Electronic Supplementary Information for

Halide inhibition of the copper-catalysed azide-alkyne cycloaddition

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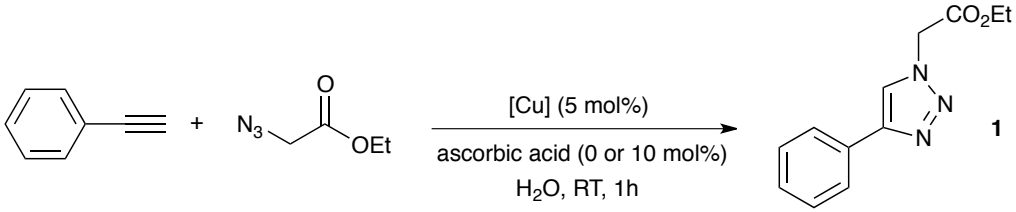
General experimental considerations

Proton nuclear magnetic resonance (^{1}H NMR) and proton-decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 400 MHz spectrometer. ^{1}H and ^{13}C NMR Spectra were assigned as fully as possible using COSY, HSQC, and DEPT-135 experiments. All chemical shifts are quoted on the δ scale in ppm using residual solvent as the internal standard (^{1}H NMR: $CDCl_3$ = 7.26; DMSO-d_6 = 2.50; and ^{13}C NMR: $CDCl_3$ = 77.0; DMSO-d_6 = 39.5). Coupling constants (*J*) are reported in hertz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, and a = apparent. Infrared (IR) spectra were recorded on a Fourier Transform spectrophotometer using thin films on NaCl plates for liquids and oils and KBr discs for solids and crystals. Absorption maxima (υ_{max}) are reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were recorded on an electrospray ionization mass spectrometer with atmospheric pressure chemical ionization (APCI) capability and an orbitrap mass analyzer. Accurate mass (m/z) values are reported in Daltons. Thin layer chromatography (TLC) was carried out using aluminum backed 200 μm silica plates impregnated with a UV_{254} fluorophore. Visualization of the silica plates was achieved using a UV lamp (λ_{max} = 254 nm), and/or ammonium molybdate (5% in 2M H_2SO_4), and/or potassium permanganate (5% $KMnO_4$ in 1M NaOH with 5% potassium carbonate). Flash column chromatography was carried out using 60 Å, 40-63 mm silica gel. All solvents and reagents were used as received from commercial suppliers. Deionized water was used for chemical reactions unless otherwise indicated. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40-60 ºC. Brine refers to a saturated solution of sodium chloride. Anhydrous magnesium sulfate ($MgSO_4$) was used as a drying agent after reaction workup, as indicated. In instances where starting materials or reagents have been reported previously in the literature, references are provided that corroborate spectroscopic assignments and other analytical characterization.

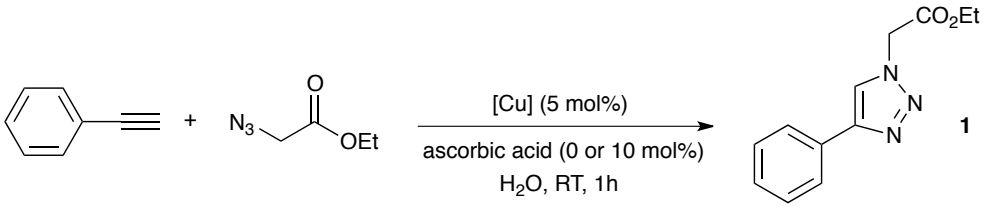
Experiments from Table 1: Catalyst screening for synthesis of triazole 1



H_2O (1.0) mL was added to a 5 mL reaction tube followed by phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL). The copper source (5 mol%) was then added to the mixture as solid. If ascorbic acid was included in the reaction mixture, it was the last component added (17 mg, 0.10 mmol). The reaction was then capped and stirred at room temperature for

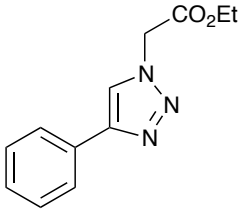
1 hour. If product precipitated, the triazole was isolated by filtration and then transferred to a clean vial. The crude triazole was then suspended in 2.0 mL NH_4OH (25%) and stirred vigorously for 1 hour to remove copper coordinated to the product. The triazole was then isolated by filtration, dried under vacuum, and characterised. If no precipitate formed in the reaction, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove as much ethanol as possible. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. Conversions were calculated from the relative integration of the $C\underline{H}_2CO_2Et$ in any unreacted ethyl azidoacetate ($\delta \sim 3.8$ ppm) and the triazole product ($\delta \sim 5.2$) in $CDCl_3$. Isolated yields and conversions are recorded below in Table S1.

Table S1:



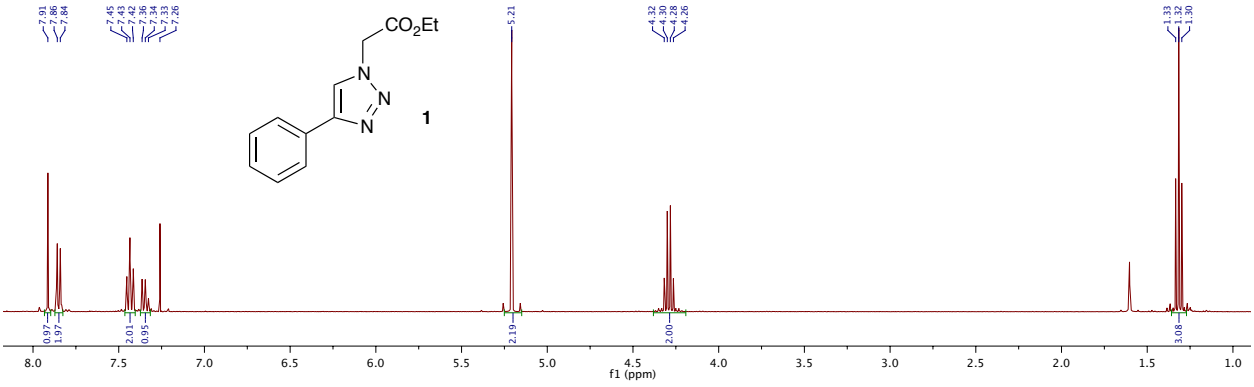
Entry	Catalyst	Ascorbic Acid	Isolated Yield or Conversion to 1
1	CuBr	10 mol%	224 mg, 97% isolated yield
2	CuBr	0 mol%	204 mg, 88% isolated yield
3	CuI	10 mol%	0% conversion, unreacted azide and alkyne in ^1H NMR
4	CuI	0 mol%	0% conversion, unreacted azide and alkyne in ^1H NMR
5	$CuCl_2$	10 mol%	52% conversion to triazole by ^1H NMR analysis
6	$CuCl_2$	0 mol%	0% conversion, unreacted azide and alkyne in ^1H NMR
7	$CuSO_4$	10 mol%	210 mg, 91% isolated yield
8	$CuSO_4$	10 mol%	100% conversion to triazole by ^1H NMR
9	$CuSO_4$	0 mol%	0% conversion, unreacted azide and alkyne in ^1H NMR
10	$Cu_2(OH)PO_4$	10 mol%	209 mg, 90% isolated yield
11	$Cu_2(OH)PO_4$	0 mol%	0% conversion, unreacted azide and alkyne in ^1H NMR
12	Cu powder (45 μm)	0 mol%	0% conversion, unreacted azide and alkyne in ^1H NMR
13	$CuNO_3$	10 mol%	173 mg, 75% isolated yield
14	$CuNO_3$	0 mol%	0% conversion, unreacted azide and alkyne in ^1H NMR

Characterization data for isolated triazole **1**:

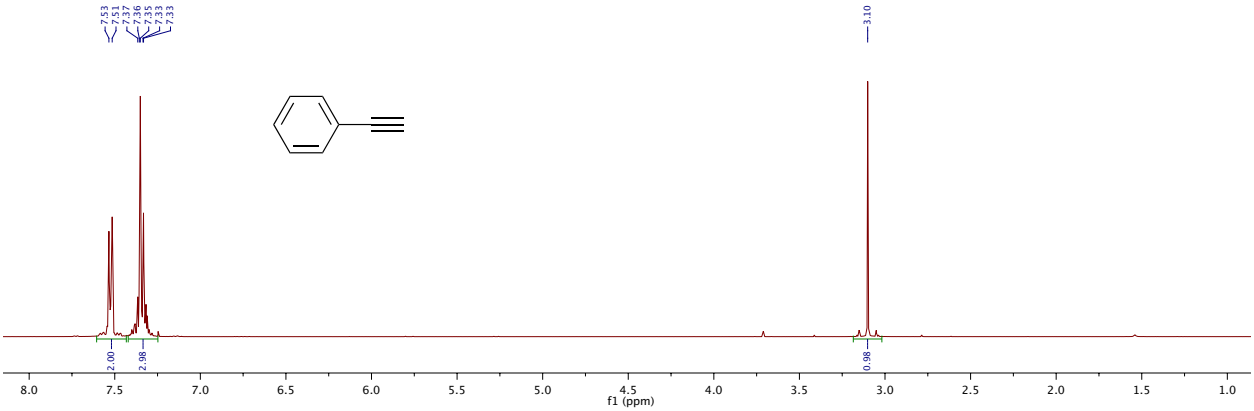


m.p. = 92-95 ºC. IR (KBr): 3134, 3103, 3003, 2948, 1755, 1467, 1442, 1348, 1216, 1199, 1145, 1076, 787, 695. ^{1}H NMR (400 MHz, DMSO-d6): 1.20 (3H, t, J = 7.1, $CH_2C\underline{H}_3$), 4.17 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 5.44 (2H, s, $C\underline{H}_2CO_2Et$), 7.32 (1H, tt, J = 7.4, 1.2, CH_{Ph}), 7.43 (2H, t, J = 7.4, CH_{Ph}) 7.84 (2H, dd, J = 7.4, 1.2, CH_{Ph}), 8.55 (1H, s, $CH_{Triazole}$). ^{13}C NMR (100 MHz, DMSO-d6): 14.4 ($CH_2\underline{C}H_3$), 51.0 ($\underline{C}H_2CO_2Et$), 62.0 ($\underline{C}H_2CH_3$), 123.2 ($CH_{triazole}$), 125.6 (CH_{Ph}), 128.4 (CH_{Ph}), 129.4 (CH_{Ph}), 131.0 (4^{o}_{Ar}), 146.8 (4^{o}_{Ar}), 167.7 (C=O). HRMS (m/z, ESI^{+}): Found 232.1056 $[M+H]^{+}$; $C_{12}H_{14}N_3O_2$ requires 232.1081. This data is consistent with that previously reported in the literature.[1] (^{1}H and ^{13}C NMR spectra in DMSO-d6 for triazole **1** are located on page S22)

^{1}H NMR (400 MHz) for triazole **1** in $CDCl_3$ (Reference spectrum for comparison to crude reaction mixtures):

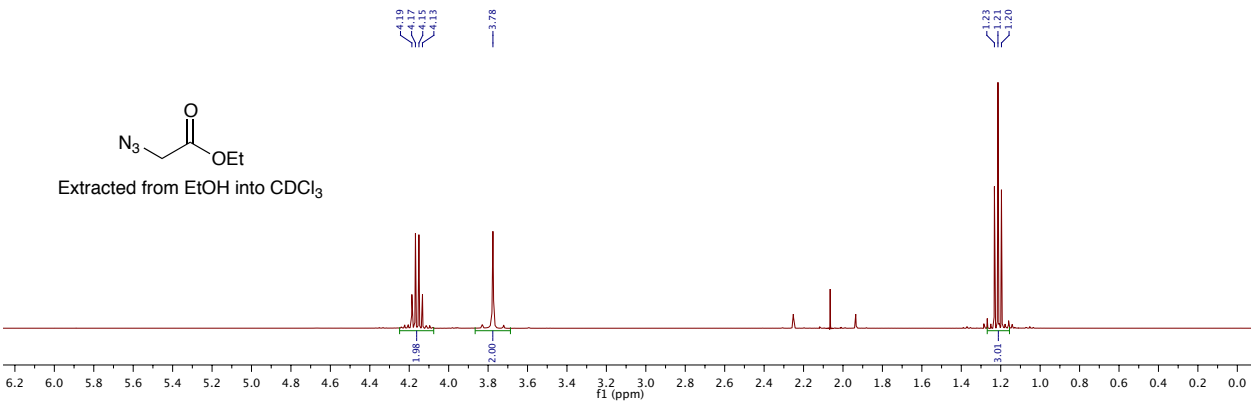


^{1}H NMR (400 MHz) for phenylacetylene in $CDCl_3$ (Reference spectrum for use in analysis of crude reaction mixtures):

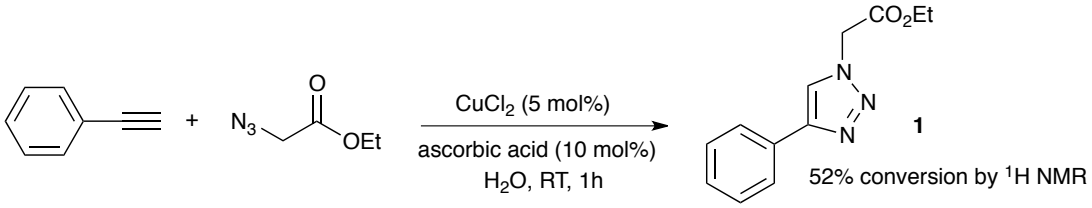


^{1}H NMR (400 MHz) for ethyl azidoacetate after extraction from ethanol with $CDCl_3$ (Reference spectrum for comparison to crude reaction mixtures):

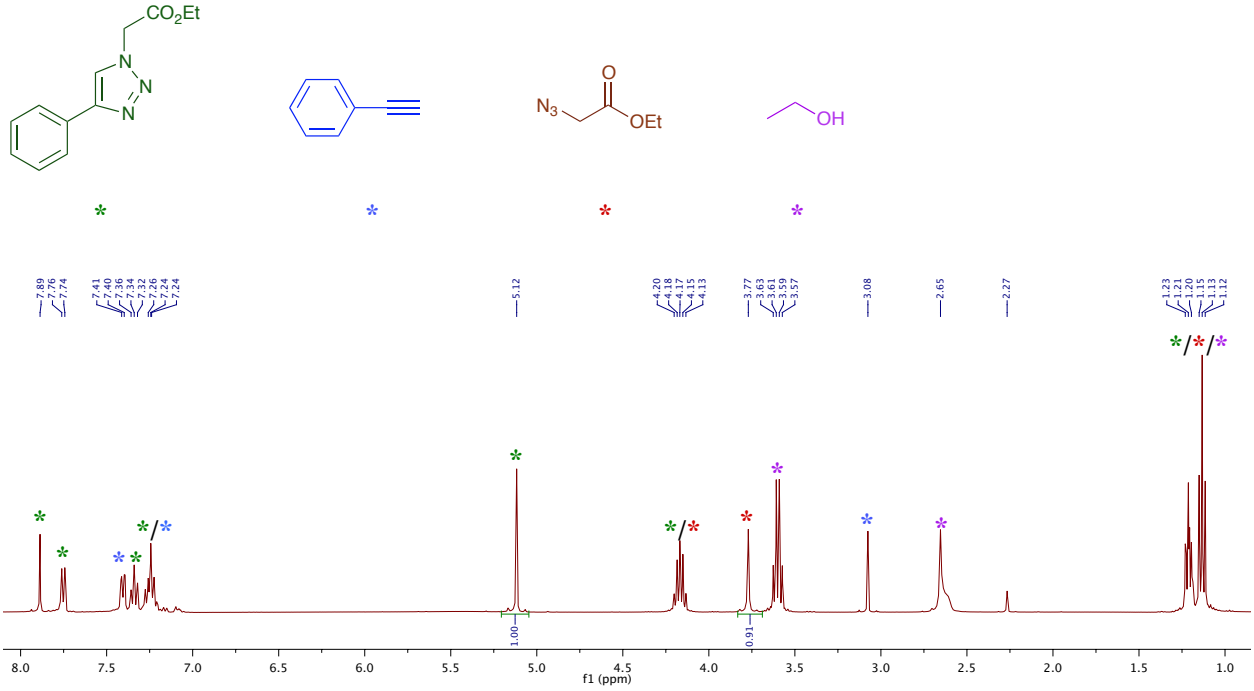
Ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL) was added to a test tube containing 1.0 mL H_2O and stirred for several minutes to homogenize. Next, $CDCl_3$ (0.7 mL) was added directly to the solution and mixed by drawing repeatedly into a pipette in order to extract the azide from the water-ethanol mixture. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the organic layer and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove as much ethanol as possible. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^{1}H NMR. The spectrum of the extracted azide is shown below:



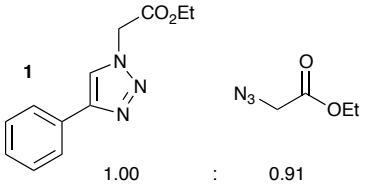
Representative NMR for conversion analysis (Entry 5, Table S1)



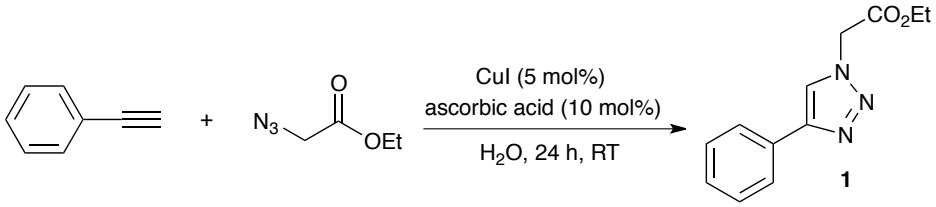
Reaction components in ^{1}H NMR of crude reaction mixture:



The relative integration of the C<u>H$_2$</u>CO$_2$Et used to determine reaction conversion is indicated above.



CuI as a catalyst in the synthesis of triazole 1 (24 hour reaction time)



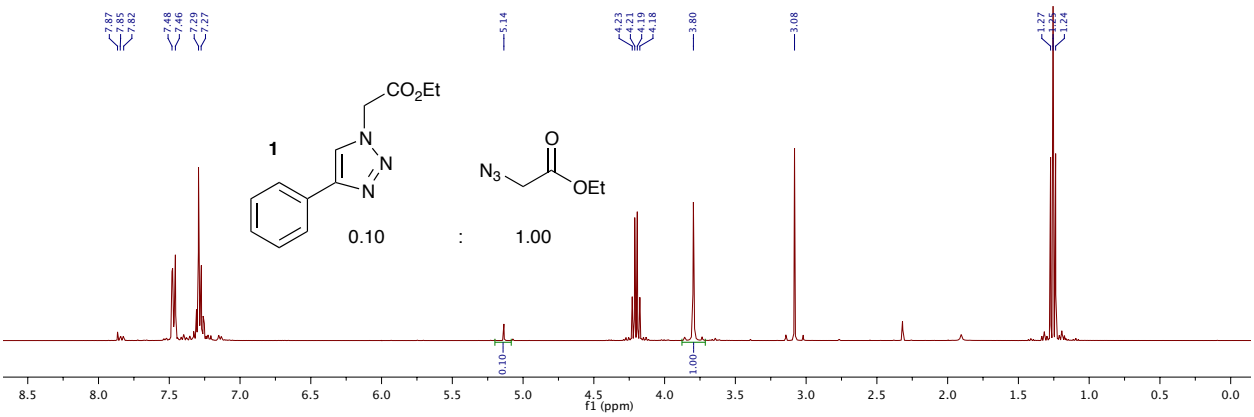
8% isolated yield
9% conversion by ^{1}H NMR

Procedure used to determine isolated yield of triazole:

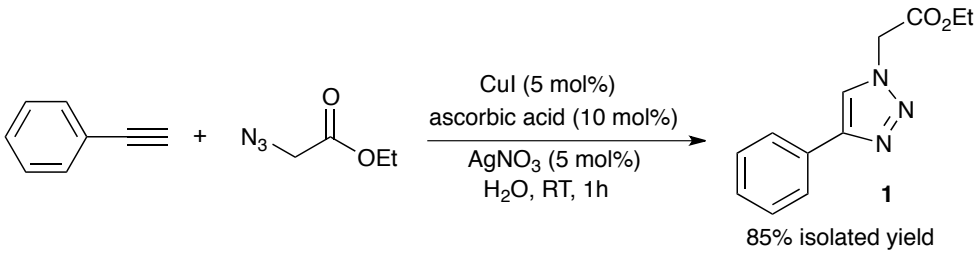
H_2O (1.0) mL was added to a 5 mL reaction tube followed by phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL). Copper(I) iodide (10 mg, 0.05 mmol) was then added to the mixture as solid. Ascorbic acid was then added as a solid (18 mg, 0.10 mmol). The reaction was then stoppered and stirred at room temperature for 24 hours. After this time, the product was isolated by filtration and dried under vacuum to provide the triazole product (20 mg, 8% yield). Spectroscopic data was identical to the triazole isolated in previous experiments.

Procedure to determine conversion to triazole **1** by ^{1}H NMR:

H_2O (1.0) mL was added to a 5 mL reaction tube followed by phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL). Copper(I) iodide (10 mg, 0.05 mmol) was then added to the mixture as solid. Ascorbic acid was then added as a solid (18 mg, 0.10 mmol). The reaction was then stoppered and stirred at room temperature for 24 hours. After this time, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove as much ethanol as possible. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^{1}H NMR that revealed 9% conversion to triazole **1**, consistent with the isolated yield reported in the previous experiment. The ^{1}H NMR spectrum is shown on the following page.



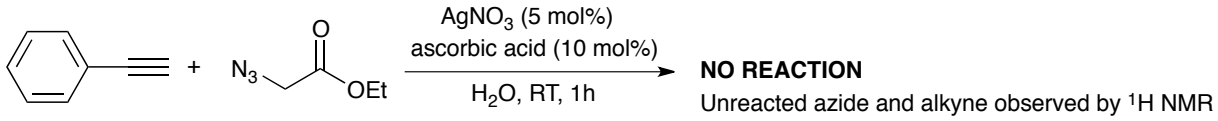
$AgNO_3$ activation of CuI in the synthesis of triazole 1



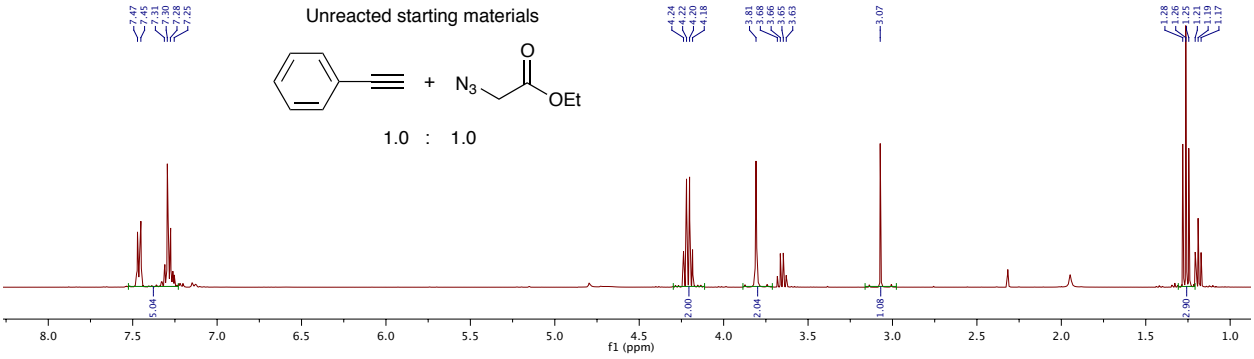
85% isolated yield

H_2O (1.0) mL was added to a 5 mL reaction tube followed by phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL). Copper(I) iodide (10 mg, 0.05 mmol) was then added to the mixture as solid followed by ascorbic acid (18 mg, 0.10 mmol). Lastly, $AgNO_3$ (9 mg, 0.05 mmol) was added and the reaction was stirred, open to air, at room temperature. The reaction gradually turned yellow over the course of the reaction and product was observed to precipitate from the reaction mixture after 1 hour. After this time, the product was isolated by filtration. The crude triazole was then suspended in 2.0 mL NH_4OH (25%) and stirred vigorously for 1 hour to remove any metals coordinated to the product. The triazole was then isolated by filtration, dried under vacuum to provide the titled compound (197 mg, 85% yield). Spectroscopic data was identical to that reported for triazole **1**.

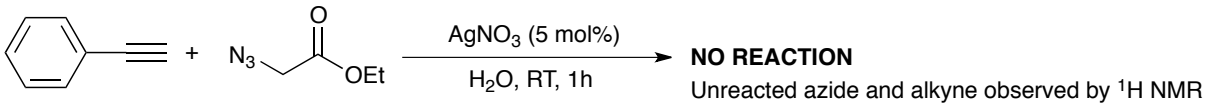
Negative control: $AgNO_3$ in the presence of ascorbic acid does not catalyse the azide-alkyne cycloaddition between phenylacetylene and ethyl azidoacetate:



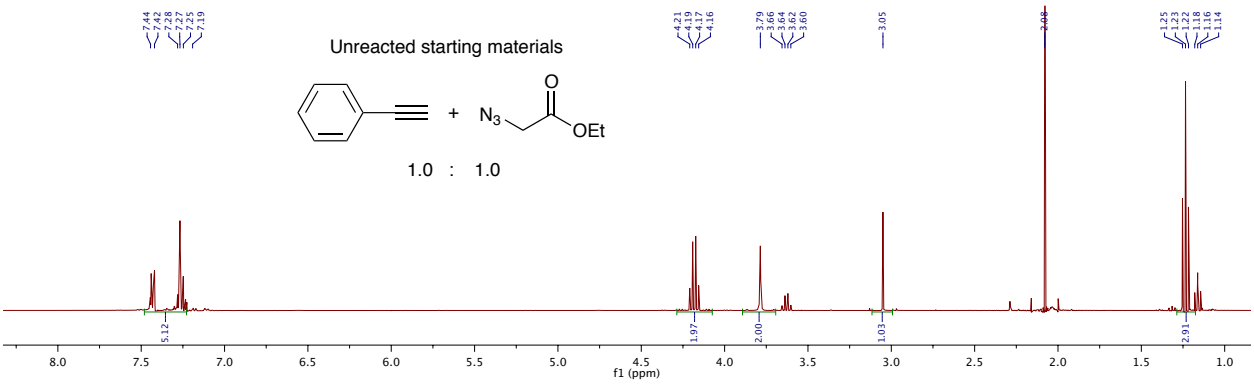
H_2O (1.0) mL was added to a 5 mL reaction tube followed by phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL). Next, ascorbic acid (18 mg, 0.10 mmol) was added to the stirred mixture followed by $AgNO_3$ (9 mg, 0.05 mmol). After 1 hour of stirring at room temperature, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove as much ethanol as possible. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. Only unreacted azide, unreacted alkyne, and ethanol were observed. No triazole was detected.



Negative control: $AgNO_3$ does not catalyse the azide-alkyne cycloaddition between phenylacetylene and ethyl azidoacetate:

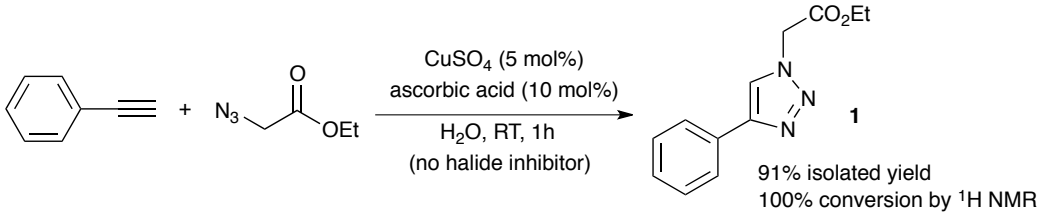


H_2O (1.0) mL was added to a 5 mL reaction tube followed by phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL). Next, $AgNO_3$ (9 mg, 0.05 mmol) was added to the stirred mixture. After 1 hour of stirring at room temperature, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove as much ethanol as possible. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. Only unreacted azide, unreacted alkyne, and ethanol were observed. No triazole was detected.



NMR study of sodium halides as inhibitors in the copper-catalysed synthesis of triazole 1

Positive control: no halides

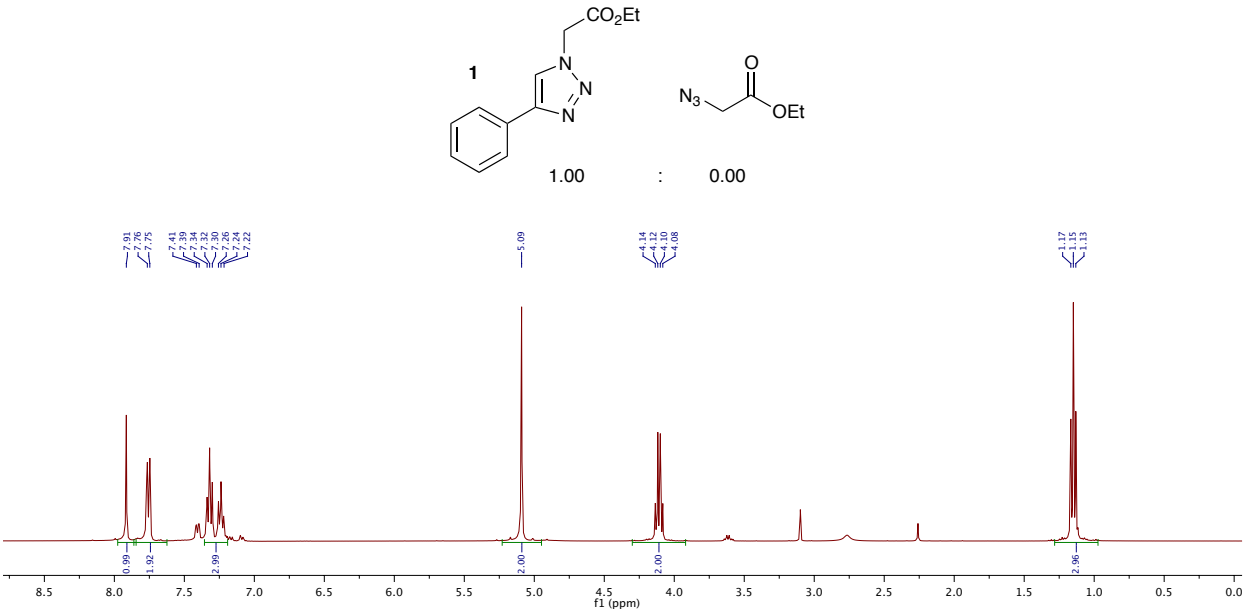


Method for determining isolated yield:

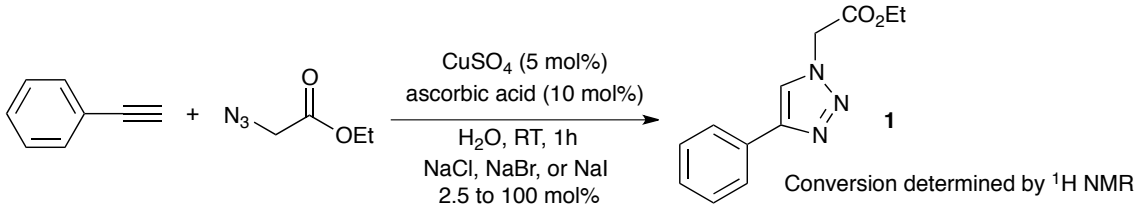
H_2O (1.0) mL was added to a 5 mL reaction tube followed by phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL). Copper(II) sulfate pentahydrate (13 mg, 0.05 mmol) was then added to the mixture as solid. Lastly, ascorbic acid was then added as a solid (18 mg, 0.10 mmol). The reaction mixture was stirred at room temperature, open to air, for 1 hour. After this time, the triazole product precipitated from the reaction mixture and was isolated by filtration. The crude triazole was then suspended in 2.0 mL NH_4OH (25%) and stirred vigorously for 1 hour to remove any metals coordinated to the product. The triazole was then isolated by filtration, dried under vacuum to provide the titled compound (210 mg, 91% yield). Spectroscopic data was identical to that reported above.

Method for determining reaction conversion by ^{1}H NMR analysis:

H_2O (1.0) mL was added to a 5 mL reaction tube followed by phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL). Copper(II) sulfate pentahydrate (13 mg, 0.05 mmol) was then added to the mixture as solid. Lastly, ascorbic acid was then added as a solid (18 mg, 0.10 mmol). The reaction mixture was stirred at room temperature, open to air, for 1 hour. After this time, the triazole product precipitated from the reaction mixture. $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove as much ethanol as possible. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^{1}H NMR. Full conversion to triazole **1** was observed and no ethyl azidoacetate was detected. The ^{1}H NMR spectrum is shown on the following page.



Halides as inhibitors in the copper-catalysed synthesis of triazole 1

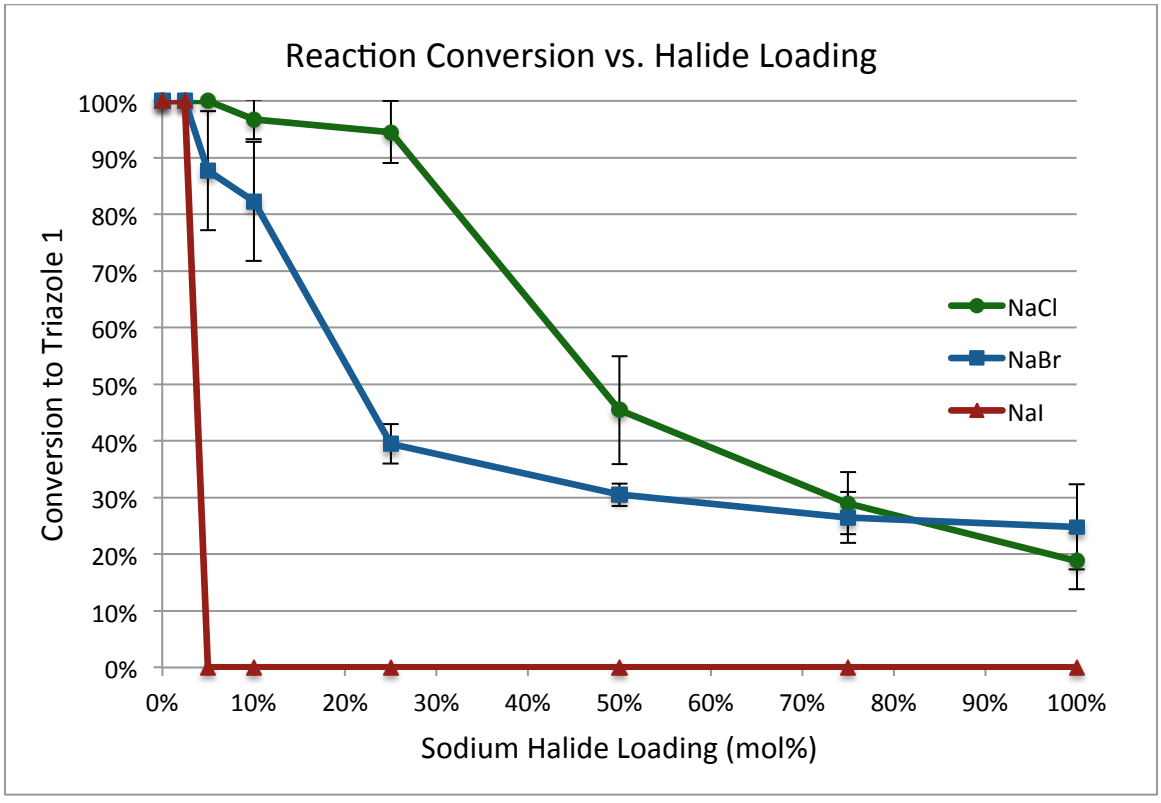


General procedure: Ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL) and phenylacetylene (0.11 mL, 1.0 mmol) were added to a 5 mL reaction tube equipped with a stir bar. Copper(II) sulfate pentahydrate (13 mg, 0.050 mmol) was then added as a solid to the stirred mixture. Next, a solution of sodium halide (NaI, NaBr, or NaCl) was added in a total volume of 1.0 mL of water. The amount of sodium halide was varied from 2.5 mol% to 100 mol% in separate experiments. Finally, ascorbic acid (18 mg, 0.010 mmol) was added and the resulting reaction was stirred vigorously, open to air, for 1 hour at room temperature. After this time, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove as much ethanol as possible. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. Conversions were calculated from the

relative integration of the $C\underline{H}_2CO_2Et$ in any unreacted ethyl azidoacetate (δ ~ 3.8 ppm) and the triazole product (δ ~ 5.2) in $CDCl_3$. Each reaction was run in triplicate at minimum. Average conversions are tabulated in Table S2. The plot below Table S2 contains error bars at ± 1 standard deviation from the mean reaction conversion. Representative ^1H NMR spectra are shown on pages S14-S16.

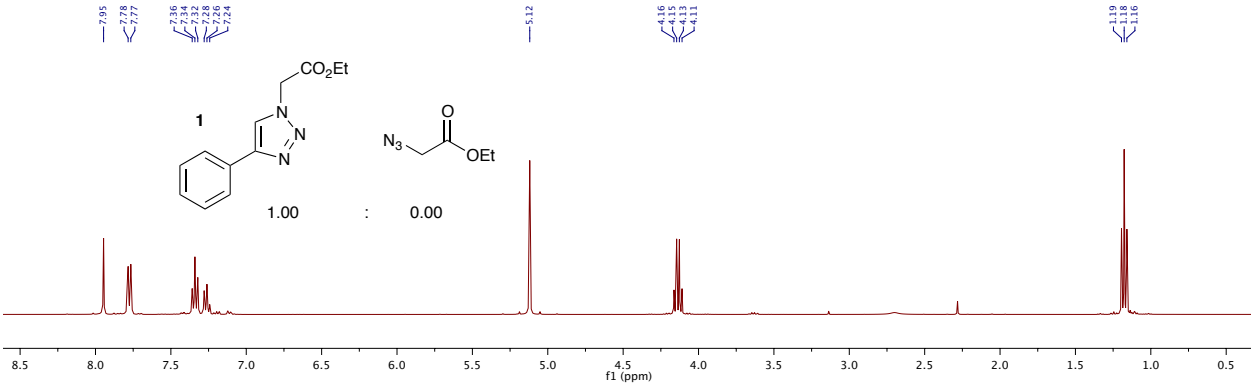
Table S2:

Inhibitor Loading	Average Conversion to Triazole 1		
(NaX mol%)	NaCl	NaBr	NaI
0%	100%	100%	100%
2.50%	100%	100%	100%
5%	100%	88%	0%
10%	97%	82%	0%
25%	95%	40%	0%
50%	45%	31%	0%
75%	29%	27%	0%
100%	19%	25%	0%

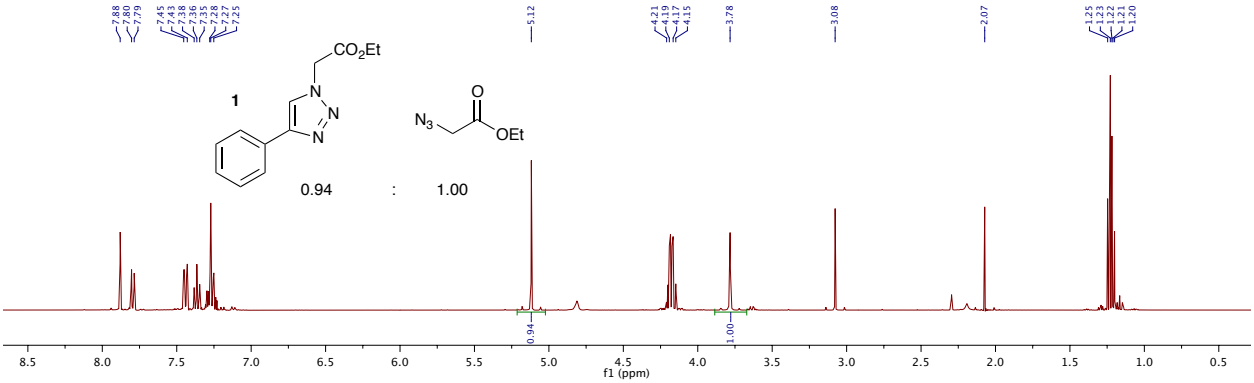


Representative ^{1}H NMR Spectra from Table S2: NaCl as an inhibitor

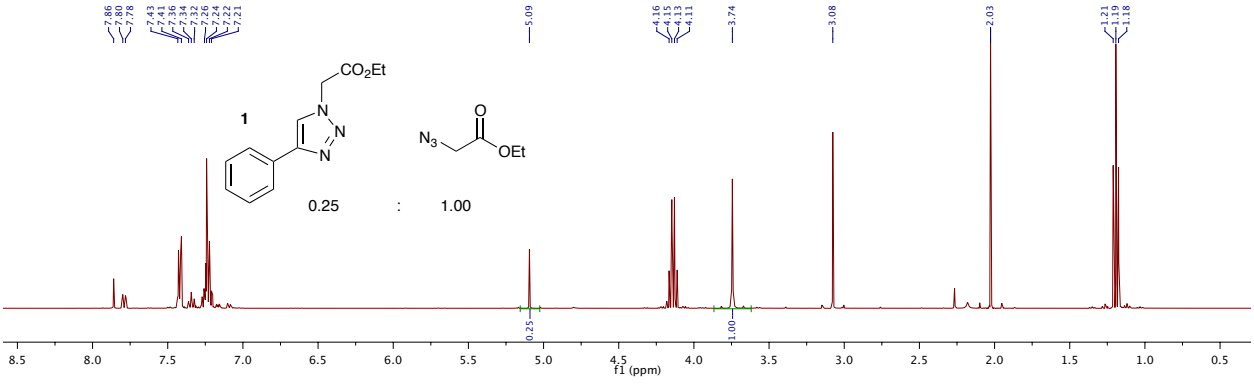
10 mol% NaCl; 100% Conversion to triazole **1**



50 mol% NaCl; 48% Conversion to triazole **1**

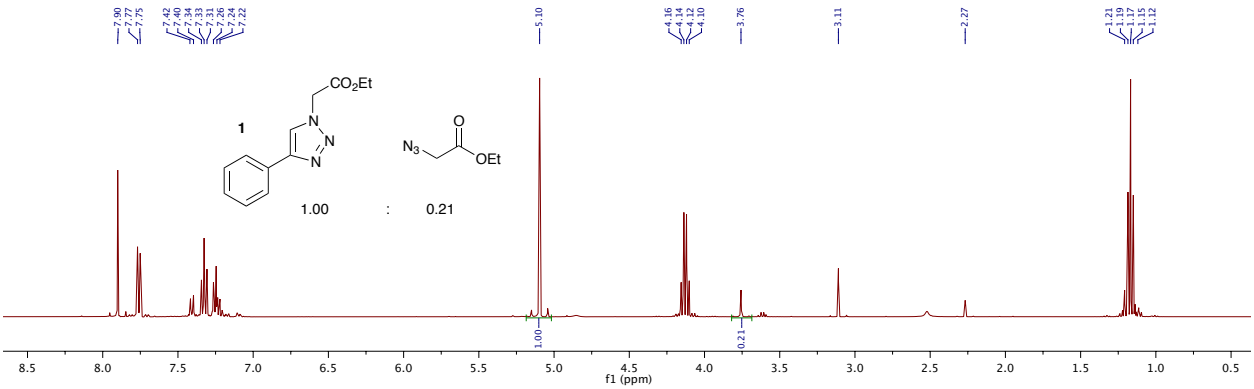


100 mol% NaCl; 20% Conversion to triazole **1**

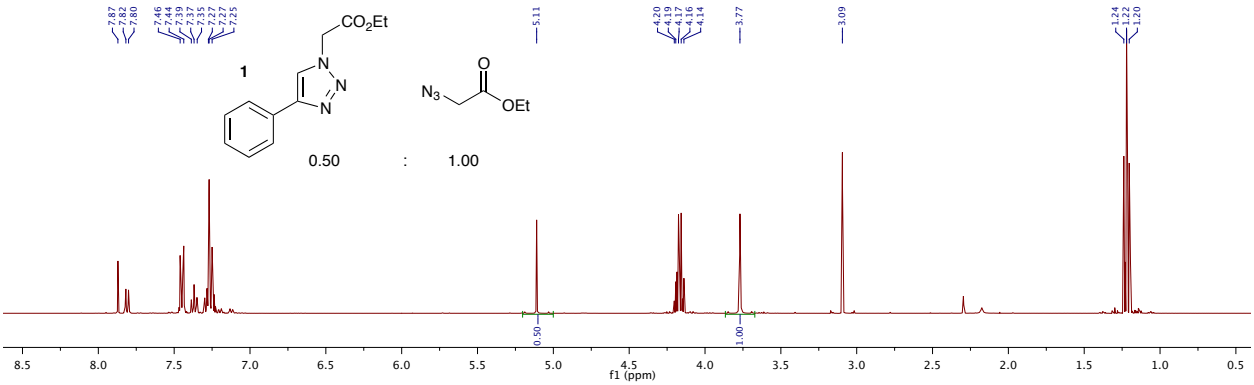


Representative ^{1}H NMR Spectra from Table S2: NaBr as an inhibitor

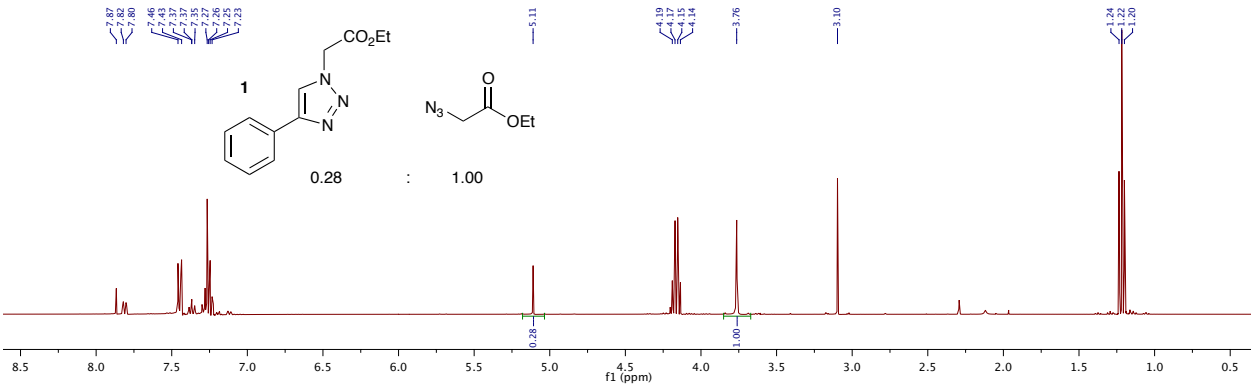
10 mol% NaBr; 83% Conversion to triazole **1**



50 mol% NaBr; 33% Conversion to triazole **1**

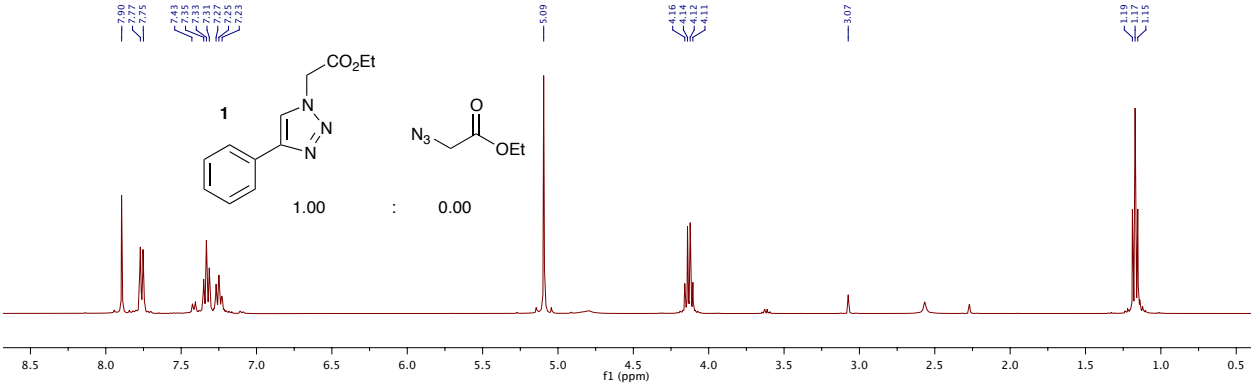


100 mol% NaBr; 22% Conversion to triazole **1**

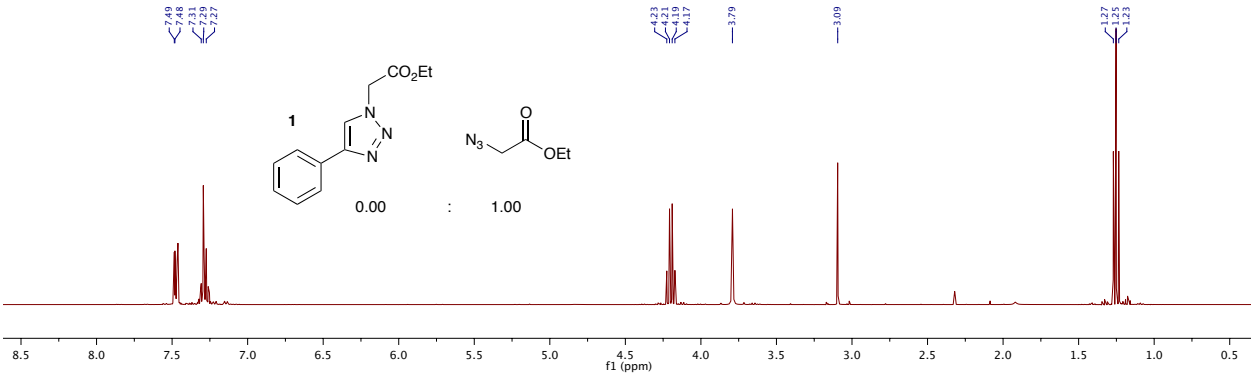


Representative ^{1}H NMR Spectra from Table S2: NaI as an inhibitor

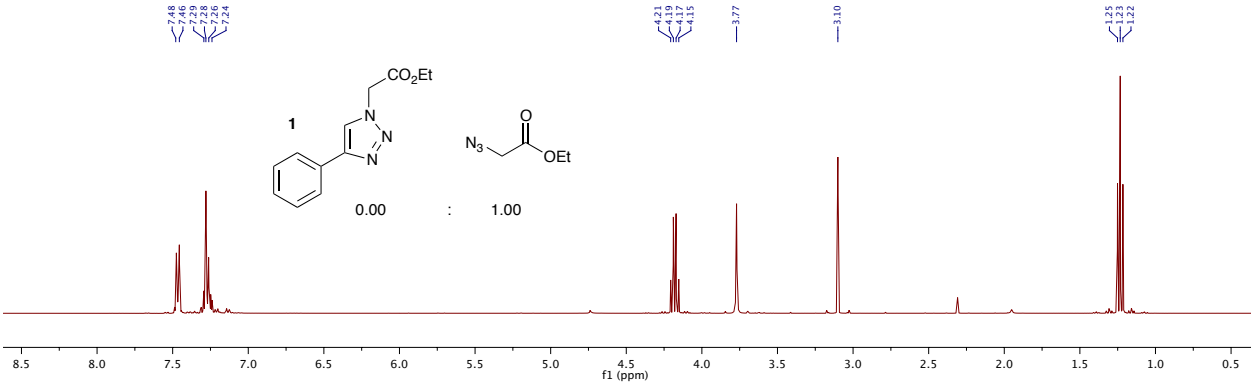
2.5 mol% NaI, 100% Conversion to triazole **1**



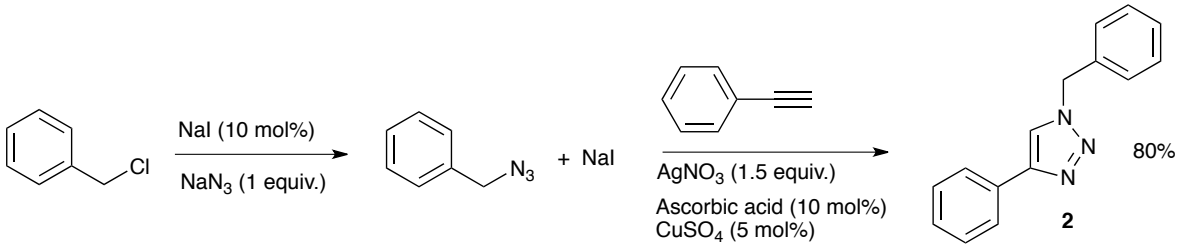
5 mol% NaI, 0% Conversion to triazole **1**



50 mol% NaI, 0% Conversion to triazole **1**



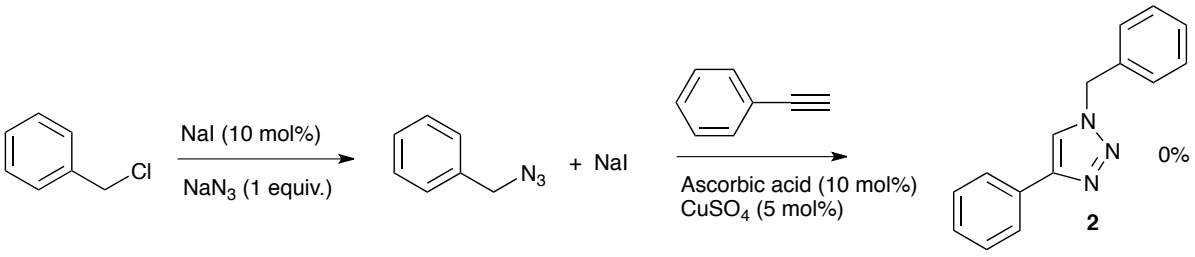
One-pot S_N2-CuACC using $AgNO_3$ halide trap in the synthesis of triazole 2



Deionized water (0.9 mL) and ethanol (1.0 mL) was added to a 5 mL reaction tube followed by benzyl chloride (0.23 mL, 1.65 mmol). Next, 0.10 mL of a 1M aqueous solution of NaI was added to the stirred mixture (0.1 mmol NaI). Sodium azide (65 mg, 1.0 mmol) was added as a solid to the reaction mixture. The reaction was then capped and stirred at room temperature for 24 hours. After this time silver nitrate (255 mg, 1.50 mmol) was added to the mixture and stirred for 30 minutes to sequester halides. Next, copper(II) sulfate pentahydrate (13 mg, 0.05 mmol) was added followed by phenyl acetylene (0.11 mL, 1.0 mmol) and ascorbic acid (18 mg, 0.10 mmol). The reaction mixture was then stirred, open to air, at room temperature for 3 hours. After this time, the mixture was transferred to a separatory funnel and diluted with EtOAc (100 mL) and water (100 mL). The organic layer was then isolated and washed with additional water (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was then purified by column chromatography (30% EtOAc in petrol) to provide the triazole **2** as a white solid (188 mg, 80% yield). Characterization data was consistent with previous reports.[1] m.p. 121-123 ºC. IR (KBr): 3121, 3095, 3063, 3030, 2922, 1496, 1466, 1454, 1442, 1356, 1224, 1205, 1075, 1049, 766, 729, 693. ^{1}H NMR (400 MHz, DMSO-d6): 5.65 (2H, s, C$\underline{H}_2$Ph), 7.30-7.40 (5H, m, CH_{Ph}), 7.43 (2H, t, J = 7.6, CH_{Ph}), 7.86 (2H, dd, J = 8.2, 1.1, CH_{Ph}), 8.65 (1H, s, $CH_{Triazole}$). ^{13}C NMR (100 MHz, DMSO-d6): 53.5 ($\underline{C}H_2$Ph), 122.0 ($CH_{Triazole}$), 125.60 (CH_{Ph}), 128.3 (2 x CH_{Ph}), 128.6 (CH_{Ph}), 129.2 (CH_{Ph}), 129.3 (CH_{Ph}), 131.1($4^o{}_{Ar}$), 136.4 ($4^o{}_{Ar}$), 147.1 ($4^o{}_{Ar}$). HRMS (m/z, ESI$^+$): Found 236.1184 $[M+H]^+$; $C_{15}H_{14}N_3$ requires 236.1182.

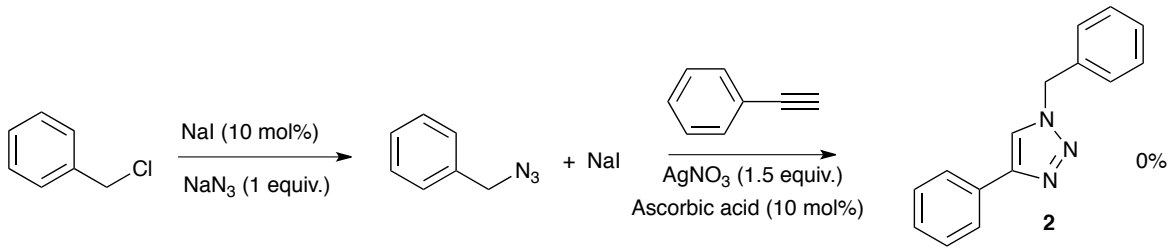
^{1}H, ^{13}C, and HSQC NMR spectra for triazole **2** are found on pages S23-S25.

One-pot S_N2-CuACC negative control reaction with no $AgNO_3$



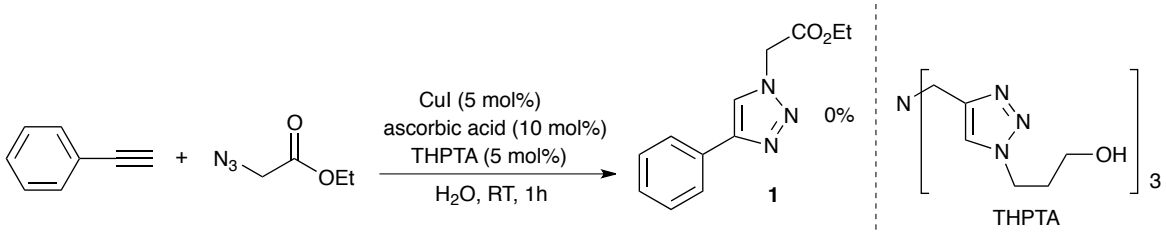
Deionized water (0.9 mL) and ethanol (1.0 mL) was added to a 5 mL reaction tube followed by benzyl chloride (0.23 mL, 1.65 mmol). Next, 0.10 mL of a 1M aqueous solution of NaI was added to the stirred mixture (0.1 mmol NaI). Sodium azide (65 mg, 1.0 mmol) was added as a solid to the reaction mixture. The reaction was then capped and stirred at room temperature for 24 hours. After this time, copper(II) sulfate pentahydrate (13 mg, 0.05 mmol) was added followed by phenyl acetylene (0.11 mL, 1.0 mmol) and ascorbic acid (18 mg, 0.10 mmol). The reaction mixture was then stirred, open to air, at room temperature for 3 hours. After this time, the mixture was transferred to a separatory funnel and diluted with EtOAc (100 mL) and water (100 mL). The organic layer was then isolated and washed with additional water (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was subject to column chromatography (30% EtOAc in petrol) as in the previous experiment, but no triazole was detected or isolated off of the column.

One-pot S_N2-CuACC negative control reaction using $AgNO_3$ but no copper



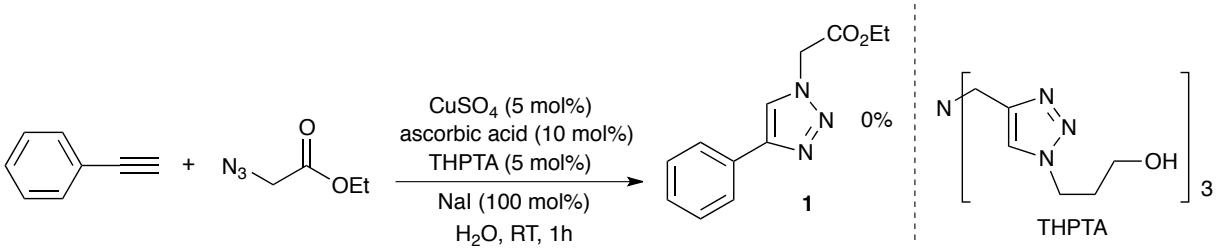
Deionized water (0.9 mL) and ethanol (1.0 mL) was added to a 5 mL reaction tube followed by benzyl chloride (0.23 mL, 1.65 mmol). Next, 0.10 mL of a 1M aqueous solution of NaI was added to the stirred mixture (0.1 mmol NaI). Sodium azide (65 mg, 1.0 mmol) was added as a solid to the reaction mixture. The reaction was then capped and stirred at room temperature for 24 hours. After this time silver nitrate (255 mg, 1.50 mmol) was added to the mixture and stirred for 30 minutes to sequester halides. After this time, phenyl acetylene (0.11 mL, 1.0 mmol) and ascorbic acid (18 mg, 0.10 mmol) were added. The reaction mixture was then stirred, open to air, at room temperature for 3 hours. After this time, the mixture was transferred to a separatory funnel and diluted with EtOAc (100 mL) and water (100 mL). The organic layer was then isolated and washed with additional water (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was subject to column chromatography (30% EtOAc in petrol) as in the previous two experiments, but no triazole was detected or isolated off of the column.

Assessment of CuI activity using the THPTA ligand in the synthesis of triazole 1



H_2O (1.0) mL was added to a 5 mL reaction tube followed by THPTA ligand (22 mg, 0.05 mmol) and CuI (10 mg, 0.05 mmol). This mixture was stirred for 10 minutes at room temperature. After this equilibration, phenylacetylene (0.11 mL, 1.0 mmol) and ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL) were added to the reaction mixture followed by ascorbic acid (18 mg, 0.10 mmol). The resulting mixture was stirred for an additional hour at room temperature. After this time, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove ethanol. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. Triazole **1** was not detected, and only unreacted azide and alkyne were recovered in the extraction.

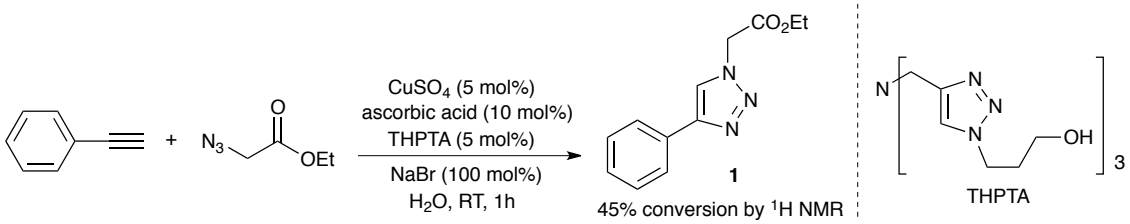
Assessment of THPTA in overcoming sodium iodide inhibition in the CuAAC



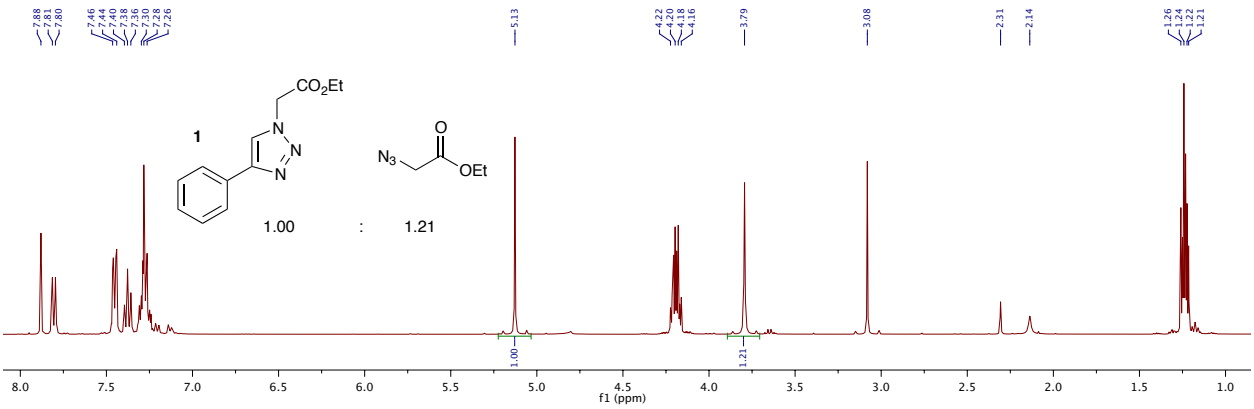
Ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL) was added to a 5 mL reaction tube followed by phenyl acetylene (0.11 mL, 1.0 mmol). Next, copper(II) sulfate pentahydrate (13 mg, 0.05 mmol) was added to the stirred mixture followed by THPTA (22 mg, 0.05 mmol). The resulting mixture was stirred for 10 minutes at room temperature before a solution of sodium iodide (1.0 mL of a 1M aqueous solution, 1 mmol NaI) was added. Finally, ascorbic acid (18 mg, 0.10 mmol) was added and the reaction was stirred at room temperature for 1 hour. After this time, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted

azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove ethanol. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. Triazole **1** was not detected, and only unreacted azide and alkyne were recovered in the extraction.

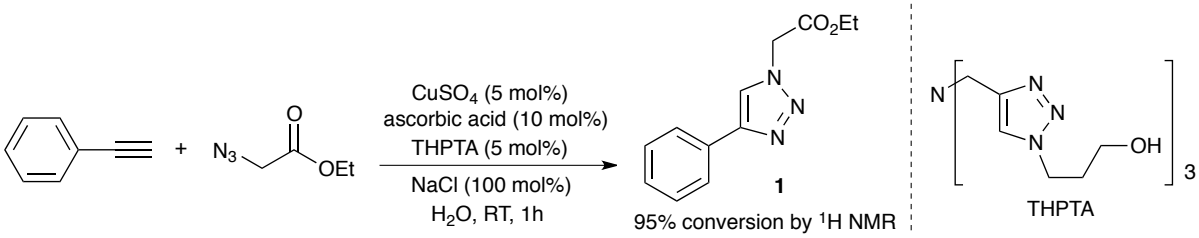
Assessment of THPTA in overcoming sodium bromide inhibition in the CuAAC



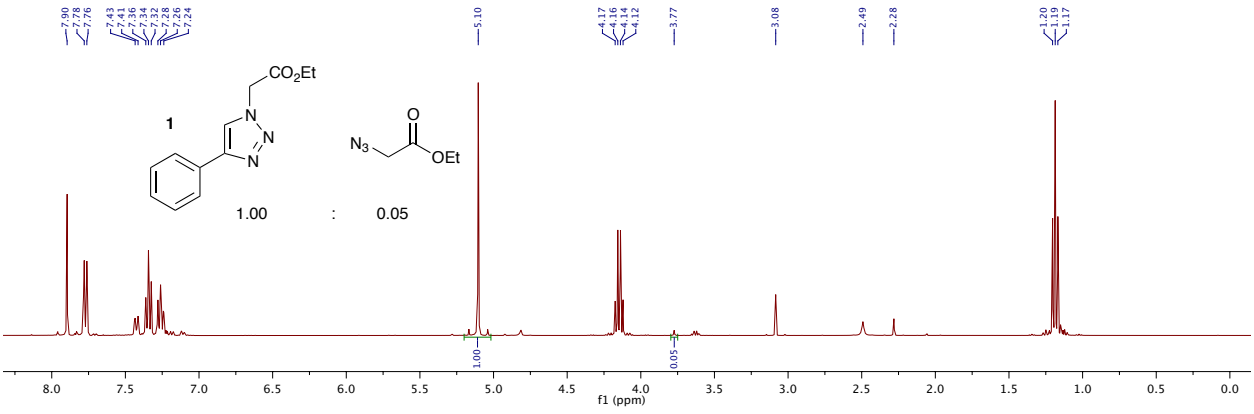
Ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL) was added to a 5 mL reaction tube followed by phenyl acetylene (0.11 mL, 1.0 mmol). Next, copper(II) sulfate pentahydrate (13 mg, 0.05 mmol) was added to the stirred mixture followed by THPTA (22 mg, 0.05 mmol). The resulting mixture was stirred for 10 minutes at room temperature before a solution of sodium bromide (1.0 mL of a 1M aqueous solution, 1 mmol NaBr) was added. Finally, ascorbic acid (18 mg, 0.10 mmol) was added and the reaction was stirred at room temperature for 1 hour. After this time, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove ethanol. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. The triazole was formed in 45% conversion.



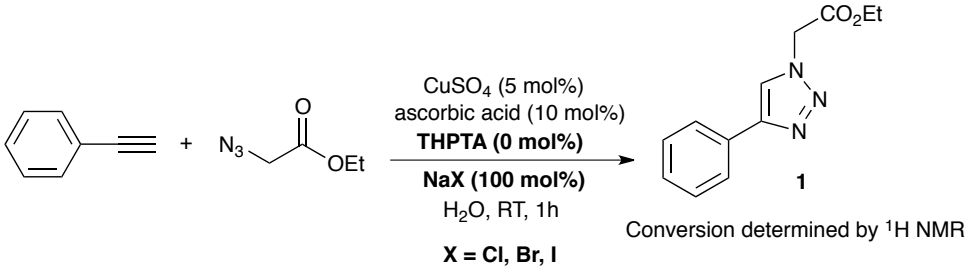
Assessment of THPTA in overcoming sodium chloride inhibition in the CuAAC



Ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL) was added to a 5 mL reaction tube followed by phenyl acetylene (0.11 mL, 1.0 mmol). Next, copper(II) sulfate pentahydrate (13 mg, 0.05 mmol) was added to the stirred mixture followed by THPTA (22 mg, 0.05 mmol). The resulting mixture was stirred for 10 minutes at room temperature before a solution of sodium chloride (1.0 mL of a 1M aqueous solution, 1 mmol NaCl) was added. Finally, ascorbic acid (18 mg, 0.10 mmol) was added and the reaction was stirred at room temperature for 1 hour. After this time, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove ethanol. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. The triazole was formed in 95% conversion.

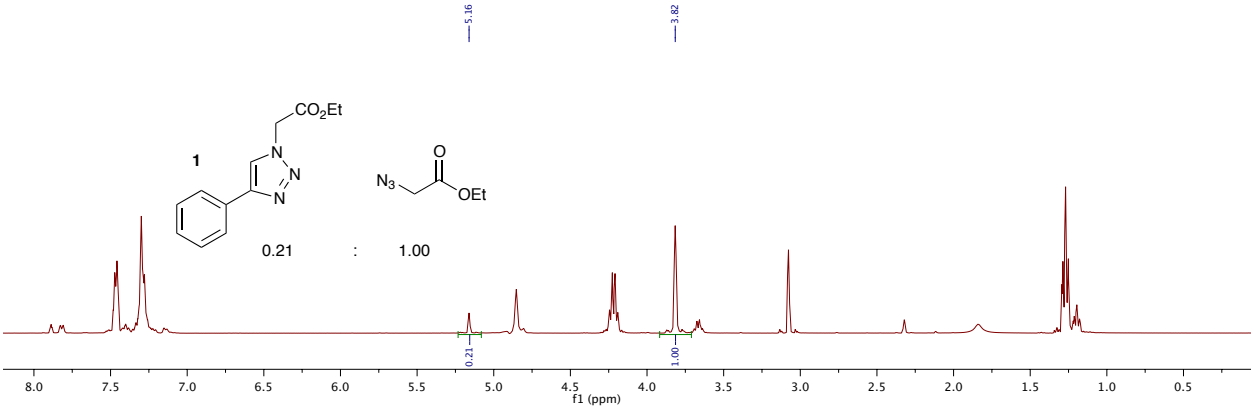


Control reactions without the THPTA ligand

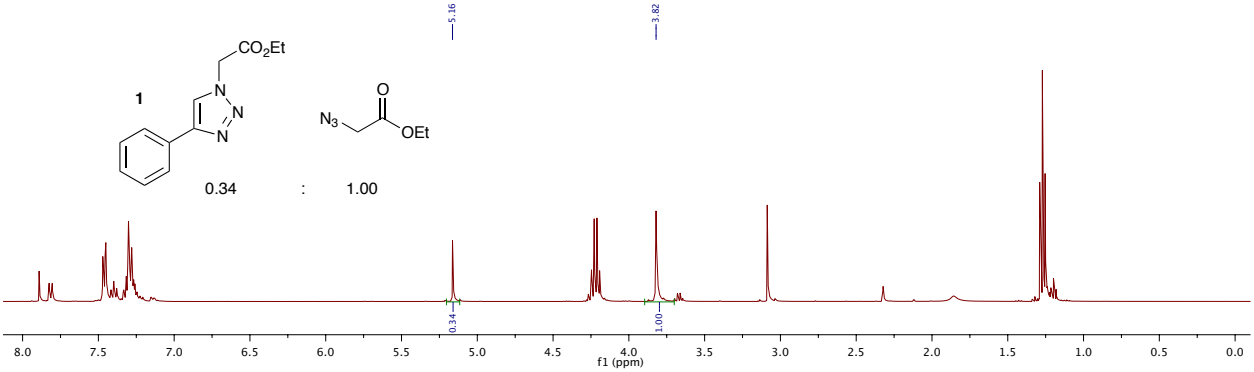


Ethyl azidoacetate (0.65 mL of a 25% solution in EtOH, 1.0 mmoL) was added to a 5 mL reaction tube followed by phenyl acetylene (0.11 mL, 1.0 mmol). Next, copper(II) sulfate pentahydrate (13 mg, 0.05 mmol) was added to the reaction vessel. The resulting mixture was stirred for 10 minutes at room temperature before a solution of sodium halide (1.0 mL of a 1M aqueous solution, 1 mmol of NaCl, NaBr, or NaI) was added. Finally, ascorbic acid (18 mg, 0.10 mmol) was added and the reaction was stirred at room temperature for 1 hour. After this time, $CDCl_3$ (0.7 mL) was added directly to the reaction and mixed by drawing repeatedly into a pipette in order to extract triazole and any unreacted azide and alkyne. Mixing was then stopped to allow the aqueous and organic layers to separate. The water layer was decanted by pipet and discarded. Deionized water (0.7 mL) was then added to the reaction vial and mixed in a similar fashion. The water layer was again decanted by pipet and discarded. The water wash was repeated two additional times to remove ethanol. After the final water layer was decanted, the $CDCl_3$ layer was analyzed directly by ^1H NMR. Reaction conversions and NMR spectra are listed on page S23.

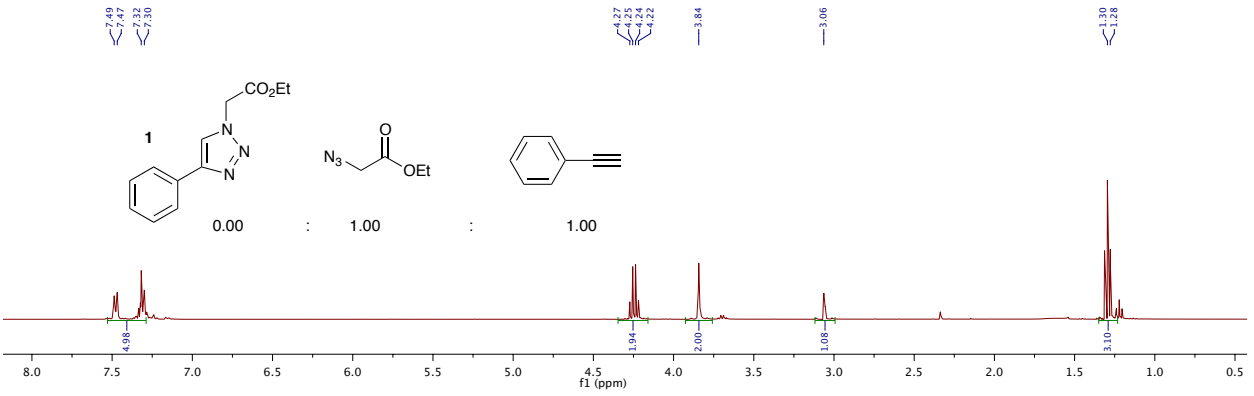
100 mol% NaCl: 17% conversion to triazole 1



100 mol% NaBr: 25% conversion to triazole 1



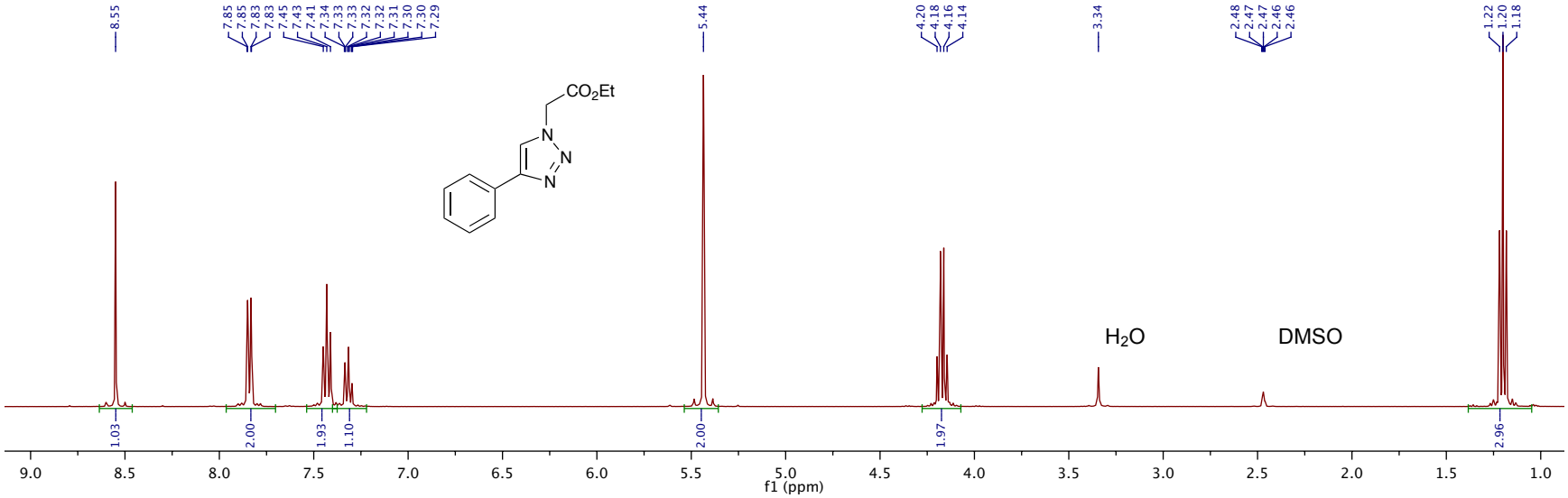
100 mol% NaI: 0% conversion to triazole 1



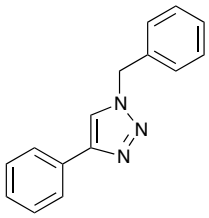
References:

1. L. S. Campbell-Verduyn, L. Mirfeizi, R. A. Dierckx, P. H. Elsinga and B. L. Feringa, *Chem. Commun.*, 2009, 2139-2141.

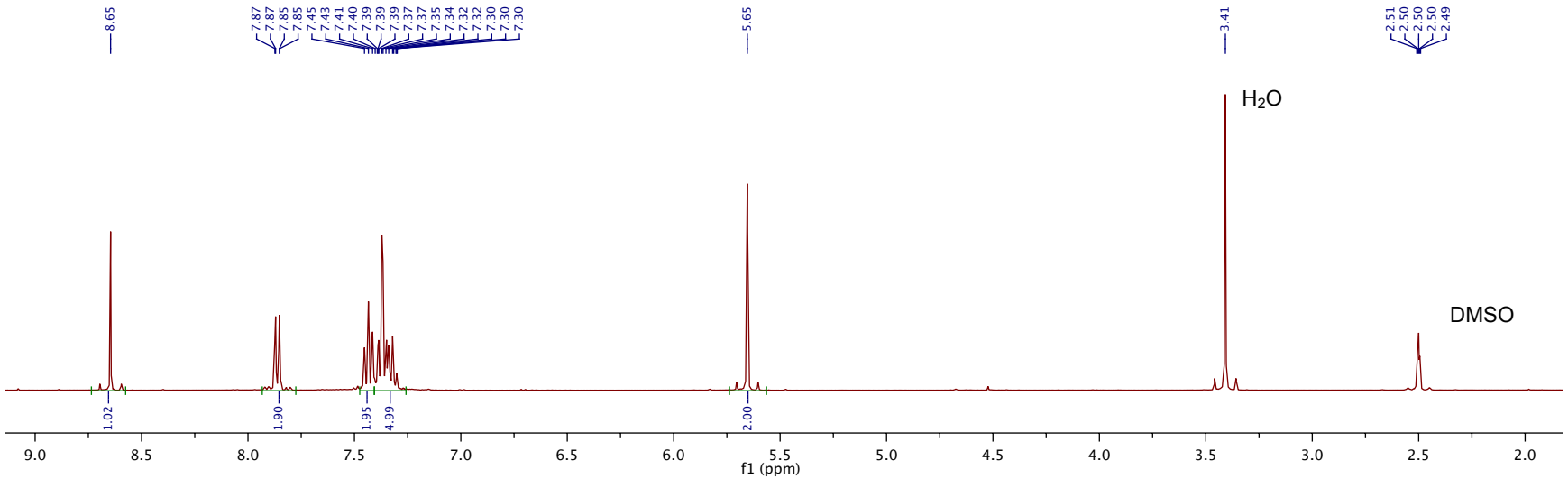
^{1}H NMR for triazole **1** (400 MHz, DMSO-d6)



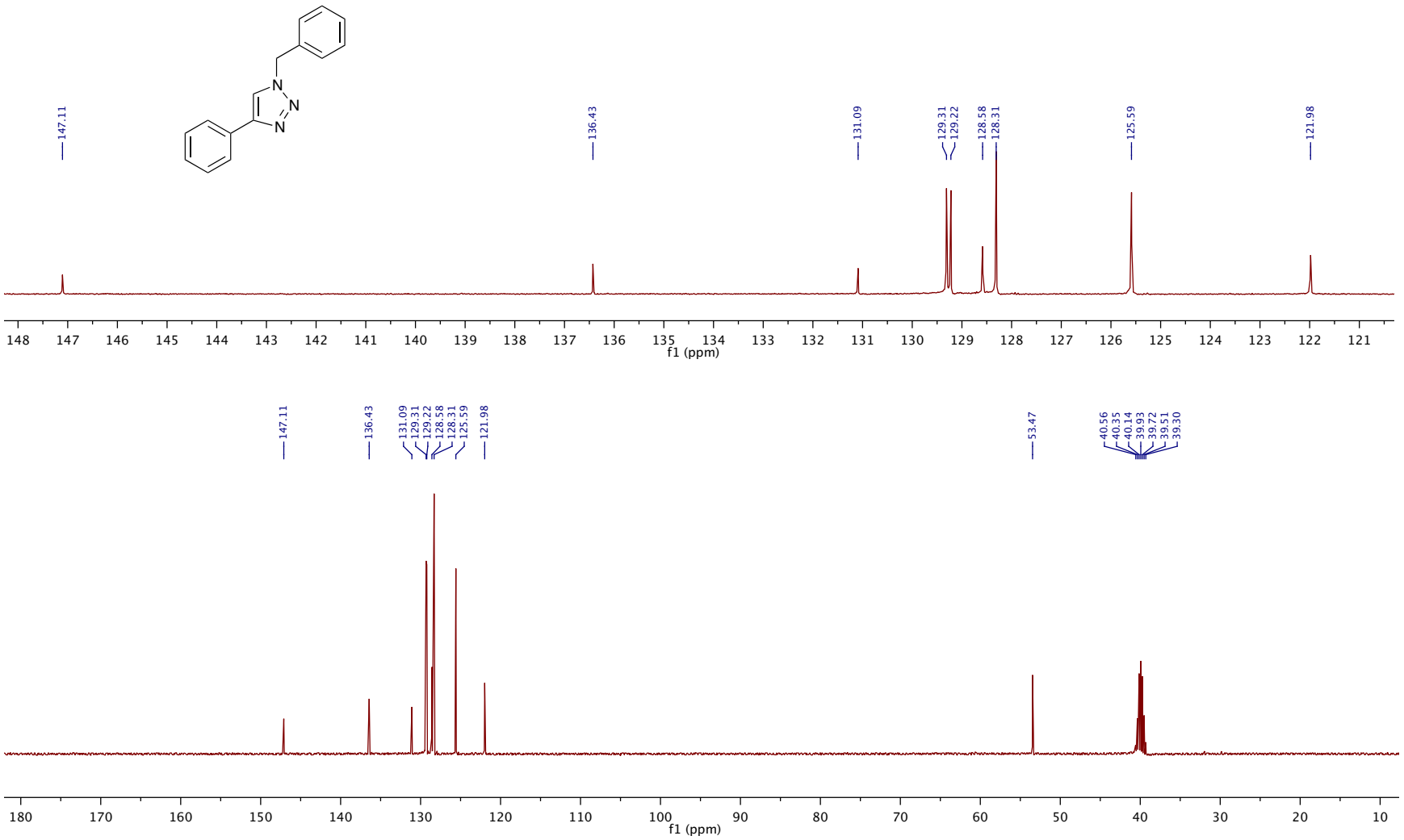
^{13}C NMR for triazole **1** (100 MHz, DMSO-d6)



^{1}H NMR for triazole **2** (400 MHz, DMSO-d6)



^{13}C NMR for triazole **2** (100 MHz, DMSO-d6)



HSQC NMR spectrum for triazole **2**