Chemical Communications

A [(NHC)CuCl] Complex as Latent Click Catalyst

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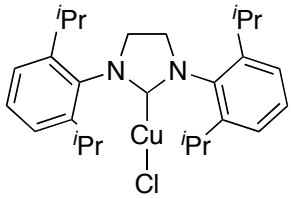
Electronic Supplementary Information

General Considerations

All reagents were used as purchased. Copper(I) chloride and potassium methoxide were stored in a glovebox under argon. 1,3-Bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolinium chloride (SIPr·HCl) was synthesized according to literature procedures.[1] ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a 400 MHz spectrometer at room temperature. Chemical shifts (δ) are reported with respect to tetramethylsilane as internal standard in ppm. Elemental analyses were performed at Centro de Microanálisis Elemental of the Universidad Complutense de Madrid (Spain).

Synthesis of [(SIPr)CuCl]



In a vial, copper(I) chloride (0.171 g, 1.5 mmol), SIPr·HCl (0.586 g, 1.37 mmol) and potassium methoxide (0.132 g, 1.88 mmol) were loaded inside a glovebox and stirred in dry toluene (4 mL) overnight at room temperature outside of the glovebox. After filtration of the reaction mixture through a plug of celite (DCM), the filtrate was mixed with pentane to form a precipitate. A second filtration afforded the title complex as a white solid (0.588 g, 80%). NMR spectra were consistent with previously reported data for this compound.[2]

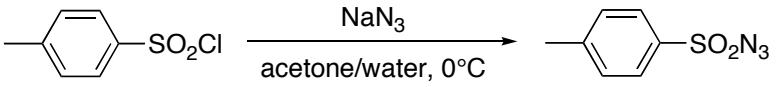
Crystallographic Information for [(SIPr)CuCl]

Crystal structure data for [(SIPr)CuCl], $C_{27}H_{38}ClCuN_2 \cdot 2CH_2Cl_2$, M = 659.44, monoclinic, a = 9.5227(11)Å, b = 16.4203(19)Å, c = 11.0548(13) Å, β = 103.810(2)°, V = 1678.6(3) Å^3; T = 150(2) K, space group $P2_1/m$, Z = 2, absorption coefficient = 1.069 mm^{-1}. Intensities were measured to a maximum 2θ of 52°, but measurements above 2θ = 45° were not significantly above background due to solvent disorder. Of 13663 reflections collected in the 2θ range 2.4°–45°, 2289 were unique reflections (R_{int} = 0.0506) and were used in all calculations. Two solvent molecules were observed to both be disordered about the crystallographic mirror plane, and were refined with geometrical constraints and 50% occupancy. An attempt to refine the structure in space group $P2_1$ also yielded disordered solvent molecules and did not significantly improve the refinement. Hydrogen atom positions were from a constrained refinement using a riding model. The final agreement factors were wR2(all data) = 0.0801, R1(all data) = 0.0379, R1(observed data) = 0.0321. CCDC 649761.

Synthesis of Azides (1)

Benzyl and alkyl azides were synthesized from the corresponding bromides by nucleophilic substitution with sodium azide in DMSO (eq. 1).[3] Tosyl azide **1l** was prepared from tosyl chloride following the procedure reported by Hiersemann (eq. 2).[4]

$$R^1\text{—Br} \xrightarrow[\text{DMSO, RT}]{NaN_3} R^1\text{—}N_3 \qquad (1)$$



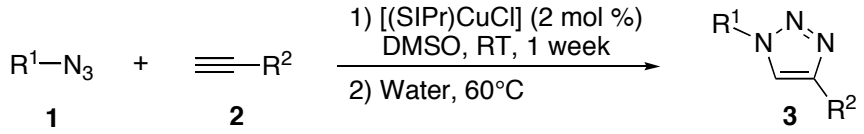
(2)

Benzyl azide **1a**,[3] 4-(azidomethyl)benzonitrile **1b**,[3,5] 1-(azidomethyl)4-nitrobenzene **1d,**[3,5] 1-azidoheptane **1e**,[3,5] 2-(2-azidoethyl)-1,3-dioxolane **1h**,[6,5] (2-azidomethyl)benzene **1i**,[7,5] 3-

azidopropan-1-ol **1k**[8] and *p*-toluenesulfonyl azide **1l**[9,4] have already been reported in the literature.

Synthesis of 1,2,3-Triazoles (3)

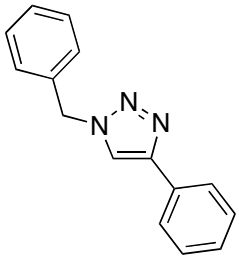
A. General Procedure for the Latent [3+2] Cycloaddition of Azides and Alkynes



1 **2** **3**

In a vial fitted with a screw cap, azide **1** (1.0 mmol), alkyne **2** (1.0 mmol), [(SIPr)CuCl] (10 mg, 2 mol %) and DMSO (1 mL) were loaded. The solution was stirred at room temperature for at least one week and controlled by GC to ensure the absence of reaction. Then, water (1 mL) was added and the reaction mixture was heated at 60°C. After total consumption of the starting azide or no further conversion, the corresponding triazole was collected by filtration and washed with water and pentane. Alternatively, **3** could be also recovered after extraction with EtOAc. In all examples, the crude products were estimated to be greater than 95% pure by ^{1}H NMR. Reported yields are isolated yields and are the average of at least two runs.

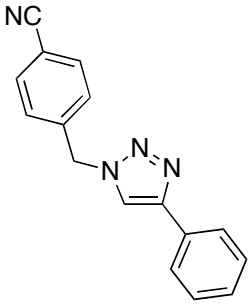
1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (3a)



Using the general procedure from 0.133 g of benzyl azide **1a** and 0.11 mL of phenylacetylene **2a**, 0.231 g of the title compound were isolated (98% yield).

Spectroscopic data for **3a** were consistent with previously reported data for this compound.[10]

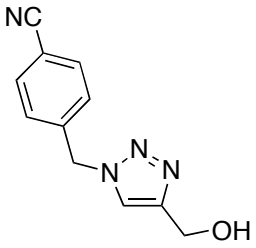
4-[(4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl]benzonitrile (3b)



Using the general procedure from 0.158 g of 4-(azidomethyl)benzonitrile **1b** and 0.11 mL of phenylacetylene **2a**, 0.233 g of the title compound were isolated (90% yield).

Spectroscopic data for **3b** were consistent with previously reported data for this compound.[10]

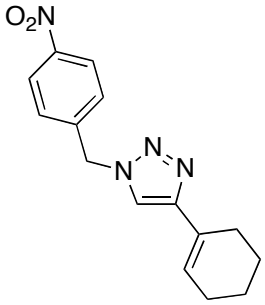
4-[(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl]benzonitrile (3c)



Using the general procedure from 0.176 g of 4-(azidomethyl)-4-nitrobenzene **1b** and 0.062 mL of propargylic alcohol **2c**, 0.167 g of the title compound were isolated (78% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (s, 1H, NC*H*=), 7.79 (d, J = 8.2 Hz, 2H, H^{Ar}), 7.51 (d, J = 8.2 Hz, 2H, H^{Ar}), 5.75 (s, 2H, NCH_2), 4.67 (d, J = 5.0 Hz, 2H, CH_2OH), 4.21 (t, J = 5.0 Hz, 1H, OH); ^{13}C NMR (100 MHz, acetone-d_6): δ = 150.1 (C, N*C*=), 142.7 (C, C^{Ar}), 133.6 (CH, C^{Ar}), 129.7 (CH, C^{Ar}), 123.5 (CH, N*C*H=), 119.1 (C, C^{Ar}), 112.9 (C, CN), 56.9 (CH_2, NCH_2), 52.5 (CH_2, CH_2OH); Elemental analysis calcd for $C_{11}H_{10}N_4O$ (214.22): C, 61.67; H, 4.71; N, 26.15. Found: C, 62.02; H, 4.55; N, 26.28.

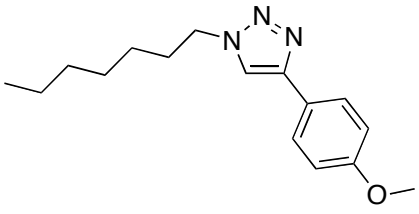
4-Cyclohexenyl-1-(4-nitrobenzyl)-1*H*-1,2,3-triazole (3d)



Using the general procedure from 0.176 g of 4-(azidomethyl)-4-nitrobenzene **1d** and 0.118 mL of 1-ethynylcyclohex-1-ene **2d**, 0.280 g of the title compound were isolated (98% yield).

Spectroscopic data for **3d** were consistent with previously reported data for this compound.[5]

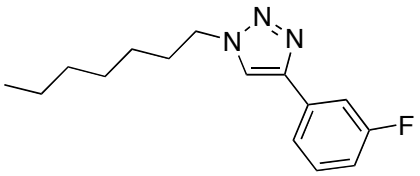
1-Heptyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (3e)



Using the general procedure from 0.176 g of 1-azidoheptane **1e** and 0.136 mL of 1-ethynyl-4-methoxybenzene **2e**, 0.262 g of the title compound were isolated (96% yield).

Spectroscopic data for **3e** were consistent with previously reported data for this compound.[5]

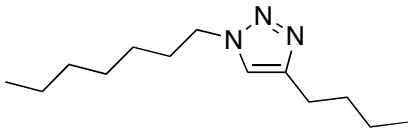
4-(3-Fluorophenyl)-1-heptyl-1*H*-1,2,3-triazole (3f)



Using the general procedure from 0.176 g of 1-azidoheptane **1e** and 0.121 mL of 1-ethynyl-3-fluorobenzene **2i**, 0.233 g of the title compound were isolated (89% yield).

Spectroscopic data for **3f** were consistent with previously reported data for this compound.[5]

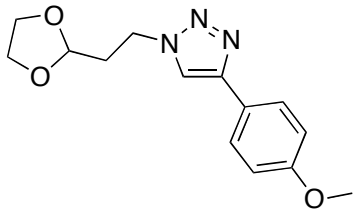
4-Butyl-1-heptyl-1*H*-1,2,3-triazole (3g)



Using the general procedure from 0.176 g of 1-azidoheptane **1e** and 0.12 mL of 1-hexyne **2g**, 0.185 g of the title compound were isolated (83% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (s broad, 1H, NC*H*=), 4.26 (t, J = 7.2 Hz, 2H, NCH_2), 2.66 (t, J = 7.6 Hz, 2H, =CCH_2), 1.93 – 1.82 (m, 2H, CH_2 heptyl), 1.70 – 1.59 (m, 2H, CH_2 butyl), 1.44 – 1.20 (m, 10H, CH_2 butyl + CH_2CH_2CH_2CH_2CH$_3$), 0.93 (t, J = 7.3 Hz, 3H, CH_3 butyl), 0.87 (t, J = 6.9 Hz, 3H, CH_3 heptyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0 (C, N*C*=), 120.2 (CH, N*C*H=C), 49.8 (CH_2, N*C*H_2), 31.31 (CH_2), 31.26 (CH_2), 30.0 (CH_2), 28.4 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 22.2 (CH_2), 22.0 (CH_2), 13.7 (CH_3), 13.5 (CH_3); Elemental analysis calcd for $C_{13}H_{25}N_3$ (223.36): C, 69.91; H, 11.28; N, 18.81. Found: C, 69.74; H, 11.32; N, 19.02.

1-(2-(1,3-Dioxolan-2-yl)ethyl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (3h)

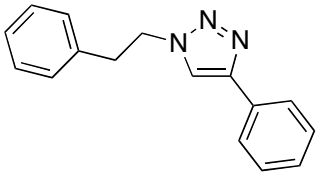


Using the general procedure 0.143 g of (2-azidoethyl)-1,3-dioxolane **1h** and 0.136 mL of 1-ethynyl-4-methoxybenzene **2e**, 0.257 g of the title compound were isolated (93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 6.8 Hz, 2H, H^{Ar}), 7.71 (s, 1H, NC*H*=), 6.95 (d, J = 6.8 Hz, 2H, H^{Ar}), 4.95 (t, J = 4.3 Hz, 1H, OC*H*O), 4.54 (t, J = 7.3 Hz, 2H, NCH_2), 4.05 – 3.91 (m, 2H, OCH_2), 3.91 – 3.84 (m, 2H, OCH_2), 3.84 (s, 3H, OCH_3), 2.34 (dt, J = 4.3; 7.3 Hz, 2H, NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (C, MeO*C*^{Ar}), 147.6 (C, N*C*=), 127.0 (CH, C^{Ar}), 123.4 (C, C^{Ar}), 119.0 (CH, N*C*H=), 114.2 (CH, C^{Ar}), 101.5 (CH, O*C*HO), 65.1 (CH_2, CH_2O), 55.3 (CH_3, OCH_3), 45.3 (CH_2,

NC*H*$_2$), 34.1 (CH_2, NCH_2C*H*$_2$); Elemental analysis calcd for $C_{14}H_{17}N_3O_3$ (275.30): C, 61.08; H, 6.22; N, 17.43. Found: C, 61.27; H, 6.33; N, 17.67.

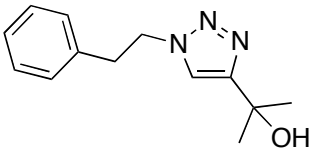
1-Phenethyl-4-phenyl-1*H*-1,2,3-triazole (3i)



Using the general procedure from 0.147 g of (2-azidoethyl)benzene **1i** and 0.11 mL of phenylacetylene **2a**, 0.232 g of the title compound were isolated (93% yield).

Spectroscopic data for **3f** were consistent with previously reported data for this compound.[10]

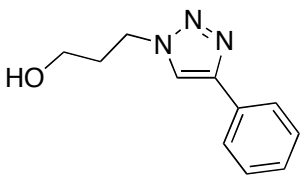
2-(1-Phenethyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (3j)



Using the general procedure from 0.147 g of (2-azidoethyl)benzene **1i** and 0.102 mL of 2-methylbut-3-yn-2-ol **2j**, 0.223 g of the title compound were isolated as a white solid after filtration (97% yield).

Spectroscopic data for **3f** were consistent with previously reported data for this compound.[5]

3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propan-1-ol (3k)

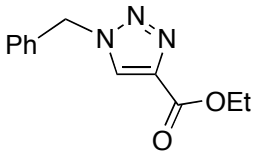


Using the general procedure from 0.101 g 3-azidopropan-1-ol **1k** and 0.11 mL of phenylacetylene **2a**, 0.169 g of the title compound were isolated (83% yield).

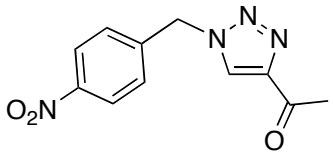
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 – 7.75 (m, 3H, H^{Ar} + NC*H*=), 7.47 – 7.27 (m, 3H, H^{Ar}), 4.55 (t, *J* = 6.8 Hz, 2H, NC*H*$_2$), 3.68 (t, *J* = 5.8 Hz, 2H, C*H*$_2$OH), 3.09 (s broad, 1H, OH), 2.20 – 2.10 (m, 2H, NCH_2C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6 (C, N*C*=), 130.4 (C, C^{Ar}), 128.8 (CH, C^{Ar}), 128.1 (CH, C^{Ar}), 125.6 (CH, C^{Ar}), 120.3 (CH, N*C*H=), 58.4 (CH_2, NC*H*$_2$), 47.0 (CH_2, C*H*$_2$OH), 32.6 (CH_2, NCH_2C*H*$_2$); Elemental analysis calcd for $C_{11}H_{13}N_3O$ (203.24): C, 65.01; H, 6.45; N, 20.68. Found: C, 65.31, H, 6.43, H, 20.80.

Unsuitable Couples for Latent Catalysis

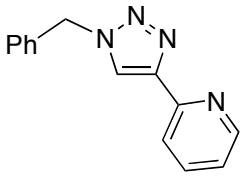
In some cases, generally when highly activated alkynes toward cycloaddition were used, formation of the corresponding triazoles was observed during the latent period (one week at room temperature in DMSO, in the presence of 2 mol % of [(SIPr)CuCl]) . Examples are given below, reaction times were not optimized. The formation of two regioisomers in the first case implies that it is not, at least not totally, a copper-catalyzed transformation.



5 days, RT
^{1}H NMR Conversion = 91%
1,4-triazole:1,5-triazole = 93:7



6 days, RT
^{1}H NMR Conversion = 100%
Yield = 93%



6 days, RT
^{1}H NMR Conversion = 100%
Yield = 100%

Optimization of Water Volume

In a vial fitted with a septum screw cap, benzyl azide **1a** (133 mg, 1.0 mmol), phenylacetylene **2a** (0.11 mL, 1.0 mmol), [(SIPr)CuCl] (10 mg, 2 mol %) and 1 mL of anhydrous DMSO were loaded. Then, water (x mL) was added through the septum and the reaction mixture was heated at 60°C. The reactions were monitored by GC, the different reaction rates are presented in Figure 1.

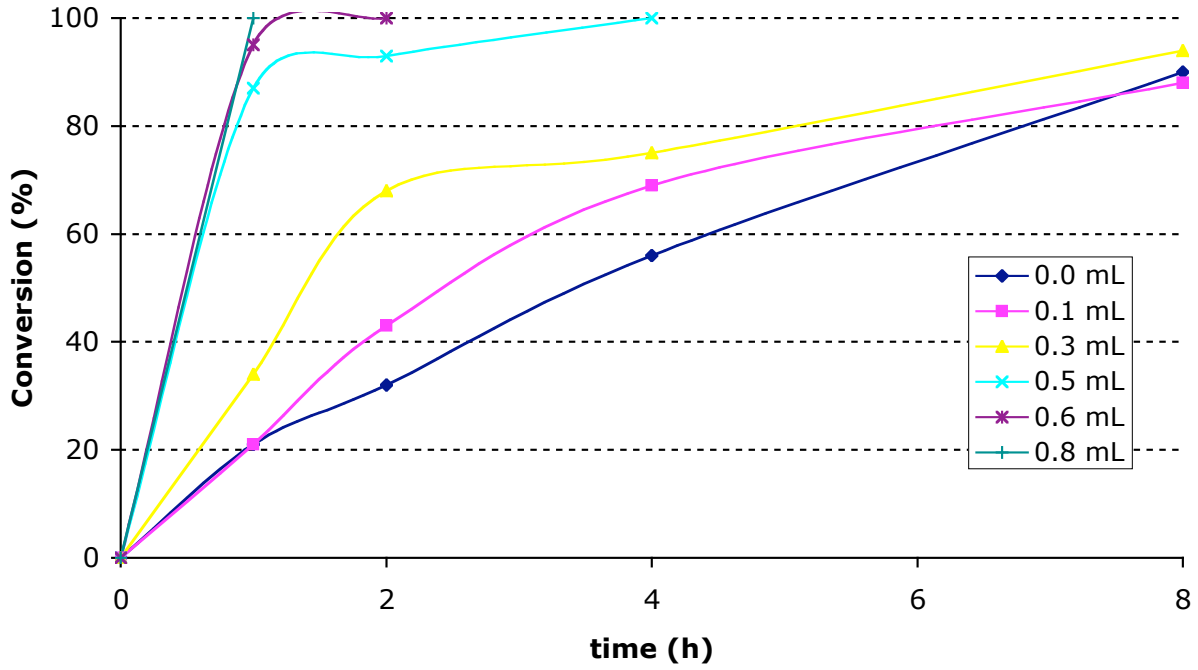


Fig. 1. Influence of the water volume for catalyst activation

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