'Click for PET'

Campbell-Verduyn, Lachlan Schuyler

Chapter 3
Ligand Accelerated Copper(I)-Catalyzed Azide-Alkyne Cycloadditions

A new catalytic system using the phosphoramidite ligand MonoPhos was developed for the purpose of achieving rate acceleration of the copper catalyzed 1,3-dipolar cycloaddition of azides and alkynes. This methodology was optimized to achieve dramatic rate enhancement and applied for the ligation of [^{18}F]-containing prosthetic groups for positron emission tomography. Phosphoramidites proved to be excellent rate accelerating, high yielding ligands.

Part of this chapter was published:
L. S. Campbell-Verduyn, L. Mirfeizi, R. A. Dierckx, P. H. Elsinga, B. L. Feringa, *Chem. Commun.* **2009**, *16*, 2139-2141.

Radiolabelling procedures were performed by Leila Mirfeizi.[1]

[1] Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen

3.1 Introduction

Following pioneering work by Huisgen,[1a] the discovery by Sharpless *et al*[1b] and Meldal *et al*[1c] in 2002 that copper(I) catalyzes the 1,3-dipolar cycloaddition of azides and alkynes to form 1,4-disubstituted triazoles (CuAAC) 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 for medicinal and biological applications, amongst others.[2]

One such application has been the labelling of biological targets with short lived radioisotopes for nuclear imaging by positron emission tomography (see Chapter 1, Section 1.9). It is crucial in the area of radiolabelling to have reaction times that are as short as possible to conserve the maximum amount of radioactivity, which is constantly decaying with time. Publications describing the application of the CuAAC to [^{18}F]-labelling have demonstrated that to achieve such desired reaction times, elevated copper concentrations (ranging from 50 mol % to several equivalents) must be used.[3] However, such large excesses of copper salts are less than ideal as copper can contaminate the resulting tracer which is to be injected in living organisms. As copper is cytotoxic, this is a potential drawback of the methodology. Alternatives to such high copper concentrations for the acceleration of the CuAAC are desirable. One possible option to accelerate the reaction without resorting to elevated copper concentrations would be to use ligands. Although the reaction proceeds smoothly on its own, several ligand systems have shown to promote rate enhancement of the CuAAC.[4] Most notably polytriazolylamine tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine **1** (TBTA) has proven to sufficiently enhance the reaction rate to allow for lower catalyst loadings (Figure 1).[5] Although TBTA (**1**) remains the most widely used ligand,[3,6] related examples have since emerged including the water soluble sulfonated bathophenanthroline (**2**),[4] benzimidazoles (**3**),[7] pybox ligands (**4**),[8] phosphites,[9] NHC carbenes (**5**)[10] and histidine derivatives (**6**).[11] Most of these ligands show acceleration that, while significant, still falls short of the required reaction times for labelling with short-lived radioisotopes. Others still require high catalyst loadings or the assistance of higher temperatures[12] and while NHC carbenes have demonstrated very effective acceleration, their use may be limited by their challenging synthetic route.[13]

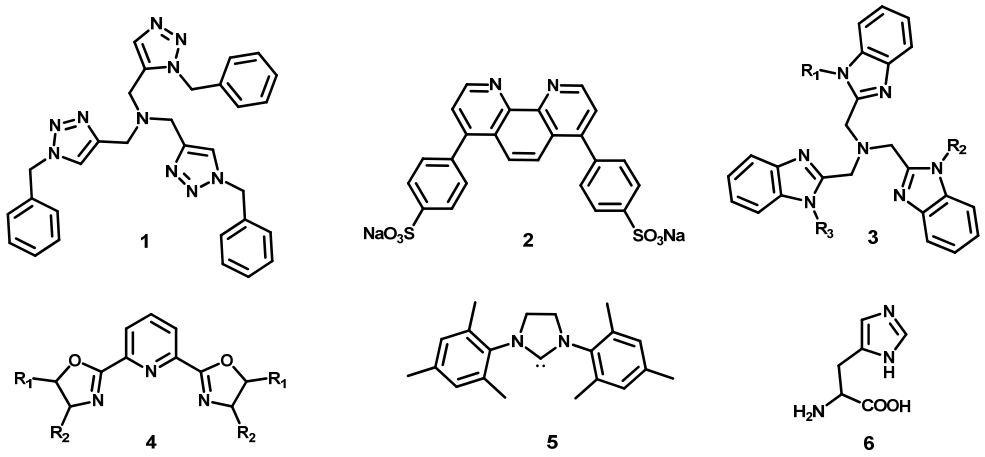
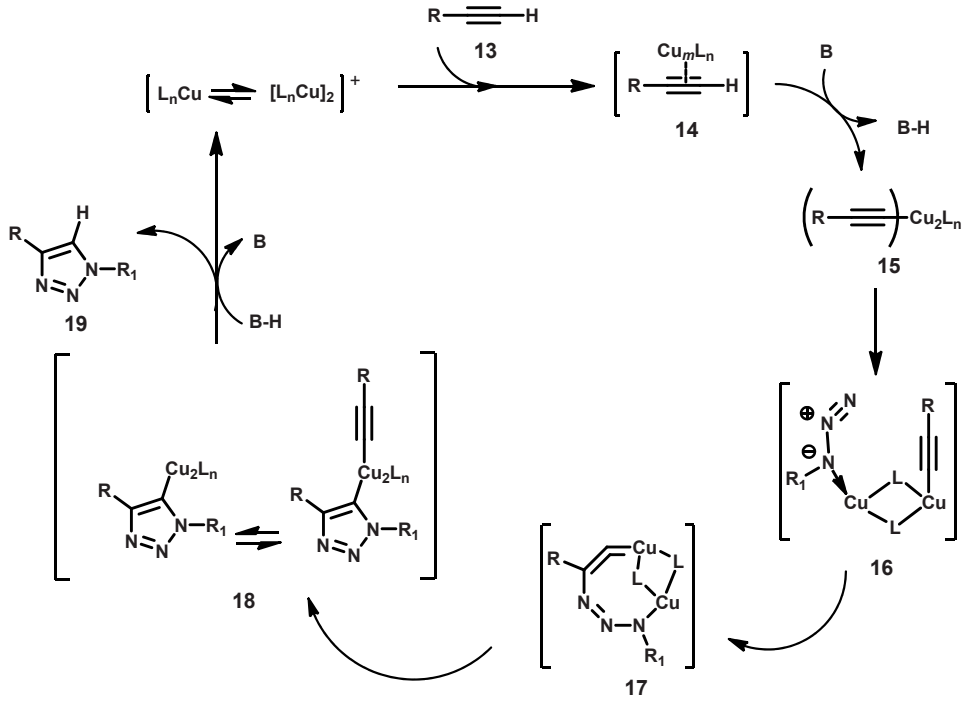


Figure 1 Ligands used to promote the CuAAC

It is widely accepted that the addition of a ligand in the CuAAC serves two purposes. In one instance, it stabilizes the oxidation state of Cu(I), protecting it from being oxidized by various external species.[4] This allows for a high level of the catalytically active complexes in solution. It is also suggested that a variety of Cu(I) complexes exist in the reaction medium and that the presence of ligands can alter the equilibrium between the multi-nuclear copper complexes, dissociating stable clusters to help form active complexes.[4] Recent investigations into the proposed mechanism of the copper(I)-catalyzed azide alkyne cycloaddition unearthed a complex set of data that led to the conclusion that there are multiple species involved in ligand accelerated catalysis, which may depend on any number of factors (Scheme 1).[14] Variation of reaction conditions (pH, concentration, solvent) proved to have a very pronounced effect on the efficiency of a given ligand in accelerating triazole formation. This is indicative of sensitive cluster formation which in turn has a large impact on the catalytic efficiency.



Scheme 1 Proposed mechanism cycle of the CuAAC[15]

Phosphoramidites[16] (Figure 2) are used as monodentate ligands for copper in a number of stereoselective transformations and have demonstrated strong ligand accelerating effects.[17] They contain a trivalent phosphorus, and differ from other phosphorus ligands in that they contain two P-O bonds and one P-N bond. They typically have electronic donor-acceptor properties that lie in a range between those of arylphosphites and arylphosphines. Both the nitrogen and the phosphorus atoms have one lone pair of electrons, and they can bind either in a monodentate fashion through the phosphorus or in bidentate fashion with extra coordination achieved by cyclometallation or by coordination from a substitution on the amine.[15] Phosphoramidites have shown to coordinate to a wide variety of transition metals including copper. They are inexpensive, easily modified, remarkably stable and readily accessible ligands.[18] Their facile modularity makes them an appealing class of ligands as the properties of the ligands and thus of the metal-ligand complex are more readily tuned for specific applications.[19]

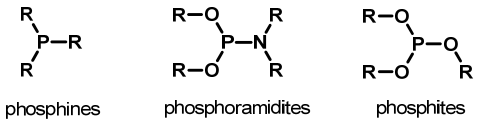


Figure 2 Phosphorus ligands

3.2 Goal

Our interest in applying the CuAAC 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 CuAAC reactions lack an appropriate time scale for [^{18}F]-radiolabelling in the absence of high copper concentrations or of numerous equivalents of nitrogen containing base.[20] To achieve the broader goal of implementing 'click' chemistry into the toolbox of accessible reactions for radiolabelling, acceleration of the standard reaction is required. The goal of this project is to develop a ligand accelerated system that is robust and simple to use but that gives the desired rates of reaction and that allows for lower concentrations of substrates to be used, facilitating purification of the desired tracer. We set for ourselves a benchmark of 10 to 15 min reaction times. Full conversion is not necessarily a requirement for successful conditions if the first 10-15 min are high yielding.

3.3 Condition Optimization

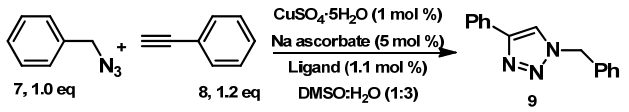
Based on the existing examples of rate accelerating ligands present in the literature, a variety of nitrogen and phosphorus containing ligands were screened in an attempt to find a new ligand system to provide the desired rate acceleration. A model reaction of benzyl azide **7** with phenylacetylene **8** was used for preliminary screening of ligand effects. The initial screening was performed using 1 mol % of $CuSO_4 \cdot 5H_2O$ (reduced *in situ* to Cu(I) with 5 mol % sodium ascorbate) because this provided a reaction time of 30 h to reach full conversion. This was a time frame that was sufficiently long to allow us to ascertain if the addition of a ligand had an effect on the rate.

A vast array of phosphorus and nitrogen containing ligands were tested (Table 1). Chiral ligands were used in their racemic form. 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. DMSO also helps prevent copper from being saturated by the ligand by binding competitively to the copper center, and also prevents inhibitory aggregation.[21] In the absence of a ligand, the reaction under the selected conditions only achieves 88 % conversion after 24 h (entry 1). After approximately 30 h, the ligand free reaction reaches completion. Using tertiary amine **L1** as a ligand significantly decreases the

overall reaction time, achieving full conversion after 4 h (entry 2). A secondary amine **L2** bearing the same bipyridyl group and a benzylic phenol proved to have a detrimental effect on the progress of the reaction compared with ligand-free conditions (entry 3). The bulky diimino ligand **L3** showed similarly poor results (entry 4), as did the bipyridyl containing, phenolic secondary amine **L4** (entry 5). Pyridine-2,6-diyldimethanol **L5** also slowed the reaction, reducing the conversion to 27 % after 24 h (entry 6) and the addition of *N*',*N*',*N*'-trimethyl-1,4,7- triazacyclononane **L6** (MeTACN) resulted in no conversion at all, even after 24 h (entry 7). More encouraging results were achieved with phosphorus containing ligands. Triphenyl phosphine **L7** and triphenyl phosphite **L8** (entries 8 and 9) showed modest acceleration, reducing the time to full conversion to 10 h. The use of more rigid BINAP **L9** (entry 10) proved to have a stronger accelerating effect, reducing the reaction time to 4 h. Given the positive effect of the tertiary nitrogen containing ligands, as well as the more rigid phosphorus containing BINAP ligand, a simple phosphoramidite ligand was tested. The use of MonoPhos **L10** (entry 11) showed a dramatic rate accelerating effect, decreasing the reaction time to 2 h and yielding the cycloadduct nearly quantitatively.

One of the key advantages of phosphoramidites as a class of ligands is their modularity.[16] Both the phosphorus backbone and the amine can be varied to a wide degree. Given the positive result that was achieved using MonoPhos, a more thorough screening of phosphoramidites was undertaken (Table 2). MonoPhos was synthesized with *(R)*-BINOL, *(S)*-BINOL and racemic 1,1'-bi-2-naphthol (BINOL). All three ligands were compared in the CuAAC and proved to give identical results. Thus all subsequent phosphoramidites were synthesized as racemates. Diethyl phosphoramidite **L11** (entry 3) gave similar acceleration as did the more sterically hindered diisopropyl phosphoramidite **L12** (entry 4). Increasing the length of the amine alkyl chains (**L13**) proved to decrease the rate of the reaction (entry 5) as did the use of cyclic PipPhos **L14** (entry 6). Benzylic substituents at the amine moiety (**L15**) also increased the reaction time. Curious as to the effect of the diol backbone of the ligand upon the reaction rate, we investigated several variations and found that both a simple catechol-based phosphoramidite **L16** and the less rigid dibenzyl phosphoramidite **L17** gave less favourable results than MonoPhos **L10** (entries 8 and 9). Oxidized MonoPhos **L18** (entry 10) also gave comparatively long reaction times and lower yields. We concluded that the rigid backbone is a factor in the effectiveness of the ligand on this system. In all cases the sole product obtained was the 1,4-regioisomer.

Table 1 Initial screening of ligands for CuAAC



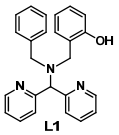
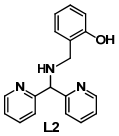
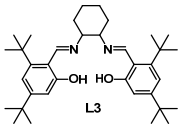
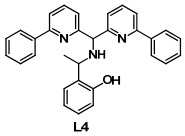
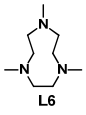
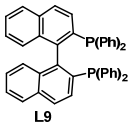
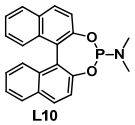
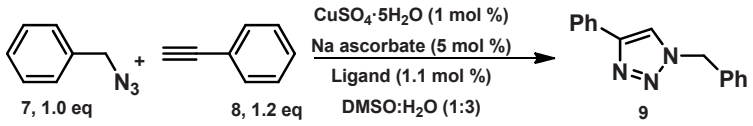
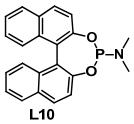
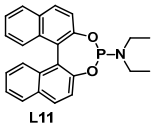
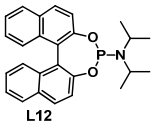
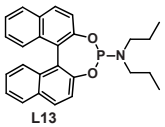
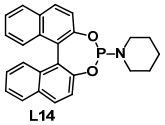
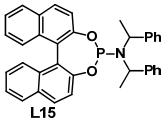
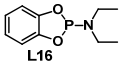
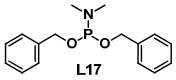
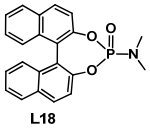
	Ligand	Time (h)	Conversion (Yield)
1	None	24	88
2	 L1	4	100 (90)
3	 L2	24	17
4	 L3	24	18
5	 L4	24	70
6	 L5	24	27
7	 L6	24	0
8	$P(Ph)_3$ L7	10	100 (96)
9	$P(OPh)_3$ L8	10	100 (93)
10	 L9	4	100 (78)
11	 L10	2	100 (98)

Table 2 Screening of phosphoramidite ligands in the ligand enhanced CuAAC

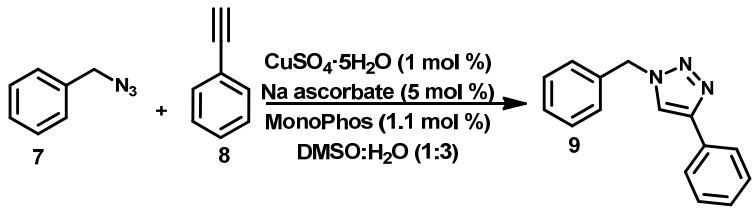


	Ligand	Time[a] (h)	Yield[b] (%)
1	None	30	88
2	 L10	2	98
3	 L11	2	90
4	 L12	2	93
5	 L13	2.5	97
6	 L14	7	86
7	 L15	5	91
8	 L16	4	85
9	 L17	10	75
10	 L18	15	58

[a]To full conversion. [b]Isolated yield.

Proceeding with MonoPhos as a ligand, further reaction parameters were explored. Varying the concentration first of the azide and then of the alkyne indicated that a four-fold excess of either substrate initially improves rates; after 10 min conversions were 47 and 80%, respectively (Table 3). An excess of alkyne proved to be a superior choice for overall rate enhancement, reducing the total reaction time from 2 h to 30 min. In view of our goal to achieve a fast method for radiolabelling we subsequently work with an excess of alkyne. Although 4.0 eq showed dramatic acceleration, we opted to work with 2.0 eq of alkyne in all subsequent experiments, as 4.0 eq is quite excessive. We also found that by adding 1 mol % of MeTACN (**L6**) the reaction could be stopped with no further conversion to the product.[22]

Table 3 Effect of relative substrate concentration

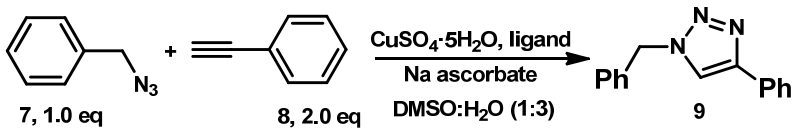


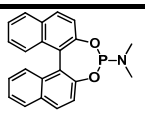
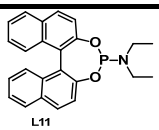
7 8 9

Eq. Azide	Eq. Alkyne	% Conversion at 10 min	Time to Completion
1.0	1.0	15	2 h
4.0	1.0	47	2.5 h
1.0	4.0	80	30 min

Increasing the catalyst loading had the expected effect of enhancing the rate of the reaction. From 1 to 5 to 10 mol %, it was possible to significantly decrease the reaction time to achieve full completion within 30 min with MonoPhos **L10** (Table 4). Performing the same experiments with diethyl phosphoramidite **L11** demonstrated the same trend, as the amount of copper was increased, the time to completion decreased. Comparing the results from entries 1-3 and entries 4-6, it is clear that MonoPhos **L11** has superior accelerating effects on this system. Increasing the copper concentrations above 10 mol % gave rise to copper clusters precipitating out of solution.

Table 4 Effect of catalyst loading upon reaction time

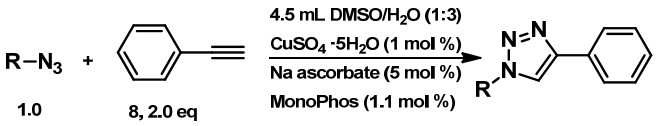


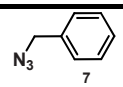
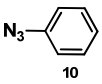
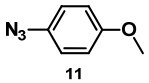
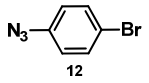
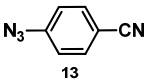
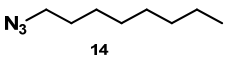
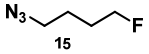
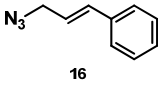
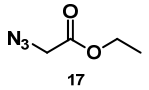
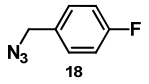
	Cu:Ligand (mol %)	Ligand	Conversion at 10 min (%)	Time (min)[a]	Yield[b] (%)
1	1:1.1	 L10	21	60	91
2	5:5.5		45	40	93
3	10:11		60	30	92
4	1:1.1	 L11	16	100	90
5	5:5.5		38	80	95
6	10:11		43	40	89

[a]For completion. [b]Isolated yield.

Following these initial investigations, the substrate scope of the reaction was explored. The CuAAC proceeded very smoothly with a wide variety of azides (Table 5). Using 2.0 eq of phenylacetylene **8**, benzyl azide **9** can be transformed into triazole **11** but now within an hour (Table 5, entry 1) rather than the two hours required when only 1.0 equivalent of **8** was used (Table 2 entry 2). Phenylazide **10** gave the slowest reaction, taking 4 h to proceed to completion (entry 2) whereas phenylazides with methoxy (**11**), bromo (**12**), and cyano (**13**) substituents at the *para* position reacted fully within 2 h (entries 3, 4 and 5). 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. [23] Alkyl substrates 1-azidooctane **14** and 1-azido-4-fluorobutane **15** also gave fast conversions and excellent yields (entries 6 and 7). Unsaturated and ester functionalized azides **16** and **17** reacted very quickly to produce triazoles set for further functionalization (entries 8 and 9). Of particular interest to us were the rapid conversions of the fluorine containing aryl and alkyl azides to their corresponding triazoles (entries 7 and 10). [^{18}F]-labelled analogues of these compounds have been prepared to label target compounds using this rapid 'click' protocol.[24] In general it seems that the MonoPhos accelerated CuAAC tolerates a wide range of azides with just slight variations in reaction time.

Table 5 Azide scope for the azide-alkyne cycloaddition

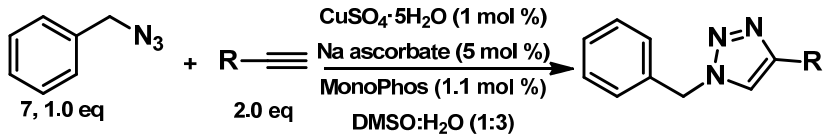


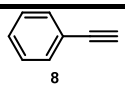
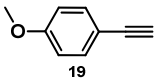
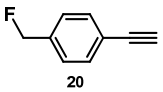
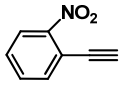
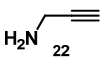
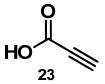
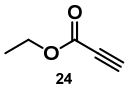
	Azide	Time[a] (h)	Yield[b] (%)
1	 7	1	91
2	 10	4	88
3	 11	2	80
4	 12	2	71
5	 13	2	81
6	 14	2.5	99
7	 15	1.5	90
8	 16	1.5	96
9	 17	0.75	83
10	 18	1.5	84

[a]Time to completion. [b]Isolated yield.

A similar investigation of the alkyne scope revealed significant differences in the rates of various substrates (Table 6) 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 (see Chapter 1, section 1.3).[4]

Table 6 Alkyne scope for the [3+2] azide-alkyne cycloaddition



	Alkyne	Time[a] (h)	Yield[b] (%)
1	 8	1	91
2	 19	1.5	86
3	 20	2	93
4	 21	5	62
5	 22	1	65[c]
6	 23	1	59[d]
7	 24	2	87

[a]Time to full conversion. [b]Isolated yield. [c]Reaction only reaches 70 % conv. [d] Isolated yield after reaction completion (13 h).

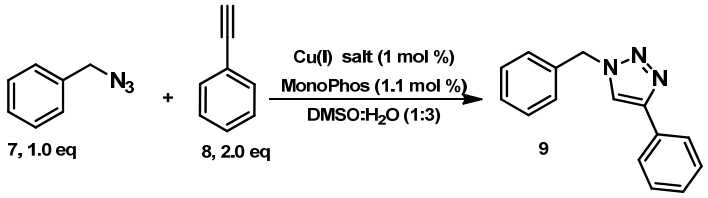
Compared with the model substrate phenylacetylene **8** (entry 1), 1-ethynyl-4-methoxybenzene **19** and 1-ethynyl-4-fluoromethylbenzene **20** had slightly longer reaction times but still reacted rapidly to provide good yields (entries 2 and 3). An electron withdrawing group in the *ortho* position of the phenyl ring (**21**) seemed to have a negative effect on the rate (entry 4), however we also noted in the course of this reaction that the solubility of the substrate was poor. Reaction with propargyl amine **22** (entry 5) showed very rapid conversion to the corresponding triazole in the first hour (70 %), 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 in fact used by Sharpless *et al* in a previous study to catalyze the [3+2] cycloaddition of azides and alkynes.[4] With nearly one

full equivalent of the triazole product with respect to catalytic amounts of copper the metal center risks saturation and inhibition of any further catalysis. Propiolic acid **23** (entry 6) showed similar behaviour, reaching 55% conversion after 1 h and then requiring a further 12 h to reach full conversion. However an ester substituted alkyne **24** reacted smoothly (entry 7). Thus we suspect some coordination of the copper by the free acid of the substrate or of the triazole product, inhibiting the reaction.

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 exclude the use of water due to the inherent thermodynamic instability of Cu(I), resulting in its easy oxidation to Cu(II).[25] Thus 'click' reactions using Cu(I) salts require an equivalent of nitrogen containing base to promote the reaction in the absence of water (which normally serves to deprotonate the terminal alkyne to form the acetylide).[15] A greater likelihood of side product formation is observed in cases where Cu(I) salts are used.[15,26]

It was anticipated that MonoPhos **L10** might stabilize the catalytically active Cu(I) oxidation state. A range of readily available Cu(I) salts were tested in aqueous solution (Table 7) and indeed they gave excellent reaction times and yields, with no evidence of side product formation (alkyne-alkyne homocoupling for instance) detected. Thus the presence of MonoPhos appears to have the effect of stabilizing the copper(I) oxidation state sufficiently to allow the reaction to proceed in aqueous solution.

Table 7 [3+2] Cycloaddition with copper (I) salts

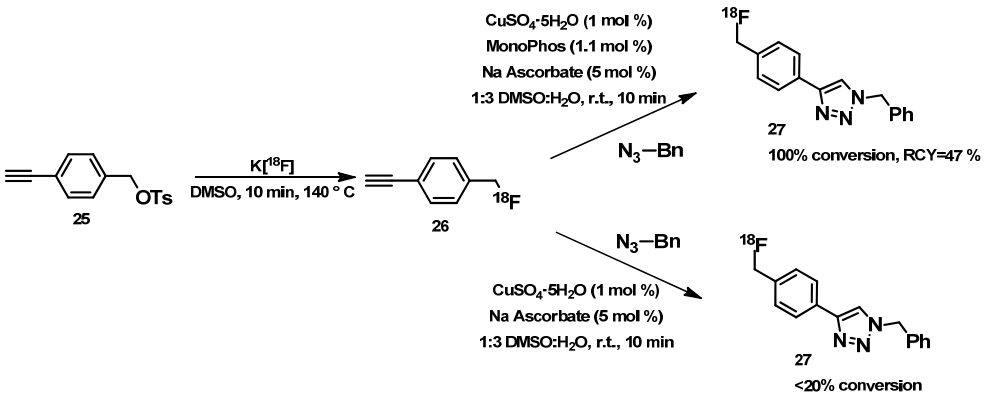


Copper Salt	Time[a] (h)	Yield (%)
CuCl	1	99
CuBr	2	94
CuI	3.5	89
CuBr·DMS	1	95

[a]To full conversion.

To test our methodology on the required time scale of radiolabelling, we synthesized [^{18}F]-fluorinated 1-ethynyl-4-(fluoromethyl)benzene **26** (Scheme 2). After fluorination, it was ligated to benzyl azide **7** in the presence of $CuSO_4 \cdot 5H_2O$ (1 mol %) and MonoPhos (1.1 mol %). Full conversion to the labelled triazole **27** was detected after 10 min (as

determined by HPLC and radio-TLC). Under identical conditions but in the absence of ligand, only low conversion to triazole **27** was detected (< 20%).



Scheme 2 Synthesis of [^{18}F]-labelled triazole **27** (RCY=radiochemical yield)

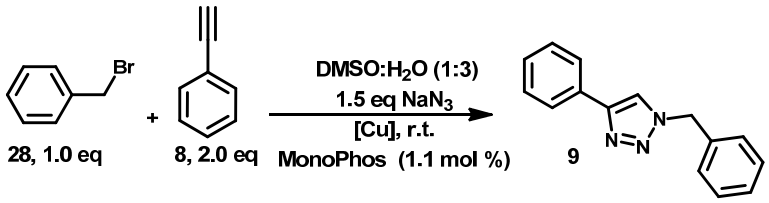
3.4 System Limitations

Several attempts were made to expand the use of the newly developed methodology. In this section, several instances in which the system failed to give the desired result and where other ligand systems proved successful are outlined.

Inorganic azides are often considered to be toxic, and potentially explosive compounds.[27] Generally organic azides can be exempted from such qualities, but there are some dangers which are associated with low molecular weight azides, as well with the synthesis of some organic azides. This is particularly true in instances where elevated temperatures are required for azide formation, and in those when the azide is formed through the use of triflyl azide or via copper catalyzed coupling. Metallic azide complexes are known to be shock sensitive.[27] As a result, interest in developing or extending systems to allow for one-pot formation of azides for tandem 'clicking' to alkynes has emerged.[28] This would allow for the desired triazole product to be accessed starting simply from, for instance, the corresponding halides. Some simple reactions were performed, to test the possible extension of our methodology to a one-pot system (Table 8). One equivalent of benzyl bromide **28** and two equivalents of phenylacetylene **8** were dissolved in a water/DMSO mixture (3:1). To this solution was added 1.5 equivalents of sodium azide, 1 mol % of CuCl and 1.1 mol % of MonoPhos. The reaction mixture was allowed to stir at room temperature. After 1 h, only traces of product were detected, and after 4 and 17 h respectively, only 10 and 12% product formation was observed. The one-pot reaction was also attempted using $CuSO_4 \cdot 5H_2O$ with a reducing agent, sodium ascorbate, along with

MonoPhos and sodium azide. This proved to give even less conversion to the product. With little doubt, the goal could be achieved using elevated temperatures or catalyst loadings, or through the use of microwave as described in literature,[29] however the goal of these experiments was to see whether the increased reactivity seen in the classic 'click' reaction using phosphoramidite ligands could translate into useful extra reactivity in other scenarios.

Table 8 One-pot azide formation and subsequent 'click' reaction

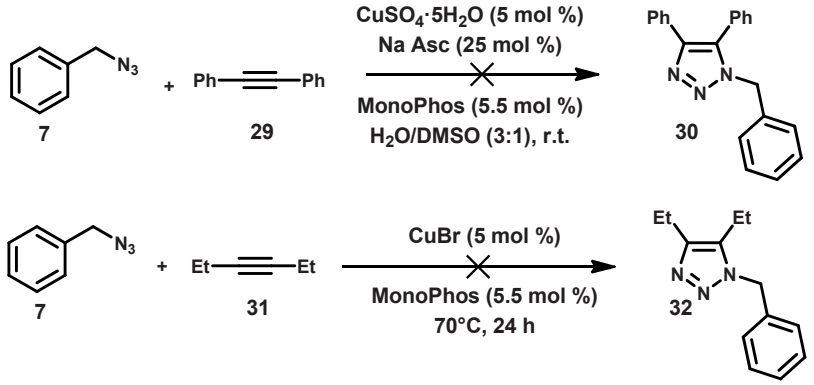


Conditions	Time (h)	Conversion
CuCl (1 mol %)	1	Traces
MonoPhos (1.1 mol %)	4	10
NaN_3 (1.5 eq)	17	12
$CuSO_4 \cdot 5H_2O$ (2 mol %)	1	Traces
MonoPhos (2.2 mol %)	15	Traces
Na Ascorbate (10 mol %)		
NaN_3 (1.5 eq)		

While it is generally accepted that the copper catalyzed [3+2] cycloaddition of azides and alkynes proceeds through the formation of the copper-acetylide species (Chapter 1, Section 1.3), the use of NHC carbene ligand copper complexes has been shown to allow access to cyclization with internal alkynes.[10] The authors suggest that rather than the formation of the copper-acetylide, the copper-NHC catalyzed cycloaddition with internal alkynes proceeds through a π-alkyne complex. Spectroscopic studies give evidence of very strong π-backbonding[30] in the copper NHC complex, and they claim that the strong sigma-donating nature of the ligands yields the resulting effect of sufficiently activating the alkyne by π-complexation. Given these findings, we were curious to test the phosphoramidite copper complex system to ascertain whether it activated the alkyne in a similar fashion to the NHC carbenes.

Subjecting diphenylacetylene **29** to the standard reaction conditions (Scheme 3) gave no formation of triazole **30** after more than 48 h. We decided to test more robust reaction conditions, namely those reported in the literature, and changed the substrate in question to

diethylacetylene **31**, which is known to be a less reactive alkyne for the thermally driven, uncatalyzed [3+2] cycloaddition with azides.[10] Thus the reaction mixture could be heated without fear that the thermally driven triazole product would be formed. Diethylacetylene **31** was subjected to CuBr and MonoPhos (5 and 5.5 mol %, respectively) in a DMSO/H_2O water mixture (1:3) at 70°C for 24 h, at which point no evidence of triazole **32** formation was detected. It seems that in contrast to the results observed using NHC carbene ligands, MonoPhos does not catalyze the cycloaddition of internal alkynes.

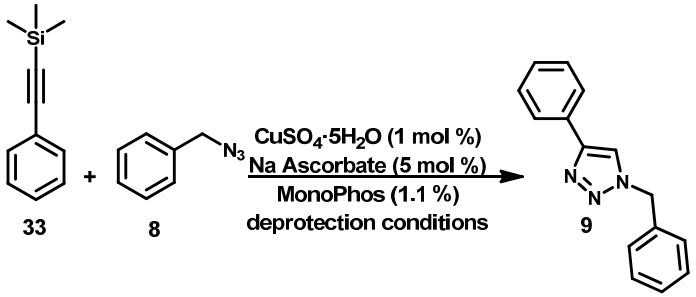


Scheme 3 Reactions with selected internal alkynes

A final limitation to the system arose in the form of a two-step one-pot deprotection of a silyl protected alkyne and subsequent CuAAC. Terminal alkynes are often masked during synthetic transformations to protect them from transition metals or organometallic reagents. Silyl groups are commonly used to provide this protection and can be removed with relative ease using fluoride anions, basic conditions or Lewis acids.[31] For the sake of synthetic versatility, it can be advantageous to have a one-pot, high yielding procedure to liberate a masked alkyne and allow it to undergo cyclization with an azide without having to purify and isolate the intermediate terminal alkyne. Existing examples of systems show that using a catalytic amount (20 mol %) of $AgBF_4$ in a water/tert-butyl alcohol mixture along with $CuSO_4$ (10 mol %) and sodium ascorbate (20 mol %) at 35°C for 18 h can produce the corresponding triazoles from the silyl protected alkyne substrates in high yields.[32] Triethylamine in combination with heating to 50°C or accompanied by microwave heating can produce the same effect.[26]

As a model reaction, trimethyl(phenylethynyl)silane **33** and benzyl azide **7** were stirred in the presence of 1 mol % $CuSO_4·5H_2O$, along with 5 mol % of sodium ascorbate and 1.1 mol % of MonoPhos (unless otherwise indicated). The reaction mixture was subjected to a variety of deprotection conditions (Table 9).

Table 9 One-pot desilylation and subsequent 'click' reaction



	Deprotection Conditions	Product Yield (%)
1	None	0
2	Ag_2O (0.5 eq), Bu_4NCl (1.1 eq), rt, 20 h	20
3	KF/18-crown-6 (1.1 eq), THF/H_2O, rt, 20 h	0
4	K_2CO_3 (1.1 eq), methanol, rt, 20 h	0
5	K_2CO_3 (1.1 eq), methanol/H_2O, rt, 20 h	0
6	TBAF (1.0-5.0 eq), H_2O	0
7	DMI, 80°C, CuBr (1.1 eq)	0

In the absence of any additives, after 20 h at room temperature, no triazole product was detected (entry 1). This was as expected given that the silyl group prevents the formation of the copper-acetylide species. Using 0.5 eq of Ag_2O in the presence of 1.1 eq of Bu_4NCl it was possible to isolate 20 % triazole after 20 h. KF/18-crown-6 were used to provide a fluoride ion to deprotect the silyl group, however, after 20 h at room temperature, no product was isolated. The presence of H_2O in this case may have prevented the desired deprotection due to formation of hydrogen bonds between the fluoride anion and the water molecules. Potassium carbonate was used in a methanol solution as well as in a water/methanol (1:1) solution, but no triazole product was detected after 20 h in either case. Tetrabutylammonium fluoride (TBAF) was also used as a fluoride source, with the concentration varying from 1.0-5.0 eq, but again no triazole product was detected. A final attempt was made to perform an alkynyl transfer in 1,3-dimethyl-2-imidazolidinone (DMI) which has been shown to facilitate this transfer from silane to copper, [25] however, this again yielded none of the desired product. Although the copper-MonoPhos system is rigorous in some respects, in others, further optimization would be needed to make the system applicable to a wider variety of challenging systems.

3.5 Conclusions

Phosphoramidite copper complexes have been applied to the azide alkyne [3+2] cycloaddition and shown to enhance the rate of the reaction. The presence of the ligand appears to stabilize the catalytically active Cu(I) oxidation state to the extent that Cu(I) salts can be used in aqueous systems without any apparent loss of reactivity. 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. It was demonstrated that on a 10 min time scale, the presence of 1 mol % of ligand was crucial for achieving the desired conversions and yields.

3.6 Experimental Section

General Information

$CuSO_4 \cdot 5H_2O$, CuCl, CuBr, CuBr·DMS, sodium ascorbate and dimethyl sulfoxide were purchased from Aldrich and used as received. Conversion of reactions was determined by GC-MS (GC HP6890, MS HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA) or by ^{1}H NMR. Phosphoramidites were synthesized as described in the literature.[16]

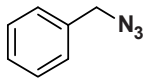
Safety

Working with azides should always be done carefully. Organic azides, particularly those of low molecular weight, or with high nitrogen content, are potentially explosive. Heat, light and pressure can cause decomposition of the azides. Furthermore, the azide ion is toxic, and sodium azide should always be handled while protected with gloves. Heavy metal azides are particularly unstable, and may explode if heated or shaken.

Experimental Procedure for the Preparation of Azides

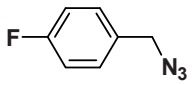
General Procedure A: To a stirred solution of the corresponding bromide (1.0 eq) in a 50 mL water/acetone mixture (1:4) was added NaN_3 (1.5 eq). The resulting suspension was stirred at room temperature for 24 h. DCM was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3 x 10 mL aliquots of DCM and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the azide was sufficiently pure to use without further purification. In the case of the synthesis of 1-azidooctane, DMSO was used as solvent and the reaction was quenched with water. The characterization of all azides synthesized was in accordance with published spectroscopic data.[27]

Benzyl azide



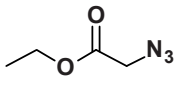
Yellow oil. From 2.5 mmol benzyl bromide, 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.43 (m, 5H), 4.35 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 135.5, 129.3, 128.3, 128.2, 54.8.

1-(Azidomethyl)-4-fluorobenzene



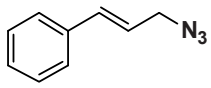
Pale yellow oil. From 2.5 mmol 1-(bromomethyl)-4-fluorobenzene, 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.39 (m, 2H), 7.00-7.11 (m, 2H), 4.30 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 162.5 (d, *J*=1307 Hz), 131.4, 129.9 (d, J= 45.2 Hz), 115.7 (d, *J*=110.0 Hz), 54.0; ^{19}F NMR (200 MHz, $CDCl_3$): δ -112.3.

Ethyl 2-azidoacetate



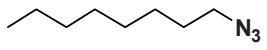
Colorless oil. From 2.5 mmol ethyl bromoacetate, 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, *J*=6.8 Hz, 2H), 3.77 (d, *J*= 1.2 Hz, 2H), 1.20 (td, *J*=7.2, 1.2 Hz, 3H). ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 168.1, 61.5, 50.0, 13.8.

Cinnamyl azide



Colorless oil. From 2.5 mmol cinnamyl bromide, 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.45 (m, 5H), 6.67 (d, *J*=16 Hz, 1H), 6.26 (dt, *J*=16, 6.4 Hz, 1H), 3.95 (d, *J*=6.4 Hz, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 135.7, 134.5, 128.7, 128.2, 126.7, 122.4, 53.0; HRMS (EI) calcd for $C_9H_9N_3$ 159.0796, found 159.0790.

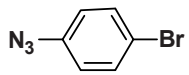
1-Azidooctane



Clear yellow oil. From 3.0 mmol of 1-bromooctane, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.21 (t, *J*=6.8 Hz, 2H), 1.56 (q, *J*=6.8 Hz, 2H), 1.24-1.34 (m, 10 H), 0.85 (t, *J*= 6.4 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 51.5, 31.8, 29.2, 29.2, 28.9, 26.8, 22.7, 14.1.

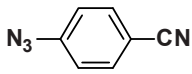
General Procedure B: To a stirred solution of the corresponding aromatic amine (1.0 eq) in acetonitrile (0.5 M) at 0ºC was added tert-butyl nitrite (1.5 eq), followed by azidotrimethylsilane (1.2 eq) in a dropwise fashion. The roundbottom flask was then removed from the ice bath and the mixture allowed to warm to room temperature and stir for a further 2 h. Solvent was removed under reduced pressure and the azides were purified by column chromatography (pentane/ether 1:1).

1-Azido-4-bromobenzene



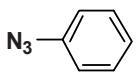
Yellow-orange solid. From 2.0 mmol 4-bromoaniline, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J*=6.8 Hz, 2H), 6.89 (d, *J*= 8.8 Hz, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 139.1, 132.7, 120.5, 117.7.

4-Azidobenzonitrile



Orange solid. From 3.0 mmol 4-aminobenzonitrile, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (td, *J*= 9.6, 2.0 Hz, 2H), 7.05 (td, *J*= 9.6, 0.8 Hz, 2H) ; ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 144.5, 133.5, 119.5, 118.2, 108.0.

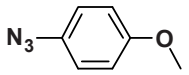
Azidobenzene



Pale yellow oil. From 3.0 mmol aniline, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36-7.41 (m, 2H), 7.15-7.20 (m, 1H), 7.05-7.08 (m, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 140.0, 129.7, 124.8, 118.9.

General Procedure C: A mixture of aryl iodide (1.0 eq), sodium azide (1.2 eq), copper(I) iodide (0.1 eq), L-proline (0.2 eq) and sodium hydroxide (0.2 eq) was prepared in DMSO (5 mL). The reaction mixture was sealed in a roundbottom flask under nitrogen atmosphere and heated to 60ºC for 6 h. The reaction mixture was partitioned between ethyl acetate and water (1:1). The organic layer was collected and the aqueous layer extracted twice with ethyl acetate (2 x 15 mL). The layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give an oil which was purified by column chromatography to yield the pure products (pentane/ether 1:1).

1-Azido-4-methoxybenzene

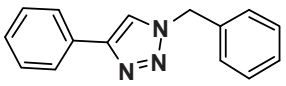


Dark orange solid. From 2.0 mmol iodoanisole, 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.4 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 156.9, 132.2, 119.9, 115.0, 55.4.

General Procedure for the Synthesis of 1,4-Disubstituted Triazoles: In a sample vial, 5.6 x 10^{-3} mmol of $CuSO_4 \cdot 5H_2O$ and 2.8 x 10^{-2} mmol sodium ascorbate were dissolved in 1.2 mL distilled water. To the sample vial was added 6.2 x 10^{-3} mmol of MonoPhos in 0.4 mL DMSO. The resulting solution was vigorously stirred for 15 min. The solution was then added to a 25 mL oven-dried roundbottom flask containing 0.56 mmol of azide and 1.12 mmol of alkyne in 3 mL of a DMSO:H_2O mixture (1:3). The roundbottom flask was sealed and the reaction mixture was vigorously stirred. Reaction progress was monitored by ^{1}H NMR. Upon reaction completion, 10 mL of H_2O was added to the reaction mixture. For

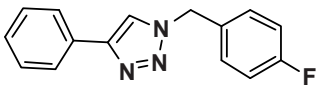
solid products, the reaction mixture was placed in an ice bath and the precipitated solid product was filtered and washed with 3 x 5 mL of cold water. For oil products, the resulting reaction mixture was extracted with 3 x 15 mL of dichloromethane. The organic layers were combined and dried over $MgSO_4$ and the solvent was removed by vacuum evaporation. Crude oils were purified using silica gel chromatography (pentane:ether 1:1). Data for triazoles characterized by NMR only are in accordance with literature spectroscopic data.[33]

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole



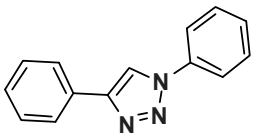
White solid: mp 128-130ºC. 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J*=7.2 Hz, 2H), 7.66 (s, 1H), 7.32-7.42 (m, 8H), 5.58 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 148.0, 135.0, 130.7, 129.1, 128.9, 128.7, 128.2, 128.1, 125.7, 120.1, 41.0. HRMS (EI) calcd for $C_{15}H_{13}N_3$ 235.1109, found 235.1098.

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

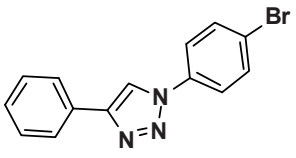


White solid: mp 129-131ºC. 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J*=7.2 Hz, 2H), 7.67 (s, 1H), 7.37 (t, *J*=7.2 Hz, 2H), 7.25-7.28 (m, 3H), 7.03 (t, *J*=8.8 Hz, 2H), 5.49 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 163.0 (d, *J*=248 Hz) , 148.5, 130.8 (d, *J*=3.0 Hz), 130.6, 130.2 (d, *J*=9.0 Hz), 129.0, 128.4, 125.9, 119.7, 116.3 (d, *J*=21 Hz), 53.6; ^{19}F NMR (200 MHz, $CDCl_3$): δ -113.1 (m).

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



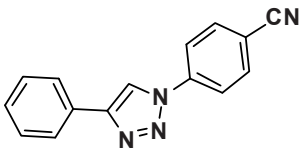
Pale yellow solid: mp 183-184ºC. 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.92 (dt, *J*=8.0, 1.6 Hz, 2H), 7.79 (dt, *J*=8.4, 1.2 Hz, 2H), 7.55 (tt, *J*=8.4, 1.6 Hz, 2H), 7.43-7.48 (m, 3H), 7.38 (tt, *J*=7.6, 0.8 Hz, 1H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 148.8, 137.4, 130.6, 130.2, 129.3, 129.2, 128.8, 126.2, 120.9, 118.0.



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

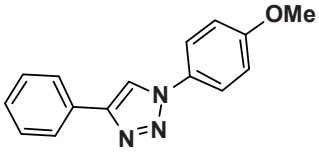
White solid: mp 231ºC. 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J*=3.2 Hz, 1H), 7.91 (dq, *J*= 6.4, 3.2 Hz, 2H), 7.68-7.70 (m, 4H), 7.47 (tt, *J*= 8.0, 1.6 Hz, 2H), 7.40 (dt, *J*=8.0, 1.6 Hz, 1H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 149.1, 133.3, 136.4, 130.4, 129.4, 129.0, 126.3, 122.8, 122.3, 117.7. HRMS (EI) calcd for $C_{14}H_{10}N_3Br$ 300.0131, found 300.0130.

4-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile



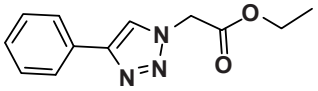
Pale yellow solid: mp 234 ºC. 81% yield. ^{1}H NMR (400 MHz, d6-DMSO): δ 9.45 (s, 1H), 8.15 (q, *J*= 8.1 Hz, 4H), 7.93 (d, *J*= 7.8 Hz, 2H), 7.50 (t, *J*= 7.8 Hz, 2H), 7.36-7.41 (m, 1H); ^{13}C NMR (100.59 MHz, d6-DMSO): δ 148.4, 140.2, 135.0, 130.5, 129.8, 129.2, 126.1, 121.0, 120.5, 118.8, 111.7. HRMS (EI) calcd for $C_{15}H_{10}N_4$ 247.0978, found 247.0977.

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



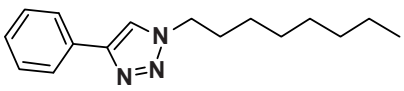
Pale yellow solid: mp 160-161ºC. 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.90 (d, *J*=7.6 Hz, 2H), 7.69 (d, *J*=9.2 Hz, 2H), 7.46 (t, *J*=7.6 Hz, 2H), 7.36 (t, *J*=7.6, 1.2 Hz, 1H), 7.04 (d, *J*=8.4 Hz , 2H), 3.88 (s, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 160.2, 148.6, 130.9, 130.8, 129.3, 128.7, 126.2, 122.6, 118.2, 115.2, 56.0. HRMS (EI) calcd for $C_{16}H_{15}N_3O$ 265.1215, found 265.1215.

Ethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate



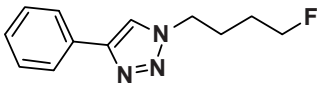
White solid: mp 99ºC. 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.84 (d, *J*=7.2 Hz, 2H), 7.43 (t, *J*=7.2 Hz, 2H), 7.34 (t, *J*=7.2 Hz, 1H), 5.20 (s, 2H), 4.28 (q, *J*=6.8 Hz, 2H), 1.31 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 166.5, 148.4, 130.6, 129.1, 128.5, 126.0, 121.3, 62.7, 51.2, 14.3.

1-Octyl-4-phenyl-1*H*-1,2,3-triazole



White solid: mp 74-75ºC. 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J*=7.2 Hz, 2H), 7.73 (s, 1H), 7.36 (t, *J*=7.2 Hz, 2H), 7.27 (t, *J*=7.2 Hz, 1H), 4.32 (t, *J*=7.2 Hz, 2H), 1.87 (br s, 2H), 1.20-1.27 (m, 10H), 0.82 (t, *J*=3.2 Hz, 3H) ; ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 147.7, 130.9, 128.9, 128.1, 125.7, 119.7, 50.5, 31.8, 30.4, 29.1, 29.0, 26.6, 22.7, 14.2.

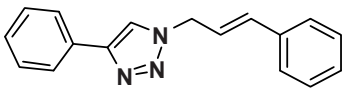
1-(4-Fluorobutyl)-4-phenyl-1*H*-1,2,3-triazole



White solid: mp 54-55ºC. 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J*=10 Hz, 2H), 7.76 (s, 1H), 7.42 (t, *J*=10 Hz, 2H), 7.30-7.35 (m, 1H), 4.56 (t, *J*=7.2 Hz, 1H), 4.38-4.47 (m, 3H), 2.05-2.15 (m, 2H), 1.65-1.82 (m, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$):

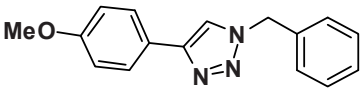
δ 148.1, 130.8, 129.1, 128.4, 125.9, 119.7, 83.5 (d, *J*=330.1 Hz), 50.1, 27.3 (d, *J*=91.3 Hz), 27.2. HRMS (EI) calcd for $C_{12}H_{14}N_3F$ 219.1172, found 219.1169.

1-Cinnamyl-4-phenyl-1*H*-1,2,3-triazole



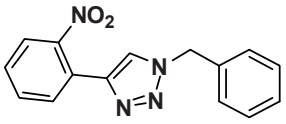
Pale yellow solid: mp 134ºC. 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.82 (d, *J*=6.8 Hz, 2H), 7.40-7.44 (m, 4H), 7.27-7.37 (m, 4H), 6.70 (d, *J*= 15.6 Hz, 1H), 6.37 (dt, *J*= 16.0 Hz, 6.4 Hz, 1H), 5.17 (d, 6.8 Hz, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 148.4, 135.7, 135.6, 130.8, 129.1, 129.0, 128.8, 128.4, 127.0, 126.0, 122.2, 119.6, 52.7.

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

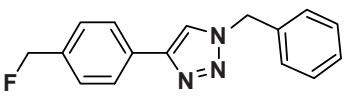


Pale yellow solid: mp 143-144ºC. 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J*=8.8 Hz, 2H), 7.56 (s, 1H), 7.35-7.75 (m, 3H), 7.29-7.34 (m, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 5.55 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 159.9, 148.4, 135.1, 129.4, 129.0, 128.3, 127.3, 123.6, 119.0, 114.5, 55.5, 54.5.

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



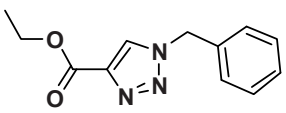
Pale yellow solid: mp 110-112ºC. 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J*=7.6 Hz, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 7.73 (s, 1H), 7.63 (t, *J*=7.6 Hz, 1H), 7.47 (t, *J*=8.0 Hz, 1H), 7.34-7.40 (m, 3H), 7.28-7.31 (m, 2H), 5.58 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 148.4, 142.7, 134.6, 132.8, 131.3, 129.4, 129.2, 129.1, 128.3, 124.9, 124.3, 123.2, 54.6. HRMS (EI) calcd for $C_{15}H_{12}N_4O_2$ 281.1033, found 281.1030.



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

White solid: mp 127-130ºC. 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J*=7.6 Hz, 2H), 7.67 (s, 1H), 7.31-7.42 (m, 7H), 5.58 (s, 2H), 5.38 (d, *J*=4.8 Hz, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 148.0, 136.3 (d, *J*=16 Hz), 134.9, 131.3 (d, *J*=3.1 Hz), 129.5, 129.1, 128.3, 128.2 (d, *J*=5.3 Hz), 126.1, 120.0, 84.6 (d, *J*=166 Hz), 54.5. ^{19}F NMR (200 MHz, $CDCl_3$): δ 58.2 (t, *J*=25 Hz). HRMS (EI) calcd for $C_{16}H_{14}N_3F$ 268.1245, found 268.1243.

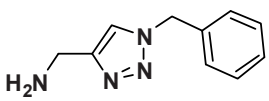
Ethyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate



White solid: mp 83-85ºC. 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.36 (br s, 3H), 7.25-7.28 (m, 2H), 5.56 (s, 2H), 4.36 (q, *J*=6.8 Hz, 2H), 1.35 (t, *J*=6.8 Hz, 3H);

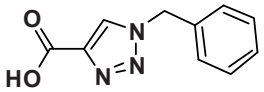
^{13}C NMR (100.59 MHz, $CDCl_3$): δ 160.9, 140.8, 134.0, 129.5, 129.3, 128.5, 127.6, 61.5, 54.7, 14.5.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methanamine



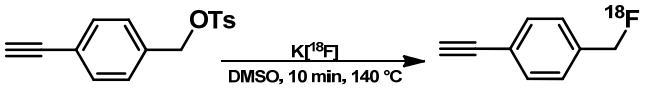
White solid: mp 109-112ºC. 65% yield. ^{1}H NMR (400 MHz, DMSO): δ 7.91 (s, 1H), 7.28-7.34 (m, 5H), 5.54 (s, 2H), 4.15 (s, 2H); ^{13}C NMR (100.59 MHz, DMSO): δ 147.0, 136.9, 129.4, 128.7, 123.3, 122.7, 53.4, 40.1. HRMS (EI) calcd for $C_{10}H_{12}N_4$ 189.1135, found 189.1135.

1-Benzyl-1*H*-1,2,3-triazole-4-carboxylic acid



White solid: mp 128ºC. 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.33-7.38 (m, 5H), 5.64 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 162.1, 140.4, 135.2, 128.9, 128.6, 128.3, 128.1, 54.0. HRMS (EI) calcd for $C_{10}H_9N_3O_2$ 204.0768, found 204.0768.

Radiolabelling Procedure



[^{18}F]-fluoride in [^{18}O]-enriched H_2O was captured on a QMA light Sep-Pak cartridge. The [^{18}F]-fluoride was eluted with 4.5 mg of potassium bicarbonate. 20 mg of Kryptofix was subsequently added. Under argon atmosphere, the fluoride was dried three times with 0.5 mL of pure acetonitrile at 130°C. The dried [^{18}F]-fluoride was then added to 3.0 mg of 4-ethynylbenzyl 4-methylbenzenesulfonate in 0.5 mL dry DMSO. The solution was allowed to react for 10 min at 140°C. The labeled product was adsorbed on a light C18 Sep-Pak cartridge and eluted with 5 mL pure methanol. The Sep-Pak eluate was then treated with semi-preparative HPLC on a C18-reversed phase column (mobile phase 60/40 methanol/water, retention time=12 min). For conditions of the 'click' reaction, refer to the General Procedure. Conversion of the reaction was monitored by radio-TLC.

3.7 References and Notes

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