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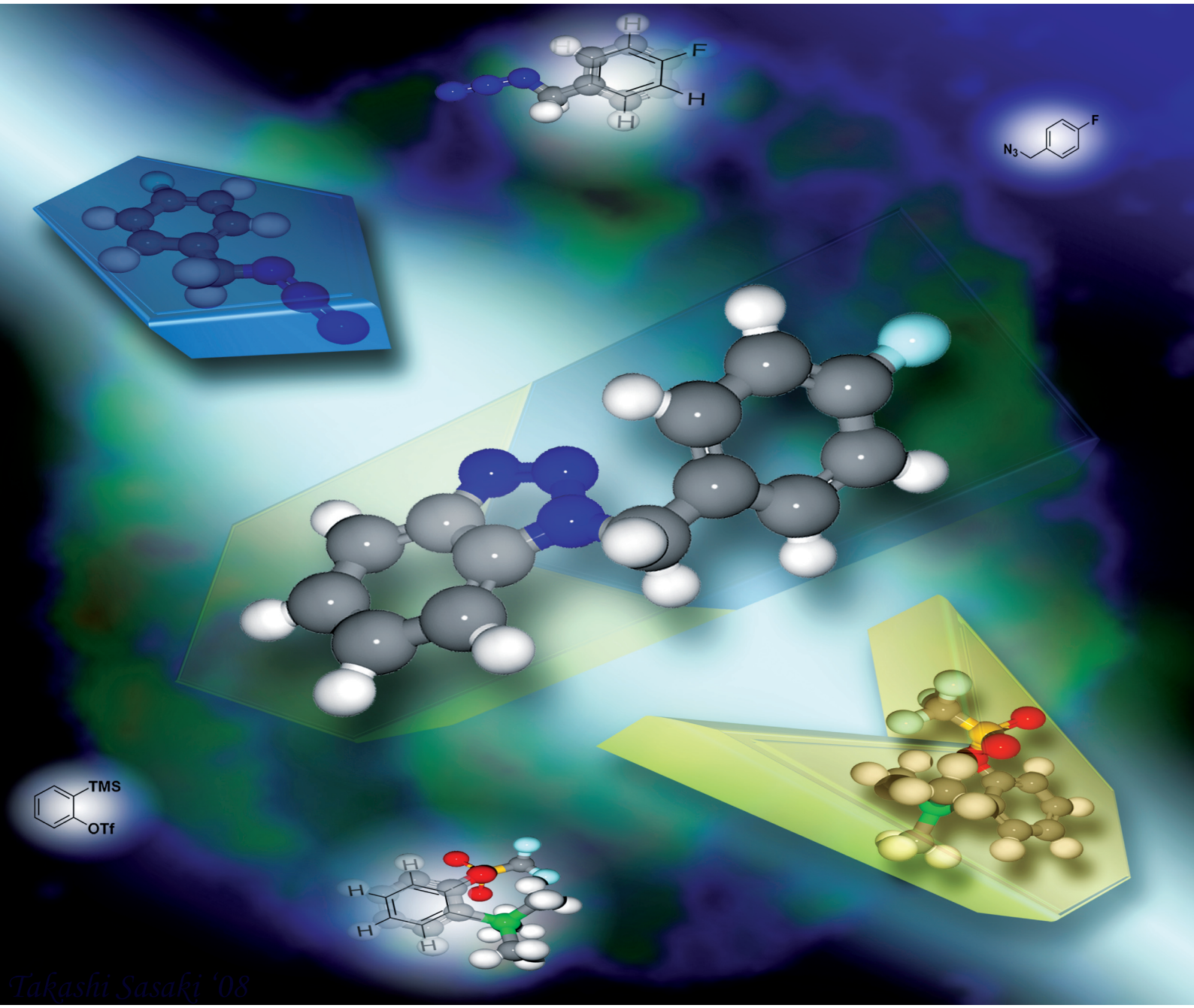

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Copper-free 'click': 1,3-dipolar cycloaddition of azides and arynes†

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Arynes formed through fluoride-promoted *ortho*-elimination of *o*-(trimethylsilyl)aryl triflates can undergo [3 + 2] cycloaddition with various azides to form substituted benzotriazoles. The rapid reaction times and mild conditions make this an attractive variation of the classical 'click' reaction of azides and alkynes.

The discovery by Sharpless *et al.* in 2001 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 combinatorial method for functionalized moieties.[1] Significant progress has been made in the application of this methodology to the areas of materials science, drug discovery, polymer chemistry and bioconjugation, among others.[2] Limitations arise in the field of bioconjugation and *in vivo* imaging due to the toxicity of copper. Furthermore, in the absence of copper, the reaction necessitates elevated temperatures or pressures which are incompatible with most living systems.[3] The rarity and inertness of azides and alkynes in biological environments make them ideal bioorthogonal markers, highlighting the importance of developing copper-free 'click' reactions.

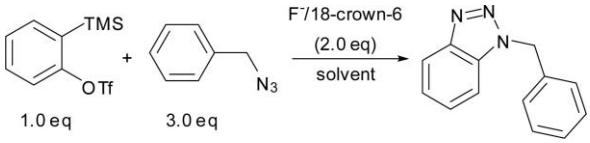
To date, promising alternatives for alkyne activation have been discovered; activation of the substrate *via* electron-withdrawing functionalities adjacent to the triple bond serves to increase reaction rates in the absence of copper[4], as does the use of severely strained acetylenes.[5] In our investigation into accelerated 'click' reactions using new systems, we touched upon the annulation of arynes by azides. Herein lies the potential for [3 + 2] cycloaddition in the absence of copper while retaining those benefits commonly associated with 'click' reactions – namely regioselective, fast reactions under mild conditions. We report here our preliminary results of a new, fast, and versatile copper-free click reaction.

Arynes, particularly benzynes, have proven to be useful reactive intermediates for synthetic organic chemists. They are kinetically unstable, highly strained molecules that readily undergo nucleophilic coupling with various neutral species to form complex organic molecules.[6]

Benzyne has traditionally been formed from the diazonium carboxylate intermediate obtained by refluxing anthranilic acid with an organic nitrite. The harsh conditions severely hinder the scope of this reaction, and milder methods were subsequently developed.[7] Thus came examples generating arynes from *o*-(trimethylsilyl)aryliodonium salts; a gentler method, but involving a difficult synthesis of the precursors limiting the possibilities for functionalization.[8] Other examples include benzobisoxadisiloles as precursors of benzdiynes[9] and two-step deprotonation and dehalogenation of aromatic halogen compounds.[10] Currently, the mildest way to form the benzyne intermediate is to use fluoride-induced *ortho*-elimination of *o*-(trimethylsilyl)aryl triflates, which can easily be prepared with various substituents on the arene ring.[11]

Beginning with the cycloaddition of benzyl azide and commercially available *o*-(trimethylsilyl)phenyl triflate, we investigated the use of differing fluoride sources in a range of solvents for benzyne generation (Table 1). Fluoride salts in combination with a complementary crown ether were tested, as was tetrabutylammonium fluoride (TBAF). KF paired with 18-crown-6 induced full conversion to the benzotriazole at room temperature in all solvents tested with good yields (entries 1–5). CsF and 18-crown-6 gave faster reaction times, if somewhat lower yields (entries 8–10). TBAF provides an alternative to fluoride salts, but both the reaction time and yield were less favourable (entry 6). NaF in combination with 15-crown-5 gave no product conversion, nor did the reaction proceed in water even after 48 h. In both cases it was possible to recover the azide starting material quantitatively as well as the majority of the benzyne precursor. This led us to conclude that no formation of the benzyne intermediate occurs.

Table 1 Reaction optimization[a]



	Fluoride source	Solvent	T/°C	Time/h	Yield[b] (%)
1	KF/18-crown-6	THF	rt	4	85
2[c]	KF/18-crown-6	THF	rt	29	80
3	KF/18-crown-6	THF	60	1	71
4	KF/18-crown-6	DCM	rt	8	72
5	KF/18-crown-6	MeCN	rt	3	87
6	TBAF	THF	rt	20	69
7	NaF/15-crown-5	THF	rt	24	0
8	CsF/18-crown-6	THF	rt	1.5	70
9	CsF/18-crown-6	DCM	rt	30	58
10	CsF/18-crown-6	MeCN	rt	0.5	77
11	CsF/18-crown-6	H_2O	rt	40	0

[a] All reaction were carried out on a 0.2 mmol scale in 0.05M concentration. [b] Average isolated yields from two or more experiments. [c] Reaction was carried out using 1.2 eq of azide.

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Reducing the equivalents of azide (entry 2) prolongs the reaction, and causes a slight drop in yield. At reflux the reaction proceeds to completion in one hour, but the yield is lower (entry 3), as it is in DCM (entry 4). In cases with lower yields, the decrease can generally be attributed to degradation of the benzyne precursor. Acetonitrile appears to have an accelerating effect on the reaction, shortening conversion times for both KF and CsF. The latter reaction is particularly satisfying, showing full conversion in 30 min (entry 10). These conditions were thus chosen for all subsequent experiments.

Having established a methodology to obtain rapid conversion to benzotriazole, we were interested in the effect of the crown ether upon the reaction time (Table 2).

As recorded in Table 2, the optimal ratio of crown ether to fluoride salt is 1 : 1. An extra equivalent of crown ether appears to have an inhibitory effect, and the absence of crown ether significantly decreases the reaction rate. In THF, virtually no product was formed even after 48 h in the absence of crown ether. In MeCN, after 48 h, the reaction reached completion, but the yield was dramatically reduced. Reaction entries 3 and 5 were performed with our regular reaction conditions using an excess of azide, but were also attempted with a slight excess (1.2 eq) of the *o*-(trimethylsilyl)phenyl triflate. The concentration of the reaction mixture was varied from 0.05 M to 2.0 M with no significant improvement of conversion rates or yields.[12]

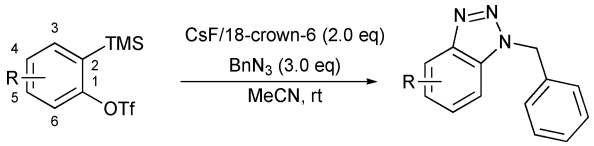
Having confirmed the optimized reaction conditions, we subsequently tested different aryne precursors (Table 3). Slightly better yields are achieved with an electron-donating methoxy substituent at carbon 3 with full conversion in a matter of minutes (entry 3). The unsymmetrical benzyne precursor yields a single regioisomer with the benzyl on the nitrogen remote to the substituent. A naphthalene derivative can also be used; the reaction is thus not limited to benzyne precursors (entry 2). In the case of cycloaddition with the naphthyl precursor a mixture of regioisomers (2 : 1) is observed. Preference is given to the product in which the benzyl group is positioned at the less sterically hindered position 2.

Table 2 Effect of crown ether

	Fluoride source	Solvent	Time/h	Yield[a] (%)
1	CsF/18-crown-6 (1 : 1)	THF	1.5	70
2	CsF/18-crown-6 (1 : 2)	THF	20	67
3	CsF	THF	48	2[b]
4	CsF/18-crown-6 (1 : 1)	MeCN	0.5	77
5	CsF	MeCN	48	46

[a] Isolated yield. [b] Percent conversion as determined by GC.

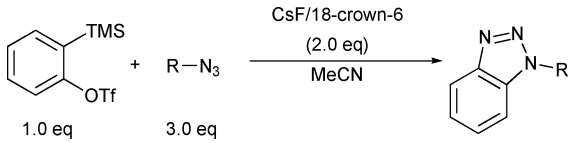
Table 3 Substituted aryne precursors

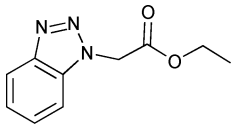
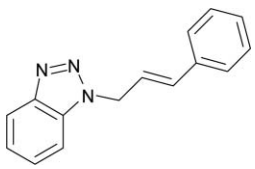
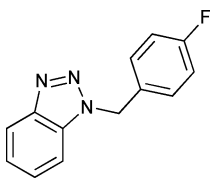


	R	Time/h	Yield[a] (%)
1	H	0.50	56
2	3,4-$(CH)_4$	0.25	75[b]
3	3-MeO	0.25	84

[a] Isolated yield. [b] 2 : 1 regioselectivity.

Table 4 Click reaction with functionalized azides



	R	Product	Time/h	Yield[a] (%)
1	EtO_2CCH_2–		1	82
2	Cinnamyl		1.5	78
3	*p*-Fluorobenzyl		0.5	59

[a] Isolated yield.

To further ensure the generality of the reaction, some selected and particularly challenging azides were tested under the optimized reaction conditions (Table 4).

The reaction proceeds effectively with a non-aromatic functionalized azide (entry 1), and the presence of alkenes is tolerated (entry 2). Both products were isolated in good yields with reaction times of less than 2 h with no side product formation observed. An electron-deficient fluoroazide (entry 3) reacts completely in 30 min. An ^{18}F-labelled analogue of this azide could be used to apply this fast coupling protocol in radiolabelling for imaging technologies such as ^{18}F PET.[13]

This method for the development of various substituted and functionalized benzotriazoles fulfills many of the requirements necessary to classify any given reaction as a 'click' reaction. It has rapid conversion times, proceeds at room temperature in air and produces a single product in good yields. The extension of this versatile methodology to more significant substrates is currently under study.[13]

Acknowledgements

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12 Note: In a recent paper in *Organic Letters* (F. Shi, J. Waldo, Y. Chen and R. C. Larock, *Org. Lett.*, 2008, **10**, 2409) similar work was reported in the absence of crown ether. Our attempts to reproduce these results revealed that either virtually no reaction was observed (with THF as solvent), or excessively long reaction times (48 h with MeCN as solvent) were needed. In contrast, the addition of crown ether is essential for fast reaction times, as shown in the current paper.
13 Study in progress.