph/*c*-Hex pattern (**9k**, entry 42) raised the question as to the role of the aromatic ring, namely whether imines with two electronically different aromatic groups could also be reduced enantioselectively.[22,23] To this end, we examined imine **9n**, with two essentially isosteric but electronically opposite aromatic systems. The latter derivative turned out to be reduced readily but the product was almost racemic (entry 45), showing that the electronics in this imine reduction plays a negligible role compared to steric effects.

A functional group in the side chain of the imine was another feature to be explored as its presence would considerably broaden the synthetic utility of this chemistry. Therefore, the chloromethyl imines **10a**−**i** were prepared (vide supra) and investigated. Their reduction proceeded very well and afforded the corresponding amines in >90% ee (entries 46−54). The resulting amino chlorides **15a**−**i** were then cyclized to the corresponding aziridines on treatment with *t*-BuOK.[9d] It is pertinent to note that the preparation of the sensitive chloro imines **10a**−**i** from the corresponding α-chloro ketones was not entirely free of problems: while the electron-neutral and electron-poor imines **10a**−**c** were synthesized and isolated as individual substances, their electron-rich counterparts **10g**,**h** could not be obtained as pure compounds, since the reaction did not proceed to completion. Therefore, in the latter instances, we chose to generate the imine in situ, using an excess of the chloro ketone, to make sure that all the anisidine was consumed in the reaction, as its presence in the reduction step was known[9d] to be detrimental to the enantioselectivity. Details of this two-step one-pot protocol were revealed in our preliminary communication.[9d]

SCHEME 2. Reaction of 10j−n to 31j−n



X = CN, CO^2Et (see Table 1).

An attempted switch from the CH_2Cl group of the latter set of imines to the analogous CH_2CN derivatives created a new situation owing to the π-system of the C≡N: thus, instead of the desired imines **10j**,**k**, the corresponding conjugated enamines **31j**,**k** were actually obtained (Scheme 2) on reaction of the β-keto nitriles with anisidine. Nevertheless, in the presence of a trace of a Brønsted acid, the enamines could be equilibrated with the imine (although the enamine species would still prevail in the mixture). After a series of experiments, addition of acetic acid (1 equiv) was identified as a healthy compromise between reactivity and selectivity: the reduction, carried out in its presence, afforded the expected β-amino nitriles **15j**,**k** in high yields and enantioselectivities (87% ee, entries 55 and 56). A single crystallization of **15j** from hexane furnished an enantiopure product (99.9% ee). Reduction of the analogous enamines, generated from β-keto esters (**31*l*−n**), afforded the expected β-amino esters **15*l*−n** (again via the corresponding imines **10*l*−n**, generated in situ by the AcOH-catalyzed equilibration) also in high yields and enantioselectivities (88−90% ee, entries 57−59). A single crystallization of the β-amino ester **15*l*** from hexane increased its enantiopurity from 89% ee (entry 57) to 99.8% ee. Finally, with the lower homologue **10o**, lacking the CH_2 group, the problem of enamine−imine dichotomy was eliminated but the enantioselectivity proved to be rather low (59% ee, entry 60). On the other hand, the higher homologue **10p** was reduced with high enantioselectivity again (88% ee, entry 61).

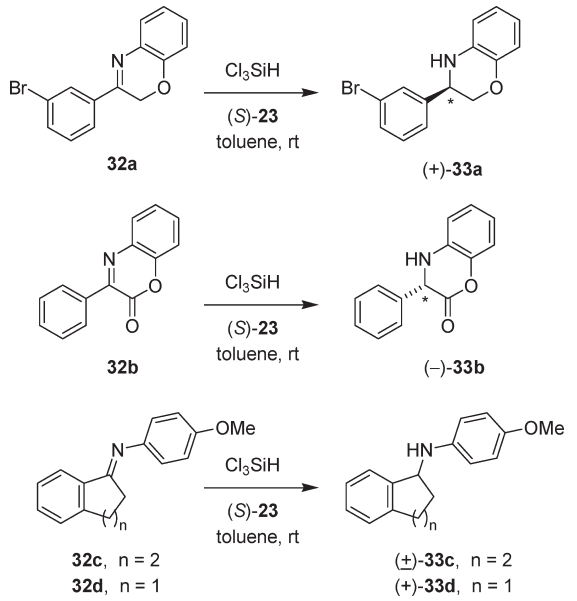
Reduction of the cyclic imines **32a**−**d** (Scheme 3), closely related to the acyclic imines **6**−**10**, was briefly investigated. In spite of the familiar structural features, namely the *N*-aryl substituent, the phenyl group in the position of the original R^1 substituent, and a functional group or an extended carbon chain (R^2), the reduction turned out to proceed with much lower enantioselectivities than those observed for the acyclic imines. Thus, **32a** and **32b** afforded the respective amines **33a** and **33b** with 25% ee and 46% ee (entries 62 and 63), interestingly of opposite configuration to each other.[24] The tetralone-derived imine **32c**, which can be regarded as a cyclic analogue of **9a**, produced racemic amine **33c** (entry 64) and the indanone-derived imine **32d** was reduced to amine **33d** with 10% ee (entry 65). The latter results strongly suggest

(22) For an enantioselective reduction of isosteric, electronically biased ketones, see: (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett*. **1995**, *36*, 9153. (b) Corey, E. J.; Helal, C. J. *Tetrahedron Lett*. **1996**, *37*, 5675.

(23) For a review, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987.

(24) The absolute configuration of **33a**,**b** was inferred by comparison of the HPLC trace and optical rotation of our products with those obtained by Rueping.[8d] The original assignment was made by Rueping by X-ray crystallography for one of the members of the series and was then extrapolated to the rest of the set.[8d] Hence, the configuration of **33a**,**b** has not been rigorously proven but is likely to be as shown in Scheme 3, i.e., (*R*)-(+)-**33a** and (*S*)-(−)-**33b**.

SCHEME 3. Asymmetric Reduction of Selected Cyclic Ketimines



that highly enantioselective reduction occurs in a conformation that is attainable by the noncyclic imines **6**−**10** but which is not available for the rigid cyclic structures, in particular **32c**,**d**.

Other Organocatalysts for the Reduction of Imines with Trichlorosilane. To complete this study, we present a comparison of our findings with the highlights of the results attained with catalysts **24**−**30** (Chart 2), as published by the groups of Matsumura,[12] Sun,[13] and Zhang.[14] These groups have studied more limited sets of substrate imines and from their work we have selected representative examples (Table 2), which are further limited for the sake of space to the imines derived from acetophenone (**6a**,**b**), its cyclohexyl analogue (**7c**), the cinnamyl analogue (**7a**), and those with a functional group (**10*l*,o**). Unfortunately, some of the authors did not reveal the absolute configuration of their products, which makes the comparison less straightforward.[25]

Clearly, the highest enantioselectivities were attained for the acetophenone-derived imines **6a**,**b** with the pipecolinic acid-derived catalyst **25** (Table 2, entries 2 and 3), which resonates with our results (Table 1, entries 3−5). The proline-derived formamide **24**[12a] exhibited rather lower enantioselectivities (compare entry 1 in Table 2, with entry 1 in Table 1). The pipecolinic acid-derived catalyst **25**[13a] gave slightly higher enantioselectivities with the cinnamyl and cyclohexyl derivatives **7a** and **7c′** (Table 2, entries 4 and 5) than did our Sigamide (Table 1, entries 12, 13, and 14). On the other hand, the level of asymmetric induction attained with catalysts **26** and **28**[12b,13b,c] (Table 2, entries 6−10) was lower than that observed for Sigamide (Table 1, entries 3−5, 57, and 60). The α-picolinic amide **29**[14a] approached the selectivity attained with **23** and **25** in the case of the acetophenone-derived imines **6a**,**b** (Table 2, entries 11−13) but was no match in the case of the cyclohexyl derivative **7c** (compare Table 2, entry 14 with Table 1, entry 14 and Table 2, entry 5). Finally, the sulfinamide **30**[13f] has shown consistently high enantioselectivities with imines derived from acetophenone and its congeners (≤96−97% ee; Table 2, entry 15). However, this catalyst is noteworthy for its efficiency with imines derived from nonaromatic amines, such as $PhCH_2NH_2$; other *N*-alkyl imines exhibited rather lower selectivities.[13f] Unfortunately, comparison with catalyst **25**[13a] is hampered by the fact that the authors did not reveal the configuration of the resulting amine.

From the limited data reported by Matsumura,[12] Sun,[13] and Zhang,[14] the pipecolinic acid-derived catalyst **25** and the sulfinamide **30** appear to exhibit the highest enantioselectivities, similar to those attained by us with Sigamide **23**. However, our substrate portfolio is now much broader (Table 1) so that a more detailed comparison cannot be made at present. Furthermore, Sigamide performed consistently well at our standard 5 mol % loading and in selected examples was shown to operate with the same efficiency even when as little as 1 mol % had been used. Most of the catalysts listed in Table 2 were used at 10−20 mol % loading, although some cases with 5 mol % were also reported. Finally, our reductions were carried out at room temperature, whereas most experiments listed in Table 2 were run at 0 °C or below.

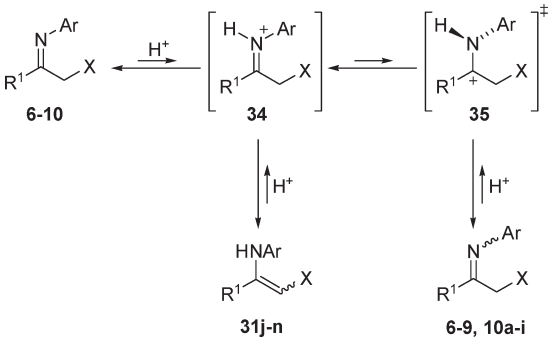
Mechanistic Considerations. Our experiments, in conjunction with those reported by Sun,[13a,b,e,f] indicate that the Lewis base-catalyzed imine reduction with trichlorosilane is not affected by isomeric nonhomogeneity of the starting imines. Thus, for example, imines **9h**−**j**, which exist as 5:2 to 5:3 (*E*/*Z*) mixtures, were reduced to the corresponding amines with 94−97% ee (Table 1, entries 39−41). Apparently, traces of HCl, naturally present in the moisture-sensitive Cl_3SiH, trigger an (*E*/*Z*) equilibration of imines **6**−**10**, which is faster than the reduction (Scheme 4).

Brønsted acid-catalyzed isomerization of compounds containing C=N bonds is a well-known process. The generally accepted mechanism involves the initial protonation of the imine nitrogen to generate trace amounts of the iminium ion **34**, followed either by rotation about the C−N bond (**35**) or via a nucleophilic attack by the acid counterion to produce the corresponding tetrahedral intermediate, which undergoes rotation/proton exchange on nitrogen and subsequent elimination to give the other isomer.[26] An analogous (*Z*/*E*) isomerization mechanism, i.e., protonation at the α-position to give the iminium ion **34**, rotation around the C−C bond, and proton elimination, can be envisaged in the case of β-enamino nitriles and esters **31j**−**n**. As discussed above, the β-enamino esters **31*l***−**n** were obtained as the (*Z*)-isomers, which are apparently more stable owing to an intramolecular hydrogen bonding between the N−H and the ester carbonyl group. In the case of **31*l***, no signs of isomerization in the presence of acetic acid (2 equiv) could be detected by NMR spectroscopy. By contrast, the β-enamino nitriles **31j**,**k** readily equilibrate to a mixture of (*Z*/*E*) isomers, e.g., **31j** isomerizes to a mixture of isomers (~2.6:1) in $CDCl_3$ solutions overnight even without an external source of protons.[9g]

(25) In some cases, where neither the absolute configuration nor the optical rotations were stated in the paper, the configuration could be deduced by comparison of the mobilities of our own samples on chiral HPLC columns with those that could be extracted from the relevant Supporting Information.

(26) (a) Jennings, W. B.; Al-Showiman, S.; Tolley, M. S.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, *1535*. (b) Johnson, J. E.; Morales, N. M.; Gorczyca, A. M.; Dolliver, D. D.; McAllister, M. A. *J. Org. Chem.* **2001**, *66*, 7979.During the preparation of this manuscript, a similar discussion of the role of Brønsted acids on the reduction of imines with Hantzsch dihydropyridines appeared: (c) Marcelli, T.; Hammar, P.; Himo, F. *Chem.—Eur. J.* **2008**, *14*, 8562.

SCHEME 4. Imine (*E*/*Z*) and Imine/Enamine Equilibration



Apparently, in the case of imines **6**−**8**, and **9a**−**m**, it is the more stable (*E*) isomer that is reduced from the *re*-face to give the (*S*) enantiomer. Accordingly, for chloro imines **10a**−**i** the (*Z*) isomer is reduced from the enantiotopic *si*-face to give the (*R*) enantiomer (note the change of Cahn−Ingold−Prelog priorities here!). On the other hand, the complete absence of steric preference for (*E*) or (*Z*) isomer may account for the loss of enantioselectivity and formation of a racemic product in the case of imine **9n**.

We suspected that protonation would not only catalyze the isomerization, but may also contribute to the nonselective background reaction by enhancing the electrophilicity of the imines (via **34**). Therefore the effect of a few acidic and basic additives on the reduction of imines **6b** and **10*l***, catalyzed by Sigamide (**23**), was briefly investigated (Table 3). Reduction of ketimine **6b** in the presence of triflic acid (0.1 equiv) led to a minor decrease of enantioselectivity (91% ee, Table 3, entry 1; compare with 94% ee, Table 1, entry 3); enantioselectivity was further reduced in the presence of a stoichiometric amount of methanol, which apparently hydrolyzes Cl_3SiH to produce HCl (Table 3, entry 2). In the case of β-enamino nitriles and esters **31j**−**n** (reacting as their imine isomers **10j**−**n**), addition of acetic acid (1 equiv) was found to have a beneficial effect on reactivity at the slight expense of enantioselectivity (vide supra).[9g] Increased amounts of acetic acid in the reduction of **10*l***/**31*l*** also slightly eroded the enantioselectivity (Table 3, entry 3; compare with Table 1, entry 57), whereas the reduction, carried out in the presence of the stronger trifluoroacetic acid, afforded a completely racemic amine **15*l*** (Table 3, entry 4).

By contrast, proton scavengers, such as *i*-Pr_2EtN (Hünig's base) or 1,8-bis(dimethylamino)naphthalene (proton sponge), were found to slow down the reaction dramatically and to ruin the enantioselectivity (Table 3, entries 5 and 6). An analogous effect of a stoichiometric amount of 2,6-lutidine has been reported recently[13g] without a detailed explanation. However, the beneficial effect of substoichiometric amounts of the latter base on enantioselectivity, reported by Sun,[13g] was not observed with our model compounds (Table 3, entry 7; compare with Table 1, entry 3).

The complete loss of reactivity in the presence of stoichiometric amounts of a base implies the involvement of a Brønsted acid in the catalytic cycle. This hypothesis is supported by the observation that addition of acetic acid (1.5 equiv) to the reaction mixture, first "poisoned" with proton sponge (1 equiv), completely restored the reactivity, providing amine **11b** in 92% yield and 87% ee (Table 3, entry 8).

The key importance of H^+ (at low concentrations) for the reaction to occur suggests that protonated imines, i.e., the corresponding iminium ions **34**, might be the actual species reduced by trichlorosilane. It can be speculated that the protonated species **34** coordinates to the catalyst, e.g., via hydrogen bonding to the anilide carbonyl group (**36**; Chart 3). Trichlorosilane apparently is activated by coordination to the formamide carbonyl group to form a pentacoordinated silicon species. However, increasing the concentration of Brønsted acid in the reaction mixture leads to an erosion of enantioselectivity due to the competing nonselective reduction (**37**). In the case of **7e** and **9*l***, it is likely that steric hindrance, exerted by the bulky *t*-Bu substituent (**38**), impedes the protonation and/or coordination to the catalyst, resulting in low reactivity and enantioselectivity. Comparison with the results obtained in the reduction of cyclic imines **32a**−**d** (Table 1, entries 62−65) strongly suggests that highly enantioselective reduction occurs in a conformation that is attainable by the noncyclic imines **6**−**10** but which is not available for the rigid cyclic structures (**39**). Molecular modeling[27] and the available crystallographic data for ketimines[28] indicate that the *N*-aryl moiety adopts a nearly perpendicular conformation with respect to the C=N bond, whereas the aromatic R^1 group is coplanar with it. It is likely that in the transition state the iminium ion **34** adopts a conformation where the R^1 group is not coplanar with the C=N bond to minimize the steric interaction with the catalyst as well as the interaction of the ortho substituent of the R^1 group with the proton at the nitrogen. Clearly, such a conformation cannot be attained by cyclic imines **32c**,**d**, where the aromatic R^1 group is locked in the coplanar arrangement **39**. Furthermore, the reduced conformational mobility of the *N*-aryl moiety, which is nearly coplanar with the C=N bond in imines **32a**,**b**, has a similar effect, i.e., the reduction proceeds with much lower enantioselectivities than those observed for the acyclic imines.

It is pertinent to note that the proline-derived catalyst **24**, which has the same absolute configuration as our Kenamide (**17**) and Sigamide (**23**), induced the formation of (*R*)-**11a**,[12a] i.e., of the opposite enantiomer to that produced by our catalysts. The latter result suggests that these two types of catalysts assume a different conformation on coordination of the silicon. This is partially supported by single crystal X-ray analysis of Kenamide (**17**) and catalysts **40** and **41** (Chart 4).

The *N*-methyl moiety of catalyst **17** is crucial for the enantioselectivity, presumably by controlling the spatial orientation of the formamide group and relaying the stereochemical information from the chiral center.[9b] The dihedral angle $CH_3-N-CH-R$, which reflects the magnitude of the chiral relay, was found to be ca. 60° in Kenamide **17** in the crystal (Table 4). For the *tert*-leucine-derived catalyst **40**, which showed a marginally reduced efficiency (≤83% ee),[9b] the corresponding dihedral angle $CH_3-N-CH-R$ was ~88°. The crystals of the phenylalanine-derived catalyst **41**, exhibiting a further reduced level of asymmetric induction (≤49% ee),[9b] contain two crystallographically independent

(27) SPARTAN '04 for Windows; Wavefunction, Inc., 1840 Von Karman Avenue, Suite 370, Irvine, CA 92612.

(28) For the X-ray structure of **32d**, see ref 4c. For the X-ray structure of 3,5-dimethyl-*N*-[(*E*)-1′-(4′-nitrophenyl)ethylidene]aniline, see: Yang, X.-Y.; Li, Y.-F.; Zheng, J.; Jian, F.-F. *Acta Crystallogr.* **2007**, *E63*, No. o1611.

TABLE 2. Examples of the Reduction of Selected Ketimines with Trichlorosilane, Catalyzed by Lewis Bases 24−30[a]

entry	catalyst (mol %)	imine	R^1	R^2	Ar	temp (°C)	solvent	yield (%)	imine (% ee)[b]	ref
1	**24** (10)	**6a**	Ph	Me	Ph	rt	CH_2Cl_2	52	66 (*R*)	12a
2	**25** (5)	**6a**	Ph	Me	Ph	0	CH_2Cl_2	87	94	13a
3	**25** (10)	**6b**	Ph	Me	4-MeO-C_6H_4	0	CH_2Cl_2	98	92	13a
4	**25** (10)	**7a**	PhCH=CH	Me	Ph	0	CH_2Cl_2	81	87	13a
5	**25** (10)	**7c′**	*c*-C_6H_{11}	Me	2-MeO-C_6H_4	0	CH_2Cl_2	75	87	13a
6	**26** (10)	**6a**	Ph	Me	Ph	−20	CH_2Cl_2	95	89	13a
7	**28** (10)	**6a**	Ph	Me	Ph	rt	CH_2Cl_2	86	73 (*S*)	12b
8	**28** (10)	**6b**	Ph	Me	4-MeO-C_6H_4	rt	CH_2Cl_2	90	75 (*S*)	12b
9	**28** (10)	**10l**	Ph	CH_2CO_2Et	H	rt	CH_2Cl_2	65	41 (*S*)	12b
10	**28** (10)	**10o**	Ph	CO_2Me	Ph	rt	CH_2Cl_2	80	45 (*R*)[c]	12b
11	**29** (10)	**6a**	Ph	Me	Ph	0	$CHCl_3$	90	86 (*R*)	14a
12	**29** (20)	**6a**	Ph	Me	Ph	−10	$CHCl_3$	88	92 (*R*)	14a
13	**29** (20)	**6b**	Ph	Me	4-MeO-C_6H_4	−10	$CHCl_3$	90	93 (*R*)[d]	14a
14	**29** (20)	**7c**	*c*-C_6H_{11}	Me	4-MeO-C_6H_4	−10	$CHCl_3$	71	61	14a
15	**30** (10)	**6i**	Ph	Me	CH_2Ph	0	toluene	98	96 (*R*)	13f

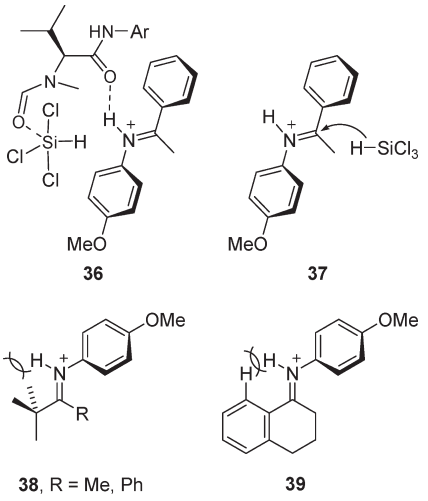
[a]The reactions were carried out under similar condition as our own experiments (Table 1 and Experimental Section). [b]The absolute configuration was either stated by the authors or deduced by us (ref 25). [c]Note the change in the preference of the substituents in the Cahn−Ingold−Prelog system. [d]The configuration can be assumed to be (*R*) but direct evidence has not been provided.

TABLE 3. Reduction of Ketimines 6b and 10*l* with Trichlorosilane in the Presence of Additives, Catalyzed by Sigamide (*S*)-23 (5 mol %)[a]

entry	imines **6**−**10**	R^1	R^2	additive	amine **11b** and **15*l***	yield (%)	**11b** and **15*l*** (% ee)
1	**6b**	Ph	Me	CF_3SO_3H (0.1 equiv)	**11b**	90	91
2	**6b**	Ph	Me	MeOH (1 equiv)	**11b**	90	84
3	**10*l***	Ph	CH_2CO_2Et	CH_3CO_2H (1.5 equiv)	**15*l***	95	85
4	**10*l***	Ph	CH_2CO_2Et	CF_3CO_2H (1 equiv)	**15*l***	89	0
5	**6b**	Ph	Me	*i*-Pr_2EtN (1 equiv)	**11b**	trace	0
6	**6b**	Ph	Me	proton sponge (1 equiv)	**11b**	0	−
7	**6b**	Ph	Me	2,6-lutidine (0.3 equiv)	**11b**	73	92
8	**6b**	Ph	Me	proton sponge (1 equiv), then CH_3CO_2H (1.5 equiv)	**11b**	92[b]	87

[a]The reaction was carried out at 0.2 mmol scale with 2.0 equiv of Cl_3SiH at 18 °C for 16 h in toluene. [b]Acetic acid (1.5 equiv) was added after 10 min.

CHART 3



species, which differ in the dihedral angle quite substantially (~48° and 67°). The X-ray structure of the proline-derived catalyst **24** is not available for comparison; however, the corresponding dihedral angle $CH_2-N-CH-CH_2$ in the structurally related acetamide **42** was reported to be much smaller (7.66°).[29] Although the solid-state data may not be directly used for the interpretation of the behavior of molecules in a solution, the dramatically different conformation of the flexible catalysts **17**, **40**, and **41** vs. that of the rigid **42** can be assumed to be reflected, to some extent, in the solution. Hence, the reversed sense of asymmetric induction for those two types of catalysts can be attributed to the constrained character of **24** as opposed to the flexibility of catalysts **17** and **40**, which apparently prefer a different conformation. The flexibility of the valine-derived catalysts, combined with the chiral relay effect of the *N*-Me group, presumably allows an optimal conformation in the transition state. The valine-derived catalysts (*S*)-**17** and (*S*)-**23** and the proline-derived analogue (*S*)-**24**[12a] thus represent the two

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CHART 4

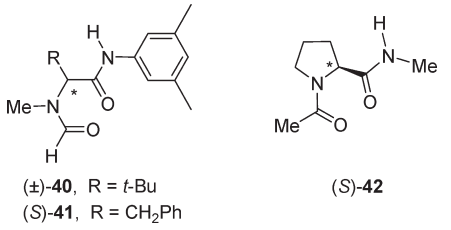

TABLE 4. Crystallographic Data for Amides 17 and 40−42

catalyst	dihedral angle CH_3-N-C^*H-R, deg
(*S*)-**17**[a]	58.08, 62.75, 58.78
(±)-**40**	88.32
(*S*)-**41**[b]	48.23, 67.33
(*S*)-**42**[c]	7.66[d]

[a]Three crystallographically independent molecules in the unit cell. [b]Two crystallographically independent molecules in the unit cell. [c]Reference 29. [d]Dihedral angle $CH_2-N-C^*H-CH_2$.

extremes, favoring the formation of (*S*)-**11a** (≤92% ee) and (*R*)-**11a** (≤66% ee), respectively.

Conclusions

We have demonstrated the broad scope of the reduction of ketimines with trichlorosilane catalyzed by the Lewis-basic Sigamide **23** (Scheme 1 and Table 1). High enantioselectivity (typically ≥90% ee) was observed across the spectrum of aromatic, heteroaromatic, and aliphatic substrates, which may contain additional functional groups. The reaction proceeds in toluene at room temperature overnight with 1−5 mol % of the catalyst. Hence, our protocol compares favorably with its alternatives, such as catalytic hydrogenation (which requires high-pressure equipment in the case of imines),[3,6] or reduction with Hantzsch dihydropyridine catalyzed by chiral acids.[8] Furthermore, our catalytic process is complementary to the Cu-catalyzed hydrosilylation developed by Lipshutz,[4f−h] which favors a 1,4-addition to α,β-unsaturated imines, whereas our system is 1,2-selective (Table 1, entries 12 and 13). Current limitations are relatively few: (1) the reaction exhibits very low enantioselectivity with imines derived from pyridine (Table 1, entries 17 and 18) but a remedy to this flaw was found (Table 1, entry 19); (2) reduction of ketimines derived from diaryl ketones gives practically racemic products even if the two aryl groups differ in their electronics (Table 1, entry 45); (3) the current system only works efficiently with imines derived from aromatic amines (e.g., aniline and anisidine),[30] nevertheless, the anisidine-derived amines can be oxidatively deprotected to produce primary amines;[9g] and (4) imines derived from cyclic ketones exhibit low enantioselectivity. Some of these limitation are now being addressed in this Laboratory and the results will be communicated in due course.

Trichlorosilane, a nonexpensive stoichiometric reducing agent, is relatively easy to handle under anhydrous (but not necessarily anaerobic) conditions. The aqueous workup produces NaCl and SiO_2, two benign inorganics, which in conjunction with the use of toluene as the optimal solvent renders this method environmentally acceptable.

Experimental Section

The commercially unavailable ketones required for the preparation of imines **7b**,[31] **8c**,[32] **8e**,[33] **8j** and **8k**,[34] **8n**,[35,36] **8m** and **9m**,[36,37] **9b**−**e** and **9h**,[37] and **9n**[38] were synthesized according to the published procedures. In this section, only the general procedures are shown. The analytical data for the imines and amines and copies of their NMR spectra and HPLC traces are given in the Supporting Information; some of these are known[3g,p,8d,9g,39−47] but were often prepared by different procedures.

General Procedure for the Preparation of Imines: Method A. Molecular sieves (5 Å; 6.25 g) were added to a solution of the ketone (5.00 mmol; 1 equiv) and *p*-anisidine (770 mg, 6.25 mmol; 1.25 equiv) in anhydrous toluene (25 mL) and the reaction mixture was heated under reflux for 5 h. The mixture was then cooled, the sieves were filtered off, the filtrate was evaporated, and the residue was purified by flash chromatography on a silica gel column (pretreated overnight with 10% triethylamine in petroleum ether) with a petroleum ether−ethyl acetate mixture (100:0 to 60:40).

Method B. A solution of the ketone (5.0 mmol; 1 equiv), *p*-anisidine (647 mg, 5.25 mmol, 1.05 equiv), and *p*-toluenesulfonic acid (47 mg, 0.25 mmol, 5 mol %) in anhydrous benzene (25 mL) was heated under reflux with a Dean−Stark trap for 10 h, then cooled and evaporated to dryness. The residue was purified by flash chromatography on a silica gel column (treated overnight with 10% triethylamine in petroleum ether) with a petroleum ether−ethyl acetate mixture (100:0 to 90:10).

Method C[18]**.** A 1.0 M solution of titanium(IV) chloride in CH_2Cl_2 (3.0 mL, 3.0 mmol, 1 equiv) was added dropwise to a precooled (0 °C) solution of the ketone (3.0 mmol, 1 equiv) and *p*-anisidine (1.11 g, 9.0 mmol, 3 equiv) in anhydrous ether and the reaction mixture was heated to reflux overnight. The mixture was then cooled to room temperature and filtered, then the solid material was washed with anhydrous ether. The filtrate was then washed with a KOH solution (2 M, 15 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were dried over K_2CO_3 and evaporated. The crude mixture was purified on a silica gel column (30 mL) (treated overnight with 10% triethylamine in petroleum ether) in a petroleum ether−Et_3N mixture (99:1).

Method D[9g,20]**.** A solution of the corresponding ketonitrile (5.0 mmol, 1 equiv) and *p*-anisidine (800 mg, 6.5 mmol, 1.3 equiv) or aniline (605 mg, 6.5 mmol, 1.3 equiv) in glacial acetic acid (2.9 mL) was stirred at 80 °C for 6 h under an argon atmosphere. The reaction mixture was then cooled to room temperature and the precipitated solid was filtered off, washed with glacial acetic acid, vacuum dried, and used without further purification (**31j**) or after an additional recrystallization from aqueous methanol (**31k**).

Method E[21]**.** A solution of the corresponding ketoester (5.0 mmol, 1 equiv), *p*-anisidine (677 mg, 5.5 mmol, 1.1 equiv), and *p*-toluenesulfonic acid (95 mg, 0.5 mmol, 10 mol %) in dry ethanol (5 mL) was refluxed for 24−48 h under an argon atmosphere, then cooled and evaporated to dryness. Solid residues were directly purified by crystallization. Oily residues were dissolved in dichloromethane (20 mL) and washed with water (10 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated,

(30) This limitation seems to have been eliminated by the sulfinamide catalyst **30** and partly by the α-picolinamide **29**.

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then the residue was purified by column chromatography on silica gel.

Methyl (*E*)-4-(*N*-4′-Methoxyphenylimino)-4-phenylbutanoate (10p). Method B (60%; chromatographic purification with a 97:3 mixture of petroleum ether and AcOEt): yellow crystals; mp 62−63 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ∼7:3 ratio; the minor one is marked with an *) δ 2.42−2.47 (m, 2H), 2.81* (dd, J = 7.0, 6.9 Hz, 0.86H), 3.00−3.07 (m, 2.86H), 3.60 (s, 3H), 3.698* (s, 1.29H), 3.701* (s, 1.29H), 3.82 (s, 3H), 6.51−6.55* (m, 0.86H), 6.63−6.67* (m, 0.86H), 6.71−6.75 (m, 2H), 6.89−6.92 (m, 2H), 7.98−7.12* (m, 0.86H), 7.20−7.24* (m, 1.29H), 7.42−7.47 (m, 3H), 7.85−7.90 (m, 2H); ^{13}C NMR δ 25.18 (CH_2), 30.30* (CH_2), 31.99 (CH_2), 35.50* (CH_2), 51.67* (CH_3), 51.86 (CH_3), 55.28* (CH_3), 55.47 (CH_3), 113.77* (2 × CH), 114.45 (2 × CH), 120.08 (2 × CH), 122.12* (2 × CH), 127.49 (2 × CH), 127.78* (2 × CH), 128.20* (2 × CH), 128.47* (CH), 128.66 (2 × CH), 137.91 (C), 137.99* (C), 143.74* (C), 144.31 (C), 155.69* (C), 156.00 (C), 168.29 (C), 169.20* (C), 172.40 (C), 173.80* (C); IR ν 3020, 2951, 2834, 11735, 1630, 1503, 1439, 1287, 1241 cm^{-1}; MS (CI/isobutane) m/z (%) 298 [(M + H)$^+$, 100]; HRMS (CI/isobutane) 298.1441 ($C_{18}H_{20}NO_3$ requires 298.1443).

General Procedure for Enantioselective Reduction of Imines. Trichlorosilane (40 μL, 0.4 mmol, 2 equiv) was added dropwise to a cooled solution (0 °C) of the imine (0.2 mmol, 1 equiv) and catalyst (0.01 mmol, 0.05 equiv) in anhydrous toluene (2 mL) under an argon atmosphere and the reaction mixture was allowed to stir at room temperature (15−20 °C) for 24 h (unless otherwise stated). Then the reaction mixture was diluted with ethyl acetate (5 mL) and quenched with a saturated $NaHCO_3$ solution (20 mL) and the layers were separated. The aqueous layer was extracted with AcOEt (2 × 5 mL), the combined organic phase was washed with water (2 × 15 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash chromatography on a silica gel column (25 mL) with a petroleum ether−ethyl acetate mixture (98:2 to 85:15). The yields and enantioselectivities are given in Table 1. The absolute configuration of the amines was established by comparison of their optical rotation (measured in $CHCl_3$) with the literature data and/or by comparison of their HPLC behavior with that of the authentic samples.

(−)-Methyl 4-[*N*-(4′-Methoxyphenyl)amino]-4-phenylbutanoate (15p). 15p was obtained as a yellow oil, isolated as a more polar component from the reduction of **10p**: mp 59−60 °C (hexane/CH_2Cl_2); $[\alpha]_D$ −13.5 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03−2.19 (m, 2H), 2.41 (dd, J = 7.3, 7.2 Hz, 3H), 3.66 (s, 3H), 3.69 (s, 3H), 3.98 (br s, 1H), 4.30 (dd, J = 7.2, 6.5 Hz, 1H), 6.45−6.49 (m, 2H), 6.66−6.70 (m, 2H), 7.21−7.25 (m, 1H), 7.29−7.34 (m, 4H); ^{13}C NMR δ 31.06 (CH_2), 33.32 (CH_2), 51.77 (CH_3), 55.75 (CH_3), 58.52 (CH), 114.60 (2 × CH), 114.77 (2 × CH), 126.46 (2 × CH), 127.21 (CH), 128.71 (2 × CH), 141.39 (C), 143.33 (C), 151.97 (C), 174.07 (C); IR ν 3394, 3025, 3005, 2951, 2833, 1733, 1513, 1452, 1237 cm^{-1}; MS (EI) m/z (%) 299 (M$^{+\bullet}$, 30), 212 (100), 117 (23), 85 (52), 83 (80); HRMS (EI) 299.1518 ($C_{18}H_{21}NO_3$ requires 299.1521); HPLC analysis [Chiralpak IB, hexane−propan-2-ol (90:10), 0.75 mL/min, t_{minor} = 16.52 min, t_{major} = 28.60 min] showed 88% ee.

2-Methoxy-1-(4′-methoxyphenyl)-5-phenyl-1*H*-pyrrole. The title compound was obtained as white crystals, isolated in 27% yield as a less polar component along with **15p**: mp 101−102 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.81 (s, 3H), 5.45 (d, J = 3.7 Hz, 1H), 6.26 (d, J = 3.7 Hz, 1H), 6.84−6.88 (m, 2H), 7.03−7.16 (m, 7H); ^{13}C NMR δ 54.30 (CH_3), 56.71 (CH_3), 82.86 (CH), 105.73 (CH), 112.92 (2 × CH), 124.24 (CH), 125.80 (C), 126.13 (2 × CH), 126.95 (2 × CH), 128.10 (2 × CH), 129.00 (C), 132.24 (C), 149.12 (C), 157.39 (C); IR ν 3019, 2956, 2931, 2832, 1599, 1564, 1515, 1454, 1420, 1294, 1250, 1216 cm^{-1}; MS (EI) m/z (%) 279 (M$^{+\bullet}$, 55), 264 (100), 193 (10), 103 (10), 77 (16); HRMS (EI) 279.1258 ($C_{18}H_{17}NO_2$ requires 279.1259).

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Note Added in Proof. (1) Coordination of pyridine to the silicon atom of Cl_2SiHR, relevant to the behavior of the pyridine derivatives **8a**−**c** (Table 1, entries 17−19), has been demonstrated by X-ray crystallography and solution studies: Fester, G. W.; Wagler, J.; Brendler, E.; Böhme, U.; Gerlach, D.; Kroke, E. *J. Am. Chem. Soc.* **2009**, *131*, 6855. (2) A recent mechanistic and computational study on the reduction of imines with Cl_3SiH, catalyzed by a series of amides, including some of those discussed in this paper, suggests that the catalyst not only coordinates to the reagent but also acts as a proton donor to the imine in the transition structure: Zhang, Z.; Rooshenas, R.; Hausmann, H.; Schreiner, P. R. *Synthesis* **2009**, 1531. However, this mechanistic picture does not take into account the role of the added Brønsted acid observed in our experiments.

Supporting Information Available: Experimental methods, ^{1}H and ^{13}C NMR spectra for new compounds, crystallographic data for **17** and **40**−**41** in CIF format, and HPLC traces for chiral amines. This material is available free of charge via the Internet at http://pubs.acs.org.