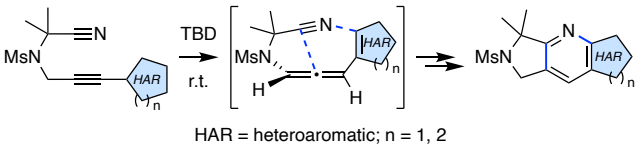
Intramolecular Cyclization of Alkynylheteroaromatic Substrates Bearing a Tethered Cyano Group: A Strategy for Accessing Fused Pyridoheterocycles

Niklas Kraemer, Erin M. Eason, and Thomas R. Hoye*

Department of Chemistry, 207 Pleasant St. SE, University of Minnesota, Minneapolis, Minnesota 55455 USA

Supporting Information Placeholder

ABSTRACT: Heterocyclic substrates containing a conjugated alkyne and a pendant nitrile were shown to cyclize in an overall tetradehydro-Diels–Alder reaction to give products in which the initial heterocycle bears a newly fused pyridine ring. Base-promoted tautomerization of the alkyne to its isomeric allene allows this process to occur at ambient temperature. DFT studies support many of the mechanistic interpretations of the overall results.



INTRODUCTION

Heteroaromatic moieties are valuable building blocks in the pharmaceutical industry. When incorporated into ligands, they reduce conformational freedom and provide anchor points for binding to biomacromolecules. Representative drug candidates or approved pharmaceuticals that contain a fused pyridoheterocyclic substructure are shown in Figure 1a. The immunomodulatory agent sotirimod (**1**) [1] contains a 1,5-napthyridine (pyridopyridine) heteroaromatic core. Anagliptin (**2**, Suiny®),[2] a DPP-4 inhibitor approved in Japan to treat type 2 diabetes, features a pyridopyrazole moiety. The pyridoimidazole derivative sulmazole (**3**, Vardax®)[3] exhibits favorable vasodilator effects. Sitravatinib (**4**),[4] a receptor tyrosine kinase inhibitor currently undergoing late stage clinical trials, contains a central pyridothiophene core. New methods for constructing compounds with pyridine rings fused to another heterocycle are of interest.

Previously we have reported the net-[4 + 2]-cycloaddition of an in situ-generated allenyl arene with a pendant alkyne or nitrile, which generates a naphthalene or quinoline derivative.[5] We wanted to expand the types of substrates amenable for this cyclization reaction with the goal of producing useful classes of heterocyclic compounds by a novel and complementary method. More specifically, if the C_{sp2}=C_{sp2} bond endocyclic to the aromatic ring bearing the alkyne in a substrate is within a heteroaromatic ring (HAR), such as the 2-pyridine **5a**, a wider variety of heterocyclic products can be envisioned. We anticipate that, as with the previous study, we would be able to isomerize the alkyne in substrates such as **5a** to their tautomeric allenes (cf. **6a**) upon treatment with base (Figure 1b). These allenyl HARs, in turn, should undergo the net-[4 + 2]-cycloaddition to engage the pendant nitrile and produce pyridine derivatives that have incorporated the HAR (cf. **7a**), now fused to the newly created pyridine ring.

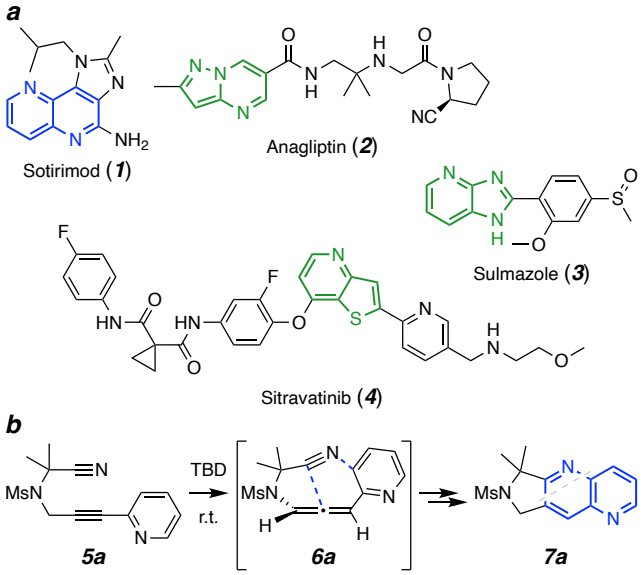


Figure 1. (a) Biologically significant compounds containing pyrido-fused heteroaromatics. (b) Current work examining the cyclization of allenyl heteroaromatics with pendant nitriles.

RESULTS AND DISCUSSION

The alkynyl HAR substrates **5** feature a common three-atom linker with a central methanesulfonamide and gem-dimethyl moiety adjacent to the pendant nitrile. This design leverages the Thorpe–Ingold (or gem-disubstituent) effect, likely increasing the rate of cyclization.[6] The various HAR substrates were synthesized from the common alkyne precursor **8** by a Sonogashira reaction with a variety of iodo- or bromo-HARs **9a-j** (Figure 2a).[7] The alkynes **5a-j** are thermally stable at, and well past, room temperature. For example, when **5f** was heated even to ca. 250 °C overnight in the absence of

added base, no thermal tetradehydro-Diels–Alder reaction was observed (and a substantial amount of **5f** was recovered).[8] When these alkynyl-HARs were exposed to the non-nucleophilic base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) at ambient temperature, products **7a-j** were formed in very good to excellent yields (Figure 2b). This suggested that intermediate allenes **6a-j** were being generated, thereby enabling engagement with the pendant nitrile and cycloisomerization to the dearomatized species **10a-j**. Final tautomerization would then lead to **7a-j**.

Substrates **5a-d** all contain a terminal pyridine ring. Cyclizations of **5a** and **5d** to give the pyridopyridines **7a** and **7d** proceeded very efficiently (85% and 88% yield, respectively). The 3-alkynylpyridine substrate **5b** contains two different aromatic carbon atoms, C2 and C4 in the 3-pyridinyl moiety, that could participate in the cyclization. Both possible regioisomers, the 1,6-naphthyridine **7b-maj** and the 1,8-naphthyridine **7b-min** were formed (ca. 7:3 ratio) in a combined near-quantitative yield. We also observed a small preference in the cyclization of the 2-fluoro-4-pyridinyl substrate **5c**. Isomer **7c-maj**, which arises from cyclization upon C3 *ortho* to F, was slightly favored (ca. 7:4 ratio) over cyclization to C5 leading to **7c-min**.

Additional HAR moieties were examined to demonstrate some of the generality of this approach for synthesizing interesting heterocyclic skeletons. For example, treatment of the 2-alkynylpyrazine **5e** with TBD resulted in the formation of the pyrido[2,3-*b*]pyrazine derivative **7e** in 75% yield within an hour at room temperature (75% on a 1 mmol scale). The 2-alkynylthiophene precursor **5f** likewise cyclized rapidly to give the pyridothiophene **7f** in excellent yield. An analogous cyclization of this substrate was performed in deuterated chloroform, resulting in the partial deuteration of **7f** shown in Figure 2c. A control experiment in which all-protio **7f** was incubated in $CDCl_3$ containing TBD showed no proton/deuterium exchange of the cyclized product after 24 h. The presence of deuterium at C8 in **7f** results from the initial base-mediated tautomerization of the alkyne to the allene via the ion pair **5f**$^-$•**TBD**$^+$. During the rearomatization process of the intermediate **10f** the methylene carbon is reestablished whereby either a protium or deuterium is incorporated from another molecule of **TBDH**/**D**$^+$. The imidazole derivative **5g**, was the slowest substrate to react, furnishing the pyridoimidazole product **7g** over the course of three weeks at room temperature. Presumably the electron-rich imidazolyl group slows the rate of the initial deprotonation by TBD (cf. **5f** to **5f**$^-$).

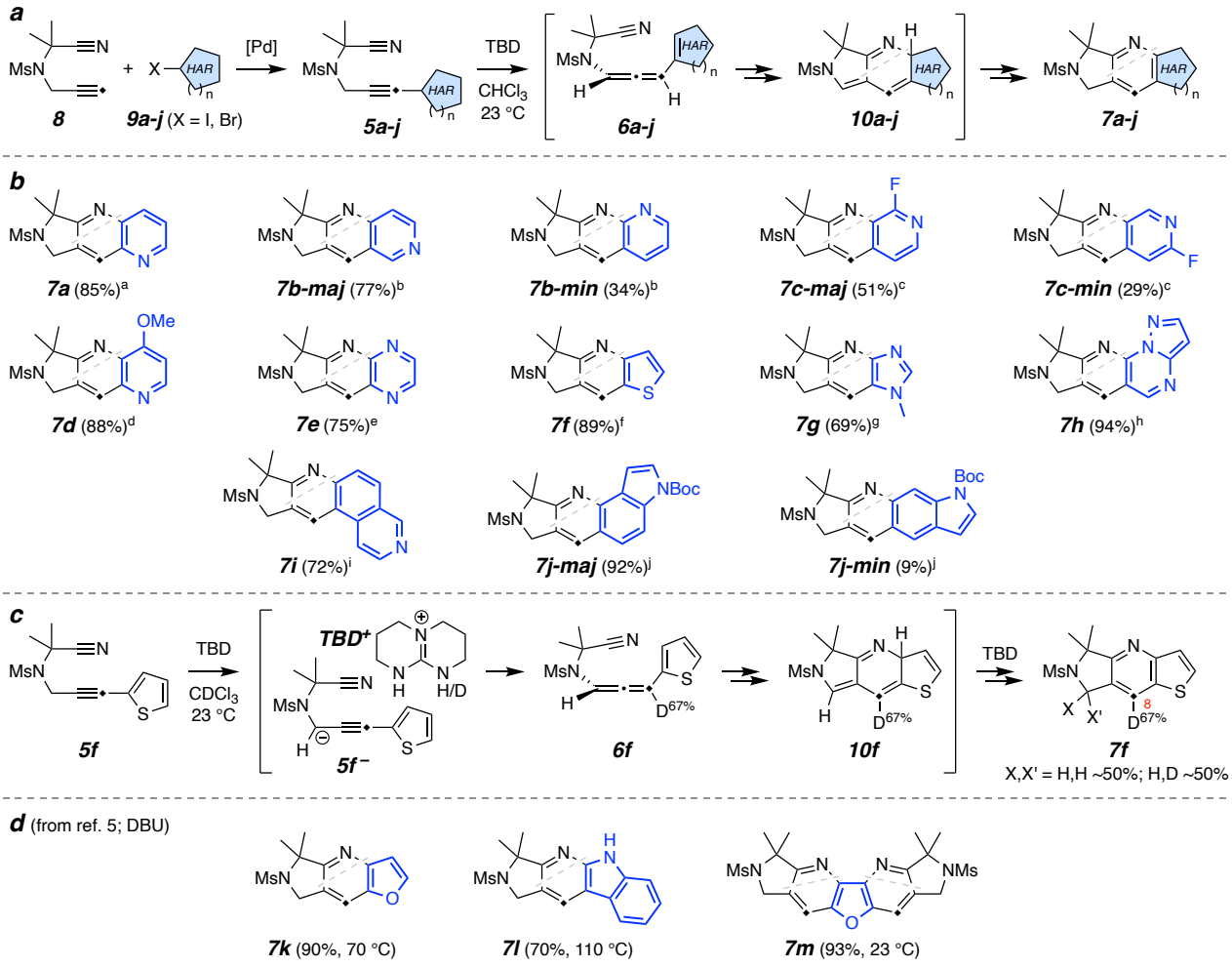


Figure 2. (a) Synthesis and cyclization of alkynyl heteroaromatic substrates **5a-j** to produce pyrido-fused heterocycles **7a-j**. [**5a-j**: **a**, 2-pyridinyl; **b**, 3-pyridinyl; **c**, 2-fluoro-4-pyridinyl; **d**, 4-methoxy-2-pyridinyl; **e**, 2-pyrazinyl; **f**, 2-thiophenyl; **g**, 1-methyl-2-imidazolyl; **h**, 6-pyrazolo[1,5-*a*]pyrimidinyl; **i**, 5-isoquinolinyl; **j**, *N*-Boc-5-indolyl] (b) Structure and isolated yield of **7a-j**. [a]24 h. [b]2.5 h. [c]2 h. [d]2.5 h. [e]1 h; 75% on a 1 mmol scale, 12 min. [f]1 h. [g]22 d. [h]24 h. [i]12 h. [j]24 h. (c) Deuterium incorporation observed in the cyclization of **5f**. (d) Additional HAR compounds reported in ref. 5.

Several substrates containing terminal bicyclic HARs were also studied. The pyrazolo[1,5-*a*]pyrimidine **5h** cyclized to give a single regioisomer **7h** in excellent yield. DP4+, a probability analysis that compares calculated NMR chemical shifts of all possible isomers with the experimentally obtained ^{1}H and ^{13}C shifts, was performed to assign its structure as the indicated angular cyclization regioisomer over the alternative linear product [see Supporting Information (SI) for details].[9] The 5-alkynylisoquinoline substrate **5i** underwent the net-[4 + 2]-cycloaddition to give **7i** in 72% yield. A second possible regioisomer made by cyclization onto the ring fusion carbon adjacent to the alkyne was not observed; this would have led to a dearomatized product. Finally, the indole derivative **5j** cyclized to give two regioisomers, **7j-maj** and **7j-min**, in near-quantitative yield in an ca. 10:1 ratio. The regioselectivity observed in this case presumably reflects a higher degree of aromaticity within the pyrrole substructure that can be maintained in the rate-limiting step for formation of **7j-maj**.

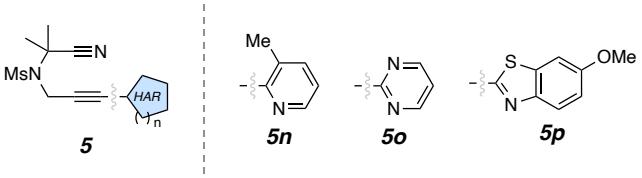


Figure 3. Substrates that failed to cyclize.

We looked at several substrates that were blocked from undergoing the final rearomatization process because of the absence of the sp^{3}CH proton in **10** (Figure 2a). Might these give rise to products similar to **10**, thereby reflecting mechanistic overlap with the initial stages of the reaction manifold? The alkynyl HARs examined, **5n**–**5p**, are shown in Figure 3. To generate an intermediate analogous to **10** would require the nitrogen atom of the cyano group to engage either a methylated carbon atom (cf. C3 in **5n**) or a heteroatom. Upon treatment with base, each of these compounds were consumed over time but none gave rise to tractable product mixtures (see SI). The reluctance to form a N–N bond is consistent with the absence of such products in the reactions leading to **7a**,**d**,**e** (Figure 2b).

For several of the substrates (**5a-j**), we attempted to detect an intermediate allene by in situ NMR monitoring but were never successful. We had also examined **11a** in our earlier study, but the intermediate allene was not observed in that instance as well.[5] These results implied that the rate-limiting step for these reactions is generation of the allenes and not the subsequent, more rapid cyclization events.

We now report that the *p*-cyanophenyl terminated analog **11b**, *lacking the gem-dimethyl groups* present in **11a**, has allowed us for the first time to detect the intermediate allene species. The reaction of the benzonitrile derivative **11b**, when treated with ca. 0.5 equiv of TBD in benzene-d_6, was monitored by ^{1}H NMR spectroscopy (Figure 4). Interpretation of a similar experiment in CDCl3 was complicated by concomitant deuterium incorporation, a complication that was avoided using benzene-d_6 as the solvent. Minutes after adding TBD a new set of resonances had begun to emerge. Key to assigning the structure to this intermediate as the allene **12b** were the diastereotopic methylene protons (H_a and H_b) alpha to the pendant nitrile group. These showed a geminal coupling constant of J = 18.1 Hz. Additionally, the resonance for one allene proton (H_d) was clearly visible at 6.26 ppm (J = 6.0 Hz). The second allene proton (H_c) could be discerned at 6.74 ppm, overlapping with a new (non-first order) doublet of the 1,4-disubstituted benzonitrile moiety in the allene. Observation of **12b** marked the first time we could detect the transient allene intermediate prior to its cyclization. The half-life for the base-mediated alkyne to allene tautomerization was seen to be ca. 20 min under these reaction conditions. Gradually the cyclization of the allene **12b** to the quinoline derivative **13b** interceded. For example, even at just 10 minutes after adding base to the reaction mixture, resonances corresponding to the product **13b** (<1%) were first detected. A meaningful half-life for the cyclization of **12b** to **13b** could not be judged, because the product **13b** crystalized from solution as the reaction progressed, complicating the analysis.

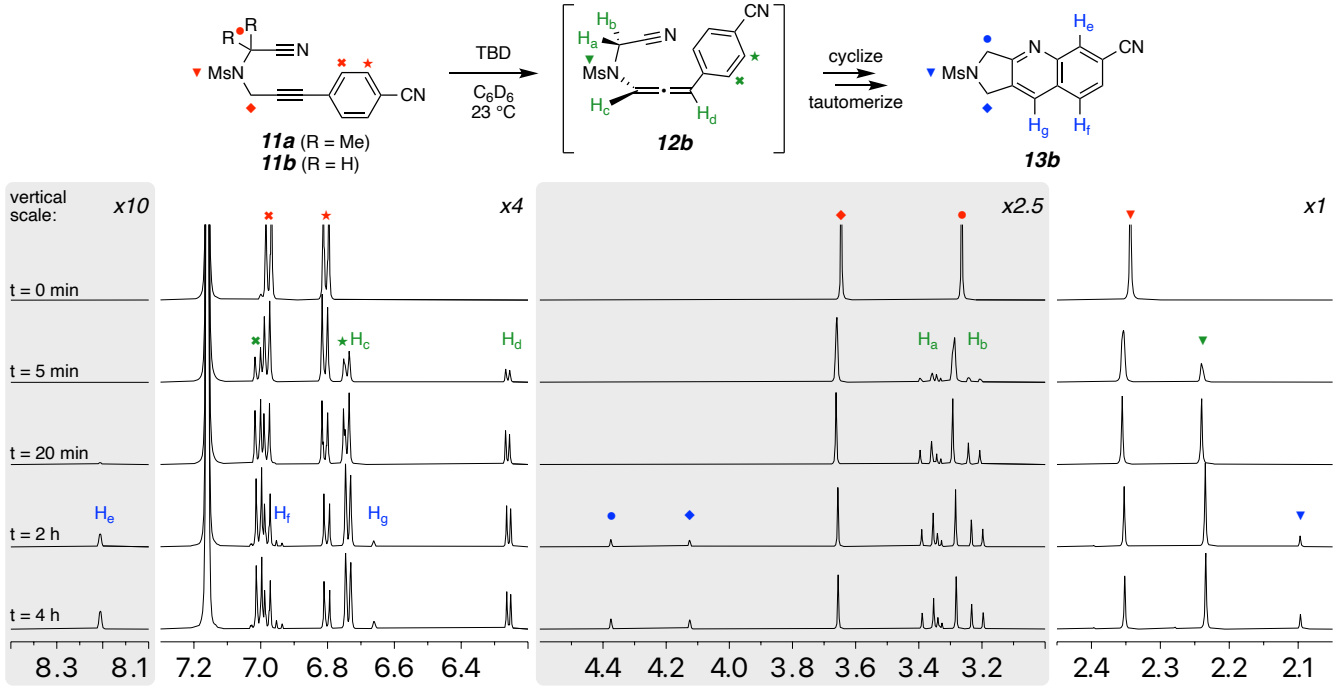


Figure 4. Cyclization of **11b** at ambient temperature via the observable allene **12b** to give the quinoline **13b** as monitored by ^{1}H NMR spectroscopy. The vertical scales of each different vertical panel has been adjusted to more easily identify the onset of appearance of resonances for **12b** and **13b**.

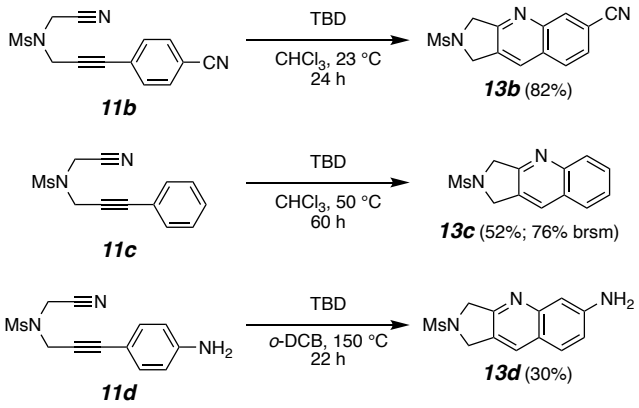


Figure 5. Cyclization of substrates lacking a gem-dimethyl moiety.

The ability to observe the allene intermediate using **11b** and not **11a** presumably reflects the slower rate of the cycloisomerization of the former because of i) the absence of the gem-dimethyl (Thorpe–Ingold) effect operative in the reaction of **11a** and ii) the need to overcome greater resonance energy present in the arene moiety compared to that in the heterocyclic analogs where, again, we were unable to detect the allene.[10]

In addition to the benzonitrile **11b**, we synthesized two other substrates lacking the geminal dimethyl groups in the linker and examined their cyclization (Figure 5). Upon treatment with base, we observed a significant decrease in reactivity at room temperature for both the phenyl analog **11c** and the electron rich aniline compound **11d** compared to the electron withdrawing benzonitrile substrate **11b**. These observations were consistent with the reactivity we previously reported for the gem-dimethylated analogs of **11b-11d** and are reflective of a slower tautomerization to the requisite allene intermediates **12**.[5]

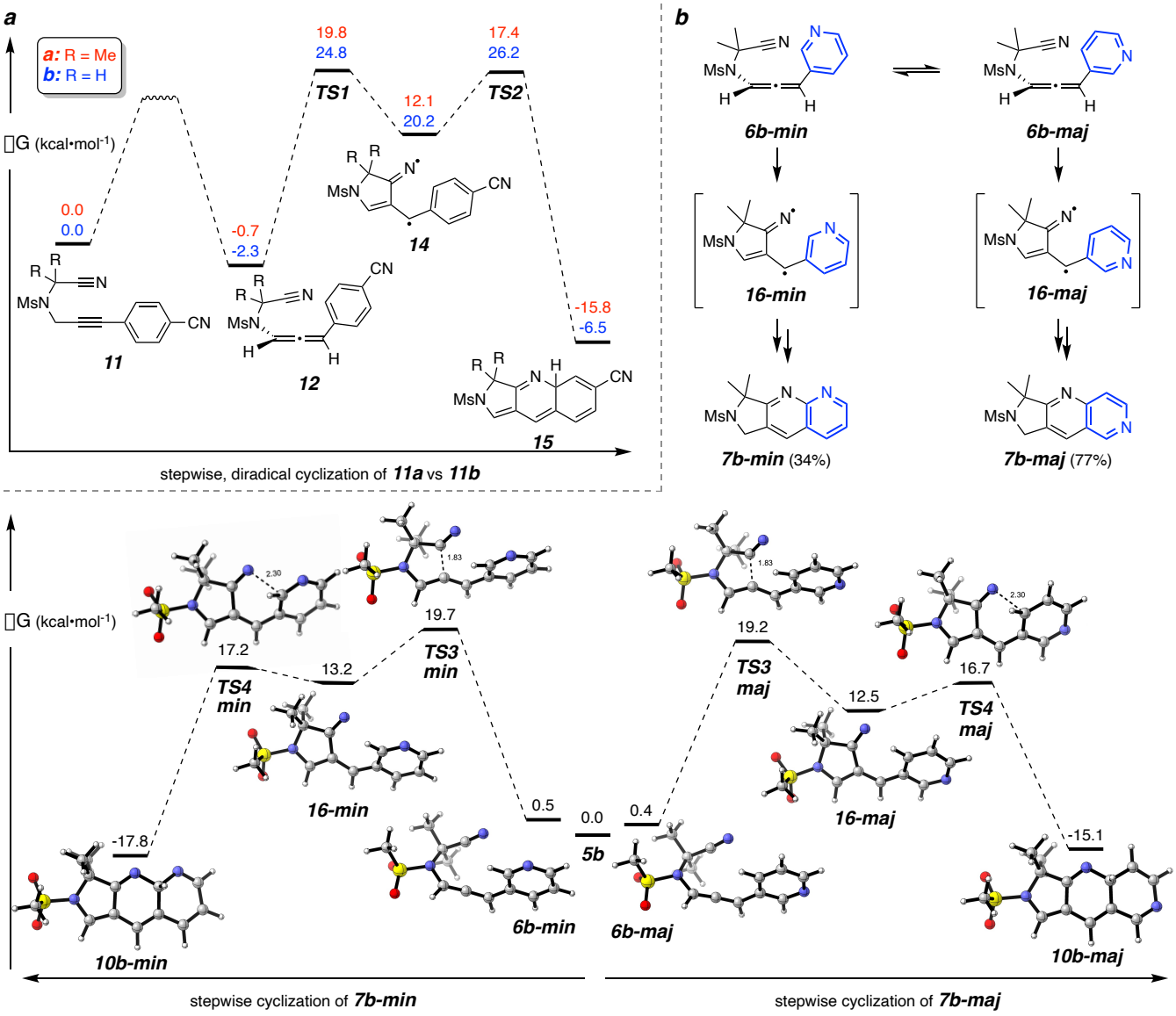


Figure 6. DFT calculations done at the [SMD(chloroform)//(U)MN15/6-311+G(d,p)//(U)MN15/6-31G(d)] level of theory. (a) Comparison of the stepwise, diradical cyclization of **11a** vs **11b**. (b) Examining the origin of regioselectivity in the cycloisomerization of the 3-alkynylpyridine **5b**, the tautomer of allenes **6b**, to give **7b-min** and **7b-maj**.

To better understand the energetic differences required to achieve cyclization of **11a** vs **11b**, we undertook density functional theory (DFT) calculations. We were unable to find a concerted transition state structure (TSS) connecting either of the allenes **12** with its corresponding dearomatized intermediate **15**.[11] Stepwise, diradical cyclizations are shown in Figure 6a [energies in kcal mol^{-1} of **11a** (R = Me) on top, in red, and **11b** (R = H) on the bottom, in blue]. We found that each of the reactive allene conformers **12a** or **12b** was slightly lower in energy than its precursor alkyne **11a** or **11b** (-0.7 or -2.3 kcal mol^{-1}, respectively). Given our inability to observe **12a**, we can surmise that the base-mediated alkyne to allene isomerization is the rate-determining step for substrates containing the gem-dimethyl linker.[12] The first bond formation step proceeds with a 20.5 vs 27.1 kcal mol^{-1} barrier to give **14a** or **14b**, respectively. Both of the TSSs **TS1** exhibit expectation values of the total spin($\langle S^2 \rangle$) of zero, i.e., containing no diradical character. This observation is indicative of a post-transition state conical intersection, where, in this case, the energy along a zwitterionic pathway is lower in energy than the diradical pathway up to and past the TSS, yet a crossover occurs after the TSS along the reaction coordinate, with the diradical product being lower in energy than the analogous zwitterion.[13] Examining the intrinsic reaction coordinate (IRC) shows a crossover of the zwitterionic to a diradical species after the TSSs (see SI for additional details). A second, exergonic bond forming step follows with a 5.3 kcal mol^{-1} barrier for the gem-dimethyl containing diradical **14a** to give the dearomatized intermediate **15a**. In contrast, the non-methylated diradical **14b**, is seen to be formed from the allene **12b** in a pre-equilibrium event; C–N bond formation is the rate-determining step leading to **15b**. The significantly higher overall barrier for **12b** to cyclize to **15b** is consistent with the observation of allene **12b** seen in Figure 4.

We also performed DFT calculations to investigate the subtle regioselectivity in the cyclization of the 3-alkynylpyridine substrate **5b** (Figure 6b).[14] The $\Delta\Delta G^{\ddagger}$ between the rate-limiting, initial bond closure via **TS3-min** and **TS3-maj** leading to the diradical **16-min** or **16-maj**, was calculated to be a mere 0.5 kcal mol^{-1}, aligning well with the experimentally observed ca. 7:3 distribution of products. The C–C bond rotation interconverting the diradical conformers **16-maj** and **16-min** was found to have a slightly higher barrier (17.4 kcal mol^{-1}) compared to either of the second bond forming TSSs (**TS4-maj** or **-min**). An analogous study of the cyclization of the 2-alkynylpyridine derivative **5a**, which experimentally showed exclusive cyclization onto C3 rather than N1 of the pyridine ring, could also be recapitulated by DFT ($\Delta\Delta G^{\ddagger}$ 2.2 kcal mol^{-1}, see Figures S10 and S11, SI).

CONCLUSION

In conclusion, we have synthesized a variety of interesting pyrido-fused HAR derivatives under ambient, basic conditions. Key to this transformation is the TBD-catalyzed tautomerization of the alkynyl-HAR substrates to give an allene intermediate, which readily undergoes a net-[4 + 2]-cycloaddition with the pendant nitrile. By removing the gem-dimethyl moiety in the methanesulfonamide linker, we were able to slow the cyclization reaction to allow for the direct observation of a steady-state level of the key allene intermediate by ^{1}H NMR analysis. DFT computational studies supported many of these mechanistic aspects.

EXPERIMENTAL SECTION

General experimental protocols. "^{1}H NMR and ^{13}C spectra were obtained on a Bruker Avance III HD 400, a Bruker Avance III HD 500, or a Bruker Avance III 500 spectrometer. Chemical shifts are referenced to TMS at δ 0.00 ppm for spectra in $CDCl_3$ solution. A non-first order multiplet (nfom), a non-first order doublet (nfod), or a non-first order triplet (nfot) in a ^{1}H NMR spectrum is specifically denoted as such. Apparent (i.e., not the actual) coupling constant for non-first order coupling is signified by J_{app}. Multiplets are listed as: chemical shift (ppm) [multiplicity, coupling constant(s) in Hz, integral value (to the nearest integer), and assignment of the substructural environment either by indicating neighboring atoms or by using the numbering of the carbon atom to which the proton is attached]. Coupling constant analysis of first-order multiplets was done using previously published methods.[15]" [16] ^{1}H NMR spectra recorded in benzene-d_6 were referenced to the shift of C_6HD_5 (d = 7.16 ppm). ^{19}F NMR spectra were referenced to an internal standard of hexafluorobenzene (d = -164.9 ppm). "^{13}C NMR chemical shifts are taken from the 1D spectrum and referenced to δ 77.16 ppm for spectra in $CDCl_3$ solution."[16] Structural assignments for **7j-maj**, **7j-min**, **13b**, and **13d** were made with the aid of additional information from HSQC and HMBC experiments.

"Infrared (IR) spectra were taken in the attenuated total reflectance (ATR) mode on a Bruker Alpha II Spectrometer. Absorption maxima are given in cm^{-1}. The samples were prepared as thin films from neat material or by evaporation of a DCM solution on the diamond window.

High-resolution mass spectrometry (HRMS) was performed on a Thermo Orbitrap Velos instrument in ESI-TOF mode having a mass accuracy of ≤3 ppm. The samples were injected directly into the ion source. Pierce™ LTQ was used as an external calibrant."[16] Additional HRMS data were obtained on an Agilent 7200 GC/QTOF-MS on a J&W Scientific 60 m DB-5 capillary column with a mass accuracy of ≤5 ppm.

"Thin layer chromatography (TLC) was carried out using silica-gel coated, plastic or aluminum plates that were visualized by UV, or when necessary, by staining with a $KMnO_4$ solution and heating.

Melting points were measured using a Köfler hot-stage and are uncorrected. The crystalline nature or solids was judged by the refraction of light (aka, twinkling) observed with a polarizing microscope.

Medium pressure liquid chromatography (MPLC) was used to purify most new compounds. The apparatus was constructed with a HPLC pump (Waters model 510), differential refractive index detector (Waters R403), and UV detector (Gilson 112 UV). Hand-packed silica gel columns (Teledyne RediSep Rf Gold®; normal-phase, 20-40 μm, 60 Å pore size) were used. Preparative flash chromatography was done on Agela silica gel (230-400 mesh).

Reaction temperatures refer to the temperatures of an external heating oil bath. Reactions conducted at temperatures higher than that of the boiling point of the solvent, were done in a screw-top culture tube that was sealed with an inert Teflon®-lined cap."[16]

Chloroform was used as the solvent for many of the cycloisomerization reactions. A small portion (e.g. 50 mL) was

passed through a column of flash chromatography silica gel (ca. 20 mL) immediately before use to remove ethanol stabilizer.

Unless otherwise indicated all compounds were obtained commercially and used directly as received.

General Procedure A: Sonogashira Coupling Reaction. To an appropriately sized culture tube was added a terminal alkyne, aryl iodide or bromide, base, and solvent (amounts specified in each procedure). The headspace of the reaction vessel was flushed with N_2. A Pd catalyst and CuI were added, the culture tube was sealed with a Teflon®-lined cap, and the reaction mixture was stirred at room temperature or reflux. Upon consumption of the starting materials (GC monitoring), the reaction was quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous portion was extracted using dichloromethane (3x). The combined organic layers were dried using sodium sulfate and filtered. The filtrate was concentrated and the residue was purified by flash column chromatography or MPLC using an appropriate elution solvent.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(pyridin-2-yl)prop-2-yn-1-yl)methanesulfonamide (5a).** Following general procedure A, the alkynylnitrile **8**[17] (40 mg, 0.2 mmol), 2-bromopyridine (**9a**, 95 mL, 0.24 mmol), triethylamine (140 mL, 1.0 mmol), toluene (2 mL, 0.12 M), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and CuI (4 mg, 0.02 mmol) were used to prepare the pyridine derivative **5a**. The reaction mixture was stirred at 95 °C for 4 h, and the organic residue was purified by flash column chromatography (hexanes:EtOAc 1:1) to give brown rod-like crystals (27 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, *H*6), 7.68 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H, *H*4), 7.47 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H, *H*3), 7.28 (ddd, *J* = 7.7, 4.9, 1.3 Hz, 1H, *H*5), 4.50 (s, 2H, CH_2), 3.27 (s, 3H, MsCH_3), and 1.99 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.4, 142.2, 136.5, 127.4, 123.7, 120.7, 85.8, 83.3, 53.9, 41.7, 36.5, and 29.3. IR (neat): 2994 (C_{sp3}–H), 2916 (C_{sp3}–H), 1328 (SO_2NR_2), and 1145 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{13}H_{16}N_3O_2S^+$ 278.0958; Found 278.0955. TLC: R_f 0.37 (hexanes:EtOAc, 1:1). mp: 48–51 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(pyridin-3-yl)prop-2-yn-1-yl)methanesulfonamide (5b).** Following general procedure A, the alkynylnitrile **8**[17] (0.11 g, 0.55 mmol), 3-bromopyridine (**9b**, 48 mL, 0.5 mmol), triethylamine (0.349 mL, 2.5 mmol), THF (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), and CuI (9 mg, 0.05 mmol) were used to prepare the pyridine derivative **5b**. The reaction mixture was stirred at 80 °C for 28 h, and the organic residue was purified by MPLC (hexanes:EtOAc 1:3) to give yellow cubic crystals (34 mg, 24% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (dd, *J* = 2.2, 1.0 Hz, 1H, *H*2), 8.58 (dd, *J* = 4.9, 1.7 Hz, 1H, *H*6), 7.76 (dt, *J* = 7.9, 1.7 Hz, 1H, *H*4), 7.28 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H, *H*5), 4.50 (s, 2H, CH_2), 3.24 (s, 3H, MsCH_3), and 1.99 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.4, 149.6, 138.8, 123.3, 120.7, 119.0, 86.8, 83.4, 53.8, 41.6, 36.9, and 29.3. IR (neat): 3033 (C_{sp2}–H), 2989 (C_{sp3}–H), 2933 (C_{sp3}–H), 2232 (C ≡ N), 1328 (SO_2NR_2), and 1143 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] $C_{13}H_{16}N_3O_2S^+$ 278.0958; Found 278.0953. TLC: R_f 0.28 (hexanes:EtOAc, 1:4). mp: 65–67 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(2-fluoropyridin-4-yl)prop-2-yn-1-yl)methanesulfonamide (5c).** Following general procedure A, the alkynylnitrile **8**[17] (0.11 g, 0.55 mmol), the bromopyridine **9c** (88 mg, 0.5 mmol), diisopropylethylamine (0.261 mL, 1.5 mmol), dimethylformamide (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), and CuI (9 mg, 0.05 mmol) were used to prepare the pyridine derivative **5c**. The reaction mixture was stirred at 23 °C for 24 h, and the organic residue was purified by flash column chromatography (hexanes:EtOAc 4:1) to give yellow cubic crystals (63.2 mg, 43% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (ddd, *J* = 5.2, 0.8, 0.8 Hz, 1H, *H*6), 7.22 (ddd, *J* = 5.1, 1.9, 1.2 Hz, 1H, *H*5), 6.98 (ddd, *J* = 2.1, 1.2, 0.8 Hz, 1H, *H*3), 4.51 (s, 2H, CH_2), 3.22 (s, 3H, MsCH_3), and 1.98 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 163.8 (d, $^1J_{CF}$ = 239.4 Hz, *C*2), 148.2 (d, $^3J_{CF}$ = 15.7 Hz, *C*6), 134.8 (d, $^3J_{CF}$ = 9.4 Hz, *C*4), 123.5 (d, $^4J_{CF}$ = 4.5 Hz, *C*5), 120.6 (*C*≡N), 111.8 (d, $^2J_{CF}$ = 39.4 Hz, *C*3), 89.4 (*C*≡CAr), 82.8 (d, $^4J_{CF}$ = 5.0 Hz, C≡*C*Ar), 53.8 (*C*(CH$_3$)$_2$), 41.7 (MsCH$_3$), 36.8 (*C*H$_2$), and 29.2 [C(*C*H$_3$)$_2$]. ^{19}F NMR (471 MHz, $CDCl_3$): δ -69.9 (s, 1F, *F*2). IR (neat): 3072 (C_{sp2}–H), 3002 (C_{sp2}–H), 2927 (C_{sp3}–H), 2235 (C ≡ N), 1325 (SO_2NR_2), and 1143 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{13}H_{15}FN_3O_2S^+$ 296.0864; Found 296.0856. TLC: R_f 0.30 (hexanes:EtOAc, 1:1). mp: 104–106 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(4-methoxypyridin-2-yl)prop-2-yn-1-yl)methanesulfonamide (5d).** Following general procedure A, the alkynylnitrile **8**[17] (0.11 g, 0.55 mmol), the bromopyridine **9d** (94 mg, 0.5 mmol), triethylamine (0.349 mL, 2.5 mmol), THF (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), and CuI (9 mg, 0.05 mmol) were used to prepare the pyridine derivative **5d**. The reaction mixture was stirred at 90 °C for 17 h, and the organic residue was purified by MPLC (hexanes:EtOAc 1:2) to give pale yellow rod-like crystals (56 mg, 37% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (dd, *J* = 5.8, 0.6 Hz, 1H, *H*6), 7.02 (dd, *J* = 2.6, 0.6 Hz, 1H, *H*3), 6.80 (dd, *J* = 5.8, 2.6 Hz, 1H, *H*5), 4.48 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.26 (s, 3H, MsCH_3), and 1.99 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165.9, 151.5, 143.3, 120.8, 113.5, 110.3, 85.9, 82.8, 55.5, 53.9, 41.7, 36.5, and 29.3. IR (neat): 2941 (C_{sp3}–H), 2865 (C_{sp3}–H), 2240 (C ≡ N), 1332 (SO_2NR_2), and 1147 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{14}H_{18}N_3O_3S^+$ 308.1063; Found 308.1059. TLC: R_f 0.24 (EtOAc). mp: 70–73 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(pyrazin-2-yl)prop-2-yn-1-yl)methanesulfonamide (5e).** Following general procedure A, the alkynylnitrile **8**[17] (0.11 g, 0.55 mmol), 2-bromopyrazine (**9e**, 45.2 mL, 0.5 mmol), diisopropylethylamine (0.261 mL, 1.5 mmol), DMF (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), and CuI (9 mg, 0.05 mmol) were used to prepare the pyrazine derivative **5e**. The reaction mixture was stirred at 23 °C for 3 d, and the organic residue was purified by flash column chromatography (hexanes:EtOAc 1:1) to give orange cubic crystals (0.1016 g, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, *J* = 1.6 Hz, 1H, *H*3), 8.57 (dd, *J* = 2.6, 1.6 Hz, 1H, *H*5), 8.55 (d, *J* = 2.6 Hz, 1H, *H*6), 4.54 (s, 2H, CH_2), 3.27 (s, 3H, MsCH_3), and 2.00 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.6, 144.6, 143.8, 138.9, 120.5, 87.5, 82.6, 53.9, 41.8, 36.2, and 28.9. IR (neat): 3066 (C_{sp2}–H), 2996 (C_{sp3}–H), 2935 (C_{sp3}–H), 2231 (C≡N), 1333 (SO_2NR_2), and 1146 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{15}N_4O_2S^+$ 279.0910; Found 279.0902. TLC: R_f 0.16 (hexanes:EtOAc, 1:1). mp: 76–79 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(thiophen-2-yl)prop-2-yn-1-yl)methanesulfonamide (5f).** Following general procedure A, the alkynylnitrile **8**[17] (60 mg, 0.30 mmol), 2-bromothiophene (**9f**, 41 mL, 0.43 mmol), triethylamine (2.0 mL, 1.5 mmol), tetrahydrofuran (4 mL, 0.075 M), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.015 mmol), and CuI (3 mg, 0.015 mmol) were used to prepare the thiophene derivative **5f**. The reaction mixture was stirred at room temperature for 21 h, and

the organic residue was purified by flash column chromatography (hexanes:EtOAc 4:1) to give **5f** as cream-colored rod-like crystals (42 mg, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 5.1, 1.2 Hz, 1H, *H*5 or *H*3), 7.25 (dd, *J* = 3.7, 1.3 Hz, 1H, *H*3 or *H*5), 6.99 (dd, *J* = 5.2, 3.8 Hz, 1H, *H*4), 4.48 (s, 2H, CH_2), 3.23 (s, 3H, MsCH_3), and 1.97 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 133.0, 128.1, 127.3, 121.5, 120.6, 87.3, 80.2, 53.9, 41.6, 36.9, 29.8, and 29.2. IR (neat): 2957 (Csp3–H), 2921 (Csp3–H), 2851 (Csp3–H), 1325 (SO_2NR_2), and 1144 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{15}N_2O_2S_2^+$ 283.0569; Found 283.0563. TLC: R_f 0.24 (hexanes:EtOAc, 3:1). mp: 37–39 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(1-methyl-1*H*-imidazol-5-yl)prop-2-yn-1-yl)methanesulfonamide (5g).** Following general procedure A, the alkynylnitrile **8**[17] (0.11 g, 0.55 mmol), the bromoimidazole **9g** (81 mg, 0.5 mmol), triethylamine (0.349 mL, 2.5 mmol), DMF (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), and CuI (9 mg, 0.05 mmol) were used to prepare the imidazole derivative **5g**. The reaction mixture was stirred at 80 °C for 22 h, and the organic residue was purified by MPLC (5% MeOH in DCM) to give orange cubic crystals (27.4 mg, 20% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (br s, 1H, *H*2), 7.29 (br s, 1H, *H*4), 4.52 (s, 2H, CH_2), 3.69 (s, 3H, NCH_3), 3.20 (s, 3H, MsCH_3), and 1.97 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.9, 135.6, 120.6, 114.9, 91.1, 74.9, 54.0, 41.9, 37.1, 32.3, and 29.1. IR (neat): 3019 (C_{sp2}–H), 2971 (C_{sp3}–H), 2918 (C_{sp3}–H), 2239 (C≡N),1323 (SO_2NR_2), and 1137 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{17}N_4O_2S^+$ 281.1067; Found 281.1055. TLC: R_f 0.17 (5% MeOH in DCM). mp: 106–109 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(pyrazolo[1,5-*a*]pyrimidin-6-yl)prop-2-yn-1-yl)methanesulfonamide (5h).** Following general procedure A, the alkynylnitrile **8**[17] (40 mg, 0.2 mmol), the aryl bromide **9h** (48 mg, 0.24 mmol), triethylamine (140 mL, 1.0 mmol), toluene (2 mL, 0.12 M), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and CuI (4 mg, 0.02 mmol) were used to prepare the nitrile **5h**. The reaction mixture was stirred and heated at 95 °C for 4 h, and the organic residue was purified by flash column chromatography (hexanes:EtOAc 1:1) to give **5h** as a cream-colored flaky powder (34 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (dd, *J* = 2.1, 0.9 Hz, 1H, *H*7), 8.47 (d, *J* = 2.2 Hz, 1H, *H*5), 8.18 (d, *J* = 2.4 Hz, 1H, *H*2), 6.74 (dd, *J* = 2.3, 1.0 Hz, 1H, *H*3), 4.53 (s, 2H, CH_2), 3.24 (s, 3H, MsCH_3), and 1.99 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 150.6, 147.4, 146.7, 137.8, 120.7, 104.4, 98.3, 87.7, 79.9, 53.9, 41.8, 37.0, and 29.3. IR (neat): 3074 (C_{sp2}–H), 2987 (C_{sp3}–H), 2923 (C_{sp3}–H), 2240 (C≡N), 1331 (SO_2NR_2), and 1143 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{14}H_{16}N_5O_2S^+$ 318.1019; Found 318.1017. TLC: R_f 0.38 (hexanes:EtOAc, 1:1). mp: 127–129 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(isoquinolin-5-yl)prop-2-yn-1-yl)methanesulfonamide (5i).** Following general procedure A, the alkynylnitrile **8**[17] (40 mg, 0.2 mmol), 5-iodoisoquinoline (**9i**, 61mg, 0.24 mmol), triethylamine (140 mL, 1.0 mmol), acetonitrile (2 mL, 0.12 M), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and CuI (4 mg, 0.02 mmol) were used to prepare the quinoline derivative **5i**. The reaction mixture was stirred at room temperature for 4 h, and the organic residue was purified by MPLC (hexanes:EtOAc 1:3) to give **5i** as cream-colored flaky crystals (37 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.28 (d, J = 1.1 Hz, 1H, *H*1), 8.64 (d, *J* = 5.9 Hz, 1H, *H*3), 8.03 (ddd, *J* = 5.9, 1.0, 1.0 Hz, 1H, *H*4), 8.00 (ddd, *J* = 8.3, 1.1, 1.1 Hz, 1H, *H*8), 7.90 (dd, *J* = 7.2, 1.2 Hz, 1H, *H*6), 7.58 (dd, *J* = 8.3, 7.2 Hz, 1H, *H*7), 4.64 (s, 2H, CH_2C≡C), 3.27 (s, 3H, MsCH_3), and 2.04 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.0, 144.5, 136.2, 135.0, 129.0, 128.4, 126.9, 120.7, 118.9, 118.5, 89.4, 83.3, 54.1, 41.8, 37.1, and 29.3. IR (neat): 2937 (C_{sp3}–H), 1337 (SO_2NR_2), and 1147 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{18}N_3O_2S^+$ 328.1114; Found 328.1109. TLC: R_f 0.4 (hexanes:EtOAc, 1:3). mp: 131–135 °C.

***tert*-Butyl 5-(3-(*N*-(2-cyanopropan-2-yl)methylsulfonamido)prop-1-yn-1-yl)-1*H*-indole-1-carboxylate (5j).** Following general procedure A, the alkynylnitrile **8**[17] (40 mg, 0.2 mmol), iodoindole **9j** (82 mg, 0.24 mmol), triethylamine (140 mL, 1.0 mmol), dichloromethane (2 mL, 0.12 M), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and CuI (4 mg, 0.02 mmol) were used to prepare the indole derivative **5j**. The reaction mixture was stirred at room temperature for 24 h, and the organic residue was purified by flash column chromatography (hexanes:EtOAc 3:1) to give a brown viscous oil (25 mg, 30% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (br d, *J* = 8.6 Hz, 1H, *H*7), 7.67 (dd, *J* = 1.7, 0.7 Hz, 1H, *H*4), 7.62 (dd, *J* = 3.8, 0.5 Hz, 1H, *H*2), 7.37 (dd, *J* = 8.6, 1.7 Hz, 1H, *H*6), 6.54 (d, *J* = 3.8, 0.8 Hz, 1H, *H*3), 4.49 (s, 2H, CH_2), 3.28 (s, 3H, MsCH_3), 2.00 [s, 6H, MsNC(CH_3)$_2$], and 1.67 [s, 9H, C(CH_3)$_3$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 149.5, 135.3, 130.7, 127.6, 127.2, 124.7, 120.8, 115.8, 115.5, 107.1, 87.5, 84.4, 81.9, 53.7, 41.3, 36.9, 29.4, and 28.3. IR (neat): 2980 (C_{sp3}–H), 2231 (C≡N), 1732 (C=O), 1338 (SO_2NR_2), and 1149 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{21}H_{26}N_3O_4S^+$ 416.1639; Found 416.1637. TLC: R_f 0.34 (hexanes:EtOAc, 3:1).

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(3-methylpyridin-2-yl)prop-2-yn-1-yl)methanesulfonamide (5n).** Following general procedure A, the alkynylnitrile **8**[17] (0.11 g, 0.55 mmol), the bromopyridine **9n** (56 mg, 0.5 mmol), triethylamine (0.349 mL, 2.5 mmol), THF (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), and CuI (9 mg, 0.05 mmol) were used to prepare the pyridine derivative **5n**. The reaction mixture was stirred at 80 °C for 28 h, and the organic residue was purified by MPLC (hexanes:EtOAc 1:3) to give red cubic crystals (60 mg, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (ddq, *J* = 4.8, 1.7, 0.6 Hz, 1H, *H*6), 7.53 (ddq, *J* = 7.8, 1.7, 0.8 Hz, 1H, *H*4), 7.19 (ddq, *J* = 7.8, 4.8, 0.5 Hz, 1H, *H*5), 4.54 (s, 2H, CH_2), 3.26 (s, 3H, MsCH_3), 2.46 (ddd, *J* = 0.7, 0.5, 0.5 Hz, 3H, ArCH_3), and 2.00 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.7, 141.9, 137.4, 136.4, 123.6, 120.6, 87.0, 84.6, 54.1, 41.9, 36.5, 29.2, and 19.6. IR (neat): 2999 (C_{sp3}–H), 2924 (C_{sp3}–H), 2866 (C_{sp3}–H), 1332 (SO_2NR_2), and 1146 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{14}H_{18}N_3O_2S^+$ 292.1114; Found 292.1110. TLC: R_f 0.40 (EtOAc). mp: 74–77 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(pyrimidin-2-yl)prop-2-yn-1-yl)methanesulfonamide (5o)**

Following general procedure A, the alkynylnitrile **8**[17] (100 mg, 0.5 mmol), the aryl bromide **9o** (159 mg, 1.0 mmol), triethylamine (349 mL, 2.5 mmol), dimethylformamide (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), and CuI (9 mg, 0.05 mmol) were used to prepare the nitrile **5o**. The reaction mixture was stirred at 100 °C for 3 d, and the organic residue was purified by MPLC (hexanes:EtOAc 2:9) to give cream-colored cubic crystals (18.1 mg, 13% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, *J* = 4.9 Hz, 2H, *H*4+6), 7.29 (t, *J* = 4.9 Hz, 1H, *H*5), 4.51 (s, 2H, CH_2), 3.30 (s, 3H, MsCH_3), and 1.99 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 157.5, 152.2, 120.7, 120.5, 84.8, 82.2, 54.2, 42.1, 36.0, and 29.0. IR (neat): 3021 (C_{sp2}–H), 2975 (C_{sp3}–H), 2238 (C≡N), 1330 (SO_2NR_2), and 1145 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M

+ H^+] Calcd for $C_{12}H_{15}N_4O_2S^+$ 279.0910; Found 279.0904. TLC: R_f 0.12 (hexanes:EtOAc, 1:1). mp: 170–172 °C.

***N*-(2-Cyanopropan-2-yl)-*N*-(3-(6-methoxybenzo[*d*]thiazol-2-yl)prop-2-yn-1-yl)methanesulfonamide (5p).** Following general procedure A, the alkynylnitrile **8**[17] (150 mg, 0.75 mmol), the aryl iodide **9p**[18] (146 mg, 0.5 mmol), triethylamine (349 mL, 2.5 mmol), dimethylformamide (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), and CuI (9 mg, 0.05 mmol) were used to prepare the nitrile **5p**. The reaction mixture was stirred at 100 °C for 19 h, and the organic residue was purified by MPLC (hexanes:EtOAc 1:1) to give **5p** as cream-colored cubic crystals (66.7 mg, 37% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 9.1, 0.5 Hz, 1H, *H*4), 7.28 (dd, *J* = 2.6, 0.5 Hz, 1H, *H*7), 7.13 (dd, *J* = 9.0, 2.6 Hz, 1H, *H*5), 4.55 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.26 (s, 3H, MsCH_3), and 1.99 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.1, 147.3, 144.2, 137.0, 124.5, 120.4, 117.0, 103.4, 89.7, 79.7, 55.9, 54.2, 42.1, 36.4, and 29.0. IR (neat): 3016 (C_{sp2}–H), 2989 (C_{sp3}–H), 2936 (C_{sp3}–H), 1325 (SO_2NR_2), and 1141 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{16}H_{18}N_3O_3S_2^+$ 364.0784; Found 364.0778. TLC: R_f 0.53 (hexanes:EtOAc, 1:1). mp: 155–160 °C.

6,6-Dimethyl-7-(methylsulfonyl)-7,8-dihydro-6*H*-pyrrolo[3,4-*b*][1,5]naphthyridine (7a). A solution of nitrile **5a** (14 mg, 0.05 mmol) and TBD (3 mg, 0.025 mmol) in $CHCl_3$ (0.5 mL, 0.1 M) was allowed to stir at 23 °C. After 24 h the solution was concentrated and the organic residue was purified by flash column chromatography in (hexanes:EtOAc 1:6) to give **7a** as cream-colored rod-like crystals (12 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.97 (dd, *J* = 4.1, 1.6 Hz, 1H, *H*2), 8.40 (ddd, *J* = 8.6, 1.7, 0.8 Hz, 1H, *H*4), 8.26 (td, *J* = 1.5, 0.9 Hz, 1H, *H*9), 7.65 (dd, *J* = 8.6, 4.2 Hz, 1H, *H*3), 4.87 (d, *J* = 1.5, 2H, CH_2), 3.05 (s, 3H, MsCH_3), and 1.88 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.8, 151.2, 144.2, 143.6, 137.3, 131.5, 129.7, 124.4, 68.8, 50.2, 40.3, and 27.7. IR (neat): 2992 (C_{sp3}–H), 2956 (C_{sp3}–H), 2922 (C_{sp3}–H), 2852 (C_{sp3}–H), 1324 (SO_2NR_2), and 1162 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{13}H_{16}N_3O_2S^+$ 278.0958; Found 278.0956. TLC: R_f 0.25 (hexanes:EtOAc, 1:6). mp: 161–164 °C.

3,3-Dimethyl-2-(methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*][1,6]naphthyridine (7b-maj). A solution of nitrile **5b** (16.3 mg, 0.06 mmol) and TBD (4 mg, 0.03 mmol) in $CHCl_3$ (1.18 mL, 0.05 M) was allowed to stir at 23 °C. After 2.5 h the solution was concentrated and the organic residue was purified by MPLC (hexanes:EtOAc 1:4) to give, in order of elution, **7b-min** as cream rod-like crystals (5.5 mg, 34% yield) and **7b-maj** as cream cubic crystals (12.5 mg, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.28 (d, *J* = 1.0 Hz, 1H, *H*8), 8.76 (d, *J* = 6.0 Hz, 1H, *H*6), 8.17 (td, *J* = 1.5, 0.9 Hz, 1H, *H*9), 7.93 (ddd, *J* = 6.0, 0.9, 0.9 Hz, 1H, *H*5), 4.85 (d, *J* = 1.5, 2H, CH_2), 3.05 (s, 3H, MsCH_3), and 1.88 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.7, 152.8, 151.1, 147.1, 129.9, 127.7, 123.2, 122.2, 69.0, 50.2, 40.4, and 27.6. IR (neat): 3045 (C_{sp2}–H), 2999 (C_{sp3}–H), 2919 (C_{sp3}–H), 2863 (C_{sp3}–H), 1323 (SO_2NR_2), 1138 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{13}H_{16}N_3O_2S^+$ 278.0958; Found 278.0954. TLC: R_f 0.09 (EtOAc). mp: 231–235 °C.

8,8-Dimethyl-7-(methylsulfonyl)-7,8-dihydro-6*H*-pyrrolo[3,4-*b*][1,8]naphthyridine (7b-min). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.12 (dd, *J* = 4.3, 2.0 Hz, 1H, *H*2), 8.23 (dd, *J* = 8.1, 2.0 Hz, 1H, *H*4), 8.09 (t, *J* = 1.4 Hz, 1H, *H*5), 7.53 (dd, *J* = 8.1, 4.3 Hz, 1H, *H*3), 4.86 (d, *J* = 1.4, 2H, CH_2), 3.05 (s, 3H, MsCH_3), and 1.92 [s, 6H, C(CH_3)$_2$]. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 156.6, 153.7, 137.3, 131.2, 127.3, 122.4, 122.2, 69.2, 50.2, 40.3, and 27.6. IR (neat): 3029 (C_{sp2}–H), 2994 (C_{sp3}–H), 2929 (C_{sp3}–H), 2859 (C_{sp3}–H), 1325 (SO_2NR_2), and 1146 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{13}H_{16}N_3O_2S^+$ 278.0958; Found 278.0954. TLC: R_f 0.16 (EtOAc). mp: 131–135 °C.

5-Fluoro-3,3-dimethyl-2-(methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*][1,7]naphthyridine (7c-maj). A solution of nitrile **5c** (39.6 mg, 0.13 mmol) and TBD (9.3 mg, 0.07 mmol) in $CHCl_3$ (2.6 mL, 0.05 M) was allowed to stir at 23 °C. After 2 h the solution was concentrated and the organic residue was purified by MPLC (hexanes:EtOAc 1:1) to give, in order of elution, **7c-min** as yellow cubic crystals (11.3 mg, 29% yield) and **7c-maj** as yellow cubic crystals (20.2 mg, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 5.7, 1.4 Hz, 1H, *H*7), 8.07 (td, *J* = 1.5, 1.1 Hz, 1H, *H*9), 7.56 (dd, *J* = 5.7, 1.1 Hz, 1H, *H*8), 4.86 (d, *J* = 1.5 Hz, 2H, CH_2), 3.05 (s, 3H, MsCH_3), and 1.89 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.3 (*C*3a), 159.6 (d, $^1J_{CF}$ = 252.2 Hz, *C*5), 140.3 (d, $^3J_{CF}$ = 15.3 Hz, *C*7), 134.6 (d, J_{CF} = 4.4 Hz, *C*8a), 133.4 (d, $^2J_{CF}$ = 28.5 Hz, *C*4a), 131.8 (*C*9a), 128.7 (d, J_{CF} = 3.6 Hz, *C*8 or *C*9), 119.1 (d, J_{CF} = 5.5 Hz, *C*8 or *C*9), 69.0 (*C*(CH_3)$_2$), 50.3 (*C*H$_2$), 40.5 (MsCH$_3$), and 27.7 (C(CH_3)$_2$). ^{19}F NMR (471 MHz, $CDCl_3$): δ -75.7 (s, 1F, *F*5). IR (neat): 3009 (C_{sp2}–H), 2978 (C_{sp3}–H), 2941 (C_{sp3}–H), 1327 (SO_2NR_2), and 1140 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{13}H_{15}FN_3O_2S^+$ 296.0864; Found 296.0857. TLC: R_f 0.10 (hexanes:EtOAc, 1:1). mp: 181–185 °C.

7-Fluoro-3,3-dimethyl-2-(methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*][1,7]naphthyridine (7c-min). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.20 (dd, *J* = 1.5, 0.8 Hz, 1H, *H*5), 8.01 (td, *J* = 1.5, 0.9 Hz, 1H, *H*9), 7.26 (d, *J* = 0.8 Hz, 1H, *H*8), 4.84 (d, *J* = 1.6 Hz, 2H, CH_2), 3.05 (s, 3H, MsCH_3), and 1.87 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 167.6 (*C*3a), 161.1 (d, $^1J_{CF}$ = 236.8 Hz, *C*7), 152.6 (d, $^3J_{CF}$ = 16.0 Hz, *C*5), 142.2 (d, $^4J_{CF}$ = 3.2 Hz, *C*4a), 134.4 (d, $^3J_{CF}$ = 9.5 Hz, *C*8a), 131.4 (*C*9a), 128.2 (d, $^4J_{CF}$ = 6.5 Hz, *C*9), 102.6 (d, $^2J_{CF}$ = 38.1 Hz, *C*8), 68.7 (*C*(CH_3)$_2$), 50.1 (*C*H$_2$), 40.5 (MsCH$_3$), and 27.6 (C(CH_3)$_2$). ^{19}F NMR (471 MHz, $CDCl_3$): δ -79.1 (s, 1F, *F*7). IR (neat): 3008 (C_{sp2}–H), 2982 (C_{sp3}–H), 2934 (C_{sp3}–H), 1335 (SO_2NR_2), and 1146 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{13}H_{15}FN_3O_2S^+$ 296.0864; Found 296.0858. TLC: R_f 0.20 (hexanes:EtOAc, 1:1). mp: 177–182 °C.

4-Methoxy-6,6-dimethyl-7-(methylsulfonyl)-7,8-dihydro-6*H*-pyrrolo[3,4-*b*][1,5]naphthyridine (7d). A solution of nitrile **5d** (25.9 mg, 0.08 mmol) and TBD (6 mg, 0.04 mmol) in $CHCl_3$ (1.69 mL, 0.05 M) was allowed to stir at 23 °C. After 2.5 h the solution was concentrated and the organic residue was purified by MPLC (hexanes:EtOAc 1:4) to give **7d** as yellow cubic crystals (22.9 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, *J* = 5.2 Hz, 1H, *H*2), 8.21 (t, *J* = 1.5 Hz, 1H, *H*9), 6.99 (d, *J* = 5.3 Hz, 1H, *H*3), 4.85 (d, *J* = 1.5, 2H, CH_2), 4.14 (s, 3H, OCH_3), 3.04 (s, 3H, MsCH_3), and 1.90 [s, 6H, C(CH_3)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165.3, 162.1, 152.1, 144.3, 137.3, 131.4, 130.0, 103.9, 69.0, 56.6, 50.1, 40.3, and 27.8. IR (neat): 2982 (C_{sp3}–H), 2932 (C_{sp3}–H), 2850 (C_{sp3}–H), 1321 (SO_2NR_2), and 1140 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H^+] Calcd for $C_{14}H_{18}N_3O_3S^+$ 308.1063; Found 308.1058. TLC: R_f 0.09 (EtOAc). mp: 240–245 °C.

6,6-Dimethyl-7-(methylsulfonyl)-7,8-dihydro-6*H*-pyrrolo[3',4':5,6]pyrido[2,3-*b*]pyrazine (7e). A solution of nitrile **5e** (17.5 mg, 0.06 mmol) and TBD (4.4 mg, 0.03 mmol) in $CHCl_3$ (1.2 mL, 0.05 M) was allowed to stir at 23 °C. After 1 h the solution was concentrated and the organic residue was purified by

flash column chromatography (EtOAc) to give **7e** as yellow cubic crystals (13.1 mg, 75% yield). In a larger scale experiment, the nitrile **5e** (0.264 g, 0.95 mmol) was dissolved in $CHCl_3$ (19.0 mL, 0.05 M). TBD (66.0 mg, 0.47 mmol) was added to the stirring solution at 23 °C. Within seconds the solution turned dark green and after 12 min the solution was concentrated and the organic residue was purified by flash column chromatography (EtOAc) to give **7e** as yellow cubic crystals (0.197 g, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.06 (d, *J* = 1.8 Hz, 1H, *H*2 or *H*3), 8.96 (d, *J* = 1.8 Hz, 1H, *H*2 or *H*3), 8.35 (t, *J* = 1.5 Hz, 1H, *H*9), 4.92 (d, *J* = 1.5 Hz, 2H, C*H*$_2$), 3.06 (s, 3H, MsC*H*$_3$), and 1.93 [s, 6H, C(C*H*$_3$)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.6, 151.7, 147.6, 146.1, 138.1, 132.7, 131.2, 69.0, 50.1, 40.5, and 27.6. IR (neat): 3007 (Csp2–H), 2938 (Csp3–H), 1315 (SO_2NR_2), and 1140 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{15}N_4O_2S^+$ 279.0910; Found 279.0905. TLC: R$_f$ 0.21 (EtOAc). mp: blackening onset at 212 °C.

5,5-Dimethyl-6-(methylsulfonyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]thieno[2,3-*e*]pyridine (7f). A solution of nitrile **5f** (5.0 mg, 0.02 mmol) and TBD (3.0 mg, 0.02 mmol) in C**D**Cl_3 (0.55 mL, 0.04 M) was allowed to stand at room temperature. After 1 h the solution was concentrated and the organic residue was purified by MPLC (hexanes:EtOAc 3:1) to give **7f** as cream-colored, rod-like crystals (4.4 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 0.3H, *H*8), 7.78 (d, *J* = 5.6 Hz, 1H, *H*2), 7.56 (d, *J* = 5.6 Hz, 1H, *H*3), 4.77 (s, 1H, C7*H*$_2$), 4.76 (br s, 0.5H, C7*H*D), 3.02 (s, 1.8H, MsC*H*$_3$), 3.01 (t, J_{HD} = 2.0 Hz, 0.8H, MsC*H*$_2$D), 2.99 (br m, 0.2H, MsC*H*D$_2$), and 1.84 [s, 6H, C(C*H*$_3$)$_2$]. IR (neat): 3075 (C_{sp2}–H), 3021 (C_{sp2}–H), 2923 (C_{sp3}–H), 2853 (C_{sp3}–H), 1318 (SO_2NR_2), and 1146 (SO_2NR_2) cm^{-1}. HRMS (EI-TOF) *m/z*: [M$^+$ - CH$_3^\bullet$] Calcd for $C_{11}H_{10}DN_2O_2S_2^{\bullet+}$ 268.0319; Found 268.0318 (mono-deuterated product). TLC: R$_f$ 0.21 (hexanes:EtOAc, 1:1). mp: 170–172 °C.

An analogous experiment performed in C**H**Cl_3 gave a sample of all-protio **7f** from which the following NMR data were obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (td, *J* = 1.2, 0.9 Hz, 1H, *H*8), 7.77 (d, *J* = 5.6 Hz, 1H, *H*2), 7.56 (dd, *J* = 5.6, 0.9 Hz, 1H, *H*3), 4.77 (d, *J* = 1.3 Hz, 2H, C*H*$_2$), 3.02 (s, 2H, MsC*H*$_3$), and 1.84 [s, 6H, C(C*H*$_3$)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 163.0, 156.5, 132.7, 131.2, 125.0, 124.8, 123.3, 68.8, 50.5, 40.1, and 27.8. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{15}N_2O_2S_2^+$ 283.0569; Found 283.0563 (all protio product).

1,5,5-Trimethyl-6-(methylsulfonyl)-1,5,6,7-tetrahydroimidazo[4,5-*b*]pyrrolo[3,4-*e*]pyridine (7g). A solution of nitrile **5g** (10.0 mg, 0.036 mmol) and TBD (2.5 mg, 0.018 mmol) in $CHCl_3$ (0.72 mL, 0.05 M) was allowed to stir at 23 °C. After 22 d the solution was concentrated and the organic residue was purified by MPLC (5% MeOH in DCM) to give **7g** as white cubic crystals (6.9 mg, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H, *H*2), 7.61 (t, *J* = 1.2 Hz, 1H, *H*8), 4.79 (d, *J* = 1.1 Hz, 2H, C*H*$_2$), 3.89 (s, 3H, NC*H*$_3$), 3.01 (s, 3H, MsC*H*$_3$), and 1.84 [s, 6H, C(C*H*$_3$)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.1, 157.1, 146.3, 126.7, 122.2, 112.4, 68.9, 50.8, 40.0, 31.8, and 28.0. IR (neat): 3099 (Csp2–H), 2927 (Csp3–H), 1321 (SO_2NR_2), and 1144 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{17}N_4O_2S^+$ 281.1067; Found 281.1056. TLC: R$_f$ 0.14 (5% MeOH in DCM). mp: 240–244 °C.

9,9-Dimethyl-8-(methylsulfonyl)-8,9-dihydro-7*H*-pyrazolo[1,5-*a*]pyrrolo[3',4':5,6]pyrido[3,2-*e*]pyrimidine (7h). A solution of nitrile **5h** (16 mg, 0.05 mmol) and TBD (3 mg, 0.025 mmol) in $CHCl_3$ (0.5 mL, 0.1 M) was allowed to stir at 23 °C. After 24 h the solution was concentrated and the organic residue was purified by flash column chromatography (hexanes:EtOAc 1:5) to give **7h** as a cream-colored, thread-like powder (15 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H, *H*5), 8.26 (d, *J* = 2.2 Hz, 1H, *H*2), 8.19 (t, *J* = 1.2 Hz, 1H, *H*6), 6.93 (d, *J* = 2.1 Hz, 1H, *H*3), 4.86 (d, *J* = 1.2 Hz, 2H, C*H*$_2$), 3.05 (s, 3H, MsC*H*$_3$), and 1.95 [s, 6H, C(C*H*$_3$)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.7, 150.8, 148.3, 147.0, 144.8, 132.0, 126.0, 113.2, 101.5, 69.8, 50.3, 40.4, and 27.7. IR (neat): 3123 (C_{sp2}–H), 2957 (C_{sp3}–H), 2925 (C_{sp3}–H), 2853 (C_{sp3}–H), 1320 (SO_2NR_2), and 1142 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{14}H_{16}N_5O_2S^+$ 318.1019; Found 318.1016. TLC: R$_f$ 0.21 (hexanes:EtOAc, 1:5). mp: 204–210 °C.

8,8-Dimethyl-9-(methylsulfonyl)-9,10-dihydro-8*H*-pyrrolo[3,4-*b*][4,7]phenanthroline (7i). A solution of nitrile **5i** (25 mg, 0.075 mmol) and TBD (5 mg, 0.0375 mmol) in $CHCl_3$ (0.8 mL, 0.09 M) was allowed to stir at 23 °C. After 12 h the solution was concentrated and the organic residue was purified by flash column chromatography (hexanes:EtOAc 1:3) to give **7i** as a cream-colored flaky powder (18 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.34 (d, *J* = 1.0 Hz, 1H, *H*4), 8.84 (td, *J* = 1.3, 0.6 Hz, 1H, *H*11), 8.83 (d, *J* = 5.7 Hz, 1H, *H*2), 8.37 (d, *J* = 5.8 Hz, 1H, *H*1), 8.12 (dd, *J* = 9.1, 0.6 Hz, 1H, *H*6), 8.09 (d, *J* = 9.1 Hz, 1H, *H*5), 4.93 (d, *J* = 1.3 Hz, 2H, C*H*$_2$), 3.06 (s, 3H, MsC*H*$_3$), and 1.91 [s, 6H, C(C*H*$_3$)$_2$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 167.3, 152.1, 150.1, 145.8, 134.4, 129.9, 129.0, 126.7, 126.6, 125.7, 123.3, 116.0, 69.2, 50.7, 40.3, and 27.7. IR (neat): 2983 (C_{sp3}–H), 2923 (C_{sp3}–H), 2852 (C_{sp3}–H), 1314 (SO_2NR_2), and 1139 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{18}N_3O_2S^+$ 328.1114; Found 328.1111. TLC: R$_f$ 0.25 (hexanes:EtOAc, 1:3). mp: 185–190 °C.

***tert*-Butyl 9,9-dimethyl-8-(methylsulfonyl)-8,9-dihydrodipyrrolo[3,4-*b*:2',3'-*h*]quinoline-3(7*H*)-carboxylate (7j-maj).** A solution of the nitrile **5j** (12 mg, 0.03 mmol) and TBD (2 mg, 0.015 mmol) in $CHCl_3$ (0.55 mL, 0.05 M) was allowed to stir at 23 °C. After 24 h the solution was concentrated and the organic residue was purified by MPLC (hexanes:EtOAc 3:1) to give, in order of elution, **7j-maj** as a cream-colored, powdery crystals (11 mg, 92% yield) and **7j-min** as white rod-like crystals (1.1 mg, 9% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (br d, *J* = 9.0 Hz, 1H, *H*4), 8.07 (t, *J* = 1.3 Hz, 1H, *H*6), 7.72 (d, *J* = 3.6 Hz, 1H, *H*2), 7.66 (d, *J* = 9.0 Hz, 1H, *H*5), 7.41 (dd, *J* = 3.6, 0.8 Hz, 1H, *H*1), 4.83 (d, *J* = 1.3 Hz, 2H, C*H*$_2$), 3.04 (s, 3H, MsC*H*$_3$), 1.90 [s, 6H, MsNC(C*H*$_3$)$_2$], and 1.72 [s, 9H, C(C*H*$_3$)$_3$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 164.9 (*C*9a), 149.8 (*C*=O), 143.6 (*C*10a), 134.9 (*C*3a, v. weak in 1D spectrum but strong correlations in the HMBC), 130.1 (*C*6), 127.5 (*C*10b), 125.1 (*C*2), 124.3 (*C*5a or *C*6a), 124.1 (*C*5a or *C*6a), 123.9 (*C*5), 116.4 (*C*4), 106.6 (*C*1), 84.5 (Me$_3$*C*O), 69.1 (*C*9), 50.6 (*C*7), 40.1 (*C*H$_3$SO$_2$), 28.3 [*C*(CH$_3$)$_3$], and 27.9 [C9(*C*H$_3$)$_2$]. (Assignments based on interpretation of the HSQC and HMBC spectra) IR (neat): 3133 (C_{sp2}–H), 2923 (C_{sp3}–H), 2852 (C_{sp3}–H), 1724 (C=O), 1328 (SO_2NR_2), and 1126 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{21}H_{26}N_3O_4S^+$ 416.1639; Found 416.1636. TLC: R$_f$ 0.75 (hexanes:EtOAc, 1:1). mp: 162–165 °C.

***tert*-Butyl 8,8-dimethyl-7-(methylsulfonyl)-7,8-dihydrodipyrrolo[3,4-*b*:3',2'-*g*]quinoline-1(6*H*)-carboxylate (7j-min).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (br s, 1H, *H*10), 8.08 (td, *J* = 1.3, 0.9 Hz, 1H, *H*5), 7.96 (d, *J* = 0.8 Hz, 1H, *H*4), 7.80 (br d, *J* = 3.9 Hz, 1H, *H*2), 6.71 (dd, *J* = 3.9, 0.9 Hz, 1H, *H*3), 4.82 (d, *J* = 1.4 Hz, 2H, C*H*$_2$), 3.04 (s, 3H, MsC*H*$_3$), 1.88 [s, 6H, C8(C*H*$_3$)$_2$],

and 1.73 [s, 9H, C(CH_3)$_3$]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 164.9 (C8a), 146.4 (*C*9a), 137.0, 130.1, 129.7, 124.1 (C5a), 130.2 (*C*2), 129.8 (*C*5), 118.2 (*C*4), 113.9 (*C*10), 107.0 (*C*3), 84.2 (Me_3CO), 68.8 (*C*8), 50.4 (*C*6), 40.3 (CH_3SO_2), 28.5 [OC(CH_3)$_3$], and 27.7 [C8(CH_3)$_2$]. (From the HSQC spectrum. From the HMBC spectrum. Boc carbonyl not observable.) HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{21}H_{26}N_3O_4S^+$ 416.1639; Found 416.1632. TLC: R_f 0.52 (hexanes:EtOAc, 1:1). mp: >240 °C.

***N*-(Cyanomethyl)-*N*-(3-(4-cyanophenyl)prop-2-yn-1-yl)methanesulfonamide (11b).** Following general procedure A, the alkynylnitrile **S2** (see SI, 85 mg, 0.5 mmol), 4-iodobenzonitrile (120 mg, 0.6 mmol), triethylamine (350 mL, 2.5 mmol), acetonitrile (5 mL, 0.1 M), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), and CuI (10 mg, 0.05 mmol) were used to prepare the sulfonamide **11b**. The reaction mixture was stirred at 23 °C for 60 h, and the organic residue was purified by flash column chromatography (hexanes:EtOAc 1:1) to give cream-colored flakey crystals (95 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (nfod, J_{app} = 8.4 Hz, 2H, *o*- or *m*-Ar C≡C), 7.57 (nfod, J_{app} = 8.4 Hz, 2H, *o*- or *m*-Ar C≡C), 4.47 (s, 2H, CH_2C≡C), 4.37 (s, 2H, CH_2CN), and 3.13 (s, 3H, MsCH_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 132.4, 132.3, 126.3, 118.2, 114.5, 112.9, 86.1, 84.8, 39.4, 39.1, and 36.0. IR (neat): 3090 (C_{sp2}–H), 3000 (C_{sp2}–H), 2965 (C_{sp3}–H), 2226 (C≡N), 1320 (SO_2NR_2), and 1156 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{13}H_{12}N_3O_2S^+$ 274.0645; Found 274.0644. TLC: R_f 0.52 (hexanes:EtOAc, 1:1). mp: 94–96 °C.

***N*-(Cyanomethyl)-*N*-(3-phenylprop-2-yn-1-yl)methanesulfonamide (11c).** Following general procedure A, the alkynylnitrile **S2** (see SI, 85 mg, 0.50 mmol), iodobenzene (65 mL, 0.6 mmol), triethylamine (350 mL, 0.50 mmol), acetonitrile (5 mL, 0.10 M), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), and CuI (10 mg, 0.05 mmol) were used to prepare the sulfonamide **11c**. The reaction mixture was stirred at room temperature for 60 h, and the organic residue was purified by flash column chromatography (hexanes:EtOAc 4:1) to give yellow flakey crystals (92 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.44 (nfom, 2H, *o*-Ar), 7.39–7.31 (m, 3H, *m*- and *p*-Ar), 4.44 (s, 2H, CH_2C≡C), 4.37 (s, 2H, CH_2CN), and 3.12 (s, 3H, MsCH_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 131.9 (ArC_o), 129.4 (ArC_p), 128.7 (ArC_m), 121.5 ($C_{sp}C_{Ar}$), 114.5 (CH_2CN), 88.0 (ArC_{sp}), 80.3 ($ArCC_{sp}$), 39.2 (CH_3S), 39.1 (CH_2C≡C), and 35.8 (CH_2CN). IR (neat): 3015 (C_{sp2}–H), 2989 (C_{sp3}–H), 2951 (C_{sp3}–H), 2245 (C≡N), 1323 (SO_2NR_2), and 1149 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{13}N_2O_2S^+$ 249.0692; Found 249.0689; [M + Na$^+$] Calcd for $C_{12}H_{12}N_2NaO_2S^+$ 271.0512; Found 271.0510. TLC: R_f 0.32 (hexanes:EtOAc, 3:1). mp: 70–72 °C.

***N*-(3-(4-Aminophenyl)prop-2-yn-1-yl)-*N*-(cyanomethyl)methanesulfonamide (11d).** Following general procedure A, the alkynylnitrile **S2** (see SI, 34 mg, 0.20 mmol), 4-iodoaniline (40 mg, 0.18 mmol), triethylamine (139 mL, 1.0 mmol), acetonitrile (1 mL, 0.2 M), $Pd(PPh_3)_2Cl_2$ (4.2 mg, 0.006 mmol), and CuI (2.3 mg, 0.012 mmol) were used to prepare the sulfonamide **11d**. The reaction mixture was stirred at 90 °C for 5 h, and the organic residue was purified by flash column chromatography (1% MeOH in DCM) to give orange rod-like crystals (20 mg, 42% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (nfod, J_{app} = 8.5 Hz, 2H, *o*-Ar), 6.60 (nfod, J_{app} = 8.6 Hz, 2H, *m*-Ar), 4.41 (s, 2H, CH_2C≡C), 4.36 (s, 2H, CH_2CN), 3.86 (br s, 2H, NH_2), and 3.10 (s, 3H, MsCH_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.6, 133.4, 114.8, 114.6, 110.6, 88.8, 78.0, 39.3, 39.0, and 35.7. IR (neat): 3474 (NH_2), 3382 (NH_2), 2925 (C_{sp3}–H), 2204 (C≡N), 1311 (SO_2NR_2), and 1150 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{14}N_3O_2S^+$ 264.0801; Found 264.0797. TLC: R_f 0.35 (1% MeOH in DCM). mp: 117–120 °C.

2-(Methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline-6-carbonitrile (13b). A solution of methanesulfonamide **11b** (10.6 mg, 0.04 mmol) and TBD (5.4 mg, 0.04 mmol) in $CHCl_3$ (0.78 mL, 0.05 M) was allowed to stir at 23 °C. After 24 h the solution was concentrated and the organic residue was purified by MPLC (5% MeOH in DCM) to give **13b** as white cubic crystals (8.7 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (dt, *J* = 1.6, 0.8 Hz, 1H, *H*5), 8.10 (nfom, 1H, *H*9), 7.93 (dd, *J* = 8.5, 0.7 Hz, 1H, *H*8), 7.73 (dd, *J* = 8.4, 1.6 Hz, 1H, *H*7), 4.93 (nfom, 2H, *H*1), 4.88 (nfom, 2H, *H*3), and 2.99 (s, 3H, MsCH_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.0 (*C*3a), 147.3 (*C*4a), 135.2 (*C*5), 131.0 (*C*9a), 130.2 (*C*9), 129.5 (*C*8), 128.9 (*C*8a), 127.9 (*C*7), 118.1 (*C*N), 113.4 (*C*6), 53.5 (*C*3), 51.7 (*C*1), and 36.4 ($MsCH_3$). (From the HSQC spectrum. From the HMBC spectrum.) IR (neat): 3065 (C_{sp2}–H), 3019 (C_{sp2}–H), 2923 (C_{sp3}–H), 2227 (C≡N), 1326 (SO_2NR_2), and 1141 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{13}H_{12}N_3O_2S^+$ 274.0645; Found 274.0643. TLC: R_f 0.43 (5% MeOH in DCM). mp: blackening onset at 110 °C (fully charred by ~200 °C).

2-(Methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (13c). A solution of methanesulfonamide **11c** (25 mg, 0.1 mmol) and TBD (14 mg, 0.1 mmol) in $CHCl_3$ (1 mL, 0.1 M) was allowed to stir at 50 °C. After 60 h the solution was concentrated and the organic residue was purified by MPLC (hexanes:EtOAc 3:1) to give **13c** as cream-colored, rod-like crystals (13 mg, 52% yield) along with recovered starting material **11c** (8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (dddd, *J* = 8.5, 0.9, 0.9, 0.9 Hz, 1H, *H*5), 8.05 (td, *J* = 1.2, 1.2 Hz, 1H, *H*9), 7.84 (ddd, *J* = 8.2, 1.7, 0.6 Hz, 1H, *H*8), 7.74 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, *H*6), 7.57 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, *H*7), 4.90 (td, *J* = 1.2, 1.2 Hz, 2H, *H*1), 4.86 (nfom, 2H, *H*3), and 2.96 (s, 3H, MsCH_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.7, 148.4, 130.3, 130.1, 129.1, 128.1, 128.0, 127.5, 127.0, 53.7, 51.8, and 35.7. IR (neat): 3054 (C_{sp2}–H), 3007 (C_{sp2}–H), 2960 (C_{sp3}–H), 1314 (SO_2NR_2), and 1146 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{13}N_2O_2S^+$ 249.0692; Found 249.0688. TLC: R_f 0.18 (hexanes:EtOAc, 1:1). mp: 180–185 °C.

2-(Methylsulfonyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-6-amine (13d). A solution of methanesulfonamide **11d** (2.7 mg, 0.01 mmol) and TBD (1.4 mg, 0.01 mmol) in *o*-dichlorobenzene (1.0 mL, 0.01 M) was sealed in a screw-capped, Teflon-lined, threaded vial and allowed to stir at 150 °C. After 22 h the solution was concentrated and the organic residue was purified by flash column chromatography (EtOAc) to give **13d** as a red amorphous solid (0.8 mg, 30% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (td, *J* = 1.2, 1.0 Hz, 1H, *H*9), 7.61 (d, *J* = 8.7 Hz, 1H, *H*8), 7.15 (ddd, *J* = 2.4, 0.6, 0.6 Hz, 1H, *H*5), 6.99 (dd, *J* = 8.7, 2.4 Hz, 1H, *H*7), 4.82 (td, *J* = 1.3, 1.2 Hz, 2H, *H*1), 4.77 (t, *J* = 1.3 Hz, 2H, *H*3), 4.12 (br s, 2H, NH_2), and 2.93 (s, 3H, MsCH_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.8, 150.4, 148.3, 130.1, 129.2, 124.3, 121.4, 118.9, 109.0, 53.9, 51.9, and 35.4. (From the HSQC spectrum. From the HMBC spectrum.) IR (neat): 3453 (NH_2), 3301 (NH_2), 2921 (C_{sp3}–H), 1323 (SO_2NR_2), and 1140 (SO_2NR_2) cm^{-1}. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{12}H_{14}N_3O_2S^+$ 264.0801; Found 264.0790. TLC: R_f 0.19 (EtOAc). mp: turned black with decomposition at ~170 °C.

COMPUTATIONAL METHODS

A conformational search was conducted for all ground state structures using the Schrödinger software package.[19] Specifically, candidate conformers were generated with MacroModel using the OPLS_2005 force field in Maestro (Maestro Version 12.9.137, MMshare Version 5.5.137, Release 2021-3, Platform Linux-x86_64). Gaussian 16[20] was used to conduct all DFT calculations. All conformers generated by the conformational search were subjected to a geometry optimization and frequency calculation (298 K) using the ultrafine integration grid at the (U)MN15[21]/6-31G(d) level of theory with SMD(chloroform) solvation.[22] Transition state structures (TSSs) were found by first scanning the bond length of the respective bond(s) being formed or broken, followed by subjecting the geometry obtained from the highest energy step in the scan calculation to a TS calculation at the same level of theory as described above. The identity of all TSSs were confirmed to contain a single imaginary frequency. An intrinsic reaction coordinate (IRC)[23] calculation was also performed to ensure that the TSSs connected the corresponding reactant to the product. The reactive allene conformer was identified by performing a geometry optimization and frequency calculation for the allene obtained in the final step (of ten) of the IRC for the TSS for the first bond-formation leading to the diradical intermediate. Single point energy calculations were conducted for all reactive, intermediate conformers and TSSs at the (U)MN15[21]/6-311+G(d,p) level of theory using the ultrafine integration grid and SMD(chloroform) solvation.[22] Full reaction coordinates that include all stationary structures are given in the SI for each system investigated, followed by the output from the IRC calculation for each TSS. Furthermore, for each calculated structure in the reaction coordinate, the following data are provided: (1) a CYLview20[14]-generated three-dimensional image of the optimized structure, (2) the thermal correction to "Gibbs Free Energy" obtained from the geometry optimization and frequency calculation, (3) the energy obtained from the single point energy calculation done using a larger basis set, (4) the spin expectation value $\langle S^2 \rangle$ for any structure containing radical character, (5) the imaginary frequency for each TSS, and (6) the Cartesian coordinates for each stationary point.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of NMR spectra as well as selected experimental details as well as computational details for stationary points on the PESs (PDF)

FAIR data consisting of raw NMR FID files are given for compounds **5a–j**, **5n–p**, **7a–j**, **11b-d**, **13b-d**, and **S2** (FID for Publication.zip)

AUTHOR INFORMATION

Corresponding Author

* hoye@umn.edu

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. /

Notes

The authors have no competing interests.

ACKNOWLEDGMENT

N.K. and E.M.E. appreciate support from an NSF GRFP (Award #2237827) and a summer Lando Fellowship, respectively. This research was supported by a grant from the United States National Science Foundation (CHE-2155042). NMR spectral data were recorded using an instrument funded by the NIH Shared Instrumentation Grant program (S10OD011952). High resolution mass spectrometric data were obtained at the University of Minnesota Masonic Cancer Center using instrumentation partially funded by an NIH Cancer Center Support Grant (CA-77598). Computational studies were done using software and hardware facilities provided by the University of Minnesota Supercomputing Institute (MSI).

REFERENCES

[1] Krepski, L. R.; Marszalek, G. J.; Mackey, S. S.; Gerster, J. F. Method for 1*H*-imidazo[4,5-*c*]pyridines and analogs thereof. International Patent WO2007035935A1, March 29, 2007.

[2] Kato, N.; Oka, M.; Murase, T.; Yoshida, M.; Sakairi, M.; Yamashita, S.; Yasuda, Y.; Yoshikawa, A.; Hayashi, Y.; Makino, M.; Takeda, M.; Mirensha, Y.; Kakigami, T. Discovery and pharmacological characterization of N-[2-({2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}amino)-2-methylpropyl]-2-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide hydrochloride (anagliptin hydrochloride salt) as a potent and selective DPP-IV inhibitor. *Bioorg. Med. Chem.* **2011**, *19*, 7221–7227.

[3] Parsons, W. J.; Ramkumar, V.; Stiles, G. L. The new cardiotonic agent sulmazole is an A1 adenosine receptor antagonist and functionally blocks the inhibitory regulator, G_i. *Mol. Pharmacol.* **1988**, *33*, 441–448.

[4] Patwardhan, P. P.; Ivy, K. S.; Musi, E.; de Stanchina, E.; Schwartz, G. K. Significant blockade of multiple receptor tyrosine kinases by MGCD516 (Sitravatinib), a novel small molecule inhibitor, shows potent anti-tumor activity in preclinical models of sarcoma. *Oncotarget* **2016**, *7*, 4093–4109.

[5] Kraemer, N.; Naredla, R. R.; Hoye, T. R. In situ allene formation via alkyne tautomerization to promote [4 + 2]-cycloadditions with a pendant alkyne or nitrile. *Org. Lett.* **2022**, *24*, 2327–2331.

[6] For the importance of the Thorpe–Ingold effect in the context of a related Diels–Alder cyclization see: (a) Camedda, N.; Bigi, F.; Maggi, R.; Maestri, G. Sequential strategies to trigger mild dearomative Diels–Alder cyclizations. *Org. Lett.* **2023**, *25*, 2233–2237. For a general review see: (b)Jung, M. E.; Piizzi, G. *gem*-Disubstituent effect: Theoretical basis and synthetic applications. *Chem. Rev.* **2005**, *105*, 1735–1766.

[7] Chinchilla, R.; Nájera, C. The Sonogashira reaction: A booming methodology in synthetic organic chemistry. *Chem. Rev.* **2007**, *107*, 874–922.

[8] Wessig, P.; Muller, G. The dehydro-Diels–Alder reaction. *Chem. Rev.* **2008**, *108*, 2051–2063.

[9] (a) Smith, S. G.; Goodman, J. M. Assigning stereochemistry to single diastereoisomers by GIAO NMR calculation: The DP4 probability. *J. Am. Chem. Soc.* **2010**, *132*, 12946–12959. (b) Grimblat, N.; Zanardi, M. M.; Sarotti, A. M. Beyond DP4: An improved probability for the stereochemical assignment of isomeric compounds using quantum chemical calculations of NMR shifts. *J. Org. Chem.* **2015**, *80*, 12526–12534.

[10] Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. Aromaticity as a cornerstone of heterocyclic chemistry. *Chem. Rev.* **2004**, *104*, 2777–2812.

[11] Systematic, concomitant scanning of the two possible bond cleavages that can return the cycloadduct **15** to its allene precursor **12** identified only species that were higher in energy than that of either **TS1** or **TS2** (see Figures S4 and S6 in the SI for details).

[12] dos Passos Gomes, G.; Morrison, A. E.; Dudley, G. B.; Alabugin, I. V. Optimizing amine-mediated alkyne–allene isomerization to improve benzannulation cascades: Synergy between theory and experiments. *Eur. J. Org. Chem.* **2019**, *2019*, 512–518.

[13] (a) Nguyen, Q. N. N.; Tantillo, D. J. When to let go–diradical intermediates from zwitterionic transition state structures? *J. Org. Chem.* **2016**, *81*, 5295–5302. (b) Stumetz, K. S.; Nadeau, J. T.; Cremeens, M. E. Potential nonadiabatic reactions: Ring-opening 4,6-dimethylidenebicyclo[3.1.0]hex-2-ene derivatives to aromatic reactive intermediates. *J. Org. Chem.* **2013**, *78*, 10878–10884. (c) Hughes, T. S.; Carpenter, B. K. Parallel mechanisms for the cycloaromatization of enyne allenes. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2291–2298.

[14] Three-dimensional images of optimized structures generated using the *CYLView* software package. Legault, C. Y., *CYLview20*; Université de Sherbrooke, 2020 (http://www.cylview.org; accessed 6-20-23).

[15] (a) Hoye, T. R; Hanson, P. R.; Vyvyan, J. R. A practical guide to first-order multiplet analysis in 1H NMR spectroscopy. *J. Org. Chem.* **1994**, *59*, 4096–4103. (b) Hoye, T. R.; Zhao, H. A method for easily determining coupling constant (*J*) values: An addendum to "A practical guide to first-order multiplet analysis in 1H NMR spectroscopy." *J. Org. Chem.* **2002**, *67*, 4014–4016.

[16] From the supporting information in ref 5.

[17] Wang, T.; Naredla, R. R.; Thompson, S. K.; Hoye, T. R. The pentadehydro-Diels–Alder reaction. *Nature* **2016**, *532*, 484–488.

[18] Xie, A.; Cao, M.; Liu, Y.; Feng, L.; Hu, X.; Dong, W. The synthesis of tetrazoles in nanometer aqueous micelles at room temperature. *Eur. J. Org. Chem.* **2014**, 436–441.

[19] *Schrödinger Release 2023-1*: MacroModel; Schrödinger, LLC: New York, NY, 2021.

[20] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, Revision C.01, Gaussian, Inc., Wallingford CT, 2019.

[21] Yu, H. S.; He, X.; Li, S. L.; Truhlar, D. G. MN15: A Kohn–Sham global-hybrid exchange–correlation density functional with broad accuracy for multi-reference and single-reference systems and noncovalent interactions. *Chem. Sci.* **2016**, *7*, 5032–5051.

[22] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B.* **2009**, *113*, 6378–6396.

[23] Fukui, K. The path of chemical reactions - the IRC approach. *Acc. Chem. Res.* **1981**, *14*, 363–368.