Asymmetric Conjugate Addition of Ketones to β -Nitrostyrenes by means of 1,2-Amino Alcohol-derived Prolinamides as Bifunctional Catalysts

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Abstract

Different L-prolinamides **21**, prepared from L-proline and chiral β -amino alcohols are active bifunctional catalysts for the direct nitro-Michael addition of ketones to β -nitrostyrenes. In particular, catalyst **21e** prepared from L-proline and (1*S*,2*R*)-*cis*-1-amino-2-indanol exhibits the highest catalytic performance working in polar aprotic solvents such as NMP especially in the presence of 20 mol% of acid additives such as 4-nitrobenzoic acid or under microwave heating. High *syn*-diastereoselectivities (up to 94% *de*) and good enantioselectivities (up to 80% *ee*) are obtained at r.t. Moreover,

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catalyst **21e** can be easily recovered and reused. ESI-MS studies are used to characterize the intermediates assumed for the catalytic cycle. The stereochemical control attending Michael addition reactions between ketones and nitrostyrenes catalyzed by prolinamide derivatives **21** have been investigated using computational density functional methods. Transition state structures for the rate-limiting C–C bond-forming step are calculated. Analysis of these structures indicates that hydrogen bonding plays an important role in catalysis and that the energy barrier for *Re*-face attack to form *syn*-(4*S*,5*R*) products is lower than that for the *Si*-face attack leading to *syn*-(4*R*,5*S*) products.

Introduction

Organocatalytic asymmetric carbon-carbon and carbon-heteroatom bond-forming reactions have been extensively investigated in recent years.^[1] The conjugate Michael addition^[2] plays a particularly important role among the numerous asymmetric carbon-carbon bond forming reactions since it represents one of the most elegant and attractive ways to introduce chirality into a Michael acceptor.^[3] Particularly interesting and challenging is the asymmetric conjugate addition of a carbon nucleophile to a nitroalkene since it represents a very useful synthetic method for the preparation of chiral nitroalkanes with at least two vicinal stereogenic centers in a single step. Chiral nitroalkanes are valuable building blocks in organic synthesis because they can be transformed into a wide variety of different functional groups such as amines, ketones, carboxylic acids, nitrile oxides, etc.^[4] Barbas,^[5] and List^[6] independently reported the first organocatalytic addition of ketones to *trans*- β -nitrostyrene using L-proline (**1**) as catalyst with good yields but very low enantioselectivities (0 to 23% *ee*). A related study by Enders showed a strong solvent effect in the reaction since in MeOH the enantioselectivity could be increased to 76% for the major *syn* diastereomer in the reaction between 3-pentanone and *trans*- β -nitrostyrene employing a 20 mol% of L-proline as catalyst.^[7] Since these preliminary studies, very effective catalytic systems (**2-20**)^[8-26] have been developed for the asymmetric Michael reaction of ketones with nitroalkenes being the process generally *syn*-selective (Scheme 1). Best improvements to this reaction have been mostly achieved using pyrrolidine-based catalytic derivatives. However, chiral acyclic primary amines such as **10**, thiourea-amine bifunctional catalysts such as **8**, **12**, **13**, **16** and **17**, and small dipeptides such as **9** have been also shown to be very effective catalyst as shown in Scheme 1 for the addition of ketones to

trans- β -nitrostyrene. Moreover, some of these catalysts have some important features to emphasize such as bipyrrrolidine **2**, which is a very active organocatalyst for the *anti*-conjugate addition of α -hydroxyketones to nitrostyrenes.^[8] A similar sense of relative stereoinduction has been shown by chiral primary amine-thiourea catalysts **13**^[19] and **17**^[23] developed by Tsogoeva and Jacobsen, respectively, in the conjugate addition of acyclic ketones to nitroolefins giving predominantly the *anti* Michael adducts due to the participation of a *Z*-enamine intermediate. Catalysts **4**,^[10b] **16**,^[22] **19**,^[25] and **20**^[26] are very effective systems to perform the Michael addition under aqueous conditions such as brine (catalyst **4**) or neat water. On the other hand, the chiral imidazolium salt **15**^[21] performs much better than other chiral pyrrolidine catalysts in ionic liquids as reaction media. Furthermore, catalyst **15** and the fluorous sulfonamide **19** can be easily recycled by precipitation and fluorous solid-phase extraction, respectively, and reused without significant loss of activity and stereoselectivity.

Scheme 1. Enantioselective conjugate addition of ketones to *trans*- β -nitrostyrene

L-Prolinamide and derivatives have been shown as highly efficient catalysts for the direct aldol reaction of aldehydes with simple ketones in organic,^[27] ionic,^[28] and aqueous solvents.^{[27n],[29]} This type of organocatalysts have been also demonstrated to promote the enantioselective α -hydroxyamination reaction of α -branched aldehydes with good yields and moderate enantioselectivities^[30] as well as the α -selenylation of aldehydes^[31] and ketones^[31b] and the α -chlorination of aldehydes.^[32]

The initial aim in our organocatalysis program was to design several amino alcohol-derived organocatalysts where the amide and hydroxyl groups were expected to interact via double hydrogen bonding with the nitro group of the electrophile in order to enhance their reactivity as depicted in Scheme 2. A transient activation of the ketone donor through formation of an enamine on the secondary amino group was also anticipated.^[33] In a recent preliminary paper^[34] we indeed reported that amino alcohol-derived prolinamides **21** presumably serve as bifunctional organocatalysts for Michael addition reactions between 3-pentanone and β -nitrostyrenes with high levels of *syn*-diastereoselectivity (up to 94%) and good enantioselectivities (up to 80% *ee*) working under room temperature conditions and with polar non-protic solvents such as NMP. One of the main drawbacks of these catalysts was the long reaction times required to completion (4 days). Herein, the full account of our studies aimed to improve the catalytic performance of the system and to explore the full scope and the mechanism of this process are described.

Scheme 2. L-Prolinamide-derived bifunctional organocatalysts

Results and Discussion

Catalysts **21** were prepared in good to excellent yields from Cbz- or Fmoc-L-proline or Cbz-4-hydroxy-L-proline and the corresponding commercially available chiral amines and β -amino alcohols through the reaction sequence shown in Scheme 3. β -Amino alcohols employed in the preparation of catalysts **21i**^[35] and **21n**^[36] were synthesized according to literature procedures from (1*S*,2*R*)-*cis*-1-amino-2-indanol and (1*R*,*E*)-camphorquinone-3-oxime, respectively. Very recently, Córdova has demonstrated that simple amides derived from primary amino acids such as alanine (see **10** in Scheme 1) efficiently catalyze the direct enantioselective addition of ketones to

nitrostyrenes.^[16] For this reason, catalyst **23** was also prepared from Boc-L-alanine following the synthetic sequence shown in Scheme 4.

Scheme 3. Synthesis of bifunctional organocatalysts **21a-n**

Scheme 4. Synthesis of bifunctional organocatalyst **23**

We first elucidated the parameters that could play a role in the selectivity of the reaction. Organocatalysts (20 mol%) were then examined for their ability to mediate the stereoselective Michael addition between 3-pentanone (**25a**, 4 mmol) and *trans*- β -nitrostyrene (**26a**, 0.4 mmol) in a typical polar protic solvent such as MeOH^[37] (0.2 mL: 0.5 mL of solvent/mmol of **26a**) at r.t. to give *syn*- and *anti*-adducts **27aa** (Scheme 5, solvent = MeOH and Table 1). α -Methyl-L-proline (**28**), *trans*-4-hydroxy-L-proline (**29**), and *trans*-4-TBDMSO-L-proline (**30**) were also included in the study (Figure 1).

Scheme 5. Michael addition between 3-pentanone and *trans*- β -nitrostyrene

Table 1. Asymmetric 1,4-addition of 3-pentanone to β -nitrostyrene. Catalyst study.^[a]

Entry	Catalyst	<i>t</i> (d)	Conv. (%) ^[b]	<i>Dr</i> ^{[b],[c]}	<i>Ee</i> (%) ^[d]
1	21a	2	87	92/8	39
2	21b	1.5	96	85/15	52
3	21c	1	>99	83/17	36
4	21d	6	80	89/11	42
5	21e	3	95	93/7	64
6	<i>ent</i> - 21e	3	99	91/9	62 ^[e]
7	21f	3	48	91/9	48
8	21g	3	>99	87/13	64
9	21h	4.5	>99	85/15	64
10	21i	3	>99	88/12	34
11	21j	2	>99	88/12	38
12	21k	3	48	82/18	32
13	21l	3	>99	92/8	53
14	21m	2	>99	86/14	52
15	21n	3	>99	86/14	56
16	23	6	<5	— ^[f]	— ^[f]
17	28	4	<5	— ^[f]	— ^[f]

18	29	6	<5	— ^[f]	— ^[f]
19	30	4.5	58	81/19	38
20	21e ^[g]	9	37	90/10	52
21	21e ^[h]	9	98	90/10	58
22	21e ^[i]	3	99	89/11	56

^[a] A mixture of the corresponding catalyst (20 mol%), 3-pentanone (4 mmol), and *trans*- β -nitrostyrene (0.4 mmol) were stirred in MeOH (0.2 mL) at r.t. for the time indicated in the Table. ^[b] Determined by ¹H NMR and/or GC analysis. ^[c] *Syn/anti* ratio. ^[d] *Ee* for the *syn* diastereoisomer. Determined by chiral-phase HPLC analysis. ^[e] The enantiomer *syn*-(4*R*,5*S*)-**27aa** was obtained. ^[f] Not determined. ^[g] 5 mol% of **21e** was used. ^[h] 10 mol% of **21e** was used. ^[i] 15 mol% of **21e** was used.

Figure 1. Proline-derived organocatalysts **28-30**

Most of L-prolinamides exhibited high catalytic activities for the reaction to give the *syn* adduct **27aa** as a favored product. Prolinamides **21a** and **21b**, derived from 1,2-diphenyl-2-aminoethanol, which have been successfully used in the direct aldol reaction of ketones with aldehydes,^[27a,b,e,i,q] showed good activity with high reaction conversions and good diastereoselectivity, *syn/anti*: 92/8 and 85/15, respectively, and enantioselectivity 39 and 52% *ee* for the major diastereomer, respectively (Table 1, entries 1 and 2). Catalyst **21c**, derived from (*R*)-2-phenyl-2-aminoethanol, with a primary alcohol unit group, showed very high catalytic activity to afford after 1 d the Michael adduct **27aa** in high yield but with lower diastereo- and enantioselectivity (*syn/anti*: 83/17, 36% *ee*) (Table 1, entry 3). The presence of the chiral hydroxyl moiety seems to be important for the selectivity of the process. This was further supported with catalyst **21d**, derived from 2-aminophenol, which gave a 42% *ee* for the *syn* adduct after 6 d (Table 1, entry 4). The reaction time decreased to 3 d and a noticeable increase in yield (95%) and enantioselectivity (64% *ee*) was obtained with (1*S*,2*R*)-*cis*-1-amino-2-indanol-derived prolinamide **21e** (Table 1, entry 5). This result demonstrated that increasing the conformational rigidity of the amino alcohol moiety seemed to be beneficial for the selectivity of the process. This was probably due to the more favored double hydrogen-bonding interactions of the more rigid derivative **21e** with the

electrophile. Diastereomeric catalysts **21e**, **21j**, **21l** and **21m**, showed very high catalytic activities in the 1,4-addition (Table 1, entries 5, 11, 13, and 14), the highest enantioselectivity (64% *ee*) being observed with prolinamide **21e**. This finding indicated that the (1*S*,2*R*) configuration of the chiral 1-aminoindanol matched the (*S*)-configuration of the L-proline to enhance the stereochemical control of the reaction. On the other hand, catalyst *ent*-**21e**, prepared from D-proline and (1*R*,2*S*)-*cis*-1-amino-2-indanol, gave the enantiomeric (4*R*,5*S*)-*syn*-adduct **27aa** in a 62% *ee* (Table 1, entry 6). This experiment also showed that the enantioselectivity of the process was controlled by the proline moiety since diastereomeric catalysts *ent*-**21e** and **21l**, derived from (1*R*,2*S*)-*cis*-1-amino-2-indanol and L- and D-proline, respectively, afforded the corresponding enantiomers of the *syn* adduct **27aa** (Table 1, entries 6 and 13). Catalysts **21f** and **21k**, derived from L-proline and (*R*)- and (*S*)-1-aminoindane, respectively, mediated the formation of the Michael product **27aa** in lower yields (48%) and enantioselectivities, 48 and 32%, respectively, (Table 1, entries 7 and 12) than the corresponding aminoalcohol-derived prolinamides **21e**, **21j**, **21l**, and **21m**. These results and the very low enantioselectivity (34% *ee*) observed with *N*-methylated derivative **21i** (Table 1, entry 10) visibly showed that the presence of the hydroxyl group and a hydrogen in the amido group were important for a good conversion and selectivity in the 1,4-addition. Catalysts **21g** and **21h**, derived from *trans*-L-4-hydroxyproline, afforded similar levels of enantioselection than the L-proline derivative **21e** but lower diastereoselectivities (Table 1, entries 8 and 9). Catalysts **21l** and **21n** gave very similar results in terms of activity and enantioselectivity (Table 1, entries 13 and 15). This seemed to point to a negligible effect of the steric bulkiness of the amide group of the organocatalysts in the reaction outcome.

Although amides derived from simple primary amino acids such as alanine have been shown to efficiently catalyze the direct enantioselective addition of ketones to nitrostyrenes,^[16] L-alanine amide **24** failed to give any product in the 1,4-addition of 3-pentanone to β -nitrostyrene under the tested reaction conditions (Table 1, entry 16). Proline has been previously shown to promote the Michael addition of ketones to nitrostyrene in MeOH as solvent.^[7] In contrast, α -methyl-L-proline (**28**), a very efficient organocatalyst for the intramolecular α -alkylation of aldehydes,^[38] was not effective in the 1,4-addition after long reaction periods (Table 1, entry 17). Similar result was observed when *trans*-4-hydroxy-L-proline (**29**) was used as promoter, probably due to

solubility problems (Table 1, entry 18). *trans*-4-TBDMSO-L-proline (**30**) has been presented as a valid alternative to proline and proline derivatives in different asymmetric organocatalytic processes due to its high solubility in organic solvents.^[39] However, the catalytic activity of **30** in the conjugate addition of 3-pentanone to nitrostyrene in MeOH resulted very low affording **27aa** in a 58% conversion and 38% *ee* for the major *syn* isomer (Table 1, entry 19).

The effect of the catalyst loading on the reaction efficiency was also evaluated employing **21e**. The enantioselectivity of the process was in general slightly sensitive to the catalyst loading, affording the best results in terms of yield and selectivity with a 20 mol% of catalyst, as routinely employed (Table 1, compare entries 5 and 20-22). As conclusion, the catalyst study showed prolinamide **21e** as the most selective organocatalyst in the process. It also demonstrated that the amide and the hydroxy groups are certainly involved in the catalysis and stereoselection of the 1,4-addition, probably through hydrogen bonding interactions.

Encouraged by these initial results, and due to the levels of reaction efficiency observed with prolinamide **21e**, we selected this catalyst for further studies of the direct asymmetric addition of ketone **25a** to β -nitrostyrene **26a** (Scheme 5, catalyst = **21e** and Table 2). With respect to the nucleophile stoichiometry required for optimal results, a ten fold excess of ketone gave the best results (Table 2, entries 1–3). We next screened a range of solvents for the reaction catalyzed by prolinamide **21e** (Table 2, entries 5–24). Bulkier polar protic alcohols such as *i*PrOH and *t*BuOH were much less effective affording lower conversions and selectivities (Table 2, entries 5–6). Non-polar solvents such as toluene slowed down the reaction to 8 d affording *syn*-**27aa** in a 56% *ee* (Table 2, entry 7). Furthermore, we observed the formation of the regioisomer **31** (Figure 2) in very low yields (8%, GC analysis), which resulted from the Michael addition to the carbon in α position to the nitro group. This by-product was not observed when polar protic solvents were used (Table 2, compare entries 1–7). The use of CHCl₃ and CH₃CN gave similar results to MeOH with respect to diastereo- and enantioselectivity detecting again the formation in small amounts (5%, GC analysis) of the regioisomeric compound **31** (Figure 2, Table 2, entries 8 and 9). The employment of protic solvents seemed then beneficial to avoid the formation of **31**. Increasing notably the polarity of the reaction medium with DMF provided a noticeable increase in selectivity (76% *ee*), being very important the amount of solvent used in the process since no conversion was observed when 5 mL of DMF/mmol of **26a** were used instead of 0.5 mL/mmol of the limiting

reagent (Table 2, entries 10 and 11). Again small amounts (5%) of **31** were detected by GC. Similar *ee*'s were obtained for DMSO, DMAc and NMP although the best combination of yield, diastereo- and enantioselectivity was obtained with the latest solvent though employing longer reaction times (Table 2, entries 12–14).

Figure 2. Regioisomeric product obtained in non-protic solvents

The reaction time could be reduced from 7 to 3 d by adding the electrophile to the reaction mixture after stirring for 20 min the ketone and the catalyst in NMP at r.t. (Table 2, compare entries 14 and 15). From this point all the experiments were performed in this manner. The presence of water has been shown to appreciably accelerate and improve the stereoselectivity in different organocatalyzed processes by facilitating hydrogen bonding and proton transfer. When the **21e**-catalyzed reaction between 3-pentanone and β -nitrostyrene was carried out employing anhydrous NMP (Table 2, entry 16), similar selectivities were observed but the 1,4-addition took two extra days. This showed that the presence of small amounts of water (H_2O content in the initially employed commercial NMP: 0.05%, Table 2, entry 15) had a beneficial effect over the reaction rate.

Table 2. Asymmetric 1,4-addition of 3-pentanone to β -nitrostyrene catalyzed by **21e**.

Reaction conditions study.^[a]

Entry	Solvent	<i>t</i>	Conv (%) ^[b]	<i>Dr</i> ^{[b],[c]}	<i>Ee</i> (%) ^[d]
1	MeOH	3 d	95	93/7	64
2	MeOH ^[e]	5 d	62	75/25	— ^[f]
3	MeOH ^[g]	5 d	30	75/25	— ^[f]
4	MeOH ^[h]	7 d	64	93/7	58
5	<i>i</i> PrOH	4 d	71	88/12	57
6	<i>t</i> BuOH	4 d	40	90/10	53
7	Toluene	8 d	91 (8)	91/9	56
8	CHCl_3	3 d	97 (5)	91/9	58

9	CH ₃ CN	7 d	95 (5)	90/10	65
10	DMF	10 d	95 (5)	92/8	76
11	DMF ^[i]	10 d	<5	— ^[f]	— ^[f]
12	DMSO	4 d	90 (10)	86/14	73
13	DMAc	7 d	70 (9)	88/12	79
14	NMP	7 d	95 (5)	90/10	79
15	NMP ^[j]	3 d	78 (9)	91/9	77
16	NMP ^[k]	5 d	76 (8)	90/10	77
17	NMP/H ₂ O ^[l]	6 d	63 (5)	90/10	70
18	NMP/H ₂ O ^[m]	6 d	95 (5)	90/10	72
19	NMP/H ₂ O ^[n]	6 d	84 (5)	92/8	76
20	NMP/MeOH ^[o]	3 d	95	91/9	69
21	NMP/DMSO ^[p]	4 d	94 (5)	86/14	75
22	[bmim][PF ₆]	3 d	90	87/13	62
23	—	4 d	65	87/13	60
24	NMP ^[q]	2.5 h	99	90/10	72

^[a] A mixture of **21e** (20 mol%), 3-pentanone (4 mmol), and *trans*- β -nitrostyrene (0.4 mmol) was stirred in the corresponding solvent (0.2 mL) at r.t. for the time indicated in the Table. ^[b] Determined by ¹H NMR and/or GC analysis. In parenthesis GC yield of compound **31**. ^[c] *Syn/anti* ratio. ^[d] *Ee* for the *syn* diastereomer. Determined by chiral-phase HPLC analysis. ^[e] 5 equiv of ketone were used. ^[f] Not determined. ^[g] 1 equiv of ketone was used. ^[h] 40 equiv of ketone were used. ^[i] 5 mL of DMF/mmol of **26a** were used. ^[j] **26a** was added to the reaction mixture after 20 min. ^[k] Anhydrous NMP was used. ^[l] 0.5 mL of solvent (NMP/H₂O: 1/1)/mmol of **26a** were used (14 equiv of H₂O). ^[m] 0.75 mL of solvent (NMP/H₂O: 2/1)/mmol of **26a** were used (14 equiv of H₂O). ^[n] 0.6 mL of solvent (NMP/H₂O: 5/1)/mmol of **26a** were used (5 equiv of H₂O). ^[o] 0.5 mL of solvent (NMP/MeOH: 1/1)/mmol of **26a** were used. ^[p] 0.5 mL of solvent (NMP/DMSO: 1/1)/mmol of **26a** were used. ^[q] The reaction was performed under microwave irradiation (15 W, 48 °C).

Since we had demonstrated a dramatic solvent and concentration effect in the reaction scope, a deep study was then performed in NMP varying the concentration of the reaction and the amount of water present in the reaction. The representative results are collected in Table 2, entries 17–21. The study demonstrated that the best results were indeed obtained with the commercially available NMP (0.05% H₂O) which represents 0.014 mmol H₂O/mmol **26a** (Table 2, entry 15). Other different combinations of solvents such as NMP/MeOH and NMP/DMSO did not improve the results obtained so far either (Table 2, entries 20–21) with the exception that the presence of MeOH as cosolvent circumvent the formation of **31** again (entry 20). We also tested the

employment of the ionic liquid [bmim][PF₆] as reaction medium, but lower diastereo- and enantioselectivities were obtained (Table 2, entry 22). Solventless conditions (Table 2, entry 23) led to the formation of **27aa** in a 65% conversion and 60% *ee* for the major *syn* isomer (*syn/anti*: 87/13). Finally, a very fast reaction was achieved under microwave irradiation (15 W, 48 °C) still preserving good diastereo- and enantioselectivities (Table 2, entry 24). Then, **21e** (20 mol%), NMP as solvent (0.5 mL/mmol of **26a**) at r.t. were the new established reaction conditions for the conjugate addition of 3-pentanone (10 mmol) to *trans*- β -nitrostyrene (1 mmol).^[40]

In order to further decrease the long reaction times we studied the influence of an acid as additive in the model reaction between 3-pentanone and *trans*- β -nitrostyrene (Table 3). It has been previously demonstrated that the presence of an acidic additive in the reaction results beneficial in terms of activity due to acceleration of enamine formation.^{[27n],[33],[41]} Thus, we started our additive study employing substoichiometric amounts (20 mol%) of different organic acids (Table 3, entries 1–10). Among the carboxylic acids, 4-nitrobenzoic acid gave the best results in terms of rate (1 d), yield (full conversion) and selectivity (Table 3, compare entries 1–7). In the presence of this cocatalyst and using anhydrous NMP, the reaction rate and the enantioselectivity of the process were lower which clearly demonstrated that the water present in the employed commercial non-anhydrous NMP was also necessary to obtain good activities and selectivities when using acid as cocatalyst (Table 3, entries 5 and 6). Interestingly, the acid additives also avoided the formation of byproduct **31** (Figure 2). Benzenesulfonic acid did not promote the reaction at all (Table 3, entry 8). Both enantiomers of 2-phenylpropionic acid were also tested with the aim of detecting a possible influence on the selectivity of the process of a chiral proton source. Unfortunately, no improvement on the selectivity was observed (Table 3, entries 9 and 10). Very recently, chiral Brønsted acid 1,1'-bi-(2-naphthol) has been shown to improve the enantioselectivity of the L-proline catalyzed direct aldol reaction when used as chiral additive through hydrogen bonding activation.^[42] We then performed the reaction in the presence of (*R*)- or (*S*)-1,1'-bi-(2-naphthol) (5 mol%) anticipating a possible multicomponent chiral catalytic system of higher efficiency. However, very similar results were obtained in both cases slightly decreasing the rate and selectivity of the reaction (Table 3, entries 11 and 12). In the absence of acid, (*S*)-bi-2-naphthol (5 mol%) did not show any improvement (Table 3, compare entries 12 and 13) which indicated a negligible effect of this additive in the reaction scope.

Table 3. Asymmetric 1,4-addition of 3-pentanone to β -nitrostyrene catalyzed by **21e**.Additive study.^[a]

Entry	Additive	<i>t</i> (d)	Conv (%) ^[b]	<i>Dr</i> ^{[b],[c]}	<i>Ee</i> (%) ^[d]
1	—	3	78	91/9	77
2	AcOH	2	97	95/5	75
3	PhCO ₂ H	1	75	90/10	75
4	PhCO ₂ H ^[e]	6	50	97/3	78
5	4-NO ₂ C ₆ H ₄ CO ₂ H	1	99	95/5	78
6	4-NO ₂ C ₆ H ₄ CO ₂ H ^[f]	2	97	94/6	70
7	2,4-(NO ₂) ₂ C ₆ H ₃ CO ₂ H	2	84	93/7	76
8	PhSO ₃ H	6	<5	— ^[g]	— ^[g]
9	(<i>R</i>)-(-)-2-phenylpropionic acid	1	65	93/7	76
10	(<i>S</i>)-(+)-2-phenylpropionic acid	1	72	93/7	74
11	(<i>R</i>)-1,1'-bi-(2-naphthol) ^[h]	4	>99	90/10	74
12	(<i>S</i>)-1,1'-bi-(2-naphthol) ^[i]	2	>99	93/7	76
13	(<i>S</i>)-1,1'-bi-(2-naphthol) ^[j]	4	99	91/9	73

^[a] A mixture of catalyst **21e** (20 mol%), the additive (20 mol%), and 3-pentanone (4 mmol) was stirred in NMP (0.2 mL) for 20 min at r.t. Then, the β -nitrostyrene (0.4 mmol) was added to the mixture and the reaction was stirred at r.t. for the time indicated in the Table. ^[b] Determined by ¹H NMR and/or GC analysis. ^[c] *Syn/anti* ratio. ^[d] *Ee* for the *syn* diastereoisomer. Determined by chiral-phase HPLC analysis. ^[e] The reaction was performed at 0°C. ^[f] Anhydrous NMP was used as solvent. ^[g] Not determined. ^[h] 5 Mol% of (*R*)-Binol and 5 mol% of 4-nitrobenzoic acid were used. ^[i] 5 Mol% of (*S*)-Binol and 5 mol% of 4-nitrobenzoic acid were used. ^[j] 5 Mol% of (*S*)-Binol was used.

Under the established best reaction conditions [**21e** (20 mol%) as catalyst, 4-nitrobenzoic acid (20 mol%) as additive and NMP as solvent at r.t.] various ketones and nitrostyrenes were evaluated as substrates (Scheme 6 and Table 4). The reaction appeared quite general with respect to the nature of the aromatic Michael acceptor. Generally, good yields and good diastereo- and enantioselectivities were observed. The introduction of electron-withdrawing or electron-donating groups on the aromatic ring of the nitrostyrene did not affect the enantioselectivities. Thus, 4-tolyl, 4-chloro, 4-methoxy, and 3,5-dichlorosubstituted nitrostyrene derivatives gave compounds **27ab–27ae** in 64–83% yields, 91/9 to 97/3 diastereomeric ratios and 76 to 81% enantioselectivities in 1.5 d reaction time (Table 4, entries 2–5). However, in the case of the 2-(trifluoromethyl)phenyl derivative a 59% *ee* for the major diastereoisomer

(*syn/anti*: 99/1) *syn*-**27af** was obtained (Table 4, entry 6). When 2-chloronitrostyrene was used as a Michael acceptor, the corresponding Michael adduct **27ag** was obtained in 75% yield and 78% *ee* (Table 4, entry 7). In general, the *syn*-diastereoselectivity was slightly higher when electron-poor nitrostyrenes were used (Table 4, entries 5 and 6).

Scheme 6. Michael addition of ketones to β -nitrostyrenes

Table 4. Asymmetric 1,4-addition of ketones to nitrostyrenes catalyzed by **21e**.^[a]

Entry	R ¹	R ²	Ar	Solvent	<i>t</i> (d)	Conv. (%) ^[b]	No.	<i>syn/anti</i> ^[c]	<i>Ee</i> (%) ^[d]
1	Et	Me	Ph	NMP	1	99 (76)	27aa	95/5	78 ^[e]
2	Et	Me	4-MeC ₆ H ₄	NMP	1.5	94 (64)	27ab	91/9	76
3	Et	Me	4-ClC ₆ H ₄	NMP	1.5	>99 (75)	27ac	92/8	79
4	Et	Me	4-MeOC ₆ H ₄	NMP	1.5	86 (74)	27ad	93/7	81
5	Et	Me	3,5-(Cl) ₂ C ₆ H ₃	NMP	1.5	>99 (83)	27ae	97/3	78
6	Et	Me	2-CF ₃ C ₆ H ₄	NMP	1.5	>99 (75)	27af	99/1	59
7	Et	Me	2-ClC ₆ H ₄	NMP	1	>99 (75)	27ag	97/3	78
8	-(CH ₂) ₄ -		Ph	MeCN	1	>99 (80)	27ba	90/10	65 ^[f]
9	Me	OH	Ph	CH ₂ Cl ₂	2	>99 (64)	27ca	65/35	41 ^[g]
10	Me	Me	Ph	DMSO	1.5	>99 (80)	27da ^[h]	90/10	54 ^[i]

^[a] A mixture of catalyst **21e** (20 mol%), 4-nitrobenzoic acid (20 mol%), and 3-pentanone (4 mmol) were stirred in the corresponding solvent (0.2 mL) for 20 min at r.t. Then, the nitrostyrene (0.4 mmol) was added to the mixture and the reaction was stirred at r.t. for the time indicated in the Table. ^[b] Determined by ¹H NMR and/or GC analysis over the crude reaction mixture. In brackets, isolated yield after flash chromatography for the mixture of diastereoisomers. ^[c] Determined by ¹H NMR and/or GC analysis over the crude reaction mixture. ^[d] *Ee* for the *syn* diastereoisomer. Determined by chiral-phase HPLC analysis. Absolute configuration not determined except for **27aa**. ^[e] Similar results were obtained with recycled **21e** (88% yield, *syn/anti*: 91/9, 78% *ee*). ^[f] A 16% *ee* was obtained when NMP was used as solvent. ^[g] 35% *ee* for the *anti* isomer. ^[h] *Syn/anti/iso*: 54/6/40. ^[i] 5% *Ee* for the *anti* isomer; 76% *ee* for the *iso* isomer.

Next, we examined other ketone donors in the Michael reaction with *trans*- β -nitrostyrene (Scheme 6, Table 4). For each nucleophile a full solvent study was carried

out since we observed enormous differences in reactivity and selectivity depending of the solvent employed.^[43] In Table 4 entries (7–10) we have recovered the results under the optimized reaction conditions for the new ketones studied. The conjugate addition of cyclohexanone as a Michael donor catalyzed by 20 mol% of **21e** proceeded with good diastereoselectivity (*syn/anti*: 90/10) and moderate selectivity 65% *ee* when using MeCN as solvent (Table 4, entry 8). Surprisingly, NMP led to a very low 16% *ee* in this particular case. The conjugate reaction between hydroxyacetone and nitrostyrene was regioselective for all the studied reaction conditions,^[43] CH₂Cl₂ being the solvent which gave better results in terms of enantioselectivity. As depicted in the entry 9 of Table 4, the reaction was less *syn*-selective than previously observed giving a 65/35 *syn/anti* relationship with low enantioselectivities for both isomers (41% *ee* for *syn*-**27ca** and 35% *ee* for *anti*-**27ca**). On the other hand, the **21e**-catalyzed Michael addition of butanone with nitrostyrene mainly gave the *iso* isomer in moderate to good enantioselectivities^[43] giving the best result in DMSO (Table 4, entry 10, Scheme 7).

Scheme 7. Michael addition of butanone to *trans*-β-nitrostyrene

It is worthy to mention that prolinamide catalyst **21e** could be easily recovered (80% recovery) from the reaction mixture after extractive acid-base workup and reused after flash chromatography with similar results (Table 4, entry 1) since no loss of optical activity was detected in the organocatalyst $\{[\alpha]_D^{20} = -24.4$ (*c* 1.0, CH₂Cl₂) $\}$.

With respect to the reaction mechanism, it is accepted that when primary or secondary chiral amines are used as organocatalysts, the reaction clearly involves an enamine pathway. The existence of the enamine intermediate **I** in the **21e**-catalyzed Michael addition of 3-pentanone to β-nitrostyrene was confirmed employing the ESI-MS method (Scheme 8, Figure 3). Under the typical reaction conditions, enamine **I**H⁺ (*m/z* = 315.1) was detected after stirring for 20 min the organocatalyst **21e** (20 mol%), 3-pentanone (1 mmol) and 4-NO₂C₆H₄CO₂H (20 mol%) employing MeOH as solvent (Figure 3a). To this solution was then added *trans*-β-nitrostyrene (0.1 mmol) and the

mixture was injected after 0.2 min. The formation of intermediate **II** ($m/z = 464.3$) (Scheme 8) was a fast reaction since it was immediately detected in the mixture by ESI-MS (Figure 3b). This meant that enamine **I** attacks the electrophile probably activated by hydrogen bonding by the amide moiety to give intermediate **II**. We could also intercept^[43] the adduct ion **III** $\cdot\text{H}^+$ (m/z 396.2, Scheme 8) formed by a reversible Michael addition of **21e** to the electrophile. The last step of the catalytic cycle involves the regeneration of **21e** by hydrolysis facilitated by the small amounts of water present in the solvent.

Scheme 8. Proposed mechanism for the **21e**-catalyzed Michael addition

Figure 3. ESI/MS-(+) spectra of the intermediates a) IH^+ , b) II^+ (see Scheme 8).

Figure 4 indicates the relationship between the *ee* value of the catalyst **21e** used in the Michael reaction and the *ee* value of the Michael adduct **27aa**. The observed linearity suggested that the active catalyst in this process is a monomeric species.^[44] The *syn*-diastereoselectivity and the absolute configuration observed can be reasonably explained through the acyclic synclinal transition state assembly **A** proposed by Seebach,^[45] assuming intramolecular hydrogen bonding (Scheme 8).

Figure 4. Observation of nonlinear effect of **21e** with **27aa**.

Computational Studies:

To explain the predominant production of (4*S*,5*R*)-*syn*-adduct, we have computationally^[46] located and studied the transition states for the formation of both enantiomers by DFT^[47] at B3LYP/6-31G* level.^[48] For computational simplicity reasons, we have chosen the non-substituted prolinamide **32** as a model catalyst for the reaction between 3-pentanone **25a** and 1-nitropropene **33** (Figure 5). Since the formation of the enamine and the final hydrolysis of the Michael addition adduct are fast and have no effect on the rate and stereoselectivity of the reaction,^[49] we focused on the study of the transition states involved in the rate-limiting step, the nucleophilic attack of the enamines **34** to 1-nitropropene. For the calculation of the activation barriers of those reactions, it was also necessary to determine the energies of the reactant hydrogen bond complexes formed between the enamines and 1-nitropropene.

Figure 5. Model reaction used for the DFT computational studies.

The enamine can be found in two different conformations, *syn*-**34** and *anti*-**34**. For each of them, two different transition states exist for the approach of the nitropropene to the diastereotopical *Re* and *Si* faces of the enamine, resulting in the formation of four different transition states, two for each enantiomer (Figure 6). The two transition states arising from the *anti* enamine (TS_A and TS_B) can benefit from the hydrogen bonding activation with the NH and OH present in the prolinamide and our initial hypothesis was that this interaction might contribute to a lowering in the energy barriers, resulting in faster reaction rates. Meanwhile, reaction through *syn* enamine conformations would only occur in an *uncatalyzed* way, without the help of hydrogen bonding activation (TS_C and TS_D). We located the four possible transition states and found that the lowest in energy (15.0 kcal/mol) corresponds to TS_A, the one that leads to the experimentally observed *syn*-(4*S*,5*R*) enantiomer. According to our initial hypothesis, this result shows that both NH and OH in the catalyst activate the nitroalkene by the concurrence of up to three hydrogen bonds, favoring the approach of the nitroalkene from the *Re* face of the *anti* enamine. The minor enantiomer *syn*-(4*R*,5*S*) is formed through *Si* approach of the nitroalkene to the *anti* enamine (TS_B), whose activation energy is 16.4 kcal/mol. The difference between TS_A and TS_B accounts for 1.4 kcal/mol, corresponding to a computed $\approx 10:1$ selectivity ($\approx 80\%$ *ee*) in favor of the *syn*-(4*S*,5*R*) enantiomer.

The other two transition states (TS_C and TS_D) do not show hydrogen bonding activation. Therefore, their activation barriers are much higher than those of their activated counterparts TS_C $\gg$ TS_A and TS_D $\gg$ TS_B. Interestingly, there is an inverse relationship between the distance of the two bond-forming carbon atoms (C1---C2) and the reaction rate. The fastest reaction corresponds to the earliest transition state TS_A ($\delta_{C1-C2} = 2.13$ Å) and the slowest reaction to the latest transition state TS_D ($\delta_{C1-C2} = 1.94$ Å).

TS_A (*anti-Re*): 15.0 kcal/mol

TS_B (*anti-Si*): 16.4 kcal/mol

TS_C (*syn-Re*): 18.2 kcal/mol

TS_D (*syn-Si*): 27.6 kcal/mol

Figure 6. Transition state geometries and activation energies for the reaction between **25a** and **32**, calculated at B3LYP/6-31G*.

The reasons for the observed stereoselectivity are understandable in view of the hydrogen bonding differences between TS_A and TS_B and the data shown in Table 5. In both cases we can distinguish up to three hydrogen bonds (two of them strong and one weak) between the two oxygen atoms of the nitro group and the NH and OH in the prolinamide. The rigidity and steric congestion of the proline-based enamine allows for a clear differentiation in the strength of those interactions. In TS_A, one of the oxygens of the nitro (O1) is able to form two strong hydrogen bonds with H-N3 (2.03 Å) and especially with H-O3 (1.88 Å), whereas TS_B shows two relatively weaker bonds, with larger distances for O1---H-N3 (2.11 Å) and O2---H-O3 (2.09 Å). In both cases, there is a third very weak hydrogen bond with H-N3 (distances $\approx$ 2.5 Å), but it can be considered that this interaction is less important in the activation of the nitro group. Finally, the distances between O2---H-O3 in TS_A and O1---H-O3 in TS_B are too large

(>2.7 Å) to describe them as hydrogen bonds, although they still can represent positive electrostatic interactions. These data suggest that the strength difference of the hydrogen bonds in TS_A and TS_B is responsible for the computed facial selectivity. Noteworthy, the source of the chirality in these models is only the stereogenic center at position 2 of the pyrrolidine ring. We have not included the chirality in the hydroxyethylamino group of the prolinamide. Therefore, by appropriate choice of the substituent and the matched relative configuration we can further modulate the stereoselectivity of the reaction.

Table 5. Activation energies and interatomic distances for the transition states calculated at B3LYP/6-31G* level

	TS _A	TS _B	TS _C	TS _D
Activation energies ^[a]	15.0	16.4	18.2	27.6
Distances ^[b]				
C1---C2	2.129	2.095	2.012	1.945
N1---N2	3.260	3.103	---	---
O1---H-N3	2.028	2.109	---	---
O1---H-O3	1.885	2.845	---	---
O2---H-N3	2.589	2.557	---	---
O2---H-O3	2.720	2.093	---	---

^[a] Activation energies in kcal/mol calculated at B3LYP/6-31G*+ZPVE. ^[b] Distances in Å.

Conclusions

From the studies carried out about the direct enantioselective conjugate addition of ketones to β -nitrostyrenes catalyzed by 1,2-amino alcohol-derived prolinamides, it can be concluded that these organocatalysts promote the *syn*-diastereo- and enantioselective Michael addition of ketones to nitrostyrenes in polar aprotic solvents such as NMP. From a wide variety of prolinamide derivatives, the best catalyst **21e**, derived from L-proline and (1*S*,2*R*)-*cis*-1-amino-2-indanol, gave a diastereomeric excess of up to 94% and up to 80% *ee* of the *syn* adduct. High reaction rates could be achieved employing acid additives such as 4-nitrobenzoic acid or under microwave irradiation conditions. Both the amide hydrogen and the chiral hydroxyl group of the catalysts play an important role in the process. Furthermore, prolinamide catalysts can be recovered and reused. From ESI-MS experiments on the Michael reaction between 3-pentanone and *trans*- β -nitrostyrene catalyzed by **21e** it was possible to characterize all the

intermediates assumed for the catalytic cycle. Computational studies at B3LYP/6-31G* level have been conducted on a model reaction, confirming the initial hypothesis that hydrogen bonding plays a crucial role on the activation of the nitroalkene, and helps to discriminate between the two diastereofacial approaches. The computationally favored transition state TS_A presents the strongest hydrogen bonds and, in accordance with the experimental results, leads to the observed major *syn*-(4*S*,5*R*) enantiomer.

Further studies on the scope of prolinamide-derived catalysts **21** in Michael and other organocatalytic asymmetric C–C bond-forming reactions are currently underway.

Experimental Section

General. Melting points were obtained with a *Reichert Thermovar* apparatus and were not corrected. IR data were collected on a FTIR apparatus, *Nicolet Impact 400D-FT*, and peaks are reported in cm⁻¹. Specific rotations were determined at 20 °C with a *Perkin–Elmer 341* digital polarimeter. Enantiomeric excesses were determined using a *Shimadzu HPLC* (LC-10AD pump and SPD-10a detector), *JASCO HPLC* (PU-2089 Plus pump, MD-2010 Plus detector and an AS-2059 Plus automatic injector) or *Agilent 1100 Series HPLC* (G1311A Quat Pump, DAD G1315B detector and an automatic injector). For each new compound, wavelength, solvent mixture, flow rate, column used, retention time and major enantiomer (in bold) are stated. NMR spectra were recorded on a *Bruker AC-300* (300 MHz for ¹H NMR and 75 MHz for ¹³C NMR) using CDCl₃ as solvent and TMS as internal standard unless otherwise noted; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a *Shimadzu QP-5000* and *Agilent 5973* spectrometers and DIP (Direct Insertion Probe) mass spectra were obtained on a *Agilent 5973* spectrometer, fragment ions *m/z* with relative intensities (%) in parenthesis. HRMS were performed in a *Finnigan MAT 95S spectrometer*. ESI-MS experiments were carried out with an *Agilent 1100 Series LC/MSD Trap “SL”* mass spectrometer equipped with an ESI source. Analytical TLC was visualized with UV light at 254 nm. Thin layer chromatography was carried out on TLC aluminium sheets with silica gel 60 F₂₅₄ (Merck). For flash chromatography silica gel 60 (0.040-0.063mm) was employed in a Büchi Pump system (Controller C–610 y Module C–601). Microwave experiments were performed using a *CEM DISCOVER Synthesis unit*. Reactions under inert atmosphere (argon) were performed in oven-dried glass-ware, sealed with a rubber septum, using anhydrous solvents.

Typical procedure for the synthesis of 22 and 24: To a 0 °C solution of the corresponding *N*-protected-L-proline derivative (Scheme 3) or *N*-protected-L-alanine (8.0 mmol) (Scheme 4) and TEA (8.0 mmol) in THF (30 ml) was added dropwise ethyl chloroformate (8.0 mmol) for 15 min. After the solution was stirred at 0 °C for 30 min, the corresponding amine (8.0 mmol) was added dropwise for 15 min. The resulting solution was stirred for 1 h at 0 °C and at r.t. for another 16 h, and then refluxed for 3 h. After cooling down to r.t., the solution was diluted with EtOAc. After filtration and removal the solvent under reduced pressure, the corresponding *N*-protected amides **22a-n**, and **24** were obtained and used in the next step without further purification.

Experimental procedure for the synthesis of compound 21a: Piperidine (0.56 ml, 5.64 mmol) was added to a 0 °C solution of Fmoc-**22a** (1.5 g, 2.82 mmol) in CH₃CN (30 ml). The resulting mixture was maintained at 0 °C for 30 min, and at r.t. for 3 h and then concentrated. The crude residue was purified by recrystallization in EtOH to give pure **21a**.

Typical procedure for the synthesis of compounds 21b-n: Compounds Cbz-**22b-n** (1g), 5% Pd/C (0.1g, 10% weight) and MeOH (30 mL) were mixed in a 100 mL two necks bottom flask. After stirred under hydrogen (1 atm) for 1 h, the solution was filtered through a pad of celite. After removal the solvent, the resulting residue was purified by: recrystallization (**21b**, **21c**, **21d**, **21e**, **21g**, **21i**, **21j**, **21l**, and **21m**) or by flash chromatography (EtOAc) (**21f**, **21h**, **21k**, and **21n**).

Experimental procedure for the synthesis of compound 23. Boc-L-alanine (440 mg, 1.25 mmol) was stirred in a 4 M hydrogen chloride solution in dioxane (5 ml) for 30 min and then extracted with EtOAc (3 × 15 ml). The aqueous phase was treated with 15% NaOH until pH 10 and then extracted with EtOAc (3 × 15 ml). The organic layer was dried over anhydrous MgSO₄, filtered off and the solvent was evaporated at low pressure to give product **23** pure by ¹H NMR.

(2S)-N-[(1S,2R)-2-Hydroxy-1,2-diphenylethyl]pyrrolidine-2-carboxamide (21a).

White solid; *M.p.* 144 °C (EtOH); $[\alpha]_D^{20}$ -19.5 (c 1.0, MeOH); *R_f* (MeOH/EtOAc: 1/1) 0.48; IR ν (KBr) 3325, 3299 (N-H, O-H), 1687 (C=O), 1044, 1024 (C-O) cm⁻¹; ¹H NMR δ 1.58–1.67 (m, 2 H, CH₂CH₂NH), 1.75–1.85 (m, 1 H, CH₂CHCO), 1.96–2.10 (m, 1 H, CH₂CHCO), 2.57 (s, 2 H, OH, NH), 2.79–2.87 (dt, *J* = 10.3, 6.3 Hz, 1 H, CH₂N), 2.93–3.01 (dt, *J* = 10.2, 6.7 Hz, 1 H, CH₂NH), 3.72–3.77 (dd, *J* = 9.0, 5.3 Hz, 1 H, CHCO), 5.4 (d, *J* = 4.2 Hz, 1 H, CHOH), 5.25–5.29 (dd, *J* = 8.6, 4.0 Hz, 1 H,

PhCHNH), 6.98–7.26 (m, 10 H, ArH), 8.43–8.46 (d, J = 8.4 Hz, 1 H, NHCO) ppm; ^{13}C NMR δ 26.1 ($\text{CH}_2\text{CH}_2\text{NH}$), 30.5 (CH_2CHCO), 47.2 (CH_2NH), 59.1 (NCHPh), 60.5 (CHCO), 77.5 (OCHPh), 126.7, 127.48, 127.54, 127.6, 127.8, 128.1 (ArCH), 137.5, 139.7 (ArC), 175.4 ($\text{C}=\text{O}$) ppm; MS m/z 292 [$\text{M}^+ - \text{H}_2\text{O}$, 4%], 290 (28), 201 (27), 194 (20), 184 (34), 183 (53), 181 (10), 180 (54), 179 (13), 178 (12), 165 (11), 156 (13), 90 (13), 89 (19), 77 (12), 70 (100); HRMS calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ [M^+] 310.1681, [$\text{M}^+ - \text{H}_2\text{O}$] 292.1565, found 292.1546.

(2S)-N-[(1R,2S)-2-Hydroxy-1,2-diphenylethyl]pyrrolidine-2-carboxamide (21b).

White solid; *M.p.* 70 °C (EtOAc/MeOH, Δ); $[\alpha]_D^{20}$ –23.8 (c 0.52, EtOH); R_f (MeOH/EtOAc: 1/1) 0.43; IR ν (KBr) 3325, 3299 (N–H, O–H), 1687 ($\text{C}=\text{O}$), 1044, 1024 ($\text{C}-\text{O}$) cm^{-1} ; ^1H NMR (CD_3OD) δ 1.79–1.95 (m, 3 H, $2 \times \text{CH}_2\text{CH}_2\text{NH}$, $1 \times \text{CH}_2\text{CHCO}$), 2.21–2.39 (m, 1 H, CH_2CHCO), 3.09–3.39 (m, 2 H, CH_2NH), 3.62–3.64 (m, 1 H, CHCO), 5.26 (d, J = 6.5 Hz, 1 H, CHOH), 5.45 (d, J = 6.5 Hz, 1 H, PhCHNH), 7.56 (br s, 10 H, ArH) ppm; ^{13}C NMR δ 26.9 ($\text{CH}_2\text{CH}_2\text{NH}$), 31.8 (CH_2CHCO), 47.9 (CH_2NH), 59.7 (NCHPh), 61.5 (NCHCO), 77.4 (OCHPh), 128.1, 128.3, 128.6, 128.96, 128.99, 129.1, 129.2 (ArCH), 140.6, 142.7 (ArC), 176.6 ($\text{C}=\text{O}$) ppm; MS m/z 292 [$\text{M}^+ - \text{H}_2\text{O}$, 5%], 290 (39), 288 (15), 281 (14), 208 (11), 207 (45), 201 (35), 196 (11), 195 (11), 194 (28), 180 (61), 184 (51), 183 (75), 181 (13), 179 (24), 178 (23), 165 (23), 156 (21), 130 (10), 129 (11), 117 (19), 116 (12), 106 (11), 105 (19), 104 (19), 91 (24), 90 (20), 89 (29), 77 (23), 70 (100); HRMS calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ [M^+] 310.1681, found 310.1661.

(2S)-N-[(R)-2-Hydroxy-1-phenylethyl]pyrrolidine-2-carboxamide (21c).

White solid; *M.p.* 125 °C (EtOH/hexane); $[\alpha]_D^{20}$ –86.9 (c 1.0, CH_2Cl_2); R_f (MeOH/EtOAc: 1/1) 0.50; IR ν (KBr) 3306 (N–H, O–H), 1648 ($\text{C}=\text{O}$), 1077, 1062 ($\text{C}-\text{O}$) cm^{-1} ; ^1H NMR (CD_3OD) δ 1.67–1.84 (m, 2 H, $\text{CH}_2\text{CH}_2\text{NH}$), 1.87–1.98 (m, 1 H, CH_2CHCO), 2.01–2.22 (m, 1 H, CH_2CHCO), 2.91–3.04 (m, 2 H, CH_2NH), 3.43 (br s, 2 H, OH, NH), 3.77–3.82 (m, 3 H, $2 \times \text{CH}_2\text{OH}$, $1 \times \text{CHCO}$), 4.97–5.03 (m, 1 H, PhCH), 7.25–7.37 (m, 5 H, ArH), 8.30 (d, J = 7.8 Hz, 1 H, NHCO) ppm; ^{13}C NMR δ 26.0 ($\text{CH}_2\text{CH}_2\text{NH}$), 30.8 (CH_2CHCO), 47.1 (CH_2NH), 56.1 (CHPh), 60.4 (CHCO), 66.8 (CH_2OH), 126.6, 127.7, 128.7 (ArCH), 139.0 (ArC), 175.5 ($\text{C}=\text{O}$) ppm; MS m/z 216 [$\text{M}^+ - \text{H}_2\text{O}$, 28%], 214 (23), 206 (19), 201 (19), 199 (17), 198 (25), 184 (16), 183 (30), 174 (59), 160 (60), 156 (10), 120 (72), 119 (27), 118 (17), 117 (13), 105 (17), 104 (100), 103 (26), 96 (10), 91 (27), 90 (16), 89 (22), 83 (11), 78 (14), 77 (22), 70 (52), 69 (14), 68 (24), 55 (10), 51

(10); C₁₃H₁₈N₂O₂ (234.29): calcd. C 66.64, H 7.74, N 11.96, O 13.66; found C 66.65, H 7.94, N 11.84.

(S)-N-(2-Hydroxyphenyl)pyrrolidine-2-carboxamide (21d). Yellow solid; *M.p.* 170 °C (EtOH, Δ); $[\alpha]_D^{20}$ -45.6 (c 1.0, CH₂Cl₂); *R_f* (EtOAc) 0.22; IR ν (KBr) 3220, 3357 (N–H, O–H), 1641 (C=O), 1092 (C–O) cm⁻¹; ¹H NMR (DMSO) δ 1.56–1.65 (m, 2 H, CH₂CH₂NH), 1.73–1.84 (m, 1 H, CH₂CHCO), 1.97–2.09 (m, 1 H, CH₂CHCO), 2.71–2.79 (m, 1 H, CH₂NH), 2.90–2.98 (m, 1 H, CH₂NH), 3.7 (dd, *J* = 5.2, 8.9 Hz, 1 H, CHCO), 6.71–6.86 (m, 4 H, ArH), 8.17 (d, *J* = 7.96 Hz, 1 H, NHCO) ppm; ¹³C NMR (DMSO) δ 26.0, (CH₂CH₂NH), 30.3 (CH₂CHCO), 46.6 (CH₂NH), 60.8 (CHCO), 114.5, 118.6, 119.0, 123.2 (ArCH), 126.3 (NHC), 146.0 (COH), 173.0, (C=O) ppm; MS *m/z* 206 [M⁺, 2%], 70 (100); HRMS calcd. for C₁₁H₁₄N₂O₂ [M⁺] 206.1055, found 206,1064.

(2S)-N-[(1S,2R)-2,3-Dihydro-2-hydroxy-1H-inden-1-yl]pyrrolidine-2-carboxamide (21e). White solid, *M.p.* 169 °C (EtOAc/MeOH, Δ); $[\alpha]_D^{20}$ -24.6 (c 1.0, CH₂Cl₂); *R_f* (MeOH/EtOAc: 1/1) 0.61; IR ν (KBr) 3336, 3295 (N–H, O–H), 1633 (C=O), 1066, 1090 (C–O) cm⁻¹; ¹H NMR δ 1.63–1.83 (m, 2 H, CH₂CH₂NH), 1.93–2.03 (m, 1 H, CH₂CHCO), 2.12–2.21 (m, 1 H, CH₂CHCO), 2.54 (br s, 1 H, OH), 2.81–2.98 (m, 3 H, 1 × CH₂CHOH, 2 × CH₂NH), 3.14 (dd, *J* = 16.5, 5.1 Hz, 1 H, CH₂CHOH), 3.77 (dd, *J* = 9.0, 5.3 Hz, 1 H, CHCO), 4.61 (dt, *J* = 5.1, 2.3 Hz, 1 H, CHOH), 5.31 (dd, *J* = 8.7, 4.9 Hz, 1 H, NCHCH), 7.14–7.26 (m, 4 H, ArH), 8.13 (d, *J* = 8.5 Hz, 1 H, NHCO) ppm; ¹³C NMR δ 26.2 (CH₂CH₂NH), 31.1 (CH₂CHCO), 39.6 (CH₂CHOH), 47.2 (CH₂NH), 57.0 (CHCHNH), 60.7 (CHCO), 73.6 (CHOH), 124.1, 125.3, 127.0, 128.1 (ArCH), 140.2, 140.8 (ArC), 176.2 (C=O) ppm; MS *m/z* 228 [M⁺ – H₂O, 33%], 211 (11), 210 (13), 186 (69), 173 (63), 133 (12), 132 (39), 131 (12), 130 (11), 117 (13), 116 (100), 115 (84), 103 (11), 85 (29), 77 (10), 70 (34), 68 (12); C₁₄H₁₈N₂O₂ (246.30): calcd. C 68.27, H 7.37, N 11.37, O 12.99; found C 68.37, H 7.47, N 11.72.

(2S)-N-[(R)-2,3-Dihydro-1H-inden-1-yl]pyrrolidine-2-carboxamide (21f). Yellow oil; *R_f* (EtOAc/MeOH: 2/1) 0.36; $[\alpha]_D^{20}$ +23.4 (c 1.0, CH₂Cl₂); IR ν (neat) 3294 (N–H), 1654 (C=O) cm⁻¹; ¹H NMR δ 1.67–1.85 (m, 3 H, 2 × CH₂CH₂NH, 1 × CH₂CH₂C), 1.97–2.26 (m, 3 H, 2 × CH₂CHCO, 1 × CH₂NH), 2.54–2.64 (m, 1 H, CH₂CH₂C), 2.81–3.03 (m, 4 H, 2 × CH₂CH₂C, 2 × CH₂NH), 3.80 (dd, *J* = 9.2, 5.2 Hz, 1 H, CHCO), 5.46 (dd, *J* = 16.7, 8.3 Hz, 1 H, CHNHCO), 7.17–7.26 (m, 4 H, ArH), 7.88 (d, *J* = 8.11 Hz, 1 H, NHCO) ppm; ¹³C NMR δ 26.2 (CH₂CH₂NH), 30.2 (CH₂CH₂C), 31.1 (CH₂CHCO), 34.1 (CH₂CH₂C), 47.2 (CH₂NH), 53.8 (CHNHCO), 60.5 (CHCO), 123.7, 124.7, 126.7,

127.7 (ArCH), 143.2, 143.6 (ArC), 175.2 (C=O) ppm; MS m/z 230 [M^+ , <1%], 115 (10), 70 (100); HRMS calcd. for $C_{14}H_{18}N_2O$ [M^+] 230.1419, found 230.1430.

(2S,4R)-N-[(1S,2R)-2,3-Dihydro-2-hydroxy-1H-inden-1-yl]-4-hydroxypyrrolidine-2-carboxamide (21g). Pale yellow solid; *M.p.* 142 °C (EtOAc, Δ); R_f (EtOAc/MeOH: 2/1) 0.41; $[\alpha]_D^{20} +15.3$ (c 1.0, MeOH); IR ν (KBr) 3358, 3323 (N–H, O–H), 1651 (C=O), 1097, 1060, 1039 (C–O); 1H NMR (CD_3OD) δ 1.78–1.86 (m, 1 H, CH_2CHCO), 2.10–2.17 (m, 1 H, CH_2CHCO), 2.76–2.81 (m, 3 H, $2 \times CH_2NH$, $1 \times CHCH_2C$), 3.02 (dd, $J = 16.4, 5.0$ Hz, 1 H, $CHCH_2C$), 3.89 (t, $J = 16.7$ Hz, 1 H, $CHCO$), 4.24 (br d, $J = 2.5$, 1 H, CH_2CHCH_2), 4.41 (dt, $J = 5.0, 1.3$ Hz, 1 H, CH_2CHCH), 5.12 (d, $J = 5.0$ Hz, 1 H, $CHCHNH$), 7.01–7.13 (m, 4 H, ArH) ppm; ^{13}C NMR δ 40.7 (CH_2NH), 41.0 ($CHCH_2CH$), 55.9 ($CHCH_2C$), 58.1 ($CHCHNH$), 60.8 (CH_2CHCO), 73.6 ($CHOH$), 74 ($CHOH$), 124.8, 126.2, 127.8, 128.9 (ArCH), 141.7, 142.3 (ArC), 177.7 (C=O) ppm; MS m/z 244 [$M^+ - H_2O$, <1%], 216 (24), 215 (19), 211 (24), 210 (37), 201 (10), 188 (26), 187 (75), 186 (64), 133 (20), 132 (21), 131 (11), 117 (13), 116 (100), 115 (81), 87 (13), 86 (34), 85 (28); HRMS calcd. for $C_{14}H_{18}N_2O_3$ [M^+] 262.1317, [$M^+ - 17$] 245.1296, found 245.1293.

(2S,4R)-4-(tert-Butyldimethylsilyloxy)-N-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-pyrrolidine-2-carboxamide (21h). White solid; *M.p.* 138–140 °C (EtOAc); $[\alpha]_D^{20} +8.5$ (c 0.65, MeOH); R_f (EtOAc) 0.36; IR ν (KBr) 3408, 3290 (N–H, O–H), 1655 (C=O), 1090, 1053, (C–O); 1H NMR δ 0.06, 0.08 [2s, 6 H, $(CH_3)_2$], 0.87 [s, 9 H, $C(CH_3)_3$], 1.92–2.04 (m, 1 H, CH_2CHCO), 2.24–2.32 (m, 1 H, CH_2CHCO), 2.45 (br s, 2 H, OH, CONH), 2.72–2.77 (m, 1 H, CH_2N), 2.85–2.89 (m, 1 H, CH_2N), 2.93–2.99 (m, 1 H, CH_2CHOH), 3.13–3.20 (m, 1 H, CH_2CHOH), 4.05 (t, $J = 8.3$ Hz, 1 H, $CHCO$), 4.38 (br s, 1 H, OH), 4.63–4.67 (m, 1 H, $CHOH$), 5.33 (dd, $J = 8.6, 5.1$ Hz, 1 H, $CHCHN$), 7.14–7.26 (m, 4 H, ArH), 8.20 (d, $J = 8.4$ Hz, 1 H, $NHCO$) ppm; ^{13}C NMR δ –4.8, –4.7 [$Si(CH_3)_2$], 18.0 [$C(CH_3)_3$], 25.7, 25.8 [$C(CH_3)_3$], 39.6 (CH_2N), 40.4 (CH_2CHCO), 55.9 (CH_2CHOH), 57.0 ($CHCHN$), 59.9 ($CHCO$), 73.6 ($CHOH$), 73.9 ($CHOTBDMS$), 124.2, 125.4, 127.1, 128.2 (ArCH), 140.2, 140.7 (ArC), 175.9 (C=O) ppm; MS m/z 358 [$M^+ - H_2O$, 8%], 302 (13), 301 (54), 226 (12), 210 (46), 201 (14), 200 (100), 186 (19), 173 (20), 132 (11), 131 (12), 117 (11), 116 (90), 115 (42), 81 (70), 75 (15), 73 (17), 68 (11); HRMS calcd. for $C_{20}H_{32}N_2O_3Si$ [M^+] 376.2182, [$M^+ - H_2O$] 358.2088, found 358.2083.

(2S)-N-[(1S,2R)-2,3-Dihydro-2-hydroxy-1H-inden-1-yl]-N-methylpyrrolidine-2-carboxamide (21i). Yellow solid; *M.p.* 156–158 °C (EtOAc/hexane); $[\alpha]_D^{20}$ –29.0 (c 1.0, CH₂Cl₂); *R_f* (MeOH) 0.27; IR ν (KBr) 3249, 3065 (N–H, O–H), 1628 (C=O), 1100 (C–O) cm^{–1}; ¹H NMR (rotamers mixture) δ 1.72–2.27 (m, 8 H, 4 $\times$ CH₂CH₂N, 4 $\times$ CH₂CHCO), 2.62 (s, 3 H, CH₃), 2.73 (s, 3 H, CH₃), 2.80–3.09 (m, 4 H, 2 $\times$ CH₂CHOH, 2 $\times$ CH₂N), 3.97 (dd, *J* = 9.1, 6.3 Hz, 1 H, CHCO), 4.31 (t, *J* = 7.2 Hz, 1 H, CHCO), 4.76 (m, 2 H, CHOH), 5.30 (d, *J* = 7.0 Hz, 1 H, NCHCH) 5.85 (d, *J* = 6.9 Hz, 1 H, NCHCH), 7.19–7.35 (m, 8 H, ArH) ppm; ¹³C NMR δ 26.5, 26.6 (CH₂CH₂N), 30.0, 30.1 (CH₂CHCO), 31.3, 32.1 (CH₃), 39.9, 40.1 (CH₂CHOH), 47.1, 47.8 (CH₂N), 58.2, 58.8 (CHCHN), 61.5, 63.5 (CHCO), 71.8, 72.4 (CHOH), 125.2, 125.4, 125.6, 125.9, 127.2, 128.7, 128.9, (ArCH), 138.0, 138.2, 141.3, 141.6 (ArC), 173.8, 176.1 (C=O) ppm; MS *m/z* 242 [*M*⁺ – H₂O, 7%], 175 (10), 174 (81), 146 (10), 145 (13), 144 (16), 133 (17), 117 (13), 116 (78), 115 (100), 98 (16); HRMS calcd. for C₁₅H₂₀N₂O₂ [*M*⁺], 260.1525, [*M*⁺ – H₂O] 242.1408, found 242.1411.

(2S)-N-[(1R,2R)-2,3-Dihydro-2-hydroxy-1H-inden-1-yl]pyrrolidine-2-carboxamide (21j). White solid; *M.p.* 165 °C (EtOAc, Δ); $[\alpha]_D^{20}$ +78.8 (c 1.0, CH₂Cl₂); *R_f* (MeOH/EtOAc: 1/1) 0.31; IR ν (KBr) 3384, 3292 (N–H, O–H), 1659 (C=O), 1080 (C–O) cm^{–1}; ¹H NMR δ 1.67–1.76 (m, 2 H, CH₂CH₂N), 1.93–2.05 (m, 1 H, CH₂CHCO), 2.13–2.26 (m, 1 H, CH₂CHCO), 2.50–3.50 (br s, 1 H, OH), 2.82–3.06 (m, 3 H, 1 $\times$ CH₂CHOH, 2 $\times$ CH₂N), 3.29 (dd, *J* = 15.8, 7.6 Hz, 1 H, CH₂CHOH), 3.85 (dd, *J* = 8.9, 5.2 Hz, 1 H, CHCO), 4.36 (dd, *J* = 15.1, 7.6 Hz, 1 H, CHOH), 5.03 (t, *J* = 5.5 Hz, 1 H, NCHCH), 7.22–7.28 (m, 4 H, ArH), 8.29 (br s, 1 H, NHCO) ppm; ¹³C NMR δ 26.2 (CH₂CH₂N), 30.9 (CH₂CHN), 38.4 (CH₂CHOH), 47.3 (CH₂N), 60.3 (CHCHN), 63.4 (CHCO), 81.7 (CHOH), 122.9, 125.2, 127.2, 128.5 (ArCH), 139.3, 140.6 (ArC), 178.0 (C=O) ppm; MS *m/z* 246 [*M*⁺, <1%], 70 (100); HRMS calcd. for C₁₄H₁₈N₂O₂ [*M*⁺] 246.1368, found 246.1359.

(2S)-N-[(S)-2,3-Dihydro-1H-inden-1-yl]pyrrolidine-2-carboxamide (21k). Yellow oil; $[\alpha]_D^{20}$ –76.4 (c 1.0, CH₂Cl₂); *R_f* (EtOAc/MeOH: 2/1) 0.3; IR ν (neat) 3294 (N–H), 1656 (C=O) cm^{–1}; ¹H NMR δ 1.65–1.82 (m, 3 H, 2 $\times$ CH₂CH₂N, 1 $\times$ CH₂CH₂C), 1.88–1.99 (m, 1 H, CH₂CHCO), 2.10–2.23 (m, 2 H, 1 $\times$ CH₂NH, 1 $\times$ CH₂CHCO), 2.53–2.64 (m, 1 H, CH₂CH₂C), 2.80–3.03 (m, 4 H, 2 $\times$ CCH₂CH₂, 2 $\times$ CH₂N), 3.79 (dd, *J* = 9.0, 5.3 Hz, 1 H, CHCO), 5.42 (dd, *J* = 16.1, 7.9 Hz, 1 H, CHNHCO), 7.17–7.27 (m, 4 H, ArH), 7.87 (d, *J* = 7.2 Hz, 1 H, NHCO) ppm; ¹³C NMR δ 26.1 (CH₂CH₂CH₂), 30.2

(CH₂CH₂C), 30.8 (CH₂CHCO), 34.2 (CH₂CH₂C), 47.2 (NCH₂), 53.9 (CONHCH), 60.5 (CHCO), 124.0, 124.7, 126.6, 127.7 (ArCH), 143.3, 143.7 (ArC), 175.2 (C=O) ppm; MS *m/z* 230 [*M*⁺, <1%], 115 (10), 70 (100); HRMS calcd. for C₁₄H₁₈N₂O [*M*⁺] 230.1419, found 230.1415.

(2*S*)-*N*-[(1*R*,2*S*)-2,3-Dihydro-2-hydroxy-1*H*-inden-1-yl]pyrrolidine-2-carboxamide (21*l*). White solid; *M.p.* 145 °C (EtOAc/MeOH); [*α*]_D²⁰ −6.9 (c 1.0, CH₂Cl₂); *R*_f (MeOH/EtOAc: 1/1) 0.27; IR *ν*(KBr) 3302, 3190 (N–H, O–H), 1645 (C=O), 1055 (C–O) cm^{−1}; ¹H NMR *δ* 1.61–1.82 (m, 2 H, CH₂CH₂N), 1.89–2.03 (m, 1 H, CH₂CHN), 2.08–2.20 (m, 1 H, CH₂CHN), 2.85 (br s, 1 H, OH), 2.88–2.96 (m, 3 H, 1 × CH₂CHOH, 2 × CH₂CH₂N), 3.13 (dd, *J* = 16.4, 5.1 Hz, 1 H, CH₂CHOH), 3.76 (dd, *J* = 8.7, 5.6 Hz, 1 H, CHCO), 4.59 (dt, *J* = 5.4, 2.9 Hz, 1 H, CHOH), 5.27 (dd, *J* = 8.3, 5.2 Hz, 1 H, NCHCH), 7.22–7.27 (m, 4 H, ArH), 7.93 (d, *J* = 8.1 Hz, 1 H, NHCO) ppm; ¹³C NMR *δ* 26.2 (CH₂CH₂N), 31.1 (CH₂CHN), 39.6 (CHCH₂C), 47.2 (CH₂CH₂N), 57.3 (CHCHN), 60.8 (CHCO₂), 73.5 (CHOH), 124.5, 125.3, 127.0, 128.2 (ArCH), 140.4, 140.8 (CAr), 175.9 (C=O) ppm; MS *m/z* 228 [*M*⁺ − H₂O, 28%], 210 (13), 207 (11), 186 (69), 198 (15), 197 (21), 186 (58), 173 (52), 133 (13), 132 (51), 131 (27), 130 (40), 117 (16), 116 (100), 115 (98), 104 (41), 103 (21), 85 (23), 78 (11), 77 (17), 70 (30), 68 (15). HRMS calcd. for C₁₄H₁₈N₂O₂ [*M*⁺] 246.1368, [*M*⁺ − H₂O] 228.1274, found 228.1248.

(2*S*)-*N*-[(1*S*,2*S*)-2,3-Dihydro-2-hydroxy-1*H*-inden-1-yl]pyrrolidine-2-carboxamide (21*m*). White solid; *M.p.* 149–150 °C (EtOAc/MeOH, Δ); [*α*]_D²⁰ −78.4 (c 1.0, CH₂Cl₂); *R*_f (MeOH/EtOAc: 1/1) 0.28; IR *ν*(KBr) 3268, 3073 (N–H, O–H), 1652 (C=O), 1085, 1064 (C–O) cm^{−1}; ¹H NMR *δ* 1.71–1.89 (m, 2 H, CH₂CH₂N), 1.95–2.04 (m, 1 H, CH₂CHN), 2.15–2.28 (m, 1 H, CH₂CHN), 1.71–2.04 (br s, 1 H, OH), 2.90–3.11 (m, 3 H, 1 × CCH₂CH, 2 × CH₂CH₂N), 3.29 (dd, *J* = 15.7, 7.7 Hz, 1 H, CCH₂CH), 3.84 (dd, *J* = 9.0, 5.3 Hz, 1 H, CHCO), 4.39 (dd, *J* = 15.2, 7.9 Hz, 1 H, CHOH), 5.05 (t, *J* = 5.5 Hz, 1 H, NCHCH), 7.15–7.27 (m, 4 H, ArH), 8.25 (br s, 1 H, NHCO) ppm; ¹³C NMR *δ* 26.3 (CH₂CH₂N), 30.6 (CH₂CHN), 38.3 (CHCH₂C), 47.2 (CH₂CH₂N), 60.3 (CHCHN), 63.0 (CHCO), 81.4 (CHOH), 122.7, 125.1, 127.1, 128.3 (ArCH), 139.4, 140.3 (ArC), 177.6 (C=O) ppm; MS *m/z* 246 [*M*⁺, <1%], 70 (100); HRMS calcd. for C₁₄H₁₈N₂O₂ [*M*⁺] 246.1368, found 246.1372.

(2*S*)-*N*-(3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolidine-2-carboxamide (21*n*). White solid; *M.p.* 156° C (EtOAc); [*α*]_D²⁰ +101.5 (c 0.3 CH₂Cl₂); *R*_f (MeOH/EtOAc: 1/1) 0.32; IR *ν*(KBr) 3410, 3312 (N–H, O–H), 1630 (C=O), 1122,

1099 (C–O) cm^{-1} ; ^1H NMR δ 0.81 (s, 3 H, CH_3CCH_3), 0.92 (s, 3 H, CH_3CCH_3), 1.10 (s, 3 H, CH_2CCH_3), 1.04–1.2 (m, 2 H, $1 \times \text{CCH}_2\text{CH}_2$, $1 \times \text{CCH}_2\text{CH}_2$), 1.45–1.53 (m, 1 H, CCH_2CH_2), 1.63–1.80 (m, 3 H, $1 \times \text{CCH}_2\text{CH}_2$, $2 \times \text{CH}_2\text{CH}_2\text{CH}_2$), 1.87–2.05 (m, 1 H, NCHCH_2), 2.07–2.21 (m, 4 H, $2 \times \text{NCHCH}_2$, $1 \times \text{OH}$, $1 \times \text{NHCHCH}$), 2.87–3.04 (m, 2 H, CH_2NH), 3.67–3.73 (m, 2 H, $1 \times \text{NCHCH}_2$, $1 \times \text{NCHCH}$), 3.85 (d, $J = 8.1$ Hz, 1 H, CHOH), 7.98 (br s, 1 H, CONH) ppm; ^{13}C NMR δ 11.2, 20.8, 21.3 (CH_3), 26.2, 26.3 (CCH_2CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$), 31.1 (NCHCH_2), 33.4 (CCH_2CH_2), 47.1 (CH_3CCH_3), 47.3 (CH_2N), 49.1 (CH_2CCH_3), 50.1 (CHCH_3), 57.9, 60.5 (NHCH), 80.6 (CHOH), 175.5 (C=O) ppm; MS m/z 266 [M^+ , <1%], 70 (100); HRMS calcd. for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_2$ [M^+] 266.1994, [$\text{M}^+ - \text{H}_2\text{O}$] 248.1878, found 248.1848.

(2R)-N-[(1R,2S)-2,3-Dihydro-2-hydroxy-1H-inden-1-yl]pyrrolidine-2-carboxamide (ent-21e) White solid; *M.p.* 169 °C (EtOAc/MeOH); $[\alpha]_D^{20} +24.6$ (c 1.0, CH_2Cl_2); R_f (MeOH/EtOAc: 1/1) 0.61; IR ν (KBr) 3336, 3295 (N–H, O–H), 1633 (C=O), 1066, 1090 (C–O) cm^{-1} ; ^1H NMR δ 1.69–1.86 (m, 2 H, $\text{CH}_2\text{CH}_2\text{N}$), 1.97–2.06 (m, 1 H, CH_2CHN), 2.08–2.28 (m, 1 H, CH_2CHN), 1.69–2.28 (br s, 1 H, OH), 2.81–3.05 (m, 3 H, $1 \times \text{CH}_2\text{CHOH}$, $2 \times \text{CH}_2\text{CH}_2\text{N}$), 3.18 (dd, $J = 16.4$, 5.2 Hz, 1 H, CH_2CHOH), 3.84 (dd, $J = 9.1$, 5.2 Hz, 1 H, CHCO), 4.65 (dt, $J = 5.1$, 2.3 Hz, 1 H, CHOH), 5.34 (dd, $J = 8.7$, 5.1 Hz, 1 H, NCHCH), 7.17–7.27 (m, 4 H, ArH), 8.15 (d, $J = 7.8$ Hz, 1 H, CONH) ppm; ^{13}C NMR δ 26.2 ($\text{CH}_2\text{CH}_2\text{N}$), 31.1 (CH_2CHN), 39.6 (CH_2CHOH), 47.2 ($\text{CH}_2\text{CH}_2\text{N}$), 57.0 (NCHCH), 60.7 (CHCO), 73.6 (CHOH), 124.1, 125.3, 127.0, 128.1 (ArCH), 140.2, 140.9 (ArC), 176.2 (C=O) ppm; MS m/z 228 [$\text{M}^+ - \text{H}_2\text{O}$, 34%], 226 (15), 211 (11), 210 (13), 198 (17), 197 (28), 186 (67), 173 (60), 133 (12), 132 (37), 131 (26), 130 (38), 117 (13), 116 (100), 115 (94), 104 (44), 103 (21), 85 (26), 77 (16), 70 (33), 68 (13); HRMS calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$ [M^+] 246.1368, found 246.1361.

(2S)-2-amino-N-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)propanamide (23). Pale yellow solid; *M.p.* 143–144 °C (EtOAc); $[\alpha]_D^{20} +34.0$ (c 1.0, CH_2Cl_2); R_f (MeOH/EtOAc: 1/1) 0.45; IR ν (KBr) 3295 (N–H, O–H), 1641 (C=O), 1054, 1086 (C–O) cm^{-1} ; ^1H NMR (400Mz) δ 1.37 (d, $J = 6.8$ Hz, 3 H, CH_3), 2.21 (br s, 3 H, $2 \times \text{NH}_2$, $1 \times \text{OH}$), 2.92 (dd, $J = 16.4$, 1.8 Hz, 1 H, CH_2), 3.14 (dd, $J = 16.4$, 5.3 Hz, 1 H, CH_2), 3.53 (q, $J = 6.8$ Hz, 1 H, CHCH_3), 4.58 (dt, $J = 5.2$, 2.5 Hz, 1 H, CHOH), 5.29 (dd, $J = 8.5$, 5.2 Hz, 1 H, CHNH), 7.21–7.27 (m, 4 H, ArH), 7.75 (d, $J = 8.1$ Hz, 1 H, NHCO) ppm; ^{13}C NMR δ 21.8 (CH_3), 39.6 (CH_2), 50.9 (CHNH_2), 57.1 (CHNH), 73.5 (CHOH), 124.3, 125.2, 127.0, 128.1 (ArCH), 140.2, 140.7 (ArC), 176.6 (C=O) ppm; MS m/z 202

[$M^+ - H_2O$, 24%], 188 (13), 187 (99), 133 (12), 132 (22), 116 (68), 115 (100), 103 (10); HRMS calcd. for $C_{12}H_{16}N_2O_2$ [M^+] 220.1212 found 220.1219.

Typical procedure for the Michael addition of ketones to β -nitrostyrenes. A mixture of catalyst **21** (0.08 mmol), 4-nitrobenzoic acid (0.08 mmol) and the corresponding ketone (4 mmol) in NMP (0.2 ml) was stirred for 20 min at 25 °C. Then, the corresponding nitrostyrene (0.4 mmol) was added to the mixture and the reaction was stirred at 25 °C for the reaction time stated in Tables. The reaction mixture was quenched with water (2 mL) and extracted with EtOAc (3×2 mL). The organic layers were washed with water (3×2 mL) in order to remove NMP, dried over anhydrous $MgSO_4$, filtered off and the solvent was evaporated at low pressure to give crude products which were purified by flash chromatography (hexane/EtOAc: 18/1, 3.5 mL/min) giving pure *syn*-**27**.

Compounds **27aa**,^[7] **27ba**,^[11] **27ca**,^[8b] **27da**,^[8a] have been previously described and spectroscopic data were in agreement with published. See supporting information for HPLC separation conditions.

***syn*-4-Methyl-6-nitro-5-*p*-tolylhexan-3-one (27ab).** Colourless oil; $[\alpha]_D^{20} +14.8$ (c 1.0, CH_2Cl_2) for 74% *ee*; R_f (Hexane/EtOAc: 5/1) 0.39; IR ν (neat) 1552 (NO_2), 1704 ($C=O$) cm^{-1} ; 1H NMR (400 MHz) δ 0.96 (d, $J = 7.3$ Hz, 3 H, CH_3CH), 1.07 (t, $J = 7.3$ Hz, 3 H, CH_3CH_2), 2.31 (s, 3 H, CH_3Ar), 2.41 (dq, $J = 18.2, 7.3$ Hz, 1 H, CH_2CH_3), 2.61 (dq, $J = 17.9, 7.1$ Hz, 1 H, CH_2CH_3), 2.93–3.00 (m, 1 H, $CHCH_3$), 3.65 (dt, $J = 9.3, 5.0$ Hz, 1 H, $CHAr$), 4.57 (dd, $J = 12.4, 4.8$ Hz, 1 H, CH_2NO_2), 4.64 (dd, $J = 12.4, 9.1$ Hz, 1 H, CH_2NO_2), 7.04 (d, $J = 8.1$ Hz, 2 H, ArH), 7.12 (dd, $J = 7.8$ Hz, 2 H, ArH) ppm; ^{13}C NMR δ 7.6 (CH_3CH_2), 16.2 (CH_3CH), 21 (CH_3Ar), 35.4 (CH_2CO), 45.7 ($CHAr$), 48.3 ($CHCO$), 78.4 (CH_2NO_2), 127.7, 129.6 ($ArCH$), 134.4, 137.6 (ArC), 213.7 ($C=O$) ppm; MS m/z : 249 [M^+ , <1%], 202 (13), 187 (17), 173 (67), 146 (13), 145 (18), 132 (14), 131 (19), 118 (42), 117 (30), 115 (17), 105 (15), 91 (17), 57 (100); HRMS calcd. for $C_{14}H_{19}NO_3$ 249.1365 [M^+], found 249.1356; HPLC (Chiralcel OD-H, 1 mL/min, Hexane/*i*-PrOH: 99/1, λ 254 nm), $t_{Rmaj} = 13.3$ min, $t_{Rmin} = 17.7$ min.

***syn*-5-(4-Chlorophenyl)-4-methyl-6-nitrohexan-3-one (27ac).** Colourless oil; $[\alpha]_D^{20} +5.7$ (c 1.0, CH_2Cl_2) for 78% *ee*; R_f (Hexane/EtOAc: 5/1) 0.2; IR ν (neat.) 1553 (NO_2), 1711 ($C=O$) cm^{-1} ; 1H NMR (400 MHz) δ 0.96 (d, $J = 7.1$ Hz, 3 H, CH_3CH), 1.07 (t, $J = 7.1$ Hz, 3 H, CH_3CH_2), 2.41 (dq, $J = 17.9, 7.1$ Hz, 1 H, CH_2CH_3), 2.62 (dq, $J = 17.9, 7.1$ Hz, 1 H, CH_2CH_3), 2.95 (dq, $J = 9.3, 7.2$ Hz, 1 H, $CHCH_3$), 3.69 (dt, $J = 9.3,$

4.9 Hz, 1 H, CHAr), 4.58 (dd, $J = 12.4, 4.8$ Hz, 1 H, CH₂NO₂), 4.64 (dd, $J = 12.4, 9.0$ Hz, 1 H, CH₂NO₂), 7.11 (d, $J = 8.3$ Hz, 2 H, ArH), 7.31 (dd, $J = 6.6$ Hz, 2 H, ArH) ppm; ¹³C NMR δ 7.6 (CH₃CH₂), 16.2 (CH₃CH), 35.4 (CH₂CO), 45.4 (CHAr), 48.1 (CHCO), 78.0 (CH₂NO₂), 129.2, 129.3 (ArCH), 133.8, 136.0 (ArC), 213.1 (C=O) ppm; MS m/z : 269 [$M^+ - \text{CH}_3\text{CH}_2$, <1%], 193 (19), 138 (18), 115 (10), 57 (100); HRMS calcd. for C₁₃H₁₆ClNO₃ [M^+] 269.0819, [$M^+ - \text{NO}_2$] 223.0884, found 223.0874; HPLC (Chiralcel OD-H, 1mL/min, Hexane/*i*-PrOH: 99/1, λ 254 nm), $t_{\text{Rmaj}} = 22.6$ min, $t_{\text{Rmin}} = 25.8$ min.

***syn*-5-(4-Methoxyphenyl)-4-methyl-6-nitrohexan-3-one (27ad).** White solid; *M.p.* 124 °C (EtOAc/pentane); $[\alpha]_D^{20} -10.1$ (c 1.0, CH₂Cl₂) for 73% *ee*; R_f (Hexane/EtOAc: 5/1) 0.29; IR ν (KBr) 1245 (Ar–O–C), 1552 (NO₂), 1705 (C=O) cm⁻¹; ¹H NMR δ 1.38 (d, $J = 7.2$ Hz, 3 H, CH₃CH), 1.48 (t, $J = 7.3$ Hz, 3 H, CH₃CH₂), 2.83 (dq, $J = 18.0, 7.2$ Hz, 1 H, CH₂CH₃), 3.03 (dq, $J = 18.1, 7.2$ Hz, 1 H, CH₂CH₃), 3.37 (dq, $J = 9.5, 7.2$ Hz, 1 H, CHCH₃), 4.06 (dt, $J = 9.0, 5.1$ Hz, 1 H, CHAr), 4.2 (s, 3 H, OCH₃) 4.95–5.08 (m, 2 H, CH₂NO₂), 7.27 (d, $J = 8.6$ Hz, 2 H, ArH), 7.49 (d, $J = 8.6$ Hz, 2 H, ArH) ppm; ¹³C NMR δ 7.6 (CH₃CH₂), 16.2 (CH₃CH), 35.4 (CH₂CO), 45.3 (CHAr), 48.5 (CHCO) 55.2 (OCH₃), 78.5 (CH₂NO₂), 114.3, 128.9 (ArCH), 129.4, 159.1 (ArC), 213.7 (C=O) ppm; MS m/z 265 [M^+ , 4%], 218 (26), 203 (17), 189 (52), 162 (11), 161 (10), 135 (13), 134 (100), 121 (10), 119 (11), 91 (14), 57 (77); C₁₄H₁₉NO₄ (265.31): calcd. C 63.38, H 7.22, N 5.28, O 24.12; found C 63.26, H 7.34, N 5.27; HPLC (Chiralcel OD-H, 1mL/min, Hexane/*i*-PrOH: 99/1, λ 254 nm), $t_{\text{Rmaj}} = 21.4$ min, $t_{\text{Rmin}} = 27.4$ min.

***syn*-5-(3,5-Dichlorophenyl)-4-methyl-6-nitrohexan-3-one (27ae).** Yellow oil; $[\alpha]_D^{20} -24.4$ (c 1.0, CH₂Cl₂) for 72% *ee*; R_f (Hexane/EtOAc: 5/1) 0.31; IR ν (neat) 1556 (NO₂), 1712 (C=O) cm⁻¹; ¹H NMR δ 1.02 (d, $J = 7.2$ Hz, 3 H, CH₃CH), 1.06 (t, $J = 7.2$ Hz, 3 H, CH₃CH₂), 2.39 (dq, $J = 18.1, 7.2$ Hz, 1 H, CH₂CH₃), 2.64 (dq, $J = 18.1, 7.2$ Hz, 1 H, CH₂CH₃), 3.10–3.20 (m, 1 H, CHCH₃), 4.24 (dt, $J = 9.0, 4.2$ Hz, 1 H, CHAr), 4.61 (dd, $J = 12.8, 4.2$ Hz, 1 H, CH₂NO₂), 4.82 (dd, $J = 12.8, 8.7$ Hz, 1 H, CH₂NO₂), 7.11 (d, $J = 8.4$ Hz, 1 H, ArH), 7.22–7.27 (m, 1 H, ArH), 7.44 (d, $J = 2.2$ Hz, 1 H, ArH) ppm; ¹³C NMR δ 7.6 (CH₃CH₂), 16.1 (CH₃CH), 35.5 (CH₂CO), 41.7 (CHAr), 46.8 (CHCO), 76.4 (CH₂NO₂), 127.7, 129.4, 130.2 (ArCH), 133.8, 134.2, 135.2 (ArC), 213.0 (C=O) ppm; MS m/z : 303 [M^+ , <1%], 261 (14), 199 (11), 186 (11), 172 (11), 57 (100); HRMS calcd. for C₁₃H₁₅Cl₂NO₃ [M^+] 303.0429, found 303.0421; HPLC (Chiralcel OD-H, 1mL/min, Hexane/*i*-PrOH: 99/1, λ 254 nm), $t_{\text{Rmaj}} = 13.9$ min, $t_{\text{Rmin}} = 17$ min.

***syn*-4-Methyl-6-nitro-5-[2-(trifluoromethyl)phenyl]hexan-3-one (27af).** Yellow oil; $[\alpha]_D^{20}$ -4.5 (c 1.0, CH₂Cl₂) for 50% *ee*; *R_f* (Hexane/EtOAc: 5/1) 0.25; IR ν (neat) 1556 (NO₂), 1713 (C=O) cm⁻¹; ¹H NMR δ 0.97 (d, *J* = 7.2 Hz, 3 H, CH₃CH), 1.09 (t, *J* = 7.3 Hz, 3 H, CH₃CH₂), 2.48 (dq, *J* = 18.1, 7.3 Hz, 1 H, CH₂CH₃), 2.67 (dq, *J* = 18.1, 7.2 Hz, 1 H, CH₂CH₃), 3.21–3.31 (m, 1 H, CHCH₃), 4.06–4.15 (m, 1 H, CHAr), 4.58 (dd, *J* = 11.8, 4.0 Hz, 1 H, CH₂NO₂), 4.82 (dd, *J* = 11.8, 6.7 Hz, 1 H, CH₂NO₂), 7.28 (d, *J* = 7.8 Hz, 1 H, ArH), 7.41 (t, *J* = 7.6 Hz, 1 H, ArH), 7.54 (t, *J* = 7.5 Hz, 1 H, ArH), 7.72 (d, *J* = 7.8 Hz, 1 H, ArH) ppm; ¹³C NMR δ 7.5 (CH₃CH₂), 16.4 (CH₃CH), 35.4 (CH₂CO), 40.8 (CHAr), 47.7 (CHCO), 77.9 (CH₂NO₂), 122.3 (CF₃), 125.9 (ArC), 126.7, 127.8 (ArCH), 129.3 (ArC), 132.4 (ArCH), 136.8 (ArC), 213.3 (C=O) ppm; MS *m/z*: 303 [M⁺ – CH₃CH₂, <3%], 199 (42), 186 (17), 178 (11), 159 (13), 151 (10), 57 (100); HRMS calcd. for C₁₄H₁₆F₃NO₃ [M⁺] 303.1082, [M⁺ – CH₃CH₂] 274.0686, found 274.0710. HPLC (Chiralcel OD-H, 1mL/min, Hexane/*i*-PrOH: 99/1, λ 254 nm), *t*_{Rmaj} = 8.8 min, *t*_{Rmin} = 11.5 min.

***syn*-5-(2-Chlorophenyl)-4-methyl-6-nitrohexan-3-one (27ag).** Colourless oil; $[\alpha]_D^{20}$ +21.5 (c 1.0, CH₂Cl₂) for 78% *ee*; *R_f* (Hexane/EtOAc: 5/1) 0.4; IR ν (neat.) 1557 (NO₂), 1713 (C=O) cm⁻¹; ¹H NMR (400 MHz) δ 1.02 (d, *J* = 7.2 Hz, 3 H, CH₃CH), 1.06 (t, *J* = 7.2 Hz, 3 H, CH₃CH₂), 2.38 (dq, *J* = 17.9, 7.2 Hz, 1 H, CH₂CH₃), 2.62 (dq, *J* = 17.9, 7.2 Hz, 1 H, CH₂CH₃), 3.16–3.24 (m, 1 H, CHCH₃), 4.30 (dt, *J* = 9.2, 4.4 Hz, 1 H, CHAr), 4.63 (dd, *J* = 12.7, 4.4 Hz, 1 H, CH₂NO₂), 4.85 (dd, *J* = 12.7, 8.8 Hz, 1 H, CH₂NO₂), 7.15–7.27 (m, 3 H, ArH), 7.41 (d, *J* = 9.4 Hz, 1 H, ArH) ppm; ¹³C NMR δ 7.6 (CH₃CH₂), 16.1 (CH₃CH), 35.5 (CH₂CO), 42.1 (ArCH), 46.9 (CHCO), 76.6 (CH₂NO₂), 127.3, 128.9, 128.5, 130.4 (ArCH), 134.5, 135.1 (ArC), 213.3 (C=O) ppm; MS *m/z*: 234 [M⁺ – Cl, 54%], 167 (11), 165 (30), 152 (22), 138 (13), 131 (10), 130 (15), 129 (12), 125 (15), 115 (17), 103 (14), 57 (100); HRMS calcd. for C₁₃H₁₆ClNO₃ [M⁺] 269.0819, [M⁺ – Cl] 234.1125, found 234.1151; HPLC (Chiralcel OD-H, 1mL/min, Hexano/*i*-PrOH: 99/1, λ 210 nm), *t*_{Rmaj} = 11.2 min, *t*_{Rmin} = 14.3 min.

4-Methyl-5-nitro-6-phenylhexan-3-one (31). Yellow oil; *R_f* (hexano/EtOAc: 6/1) 0.49; IR ν (neat.) 1558 (NO₂), 1714 (C=O) cm⁻¹; ¹H NMR δ 1.06 (t, *J* = 7.3 Hz, 3 H, CH₃CH₂), 1.18 (d, *J* = 7.0 Hz, 3 H, CH₃CH), 2.30–2.46 (m, 3 H, 2 × CH₂Ph, 1 × CHCH₃), 2.50–2.68 (m, 2 H, CH₂CH₃), 5.45 (t, *J* = 7.64 Hz, 1 H, CHNO₂), 7.36–7.47 (m, 5 H, ArH) ppm; ¹³C NMR δ 7.7 (CH₃CH₂), 17.8 (CH₃CH), 34.8 (CH₂), 36.5 (CH₂), 42.6 (CHCO), 89.8 (CH₂NO₂), 127.6, 129.0, 129.9 (ArCH), 134.3 (ArC), 213.4

(C=O) ppm; MS m/z 207 [$M^+ - H_2O$, <1%], 189 (46), 131 (58), 117 (14), 115 (2), 114 (11), 91 (13), 57 (34). HRMS calcd. for $C_{13}H_{17}NO_3$ [M^+] 235.1208, [$M^+ - NO_2$] 189.1274, found 189.1265.

Supporting Information (see footnote on the first page of this article): typical procedure for the Michael addition under microwave irradiation and solvent screening for the Michael addition of ketones **25b**, **25c**, and **25d** to β -nitrostyrene. Typical procedure for recovery of catalyst **21e** and ESI-MS (+) experiments and spectra. Cartesian coordinates for transition states and reactant complexes and HPLC separation conditions are included.

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References

- [1] a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748. b) B. List, *Tetrahedron*, **2002**, *58*, 5573–5590. c) R. O. Duthaler, *Angew. Chem. Int. Ed.* **2003**, *42*, 975–978. d) *Acc. Chem. Res.* **2004**, *37* (8), special issue on organocatalysis. e) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. f) A. Berkessel, H. Gröger, In *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH: Weinheim, 2004. g) P. M. Pihko, *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064. h) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724. i) *Tetrahedron* **2006**, *62* (2–3), Tetrahedron symposium-in-Print on Organocatalysis in Organic Synthesis.
- [2] A. Perlmutter, *Conjugative Additions in Organic Synthesis*, Pergamon Press: Oxford, 1992.

- [3] For reviews on catalytic asymmetric Michael additions, see: a) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061. b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196. c) S. C. Jha, N. N. Joshi, *Arkivoc* **2002**, *vii*, 167–196. d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–972. e) D. Almaši, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry*, **2007**, In press (doi:10.1016/j.tetasy.2007.01.023)
- [4] a) N. Ono, *The Nitro Group in Organic Synthesis* Wiley-VCH: New York, **2001**. b) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.
- [5] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.
- [6] B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425.
- [7] D. Enders, A. Seki, *Synlett* **2002**, 26–28.
- [8] a) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147–1168. b) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559–2561.
- [9] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559.
- [10] a) J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Synthesis* **2004**, 1509–1521. b) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967.
- [11] A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96.
- [12] C. E. T. Mitchell, A. J. A. Cobb, S. V. Ley, *Synlett* **2005**, 611–614.
- [13] D. Terakado, M. Takano, T. Oriyama, *Chem. Lett.* **2005**, *34*, 962–963.
- [14] S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, 4995–5000.
- [15] Y. Xu, W. Zou, H. Sundén, I. Ibrahim, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 418–424.
- [16] Y. Xu, A. Córdova, *Chem. Commun.* **2006**, 460–462.

- [17] M.-K. Zhu, L. F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Tetrahedron: Asymmetry* **2006**, *17*, 491–493.
- [18] D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826–832.
- [19] S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451–1453.
- [20] J. Wang, H. Li, B. Lou, L. Zu, H. Guo, W. Wang, *Chem. Eur. J.* **2006**, *12*, 4321–4332.
- [21] S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097.
- [22] C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904.
- [23] H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171.
- [24] S. V. Pansare, K. J. Pandya, *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625.
- [25] L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079.
- [26] S. Luo, X. Mi, S. Liu, H. Xu, J.-P. Cheng, *Chem. Commun.* **2006**, 3687–3689.
- [27] a) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263. b) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755–5760. c) Z. Tang, Z.-H. Yang, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Org. Lett.* **2004**, *6*, 2285–2287. d) S. Tanimori, T. Naka, M. Kirihata, *Synth. Commun.* **2004**, *34*, 4043–4048. e) Z. Tang, Z.-H. Yang, X.-H. Cheng, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289. f) J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan, W.-J. Xiao, *Org. Lett.* **2005**, *7*, 4543–4545. g) D. Gryko, R. Lipiński, *Adv. Synth. Catal.* **2005**, *347*, 1948–1952. h) S. Samanta, J. Liu, R. Dodda, C.-G. Zhao, *Org. Lett.* **2005**, *7*, 5321–5323. i) L. He, Z. Tang, L. F. Cun, A.-Q. Mi, Y.-Z. Jiang, L. Z. Gong, *Tetrahedron* **2006**, *62*, 346–351. j) M. Jiang, S.-F. Zhu, Y. Yang, L.-Z. Gong, X.-G. Zhou, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2006**, *17*, 384–387. k) Z. Tang, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Org. Lett.* **2006**, *8*, 1263–1266. l) G. Guillena, M. C. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 729–733. m) G. Guillena, M. C. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 1027–1031. n) G. Guillena, M. C. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 1493–1497. o) D. Gryko, B.; Kowalczyk, L. Zawadzki, *Synlett* **2006**, 1059–1062. p) S. Samanta, C.-G. Zhao, *J. Am. Chem. Soc.* **2006**, *128*, 7442–7443. q) M. Raj, Vishnumaya S. K. Ginotra, V. K. Singh,

- Org. Lett.* **2006**, *8*, 4097–4099. r) J.-R. Chen, X.-Y. Li, X.-N. Xing, W.-J. Xiao, *J. Org. Chem.* **2006**, *71*, 8198–8202.
- [28] H.-M. Guo, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2005**, 1450–1452.
- [29] S. S. Chimni, D. Mahajan, V. V. S. Babu, *Tetrahedron Lett.* **2005**, *46*, 5617–5619.
- [30] H.-M. Guo, L. Cheng, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2006**, 429–431.
- [31] a) W. Wang, J. Wang, H. Li, *Org. Lett.* **2004**, *6*, 2817–2820. b) J. Wang, H. Li, Y. Mei, B. Lou, D. Xu, D. Xie, H. Guo, W. Wang, *J. Org. Chem.* **2005**, *70*, 5678–5687.
- [32] N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791.
- [33] a) J. Hine, *Acc. Chem. Res.* **1978**, *11*, 1–7. b) J. Hine, Y. Chou, *J. Org. Chem.* **1981**, *46*, 649–652. c) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570–579.
- [34] D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 2064–2068.
- [35] Z. J. Song, M. Zhao, R. Desmond, P. Devine, D. M. Tschaen, R. Tillyer, L. Frey, R. Heid, F. Xu, B. Foster, J. Li, R. Reamer, R. Volante, E. J. J. Grabowski, U. H. Dolling, P. J. Reider, S. Okada, Y. Kato, E. Mano, *J. Org. Chem.* **1999**, *64*, 9658–9667.
- [36] R. E. Gawley, P. Zhang, *J. Org. Chem.* **1996**, *61*, 8103–8112.
- [37] Alcoholic solvents have been previously shown to be very effective for the organocatalytic addition of ketones to nitroolefins, See reference: 7.
- [38] N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450–451.
- [39] For the asymmetric α -aminooxylation, *O*-nitroso-aldol/Michael and Mannich reactions with carbonyl compounds, see: Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshino, *Adv. Synth. Catal.* **2004**, *346*, 1435–1439. For the asymmetric Michael reaction of aldehydes and nitroalkanes, see: Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215. For the asymmetric Mannich reaction, see: D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem. Int. Ed.* **2005**, *44*,

4079–4083. For the α -fluorination of aldehydes and ketones, see: D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 991–993. For the asymmetric aldol reaction in the synthesis of carbohydrates, see: C. Grondal, D. Enders, *Tetrahedron* **2006**, 62, 329–337.

- [40] At this point, catalysts **21f** and **21g** were also tested in order to confirm **21e** as the best choice as well as the reaction conditions: **21f** (6d, 65%, *syn/anti*: 84/14, 74% *ee*), **21g** (7d, 45%, *syn/anti*: 80/20, 78% *ee*)
- [41] a) M. E. Kuehne, *J. Am. Chem. Soc.* **1959**, 81, 5400–5404. b) T. A. Spencer, H. S. Neel, D. C. Ward, K. L. Williamson, *J. Org. Chem.* **1966**, 31, 434–436. c) R. B. Woodward, *Pure Appl. Chem.* **1968**, 17, 519–547. d) Z. G. Hajos, D. R. Parrosh, *J. Org. Chem.* **1974**, 39, 1612–1615.
- [42] Y. Zhou, Z. Shah, *Tetrahedron: Asymmetry* **2006**, 17, 1671–1677.
- [43] See supporting information.
- [44] C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, 37, 2922–2959.
- [45] D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, 64, 1413–1423.
- [46] Calculations were carried out using the Gaussian 03 suite of programs: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian 03, Revision C.02, Gaussian, Inc., Wallingford CT, **2004**.
- [47] R. G. Parr, W. Yang, In *Density-Functional Theory of Atoms and Molecules*, Oxford, New York, 1989.

- [48] a) C. Lee, W. Yang, R. G. Parr *Phys. Rev. B* **1988**, *37*, 785–789. b) A. D. Becke *Phys. Rev. A* **1988**, *38*, 3098–3100. c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652. d) W. Kohn; A. D. Becke; R. G. Parr *J. Phys. Chem.* **1996**, *100*, 12974–12980.
- [49] J. L. Reymond, *J. Mol. Catal. B* **1998**, *5*, 331–337. See also ref. [21].