

(S)-Binam-L-prolinamide as organocatalyst for the enantioselective conjugate addition of α -alkoxyketones to β -nitrostyrene derivatives

Gabriela Guillena,* Carmen Nájera, Santiago F. Vióquez and Miguel Yus

Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO),

Universidad de Alicante, Apartado 99, 03080 Alicante, Spain

E-mail: gabriela.guillena@ua.es, cnajera@ua.es

Dedicated to Professor Julio Alvarez-Builla on occasion of his 65th birthday

Abstract

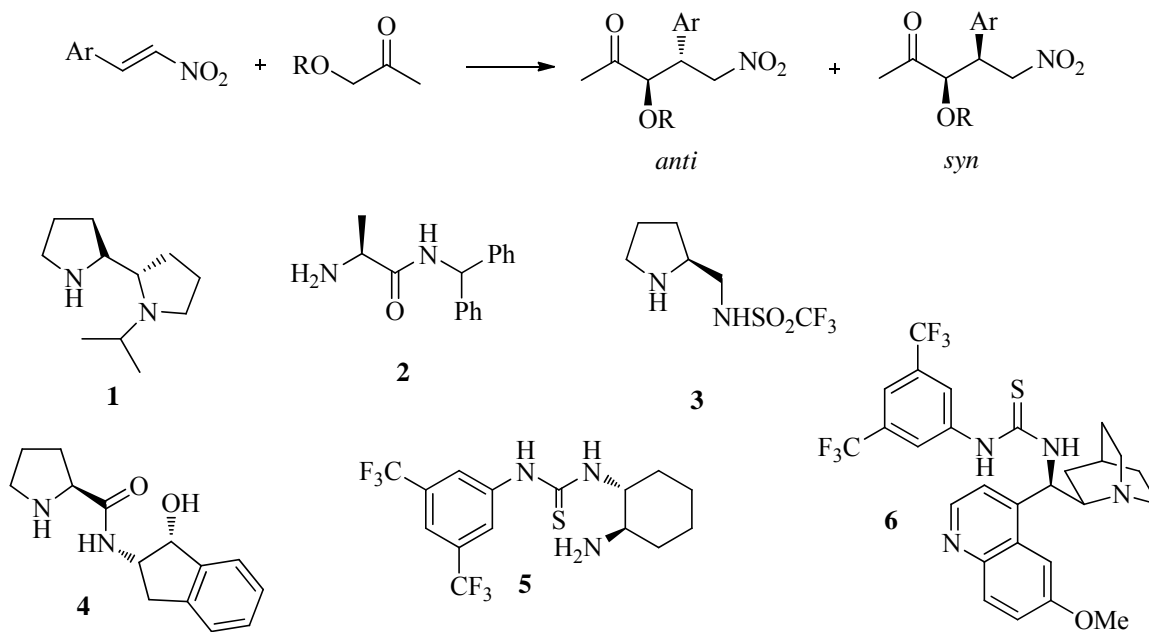
(S)-Binam-L-prolinamide (20 mol%) catalyze the enantioselective Michael addition of several α -alkoxyketones to different β -nitrostyrene derivatives. In the study of the optimization of the reaction conditions it was found surprisingly that hexane is the solvent of choice to carry out such transformation. Under these reaction conditions, the corresponding highly functionalized products were obtained in good yields (up to 90%), mainly as *syn*-diastereomers with moderate diastereo- and enantioselectivities.

Keywords: Asymmetric synthesis, conjugate addition, nitroolefins, organocatalysis, prolinamides

Introduction

Asymmetric conjugate additions of nucleophiles to electron-poor alkenes, also known as Michael-type reactions, are one of the most important and attractive C-C bond formation reactions, which allows the synthesis of useful products in a stereocontrolled manner.¹ Several strategies could be applied to achieve this task, with the use of catalytic methods being the most attractive alternative to produce these compounds with high selectivity and efficiency.² Numerous advances in the use of chiral transition metal catalysts have been achieved for this purpose in the last century.³ On the other hand, the use of metal-free processes, so-called organocatalysis,⁴ has emerged in the last decade as a powerful environmentally benign strategy to perform this reaction,⁵ as well as other C-C or C-heteroatom⁶ bond formation reactions. This procedure has several advantages related to handling, cost and safety issues due to the stability and availability of the catalysts, less demanding reaction conditions required compared to the use of transition metal catalysts and reduced toxicity of the final products, proving a highly efficient chemical process for the synthesis of complex

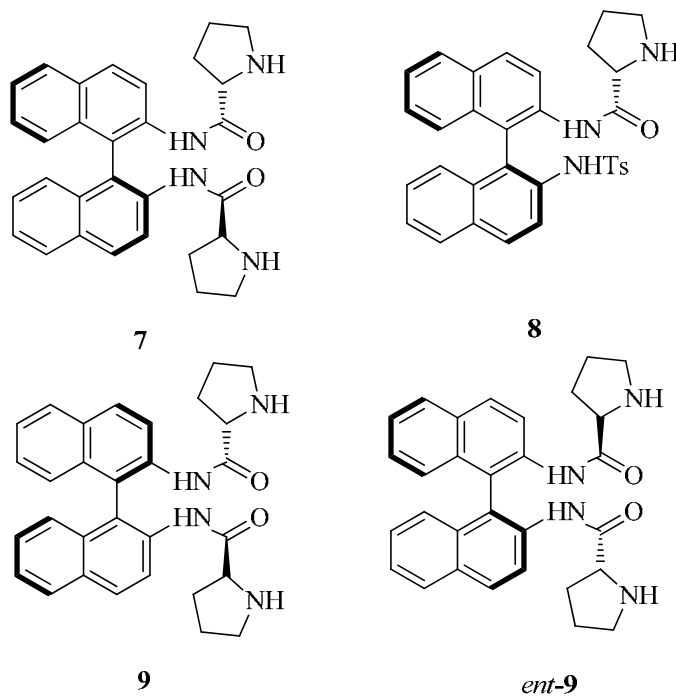
molecules.⁷ In this context, the asymmetric 1,4-addition of ketones and aldehydes to nitrostyrenes led to the formation of interesting chiral γ -nitrocarbonyl compounds bearing at least two stereogenic centers. These chiral compounds are valuable building blocks in organic synthesis, since the nitro functionality can easily be transformed into a carboxylic acid, ketone, nitrile oxide, or amine, etc.⁸ However, the use of α -alkoxyketones as nucleophiles, which in the aldol⁹ and Mannich¹⁰ organocatalyzed reactions has led to high regioselectivities and stereoselectivities, gave diverse results when they were used as donors in the Michael addition to nitrostyrenes. Thus, while the use of the bypyrrolidine **1** (15 mol%, Scheme 1) as catalyst in the reaction between α -hydroxyacetone to aromatic nitroolefins in chloroform gave mainly the *anti*-isomer in excellent enantioselectivities after 7 d at room temperature (56-82% de, 96-98% ee), the use of α -methoxyacetone (R = Me) under similar reaction conditions provided the *syn*-isomer as the main product (66% de) with moderate enantioselectivity (69% ee).¹¹ When the reaction was carried out in *N*-methylpyrrolidinone (NMP) as solvent in the presence of 10 equiv of water and *p*-methylphenylsulphonic acid (15% mol) using the primary amine **2** (30 mol%) as catalyst in the reaction between α -hydroxyacetone and β -nitrostyrene, the *anti*-isomer (33% de) was achieved as the main product with low enantioselectivity (29% ee).¹² The use of catalyst **3** (20 mol% in isopropanol at 0 °C)¹³ and prolinamide **4** (20 mol% in the presence of 20 mol% of *p*-nitrobenzoic acid in CH₂Cl₂ at rt),¹⁴ led mainly to the formation of the *syn*-isomer (de up to 50%) in moderate enantioselectivity (ee up to 46% ee). However, improved results were obtained when sulphonamide **3** as catalyst and *tert*-butyldimethylsilyl protected α -hydroxyacetone (R = TBDMS in Scheme 1)



Scheme 1. Michael reaction between α -alkoxyacetones and β -nitrostyrenes.

were used in this transformation (90% de and 86% ee). Also, the use of thiourea derivatives as catalysts in the reaction between α -methoxyacetone and β -nitrostyrene provided different results. Thus, while compound **5** (20 mol%) in the presence of 4-(dimethylamino)pyridine (DMAP, 20 mol%) in chloroform at room temperature gave the *anti*-isomer in low diastereoselectivity (33% de) and moderate enantioselectivity (41% ee),¹⁵ the use of the quinidine thiourea **6** in combination with proline (5 mol% of each) in benzene at rt led mainly to the formation of the *syn*-isomer in moderate diastereoselectivity (64% de) and high enantioselectivity (90% ee).¹⁶

As in the direct aldol reaction catalyzed by Binam-prolinamides such as **7**¹⁷ and **8**¹⁸ between aldehydes and alkoxyacetones provided the expected products with high regio-, diastereo- and enantioselectivity using different reaction media,^{17d,e,i} including solvent-free reaction conditions,^{17j,k} we thought that the application of these catalyst to the Michael addition of α -alkoxyketones as nucleophiles to β -nitrostyrene derivatives would be of interest.



Results and Discussion

Catalysts (*S_a*)-Binam-L-Pro **7** and *N*-tosyl-*(S_a)*-Binam-L-Pro **8** were synthesized as previously described^{17a,18b} starting from 2,2'-diamino-1,1'-binaphthalene (Binam) and L-proline. Also the diastereomeric catalysts **9** and *ent-9* were prepared following similar procedures. The optimization of the reaction conditions were performed by the addition of α -methoxyacetone to β -nitrostyrene as reaction model (Table 1), using 20 mol% of catalyst **7** and NMP as solvent. We have previously found for the aldol reaction that a high acceleration was achieved when the reaction was co-catalyzed by a carboxylic acid,^{17,18} therefore 20 mol% of *p*-nitrobenzoic acid was added as

cocatalyst at room temperature, achieving the expected product only after 6 h. nearly in a quantitative yield but with a moderate *syn*-diastereoselectivity (38% de) and with low enantioselectivity (Table 1, entry 1).

Table 1. Optimization of the reaction conditions for the Michael addition of α -methoxyacetone to β -nitrostyrene^a

Reaction scheme: $\text{MeO}-\text{CH}_2-\text{C}(=\text{O})-\text{CH}_3$ (10) + $\text{Ph}-\text{CH}=\text{CH}-\text{NO}_2$ (11) $\xrightarrow[\text{solvent, T (}^\circ\text{C)}]{\text{cat. (20\% mol), acid (\% mol)}}$ syn-12aa + anti-12aa

Entry	Cat. (% mol)	Solvent (μL)	T ($^\circ\text{C}$)	t (h)	Conv. (%) ^b	dr (<i>anti/syn</i>) ^c	ee (%) ^d
1	7	NMP (100)	25	6	98	31:69	26
2	7	NMP (100)	0	6	80	32:68	30
3 ^e	7	NMP (100)	0	6	92	25:75	32
4 ^e	7	NMP (100)	-40	24	34	-	-
5 ^e	8	NMP (100)	0	6	66	35:65	26
6 ^e	9	NMP (100)	0	6	88	34:66	25
7 ^e	<i>ent-9</i>	NMP (100)	0	6	75	33:67	-20
8 ^f	7	NMP (100)	0	6	90	23:77	30
9 ^g	7	NMP (100)	0	6	83	29:71	27
10 ^h	7	NMP (100)	0	6	90	30:70	32
11 ^h	7	<i>i</i> -PrOH (100)	-40	19	90	28:72	39
12 ^h	7	THF (100)	-40	24	76	32:68	56
13 ^h	7	Hexane (100)	-40	24	90	19:81	60
14 ^h	7	Toluene (100)	-40	24	83	27:73	55
15 ^h	7	-	-40	19	85	21:79	52

^aThe reactions were carried out using β -nitrostyrene (0.25 mmol), α -methoxyacetone (1.25 mmol), catalyst (20% mol) and acid (20% mol).

^bConversion based on the unreacted β -nitrostyrene determined by ^1H NMR of the crude mixture.

^cDetermined by ^1H NMR of the crude mixture.

^dDetermined by HPLC for the *syn*-isomer.

^e10 mol% of acid was used.

^fBenzoic acid (10 mol%) was used.

^gAcetic acid (10 mol%) was used.

^hThe reaction was carried out in the absence of acid.

In order to increase the enantioselectivity of the process, the temperature was decreased to 0 °C, which led only to a slightly increase of the enantioselectivity of the product (Table 1, entry 2). The use of an excessive amount of acid could have a detrimental effect on the results, thus this amount was reduced to 10 mol%, and a small improvement of the diastereo- and enantioselectivity was observed under these new reaction conditions (Table 1, entry 3). A further decrease of the reaction temperature to -40 °C was attempted, but unfortunately under these reaction conditions, a low conversion was observed (Table 1, entry 4). Next, the influence of the structure of the catalyst was evaluated by performing the reaction under similar conditions but using compound **8** (20 mol%), leading to poorer results in terms of conversion, diastereo- and enantioselectivity (Table 1, entry 5). Then, the effect of the axial stereoelement in the stereochemical outcome of the reaction was studied. Thus, when the diastomeric catalyst (*R_a*)-Binam-L-Pro **9** was used, the product *syn*-**12aa** was obtained with high conversion (88%), although with lower diastereo- and enantioselectivity (Table 1, entry 6), showing that catalyst **7** was the matched diastereomer to perform this transformation. The use of the corresponding enantiomeric catalyst *ent*-**9** (20 mol%) under similar reaction conditions led, as expected, to the product *syn*-**12aa** but with opposite configuration (Table 1, entry 7). Once the best catalyst **7** was found, the effect of the addition of a carboxylic acid as cocatalyst was evaluated. Thus, when weak acids, such as benzoic or acetic acid were used (10 mol%) the achieved results were not improved (Table 1, entries 8 and 9). Furthermore, when the reaction was performed in the absence of acid, similar results to those achieved in the presence of 10 mol% of *p*-nitrobenzoic acid were obtained (Table 1, compare entries 3 and 10), showing that for this transformation the use of an acid as cocatalysts was not necessary. Under these new reaction conditions (20 mol% of catalyst **7**), the use of a different solvent to perform the reaction was tested. Thus, the reaction in isopropanol at -40 °C gave after 19 h the expected product *syn*-**12aa** (44% de) with a small increase of the achieved enantioselectivity (Table 1, entry 11). The use of a less polar solvent such THF, hexane or toluene (Table 1, entries 12-14) led to a further improvement of the enantioselectivity, with the best results (62% de, 60% ee) being obtained using hexane as reaction medium (Table 1, entry 13). This transformation could be also performed under solvent-free conditions at -40 °C, although a slightly lower conversion (85%), diastereo- (58% de) and enantioselectivity (52% ee) were achieved under these reaction conditions (Table 1, entry 15).

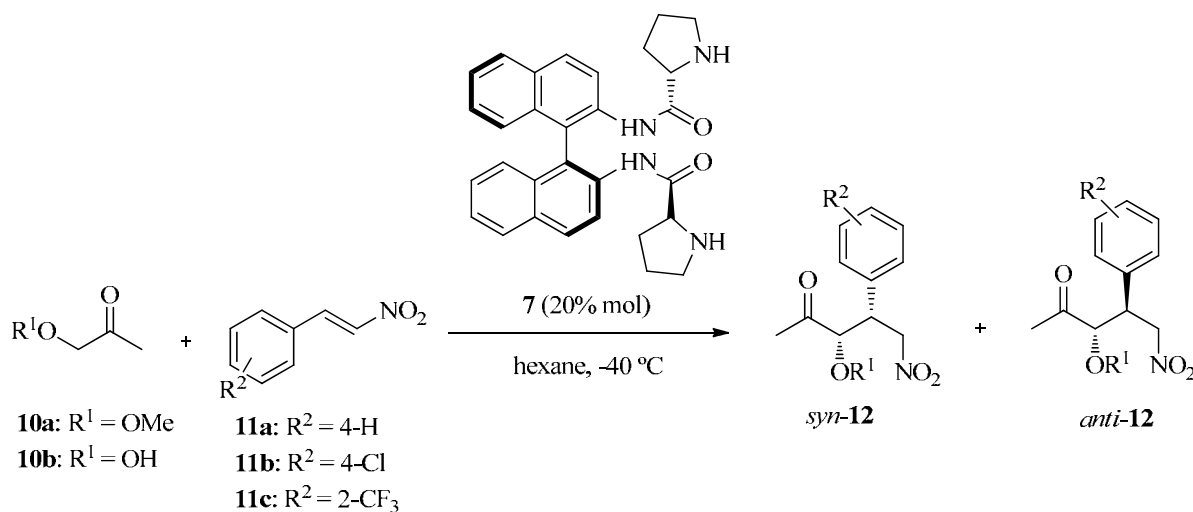
Under the optimal reaction conditions, 20 mol% of catalyst **7** in hexane at -40 °C (Table 1, entry 13), the reaction were performed using α -methoxyacetone and α -hydroxyacetone as nucleophiles and several β -nitrostyrene derivatives as Michael acceptors (Table 2).

The use of α -methoxyacetone as nucleophile in the Michael reaction with several β -nitrostyrene derivatives gave mainly the corresponding *syn*-isomers, with moderate diastereo- and enantioselectivity (Table 2, entries 1-3). Surprisingly, the reaction with β -nitrostyrene derivatives containing electron-withdrawing groups, was slower than the reaction with **11a** (Table 2, entries 2 and 3). Thus, the reaction of 1-chloro-4-(2-nitrovinyl)benzene **11b** with α -methoxyacetone **10a** gave product **12ab** after 48 h in 82% yield, with moderate diastereo- and enantioselectivity (54% de and 40% ee, Table 2, entry 2). Better enantioselectivity (60% ee) was achieved after 48h for the product **12ac** mainly as the *syn*-isomer (24% de, Table 2, entry 3). For all these compound, the

obtained enantioselectivities for the corresponding *anti*-isomers were superior to those achieved for the *syn*-product, being obtained with up to 82% ee for *anti*-**12ac**.

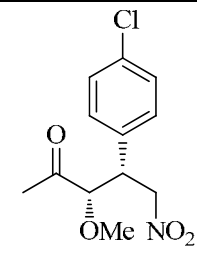
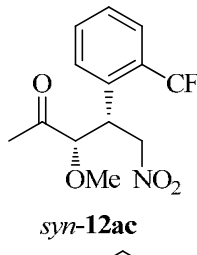
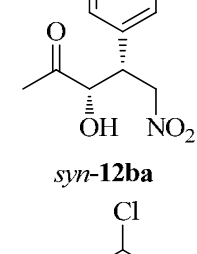
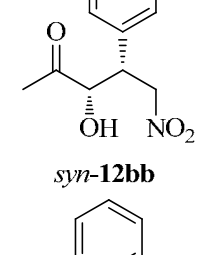
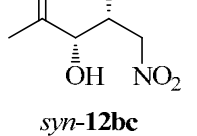
When α -hydroxyacetone **10b** was used as Michael donor in the reaction with different β -nitrostyrene derivatives, the reaction must be performed at 0 °C, because at lower temperatures the process was too slow. Under these reaction conditions, the use of β -nitrostyrene **11a** as electrophile led mainly to the formation of *syn*-**12ba** (54% de) in good yield (87%) albeit with moderate enantioselectivity (54% ee, Table 2, entry 4). The use of compound **11b** as Michael acceptor gave the corresponding α -hydroxy- γ -nitropentane derivative **12bb** in low diastereo- and enantioselectivity (30% de, 36% ee), while the use of β -nitrostyrene derivative **11c** led mainly to *syn*-**12bc** in 50% de and 46% ee (Table 1, entries 5 and 6). As in the previous cases, the achieved enantioselectivities for the corresponding *anti*-isomers were higher compared to the major *syn*-isomer. For these compounds, the separation of both diastereoisomers was possible by column chromatography.

Table 2. Michael addition of α -alkoxyacetones to β -nitrostyrenes^a



Entry	Major Product	t (h)	Yield (%) ^b	dr (<i>anti</i> / <i>syn</i>) ^c	ee _{syn} (%) ^d	ee _{anti} (%) ^d
1	 <i>syn</i> - 12aa	24	90	19:81	60	62

Table 2. Continued

Entry	Major Product	t (h)	Yield (%) ^b	dr (<i>anti/syn</i>) ^c	ee _{syn} (%) ^d	ee _{anti} (%) ^d
2	 <i>syn-12ab</i>	48	82	23:77	40	66
3	 <i>syn-12ac</i>	48	90	38:62	60	82
4 ^e	 <i>syn-12ba</i>	27	87	23:77	54	60
5 ^e	 <i>syn-12bb</i>	21	90	35:65	36	55
6 ^e	 <i>syn-12bc</i>	23	90	25:75	46	82

^aThe reactions were carried out using β -nitrostyrene derivative (0.25 mmol), α -alkoxyketone (1.25 mmol), catalyst **7** (20% mol) in *n*-hexane at -40°C, otherwise stated.

^bYield after purification by column chromatography.

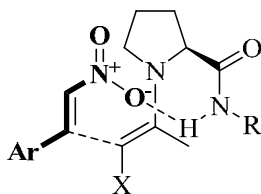
^cDetermined by ¹H NMR of the crude mixture.

^dDetermined by HPLC.

^eThe reaction was carried out at 0 °C

Finally, other alkyl ketones such as cyclohexanone, acetone, butanone or 3-pentanone were used as nucleophiles in the Michael addition to β -nitrostyrene. Although, the corresponding addition products were formed in good yields, for all tested reaction conditions in the case of cyclohexanone and acetone, only racemic mixtures were obtained. For butanone and 3-pentanone, the best results were obtained in NMP as solvent in the presence of 20 mol% of catalyst **4** and 20 mol% of *p*-nitrobenzoic acid at room temperature achieving the expected *syn*-products in high diastereoselectivity (80% de) but in only 28% and 49% ee, respectively.

The previously reported X-ray structure for catalyst **7**^{17k} gave a dihedral angle between the both naphthyl groups in the catalyst of 81.51°. Furthermore, the results of the ESI-MS mechanistic studies for the aldol reaction^{17k} showed that both proline residues present in the catalyst were involved in the formation of the enamine intermediate but only one of the enamine reacted with the electrophile. Based on these previous observations and the present experimental results, a model for the transition state, involving the enamine intermediate with only one intramolecular hydrogen bond of the hydrogen of the amide group with the nitro group of the electrophile could be proposed.



As conclusion, the catalyst **7** (20 mol%) was able to promote the enantioselective Michael addition of several α -alkoxyketones to different β -nitrostyrene derivatives. The reaction was carried out in *n*-hexane as solvent at -40 °C or 0 °C depending on the nucleophilic α -alkoxyketones used. Good yields (87-90%) were obtained for the corresponding α -hydroxy- γ -nitropentane derivatives. Under these reaction conditions, moderate diastereoselectivities were achieved (up to 62% de), although in most cases it was possible to isolate both diastereoisomers. While the enantioselectivities obtained for the minor *anti*-isomers were high (up to 82% ee), those reached for the major *syn*-isomers were only moderate (up to 60% ee).

Experimental Section

General. All reactions for the catalyst preparation were carried out under argon. NMP, THF, *i*-PrOH, CH₂Cl₂, *n*-hexane and toluene and all others reagents were commercially available and used without further purification. Catalysts **7**,^{17a} **8**^{18b}, **9**^{17a} and *ent*-**9**^{17a} were prepared according to the previously reported procedures. Only the structural most important peaks of the IR spectra (recorded on a Nicolet Impact 400D) are listed. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using CDCl₃ as solvent and TMS as internal standard. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were

performed on a Agilent 1100 series equipped with a chiral column (detailed for each compound below), using mixtures of *n*-hexane/isopropyl alcohol (IPA) as mobile phase, at 25 °C. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualised under UV light ($\lambda=254$ nm). For flash chromatography we employed Merck silica gel 60 (0.063-0.2 mm). HRMS was carried out in the Research Technical Services of the University of Alicante.

General procedure for the Michael reaction

To a mixture of catalyst **7** (0.024 g, 0.05 mmol) and the β -nitrostyrene derivative (0.25 mmol) in *n*-hexane (100 μ L) was added the corresponding α -alkoxyketone (0.5 mmol) at 0 or -40 °C. The resulting mixture was stirred at the corresponding temperature until β -nitrostyrene derivative consumption (TLC monitored). The crude reaction mixture was dissolved in CH₂Cl₂ and purified by column chromatography (hexane/ethyl acetate 9:1) to give the pure addition products. Spectroscopic and physical data for products **12**, as well as literature reference for known products, follow:

(3S,4R)-syn-3-Methoxy-5-nitro-4-phenylpentan-2-one (syn-12aa).^{11a} Colourless oil; R_f = 0.32 (hexane/ethyl acetate 4:1); ¹H NMR (300 MHz, CDCl₃): δ 1.77 (s, 3H, OCCH₃), 3.45 (s, 3H, OCH₃), 3.80-3.93 (m, 2H, CHAr and CHO), 4.66 (dd, *J* = 6.8 Hz, 12.9 Hz, 1H, HCHNO), 4.93 (dd, *J* = 8.4, 12.9 Hz, 1H, HCHNO), 7.20-7.37 (5H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 26.6 (OCCH₃), 46.3 (CHAr), 59.8 (OCH₃), 76.5 (CH₂NO₂), 86.7 (CHOCH₃), 128.3 (ArCH), 128.4 (2xArCH), 128.9 (2xArCH), 134.4 (ArC), 209.9 (C=O).

(3S,4S)-anti-3-Methoxy-5-nitro-4-phenylpentan-2-one (anti-12aa).^{11a} Colourless oil; R_f = 0.35 (hexane/ethyl acetate 4:1) ¹H NMR (300 MHz, CDCl₃): δ 2.03 (s, 3H, OCCH₃), 3.67 (s, 3H, OCH₃), 3.78-3.91 (m, 2H, CHAr and CHO), 4.72 (dd, *J* = 6.8, 13.2 Hz, 1H, HCHNO), 4.84 (dd, *J* = 5.6, 13.4 Hz, 1H, HCHNO), 7.23-7.38, 5H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 26.2 (OCCH₃), 45.9 (CHAr), 58.8 (OCH₃), 76.7 (CH₂NO₂), 88.1 (CHOCH₃), 128.1 (2xArCH), 128.4 (ArCH), 129.1 (2xArCH), 135.5 (ArC), 208.1 (C=O).

HPLC (Chiralpak AD; 1.0 mL/min; 96:4 hex/IPA, 210 nm); t_{Rmajor} (*anti-12aa*) = 35.4, t_{Rminor} (*anti-12aa*) = 59.2; t_{Rmajor} (*syn-12aa*) = 20.3, t_{Rminor} (*syn-12aa*) = 30.4.

4-(4-Chlorophenyl)-3-methoxy-5-nitropentan-2-one (anti-12ab/syn-12ab). Colourless oil; R_f = 0.36 (hexane/ethyl acetate 4:1); IR (film): ν 3305, 3170, 2918, 2833, 1718, 1550, 1491, 1377, 1310, 1186, 1092, 841 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.83 (s, 3H, OCCH₃), 3.46 (s, 3H, OCH₃), 3.86-3.93 (m, 2H, CHAr and CHO), 4.63 (dd, *J* = 12.9, 6.8 Hz, 1H, HCHNO), 4.89 (dd, *J* = 12.9, 8.1 Hz, 1H, HCHNO), 7.21 (d, *J* = 8.6 Hz, 2H, ArH), 7.29 (d, *J* = 8.6 Hz, 2H, ArH); ¹³C RMN (75 MHz, CDCl₃): δ 26.6 (OCCH₃), 45.6 (CHAr), 59.8 (OCH₃), 76.4 (CH₂NO₂), 86.5 (CHOCH₃), 129.0 (ArCH), 129.4 (ArCH), 132.8 (ArC), 134.4 (ArC), 209.4 (C=O); HRMS (*m/z*): calculated for C₁₄H₁₆NO₇ (M⁺): 271.0611; found 275.0581

HPLC (Chiralpak AD; 1.0 mL/min; 90:10 Hex/IPA, 210 nm); t_{Rminor} (*anti-12ab*) = 9.34, t_{Rmajor} (*anti-12ab*) = 10.1; t_{Rmajor} (*syn-12ab*) = 7.1, t_{Rminor} (*syn-12ab*) = 7.8.

(3S,4R)-syn-3-Methoxy-5-nitro-4-(2-trifluoromethyl)phenylpentan-2-one (syn-12ac). Colourless oil; $R_f = 0.26$ (hexane/ethyl acetate 4:1); IR (film): ν 3345, 3180, 2960, 2837, 1716, 1555, 1455, 1377, 1310, 1260, 1161, 1106, 1032, 773 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 1.95 (s, 3H, OCCH_3), 3.45 (s, 3H, OCH_3), 4.11 (d, $J = 4.7$ Hz, 1H, ArCH), 4.53-4.45-4.56 (m, 2H, CHO and HCHNO), 4.93 (dd, $J = 11.2, 2.6$ Hz, 1H, HCHNO), 7.41 (t, $J = 7.7$ Hz, 1H, ArH), 7.58-7.48(m, 1H, ArH), 7.68 (d, $J = 7.9$ Hz, 1H, ArH), 7.85 (d, $J = 7.9$ Hz, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3): δ 26.7 (OCCH_3), 40.3 (CHAr), 59.7 (OCH_3), 75.6 (CH_2NO_2), 85.7 (CHOCH_3), 126.4 (ArCH), 128.3 (ArC), 129.5 (ArCH), 130.2 (ArCH), 132.3 (ArCH), 133.5 (ArC), 206.8 (C=O). HRMS (m/z) calculated for $\text{C}_{14}\text{H}_{16}\text{NO}_7$ (M^+): 305.0875; found 305.0970.

(3S,4S)-anti-3-Methoxy-5-nitro-4-(2-trifluoromethyl)phenylpentan-2-one (anti-12ac). Colourless oil; $R_f = 0.27$ (hexane/ethyl acetate 4:1); IR (film): ν 3345, 3180, 2960, 2837, 1716, 1555, 1455, 1377, 1310, 1260, 1161, 1106, 1032, 773 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.24 (s, 3H, OCCH_3), 3.37 (s, 3H, OCH_3), 3.96 (d, $J = 5.0$ Hz, 1H, CHAr), 4.39 (dd, $J = 12.7, 5.7$ Hz, 1H, CHO), 4.77 (ddd, $J = 19.2, 13.3, 6.6$ Hz, 2H, CH_2NO), 7.46 (t, $J = 7.0$ Hz, 1H, ArH), 7.52-7.67 (m, 2H, ArH), 7.73 (d, $J = 8.0$ Hz, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3): δ 26.0 (OCCH_3), 40.1 (CHAr), 59.4 (OCH_3), 75.2 (CH_2NO_2), 87.5 (CHOCH_3), 126.5 (ArCH), 126.7 (ArCH), 128.3 (ArC), 129.5 (ArCH), 132.3 (ArCH), 134.9 (ArC), 207.0 (C=O); HRMS (m/z) calculated for $\text{C}_{14}\text{H}_{16}\text{NO}_7$ (M^+): 305.0875; found 305.0974.

HPLC (Chiralpak AD; 1.0 mL/min; 96:4 Hex/IPA, 210 nm); t_{Rminor} (*anti-12ac*) = 22.6, t_{Rmajor} (*anti-12ac*) = 35.8; t_{Rmajor} (*syn-12ac*) = 17.0, t_{Rminor} (*syn-12ac*) = 18.7.

(3S,4R)-syn-3-Hydroxy-5-nitro-4-phenylpentan-2-one (syn-12ba).^{11a} Colourless oil; $R_f = 0.22$ (hexane/ethyl acetate 4:1); ^1H NMR (300 MHz, CDCl_3): δ 2.17 (s, 3H, OCCH_3), 3.75 (d, $J = 4.8$ Hz, 1H, CHAr), 4.03 (dt, $J = 3.0, 7.6$ Hz, 1H, CHOH), 4.66 (dd, $J = 6.8, 12.9$ Hz, 1H, HCHNO), 4.93 (dd, $J = 8.4, 12.9$ Hz, 1H, HCHNO), 7.20-7.37 (5H, ArH); ^{13}C NMR (75 MHz, CDCl_3): δ 25.5 (OCCH_3), 45.7 (CHAr), 76.7 (CH_2NO_2), 77.1 (CH-OH), 128.5 (2x ArCH), 128.7 (ArCH), 128.9 (2x ArCH), 133.8 (ArC), 206.3 (C=O).

(3S,4S)-anti-3-Hydroxy-5-nitro-4-phenylpentan-2-one (anti-12ba).^{11a} Colourless oil; $R_f = 0.24$ (hexane/ethyl acetate 4:1); ^1H NMR (300 MHz, CDCl_3): δ 2.03 (s, 3H, OCCH_3), 3.78-3.91 (m, 2H, CHAr and OH), 4.40-4.43 (m, 1H, CHOH), 4.74 (dd, $J = 7.1, 13.4$ Hz, 1H, HCHNO), 5.03 (dd, $J = 7.8, 13.4$ Hz, 1H, HCHNO), 7.23-7.40 (m, 5H, ArH); ^{13}C NMR (75 MHz, CDCl_3): δ 26.2 (OCCH_3), 45.9 (CHAr), 76.7 (CH_2NO_2), 88.1 (CHOCH_3), 128.1 (2x ArCH), 128.4 (ArCH), 129.1 (2x ArCH), 135.5 (ArC), 208.1 (C=O).

HPLC (Chiralpak AD; 1.0 mL/min; 96:4 Hex/IPA, 210 nm); t_{Rminor} (*anti-12ba*) = 98.4, t_{Rmajor} (*anti-12ba*) = 104.6; t_{Rminor} (*syn-12ba*) = 49.7, t_{Rmajor} (*syn-12ba*) = 104.6.

(3S,4R)-syn-4-(4-Chlorophenyl)-3-hydroxy-5-nitropentan-2-one (syn-12bb).^{11a} Colourless oil; $R_f = 0.36$ (hexane/ethyl acetate 4:1); ^1H NMR (300 MHz, CDCl_3): δ 2.21 (s, 3H, OCCH_3), 3.78 (d, $J = 4.6$ Hz, 1H, OH), 4.05 (dt, $J = 2.8, 7.6$ Hz, 1H, CHAr), 4.56 (dd, $J = 3.2, 4.7$ Hz, 1H, CHOH), 4.75 (dd, $J = 7.5, 13.6$ Hz, 1H, HCHNO), 5.02 (dd, $J = 7.6, 13.6$ Hz, 1H, HCHNO), 7.21-7.31 (m, 2H, ArH), 7.33-7.40 (m, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3): δ 28.3 (OCCH_3), 45.1 (CHAr),

76.8 (CH₂NO₂), 76.9 (CH-OH), 129.1 (2xArCH), 129.7 (ArCH), 132.2 (2xArCH), 134.7(ArC), 205.9 (C=O).

(3S,4S)-anti-4-(4-Chlorophenyl)-3-hydroxy-5-nitropentan-2-one (anti-12bb).^{11a} Colourless oil; R_f = 0.38 (hexane/ethyl acetate 4:1); ¹H NMR (300 MHz, CDCl₃): δ 2.19 (s, 3H, O=CCH₃), 3.79 (d, *J* = 4.9 Hz, 1H, OH), 3.89 (ddd, *J* = 4.5, 6.0, 8.3 Hz, 1H, CHAr), 4.39 (t, *J* = 4.8 Hz, 1H, CHOH), 4.64 (dd, *J* = 8.6, 13.6 Hz, 1H, HCHNO), 4.77 (dd, *J* = 6.0, 13.6 Hz, 1H, HCHNO), 7.03-7.45 (m, 5H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 26.3 (OCCH₃), 46.1 (CHAr), 75.7 (CH₂NO₂), 78.4 (CHOCH₃), 129.4 (2xArCH), 129.64 (2xArCH), 134.4 (ArC), 135.8 (ArC), 207.4 (C=O).

HPLC (Chiralpak AS; 1.0 mL/min; 90:10 Hex/IPA, 210 nm); t_{Rminor} (*anti-12bb*) = 28.8, t_{Rmajor} (*anti-12bb*) = 38.3; t_{Rminor} (*syn-12bb*) = 26.1, t_{Rmajor} (*syn-12bb*) = 56.1.

(3S,4R)-syn-3-Hydroxy-5-nitro-4-((2-trifluoromethyl)phenyl)pentan-2-one (syn-12bc).^{11a} Colourless oil; R_f = 0.20 (hexane/ethyl acetate 4:1); ¹H NMR (300 MHz, CDCl₃): δ 2.07 (s, 3H, OCCH₃), 3.94-4.03 (m, 1H, OH), 4.50-4.60 (m, 2H, CHAr and CHOH), 4.68-4.75 (m, 1H, HCHNO), 5.08-5.03 (m, 1H, HCHNO), 7.42-7.56 (m, 2H, ArH), 7.71 (d, *J* = 7.3 Hz, 1H, ArH), 7.85 (d, *J* = 7.8 Hz, 2H, ArH); ¹³C RMN (75 MHz, CDCl₃): δ 25.3 (OCCH₃), 39.4 (CHAr), 75.6 (CH₂NO₂), 76.4 (CH-OH), 128.4 (2xArCH), 129.8 (ArCH), 132.7 (ArCH), 133.4(ArC), 206.8 (C=O).

(3S,4S)-anti-3-Hydroxy-5-nitro-4-((2-trifluoromethyl)phenyl)pentan-2-one (anti-12bc).^{11a} Colourless oil; R_f = 0.23 (hexane/ethyl acetate 4:1); ¹H NMR (300 MHz, CDCl₃): δ 2.37 (s, 3H, OCCH₃), 4.37 (s, 1H, OH), 4.50-4.60 (m, 2H, CHAr and CHOH), 4.61 (dd, *J* = 6.3, 13.7 Hz, 1H, HCHNO), 4.77 (dd, *J* = 7.3, 13.9 Hz, 1H, HCHNO), 7.39-7.56 (m, 1H, ArH), 7.63 (t, *J* = 7.6 Hz, 1H, ArH), 7.75 (d, *J* = 8.2 Hz, 1H, ArH); 7.78 (d, *J* = 7.8 Hz, 1H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 25.3 (O=CCH₃), 40.1 (CHAr), 73.8 (CH₂NO₂), 78.5 (CH-OH), 124.4 (ArCH), 129.8 (ArCH), 132.7 (ArCH), 133.4(ArC), 206.9 (C=O).

HPLC (Chiralpak OD; 1.0 mL/min; 90:10 Hex/IPA, 210 nm); t_{Rminor} (*anti-12bc*) = 16.6, t_{Rmajor} (*anti-12bc*) = 23.5; t_{Rmajor} (*syn-12bc*) = 9.4, t_{Rminor} (*syn-12bc*) = 11.0

Acknowledgments

This research was supported by the Ministerio de Ciencia e Innovación (Projects CTQ2007-62771/BQU, CTQ2007-65218/BQU and Consolider Ingenio 2010 CSD2007-00006), the Generalitat Valenciana (Project PROMETEO/2009/039, FEDER) and the University of Alicante (UA). S. F. V. thanks the UA for a predoctoral contract.

References

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

2. (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233. (c) Trost B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (d) Trost, B. M.; Frederiksen, M. U.; Mathias, U.; Rudd, M. T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6630. (e) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem Int. Ed.* **2007**, *47*, 2358. (f) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611.
3. (a) Christoffers, J.; Korielly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279-1300. (b) López, F.; Feringa, B. L. In *Asymmetric Synthesis 2nd Edn.* Christmann; M.; Bräse S, Eds.; Wiley-VCH: Weinheim, 2008, pp 83-89.
4. For selected comprehensive books and reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (c) Kočovský, P.; Malkov, A. V. *Tetrahedron* **2006**, *62*, 255 (thematic issue on Organocatalysis in Organic Synthesis, no. 2-3). (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (e) *Enantioselective Organocatalysis*, Dalko, P. I. Ed.; Wiley-VCH: Weinheim, 2007. (f) List, B. *Chem. Rev.* **2007**, *107*, 5413 (Special Issue in Organocatalysis). (g) de Figueiredo, R. M.; Marcia, R.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575. (h) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 493. (i) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 757. (j) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (k) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.
5. (a) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1071. (c) Vicario J. L.; Badia, D.; Carillo L. *Synthesis* **2007**, 2065.
6. (a) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (b) Guillena, G.; Ramón D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.
7. (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (b) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693.
8. (a) Ono, N. *The Nitro Group in Organic Synthesis*. Wiley-VCH: New York, 2001. (b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.
9. For recent selected reviews on organocatalyzed aldol reactions, see: (a) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (b) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131. (c) Zlotin, S. G.; Kucherenko, A. S.; Beletskaya, I. P. *Russ. Chem. Rev.* **2009**, *78*, 737. (d) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600.
10. For selected reviews on organocatalyzed Mannich reactions, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580. (b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (c) Verkade, J. M. M.; vanHemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29.
11. (a) Andrey, A.; Alexakis, A.; Bernardinelli, G. *Org. Lett* **2003**, *5*, 2559. (b) Andrey, A.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (c) Mossé, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577.

12. (a) Xu, Y.; Córdova, A. *Chem. Commun.* **2006**, 460. (b) Xu, Y.; Zou, W.; Sundén H.; Ibrahim, I.; Córdova, A. *Adv. Synth. Catal.* **2006**, 348, 418.
13. Wang, J.; LI, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, 12, 4321.
14. Almaşi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nagel, Y.; Nájera, C. *Eur. J. Org. Chem.* **2007**, 2328.
15. Zhang, X.-j.; Liu, S.-p.; Lao, J.-h.; Du, G.-j.; Yan, M.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2009**, 20, 1451.
16. Mandal, T.; Zhao, C.-G. *Angew. Chem. Int. Ed.* **2008**, 47, 7714.
17. (a) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, 17, 729. (b) Gryko, D.; Kowalczyk, B.; Zawadzki, L. *Synlett* **2006**, 1059. (c) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, 17, 1493; *corrigendum: Tetrahedron: Asymmetry* **2007**, 18, 1031. (d) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, 17, 1027; *corrigendum: Tetrahedron: Asymmetry* **2007**, 18, 1030. (e) Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron: Asymmetry* **2006**, 17, 2754. (f) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, 18, 1272. (g) Ma, G.-N.; Zhang, Y.-P.; Shi, M. *Synthesis* **2007**, 197. (h) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, 9, 1247. (i) Guillena, G.; Hita, M. C.; Nájera, C. *Arkivoc* **2007**, (iv), 260; *corrigendum: Arkivoc* **2007**, (i), 146. (j) Guillena, G.; Hita, M. C.; Nájera, C.; Vióquez, S. F. *Tetrahedron: Asymmetry* **2007**, 18, 2300. (k) Guillena, G.; Hita, M. C.; Nájera, C.; Vióquez, S. F. *J. Org. Chem.* **2008**, 73, 5933. (l) Kucherenko, A. S.; Syutkin, D. E.; Zlotin, S. G. *Russ. Chem. Bull.* **2008**, 57, 591.
18. (a) Guillena, G.; Nájera, C.; Vióquez, S. F. *Synlett* **2008**, 3031. (b) Bradshaw, B.; Etxebarria-Jardi, G.; Bonjoch, J.; Vióquez, S. F.; Guillena, G.; Nájera, C. *Adv. Synth. Catal.* **2009**, 351, 2482.