Supporting Information

A Novel Imidazolidine-Tetrazole Organocatalyst for Asymmetric Conjugate Addition of Nitroalkanes

by

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Synthesis of 5-(4-benzyl-1-methyl-imidazolidin-2-yl)-1H-tetrazole (1). Caution: This procedure should only be conducted in well ventilated hood as the hydrazoic acid formed in the reaction is very toxic. In a three-necked flask containing an addition funnel, thermometer, stirring bar, and gas outlet tube, a paste is prepared from equal weights of technical NaN₃ (13.0 g, 200 mmol, 2 eq) and warm water (Caution: azides are explosive in the presence of heavy metals). To this paste, CHCl₃ is added (80 mL) and the mixture is cooled to 0 °C. While the mixture is stirred and cooled, concentrated H₂SO₄ is added dropwise (5.3 mL, 1 mol of H₂SO₄ for 2 moles of NaN₃). The temperature should not exceed 10 °C. After the addition of the acid, the organic layer is decanted and dried over anhydrous Na₂SO₄ and filtered. After that a solution of diethoxy acetonitrile (12.9 g, 100 mmol) in dry pyridine 8.0 mL is added into the HN₃ solution at ambient temperature and is stirred for 120 h. The solvent is evaporated and 30 mL of Na₂CO₃ solution (sat. aq.) is added. The solution is washed twice with 5 mL of Et₂O. The aqueous phase is acidified with 4N HCl until pH 1.5-2.0 and extracted 5 times with 10 mL of Et₂O. The organic phase is dried with anhydrous Na₂SO₄, filtered and the solvent is evaporated to give 5-diethoxymethyl-1H-tetrazole (12.0 g, 70% yield).

In a flask containing 5-diethoxymethyl-1H-tetrazole (8.6 g, 50 mmol) 4N HCl is added (1.2 eq, 15.0 mL) and stirred for 48 h. The solvent was removed under vacuum and 1H-tetrazole-5-carbaldehyde was obtained as a white solid after crystallization in boiling THF-pentane (2.9 g, 60% yield). Condensation with an equimolar amount of N-methyl-3-phenylpropane-1,2-diamine¹ was performed in CH₂Cl₂ at ambient temperature for 24 hours, after which the solvent was evaporated and the crude product was purified by column chromatography on silica gel using AcOEt:MeOH 70:30 to give 5-(4-benzyl-1-methyl-imidazolidin-2-yl)-1H-tetrazole (5.5 g, 77%). [α]D = -33.6 (c = 1.01, EtOH). ¹H-NMR (400 MHz, DMSO-d₆) δ 2.49 (s, 3H), 2.52-2.54 (m, 1H), 2.78-2.87 (m, 2H), 2.93 (dd, J = 7.2, 14.0 Hz, 1H), 3.16-3.20 (m, 1H), 3.84-3.91 (m, 1H), 4.07 (s, 1H), 5.26 (s, 1H), 7.17-7.30 (m, 5H); ¹³C-NMR (100MHz, DMSO-d₆) δ 38.2, 38.3, 59.1, 126.9, 129.0, 129.7, 139.3, 157.5; HMRS m/z 267.1340 (M + Na⁺), calc for C₁₂H₁₆N₆Na⁺ 267.1334.

General procedure for the organocatalytic Michael reaction. In a ordinary test tube equipped with a magnetic stirring bar, 0.5 mmol of enone and catalyst (0.1mmol) was added to 1.0 mL of the nitroalkane, and the reaction mixture stirred at ambient temperature for the time indicated in the table. The crude mixture was purified by FC on silica gel after evaporation of the nitroalkane.¹
5-Methyl-5-nitro-4-phenylhexan-2-one (3a). Enantiomers were separated by GC using a Chirasil Dex-CB chiral stationary phase. Temperature program: from 70 °C to 150 °C at a rate of 10 °C/min. R\textsubscript{t} (min): 24.16 (minor enantiomer); 24.56 (major enantiomer).

6-Methyl-6-nitro-5-phenylheptan-3-one (3b). Enantiomers were separated by GC using a Chirasil Dex-CB chiral stationary phase. Temperature program: from 70 °C to 155 °C at a rate of 10 °C/min. R\textsubscript{t} (min): 25.86 (minor enantiomer); 26.38 (major enantiomer).

4-(4-Chlorophenyl)-5-methyl-5-nitrohexan-2-one (3c). [\(\alpha\)\textsubscript{D}] = -35.0 (c = 1.0, EtOH). Lit.\textsuperscript{1} [\(\alpha\)\textsubscript{D}] = -38.0 (c = 1.0, EtOH). Enantiomers were separated by HPLC on Daicel Chiralpack AD column with hexane/i-PrOH (90:10) as eluent: R\textsubscript{t} (min): 9.63 (minor enantiomer); 10.56 (major enantiomer).

4-(4-Hydroxyphenyl)-5-methyl-5-nitrohexan-2-one (3d). Enantiomers were separated by HPLC on Daicel Chiralpack AD column with hexane/i-PrOH (90:10) as eluent: R\textsubscript{t} (min): 20.45 (major enantiomer); 22.33 (minor enantiomer).

4-(4-Chlorophenyl)-5-methyl-5-nitrohexan-2-one (3e). Enantiomers were separated by HPLC on Daicel Chiralpack AD column with hexane/i-PrOH (90:10) as eluent: R\textsubscript{t} (min): 20.75 (minor enantiomer); 28.00 (major enantiomer).

5-Methyl-5-nitro-4-(4-nitrophenyl)hexan-2-one (3f). Enantiomers were separated by HPLC on Daicel Chiralpack AD column with hexane/i-PrOH (98:2) as eluent: R\textsubscript{t} (min): 10.72 (minor enantiomer); 11.71 (major enantiomer).

5-Nitro-4-phenylpentan-2-one (3g). In the case of major Rf diastereoisomer, enantiomers were separated by GC using a Chirasil-Dex G-TA chiral stationary phase. Temperature program: from 70 °C to 160 °C at a rate of 10 °C/min. R\textsubscript{t} (min): 27.80 (minor enantiomer); 28.22 (major enantiomer).

2-Nitro-5-oxo-3-phenylhexanoic Acid Ethyl Ester (3i). Enantiomeric excess was determined after decarboxylation.

4-(1-Nitrocyclopentyl)-4-phenylbutan-2-one (3j). Enantiomers were separated by HPLC on Daicel Chiralpack AS column with hexane/i-PrOH (90:10) as eluent: R\textsubscript{t} (min): 8.38 (minor enantiomer); 12.60 (major enantiomer).

4-(1-Nitrocyclohexyl)-4-phenylbutan-2-one (3k). Enantiomers were separated by HPLC on Daicel Chiralpack AS column with hexane/i-PrOH (90:10) as eluent: R\textsubscript{t} (min): 6.89 (minor enantiomer); 9.49 (major enantiomer).

(-)-3-Nitromethyl-cyclopentanone (3l). \([\alpha]_D = -58.0 \text{ (c = 1.1, CHCl}_3\)). Lit.\(^2\) \([\alpha]_D = +66.9 \text{ (c = 0.6, CHCl}_3\));
The enantiomeric excess was determined by the method of Hanessian and Pham.\(^2\)

(-)-3-Nitromethyl-cyclohexanone (3m). \([\alpha]_D = -7.2 \text{ (c = 1.7, CHCl}_3\)). Lit.\(^2\) \([\alpha]_D = +8.1 \text{ (c = 1.8, CHCl}_3\)).
Enantiomers were separated by GC using a Chirasildex G-TA chiral stationary phase. Temperature program:
from 70 °C to 120 °C at a rate of 10 °C/min. \(R_t\) (min): 58.48 (minor enantiomer); 59.90 (major enantiomer).

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[Chemical structure diagram of compound 1 with ppm (f1) scale from 175 to 25 ppm and intensity scale from 0 to 25000]