

Multicomponent Click Synthesis of 1,2,3-Triazoles from Epoxides in Water Catalyzed by Copper Nanoparticles on Activated Carbon^S

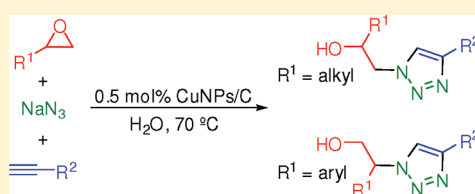
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S Supporting Information

ABSTRACT: Copper nanoparticles on activated carbon have been found to effectively catalyze the multicomponent synthesis of β -hydroxy-1,2,3-triazoles from a variety of epoxides and alkynes in water. The catalyst is easy to prepare, reusable at a low copper loading (0.5 mol %), and exhibits higher catalytic activity than some commercially available copper sources. The regio- and stereochemistry of the reaction has been revised and unequivocally established on the basis of X-ray crystallographic analyses. An NMR experiment has been implemented for the rapid and unmistakable determination of the regiochemistry of the process. Some mechanistic aspects of the reaction have been also undertaken which unveil the participation of copper(I) acetylides.



INTRODUCTION

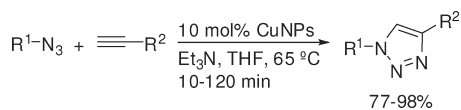
The Huisgen 1,3-dipolar cycloaddition of azides and alkynes¹ has become a synthetic cornerstone since the paramount discovery by the groups of Meldal² and Sharpless³ of its copper(I)-catalyzed version (CuAAC).⁴ The superb reliability of the CuAAC reaction has increasingly attracted the attention from a diverse range of the areas of chemistry.⁵ As a result, a plethora of methods have been developed around this reaction with the aim to increase efficiency. Among them, we consider of special interest those which combine three important aspects in modern synthetic organic chemistry, namely, (a) multicomponent synthesis;⁶ the in situ generation of organic azides in the presence of the alkyne (three-component alkyne–azide cycloaddition) minimizes hazards derived from the isolation and handling of the former, avoiding the time-consuming and waste generation of an additional synthetic step; (b) heterogeneous catalysis,⁷ especially involving metal nanoparticles,⁸ which offers several advantages over the homogeneous counterpart, such as easy recovery, easy recycling, and enhanced stability of the catalyst; and (c) reactions in water,⁹ the solvent used by nature for biological chemistry which can make synthetic processes cheaper, safer, and greener. In this regard, some reports on the copper-catalyzed multicomponent synthesis of triazoles from organic halides in water, using heterogeneous catalysts, have appeared in the literature.¹⁰

The azidolysis of epoxides¹¹ and the CuAAC have in common some inherent attributes which perfectly fit the set of stringent criteria required for click chemistry, in the terms coined by Sharpless et al.¹² Therefore, it is not surprising that, in recent years, an increasing interest emerged on the multicomponent synthesis of 1,2,3-triazoles through the in situ generation of azidoalcohols and further cycloaddition with alkynes.^{13,14} The resulting products possess a 1-(hydroxyethyl)-1*H*-1,2,3-triazole

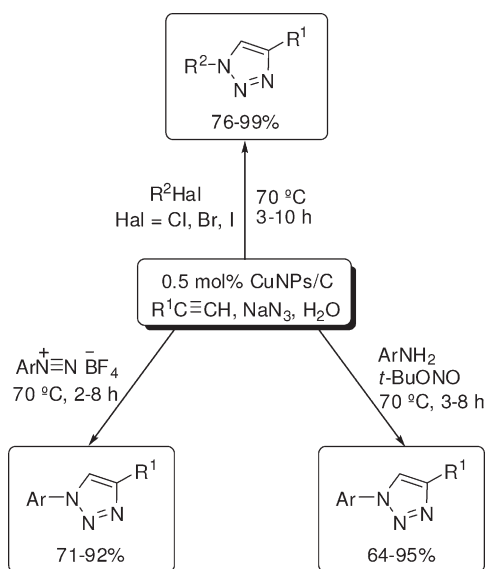
moiety which is also present in peptide surrogates of HIV-1 protease inhibitors.¹⁵ The pioneering work in this field involved homogeneous catalysis with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (10 mol %)/sodium ascorbate (20 mol %)/ H_2O ,^{13a} CuI (5 mol %)/PEG-400,^{13b} and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (10 mol %)/ H_2O .^{13c} Although the reactions were carried out in one pot, the whole process was sequential; therefore, the formation of the azidoalcohol needed monitoring before the addition of the alkyne. It is worthy to note the one-pot enantioselective biocatalytic azidolysis of aromatic epoxides, linked to the dipolar cycloaddition with alkynes, reported by the group of Feringa.¹⁶ Some heterogeneous catalytic systems have been developed recently, including porphyrinatocopper nanoparticles on activated multiwalled carbon nanotubes (5 mol %)/ H_2O ,^{14a} $\text{Cu}[\text{N}^2, \text{N}^6\text{-bis}(2\text{-hydroxyphenyl})\text{pyridine-2,6-dicarboxamidate}]\text{H}_2\text{O}$ (5 mol %)/ascorbic acid (20 mol %)/ H_2O ,^{14b} and copper(I)-modified zeolites (8 mol %)/ H_2O .^{14c} In these cases, the catalyst could be easily recovered exhibiting a high recycling capability. Despite the fact of the mild reaction conditions generally applied, there are still some issues that need improvement in order to make the processes more effective: (a) the regioselectivity, which is not always as high as desired; (b) the purification of products, some methodologies requiring column chromatography; (c) to reduce the amounts of copper in solution should be also a priority, particularly for biological applications; and (d) the long and tedious procedures usually required for the heterogenization of copper, which preclude the widespread utilization of this type of catalysts. We can conclude that easy-to-prepare and versatile heterogeneous copper catalysts

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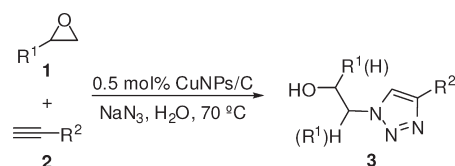
Scheme 1. 1,3-Dipolar Cycloaddition of Organic Azides and Terminal Alkynes Catalyzed by Unsupported Copper Nanoparticles



Scheme 2. Multicomponent Synthesis of 1,2,3-Triazoles from Organic Halides, Aryldiazonium Salts, and Aromatic Amines Catalyzed by Copper Nanoparticles Supported on Activated Carbon



Scheme 3. General Conditions for the Multicomponent Synthesis of Triazoles from Epoxides



azidolysis of epoxides and 1,3-dipolar cycloaddition with alkynes. Special attention is dedicated to the regio- and stereochemical course of the reaction, a topic that has not been properly addressed hitherto and that has led to an incorrect assignment of the reaction products. An NMR experiment for the determination of the regioselectivity of the reaction and some mechanistic studies are also presented.

RESULTS AND DISCUSSION

Preparation of the Catalyst. The copper catalyst was readily available by mixing activated carbon with a recently prepared suspension of CuNPs. The latter was obtained in a few minutes from anhydrous copper(II) chloride, lithium metal, and a catalytic amount of DTBB (10 mol %) in THF at room temperature. In contrast with most heterogeneous catalysts, our catalyst was ready for use as prepared, after filtration and drying, without any further pretreatment. The catalyst was fully characterized by different means, which revealed the presence of oxidized spherical nanoparticles (Cu₂O and CuO) dispersed on the active carbon support with an average size of ca. 6 ± 2 nm.²¹

Multicomponent Synthesis of Triazoles from Epoxides and Alkynes in Water. All reactions were performed with 0.5 mol % of CuNPs/C, the copper loading being 10-fold lower than the lowest previously published by others.^{13,14,16} Preliminary experiments with styrene oxide, phenylacetylene, and sodium azide in water allowed us to select a reaction temperature of 70 °C as the most convenient in order to achieve high conversions. A control experiment under the above conditions but in the presence of only activated carbon (without copper) gave no trace of the corresponding triazole after 24 h. This result confirms the essential role of copper and practically discards any catalytic effect of the support. A series of commercially available epoxides and alkynes were subjected to the azidolysis–cycloaddition process in water at 70 °C (Scheme 3, Table 1).

We first studied the reaction of alkyl-substituted epoxides with phenylacetylene (Table 1, entries 1–4). The monosubstituted epoxides bearing an alkyl and alkenyl chain **1a** and **1b** reacted relatively fast, affording triazoles **3aa** and **3ba**, respectively, in high yields (Table 1, entries 1 and 2). Glycidyl phenyl ether (**1c**) also reacted nicely, whereas the 1,1-disubstituted vinyl oxirane **1d** furnished a 5:1 mixture of *E/Z* diastereoisomers (Table 1, entries 3 and 4). Bicyclic epoxides derived from cyclic olefins were shown to be more reluctant to react. For instance, higher temperature was necessary to get a high yield in the transformation of cyclohexene oxide (**1e**) into hydroxytriazole **3ea** (Table 1, entry 5). Moreover, cyclooctane oxide (**1f**) remained unchanged even after prolonged heating (Table 1, entry 6). This result, however, is not so unexpected since the azidolysis of cyclooctane oxide was already described as problematic by others.²²

Then we explored the reactivity of aryl-substituted oxiranes with phenylacetylene (Table 1, entries 7–10). Both styrene

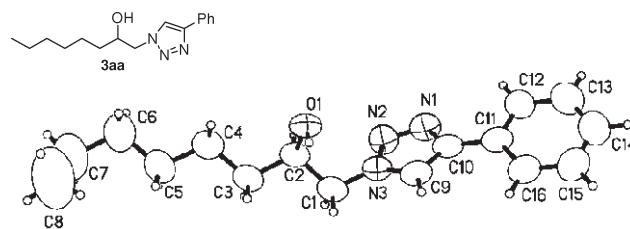
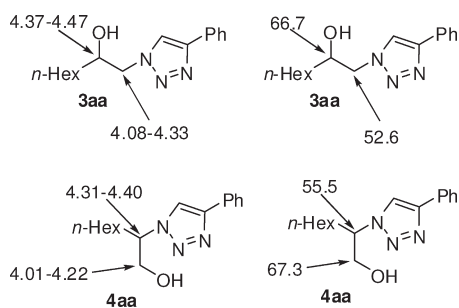
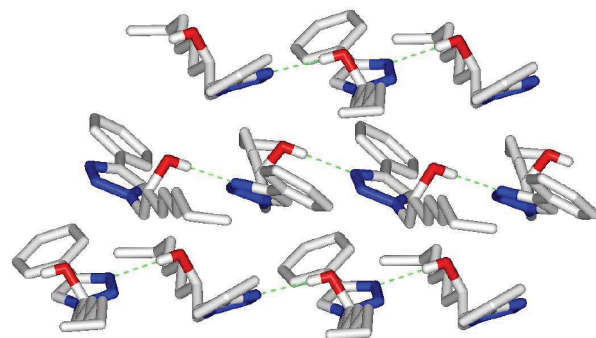
that can contribute to the advancement of the multicomponent synthesis of triazoles from epoxides in water are welcome.

Our interest on the preparation and reactivity of active metals and nanoparticles¹⁷ led us to the generation of a form of active copper [obtained from CuCl₂·2H₂O, metal lithium, and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) in THF at room temperature] and its application to the reduction of manifold organic functionalities.¹⁸ We discovered that copper nanoparticles (CuNPs) were formed either from CuCl₂·2H₂O or anhydrous CuCl₂ under the aforementioned conditions. Trying to expand the use of these nanoparticles,¹⁹ we were immersed in the field of click chemistry in 2009. We found out that 10 mol % of unsupported CuNPs catalyzed the 1,3-dipolar cycloaddition of organic azides and terminal alkynes in remarkable short reaction times (Scheme 1).²⁰ The presence of triethylamine was, however, mandatory for the reaction to occur, and the CuNPs could not be reused since they underwent dissolution. A second generation of catalysts was introduced by immobilization of the CuNPs on different inorganic supports. In particular, we developed a highly versatile catalyst, consisting of oxidized copper nanoparticles on activated carbon (CuNPs/C), for the multicomponent synthesis of 1,2,3-triazoles from organic halides, aryldiazonium salts, and anilines in water (Scheme 2).²¹ One example of other azide precursors, such as an epoxide and alkene, was also reported. We wish to present herein our results on the performance and scope of the CuNPs/C in the domino

Table 1. Multicomponent Synthesis of Hydroxytriazoles from Epoxides Catalyzed by CuNPs/C in Water^a

Entry	Epoxide	Alkyne	t (h)	Triazole	Yield (%) ^b
1			2		88
2			2		90
3			4		89
4			4		81 ^c
5			8		93 ^d
6			24		0
7			8		93
8			8		82
9			16		76
10			16		70
11			4		89
12			4		81
13			8		79
14			16		84
15			20 8 ^d		64 81 ^d

^a Reaction conditions: **1** (1 mmol), **2** (1 mmol), NaN₃ (1.1 mmol), CuNPs/C (0.5 mol %), H₂O, 70 °C. ^b Isolated yield. ^c E/Z 5:1. ^d Reaction at 100 °C.

Scheme 4. Computer-Estimated ^1H and ^{13}C NMR Chemical Shifts (in ppm) for 3aa and 4aa

Figure 1. Plot showing the X-ray structure and atomic numbering for compound 3aa.

Figure 2. Intermolecular hydrogen bonding between molecules of 3aa in the crystal. The hydrogen atoms, except the hydroxyl group hydrogen atoms, have been omitted for clarity.

oxide (**1g**) and 4-chlorostyrene oxide (**1h**) exhibited similar reactivity, providing the corresponding triazoles in good yields (Table 1, entries 7 and 8) and with opposite regioselectivity to that displayed by the alkyl-substituted oxiranes (Table 1, entries 1–3). The *meso*-epoxide **1i** and racemic **1j** gave rise to the 1,2-diphenyl-2-hydroxyethyl-substituted triazoles **3ia** and **3ja** (Table 1, entries 9 and 10). In these cases, longer reaction times were required and lower yields than the average were recorded. The methodology was proven to be equally effective for alkyl- and cycloalkyl-substituted alkynes, such as oct-1-yne (**2b**) and cyclohexylacetylene (**2c**), which manifested the same reactivity pattern (Table 1, entries 11 and 12). The presence of a heterocyclic moiety in the alkyne (**2d**) was compatible with the reactions conditions leading to the pyridyl-substituted product **3gd** (Table 1, entry 13). The reaction of 1,3-diethynylbenzene (**2e**) with the enantiomerically pure (*R*)-**1g** produced the structurally interesting C_2 -symmetric bis(hydroxytriazole) **3ge** in high yield (Table 1, entry 14). Finally, a triazole bearing two nonaromatic substituents (**3bf**) was obtained from unsaturated epoxide **1b** and hex-1-yne (**2f**) in moderate yield at 70 °C and good yield at 100 °C (Table 1, entry 15).

Regio- and Stereochemistry of the Reaction. It must be highlighted that the multicomponent synthesis of hydroxytriazoles catalyzed by CuNPs/C was regioselective with regard to both the azidolysis of the epoxide and the 1,3-dipolar cycloaddition of the in situ generated azidoalcohols with terminal alkynes. In the latter case, and in contrast with some other methodologies,^{13a,14c} the 1,4-disubstituted 1,2,3-triazoles were the only products observed, with no trace of the regioisomeric 1,5-disubstituted 1,2,3-triazoles being detected. The attention devoted by some research groups to the regiochemistry of the cycloaddition has been to the detriment of the analysis of the regioselectivity in the oxirane ring opening. The fact that some of the results have been misunderstood has had, consequently, a confusing effect on the reader. We would like to address this subject by taking advantage of the crystalline nature of the triazoles synthesized. We have selected some examples to unequivocally assign both the regio- and stereochemistry of the products on the basis of X-ray crystallography.

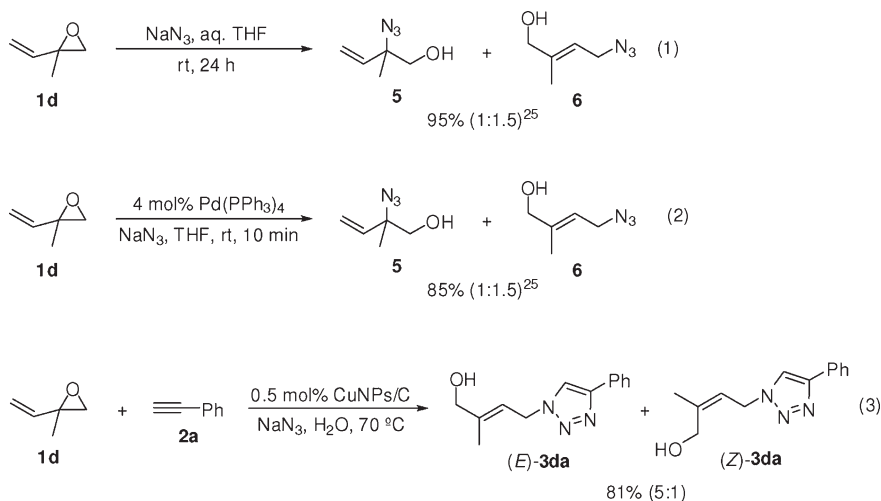
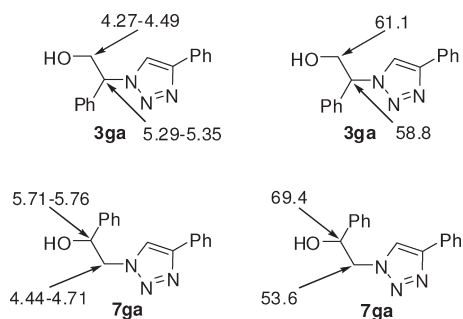
Concerning the monosubstituted oxiranes, the β -hydroxytriazole derived from oct-1-ene oxide (**3aa**) was used as a model compound for this study. The ^1H and ^{13}C NMR chemical shifts of the key nuclei involved in the regiochemical outcome were computer estimated for **3aa** and its regioisomer **4aa** (Scheme 4). According to these values, an assignment based on the ^1H and proton-decoupled ^{13}C NMR spectra might be somewhat ambiguous. The assignment of the ^1H NMR signals must be especially

awkward due to the overlapping of the chemical shifts and the identical multiplicity of CH-Het and CH_2 -Het in both regioisomers. A DEPT 135° experiment, however, would be helpful in the case of the ^{13}C NMR spectrum. X-ray crystallographic analysis²³ demonstrated that triazole **3aa** derived from the nucleophilic attack of the azide ion to the less hindered position of the oxirane ring (Figure 1). This result is in agreement with the previously reported azidolysis of alkyl-monosubstituted oxiranes.²² Interestingly, intermolecular hydrogen bonding was observed in the crystal structure of **3aa** (Figure 2). The fact that the (*R*)-**3aa** and (*S*)-**3aa** enantiomers alternate positions within the same molecular row favors the formation of hydrogen bonds between the OH and the 2-N or 3-N of the triazole unit, with the two latter also participating in an alternate manner. The hydrogen bonds were unsymmetrical, with the hydrogen being covalently bonded to the oxygen and hydrogen bonded to the nitrogen.²⁴ In all cases, constant values of 2.12 Å for the $\text{OH}\cdots\text{N}$ bond (hydrogen-to-nitrogen distance) and 2.98 Å for the $\text{O}-\text{H}\cdots\text{N}$ bonds (oxygen-to-nitrogen distance) were measured.

The reaction with isoprene monoepoxide (**1d**) was particularly interesting because it provided the regioisomer **3da**, arising from an $\text{S}_{\text{N}}2'$ process, as a 5:1 *E/Z* diastereomeric ratio (Scheme 5). Contrary to this behavior, a lack of regioselectivity was reported for both the uncatalyzed and palladium-catalyzed azidolyses of **1d**,²⁵ equilibration between the tertiary and primary allylic azides occurs, with the primary reacting selectively because of steric reasons, as noted by the group of Sharpless and Fokin.²⁶

Cyclohexene oxide (**1e**) gave, as expected and published by others,^{13,14} the *trans*- β -hydroxytriazole **3ea**, the stereochemistry being deduced from the ^1H NMR coupling constants of the ring protons. The synthesis of triazoles from styrene oxide, however, is rather controversial and requires careful examination and interpretation of the spectroscopic data. As depicted in Scheme 6,

Scheme 5. Azidolysis and Domino Azidolysis–Cycloaddition of Epoxide 1d

Scheme 6. Computer-Estimated ¹H and ¹³C NMR Chemical Shifts (in ppm) for 3ga and 7ga

the key protons resulting from the regiochemistry of the reaction appear within a near range of chemical shifts for regioisomers **3ga** and **7ga**. Furthermore, the CH₂O and CHN are practically indistinguishable by ¹³C NMR in **3ga**, making dubious any assignment unless a sample of the regioisomer **7ga** is available for comparison. Table 2 shows the inconsistency of the melting point and ¹H and ¹³C NMR data reported by different groups with the structure proposed; that is, similar melting point and NMR data are correlated with different regioisomers or totally unlike data appear for the same regioisomer. In order to disclose the regio- and stereochemical course of our multicomponent synthesis of triazoles from aryl-substituted oxiranes, enantiomerically pure styrene oxide (*R*)-**1g** was allowed to react with sodium azide and phenylacetylene (**2a**) under the standard conditions. The β-hydroxytriazole attained was derivatized to the corresponding mesylate (*S*)-**8**, and its regiochemistry and absolute stereochemistry were unequivocally established by X-ray crystallography (Figure 3). We can, therefore, assert that the process is regiospecific, with the exclusive attack of nitrogen occurring to the benzylic position of the oxirane, and stereospecific, through a typical S_N2 pathway (i.e., with inversion of the configuration).

To the best of our knowledge, the multicomponent synthesis of 1,2,3-triazoles from the stilbene oxides has been never

accomplished. We applied our methodology to both *cis*- and *trans*-stilbene oxide (Table 1, entries 9 and 10). In these cases, the stereochemistry of the ring opening also followed the pattern of a sole S_N2 mechanism, as confirmed by the X-ray structure of the triazole **3ia** derived from *cis*-stilbene oxide (**1i**) (Figure 4).

NMR Experiments. We next searched for a fast and reliable way to ascertain the regiochemistry of the multicomponent synthesis of triazoles from monosubstituted epoxides once it was confirmed by X-ray crystallography. We believed that the ¹H NMR signal of the OH of the triazoles **3** could be used as an adequate probe for this purpose whenever it is visible and does not overlap other signals. The idea was to use a solvent which allowed detecting the coupling of the OH with the protons attached to the α-carbon atom. In this way, the OH of secondary alcohols, produced by nucleophilic attack on the less hindered position of the oxirane ring, would manifest as a doublet (d). On the other hand, the OH of primary alcohols, obtained by nucleophilic ring opening at the most substituted position, should be brought into view as a doublet of doublets (dd), given that the two methylene protons (CH₂OH) are diastereotopic. This information is not so evident from Table 1, where the OH was normally described as either a singlet or a multiplet. An array of deuterated solvents was tested using triazole **3ga** as a model compound, with the position of the OH signal being identified by the addition of D₂O to the sample (Figure 5). In principle, DMSO-*d*₆ does not seem to be an appropriate solvent because the OH appears as a broad singlet due to the rapid exchange of the proton, probably favored by the trace of water contained in the solvent which is difficult to eliminate. This proton shows up as a triplet in CD₃CN at 3.40 ppm, although strictly it must be a partially overlapped doublet of doublets. No OH peak, except that of residual water present in commercial CDCl₃ or in the sample, was observed when using this solvent as received. However, when the CDCl₃ was previously passed through a short silica column, a clear dd was displayed in the spectrum. In this case, the CHCH₂ moiety evolved from three dd with wet CDCl₃ into a dd (5.67 ppm) and two ddd (4.63 and 4.23 ppm) with anhydrous CDCl₃. The spectrum recorded in CD₃CN pointed out a similar trend for this moiety.

Table 2. Reported Data in the Literature for Regioisomers **3ga** and **7ga**

mp (°C)	¹ H NMR (ppm) ^a	¹³ C NMR (ppm) ^b	structure	ref
131			3ga	13a
158	DMSO- <i>d</i> ₆ : 4.40 (q), 4.63 (dd), 5.05 (<i>m</i>), 5.65 (d)	57.3, 71.9	3ga	13b
	CDCl ₃ /DMSO- <i>d</i> ₆ : 4.15 (<i>m</i>), 4.40 (<i>m</i>), 5.03 (<i>t</i>), 5.80 (dd)		3ga	13c
126	CDCl ₃ : 3.62 (<i>s</i>), 4.15 (dd), 4.56 (dd), 5.60 (dd)	64.7, 67.3	7ga	14a, 14b
156.5	CDCl ₃ : 3.61 (<i>s</i>), 4.46 (q), 4.65 (d), 5.24 (d)	57.6, 72.3	7ga	16

^a Chemical shifts correspond to the CH₂CH moiety (one ¹H each) and OH (in italics, tentatively assigned by us). ^b Chemical shifts correspond to the CH₂CH moiety.

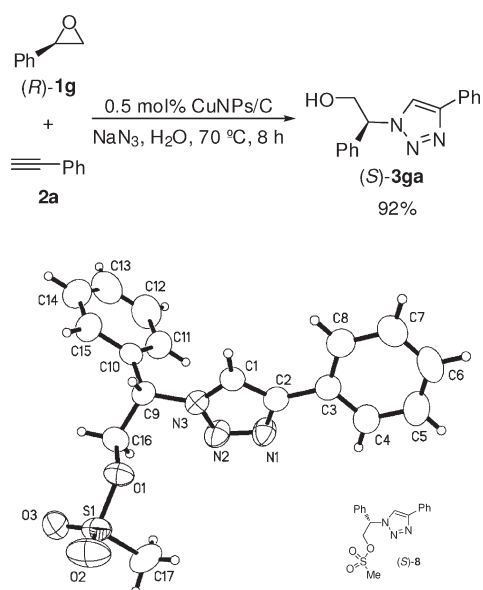


Figure 3. Synthesis of triazole (*S*)-**3ga** and plot showing the X-ray structure and atomic numbering for compound (*S*)-**8**.

A parallel study was undertaken, using the secondary alcohol **3aa** as a model molecule, with the solvents which better exhibited the multiplicity of the OH above (Figure 6). Disappointingly, neither wet nor anhydrous CDCl₃ was a useful solvent, with the OH being manifested in both cases as a broad singlet. In contrast, CD₃CN enabled the OH signal to be resolved as a well-defined doublet. Therefore, CD₃CN was considered to be the solvent of choice for the ¹H NMR spectra of both primary and secondary alcohols. It was gratifying to see that all triazoles synthesized in this article, which were subjected to the above experiment, displayed the aforementioned NMR patterns for the hydroxy group, that is, a triplet (*J* ~ 6.0 Hz) for primary alkyl, a doublet (*J* ~ 5.5 Hz) for secondary alkyl, and a doublet (*J* ~ 9.0 Hz) for secondary benzyl β-hydroxyalcohols (see the Experimental Section for details).

The experiments described above are conclusive enough to be utilized as a tool in the unmistakable determination of the regiochemistry of the title reaction. Therefore, we are now in a position to assess the structure assignment of the β-hydroxytriazoles reported

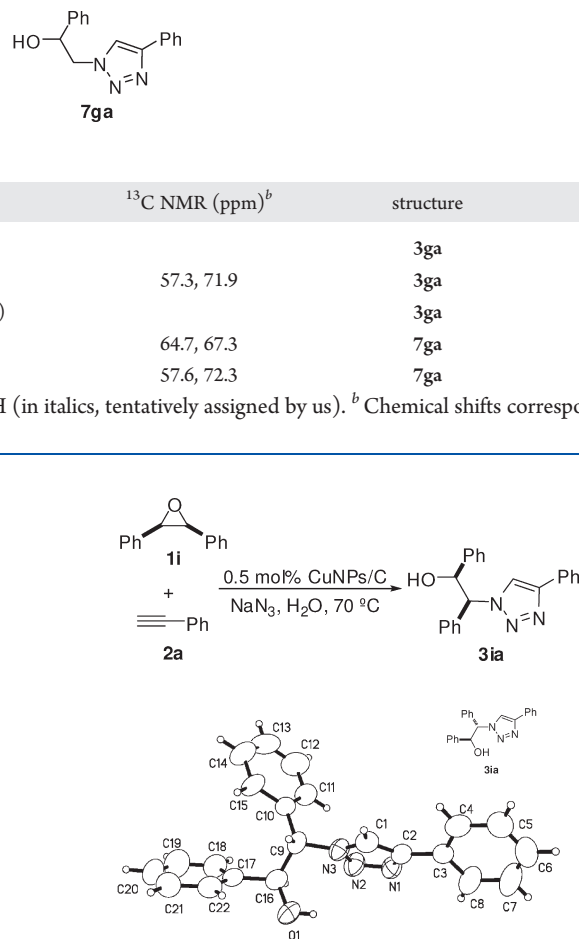


Figure 4. Synthesis of triazole **3ia** and plot showing its X-ray structure and atomic numbering.

in the literature (Table 2). Structures in refs 13a and 13c are right, although only based on the melting point and ¹H NMR data, respectively. Reference 13b is wrong, and the product obtained by the authors is **7ga** instead of **3ga**. References 14a and 14b are also wrong; in these publications, the authors prepared compound **3ga** instead of **7ga**, and accordingly, the structures drawn for the twelve^{14a} and fifteen^{14b} examples of β-hydroxytriazoles derived from styrene oxide are incorrect. Finally, ref 16 is right. In our opinion, these findings open a new debate about which factors govern the regioselectivity in the step of the azidolysis of the epoxide for every particular case, as it is known that both regioisomers are accessible for aryl epoxides.

Stability and Recycling of the Catalyst. The catalyst was handled in air, and all of the experiments were carried out without air exclusion; these are advantages that make the process operationally simple. Furthermore, in all cases, the progress of the reaction could be followed visually. Once the reaction ended, a nearly spherical solid piece at the surface of a transparent and colorless solution was observed, where the triazole was in the core of the solid covered by the catalyst.^{21b} It is worthwhile mentioning that, despite the fact that a small amount of catalyst was utilized, it could be easily recovered by filtration (after treating with ethyl acetate) and reused. We noted a progressive decrease in the isolated yield of triazole **3ga** along four consecutive cycles (Figure 7). The

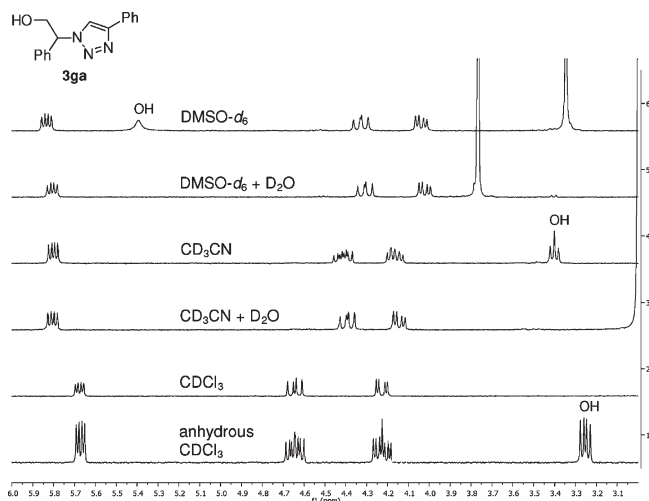


Figure 5. ^1H NMR region for the CHCH_2OH moiety of **3ga** in different solvents.

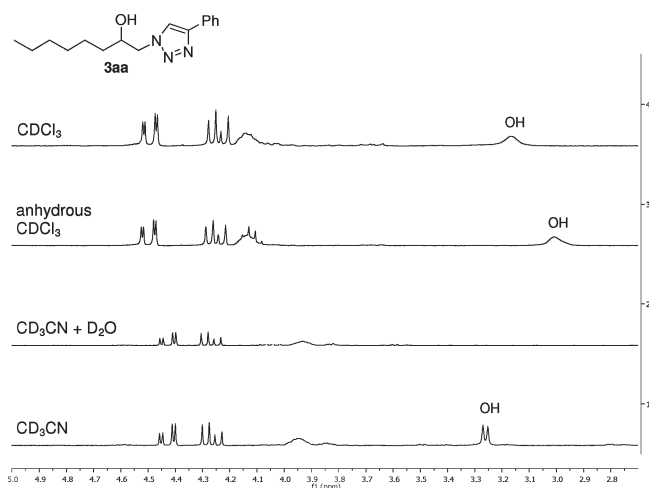


Figure 6. ^1H NMR region for the NCH_2CHOH moiety of **3aa** in different solvents.

copper in the aqueous solution from the first to the second cycle was detected to be 80 ppb (ICP-MS), which practically rules out any loss of catalytic activity by metal leaching. However, a loss of catalyst mass of approximately 2 mg was measured after each cycle. This amount, retained by the fitted glass filter during filtration, represents a 10% of the starting amount of catalyst (20 mg) in the first cycle and larger in the subsequent cycles. This fact could account for the tendency observed in the recycling experiments. Nevertheless, a fair isolated yield of 70% was recorded after the fourth cycle. We must remark that the aforementioned aqueous solution obtained after filtration (with 80 ppb Cu) was proven to be totally inactive in the three-component synthesis of triazole **3ga**. Although this experiment points to a process of heterogeneous nature, we cannot dismiss that the support acts as a reservoir for metal species that leach into solution and readsorb (the release–recapture mechanism). This kind of process, however, has been mainly proven to occur for nanoparticle suspensions of the catalytically active group VIII transition metals.²⁷ More recently, significant leaching of copper metal was observed in the Cu/C-catalyzed

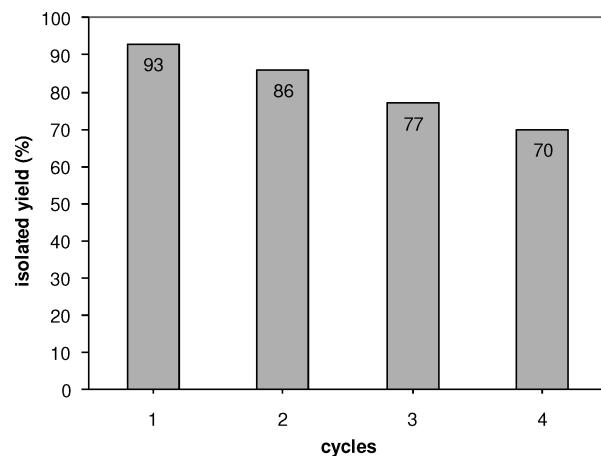
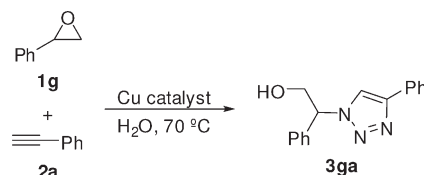


Figure 7. Recycling of the CuNPs/C in the synthesis of the triazole **3ga**.

Table 3. Three-Component Synthesis of β -Hydroxytriazoles from Epoxides Catalyzed by Different Copper Catalysts^a



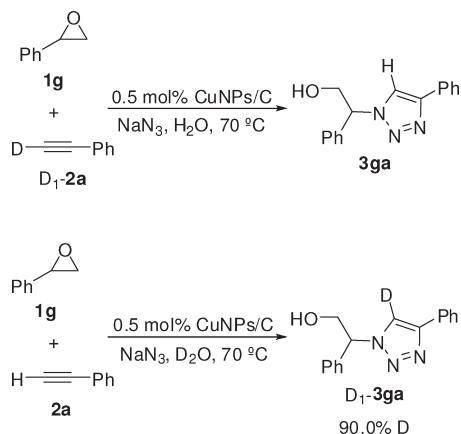
entry	catalyst	mol (%)	<i>t</i> (h)	yield (%) ^b
1	Cu	10	24	0
2	CuO	10	24	0
3	Cu ₂ O	10	24	50
4	CuCl	10	24	79
5	CuCl	1	24	77
6	CuCl ₂	10	24	64
7	CuCl ₂	1	24	20
8	CuNPs/C	0.5	8	93

^a Reaction conditions: **1g** (1 mmol), **2a** (1 mmol), NaN₃ (1.1 mmol), catalyst in H₂O at 70 °C. ^b Yield determined by ^1H NMR of the reaction crude.

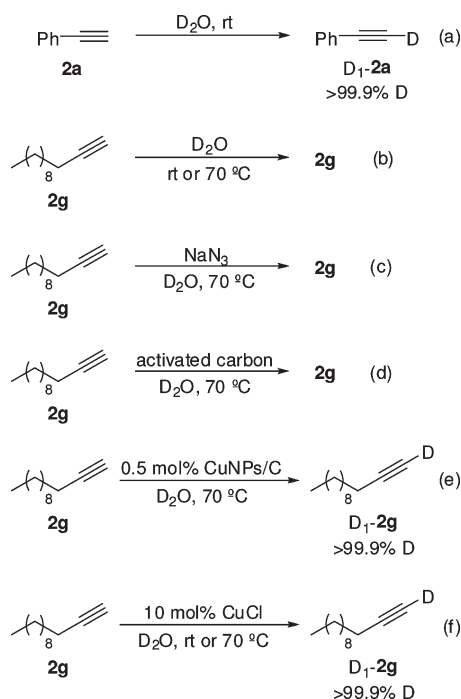
cycloaddition of benzyl azide and phenylacetylene in acetone under continuous flow conditions (170 °C, 20 bar, 1.5 mL min⁻¹).²⁸

Comparison with Other Catalysts. We work on the principle that any laboratory-made catalyst should be more efficient than commercially available catalysts used for the same purpose. Otherwise, it is difficult to economically justify the time, materials, and human resources employed during its preparation. Taking into account this premise, we undertook a comparative study on the reactivity of the CuNPs/C with different commercially available copper sources (Table 3). The standard conditions were applied to the reaction of styrene oxide (**1g**), sodium azide, and phenylacetylene (**2a**) at different catalyst loading. Copper metal and CuO were inactive (Table 3, entries 1 and 2, respectively), whereas Cu₂O gave rise to the expected triazole **3ga** in 50% yield (Table 3, entry 3). CuCl was the best of the commercial catalysts, albeit prolonged heating was necessary and the conversion was not as high as desirable (Table 3, entries 4 and 5). The conversion dropped for CuCl₂, especially when reducing

Scheme 7. Deuterium-Labeling Experiments in the CuNPs/C-Catalyzed Multicomponent Synthesis of β -Hydroxytriazole 3ga



Scheme 8. Deuteration Experiments in the Ionization of Terminal Alkynes 2a and 2g³⁶



the catalyst loading to 1 mol % (Table 3, entries 6 and 7). Therefore, the nanosized character of our catalyst seems to play a decisive role in its high performance (Table 3, entry 8). Very recently, it has been disclosed that defect sites on CuNPs can induce intense dissociation of water to form atomic oxygen, which might somehow participate in the redox mechanism of the reaction.²⁹ This fact, together with the large surface-to-volume ratio of the nanocatalyst and its distribution on the support, could account for the behavior of the CuNPs/C when compared with the commercial bulk catalysts.

Some Mechanistic Aspects. The general mechanism for the CuAAC has been a subject of intense debate.³⁰ The principal discussion arises from whether copper acetylides or copper

π -complexes are the real intermediates. On the other hand, although the formation a molecular copper(I) triazolide complex has been often postulated, only Straub et al. isolated this type of complex as a direct evidence for the existence of such structures as intermediates in the click reaction.^{30d} Final protonolysis of this type of intermediate would render the triazole product. Recently, we have experimentally demonstrated (based on different observations, specific reactions, and deuteration experiments) that copper(I) acetylides are the true intermediate species in the CuAAC involving unsupported CuNPs in the presence of triethylamine and THF as solvent.^{20b} To the best of our knowledge, however, this kind of research has been tackled neither for supported CuNPs nor for the multicomponent synthesis of triazoles from epoxides. In order to gain an insight into the mechanism of the title reaction, we carried out two deuteration experiments with styrene oxide (**1g**) and phenylacetylene (**2a**) (Scheme 7): (a) the reaction with deuterated phenylacetylene **2a-d₁** afforded the nondeuterated triazole **3ga**; (b) the reaction with nondeuterated phenylacetylene (**2a**) in D₂O led to triazole **3ga-d₁** with 90% deuterium incorporation. The participation of copper π -complexes would yield **3ga-d₁** in experiment (a) because the C_{sp}-deuterium bond would not dissociate in any step of the catalytic cycle. Therefore, these results suggest that both copper(I) phenylacetylide and the corresponding copper(I) β -hydroxytriazolide are the true intermediates in this methodology.³¹

Another aspect which remains unclear in the CuAAC is how the copper(I) acetylide is generated. We demonstrated that the formation of phenylacetylide was favored when triethylamine was present in an organic solvent, such as THF.^{20b} In aqueous solvents, however, the scenario is different and requires a thorough survey. In a recent mechanistic study,^{30g} it was invoked that sodium ascorbate functions as a base to deprotonate the terminal alkyne in a 1:1 *t*-BuOH/H₂O solvent mixture. The ionization constant values, however, do not seem to support this assertion as, if the case, ascorbate (pK_a = 4.04)³² should deprotonate water (pK_a = 13.995)³² rather than phenylacetylene (pK_a = 20.0).³³ Since our catalytic system is simply composed of CuNPs/C and water, with no base, a series of labeling experiments were conducted in order to study how feasible the ionization of terminal alkynes in water was (Scheme 8). It was very interesting to prove that, despite the Δ pK_a between phenylacetylene and water, ionization of phenylacetylene in D₂O readily occurred at room temperature with quantitative incorporation of deuterium (Scheme 8, eq a). This method of preparation of deuteriophenylacetylene (**2a-d₁**) is much more convenient than the classical one through the corresponding Grignard derivative.³⁴ The less acidic dodec-1-yne (**2g**) was not as prone to ionization as phenylacetylene either at room temperature or at 70 °C (Scheme 8, eq b). Control experiments with the different components of our catalytic system brought to light that neither sodium azide nor the support exerted any ionization effect on **2g** (Scheme 8, eqs c and d). We were delighted to observe quantitative incorporation of deuterium in the presence of the CuNPs (Scheme 8, eq e). Furthermore, the same outcome was obtained with commercial copper(I) chloride, with the concomitant formation of a yellow solid that could be ascribed to the respective copper(I) acetylide (Scheme 8, eq f). This solid was not observed in experiment (e) (Scheme 8) due to the lower amount of copper present in a black suspension and/or to the fact that the copper acetylide remains anchored to the heterogeneous catalyst. In view of these results, it seems reasonable to propose that, in the absence of base, CuNPs enhance the acidity of the

terminal alkyne in water, by coordination to the carbon–carbon triple bond,³⁵ enabling the formation of the corresponding copper(I) acetylide. This finding highlights the double role that CuNPs can play in the base-free CuAAC and, in particular, in the multi-component synthesis of β -hydroxytriazoles from epoxides.

CONCLUSION

We have demonstrated for the first time that copper nanoparticles can catalyze the multicomponent synthesis of triazoles from epoxides. A wide range of β -hydroxytriazoles have been synthesized from epoxides, sodium azide, and terminal alkynes in water with CuNPs/C as catalyst at low metal loading (0.5 mol %). The methodology developed is regioselective with respect to both the azidolysis of the epoxide and the 1,3-dipolar cycloaddition as follows: (a) monoalkyl-substituted oxiranes give rise to secondary β -hydroxytriazoles; (b) an S_N2' mechanism governs the regiochemistry for vinyl epoxides; (c) monoaryl-substituted oxiranes lead to primary β -hydroxytriazoles with inversion of the configuration; and (d) 1,4-disubstituted triazoles are solely formed. The regio- and stereochemistry have been unequivocally established on the basis of X-ray crystallographic analysis. Moreover, we realized that three of the six publications dealing with this topic have mistakenly assigned the regiochemistry of the products. A simple ^1H NMR experiment in CD_3CN has been proposed to rapidly and reliably disclose the regiochemical outcome in this type of reaction. In addition, the catalyst could be recycled, with negligible leaching, and reused along four cycles, providing excellent-to-good yields of the product. Finally, deuteration experiments unveiled the double role played by the CuNPs (i.e., alkyne activation for the acetylide formation and catalysis for the 1,3-dipolar cycloaddition) as well as the very likely participation of copper(I) acetylides and triazolides as reaction intermediates.

EXPERIMENTAL SECTION

General: Anhydrous copper(II) chloride (97%, Aldrich), lithium powder (MEDALCHEMY S.L.), DTBB (4,4'-di-*tert*-butylbiphenyl, Aldrich), activated charcoal (Norit CA1, Aldrich), and sodium azide were commercially available. All of the starting materials, deuterated solvents, and other reagents were commercially available of the best grade and were used without further purification. THF was dried in a solvent purification system using an alumina column. Mesylation of (S)-**3ga** to give (S)-**8** was done following a standard procedure. Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 20 °C. Concentrations (*c*) are given in g/100 mL and [α] values are given in units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. NMR spectra were recorded at 300 or 400 MHz for ^1H NMR and 75 or 100 MHz for ^{13}C NMR; peak assignments were done on the basis of DEPT experiments, chemical shift estimation, and the information obtained from the X-ray crystallographic analysis; chemical shifts are given in (δ) parts per million and coupling constants (*J*) in hertz. Infrared analysis was performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1} . Mass spectra (EI) were obtained at 70 eV; and fragment ions in *m/z* with relative intensities (%) in parentheses. HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV. Column chromatography was performed using silica gel 60 of 40–60 μm (hexane/EtOAc as eluent). ^1H and ^{13}C NMR data were estimated with the ACD/Laboratories 6.0 program.

Typical Procedure for the Preparation of CuNPs/C: Anhydrous copper(II) chloride (135 mg, 1 mmol) was added to a suspension

of lithium (14 mg, 2 mmol) and 4,4'-di-*tert*-butylbiphenyl (DTBB, 27 mg, 0.1 mmol) in THF (2 mL) at room temperature under an argon atmosphere. The reaction mixture, which was initially dark green, rapidly changed to black, indicating that the suspension of CuNPs was formed. This suspension was diluted with THF (18 mL) followed by the addition of the activated carbon (1.28 g). The resulting mixture was stirred for 1 h at room temperature, filtered, and the solid successively washed with water (20 mL) and THF (20 mL) and dried under vacuum.

General Procedure for the CuNP/C-Catalyzed Synthesis of β -Hydroxytriazoles from Epoxides in Water: NaN_3 (72 mg, 1.1 mmol), the epoxide (1 mmol), and the alkyne (1 mmol) were added to a suspension of CuNPs/C (20 mg, 0.5 mol % Cu) in H_2O (2 mL). The reaction mixture was warmed to 70 °C and monitored by TLC until total conversion of the starting materials. Water (30 mL) was added to the resulting mixture, followed by extraction with EtOAc (3×10 mL). The collected organic phases were dried with anhydrous MgSO_4 , and the solvent was removed in vacuo to give the corresponding triazoles **3**, which did not require any further purification. Only triazoles (S)-**3ga** and (S,S')-**3ge** were submitted to column chromatography in order to get an accurate optical rotation.

1-(4-Phenyl-1H-1,2,3-triazol-1-yl)octan-2-ol³⁷ (3aa): White solid; R_f 0.55 (hexane/EtOAc, 3:2); mp 125.5–127.0 °C; ^1H NMR (300 MHz, CD_3CN) δ 8.12 (s, 1H), 7.85 (d, $^3J(\text{H,H}) = 7.8$ Hz, 2H; Ar–H), 7.44 (t, $^3J(\text{H,H}) = 7.8$ Hz, 2H; Ar–H), 7.34 (t, $^3J(\text{H,H}) = 7.8$ Hz, 1H; Ar–H), 4.43 (dd, $^2J(\text{H,H}) = 14.0$ Hz, $^3J(\text{H,H}) = 3.5$ Hz, 1H; CHHN), 4.27 (dd, $^2J(\text{H,H}) = 14.0$ Hz, $^3J(\text{H,H}) = 7.6$ Hz, 1H; CHHN), 4.00–3.88 (m, 1H; CHO), 3.47 (d, $^3J(\text{H,H}) = 5.4$ Hz, 1H; OH), 1.53–1.15 (m, 10H; $5 \times \text{CH}_2$), 0.88 (t, $^3J(\text{H,H}) = 6.6$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3CN) δ 147.4 (NCCH), 130.2 (ArC), 128.8, 128.1, 125.6 ($5 \times \text{ArCH}$), 121.1 (CHN), 70.5 (CHO), 56.2 (CH_2N), 34.4, 31.7, 29.1, 25.4, 23.0 [$(\text{CH}_2)_5$], 14.0 (CH_3); IR (neat) $\tilde{\nu}$ 693, 771, 828, 983, 1089, 1142, 1227, 1464, 1602, 2854, 2915, 3135, 3229; MS (70 eV) *m/z* (%) 273 (20) [M^+], 146 (33), 132 (25), 118 (13), 117 (100), 105 (10), 103 (18), 102 (32), 89 (10), 77 (10), 69 (24), 55 (18), 43 (15), 41 (13); HRMS (EI) *m/z* calcd for $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}$ 273.1841, found 273.1850.

1-(4-Phenyl-1H-1,2,3-triazol-1-yl)hex-5-en-2-ol (3ba): White solid; R_f 0.43 (hexane/EtOAc, 1:1); mp 104.9–107.9 °C; ^1H NMR (400 MHz, CD_3CN) δ 8.11 (s, 1H), 7.86 (d, $^3J(\text{H,H}) = 7.5$ Hz, 2H; Ar–H), 7.44 (t, $^3J(\text{H,H}) = 7.5$ Hz, 2H; Ar–H), 7.34 (t, $^3J(\text{H,H}) = 7.5$ Hz, 1H; Ar–H), 5.93–5.81 (m, 1H; $\text{CH}=\text{CH}_2$), 5.06 (dd, $^3J(\text{H,H}) = 12.9$ Hz, $^2J(\text{H,H}) = 1.2$ Hz, 1H; $\text{CHH}=\text{CH}$), 4.98 (dd, $^3J(\text{H,H}) = 7.8$ Hz, $^2J(\text{H,H}) = 1.2$ Hz, 1H; $\text{CHH}=\text{CH}$), 4.45 (dd, $^2J(\text{H,H}) = 14.0$ Hz, $^3J(\text{H,H}) = 3.6$ Hz, 1H; CHHN), 4.30 (dd, $^2J(\text{H,H}) = 14.0$, $^3J(\text{H,H}) = 7.6$ Hz, 1H; CHHN), 4.03–3.93 (m, 1H; CHO), 3.27 (d, $^3J(\text{H,H}) = 5.6$ Hz, 1H; OH), 2.30–2.10 (m, 4H; $2 \times \text{CH}_2$); ^{13}C NMR (100 MHz, CD_3CN) δ 147.7 (NCCH), 139.3 ($\text{CH}=\text{CH}_2$), 132.3 (ArC), 129.9, 128.8, 126.3 ($5 \times \text{ArCH}$), 122.6 (CHN), 115.4 ($\text{CH}_2=\text{CH}$), 70.2 (CHO), 56.8 (CH_2N), 34.3, 30.3 ($2 \times \text{CH}_2$); IR (neat) $\tilde{\nu}$ 693, 771, 832, 921, 983, 1097, 1227, 1443, 1472, 1639, 2919, 2939, 3143, 3241; MS (70 eV) *m/z* (%) 243 (20) [M^+], 214 (15), 158 (215), 156 (130), 146 (26), 132 (10), 130 (33), 118 (12), 117 (100), 105 (16), 104 (10), 103 (34), 102 (55), 91 (10), 90 (15), 89 (22); HRMS (EI) *m/z* calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}$ 243.1372, found 243.1350.

1-Phenoxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propan-2-ol^{14b} (3ca): Pale yellow solid; mp 125.0–127.0 °C; ^1H NMR (400 MHz, CD_3CN) δ 8.15 (s, 1H), 7.86 (d, $^3J(\text{H,H}) = 7.5$ Hz, 2H; Ar–H), 7.44 (td, $^3J(\text{H,H}) = 7.5$ Hz, $^4J(\text{H,H}) = 1.6$ Hz, 2H; Ar–H), 7.40–7.17 (m, 3H; Ar–H), 7.08–6.72 (m, 3H; Ar–H), 4.66 (dd, $^2J(\text{H,H}) = 14.1$ Hz, $^3J(\text{H,H}) = 3.8$ Hz, 1H; CHHN), 4.52 (dd, $^2J(\text{H,H}) = 14.1$, $^3J(\text{H,H}) = 7.6$ Hz, 1H; CHHN), 4.43–4.27 (m, 1H; CHO), 4.09–3.87 (m, 2H; CH_2O), 3.75 (d, $^3J(\text{H,H}) = 5.4$ Hz, 1H; OH); ^{13}C NMR (100 MHz, CD_3CN) δ 159.6 (NCCH), 147.8, 132.1 ($2 \times \text{ArC}$), 130.5, 129.9, 128.9, 126.3, 122.8, 122.0 ($10 \times \text{ArCH}$), 115.5 (NCCH), 70.1 (CH_2O), 69.5 (CHO), 53.9 (CH_2N).

(**E**)-2-Methyl-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)but-2-en-1-ol²⁶
 [(**E**)-**3da**]: Yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.74–7.66 (m, 3H; 2 × Ar–H, CHN), 7.35 (t, ³J(H,H) = 7.2 Hz, 2H; Ar–H), 7.31–7.23 (m, 1H; Ar–H), 5.70 (t, ³J(H,H) = 7.6 Hz, 1H; CH=CCH₃), 4.92 (d, ³J(H,H) = 7.2 Hz, 2H; CH₂N), 4.06 (br s, 2H; CH₂O), 1.67 (s, 3H; CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 147.5 (NCCH), 142.3 (CH₃C=CH), 130.2 (ArC), 128.6, 127.9, 125.4 (5 × ArCH), 119.4 (NCCH), 115.9 (CH=CCH₃), 66.5 (CH₂O), 47.4 (CH₂N), 13.7 (CH₃).

(**Z**)-2-Methyl-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)but-2-en-1-ol²⁶
 [(**Z**)-**3da**]: Yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.76 (s, 1H; CHN), 7.74–7.66 (m, 2H; Ar–H), 7.39–7.31 (m, 2H; Ar–H), 7.31–7.23 (m, 1H; Ar–H), 5.45 (t, ³J(H,H) = 7.5 Hz, 1H; CH=CCH₃), 5.01 (d, ³J(H,H) = 7.5 Hz, 2H; CH₂N), 4.26 (br s, 2H; CH₂O), 1.77 (s, 3H; CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 147.5 (NCCH), 142.5 (CH₃C=CH), 130.2 (ArC), 128.6, 127.9, 125.4 (5 × ArCH), 119.7, 119.2 (NCCH, CH=CCH₃), 60.9 (CH₂O), 47.2 (CH₂N), 21.5 (CH₃).

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)cyclohexanol^{13a,30e} (**3ea**):
 White solid; mp 167.8–171.8 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.58 (s, 1H; NCH=C), 7.85 (d, ³J(H,H) = 7.5 Hz, 2H; Ar–H), 7.45 (t, ³J(H,H) = 7.5 Hz, 2H; Ar–H), 7.32 (dt, ³J(H,H) = 7.5 Hz, ⁴J(H,H) = 1.2 Hz, 1H; Ar–H), 5.00 (d, ³J(H,H) = 5.8 Hz, 1H; OH), 4.24 (ddd, ³J(H,H) = 12.1 Hz, ³J(H,H) = 9.9 Hz, ³J(H,H) = 4.2 Hz, 1H; CH₂CHN), 3.85–3.65 (m, 1H; CHO), 2.13–1.11 (m, 8H; 4 × CH₂); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 145.6 (NCCH), 131.2 (ArC), 128.9, 127.6, 122.9 (5 × ArCH), 120.5 (NCCH), 71.3 (CHO), 66.0 (CHN), 34.7, 31.9, 24.4, 23.9 (4 × CH₂).

2-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol^{13a,c} (**3ga**):
 Pale yellow solid; *R*_f 0.63 (hexane/EtOAc, 3:7); mp 125.0–127.0 °C; ¹H NMR (300 MHz, CD₃CN) δ 8.26 (s, 1H; NCH=C), 7.86 (d, ³J(H,H) = 7.3 Hz, 2H; Ar–H), 7.44 (t, ³J(H,H) = 7.3 Hz, 2H; Ar–H), 7.40–7.31 (m, 6H; Ar–H), 5.80 (dd, ³J(H,H) = 8.7 Hz, ³J = 4.7 Hz, 1H; CHCH₂), 4.46–4.36, 4.21–4.12 (2 m, 2H; CH₂), 3.40 (t, ³J(H,H) = 6.5 Hz; 1H; OH); ¹³C NMR (75 MHz, CD₃CN) δ 147.8 (NCCH), 138.1, 131.9 (2 × ArC), 129.9, 129.8, 129.5, 128.9, 128.2, 126.4 (10 × ArCH), 121.6 (NCCH), 67.6 (CHCH₂), 64.7 (CH₂); IR (neat) $\tilde{\nu}$ 685, 700, 713, 757, 1026, 1050, 1079, 1148, 1212, 1361, 1436, 1457, 1497, 2939, 3032, 3087, 3123, 3478; MS (70 eV) *m/z* (%) 265 (22) [M⁺], 207 (14), 206 (86), 178 (17), 146 (10), 117 (30), 116 (100), 104 (42), 103 (40), 102 (17), 91 (17), 90 (11), 89 (27), 77 (26).

(**S**)-2-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol [(**S**)-**3ga**]: The same physical and spectroscopic data as described for racemic **3ga**; [α]_D²⁰ +14.5 (c 1.0, CHCl₃); HRMS (EI) *m/z* calcd for C₁₆H₁₅N₃O 265.1215, found 265.1213.

2-(4-Chlorophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol (**3ha**): White solid; *R*_f 0.65 (hexane/EtOAc, 3:7); mp 139.6–142.1 °C; ¹H NMR (300 MHz, CD₃CN) δ 8.21 (s, 1H; NCH=C), 7.8 (d, ³J(H,H) = 7.5 Hz, 2H; Ar–H), 7.46–7.27 (m, 7H; Ar–H), 5.76 (dd, ³J(H,H) = 9.0 Hz, ³J(H,H) = 3.0 Hz, 1H; CHCH₂), 4.39–4.27, 4.17–4.07 (2 m, 2H; CH₂), 3.38 (t, ³J(H,H) = 6.0 Hz, 1H; OH); ¹³C NMR (75 MHz, CD₃CN) δ 148.0 (NCCH), 137.0, 134.8, 131.9 (3 × ArC), 130.1, 129.8, 129.7, 129.0, 126.4 (9 × ArCH), 121.7 (NCCH), 66.8 (CHCH₂), 64.6 (CH₂); IR (neat) $\tilde{\nu}$ 691, 730, 764, 819, 1015, 1050, 1092, 1223, 1432, 1460, 1492, 2938, 3085, 3331; MS (70 eV) *m/z* (%): 301 (4) [M⁺ + 2], 299 (13) [M⁺], 242 (16), 240 (41), 138 (18), 137 (10), 117 (23), 116 (100), 102 (18), 91 (15), 89 (23); HRMS (EI) *m/z* calcd for C₁₆H₁₄ClN₃O 299.0825, found 299.0830.

(1*S**,2*R**)-1,2-Diphenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol (**3ia**): White solid; *R*_f 0.63 (hexane/EtOAc, 1:1); mp 209.0–212.0 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.96 (s, 1H; NCH=C), 7.87 (d, ³J(H,H) = 7.2 Hz, 2H; Ar–H), 7.49–7.39 (m, 4H; Ar–H), 7.37–7.30 (m, 3H; Ar–H), 7.25–7.17 (m, 6H; Ar–H), 6.04 (d, ³J(H,H) = 4.8 Hz, 1H; NCHCH), 5.97 (d, ³J(H,H) = 8.7 Hz, 1H; OH), 5.58 (dd, ³J(H,H) = 8.7 Hz, ³J(H,H) = 4.8 Hz, 1H; CHO); ¹³C

NMR (75 MHz, DMSO-*d*₆) δ 146.0 (NCCH), 141.6, 137.2, 130.9 (3 × ArC), 128.9, 128.4, 128.2, 128.0, 127.9, 127.8, 127.5, 127.2, 125.1 (15 × ArCH), 121.2 (NCCH), 74.3 (CHO), 70.5 (NCHCH); IR (neat) $\tilde{\nu}$ 697, 750, 771, 1048, 1207, 1231, 1435, 1455, 2854, 2923, 3029, 3082, 3429; MS (70 eV) *m/z* (%) 341 (0.3) [M⁺], 236 (15), 235 (85), 207 (20), 206 (100), 180 (11), 179 (12), 178 (21), 130 (10), 116 (16), 107 (10), 105 (20), 102 (23), 91 (10), 79 (15), 77 (28); HRMS (EI) *m/z* calcd for C₂₂H₁₉N₃O 341.1528, C₁₅H₁₃N₃ 235.1109, found 235.1136.

(1*S**,2*R**)-1,2-Diphenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol (**3ja**): White solid; *R*_f 0.68 (hexane/EtOAc, 1:1); mp 206.5–211.0 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.71 (s, 1H; NCH=C), 7.72 (d, ³J(H,H) = 8.5 Hz, 2H; Ar–H), 7.66 (d, ³J(H,H) = 8.5 Hz, 2H; Ar–H), 7.44–7.12 (m, 11H; Ar–H), 5.98 (d, ³J(H,H) = 4.8 Hz, 1H; NCHCH), 5.89 (d, ³J(H,H) = 9.0 Hz, 1H; OH), 5.54 (dd, ³J(H,H) = 9.0 Hz, ³J(H,H) = 4.8 Hz, 1H; CHO); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 146.3 (NCCH), 142.3, 137.9, 130.9 (3 × ArC), 129.2, 128.9, 128.6, 128.4, 128.2, 128.1, 127.9, 127.2, 125.3 (15 × ArCH), 121.1 (NCCH), 74.0 (CHO), 69.8 (NCHCH); IR (neat) $\tilde{\nu}$ 701, 746, 766, 1451, 2850, 2919, 3078, 3123, 3421; MS (70 eV) *m/z* (%) 341 (0.3) [M⁺], 236 (15), 235 (89), 207 (19), 206 (100), 179 (10), 178 (20), 130 (10), 116 (14), 107 (11), 105 (21), 102 (22), 79 (14), 77 (26); HRMS (EI) *m/z* calcd for C₂₂H₁₉N₃O 341.1528, C₁₅H₁₃N₃ 235.1109, found 235.1092.

2-(4-Hexyl-1*H*-1,2,3-triazol-1-yl)-2-phenylethanol^{13a} (**3gb**):
 Pale yellow solid; mp 64.2–66.3 °C; ¹H NMR (300 MHz, CD₃CN) δ 7.60 (s, 1H; NCH=C), 7.42–7.26 (m, 5H; Ar–H), 5.68 (dd, ³J(H,H) = 8.7 Hz, ³J(H,H) = 4.8 Hz, 1H; CHCH₂), 4.40–4.28, 4.15–4.03 (2 m, 2H; CH₂), 3.32 (t, ³J(H,H) = 5.9 Hz, 1H; OH), 2.53 (t, ³J(H,H) = 7.7 Hz, 2H; CH₂CN), 1.69–1.55 (m, 2H; CH₂), 1.37–1.23 (m, 6H; 3 × CH₂), 0.81 ppm (t, ³J(H,H) = 7.0 Hz, 3H; CH₃); ¹³C NMR (75 MHz, CD₃CN) δ 152.1 (NCCH), 137.8 (ArC), 129.7, 129.5, 128.4 (5 × ArCH), 121.3 (NCCH), 66.7 (CHCH₂), 65.3 (CH₂O), 35.1, 29.3, 28.9, 26.3, 22.4 (5 × CH₂), 13.9 (CH₃).

2-(4-Cyclohexyl-1*H*-1,2,3-triazol-1-yl)-2-phenylethanol (**3gc**): White solid; *R*_f 0.48 (hexane/EtOAc, 3:7); mp 128.2–131.8 °C; ¹H NMR (300 MHz, CD₃CN) δ 7.60 (s, 1H; NCH=C), 7.42–7.26 (m, 5H; Ar–H), 5.68 (dd, ³J(H,H) = 8.7 Hz, ³J(H,H) = 4.8 Hz, 1H; NCHCH₂), 4.40–4.28, 4.15–4.03 (2 m, 2H; CH₂O), 3.32 (t, ³J(H,H) = 5.9 Hz, 1H; OH), 2.77–2.65 (m, 1H; CH₂CHCH₂), 1.83–1.65 (m, 4H; 2 × CH₂CH₂CH), 1.46–1.34 (m, 4H; 2 × CH₂CH₂CH), 1.29–1.18 ppm [m, 2H; (CH₂)₂CH₂(CH₂)₂]. ¹³C NMR (75 MHz, CD₃CN) δ 153.4 (NCCH), 138.5 (ArC), 129.8, 129.4, 128.2 (5 × ArCH), 120.9 (NCCH), 65.0 (CH₂O), 64.7 (NCHCH₂), 36.1 (CH₂CHCH₂), 33.8, 26.9, 26.8 [(CH₂)₅]; IR (neat) $\tilde{\nu}$ 697, 756, 889, 1067, 1448, 2849, 2923, 3061, 3117, 3233; MS (70 eV) *m/z* (%) 271 (23) [M⁺], 213 (18), 212 (100), 149 (21), 130 (12), 123 (10), 122 (14), 121 (64), 109 (12), 104 (37), 103 (72), 95 (14), 94 (12), 93 (12), 91 (58), 81 (17), 80 (39), 79 (27), 78 (10), 77 (36), 69 (10), 67 (27), 65 (11), 56 (13), 55 (18), 43 (13), 41 (21); HRMS (EI) *m/z* calcd for C₁₆H₂₁N₃O 271.1685, found 271.1685.

2-Phenyl-2-[4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]ethanol (**3gd**): White solid; *R*_f 0.26 (hexane/EtOAc, 1:9); mp 112.7–115.3 °C; ¹H NMR (300 MHz, CD₃CN) δ 8.52–8.47 (m, 1H; Ar–H), 8.35 (s, 1H; NCH=CN), 8.02 (dt, ³J(H,H) = 7.8 Hz, ⁴J(H,H) = 1.1 Hz, 1H; Ar–H), 7.76 (td, ³J(H,H) = 7.8 Hz, ⁴J(H,H) = 1.8 Hz, 1H; Ar–H), 7.34–7.27 (m, 4H; Ar–H), 7.21 (ddd, ³J(H,H) = 7.5 Hz, ³J(H,H) = 5.0 Hz, ⁴J(H,H) = 1.2 Hz, 1H; Ar–H), 5.77 (dd, ³J(H,H) = 8.7 Hz, ³J(H,H) = 4.7 Hz, 1H; CHCH₂), 4.43–4.32, 4.17–4.06 (2 m, 2H; CH₂), 3.44 ppm (t, ³J(H,H) = 6.0 Hz, 1H; OH); ¹³C NMR (75 MHz, CD₃CN) δ 151.4 (NCCHN), 150.6 (ArCH), 148.8, 138.0 (2 × ArC), 137.9, 129.8, 129.5, 128.2, 123.8, 123.5 (8 × ArCH), 120.6 (NCCHN), 67.7 (NCHCH₂), 64.6 ppm (CH₂); IR (neat) $\tilde{\nu}$ 704, 727, 783, 846, 1004, 1057, 1077, 1084, 1200, 1209, 1235, 1246, 1310, 1422, 1475, 1602, 2845, 2906, 3134; MS (70 eV) *m/z* (%) 266 (15) [M⁺], 235 (21), 208 (17), 207 (100), 180 (28), 118 (34), 119 (29), 105 (13), 104 (36), 103 (44),

91 (25), 90 (12), 79 (13), 78 (29), 77 (28), 51 (13); HRMS (EI) m/z calcd for $C_{15}H_{14}N_4O$ 266.1168, found 266.1164.

(2S,2S')-2,2'-[4,4'-(1,3-Phenylene)bis(1H-1,2,3-triazole-4,1-diyl)]bis(2-phenylethanol) [(S,S')-3ge]: White solid; R_f 0.35 (hexane/EtOAc, 1:4); mp 74.5–79.1 °C; $[\alpha]_D^{20} +10.6$ (c 1.0, $CHCl_3$); 1H NMR (300 MHz, CD_3CN) δ 8.33 (s, 2H, 2 \times NCH=C), 8.31 (t, $^4J(H,H) = 1.8$ Hz, 1H; Ar–H), 7.81 (dd, $^3J(H,H) = 7.8$ Hz, $^4J(H,H) = 1.8$ Hz, 2H; Ar–H), 7.48 (t, $^3J(H,H) = 7.8$ Hz, 1H; Ar–H), 7.40–7.33 (m, 10H; Ar–H), 5.82 (dd, $^3J(H,H) = 8.7$ Hz, $^3J(H,H) = 4.5$ Hz, 2H; 2 \times $CHCH_2$), 4.48–4.38, 4.22–4.13 (2 m, 4H; 2 \times CH_2), 3.54 (t, $^3J(H,H) = 5.8$ Hz, 2H; 2 \times OH); ^{13}C NMR (75 MHz, CD_3CN) δ 147.6 (2 \times NCCH), 138.0, 132.6 (4 \times ArC), 130.5, 129.8, 129.5, 128.2, 125.8, 123.3 (14 \times ArCH), 121.9 (2 \times NCCH), 67.7 (2 \times $CHCH_2$), 64.7 (2 \times CH_2); IR (neat) $\tilde{\nu}$ 695, 759, 792, 1052, 1230, 1372, 1455, 2924, 3133, 3309; MS (70 eV) m/z (%) 452 (23) [M^+], 394 (13), 347 (12), 304 (18), 303 (65), 291 (12), 286 (35), 273 (11), 258 (11), 257 (22), 245 (26), 244 (19), 243 (12), 230 (12), 217 (12), 216 (11), 202 (10), 184 (38), 171 (30), 155 (23), 154 (20), 140 (13), 128 (13), 121 (27), 115 (10), 104 (27), 103 (100), 91 (29), 89 (10), 79 (14), 77 (49); HRMS (EI) m/z calcd for $C_{26}H_{24}N_6O_2$ 452.1961, found 452.1958.

1-(4-n-Butyl-1H-1,2,3-triazol-1-yl)hex-5-en-2-ol (3bf): Yellow oil; R_f 0.61 (hexane/EtOAc, 1:4); 1H NMR (300 MHz, CD_3CN) δ 7.40 (s, 1H; NCH=C), 5.72 (ddt, $^3J(H,H) = 17.2$ Hz, $^3J(H,H) = 10.3$ Hz, $^3J(H,H) = 6.6$ Hz, 1H; $CH=CH_2$), 4.92 (dq, $^3J(H,H) = 17.1$, $^2J(H,H) = 4.7$ Hz, 1H; $CHH=CH$), 4.80 (dq, $^3J(H,H) = 10.3$ Hz, $^3J(H,H) = 10.4$ Hz, $^2J(H,H) = 4.7$ Hz, 1H; $CHH=CH$), 4.22 (dd, $^2J(H,H) = 14.0$ Hz, $^3J(H,H) = 3.6$ Hz, 1H; $CHHN$), 4.08 (dd, $^2J(H,H) = 14.0$ Hz, $^3J(H,H) = 7.4$ Hz, 1H; $CHHN$), 3.85–3.73 (m, 1H; CHO), 3.24 (d, $^3J(H,H) = 5.4$ Hz, 1H; OH), 2.53 (t, $^3J(H,H) = 7.7$ Hz, 2H, CH_2CN), 2.13–1.93 (m, 2H; $CH_2CH=CH_2$), 1.72–1.56 (m, 6H; CH_2CH_2CHO , $CH_2CH_2CH_3$), 0.81 (t, $^3J(H,H) = 7.2$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3CN) δ 148.4 (NCCH), 139.3 ($CH=CH_2$), 123.2 (NCCH), 115.3 ($CH_2=CH$), 70.3 (CHO), 56.4 (CH_2N), 34.4, 32.4, 30.2, 25.8, 22.9 (5 \times CH_2), 14.1 (CH_3); IR (neat) $\tilde{\nu}$ 910, 994, 1053, 1133, 1219, 1456, 1551, 1640, 2859, 2931, 3077, 3289; MS (70 eV) m/z (%) 223 (11) [M^+], 181 (10), 168 (11), 166 (11), 152 (23), 139 (17), 138 (33), 126 (27), 110 (61), 98 (23), 97 (11), 96 (23), 95 (11), 94 (10), 83 (18), 82 (36), 81 (82), 80 (21), 79 (22), 69 (20), 68 (53), 67 (27), 57 (28), 56 (17), 55 (63), 54 (40), 53 (19), 44 (17), 43 (100), 42 (17), 41 (91); HRMS (EI) m/z calcd for $C_{12}H_{21}N_3O$ 223.1685, found 223.1683.

5-Deuterio-2-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanol (90% D) (3ga-d₁): Yellow solid; R_f 0.66 (hexane/EtOAc, 1:4); mp 122.4–124.4 °C; 1H NMR (300 MHz, CD_3CN) δ 7.88–7.83 (m, 2H; Ar–H), 7.48–7.30 (m, 8H; Ar–H), 5.80 (dd, $^3J(H,H) = 8.7$ Hz, $^3J(H,H) = 4.8$ Hz, 1H; $CHCH_2$), 4.47–4.36, 4.21–4.11 (2 m, 2H; CH_2), 3.43 (t, $^3J(H,H) = 6.2$ Hz, 1H; OH); ^{13}C NMR (75 MHz, CD_3CN) δ 147.8 (NCCH), 138.1, 132.0 (2 \times ArC), 129.9, 129.8, 129.5, 128.9, 128.2, 126.4 (10 \times CH), 121.6 (t, $^1J(C,D) = 58.1$ Hz, CD), 67.7 ($CHCH_2$), 64.7 (CH_2); IR (neat) $\tilde{\nu}$ 692, 724, 754, 768, 776, 1024, 1051, 1220, 1455, 1475, 1606, 3029, 3060, 3301; MS (70 eV) m/z (%): 266 (28) [M^+], 208 (14), 207 (81), 206 (11), 179 (13), 147 (11), 118 (28), 117 (100), 116 (11), 105 (10), 104 (55), 103 (52), 91 (23), 90 (12), 89 (23), 77 (31), 51 (10); HRMS (EI) m/z calcd for $C_{16}H_{14}DN_3O$ 266.1278, found 266.1279.

(S)-2-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl methanesulfonate [(S)-8]: White solid; R_f 0.51 (hexane/EtOAc, 1:1); mp 184.1–186.1 °C; $[\alpha]_D^{20} -7.2$ (c 0.4, acetone); 1H NMR (300 MHz, CD_3CN) δ 8.25 (s, 1H; NCH=C), 7.89–7.81 (m, 2H; Ar–H), 7.49–7.31 (m, 8H; Ar–H), 6.11 (dd, $^3J(H,H) = 9.6$, $^3J(H,H) = 4.8$ Hz, 1H; $CHCH_2$), 5.17 (dd, $^2J(H,H) = 11.0$ Hz, $^3J(H,H) = 9.3$ Hz, 1H; $CHHO$), 4.84 (dd, $^2J(H,H) = 11.0$ Hz, $^3J(H,H) = 4.8$ Hz, 1H; $CHHO$), 2.99 (s, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3CN) δ 148.9 (NCCH), 136.5, 132.1 (2 \times ArC), 130.8, 130.6, 130.4, 129.7, 128.9, 127.0 (10 \times ArCH),

122.4 (NCCH), 71.2 ($CHCH_2$), 64.7 (CH_2), 38.1 (CH_3); IR (neat) $\tilde{\nu}$ 694, 762, 813, 881, 966, 993, 1169, 1182, 1343, 2922, 3023; MS (70 eV) m/z (%) 343 (6) [M^+], 236 (13), 206 (16), 117 (11), 116 (59), 105 (13), 104 (100), 103 (27), 102 (11), 91 (26), 89 (16), 80 (14), 78 (12); HRMS (EI) m/z calcd for $C_{17}H_{17}N_3O_3S$ 343.0991, $C_9H_{11}O_3S$ 199.0429, found 199.0441.

1-Deuteriododec-1-yne (2g-d₁): Yellow liquid; R_f 0.83 (hexane); 1H NMR (400 MHz, $CDCl_3$) δ 2.18 (t, $^3J(H,H) = 7.2$ Hz, 2H; CH_2C), 1.52 (quintet, $^3J(H,H) = 7.1$ Hz, 2H; CH_2CH_2C), 1.43–1.34 (m, 2H; $CH_2CH_2CH_2C$), 1.32–1.19 [m, 12H; (CH_2)₆CH₃], 0.88 (t, $^3J(H,H) = 6.8$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, CCl_3D) δ 84.3 (t, $^2J(C,D) = 27.8$ Hz, $C\equiv CD$), 67.8 (t, $^1J(C,D) = 149.4$ Hz, $DC\equiv C$), 31.9, 29.6, 29.5, 29.3, 29.1, 28.8, 28.5, 22.7, 18.4 (9 \times CH_2), 14.1 (CH_3); IR (film) $\tilde{\nu}$ 721, 1464, 2597, 2854, 2923; MS (70 eV) m/z (%) 167 (0.1) [M^+], 110 (13), 97 (16), 96 (46), 95 (12), 83 (43), 82 (100), 81 (38), 80 (15), 70 (11), 69 (39), 68 (48), 67 (48), 57 (16), 56 (19), 55 (48), 54 (17); HRMS (EI) m/z calcd for $C_{12}H_{21}D$ 167.1784, $C_{11}H_{18}D$ 152.1550, found 152.1535.

ASSOCIATED CONTENT

S Supporting Information. 1H and ^{13}C NMR spectra of triazoles 3; CIF files of the X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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DEDICATION

[§]Dedicated to Professor Francisco Palacios on the occasion of his 60th birthday.

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