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One-Pot Synthesis of 3-Azido- and 3-Aminopiperidines by Intramolecular Cyclization of Unsaturated Amines

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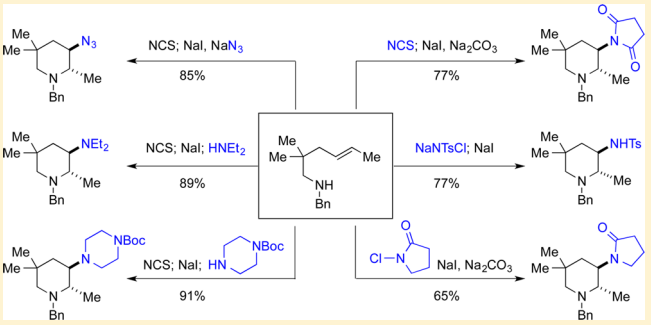
Supporting Information

ABSTRACT: A highly efficient one-pot synthesis of 3-azidopiperidines has been achieved by an intramolecular cyclization of unsaturated amines that allows for the nucleophilic installation of an azide moiety. This method unlocks the versatile employment of the azide functionality in the preparation and biological studies of piperidine-containing structures. This strategy has been expanded for the direct incorporation of a variety of nitrogen nucleophiles, and thus it provides a rapid and modular synthesis of 3-amino and 3-amidopiperidines of important pharmaceutical and biological relevance. Particularly noteworthy is that the regioselectivity of this transformation enables the formation of the anti-Markovnikov-type adduct, complementing Markovnikov-based olefin amino functionalization methods.



INTRODUCTION

Piperidine-based structures have attracted continuous interest due to their widespread existence in natural products[1] (e.g., slaframine and prosophylline), medicine (e.g., pethidine), and molecules of important biological activities[2] (e.g., IdeS inhibitor;[2a] σ_1 receptor ligand;[2e] and CP-99,994,[2b] an NK1 receptor antagonist) (Figure 1). These compounds hold remarkable promise for the treatment of osteoporosis, rheumatoid arthritis, depressive and mnemonic disorders, anxiety, and Alzheimer's disease, demonstrating the importance of piperidines in biology and medicine. Therefore, rapid access of piperidine skeletons from readily available acyclic alkenes is extremely valuable.[3−5] Particularly useful are alkene amino-functionalizations that enable the incorporation of a chemical reporter (e.g., fluorine-18 for PET imaging) onto the resulting piperidine ring; such functionalities will provide a chemical approach toward understanding the mode of action of bioactive piperidine-containing molecules as well as their clinical potential.[6]

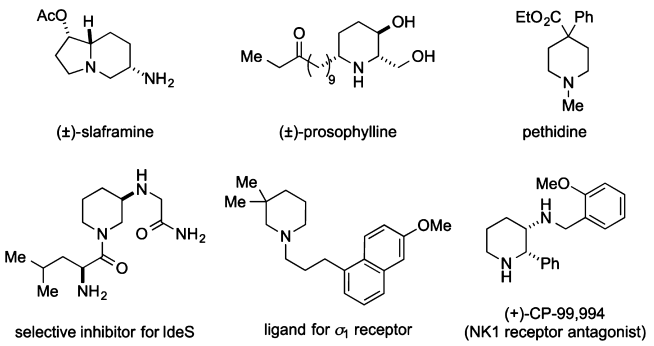


Figure 1. Examples of piperidine-containing natural products, medicine, and biologically active compounds.

Our group has been interested in developing new chemical methods that allow for the installation of such a chemical reporter onto the piperidine ring. Toward this, we recently developed a one-pot synthesis of 3-fluoropiperidines (Scheme 1, Nu = F).[7] That reaction involves an initial amino cyclization step of an *N*-iodoamine intermediate **I** formed *in situ*,[8] the subsequent rearrangement of pyrrolidine **II** to the aziridinium intermediate[9] **III**, followed by the nucleophilic ring-opening by a fluoride ion to give the final product. Herein we report our studies on extending this strategy for the incorporation of an azide functionality onto the piperidine ring (Scheme 1, Nu = N_3). Such a general approach to access an azidopiperidine ring will be highly valued as the azide functionality has been proven to be the most versatile bioorthogonal chemical reporter in chemical biology and one of the most useful building blocks in organic synthesis.[10−12] For example, the introduced azide will enable the covalent conjugation of an azidopiperidine molecule to facilitate the identification of its cellular targets.[10,11] Furthermore, the diverse reactivity of the azide moiety will allow for rapid structural functionalization to an extensive range of derivatives.[12] Although many methods have been developed to prepare piperidine-containing structures, a direct method for the incorporation of an azide onto the piperidine ring remains absent, impeding the biological exploration of these privileged compounds. In this contribution, we describe our development of a modular one-pot synthesis of 3-azidopiperidines starting

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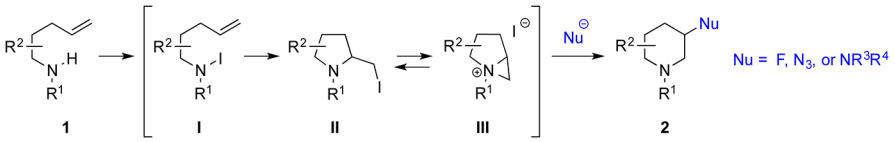
Scheme 1. Synthesis of 3-Functionalized Piperidines

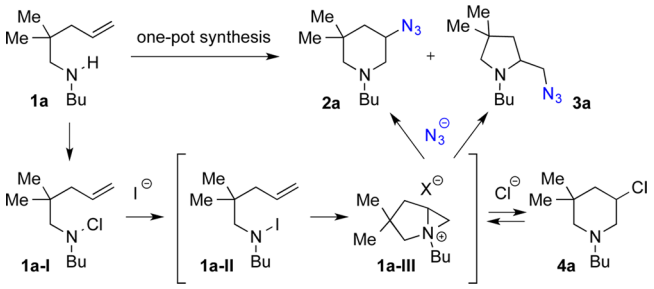


from unsaturated amines. Auxiliary transformations of the azido group on the piperidine ring demonstrate the great potential of this approach in the synthesis and biological studies of piperidine-based molecules. Additionally, this strategy has been extended as a general approach to incorporate a variety of nitrogen nucleophiles for the preparation of 3-amino-piperidines, which are found widely in natural products and biologically active compounds (Figure 1). *N*-Chloroamides, acting as both the halogenation source and the nucleophilic nitrogen source, offer an appealing dual role in this formal olefin diamination reaction. Importantly, this transformation provides the anti-Markovnikov-type adducts, uniquely complementing traditional Markovnikov-based intramolecular amination methods.[4,5]

RESULTS AND DISCUSSION

Our studies began with establishing effective conditions for the formation of 3-azidopiperidine **2a** from model substrate **1a** (Table 1). On the basis of our earlier work,[7] NaI was found to be effective as a catalyst to convert the *N*-chloramine precursor **1a-I** to 3-chloropiperidine **4a** in the absence of an external nucleophile. In the presence of NaN_3, the nucleophilic ring-opening with azide outcompeted the reversible reaction with chloride,[8] leading to the formation of the desired 3-azidopiperidine **2a** (entry 1). MeCN was found to be the most effective solvent in the initial screenings.[13] Next, we focused on developing a simple one-pot protocol that would directly transform amine precursors to 3-azidopiperidines. Toward this, *N*-chloramine **1a-I** was formed upon the treatment of **1a** with *N*-chlorosuccinimide (NCS); addition of NaI and NaN_3 to this solution led to the formation of **2a** in excellent yield, although a longer reaction time is required (entries 2−4). Even with only 1.2 equiv of NaN_3, **2a** was formed in 92% yield (entry 3). The control experiment suggests the essential role of NaI in promoting this transformation (entry 4). It should be noted that, in all conditions, the *exo*-ring-opened pyrrolidine **3a** was not detected. Thus, its regioselectivity profile for 6-*endo*-cyclization products[14] complements traditional Markovnikov-based intramolecular amination reactions of similar olefin substrates.[4,5,15]

Table 1. Condition Optimization for the Synthesis of 3-Azidopiperidine 2a[a]



entry	alkene	NCS (equiv)	NaI (mol %)	NaN_3 (equiv)	**2a** (%)[b]
1	**1a-I**	–	5	2.0	69
2	**1a**	1.0	5	2.0	93
3	**1a**	**1.0**	**5**	**1.2**	**92**
4	**1a**	1.0	–	1.2	--[c]

[a]Conditions. Entry 1: **1a-I** (1.0 equiv, 0.1 mmol, 0.18 M), (0.05 equiv), MeCN, 50 °C, 8 h. Entries 2−4: **1a** (1.0 equiv, 0.09 mmol, 0.1 M), MeCN, 24 °C, 2 h; then 60 °C, 48 h. [b]NMR yields. No **3a** detected. Determined by ^{1}H NMR spectroscopy using either DMF or CH_2Br_2 as an internal standard. [c]Neither **2a** nor **4a** formed; only **1a-I** was observed.

With effective conditions identified, we examined the generality and efficiency of this one-pot synthesis of 3-azidopiperidines on a range of substrates with different substitutions on the nitrogen atom, olefin moiety, and alkyl backbone (Table 2). For **1a−1c**, pentenyl substrates bearing different substitutions on the nitrogen, all formed 3-azidopiperidine products with excellent regioselectivity and yields (entries 1−3). Disubstituted olefins **1d−1h** also efficiently generated the 3-azidopiperidine products with high regioselectivity and diastereoselectivity (entries 4−8). In particular, the *Z*-alkene gave exclusively the cyclic *cis*-amine and the *E*-alkene provided only the *trans* product. The low yield in the case of the trisubstituted alkene **1i** suggested that steric hindrance affects the efficiency of this transformation (entry 9). Additionally, we examined the effect of the substitution on the backbone, including both acyclic and cyclic substrates (entries 10−16). Substrate **1j**, which lacks substitution on the backbone, smoothly afforded β-azido heterocycles with little regioselectivity. For substrates **1k−1m**, with a methyl substitution at the α-, β-, and γ-positions relative to the nitrogen atom respectively, all provided the desired 3-azidopiperidine products (entries 11−13). The observed stereochemical outcome suggests the regioselectivity of this transformation is influenced by substitutions on the backbone and that substitution at the β-position favors the *endo* nucleophilic ring-opening.[16] For cyclic substrates, **1n** with a cyclopropane at the β-position provided the spiro products with modest *endo* selectivity (entry 14). Comparatively, cyclic substrates **1o−1p** afforded 3-azidopiperidine bicyclic products in good yields (entries 15−16). Finally, the reaction of hexenyl substrate **1q** slightly favored the formation of *endo* product **2q**, providing β-azidoazapane under the standard conditions (entry 17).

To further explore the applications of this method, we examined the transformation of 3-azidopiperidine **2h** into differently functionalized piperidine derivatives (Scheme 2). First, **2h** was exposed to reduction conditions to transform the azido group to an amino functionality.[17] The primary amine **5** was formed in 91% yield when **2h** was treated with PPh_3 in the presence of water, while the secondary amine **6** was obtained in 54% yield when **2h** was treated with PMe_3 followed by the addition of aldehyde and $NaBH_4$. Rather, free diamine **7** was obtained in 87% yield upon the hydrogenolysis of **2h** with Pd/C, resulting from the simultaneous reduction of the azide group and removal of the benzyl group in a single step. 1,2,3-Triazole **8** was formed in 99% yield by a facile 1,3-dipolar cycloaddition

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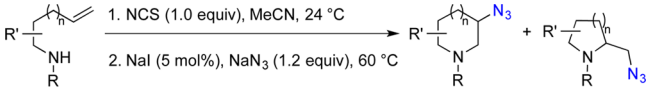
Table 2. One-Pot Synthesis of 3-Azidopiperidines from Unsaturated Amines[a]



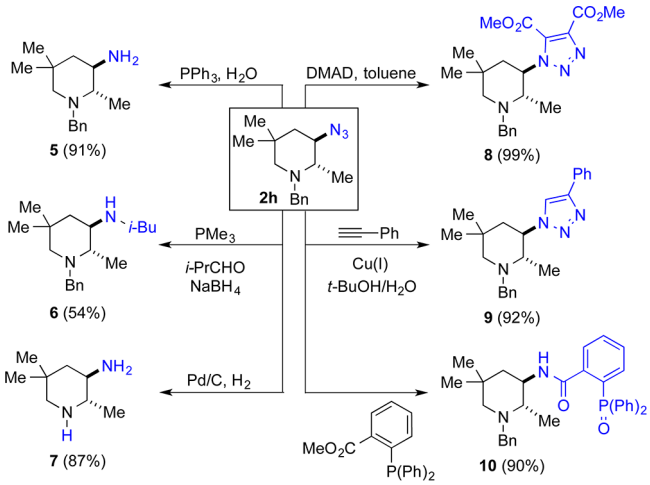
1 2 3

entry	amine	product			yield(%)[b]	2:3 (dr)[c]
1	1a	2a	R = Bu		92	2a only
2	1b	2b	R = *t*-Bu		90	2b only
3	1c	2c	R = Bn		95	2c only
4	1d	2d			69	2d only
5	1e	2e	R = Bu		63	6:1
6	1f	2f	R = *t*-Bu		60	2f only
7	1g	2g	R = Bu		76	2g only
8	1h	2h	R = Bn		89	2h only
9	1i	2i			28	2i only
10	1j	2j		3j	68	1:1.3
11	1k	2k		3k	92	6:1 (2k: 6.9:1) (3k: 1:1)
12	1l	2l		3l	56	1:1.8 (2l: 3.3:1) (3l: 1:1)
13	1m	2m		3m	68	1:1.2 (2m: *trans* only) (3m: 1:1)
14	1n	2n		3n	80	1.8:1
15	1o	2o			90	11:1 (2o: 4.3:1)
16	1p	2p			70	24:1 (2p:1.2:1)
17	1q	2q		3q	55	1.3:1

[a]Reactions conditions: **1** (1.0 equiv, 0.3 mmol, 0.1 M), NCS (1.0 equiv), 24 °C, 2 h; NaI (0.05 equiv), NaN_3 (1.2 equiv), 60 °C, 48 h. [b]Isolated yields. [c]Regioselectivity (**2**:**3**) and diastereoselectivity (dr) were determined by ^{1}H NMR spectroscopy with DMF as a quantitative internal standard and confirmed by GC/MS analysis of the reaction mixture. Major diastereomer is shown.

of **2h** with dimethyl acetylenedicarboxylate (DMAD). These representative transformations exhibit the versatility of azide as a useful synthetic handle. Next, azidopiperidine **2h** was subjected to the two most widely used bioorthogonal reactions; the azide−alkyne click chemistry[10f] of **2h** with phenyl acetylene in a mixture of water and *tert*-butanol proceeded smoothly to

Scheme 2. Derivatization of the Azide Group for Functionalization and Bioorthogonal Labeling of Piperidines



give triazole **9** in 92% yield, while the Staudinger ligation[18] of **2h** formed the desired product **10** in 90% yield. These successes suggest the potential applications of this one-pot synthesis of 3-azidopiperidines for molecular labeling of bioactive molecules containing the piperidine motif.

Using this aminocyclization/ring-opening strategy, we subsequently examined the use of amines as nucleophiles for their direct incorporation onto substrates **1f** and **1h** (Table 3). Encouragingly, both acyclic and cyclic amines were successfully introduced onto the piperidine in excellent yields under slightly modified conditions (entries 1−2). Next we looked into the scope of other heteroatom nucleophiles such as acetate, thiocyanate, and cyanide in the reactions of **1f** and **1h**, respectively. With NaOAc as the nucleophile, the desired 3-acetopiperidine products **15** and **16** were readily formed (entry 3), demonstrating the potential extension of this method in preparing 3-oxygenated piperidines (e.g., natural product prosophylline, Figure 1). When NaSCN was used, the expected 3-thiocyanatopiperidine was not detected in either reaction of **1f** or **1h**. Interestingly, thiourea **17** was formed in the reaction of **1f**, and 3-isothiocyanatopiperidine **18** was formed from **1h** (entry 4). Both results suggest that nitrogen nucleophilic ring-opening outcompetes sulfur ring-opening under current conditions.[19] Particularly interestingly, the 3-isothiocyanatopiperidine intermediate from **1f** readily formed a cyclic thiourea **17** upon the cleavage of a *tert*-butyl group. The reaction with NaCN gave a 1:1 mixture of 3-cyanopiperidine (e.g., **19**, **21**) and 3-succinylpiperidine (e.g., **20**, **22**) (entry 5). This outcome suggests that succinimide (pK_a = 14.7), formed as a byproduct from NCS in the chlorination step, can serve as an effective nucleophile for the ring-opening step in the presence of a base such as NaCN (HCN, pK_a = 12.7).

Intrigued by the dual role of NCS as both the chlorinating reagent and nucleophile source in the formation of 3-succinylpiperidine (**20** and **22**), we decided to further explore this atom-efficient transformation in the reaction of alkene **1h** with NCS using the non-nucleophilic base Na_2CO_3 (Scheme 3). With succinimide as the sole nucleophile for the ring-opening step, 3-succinylpiperidine **22** efficiently formed in 77% yield. To determine if other *N*-chloroamides could also promote such a tandem chlorination/cyclization/nucleophilic ring-opening reaction, we applied chloramine-T (TsNClNa) and *N*-chloropyrrolidinone[20] to similar reactions with **1h**. Both

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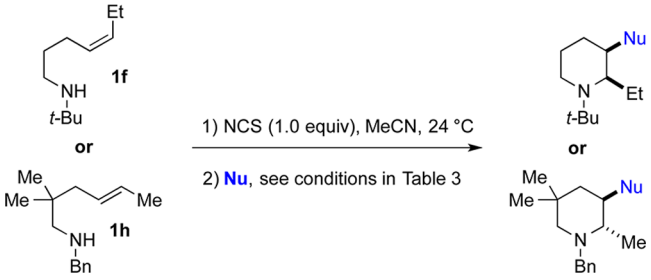
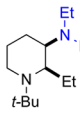
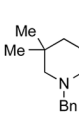
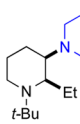
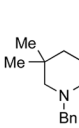
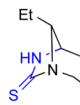
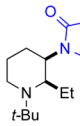
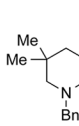
Table 3. Synthesis of 3-Functionalized Piperidines Using N, O, and C-Nucleophiles[a]



entry	conditions for step 2	product from **1f** (yield)[b]	product from **1h** (yield)[b]
1	NaI (5 mol%), 60 °C; $HNEt_2$ (2.5 equiv), 60 °C	 **11** (53%)	 **12** (89%)
2	NaI (5 mol%), 60 °C; $HN(CH_2CH_2)_2NBoc$ (2.5 equiv)	 **13** (57%)	 **14** (91%)
3	NaI (5 mol%), NaOAc (1.2 equiv) 60 °C	 **15** (55%)	 **16** (84%)
4	NaI (5 mol%), NaSCN (1.2 equiv), 60 °C	 **17** (31%)	 **18** (83%)
5	NaI (5 mol%), NaCN (1.2 equiv), 60 °C	 **19**  **20**	 **21**  **22**
		19: **20** = 1:1 (57%)[c]	**21**: **22** = 1:1 (83%)[c]

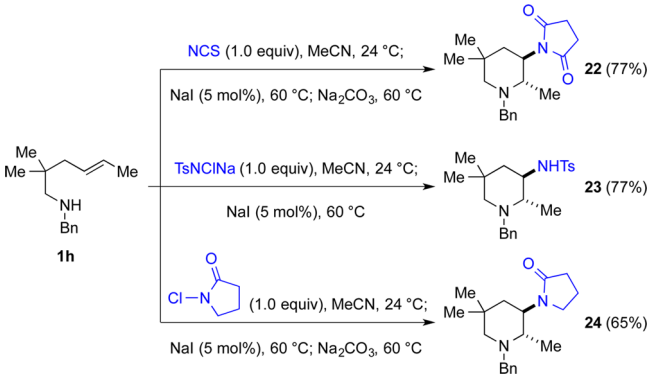
[a]Reaction conditions. step 1: **1f** or **1h** (1.0 equiv, 0.3 mmol, 0.1 M), NCS (1.0 equiv), 24 °C, 2 h; step 2: listed in Table 3. [b]Isolated yields. [c]Yields and ratios were determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

reactions provided the desired products, sulfonamide **23** and 3-amidopiperidine **24**, in 77% and 65% yield, respectively. Additional base was not even needed in the reaction of chloramine T. These results not only demonstrate the atom-efficiency of this tandem transformation but also establish the applicability of using nonacidic amides (pyrrolidinone pK_a = 24) as nucleophiles for an effective and modular synthesis of 3-amidopiperidines. It is particularly notable that all of these reactions continued to form the anti-Markovnikov-type product exclusively, providing opposite regioselectivity when compared to most olefin intramolecular amination reactions.[4,5]

CONCLUSION

In summary, we have developed a one-pot synthesis of 3-functionalized piperidines starting from unsaturated amines. The wide substrate scope and adaptability of the protocol will greatly expedite the preparation of 3-azido, 3-amino, and 3-

Scheme 3. One-Pot Synthesis of 3-Amidopiperidines from Unsaturated Amine 1h



amidopiperidines, which allows for the rapid access of piperidine-based natural products and biologically active compounds containing such functionalities. Particularly useful is the introduction of the azide as a versatile bioorthogonal chemical reporter, greatly facilitating the biological studies of this privileged structure. It is noteworthy that this formal intramolecular olefin amino-functionalization provides anti-Markovnikov-type adducts, uniquely complementing traditional Markovnikov-based olefin functionalizations.

EXPERIMENTAL SECTION

General Experiement Information. Unless otherwise noted, reactions were performed without exclusion of air or moisture. All commerially available reagents and solvents were used as received unless otherwise stated. *N*-chlorosuccinimide (NCS) was recrystallized from boiling water then dried under a vacuum and stored in a desiccator. Sodium thiosulfate was dried under a vacuum at 60 °C before use. Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with 0.25 mm of 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nmol). TLC plates were visualized by exposure to ultraviolet light and/or exposure to $KMnO_4$ stain. Organic solutions were concentrated *in vacuo* using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade). Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) and 400 or 500 MHz. All values for proton chemical shifts are reported in parts per million (δ) and are referenced to the residual protium in $CDCl_3$ (δ 7.26). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in $CDCl_3$ (δ 77.0). Infrared spectroscopic data are reported in wavenumbers (cm^{-1}), and only selected peaks are reported. High-resolution mass spectra were obtained using a liquid chromatography−electrospray ionization and time-of-flight mass spectrometer.

General Procedure for the One-Pot Azido-Cyclization Reactions. To a solution of unsaturated amine (0.3 mmol, 1 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1 equiv). The reaction solution was allowed to stir in the dark for 2 h, after which NaI (0.015 mmol, 0.05 equiv) and NaN_3 (0.36 mmol, 1.2 equiv) were added. The solution was then immediately heated to 60 °C and allowed to stir for 48 h. After cooling down to room temperature, the reaction mixture was diluted with an aqueous solution of NaOH (7 mL, 0.4 M) and extracted with hexanes (10 mL × 4). The hexane layers

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were combined and washed with an aqueous solution of NaOH (1.25 M, 5 mL) followed by brine (15 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by either column chromatography or Kugelrohr distillation.

5-Azido-1-butyl-3,3-dimethylpiperidine (2a). Isolation by Kugelrohr distillation; Clear liquid (57.8 mg, 92%); R_f = 0.55 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (ddt, J = 11.4, 10.5, 4.5 Hz, 1H), 2.98 (ddt, J = 10.5, 4.5, 1.7 Hz, 1H), 2.38 (dt, J = 11.1, 1.7 Hz, 1H), 2.35−2.23 (m, 2H), 1.74 (t, J = 10.5 Hz, 1H), 1.71 (ddt, J = 12.5, 4.5, 1.7 Hz, 1H), 1.65 (d, J = 11.1 Hz, 1H), 1.47−1.37 (m, 2H), 1.32 (sextet, J = 7.3 Hz, 2H), 1.09 (t, J = 12.0 Hz, 1H), 1.01 (s, 3H), 0.93 (s, 3H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 65.0, 58.5, 57.9, 55.6, 42.8, 31.6, 29.4, 29.1, 25.6, 20.5, 14.0; FTIR (thin film), cm^{-1} 2954, 2929, 2092, 1247; HRMS-ESI (m/z) calcd for $C_{11}H_{23}N_4$ ([M + H]$^+$): 211.1917; found: 211.1919.

5-Azido-1-(*tert*-butyl)-3,3-dimethylpiperidine (2b). Isolation by Kugelrohr distillation; Clear liquid (55.3 mg, 90%); R_f = 0.56 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48 (ddt, J = 11.1, 10.4, 4.3 Hz, 1H), 3.16 (ddt, J = 10.4, 4.3, 1.9 Hz, 1H), 2.50 (dt, J = 11.1, 1.9 Hz, 1H), 1.84 (t, J = 10.4 Hz, 1H), 1.78 (d, J = 11.1 Hz, 1H), 1.71 (ddt, J = 12.3, 4.3, 1.9 Hz, 1H), 1.07 (t, J = 11.7 Hz, 1H), 1.03 (s, 9H), 0.99 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 57.9, 56.7, 53.3, 51.5, 43.1, 31.5, 29.4, 26.4 (3C), 25.3; FTIR (thin film), cm^{-1} 2089, 1362, 1251, 1225; HRMS-ESI (m/z) calcd for $C_{11}H_{23}N_4$ ([M + H]$^+$): 211.1917; found: 211.1918.

5-Azido-1-benzyl-3,3-dimethylpiperidine (2c). Isolation by Kugelrohr distillation; Clear liquid (69.6 mg, 95%); R_f = 0.52 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.22 (m, 5H), 3.61 (ddt, J = 11.5, 10.5, 4.5 Hz, 1H), 3.52 (d, J = 13.5 Hz, 1H), 3.47 (d, J = 13.5 Hz, 1H), 2.99 (ddt, J = 10.5, 4.5, 2.0 Hz, 1H), 2.36 (dt, J = 10.8, 2.0 Hz, 1H), 1.83 (t, J = 10.5 Hz, 1H), 1.74 (ddt, J = 12.5, 4.5, 2.0 Hz, 1H), 1.72 (d, J = 10.8 Hz, 1H), 1.13 (t, J = 12.0 Hz, 1H), 1.05 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 128.6 (2C), 128.2 (2C), 127.0, 64.7, 62.5, 58.1, 55.5, 42.8, 31.8, 29.2, 25.5; FTIR (thin film), cm^{-1} 2092, 1254, 737, 697; HRMS-ESI (m/z) calcd for $C_{14}H_{21}N_4$ ([M + H]$^+$): 245.1761; found: 245.1761.

3-Azido-1-isobutyl-3,5,5-trimethylpiperidine (2d). Isolation by Kugelrohr distillation; Clear liquid (46.3 mg, 69%); R_f = 0.75 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (dt, J = 11.9, 1.8 Hz, 1H), 2.32 (dt, J = 10.9, 1.8 Hz, 1H), 2.03 (d, J = 7.4 Hz, 2H), 1.93 (d, J = 11.9 Hz, 1H), 1.76 (septet, J = 6.6 Hz, 1H), 1.73 (d, J = 10.9 Hz, 1H), 1.52 (dt, J = 14.1, 1.8 Hz, 1H), 1.25 (s, 3H), 1.15 (d, J = 14.1 Hz, 1H), 1.14 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.89 (s, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.4, 66.1, 63.3, 60.4, 47.1, 31.3, 29.9, 26.8, 26.3, 25.9, 20.8, 20.6; FTIR (thin film), cm^{-1} 2952, 2098, 1258, 1100; HRMS-ESI (m/z) calcd for $C_{12}H_{25}N_4$ ([M + H]$^+$): 225.2074; found: 225.2074.

***cis*-3-Azido-1-butyl-2-ethylpiperidine (2e) and 2-(1-azidopropyl)-1-butylpyrrolidine (3e).** Isolation by column chromatography (10% ethyl acetate−hexanes); Yellow liquid (39.6 mg, 63%, 6:1 ratio); R_f = 0.14 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (dt, J = 6.3, 3.3 Hz, 1H, **2e**), 3.12 (dt, J = 9.7, 4.3 Hz, 1H, **3e**) 3.06 (ddd, J = 10.0, 5.2, 3.1 Hz, 1H, **3e**), 2.80−2.69 (m, 1H, **2e**; m, 1H, **3e**), 2.64 (dt, J = 9.0, 5.0 Hz, 1H, **3e**), 2.56 (t, J = 7.6 Hz, 2H, **2e**), 2.42−2.28 (m, 2H, **2e**; m, 2H, **3e**), 2.22 (q, J = 8.3 Hz, 1H, **3e**), 1.94−1.84 (m, 1H, **2e**), 1.84−1.21 (m, 9H, **2e**; m, 9H, **3e**), 1.01 (t, J = 7.4 Hz, 3H, **3e**), 0.94 (t, J = 7.4 Hz, 3H, **2e**), 0.91 (t, J = 7.4 Hz, 3H, **3e**), 0.90 (t, J = 7.2 Hz, 3H, **2e**); ^{13}C NMR (125 MHz, $CDCl_3$, **2e**): δ 63.4, 58.9, 53.1, 49.8, 27.6, 27.4, 21.5, 20.7, 19.8, 14.0, 11.6; ^{13}C NMR (125 MHz, $CDCl_3$, **3e**): δ 68.5, 67.1, 56.5, 54.4, 31.3, 27.7, 27.2, 24.2, 23.2, 20.5, 11.4; FTIR (thin film), cm^{-1} 2956, 2931, 2091, 1255; HRMS-ESI (m/z) calcd for $C_{11}H_{23}N_4$ ([M + H]$^+$): 211.1917; found: 211.1918.

***cis*-3-Azido-1-(*tert*-butyl)-2-ethylpiperidine (2f).** Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (38.0 mg, 60%); R_f = 0.44 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (dt, J = 11.7, 4.7 Hz, 1H), 3.18−3.13 (m, 1H), 2.85−2.78 (m, 1H), 2.46 (td, J = 12.9, 2.7 Hz, 1H), 1.86−1.76 (m, 1H), 1.62−1.38 (m, 5H), 1.11 (s, 9H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 62.4, 57.3, 54.2, 38.2, 29.5 (3C), 25.9, 25.0, 17.4, 12.8; FTIR (thin film), cm^{-1} 2970, 2094, 1254, 1219; HRMS-ESI (m/z) calcd for $C_{11}H_{23}N_4$ ([M + H]$^+$): 211.1917; found: 211.1916.

***trans*-3-Azido-1-butyl-2,5,5-trimethylpiperidine (2g).** Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (51.4 mg, 76%); R_f = 0.59 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (ddd, J = 11.9, 9.4, 4.7 Hz, 1H), 2.66 (ddd, J = 13.2, 9.0, 6.6 Hz, 1H), 2.42 (dd, J = 11.5, 2.3 Hz, 1H), 2.36 (ddd, J = 13.2, 8.5, 5.4 Hz, 1H), 1.96 (dq, J = 9.4, 6.1 Hz, 1H), 1.93 (d, J = 11.5 Hz, 1H), 1.78 (ddd, J = 12.6, 4.7, 2.3 Hz, 1H), 1.46−1.21 (m, 4H), 1.23 (t, J = 12.3 Hz, 1H), 1.19 (d, J = 6.1 Hz, 3H), 1.02 (s, 3H), 0.92 (s, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 63.8, 62.5, 60.8, 52.7, 42.7, 31.0, 29.4, 27.2, 25.1, 20.6, 16.3, 14.0; FTIR (thin film), cm^{-1} 2954, 2929, 2097, 1257; HRMS-ESI (m/z) calcd for $C_{12}H_{25}N_4$ ([M + H]$^+$): 225.2074; found: 225.2076.

***trans*-3-Azido-1-benzyl-2,5,5-trimethylpiperidine (2h).** Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (69.3 mg, 89%); R_f = 0.37 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.20 (m, 5H), 4.12 (d, J = 13.9 Hz, 1H), 3.21 (ddd, J = 11.7, 9.3, 4.7 Hz, 1H), 3.08 (d, J = 13.9 Hz, 1H), 2.34 (dd, J = 11.5, 2.3 Hz, 1H), 2.06 (dq, J = 9.3, 6.1 Hz, 1H), 1.81 (ddd, J = 12.7, 4.7, 2.3 Hz, 1H), 1.74 (d, J = 11.5 Hz, 1H), 1.31 (d, J = 6.1 Hz, 3H), 1.28 (t, J = 12.2, 1H), 1.00 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 128.4 (2C), 128.1 (2C), 126.1, 63.7, 62.4, 61.6, 57.4, 42.7, 31.0, 29.2, 24.9, 16.9; FTIR (thin film), cm^{-1} 2095, 1255, 737, 697; HRMS-ESI (m/z) calcd for $C_{15}H_{23}N_4$ ([M + H]$^+$): 259.1917; found: 259.1911.

3-Azido-1-benzyl-2,2,5,5-tetramethylpiperidine (2i). Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (22.7 mg, 28%); R_f = 0.74 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.19 (m, 5H), 4.08 (d, J = 14.3 Hz, 1H), 3.47 (dd, J = 12.5, 4.7 Hz, 1H), 3.03 (d, J = 14.3 Hz, 1H), 2.10 (d, J = 12.1 Hz, 1H), 2.04 (dd, J = 12.1, 2.0 Hz, 1H), 1.62 (ddd, J = 12.9, 4.7, 2.0 Hz, 1H), 1.46 (t, J = 12.7 Hz, 1H), 1.31 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 128.1 (2C), 128.0 (2C), 126.5, 65.1, 58.1, 57.5, 53.1, 38.9, 31.0, 29.3, 26.8, 25.1, 9.6; FTIR (thin film), cm^{-1} 2953, 2097, 1452, 1254, 733, 697; HRMS-ESI (m/z) calcd for $C_{16}H_{25}N_4$ ([M + H]$^+$): 273.2074; found: 273.2068.

3-Azido-1-benzylpiperidine (2j). Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (19.3 mg, 30%); R_f = 0.22 (10% ethyl acetate−

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hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.23 (m, 5H), 3.53 (s, 2H), 3.49 (tt, J = 9.1, 4.1 Hz, 1H), 2.82 (ddt, J = 10.8, 4.1, 1.5 Hz, 1H), 2.62 (dtt, J = 11.3, 3.3, 1.5 Hz, 1H), 2.20−2.06 (m, 2H), 1.93 (dqt, J = 12.6, 4.1, 1.5 Hz, 1H), 1.82−1.73 (m, 1H), 1.64−1.52 (m, 1H), 1.45−1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 129.0 (2C), 128.2 (2C), 127.1, 62.9, 57.5, 57.3, 53.0, 29.5, 23.3; FTIR (thin film), cm^{-1} 2089, 1256, 736, 697; HRMS-ESI (m/z) calcd for $C_{12}H_{17}N_4$ ([M + H]$^+$): 217.1448; found: 217.1446. These data are consistent with published data.[5d]

2-(Azidomethyl)-1-benzylpyrrolidine (3j). Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (25.0 mg, 38%); R_f = 0.29 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.21 (m, 5H), 4.00 (d, J = 13.0 Hz, 1H), 3.43 (d, J = 13.0 Hz, 1H), 3.27 (dd, J = 12.4, 5.9 Hz, 1H), 3.17 (dd, J = 12.4, 4.0 Hz, 1H), 3.00−2.94 (m, 1H), 2.80−2.72 (m,1H), 2.28−2.20 (m, 1H), 2.01−1.91 (m, 1H), 1.84−1.67 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.4, 128.7 (2C), 128.3 (2C), 127.0, 63.2, 59.4, 54.6, 54.5, 29.0, 23.1; FTIR (thin film), cm^{-1} 2091, 1452, 1270, 736, 697; HRMS-ESI (m/z) calcd for $C_{12}H_{17}N_4$ ([M + H]$^+$): 217.1448; found: 217.1448. These data are consistent with published data.[5d]

***cis*-3-Azido-1-benzyl-5-methylpiperidine (2k).** Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (43.9 mg, 69%); R_f = 0.37 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.23 (m, 5H), 3.54 (d, J = 13.3 Hz, 1H), 3.52 (d, J = 13.3 Hz, 1H), 3.46 (ddt, J = 11.5, 10.6, 4.4 Hz, 1H), 3.02 (ddt, J = 10.6, 4.4, 1.7 Hz, 1H), 2.78 (ddt, J = 10.9, 3.7, 1.7 Hz, 1H), 2.05 (dtt, J = 12.6, 4.4, 1.7 Hz, 1H), 1.83−1.69 (m, 1H), 1.78 (d, J = 10.6 Hz, 1H), 1.54 (t, J = 10.9 Hz, 1H), 0.94 (q, J = 12.0 Hz, 1H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 129.0 (2C), 128.3 (2C), 127.1, 62.7, 60.5, 57.5, 57.4, 38.3, 29.9, 19.0; FTIR (thin film), cm^{-1} 2090, 1263, 738, 697; HRMS-ESI (m/z) calcd for $C_{13}H_{19}N_4$ ([M + H]$^+$): 231.1604; found: 231.1608.

***trans*-5-Azido-1-benzyl-2-methylpiperidine (2l) and *cis*-5-azido-1-benzyl-2-methyl-piperidine (2l′).** Isolation by column chromatography (0.5% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (14.5 mg, 21%, 3.3:1 ratio); R_f = 0.28 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.21 (m, 5H, **2l**; m, 5H, **2ĺ**), 4.04 (d, J = 13.4 Hz, 1H, **2l**), 3.87 (tt, J = 10.8, 4.0 Hz, 1H, **2l**), 3.84 (d, J = 13.4 Hz, 1H, **2ĺ**), 3.55−3.49 (m, 1H, **2ĺ**), 3.39 (d, J = 13.4 Hz, 1H, **2ĺ**), 3.19 (d, J = 13.4 Hz, 1H, **2l**), 3.06 (ddd, J = 10.8, 4.0, 2.0 Hz, 1H, **2l**), 2.68−2.59 (m, 2H, **2ĺ**), 2.08 (t, J = 10.8 Hz, 1H, **2l**), 2.31−2.26 (m, 1H, **2l**), 2.22−2.15 (m, 1H, **2l**), 1.79−1.52 (m, 2H, **2l**; m, 5H, **2ĺ**), 1.47−1.39 (m, 1H, **2l**), 1.18 (d, J = 6.1 Hz, 3H, **2l**), 1.12 (d, J = 6.3 Hz, 3H, **2ĺ**); ^{13}C NMR (125 MHz, $CDCl_3$, found **2l** and **2ĺ**): δ 138.7, 128.9 (2C), 128.8 (2C), 128.3 (2C), 128.2 (2C), 126.9, 65.8, 60.1, 58.4, 57.5, 56.1, 55.7, 53.4, 35.5, 34.4, 20.0, 15.3; FTIR (thin film), cm^{-1} 2096, 1453, 1063, 785, 759, 734, 697; HRMS-ESI (m/z) calcd for $C_{13}H_{19}N_4$ ([M + H]$^+$): 231.1604; found: 231.1603.

***trans*-3-Azido-1-benzyl-4-methylpiperidine (2m) and 2-(azidomethyl)-1-benzyl-3-methylpyrrolidine (3m).** Isolation by column chromatography (0.1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (34.4 mg, 50%); R_f = 0.30 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.21 (m, 5H, **2m**; m, 5H, **3m**), 4.04 (d, J = 13.2 Hz, 1H, **2m**), 3.53 (s, 2H, **2m**), 3.40 (dd, J = 12.6, 4.9 Hz, 1H, **3m**), 3.39 (d, J = 13.2 Hz, 1H, **3m**), 3.20 (dd, J = 12.6, 4.1 Hz, 1H, **3m**), 3.08 (ddd, J = 10.7, 4.2, 1.7 Hz, 1H, **2m**), 2.99 (td, J = 10.1, 4.2 Hz, 1H, **2m**), 2.94−2.90 (m, 1H, **3m**), 2.38−2.25 (m, 2H, **3m**), 2.16−2.07 (m, 1H, **3m**), 1.99−1.92 (m, 1H, **2m**; m, 1H, **3m**), 1.93 (t, J = 10.4 Hz, 1H, **2m**), 1.71−1.66 (m, 1H, **2m**), 1.42−1.32 (m, 2H, **2m**; m, 1H, **3m**), 1.06 (d, J = 6.0 Hz, 3H, **2m**), 1.04 (d, J = 6.9 Hz, 3H, **3m**); ^{13}C NMR (125 MHz, $CDCl_3$, **2m**): δ 129.0 (2C), 128.7 (2C), 128.3 (2C), 127.2 (2C), 64.5, 62.7, 57.4, 52.9, 36.2, 32.7, 18.6; FTIR (thin film), cm^{-1} 2925, 2093, 1454, 1256, 739, 698; HRMS-ESI (m/z) calcd for $C_{12}H_{19}N_4$ ([M + H]$^+$): 231.1604; found: 231.1602.

2-(Azidomethyl)-1-benzyl-3-methylpyrrolidine (3m′). Isolation by column chromatography (0.1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (12.6 mg, 18%); R_f = 0.38 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.21 (m, 5H), 3.99 (d, J = 13.1 Hz, 1H), 3.56 (d, J = 13.1 Hz, 1H), 3.25 (dd, J = 12.6, 6.1 Hz, 1H), 3.12 (dd, J = 12.6, 4.7 Hz, 1H), 2.98 (ddd, J = 9.1, 6.9, 2.0 Hz, 1H), 2.82 (ddd, J = 8.3, 6.1, 4.7 Hz, 1H), 2.36−2.24 (m, 2H), 1.86 (dtd, J = 12.1, 6.7, 2.0 Hz, 1H), 1.50 (dtd, J = 12.1, 10.1, 6.9 Hz, 1H), 1.04 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 128.7 (2C), 128.2 (2C), 126.9, 65.0, 59.9, 53.0, 52.0, 35.5, 32.9, 15.0; FTIR (thin film), cm^{-1} 2925, 2093, 1452, 1309, 1271, 739, 699; HRMS-ESI (m/z) calcd for $C_{12}H_{19}N_4$ ([M + H]$^+$): 231.1604; found: 231.1601.

7-Azido-5-benzyl-5-azaspiro[2.5]octane (2n). Isolation by column chromatography (0.5% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (37.7 mg, 52%); R_f = 0.20 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.22 (m, 5H), 3.62 (tt, J = 9.1, 4.1 Hz, 1H), 3.57 (d, J = 13.2 Hz, 1H), 3.50 (d, J = 13.2 Hz, 1H), 2.95 (dd, J = 10.7, 4.1 Hz, 1H), 2.26−2.19 (m, 1H), 2.22 (d, J = 11.2 Hz, 1H), 1.99 (d, J = 11.2 Hz, 1H), 1.63 (dd, J = 12.9, 9.1 Hz, 1H), 1.44 (dd, J = 12.9, 4.1 Hz, 1H), 0.43−0.32 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 128.9 (2C), 128.3 (2C), 127.1, 62.4, 61.0, 57.6, 56.8, 38.7, 16.4, 12.2, 10.3; FTIR (thin film), cm^{-1} 2926, 2094, 1242, 740, 698; HRMS-ESI (m/z) calcd for $C_{14}H_{19}N_4$ ([M + H]$^+$): 243.1604; found: 243.1604.

6-(Azidomethyl)-5-benzyl-5-azaspiro[2.4]heptane (3n). Isolation by column chromatography (0.5% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (20.6 mg, 28%); R_f = 0.24 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.21 (m, 5H), 4.06 (d, J = 13.0 Hz, 1H), 3.44 (d, J = 13.0 Hz, 1H), 3.38 (dd, J = 12.4, 5.9 Hz, 1H), 3.34 (dd, J = 12.4, 4.2 Hz, 1H), 3.02 (dddd, J = 8.2, 6.2, 5.9, 4.2 Hz, 1H), 2.59 (d, J = 9.1 Hz, 1H), 2.51 (d, J = 9.1 Hz, 1H), 2.06 (dd, J = 12.5, 8.2 Hz, 1H), 1.65 (dd, J = 12.5, 8.2 Hz, 1H), 0.59−0.40 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 128.7 (2C), 128.3 (2C), 127.0, 64.4, 62.7, 59.7, 54.3, 38.4, 19.8, 14.1, 9.4; FTIR (thin film), cm^{-1} 2092, 1452, 1275, 737, 698; HRMS-ESI (m/z) calcd for $C_{14}H_{19}N_4$ ([M + H]$^+$): 243.1604; found: 243.1605.

3-Azido-1-benzyl-*trans*-decahydroquinoline (2o). Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Yellow liquid (67.2 mg, 83%); R_f = 0.38 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.21 (m, 5H), 4.09 (d, J = 13.6 Hz, 1H), 3.40 (ddt, J = 11.6, 10.9, 4.4 Hz, 1H), 3.22 (d, J = 13.6 Hz, 1H), 2.97 (ddd, J = 10.9, 4.4, 2.2 Hz, 1H), 2.29−2.21 (m, 1H), 1.98−1.92 (m, 1H), 1.88−1.78 (m, 1H), 1.86 (t, J = 10.9 Hz, 1H), 1.74 (ddd, J = 10.7, 9.5, 3.6 Hz, 1H), 1.71−1.63 (m, 2H), 1.38−1.23 (m, 3H), 1.17−1.05 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 128.9 (2C), 128.2 (2C), 126.9, 65.7, 57.3, 57.0, 56.5, 40.6, 37.7, 32.7, 30.3, 25.8, 25.5; FTIR (thin film), cm^{-1} 2922,

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2091, 1253, 738, 697; HRMS-ESI (m/z) calcd for $C_{16}H_{23}N_4$ ($[M + H]^+$): 271.1917; found: 271.1917.

3-Azido-1-benzyl-*cis*-decahydroquinoline (2p). Isolation by column chromatography (0.5% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (30.1 mg, 37%); R_f = 0.50 (10% ethyl acetate−hexanes); R_f = 0.50 (10% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.21 (m, 5H), 3.74 (d, J = 13.6 Hz, 1H), 3.58 (d, J = 13.6 Hz, 1H), 3.48 (tt, J = 11.0, 5.0 Hz, 1H), 2.72 (dt, J = 11.1, 4.6 Hz, 1H), 2.66 (ddd, J = 11.0, 5.0, 1.2 Hz, 1H), 2.35 (t, J = 11.0 Hz, 1H), 2.06 (tq, J = 8.0, 4.6 Hz, 1H), 1.82−1.52 (m, 7H), 1.45−1.39 (m, 1H), 1.36−1.27 (m, 1H), 1.19−1.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.4, 128.4 (2C), 128.2 (2C), 126.9, 58.5, 58.2 (2C), 49.5, 34.5, 31.1, 29.9, 25.3, 21.0, 17.7; FTIR (thin film), cm^{-1} 2925, 2091, 1253, 736, 697; HRMS-ESI (m/z) calcd for $C_{16}H_{23}N_4$ ($[M + H]^+$): 271.1917; found: 271.1917.

3-Azido-1-benzylazepane (2q). Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (21.2 mg, 31%); R_f = 0.35 (10% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.21 (m, 5H), 3.73 (d, J = 13.5 Hz, 1H), 3.66 (d, J = 13.5 Hz, 1H), 3.49 (tt, J = 7.8, 4.4 Hz, 1H), 2.87 (dd, J = 13.8, 4.4 Hz, 1H), 2.69 (dd, J = 13.8, 7.8 Hz, 1H), 2.63 (t, J = 6.0 Hz, 2H), 2.09−1.99 (m, 1H), 1.80−1.51 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 128.6 (2C), 128.2 (2C), 127.0, 63.1, 61.4, 59.1, 55.9, 32.9, 29.0, 22.2; FTIR (thin film), cm^{-1} 2922, 2089, 1452, 1251, 966, 735, 697; HRMS-ESI (m/z) calcd for $C_{13}H_{19}N_4$ ($[M + H]^+$): 231.1904; found: 231.1906.

2-(Azidomethyl)-1-benzylpiperidine (3q). Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear liquid (16.5 mg, 24%); R_f = 0.25 (10% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.20 (m, 5H), 4.00 (d, J = 13.5 Hz, 1H), 3.33 (d, J = 13.5 Hz, 1H), 3.50 (dd, J = 12.7, 5.8 Hz, 1H), 3.47 (dd, J = 12.7, 4.0 Hz, 1H), 2.77 (dt, J = 12.1, 4.3 Hz, 1H), 2.51 (ddt J = 8.6, 5.8, 4.0 Hz, 1H), 2.09 (ddd J = 12.1, 9.2, 3.4 Hz, 1H), 1.79−1.64 (m, 2H), 1.62−1.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.1, 128.7 (2C), 128.2 (2C), 126.9, 60.2, 58.5, 53.0, 51.5, 29.4, 25.0, 23.1; FTIR (thin film), cm^{-1} 2933, 2092, 1270, 734, 698; HRMS-ESI (m/z) calcd for $C_{13}H_{19}N_4$ ($[M + H]^+$): 231.1904; found: 231.1906.

***trans*-1-Benzyl-2,5,5-trimethylpiperidin-3-amine (5).**[17a,b] A solution of **2h** (38.8 mg, 0.15 mmol, 1.0 equiv) and triphenylphosphine (59.0 mg, 0.225 mmol, 1.5 equiv) in water (18.9 μL, 1.05 mmol, 7 equiv) and THF (3 mL) was refluxed for 5 h. After cooling down to room temperature, the reaction was concentrated *in vacuo*. The residue was purified by column chromatography (10% methanol−dichloromethane) to produce **5** as a clear liquid (34.9 mg, 93%). R_f = 0.14 (10% methanol−dichloromethane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.18 (m, 5H), 4.12 (d, J = 13.9 Hz, 1H), 3.08 (d, J = 13.9 Hz, 1H), 2.63 (ddd, J = 11.4, 8.6, 4.6 Hz, 1H), 2.34 (dd, J = 11.3, 2.4 Hz, 1H), 1.81 (dq, J = 8.6, 6.0 Hz, 1H), 1.72 (d, J = 11.3 Hz, 1H), 1.60 (ddd, J = 12.6, 4.6, 2.4 Hz, 1H), 1.27 (d, J = 6.0 Hz, 2H), 1.24 (s, br, 2H), 0.99 (s, 3H), 0.98 (dd, J = 11.4, 11.3 Hz, 1H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 128.4 (2C), 128.0 (2C), 126.4, 65.3, 64.4, 57.8, 51.7, 41.7, 30.7, 29.6, 25.3, 16.5; FTIR (thin film), cm^{-1} 2949, 1452, 1368, 1122, 736, 697; HRMS-ESI (m/z) calcd for $C_{15}H_{25}N_2$ ($[M + H]^+$): 233.2012; found: 233.2011.

***trans*-1-Benzyl-*N*-isobutyl-2,5,5-trimethylpiperidin-3-amine (6).**[17c,d] To a solution of **2h** (38.8 mg, 0.15 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1.5 mL), was added a solution of trimethylphosphine in toluene (0.3 mL, 1.0 M, 0.3 mmol, 2.0 equiv) under nitrogen atmosphere. The solution was allowed to stir at room temperature for 1.75 h. Then isobutylaldehyde (34.0 μL, 0.375 mmol, 2.5 equiv) was added to the solution. The reaction was allowed to stir at room temperature for 4.25 h and was then concentrated *in vacuo*. The concentrated residue was dissolved in MeOH (2 mL) and placed in a 0 °C ice bath. To the resulting solution was added solid $NaBH_4$ (17.0 mg, 0.45 mmol, 3.0 equiv), and the reaction mixture was stirred for 10 min at 0 °C. The reaction was warmed to room temperature, and after 1 h, the reaction mixture was quenched with a saturated solution of $NaHCO_3$. The reaction mixture was diluted with water (15 mL) and extracted with Et_2O (15 mL × 4). The ether layers were combined, dried over K_2CO_3, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% methanol−dichloromethane) to give **6** as a yellow oil (23.1 mg, 54%). R_f = 0.66 (20% methanol−dichloromethane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.16 (m, 5H), 4.08 (d, J = 13.9 Hz, 1H), 3.10 (d, J = 13.9 Hz, 1H), 2.53−2.48 (m, 1H), 2.39−2.24 (m, 3H), 1.97 (dq, J = 8.4, 6.0 Hz, 1H), 1.73 (ddd, J = 10.5, 4.5, 2.2 Hz, 1H), 1.72 (d, J = 11.2 Hz, 1H), 1.66 (septet, J = 6.6 Hz, 1H), 1.28 (d, J = 6.0 Hz, 3H), 0.96 (s, 3H), 0.94 (s, br, 1H), 0.93−0.88 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.6, 128.4 (2C), 128.0 (2C), 126.4, 63.9, 62.7, 58.1 (2C), 55.9, 44.5, 30.6, 29.6, 28.9, 25.6, 20.8, 20.7, 16.2; FTIR (thin film), cm^{-1} 2950, 1453, 1364, 1123, 735, 697; HRMS-ESI (m/z) calcd for $C_{19}H_{33}N_2$ ($[M + H]^+$): 289.2638; found: 289.2635.

***trans*-2,5,5-Trimethylpiperidin-3-amine (7).**[21] To a solution of **2h** (38.8 mg, 0.15 mmol, 1.0 equiv) in MeOH (3 mL) under nitrogen, was added palladium on carbon (23.2 mg, 10 wt %, 0.0225 mmol, 0.15 equiv). The reaction mixture was purged and refilled with hydrogen. After 2 h, the reaction mixture was diluted with MeOH and filtered through Celite. The filtrate was concentrated *in vacuo* to give **7** as a light-yellow liquid (18.6 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.53 (dd, J = 12.2, 2.5 Hz, 1H), 2.41 (d, J = 12.2 Hz, 1H), 2.38 (ddd, J = 11.5, 9.1, 4.1 Hz, 1H), 2.11 (dq, J = 9.1, 6.3 Hz, 1H), 1.58 (ddd, J = 12.9, 4.1, 2.5 Hz, 1H), 1.41 (s, br, 3H), 1.14 (d, J = 6.3 Hz, 3H), 0.98 (t, J = 12.2 Hz, 1H), 0.98 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.0, 58.2, 52.1, 47.9, 32.1, 29.5, 24.5, 19.2; FTIR (thin film), cm^{-1} 2949, 2903, 1459, 789, 714, 606; HRMS-ESI (m/z) calcd for $C_8H_{19}N_2$ ($[M + H]^+$): 143.1543; found: 143.1541.

Dimethyl 1-(*trans*-1′-Benzyl-2′,5′,5′-trimethylpiperidin-3′-yl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (8).[22] A solution of **2h** (38.8 mg, 0.15 mmol, 1.0 equiv) and dimethyl acetylenedicarboxylate (55.3 μL, 0.45 mmol, 3.0 equiv) in toluene (1.5 mL) was refluxed under nitrogen for 24 h. After cooling down to room temperature, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by column chromatography (25% diethyl ether−hexanes) to give **8** as a clear oil (59.6 mg, 99%). R_f = 0.25 (25% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.19 (m, 5H), 4.74 (ddd, J = 12.6, 9.8, 4.4 Hz, 1H), 4.18 (d, J = 13.7 Hz, 1H), 4.03 (s, 3H), 3.97 (s, 3H), 3.16 (d, J = 13.7 Hz, 1H), 3.02 (dq, J = 9.8, 6.0 Hz, 1H), 2.46 (dd, J = 11.6, 2.2 Hz, 1H), 2.00 (d, J = 11.6 Hz, 1H), 1.99 (t, J = 12.6 Hz, 1H), 1.81 (ddd, J = 12.6, 4.4, 2.2 Hz, 1H), 1.09 (s, 3H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 159.3, 139.6, 138.8, 131.2, 128.3 (2C), 128.2 (2C), 126.8, 64.0, 62.6, 61.1, 57.3, 53.5, 52.6, 45.0, 31.2, 29.0, 24.2, 16.3; FTIR (thin film), cm^{-1} 1731, 1213, 734,

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698; HRMS-ESI (m/z) calcd for $C_{21}H_{29}N_4O_4$ ([M + H]$^+$): 401.2183; found: 401.2178.

***trans*-1-Benzyl-2,5,5-trimethyl-3-(4′-phenyl-1*H*-1′,2′,3′-triazol-1-yl)piperidine (9).**[10f] To a suspension of **2h** (38.8 mg, 0.15 mmol, 1.0 equiv) in water (0.3 mL) and *tert*-butanol (0.3 mL) were added phenylacetylene (16.5 μL, 0.15 mmol, 1.0 equiv), sodium ascorbate (30.0 mg, 0.015 mmol, 0.1 equiv), and $CuSO_4{\cdot}5H_2O$ (0.8 mg, 0.003 mmol, 0.02 equiv). The suspension was stirred vigorously and heated to 60 °C. After 15 h, a light-pink solid had precipitated out of solution. The solid was filtered and washed with copious amounts of water to give **9** as a light-pink solid (49.6 mg, 92%). R_f = 0.54 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.81 (m, 2H), 7.76 (s, 1H), 7.46−7.40 (m, 2H), 7.37−7.30 (m, 6H), 4.58 (ddd, J = 12.5, 9.8, 4.7 Hz, 1H), 4.19 (d, J = 13.8 Hz, 1H), 3.19 (d, J = 13.8 Hz, 1H), 2.68 (dq, J = 9.8, 6.0 Hz, 1H), 2.50 (dd, J = 11.7, 2.2 Hz, 1H), 1.98 (d, J = 11.7 Hz, 1H), 1.91 (ddd, J = 12.7, 4.7, 2.2 Hz, 1H), 1.82 (t, J = 12.6 Hz, 1H), 1.12 (s, 3H), 1.02 (d, J = 6.0 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 139.5, 130.7, 128.8 (2C), 128.4 (2C), 128.2 (2C), 128.1, 126.8, 125.6 (2C), 118.2, 64.1, 62.5, 62.1, 57.5, 45.2, 31.1, 29.1, 24.6, 16.3; FTIR (neat), cm^{-1} 1370, 1049, 908, 766, 731, 693; HRMS-ESI (m/z) calcd for $C_{23}H_{29}N_4$ ([M + H]$^+$): 361.2387; found: 361.2387.

***N*-(*trans*-1′-Benzyl-2′,5′,5′-trimethylpiperidin-3′-yl)-2-(diphenylphosphoryl)benzamide (10).**[18] A solution of **2h** (38.8 mg, 0.15 mmol, 1.0 equiv) and methyl 2-(diphenylphosphino)benzoate (48.0 mg, 0.15 mmol, 1.0 equiv) in MeCN (1.32 mL) and water (0.11 mL) was heated at 37 °C for 48 h. The reaction mixture was concentrated *in vacuo*. The crude residue was immediately purified by column chromatography (6% methanol−dichloromethane) to give **10** as a light-yellow solid (72.4 mg, 90%). R_f = 0.32 (4% methanol−dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (d, br, J = 8.9 Hz, 1H), 8.19−8.15 (m, 1H), 7.66 (tt, J = 7.6, 1.6 Hz, 1H), 7.64−7.54 (m, 5H), 7.53−7.44 (m, 5H), 7.37 (tt, J = 7.6, 1.6 Hz, 1H), 7.31−7.16 (m, 5H), 7.05−6.98 (m, 1H), 4.05 (d, J = 13.9 Hz, 1H), 3.86−3.77 (m, 1H), 3.01 (d, J = 13.9 Hz, 1H), 2.24 (dd, J = 11.2, 2.1 Hz, 1H), 2.03 (dq, J = 9.5, 6.0 Hz, 1H), 1.70 (d, J = 11.2 Hz, 1H), 1.02−0.92 (m, 2H), 0.94 (d, J = 6.0 Hz, 3H), 0.89 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3 (d, $^3J_{P-C}$ = 3.0 Hz), 141.6 (d, $^2J_{P-C}$ = 7.7 Hz), 140.4, 133.6 (d, $^3J_{P-C}$ = 12.2 Hz), 132.7, 132.4 (2C), 132.3 (d, $^2J_{P-C}$ = 10.2 Hz, 2C), 132.2 (d, $^2J_{P-C}$ = 10.2 Hz, 2C), 132.0 (d, $^2J_{P-C}$ = 10.2 Hz), 131.6 (d, $^1J_{P-C}$ = 107.5 Hz), 131.2 (d, $^1J_{P-C}$ = 107.5 Hz), 129.8 (d, $^3J_{P-C}$ = 12.0 Hz), 128.8 (d, $^3J_{P-C}$ = 12.2 Hz, 2C), 128.7 (d, $^3J_{P-C}$ = 12.2 Hz, 2C), 128.4 (2C), 128.0 (2C), 127.9 (d, $^1J_{P-C}$ = 90.3 Hz), 126.4, 63.7, 61.7, 57.6, 51.3, 43.2, 30.6, 29.2, 24.7, 16.4; FTIR (neat), cm^{-1} 1650, 1118, 723, 693; HRMS-ESI (m/z) calcd for $C_{34}H_{38}N_2O_2P$ ([M + H]$^+$): 537.2665; found: 537.2663.

General Procedure for the One-Pot Nucleophile-Cyclization Reactions in Table 3. *General Procedure for Entries 1−2 in Table 3.* To a solution of unsaturated amine **1f** or **1h** (0.3 mmol, 1 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1 equiv). The reaction solution was allowed to stir in the dark for 1 h, after which NaI (0.015 mmol, 0.05 equiv) was added, and the solution was immediately heated to 60 °C. After 2.5 h, the amine nucleophile (0.75 mmol, 2.5 equiv) was added. The reaction was monitored by TLC until determined complete and was then diluted with EtOAc (40 mL). The organic layer was washed with aqueous solutions of NaOH (1.0 M, 10 mL × 2) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. The crude residue was then purified by either column chromatography or Kugelrohr distillation.

***cis*-1-(*tert*-Butyl)-*N*,*N*,2-triethylpiperidin-3-amine (11).** Isolation by column chromatography (7.5% methanol−1% NH_4OH−dichloromethane); White solid (38.4 mg, 53%); R_f = 0.19 (25% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (dt, J = 8.0, 4.1 Hz, 1H), 2.86−2.80 (m, br, 1H), 2.65 (dq, J = 13.8, 7.1 Hz, 2H), 2.60 (dq, J = 13.8, 7.1 Hz, 2H), 2.60−2.49 (m, 2H), 1.78−1.71 (m, br, 1H), 1.54−1.36 (m, 5H), 1.12 (s, 9H), 0.96 (t, J = 7.1 Hz, 6H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 60.6, 56.1, 54.0, 42.1 (2C), 38.7, 29.9 (3C), 26.5, 24.1, 17.2, 12.9, 11.4 (2C); FTIR (thin film), cm^{-1} 2967, 2931, 1215; HRMS-ESI (m/z) calcd for $C_{15}H_{33}N_2$ ([M + H]$^+$): 241.2638; found: 241.2634.

***trans*-1-Benzyl-*N*,*N*-diethyl-2,5,5-trimethylpiperidin-3-amine (12).** Isolation by Kugelrohr distillation; Clear liquid (77.4 mg, 89%); R_f = 0.16 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.18 (m, 5H), 4.17 (d, J = 13.9 Hz, 1H), 3.01 (d, J = 13.9 Hz, 1H), 2.55 (dq, J = 12.8, 7.1 Hz, 2H), 2.52 (ddd, J = 12.5, 11.2, 4.0 Hz, 1H), 2.30 (dq, J = 12.8, 7.1 Hz, 2H), 2.29 (dd, J = 11.2, 2.7 Hz, 1H), 2.06 (dq, J = 9.6, 6.0 Hz, 1H), 1.61 (d, J = 11.2 Hz, 1H), 1.43 (ddd, J = 12.5, 4.0, 2.7 Hz, 1H), 1.33 (d, J = 6.0 Hz, 3H), 1.05 (t, J = 12.5 Hz, 1H), 1.00 (t, J = 7.1 Hz, 6H), 0.96 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.8, 128.4 (2C), 128.0 (2C), 126.3, 64.7, 60.5, 59.0, 58.5, 43.9 (2C), 35.5, 30.4, 30.1, 24.7, 17.1, 14.9 (2C); FTIR (thin film), cm^{-1} 2966, 2926, 737, 697; HRMS-ESI (m/z) calcd for $C_{19}H_{33}N_2$ ([M + H]$^+$): 289.2638; found: 289.2644 .

***tert*-Butyl-4-(*cis*-1′-(*tert*-butyl)-2′-ethylpiperidin-3′-yl)-piperazine-1-carboxylate (13).** Isolation by column chromatography (5% methanol−1% NH_4OH−dichloromethane); Yellow oil (63.5 mg, 53%); R_f = 0.39 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (t, J = 5.0 Hz, 4H), 3.24−3.19 (m, 1H), 2.80 (dt, J = 13.1, 3.6 Hz, 1H), 2.51 (ddd, J = 13.6, 11.8, 2.9 Hz, 1H), 2.43 (t, J = 5.0 Hz, 4H), 2.20 (dt, J = 11.8, 4.2 Hz, 1H), 1.80−1.74 (m, 1H), 1.61−1.25 (m, 5H), 1.45 (s, 9H), 1.10 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C): δ 154.8, 79.3, 64.9, 55.4, 54.2, 50.2 (2C), 44.2 (2C), 38.7, 29.7 (3C), 28.5 (3C), 26.1, 23.6, 17.8, 12.9; FTIR (thin film), cm^{-1} 2967, 1699, 1365, 1250, 1171; HRMS-ESI (m/z) calcd for $C_{20}H_{40}N_3O_2$ ([M + H]$^+$): 354.3115; found: 354.3118.

***tert*-Butyl-4-(*trans*-1′-benzyl-2′,5′,5′-trimethylpiperidin-3′-yl)piperazine-1-carboxylate (14).** Isolation by column chromatography (5% ethyl acetate−1% NH_4OH−hexanes); Clear oil (110.0 mg, 91%); R_f = 0.63 (25% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.19 (m, 5H), 4.15 (d, J = 13.8 Hz, 1H), 3.45−3.31 (m, 4H), 3.01 (d, J = 13.8 Hz, 1H), 2.60−2.52 (m, 2H), 2.41 (ddd, J = 12.5, 9.7, 3.8, 1H), 2.37−2.32 (m, 2H), 2.30 (dd, J = 11.3, 2.3 Hz, 1H), 2.10 (dq, J = 9.7, 6.0 Hz, 1H), 1.61 (d, J = 11.3 Hz, 1H), 1.48−1.43 (m, 1H), 1.46 (s, 9H), 1.34 (d, J = 6.0 Hz, 3H), 1.05 (t, J = 12.5 Hz, 1H), 0.95 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C): δ 154.9, 140.7, 128.5 (2C), 128.0 (2C), 126.4, 79.3, 64.7, 64.2, 59.9, 58.4, 48.8 (2C), 44.5 (2C), 35.8, 30.4, 30.0, 28.5 (3C), 24.7, 16.8; FTIR (thin film), cm^{-1} 1695, 1365, 1246, 1173, 1119; HRMS-ESI (m/z) calcd for $C_{24}H_{40}N_3O_2$ ([M + H]$^+$): 402.3114; found: 402.3114.

General Procedure for Entries 3−4 in Table 3. To a solution of unsaturated amine **1f** or **1h** (0.3 mmol, 1 equiv) in

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anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1 equiv). The reaction solution was stirred in the dark for 1 h. Then nucleophile (NaOAc or NaSCN, 0.36 mmol, 1.2 equiv) and NaI (0.015 mmol, 0.05 equiv) were added. The solution was then heated at 60 °C for 48 h. After cooling down to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with hexanes (10 mL × 4). The hexane layers were combined and washed with aqueous solutions of NaOH (1.0 M, 10 mL × 2) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the crude residue was then purified by either column chromatography or Kugelrohr distillation.

***cis*-1-(*tert*-Butyl)-2-ethylpiperidin-3-yl acetate (15).** Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); White solid (37.6 mg, 55%); R_f = 0.56 (20% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 4.88 (dt, J = 11.6, 5.0 Hz, 1H), 3.27−3.21 (m, 1H), 2.83−2.77 (m, 1H), 2.48 (ddd, J = 13.3, 11.9, 3.2 Hz, 1H), 2.02 (s, 3H), 1.77−1.71 (m, 1H), 1.64−1.43 (m, 5H), 1.11 (s, 9H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 73.9, 55.8, 54.0, 38.3, 29.6 (3C), 25.8, 25.4, 21.4, 17.5, 12.6; FTIR (thin film), cm^{-1} 2959, 1733, 1366, 1240, 1217, 1030; HRMS-ESI (m/z) calcd for $C_{13}H_{26}NO_2$ ($[M + H]^+$): 228.1958; found: 228.1958.

***trans*-1-Benzyl-2,5,5-trimethylpiperidin-3-yl acetate (16).** Isolation by Kugelrohr distillation; White solid (69.2 mg, 84%); R_f = 0.34 (10% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.19 (m, 5H), 4.74 (ddd, J = 10.5, 8.8, 4.8 Hz, 1H), 4.09 (d, J = 13.8 Hz, 1H), 3.12 (d, J = 13.8 Hz, 1H), 2.34 (dd, J = 11.3, 2.0 Hz, 1H), 2.26 (dq, J = 8.8, 6.1 Hz, 1H), 2.06 (s, 3H), 1.77 (ddd, J = 12.2, 4.8, 2.0 Hz, 1H), 1.77 (d, J = 11.3 Hz, 1H), 1.16 (d, J = 6.1 Hz, 3H), 1.15 (dd, J = 12.5, 10.5 Hz, 1H), 1.01 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 140.0, 128.4 (2C), 128.1 (2C), 126.6, 63.5, 60.7, 57.4, 42.6, 31.1, 29.1, 25.5, 21.3, 15.4; FTIR (thin film), cm^{-1} 1734, 1368, 1238, 1029; HRMS-ESI (m/z) calcd for $C_{17}H_{26}NO_2$ ($[M + H]^+$): 276.1958; found: 276.1964.

***cis*-8-Ethyl-1,6-diazabicyclo[3.2.1]octane-7-thione (17).** Isolation by column chromatography (20% ethyl acetate−hexanes to 40% ethyl acetate−hexanes); Orange oil (15.6 mg, 31%); R_f = 0.14 (25% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, br, 1H), 3.90 (dt, J = 11.6, 8.0 Hz, 1H), 3.68 (dt, J = 9.9, 5.4 Hz, 1H), 3.61 (tdd, J = 6.3, 5.4, 1.0 Hz, 1H), 3.31 (ddd, J = 11.6, 9.2, 3.7 Hz, 1H), 2.15−1.87 (m, 3H), 1.72−1.44 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.4, 68.9, 62.2, 46.7, 30.8, 28.4, 25.5, 9.7; FTIR (thin film), cm^{-1} 3201, 2961, 1459, 1421, 1318, 1256; HRMS-ESI (m/z) calcd for $C_8H_{15}N_2S$ ($[M + H]^+$): 171.0950; found: 171.0949.

***trans*-1-Benzyl-3-isothiocyanato-2,5,5-trimethylpiperidine (18).** Isolation by column chromatography (1% ethyl acetate−1% NH_4OH−hexanes); Clear oil (68.3 mg, 83%); R_f = 0.59 (10% ethyl acetate−hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 7.39−7.21 (m, 5H), 4.10 (d, J = 13.8 Hz, 1H), 3.57 (ddd, J = 11.6, 9.0, 4.4 Hz, 1H), 3.12 (d, J = 13.8 Hz, 1H), 2.34 (dd, J = 11.4, 2.0 Hz, 1H), 2.29 (dq, J = 9.0, 6.1 Hz, 1H), 1.90 (ddd, J = 12.9, 4.4, 2.0 Hz, 1H), 1.79 (d J = 11.4 Hz, 1H), 1.45 (dd, J = 12.9, 11.6 Hz, 1H), 1.35 (d, J = 6.1 Hz, 3H), 0.96 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.7, 131.0, 128.6 (2C), 128.5 (2C), 127.1, 63.7, 62.5, 59.4, 57.6, 45.3, 31.2, 29.1, 25.1, 17.3; FTIR (thin film), cm^{-1} 2055 (broad), 1452, 1365, 1125, 722, 697; HRMS-ESI (m/z) calcd for $C_{16}H_{23}N_2S$ ($[M + H]^+$): 275.1576; found: 275.1579.

General Procedure for Entry 5 in Table 3. To a solution of unsaturated amine **1f** or **1h** (0.3 mmol, 1 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1 equiv). The reaction solution was allowed to stir in the dark for 1 h, after which NaI (0.015 mmol, 0.05 equiv) was added, and the solution was immediately heated to 60 °C. After 2.5 h, NaCN (0.36 mmol, 1.2 equiv) was added. The reaction was monitored by TLC until determined complete. Then the reaction mixture was diluted with water (10 mL) and extracted with hexanes (10 mL × 4). The hexane layers were combined and washed with aqueous solutions of NaOH (1.0 M, 10 mL × 2) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. The crude residue was then purified by column chromatography.

***cis*-1-(*tert*-Butyl)-2-ethylpiperidin-3-carbonitrile (19).** Isolation by column chromatography (2% ethyl acetate−hexanes); Clear oil (9.0 mg, 15%, mass loss due to the volatility); R_f = 0.46 (25% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 3.33 (dt, J = 7.4, 4.7 Hz, 1H), 2.95−2.88 (m, br, 1H), 2.78 (dt, J = 12.9, 4.2 Hz, 1H), 2.59 (ddd, J = 13.9, 12.9, 3.0 Hz, 1H), 1.99−1.91 (m, br, 1H), 1.83 (qd, J = 13.0, 4.5 Hz, 1H), 1.80−1.59 (m, 2H), 1.52−1.45 (m, br, 1H), 1.41−1.29 (m, 1H), 1.11 (s, 9H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 122.3, 54.7, 54.3, 38.1, 31.7, 29.6 (3C), 24.7, 24.0, 19.6, 12.5; FTIR (thin film), cm^{-1} 2962, 1361, 1219, 1204; HRMS-ESI (m/z) calcd for $C_{12}H_{23}N_2$ ($[M + H]^+$): 195.1856; found: 195.1856.

1-(*cis*-1′-(*tert*-Butyl)-2′-ethylpiperidin-3′-yl)-succinimide (20). Isolation by column chromatography (25% ethyl acetate−1% NH_4OH−hexanes); Yellow oil (20.0 mg, 25%); R_f = 0.51 (50% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 4.22 (dt, J = 13.5, 4.1 Hz, 1H), 3.16−3.10 (m, 1H), 2.97−2.80 (m, 2H), 2.68−2.58 (m, 1H), 2.63 (s, br, 4H), 1.80−1.68 (m, 1H), 1.66−1.53 (m, 2H), 1.44 (qt, J = 12.9, 4.2 Hz, 1H), 1.30−1.18 (m, 1H), 1.15 (s, 9H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0 (2C), 56.3, 55.4, 54.2, 38.5, 30.0 (3C), 28.1 (2C), 26.8, 22.6, 18.3, 12.3; FTIR (thin film), cm^{-1} 1691, 1368, 1159, 700; HRMS-ESI (m/z) calcd for $C_{15}H_{27}N_2O_2$ ($[M + H]^+$): 267.2067; found: 267.2072.

***trans*-1-Benzyl-2,5,5-trimethylpiperidine-3-carbonitrile (21).** Isolation by column chromatography (2% ethyl acetate−1% NH_4OH−hexanes); Clear oil (30.7 mg, 42%); R_f = 0.62 (25% ethyl acetate−hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−7.21 (m, 5H), 4.11 (d, J = 13.7 Hz, 1H), 3.11 (d, J = 13.7 Hz, 1H), 2.64 (ddd, J = 12.6, 9.7, 4.1 Hz, 1H), 2.41 (dq, J = 9.7, 6.1 Hz, 1H), 2.36 (dd, J = 11.5, 2.3 Hz, 1H), 1.79 (ddd, J = 13.2, 4.1, 2.3 Hz, 1H), 1.78 (d, J = 11.5 Hz, 1H), 1.50 (t, J = 12.9 Hz, 1H), 1.42 (d, J = 6.1 Hz, 3H), 0.96 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 128.3 (2C), 128.2 (2C), 126.8, 121.9, 63.5, 58.9, 57.5, 41.1, 33.8, 30.4, 28.7, 24.2, 18.6; FTIR (thin film), cm^{-1} 2953, 1453, 1127, 740, 698; HRMS-ESI (m/z) calcd for $C_{16}H_{23}N_2$ ($[M + H]^+$): 243.1856; found: 243.1857.

***N*-(*trans*-1-Benzyl-2,5,5-trimethylpiperidin-3-yl)-succinimide (22).** To a solution of unsaturated amine **1h** (0.3 mmol, 1 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1 equiv). The reaction solution was allowed to stir in the dark for 1 h, after which NaI (0.015 mmol, 0.05 equiv) was added, and the solution was immediately heated to 60 °C. After 2.5 h, Na_2CO_3 (0.36 mmol, 1.2 equiv) was added. The reaction was monitored by TLC until determined complete.

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Then the reaction mixture was diluted with water (10 mL) and extracted with hexanes (10 mL × 4). The hexane layers were combined and washed with aqueous solutions of NaOH (1.0 M, 10 mL × 2) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. The crude residue was then purified by column chromatography (20% ethyl acetate−hexanes) to give **22** as a white solid (72.6 mg, 77%). R_f = 0.40 (40% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.19 (m, 5H), 4.17 (ddd, J = 13.0, 10.1, 4.4 Hz, 1H), 4.14 (d, J = 13.8 Hz, 1H), 3.06 (d, J = 13.8 Hz, 1H), 3.01 (dq, J = 10.1, 6.1 Hz, 1H), 2.68 (s, br, 4H), 2.34 (dd, J = 11.5, 2.3 Hz, 1H), 2.07 (t, J = 12.6 Hz, 1H), 1.90 (d J = 11.5 Hz, 1H), 1.28 (ddd, J = 12.3, 4.4, 2.3 Hz, 1H), 1.06 (s, 3H), 1.02 (d, J = 6.1 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3 (2C), 140.4, 128.3 (2C), 128.1 (2C), 126.5, 64.2, 57.6, 57.0, 53.6, 39.7, 31.1, 29.2, 28.0 (2C), 24.5, 16.6; FTIR (thin film), cm^{-1} 1699, 1390, 1369, 1193, 1148, 735; HRMS-ESI (m/z) calcd for $C_{19}H_{27}N_2O_2$ ([M + H]$^+$): 315.2067; found: 315.2072.

***N*-(*trans*-1-Benzyl-2,5,5-trimethylpiperidin-3-yl)-tosylsulfonamide (23).** To a solution of **1h** (21.7 mg, 0.1 mmol, 1 equiv) in anhydrous MeCN (1 mL) was added $TsNClNa{\cdot}3H_2O$ (28.2 mg, 0.1 mmol, 1 equiv). The reaction solution was allowed to stir in the dark for 1 h, and then NaI (0.7 mg, 0.005 mmol, 0.05 equiv) was added. The reaction was then immediately heated to 60 °C and allowed to stir for 2 h. Then the reaction was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), and filtered through Celite. The filtrate was concentrated *in vacuo*, and the crude residue was then purified by column chromatography (10% ethyl acetate−hexanes) to give **23** as a colorless oil (29.6 mg, 77%). R_f = 0.32 (25% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 2H), 7.33−7.20 (m, 7H), 4.34 (d, J = 9.5 Hz, 1H), 3.39 (d, J = 13.6 Hz, 1H), 3.15 (tdd, J = 9.5, 7.6, 4.4 Hz, 1H), 3.13 (d, J = 13.6 Hz, 1H), 2.42 (s, 3H), 2.27 (dd, J = 11.5, 1.5 Hz, 1H), 2.02 (dq, J = 7.6, 6.2 Hz, 1H), 1.74 (d, J = 11.5 Hz, 1H), 1.39 (ddd, J = 13.1, 4.4, 1.5 Hz, 1H), 1.12 (d, J = 6.2 Hz, 3H), 1.00 (dd, J = 13.1, 9.5 Hz, 1H), 0.83 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C): δ 143.1, 139.8, 138.6, 129.6 (2C), 128.5 (2C), 128.2 (2C), 127.1 (2C), 126.8, 62.1, 61.2, 58.2, 54.8, 44.0, 30.7, 28.9, 26.2, 21.4, 14.2; FTIR (thin film), cm^{-1} 1153, 732, 663, 564; HRMS-ESI (m/z) calcd for $C_{22}H_{31}N_2O_2S$ ([M + H]$^+$): 387.2101; found: 387.2103.

1-(*trans*-1′-Benzyl-2′,5′,5′-trimethylpiperidin-3′-yl)-pyrrolidin-2-one (24). To a solution of **1h** (65.2 mg, 0.3 mmol, 1 equiv) in anhydrous MeCN (3 mL) was added *N*-chloro-2-pyrrolidinone[20] (35.9 mg, 0.3 mmol, 1 equiv). The reaction solution was allowed to stir in the dark for 1 h. NaI (2.2 mg, 0.015 mmol, 0.05 equiv) was then added, and the solution was immediately heated to 60 °C and allowed to stir for 2 h. Na_2CO_3 (38.2 mg, 0.36 mmol, 1.2 equiv) was then added, and the reaction was allowed to stir for an additional 72 h. The reaction was cooled down to room temperature, diluted with EtOAc (40 mL), and placed into a separatory funnel. The organic layer was washed with aqueous solutions of NaOH (1.0 M, 10 mL × 2) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The crude residue was then purified by column chromatography (25% ethyl acetate−hexanes) to give **24** as a slightly yellow solid (58.2 mg, 65%). R_f = 0.14 (40% ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C): δ 7.33−7.19 (m, 5H), 4.15 (d, J = 13.9 Hz, 1H), 4.14−4.06 (m, 1H), 3.39−3.24 (m, 1H), 3.29−2.24 (m, 1H), 3.04 (d, J = 13.9 Hz, 1H), 2.43−2.34 (m, 3H), 2.28−2.21 (m, 1H), 2.02−1.96 (m, 2H), 1.71 (d, J = 11.4 Hz, 1H), 1.40 (ddd, J = 12.4, 4.6, 2.2 Hz, 1H), 1.35 (dd, J = 12.4, 12.3 Hz, 1H), 1.14 (d, J = 6.0 Hz, 3H), 1.08 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 140.2, 128.4 (2C), 128.1 (2C), 126.6, 64.8, 59.5, 58.1, 52.2, 43.2, 41.1, 31.5, 30.9, 29.5, 24.8, 18.6, 16.4; FTIR (thin film), cm^{-1} 2949, 1684, 1420, 1283, 1268; HRMS-ESI (m/z) calcd for $C_{19}H_{29}N_2O$ ([M + H]$^+$): 301.2274; found: 301.2273.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional screening data and copies of ^{1}H and ^{13}C NMR spectra for new compounds. 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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