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Azetidine-derived bifunctional organocatalysts for Michael reactions

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ABSTRACT

2-Cyano azetidines, easily accessible from β-amino alcohols, are precursors of stereodefined homochiral azetidinic or pyrrolidinic 1,2-diamines. A small library of these original diamines was screened as precatalysts for the enantioselective addition of 1,3-dicarbonyl compounds onto β-nitro styrenes. An azetidinic diamine derived from (−)-ephedrine and derivatized as a thiourea was found to catalyze the conjugate addition of acetylacetone with good levels of enantioselectivities (up to 84% ee). Interestingly, the absolute configuration of the Michael adduct depends on the nature of the 1,3 dicarbonyl nucleophile (diethyl malonate or acetylacetone), which is indicative of a different mechanism involved in the reaction of these two nucleophiles.

1. Introduction

Since the seminal work of Takemoto[1] who first reported thioureas acting as very efficient bifunctional organocatalysts for the enantioselective addition of 1,3-dicarbonyl compounds onto nitroolefins, this reaction has become a standard for the evaluation of newly designed organocatalysts.[2] Thus, continuous efforts have been made to synthesize new ureas or other hydrogen bond donors from accessible members of the chiral pool, such as amino acids,[3] carbohydrates,[4] cinchona-derived alkaloids,[5] or other more sophisticated scaffolds.[6] The basic subunit found in the majority of these organocatalyst is a chiral 1,2-diamine in which one of the amino moieties will be part of a urea, which activates the electrophile through a hydrogen bond, while the other one, as a tertiary amine, will concomitantly act as a base for nucleophile activation.[7] Therefore, new classes of chiral and stereodefined 1,2-diamines readily available from the chiral pool are important for the screening of such new catalysts. We have reported that 2-cyano azetidines **1**, easily accessible from β-amino alcohols[8] are ideal precursors for a wide range of 1,2-diamines either by simple $LiAlH_4$ reduction, to give primary amines **2** or through a one pot two-step procedure leading to *anti*-diamine **3**.[9,10] Furthermore, these strained 2-alkylamino azetidines can be rearranged into 3-amino pyrrolidines **4**.[10] Thus, starting from readily available amino alcohols, a library of stereodefined 1,2-diamines can be easily synthesized and screened in this reaction (Fig. 1).

As part of our program directed toward the development of azetidines,[11] we herein report the screening of thioureas derived from these heterocyclic diamines as new organocatalysts for the conjugate addition of 1,3-dicarbonyl compounds onto nitroolefins. We also demonstrate herein that efficient catalysts can be discovered starting from commercially available amino alcohols, such as (1*R*,2*S*)-ephedrine **5** and (1*S*,2*S*)-pseudoephedrine **6**, and that the direction of the enantioselectivity of this reaction can be reversed according to the nature of the 1,3-dicarbonyl nucleophile, which at first sight is unexpected.

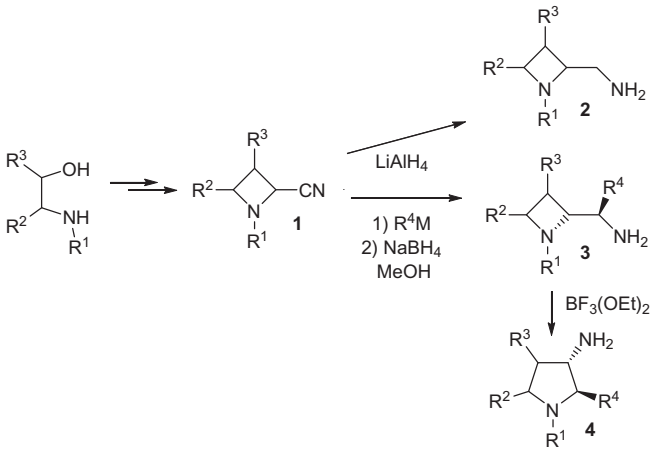

Figure 1. Azetidinic and pyrrolidinic 1,2-diamines are accessible from β-amino alcohols.

2. Results and discussion

2.1. Synthesis of catalysts

As previously described, 2-cyano azetidines **7**–**8** and **9**–**10** are easily prepared[8] in gram quantities from **5** and **6**, respectively.

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Reduction of the cyano group with $LiAlH_4$ gave **11**–**14**, while addition of PhMgBr followed by reduction gave *anti*-diamine **15**–**18**. Three of the latter were also rearranged into 3-aminopyrrolidines **19**–**21**.[10] These amines were then transformed in quantitative yields, as judged by NMR into their urea derivatives by reaction with 3,5-bis trifluoromethyl isothiocyanate in toluene at room temperature for 15mn. These ureas were isolated in the case of azetidine **12** and pyrrolidine **20** (see Section 4) but it was shown that in situ generation of the urea prior to the Michael reaction instead of external addition of the catalyst was equally efficient in terms of yield and enantioselectivity. Therefore, the above amines can be considered as 'pre-catalysts' and have been used as such in this work (see Fig. 2).

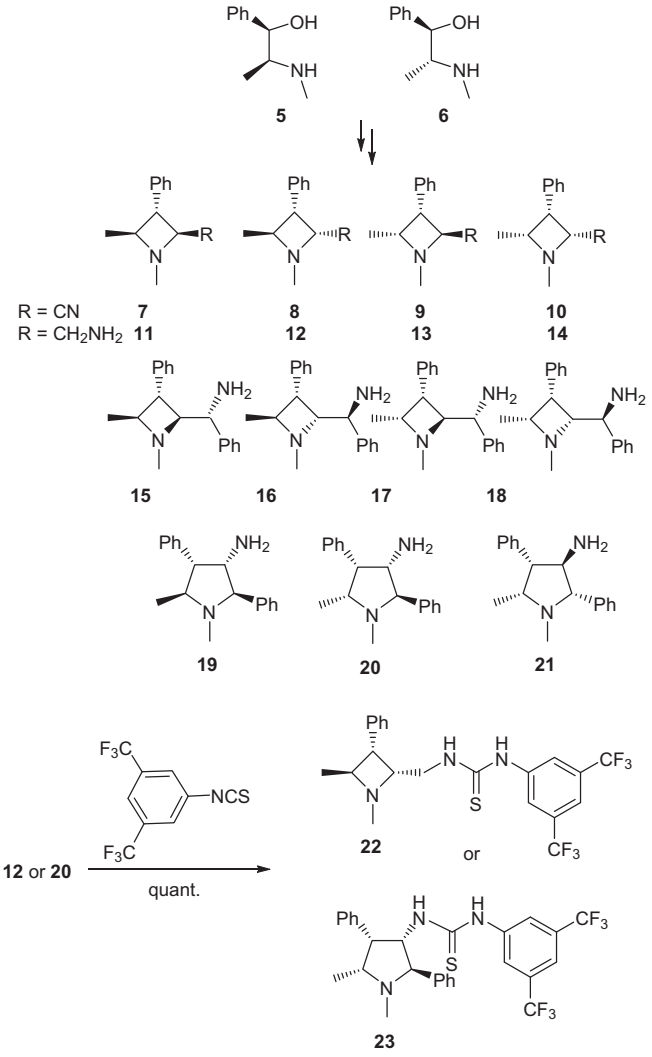


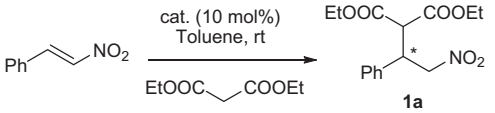
Figure 2. Structure of ephedrine-derived azetidinic and pyrrolidinic 1,2-diamines screened in this work.

2.2. Screening of the catalyst

Having a small library of diamines in hand, these compounds were evaluated in the standard reaction of diethyl malonate reacting with β-nitrostyrene in toluene at room temperature to give adduct **1a**. The results are shown in Table 1.

This first set of experiments demonstrates that both the nature of the aza-heterocycle (azetidine or pyrrolidine), and relative configurations of the substituents on these scaffolds have a profound influence on the efficiency of this reaction. Only azetidinic diamine **12**, (entry 2) derived from (−)-ephedrine displayed high catalytic activity, and produced the Michael adduct in reasonable time and yield, albeit with moderate enantioselectivity. Pyrrolidinic diamines **19**–**21** proved completely inefficient in this reaction. The enantioselectivity of the reaction appeared to be governed by the configuration of the C-2 center of the azetidine (compare entries 1/2 and 6/7).

Table 1
Screening of the catalyst



Entry	Pre-catalyst	Time (h)	Yield[a] (%)	er (*S*:*R*)[b]
1	**11**	192	63	33:67
2[c]	**12**	20	77	68:32
3	**13**	72	71	35:65
4	**14**	192	—[d]	nd
5	**15**	192	—[d]	nd
6	**16**	192	38	38:62
7	**17**	192	26	61:39
8	**18**	192	—[d]	nd
9	**19**	48	No reaction	—
10	**20**	48	No reaction	—
11	**21**	48	No reaction	—

[a] Yield of isolated product.
[b] Determined by HPLC (see Section 4).
[c] The same results were obtained with in situ generated, or externally added catalyst.
[d] Conversion was below 20%.

2.3. Optimization with catalyst 12

Thus we focused on diamine **12** to optimize its catalytic activity by varying the nature of the solvent and of the nucleophile. These experiments appear in Table 2.

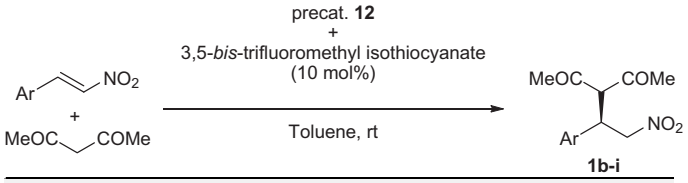
This second set of experiments showed that toluene was indeed the best solvent for this reaction. In this solvent, variation of the nature of the nucleophile showed more contrasting results: malononitrile gave a racemic adduct, and Meldrum's acid reacted sluggishly and produced the adduct with low ee; but both rates and enantioselectivity were nicely improved when acetylacetone was used as the nucleophile (entry 5). In this case, the Michael reaction was completed in 6 h, giving the adduct with 76% ee. Unexpectedly, the absolute configuration of the major Michael adduct was reversed compared to the experiment with diethylmalonate (Table 1, entry 2). Finally, a last set of experiments was conducted by varying the nature of the β-nitrostyrene, using precatalyst **12**, and acetylacetone as the nucleophile. These experiments are shown in Table 3, and they demonstrate the scope of this reaction, which remains unaffected by the electronic effects on the aromatic ring. However, a slight decrease in enantioselectivity was noticed for *meta*- and *para*-substituted benzene rings.

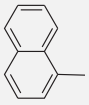
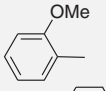
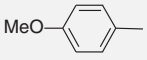
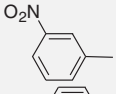
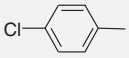
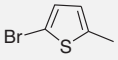
Table 2
Screening of solvent and nucleophile with precatalyst **12**

Entry	Solvent/nucleophile	Time (h)	Yield[a] (%)	er (*S*:*R*)[b]
1	Diethyl malonate/DCM	72	61	70:30
2	Diethyl malonate/diethyl ether	72	69	71:29
3	Diethyl malonate/MeCN	168	26	65:35
4	Malononitrile/toluene	6	57	50:50
5	Acetylacetone/toluene	6	63	12:88
6	Meldrum's acid/toluene	144	40	40:60[c]

[a] Yield of isolated product.
[b] Determined by HPLC (see Section 4).
[c] Determined after chemical correlation to diethylmalonate adduct.[1b]

Table 3
Scope for different β-nitrostyrene with precatalyst **12** and acetylacetone



Entry	Ar	Time (h)	Yield[a] (%)	er (*S*:*R*)[b]
1		6	63 **1b**	12:88
2		24	74 **1c**	10:90
3		24	78 **1d**	8:92
4		24	79 **1e**	17:83
5		24	67 **1f**	7:93
6		24	79 **1g**	17:83
7		24	65 **1h**	15:85
8		3	62 **1i**	13:87

[a] Yield of isolated product.
[b] Determined by HPLC (see Section 4).

3. Conclusion

In this study, we have demonstrated that efficient catalysts can be discovered by screening a library of 1,2-diamines prepared from 2-cyano azetidines.[11] These azetidines are easily accessed from commercially available β-amino alcohols, and they are convenient scaffolds for molecular diversity.[12] An interesting finding in this study is the reversal of the absolute configuration in the Michael adduct produced, when diethylmalonate or acetylacetone is used. To the best of our knowledge, this observation is unprecedented since Takemoto[1] first reported that his cyclohexylamine-derived catalyst induced the same absolute configuration in the Michael adduct with diethyl malonate and acetylacetone.[13] In our case, this inversion suggests that a completely different mode of activation is operating depending on the nature of these nucleophiles. As a matter of fact, experimental, theoretical, and mechanistical studies of this reaction have witnessed the emergence of two possible mechanisms: Takemoto initially proposed that (with malonate as a nucleophile), the ternary complex leading to the more favorable transition state involves binding of the nitrostyrene with the urea through H-bonding, and concommitent deprotonation of the enol form of the malonate by the proximate tertiary amine, as schematized in Figure 3A, with catalyst derived from **12**. This route was later confirmed by Liu et al.[14] by DFT calculations. The same year, Pápai[15] proposed an alternative route (with acetylacetone), involving an inverted scenario, that is, binding of the nitrostyrene to the ammonium resulting from the enolization of the 1,3-diketone, and binding of the enolate to the urea (Fig. 3B). This change in scenario, which is logical, considering the differences of pK_a values for these nucleophiles can of course induce a change in enantioselectivity if the prochiral face of the electrophile remains the same (which was not the case in Pápai's calculation). Thus, our experimental results provide indirect suspicion that these different mechanisms are indeed operating in our case and demonstrate that the nature of the 1,3-dicarbonyl nucleophile can have a profound influence on the enantioselectivity of the related reactions. It should be noted that the same direction of enantioselection is observed for acetylacetone (pK_a 9), and Meldrum' acid (pK_a 4.97) (Table 2, entry 6), which is also indicative of the same mechanism operating with these two acidic nucleophiles compared to diethylmalonate (pK_a 13).

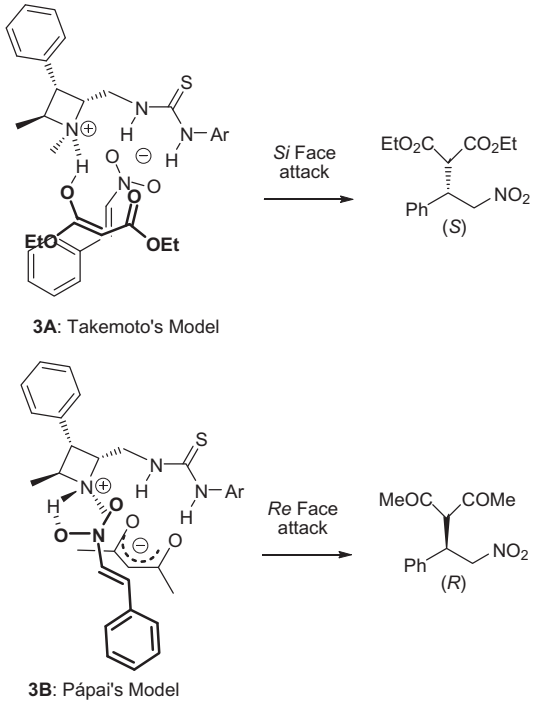


Figure 3. Takemoto (**3A**) and Pápai's (**3B**) models account for our observed reversal of enantioselectivity.

Work is currently in progress in our group in order to screen other members of this class of heterocycles in organocatalyzed reactions.

4. Experimental

4.1. General

Amino azetidines and pyrrolidines **11**–**21** were prepared following our previously reported procedures (see Section 1). All chemicals were used as received unless otherwise noted. Toluene was dried by a dehydrating system MB-SPS 800 (Mbraun). ^{1}H and ^{13}C NMR spectra were collected on a Bruker Avance 300 NMR spectrometer. High resolution mass spectra (HR-MS) were obtained on a Waters Micromass Q-Tof Micro instrument. Optical rotations were determined on a Perkin Elmer 341 polarimeter. Enantiomeric excesses were measured by HPLC at room temperature using Jasco PU-2089 pump equipped with UV detector and Chiralpak AD-H (4.6 mm × 250 mm), AD (4.6 mm × 250 mm), AS-H (4.6 mm × 250 mm).

4.2. Synthesis of catalysts

4.2.1. 1-((2*R*,3*S*,4*S*)-3-Phenyl-1,2,4-trimethylazetidinic)-3-(3,5-bis(trifluoromethyl)phenyl) thiourea 22

Under an argon atmosphere, to a solution of (2*R*,3*S*,4*S*)-2-(1-aminomethyl)-1,4-dimethyl-3-phenyl-azetidine **12** (160 mg, 0.84 mmol)

in dry toluene (9.5 mL) was added 3,5-bis-(trifluoromethyl)phenyl isothiocyanate (1.0 equiv, 228 mg). After the reaction mixture was stirred for 30 min at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (10:90, MeOH/CH_2Cl_2, R_f = 0.46) to give the desired thiourea **22** as pale yellow amorphous solid (169 mg, 41%); mp 84–86 °C. $[\alpha]_D^{25} = +12.7$ (*c* 1.2, CH_2Cl_2); FTIR ν_{max} 3250, 3097, 2927, 2852, 1594, 1472, 1373, 1274, 1167, 1123, 881, 840, 726, 702, 681 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.09 (m, 8H), 5.22 (br s, 2H), 4.12 (m, 1H), 3.28 (dd, *J* = 10.9 Hz, *J* = 6.8 Hz, 1H), 3.10 (dd, *J* = 10.9 Hz, *J* = 8.8 Hz, 1H), 2.97 (dd, *J* = 6.6 Hz, *J* = 10.7 Hz 1H), 2.87 (m, 1H), 2.36 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 150.2, 137.7, 132.6, 132.2, 131.8, 129.2, 128.9, 128.8, 127.8, 125.1, 122.0, 116.2, 58.5, 54.8, 52.6, 50.8, 32.9, 15.5; HRMS (ESI) *m/z* calcd for $C_{21}H_{21}F_6N_3S$ $[M+H]^+$: 462.1439, found: 462.1432.

4.2.2. 1-((2*R*,3*S*,4*R*,5*R*)-1,5-Dimethyl-2,4-diphenylpyrrolidinic)-3-(3,5-bis(trifluoromethyl)phenyl) thiourea 23

Under an argon atmosphere, to a solution of (2*R*,3*S*,4*R*,5*R*)-3-amino-1,5-dimethyl-2,4-diphenyl-pyrrolidine **20** (118 mg, 0.45 mmol) in toluene (6.6 mL) was added 3-(-bis(trifluoromethyl)phenyl isothiocyanate (1.0 equiv, 122 mg). After the reaction mixture was stirred for 30 min at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (30:70, AcOEt/pentane, R_f = 0.68) to give a viscous yellow oil **23** (133 mg, 61%). $[\alpha]_D^{25} = +68.5$ (*c* 0.2, CH_2Cl_2); FTIR ν_{max} 3300, 3031, 2932, 2780, 1525, 1380, 1171, 1125, 884, 846, 762, 699, 681 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.49–7.15 (m, 13H), 5.80 (br s, 1H), 5.23 (br s, 1H), 4.08 (br s, 1H), 3.73 (br s, 1H), 3.64 (m, 1H), 2.02 (s, 3H), 0.86 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 130.4, 128.7, 123.8, 119.1, 72.6, 65.1, 61.4, 51.8, 34.5, 15.1; HRMS (ESI) *m/z* calcd for $C_{27}H_{25}F_6N_3S$ $[M+H]^+$: 538.1752, found: 538.1732.

4.3. General procedure for enantioselective Michael addition of 1,3 dicarbonyl compounds to nitroolefins

4.3.1. (*R*)-3-(1-(3-Nitrophenyl)-2-nitroethyl)pentane-2,4-dione 1g

To a stirred solution of (2*R*,3*S*,4*S*)-2-(1-amino-methyl)-1,4-dimethyl-3-phenyl-azetidine **12** (0.1 equiv, 12 mg) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.1 equiv, 17 mg) in dry toluene (0.9 mL) were added after 30 min a solution of (*E*)-1-nitro-3-(2-nitro-vinyl)-benzene (123 mg, 0.6 mmol) in dry toluene (0.5 mL) and acetylacetone (2 equiv, 128 mg) under an argon atmosphere. Upon consumption of nitroolefin substrate in 24 h (monitored by TLC), the reaction mixture was concentrated and purified by preparative TLC (25:75, AcOEt/pentane, R_f = 0.20) to yield **1g** as an orange oil (147 mg, 79%). $[\alpha]_D^{25} = -21.7$ (*c* 1.3, CH_2Cl_2); FTIR ν_{max} 3069, 2963, 2919, 1716, 1548, 1527, 1349, 1250, 1171, 1142, 912, 738, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.17–8.13 (m, 2H), 7.60–7.51 (m, 2H), 4.77–4.65 (m, 2H), 4.47 (d, *J* = 12 Hz, 1H), 4.40 (m, 1H), 2.33 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 200.1, 148.5, 138.5, 134.5, 130.3, 123.5, 122.7, 77.4, 69.9, 42.2, 30.5, 30.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2O_6$ $[M+Na]^+$: 317.0750, found: 317.075. HPLC [CHIRALPAK®AS-H, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 215 nm, retention times: (minor) 31.0 min, (major) 50.2 min].

4.3.2. (*R*)-3-(1-(5-Bromothienyl)-2-nitroethyl)pentane-2,4-dione 1i

To a stirred solution of (2*R*,3*S*,4*S*)-2-(1-amino-methyl)-1,4-dimethyl-3-phenyl-azetidine **12** (0.1 equiv, 12 mg) and 3,5-bis-(trifluoromethyl)phenyl isothiocyanate (0.1 equiv, 17 mg) in dry toluene (0.9 mL) were added after 30 min a solution of (*E*)-5-bromo-2-(2-nitro-vinyl)-thiophene (150 mg, 0.6 mmol) in dry toluene (0.5 mL) and acetylacetone (2 equiv, 128 mg) under an argon atmosphere. Upon consumption of the nitroolefin substrate after 6 h (monitored by TLC), the reaction mixture was concentrated and purified by preparative TLC (25:75, AcOEt/pentane, R_f = 0.10) to yield a brown powder **1i** (132 mg, 62%). mp 67 °C; $[\alpha]_D^{25} = -30.0$ (*c* 0.2, CH_2Cl_2); FTIR ν_{max} 3080, 2922, 1726, 1547, 1430, 1361, 1251, 1142, 963, 795 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.89–6.87 (d, *J* = 4 Hz, 1H), 6.67–6.65 (d, *J* = 4 Hz, 1H), 4.65–4.62 (m, 2H), 4.41 (m, 1H), 4.34 (d, *J* = 10 Hz, 1H), 2.30 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 200.4, 140.1, 130.1, 127.6, 112.6, 78.0, 70.4, 38.5, 30.6, 29.9; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}BrNO_4S$ $[M+Na]^+$: 355.9568, found: 355.9573. HPLC [CHIRALPAK® AD, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 244 nm, retention times: (minor) 10.2 min, (major) 12.8 min].

4.3.3. (*S*)-Ethyl-2-(carboxyethyl)-4-nitro-3-phenylbutyrate 1a

Colorless needles.[1a] ^1H NMR (300 MHz, CDCl3) δ 7.42–7.10 (m, 5H), 4.93 (dd, *J* = 4.6, 13.1 Hz, 1H), 4.86 (dd, *J* = 9.2, 13.1 Hz, 1H), 4.33–4.15 (m, 3H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.82 (d, *J* = 9.5 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); HPLC [CHIRALPAK® AD-H, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 213 nm, retention times: (major) 12.6 min, (minor) 34.8 min].

4.3.4. (*R*)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione 1b

White solid;[6a] mp 114–116 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.18 (m, 5H), 4.58–4.67 (m, 2H), 4.36–4.40 (d, *J* = 10.8 Hz, 1H), 4.21–4.28 (m, 1H), 2.30 (s, 3H), 1.94 (s, 3H); HPLC [CHIRALPAK® AS-H, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 215 nm, retention times: (minor) 15.0 min, (major) 24.9 min].

4.3.5. (*R*)-3-(1-Naphthalen-1-yl)-2-nitroethyl)pentane-2,4-dione 1c

Yellow viscous oil.[4a] ^1H NMR (300 MHz, $CDCl_3$,) δ 8.18–7.27 (m, 7H), 5.20 (m, 1H), 4.81 (dd, *J* = 12.0, *J* = 6.6 Hz, 1H), 4.75–4.68 (m, 2H), 2.31 (s, 3H), 1.86 (s, 3H); HPLC [CHIRALPAK® AS-H, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 215 nm, retention times: (minor) 17.1 min, (major) 23.4 min].

4.3.6. (*R*)-3-(1-(2-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione 1d

Orange viscous oil.[6d] ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.25 (m, 1H), 7.09–7.07 (m, 1H), 6.88–6.92 (m, 2H), 4.82–4.75 (m, 1H), 4.61–4.49 (m, 3H), 3.89 (s, 3H)), 2.28 (s, 3H), 1.94 (s, 3H); HPLC [CHIRALPAK® AS-H, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 215 nm, retention times: (minor) 14.7 min, (major) 15.0 min].

4.3.7. (*R*)-3-(1-(4-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione 1e

Pale yellow solid;[4a] mp 117 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.61–4.57 (m, 2H), 4.35 (d, *J* = 11.0 Hz, 1H), 4.24–4.18 (m, 1H), 3.78 (s, 3H), 2.29 (s, 3H; CH3), 1.95 (s, 3H); HPLC [CHIRALPAK® AD, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 215 nm, retention times: (minor) 13.6 min, (major) 19.9 min].

4.3.8. (*R*)-3-(1-(2-Nitrophenyl)-2-nitroethyl)pentane-2,4-dione 1f

Pale yellow solid;[6c] mp 112–114 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.0, *J* = 1.4 Hz, 1H), 7.58–7.36 (m, 3H), 4.97 (dd, *J* = 13.3, *J* = 7.1 Hz, 1H), 4.84 (dd, *J* = 13.3, *J* = 3.7 Hz, 1H), 4.73 (ddd, *J* = 8.7, *J* = 7.2, *J* = 3.7 Hz, 1H), 4.67 (d, *J* = 8.7 Hz, 1H), 2.31 (s, 3H), 2.13 (s, 3H); HPLC [CHIRALPAK® AS-H, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 215 nm, retention times: (minor) 27.3 min, (major) 28.4 min].

4.3.9. (*R*)-3-(1-(4-Chlorophenyl)-2-nitroethyl)pentane-2,4-dione 1h

Pale yellow solid;[4a] mp 121 °C. ^{1}H NMR (300 MHz, CDCl3) δ 7.30 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 4.60 (d, J = 5.7 Hz, 2H), 4.32 (d, J = 10.8 Hz, 1H), 4.26–4.18 (m, 1H), 2.29 (s, 3H), 1.97 (s, 3H); HPLC [CHIRALPAK® AD, 2-propanol/heptane = 20/80, 0.8 mL/min, λ = 215 nm, retention times: (minor) 12.9 min, (major) 30.6 min].

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References

1. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
2. Takemoto, Y.; Miyabe, H. *Chimia* **2007**, *61*, 269–275.
3. Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171.
4. (a) Gao, P.; Wang, C.; Wu, Y.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2008**, 4563–4566; (b) Pu, X.; Li, P.; Peng, F.; Li, X.; Zhang, H.; Shao, Z. *Eur. J. Org. Chem.* **2009**, 4622–4626.
5. (a) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367–6370; (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969; (c) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929–931; (d) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932–4933; (e) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049.
6. (a) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713–4716; (b) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455; (c) Malerich, J.; Hagihara, K.; Rawal, H. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417; (d) Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. *Chem. Commun.* **2008**, 1431–1433; (e) Peng, F.-Z.; Shao, Z.-H.; Fan, B.-M.; Song, H.; Li, G.-P.; Zhang, H.-B. *J. Org. Chem.* **2008**, *73*, 5202–5205; (f) Jiang, X.; Zhang, Y.; Liu, X.; Zhang, G.; Lai, L.; Wu, L.; Zhang, J.; Wang, R. *J. Org. Chem.* **2009**, *74*, 5562–5567; (g) Almasi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nàjera, C. *J. Org. Chem.* **2009**, *74*, 6163–6168; (h) McGarraugh, P. G.; Brenner, S. E. *Tetrahedron* **2009**, *65*, 449–455; (i) Thai, K.; Gravel, M. *Tetrahedron: Asymmetry* **2010**, *21*, 751–755.
7. For selected reviews on this topic, see: (a) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743; (c) Dondoni, A.; Massy, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660; (d) Zhang, Z. G.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.
8. Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297–302.
9. Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Eur. J. Org. Chem.* **2004**, 3893–3897.
10. Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861–5864.
11. For other applications of azetidines as ligands in enantioselective catalysis, see: Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem.* **2004**, *1*, 133–148. and references cited therein.
12. Couty, F.; Evano, G. *Synlett* **2009**, 3053–3064.
13. In the initial report of Takemoto (Ref. 1b), the absolute configuration of the acetylacetone adduct on β-nitrostyrene was not determined. It was later on determined by Wang et al. (Ref. 6a) to be (*R*) by chemical correlation to (*R*)-α-phenyl-β-alanine.
14. Zhu, R.; Zhang, D.; Wu, J.; Liu, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1611–1616.
15. Hamza, A.; Schubert, G.; Soos, T.; Pàpai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.