Supporting Information

To accompany

Organocatalytic Asymmetric Aza-Nazarov Cyclization of an Azirine Accompanied by a Kinetic Resolution

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General Experimental:

$^1$H NMR and $^{13}$C NMR spectra were recorded either at 300 MHz ($^1$H) and 75 MHz ($^{13}$C) or at 500 MHz ($^1$H) and 125 MHz ($^{13}$C). Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, i.e. 7.26/77.0 for CDCl$_3$ or 3.30/49.0 for CD$_3$OD. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). Thin layer chromatography (TLC) was performed on glass plates 250 µm, particle size 5-17 µm, pore size 60 Å. Flash column chromatography was performed on silica gel, 200-400 mesh or premium silica gel, 60 Å, 40-75 µm. All moisture sensitive reactions were performed under a static atmosphere of nitrogen or argon in oven dried or flame dried glassware. Purity and homogeneity of all materials was determined from TLC, $^1$H NMR, $^{13}$C NMR, and HPLC.
Screening of catalysts

In addition to 7, catalysts A, B, C and D were examined for activity. Catalyst A gave results that were essentially the same as with 7, whereas catalysts B-D did not lead to any reaction of 4, indicating the importance of the primary amino group.
(E)-2-(tert-butylimethylsilyl)oxy-3-methyl-4-phenylbut-3-enenitrile (1)

To a stirred solution of α-methylcinnamaldehyde (5.24 g, 35.8 mmol, 1.0 eq) in CH$_3$CN (180 mL), was added sequentially KCN (18.6 g, 286.4 mmol, 8.0 eq), TBSCI (6.49 g, 42.9 mmol, 1.2 eq) and ZnI$_2$ (1.14 g, 3.6 mmol, 10 mol %) at 21°C. After 18 h, the mixture was quenched with H$_2$O and extracted with EtOAc. The combined organic layers were dried over anhydrous Na$_2$SO$_4$. Filtration and evaporation in vacuo followed by column chromatography (silica gel, hexane to 50:1 hexane/EtOAc) provided cyanohydrin 1 (9.24 g, 90% yield) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.34–7.23 (m, 5H), 6.66 (s, 1H), 4.91 (s, 1H), 1.96 (s, 3H), 0.92 (br s, 9H), 0.20 (s, 3H), 0.15 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 135.9, 132.6, 128.8, 128.7, 128.1, 127.3, 118.6, 67.6, 25.4, 18.0, 13.4, −5.3.

(2Z,5E)-ethyl 3-amino-4-(tert-butylimethylsilyl)oxy-2-ethyl-5-methyl-6-phenylhexa-2,5-dienoate (2)

To a stirred suspension of activated Zn dust (680 mg, 10.4 mmol, 3.0 eq) in THF (9 mL) under reflux, a solution of cyanohydrin 1 (1.00 g, 3.4 mmol, 1.0 eq) in THF (3 mL) was transferred by cannula. Then ethyl-2-bromobutyrate (0.90 mL, 6.0 mmol, 1.8 eq) was added dropwise over a period of 1 h while maintaining steady reflux. After an additional hour the reaction mixture was cooled to 21°C and poured into a vigorously stirred mixture of 50% aq K$_2$CO$_3$ (5 mL) and THF (25 mL). After 30 min the clear solution was decanted off, dried over anhydrous Na$_2$SO$_4$. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 50:1 hexane/EtOAc) provided enamino ester 2 (1.12 g, 80% yield) as a clear oil. IR (neat) 3482, 3313, 2955, 2858, 1660, 1595, 1510, 1236, 1064, 873, 749 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36–7.39 (m, 3H), 7.26–7.23 (d, $J$ = 8.4 Hz, 2H), 6.54 (br s, 1H), 5.08 (s, 1H), 4.15 (q, $J$ = 7.2 Hz, 2H), 2.47-2.10 (m, 2H), 1.81 (s, 3H), 1.28 (t, $J$ = 7.2 Hz, 3H), 0.96–0.90 (m, 12 H), 0.14 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.6, 158.1, 137.0, 136.9, 128.7, 128.0, 126.6, 93.8, 76.0, 58.5, 25.6, 18.8, 18.0, 14.8, 14.4, 12.5, −4.8, −5.3; HRMS (EI) calcd. for C$_{23}$H$_{37}$NO$_3$Si: 403.2542 found: 403.2539.
(2Z,5E)-ethyl 3-amino-2-ethyl-5-methyl-4-oxo-6-phenylhexa-2,5-dienoate (5)

Tetrabutylammonium fluoride monohydrate (587 mg, 1.86 mmol, 1.5 eq) was added to a stirred solution of enamino ester 2 (500 mg, 1.24 mmol, 1.0 eq) in THF (6 mL) at 0 °C. After stirring at this temperature for 20 min, the reaction was quenched by addition of water. The mixture was extracted with EtOAc, and the combined organic layers were washed with water, brine and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo followed by short column chromatography (silica gel, 4:1 hexane/EtOAc) provided alcohol 3 (quantitative yield) as a pale yellow oil. SO₃/pyridine complex (591 mg, 3.72 mmol, 3.0 eq), DMSO (0.26 mL, 3.72 mmol, 3.0 eq), N,N-diisopropylethylamine (1.33 mL, 7.43 mmol, 6.0 eq) was added to a solution of the above alcohol 3 in CH₂Cl₂ (6 mL) at 0 °C. The solution was stirred at this temperature for 20 min. Then water was added and aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with water, brine and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 10:1 hexane/EtOAc) provided aminodienone 5 (215 mg, 60% yield, overall for 2 steps) as a yellow oil. IR (film) 3360, 2926, 1788, 1659, 1605 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 7.65 (s, 1H), 7.50 (d, J = 7.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.12 (s, 3H), 1.97 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CD₃OD) δ 198.1, 171.6, 158.0, 147.2, 136.5, 131.2, 130.6, 129.7, 126.3, 95.9, 60.2, 22.1, 15.5, 14.9, 12.2; HRMS (EI) calcd for C₁₇H₂₁NO₃ (M⁺) 287.1521, found 287.1510.

Ethyl 2-ethyl-3-((E)-2-methyl-3-phenylacryloyl)-2H-azirine-2-carboxylate (4)

To a solution of the aminodienone 5 (200 mg, 0.67 mmol, 1.0 eq) in 1,2-dichlorethane (7 mL) was added Phl(OAc)₂ (336 mg, 1.04 mmol, 1.5 eq) in a portionwise at 0°C. After the stirring at this temperature for 30 min the cooling bath was removed and stirring was continued at 21°C for 1 h. Upon completion of the reaction, the reaction mixture was filtered through a pad of Celite® and the pad was washed with EtOAc. The filtrate was concentrated in vacuo followed by column
chromatography (silica gel, 20:1 hexane/ EtOAc) provided azirine 4 (111 mg, 56% yield) as a yellow oil. IR (neat) 2976, 1720, 1682, 1448, 1256, 1214, 1015, 694 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.15 (s, 1H), 7.54–7.57 (m, 2H), 7.42–7.49 (m, 3H), 4.19 (q, \(J = 7.2\) Hz, 2H), 2.25 (s, 3H), 2.16 (qd, \(J = 7.5, 3.0\) Hz, 2H), 1.25 (t, \(J = 7.2\) Hz, 3H), 0.89 (t, \(J = 7.5\) Hz, 3H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 184.9, 171.3, 163.9, 148.6, 135.8, 134.8, 130.6, 130.1, 128.7, 61.7, 44.3, 23.2, 14.2, 12.5, 10.0; HRMS (EI) calcd for C\(_{17}\)H\(_{19}\)NO\(_3\): 285.1365 found 285.1365.

(2S,6S)-ethyl 2-ethyl-1,2,3,6-tetrahydro-4-hydroxy-5-methyl-3-oxo-6-phenylpyridine-2-carboxylate (6)

To a solution of the azirine 4 (28.5 mg, 0.10 mmol 1.0 eq) in MeCN (130 \(\mu\)L) was added water (1.0 M in MeCN, 120 \(\mu\)L, 0.12 mmol. 1.2 eq), 1,2-diamine 7 (1.0 M in CH\(_2\)Cl\(_2\), 20 \(\mu\)L, 0.02 mmol, 20 mol %) at 21°C. After stirring at this temperature for 9 days brine was added and the whole was extracted with EtOAc. The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\). Filtration and evaporation in vacuo followed by column chromatography (silica gel, 20:1 hexane/EtOAc) provided piperidinone 6 (8.5 mg, 28% yield) as a colorless oil and optically active azirine 4 (10.4 mg, 36% yield, [\(\alpha\)]\(_D\)\(^{23}\) +5.4 (c 0.58, MeOH)) as a colorless oil.

Compound (+)-6: [\(\alpha\)]\(_D\)\(^{25}\) = +57.5 (c = 0.36, CHCl\(_3\)); IR (neat) 3425, 2979, 2937, 1730, 1678, 1652, 1452, 1388, 1237 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.19–7.34 (m, 5H), 6.13 (s, 1H), 4.57 (s, 1H), 3.86–4.00 (m, 2H), 2.63 (s, 1H), 1.87–1.96 (m, 2H), 1.63 (s, 3H), 1.11 (t, \(J = 7.2\) Hz, 3H), 0.96 (t, \(J = 7.2\) Hz, 3H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 190.4, 170.1, 142.8, 140.7, 130.2, 129.2, 128.9, 128.5, 68.8, 62.1, 59.4, 27.3, 14.6, 14.1, 8.9; HRMS (ESI+) calcd. for C\(_{17}\)H\(_{22}\)NO\(_4\) (M+H) 304.1549, found 304.1535; Chiral HPLC (5% i-PrOH / Hexanes, Chiralcel AD-H\({\text{\textregistered}}\), 4.6 mm x 250 mm, UV detection at 261 nm, 1 mL/min) \(t_R = 12.2\) min (major), \(t_R = 15.1\) min (minor).
(2S,6S,4(1S))-ethyl 2-ethyl-1,2,3,6-tetrahydro-4-(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl)oxy-5-methyl-3-oxo-6-phenylpyridine-2-carboxylate (8)

(−)-Camphanoyl chloride (5.9 mg, 27.8 µmol, 2 eq) was added to a stirred solution of piperidone 6 (4.0 mg, 13.9 µmol, 1.0 eq) and DMAP (6.8 mg, 55.6 µmol, 4 eq) in CH₂Cl₂ (1 mL) at 0 °C. After stirring at 21°C for 30 min, the reaction was quenched by addition of water and the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with 10% aq HCl solution, saturated aq NaHCO₃, and brine and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo followed by column chromatography (silica gel, 4:1 hexane/EtOAc) provided camphanic ester 8 (6.0 mg, 92% yield) as a white solid. Dissolution in EtOAc and slow diffusion of hexane in a sealed vessel yielded a colorless crystal suitable for single crystal X-ray analysis. ¹H NMR (500 MHz, CDCl₃) δ 7.33–7.42 (m, 5H), 4.68 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 2.80 (br s, 1H), 2.56 (m, 1H), 1.95–2.18 (m, 4H), 1.73 (m, 1H), 1.64 (s, 3H), 1.21 (s, J = 7.2 Hz, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 186.4, 178.0, 169.3, 165.0, 147.3, 139.6, 139.3, 129.3, 128.7, 128.3, 91.0, 70.0, 62.0, 59.9, 55.0, 54.8, 30.9, 28.9, 26.0, 16.6, 15.2, 13.9, 9.6, 8.5; HRMS (EI) calcd for C₂₇H₃₃NO₇ (M⁺) 483.2257, found 483.2243.