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New Chiral Lewis Bases Derived from L-Pipecolinic Acid Showing Stereocontrol Highly Dependent on the Catalyst Design in the Hydrosilylation of *N*-Phenyl Ketimines

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Chiral L-pipecolinic acid based catalysts, the *N*-functionalized pipecolinamides **4a**–**h** and **5a**–**e**, have been obtained in a straightforward two-step synthesis starting from Boc-L-pipecolinic acid. The catalysts form a complex with trichlorosilane, which proved to be effective for the enantioselective addition to the standard *N*-phenylimine substrate **6**. We have tested the enantioselectivity of the ligands to establish the influence of *N*- and *O*-functionalization on the chiral α-amino acid. Whereas the *N*-formylpipecolinamides give rise to *R*-configured amines, the opposite result was obtained by using the urea-pipecolinamide **5c**, which proved to be an efficient activator of trichlorosilane. The observed reactivities and stereoselectivities have been rationalized not only on the basis of the conformational dependence of the ligands, but also by noncovalent interactions, which has allowed the structures of the transition states to be deduced.

Introduction

Lewis bases such as tertiary amines[1] or DMF[2] are known to activate trichlorosilane in the reduction of ketimines to amines.[3] It has been confirmed by ^{29}Si NMR spectroscopy that the intermediacy of a hexacoordinate species is the origin of this activation. These extracoordinated adducts have been shown to be more unstable than the tetracoordinate species[4] and this effect could also facilitate catalyst turnover if a Lewis base is employed in catalytic amounts. In addition, the increase of the natural atomic charge on the silicon atom of the hexacoordinate species compared with the tetracoordinate precursor results in an increase in the Lewis acidity, allowing the largest polarization of the surrounding groups to be transferred.[5]

Thus, taking into account these observations, it is not surprising that chiral formamides have emerged as candidates for the development of the asymmetric organocatalytic reduction of ketimines, an environmentally friendly approach. Matsumura and co-workers reported the first organocatalytic enantioselective reduction method based on *N*-formylproline derivatives using trichlorosilane as the hydrosilylation reagent and the catalyst **1** (Figure 1).[6] The enantioselectivity was moderate [55% *ee* and 91% yield of the (*R*)-1-methylbenzylamine product at room temperature using DCM as solvent].

More recently, a new activator for Cl_3SiH based on L-valine (compound **2**; Figure 1), the best catalyst of a set of α-amino acids, was reported.[7,8] Compound **2** exhibited a high enantioselectivity (up to 98% *ee* in the *S* amine), but only a moderate reactivity (49% yield) in $CHCl_3$ at –20 °C. On the other hand, Sun and co-workers found that compound **3a** displayed a significantly higher reactivity (94% yield in CH_2Cl_2 at 0 °C) and selectivity (73% *ee* in the *R*

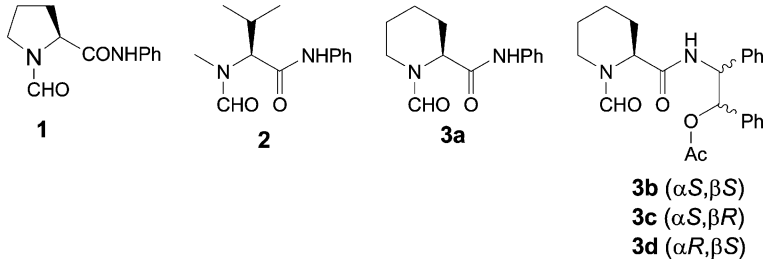

Figure 1. Structures of previously reported catalysts.

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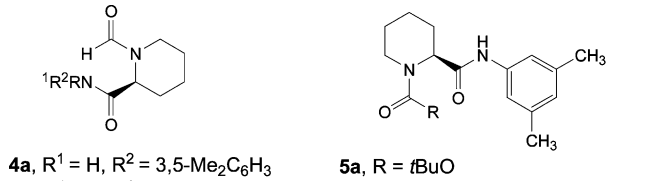
amine) than its congener **1** (Figure 1).[9,10] This observation prompted them to prepare compounds **3b**–**d**, starting from L-pipecolinic acid, to examine their catalytic efficiency. Of these, **3b** and **3c** were the most reactive (97% yields) and also the most selective (up to 94% *ee*), whereas the α-*R*-configured stereoisomer **3d** afforded the *R* amine in 71% yield and 47% *ee*.

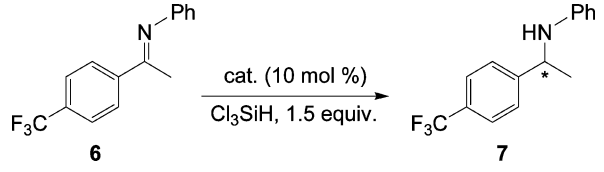
Encouraged by these results, we have prepared a series of new *N*-formamide catalysts **4a**–**h** and **5a**–**e** (Figure 2) starting from commercially available L-*N*-Boc-pipecolinic acid and tested their catalytic effects in the model reaction of **6** with Cl_3SiH (on a scale of 0.2 mmol of **6** in 1 mL of $CHCl_3$ at –20 °C and with 10 mol-% of catalyst; Figure 3). Our aim was to identify the role of the structural effects of these Lewis bases in order to shed light on the origin of the asymmetric induction.



4a, R^1 = H, R^2 = 3,5-$Me_2C_6H_3$
4b, R^1 = H, R^2 = $C_6H_5CH_2$
4c, R^1 = H, R^2 = *p*-$MeOC_6H_4CH_2$
4d, R^1 = H, R^2 = *p*-$ClC_6H_4CH_2$
4e, R^1 = H, R^2= 2-$pyCH_2$
4f, R^1 = H, R^2 = $C_6H_5CH_2CH_2$
4g, R^1-R^2 = -$(CH_2)_5$-
4h, R^1-R^2 = -$(CH_2)_2$-O-$(CH_2)_2$-

5a, R = *t*BuO
5b, R = PhO
5c, R = 3,5-$Me_2C_6H_3NH$
5d, R = (2*R*)-*N*-formylpiperidin-2-yl
5e, R = (2*S*)-*N*-formylpiperidin-2-yl

Figure 2. Structures of the catalysts.



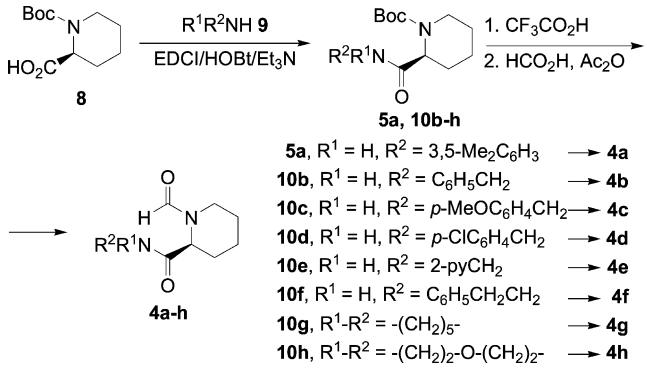
6 **7**

Figure 3. Benchmark reaction to evaluate the catalysts **4a**–**h** and **5a**–**e**.

Results and Discussion

Synthesis and Structural Analysis of Catalysts 4a–h and 5a–e

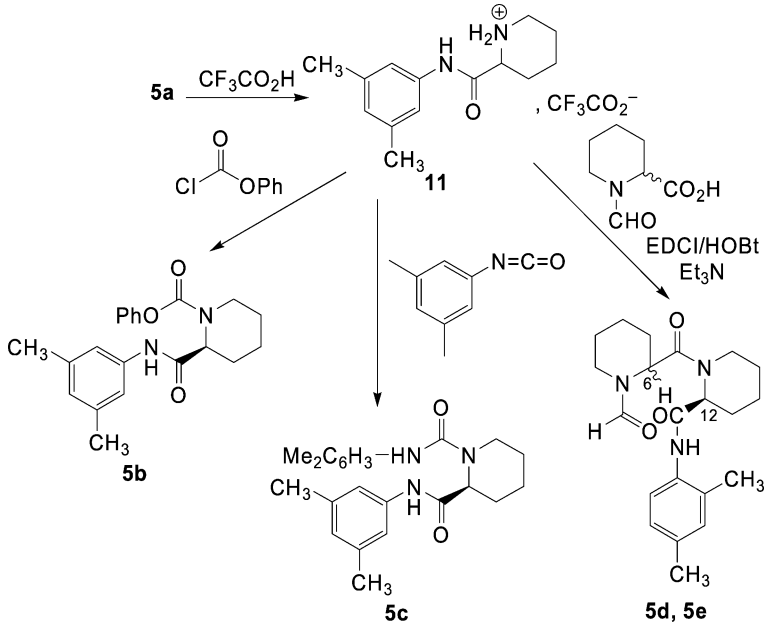
Both the *N*-formylpipecolinamides **4a**–**h** and the *N*-functionalized pipecolinamides **5a**–**e** were prepared from L-*N*-Boc-pipecolinic acid **8**. The synthesis of the catalysts **4a**–**h** commenced with the amidation of the acid using the carbodiimide method. Next, Boc deprotection (with TFA) of the amides **5a** and **10b**–**h** was followed by formylation with a mixed anhydride generated in situ from formic acid and acetic anhydride to give the desired *N*-formylpipecolinamides **4a**–**h** (Scheme 1).



8 **5a, 10b-h** **4a-h**

5a, R^1 = H, R^2 = 3,5-$Me_2C_6H_3$ → **4a**
10b, R^1 = H, R^2 = $C_6H_5CH_2$ → **4b**
10c, R^1 = H, R^2 = *p*-$MeOC_6H_4CH_2$ → **4c**
10d, R^1 = H, R^2 = *p*-$ClC_6H_4CH_2$ → **4d**
10e, R^1 = H, R^2 = 2-$pyCH_2$ → **4e**
10f, R^1 = H, R^2 = $C_6H_5CH_2CH_2$ → **4f**
10g, R^1-R^2 = -$(CH_2)_5$- → **4g**
10h, R^1-R^2 = -$(CH_2)_2$-O-$(CH_2)_2$- → **4h**

Scheme 1. Synthesis of the catalysts **4a**–**h**.



5b **5c** **5d, 5e**

Scheme 2. Synthesis of catalysts **5b**–**e**.

All compounds **4a**–**h** were isolated and purified by LC in high-to-moderate yields (73–98%). Their characterization by ^{1}H and ^{13}C NMR spectroscopy was unequivocal. The NMR assignments were accomplished by analysis of the two-dimensional homonuclear COSY spectra and the heteronuclear HMQC correlations.

The synthesis of catalysts **5b** and **5c** required the isolation of the free amine **11** (as the trifluoroacetate salt), which was transformed into the carbamate **5b** by treatment with phenyl chloroformate or into the urea derivative **5c** by using 3,5-dimethylphenyl isocyanate (Scheme 2).[11] In our hands, attempts to synthesize the dipeptide **5e** from L-*N*-Boc-pipecolinic acid **8** and the amine **11** failed during the one-pot transformation of the isolated *N*-Boc derivative of **5e** (deprotection and formylation). However, a mixture of the diastereoisomeric catalysts **5d** and **5e** was obtained from the amine **11** and *rac*-*N*-formylpipecolinic acid using the carbodiimide method. Both epimeric compounds were separated by LC and their structures were determined by ^{1}H and ^{13}C NMR analysis. In fact, these compounds displayed large differences in their ^{1}H NMR spectra. Thus, the minor isomer **5e** was produced as a mixture of two or more rotamers, whereas the major isomer **5d** was obtained as a sole rotamer. In addition, the isomer **5d** displayed different coupling patterns for the hydrogen atom bonded at carbon C-6 (δ = 4.91 ppm; t, $^3J_{H,H}$ = 5.0 Hz) and the hydrogen attached to C-12 (δ = 5.37 ppm; dt, $^3J_{H,H}$ = 5.6, 1.8 Hz, $^4J_{H,H}$ = 1.8 Hz). In contrast, the corresponding two protons of the major rotamer of **5e** showed identical coupling patterns (6-H: δ = 5.39 ppm; d, $^3J_{H,H}$ = 6.2 Hz; 12-H: δ = 5.22; d, $^3J_{H,H}$ = 5.9 Hz), whereas the minor rotamer exhibited different patterns (6-H; δ = 5.08 ppm; dd, ^3J = 5.9 Hz, $^4J_{H,H}$ = 2.2 Hz; 12-H; δ = 4.63 ppm; d, $^3J_{H,H}$ = 4.2 Hz). In this case, the broad signals observed indicate coalescence with other signals belonging to other rotamers.

To establish the absolute configuration of the two stereoisomers, a conformational search was made for the 6*R*,12*S* and 6*S*,12*S* isomers. As a preliminary step, eight conformers of each were constructed by turning N–CO linkages around the amide group (2^3) and computed by using the molecular mechanics force-field MM$^+$ implemented in Hyperchem.[12] Three conformations were selected in each case and optimized by PM3 semi-empirical calculations[13] implemented in Gaussian03.[14] These calculated structures were used as the starting point for complete geometry optimization by DFT at the B3LYP/6-31G(d) level of theory.[15,16] According to the results, a unique conformer was unequivocally selected for the 6*R*,12*S* isomer (≥ 96%; Figure 4) and three were finally considered for the 6*S*,12*S* isomer (A: 35.2%; B: 24.9%; C: 39.9%; Figure 5).

These structures show the equatorial position of the 6-H and 12-H atoms, as suggested from the values of their vicinal coupling constants ($^3J_{H,H}$ = 4.2–6.2 Hz). Furthermore, the calculated parameters are in agreement with the different behavior of the two epimers. Thus, because compound **5d** is monoconformational with regard to **5e**, it fitted the calculated structure of 6*R*,12*S*. In fact, this structure exhibits a short distance (2.02 Å) between the oxygen atom

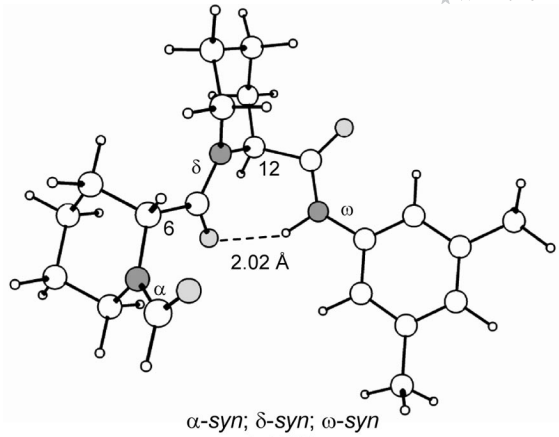


Figure 4. Calculated parameters and geometry of the 6*R*,12*S* isomer. The *syn*/*anti* notation takes into account the two relative positions of the carbonyl group with regard to the substituent of the nitrogen atom in the amide.

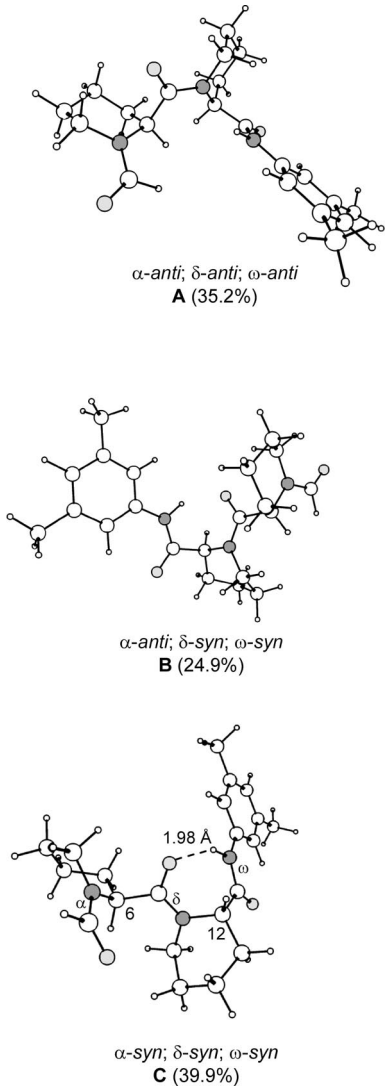


Figure 5. Calculated parameters and geometry for the rotamers of the 6*S*,12*S* isomer. For the *syn*/*anti* notation, see Figure 4.

at the carbonyl group (δ) and the hydrogen atom of the amide group (ω), making possible a hydrogen bond between them (Figure 4). Because of this, the different coupling patterns for 6-H and 12-H can be rationalized in terms of the long-range coupling observed for the hydrogen 12-H, which is missing for 6-H. Thus, two eq–ax couplings ($^3J_{H,H}$ = 5.6 Hz and $^3J_{H,H}$ = 1.8 Hz, the coupling constant of the latter being similar to that of a long-range coupling $^4J_{H,H}$ like a pseudo-azaallylic coupling with N_ω–H) are in agreement with the coupling pattern observed for 12-H (dt). A similar value for the coupling constant of 6-H with the two hydrogen atoms of the adjacent CH_2 group is in agreement with the observed 6-H coupling pattern (t; see above).

Unfortunately, a correlation analysis for the epimer **5e** based on the coupling patterns of the 6-H and 12-H atoms did not provide much insight into this issue. However, the structure of **5e** was determined unequivocally from its conformational analysis (Figure 5).

Asymmetric Reduction of Ketimine 6 with Cl_3SiH Activated by Chiral Catalysts 4a–h and 5a–e

Ketimine **6**, derived from 4-(trifluoromethyl)acetophenone and aniline, was reduced with Cl_3SiH in the presence of different loadings of catalyst **4a** in several different solvents and reaction conditions (Table 1). The optimal result was obtained with 1.5 equiv. of Cl_3SiH on the 0.2 mmol scale in 1.0 mL of $CHCl_3$ at –20 °C over 24 h using 10 mol-% of the catalyst (entry 5). The lowest effective catalyst loading was 5 mol-%, but the reaction was slower (entry 4). On the other hand, the highest reactivity observed in toluene was accompanied by an unacceptable loss of selectivity (entry 1). Furthermore, lowering the reaction temperature to –40 °C had a negative effect on both the selectivity and the reactivity, which were significantly decreased (entry 6).

Table 1. Asymmetric reduction of ketimine **6** with Cl_3SiH in the presence of **4a**.[a]

Entry	Solvent	Cat. loading [mol-%]	*T* [°C]	*t* [h]	% Yield[b]	% *ee*[c,d]
1	toluene	10	20	8	92	53
2	DCM	10	20	8	73	64
3	$CHCl_3$	10	20	8	70	66
4	$CHCl_3$	5	–20	32	84	76
5	$CHCl_3$	10	–20	24	94	76
6	$CHCl_3$	10	–40	24	90	67

[a] The reaction was carried out on the 0.2 mmol scale in 1.0 mL of solvent with 1.5 equiv. of Cl_3SiH. [b] Determined by ^1H NMR analysis of the reaction crudes. [c] Determined by chiral GC. [d] The products were *R*-configured, as revealed by comparison of their optical rotations with the literature data.[7a]

Compound **4a** exhibited the same enantioselectivity as its analogue **3a** (Figure 1), as could be expected, and a significantly higher selectivity than the L-proline derivative **1** (Figure 1) with the same configuration of the product (*R*). In addition, it was much more reactive than the L-valine derivative **2**, but it exhibited lower and opposite enantioselectivity (Figure 1). These results are intriguing and suggest that the stereocontrol is strongly dependent on the structural features of the catalyst.

In spite of the modest selectivity of **4a** and because its reactivity was high, it seems that selection of the L-pipecolinic scaffold could be a good strategy for achieving a long-range chiral induction by changing the side-chains. Thus, catalyst design could be rationalized.

The role of the amide functionality in the catalyst was elucidated with the aid of amides **4a**–**h** (Table 2). Catalyst **4a**, with an aniline moiety, was found to be less efficient than the benzylamine analogue **4b** (entries 1 and 2). In addition, *p*-methoxy and *p*-chloro substituents on the phenyl group of **4b** gave lower yields and similar enantioselectivities to the parent compound (entries 3 and 4 vs. 2). In contrast, a significantly reduced efficacy was observed for the 2-pyridinylmethyl analogue **4e** (entry 5), which suggests interference by the pyridine moiety. Surprisingly, the homologue of the parent catalyst **4b**, the 2-phenylethylamine derivative **4f**, gave a moderate yield and good selectivity (entry 6), whereas the tertiary amides **4g** and **4h**, in spite of their catalytic efficiency, exhibited a low level of enantioselectivity (entries 7 and 8).

Table 2. Asymmetric reduction of ketimine **6** with Cl_3SiH in the presence of **4a**–**h**.[a]

Entry	Cat.	% Yield[b]	% *ee*[c,d]
1	(–)-**4a**	94	76
2	(–)-**4b**	100	85
3	(–)-**4c**	72	86
4	(–)-**4d**	71	87
5	(–)-**4e**	57	15
6	(–)-**4f**	70	84
7	(–)-**4g**	100	24
8	(–)-**4h**	81	18

[a] The reaction was carried out on the 0.2 mmol scale in 1.0 mL of $CHCl_3$ and with 10 mol-% of the catalyst at –20 °C for 24 h. [b] Determined by ^1H NMR analysis of the reaction crudes. [c] Determined by chiral GC. [d] The products were *R*-configured as revealed by comparison of their optical rotations with the literature data.[7a]

While our initial work was in progress, Matsumura and co-workers reported another catalyst based on L-proline in which the formamide group in the original structure of **1** (Figure 1) was replaced with picolinoylamide and the anilide moiety with a diphenylcarbinol segment.[17] The new catalyst **12** (Figure 6) exhibited increased enantioselectivity and, compared with **1**, induced the opposite configuration in the products [77% *ee* of (*S*)-1,*N*-diphenylethylamine in DCM at 0 °C]. This was the first set of data to show that the presence of an *N*-formyl group is not always essential in the catalyst. At the same time, another catalyst, **13**, based on 2-pyridinyl-2-oxazoline (Figure 6), which exhibits a high efficiency in the reduction of *N*-arylimines and ketones, was reported.[18] Likewise, Sun and co-workers recently reported that the catalyst **14** (Figure 6) gives high enantioselectivities (up to 99.6% *ee*) in unprecedented long-range chiral induction of aromatic *N*-alkyl ketimines.[19]

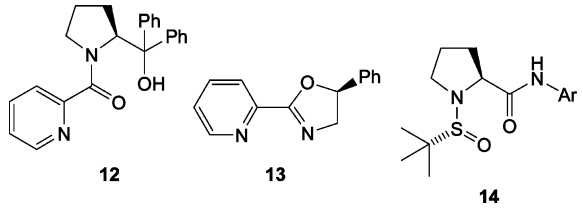


Figure 6. Second generation of catalysts bearing coordinative centers other than the formamide moiety.

Therefore, to improve the efficacy and the stereocontrol of the L-pipecolinic acid based catalysts we investigated the role of *N*-functionalized pipecolinamides like **5a**–**c** in the reduction of imine **6** with Cl_3SiH (Table 3, entries 2–4).

Table 3. Asymmetric reduction of ketimine **6** with Cl_3SiH in the presence of **5a**–**d**.[a]

Entry	Cat.	% Yield[b]	% *ee*[c] (conf.)[d]
1[e]	**4a**	94	76 (*R*)
2	**5a**	<5	–
3	**5b**	<5	–
4	**5c**	56	67 (*S*)
5	**5d**	84	32 (*S*)
6	**5e**	56	9 (*R*)

[a] The reaction was carried out on a 0.2 mmol scale in 1.0 mL of solvent with 1.5 equiv. of Cl_3SiH at –20 °C for 24 h. [b] Determined by ^1H NMR analysis of the reaction crudes. [c] Determined by chiral GC. [d] The configuration of the enantiomer in excess was revealed by comparison of the optical rotation of the reaction crudes with literature data[7a] and also by comparison of the retention times of chiral amines with samples of known composition like that in entry 1. [e] The analysis of this sample is included for comparison.

Furthermore, because tertiary alkyl amides like **4g** and **4h** turned out to be efficient in catalysis, but fruitless in stereocontrol (Table 2, entries 7 and 8), we attempted to improve their enantiodifferentiation by the inclusion of a second chiral moiety of pipecolinamide in the framework of the catalyst, for example, **5d** and **5e** (Table 3, entries 5 and 6).

Compounds **5a** and **5b** (Table 3, entries 2 and 3) proved to be inert in the catalysis reaction. This could be ascribed to the steric congestion close to the carbonyl group, but the urea derivative **5c** (entry 4), in spite of its similar steric properties in comparison with **5b**, was efficient, not only in conversion but also in stereocontrol. Note that the sense of induction changed with regard to that observed in the parent compound **4a** (entry 1). This is isolated but interesting behavior that indicates another mechanistic pathway, possibly based on the interaction between the Brønsted acidic NH group of the urea moiety and the basic nitrogen atom of the imine (see below).

The dipeptide amides **5d** and **5e** (entries 5 and 6) induced opposite selectivity due to the change in the configuration of the *N*-formylpipecolinic moiety (*R* vs. *S*), but the selectivity was significantly reduced. It seems that the big distance between this coordinative bidentate unit and the group bearing the aniline moiety causes the decrease in the selectivity relative to the parent compound **4a** (entry 1). This is an important feature to be taken into account as arene–arene interactions and hydrogen bonds are responsible for enhancing stereocontrol (see below).[20]

Transition-State Models for the Catalytic Hydrosilylation of *N*-Phenyl Ketimine 6 Using the L-Pipecolinic Acid Based Catalysts

To rationalize our results and others related to them, two transition states should be considered. Thus, TS$^{\neq}$ **A** and **B** (Figure 7) based on the catalyst **4a** can be proposed on the basis of the following considerations.

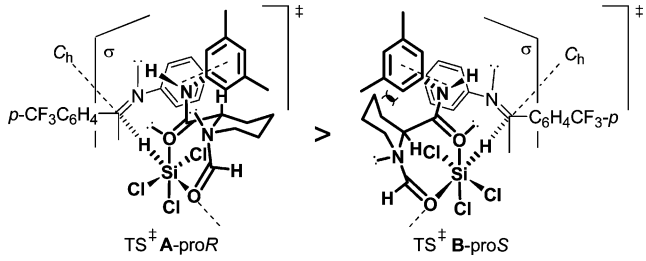


Figure 7. Relative stability of the competitive transition states **A** and **B** postulated for the hydrosilylation of the imine **6** in the presence of the catalyst **4a**. Generalizations can be made for related transition states of the catalysts **4a**–**f** in Table 2.

1) The extracoordination of the silicon atom enables the transfer of the hydride ligand to the electrophilic site of the imine group. From a steric and orbital viewpoint, it seems that the transfer through an *anti* approach occurs easily in the newly occupied position in the hexacoordinate complex.[21]

2) In both geometrical approaches of the configured (*E*)-imine (*Si* face, pro-*R*, and *Re* face, pro-*S*),[22,23] two stabilizing interactions between the secondary amide group (NH and arene) in the catalyst and the *N*-phenylimine moiety in the substrate could be involved (Figure 7).[7] Validation of the approaches arises from the nonrestrained rotation of the nodal plane of the imine group around the perpendicular axis matching the trajectory to the incoming nucleophile. Note that *R* stereoselectivity will be enhanced by increasing the flexibility of the amide skeleton, as in the benzyl and phenylethylamides **4b**–**d** and **4f** (see above).

3) Inspection of the two transition states **A** and **B** (Figure 7) suggests that the kinetic bias to the *R*-configured enantiomer derives primarily from the minimal steric congestion at the coordination site relative to the pro-*S* bias. Each of these transition states corresponds to the C=O ligand in a pseudo-equatorial and -axial orientation which induces changes in their ability to coordinate and thus affects the relative rates of the complexes to transfer the hydride.

The results obtained with the catalysts **5d** and **5e** (Table 3, entries 5 and 6) can be explained in an analogous way. Because they are epimers at the coordinative *N*-formylpiperidine unit, the selectivities are opposite (Figure 8, a,b). Note also that insertion of a second *S*-configured moiety, the L-pipecolinic carboxamide, led to a dramatic reduction

in the selectivity. There appears to be a close correlation between the steric hindrance of the catalysts and the ability of the imine moiety to adopt a conformation about the C_n axis that allows arene–arene and hydrogen-bond interactions to develop.

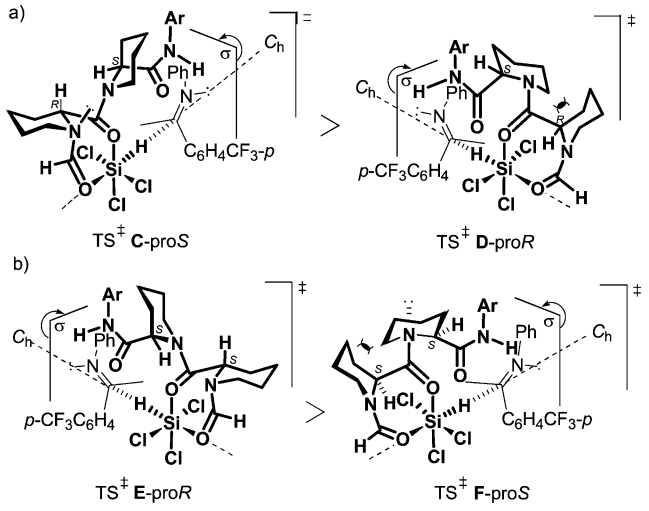


Figure 8. Relative stability of the competitive transitions states postulated for the hydrosilylation of the imine **6** in the presence of the catalysts a) **5d** and b) **5e**.

The striking results observed with the L-valine catalyst **2**[7] (Figure 1) can be explained on similar bases. In this case, the nitrogen atom in the amino acid moiety is not confined to a ring as is the case in **4a** making possible the free rotation of the C–N bond or a nitrogen inversion. A Newman projection can give more insight into the role of the inversion of the configuration of the nitrogen atom in the transition state pro*S* of catalyst **3a** in comparison with the catalyst **4a** (Figure 9). Thus, the bulkiest *i*Pr group can be arranged *anti* with respect to the coordinative C=O in the TS≠ **H** (pro*S*), whereas it adopts a *syn* orientation in the TS≠ **G** (pro*R*). Thus, the relative stability of TS≠ **G** (pro*R*) and TS≠ **H** (pro*S*) is modified with respect to that of **4a** (Figure 7) by a simple conformational effect in the catalysts.

Finally, to account for the opposite direction of selectivity (*ee* 67% *S*) obtained with the catalyst **5c** (Table 3), another approach to the imine substrate complex had to be proposed. Thus, the greater Brønsted acidic character of the NH group of the urea moiety compared with the NH group of the amide (pK_a of urea: 13.90 vs. pK_a of acetamide: 17.0) [24–26] could be responsible for the double role that the urea function could play by coordinating the silicon atom of the reagent and also the basic nitrogen of the imine (through a hydrogen bond). Both effects are mutually enforced and, in addition, the hydrogen transfer from the complex must be *anti* with respect to the other site of coordination. Thus, the different steric demands of the urea moiety in the two competitive transition states are considered as the most important factor determining the selectivity (Figure 10). Therefore, the transition state TS≠ **I** (pro*S*) is more stable than the TS≠ **J** (pro*R*) due to the pseudo-axial character of

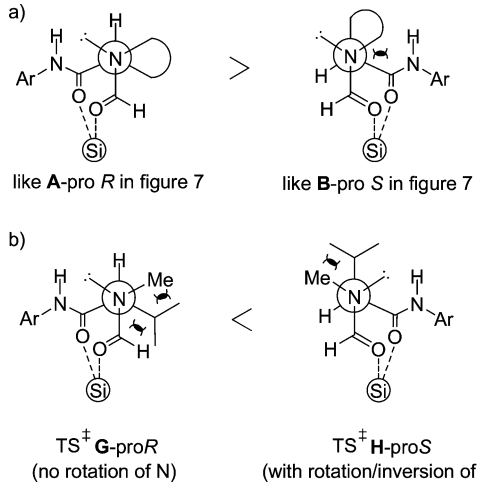


Figure 9. Relative stability of the competitive transition states postulated for the hydrosilylation of the imine **6** in the presence of the catalysts a) **4a** and b) **2**.[7]

the urea group in the latter complex, regardless of the other steric interactions on the other coordinative groups (carbonyl group of the amide moiety).

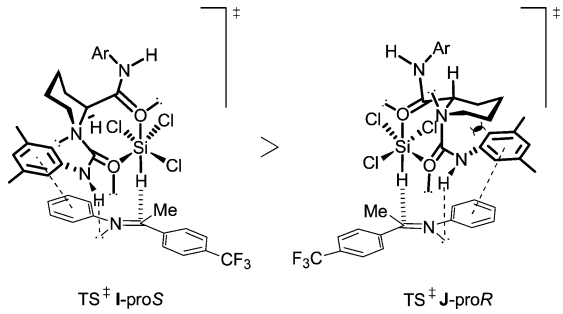


Figure 10. Relative stability of the competitive transition states postulated for the hydrosilylation of the imine **6** in the presence of the catalyst **5c**.

Conclusions

We have developed L-pipecolinic acid derived *N*-formamides and other derivatives as new Lewis basic organocatalysts for the hydrosilylation of a standard *N*-phenyl ketimine substrate. The sense of stereoselectivity was *R* in the amine provided that *S* was the configuration of the *N*-formamide (unlike stereoinduction).[27] The stereocontrol depends on the structure of the 2-carboxylic amide group, and the benzyl and β-phenylethyl amides afforded the best stereochemistries (up to 87% *ee*), whereas tertiary aliphatic amides were efficient in catalysis but fruitless in stereocontrol.

Accordingly, it seems that the arene–arene interaction and the hydrogen bond between the ligand and the *N*-phenyl group of the ketimine are crucial for improving stereocontrol, as was indicated by Malkov et al.[7a] They form a partnership that enables the bidentate ligands to adopt two reactive conformations in which the silicon atom has

different abilities to attain extracoordination in the active complexes and thus to release the hydride ligand in the competitive transition states.

This working hypothesis matches the like stereoinduction observed with analogous α-amino acid based catalysts[7] and it could be a good theoretical tool for designing other catalysts.

Furthermore, we obtained an unprecedented reversal in stereoselectivity by using the urea-amide derivative **5c**, which was efficient in catalysis (up to 67% *ee* in *S* amine). A mechanistic change involving a new interaction between the N–H group of the urea and the Brønsted basic nitrogen of the ketimine could be responsible for changing the stereopreference to pro*S*. This finding marks a nexus between the first generation of catalysts based in *N*-formamide templates and the second one based on other coordinative centers.[17–19,28]

The mechanistic aspects of these catalysts are under study and will be reported in due course.

Experimental Section

General Methods: Melting points were determined with a Gallenkamp apparatus in open capillary tubes and are uncorrected. Optical rotations were measured at room temperature (20–23 °C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). Infrared spectra were recorded with a Bruker Tensor 27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker AC 300 spectrometer (^{1}H, 300.13 MHz; ^{13}C, 75.42 MHz). The chemical shifts (δ/ppm) are referenced to TMS (^{1}H) or deuteriated chloroform (^{13}C). The coupling constants (J) are reported in Hz. The multiplicities in the ^{1}H NMR spectra are indicated as s (singlet), d (doublet), t (triplet), dt (doublet of triplets), and m (multiplet), Elemental analyses were performed with a Perkin–Elmer 2400 CHN analyzer. The accurate mass electrospray ionization (ESI) mass spectra were measured with a Bruker APEX Qe 4.7T mass spectrometer.

All reactions in nonaqueous media were carried out in flame-dried glassware under argon. Reagents and solvents were handled by using standard syringe techniques. Diethyl ether and toluene were distilled from sodium and benzophenone, dichloromethane and chloroform from P_2O_5, and triethylamine from CaH_2. All starting materials and reagents such as HOBt hydrate (*N*-hydroxybenzotriazole) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) were commercially available research-grade chemicals and used without further purification. Silica gel 60 F_{254} was used for TLC and the spots were detected by UV or with an acidic solution of vainilline in ethanol (4-hydroxy-3-methoxybenzaldehyde/H_2SO_4/EtOH = 2:1:100) or phosphomolybdic acid solution in ethanol (PPM). Flash column chromatography was carried out on silica gel (230–400 ASTM mesh).

The products were identified by IR and NMR analysis and their purity was verified by elemental analysis. The imine **6** is a known compound[7a] and was prepared according the reported procedure. Amines **7** are known compounds and their absolute configurations were established by reference to literature data.[7a]

General Procedure for the Synthesis of *N*-Formylpipecolinamides 4a–h: Amine **9** (1.57 mmol), triethylamine (285 μL, 1.96 mmol), HOBt (300 mg, 1.70 mmol), and EDCI (327 mg, 1.70 mmol) were added to a solution of L-*N*-Boc-pipecolinic acid **8** (300 mg, 1.31 mmol) in dichloromethane (13 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 mL) and the solution was washed with water (20 mL), aqueous HCl (0.5 M, 2 × 20 mL), saturated aqueous $NaHCO_3$ solution (2 × 20 mL), and brine (20 mL), and dried with anhydrous $MgSO_4$. The solvents were removed under reduced pressure to give pure amide (TLC) **5a** and **10b**–**h**.

Compound **10** (1.11 mmol) was dissolved in trifluoroacetic acid (2.15 mL) and stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue was dissolved in formic acid (1.6 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (0.9 mL) was added dropwise and the mixture was stirred at room temperature overnight. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel to give the pure catalyst **4**.

Catalyst 4a: White solid; yield 75%, 217 mg. $[\alpha]_D^{20}$ = –264.2 (c = 1.0, $CHCl_3$); m.p. 38–40 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.38–1.62 (m, 2 H, $NCH_2CH_2CH_2CH_2$), 1.74–1.85 (m, 2 H, $NCH_2CH_2CH_2$), 1.85–2.02 (m, 1 H, $NCH_2CH_2CH_2$), 2.28 (s, 6 H, CH_3), 2.28–2.38 (m, 1 H, $NCHCH_2$), 3.28 (td, $^2J_{H,H}$ = 13.2, $^3J_{H,H}$ = 13.2, 2.8 Hz, 1 H, NCH_2), 3.60 (dd, $^2J_{H,H}$ = 13.2, $^3J_{H,H}$ = 4.7 Hz, 1 H, NCH_2), 5.10 (d, $^3J_{H,H}$ = 5.8 Hz, 1 H, NCH), 6.75 (s, 1 H, CHAr), 7.14 (s, 2 H, CHAr), 8.02 (s, 1 H, NH), 8.18 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.8 ($NCH_2CH_2CH_2$), 21.3 (CH_3), 24.7 ($NCHCH_2$), 25.5 (NCH_2CH_2), 44.5 (NCH_2), 57.5 (NCH), 117.5 (CHAr), 126.0 (CHAr), 137.5 (CAr), 138.7 (CAr), 163.0 (CHO), 168.2 (CONH) ppm. IR (ATR): $\tilde{\nu}$ = 3295, 1659, 1432, 1214, 755 cm^{-1}. $C_{15}H_{20}N_2O_2$ (260.33): calcd. C 69.20, H 7.74, N 10.76; found C 69.44, H 7.41, N 10.71. HRMS (ESI): calcd. for $C_{15}H_{20}N_2O_2$ $[M - H]^+$ 259.14520; found 259.14445.

Catalyst 4b: White solid; yield 80%, 219 mg. $[\alpha]_D^{20}$ = –196.5 (c = 0.3, $CHCl_3$); m.p. 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): major rotamer (73%): δ = 1.22–1.78 (m, 5 H, $NCH_2CH_2CH_2CH_2$), 2.29 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H, $NCHCH_2$), 3.22 (td, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 13.1, 2.9 Hz, 1 H, NCH_2), 3.46 (dd, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 4.5 Hz, 1 H, NCH_2), 4.38 (ABX system, $^2J_{H,H}$ = 14.8, $^3J_{H,H}$ = 5.7 Hz, 1 H, $NHCH_2$), 4.41 (ABX system, $^2J_{H,H}$ = 14.8, $^3J_{H,H}$ = 6.0 Hz, 1 H, $NHCH_2$), 4.96 (d, $^3J_{H,H}$ = 5.7 Hz, 1 H, NCH), 6.75 (s, 1 H, NH), 7.17–7.35 (m, 5 H, CHAr), 7.96 (s, 1 H, CHO) ppm; minor rotamer (27%): δ = 1.22–1.78 (m, 5 H, $NCH_2CH_2CH_2CH_2$), 2.51 (d, $^2J_{H,H}$ = 10.0 Hz, 1 H, $NCHCH_2$), 2.60 (td, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 12.9, 2.9 Hz, 1 H, NCH_2), 4.06 (d, $^3J_{H,H}$ = 3.7 Hz, 1 H, NCH), 4.21 (d, $^2J_{H,H}$ = 12.9 Hz, 1 H, NCH_2), 4.37 (ABX system, $^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 5.6 Hz, 1 H, $NHCH_2$), 4.49 (ABX system, $^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 6.2 Hz, 1 H, $NHCH_2$), 7.17–7.35 (m, 6 H, CHAr, NH), 7.85 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): major rotamer: δ = 20.9 (NCH_2CH_2*), 25.3 ($NCHCH_2$), 25.5 ($NCH_2CH_2CH_2$*), 43.3 ($NHCH_2$), 44.4 (NCH_2), 50.8 (NCH), 127.2, 127.4, 128.5 (CHAr), 138.2 (CAr), 162.4 (CHO), 169.6 (CONH) ppm; minor rotamer: δ = 20.9 (NCH_2CH_2*), 25.3 ($NCHCH_2$), 25.5 ($NCH_2CH_2CH_2$*), 43.3 ($NHCH_2$), 44.4 (NCH_2), 50.8 (NCH), 127.2, 127.4, 128.5 (CHAr), 138.2 (CAr), 162.4 (CHO), 169.6 (CONH) ppm (the assignments marked with an asterisk are interchangeable). IR (ATR): $\tilde{\nu}$ = 3307, 2940, 2861, 1655 cm^{-1}. $C_{14}H_{18}N_2O_2$ (246.30): calcd. C 68.27, H 7.37, N 11.37; found C 68.33, H 7.42, N 11.33. HRMS (ESI): calcd. for $C_{14}H_{18}N_2O_2$ $[M + Na]^+$ 269.12605; found 269.12678.

Catalyst 4c: Colorless oil; yield 81%, 248 mg. $[\alpha]_D^{20}$ = –169.8 (c = 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): major rotamer (72%): δ = 1.25–1.84 (m, 5 H, $NCH_2CH_2CH_2CH_2$), 2.34 (d, $^3J_{H,H}$

= 13.7 Hz, 1 H, NCHCH_2), 3.20 (td, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 13.1, 2.9 Hz, 1 H, NCH_2), 3.53 (dd, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 4.0 Hz, 1 H, NCH_2), 3.80 (s, 3 H, CH_3O), 4.33 (ABX system, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 5.5 Hz, 1 H, NHCH_2), 4.40 (ABX system, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 5.7 Hz, 1 H, NHCH_2), 5.01 (d, $^3J_{H,H}$ = 6.1 Hz, 1 H, NC*H*), 6.25 (s, 1 H, N*H*), 6.86 (AA′XX′ system, $^3J_{H,H}$ = 8.6 Hz, 2 H, C*H*Ar), 7.17 (AA′XX′ system, $^3J_{H,H}$ = 8.6 Hz, 2 H, C*H*Ar), 8.11 (s, 1 H, C*H*O) ppm; minor rotamer (28%): δ = 1.25–1.84 (m, 5 H, NCH$_2$CH_2CH_2CH_2), 2.56–2.59 (m, 1 H, NCHCH_2), 2.61 (td, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 12.9, 3.3 Hz, 1 H, NCH_2), 3.81 (s, 3 H, CH_3O), 4.19 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, NC*H*), 4.30–4.52 (m, 3 H, NCH_2, NHCH_2), 6.31 (s, 1 H, N*H*), 6.87 (AA′XX′ system, $^3J_{H,H}$ = 8.6 Hz, 2 H, C*H*Ar), 7.19 (AA′XX′ system, $^3J_{H,H}$ = 8.6 Hz, 2 H, C*H*Ar), 8.08 (s, 1 H, C*H*O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): major rotamer: δ = 20.9 (NCH$_2$CH$_2$*C*H$_2$), 25.3 (NCH*C*H$_2$), 25.5 (NCH$_2$*C*H$_2$), 42.7 (NH*C*H$_2$), 44.3 (N*C*H$_2$), 50.8 (N*C*H), 55.1 (*C*H$_3$O), 113.8 (*C*HAr), 128.8 (*C*HAr), 130.2 (*C*Ar), 158.7 (*C*HAr), 162.4 (*C*HO), 169.5 (*C*ONH) ppm; minor rotamer: δ = 21.1 (NCH$_2$CH$_2$*C*H$_2$), 24.4 (NCH$_2$*C*H$_2$), 26.7 (NCH*C*H$_2$), 38.4 (N*C*H$_2$), 43.1 (NH*C*H$_2$), 55.1 (*C*H$_3$O), 57.7 (N*C*H), 113.8 (*C*HAr), 129.1 (*C*HAr), 130.3 (*C*Ar), 158.8 (*C*HAr), 162.4 (*C*HO), 169.0 (*C*ONH) ppm. IR (ATR): $\tilde{\nu}$ = 3307, 2926, 2855, 1655, 1513, 1246 cm^{-1}. $C_{15}H_{20}N_2O_3$ (276.33): calcd. C 65.20, H 7.30, N 10.14; found C 65.14, H 7.22, N 10.18. HRMS (ESI): calcd. for $C_{15}H_{20}N_2O_3$ [M – CO + H]$^+$ 249.15975; found 249.15892.

Catalyst 4d: White solid; yield 79%, 246 mg. $[a]_D^{20}$ = –175.0 (*c* = 0.2, $CHCl_3$); m.p. 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): major rotamer (78%): δ = 1.16–1.72 (m, 5 H, NCH$_2$CH_2CH_2CH_2), 2.22 (d, $^2J_{H,H}$ = 13.5 Hz, 1 H, NCHCH_2), 3.15 (td, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 13.1, 2.8 Hz, 1 H, NCH_2), 3.42 (dd, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 4.0 Hz, 1 H, NCH_2), 4.27 (ABX system, $^2J_{H,H}$ = 15.1, $^3J_{H,H}$ = 5.5 Hz, 1 H, NHCH_2), 4.30 (ABX system, $^2J_{H,H}$ = 15.1, $^3J_{H,H}$ = 5.7 Hz, 1 H, NHCH_2), 4.88 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, NC*H*), 6.81 (s, 1 H, N*H*), 7.09 (AA′BB′ system, $^3J_{H,H}$ = 8.5 Hz, 2 H, C*H*Ar*), 7.19 (AA′BB′ system, $^3J_{H,H}$ = 8.5 Hz, 2 H, C*H*Ar*), 7.91 (s, 1 H, C*H*O) ppm (the assignments marked with an asterisk are interchangeable); minor rotamer (22%): δ = 1.16–1.72 (m, 5 H, NCH$_2$CH_2CH_2CH_2), 2.43–2.52 (m, 1 H, NCHCH_2), 2.50 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 13.0, 3.4 Hz, 1 H, NCH_2), 4.06 (d, $^3J_{H,H}$ = 3.2 Hz, 1 H, NC*H*), 4.12 (dd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 3.7 Hz, 1 H, NCH_2), 4.25 (ABX system, $^2J_{H,H}$ = 14.6, $^3J_{H,H}$ = 5.3 Hz, 1 H, NHCH_2), 4.40 (ABX system, $^2J_{H,H}$ = 14.6, $^3J_{H,H}$ = 6.0 Hz, 1 H, NHCH_2), 7.13 (AA′BB′ system, $^3J_{H,H}$ = 9.2 Hz, 2 H, C*H*Ar*), 7.20 (AA′BB′ system, $^3J_{H,H}$ = 9.2 Hz, 2 H, C*H*Ar*), 7.41 (s, 1 H, N*H*), 7.83 (s, 1 H, C*H*O) ppm (the assignments marked with an asterisk are interchangeable). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): major rotamer: δ = 20.9 (NCH$_2$CH$_2$*C*H$_2$), 25.3 (NCH*C*H$_2$), 25.5 (NCH$_2$*C*H$_2$), 42.6 (NH*C*H$_2$), 44.4 (N*C*H$_2$), 50.8 (N*C*H), 128.6, 128.9 (*C*HAr), 133.0 (*C*Ar), 136.8 (*C*Ar), 162.5 (*C*HO), 169.8 (*C*ONH) ppm; minor rotamer: δ = 21.1 (NCH$_2$CH$_2$*C*H$_2$), 24.4 (NCH*C*H$_2$), 26.7 (NCH*C*H$_2$), 38.5 (N*C*H$_2$), 43.0 (NH*C*H$_2$), 57.8 (N*C*H), 128.6, 129.2 (*C*HAr), 133.1 (*C*Ar), 136.9 (*C*Ar), 162.5 (*C*HO), 169.2 (*C*ONH) ppm. IR (ATR): $\tilde{\nu}$ = 3307, 2931, 2859, 1655 cm^{-1}. $C_{14}H_{17}ClN_2O_2$ (280.75): calcd. C 59.89, H 6.10, N 9.98; found C 59.98, H 6.16, N 9.93. HRMS (ESI): calcd. for $C_{14}H_{17}ClN_2O_2$ [M + Na]$^+$ 303.08708; found 303.08695.

Catalyst 4e: Colorless oil; yield 73%, 200 mg. $[a]_D^{20}$ = –99.6 (*c* = 0.26, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): major rotamer (76%): δ = 1.29–1.77 (m, 5 H, NCH$_2$CH_2CH_2CH_2), 2.32 (d, $^3J_{H,H}$ = 11.8 Hz, 1 H, NCHCH_2), 3.27 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 13.0, 2.9 Hz, 1 H, NCH_2), 3.54 (dd, $^3J_{H,H}$ = 13.6, 4.5 Hz, 1 H, NCH_2), 4.57 (d, $^3J_{H,H}$ = 5.6 Hz, 2 H, NHCH_2), 5.04 (d, $^3J_{H,H}$ = 5.1 Hz, 1 H, NC*H*), 7.32 (dd, $^3J_{H,H}$ = 7.8, 5.1 Hz, 1 H, NCHCH_{py}), 7.42 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, NCCH_{py}), 7.70–7.80 (br. s, 1 H, N*H*), 7.81 (td, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.9 Hz, 1 H, NCCHCH_{py}), 8.11 (s, 1 H, C*H*O), 8.53 (dd, $^3J_{H,H}$ = 5.1, $^4J_{H,H}$ = 1.9 Hz, 1 H, NCH_{py}) ppm; minor rotamer (24%): δ = 1.29–1.77 (m, 5 H, NCH$_2$CH_2CH_2CH_2), 2.46 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, NCHCH_2), 2.78 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 13.0, 3.4 Hz, 1 H, NCH_2), 4.23 (d, $^3J_{H,H}$ = 4.9 Hz, 1 H, NC*H*), 4.34 (dd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 3.9 Hz, 1 H, NCH_2), 4.50–4.67 (m, 2 H, NHCH_2), 7.27–7.44 (m, 2 H, NCCH_{py}, NCHCH_{py}), 7.75 (t, $^3J_{H,H}$ = 5.1 Hz, 1 H, NCCHCH_{py}), 8.08 (s, 1 H, C*H*O), 8.53 (dd, $^3J_{H,H}$ = 5.1, $^4J_{H,H}$ = 1.9 Hz, 1 H, NCH_{py}), 11.64 (s, 1 H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): major rotamer: δ = 21.0 (NCH$_2$*C*H$_2$*), 25.4 (NCH$_2$CH$_2$*C*H$_2$*), 25.5 (NCH*C*H$_2$*), 43.3 (NH*C*H$_2$), 44.4 (N*C*H$_2$), 51.0 (N*C*H), 123.1 (NCH*C*H$_{py}$), 123.3 (NC*C*H$_{py}$), 139.1 (NCCH*C*H$_{py}$), 146.9 (N*C*H$_{py}$), 155.6 (*C*$_{py}$), 162.5 (*C*HO), 170.0 (*C*ONH) ppm (the assignments marked with an asterisk are interchangeable); minor rotamer: δ = 21.1 (NCH$_2$*C*H$_2$*), 24.4 (NCH$_2$CH$_2$*C*H$_2$*), 27.0 (NCH*C*H$_2$*), 38.4 (N*C*H$_2$), 43.7 (NH*C*H$_2$), 57.7 (N*C*H), 122.9 (NC*C*H$_{py}$§), 122.9 (NCH*C*H$_{py}$§), 138.5 (NCCH*C*H$_{py}$), 147.5 (N*C*H$_{py}$), 155.4 (*C*$_{py}$), 162.5 (*C*HO), 169.9 (*C*ONH) ppm (the assignments marked with an asterisk and the symbol § are interchangeable). IR (ATR): $\tilde{\nu}$ = 3307, 2931, 2941, 2862, 1660 cm^{-1}. $C_{13}H_{17}N_3O_2$ (247.29): calcd. C 63.14, H 6.93, N 16.99; found C 63.08, H 6.99, N 17.05. HRMS (ESI): calcd. for $C_{13}H_{17}N_3O_2$ [M]$^+$ 247.13210; found 247.13190.

Catalyst 4f: Colorless oil; yield 80%, 231 mg. $[a]_D^{20}$ = –129.9 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): major rotamer (71%): δ = 1.21–1.74 (m, 5 H, NCH$_2$CH_2CH_2CH_2), 2.24 (d, $^3J_{H,H}$ = 13.1 Hz, 1 H, NCHCH_2), 2.70 (ABX$_2$ system, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 7.2 Hz, 1 H, NHCH$_2$CH_2), 2.85 (ABX$_2$ system, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 7.0 Hz, 1 H, NHCH$_2$CH_2), 2.96 (td, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 13.1, 2.6 Hz, 1 H, NCH_2), 3.32–3.40 (m, 1 H, NCH_2), 3.42 (ABX$_3$ system, $^2J_{H,H}$ = 13.4, $^3J_{H,H}$ = 6.6 Hz, 1 H, NHCH_2), 3.55 (ABX$_3$ system, $^2J_{H,H}$ = 13.4, $^3J_{H,H}$ = 6.8 Hz, 1 H, NHCH_2), 4.88 (d, $^3J_{H,H}$ = 5.9 Hz, 1 H, NC*H*), 6.30 (s, 1 H, N*H*), 7.12–7.31 (m, 5 H, C*H*Ar), 7.92 (s, 1 H, C*H*O) ppm; minor rotamer (29%): δ = 1.21–1.74 (m, 5 H, NCH$_2$CH_2CH_2CH_2), 2.37 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 13.0, 3.3 Hz, 1 H, NCH_2), 2.49 (d, $^3J_{H,H}$ = 11.4 Hz, NCHCH_2), 2.71–2.91 (m, 2 H, NHCH$_2$CH_2), 3.32–3.71 (m, 2 H, NHCH_2), 4.03 (d, $^3J_{H,H}$ = 3.7 Hz, 1 H, NC*H*), 4.15 (d, $^3J_{H,H}$ = 13.0 Hz, 1 H, NCH_2), 6.78 (s, 1 H, N*H*), 7.12–7.31 (m, 5 H, C*H*Ar), 7.79 (s, 1 H, C*H*O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): major rotamer: δ = 20.8 (NCH$_2$CH$_2$*C*H$_2$*), 25.1 (NCH*C*H$_2$), 25.5 (NCH$_2$*C*H$_2$*), 35.3 (NHCH$_2$*C*H$_2$), 40.3 (NH*C*H$_2$), 44.1 (N*C*H$_2$), 50.7 (N*C*H), 126.3 (*C*HAr), 128.4 (*C*HAr§), 128.6 (*C*HAr§), 138.6 (*C*Ar), 162.2 (*C*HO), 169.5 (*C*ONH) ppm (the assignments marked with an asterisk and the symbol § are interchangeable); minor rotamer: δ = 20.9 (NCH$_2$*C*H$_2$*), 24.3 (NCH$_2$CH$_2$*C*H$_2$*), 26.6 (NCH*C*H$_2$), 35.1 (NHCH$_2$*C*H$_2$), 38.1 (N*C*H$_2$), 40.6 (NH*C*H$_2$), 57.7 (N*C*H), 126.3 (*C*HAr), 128.4 (*C*HAr§), 128.7 (*C*HAr§), 138.6 (*C*Ar), 162.3 (*C*HO), 169.1 (*C*ONH) ppm (the assignments marked with an asterisk and the symbol § are interchangeable). IR (ATR): $\tilde{\nu}$ = 3325, 2931, 2859, 1656, 1530, 1400 cm^{-1}. $C_{15}H_{20}N_2O_2$ (260.33): calcd. C 69.20, H 7.74, N 10.76; found C 69.27, H 7.79, N 10.84. HRMS (ESI): calcd. for $C_{15}H_{20}N_2O_2$ [M + Na]$^+$ 283.14170; found 283.14145.

Catalyst 4g: Colorless oil; yield 96%, 239 mg. $[a]_D^{20}$ = –41.1 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.34–1.95 (m, 12 H, NCH$_2$CH_2CH_2CH_2CH, NCH$_2$CH_2CH_2CH_2CH$_2$), 3.29–3.66 (m, 5 H, NCH_2, CH_2NCH_2), 3.75 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 2.8 Hz, 1 H, NCH_2), 5.30 (d, $^3J_{H,H}$ = 6.2 Hz, 1 H, NC*H*), 8.04 (s, 1 H, C*H*O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.5 (NCH$_2$*C*H$_2$*), 24.4 (NCH$_2$CH$_2$*C*H$_2$*), 25.6 (NCH*C*H$_2$*), 25.9, 26.3, 26.6 (NCH$_2$*C*H$_2$*C*H$_2$*C*H$_2$CH$_2$), 43.2 (*C*H$_2$NCH$_2$§), 44.4

(N*C*H$_2$), 46.6 (CH$_2$N*C*H$_2$§), 47.3 (N*C*H), 161.7 (*C*HO), 169.1 (*C*ON) ppm (the assignments marked with an asterisk and the symbol § are interchangeable). IR (ATR): $\tilde{\nu}$ = 1645 cm^{-1}. $C_{12}H_{20}N_2O_2$ (224.30): calcd. C 64.26, H 8.99, N 12.49; found C 64.21, H 8.96, N 12.44. HRMS (ESI): calcd. for $C_{12}H_{20}N_2O_2$ [M + Na]$^+$ 247.14170; found 247.14057.

Catalyst 4h: Colorless oil; yield 76%, 191 mg. $[\alpha]_D^{20}$ = –19.6 (*c* = 0.24, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.30–1.93 (m, 6 H, NCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH), 3.40–3.73 (m, 10 H, NC*H*$_2$, NC*H*$_2$C*H*$_2$OC*H*$_2$C*H*$_2$), 5.26 (d, $^3J_{H,H}$ = 6.6 Hz, 1 H, NC*H*), 8.03 (s, 1 H, C*H*O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.3 (NCH$_2$CH$_2$*C*H$_2$), 25.8 (NCH$_2$*C*H$_2$), 26.3 (NCH*C*H$_2$), 42.2 (N*C*H$_2$CH$_2$O*), 44.3 (N*C*H$_2$), 46.1 (N*C*H$_2$CH$_2$O*), 47.0 (NC*H*), 66.5 (*C*H$_2$O§), 66.7 (*C*H$_2$O§), 161.8 (*C*HO), 169.4 (*C*ON) ppm (the assignments marked with an asterisk and the symbol § are interchangeable). IR (ATR): $\tilde{\nu}$ = 3472, 2929, 2857, 1650, 1424 cm^{-1}. $C_{11}H_{18}N_2O_3$ (226.27): calcd. C 58.39, H 8.02, N 12.38; found C 58.33, H 7.90, N 12.44. HRMS (ESI): calcd. for $C_{11}H_{18}N_2O_3$ [M]$^+$ 226.13170; found 226.13250.

Synthesis of Catalysts 5b and 5c from Compound 5a: Compound **5a** (377 mg, 1.13 mmol) was dissolved in trifluoroacetic acid (2.4 mL) and the mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue was dissolved in diethyl ether to give **11** as a white solid (90% yield, 352 mg).

Catalyst 5b: Phenyl chloroformate (37 μL, 0.289 mmol) was added dropwise to a suspension of **11** (100 mg, 0.289 mmol) and $NaHCO_3$ (39 mg, 0.462 mmol) in dry acetonitrile (1.5 mL) at 0 °C and the mixture was stirred at room temperature for 16 h. Then $CHCl_3$ (5 mL) and 5% aq. Na_2SO_4 (2 mL) were added to the reaction mixture and the organic phase was washed with water and dried with anhydrous Na_2SO_4. After removal of the solvent under reduced pressure the residue was purified by column chromatography on silica gel to give the pure amide-carbamate **5b** as a colorless solid (38% yield, 39 mg). $[\alpha]_D^{20}$ = –144.3 (*c* = 0.25, $CHCl_3$); m.p. 72–74 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.52–1.95 (m, 5 H, NCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$), 2.31 (s, 6 H, C*H*$_3$), 2.28–2.52 (m, 1 H, NCHC*H*$_2$), 3.02–3.31 (m, 1 H, NC*H*$_2$), 4.31 (dd, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 3.7 Hz, 1 H, NC*H*$_2$), 4.98 (s, 1 H, NC*H*), 6.78 (s, 1 H, C*H*Ar), 7.17 [s, 2 H, C*H*(NAr)], 7.13–7.23 [m, 2 H, C*H*(NAr)], 7.24 [t, $^3J_{H,H}$ = 7.7 Hz, 1 H, C*H*(OPh)], 7.40 [t, $^3J_{H,H}$ = 7.7 Hz, 2 H, C*H*(OPh)], 8.03 (s, 1 H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.1 (NCH$_2$CH$_2$*C*H$_2$), 21.3 (*C*H$_3$), 24.9 (NCH*C*H$_2$), 25.5 (NCH$_2$*C*H$_2$), 42.9 (N*C*H$_2$), 55.1 (N*C*H), 117.6 [*C*H(NAr)], 121.6 [*C*H(OPh)], 125.6 [*C*H(OPh)], 126.1 [*C*H(NAr)], 129.4 [*C*H(OPh)], 137.4 [*C*(NAr)], 138.7 [*C*(NAr)], 151.1 [*C*(OPh)], 155.7 (N*C*OO), 168.9 (*C*ONH) ppm. IR (ATR): $\tilde{\nu}$ = 3327, 1696, 1203 cm^{-1}. $C_{21}H_{24}N_2O_3$ (352.43): calcd. C 71.57, H 6.86, N 7.95; found C 71.68, H 6.79, N 7.88. HRMS (ESI): calcd. for $C_{21}H_{24}N_2O_3$ [M + Na]$^+$ 375.16791; found 375.16698.

Catalyst 5c: Triethylamine (32 μL, 0.218 mmol) was added to a suspension of **11** (50 mg, 0.145 mmol) in dichloromethane (0.75 mL) and the mixture was stirred for 45 min at room temperature. Then a solution of 3,5-dimethylphenyl isocyanate (21 mg, 0.145 mmol) in dry dichloromethane (0.3 mL) was added dropwise and the reaction mixture was stirred at room temperature for 2 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel to give pure urea-amide **5c** as a colorless solid (58% yield, 32 mg). $[\alpha]_D^{20}$ = –155.7 (*c* = 1.0, $CHCl_3$); m.p. 137–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.41–1.94 (m, 5 H, NCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$), 2.23–2.29 (m, 1 H, NCHC*H*$_2$), 2.27 (s, 3 H, CH$_3$*), 2.29 (s, 3 H, CH$_3$*), 3.23 (td, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 2.1 Hz, 1 H, NC*H*$_2$), 3.71 (dt, $^3J_{H,H}$ = 13.1, 3.4 Hz, 1 H, NC*H*$_2$), 5.05 (d, $^3J_{H,H}$ = 4.9 Hz, 1 H, NC*H*), 6.64 (d, $^3J_{H,H}$ = 3.2 Hz, 1 H, CONH), 6.73 (s, 2 H, C*H*Ar), 7.02 (s, 2 H, C*H*Ar), 7.16 (s, 2 H, C*H*Ar), 8.61 (s, 1 H, NCONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.1 (NCH$_2$CH$_2$*C*H$_2$), 21.26 (*C*H$_3$*), 21.32 (*C*H$_3$*), 24.9 (NCH$_2$*C*H$_2$), 25.3 (NCH*C*H$_2$), 43.6 (N*C*H$_2$), 54.4 (N*C*H), 117.5, 118.2, 125.4, 125.7 (*C*HAr), 137.7, 138.3, 138.5, 138.8 (*C*Ar) 156.6 (N*C*ONH), 170.0 (*C*ONH) ppm (the assignments marked with an asterisk are interchangeable). IR (ATR): $\tilde{\nu}$ = 3308, 1710, 1640, 1614, 1545, 1431, 842, 754 cm^{-1}. $C_{23}H_{29}N_3O_2$ (379.50): calcd. C 72.79, H 7.70, N 11.07; found C 72.71, H 7.65, N 11.11. HRMS (ESI): calcd. for $C_{23}H_{29}N_3O_2$ [M + Na]$^+$ 402.21520; found 402.21386.

Synthesis of Catalysts 5d and 5e from *rac*-1-Formylpiperidin-2-Carboxylic Acid: Acetic anhydride (0.91 mL, 8.13 mmol) was added dropwise to a solution of L-pipecolinic acid (150 mg, 1.16 mmol) in formic acid (1.6 mL) at 0 °C and the reaction mixture was stirred at room temperature overnight. Then it was concentrated under reduced pressure and the residue {$[\alpha]_D^{20}$= 0 (*c* = 0.2, $CHCl_3$)} was used without purification in the following transformation.

Triethylamine (104 μL, 0.72 mmol), compound **11** (99 mg, 0.286 mmol), HOBt (66 mg, 0.372 mmol), and EDCI (72 mg, 0.372 mmol) were added dropwise to a solution of the crude product (45 mg, 0.286 mmol) in dry dichloromethane (2.8 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (25 mL) and the solution was washed with water, aqueous HCl (0.5 M, 2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine (15 mL), and dried with anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:1 v/v) to give two fractions that were identified as **5d** and **5e** from spectroscopic data (60% over yield).

Catalyst 5d: White solid; yield 43%, 46 mg. $[\alpha]_D^{20}$ = –53.7 (*c* = 0.9, $CHCl_3$); m.p. 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.40–2.02 (m, 11 H, CHONCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$, NCH$_2$C*H*$_2$-C*H*$_2$C*H*$_2$), 2.28 (s, 6 H, C*H*$_3$), 2.52 (d, $^3J_{H,H}$ = 13.6 Hz, 1 H, NCHC*H*$_2$), 3.18 (td, $^2J_{H,H}$ = 13.3, $^3J_{H,H}$ = 13.3, 2.5 Hz, 1 H, NC*H*$_2$), 3.50 (dt, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 4.5 Hz, 1 H, CHONC*H*$_2$), 3.76 (dd, $^2J_{H,H}$ = 12.9, $^3J_{H,H}$ = 3.5 Hz, 1 H, CHONC*H*$_2$), 3.82 (dt, $^2J_{H,H}$ = 13.3, $^3J_{H,H}$ = 3.0 Hz, 1 H, NC*H*$_2$), 4.91 (t, $^3J_{H,H}$ = 5.0 Hz, 1 H, CHONC*H*), 5.37 (dt, $^3J_{H,H}$ = 5.6, $^3J_{H,H}$ = $^4J_{H,H}$ = 1.8 Hz, 1 H, NC*H*), 6.72 (s, 2 H, C*H*Ar), 7.30 (s, 1 H, C*H*Ar), 8.13 (s, 1 H, C*H*O), 8.31 (s, 1 H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.5 (NCH$_2$CH$_2$*C*H$_2$), 21.0 (CHONCH$_2$CH$_2$*C*H$_2$), 21.4 (*C*H$_3$), 25.1 (NCH*C*H$_2$), 25.2 (CHONCH$_2$*C*H$_2$), 25.7 (NCH$_2$*C*H$_2$), 26.4 (CHONCH*C*H$_2$), 43.9 (N*C*H$_2$), 44.8 (CHON*C*H$_2$), 50.2 (CHON*C*H), 53.2 (N*C*H), 117.9, 125.8 (*C*HAr), 137.9, 138.3 (*C*Ar), 162.8 (*C*HO), 168.3 (*C*ONH), 171.1 (*C*ON) ppm. IR (ATR): $\tilde{\nu}$ = 3306, 2940, 2859, 1652, 1425 cm^{-1}. $C_{21}H_{29}N_3O_3$ (371.47): calcd. C 67.90, H 7.87, N 11.31; found C 67.82, H 7.85, N 11.26. HRMS (ESI): calcd. for $C_{21}H_{29}N_3O_3$ [M + Na]$^+$ 394.21011; found 394.20896.

Catalyst 5e: Colorless oil; yield 17%, 18 mg. $[\alpha]_D^{20}$ = –185.2 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): major rotamer: δ = 1.38–2.07 (m, 10 H, CHONC*H*$_2$C*H*$_2$C*H*$_2$, NC*H*$_2$C*H*$_2$C*H*$_2$), 2.03 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CHONCHC*H*$_2$), 2.27–2.32 (m, 1 H, NCHC*H*$_2$), 2.29 (s, 6 H, C*H*$_3$), 3.15 (td, $^2J_{H,H}$ = 13.2, $^3J_{H,H}$ = 13.2, 2.4 Hz, 1 H, NC*H*$_2$), 3.52–3.61 (m, 1 H, CHONC*H*$_2$), 3.67 (td, $^2J_{H,H}$ = 12.6, $^3J_{H,H}$ = 12.6, 2.7 Hz, 1 H, CHONC*H*$_2$), 3.78–3.88 (m, 1 H, NC*H*$_2$), 5.22 (d, $^3J_{H,H}$ = 5.9 Hz, 1 H, NC*H*), 5.39 (d, $^3J_{H,H}$ = 6.2 Hz, 1 H, CHONC*H*), 6.75 (s, 1 H, C*H*Ar), 7.12 (s, 2 H, C*H*Ar), 8.04 (s, 1 H, N*H*), 8.11 (s, 1 H, C*H*O) ppm; minor

rotamer: δ = 1.38–2.07 (m, 11 H, CHONCH_2CH_2CH_2, NCH_2CH_2CH_2), 2.30 (s, 6 H, CH_3), 2.56 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H, NCHCH_2), 2.63 (td, $^2J_{H,H}$ = 13.3, $^3J_{H,H}$ = 13.3, 2.8 Hz, 1 H, NCH_2), 3.52–3.61 (m, 1 H, CHONCH_2), 3.78–3.88 (m, 1 H, CHONCH_2), 4.58–4.64 (m, 1 H, NCH_2), 4.63 (d, $^3J_{H,H}$ = 4.2 Hz, 1 H, NCH), 5.08 (dd, $^3J_{H,H}$ = 5.9, 2.2 Hz, 1 H, CHONCH), 6.75 (s, 1 H, CHAr), 7.37 (s, 2 H, CHAr), 8.09 (s, 1 H, CHO), 8.82 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): major rotamer: δ = 20.2 (NCH$_2$CH$_2$CH_2), 20.5 (CHONCH$_2$CH$_2$CH_2), 21.3 (CH_3), 25.0 (NCH$_2$CH_2), 25.3 (NCHCH$_2$), 25.88 (CHONCHCH$_2$), 25.94 (CHONCH$_2$CH_2), 43.8 (NCH$_2$), 44.5 (CHONCH_2), 48.1 (CHONCH), 53.2 (NCH), 117.4, 125.9 (CHAr), 137.6, 138.7 (CAr), 161.6 (CHO), 168.9 (CONH), 171.9 (CON) ppm; minor rotamer: δ = 19.9 (CHONCH$_2$CH$_2$CH_2), 20.6 (NCH$_2$CH$_2$CH_2), 21.4 (CH_3), 24.6 (CHONCH$_2$CH_2), 24.9 (NCH$_2$CH_2), 25.6 (CHONCHCH$_2$), 26.8 (NCHCH$_2$), 39.9 (NCH_2), 44.0 (CHONCH_2), 48.4 (CHONCH), 57.1 (NCH), 126.0, 126.0 (CHAr), 137.9, 138.4 (CAr), 163.5 (CHO), 167.3 (CONH), 170.2 (CON) ppm. IR (ATR): $\tilde{\nu}$ = 3352, 2931, 2857, 1656, 1643 cm^{-1}. $C_{21}H_{29}N_3O_3$ (371.47): calcd. C 67.90, H 7.87, N 11.31; found C 67.80, H 7.82, N 11.33. HRMS (ESI): calcd. for $C_{21}H_{29}N_3O_3$ [M + Na]$^+$ 394.21011; found 394.20555.

General Procedure for the Catalytic Hydrosilylation of Ketimine 6: Trichlorosilane (154 μL, 1.5 mmol) was added dropwise to a stirred solution of ketimine **6** (1 mmol) and the catalyst (0.1 mmol) in anhydrous solvent (Tables 1–3) at –20 °C (or at –40 °C; see Table 1) and the mixture was stirred for 24 h under argon. The reaction was quenched with a saturated solution of $NaHCO_3$ (20 mL) and the product **7** was extracted with ethyl acetate (3 × 70 mL). The extract was washed with brine, dried with anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. The yields and *ee*s are given in Tables 1–3.

Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.54 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3), 4.09 (s, 1 H, NH), 4.54 (q, $^3J_{H,H}$ = 6.8 Hz, 1 H, CH), 6.48 (dd, $^3J_{H,H}$ = 8.5, $^4J_{H,H}$ = 1.0 Hz, 2 H, CHAr), 6.68 (tt, $^3J_{H,H}$ = 7.4, $^4J_{H,H}$ = 1.0 Hz, 1 H, CHAr), 7.11 (dd, $^3J_{H,H}$ = 8.5, 7.4 Hz, 2 H, CHAr), 7.50 (AA′XX′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, CHAr), 7.59 (AA′XX′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.0 (CH_3), 53.3 (CH), 117.7 (CHAr), 118.6 (c, $^1J_{C,F}$ = 248.0 Hz, CF_3), 125.7 (d, $^3J_{C,F}$ = 3.8 Hz, CHAr), 126.2 (CHAr), 129.2 (CHAr), 133.3 (CAr), 138.1 (c, $^2J_{C,F}$ = 29.8 Hz, CAr), 142.4 (CAr), 146.8 (CAr) ppm in agreement with the literature data.[7a] IR (ATR): $\tilde{\nu}$ = 3408, 1236, 1162, 750, 694 cm^{-1}. $C_{15}H_{14}F_3N$ (265.27): calcd. C 67.91, H 5.32, N 5.28; found C 67.80, H 5.41, N 5.33. Chiral GC-CYCLODEX-B (30 m × 0.252 mm × 0.25 μm); temperature: 125 °C for 2 min, then 1 °C/min to 200 °C: t_{imine} = 32.4 min, t_S = 35.7 min, t_R = 36.0 min.

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