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[(NHC)$_2$Cu]X Complexes as Efficient Catalysts for Azide-Alkyne Click Chemistry at Low Catalyst Loadings**

Silvia Díez-González and Steven P. Nolan**

In 2001, Sharpless and co-workers defined the concept of 'Click Chemistry' and the criteria for a transformation to be considered as 'Click'.[1] Since then, the copper-catalyzed reaction of azide and alkyne to produce 1,2,3-triazoles regioselectively[2] (1,3-dipolar Huisgen cycloaddition[3]) has become the best Click reaction to date. Thanks to its mild conditions and high efficiency, this reaction has found a myriad of applications in biology and material science.[4] Less attention has been focused on the development of novel copper(I)-based well-defined systems[5,6,7] and to the amount of copper used.[8] This last point is extremely important for future industrial applications and it might be one of the last challenges to overcome for this transformation.

We recently reported the remarkable activity of [(NHC)CuX] complexes (NHC = N-heterocyclic carbene; X = Cl, Br) in this cycloaddition reaction[9] and this catalytic system has already been applied to the preparation of triazole-containing carbanucleosides,[10] porphyrins[11] or platinum-based anticancer drugs.[12]

On the other hand, we have also studied a family of cationic NHC-containing complexes of general formulae [(NHC)$_2$Cu]X (X = PF_6, BF_4).[13] Interestingly, during the examination of their activity in the hydrosilylation of ketones we observed an enhanced reactivity of these complexes when compared to their neutral analogues [(NHC)CuCl].[14] This improved activity was rationalized via a more efficient activation pathway of the cationic pre-catalyst. Additionally, the second NHC ligand was found to have an active role in the catalytic cycle.

Since under hydrosilylation conditions one NHC ligand is displaced by the base in the reaction mixture, we wondered if an alkyne could play a similar role to produce the active copper acetylide species, from [(NHC)$_2$Cu]X species (Figure 1).

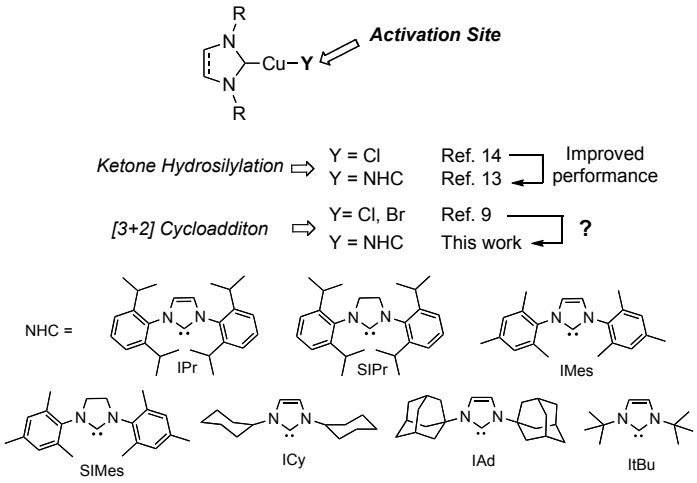

Figure 1. Catalyst design

We investigated the activity of complexes [(NHC)$_2$Cu]X **1**–**7** in the Huisgen cycloaddition with benzyl azide and phenylacetylene as model substrates (Table 1). Reactions were conducted in water with 2 mol % of copper catalyst and results are presented in Table 1. SIMes-containing complexes **4a** and **4b** displayed only poor activities under these conditions, in contrast with our previous studies dealing with [(NHC)CuX] complexes.[9] This lack of reactivity cannot be simply correlated with the medium steric bulk of the SIMes ligand since complexes **7a** and **7b**, bearing very bulky ItBu ligands, were also found ineffective.[15] [(ICy)$_2$Cu]PF_6 **5a** provided the best result and the cycloaddition reached completion in 90 min. Of note, no general trend of reactivity was found in this reaction considering the counterion of the metal complex. Further optimization with complex **5a** showed that acetonitrile, instead of water, was the most suitable solvent for this transformation.[16] Moreover, the reaction was found to proceed smoothly under neat conditions and in this case, the catalytic loading could be significantly reduced.

The scope of this reaction was then examined with 0.5 mol % of **5a** under neat conditions at room temperature. Results are presented in Scheme 1. All reactions proceeded smoothly to completion in short reaction times (from minutes to 9 h) and triazoles **8** were isolated in excellent yields and high purity after simple filtration or evaporation. It is important to note that following the 'Click laws', no precautions to exclude oxygen or moisture were taken in any of these reactions. No copper disproportionation with precipitation of metallic copper, or copper oxidation were observed under the optimized reaction conditions which shows, once more, the high ability of NHCs to stabilize copper(I) species.[17]

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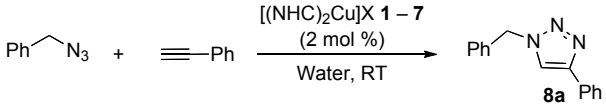
Table 1. Catalyst screening[a]



$[(NHC)_2Cu]PF_6$		time (h)	Conv. (%)
$[(IPr)_2Cu]PF_6$	**1a**	18	71
$[(SIPr)_2Cu]PF_6$	**2a**	5	100
$[(IMes)_2Cu]PF_6$	**3a**	6	100
$[(SIMes)_2Cu]PF_6$	**4a**	18	5
$[(ICy)_2Cu]PF_6$	**5a**	1.5	99
$[(IAd)_2Cu]PF_6$	**6a**	5	100
$[(ItBu)_2Cu]PF_6$	**7a**	18	76

$[(NHC)_2Cu]BF_4$		time (h)	Conv. (%)
$[(IPr)_2Cu]BF_4$	**1b**	8	100
$[(SIPr)_2Cu]BF_4$	**2b**	5	100
$[(IMes)_2Cu]BF_4$	**3b**	6	100
$[(SIMes)_2Cu]BF_4$	**4b**	18	13
$[(ICy)_2Cu]BF_4$	**5b**	5	95
$[(IAd)_2Cu]BF_4$	**6b**	3	100
$[(ItBu)_2Cu]BF_4$	**7b**	18	35

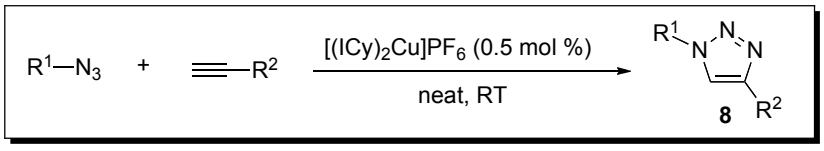
[a] NMR Conversions are average of at least two independent runs.

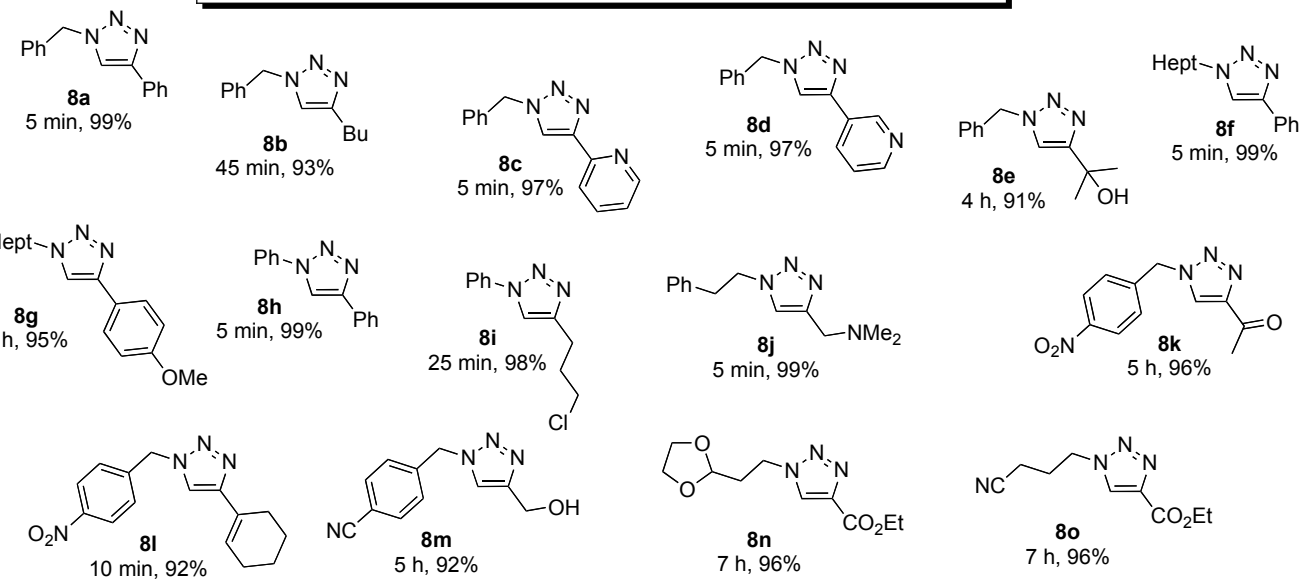
Electron-rich, electron-poor and/or hindered alkynes were found to be suitable cycloaddition partners as well as enynes. Benzyl, alkyl and aryl azides were successfully employed. A number of functional groups were tolerated such as alcohol, ketone, ester, amine, pyridine, nitrile and halogen. Of note, no direct correlation can be drawn between the electronic nature of the reactants and the outcome of the reaction. Actually, as we had previously observed,[9] the physical state of the reaction product is crucial and oily or low melting-point triazoles led to longer reaction times. In these cases, improved results were obtained by simply increasing the reaction temperature to 40°C.[18]

The great activity of this catalytic system naturally led us to examine the possibility of further reducing the amount of metal used in this transformation. Using again benzyl azide and phenylacetylene as model substrates and under neat conditions, we tested different catalyst loadings at various temperatures. In this particular case, reactions carried out at 40°C or 50°C were found faster than the ones performed at room temperature and allowed for the lowest catalyst loadings.[19] However, minor formation of the 1,5-disubstituted triazole regioisomeric to **8a** was systematically observed by GC and ^{1}H NMR after prolonged reaction times (i.e. 8 h at 40°C and 5 h at 50°C), clearly showing that extreme caution is required to avoid undesired thermal processes. Results obtained for a number of triazoles are presented in Table 2.

In all cases, loadings of **5a** could at least be lowered to 300 ppm at room temperature or to 100 ppm at 40°C. Under these challenging conditions, good conversions were still reached after short to reasonable reaction times. The best results were obtained for triazole **8a**, and copper loadings as low as 40 ppm led to a remarkable turnover number (TON) over 20 000 and a turnover frequency over 5 000 h^{-1}.[20] It is important to note that under these reaction conditions, our previous catalyst [(SIMes)CuBr] led to no conversion after 24 h.

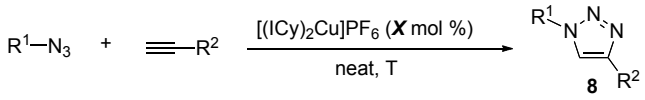
To gain some insight into the activation pathway of the pre-catalyst, we next carried out a number of stoichiometric experiments. Whereas no interaction was observed between benzyl azide and **5a** in CD_3CN, the same copper complex was completely consumed in minutes in the presence of phenylacetylene. The equimolar formation of two novel species was evidenced by ^{1}H NMR (Figure 2). One of them was unequivocally identified as $ICy{\cdot}HPF_6$ **B** by comparison with a pure sample.[21] The second species could also be cleanly isolated and identified as a mono nuclear copper(I) acetylide **A** by NMR. To unambiguously determine the nature of **A**, we carried out the same reaction with IPr-containg complex **1a**. In this case, no reaction was observed at room temperature. However, after overnight heating at 80°C the formation of two new species was observed, as well as remaining starting material. The new products were separated and identified as the known [(IPr)CuC≡CPh][22] and $IPr{\cdot}HPF_6$. Hence, it appears that one of the NHC ligands on the copper center can act as a base, deprotonating the alkyne, to initiate the catalytic cycle.





Scheme 1. [(ICy)$_2$Cu]PF$_6$-catalyzed formation of triazoles

Table 2. [(ICy)$_2$Cu]PF$_6$-catalyzed synthesis of triazoles at low catalyst loadings[a]



Triazole **8**	T	[Cu] (ppm)	Time (h)	Conv. (%)	TON
8a	RT	50	48	80	16000
	40°C	50	8	89	17800
	50°C	40	4	81	20250
8d	RT	75	6	91	12133
8f	RT	200	20	72	3600
8i	RT	300	43	85	2833
	40°C	100	18	70	7000
8j	RT	300	40	45	1500
	40°C	100	18	71	7100

[a] GC Conversions are average of at least two independent runs.

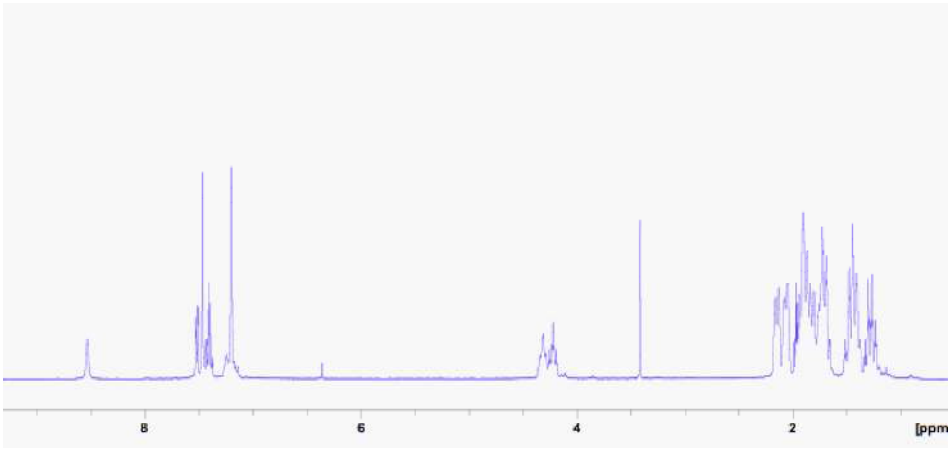
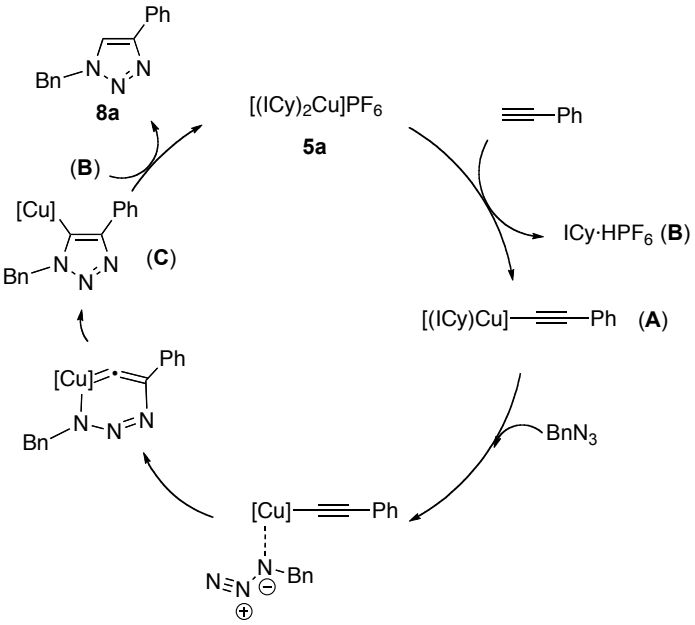


Figure 2. Reaction of **5a** with phenylacetylene, ^{1}H NMR spectrum.

The mechanism proposed for this transformation is depicted in Scheme 2. Bis-NHC complex **5a** would be transformed into an acetylide **A** and an azolium salt **B** by reaction with the alkyne. After the interaction of **A** and the azide, the reaction would follow the pathway commonly accepted for this transformation[23] to form a triazolide intermediate **C** that upon reaction with the azolium salt **B** would lead to the formation of the expected triazole **8a** and the regeneration of the catalyst.



Scheme 2. Postulated mechanism

In an attempt to isolate intermediate **C**, isolated **A** complex was reacted with benzyl azide in CD_3CN. However, only the formation of a complex mixture of unknown products was observed as well as a considerable precipitation of presumably copper salts. We attribute this result to the extreme instability of **C** in the absence of a protic source. On the contrary, when a mixture of **A** and **B** was reacted with the azide, a clean formation of triazole **8a** was obtained, along with the regeneration of [(ICy)$_2$Cu]PF$_6$.

Further experiments to isolate the triazolide intermediate **C** had limited success. The reaction of **5a** with an equimolar amount of phenylacetylene and a slight excess of benzyl azide in acetonitrile led either to the decomposition of the reaction mixture or to the direct formation of triazole **8a**. Nevertheless, we were able to observe by ^{1}H NMR the consumption of the starting materials as well as the formation of a new compound. The spectrum of the new species could be attributed to **C**,[19] but its minor formation along with its high instability precluded its full characterization. Moreover, it is important to note that upon acidic hydrolysis this crude mixture rapidly evolved to triazole **8a** and ICy·HPF$_6$. These findings are in line with the work of Straub and co-workers, who recently isolated a related triazolide complex and showed the crucial importance of an extremely encumbered environment around the metal center to stabilize such complexes.[24]

In conclusion, we have developed a novel catalytic system, [(ICy)$_2$Cu]PF$_6$ **5a** without solvent, for the [3+2] cycloaddition of azides and alkynes under Click conditions. This system has been shown to be broad in scope and highly efficient (TOFs up to 5 000 h^{-1}) even at very low catalyst loadings (down to 40 ppm).

Furthermore, preliminary mechanistic studies have shown the ability of the NHC ligand on the copper center to act as a base, deprotonating the starting alkyne to initiate the catalytic cycle. Further applications of this catalyst system, especially in its low catalyst loading version, are currently under investigations in our laboratory.

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[16] During the optimization studies, complete conversions were obtained with DMSO (2 h), water (1.5 h), DMF (1.5 h), THF (1 h), acetone (0.5 h) and MeCN (0.2 h) in the presence of 2 mol % of **5a**. Sluggish reactions were observed when using alcohols as solvents.

[17] For a review, see: S. Díez-González, S. P. Nolan, *Synlett* **2007**, 2158–2167.

[18] For instance, when the reactions were carried out at 40°C, triazole **8g** was produced quantatively in 3 h, instead of 9 h. For triazoles **8n** and **8o**, a reaction time of only 90 min was required.

[19] For further details, see the Supporting Information.

[20] Vincent and co-workers recently reported a copper(I)-tren catalyst that allowed for high TONs, up to 54 000 for the preparation of **8a** at 60°C for 24 h in the absence of solvent. However, during our studies and for the same triazole, we have observed the non-negligible formation of the 1,5-regioisomer at 50°C after only 5 h. See ref. 13b.

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Entry for the Table of Contents

La Click, c'est chic!

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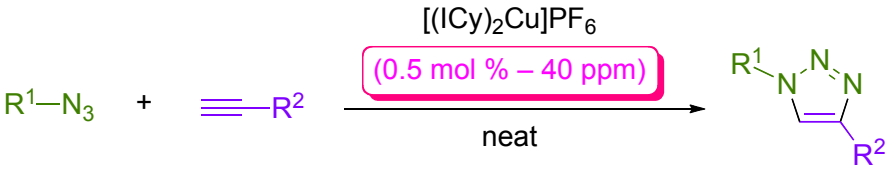
[$(NHC)_2Cu$]X Complexes as Efficient Catalysts for Azide-Alkyne Click Chemistry at Low Catalyst Loadings



A novel catalytic system, based on a [$(NHC)_2Cu$]X complex, was developed for the [3+2] cycloaddition reaction of azides and alkynes under Click conditions. This system is broad in scope and highly efficient (TOFs up to 5 000 h^{-1}) even at very low catalyst loadings (down to 40 ppm). Furthermore, preliminary mechanistic studies suggest a specific catalyst activation pathway toward the cycloaddition.

Angew. Chem. Int. Ed.

[(NHC)$_2$Cu]X Complexes as Efficient Catalysts for Azide-Alkyne Click Chemistry at Low Catalyst Loadings

Supporting Information

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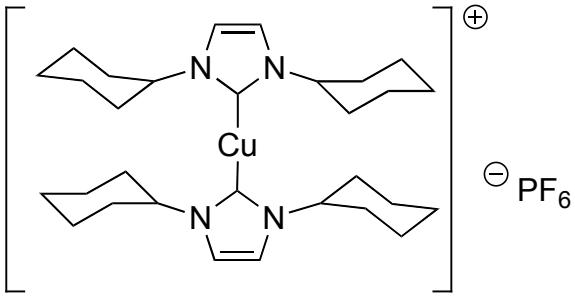
SOMMAIRE

General Considerations

All reagents were used as purchased. Tetrakis(acetonitrile)copper(I) hexafluorophosphate,[i] and ICy·HCl were synthesized according to literature procedures.[ii] All reported yields are isolated yields and are average of at least two runs. ^{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. Assignments of some ^{1}H and ^{13}C NMR signals rely on COSY and/or HMBC experiments. ^{31}P NMR experiments were calibrated with H_3PO_4 as external standard. Elemental analyses were performed at Centro de Microanálisis Elemental of the Universidad Complutense de Madrid (Spain). High Resolution Mass Spectra (HRMS) were performed by the High Resolution Mass Spectromety Service at the Institute of Chemical Research of Catalonia.

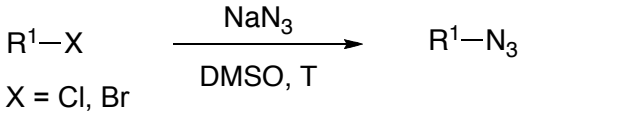
Synthesis of $[(ICy)_2Cu]PF_6$



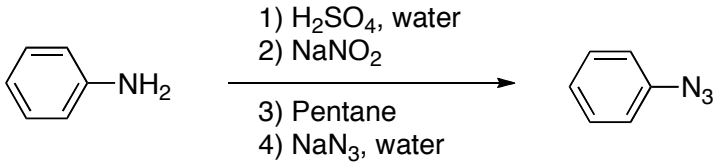
In a vial fitted with a screw cap, tetrakis(acetonitrile)copper(I) hexafluoro phosphate (0.186 g, 0.5 mmol), ICy·HCl (0.268 g, 1 mmol) and NaO-*t*-Bu (0.127 g, 1.3 mmol), were loaded inside a glovebox and stirred in dry THF (12 mL) outside the glovebox for 15 h. After filtering the reaction mixture through a plug of celite (acetone), the filtrate was mixed with pentane to form a precipitate. A second filtration led to the isolation of the title compound as a white solid (0.250 g, 75%). Spectroscopic data for this complex were consistent with previously reported data.[iii]

Synthesis of Azides

Alkyl azides were synthesized at room temperature from the corresponding bromides or chlorides by nucleophilic substitution with sodium azide in DMSO (eq. 1).[iv] Phenyl azide was prepared following a previously reported combination[v] of the methods described by Nölting[vi] and Lindsay[vii] (eq. 2).

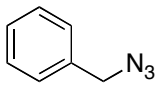


(1)



(2)

Benzyl azide

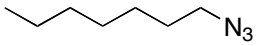


From benzyl bromide (3.6 mL, 30 mmol) and following the Alvarez procedure[4] (1 h, RT), 3.77 g of the title compound were isolated as a light yellow oil after extraction (94%).

Spectroscopic data for the title compound were consistent with the previously reported ones.[4]

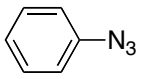
1-Azidoheptane

From 1-bromoheptane (4.7 mL, 30 mmol) and following the Alvarez procedure[4] (5 h, RT), 3.71 g of the title compound were isolated as a light yellow oil after extraction (88%).



Spectroscopic data for the title compound were consistent with the previously reported ones.[viii]

Phenyl azide

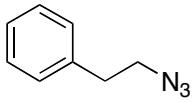


From aniline (6.20 g, 70 mmol) and following the Cwiklicki procedure,[5] 6.70 g of the title compound were isolated as a light yellow oil after extraction (80%).

Spectroscopic data for the title compound were consistent with the previously reported ones.[5,8]

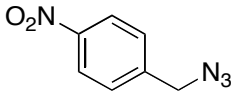
(2-Azidoethyl)benzene

From (2-bromoethyl)benzene (4.0 mL, 30 mmol) and following the Alvarez procedure[4] (5 h, RT), 4.14 g of the title compound were isolated as a light yellow oil after extraction (94%).



Spectroscopic data for the title compound were consistent with the previously reported ones.[ix,8]

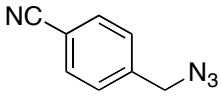
1-(Azidomethyl)4-nitrobenzene



From 1-(bromomethyl)-4-nitrobenzene (6.18 g, 30 mmol) and following the Alvarez procedure[4] (4 h, RT), 4.95 g of the title compound were isolated as a bright yellow oil after extraction (94%).

Spectroscopic data for the title compound were consistent with the previously reported ones.[8]

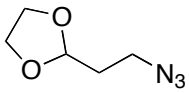
4-(Azidomethyl)benzonitrile



From 4-(bromomethyl)benzonitrile (1.96 g, 10 mmol) and following the Alvarez procedure[4] (3 h, RT), 1.48 g of the title compound were isolated as a light yellow oil after extraction (94%).

Spectroscopic data for the title compound were consistent with the previously reported ones.[8]

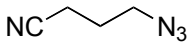
2-(2-Azidoethyl)-1,3-dioxolane



From 2-(2-bromoethyl)-1,3-dioxolane (1.34 mL, 10 mmol) and following the Alvarez procedure[4] (14 h, RT), 1.41 g of the title compound were isolated as a light yellow oil after extraction (99%).

Spectroscopic data for the title compound were consistent with the previously reported ones.[x,8]

4-Azidobutanenitrile

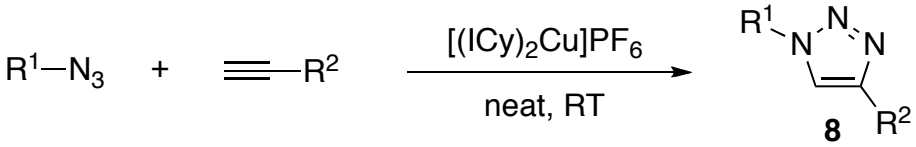


From 4-chlorobutanenitrile (2.2 mL, 25 mmol) and following following the Alvarez procedure[4] (14 h, 60°C), 2.00 g of the title compound were isolated as a light yellow oil after extraction (80%)

Spectroscopic data for the title compound were consistent with the previously reported ones.[xi]

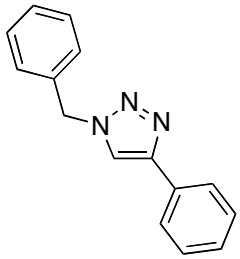
Synthesis of 1,2,3-Triazoles (8)

General Procedure for the [3+2] Cycloaddition of Azides and Terminal Alkynes



In a vial fitted with a screw cap, azide (1.0 mmol), alkyne (1.05 mmol) and $[(ICy)_2Cu]PF_6$ **5a** (3.4 mg, 0.5 mol %) were loaded. The reaction was allowed to proceed at room temperature and monitored by ^{1}H NMR or GC analysis of aliquots. After total consumption of the starting azide, the solid product was simply dissolved in EtOAc and concentrated or alternatively collected by filtration and washed with pentane. 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.

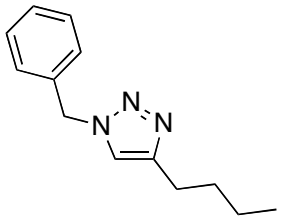
1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (8a)



Using the general procedure from 0.125 mL of benzyl azide and 0.11 mL of phenylacetylene and after 5 min of reaction, 0.234 g of the title compound were isolated as a white solid after evaporation of EtOAc (99% yield).

Spectroscopic data for **8a** were consistent with previously reported data for this compound.[xii]

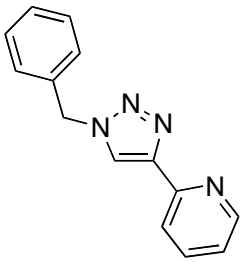
1-Benzyl-4-butyl-1*H*-1,2,3-triazole (8b)



Using the general procedure from 0.125 mL of benzyl azide and 0.118 mL of 1-hexyne and after 45 min of reaction, 0.301 g of the title compound were isolated as a white solid after evaporation of EtOAc (93% yield).

Spectroscopic data for **8b** were consistent with previously reported data for this compound.[xiii]

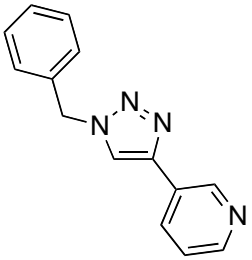
2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)pyridine (8c)



Using the general procedure from 0.125 mL of benzyl azide and 0.11 mL of 2-ethynylpyridine and after 5 min of reaction, 0.230 g of the title compound were isolated as a white solid after evaporation of EtOAc (97% yield).

Spectroscopic data for **8c** were consistent with previously reported data for this compound.[xiv]

3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)pyridine (8d)



Using the general procedure from 0.125 mL of benzyl azide and 0.113 g of 2-ethynylpyridine and after 5 min of reaction, 0.222 g of the title compound were isolated as an off-white solid after filtration and washing with pentane (97% yield).

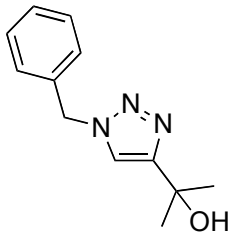
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (s broad, 1H, H^{pyr}), 8.57 (s broad,

1H, H^{pyr}), 8.18 (d, J = 7.92 Hz, H^{pyr}), 7.75 (s, 1H, N–CH=C), 7.44-7.31 (m, 6H, $5H^{Ph}$ + $1H^{pyr}$), 5.61 (s, 2H, $PhCH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2 (CH, CH^{pyr}), 147.0 (CH, CH^{pyr}), 145.2 (C, =C–pyr), 134.3 (C, C^{Ar}), 132.9 (CH, CH^{pyr}), 129.2 (CH, CH^{Ph}), 128.9 (CH, CH^{Ph}), 128.1 (CH, CH^{Ph}), 126.7 (C, C^{Ar}), 123.7 (CH, CH^{pyr}), 119.8 (CH, *C*H=C–pyr), 54.4 (CH_2, Ph–CH_2).

Elemental analysis calcd for $C_{14}H_{12}N_4$ (236.11): C, 71.17; H, 5.12; N, 23.71. Found: C, 71.14; H, 5.16; N, 23.37.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (8e)

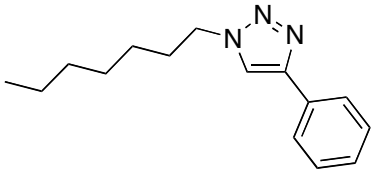


Using the general procedure from 0.125 mL of benzyl azide and 0.102 mL of 2-methylbut-3-yn-2-ol and after 4 h of reaction, 0.198 g of the title compound were isolated as a white solid after evaporation of EtOAc (91% yield).

Spectroscopic data for **8c** were consistent with previously reported data for this compound.[12]

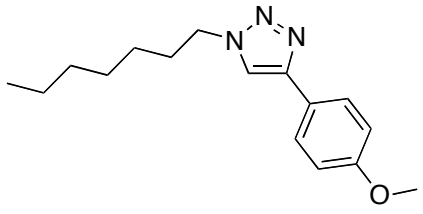
1-Heptyl-4-phenyl-1*H*-1,2,3-triazole (8f)

Using the general procedure from 0.176 g of 1-azidoheptane and 0.11 mL of phenylacetylene and after 5 min of reaction, 0.240 g of the title compound was isolated as a white solid after evaporation of EtOAc (99% yield).



Spectroscopic data for **8c** were consistent with previously reported data for this compound.[8]

1-Heptyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (8g)

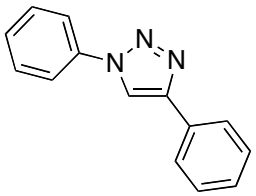


Using the general procedure from 0.176 g of 1-azidoheptane and 0.136 mL of 1-ethynyl-4-methoxybenzene and after 9 h of reaction, 0.259 g of the title compound was isolated as a white solid after evaporation of EtOAc (95% yield).

Spectroscopic data for **8c** were consistent with previously reported data for this compound.[8]

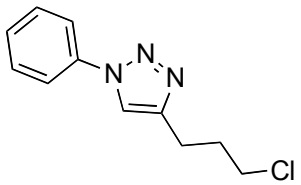
1,4-Diphenyl-1*H*-1,2,3-triazole (8h)

Using the general procedure from 0.119 g of phenyl azide and 0.11 mL of phenylacetylene and after 5 min of reaction, 0.220 g of the title compound was isolated as a white solid after evaporation of EtOAc (99% yield).



Spectroscopic data for **8h** were consistent with previously reported data for this compound.[xv]

4-(3-Chloropropyl)-1-phenyl-1*H*-1,2,3-triazole (8i)



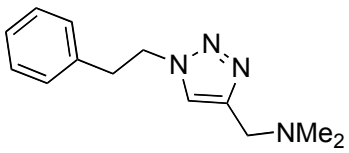
Using the general procedure from 0.119 g of phenyl azide and 0.115 mL of 5-chloropent-1-yne and after 25 min of reaction, 0.218 g of the title compound was isolated as a white solid after evaporation of EtOAc (98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H, CH=C), 7.76 – 7.73 (m, 2H, H^{Ph}), 7.56 – 7.51 (m, 2H, H^{Ph}), 7.46 – 7.42 (m, 1H, H^{Ph}), 3.64 (t, J = 5.1 Hz, 2H, CH_2Cl), 3.00 (t, J = 5.8 Hz, 2H, $=CCH_2$), 2.26 (quintet, J = 5.4 Hz, $CH_2CH_2CH_2Cl$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0 (C, $=CCH_2$), 137.1 (C, C^{Ph}), 129.7 (CH, C^{Ph}), 128.5 (CH, C^{Ph}), 120.4 (CH, C^{Ph}), 119.3 (CH, $CH=CCH_2$), 44.1 (CH_2, CH_2Cl), 31.7 ($=CCH_2$), 22.6 (CH_2, $CH_2CH_2CH_2Cl$).

HRMS calculated for $C_{11}H_{13}ClN_3$: 222.0798. Found: 222.0791($[M+H]^+$).

***N*,*N*-Dimethyl-1-(1-phenethyl-1*H*-1,2,3-triazol-4-yl)methanamine (8j)**



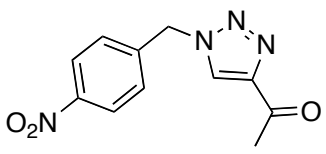
Using the general procedure from 0.147 g of phenethyl azide and 0.118 mL of *N*,*N*-dimethylprop-2-yn-1-amine and after 5 min of reaction, 0.224 g of the title compound was isolated as a yellow oil after evaporation of EtOAc (97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.21 (m, 4H, H^{Ar} + CH=C), 7.09 (d, J = 6.6 Hz, 2H, H^{Ar}), 4.58 (t, J = 7.2 Hz, 2H, Ph–CH_2–CH_2), 3.56 (s, 2H, CH_2NMe_2), 3.21 (t, J = 7.2 Hz, 2H, Ph–CH_2–CH_2), 2.22 (s, 6H, NMe_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9 (C, C^{Ph}), 137.0 (C, CH=*C*), 128.8 (CH, C^{Ph}), 128.6 (CH, C^{Ph}), 127.0 (CH, C^{Ph}), 122.7 (CH, *C*H=C), 54.3 (CH_2NMe_2), 51.6 (Ph–CH_2–CH_2), 45.0 (Ph–CH_2–CH_2), 36.7 (CH_3, NMe).

HRMS calculated for $C_{13}H_{19}N_4$: 231.1610. Found: 231.1609 ($[M+H]^+$).

1-[1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]ethanone (8k)



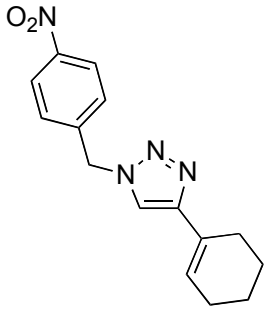
Using the general procedure from 0.176 g of 4-(azidomethyl)-4-nitrobenzene and 0.086 mL of but-3-yn-2-one and after 5 h of reaction, 0.235 g of the title compound was isolated as a white solid after evaporation of EtOAc (96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 8.6 Hz, 2H, H^{Ar}), 8.06 (s, 1H, N–CH=), 7.45 (d, J = 8.6 Hz, 2H, H^{Ar}), 5.70 (s, 2H, N–CH_2), 2.71 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6 (C, C=O), 147.7 (C, C^{Ar}), 148.3 (C, C^{Ar}), 140.6 (C, =*C*–C=O), 128.8 (CH, C^{Ar}), 125.5 (CH, NC*H*=C–C=O), 53.4 (CH2, Ar*C*H_2), 27.1 (CH_3).

Elemental analysis calcd for $C_{11}H_{10}N_4O_3$ (246.22): C, 53.66; H, 4.09; N, 22.75. Found: C, 53.70; H, 4.23; N, 22.66.

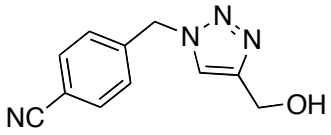
4-Cyclohexenyl-1-(4-nitrobenzyl)-1*H*-1,2,3-triazole (8l)



Using the general procedure from 0.176 g of 4-(azidomethyl)-4-nitrobenzene and 0.118 mL of 1-ethynylcyclohex-1-ene and after 10 min of reaction, 0.262 g of the title compound was isolated as a light yellow solid after evaporation of EtOAc (92% yield).

Spectroscopic data for **8c** were consistent with previously reported data for this compound.[8]

4-{[4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]methyl}benzonitrile (8m)



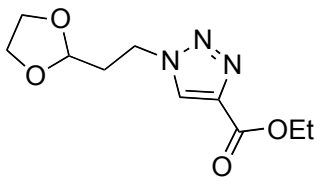
Using the general procedure from 0.158 g of 4-(azidomethyl)benzonitrile and 0.062 mL of prop-2-yn-1-ol and after 5 h of reaction, 0.262 g of the title compound was isolated as a light yellow solid after evaporation of EtOAc (92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 6.8 Hz, 2H, H^{Ar}), 7.52 (s, 1H, NCH=), 7.36 (d, *J* = 6.8 Hz, 2H, H^{Ar}), 5.61 (s, 2H, ArCH_2), 4.82 (d, *J* = 3.7 Hz, CH_2OH), 2.13 (t broad, *J* = 3.7 Hz, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7 (C, =*C*CH_2OH), 139.7 (C, C^{Ar}), 132.9 (CH, CH^{Ar}), 128.4 (CH, CH^{Ar}), 121.8 (CH, *C*H=CCH_2OH), 118.1 (C, CN), 112.8 (C, C^{Ar}), 56.5 (CH_2, ArCH_2), 53.4 (CH_2, CH_2OH).

HRMS calculated for $C_{11}H_{11}N_4O$: 215.0933. Found: 215.0935 ($[M+H]^+$).

Ethyl 1-(2-(1,3-dioxolan-2-yl)ethyl)-1*H*-1,2,3-triazole-4-carboxylate (8n)



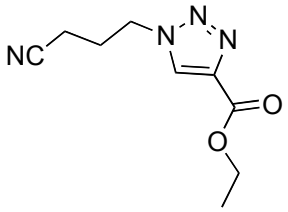
Using the general procedure from 0.143 g of 2-(2-azidoethyl)-1,3-dioxolane and 0.106 mL of ethyl propiolate and after 7 h of reaction, 0.232 g of the title compound was isolated as a light yellow oil after filtration and washing with pentane (96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1H, CH=C), 4.93 (t, *J* = 4.1 Hz, 1H, O–CH–O), 4.58 (t, *J* = 7.1 Hz, CH_2–CH_2–N), 4.44 (q, *J* = 7.1 Hz, OC$H_2$$CH_3$), 4.03 – 3.94 (m, 2H, O–CH_2–CH_2–O), 3.94 – 3.83 (m, 2H, O–CH_2–CH_2–O), 2.34 (dt, *J* = 4.1; 7.1 Hz, CH–CH_2–CH_2), 1.42 (t, *J* = 7.1 Hz, OCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (C, C=O), 139.3 (C, =*C*–CO_2Et), 127.5 (CH, CH=C), 127.5 (CH, O–CH–O), 64.55 (CH_2, O–CH_2–CH_2–O), 64.48 (CH_2, O–CH_2–CH_2–O), 60.6 (CH_2, O*C*H_2–CH_3), 45.0 (CH_2, CH_2–*C*H_2–N), 33.2 (CH_2, *C*H_2–CH_2–N), 13.7 (CH_3)

HRMS calculated for $C_{10}H_{16}N_3O_4$ 222.1141. Found: 222.1133.

Ethyl 1-(3-cyanopropyl)-1*H*-1,2,3-triazole-4-carboxylate (8o)



Using the general procedure from 0.110 g of 4-azidobutanenitrile and 0.106 mL of ethyl propiolate and after 7 h of reaction, 0.195 g of the title compound were isolated as a white solid after evaporation of EtOAc (96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1H, N–CH=), 4.59 (t, *J* = 6.5 Hz, CH_2–C*H*$_2$–N), 4.44 (q, *J* = 7.1 Hz, OCH_2), 2.45 (t, *J* = 6.0 Hz, NC–CH_2), 2.36 (quintet, *J* = 6.9 Hz, C*H*$_2$$CH_2$–N), 1.42 (t, *J* = 7.1 Hz, OCH_2C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4 (C, C=O), 140.6 (C, =*C*–C=O), 127.9 (CH, NCH=), 117.9 (C, CN), 61.3 (CH_2, OCH_2), 48.6 (CH_2, CH_2–*C*H_2–N), 25.7 (CH_2, *C*H_2–CH_2–N), 14.5 (CH_2, NC–*C*H_2), 14.2 (CH_3).

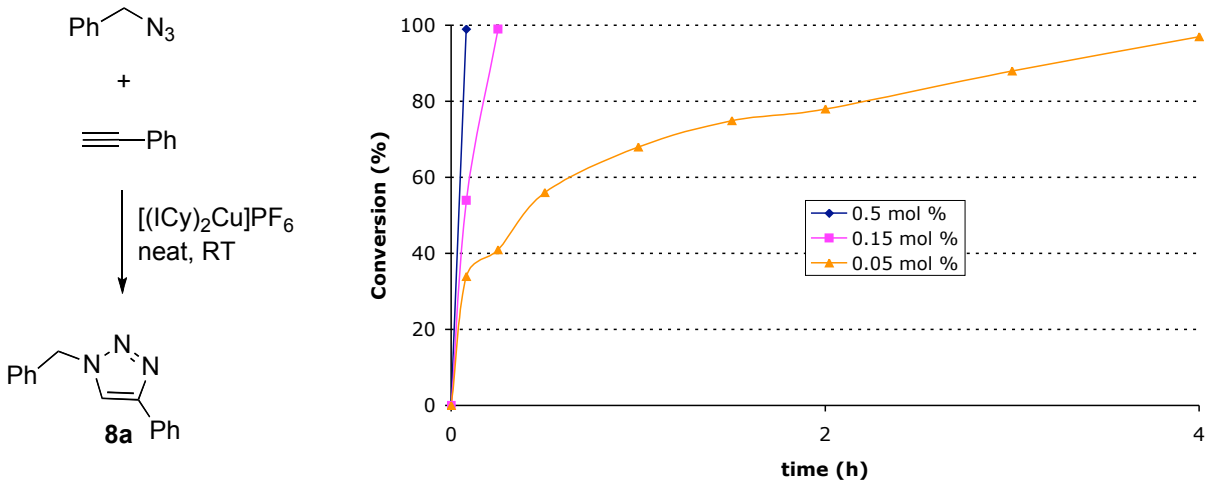
HRMS calculated for $C_9H_{12}N_4O_2Na$: 231.0858. Found: 231.0859 ($[M+Na]^+$)

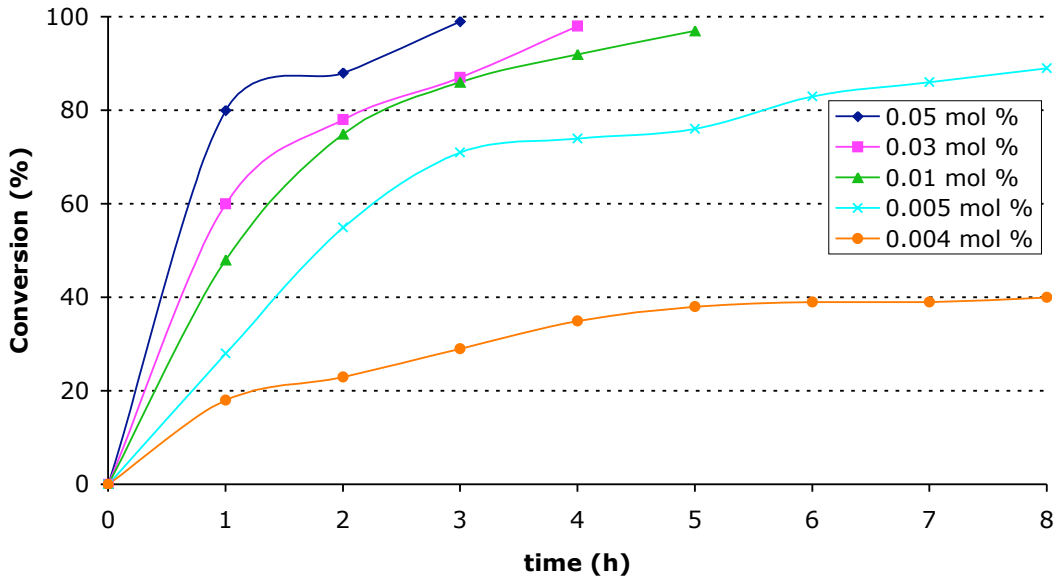
Low Catalyst Experiments

General Procedure for the [3+2] Cycloaddition of Azides and Terminal Alkynes at Low Catalyst Loading

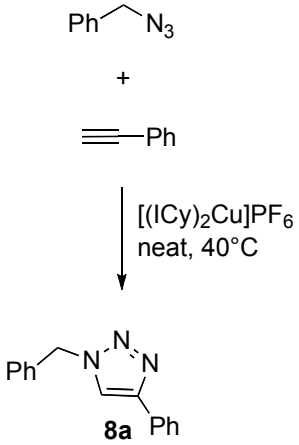
In a vial fitted with a screw cap, the required amount of a freshly prepared solution 0.025 M of $[(ICy)_2Cu]PF_6$ **5a** in MeCN was introduced and the solvent evaporated under a flux of compressed air. Then, azide (1.0 mmol), and alkyne (1.05 mmol) were loaded. The reaction was allowed to proceed at room temperature and monitored by GC analysis of aliquots with hexamethylbenzene as internal standard.

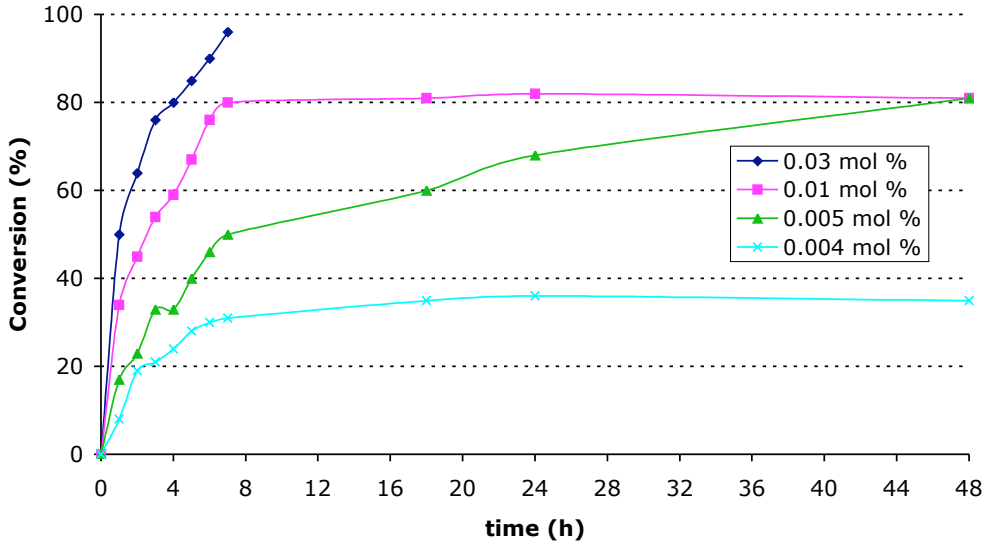
Model reaction at room temperature:





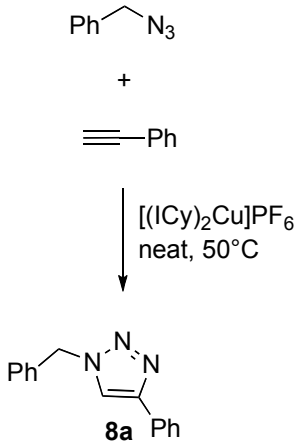
Model reaction at 40°C

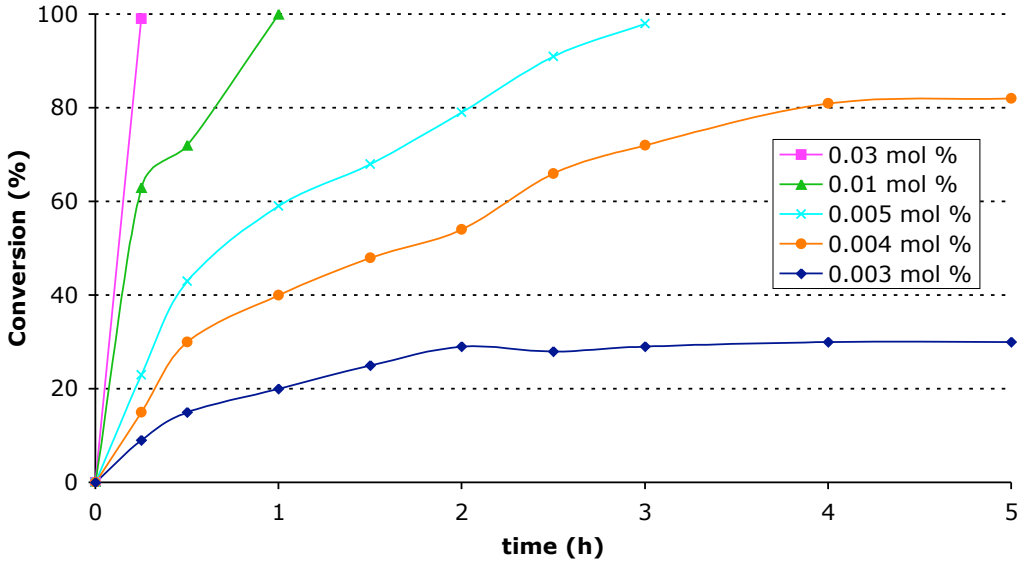




The formation of the 1,5-disubstituted triazole, regioisomer to ***8a****, was observed on GC and* ^{1}H *NMR for reaction times longer than 8 h.*

Model reaction at 50°C

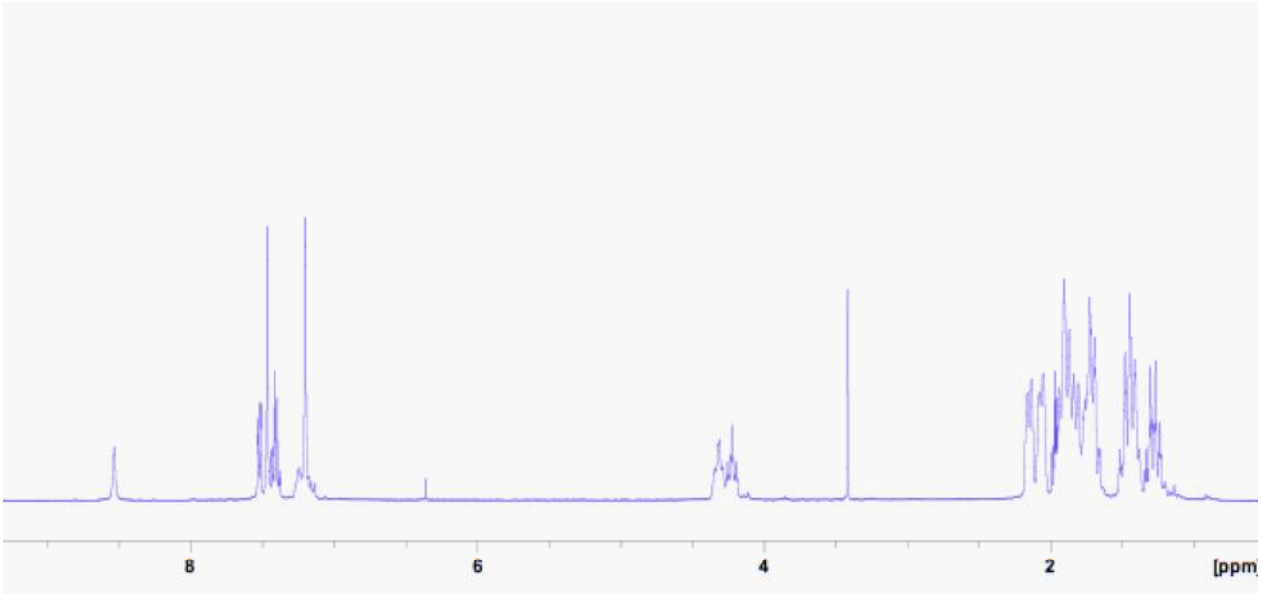




The formation of the 1,5-disubstituted triazole, regioisomer to ***8a****, was observed on GC and* ^{1}H *NMR for reaction times longer than 5 h.*

Mechanistic Studies

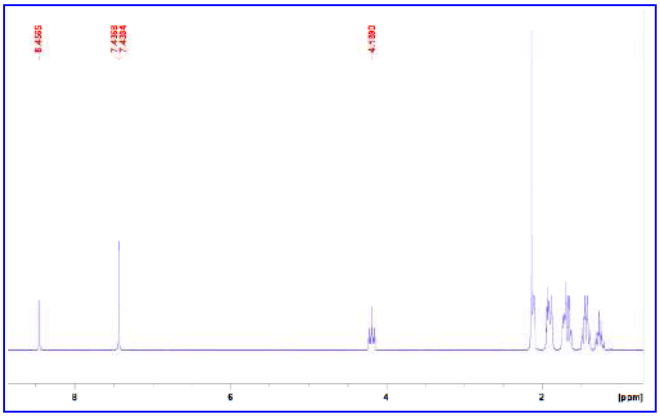
· ***Stoichiometric Reaction 1:***

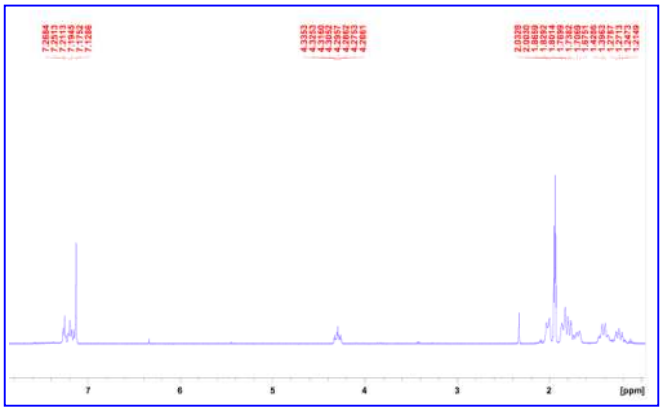


1) Evaporation
2) Toluene

Precipitate

Filtrate





[(ICy)CuC≡CPh] (A)

^{1}H NMR (400 MHz, CD_3CN): δ = 7.29 – 7.23 (m, 2H, H^{Ar}), 7.23 – 7.14 (m, 3H, H^{Ar}), 7.13 (s, 2H, N–CH=), 4.35 – 4.24 (m, 2H, NCH^{Cy}), 2.06 – 1.97 (m, 4H, CH_2^{Cy}), 1.90 – 1.75 (m, 8H, CH_2^{Cy}), 1.75 – 1.65 (m, 2H, CH_2^{Cy}), 1.50 – 1.32 (m, 4H, CH_2^{Cy}), 1.32 – 1.17 (m, 2H, CH_2^{Cy}).

^{13}C NMR (100 MHz, CD_3CN): δ = 178.8 (C, NCN), 132.4 (CH, CH^{Ph}), 130.3 (CH, CH^{Ph}), 129.3 (C), 129.4 (CH, CH^{Ph}), 126.6 (C), 119.4 (CH, NCH=), 108.2 (C, CuC*C*Ph), 62.2 (CH, CH^{Cy}), 35.8 (CH_2, CH_2^{Cy}), 26.7 (CH_2, CH_2^{Cy}), 26.3 (CH_2, CH_2^{Cy}).

ICy·HPF$_6$ (B)

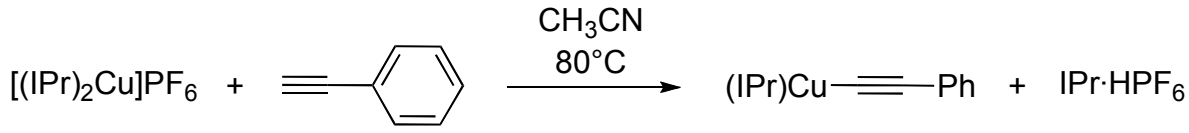
Spectroscopic data in acetone-d$_6$ were consistent with the reported ones.[xvi]

^{1}H NMR (400 MHz, CD_3CN): δ = 8.46 (s, 1H, NCHN), 7.43 (s, 2H, NCH=), 2.19 (tt, 2H, *J* = 3.8, 11.9 Hz, NCH^{Cy}), 2.16 – 2.08 (m, 4H, CH_2^{Cy}), 1.97 – 1.84 (m, 4H, CH_2^{Cy}), 1.78 – 1.60 (m, 6H, CH_2^{Cy}), 1.52 – 1.37 (m, 4H, CH_2^{Cy}), 1.33 – 1.19 (m, 2H, CH_2^{Cy}).

^{13}C NMR (100 MHz, CD_3CN): δ = 133.9 (CH, NCHN), 122.0 (CH, NCH=), 61.1 (CH, CH^{Cy}), 34.1 (CH_2, CH_2^{Cy}), 26.0 (CH_2, CH_2^{Cy}), 25.8 (CH_2, CH_2^{Cy}).

^{31}P NMR (162 MHz, CD_3CN): δ = -141.5 (m)

· ***Stoichiometric Reaction 2:***



In a round-bottom-flask, [(IPr)$_2$Cu]PF$_6$ **1a** (200 mg, 0.2 mmol), phenylacetylene (100 μL, 0.9 mmol) and MeCN (1.5 mL) were loaded under argon atmosphere. The resulting solution was heated at 80°C for 16 h. The ^{1}H NMR of the reaction mixture showed the presence of **1a**, the copper acetylide and IPr·HPF$_6$ in a ratio 30 : 33 : 37. Inside a glovebox, the solvent was evaporated and the resulting precipitate was washed with toluene. Concentration of the filtrate yield 31 mg of [(IPr)CuC≡CPh].

[(IPr)CuC≡CPh]

Whereas the ^{1}H NMR spectrum was in accordance with the one in the literature, we did not observed any resonance at 101.0 ppm in the ^{13}C spectrum, originally assigned to an acetylide carbon.[xvii] Straub and co-workers recently suggested, based on theoretical calculations, that such resonance should be found around 130 ppm instead.[xviii] The original report actually contained such resonance and therefore the identity of the title compound is not doubtful. The reported data simply contained an extra signal, probably due to an impurity.

^{13}C NMR (100 MHz, C_6D_6): δ = 184.4 (C, NCN), 146.0, 135.2, 132.7, 131.0, 128.9, 125.2, 124.6, 123.1, 122.9, 105.4 (C, CuC*C*Ph), 29.4(CH, C*H*CH_3), 25.6 (CH_3), 24.0 (CH_3).

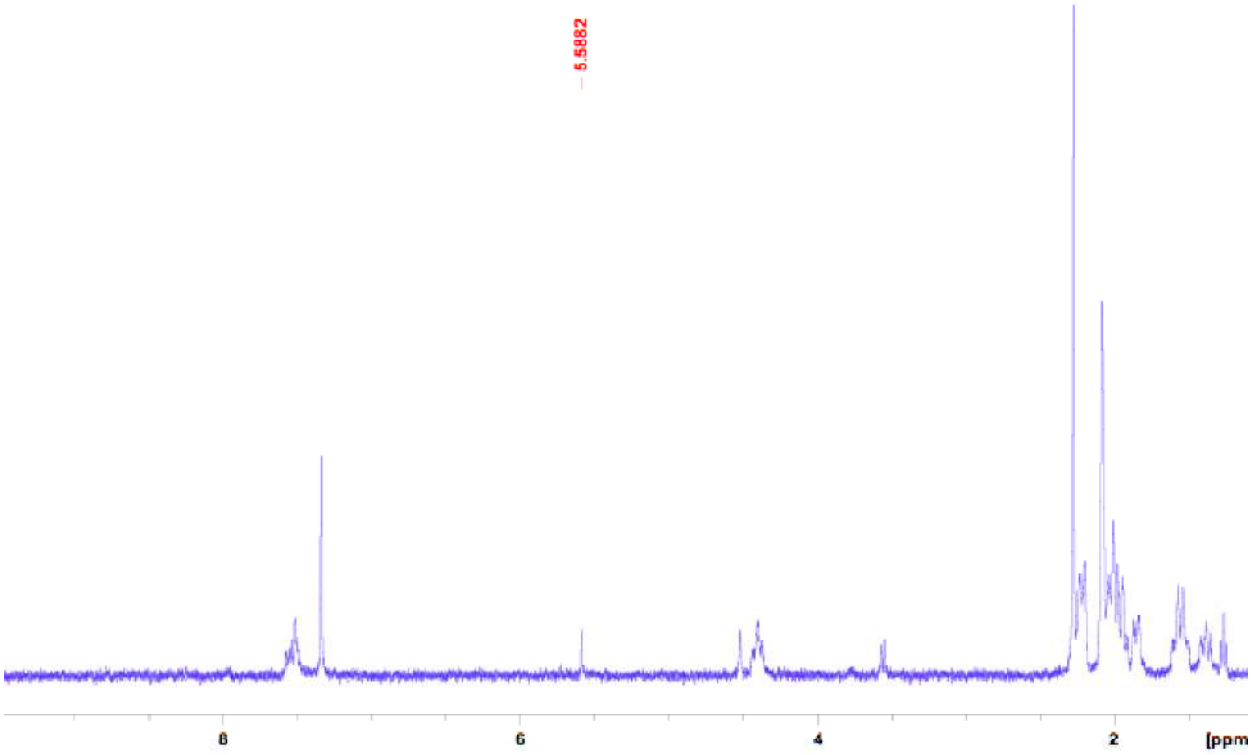
IPr·HPF$_6$

^{1}H NMR (400 MHz, CD_3CN): δ = 9.07 (s, 1H, NCHN), 7.88 (s, 2H, NCH=), 7.65 (t, 2H, *J* = 7.8 Hz, H^{Ar}), 7.46 (d, 4H, *J* = 7.8 Hz, H^{Ar}), 2.40 (sept, 4H, *J* = 6.8 Hz, C*H*CH_3), 1.26 (d, 12H, *J* = 6.8 Hz, CH_3), 1.18 (d, 12H, *J* = 6.8 Hz, CH_3).

^{13}C NMR (100 MHz, CD_3CN): δ = 146.4 (CH, NCHN), 139.0 (C), 133.3 (CH, CH^{Ar}), 130.9 (C), 126.9 (CH, CH^{Ar}), 125.8 (CH, NCH=), 30.0 (CH, *C*HCH_3), 24.6 (CH_3), 23.9 (CH_3).

^{31}P NMR (162 MHz, CD_3CN): δ = -141.5 (m)

· ***Stoichiometric Reaction 3:***



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