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Cyanide Anion as a Leaving Group in Nucleophilic Aromatic Substitution: Synthesis of Quaternary Centers at Azine Heterocycles

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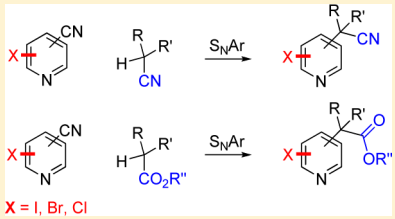
Supporting Information

ABSTRACT: Nucleophilic aromatic substitution of 2- or 4-cyanoazines with the anions derived from aliphatic α,α-disubstituted esters and nitriles leads to displacement of the cyanide function. Enabling cyanides to be used as highly active leaving groups in S_NAr reactions provides additional flexibility in starting materials for synthesis. We show that, in many cases, the cyanide leaving group is displaced preferentially in the presence of halogens. The resulting heteroaryl iodides, bromides, and chlorides subsequently can be used as handles for further chemical diversification.



The classical method of forging aliphatic carbon−carbon bonds to arenes by electrophilic aromatic substitution (S_EAr) onto alkyl halides continues to be of general use over 130 years after its discovery by Friedel and Crafts.[1] While nucleophilic aromatic substitution (S_NAr) has been used extensively to secure aryl linkages to heteroatoms,[2] studies describing the use of S_NAr to furnish carbon−carbon bonds without using stabilized carbanions derived from malonates have only been reported recently.[3−5]

In 2005, Klapars and Waldman at Merck identified the first highly effective aliphatic α-nitrile arylation, spanning a broad spectrum of heteroaryl halide acceptors.[3a] Previously, quaternary motifs of this type were accessed by palladium-catalyzed reactions of enolates with aryl halides, a reaction type with very few heteroaromatic examples (Figure 1).[6] Shortly after this initial publication, another Merck group demonstrated that heteroaryl halogen electrophiles could also be intercepted by ester enolates under similar conditions.[4] In 2009, during a medicinal chemistry campaign that utilized the Klapars and Waldman α-nitrile arylation method, a third Merck group noted unintentional displacement of a nitrile functional group on the pyridine electrophile.[5] Herein, we report further studies on the use of the cyanide leaving group in forming quaternary centers via S_NAr chemistry.[7−11]

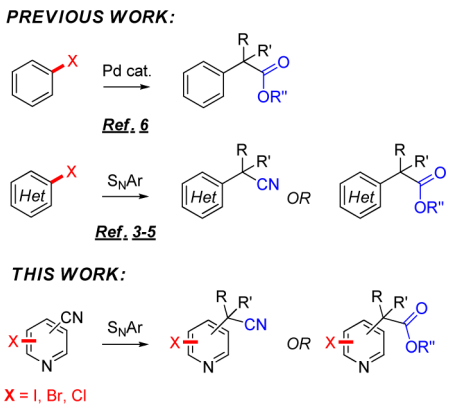


Figure 1. Literature precedent for the formation of quaternary bonds to arenes.

We now show that S_NAr reaction of the potassium and lithium anions derived from aliphatic α,α-disubstituted esters and nitriles with 2- or 4-cyanoazines leads to products with overall *ipso* substitution of the carbonitrile. In nearly all cases, reaction pathways such as addition to the arylnitrile carbon or competing displacement of halide functional groups do not occur. Aryl halides are by far the most commonly used leaving groups for S_NAr chemistry and are critical handles for late-stage molecular diversification of arenes. Thus, halide-sparing transformations such as the reaction presented here constitute valuable additions to the synthetic chemist's toolbox.

As depicted in Table 1, quaternary azine α-nitriles can be obtained in good yield by this operationally simple method. This type of motif has recently seen utility in drug discovery settings[12] for which there existed no practical synthetic approach before the work by Merck.[3a,5] In a typical example, an equimolar quantity of cyanoazine and aliphatic nitrile in tetrahydrofuran at −78 °C is treated with 1.1 equiv of lithium bis(trimethylsilyl)amide and allowed to warm to room temperature. Our work demonstrates the use of both acyclic α,α-disubstituted nitriles as well as cyclic nitriles with 3- to 7-membered rings. For example, isonicotinonitrile reacts in high yield with cyclohexane carbonitrile (entry 1, 71%), *tert*-butyl 3-cyanoazetidine-*N*-carboxylate (entry 2, 78%), and tetrahydropyran carbonitrile (entry 4, 94%). For other halogen-containing isonicotinonitrile electrophiles, we were able to include chlorides at C2 (entry 9, 80% on gram-scale), C3 (entry 7, 82%), and C3/C5 (entry 3, 47%), as well as C3 bromides (entry 5, 71%) and iodides (entries 6 and 8, 75% and 60%, respectively). Surprisingly, α-lithiated aliphatic nitriles with a heteroatom on the β-carbon do not appear to undergo

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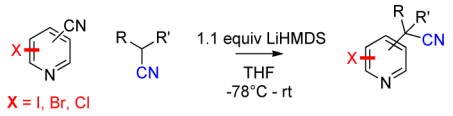
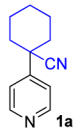
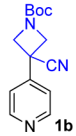
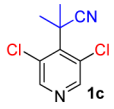
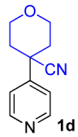
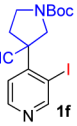
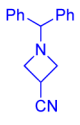
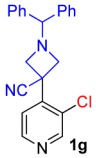
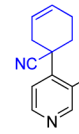
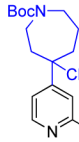
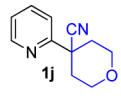
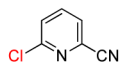
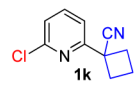
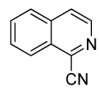
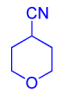
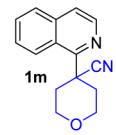
Table 1. S_NAr Reaction Scope of Aliphatic α,α-Disubstituted Nitriles with Cyanoazines[a]



entry	azine	nitrile	product	% yield
1			 **1a**	71[b]
2			 **1b**	78
3			 **1c**	47
4			 **1d**	94
5			 **1e**	71
6			 **1f**	75[b]
7			 **1g**	82
8			 **1h**	60
9			 **1i**	90 (80)[c]
10			 **1j**	62
11			 **1k**	45
12			 **1l**	39
13			 **1m**	97
14			**1n**	37

[a]Conditions: The azine (1 mmol) and cyanide (1 mmol) were weighed into a vial, capped with a septum, and purged with nitrogen gas. Anhydrous THF (5 mL) was added, and the mixture was cooled to −78 °C while stirring. LiHMDS (1.1 mL, 1.0 M in THF) was added before removal of the cooling bath and the reaction mixture allowed to warm to room temperature. [b]1.4 equiv of LiHMDS. [c]Gram scale (4.5 mmol).

spontaneous ring-opening to any appreciable extent (entries 2, 6, and 7). For reactions of picolinonitriles, which are generally less reactive than the isonicotinonitriles, compound **1j** is obtained in 62% yield (entry 10) and volatile fragment **1l** in 39% yield (entry 12). We also were able to preserve a chloride at C6, as exemplified by cyclobutane **1k** (entry 11, 45%). Isoquinoline 1-carbonitrile is a highly reactive electrophile,[13] whereby compound **1m** is obtained in almost quantitative yield (entry 13, 97%) and we were able to obtain cyclopropane **1n** (entry 14, 37%) despite cyclopropyl carbonitrile displaying only trace reactivity with 2- and 4-cyanopyridines.[14]

In the above reactions, small amounts of product resulting from competitive halide displacement or direct attack on the arylnitrile carbon[15] were detected by HPLC−MS but were not isolated.[16] However, these byproducts do not make up the mass balance difference for entries in which the yield was moderate. Instead, we noticed that lower yields often result from decomposition of products and reactants, potentially due to extraneous base, as previously observed in the S_NAr studies by Klapars and Waldman.[3a] Therefore, extended reaction times should be avoided whenever possible; typically, the reaction is complete within 3 h.

In extending the current transformation to nucleophilic additions of aliphatic esters, only trace reactivity was observed with lithium bis(trimethylsilyl)amide. After screening several additives,[17] we discovered that simply switching to sodium or potassium bis(trimethylsilyl)amide provided higher conversions to product, with the highest levels being reached with potassium bis(trimethylsilyl)amide. Futhermore, we did not isolate or detect any products from competitive Claisen condensation onto the product ester.

Thus, reaction of isonicotinonitrile with ethyl cyclobutanecarboxylate provides volatile compound **2a** in 60% yield (Table 2, entry 1). Isonicotinonitrile also reacts with a cyclic alkenyl methyl ester to afford compound **2c** (entry 3, 57%). Pyridyl halides are retained, providing moderate yields of cyano-selective substitution products in reactions with cyclic lactones (entry 2, 36%), benzyl carbamate-protected piperidines (entry

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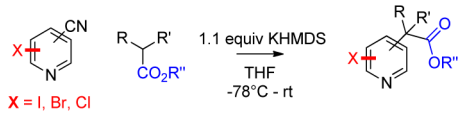
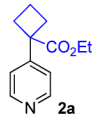
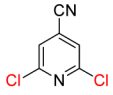
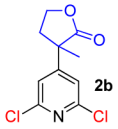
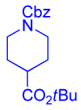
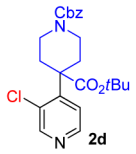
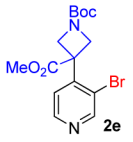
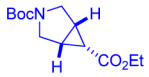
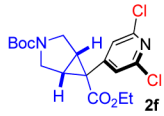
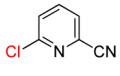
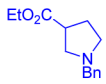
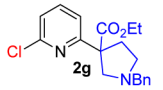
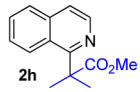
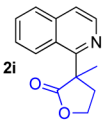
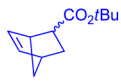
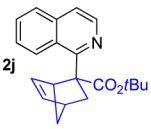
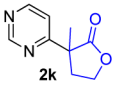
Table 2. S_NAr Reaction Scope of Aliphatic α,α-Disubstituted Esters with Cyanoazines[a]



entry	azine	ester	product	% yield
1			 **2a**	60
2			 **2b**	36
3			 **2c**	57
4			 **2d**	28
5			 **2e**	39
6			 **2f**	44[b]
7			 **2g**	54
8			 **2h**	55
9			 **2i**	94
10			 **2j**	40
11			 **2k**	62

[a]Conditions: The azine (1 mmol) and cyanide (1 mmol) were weighed into a vial, capped with a septum, and purged with nitrogen gas. Anhydrous THF (2.5 mL) was added, and the mixture was cooled to −78 °C while stirring. KHMDS (2.2 mL, 0.5 M in toluene) was added before removal of the cooling bath and the reaction mixture allowed to warm to room temperature. [b]1.4 equiv of LiHMDS.

4, 28%), *tert*-butyl carbamate protected azetidines (entry 5, 39%), and most notably, a [3.1.0]azabicyclic cyclopropane ester, affording **2f** as a single diastereomer (entry 6, 44%). The chloro substituent also remains intact following substitution of 6-chloropicolinonitrile with ethyl *N*-benzylpyrrolidine-3-carboxylate (entry 7, 54%).[18] The isoquinoline 1-carbonitrile system is receptive to nucleophilic attack from methyl isobutyrate (entry 8, 55%), α-methyl-γ-butyrolactone (entry 9, 94%), and a *tert*-butyl carboxylate derived from norbornene, affording bicycle **2j** as a single diastereomer (entry 10, 40%). We were additionally able to apply our method to pyrimidine-4-carbonitrile (entry 11, 62%), implying the possibility of extending cyano-S_NAr chemistry to diazines and other heteroaromatic scaffolds.[19]

The synthetic utility of aromatic iodides and bromides for molecular diversification is well recognized (transition-metal-catalyzed cross couplings, lithium−halogen exchange, etc.). Therefore, the ability to preserve halides during our cyano-selective S_NAr reaction has great value. Recently, there has been a surge in research toward highly active metal catalysts that operate on less reactive arene functions such as chlorides. We highlight some of these types of Pd(0)-catalyzed cross-couplings in Scheme 1. Using the conditions of Dreher and Molander, compound **1i** undergoes smooth *B*-alkyl Suzuki coupling with potassium cyclopropyltrifluoroborate to provide **3a** in 94% yield.[20] Biaryl carbon−carbon bond formation is also achieved with 2-aminopyrimidine-5-boronic acid pinacol ester under the conditions of Guram (**3b**, 56%).[21] In terms of carbon−nitrogen bond formation, 2-aminopyridine participates in a Buchwald−Hartwig reaction under the conditions of Yin to afford bis-2-pyridylamine **3c** in 93% yield.[22] Finally, the recently reported conditions of Beller, which did not comment on the use of secondary alcohols, were successfully employed in engaging 2-propanol to secure a carbon−oxygen linkage (**3d**, 56%).[23,24]

As demonstrated here, azine carbonitriles undergo nucleophilic aromatic substitution with carbon-based enolates with net loss of the cyano functional group. Current limitations include the incompatibility of unsubstituted and α-monosubstituted nitriles and esters such as acetonitrile, propionitrile, *tert*-butyl propionate, and diethyl malonate. Under the current conditions, α,α-disubstituted amides and phosphonates also did not afford S_NAr product.[25] Further work may seek to address these issues as well as expanding the range of nucleophilic acceptors to other unsaturated heterocyclic cyanides.

EXPERIMENTAL SECTION

General Procedure for S_NAr Reactions A (Table 1). WARNING: We did not discount the possibility that toxic hydrogen cyanide gas may be formed either under the reaction conditions or upon workup. As this could lead to a potentially fatal outcome, we advise that extreme caution be used, especially if the reaction is conducted on larger scale.

The azine (1 equiv) and, if solid, nitrile (1 equiv) were weighed into a vial and purged with nitrogen gas. Anhydrous THF (5 mL) was added, and the mixture was cooled to −78 °C (dry ice, acetone) with stirring. If the nitrile was a liquid, it was added at this point. Lithium bis(trimethylsilyl)amide (1.1 equiv, 1.0 M in THF [untitrated]) was added before removal of the cooling bath and the reaction mixture

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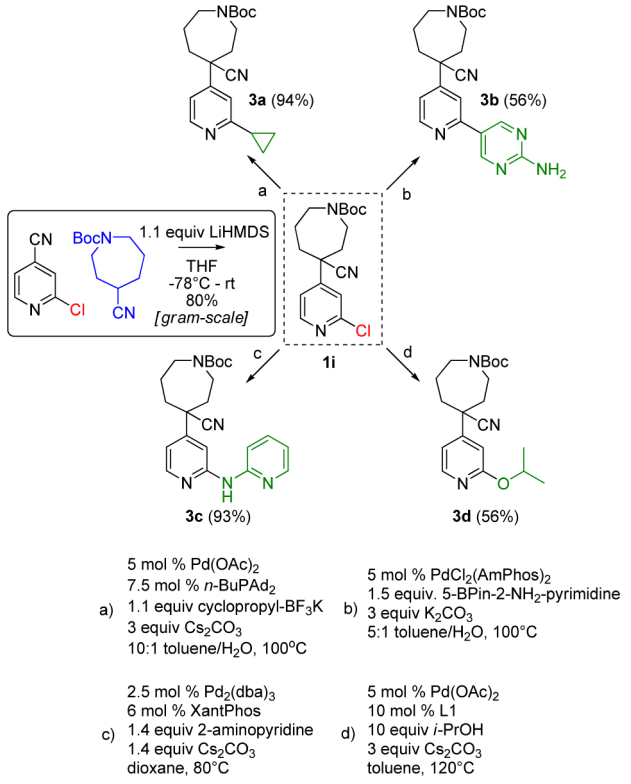
Scheme 1. Pd(0)-Catalyzed C−C, C−N, and C−O Functionalization of a Chloroazine



allowed to warm to rt. After completion as determined by TLC or UPLC analysis, the mixture was quenched with satd aq NH_4Cl and diluted with CH_2Cl_2, and the layers were partitioned. The aqueous layer was extracted with CH_2Cl_2 (2×), and the organic phases were combined, dried ($MgSO_4$), and concentrated to dryness. The resulting residue was purified by flash chromatography using the stated eluent system.

*1-(Pyridin-4-yl)cyclohexanecarbonitrile (**1a**).* Procedure A: cyclohexanecarbonitrile (109 mg, 1.00 mmol) and isonicotinonitrile (104 mg, 1.00 mmol) were reacted with LiHMDS (1.4 mL, 1.4 equiv) for 1.5 h. Flash chromatography (CH_2Cl_2/MeOH 100:0−95:5) afforded **1a** as a white solid (132 mg, 71%); R_f = 0.29 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65−8.61 (m, 2H), 7.45−7.39 (m, 2H), 2.17−2.10 (m, 2H), 1.92−1.72 (m, 7H), 1.36−1.24 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 150.1, 121.4, 120.7, 44.3, 36.7, 24.8, 23.3; HRMS m/z calcd for $C_{12}H_{14}N_2$ $[M + H]^+$ 187.1230, found 187.1218.

*tert-Butyl 3-Cyano-3-(pyridin-4-yl)azetidine-1-carboxylate (**1b**).* Procedure A: *tert*-Butyl 3-cyanoazetidine-1-carboxylate (182 mg, 1.00 mmol) and isonicotinonitrile (104 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 1.5 h. Flash chromatography (CH_2Cl_2/MeOH 100:0−95:5) afforded **1b** as a white solid (203 mg, 78%): R_f = 0.24 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75−8.71 (m, 2H), 7.55−7.50 (m, 2H), 4.65 (d, J = 8.8 Hz, 2H), 4.21 (d, J = 8.8 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 151.0, 145.4, 120.2, 119.3, 81.5, 60.8 (br), 33.9, 28.3; HRMS m/z calcd for $C_{14}H_{17}N_3O_2$ $[M + H]^+$ 260.1394, found 260.1399.

*2-(3,5-Dichloropyridin-4-yl)-2-methylpropanenitrile (**1c**).* Procedure A: isobutyronitrile (69 mg, 1.00 mmol) and 3,5-dichloroisonicotinonitrile (173 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 1.5 h. Flash chromatography (heptanes/EtOAc 100:0−80:20) afforded **1c** as a white solid (101 mg, 47%): R_f = 0.38 (Heptanes/EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 2H), 2.08 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 141.6, 131.3, 122.6, 38.3, 28.4; HRMS m/z calcd for $C_9H_8N_2Cl_2$ $[M + H]^+$ 215.0137, found 215.0165.

*4-(Pyridin-4-yl)tetrahydro-2H-pyran-4-carbonitrile (**1d**).* Procedure A: Tetrahydro-2*H*-pyran-4-carbonitrile (333 mg, 3.00 mmol) and isonicotinonitrile (312 mg, 3.00 mmol) were reacted with LiHMDS (3.3 mL) for 2.5 h. After workup, the compound was pure, affording **1d** as a off-white solid (533 mg, 94%): R_f = 0.29 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70−8.66 (m, 2H), 7.45−7.40 (m, 2H), 4.15−4.08 (m, 2H), 3.94−3.87 (m, 2H), 2.18−2.09 (m, 2H), 2.06−2.00 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 148.4, 120.6, 120.5, 64.7, 41.9, 36.0; HRMS m/z calcd for $C_{11}H_{12}N_2O$ $[M + H]^+$ 189.1022, found 189.1023.

*2-(3-Bromopyridin-4-yl)-2-methylbutanenitrile (**1e**).* Procedure A: 2-Methylbutanenitrile (83 mg, 1.00 mmol) and 3-bromoisonicotinonitrile (183 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 3 h. Flash chromatography (heptanes/EtOAc 100:0−80:20) afforded **1e** as a clear oil (169 mg, 71%): R_f = 0.23(heptanes/EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.56 (d, J = 5.5 Hz, 1H), 7.53 (d, J = 5.5 Hz, 1H), 2.57−2.43 (m, 1H), 2.14−2.03 (m, 1H), 1.90 (s, 3H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 149.0, 145.6, 123.7, 121.5, 119.6, 44.2, 30.9, 24.1, 9.8; HRMS m/z calcd for $C_{10}H_{11}N_2Br$ $[M + H]^+$ 239.0178, found 239.0173.

*tert-Butyl 3-cyano-3-(3-iodopyridin-4-yl)pyrrolidine-1-carboxylate (**1f**).* Procedure A: *tert*-Butyl 3-cyanopyrrolidine-1-carboxylate (196 mg, 1.00 mmol) and 3-iodoisonicotinonitrile (230 mg, 1.00 mmol) were reacted with LiHMDS (1.4 mL, 1.4 equiv) for 1.5 h. Flash chromatography (CH_2Cl_2/MeOH 100:0−95:5) afforded **1f** as a brown solid (132 mg, 75%): R_f = 0.28 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.59 (d, J = 5.2 Hz, 1H), 7.25 (d, J = 5.2 Hz, 1H), 4.56−4.42 (m, 1H), 3.85 (m, 1H), 3.77−3.51 (m, 2H), 2.89−2.82 (m, 1H), 2.70−2.61 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, 335 K) δ 160.8, 153.8, 149.7, 145.5, 122.5, 118.8, 96.0, 80.8, 54.3, 43.9, 36.2, 35.6, 28.5; HRMS m/z calcd for $C_{15}H_{18}N_3O_2I$ $[M + H]^+$ 400.0516, found 400.0497.

*1-Benzhydryl-3-(3-chloropyridin-4-yl)azetidine-3-carbonitrile (**1g**).* Procedure A: 1-Benzhydrylazetidine-3-carbonitrile (248 mg, 1.00 mmol) and 3-chloroisonicotinonitrile (139 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 2.5 h. Flash chromatography (heptanes/EtOAc 100:0−60:40) afforded **1g** as a white solid (296 mg, 82%): R_f = 0.26 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.52 (d, J = 5.0 Hz, 1H), 7.45−7.41 (m, 4H), 7.34−7.26 (m, 4H), 7.24−7.19 (m, 2H), 7.07 (d, J = 5.0 Hz, 1H), 4.33 (s, 1H), 4.07−4.02 (m, 2H), 3.44−3.39 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 148.6, 142.8, 140.5, 131.1, 128.9, 127.8, 127.3, 122.1, 120.2, 77.5, 61.9, 34.5; HRMS m/z calcd for $C_{22}H_{18}N_3Cl$ $[M + H]^+$ 360.1262, found 360.1270.

*1-(3-Iodopyridin-4-yl)cyclohex-3-enecarbonitrile (**1h**).* Procedure A: Cyclohex-3-enecarbonitrile (107 mg, 1.00 mmol) and 3-iodoisonicotinonitrile (230 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 4 h. Flash chromatography (heptanes/EtOAc 100:0−70:30) afforded **1h** as a white solid (187 mg, 60%): R_f = 0.25 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.55 (d, J = 5.4 Hz, 1H), 7.37 (d, J = 5.4 Hz, 1H), 5.89 (d, J = 10.0 Hz, 1H), 5.78 (d, J = 10.0 Hz, 1H), 3.11 (d, J = 17.3 Hz, 1H), 2.66 (d, J = 17.3 Hz, 1H), 2.56−2.45 (m, 2H), 2.40−2.27 (m, 1H), 2.21−2.05 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 149.6, 147.9, 127.5, 122.8, 122.3, 119.9, 95.3, 42.1, 34.0, 29.9, 22.8; HRMS m/z calcd for $C_{12}H_{11}N_2I$ $[M + H]^+$ 311.0040, found 311.0075.

*tert-Butyl 4-(2-Chloropyridin-4-yl)-4-cyanoazepane-1-carboxylate (**1i**).* Procedure A: *tert*-Butyl 4-cyanoazepane-1-carboxylate (1.00 g, 4.45 mmol) and 2-chloroisonicotinonitrile (618 mg, 4.45 mmol) were reacted with LiHMDS (4.9 mL) for 2 h. Flash chromatography (heptanes/EtOAc 100:0−70:30) afforded **1i** as a clear viscous oil (1.20 g, 80%); R_f = 0.23 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$, 335 K) δ 8.41 (d, J = 5.3 Hz, 1H), 7.42 (d, J = 1.7 Hz, 1H), 7.30 (dd, J = 5.3, 1.7 Hz, 1H), 4.15−3.77 (m, 1H), 3.77−3.61 (m, 1H), 3.51−3.20 (m, 2H), 2.20−1.93 (m, 6H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, 335 K) δ 155.4 (br), 153.6, 152.8, 150.6, 121.1, 120.1, 119.2, 80.3, 46.9, 45.3 (br), 42.9, 41.0 (br), 36.9 (br), 28.6, 24.5; HRMS m/z calcd for $C_{17}H_{22}N_3O_2Cl$ $[M + H]^+$ 336.1473, found 336.1461.

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*4-(Pyridin-2-yl)tetrahydro-2H-pyran-4-carbonitrile (**1j**).* Procedure A: Tetrahydro-2*H*-pyran-4-carbonitrile (111 mg, 1.00 mmol) and picolinonitrile (104 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 2 h. Flash chromatography (CH_2Cl_2/MeOH 100:0−95:5) afforded **1j** as a white solid (116 mg, 62%): R_f = 0.50 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65−8.61 (m, 1H), 7.80−7.74 (m, 1H), 7.61−7.57 (m, 1H), 7.32−7.25 (m, 1H), 4.12−4.06 (m, 2H), 3.94−3.85 (m, 2H), 2.41−2.33 (m, 2H), 2.08−2.02 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 149.7, 137.4, 123.2, 121.6, 120.4, 64.8, 44.1, 35.2; HRMS *m*/*z* calcd for $C_{11}H_{12}N_2O$ $[M + H]^+$ 189.1022, found 189.1012.

*1-(6-Chloropyridin-2-yl)cyclobutanecarbonitrile (**1k**).* Procedure A: cyclobutanecarbonitrile (81 mg, 1.00 mmol) and 6-chloropicolinonitrile (138 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 3 h. Flash chromatography (heptanes/EtOAc 100:0−80:20) afforded **1k** as a clear oil (86 mg, 45%): R_f = 0.47 (Heptanes/EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.66 (m, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 2.95−2.86 (m, 2H), 2.77−2.68 (m, 2H), 2.46−2.35 (m, 1H), 2.21−2.12 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 151.5, 139.6, 123.6, 123.3, 119.1, 41.7, 33.7, 16.9; HRMS *m*/*z* calcd for $C_{10}H_9N_2Cl$ $[M + H]^+$ 193.0527, found 193.0520.

*2-Methyl-2-(pyridin-2-yl)propanenitrile (**1l**).* Procedure A: Isobutyronitrile (69 mg, 1.00 mmol) and picolinonitrile (104 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 3 h. Flash chromatography (heptanes/EtOAc 100:0−70:30) afforded **1l** as a colorless liquid (57 mg, 39%): R_f = 0.47 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.2 Hz, 1H), 7.77−7.71 (m, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.26−7.23 (m, 1H), 1.77 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 149.5, 137.2, 124.3, 122.8, 119.8, 39.5, 27.8; HRMS *m*/*z* calcd for $C_9H_{10}N_2$ $[M + H]^+$ 147.0917, found 147.0931.

Note: This compound was somewhat volatile under high vacuum.

*4-(Isoquinolin-1-yl)tetrahydro-2H-pyran-4-carbonitrile (**1m**).* Procedure A: Tetrahydro-2*H*-pyran-4-carbonitrile (111 mg, 1.00 mmol) and isoquinoline-1-carbonitrile (111 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 1.5 h. After workup, the compound was pure, affording **1m** as a white solid (232 mg, 97%): R_f = 0.31 (heptanes/EtOAc, 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.5 Hz, 1H), 8.49 (d, *J* = 5.6 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.75−7.64 (m, 3H), 4.17−4.03 (m, 4H), 2.56−2.43 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.2, 141.1, 137.3, 130.0, 128.4, 127.6, 125.4, 124.7, 122.0, 121.8, 64.5, 42.0, 35.4; HRMS *m*/*z* calcd for $C_{15}H_{14}N_2O$ $[M + H]^+$ 239.1179, found 239.1200.

*1-(Isoquinolin-1-yl)cyclopropanecarbonitrile (**1n**).* Procedure A: Cyclopropanecarbonitrile (67 mg, 1.00 mmol) and isoquinoline-1-carbonitrile (154 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 3 h. Flash chromatography (CH_2Cl_2/MeOH 100:0−95:5) afforded **1n** as a yellow solid (73 mg, 37%): R_f = 0.24 (heptanes/EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62−8.57 (m, 1H), 8.42 (d, *J* = 5.7 Hz, 1H), 7.91−7.86 (m, 1H), 7.78−7.72 (m, 2H), 7.65 (d, *J* = 6.2 Hz, 1H), 1.89−1.85 (m, 2H), 1.80−1.76 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 141.6, 136.7, 130.6, 128.2, 127.6, 127.3, 125.0, 122.7, 121.8, 16.0, 14.4; HRMS *m*/*z* calcd for $C_{13}H_{10}N_2$ $[M + H]^+$ 195.0917, found 195.0948.

General Procedure for S_NAr Reactions B (Table 2). The azine (1 equiv) and, if solid, ester (1 equiv) were weighed into a vial and purged with nitrogen gas. Anhydrous THF (2.5 mL) was added and the mixture was cooled to −78 °C (dry ice, acetone) with stirring. If the ester was a liquid, it was added at this point. Potassium bis(trimethylsilyl)amide (1.1 equiv, 0.5 M in toluene [untitrated]) was added before removal of the cooling bath and the reaction mixture allowed to warm to rt. After completion as determined by TLC or UPLC analysis, the mixture was quenched with satd aq NH_4Cl and diluted with CH_2Cl_2, and the layers were partitioned. The aqueous layer was extracted with CH_2Cl_2 (2×), and the organic phases were combined, dried ($MgSO_4$), and concentrated to dryness. The resulting residue was purified by flash chromatography using the stated eluent system.

*Ethyl 1-(Pyridin-4-yl)cyclobutanecarboxylate (**2a**).* Procedure B: Ethyl cyclobutanecarboxylate (128 mg, 1.00 mmol) and isonicotinonitrile (104 mg, 1.00 mmol) were reacted with KHMDS (2.2 mL) for 1 h. Flash chromatography (CH_2Cl_2/MeOH, 100:0−95:5) afforded **2a** as an orange oil (125 mg, 60%): R_f = 0.30 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57−8.54 (m, 2H), 7.24−7.20 (m, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 2.88−2.81 (m, 2H), 2.52−2.44 (m, 2H), 2.14−2.04 (m, 1H), 1.95−1.83 (m, 1H), 1.18 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 152.5, 149.8, 121.5, 61.3, 51.9, 32.0, 16.7, 14.0; HRMS *m*/*z* calcd for $C_{12}H_{15}NO_2$ $[M + H]^+$ 206.1176, found 206.1176.

Note: This compound was somewhat volatile under high vacuum.

*3-(2,6-Dichloropyridin-4-yl)-3-methyldihydrofuran-2(3H)-one (**2b**).* Procedure B: 3-Methyldihydrofuran-2(3*H*)-one (128 mg, 1.00 mmol) and 2,6-dichloroisonicotinonitrile (173 mg, 1.00 mmol) were reacted with KHMDS (2.2 mL) for 2.5 h. Flash chromatography (heptanes/EtOAc 100:0−70:30) afforded **2b** as a white solid (88 mg, 36%); R_f = 0.28 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, CDCl3) δ 7.39 (s, 2H) 4.44−4.39 (m, 1H), 4.33−4.28 (m, 1H), 2.70−2.64 (m, 1H), 2.52−2.45 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 156.1, 151.3, 120.7, 65.0, 46.8, 36.6, 25.0; HRMS *m*/*z* calcd for $C_{10}H_9NO_2Cl_2$ $[M + Na]^+$ 267.9903, found 267.9923.

*Methyl 1-(Pyridin-4-yl)cyclopent-3-enecarboxylate (**2c**).* Procedure B: Methyl cyclopent-3-enecarboxylate (126 mg, 1.00 mmol) and isonicotinonitrile (104 mg, 1.00 mmol) were reacted with KHMDS (2.2 mL) for 2 h. Flash chromatography (CH_2Cl_2/MeOH 100:0−90:10) afforded **2c** as an orange solid (115 mg, 57%): R_f = 0.51 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60−8.46 (m, 2H), 7.25−7.16 (m, 2H), 5.80−5.70 (m, 2H), 3.67 (s, 3H), 3.42−3.31 (d, *J* = 17.8 Hz, 2H), 2.74 (d, *J* = 17.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 152.6, 149.9, 128.8, 121.6, 57.7, 52.8, 42.6; HRMS *m*/*z* calcd for $C_{12}H_{13}NO_2$ $[M + H]^+$ 204.1019, found 204.1045.

*1-Benzyl 4-tert-Butyl 4-(3-Chloropyridin-4-yl)piperidine-1,4-dicarboxylate (**2d**).* Procedure B: 1-Benzyl 4-*tert*-butyl piperidine-1,4-dicarboxylate (319 mg, 1.00 mmol) and 3-chloroisonicotinonitrile (139 mg, 1.00 mmol) were reacted with KHMDS (2.2 mL) for 3 h. Flash chromatography (heptanes/EtOAc 100:0−60:40) afforded **2d** as a colorless oil (121 mg, 28%): R_f = 0.22 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.48 (d, *J* = 5.1 Hz, 1H), 7.37−7.30 (m, 5H), 7.26−7.24 (m, 1H), 5.14 (s, 2H), 4.04−3.80 (m, 2H), 3.62−3.36 (m, 2H), 2.54−2.40 (m, 2H), 2.08−1.78 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 155.3, 150.8, 149.5, 148.3, 136.7, 131.4, 128.5, 128.1, 128.0, 121.8, 82.1, 67.2, 49.2, 40.3 (br), 32.0, 27.8; HRMS *m*/*z* calcd for $C_{23}H_{27}N_2O_4Cl$ $[M + H]^+$ 431.1732, found 431.1709.

*1-tert-Butyl 3-Methyl 3-(3-Bromopyridin-4-yl)azetidine-1,3-dicarboxylate (**2e**).* Procedure B: 1-*tert*-Butyl 3-methyl azetidine-1,3-dicarboxylate (215 mg, 1.00 mmol) and 3-bromoisonicotinonitrile (183 mg, 1.00 mmol) were reacted with KHMDS (2.2 mL) for 11 h. Flash chromatography (heptanes/EtOAc 100:0−50:50) afforded **2e** as a clear oil (144 mg, 39%): R_f = 0.31 (Heptanes/EtOAc 50:50); ^{1}H NMR (500 MHz, $CDCl_3$, 335 K) δ 8.70 (d, *J* = 1.9 Hz, 1H), 8.57 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.24 (d, *J* = 4.9 Hz, 1H), 4.57 (d, *J* = 8.8 Hz, 2H), 4.30 (d, *J* = 8.8 Hz, 2H), 3.73 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, 335 K) δ 171.4, 155.9, 152.8, 148.7, 147.3, 123.3, 121.7, 80.4, 57.0 (br), 53.3, 48.3, 28.4; HRMS *m*/*z* calcd for $C_{15}H_{19}N_2O_4Br$ $[M + H]^+$ 371.0601, found 371.0586.

(1R,5S*,6S*)-3-tert-Butyl 6-ethyl 6-(2,6-Dichloropyridin-4-yl)-3-azabicyclo[3.1.0]hexane-3,6-dicarboxylate (**2f**).* Procedure B: (1*R**,5*S**,6*S**)-3-*tert*-Butyl 6-ethyl 3-azabicyclo[3.1.0]hexane-3,6-dicarboxylate (158 mg, 0.619 mmol) and 2,6-dichloroisonicotinonitrile (132 mg, 0.742 mmol) were reacted with LiHMDS (1.4 mL, 1.4 equiv) for 17 h. Flash chromatography (heptanes/EtOAc, 100:0−70:30) afforded **2f** as a yellow solid (110 mg, 44%): R_f = 0.32 (Heptanes/EtOAc, 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.03 (d, *J* = 11.3 Hz, 1H), 3.94 (d, *J* = 11.3 Hz, 1H), 3.50−3.40 (m, 2H), 2.14−2.03 (m, 2H), 1.42 (s, 9H), 1.33−1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 153.9, 153.3, 150.9, 121.2, 80.1, 62.0, 46.0 (br), 35.3, 30.3 (br), 28.3, 14.1; HRMS *m*/*z* calcd for $C_{18}H_{22}N_2O_4Cl_2$ $[M + H]^+$ 401.1029, found 401.1012.

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*Ethyl 1-Benzyl-3-(6-Chloropyridin-2-yl)pyrrolidine-3-carboxylate (**2g**).* Procedure B: Ethyl 1-benzylpyrrolidine-3-carboxylate (233 mg, 1.00 mmol) and 6-chloropicolinonitrile (139 mg, 1.00 mmol) were reacted with KHMDS (2.2 mL) for 19.5 h. Flash chromatography (heptanes/EtOAc 100:0−70:30) afforded **2g** as a yellow oil (186 mg, 54%): R_f = 0.32 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.8, 7.8 Hz, 1H), 7.36−7.29 (m, 4H), 7.26−7.22 (m, 2H), 7.17 (d, J = 7.4 Hz, 1H), 4.23−4.07 (m, 2H), 3.72−3.63 (m, 2H), 3.33 (d, J = 9.7 Hz, 1H), 3.06 (d, J = 9.7 Hz, 1H), 2.91−2.76 (m, 2H), 2.76−2.68 (m, 1H), 2.43−2.34 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.9, 162.8, 150.2, 139.0, 139.0, 128.5, 128.2, 126.9, 122.4, 119.8, 62.0, 61.4, 60.1, 59.7, 53.5, 34.6, 14.0; HRMS m/z calcd for $C_{19}H_{21}N_2O_2Cl$ $[M + H]^+$ 345.1364, found 345.1345.

*Methyl 2-(Isoquinolin-1-yl)-2-methylpropanoate (**2h**).* Procedure B: Methyl isobutyrate (102 mg, 1.00 mmol) and isoquinoline-1-carbonitrile (154 mg, 1.00 mmol) were reacted with KHMDS (2.2 mL) for 3 h. Flash chromatography (heptanes/EtOAc 100:0−70:30) afforded **2h** as a white solid (127 mg, 55%): R_f = 0.43 (heptanes/EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50−8.43 (m, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.84−7.77 (m, 1H), 7.64−7.57 (m, 1H), 7.56−7.49 (m, 2H), 3.58 (s, 3H), 1.80 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 161.5, 141.0, 136.8, 129.3, 128.0, 127.1, 126.2, 124.8, 120.5, 52.4, 49.7, 26.7; HRMS m/z calcd for $C_{14}H_{15}NO_2$ $[M + H]^+$ 230.1176, found 230.1211.

*3-(Isoquinolin-1-yl)-3-methyldihydrofuran-2(3H)-one (**2i**).* Procedure B: 3-Methyldihydrofuran-2(3*H*)-one (300 mg, 3.00 mmol) and isoquinoline-1-carbonitrile (463 mg, 3.00 mmol) were reacted with KHMDS (6.6 mL) for 2 h. Flash chromatography (heptanes/EtOAc 100:0−70:30) afforded **2i** as a white solid (641 mg, 94%): R_f = 0.23 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47−8.43 (m, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.70−7.65 (m, 1H), 7.64−7.58 (m, 2H), 4.46−4.40 (m, 1H), 4.29−4.23 (m, 1H), 3.23−3.15 (m, 1H), 2.54−2.47 (m, 1H), 1.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.1, 158.6, 140.9, 137.6, 129.7, 128.5, 127.2, 125.3, 125.2, 121.2, 65.7, 51.7, 38.0, 23.4; HRMS m/z calcd for $C_{14}H_{13}NO_2$ $[M + H]^+$ 228.1019, found 228.1004.

Racemic (1S,2S*,4S*)-tert-Butyl 2-(Isoquinolin-1-yl)-bicyclo[2.2.1]hept-5-ene-2-carboxylate (**2j**).* Procedure B: Racemic *tert*-butyl-5-norbornene-2-carboxylate (194 mg, 1.00 mmol) and isoquinoline-1-carbonitrile (154 mg, 1.00 mmol) were reacted with KHMDS (2.2 mL) for 3 h. Flash chromatography (heptanes/EtOAc 100:0−90:10) afforded **2j** as a clear oil (129 mg, 40%): R_f = 0.41 (heptanes/EtOAc 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 5.7 Hz, 1H), 8.20 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.64−7.59 (m, 1H), 7.54−7.48 (m, 2H), 6.52−6.45 (m, 1H), 6.14−6.07 (m, 1H), 4.23−4.17 (m, 1H), 3.03−2.90 (m, 1H), 2.74−2.64 (m, 1H), 2.02−1.91 (m, 1H), 1.72−1.62 (m, 2H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 162.6, 141.2, 140.9, 136.7, 133.1, 129.3, 127.5, 127.4, 126.7, 126.3, 119.7, 80.4, 60.8, 50.9, 49.5, 43.5, 38.9, 27.7; HRMS m/z calcd for $C_{21}H_{23}NO_2$ $[M + H]^+$ 322.1802, found 322.1790.

*3-Methyl-3-(pyrimidin-4-yl)dihydrofuran-2(3H)-one (**2k**).* Procedure B: 3-Methyldihydrofuran-2(3*H*)-one (100 mg, 1.00 mmol) and pyrimidine-4-carbonitrile (105 mg, 1.00 mmol) were reacted with LiHMDS (1.1 mL) for 3.5 h. Flash chromatography (CH_2Cl_2/MeOH 100:0−95:5) afforded **2k** as an off-white solid (111 mg, 62%): R_f = 0.26 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (d, J = 1.5 Hz, 1H), 8.75 (d, J = 5.3 Hz, 1H), 7.60 (dd, J = 5.3, 1.5 Hz, 1H), 4.47−4.31 (m, 2H), 3.15−3.04 (m, 1H), 2.43−2.30 (m, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 168.4, 158.6, 157.7, 118.4, 65.9, 49.5, 35.48, 23.5; HRMS m/z calcd for $C_9H_{10}N_2O_2$ $[M + H]^+$ 179.0815, found 179.0805.

*tert-Butyl 4-Cyano-4-(2-cyclopropylpyridin-4-yl)azepane-1-carboxylate (**3a**).* Into a vial were weighed *tert*-butyl 4-(2-chloropyridin-4-yl)-4-cyanoazepane-1-carboxylate (111 mg, 0.333 mmol), palladium(II) acetate (3.7 mg, 5 mol %), *n*-butyldi-1-adamantylphosphine (8.9 mg, 7.5 mol %), potassium cyclopropyltrifluoroborate (54.1 mg, 0.366 mmol), and cesium carbonate (325 mg, 1.00 mmol). The vial contents were purged with nitrogen gas before addition of distilled water (0.15 mL) and toluene (1.5 mL), and the vial was sealed. The reaction mixture was stirred at 100 °C for 17 h. After the mixture was concentrated to dryness, purification via flash chromatography (heptanes/EtOAc 100:0−70:30) afforded **3a** as a colorless oil (107 mg, 94%): R_f = 0.31 (heptanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47−8.42 (m, 1H), 7.27−7.25 (m, 1H), 7.11−7.06 (m, 1H), 4.12−3.78 (m, 1H), 3.77−3.60 (m, 1H), 3.47−3.23 (m, 2H), 2.24−1.92 (m, 7H), 1.50 (br s, 9H), 1.13−0.98 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1 (br), 155.4 (br), 150.1, 150.0 (br), 120.8, 118.2, 117.0 (br), 80.1 (br), 46.9 (br), 45.3 (br), 42.6 (br), 41.0 (br), 37.0 (br), 28.5, 24.2 (br), 17.3 (br), 10.3 (br); HRMS m/z calcd for $C_{20}H_{27}N_3O_2$ $[M + H]^+$ 342.2176, found 342.2165.

*tert-Butyl 4-(2-(2-Aminopyrimidin-5-yl)pyridin-4-yl)-4-cyanoazepane-1-carboxylate (**3b**).* Into a vial were weighed *tert*-butyl 4-(2-chloropyridin-4-yl)-4-cyanoazepane-1-carboxylate (113 mg, 0.337 mmol), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium(II) (11.9 mg, 5 mol %), 2-aminopyrimidine-5-boronic acid pinacol ester (112 mg, 0.506 mmol), and potassium carbonate (140 mg, 1.01 mmol). The vial contents were purged with nitrogen gas before addition of distilled water (0.2 mL) and toluene (1.1 mL), and the vial was sealed. The reaction mixture was stirred at 100 °C for 19 h. After the mixture was concentrated to dryness, purification via flash chromatography (CH_2Cl_2/MeOH 100:0−90:10) afforded **3b** as a white solid (73.9 mg, 56%): R_f = 0.27 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (500 MHz, DMSO-d_6, 335 K) δ 8.96 (s, 2H), 8.64 (d, J = 5.2 Hz, 1H), 7.92 (d, J = 1.7 Hz, 1H), 7.42 (dd, J = 5.2, 1.7 Hz, 1H), 6.91 (br s, 2H), 3.80−3.31 (m, 4H), 2.41−1.87 (m, 6H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6, 335 K) δ 163.5, 156.4, 154.2, 153.7, 151.3, 150.1, 120.6, 120.6 (br), 118.3, 114.9, 78.6, 44.5, 42.1 (br), ~39.6 (under DMSO), 37.0 (br), 38.2, 37.0 (br), 28.0, 24.8; HRMS m/z calcd for $C_{21}H_{26}N_6O_2$ $[M + H]^+$ 395.2190, found 395.2181.

*tert-Butyl 4-Cyano-4-(2-(pyridin-2-ylamino)pyridin-4-yl)azepane-1-carboxylate (**3c**).* Into a vial were weighed *tert*-butyl 4-(2-chloropyridin-4-yl)-4-cyanoazepane-1-carboxylate (111 mg, 0.330 mmol), 2-aminopyridine (43.5 mg, 0.462 mmol), tris(dibenzylideneacetone)dipalladium(0) (7.6 mg, 2.5 mol %), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (11.5 mg, 6 mol %), and cesium carbonate (150 mg, 0.462 mmol). The vial was purged with nitrogen gas before anhydrous 1,4-dioxane (1.32 mL, 0.25 M) was injected and the vessel sealed. The reaction mixture was stirred at 80 °C for 17 h before being cooled to rt, filtered through Celite, and rinsed with CH_2Cl_2. After concentration, flash column chromatography (CH_2Cl_2/MeOH, 100:0−95:5) afforded **3c** as a colorless liquid (120 mg, 93%): R_f = 0.28 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (500 MHz, $CDCl_3$, 335 K) δ 8.30−8.21 (m, 2H), 7.90 (br s, 1H), 7.88−7.77 (m, 1H), 7.61−7.56 (m, 1H), 7.51−7.38 (m, 1H), 6.91 (m, 1H), 6.88−6.83 (m, 1H), 4.13−3.80 (m, 1H), 3.79−3.59 (m, 1H), 3.45 (ddd, J = 12.0, 4.3 Hz, 4.3 Hz, 1H), 3.42−3.25 (m, 1H), 2.22−1.97 (m, 6H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz, 335 K) δ 155.4 (br), 155.0, 154.0, 152.3, 148.7, 147.9, 137.8, 120.9, 116.8, 113.1, 112.0, 108.2, 80.0, 47.2 (br), 45.5 (br), 43.0 (br), 40.8 (br), 37.1 (br), 28.6, 24.4 (br); HRMS m/z calcd for $C_{22}H_{27}N_5O_2$ $[M + H]^+$ 394.2237, found 394.2214.

*tert-Butyl 4-Cyano-4-(2-isopropoxypyridin-4-yl)azepane-1-carboxylate (**3d**).* Into a vial were weighed *tert*-butyl 4-(2-chloropyridin-4-yl)-4-cyanoazepane-1-carboxylate (108 mg, 0.323 mmol), palladium(II) acetate (3.6 mg, 5 mol %), 5-(di(adamantan-1-yl)phosphino)-1′,3′,5′-triphenyl-1′*H*-1,4′-bipyrazole (20 mg, 10 mol %), and cesium carbonate (315 mg, 0.969 mmol). The vial was purged with nitrogen gas before injection of anhydrous toluene (1.6 mL) and anhydrous 2-propanol (250 μL, 3.23 mmol), and the vessel was sealed. The reaction mixture was stirred at 120 °C for 19 h before being cooled to rt, filtered through Celite, and rinsed with CH_2Cl_2. After concentration, flash column chromatography (heptanes/EtOAc 100:0−75:25) afforded **3d** as a colorless liquid (65 mg, 56%): R_f = 0.29 (heptanes/EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 5.1 Hz, 1H), 6.88 (d, J = 5.1 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 5.31 (hept, J = 6.2 Hz, 1H), 4.13−3.76 (m, 1H), 3.76−3.57 (m, 1H), 3.49−3.16 (m, 2H), 2.16−1.92 (m, 6H), 1.49 (s, 9H), 1.34 (d, J = 6.2

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Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz, 335 K) δ 164.4, 155.4, 153.0, 147.9, 120.8, 113.2, 108.3, 80.0, 68.6, 46.8, 45.4, 42.9, 40.9, 37.1, 28.6, 24.4, 22.1; HRMS m/z calcd for $C_{20}H_{29}N_3O_3$ $[M + H]^+$ 360.2282, found 360.2274.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **1a−n**, **2a−k**, **3a−d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Professor Keith Fagnou (1971−2009).

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(13) Reactions with quinoline-2-carbonitrile did not afford full conversion under these reaction conditions, and isolation was not attempted.

(14) Difficulties associated with S_NAr reactions using cyclopropanecarbonitrile have already been discussed by Klapars and Waldman. See ref 3a.

(15) Mechanistically, the title reaction may actually proceed via nucleophilic attack at the carbonitrile carbon first, followed by a 1,2-alkyl migration onto the arene with accompanying extrusion of the cyanide anion. We thank Steven T. Staben for pointing this out. It is important to note, however, that we have not made attempts to confirm that unmodified cyanide anion is produced during the course of the reaction. Additionally, no rate studies have been conducted in order to shed light on the mechanistic details. See: Bunnett, J. F.; Garbisch, E. W., Jr.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385−391.

(16) Direct attack on the carbonitrile carbon is the sole pathway observed for the reaction of ethylmagnesium bromide with 1-isoquinoline carbonitrile, as determined by HPLC−MS analysis of the reaction mixture.

(17) No improvements are seen in the presence of lithium chloride, copper(II) trifluoromethanesulfonate, scandium(III) trifluoromethanesulfonate, boron trifluoride etherate, or tetramethylethylenediamine.

(18) Interestingly, reaction of ethyl *N*-benzylpyrrolidine-3-carboxylate with 3,5-dichloroisonicotinonitrile leads exclusively to chloro displacement (82%).

(19) We were not able to successfully employ 2-cyanopyrazine or 3-cyanopyridazine.

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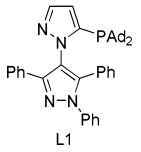

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(24) In the control experiment, no reaction occurs in the absence of palladium(II) acetate, ruling out the possibility of an S_NAr pathway.
(25) Neither *N,N*-dimethylisobutyramide or cyclohexyldimethylphosphonate provide the desired product with isonicotinonitrile using LiHMDS, KHMDS, or LDA, as determined by HPLC−MS analysis of the reaction mixture.