Divergent Nickel-Catalysed Ring-Opening–Functionalization of Cyclobutanone Oximes with Organozincs

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2 General Experimental Details

All required fine chemicals were used directly without purification unless stated otherwise. All air and moisture sensitive reactions were carried out under nitrogen atmosphere using standard Schlenk manifold technique. THF was distilled from sodium/benzophenone, O-(2,4-dinitrophenyl)hydroxylamine was purchased by Fluorochem and used without further purification. $^1$H and $^{13}$C Nuclear Magnetic Resonance (NMR) spectra were acquired at various field strengths as indicated and were referenced to CHCl$_3$ (7.26 and 77.1 ppm for $^1$H and $^{13}$C respectively). $^1$H NMR coupling constants are reported in Hertz and refer to apparent multiplicities and not true coupling constants. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, sx = sextet, sp = septet, m = multiplet, dd = doublet of doublets, etc.), proton assignment (determined by 2D NMR experiments: COSY, HSQC and HMBC) where possible. High-resolution mass spectra were obtained using a JEOL JMS-700 spectrometer or a Fissions VG Trio 2000 quadrupole mass spectrometer. Spectra were obtained using electron impact ionization (EI) and chemical ionization (CI) techniques, or positive electrospray (ES). Infra-red spectra were recorded using a JASCO FT/IR 410 spectrometer or using an ATI Mattson Genesis Seris FTIR spectrometer as evaporated films or liquid films. Analytical TLC: aluminum backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F254. Compounds were visualized by exposure to UV-light or by dipping the plates in permanganate (KMnO$_4$) stain followed by heating. Flash column chromatography was performed using Merck Silica Gel 60 (40–63 µm). All mixed solvent eluents are reported as v/v solutions.
3 Starting Material Synthesis

Preparation of nickel(II)(4,4'-di-tert-butyl-2,2'-bipyridine)(Br)_2

This has been prepared according to literature procedures.\textsuperscript{1, 2}

Preparation of Organozinc Reagents

Stock solutions of the following organozincs have been prepared according to the procedures reported in the literature, from the corresponding commercially available Grignard reagents.\textsuperscript{3} All the solutions of Grignard reagents used for the synthesis were titrated before use, according to the procedure reported in the literature.\textsuperscript{4}

Preparation of starting material 1, 3 and 4 – General Procedure 1

A solution of the ketone (1.0 equiv.) in EtOH (0.1 M) was treated with the O-(2,4-dinitrophenyl)hydroxylamine (1.0 equiv.) and HCl (1-3 drops). Upon addition of HCl the mixture became yellow and over time the product crystallized out. Once the reaction was judged complete by TLC analysis the pure product was filtered washing with cold EtOH and dried under high vacuum for 2 h.
Cyclobutanone-O-(2,4-dinitrophenyl)-oxime (1)

Following GP1, cyclobutanone (700 mg, 10.0 mmol) gave 1 (49%) as a pale yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.86 (1H, d, $J = 2.7$ Hz), 8.40 (1H, dd, $J = 9.4, 2.8$ Hz), 7.87 (1H, d, $J = 9.4$ Hz), 3.21 (2H, t, $J = 8.1$ Hz), 3.12 (2H, t, $J = 8.0$ Hz), 2.16 (2H, p, $J = 8.1$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 169.4, 157.7, 140.6, 135.9, 129.4, 122.2, 117.1, 32.3, 31.6, 14.6; HRMS (APCI): Found MH$^+$ 252.0612 C$_{10}$H$_{10}$N$_3$O$_5$ requires 252.0615.

tert-Butyl-2-((2,4-dinitrophenoxylimino)-7-azaspiro[3.5]nonane-7-carboxylate (3)

Following GP1, tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (717 mg, 3.0 mmol) gave 3 (40%) as a pale yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.86 (1H, d, $J = 2.7$ Hz), 8.41 (1H, dd, $J = 9.4, 2.7$ Hz), 7.87 (1H, d, $J = 9.4$ Hz), 3.45 (2H, dt, $J = 11.3, 5.4$ Hz), 3.37 (2H, dt, $J = 13.7, 5.7$ Hz), 2.95 (2H, s), 2.85 (2H, s), 1.68 (4H, t, $J = 5.6$ Hz), 1.47 (9H, s); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 165.1, 157.3, 154.7, 140.6, 135.8, 129.3, 122.1, 117.0, 79.8, 42.0, 41.6, 36.3, 33.6, 28.4; HRMS (HESI): Found MNa$^+$ 443.1522 C$_{15}$H$_{24}$N$_4$O$_7$Na requires 443.1537.

3-(Benzyloxy)cyclobutan-1-one-O-(2,4-dinitrophenyl)-oxime (4)

Following GP1, 3-(benzyloxy)cyclobutan-1-one (352 mg, 2.0 mmol) gave 4 (26%) as a pale yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.86 (1H, d, $J = 2.6$ Hz), 8.40 (1H, dd, $J = 9.4, 2.6$ Hz), 7.86 (1H, d, $J = 9.3$ Hz), 7.43–7.29 (5H, m), 4.55 (1H, d, $J = 11.6$ Hz), 4.51 (1H, d, $J = 11.6$ Hz), 4.31 (1H, p, $J = 6.5, 6.0$ Hz), 3.58–3.43 (1H, m), 3.40–3.28 (1H, m), 3.22–3.05
(2H, m); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 163.4, 157.5, 140.8, 137.1, 135.9, 129.4, 128.8, 128.3, 128.1, 122.2, 117.1, 71.4, 66.7, 40.8, 40.1; HRMS (APCI): Found MH\(^+\) 358.1033 C\(_{17}\)H\(_{15}\)N\(_3\)O\(_6\) requires 358.1034.
4  Ring-Opening-Functionalization

General procedure for the ring-opening–functionalization – GP2

\[
\text{N-OAr} + (R_1)_2\text{Zn}_{\text{THF–DMF (1:1), r.t.}} \rightarrow R^N\text{C}R^\text{NC}Me
\]

An oven-dried 10 mL crimp-cap microwave vial equipped with a stirring bar was charged with the aryl oxime (0.1 mmol, 1.0 equiv.), and dtbpy•NiBr\(_2\) (5 mg, 2 µmol, 20 mol%), sealed, evacuated and refilled with N\(_2\) for three times. Then DMF and a solution of organozinc in THF (0.1 mmol, 1.0 equiv.) were added (DMF:THF = 1:1, 0.05 M). The reaction was stirred at room temperature for 16 h, then the crude was filtered through a silica plug eluting with EtOAc. The solution was washed with H\(_2\)O (5 mL x 3), and brine (5 ml x 1), dried (MgSO\(_4\)), filtered and evaporated. Purification by column chromatography on silica gel gave the corresponding product.

Nonanenitrile (2)

Following GP2, 1 gave 2 (65%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 2.33 (2H, t, \(J = 7.1\) Hz), 1.66 (2H, p, \(J = 7.2\) Hz), 1.50–1.37 (2H, m), 1.36–1.20 (8H, m), 0.87 (3H, t); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 120.0, 31.8, 29.1, 28.9, 28.8, 25.5, 22.7, 17.3, 14.2. Data in accordance with the literature.

7,11-Dimethylundecanenitrile (5)

Following GP2, 1 gave 5 (61%) as an oil. \(R_f\) 0.90 [petrol:EtOAc (8:2)]; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 2.33 (2H, t, \(J = 7.1\) Hz), 1.66 (2H, p, \(J = 7.3\) Hz), 1.59–1.48 (1H, m), 1.47–1.33 (4H, m), 1.33–1.18 (5H, m), 1.17–0.99 (4H, m), 0.92–0.75 (9H, m); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 120.0, 39.5, 37.4, 36.8, 32.8, 29.2, 28.1, 26.4, 25.6, 24.9, 22.9, 22.8, 19.8, 17.3; HRMS (ASAP): Found MH\(^+\) 210.2212 C\(_{14}\)H\(_{28}\)N requires 210.2216.

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4-Cyclopentylbutanenitrile (6)

Following GP2, 1 gave 6 (15%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.33 (2H, t, $J = 7.1$ Hz), 1.84–1.73 (3H, m), 1.71–1.36 (10H, m); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 120.0, 39.5, 35.3, 32.7, 25.3, 24.8, 17.5. Data in accordance with the literature.\(^6\)

tert-Butyl 4-(Cyanomethyl)-4-ethylpiperidine-1-carboxylate (7)

Following GP2, 1 gave 7 (79%) as an oil. R$_f$ 0.50 [petrol:EtOAc (7:3)]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.53–3.27 (4H, m), 2.34 (2H, br s), 1.61–1.54 (2H, m), 1.53–1.47 (2H, m), 1.45 (9H, s), 1.34–1.22 (2H, m), 0.88 (3H, t, $J = 7.6$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 154.9, 117.7, 79.9, 34.3, 33.9, 29.8, 29.1, 28.6, 25.7, 7.4; HRMS (HESI): Found MNa$^+$ 275.1721 C$_{12}$H$_{24}$N$_2$O$_2$Na requires 275.1730.

tert-Butyl 4-(Cyanomethyl)-4-propylpiperidine-1-carboxylate (8)

Following GP2, 1 gave 8 (46%) as an oil. R$_f$ 0.50 [petrol:EtOAc (7:3)]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.44–3.35 (4H, m), 2.34 (2H, s), 1.56–1.46 (6H, m), 1.45 (9H, s), 1.32–1.23 (2H, m), 0.95 (3H, t, $J = 7.2$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 154.9, 117.8, 79.9, 39.1, 34.3, 28.6, 28.5, 26.2, 16.3, 14.7; HRMS (ASAP): Found MNa$^+$ 289.1874 C$_{15}$H$_{26}$N$_2$O$_2$Na requires 289.1886.

tert-Butyl 4-(Cyanomethyl)-4-(cyclopropylmethyl)piperidine-1-carboxylate (9)

Following GP2, 1 gave 9 (91%) as an oil. R$_f$ 0.50 [petrol:EtOAc (7:3)]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.52–3.27 (4H, m), 2.50 (2H, s), 1.65–1.58 (2H, m), 1.58–1.51 (2H, m), 1.45 (9H, s), 1.47–1.42 (2H, m), 0.67–0.56 (1H, m), 0.56–0.47 (2H, m), 0.22–0.10 (2H, m); $^{13}$C NMR
(126 MHz, CDCl₃) δ 154.9, 118.0, 79.9, 41.6, 35.6, 34.5, 29.8, 28.6, 26.2, 5.4, 4.7; HRMS (ASAP): Found MH⁺ 279.2065 C₁₆H₂₇N₂O₂ requires 279.2067.

3-(Benzyloxy)pentanenitrile (10)

Following GP2, 1 gave 10 (63%) as an oil. Rf 0.80 [petrol:EtOAc (9:1)]; ¹H NMR (500 MHz, CDCl₃) δ 7.42–7.28 (5H, m), 4.63 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 11.6 Hz), 3.64 (1H, p, J = 5.9 Hz), 2.55 (2H, d, J = 5.6 Hz), 1.82–1.63 (2H, m), 0.97 (3H, t, J = 7.4 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 137.7, 128.6, 127.9, 117.8, 75.9, 72.0, 27.1, 22.8, 22.7, 9.4; HRMS (ASAP): Found MH⁺ 190.1223 C₁₂H₁₆NO requires 190.1226.

3-(Benzyloxy)hexanenitrile (11)

Following GP2, 1 gave 11 (21%) as an oil. Rf 0.80 [petrol:EtOAc (9:1)]; ¹H NMR (500 MHz, CDCl₃) δ 7.41–7.29 (5H, m), 4.64 (1H, d, J = 11.5 Hz), 4.56 (1H, d, J = 11.5 Hz), 3.69 (1H, p, J = 6.0 Hz), 2.55 (2H, d, J = 5.6 Hz), 1.80–1.65 (1H, m), 1.65–1.57 (1H, m), 1.51–1.34 (2H, m), 0.93 (3H, t, J = 7.3 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 137.6, 128.5, 127.8, 117.7, 74.3, 71.9, 36.4, 29.7, 23.0, 18.3, 13.9; HRMS (ASAP): Found MH⁺ 204.1385 C₁₃H₁₈NO requires 204.1388.

3-(Benzyloxy)-4-cyclopropylbutanenitrile (12)

Following GP2, 1 gave 12 (76%) as an oil. Rf 0.80 [petrol:EtOAc (9:1)]; ¹H NMR (500 MHz, CDCl₃) δ 7.44–7.28 (5H, m), 4.64 (1H, d, J = 12.2 Hz), 4.61 (1H, d, J = 12.1 Hz), 3.78 (1H, p, J = 5.9 Hz), 2.77–2.54 (2H, m), 1.71 (1H, dt, J = 13.3, 6.3 Hz), 1.48 (1H, dt, J = 13.9, 6.7 Hz), 0.83–0.66 (1H, m), 0.58–0.42 (2H, m), 0.22–0.02 (2H, m); ¹³C NMR (126 MHz, CDCl₃) δ 137.8, 128.6, 127.9, 117.9, 75.2, 72.0, 38.9, 23.0, 7.0, 4.8, 4.6; HRMS (ASAP): Found MH⁺ 216.1379 C₁₄H₁₈NO requires 216.1383.
4-Phenylbutanenitrile (13)

Following GP2, 1 gave 13 (83%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31 (2H, t, $J = 7.5$ Hz), 7.23 (1H, t, $J = 7.4$ Hz), 7.19 (2H, d, $J = 7.6$ Hz), 2.78 (2H, t, $J = 7.4$ Hz), 2.32 (2H, t, $J = 7.1$ Hz), 1.99 (2H, p, $J = 7.2$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 139.8, 128.8, 128.6, 126.7, 119.6, 34.5, 27.1, 16.5. Data in accordance with the literature.$^7$

4-(o-Tolyl)butanenitrile (15)

Following GP2, 1 gave 15 (78%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.20–7.09 (4H, m), 2.84–2.66 (2H, t, $J = 7.1$ Hz), 2.37 (2H, t, $J = 7.1$ Hz), 2.32 (3H, s), 2.00–1.90 (2H, m); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.1, 136.1, 130.7, 129.1, 126.8, 126.3, 119.7, 32.0, 25.8, 19.4, 16.9. Data in accordance with the literature.$^8$

4-(2-Methoxyphenyl)butanenitrile (16)

Following GP2, 1 gave 16 (84%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.22 (1H, t, $J = 7.7$ Hz), 7.13 (1H, d, $J = 7.2$ Hz), 6.90 (1H, t, $J = 7.4$ Hz), 6.86 (1H, d, $J = 8.2$ Hz), 3.83 (3H, s), 2.77 (2H, t, $J = 7.3$ Hz), 2.31 (2H, t, $J = 7.2$ Hz), 1.96 (2H, p, $J = 7.2$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 157.5, 130.2, 128.2, 127.8, 120.5, 119.9, 110.3, 55.2, 29.3, 25.5, 16.6. Data in accordance with the literature.$^8$

4-(Thiophen-2-yl)butanenitrile (14)

Following GP2, 1 gave 14 (78%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.17 (1H, d, $J = 5.0$ Hz), 7.00–6.91 (1H, m), 6.84 (1H, d, $J = 3.4$ Hz), 3.01 (2H, t, $J = 7.2$ Hz), 2.37 (2H, t, $J = 7.1$ Hz), 2.03 (2H, p, $J = 7.1$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 142.2, 127.1, 125.4, 124.0, 119.4, 28.6, 27.4, 16.4. Data in accordance with the literature.$^9$
Hex-5-enenitrile (17)

Following **GP2**, **1** gave **17** (24%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.85–5.64 (1H, m), 5.16 – 5.01 (2H, m), 2.35 (2H, t, $J = 7.2$ Hz), 2.22 (2H, q, $J = 6.9$ Hz), 1.80–1.74 (2H, m); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 136.1, 119.7, 116.8, 32.5, 24.6, 16.4. Data in accordance with the literature.$^{10}$

tert-Butyl-4-allyl-4-(cyanomethyl)piperidine-1-carboxylate (18)

Following **GP2**, **1** gave **18** (75%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.73 (1H, ddt, $J = 20.1$, 9.4, 7.6 Hz), 5.24–5.13 (2H, m), 3.41 (4H, t, $J = 5.8$ Hz), 2.33 (2H, s), 2.26 (2H, d, $J = 7.6$ Hz), 1.63 – 1.46 (4H, m), 1.45 (4H, s); $^{13}$C NMR (126 MHz, CDCl$_3$, conformers) $\delta$ 154.9, 131.9, 120.2, 117.6, 79.9, 40.82, 40.80, 40.78, 39.7 (broad), 39.0 (broad), 34.6, 34.1 (broad), 28.6, 28.5, 26.14, 26.11, 26.09. Data in accordance with the literature [Takeda Pharmaceutical Company Limited - EP2123652, 2009, A1]

Hex-5-ynenitrile (19)

Following **GP2**, **1** gave **19** (40%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.53 (2H, t, $J = 7.3$ Hz), 2.38 (2H, t, $J = 6.7$ Hz), 2.14–2.05 (1H, m), 1.86 (2H, p, $J = 6.0$ Hz). Data in accordance with the literature.$^{11}$

tert-Butyl 4-(cyanomethyl)-4-(prop-2-yn-1-y1)piperidine-1-carboxylate (20)

Following **GP2**, **1** gave **20** (54%) as an oil. $R_f$ 0.50 [petrol:EtOAc (7:3)]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.57–3.44 (2H, m), 3.37–3.25 (2H, m), 2.53 (2H, s), 2.41 (2H, d, $J = 2.7$ Hz), 2.10 (1H, t, $J = 2.6$ Hz), 1.71–1.59 (4H, m), 1.46 (9H, s); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 154.8, 117.3, 80.1, 79.1, 72.6, 34.8, 33.5, 31.1, 28.6, 26.6, 21.2; HRMS (ASAP): Found MH$^+$ 263.1749 C$_{15}$H$_{23}$N$_2$O$_2$ requires 263.1754.
5 NMR Spectra

1 $^1$H NMR (500 MHz, CDCl$_3$)

$^1$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^1$C NMR (126 MHz, CDCl$_3$)
4^1H NMR (500 MHz, CDCl$_3$)

4^13C NMR (126 MHz, CDCl$_3$)
$^{1}H\text{ NMR (500 MHz, CDCl}_{3}\text{)}$

$^{13}C\text{ NMR (126 MHz, CDCl}_{3}\text{)}$
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
6 $^1$H NMR (500 MHz, CDCl$_3$)

6 $^{13}$C NMR (126 MHz, CDCl$_3$)
$^7$H NMR (500 MHz, CDCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$)

$^7$C NMR (126 MHz, CDCl$_3$)

$^1$C NMR (126 MHz, CDCl$_3$)
8$^1$H NMR (500 MHz, CDCl$_3$)

8$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$10^{1}H$ NMR (500 MHz, CDCl$_3$)

$10^{13}C$ NMR (126 MHz, CDCl$_3$)
$^{11}$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^{12}\text{H NMR} \ (500 \text{ MHz, CDCl}_3)$

$^{13}\text{C NMR} \ (126 \text{ MHz, CDCl}_3)$
$^{13}$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^{15}$H NMR (500 MHz, CDCl$_3$)

$^{15}$C NMR (126 MHz, CDCl$_3$)
$^{16}$H NMR (500 MHz, CDCl$_3$)

$^{16}$C NMR (126 MHz, CDCl$_3$)
$^{14}$H NMR (500 MHz, CDCl$_3$)

$^{14}$C NMR (126 MHz, CDCl$_3$)
\[ 1^3C \text{ NMR (126 MHz, CDCl}_3) \]

\[ 1^H \text{ NMR (500 MHz, CDCl}_3) \]
$^{20}$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
6 References: