Supporting Information

Synthesis of Cyanamides via a One Pot Oxidation-Cyanation of Primary and Secondary Amines

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Table of Contents

1. General Experimental Details 2
2. Characterization of N-Chloro-1-arylethan-1-amines 4
3. General Cyanation Procedure 5
4. Synthesis of Cyanamides, 2-Aminooxazolidines, 2-Aminooxazoles and -imidazoles 6
5. Results with Additional Substrates 16
6. Optimization and Synthesis of Cyanamide 2 17
   6.1. Oxidation of Amine 1 with NCS 17
   6.2. Oxidation of Amine 1 with NBS 17
   6.3. Optimization of the Cyanation of Amine 1 18
   6.4. Synthesis of Cyanamide 2 18
7. Mechanistic Experiments 19
   7.1. Reaction Profile for the Formation of Cyanamide 5 19
   7.2. Determination of the Kinetic Order of Zn(CN)₂ 20
   7.3. Hammett Study 22
   7.4. Control Experiments 24
   7.5. Characterization of the Major Side Product in the Cyanation of 1-Arylethan-1-amines 29
   7.6. Proposed Mechanism 31
8. ¹H and ¹³C NMR Spectra 32
1. General Experimental Details

Unless otherwise noted, all reactions were performed under an N₂-atmosphere. Heating of reaction mixtures was performed using a temperature controlled hotplate equipped with stirring and an active thermocouple. Stirring of reaction mixtures was performed using magnetic stirring, unless noted otherwise. Evaporation and concentration in vacuo was done using variable vacuum via a vacuum controlled (ca. 400–40 mmHg) rotary evaporator. Column chromatography was done using a Teledyne ISCO CombiFlash® Rf+ chromatography system using prepacked single-use silica packed cartridges (RediSep Rf Gold Normal-Phase Silica, 20–40 micron average particle size, 60 Å average pore size).

Materials. Reagents were purchased in reagent grade from commercial suppliers and used without further purification, unless otherwise described. Anhydrous solvents (acetonitrile and ethyl acetate) were obtained from Sigma-Aldrich as part of their Sure/Seal™ bottles product line. NMR kinetic experiments utilized CD₃CN (99% D) which was purchased from Acros Organics. THF-d₈ (99.5% D), CD₂Cl₂ (99.8% D), CD₃OD (99.8% D), DMSO-d₆ (99.9% D) were purchased from Cambridge Isotope Laboratories in sealed ampules and used as received. CDCl₃ (99.8% D) was purchased from Cambridge Isotope Laboratories in 100 mL bottles and used as received.

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) spectra, carbon nuclear magnetic resonance (¹³C NMR) spectra and proton-decoupled fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded at 25 °C on a Bruker 500 MHz AVANCE III HD spectrometer equipped with a SmartProbe. A diffusion (DOSY) NMR experiment was performed at 25°C using a Bruker 600 MHz AVANCE III HD spectrometer equipped with a triple resonance (HCN) helium-cooled cryoprobe. Chemical shifts for proton and carbon are reported in parts per million downfield from tetramethylsilane and are referenced to residual resonances of the NMR solvent according to values reported in the literature.¹ ¹⁹F chemical shifts were referenced according to IUPAC recommendations² using the ξₓ value of 94.094011 for CCl₃F. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (J) quoted in hertz (Hz) and integration. Reaction optimization for amine 4 was performed by quantitative ¹H NMR using the following parameters: D1 = 60 s, NS = 8 and CH₂Br₂ as internal standard. The convection-compensated, dstepgp3s pulse sequence³ was used for diffusion NMR measurements with the following parameters: NS = 16, D1 = 3 s, D20 (Δ) = 60 ms, P30 (δ/2) = 1 ms, and gradient amplitudes (g) from 2% to 98% in 16 increments (t1). The DOSY spectrum was generated using Bruker’s Dynamics Center, version 2.3, by fitting the peak intensity data to the following equation,

\[ f(g) = I_0 \times e^{-\gamma^2 g^2 \Delta (\Delta g)^2 + D} \]

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¹ Fulmer, G. R.; Miller, A. J. M. Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M. Bercaw, J. E.; Goldberg, K. I. *Organometallics* 2010, 29, 2176.
² R.K. Harris, E.D. Becker, S.M. Cabral de Menezes, R. Goodfellow, and P. Granger, "NMR Nomenclature. Nuclear Spin Properties and Conventions for Chemical Shifts (IUPAC Recommendations 2001)". Pure and Applied Chemistry 73, 1795-1818 (2001).
³ Jerschow, A.; Mueller, N. *J. Magn. Reson. A* 1997, 125, 372.
where $I_0$ is the initial peak intensity, $\gamma$ is proton’s gyromagnetic ratio, $g$ is gradient amplitude, $\delta$ is twice the gradient pulse length (2 ms), $\Delta$ is diffusion time (60 ms), and $D$ are the diffusion coefficients.

Reaction optimization for amine 1 was performed by HPLC analysis using an Agilent 1100 system equipped with a UV detector ($\lambda = 254$ nm) and an Ascentis Express C18 column (10 cm x 4.6 mm, 2.7 μm) operating at 40 °C with a flow of 1 mL/min. The binary eluent mixture of eluent A = 0.1% v/v H$_3$PO$_4$ in H$_2$O and eluent B = CH$_3$CN was used with a 8 min gradient starting from 95%A and 5%B to 5%A and 95% B.

Infrared spectra were recorded on a Thermo Fisher Scientific Nicolet iS50 FTIR spectrometer equipped with a diamond ATR attachment. The wave numbers ($\nu$) of recorded IR signals are quoted in cm$^{-1}$.

**UPLC Method for HRMS.** HRMS sample analysis performed using Waters Acquity UPLC system interfaced with a Waters Xevo G2 QToF ESI with the source temperature set to 120 °C. Samples were dissolved in DMSO at 1 mM concentration and 1 μL injection volumes were used. The Waters UPLC was equipped with an ACQUITY UPLC™ BEH C18 Column (130Å pore size, 1.7 μm practical size, 2.1 mm internal diameter × 50 mm length) operating at 40 °C with a 0.6 mL/min flow rate of a binary eluent mixture (eluent A and B, prepared as described below). The 3 min method used the following eluent gradient: gradient from 95%A, 5%B at $t = 0$ min to 0.0%A, 100%B at $t = 1.60$ min, followed by a hold of that eluent mixture until 2.10 min, and a subsequent gradient to achieve 95% A and 5%B at $t = 2.30$ min and final hold until $t = 2.70$ min. Two different eluent systems were used: (system 1) eluent A = 0.1% v/v formic acid in H$_2$O, eluent B = 0.1% v/v formic acid in CH$_3$CN; (system 2) eluent A = 0.1% v/v NH$_4$OH in H$_2$O, eluent B = 0.1% v/v NH$_4$OH in CH$_3$CN.

**Abbreviations.** ATR = Attenuated total reflectance, AY = assay yield (yield determined using an analytical method and referenced to an internal standard), ESI = electrospray ionization, EtOAc = ethyl acetate, HPLC = high pressure liquid chromatography, HRMS = high resolution mass spectrometry, NBS = N-bromosuccinimide, NCS = N-chlorosuccinimide, PTFE = polytetrafluoroethylene, QToF = quadrupole time of flight, RDS = rate determining step, 2-Me THF = 2-methyltetrahydrofuran, THF = tetrahydrofuran.
2. Characterization of N-Chloro-1-arylethan-1-amines

\[ \text{N-chloro-1-phenylethan-1-amine } \text{4-Cl} \]

1-phenylethan-1-amine (26 µL, 0.2 mmol, 1.0 equiv.) was added to a cooled solution of NCS (27 mg, 0.2 mmol, 1.05 equiv.) in CD$_3$CN (1.8 mL) in an 8 mL vial equipped stir bar. The mixture was stirred for 5 min and then transferred to an NMR tube to characterize the crude N-chloroamine 4-Cl.

$^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 7.37 – 7.28 (m, 5H), 5.19 (br s, NH), 4.14 – 4.09 (m, 1H), 1.40 (d, $J = 6.7$ Hz, 3H) ppm; $^{13}$C NMR (126 MHz, CD$_3$CN) $\delta$ 144.0, 129.4, 128.6, 127.9, 65.1, 22.0 ppm.

**Figure S1.** $^1$H NMR (500 MHz) spectra of 4-Cl (top) and 1-phenylethan-1-amine (bottom) in CD$_3$CN.
**N-chloro-1-(4-methylphenyl)ethan-1-amine.** 1-(4-methylphenyl)ethan-1-amine (15 μL, 0.1 mmol, 1.0 equiv.) was added to a cooled solution of NCS (13 mg, 0.2 mmol, 1.05 equiv.) in CD$_3$CN (0.9 mL) in an 8 mL vial equipped stir bar. The mixture was then stirred for 5 min and then transferred to an NMR tube to characterize the crude N-chloroamine.

$^1$H NMR (500 MHz, CD$_3$CN) δ 7.25 – 7.23 (m, 2H), 7.18 – 7.17 (m, 2H), 5.14 (br s, NH), 4.10 – 4.05 (m, 1H), 2.32 (s, 3H), 1.38 (d, J = 6.7 Hz, 3H) ppm; $^{13}$C NMR (126 MHz, CD$_3$CN) δ 140.9, 138.4, 130.0, 127.9, 64.8, 21.8, 21.1 ppm.

**N-chloro-1-(4-bromophenyl)ethan-1-amine.** 1-(4-bromophenyl)ethan-1-amine (14 μL, 0.1 mmol, 1.0 equiv.) was added to a cooled solution of NCS (13 mg, 0.2 mmol, 1.05 equiv.) in CD$_3$CN (0.9 mL) in an 8 mL vial equipped stir bar. The mixture was then stirred for 5 min and then transferred to an NMR tube to characterize the crude N-chloroamine.

$^1$H NMR (500 MHz, CD$_3$CN) δ 7.53 – 7.51 (m, 2H), 7.30 – 7.28 (m, 2H), 5.2 (br s, NH), 4.13 – 4.08 (m, 1H), 1.37 (d, J = 6.6 Hz, 3H) ppm; $^{13}$C NMR (126 MHz, CD$_3$CN) δ 143.3, 132.4, 130.0, 121.8, 64.5, 21.9 ppm.

### 3. General Cyanation Procedure

A 20 mL vial equipped with a magnetic stir bar was charged with NCS (136 mg, 1.5 mmol, 1.05 equiv.) and Zn(CN)$_2$ (118 mg, 1.0 mmol, 1.0 equiv.). Acetonitrile (9 mL) and water (0.9 mL) were added under inert atmosphere and the suspension was cooled to 0 °C. The amine (1.0 mmol, 1.0 equiv.) was added in one portion and the mixture was stirred at room temperature at 600-1000 rpm for 16 h. The suspension was filtered over a 2 cm plug of celite and the plug was rinsed with ~ 20 mL EtOAc. The filtrate was washed with 20 mL of water and a 20% aqueous NaCl solution, dried over MgSO$_4$ and then concentrated in vacuo. The crude product was purified by flash chromatography.
4. Synthesis of Cyanamides, 2-Aminoazolidines, 2-Aminoazoles and -imidazoles

**N-(1-phenylethyl)cyanamide 5.** Following the general procedure, 1-phenylethan-1-amine (1.06 mL, 8.25 mmol, 1.00 equiv.) was reacted with NCS (1.16 g, 8.66 mmol, 1.05 equiv.) and Zn(CN)_2 (969 mg, 8.25 mmol, 1.00 equiv.) in acetonitrile (74 mL) and water (7.4 mL) for 16 h. The crude product was purified by flash chromatography (hexanes/EtOAc 85/15 – 60/40) to obtain 5 as a light brown oil in 930 mg and 77% yield.

\[ \text{NMR (500 MHz, CD}_2\text{Cl}_2 \delta 7.41–7.32 \text{ (m, 5H), 4.43–4.38 \text{ (m, 1H), 4.13 \text{ (br s, NH), 1.54 \text{ (dd, J = 6.8 Hz, 0.7 Hz, 3H ppm; C NMR (126 MHz, CD}_2\text{Cl}_2 \delta 142.1, 129.2, 128.6, 126.6, 115.2, 56.0, 22.3 ppm; ESI}^+ \text{ HRMS m/z calcd. for [C}_9\text{H}_7\text{N}_2\text{]_2 ([2M + H]^+) 293.1761, found 293.1778; IR } \nu 3183, 2976, 2211 (\text{C≡N), 1611, 1512, 1377, 1244, 830, 638 cm}^{-1}. \]

**N-(1-(4-methoxyphenyl)ethyl)cyanamide 6.** Following the general procedure 1-(4-methoxy phenyl)ethan-1-amine (454 mg, 3.00 mmol, 1.00 equiv.) was reacted with NCS (421 mg, 3.15 mmol, 1.05 equiv.) and Zn(CN)_2 (352 mg, 3.00 mmol, 1.00 equiv.) in acetonitrile (27 mL) and water (2.7 mL) for 16 h. The crude product was purified by flash chromatography (hexanes/EtOAc 100/0 – 60/40) to obtain 6 as a light brown oil product in 220 mg and 41 % yield.

\[ \text{NMR (500 MHz, CD}_2\text{CN \delta 7.33 – 7.31 \text{ (m, 2H), 6.97 – 6.95 \text{ (m, 2H), 4.99 \text{ (br s, NH), 4.39 – 4.34 \text{ (m, 1H), 3.82 \text{ (s, 3H), 1.46 \text{ (d, J = 6.7 Hz, 3H ppm; C NMR (126 MHz, CD}_2\text{CN \delta 160.4, 135.3, 128.6, 116.4, 114.9, 55.9, 55.5, 22.4 ppm; ESI}^+ \text{ HRMS m/z calcd. for [C}_{10}\text{H}_{12}\text{N}_2\text{]_2 ([2M + H]^+) 353.1971, found 353.1986; IR } \nu 3193, 2972, 2210 (\text{C≡N), 1611, 1512, 1377, 1244, 830, 638 cm}^{-1}. \]

**N-(1-(3-bromophenyl)ethyl)cyanamide 7.** Following the general procedure, 1-(3-bromophenyl)ethan-1-amine (187 mg, 0.89 mmol, 1.00 equiv.) was reacted with NCS (121 mg, 0.90 mmol, 1.05 equiv.) and Zn(CN)_2 (105 mg, 0.89 mmol, 1.00 equiv.) in acetonitrile (8.0 mL) and water (0.8 mL) for 25 h. The crude product was purified by flash chromatography (hexanes/EtOAc 95/5 – 70/30) to obtain 7 as a colorless oil in 139.7 mg and 69% yield.

\[ \text{NMR (500 MHz, CD}_2\text{CN \delta 7.55 \text{ (s, 1H), 7.50 – 7.49 \text{ (m, 1H), 7.36–7.30 \text{ (m, 2H), 5.11 \text{ (br s, NH), 4.40 – 4.35 \text{ (m, 1H), 1.45 \text{ (d, J = 6.8 Hz, 3H ppm; C NMR (126 MHz, CD}_2\text{CN \delta 146.1, 131.9, 131.7, 130.3, 126.3, 123.1, 116.0, 55.4, 22.2 ppm; ESI}^+ \text{ HRMS m/z calcd. for [C}_9\text{H}_9\text{BrN}_2\text{]_2 ([2M + H]^+) 450.9951, found 450.9969; IR } \nu 3334, 2973, 2217, 1676, 1592, 1335, 1205, 1070, 780, 713, 692 cm}^{-1}. \]

S6
\textit{N-(2,3-dihydro-1H-inden-1-yl)cyanamide} 8. Following the general procedure, 2,3-dihydro-1H-inden-1-amine (400 mg, 3.00 mmol, 1.00 equiv.) was reacted with NCS (421 mg, 3.15 mmol, 1.05 equiv.) and Zn(CN)\textsubscript{2} (352 mg, 3.00 mmol, 1.00 equiv.) in acetonitrile (24 mL) and water (2.4 mL) for 16 h. The crude product was purified by flash chromatography (hexanes/EtOAc 100/0 – 50/50) to obtain 8 as a white solid in 320 mg and 67% yield.

\textbf{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3})} δ 7.44 – 7.42 (m, 1H), 7.30 – 7.26 (m, 3H), 4.79 – 4.75 (m, 1H), 3.64 (br s, NH), 3.10 – 3.04 (m, 1H), 2.91 – 2.85 (m, 1H), 2.60 – 2.53 (m, 1H), 2.11 – 2.05 (m, 1H) ppm; \textbf{\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3})} δ 143.5, 141.0, 129.2, 127.3, 125.3, 124.4, 115.1, 61.6, 33.8, 20.1 ppm; \textbf{ESI\textsuperscript{+} HRMS} m/z calcd. for \([\text{C}_{10}\text{H}_{10}\text{N}_{2}]^{2+}\) 317.1761, found 317.1767; \textbf{IR} ν 3238, 2965, 2213 (C≡N), 1457, 1335, 1299, 1164, 767, 742 cm\textsuperscript{-1}.

\textit{4-phenylbutylcyanamide} 9. Following the general procedure, 4-phenylbutylamine (0.32 mL, 2.00 mmol, 1.00 equiv.) was reacted with NCS (270 mg, 2.02 mmol, 1.01 equiv.) and Zn(CN)\textsubscript{2} (235 mg, 2.00 mmol, 1.00 equiv.) in acetonitrile (18 mL) and water (1.8 mL) for 16 h. The crude product was purified by flash chromatography (hexanes/EtOAc 80/20 – 50/50) to obtain 9 as a colorless liquid in 188 mg and 54% yield.\textsuperscript{4}

\textbf{\textsuperscript{1}H NMR (500 MHz, CD\textsubscript{2}Cl\textsubscript{2})} δ 7.30 – 7.27 (m, 2H), 7.20 – 7.17 (m, 3H), 3.63 (br s, NH), 3.07 (q, J = 6.7 Hz, 2H), 2.65 (t, J = 7.4 Hz, 1H), 1.72 – 1.59 (m, 4H) ppm; \textbf{\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3})} δ 142.4, 128.7, 128.7, 126.2, 116.4, 46.6, 35.7, 29.7, 28.5 ppm; \textbf{ESI\textsuperscript{+} HRMS} m/z calcd. for \(\text{C}_{14}\text{H}_{14}\text{N}_{2}\) ([M\textsuperscript{+}]\textsuperscript{+}) 173.1084, found 173.1081; \textbf{IR} ν 3201, 3026, 2931, 2859, 2215 (C≡N), 1603, 1495, 1452, 1362, 1152, 746, 698 cm\textsuperscript{-1}.

\textit{N-benzyl-N-methylcyanamide} 10.\textsuperscript{5} Following the general procedure, \(N\)-methylbenzylamine (242 mg, 2.00 mmol, 1.00 equiv.) was reacted with NCS (280 mg, 2.10 mmol, 1.05 equiv.) and Zn(CN)\textsubscript{2} (235 mg, 2.00 mmol, 1.00 equiv.) in acetonitrile (17 mL) and water (1.7 mL) for 16 h. The crude yield of 85% was determined by quantitative \textbf{\textsuperscript{1}H NMR (d1 = 60 s, NS = 8)} using CH\textsubscript{3}Br\textsubscript{2} as internal standard. The crude product was purified by flash chromatography (hexanes/EtOAc 100/0 – 50/50) to obtain 10 as a colorless oil in 130 mg and 45% yield.

\textsuperscript{4} For the synthesis of \textit{N-cyano-2-phenylethylamine}, a compound related to 9, with BrCN, see: Klein, P. J.; Christiaans, J. A. M.; Metaxas, A.; Schuit, R. C.; Lammertsma, A. A.; van Berckel, B. N. M., Windhorst, A. D. \textit{Bioorg. Med. Chem.}, \textbf{2015}, 23, 1189.

\textsuperscript{5} Ayres, J. N.; Ling, K. B.; Morrill, L. C. \textit{Org. Lett.}, \textbf{2016}, 18, 5528.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.39 – 7.32 (m, 5H), 4.16 (s, 2H), 2.78 (s, 3H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 134.5, 129.1, 128.8, 128.5, 119.0, 57.3, 37.9 ppm; ESI\(^+\) HRMS m/z calcd. for C\(_8\)H\(_{10}\)N\(_2\) ([M + H]\(^+\)) 147.0922, found 147.0925; IR \(\nu\) 2281, 2208 (C≡N), 1454, 1141, 1027, 732, 662 cm\(^{-1}\).

**N-methyl-N-phenethylcyanamide 11.** Following the general procedure, N-methyl-2-phenylethan-1-amine (0.29 mL, 2.00 mmol, 1.00 equiv.) was reacted with NCS (270 mg, 2.02 mmol, 1.01 equiv.) and Zn(CN)\(_2\) (235 mg, 2.00 mmol, 1.00 equiv.) in acetonitrile (18 mL) and water (1.8 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 95/5 – 70/30) to obtain 12 as a colorless liquid in 269 mg and 84% yield.\(^6\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.31 (m, 2H), 7.26 – 7.24 (m, 3H), 3.21 (t, \(J = 7.5\) Hz, 2H), 2.93 (t, \(J = 7.5\) Hz, 2H), 2.81 (s, 3H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 138.3, 129.1, 129.0, 127.1, 118.5, 54.7, 39.5, 34.1 ppm; ESI\(^+\) HRMS m/z calcd. for C\(_{10}\)H\(_{12}\)N\(_2\) ([M + H]\(^+\)) 161.1073, found 161.1076; IR \(\nu\) 3028, 2926, 2208 (C≡N), 1497, 1453, 1374, 1141, 1058, 1030, 745, 698 cm\(^{-1}\).

\(^{3,4}\)-dihydroisoquinoline-2(1H)-carbonitrile 12.\(^5\) Following the general procedure, 1,2,3,4-tetrahydroisoquinoline (126 \(\mu\)l, 1 mmol, 1.0 equiv.) was reacted with NCS (136 mg, 1.05 mmol, 1.05 equiv.) and Zn(CN)\(_2\) (118 mg, 1.0 mmol, 1.0 equiv.) in acetonitrile (9 mL) and water (0.9 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/ – 60/40) to obtain 12 as an off white solid in 120 mg and 80% yield.\(^7\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.22 – 7.20 (m, 2H), 7.15 – 7.14 (m, 1H), 7.06 – 7.04 (m, 1H), 4.42 (s, 2H), 3.50 (t, \(J = 5.9\) Hz, 2H), 2.97 (t, \(J = 5.9\) Hz, 2H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 132.8, 130.9, 129.4, 127.4, 126.9, 126.1, 118.2, 50.2, 46.9, 27.8 ppm; ESI\(^+\) HRMS m/z calcd. for C\(_{10}\)H\(_{10}\)N\(_2\) ([M + H]\(^+\)) 159.0922, found 159.0932; IR \(\nu\) 2922, 2200 (C≡N), 1496, 1433, 1374, 1132, 772, 638 cm\(^{-1}\).

**4-phenylpiperidine-1-carbonitrile 13.** Following the general procedure, 4-phenylpiperidine (484 mg, 3 mmol, 1.0 equiv.) was reacted with NCS (421 mg, 3.15 mmol, 1.05 equiv.) and Zn(CN)\(_2\) (353 mg, 3.0 mmol, 1.0 equiv.) in acetonitrile (26 mL) and water (2.6 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 70/30) to obtain 13 as a white solid in 419 mg and 75% yield.

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\(^6\) For the synthesis of compound 11 with BrCN, see: Hua, G.; Du, J.; Slawin, A. M. Z.; Woollins, J. D. *Molecules* 2017, 22, 46.

\(^7\) For the synthesis of 12 with BrCN, see: Ried, W.; Kümbel, B.; Tauer, M. L. *Liebigs Ann. Chem.* 1984, 564.
1H NMR (500 MHz, CDCl₃) δ 7.40 – 7.31 (m, 2H), 7.29–7.24 (m, 3H), 3.60 – 3.56 (m, 2H), 3.23 – 3.17 (m, 2H), 2.69 – 2.63 (m, 1H), 1.93 – 1.88 (m, 4H) ppm; 13C NMR (126 MHz, CDCl₃) δ 144.6, 128.7, 126.8, 126.6, 118.3, 50.1, 41.3, 32.0 ppm; ESI+ HRMS m/z calcd. for C₁₂H₁₄N₂ ([M + H]+) 187.1235, found 187.1239; IR ν 2926, 2206 (C≡N), 1431, 1266, 1022, 908, 752, 730, 697, 637 cm⁻¹.

1,4-dioxa-8-azaspiro[4.5]decane-8-carbonitrile 14. Following the general procedure, 1,4-dioxa-8-azaspiro[4.5]decane (286 mg, 2 mmol, 1.0 equiv.) was reacted with NCS (280 mg, 2.1 mmol, 1.05 equiv.) and Zn(CN)₂ (235 mg, 2.0 mmol, 1.0 equiv.) in acetonitrile (17 mL) and water (1.7 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 70/30) to obtain 14 as a white solid in 200 mg and 60% yield.⁸

1H NMR (500 MHz, CDCl₃) δ 3.96 (s, 4H), 3.34 – 3.32 (m, 4H), 1.80 – 1.77 (m, 4H) ppm; 13C NMR (126 MHz, CDCl₃) δ 118.1, 105.6, 64.7, 48.1, 34.3 ppm; ESI+ HRMS m/z calcd. for C₈H₁₂N₂O₂ ([M + H]+) 169.0977, found 169.0985; IR ν 2960, 2204 (C≡N), 1378, 1227, 1067, 942, 788, 687, 619 cm⁻¹.

4-(hydroxymethyl)piperidine-1-carbonitrile 15. Following the general procedure, piperidin-4-ylmethanol (346 mg, 3 mmol, 1.0 equiv.) was reacted with NCS (421 mg, 3.15 mmol, 1.05 equiv.) and Zn(CN)₂ (352 mg, 3.0 mmol, 1.0 equiv.) in acetonitrile (26 mL) and water (2.6 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 0/100) to obtain 15 as a thick colorless oil in 220 mg and 55% yield.

1H NMR (500 MHz, CDCl₃) δ 3.49 (d, J = 6.4 Hz, 2H), 3.45 – 3.42 (m, 2H), 3.03 – 2.98 (m, 2H), 1.77 – 1.74 (m, 3H), 1.64 – 1.55 (m, 1H), 1.40 – 1.32 (m, 2H) ppm; 13C NMR (126 MHz, CDCl₃) δ 118.5, 67.0, 49.5, 37.5, 27.7 ppm; ESI+ HRMS m/z calcd. for C₇H₁₂N₂O ([M + H]+) 141.1022, not detected, compound is unstable; IR ν 3031, 2956, 2212 (C≡N), 1508, 1492, 1290, 1225, 1018, 821, 738, 638 cm⁻¹.

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⁸ For the synthesis of 14 with BrCN, see: Heckel, A.; Blum, A.; Breitfelder, S.; Himmelsbach, F.; Langkopf, E.; Nosse, B.; Wellenzohn, B.; Ashweek, N. J.; Harriott, N. Preparation of N-cyclopropyl-N-(heteroarylpiperidinyl)benzamides as GPR119 modulators. Int. Patent WO 20121234399 A1, September 20, 2012.

⁹ Fang, J.; Tang, J.; Carpenter, A. J.; Peckham, G.; Conlee, C. R.; Du, K. S.; Katamreddy, S. R. Preparation of piperidine derivatives as GPR119 agonists for treating metabolic disorders. Int. Patent WO 2008/070692 A2, June 12, 2008. Reference uses BrCN as cyanation reagent.
To further confirm the formation of 4-(hydroxymethyl)piperidine-1-carbonitrile 15, (1-(3-methyl-1,2,4-oxadiazol-5-yl) piperidin-4-yl) methanol was prepared following a literature procedure. Zinc Chloride (97 mg, 0.71 mmol, 1.0 equiv) was added to 4-(hydroxymethyl)piperidine-1-carbonitrile 15 (100 mg, 0.71 mmol, 1.0 equiv.) and N-hydroxyacetimidamide (52.8 mg, 0.71 mmol, 1.0 equiv.) in ethanol (1 mL) at room temperature and the reaction mixture was stirred at room temperature for 2 h. Conc. HCl (0.330 mL) was added and the reaction mixture was stirred at 90 °C for 4 h. The reaction mixture was then concentrated, basified with sat. aq. NaHCO₃ and the product was extracted with dichloromethane. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to afford the crude product. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 0/100) to afford the title compound in 52 mg and 37% yield.

**1H NMR (500 MHz, CDCl₃)** δ 4.17 – 4.14 (m, 2H), 3.54 – 3.53 (m, 2H), 3.09 – 3.03 (m, 2H), 2.21 (s, 3H), 1.85 – 1.83 (m, 2H), 1.77 – 1.72 (m, 1H), 1.35 – 1.27 (m, 2H) ppm; **13C NMR (126 MHz, CDCl₃)** δ 170.9, 167.9, 67.4, 46.2, 38.2, 28.2, 12.1 ppm; **ESI+ HRMS** m/z calcd. for C₉H₁₅N₃O₂ ([M + H]+) 198.1242, found 198.1248; **IR** ν 3367, 2922, 2858, 1617, 1549, 1421, 1327, 1217, 1037, 896, 749, 707 cm⁻¹.

4-(4-cyanophenyl)piperidine-1-carbonitrile 16. Following the general procedure 4-(piperidin-4-yl)benzonitrile was reacted with NCS (75 mg, 0.56 mmol, 1.05 equiv.) and Zn(CN)₂ (63 mg, 0.53 mmol, 1.0 equiv.) in acetonitrile (5 mL) and water (0.5 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 70/30) to obtain 16 as a white solid in 82 mg and 72% yield.

**1H NMR (500 MHz, CD₂CN)** δ 7.68 – 7.67 (m, 2H), 7.43 – 7.41 (m, 2H), 3.49 – 3.47 (m, 2H), 3.19 – 3.13 (m, 2H), 2.78 – 2.74 (m, 1H), 1.85 – 1.74 (m, 4H) ppm; **13C NMR (126 MHz, CD₂CN) δ** 152.0, 133.5, 128.8, 119.8, 119.1, 111.0, 50.6, 41.8, 32.2 ppm; **ESI+ HRMS** m/z calcd. for C₉H₁₂N₂O₂ ([M + H]+) 212.1187, found 212.1193; **IR** ν 2943, 2919, 2865, 2228 (C≡N), 2208 (C≡N), 1608, 1508, 1387, 1252, 1141, 1090, 985, 862, 830, 726 cm⁻¹.

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**References:**

10 Barba, O.; Bell, J. C.; Dupree, T. B.; Fry, P. T.; Bertram, L. S.; Frye, M. C. T.; Gattrell, W.; Jeevaratnam, R. P.; Keily, J.; Krulke, T. M.; Mcdonald, R. W.; Morgan, T.; Rasamison, C. M.; Schofield, K. L.; Stewart, A. J. W.; Swain, S. A.; Withall, D. M. Cycloamino derivatives as GPR119 Antagonists. Int. Patent WO 2011/147951 A1, December 1, 2011.

11 Eastwood, P. R. *Tetrahedron Lett.* 2000, 41, 3705.
2-phenylpyrrolidine-1-carbonitrile 17. Following the general procedure, 2-phenylpyrrolidine (442 mg, 3 mmol, 1.0 equiv.) was reacted with NCS (421 mg, 3.15 mmol, 1.05 equiv.) and Zn(CN)₂ (352 mg, 3.0 mmol, 1.0 equiv.) in acetonitrile (26 mL) and water (2.6 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 90/10 – 70/30) to obtain 17 as a light brown solid in 262 mg and 51% yield.

\[ ^1H \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.38 – 7.35 (m, 2H), 7.32 – 7.28 (m, 3H), 4.65 (t, 1H, J = 7.1 Hz), 3.72 – 3.68 (m, 1H), 3.60 – 3.55 (m, 1H), 2.34 – 2.31 (m, 1H), 2.05 – 1.98 (m, 2H), 1.90 – 1.84 (m, 1H) ppm; \]

\[ ^{13}C \text{NMR} (126 \text{ MHz, CDCl}_3) \delta 139.8, 128.9, 128.2, 126.4, 117.0, 66.0, 51.6, 35.7, 24.9 \text{ ppm; ESI}^+ \text{ HRMS m/z calcd. for } C_{11}H_{12}N_2([M + H]^+) 173.1078, \text{found } 173.1081; \]

\[ \text{IR } \nu 2975, 2881, 2204 (C≡N), \nu 1648 - 1595 (C=N), \nu 1537, 1345, 702 (N–C=O). \]

(S)-N-(1-cyanopyrrolidin-3-yl)-N-methyl-2-nitrobenzenesulfonamide 18. Following the general procedure (S)-N-methyl-2-nitro-N-(pyrrolidin-3-yl)benzenesulfonamide 12 (200 mg, 0.70 mmol, 1.0 equiv.) was reacted with NCS (98 mg, 0.73 mmol, 1.05 equiv.) and Zn(CN)₂ (82 mg, 0.7 mmol, 1.0 equiv.) in acetonitrile (6 mL) water (0.6 mL) for 24 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 60/40) to obtain 18 as a colorless oil 170 mg and 78 % yield.

\[ ^1H \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 8.07 – 8.05 (m, 1H), 7.77 – 7.71 (m, 2H), 7.68 – 7.66 (m, 1H), 4.73 – 4.67 (m, 1H), 3.59 – 3.54 (m, 2H), 3.43 – 3.39 (m, 1H), 3.32 – 3.29 (m, 1H), 2.86 (s, 3H), 2.25 – 2.18 (m, 1H), 2.01 – 1.96 (m, 1H) ppm; \]

\[ ^{13}C \text{NMR} (126 \text{ MHz, CDCl}_3) \delta 158.0, 134.2, 132.2, 132.1, 131.5, 124.6, 116.4, 56.1, 51.4, 49.5, 29.2, 28.5 \text{ ppm; ESI}^+ \text{ HRMS m/z calcd. for } C_{16}H_{11}N_2O_2; ([M + H]^+) 311.0814, \text{found } 311.0814; \]

\[ \text{IR } \nu 2943, 2208 (C≡N), 1714, 1540, 1346, 1158, 985, 884, 852, 777, 740 \text{ cm}^{-1}. \]

N-(4-chlorophenyl)cyanamide 19. Following the general procedure, 4-chloroaniline (383 mg, 3 mmol, 1.0 equiv.) was reacted with NCS (421 mg, 3.15 mmol, 1.05 equiv.) and Zn(CN)₂ (353 mg, 3.0 mmol, 1.0 equiv.) in acetonitrile (28 mL) and water (2.8 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 80/20) to obtain 19 as a light brown solid in 260 mg and 57% yield. 14

12 The compound was prepared from (S)-N-boc-3-amino-pyrrolidine following a literature procedure: Kodama, T.; Tamura, M.; Oda, T.; Yamazaki, Y.; Nishikawa, M.; Takemura, S.; Doi, T.; Kyotani, Y.; Ohkuchi, M. Preparation of 1-[(pyridine-4-yl)methyl]-4-piperidinamines as cell adhesion inhibitors for treatment of inflammatory diseases. US Patent 6395753 B1, May 28, 2002.

13 Lin, C.-C.; Hsieh, T.-H.; Liao, P.-Y.; Liao, Z.-Y.; Chang, C.-W.; Shih Y.-C.; Yeh, W.-H.; Chien T.-C. Org. Lett. 2014, 16, 892.

14 For the synthesis of 19 and 20 with BrCN, see: Rao, B.; Zeng, X. Org. Lett. 2014, 16, 314.
$^1$H NMR (500 MHz, DMSO-d$_6$) δ 10.3 (br s, NH), 7.40 – 7.39 (m, 2H), 6.98 – 6.96 (m, 2H) ppm; $^{13}$C NMR (126 MHz, DMSO-d$_6$) δ 137.7, 129.6, 126.2, 116.7, 111.7 ppm; ESI$^+$ HRMS m/z calcd. for C$_8$H$_7$ClN$_2$ ([M + H]$^+$) 153.0219, found 153.0217; IR ν 3134, 2950, 2227 (C≡N), 1600, 1489, 1253, 1009, 829, 619 cm$^{-1}$.

$N$-(4-trifluorophenyl)cyanamide 20. Following the general procedure, 4-trifluoroaniline (329 mg, 2.00 mmol, 1.00 equiv) was reacted with NCS (270 mg, 2.02 mmol, 1.01 equiv.) and Zn(CN)$_2$ (235 mg, 1.00 mmol, 1.0 equiv.) in acetonitrile (18 mL) and water (1.8 mL) for 68 h. The crude product was purified by flash chromatography (hexane/EtOAc 95/5 – 80/20) to obtain 20 as a rose solid in 220 mg and 59% yield.

$^1$H NMR (500 MHz, CD$_2$Cl$_2$) δ 7.63 (d, $J$ = 8.5 Hz, 2H), 7.14 (d, $J$ = 8.5 Hz, 2H), 6.50 (br s, 1H) ppm; $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 141.2 (s, 1C), 127.7 (q, $J_{CF}$ = 3.9 Hz, 2C), 126.2 (q, $J_{CF}$ = 33.0 Hz, 1C), 124.6 (q, $J_{CF}$ = 271.2 Hz, 1C), 116.0 (s, 2C), 110.3 (s, 1C) ppm; $^{19}$F NMR (470 MHz, CD$_2$Cl$_2$) δ -62.4 ppm; ESI$^+$ HRMS m/z calcd. for C$_8$H$_5$F$_3$N$_2$ ([M + H]$^+$) 185.0332, found 185.0330; IR ν 3147, 3089, 2969, 2901, 2237 (C≡N), 1616, 1525, 1413, 1326, 1260, 1163, 1104, 1063, 1014, 831 cm$^{-1}$.

$N$-benzyl-$N$-phenylcyanamide 21. Following the general procedure, N-benzylaniline (366 mg, 2 mmol, 1.0 equiv) was reacted with NCS (280 mg, 2.1 mmol, 1.05 equiv.) and Zn(CN)$_2$ (235 mg, 2.0 mmol, 1.0 equiv.) in acetonitrile (18 mL) and water (1.8 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 70/30) to obtain 21 as a white solid in 320 mg and 77% yield.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.39 – 7.32 (m, 7H), 7.14 – 7.12 (m, 2H), 7.10 – 7.07 (m, 1H), 4.81 (s, 2H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) δ 140.0, 134.4, 129.8 (2C), 129.2, 128.7, 127.5, 123.8, 116.2, 53.9 ppm; ESI$^+$ HRMS m/z calcd. for C$_{14}$H$_{12}$N$_2$ ([M + H]$^+$) 209.1078, found 209.1078; IR ν 3030, 2217 (C≡N), 1598, 1493, 1369, 1233, 745, 720, 685, 649 cm$^{-1}$.

$N$-benzyl-$N$-(4-methoxyphenyl)cyanamide 22. Following the general procedure, N-benzyl-4-methoxyaniline (640 mg, 3 mmol, 1.0 equiv.) was reacted with NCS (421 mg, 3.15 mmol, 1.05 equiv.) and Zn(CN)$_2$ (352 mg, 3.0 mmol, 1.0 equiv.) in acetonitrile (26 mL) and water (2.6 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 70/30) to obtain 22 as a white solid in 380 mg and 53% yield.

15 Ayres, J. N.; Ashford, M. W.; Stöckl, Y.; Prudhomme, V.; Ling, K. B.; Platts, J. A.; Morrill, L. C. Org. Lett. 2017, 19, 3835.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39 – 7.33 (m, 5H), 7.06 – 7.05 (m, 2H), 6.87 – 6.85 (m, 2H), 4.73 (s, 2H), 3.77 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 156.4, 134.6, 133.3, 129.1 (2C), 128.6, 127.6, 118.4, 115.0, 55.7, 54.8 ppm; ESI$^+$ HRMS m/z calcd. for C$_{15}$H$_{14}$N$_2$ ([M + H]$^+$) 239.1184, found 239.1180; IR v 3395, 2956, 2211 (C≡N), 1508, 1452, 1369, 1209, 1039, 820, 701, 638 cm$^{-1}$.

![Chemical Structure](image1)

**N-benzyl-N-(p-tolyl)cyanamide 23.** Following the general procedure, N-benzyl-4-methylaniline (435 mg, 2.20 mmol, 1.0 equiv.) was reacted with NCS (309 mg, 2.31 mmol, 1.05 equiv.) and Zn(CN)$_2$ (259 mg, 3.0 mmol, 1.0 equiv.) in acetonitrile (17 mL) and water (1.7 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 80/20) to obtain 23 as a light brown solid in 355 mg and 72% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.40 – 7.31 (m, 5H), 7.14 – 7.12 (m, 2H), 7.03 – 7.01 (m, 2H), 4.77 (s, 2H), 2.30 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 137.5, 134.6, 133.5, 130.3, 129.2, 128.6, 127.5, 116.3, 114.4, 54.0 ppm; ESI$^+$ HRMS m/z calcd. for C$_{15}$H$_{14}$N$_2$ ([M + H]$^+$) 223.1230, found 223.1230; IR v 3029, 2923, 2216 (C≡N), 1509, 1453, 1273, 1224, 1178, 1024, 932, 813, 736, 692 cm$^{-1}$.

![Chemical Structure](image2)

**N-benzyl-N-(4-chlorophenyl)cyanamide 24.** Following the general procedure, N-benzyl-4-chloroaniline (435 mg, 2.00 mmol, 1.0 equiv.) was reacted with NCS (280 mg, 2.01 mmol, 1.05 equiv.) and Zn(CN)$_2$ (235 mg, 2.00 mmol, 1.0 equiv.) in acetonitrile (17 mL) and water (1.7 mL) for 16 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 70/30) to obtain 24 as a light brown solid in 376 mg and 78% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39 – 7.33 (m, 5H), 7.30 – 7.27 (m, 2H), 7.07 – 7.04 (m, 2H), 4.78 (s, 2H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.6, 133.9, 129.8, 129.3, 129.2, 128.8, 127.4, 117.5, 113.6, 54.0 ppm; ESI$^+$ HRMS m/z calcd. for C$_{15}$H$_{14}$CN$_2$ ([M + H]$^+$) 243.0689, found 243.0676; IR v 3065, 2216 (C≡N), 1509, 1453, 1273, 1224, 1178, 1024, 932, 813, 736, 639 cm$^{-1}$.

![Chemical Structure](image3)

**N-benzyl-N-(pyridin-2-yl)cyanamide 25.** Following the general procedure, N-benzylpyridin-2-amine (336 mg, 2.00 mmol, 1.00 equiv.) was reacted with NCS (280 mg, 2.10 mmol, 1.05 equiv.) and Zn(CN)$_2$ (235 mg, 2.00 mmol, 1.00 equiv.) in acetonitrile (18 mL) and water (1.8 mL) at 40 °C for 96 h. The crude product was purified by flash chromatography (hexane/EtOAc 95/5 – 80/20) to obtain 25 as a white solid in 270 mg and 64% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.34 – 8.33 (m, 1H), 7.70 – 7.67 (m, 1H), 7.44 – 7.42 (m, 2H), 7.38 – 7.31 (m, 3H), 7.22 – 7.20 (m, 1H), 7.02 – 6.99 ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 151.8, 148.2, 138.8, 135.1, 128.9, 128.5, 128.5, 118.8, 112.9, 101.4, 96.6 ppm; ESI$^+$ HRMS m/z calcd.
for C\textsubscript{13}H\textsubscript{11}N\textsubscript{3} ([M + H\textsuperscript{+}]\textsuperscript{+}) 210.1031, found 210.1041; IR \nu 3029, 2222 (C=\text{N}), 1607, 1452, 1153, 769, 721, 692 cm\textsuperscript{-1}.

8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-amine 26. Following the general procedure, 1-amino-2,3-dihydro-1H-inden-2-ol (448 mg, 3.00 mmol, 1.00 equiv.) was reacted with NCS (421 mg, 3.15 mmol, 1.05 equiv.) and Zn(CN)\textsubscript{2} (352 mg, 3.00 mmol, 1.00 equiv.) in acetonitrile (22 mL) and water (2 mL) for 16 h. The crude product was purified by flash chromatography (hexanes/EtOAc 100/0 to 0/100) to obtain 26 as a white solid in 360 mg and 69% yield.

\textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}OD) \delta 7.48 (br s, 1H), 7.17 (br s, 2H), 7.03 (br s, 1H), 5.47 (s, 2H), 3.38 – 3.44 (m, 1H), 3.17 (d, \textit{J} = 17.8 Hz, 1H) ppm; \textsuperscript{13}C NMR (126 MHz, CD\textsubscript{3}OD) \delta 165.8, 141.7, 140.6, 129.9, 128.1, 127.0, 126.1, 86.3, 72.1, 39.2 ppm; ESI\textsuperscript{+} HRMS m/z calcd. for C\textsubscript{10}H\textsubscript{10}N\textsubscript{2}O ([M + H\textsuperscript{+}]\textsuperscript{+}) 175.0871, found 175.0880; IR \nu 3415, 3284, 1683, 1462, 1034, 751 cm\textsuperscript{-1}.

6-chlorobenzo[d]oxazol-2-amine 27. Following the general procedure 2-amino-5-chlorophenol (287 mg, 2.00 mmol, 1.00 equiv.) was reacted with NCS (280 mg, 2.10 mmol, 1.05 equiv.) and Zn(CN)\textsubscript{2} (235 mg, 2.00 mmol, 1.00 equiv.) in acetonitrile (17 mL) and water (1.7 mL) for 24 h. The crude product was purified by flash chromatography (hexane/EtOAc 100/0 – 70/40) to obtain 27 as a light brown solid in 230 mg and 68 % yield.

\textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6}) \delta 7.53 (s, 2H), 7.48 (d, \textit{J} = 1.9 Hz, 1H), 7.17 (d, \textit{J} = 8.3 Hz, 1H), 7.13 (dd, \textit{J} = 8.3 Hz, \textit{J} = 1.9 Hz, 1H) ppm; \textsuperscript{13}C NMR (126 MHz, DMSO-d\textsubscript{6}) \delta 163.3, 148.2, 142.7, 123.7, 123.5, 115.8, 109.1 ppm; ESI\textsuperscript{+} HRMS m/z calcd. for C\textsubscript{8}H\textsubscript{12}N\textsubscript{2}O\textsubscript{2} ([M + H\textsuperscript{+}]\textsuperscript{+}) 169.1068, found169.0172; IR \nu 3446, 3363, 3279, 2942, 2864, 2206, 1663, 1465, 1386, 1252, 1089, 985, 955, 861, 830, 808 cm\textsuperscript{-1}.

6-Nitro-1H-benzo[d]imidazol-2-amine 28.\textsuperscript{16} Following the general procedure 4-nitro-1,2-benzenediamine (313 mg, 2.00 mmol, 1.00 equiv.) was reacted with NCS (270 mg, 2.02 mmol, 1.01 equiv.) and Zn(CN)\textsubscript{2} (235 mg, 2.00 mmol, 1.00 equiv.) in acetonitrile (18 mL) and water (1.8 mL) for 72 h. The crude product was purified by flash chromatography (dichloromethane/MeOH 100/0 – 90/10) followed by trituration with MeOH to obtain 28 as a brown solid in169 mg and 48% yield.

\textsuperscript{16} Li, Y.-F.; Wang, G.-F.; Luo, Y.; Huang, W.-G.; Tang, W.; Feng, C.-L.; Shi, L.-P.; Ren, Y.-D.; Zuo, J.-P.; Lu, W. Eur. J. Med. Chem. 2007, 42, 1358. Reference uses BrCN as cyanation reagent.
$^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 11.76 (br s, 1H), 8.08 (br s, 1H), 7.94 (dd, $J = 8.7$ Hz, $J = 2.1$ Hz, 1H), 7.34 (d, $J = 8.7$ Hz, 1H), 7.28 (br s, 2H) ppm; $^{13}$C NMR (151 MHz, DMSO-d$_6$) $\delta$ 158.2, 143.3, 140.9, 135.8, 117.4, 111.6, 106.9 ppm; ESI$^+$ HRMS m/z calcd. for C$_7$H$_6$N$_4$O$_2$ ([M + H]$^+$) 179.0564, found 179.0569; IR $\nu$ 3404, 3322, 1645, 1624, 1608, 1565, 1509, 1474, 1337, 1292, 1070, 881, 824, 757, 738, 706 cm$^{-1}$.

*N-(1-(p-tolyl)ethyl)cyanamide* 29. Following the general procedure, 1-(4-methylphenyl)ethan-1-amine (250 mg, 2.0 mmol, 1.0 equiv.) was reacted with NCS (280 mg, 2.1 mmol, 1.05 equiv.) and Zn(CN)$_2$ (235 mg, 2.0 mmol, 1.0 equiv.) in acetonitrile (17 mL) and water (1.7 mL) for 16 h. The crude product was purified by flash chromatography (hexanes/EtOAc 100/0 – 80/20) to obtain 29 as a light brown oil in 260 mg and 81% yield.

$^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 7.27 – 7.25 (m, 2H), 7.22 – 7.20 (m, 2H), 5.01 (br s, NH), 4.37 – 4.33 (m, 1H), 1.45 (d, $J = 7.0$ Hz, 3H) ppm; $^{13}$C NMR (126 MHz, CD$_3$CN) $\delta$ 140.4, 138.8, 130.3, 127.2, 116.4, 55.8, 22.4, 21.1 ppm; ESI$^+$ HRMS m/z calcd. for C$_{10}$H$_8$N$_2$ ([M + H]$^+$) 161.1073, not detected, compound is unstable; IR $\nu$ 3185, 2976, 2922, 2211 (C≡N), 1515, 1448, 1377, 1159, 816 cm$^{-1}$.

$^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 11.76 (br s, 1H), 8.08 (br s, 1H), 7.94 (dd, $J = 8.7$ Hz, $J = 2.1$ Hz, 1H), 7.34 (d, $J = 8.7$ Hz, 1H), 7.28 (br s, 2H) ppm; $^{13}$C NMR (151 MHz, DMSO-d$_6$) $\delta$ 158.2, 143.3, 140.9, 135.8, 117.4, 111.6, 106.9 ppm; ESI$^+$ HRMS m/z calcd. for C$_7$H$_6$N$_4$O$_2$ ([M + H]$^+$) 179.0564, found 179.0569; IR $\nu$ 3404, 3322, 1645, 1624, 1608, 1565, 1509, 1474, 1337, 1292, 1070, 881, 824, 757, 738, 706 cm$^{-1}$.

*N-(1-(p-bromo)phenyl)ethyl)cyanamide* 30. Following the general procedure, 1-(4-bromophenyl)ethan-1-amine (400 mg, 2.0 mmol, 1.0 equiv.) was reacted with NCS (280 mg, 2.1 mmol, 1.05 equiv.) and Zn(CN)$_2$ (235 mg, 2.0 mmol, 1.0 equiv.) in acetonitrile (17 mL) and water (1.7 mL) for 24 h. The crude product was purified by flash chromatography (hexanes/EtOAc 100/0 – 70/30) to obtain 30 as a light yellow oil in 300 mg and 67% yield.

$^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 7.56 – 7.54 (m, 2H), 7.31 – 7.29 (m, 2H), 5.10 (br s, NH), 4.40 – 4.35 (m, 1H), 1.45 (d, $J = 6.9$ Hz, 3H) ppm; $^{13}$C NMR (126 MHz, CD$_3$CN) $\delta$ 142.8, 132.7, 129.4, 122.2, 116.1, 55.4, 22.2 ppm; ESI$^+$ HRMS m/z calcd. for C$_9$H$_9$BrN$_2$ ([M + H]$^+$) 223.0022, not detected, compound is unstable; IR $\nu$ 3183, 2976, 2901, 2213 (C≡N), 1489, 1406, 1073, 1009, 822 cm$^{-1}$.
5. Results with Additional Substrates

Figure S2: All substrates were tested following the general procedure.

- **Figure S2**: All substrates were tested following the general procedure.
6. Optimization and Synthesis of Cyanamide 2

6.1. Oxidation of Amine 1 with NCS.

(R)-N-(3-(2-chloroamido-1-(N-methylsulfamoyl)propan-2-yl)-4-fluorophenyl)-5-fluoropicolinamide 1-Cl. A 8 mL vial was charged with 1\footnote{1 was prepared as reported in: Thaisrivongs, D. A.; Morris, W. J.; Tan, L.; Song, Z. J.; Lyons, T. W.; Waldman, J. H.; Naber, J. R.; Chen, W.; Chen, L.; Zhang, B.; Yang, J. Org. Lett. 2018, 20, 1568.} (97.9 wt%, 39 mg, 0.1 mmol, 1.00 equiv.) and NCS (13 mg, 0.105 mmol, 1.05 equiv.). CD$_3$CN (0.9 mL) was added and the mixture was stirred at room temperature for 24 h and then transferred to an NMR tube to characterize the crude N-chloroamine 1-Cl.

$^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 9.96 (s, 1H, NH), 8.54 (d, $J = 2.7$ Hz, 1H), 8.27 (dd, $J = 8.7$ Hz, $J = 4.6$ Hz, 1H), 7.93 – 7.89 (m, 1H), 7.88 – 7.82 (m, 1H), 7.74 (td, $J = 8.7$ Hz, $J = 2.7$ Hz, 1H), 7.12 (dd, $J = 12.4$ Hz, $J = 8.9$ Hz, 1H), 5.68 (s, 1H, NH), 5.08 – 5.06 (m, 1H, NH), 3.78 (d, $J = 14.7$ Hz, 1H), 3.68 (d, $J = 14.7$ Hz, 1H), 3.67 (d, $J = 5.0$ Hz, 3H), 1.82 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CD$_3$CN) $\delta$ 162.5, 162.4 (d, $J = 258.9$ Hz), 158.2, 158.1 (d, $J = 243.6$ Hz), 147.3 (d, $J = 3.8$ Hz), 137.7 (d, $J = 25.7$ Hz), 135.4 (d, $J = 2.5$ Hz), 129.9 (d, $J = 11.2$ Hz), 125.4 (d, $J = 27.7$ Hz), 125.4 (d, $J = 2.7$ Hz), 122.5 (d, $J = 9.1$ Hz), 121.6 (d, $J = 3.8$ Hz), 117.4 (d, $J = 25.5$ Hz), 63.1 (d, $J = 3.4$ Hz), 56.2 (d, $J = 5.5$ Hz), 29.5, 24.8 (d, $J = 3.3$ Hz) ppm; $^{19}$F NMR (470 MHz, CD$_3$CN) $\delta$ -117.15, -123.72 ppm.

Reacting 1-Cl in acetonitrile/H$_2$O 9/1 with NaCN (1 equiv.) resulted in a 34% yield of 2 after stirring the mixture at 50 °C for 18 h. The yield was determined by HPLC using biphenyl as an internal standard. Due to the poor reactivity, the cyanation of 1 using NCS was not further explored.

6.2. Oxidation of Amine 1 with NBS.

(R)-N-(3-(2-bromoamido-1-(N-methylsulfamoyl)propan-2-yl)-4-fluorophenyl)-5-fluoropicolinamide 1-Br. A 8 mL vial was charged with 1 (97.9 wt%, 39 mg, 0.1 mmol, 1.00 equiv.) and NBS (18.6 mg, 0.105 mmol, 1.05 equiv.). CD$_3$CN (0.9 mL) was added and the mixture was stirred at room temperature for 10 min and then transferred to an NMR tube to characterize the crude N-bromoamine 1-Br.

$^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 9.96 (br s, 1H, NH), 8.54 (d, $J = 2.7$ Hz, 1H), 8.27 (dd, $J = 8.7$ Hz, $J = 4.6$ Hz, 1H), 7.93 – 7.89 (m, 1H), 7.88 – 7.82 (m, 1H), 7.74 (td, $J = 8.7$ Hz, $J = 2.7$ Hz, 1H), 7.12 (dd, $J = 12.4$ Hz, $J = 8.9$ Hz, 1H), 5.68 (s, 1H, NH), 5.08 – 5.06 (m, 1H, NH), 3.78 (d, $J = 14.7$ Hz, 1H), 3.68 (d, $J = 14.7$ Hz, 1H), 3.67 (d, $J = 5.0$ Hz, 3H), 1.82 (s, 3H) ppm; $^{13}$C NMR (126 MHz, CD$_3$CN) $\delta$ 162.5, 162.4 (d, $J = 258.9$ Hz), 158.2, 158.1 (d, $J = 247.2$ Hz), 147.2 (d, $J = 3.4$ Hz), 137.7 (d, $J = 25.7$ Hz), 135.3, 130.0, 125.4 (d, $J = 27.0$ Hz), 125.4 (d, $J = 1.9$ Hz), 122.6, 121.7, 117.4 (d, $J = 25.6$ Hz), 62.7, 56.9, 29.5, 25.8 ppm; $^{19}$F NMR (470 MHz, CD$_3$CN) $\delta$ -117.15, -123.70 ppm. ESI$^+$ HRMS $m/z$ calcld. for C$_{16}$H$_{12}$BrF$_2$N$_2$O$_5$S ($[M + Na]^+$) 485.0065, found 484.9741.
6.3. Optimization of the Cyanation of Amine 1

The reaction conditions for the cyanation of 1 were carried out on 0.1 mmol scale following the general cyanation procedure. Assay yields for 2 were determined by HPLC using biphenyl as internal standard.

Table S1:

| Solvent          | MeCN | 2-Me-THF | EtOAc |
|------------------|------|----------|-------|
| Temperature      |      |          |       |
| 22 °C            | 30 °C| 30 °C    | 30 °C 50 °C |
| Time             | Yield of 2 [%] |
| 17 h             | 43  | 34       | 55    | 63  | 50  |
| 24 h             | 49  | 42       | 63    | 68  | 49  |
| 48 h             | 56  | 49       | 65    | 73  | 47  |

*The assay yield of 2 was determined by HPLC.

6.4. Synthesis of Cyanamide 2

(R)-N-(3-(2-cyanamido-1-(N-methylsulfamoyl)propan-2-yl)-4-fluorophenyl)-5-fluoropicolinamide 2. Following the general procedure, 1 (97.9 wt%, 769 mg, 1.96 mmol, 1.00 equiv.) was reacted with NBS (360 mg, 2.10 mmol, 1.05 equiv.) and Zn(CN)₂ (235 mg, 2.00 mmol, 1.00 equiv.) in EtOAc (18 mL) and water (1.8 mL) at 30 °C for 72 h. The crude yield of 80% was determined by quantitative ¹H NMR (d1 = 60 s, NS = 8) using CH₂Br₂ as internal standard. The crude product was further purified by flash chromatography (hexanes/EtOAc 60/40 – 20/80, then CH₂Cl₂/EtOAc 9/1 – 7/3) to obtain 2 as a white solid in 536 mg and 67% yield.

¹H NMR (500 MHz, CDCl₃) δ. 9.90 (s, 1H, NH), 8.47 (d, J = 2.7 Hz, 1H), 8.32 (dd, J = 8.7 Hz, J = 4.5 Hz, 1H), 8.01 – 7.98 (m, 1H), 7.68 (dd, J = 7.1 Hz, J = 2.6 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.15 (dd, J = 11.7 Hz, J = 8.8 Hz, 1H), 6.24 (s, 1H, NH), 4.03 (d, J = 15.0 Hz, 1H), 3.90 (q, J = 5.0 Hz, 1H, NH), 3.44 (d, J = 15.0 Hz, 1H), 2.57 (d, J = 5.0 Hz, 3H), 1.90 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 161.6, 161.6 (d, J = 262.1 Hz), 156.2 (d, J = 243.4 Hz), 145.7 (d, J = 3.9 Hz), 136.9 (d, J = 25.5 Hz), 134.7 (d, J = 2.5 Hz), 128.2 (d, J = 13.1 Hz), 124.6 (d, J = 1.8 Hz), 124.5 (d, J = 14.8 Hz), 122.3 (d, J = 8.7 Hz), 119.5 (d, J = 3.3 Hz), 117.3 (d, J = 25.0 Hz), 113.0, 58.1 (d, J = 5.2 Hz), 57.4 (d, J = 4.5 Hz), 29.1, 26.4 (d, J = 4.6 Hz) ppm; ¹⁹F NMR (470 MHz, CD₃CN) δ -116.01, -120.76 ppm; ESI- HRMS m/z calcd. for C₁₇H₁₇F₂N₂O₃S ([M + H]⁺) 410.1093, found 410.1108; IR ν 3284, 2217, 1707, 1673, 1535, 1472, 1408, 1317, 1222, 819, 640 cm⁻¹.
7. Mechanistic Experiments

7.1. Reaction Profile for the Formation of Cyanamide 5

![Reaction Scheme]

A 20 mL vial equipped with a magnetic stir bar was charged with Zn(CN)$_2$ (117 mg, 1.00 mmol, 1.00 equiv.) NCS (135 mg, 1.01 mmol, 1.01 equiv.), CD$_3$CN (9 mL) and CH$_2$Br$_2$ (70 μL, 1.0 mmol, 1.0 equiv.) The vial was cooled in an ice bath, 1-phenylethan-1-amine (4) (129 μL, 1.00 mmol, 1.00 equiv.) was added and the mixture was stirred for 5 – 10 min at 500 rpm. Water (0.9 mL) was added and a ~0.2 mL aliquot ($t_0$ sample) was immediately taken. The vial was then stirred at room temperature at 600 rpm. The reaction was sampled every hour. Each aliquot ($t_0 - 16$ h) was dried over Na$_2$SO$_4$ and filtered through a 0.45 μm PTFE syringe filter into a NMR tube using CD$_3$CN as an eluent. The yield of 5 was determined by quantitative $^1$H NMR (D1 = 60 s, NS = 8) with respect to CH$_2$Br$_2$ as internal standard.

Table S2: $^1$H NMR yield of 5 converted to concentration [mol/L].

| Time [h] | Time [s] | AY 5 [%] | conc. 5 [mol/L] |
|----------|----------|----------|-----------------|
| 0        | 0        | 0        | 0               |
| 1        | 3600     | 4        | 0.0040          |
| 2        | 7200     | 7        | 0.0071          |
| 3        | 10800    | 15       | 0.0152          |
| 4        | 14400    | 18       | 0.0182          |
| 5        | 18000    | 26       | 0.0263          |
| 6        | 21600    | 30       | 0.0303          |
| 7        | 25200    | 33       | 0.0333          |
| 8        | 28800    | 40       | 0.0404          |
| 16       | 57600    | 80       | 0.0808          |

Figure S3: Zero order reaction profile of 5.
7.2. Determination of the Kinetic Order of Zn(CN)$_2$

The procedure described in 7.1. was repeated using either Zn(CN)$_2$ (88 mg, 0.75 mmol, 0.75 equiv.) or Zn(CN)$_2$ (59 mg, 0.50 mmol, 0.50 equiv.). Each aliquot ($t_0 - 8$ h) was dried over Na$_2$SO$_4$ and filtered through a 0.45 μm PTFE syringe filter into a NMR tube using CD$_3$CN as an eluent. The yield of 5 was determined by quantitative $^1$H NMR (D$_1 = 60$ s, NS = 8) with respect to CH$_2$Br$_2$ as internal standard.

**Table S3: $^1$H NMR yield of 5 converted to concentration [mol/L].**

| Time [h] | Time [s] | 1 equiv. | 0.75 equiv. | 0.5 equiv. |
|----------|----------|----------|-------------|------------|
|          |          | AY [%]   | conc. [mol/L] | AY [%] | conc. [mol/L] | AY [%] | conc. [mol/L] |
| 0        | 0        | 0        | 0           | 0        | 0           | 0        | 0 |
| 1        | 3600     | 4        | 0.0040      | 3        | 0.0030      | 4        | 0.0039 |
| 2        | 7200     | 7        | 0.0071      | 9        | 0.0090      | 10       | 0.0099 |
| 3        | 10800    | 15       | 0.0152      | 14       | 0.0140      | 14       | 0.0138 |
| 4        | 14400    | 18       | 0.0182      | 20       | 0.0200      | 19       | 0.0188 |
| 5        | 18000    | 26       | 0.0263      | 23       | 0.0230      | 23       | 0.0227 |
| 6        | 21600    | 30       | 0.0303      | 29       | 0.0290      | 26       | 0.0258 |
| 7        | 25200    | 33       | 0.0333      | 34       | 0.0339      | 31       | 0.0317 |
| 8        | 28800    | 40       | 0.0404      | 39       | 0.0390      | 36       | 0.0367 |

**Figure S4: Initial rate for 1 equiv. Zn (CN)$_2$ ($k = 1.37 \cdot 10^6$ mol/L·s$^{-1}$)**

![Initial rate for 1 equiv. Zn (CN)$_2$](image)
**Figure S5:** Initial rate for 0.75 equiv. Zn (CN)$_2$ ($k = 1.34 \cdot 10^6$ mol/L·s$^{-1}$)

![Graph showing initial rate for 0.75 equiv. Zn (CN)$_2$.](image)

**Figure S6:** Initial rate for 0.5 equiv. Zn (CN)$_2$ ($k = 1.26 \cdot 10^6$ mol/L·s$^{-1}$)

![Graph showing initial rate for 0.5 equiv. Zn (CN)$_2$.](image)
7.3. Hammett Study

The procedure described in 7.1. was repeated using either 1-(4-methylphenyl)ethan-1-amine (152 μL, 1.00 mmol, 1.00 equiv.) or 1-(4-bromophenyl)ethan-1-amine (143 μL, 1.00 mmol, 1.00 equiv.). Each aliquot (t₀ – 8 h) was dried over Na₂SO₄ and filtered through a 0.45 μm PTFE syringe filter into a NMR tube using CD₃CN as an eluent. The yields of cyanamides 4, 29 and 30 were determined by qualitative ¹H NMR (D1 = 60 s, NS = 8) with respect to CH₂Br₂ as internal standard.

Table S4: ¹H NMR yield of cyanamides converted to concentration [mol/L].

| Time [h] | Time [s] | R = H (4) | R = Me (29) | R = Br (30) |
|----------|----------|-----------|-------------|-------------|
|          |          | AY [%]    | conc. [mol/L] | AY [%] | conc. [mol/L] | AY [%] | conc. [mol/L] |
| 0        | 0        | 0         | 0            | 0         | 0            | 0       | 0 |
| 1        | 3600     | 4         | 0.0040       | 3         | 0.0030       | 2       | 0.0021 |
| 2        | 7200     | 7         | 0.0071       | 13        | 0.0135       | 4       | 0.0042 |
| 3        | 10800    | 15        | 0.0152       | 20        | 0.0198       | 7       | 0.0075 |
| 4        | 14400    | 18        | 0.0182       | 26        | 0.0261       | 7       | 0.0075 |
| 5        | 18000    | 26        | 0.0263       | 30        | 0.0302       | 13      | 0.0127 |
| 6        | 21600    | 30        | 0.0303       | 37        | 0.0375       | 15      | 0.0148 |
| 7        | 25200    | 33        | 0.0333       | 40        | 0.0406       | 19      | 0.0191 |
| 8        | 28800    | 40        | 0.0404       | 49        | 0.0490       | 22      | 0.0223 |

Figure S7: Initial rate for R = H (k = 1.37·10⁶ mol/L·s⁻¹)
**Figure S8:** Initial rate for $R = \text{Me}$ ($k = 1.7 \cdot 10^6 \text{ mol/L} \cdot \text{s}^{-1}$)

![Graph showing initial rate for $R = \text{Me}$](image)

**Figure S9:** Initial rate for $R = \text{Br}$ ($k = 0.72 \cdot 10^6 \text{ mol/L} \cdot \text{s}^{-1}$)

![Graph showing initial rate for $R = \text{Br}$](image)

**Table S5:** log ($k_x/k_H$) values for Hammett plot.

| $R$ | $k$ [mol/L·s] | $\sigma_{para}$ | log ($k_x/k_H$) |
|-----|---------------|-----------------|-----------------|
| Me  | 1.696         | -0.17           | 0.093           |
| H   | 1.370         | 0               | 0               |
| Br  | 0.719         | 0.23            | -0.280          |
7.4. Control & Cross-Over Experiments

Background reaction between NCS and Zn(CN)₂

A J-Young NMR tube was charged with Zn(CN)₂ (12 mg, 0.1 mmol, 1.0 equiv.) and NCS (13 mg, 0.1 mmol, 1.0 equiv.). CD₃CN (0.9 mL) and water (9 μL) were added and the slurry was allowed to stand (with frequent shaking) at room temperature for 8 h before ¹H and ¹³C NMR analysis.

44% conversion of NCS to succinimide was observed by ¹H NMR (Figure S10). The formation of ClCN was confirmed by ¹³C NMR upon comparison with a mixture of Zn(CN)₂ in CD₃CN/H₂O (Figure S11). The observed chemical shift for ClCN 96.68 ppm is consistent with the previously reported value of 95.45 ppm for neat ClCN at 10 °C.¹⁸

Figure S10: ¹H NMR (600 MHz, CD₃CN) of the background reaction after 8 h showing 44% conversion of NCS to succinimide.

¹⁸ Henderson, T.J; Cullinan, D. B. Magn. Reson. Chem. 2007; 45, 954.
Figure S11: $^{13}$C NMR (150 MHz, CD$_3$CN) of the background reaction after 8 h compared to a mixture of Zn(CN)$_2$ in CD$_3$CN/H$_2$O.

Oxidation of N-benzylaniline (31) with NCS

A 20 mL vial was charged with N-benzylaniline (31) (92 mg, 0.5 mmol, 1.0 equiv.) and NCS (70 mg, 0.53 mmol, 1.05 equiv.). CD$_3$CN (4.5 mL) and CH$_2$Br$_2$ (35 μL, 0.5 mmol, 1.0 equiv.) were added and the solution was stirred at room temperature for 5 min. Then, a ~0.6 mL aliquot was transferred to a NMR tube and the mixture was monitored by quantitative $^1$H NMR (D1 = 60 s, NS = 8) after 1 h and then every 2 h for 15 h.

Formation of N-benzyl-N-chloroaniline could not be observed. Instead slow formation of N-benzyl-p-chloroaniline (24) (12%) and N-benzyl-o-chloroaniline$^{19}$ (5%) was detected.

$^{19}$ Barraza, S. J.; Denmark, S. E. Synlett 2017, 28, 2891.
Figure S12: $^1$H NMR of the crude mixture after 1 h and 15 h. Arrows indicate benzylic protons of $N$-benzyl-$\alpha$-chloroaniline (4.45 ppm) and $N$-benzyl-$\beta$-chloroaniline (24) (4.30 ppm).

Oxidation of $N$-benzylaniline (31) with 4-Cl

A 8 mL vial was charged with NCS (83 mg, 0.63 mmol, 1.25 equiv.) and CD$_3$CN (2.4 mL). The vial was then cooled in an ice bath. 1-Phenylethan-1-amine (4) (77 µL, 0.6 mmol, 1.2 equiv.) was added and the solution was stirred for 5 – 10 min. A separate 20 mL vial was charged with $N$-benzylaniline (31) (92 mg, 0.5 mmol, 1.0 equiv.) and CD$_3$CN (2.5 mL). 2 mL of the cooled, in situ prepared $N$-chloro-1-phenylethan-1-amine (4-Cl) solution (equal to ~ 1 equiv. of $N$-chloroamine) was added to the $N$-benzylaniline solution. CH$_2$Br$_2$ (35 µL, 0.5 mmol, 1.0 equiv.) was added and the solution was stirred at room temperature for 5 min. Then, a ~0.6 mL aliquot was transferred to a NMR tube and the mixture was monitored by quantitative $^1$H NMR (d1 = 60 s, NS = 8) after 1 h and then every 2 h for 15 h.
Formation of N-benzyl-N-chloroaniline could not be observed. 94% of N-benzylaniline (31) remained unreacted. The remainder (~6%) was found to be converted to N-benzyl-o-chloroaniline and N-benzyl-p-chloroaniline (24). N-chloro-1-phenylethan-1-amine (4-Cl) slowly decomposed to another unidentified species.

**Figure S13:** $^1$H NMR of the reaction mixture after 1 h and 15 h. Arrows indicate N-benzyl-o-chloroaniline, N-benzyl-p-chloroaniline (24) and an unidentified decomposition product of 4.

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**Cross-Over Experiment**

A 8 mL vial was charged with NCS (21 mg, 0.158 mmol, 1.58 equiv.) and CD$_3$CN (0.75 mL). The vial was then cooled in an ice bath. 1-Phenylethan-1-amine (4) (21 μL, 0.158 mmol, 1.58 equiv.) was added and the solution was stirred for 5 – 10 min. A separate 20 mL vial was charged with Zn(CN)$_2$ (12 mg, 0.1 mmol, 1.0 equiv.), N-benzylaniline (31) (92 mg, 0.5 mmol, 1.0 equiv.) and CD$_3$CN (0.4 mL). 0.5 mL of the cooled, *in situ* prepared N-chloro-1-phenylethan-1-amine (4-Cl) solution (equal to ~ 1.05 equiv. of N-chloroamine) was added to the N-benzylaniline solution. CH$_3$Br$_2$ (7 μL, 0.1 mmol, 1.0 equiv.) was added.
added and a ~0.2 mL aliquot (t₀ sample) was immediately taken. The aliquot was filtered through a 0.45 μm PTFE syringe filter into a NMR tube using CD₃CN as eluent. To the remaining solution water (70 μL) was added and the mixture was stirred at room temperature. After 17 h, a ~0.2 mL aliquot was filtered through a 0.45 μm PTFE syringe filter into a NMR tube using CD₃CN as eluent. Both samples were analyzed by quantitative ¹H NMR (D₁ = 60 s, NS = 8).

With the t₀ sample, the starting ratio of N-benzylaniline (31) to N-chloro-1-phenylethan-1-amine (4-Cl) was confirmed as 1:1 and the initial concentration of each amine compared to the internal standard CH₂Br₂ was determined.

After 17 h, 32% of N-benzylaniline (31) was converted to the desired N-cyano-N-benzylamine (21). 4% of 31 was chlorinated at the aniline ring and 64% of 31 remained unreacted. 58% of N-chloroamine 4-Cl was converted to cyanamide 5, 37% was reduced to 1-phenylethan-1-amine 4 and 5% of 4-Cl remained unreacted (see part 7.5. for further details).

Figure S14: ¹H NMR of the reaction mixture at t₀ and 17 h.
7.5. Characterization of the Major Side Product in the Cyanation of 1-Arylethan-1-amines

Reactions of 1-arylethan-1-amines always generate 10 – 15% of an unknown impurity with a characteristic benzylic proton signal at around 4.45 ppm. In order to characterize the impurity the crude reaction mixture of 1-(p-bromophenyl)ethan-1-cyanamide was analyzed.

**Titration Experiment and $^1$H DOSY experiment**

Following the general procedure, 1-(4-bromophenyl)ethan-1-amine (72 μL, 0.5 mmol, 1.0 equiv.) was reacted with NCS (67 mg, 0.51 mmol, 1.01 equiv.) and Zn(CN)$_2$ (59 mg, 0.5 mmol, 1.0 equiv.) in CD$_3$CN (4.5 mL) and water (0.45 mL) for 24 h. A 0.6 mL aliquot was dried over Na$_2$SO$_4$ and filtered through a 0.45 μm PTFE syringe filter into a NMR tube using CD$_3$CN as eluent. The sample was analyzed by quantitative $^1$H NMR ($D_1 = 60$ s, $NS = 8$).

Full consumption of the N-chloroamine was observed. The desired cyanamide (benzylic proton at 4.36 ppm) was formed in a 8.1 / 1 ratio with an unknown impurity (benzylic proton at 4.43 ppm).

1-(4-bromophenyl)ethan-1-amine (13 mg, ~1.2 equiv.) was added to the NMR sample and a quantitative $^1$H NMR ($D_1 = 60$ s, $NS = 8$) measurement was repeated.

The impurity peak at 4.43 ppm converged with the starting material peak at 4.21 ppm suggesting that the impurity is in fact the starting material, 1-(4-bromophenyl)ethan-1-amine.

Additionally, the starting material peak at 4.21 ppm appears to be more downfield compared to the $^1$H NMR shift of the benzylic proton of 1-(4-bromophenyl)ethan-1-amine alone.

This observation is in line with a fast equilibrium between bound and unbound amine to ZnCl$_2$ or Zn(CN)Cl in solution.

The hypothesis that the peak at 4.43 ppm is the result of amine starting material bound to ZnCl$_2$ or Zn(X)Cl (X = CN, OH) in solution was further supported by a $^1$H DOSY NMR experiment of the reaction mixture. The experiment showed a slower diffusion coefficient for the starting material peak at 4.43 ppm than for the cyanamide product at 4.36 ppm which is consistent with the starting material being complexed to a zinc salt.
**Figure S15:** $^1$H NMR at 500 MHz of the reaction mixture after 24 h with and without additional starting material added.

**Figure S16:** $^1$H DOSY NMR at 600 MHz of the reaction mixture after 24 h.
7.6. Proposed Mechanism:
The observed zero order in amine 4 and Zn(CN)$_2$ as well as negative $\rho$ value from the Hammett plot are in agreement with a mass transfer limited scenario in which coordination of the $N$-chloroamine to Zn(CN)$_2$ affects dissolution and thus the rate of the reaction (Scheme S1).

**Scheme S1:**

The kinetic data could also be explained with rate determining $S_N2$-type step from a stable Zn(CN)$_2$ – $N$-chloroamine complex (Scheme S2).

**Scheme S2:**

Based on the results of the control and cross-over experiments in 6.4., a mass transfer limited scenario seems more likely. Moreover, the cross-over experiment suggests the *in situ* formation of cyanogen chloride. The latter would also explain the recovery of ~10% starting material (see 6.5.) during the reaction of $N$-chloroamines with Zn(CN)$_2$.

**Scheme S3:**
8. $^1$H and $^{13}$C NMR

Figure S17. $^1$H NMR (500 MHz) spectrum of 4-Cl in CD$_3$CN (succinimide at 2.61 ppm).

Figure S18. $^{13}$C NMR (126 MHz) spectrum of 4-Cl in CD$_3$CN (succinimide at 179.4 and 30.4 ppm).
Figure S19. $^1$H NMR (500 MHz) spectrum in CD$_3$CN (succinimide at 2.61 ppm).

Figure S20. $^{13}$C NMR (126 MHz) spectrum in CD$_3$CN (succinimide at 179.4 and 30.4 ppm).
Figure S21. $^1$H NMR (500 MHz) spectrum in CD$_3$CN (succinimide at 2.61 ppm).

Figure S22. $^{13}$C NMR (126 MHz) spectrum in CD$_3$CN (succinimide at 179.4 and 30.4 ppm).
Figure S23. $^1$H NMR (500 MHz) spectrum of 5 in CD$_2$Cl$_2$.

Figure S24. $^{13}$C NMR (126 MHz) spectrum of 5 in CD$_2$Cl$_2$. 
Figure S25. $^1$H NMR (500 MHz) spectrum of 6 in CD$_3$CN.

Figure S26. $^{13}$C NMR (126 MHz) spectrum of 6 in CD$_3$CN.
Figure S27. $^1$H NMR (500 MHz) spectrum of 7 in CD$_3$CN.

Figure S28. $^{13}$C NMR (126 MHz) spectrum of 7 in CD$_3$CN.
Figure S29. $^1$H NMR (500 MHz) spectrum of 8 in CDCl$_3$.

Figure S30. $^{13}$C NMR (126 MHz) spectrum of 8 in CDCl$_3$. 
Figure S31. $^1$H NMR (500 MHz) spectrum of 9 in CD$_2$Cl$_2$.

Figure S32. $^{13}$C NMR (126 MHz) spectrum of 9 in CD$_2$Cl$_2$. 
Figure S33. $^1$H NMR (500 MHz) spectrum of 10 in CDCl$_3$.  

Figure S34. $^{13}$C NMR (126 MHz) spectrum of 10 in CDCl$_3$.  

S40
Figure S35. $^1$H NMR (500 MHz) spectrum of 11 in CD$_2$Cl$_2$.

Figure S36. $^{13}$C NMR (126 MHz) spectrum of 11 in CDCl$_3$. 
Figure S37. $^1$H NMR (500 MHz) spectrum of 12 in CDCl$_3$.

Figure S38. $^{13}$C NMR (126 MHz) spectrum of 12 in CDCl$_3$. 
Figure S39. $^1$H NMR (500 MHz) spectrum of 13 in CDCl$_3$.

Figure S40. $^{13}$C NMR (126 MHz) spectrum of 13 in CDCl$_3$. 
Figure S41. $^1$H NMR (500 MHz) spectrum of 14 in CDCl$_3$.

Figure S42. $^{13}$C NMR (126 MHz) spectrum of 14 in CDCl$_3$. 
Figure S43. $^1$H NMR (500 MHz) spectrum of 15 in CDCl$_3$.

Figure S44. $^{13}$C NMR (126 MHz) spectrum of 15 in CDCl$_3$. 
Figure S45. $^1$H NMR (500 MHz) spectrum of the 1,2,4-oxadiazole in CDCl$_3$.

Figure S46. $^{13}$C NMR (126 MHz) spectrum of the 1,2,4-oxadiazole in CDCl$_3$. 
Figure S47. $^1$H NMR (500 MHz) spectrum of 16 in CD$_3$CN.

![H NMR spectrum of 16 in CD$_3$CN]

Figure S48. $^{13}$C NMR (126 MHz) spectrum of 16 in CD$_3$CN.

![C NMR spectrum of 16 in CD$_3$CN]
Figure S49. $^1$H NMR (500 MHz) spectrum of 17 in CDCl$_3$.

Figure S50. $^{13}$C NMR (126 MHz) spectrum of 17 in CDCl$_3$. 
Figure S51. $^1$H NMR (500 MHz) spectrum of 18 in CDCl$_3$.

Figure S52. $^{13}$C NMR (126 MHz) spectrum of 18 in CDCl$_3$. 
Figure S53. $^1$H NMR (500 MHz) spectrum of 19 in DMSO-$d_6$.

Figure S54. $^{13}$C NMR (126 MHz) spectrum of 19 in DMSO-$d_6$. 
Figure S55. $^1$H NMR (500 MHz) spectrum of 20 in CD$_2$Cl$_2$.

Figure S56. $^{13}$C NMR (126 MHz) spectrum of 20 in CD$_2$Cl$_2$. 
Figure S57. $^{19}$F NMR (470 MHz) spectrum of 20 in CD$_2$Cl$_2$. 
Figure S58. $^1$H NMR (500 MHz) spectrum of 21 in CDCl$_3$.

Figure S59. $^{13}$C NMR (126 MHz) spectrum of 21 in CDCl$_3$. 
Figure S60. $^1$H NMR (500 MHz) spectrum of 22 in CDCl$_3$.

Figure S61. $^{13}$C NMR (126 MHz) spectrum of 22 in CDCl$_3$. 
Figure S62. $^1$H NMR (500 MHz) spectrum of 23 in CDCl$_3$.

Figure S63. $^{13}$C NMR (126 MHz) spectrum of 23 in CDCl$_3$. 
Figure S64. $^1$H NMR (500 MHz) spectrum of 24 in CDCl$_3$.

Figure S65. $^{13}$C NMR (126 MHz) spectrum of 24 in CDCl$_3$. 
Figure S66. $^1$H NMR (500 MHz) spectrum of 25 in CDCl$_3$.

Figure S67. $^{13}$C NMR (126 MHz) spectrum of 25 in CDCl$_3$. 

S57
Figure S68. $^1$H NMR (500 MHz) spectrum of 26 in CD$_3$OD.

Figure S69. $^{13}$C NMR (126 MHz) spectrum of 26 in CD$_3$OD.
Figure S70. $^1$H NMR (500 MHz) spectrum of 27 in DMSO-$d_6$.

Figure S71. $^{13}$C NMR (126 MHz) spectrum of 27 in DMSO-$d_6$. 
Figure S72. $^1$H NMR (500 MHz) spectrum of 28 in DMSO-d$_6$.

Figure S73. $^{13}$C NMR (151 MHz) spectrum of 28 in DMSO-d$_6$. 
Figure S74. $^1$H NMR (500 MHz) spectrum of 29 in CD$_3$CN.

Figure S75. $^{13}$C NMR (126 MHz) spectrum of 29 in CD$_3$CN.
Figure S76. $^1$H NMR (500 MHz) spectrum of 30 in CD$_3$CN.

Figure S77. $^{13}$C NMR (126 MHz) spectrum of 30 in CD$_3$CN.
Figure S78. $^1$H NMR (500 MHz) spectrum of 1-Cl in CD$_3$CN (succinimide at 2.61 ppm).

Figure S79. $^{13}$C NMR (126 MHz) spectrum of 1-Cl in CD$_3$CN (succinimide at 179.4 and 30.4 ppm).
Figure S80. $^{19}$F NMR (470 MHz) spectrum of 1-Cl in CD$_3$CN.

Figure S81. $^1$H NMR (500 MHz) spectrum of 1-Br in CD$_3$CN (succinimide at 2.61 ppm).
**Figure S82.** $^{13}$C NMR (126 MHz) spectrum of 1-Br in CD$_3$CN (succinimide at 179.4 and 30.4 ppm).

**Figure S83.** $^{19}$F NMR (470 MHz) spectrum of 1-Br in CD$_3$CN.
Figure S84. $^1$H NMR (500 MHz) spectrum of 2 in CDCl$_3$.

Figure S85. $^{13}$C NMR (126 MHz) spectrum of 2 in CDCl$_3$. 
Figure S86. $^{19}$F NMR (470 MHz) spectrum of 2 in CDCl$_3$. 