Optically Active α-Phenylethylamine as Efficient Organocatalyst in the Solvent-free Reactions Between 2,3-Butanedione and Conjugated Nitroolefins

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ABSTRACT (*R*)-(+) and (*S*)-(−)-1-phenylethylamine have been shown to promote highly diastereoselective and complementary enantioselective formal [3 + 2]carbocyclization reactions between 2, 3-butanedione and conjugated nitroalkenes with formation of enantiomerically rich 2-hydroxy-3-nitrocyclopentanone derivatives. The reactions were carried out both in solvent and under solvent-free conditions. The absolute configurations of the products were assigned by X-ray and circular dichroism spectra analyses. *Chirality 00:000–000, 2012.*

KEY WORDS: primary amine organocatalysis; five-membered ring β-nitro-α-ketols; fully conjugated nitrocyclopentenone; solvent-free reactions

INTRODUCTION

The interest in asymmetric organocatalysis[1–12] has rapidly increased since the pioneering works of List, Barbas, and their coworkers in 2001.[13,14] The reactions between carbonyl compounds and nitroolefins have been among the most studied reactions.[15–28] Conjugated nitroalkenes are highly reactive and provide easy access to interesting intermediates due to the synthetic versatility of the nitro group.[29–35] However, while several examples are reported on organocatalyzed conjugated addition of 1,3-dicarbonyl compounds to nitroalkenes,[36–44] only a few cases can be found in the literature regarding the same reaction with 1,2-dicarbonyl compounds,[7,45,46] namely with 1,2-cyclohexanedione[45,46] and α-ketoanilides.[7]

Several years ago,[47–49] (*S*)-(−)-1-phenylethylimine **2** derived from 2,3-butanedione **1** and (*S*)-(−)-1-phenylethylamine (Scheme 1) has been found to react with cyclic and acyclic nitroolefins **3a–d**, both in solvent and under solvent-free conditions, to give products of carbocyclization reactions (−)-**4a–d**. The imine intermediates (−)-**4b–d** were converted into the corresponding α-ketols (+)-**5b–d**, either by acid hydrolysis under mild conditions or by oxidation of the C=N bond followed by acidic treatment. This reaction sequence was highly diastereoselective and enantioselective, as the final ketols were single isomers.[49] Acid-catalyzed hydrolysis of (−)-**4a** did not proceed, and the pentalenone derivative (+)-**5a** had to be prepared by a different route.[50]

MATERIAL AND METHODS

General

Infrared (IR) spectra were recorded on a Jasco FT/IR 200 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were run on a Jeol EX-400 (400 MHz) spectrometer (100.1 MHz for carbon) and on a Jeol 270 spectrometer (67.5 MHz for carbon) by using deuteriochloroform as the solvent and tetramethylsilane as an internal standard, unless otherwise stated. Chemical shifts are expressed in parts per million (δ). Coupling constants are given in Hz. Signal attribution of products was made by heteronuclear single-quantum COSY (COrrelation SpectroscopY), and the relative configuration of the same compounds was determined by difference nuclear Overhauser effect experiments. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter, at 25 °C. circular dichroism (CD) spectra were recorded on a Jasco J-700A spectropolarimeter (0.1 cm cell) at 20 °C. Optical rotations are quoted in units of 10^{-1} deg cm^2 g^{-1}. High performance liquid chromatograms (HPLC) were obtained on a Hewlett-Packard series 1100 instrument, Knauer UV detector, from a chiral column Lux 5 μ Cellulose-2 with a Cellulose tris(3-chloro-4-methylphenylcarbammate) chiral stationary phase, eluent: *n*-hexane/isopropanol 75:25, detector UV 220 nm. Chiral High Resolution gas liquid chromatography analyses were run on a Shimadzu GC-14B instrument, the capillary columns being Chiraldex™ type G-TA, β-cyclodextrin (40 m × 0.25 mm) (carrier gas Helium, 180 KPa, split 1:100) at 150° isotherm; thin-layer chromatographies were performed on Polygram® Sil G/UV254 silica gel precoated plastic sheets (eluent: light petroleum–ethyl acetate). Flash chromatography[51] was run on silica gel, 230−400 mesh ASTM (Kieselgel 60, Merck), using light petroleum 40–70 °C/ethyl acetate mixtures as the eluent. Mass spectrometries (MS) were performed on an ion trap Finnigan GCQ (70 eV) spectrometer. Elemental analyses were determined on a Carlo Erba 1106 instrument at the Department of Chemical Sciences and Technologies of the University of Udine, Italy. 2,3-Butanedione, β-nitrostyrene, (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine, (*S*)-(−)-5-(2-pyrrolidinyl)-1*H*-tetrazole, (*S*)-(−)-α,α-diphenylprolinol trimethylsilyl ether, and L-proline were purchased from Sigma Aldrich. 1-Nitrocyclopentene,[52] 1-nitrocyclohexene,[52] 2-nitro-1-phenylpropene,[53] and 3-bromo-β-nitrostyrene[54] were prepared by literature procedures.

Syntheses

General procedure for the organocatalyzed reactions. To a mixture of freshly distilled 2,3-butanedione (1.0 mmol) and the appropriate nitroolefin (1.0 mmol) in isopropanol (10 ml) the catalyst (0.2 mmol) was added. When an acid was used in conjunction with the organocatalyst, they were added to the reactants as a 1:1 preformed mixture. The reaction mixture was kept under stirring at room temperature. When the reaction did not go to completion, it was stopped when the NMR analysis revealed a constant ratio between a signal of the nitroolefin and the nitromethine signal of the major product whose ratio was evaluated using an internal standard. The solvent was eliminated and the reaction

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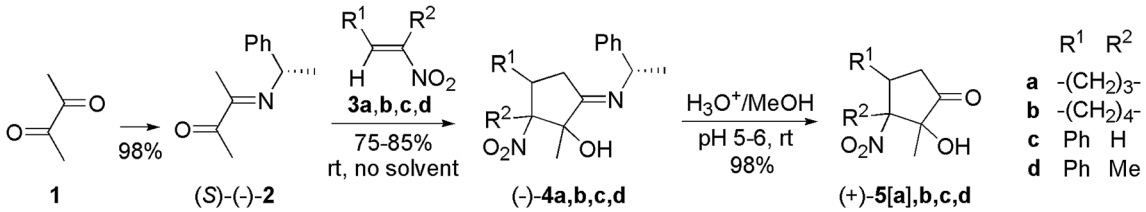


1 (S)-(-)-2 (-)-4a,b,c,d (+)-5[a],b,c,d

Scheme 1. Formation of optically active α-ketols from (*S*)-(−)-1-phenylethylimine **2** and nitroolefins **3a–d**.

products were separated on column chromatography, using light petroleum–ethyl acetate in 5:1 ratio as the eluent.

(1*R*,3*aR*,6*aR*)-(+)-1-*Hydroxy*-1-*methyl*-6*a*-*nitrohexahydro*-1*H*-*pentalen*-2-*one* [(+)-*5a*].[50] $[\alpha]_D^{25}$ = +32 (c 0.25, CH_3OH), 90% e.e.; CD (0.0082 M, CH_3OH), $\Delta\varepsilon_{308}$ = +0.974; $\Delta\varepsilon_{265}$ = −0.319; high-resolution gas chromatography (HRGC) (β-cyclodextrin, 150 °C): (+)-**5a**, 30.4 min, (−)-**5a**, 31.1 min.

(1*S*,3*aR*,6*aR*)-(+)-1-*Hydroxy*-1-*methyl*-6*a*-*nitrohexahydro*-1*H*-*pentalen*-2-*one* [(+)-*6a*].[50] $[\alpha]_D^{25}$ = +23.5 (c 0.8, CH_3OH), 89% e.e. CD (0.0078 M, CH_3OH), $\Delta\varepsilon_{305}$ = +1.01; $\Delta\varepsilon_{252}$ = −0.48; HRGC (β-cyclodextrin, 150 °C): (−)-**6a**, 45.4 min, (+)-**6a**, 46.7 min.

(1*R*,3*aR*,7*aR*)-(+)-1-*Hydroxy*-1-*methyl*-7*a*-*nitrooctahydro*-2*H*-*inden*-2-*one* [(+)-*5b*].[48] $[\alpha]_D^{25}$ = +114 (c 0.33, CH_3OH), 92% e.e. CD (0.0155 M, CH_3OH), $\Delta\varepsilon_{310}$ = +2.39; $\Delta\varepsilon_{274}$ = −0.41. HRGC (β-cyclodextrin, 150 °C): (+)-**5b**, 96.7 min, (−)-**5b**, 100.7 min.

(1*S*,3*aR*,7*aR*)-(+)-1-*Hydroxy*-1-*methyl*-7*a*-*nitrooctahydro*-2*H*-*inden*-2-*one* [(+)-*6b*].[48] $[\alpha]_D^{25}$ = +60 (c 0.18, CH_3OH), >99% e.e. CD (0.0084 M, CH_3OH), $\Delta\varepsilon_{306}$ = +2.30; $\Delta\varepsilon_{272}$ = −0.40. HRGC (β-cyclodextrin, 150 °C): (−)-**6b**, 50.7 min, (+)-**6b**, 52.3 min.

(2*R*,3*R*,4*R*)-(+)-2-*Hydroxy*-2-*methyl*-3-*nitro*-4-*phenylcyclopentanone* [(+)-*5c*].[47] ^{13}C NMR (67.8 MHz, CD_3OD) δ, ppm: 210.8 (s, CO), 140.5 (s, Ph), 129.9 (2d, Ph), 128.6 (2d, Ph), 128.5 (d, Ph), 95.8 (d, C-3), 77.9 (s, C-2), 43.6 (t, C-5), 42.2 (d, C-4), 20.2 (q, CH_3); $[\alpha]_D^{25}$ = +133.6 (c, 0.1 $CHCl_3$), 99% e.e. [lit.[49] $[\alpha]_D^{25}$ = +134.0 (c 0.1, $CHCl_3$), 99% e.e.]; UV (1.45×10^{-4} M, CH_3OH), nm, 212.0 (ε, 8090), 224.0 (ε, 2772); CD (0.006 M, CH_3OH), $\Delta\varepsilon_{312}$ = +2.2; $\Delta\varepsilon_{276}$ = −1.2; $\Delta\varepsilon_{232}$ = +1.8).

High performance liquid chromatograms (flow rate, 1 ml/min, pressure 34 bar): (+)-**5c**, 7.31 min, (−)-**5c**, 7.68 min.

With the use of (*R*)-(+)-1-phenylethylamine as the catalyst (20 mol%), ketol (−)-**5c** was isolated, $[\alpha]_D^{25}$ = −134.0 (c 0.1, $CHCl_3$), 99% e.e. CD (0.01 M, CH_3OH), $\Delta\varepsilon_{312}$ = −2.2; $\Delta\varepsilon_{276}$ = +1.2; $\Delta\varepsilon_{232}$ = −1.8).

With the use of (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/trifluoroacetic acid (2PMP/TFA) as the catalyst (20 mol%), ketol (+)-**5c** was isolated, $[\alpha]_D^{25}$ = +91.6 (c, 0.1 $CHCl_3$), 68% e.e.

(2*S*,3*R*,4*R*)-(+)-2-*Hydroxy*-2-*methyl*-4-*phenyl*-3-*nitrocyclopentanone* [(+)-*6c*]. Compound (+)-**6c** was isolated from the reaction catalyzed by (*S*)-(+)-1-2PMP/TFA as a white crystalline solid, m.p. 142–143 °C, from *n*-heptane-ethyl acetate; R_f: 0.31, eluent: light petroleum–ethyl acetate 3:1; IR (nujol) 3506 (OH), 1755 (CO), 1600, 1590, 698, 675 cm^{-1} (Ph), 1546, 1365 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.35 (m, 5H, Ph), 5.20 (d, J = 10.1 Hz, 1H, H-3), 4.03 (dt, $J_1 = J_2$ = 11.3 Hz, J_3 = 10.1 Hz, 1H, H-4), 3.16 (dd, J_1 = 9.9 Hz, J_2 = 19.8 Hz, 1H, H-5 *trans* to Ph), 3.05 (1H, bs, OH), 2.67 (dd, J_1 = 11.3 Hz, J_2 = 19.8 Hz, 1H, H-5 *cis* to Ph), 1.37 (s, 1H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 210.4 (s, CO), 137.5 (s, Ph), 129.3 (2d, Ph), 128.3 (d, Ph), 127.2 (2d, Ph), 96.3 (d, C-3), 80.4 (s, C-2), 41.4 (t, C-5), 39.8 (d, C-4), 19.7 (q, CH_3). MS (70 eV): 235 ($M^{+\bullet}$, <1), 187 (5, M–OH–NO), 160 (10), 159 (14, 187–CO), 147 (72), 145 (35), 131 (46), 129 (100), 117 (42), 103 (14), 91 (15), 77 (13); Anal. calc. for $C_{12}H_{13}NO_4$: C, 61.27, H, 5.57, N, 5.95. Found: C, 60.44, H, 5.41, N, 5.53; $[\alpha]_D^{25}$ = +22.2 (c, 0.22 $CHCl_3$), 81% e.e.; HPLC (flow rate, 1 ml/min, pressure 30 bar): (+)-**6c**, 8.59 min, (−)-**6c**, 9.22 min.

(2*S*,3*S*,4*R*)-(−)-2-*Hydroxy*-2-*methyl*-4-*phenyl*-3-*nitrocyclopentanone* [(−)-*7c*]. Compound (−)-**7c** was isolated from the reaction catalyzed by 2PMP/TFA as a pale yellow solid, m.p. 127–128 °C, from *n*-heptane-ethyl acetate; R_f: 0.12, eluent: light petroleum–ethyl acetate 3:1; IR (nujol) 3414 (OH), 1754 (CO), 1601, 1590, 700, 670 (Ph), 1552, 1365 cm^{-1} (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.30 (m, 5H, Ph), 5.18 (d, J = 5.7 Hz, 1H, C-3), 3.97 (dt, $J_1 = J_2$ = 11.3 Hz, J_3 = 5.7 Hz, 1H, C-4), 3.22 (dd, J_1 = 19.6 Hz, J_2 = 10.6 Hz, 1H, H-5 *cis* to Ph), 3.09 (bs, 1H, OH), 2.92 (dd, J_1 = 19.6 Hz, J_2 = 10.0 Hz, 1H, H-5 *trans* to Ph), 1.53 (s, 1H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 212.5 (s, CO), 134.4 (s, Ph), 129.2 (2d, Ph), 128.5 (d, Ph), 127.1 (2d, Ph), 96.0 (d, C-3), 80.5 (s, C-2), 40.7 (d, C-4), 35.2 (t, C-5), 22.6 (q, CH_3). MS (70 eV): 235 ($M^{+\bullet}$, <1), 187 (5, M–OH–NO), 160 (11), 159 (12, 187–CO), 147 (71), 145 (35), 131 (46), 129 (100), 117 (42), 103 (14), 91 (15), 77 (13); Anal. calc. for $C_{12}H_{13}NO_4$: C, 61.27, H, 5.57, N, 5.95. Found: C, 60.99, H, 5.52, N, 5.67. $[\alpha]_D^{25}$ = −45.0 (c, 0.04 $CHCl_3$), 71% e.e.; HPLC (flow rate, 1 ml/min, pressure 34 bar): (+)-**7c**, 19.40 min, (−)-**7c**, 20.85 min.

(2*R*,3*R*,4*R*)-(+)-2-*Hydroxy*-2,3-*dimethyl*-3-*nitro*-4-*phenylcyclopentanone* [(+)-*5d*].[47] R_f 0.75 (eluent: ethyl acetate-light petroleum gradient from 15:85 to 20:80): M.p. 172–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.35 (m, 3H, Ph), 7.17 (m, 2H, Ph), 3.88 (dd, J_1 = 11.0 Hz, J_2 = 9.9 Hz, 1H, H-4), 3.11, 2.96 (part AB of an ABX system, J_{AB} = 19.2 Hz, J_{AX} = 11.0 Hz, J_{BX} = 9.9 Hz, 2H, 2 H-5), 1.60 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 209.4 s, 134.2 (s), 129.0 (2d), 128.6 (d), 128.2 (2d), 99.2 (s), 79.8 (s), 48.6 (d), 38.0 (t), 15.9 (q), 14.0 (q); $[\alpha]_D^{25}$ = +25 (c 0.1, $CHCl_3$), 71% e.e.; CD (c 0.004, $CHCl_3$): ε_{304} +1.657; ε_{273} −0.319; ε_{248} +0.756. HRGC (β-cyclodextrin, 150 °C): (+)-**5d**, 249.1 min, (−)-**5d**, 254.8 min.

(2*S*,3*R*,4*R*)-(+)-2-*Hydroxy*-2,3-*dimethyl*-3-*nitro*-4-*phenylcyclopentanone* [(+)-*6d*]. R_f 0.25 (eluent: ethyl acetate-light petroleum gradient 15:85 to 20:80); M.p. 149 °C; ^{1}H NMR δ, ppm: 7.35 (m, 3H, Ph), 7.17 (m, 2H, Ph), 3.57 (t, J = 10.4 Hz, 1H, H-4), 3.11 (dd, J_1 = 10.4 Hz, J_2 = 19.6 Hz, 1H, H-5 *cis* to Ph), 2.91 (dd, J_1 = 10.4 Hz, J_2 = 19.6 Hz, 1H, H-5 *trans* to Ph), 1.63 (s, 3H, CH_3), 1.41 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 209.4 s, 134.2 (s), 129.0 (2d), 128.6 (d), 128.2 (2d), 99.2 (s), 79.8 (s), 48.6 (d), 38.0 (t), 15.9 (q), 14.0 (q); $[\alpha]_D^{25}$ = −43.4 (c 0.65, $CHCl_3$), $[\alpha]_D^{25}$ = −59.4 (c 0.325, CH_3OH), 89% e.e.; CD (c 0.013, $CHCl_3$): ε_{297} +2.370; ε_{257} −2.266; ε_{233} −1.139; HRGC (β-cyclodextrin, 150 °C): (+)-**6d**, 181.8 min, (−)-**6d**, 185.0 min.

(2*R*,3*R*,4*R*)-(+)-4-(3-*bromophenyl*)-2-*hydroxy*-2-*methyl*-3-*nitrocyclopentanone* [(+)-*8*)]. Ketol (+)-**8** was isolated from the reaction catalyzed by (*S*)-(−)-1-phenylethylamine as a white crystalline solid, m.p. 131–132 °C, from *n*-heptane–ethyl acetate; R_f: 0.57, eluent: light petroleum–ethyl acetate 6:1; IR (nujol) 3428 (OH), 1595, 651 (Ar), 1759 (CO), 1557, 1382, 1364, 1356 cm^{-1} (NO_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.45 (m, 2H, *o*- to Br ArH), δ 7.25 (m, 2H, ArH), 4.85 (d, J = 9.5 Hz, 1H, H-3), 4.33 (dt, $J_1 = J_2$ = 11.4 Hz, J_3 = 9.5 Hz, 1H, H-4), 3.17 (dd, J_1 = 9.5 Hz, J_2 = 19.4 Hz, 1H, H-5 *trans* to Ph), 2.60 (dd, J_1 = 11.4 Hz, J_2 = 19.4 Hz, 1H, H-5 *cis* to Ph), 2.53 (bs, 1H, OH), 1.57 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 207.9 (s, CO), 140.1 (s), 131.5 (d, Ar), 130.8 (d, Ar), 130.2 (d, Ar), 126.7 (d, Ar), 123.3 (s, Ar), 94.3 (d, C-3), 41.5 (d, C-4), 40.5 (t, C-5), 21.2 (q, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ, ppm: 210.1 (s, CO), 143.3 (s), 131.9 (d, Ar), 131.7 (d, Ar), 131.6 (d, Ar), 127.7 (d, Ar), 123.7 (s, Ar), 95.3 (d, C-3), 77.8 (s, C-2), 43.5 (d, C-4), 42.0 (t, C-5), 20.0 (q, CH_3); MS (70 eV): 285, 283 (0.5, M –30), 227, 225 (100), 211, 209 (30), 197, 195 (9), 145 (60), 128 (35). Anal. calc. for $C_{12}H_{12}NO_4Br$: C, 45.88, H, 3.85, N, 4.46. Found: C, 46.46, H, 3.91, N, 4.33; $[\alpha]_D^{25}$ = +103.3 (c, 0.18, $CHCl_3$), 90% e.e.; CD (0.0025 M, CH_3OH), ε_{310} = +2.6; ε_{277} = −1.8; ε_{232} = +1.6. HPLC (flow rate, 1 ml/min, pressure 29 bar): (+)-**8**, 8.20 min, (−)-**8**, 8.94 min.

(*R*)-(−)-2-*Methyl*-3-*nitro*-4-*phenylcyclopent*-2-*en*-1-*one* [(−)-*9*)] The crude mixture of ketols obtained from the reaction between diacetyl and β-nitrostyrene, catalyzed by (*S*)-(−)-1-phenylethylamine, was acetylated in chloroform with acetic anhydride (25 eq.), in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA), at 0 °C. The mixture was stirred at room temperature for 24 h. The reaction mixture was washed

five times with a 5% solution of sodium bicarbonate and then with water and dried on anhydrous sodium sulfate. After elimination of the solvent, the resulting semisolid material was purified on column chromatography to give (*2R,3R,4R*)-*2-acetoxy-2-methyl-3-nitro-4-phenylcyclopentanone*, as an oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ, ppm: 7.36 (m, 3H, Ph), 7.25 (m, 2H, Ph), 4.97 (d, J = 11.0 Hz, 1H, H-3), 4.56 (ddd, J_1 = 11.0 Hz, J_2 = 8.8 Hz, J_3 = 12.1 Hz, 1H, H-4), 3.33 (dd, J_1 = 8.8 Hz, J_2 = 19.0 Hz, 1H, H-5 *trans* to Ph), 2.53 (dd, J_1 = 12.1 Hz, J_2 = 19.0 Hz, 1H, H-5 *cis* to Ph), 2.08 (s, 3H, CH_3CO), 1.67 (s, 1H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ, ppm: 205.7 (s, CO), 170.2 (s, COO), 138.2 (s, Ph), 129.2 (2d, Ph), 128.1 (d, Ph), 127.1 (2d, Ph), 95.8 (d, C-3), 78.9 (s), 42.8 (t, C-5), 42.6 (d, C-4), 22.9 (q, CH_3CO), 21.3 (q, CH_3). The acetylated ketol thus formed was dissolved in chloroform, and a catalytic amount of 4-dimethylaminopyridine (DMAP) was added. After 8 h, the α,β-unsaturated ketone (–)-**9** was formed in quantitative yield and purified on column chromatography. It solidified on standing, m.p. 91–92 °C, R_f: 0.67, eluent: light petroleum–ethyl acetate 3:1; IR (neat) 3065, 3031, 1602, 733, 700 (Ph), 1727 (CO), 1556 (CC), 1525, 1356 cm^{-1} (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.30 (m, 3H, Ph), 7.15 (bd, 2H, Ph), 4.62 (d quintet, $J_{4,5}$ = 7.3 Hz, $J_{4,5}$ = $J_{4,Me}$ = 2.2 Hz, 1H, H-4), 3.20 (dd, J_1 = 19.4 Hz, J_2 = 7.3 Hz, 1H, H-5), 2.66 (dd, J_1 = 19.4 Hz, J_2 = 2.2 Hz, 1H, H-5), 2.20 (d, J = 2.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 204.7 (s, CO), 169.7 (s, C-3), 140.2 (s, C-2), 138.1 (s), 129.3 (2d, Ph), 128.0 (d, Ph), 126.9 (2d, Ph), 45.2 (t, C-5), 43.2 (d, C-4), 9.4 (q, CH_3); MS: 217 (36, $M^{+\bullet}$), 187 (100, M–NO), 145 (18), 141 (25), 128 (62). Anal. calc. for $C_{12}H_{11}NO_3$: C, 66.35, H, 5.10, N, 6.45. Found: C, 66.20, H, 5.27, N, 6.52. $[\alpha]_D^{25}$ = –4.64 (c 0.54, CH_3OH), 90% e.e.; UV (2.5×10^{-4} M, CH_3OH) nm, 214.0 (ε 7408), 257.0 (ε 5608); CD (2.5×10^{-4} M, CH_3OH), ε_{354} = +2.3; ε_{261} = –5.8; ε_{228} = +2.4. HPLC (flow rate, 1 ml/min, pressure 29 bar): (+)-**9**, 11.59 min, (–)-**9**, 12.55 min.

(*R*)-(–)-4-(3-*Bromophenyl*)-*2-methyl-3-nitrocyclopent-2-en-1-one* [(–)-*10*]. The same procedure applied on compound (+)-**8** gave the α,β-unsaturated ketone (–)-**10**, R_f: 0.68, eluent: light petroleum–ethyl acetate 3:1; IR (neat) 3065, 3031, 1602, 733, 700 (Ph), 1727 (CO), 1556 (CC), 1525, 1356 cm^{-1} (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.42 (bd, J = 8.4 Hz, 1H, ArH), 7.30 (t, J = 1.6 Hz, 1H, ArH), 7.20 (t, J = 7.7 Hz, 1H, ArH), 7.09 (bd, J = 7.7 Hz, 1H, ArH), 4.52 (d quintet, $J_{4,5}$ = 7.7 Hz, $J_{4,5}$ = $J_{4,Me}$ = 2.2 Hz, 1H, H-4), 3.20 (dd, J_1 = 19.4 Hz, J_2 = 7.7 Hz, 1H, H-5), 2.63 (dd, J_1 = 19.4 Hz, J_2 = 2.2 Hz, 1H, H-5), 2.20 (d, J = 2.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 204.0 (s, CO), 168.8 (s, C-3), 141.0 (s, C-2), 140.5 (s), 131.3 (d, Ar), 130.8 (d, Ar), 130.0 (d, Ar), 125.5 (s, Ar), 123.3 (d, ArH), 44.9 (t, C-5), 42.7 (d, C-4), 9.6 (q, CH_3). MS: 297, 295 (48, $M^{+\bullet}$), 267, 265 (92, M–NO), 209, 207 (28), 186 (30), 158 (28), 141 (30), 128 (100). $[\alpha]_D^{25}$ = –20 (c 0.06, CH_3OH), 72% e.e. CD (2.0×10^{-4} M, CH_3OH), ε_{354} = +3.6; ε_{267} = –11.6; ε_{226} = +3.3). HPLC (flow rate, 1 ml/min, pressure 37 bar): (+)-**10**, 9.82 min, (–)-**10**, 10.73 min.

Crystal Structure Determinations

Diffraction data for the structures reported were collected at room temperature on a Nonius DIP-1030H system (Mo-Kα radiation, λ = 0.71073 Å). All the structures were solved by direct methods and refined by the full-matrix least-squares method based on F^2 with all observed reflections.[55] The calculations were performed using the WinGX System, Ver 1.80.05.[56]

Crystal data for compound 5c. $C_{12}H_{13}NO_4$, fw = 235.23 g mol^{-1}, orthorhombic, $P\ 2_12_12_1$, a = 5.558(2), b = 13.267(4), c = 15.786(4) Å, V = 1164.0(6) Å^3, Z = 4, D_{calcd} = 1.342 g/cm^3, μ(Mo-Kα) = 0.102 mm^{-1}, F(000) = 496, = 23.25°. Final $R1$ = 0.0304, $wR2$ = 0.0629, GOF = 0.859 for 156 parameters and 1606 unique reflections, of which 1075 with $I > 2\sigma(I)$, residuals in F map 0.112, –0.119 e. Å^{-3}.

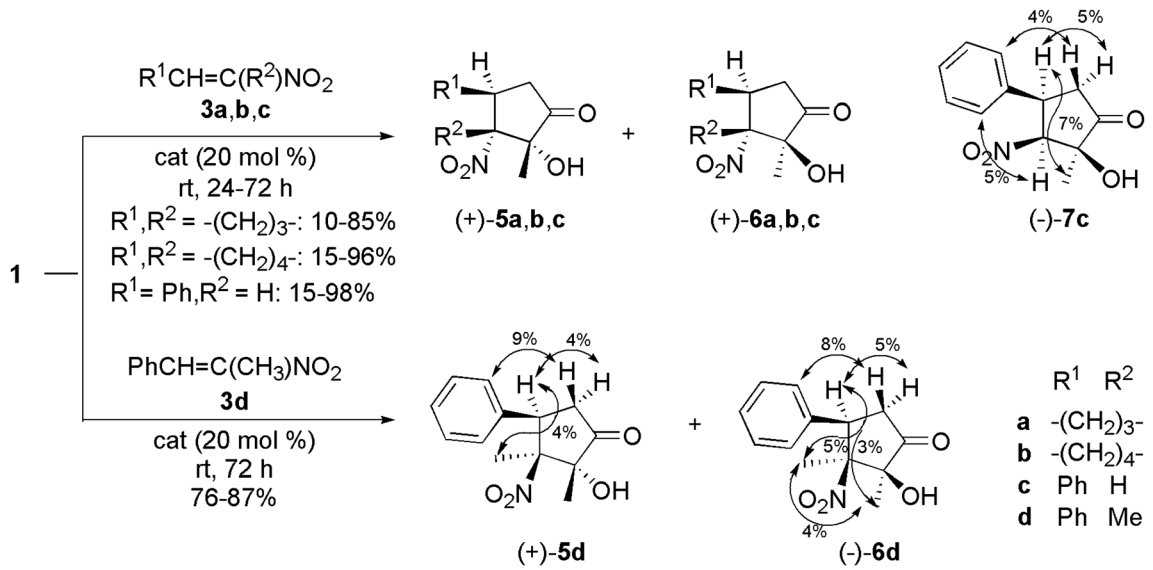
Crystal data for compound 6c. $C_{12}H_{13}NO_4$, fw = 235.23 g mol^{-1}, orthorhombic, $P\ 2_12_12_1$, a = 5.380(2), b = 13.220(3), c = 16.388(3) Å, V = 1165.6(6) Å^3, Z = 4, D_{calcd} = 1.341 g/cm^3, μ(Mo-Kα) = 0.101 mm^{-1}, F(000) = 496, = 25.31°. Final $R1$ = 0.0346, $wR2$ = 0.0670, GOF = 0.775 for 156 parameters and 1923 unique reflections, of which 1016 with $I > 2\sigma(I)$, residuals in F map 0.097, –0.135 e. Å^{-3}.

Crystal data for compound (+)-8. $C_{12}H_{12}BrNO_4$, fw = 314.14 g mol^{-1}, monoclinic, C 2, a = 18.674(4), b = 5.672(2), c = 15.126(3) Å, β = 125.16 (3)°, V = 1309.9(6) Å^3, Z = 4, D_{calcd} = 1.593 g/cm^3, μ(Mo-Kα) = 3.144 mm^{-1}, F(000) = 632, = 25.66°. Final $R1$ = 0.0397, $wR2$ = 0.0797, GOF = 0.836 for 165 parameters and 2098 unique reflections, of which 1274 with $I > 2\sigma(I)$, residuals in F map 0.375, –0.350 e. Å^{-3}. Flack parameter 0.035(17).

RESULTS AND DISCUSSION

In the light of the aforementioned findings, we performed the reactions between 2,3-butanedione and nitroolefins under organocatalytic conditions both in solvent and under solvent-free conditions.

The same nitroolefins were used as electrophiles, namely 1-nitrocyclopentene **3a**, 1-nitrocyclohexene **3b**, β-nitrostyrene **3c**, and 1-nitro-2-phenylpropene **3d** (Scheme 2). (*R*)-(+)- and (*S*)-(–)-1-phenylethylamine, L-proline, (*S*)-(–)-5-(2-pyrrolidinyl)-1H-tetrazole and (S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine



Scheme 2. Organocatalyzed reactions of 2,3-butanedione **1** with the nitroolefins **3a–d**.

in conjunction with an acid. Of the solvents checked, namely dimethyl sulfoxide, tetrahydrofuran, $CHCl_3$, CH_3OH, and isopropanol, only the alcohols gave satisfactory results, and among them, isopropanol furnished the products with higher enantiomeric excess. Organocatalysts and solvents were first checked for the reaction between 2,3-butanedione and β-nitrostyrene **3c**, and the conditions that gave the best results were then used for the other nitroolefins. The reactions were monitored with ^{1}H NMR to determine the degree of conversion, and they were stopped when they did not proceed any further.

The reaction of 2,3-butanedione **1** with the nitroolefins **3a–d** in the presence of the organocatalyst (20 mol%), both in isopropanol and without solvent, produced the corresponding α-ketols (+)-**5a–d**, accompanied in most cases by a certain amount of their diastereomers (+)-**6a–c** and (−)-**6d**. With β-nitrostyrene **3c** and, as a catalyst, (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine coupled with an acid, a third diastereomer (−)-**7c** was isolated. The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures, and the enantiomeric excesses of the products were determined either by HPLC or HRGC on chiral columns. The reactions carried out in the absence of solvent were cleaner than those performed in solvent with the exception of the reaction with 1-nitrocyclopentene, which was very sensitive to basic conditions. On the contrary, the reactions carried out in isopropanol were characterized by a low catalyst turnover, probably because of the formation of the relatively stable and unreactive hemiaminal species.[57] When the reaction was carried out in the absence of solvent, a twofold increase in the molar amount of 2,3-butanedione did not make significative changes into yields and diastereoselectivities or enantioselectivities, but it proved helpful in dissolving the nitroolefin when this latter was solid.

In all cases, the final product was the corresponding enantiomerically enriched α-ketol, **5** and/or **6**. However, in the reaction with 1-phenyl-1-nitropropene **3d**, a small amount of the imine intermediates was present in the crude reaction mixture, owing to the fact that they were not completely hydrolyzed under the conditions used. As a consequence, the catalyst was partially "sequestered", resulting in a slightly lower total yield.

Under basic conditions (pH 8), the enantiomerically enriched compounds **5b–d** were partially converted into their respective diastereomers **6b–d**, thus demonstrating that they were formed under kinetic formation. In the reaction with 1-nitrocyclopentene, the product of kinetic formation was **6a** that partially was converted into **5a** even on standing in solution at room temperature.

Diastereoisomers **5**, **6**, and **7** were assigned the relative configurations shown in Scheme 2. Stereochemical assignments were made either by means of nuclear Overhauser effect measurements (whose results are reported in Scheme 2 for **5d**, **6d**, and **7c**) or on the basis of single crystal X-ray structural determinations that were performed on compounds **5c**, **6c** (Fig. 1a and b), and **6b**.[48]

The *trans* configuration between R^1 and the nitro group present in the original nitroolefins was maintained in all products except in those derived from 2-nitro-1-phenylpropene. In fact, in spite of the fact that the configuration of the nitroolefin **3d** is *E*, in compounds (+)-**5d** and (−)-**6d**, the phenyl group and NO_2 are in *cis* relationship, evidently for steric reasons. This constitutes evidence for a two-step reaction mechanism (Scheme 3).

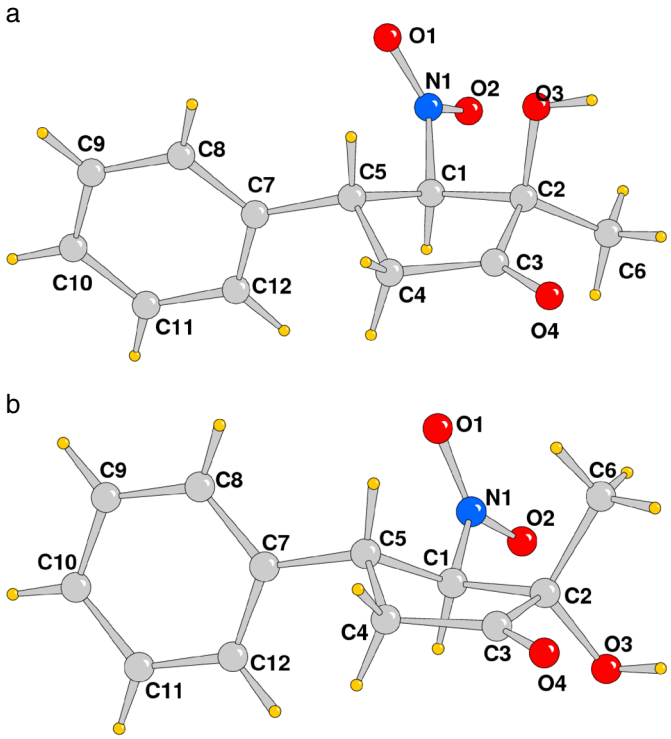


Fig. 1. Oak Ridge Thermal-Ellipsoid Plot Program (ORTEP) P diagrams of compounds (a) (±)-**5c** and (b) (±)-**6c**.

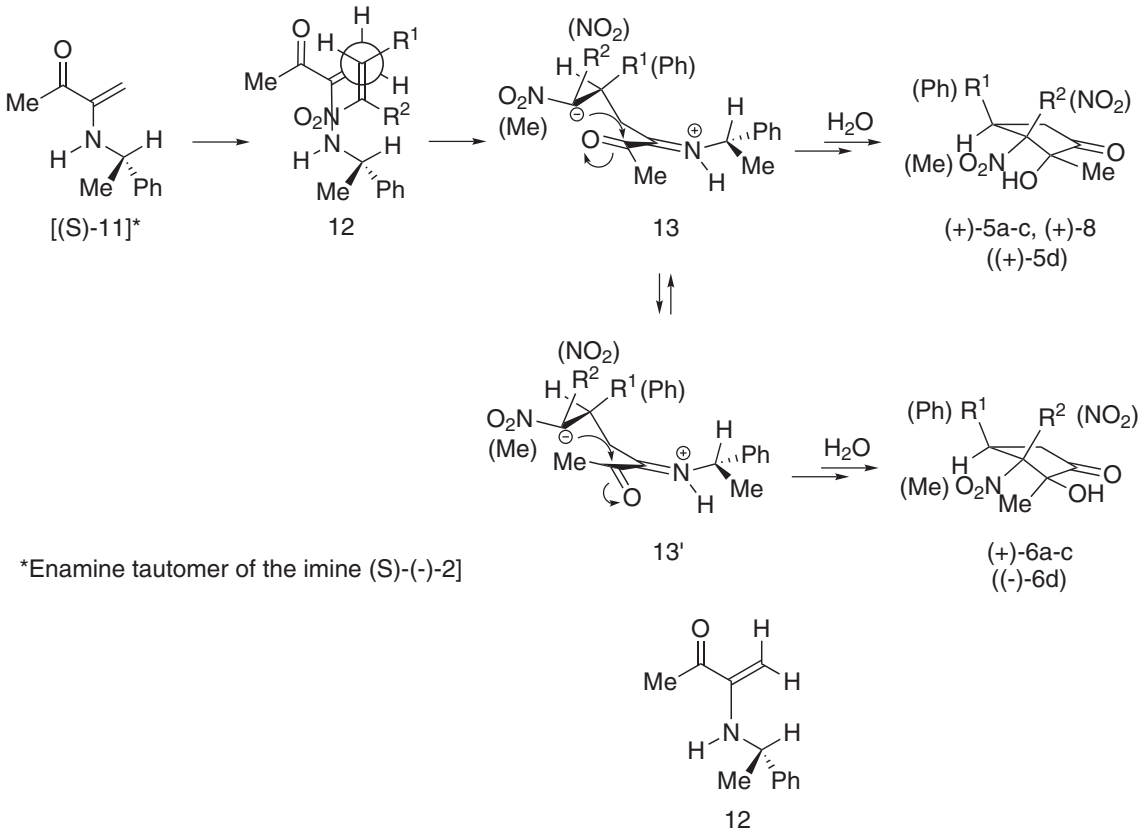
The main results relative to the organocatalyzed reactions are summarized in Tables 1 and 2.

It is evident that the most efficient catalyst was the primary amine 1-phenylethylamine (Table 1, Entries 1–5), both in the presence and absence of solvent. The observed diastereoselectivity was good for all nitroolefins with the exception of 1-nitrocyclopentene. In that case, the initially formed isomer (+)-**6a** rapidly interconverted into (+)-**5a** to reach the final equilibrium ratio of 60:40 in favor of **6a**. When a preformed mixture of (*S*)-(−)-1-phenylethylamine and TFA was used in the reaction between diacetyl and β-nitrostyrene **3c**, diastereoselectivity and enantioselectivity was good only when the reaction was performed in the absence of solvent (Entry 6). On the contrary, in isopropanol, the conversion was only 3% after 96 h.

L-proline (Table 2, Entries 1–4) was only partially efficient as an organocatalyst, as yields and enantioselectivities were low and **3d** did not react. The poor reactivity observed for the other nitroolefins was due to the fact that the reactions took a different course, yielding mainly pyrrolizidine derivatives.[58] When a preformed mixture of L-proline and TFA was used in the reaction between diacetyl and β-nitrostyrene **3c**, conversion was very poor (4%) after 96 h (Table 2, Entry 5).

With (*S*)-(−)-5-(2-pyrrolidinyl)-1H-tetrazole (Entry 11), conversion and enantioselectivity were very low, while with (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine, used in conjunction with different acids (Entries 5–10), conversions were good only for TFA, as found by Betancort and Barbas,[14] but diastereoselectivities were low.

It is important to underline that in an analogous experiment performed by D. Ding and coworkers[46] with diacetyl and β-nitrostyrene, in the presence of a quinine-derived thiourea as the organocatalyst, no product was obtained. This highlights the importance of a screening for the best organocatalyst.



Scheme 3. Mechanism proposed for the Michael–Henry tandem reaction.

TABLE 1. Reactions between 2,3-butanedione 1 and conjugated nitroolefins 3a–d[a] catalyzed by (*S*)-(−) and (*R*)-(+)-1-phenylethylamine and L-proline with and without acid

Entry	Catalyst	Nitroolefin	Products	Isopropanol			No solvent		
				5/6[b]	e.e. %[c]	Yield[d]	**5/6**[b]	e.e. %[c]	Yield[d]
1	(*S*)-1-phenylethylamine	**3a**	(+)-**5a**	1:9	90	55	1:6	85	85
			(+)-**6a**		92			84	
2		**3b**	(+)-**5b**	4:1	92	75	99:1	96	96
			(+)-**6b**		99				
3		**3c**	(+)-**5c**	15.7:1	99	65	99:1	>99	98
			(+)-**6c**		n.d.[e]				
4		**3d**	(+)-**5d**	13.3:1	85	76	2.3:1	89	87
			(−)-**6d**		73			71	
5	(*R*)-1-phenylethylamine	**3c**	(−)-**5c**	13.3:1	99	62			
			(−)-**6c**		n.d.[e]				
6	(*S*)-1-phenylethylamine/TFA	**3c**	(+)-**5c**			4% conv.	24:1	95	35
			(+)-**6c**						

[a]In the experiments performed in isopropanol (5 ml), the reagents were in 1:1 molar ratio and 20 mol% cat. on a 3 mmol scale. The solvent-free experiments were carried out on a 1 mmol scale. With ®-nitrostyrene and 2-nitro-1-phenylpropene, a twofold amount of 2,3-butanedione was used to allow the formation of a homogeneous solution.
[b]Determined by ^{1}H NMR of the crude mixture.
[c]Determined either by chiral high performance liquid chromatograms or by chiral high-resolution gas chromatography of the isolated diastereomer.
[d]Yield of isolated major isomer.
[e]Not determined.

The absolute configuration of the products was determined by X-ray analysis performed on compound (+)-**8** (Fig. 2), analogous to (+)-**5c**, and by analysis of the respective CD curves.

Compound (+)-**8** was isolated as a single isomer from the reaction between the imine (*S*)-(−)-**2** and *m*-bromo-β-nitrostyrene, under solvent-free conditions, followed by acidic hydrolysis. Its enantiomeric excess was 95%, and its absolute configuration was (2*R*,3*R*,4*R*) (Flack parameter 0.035(17)) (Fig. 3). The same product (+)-**8**, with 90% e.e., was obtained under organocatalytic conditions from diacetyl **1** and *m*-bromo-β-nitrostyrene, in the presence of (*S*)-(−)-1-phenylethylamine.

TABLE 2. Reactions between 2,3-butanedione 1 and conjugated nitroolefins 3a–d[a] catalyzed by (*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine in conjunction with various acids and (*S*)-(−)-5-(2-pyrrolidinyl)-1*H*-tetrazole

Entry	Catalyst	Nitroolefin	Products	**5/6/7**[b]	e.e. %[c]	Yield[d]
1	L-proline	**3a**	(+)-**5a**	9:1:0	30	10
			(+)-**6a**		30	n.d.[e]
2		**3b**	(+)-**5b**	9:1:0	40	15
			(+)-**6b**		24	
3		**3c**	(+)-**5c**	99:1:0	31	15
4		**3d**	No reaction			
5	(*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/trifluoroacetic acid	**3a**	(+)-**5a**	9:1:0	34	65
			(+)-**6a**		73	
6		**3b**	(+)-**5b**	1.3:1:0	16	73
			(+)-**6b**		89	
7		**3c**	(+)-**5c**	1.9:1.4:1	68	85
			(+)-**6c**		81	
			(−)-**7c**		71	
8		**3d**	(+)-**5d**	1:2.3:0	61	87
			(−)-**6d**		56	
9	(*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine/*p*-toluenesulfonic acid	**3c**	(+)-**5c**	5.7:1:7.6	83	30
			(+)-**6c**		83	
			(−)-**7c**			
10	(*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine/10-camphorsulfonic acid	**3c**	(+)-**5c**	2.7:1:2.8	24	45
			(+)-**6c**		63	
			(−)-**7c**		n.d.[e]	
11	(*S*)-(−)-5-(2-pyrrolidinyl)-1*H*-tetrazole	**3c**	(+)-**5c**	5.7:0:1	24	20
			(−)-**7c**		n.d.	

[a]In the experiments performed in isopropanol (5 ml), the reagents were in 1:1 molar ratio and 20 mol% cat. on a 3 mmol scale.
[b]Determined by ^{1}H NMR of the crude mixture.
[c]Determined either by chiral high performance liquid chromatograms or by chiral high-resolution gas chromatography of the isolated diastereomer.
[d]Yield of isolated major isomer.
[e]Not determined.

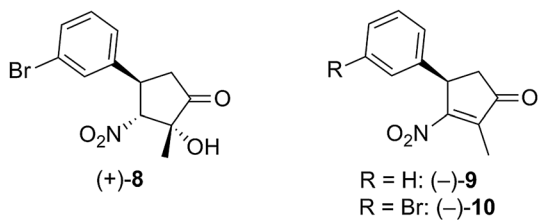


Fig. 2. α-Ketol (+)-**8** and dehydration derivatives (−)-**9** and (−)-**10**.

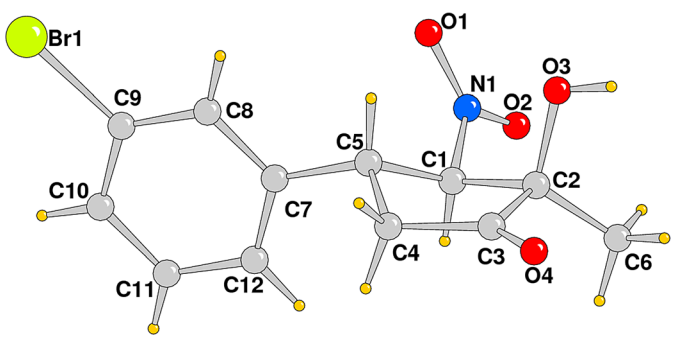


Fig. 3. ORTEP diagram of compound (+)-**8**.

The CD curve of the α-ketol (+)-**5c** was essentially superimposable on that of (+)-**8** [(+)-**5c**: ε_{312} +2.17, ε_{277} −1.20, ε_{232} +1.81; (+)-**8**: ε_{310} +2.60, ε_{277} −1.77, ε_{232} +1.82], and therefore, it was assigned the same (2*R*,3*R*,4*R*) absolute configuration. The bicyclic α-ketols (+)-**5a** and (+)-**5b** showed very similar CD curves, and they were also assigned the same absolute configuration.

As a corollary to these reactions, the dehydration reaction of the α-ketols (+)-**5c** and (+)-**8** to the respective cyclopentenones (−)-**9** and (−)-**10** (Fig. 2) should be mentioned. This was quantitatively accomplished via acetylation of the hydroxy group with acetic anhydride in the presence of trace amounts of PTSA,[59] followed by treatment with DMAP at room temperature for 6 h.[60]

As to the reaction mechanism, three consecutive stereocenters are formed in this reaction. The stereoselectivity of the reaction is related to the initial Michael reaction, which creates the stereocentre bearing the R^1 residue, and to the subsequent intramolecular Henry reaction, which generates the other two stereocentres. The mechanism proposed for the organocatalyzed reactions described is depicted in Scheme 3. The reactivity of the imine intermediate (*S*)-(−)-**2** is to be ascribed to its cross-conjugated enaminone tautomer form (*S*)-**11**. As the configuration of the products is strictly related to the configuration of the α-phenylethyl moiety, in the topological approach of the reagents, the amine component should be opposite to the acetyl group, as depicted in **12**. As a consequence, the firstly formed stereocentre should be (*R*). Subsequent collapse of the carbanion onto the carbonyl carbon atom in the dipolar intermediate **13** (groups in parenthesis for **3d**) would generate the other two stereocentres. The orientation of the acetyl group, as depicted in Scheme 3, would generate compounds (+)-**5a–d** and (+)-**8**, while its rotation around the OC–CN^+ single bond would afford their optically active diastereomers **6a–d**, after hydrolysis of the respective cyclic iminium forms

derived from closure of intermediates **13** and **13′**. Formation of (−)-**7c** would occur via inversion of the carbanion and its collapse onto the acetyl carbonyl group, followed by hydrolysis of the corresponding derivative. The inversion of diastereoselectivity observed for the products derived from 1-nitrocyclopentene **3a** with respect to the other nitroolefins (Table 1, Entry 1) might be ascribed to a less steric requirement of the nitrocyclopentane ring that could favor the dipolar intermediate **13′**, in which the interaction between the methyl group of the diacetyl moiety and the iminium group are reduced.

CONCLUSIONS

In conclusion, although the organocatalytic action of chiral nonracemic compounds possessing a primary amino group is well known,[26–29,61–64] this is the first example of an organocatalyzed intramolecular tandem Michael–Henry reaction involving diacetyl and conjugated nitroalkenes, leading to chiral nonracemic polyfunctionalized cyclopentanone derivatives. Interestingly, these reactions seem more satisfactory when carried out in the absence of solvent, even when the nitroolefins are in the solid state, as is the case of β-nitrostyrene, *m*-bromo-β-nitrostyrene, and 2-nitro-1-phenylpropene.

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