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Method for Assigning Structure of 1,2,3-Triazoles

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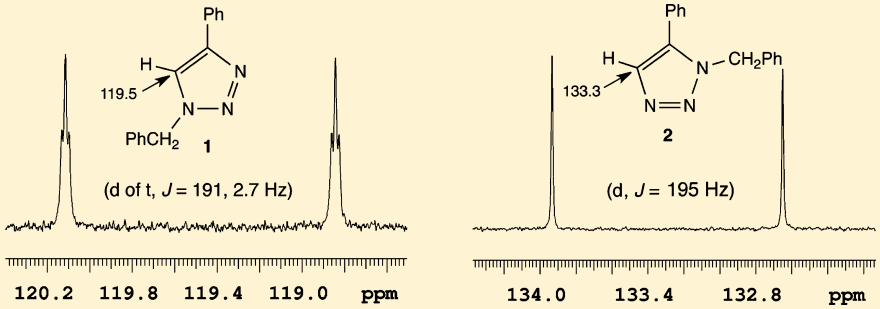
Supporting Information



ABSTRACT: 1,4-Disubstituted-1*H*-1,2,3-triazoles **1** can easily be distinguished from the isomeric 1,5-disubstituted-1*H*-1,2,3-triazoles **2** by simple one-dimensional ^{13}C NMR spectroscopy using gated decoupling. The C_5 signal of **1** appears at δ ~120 ppm, while the C_4 signal of **2** appears at δ ~133 ppm. Computational studies also predict the upfield shift of C_5 of **1** relative to C_4 in **2**.

Triazoles are a class of compounds of much recent interest. They are generally prepared by cycloaddition reactions of azides with alkynes. The original thermal cycloaddition reaction discovered by Huisgen[1] has been largely supplanted by copper-catalyzed reactions of azides with alkynes, which give 1,4-disubstituted-1*H*-1,2,3-triazoles of general structure **1**.[2,3] References to this copper-catalyzed reaction, since Sharpless first introduced the concept of the "Click Reaction" in 2001,[4] are too numerous to list. Hence, a few general reviews are given.[5] The regioisomeric 1,5-disubstituted-1*H*-1,2,3-triazoles **2** can often be prepared by a ruthenium-catalyzed reaction,[6] or by addition of acetylide anions to azides.[7] The structures of many of these triazoles were proven by X-ray crystallographic analysis[2,6] or by more sophisticated NMR methods including NOE,[2,3] HMQC, HSQC, and HMBC[8] studies. While structures of triazoles in the Sharpless/Fokin studies and in certain other studies have been rigorously demonstrated, in many subsequent studies in the literature, the structures of triazoles are not "proven" but are simply assigned using the assumption that Cu catalysis gives isomers of type **1**, while Ru catalysis gives type **2** isomers. While these assumptions are most likely correct, a simple method for verification of structure is desirable.

X-ray, NOE, and multidimensional NMR techniques are powerful methods for structure elucidation. However, they are not always routine, rapid, simple, or inexpensive techniques. As part of another investigation, we have generated a number of isomeric triazoles for mechanistic studies. We therefore wanted a simple protocol for rapidly distinguishing between the isomeric triazoles **1** and **2**. We now report that structures can be easily assigned from simple 1-dimensional ^{13}C NMR data.

Figure 1 shows an expanded region of the ^{13}C NMR spectrum of triazole **1a** prepared by a Cu catalyzed reaction. Spectrum A is the standard proton decoupled spectrum, while spectrum B uses the relatively old and simple gated decoupling sequence (decoupler off during acquisition), where coupling to neighboring hydrogens is observed. Identification of the C_5 carbon signal of **1a** is straightforward due to the relatively large C−H coupling constant of 191 Hz. The corresponding C−H coupling constants for aromatic carbons are much smaller (~155 Hz). The doublet of triplets (J = 191, 2.7 Hz) at δ 119.5 is due to the C_5 carbon coupled to the directly bonded hydrogen and 3-bond coupled to the two benzylic hydrogens.

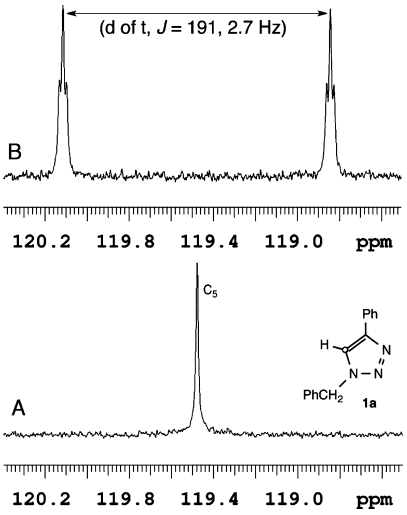


Figure 1. (A) Expanded ^{13}C NMR of **1a**. (B) ^{1}H coupled ^{13}C NMR of **1a**.

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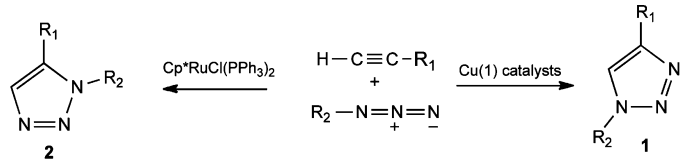


This rapid "low tech" experiment gives the same coupling information as the more tedious HMQC and HMBC methods. It also gives precise values of coupling constants, which are used to readily assign the C_5 signal. The single frequency decoupled spectrum (not shown), where the benzylic hydrogens at δ = 5.57 ppm in the ^{1}H NMR spectrum are irradiated, confirms that the triplet is due to long-range coupling to the benzylic hydrogens. This verifies that the carbon signal at δ 119.5 is indeed due to the C_5 carbon of **1a**.

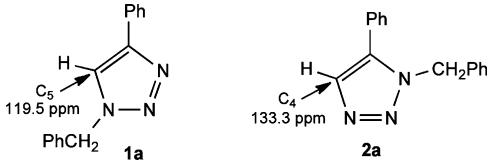


Figure 2 shows an expanded region of the ^{13}C NMR spectrum of the isomeric triazole **2a**. The signal at δ = 133.3

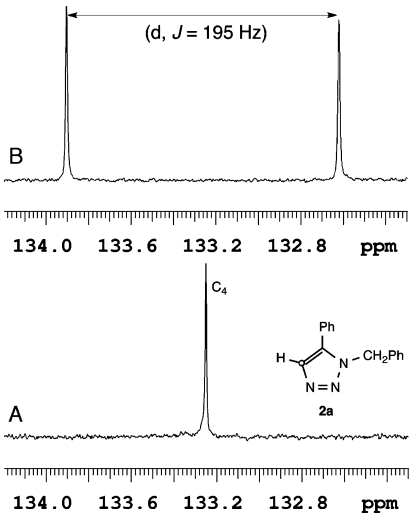


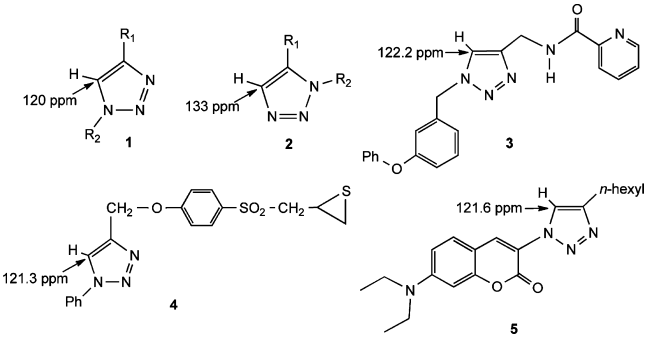
Figure 2. (A) Expanded ^{13}C NMR of **2a**. (B) ^{1}H coupled ^{13}C NMR of **2a**.

ppm is due to the C_4 carbon, and this is confirmed by the gated decoupling experiment that shows a doublet (J = 195 Hz) due to the directly attached hydrogen. The 4-bond coupling to the benzylic hydrogens is not observed. These ^{13}C spectra are easy to acquire and may be obtained in less that one hour using routine techniques.

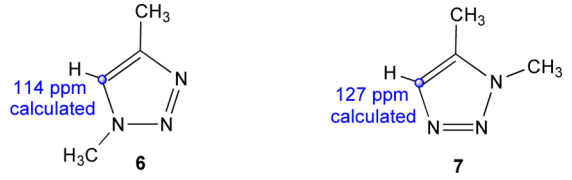
We have now prepared and analyzed the 19 pairs of triazoles in Table 1 by these simple ^{13}C NMR methods. In all of these triazoles, the C_5 carbon of **1** is always further upfield than the C_4 carbon of **2**. The average chemical shift of C_5 for triazoles **1a**–**1o** is δ = 120 ± 3 ppm, while the shift of C_4 is δ = 133 ± 3 ppm for **2a**–**2o**. The previously reported triazoles **3**,[9] **4**,[10] and **5**[11] (whose structures were based solely on the copper-catalyzed synthetic method) have also been analyzed, and the C_5 shifts also fall within the δ = 120 ± 3 ppm range.

Table 1. ^{13}C Shifts of C_5 of Triazole 1 and C_4 of Triazole 2

substrates	R_1	R_2	C_5 of **1** (ppm)	C_4 of **2** (ppm)
1a/2a	Ph	$PhCH_2$	119.5	133.3
1b/2b	Ph	*n*-hexyl	119.2	133.0
1c/2c	*n*-Bu	$PhCH_2$	120.4	132.5
1d/2d	*n*-Bu	*n*-hexyl	120.3	131.9
1e/2e	CH_2OAc	$PhCH_2$	123.6	135.3
1f/2f	$C(OH)Me_2$	$PhCH_2$	119.0	130.9
1g/2g	Ph	Ph	117.6	133.4
1h/2h	*n*-Bu	Ph	118.8	132.3
1i/2i	$C(OH)Ph_2$	*n*-hexyl	122.3	134.8
1j/2j	CH_2OPh	$PhCH_2$	122.6	134.6
1k/2k	Ph	$PhCOCH_2$	121.5	132.9
1l/2l	Ph	cyclohexyl	117.3	132.6
1m/2m	*n*-Bu	cinnamyl	120.3	132.4
1n/2n	$CH(OEt)_2$	$PhCH_2$	121.8	134.9
1o/2o	CH_2OH	$PhCH_2$	121.6	136.3
1p/2p	CHO	$PhCH_2$	125.1	141.2
1q/2q	CO_2Et	$PhCH_2$	127.3	138.2
1r/2r	$COCH_3$	$PhCH_2$	125.2	138.6
1s/2s	OEt	$PhCH_2$	105.9	113.8



Computational Studies. While ^{13}C chemical shifts of the C_5 and C_4 carbons of **1** and **2** appear to be a reliable empirical method of assigning structure, we sought a theoretical basis for these shifts. GIAO calculated shifts[12] (B3LYP/6-31G* level) of C_5 and C_4 for compounds **6** and **7** are δ = 114 and 127 ppm, respectively. These calculated values are about 6 ppm upfield from the experimental values for **1** and **2**. However, there is still a large difference (13 ppm) between C_5 of **6** and C_4 of **7**. This calculated difference is completely consistent with the experimental findings.



Why is the C_5 carbon in isomer **1** further upfield than C_4 in isomer **2**? A valence bond approach can rationalize this observation. While there are a number of resonance contributors in **1**, consider the important form **1y** (which

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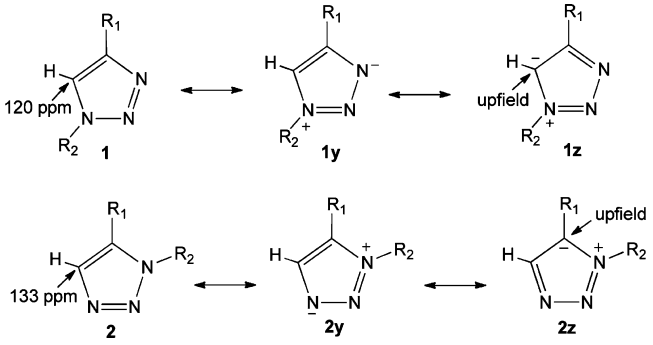
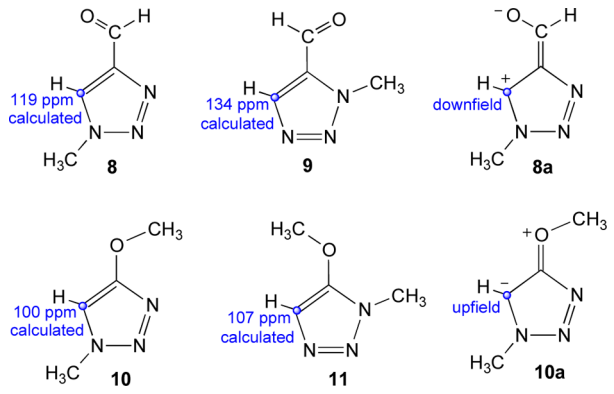
places formal negative charge on the more electronegative nitrogen N_3) and form **1z**. The upfield position of the C_5 carbon in **1** can be attributed to resonance donation from the N_1 nitrogen, which places formal negative charge on N_3 and consequently on C_5 carbon. Analogous resonance donation from N_1 in isomer **2** does not place formal negative charge on C_4. Instead, the quarternary C_5 of isomer **2** is predicted to be shifted upfield (form **2z**). This is indeed the case experimentally, where C_5 of isomers **2** are all upfield relative to the analogous quaternary carbons C_4 in isomers **1**.

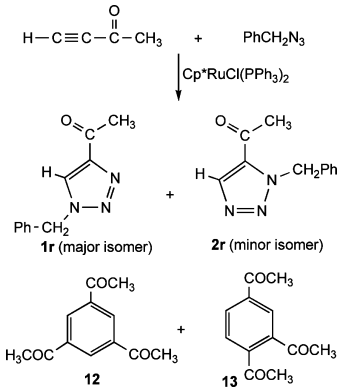


Exceptions. Carbonyl containing substrates **1p**−**1r** give C_5 shifts that are about 6 ppm downfield from the δ = 120 ± 3 ppm range. The isomeric substrates **2p**−**2r** follow a similar trend, and shifts are also about 6 ppm downfield from the δ = 133 ± 3 ppm range. Computational predictions agree with these experimental findings and B3LYP/6-31G* GIAO calculated shifts in aldehydes **8** and **9** are 5 and 7 ppm downfield, respectively, from calculated shifts in **6** and **7**. Standard carbonyl group resonance effects, as in **8a**, account for the further downfield shifts of C_5 in carbonyl containing substrates **1p**−**1r**, as well as the further downfield shifts of C_4 in **2p**−**2r**.



Other triazoles, where chemical shifts of C_5 and C_4 lie outside of the "expected" range, are the ethoxy-substituted triazoles **1s** and **2s**, where the observed shifts are δ = 105.9 and 113.8 ppm, respectively. Computational studies on triazoles **10** and **11** predict that the C_5 and C_4 carbons of these triazoles will be shifted upfield. Resonance interactions, as in **10a**, account for these upfield shifts.

Applications. During the attempted synthesis of **2r**, we carried out the $Cp^*RuCl(PPh_3)_2$ catalyzed reaction of $PhCH_2N_3$ with 1-propyn-3-one. This is a complex reaction, where significant amounts of the alkyne trimers **12** and **13** were formed. The major triazole isolated was **1r** and not the expected isomer **2r**. This example illustrates the need to assign structure based on some experimental method, and not simply to assign structure based on the catalyst used.



A comment on the structure of phenyl-1,2,3-triazole[8a,13] is appropriate. This triazole has been shown at various times as tautomer **14**, **15**, or **16**.[14] What then is the correct structure? The actual ^{13}C NMR spectrum of phenyl-1,2,3-triazole in $CDCl_3$ shows a doublet (J = 190 Hz) at δ = 129.2 ppm and a singlet at δ = 146.9 ppm. These values are not consistent with either structure **14** or **15**. Shown in Figure 3 are the B3LYP/6-31G* GIAO calculated ^{13}C shifts of the appropriate carbons of **14**-**16**, as well as the relative energies. Since actual shifts are about 6 ppm downfield from the GIAO calculated shifts, the observed ^{13}C shifts implicate tautomer **16** as the actual structure. Further evidence for tautomer **16** as the actual structure comes from the calculated energies of these tautomers. The lowest energy tautomer is **16**, which lies 4.3 and 5.0 kcal/mol lower than **14** and **15**, respectively. Consequently, one would expect **16** to predominate in any equilibrium, while **14** and **15** should not be observable by NMR.

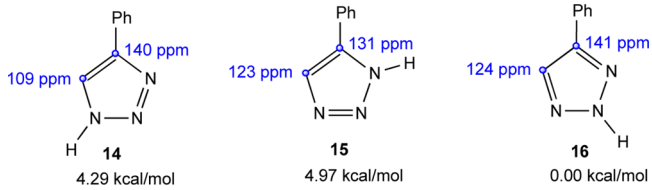


Figure 3. B3LYP/6-31G* GIAO calculated ^{13}C shifts and relative energies of tautomeric triazoles **14**−**16**.

In summary, 1,4-disubstituted-1*H*-1,2,3-triazoles **1** show a characteristic ^{13}C signal at δ ~120 ppm for C_5, while C_4 in the isomeric 1,5-disubstituted-1*H*-1,2,3-triazoles **2** appears at δ ~133 ppm. These ^{13}C signals are readily identified by the large 1-bond C−H coupling constant in the gated decoupled ^{13}C NMR spectrum. B3LYP/6-31G* GIAO computational studies agree with this trend, although calculated shifts are consistently about 6 ppm upfield from actual values. This combination of ^{13}C NMR and computational observations offers a simple method for distinguishing between triazoles **1** and **2**.

EXPERIMENTAL SECTION

General. NMR spectra were recorded on a Varian DirectDrive 600 MHz spectrometer. HRMS measurements were carried out using a Bruker MicroTOF-II spectrometer (electrospray ionization source with time-of-flight mass analyzer).

Preparation of Triazoles 1 by Cu(I)-Catalyzed Reactions. Method 1. General Comments. Triazoles **1** were prepared by the

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copper(I)-catalyzed cycloaddition of the appropriate alkynes and azides using a water/CH_2Cl_2 solvent system.[15] The presence of traces of copper in triazoles **1** prepared by this $CuSO_4$/sodium ascorbate method broadens C_5 (as well as C_4) and can make identification of these ^{13}C signals problematic. Hence it is necessary to remove traces of copper impurities by passing the sample through a small amount of silica gel. Alternatively, addition of a small amount of Et_3N to the sample sharpens the ^{13}C signals. Triazoles **1a**,[16] **1b**,[17] **1c**,[18] **1e**,[19] **1f**,[20] **1g**,[21] **1h**,[22] **1j**,[23] **1k**,[24] **1l**,[22] **1n**,[25] **1o**,[26] **1p**,[27] **1q**,[28] **1r**,[29] and **1s**,[30] have been previously reported. Triazoles **1d**, **1i**, and **1m** have not been previously reported. The following procedure for the preparation of **1d** is representative.

Preparation of Triazole ***1d****. Method 1.* A solution of 209 mg (1.65 mmol) of *n*-hexyl azide and 175 mg (2.13 mmol) of 1-hexyne in 4 mL of CH_2Cl_2 was stirred and 3 mL of water was added followed by 54 mg of $CuSO_4{\cdot}5H_2O$. Sodium ascorbate (150 mg) was then added in small portions and the mixture was stirred for 24 h at room temperature. The CH_2Cl_2 phase was then separated and dried over $MgSO_4$. After filtration, the solvent was removed using a rotary evaporator and the residue was chromatographed on 3 g of silica gel. The column was eluted with increasing amounts of ether in pentane. Triazole **1d** (322 mg; 94% yield) eluted with 75% ether in pentane. ^1H NMR ($CDCl_3$) δ 7.24 (s, 1 H), 4.30 (t, J = 7.3 Hz, 2 H), 2.71 (t, J = 7.7 Hz, 2 H), 1.88 (m, 2 H), 1.65 (m, 2 H), 1.39 (m, 2 H), 1.31 (m, 6 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 148.4, 120.3, 150.2, 31.6, 31.2, 30.3, 26.2, 25.4, 22.4, 22.3, 13.9, 13.8. HRMS (ESI) (MH^+) calcd for $C_{12}H_{24}N_3$ 210.1965, found 210.1994.

Triazole ***1i****.* This triazole was prepared in 98% yield by Method 1. ^1H NMR ($CDCl_3$) δ 7.36–7.24 (m, 10 H), 7.07 (s, 1 H), 4.28 (t, J = 7.4 Hz, 2 H), 3.96 (bs, 1 H), 1.86 (m, 2 H), 1.34–1.26 (m, 6 H), 0.87 (t, J = 7 Hz, 3 H). Irradiation of the 2 H triplet at δ = 4.28 ppm gives a 7% NOE of the 1 H singlet at δ = 7.07 ppm. ^{13}C NMR ($CDCl_3$) δ 153.9, 145.8, 128.0, 127.4, 127.2, 122.3, 50.4, 31.0, 30.2, 26.1, 22.4, 13.9. HRMS (ESI) (MH^+) calcd for $C_{21}H_{26}N_3O$ 336.2070, found 336.2098.

Triazole ***1m****.* This triazole was prepared in 90% yield by Method 1. ^1H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5 H), 7.32 (s, 1 H), 6.63 (d, J = 15.8 Hz, 1 H), 6.33 (d of t, J = 15.8, 6.6 Hz, 1 H), 5.08 (d of d, J = 6.7, 1.4 Hz, 2 H), 2.71 (t, J = 7.5 Hz, 2H), 1.64 (m, 2 H), 1.37 (m, 2 H), 0.92 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 148.8, 135.6, 135.0, 128.7, 128.5, 126.7, 122.3, 120.3, 52.2, 31.6, 25.4, 22.3, 13.8. HRMS (ESI) (MH^+) calcd for $C_{15}H_{20}N_3$ 242.1652, found 242.1678.

Preparation of Triazoles 2 by Cp*RuCl(PPh$_3$)$_2$-Catalyzed Reactions. Method 2. Triazoles **2a**,[6a] **2b**,[31] **2c**,[6a] **2e**, **2f**,[6a] **2i**, **2j**, **2l**,[7a] **2m**, **2n**, **2q**,[32] and **2s**[33] were prepared by the Cp*RuCl(PPh_3)$_2$-catalyzed cycloaddition of the appropriate alkynes and azides.[6] The following procedures for the preparation of **2i** and **2n** are representative.

Preparation of Triazole ***2i****. Method 2.* *n*-Hexylazide (73 mg; 0.57 mmol) and 1,1-diphenylprop-2-yn-1-ol (101 mg; 0.49 mmol) were placed in a 10 mL flask under argon and 2.5 mL of C_6H_6 was added. The mixture was stirred as 8 mg of Cp*RuCl(PPh_3)$_2$ was added and the flask was heated to reflux under argon. After 100 min, 0.75 g of silica gel was added to the mixture and the C_6H_6 was the removed using a rotary evaporator. The solid residue was added to a chromatography column prepared from 4 g of silica gel. The column was eluted with increasing amounts of ether in pentane. The triazole **2i** (126 mg, 77% yield) eluted with 50% ether in pentane as a white solid, mp 125–126 °C. ^1H NMR ($CDCl_3$) δ 7.37–7.30 (m, 3 H), 7.26–7.20 (m, 2 H), 6.88 (s, 1 H), 4.12 (m, 2 H), 3.83 (s, 1 H), 1.65 (m, 2 H), 1.19 (m, 2 H), 1.12 (m, 4 H), 0.82 (t, J = 7.2 Hz, 3 H). Irradiation of the 2 H multiplet at δ = 4.12 ppm gives no NOE of the 1 H singlet at δ = 6.88 ppm. ^{13}C NMR ($CDCl_3$) δ 143.8, 141.6, 134.8, 128.4, 128.2, 126.9, 76.3, 49.7, 31.2, 29.5, 26.3, 22.4, 14.0. HRMS (ESI) (MH^+) calcd for $C_{21}H_{26}N_3O$ 336.2070, found 336.2065.

Preparation of Triazole ***2n****. Method 2.* Benzyl azide (113 mg; 0.85 mmol) was placed in a 10 mL flask under argon and 2 mL of C_6H_6 was added. Propiolaldehyde diethyl acetal (128 mg; 1.00 mmol) in 0.5 mL of C_6H_6 was then added followed by 8.8 mg of Cp*RuCl(PPh_3)$_2$. The mixture was then heated to reflux under argon for 4 h. About half of the C_6H_6 was the removed using a rotary evaporator and the residue was chromatographed on 6 g of silica gel (column packed with 10% ether in pentane). The column was eluted with increasing amounts of ether in pentane. The triazole **2n** (183 mg, 83% yield) eluted with 50% ether in pentane. ^1H NMR ($CDCl_3$) δ 7.70 (s, 1 H), 7.36–7.27 (m, 3 H), 7.25–7.21 (m, 2 H), 5.63 (s, 2 H), 5.42 (d, J = 0.6 Hz, 1 H), 3.46 (m, 4 H), 1.15 (t, J = 7.0 Hz, 6 H). ^{13}C NMR ($CDCl_3$) δ 134.9, 134.8, 134.0, 128.8, 128.2, 127.5, 94.4, 61.3, 52.4, 14.9. HRMS (ESI) (MH^+) calcd for $C_{14}H_{20}N_3O_2$ 262.1550, found 262.1559.

Triazole ***2e****.* This triazole was prepared in 94% yield by Method 2. ^1H NMR ($CDCl_3$) δ 7.73 (s, 1 H), 7.38–7.29 (m, 3 H), 7.19–7.15 (m, 2 H), 5.63 (s, 2 H), 5.02 (s, 2 H), 1.93 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 170.0, 135.3, 134.6, 131.6, 129.0, 128.4, 127.1, 53.4, 52.2, 20.4. HRMS (ESI) (MH^+) calcd for $C_{12}H_{13}N_3O_2$ 232.1086, found 232.1096.

Triazole ***2j****.* This triazole was prepared in 67% yield by Method 2. ^1H NMR ($CDCl_3$) δ 7.72 (s, 1 H), 7.33–7.26 (m, 5 H), 7.23–7.15 (m, 2 H), 7.04–6.99 (m, 1 H), 6.85–6.81 (m, 2 H), 5.65 (s, 2 H), 4.90 (s, 2 H). ^{13}C NMR ($CDCl_3$) δ 157.5, 134.6, 134.4, 132.3, 129.7, 129.0, 128.5, 127.6, 122.0, 114.6, 58.3, 52.6. HRMS (ESI) (MH^+) calcd for $C_{16}H_{15}N_3O$ 266.1288, found 266.1301.

Triazole ***2m****.* This triazole was prepared in 68% yield by Method 2. ^1H NMR ($CDCl_3$) δ 7.49 (s, 1 H), 7.36–7.24 (m, 5 H), 6.46 (d, J = 15.9 Hz, 1 H), 6.29 (d of t, J = 15.9, 6.0 Hz, 1 H), 5.08 (d of d, J = 6.0, 1.5 Hz, 2 H), 2.64 (t, J = 7.6 Hz, 2 H), 1.65 (m, 2 H), 1.40 (m, 2 H), 0.93 (t, J = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 137.4, 135.6, 133.6, 132.4, 128.7, 128.3, 126.5, 122.6, 49.8, 30.1, 22.8, 22.3, 13.7. HRMS (ESI) (MH^+) calcd for $C_{15}H_{20}N_3$ 242.1652, found 242.1665.

Preparation of Triazoles 2 by Reaction of Magnesium Acetylides with Azides. Method 3. Triazoles **2d**, **2g**,[7a] and **2h** were prepared by the reaction of the appropriate magnesium acetylide and azides.[7a] The following procedure for the preparation of **2d** is representative.

Ethylmagnesium bromide (1.50 mL of a 1.0 M solution in THF; 1.50 mmol) was placed in flask under argon and a solution of 122 mg of 1-hexyne (1.49 mmol) in 0.5 mL THF was added dropwise at 0 °C. The mixture was warmed to room temperature and after 1.5 h, 205 mg of *n*-hexyl azide (1.61 mmol) in 0.5 mL THF was added dropwise. After 7 h at room temperature, the mixture was cooled in ice and quenched with aqueous ammonium bromide solution. The mixture transferred to a separatory funnel using ether and the organic phase was washed with saturated salt solution. After drying over a mixture of Na_2SO_4 and $MgSO_4$, the solution was filtered and the solvent was removed using a rotary evaporator. The residue was chromatographed on 2.5 g of silica gel and the column was eluted with increasing amounts of ether in pentane. The triazole **2d** (208 mg; 67% yield) eluted with 70% ether in pentane. ^1H NMR ($CDCl_3$) δ 7.44 (s, 1 H), 4.24 (t, J = 7.4 Hz, 2 H), 2.62 (t, J = 7.6 Hz, 2 H), 1.88 (m, 2 H), 1.66 (m, 2 H), 1.43 (m, 2 H), 2.32 (m, 6 H), 0.97 (t, J = 7.3 Hz, 3 H), 0.89 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 136.8, 132.0, 47.7, 31.2, 30.3, 30.1, 26.3, 22.9, 22.5, 22.3, 14.0, 13.7. HRMS (ESI) (MH^+) calcd for $C_{12}H_{24}N_3$ 210.1965, found 210.1990.

Triazole ***2h****.* This triazole was prepared in 70% yield by Method 3. ^1H NMR ($CDCl_3$) δ 7.59 (s, 1 H), 7.57–7.48 (m, 3 H), 7.46–7.42 (m, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.58 (m, 2 H), 1.33 (m, 2 H), 0.88 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 138.2, 136.4, 132.3, 129.42, 129.41, 125.2, 30.3, 23.3, 22.1, 13.6. HRMS (ESI) (MH^+) calcd for $C_{12}H_{16}N_3$ 202.1339, found 202.1362.

Preparation of Triazole ***2k****.* Triazole **2k** was prepared by the Cp*Ru(PPh_3)$_2$Cl catalyzed cycloaddition of phenylacetylene with the dimethylacetal of $PhCOCH_2N_3$, followed by hydrolysis of the resultant triazole acetal. α-Azidoacetophenone dimethyl acetal (174 mg; 0.84 mmol) was placed in a flask under argon and 2 mL of C_6H_6 was added. Phenylacetylene (94 mg; 0.92 mmol) in 1 mL of C_6H_6 was then added followed by 9.5 mg of Cp*RuCl(PPh_3)$_2$. The mixture was then refluxed under argon for 5.5 h. About 1 g of silica gel was added to the mixture and the C_6H_6 was the removed using a rotary evaporator. The residue was chromatographed on 4 g of silica gel. The column was eluted with increasing amounts of ether in pentane. The dimethylacetal derivative of triazole **2k** (179 mg, 69% yield) eluted

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with 50% ether in pentane. ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.31 (m, 1 H), 7.23 (m, 2 H), 7.14 (m, 2 H), 7.01 (m, 2 H), 6.89 (m, 2 H), 6.66 (m, 2 H), 4.72 (s, 2 H), 3.33 (s, 6 H). ^{13}C NMR ($CDCl_3$) δ 138.9, 137.2, 132.4, 128.7, 128.6, 128.5, 128.3, 128.0, 126.7, 101.7, 51.1, 49.3.

A solution of 170 mg (0.55 mmol) of the acetal prepared above in 5 mL of THF was stirred as 2.0 g of 3% H_2SO_4 in water was added dropwise. The mixture was then heated at reflux for 20 h and then solid $NaHCO_3$ was then added to neutralize the H_2SO_4. The organic phase was then decanted and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration the solvent was removed using a rotary evaporator. This residue was dissolved in CH_2Cl_2 and filtered through 1.8 g of silica gel in a column. The triazole **2k** (110 mg; 76% yield) eluted with CH_2Cl_2. ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2 H), 7.79 (s, 1 H), 7.64 (m, 1 H), 7.51 (m, 2 H), 7.44−7.39 (m, 3 H), 7.37−7.32 (m, 2 H), 5.81 (s, 2 H). ^{13}C NMR ($CDCl_3$) δ 190.8, 139.2, 134.4, 134.0, 133.1, 129.7, 129.11, 129.07, 128.6, 128.1, 126.7, 54.0. HRMS (ESI) (MH^+) calcd for $C_{16}H_{14}N_3O$ 264.1131, found 264.1152.

Preparation of Triazole ***2p***. Triazole **2p**[34] was prepared by hydrolysis of **2n**. A solution of 154 mg (0.59 mmol) of the acetal **2n** in 10 mL of THF was stirred as 2.7 g of 3% H_2SO_4 in water was added dropwise. The stirred solution was heated for 41 h at 50−52 °C and the mixture was then neutralized with $NaHCO_3$. Most of the THF was removed using a rotary evaporator and 4 mL of water and 7 mL of CH_2Cl_2 was added. The CH_2Cl_2 phase was dried over Na_2SO_4, filtered, and the solvent was removed using a rotary evaporator to give 111 mg (100% yield) of aldehyde **2p**.[34] ^{1}H NMR ($CDCl_3$) δ 9.95 (s, 1 H), 8.25 (s, 1 H), 7.37−7.28 (m, 5 H), 5.90 (s, 2 H). ^{13}C NMR ($CDCl_3$) δ 178.2, 141.2, 134.4, 133.4, 128.9, 128.7, 128.2, 53.8.

Preparation of Triazole ***2o***. Triazole **2o**[35] was prepared by $NaBH_4$ reduction of **2p**. A solution of 17 mg (0.091 mmol) of aldehyde **2p** in 1 mL of methanol was cooled in a water bath to 15 °C as 15 mg of solid $NaBH_4$ (0.41 mmol) was added in small portions. After stirring for 4 h at room temperature, the methanol was removed using a rotary evaporator. A few drops of 10% HCl in water were added followed by 1 mL of water and the mixture was extracted with 3 mL of CH_2Cl_2. The CH_2Cl_2 extract was dried over Na_2SO_4 and the solvent was removed using a rotary evaporator to give 15 mg (87% yield) of triazole **2o**.[35] ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1 H), 7.35−7.28 (m, 3 H), 7.25−7.21 (m, 2 H), 5.63 (s, 2 H), 4.58 (s, 2 H). ^{13}C NMR ($CDCl_3$) δ 136.3, 134.8, 133.2, 129.0, 128.4, 127.6, 53.1, 46.0.

Preparation of Triazole ***2r***. Triazole **2r**[36] was prepared by addition of CH_3MgBr to **2p** followed by PCC oxidation of the resultant alcohol. Tetrahydrofuran (2 mL) was placed in a flask under argon and 1.4 mL of 0.75 M CH_3MgI in ether (1.05 mmol) was added. A solution of 105 mg of triazole **2p** (0.56 mmol) in 2 mL of THF was added dropwise to the stirred solution. The mixture was then warmed at 35 °C for 10 min, cooled in a water bath, and then quenched with aqueous ammonium bromide solution. The organic phase was separated, dried using Na_2SO_4, and the solvent was removed using a rotary evaporator. The residue was dissolved in CH_2Cl_2 and redried using Na_2SO_4. Solvent removal using a rotary evaporator gave 93 mg of crude alcohol product that was used directly in the next step.

A solution of the alcohol prepared above (84 mg; 0.46 mmol) in 2 mL of CH_2Cl_2 was stirred as 103 mg of pyridinium chlorochromate (0.48 mmol) was added in small portions. After stirring for 6 h at room temperature, 5 mL of ether was added to the dark mixture and the organic phase was filtered through a small amount of silica gel in a pipet. The solvent was then removed using a rotary evaporator to give 40 mg (48% yield) of triazole **2r**.[36] ^{1}H NMR ($CDCl_3$) δ 8.16, 7.38−7.27 (m, 5 H), 5.90 (s, 2 H), 2.53 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 187.1, 136.6, 134.9, 133.1, 128.7, 128.4, 128.2, 53.6, 28.8.

■ ASSOCIATED CONTENT

Supporting Information

Complete ref 12, the B3LYP/6-31G* calculated structures, energies, and Cartesian coordinates of **6**, **7**, **8**, **9**, **10**, **11**, **14**, **15**, and **16**, and ^{1}H and ^{13}C NMR spectra of triazoles **1a**−**1s**, **2a**−**2s**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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