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Stereoselective nucleophilic addition to imines catalyzed by chiral bifunctional thiourea organocatalysts

Alessandra Puglisi, Maurizio Benaglia *, Rita Annunziata, Davide Rossi

Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano, via Golgi 19, I-20133 Milano, Italy

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ABSTRACT

A new and easy synthesis of chiral bifunctional organic catalysts obtained by the combination of (*S*)-*t*-leucine-derivatives with (1*R*,2*R*)-*trans*-1,2-diamino-cyclohexane was developed. A few compounds, representatives of a class of organocatalysts containing a thiourea group and a tertiary amino group connected through a chiral backbone, have been successfully synthesized. The catalytic behaviour of such bifunctional chiral molecules, either neutral or protonated species, was investigated in the addition of acetylacetone to β-nitrostyrene as a model reaction. Using the best conditions, high yields and enantioselectivities of up to 85% were obtained. The same metal free catalysts were then employed in the addition of activated nucleophiles to imines: in the reaction of 1,3-diketones with *N*-CBz imines, the products were isolated in up to 61% ee, while in the reaction with diethyl malonate enantioselectivities up to 71% were reached.

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1. Introduction

Among the different chiral compounds capable of donating one or more hydrogen bonds and therefore catalyzing stereoselective reactions[1] are phosphoric acids,[2] diols,[3] thiourea derivatives[4] and, less often, carboxylic acids.[5] Over the last few years, the class of thiourea catalysts was further expanded upon through the development of bifunctional catalytic systems,[6] whereby the thiourea group is usually coupled to a chiral Lewis base in order to exert a greater degree of stereocontrol over the reaction.

Different chiral scaffolds have been used to build multifunctional organic catalysts,[7] including cinchona alkaloids[8] and binaphthyl diamines;[9] in this context, 1,2-*trans*-diamino cyclohexane has shown an extraordinary ability to act as chiral linker connecting two catalytic cycles.[10] Following his fundamental work in the field of urea and thiourea-based monofunctional catalysts,[11] Jacobsen has recently developed novel bifunctional organocatalysts of type **A** (Fig. 1), where the thiourea group is connected through the 1,2-*trans*-diamino cyclohexane scaffold to a Lewis basic catalytic site.[12] Takemoto developed a very successfull and versatile catalyst of type **B** (Fig. 1) which is able to promote several reactions,[6] including Mannich, aza-Henry and more recently Petasis-type reactions.[13]

Differently modified Jacobsen's catalysts have been widely used for various reactions, but surprisingly the very simple *N,N*-dimethyl-substituted catalyst **C** (Fig. 1) has only found application in the kinetic resolution of oxazinones.[14] We decided to explore the catalytic behaviour of catalyst type **C** in different reactions,

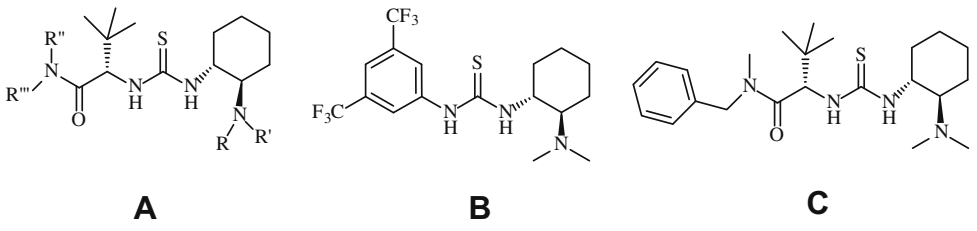

Figure 1. Multifunctional chiral organocatalysts **A–C**.

* Corresponding author. Tel.: +39 025031 4171; fax: +39 025031 4159.
E-mail address: maurizio.benaglia@unimi.it (M. Benaglia).

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namely the addition of acetylacetone to nitrostyrene and the reactions of *N*-CBz imines with 1,3-diketones and diethyl malonate. Herein, we report a new easy synthesis in a few steps of chiral bifunctional organic catalysts obtained by combination of (*S*)-*t*-leucine-derivatives with (1*R*,2*R*)-*trans*-1,2-diamino-cyclohexane and the results of the investigation of such compounds as chiral organocatalysts.

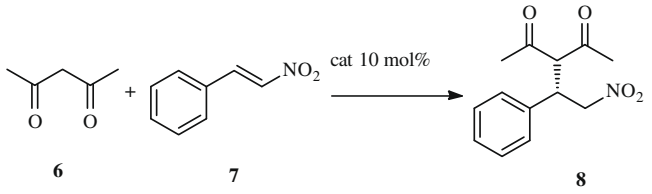
2. Results and discussion

The reported synthesis of catalyst type **C** involves the condensation of a *t*-leucine-derived isothiocyanate with *N,N*-dimethyl-1,2-diamino-*trans*-cyclohexane, a non-commercially available compound, that has to be synthesized with a tedious, four-step synthetic procedure. When we started our investigation, we thought that an easier preparation of this class of molecules would have been desirable and that the direct reaction of the chiral diamine with he isothiocyanate, followed by bis N-methylation, would have represented an attractive alternative approach to the known procedure; the planned synthetic pathway is outlined in Scheme 1.

Following the general procedure, the condensation of *N*-methyl benzylamine with N-protected Boc (*S*)-*t*-leucine **1** afforded in quantitative yield, the *N*-benzyl, *N*-methyl amide of (*S*)-*t*-leucine **2a**, which was converted to the corresponding isothiocyanate **3a**, and this was immediately reacted with (1*R*,2*R*)-1,2-diamino cyclohexane to afford the bifunctional amino thiourea **4a** in 65% yield. Finally, reductive amination with formaldehyde and sodium borohydride, followed by treatment with acetic acid, allowed us to isolate *N,N*-dimethyl amino derivative **5a** in 61% yield after chromatographic purification.[15]

Bifunctional catalysts, such as **5**, present several points of structural variation, such as the substituents at the amide group, the amino acid, and the residues on the amine group; however, on the basis of the reported work by Jacobsen et al.,[11] at this preliminary stage of investigation we decided to study slight modifications only at the (*S*)-*t*-leucine amide nitrogen. It has been already demonstrated that even minor changes in the substitution pattern at the aminoacid amino group may have dramatic effects on the stereoselectivity of the process.[16] Therefore, following the general synthetic procedure pictured in Scheme 1, three other catalysts **5b**, **5c**, **5d** were prepared starting from methyl amine, *N,N*-dimethyl amine and benzyl amine, respectively.[15]

The catalytic activity of compounds **5a**–**d** was first evaluated in the model reaction between *trans* β-nitrostyrene **6** and acetyl acetone **7** (Scheme 2); the reaction was typically performed in the presence of 10 mol % of catalyst for 12 h in different solvents and temperatures; the results obtained with chiral bifunctional catalysts of type **5** are reported in Table 1.



6 7 8

Scheme 2. Addition of acetyl acetone to β-nitrostyrene.

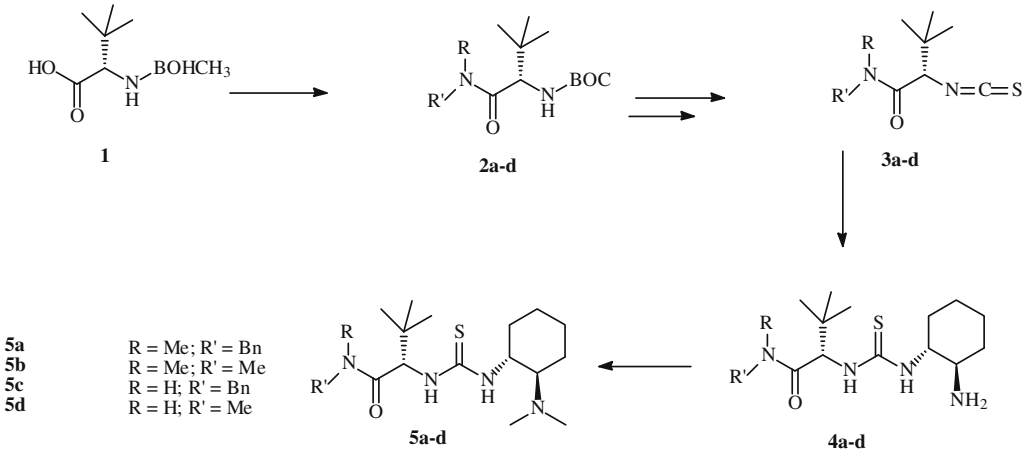
Table 1
Stereoselective addition of acetylacetone to *trans*-β-nitrostyrene promoted by **5a–5d** catalysts

Entry	Catalyst	Solvent	Yield[a] (%)	ee[b] (%)
1	**5a**	Et_2O	93	71
2	**5b**	Et_2O	98	75
3	**5c**	Et_2O	73	70
4	**5d**	Et_2O	85	53
5	**5a**	DME	60	65
6	**5b**	DME	64	58
7	**5c**	DME	40	54
8[c]	**5a/H$^+$**	Et_2O	90	85
9	**5b/H$^+$**	Et_2O	95	75

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Daicel ChiralPak AD); (*R*)-enantiomer was obtained as major product.
[c] See text and Section 4.

The first experiments in diethyl ether at room temperature showed that all four catalysts were able to efficiently promote the reaction, affording product **8** in yields higher than 73% (Table 1, entries 1–4). For the enantioselectivity, catalysts **5a** and **5b** offered the best performance, leading to the product in 71% and 75% ee, respectively (entries 1 and 2). By running the reaction in dimethoxyethane (DME), only catalyst **5a** maintained a good level of stereoselectivity (65% ee), while other catalysts gave inferior results (entries 5–7). Any attempt to improve the enantioselection of the process, by changing solvents and reaction temperature, failed.

Therefore, we decided to test a protonated species to act as a catalyst for the reaction; by a proper modification in the basic work-up of the last step of the synthetic sequence of Scheme 1, the *N,N*-bis methylation of amines **4a** and **4b**, a charged species



1 2a-d 3a-d 5a-d 4a-d

Scheme 1. Synthetic sequence for catalysts **5**.

was isolated by chromatographic purification, containing the acetate salts of **5a** and **5b**, that was completely characterized by mass spectrometry and NMR spectroscopy.[17] While adduct **5bH$^+$-AcO$^-$** catalyzed the addition of acetyl acetone to *trans*-β-nitrostyrene with a chemical and stereochemical efficiency similar to those obtained with the neutral species (95% yield and 75% ee, Table 1, entry 9), catalyst **5aH$^+$-AcO$^-$** showed a marked improvement compared to neutral **5a**, affording product **8** in 90% yield and 85% ee (Table 1, entry 8). The protonated species **5aH$^+$-AcO$^-$** was then selected as the catalyst of choice for further studies; the results are collected in Table 2.

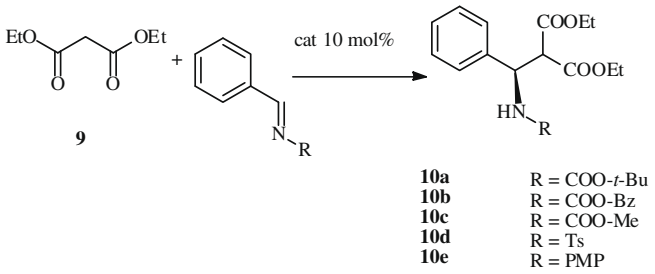
Table 2
Stereoselective addition of acetylacetone to *trans*-β-nitrostyrene promoted by **5a/AcOH** catalyst

Entry	Solvent	Temperature (°C)	Reaction time (h)	Yield[a] (%)	ee[b] (%)
1[c]	Et_2O	25	12	93	71
2	Et_2O	25	12	90	85
3	THF	25	12	63	69
4	DME	25	12	61	80
5	Dioxane	25	12	65	67
6	DCM	25	12	61	45
7	CH_3CN	25	12	11	61
8	Toluene	25	12	65	67
9	Et_2O	0	12	85	51
10	Et_2O	−20	12	60	50
11	DME	0	12	39	75

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Daicel ChiralPak AD); (*R*)-enantiomer was obtained as the major product.
[c] Neutral catalyst was employed.

The charged catalytic system **5aH$^+$-AcO$^-$** worked well in ether solvents; not only in diethyl ether, but also in THF and dioxane with good levels of enantioselectivity being reached; in dimethoxyethane, the product was obtained in 85% ee (Table 2, entries 2–5). By running the reaction in other solvents, such as dichloromethane, acetonitrile or toluene, a decrease in chemical yield and enantioselectivity was observed (Table 2, entries 5–8). Lowering the reaction temperature did not allow us to improve the enantioselectivity of the process (Table 2, entries 9–11).

In order to further explore the catalytic behaviour of adduct **5aH$^+$-AcO$^-$** in more challenging transformations, the addition of activated nucleophiles to imines was studied; in particular, we focused our attention on reactions of imines with 1,3-diketones and 1,3-dicarboxylic esters (Scheme 3).



Scheme 3. Addition of diethyl malonate to imines.

The addition of diethyl malonate to different benzaldehyde imines was investigated; the reaction was typically performed in dichloromethane at room temperature for 12 h in the presence of 10 mol % of catalyst **5aH$^+$-AcO$^-$**; the results are reported in Table 3.

While *N*-BOC imine did not react very well and product **10a** was isolated in only 15% yield (Table 3, entry 1), *N*-carbomethoxy and *N*-carbobenzyloxy imines gave more interesting results; the products **10c** and **10b** were isolated in 41% and 53% yield, respectively; the enantioselectivities of the reaction were 51% and 61% for **10c** and **10b**, respectively (Table 3, entries 2 and 3). Other imines gave less satisfactory results, such as *N*-tosyl imine (Table 3, entry 4) or did not react at all, such as *N*-4-methoxyphenyl imine (Table 3, entry 5). Running the reaction with *N*-CBz imine at lower temperature did not cause any increase in enantioselectivity (Table 3, entry 6).

Table 3
Stereoselective addition of diethyl malonate to imines promoted by **5a/AcOH** catalyst in dichloromethane

Entry	R	Temperature (°C)	Reaction time (h)	Yield[a] (%)	ee[b] (%)
1	COO-*t*Bu	25	12	15	n.d.
2	COO-Bz	25	12	53	61
3	COO-Me	25	12	41	51
4	Ts	25	12	40	15
5[c]	4-OMe-Ph	25	12	—	—
6	COO-Bz	0	40	45	55
7[c]	COO-Bz	25	12	81	63

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Daicel ChiralPak AD and ChiralPak IB); (*S*)-enantiomer was obtained as major product.
[c] Neutral catalyst was employed.

It is worth mentioning that for this reaction, the neutral catalyst **5a** showed superior results to the protonated species; indeed **5a**, catalyzed the addition of diethyl malonate to *N*-Cbz imine of benzaldehyde at room temperature in dichloromethane in 81% yield and 63% ee.

Other reaction solvents for the reaction promoted by **5aH$^+$-AcO$^-$** were briefly examined (Table 4).[18]

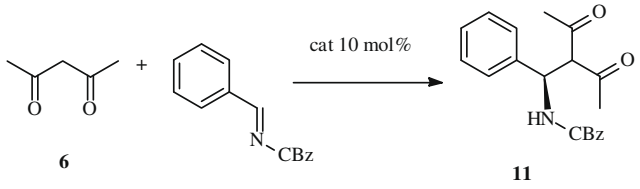
For this reaction, diethyl ether (like other ethereal solvents) was not a suitable reaction medium, since product **10b** was isolated with lower enantioselectivities than in dichloromethane (Table 4, entries 2–4 vs entry 1). Acetonitrile was shown not to be the solvent of choice (Table 4, entry 5), while the best result was obtained by running the reaction in toluene; in this case, catalyst **5aH$^+$-AcO$^-$** was able to promote the addition of diethyl malonate to *N*-Cbz imine of benzaldehyde in 60% yield and 71% ee.

Table 4
Stereoselective addition of diethyl malonate to *N*-CBz imine catalyzed by **5a/AcOH** catalyst

Entry	Solvent	Reaction time (h)	Temperature (°C)	Yield[a] (%)	ee[b] (%)
1	DCM	12	25	53	61
2	Et_2O	12	25	55	43
3	DME	12	25	58	33
4	THF	12	25	63	11
5	CH_3CN	12	25	67	33
6	Toluene	12	25	60	71
7[c]	DCM	12	25	<10	—

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Daicel ChiralPak AD); (*S*)-enantiomer was obtained as major product.
[c] Reaction without catalyst.

Preliminary experiments were also performed on the organocatalyzed acetyl acetone addition to *N*-Cbz imine of benzaldehyde (Scheme 4); the results are collected in Table 5.



Scheme 4. Addition of acetyl acetone to imines.

As shown in Table 5 for the **5aH$^+$-AcO$^-$** catalyzed reaction, toluene and diethyl ether behaved similarly as reaction solvents, leading to product **11** in good yield and comparable low enantioselectivities (Table 5, entries 1 and 2). Better results were obtained by working in toluene with neutral catalyst **5a**; in this case, after 12 h reaction at 25 °C, the product was isolated in 80% yield and 55% ee (Table 5, entry 3). Enantioselectivity was increased by lowering the reaction temperature; at −40 °C, bifunctional catalyst **5a** was able to promote the acetyl acetone addition to *N* Cbz imine in 40% yield and 61% ee, even if longer reaction times were required (Table 5, entry 5). It should be noted that catalyst **5b** also promoted the reaction with decent chemical efficiency and 53% ee (Table 5, entry 6).

Table 5
Stereoselective addition of acetyl acetone to *N*-CBz imine of benzaldehyde

Entry	Catalyst	Solvent	Reaction time (h)	Temperature (°C)	Yield[a] (%)	ee[b] (%)
1	**5a/ AcOH**	Et_2O	12	25	67	33
2	**5a/ AcOH**	Toluene	12	25	63	40
3	**5a**	Toluene	12	25	80	55
4	**5a**	Toluene	18	−20	70	57
5	**5a**	Toluene	60	−40	40	61
6	**5b**	Toluene	60	−40	42	53
7	—	Toluene	18	−20	54	—

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Daicel ChiralPak AD); (*S*)-enantiomer was obtained as major product.

At this stage, it is really difficult to propose any hypothesis of the rationalization of the stereochemical course of the reaction, also in view of the fact that the present multifunctionalized catalysts probably present more than one possible reaction mechanism. Compounds **5** are thought to operate as bifunctional catalysts; for example, in the acetyl acetone addition to *trans*-β-nitrostyrene, it is quite reasonable to postulate transition state type **A**, as depicted in Figure 2. The nitrostyrene activation through the double hydrogen bond coordination with a thiourea group and deprotonation of 1,3-diketone by the basic amino group of 1,2-diaminocylohexane moiety should keep the two reagents close enough to allow the catalyst to control the absolute stereochemistry of the process. However, in the case of protonated catalyst **5aH$^+$-AcO$^-$**, different mechanisms of the reaction could be proposed; in this case, the enolic form of acetyl acetone would attack nitrostyrene; key features of hypothetic transition state **B** are the coordination of the nitro group by thiourea hydrogen atoms in combination with a hydrogen bond between ammonium cyclohexyl-*N*,*N*-dimethyl ammonium salt and acetyl acetone (Fig. 2).

Similar considerations may apply to the addition of activated nucleophiles to imines. It can be hypothesized that a coordination of two hydrogen atoms of thiourea to a carbobenzyloxy group at the imine nitrogen might be present (Fig. 3); once again in the case of neutral catalysts model **A** can be proposed, while stereoselection model **B** can be invoked for protonated catalytic species. The fact that catalysts showed their best performance in an apolar solvent, such as toluene, is in agreement with the proposed stereochemical models that rely on the formation of an extensive hydrogen bonding network. It is more difficult to explain why diethyl ether is a better solvent for the addition to nitrostyrene; however, it should be mentioned that any attempt of rationalization is hampered by the observation that catalyst **5aH$^+$-AcO$^-$** is poorly soluble in diethyl ether.[19]

As mentioned before, it is likely that the catalysts do not have a single unambiguous mechanism of action; it should also be noted that in the acetyl acetone addition to the imine, the analysis is further complicated by the strong background reaction that is still present at low temperatures (Table 5, entry 7).

3. Conclusions

In conclusion, a new and easy synthesis in a few steps of chiral bifunctional organic catalysts obtained by combination of

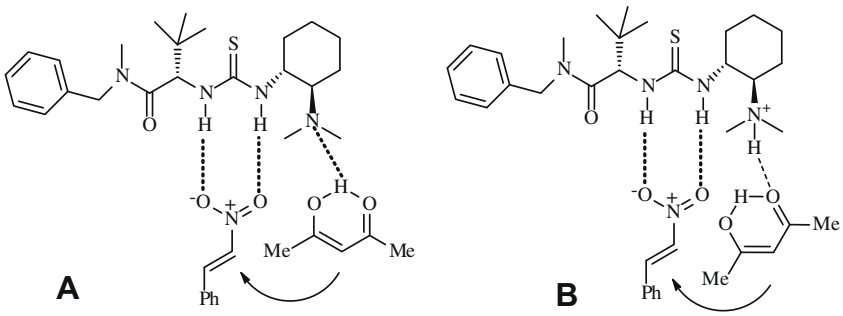


Figure 2. Proposed stereoselection models for acetyl acetone addition to β-nitrostyrene.

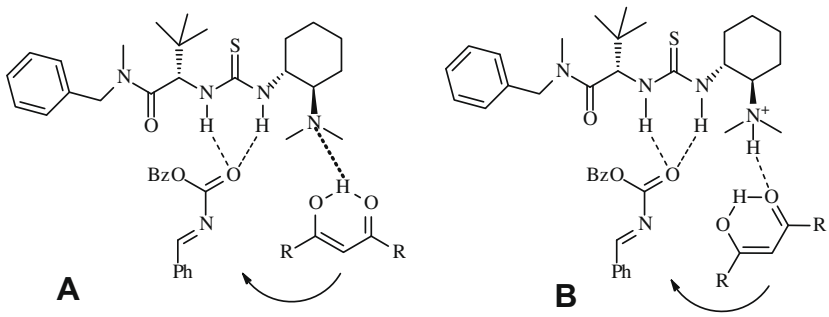


Figure 3. Proposed stereoselection models for addition to imines.

(*S*)-*t*-leucine-derivatives with (1*R*,2*R*)-*trans*-1,2-diamino-cyclohexane has been developed. The catalytic behaviour of such bifunctional chiral molecules, either neutral or protonated species, was investigated in the addition of acetylacetone to nitrostyrene as model reaction. Under the best conditions, high yields and enantioselectivities of up to 85% were obtained. The same metal free catalysts were then employed in the addition of activated nucleophiles to imines: in the reaction of 1,3-diketones with *N*-CBz imines, the products were isolated in up to 61% ee, while in the reaction with diethyl malonate, enantioselectivities of up to 71% were reached.

4. Experimental

4.1. General methods

All commercially available reagents including dry solvents were used as received. Dry CH_2Cl_2 was distilled under nitrogen over CaH_2. Organic extracts were dried over sodium sulfate, filtered and concentrated under vacuum using a rotatory evaporator. Non-volatile materials were dried under high vacuum. Reactions were monitored by thin-layer chromatography on pre-coated Merck Silica Gel 60 F254 plates, and were visualized either by UV or by staining with a solution of cerium sulfate (1 g) and ammonium heptamolybdate tetrahydrate (27 g) in water (469 mL) and concentrated sulfuric acid (31 mL). Flash chromatography was performed on Fluka Silica Gel 60 or on Merck basic alumina activity I, deactivated with 3% water. ^{1}H NMR spectra were recorded on a Bruker AC 300 or Bruker AMX 300 instruments at 300 MHz in $CDCl_3$ unless otherwise stated, and were referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz, and were referenced to 77.0 ppm in $CDCl_3$. Optical rotations were measured with Perkin–Elmer 241 polarimeter.

4.1.1. Synthesis of amide 2a

A 100 mL, two-necked round bottom flask was charged with *t*-leucine (1 g, 4.32 mmol, 1 equiv), 1-hydroxybenzotriazole hydrate (HOBt, 1.75 g, 12.97 mmol, 3 equiv) and 35 mL of anhydrous $CHCl_3$ under nitrogen. After 5 min of stirring, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC, 2.49 g, 12.97 mmol, 3 equiv) and *N*-methyl-benzylamine were added, and the reaction mixture was stirred at 23 °C for 18 h. Next 1 M HCl (20 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the organic phases were washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL) and dried over Na_2SO_4. Solvent removal in vacuo afforded analytically pure amide (4.30 mmol, >98% yield) as a thick oil that was used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a 4:1 mixture of rotamers: the major is indicated): δ 7.35–7.15 (m, 5H, Ar*H*), 5.35 (br, 1H, C*H*), 4.65 (B part of a AB system, d, *J* = 3.3 Hz, 1H, CH_2Ph), 4.50 (A part of a AB system, d, *J* = 3.3 Hz, 1H, CH_2Ph), 3.05 (s, 3H, NCH_3), 1.40 (s, 9H, COOC(CH_3)$_3$), 1.0 (s, 9H, CHC(CH_3)$_3$).

4.1.2. Synthesis of isothiocyanate 3a

The crude amide (724 mg, 2.17 mmol, 1 equiv) was dissolved in dichloromethane (12 mL) after which trifluoroacetic acid (TFA, 2.5 mL, 32.51 mmol, 15 equiv) was added. The reaction mixture was stirred at 23 °C until the disappearance of the starting material, as monitored by TLC (1 h). The reaction mixture was carefully quenched with a saturated aqueous solution of sodium bicarbonate; the aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give analytically pure free amine (448 mg, 1.91 mmol, 88% yield) as a white solid that was used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a 5:1 mixture of rotamers: the major is indicated): δ 7.35–7.15 (m, 5H, Ar*H*), 5.35 (br, 1H, C*H*), 4.65 (B part of a AB system, d, *J* = 3.3 Hz, 1H, CH_2Ph), 4.50 (A part of a AB system, d, *J* = 3.3 Hz, 1H, CH_2Ph), 3.05 (s, 3H, NCH_3), 1.0 (s, 9H, CHC(CH_3)$_3$).

The crude amine (448 mg, 1.91 mmol, 1 equiv) was dissolved in a mixture of dichloromethane and saturated aqueous sodium bicarbonate solution (1:1, 50 mL), and allowed to stir in an ice-bath until 5 °C. Once at 5 °C, the stirring was stopped, and the layers allowed to separate. Thiophosgene (0.162 mL, 2.10 mmol, 1.1 equiv) was rapidly added to the dichloromethane layer via syringe. The reaction mixture was stirred at 5 °C for 30 min. The layers were then partitioned, and the aqueous layer was extracted with dichloromethane (3 × 30 mL); the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give analytically pure isothiocianate **3** (522 mg, 1.89 mmol, 99% yield) as a yellow oil, which was used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a 5:1 mixture of rotamers: the major is indicated): δ 7.35–7.15 (m, 5H, Ar*H*), 5.35 (br, 1H, C*H*), 4.65 (B part of a AB system, d, *J* = 3.3 Hz, 1H, CH_2Ph), 4.50 (A part of a AB system, d, *J* = 3.3 Hz, 1H, CH_2Ph), 3.05 (s, 3H, NCH_3), 1.0 (s, 9H, CHC(CH_3)$_3$).

4.1.3. Synthesis of thiourea 4a

Crude isothiocyanate **3a** (522 mg, 1.89 mmol, 1 equiv) was dissolved in dichloromethane (20 mL) under nitrogen; (*R*,*R*)-diaminocyclohexane (258 mg, 2.27 mmol, 1.2 equiv) was then added, and the reaction mixture was allowed to stir at 23 °C until the disappearance of isothiocyanate as monitored by TLC (2 h). Solvent removal in vacuo afforded crude thiourea **4a**, which was purified by flash chromatography on silica gel (3 × 16 cm silica, CH_2Cl_2/CH_3OH 9:1, then CH_2Cl_2/CH_3OH 9:1 + 1% TEA, R_f = 0.26, ninhydrin TLC visualization) to give pure thiourea **4** (312 mg, 0.80 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a 4:1 mixture of rotamers: the major is indicated): δ 7.42–7.20 (m, 5H, Ar*H*), 5.50 (d, *J* = 7.5 Hz, 1H, C*H*), 4.98 (B part of a AB system, d, *J* = 14.5 Hz, 1H, CH_2Ph), 4.28 (A part of a AB system, d, *J* = 14.5 Hz, 1H, CH_2Ph), 3.22 (s, 3H, NCH_3), 2.57 (m, 1H, C*H*(NH_2)), 2.38 (br, 2H, NH_2), 2.05 (d, *J* = 12.0 Hz, C*H*N thiourea), 1.88 (d, *J* = 10.0 Hz, 2H, CH_2(CHNH_2)), 1.71 (m, 3H, CH_2(CHNH_2), CH_2(CHN)), 1.33–1.19 (m, 4H, CH_2 cycl), 1.09 (s, 9H, C(CH_3)$_3$).

4.1.4. Synthesis of catalyst 5a

Thiourea **4a** (312 mg, 0.80 mmol, 1 equiv) was dissolved in THF (16 mL); formaldehyde (37% aqueous solution, 0.72 mL, 9.60 mmol, 12 equiv) was then added, and the reaction mixture was allowed to stir at 50 °C for 15 h. The mixture was then cooled to 23 °C, and $NaCNBH_3$ (350 mg, 5.6 mmol, 7 equiv) was added; the reaction mixture was stirred at 23 °C for 2 h. Acetic acid (1.3 mL) was then added, and the reaction mixture heated at 50 °C for an additional 4 h. After this time, the reaction mixture was cooled to 23 °C and 1 M NaOH was added until pH > 12; the layers were then partitioned, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford a crude product, which was purified by flash chromatography on silica gel (3 × 16 cm silica, CH_2Cl_2/CH_3OH 95:5, CH_2Cl_2/CH_3OH 9:1, then CH_2Cl_2/CH_3OH 9:1 + 1% TEA, R_f = 0.37, ninhydrin TLC visualization) to give pure thiourea (201 mg, 0.48 mmol, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a 4:1 mixture of rotamers: the major is indicated): δ 7.37–7.26 (m, 5H, Ar*H*), 7.14 (d,*J* = 9.1 Hz, 1H, N*H*CS) 7.03 (br s, 1H, CSN*H* cy), 5.60 (d, *J* = 9.1 Hz, 1H, C*H*), 4.76 (B part of a AB system, d, *J* = 14.6 Hz, 1H, CH_2Ph), 4.50 (A part of a AB system, d, *J* = 14.6 Hz, 1H, CH_2Ph), 3.78 (m, 1H, C*H*NH), 3.21 (s, 3H, NCH_3), 2.58 (m, 1H, C*H*N(CH_3)$_2$),

2.46 (m, 1H, CH_2CHNH), 2.34 (s, 6H, N(CH_3)$_2$), 1.91 (m, 1H, CH_2CHN(CH$_3$)$_2$), 1.87 (m, 1H, CH), 1.73 (m, 1H, CH), 1.3–1.2 (m, 4H, CH), 1.09 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, compound exists as a 4:1 mixture of rotamers: the major is indicated): δ 182.8, 172.4, 136.9, 128.5, 128.1, 127.3, 66.9, 60.5, 55.3, 51.3, 40.0, 36.1, 35.9, 33.0, 26.8, 24.9, 24.6, 22.0. MS-ESI$^+$: *m/z* 419 [M+H]$^+$, Elem. Anal. Calcd for $C_{23}H_{38}N_4OS$: C, 65.99; H, 9.15; N, 13.38, S, 7.66. Found: C, 66.05; H, 9.17; N, 13.37, S, 7.69.

4.1.5. Isolation of catalyst 5aH$^+$-AcO$^-$

Thiourea **4a** (312 mg, 0.80 mmol, 1 equiv) was dissolved in THF (16 mL); formaldehyde (37% aqueous solution, 0.72 mL, 9.60 mmol, 12 equiv) was then added, and the reaction mixture was allowed to stir at 50 °C for 15 h. The mixture was then cooled to 23 °C, and $NaCNBH_3$ (350 mg, 5.6 mmol, 7 equiv) was added; the reaction mixture was stirred at 23 °C for 2 h. Acetic acid (1.3 mL) was then added, and the reaction mixture heated at 50 °C for additional 4 h. After this time, the reaction mixture was cooled to 23 °C and 1 M NaOH was added until pH 8 was reached; the layers were then partitioned, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford crude product that was purified by flash chromatography on silica gel (3 × 16 cm silica, CH_2Cl_2/CH_3OH 95:5, CH_2Cl_2/CH_3OH 9:1, then CH_2Cl_2/CH_3OH 9:1 + 3% TEA, R_f = 0.31, ninhydrin TLC visualization) to give pure thiourea (201 mg, 0.45 mmol, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a 3:1 mixture of rotamers: the major is indicated): δ 9.00 (d, *J* = 9.1 Hz, 1 H, N*H*CS), 7.35–7.25 (m, 5H, Ar*H*), 7.43 (br s, 1H, CSN*H* cy), 4.90 (d, *J* = 9.1 Hz, 1H, C*H*), 4.75 (B part of a AB system, d, *J* = 13.6 Hz, 1H, CH_2Ph), 4.71 (m, 1H, C*H*NH), 4.50 (A part of a AB system, d, *J* = 13.6 Hz, 1H, CH_2Ph), 3.55 (m, 1H, C*H*N(CH$_3$)$_2$), 3.31 (s, 3H, NCH_3), 2.51 (m, 1H, CH_2CHNH), 2.75 (s, 6H, N(CH_3)$_2$), 2.11 (m, 1H, CH_2CHN(CH$_3$)$_2$), 1.97 (m, 1H, C*H*), 1.77 (m, 1H, C*H*), 1.3–1.2 (m, 4H, C*H*), 1.12 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, compound exists as a 3:1 mixture of rotamers: the major is indicated): δ 183.3, 172.8, 136.5, 128.4, 128.0, 127.3, 68.7, 61.5, 53.3, 51.8, 40.0, 36.3, 32.3, 26.9, 24.3, 23.8, 23.1. MS-ESI$^+$: *m/z* 420 [M+H]$^+$.

Catalysts **5b**, **5c** and **5d** were prepared according to the general procedure reported for catalyst **5a**.

Catalyst **5b**: (flash chromatography, 3 × 16 cm alumina, CH_2Cl_2/CH_3OH 9:1, then CH_2Cl_2/CH_3OH 9:1 + 1% TEA, R_f = 0.15, ninhydrin TLC visualization). $[\alpha]_D^{23} = +9.5$ (*c* 1.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, *J* = 9.5 Hz, 1H, CHN*H*CS), 6.65 (br s, 1H, CSN*H*), 5.59 (d, *J* = 9.5 Hz, 1H, C*H*), 3.55 (m, 1H, C*H*NHCS), 3.22 (s, 3H, N(CH_3)$_2$CO), 2.93 (s, 3H, N(CH_3)$_2$CO), 2.58 (m, 1H, C*H*N(CH$_3$)$_2$), 2.40 (m, 1H, NHCHCH_2), 2.32 (m, 1H, C*H*N(CH$_3$)$_2$), 2.20 (s, 6H, N(CH_3)$_2$), 1.90 (m, 1H, CH_2CHN(CH$_3$)$_2$), 1.80 (m, 1H, CH_2CHN(CH$_3$)$_2$), 1.77 (m, 1H, CH_2CH$_2$CHNH), 1.67 (m, 1H, CH_2CH$_2$CHN(CH$_3$)$_2$), 1.20 (m, 3H, CH_2CHN(CH$_3$)$_2$, CH_2CH$_2$ CHN(CH$_3$)$_2$ and CH_2CH$_2$CHNH), 1.13 (m, 1H, NHCHCH_2), 1.02 (s, 9H, CHC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.5, 172.1, 66.7, 60.0, 55.5, 40.2, 38.5, 36.0, 35.5, 33.0, 26.7, 25.0, 24.6, 22.0. MS-ESI$^+$: *m/z* 343 [M+H]$^+$, Elem. Anal. Calcd for $C_{17}H_{34}N_4OS$: C, 59,61; H, 10.00; N, 16.36, S, 9.36. Found: C, 59.65; H, 10.03; N, 16.29, S, 9.31.

Catalyst **5c**: (flash chromatography, 3 × 16 cm alumina, CH_2Cl_2/CH_3OH 95:5 then CH_2Cl_2/CH_3OH 9:1, R_f = 0.34, ninhydrin TLC visualization). $[\alpha]_D^{23} = -6.5$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H, Ar*H*), 6.65 (br s, 1H, N*H*CS), 6.52 (br s, 1H, CSN*H* cy), 4.80 (br, 1H, C*H*), 4.45 (B part of a AB system, d, *J* = 13.0 Hz, 1H, CH_2Ph), 4.30 (A part of a AB system, d, *J* = 13.0 Hz, 1H, CH_2Ph), 3.75 (m, 1H, C*H*NHCS), 2.42 (m, 2H, C*H*N(CH$_3$)$_2$ and CH_2CHNH), 2.20 (s, 6H, N(CH_3)$_2$), 1.90 (m, 1H, CH_2CHN(CH$_3$)$_2$), 1.80 (m, 1H, CH_2CH$_2$CHNH), 1.73 (m, 1H, CH_2CH$_2$CHN(CH$_3$)$_2$), 1.20 (m, 1H, CH_2CHN(CH$_3$)$_2$), 1.15 (m, 3H, CH_2CH$_2$CHN(CH$_3$)$_2$, CH_2CH$_2$CHNH and CH_2CHNH), 1.05 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.5, 171.0, 138.0, 128.7, 128.4, 127.4, 66.8, 66.2, 55.7, 43.5, 40.2, 34.7, 33.1, 27.0, 24.9, 24.6, 22.0. MS-ESI$^+$: *m/z* 405 [M+H]$^+$, Elem. Anal. Calcd for $C_{22}H_{36}N_4OS$: C, 65.31; H, 8.97; N, 13.85, S, 7.92. Found: C, 65.29; H, 8.93; N, 13.89, S, 7.93.

Catalyst **5d**: (flash chromatography, 3 × 16 cm silica, CH_2Cl_2/CH_3OH 95:5, then CH_2Cl_2/CH_3OH 9:1, then CH_2Cl_2/CH_3OH 9:1 + 1% TEA, R_f = 0.50, ninhydrin TLC visualization). $[\alpha]_D^{23} = +1.5$ (*c* 1.01, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.0 (br, 1H, CHN*H*CS), 6.02 (br, 1H, *H*NCH$_3$), 4.75 (br, 1H, C*H*), 3.65 (m, 1H, C*H*NHCS), 2.84 (d, *J* = 4.9 Hz, 3H, NHCH_3), 2.50 (m, 1H, C*H*N(CH$_3$)$_2$), 2.30 (s, 3H, N(CH_3)$_2$), 2.26 (s, 3H, N(CH_3)$_2$), 2.33 (m, 1H, NHCHCH_2), 1.90 (m, 1H, CH_2CHN(CH$_3$)$_2$), 1.87 (m, 1H, CH_2CH$_2$CHNH), 1.77 (m, 1H, CH_2CH$_2$CHN(CH$_3$)$_2$), 1.30 (m, 2H, CH_2CH$_2$CHNH and CH_2CH$_2$-CHN(CH$_3$)$_2$),1.23 (m, 1H, CH_2CHN(CH$_3$)$_2$),1.20 (m, 1H, NHCHCH_2), 1.10 (s, 9H, CHC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.8, 171.4, 66.9, 66.2, 55.8, 40.2, 34.7, 33.1, 26.8, 26.0, 25.0, 24.5, 22.0. MS-ESI$^+$: *m/z* 329 [M+H]$^+$, Elem. Anal. Calcd for $C_{16}H_{32}N_4OS$: C, 58.50; H, 9.82; N, 17.05, S, 9.76. Found: C, 58.55; H, 9.83; N, 16.99, S, 9. 71.

4.2. General procedure for Michael addition reaction of 2,4-pentanedione to *trans*-β-nitrostyrene

Thiourea catalyst **5a** (8.4 mg, 0.02 mmol, 0.1 equiv) and *trans*-β-nitrostyrene (30 mg, 0.20 mmol, 1 equiv) were charged in a 10 mL round bottom flask under nitrogen. Next Et_2O (0.5 mL) was added, and after 5 min of stirring at 23 °C, 2,4-pentanedione (0.023 mL, 0.22 mmol, 1.1 equiv) was added via syringe. The reaction mixture was stirred at 23 °C for 18 h, then the solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel (1 × 16 cm silica, petroleum ether/AcOEt 7:3, R_f = 0.25) to afford pure 3-((*R*)-2-nitro-1-phenylethyl)pentane-2,4-dione (45 mg, 0.18 mmol, 90% yield). ^{1}H NMR (300 MHz, CDCl3): δ 7.35–7.1 (m, 5H), 4.65–4.55 (m, 2H), 4.3 (d, *J* = 10.9 Hz, 1H), 4.2 (m, 1H), 2.3 (s, 3H), 1.9 (s, 3H). HPLC (Daicel Chiralpak AD, hexane/*i*-propanol 85:15, flow rate = 1 mL/min, *P* = 22 bar, λ = 210 nm): t_{minor} = 9.6 min, t_{major} = 12.8 min, ee = 85%. $[\alpha]_D^{20} = -14.0$ (*c* 0.1, $CHCl_3$). Data are in agreement with those reported by Wang et al.[20]

4.3. General procedure for Mannich reaction of diethyl malonate to imines

Thiourea catalyst **5a** (8 mg, 0.019 mmol, 0.1 equiv) and imine (0.19 mmol, 1 equiv) were charged in a 10 mL round bottom flask under nitrogen. Toluene (0.5 mL) was added, and after 5 min of stirring at indicated temperature, diethyl malonate (0.058 mL, 0.38 mmol, 2 equiv) was added via syringe. The reaction mixture was stirred at the indicated temperature for the appropriate time, then the solvent was evaporated in vacuo and the crude was purified by flash chromatography on silica gel.

4.3.1. *N*-Cbz product 10b

(1 × 16 cm silica, petroleum ether/AcOEt 85:15, R_f = 0.17, cerium sulfate-ammonium molybdate TLC visualization). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4–7.2 (m, 10H), 6.45 (d, 1H), 5.55 (m, 1H), 5.05 (dd, 2H), 4.2–4.0 (m, 4H), 3.85 (d, 1H), 1.2 (t, 3H), 1.1 (t, 3H). HPLC (Daicel Chiralpak IB, hexane/*i*-propanol 98:2, flow rate = 0,8 mL/min, *P* = 27 bar, λ = 210 nm): t_{minor} = 41.7 min, t_{major} = 44.3 min. $[\alpha]_D^{20} = +6.1$ (*c* 0.1, $CHCl_3$). (*S*)-enantiomer.

Data are in agreement with those reported by Yamaoka et al.[21]

4.3.2. *N*-Boc product 10a

(1 × 16 cm silica, petroleum ether/AcOEt 7:3, R_f = 0.25) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3 (m, 5H), 6.25 (br s, 1H), 5.4 (br s, 1H), 4.35–4.25 (m, 4H), 4.1 (d, 1H), 3.7 (s, 3H), 1.5 (t, 3H), 1.25 (t, 9H), 1.15 (t,

3H). HPLC (Daicel Chiralpak AD, hexane/*i*-propanol 8:2, flow rate = 0.8 mL/min, $P = 17$ bar, $\lambda = 210$ nm) $t_{minor} = 11.2$ min, $t_{major} = 12.8$ min. (*S*)-enantiomer.

4.3.3. *N*-Ts product 10d

(1×16 cm silica, petroleum ether/AcOEt 85:15, $R_f = 0.20$, cerium sulfate-ammonium molybdate TLC visualization). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, 2H), 7.20–7.10 (m, 7H), 6.35 (d, 1H), 5.20 (dd, 1H), 4.20–4.0 (m, 4H), 2.36 (s, 3H), 1.2 (m, 6H). HPLC (Daicel Chiralpak IB, hexane/*i*-propanol 95:5, flow rate = 0.8 mL/min, $P = 29$ bar, $\lambda = 210$ nm): $t_{minor} = 30.9$ min, $t_{major} = 34.6$ min. (*S*)-enantiomer.

4.3.4. *N*-COOMe product 10c

(1.5×14 cm silica, petroleum ether/AcOEt 85:15, $R_f = 0.10$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 6.40 (br s, 1H), 5.55 (br s, 1H), 4.25–4.0 (m, 4H), 3.85 (d, 1H), 3.70 (s, 3H), 1.25 (t, 3H), 1.15 (t, 3H). HPLC (Daicel Chiralpak AD, hexane/*i*-propanol 80:20, flow rate = 0.8 mL/min, $P = 18$ bar, $\lambda = 210$ nm): $t_{minor} = 16.5$ min, $t_{major} = 20.5$ min. (*S*)-enantiomer.

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References

1. Reviews: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062.
2. Reviews: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999; (b) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909; (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
3. McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6130, and references cited therein.
4. (a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418; (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.
5. Hashimoto, T.; Maruoka, K. J. *Am. Chem. Soc.* **2007**, *129*, 10054, and references cited therein.
6. Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.
7. For selected very recent examples see: (a) Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606; (b) Andres, J. M.; Manzano, R.; Pedrosa, R. *Chem. Eur. J.* **2008**, *14*, 5116; (c) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 46; (d) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110; (e) Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. *Chem. Commun.* **2008**, 1431.
8. See: Connon, S. J. *Chem. Commun.* **2008**, 2499, and references cited therein.
9. Review: Yu, X.; Wang, W. *Chem. Asian. J.* **2008**, *3*, 516.
10. For selected very recent examples see: (a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Muller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 817; (b) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878; (c) Yakalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 418 and references cited therein.
11. Review: Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.
12. See for example: (a) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366; (b) Huang, H.; Jacobsen, E. N. . *J. Am. Chem. Soc.* **2006**, *128*, 7170.
13. Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686.
14. Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7466.
15. See Section 4 for further details about the isolation, purification and characterization of **5a** and all new compounds.
16. See for example: Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964. and review 4b.
17. See Section 4 for detailed description of the synthesis and characterization of the acetic adduct of compound **5a**.
18. All attempts to improve the enantioselection of reactions promoted by neutral **5a** were unsuccessful.
19. The possibility that in diethyl ether adduct **5a**/**AcOH** operates at least in part in heterogeneous catalysis conditions cannot be ruled out.
20. Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.
21. Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, *16*, 2571.