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Enzyme- and ruthenium-catalyzed dynamic kinetic resolution involving cascade alkoxycarbonylations for asymmetric synthesis of 5-Substituted *N*-Aryloxazolidinones

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ABSTRACT

Asymmetric synthesis of *N*-aryloxazolidinones *via* dynamic kinetic resolution was developed. A ruthenium-based catalyst was used in the racemization of *β*-anilino alcohols, while *Candida antarctica* lipase B (CAL-B) was applied for two selective alkoxycarbonylations operating in cascade. Various *N*-aryloxazolidinone derivatives were obtained in high yields and good enantiopurities.

Introduction

N-Aryloxazolidinones constitute a class of attractive structures that show wide presence in pharmaceuticals, such as antimicrobials, MAO inhibitors, and HIV-1 protease inhibitors [1–5], Current syntheses of enantiopure *N*-aryloxazolidinones are generally based on Cu-catalyzed intermolecular *N*-arylation of chiral oxazolidinones [6–8], where the parent oxazolidinones can be prepared by, *e.g.*, cyclization of enantioenriched 1,2-aminoalcohols *via* the Mitsunobu reaction [9], intermolecular, stereospecific nucleophilic ring-opening of aziridine-2-carboxamides [10], aminolytic kinetic resolution of epoxides [11], regioselective alkylation-cyclization of aryl *N*-lithiocarbamates [12], or enzymatic desymmetrization of *N*-Boc-serinols [13]. In these sequential transformation processes, however, racemization of the compounds were occasionally observed. Although the synthesis of racemic *N*-aryloxazolidinones has been demonstrated [14], the direct, high-yielding formation of the corresponding enantiopure structures, especially the 5-substituted heterocycles, has not been established. This has been addressed in the present study, where, in continuation to our work on enzyme-catalyzed heterocycle formations [15–23], we report a novel asymmetric synthesis protocol of 5-substituted *N*-aryloxazolidinones based on dynamic kinetic resolution (DKR) through racemization and two sequential enzyme-catalyzed processes (Fig. 1).

Experimental

General methods

DKR and racemization reactions were carried out under dry argon atmosphere using standard Schlenk techniques. Reagents were obtained from commercial suppliers and used as received. *Candida antarctica* lipase B (CAL-B) preparation was purchased from Sigma-Aldrich. Ruthenium catalyst **5** was synthesized according to a literature procedure. [24] ^{1}H and ^{13}C NMR data were recorded on Bruker Avance 400 or Bruker Avance 500 spectrometers. Chemical shifts are reported as δ values (ppm) with $CHCl_3/CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.0) as an internal references. *J*-values are given in hertz (Hz). Optical rotations were measured with a polarimeter equipped with an Na lamp. Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on an HP-Agilent 1110 Series controller and a UV detector, using a Daicel Chiralpak OD-H or Chiralcel OJ column (4.6 × 250 mm, 10 μm). Solvents for HPLC use were of spectrometric grade. Thin layer chromatography (TLC) was performed on precoated Polygram® SIL G/UV 254 silica plates (0.20 mm, Macherey-Nagel), visualized with UV-detection. Flash column chromatography was performed on silica gel 60, 0.040-0.063 mm (SDS).

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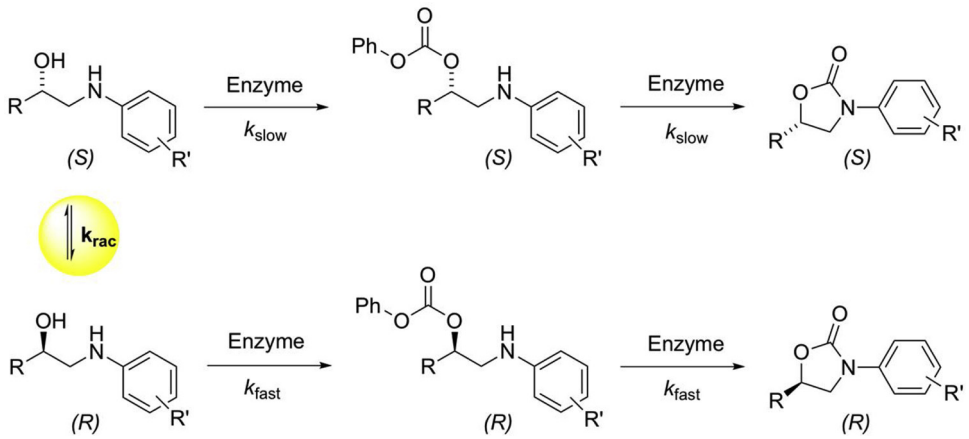


Fig. 1. DKR-based asymmetric synthesis of 5-substituted N-aryloxazolidinones.

*General procedure for synthesis of β-aminoalcohols **1a-1i***

LiBr (0.1 mmol) was added to a stirred mixture of respective epoxide (2 mmol) and aniline (2 mmol) under nitrogen atmosphere, and the solution was stirred at r.t. for 4 h. The reaction mixture was diluted with water (10 mL) and extracted twice with diethyl ether (15 mL each). The combined organic layer was dried over $MgSO_4$ and removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 3:1).

1-(phenylamino)propan-2-ol (1a) [25]. Yellow oil, yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.25 (d, J = 6.2 Hz, 3H, CH_3), 2.01 (br, 1 H), 2.98 (dd, J_1 = 13.1 Hz, J_2 = 8.6 Hz, 1H, CH_2), 3.20 (dd, J_1 = 12.9 Hz, J_2 = 3.4 Hz, 1H, CH_2), 4.0 (m, 1H, CH), 6.66 (d, J = 8.6 Hz, 2H, 2CH), 6.77 (t, J = 7.4 Hz, 1H, CH), 7.23 (t, J = 7.9 Hz, 2H, 2CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 20.8, 51.6, 66.3, 113.3, 117.8, 129.3, 148.2.

1-(phenylamino)butan-2-ol (1b) [26]. White solid, yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.02 (t, J = 7.3 Hz, 3H, CH_3), 1.56 (m, 2H, CH_2), 2.57 (br, 1 H), 2.99 (dd, J_1 = 12.9 Hz, J_2 = 8.4 Hz, 1H, CH_2), 3.26 (dd, J_1 = 12.7 Hz, J_2 = 3.2 Hz, 1H, CH_2), 3.75 (m, 1H, CH), 3.97 (br, 1 H), 6.66 (d, J = 7.7 Hz, 2H, 2CH), 6.77 (t, J = 7.7 Hz, 1H, CH), 7.22 (t, J = 7.7 Hz, 2H, 2CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 10.0, 27.9, 49.9, 71.8, 113.4, 117.9, 129.3, 148.4.

1-(4-chlorophenylamino)butan-2-ol (1c) [27]. White solid, yield: 71%. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 1.01 (t, J = 7.5 Hz, 3H, CH_3), 1.55 (m, 2H, CH_2), 1.80 (br, 1 H), 2.98 (dd, J_1 = 12.9 Hz, J_2 = 8.5 Hz, 1H, CH_2), 3.23 (dd, J_1 = 12.8 Hz, J_2 = 3.2 Hz, 1H, CH_2), 3.76 (m, 1H, CH), 4.01 (br, 1 H), 6.56 (d, J = 8.9 Hz), 7.12 (d, J = 8.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 10.1, 28.2, 50.0, 71.9, 114.5, 122.6, 129.3, 147.1.

1-(4-chlorophenylamino)propan-2-ol (1d) [28]. Yellow solid, yield: 77%. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 1.26 (d, J = 6.3 Hz, 3H, CH_3), 2.09 (br, 1 H), 2.98 (dd, J_1 = 13.3 Hz, J_2 = 8.7 Hz, 1H, CH_2), 3.20 (dd, J_1 = 13.0 Hz, J_2 = 3.6 Hz, 1H, CH_2), 4.03 (m, 1H, CH), 6.58 (d, J = 8.8 Hz, 2H, 2CH), 7.12 (d, J = 8.8 Hz, 2H, 2CH); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 21.1, 52.1, 66.5, 114.6, 122.9, 129.3, 146.8.

1-(4-fluorophenylamino)propan-2-ol (1e) [29]. Yellow solid, yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.26 (d, J = 6.3 Hz, 3H, CH_3), 2.06 (br, 1 H), 2.95 (dd, J_1 = 12.5 Hz, J_2 = 8.6 Hz, 1H, CH_2), 3.18 (dd, J_1 = 13.1 Hz, J_2 = 3.3 Hz, 1H, CH_2), 3.87 (br, 1 H), 4.0 (m, 1H, CH), 6.58 (q, J = 4.5 Hz, 2H, 2CH), 6.89 (t, J = 8.8 Hz, 2H, 2CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 21.0, 52.4, 66.4, 114.2, 114.3, 115.7, 115.9, 144.7, 155.0, 157.3.

1-(3-fluorophenylamino)propan-2-ol (1f) [30]. Colorless oil, yield: 42%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.25 (d, J = 6.3 Hz, 3H, CH_3), 2.19 (br, 1 H), 2.96 (dd, J_1 = 13.2 Hz, J_2 = 8.4 Hz, 1H, CH_2), 3.18 (dd, J_1 = 13.0 Hz, J_2 = 3.3 Hz, 1H, CH_2), 4.01 (m, 1H, CH), 4.18 (br, 1 H), 6.31 (d, J = 11.7 Hz, 1H, CH), 6.38˜6.43 (m, 2H, 2CH), 7.09 (q, J = 7.7 Hz, 1H, CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 21.0, 51.5, 66.5, 99.7, 100.0, 104.1, 104.3, 109.1, 109.2, 130.4, 130.5, 150.1, 150.3, 163.0, 165.4.

1-(2-fluorophenylamino)propan-2-ol (1 g) [31]. Brown oil, yield: 59%. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 1.27 (d, J = 6.3 Hz, 3H, CH_3), 2.55 (br, 1 H), 3.03 (dd, J_1 = 12.9 Hz, J_2 = 8.4 Hz, 1H, CH_2), 3.22 (dd, J_1 = 12.9 Hz, J_2 = 3.5 Hz, 1H, CH_2), 4.03 (m, 1H, CH), 6.64 (q, J = 6.9 Hz, 1H, CH), 6.72 (t, J = 8.4 Hz, 1H, CH), 6.96˜7.01 (m, 2H, 2CH); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 20.9, 51.3, 66.5, 112.60, 112.62, 114.6, 114.7, 117.2, 117.3, 124.64, 124.67, 136.73, 136.82, 150.9, 152.8.

1-(4-methoxyphenylamino)propan-2-ol (1 h) [31]. Yellow solid, yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.25 (d, J = 6.5 Hz, 3H, CH_3), 2.19 (br, 1 H), 2.94 (dd, J_1 = 13.0 Hz, J_2 = 8.6 Hz, 1H, CH_2), 3.18 (dd, J_1 = 12.7 Hz, J_2 = 3.1 Hz, 1H, CH_2), 3.75 (s, 3H, CH_3), 3.99 (m, 1H, CH), 6.63 (d, J = 8.8 Hz, 2H, 2CH), 6.78 (d, J = 8.9 Hz, 2H, 2CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 20.9, 52.8, 55.8, 66.4, 114.8, 114.9, 142.4, 152.4.

1-chloro-3-(phenylamino)propan-2-ol (1i) [26]. White solid, yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 3.14 (dd, J_1 = 13.4 Hz, J_2 = 7.5 Hz, 1H, CH_2), 3.30 (dd, J_1 = 13.4 Hz, J_2 = 4.4 Hz, 1H, CH_2), 3.45 (br, 1 H), 3.56 (m, 2H, CH_2), 3.99 (m, 1H, CH), 6.62 (d, J = 8.4 Hz, 2H, CH), 6.75 (t, J = 6.9 Hz, 1H, CH), 7.18 (t, J = 7.5 Hz, 2H, 2CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 47.2, 47.6, 69.9, 113.3, 118.3, 129.4, 147.8.

*General procedure for synthesis of racemic N-aryloxazolidinones **4a-4i***

β-aminoalcohol **1a-1i** (0.08 mmol), diphenyl carbonate (0.1 mmol), NaH (0.16 mmol, 60% in oil) and THF (1 mL) were added into a 5 mL flask. The solution was stirred at r.t. for 6 h. TLC was used to monitor the reaction progress. CH_2Cl_2 was subsequently added, and the aqueous layer was extracted three times (3 mL CH_2Cl_2 each). The combined organic layer was dried over $MgSO_4$ and removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 6:1).

Procedure for kinetic resolution

β-aminoalcohol **1a-1i** (0.05 mmol), diphenyl carbonate (0.15 mmol) and dry toluene (0.6 mL) were added into a 1.5 mL sealed-cap vial containing CAL-B (30 mg) and 4 Å molecular sieves (20 mg). CAL-B was dried under vacuum for at least two days before use. The vial was kept at r.t. without stirring, and ^{1}H NMR was used to monitor the reaction progress. After a specific time, the reaction mixture was filtered through a cotton-stoppered pipette. CH_2Cl_2 was subsequently added, and the aqueous layer was extracted three times (3 mL CH_2Cl_2 each). The

combined organic layer was dried over $MgSO_4$ and removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 6:1).

Racemization of (S)-1a

Ruthenium catalyst **5** (1.2 mg, 0.0019 mmol) was added to a Schlenk tube. Dry toluene (0.4 mL) was added, and the resulting solution was stirred. A THF solution of *t*-BuOK (3.75 μL, 0.5 M in dry THF, 0.0019 mmol) was added to the reaction mixture. After 6 min stirring, *(S)*-1-(phenylamino)propan-2-ol (*(S)*-**1a**) (5.7 mg, 0.0375 mmol) dissolved in dry toluene (0.1 mL) was added to the reaction mixture, and the reaction was heated to the appropriate temperature. Samples for HPLC analysis were collected with a syringe after 2, 5, 10, 30, 60, and 90 min. HPLC: Chiralpak OD-H column, Hex:^{i}PrOH = 9 : 1, 0.5 mL/min, t_{R1} = 25.3 min, t_{R2} = 30.7 min.

Procedure for dynamic kinetic resolution

Ruthenium catalyst **5** (4.8 mg, 0.0075 mmol), CAL-B (15 mg), and $CaCl_2$ (8.3 mg, 0.075 mmol) were added to a Schlenk tube. Dry toluene (0.7 mL) was added, and the resulting solution was stirred. A THF solution of *t*-BuOK (15 μL, 0.5 M in dry THF, 0.0075 mmol) was added to the reaction mixture. After 6 min of stirring, *rac*-**1** (0.075 mmol) dissolved in dry toluene (0.1 mL) was added to the reaction mixture. After an additional 4 min, diphenyl carbonate (48.2 mg, 0.225 mmol) dissolved in dry toluene (0.2 mL) was added. SiO_2 was added under flow of dry nitrogen and the resulting reaction was heat to 50 °C. After a certain time, the reaction mixture was filtered and solvent was removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 6:1).

5-methyl-3-phenyloxazolidin-2-one (4a) [32]. Conversion: 100%, enantiomeric excess (*ee*): 90%, determined by HPLC analysis: Chiral OD-H, Hex:^{i}PrOH = 9 : 1, 0.5 mL/min, detection 210 nm, t_{R1} = 27.7 min, t_{R2} = 34.0 min, white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.54 (d, J = 6.3 Hz, 3H, CH_3), 3.63 (t, J = 8.1 Hz, 1H, CH_2), 4.12 (t, J = 8.5 Hz, 1H, CH_2), 4.79 (m, 1H, CH), 7.14 (t, J = 7.5 Hz, 1H, CH), 7.38 (t, J = 7.5 Hz, 2H, 2CH), 7.53 (d, J = 8.1 Hz, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 21.0, 52.1, 69.8, 118.3, 124.1, 129.3, 138.5, 155.0.

5-ethyl-3-phenyloxazolidin-2-one (4b) [33]. Conversion: 96%, enantiomeric excess (*ee*): 95%, determined by HPLC analysis: Chiral OD-H, Hex:^{i}PrOH = 9 : 1, 0.5 mL/min, detection 210 nm, t_{R1} = 25.6 min, t_{R2} = 32.5 min, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 1.08 (t, J = 7.3 Hz, 3H, CH_3), 1.74˜1.94 (m, 2H, CH_2), 3.67 (t, J = 7.8 Hz, 1H, CH_2), 4.09 (t, J = 8.6 Hz, 1H, CH_2), 4.59 (m, 1H, CH), 7.13 (t, J = 7.4 Hz, 1H, CH), 7.38 (t, J = 7.9 Hz, 2H, 2CH), 7.54 (d, J = 7.9 Hz, 2H, 2CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 8.9, 28.2, 50.3, 74.3, 118.3, 124.2, 129.2, 138.5, 155.1.

3-(4-chlorophenyl)-5-ethyloxazolidin-2-one (4c) [30]. Conversion: quant., enantiomeric excess (*ee*): 92%, determined by HPLC analysis: Chiral OJ, Hex:^{i}PrOH = 8 : 2, 1 mL/min, detection 210 nm, t_{R1} = 19.0 min, t_{R2} = 23.3 min, white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.07 (t, J = 7.6 Hz, 3H, CH_3), 1.85 (m, 2H, CH_2), 3.64 (t, J = 7.8 Hz, 1H, CH_2), 4.06 (t, J = 8.6 Hz, 1H, CH_2), 4.59 (m, 1H, CH), 7.33 (d, J = 8.9 Hz, 2H, 2CH), 7.50 (d, J = 9.0 Hz, 2H, 2CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 8.9, 28.2, 50.2, 74.3, 119.4, 129.2, 129.3, 137.2, 155.0.

3-(4-chlorophenyl)-5-methyloxazolidin-2-one (4d) [34]. Conversion: quant., enantiomeric excess (*ee*): 84%, determined by HPLC analysis: Chiral OJ, Hex:^{i}PrOH = 8 : 2, 1 mL/min, detection 210 nm, t_{R1} = 27.6 min, t_{R2} = 32.3 min, white solid. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 1.54 (d, J = 6.3 Hz, 3H, CH_3), 3.60 (t, J = 7.9 Hz, 1H, CH_2), 4.10 (t, J = 8.5 Hz, 1H, CH_2), 4.79 (m, 1H, CH), 7.33 (d, J = 8.9 Hz, 2H, 2CH), 7.48 (d, J = 8.9 Hz, 2H, 2CH); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 20.9, 52.0, 69.8, 119.5, 129.3, 137.2, 154.9.

3-(4-fluorophenyl)-5-methyloxazolidin-2-one (4e) [30]. Conversion: quant., enantiomeric excess (*ee*): 84%, determined by HPLC analysis: Chiral OJ, Hex:^{i}PrOH = 8 : 2, 0.5 mL/min, detection 210 nm, t_{R1} = 42.7 min, t_{R2} = 46.2 min, white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.54 (d, J = 6.2 Hz, 3H, CH_3), 3.61 (t, J = 8.0 Hz, 1H, CH_2), 4.09 (t, J = 8.6 Hz, 1H, CH_2), 4.79 (m, 1H, CH), 7.07 (t, J = 8.5 Hz, 2H, 2CH), 7.49 (dd, J_1 = 88 Hz, J_2 = 4.7 Hz, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 20.9, 52.3, 69.7, 115.8, 116.0, 120.0, 120.1, 134.6, 134.7, 155.2, 158.2, 160.6.

3-(3-fluorophenyl)-5-methyloxazolidin-2-one (4f) [30]. Conversion: 97%, enantiomeric excess (*ee*): 78%, determined by HPLC analysis: Chiral OD-H, Hex:^{i}PrOH = 9 : 1, 0.5 mL/min, detection 210 nm, t_{R1} = 28.2 min, t_{R2} = 31.7 min, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.54 (d, J = 6.1 Hz, 3H, CH_3), 3.60 (t, J = 7.8 Hz, 1H, CH_2), 4.11 (t, J = 8.4 Hz, 1H, CH_2), 4.80 (m, 1H, CH), 6.84 (td, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1H, CH_2), 7.23 (d, J = 8.9 Hz, 1H, CH), 7.31 (q, J = 7.5 Hz, 1H, CH), 7.42 (dt, J_1 = 11.8 Hz, J_2 = 2.2 Hz, 1H, CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 20.9, 52.0, 69.8, 105.8, 106.0, 110.7, 110.9, 113.3, 113.4, 130.3, 130.4, 140.1, 140.2, 154.7, 162.0, 164.5.

3-(2-fluorophenyl)-5-methyloxazolidin-2-one (4 g) [30]. Conversion: quant., enantiomeric excess (*ee*): 85%, determined by HPLC analysis: Chiral OJ, Hex:^{i}PrOH = 8 : 2, 0.5 mL/min, detection 210 nm, t_{R1} = 31.1 min, t_{R2} = 33.9 min, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 1.54 (d, J = 6.3 Hz, 3H, CH_3), 3.66 (t, J = 8.0 Hz, 1H, CH_2), 4.12 (t, J = 8.3 Hz, 1H, CH_2), 4.82 (m, 1H, CH), 7.11˜7.19 (m, 2H, 2CH), 7.23 (t, J = 5.6 Hz, 1H, CH), 7.55 (td, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H, CH); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 20.7, 53.9, 71.3, 116.7, 116.9, 124.8, 125.6, 127.2, 128.2, 128.3, 156.0, 156.2, 157.9.

3-(4-methoxyphenyl)-5-methyloxazolidin-2-one (4 h) [35]. Conversion: 88%, enantiomeric excess (*ee*): 81%, determined by HPLC analysis: Chiral OD-H, Hex:^{i}PrOH = 9 : 1, 0.5 mL/min, detection 210 nm, t_{R1} = 47.4 min, t_{R2} = 50.8 min, white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.52 (d, J = 6.2 Hz, 3H, CH_3), 3.59 (t, J = 7.7 Hz, 1H, CH_2), 3.80 (s, 3H, CH_3), 4.08 (t, J = 8.5 Hz, 1H, CH_2), 4.77 (m, 1H, CH), 6.90 (d, J = 9.1 Hz, 2H, 2CH), 7.42 (d, J = 9.1 Hz, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 20.8, 52.5, 55.7, 69.6, 114.4, 120.3, 131.7, 155.4, 156.4.

5-(chloromethyl)-3-phenyloxazolidin-2-one (4i) [32]. Conversion: 87%, enantiomeric excess (*ee*): 71%, determined by HPLC analysis: Chiral OD-H, Hex:^{i}PrOH = 9 : 1, 0.5 mL/min, detection 210 nm, t_{R1} = 40.5 min, t_{R2} = 44.1 min, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 3.77 (m, 2H, CH_2), 3.98 (dd, J_1 = 9.2 Hz, J_2 = 5.7 Hz, 1H, CH_2), 4.18 (t, J = 9.2 Hz, 1H, CH_2), 4.88 (m, 1H, CH), 7.16 (t, J = 7.6 Hz, 1H, CH), 7.40 (t, J = 7.9 Hz, 2H, 2CH), 7.55 (d, J = 7.9 Hz, 2H, 2CH); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 44.7, 48.4, 71.0, 118.5, 124.6, 129.4, 137.9, 154.1.

Results and discussion

We previously reported the sequential kinetic resolution (KR) of 1,2-anilinoalcohols towards cyclic *N*-aryloxazolidinones, where diphenyl carbonate acts as a double acyl donor [36]. The reaction was shown to possess wide substrate compatibility, however displaying some limitations due to the applied KR protocol. To address this challenge, an additional racemization catalyst was introduced in the present process (Scheme 1, yellow part), leading to an improved dynamic kinetic resolution protocol. DKR can in this context lead to high conversions while maintaining high enantiopurities, and has been widely applied in organic synthesis and used for large-scale production in industry [37–42]. However, no reports on DKR-systems for 1,2-anilinoalcohols have been presented. A major issue in chemoenzymatic DKR is the compatibility of the racemization catalyst, which may be deactivated by the enzyme, the substrates/products, or the reaction conditions. For example, in the development of a DKR-protocol for aminoalcohols, Bäckvall and co-workers found severe deactivation of the ruthenium-based racemization catalyst [43,44], which could be attributed to

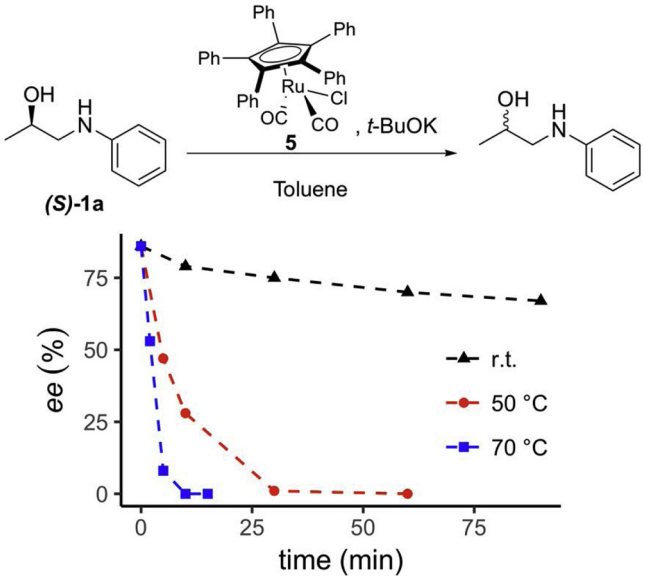


Fig. 2. Racemization of (*S*)-**1a** at different temperatures.

bidentate coordination of the substrates to the ruthenium center [45,46]. Thus, protection of the amino group was required for the transformation to proceed successfully. In the present study, however, we reasoned that this complication would be less pronounced, owing to the weaker coordination of anilines to the ruthenium center, compared to alkyl amines. The presence of the aryl ring would thus prohibit potential bidentate coordination towards the ruthenium center due to enhanced steric hindrance as well as the reduced nucleophilicity. Sterically crowded ruthenium-based catalysts would then be applicable in the present case.

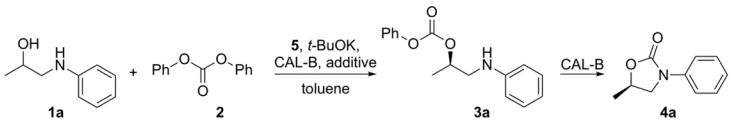
To support this hypothesis, enantioenriched 1,2-anilinoalcohol *(S)*-**1a** (84% *ee*) was examined in toluene with ruthenium catalyst **5**, conveniently and efficiently prepared in 86% isolated yield [24]. No by-products were detected by ^{1}H NMR within 24 h, thus indicating good compatibility of the ruthenium racemization catalyst with 1,2-anilinoalcohols. The racemization process was subsequently performed at different temperatures: room temperature, 30 °C, 50 °C and 70 °C, and monitored by HPLC. As indicated in Fig. 2, higher temperatures led to acceleration of the racemization process, with the transformation at 70 °C being finished within 20 min. This is comparable to the results for other alcohols using the same catalyst [47,48].

Next, the DKR protocol was optimized with respect to enzyme loading, additives, and temperature (Table 1). In general, transformation of the starting material (**1a**) into intermediate **3a** was observed within 8 h, whereas the cyclization process of the intermediate to the final oxazolidinone product proceeded slower. The temperature screen indicated an optimal temperature at 50 °C, with full conversion to the oxazolidinone and 88% *ee* within 66 h (Table 1, entries 1–4). Interestingly, the *ee* of intermediate **3a** was recorded to 60% after complete conversion of the starting material. The considerably higher *ee* of the final product thus indicates an enzyme-catalyzed, stereospecific cyclization process in addition to the stereoselective alkoxycarbonylation step. Either lowering or increasing the catalyst loading led to lower conversions or poorer *ees* (Table 1, entries 5–6).

The additive salts (K_2CO_3, Na_2CO_3, Na_2SO_4, $CaCl_2$) influenced the *ee* only slightly, but otherwise increased the reaction rates to some extent. For enzymatic reactions in nonpolar organic solvents, inorganic salts have been reported to impact the selectivities of the enzymes, mediated by tuning the water content (described as the water activity, a_w) *via* their equilibria between free water molecules and salt-hydrate pairs [49–51]. The use of calcium chloride (a_w ~ 0.04 at 20 °C) [51], instead of sodium carbonate (a_w ~ 0.7 at 20 °C) [51], potassium carbonate (a_w ~ 0.4 at 20 °C) [52], or sodium sulfate (a_w ~ 0.8 at 20 °C), thus resulted in slightly higher enantiopurities (Table 1, entries 6, 8, 10, 11). Of the salts evaluated, $CaCl_2$ displays the lowest a_w, indicating that the enantioselectivity of CAL-B increased at lower a_w in toluene (Table 1, entries 6, 8–10). This is consistent with the trends in previous reports [53,54]. The presence of SiO_2 also produced positive effects on the chiral discrimination (Table 1, entries 6–7, 12–13), as shown in similar enzymatic heterocylizations [15].

Although the cyclization step displayed lower rates, it proved to be a

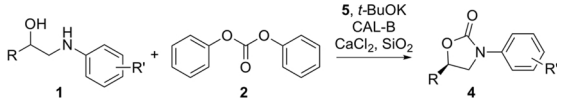
Table 1
Optimization of the DKR process of 1-(phenylamino)propan-2-ol (**1a**).[a].

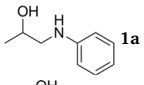
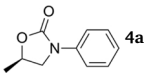
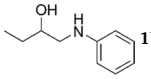
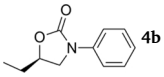
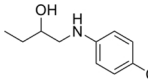
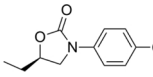
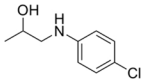
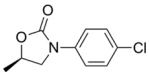
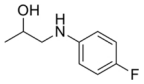
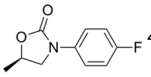
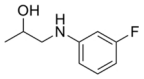
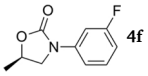
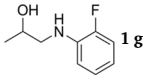
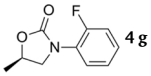
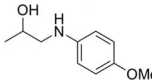
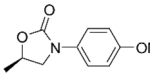
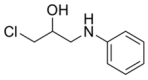
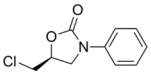


Entry	Lipase (mg)	Additive	T (°C)	Time (h)	Conv. (%)[b]	*ee* (%)[c]
1	15	Na_2CO_3	70	43	98	85
2	15	Na_2CO_3	60	58	97	86
3	15	Na_2CO_3	50	66	quant.	88
4	15	Na_2CO_3	40	97	quant.	74
5	7.5	Na_2CO_3	70	17	25	81
6	30	Na_2CO_3	70	17	quant.	82
7	30	Na_2CO_3, SiO_2	70	19	99	84
8	30	$CaCl_2$	70	23	quant.	86
9	30	4 Å MS	70	22	97	79
10	30	K_2CO_3	70	23	quant.	81
11	30	Na_2SO_4	70	23	quant.	75
12[d]	15	$CaCl_2$ SiO_2	50	18	quant.	90
13	15	$CaCl_2$ SiO_2	50	69	quant.	89
14[e]	15	$CaCl_2$ SiO_2	50	65	quant.	26

[a] Reaction conditions: compound **1** (0.075 mmol), compound **2** (0.225 mmol), Ru-catalyst **5** (0.0075 mmol), *t*-BuOK (0.5 M in THF), CAL-B preparation, additives (0.075 mmol or 20 mg [4 Å MS or SiO_2]), in toluene (1 mL). [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis using Chiralpak OD-H chiral column. [d] Temperature increased to 70 °C following complete conversion of all starting materials to intermediate. [e] Reaction performed without Ru-catalyst and *t*-BuOK.

Table 2
DKR of different substrates.[a].



Entry	Substrate	Product	Time	Conv.(%)[b]	*ee* (%)[c]
1	 **1a**	 **4a**	18 h	quant. (89[d])	90
2[f]	 **1b**	 **4b**	42 h	96	95
3	 **1c**	 **4c**	47 h	quant.	92
4	 **1d**	 **4d**	27 h	quant.	84
5	 **1e**	 **4e**	42 h	quant.	84
6	 **1f**	 **4f**	42 h	97	78
7	 **1 g**	 **4 g**	7 d	quant.	85
8	 **1 h**	 **4 h**	30 h	88	81
9	 **1i**	 **4i**	6 d	87	71

[a] Reaction conditions: compound **1** (0.05 mmol), compound **2** (0.15 mmol), SiO_2 (20 mg), CAL-B preparation (15 mg), Ru-catalyst **5** (0.0075 mmol), *t*-BuOK (0.5 M in THF), $CaCl_2$ (20 mg) in toluene (1 mL) at 50 °C. Average values, each reaction carried out ≥ 2 times. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis using Chiralpak OD-H or OJ chiral column. [d] Isolated yield from reaction at 0.4 mmol scale. [e] For substrates **1c**, **1d**, **1e**, **1f**, **1i**, temperature increased to 70 °C following complete conversion of starting materials to intermediate. [f] 30 mg CAL-B preparation.

CAL-B-catalyzed process that could be accelerated at higher temperature. Thus, an increase in reaction temperature to 70 °C, following complete conversion from the substrate aniline to intermediate **3a**, led to a significantly shortened overall process time without loss of reaction selectivity (Table 1, entry 12). In comparison, the process performed in the absence of the ruthenium catalyst resulted in product formation with only 26% *ee*.

Finally, the developed DKR protocol was applied to a range of other 1,2-anilinoalcohol derivatives to further evaluate the scope of the process. The results are displayed in Table 2, and as can be seen, most of the substrates could be transformed into the corresponding oxazolidinone species through the DKR process with excellent conversions and up to excellent *ees*. Under the conditions developed, the protocol displayed the best results for the *O*-ethyl substrate (95% *ee*, Table 2, entry 2). Halogen substituents at different positions of the aniline ring also proved highly compatible with the protocol (Table 2, entries 3–7). These results show high tolerance of halogen atoms in the phenyl ring, thus enabling further modification of the enantioenriched *N*-aryloxazolidinones. Interestingly, the *ortho*-fluorine substrate was considerably more sluggishly transformed in the process, however still resulting in excellent conversion and good *ee* (85%, Table 2, entry 7). A *para*-methoxy group on the aniline ring led to a comparably good *ee* value, albeit slight deactivation of the racemization catalyst was expected, also resulting in lower conversion (Table 2, entry 8).

Conclusions

In summary, a DKR protocol for the transformation of 1,2-anilinoalcohol substrates to enantioenriched 5-substituted *N*-aryloxazolidinones was developed. The protocol employed a ruthenium complex as racemization catalyst, combined with CAL-B-catalyzed inter- and intramolecular alkoxycarbonylation in two stereoselective steps. Various *N*-aryloxazolidinone analogs carrying different functional groups were obtained with up to excellent *ees* and generally excellent conversions. Aniline structures showed high compatibility with the ruthenium-catalyzed racemization process, enabling direct application of 1,2-aminoalcohols in DKR without pre-protection. In combination with directed evolution-type protocols, the developed DKR protocol shows high potential for further optimization of the enantioenrichment process. Furthermore, 1,3-anilinoalcohol substrates may be applied to obtain oxazinanones, a venue we are currently pursuing.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

online version, at doi:https://doi.org/10.1016/j.mcat.2019.03.020.

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