The First Catalytic Highly Enantioselective Alkylation of Ketimines—A Novel Approach to Optically Active Quaternary α-Amino Acids

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Abstract: A series of novel ketimines with intrinsic protecting group anchoring was synthesized and allowed to react with various silylketene acetals in the presence of 5–10 mol% of a chiral $Zn(OTf)_2$-(*R,R*)-Ph-pybox-aqua complex. The corresponding optically active quaternary α-amino acid derivatives were obtained in high yields and with enantioselectivities ranging from 34% up to 95% *ee*. The catalyst was studied by ^1H NMR spectroscopy and X-ray crystallography, and a dynamic equilibrium of two species was identified in solution. These are a homochiral 1:2 metal–ligand complex and a 1:1 metal–ligand complex, of which the latter is expected to be the actual catalyst of the diastereo- and enantioselective reaction. A strong positive nonlinear effect was observed due to the formation of a catalytically inactive 1:2 metal–ligand hetero-chiral complex. On the basis of DFT calculations and the absolute stereochemistry of the products, simultaneous coordination of the imino electrophile and a single molecule of H_2O to the chiral Lewis acid complex is proposed. Coordination of the imine-nitrogen atom in the axial position of an octahedral complex can account for the facial selectivity as well as the diastereoselectivity observed.

Keywords: α-amino acids · alkylation · asymmetric catalysis · zinc

Introduction

The construction of a quaternary chiral carbon center by a catalytic enantioselective process is a difficult and challenging task in synthetic organic chemistry.[1] In particular, the asymmetric synthesis of quaternary α-amino acid derivatives has recently attracted considerable attention.[2] Some quaternary α-amino acids are naturally occurring or are structural components of natural products that have interesting biological properties such as antibiotics.[3] As a result of the tetrasubstituted asymmetric carbon atom, the stereogenic center is considerably more stable than that in α-amino acid derivatives with α-protons. Problems of metabolic degradation of, for example, peptidomimetics may thereby be avoided. Moreover, α,α-disubstituted α-amino acids exert a remarkable influence on the conformation of peptides, into which they are incorporated.[4] By preorganizing the optimum conformation for binding of a given receptor, significant enhancement of biological activity can be expected. Finally, non-natural α-aryl-α-alkyl-α-amino acid derivatives have shown strong inhibitory effects on aldose reductases and various other enzymes.[5]

Only a few catalytic processes for the synthesis of optically active quaternary α-amino acids have been developed, such as the organocatalyzed Steglich rearrangement,[6] palladium- and molybdenum-catalyzed allylic substitution using prochiral aza-nucleophiles,[7] cyanation reactions of ketimines,[8] as well as aldol reactions of α-isocyanocarboxylates.[9] Despite the fact that electron-deficient α-ketimino esters would constitute an elegant precursor of quaternary α-amino acids, the catalytic enantioselective alkylation of such compounds has to the best of our knowledge not been reported. Asymmetric Lewis acid catalysis using aldimines derived from glyoxylic aldehydes as electrophiles has been used in various C–C bond-forming reactions to afford optically active tertiary α-amino acid derivatives.[10] However, a specific catalytic system cannot unambiguously be expanded to include ketimines for the following reasons: i) imines bearing α-protons are susceptible to form enamines in the presence of Brønsted or Lewis acids, ii) the equilibrium of the flexible imine double bond is often shifted towards the *Z* isomer and thereby render difficult a constrained and rigid bidentate coordination to a Lewis acid complex (Scheme 1), iii) a characteristic and fundamental problem re-

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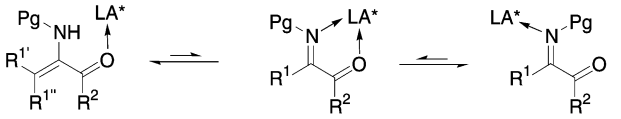
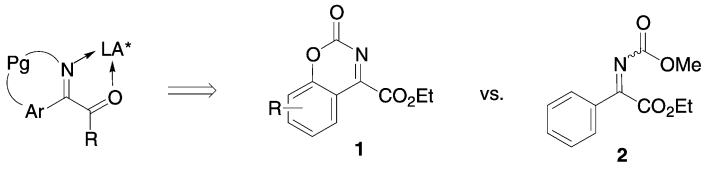


Scheme 1. Isomerization of imines derived from α-dicarbonyl compounds.

lated to the use of ketimine substrates is steric hindrance. The disubstituted carbon atom of a prochiral imine double bond is much less reactive than the carbon atom of the C=N double bond in aldimines, due to steric repulsions during the C–C bond formation. Herein we present the development of the first Lewis acid catalyzed enantioselective alkylation of imines derived from ketones.

Results and Discussion

Concept and synthesis of ketimine substrates: Motivated by the aforementioned facts, we decided to undertake the synthesis of a series of ketimines, with *intrinsic protective group anchoring*, illustrated by the general concept outlined in Scheme 2. By anchoring the nitrogen protecting group by

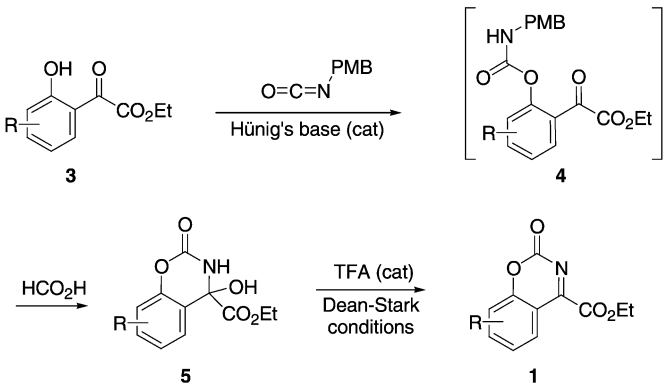


Scheme 2. The concept of *intrinsic protecting group anchoring*.

means of an aryl substituent, the degree of rotational freedom, as well as possible imine double bond isomerization, is minimized, rendering a beneficial preorganized structure for bidentate Lewis acid activation. Moreover, the problem of enamine formation is also circumvented. The general imine architecture **1** was envisioned as a promising substrate candidate because the intrinsically bound carbamate protecting group would effect a highly electron-deficient imine double bond and concurrently serve as a readily removable moiety in the accompanying products (see below).

The general synthesis of novel ketimine electrophiles **1a–f** is presented in Scheme 3. Reaction of acylated phenols **3** (see Supporting Information) with *p*-methoxybenzyl isocyanate in the presence of a catalytic amount of Hünig's base affords the intermediate **4** in high yields. Depending on the substitution pattern of the aromatic nucleus, the intermediate spontaneously, or upon dissolution in formic acid, cyclizes to the imine hydrates **5**. Finally, dehydration under Dean–Stark conditions in the presence of a catalytic amount of trifluoroacetic acid (TFA) yields the ketimines **1** in quantitative yields.

Imine **1a** (R = H) reacted in a number of different C–C bond-forming processes such as allylation, Friedel–Crafts-, Diels–Alder-, ene-, aza-Henry- and Mannich-type reactions catalyzed by Lewis acids such as $Cu(OTf)_2$, $CuPF_6$,



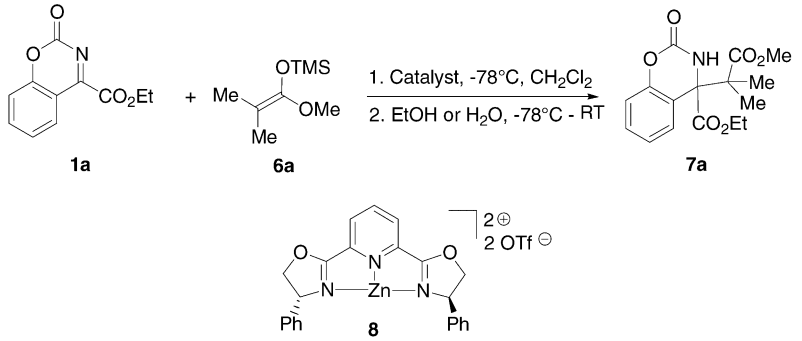
Scheme 3. Synthesis of ketimines **1**.

$Zn(OTf)_2$, $Sc(OTf)_2$, $Sn(OTf)_2$, and $Ni(ClO_4)_2$. In comparison, verifying the potency of the concept "*intrinsic protecting group anchoring*," imine **2** (non-anchored protecting group) was found to be unreactive when similar nucleophiles and reaction conditions were employed. Further studies of the reactivity of ketimine **1a** were focused on the Mannich reaction, which is one of the most widely utilized chemical transformations for the synthesis of nitrogen-containing compounds.[11] Herein we report the development of the first catalytic enantioselective Mannich reaction of imines derived from ketones, which provides a direct access to optically active quaternary α- and β-amino acid derivatives.[10a–d,12]

Catalyst optimization: An extensive catalyst screening program revealed that a complex of $Zn(OTf)_2$ and (*R,R*)-Ph-pybox[13] was a promising catalyst for the reaction between imine **1a** and ketene acetal **6a** (100% yield, 72% *ee*) [Eq. (1); Table 1, entry 3].[14] The presence of a catalytic amount of H_2O proved to be essential to obtain a consistently high reactivity and enantioselectivity of the catalyst. Employing 10 mol% of the (*R,R*)-Ph-pybox-$Zn(OTf)_2$ catalyst **8** in the presence of 5 mol% H_2O, the Mannich base **7a** was isolated in 97% yield with 80% *ee* (Table 1, entry 4). The enantioselectivity was significantly improved from 80% to 95% *ee* by slowly adding **6a** to a solution of **1a** and the catalyst, as well as by adding a stoichiometric amount of H_2O relative to $Zn(OTf)_2$ (Table 1, entries 5 and 6). At the present stage we believe that product–catalyst dissociation is the rate-determining step of the catalytic cycle,[15] and that by slow addition of one of the reaction components a racemic background reaction catalyzed by transient silyl species is avoided.[16] Interestingly, by performing the reaction under strictly dry conditions and with slow addition of the nucleophile, the reactivity of the catalytic system is reduced and a substantial drop in enantioselectivity is observed (Table 1, entry 8 versus entry 3). Finally, imine **1a** underwent a clean reaction with **6a** in the presence of only 5 mol% catalyst without compromising the yield and enantioselectivity significantly (98% yield, 93% *ee*) (Table 1, entry 9).

Reaction scope: With the optimized reaction conditions in hand, a number of silylketene acetals were tested as sub-

Table 1. Results for the catalytic asymmetric Mannich reaction of **1a** with silylketene acetal **6a**.



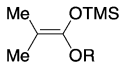
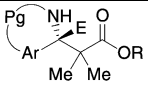
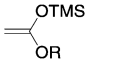
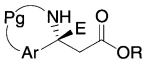
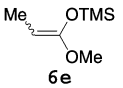
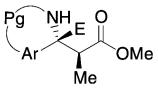
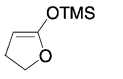
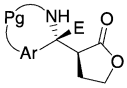
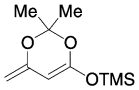
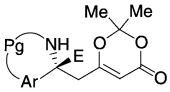
(1)

Entry	Catalyst	[mol %]	Additive [mol %]	Time [h]	Yield[a] [%]	*ee*[b] [%]	Config.
1	–	–	–	20[c]	5	–	
2	$Zn(OTf)_2$	10	–	20[c]	60	–	
3	**8**	10	–	20[c]	100	72	(*S*)
4	**8**	10	H_2O/5	20[c]	97	80	(*S*)
5[d]	**8**	10	H_2O/5	2.5	100	94	(*S*)
6[d]	**8**	10	H_2O/10	2.5	100	95	(*S*)
7[d]	**8**	10	H_2O/20	2.5	83[e]	84	(*S*)
8[d]	**8**	10	–	2.5	58	15	(*S*)
9[d]	**8**	5	H_2O/5	4.0	98	93	(*S*)

[a] Yield of isolated product. [b] *ee* determined by chiral HPLC. [c] Arbitrary reaction time. [d] Dropwise addition of **6a** over the course of 2 h. [e] 16% of hydrated imine was detected by HPLC.

strates for the Mannich reaction with ketimine **1a** and the results are presented in Table 2. The two silylketene acetals **6a**,**b** both underwent a highly enantioselective reaction with **1a**, and the Mannich adducts were obtained with excellent enantiomeric excesses of 95% and 94%, respectively. Both the ethyl and phenyl acetate derived silylketene acetals **6c**,**d** reacted smoothly, affording the product **7c**,**d** in high yields and with 95% and 92% *ee*, respectively. α-Mono-substituted substrates may also be employed as for example, the isomeric mixture of (*E*)- and (*Z*)-propionate-derived silylketene acetal **6e** provided the Mannich product **7e** in quantitative yield, with high diastereoselectivity and enantioselectivity (*syn*/*anti* (1:8.3), *anti*: 93% *ee*). The geometrically restricted butyrolactone-derived silylketene acetal **6f** afforded Mannich base **7f** in quantitative yield with a high enantioselectivity of 95% *ee*, although with moderate diastereoselectivity (*syn*/*anti* (1:4.6)). Finally, the generality of the reaction was demonstrated by the reaction of **1a** with dioxolinone derivative **6g** (quantitative yield, 88% *ee*). The latter result is interesting from a mechanistic point of view; the observed similar high level of enantioselectivity compared with the results obtained with nonconjugated silylketene acetals indicates an open transition state with linear approach of the nucleophile as simultaneous C–C bond formation and silyl transfer of the TMS group of **6g** to the imine-nitrogen atom is most unlikely. A detailed discussion of the reaction mechanism follows in the next section.

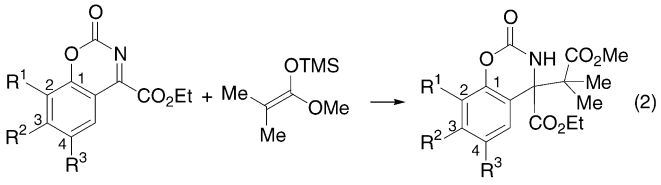
Table 2. Reactions of various silylketene acetals and conjugated dienes (**6a–g**) with ketimine **1a** under optimized reaction conditions.[a]

Nucleophile	Product	Yield[b]	d.r.[c]	*ee*[d]
				
6a R = Me	**7a**,**b**	> 99	–	95
6b R = Et		79	–	94
				
6c R = Et	**7c**,**d**	> 99	–	95
6d R = Ph		90	–	92
				
6e E/Z 73:27	*anti*-**7e**	> 99[e]	1:8.3	52/93
				
6f	*anti*-**7f**	> 99[e]	1:4.6	85/95
				
6g	**7g**	> 99	–	88

[a] 10 mol% $Zn(OTf)_2 \cdot H_2O$, 11 mol% (*R*,*R*)-Ph-pybox, CH_2Cl_2, −78°C, 2.5 h, slow addition of nucleophile to a solution of imine **1a** and catalyst. E = CO_2Et. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy of the crude product mixture. [d] *ee* determined by chiral HPLC (see Supporting Information for details). [e] Combined yield of the two diastereomers.

Finally, a representative selection of substituted ketimines, conforming to the principle of *intrinsic protecting group anchoring*, were synthesized and evaluated as substrates in the present Lewis acid catalyzed asymmetric Mannich reaction. The reactions with silylketene acetal **6a** were carried out under the optimized reaction conditions with either 2.0 or 4.0 h slow addition of the nucleophile depending on the exact substitution patters of the imino electrophile. The results are presented in Table 3 [Eq. (2)]. Imines substituted with electron-donating methyl- or methoxy-groups in the 4-position of the aromatic nucleus underwent a clean reaction with **6a** affording the corresponding Mannich products **7h**,**i** in high yields and with optical purities of 84% and 93% *ee*, respectively (Table 3, entries 2 and 3). Imines with electron-withdrawing substituents such as fluorine and chlorine in the 4-position were also employed as substrates and gave the Mannich adducts **7j**,**k** in high yields (86% and > 99%) and with enantioselectivities of 89% and 93% *ee*, respectively (Table 3, entries 4 and 5). A clean reaction of imine **1f** (3-methoxy) with silylketene acetal **6a** was also observed, however, the optical purity of the corresponding product **7l** dropped to 34% *ee* (Table 3, entry 6). The dramatic impact on the enantioselectivity of substitu-

Table 3. Results for the catalytic asymmetric Mannich reaction of ketimines **1a–g** with silylketene acetal **6a**.[a]



1a-g **6a** **7a,h-m**

Entry	Imine	R^1	R^2	R^3	Product	Yield[b][%]	*ee*[c][%]
1[d]	**1a**	H	H	H	**7a**	>99	95
2[e]	**1b**	H	H	Me	**7h**	>99	84
3[e]	**1c**	H	H	OMe	**7i**	93	91
4[d]	**1d**	H	H	F	**7j**	86	89
5[d]	**1e**	H	H	Cl	**7k**	>99	93
6[e]	**1f**	H	OMe	H	**7l**	>99	34
7[e]	**1g**		$-C_4H_4-$		**7m**	93	80

[a] 10 mol% $Zn(OTf)_2 \cdot H_2O$, 11 mol% (*R,R*)-Ph-pybox, CH_2Cl_2, −78°C. [b] Yield of isolated product. [c] *ee* determined by chiral HPLC. [d] Slow addition of nucleophile to a solution of ketimine and catalyst over the course of 2.0 h. [e] Slow addition of nucleophile to a solution of ketimine and catalyst over the course of 4.0 h.

tion in the 3-position is most likely an electronic effect as the reaction of imine **1g** derived from 1-naphthol provided the Mannich base **7m** in 93% yield and with a good enantioselectivity of 80% *ee*.

Reaction mechanism: To understand the nature of the catalyst, a systematic ^1H NMR study was undertaken (Figure 1). Figure 1a-A shows the ^1H NMR spectrum of (*R,R*)-Ph-pybox **9** dissolved in CD_2Cl_2 with the resonance region around H_a expanded. When $Zn(OTf)_2$ and (*R,R*)-Ph-pybox (1.1 equiv) were dissolved in CD_2Cl_2, two distinct complexes could be detected in a ratio of 1:1.6, and ES-MS analysis of the NMR sample identified the two structures **8** and **10** (Figure 1a-B; see Supporting Information). Furthermore, the addition of TBME to a catalyst solution (1:1.1, Zn/ligand) in CH_2Cl_2 gave suitable crystals for X-ray analysis, from which the structure of the major species was assigned as **10** (Figure 1b).[17] The ^1H NMR spectrum of the crystalline precipitate **10** corresponded to the major species in the catalyst solution. In the ^1H NMR spectrum recorded after mixing $Zn(OTf)_2$ and two equivalents of (*R,R*)-Ph-pybox in CD_2Cl_2, only resonance signals corresponding to the homochiral $Zn(OTf)_2$-((*R,R*)-Ph-pybox)$_2$ complex **10** were observed (Figure 1a-C). Finally, addition of 2.6 equivalents of ligand relative to the $Zn(OTf)_2$ present, led to the reappearance of resonance signals corresponding to free (*R,R*)-Ph-pybox in the ^1H NMR spectrum (Figure 1a-D).

It has been found that the ratio between **8** and **10** is a dynamic equilibrium, sensitive to the exact reaction conditions [Eq. (3); Table 4]. The use of a polar and coordinating solvent stabilized the Lewis acidic complex **8** and consequently the equilibrium constant *K* was changed from 1.6 in CH_2Cl_2 to 1.1 in for example, MeCN (Table 4, entry 2 versus entry 1). Addition of 10 equivalents of imine **1a**, which resembles the initial conditions of a catalytic reaction, did not significantly change the equilibrium, but interestingly, a sub-

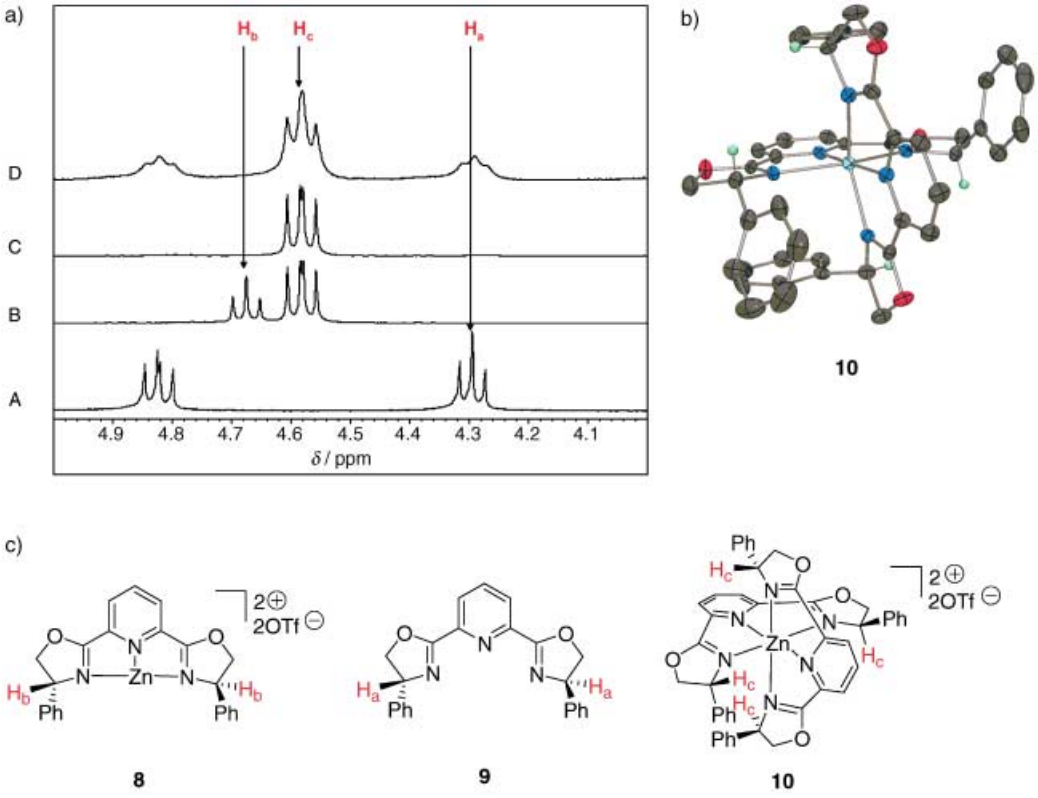


Figure 1. a) ^1H NMR studies of Zn^{II}-(*R,R*)-Ph-pybox complexes. A: (*R,R*)-Ph-pybox; B: $Zn(OTf)_2$/(*R,R*)-Ph-pybox (1:1.1); C: $Zn(OTf)_2$/(*R,R*)-Ph-pybox (1:2.0); D: $Zn(OTf)_2$/(*R,R*)-Ph-pybox (1:2.6). b) The X-ray structure of **10**, and c) the structures **8–10** assigned in the ^1H NMR spectra; see text for details.

stantial stabilization of **8** was effected by the addition of one equivalent of H_2O or HFIP to the catalyst solution (Table 4, entries 4 and 5). In this context, it should be noted that the octahedral homo-chiral $Zn(OTf)_2$-((*R,R*)-Ph-pybox)$_2$ complex **10** showed low catalytic activity affording racemic products.

The dramatic effect of additives on the ratio between the two zinc–pybox complexes indicated that the stoichiometry of ligand and $Zn(OTf)_2$ might be important for the outcome of the catalytic enantioselective Mannich reaction. However, the optimal ratio cannot unambiguously be calculated on the basis of numerical values such as those presented in Table 4 due to the formation of strongly Lewis basic intermediates and changing concentrations of reaction components as the reaction proceeds. A series of catalysts prepared with different ratios of $Zn(OTf)_2$ and (*R*)-Ph-pybox was evaluated for its catalytic and enantioselective properties in the model reaction of imine **1a** with **6a** under dry as well as "wet" reaction conditions. The results are presented in Figure 2. Under dry reaction conditions the best result in terms of both yield and enantioselectivity was obtained by applying a catalyst prepared from $Zn(OTf)_2$ and (*R,R*)-Ph-pybox in the ratio 1:1.1. The Mannich product was formed

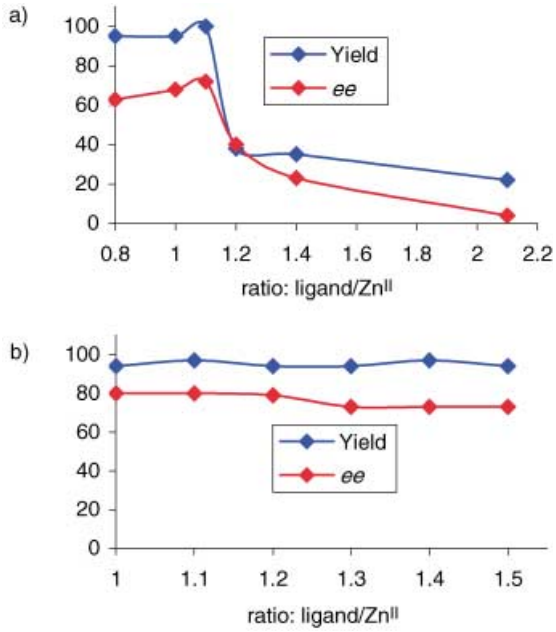
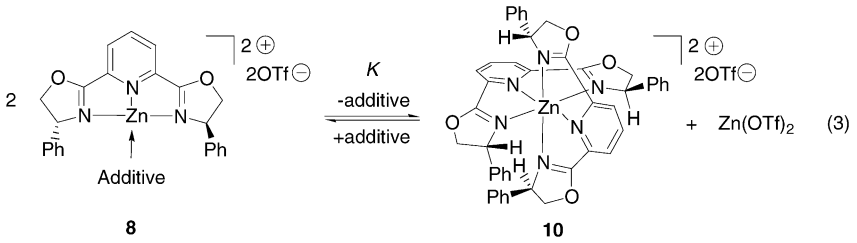


Figure 2. Reactions of imine **1a** with silylketene acetal **6a** under strictly dry conditions (a) and in the presence of 5 mol% H_2O (b).

Table 4. Effect of additives on the ration between **8** and **10**.



8 **10**

Entry	Solvent	Additive	Equiv (rel. to Zn)	*K*
1	CH_3CN	none	–	1.1
2	CH_2Cl_2	none	–	1.6
3	CH_2Cl_2	imine	10	1.4
4	CH_2Cl_2	H_2O	1	1.0
5	CH_2Cl_2	HFIP	1	0.5

in quantitative yield with 72% *ee*. Increasing the amount of ligand caused a rapid drop in both yield and enantioselectivity (Figure 2a). Notably, the shape of the two curves is almost identical, which implies that the most active complex in solution also possesses good enantioseletive properties. Clearly, the addition of H_2O resulted in a consistently highly reactive catalyst and the level of enantioselectivety was also improved. Moreover, the impact of Lewis acid/ligand ratio on the outcome of the reaction was also strongly minimized as both the yields and enantioselectivities were almost identical at values ranging from 1.0 up to 1.5 (Figure 2b).

In conclusion, complex **8** is believed to be the actual catalyst of the present enantioselective Mannich reaction with H_2O most likely associated to the Zn^{II} center of the chiral Lewis acid complex.

The phenomena of nonlinear effects (NLE) in the field of asymmetric catalysis has attracted much attention, in particular as an informative tool for mechanistic investigations.[18] In light of the identified homo-chiral $Zn(OTf)_2$-((*R,R*)-Ph-pybox)$_2$ complex **10** (vide supra), a series of experiments was performed to determine whether NLE were operating in the present study. Mannich reactions of ketimine **1a** and silylketene acetal **6a** were carried out in the presence of Lewis acid complexes prepared from $Zn(OTf)_2$ and Ph-pybox with optical purities ranging from 0–100% *ee*.[19] A strong chiral amplification was observed; for example, employment of a catalyst of 30% *ee* afforded the Mannich product in high yield (>90%) with 90% *ee* (Figure 3a). To identify 1:2 metal–ligand complexes, a solution of $Zn(OTf)_2$, (*R,R*)-Ph-pybox, and (*S,S*)-Ph-pybox (1:0.55:0.55) in CD_2Cl_2 was analyzed by ^1H NMR spectroscopy. Resonance signals corresponding to a single metal–ligand species were observed. The structure was assigned by X-ray crystal structure analysis as the hetero-chiral complex of one zinc atom coordinating two pybox-ligands (**11**, Figure 3b).[20] The 1:2 metal–ligand complex is almost insoluble in organic solvents and is therefore expected to serve as a catalytically inactive reservoir of the minor enantiomer of the chiral ligand. Notably, depending on the choice of metal cation and the substitution pattern of the pybox ligand, diastereomeric mixtures of 1:2 metal–pybox complexes have been observed.[21] The stoichiometry of ligand and Lewis acid employed in the present catalytic reaction (1:1.1) eventually implies that unligated

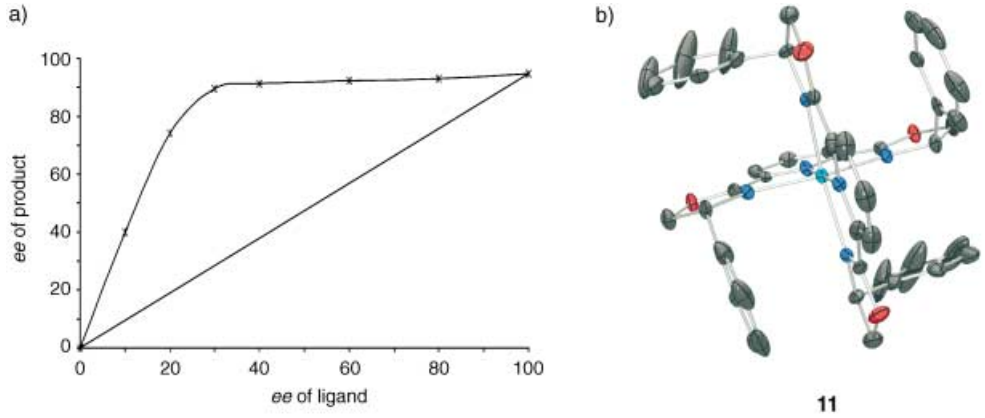


Figure 3. a) Nonlinear effects in the reaction of **1a** with **6a** catalyzed by Lewis acid complexes prepared from $Zn(OTf)_2 \cdot H_2O$ (10 mol %) and Ph-pybox (11 mol %). The silylketene acetal is added dropwise over the course of 2.0 h. b) The X-ray structure of **11**.

$Zn(OTf)_2$ is present as the reaction proceeds. However, the Lewis acidity of $Zn(OTf)_2$ is most likely significantly reduced by the coordination of the added H_2O during the catalyst preparation as well as the coordination of intermediate Lewis basic reaction products.[22]

Enantioselectivity: The experimental observations (vide supra) obtained during the catalyst optimization and mechanistic studies seem to indicate that both the imine and a single molecule of H_2O simultaneously coordinate to the catalyst in the transition state. The geometries of the two proposed intermediates **12a** and **12b** (Figure 4) were optimized by using DFT calculations.[23]

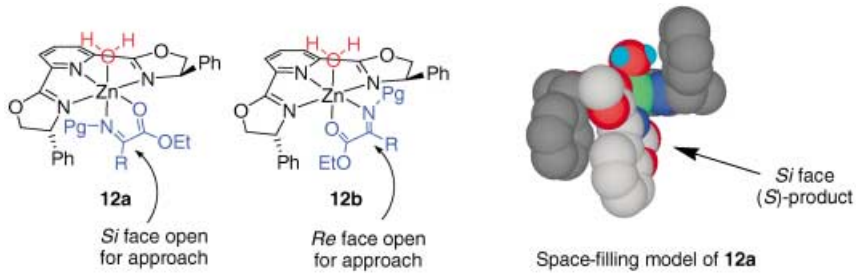


Figure 4. Substrate–catalyst coordination.

In both cases, the chiral zinc(II) complex effectively discriminates the two faces of the ketimine substrate. The sense of induction predicted by **12a** and **12b** is opposite ((*S*) versus (*R*), respectively) and interestingly, the energies of the two intermediates differ by only 0.3 kcal mol^{-1} in favor of **12a**. However, a closer examination of the optimized geometries revealed a stronger coordination of the imine-nitrogen atom when coordinating the axial site of the chiral Lewis acid complex (**12a**). The bond length between the metal center and the imine-nitrogen atom is 0.10 Å shorter than when the imine-nitrogen atom coordinates the catalyst in the ligand plane (**12b**). Finally, the exposed *Si* face of the imine shown in **12a** is considerably less hindered for approach of the nucleophile than the open *Re* face of **12b**. In conclusion, despite the calculated small energy difference of the two complexes, the mode of coordination outlined in **12a** is considered the most likely geometry, which also can account for the sense of absolute configuration observed experimentally (see below).

Diastereoselectivity: The diastereoselectivity observed in the reaction of imine **1a** with silylketene acetals **6e** and **6f** can be rationalized by an attack of the nucleophile on the proposed imine–zinc(II) complex **12a** through an open transition state. Of the three possible transition states that lead to the observed relative stereochemistry, the linear antiperiplanar approach **13** (Figure 5) has the fewest destabilizing substrate–substrate *gauche* interactions and the smallest substrate–catalyst steric interaction. The smallest substituent (H) of the nucleophile orients towards the phenyl group of the chiral ligand, the medium-sized substituent (R^2) overlaps the aryl moiety of the imine, and finally the largest moiety of the nucleophile points away from the crowded reaction site. It is proposed that the difference in diastereoselectivity observed for the two substrates **6e** and **6f** (1:8 versus 1:5) can be

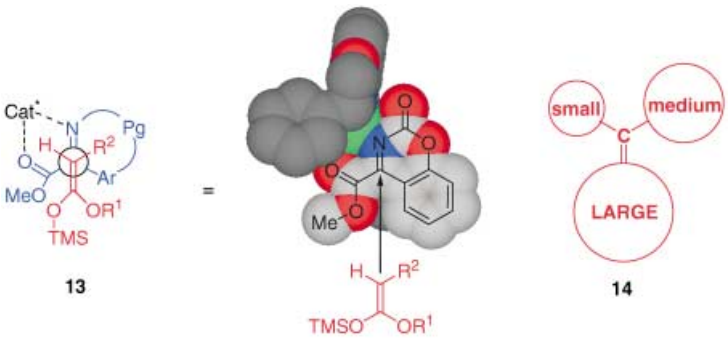
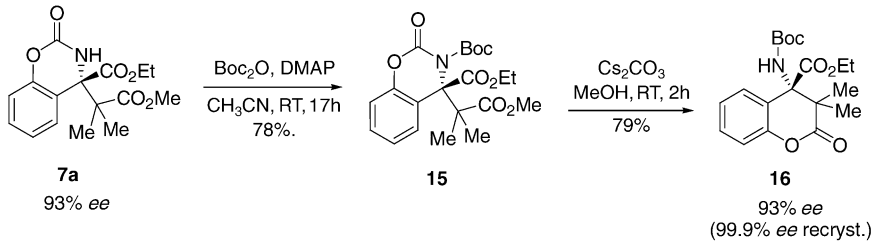


Figure 5. Model for diastereoselective approach of silylketene acetal.

explained by the general substrate architecture **14**. A substantial size differentiation of the substituents of the silylketene acetal may be necessary to obtain high diastereoselectivity.

Product modifications: A selective *N*-protecting group adjustment leading to optically active lactones is presented in Scheme 4. *tert*-Butyloxycarbonyl(Boc) protection of Mannich base **7a** facilitated basic solvolysis of the phenoxy carbamate structure **15**, and subsequent spontaneous cyclization of the resulting phenol afforded lactone **16** in high yield.[24] The absolute stereochemistry of **7a** was determined by X-ray analysis of an *N*-trichloroacetyl derivative of **16** (compound **17**, see Supporting Information).



Scheme 4. Synthesis of optically pure lactone from Mannich adduct **7a**.

Conclusion

In conclusion, we have demonstrated that a novel complex of $Zn(OTf)_2 \cdot H_2O$ and the commercially available (*R,R*)-Phpybox ligand catalyzes the first highly enantioselective alkylation of ketimines. By introduction of the concept of *intrinsic protecting group anchoring,* several imines and silylketene acetals have successfully been employed as substrates affording optically active quaternary α-amino acid derivatives in excellent yields and with high enantioselectivities. The nature of the catalyst system has been studied by X-ray analysis, ^{1}H NMR spectroscopy, and mass spectrometry, as well as NLE experiments. Finally, on the basis of DFT calculations and the determined absolute configuration of the products, a simultaneous coordination of the imino electrophile and a single molecule of H_2O to the chiral Lewis acid catalyst is proposed. The optimized intermediate can account for both the enantioselectivity as well as the diastereoselectivity experimentally observed. Experiments are currently in progress to establish the generality of the novel catalyst and the concept of *intrinsic protecting group anchoring* in other C–C bond-forming reactions.[25]

Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield from TMS ($\delta = 0$ ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$ ppm) for ^{13}C NMR. Solvents were dried according to standard procedures. Flash chromatography (FC) was carried out using the FlashMaster II from Jones Chromatography with columns containing Merck silica gel 60 (230–400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by HPLC using Daciel Chiralcel OJ/OD or Daicel Chiralpak AD/AS columns with *i*PrOH/hexane as the eluent system.

Materials: Imine **2** was prepared according to the literature procedure.[26] Silylketene acetals **6a** and **6e** were purchased from Aldrich and TCI, respectively, and used as received. Silylketene acetals **6b**,[27] **6c**,[28] **6d**,[29] **6f**[30] and **6g**[31] were prepared according to literature procedures. 4-Methoxybenzyl isocyanate was purchased from Aldrich and used as received.

General procedure for the synthesis of ketimine hydrates (5a): *para*-Methoxybenzyl isocyanate (0.21 mL, 1.46 mmol) and Hünig's base (12 μL, 0.13 mmol) were added to a stirred solution of **3a** (252 mg, 1.30 mmol) in Et_2O (3.0 mL) at room temperature. Stirring was continued for 2 h, followed by evaporation of the solvent. The crude product was dissolved in formic acid (5 mL) and stirred at ambient temperature for 16 h, then heated to 60 °C for 5 h, before being concentrated in vacuo. The imine hydrate was purified by FC (acetone/pentane 3:7) to give the title compound as a white crystalline material (208 mg, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$–7.37 (m, 2H; Ar*H*), 7.20 (t, $J = 7.6$ Hz, 1H; ArH), 7.11 (d, $J = 8.1$ Hz, 1H; Ar*H*), 7.04 (br s, 1H; N*H*), 5.28 (br s, 1H; O*H*), 4.32–4.19 (m, 2H; OCH_2CH_3), 1.22 ppm (t, $J = 7.2$ Hz, 3H; OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.3$, 149.1, 148.7, 131.3, 125.6, 125.0, 118.4, 116.6, 81.2, 64.0, 13.8 ppm; HRMS $C_{11}H_{11}NO_5$ $[M+Na]^+$; calcd: 260.0535, found: 260.0533.

General procedure for the synthesis of ketimines 1a–g: Imine hydrate, toluene and TFA (5 mol %) were added to a round-bottomed flask equipped with a magnetic stirring bar, and a Dean–Stark condenser. The slurry was heated to reflux temperature and heating was continued until full conversion of the hydrate was detected by ^{1}H NMR spectroscopy (1–2.5 h). The toluene was distilled off and the resulting oil placed under high vacuum for 2 h leaving the highly hygroscopic ketimines as off-white or yellow solids in quantitative yields.

Imine ***1a***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (dd, $J = 8.5$, 1.5 Hz, 1H; Ar*H*), 7.82 (d, $J = 7.7$ Hz, 1H; Ar*H*), 7.42–7.36 (m, 2H; Ar*H*), 4.53 (q, $J = 7.2$ Hz, 2H; OCH_2CH_3), 1.46 ppm (t, $J = 7.2$ Hz, 3H; OCH_2CH_3).

Imine ***1b***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$ (s, 1H; Ar*H*), 7.61 (dd, $J = 8.7$, 2.4 Hz, 1H; Ar*H*), 7.27 (d, $J = 7.27$ Hz, 1H; Ar*H*), 4.52 (q, $J = 7.3$ Hz, 2H; OCH_2CH_3), 2.43 (s, 1H; $ArCH_3$), 1.45 ppm (t, $J = 7.1$ Hz, 3H; OCH_2CH_3).

Imine ***1c***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 3.1$ Hz, 1H; Ar*H*), 7.41 (dd, $J = 9.2$, 3.1 Hz, 1H; Ar*H*), 7.33 (d, $J = 9.2$ Hz, 1H; Ar*H*), 4.54 (q, $J = 7.2$ Hz, 2H; OCH_2CH_3), 3.88 (s, 3H; OCH_3), 1.48 ppm (t, $J = 7.2$ Hz, 3H; OCH_2CH_3).

Imine ***1d***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (dd, $J = 8.0$, 3.0 Hz, 1H; Ar*H*), 7.55 (ddd, $J = 9.2$, 7.7, 3.0 Hz, 1H; Ar*H*), 7.40 (dd, $J = 9.2$, 4.4 Hz, 1H; Ar*H*), 4.54 (q, $J = 7.0$ Hz, 2H; OCH_2CH_3), 1.47 ppm (t, $J = 7.2$ Hz, 3H; OCH_2CH_3).

Imine ***1e***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.13$ (d, $J = 2.5$ Hz, 1H; Ar*H*), 7.76 (dd, $J = 8.9$, 2.4 Hz, 1H; Ar*H*), 7.36 (d, $J = 8.9$ Hz, 1H; Ar*H*), 4.55 (q, $J = 7.3$ Hz, 2H; OCH_2CH_3), 1.48 ppm (t, $J = 7.3$ Hz, 3H; OCH_2CH_3).

Imine ***1f***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (d, $J = 9.1$ Hz, 1H; Ar*H*), 6.91 (dd, $J = 9.2$, 2.6 Hz, 1H; Ar*H*), 6.80 (d, $J = 2.5$ Hz, 1H; Ar*H*), 4.51 (q, $J = 7.2$ Hz, 2H; OCH_2CH_3), 3.95 (s, 3H; OCH_3), 1.46 ppm (t, $J = 7.3$ Hz, 3H; OCH_2CH_3).

Imine ***1g***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.60$ (d, $J = 8.6$ Hz, 1H; Ar*H*), 8.00–7.87 (m, 2H; Ar*H*), 7.88 (t, $J = 7.5$ Hz, 1H; Ar*H*), 7.76–7.70 (m, 2H; Ar*H*), 4.57 (q, $J = 7.2$ Hz, 2H; OCH_2CH_3), 1.49 ppm (t, $J = 7.2$ Hz, 3H; OCH_2CH_3).

General procedure for catalytic enantioselective reaction of imines 1a–f with silylketene acetals: To a flame-dried Schlenk tube equipped with a magnetic stirring bar was added $Zn(OTf)_2$ (7.3 mg, 0.020 mmol), which was gently dried with a heat-gun under vacuum. After cooling to room temperature, (*R*)-Ph-pybox (8.1 mg, 0.022 mmol) was added and stirred for an additional 1 h under vacuum. Wet CH_2Cl_2 (0.22 mL, H_2O: 1660 ppm) was added and stirring continued for 1 h at ambient temperature followed by addition of imine (1.0 mL, 0.2 M in CH_2Cl_2). After an additional 30 min of stirring the solution was cooled to −78 °C. At that temperature a solution of the silylketene acetal (1.2 equiv in 1 mL CH_2Cl_2) was added drop wise over the course of 2 h and subsequently quenched with H_2O (0.2 mL) after 2.5 h. The reaction mixture was left to warm to room temperature and filtered through a plug of silica gel (15 cm silica gel, eluent: 50 mL 30 % Et_2O in CH_2Cl_2), concentrated in vacuo and purified by FC.

7a: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (90/10); flow rate 1.0 mL min^{-1}; τ_{major} = 8.2 min; τ_{minor} = 10.5 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.0 Hz, 1H; Ar*H*), 7.36 (t, *J* = 7.7 Hz, 1H; Ar*H*), 7.13 (t, *J* = 7.8 Hz, 1H; Ar*H*), 6.98 (d, *J* = 8.2 Hz, 1H; Ar*H*), 6.50 (s, 1H; N*H*), 4.30–4.13 (m, 2H; OCH_2), 3.71 (s, 3H; OCH_3), 1.47 (s, 3H; CH_3), 1.25 (dt, *J* = 1.6, 7.1 Hz, 3H; CH_2CH_3), 1.17 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 169.6, 150.2, 149.4, 130.5, 127.7, 123.8, 117.1, 114.4, 67.6, 62.6, 53.5, 52.6, 22.7, 22.2, 13.8 ppm; $[\alpha]_D^{RT}$ = +118 (*c* = 1.0 in $CHCl_3$), (95 % *ee*); HRMS $C_{16}H_{19}NO_6$ [*M*+Na]$^+$; calcd: 344.1110, found: 344.1122.

7b: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (90/10); flow rate 1.0 mL min^{-1}; τ_{major} = 6.8 min; τ_{minor} = 8.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.0 Hz, 1H; Ar*H*), 7.35 (t, *J* = 7.8 Hz, 1H; Ar*H*), 7.12 (t, *J* = 7.7 Hz, 1H; Ar*H*), 7.08 (d, *J* = 8.1 Hz, 1H; Ar*H*), 6.49 (s, 1H; N*H*), 4.28–4.10 (m, 4H; 2 × (OCH_2)), 1.47 (s, 3H; CH_3), 1.29–1.24 (m, 6H; 2 × (CH_2CH_3)), 1.16 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 169.7, 150.2, 149.4, 130.4, 127.6, 123.7, 117.0, 114.5, 67.6, 62.5, 61.6, 53.4, 22.7, 22.2, 13.9, 13.8 ppm; $[\alpha]_D^{RT}$ = +111 (*c* = 1.0 in $CHCl_3$), (94 % *ee*); HRMS $C_{17}H_{21}NO_6$ [*M*+Na]$^+$; calcd: 358.1267, found: 358.1258.

7c: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (95/5); flow rate 1.0 mL min^{-1}; τ_{major} = 39.5 min; τ_{minor} = 54.5 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.32 (m, 2H; Ar*H*), 7.08 (t, *J* = 7.3 Hz, 1H; Ar*H*), 7.00 (d, *J* = 8.8 Hz, 1H; Ar*H*), 6.58 (s, 1H; N*H*), 4.04–4.22 (m, 4H; 2 × (OCH_2)), 3.59 (d, *J* = 17.2 Hz, 1H; CH_2), 2.79 (d, *J* = 17.2 Hz, 1H; CH_2), 1.21 (t, *J* = 7.0 Hz, 3H; CH_3), 1.16 ppm (t, *J* = 7.0 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.5, 148.9, 148.9, 130.6, 124.8, 124.8, 117.2, 117.1, 62.9, 61.6, 61.2, 44.1, 14.0, 13.8 ppm; $[\alpha]_D^{RT}$ = +162 (*c* = 1.0 in $CHCl_3$), (95 % *ee*); HRMS $C_{15}H_{17}NO_6$ [*M*+Na]$^+$; calcd: 330.0954, found: 330.0949.

7d: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (85/15); flow rate 1.0 mL min^{-1}; τ_{major} = 22.5 min; τ_{minor} = 27.5 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.36 (m, 4H; Ar*H*), 7.21 (t, *J* = 7.5 Hz, 1H; Ar*H*), 7.13 (t, *J* = 7.5 Hz, 1H; Ar*H*), 7.07–7.01 (m, 3H; Ar*H*), 6.51 (s, 1H; N*H*), 4.24–4.07 (m, 2H; OCH_2), 3.86 (d, *J* = 17.9 Hz, 1H; CH*H*), 3.08 (d, *J* = 17.9 Hz, 1H; CH*H*), 1.16 ppm (t, *J* = 7.1 Hz, 3H; CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 169.6, 149.9, 149.0, 148.8, 130.9, 129.6, 126.5, 125.0, 124.8, 121.2, 117.4, 116.8, 63.3, 61.4, 44.5, 13.9 ppm; $[\alpha]_D^{RT}$ = +133 (*c* = 1.0 in $CHCl_3$), (92 % *ee*); HRMS $C_{19}H_{17}NO_6$ [*M*+Na]$^+$; calcd: 378.0954, found: 378.0969.

anti-**7e**: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (90/10); flow rate 1.0 mL min^{-1}; τ_{major} = 13.0 min; τ_{minor} = 26.0 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.7 Hz, 1H; Ar*H*), 7.26 (t, *J* = 7.3 Hz, 1H; Ar*H*), 7.08 (t, *J* = 7.3 Hz, 1H; Ar*H*), 6.98 (d, *J* = 8.1 Hz, 1H; Ar*H*), 6.93 (s, 1H; N*H*), 4.21 (m, 2H; OCH_2), 3.38–3.46 (m, 4H, OCH_3; CH), 1.24 (t, *J* = 7.7 Hz, 3H; CH_3), 1.18 ppm (d, *J* = 5.1 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 169.3, 149.7, 149.0, 130.3, 126.0, 124.4, 116.8, 116.7, 65.0, 63.1, 52.0, 48.9, 13.9, 12.4 ppm; $[\alpha]_D^{RT}$ = +50 (*c* = 1.0 in $CHCl_3$), (93 % *ee*); HRMS $C_{15}H_{17}NO_6$ [*M*+Na]$^+$; calcd: 330.0954, found: 330.0951.

syn-**7e**: The *ee* was determined by HPLC using a Daicel Chiralcel AD column (hexane/*i*PrOH (95/5); flow rate 1.0 mL min^{-1}; τ_{major} = 20.1 min; τ_{minor} = 28.2 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.34 (m, 2H; Ar*H*), 7.09 (t, *J* = 7.7 Hz, 1H; Ar*H*), 7.01 (d, *J* = 8.0 Hz, 1H; Ar*H*), 6.50 (s, 1H; N*H*), 4.12 (m, 2H; OCH_2), 3.69 (s, 3H; OCH_3), 3.58 (q, *J* = 7.3 Hz, 1H; C*H*), 1.15 (t, *J* = 7.3, 3H; CH_3), 1.05 ppm (d, *J* = 7.7 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 171.1, 149.8, 149.2, 130.6, 124.9, 124.6, 117.3, 115.5, 65.4, 62.9, 52.6, 46.5, 13.8, 11.7 ppm; $[\alpha]_D^{RT}$ = + 78 (*c* = 1.0 in $CHCl_3$), (52 % *ee*); HRMS $C_{15}H_{17}NO_6$ [*M*+Na]$^+$; calcd: 330.0954, found: 330.0949.

anti-**7f**: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (90/10); flow rate 1.0 mL min^{-1}; τ_{major} = 14.6 min; τ_{minor} = 30.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.0 Hz, 1H; Ar*H*), 7.31 (t, *J* = 8.0 Hz, 1H; Ar*H*), 7.14 (t, *J* = 7.3 Hz, 1H; Ar*H*), 7.01 (d, *J* = 7.3, 1H; Ar*H*), 5.83 (s, 1H; N*H*), 4.14–4.40 (m, 4H; C*H*, OC*H*H, OCH_2), 4.07 (dd, *J* = 8.8, 12.8 Hz, 1H; OC*H*H), 2.11 (m, 1H; C*H*H), 1.96 (m, 1H; C*H*H), 1.23 ppm (t, *J* = 7.0 Hz, 3H; OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 169.7, 149.0, 148.9, 130.8, 125.3, 125.1, 117.2, 115.5, 66.8, 63.4, 49.4, 24.1, 13.8 ppm; $[\alpha]_D^{RT}$ = +122 (*c* = 1.0 in $CHCl_3$), (95 % *ee*); HRMS $C_{15}H_{15}NO_6$ [*M*+Na]$^+$; calcd: 328.0797, found: 328.0812

syn-**7f**: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (70/30); flow rate 1.0 mL min^{-1}; τ_{major} = 18.8 min; τ_{minor} = 23.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (s, 1H; N*H*), 7.28–7.38 (m, 2H; Ar*H*, 7.11 (t, *J* = 8.1 Hz, 1H; Ar*H*), 7.04 (d, *J* = 8.4 Hz, 1H; Ar*H*), 4.34 (t, *J* = 9.2 Hz, 1H; OC*H*H), 4.08–4.30 (m, 3H; OCH_2, C*H*), 3.41 (dd, *J* = 9.2, 11.4 Hz, 1H; OC*H*H), 2.52 (m, 1H; C*H*H), 2.29 (m, 1H; C*H*H), 1.22 ppm (t, J = 7.0 Hz, 3H; OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 169.0, 149.4, 149.3, 130.7, 125.5, 124.8, 117.2, 115.8, 66.3, 63.6, 63.4, 49.7, 25.1, 13.9 ppm; $[\alpha]_D^{RT}$ = +60 (*c* = 1.0 in $CHCl_3$), (85 % *ee*); HRMS $C_{15}H_{15}NO_6$ [*M*+Na]$^+$; calcd: 328.0797, found: 328.0796.

7g: The *ee* was determined by HPLC using a Daicel Chiralcel OJ column (hexane/*i*PrOH (70/30); flow rate 1.0 mL min^{-1}; τ_{major} = 15.8 min; τ_{minor} = 23.0 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.7 Hz, 1H; Ar*H*), 7.30 (t, *J* = 7.0 Hz, 1H; Ar*H*), 7.10–7.15 (m, 2H; Ar*H* and N*H*), 7.00 (d, *J* = 5.4 Hz, 1H; Ar*H*), 5.26 (s, 1H; C*H*), 4.15 (m, 2H; OCH_2), 3.20 (d, *J* = 15.0 Hz, 1H; C*H*H), 3.08 (d, *J* = 15.0 Hz; C*H*H), 1.40 (s, 6H; 2 × (CH_3)), 1.18 ppm (t, *J* = 7.0 Hz, 3H; OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 165.0, 160.2, 149.6, 148.9, 130.69, 126.0, 124.7, 116.9, 116.7, 106.9, 97.6, 63.2, 62.3, 42.0, 24.8, 24.2, 13.8 ppm; $[\alpha]_D^{RT}$ = +61 (*c* = 1.0 in $CHCl_3$), (88 % *ee*); HRMS $C_{18}H_{19}NO_7$ [*M*+Na]$^+$; calcd: 384.1059, found: 358.1053.

7h: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (90/10); flow rate 1.0 mL min^{-1}; τ_{major} = 6.2 min; τ_{minor} = 7.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (s, 1H; Ar*H*), 7.14 (d, *J* = 8.6 Hz, 1H; Ar*H*), 7.00 (d, *J* = 8.6 Hz, 1H; Ar*H*), 6.46 (br s, 1H; N*H*), 4.30–4.11 (m, 2H; OCH_2), 3.70 (s, 3H; OCH_3), 2.30 (s, 3H; $ArCH_3$), 1.48 (s, 3H; CH_3), 1.25 (t, *J* = 7.2 Hz, 3H; CH_2CH_3), 1.14 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 169.6, 149.6, 148.0, 133.4, 131.1, 127.6, 116.8, 113.9, 67.5, 62.5, 53.5, 52.6, 22.7, 22.1, 20.9, 13.8 ppm; $[\alpha]_D^{RT}$ = +96.3 (*c* = 1.0 in $CHCl_3$), (84 % *ee*); HRMS $C_{17}H_{21}NO_6$ [*M*+Na]$^+$; calcd: 358,1267, found: 358.1273.

7i: The *ee* was determined by HPLC using a Daicel Chiralcel OJ column (hexane/*i*PrOH (95/5); flow rate 1.0 mL min^{-1}; τ_{major} = 21.0 min; τ_{minor} = 25.4 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, *J* = 9.0 Hz, 1H; Ar*H*), 6.95 (d, *J* = 2.7 Hz, 1H; Ar*H*), 6.90 (dd, *J* = 9.0, 2.8 Hz, 1H; Ar*H*), 6.43 (br s, 1H; N*H*), 4.31–4.14 (m, 2H; OCH_2CH_3), 3.77 (s, 3H; OCH_3), 3.72 (s, 3H; OCH_3), 1.51 (s, 3H; CH_3), 1.27 (t, *J* = 7.3 Hz, 3H; OCH_2CH_3), 1.18 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 169.5, 155.4, 149.7, 144.1, 117.8, 115.8, 115.1, 112.7, 67.6, 62.6, 55.6, 53.6, 52.6, 22.8, 22.1, 13.8 ppm; $[\alpha]_D^{RT}$ = +76.0 (*c* = 1.0 in $CHCl_3$), (91 % *ee*); HRMS $C_{17}H_{21}NNaO_7$ [*M*+Na]$^+$; calcd: 374.1216, found: 374.1220.

7j: The *ee* was determined by HPLC using a Daicel Chiralcel OJ column (hexane/*i*PrOH (90/10); flow rate 1.0 mL min^{-1}; τ_{major} = 6.6 min; τ_{minor} = 8.7 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (dd, *J* = 9.5, 2.2 Hz, 1H; Ar*H*), 7.09–7.04 (m, 2H; Ar*H*), 6.51 (br s, 1H; N*H*), 4.33–4.14 (m, 2H; OCH_2CH_3), 3.71 (s, 3H; OCH_3), 1.48 (s, 3H; CH_3), 1.27 (t, *J* = 7.1 Hz, 3H; OCH_2CH_3), 1.17 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 169.2, 159.4, 157.0, 149.1, 146.3, 118.5, 118.4, 117.7, 117.4, 116.0, 115.9, 114.6, 114.3, 67.4, 62.9, 53.7, 52.7, 22.6, 22.0, 13.8 ppm; $[\alpha]_D^{RT}$ = + 122.2 (*c* = 1.0 in $CHCl_3$), (89 % *ee*); HRMS $C_{16}H_{18}FNO_6$ [*M*+Na]$^+$; calcd: 362,1016, found: 362.1012.

7k: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (90/10); flow rate 1.0 mL min^{-1}; τ_{major} = 8.3 min;

τ_{minor} = 11.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 2.6 Hz, 1H; Ar*H*), 7.34 (dd, J = 8.8, 2.6 Hz; Ar*H*), 7.05 (d, J = 8.8 Hz, 1H; Ar*H*), 6.45 (brs, 1H; N*H*), 4.35–4.17 (m, 2H; OCH_2CH_3), 3.73 (s, 3H; OCH_3), 1.50 (s, 3H; CH_3), 1.30 (t, J = 7.1 Hz, 3H; OCH_2CH_3), 1.18 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 169.1, 148.82, 148.78, 130.6, 129.1, 127.5, 118.4, 116.1, 67.3, 62.9, 53.6, 52.7, 22.5, 22.0, 13.8 ppm; $[\alpha]_D^{RT}$ = +80.2 (c = 1.0 in $CHCl_3$), (93% *ee*); HRMS $C_{16}H_{18}ClNNaO_6$ $[M+Na]^+$; calcd: 378.0720, found: 378.0718.

7l: The *ee* was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH (90/10); flow rate 1.0 mL min^{-1}; τ_{major} = 9.6 min; τ_{minor} = 11.6 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 9.3 Hz, 1H; Ar*H*), 6.69 (dd, J = 8.9, 2.7 Hz, 1H; Ar*H*), 6.61 (d, J = 2.7 Hz, 1H; Ar*H*), 6.45 (brs 1 h; NH), 4.30–4.13 (m, 2H; OCH_2CH_3), 3.81 (s, 3H; OCH_3), 3.71 (s, 3H; OCH_3), 1.48 (s, 3H; CH_3), 1.26 (t, J = 7.2 Hz, 3H; OCH_2CH_3), 1.16 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 169.7, 161.0, 151.2, 149.3, 128.5, 110.5, 106.2, 101.6, 67.2, 62.4, 55.5, 53.4, 52.5, 22.6, 22.0, 13.8 ppm; $[\alpha]_D^{RT}$ = +34.3 (c = 1.0 in $CHCl_3$), (34% *ee*); HRMS $C_{17}H_{21}NO_7$ $[M+Na]^+$; calcd: 374.1216, found: 374.1213.

7m: The *ee* was determined by HPLC using a Daicel Chiralcel OJ column (hexane/*i*PrOH (95/5); flow rate 1.0 mL min^{-1}; τ_{major} = 14.8 min; τ_{minor} = 26.7 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38–8.33 (m, 1H; Ar*H*), 7.86–7.81 (m, 1H; Ar*H*), 7.63–7.57 (m, 3H; Ar*H*), 7.43 (d, J = 10.1 Hz, 1H; Ar*H*), 6.63 (brs, 1H; N*H*), 4.33–4.16 (m, 2H; OCH_2), 3.76 (s, 3H; OCH_3), 1.55 (s, 3H; CH_3), 1.26 (t, J = 7.2 Hz, 3H; CH_2CH_3), 1.24 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 169.8, 149.4, 145.9, 134.0, 127.8, 127.2, 126.9, 123.4, 123.2, 123.1, 121.8, 109.0, 68.2, 62.6, 53.6, 52.6, 22.8, 22.3, 13.8 ppm; $[\alpha]_D^{RT}$ = 147.0 (c = 1.0 in $CHCl_3$), (80% *ee*); HRMS $C_{20}H_{21}NO_6$ $[M+Na]^+$; calcd: 394.1267 found: 394.1279.

15: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, J = 8.1 Hz, 1H; Ar*H*), 7.10 (t, J = 7.7 Hz, 1H; Ar*H*), 7.01 (d, J = 8.1 Hz, 1H; Ar*H*), 4.15 (m, 1H; OCH_2), 3.94 (m, 1H; OCH_2), 3.56 (s, 3H; OCH_3), 1.44 (s, 9H; O*t*Bu), 1.37 (s, 3H; CH_3), 1.27 (s, 3H; CH_3), 1.06 ppm (t, J = 7.0 Hz, 1H; OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 169.5, 153.7, 150.4, 130.3, 126.7, 123.9, 119.9, 117.0, 80.4, 66.0, 63.1, 46.0, 28.1, 22.6, 19.8, 13.5 ppm; HRMS $C_{21}H_{27}NO_8$ $[M+Na]^+$; calcd: 444.1634 found: 444.16345.

16: The *ee* was determined by HPLC using Daicel Chiralcel OJ column (hexane/*i*PrOH (90/10); flow rate 0.5 mL min^{-1}; τ_{major} = 27.9 min; τ_{minor} = 48.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, J = 7.7 Hz, 1H; Ar*H*), 7.27 (d, J = 7.7 Hz, 1H; Ar*H*), 7.13 (t, J = 7.9 Hz, 1H; Ar*H*), 7.08 (d, J = 8.2 Hz, 1H; Ar*H*), 5.73 (s, 1H; N*H*), 4.22–4.06 (m, 2H; OCH_2), 1.43 (s, 9H; $C(CH_3)_3$), 1.36 (s, 1H; CH_3), 1.29 (s, 1H; CH_3), 1.14 ppm (t, J = 7.2 Hz, 1H; OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 169.5, 153.7, 150.4, 130.3, 126.7, 123.9, 119.9, 117.0, 80.4, 66.0, 63.1, 46.0, 28.1, 22.6, 19.8, 13,5 ppm; IR (KBr): $\tilde{\nu}$ = 3361, 2991, 2976, 1767, 1724, 1518, 1485, 1458, 1391, 1364, 1286, 1268, 1237, 1221, 1170, 1119, 1093, 1064, 1043, 1027, 960, 923, 896, 855, 776, 764, 740, 670, 650, 632, 486, 471 cm^{-1}; $[\alpha]_D^{RT}$ = −112 (c = 1.0 in $CHCl_3$), (93% *ee*); HRMS $C_{19}H_{25}NO_6$ $[M+Na]^+$; calcd: 386.1580 found: 386.1581.

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[1] For recent reviews on asymmetric synthesis of quaternary carbon centers see: a) M. Cristoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; b) E. J. Corey, A . Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401.

[2] For review see for example: C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599.

[3] a) G. Fenteany, R. F. Standaert, W. S. Lane, S. Choi, E. J. Corey, S. L. Schreiber, *Science* **1995**, *268*, 726–731; b) G. Jung, H. Brüchner, H. Schmidt in *Structure and Activity of Natural Peptides*, (Eds.: W. Voelter, G. Wietzel), de Gruyter, Berlin, **1981**; c) D. Kluepfel, J. F. Bagli, H. Baker, M. P. Charest, A. Kudelski, S. N. Sehgal, C. J. Vézina, *J. Antibiot.* **1972**, 25, 109–115; d) M. Oka, N. Kato, *J. Enzyme Inhib.* **2001**, *16*, 465–473.

[4] a) P. K. C. Paul, M. Sukumar, R. Bardi, A. M. Piazzesi, G. Valle, C. Toniolo, P. Balaram, *J. Am. Chem. Soc.* **1986**, *108*, 6363–6370; b) M. Altorfer, C. Lehmann, P. Schönholzer, K. Müller, *J. Org. Chem.* **1996**, *61*, 4080–4086, and references therein.

[5] See for example: a) R. Sarges, J. Bordner, B. W. Donimy, M. J. Peterson, E. B. Whipple, *J. Med. Chem.* **1985**, *28*, 1716–1720; b) T. Yamaguchi, K. Miura, T. Usui, R. Unno, Y. Matsumoto, M. Fukushima, K. Mizuno, Y. Kondo, Y. Baba, M. Kurono, *Arzneim.-Forsch.* **1994**, *44*, 344–348; c) H. U. Stilz, B. Jablonka, M. Just, J. Knolle, E. F. Paulus, G. Zoller, *J. Med. Chem.* **1996**, *39*, 2118–2122; d) N. Hotta, T. Touota, K. Matsuoka, Y. Shigeta, R. Kikkiwa, T. Kaneko, A. Takahashi, K. Sugimura, Y. Koike, J. Ishii, N. Sakamoto, *Diabetes Care* **2001**, *24*, 1776–1782.

[6] J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.

[7] a) Y. Ito, R. Kuwano, *J. Am. Chem. Soc.* **1999**, *121*, 3236–3237; b) B. M. Trost, X. Ariza, *Angew. Chem.* **1997**, *109*, 2749–2751; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2635–2637; c) B. M. Trost, X. Ariza, *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737; d) B. M. Trost, K. Dogra, *J. Am. Chem. Soc.* **2002**, *124*, 7256–7257.

[8] a) E. N. Jacobsen, P. Vachal, *Org. Lett.* **2000**, *2*, 867–870; b) E. N. Jacobsen, P. Vachal, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014; c) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784–10785; d) J. J. Burne, M. Chavarot, P. Y. Chavant, Y. Vallée, *Tetrahedron Lett.* **2000**, *41*, 873–876; e) M. Chavarot, J. J. Burne, P. Y. Chavant, Y. Vallée, *Tetrahedron: Asymmetry* **2001**, *12*, 1147–1150.

[9] Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, T. Hayashi, *Tetrahedron* **1988**, *44*, 5253–5262.

[10] For Lewis acid catalyzed enantioselective addition reactions of imines derived from α-dicarbonyl compounds, see for example: a) A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2003**, *36*, 10–19; b) A. Fujii, E. Hagawara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458; Kobayashi, T. Hamada, K. Manabe, *J. Am. Chem. Soc.* **2002**, *124*, 5640–5641; d) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339; e) H. Kagoshima, T. Uzawa, T. Akiyama, *Chem. Lett.* **2002**, 298–299; f) *Chem. Eur. J.* **2000**, *6*, 2435–2448; g) S. Saaby, P. Bayón, S. P. Aburel, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4352–4361, and references therein.

[11] For review, see: a) E. F. Kleinmann, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Flemming), Pergamon Press, Oxford, **1991**, *Vol 2*, Chapter 4.1, p. 893; b) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.

[12] For Lewis acid catalyzed enantioselective Mannich reactions of aldimines, see: a) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154; b) M. Ueno, H. Ishitani, S. Kobayashi, *Org. Lett.* **2002**, *4*, 3395–3397; c) S. Xue, S. Yu, Y. Deng, W. D. Wulff, *Angew. Chem.* **2001**, *113*, *2331–2334; Angew. Chem. Int. Ed.* **2001**, *40*, 2271–2274; d) S. Kobayashi, R. Matsubara, H. Kitagawa, *Org. Lett.* **2002**, *4*, 143–145; e) S. Kobayashi, R. Matsubara, Y. Nakamura, H. Kitagawa, M. Sugiura, *J. Am. Chem. Soc.* **2003**, *125*, 2507–2515; f) S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307–310; g) S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron* **1999**, *55*, 8857–8867; h) S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713; i) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, *3083–3085; Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; j) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583–2591; for Lewis base catalyzed enantioselective Mannich reactions of aldimines, see k) K. Tomioka, H. Fujieda, S. Hayashi, M. A. Hussein, T. Kambara, Y. Nomura, M. Kanai, K. Koga, *Chem. Commun.* **1999**, 715–716; l) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061; organocatalyzed enantioselective Mannich reactions of aldimines, see: m) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; n) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; o) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833; p) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843;

q) A. Córdova, S. Watanaba, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867; r) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

[13] (*R,R*)-Ph-pybox: 2,6-Bis[4′-(*R*)-phenyloxazolin-2′-yl]-pyridine. For review, see: G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119–3154. For leading references to the application of pybox ligands in asymmetric catalysis see: a) H. Nishiama, M. Kondo, T. Nakamura, K. Itoh, *Organometallics* **1991**, *10*, 500–508. b) D. A. Evans, D. M. Barnes, J. F. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.

[14] A complex of $Zn(OTf)_2$ and (*R,R*)-Ph-DBFOX in CH_2Cl_2 at −78 °C catalyzed the reaction of imine **1a** and silylketene acetal **6a** in 77% yield and with 77% *ee*. Catalysts prepared from Lewis acids such as $Cu(OTf)_2$, $CuPF_6$, $Mg(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_2$, $Sn(OTf)_2$ and $Ni(ClO_4)_2$ complexed with chiral ligands of the phosphino-oxazoline-, bisoxazoline- or BINAP-types catalyzed the reaction of imine **1a** and silylketene acetal **6a** in high yields, but in general with low enantioinduction.

[15] S. Kobayashi, Y. Fujishita, T. Mukaiyama, *Chem. Lett.* **1990**, 1455–1458.

[16] In the presence of 5 mol% TMSOTf in CH_2Cl_2, the Mannich reaction of **1a** with **6a** proceeds in quantitative yield in less than 2 h at −78 °C.

[17] CCDC-207535 contains the supplementary crystallographic data for compound **10**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

[18] For review, see: a) C. Girard, H. G. Kagan, *Angew. Chem.* **1998**, *110*, *3088–3127; Angew. Chem. Int. Ed.* **1998**, *37*, 2923–2959; b) H. B. Kagan, T. O. Luukas, in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2000**, Chapter 4.1, pp. 1–16.

[19] The catalysts were prepared by stirring $Zn(OTf)_2$ (10 mol%), H_2O (1.0 equiv rel. to zinc), (*R,R*)-Ph-pybox and (*S,S*)-Ph-pybox (totally 11 mol% and with molar ratios corresponding to the desired level of optical purity) in CH_2Cl_2 for 1 h and then cooled to −78 °C.

[20] CCDC-214298 contains the supplementary crystallographic data for compound **11**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

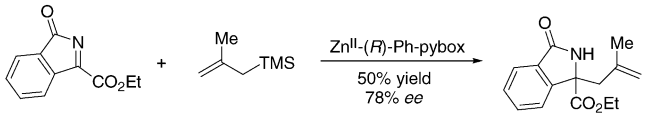
[21] a) H. C. Aspinall, N. Greeves, *J. Organomet. Chem.* **2002**, *647*, 151–157; b) C. Provent, G. Bernardinelli, A. F. Williams, N. Vulliermet, *Eur. J. Inorg. Chem.* **2001**, 1963–1967; c) M. Jiang, S. Dalgarno, C. A. Kilner, M. A. Halcrow, T. P. Kee, *Polyhedron* **2001**, *20*, 2151–2162.

[22] MS-analysis showed the existence of a **7a**-Zn–OH complex in the crude product mixture.

[23] Density functional theory (DFT) calculations were performed by using the Gaussian 98 software. The B3LYP method and the 6-31G(D,P) basis set were chosen. (Gaussian 98, Revision A.7, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian Inc., Pittsburgh PA, **1998**).

[24] Loss of optical purity was not detected throughout the transformation shown in Scheme 4.

[25] Example of a catalytic asymmetric allylation of a novel ketimine electrophile with intrinsic protecting group anchoring.



[26] J. P. Versleijen, M. S. Sanders-Hovens, S. A. Vanhommerig, J. A. Vekemans, E. M. Meijer, *Tetrahedron* **1993**, *49*, 7793–7802.

[27] E. Juaristi, J. S. Cruz-Sánches, *J. Org. Chem.* **1988**, *53*, 3334–3338.

[28] Y. Kita, J. Segawa, J. Haruta, H. Yasuda, Y. Tamura, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1099–1104.

[29] N. Slougui, G. Rousseau, *Synth. Commun.* **1987**, *17*, 1–11.

[30] a) G. M. Rubottom, J. M. Gruber, R. Marrero, H. D. Juve, Jr., C. W. Kim, *J. Org. Chem.* **1983**, *48*, 4940–4944; b) T. V. Rajababu, *J. Org. Chem.* **1984**, *49*, 2083–2089.

[31] J. G. Grunwell, A. Karipides, C. T. Wigal, S. W. A. Clayton, F. J. Fleitz, M. Daffner, J. E. Stevens, *J. Org. Chem.* **1991**, *56*, 91–95.

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