Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Dynamic Combinatorial Resolution: Direct Asymmetric Lipase-Mediated Screening of a Dynamic Nitroaldol Library

Pornrapee Vongvilai, Marcus Angelin, Rikard Larsson, Olof Ramström*

KTH - Royal Institute of Technology, Department of Chemistry, Teknikringen 30, S-10044 Stockholm, Sweden; Email: ramstrom@kth.se

General

Reagents were purchased from commercial sources and used as received. ^{1}H- and ^{13}C-NMR data were recorded on a Bruker Avance 400 spectrometer at 400 (100) MHz and/or a Bruker Avance DMX 500 at 500 (125) MHz respectively. Chemical shifts are reported as δ values (ppm) with $CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.0) as internal standard. *J* values are given in Hertz (Hz). Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on HP-Agilent 1110 Series instrumentation and a UV detector, using a Daicel Chiralpak OD-H column (46×250 mm, 5 μm). Solvents for HPLC use were spectrometric grade. Melting points were analyzed using a Stuart Scientific melting point apparatus SMP3. Thin layer chromatography (TLC) was performed on precoated Polygram® SIL G/UV_{254} silica plates (0.20 mm, Macherey-Nagel) and visualized by UV-detection. Flash column chromatography was performed on silica gel 60, 0.040-0.063 mm (SDS). HRMS was performed by Instrumentstationen, Kemicentrum, Lund University, Sweden.

Generation of DCLs and lipase-mediate screening

The nitroaldol DCLs were generated by using five different aldehydes (**1** to **5**, 0.1 mmol each), together with 1 equivalent of 2-nitropropane (8.9 mg, 0.1 mmol) in dry toluene (0.5 mL). DCL generation was initiated by addition of 10 equivalents of dry triethylamine (101 mg, 1 mmol) at 40°C. The library was followed by ^{1}H NMR at 298K, by addition of aliquots (10 µL) from the reaction mixture to $CDCl_3$ (0.55 mL). For the lipase-mediate screening, *Pseudomonas cepacia* (PS-C I, immobilized on ceramic, Sigma-Aldrich EC 3.1.1.3, 160 mg) together with ground 4 Å molecular sieves (20 mg), and five equivalents of *p*-chlorophenyl acetate (85 mg, 0.5 mmol) were added. The reaction was performed at 40°C without stirring under argon atmosphere, followed by ^{1}H NMR.

***p*-chlorophenyl acetate[1]**

Acetyl chloride (5.5 mmol) was added dropwise to a solution of 4-chlorophenol (0.643 g, 5.0 mmol), triethylamine (1.52 g, 15 mmol), and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature overnight. The solution was washed with diluted HCl (3 × 8 mL), and the combined aqueous phases were reextracted with ether (3 × 8 mL). The combined organic phases were washed with saturated $NaHCO_3$ (aq, 5 mL), and brine (4 mL), and dried over $MgSO_4$. The solvent was concentrated in vacuo, and the crude mixture was purified on silica (CH_2Cl_2/hexane, 7:3 (v/v)). Colorless oil; ^{1}H NMR ($CDCl_3$) δ = 2.29 (s, 3H), 7.03 (d, 2H, *J* = 8.8 Hz), 7.34 (d, 2H, *J* = 8.8 Hz).

2-methyl-2-nitro-1-(3-nitrophenyl)propyl acetate (3-6 ester)

3-nitrobenzaldehyde (**3**) (37.75 mg, 0.25 mmol) was dissolved in $CHCl_3$ (0.5 ml) followed by adding 2-nitropropane (**6**) (111.25 mg, 1.25 mmol) and triethylamine (75.75 mg, 0.75 mmol) and stirred at room temperature for 3 h. The reaction was acidified with diluted HCl, extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic layers washed with brine (2 × 1 mL). The organic phase was dried with $MgSO_4$ and the solvent evaporated. The crude mixture was dissolved in dry pyridine (1 mL) followed by addition of 5 equivalents of acetic anhydride (127.5 mg, 1.25 mmol). The reaction was stirred at room temperature for 6 h and work-up as above provided the corresponding crude racemic mixture of compound **3-6 ester**. The crude

mixture was purified by column chromatography with isocratic system CH_2Cl_2/Hexane (7:3 (*v*/*v*)) as an eluent to yield compound **3-6 ester.** 60 mg. Colorless amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.52 (3H, s), 1.66 (3H, s), 2.13 (3H, s), 6.39 (1H, s), 7.58 (1H,dd, *J* = 7.8, 8.0 Hz), 7.66 (1H,d, *J* = 7.8 Hz), 8.20 (1H, brs), 8.24 (1H, brd, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ = 20.3, 20.7, 23.8, 77.8, 89.6, 122.3, 124.1, 129.7, 133.7, 137.3, 148.3, 168.8; HRMS (ESI-TOF): 300.1182 ($[M+NH_4]^+$, $C_{12}H_{18}N_3O_6^+$; calc. 300.1190).

2-methyl-2-nitro-1-(4-(trifluoromethyl)phenyl)propyl acetate (**1-6 ester)**

Prepared using the same protocol as for compound **3-6 ester**. 67 mg. Colorless solid. m.p. 108–110°C; ^{1}H NMR ($CDCl_3$) δ = 1.50 (3H, s), 1.64 (3H, s), 2.10 (3H, s), 6.35 (1H, s), 7.46 (2H, d, *J* = 8.0 Hz), 7.64 (2H, d, *J* = 8.0 Hz; ^{13}C NMR ($CDCl_3$) δ = 20.1, 20.7, 24.1, 77.8, 89.7, 122.4, 125.5, 128.0, 131.1, 131.4, 139.1, 168.8; HRMS (ESI-TOF): 323.1211 ($[M+NH_4]^+$, $C_{13}H_{18}F_3N_2O_4^+$; calc. 323.1213).

Determination of enantiomeric purity

The ee:s of final products **1-6 ester** and **3-6 ester**, were determined by analytical HPLC utilizing a chiral normal-phase column (OD-H; Isopropanol/hexane, 1:99; flow rate 0.5 mL/min): racemic **1-6 ester** t_R 23 and 24 min; racemic **3-6 ester** t_R 60 and 65 min.

(*S*)-(-)-MTPA ester of 7-6 [2]

A reaction mixture consisting of **7-6** (4 mg) resulting from the kinetic resolution by enzyme-lipase PS-C I (90% ee), pyridine (0.5 mL), and (*R*)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride (20 mg) was left standing at room temperature for 40 h. The mixture was acidified with dilute HCl and extracted with EtOAc (3 × 1 mL), and washed with brine. The EtOAc layer was dried, yielding the (*S*)-(-)-MTPA ester of **7-6a** (2 mg). Colorless oil: ^{1}H NMR ($CDCl_3$) δ = 1.47 (3H, s), 1.60 (3H, s), 3.41 (3H, s, OMe), 6.65 (1H, s), 7.38 (3H, m, aromatic protons of MTPA), 7.40 (2H, m, aromatic protons of MTPA), 7.44 (2H, d, *J* = 8.5 Hz), 8.23 (2H, d, *J* = 8.5 Hz).

(*R*)-(+)-MTPA ester of 7-6 [2]

Preparation of the (*R*)-(+)-MTPA ester of **7**-**6** from (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride was performed in the same manner as that of the (*S*)-(-)-MTPA ester derivative. Colorless oil: ^{1}H NMR ($CDCl_3$) δ = 1.48 (3H, s), 1.55 (3H, s), 3.45 (3H, s, OMe), 6.57 (1H, s), 7.28 (2H, d, *J* = 7 Hz), 7.37 (3H, m, aromatic protons of MTPA), 7.42 (2H, m, aromatic protons of MTPA)**,** 8.16 (2H, d, *J* = 7 Hz).

References

1. Fransson A-B L; Xu Y; Leijondahl K; Bäckvall J-E. *J. Org. Chem.* **2006**, *71*, 6309 -6316.
2. Seephonkai P; Isaka M; Kittakoop P; Boonudomlap U; Thebtaranonth Y. *J. Antibiot.* **2004**, *57*, 10-16.