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Fused Polycyclic Compounds via Cycloaddition of 4-(1′-Cyclohexenyl)-5-iodo-1,2,3-triazoles with 4-Phenyl-1,2,4-triazoline-3,5-dione: The Importance of a Sacrificial Iodide Leaving Group

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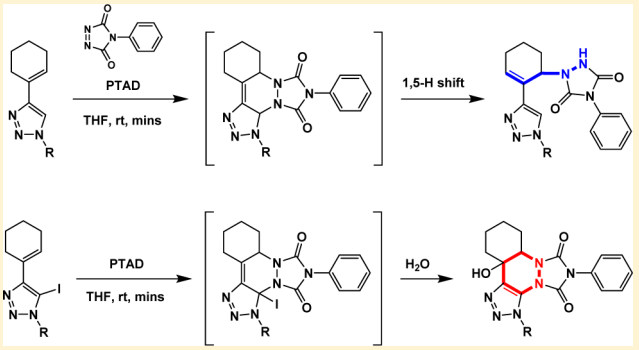
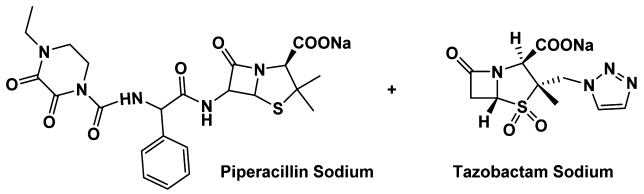
Supporting Information

ABSTRACT: 4-(1′-Cyclohexenyl)-5-iodo-1,2,3-triazole and 4-phenyl-1,2,4-triazoline-3,5-dione undergo a formal Diels−Alder reaction, which following an S_N2' solvolysis process to displace the iodo group affords a fused polycyclic compound.

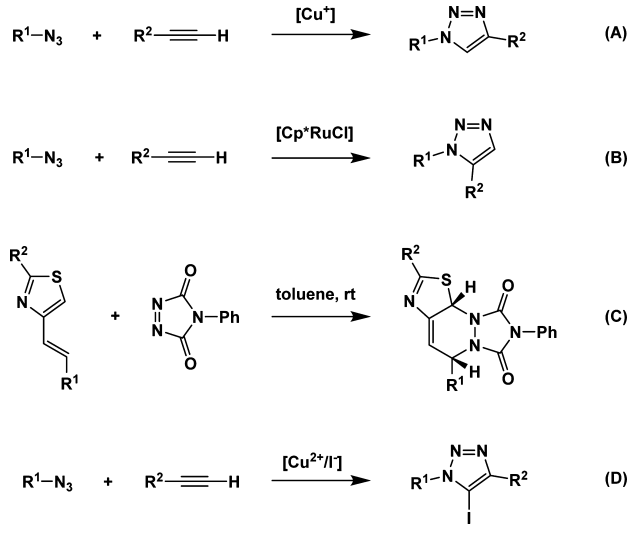


1,2,3-Triazoles are increasingly valuable compounds in the areas of medicinal and bioconjugate chemistry because of their ease of synthesis, chemical stability, and potential biological activities.[1] As an example of the potential of 1,2,3-triazoles as pharmaceuticals, the combinatorial drug Zosyn (Chart 1) marketed by Pfizer has a 1,2,3-triazolyl-containing component. The current synthetic methods offer rapid access to both 1,4- and 1,5-disubstituted 1,2,3-triazoles from copper(I)- or ruthenium(II)-mediated azide−alkyne cycloadditions (Schemes 1A and 1B, respectively) with broad substrate scopes.[2−4] In comparison, the regioselective preparation of 1,4,5-trisubstituted-1,2,3-triazoles, which would further enhance the functional versatility of 1,2,3-triazolyl-containing substances, is relatively underdeveloped. Several methods for preparing 5-iodo-1,2,3-triazoles, which can be further elaborated using palladium-catalyzed cross-coupling reactions, are available.[5−9] The de novo synthesis of 1,4,5-trisubstituted 1,2,3-triazoles via an amine-catalyzed reaction between a ketone and an aromatic azide was recently reported.[10−12] Another strategy is post-synthetic functionalization of the C5 position of 1,4-disubstituted 1,2,3-triazoles via transition metal-mediated processes.[13−17]

Chart 1. Zosyn



Scheme 1. Known Reactions Mentioned in the Text: (A) Copper(I)-Catalyzed Azide−Alkyne Cycloaddition;[2,3] (B) Ruthenium(II)-Catalyzed Azide−Alkyne Cycloaddition;[4] (C) Hetero-Diels−Alder Reaction of 4-Alkenylthiazole and 1,2,4-Triazoline-3,5-dione;[18] and (D) 5-Iodo-1,2,3-triazole Formation from Azide and Alkyne[9]



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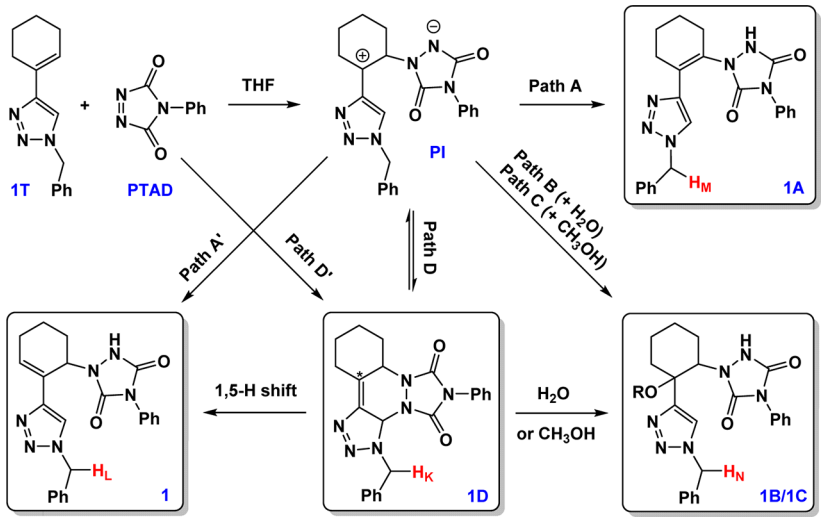
Scheme 2. Postulated Mechanisms of the Reaction between 1T and PTAD[a]



[a]Ph = phenyl. Paths A and A′, proton transfer; paths B and C, solvolysis (**1B**, R = H; **1C**, R = CH_3) of the PI intermediate; paths D and D′, indirect and direct formation of the Diels–Alder intermediate **1D**. Path A′ from **PI** and/or 1,5-H shift from **1D** affords the major product **1**.

The reaction of a 4-alkenylthiazole with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[19] was reported to afford a polyheterocyclic compound through a concerted Diels–Alder (D–A) pathway (Scheme 1C).[18] The structural similarity between thiazole and 1,2,3-triazole led us to hypothesize that 4-alkenyl-1,2,3-triazoles may also undergo D–A reactions with dienophiles, resulting in fused heterocycles via functionalization of the C5 position with a 100% atom economy.

However, 4-(1′-cyclohexenyl)-1,2,3-triazoles react with PTAD in THF at room temperature to afford primarily the ene reaction products,[20] as is typically observed in reactions between an alkene and PTAD.[21] The details of the reaction between 1,2,3-triazole **1T** and PTAD are illustrated in Scheme 2. In addition to the ene product **1**, compound **1A** was observed as a minor side product.[22] If water was not carefully excluded, the water adduct **1B** was also observed. When water was intentionally added to the reaction mixture in CH_3CN up to 25%, the amount of water adduct **1B** as a mixture of two diastereomers rose to 34% (Figure S1 in Supporting Information). The reaction conducted in CH_3OH affords the CH_3OH adduct **1C**, also as a mixture of two diastereomers. The structure of the major diastereomer **1C** was confirmed via single crystal X-ray crystallography (Figure 1).[23]

The observation of the solvent adducts **1B** and **1C** in diastereomeric mixtures leads to the formulation of a stepwise mechanism involving a polar intermediate (**PI** in Scheme 2). The electrophilic addition of PTAD to an alkene, a diene, or an arene may involve a zwitterionic intermediate.[24−28] As proposed in Scheme 2, following the addition of PTAD to **1T**, the zwitterionic intermediate **PI** containing a benzylic-like cation may undergo proton transfer (paths A and A′) to afford enamide **1A** and major product **1**,[29] or solvolysis to give **1B** or **1C** in a mixture of diastereomers. In addition to these pathways, the **PI** may choose ring closure to give the formal Diels–Alder product **1D**, which tautomerizes to the major ene reaction product **1** or undergoes stereospecific S_N2' solvolysis due to the propensity of the urazolyl as a leaving group to give **1B** or **1C** as single diastereomers.

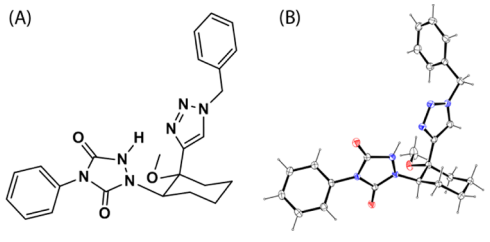


Figure 1. (A) ChemDraw and (B) ORTEP views of the major diastereomer of compound **1C** (30% ellipsoids). Hydrogen and carbon, black; nitrogen, blue; oxygen, red.

Alternatively, as suggested by a reviewer, the D–A product **1D** may form first from **1T** and PTAD via path D′ (Scheme 2). Intermediate **1D** may equilibrate with the zwitterionic intermediate **PI**, which provides pathways to reach **1A** and **1B**/**1C** as mixtures of diastereomers. The 1,5-hydride shift pathway is available to **1D** to afford the major product **1**. In contrast to the pathway described in the previous paragraph, in which the formation of **PI** precedes the D–A intermediate **1D**, the alternative pathway has the D–A intermediate formation first, which then subsequently transforms to the **PI** intermediate in a reversible reaction (path D). The reaction between **1T** and PTAD in methanol results in predominantly one diastereomer (84%, Figures S2 and S3 in the Supporting Information), of which the triazolyl and urazolyl groups are *cis* to each other (Figure 1). This observation supports the mechanism involving the initial formation of D–A intermediate **1D**, which rapidly undergoes the stereospecific S_N2' methanolysis to afford diastereomer **1C** shown in Figure 1. The minor diastereomer can be attributed to the S_N1 methanolysis from the **PI** intermediate produced via the reversible path D (Scheme 2).

The intermediary of the formal D–A product **1D** is supported by the ^{1}H NMR time-course experiment (Figure 2). Compound **1T** (^{1}H NMR spectrum in THF-d_8 is shown in Figure S6 in the Supporting Information) reacts rapidly with PTAD in THF-d_8 to afford **1D** within the time required to acquire the first ^{1}H NMR spectrum after the initial mixing, ca. 75 s. The two doublets at 5.42 and 5.27 ppm (Figure 2) are assigned to the diastereotopic H_K of the D–A intermediate **1D**

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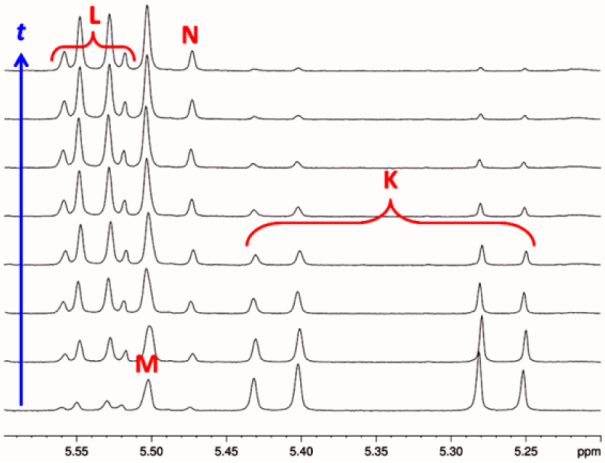


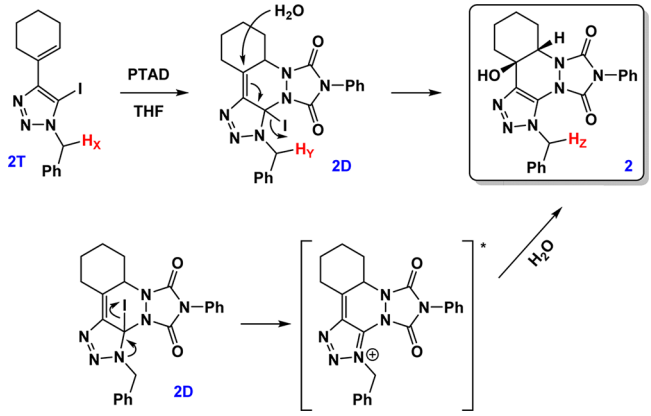
Figure 2. Benzylic proton regions of ^{1}H NMR spectra (500 MHz, THF-d_8) of the reaction of **1T** (0.05 mmol) with PTAD (0.05 mmol) over the first 10 min, after which no apparent change of the spectrum was observed. Peak assignments (K, L, M, N) are shown in Scheme 2. The Supporting Information contains an expansion (Figure S4) and additional peak assignments (Figure S5).

(Scheme 2). The two doublets subsequently convert to a new AB spin system slightly downfield that are assigned to the benzylic H_L (5.55 and 5.53 ppm) of the isolated ene product **1**. The minor product **1A**, of which the singlet benzylic H_M (5.50 ppm) is shown in Figure 2, appears simultaneously with intermediate **1D**. The formation of the zwitterionic intermediate **PI**, which is the precursor of **1A**, is therefore very rapid either directly from **1T** and PTAD or from **1D** via a fast equilibrium. At this moment, we are not able to distinguish these two scenarios. The hydrolyzed side product **1B** has a delayed appearance (benzylic H_N in Figure 2), which suggests that in addition to the direct hydroxylation of the zwitterionic intermediate **PI**, nucleophilic attack of water at C* in **1D** (Scheme 2) displaces the urazolyl group at the C5 position of the triazole ring via an S_N2' pathway.

We concluded on the basis of the above data that contrary to our initial intention of a D−A type reaction, the reaction between 4-(1′-cyclohexenyl)-1,2,3-triazole and PTAD is unsuccessful in functionalizing the C5 position of a 1,2,3-triazole. The mechanistic information revealed in these experiments, however, led to the formulation of a new strategy for achieving our original objective. In Scheme 2, solvolysis of the D−A intermediate **1D** results in the opening of the six-membered ring because of the propensity of the urazolyl moiety as a leaving group. A surrogate leaving group preinstalled at the C5 position may also facilitate the solvolysis but would retain the polycyclic core of **1D**, hence the functionalization at the C5 position.

The 5-iodo-1,2,3-triazole **2T** (Scheme 3) was prepared via a recently reported method, in which mixing $Cu(ClO_4)_2{\cdot}6H_2O$ and NaI or KI produces copper(I) catalyst and triiodide electrophile to collectively mediate the one-step 5-iodo-1,2,3-triazole formation from an alkyne and an azide (Scheme 1D).[9] In the reactions affording **2T**−**11T**, an accelerating ligand TBTA[30,31] was required.[9] The reaction of **2T** with PTAD was monitored via ^{1}H NMR spectroscopy. Similar to **1T**, the reaction initially affords the D−A product (**2D**, Scheme 3), which was observed in the spectra collected during the early stage of the reaction at 5 °C (green in Figure 3). **2D** subsequently transforms into the more stable compound **2** (red

Scheme 3. Reaction of 5-Iodo-1,2,3-triazole 2T with PTAD in THF To Afford 2[a]



[a]Benzylic protons X, Y, and Z are marked in Figure 3. The addition of $AgNO_3$ may aid the elimination of iodide in the bottom route to reach the cationic intermediate.

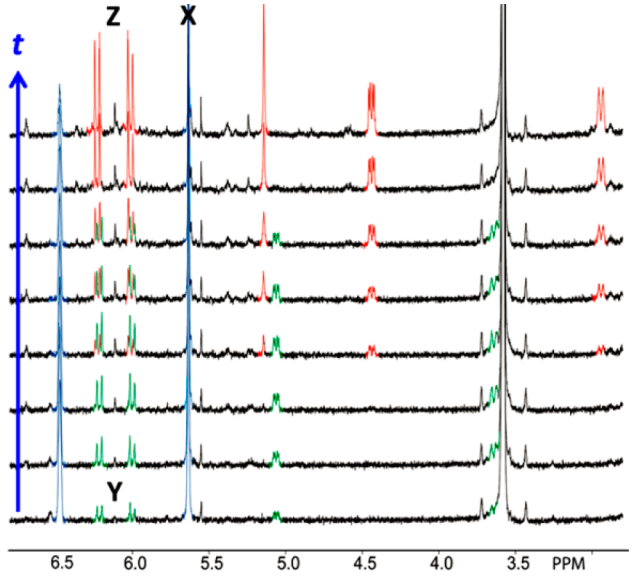


Figure 3. ^{1}H NMR spectra (500 MHz, THF-d_8) of the reaction between **2T** (0.04 mmol) and PTAD (0.05 mmol) over the first 10 min at 5 °C. The reaction did not reach completion when the experiment was terminated. X, Y, and Z are marked in Scheme 3. **2T**, blue; **2D**, green; **2**, red.

in Figure 3), which was characterized via single crystal X-ray crystallography (Figure 4). Hydrolysis of **2D** occurs either via a concerted S_N2' pathway or following the formation of a cationic

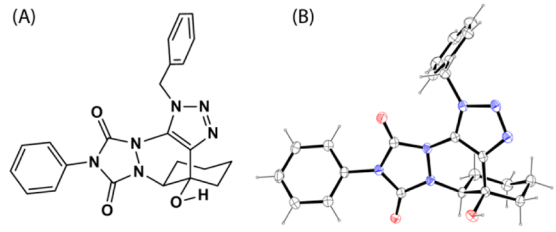


Figure 4. (A) ChemDraw and (B) ORTEP views of compound **2** (30% ellipsoids). Hydrogen and carbon, black; nitrogen, blue; oxygen, red.

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intermediate after eliminating the iodide, especially when assisted by $AgNO_3$ (Scheme 3). Therefore, different from **1T**, instead of the urazolyl group, iodide from **2T** is displaced from either route to afford the fused polycyclic compound **2** (Scheme 3).

A few other 4-(1′-cyclohexenyl)-5-iodo-1,2,3-triazoles were subjected to this procedure to afford fused tetracyclic products in modest to good yields (Table 1). $AgNO_3$ is not required, but it may increase the yield presumably by aiding the departure of the iodo group or by scavenging the formed iodide. The addition of water (Figure S7 in the Supporting Information) to the reaction mixture hampers the reaction by consuming PTAD. 5-Iodo-1,2,3-triazoles (e.g., **2T**) appear to have a lower reactivity than 5-proto-1,2,3-triazoles (e.g., **1T**) toward PTAD. The side reactions between other nucleophiles in the reaction system and PTAD consequently become significant, leading to the moderate isolated yields in many cases.

In conclusion, we have demonstrated that the C5 position of a 4-(1′-cyclohexenyl)-5-iodo-1,2,3-triazole can be further functionalized via a reaction with PTAD to afford a polyheterocyclic structure. The appearance of a zwitterionic intermediate in the reaction mechanism is supported by the analysis of product distributions. A formal Diels–Alder intermediate was observed using ^{1}H NMR spectroscopy, the formation of which either precedes or follows the formation of the zwitterionic intermediate. Subsequent S_N2' solvolysis of the Diels–Alder intermediate leads to the formation of polycyclic compounds at the expense of the iodide as the leaving group. Without the 5-iodo group, a more typical ene reaction product is afforded without functionalization at the C5 position.

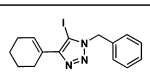
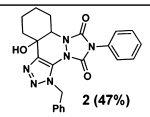
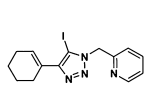
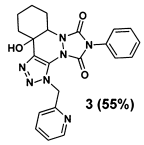
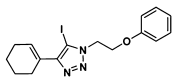
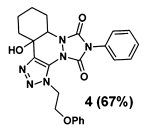
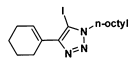
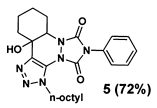
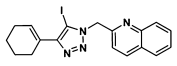
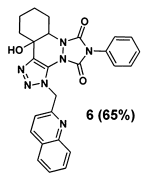
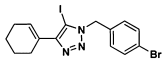
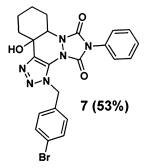
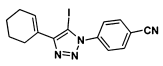
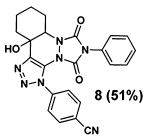
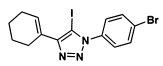
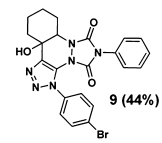
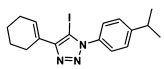
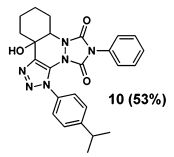
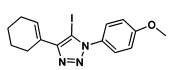
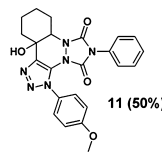
EXPERIMENTAL SECTION

Warning! *Low-molecular-weight organic azides and copper(II) perchlorate used in this study are potentially explosive. Appropriate protective measures should always be taken when handling these compounds.* Solvents and reagents were purchased from various commercial sources and were used without further purification. $Cu(ClO_4)_2{\cdot}6H_2O$ was placed in a vacuum oven at 40 °C for 16 h and was stored in a dry keeper before use. ^{1}H NMR kinetic experiments were conducted on a 500 MHz NMR spectrometer. Characterizations of new compounds were performed on 300 or 500 MHz NMR spectrometers. $CDCl_3$ was treated with alumina gel before use. All chemical shifts are reported in δ units relative to tetramethylsilane. Flash chromatography was performed using alumina (80–200 mesh) or silica gel as the stationary phase. The organic azides were prepared using known procedures.[32,33] The acceleratory ligand tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-amine (TBTA) was prepared according to a published procedure.[31]

Compounds 1, 1A, and 1B. Compound **1T** (121 mg, 0.506 mmol) was added to a 5 mL flame-dried round-bottom flask equipped with a stir bar. PTAD (94 mg, 0.54 mmol) was added to the flask, which was then sealed with a septum. Dry THF (2.5 mL) was added via a syringe, and the reaction mixture was allowed to stir at rt. The indicative red color of PTAD faded within 4 min to a pale pink, and after 9 min the pink color disappeared. The two products (**1** and **1A**) were separated on a silica column eluted with ethyl acetate in CH_2Cl_2 (0–50%) to afford the major product **1** in 31% yield as an amorphous solid (64 mg, 0.15 mmol). The minor product **1A** was isolated in <5% yield as an amorphous solid.

Major Product **1**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (s(b), 1H), 7.51 (s, 1H), 7.50 (d, J = 4.4 Hz, 4H), 7.41 (t, J = 4.3 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 1.8 Hz, 2H), 7.29–7.27 (m, 2H), 6.84 (td, J = 2.4, 1.5 Hz, 1H), 5.55 (d, J = 15 Hz, 1H), 5.48 (d, J = 15 Hz, 1H), 5.13 (m, 1H), 2.31–2.21 (m, 2H), 2.18–2.12 (m, 1H), 2.12–2.04 (m, 1H), 2.01–1.92 (m, 1H), 1.83–1.66 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1 (q), 152.4 (quaternary), 146.3 (quaternary), 134.5 (CH), 133.8 (quaternary), 131.5 (quaternary), 129.2 (CH), 129.1

Table 1. Structures and Isolated Yields of 4-(1′-Cyclohexenyl)-5-iodo-1,2,3-triazoles and Major Products of the Subsequent Reactions with PTAD

entry	5-iodo-1,2,3-triazole[a]	cyclization product[b]
1	 2T (57%)	 2 (47%)
2	 3T (59%)	 3 (55%)
3	 4T (63%)	 4 (67%)
4	 5T (52%)	 5 (72%)
5	 6T (60%)	 6 (65%)
6	 7T (81%)	 7 (53%)
7	 8T (42%)	 8 (51%)
8	 9T (64%)	 9 (44%)
9	 10T (50%)	 10 (53%)
10	 11T (67%)	 11 (50%)

[a]1-Ethynylcyclohexene (5 mmol), azide (5 mmol), THF (50 mL), TEA (5 mmol), NaI (20 mmol), TBTA (0.3 mmol), and $Cu(ClO_4)_2{\cdot}6H_2O$ (10 mmol), rt. [b]5-Iodo-1,2,3-triazole (0.5 mmol), THF (2.5 mL), and PTAD (0.55 mmol), rt. $AgNO_3$ (0.5 mmol) assists the reaction in several cases.

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(CH), 128.8 (CH), 128.0 (CH), 128.0 (CH), 125.4 (CH), 123.9 (quaternary), 119.7 (CH), 54.2 (CH_2), 52.0 (CH), 26.9 (CH_2), 24.9 (CH_2), 19.3 (CH_2). HRMS (EI, double-focusing): m/z [M^+] calcd for $C_{23}H_{22}N_6O_2$ 414.1804, found 414.1796.

Minor Product ***1A***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (s(b), 1H), 7.59−7.45 (m, 5H), 7.44−7.35 (m, 4H), 7.33−7.24 (m, 2H), 5.51 (s, 2H), 2.47 (s, 2H), 2.58 (s, 2H), 1.90−1.70 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5 (quaternary), 151.5 (quaternary), 146.0 (quaternary), 134.2 (quaternary), 131.5 (quaternary), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.8 (quaternary), 128.1 (CH), 128.0 (quaternary), 125.6 (CH), 121.9 (CH), 54.3 (CH_2), 29.2 (CH_2), 25.6 (CH_2), 22.2 (CH_2), 21.8 (CH_2). HRMS (EI, double-focusing): m/z [M^+] calcd for $C_{23}H_{22}N_6O_2$ 414.1804, found 414.1804.

Minor Product ***1B*** *from Hydrolysis*. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (s(b), 1H), 7.67 (s, 1H), 7.52−7.45 (m, 4H), 7.39 (m, 5H), 7.30 (m, 1H), 5.54 (d, J = 14.8 Hz, 2H), 4.90 (s(b), 1H), 4.50 (dd, J = 8.1, 4.3 Hz, 1H), 2.30 (m, 1H), 2.05 (m, 1H), 1.95 (m, 2H), 1.81 (m, 2H), 1.52 (m, 1H), 1.13 (m, 1H). HRMS (EI, double-focusing): m/z [M^+] calcd for $C_{23}H_{24}N_6O_3$ 432.1910, found 432.1905.

Preparative Synthesis of 1C. Compound **1T** (120 mg, 0.501 mmol) was added to a flame-dried 10 mL round-bottom flask equipped with a stir bar. PTAD (95 mg, 0.54 mmol) was added as a solid, and the flask was sealed with a septum. CH_3OH (2.5 mL) was added via a syringe. Within 15 min of mixing, the red color of PTAD disappeared and the reaction was stopped via dilution with CH_2Cl_2 (3 mL). Upon solvent removal, the reaction mixture was separated on a silica column eluted with ethyl acetate in CH_2Cl_2 (0−100%). The CH_3OH adduct (**1C**) was isolated in <10% yield as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.40 (s, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.57 (s, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.45 (d, J = 6.2 Hz, 2H), 7.39 (tt, J = 4.8, 1.2 Hz, 1H), 7.34−7.31 (m, 2H), 5.66 (d, J = 14.9 Hz, 1H), 5.59 (d, J = 13.9 Hz, 1H), 4.66 (dd, J = 8.4, 4.0 Hz, 1H), 3.23 (s, 3H), 2.29 (d, J = 14.6 Hz, 1H), 2.05 (qd, J = 8.0, 3.6 Hz, 1H), 1.99 (m, 1H), 1.84 (d, J = 12.4 Hz, 1H), 1.78 (d, J = 12.4 Hz, 1H), 1.52 (qt, J = 5.1, 4.4 Hz, 1H), 1.13 (qt, J = 5.6, 3.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 152.8, 147.4, 134.0, 131.8, 129.4, 129.1, 129.05, 128.1, 127.9, 125.7, 123.8, 61.0, 54.6, 50.5, 41.0, 35.7, 28.1, 25.4, 22.9. HRMS (ESI-TOF): m/z [M + H^+] calcd for $C_{24}H_{27}O_3N_6$ 447.2145, found 447.2145.

Compound 2T. This is a representative procedure for preparing **2T**−**11T**. Benzylazide (676.1 mg, 5.08 mmol) and 1-ethynylcyclohexene (547.0 mg, 5.15 mmol) were dissolved in THF (50 mL) in a 100 mL round-bottom flask equipped with a stir bar. Triethylamine (520 mg, 5.14 mmol) was added, followed by NaI (3.2 g, 21 mmol). The mixture was allowed to stir at rt for ∼5 min before a catalytic amount of TBTA (174 mg, 0.33 mmol) and $Cu(ClO_4)_2{\cdot}6H_2O$ (3.75 g, 10.1 mmol) were added sequentially. The reaction mixture was stirred at rt for an additional 18 h before it was diluted with ethyl acetate and 10% NH_4OH solution and transferred to a separatory funnel. The product was extracted with ethyl acetate (30 mL × 3), washed with saturated brine, and dried over Na_2SO_4. Upon solvent removal, compound **2T**[34] was isolated on an alumina column eluted with CH_2Cl_2 in hexanes (0−75%) in 57% yield as an amorphous solid (1.04 g, 2.9 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 7.2 Hz, 2H), 7.37 (t, J = 1.6 Hz, 1H), 7.30 (d, J = 5.7 Hz, 2H), 6.49 (sept, 1H), 5.65 (s, 2H), 2.62−2.58 (m, 2H), 2.28−2.24 (m, 2H), 1.84−1.79 (m, 2H), 1.74−1.69 (m, 2H).

Compound 3T. Representative procedure in 59% yield as an amorphous solid (215 mg, 0.59 mmol). ^{1}H NMR (500 MHz, CD_3CN): δ 8.56 (s, 1H), 7.77 (td, J = 6.0, 1.7 Hz, 1H), 7.33 (t, J = 6.4 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 6.48 (m, 1H), 5.72 (s, 2H), 2.59−2.53 (m, 2H), 2.29−2.22 (m, 2H), 1.84−1.80 (m, 2H), 1.74−1.68 (m, 2H). ^{13}C NMR (125 MHz, CD_3CN): δ 154.8, 151.2, 149.5, 137.1, 128.4, 128.0, 123.1, 121.7, 76.9, 27.1, 25.0, 22.5, 21.7. HRMS (CI, double-focusing, isobutane reagent gas): m/z [M + H]$^+$ calcd for $C_{14}H_{16}N_4I$ 367.0420, found 367.0433.

Compound 4T. Representative procedure (KI in place of NaI) in 63% yield as an amorphous solid (50 mg, 0.13 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30−7.24 (m, 2H), 6.96 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 6.42 (m, 1H), 4.79 (t, J = 5.5 Hz, 2H), 4.41 (t, J = 5.5 Hz, 2H), 2.60−2.49 (m, 2H), 1.81−1.65 (m, 4H). ^{13}C NMR (125 MHz, CD_3CN): δ 158.2, 129.5, 128.4, 128.1, 121.3, 117.2, 114.6, 77.1, 66.3, 49.8, 27.1, 25.0, 22.4, 21.7. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{16}H_{19}N_3IO$ 396.05728, found 396.05655.

Compound 5T. Representative procedure in 52% yield as an amorphous solid (246 mg, 0.64 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46 (m, 1H), 4.42−4.39 (m, 2H), 2.61−2.56 (m, 2H), 2.29−2.23 (m, 2H), 1.97−1.90 (m, 2H), 1.85−1.79 (m, 2H), 1.75−1.69 (m, 3H), 1.43−1.26 (m, 9H), 0.92 (t, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.1, 128.4, 128.2, 74.6, 50.7, 31.7, 29.9, 29.1, 29.0, 27.3, 26.4, 25.4, 22.7, 22.6, 22.0, 14.1. HRMS (EI, double-focusing): m/z [M]$^+$ calcd for $C_{16}H_{27}IN_3$ 388.1250, found 388.1257.

Compound 6T. Representative procedure in 60% yield as an amorphous solid (288 mg, 0.69 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.40 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.78 (td, J = 5.4, 1.5 Hz, 1H), 7.62 (td, J = 5.8, 1.2 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 6.49 (pent, J = 1.9 Hz, 1H), 5.97 (s, 2H), 2.54−2.49 (m, 2H), 2.23−2.17 (m, 2H), 1.76−1.70 (m, 2H), 1.66−1.60 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 155.7, 150.6, 147.4, 137.9, 130.5, 129.1, 128.6, 128.4, 127.5, 127.3, 127.2, 119.7, 80.9, 55.9, 27.3, 25.3, 22.7, 22.0. HRMS (CI, double-focusing, isobutane reagent gas): m/z [M + H]$^+$ calcd for $C_{18}H_{18}IN_4$ 417.0576, found 417.0586.

Compound 7T. Representative procedure in 81% yield as an amorphous solid (317 mg, 0.71 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.59 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.44 (pent, J = 1.8 Hz, 1H), 2.49−2.44 (m, 2H), 2.21−2.16 (m, 2H), 1.74−1.70 (m, 2H), 1.65−1.58 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 150.7, 135.4, 132.2, 130.0, 128.5, 127.5, 121.6, 80.1, 53.1, 27.3, 25.3, 22.7, 22.0. HRMS (CI, double-focusing, isobutane reagent gas): m/z [M + H]$^+$ calcd for $C_{15}H_{16}BrN_3I$ 443.9572, found 443.9580.

Compound 8T. Representative procedure in 42% yield as an amorphous solid (157 mg, 0.42 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.15 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H), 6.50 (s, 1H), 2.55−2.49 (m, 2H), 2.27−2.21 (m, 2H), 1.79−1.72 (m, 2H), 1.69−1.62 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 151.4, 140.8, 134.2, 128.6, 128.2, 128.1, 118.4, 113.4, 81.4, 27.5, 25.4, 22.7, 22.0. HRMS (CI, double-focusing, isobutane reagent gas): m/z [M + H]$^+$ calcd for $C_{15}H_{14}IN_4$ 377.0263, found 377.0270.

Compound 9T. Representative procedure in 64% yield as an amorphous solid (127 mg, 0.30 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 6.52−6.46 (m, 1H), 2.63−2.55 (m, 2H), 2.30−2.21 (m, 2H), 1.87−1.66 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 151.0, 136.6, 132.9, 129.2, 128.3, 128.2, 123.8, 81.7, 27.4, 25.4, 22.7, 22.0. HRMS (CI, double-focusing, isobutane reagent gas): m/z [M + H]$^+$ calcd for $C_{14}H_{14}N_3BrI$ 429.9416, found 429.9415.

Compound 10T. Representative procedure in 50% yield as an amorphous solid (227 mg, 0.58 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.50 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 6.50 (s, 1H), 3.04 (pent, J = 6.9 Hz, 1H), 2.57−2.48 (m, 2H), 2.27−2.18 (m, 2H), 1.79−1.70 (m, 2H), 1.70−1.62 (m, 2H), 1.28 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 151.0, 150.7, 135.2, 128.4, 128.0, 127.7, 127.0, 81.9, 33.7, 27.4, 25.3, 24.2, 22.7, 22.0. HRMS (CI, double-focusing, isobutane reagent gas): m/z [M + H]$^+$ calcd for $C_{17}H_{21}IN_3$ 394.0780, found 394.0792.

Compound 11T. Representative procedure in 67% yield as an amorphous solid (282 mg, 0.74 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 6.54 (sept, J = 1.8 Hz, 1H), 2.68−2.62 (m, 2H), 2.33−2.27 (m, 2H), 1.89−1.82 (m, 2H), 1.79−1.72 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.7, 150.5, 130.3, 128.6, 128.5, 127.9, 114.9, 82.2, 56.1, 27.4, 25.4, 22.7, 22.0. HRMS (CI, double-focusing, isobutane reagent gas): m/z [M + H]$^+$ calcd for $C_{15}H_{17}OIN_3$ 382.0417, found 382.0429.

Compound 2. This is a representative procedure for preparing **2**−**11** from **2T**−**11T**, respectively. Compound **2T** (184.2 mg, 0.50 mmol), $AgNO_3$ (85.1 mg, 0.50 mmol), and dry THF (2 mL) were added to a 5 mL flame-dried round-bottom flask equipped with a stir bar, and the flask was sealed with a septum. PTAD (95.9 mg, 0.55 mmol) was weighed into a separate container and dissolved with dry

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THF (0.5 mL). The PTAD solution was then added dropwise via a syringe to the reaction flask over ~45 min at a rate such that the red color had completely vanished between drops. The reaction mixture was allowed to stir for an additional 60 min at rt before it was diluted with CH_2Cl_2 and filtered through a small plug of silica gel to remove the inorganic materials. The crude product was purified on a silica column on which the less polar impurities were removed with an isocratic portion of CH_2Cl_2. The product was recovered via elution of 20−25% ethyl acetate in CH_2Cl_2 in 47% yield as an amorphous solid (100.3 mg, 0.233 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (m, 4H), 7.46 (m, 3H), 7.31 (m, 3H), 6.26 (d, J = 15.4 Hz, 1H), 6.05 (d, J = 14.6 Hz, 1H), 4.55 (dd, J = 7.1, 5.4 Hz, 1H), 3.11 (d, J = 13.4 Hz, 1H), 3.00 (s, 1H), 1.93−1.70 (m, 4H), 1.43 (qt, J = 6.8, 3.8 Hz, 1H), 1.81 (qt, J = 6.8, 3.8 Hz, 1H), 0.92 (qd, J = 9.8, 3.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.0 (quaternary), 148.1 (quaternary), 134.8 (quaternary), 133.0 (quaternary), 130.5 (quaternary), 129.4 (CH), 129.3 (CH), 128.9 (CH), 128.4 (CH), 127.7 (CH), 125.8 (CH), 68.4 (CH), 59.3 (CH_2), 54.3 (CH_2), 35.1 (CH_2), 27.9 (CH_2), 24.0 (CH_2), 22.6 (CH_2). HRMS (EI, double-focusing): m/z $[M]^+$ calcd for $C_{23}H_{22}N_6O_3$ 430.1754, found 430.1756.

Compound 3. Representative procedure in 55% yield as an amorphous solid (120.1 mg, 0.278 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (d, J = 4.7 Hz, 1H), 7.67 (td, J = 6.0, 1.8 Hz, 1H), 7.47−7.41 (m, 4H), 7.41−7.37 (m, 1H), 7.21 (dd, J = 5.1, 2.6 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 6.38 (d, J = 16.4 Hz, 1H), 6.06 (d, J = 15.8 Hz, 1H), 4.54 (dd, J = 7.4, 5.0 Hz, 1H), 4.28 (s, 1H), 3.06 (d, J = 12.2 Hz, 1H), 1.93 (d, J = 14.5 Hz, 1H), 1.84 (td, J = 8.8, 4.1 Hz, 1H), 1.77−1.69 (m, 2H), 1.41 (qt, J = 12.9, 3.6 Hz, 1H), 1.31−1.12 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5 (quaternary), 149.5 (CH), 149.0 (quaternary), 147.7 (quaternary), 136.9 (CH), 132.8 (quaternary), 130.6 (quaternary), 130.4 (quaternary), 129.3 (CH), 128.7 (CH), 125.8 (CH), 122.9 (CH), 121.4 (CH), 68.3 (quaternary), 59.6 (CH), 55.4 (CH_2), 35.0 (CH_2), 27.7 (CH_2), 24.1 (CH_2), 22.6 (CH_2). HRMS (EI, double-focusing): m/z $[M]^+$ calcd for $C_{22}H_{21}O_3N_7$ 431.1706, found 431.1704.

Compound 4. Representative procedure in 67% yield as an amorphous solid (102 mg, 0.22 mmol). $AgNO_3$ was not used in this case. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52−7.41 (m, 5H), 7.26 (t, J = 7.3 Hz, 2H), 6.97 (t, J = 6.4 Hz, 1H), 6.80 (d, J = 7.8 Hz, 2H), 5.58 (dt, J = 6.3, 2.1 Hz, 1H), 5.04 (dt, J = 5.5, 4.3 Hz, 1H), 4.50 (d, J = 5.2 Hz, 1H), 4.43 (t, J = 4.9 Hz, 2H), 4.13 (s, 1H), 3.00 (d, J = 14.1 Hz, 1H), 1.85 (d, J = 12.3 Hz, 1H), 1.79 (td, J = 8.6, 4.9 Hz, 1H), 1.69 (d, J = 15.3 Hz, 1H), 1.60 (d, J = 15 Hz, 1H), 1.63 (qt, J = 12.9, 4.9 Hz, 1H), 1.06 (qt, J = 12.9, 4.3 Hz, 1H), 0.92 (qd, J = 9.2, 4.3 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 158.0, 148.9, 147.9, 132.5, 130.5, 130.1, 129.6, 129.3, 128.8, 125.8, 121.4, 114.5, 68.3, 66.4, 59.4, 50.6, 34.9, 27.8, 24.0, 22.4. HRMS (EI, double-focusing): m/z $[M]^+$ calcd for $C_{24}H_{24}N_6O_4$ 460.1859, found 460.1863.

Compound 5. Representative procedure in 72% yield as an amorphous solid (164 mg, 0.36 mmol). $AgNO_3$ was not used in this case. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 4.2 Hz, 4H), 7.46 (t, J = 4.7 Hz, 1H), 4.99−4.92 (m, 1H), 4.81−4.73 (m, 1H), 4.58 (dd, J = 7.4, 5.0 Hz, 1H), 3.36 (s, 1H), 3.08 (d, J = 15.0 Hz, 1H), 1.90−1.71 (m, 4H), 1.52−1.39 (m, 1H), 1.24−1.05 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.2 (quaternary), 148.1 (quaternary), 132.6 (quaternary), 130.6 (quaternary), 129.3 (CH), 129.2 (quaternary), 128.8 (CH), 125.6 (CH), 68.4 (quaternary), 59.5 (CH), 51.5 (CH_2), 35.1 (CH_2), 31.7 (CH_2), 30.0 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.0 (CH_2), 26.4 (CH_2), 24.0 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{24}H_{33}N_6O_3$ 453.2614, found 453.2601.

Compound 6. Representative procedure in 65% yield as an amorphous solid (147 mg, 0.31 mmol). $AgNO_3$ was not used in this case. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.68 (td, J = 5.5, 1.4 Hz, 1H), 7.55 (td, J = 6.9, 1.2 Hz, 1H), 7.42−7.34 (m, 5H), 7.29 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 16.6 Hz, 1H), 6.19 (d, J = 16.6 Hz, 1H), 4.59 (dd, J = 6.8, 4.5 Hz, 1H), 4.16 (s, 1H), 3.14 (d, J = 14.7 Hz, 1H), 2.02−1.95 (m, 1H), 1.95−1.80 (m, 3H), 1.60−1.44 (m, 2H), 1.38−1.27 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5 (quaternary), 148.8 (quaternary), 147.7 (quaternary), 147.5 (quaternary), 137.1 (CH), 132.8 (quaternary), 130.9 (quaternary), 130.5 (quaternary), 129.9 (CH), 129.2 (CH), 128.9 (CH), 128.6 (CH), 127.8 (CH), 127.5 (quaternary), 126.7 (CH), 125.8 (CH), 118.7 (CH), 68.5 (quaternary), 59.6 (CH), 55.8 (CH_2), 35.2 (CH_2), 27.8 (CH_2), 24.2 (CH_2), 22.7 (CH_2). HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{26}H_{24}N_7O_3$ 482.1941, found 482.1955.

Compound 7. Representative procedure in 53% yield as an amorphous solid (134 mg, 0.26 mmol). $AgNO_3$ was not used in this case. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54−7.43 (m, 7H), 7.17 (d, J = 6.4 Hz, 2H), 6.17 (d, J = 5.1 Hz, 1H), 5.94 (d, J = 5.1 Hz, 1H), 4.52 (dd, J = 7.4, 5.0 Hz, 1H), 3.69 (s, 1H), 3.06 (d, J = 3.1 Hz, 1H), 1.93−1.67 (m, 4H), 1.40 (q, J = 13.5 Hz, 1H), 1.12 (q, J = 13.6 Hz, 1H), 0.88 (q, J = 12.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9 (quaternary), 148.1 (quaternary), 133.8 (quaternary), 133.1 (quaternary), 132.0 (CH), 130.4 (quaternary), 129.6 (CH), 129.4 (CH), 129.2 (quaternary), 128.9 (CH), 125.8 (CH), 125.6 (quaternary), 122.6 (quaternary), 68.4 (quaternary), 59.3 (CH), 53.7 (CH_2), 35.0 (CH_2), 27.9 (CH_2), 24.0 (CH_2), 22.6 (CH_2). HRMS (EI, double-focusing): m/z $[M]^+$ calcd for $C_{23}H_{21}O_3BrN_6$ 508.0859, found 508.0846.

Compound 8. Representative procedure in 51% yield as an amorphous solid (113 mg, 0.26 mmol). $AgNO_3$ was not used in this case. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 6.4 Hz, 2H), 7.73 (d, J = 8.9 Hz, 2H), 7.41−7.37 (m, 2H), 7.36−7.32 (m, 3H), 4.61 (dd, J = 7.5, 4.9 Hz, 1H), 4.02 (d, J = 4.9 Hz, 1H), 2.05−2.01 (m, 1H), 1.84−1.70 (m, 3H), 1.46−1.35 (m, 1H), 1.28−1.11 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.3 (quaternary), 148.6 (quaternary), 140.1 (quaternary), 133.2 (quaternary), 133.1 (CH), 130.2 (quaternary), 129.7 (quaternary), 129.4 (CH), 129.0 (CH), 125.7 (CH), 124.6 (CH), 117.8 (quaternary), 113.3 (quaternary), 68.8 (quaternary), 59.4 (CH), 34.9 (CH_2), 28.6 (CH_2), 24.1 (CH_2), 22.5 (CH_2). HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{23}H_{19}N_7O_3$ 442.1628, found 442.1633.

Compound 9. Representative procedure in 44% yield as an amorphous solid (39 mg, 0.08 mmol). $AgNO_3$ was not used in this case. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.45−7.33 (m, 5H), 4.67 (dd, J = 12, 6.0 Hz, 1H), 3.15 (d, J = 12 Hz, 1H), 2.63 (s, 1H), 1.92−1.76 (m, 4H), 1.53−1.43 (m, 1H), 1.32−1.20 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4 (quaternary), 148.4 (quaternary), 135.9 (quaternary), 133.0 (quaternary), 132.3 (CH), 130.3 (quaternary), 129.7 (quaternary), 129.3 (CH), 128.9 (CH), 125.8 (CH), 125.7 (CH), 123.7 (quaternary), 68.8 (quaternary), 59.5 (CH), 35.0 (CH_2), 28.5 (CH_2), 24.2 (CH_2), 22.6 (CH_2). HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{22}H_{20}BrN_6O_3$ 495.0780, found 495.0781.

Compound 10. Representative procedure in 53% yield as an amorphous solid (117.5 mg, 0.26 mmol). $AgNO_3$ was not added in this case. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, J = 8.5 Hz, 2H), 7.44−7.35 (m, 7H), 4.68 (dd, J = 7.6, 4.9 Hz, 1H), 3.91 (s, 1H), 3.10 (d, J = 11.6 Hz, 1H), 3.02 (pent, J = 6.9 Hz, 1H), 2.05 (d, J = 16.2 Hz, 1H), 1.88 (td, J = 9.5, 3.9 Hz, 1H), 1.83−1.75 (m, 2H), 1.53−1.42 (m, 1H), 1.32 (d, J = 7.0 Hz, 6H), 1.30−1.20 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.4 (quaternary), 149.6 (quaternary), 148.4 (quaternary), 134.6 (quaternary), 133.0 (quaternary), 130.5 (quaternary), 129.6 (quaternary), 129.3 (CH), 128.7 (CH), 127.1 (CH), 125.9 (CH), 124.0 (CH), 68.8 (quaternary), 59.5 (CH), 35.0 (CH_2), 33.9 (CH_3), 28.6 (CH_2), 24.2 (CH_2), 23.9 (CH), 23.8 (CH), 22.6 (CH_2). HRMS (ESI-TOf): m/z $[M + H]^+$ calcd for $C_{25}H_{27}N_6O_3$ 459.2145, found 459.2161.

Compound 11. Representative procedure in 50% yield as an amorphous solid (111 mg, 0.25 mmol). $AgNO_3$ was not used in this case. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 9.0 Hz, 2H), 7.44−7.36 (m, 5H), 7.01 (d, J = 9.0 Hz, 2H), 4.67 (dd, J = 7.5, 5.0 Hz, 1H), 3.88 (s, 3H), 3.11 (d, J = 11.8 Hz, 1H), 2.05 (d, J = 10.0 Hz, 1H), 1.93−1.76 (m, 3H), 1.54−1.42 (m, 1H), 1.33−1.21 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3 (quaternary), 149.5 (quaternary), 148.1 (quaternary), 132.8 (quaternary), 130.4 (quaternary), 129.9 (quaternary), 129.8 (quaternary), 129.3 (CH), 128.7 (CH), 125.9 (CH), 125.8 (CH), 114.2 (CH), 68.7 (quaternary), 59.5 (CH), 55.5

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(CH_3), 35.0 (CH_2), 28.5 (CH_2), 24.2 (CH_2), 22.6 (CH_2). HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{23}H_{23}N_6O_4$ 447.1781, found 447.1796.

Representative Procedure of the ^{1}H NMR Time-Course Experiments. THF-d_8 (0.5 mL) was added to an NMR tube equipped with a mixing bulb and a cap. After the tube had been sealed, it was immersed in a dewar that contained dry ice and acetone. After cooling at −78 °C for several minutes, the NMR tube was inserted into the NMR spectrometer and the solvent was locked and shimmed upon. The NMR tube was quickly removed and reintroduced to the −78 °C dewar. Compound **1T** (11.3 mg, 0.05 mmol) and PTAD (6.7 mg, 0.05 mmol) were transferred from a 0.5 dram vial to the NMR tube. The sample was quickly mixed by inversion and reinserted into the spectrometer. Spectra were recorded every 75 s (Figure 2).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of reported compounds, an expanded figure depicting the ^{1}H NMR time-course experiment, additional informative ^{1}H NMR spectra of crude reaction mixtures, and .cif file of **1C** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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