A Highly Chemoselective and Enantioselective Aza-Henry Reaction of Cyclic $\alpha$-Carbonyl Ketimines under Bifunctional Catalysis

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General Methods

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300 and 75 MHz for $^1$H and $^{13}$C, respectively. Chemical shifts ($\delta$) are reported in ppm relative to residual solvent signals (CHCl$_3$, 7.26 ppm for $^1$H NMR, CDCl$_3$, 77.0 ppm). $^{13}$C-NMR spectra were acquired on a broad band decoupled mode. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or KMnO$_4$ dip. Purification of reaction products was carried out by flash chromatography (FC) using silica gel Merck-60. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excesses (ee) of products were determined by chiral stationary phase HPLC (Daicel Chiralcel IC column).

Materials. Commercially available nitroalkanes 2, catalysts 6, and 7 and solvents were used without further purification. 2-Aryl-3H-indol-3-ones 1a-j, $^1$ catalysts 4a-e$^2$ and 5$^3$ were synthesized according to the literature.

tert-Butyl 3-oxo-1'H,3H-2,3'-biindole-1'-carboxylate (1j):

The product was obtained following the reported procedure$^1$ as red solid (45% yield) after FC (eluent 1/1; hexane/AcOEt); $^1$H-NMR (CDCl$_3$): $\delta$ = 8.68 (s, 1H), 8.50-8.47 (m, 1H), 8.11-8.08 (m, 3H), 6.98 (d, $J$ = 8.2 Hz, 1H), 6.84 (t, $J$ = 7.7 Hz, 1H), 5.88 (s, 1H), 7.40 (t, $J$ = 7.3 Hz, 3H), 7.32-7.28 (m, 3H), 7.08 (t, $J$ = 7.5 Hz, 1H), 1.63 (s, 9H). $^{13}$C-NMR (CDCl$_3$): $\delta$ = 194.1, 162.1, 158.1, 149.0, 136.9, 135.1, 132.3, 128.1, 127.4, 125.7, 125.6, 124.1, 123.3, 122.7, 121.8, 115.2, 111.3, 85.0, 28.1. HRMS: calculated for C$_{21}$H$_{18}$N$_2$O$_3$ [M]$^+$ 346.1317; found 346.1319.

 Experimental Procedures and Characterizations

General Procedure for the synthesis of compounds 3. To an ordinary vial charged with corresponding 2-aryl-3H-indol-3-ones 1a-i (0.2 mmol) was added the catalyst 4e (10 mol%), and the corresponding nitroalkane 3 (2.0 mmol) in p-xilene (0.72 mL). The reaction mixture was stirring at room temperature for 48 h. Once the reaction was finished (followed by TLC), the crude was directly charged and purified by FC, affording pure products.

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(S)-2-(Nitromethyl)-2-phenylindolin-3-one (3a):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (90% yield) after FC (eluent 5/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IC column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 18.2 \text{ min} \), \( \tau_{\text{major}} = 20.1 \text{ min} \) (e.r. = 95:5). \([\alpha]^{20}_D = -322.0 \) (c = 0.4 in CHCl3); 1H-NMR (CDCl3): \( \delta = 7.56-7.47 \) (m, 4H), 7.32-7.29 (m, 3H), 6.98 (d, \( J = 8.2 \text{ Hz} \), 1H), 6.84 (t, \( J = 7.7 \text{ Hz} \), 1H), 5.88 (s, 1H), 5.19 (d, \( J = 13.7 \text{ Hz} \), 1H), 4.75 (d, \( J = 13.7 \text{ Hz} \), 1H). 13C-NMR (CDCl3): \( \delta = 196.2, 160.1, 138.3, 134.4, 129.2, 128.8, 125.8, 125.1, 120.1, 118.3, 112.2, 80.3, 69.2 \). HRMS: calculated for C15H12N2O3 [M]\(^+\) 268.0848; found 268.0837.

(S)-2-(Nitromethyl)-2-(p-tolyl)indolin-3-one (3b):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (93% yield) after F-C (eluent 5/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IC column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 22.9 \text{ min} \), \( \tau_{\text{major}} = 19.1 \text{ min} \) (e.r. = 91:9). \([\alpha]^{20}_D = -331.1 \) (c = 0.35 in CHCl3); 1H-NMR (CDCl3): \( \delta = 7.50 \) (d, \( J = 7.7 \text{ Hz} \), 1H), 7.44 (td, \( J_1 = 7.0, 1.3 \text{ Hz} \), 1H), 7.32 (d, \( J = 9.0 \text{ Hz} \), 2H), 7.08 (d, \( J = 9.0 \text{ Hz} \), 2H), 6.93 (d, \( J = 8.3 \text{ Hz} \), 1H), 6.79 (t, \( J = 7.0 \text{ Hz} \), 1H), 5.80 (s, 1H), 5.12 (d, \( J = 15.0 \text{ Hz} \), 1H), 4.70 (d, \( J = 15.0 \text{ Hz} \), 1H), 2.22 (s, 3H). 13C-NMR (CDCl3): \( \delta = 196.5, 160.1, 138.7, 138.2, 131.4, 130.0, 125.9, 125.4, 120.4, 118.5, 112.2, 80.2, 69.2, 21.0 \). HRMS: calculated for C16H14N2O3 [M]\(^+\) 282.1004; found 282.0996.

(S)-2-(4-Ethylphenyl)-2-(nitromethyl)indolin-3-one (3c):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (93% yield) after F-C (eluent 6/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IC column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 18.6 \text{ min} \), \( \tau_{\text{major}} = 22.4 \text{ min} \) (e.r. = 92:8). \([\alpha]^{20}_D = -390.1 \) (c = 0.15 in CHCl3); 1H-NMR (CDCl3): \( \delta = 7.51 \) (d, \( J = 7.7 \text{ Hz} \), 1H), 7.48 (td, \( J = 7.0, 1.3 \text{ Hz} \), 1H), 7.36 (d, \( J = 9.0 \text{ Hz} \), 2H), 7.13 (d, \( J = 9.0 \text{ Hz} \), 2H), 6.94 (d, \( J = 8.3 \text{ Hz} \), 1H), 6.81 (t, \( J = 7.0 \text{ Hz} \), 1H), 5.77 (s, 1H), 5.40 (d, \( J = 12.0 \text{ Hz} \), 1H), 4.72 (d, \( J = 12.0 \text{ Hz} \), 1H), 2.53 (q, \( J = 6.0 \text{ Hz} \), 2H), 1.12 (t, \( J = 6.0 \text{ Hz} \), 3H). 13C-NMR (CDCl3): \( \delta = 195.9, 159.6, 144.5, 137.7, 131.1, 128.3, 125.3, 124.6, 119.6, 118.0, 111.7, 79.8, 68.7, 27.9, 14.8 \). HRMS: calculated for C17H16N2O3 [M]\(^+\) 296.1161; found 296.1153.
(S)-2-(4-Methoxyphenyl)-2-(nitromethyl)indolin-3-one (3d):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (95% yield) after FC (eluent 5/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak ID column [hexane/iPrOH (80:20)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 18.6 \text{ min} \), \( \tau_{\text{major}} = 23.4 \text{ min} \) (e.r. = 85:15). \( \alpha \)\text{D} = -158.4 (c = 0.19 in CHCl3); \( \delta \)-H-NMR (CDCl3): \( \delta = 7.51 \text{ (d, } J = 7.7 \text{ Hz, 1H)}, 7.45 \text{ (td, } J_1 = 7.4, J_2 = 0.9 \text{ Hz, 1H)}, 7.37 \text{ (d, } J = 9.0 \text{ Hz, 2H)}, 6.80 \text{ (d, } J = 9.0 \text{ Hz, 2H)}, 6.93 \text{ (d, } J = 8.2 \text{ Hz, 1H)}, 6.807 \text{ (t, } J = 6.9 \text{ Hz, 1H}), 5.79 \text{ (s, 1H)}, 5.10 \text{ (d, } J = 12.0 \text{ Hz, 1H}), 4.68 \text{ (d, } J = 12.0 \text{ Hz, 1H)}, 3.69 \) (s, 3H). \( 13 \)-C-NMR (CDCl3): \( \delta = 196.5, 160.0, 138.2, 126.5, 126.2, 125.8, 102.1, 118.5, 114.6 (2C), 112.2, 80.46, 68.7, 55.3. \) HRMS: calculated for C16H14N2O4 [M]+ 298.0954; found 298.0954.

(S)-2-(4-Fluorophenyl)-2-(nitromethyl)indolin-3-one (3e):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (93% yield) after FC (eluent 5/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IC column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 15.0 \text{ min}, \tau_{\text{major}} = 13.2 \text{ min} \) (e.r. = 91:9). \( \alpha \)\text{D} = -415.6 (c = 0.14 in CH2Cl2); \( \delta \)-H-NMR (CDCl3): \( \delta = 7.53-7.46 \) (m, 4H), 6.98 (t, \( J = 8.51 \text{ Hz, 3H} \)), 6.83 (t, \( J = 7.55 \text{ Hz, 1H} \)), 5.88 (s, 1H), 5.12 (d, \( J = 15.0 \text{ Hz, 1H} \)), 4.63 (d, \( J = 15.0 \text{ Hz, 1H} \)). \( 13 \)-C-NMR (CDCl3): \( \delta = 196.0, 164.7, 160.9 \) (d, \( J_{\text{C,F}} = 426 \text{ Hz} \)), 138.6, 130.1 (d, \( J_{\text{C,F}} = 12.0 \text{ Hz} \)), 127.2 (d, \( J_{\text{C,F}} = 36.0 \text{ Hz} \)), 125.9, 120.4, 118.2, 116.1 (d, \( J_{\text{C,F}} = 87 \text{ Hz} \)), 112.3, 80.5, 68.7. HRMS: calculated for C15H11FN2O3 [M]+ 286.0754; found 286.0765.

(S)-2-(4-Chlorophenyl)-2-(nitromethyl)indolin-3-one (3f):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (81% yield) after FC (eluent 5/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IC column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 14.2 \text{ min}, \tau_{\text{major}} = 12.3 \text{ min} \) (e.r. = 93:7). \( \alpha \)\text{D} = -305.1 (c = 0.4 in CHCl3); \( \delta \)-H-NMR (CDCl3): \( \delta = 7.52-7.41 \) (m, 2H), 7.44 (d, \( J = 9.0 \text{ Hz, 2H} \)), 7.26 (d, \( J = 9.0 \text{ Hz, 2H} \)), 6.97 (d, \( J = 8.2 \text{ Hz, 1H} \)), 6.83 (t, \( J = 7.5 \text{ Hz, 1H} \)), 5.89 (s, 1H), 5.12 (d, \( J = 15.0 \text{ Hz, 1H} \)), 4.63 (d, \( J = 15.0 \text{ Hz, 1H} \)). \( 13 \)-C-NMR (CDCl3): \( \delta = 195.7, 160.1, 138.6, 135.1, 133.0, 129.3, 126.7, 125.9, 120.4, 118.0, 112.4, 80.3, 68.8. \) HRMS: calculated for C15H11N2O3Cl [M]+ 302.0458; found 302.0468.
(S)-2-(2-Bromophenyl)-2-(nitromethyl)indolin-3-one (3g):

The product was obtained following the standard procedure using catalyst 4e as yellow solid (81% yield) after FC (eluent 7/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IC column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 21.7 \text{ min}, \tau_{\text{major}} = 24.1 \text{ min} \) (e.r. = 2:98). \([\alpha]_{20}^D = -346.7 \) (c = 0.15 in CHCl$_3$). Mp: 198-200 °C. \(^1\)H-NMR (CDCl$_3$): \( \delta = 7.69 \) (d, \( J = 9.0 \) Hz, 1H), 7.64-7.61 (m, 1H), 7.48 (m, 2H), 7.25 (m, 2H), 6.87-6.81 (m, 2H), 6.24 (s, 1H), 5.45 (d, \( J = 12.0 \) Hz, 1H), 4.96 (d, \( J = 12.0 \) Hz, 1H). \(^1\)C-NMR (CDCl$_3$): \( \delta = 195.9, 158.9, 137.0, 134.8, 131.5, 129.7, 128.9, 127.9, 124.1, 121.7, 119.4, 119.2, 111.9, 76.9, 68.8 \). HRMS: calculated for C$_{15}$H$_{11}$BrN$_2$O$_3$ [M]+ 345.9953; found 345.9939.

(S)-2-(Naphthalen-2-yl)-2-(nitromethyl)indolin-3-one (3h):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (>99% yield) after FC (eluent 5/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IC column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 20.6 \text{ min}, \tau_{\text{major}} = 23.8 \text{ min} \) (e.r. = 92:8). \([\alpha]_{20}^D = -341.0 \) (c = 1.0 in CH$_2$Cl$_2$); \(^1\)H-NMR (CDCl$_3$): \( \delta = 7.99 \) (d, \( J = 1.8 \) Hz, 1H), 7.84 (d, \( J = 8.8 \) Hz, 1H), 7.81-7.79 (m, 2H), 7.64 (dd, \( J = 8.7, 2.0 \) Hz, 1H), 7.60 (d, \( J = 7.9 \) Hz, 1H), 7.59-7.53 (m, 1H), 7.51-7.45 (m, 2H), 7.07 (d, \( J = 8.2 \) Hz, 1H), 6.70 (t, \( J = 7.7 \) Hz, 1H), 6.05 (s, 1H), 5.35 (d, \( J = 15.0 \) Hz, 1H), 4.87 (d, \( J = 15.0 \) Hz, 1H). \(^1\)C-NMR (CDCl$_3$): \( \delta = 196.2, 160.2, 138.4, 133.2, 133.2, 131.8, 129.3, 128.3, 128.3, 127.6, 126.8, 126.7, 125.9, 124.7, 122.5, 120.2, 118.5, 112.4, 80.4, 69.4 \). HRMS: calculated for C$_{19}$H$_{14}$N$_2$O$_3$ [M]+ 318.1004; found 318.1007.

(S)-2-([1,1'-Biphenyl]-4-yl)-2-(nitromethyl)indolin-3-one (3i):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (37% yield) after FC (eluent 5/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IA column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \( \tau_{\text{minor}} = 34.9 \text{ min}, \tau_{\text{major}} = 52.3 \text{ min} \) (e.r. = 92:8). \([\alpha]_{20}^D = -415.6 \) (c = 0.14 in CH$_2$Cl$_2$); \(^1\)H-NMR (CDCl$_3$): \( \delta = 7.62-7.52 \) (m, 9H), 7.42 (t, \( J = 7.0 \) Hz, 1H), 7.35 (d, \( J = 8.2 \) Hz, 1H), 6.90 (t, \( J = 7.6 \) Hz, 1H), 5.94 (s, 1H), 5.29 (d, \( J = 12.0 \) Hz, 1H), 4.81 (d, \( J = 12.0 \) Hz, 1H). \(^1\)C-NMR (CDCl$_3$): \( \delta = 196.1, 160.1, 141.8, 140.1, 138.4, 133.3, \)
128.8, 127.9, 127.7, 127.1, 125.9, 125.6, 120.3, 118.4, 112.3, 80.3, 69.2. HRMS: calculated for C\textsubscript{21}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3} [M]+ 344.1161; found 344.1154.

\textit{(S)-tert-Butyl 2-(nitromethyl)-3-oxo-2,3'-biindoline-1'-carboxylate (3j)}:

The product was obtained following the standard procedure using catalyst \textit{4e} as yellow oil (52% yield) after FC (eluent 5/1; hexane/AcOEt). The \textit{ee} was determined by HPLC using a Chiralpak IC column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \(\tau_{major} = 19.5 \text{ min, } \tau_{minor} = 21.5 \text{ min (e.r. = 80:20). } [\alpha]^{20}_D = -49.3 \text{ (c = 0.75 in CH}_2\text{Cl}_2); ^1\text{H-NMR (CDCl}_3): \delta = 8.09 \text{ (d, } J = 8.3 \text{ Hz, 1H), 7.64-7.58 (m, 3H), 7.50 (t, } J = 8.3 \text{ Hz, 1H), 7.26 (t, } J = 8.3 \text{ Hz, 1H), 7.15 (d, } J = 7.2 \text{ Hz, 1H), 6.94 (d, } J = 8.2 \text{ Hz, 1H), 6.88 (t, } J = 7.8 \text{ Hz, 1H), 5.62 (sb, 1H), 5.26 (d, } J = 13.2 \text{ Hz, 1H), 4.86 (d, } J = 13.2 \text{ Hz, 1H), 1.58 (s, 9H).} ^{13}\text{C-NMR (CDCl}_3): \delta = 194.6, 160.1, 138.3, 135.9, 126.9, 125.7, 125.1, 124.4, 123.2, 120.6, 119.9, 119.6, 115.9, 114.4, 112.9, 84.6, 79.2, 77.2, 66.6, 28.1. HRMS: calculated for C\textsubscript{22}H\textsubscript{21}N\textsubscript{3}O\textsubscript{5} [M]+ 407.1481; found 407.1481.

\textit{(S)-2-[\textit{(S/R)}-1-Nitroethyl]-2-phenylindolin-3-one (3k/3k')}:

These products were obtained as a mixture of diastereoisomers (dr=3:1) following the standard procedure using catalyst \textit{4e}. \textit{Major diasterisomer}: it was isolated as a yellow oil in 73% yield after FC (eluent 6/1; hexane/AcOEt). The \textit{ee} was determined by HPLC using a Chiralpak IA column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \(\tau_{minor} = 8.3 \text{ min, } \tau_{major} = 7.3 \text{ min (e.r. = 91:9). } [\alpha]^{20}_D = -276.5 \text{ (c = 0.78 in CH}_2\text{Cl}_2); ^1\text{H-NMR (CDCl}_3): \delta = 7.54-7.21 (m, 7H), 7.02 (d, } J = 8.3 \text{ Hz, 1H), 6.78-6.73 (m, 1H), 6.00 (sb, 1H), 5.46 (q, } J = 6.5 \text{ Hz, 1H), 1.64 (d, } J =4.0 \text{ Hz, 3H).} ^{13}\text{C-NMR (CDCl}_3): \delta =195.7, 160.4, 137.6, 134.6, 128.2, 127.9, 124.6, 124.4, 118.7, 117.5, 111.1, 87.4, 71.3, 14.1. \textit{Minor diasterisomer}: it was isolated as yellow oil in 24% yield after FC (eluent 6/1; hexane/AcOEt). The \textit{ee} was determined by HPLC using a Chiralpak IA column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; \(\tau_{minor} = 42.0 \text{ min, } \tau_{major} = 31.0 \text{ min (e.r. = 89:11). } [\alpha]^{20}_D = -168.8 \text{ (c = 0.40 in CH}_2\text{Cl}_2); ^1\text{H-NMR (CDCl}_3): \delta = 7.49-1.17 (m, 7H), 7.0 (d, } J = 8.1 \text{ Hz, 1H), 6.95-6.78 (m, 1H), 5.43(q, } J = 6.1 \text{ Hz, 1H), 5.26 (sb, 1H), 1.24 (d, } J = 3.2 \text{ Hz, 1H).} ^{13}\text{C-NMR (CDCl}_3): 180.1, 144.2, 121.2, 118.3, 112.3, 111.8, 109.8, 109.1, 104.1, 103.3, 95.7, 69.6, 55.6, 12.3. HRMS: calculated for C\textsubscript{16}H\textsubscript{14}N\textsubscript{2}O\textsubscript{3} [M]+ 282.1000; found 282.1011.
(S)-2-(2-Nitropropan-2-yl)-2-phenylindolin-3-one (3l):

The product was obtained following the standard procedure using catalyst 4e as yellow oil (87% yield) after FC (eluent 6/1; hexane/AcOEt). The ee was determined by HPLC using a Chiralpak IA column [hexane/iPrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{minor}} = 11.8 \text{ min, } \tau_{\text{major}} = 9.8 \text{ min (e.r. = 56:44).}$ $^1$H-NMR (CDCl$_3$): $\delta = 7.62 - 7.18 \text{ (m, 7H), } 6.88 \text{ (d, } J = 8.7 \text{ Hz , 1H), } 6.76 - 6.71 \text{ (m, 1H), } 2.01 \text{ (s, 6H).}$ $^{13}$C-NMR (CDCl$_3$): $\delta = 196.8, 159.5, 137.8, 133.6, 128.7, 128.1, 127.4, 125.1, 120.6, 119.4, 111.8, 94.2, 71.8, 22.8, 21.0$. HRMS: calculated for C$_{17}$H$_{16}$N$_2$O$_3$ [M$^+$] $296.1161$; found $296.1246$. 
Spectra of compounds 1j and 3a-l
Major diastereoisomer
Minor diastereoisomer

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HPLC chromatograms of compound 3a-k
Figure 1. ORTEP of the compound 3g.\textsuperscript{4}

\textsuperscript{4} The structure of a compound derived 3g was determined by X-ray crystal analysis. Complete structural data have been deposited at the CCDC (CCDC 884937).