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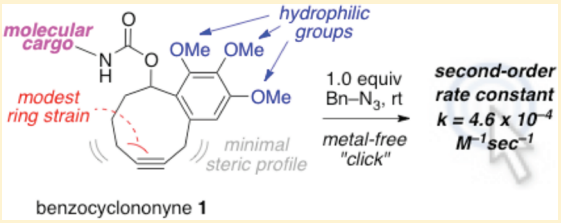
Strain-Promoted Azide–Alkyne Cycloadditions of Benzocyclononynes

Jumreang Tummatorn,† Paratchata Batsomboon, Ronald J. Clark, Igor V. Alabugin, and Gregory B. Dudley*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States

Supporting Information

ABSTRACT: Preliminary studies related to the design and development of new cycloalkyne reagents for metal-free click coupling are reported. Cyclononynes are more stable than cyclooctynes, and the robust benzocyclononyne platform offers spontaneous reactivity toward azides at rates competitive with other azidophiles that have been employed for metal-free click coupling. Benzocyclononynes (e.g., **1**) provide valuable insight into the design of new cycloalkynes for strain-promoted azide–alkyne cycloaddition (SPAAC) couplings for applications in which side reactions and decomposition of the reagent must be kept to a minimum.



The azide–alkyne cycloaddition (AAC) is the prototypical example of what has come to be known as "click" chemistry, or organic coupling reactions that meet specific criteria for performance efficiency.[1] Azides are superb click partners: small, easy to introduce, stable to many common reaction conditions, and reactive as 1,3-dipoles in the AAC reaction among others.

The AAC reaction is exothermic but slow under ambient conditions. Two recent strategies, copper catalysis and ring strain, have emerged to overcome kinetic barriers and propel the AAC reaction to the forefront of molecular sciences.[2] The copper-catalyzed azide–alkyne cycloaddition (CuAAC) of terminal alkynes delivers 1,4-disubstituted 1,2,3-triazoles in a regiocontrolled manner. The impact of this process can hardly be overstated. However, the need for a copper catalyst makes the CuAAC process nonideal for bioorthogonal coupling[3] and for many applications in inorganic/nanomaterials science.[4]

The strain-promoted azide–alkyne cycloaddition (SPAAC) takes advantage of ground-state destabilization (strain) to accelerate triazole formation under ambient or physiological conditions.[5] The metal-free SPAAC process is rapidly evolving in myriad directions, increasing demand for cycloalkyne tools. Current SPAAC tools are based on the cyclooctyne (OCT) platform (Figure 1; strained cycloalkenes also merit attention).[6] Cyclooctyne offers "explosive"[7a] reactivity toward azides but also "is air-sensitive and rearranges and polymerizes easily."[7b] From there, reactivity can be enhanced beyond the level at which the reagent can be isolated in pure form.[8]

Design and synthesis of cycloalkynes that are stable to diverse chemical environments and yet spontaneously reactive toward azides is thus an important current challenge. This challenge represents a methodological convergence of two of our long-standing interests: organic reagents[9] and high-value alkynes.[10,11] We recently disclosed a strategy for preparing

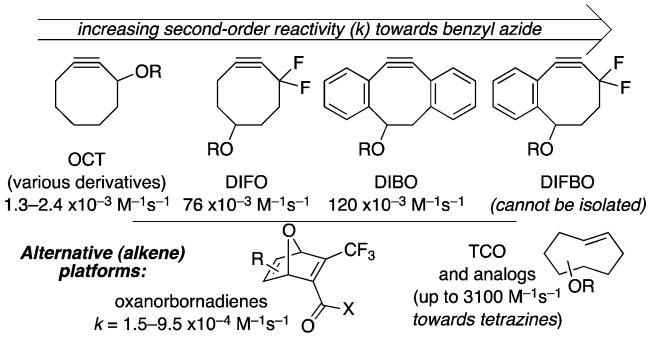


Figure 1. Selected SPAAC reagents based on cyclooctyne (OCT) and alternative alkene platforms for metal-free click coupling.

medium-ring cycloalkynes by ring expansion of vinylogous acyl triflates (e.g., **2** → **3**, Scheme 1)[10c] and now turn our attention to the design and synthesis of cycloalkynes for SPAAC coupling.

Considering that cyclooctyne stability can be a limiting factor,[7] we reasoned that SPAAC reactions of cyclononynes should be investigated, perhaps by taking advantage of lessons learned in the development of cyclooctyne reagents. Our hypothesis is that benzocyclononynes will provide a balance of stability and reactivity not available using the cyclooctyne platform. We focus on benzocyclononynes (cf. **3**, Scheme 1) because (i) fused benzene rings enhance SPAAC reactivity,[6a] (ii) a methylene spacer between the benzene ring and the alkyne minimizes steric repulsion in the SPAAC transition state,[12] and (iii) our modular assembly of cycloalkynes[10c] conveniently provides benzocyclononynes. Robust, reactive,

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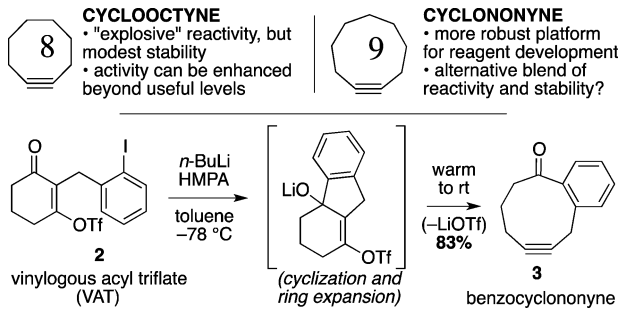
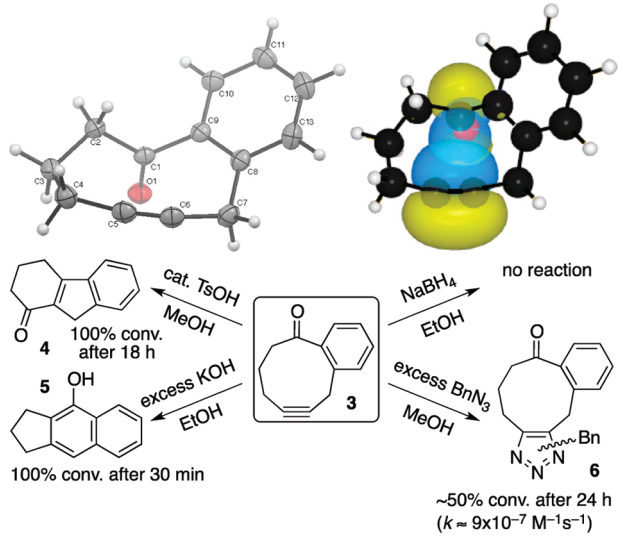
Scheme 1. Cyclooctyne, Cyclononyne Platforms, and the Preparation of Benzocyclononyne Ketone 3



and user-friendly cycloalkyne tools may enable SPAAC chemistry to grow in much the same way as the advent of ruthenium alkylidene catalysts helped accelerate the development of olefin metathesis chemistry.[13] Preliminary studies into the SPAAC coupling of benzocyclononynes are described herein.

Studies on cycloalkynone **3**[10c] provide important insights into cycloalkyne structure–activity relationships (Scheme 2).

Scheme 2. X-ray Structure, NBO Analysis Showing Transannular $\pi \rightarrow \pi^*$ Interaction, and Reactions of Ketone 3

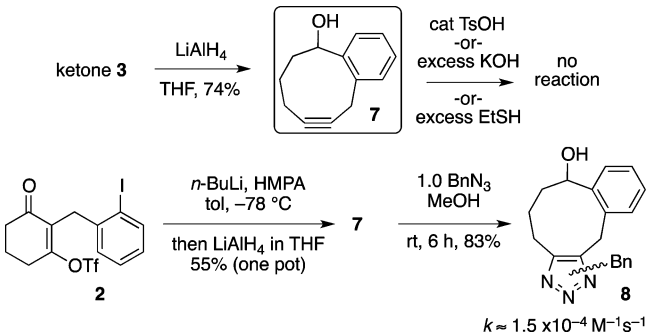


The crystal structure of **3** shows (i) the proximity (2.69 Å) and perpendicular orientation of the ketone (C1) to the alkyne (C5–C6), and (ii) the lack of conjugation between the ketone and the aromatic ring: the in-plane alkyne π-orbital is in near-perfect Bürgi–Dunitz alignment for transannular interaction with the ketone π^*-orbital. NBO analysis of **3** (B3LYP/6-31G(d,p) level) also points to transannular alkyne–ketone interaction (Scheme 2).[14]

Chemical reactivity of keto-alkyne **3** is best understood in the context of this interaction. Transannular keto-alkyne cyclization[15] is induced by either acid (**3** → **4**, Scheme 2) or base (**3** → **5**), but the ketone resisted reduction with $NaBH_4$. These observations suggest that keto-alkyne **3** is prone to cyclization but unusually stable to external reagents. Nonetheless, the alkyne showed modest reactivity with benzyl azide (**3** → **6**) at room temperature.[16]

Reduction of ketone **3** with $LiAlH_4$ provided alcohol **7**; note that ring expansion and reduction may be combined into a one-pot process (**2** → **7**, Scheme 3). Compared to ketone **3**, alcohol

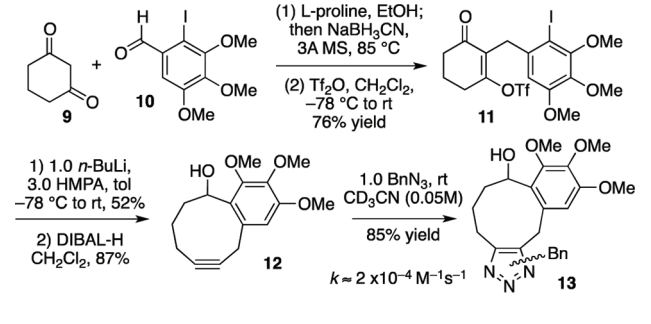
Scheme 3. Stability and Reactivity of Alcohol 7

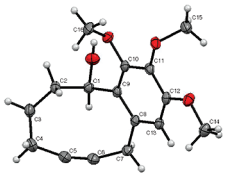


7 is more stable to acid and base and ca. 150-fold more reactive toward benzyl azide (**7** → **8**), providing an 83% yield of regioisomeric[16] triazoles **8** after 6 h at room temperature. This increase in reactivity is atypical SPAAC behavior, because changing an sp^2-center to an sp^3-center should decrease reactivity.[6] We invoke the transannular $\pi \rightarrow \pi^*$ interaction in ketone **3** (or rather its absence in alcohol **7**) to explain the increased acid/base-stability and azide-reactivity of **7**. The reactivity of **7** is similar to activated oxanorbornadienes (cf. Figure 1),[17] which have been employed for bioorthogonal ligation and radiolabeling, and about 10-fold less than OCT,[5] the starting point in the development of cyclooctyne-based reagents for metal-free click chemistry.

From these initial studies, we proceed with the synthesis of new cyclononynes for SPAAC coupling (Scheme 4). Concerns

Scheme 4. Synthesis and X-ray Structure of Cycloalkynol 12





have been raised regarding the lipophilicity of certain SPAAC reagents,[6a] so we increase hydrophilicity by adding methoxy groups around the aromatic ring (except in the position closest to the alkyne, to avoid the risk of negative steric interactions with the approaching azide[12]). This structural modification also reduces costs, as aldehyde **10**[18] is more accessible than 2-iodobenzaldehyde.

The synthesis of cycloalkynol **12** begins with vinylogous acyl triflate **11**, prepared in our usual manner (Scheme 4).[10c]

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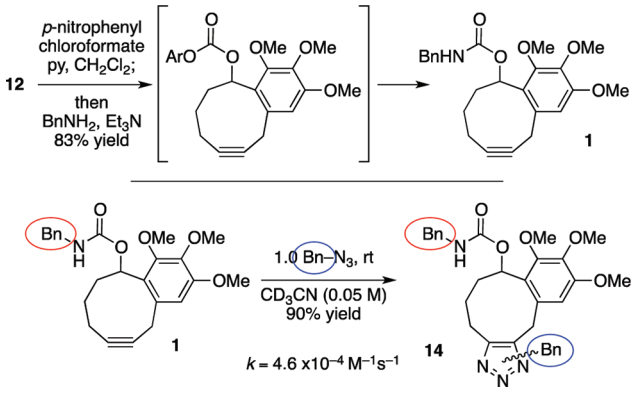
Tandem cyclization/ring expansion was initiated by iodine–lithium exchange, followed by ketone reduction with DIBAL-H. This sequence will benefit from further optimization, but for now reliably provides **12** in ca. 35% overall yield. Once prepared, crystalline **12** is routinely stored in glass vials in a lab refrigerator, where thus far it has proven to be indefinitely stable.

The alcohol group of **12** provides a handle for attachment of molecular cargo (e.g., fluorescent probes, radiolabels, etc.) for delivery using SPAAC coupling. Using benzylamine as model cargo, we prepared carbamate **1** (via the *p*-nitrophenyl carbonate) for kinetic analysis (Scheme 5). Other amine-tagged functionality can be attached in an analogous manner, as will be described in future reports.

Scheme 5. Model Functionalization of 12 and "Click" Reactivity of Carbamate 1



The second-order rate constant for the reaction of **1** with benzyl azide is 4.6×10^{-4} M^{-1} s^{-1}. This level of reactivity surpasses many oxanorbornadiene reagents and lands within an order of magnitude of OCT (2.4×10^{-3} M^{-1} s^{-1}), indicating that this cyclononyne platform may be sufficiently reactive for applications in metal-free click chemistry. Further development of these reagents appears promising.

In conclusion, the benzocyclononyne platform can provide useful levels of SPAAC reactivity. This preliminary communication addresses the rapidly growing demand for cycloalkyne tools for metal-free click coupling. We anticipate that cycloalkynol **12** will be valuable for applications in which problematic background reactivity, i.e., decomposition and/or side reactions with other functional groups, outweighs the advantages of hyperfast coupling with azides. We expect more reactive variants of benzocyclononyne to be identified going forward by rechanneling insights from the development of cyclooctyne reagents. Our efforts are progressing on several fronts, including (i) optimization of the synthesis of cycloalkynol **12**, (ii) elucidating[19] and applying new design principles for the development of more reactive benzocyclononyne derivatives, and (iii) collaborative application of benzocyclononynes to current challenges in chemical biology and inorganic/nanomaterials science.

EXPERIMENTAL SECTION

2,3,4,9-Tetrahydro-1*H*-fluoren-1-one (4, Cyclization of 3[10c] under Acidic Conditions). Cycloalkynone **3** (9.0 mg, 0.05 mmol) and *p*-TsOH (0.93 mg, 0.0049 mmol) were stirred in MeOH (1 mL) at rt for 18 h. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (2 × 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica (20% EtOAc/hexanes) to give **4**, 7.8 mg (87%), as a white solid, mp 92–93 °C. IR (neat): ν_{max} 2935, 1650,1394, 1138, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.51 (m, 2H), 7.42–7.36 (m, 2H), 3.62 (t, 2H, J = 3.0 Hz), 2.82 (tt, 2H, J = 6.0, 3.0 Hz), 2.58 (t, 2H, J = 6.1 Hz), 2.23 (pentet, 2H, J = 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 160.2, 145.0, 142.3, 138.7, 128.8, 126.9, 124.8, 121.7, 38.2, 35.0, 23.6, 23.0. HRMS (EI^+) calcd for $C_{13}H_{12}O$ $(M)^+$ 184.0888; found 184.0888.

2,3-Dihydro-1*H*-cyclopenta[*b*]naphthalen-4-ol (5, Cyclization of 3 under Basic Conditions). Cycloalkynone **3** (21.6 mg, 0.12 mmol) in 2 M KOH in EtOH (2 mL) was stirred at rt for 30 min. Purification as described above for **4** gave compound **5**, 10.5 mg (49%), as a white solid, mp 72–75 °C. IR (neat): ν_{max} 3329, 2944, 1579, 1281, 1087, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.07 (m, 1H), 7.71–7.70 (m, 1H), 7.41–7.37 (m, 2H), 7.30 (s, 1H), 4.94 (s, 1H), 3.07 (td, 2H, J = 7.7, 1.0 Hz), 2.95 (t, 2H, J = 7.2 Hz), 2.19 (p, 2H, 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 144.3, 134.5, 127.3, 125.4. 124.1, 123.7, 123.2, 120.9, 114.9, 33.1, 28.3, 25.9.

Cycloalkynol 7. To a solution of cyclononyne **3** (91 mg, 0.49 mmol) in THF (10 mL) at 0 °C was added $LiAlH_4$ (19.0 mg, 0.49 mmol). The mixture was stirred for 30 min, and then 2 M NaOH was added (50 μL), followed by $MgSO_4$. After additional stirring for 15 min, the reaction mixture was filtered and concentrated. The crude product was purified by chromatography on silica (30% EtOAc/hexanes) to give compound **7**, 67.7 mg (74%), as a yellow oil. IR (neat): ν_{max} 3377, 2933, 1452, 1437, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 7.7 Hz), 7.30 (t, 1H, J = 7.5 Hz), 7.16 (t, 1H, J = 7.6 Hz), 7.05 (d, 1H, J = 7.5 Hz), 5.70 (t, 1H, J = 4.7 Hz), 3.90 (dt, 1H, J = 18.2, 3.2 Hz), 3.13 (d, 1H, J = 18.2 Hz), 2.27–2.17 (m, 2H), 2.14–2.07 (m, 1H), 2.01–1.91 (m, 1H), 1.89–1.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 136.0, 128.9. 127.5, 126.9, 126.3, 90.6, 89.1, 72.3, 40.5, 27.2, 25.6, 19.7. HRMS (EI^+) calcd for $C_{13}H_{13}O$ $(M - H)^+$ 185.0966; found 185.0966.

2-(2-Iodo-3,4,5-trimethoxybenzyl)-3-oxocyclohex-1-enyl Trifluoromethanesulfonate (11). Reductive condensation of 1,3-cyclohexanedione (**9**) with aldehyde **10**[18] according to our general procedure[10c] gave VAT **11**, 780 mg (76%), as colorless crystals, mp 60–61 °C. IR (neat): ν_{max} 2940, 1670, 1480, 1417, 1388, 1330, 1213, 1137, 984 cm^{-1}. ^1H NMR (400 MHz) δ 6.43 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.77 (s, 2H), 2.86 (t, 2H, J = 6.2 Hz), 2.54 (t, 2H, J = 6.4 Hz), 2.16 (pt, 2H, J = 6.4 Hz). ^{13}C NMR (100 MHz) δ 196.8, 163.1, 153.4, 153.2, 140.7, 135.7, 130.1, 118.4 (q, J_{CF} = 304 Hz), 108.5, 88.3, 60.9, 60.7, 56.0, 36.8, 35.0, 28.9, 20.6. HRMS (EI^+) calcd for $C_{17}H_{18}F_3IO_7S$ $(M)^+$ 549.9770; found 549.9778.

Cycloalkynol 12. Tandem cyclization/ring expansion of VAT **11** according to our general procedure[10c] gave the corresponding cycloalkynone in 52% yield as colorless crystals, mp 91–92 °C. IR (neat): ν_{max} 1938, 1689, 1596, 1400, 1323, 1122, 997 cm^{-1}. ^1H NMR (400 MHz) δ 6.44 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83–3.81 (m, 1H), 3.09 (dd, 1H, J = 19.1, 1.4 Hz), 2.87–2.80 (m, 1H), 2.75–2.64 (m, 2H), 2.27–2.13 (m, 2H), 2.06–2.00 (m, 1H). ^{13}C NMR (100 MHz) δ 208.7, 153.0, 150.1, 140.3, 133.8, 131.3, 108.4, 90.0, 88.5, 61.3, 60.8, 56.1, 43.1, 27.6, 24.2, 18.8. HRMS (EI^+) calcd for $C_{16}H_{18}O_4$ $(M)^+$ 274.1205; found 274.1204. This cycloalkynone intermediate (193 mg, 0.70 mmol) was dissolved in CH_2Cl_2 (8.4 mL) at −78 °C and treated dropwise with DIBAL (2.10 mL, 1 M in toluene, 2.1 mmol). After 30 min at −78 °C, the reaction mixture was quenched by addition of 2 M NaOH (1.8 mL) at −78 °C and followed by $MgSO_4$. After additional stirring for 15 min, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica (20–30% EtOAc/hexanes) to provide cycloalkynol **12**, 170 mg (87%), as colorless crystals, mp 85–86 °C. IR (neat): ν_{max} 2996, 2397, 1598, 1494, 1321, 1117 cm^{-1}. ^1H NMR (400 MHz) δ 6.40 (s, 1H) 5.48–5.43 (m, 1H), 4.00 (s, 3H), 3.90 (dt, 1H, J = 7.6, 2.9 Hz), 3.84 (s, 3H), 3.83 (s, 3H), 2.98 (dd, 1H, J = 18.2, 1.2 Hz), 2.27–2.13 (m, 3H), 2.10–1.90 (m, 3H). ^{13}C NMR (100 MHz) δ 152.9, 151.7, 141.2, 132.4, 131.2, 108.6, 09.5, 88.7, 73.5, 61.3, 60.7, 56.0, 42.0, 27.4, 26.1, 19.9. HRMS (EI^+) calcd for $C_{16}H_{20}O_4$ $(M)^+$ 276.1362; found 276.1362.

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Carbamate 1. A solution of 4-nitrophenyl chloroformate (25 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added dropwise via syringe to a solution of benzocyclononye **12** (30.8 mg, 0.115 mmol) and pyridine (22.5 μL) in CH_2Cl_2 (0.65 mL) at 0 °C. The resulting mixture was stirred for 10 h at rt and cooled to 0 °C, and then Et_3N (48 μL, 0.34 mmol) and benzylamine (24 μL, 0.22 mmol) were added slowly via syringe. The resulting mixture was stirred for 6 h at rt and then diluted with EtOAc (5 mL). The solution was washed with 1 M $KHSO_4$ (2 × 5 mL), saturated $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and the residue was purified by chromatography on silica (20−25% EtOAc/hexanes) to furnish 39.1 mg (83%) of **1** as a white solid, mp 95−96 °C. IR (neat): ν_{max} 3266, 2936, 1707, 1685, 1597, 1493, 1454, 1434, 1323, 1239, 1196, 1171 cm^{-1}. ^1H NMR (400 MHz) δ 7.29−7.21 (m, 5H), 6.69 (t, 1H, J = 5.47 Hz), 6.43 (s, 1H,), 5.07 (br s, 1H), 4.38−4.18 (m, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.84 (s, 3H), 2.91 (d, 1H, J = 17.7 Hz), 2.34−2.19 (m, 4H), 1.94−180 (m, 1H), 1.77−1.76 (m, 1H). ^{13}C NMR (100 MHz) δ 156.7, 154.0, 152.0, 141.4, 138.4, 135.8, 128.5, 127.31, 127.26, 126.8, 107.9, 91.8, 90.9, 74.5, 60.9, 60.5, 55.7, 44.9, 35.5, 26.9, 26.2, 19.9. HRMS (EI^+) calcd for $C_{24}H_{27}NO_5Na$ $(M + Na)^+$ 432.1787; found 432.1770.

General Procedure for the Synthesis of Triazole Derivatives 8, 13, and 14. Cycloalkynol **7**, **11**, or **1** (1.0 equiv) and benzyl azide (1.0 equiv) were stirred in CH_3CN (0.05 M) at rt for 36 h and then concentrated under reduced pressure. The residue was purified by chromatography on silica (20% MeOH/$CHCl_3$) to give triazole regioisomers.[16]

Triazoles ***8***. Reaction stirred in MeOH (0.5 M) for 6 h. Yield 43 mg (83%), colorless oil. IR (neat): ν_{max} 3368, 2937, 1455, 1240, 1044, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (br s) 7.36−7.03 (m), 6.84 (br s), 5.62 (d, part of AB, J_{AB} = 16.2 Hz), 5.45 (d, B part AB, J_{AB} = 15.6 Hz), 5.39 (d, A part AB, J_{AB} = 15.6 Hz), 5.31 (B part AB, J_{AB} = 15.6 Hz), 5.18 (br s), 4.99 (br s), 4.16 (br s), 4.04 (s), 4.01 (s), 3.85 (br s), 3.00 (br s), 2.58 (br d, J = 12.0 Hz), 2.34 (br s), 1.90 (br s), 1.75−1.62 (m), 1.50 (br s), 1.30 (br s), 0.97−0.91 (m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 144.6 (br), 143.4 (br), 132.5, 131.0 (br), 130.6 (br), 129.0, 128.8, 128.2, 128.1, 127.8 (br), 127.1, 126.8, 126.7, 51.9, 51.7, 30.1, 27.6, 24.5, 23.3, 22.2, 19.2. HRMS (EI^+) calcd for $C_{20}H_{21}ON_3$ $(M)^+$ 319.1685; found 319.1689.

Triazoles ***13***. Yield 7.3 mg (85%), colorless oil. IR (neat): ν_{max} 3380, 2938, 1734, 1597, 1495, 1455, 1323, 1267, 1239, 1120, 1001 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (s), 7.33−7.27 (m), 7.12−7.09 (m), 6.74, 5.91 (br s), 5.73 (d, A part AB, J_{AB} = 16.2 Hz), 5.48 (d, B part AB, J_{AB} = 16.2 Hz), 5.45 (d, A part AB, J_{AB} = 15.8 Hz), 5.37 (d, B part AB, J_{AB} = 15.8 Hz), 5.26 (s), 4.07 (s), 4.04 (s), 3.89 (s), 3.88 (s), 3.85 (s), 3.81 (s), 3.82 (s), 3.62 (s), 2.69 (br s), 2.53 (br s), 2.02 (br s), 1.86−1.82 (m), 1.77 (br s), 1.67 (br s), 1.46 (br s), 1.26 (br s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 151.8, 151.5, 145.3, 144.5 (br s), 141.5, 140.9, 135.4, 135.3, 132.7, 131.7, 129.0, 128.9, 128.24, 128.20, 127.3 (br s), 126.9, 126.8 (br s), 110 (br s), 67.7 (br s), 61.5, 61.4, 60.7, 60.6, 30.6, 27.9 (br s), 25.0, 23.7, 22.0, 19.0. HRMS (EI^+) calcd for $C_{23}H_{27}N_3O_4Na$ $(M + Na)^+$ 432.1899; found 432.1912.

Triazoles ***14***. Yield 34 mg (90%), colorless oil. IR (neat): ν_{max} 3328, 2936, 1710, 1596, 1496, 1455, 1412, 1328, 1126, 1027 cm^{-1}. ^1H NMR (600 MHz, CD_3CN) δ 7.61 (s), 7.39 (br s), 7.33−7.27 (m), 7.24 (d, 7.9 Hz), 7.10 (d, 7.0 Hz), 6.66 (s), 6.39 (d, A part AB, J_{AB} = 6.8 Hz), 6.38 (d, B part AB, J_{AB} = 6.8 Hz), 6.17 (s), 6.07 (br s), 5.88 (br s), 5.67 (d, A part AB, J_{AB} = 15.8 Hz), 5.61 (d, A part AB, J_{AB} = 15.8 Hz), 5.46 (d, A part AB, J_{AB} = 15.9 Hz), 5.36 (d, A part AB, J_{AB} = 15.8 Hz), 4.28−4.19 (m), 3.84 (s), 3.83 (s), 3.77 (s), 3.76 (s), 3.63 (s), 2.52 (d), 2.04 (br s), 1.90 (br s), 1.76 (br s), 1.60 (br s), 1.44 (br s), 1.29 (s) 0.98 (br). ^{13}C NMR (125 MHz, CD_3CN) δ 157.1 (br), 154.6, 153.2 (br), 145.8 (br), 145.4 (br), 142.2 (br), 140.64, 140.58, 137.3, 137.2, 133.9 (br), 131.5, 129.9, 129.7, 129.3, 129.0, 128.9, 127.99, 127.96, 127.89, 127.85, 69.7, 62.04, 62.01, 61.1, 61.0, 56.5, 56.4, 52.4, 51.9, 45.1, 32.0. 30.3 (br), 30.0 (br), 29.3 (br), 25.3 (br), 23.9, 22.8, 19.5. HRMS (EI^+) calcd for $C_{31}H_{34}N_4O_5Na$ $(M + Na)^+$ 565.2427; found 565.2424.

General Procedure for Kinetic Experiments. All kinetic experiments were conducted under second order conditions, using a 1:1 molar ratio of cycloalkynes and azide. The second order rate constants were obtained by plotting the inverse concentration versus time in seconds. The cycloalkyne derivatives **1**, **3**, **7**, and **12** (1.0 equiv), benzyl azide (1.0 equiv), and the internal standard (1.0 equiv) were dissolved in CD_3CN (0.05 M) at rt (~25 °C) in an NMR tube; ^1H NMR spectra were acquired immediately and every 2 h. Note that the reaction with cycloalkynone **3** was conducted at higher concentration (1.0 M). The internal standards for each experiment were as follows: **1**, 1-bromo-3,5-dimethylbenzene; **3** and **7**, 1-bromo-3,5-dimethoxybenzene; and **12**, 2-bromoanisole.

■ ASSOCIATED CONTENT

Supporting Information

X-ray files in CIF format, ORTEP plots, plots of kinetic data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org. The supplementary crystallographic data for compounds **3** and **12** have also been deposited with the Cambridge Crystallographic Data Centre (CCDC 847775 and 847776, respectively). These data can be obtained free of charge via the Internet at http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gdudley@chem.fsu.edu.

Present Address

[†]Chulabhorn Research Institute, Bangkok, Thailand.

Notes

The authors declare no competing financial interest.

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