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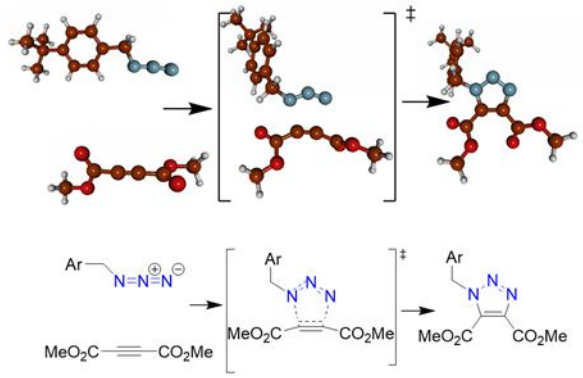
Abstract:

The thermal (3+2) dipolar azide-alkyne cycloaddition, proceeding without copper or strained alkynes, is an underutilized ligation with potential applications in materials, bioorganic, and synthetic chemistry. Herein we investigate the effects of alkyne substitution on the rate of this reaction, both experimentally and computationally. Electron-withdrawing groups accelerate the reaction, providing a range of relative rates from 1.0 to 2100 between the slowest and fastest alkynes studied. Unexpectedly, aryl groups conjugated to the alkyne significantly retard the reaction rate. In contrast, a sulfonyl, ester-substituted alkyne is reactive enough that it couples with an azide at room temperature in a few hours. This reactivity scale should provide a guide to those who wish to use this ligation under mild conditions.



Introduction:

Azides are rare in nature, and participate in relatively few reactions.[1] This property makes them useful for chemoselective functionalization. The dipolar (3+2) azide-alkyne thermal cycloaddition reaction, first utilized by Michael,[2] and later studied extensively by Huisgen,[3] provides a way to attach an alkyne-functionalized molecule to an azide-functionalized partner in the presence of other reactive groups. The copper-catalyzed variant, introduced by Sharpless[1] and Meldal,[4] provides the benefit of very mild reaction conditions, including room-temperature reactivity and the ability to use water as a solvent. These benefits have propelled the copper-catalyzed reaction to great popularity, eclipsing that of the original.[5] However, concerns about residual copper, which can be toxic and can interfere with electronic applications, have led to renewed interest in the metal-free azide-alkyne cycloaddition.

Bertozzi's cyclooctynes[6] use ring strain as a driving force to eliminate the need for a catalyst. The addition of electron-withdrawing fluorine atoms further enhances their reactivity. These molecules have found great success, especially for *in vivo* applications. However, an easier-to-synthesize alternative to cyclooctynes would widen the applicability of the metal-free reaction. To this end, electron-poor linear alkynes are a topic of this investigation.

Because the reaction is controlled by a HOMO (azide) - LUMO (alkyne) interaction, electron-withdrawing groups that lower the LUMO of the alkyne can be used to accelerate the reaction.[7] Acetylene diesters and monoesters have been shown to react with azides at room temperature.[8] Sulfone-substituted alkynes also react quickly with azides at room temperature, although they suffer from Michael addition side reactions in the presence of nucleophiles.[9] Acetylenic sulfones have also successfully been used as dipolarophiles in a range of other 1,3-dipolar cycloadditions.[10] Our lab has used acetylene diesters and monoesters as linkages to covalently attach plasticizers to the backbone of azide-functionalized PVC.[11,12]

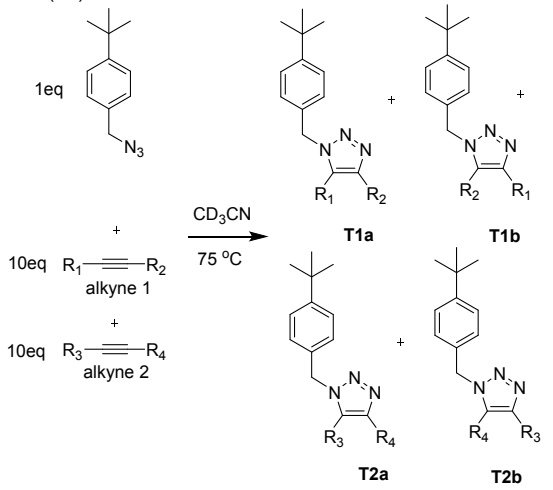
Brook[7] used competition experiments to probe the relative reactivity of several alkynes with different electron-withdrawing groups, with the goal of chemoselectively crosslinking or functionalizing polysiloxane elastomers. Herein we further probe the effects of various groups on alkynes in the metal-free azide-alkyne cycloaddition via competition experiments and by density functional theory. By generating a scale of relative reactivities, this fundamental ligation reaction will find broader usage in synthesis, materials, and biomedical applications.

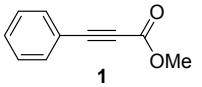
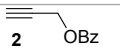
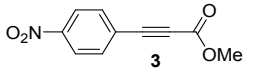
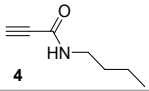
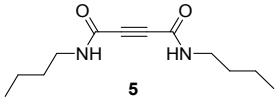
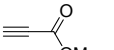
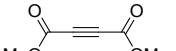
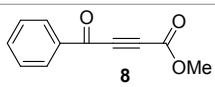
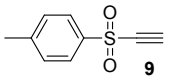
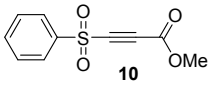
Results and Discussion:

To compare the relative rates of the cycloaddition reaction, alkynes with similar expected rates were selected pairwise and heated to 75 °C in CD_3CN in an NMR tube with a limiting amount of 4-*t*-butylbenzyl azide. A 1 : 10 : 10 ratio of azide : alkyne 1 : alkyne 2 was chosen to approximate pseudo-first order conditions. The competition reaction between nitrophenyl alkyne **3** and acetylene diamide **5** was monitored over time, confirming that the product ratio

did not change as a function of conversion. Based on this result, all other product ratios were measured after all of the azide had been consumed. Each competition experiment was done in duplicate, and the average of the product ratios, corrected for initial ratios, was used to construct the relative rate scale shown in **Table 1**. Authentic samples of individual alkyne + azide triazole products were prepared: regioisomers were separated chromatographically when possible. In the case of alkyne **8**, the identity of the two regioisomers was determined by NOE experiments. In general, the triazole product of alkyne **1** is designated as **T1** for Triazole 1, with regioisomers labelled as **T1a** and **T1b** when applicable.

Table 1. Results of competition experiments with t-butylbenzyl azide (**A1**)

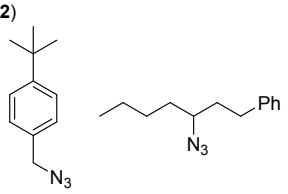


Alkyne	Relative rate[a]
 **1**	1.0
 **2**	1.4
 **3**	3.7
 **4**	8.8
 **5**	15
 **6**	25
 **7**	130
 **8**	150
 **9**	340
 **10**	2100

[a] The relative rate of alkyne **1** with 4-*t*-butylbenzyl azide is defined as 1.0. Unsymmetrical alkynes form two regioisomeric products **a** and **b**; for simplicity, the overall relative rates are defined by the sum of both regioisomers formed from each alkyne.

The results were mainly as expected, with stronger electron-withdrawing groups leading to more reactive alkynes. Pleasingly, the sulfonyl, ester-substituted alkyne **10** reacts considerably faster than the commonly used diester alkyne **7**. As the cycloaddition with sulfonyl alkyne **10** is rapid, it was examined in a room temperature reaction with 4-*t*-butylbenzyl azide, reaching 92% completion in 5 hours. The two alkynes that did not match expectations were the aryl-substituted alkynes **1** and **3**. Although the nitrophenyl group in **3** is expected to be electron-withdrawing, it did not outcompete the mono-ester **6**, which has a hydrogen in place of the nitrophenyl group. The low reactivity of the phenyl-substituted alkyne **1** was the most surprising: the phenyl ring seems to overwhelm the electron-withdrawing effect of the ester, making it slower than the completely unactivated alkyne **2**.

Table 2. Results of competition experiments with 3-azido-1-phenylheptane (**A2**)



A1 **A2**

Alkyne pair	Ratio with 1° benzylic azide **A1**	Ratio with 2° alkyl azide **A2**
6 vs **3**	6.8 : 1.0	7.9 : 1.0
7 vs **6**	5.2 : 1.0	5.6 : 1.0
10 vs **7**	16.3 : 1	24.4 : 1.0

[a] Unsymmetrical alkynes form two regioisomeric products **a** and **b**; for simplicity, the overall relative rates are defined by the sum of both regioisomers formed from each alkyne.

To investigate azide scope, selected alkynes were also reacted with a secondary alkyl azide, 3-azido-1-phenylheptane (**Table 2**). The relative rates are similar to those found with *t*-butylbenzyl azide, indicating general applicability of the results to other azides.

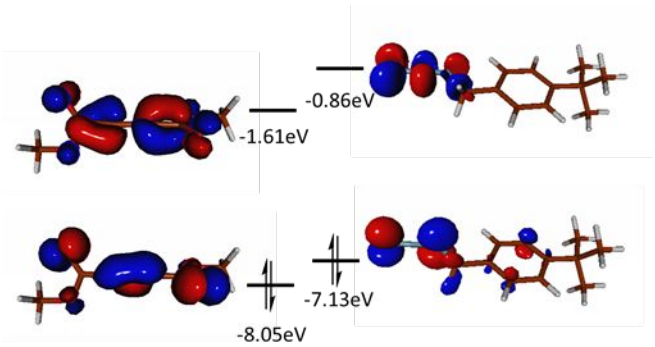
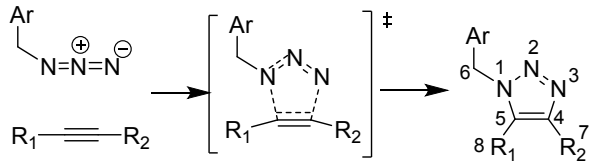


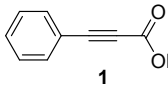
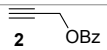
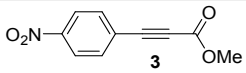
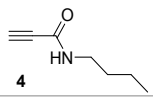
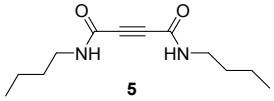
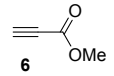
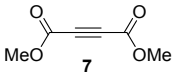
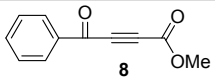
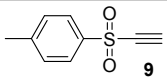
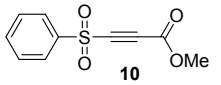
Figure 1. HOMO and LUMO of dimethyl acetylenedicarboxylate (**7**) and 4-*t*-butylbenzyl azide

In order to better understand these results, the transition states of each reaction with t-butylbenzyl azide were modeled at the B3LYP/6-31G* level. The results are shown in **Table 3.** Activation energies were in qualitative agreement with the experimental reactivity order. The energy level of the LUMO of each alkyne was calculated and compared. Lower LUMOs generally correlate with lower energy barriers, however this failed to explain the sluggish reactivity of the aryl-substituted alkynes **1** and **3**. In all cases, the HOMO (azide) - LUMO (alkyne) gap was smaller than the HOMO (alkyne) - LUMO (azide) gap (**Figure 1**).

Table 3. Results of DFT calculations

Ar = 4-*t*-Bu-Ph



Alkyne	E_a[a] (kcal/mol)	Alkyne LUMO (eV)	Change in bond order[a,b]
 **1**	20.7	-1.83	-0.049
	20.7		-0.026
 **2**	19.6	0.52	-0.025
	19.0		-0.033
 **3**	19.6	-1.54	-0.039
	19.8		-0.034
 **4**	17.5	-0.83	-0.017
	18.1		-0.032
 **5**	17.6	-1.11	-0.025
	16.1	-1.35	+0.006
 **6**	17.7		-0.026
 **7**	15.8	-1.61	+0.004
 **8**	16.9	-1.54	-0.008
	15.9		+0.018
 **9**	14.5	-1.46	-0.001
	15.1		-0.019
 **10**	13.5	-2.06	+0.004
	15.1		-0.010

[a] Two energies and two bond orders are shown for unsymmetrical alkynes, referring to the two regioisomers formed. [b] Bond order is the sum of bonds between atoms 4-7 and 5-8, change in bond order is measured from the starting material to the transition state.

One hypothesis for the low reactivity of the aryl-substituted alkynes is that the transition state geometry forces the aryl rings out of conjugation with the alkyne, destabilizing the transition state. This would be consistent with the results of Hosoya,[13] who found that phenyl azide is less reactive than a 2,6-disubstituted phenyl azide that cannot participate in aryl-azide resonance due to steric interactions. To investigate this, the Wiberg bond indices[14] were measured in the starting materials, transition states, and products. A decrease in the bond index at the transition state correlated with higher activation energies, including aryl alkynes **1** and **3**. It is possible that the aryl rings are not able to act as electron-withdrawing groups at the transition state due to geometry constraints, while the other electron-withdrawing groups continue to remove electron density throughout the reaction coordinate.

Conclusion:

Alkynes with various substituents were compared to determine their relative rates in reacting with a model azide to form a triazole ring. Electron-withdrawing groups were found to enhance the rate of the metal-free azide-alkyne cycloaddition. However, aryl-substituted alkynes react slower than expected, probably due to a loss of conjugation at the transition state. DFT calculations support this explanation. The reactivity of ketone, ester substituted alkyne **8** did not differ much from that of the more commonly utilized diester **7**, but the sulfonyl, ester-substituted alkyne **10** reacts 16 times faster than the diester and 1500 times faster than unactivated alkyne **2**. Derivatives of this sulfonyl, ester alkyne may find large applicability for ligation under very mild conditions. These findings should also lead to the rational design of other highly reactive alkynes for the metal-free azide-alkyne cycloaddition.

Experimental Section:

Materials and General Methods

All reagents and solvents were used as received unless otherwise noted. Dry tetrahydrofuran (THF) was obtained by distillation over sodium and benzophenone. Dry CH_2Cl_2 was obtained by distillation over CaH_2. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III HD 4 channel 500 MHz Oxford Magnet NMR spectrometer with Automation. NOE experiments were recorded on a Bruker Avance III HD 800 MHz NMR Spectrometer with cryoprobe at 4 °C. FTIR spectra were taken in $CDCl_3$ and recorded with a Perkin Elmer Spectrum One spectrometer in NaCl microsolution cells. HRMS was recorded with a Thermo Scientific LTQ-Orbitrap Velos Pro Mass Spectrometer. Calculations were performed using the B3LYP functional and the 6-31G* basis set using the Gaussian09 suite of software.[15] Transition states were confirmed to have 1 negative frequency and energy minima were confirmed to have no negative frequencies. Energies were corrected for zero-point energies. Solvent was simulated using the polarizable continuum model (acetonitrile, ε = 35.688).

Preparation of 4-*t*-butylbenzyl azide (A1)[16]

NaN_3 (15 g, 230.73 mmol) was dissolved in 80 mL of water, then stirred with 40 g of Amberlite® IRA-400 for 1 h. The resulting beads were filtered, washed with water (80 mL) and EtOH (50 mL) to give charged Amberlite-N_3. 4-*t*-Butylbenzyl bromide (4.02 g, 17.7 mmol) and Amberlite-N_3 (40 g) were combined in CH_3CN (60 mL) and stirred for 5 h at room temperature. The reaction was monitored by TLC. Mixture was filtered, the filtrate was concentrated under vacuum, dissolved in Et_2O, dried over $MgSO_4$ and concentrated under vacuum, yielding 3.178 g of slightly yellow liquid (94.9% yield). R_f = 0.85 (4:1 hexanes/ethyl acetate UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 4.34 (s, 1H), 1.36 (s, 4H) ppm.

Preparation of 3-hydroxy-1-phenylheptane[17]

Following the procedure of Earla,[17] to a solution of 3-phenylpropionaldehyde (2.133 g, 15.89 mmol) in dry THF (40mL) was added *n*-butyllithium (1.6 M in hexanes, 12.9 mL) under nitrogen at -78 °C. The reaction mixture was warmed to room temperature and stirred for 20 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL), H_2O (50 mL) was added, and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (3x 25 mL), and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum to give 2.661 g (88.0%) of the product as a colorless liquid, which was used without purification in the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ =7.31 (t, *J* = 7.3 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 3.66 (tt, *J* = 8.1, 4.5 Hz, 1H), 2.83 (m, 1H), 2.70 (m, 1H), 1.80 (m, 2H), 1.51 (m, 1H), 1.41 (m, 2H), 1.36 (m 3H), 0.93 (t, *J* = 7.0 Hz, 3H) ppm.

1-Phenylheptan-3-yl methanesulfonate (A2')

To a solution of 3-hydroxy-1-phenylheptane (633 mg, 3.29 mmol) and NEt_3 (0.55 mL, 4.0 mmol) in Et_2O (5 mL) at 0 °C was dropwise added methanesulfonyl chloride (0.30 mL, 3.9 mmol). The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was diluted with brine (20 mL) and extracted with Et_2O (3x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to give 906 mg (94.6%) of the product as a colorless liquid.

R_f = 0.53 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 7.5 Hz, 2H), 7.23 (m, 3H), 4.79 (tt, *J* = 4.1, 9.2 Hz, 1H), 3.02 (s, 3H), 2.75 (m, 2H), 2.04 (m, 2H), 1.78 (m, 2H), 1.38 (m, 2H), 0.94 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C{^{1}H} and DEPT NMR (126 MHz, $CDCl_3$): δ = 140.9(C), 128.53(CH), 128.33(CH), 126.15(CH), 83.41(CH_3), 38.74(CH), 36.14(CH_2), 34.22(CH_2), 31.30(CH_2), 27.01(CH_2), 22.46(CH_2), 13.90 (CH_3) ppm; IR (NaCl, $CDCl_3$): ν = 1353, 1333, 1174 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{22}SO_3Na$ $[M+Na]^+$ 293.1182, found 293.1177.

3-azido-1-phenylheptane (A2) [17]

In a modified procedure of Earla[17], to a solution of 1-phenylheptan-3-yl methanesulfonate (291 mg, 1.00 mmol) in DMF (5 mL) under nitrogen was added NaN_3 (196.0 mg, 3.015 mmol). The mixture was heated to 70 °C and stirred for 2 h. The reaction was cooled to room temperature, brine (15 mL) was added, and the product was extracted with Et_2O (3x 15 mL). The combined organic extracts were washed with brine (3x 30 mL), dried over $MgSO_4$, and concentrated under vacuum to give 204 mg (93.8%) of the product as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ =7.32 (t, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 2H), 3.27 (tt, *J* = 7.2, 5.4 Hz, 1H), 2.82 (m, 1H), 2.71 (m, 1H), 1.85 (m, 2H), 1.58 (m, 2H), 1.45 (m, 1H), 1.36 (m, 3H), 0.94 (t, *J* = 7.1 Hz, 3H) ppm.

Synthesis of Alkynes

Preparation of prop-2-yn-1-yl benzoate (2)[18]

Following the method of Buono,[18] to a solution of propargyl alcohol (1.00 mL, 17.3 mmol) and triethylamine (4.2 mL, 30 mmol) in CH_2Cl_2 (35 mL), benzoyl chloride (1.75 mL, 15.1 mmol) was added dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 28 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 5% HCl (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by chromatography on silica gel (eluent EtOAc/hexanes 10:90) to afford the product as a clear oil (2.26 g, 93.4%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 4.95 (d, *J* = 2.5 Hz, 2H), 2.54 ppm (d, *J* = 2.8 Hz, 1H).

Preparation of methyl 4-(4-nitrophenyl)-2-butynoate (3) [19]

Following the procedure of Ipatkschi,[20] to a flame-dried 50 mL round bottom flask were added 1-iodo-4-nitrobenzene (0.300 g, 1.21 mmol), methyl propiolate (0.405 mg, 4.81 mmol), and 6 mL of dry THF. Bis-triphenylphosphinyl palladium (II) chloride (0.017 g, 0.024 mmol), copper (I) iodide (0.009 g, 0.05 mmol), and potassium carobonate (0.333 g, 2.41 mmol) were added to the reaction mixture and stirred for 2 h at 65 °C under nitrogen. The THF was evaporated and the crude residue was extracted with diethyl ether (3x 40 mL). The organic layer was concentrated under vacuum to give 0.2987 g of crude product, which was purified by silica gel column chromatography to give the product as a yellow powder (0.2034 g, 81.9% yield). R_f = 0.53 (4:1 hexanes:ethyl acetate, UV and $KMnO_4$); m.p. 113-115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 3.89 ppm (s, 3H).

Preparation of *N*-butylpropiolamide (4).

In a modified procedure of Kunishima,[21] a mixture of propiolic acid (140.1 mg, 2.000 mmol) and butylamine (160.9 mg, 2.199 mmol) in THF (10 mL) was stirred at room temperature for 10 min. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (608.8 mg, 2.2 mmol) was added to the mixture and stirred at room temperature overnight. The next day, the reaction mixture was poured into water and extracted with diethyl ether (3 x 10mL). The combined organic phase was washed successively with saturated sodium carbonate (10 mL), water (10 mL), 1 M HCl (10 mL), water (10 mL), brine (10 mL) and dried over $MgSO_4$. The crude product was purified by silica gel column using 3:2 hexanes:ethyl acetate to give 91.8 mg (36.7%) of *N*-butylpropiolamide as a colorless liquid. R_f = 0.50 (3:2 hexanes:ethyl acetate, $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$): δ =

5.89 (bs, 1H), 3.33 (td, *J* = 7.2, 5.9 Hz, 2H), 2.79 (s, 1H), 1.54 (p, *J* = 7.4 Hz, 2H), 1.39 (h, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 152.18 (C), 79.2 (apparent CH due to long-range coupling), 72.9 (CH), 39.6 (CH_2), 31.2 (CH_2), 20.0 (CH_2), 13.6 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 3437, 3302, 2114, 1659 cm^{-1}; HRMS (ESI): m/z calcd for $C_7H_{12}NO$ $[M+H]^+$ 126.0913, found 126.0924.

Preparation of *N,N'*-dibutyl-2-butynediamide (5) [22]

In a modified procedure of Kunishima,[21] to a 25 mL 2-neck round bottom flask was added acetylenedicarboxylic acid (285.8 mg, 2.506 mmol) and *N*-methylpyrrolidinone (NMP) (5.0 mL) at 0 °C. To this solution was added a solution of *n*-butylamine (0.59 mL, 6.0 mmol) in NMP (2.5 mL). After stirring at 0 °C for 10 min, DMTMM (1.9387 g, 7.0060 mmol) was added to the reaction mixture. The reaction was stirred at 0 °C for 5 h, then partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (50 mL), saturated $NaHCO_3$ (50 mL), 1M HCl (50 mL), and brine (50 mL x2). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude residue. The residue was dissolved in THF, refluxed, then cooled to RT and then to -20 °C overnight to give the product as a precipitate: filtration afforded a white powder (269.5 mg 48%). R_f = 0.35 (2:3 ethyl acetate:hexanes, $KMnO_4$); m.p. 141-142 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.04 (bs, 1H), 3.34 (td, *J* = 7.2, 6.0 Hz, 2H), 1.54 (p, *J* = 7.3 Hz, 2H), 1.38 (h, *J* = 7.3 Hz, 2H), 0.96 ppm (t, *J* = 7.4 Hz, 3H).

Preparation of methyl 4-hydroxy-4-phenyl-2-butynoate[23]

Following the procedure of Sames,[23] 25 mL of dry THF was added to a flame-dried 250 mL round bottom flask and cooled to –78 °C. Lithium bis-trimethylsilylamide (10.1 mL, 1.3 M in THF, 13 mmol) was added and cooled for 20 minutes. Methyl propiolate (1.1 mL, 12 mmol) was added dropwise to the reaction mixture and stirred at -78 °C for one h, benzaldehyde (1.34 mL, 13.1 mmol) was added and stirred for an additional 2 hours. The reaction mixture was allowed to warm to room temperature, then quenched with saturated aqueous NH_4Cl (10 mL) and extracted with $CHCl_3$ (3x 10 mL). The organic layer was concentrated under vacuum to give 2.37 g of crude product, which was purified by column chromatography to give 2.00 g of the product as a white powder (88%). R_f = 0.70 (4:1 hexanes:ethyl acetate, $KMnO_4$ and UV); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.1 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 6.9 Hz, 1H), 5.58 (s, 1H), 3.81 ppm (s, 3H).

Preparation of methyl 4-oxo-4-phenyl-2-butynoate (8) [23]

Following the procedure of Sames,[23] a solution of 0.3 M Dess-Martin Periodinane (792.6 mg, 1.877 mmol) in 6 mL CH_2Cl_2 was added dropwise to a solution of methyl 4-hydroxy-4-phenyl-2-butynoate (273.2 mg, 1.444 mmol) in 3 mL of dry CH_2Cl_2 at room temperature under nitrogen. After 1 h, the reaction was quenched by slow addition of saturated aqueous sodium bicarbonate (10 mL). The resulting mixture was stirred for 15 minutes, then extracted with CH_2Cl_2 (2x 10 mL). The organic layer was dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography to give 255.9 mg of the product as a white powder (94.17% yield). R_f = 0.61 (4:1 hexanes:ethyl acetate, $KMnO_4$ and UV); m.p. 64-65 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.2 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 3.92 ppm (s, 3H).

Preparation of diphenyl thiosulfate[24]

Following a modified procedure from Takeda,[24] diphenyl disulfide (3.70 g, 16.9 mmol) was dissolved in 27 mL of glacial acetic acid. Hydrogen peroxide (30% in water, 3.5 mL, 34 mmol) was added dropwise. The mixture was stirred for 24 h, diluted with water (50 mL), extracted with chloroform (2 x 50 mL), and washed with saturated sodium bicarbonate (50 mL). The organic layer was dried over sodium sulfate, and concentrated under vacuum to give the crude product. Purification by column chromatography (0 to 40% ethyl acetate in hexanes) gave the product as brown crystals: 3.68 g (86.9% yield). $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 142.9, 136.6, 133.7, 131.45, 129.5, 128.9, 127.8, 127.5 ppm.

Preparation of methyl 3-(phenylsulfanyl)-2propynoate[24]

Following the procedure of Takeda, [24] methyl propiolate (0.93 mL, 10.5 mmol) was dissolved in 20 mL of dry THF at -78 °C. Lithium bis(trimethylsilyl)amide (1.3 M in THF, 8 mL, 10.5 mmol) was added and stirred for 30 min. Diphenyl thiosulfate (2.553 g, 10.20 mmol) in 20 mL dry THF was added dropwise. The mixture was warmed to room temperature and stirred for 2 h, then quenched with water (30 mL), and extracted with diethyl ether (2x 30 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum to give the crude product which was purified by silica gel column chromatography to give a yellow oil: 784 mg, 39.9% yield. R_f = 0.76 (1:4 ethyl acetate:hexanes, UV and $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 6.5 Hz, 1H), 3.84 (s, 3H) ppm.

Preparation of Methyl 3-(phenylsulfonyl)-2-propynoate (10)[24]

Following the procedure of Takeda,[24] methyl 3-(phenylsulfanyl)-2-propynoate (600 mg, 3.12 mmol) was dissolved in 20 mL of CH_2Cl_2. *m*CPBA (3.0 g, 55% by weight, 9.6 mmol) dissolved in 40 mL of CH_2Cl_2 was added. The solution was stirred for 2 h, then quenched with solid $NaHSO_3$ (2 g), washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The crude product was purified by silica gel column chromatography (ethyl acetate/hexanes) to give 180.8 mg of a yellow oil, 25.8.% yield. R_f = 0.37 (1:4 ethyl acetate:hexanes, UV and $KMnO_4$); ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.1 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 2H), 3.84ppm (s, 3H) ppm.

Preparation of Authentic Triazoles

Ethyl 1-(4-*t*-butylbenzyl)-5-phenyl-1,2,3-triazole-4-carboxylate and Ethyl 1-(4-*t*-butylbenzyl)-4-phenyl-1,2,3-triazole-5-carboxylate, T1a and T1b

Ethyl phenylpropiolate (188.5 mg, 1.082 mmol) and 4-*t*-butylbenzyl azide (306.5 mg, 1.619 mmol) were combined in 2 mL of CH_3CN and heated to 75 °C for 14 days. The product was purified by silica gel column chromatography (5% to 40% ethyl acetate in hexanes) to give 293.3 mg (74.58%) of the two regioisomeric triazole products, separable: 185.4 mg of **T1a** as a clear oil, and 111.9 mg of **T1b** as a white powder.

T1a (regioisomer not identified):

Clear liquid. R_f = 0.67 (4:1 hexanes:ethyl acetate, UV); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.78 – 7.68 (m, 2H), 7.47 – 7.42 (m, 3H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.93 (s, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.32 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 159.2(C), 151.4(C), 150.4(C), 132.2(C), 130.4(C), 129.4(CH), 128.9(CH), 127.9(CH), 127.8(CH), 125.7(CH), 124.1(C), 61.8(CH_2), 53.8(CH_2), 34.6(C), 31.3(CH_3), 13.7 (CH_3) ppm; IR (NaCl, $CDCl_3$) v = 1720 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{26}N_3O_2$ $[M+H]^+$ 364.2020, found 364.2047.

T1b (regioisomer not identified):

White powder. R_f = 0.29 (4:1 hexanes:ethyl acetate, UV); m.p. 70-71 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.52 (t, *J* = 7.4 Hz, 1H),

7.46 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 6.9 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.41 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.29 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 161.0(C), 151.5(C), 141.2(C), 137.1(C), 131.6(C), 130.0(CH), 129.9(CH), 128.5(CH), 127.4(CH), 126.1(C), 125.7(CH), 60.9(CH_2), 51.9(CH_2), 34.6(C), 31.2(CH_3), 14.1 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1725 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{26}N_3O_2$ $[M+H]^+$ 364.2020, found 364.2012.

1-(4-*t*-butylbenzyl)-1,2,3-triazol-4-ylmethyl benzoate and 1-(4-*t*-butylbenzyl)-1,2,3-triazol-5-ylmethyl benzoate, T2a and T2b

Propargyl benzoate (24.0 mg, 0.149 mmol) and 4-*t*-butylbenzyl azide (41.4 mg, 0.219 mmol) were combined in 2 mL of CH_3CN and heated to 75 °C for 14 days. Attempts to separate the two regioisomers by column chromatography were unsuccessful, providing 11.49 mg (22.1% yield) of the mixture (6.8 : 1 ratio by ^{1}HNMR) as a white powder. R_f = 0.27, 0.21 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR of major isomer (500 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.63 (s, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 5.51 (s, 2H), 5.47 (s, 2H), 1.33 (s, 9H), ppm; ^{1}H NMR of minor isomer (500 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.0 Hz 2H), 7.84 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 5.68 (s, 2H), 5.31 (s, 2H), 1.28 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR of major isomer (126 MHz, CDCl3): δ = 166.4(C), 152.0(C), 143.3 (C), 133.2(CH), 131.3(C), 129.77(C), 129.75(CH), 128.4(CH), 128.0(CH), 126.1(CH), 123.8(CH), 58.1 (CH_2), 54.0(CH_2), 34.7(C), 31.3(CH_3), ppm; $^{13}C\{^1H\}$ and DEPT NMR of minor isomer (126 MHz, CDCl3): δ = 165.7(C), 151.6(C), 143.3 (C), 133.6(CH), 131.4(C), 129.70(CH), 129.0(C), 128.5(CH), 127.1(CH), 126.0(CH), 123.8 (C), 52.2(CH_2), 54.1(CH_2), 34.6(C), 31.2(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1719 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{24}N_3O_2$ (M+H) 350.1863, found 350.1889.

Methyl 1-(4-*t*-butylbenzyl)-5-(4-nitrophenyl)-1,2,3-triazole-4-carboxylate and Methyl 1-(4-*t*-butylbenzyl)-4-(4-nitrophenyl)-1,2,3-triazole-5-carboxylate T3a and T3b

A solution of methyl (4-nitrophenyl)propiolate (26.7 mg, 0.13 mmol) and *t*-butylbenzyl azide (36.0 mg, 0.19 mmol) dissolved in 2.0 mL CH_3CN was heated to 75 °C. TLC was checked at 120 h (5 days) and indicated that the reaction was done. The mixture was purified by column chromatography (19:1 to 4:1 hexanes:ethyl acetate) to afford 46.3 mg (0.093 mmol, 93%) of triazole product, separable: (20.8 mg of **T3a**, 25.5 mg of **T3b**).

T3a (regioisomer not identified):

Brown crystals, R_f = 0.43 (4:1 hexanes:ethyl acetate, UV); m.p. 132-136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.6 Hz, 2H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.94 (s, 2H), 3.86 (s, 3H), 1.32 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 159.0(C), 151.8(C), 148.3(C), 148.0(C), 136.7(C), 131.7(C), 130.2(CH), 127.8(CH), 125.8(CH), 124.7(C), 123.3(CH), 54.2(CH_2), 52.6(CH_3), 34.6(C), 31.3(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1731, 1524, 1348 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{23}N_4O_4$ $[M+H]^+$ 395.1715, found 395.1706.

T3b (regioisomer not identified):

Yellow crystals. R_f = 0.12 (4:1 hexanes:ethyl acetate, UV); m.p. 147-148 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 5.45 (s, 2H), 3.87 (s, 3H), 1.30 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 161.0(C), 152.1(C), 148.7(C), 139.1(C), 137.4(C), 132.6(C), 131.1(CH), 130.9(C), 127.3(CH), 126.0(CH), 123.6(CH), 52.5(CH_2), 52.2(CH_3), 34.6(C), 31.2 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1730, 1528, 1350 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{23}N_4O_4$ $[M+H]^+$ 395.1715, found 395.1704.

***N*-butyl 1-(4-*t*-butylbenzyl)-1,2,3-triazole-4-carboxamide and *N*-butyl 1-(4-*t*-butylbenzyl)-1,2,3-triazole-5-carboxamide, T4a and T4b**

solution of *n*-butyl propiolamide (20.0 mg, 0.160 mmol) and *t*-butylbenzyl azide (45.4 mg, 0.240 mmol) dissolved in 2.0 mL of $CHCl_3$ was heated to 75 °C. The reaction was monitored by TLC. After 168 h (7 days), the reaction was complete. Attempts to separate the two regioisomers by column chromatography were unsuccessful, providing 44.0 mg (0.139 mmol, 86.8%) of the triazole mixture (2.2 : 1 ratio of isomers by ^{1}HNMR) as a brown liquid. R_f = 0.07, 0.21 (CH_2Cl_2, UV); ^{1}H NMR of major isomer (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.52 (s, 2H), 3.44 (q, *J* = 6.7 Hz, 2H), 1.60 (p, *J* = 7.3 Hz, 2H), 1.42 (h, *J* = 6.9 Hz, 3H), 1.33 (s, 9H), 0.95 ppm (t, *J* = 7.3 Hz, 3H); ^{1}H NMR of minor isomer (500 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 2.2 Hz, 2H), 5.91 (s, 2H), 3.39 (q, *J* = 6.8 Hz, 2H), 1.52 (q, *J* = 7.5 Hz, 2H),1.29 (s, 9H), 0.93 ppm (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ and DEPT NMR of major isomer (126 MHz, $CDCl_3$): δ = 160.0(C), 152.3(C), 143.7(C), 132.4(C), 130.7(C), 128.2(CH), 126.2(CH), 54.2(CH_2), 38.9(CH_2), 34.7(C), 31.6(CH_2), 31.23(CH), 20.05(CH_2), 13.72(CH_3) ppm; $^{13}C\{^1H\}$ and DEPT NMR of minor isomer (126 MHz, $CDCl_3$): δ = 158.0(C), 151.3(C), 133.4(C), 133.3(C), 128.1(CH), 125.6(CH), 125.2(CH), 52.7(CH_2), 39.5(CH_2), 34.5(C), 31.4(CH_2), 31.25(CH), 20.0(CH_2), 13.70 (CH_3); IR (NaCl, $CDCl_3$): v = 3419, 1664 cm^{-1}; HRMS (ESI): m/z calcd for $C_{18}H_{27}N_4O$ $[M+H]^+$ 315.2179, found 315.2209.

***N,N'*-Bis-(*n*-butyl) 1-(4-*t*-butylbenzyl)-1,2,3-triazole-4,5-dicarboxamide, T5**

Bis-(*n*-butyl)-acetylenediamide (26.9 mg, 0.120 mmol) and *t*-butylbenzyl azide (34.1 mg, 0.180 mmol) were combined in 2 mL of CH_3CN and heated to 75 °C. TLC was checked at 72 h and indicated that the reaction was complete. The mixture was purified by column chromatography (19:1 to 4:1 hexanes:ethyl acetate) to give 38.6 mg (0.0933 mmol, 77.8 %) of the title compound as white crystals. R_f= 0.35 (9:1 hexanes:ethyl acetate, UV); m.p. 76-78 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.15 (s, 2H), 3.48 (q, *J* = 6.8 Hz, 2H), 3.42 (td, *J* = 7.2, 5.4 Hz, 2H), 1.64 (p, *J* = 7.1 Hz, 2H), 1.63 (p, *J* = 7.1 Hz, 2H), 1.45 (h, *J* = 7.5 Hz, 2H), 1.40 (h, *J* = 7.5 Hz, 2H) 1.30 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 161.5(C), 156.6(C), 151.2(C), 138.7(C), 132.5(C), 130.8(C), 128.2(CH), 125.6(CH), 53.9(CH_2), 39.4(CH_2), 39.3(CH_2), 34.5 (C), 31.4(CH_2), 31.3(CH_3), 31.2(CH_2), 20.2(CH_2), 20.1(CH_2), 13.8(CH_3), 13.7(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 3409, 3221, 1672, 1649 cm^{-1}; HRMS (ESI): m/z calcd for $C_{23}H_{36}N_5O_2$ $[M+H]^+$ 414.2865, found 414.2855.

Methyl 1-(4-*t*-butylbenzyl)-1,2,3-triazole-4-carboxylate and methyl 1-(4-*t*-butylbenzyl)-1,2,3-triazole-5-carboxylate, T6a and T6b

A solution of methyl propiolate (15.6 mg, 0.186 mmol) and *t*-butylbenzyl azide (49.4 mg, 0.261 mmol) dissolved in 2.0 mL of CH_3CN was heated to 75°C. TLC was checked at 24 h and indicated that the reaction was done. The mixture was purified by column chromatography (0% to 60% ethyl acetate in hexanes) to afford 25.4 mg (0.0929 mmol, 50.0%) total of two regioisomers, consisting of 5.5 mg of **T6a**, and 19.9 mg of **T6b**.

T6a (regioisomer not identified):

Yellow liquid R_f = 0.36 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (s, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.31

(d, *J* = 8.4 Hz, 2H), 5.91 (s, 2H), 3.92 (s, 3H), 1.31 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 158.9(C), 151.5(C), 131.9(C), 127.9(CH), 125.7(CH), 53.1(CH_2), 52.4(CH_3), 34.6(C), 31.3 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1727 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{20}N_3O_2$ (M+H) 274.1550, found 274.1578

T6b (regioisomer not identified):

White crystals, R_f = 0.12 (4:1 hexanes:ethyl acetate, UV); m.p. 120-121 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.98 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.56 (s, 2H), 3.94 (s, 3H), 1.34 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 161.2(C), 152.4(C), 140.2(C), 130.6(C), 128.2(CH), 127.3(CH), 126.3(CH), 54.2(CH_2), 52.2(CH_3), 34.7(C), 31.2 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1731 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{20}N_3O_2$ (M+H) 274.1550, found 274.1576.

Dimethyl 1-(4-*t*-butylbenzyl)-1,2,3-triazole-4,5-dicarboxylate, T7

A solution of dimethyl acetylenedicarboxylate (21.1 mg, 0.15 mmol) and *t*-butylbenzyl azide (42.5 mg, 0.22 mmol) dissolved in 2.0 mL of CH_3CN was heated to 75 °C. TLC was checked at 24 h and indicated that the reaction was done. The mixture was purified by column chromatography (10% to 70% ethyl acetate in hexanes) to afford 50.4 mg (0.15 mmol, 100%) of the title compound as a brown liquid. R_f = 0.29 (4:1 hexanes:ethyl acetate, UV); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 5.78 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H), 1.30ppm (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$) δ = 160.5(C), 158.9(C), 152.0(C), 140.1(C), 130.9(C), 129.8(C), 127.9(CH), 125.9(CH), 53.7(CH_2), 53.3(CH_3), 52.7(CH_3), 34.6(C), 31.2 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1735 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{22}N_3O_4$ $[M+H]^+$ 332.1605, found 332.1599.

Methyl 1-(4-*t*-butylbenzyl)-5-phenyloxomethyl-1,2,3-triazole-4-carboxylate (T8a) and Methyl 1-(4-*t*-butylbenzyl)-4-phenyloxomethyl-1,2,3-triazole-5-carboxylate (T8b)

A solution of methyl 4-oxo-4-phenyl-2-butynoate (26.0 mg, 0.138 mmol) and *t*-butylbenzyl azide (39.0 mg, 0.206 mmol) dissolved in 2.0 mL of CH_3CN was heated to 75°C. TLC was checked at 24 h and showed that the reaction was done. The mixture was purified by column chromatography (10% to 40% ethyl acetate in hexanes) afforded 45.0 mg (0.125 mmol, 90.6%) total of product, which were separable: 22.0mg of **T8a**, and 23.0 mg of **T8b** as white solids.

Regioisomer T8a:

White crystals, R_f = 0.31 (4:1 hexanes:ethyl acetate, UV); m.p. 100-102 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (t, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 5.60 (s, 2H), 3.69 (d, *J* = 0.7 Hz, 3H), 1.16ppm (s, 9H); irradiation at 5.60 ppm results in NOE enhancement of signal at 7.46 ppm, but none at 3.69 ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 186.7(C), 160.2(C), 152.0(C), 138.8(C), 137.1(C), 135.8(C), 134.5(CH), 130.3(C), 129.1(CH), 128.52(CH), 128.51(CH), 125.7(CH), 53.3(CH_2), 52.2(CH_3), 34.5(C), 31.1 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1732, 1671 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{24}N_3O_3$ $[M+H]^+$ 378.1812, found 378.1802.

Regioisomer T8b:

White crystals, R_f = 0.43 (4:1 hexanes:ethyl acetate, UV); m.p. 99-105 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 5.88 (s, 2H), 3.78 (s, 3H), 1.33 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 186.6(C), 159.0(C), 151.9(C), 147.6(C), 136.3(C), 133.8(CH), 131.1(C), 130.4(CH), 128.8(CH), 128.5(C), 128.1(CH), 125.9(CH), 53.5(CH_2), 53.0(CH_3), 34.6(C), 31.3 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1735, 1673 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{24}N_3O_3$ $[M+H]^+$ 378.1812, found 378.1806.

1-(4-*t*-Butylbenzyl)-4-(4-methylphenylsulfonyl)-1,2,3-triazole and 1-(4-*t*-butylbenzyl)-5-(4-methylphenylsulfonyl)-1,2,3-triazole, T9a and T9b

Ethynyl *p*-tolylsulfone (24.8 mg, 0.138 mmol) and *t*-butylbenzyl azide (38.1 mg, 0.201 mmol) were dissolved in 2 mL of CH_3CN and heated to 75 °C for 5 h. The mixture was cooled to 0 °C to produce 25.3 mg of **T9b** as a white precipitate, then 6.8 mg of **T9a** as a white solid was isolated by silica gel column chromatography (0% to 40% ethyl acetate in hexanes) to give 32.0 mg (63.0%) of total product.

T9a (regioisomer not identified):

White solid. R_f = 0.26 (4:1 hexanes:ethyl acetate, UV); m.p. 152-154 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 5.82 (s, 2H), 2.39 (s, 3H), 1.31 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 151.6(C), 145.5(C), 137.7(CH), 137.3(C), 136.5(C), 130.8(C), 129.9(CH), 127.6(CH), 127.4(CH), 125.6(CH), 52.9(CH_2), 34.6(C), 31.3(CH_3), 21.7(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1339, 1148 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{24}N_3SO_2$ $[M+H]^+$ 370.1579, found 370.1573.

T9b (regioisomer not identified):

White solid. R_f = 0.15 (4:1 hexanes:ethyl acetate, UV); m.p. 252-255 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.4 Hz, 2H), 7.95 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.51 (s, 2H), 2.44 (s, 3H), 1.35 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 152.8(C), 149.5(C), 145.0(C), 137.1(C), 129.9(CH), 129.8(C), 128.4(CH), 128.2(CH), 126.4(CH), 125.4(CH), 54.6(CH_2), 34.8(C), 31.2(CH_3), 21.7(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1331, 1158 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{24}N_3SO_2$ $[M+H]^+$ 370.1579, found 370.1577.

Methyl 1-(4-*t*-butylbenzyl)-5-phenylsulfonyl-1,2,3-triazole-4-carboxylate and Methyl 1-(4-*t*-butylbenzyl)-4-phenylsulfonyl-1,2,3-triazole-5-carboxylate, T10a and T10b

Methyl 3-(phenylsulfonyl)-2-propynoate (28.1 mg, 0.12 mmol) and *t*-butylbenzyl azide (34.3 mg, 0.181 mmol) were dissolved in 2 mL of CH_3CN and heated to 75 °C for 1 h. The mixture was purified by silica gel column chromatography (5% to 40% ethyl acetate in hexanes), 19.2 mg (37.0%) (5.5 mg of **T10a**, 13.7 mg of **T10b**)

T10a (regioisomer not identified):

Colorless crystals. R_f = 0.14 (4:1 hexanes:ethyl acetate, UV); m.p. 99-113 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.09 (s, 2H), 3.96 (s, 3H), 1.35 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 159.5(C), 152.1(C), 140.5(C), 139.0(C), 137.4(C), 134.5(CH), 131.1(C), 128.8(CH), 128.5(CH), 127.7(CH), 125.9(CH), 54.5(CH_2), 52.9(CH), 34.7(C), 31.4 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1742, 1350, 1172 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{24}N_3SO_4$ $[M+H]^+$ 414.1482, found 414.1518.

T10b (regioisomer not identified):

Colorless viscous liquid. R_f = 0.17 (4:1 hexanes:ethyl acetate, UV); ^1H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 7.4 Hz, 2H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 5.80 (s, 2H), 3.99 (s, 3H), 1.31 (s, 9H) ppm; $^{13}C\{^1H\}$ and DEPT NMR (126 MHz, $CDCl_3$): δ = 157.6(C), 152.2(C), 149.4(C), 139.4(C), 134.2(CH), 130.4(C), 129.1(CH), 128.9(CH), 128.2(CH), 127.6(C), 125.9(CH), 54.2(CH_2), 53.5(CH), 34.7(C), 31.2 (CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1740, 1330, 1163 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{24}N_3SO_4$ $[M+H]^+$ 414.1482, found 414.1521.

Methyl 1-(1-phenylheptan-3-yl)-5-(4-nitrophenyl)-1,2,3-triazole-4-carboxylate and methyl 1-(1-phenylheptan-3-yl)-4-(4-nitrophenyl)-1,2,3-triazole-5-carboxylate, T11a and T11b

Methyl 4-nitrophenylpropiolate (26.8 mg, 0.131 mmol) and 3-azido-1-phenylheptane (41.2 mg, 0.190 mmol) were dissolved in 2 mL of CH_3CN and heated to 75 °C for 10 days. The mixture was purified by silica gel column chromatography (0% to 40% ethyl acetate in hexanes) to give 35.1 mg (63.4%) of total product, 12.9 mg of **T11a**, 22.2 mg of **T11b** as colorless liquids.

T11a (regioisomer not identified)

Colorless liquid. R_f = 0.48 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 2H), 5.20 (tt, *J* = 9.5, 4.9 Hz, 1H), 3.83 (s, 3H), 2.61 (m, 1H), 2.56 (m, 2H), 2.31 (m, 1H), 2.20 (m, 1H), 1.99 (m, 1H), 1.31 (m, 3H), 1.12 (m, 1H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} and DEPT NMR (126 MHz, $CDCl_3$): δ = 159.5(C), 147.9(C), 147.2(C), 140.4(C), 136.9(C), 130.1(CH), 128.5(CH), 128.3(CH), 126.2(CH), 126.0(C), 123.3(CH), 61.6(CH), 52.6(CH_3), 36.5(CH_2), 35.6(CH_2), 32.2(CH_2), 28.0(CH_2), 22.3(CH_2), 13.9(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1728, 1524, 1349 cm^{-1}; HRMS (ESI): m/z calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$ 423.2027, found 423.2016.

T11b (regioisomer not identified)

Colorless liquid. R_f = 0.30 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.21 (m, 3H), 7.04 (d, *J* = 6.8 Hz, 2H), 4.08 (tt, *J* = 9.4, 5.3 Hz, 1H), 3.87 (s, 3H), 2.49 (m, 3H), 2.32 (m, 1H), 2.11 (m, 1H), 1.91 (m, 1H), 1.18 (m, 2H), 1.03 (m, 2H) 0.83 (t, *J* = 7.3 Hz, 1H) ppm; ^{13}C{^{1}H} and DEPT NMR (126 MHz, $CDCl_3$): δ = 161.2(C), 148.6(C), 139.8(C), 132.8(C), 131.1(CH), 128.7(CH), 128.2(CH), 126.5(CH), 123.7(CH), 59.4(CH), 52.2(CH_3), 36.4(CH_2), 35.0(CH_2), 31.9(CH_2), 28.1(CH_2), 22.2(CH_2), 13.7(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1728, 1528, 1350 cm^{-1}; HRMS (ESI): m/z calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$ 423.2027, found 423.2014.

Methyl 1-(1-phenylheptan-3yl)-1,2,3-triazole-4-carboxylate and methyl 1-(1-phenylheptan-3-yl)-1,2,3-triazole-5-carboxylate, T12a and T12b

Methyl propiolate (21.8 mg, 0.259 mmol) and 3-azido-1-phenylheptane (36.3 mg, 0.167 mmol) were dissolved in 2 mL of CH_3CN and heated to 75 °C for 36 h. The mixture was purified by silica gel column chromatography (0% to 40% ethyl acetate in hexanes) to give 26.3 mg (52.2%) of total product: 4.2 mg of **T12a**, 22.1 mg of **T12b** as colorless liquids.

T12a (regioisomer not identified)

Colorless liquid. R_f = 0.50 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (s, 1H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 2H), 5.38 (tt, *J* = 9.5, 4.8 Hz, 1H), 3.91 (s, 3H), 2.49 (m, 3H), 2.24 (m, 1H), 2.15 (m, 1H), 1.94 (m, 1H), 1.29 (m, 2H), 1.24 (m, 1H), 1.03 (m, 1H) 0.85 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} and DEPT NMR (126 MHz, $CDCl_3$): δ = 159.1(C), 140.7(C), 137.7(CH), 128.4(CH), 128.3(CH), 126.1(CH), 60.7(CH), 52.3(CH_3), 36.8(CH_2), 35.5(CH_2), 32.2(CH_2), 27.9(CH_2), 22.3(CH_2), 13.8(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1735 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{24}N_3O_2$ $[M+H]^+$ 302.1858, found 302.1857.

T12b (regioisomer not identified)

Colorless liquid. R_f = 0.24 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 2H), 4.53 (tt, *J* = 9.6, 5.0 Hz, 1H), 3.98 (s, 3H), 2.47 (m, 2H), 2.30 (m, 1H), 2.23 (m, 1H), 1.91 (m, 2H), 1.28 (m, 2H), 1.19 (m, 1H), 1.02 (m, 1H), 0.84 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} and DEPT NMR (126 MHz, $CDCl_3$): δ = 161.3(C), 140.0(C), 128.6(CH), 128.3(CH), 126.3(CH), 126.2(CH), 62.1(CH), 52.2(CH_3), 37.0(CH_2), 35.4(CH_2), 32.0(CH-$_2$), 27.9(CH_2), 22.1(CH_2), 13.8(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1725 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{24}N_3O_2$ $[M+H]^+$ 302.1858, found 302.1859.

Dimethyl 1-(1-phenylheptan-3-yl)-1,2,3-triazole-4,5-dicarboxylate, T13

Dimethyl acetylenedicarboxylate (30.2 mg, 0.213 mmol) and 3-azido-1-phenylheptane (30.4 mg, 0.140 mmol) were dissolved in 2 mL of CH_3CN and heated to 75 °C for 24 h. The mixture was purified by silica gel column chromatography (0% to 40% ethyl acetate in hexanes) to give 42.8 mg (85.2%) of **T13** as a colorless liquid.

T13

Colorless liquid. R_f = 0.33 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 2H), 4.75 (tt, *J* = 9.6, 4.9 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 2.53 (m, 1H), 2.47 (m, 2H), 2.22 (m, 1H), 2.11 (m, 1H), 1.91 (m, 1H), 1.26 (m, 2H), 1.21 (m, 1H), 1.04 (m, 1H), 0.84 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} and DEPT NMR (126 MHz, $CDCl_3$): δ = 160.6(C), 159.4(C), 140.2(C), 138.9(C), 131.6(C), 128.5(CH), 128.3(CH), 126.2(CH), 61.8(CH), 53.4(CH_3), 52.6(CH_3), 36.5(CH_2), 35.2(CH_2), 32.0(CH_2), 27.8(CH_2), 22.1(CH_2), 13.8(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1737 cm^{-1}; HRMS (ESI): m/z calcd for $C_{19}H_{26}N_3O_4$ $[M+H]^+$ 360.1913, found 360.1925.

Methyl 1-(1-phenylheptan-3-yl)-4-phenylsulfonyl-1,2,3-triazole-5-carboxylate and methyl 1-(1-phenylheptan-3-yl)-5-phenylsulfonyl-1,2,3-triazole-4-carboxylate, T14a and T14b

Methyl phenylsulfonylpropiolate (32.3 mg, 0.144 mmol) and 3-azido-1-phenylheptane (49.4 mg, 0.227 mmol) were dissolved in 2 mL of CH_3CN and heated to 75 °C for 5h. Attempts to separate the regioisomers by column chromatography were unsuccessful, but produced 27.8 mg (43.6%) of total product as a colorless liquid (2.2 : 1 ratio of isomers by ^{1}HNMR). R_f = 0.43, 0.38 (4:1 hexanes:ethyl acetate, UV); ^{1}H NMR of major regioisomer (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.7 Hz, 2H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 7.3 Hz, 2H), 4.91 (tt, *J* = 9.3, 5.0 Hz, 1H), 3.98 (s, 1H), 2.46 (m, 3H), 2.26 (m, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.23 (m, 3H), 1.01 (m, 1H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm; ^{1}H NMR of minor regioisomer (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.8 Hz, 2H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 2H), 5.30 (tt, *J* = 8.3, 5.1 Hz, 1H), 4.01 (s, 3H), 2.46 (m, 2H), 2.26 (m, 2H), 2.06 (m, 1H), 1.93 (m, 1H), 1.23 (m, 2H), 1.09 (m, 1H), 0.90 (m, 1H), 0.80 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C{^{1}H} and DEPT NMR of major regioisomer (126 MHz, $CDCl_3$): δ = 157.9(C), 148.3(C), 139.9(C), 139.66(C), 134.1(CH), 129.1(CH), 128.7(CH), 128.50(CH), 128.17(CH), 126.26(CH), 62.3(CH), 53.6(CH_3), 36.1(CH_2), 35.3(CH_2), 32.0(CH_2), 27.8(CH_2), 22.2(CH_2), 13.74(CH_3) ppm; ^{13}C{^{1}H} and DEPT NMR of minor regioisomer (126 MHz, $CDCl_3$): δ = 160.3(C), 140.3(C), 139.61(C), 137.7(C), 134.9(CH), 129.5(CH), 129.3(C), 128.52(CH), 128.4(CH), 128.23(CH), 126.24(CH), 62.7(CH), 53.2(CH_3), 37.2(CH_2), 35.4(CH_2), 32.1(CH_2), 27.9(CH_2), 22.3(CH_2), 13.77(CH_3) ppm; IR (NaCl, $CDCl_3$): v = 1741, 1334, 1163 cm^{-1}; HRMS (ESI): m/z calcd for $C_{23}H_{28}N_3SO_4$ $[M+H]^+$ 442.1795, found 442.1780.

Room temperature cycloaddition

Methyl 3-(phenylsulfonyl)-2-propynoate (41.7 mg, 0.186 mmol) and *t*-butylbenzyl azide (31.4 mg, 0.166 mmol) were combined in 0.6 mL CD_3CN at room temperature. At time zero, the azide : alkyne ratio was 1.0 : 0.68 based on integrations of azide C**H$_2$**Ar (δ = 4.36, I = 2.00), sulfone OC**H$_3$** (δ = 3.82, I = 2.04). After 5 hours, 92% of the alkyne had been converted to triazole, based on integrations of **T10a** OC**H$_3$** (δ = 3.93, I = 1.90), **T10b** OC**H$_3$** (δ = 3.91, I = 1.40), and **10** OC**H$_3$** (δ = 3.82, I = 0.29).

Competition Experiments with *t*-butylbenzyl azide: A representative procedure for the competition experiments is as follows.

Amide (4) vs Nitroaryl (3)

N-butyl propiolamide (23 mg, 0.18 mmol), methyl 4-nitrophenylpropiolate (37 mg, 0.18 mmol), and 4-*t*-butylbenzyl azide (3.4 mg, 0.018 mmol) were combined in 0.60 mL of CD_3CN in an NMR tube. NMR of the initial solution revealed a ratio of azide : amide : nitro of 1 : 8.3 : 9.9, based on integrations of azide C**H$_2$**Ar (δ = 4.35, I = 2.00), amide C**H$_2$**NH (δ = 3.19, I = 17.98), amide CC**H** (δ = 3.16, I = 6.84), and nitro OC**H$_3$** (δ = 3.84, I = 29.81).The reaction mixture was heated to 75 °C in an oil bath. After 5 days, NMR confirmed all of the azide had been consumed.

The ratio of products was amide : nitro 2.2 : 1.0, based on integrations of the benzylic protons of **T4a** (δ = 5.55, I = 3.80), **T4b** (δ = 5.88, I = 1.70), **T3b** (δ = 5.46, I = 1.54), and **T3a** (δ = 5.91, I =1.00).

Amide (4) vs Benzoyl (2)

The initial ratio of azide : amide : benzoyl was 1.0 : 8.7 : 13.1, based on integrations of C**H**$_2$Ar (δ = 4.35, I = 2.00), amide C**H**$_2$NH plus amide CC**H** (overlapping, δ = 3.19, I = 26.18), and benzoyl OC**H**$_2$ (δ = 4.94, I = 26.23). The ratio of products was amide : benzoyl 4.7:1, based on integrations of the bezylic protons of **T2b** (δ = 5.66, I = 0.24, δ = 5.39, I = 0.27) **T2a** (δ = 5.54, I = 0.55, δ = 5.42, I = 0.44), **T4b** (δ = 5.90, I = 1.00), and **T4a**(δ = 5.56, I = 2.52).

Ester (6) vs Diamide (5)

The intial ratio of azide : ester : diamide was 1.0 : 14.6 : 12.4, based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), ester OC**H**$_3$ (δ = 3.78, I = 43.84), and diamide C**H**$_2$NH (δ = 3.23, I = 49.40). The ratio of products was ester : diamide 2.2 : 1.0, based on integrations of the benzylic protons of **T7** (δ = 6.09, I = 1.00), **T6a** (δ = 5.89, I = 0.31), and **T6b** (δ = 5.58, I = 1.90).

Ketone (8) vs Diester (7)

The initial ratio of azide : ketone : diester was 1.0 : 12.5 : 12.4 , based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), ketone OC**H**$_3$ (δ = 3.89, I = 37.54), and diester OC**H**$_3$ (δ = 3.84, I = 74.66). The ratio of products was ketone : diester 1.1 : 1.0, based on integrations of the benzylic protons of **T7** (δ = 5.73, I = 1.32), **T8b** (δ = 5.86, I = 1.00), and **T8a** (δ = 5.57, I = 0.46).

Diester (7) vs Ester (6)

The initial ratio of azide : diester : ester was 1.0 : 11.6 : 9.0, based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), diester OC**H**$_3$ (δ = 3.84, I = 69.88), and ester OC**H**$_3$ (δ = 3.78, I = 27.00). The ratio of products was diester : ester 6.4 : 1.0, based on integrations of the benzylic protons of **T6a** (δ = 5.89, I = 0.16), **T6b** (δ = 5.58, 1.00), and **T7** (δ = 5.73, I = 7.42).

Ketone (8) vs Ester (6)

The initial ratio of azide : ketone : ester was 1.0 : 11.7 : 20.3, based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), ketone OC**H**$_3$ (δ = 3.89, I = 35.23), and ester OC**H**$_3$ (δ = 3.78, I = 60.95). The ratio of products was ketone : ester 2.7 : 1.0, based on integrations of the benzylic protons of **T6a** (δ = 5.88, I = 0.09), **T6b** (δ = 5.58, I = 0.43), **T8b** (δ = 5.86, I = 1.00), and **T8a** (δ = 5.57, I = 0.41 overlap).

Sulfone Ester (10) vs Diester (7)

The initial ratio of azide : sulfone : diester was 1.0 : 11.1 : 11.1, based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), sulfone OC**H**$_3$ (δ = 3.89, I = 33.18), and diester OC**H**$_3$ (δ = 3.78, I = 66.35). The ratio of products was sulfone : diester 17.2 : 1.0, based on integrations of the benzylic protons of **T7** (δ = 5.74, I = 0.13), **T10b** (δ = 5.74, I = 1.22), and **T10a** (δ = 6.03, I = 1.00).

Diamide (5) vs Nitroaryl (4)

The initial ratio of azide : diamide : nitro was 1.0 : 12.7 : 13.3, based on integrations of azide C**H**$_2$Ar (δ = 4.35, I = 2.00), diamide C**H**$_2$NH (δ = 3.22, I = 50.75), and nitro OC**H**$_3$ (δ = 3.85, I = 39.97). The ratio of products was diamide : nitro 4.3 : 1.0, based on integrations of the benzylic protons of **T3a** (δ = 5.91, I = 0.09), **T3b** (δ = 5.47, 0.14), and **T5** (δ = 6.08, I = 1.00).

Benzoyl (2) vs Phenyl (1)

The initial ratio of azide : benzoyl : phenyl was 1.0 : 7.8 : 9.5, based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), benzoyl OC**H**$_2$ (δ = 4.94, I = 15.59), and phenyl OC**H**$_2$ (δ = 4.28, I = 18.90). The ratio of products was benzoyl : phenyl 1.2 : 1.0, based on integrations of the benzylic protons of **T1a** (δ = 5.89, I = 0.25), **T1b** (δ = 5.42, I = 0.50, overlap), **T2b** (δ = 5.66, I = 0.28, δ = 5.39, I = 0.31), and **T2a** (δ = 5.53, I = 0.59, δ = 5.42, I = 0.60, overlap).

Sulfone (9) vs Ester (6)

The initial ratio of azide : sulfone : ester was 1.0 : 10.1 : 10.1 , based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), sulfone CC**H** (δ = 4.12, I = 10.12), and ester CC**H** (δ = 3.40, I = 10.05). The ratio of products of sulfone : ester was 10.6 : 1.0, based on integrations of the benzylic protons of **T9a** (δ = 5.79, I = 1.64), **T9b** (δ = 5.55, I = 10.07), **T6a** (δ = 5.89, I = 0.10), and **T6b** (δ = 5.58, I = 1.00).

Sulfone (9) vs Diester (7)

The initial ratio of azide : sulfone : diester was 1 : 8.2 : 8.2, based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), sulfone CC**H** (δ = 4.12, I = 8.19), and diester OC**H**$_3$ (δ = 3.84, I = 49.05). The ratio of products of sulfone : diester was 2.6 : 1.0, based on integrations of the benzylic protons of **T9a** (δ = 5.79, I = 0.33), **T9b** (δ = 5.55, I = 2.29), and **T7** (δ = 5.73, I = 1.00).

Competition Experiments with 3-azido-1-phenylheptane:

Ester (6) vs Nitro (3)

The initial ratio of azide : ester : nitro was 1 : 9.5 : 10.2, based on integrations of azide C**H**N_3 (δ = 3.33, I = 1.00), ester OC**H**$_3$ (δ = 3.77, I = 28.58), and nitro OC**H**$_3$ (δ = 3.85, I = 30.68). The ratio of products of ester : nitro was 7.4 : 1.0, based on integrations of the protons alpha to the triazole of **T11a** (δ = 5.20, I = 1.00), **T11b** (δ = 4.10, I = 1.24), **T12a** (δ = 5.33, I = 2.36), and **T12b** (δ = 4.58, I = 14.17).

Diester (7) vs Ester (6)

The initial ratio of azide : diester : ester was 1 : 6.1 : 7.0, based on integrations of azide C**H**N_3 (δ = 3.34, I = 1.00), ester OC**H**$_3$ (δ = 3.77, I = 20.91), and diester OC**H**$_3$ (δ = 3.84, I = 36.66). The ratio of products of diester : ester was 4.9 : 1.0, based on integrations of the protons alpha to the triazole of **T12a** (δ = 5.33, I = 0.14), **T12b** (δ = 4.58, I = 1.00), and **T13** (δ = 4.72, I = 5.55).

Sulfone Ester (10) vs Diester (7)

The initial ratio of azide : sulfone ester : diester was 1 : 7.6 : 9.7, based on integrations of azide C**H**N_3 (δ = 3.33, I = 1.00), sulfone ester OC**H**$_3$ (δ = 3.82, I = 22.67), and diester OC**H**$_3$ (δ = 3.84, I = 58.14). The ratio of products of sulfone ester : diester was 19.0 : 1.0, based on integrations of the protons alpha to the triazole of **T14a** (δ = 5.17, I = 6.76), **T14b** (δ = 4.80, I = 12.25), and **T13** (δ = 4.72, I = 1.00).

Time-based competition

Methyl 4-nitrophenylpropiolate (16.5 mg, 0.0804 mmol), bis-*N*-butyl acetylenediamide (20.2 mg, 0.0901 mmol), and 4-*t*-butylbenzyl azide (1.7 mg, 0.0090 mmol) were combined in 0.60 mL of CD_3CN. NMR of the initial solution revealed a ratio of azide : diamide:nitro of 1.0 : 9.1 : 9.6, based on integrations of azide C**H**$_2$Ar (δ = 4.36, I = 2.00), diamide C**H**$_2$NH (δ = 3.23, I = 18.19), and nitro OC**H**$_3$ (δ = 3.85, I = 14.40). The reaction mixture was heated to 75 °C in an oil bath.

After 30 min, 8.6% of the azide had been consumed, and the product ratio was diamide : nitro 5.0 : 1.0, based on integrations of the benzylic protons of azide (δ = 4.35 , I = 12.76), **T5** (δ = 6.08, I = 1.00), **T3a** (δ = 5.91, I = 0.08), and **T3b** (δ = 5.47, I = 0.12).

After 2 h, 29% of the azide had been consumed, and the product ratio was diamide : nitro 4.8 : 1.0, based on integrations of the benzylic protons of azide (δ = 4.35 , I = 3.00), **T5** (δ = 6.08, I = 1.00), **T3a** (δ = 5.91, I = 0.09), and **T3b** (δ = 5.47, I = 0.12).

After 15 h, 93% of the azide had been consumed, and the product ratio was diamide : nitro 4.8 : 1.0, based on integrations of the benzylic protons of azide (δ = 4.35 , I = 0.09), **T5** (δ = 6.08, I = 1.00), **T3a** (δ = 5.91, I = 0.09), and **T3b** (δ = 5.47, I = 0.12).

After 42 h, no azide starting material was detected, and the product ratio was diamide : nitro 4.8 : 1.0, based on integrations of the benzylic protons of **T5** (δ = 6.08, I = 1.00), **T3a** (δ = 5.91, I = 0.09), and **T3b** (δ = 5.47, I = 0.12).

Supporting Information:

Supporting information is available:

^{1}H and ^{13}CNMR spectra, Integrations used to determine product ratios, diastereomeric ratios, Wiberg bond indices, and atom coordinates.

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