Asymmetric conjugate addition of ketones to nitroalkenes catalyzed by chiral bifunctional sulfamides

Sheng-ping Liu, Xue-jing Zhang, Jin-hua Lao and Ming Yan*

Industrial Institute of Fine Chemicals and Synthetic Drugs, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510080, China
E-mail: yanming@mail.sysu.edu.cn

Abstract
Chiral bifunctional sulfamides were found to be efficient catalysts for the conjugate addition of ketones to nitroalkenes. Moderate to good enantioselectivities and yields were achieved for the reaction of acetone with a variety of β-aryl-nitroethylenes. Base additives were found to be more efficient than acid additives for the transformation. The reaction of methoxyacetone and cyclopentanone also provided the adducts with moderate enantioselectivities, however in low chemical yields.

Keywords: Chiral sulfamide, organocatalysis, nitroalkenes, ketone, conjugate addition

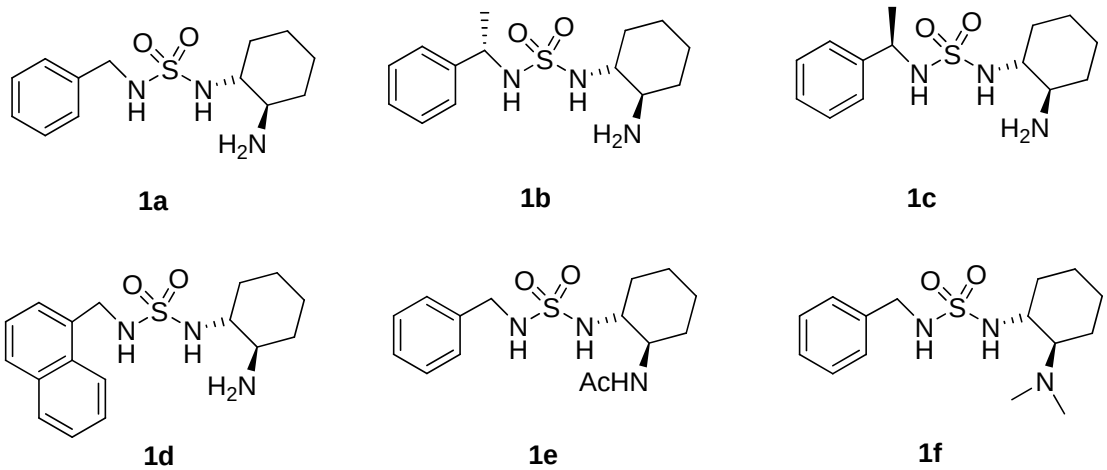
Introduction

In recent years asymmetric organocatalysis has emerged as a powerful tool for the synthesis of optically active compounds.[1] A large number of asymmetric reaction have been achieved using chiral amines, thioureas (ureas) and other organic small molecules as the catalysts. Chiral bifunctional organocatalysts, which are capable of simultaneously activation of both the electrophiles and the nucleophiles, have proved to be superior for many asymmetric transformations.[2-3] Chiral bifunctional thiourea-amine catalysts, developed by Jacobsen[4] and the others[5-6], were found to be highly efficient for the conjugate addition of aldehydes and ketones to nitroalkenes. Excellent enantioselectivities and yields were achieved and the reaction provided an efficient strategy to prepare chiral γ-nitro ketones.[7-8] However the preparation of these thiourea-amine catalysts generally requires tedious synthetic procedures, and the catalytic activity remains to be improved. Recently we developed a novel kind of chiral bifunctional sulfamide organocatalysts. The catalysts were readily prepared from amines and chiral cyclohexane-1,2-diamine with catechol sulfate. The stronger acidity of N-H bond of the sulfamide than the corresponding thiourea is expected to improve the catalytic activity. Excellent

enantioselectivities and yields were obtained for the conjugate addition of aldehydes to nitroalkenes.[9] As an extended study of the chiral sulfamide catalysts, herein we report their application in the asymmetric conjugate addition of ketones to nitroalkenes.

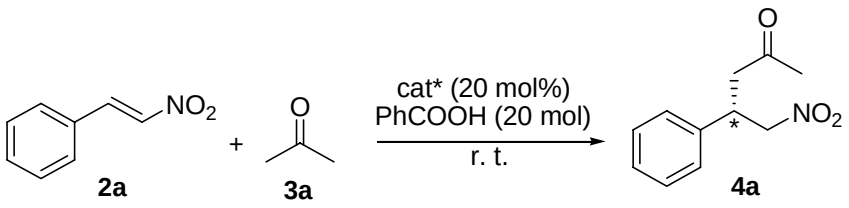
Results and Discussion

Chiral sulfamides **1a-1f** were prepared according to previously reported procedures.[9] The conjugate addition of acetone to *trans*-β-nitrostyrene **2a** was carried out in the presence of **1a-1f** and the results are summarized in Table 1. Although **1a** was found to be highly efficient for the asymmetric conjugate addition of aldehydes to nitroalkenes,[9] it provided the adduct product **4a** in low yield and with moderate enantioselectivity (Table 1, entry 1). The yield was improved significantly by the addition of 20 mol% benzoic acid (Table 1, entry 2). It is noted that in the **1a**-catalyzed addition of aldehydes to nitroalkenes, acid additives were detrimental and only base additives were efficient.[9] The result implicated some inherent difference between the reaction of ketones and aldehydes. Sulfamides **1b**, **1c** and **1d** were also efficient for the reaction (Table 1, entries 3-5). Sulfamide **1b**, derived from (*S*)-1-phenylethylamine and (*R*,*R*)-cyclohexane-1,2-diamine, provided slightly better enantioselectivity and yield than **1a**. In comparison, sulfamide **1c** derived from (*R*)-1-phenylethylamine and (*R*,*R*)-cyclohexane-1,2-diamine, provided the adduct **4a** in the same absolute configuration and with slightly lower enantioselectivity. The fact suggests that the enantioselective induction is mainly controlled by the chiral cyclohexanediamine unit. The additional chiral center only exerts small effects on the enantioselectivity. Sterically demanding **1d** provided **4a** with lower yield and enantioselectivity. Sulfamide **1e** and **1f** were totally inefficient for the reaction (Table 1, entries 6-7). The result confirms the importance of the primary amino group for the catalytic activity.



Scheme 1

Table 1. The screening of chiral sulfamides **1a-1f** [a]



Entry	Catalyst	Time (h)	Yield (%)[b]	Ee (%)[c,d]
1[e]	**1a**	79	37	64
2	**1a**	60	81	64
3	**1b**	60	84	66
4	**1c**	60	82	61
5	**1d**	60	61	51
6	**1e**	72	n.r.[f]	-
7	**1f**	72	n.r.[f]	-

[a] The reactions were carried out with **2a** (0.15 mmol), **1a-1f** (0.03 mmol) in acetone (0.3 mL).
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] The absolute configuration of **4a** was assigned to be *S* by comparing the optical rotation with the reported data.
[e] The reaction was carried out without benzoic acid.
[f] No reaction.

A number of solvents were then screened using **1b** as the catalyst and the results are listed in Table 2. The reaction solvent exerted significant effect on the yield and enantioselectivity. Generally the polar solvents resulted in lower yields and enantioselectivities (Table 2, entries 1-4). Water could also be used as the reaction solvent and provided the product with good enantioselectivity (71% ee), however in low yield (Table 2, entry 2). The best yield (87%) was achieved in ether (Table 2, entry 6), however the best enantioselectivity (84% ee) was obtained in toluene (Table 2, entry 9). Thus Et_2O and toluene were selected for further optimization study.

Table 2. The effect of reaction solvents[a]

Entry	Solvent	Yield (%)	Ee (%)
1	DMF	74	24
2	H_2O	42	71
3	MeOH	68	55
4	CH_3CN	39	50
5	THF	84	54
6	Et_2O	87	74
7	$CHCl_3$	64	46
8	CH_2Cl_2	74	74
9	toluene	55	84

[a] The reactions were carried out at room temperature with **2a** (0.15 mmol), **1b** (0.03 mmol), PhCOOH (0.03 mmol), acetone (0.2 mL) in solvent (0.4 mL).

In the organocatalytic conjugate addition of ketones to nitroalkenes, Brønsted acids were generally used as the efficient additives.[10] However in our recent study of asymmetric conjugate addition of aldehydes to nitroalkenes catalyzed by chiral sulfamides, bases such as DIPEA and DMAP, were found to be extremely efficient additives.[9] To obtain a clear understanding of the additive effect, a range of acid and base additives were examined in the reaction of **2a** with acetone. The results are summarized in Table 3. Initially benzoic acid, acetic acid, *p*-nitro-benzoic acid, trifluoroacetic acid and (*d*)-camphor-10-sulfonic acid were studied in toluene (Table 3, entries 1-5). *p*-Nitro-benzoic acid provided the product **4a** with good enantioselectivity, but the yield was poor. Trifluoroacetic acid and (*d*)-camphor-10-sulfonic acid were inefficient and no product could be obtained. Base additives such as imidazole, DIPEA, TEA and DMAP, were also examined (Table 3, entries 6-9). Imidazole provided **4a** with good yield and enantioselectivity. DMAP afforded better enantioselectivity, however in lower yield. DIPEA and TEA provided **4a** in low yields (Table 3, entries 8 and 9). Furthermore the acid and base additives were examined in ether and similar results were observed (Table 3, entries 10-18). Finally imidazole/ether system was selected for further study (Table 3, entry 15).

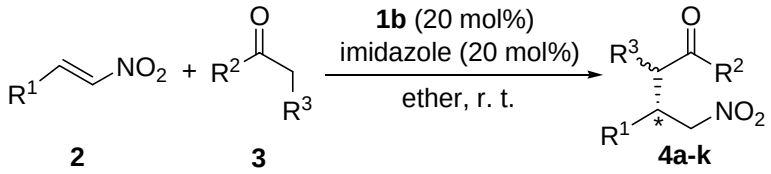
Table 3. The effect of additives[a]

Entry	Solvent	Additive	Yield (%)	Ee (%)
1	toluene	PhCOOH	55	84
2	toluene	AcOH	13	74
3	toluene	*p*-$NO_2C_6H_4COOH$	18	86
4	toluene	CF_3COOH	-	-
5	toluene	Camphor-10-sulfonic acid	-	-
6	toluene	Imidazole	80	78
7	toluene	DMAP	58	86
8	toluene	DIPEA	36	77
9	toluene	Et_3N	13	76
10	Et_2O	PhCOOH	87	74
11	Et_2O	AcOH	32	62
12	Et_2O	*p*-$NO_2C_6H_4COOH$	47	70
13	Et_2O	CF_3COOH	10	73
14	Et_2O	Camphor-10-sulfonic acid	5	70
15	Et_2O	Imidazole	73	84
16	Et_2O	DMAP	32	67
17	Et_2O	DIPEA	6	64
18	Et_2O	Et_3N	-	-

[a] The reactions were carried out at room temperature with **2a** (0.15 mmol), **1b** (0.03 mmol), additive (0.03 mmol), acetone (0.2 mL) in solvent (0.4 mL).

The scope of the reaction was studied with a variety of β-aryl-nitroethylenes and ketones and the results are summarized in Table 4. The reaction of substituted β-phenyl-nitroethylenes with acetone provided the adducts with moderate yields and enantioselectivities (table 4, entries 2-7). *ortho*, *meta* and *para*-chlorophenyl-nitroethylene afforded the product with similar enantioselectivity and yield (Table 4, entries 2-4). 2-Nitrophenyl-nitroethylene **2e** gave the product with moderate enantioselectivity and in low yield. 4-Methoxylphenyl-nitroethylene **2f** and 4-methylphenyl-nitroethylene **2g** provided the products in the same yield, but **2f** afforded better enantioselectivity. Heteroaryl-nitroethylenes, such as **2h** and **2i**, were also applicable in the transformation. The corresponding adducts were obtained with good yields and moderate enantioselectivities (Table 4, entry 8-9). While methoxyacetone was used in the reaction with **2a**, two diastereoisomeric adducts were obtained with moderate enantioselectivity and yield (Table 4, entry 10). The reaction of cyclopentanone gave the adduct with good enantioselectivity, however in low yield (Table 4, entry 11).

Table 4. The reaction of β-aryl-nitroethylenes and ketones catalyzed by **1b**[a]



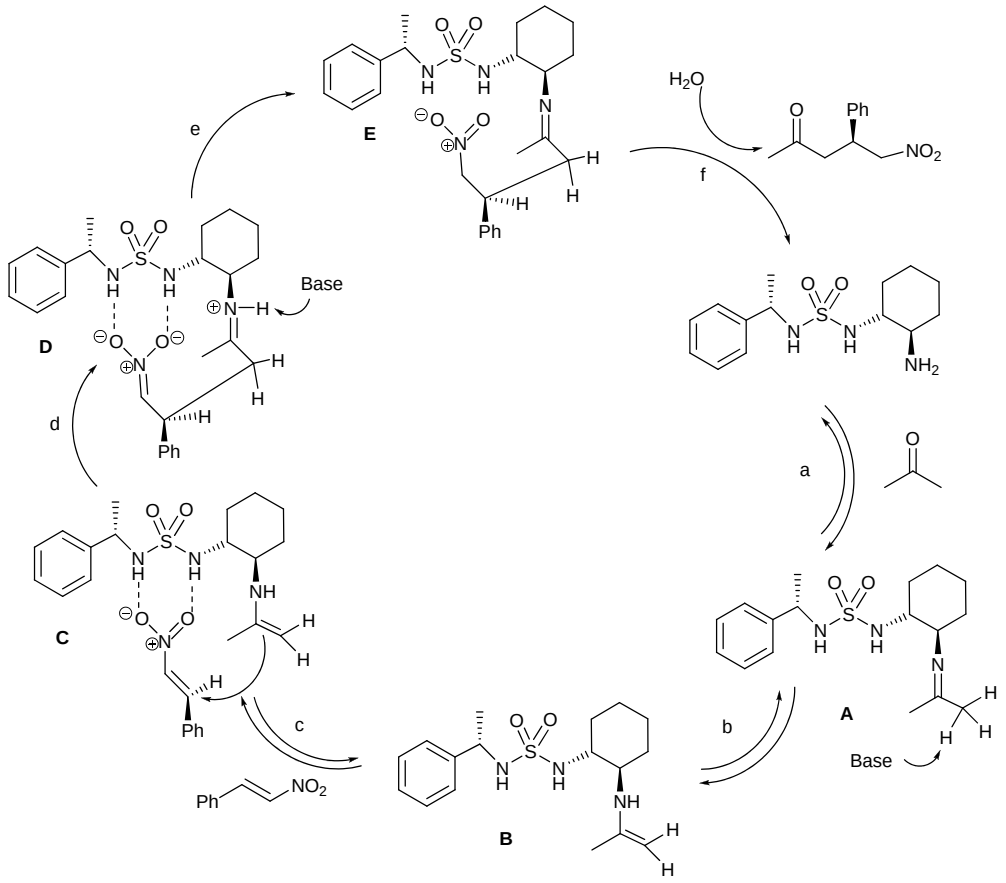
Entry	R^1	R^2	R^3	Time (h)	Product (yield %)[b]	Ee (%)[c]
1	Ph, **2a**	CH_3	H	60	**4a** (73)	84
2	2-Cl-Ph, **2b**	CH_3	H	49	**4b** (56)	73
3	3-Cl-Ph, **2c**	CH_3	H	94	**4c** (66)	66
4	4-Cl-Ph, **2d**	CH_3	H	60	**4d** (60)	70
5	2-NO_2-Ph, **2e**	CH_3	H	70	**4e** (38)	75
6	4-OMe-Ph, **2f**	CH_3	H	60	**4f** (58)	84
7	4-Me-Ph, **2g**	CH_3	H	60	**4g** (58)	68
8	2-furanyl, **2h**	CH_3	H	60	**4h** (72)	75
9	2-thiophenyl, **2i**	CH_3	H	60	**4i** (70)	69
10	Ph, **2a**	CH_3	OMe	60	**4j** (58)	75/26[d]
11	Ph, **2a**	-$CH_2CH_2CH_2$-		94	**4k** (35)	84/74[e]

[a] The reactions were carried out at room temperature with **2** (0.15 mmol), **3** (0.2 mL), **1b** (0.03 mmol), imidazole (0.03 mmol) in ether (0.4 mL).
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] *Syn:anti* = 43:57 as determined by ^{1}H NMR analysis.
[e] *Syn:anti* = 43:57 as determined by ^{1}H NMR analysis.

Several other ketones, including cyclohexanone, acetophenone, 2-butanone, were examined in the reaction with β-nitrostyrene under the optimized reaction conditions, however the reactions were sluggish and almost no product was obtained. Using benzoic acid as the additive did not provide any improvements. The reactions of β-cyclohexyl nitroethylene and β-butyl

nitroethylene with acetone were also studied, but only trace of the products was obtained.

A catalytic mechanism of chiral sulfamides is proposed in Scheme 2.[5c] An imine intermediate **A** is generated from the catalyst **1b** and acetone. The tautomerization of **A** is promoted by the base additive and provides the enamine **B**. Hydrogen bonding between the nitro group of nitrostyrene with the sulfamide (intermediate **C**), increases the nucleophilicity of nitrostyrene. The neucleophilic attack of enamine occurs from *si* face of double bond and provides intermediate **D**. The consequent proton transfer and hydrolysis give the product and regenerate the catalyst **1b**. The base additive is proposed to accelerate also the proton transfer step by removing proton from the imine cation.



Scheme 2

Conclusions

In summary, chiral bifunctional sulfamides were found to be efficient catalysts for the conjugate addition of ketones to nitroalkenes. Moderate to good enantioselectivities and yields were achieved for the reaction of acetone with a variety of β-aryl-nitroethylenes. Methoxyacetone and

cyclopentanone were also applicable in the transformation with lower chemical yields. Base additives were found to be more efficient than acid additives for the reaction. Further development of more efficient chiral sulfamide catalysts is currently under investigation.

Experimental Section

General Procedures. All solvents were used as commercial anhydrous grade without further purification. All reactions were carried out under open air. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer. High-resolution mass spectra were obtained with the Thermo MAT 95XP mass spectrometer. The low resolution mass spectra were obtained at the Thermo Trace GC Ultra-DSQ. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Enantiomeric excesses were determined by HPLC using Daicel Chiralcel AS-H and OD-H column and eluting with ^{n}-hexane/^{i}-PrOH solution.

Typical procedure for the asymmetric conjugate addition

A solution of nitroalkene (0.15 mmol), **1b** (0.03 mmol), imidazole (0.03 mmol) and ketone (0.2 mL) in ether (0.4 mL) was stirred at room temperature for 60 h. The reaction solution was concentrated under vacuum. The residue was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate = 6/1) to give the product.

(*S*)-5-Nitro-4-phenylpentan-2-one (4a).[4a] White solid (73%), m.p. 114 -116 ^{o}C (lit[4a]. m.p. 120 -122.5 ^{o}C), $[\alpha]_D^{20}$ = + 1.7 (c 1.0, $CHCl_3$) (lit[4a]. $[\alpha]_D^{20}$= +2.4, c 1.03, $CHCl_3$, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (5H, m, Ar-H), 4.70 (1H, dd, J = 12.2, 6.8 Hz, CH_2NO_2), 4.60 (1H, dd, J = 12.2, 7.8 Hz, CH_2NO_2), 4.01 (1H, m, CHAr), 2.92 (2H, d, J = 7.0 Hz, CH_2), 2.13 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.4 (C=O), 138.8 (C_{quat}), 129.1 (2CH), 127.9 (CH), 127.4 (2CH), 79.5 (CH_2), 46.1 (CH), 39.0 (CH_2), 30.4 (CH_3); IR (KBr): 3040, 2950, 2920, 1715, 1546, 1384, 1362, 1162, 758, 696 cm^{-1}; MS (EI): 207.0 (M^+), 190.8, 166.9, 132.9, 91.0, 84.0. The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 1.0 mL/min); $t_{R(major)}$ = 12.1 min, $t_{R(minor)}$ = 16.0 min, 84% ee.

(*S*)-4-(2-Chlorophenyl)-5-nitropentan-2-one (**4b).** Colorless oil (56%), $[\alpha]_D^{20}$= +28.7 (c 1.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.21 (4H, m, Ar-H), 4.80-4.72 (2H, m, CH_2NO_2), 4.50-4.43 (1H, m, CHAr), 3.07 (1H, dd, J = 18.0, 7.8 Hz, CH_2CO), 2.97 (1H, dd, J = 18.0, 6.0 Hz, CH_2CO), 2.17 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.3 (C=O), 136.0 (C_{quat}), 133.7 (C_{quat}), 130.4 (CH), 129.0 (CH), 128.4 (CH), 127.4 (CH), 77.4 (CH_2), 44.5 (CH_2), 35.8 (CH), 30.2 (CH_3); IR (KBr): 2923, 2853, 1714, 1552, 1384, 1165, 1033, 753, 686 cm^{-1}; MS (EI): 241.1 (M^+), 205.9, 160.0, 158.9, 144.9, 137.9, 114.9, 76.9; HRMS (ESI) calcd for $C_{11}H_{12}NO_3Cl$ $(M+Na)^+$: 264.0403, found: 264.0401. The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 1.0 mL/min); $t_{R(major)}$ = 10.5 min, $t_{R(minor)}$ = 12.2 min, 73% ee.

(*S*)-4-(3-Chlorophenyl)-5-nitropentan-2-one (4c).[8b] Colorless oil (66%), $[\alpha]_D^{20}$= +1.2 (c 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.10 (4H, m, Ar-H), 4.69 (1H, dd, J = 12.6, 6.6 Hz, CH_2NO_2), 4.58 (1H, dd, J = 12.4, 8.0 Hz, CH_2NO_2), 4.03-3.93 (1H, m, CHAr), 2.90 (2H, d, J = 7.0 Hz, CH_2CO), 2.13 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9 (C=O), 141.0 (C_{quat}), 134.8 (C_{quat}), 130.3 (CH), 128.1 (CH), 127.6 (CH), 125.8 (CH), 79.0 (CH_2), 45.9 (CH_2), 38.6 (CH), 30.3 (CH_3); IR (KBr): 2923, 2853, 1734, 1559, 1384, 1160, 782, 695 cm^{-1}; MS (EI): 240.9 (M^+), 195.9, 193.9, 159.0, 137.9, 114.9, 76.9; HRMS (ESI) calcd for $C_{11}H_{12}NO_3Cl$ $(M+Na)^+$: 264.0403, found: 264.0385; The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 1.0 mL/min); $t_{R(major)}$ = 13.0 min, $t_{R(minor)}$ = 19.8 min, 66% ee.

(*S*)-4-(4-Chlorophenyl)-5-nitropentan-2-one (4d). [8b] White solid (60%), m.p. 88-90 °C, $[\alpha]_D^{20}$ = +2.0 (c 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (2H, d, J = 8.2 Hz, Ar-H), 7.16 (2H, d, J = 8.2 Hz, Ar-H), 4.68 (1H, dd, J = 12.4, 6.6 Hz, CH_2NO_2), 4.57 (1H, dd, J = 12.4, 7.8 Hz, CH_2NO_2), 4.00 (1H, m, CHAr), 2.89 (2H, d, J = 7.0 Hz, CH_2CO), 2.13 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0 (C=O), 137.3 (C_{quat}), 133.8 (C_{quat}), 129.3 (2CH), 128.8 (2CH), 79.2 (CH_2), 46.0 (CH_2), 38.4 (CH), 30.4 (CH_3); IR (KBr): 3029, 2948, 2924, 2853, 1913, 1717, 1553, 1491, 1384, 1362, 1166, 854, 818, 734, 715 cm^{-1}; MS (EI) : 241.1 (M^+), 193.9, 178.9, 137.9, 114.9; The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 1.0 mL/min); $t_{R(major)}$ = 12.8 min, $t_{R(minor)}$ = 19.2 min, 70% ee.

(*S*)-5-Nitro-4-(2-nitrophenyl)pentan-2-one (4e).[8a] Yellow oil (38%), $[\alpha]_D^{20}$ = -84.0 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CHCl_3$): δ 7.89 (1H, d, J = 8.0 Hz, Ar-H), 7.61-7.57 (1H, m, Ar-H), 7.47-7.37 (2H, m, Ar-H), 4.87-4.79 (2H, m, CH_2NO_2), 4.55-4.50 (1H, m, CHAr), 3.05 (2H, d, J = 6.8 Hz, CH_2CO), 2.16 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CHCl_3$): δ 204.8 (C=O), 149.9 (C_{quat}), 133.5 (C_{quat}), 133.3 (CH), 128.7 (CH), 128.6 (CH), 125.2 (CH), 77.9 (CH_2), 45.3 (CH_2), 33.9 (CH), 30.1 (CH_3); IR (KBr): 2924, 2853, 1716, 1559, 1473, 1384, 710 cm^{-1}; MS (EI): 251.9 (M^+), 206.8, 162.9, 157.0, 145.9, 129.9, 90.0, 76.9; The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 1.0 mL/min); $t_{R(major)}$ = 21.1 min, $t_{R(minor)}$ = 25.1 min, 75% ee.

(*S*)-4-(4-Methoxyphenyl)-5-nitropentan-2-one (4f).[4a,8a] White solid (58%), m.p. 86-88 °C (lit.[4a] m.p. 93.5-94.5 °C), $[\alpha]_D^{20}$ = -1.3 (c 1.8, $CHCl_3$) (lit.[4a] $[\alpha]_D^{20}$= -1.5, c 1.32, $CHCl_3$, 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (2H, d, J = 8.6 Hz, Ar-H), 6.86 (2H, d, J = 8.6 Hz, Ar-H), 4.66 (1H, dd, J = 12.2, 6.8 Hz, CH_2NO_2), 4.56 (1H, dd, J = 12.2, 7.8 Hz, CH_2NO_2), 4.01 (1H, m, CHAr), 3.78 (3H, s, OCH_3), 2.89 (2H, J = 7.0 Hz, CH_2CO), 2.10 (3H, s, CH_3); ^{13}C NMR(100 MHz, $CDCl_3$): δ 205.5 (C=O), 159.1 (C_{quat}), 130.6 (C_{quat}), 128.4 (2CH), 114.4 (2CH), 79.7 (CH_2), 55.3 (CH_3), 46.3 (CH_2), 38.4 (CH), 30.4 (CH_3); IR (KBr): 3003, 2962, 2838, 1714, 1550, 1519, 1383, 1262, 1179, 1034, 819, 730 cm^{-1}; MS (EI): 237.0 (M^+), 191.0, 190.0, 174.9, 148.0, 134.0, 90.9, 76.9; The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 1.0 mL/min); $t_{R(major)}$ = 20.9 min, $t_{R(minor)}$ = 45.8 min, 84% ee.

(*S*)-4-(4-Methylphenyl)-5-nitropentan-2-one (**4g**).[4a] White solid (58%), m.p. 65-67 °C, $[\alpha]_D^{20}$= +1.3 (c 1.6, $CHCl_3$) (lit.[4a] $[\alpha]_D^{20}$= +5.5, c 1.59, $CHCl_3$, 97% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.08 (4H, m, Ar-H), 4.67 (1H, dd, J = 12.2, 6.8 Hz, CH_2NO_2), 4.57 (1H, dd, J = 12.2, 7.6 Hz, CH_2NO_2), 4.00-3.92 (1H, m, CHAr), 2.89 (2H, d, J = 7.0 Hz, CH_2CO), 2.31 (3H, s, $ArCH_3$), 2.11 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5 (C=O), 137.6 (C_{quat}), 135.7 (C_{quat}), 129.7 (2CH), 127.2 (2CH), 79.6 (CH_2), 46.2 (CH_2), 38.7 (CH), 30.4 (CH_3), 21.0 (CH_3); IR (KBr): 3030, 3007, 2950, 2922, 1710, 1552, 1373, 1206, 805, 716 cm^{-1}; MS (EI): 221.0 (M^+), 186.9, 174.0, 158.9, 117.0, 132.0, 90.9, 76.9. The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 1.0 mL/min); $t_{R(major)}$ = 10.6 min, $t_{R(minor)}$ = 15.6 min, 68% ee.

(*R*)-4-(Furan-2-yl)-5-nitropentan-2-one (4h). [3j,4a,5b,8a] White solid (72%), m.p. 49-51 °C (lit.[4a] m.p. 54.5-56 °C), $[\alpha]_D^{20}$= +4.5 (c 1.5, $CHCl_3$) (lit[4a]. $[\alpha]_D^{20}$= +5.7, c 1.32, $CHCl_3$, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (1H, m, ArH), 6.30 (1H, m, Ar-H), 6.14 (1H, m, Ar-H), 4.70 (1H, dd, J = 12.4, 6.4 Hz, CH_2NO_2), 4.66 (1H, dd, J = 8.6, 3.0 Hz, CH_2NO_2), 4.10 (1H, m, CHAr), 2.94 (2H, d, J = 18.0, 6.4 Hz, CH_2CO), 2.18 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1 (C=O), 151.7 (C_{quat}), 142.3 (CH), 110.5 (CH), 107.1 (CH), 77.4 (CH_2), 43.5 (CH_2), 32.9 (CH), 30.2 (CH_3); IR (KBr): 3123, 3006, 2920, 1718, 1554, 1378, 1164, 1015, 742 cm^{-1}; MS (EI): 197.0 (M^+), 150.9, 149.9, 134.9, 107.9, 93.9, 76.9. The enantiomeric excess was determined by HPLC with an OD-H column (^{n}-hexane/^{i}-PrOH = 94/6, λ = 208 nm, 0.6 mL/min); $t_{R(major)}$ = 35.1 min, $t_{R(minor)}$ = 37.2 min, 75% ee.

(*R*)-5-Nitro-4-(thiophen-2-yl)pentan-2-one (4i). [3j,4a,5a-b,8a] Yellow oil (70%), $[\alpha]_D^{20}$= +6.1 (c 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (1H, d, J = 5.0 Hz, Ar-H), 6.94-6.90 (2H, m, Ar-H), 4.72 (1H, dd, J = 12.4, 6.4 Hz, CH_2NO_2), 4.61 (1H, dd, J = 12.4 , 7.4 Hz, CH_2NO_2), 4.32 (1H, m, CHAr), 2.97 (2H, d, J = 6.8 Hz, CH_2CO), 2.16 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0 (C=O), 141.6 (C_{quat}), 127.2 (CH), 125.5 (CH), 124.7 (CH), 79.7 (CH_2), 46.8 (CH_2), 34.4 (CH), 30.3 (CH_3); IR (KBr): 3108, 3006, 2920, 1715, 1551, 1431, 1380, 1166, 851, 706 cm^{-1}; MS (EI): 213.0 (M^+), 166.9. 165.9, 150.9, 123.9, 109.9, 83.9. The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 1.0 mL/min); $t_{R(major)}$ = 14.9 min, $t_{R(minor)}$ = 19.7 min, 69% ee.

5-Nitro-4-phenylpentan-1-methoxyl-2-one (4j).[4a] White solid (58%), $[\alpha]_D^{20}$ = +1.2 (c 0.7, $CHCl_3$). IR (KBr): 2930, 2830, 1715, 1556, 1382, 1109, 763, 703 cm^{-1}; MS (EI): 237.0 (M^+), 193.9, 146.9, 116.9, 103.9, 90.9, 76.9.

syn-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (3H, m, Ar-H), 7.25-7.21 (2H, m, Ar-H), 4.93 (1H, dd, J = 12.8, 8.2 Hz, CH_2NO_2), 4.65 (1H, dd, J = 12.8, 6.8 Hz, CH_2NO_2), 3.93-3.80 (2H, m, CH_2CO), 3.45 (3H, s, OCH_3), 1.78 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.9 (C=O) , 134.5 (C_{quat}), 129.0 (2CH), 128.5 (2CH), 128.4 (CH), 86.4 (CH), 76.5 (CH_2), 59.8 (CH_3), 46.3 (CH), 26.4 (CH_3). The enantiomeric excess was determined by HPLC with an OD-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 0.6 mL/min); $t_{R(minor)}$ = 13.8 min, $t_{R(major)}$ = 26.3 min, 75% ee.

anti-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (3H, m, Ar-H), 7.25-7.21 (2H, m, Ar-H),

4.86 (1H, dd, J = 13.2, 5.6 Hz, CH_2NO_2), 4.72 (1H, dd, J = 13.2, 8.6 Hz, CH_2NO_2), 3.93-3.80 (2H, m, CH_2CO), 3.38 (3H, s, OCH_3), 2.04 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1 (C=O), 135.4 (C_{quat}), 129.1 (2CH), 128.9 (2CH), 128.1 (CH), 88.2 (CH), 76.5 (CH_2), 59.8 (CH_3), 45.9 (CH), 26.2 (CH_3). The enantiomeric excess was determined by HPLC with an OD-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 0.6 mL/min); $t_{R(minor)}$ = 14.9 min, $t_{R(major)}$ = 19.6 min, 26% ee.

2-(1-phenyl-2-nitroethyl)-cyclopentanone (4k).[8m-n] White solid (35%), $[\alpha]_D^{20}$ = -3.3 (c 1.3, $CHCl_3$); IR (KBr): 3063, 3031, 2983, 2923, 2080, 1730, 1552, 1159, 1131, 785, 697 cm^{-1}; MS (EI): 233.1 (M^+), 186.1, 157.9, 129.0, 114.9, 104.0, 90.9, 76.9.

syn-isomer. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.30 (3H, m, Ar-H), 7.19-7.16 (2H, m, Ar-H), 5.02-5.00 (2H, m, CH_2NO_2), 3.86-3.81 (1H, m, CHAr), 2.55-2.49 (1H, m, CHCO), 2.34-1.43 (6H, m, $3CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.1 (C=O), 137.4 (C_{quat}), 129.0 (2CH), 128.5 (2CH), 128.0 (CH), 78.3 (CH_2), 51.4 (CH), 44.0 (CH_2), 39.3 (CH_2), 27.0 (CH), 20.6 (CH_2). The enantiomeric excess was determined by HPLC with an OD-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 0.6 mL/min); $t_{R(minor)}$ = 11.3 min, $t_{R(major)}$ = 18.4 min, 84% ee.

anti-isomer. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.30 (3H, m, Ar-H), 7.19-7.16 (2H, m, Ar-H), 5.33 (1H, dd, J = 12.8, 5.6 Hz, CH_2NO_2), 4.71 (1H, dd, J = 12.8, 10.0 Hz, CH_2NO_2), 3.73-3.67 (1H, m, CHAr), 2.43-2.36 (1H, m, CHCO), 2.34-1.43 (6H, m, $3CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.5 (C=O), 137.7 (C_{quat}), 128.9 (2CH), 128.0 (2CH), 127.9 (CH), 78.3 (CH_2), 50.5 (CH), 44.2 (CH_2), 38.7 (CH_2), 28.3 (CH), 20.3 (CH_2). The enantiomeric excess was determined by HPLC with an OD-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 208 nm, 0.6 mL/min); $t_{R(minor)}$ = 12.9 min, $t_{R(major)}$ = 14.4 min, 74% ee.

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