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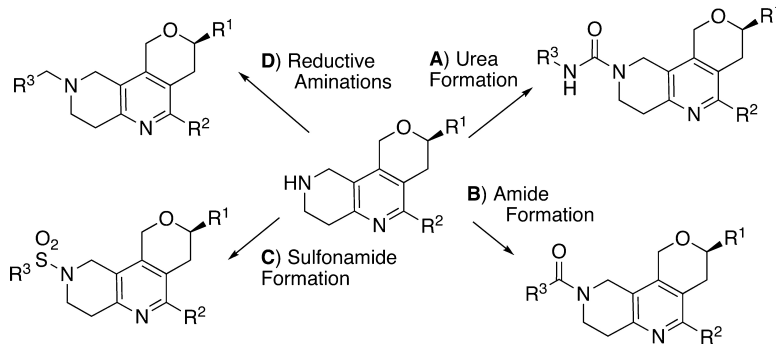

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Library Synthesis Using 5,6,7,8-Tetrahydro-1,6-naphthyridines as Scaffolds

Ya Zhou,[†] Aaron B. Beeler,[†] Sanghyun Cho,[‡] Yuehong Wang,[‡] Scott G. Franzblau,[‡] and John K. Snyder[†,*]

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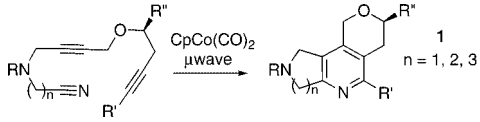
The chemistry of 5,6,7,8-tetrahydro-1,6-naphthyridine scaffolds, synthesized by intramolecular cobalt-catalyzed [2 + 2 + 2] cyclizations, has been exploited for library synthesis. Urea, amide, and sulfonamide formations were used in the synthesis of a 101-membered library. Screening of the library for antituberculosis activity revealed three lead compounds.

Introduction

We have been interested in small, unnatural heterocycles, such as tetrahydronaphthyridines, as library scaffolds,[1] and to this end, we recently reported a microwave-promoted, cobalt-catalyzed [2 + 2 + 2] cyclization (Scheme 1) to prepare pyrano-annulated 5,6,7,8-tetrahydro-1,6-naphthyridines (**1**, $n = 2$), 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridines (**1**, $n = 1$), and 6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepines (**1**, $n = 3$).[2] With multiple sites for diversification (R, R′, R″, and *n*) and low molecular weights, these compounds have several features desirable in library scaffolds. In contrast to the fully aromatized naphthyridines, which have shown significant bioactivities,[3,4] tetrahydronaphthyridines have not received significant attention. To probe the biological effects of this class of heterocycles, four tetrahydropyranonaphthyridines (Figure 1, **1**{*1*−*4*}) with different substitutions at the C6 and C8 positions were chosen as scaffolds for the preparation of a first generation library. The secondary amine at N2 was then used as the diversification point for formation of ureas, amides and sulfonamides.

Scheme 1. General [2 + 2 + 2] Cyclization to Afford Annulated Tetrahydronaphthyridines and Related Heterocycles



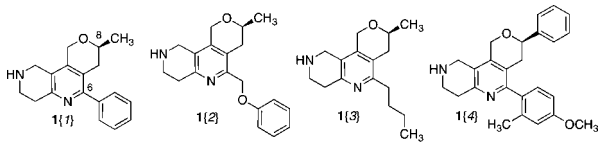
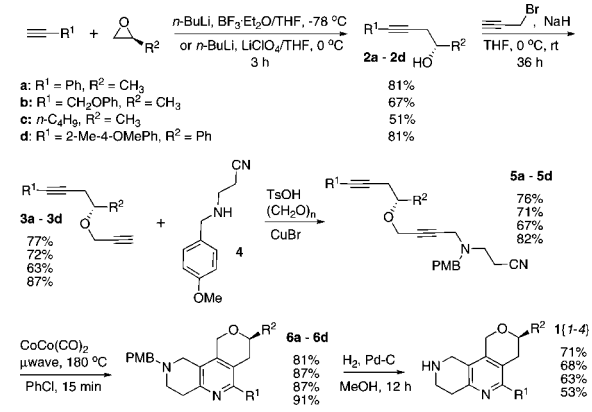


Figure 1. Four scaffolds **1**{*1*−*4*} for library synthesis.

Results and Discussion

Synthesis of Tetrahydronaphthyridine Scaffolds 1{*1*−*4*}. Following the protocols reported earlier,[2] the syntheses of scaffolds **1**{*1*−*4*} proceeded smoothly beginning with the preparation of four dialkynyl ethers **3a**−**3d** (Scheme 2). To this end, (*S*)-propylene oxide and (*S*)-styrene oxide were opened with the appropriate lithium acetylides under Lewis acid activation to afford the secondary homopropargyl alcohols **2a**−**2d**.[5,6] The preparation of alcohols **2a**−**2c** used $BF_3 \cdot OEt_2$ at −78 °C, while **2d** was synthesized at 0 °C with $LiClO_4$ as the catalyst. Propargylations of alcohols **2a**−**2d** produced dialkynyl ethers **3a**−**3d**.[7] Copper-promoted Mannich reactions[8] using *p*-methoxybenzyl-protected aminonitrile **4**, easily prepared by conjugate addition of *p*-methoxybenzylamine to acrylonitrile,[9] gave dialkynyl aminonitriles **5a**−**5d**. The [2 + 2 + 2] cyclizations of **5a**−**5d** catalyzed by $CpCo(CO)_2$ proceeded readily under microwave irradiation as previously reported,[2] giving *p*-methoxybenzyl-protected 5,6,7,8-tetrahydro-1,6-naphthyridines **6a**−**6d** in good yields. Finally, deprotection of the PMB group by Pd-catalyzed hydrogenation afforded library scaffolds **1**{*1*−*4*}.[10]

Scheme 2. Preparation of Library Scaffolds **1**{*1*−*4*}



Library Design. Diversifications of the scaffolds **1** were accomplished through three main transformations (Scheme 3): (1) urea formation with isocyanates,[11] (2) amide formation with acyl chlorides,[12] and (3) sulfonamide formation with sulfonyl chlorides.[13] Diversification reagents (isocyanates, acyl chlorides, and sulfonyl chlorides) were selected by

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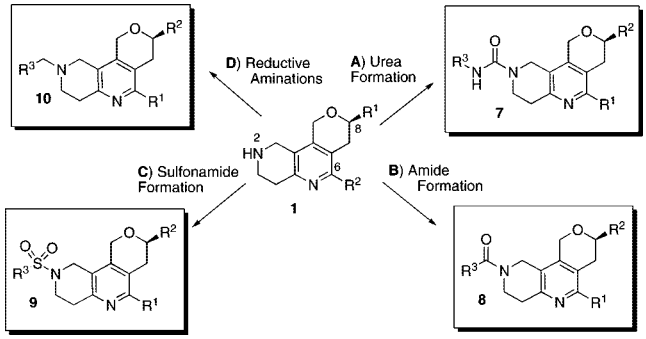
Scheme 3. Strategy for Diversification of Pyranonaphthyridine Scaffolds



enumeration of available reagents and subsequent diversity analysis of the enumerated products to determine the most dissimilar set of library members.[14] Eight reagents were selected for each diversification to afford a 96-membered library. Reductive aminations were also successful; however, the resulting tertiary amines were unstable upon long-term storage, and only five such tertiary amines were prepared. Thus, a total of 101 library members were synthesized using tetrahydronaphthyridine scaffolds **1**{*1*−*4*}.

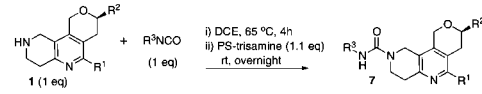
Library Synthesis. With tetrahydronaphthyridines **1**{*1*−*4*} in hand, the reaction conditions for urea formation were optimized with scaffold **1**{*1*} and three isocyanates. The reactions were carried out using 1.1 equiv of isocyanates in dichloroethane (65 °C, 4 h), followed by treatment with PS-trisamine resin[15] (1.1 equiv) at room temperature for 6 h to scavenge excess isocyanate. Upon filtration, LC/MS indicated 90−95% conversions,[16] while the NMR spectra of the crude reaction residues showed only desired urea products in most cases. The isolated yields of ureas were 91% (**7**{*1*,*1*}), 75% (**7**{*1*,*4*}), and 83% (**7**{*1*,*5*}) following flash chromatography (see Chart 1).

Using the optimized reaction conditions, we prepared a 32-membered sublibrary from scaffolds **1**{*1*−*4*} and eight commercially available isocyanates selected by the diversity analysis. The crude products were purified by mass-directed preparative HPLC to provide ureas **7**{*1*−*4*,*1*−*8*} in <10 to >98% yield with >90% purity of the library members (Chart 1).[17]

Synthesis of amides started with model studies using scaffold **1**{*1*} and acyl chlorides (1.1 equiv). The reactions proceeded readily with triethylamine as base with excess acid chloride. While full conversions of scaffold **1**{*1*} to amide products were observed by NMR, unscavenged acyl chloride was also present. With the use of PS-DMAP resin (1.5 equiv) as both catalyst and acid chloride scavenger[18] at room temperature in dichloromethane for 10 h, the reactions proceeded to completion, and upon filtration, NMR spectra indicated full conversion to the expected products with no acid chlorides detected. Following flash chromatography, the isolated yields of amides were 93% (**8**{*1*,*1*}), 75% (**8**{*1*,*2*}), 81% (**8**{*1*,*4*}), and 78% (**8**{*1*,*7*}). A 32-membered sublibrary was then prepared from tetrahydronaphthyridine scaffolds **1**{*1*−*4*} and eight commercially available acid chlorides chosen by the diversity analysis. To enhance full conversion for each reaction, a slightly higher excess of acid chlorides (1.3 equiv) and PS-DMAP resin (1.7 equiv) were used for the library synthesis. After the reactions, the PS-DMAP resin was removed by filtration, and the solvent was evaporated to afford the crude library products. Purification by mass-directed preparative HPLC provided the library members **8**{*1*−*4*,*1*−*8*} in <10 to >98% yield with >90% purity (Chart 2).[17]

Scaffold **1**{*1*} was also used in optimization studies with two sulfonyl chlorides (Chart 3). Under optimal conditions,

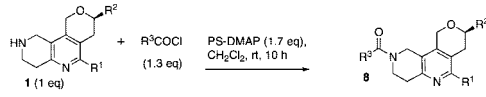
Chart 1. Urea Sublibrary Members[a]



Isocyanates \ Library Scaffolds	1{1}	1{2}	1{3}	1{4}
	7{1,1} 91% (>98%)	7{2,1} (91%)	7{3,1} (>98%)	7{4,1} (>98%)
	7{1,2} 78%	7{2,2} (>98%)	7{3,2} (>98%)	7{4,2} (67%)
	7{1,3} (>98%)	7{2,3} (>98%)	7{3,3} (>98%)	7{4,3} (>98%)
	7{1,4} 75% (>98%)	7{2,4} (>98%)	7{3,4} (73%)	7{4,4} (>98%)
	7{1,5} 83% (>98%)	7{2,5} (>98%)	7{3,5} (82%)	7{4,5} (>98%)
	7{1,6} (92%)	7{2,6} (>98%)	7{3,6} (>98%)	7{4,6} (>98%)
	7{1,7} (>98%)	7{2,7} (>98%)	7{3,7} (>98%)	7{4,7} (>98%)
	7{1,8} (<10%)	7{2,8} (<10%)	7{3,8} (<10%)	7{4,8} (>98%)

[a] Yields without parentheses are isolated yields with the library protocols for individual compounds. Yields in parentheses are LC-MS yields from library preparation.

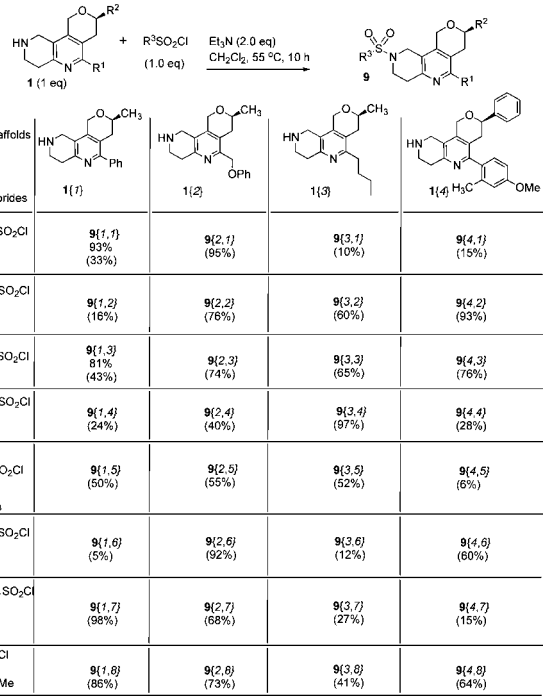
Chart 2. Amide Sublibrary Members[a]



Acid Chlorides \ Library Scaffolds	1{1}	1{2}	1{3}	1{4}
	8{1,1} 93% (85%)	8{2,1} (91%)	8{3,1} (>98%)	8{4,1} (>98%)
	8{1,2} 75% (<10%)	8{2,2} (>98%)	8{3,2} (68%)	8{4,2} (>98%)
	8{1,3} (61%)	8{2,3} (>98%)	8{3,3} (78%)	8{4,3} (>98%)
	8{1,4} 81% (73%)	8{2,4} (>98%)	8{3,4} (83%)	8{4,4} (74%)
	8{1,5} (67%)	8{2,5} (>98%)	8{3,5} (75%)	8{4,5} (76%)
	8{1,6} (68%)	8{2,6} (89%)	8{3,6} (38%)	8{4,6} (45%)
	8{1,7} 78% (27%)	8{2,7} (64%)	8{3,7} (15%)	8{4,7} (86%)
	8{1,8} (66%)	8{2,8} (72%)	8{3,8} (>98%)	8{4,8} (>98%)

[a] Yields without parentheses are isolated yields applying the library procedure for individual compounds. Yields in parentheses are LC-MS yields from library preparation.

Chart 3. Sulfonamide Sublibrary Members[a]



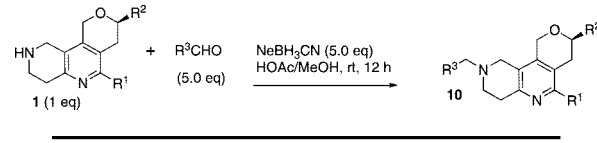
[a] Yields without parentheses are isolated yields applying the library procedure for individual compounds. Yields in parentheses are LC-MS yields from library preparation.

equal molar equivalents of **1**{*1*} and sulfonyl chlorides were allowed to react at room temperature for 4 h in the presence of triethylamine (TEA, 1 equiv). No starting material was observed by LC/MS, and the isolated yields of the desired sulfonamides after chromatography were 93% (**9**{*1*,*1*}) and 81% (**9**{*1*,*3*}). Using this protocol, we reacted the four scaffolds **1**{*1-4*} and eight commercially available sulfonyl chlorides chosen by the diversity analysis to prepare the sulfonamide sublibrary. A longer reaction time (10 h) and higher temperature (55 °C) in comparison to the model study were used to enhance conversion. After evaporation of the solvent, the crude reaction mixtures were purified by mass-directed preparative HPLC to afford the library members **9**{*1*−*4*,*1*−*8*} in <10−85% yield with >90% purity (Chart 3).[17]

Reductive aminations were also examined with these naphthyridine scaffolds **1**{*1*−*4*} using five different aldehydes (Table 1).[19] In all cases, the aminations proceeded in good to excellent yields (78−88%) to give the desired tertiary amines **10a**−**10e**. These amines, however, slowly oxidized upon prolonged storage.

Biological Activity. The libraries of ureas **7**, amides **8**, and sulfonamides **9** were screened for activity against *Mycobacterium tuberculosis* using the microplate Alamar Blue assay (MABA).[20] The MIC values, shown in Chart 4, were established after initial positive hits were identified (>80% inhibition at 10 μg/mL). Cytotoxicity assays were performed on Vero cells with IC_{50} values greater than 50 μg/mL under the assay conditions. Activities were subsequently validated in duplicate assays with resynthesized compound. Library compounds **7**{*4*,*1*}, **7**{*4*,*2*}, and **9**{*4*,*4*}, all with the 6-(4-methoxy-4-methyl)phenyl and 8-phenyl

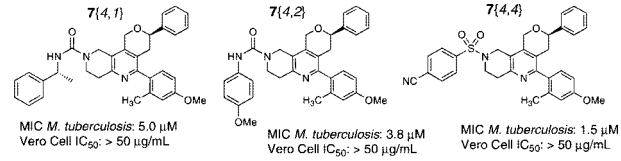
Table 1. Reductive Aminations with Scaffolds **1**{*1*−*4*}



Entry	R^1	R^2	R^3	Yield (**10**)[a]
1	Ph	Me		82% (**10a**)
2	Ph	Me		78% (**10b**)
3	CH_2OPh	Me		80% (**10c**)
4	*n*-Bu	Me		88% (**10d**)
5		Ph		88% (**10e**)

Isolated yields.

Chart 4. Bioactive Library Members



substituents of scaffold **1**{*4*} and N2 derivatized as an aryl-bearing urea or sulfonamide, showed significant activities.

Conclusions

Using the recently reported, cobalt-catalyzed [2 + 2 + 2] cyclization methodology, an efficient preparation of 5,6,7,8-tetrahydro-1,6-naphthyridine scaffolds was accomplished. Four scaffolds with secondary amine functionalities at the N2 position were then diversified through solution-phase parallel synthesis protocols to prepare arrays of ureas, amides and sulfonamide. Easy workup and LC/MS purification provided high purity library products. Screening against *M. tuberculosis* revealed three library members as lead structures for second generation library synthesis. Continuing efforts will focus on further diversifying the scaffolds for other libraries, as well as further screening of the libraries in hand for additional biological activities.

Experimental Section[21]

General Methods. Melting points were determined on a capillary melting point apparatus and are uncorrected. All ^{1}H NMR spectra were recorded at 93.94 kG (^{1}H 400 MHz), and ^{13}C NMR spectra were recorded at 70.5 kG (^{13}C 75 MHz) or 94.04 kG (^{13}C 100 MHz) at ambient temperature in $CDCl_3$, CD_3OD, or CD_3CN as indicated. Hydrogen chemical shifts are expressed in parts per million (ppm) relative to the residual protio solvent resonance in $CDCl_3$ (δ 7.24 for residual $CHCl_3$), CD_3OD (δ 3.31 for residual CHD_2OD), or CD_3CN (δ 1.94 for residual CHD_2CN). For ^{13}C spectra, the center line (δ 77.0) of the $CDCl_3$ triplet, the center line (δ 49.15) of the CD_3OD septet or the center line (δ 1.39) of the CD_3CN septet was used as the internal reference. Unless otherwise noted, each carbon resonance

represents a single carbon (relative intensity). Infrared spectra were recorded on NaCl plates prepared by depositing a solution of the sample on the NaCl plate in an appropriate, volatile solvent (typically $CHCl_3$) followed by evaporation of the solvent. Only diagnostic bands (OH, NH and CN stretching frequencies) are reported. High resolution mass spectra (HRMS) was obtained using electron impact (EIMS, 70 eV) or chemical ionization (CIMS, 140 eV) mode of ionization on a double focusing mass spectrometer, or on a quadrupolar time-of-flight (Q-TOF) mass spectrometer in either LC-electrospray (ESI-LC/MS) or atmospheric pressure chemical ionization (APCI) positive ion mode, as noted. For ESI-LC/MS, a 10 − 90% gradient CH_3CN (aqueous) solvent system was employed, 0.5 mL/min flow rate on a C_{18} column (5 μm, 4.6 i.d. × 50 mm) with nitrogen nebulizer gas, source temperature of 150 °C, desolvation temperature of 250 °C, capillary voltage of 1.6 kV, cone voltage of 38−48 V (ramp). Flash chromatography was performed on silica gel-60 (43−60 μm).[22] Optical rotation ($[\alpha]_D^{25}$) concentrations *c* are given in grams per 100 mL. Library synthesis was carried out with MiniBlock and MiniBlock XT parallel synthesis systems. The following solvents were freshly distilled immediately prior to use: THF distilled from sodium/benzophenone, methanol distilled from magnesium/iodide, and CH_2Cl_2 distilled from calcium hydride. Other commercially available starting materials and anhydrous solvents (DMF, dichloroethane, chlorobenzene) were used without further purification. The $CpCo(CO)_2$ catalyst, epoxides, propargyl bromide, all alkynes, acyl chlorides, isocyanates, and sulfonyl chlorides were commercially available. The syntheses of compounds **2a**−**2c** and **3a**−**3b** have been previously reported.[2]

Representative Procedure A. Epoxide Opening for the Preparation of 2a−2d. (S)-5-Phenylpent-4-yn-2-ol (2a). To a stirred solution of 1-ethynylbenzene (1.0 mL, 9.10 mmol) in THF (40 mL) at −78 °C, *n*-BuLi (1.6 M in hexanes, 6.3 mL, 1.1 equiv) was added dropwise. After the mixture was stirred for 1 h at −78 °C, $BF_3 \cdot OEt_2$ (1.4 mL, 1.2 equiv) was added dropwise, and the stirring was continued for an additional 15 min. (*S*)-2-Methyloxirane (0.95 mL, 13.70 mmol, 1.5 equiv) in anhydrous THF (30 mL) was then added dropwise at −78 °C. Stirring was continued for 3 h at −78 °C; then the reaction was quenched with saturated NH_4Cl solution (120 mL). The mixture was extracted with ether (3 × 150 mL), and the combined organic layers were washed with saturated brine (150 mL), dried over sodium sulfate, and the solvent removed in vacuo. The residues were purified by flash chromatography on silica gel to afford the secondary alcohol **1a** as a white solid (hexanes/EtOAc, 4:1, R_f, 0.25; 1.179 g, 81% yield): mp 62−64 °C; $[\alpha]_D^{25}$ +13.9 (*c* = 0.7, $CHCl_3$); IR (NaCl) 3342 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.44 (m, 2H), 7.29−7.32 (overlapped, 3H), 4.07 (ddq, *J* = 6.8, 5.2, 6.0 Hz, 1H), 2.64 (dd, J_{AB} = 16.5, *J* = 5.2 Hz, 1H), 2.57 (dd, J_{AB} = 16.5 Hz, *J* = 6.8 Hz, 1H), 1.85 (br s, O*H*), 1.34 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.6 (2C), 127.8, 128.2 (2C), 123.4, 86.5, 82.7, 66.4, 29.8, 22.3; CIMS (NH_3), *m*/*z* (%) 160 ($[M]^+$, 1), 131 (30), 115 (33), 83 (100), 69 (55); HRMS calcd for $C_{11}H_{13}O$ 161.0966 (APCI) *m*/*z* 161.0963 (M + H).

Representative Procedure B. Propargylation of Chiral Secondary Homopropargyl Alcohols (2 → 3, 3a−3d). (*S*)-4-(Prop-2-ynyloxy)pent-1-ynylbenzene (3a). A solution of (*S*)-5-phenylpent-4-yn-2-ol (**2a**, 0.237 g, 1.48 mmol) in THF (10 mL) was added dropwise into a suspension of sodium hydride (40.0 mg, 1.1 equiv) in THF (5 mL) at 0 °C. After the mixture was stirred for 1 h at 0 °C, a solution of propargyl bromide (0.529 g, 4.44 mmol, 3.0 equiv) in THF (5 mL) was added dropwise. The solution was allowed to warm to rt, and stirring was continued for 36 h. The reaction was quenched with water (30 mL), and the reaction mixture was extracted with ether (3 × 50 mL). The combined organic layers were washed with saturated brine (80 mL) and dried over sodium sulfate, and then the solvent removed in vacuo. The residues were purified by flash chromatography on silica gel to afford the propargyl ether **3a** as a light yellow oil (hexanes/EtOAc, 4:1, R_f, 0.73; 0.226 g, 77% yield): $[\alpha]_D^{25}$ −21.3 (*c* 2.2, $CHCl_3$); IR (NaCl) 3292, 2119, 758, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.40 (m, 2H), 7.24−7.28 (overlapped, 3H), 4.24 (ABX, J_{AB} = 15.6, J_{AX} = J_{BX} = 2.2 Hz, 2H), 3.90 (ddq, *J* = 7.0, 4.8, 6.4 Hz, 1H), 2.70 (dd, J_{AB} = 16.5, J_{BX} = 4.8 Hz, 1H), 2.53 (dd, J_{AB} = 16.5, J_{AX} = 7.0 Hz, 1H), 2.42 (t, *J* = 2.2 Hz, 1H), 1.33 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3 (2C), 128.0 (2C), 127.6, 123.4, 86.2, 82.0, 79.7, 74.0, 73.0, 55.8, 26.6, 19.3; CIMS (NH_3), *m*/*z* (%) 199 ($[M + 1]^+$, 43), 198 ($[M]^+$, 36), 197 (28), 183 (22), 155 (27), 154 (77), 143 (60), 128 (28), 115 (64), 105 (67), 83 (100); HRMS (CI, NH_3) *m*/*z* 198.1046 ($[M]^+$, 36%), calcd for $C_{14}H_{14}O$ 198.1045.

Representative Procedure C. Alkynyl Mannich Reactions (3 + 4 → 5, 5a−5d). (*S*)-3-((4-Methoxybenzyl)(4-(5-phenylpent-4-yn-2-yloxy)but-2-ynyl)amino)propanenitrile (5a). A solution of 3-(4-methoxybenzylamino)-propanenitrile (**4**, 96.0 mg, 0.5 mmol, 1.0 equiv), paraformaldehyde (61.0 mg), and *p*-toluenesulfonic acid (1.0 equiv, 96.0 mg) in dichloromethane (2 mL) was sealed in a 10 mL microwave reaction vessel (CEM Corporation) and purged with nitrogen. The reaction was heated to 60 °C with stirring for 8 h, then the solvent was removed in vacuo to afford a crude residue. (*S*)-(4-(Prop-2-ynyloxy)pent-1-ynyl)benzene (**3a**, 100.0 mg, 1.0 equiv), dissolved in THF/DMF (2:1, 3 mL), was then added into the resulting crude residue, followed by the addition of CuBr (36.0 mg, 0.5 equiv). The mixture was heated with stirring to 70 °C for 48 h. The reaction was quenched with water (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated brine and dried over sodium sulfate, and then the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel to yield dialkynyl nitrile **5a** as a yellow oil (hexanes/EtOAc, 3:1, R_f, 0.30; 153.2 mg, 76% yield): $[\alpha]_D^{25}$ −11.3 (*c* 3.46, $CHCl_3$); IR (NaCl) 2931, 1612, 1512, 1247, 1104, 1035, 758, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.25−7.21 (overlap, 5H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.28 (ABX_2, J_{AB} = 15.8 Hz, J_{AX} = $J_{AX'}$ = 1.8 Hz, 1H), 4.27 (ABX_2, J_{AB} = 15.8 Hz, J_{BX} = $J_{BX'}$ = 1.8 Hz, 1H), 3.88 (ddq, *J* = 7.1, 4.9, 6.2 Hz, 1H), 3.74 (s, 3H), 3.57 (s, 2H), 3.36 (br s, 2H), 2.81 (t, *J* = 5.8 Hz, 2H), 2.70 (dd, J_{AB} = 16.6, J_{AX} = 4.9 Hz, 1H), 2.53 (dd, J_{AB} = 16.6, J_{BX} = 7.1

Hz, 1H), 2.41 (t, $J = 5.8$ Hz, 2H), 1.32 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 131.5 (2C), 130.0 (2C), 129.7, 128.2 (2C), 127.7, 123.5, 118.6, 113.7 (2C), 86.5, 82.2, 81.9, 80.0, 73.0, 57.1, 56.2, 55.1, 48.4, 41.5, 26.8, 19.5, 16.6; HRLCMS (ESI) *m/z* 401.2235 ($[M + 1]^+$, 15%) calcd for $C_{26}H_{29}N_2O_2$ 401.2229.

Representative Procedure D. Microwave-Promoted Intramolecular Cobalt-Catalyzed [2 + 2 + 2] Cyclization (5 → 6, 6a−6d). (*S*)-2-(4-Methoxybenzyl)-8-methyl-6-phenyl-2,3,4,7,8,10-hexahydro-1*H*-pyrano[4,3-*c*][1,6]naphthyridine (6a). A solution of dialkynylnitrile **5a** (26.0 mg, 0.065 mmol) in chlorobenzene (3 mL) was added into a 10 mL microwave reaction vessel (CEM Corporation), followed by addition of catalyst $CpCo(CO)_2$ (2 μL, 0.012 mmol, 0.2 equiv). The reaction vessel was sealed and purged with nitrogen; then the resulting solution was subjected to microwave irradiation at 300 W, 180 °C, for 15 min. The volatile components were removed in vacuo, and the residue was purified by flash chromatography on silica gel to yield cyclization product **6a** (hexanes/EtOAc, 1:1, R_f, 0.25; 21.0 mg, 81% yield) as a brown solid: mp 110 °C; $[\alpha]_D^{25}$ +100.8 (*c* 1.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.31 (overlap, 5H), 7.27 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 4.71 (d, $J_{AB} = 16.4$ Hz, 1H), 4.57 (d, $J_{AB} = 16.4$ Hz, 1H), 3.79 (s, 3H), 3.67 (s, 2H), 3.56 (ddq, $J = 10.4$, 2.0, 6.0 Hz, 1H), 3.44 (br s, 2H), 3.02 (dd, $J = 6.0$, 5.6 Hz, 2H), 2.82 (ddd, $J = 11.6$, 5.6, 5.6 Hz, 1H), 2.76 (ddd, $J = 11.6$, 6.0, 6.0 Hz, 1H), 2.63 (dd, $J_{AB} = 16.4$, $J_{AX} = 10.4$ Hz, 1H), 2.49 (dd, $J_{AB} = 16.4$, $J_{BX} = 2.0$ Hz, 1H), 1.25 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 156.3, 151.6, 140.6, 140.1, 130.3 (2C), 130.1, 129.0 (2C), 128.4 (2C), 128.0, 124.3, 124.2, 113.9 (2C), 70.6, 65.4, 62.1, 55.4, 51.5, 50.0, 34.4, 32.7, 21.5; HRLCMS (ESI) *m/z* 401.2216 ($[M + 1]^+$, 48%) calcd for $C_{26}H_{29}N_2O_2$ 401.2229.

Representative Procedure E. Deprotection of PMB Group (6 → 1, 1a−1d). (*S*)-8-Methyl-6-phenyl-2,3,4,7,8,10-hexahydro-1*H*-pyrano[4,3-*c*][1,6]naphthyridine (1{*1*}). To a solution of the *p*-methoxybenzyl-protected 5,6,7,8-tetrahydro-1,6-naphthyridine **6a** (800 mg, 2.0 mmol) in MeOH (10 mL), an equal weight of 20% Pd−C and HOAc (6 μL, 5 mol%) were added. The solution was stirred under a hydrogen atmosphere at rt, monitored by TLC. After completion of the reaction (12 h), the catalyst was removed by filtration through a short silica pad, eluting with MeOH (50 mL). The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel to afford **1**{*1*} as a sticky brown oil (CH_2Cl_2/MeOH, 5:1, R_f, 0.35; 398.6 mg, 71% yield): $[\alpha]_D^{25}$ +102.0 (*c* 0.60, $CHCl_3$); IR (NaCl) 2931, 1569, 1426, 1127, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.32 (overlap, 5H), 4.76 (d, $J_{AB} = 16.4$ Hz, 1H), 4.62 (d, $J_{AB} = 16.4$ Hz, 1H), 4.58 (br, NH), 3.97 (d, $J_{AB} = 16.4$ Hz, 1H), 3.89 (d, $J_{AB} = 16.4$ Hz, 1H), 3.59 (br dq, $J = 10.6$, 6.0 Hz, 1H), 3.30 (m, 2H), 3.08 (dd, $J = 5.8$, 5.6 Hz, 2H), 2.65 (dd, $J_{AB} = 16.2$, $J_{AX} = 10.2$ Hz, 1H), 2.51 (br d, $J_{AB} = 16.2$ Hz, 1H), 1.27 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 157.1, 148.6, 142.5, 138.9, 128.6 (2C), 128.2, 128.0 (2C), 125.8, 121.0, 70.3, 64.6, 41.3, 40.9, 33.8, 28.7, 20.2; HRLCMS (ESI) *m/z* 281.1640 ($[M + 1]^+$, 100%) calcd for $C_{18}H_{21}N_2O$ 281.1654.

Preparation of Urea Sublibrary 7 (1 → 7). A MiniBlock XT reaction block hosting 48 reactor-tubes was used for library preparation. Stock solutions of scaffolds **1**{*1*−*4*} in anhydrous dichloromethane were prepared (5 mg/mL). Each scaffold was treated with eight isocyanates (Chart 1) as follows: 3.0 mL of the scaffold stock solution (15.0 mg, 1.0 equiv) and isocyanate (1.1 equiv) were placed into the reactor tube. The 4 × 8 reaction vessels in the Miniblock synthesizer were then heated to 65 °C for 4 h with stirring. PS-Trisamine (1.0 equiv, 0.13 g, Argonaut Technologies Inc., P/N 800229; lot no. 03307; 0.446 mmol/g) was then added into each reaction tube, and the reaction mixture was stirred at 50 °C overnight (12 h). The PS-trisamine resin was removed by filtration, and the filtrate was collected and transferred into a high throughput centrifugal evaporator (Genevac) to evaporate to dryness. The crude residue of each reaction was purified by mass-directed LCMS to provide the library members **7**{*1*−*4*,*1*−*8*}.

Representative of Urea Sublibrary. (*S*)-Methyl3-methyl-2-((*S*)-8-methyl-6-phenyl-2,3,4,7,8,10-hexahydro-1H-pyrano[4,3-c][1,6]naphthyridine-2-carboxamido)butanoate (**7**{*1*,*3*}, 78%). $[\alpha]_D^{25}$ +66.6 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.44 (overlap, 5H), 5.08 (d, $J = 8.0$ Hz, NH), 4.84 (d, $J_{AB} = 16.4$ Hz, 1H), 4.69 (d, $J_{AB} = 16.4$ Hz, 1H), 4.44 (overlap, 3H), 3.72 (s, 3H), 3.77−3.67 (overlap, 2H), 3.60 (m, 1H), 3.10 (ddd, $J_{AB} = 16.4$, $J = 5.6$, 5.4 Hz, 1H), 3.05 (ddd, $J_{AB} = 16.4$, $J = 5.6$, 5.4 Hz, 1H), 2.66 (dd, $J_{AB} = 16.6$, $J = 10.4$ Hz, 1H), 2.66 (dd, $J_{AB} = 16.6$, $J = 2.0$ Hz, 1H), 2.14 (m, 1H), 1.27 (d, $J = 6.0$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 157.4, 156.8, 151.0, 141.0, 139.9, 129.1 (2C), 128.6 (2C), 128.3, 125.3, 123.0, 70.7, 65.4, 58.8, 52.4, 42.1, 41.8, 34.5, 32.3, 31.6, 21.6, 19.3, 18.3; HRLCMS (ESI) *m/z* 438.2398 ($[M + 1]^+$, 100%) calcd for $C_{25}H_{32}N_3O_4$ 438.2393.

Preparation of Amide Sublibrary 8 (1 → 8). A MiniBlock synthesizer hosting 48 reactor tubes was used for library preparation. Stock solutions of scaffolds **1**{*1*−*4*} in anhydrous dichloromethane were prepared (5 mg/mL). Each scaffold was treated with eight acid chlorides (Chart 2) as follows: 3.0 mL of the scaffold stock solution (15.0 mg, 1.0 equiv), acid chloride (1.3 equiv), and PS-DMAP resin (1.7 equiv, 0.23 g, Argonaut Technologies Inc., P/N 800290; lot no. 02899; 0.35 mmol/g). The 4 × 8 reaction vessels in the Miniblock synthesizer were placed in a mechanical shaker for 10 h at rt. The PS-DMAP resin was removed by filtration, and the filtrate was collected and transferred into a high-throughput centrifugal evaporator (Genevac) to evaporate to dryness. The crude residue of each reaction was then purified by LCMS to provide the library members **8**{*1*−*4*,*1*−*8*}.

Representative of Amide Sublibrary. (*S*)-Cyclopropyl(8-methyl-6-(phenoxymethyl)-3,4,7,8-tetrahydro-1H-pyrano[4,3-c][1,6]naphthyridin-2(10H)-yl)methanone (**8**{*2*,*8*} 72%): $[\alpha]_D^{25}$ +33.0 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, rotamer ratio = 3:1 determined by integration) δ 7.27 (dd, $J = 8.8$, 7.2 Hz, 2H, major and minor rotamers), 6.98 (br d, $J = 8.8$ Hz, 2H, major and minor rotamers), 6.94 (br t, $J = 7.2$ Hz, 1H, major and minor rotamers), 5.10 (s, 2H, major and minor rotamers), 4.78 (d, $J_{AB} = 16.4$ Hz, 1H, major and minor rotamers), 4.64 (d, $J_{AB} = 16.4$ Hz, 1H, major and

minor rotamers), 4.57 (d, J_{AB} = 17.6 Hz, 1H, major and minor rotamers), 4.47 (d, J_{AB} = 17.6 Hz, 1H, major and minor rotamers), 4.02 (ddd, J_{AB} = 14.2, J = 8.2, 5.2 Hz, 0.75 H, major rotamer), 3.91 (ddd, J_{AB} = 14.2, J = 6.4, 5.2 Hz, 0.75 H, major rotamer), 3.72 (m, 0.75 H, major rotamer), 3.68 (overlap, 0.5 H, minor rotamer), 3.49 (br m, 0.25 H, minor rotamer), 3.08 (br t, J = 5.2 Hz, 1.5 H, major rotamer), 3.04 (br t, 0.5 H, minor rotamer), 2.94 (br dd, J = 7.6, 6.8 Hz, 0.5 H, minor rotamer), 2.83 (br d, J_{AB} = 16.4 Hz, 0.75 H, major rotamer), 2.67 (dd, J_{AB} = 16.4 Hz, J = 10.4 Hz, 0.75 H, major rotamer), 2.67 (overlap, 0.25 H, minor rotamer), 1.84 (m, 0.75 H, major rotamer), 1.80 (m, 0.25 H, minor rotamer), 1.33 (d, J = 6.0, 3H, major and minor rotamers), 1.00 (dd, J = 2.8, 2.8 Hz, 2H, major and minor rotamers), 0.81 (dd, J = 7.2, 3.0 Hz, 2H, major and minor rotamers); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 158.8, 151.8, 150.3, 141.6, 129.7 (2C), 127.2, 124.5, 121.3, 114.9 (2C), 70.4, 70.2, 65.3, 43.1, 41.0, 32.8, 31.9, 21.7, 11.4, 7.8 (2C); HRLCMS (ESI) m/z 379.2021 ($[M + 1]^+$, 60%) calcd for $C_{23}H_{27}N_2O_3$ 379.2022.

Preparation of Sulfonamide Sublibrary 9 (1 → 9). A Miniblock XT miniblock hosting 48 reactor tubes was used for library preparation. Stock solutions of scaffolds **1**{*1*−*4*} in anhydrous dichloromethane were prepared (5 mg/mL). Each scaffold was treated with eight sulfonyl chlorides (Chart 3) as follows: 3.0 mL of the scaffold stock solution (15.0 mg, 1.0 equiv), sulfonyl chloride (1.0 equiv), and triethylamine (3.0 equiv, 22 μL) were placed into the reactor tube. The 4 × 8 reaction vessels in the Miniblock synthesizer were then heated to 55 °C for 10 h with stirring. The reactor tubes were then placed into a high-throughput centrifugal evaporator (Genevac) to evaporate to dryness. The crude residue of each reaction was then purified by LCMS to provide the library members **9**{*1*−*4*,*1*−*8*}.

Representative of Sulfonamide Sublibrary. (*S*)-2-(3,5-Dimethylisoxazol-4-ylsulfonyl)-8-methyl-6-phenyl-2,3,4,7,8,10-hexahydro-1*H*-pyrano[4,3-*c*][1,6]naphthyridine (9{1,5} 66%): $[\alpha]_D^{25}$ +33.2 (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.46−7.38 (overlap, 5H), 4.76 (d, J_{AB} = 16.4 Hz, 1H), 4.66 (d, J_{AB} = 16.4 Hz, 1H), 4.19 (AA′, 2H), 3.62 (ddd, J = 12.0, 6.0, 6.0 Hz, 1H), 3.65−3.59 (overlap, 1H), 3.54 (ddd, J = 12.0, 6.0, 6.0 Hz, 1H), 3.14 (dd, J = 6.0, 6.0 Hz, 2H), 2.71 (s, 3H), 2.70 (dd, J_{AB} = 16.6, J = 10.0 Hz, 1H), 2.56 (dd, J_{AB} = 16.6, J = 1.8 Hz, 1H), 2.44 (s, 3H), 1.30 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 158.1, 157.5, 149.7, 140.9, 139.5, 129.0 (2C), 128.63 (2C), 128.56, 125.6, 120.8, 114.2, 70.8, 65.1, 43.3, 43.0, 34.4, 32.3, 21.6, 13.2, 11.5; HRLCMS (ESI) m/z 440.1660 ($[M + 1]^+$, 100%) calcd for $C_{23}H_{26}N_3O_4S$ 440.1664.

General Procedure A: Preparation of Tertiary Amines. Reductive Amination (1 → 10). A solution of scaffold **1**{*1*−*4*} (13.0−14.0 mg, 1.0 equiv) in MeOH (1.5 mL) was placed in a reaction vial. To this solution was added aldehyde (5.0 equiv) in MeOH (0.5 mL), followed by the addition of $NaBH_3CN$ (5.0 equiv). The pH of the reaction was adjusted to 6 by addition of HOAc. The reaction mixture was stirred at rt overnight (12 h), then quenched with saturated $NaHCO_3$ solution (5.0 mL), and extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with brine and then dried over Na_2SO_4. The solvent was removed in vacuo, and the crude residue was purified by flash chromatography on silica gel to give the desired product **10a**−**10e** (Table 1).

Representative of Tertiary Amine: (8*S*)-2-((6,6-Dimethylbicyclo[3.1.1]hept-2-en-3-yl)methyl)-8-methyl-6-phenyl-2,3,4,7,8,10-hexahydro-1*H*-pyrano[4,3-*c*][1,6]naphthyridine (10b). This was prepared according to General Procedure A, beginning with **1**{*1*} (14.0 mg, 0.050 mmol), (1*R*)-(−)-myrtenal (38 μl, 0.250 mmol, 5.0 equiv), and $NaBH_3CN$ (16.0 mg, 0.250 mmol, 5.0 equiv). Purification by flash chromatography on silica gel gave **10b** as a sticky yellow oil (hexanes/EtOAc, 1:1, R_f, 0.67; 16.1 mg, 78% yield): $[\alpha]_D^{25}$ +68.0 (*c* 0.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.32 (overlap, 5H), 5.45 (br s, 1H), 4.75 (d, J_{AB} = 16.5 Hz, 1H), 4.61 (d, J_{AB} = 16.5 Hz, 1H), 3.57 (br m, 1H), 3.39 (d, J_{AB} = 15.8 Hz, 1H), 3.33 (d, J_{AB} = 15.8 Hz, 1H), 3.12−2.97 (overlap, 4H), 2.83 (ddd, J = 11.3, 5.6, 5.6 Hz, 1H), 2.71 (ddd, J = 11.3, 5.8, 5.8 Hz, 1H), 2.63 (dd, J_{AB} = 15.8, J_{AX} = 10.6 Hz, 1H), 2.49 (br d, J_{AB} = 15.8 Hz, 1H), 2.38 (ddd, J = 8.4, 5.5, 5.5 Hz, 1H), 2.34−2.20 (overlap, 3H), 2.09 (br s, 1H), 1.26 (d, J = 6.0 Hz, 3H), 1.25 (s, 3H), 1.12 (d, J = 8.4 Hz, 1H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 151.8, 145.6, 140.6, 140.2, 129.1 (2C), 128.5 (2C), 128.1, 124.6, 124.4, 120.7, 70.7, 65.5, 64.2, 51.8, 50.5, 44.5, 41.2, 38.2, 34.5, 32.6, 32.2, 31.6, 26.4, 21.6, 21.3; HRLCMS (ESI) m/z 415.2780 ($[M + 1]^+$, 100%) calcd for $C_{28}H_{35}N_2O$ 415.2749.

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Supporting Information Available. Full characterization and ^{1}H and ^{13}C NMR spectra of all new compounds leading to library precursors, full details of the library characterization, and ^{1}H and ^{13}C NMR spectra of select library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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