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Recognition-mediated regiocontrol of a dipolar cycloaddition reaction

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Abstract—The rational design of a recognition-based system that is capable of accelerating and controlling the regiochemical outcome of a dipolar cycloaddition reaction between an azide and an alkyne is presented. The origins of the acceleration and control of the cycloaddition reactions are rationalized—using molecular mechanics calculations—in terms of the formation of a complex between the reagents which organizes and orients them prior to reaction.

The acceleration of chemical reactions, and the control of their regio- and/or stereochemical outcome through the intervention of recognition processes in solution, is a key component of enzymatic systems and has prompted synthetic chemists to design a variety[1] of unnatural systems which are capable of performing similar tasks. In principle, the location of complementary recognition sites on the reagents (**A** and **B**, Fig. 1) in a chemical reaction permits the association of these reagents through their mutually compatible recognition sites to form a complex [**A**·**B**] prior to reaction (Fig. 1). The formation of this reactive [**A**·**B**] complex renders the chemical reaction between the reagents pseudointramolecular. Thus, we might expect such reactive complexes to effect significant rate acceleration[2,3] of chemical reactions. In addition, the use of specific recognition to preassociate the reactive partners should permit the control of the stereo- and/or regiochemical outcome of the reaction through the orientation of the reagents prior to reaction. Hence, a reaction which exploits the formation of a reactive [**A**·**B**] complex might be engineered to afford a different product (**P**′) to that obtained when the reaction between **A** and **B** proceeds bimolecularly (**P**). These recognition-mediated effects on reactivity will manifest themselves when the reaction in question is under kinetic control, and the selective stabilisation of one transition state with respect to another serves to accelerate[4] the formation of one product. Recently, we have been exploring[5] the acceleration and control in solution phase reaction processes through the use of recognition-mediated processes, such as the formation of reactive [**A**·**B**] complexes.

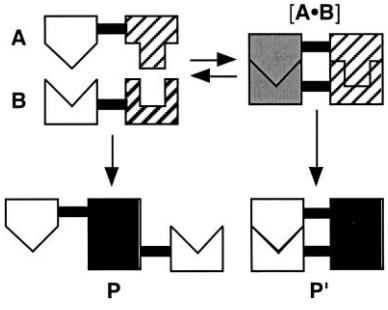

Figure 1. A bimolecular reaction between **A** and **B** affords a product **P**. Association of **A** and **B** through their complementary recognition sites affords a reactive complex [**A**·**B**]. Within this complex **A** and **B** are oriented such that reaction between them gives a product **P**′ with different regio- or stereochemistry from the bimolecular pathway.

Dipolar cycloaddition reactions are synthetically useful[6] as a result of the wide variety of 1,3-dipoles[7] available to participate in cycloaddition reactions of this type, and the potential use[8] of the resulting five-membered heterocyclic rings in natural product syntheses. Seminal work[9] by Huisgen and co-workers in the early 1960's led to the elucidation of the mechanisms, patterns of reactivity and selectivity[10] in 1,3-dipolar cycloaddition reactions. The relative reactivities of cycloaddition reactions were rationalised by Sustmann[11] who demonstrated that the interaction between the HOMO and LUMO with the smallest energy difference predominates. The extent to which each type of molecular orbital predominates can be manipulated electronically via the attachment of electron deficient or electron rich groups favouring LUMO-dipolarophile and HOMO-dipole control respectively. The reaction between an alkyne (dipolarophile) and azide (dipole) affords[12] a 1,2,3-triazole (Scheme 1). The regioselectivities of these cycloaddition reactions are generally low, and thus, if the

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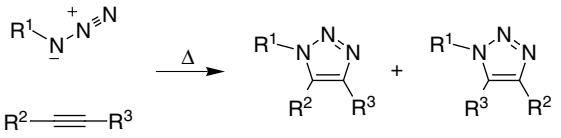


Scheme 1.

alkyne is unsymmetrical, two regioisomers will be formed in an approximately 1:1 ratio (Scheme 1). This lack of regioselectivity is a direct result of the low-lying unoccupied molecular orbitals of the C–C triple bond and, hence, leads[13] to the reaction being controlled by both dipole-HOMO and dipole-LUMO interactions simultaneously.

The improvement of the poor regioselectivity of dipolar cycloadditions involving alkynes is an attractive target for our recognition-based methodology. Accordingly, we designed (Fig. 2) the azide **1** which bears a benzo-15-crown-5 ring and alkyne **2**, which bears an ammonium cation. The mutual recognition between the ammonium cation and the crown ether should permit the formation of the [**1·2**] complex (Fig. 2). Within this complex, molecular modeling suggested (Fig. 2) that the azide and the alkyne should adopt coconformations in which the azide and alkyne are disposed in the correct orientation for reaction. Thus, we might expect the rate of the cycloaddition reaction between **1** and **2** would be accelerated by the formation of the [**1·2**] complex through the mechanism discussed above. Additionally, the regiochemistry of the cycloadduct should also be controlled. Molecular mechanics calculations[14] suggested (Fig. 3) that the 1,4-substituted triazole[15] product **3** is the only cycloadduct which is feasible from a reaction which occurs within the [**1·2**] complex. We therefore expected that

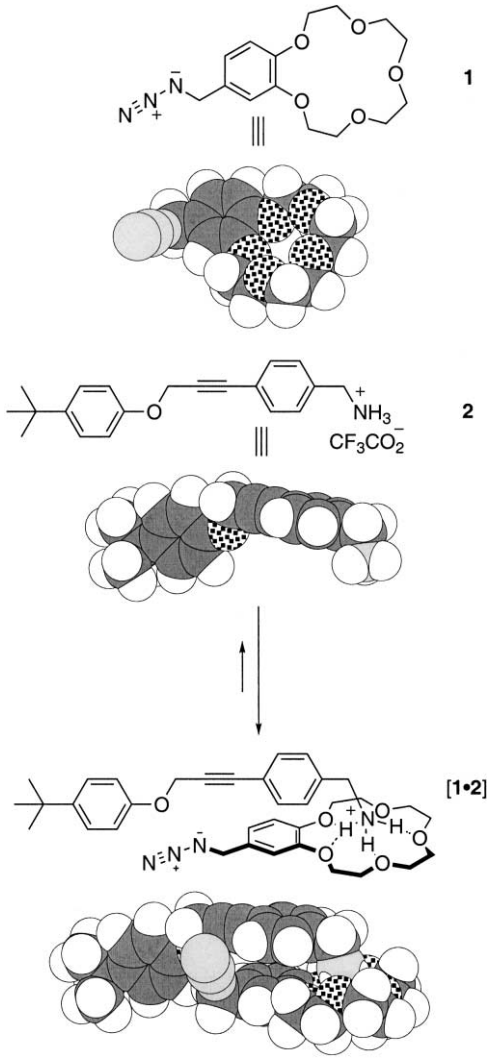


Figure 2. Azide **1** and alkyne **2** associate through their complementary recognition sites to give a reactive complex [1·2]. The CPK representations of the molecular structures of **1**, **2** and [1·2] are derived from conformational searching. C atoms are dark grey, N atoms are light grey, O atoms are speckled and H atoms are white.

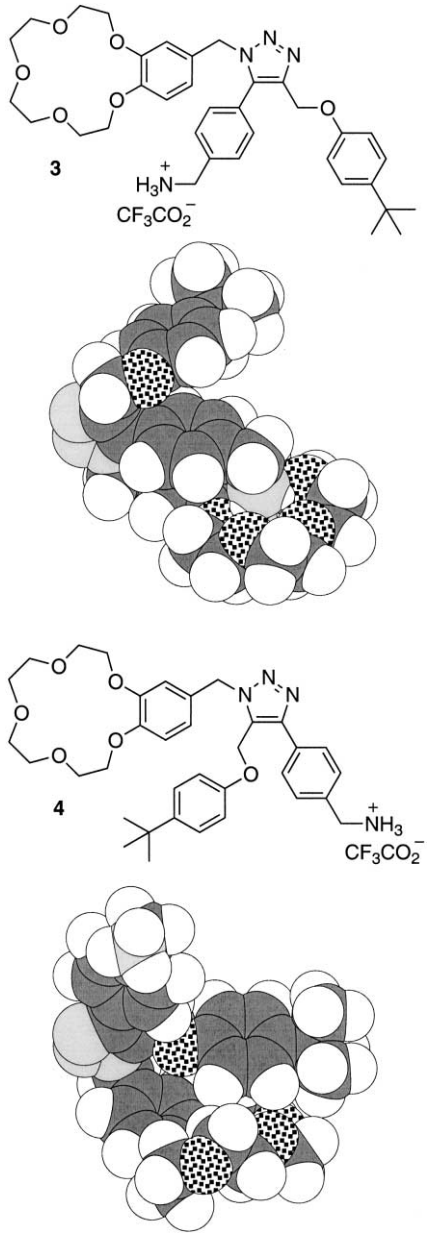
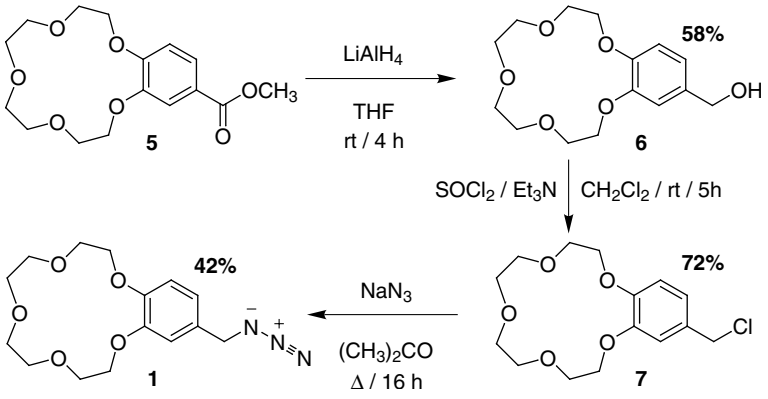
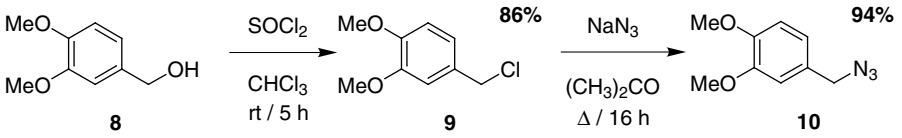


Figure 3. The regioisomeric products obtained from the reaction between **1** and **2** are **3** and **4**. Regioisomer **3** is the only plausible product from reaction between **1** and **2** in the [1·2] complex. The CPK representations of the molecular structures of **3** and **4** are derived from conformational searching. C atoms are dark grey, N atoms are light grey, O atoms are speckled and H atoms are white.



Scheme 2.



Scheme 3.

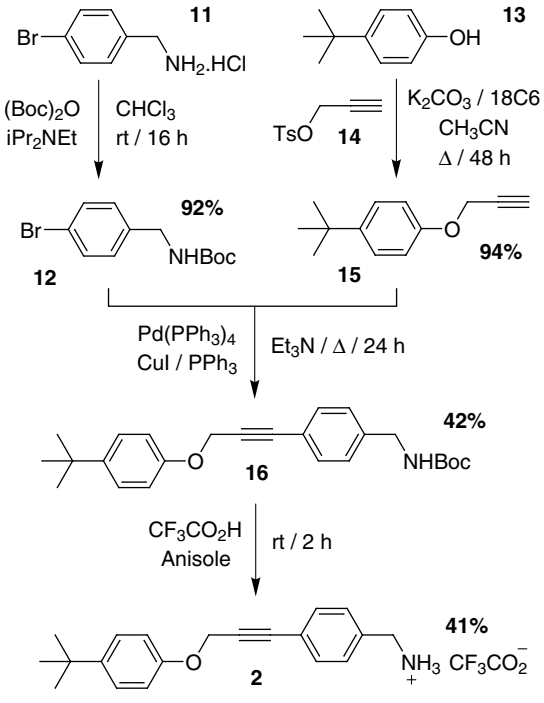
the recognition-mediated reaction should be highly selective for cycloadduct **3** (the 1,4 regioisomer) over **4** (the 1,5 regioisomer).

The preparation of the target azide dipole **1** was achieved in six steps (Scheme 2) starting from the commercially available 3,4-dihydroxybenzoic acid. 4′-Carboxy methylbenzo-15-crown-5 **5** was prepared[16] according to literature procedures and was then reduced[17] using lithium aluminium hydride to afford 4′-hydroxymethylbenzo-15-crown-5 **6** in 58% yield. Alcohol **6** was converted to the corresponding chloride **7** using thionyl chloride, the product being obtained in 72% yield after trituration at −78°C with petroleum ether and diethyl ether. The target compound, 4′-azidomethylbenzo-15-crown-5 **1** was prepared by the reaction of 4′-chloromethylbenzo-15-crown-5 **7** with sodium azide in refluxing acetone, affording the desired compound in 42% yield.

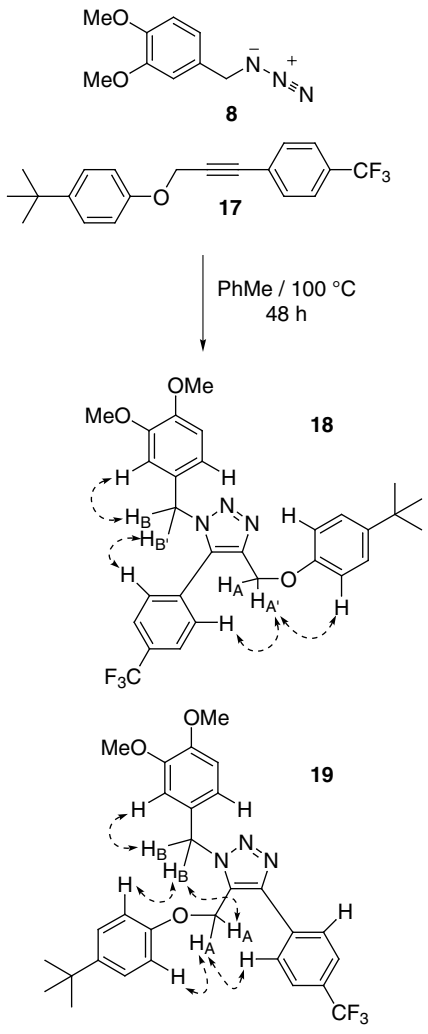
In order to make effective comparisons between the recognition-mediated reaction and the intermolecular reaction channel, it was necessary to identify a control compound, which did not possess any recognition sites, to assess the bimolecular reactivity of the azide **1**. Accordingly, we selected azide **10** as the control compound and this material was synthesised readily (Scheme 3) starting from 3,4-dimethoxybenzylalcohol **8**.

Preparation of the target alkyne dipolarophile **2** was readily achieved in three steps starting from the commercially available bromide **11** (Scheme 4). The amine hydrochloride **11** was first protected as its carbamate by the addition of *N*,*N*-diisopropylethylamine to generate the free amine *in situ*, followed by the slow addition of di-*tert*-butyldicarbonate affording **12** in 92% yield. Prop-3-yn-1-(4′-*tert*-butylphenyl)ether **15** was prepared by treatment of 4-*tert*-butyl phenol **13** with propargyl toluenesulfonate **14** under basic conditions at reflux for 2 days. Bromide **12** was then coupled with alkyne **15** using a procedure originally reported by Bumagin and co-workers[18] to afford the desired alkyne **16**. It should be noted that the dropwise addition of the alkyne is crucial in this step in order to minimise the oxidative dimerisation of the alkyne as a competitive reaction. Simple deprotection of the BOC protecting group was achieved using 5% trifluoroacetic acid, in the presence of anisole, to give the desired dipolarophile **2** in 41% yield.

In order to correctly assign the regiochemistry of the isolated triazoles in future reactions it was necesssary to



Scheme 4.



Scheme 5.

prepare pure samples of each regioisomer. Therefore, 3-(4-trifluoromethylphenyl)prop-2-yn-1-(4′-*tert*-butylphenyl)-ether **17** was reacted with 3,4-dimethoxybenzyl azide **10** at 100°C in toluene solution for 2 days (Scheme 5). After this period two products were observed by TLC, corresponding to the 1,4-substituted **18** and the 1,5-substituted **19** triazole regioisomers. Fortunately, these two products could be separated by column chromatography. We considered that the *para*-CF_3 group in **17**, which has a Hammett σ value[19] close to that of the $CH_2NH_3^+$ group would be a suitable mimic of the dipolarophile **2**, and that we could assign the regiochemistry of our final products by comparison with these model compounds.

The regiochemistry of each model product was confidently assigned using nOe experiments (Scheme 5). For example, in the case of **19**, irradiation of the resonance arising from $H_A/H_{A'}$ (centred on δ 5.15) resulted in the observation of a strong nOe in the resonance arising from $H_B/H_{B'}$ (centred on δ 5.60). The observation of this nOe suggests that this the 1,5-substituted product **19**. In support of this, irradiation of the resonance from $H_A/H_{A'}$ (centred on δ 5.01) in the 1,4-substituted regioisomer **18** did not give an observable nOe to $H_B/H_{B'}$ (centred on δ 5.46). These assignments were further confirmed by COSY, $\{^1H-^{13}C\}$ Heteronuclear Multiple Bond Correlation (HMBC) and $\{^1H-^{13}C\}$ C–H Correlation (HMQC) experiments. The assignment of the regiochemistry by nOe studies allowed the isomer ratios to be calculated using ^1H NMR spectroscopy through deconvolution of the CH_2-N resonances for the 1,4-substituted product versus the analogous CH_2-N resonances for the 1,5-substituted product in the recognition-mediated and control reaction. The progress of the recognition-mediated and control reactions could be assessed, in terms of percentage completion, by deconvolution of the CH_2-N resonances for the 1,4- and the 1,5- regioisomers against the CH_2-N resonance for the starting azide centred on δ 4.23.

Following the successful syntheses of all of the required compounds, namely **1**, **2**, **10**, a series of test experiments were performed in order to find the optimum reaction conditions for the cycloaddition. It was found that the reactions are very sensitive to the polarity of the solvent. In polar solvents such as acetonitrile no reaction occurred even after 70 hours at 90°C. As the percentage of a non-polar solvent such as 1,1,2,2-tetrachloroethane (TCE) was increased the percentage completion of the reaction also increased (Table 1). This effect is presumably a result of stabilisation of the 1,3-dipole by the polar solvent. Unfortunately, as a result of the relative insolubility of the dipolarophile **2** in TCE, it was found that it was not possible to dissolve the dipolarophile **2** at high concentrations in solvent mixtures containing less than 25% acetonitrile.[20] From these results it was concluded that the optimum conditions to analyse this recognition-mediated 1,3-dipolar

Table 1. Outcomes of 1,3-dipolar cycloaddition reactions between **1** and **2** and **2** and **10** in different solvents.

	Solvent			
Reaction[a]	d_2-TCE%[b]	CD_3CN%[c]	Isomer ratio[d] 1,4:1,5	% Completion[e]
1+**2**	75	25	90:10	10
2+**10** (Control)	75	25	60:40	2
1+**2**	87.5	12.5	97:3	30
2+**10** (Control)	87.5	12.5	57:43	12

[a] All reactions were carried out in a thermostatted heating block. In each case, the starting concentration of each reactant was 50 mM and the reactions were carried out for 67 hours at 90°C.
[b] D_2-1,1,2,2-tetrachloroethane (99.8% atom D).
[c] D-acetonitrile (99.8% atom D).
[d] Determined by deconvolution of the respective product CH_2N resonances in the 400 MHz ^1H NMR spectrum.
[e] Determined by deconvolution of the respective product CH_2N resonances in the 400 MHz ^1H NMR spectrum with respect to the CH_2N resonance of the starting azide.

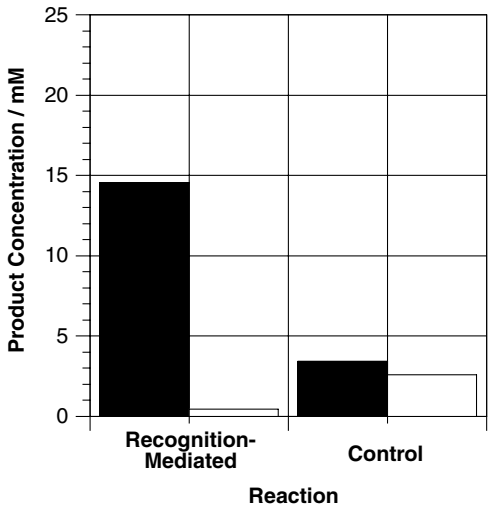
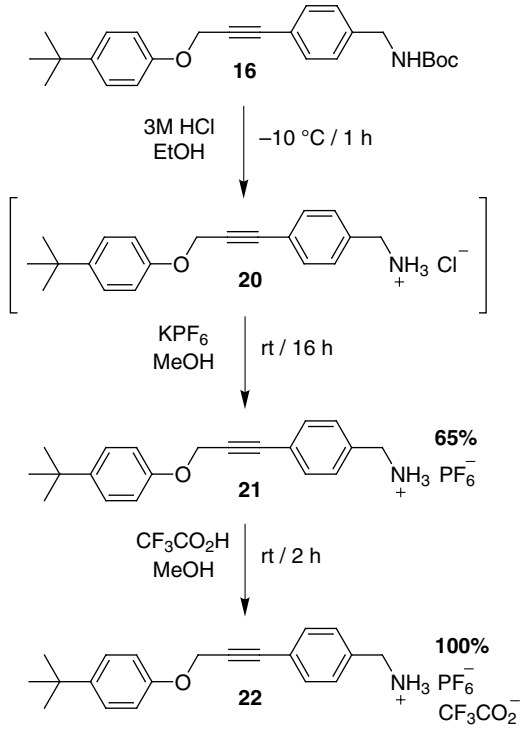


Figure 4. Product concentrations determined for the reactions between **1** and **2** (Recognition-mediated) and **2** and **10** (Control). In both cases, the starting concentration of each reactant was 50 mM and the reactions were carried out in a mixture of D_2-1,1,2,2-tetrachloroethane and D-acetonitrile (7:1) for 67 hours at 90°C. The product concentrations were determined by deconvolution of the respective product C*H*$_2$N resonances in the 400 MHz ^{1}H NMR spectrum with respect to the C*H*$_2$N resonance of the starting azide. Dark bars represent the 1,4-substituted regioisomer and light bars represent the 1,5-substituted regioisomer.



Scheme 6.

cycloaddition reaction were a concentration of 50 mM with respect to both the dipole and the dipolarophile, at a temperature of 90°C for 70 hours in a solvent mixture with the composition 87.5% D_2-TCE and 12.5% CD_3CN.

Using these optimum reaction conditions, the product ratios shown in Fig. 4 were measured for the recognition-mediated reaction between **1** and **2** and the control reaction between **2** and **10**. It is apparent from the results shown in Fig. 4 that the recognition process between the ammonium cation and the crown ether ring successfully controls the regioselectivity of this cycloaddition reaction. The ratio of the 1,4 to the 1,5 regioisomer is 97:3, compared with an approximate 1:1 ratio of regioisomers in the control reaction. Unfortunately, as a result of the high reaction temperature required, it was not possible to monitor the course of the reaction via ^{1}H NMR spectroscopy, and, hence, rate constants for the two reactions could not be determined.

Disappointingly, this system gave only modest rate enhancement (2.5-fold)—giving 30% yield of products after 67 hours for the recognition-mediated reaction, compared with 12% yield of products for the control reaction. We considered that this poor acceleration could be a result of strong ion pair association between the trifluoroacetate ion and the ammonium cation inhibiting the reaction. It was thought that this problem could be addressed by the use of an alternative counterion such as PF_6^- that does not possess any hydrogen bonding sites. Hence the dipolarophile **21** was synthesised as shown in Scheme 6. *N*-Boc-4-aminobenzylprop-2-yn-1-(4′-*tert*-butylphenyl)-ether **16** was added to a solution of 1 M HCl in ethanol and left to stir for one hour at −10°C and then for a further 30 minutes at room temperature affording the corresponding hydrochloride salt **20**. Counterion exchange of **20** using potassium hexafluorophosphate in methanol gave the target hexafluorophosphate salt **21** in good yield.

Unfortunately, dipolarophile **21** is relatively insoluble in the solvent mixture used previously. However, dipolarophile **22**, containing a mixture of the trifluoroacetate and hexafluorophosphate counterions (1:1, estimated by negative ion MALDI-tof mass spectrometry), which could be prepared readily by a simple ion-exchange extraction, was sufficiently soluble to permit some assessment of the effect of the counterion. When the reactions between **1** and **22** and **10** and **22** were performed under identical conditions to those employed previously, significantly more product (Fig. 5) was observed. However, although the recognition-mediated reaction was still significantly more selective than the control reaction, the rate enhancement with respect to the control reaction (2.4-fold) was similar to that observed with dipolarophile **2** (2.5-fold). We therefore concluded that, while the counterion has a significant effect on the reactivity of the alkyne dipolarophile, it has little effect on the efficiency of the [**A**·**B**] complex pathway.

In conclusion, we have demonstrated that [**A**·**B**] complex methodology can be applied in a logical manner to the control of the regiochemistry in a 1,3-dipolar cycloaddition reaction. The recognition-mediated reaction shows a high level of regio control, at best better than 30:1, in favour of the regioisomer predicted by molecular modelling studies. The rate acceleration achieved by the recognition-mediated process is, however, very modest. It is clear that, with relatively unreactive dipoles and dipolarophiles, such as those discussed here, the advantage gained by rendering the cycloaddition reaction pseudointramolecular through the formation of a reactive [**A**·**B**] complex is offset by the

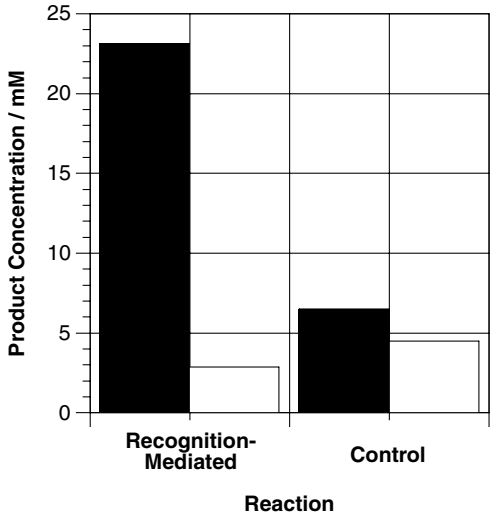


Figure 5. Product concentrations determined for the reactions between **1** and **22** (Recognition-mediated) and **10** and **22** (Control). In both cases, the starting concentration of each reactant was 50 mM and the reactions were carried out in a mixture of D_2-1,1,2,2-tetrachloroethane and D-acetonitrile (7:1) for 67 hours at 90°C. The product concentrations were determined by deconvolution of the respective product CH_2N resonances in the 400 MHz ^{1}H NMR spectrum with respect to the CH_2N resonance of the starting azide. Dark bars represent the 1,4-substituted regioisomer and light bars represent the 1,5-substituted regioisomer.

high reaction temperatures required. These high temperatures entropically disfavour the formation of the reactive [**A**·**B**] complex. We are currently seeking methods of overcoming this limitation of our methodology.

1. Experimental

1.1. General procedures

Chemicals were purchased from Aldrich or Lancaster and used as received. Solvents were purchased from Fisher Scientific and used as received unless specified. Tetrahydrofuran was distilled under nitrogen from sodium and benzophenone ketyl. Dichloromethane and acetonitrile were distilled under nitrogen from calcium hydride. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with Kieselgel 60 F_{254} (Merck 5554). Flash Chromatography was carried out using Kieselgel 60 (0.040–0.063 mm mesh, Merck 9385). Developed plates were air dried, and visualised under a UV lamp (254 nm) or using potassium permanganate (1% solution in water). Melting points were determined using an Electrothermal 9200 melting point apparatus and are uncorrected. Electron impact mass spectrometry (EIMS), chemical Ionisation (CIMS), fast atom bombardment mass spectrometry (FABMS), using a *m*-nitrobenzyl alcohol matrix, were carried out on either VG Prospec or VG Zabspec instruments. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded on either a Bruker AC300 (300 MHz), a Bruker AMX400 (400 MHz) or a Bruker DRX500 (500 MHz) spectrometer using the deuterated solvent as the lock and residual solvents as an internal reference. ^{13}C NMR spectra were recorded on a Bruker AC300 (75.5 MHz) spectrometer using the PENDANT pulse sequence, with deuterated solvent as the lock and residual solvent as internal reference. The values of all coupling constants (J) are reported in Hz.

1.2. Kinetic procedures

All solutions for kinetic studies were made up at room temperature (21°C) using volumetric flasks (2 ml± 0.02 ml). The experimental samples were prepared by dilution of the stock solutions with the appropriate deuterated solvent, using either Hamilton 1 ml, 500 μl or 250 μl gas tight syringes. Samples were analysed immediately by either 300 MHz, 400 MHz or 500 MHz ^{1}H NMR spectroscopy. Errors derived from the concentration of product, either by deconvolution or integration, are estimated to be ± 3%.

1.3. Cycloaddition AB system (50 mM)

A stock solution (100 mM) of 3-(4-benzylammonium)prop-2-yn-1-(4′-*tert*-butylphenyl)ether trifluoroacetate was made up in 75% deuterated tetrachoroethane (99.8 atom% D); 25% deuterated acetonitrile (99.8 atom% D). Stock solutions (100 mM) 4-azidobenzo-15-C-5 and 3,4-dimethoxybenzyl azide were made up in deuterated tetrachloroethane (99.8 atom% D). All solutions were stored at −12°C in a sample tube with a PTFE lined cap and sealed with parafilm. Deuterated solvents were stored in a dessicator. For the kinetic runs, 0.35 ml of azide stock solution was added to a vial containing 0.35 ml of propargyl ether stock solution and the resultant solution homogenised via shaking or sonification as necessary. The reaction mixtures were then heated to 90°C in a heating block before being transferred to a dry NMR tube for analysis via ^{1}H 400 MHz NMR (Bruker AMX400).

1.4. Synthetic procedures

1.4.1. 4-Hydroxymethylbenzo-15-crown-5 6. 4-Carboxymethyl benzo-15-crown-5 **5** (5.00 g, 1.62 mmol) in anhydrous THF (15 ml) was added dropwise to a slurry of lithium aluminium hydride (1.22 g, 31.15 mmol) in anhydrous THF (50 ml), whilst stirring vigorously under a dry nitrogen atmosphere. After the addition was complete, ethyl acetate (100 ml), H_2O (100 ml) and aqueous 1 M HCl were added slowly. The aqueous phase was then extracted with ethyl acetate (2×100 ml) and the combined organic layers dried ($MgSO_4$). The solvent was removed in vacuo affording the crude product as a yellow oil, which was purified by column chromatography (SiO_2, 1:1 v/v hexane:CH_2Cl_2) affording 4-hydroxymethylbenzo-15-crown-5 **6** as a colourless solid (2.58 g, 58%) mp 46–47°C (lit.[21] 45–47°C); δ_H (300 MHz, $CDCl_3$) 6.90–6.80 (3H, m, Ar), 4.59 (2H, s, CH_2), 4.14–4.11 (4H, m), 3.91–3.88 (4H, m), 3.75 (8H, s); δ_C (75 MHz, $CDCl_3$) 149.8 (C, quat, Ar), 149.4 (C, quat, Ar), 134.3 (C, quat, Ar), 119.2 (CH, Ar), 113.8 (CH, Ar), 112.9 (CH, Ar), 71.0 (2×CH_2), 70.5 (2×CH_2), 69.6 (2×CH_2), 69.1 (CH_2), 68.8 (CH_2), 65.2 (CH_2-OH); *m/z* (EI) 298 (M^+, 50%), 166 (56), 137 (53), 55 (55), 43 (100). (HRMS) 298.1416 (M^+ $C_{15}H_{22}O_6$ requires 298.1422).

1.4.2. 4-Chloromethylbenzo-15-crown-5 7. Triethylamine

(1.28 ml, 9.23 mmol) was added to 4-hydroxymethyl benzo-15-crown-5 **6** (2.50 g, 8.39 mmol) in CH_2Cl_2 (40 ml) and the resulting mixture was cooled to −5°C (ice/acetone bath). Thionyl chloride (0.92 ml, 12.58 mmol) in anhydrous CH_2Cl_2 (15 ml) was added dropwise whilst under a dry nitrogen atmosphere and the resulting reaction mixture was kept at −5°C for a further 45 mins before stirring at room temperature for 3 hours. The reaction mixture was washed with H_2O (100 ml), saturated aqueous $NaHCO_3$ (100 ml), aqueous 2 M HCl (100 ml) and H_2O (2×100 ml) and dried ($MgSO_4$). The solvent was removed in vacuo affording the crude product as a colourless oil which was purified via crystallisation (petroleum ether/diethyl ether 50:5 v/v) at −15°C to give 4-chloromethylbenzo-15-crown-5 **7** as a colourless solid (1.70 g, 72%) mp 62–64°C (lit.[22] 60–61°C); δ_H (300 MHz, $CDCl_3$) 6.91–6.79 (3H, m, Ar), 4.53 (2H, s, CH_2), 4.16–4.10 (4H, m), 3.92–3.88 (4H, m), 3.75 (8H, s); δ_C (75 MHz, $CDCl_3$) 149.4 (C, quat, Ar), 149.2 (C, quat, Ar), 130.5 (C, quat, Ar), 121.7 (CH, Ar), 114.4 (CH, Ar), 113.7 (CH, Ar), 71.5 (2×CH_2), 70.4 (2×CH_2), 69.5 (2×CH_2), 69.1 (CH_2), 68.7 (CH_2) 46.6 (CH_2-Cl); *m/z* (EI) 316 (M^+, 28%), 149 (100); (HRMS) 339.0975 [(M+ Na)$^+$]; $C_{15}H_{21}O_5NaCl$ requires 339.0986).

1.4.3. 4-Azidomethylbenzo-15-crown-5 1. Sodium azide (0.24 g, 3.73 mmol) was added to a stirred solution of 4-chloromethylbenzo-15-crown-5 **5** (0.74 g, 2.33 mmol) dissolved in acetone (40 ml). The resulting reaction mixture was heated to reflux for 20 hours under a dry nitrogen atmosphere. The organic phase was washed with H_2O (2×50 ml), 2 M HCl (25 ml) and dried ($MgSO_4$). The solvent was removed in vacuo affording 4-azidomethyl-benzo-15-crown-5 **1** as a cream coloured solid (0.51 g, 42%) mp 56–57.5°C; (Found; C, 55.63, H, 6.49, N, 12.99, $C_9H_{11}N_3O_2$ requires C, 55.73; H, 6.50; N, 13.00); ν_{max}/cm^{-1} 2104s (N_3), 1605 and 1590 (Ar, C=C); δ_H (300 MHz, $CDCl_3$) 6.84–6.82 (3H, m, Ar), 4.24 (2H, s, CH_2), 4.16–4.11 (4H, m), 3.92–3.89 (4H, m), 3.77–3.75 (8H, m); δ_C (75 MHz, $CDCl_3$) 149.3 (C, 2×quat, Ar), 128.4 (C, quat, Ar), 121.5 (CH, Ar), 114.1 (CH, Ar), 113.9 (CH, Ar), 71.2 (2×CH_2), 70.83 (2×CH_2), 70.6 (2×CH_2), 69.6 (CH_2), 69.1 (CH_2), 54.8 (CH_2-N_3); *m/z* (EI) 323 (M^+, 50%), 149 (100).

1.4.4. 3,4-Dimethoxybenzyl chloride 9. 3,4-Dimethoxy-benzyl alcohol **6** (8.25 g, 50 mmol) and triethylamine (7.7 ml, 55 mmol) were dissolved in dichloromethane (100 ml) before freshly distilled thionyl chloride (5.45 ml, 75 mmol) was added dropwise via syringe under a dry nitrogen atmosphere. The reaction temperature was maintained between −5°C and 0°C throughout the addition (ice/acetone bath). The reaction mixture was then left to stir for 30 minutes at 0°C, and then for a further 3 hours at room temperature, after this time, it was washed with water (50 ml), 2 M HCl (50 ml), saturated aqueous $NaHCO_3$ (50 ml) and again with water (25 ml) before drying ($MgSO_4$). The solvent was removed in vacuo, affording the crude product as a brown oil which was triturated with petroleum ether (bp 80–100°C) and diethyl ether at −78°C. The resulting colourless precipitate was filtered and washed with *n*-pentane, affording 3,4-dimethoxybenzyl chloride **9** as a colourless powder (9.33 g, 86%). mp 49–51°C (lit.[23] 51°C); δ_H (300MHz, $CDCl_3$) 6.94–6.90 (2H, m, Ar), 6.83–6.80 (1H, m, Ar), 4.56 (2H, s, CH_2), 3.89 (3H, s, CH_3), 3.87 (3H, s, CH_3); δ_C (75MHz, $CDCl_3$) 149.2 (C, quat, Ar), 149.1 (C, quat, Ar), 130.0 (C, quat, Ar), 121.2 (CH, Ar), 111.7 (CH, Ar), 111.1 (CH, Ar), 56.0 (CH_3), 55.9 (CH_3), 46.8 (CH_2-Cl); *m/z* (EI) 186 (M^+, 21%), 151 (100), 107 (12); (HRMS) 186.0443 (M^+ $C_9H_{11}O_2Cl$ requires 186.0448).

1.4.5. 3,4-Dimethoxybenzyl azide 10. Sodium azide (2.79 g, 42.90 mmol) was added to a stirred solution of 3,4-dimethoxybenzyl chloride **9** (4.86 g, 26.10 mmol) in acetone (60 ml) and the resulting reaction mixture was heated to reflux for 16 hrs under an inert nitrogen atmosphere. The product was extracted with dichloro-methane (3×100 ml) and the organic phases combined and washed with water (50 ml) before drying ($MgSO_4$). The solvent was removed in vacuo without heating, affording the crude product as a yellow oil which was purified by column chromatography (SiO_2; 2:1 v/v CH_2Cl_2: hexane) to afford 3,4-dimethoxybenzyl azide **10** as a pale yellow liquid (4.74 g, 94%). (Found; C, 55.85; H, 5.86; N, 21.75. $C_9H_{11}N_3O_2$ requires C, 55.96; H, 5.70; N, 21.76); ν_{max}/cm^{-1} 2098s (N_3), 1606 and 1592 (Ar, C=C) 1516 (COOMe); δ_H (300MHz, $CDCl_3$) 6.85–6.82 (3H, m, Ar), 4.26 (2H, s, CH_2), 3.81 (3H, s, CH_3), 3.80 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 149.2 (C, quat, Ar), 149.0 (C, quat, Ar) 127.8 (C, quat, Ar), 120.8 (CH, Ar), 111.3 (CH, Ar), 111.1 (CH, Ar), 55.9 (CH_3), 55.9 (CH_3), 54.8 (CH_2-N_3); *m/z* (EI) 193 (M^+); (HRMS) 193.0851 (M^+ $C_9H_{11}N_3O_2$ requires 193.0840).

1.4.6. *N*-Boc-4-bromobenzylamine 12. *N,N*-Diisopropyl-ethylamine (3.91 ml, 24.72 mmol) was added to a suspension of 4-bromobenzylamine hydrochloride **11** (5.00 g, 22.47 mmol) in $CHCl_3$ (100 ml) and stirred for 10 minutes under a dry nitrogen atmosphere. Di-*tert*-butyldicarbonate (4.90 g, 22.47 mmol) in c $CHCl_3$ (25 ml) was added dropwise, and the resulting reaction mixture was stirred at room temperature for 18 hrs. After this time the solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2, $CHCl_3$) to afford *N*-boc-4-bromobenzylamine **12** as a white solid (5.92 g, 92%) mp 83–84°C (lit.[24] 84–85°C); (Found; C, 50.52, H, 5.67, N, 4.94, $C_9H_{11}N_3O_2$ requires C, 50.35; H, 5.59; N, 4.96); ν_{max}/cm^{-1} 3325 and 3300 (CONH), 1682 (C=O), 1538 (C=C), 798s (C–Br); δ_H (300 MHz, $CDCl_3$) 7.45–7.42 (2H, m, Ar), 7.16–7.13 (2H, d, $^3J_{HH}$ 8.5, Ar), 4.87 (1H, b s, NH), 4.26–4.24 (2H, m, CH_2), 1.45 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 155.8 (C, quat, C=O), 138.1 (C, quat, Ar), 131.6 (2×CH, Ar), 129.3 (2×CH, Ar), 121.2 (C, quat, Ar), 44.0 (CH_2), 28.4 (3×CH_3, ^{t}Bu), 27.3 (C, quat, ^{t}Bu); *m/z* (EI) 286 (M^+, 3%), 247 (29), 186 (61), 106 (100), 58 (31).

1.4.7. Prop-3-yn-1-yl(4-*tert*-butylphenyl) ether 15. Potassium carbonate (5.28 g, 38.22 mmol) and benzo-18-crown-6 (0.34 g, 1.27 mmol) were added to a solution of propargyl toluenesulfonate **14** (5.0 g, 25.48 mmol) and 4-*tert*-butyl phenol **13** (3.80 g, 25.48 mmol) in acetonitrile (70 ml). The resulting reaction mixture was heated to reflux for 2 days after which time the organic phase was cooled, washed with water (50 ml) and extracted with CH_2Cl_2 (3×50 ml).

The combined organic phases were then dried ($MgSO_4$) and the solvent removed in vacuo to afford the crude product as a pale yellow oil. Prop-3-yn-1-yl(4-*tert*-butylphenyl) ether **15** was purified by flash column chromatography (SiO_2, 4:1 v/v hexane:CH_2Cl_2) affording a clear viscous oil (5.06 g, 94%). (Found; C, 76.32, H, 8.15. $C_{13}H_{16}O$ requires C, 76.56; H, 8.57); δ_H (300 MHz, $CDCl_3$) 7.35–7.32 (2H, d, $^3J_{HH}$ 8.8, Ar), 6.95–6.92 (2H, d, $^3J_{HH}$ 8.8, Ar), 4.68 (2H, m, CH_2), 2.58–2.56 (1H, m, C≡C–H)1.32 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 155.8 (C, quat, Ar), 144.3 (C, quat, Ar), 126.3 (2×CH, Ar), 114.4 (2×CH, Ar), 78.9 (C, terminal, C≡C), 75.4 (C, quat, C≡C), 55.9 (CH_2), 34.2 (C, quat, ^{t}Bu), 31.5 (3×CH_3, ^{t}Bu); *m/z* (EI) 188 (M^+, 29%), 173 (100), 91 (27), 39 (32).

1.4.8. *N*-Boc-4-Aminobenzylprop-2-yn-1-(4′-tert-butylphenyl)ether 16. 4-Bromo-*N*-Boc-benzylamine **12** (2.00 g, 6.99 mmol) dissolved in DMF (25 ml) and Et_3N (4.2 ml) was degassed for 20 mins by passing a constant stream of nitrogen through the reaction solvents. Tetrakis-(triphenylphosphine) palladium(0) (0.40 g, 0.35 mmol), copper iodide (0.20 g, 1.05 mmol, 0.15 equiv.) and PPh_3 (0.09 g, 0.35 mmol) were added to the constantly stirred solution whilst under a positive nitrogen atmosphere. The resulting reaction mixture was left to stir for 30 min before prop-3-yn-1-(4-*tert*-butylphenyl) ether **15** was added dropwise via syringe over 1 hour. The mixture was then heated to reflux for 50 hours after which time it was allowed to cool to room temperature before filtering through a short pad of Celite to remove metal salts. The reaction was then quenched with H_2O (100 ml) and washed with aqueous 2 M HCl (125 ml) before extracting the aqueous phase with CH_2Cl_2 (2×100 ml). The combined organic layers were then washed with H_2O (2×100 ml) and dried ($MgSO_4$) and the solvent was removed in vacuo affording the crude product as a brown oil. This residual oil was purified via column chromatography (SiO_2, 11:1 v/v hexane:ethyl acetate) affording *N*-Boc-4-aminobenzylprop-2-yn-1-(4′-tert-butylphenyl)ether **16** as a pale yellow solid (1.11 g, 42%) mp 104–106.5°C; (Found; C, 76.6; H, 7.77; N, 3.49. $C_{25}H_{31}NO_3$ requires C, 76.4; H, 7.95; N, 3.58); ν_{max}/cm^{-1} 3334 and 3328 (CONH), 1578, 1549 and 1515 (Ar, C=C); δ_H (300 MHz, $CDCl_3$) 7.42–7.39 (2H, m, Ar), 7.35–7.31 (2H, m, Ar), 7.23–7.20 (2H, m, Ar), 6.99–6.94 (2H, m, Ar), 4.88 (2H, s, CH_2), 4.83 (1H, m, NH), 4.31–4.29 (2H, m, CH_2), 1.45 (9H, s, ^{t}Bu), 1.30 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 155.6 (C, quat, C=O), 144.2 (C, quat, Ar), 138.1 (C, quat, Ar), 137.5 (C, quat, Ar), 132.1 (2×CH, Ar), 127.3 (2×CH, Ar), 126.3 (2×CH, Ar), 121.3 (C, quat, Ar), 114.4 (2×CH, Ar), 86.7 (C, quat, C≡C), 84.2 (C, quat, C≡C), 56.7 (CH_2), 56.6 (CH_2), 44.4 (C, quat, ^{t}Bu), 34.1 (C, quat, ^{t}Bu), 31.5 (3×CH_3, ^{t}Bu), 28.4 (3×CH_3, ^{t}Bu); *m/z* (CI) 411 (M^++NH_4, 88%), 355 (63), 263 (100), 207 (50), 146 (34).

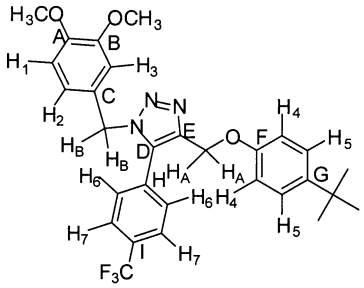
1.4.9. 3-(4-Benzylammonium)prop-2-yn-1-(4′-*tert*-butylphenyl)ether trifluoroacetate 2. *N*-Boc-4-aminobenzylprop-2-yn-1-(4′-*tert*-butylphenyl)ether **16** (0.80 g, 2.04 mmol) in anisole (0.22 ml, 2.04 mmol) was dissolved in a mixture of CH_2Cl_2/trifluoroacetic acid (30 ml: 0.52 ml / 5 % w/v) and stirred at room temperature for 17 hours under a dry nitrogen atmosphere. The solvent was removed in vacuo (without heating) affording the crude product as a yellow oil. The product was purified via crystallisation at −15°C (2:1 v/v ether:hexane) affording the product as a cream solid (0.34 g, 41%) mp 131.5–134°C. (Found; C, 64.69; H, 5.82; N, 3.36, $C_{22}H_{24}NO_3F_3$ requires C, 64.86; H, 5.90; N, 3.44); ν_{max}/cm^{-1} 3492b (NH_3^+), 121w (alkyne), 1608,1582 and 1514 (Ar, C=C), 1695 (COO^-); δ_H (300 MHz, $CDCl_3$) 8.13 (3H, b, s, NH_3^+), 7.43–7.35 (4H, m, Ar), 7.38–7.35 (2H, m, Ar), 6.97–6.94 (2H, m, Ar), 4.92 (2H, s, CH_2), 4.07 (2H, s, CH_2), 1.28 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 156.5 (C, quat, Ar), 145.2 (C, quat, Ar), 135.0 (2×quat, Ar), 131.1 (2×CH, Ar), 130.4 (2×CH, Ar), 127.4 (2×CH, Ar), 123.6 (C, quat, Ar), 115.4 (2×CH, Ar), 86.7 (C, quat, C≡C), 86.5 (C, quat, C≡C), 57.19 (CH_2), 43.8 (CH_2), 34.8 (C, quat, ^{t}Bu), 31.8 (3×CH_3, ^{t}Bu); *m/z* (FAB) 294 (M^+ - CF_3COO^-, 89%), 277 (24), 221 (100); *m/z* (MALDI) 112 (CF_3COO^-, 82%), 97 (CF_3CO^-, 100), 69 (CF_3^-, 31); (HRMS) 294.1858 (M^+ $C_{20}H_{24}NO$ requires 294.1855).

1.4.10. 3-(4-Trifluoromethyl)phenylprop-2-yn-1-(4-tert-butylphenyl) ether 17. 4-Iodobenzotrifluoride (2.72 g 10.00 mmol) was dissolved in freshly distilled diisopropylamine (80 ml) and degassed by bubbling dry nitrogen gas through the solution for 20 minutes. Palladium (II) bis-triphenylphosphine dichloride (0.42 g, 0.60 mmol), copper (II) acetate (0.11 g, 0.60 mmol) and triphenylphosphine (0.16 g, 0.60 mmol) were added successively to the constantly stirred solution under a positive nitrogen atmosphere and the mixture stirred for 2 minutes. Prop-2-yn-1-(4-*tert*-butylphenyl) ether **15** (3.65 g, 24.00 mmol, 1.2 equiv.) was added dropwise via syringe over 20 minutes and the resulting reaction mixture was heated to reflux, with stirring, for 14 hours. The mixture was cooled and filtered to remove waste solids. The solid residue was washed with dichloromethane and the filtrate collected and solvent removed in vacuo. The residue was redissolved in CH_2Cl_2 (40 ml), washed with water (15 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product purified via flash column chromatography (SiO_2, 8:1 v/v hexane:CH_2Cl_2) affording 3-(4-trifluoromethyl)phenylprop-2-yn-1-(4-tertbutylphenyl) ether **17** as a colourless solid (1.23 g, 37%) mp 88–90°C; δ_H (300MHz, $CDCl_3$) 7.61–7.50 (4H, m), 7.49–7.30 (2H, m), 7.02–6.93 (2H, m), 4.90 (2H, s), 1.41 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 155.5 (C, quat, Ar) 144.4 (C, quat, Ar), 132.1 (2×CH, Ar), 126.4 (2×CH, Ar), 125.3 (2×CH, Ar), 125.2–125.1 (CF_3), 114.5 (2×CH, Ar), 86.8 (C, quat, C≡C), 85.6 (C, quat, C≡C), 56.6 (CH_2), 34.2 (C, quat, ^{t}Bu), 31.5 (3×CH_3, ^{t}Bu); *m/z* (EI) 332 (M^+, 9%), 263 (75), 253 (100); (HRMS) 332.3589 (M^+ $C_{20}H_{19}F_3O$ requires 332.3595).

1.4.11. 1-(4-Benzyl-15-crown-5)-4-[methyl(4′-tert-butylphenyl)ether]-5-(benzylammoniumtrifluoroacetate) 1,2,3-triazole 18 and 1-(4-benzyl-15-crown-5)-5-[methyl(4′-tert-butyl-phenyl)ether]-4-(benzylammoniumtrifluoroacetate) 1,2,3-triazole 19. 4-Triflouromethylbenzylprop-2-yn-1-(4′-tert-butylphenyl)ether **17** (0.16 g, 0.48 mmol) and 3,4-dimethoxy azide **10** (0.08 g, 0.48 mmol) were dissolved in toluene (2.00 ml) and heated to reflux for 2 days under an atmosphere of dry nitrogen after which time the solvent was removed in vacuo and the two regioisomers formed separated via column chromatography (SiO_2, 3:1 v/v hexane:ethyl acetate) affording the pure 1,4 **18** and 1,5 **19**

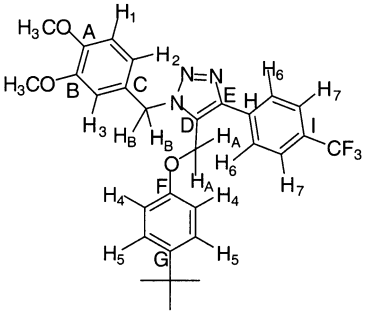
products as colourless solids (74 mg, 28% and 36 mg, 14% respectively).

1.4.12. 1-(4-Benzyl-15-crown-5)-4-[methyl(4′-tert-butylphenyl)ether]-5-(benzylammoniumtrifluoroacetate) 1,2,3-triazole 18.



δ_H (300 MHz, $CDCN_3$/TCE) 7.77–7.74 (2H, d, $^3J_{HH}$ 8.1, H_7), 7.52–7.49 (2H, d, $^3J_{HH}$ 8.1, H_6), 7.29–7.26 (2H, m, H_5), 6.84–6.81 (2H, m, H_4), 6.79–6.76 (1H, d, $^3J_{HH}$ 8.1, H_1), 6.55–6.52 (1H, dd, $^3J_{HH}$ 8.1, $^2J_{HH}$ 2.0, H_2), 5.46 (CH_2-N), 5.01 (CH_2-O), 3.73 (CH_3), 3.59 (CH_3), 1.25 (3×CH_3, *t*Bu); δ_C (125 MHz, $CDCN_3$/TCE) 156.9 (C, quat, F), 150.2 (C, quat, A or B), 150.1 (C, quat, A or B), 145.0 (C, quat, G), 142.9 (C, quat, E), 136.7 (C, quat, D), 131.9 (C, quat, H), 131.6 (2×CH, C_6), 128.8 (C, quat, C), 127.2 (2×CH, C_5), 126.2 (2×CH, C_7), 125.4 (CF_3, $^1J_{CF}$ 270.1), 121.1 (CH, C_2), 115.6 (2×CH, C_4), 112.8 (CH, C_1), 112.3 (CH, C_3), 62.2 (CH_2-O), 56.4 (CH_3), 56.2 (CH_3), 53.0 (CH_2-N), 34.7 (C, quat, *t*Bu), 31.7 (3×CH_3, *t*Bu); *m/z* (ES) 548 ([M+Na]$^+$, 100%); (HRMS) 548.2119 (M^+ $C_{29}H_{30}N_3O_3F_3Na$ requires 548.2137).

1.4.13. 1-(4-Benzyl-15-crown-5)-5-[methyl(4′-tert-butylphenyl)ether]-4-(benzylammoniumtrifluoroacetate) 1,2,3-triazole 19.



δ_H (300 MHz, $CDCN_3$/TCE) 7.89–7.86 (2H, d, $^3J_{HH}$ 8.3, H_6), 7.75–7.72 (2H, d, $^3J_{HH}$ 8.3, H_7), 7.35–7.30 (2H, m, H_5), 6.83–6.80 (5H, m, H_4, H_1, H_2, H_3), 5.60 (CH_2-N), 5.15 (CH_2-O), 3.74 (CH_3), 3.56 (CH_3), 1.27 (3×CH_3, *t*Bu); δ_C (75 MHz, $CDCN_3$/TCE) 156.5 (C, quat, F), 150.3 (2×C, quat, A/B), 146.4 (C, quat, E), 145.7 (C, quat, G), 135.9 (C, quat, H), 130.8 (C, quat, D), 130.4 (C, quat, $^3J_{CF}$ 32.1), 129.0 (2×CH, C_6), 128.5 (C, quat, C), 127.4 (2×CH, C_5), 126.8 (CH, C_7), 126.7 (CH, C_7), 125.5 (CF_3, $^1J_{CF}$ 269.6), 121.4 (CH, C_2), 115.5 (2×CH, C_4), 112.9 (CH, C_1), 112.8 (CH, C_3), 59.1 (CH_2-O), 56.4 (CH_3), 56.2 (CH_3), 53.3 (CH_2-N), 34.8 (C, quat, *t*Bu), 31.7 (3×CH_3, *t*Bu); *m/z* (ES) 548 ([M+Na]$^+$, 100%); (HRMS) 548.2146 (M^+ $C_{29}H_{30}N_3O_3F_3Na$ requires 548.2137).

1.4.14. 3-(4-Benzylammonium)prop-2-yn-1-(4′-*tert*-butylphenyl)ether chloride 20. *N*-Boc-4-aminobenzylprop-2-yn-1-(4′-*tert*-butylphenyl)ether **16** (0.25 g, 0.64 mmol) was added to a solution of 3 M HCl in ethanol and left to stir for 1 hour at −10°C. The resulting reaction mixture was then allowed to warm to room temperature and left to stir for a further 30 minutes, after which time the solvent was removed in vacuo yielding 3-(4-benzylamine hydrochloride)prop-2-yn-1-(4′-*tert*-butylphenyl)ether **20** as a colourless solid which was used without further purification. *m/z* (FAB) 294 ([M^+ - Cl], 49%), 221 (100), 128 (67).

1.4.15. 3-(4-Benzylammonium)prop-2-yn-1-(4′-*tert*-butylphenyl)ether hexaflourophosphate 21. Potassium hexaflourophosphate (0.41 g, 2.25 mmol) was added to a solution of 3-(4-benzylammonium)prop-2-yn-1-(4′-*tert*-butylphenyl)ether chloride **20** (0.18 g, 56.78 mmol) in methanol (30 ml) and the resulting reaction mixture left to stir overnight under an atmosphere of dry nitrogen. The solvent was removed in vacuo after which the residue was redissolved in water and nitromethane (v/v 10:10 ml) and left to stir for a further 30 minutes. The organic phase was isolated and washed with water before being dried over $MgSO_4$. The solvent was removed in vacuo affording the crude product as a pale yellow solid. 3-(4-benzylammonium)prop-2-yn-1-(4′-*tert*-butylphenyl)ether hexaflourophoshate **21** was obtained after recrystallisation from CH_2Cl_2:hexane as a white solid (0.16 g, 65%) mp decomposes >220°C. (Found; C, 54.76; H, 5.40; N; 3.12. $C_{20}H_{24}NOPF_6$ requires C, 54.72; H, 5.51; N, 3.20); δ_H (300 MHz, $CDCl_3$) 7.51–7.48 (6H, m, Ar), 6.98–6.94 (2H, m, Ar), 4.93 (2H, s, CH_2), 4.11 (2H, s, CH_2), 2.88 (3H, bs, NH_3^+), 1.29 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 156.4 (C, quat, Ar), 145.0 (C, quat, Ar), 142.2 (C, quat, Ar), 132.6 (2×CH, Ar), 128.2 (CH, Ar), 127.4 (2×CH, Ar), 121.5 (C, quat, Ar), 115.3 (2×CH, Ar), 87.1 (C, quat, C≡C), 85.3 (C, quat, C≡C), 57.2 (CH_2-O), 44.4 (CH_2- NH_3^+), 34.7 (C, quat, ^{t}Bu), 28.5 (3×CH_3, ^{t}Bu); *m/z* (FAB) 294 (M^+ - PF_6^-, 19%), 277 (16), 221 (100), 144 (43), 128 (59); *m/z* (MALDI) 144 (PF_6^-, 49%); (HRMS) 294.1858 (M^+ $C_{20}H_{24}NO$ requires 294.1855).

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