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ORIGINAL PAPER

1,3-Dipolar cycloaddition of benzyl azide to two highly functionalized alkynes

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Abstract Benzyl azide undergoes [3 + 2] cycloaddition when reacted with 3,3,4,4-tetraethoxybut-1-yne, a ketal, and the corresponding ketone, 1,1-diethoxybut-3-yn-2-one, in the presence of a Cu(I) salt in various solvents. The outcome is sensitive to the structure of the alkyne and the nature of the metal salt. Both alkynes give the corresponding 1,4-disubstituted 1,2,3-triazoles in up to 70% yield, but the ketone also affords a minor amount of the 1,5-disubstituted analogue. When CuI is used as catalyst, the ketal in addition furnishes some 1-benzyl-5-iodo-4-(1,1,2,2-tetraethoxyethyl)-1,2,3-triazole. On the other hand, when the reaction was carried out under Ru(II) catalysis, no 1,2,3-triazole formation was observed for any of the substrates; the ketal did not react at all, whereas the ketone underwent cyclotrimerization and gave 1,3,5-tris(2,2-diethoxyacetyl)benzene in 60% yield. No reaction occurred when the magnesium acetylide of 3,3,4,4-tetraethoxybut-1-yne was reacted with benzyl azide.

Keywords 1,2,3-Triazoles · Selective cycloaddition · Terminal alkynes · Trimerization

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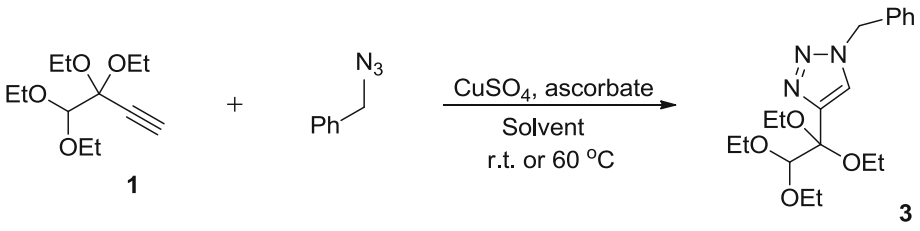
Introduction

1,2,3-Triazoles exhibit noteworthy chemical properties and biological activities, and such compounds have therefore been used in organic synthesis and applied in a variety of medicinal and industrial products for some time [1, 2]. Interestingly, the number of successful applications has increased in recent years [3–8], a development that is related to the flat structure of the triazole ring and its reluctance to react under a range of conditions [9]. This inspired us to incorporate disubstituted 1,2,3-triazole moieties, preferably with at least one polar substituent, in scaffolds to be applied in peptidomimetic studies.

Several fairly general methods are available for the synthesis of 1,2,3-triazoles [10–15], but the most versatile one is definitely the thermally induced addition of organic azides to alkynes [16–23], one of several concerted 1,3-dipolar cycloadditions studied extensively by Huisgen et al. [24–27]. This reaction exhibits a high degree of selectivity in the sense that when terminal alkynes and organic azides are used, the 1,4-disubstituted adduct predominates completely or almost completely over the corresponding 1,5-disubstituted analogue. However, several notable exceptions to this rule are known [28–30]. Thus, when Sheehan and Robinson reacted 3-phenylprop-2-ynal with phenyl azide, an approximately 5:2 mixture of the 1,5- and 1,4-diphenyl-1,2,3-triazoles was obtained in 90% total yield [28]. Furthermore, Huisgen et al. found that the reaction of methyl propynoate with the same azide under similar conditions gave the expected 1,4- and 1,5-disubstituted triazoles in a 7:1 ratio [31].

From these observations it is not straightforward to predict what would happen when we set out to make triazoles by reacting benzyl azide with two highly functionalized polar terminal alkynes, the ketal 3,3,4,4-

Scheme 1



tetraethoxybut-1-yne (**1**) [32–37] and the corresponding ketone 1,1-diethoxybut-3-yn-2-one (**2**) [33–37]. However, on the basis of discoveries of Meldal et al. [18–20] and Sharpless et al. [21–23], and results subsequently published by a large number of research groups [38–43], we expected that the addition of benzyl azide to **1** and **2** in the presence of a Cu(I) salt would result in a faster reaction, less by-product formation, and regioselective formation of 1,4-disubstituted 1,2,3-triazoles, whereas reactions carried out in the presence of [Cp*RuCl]-based complexes should furnish the corresponding 1,5-disubstituted analogues only [44–49]. As the results presented here show, these expectations were not really met.

Results and discussion

Copper-catalyzed reactions

The addition of benzyl azide to ketal **1** was first studied. Experiments were first carried out in acetonitrile, DMF, and DMSO in the absence of Cu(I) at temperatures ranging from 60 to 110°C, but cycloadducts were neither isolated nor detected. To our surprise the result was the same when reactions were performed in aqueous *tert*-butyl alcohol containing Cu(I) generated in situ from copper(II) sulfate and sodium ascorbate, reaction conditions commonly used to obtain triazoles by azide addition [10–15, 21–23, 44–47]. The outcome was the same when the temperature was elevated to 60°C and the solvent was changed to aqueous DMF. However, when dry acetonitrile or mixtures of water with chloroform, dichloromethane, or DMSO were used as solvents and $CuSO_4$/sodium ascorbate was applied as catalyst, triazole formation took place. The only product formed was 1-benzyl-4-(1,1,2,2-tetraethoxyethyl)-1*H*-1,2,3-triazole (**3**) (Scheme 1) as substantiated by spectroscopic data and an X-ray crystallography structure determination (Fig. 1), which revealed that the bond

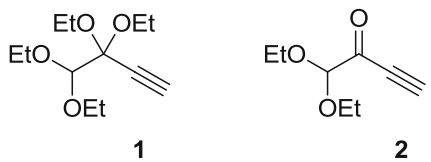


Fig. 1 The structures of the acetylenes investigated

lengths and angles were close to literature values for similar compounds [50]. Irrespective of the conditions the yield was moderate (Table 1; Fig. 2).

An alternative cuprous salt that is often used to facilitate azide cycloaddition to alkynes is copper(I) iodide, which is applied in the presence or absence of a base [51]. When this salt was employed instead of $CuSO_4$/sodium ascorbate, the yield of **3** from **1** generally increased under most conditions, although the best yield (71%, see Table 2) was only slightly higher than the best yield obtained with the $CuSO_4$-ascorbate catalyst (69%, see Table 1). A noteworthy feature is the consistent formation of an additional product, 1-benzyl-5-iodo-4-(1,1,2,2-tetraethoxyethyl)-1*H*-1,2,3-triazole (**4**, Scheme 2). The yield of **4** was low when CuI was used in the absence of base (<7%, see Table 2), but when performed in the presence of diisopropylethylamine (DIPEA) and either *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) [52], triazole **3** was not formed, whereas

Table 1 Isolated yield of triazole **3**, prepared by $CuSO_4$/ascorbate-catalyzed addition of benzyl azide to alkyne **1** for 48 h at two temperatures

Solvent	Room temperature/%	60°C
CH_3CN	44	58%
H_2O/CH_3Cl (1:3)	41	51%
H_2O/DMSO (1:3)	61	69%
H_2O/CH_2Cl_2 (1:3)	55	[a]

[a] The reaction was not run since dichloromethane boils below 60°C

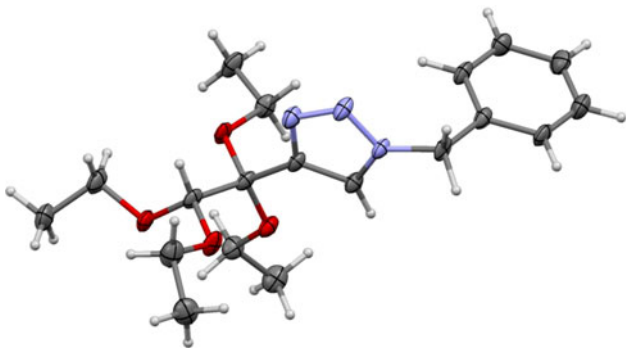


Fig. 2 Crystal structure of compound **3**; anisotropic displacement parameters are given at the 50% level

Table 2 Isolated yields of triazole **3** and 5-iodotriazole **4**, prepared by CuI-catalyzed addition of benzyl azide to alkyne **1**

Solvent	Room temperature		60°C	
	3	**4**	**3**	**4**
CH_3CN	68%	6%	71%	5%
H_2O/DMSO (1:3)	69%	3%	61%	3%
H_2O/DMF (1:3)	42%	5%	62%	7%

iodide **4** was obtained in a respectable yield (72 and 62% yield, respectively, Scheme 2).

Copper-catalyzed addition of benzyl azide to ketoalkyne **2** was then performed. On the basis of a paper published by Girard et al. [53], we expected regiospecific formation of the analogous 1,4-disubstituted triazole, and this was observed when $CuSO_4$/sodium ascorbate was used as catalyst (Table 3). The only product obtained was 1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2,2-diethoxyethanone (**5**), which was also made in 90% yield by independent synthesis (Scheme 3).

When addition of benzyl azide to ketone **2** was carried out under CuI catalysis, the outcome of the reaction changed somewhat. 1,4-Disubstituted triazole **5** was still the predominant product, but in addition the corresponding 1,5-disubstituted isomer, viz. 1-(1-benzyl-1*H*-1,2,3-triazol-5-yl)-2,2-diethoxyethanone (**6**), was obtained (Scheme 4) in up to 10% yield (Table 3, entry 8). Furthermore, unlike ketal **1**, the corresponding ketone **2** appeared not to furnish any iodotriazole, and by analyzing the crude reaction mixture with respect to the iodoketo corresponding to iodoketal **4**, viz. 1-(1-benzyl-5-iodo-1*H*-1,2,3-triazol-4-yl)-2,2-diethoxyethanone (**7**) prepared by deketalization of **4** (Scheme 5), it was proved that iodide **7** was not formed under the conditions that furnished **4** from **1**.

Scheme 2

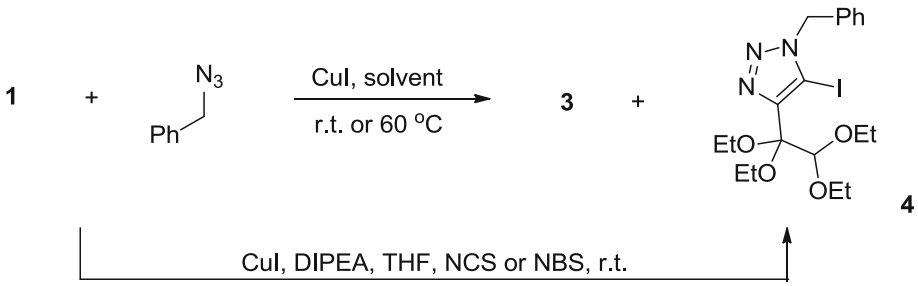
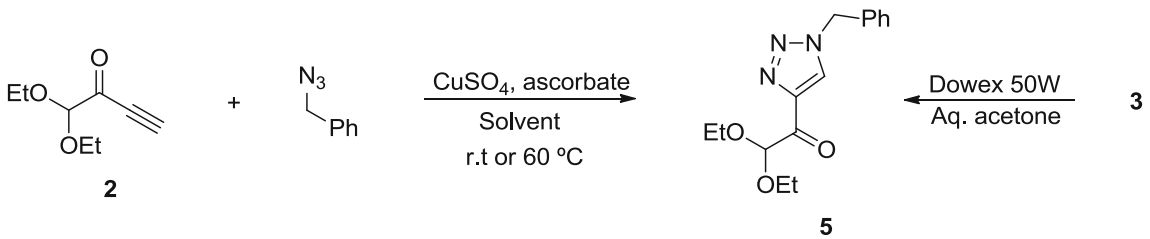


Table 3 Isolated yields of triazoles **5** and **6**, prepared by Cu(I)-catalyzed addition of benzyl azide to alkyne **2**

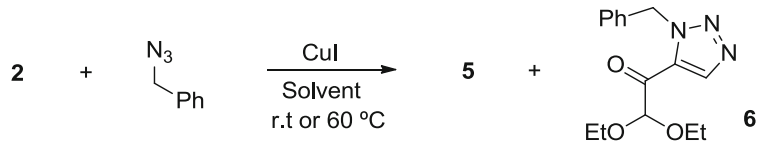
Entry	Catalyst	Solvent[a]	Room temperature		60°C	
			5	**6**	**5**	**6**
1	$CuSO_4$/ascorbate	CH_3CN	59%		61%	
2		H_2O/DMSO	61%		69%	
3		H_2O/DMF	51%		60%	
4		H_2O/CH_3Cl	48%		52%	
5		H_2O/CH_2C_{12}	70%		[b]	
6	CuI	CH_3CN	61%	3%	70%	3%
7		H_2O/DMSO	54%	3%	61%	2%
8		H_2O/DMF	52%	10%	61%	4%
9		H_2O/CH_3Cl	58%	3%	54%	5%
10		H_2O/CH_2C_{12}	59%	0%	[b]	

[a] The aqueous solvents contain 25% water by volume

[b] The reaction was not run since dichloromethane boils below 60°C



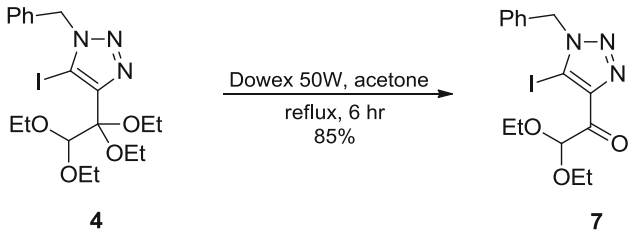
Scheme 3



Scheme 4

Table 4 Outcome of syntheses performed to obtain the 1,5-disubstituted analogues of triazoles **3** and **5**

Entry	Alkyne	Reaction conditions	Isolated compounds (yield)
1	**1**	Cp*RuCl(PPh_3)$_2$, THF 65°C, 24 h	**1** (95%) and BnN_3 (96%)
2		Cp*RuCl(PPh_3)$_2$, C_6H_6 80°C, 24 h	**1** (94%) and BnN_3 (93%)
3	**2**	Cp*RuCl(PPh_3)$_2$, THF 65°C, 4 h	**9** (55%) and BnN_3 (91%)
4		Cp*RuCl(PPh_3)$_2$, C_6H_6 80°C, 3 h	**9** (60%) and BnN_3 (88%)



Scheme 5

Ruthenium-catalyzed cycloadditions

The formation of 1,5-disubstituted triazole **6** as a by-product when alkyne **2** was reacted in the presence of CuI indicates that **6** might be formed in higher yields if the reaction is carried out under conditions that are known to favor 1,5-disubstituted 1,2,3-triazoles over 1,4-disubstituted 1,2,3-triazole. In order to achieve this the literature suggests that Cu(I) salts should be replaced by a ruthenium complex, preferably bis(triphenylphosphine)pentamethylcyclopentadienylruthenium(II) chloride (Cp*RuCl(PPh_3)$_2$) in an adequate solvent [48, 49]. After having reproduced the reaction between benzyl azide and phenylacetylene under Cp*RuCl(PPh_3)$_2$ catalysis several times and obtained 1-benzyl-5-phenyl-1,2,3-triazole (**8**) as the only product in consistently better than 85% yield, ketal **1** was reacted with benzyl azide under the same conditions. To our surprise no reaction occurred as judged from chromatographic and spectroscopic analyses, and when the reaction mixture was worked up in the usual way, both reactants were recovered in high yield (Table 4).

However, when the substrate was changed to ketone **2**, TLC analysis showed that a reaction took place. Subsequent workup revealed that all of **2** had been consumed and been converted to one product, which appeared not to be a triazole, but 1,3,5-tris(2,2-diethoxyacetyl)benzene (**9**, Fig. 3), which was obtained in 55 and 60% yield at 65 and 80°C, respectively (Table 4, entries 3 and 4). This trimer of **2** has previously been obtained by treating **2** with aqueous solutions of sodium bicarbonate [54]. The formation of **9** is not really surprising because ruthenium complexes have been proved to facilitate cyclotrimerization of electron-deficient alkynes [55, 56]. The mechanism for the reaction has not been unraveled, but a suggestion is depicted in Fig. 4.

The different behavior of **1** and **2** toward Cp*RuCl(PPh_3)$_2$ is quite indicative of the importance of the polar moiety next to the triple bond in the two alkynes. The inability of **1** to react might be due to deactivation of the catalyst by some sort of complexation involving some or all of the four oxygen atoms in the tetraethoxyethyl moiety. Alkyne **2**, on the other hand, with its conjugated ynone structural motif, has been rendered so much more prone to undergo Michael reactions that azide addition to the triple bond cannot compete. It is therefore not surprising that a thorough search of the literature reveals no publications describing 1,2,3-triazole formation by azide addition to electron-deficient carbon-carbon triple bonds similar to that found in **2**.

Regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles from terminal alkynes has also been achieved by reacting bromomagnesium acetylides with organic azides [57, 58]. After having carried out the reaction between benzyl azide and the acetylide from phenylacetylene several times and isolated 1-benzyl-5-phenyl-1,2,3-triazole (**8**) as the only product in 93% yield the acetylide from ketal **1** was reacted with benzyl azide in exactly the same way. To our disappointment the reaction failed to give any 1,2,3-triazole; instead, both benzyl azide and ketal **1** were recovered in almost quantitative yield.

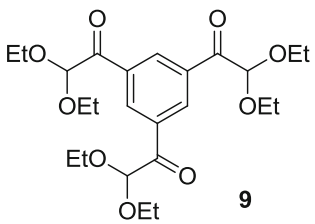


Fig. 3 The product from ruthenium-induced trimerization of ketone **2**

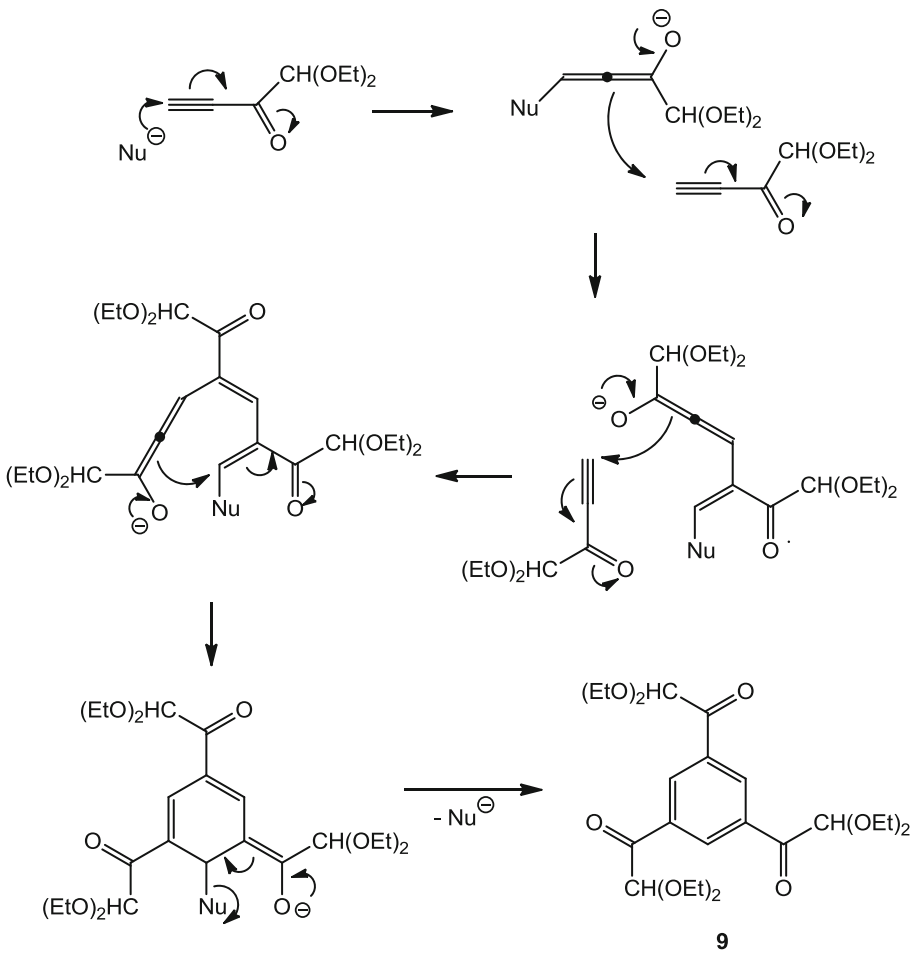


Fig. 4 A proposed mechanism for the formation of **9**; Nu^- denotes an unknown nucleophilic species derived from $Cp^*RuCl(PPh_3)_2$

Conclusion

The highly functionalized terminal alkynes 3,3,4,4-tetraethoxybut-1-yne (**1**) and 1,1-diethoxybut-3-yn-2-one (**2**) undergo [3 + 2] cycloaddition with benzyl azide in the presence of a Cu(I) salt and produce the expected 1,4-disubstituted 1,2,3-triazoles. However, both alkynes failed to give the isomeric 1,5-disubstituted 1,2,3-triazole when reacted with the same azide in the presence of ruthenium; **1** gave no product whatsoever, whereas **2** suffered trimerization and gave a benzene derivative as the only product. This clearly indicates that the ruthenium-catalyzed azide addition to alkynes is more sensitive to substituent influence than so far acknowledged in the literature.

Experimental

The IR spectra were run on a Nicolet Impact 410 infrared spectrophotometer, and the intensities are given as weak (w), medium (m), and strong (s). The NMR spectra were recorded on a Bruker Spectrospin DPX 400 MHz spectrometer; the chemical shifts are reported in ppm relative to Me_4Si, the coupling constants (*J*) in Hz, and the multiplicity as singlet (s), doublet (d), triplet (t), and multiplet (m). TLC analyses were carried out using silica gel (60 F_{254}) on aluminium sheets as stationary phase, and a mixture of hexanes and ethyl acetate as the mobile phase. Purification by flash column chromatography was performed using silica gel (230–400 mesh) as the stationary phase and a mixture of hexanes and ethyl acetate as the mobile phase. The mass spectra were obtained on a JEOL AccuTOF T100GC, operated in the DART mode, and MS-ESI spectra were obtained on a Thermo electron LTQ Orbitrap XL with an electrospray ion source (ION-MAX).

Chemicals

CuI was purchased from EMD, and all other reagents and organic solvents were purchased from Sigma-Aldrich® and used without further purification. Benzyl azide was prepared as described in the literature [59], and so were

3,3,4,4-tetraethoxybutyne (**1**), following a previously published procedure [34, 35], and 1,1-diethoxy-3-butyn-2-one (**2**), obtained by deketalization of **1** in moist acetone containing Dowex 50 W as described in the literature [35].

Cu-catalyzed addition of benzyl azide, general procedure

Terminal alkyne **1** (230 mg, 1.00 mmol) or 156 mg **2** (1.00 mmol), 146 mg benzyl azide (1.10 mmol), and either 9.3 mg $CuSO_4{\cdot}5H_2O$ (0.040 mmol)/22 mg sodium ascorbate (0.11 mmol) or 19 mg CuI (0.010 mmol) were suspended in 4 cm^3 solvent (for solvents, see Tables 1, 2, 3). The mixture was stirred vigorously at room temperature or 60°C for 48 h. For extraction one of the solvents, CH_2Cl_2, $CHCl_3$, EtOAc, or Et_2O (3 × 10–15 cm^3), was used. The combined organic fractions were dried ($MgSO_4$) and concentrated under vacuum on a rotary evaporator to give a crude product, from which pure triazoles were isolated by flash column chromatography using a 7:3 mixture of hexanes and ethyl acetate as eluent.

*Cu-catalyzed addition to **1***

1-Benzyl-4-(1,1,2,2-tetraethoxyethyl)-1H-1,2,3-triazole (**3**, $C_{19}H_{29}N_3O_4$)

Ketal **1** was reacted at room temperature under $CuSO_4$/ascorbate catalysis in water/DMSO (1:3) following the general procedure (see above) and gave 220 mg (61%) of **3** as a white solid. M.p.: 74–75.5°C; $R_f = 0.35$ (Hex/EtOAc, 7:3); IR (KBr): $\bar{\nu}$ = 3,154 (s), 2,986 (s), 2,940 (m), 2,886 (m), 2,366 (m), 2,334 (w), 1,613 (w), 1,499 (w), 1,458 (m), 1,371 (m), 1,188 (s), 1,125 (s), 1,084 (s), 979 (m), 928 (m), 842 (m), 728 (s), 687 (m) cm^{-1}; ^{1}H NMR (methanol-d_4): δ = 1.08 (6H, t, J = 7.0 Hz, 2 CH_3), 1.16 (6H, t, J = 7.0 Hz, 2 CH_3), 3.41–3.71 (8H, m, 4 OCH_2), 4.72 (1H, s, $(EtO)_2CH$), 5.57 (2H, s, $PhCH_2$), 7.29–7.36 (5H, m, Ph), 7.82 (1H, s, triazole H) ppm; ^{13}C NMR (methanol-d_4): δ = 14.6 (2 CH_3), 14.7 (2 CH_3), 53.9 ($PhCH_2$), 57.9 (2 OCH_2), 65.5 (2 OCH_2), 99.9 ($C(OEt)_2$), 104.7 ($HC(OEt)_2$), 125.5 (C), 128.1 (2 CH), 128.6 (CH), 129.1 (2 CH), 136.0 (CH), 147.3 (C) ppm; HRMS (DART): m/z calcd. for $[M + H]^+$ ($[C_{19}H_{30}N_3O_4]^+$) 364.22363, found 364.22338.

When ketal **1** was reacted at 60°C under CuI catalysis in acetonitrile following the general procedure (see above), 240 mg (71%) of **3** and 25 mg (5%) of triazole **4** were obtained. The physical data for **3** are as described above.

1-Benzyl-5-iodo-4-(1,1,2,2-tetraethoxyethyl)-1H-1,2,3-triazole (**4**, $C_{19}H_{28}IN_3O_4$)

Triazole **4** was isolated as a yellowish crystalline solid. M.p.: 83–84°C; $R_f = 0.60$ (Hex/EtOAc, 7:3); IR (KBr): $\bar{\nu}$ = 2,979 (s), 2,931 (m), 2,899 (w), 2,358 (s), 2,340 (m), 1,653 (m), 1,557 (m), 1,440 (m), 1,241 (m), 1,209 (m), 1,173 (w), 1,121 (s), 1,077 (s), 973 (s), 929 (m), 724 (s) cm^{-1}; ^{1}H NMR (methanol-d_4): δ = 1.12 (6H, t, J = 7.0 Hz, 2 CH_3), 1.24 (6H, t, J = 7.0 Hz, 2 CH_3), 3.51–3.71 (8H, m, 4 OCH_2), 4.73 (1H, s, $(EtO)_2CH$), 5.68 (2H, s, $PhCH_2$), 7.19–7.32 (5H, m, Ph) ppm; ^{13}C NMR (methanol-d_4): δ = 15.6 (2 CH_3), 15.8 (2 CH_3), 54.9 ($PhCH_2$), 58.9 (2 OCH_2), 66.5 (2 OCH_2), 100.9 ($C(OEt)_2$), 106.7 ($HC(OEt)_2$), 126.5 (C), 129.1 (2 CH), 129.7 (CH), 130.1 (2 CH), 137.1 (C), 148.4 (C) ppm; HRMS (ESI): m/z calcd. for $[M + H]^+$ ($[C_{19}H_{29}IN_3O_4]^+$) 490.11973, found 490.11950.

*Alternative synthesis of triazole **4***

Ketal **1** (230 mg, 1.00 mmol), 146 mg benzyl azide (1.10 mmol), 209 mg CuI (1.10 mmol), 129 mg diisopropylethylamine (DIPEA, 1.00 mmol), and 160 mg *N*-chlorosuccinimide (NCS, 1.20 mmol) were added to 5 cm^3 THF, and the resulting mixture was stirred vigorously at room temperature for 4 h. Extraction was carried out with EtOAc (3 × 10 cm^3). The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated under vacuum on a rotary evaporator to give a crude product. Analyses gave no indications whatsoever that triazole **3** had been formed. Isolation by flash column chromatography using a 7:3 mixture of hexanes and ethyl acetate as eluent furnished 352 mg (72%) of triazole **4** as a yellowish solid. When the reaction was repeated using 213.6 mg *N*-bromosuccinimide (NBS, 1.20 mmol) instead of NCS, the yield of **4** dropped to 302 mg (62%). In both cases the physical properties of **4** were identical to those reported above.

*Cu-catalyzed addition to **2***

1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2,2-diethoxyethanone (**5**, $C_{15}H_{19}N_3O_3$)

When ketone **2** was reacted at room temperature under $CuSO_4$/ascorbate catalysis in water/CH_2Cl_2 (1:3) following the general procedure (see above) isolation furnished 190 mg (70%) of **5** as a yellowish oil. $R_f = 0.27$ (Hex/EtOAc, 7:3); IR (film): $\bar{\nu}$ = 3,127 (m), 3,027 (w), 2,975 (s), 2,923 (m), 2,891 (m), 1,701 (s), 1,529 (s), 1,490 (m), 1,457 (m), 1,369 (m), 1,321 (w), 1,241 (s), 1,113 (m), 1,065 (m), 917 (w), 828 (m), 716 (s), 700 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.22 (6H, t, J = 7.0 Hz, 2 CH_3), 3.65–3.81 (4H, m, 2 OCH_2), 5.45 (1H, s, $(EtO)_2CH$), 5.57 (2H, s, $PhCH_2$), 7.29–7.40 (5H, m, Ph), 8.12 (1H, s, triazole H) ppm; ^{13}C NMR ($CDCl_3$): δ = 15.7 (2 CH_3), 54.9 ($PhCH_2$), 64.0 (2 OCH_2), 100.9 ($HC(OEt)_2$), 128.6 (CH), 128.9 (2

CH), 129.7 (CH), 129.8 (2 CH), 134.1 (C), 145.1 (C), 187.7 (CO) ppm; HRMS (DART): *m/z* calcd. for $[M + H]^+$ ($[C_{15}H_{20}N_3O_3]^+$) 290.15047, found 290.15251.

When ketone **2** was reacted at 60°C under CuI catalysis in acetonitrile following the general procedure (see above), isolation afforded 240 mg (70%) of **5** and 25 mg (3%) of **6**. The physical data for **5** are as described above.

1-(1-Benzyl-1H-1,2,3-triazol-5-yl)-2,2-diethoxyethanone (**6**, $C_{15}H_{19}N_3O_3$)

Triazole **6** was isolated as a greenish oil. $R_f = 0.51$ (Hex/EtOAc, 7:3); IR (film): $\bar{\nu} = 3{,}047$ (w), 2,987 (s), 2,943 (w), 2,891 (w), 1,709 (s), 1,505 (w), 1,449 (m), 1,333 (m), 1,245 (w), 1,125 (m), 1,073 (s), 921 (w), 724 (s), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.19$ (6H, t, $J = 7.0$ Hz, 2 CH_3), 3.51–3.69 (4H, m, 2 OCH_2), 4.93 (1H, s, $(EtO)_2CH$), 5.92 (2H, s, $PhCH_2$), 7.30–7.32 (5H, m, Ph), 8.47 (1H, s, triazole H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.6$ (2 CH_3), 54.4 ($PhCH_2$), 64.0 (2 OCH_2), 103.0 ($HC(OEt)_2$), 128.6 (2 CH), 128.8 (CH), 129.2 (2 CH), 130.4 (C), 135.4 (C), 140.6 (CH), 186.0 (CO) ppm; HRMS (DART): *m/z* calcd. for $[M + H]^+$ ($[C_{15}H_{20}N_3O_3]^+$) 290.15047, found 290.15017.

Alternative synthesis of ***5***

The synthesis was based on a procedure used to convert ketal **1** to ketone **2** [15]. Triazole **3** (363 mg, 1.00 mmol) was dissolved in a mixture of 18 cm^3 acetone and 0.5 cm^3 water, and 260 mg Dowex 50 W was subsequently added. The mixture was heated at reflux for 6 h and was then filtered, dried ($MgSO_4$), and concentrated. Flash-column chromatography using a 7:3 mixture of hexanes and ethyl acetate as eluent was then carried out, and 260 mg (90%) of **5** was obtained. The physical and spectroscopic data of the product are identical to those reported above.

1-(1-Benzyl-5-iodo-1H-1,2,3-triazol-4-yl)-2,2-diethoxyethanone (**7**, $C_{15}H_{18}IN_3O_3$)

The synthesis was based on a procedure used to convert ketal **1** to ketone **2** [15]. Iodotriazole **4** (489 mg, 1.00 mmol) was dissolved in a mixture of 18 cm^3 acetone and 0.5 cm^3 water, and 260 mg Dowex 50 W was subsequently added. The mixture was heated at reflux for 6 h and was then filtered, dried ($MgSO_4$), and concentrated. Flash-column chromatography using a 7:3 mixture of hexanes and ethyl acetate as eluent was then carried out, and 353 mg (85%) of the title compound was obtained as a brownish oil. $R_f = 0.50$ (Hex/EtOAc, 7:3); IR (film): $\bar{\nu} = 3{,}600$ (m), 2,975 (m), 2,931 (w), 2,891 (w), 1,713 (s), 1,497 (s), 1,461 (w), 1,445 (m), 1,421(m), 1,097 (w), 1,065 (s), 980 (m), 920 (m), 710 (m) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.28$ (6H, t, $J = 7.0$ Hz, 2 CH_3), 3.80–3.84 (4H, m, 2 OCH_2), 5.66 (2H, s, $PhCH_2$), 5.90 (1H, s, $(EtO)_2CH$), 7.31–7.38 (5H, m, Ph) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 16.8$ (2 CH_3), 55.6 ($PhCH_2$), 64.8 (2 OCH_2), 99.6 ($HC(OEt)_2$), 129.6 (2 CH), 130.3 (CH), 130.5 (2 CH), 130.7 (C), 135.0 (C), 147.2 (C), 188.4 (CO) ppm; HRMS (ESI): *m/z* calcd for $[M + H]^+$ ($[C_{15}H_{19}IN_3O_3]^+$) 416.04656; found 416.04661.

Ru-catalyzed addition of benzyl azide to ***1*** *and* ***2***

Alkyne **1** (139 mg, 0.60 mmol) or 94 mg **2** (0.60 mmol), 44 mg benzyl azide (0.33 mmol), and 4 mg $Cp^*RuCl(PPh_3)_2$ (0.005 mmol, 1 mol%) were dissolved in 5 cm^3 of either dry THF at 65°C or anhydrous benzene at 80°C. The mixture was stirred vigorously for 3–4 h or 24 h (Table 4). The solvent was removed under vacuum and left a residue that was analyzed by TLC. Flash-column chromatography with hexanes/EtOAc (9:1) as eluent afforded only the reactants benzyl azide and **1** in 93% yield or better in the reactions involving **1** (Table 4, entries 1 and 2), whereas reactions with **2** furnished unreacted benzyl azide in 88–91% yield and 1,3,5-tris(2,2-diethoxy-1-oxoethyl)benzene (**9**, Table 4, entries 5 and 6). When **2** was reacted an intractable mixture of colored compounds with unknown structures was also formed, but the compounds attached strongly to the column and could neither be isolated nor separated. Compound **9** was isolated as a colorless oil, 52 mg (55%) in THF at reflux (65°C) and 55 mg (60%) in benzene at reflux (80°C), and the spectroscopic and spectrometric data were in accordance with those of an authentic sample of the compound [23].

Mg-catalyzed addition of benzyl azide, general procedure

To the dried flask containing a solution of 0.36 cm^3 of 2.0 M EtMgBr and 5 cm^3 dry THF under nitrogen atmosphere, 183 mg **1** (0.79 mmol) was added dropwise at room temperature. The solution was heated to 50°C for 15 min and cooled to room temperature, and 96 mg benzyl azide (0.72 mmol) was added dropwise. The reaction was run at 50°C for 24 h. After quenching with 4 cm^3 aqueous NH_4Cl, extraction was carried out with EtOAc (3 × 10 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated to a colorless residue, and finally worked up by flash-column chromatography with hexanes/EtOAc (9:1) as eluent. This furnished 179 mg (98%) of ketal **1** and 93 mg (97%) of benzyl azide.

X-ray structure determination

Analysis was performed using a Bruker AXS APEXII TXS Ultra rotating anode diffractometer. A thin colorless plate

was mounted under a nitrogen stream at 123 K. Data were collected in 0.3° frames over 182° in ω at four orthogonal φ-positions. The crystal diffracted rather poorly and showed broad Bragg profiles. The raw data were processed, and the structure solved and refined using the programs contained in the Bruker AXS APEX2 software package [60].

Complete crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 811697. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)1223336033 or e-mail: deposit@ccdc.cam.ac.uk).

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