Phosphoramidite accelerated copper(I)-catalyzed [3 + 2] cycloadditions of azides and alkynes†‡

Lachlan S. Campbell-Verduyn,[a] Leila Mirfeizi,[b] Rudi A. Dierckx,[b] Philip H. Elsinga*[b] and Ben L. Feringa*[a]

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Monodentate phosphoramidite ligands are used to accelerate the copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes (CuAAC) rapidly yielding a wide variety of functionalized 1,4-disubstituted-1,2,3-triazoles; Cu(I) and Cu(II) salts both function as the copper source in aqueous solution to provide excellent yields.

Following pioneering work by Huisgen, the discovery by Sharpless *et al.* in 2002 that copper(I) catalyzes the 1,3-dipolar cycloaddition of azides and alkynes to form 1,4-disubstituted triazoles strongly contributed to the popularization of 'click' chemistry as a highly effective method for functionalization.[1] Significant progress has since been made in the application of this methodology to the areas of drug discovery, polymer chemistry, surface functionalization and to medicinal and biological applications, amongst others.[2] Our interest in applying this cycloaddition to time sensitive [^{18}F]-radiolabelling methodology for positron emission tomography (PET) led us to consider the recent advances in ligand accelerated ligations of azides and alkynes. The more general ligand-free 'click' reactions lack an appropriate rate for [^{18}F]-radiolabelling in the absence of high copper concentrations or of numerous equivalents of nitrogen containing base.[3]

Several ligand systems have shown to promote rate enhancement of the CuAAC. Most notably polytriazolylamine (TBTA) has proven to sufficiently enhance the reaction rate to allow for lower catalyst loadings.[4] Although TBTA remains the most widely used ligand,[3,5] related examples have since emerged including benzimidazoles,[6] histidine derivatives,[7] pybox ligands,[8] phosphites,[9] and NHC carbenes.[10] Most of these ligands show acceleration that, while significant, still falls short of the required reaction times for labelling with short-lived radioisotopes. Others require high catalyst loadings or the assistance of higher temperatures[11] and while NHC carbenes have demonstrated very effective acceleration, their use may be limited by their challenging synthetic route.[12]

Phosphoramidites are used as monodentate ligands for copper in a number of stereoselective transformations and have demonstrated strong ligand accelerating effects.[13] They are inexpensive, easily modified, remarkably stable and readily accessible ligands.[14] We report herein the first example of dramatic rate acceleration of the 1,3-dipolar cycloaddition of azides and alkynes using phosphoramidite ligands and the application of the developed methodology to positron emission tomography imaging precursors. Phosphoramidites prove to be excellent, high yielding, easily recovered ligands.

A model reaction of benzyl azide with phenylacetylene was used for preliminary screening of ligand effects. With 1 mol% $CuSO_4{\cdot}5H_2O$ (reduced to Cu(I) with 5 mol% sodium ascorbate), a vast array of phosphorus containing ligands were tested (Table 1). All reactions were performed in a DMSO–H_2O (1 : 3) solution, combining the rate enhancing power of water[1] with the solvation effects of DMSO.

Entry 1 shows that in the absence of ligand, the reaction requires 30 h to reach completion. We were thus delighted to see a dramatic accelerating effect upon addition of a phosphoramidite ligand. MonoPhos (entry 2) decreases the reaction time to 2 h to yield the cycloadduct quantitatively. A diethyl phosphoramidite (entry 3) gave similar acceleration but was slightly lower yielding as was a sterically hindered ligand (entry 4). Increasing the length of the amine alkyl chains proved to decrease the rate of the reaction (entry 5) as did the use of cyclic PipPhos (entry 6). Aromatic substituents at the amine moiety also increased the reaction time. Curious as to the effect of the diol backbone in the ligand upon the reaction rate we investigated several variations and found that both a simple catechol-based phosphoramidite and the less rigid dibenzyl phosphoramidite gave less favourable results than MonoPhos (entries 8 and 9). Oxidized MonoPhos (entry 10) also gave comparatively long reaction times and lower yields. Using triphenylphosphine and triphenyl phosphite as ligands (entries 11 and 12) we tested the effect of phosphorus donor properties and found modest acceleration. The use of more rigid BINAP (entry 13) proved to have a stronger accelerating effect, though still not as significant as that of the BINOL-based phosphoramidites. We concluded that the rigid backbone is a key factor in the effectiveness of our ligand. In all cases a single regioisomer of the product was obtained.

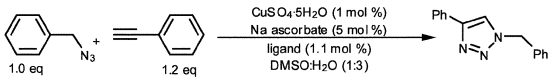
We proceeded with MonoPhos to investigate alternative reaction parameters. Varying the concentration first of the azide and then of the alkyne indicated that a fourfold excess of either substrate initially improves rates; after 10 min conversions were 47 and 80%, respectively. An excess of alkyne proved to be a superior choice for overall rate enhancement, reducing the reaction time from 2 h to 30 min. In view of the

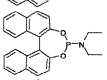
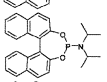
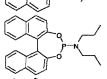
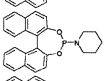
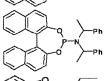
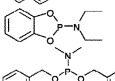
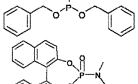
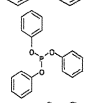
[a] *Stratingh Institute for Chemistry, University of Groningen, Groningen, The Netherlands. E-mail: b.l.feringa@rug.nl; Fax: +31 50 363 4278; Tel: +31 50 363 4296*
[b] *Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. E-mail: p.h.elsinga@ngmb.umcg.nl; Fax: +31 50 3696750; Tel: +31 50 3614850*

† Dedicated to Prof. Roeland J. M. Nolte on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: General procedures for the synthesis of azides and triazoles, ^{1}H and ^{13}C NMR data for all compounds. See DOI: 10.1039/b822994e

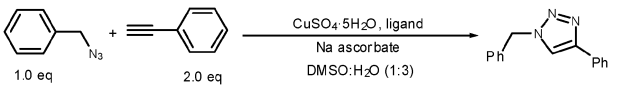
Table 1 Effect of ligand on the copper(I)-catalyzed [3 + 2] cycloaddition of phenylacetylene and benzyl azide



Entry	Ligand	Time to completion/h	Yield[a] (%)
1	none	30	88
2		2	98
3		2	90
4		2	93
5		2.5	97
6		7	86
7		5	91
8		4	85
9		10	75
10		15	58
11		10	96
12		10	93
13		4	78

[a]Isolated yield after purification by column chromatography.

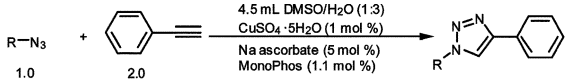
Table 2 Effect of catalyst loading upon reaction time

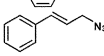
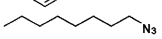


Cu (mol%)	Ligand[a]	Conv. at 10 min (%)	t/[b]min	Yield (%)[c]
1	2 (1.1%)	21	60	91
5	2 (5.5%)	45	40	93
10	2 (11%)	60	30	92
1	3 (1.1%)	16	100	90
5	3 (5.5%)	38	80	95
10	3 (11%)	43	40	89

[a] See entries 2 and 3 (Table 1). [b] For completion. [c] Isolated yield.

Table 3 Azide scope for the azide–alkyne cycloaddition



Entry	Azide	t/h	Yield[a] (%)
1		1	91
2		1.5	84
3		4	88
4		2	80
5		2	71
6		2	81
7		1.5	96
8		2.5	99
9		1.5	90
10		0.75	83

[a] Isolated yield.

goal to achieve a fast method for radiolabelling we subsequently work with 2.0 eq. of alkyne for this reason.

Increasing the catalyst loading had the expected effect of enhancing the rate of the reaction. From 1 mol% to 10 mol%, it was possible to significantly decrease the reaction time to achieve full completion within 30 min with MonoPhos (ligand 2) (Table 2). However, 1 mol% copper catalyst gives sufficiently rapid reaction times, making it unnecessary to rely on higher catalyst loadings to achieve the desired rates. Increasing the copper concentrations above 10 mol% gave rise to copper clusters precipitating out of solution.

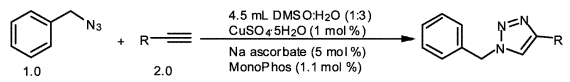
With optimized parameters in hand, we explored the substrate scope.

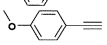
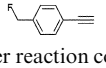
The reaction proceeded very smoothly with a wide variety of azides (Table 3). We found that phenyl azide gave the slowest reaction, taking 4 h to proceed to completion (entry 3) whereas phenylazides with methoxy, bromo, and cyano substituents at the *para* position reacted fully within 2 h (entries 4, 5 and 6). This is consistent with the recently published discovery by Finn *et al*. that electron withdrawing or donating substituents in place of both hydrogen or methyl groups on the azide substrate result in a rate increase.[15] Alkyl substrates 1-azidooctane and 1-azido-4-fluorobutane also gave fast conversions and excellent yields (entries 8 and 9). Unsaturated and ester functionalized azides reacted very quickly with no detectable evidence of side product formation (entries 7 and 10). Both resulting triazoles are primed for further functionalization. Of particular interest to us were the rapid conversions of the fluorine containing aryl and alkyl azides to their corresponding triazoles (entries 2 and 9). [^{18}F] labelled analogues of these compounds have been prepared to label target compounds using this rapid 'click' protocol.

A similar investigation of the alkyne scope revealed significant differences in the rates of various substrates (Table 4) likely due to electronic or steric effects (or both) upon the initial formation of the copper acetylide species considered the active species in the catalytic cycle.[3]

Compared with the model substrate phenylacetylene, 1-ethynyl-4-methoxybenzene and 1-ethynyl-4-fluoromethylbenzene had slightly longer reaction times but still reacted quickly with good yields (entries 2 and 7). An electron withdrawing group in the *ortho* position of the ring seemed to have a negative effect on the rate, however we noted in the course of this reaction that the solubility of the substrate was poor. We were pleased to see that an ester functionalized alkyne reacted smoothly (entry 4). Reaction with propargyl amine (entry 6) showed very rapid conversion to the corresponding triazole (70% in 1 h),

Table 4 Alkyne scope for the [3 + 2] azide-alkyne cycloaddition



Entry	Alkyne	*t*/h	Yield (%)
1		1	91
2		1.5	86
3		5	62
4		2	87
5		1	59[a]
6		1	65[b]
7		2	93

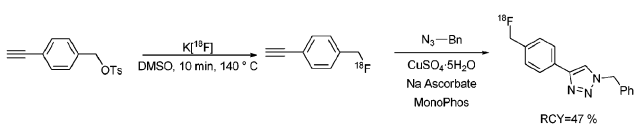
[a]Isolated yield after reaction completion (13 h). [b]Reaction only reaches 70% conv.

however, no further conversion was detected. Closer consideration of the resulting triazole led us to conclude that it is an excellent ligand for Cu(I), and was used by Sharpless *et al.* to catalyze the [3 + 2] cycloaddition of azides and alkynes.[4] With nearly one equivalent of the triazole product with respect to catalytic copper, the metal center risks saturation and inhibition of any further catalysis. Propiolic acid (entry 5) showed similar behaviour, reaching 55% conversion after 1 h and then requiring a further 12 h to reach full conversion.

As a copper source for the CuAAC, $CuSO_4{\cdot}5H_2O$ in combination with the water-soluble reducing agent sodium ascorbate is overwhelmingly favoured. Although Cu(I) salts can also be used, they require an equivalent of nitrogen containing base to promote the reaction.[2] They cannot be used in the presence of water due to the inherent thermodynamic instability of copper(I), resulting in its easy oxidation to copper(II).[16] A greater likelihood of side-product formation is observed in cases where copper(I) salts are used.[2,17]

We anticipated that the phosphoramidite might stabilize the catalytically active Cu(I) oxidation state. We tested a range of readily available copper(I) salts in aqueous solution (Table 5) and indeed found that they give excellent reaction times and yields, with no evidence of side product formation (alkyne–alkyne homocoupling for instance) detected.[2]

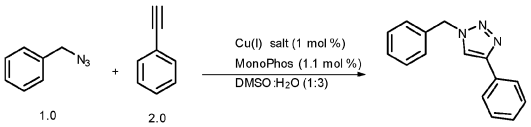
To test our methodology on the required time scale for radiolabelling, we synthesized [^{18}F]-fluorinated 1-ethynyl-4-(fluoromethyl)benzene (Scheme 1). After fluorination, it was ligated to benzyl azide in the presence of $CuSO_4{\cdot}5H_2O$ and MonoPhos. Full conversion to the labelled triazole was detected after 10 min (as determined by HPLC and radio-TLC). Under identical conditions but in the absence of ligand, only minor conversion to the triazole product was detected (<20%).



Scheme 1 Synthesis of [^{18}F]-labelled triazole (RCY = radiochemical yield).

In conclusion, we have applied phosphoramidite copper complexes to the azide–alkyne [3 + 2] cycloaddition and found that they enhance the rate of the reaction and stabilize the catalytically active copper(I) oxidation state. The system is versatile and functional group independent, a requirement in the field of 'click' chemistry. The methodology has been applied to the attachment of small [^{18}F]-labelled prosthetic groups to a model azide.

Table 5 [3 + 2] Cycloaddition with copper(I) salts



Copper salt	*t*/h	Yield (%)
CuCl	1	99
CuBr	2	94
CuI	3.5	89
CuBr·DMS	1	95

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