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

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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 *p*-nitrobenzoic acid or under microwave heating. High *syn* diastereoselectivities (up to 94 % *de*) and good enantioselectivities (up to 80 % *ee*) are obtained at room temp. Moreover, 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** has been investigated with computational density functional methods. Transition-state energies 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 *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 nitro alkene since it represents a very useful synthetic method for the preparation of chiral nitro alkanes with at least two vicinal stereogenic centres in a single step. Chiral nitro alkanes 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 with L-proline (**1**) as the catalyst with good yields but very low enantioselectivities (0–23 % *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 20 mol-% of L-proline as the catalyst.[7] Since these preliminary studies, very effective catalytic systems like **2**–**20**[8–26] have been developed for the asymmetric Michael reaction of ketones with nitro alkenes, and the process is generally *syn*-selective (Scheme 1). The best improvements to this reaction have been mostly achieved with 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** (Scheme 1) have also been shown to be very effective catalysts for the addition of ketones to *trans*-β-nitrostyrene. Moreover, some of these catalysts have some important features to emphasize such as bipyrrolidine **2**, which is a very active organocatalyst for the *anti* conjugate addition of α-hydroxy ketones to nitrostyrenes.[8] A similar sense of relative stereoinduction has been shown by the chiral, primary, amine-thiourea catalysts **13**[19] and **17**,[23] developed by Tsogoeva and Jacobsen, respectively, in the conjugate addition of acyclic ketones to nitro olefins 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 with which to perform the Michael addition under aqueous conditions such as brine

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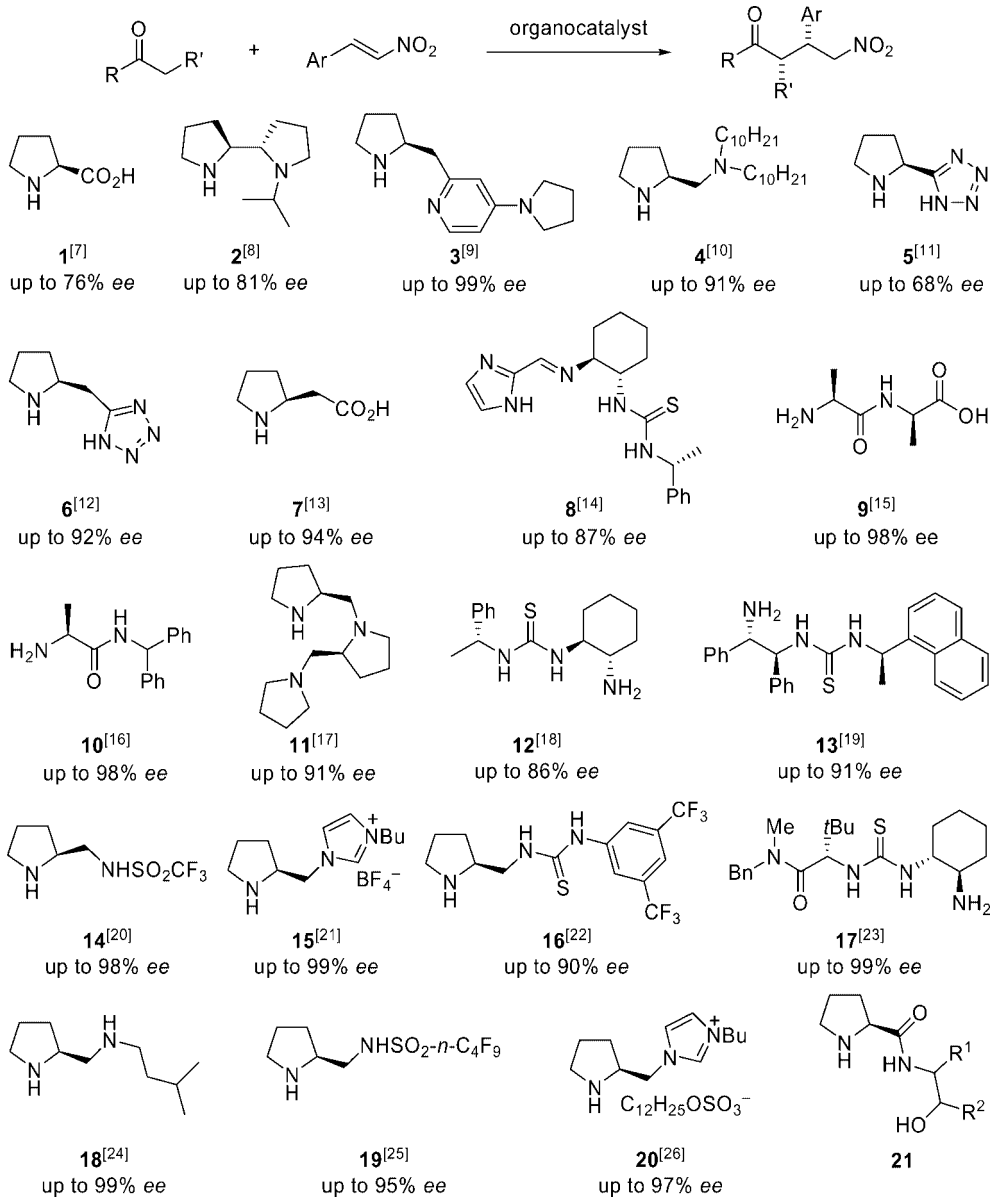


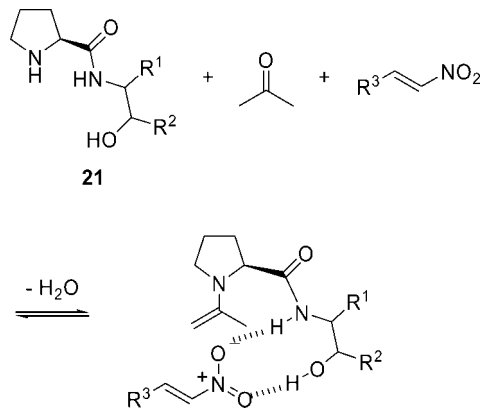
Scheme 1. Enantioselective conjugate addition of ketones to *trans*-β-nitrostyrene.

(catalyst **4**) or pure water. On the other hand, the chiral imidazolium salt **15**[21] performs much better than other chiral pyrrolidine catalysts when the reaction media is an ionic liquid. 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.

L-Prolinamide and derivatives are 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 organocatalyst also promotes 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 hydroxy groups were expected to interact by 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 the 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 aprotic solvents such as NMP. One of the

main drawbacks of these catalysts was the long reaction times required (4 d). Herein, the full account of our studies aimed at improving the catalytic performance of the system and exploring the full scope and the mechanism of this process is described.



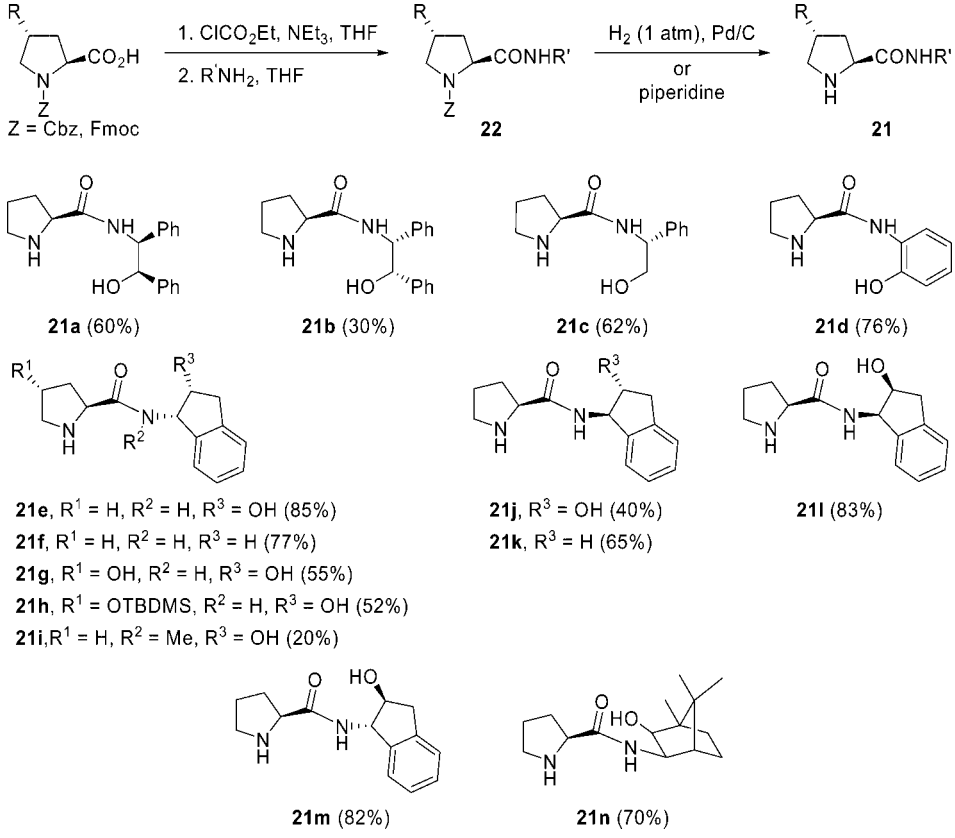
Scheme 2. L-Prolinamide-derived bifunctional organocatalysts.

Results and Discussion

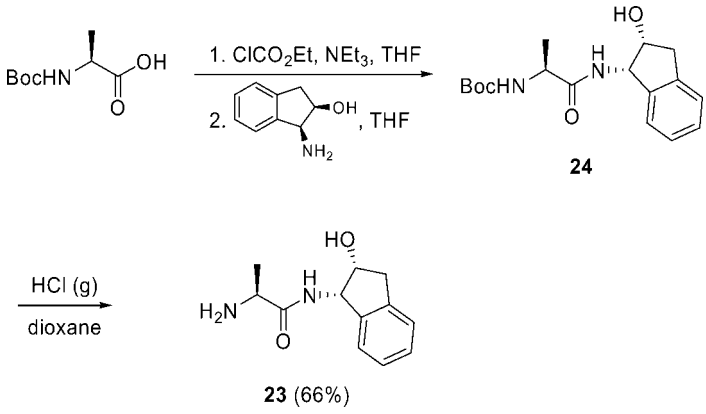
Catalysts **21** were prepared in good to excellent yields from Cbz- or Fmoc-L-proline or Cbz-4-hydroxy-L-proline and the corresponding commercially available chiral amines and β-amino alcohols through the reaction sequence shown in Scheme 3. β-Amino alcohols employed in the preparation of catalysts **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.

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 room temp. to give *syn* and *anti* adducts **27aa** (Scheme 5 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).

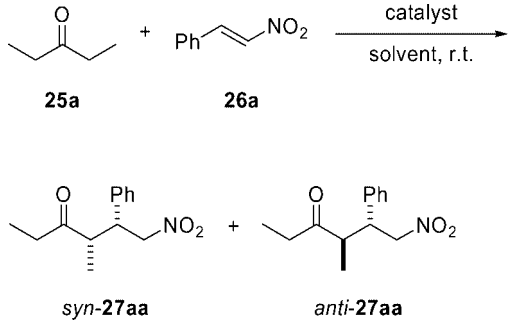
Most of the L-prolinamides exhibited high catalytic activities for the reaction and gave the *syn* adduct **27aa** as the favoured product. Prolinamides **21a** and **21b**, derived from 1,2-diphenyl-2-aminoethanol, which have been successfully used in the direct aldol reaction of ketones with aldehydes,[27a,b,e,i,q] showed good activity with high reaction conversions, good diastereoselectivity (*syn*/*anti* of 92:8 and 85:15, respectively) and enantioselectivity (39% *ee* and 52%



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



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



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	*T* [d]	Conv. [%][b]	*dr*[b,c]	*ee* [%][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	*ent*-**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 catalyst (20 mol-%), 3-pentanone (4 mmol) and *trans*-β-nitrostyrene (0.4 mmol) were stirred in MeOH (0.2 mL) at room temp. for the time indicated in the Table. [b] Determined by ^{1}H NMR and/or GC analysis. [c] *syn*/*anti* ratio. [d] *ee* for the *syn* diastereoisomer, as 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.

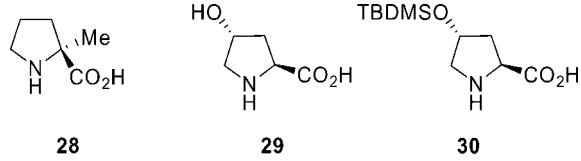


Figure 1. Proline-derived organocatalysts **28**–**30**.

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, showed very high catalytic activity and afforded, after 1 d, the Michael adduct **27aa** in high yield but with lower diastero- and enantioselectivity (*syn*/*anti* of 83:17 and 36% *ee*, Table 1, Entry 3). The presence of the chiral hydroxy moiety seems to be important for the selectivity of the process. This was further supported by 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 favoured 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 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-amino-

indane, 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 amino-alcohol-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 hydroxy group and a hydrogen in the amide 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 levels of enantioselection similar to that of 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] the 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.[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 the 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 was very low, affording **27aa** in a 58% conversion and 38% *ee* for the major *syn* isomer (Table 1, Entry 19).

The effect of catalyst loading on the reaction efficiency was also evaluated employing **21e**. The enantioselectivity of the process was, in general, slightly sensitive to catalyst loading, and the best results in terms of yield and selectivity were obtained with 20 mol-% of the catalyst, as routinely employed (Table 1, compare Entries 5 and 20–22). In conclusion, the catalyst study showed prolinamide **21e** was 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 iPrOH and tBuOH 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 α to the nitro group. This byproduct was not observed when polar protic solvents were used (Table 2, compare Entries 1–7). The use of $CHCl_3$ and CH_3CN gave similar results to MeOH with respect to diastereo- and enantioselectivity, and the formation in small amounts (5%, GC analysis) of the regioisomeric compound **31** (Figure 2, Table 2, Entries 8 and 9) was again detected. The employment of protic solvents seemed beneficial to avoid the formation of **31**. Notably, increasing the polarity of the reaction medium with DMF provided a noticeable

Table 2. Asymmetric 1,4-addition of 3-pentanone to β-nitrostyrene, catalyzed by **21e**−reaction conditions study.[a]

Entry	Solvent	*T*	Conv. [%][b]	*dr*[b,c]	*ee* [%][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*PrOH	4 d	71	88:12	57
6	*t*BuOH	4 d	40	90:10	53
7	toluene	8 d	91 (8)	91:9	56
8	$CHCl_3$	3 d	94 (5)	91:9	58
9	CH_3CN	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_2O[l]	6 d	63 (5)	90:10	70
18	NMP/H_2O[m]	6 d	95 (5)	90:10	72
19	NMP/H_2O[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 indicated solvent (0.2 mL) at room temp. for the time indicated. [b] Determined by ^1H NMR and/or GC analysis. The yield of compound **31** is shown in parenthesis, as determined by GC. [c] *syn*/*anti* ratio. [d] *ee* for the *syn* diastereomer, as 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/H_2O, 1:1)/mmol of **26a** were used (14 equiv. of H_2O). [m] 0.75 mL of solvent (NMP/H_2O, 2:1)/mmol of **26a** were used (14 equiv. of H_2O). [n] 0.6 mL of solvent (NMP/H_2O, 5:1)/mmol of **26a** were used (5 equiv. of H_2O). [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).

increase in selectivity (76% *ee*), and the amount of solvent used in the process was very important, 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* values were obtained for DMSO, DMAc and NMP, although the best combination of yield, diastereo- and enantioselectivity was obtained with the latter solvent, though longer reaction times were required (Table 2, Entries 12–14).

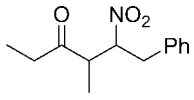


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Figure 2. Regioisomeric product obtained in non-polar solvents.

The reaction time could be reduced from 7 d to 3 d by adding the electrophile to the reaction mixture after stirring the ketone and the catalyst in NMP at room temp for 20 min (Table 2, compare Entries 14 and 15). From this point on, all subsequent 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 was 0.05%, Table 2, Entry 15) had a beneficial effect on the reaction rate.

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% H_2O) which represents 0.014 mmol H_2O/mmol **26a** (Table 2, Entry 15). Other combinations of solvents such as NMP/MeOH and NMP/DMSO did not improve the results (Table 2, Entries 20–21), except that the presence of MeOH as cosolvent circumvented the formation of **31** (Table 2, Entry 20). We also tested the ionic liquid [bmim][PF_6] as a 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* of 87:13). Finally, a very fast reaction was achieved under microwave irradiation (15 W, 48 °C) while good diastereo- and enantioselectivities were preserved (Table 2, Entry 24). Ultimately, **21e** (20 mol-%), NMP (0.5 mL/mmol of **26a**) and room temp. were established as the optimal 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 an 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 is beneficial in terms of activity due to the acceleration of enamine formation.[27n,33,41] Thus, we started our additive study by employing substoichiometric amounts (20 mol-%) of different organic acids (Table 3, Entries 1–10). Among the carboxylic acids, *p*-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 anhydrous NMP, the reaction rate and the enantioselectivity of the process were lower, which clearly demonstrated that the water present in the commercially obtained non-anhydrous NMP was also necessary to obtain good activities and selectivities with an acid cocatalyst (Table 3, Entries 5 and 6). Interestingly, the acid additives also avoided

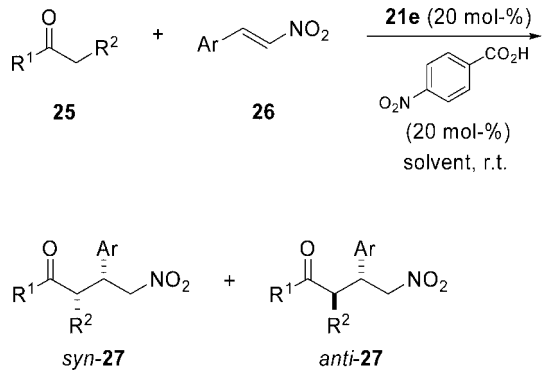
Table 3. Asymmetric 1,4-addition of 3-pentanone to β-nitrostyrene catalyzed by **21e** (additive study).[a]

Entry	Additive	*T* [d]	Conv. [%][b]	*dr*[b,c]	*ee* [%][d]
1	–	3	78	91:9	77
2	AcOH	2	97	95:5	75
3	$PhCO_2H$	1	75	90:10	75
4	$PhCO_2H$[e]	6	50	97:3	78
5	$4\text{-}NO_2C_6H_4CO_2H$	1	99	95:5	78
6	$4\text{-}NO_2C_6H_4CO_2H$[f]	2	97	94:6	70
7	$2,4\text{-}(NO_2)_2C_6H_3CO_2H$	2	84	93:7	76
8	$PhSO_3H$	6	<5	–[g]	–[g]
9	(*R*)-(–)-2-phenylpropionic acid	1	65	93:7	76
10	(*S*)-(+)-2-phenylpropionic acid	1	72	93:7	74
11	(*R*)-1,1′-bi(2-naphthol)[h]	4	>99	90:10	74
12	(*S*)-1,1′-bi(2-naphthol)[i]	2	>99	93:7	76
13	(*S*)-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 room temp. The β-nitrostyrene (0.4 mmol) was then added to the mixture, and the reaction was stirred at room temp. for the time indicated. [b] Determined by ^1H NMR and/or GC analysis. [c] *syn*/*anti* ratio. [d] *ee* for the *syn* diastereoisomer, as 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 *p*-nitrobenzoic acid were used. [i] 5 mol-% of (*S*)-Binol and 5 mol-% of *p*-nitrobenzoic acid were used. [j] 5 mol-% of (*S*)-Binol was used.

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 of a chiral proton source on the selectivity of the process. 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 through hydrogen-bonding activation when used as a chiral additive.[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-napthol) (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.

Under the established best reaction conditions [**21e** (20 mol-%) as the catalyst, *p*-nitrobenzoic acid (20 mol-%) as an additive and NMP as the solvent at room temp.], 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% yield, *dr* values from 91:9 to 97:3 and 76% to 81% *ee* values in a 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* of 99:1) *syn*-**27af** was obtained (Table 4, Entry 6). When 2-chloronitrostyrene was used as the 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.

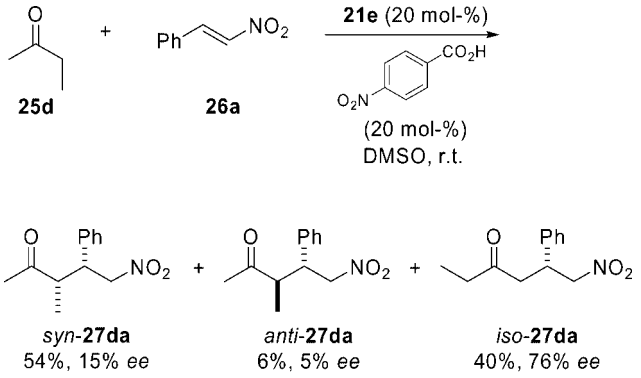
Next, we examined other ketone donors in the Michael reaction with *trans*-β-nitrostyrene (Scheme 6, Table 4). For each nucleophile, a full solvent study was carried out, since we observed enormous differences in reactivity and selectivity depending on the solvent.[43] In Table 4, Entries 7–10, we have recorded the results obtained 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* of 90:10) and moderate enantioselectivity (65% *ee*) with MeCN as the solvent (Table 4, Entry 8). Surprisingly, NMP led to a very low 16% *ee*. The conjugate reaction between hydroxyacetone and nitrostyrene was regioselective for all the studied reaction conditions,[43] CH_2Cl_2 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* with low enantioselectivit-

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

Entry	R^1	R^2	Ar	Solvent	*T* [d]	Conv. [%][b]	Product	*syn*/*anti*[c]	*ee* [%][d]
1	Et	Me	Ph	NMP	1	99 (76)	**27aa**	95:5	78[e]
2	Et	Me	4-MeC_6H_4	NMP	1.5	94 (64)	**27ab**	91:9	76
3	Et	Me	4-ClC_6H_4	NMP	1.5	>99 (75)	**27ac**	92:8	79
4	Et	Me	4-$MeOC_6H_4$	NMP	1.5	86 (74)	**27ad**	93:7	81
5	Et	Me	3,5-$(Cl)_2C_6H_3$	NMP	1.5	>99 (83)	**27ae**	97:3	78
6	Et	Me	2-$CF_3C_6H_4$	NMP	1.5	>99 (75)	**27af**	99:1	59
7	Et	Me	2-ClC_6H_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_2Cl_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-%), *p*-nitrobenzoic acid (20 mol-%) and 3-pentanone (4 mmol) was stirred in the indicated solvent (0.2 mL) for 20 min at room temp. The nitrostyrene (0.4 mmol) was then added to the mixture, and the reaction was stirred at room temp. for the time indicated. [b] Determined by ^{1}H NMR and/or GC analysis over the crude reaction mixture. The isolated yield after flash chromatography for the mixture of diastereoisomers is shown in brackets. [c] Determined by ^{1}H NMR and/or GC analysis of the crude reaction mixture. [d] *ee* for the *syn* diastereoisomer, as determined by chiral-phase HPLC analysis. The absolute configuration was not determined except for **27aa**. [e] Similar results were obtained with recycled **21e** (88% yield, *syn*/*anti* of 91:9, 78% *ee*). [f] A 16% *ee* was obtained when NMP was used as the solvent. [g] 35% *ee* for the *anti* isomer. [h] *syn*/*anti*/*iso* of 54:6/40. [i] 5% *ee* for the *anti* isomer; 76% *ee* for the *iso* isomer.

ies 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 and 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 an 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 $\{[\alpha]_D^{20} = -24.4$ ($c = 1.0$, CH_2Cl_2)$\}$.

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 by ESI-MS (Scheme 8, Figure 3). Under the typical reaction conditions, enamine **I**·H$^+$ (*m*/*z* = 315.1) was detected after stirring the organocatalyst **21e**

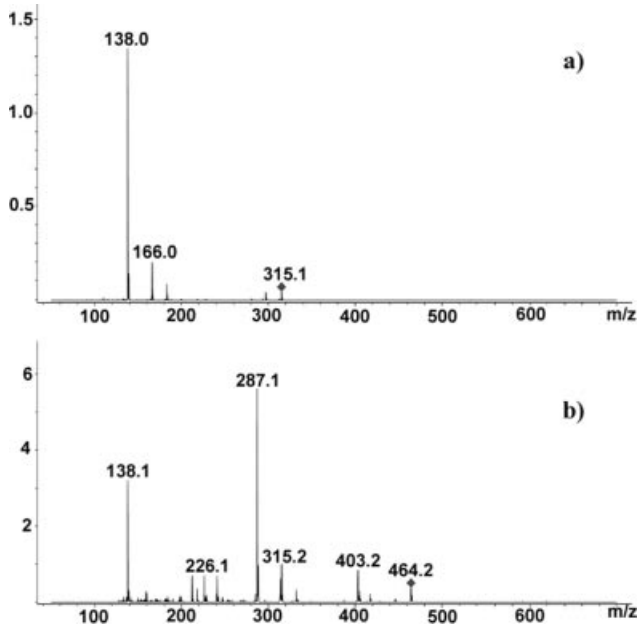
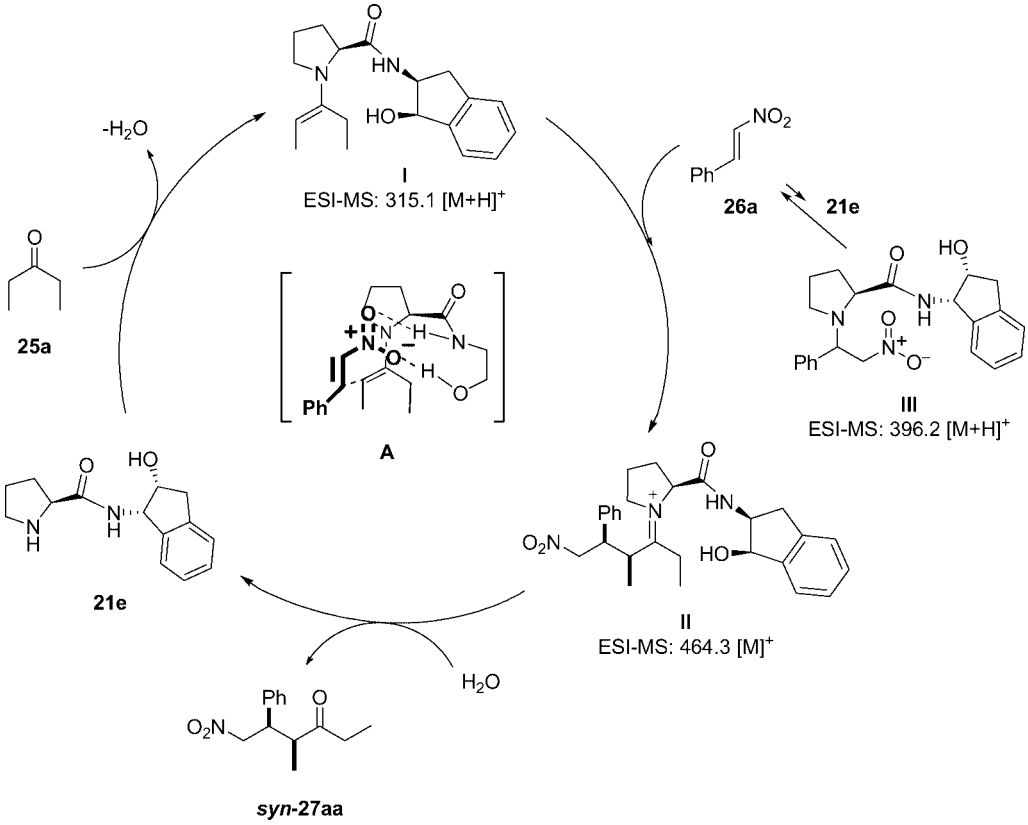


Figure 3. ESI-MS-(+) spectra of the intermediates a) **I**·H$^+$, b) **II**$^+$ (see Scheme 8).



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

(20 mol-%), 3-pentanone (1 mmol) and *p*-nitrobenzoic acid (20 mol-%) in MeOH for 20 min (Figure 3, a). To this solution was added *trans*-β-nitrostyrene (0.1 mmol), and the mixture was injected after 0.2 min. The formation of intermediate **II** (Scheme 8) was formed rapidly and was immediately detected in the mixture by ESI-MS (*m*/*z* = 464.3, Figure 3, b). This meant that enamine **I** attacked the electrophile, which was probably activated by hydrogen bonding by the amide moiety, to give intermediate **II**. We could also intercept[43] the adduct ion **III**·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.

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).

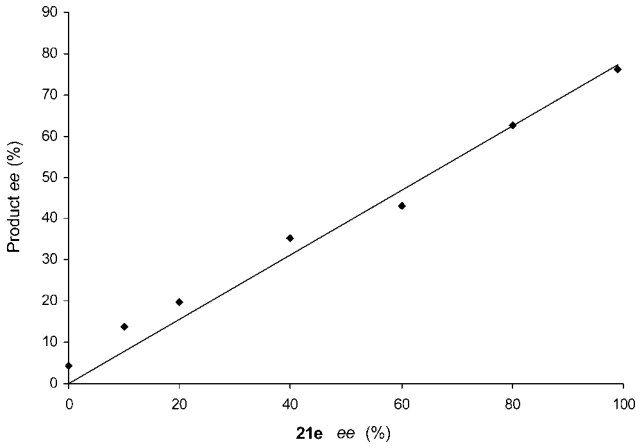


Figure 4. Observation of the linear relationship between the *ee* of **21e** and that of **27aa**.

Computational Studies

To explain the predominant production of the (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 the B3LYP/6-31G* level.[48] For computational simplicity reasons, we have chosen the unsubstituted 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** on 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.

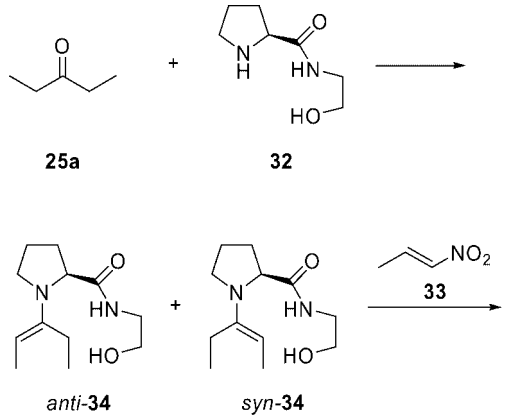


Figure 5. Model reaction used for the DFT computational studies.

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 hydrogen-bonding activation between the amide NH and the hydroxyl group 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 uncatalyzedway, without the help of hydrogen-bonding activation (TS_C and TS_D). We located the four possible transition

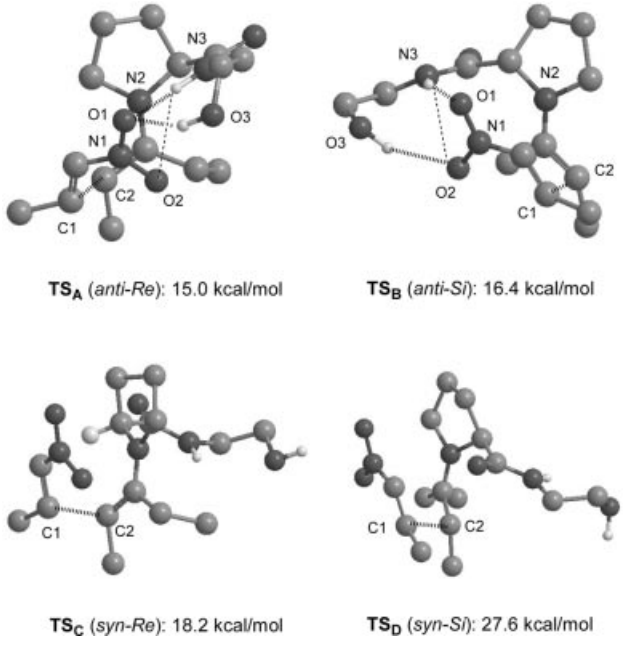


Figure 6. Transition-state geometries and activation energies for the reaction between **25a** and **32**, calculated at B3LYP/6-31G* level.

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

Entry	Transition state	Activation energies[a]	Distances[b]					
			C1···C2	N1···N2	O1···H–N3	O1···H–O3	O2···H–N3	O2···H–O3
1	TS_A	15.0	2.129	3.260	2.028	1.885	2.589	2.720
2	TS_B	16.4	2.095	3.103	2.109	2.845	2.557	2.093
3	TS_C	18.2	2.012	–	–	–	–	–
4	TS_D	27.6	1.945	–	–	–	–	–

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

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 the amide NH and the hydroxyl group in the catalyst activate the nitro alkene by the concurrence of up to three hydrogen bonds, favouring the approach of the nitro alkene from the *Re* face of the *anti* enamine. The minor enantiomer *syn*-(4*R*,5*S*) is formed through a *Si* approach of the nitro alkene 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 selectivity of ≈ 10:1 (≈ 80% *ee*) in favour 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 (activation energy: $TS_C >> TS_A$ and $TS_D >> TS_B$. Interestingly, there is an inverse relationship between the distance of the two bond-forming carbons (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 corresponds to the latest transition state TS_D ($\delta_{C1–C2}$ = 1.94 Å).

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 oxygens of the nitro group and the amide NH and hydroxyl group 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 group (O1) is able to form two strong hydrogen bonds with the amide NH (H–N3 2.03 Å) and especially with the hydroxyl group (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 (distance about 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 difference in strength of the hydrogen bonds in TS_A and TS_B is responsible for the computed facial selectivity. Of note is that the source of the chirality in these models is only the stereogenic centre 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.

Conclusions

From the studies carried out on the direct, enantioselective, conjugate addition of ketones to β-nitrostyrenes, catalyzed by 1,2-amino-alcohol-derived prolinamides, we 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 *p*-nitrobenzoic acid or under microwave irradiation conditions. Both the amide hydrogen and the chiral hydroxy 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 the B3LYP/6-31G* level have been conducted on a model reaction, confirming the initial hypothesis that hydrogen bonding plays a crucial role in the activation of the nitro alkene and helps to discriminate between the two diastereofacial approaches. The computationally favoured 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 with an 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, the wavelength of detection, solvent mixture, flow rate, column used, retention time and major enantiomer are stated. NMR spectra were recorded with a Bruker AC-300 (300 MHz for H^1 NMR and 75 MHz for ^{13}C NMR) using $CDCl_3$ as the solvent and TMS as the 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 with a Shimadzu QP-5000 and Agilent 5973 spectrometer and DIP (Direct Insertion Probe) mass spectra were obtained with an Agilent 5973 spectrometer; fragment ions are listed with relative intensities (%) in parenthesis. HRMS was performed with 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 F_{254} (Merck). For flash chromatography, silica gel 60 (0.040–0.063 mm) was employed in a Büchi Pump system (Controller C–610 with Module C–601). Microwave experiments were performed using a CEM DISCOVER Synthesis unit. Reactions under an inert atmosphere (argon) were performed in oven-dried glassware, 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 over 15 min. The resulting solution was stirred for 1 h at 0 °C and at room temp. for another 16 h and then heated at reflux for 3 h. After cooling to room temp., 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 CH_3CN (30 mL). The resulting mixture was maintained at 0 °C for 30 min and at room temp. for 3 h and then concentrated. The crude residue was purified by recrystallisation from EtOH to give pure **21a**.

Typical Procedure for the Synthesis of Compounds 21b–n: Compounds Cbz-**22b**–**n** (1 g), 5% Pd/C (0.1 g, 10 wt.-%) and MeOH (30 mL) were mixed in a 100 mL, two-necked, round-bottomed flask. After being stirred under hydrogen (1 atm) overnight, the solution was filtered through a pad of celite. After removing the solvent, the resulting residue was purified by recrystallisation (**21b**, **21c**, **21d**, **21e**, **21g**, **21i, 21j**, **21l** and **21m**) or flash chromatography with 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 hydrogen chloride (4 M 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 with anhydrous $MgSO_4$, filtered, and the solvent was evaporated at low pressure to give product **23**, which was pure by ^1H NMR spectroscopy.

(2*S*)-*N*-[(1*S*,2*R*)-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 (KBr): $\tilde{\nu}$ = 3325, 3299 (N–H, O–H), 1687 (C=O), 1044, 1024 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.58–1.67 (m, 2 H, CH_2CH$_2$NH), 1.75–1.85 (m, 1 H, CH_2CHCO), 1.96–2.10 (m, 1 H, CH_2CHCO), 2.57 (s, 2 H, OH, NH), 2.79–2.87 (dt, J = 10.3, 6.3 Hz, 1 H, CH_2N), 2.93–3.01 (dt, J = 10.2, 6.7 Hz, 1 H, CH_2NH), 3.72–3.77 (dd, J = 9.0, 5.3 Hz, 1 H, CHCO), 5.4 (d, J = 4.2 Hz, 1 H, C*H*OH), 5.25–5.29 (dd, J = 8.6, 4.0 Hz, 1 H, PhC*H*NH), 6.98–7.26 (m, 10 H, ArH), 8.43–8.46 (d, J = 8.4 Hz, 1 H, NHCO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1 (*C*H$_2$CH$_2$NH), 30.5 (*C*H$_2$CHCO), 47.2 (CH$_2$NH), 59.1 (N*C*HPh), 60.5 (*C*HCO), 77.5 (O*C*HPh), 126.7, 127.48, 127.54, 127.6, 127.8, 128.1 (ArCH), 137.5, 139.7 (ArC), 175.4 (C=O) ppm. MS: m/z (%) = 292 (4) $[M - H_2O]^+$, 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 $C_{19}H_{22}N_2O_2$ $[M]^+$ 310.1681, $[M - H_2O]^+$ 292.1565; found 292.1546.

(2*S*)-*N*-[(1*R*,2*S*)-2-Hydroxy-1,2-diphenylethyl]pyrrolidine-2-carboxamide (21b): White solid; m.p. 70 °C (EtOAc/MeOH). $[\alpha]_D^{20}$ = –23.8 (c = 0.52, EtOH); R_f(MeOH/EtOAc, 1:1) = 0.43. IR (KBr): $\tilde{\nu}$ = 3325, 3299 (N–H, O–H), 1687 (C=O), 1044, 1024 (C–O) cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 1.79–1.95 (m, 3 H, 2 CH_2CH$_2$NH, 1 CH_2CHCO), 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, C*H*OH), 5.45 (d, J = 6.5 Hz, 1 H, PhC*H*NH), 7.56 (br. s, 10 H, ArH) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 26.9 (*C*H$_2$CH$_2$NH), 31.8 *C*H$_2$CHCO), 47.9 (*C*H$_2$NH), 59.7 (N*C*HPh), 61.5 (N*C*HCO), 77.4 (O*C*HPh), 128.1, 128.3, 128.6, 128.96, 128.99, 129.1, 129.2 (ArCH), 140.6, 142.7 (ArC), 176.6 (C=O) ppm. MS: m/z (%) = 292 (5) $[M - H_2O]^+$, 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 $C_{19}H_{22}N_2O_2$ $[M]^+$ 310.1681; found 310.1661.

(2*S*)-*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 (KBr): $\tilde{\nu}$ = 3306 (N–H, O–H), 1648 (C=O), 1077, 1062 (C–O) cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 1.67–1.84 (m, 2 H, CH_2CH$_2$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 × CH_2OH, 1 × CHCO), 4.97–5.03 (m, 1 H, PhC*H*), 7.25–7.37 (m, 5 H, ArH), 8.30 (d, J = 7.8 Hz, 1 H, NHCO) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 26.0 (*C*H$_2$CH$_2$NH), 30.8 (*C*H$_2$CHCO), 47.1 (CH$_2$NH), 56.1 (CHPh), 60.4 (*C*HCO), 66.8 (CH$_2$OH), 126.6, 127.7, 128.7 (ArCH), 139.0 (ArC), 175.5 (C=O) ppm. MS: m/z (%) = 216 (28) $[M - H_2O]^+$, 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). $C_{13}H_{18}N_2O_2$ (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). $[\alpha]_D^{20}$ = –45.6 (c = 1.0, CH_2Cl_2); R_f(EtOAc) = 0.22. IR (KBr): $\tilde{\nu}$ = 3220, 3357 (N–H, O–H), 1641 (C=O), 1092 (C–O) cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 1.56–1.65 (m, 2 H, CH_2CH$_2$NH), 1.73–1.84 (m, 1 H, CH_2CHCO), 1.97–2.09 (m, 1 H, CH_2CHCO), 2.71–2.79 (m, 1 H, CH_2NH), 2.90–2.98 (m, 1 H, CH_2NH), 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. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 26.0 (*C*H$_2$CH$_2$NH), 30.3

(CH_2CHCO), 46.6 (CH_2NH), 60.8 ($CHCO$), 114.5, 118.6, 119.0, 123.2 (ArCH), 126.3 (NH*C*), 146.0 (COH), 173.0, (C=O) ppm. MS: *m*/*z* (%) = 206 (2) $[M]^+$, 70 (100). HRMS: calcd. for $C_{11}H_{14}N_2O_2$ $[M]^+$ 206.1055; found 206.1064.

(2*S*)-*N*-[(1*S*,2*R*)-2,3-Dihydro-2-hydroxy-1*H*-inden-1-yl]pyrrolidine-2-carboxamide (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 (KBr): $\tilde{\nu}$ = 3336, 3295 (N–H, O–H), 1633 (C=O), 1066, 1090 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.63–1.83 (m, 2 H, CH_2CH_2NH), 1.93–2.03 (m, 1 H, CH_2CHCO), 2.12–2.21 (m, 1 H, CH_2CHCO), 2.54 (br. s, 1 H, OH), 2.81–2.98 (m, 3 H, 1×CH_2CHOH, 2×CH_2NH), 3.14 (dd, *J* = 16.5, 5.1 Hz, 1 H, CH_2CHOH), 3.77 (dd, *J* = 9.0, 5.3 Hz, 1 H, CHCO), 4.61 (dt, *J* = 5.1, 2.3 Hz, 1 H, C*H*OH), 5.31 (dd, *J* = 8.7, 4.9 Hz, 1 H, NC*H*CH), 7.14–7.26 (m, 4 H, ArH), 8.13 (d, *J* = 8.5 Hz, 1 H, N*H*CO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_2CH_2NH), 31.1 (CH_2CHCO), 39.6 (CH_2CHOH), 47.2 (CH_2NH), 57.0 (CH*C*HNH), 60.7 (*C*HCO), 73.6 (*C*HOH), 124.1, 125.3, 127.0, 128.1 (ArCH), 140.2, 140.8 (ArC), 176.2 (C=O) ppm. MS: *m*/*z* (%) = 228 (33) $[M - H_2O]^+$, 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). $C_{14}H_{18}N_2O_2$ (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.

(2*S*)-*N*-[(*R*)-2,3-Dihydro-1*H*-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, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3294 (N–H), 1654 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.85 (m, 3 H, 2×CH_2CH_2NH, 1×CH_2CH_2C), 1.97–2.26 (m, 3 H, 2×CH_2CHCO, 1×CH_2NH), 2.54–2.64 (m, 1 H, CH_2CH_2C), 2.81–3.03 (m, 4 H, 2×CH_2CH_2C, 2×CH_2NH), 3.80 (dd, *J* = 9.2, 5.2 Hz, 1 H, CHCO), 5.46 (dd, *J* = 16.7, 8.3 Hz, 1 H, C*H*NHCO), 7.17–7.26 (m, 4 H, ArH), 7.88 (d, *J* = 8.11 Hz, 1 H, NHCO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_2CH_2NH), 30.2 (CH_2CH_2C), 31.1 (CH_2CHCO), 34.1 (CH_2CH_2C), 47.2 (CH_2NH), 53.8 (*C*HNHCO), 60.5 (*C*HCO), 123.7, 124.7, 126.7, 127.7 (ArCH), 143.2, 143.6 (ArC), 175.2 (C=O) ppm. MS: *m*/*z* (%) = 230 (<1) $[M]^+$, 115 (10), 70 (100). HRMS: calcd. for $C_{14}H_{18}N_2O$ $[M]^+$ 230.1419; found 230.1430.

(2*S*,4*R*)-*N*-[(1*S*,2*R*)-2,3-Dihydro-2-hydroxy-1*H*-inden-1-yl]-4-hydroxypyrrolidine-2-carboxamide (21g): Pale yellow solid; m.p. 142 °C (EtOAc); R_f (EtOAc/MeOH, 2:1) = 0.41. $[\alpha]_D^{20}$ = 15.3 (*c* = 1.0, MeOH). IR (KBr): $\tilde{\nu}$ = 3358, 3323 (N–H, O–H), 1651 (C=O), 1097, 1060, 1039 (C–O) cm^{-1} . ^1H NMR (300 MHz, 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×CH_2NH, 1×$CHCH_2C$), 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 Hz, 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, CHC*H*NH), 7.01–7.13 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 40.7 (CH_2NH), 41.0 ($CHCH_2CH$), 55.9 ($CHCH_2C$), 58.1 (CH*C*HNH), 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 (<1) $[M - H_2O]^+$, 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.

(2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-*N*-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-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 (KBr) $\tilde{\nu}$ = 3408, 3290 (N–H, O–H), 1655 (C=O), 1090, 1053, (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 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, C*H*CO), 4.38 (br. s, 1 H, OH), 4.63–4.67 (m, 1 H, C*H*OH), 5.33 (dd, *J* = 8.6, 5.1 Hz, 1 H, CHC*H*N), 7.14–7.26 (m, 4 H, ArH), 8.20 (d, *J* = 8.4 Hz, 1 H, N*H*CO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH*C*HN), 59.9 (*C*HCO), 73.6 (*C*HOH), 73.9 (*C*HOTBDMS), 124.2, 125.4, 127.1, 128.2 (ArCH), 140.2, 140.7 (ArC), 175.9 (C=O) ppm. MS: *m*/*z* (%) = 358 (8) $[M - H_2O]^+$, 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.

(2*S*)-*N*-[(1*S*,2*R*)-2,3-Dihydro-2-hydroxy-1*H*-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, CH_2Cl_2); R_f (MeOH) = 0.27. IR (KBr): $\tilde{\nu}$ = 3249, 3065 (N–H, O–H), 1628 (C=O), 1100 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, rotamers mixture): δ = 1.72–2.27 (m, 8 H, 4×CH_2CH_2N, 4×CH_2CHCO), 2.62 (s, 3 H, CH_3), 2.73 (s, 3 H, CH_3) 2.80–3.09 (m, 4 H, 2×CH_2CHOH, 2×CH_2N), 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, C*H*OH), 5.30 (d, *J* = 7.0 Hz, 1 H, NC*H*CH) 5.85 (d, *J* = 6.9 Hz, 1 H, NC*H*CH), 7.19–7.35 (m, 8 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 26.6 (CH_2CH_2N), 30.0, 30.1 (CH_2CHCO), 31.3, 32.1 (CH_3), 39.9, 40.1 (CH_2CHOH), 47.1, 47.8 (CH_2N), 58.2, 58.8 (CH*C*HN), 61.5, 63.5 (*C*HCO), 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 (7) $[M - H_2O]^+$, 175 (10), 174 (81), 146 (10), 145 (13), 144 (16), 133 (17), 117 (13), 116 (78), 115 (100), 98 (16). HRMS: calcd. for $C_{15}H_{20}N_2O_2$ $[M]^+$, 260.1525, $[M - H_2O]^+$ 242.1408; found 242.1411.

(2*S*)-*N*-[(1*R*,2*R*)-2,3-Dihydro-2-hydroxy-1*H*-inden-1-yl]pyrrolidine-2-carboxamide (21j): White solid; m.p. 165 °C (EtOAc). $[\alpha]_D^{20}$ = 78.8 (*c* = 1.0, CH_2Cl_2); R_f (MeOH/EtOAc, 1:1) = 0.31. IR (KBr): $\tilde{\nu}$ = 3384, 3292 (N–H, O–H), 1659 (C=O), 1080 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.76 (m, 2 H, CH_2CH_2N), 1.93–2.05 (m, 1 H, CH_2CHCO), 2.13–2.26 (m, 1 H, CH_2CHCO), 2.50–3.50 (br. s, 1 H, OH), 2.82–3.06 (m, 3 H, 1×CH_2CHOH, 2×CH_2N), 3.29 (dd, *J* = 15.8, 7.6 Hz, 1 H, CH_2CHOH), 3.85 (dd, *J* = 8.9, 5.2 Hz, 1 H, CHCO), 4.36 (dd, *J* = 15.1, 7.6 Hz, 1 H, C*H*OH), 5.03 (t, *J* = 5.5 Hz, 1 H, NC*H*CH), 7.22–7.28 (m, 4 H, ArH), 8.29 (br. s, 1 H, N*H*CO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_2CH_2N), 30.9 (CH_2CHN), 38.4 (CH_2CHOH), 47.3 (CH_2N), 60.3 (CH*C*HN), 63.4 (*C*HCO), 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 (<1) $[M]^+$, 70 (100). HRMS: calcd. for $C_{14}H_{18}N_2O_2$ $[M]^+$ 246.1368; found 246.1359.

(2*S*)-*N*-[(*S*)-2,3-Dihydro-1*H*-inden-1-yl]pyrrolidine-2-carboxamide (21k): Yellow oil. $[\alpha]_D^{20}$ = –76.4 (*c* = 1.0, CH_2Cl_2); R_f (EtOAc/MeOH, 2:1) = 0.3. IR (neat): $\tilde{\nu}$ = 3294 (N–H), 1656 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.65–1.82 (m, 3 H, 2×CH_2CH_2N, 1×CH_2CH_2C), 1.88–1.99 (m, 1 H, CH_2CHCO), 2.10–2.23 (m, 2 H, 1×CH_2NH, 1×CH_2CHCO), 2.53–2.64 (m, 1 H, CH_2CH_2C), 2.80–3.03 (m, 4 H, 2×CCH_2CH_2, 2×CH_2N), 3.79 (dd, *J* = 9.0, 5.3 Hz, 1 H, CHCO), 5.42 (dd, *J* = 16.1, 7.9 Hz, 1 H, C*H*NHCO), 7.17–7.27 (m, 4 H, ArH), 7.87 (d, *J* = 7.2 Hz, 1 H, NHCO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1 ($CH_2CH_2CH_2$), 30.2 (CH_2CH_2C), 30.8 (CH_2CHCO), 34.2 (CH_2CH_2C), 47.2 (NCH_2), 53.9 (CONH*C*H), 60.5 (*C*HCO), 124.0,

124.7, 126.6, 127.7 (ArCH), 143.3, 143.7 (ArC), 175.2 (C=O) ppm. MS: *m*/*z* (%) = 230 (<1) $[M]^+$, 115 (10), 70 (100). HRMS: calcd. for $C_{14}H_{18}N_2O$ $[M]^+$ 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 (21l): White solid; m.p. 145 °C (EtOAc/MeOH). $[\alpha]_D^{20}$ = –6.9 (*c* = 1.0, CH_2Cl_2); R_f (MeOH/EtOAc, 1:1) = 0.27. IR (KBr): $\tilde{\nu}$ = 3302, 3190 (N–H, O–H), 1645 (C=O), 1055 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.82 (m, 2 H, CH_2CH$_2$N), 1.89–2.03 (m, 1 H, CH_2CHN), 2.08–2.20 (m, 1 H, CH_2CHN), 2.85 (br. s, 1 H, OH), 2.88–2.96 (m, 3 H, 1 × CH_2CHOH, 2 × CH$_2$CH_2N), 3.13 (dd, *J* = 16.4, 5.1 Hz, 1 H, CH_2CHOH), 3.76 (dd, *J* = 8.7, 5.6 Hz, 1 H, CHCO), 4.59 (dt, *J* = 5.4, 2.9 Hz, 1 H, C*H*OH), 5.27 (dd, *J* = 8.3, 5.2 Hz, 1 H, NC*H*CH), 7.22–7.27 (m, 4 H, ArH), 7.93 (d, *J* = 8.1 Hz, 1 H, N*H*CO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (*C*H$_2$CH$_2$N), 31.1 (*C*H$_2$CHN), 39.6 (CH*C*H$_2$C), 47.2 (CH$_2$*C*H$_2$N), 57.3 (CH*C*HN), 60.8 (*C*HCO$_2$), 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 (28) $[M - H_2O]^+$, 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 $C_{14}H_{18}N_2O_2$ $[M]^+$ 246.1368, $[M - H_2O]^+$ 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 (21m): White solid; m.p. 149–150 °C (EtOAc/MeOH). $[\alpha]_D^{20}$ = –78.4 (*c* = 1.0, CH_2Cl_2); R_f (MeOH–EtOAc, 1:1) = 0.28. IR (KBr): $\tilde{\nu}$ = 3268, 3073 (N–H, O–H), 1652 (C=O), 1085, 1064 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.71–1.89 (m, 2 H, CH_2CH$_2$N), 1.95–2.04 (m, 1 H, CH_2CHN), 2.15–2.28 (m, 1 H, CH_2CHN), 1.71–2.04 (br. s, 1 H, OH), 2.90–3.11 (m, 3 H, 1 × CCH_2CH, 2 × CH$_2$CH_2N), 3.29 (dd, *J* = 15.7, 7.7 Hz, 1 H, CCH_2CH), 3.84 (dd, *J* = 9.0, 5.3 Hz, 1 H, CHCO), 4.39 (dd, *J* = 15.2, 7.9 Hz, 1 H, C*H*OH), 5.05 (t, *J* = 5.5 Hz, 1 H, NC*H*CH), 7.15–7.27 (m, 4 H, ArH), 8.25 (br. s, 1 H, NHCO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3 (*C*H$_2$CH$_2$N), 30.6 (*C*H$_2$CHN), 38.3 (CH*C*H$_2$C), 47.2 (CH$_2$*C*H$_2$N), 60.3 (CH*C*HN), 63.0 (*C*HCO), 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 (<1) $[M]^+$, 70 (100). HRMS: calcd. for $C_{14}H_{18}N_2O_2$ $[M]^+$ 246.1368; found 246.1372.

(2*S*)-*N*-(3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolidine-2-carboxamide (21n): White solid; m.p. 156 °C (EtOAc). $[\alpha]_D^{20}$ = 101.5 (*c* = 0.3 CH_2Cl_2); R_f (MeOH/EtOAc, 1:1) = 0.32. IR (KBr): $\tilde{\nu}$ = 3410, 3312 (N–H, O–H), 1630 (C=O), 1122, 1099 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (s, 3 H, CH$_3$CCH_3), 0.92 (s, 3 H, CH_3CCH$_3$), 1.10 (s, 3 H, CH$_2$CCH_3), 1.04–1.2 (m, 2 H, 1 × CCH$_2$CH_2, 1 × CCH_2CH$_2$), 1.45–1.53 (m, 1 H, CCH$_2$CH_2), 1.63–1.80 (m, 3 H, 1 × CCH_2CH$_2$, 2 × CH$_2$CH_2CH$_2$), 1.87–2.05 (m, 1 H, NCHCH_2), 2.07–2.21 (m, 4 H, 2 × NCHCH_2, 1 × OH, 1 × N*H*CHCH), 2.87–3.04 (m, 2 H, CH_2NH), 3.67–3.73 (m, 2 H, 1 × NC*H*CH$_2$, 1 × NC*H*CH), 3.85 (d, *J* = 8.1 Hz, 1 H, C*H*OH), 7.98 (br. s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 20.8, 21.3 (CH$_3$), 26.2, 26.3 (C*C*H$_2$CH$_2$, CH$_2$*C*H$_2$CH$_2$), 31.1 (NCH*C*H$_2$), 33.4 (CCH$_2$*C*H$_2$), 47.1 (CH$_3$*C*CH$_3$), 47.3 (CH$_2$N), 49.1 (CH$_2$*C*CH$_3$), 50.1 (*C*HCH$_3$), 57.9, 60.5 (NHCH), 80.6 (CHOH), 175.5 (C=O) ppm. MS: *m*/*z* (%) = 266 (<1) $[M]^+$, 70 (100). HRMS: calcd. for $C_{15}H_{26}N_2O_2$ $[M]^+$ 266.1994, $[M - H_2O]^+$ 248.1878; found 248.1848.

(2*R*)-*N*-[(1*R*,2*S*)-2,3-Dihydro-2-hydroxy-1*H*-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 (KBr): $\tilde{\nu}$ = 3336, 3295 (N–H, O–H), 1633 (C=O), 1066, 1090 (C–O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.69–1.86 (m, 2 H, CH_2CH$_2$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 × CH_2CHOH, 2 × CH$_2$CH_2N), 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, C*H*OH), 5.34 (dd, *J* = 8.7, 5.1 Hz, 1 H, NC*H*CH), 7.17–7.27 (m, 4 H, ArH), 8.15 (d, *J* = 7.8 Hz, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (*C*H$_2$CH$_2$N), 31.1 (*C*H$_2$CHN), 39.6 (*C*H$_2$CHOH), 47.2 (CH$_2$*C*H$_2$N), 57.0 (N*C*HCH), 60.7 (*C*HCO), 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 (34) $[M - H_2O]^+$, 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 $C_{14}H_{18}N_2O_2$ $[M]^+$ 246.1368; found 246.1361.

(2*S*)-2-Amino-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-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 (KBr): $\tilde{\nu}$ = 3295 (N–H, O–H), 1641 (C=O), 1054, 1086 (C–O) cm^{-1}. ^1H NMR (400 Mz, $CDCl_3$): δ = 1.37 (d, *J* = 6.8 Hz, 3 H, CH$_3$), 2.21 (br. s, 3 H, 2 × NH$_2$, 1 × 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, C*H*CH$_3$), 4.58 (dt, *J* = 5.2, 2.5 Hz, 1 H, C*H*OH), 5.29 (dd, *J* = 8.5, 5.2 Hz, 1 H, C*H*NH), 7.21–7.27 (m, 4 H, ArH), 7.75 (d, *J* = 8.1 Hz, 1 H, NHCO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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 (24) $[M - H_2O]^+$, 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), *p*-nitrobenzoic acid (0.08 mmol) and the corresponding ketone (4 mmol) in NMP (0.2 mL) was stirred for 20 min at 25 °C. The corresponding nitrostyrene (0.4 mmol) was then added to the mixture, and the reaction was stirred at 25 °C for the reaction time stated in Tables (Table 1–Table 4). 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 with anhydrous $MgSO_4$ and filtered, 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 described previously, and spectroscopic data were in agreement with those published. See the 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 (neat): $\tilde{\nu}$ = 1552 (NO_2), 1704 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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$_3$Ar), 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, C*H*CH$_3$), 3.65 (dt, *J* = 9.3, 5.0 Hz, 1 H, CHAr), 4.57 (dd, *J* = 12.4, 4.8 Hz, 1 H, CH$_2$NO$_2$), 4.64 (dd, *J* = 12.4, 9.1 Hz, 1 H, CH$_2$NO$_2$), 7.04 (d, *J* = 8.1 Hz, 2 H, ArH), 7.12 (dd, *J* = 7.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6 (*C*H$_3$CH$_2$), 16.2 (*C*H$_3$CH), 21 (CH$_3$Ar), 35.4 (*C*H$_2$CO), 45.7 (CHAr), 48.3 (*C*HCO), 78.4 (CH$_2$NO$_2$), 127.7, 129.6 (ArCH), 134.4, 137.6 (ArC), 213.7 (C=O) ppm. MS: *m*/*z* (%) = 249 (<1) $[M]^+$, 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 $C_{14}H_{19}NO_3$ $[M]^+$ 249.1365; found

249.1356; HPLC: (Chiralcel OD-H, 1 mL/min, hexane/*i*PrOH: 99:1, 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 (neat): $\tilde{\nu}$ = 1553 (NO_2), 1711 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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, C*H*CH$_3$), 3.69 (dt, *J* = 9.3, 4.9 Hz, 1 H, CHAr), 4.58 (dd, *J* = 12.4, 4.8 Hz, 1 H, CH_2NO_2), 4.64 (dd, *J* = 12.4, 9.0 Hz, 1 H, CH_2NO_2), 7.11 (d, *J* = 8.3 Hz, 2 H, ArH), 7.31 (dd, *J* = 6.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6 (*C*H$_3$CH$_2$), 16.2 (*C*H$_3$CH), 35.4 (*C*H$_2$CO), 45.4 (CHAr), 48.1 (*C*HCO), 78.0 (CH_2NO_2), 129.2, 129.3 (ArCH), 133.8, 136.0 (ArC), 213.1 (C=O) ppm. MS: *m*/*z* (%) = 269 (<1) $[M - CH_3CH_2]^+$, 193 (19), 138 (18), 115 (10), 57 (100). HRMS: calcd. for $C_{13}H_{16}ClNO_3$ $[M]^+$ 269.0819, $[M - NO_2]^+$ 223.0884; found 223.0874; HPLC: (Chiralcel OD-H, 1 mL/min, hexane/*i*PrOH: 99:1, 254 nm) t_{Rmaj} = 22.6 min, t_{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, CH_2Cl_2) for 73% *ee*; R_f (hexane/EtOAc, 5:1) = 0.29. IR (KBr): $\tilde{\nu}$ = 1245 (Ar–O–C), 1552 (NO_2), 1705 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 7.2 Hz, 3 H, CH_3CH), 1.48 (t, *J* = 7.3 Hz, 3 H, CH_3CH$_2$), 2.83 (dq, *J* = 18.0, 7.2 Hz, 1 H, CH_2CH$_3$), 3.03 (dq, *J* = 18.1, 7.2 Hz, 1 H, CH_2CH$_3$), 3.37 (dq, *J* = 9.5, 7.2 Hz, 1 H, C*H*CH$_3$), 4.06 (dt, *J* = 9.0, 5.1 Hz, 1 H, CHAr), 4.2 (s, 3 H, OCH_3) 4.95–5.08 (m, 2 H, CH_2NO_2), 7.27 (d, *J* = 8.6 Hz, 2 H, ArH), 7.49 (d, *J* = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.6 (*C*H$_3$CH$_2$), 16.2 (*C*H$_3$CH), 35.4 (*C*H$_2$CO), 45.3 (CHAr), 48.5 (*C*HCO) 55.2 (OCH_3), 78.5 (CH_2NO_2), 114.3, 128.9 (ArCH), 129.4, 159.1 (ArC), 213.7 (C=O) ppm. MS: *m*/*z* (%) = 265 (4) $[M]^+$, 218 (26), 203 (17), 189 (52), 162 (11), 161 (10), 135 (13), 134 (100), 121 (10), 119 (11), 91 (14), 57 (77). $C_{14}H_{19}NO_4$ (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, 1 mL/min, hexane/*i*PrOH 99:1, 254 nm) t_{Rmaj} = 21.4 min, t_{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, CH_2Cl_2) for 72% *ee*; R_f (hexane/EtOAc, 5:1) = 0.31. IR (neat): $\tilde{\nu}$ = 1556 (NO_2), 1712 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.2 Hz, 3 H, CH_3CH), 1.06 (t, *J* = 7.2 Hz, 3 H, CH_3CH$_2$), 2.39 (dq, *J* = 18.1, 7.2 Hz, 1 H, CH_2CH$_3$), 2.64 (dq, *J* = 18.1, 7.2 Hz, 1 H, CH_2CH$_3$), 3.10–3.20 (m, 1 H, C*H*CH$_3$), 4.24 (dt, *J* = 9.0, 4.2 Hz, 1 H, CHAr), 4.61 (dd, *J* = 12.8, 4.2 Hz, 1 H, CH_2NO_2), 4.82 (dd, *J* = 12.8, 8.7 Hz, 1 H, CH_2NO_2), 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. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.6 (*C*H$_3$CH$_2$), 16.1 (*C*H$_3$CH), 35.5 (*C*H$_2$CO), 41.7 (CHAr), 46.8 (*C*HCO), 76.4 (CH_2NO_2), 127.7, 129.4, 130.2 (ArCH), 133.8, 134.2, 135.2 (ArC), 213.0 (C=O) ppm. MS: *m*/*z* (%) = 303 (<1) $[M]^+$, 261 (14), 199 (11), 186 (11), 172 (11), 57 (100). HRMS: calcd. for $C_{13}H_{15}Cl_2NO_3$ $[M]^+$ 303.0429; found 303.0421; HPLC: (Chiralcel OD-H, 1 mL/min, hexane/*i*PrOH 99:1, 254 nm) t_{Rmaj} = 13.9 min, t_{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, CH_2Cl_2) for 50% *ee*; R_f (hexane/EtOAc, 5:1) = 0.25. IR (neat): $\tilde{\nu}$ = 1556 (NO_2), 1713 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 7.2 Hz, 3 H, CH_3CH), 1.09 (t, *J* = 7.3 Hz, 3 H, CH_3CH$_2$), 2.48 (dq, *J* = 18.1, 7.3 Hz, 1 H, CH_2CH$_3$), 2.67 (dq, *J* = 18.1, 7.2 Hz, 1 H, CH_2CH$_3$), 3.21–3.31 (m, 1 H, C*H*CH$_3$), 4.06–4.15 (m, 1 H, CHAr), 4.58 (dd, *J* = 11.8, 4.0 Hz, 1 H, CH_2NO_2), 4.82 (dd, *J* = 11.8, 6.7 Hz, 1 H, CH_2NO_2), 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. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.5 (*C*H$_3$CH$_2$), 16.4 (*C*H$_3$CH), 35.4 (*C*H$_2$CO), 40.8 (CHAr), 47.7 (*C*HCO), 77.9 (CH_2NO_2), 122.3 (CF_3), 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 (<3) $[M - CH_3CH_2]^+$, 199 (42), 186 (17), 178 (11), 159 (13), 151 (10), 57 (100). HRMS: calcd. for $C_{14}H_{16}F_3NO_3$ $[M]^+$ 303.1082, $[M - CH_3CH_2]^+$ 274.0686; found 274.0710; HPLC: (Chiralcel OD-H, 1 mL/min, hexane/*i*PrOH 99:1, 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, CH_2Cl_2) for 78% *ee*; R_f (hexane/EtOAc, 5:1) = 0.4; IR (neat): $\tilde{\nu}$ = 1557 (NO_2), 1713 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.2 Hz, 3 H, CH_3CH), 1.06 (t, *J* = 7.2 Hz, 3 H, CH_3CH$_2$), 2.38 (dq, *J* = 17.9, 7.2 Hz, 1 H, CH_2CH$_3$), 2.62 (dq, *J* = 17.9, 7.2 Hz, 1 H, CH_2CH$_3$), 3.16–3.24 (m, 1 H, C*H*CH$_3$), 4.30 (dt, *J* = 9.2, 4.4 Hz, 1 H, CHAr), 4.63 (dd, *J* = 12.7, 4.4 Hz, 1 H, CH_2NO_2), 4.85 (dd, *J* = 12.7, 8.8 Hz, 1 H, CH_2NO_2), 7.15–7.27 (m, 3 H, ArH), 7.41 (d, *J* = 9.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6 (*C*H$_3$CH$_2$), 16.1 (*C*H$_3$CH), 35.5 (*C*H$_2$CO), 42.1 (ArCH), 46.9 (*C*HCO), 76.6 (CH_2NO_2), 127.3, 128.9, 128.5, 130.4 (ArCH), 134.5, 135.1 (ArC), 213.3 (C=O) ppm. MS: *m*/*z* (%) = 234 (54) $[M - Cl]^+$, 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 $C_{13}H_{16}ClNO_3$ $[M]^+$ 269.0819, $[M - Cl]^+$ 234.1125; found 234.1151; HPLC: (Chiralcel OD-H, 1 mL/min, hexane/*i*PrOH 99:1, 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 (hexane/EtOAc, 6:1) = 0.49. IR (neat): $\tilde{\nu}$ = 1558 (NO_2), 1714 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.3 Hz, 3 H, CH_3CH$_2$), 1.18 (d, *J* = 7.0 Hz, 3 H, CH_3CH), 2.30–2.46 (m, 3 H, 2 × CH_2Ph, 1 × C*H*CH$_3$), 2.50–2.68 (m, 2 H, CH_2CH$_3$), 5.45 (t, *J* = 7.64 Hz, 1 H, $CHNO_2$), 7.36–7.47 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.7 (*C*H$_3$CH$_2$), 17.8 (*C*H$_3$CH), 34.8 (CH_2), 36.5 (CH_2), 42.6 (*C*HCO), 89.8 (CH_2NO_2), 127.6, 129.0, 129.9 (ArCH), 134.3 (ArC), 213.4 (C=O) ppm. MS: *m*/*z* (%) = 207 (<1) $[M - H_2O]^+$, 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 also the 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 the 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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