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Direct Enantioselective Michael Addition of Aldehydes to Vinyl Ketones Catalyzed by Chiral Amines

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Received December 11, 2002

Chiral amines such as (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine and the C_2-symmetric (2*S*,5*S*)-2,5-diphenylpyrrolidine can catalyze the direct enantioselective Michael addition of simple aldehydes to vinyl ketones. The conditions for this organocatalytic reaction have been optimized and it has been found that the chiral amines catalyze the formation of optically active substituted 5-keto aldehydes in good yields and enantioselectivities, using aldehydes and, e.g., methyl vinyl ketone as starting compounds. Taking into account that the chiral amine can activate the aldehyde and/or the enone, the mechanism for the reaction has been investigated. On the basis of intermediate synthesis, nonlinear effect, and theoretical investigations, the mechanism for the catalytic direct enantioselective Michael addition of aldehydes to vinyl ketones is discussed.

Introduction

Catalytic enantioselective conjugate additions are cornerstone reactions in organic chemistry.[1] This class of reactions has over the years been dominated by the application of chiral Lewis acids as catalysts and it is only recently that chiral organocatalysts[2] have been applied as catalysts for this class of enantioselective transformations.

Within the past few years the use of small organic molecules, such as chiral amines, as catalysts for a wide range of enantioselective organic reactions has been demonstrated. These organocatalytic transformations cover a wide range of reactions including Diels−Alder,[3] aldol,[4] Mannich,[5] 1,3-dipolar cycloadditions,[6] α-amination,[7] Friedel−Crafts alkylation,[8] Robinson annulation,[9] and Michael reactions.[10]

Although impressive results have been achieved in many organocatalytic asymmetric reactions, the number of reports on enantioselective Michael addition reactions where excellent enantioselectivities (>90% ee) have been obtained is limited to cyclic substrates[10e] or very low yielding reactions.[10d]

Recently, we have introduced a chiral imidazolidine as a highly enantioselective catalyst for the addition of nitroalkanes and malonates to α,β-unsaturated enones.[11] However, generally carbon nucleophiles with an active methylene center were studied in these reactions.

To the best of our knowledge there has not yet been developed an organocatalytic direct enantioselective Michael addition of simple aldehydes to vinyl ketones.[12] In this paper we present the development of the orga-

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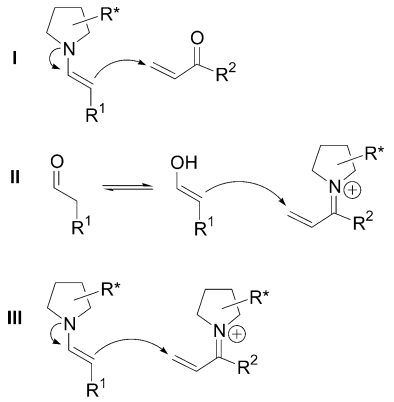
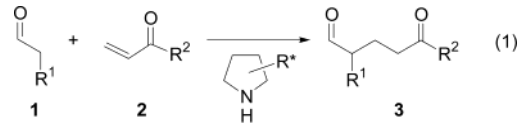
10.1021/jo026837p CCC: $25.00
Published on Web 05/01/2003

SCHEME 1



nocatalytic direct enantioselective Michael addition of aldehydes **1** to vinyl ketones **2** using chiral amines as the catalysts leading to optically active substituted 5-keto aldehydes **3** (eq 1).



A challenge for the direct enantioselective Michael addition of aldehydes to vinyl ketones is also to understand the catalytic effect of the chiral amine, i.e. does the chiral amine activate the aldehyde and/or the vinyl ketone. At least three different catalytic approaches can be envisaged: The chiral amine can activate the aldehyde with the formation of an enamine intermediate, which acts as a nucleophile attacking the vinyl ketone as outlined in Scheme 1, **I**. Another possibility is that the vinyl ketone is activated by the chiral amine with formation of an iminium ion (Scheme 1, **II**). The formation of the iminium ion generates a more electrophilic β-carbon atom of the vinyl ketone, which can react with the enol form (if present) of the aldehyde. The third possibility presented in Scheme 1 **III** is the simultaneous activation of both the aldehyde as an enamine intermediate and the vinyl ketone as an iminium ion. This approach can be considered as a double activation. The mechanism for the direct enantioselective Michael addition will be discussed on the basis of the different reaction courses presented in Scheme 1.

The optically active products formed, substituted 5-keto aldehydes **3** (eq 1) by the direct addition of aldehydes to vinyl ketones, can undergo various synthetic transformations giving, e.g., cyclohex-2-enone derivatives, which can be used as versatile starting materials for the synthesis of, e.g., optically active terpenoids,[13] and for the preparation of optically active γ-lactones,[14] which often occur in nature or as a part of natural products. Substituted 5-keto aldehydes have previously been prepared by, e.g., the 1,4-addition of masked aldehydes (i.e., piperidinone-amine)[15] or trimethylsilyl enol ether in the presence of a Lewis acid.[16]

TABLE 1. Results for the Screening of Different Chiral Amines 4a−h as Catalyst (20 mol %) for the Direct Catalytic Enantioselective Addition of 3-Phenylpropanal (1a) to Methyl Vinyl Ketone (2a) (ratio 1:3) under Neat Reaction Conditions at Room Temperature

entry	catalyst	reaction time (h)	conv[a] (%)	ee[b] (%)
1	**4a**	72	15	20
2	**4b**	36	90	15
3	**4c**	40	15	74
4	**4d**	24	55	66
5	**4e**	20	70	60
6	**4f**	40	40[c]	40
7	**4g**	18	25	64[d]
8	**4h**	18	15	73[d]

[a] Measured by ^{1}H NMR spectroscopy. [b] Determined by chiral stationary phase GC. [c] In this reaction, under both the neat conditions and in CH_2Cl_2 as the solvent, the self-aldolization product is also formed. [d] The other enantiomer relative to entries 1−6 was obtained.

Results and Discussion

A series of different chiral amines (**4a**−**i**), based on the pyrrolidine skeleton, was initially screened as catalysts for the direct enantioselective Michael addition of 3-phenylpropanal (**1a**) to methyl vinyl ketone (**2a**) under neat reaction conditions (eq 2). The results are given in Table 1.

All the chiral amines **4a**−**h** can catalyze the formation of optically active 2-benzyl-5-oxohexanal (**3a**) by the direct addition of 3-phenylpropanal (**1a)** to methyl vinyl ketone (**2a**) (Table 1). However, the catalytic and enantioselective properties of **4a**−**h** differ significantly. The highest conversion is obtained by using (*S*)-prolinol (**4b**) as the catalyst; however, the Michael-addition adduct **3a** was formed with only 15% ee (entry 2). The highest enantiomeric excess of **3a** (74% ee and 73% ee) was obtained by using (*S*)-2-[bis(phenyl)hydroxymethyl]pyrrolidine (**4c**) and the C_2-symmetric (2*S*,5*S*)-2,5-diphenylpyrrolidine (**4h**) as the catalysts, but unfortunately the conversion was very low, 15% after 40 and 18 h, respectively (entries 3 and 8). In terms of reaction time, yield, and enantioselectivity (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**4e)** gave the best results as 70% conversion (20 h) and 60% ee of **3a** was achieved (entry 5). For the reaction of other aldehydes, such as the reaction of butanal (**1b**) with **2a**, using the chiral amines **4a**−**h** as the catalysts, the trends in yield and enantioselectivity of 2-ethyl-5-oxohexanal (**3b**) were similar as those obtained for the reaction of 3-phenylbutanal (**1a**) with **2a**. The reaction of, e.g., **1b** with **2a** catalyzed by

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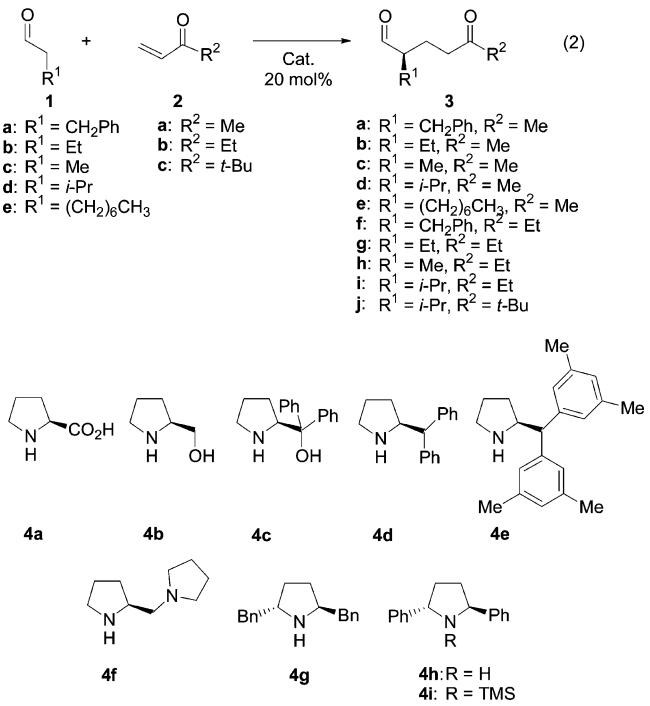


4h gave 10% conversion and 84% ee of **3b**. The chiral C_2-symmetric *N*-TMS-protected amine **4i** gave similar results in terms of enantioselectivity as 84% ee of **3b** was obtained. However, the yield of the 5-keto aldehyde obtained was, after 20 and 96 h reaction time, only 35% and 55%, respectively. Furthermore, catalyst **4i** is significantly more difficult to handle compared with the other catalysts as these are bench stable and can be used under ambient conditions, taking no precautions to exclude water. On the basis of these screening results and evaluations, the catalysts **4e** and **4h** were chosen for further development.

Several attempts to improve the conversion and enantioselectivity under the neat reaction conditions have been performed. For the reaction of butanal (**1b**) with methyl vinyl ketone (**2a**) in the presence of (2*S*,5*S*)-2,5-diphenylpyrrolidine (**4h**) as the catalyst, the presence of additives such as *i*-PrOH, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), H_2O, $La(OTf)_3$, TMSCl, and TMSOTf under various reaction conditions did not improve the yield, nor the enantiomeric excess, of 2-ethyl-5-oxohexanal (**3b)** compared to the reaction in the absence of additives where only 10% yield and 84% ee of **3b** were obtained. However, sonication of the reaction leads to a significant improvement of the reactivity as a conversion of 65% was found after 20 h and **3b** was formed in 78% ee together with a small amount (5%) of self-aldolization product.

The butanal (**1b**):methyl vinyl ketone (**2a**) ratio is, using neat conditions, important for the outcome of the reaction. A 10:1 ratio of **2a**:**1b** and application of catalyst (2*S*,5*S*)-2,5-diphenylpyrrolidine (**4h**; 20 mol %) gave 2-ethyl-5-oxohexanal (**3b**) in 15% yield and 84% ee after 72 h reaction time, while a 1:1 ratio of **1b**:**2a** improved the yield of **3b** to 60% with 65% ee in only 24 h; however, a significant amount of self-aldolization product was also formed. Changing the **2a**:**1b** ratio to 1:2 afforded only 40% yield of **3b** with an enantiomeric excess of 65% ee and a significant amount of self-aldolization product.

TABLE 2. Results for the Direct Enantioselective Michael Addition of Butanal (1b) to Methyl (2a) Vinyl Ketone Catalyzed by (*S*)-2-[Bis(3,5-dimethylphenyl)methyl]pyrrolidine (4e) and (2*S*,5*S*)-2,5-Diphenylpyrrolidine (4h; 20 mol %) in Different Solvents and Additives at Room Temperature[a]

		catalyst **4e**		catalyst **4h**	
entry	solvent	conv[b] (%)	ee[c] (%)	conv[b] (%)	ee[c] (%)
1		87	77	10	84
2	CH_2Cl_2	65	67	5	85
3	EtOH	>90	58	25	58
4	Et_2O	>90	70	28	80
5	THF	17	85	20	84
6	THF−HFIP[d]	80	79	40	78
7	THF−HFIP[e]	45	79		

[a] Reaction time 24 h. [b] Measured by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary phase GC. [d] 1 equiv of HFIP relative to butanal (**1b**) was added. [e] 0.2 equiv of HFIP relative to butanal (**1b**) was added.

The organocatalytic direct Michael addition of aldehydes to vinyl ketones can also be performed as solution reactions. Table 2 presents the reaction of butanal (**1b**) with methyl vinyl ketone (**2a**) catalyzed by (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**4e**) and (2*S*,5*S*)-2,5-diphenylpyrrolidine (**4h**) at room temperature in various solvents and additives.

The Michael addition of butanal (**1a**) to methyl vinyl ketone (**2a**) catalyzed by (*S*)-2-[bis(3,5-dimethylphenyl)-methyl]pyrrolidine (**4e**) proceeds smoothly (87% conversion) under neat conditions and 2-ethyl-5-oxohexanal (**3b**) was obtained with 77% ee (Table 2, entry 1). However, under these conditions several byproducts, which were difficult to remove from the desired product, were also formed. Among the solvents tested, the combination of THF−HFIP turned out to be the solvent composition of choice as a very clean reaction, with high conversion, takes place with the formation of **3b** having 79% ee (entry 6). A reduction of the amount of HFIP from 1 to 0.2 equiv relative to the aldehyde leads to a lower conversion (entry 7). The C_2-symmetric (2*S*,5*S*)-2,5-diphenylpyrrolidine (**4h**) catalyst generally gives higher enantioselectivity compared to **4e**; however, the catalytic properties of this catalyst under the various reaction conditions presented in entries 1−6 are not satisfactory from a synthetic point of view, as the conversions are <40%. It should also be noted that 3-phenylpropanal (**1a**), butanal (**1b**), and propanal (**1c**) all react with methyl vinyl ketone in the presence of **4h** as the catalyst in THF as the solvent; however, after 24 h of reaction time only up to 25% of the corresponding 5-keto aldehydes **3a**−**c** were obtained. The enantiomeric excesses of these 5-keto aldehydes were 75% (**3a**), 84% (**3b**), and 83% (**3c**).

A series of aldehydes **1a**−**e** has been reacted with the vinyl ketones **2a**−**c** in the presence of (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**4e**; eq 1) as the catalyst and in THF as the solvent in the presence of HFIP. The results are given in Table 3.

The different aldehydes **1a**−**e** all added smoothly to methyl vinyl ketone (**2a**) catalyzed by (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**4e**; Table 3, entries 1−5). The yields of the substituted 5-keto aldehydes are ranging from 78 to 91% and the enantiomeric excess from 64% ee (**3c**) for the reaction of propanal **1c** (entry 3) to 82% ee (**3d**) for 3-methylbutanal (**1d**; entry 4). Ethyl vinyl

TABLE 3. Results for the Direct Enantioselective Michael Addition of Aldehydes 1a−e to the Vinyl Ketones 2a−c Catalyzed by (*S*)-2-[Bis(3,5-dimethylphenyl)methyl]pyrrolidine (4e; 20 mol %) in THF−HFIP

entry	aldehyde	vinyl ketone	reaction time (h)	product; yield[a] (%)	ee[b] (%)
1	**1a**	**2a**	30	**3a**; 78	65[c]
2	**1b**	**2a**	30	**3b**; 86	79[c]
3	**1c**	**2a**	30	**3c**; 83	64[c]
4	**1d**	**2a**	80	**3d**; 91	82[c]
5	**1e**	**2a**	30	**3e**; 82	76[d]
6	**1a**	**2b**	40	**3f**; 72	58[c]
7	**1b**	**2b**	40	**3g**; 80	73[d]
8	**1c**	**2b**	40	**3h**; 85	54[c]
9	**1d**	**2b**	96	**3i**; 93	75[c]
10	**1d**	**2c**	96	**3j**; 30	50[c,e]

[a] Isolated yield. [b] Determined by chiral stationary phase GC or HPLC (see Experimental Section). [c] The 5-keto-aldehyde was used for the determination of the enantiomeric excess. [d] The acetal protected aldehyde of the 5-keto-aldehyde was used for the determination of the enantiomeric excess. [e] Neat reaction conditions.

ketone (**2b**) reacts also with the aldehydes **1a**−**d** in the direct Michael reaction with the formation of the corresponding 5-keto aldehydes **3f**−**i** in good yield and with a slight decrease in enantiomeric excess (entries 6−9) compared to that of methyl vinyl ketone. For the more sterically hindered *tert*-butyl vinyl ketone (**2c**) the reaction with 3-methylbutanal (**1d**) proceeds slightly slower than that for the other vinyl ketones and the enantiomeric excess of the corresponding 5-keto aldehydes is also lowered (entries 10).

The use of (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**4e**) as the catalyst for the direct Michael addition of aldehydes to vinyl ketones leads to formation of the (*S*) enantiomer of the 5-keto aldehydes obtained from the aldehydes **1a**,**d** and the (*R*) enantiomer of the 5-keto aldehydes formed from the aldehydes **1b**,**c**,**e**.[13,17,18] However, the use of (2*S*,5*S*)-2,5-diphenylpyrrolidine (**4h**)-catalyst gave the opposite absolute configuration of the 5-keto aldehydes formed compared to catalyst **4e**. To gain information about the mechanism for the organocatalytic enantioselective direct addition of aldehydes to vinyl ketones a series of experiments and theoretical calculations have been performed.

The enantiomeric excess of the Michael adduct **3b** obtained from the addition of butanal (**1b**) to methyl vinyl ketone (**2a**) has been investigated in the presence of 2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**4e**) having various degrees of optical purity ranging from 0% ee to 100% ee in order to investigate for nonlinear effects of the reaction.[19,20] The results from these investigations are shown in Figure 1.

Much to our surprise we have found, although small, a negative nonlinear effect for the reaction of butanal (**1b**)

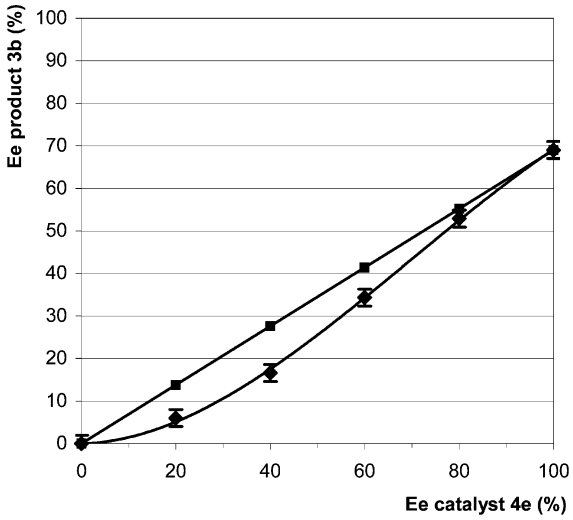
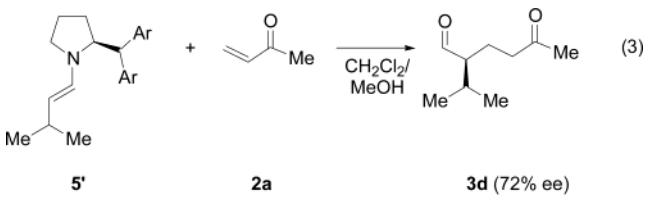


FIGURE 1. Enantiomeric excess of the Michael adduct **3b** obtained from addition of butanal (**1b**) to methyl vinyl ketone (**2a**) catalyzed by 2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**4e**) having various degrees of optical purity.

with methyl vinyl ketone (**2a**) catalyzed by 2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine (**4e**). It should be noted that Kagan et al. in their original work on nonlinear effects studying intramolecular aldol reactions catalyzed by proline also found a negative nonlinear effect.[19b] The small, but definite, convexity of the curve in Figure 1 indicates that probably more than one molecule of the chiral amine is involved in the transition state of the enantiodifferentiating step. We have also studied the reaction of **1b** with *tert*-butyl vinyl ketone (**2c**) in the presence of catalyst **4e** for nonlinear effects to investigate the influence of the more sterically hindered *tert*-butyl group on the stereochemical outcome of the reaction. However, the reaction of **2c** proceeds with a direct linearity of the enantiomeric excess of the product as a function of the enantiomeric excess of the catalyst, i.e. for this more sterically hindered substrate there is a linear effect. These results indicate that we can probably exclude the formation of an iminium ion intermediate when *tert*-butyl vinyl ketone is used as the vinyl ketone.

In relation to the different mechanistic approaches outlined in Scheme 1 we have performed a number of experiments. The chiral enamine **5′**, obtained by reaction of 3-methylbutanal (**1d**) with catalyst **4e**, was reacted with methyl vinyl ketone (**2a**; eq 3) and we were pleased to find that **5′** reacted smoothly with **2a** to give the 5-keto aldehyde **3d** in 72% ee.



Other mechanisms might also be envisaged; three of these possibilities are presented in Scheme 2.

The approach outlined in eq 4 in Scheme 2 is the enol-form of the aldehyde reacting with the iminium ion **6**. However, the addition of the enol-form of the, e.g., but-

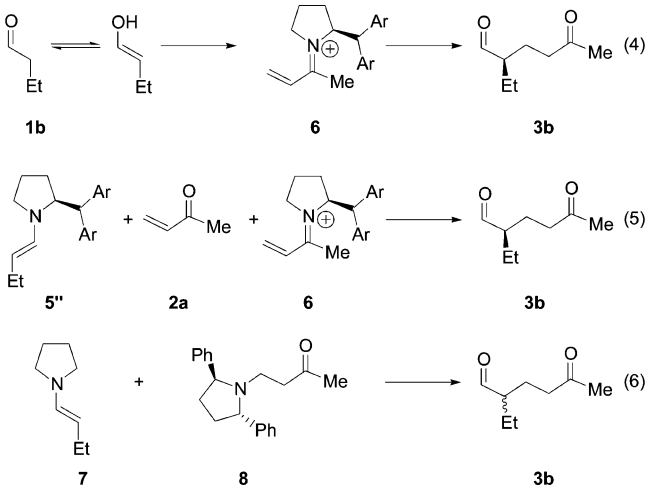
(17) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691.

(18) It should be noted that the priority of the 5-keto aldehydes changes for the different aldehydes.

(19) For a review about nonlinear effects see e.g.: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. It should also be noted that the first paper by Kagan et al. dealing with nonlinear effects was about proline-catalyzed intramolecular aldol reactions: (b) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.

(20) The reactions were carried out under neat conditions.

SCHEME 2



anal (**1b**) to the iminium ion **6**, formed from methyl vinyl ketone and the chiral amine, is probably an unlikely reaction as the keto−enol equilibrium constant is very small.[21] However, as we will present later we cannot exclude that an iminium ion is involved in the reaction course.

The reaction course proposed in eq 5 in Scheme 2, the activation of butanal (**1b**) as an enamine intermediate **5″** reacting with the vinyl ketone **2a** and the iminium ion **6**, is probably a likely process taking place for the Michael addition of the aldehydes to the less sterically hindered vinyl ketones catalyzed by the chiral amines. As demonstrated in eq 3, the enamine **5′** is a likely intermediate for the reaction. Furthermore, the small negative nonlinear effect shown in Figure 1 indicates that probably more than one molecule of the chiral amine is involved in the transition state of the reaction. To account for this we propose that the chiral amine catalyst can also react with the vinyl ketone under formation of the iminium intermediate **6** and that the enamine intermediate can add both to the vinyl ketone **2a** and **6**. The nonlinear effect observed can thus be the effect of match vs mismatch of the enamine intermediate **5** approaching the iminium intermediate **6**. One has to take into account that the concentration of **6** is small compared to the concentration of the vinyl ketone; however, **6** is significantly more reactive than the vinyl ketone.

We have observed that the chiral amine can also undergo a 1,4-addition to the vinyl ketone. This observation led us to investigate the role of this species, thus we ran the reaction of the preformed enamine **7** (in the actual reaction studied we used pyrrolidine as the amine catalyst) with the 1,4-adduct **8** (the C_2-symmetric catalyst **4h** was used and it was possible to isolate the 1,4 adduct with this amine). However, we were not able to detect the formation of the corresponding 5-keto aldehyde **3b** under various reaction conditions.

Taking into account the absolute configuration of the chiral center formed in these reactions and based on the different experiments performed we proposed that the most likely reaction course for this organocatalyzed direct addition of aldehydes to vinyl ketones is the one outlined in eq 5 in Scheme 2.

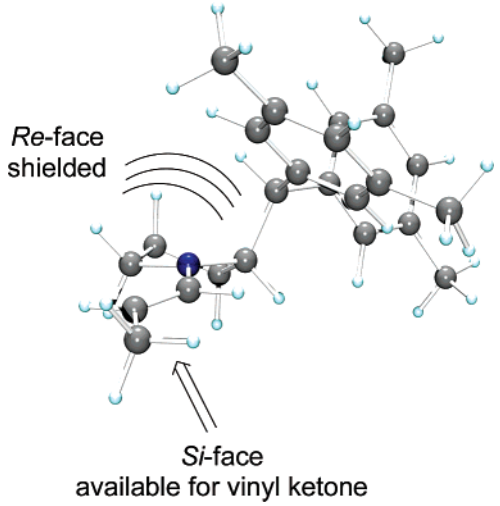
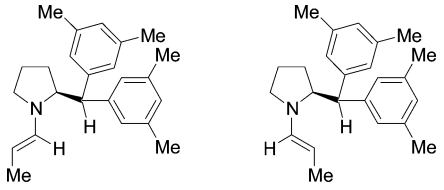


FIGURE 2. Optimized intermediate obtained from (*S*)-2-[bis-(3,5-dimethylphenyl)methyl]pyrrolidine catalyst and propanal showing the shielding of the *Re*-face of the enamine intermediate.

To gain some information about the enamine intermediate in these reactions we have performed a series of theoretical investigations. We have optimized the structure of the enamine intermediate obtained from the (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine catalyst and propanal using ab initio calculation and a 3-21G* basis set.[22] The structures of the two intermediates **5a** and **5b**



were optimized and for the former the total energy of the optimized structure was calculated to be −975.8902 au, while the latter was found to be 4 kcal/mol less stable. The former intermediate (**5a**) being the most stable is in agreement with calculations on, e.g., the intermediate in proline-catalyzed aldol reactions.[7c]

The optimized structure is shown in Figure 2 and it appears that one of the 3,5-dimethylphenyl groups of the (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine catalyst shields the *Re*-face of the enamine intermediate, while the *Si*-face is available for approach. We propose that the major reaction path is the addition of the vinyl ketone to the *Si*-face of the enamine intermediate outlined in Figure 2. However, to account for the negative nonlinear effect we cannot exclude that an iminium intermediate, probably present in a very small amount and more reactive compared to the vinyl ketone, also contributes to the reaction.

We have also tried to investigate the enantioinduction obtained when using the less active C_2-symmetric (2*S*,5*S*)-

(21) The keto−enol equilibrium constant for isobutyraldehyde is ca. 1.4×10^{-4}: Chiang, Y.; Kresge, A. J.; Walsh, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 6314.

(22) PC Spartan Plus, Version 2: Based on 3-21G* basis set optimized structures.

2,5-diphenylpyrrolidine catalyst. However, at the present stage of investigation we cannot account for the change in absolute configuration when this catalyst is used compared to (*S*)-2-[bis(3,5-dimethylphenyl)methyl]-pyrrolidine as the catalyst.

In summary, we have developed the first organocatalytic direct enantioselective Michael addition of simple aldehydes to vinyl ketones. The reaction proceeds with the formation of optically active substituted 5-keto aldehydes in good yields and enantioselectivities, using (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine as the catalyst. On the basis of a series of experimental and theoretical investigations it is proposed that the major reaction path is the addition of the vinyl ketone to the *Si*-face of the enamine intermediate formed from reaction of the aldehyde with the chiral amine catalyst.

Experimental Section

General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent, and were reported in ppm relative to $CHCl_3$ (δ 7.26) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ 77.00) for ^{13}C NMR. Coupling constants in ^{1}H NMR are in Hz. Flash chromatography (FC) was carried out with silica gel 60 (230−400 mesh). Optical rotations are reported as follows: $[\alpha]^{rt}_D$ (*c* in g per 100 mL, solvent). The enantiomeric excess (ee) of the products was determined by chiral stationary phase GC or HPLC analysis of the 5-keto aldehydes or of the corresponding cyclic acetals, obtained after the selective protection of aldehyde functionality (see below for the general procedure) as indicated in the respective entries.

Materials. All solvents and commercially available chemicals were used as received. 4,4-Dimethylpent-1-en-3-one (**2c**),[23] (*S*)-2-(diphenylmethyl)pyrrolidine (**4d**),[24] (*S*)- and (*R*)-2-[bis-(3,5-dimethylphenyl)methyl]pyrrolidine (**4e**),[24] (2*S*,5*S*)-2,5-dibenzylpyrrolidine (**4g**),[25] and (2*S*,5*S*)-2,5-diphenylpyrrolidine (**4h**[26] were prepared according to literature procedures.

General Procedure for the Catalytic Asymmetric Michael Addition to Vinyl Ketones. In an ordinary test tube equipped with a magnetic stirring bar, the catalyst (0.1 mmol) and the vinyl ketone (1.5 mmol) were dissolved in 0.5 mL of THF and the tube was closed with a rubber stopper and cooled to 0 °C. The aldehyde (0.5 mmol) was added followed by the addition of 0.5 mmol of HFIP and the mixture was allowed to warm to room temperature with stirring for the time indicated in the table. The crude reaction mixture was directly charged on the chromatography column and purified on silica.

(*S*)-2-Benzyl-5-oxo-hexanal (3a)[12a] was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 78%). Enantiomers were separated by GC with use of a Chiraldex G-TA chiral stationary phase: T_1 = 130 °C, 35 min; T_2 = 150 °C/2 °C/min; R_1 = 56 min (major), R_2 = 59 min (minor). $[\alpha]^{rt}_D$ −2.0° (*c* 2.1, $CHCl_3$, 65% ee).

(*R*)-2-Ethyl-5-oxo-hexanal (3b)[16] was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 86%). Enantiomers were separated by GC with use of a Chirasil Dex-CB chiral stationary phase: T_1 = 70 °C, 10 min; T_2 = 85 °C, 25 min/2 °C; R_1 = 28.5 min (major), R_2 = 29.1 min (minor). $[\alpha]^{rt}_D$ +7.7° (*c* 1.8, $CHCl_3$, 79% ee).

(*R*)-2-Methyl-5-oxo-hexanal (3c)[27] was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 83%). Enantiomers were separated by GC with use of a Chirasil Dex-CB chiral stationary phase: T_1 = 70 °C, 20 min; T_2 = 80 °C, 20 min/2 °C; R_1 = 28.5 min (major), R_2 = 29 min (minor). $[\alpha]^{rt}_D$ +5.4° (*c* 1.2 mg/mL, $CHCl_3$, 64% ee).

(*S*)-2-Isopropyl-5-oxo-hexanal (3d)[12a,17] was purified by FC with Et_2O/pentane and isolated as a colorless oil (yield 91%). Enantiomers were separated by GC with use of a Chirasil Dex-CB chiral stationary phase: T_1 = 90 °C, 25 min; R_1 = 23.7 min (major), R_2 = 25.3 min (minor). $[\alpha]^{rt}_D$ +39.5° (*c* 1.3, $CHCl_3$, 82% ee).

(*R*)-2-(3-Oxo-butyl)-octanal (3e)[12a] was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 82%). After the selective protection of the aldehyde functionality as a cyclic acetal, the ee was determined by HPLC with use of a Chiralpak AS column chiral stationary phase (99/1 hexane/*i*-PrOH; flow rate 0.5 mL/min; t_{minor} = 14.4 min; t_{major} = 15.3 min). $[\alpha]^{rt}_D$ +9.1° (*c* 0.73, $CHCl_3$, 76% ee).

(*S*)-2-Benzyl-5-oxo-heptanal (3f)[12a] was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 72%). The ee was determined by HPLC with use of a Chiralpak AD column chiral stationary phase (99/1 hexane/*i*-PrOH; flow rate 1 mL/min; t_{minor} = 15.6 min; t_{major} = 16.4 min). $[\alpha]^{rt}_D$ −3.4° (*c* 0.77, $CHCl_3$, 58% ee).

(*R*)-2-Ethyl-5-oxo-heptanal (3g) was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 80%). After the selective protection of the aldehyde functionality as a cyclic acetal, the enantiomers were separated by HPLC with use of a Chiralpak AS column chiral stationary phase (98/2 hexane/*i*-PrOH; flow rate 1 mL/min; t_{minor} = 6.7 min; t_{major} = 7.3 min). $[\alpha]^{rt}_D$ +6.2° (*c* 1.1, $CHCl_3$, 73% ee); ^{1}H NMR δ 0.92 (t, *J* = 7.6 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 1.48−1.88 (m, 4H), 2.14−2.22 (m, 1H), 2.37−2.45 (m, 4H), 9.54 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR δ 7.59, 11.21, 21.77, 21.86, 35.83, 39.14, 52.49, 204.81, 210.54; HRMS *m*/*z* 179.1009 (M + Na^+) calcd for $C_9H_{16}NaO_2^+$ 179.1048.

(*R*)-2-Methyl-5-oxo-heptanal (3h) was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 85%). Enantiomers were separated by GC with use of a Chirasil Dex-CB chiral stationary phase. $[\alpha]^{rt}_D$ +3.5° (*c* 1.3, $CHCl_3$, 54% ee); ^{1}H NMR δ 1.04 (t, *J* = 7.4 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.67 (td, *J* = 14.4, 6.4 Hz 1H), 1.96 (td, *J* = 14.4, 6.4 Hz 1H), 2.33−2.48 (m, 5H), 9.59 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR δ 7.70, 13.39, 24.02, 35.90, 39.07, 45.50, 204.49, 210.62; HRMS *m*/*z* 164.9265 (M + Na^+) calcd for $C_8H_{14}NaO_2^+$ 165.0891.

(*S*)-2-Isopropyl-5-oxo-heptanal (3i) was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 93%). Enantiomers were separated by GC with use of a Chirasil Dex-CB chiral stationary phase: T_1 = 70 °C, 20 min; T_2 = 90 °C, 16 min/2 °C; R_1 = 35.5 min (major), R_2 = 35.7 min (minor). $[\alpha]^{rt}_D$ +22.2° (*c* 0.8, $CHCl_3$, 75% ee); ^{1}H NMR δ 0.96 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H), 1.76−1.84 (m, 2H), 2.01−2.08 (m, 2H), 2.29−2.50 (m, 4H), 9.59 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR δ 7.70, 19.39, 19.44, 20.28, 28.32, 35.97, 39.83, 57.59, 205.46, 210.94; HRMS *m*/*z* 193.1191 (M + Na^+) calcd for $C_{10}H_{18}NaO_2^+$ 193.1204.

(*S*)-2-Isopropyl-6,6-dimethyl-5-oxo-heptanal (3j) was purified by FC with Et_2O/CH_2Cl_2 and isolated as a colorless oil (yield 30%). Enantiomers were separated by GC with use of a Chiraldex G-TA chiral stationary phase: T_1 = 70 °C, 10 min; T_2 = 110 °C, 16 min/5 °C; R_1 = 33.7 min (major), R_2 = 33.2 min (minor. $[\alpha]^{rt}_D$ +4.8° (*c* 1.1, $CHCl_3$, 50% ee); ^{1}H NMR δ 0.96 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 1.11 (s, 9H), 1.76−1.82 (m, 2H), 2.00−2.06 (m, 2H), 2.38−2.56 (m, 2H), 9.59 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR δ 19.50, 19.68, 20.31, 26.34 (3), 28.44, 34.12, 44.02, 57.70, 205.56, 215.41; HRMS *m*/*z* 221.1532 (M + Na^+) calcd for $C_{12}H_{22}NaO_2^+$ 221.1517.

General Procedure for the Selective Acetalization of Keto Aldehydes. Pure keto aldehydes (**3e** and **3g**) were dissolved in CH_2Cl_2 followed by the addition of 1.1 equiv of ethane-1,2-diol and a catalytic amount of *p*-toluensulfonic acid (0.1 equiv). After being stirred for 1 h, the reaction mixture

(23) Bates, F. X.; Donnelly, J. A.; Keegan, J. R. *Tetrahedron* **1991**, *47*, 4991.
(24) O'Hagan, D.; Tavasli, M.*Tetrahedron*: *Asymmetry* **1999**, *10*, 1189.
(25) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *43*, 9735.
(26) Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron: Asymmetry* **1995**, *6*, 409.
(27) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.

was quenched with $NaHCO_3$, extracted with Et_2O, and dried over anhydrous Na_2SO_4. ^1H NMR and GC analysis showed that the protection of the aldehyde functionality takes place with high chemoselectivity (>10 to <1).

Acknowledgment. This work was made possible by a grant from The Danish National Research Foundation.

JO026837P