A highly efficient copper(I) catalyst for the 1,3-dipolar cycloaddition of azides with terminal and 1-iodoalkynes in water: regioselective synthesis of 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles†‡

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A new water soluble Cu(I) complex that exhibits a versatile and high catalytic activity in the Huisgen cycloadditions of azides and terminal alkynes in aqueous media under mild conditions is the first well-defined Cu(I) catalyst that is active with 1-iodoalkynes in water under aerobic conditions.

Among the most genuine examples of "click chemistry",¹ the copper-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes (CuAAC)² (Scheme 1) has found wide chemical applications in many fields,^{3,4} rendering 1,2,3-triazoles under mild and neutral conditions with high efficiency.



Scheme 1 The copper-catalyzed 1,3-cycloaddition reaction (CuAAC).

Following on from the seminal catalytic systems, generally consisting of a Cu(1) species generated *in situ* from CuSO₄ and sodium ascorbate, important improvements in process efficiency have since been achieved. In particular, it was discovered that the

addition to the reaction medium of nitrogen^{5,6} or phosphorous ligands⁷ greatly improves the catalytic performance.^{8,9} Although, most of the catalytic processes proceed either in organic solvents or in mixtures with water (*i.e.* water/'BuOH), only a few CuAAC reactions have been performed in pure water as the reaction medium;^{8a,8c,8d,9} all of them, however, have used only terminal alkynes. Despite the strong acceleration effect and regioselectivity of many organic reactions in aqueous media,¹⁰ to the best of our knowledge, only one example of an efficient catalytic system for the chemo- and regioselective cycloaddition of azides with internal 1-iodoalkynes has been described to date in an aqueous medium (see Scheme 2), namely an equimolar mixture of CuI and TTTA (TTTA = tris((1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl)amine).^{6e,11}



Scheme 2 The copper-catalyzed formation of 1,4,5-trisubstituted-1,2,3-triazoles.

Since, 5-iodo-1,2,3 triazoles¹² are versatile intermediates for further functionalization, we believed it to be of interest to search for an alternative catalyst to avoid the use of polyamine ligands.¹³ Herein, we report a novel catalyst for Huisgen 1,3-dipolar cycloadditions in pure water based on a PTA-iminophosphorane Cu(1) complex (3) (PTA = 1,3,5triaza-7-phosphaadamantane).¹⁴ This complex represents the first example of an isolated copper(1) catalyst for the reaction of iodoalkynes with azides in aqueous media, the addition of which shows a remarkable activity and tolerance to functional groups, giving 1,4,5-trisubstituted-1,2,3-triazoles chemoselectively.¹⁵

The catalyst precursor (3) is readily prepared from the reaction of [Cu(NCCH₃)₄][PF₆] with hydrophilic iminophosphorane **2** (Scheme 3). Ligand **2** is accessible by attaching the water soluble aminophosphine PTA to the thiophosphoryl azide (EtO)₂P(=S)N₃ *via* a classic Staudinger-type reaction.^{16,17a} Compound **2** was fully characterized by IR and NMR spectroscopy (details are given in the ESI†). In particular, the ³¹P{¹H} NMR spectrum is very informative, showing the presence of two-well separated doublets (²*J*_{PP} = 8.9 Hz) at δ_P –27.92 and 62.38 ppm for the iminophosphorane and thiophosphoryl groups, respectively. The ¹H and ¹³C{¹H} NMR spectra display the expected signals for the PTA backbone.¹⁴ Complex **3** was isolated (81%) as an air and moisture stable white solid that is soluble in water (219 mg mL⁻¹)¹⁸ and behaves as a 1:1 electrolyte in aqueous solution ($A_M = 117 \Omega^{-1} \text{ cm}^{-2} \text{ mol}^{-1}$). The coordination of ligand

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[†] Electronic supplementary information (ESI) available: Synthesis of compounds **2–9**, experimental procedure and crystallographic data for **7a**. See DOI: 10.1039/c0gc00342e

[‡] Typical procedure for the synthesis of 1,2,3-triazoles; synthesis of diphenyl(1-(phenylthiomethyl)-1*H*-1,2,3-triazol-4-yl)methanol (**4d**): 0.0042 g (0.5 mol%) of catalyst **3** was dissolved in 2 mL of H₂O under air. 1,1-Diphenyl-2-propyn-1-ol (1 mmol, 0.208 g) and (azidomethyl)(phenyl)sulfane (1 mmol, 0.142 mL) were added in the presence of 0.012 mL (10 mol%) of 2,6-lutidine. The reaction was stirred at room temperature for 4 h, after which time a yellow powder had formed. The crude of the reaction was washed with CH₂Cl₂ (3 × 10 mL) and the combined organic fractions were concentrated by evaporation to give **4d** as a white solid (0.354 g, 95%).

Typical procedure for the synthesis of 5-iodo-1,2,3-triazoles; synthesis of 5-iodo-4-phenyl-1-(phenylthiomethyl)-1*H*-1,2,3-triazole (**7a**): 0.0168 g (2 mol%) of catalyst **3** was dissolved in 2 mL of H₂O under air. 1-lodo-phenylacetylene (1 mmol, 0.228 g) and (azidomethyl)(phenyl)sulfane (1 mmol, 0.142 mL) were added in the presence of 0.012 mL (10 mol%) of 2,6-lutidine. The reaction was stirred at room temperature for 8 h, after which time a yellow powder had formed. The crude of the reaction was washed with CH₂Cl₂ (3 × 10 mL) and the combined organic fractions were concentrated by evaporation to give **7a** as a white solid (0.377 g, 96%).



Scheme 3 Synthesis of copper(I) complex 3.

2 to copper is reflected in the ${}^{31}P{}^{1}H$ NMR spectrum of 3 by: (i) slight variations in the P=N ($\Delta \delta = 0.5$ ppm) and (RO)₂P=S $(\Delta \delta = 2.4 \text{ ppm})$ resonances with respect to those found for 2, suggesting a κ -S coordination,^{17b,c} and (ii) conversion of the doublet signals of the P=N and (RO)₂P=S groups in the free ligand into two broad signals in complex 3 (see the ESI[†]). Although the formation of the formally 1:2 adduct of the starting reagents [Cu-2ligand][PF₆] is readily deduced from their elemental analysis, the real nature of this complex can only be determined by single-crystal X-ray diffraction methods. An ORTEP-type drawing of the polymeric chain of complex 3 is shown in Fig. 1, and selected bond distances and angles are listed in the caption. The coordination sphere around the copper consists of: (i) two S-coordinated (EtO)₂P=S units, as suggested by the ${}^{31}P{}^{1}H$ NMR data, and (ii) two N-coordinated amino groups from the aminophosphine ring, displaying a distorted tetrahedral geometry (range of bond angles from 103.02(8) [N(1)-Cu(1)-S(2)] to 114.77(9)° [N(5)-Cu(1)-S(1)]). The tetracoordinated copper(I) atoms are bridged by two ligands in a κ^2 -N,S head-to-tail coordination (see Fig. 1), forming a sort of dimetala fourteen-membered ring, giving rise to a polymeric chain. The Cu(1)-S(1) and Cu(1)-S(2) bonds are very similar in length (2.314(1) and 2.320(1) Å, respectively) and compare well with those previously reported for related $P = N - P (= S)(OR)_2$ units coordinated to Cu(I).¹⁹



Fig. 1 ORTEP-type view of the structure of compound 3 showing the crystallographic labelling scheme. Hydrogen atoms, ethyl groups and PF_{6}^{-} anions have been omitted for clarity. Thermal ellipsoids are drawn at the 10% probability level. Selected bond lengths (Å): Cu(1)–S(1) = 2.314(1); Cu(1)–S(2) = 2.320(1); Cu(1)–N(1) = 2.1576(3); Cu(1)–N(5) = 2.131(4). Selected bond angles (°): N(5)–Cu(1)–N(1) = 117.92(11); N(5)–Cu(1)–S(1) = 114.77(9); N(1)–Cu(1)–S(1) = 103.77(8); N(5)–Cu(1)–S(2) = 105.16(8); N(1)–Cu(1)–S(2) = 103.02(8); S(1)–Cu(1)–S(2) = 111.71(4).

Table 1 Synthesis of 1,2,3-triazoles 4-6^a

	H_{2}^{0} R + R'N ₃ H_{2}^{0}		ol% 3 under air 2,6-lutidine		
Entry	R	R′	Product	Time/h	Yield (%) ^b
1	Ph	PhSCH ₂	4 a	6	95
2	<i>n</i> -Bu	PhSCH ₂	4b	6	94
3	Cyclohexenyl	PhSCH ₂	4c	5	93
4	C(OH)Ph ₂	PhSCH ₂	4d	4	95
5	$p-F(C_6H_4)$	PhSCH ₂	4e	4	98
6	$p-NC(C_6H_4)$	PhSCH ₂	4f	5	97
7	CO ₂ Et	PhSCH ₂	4g	3	99
8	Ph	$PhCH_2$	5a	4	94
9	<i>n</i> -Bu	PhCH ₂	5b	4	97
10	Cyclohexenyl	$PhCH_2$	5c	5	93
11	C(OH)Ph ₂	$PhCH_2$	5d	3	94
12	$p - F(C_6H_4)$	$PhCH_2$	5e	3	93
13	$p-NC(C_6H_4)$	$PhCH_2$	5f	4	97
14	CO ₂ Et	$PhCH_2$	5g	2	94
15	Ph	Adamantyl	6a	16	98
16	<i>n</i> -Bu	Adamantyl	6b	22	94
17	Cyclohexenyl	Adamantyl	6c	24	95
18	C(OH)Ph ₂	Adamantyl	6d	24	99
19	p-F(C ₆ H ₄)	Adamantyl	6e	12	96
20	$p-NC(C_6H_4)$	Adamantayl	6f	19	94
21	CO_2Et	Adamantyl	6g	8	96
^{<i>a</i>} Gene	ral conditions:	3 (0.5 mol%),	2,6-lutidi	ne (10 mo	1%), alkyne

"General conditions: 3 (0.5 mol%), 2,6-lutidine (10 mol%), alkyne (1 mmol), azide (1 mmol), 2 mL of H_2O , under air, r.t. ^{*b*} Isolated yield.

The catalytic activity of complex 3 was first evaluated using the cycloaddition of (azidomethyl)(phenyl)sulfane (PhSCH₂N₃) and phenyl acetylene as a model reaction (Table 1, entry 1). In a typical experiment, the reaction of the alkyne and the azide was catalyzed in water by using a 0.5 mol% catalyst loading of complex 3 in the presence of 2,6-lutidine to give the triazole almost quantitatively as the sole reaction product after 6 h at room temperature (as determined by GC and ¹H NMR). The addition of an amine ligand to act as a base was crucial, as no reaction was observed in its absence. The observed rate of the reaction was strongly dependent on the nature of the amine ligand. For example, the efficiency of the reaction was markedly lowered when 2,6-lutidine was replaced by pyridine, TMEDA (tetramethylethylenediamine), NEt₃ or bipyridines such as 1,10phenanthroline (see Table ESI-1 in the ESI for details[†]). It is also remarkable that the reaction proceeds at a higher rate in water than in THF (6 vs. 18 h) or in neat conditions (6 vs. 9 h), thus disclosing a new example of an accelerated organic reaction in water.¹⁰ Catalyst 3 shows a wide applicability for the CuAAC of a wide variety of alkynes with sulfanyl, benzyl and the bulky adamantyl azides, leading exclusively to 1,4-disubstituted-1,2,3 triazoles in excellent yields (Table 1). Importantly, catalyst 3 shows a high tolerance to functional groups, being compatible with the presence of alkenyl (entries 3, 10, and 17), hydroxy (entries 4, 11 and 18), fluoride (entries 5, 12 and 19), nitrile (entries 6, 13 and 20) and ester (entries 7, 14 and 21) groups. In addition, it is worth noting that the high steric demand of the adamantyl substituent does not affect the outcome of the cycloaddition.20

The catalytic activity of 3 was then tested in cycloaddition reactions with 1-iodoalkynes. To our satisfaction, the reactions

	R + R'I	2 m H ₂ O, r.t 10 mol%	nol% 3 ., under air 2,6-lutidine	K 3 nder air 3-lutidine → N R'		
Entry	R	R'	Product	Time/h	Yield (%) ^b	
1	Ph	PhSCH ₂	7a	8	96	
2	<i>n</i> -Bu	$PhSCH_2$	7b	7	93	
3	Cyclohexenyl	$PhSCH_2$	7c	6	94	
4	C(OH)Ph ₂	PhSCH ₂	7d	6	93	
5	p-F(C ₆ H ₄)	PhSCH ₂	7e	7	97	
6	p-NC(C ₆ H ₄)	PhSCH ₂	7f	6	95	
7	CO_2Et	PhSCH ₂	7g	5	96	
8	Ph	PhCH ₂	8a	6	97	
9	<i>n</i> -Bu	PhCH ₂	8b	5	94	
10	Cyclohexenyl	$PhCH_2$	8c	5	95	
11	$C(OH)Ph_2$	$PhCH_2$	8d	5	95	
12	p-F(C ₆ H ₄)	$PhCH_2$	8e	4	97	
13	p-NC(C ₆ H ₄)	$PhCH_2$	8f	6	92	
14	CO_2Et	$PhCH_2$	8g	4	94	
15	Ph	Adamantyl	9a	17	96	
16	<i>n</i> -Bu	Adamantyl	9b	29	98	
17	Cyclohexenyl	Adamantyl	9c	27	93	
18	$C(OH)Ph_2$	Adamantyl	9d	32	97	
19	p-F(C ₆ H ₄)	Adamantyl	9e	27	93	
20	p-NC(C ₆ H ₄)	Adamantyl	9f	31	97	
21	CO_2Et	Adamantyl	9g	11	92	

^{*a*} General conditions: **3** (2 mol%), 2,6-lutidine (10 mol%), alkyne (1 mmol), azide (1 mmol), 2 mL of H_2O , under air, r.t. ^{*b*} Isolated yield.

were catalyzed by 3 (2 mol%) at room temperature in pure water under air, affording quantitatively and chemoselectively the corresponding 5-iodo-1,2,3-triazoles (Table 2) in excellent yields (92-98%). This catalytic performance improves that reported previously, which required 5 mol% of the catalytic system CuI-TTTA.6c No by-products of 5-H-1,2,3-triazoles or other compounds arising from reductive dehalogenation were detected by GC. As for terminal alkynes, the reaction tolerates a diverse array of functional groups in 1-iodoalkynes (Table 2), including alkenyl (entries 3, 10, and 17), hydroxy (entries 4, 11 and 18), fluoride (entries 5, 12 and 19), nitrile (entries 6, 13 and 20) and ester (entries 7, 14 and 21) groups. Moreover, the formation of 5-iodo-1,2,3-triazoles was unambiguously confirmed by a singlecrystal X-ray diffraction study of compound 7a (see the ESI[†]).²¹ Due to the complete chemoselectivity, straightforward workup/purification of the reaction, the mild reaction conditions and the low catalyst loading, the method is highly amenable to scaling-up, and the preparation of 7a in multi-gram quantities is a representative example (see the ESI[†]).

Conclusions

In summary, we have designed a new water soluble, air-stable and highly efficient catalyst, **3**, for CuAAC reactions and the cycloaddition of 1-iodoalkynes in aqueous media under mild and aerobic conditions according to "click" laws¹ that displays a broad substrate scope and functional compatibility. It is important to note the following catalytic features: (i) Catalyst **3** is the first example of an isolated and crystallographicallycharacterized copper(1) catalyst that is active in the cycloaddition of 1-iodoalkynes with azides to give exclusively 5-iodo-1,2,3triazoles. (ii) Its high stability, which allows the reactions to be performed in air and in aqueous media, precludes either oxidation or disproportionation, which are generally associated with most copper(1) catalysts. (iii) The presence of a free thio moiety in the substrate does not deactivate the catalyst, a fact generally observed in CuAAC for functionalized substrates with donor atom groups. Since the reaction is also amenable to low catalyst loadings and is accessible on a multi-gram scale, the practical application of this methodology provides a complementary synthetic tool to familiar CuAAC, providing an important contribution to click chemistry. Further synthetic applications of this catalytic methodology in aqueous media and mechanistic studies to gain insight into the active intermediate active are presently under way.

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