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Chapter 2
1,3-Dipolar Cycloadditions of Azides and Arynes

Fluoride anion induced formation of transient benzyne intermediates in the presence of azides allows for facile access to functionalized benzotriazoles. A simple, one-pot procedure at room temperature allows for access to a variety of benzotriazoles in good yields and on a rapid time scale.

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2.1 Introduction

While 'click' reactions, as they have been defined, possess many attractive features for a wide variety of applications, the bioorthogonality of the azide-alkyne cycloadditions is of particular importance in the use of 'click' reactions in biologically relevant systems.[1] The narrow reactivity profile of the functionalities, particularly of the azide, make this reaction ideal for *in vitro* and even *in vivo* labelling.[2] However, limitations to their utility for such applications arise due to the inherent toxicity of the copper used to catalyze the reaction.[3] In the absence of copper though, the reaction of azides with alkynes requires elevated temperatures or pressures which are incompatible with most living systems.[4] This highlights the necessity for the development of copper-free 'click' reactions. To date, several intelligently conceived alternatives for alkyne activation have been utilized. The introduction of electron withdrawing functionalities adjacent to the triple bond[5] or the use of severely strained acetylenes[6] serve to sufficiently increase the reactivity of the resulting alkyne to allow for the cycloaddition with azides to occur at room temperature in the absence of copper. In this search for alternative alkyne reactivity, it is a natural segway into the investigation of the use of benzynes.

Since its discovery in 1942, *o*-benzyne **1** (1,2-dehydrobenzene) has proven to be an extremely useful reactive intermediate for synthetic organic chemists (Fig. 1).[7] As a kinetically unstable, highly strained molecule, it readily undergoes coupling reactions, participates in cycloadditions and is subjected to transition metal-catalyzed reactions with various neutral species to form complex organic molecules.[8]

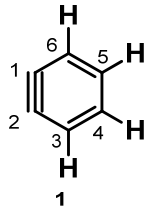

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Figure 1 Benzyne (1,2-dehydrobenzene)

A great deal of spectroscopic and theoretical study has gone into understanding the structure of *o*-benzyne **1**, and it has generally been concluded that a certain degree of triple bond character along with diradical character exists between positions 1 and 2 (Fig. 1). Thus, in a sense, these intermediates can be (and are) considered highly reactive alkynes.[9] Arynes are well known to undergo cycloadditions with a variety of substrates. Diels-Alder reactions can be performed with cyclic and acyclic heterodienes, [2+2] cycloadditions with a wide range of electron rich olefins, [4+2] cycloadditions with 1,4-dipoles, and of course [3+2] cycloadditions with 1,3-dipoles, including nitrones and azides.[6]

A key consideration in the development of aryne chemistry is the generation of the reactive intermediate and its precursor. Various methods have been developed over the years to generate this important synthetic building block. For instance, benzyne can be formed by treating an aromatic halide (**2**) with a strong base to remove the *o*-aromatic proton forming anion **3** and achieving benzyne **1** through subsequent elimination (Fig. 2, A).[10] The disadvantage of this method is that the base can often also act as a nucleophile. To avoid this problem, it is also possible to treat a dihalide substituted benzene **4** with a metal such as lithium or magnesium, followed, as in the previous case, by elimination to give benzyne **1** (Fig. 2, B).[11]

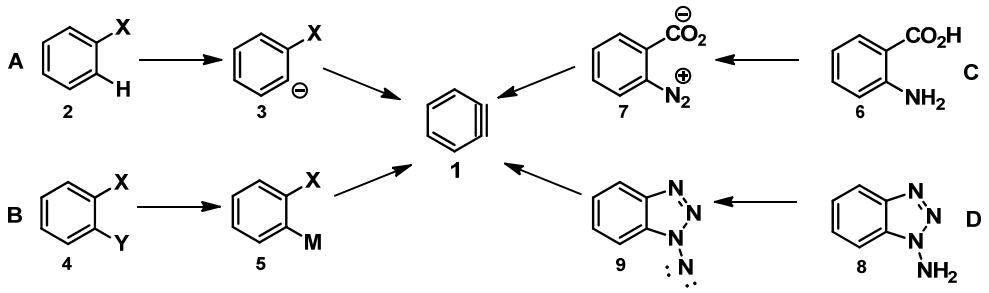
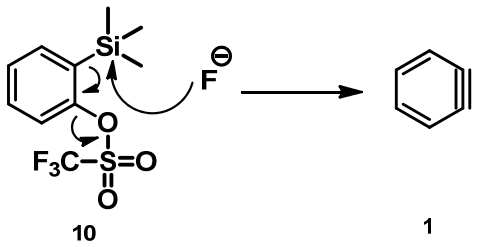


Figure 2 Various methods of generating benzyne

However, both methods A and B involve quite basic conditions which can hinder the applicability of the methodology by limiting the substrate scope to robust compounds. Furthermore, under protic conditions, formation of halobenzenes occurs very quickly relative to the alternative product route to form benzyne **1**.[12]

Benzyne **1** can also be formed from the diazonium carboxylate intermediate **7** obtained by refluxing anthranilic acid **6** with an organic nitrite (Fig. 2, C).[13] Here again, the harsh conditions severely hinder the scope of this reaction. Generation of benzyne can also be achieved by oxidation of an amino-triazole **8**, although this bears the disadvantage of requiring the presence of an oxidant (Fig. 2, D). [14] Beyond these general and widely used methods of benzyne formation, several other mild methods have been explored.[15] For instance, arynes can be generated from *o*-(trimethylsilyl)aryliodonium salts; a gentler method, but involving a difficult synthesis of the precursors limiting the possibilities for functionalization.[16] A very mild and straightforward way to form a benzyne intermediate is to use fluoride induced *ortho* elimination of *o*-(trimethylsilyl)aryl triflates **10** which can be easily prepared with various substituents on the arene ring[8] (Scheme 1). This is arguably the mildest and most versatile method of benzyne generation to date.



Scheme 1 Fluoride induced desilylation of **10** and elimination to form benzyne **1**

As mentioned above, benzotriazole formation from the cyloadditions of azides and benzynes is well documented in the literature, with examples appearing as early as 1961.[17] It has been used as a fairly standard method for the preparation of derivatized benzotriazoles over the years, with the general procedure involving refluxing anthranilic acid **6** with isoamyl nitrite to form the transient benzyne species **1** (Fig. 2, pathway C).[18] This rather harsh method of producing benzotriazoles demonstrated potential for a more modern methodology to be developed.

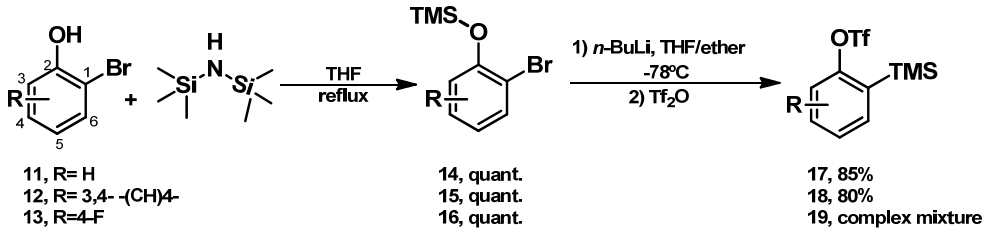
2.2 Goal

The goal of this project was to investigate the possibility of developing a general methodology for generating aryne species in a mild fashion, which would allow us to 'click', in the sense of performing a [3+2] cycloaddition, to a wide range of azides. Although it is not possible to isolate and handle them as such, arynes can be generated *in situ* and be allowed to react with an azide. With the idea that this methodology might eventually be applied in some way to the radiolabelling of relevant compounds, the speed of the reaction was to be a main focus in the methodological development. This extension to relevant biomolecules also necessitates mild reaction conditions, thus implementation of the mild fluoride induced formation of benzyne was the other focus of this synthetic methodology. The overarching goal remains the development of a copper-free [3+2] cycloaddition of azides and alkynes in the absence of copper which retains some of those benefits commonly associated with 'click' reactions – namely rapid, regioselective reactions under mild conditions.

2.3 Results and Discussion

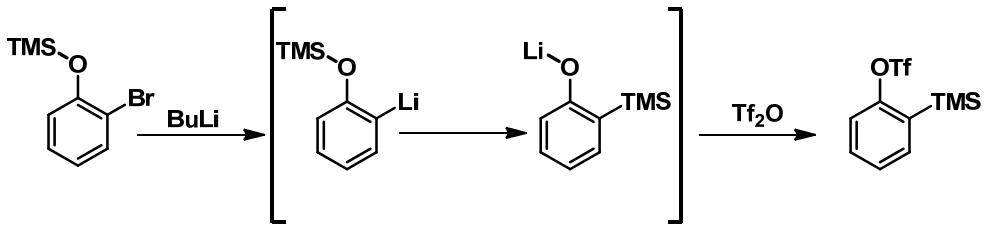
2.3.1 Synthesis of Precursors

To prepare a variety of benzyne precursors containing *ortho* substituted trimethylsilyl and triflate groups, two approaches were taken. Via Route 1, the precursor can be prepared starting from an *ortho*-bromo phenol motif (Scheme 2).



Scheme 2 Route 1 towards the preparation of benzyne precursors

By refluxing the substrate in the presence of hexamethyldisilazane (HMDS), it is possible to introduce a trimethyl silyl (TMS) group on the phenol. Silylation of alcohols and phenols through the use of HMDS is a straightforward method for silyl introduction, producing only ammonia as a side product allowing simple evaporation to be a sufficient workup.[19] This is followed by metal-halogen exchange at low temperature, migration of the TMS group from oxygen to carbon, and subsequent triflate introduction by trapping of the resulting lithium phenoxide (Scheme 3).[20]

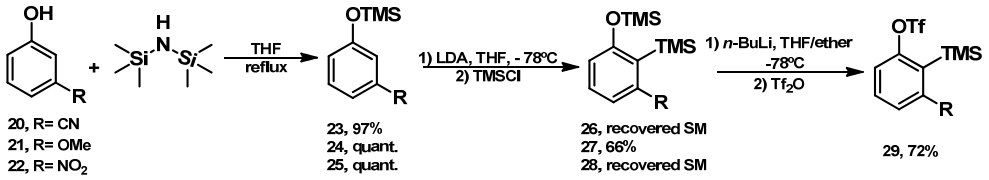


Scheme 3 Introduction of the *ortho* triflate silyl group motif

Three attempted syntheses proceeded in this fashion starting from 2-bromophenol **11**, 2-bromonaphthalen-1-ol **12** and 2-bromo-4-fluorophenol **13**, respectively (Scheme 2). The

introduction of the TMS group on the phenol functionality proceeded in quantitative yields for all three substrates. The subsequent one-pot, two-step lithiation and introduction of the triflate group gave 85 and 80% yield for the unsubstituted benzene and naphthalene precursors, respectively. However, the reaction with the silylated 2-bromo-4-fluorophenol **16** gave a complex mixture of products, with only trace amounts of the desired product.

An alternate route towards the desired precursors, Route 2 (Scheme 4), also involves the formation of a TMS protected phenol in the first step by heating the starting material at reflux in the presence of HMDS. Following this first step, the *ortho*-aromatic proton was removed using lithium diisopropyl amide (LDA) and the reaction mixture was quenched with trimethylsilyl chloride (TMSCl) to introduce a silyl group directly on the aromatic ring. This was followed by lithiation at low temperature using *n*-BuLi and addition of trifluoromethanesulfonic anhydride (Tf_2O) to introduce the desired triflate group on the phenol. This protocol was carried out on 3-hydroxybenzonitrile **20**, 3-methoxyphenol **21** and 3-nitrophenol **22**. The first step again proceeded with excellent yields for all three precursors. The subsequent deprotonation, silylation step gave the desired product **27** in 66% isolated yield for the methoxy functionalized substrate **24**. Unfortunately, in the case of the nitro and cyano derivatives **26** and **28**, it proved to be impossible in our hands to form the desired compound and almost quantitative amounts of starting material were recovered. The methoxy substrate **27** was treated with *n*-BuLi and triflic anhydride to introduce the triflate group, giving the desired benzyne precursor **29** with 72% isolated yield**.**

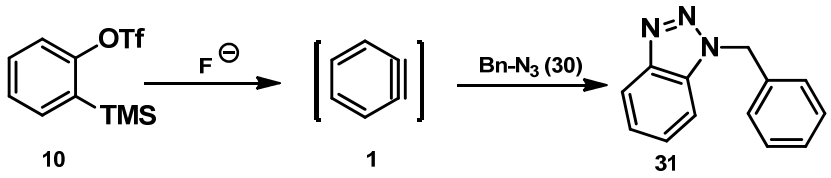


Scheme 4 Route 2 towards the preparation of benzyne precursors

2.3.2 Condition Optimization for Benzyne Formation

With a number of aryne precursors in hand, it was possible to investigate the optimal conditions for the one-pot fluoride induced benzyne formation and subsequent cycloaddition with an azide. Beginning with the cycloaddition of benzyl azide **30** and readily synthesized (as well as commercially available) *o*-(trimethylsilyl)phenyl triflate **10**, the use of differing fluoride sources was investigated in a range of solvents (Table 1).

Table 1 Reaction condition optimization[a]



10 1 31

	Fluoride Source	Eq. Fluoride	Eq. Azide	Solvent	T (°C)	Time[b] (h)	Yield[c] (%)
1	KF/18-crown-6	2.0	3.0	THF	rt	4	85
2	KF/18-crown-6	1.5	4.0	THF	rt	23	n.d.
3	KF/18-crown-6	2.0	1.2	THF	rt	29	80
4	KF/18-crown-6	2.0	3.0	THF	60	1	71
5	KF/18-crown-6	2.0	3.0	DCM	rt	8	72
6	KF/18-crown-6	2.0	3.0	MeCN	rt	3	87
7	TBAF	1.0	3.0	THF	rt	20	69[d]
8	NaF/15-crown-5	2.0	3.0	THF	rt	24	0
9	CsF/18-crown-6	2.0	3.0	THF	rt	1.5	70
10	CsF/18-crown-6	2.0	3.0	DCM	rt	30	58
11	CsF/18-crown-6	2.0	3.0	MeCN	rt	0.5	77
12	CsF/18-crown-6	2.0	3.0	H_2O	rt	48	0
13	CsF/18-crown-6	2.0	4.0	H_2O/DCM	rt	rt	0

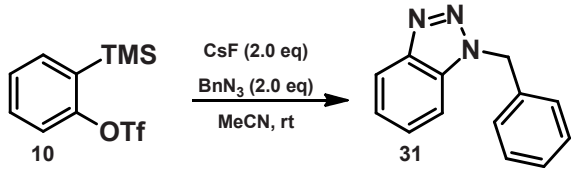
[a]All reactions were carried out on a 0.2 mmol scale in 0.05 M concentration. [b]Time until full conversion. [c]Average isolated yields from two experiments. [d]Several side products were observed in this reaction uniquely.

Fluoride salts in combination with a complementary crown ether were tested as was tetrabutyl ammonium fluoride (TBAF). KF paired with 18-crown-6 induced full conversion to benzotriazole **31** at room temperature in all solvents tested with good yields (entries 1-6). TBAF provided an alternative to fluoride salts, but both the reaction time and yield were less favourable, and unidentified side products were detected by gas chromatography analysis of the reaction mixture (entry 7). NaF in combination with 15-crown-5 gave no conversion. CsF and 18-crown-6 gave faster reaction times, if somewhat lower yields (entries 9-11). Although 18-crown-6 is known to bind with the greatest affinity to K^+, it has also been shown that it has a high binding affinity for Cs^+ as well.[21] The reaction did not proceed in water even after 48 h (entry 12), nor did it proceed in a biphasic system of H_2O and DCM (entry 13). 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 in the presence of water, perhaps due to hydration of the fluoride anion.[22]

Reducing the amount of fluoride salt (entry 2) prolonged the reaction time, while reducing the equivalents of azide (entry 3) also extended the reaction time and caused a slight drop in yield. At reflux in THF, the reaction proceeded to completion in one hour, but the yield was lower (entry 4), as it was in DCM (entry 5). In cases with lower yields, the decrease could generally be attributed to what appears to be degradation of the benzyne precursor. Acetonitrile appeared to have a positive effect on the transformation, shortening reaction times for both KF and CsF induced reactions (entries 6 and 11). The latter reaction was particularly satisfying, showing full conversion in 30 min (entry 11). These conditions (CsF/18-crown-6, MeCN, 2.0 eq of azide) were thus chosen for all subsequent experiments. Having established a methodology to obtain rapid conversion to benzotriazole **31**, the effect of the crown ether on the reaction time was investigated (Table 2).

Table 2 Effect of the crown ether



10 31

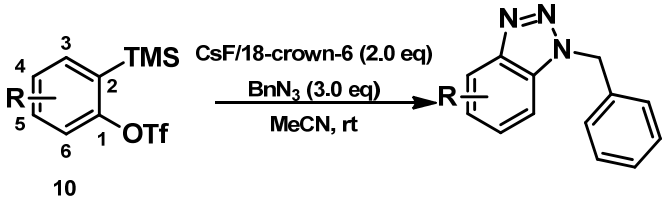
	Fluoride Source	Ratio CsF: crown ether	Solvent	Time (h)	Yield (%)
1	CsF/18-crown-6	1:1	THF	1.5	70
2	CsF/18-crown-6	1:2	THF	20	67
3	CsF	-	THF	48	2
4	CsF/18-crown-6	1:1	MeCN	0.5	77
5	CsF	-	MeCN	48	46

As demonstrated by the results in Table 2, the optimal crown ether to fluoride salt ratio is 1:1. An extra equivalent of crown ether appears to have an inhibitory effect (entry 2), and the absence of crown ether significantly decreases the reaction rate (entries 3 and 5). In THF, virtually no product was formed even after 48 h in the absence of crown ether (entry 3). In MeCN, after 48 h, the reaction managed to reach completion, but the yield was dramatically reduced (entry 5). Reaction entries 3 and 5 were performed with the optimized reaction conditions which involves using an excess of azide, but they 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.[23] We concluded from these results that the presence of crown ether is crucial to achieving rapid conversion to benzotriazoles.

Having confirmed the optimized reaction conditions, a small range of aryne precursors was tested (Table 3).

Table 3 Substrate scope



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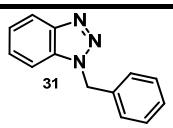
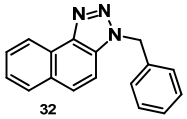
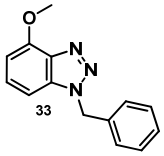
	R	Product	Time (h)	Yield (%)
1	H	 31	0.50	56
2	3,4- -$(CH)_4$-	 32	0.25	75[a]
3	3-OMe	 33	0.25	84

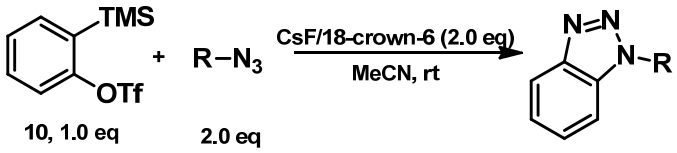
[a]2:1 regioselectivity.

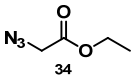
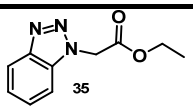
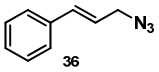
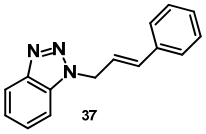
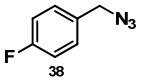
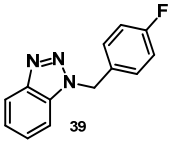
Naphthalene derivative **18** proceeded to react smoothly; the reaction is thus not limited to benzyne precursors (entry 2). In the case of cycloaddition with the naphthyl precursor **18**, a mixture of regioisomers (2:1) was observed (see section 2.6). The major product has the benzyl group positioned at the less sterically hindered position 2 as determined by ^{1}H NMR. It can be seen that good yields are achieved with an electron donating methoxy substituent at C3 (**28**) with full conversion in a matter of minutes (entry 3). The benzyne precursor **28** yielded a single regioisomer **33** with the benzyl on the nitrogen remote to the substituent. It is presumed that the selectivity is due to preferential attack at the position *meta* to the methoxy group based on both steric and electronic effects.[24]

To further ensure the generality of the reaction, some azides with particular features were tested under the optimized reaction conditions (Table 4). As can be seen from the

results, the reaction proceeds efficiently with a non-aromatic functionalized azide **34** (entry 1), and the presence of alkenes is also tolerated **36** (entry 2). Both products **35** and **37** were isolated in good yields with reaction times of less than 2 h with no side product formation observed. An electron deficient fluoroazide **38** (entry 3) reacted completely to benzotriazole **39** in 30 min. An [^{18}F] labelled analogue of this azide, developed in our group, could be used to apply this fast coupling protocol for imaging technologies such as [^{18}F]-PET.[25]

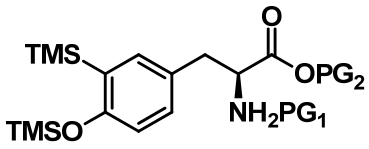
Table 4 Azide substrate scope



	Azide	Product	Time (h)	Yield (%)
1	 34	 35	1	82
2	 36	 37	1.5	78
3	 38	 39	0.5	59

2.3.3 Progress Towards a Tyrosine Precursor

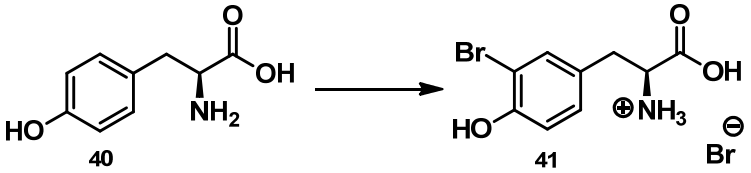
The intention of the project was to extend the methodology to a more biologically relevant substrate for possible applications in the area of [^{18}F]-radiolabelling. The goal of this part of the project was to transform an amino acid, namely tyrosine, into an aryne precursor (Scheme 5).



Scheme 5 Tyrosine based benzyne precursor (PG=protecting group)

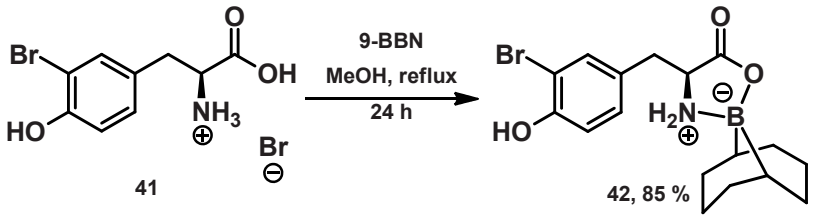
Starting from L-tyrosine (**40**), bromination was attempted using a 10:1 ratio of KBr and $KBrO_3$ in acidic conditions.[26] Even with a second addition of $KBr/KBrO_3$, the reaction never reached beyond 65% conversion, leaving approximately one third of the starting material untouched. Fortunately, a system of HBr and Br_2 in the presence of glacial acetic acid gave full conversion to the desired product **41** with 79% isolated yield.[27]

Table 5 Bromination of tyrosine



	Conditions	Result
1	$KBr/KBrO_3$ (2.0 eq/0.2 eq), HCl (0.25 M)	65% conversion
2	HBr/AcOH, Br_2	79% isolated yield

There exist a multitude of methods by which to protect the amino acid functionality for subsequent transformation. While several initial attempts were made to protect the acid and amino functionalities separately, eventually it was settled on simultaneous protection of both functionalities with one protecting group. By refluxing compound **41** in the presence of 9-borabicyclo[3,3,1]nonane (9-BBN), it was possible to form oxazaborolidinone **42** (Scheme 6).



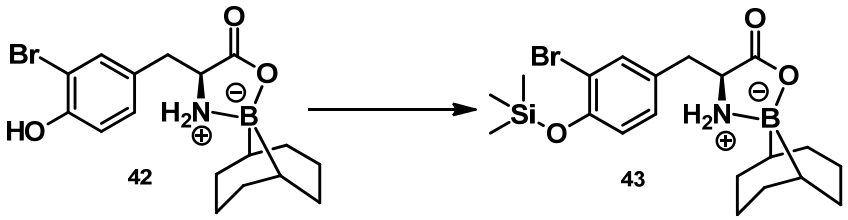
Scheme 6 Protection of tyrosine **41** with 9-BBN

This method is attractive for multiple reasons. One simple step allows for the protection of two functionalities, and yields a compound with increased solubility in organic solvents, including (in the specific case of tyrosine) THF, EtOAc, MeCN, $(CH_3)_2CO$ and MeOH amongst others. This allows for more straightforward reaction conditions to be used in subsequent steps. Although a seemingly trivial point, amino acid chemistry and particularly purification can be complicated due to lack of solubility in organic solvents. The BBN protecting group can readily be removed without epimerization of the stereogenic center using aqueous HCl or by simple exchange with ethylenediamine in MeOH.[28] The resulting protected oxazaborolidinones synthesized from a wide range of amino acids have proven to be very stable in a wide variety of reaction conditions.[29]

Further reasoning for the choice of protecting group hails from the research on BBN protected amino acids that have been shown to be selectively uptaken in melanoma cancer cells, providing a handle for boron neutron capture therapy for cancer.[30]

Following protection of the amino acid functionality, it was necessary to introduce the *ortho* substituted silyl and triflate groups. Initially, it was attempted to introduce these functionalities via Route 1 as previously described in this chapter (section 2.1, Scheme 2).

Table 6 Attempts to protect the phenol with a TMS-group

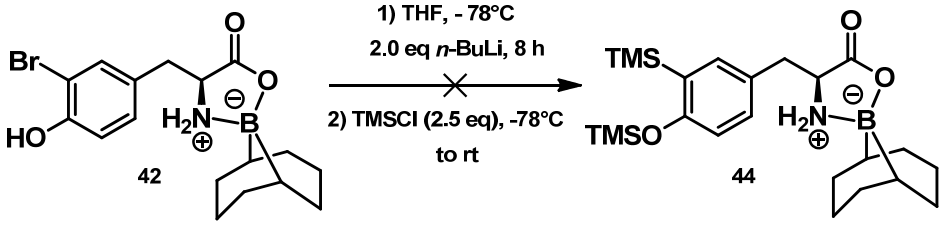


	Conditions	Comments
1	HMDS (1.1 eq), reflux	Partial BBN deprotection
2	TMSCl (1.2 eq), Et_3N (2.0 eq)	48 h, 50% conversion, cleaved upon purification by column
3	TMSOTf (1.2 eq), -10°C, Et_3N (1.1 eq), THF	Small scale: full conversion in 15 min Large scale: thick, gelatinous substance formed

Thus, **42** was heated at reflux in the presence of HMDS, but this had the effect of inducing partial removal of the BBN protecting group, even when the reaction was closely monitored (Table 6, entry 1). A second approach was taken to introduce TMS by deprotonating phenol **42** in the presence of trimethylsilyl chloride (TMSCl).[31] Two equivalents of triethyl amine were added, the extra equivalent serving as an HCl scavenger to prevent BBN deprotection. Although this did yield the desired product **43**, it was not possible to reach more than 50% conversion, despite longer reaction times (entry 2). Purification by column chromatography on silica gel resulted in cleavage of the silyl group, and the starting material was recovered in nearly quantitative amounts. A third attempt was made using trimethyl silyl triflate (TMSOTf). The increased reactivity of the silyl triflate reagent (entry 3) should allow for full conversion, making column chromatography and thus cleavage of the silyl group avoidable. Reacting **42** with 1.2 eq of TMSOTf at lower temperatures in the presence of triethyl amine did give full conversion to **43** when performed on a small scale (0.08 mmol). Unfortunately, when scaled up to 2.0 mmol, the reaction failed, and instead of product **43**, a thick white product resembling a polymeric mixture was formed. Attempts to vary the concentration and manner of addition of the reagents failed to give a different outcome.

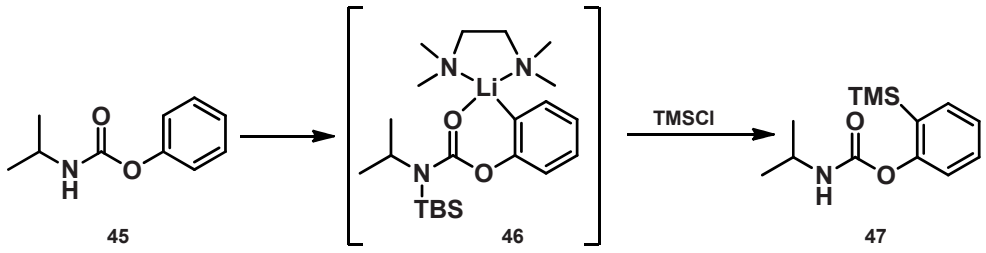
O-bromophenol **11** was then subjected, as a model substrate, to all three sets of conditions listed in Table 6 to determine whether the conditions or the substrate were proving to be problematic. Full conversion to the expected silylated phenol was seen in all cases, and it was possible to work up and purify the resulting compound by column chromatography without cleavage of the silyl group. Thus it is not a matter of the phenol or the *o*-bromine functionality, but rather a substrate specific problem.

Given the failure of this approach to yield the desired compound, we tried to introduce silyl groups both on the phenol and in the position *ortho* to it. Thus compound **42** was treated with 2.0 eq of *n*-BuLi in THF at -78°C, and quenched with TMSCl in an attempt to synthesize compound **44** (Scheme 7).



Scheme 7 Attempted synthesis of **44**

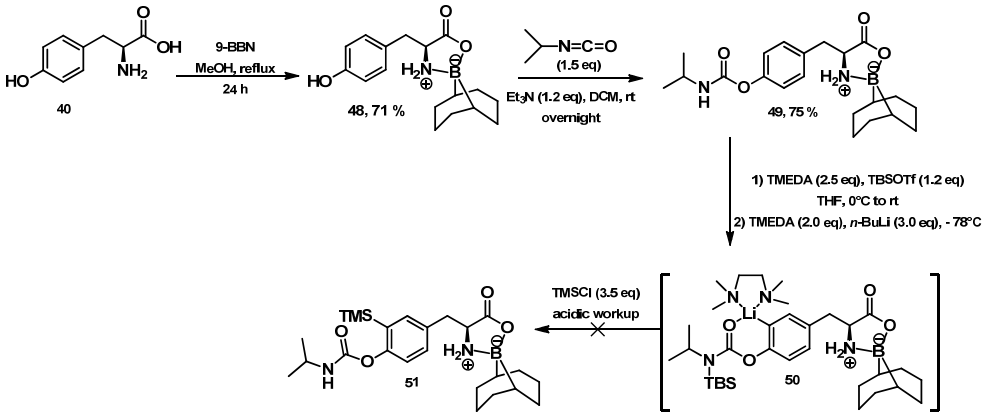
The reaction was also performed using *sec*-BuLi (both with 2.0 and 4.0 eq) as well as *tert*-BuLi (2.0 and 4.0 eq), however in all cases, only starting material **42** was recovered.
As this work was being performed, a new methodology to achieve the desired functionality for a simple benzyne precursor was published.[32] In this study, the authors made use of directed-metalation chemistry to introduce a TMS group directly in the *ortho* position starting from phenol and using arylcarbamate intermediates (Scheme 8).



Scheme 8 Literature route to 2-(trimethylsilyl)phenyl trifluoromethanesulfonate[32]

Starting from phenol, monoalkylated carbamate **45** was prepared. This underwent N-silylation to protect the free amine, which in the same pot underwent *ortho*-lithiation to give intermediate species **46**, which yields **47** when the reaction is quenched with TMSCl. After subsequent deprotection, the triflate group is introduced to yield the desired benzyne precursor **10**.

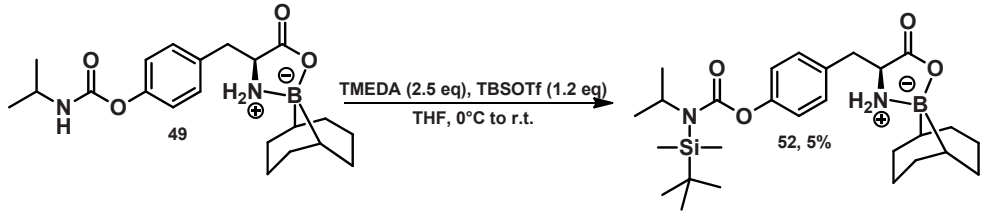
This synthetic methodology was applied to our tyrosine system (Scheme 9). Starting from L-tyrosine **40**, protected amino acid **48** can subsequently be prepared as before by refluxing in MeOH in the presence of 9-BBN. **48** was treated with triethylamine (1.2 eq) in the presence of 1.5 eq of isopropyl isocyanate to yield the target carbamate **49** in 75% isolated yield.



Scheme 9 Attempted synthesis of carbamate **51**

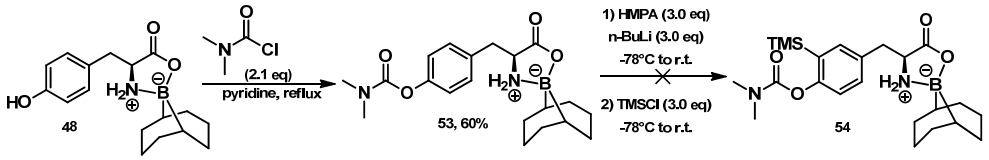
Carbamate **49** was then treated with *N, N, N', N'*-tetramethylethylenediamine (TMEDA) and TBSOTf to form the *N*-silyl derivative. In the same pot, the reaction mixture was treated with *n*-BuLi/TMEDA to form the lithium chelate **50**. Treatment with TMSCl followed by acidic workup yielded only starting material **49** in nearly quantitative amounts after purification, with no evidence of product **51**.

When the reaction was attempted in a stepwise manner (Scheme 10), it was determined that the *N*-silylated product **52** was only produced with a yield of 5%, the remaining being starting material **49**.



Scheme 10 *N*-Silylation of carbamate **49**

Further attempts to improve the yield of carbamate **52** by using a variety of bases proved futile. It was decided to proceed with a dialkylated carbamate to avoid the need to introduce the silyl group (Scheme 11). Thus protected tyrosine **48** was reacted with carbamoyl chloride to make carbamate **53** in 60% yield. **53** was then treated with *n*-BuLi and hexamethylphosphoramide (HMPA) to undergo *ortho*-lithiation followed by trapping with TMSCl. Unfortunately this yielded none of the desired product **54** and starting material was recovered. The reaction was performed again using *tert*-BuLi in the place of *n*-BuLi, but unfortunately this had no effect on the outcome.



Scheme 11 Synthesis with dialkylated carbamate protecting group

Given the repeated failure of simple reactions to be performed on either the brominated, or simple phenolic oxazaborolidinone, it can be concluded that the protected amino acid functionality is creating problems. Attempts to find examples in the literature in which these BBN protected amino acids were subjected to similar conditions successfully were sought out, but we failed to discover any. We suspect that deprotonation of one of the amino protons of the oxazaborolidinone occurs first, creating a negatively charged molecule. This could be an explanation for the failure for further anionic chemistry to be performed. The design of the molecule should be reconsidered, particularly the choice of the protecting group.

2.4 Conclusions

A new synthetic methodology has been outlined in this chapter to produce benzotriazoles using simple and mild reaction conditions. We focused on developing a general methodology using fluoride induced formation of benzyne and optimized the conditions to allow it to proceed in one pot at room temperature. Although this reaction clearly does not fulfill all of the necessary requirements to be a 'click' reaction in and of itself, it does provide a copper free alternative. It proceeds rapidly at room temperature, and the experimental procedure is very straightforward. There are functional limitations regarding the benzyne precursor.

Since the completion of this project, various articles have been published directly relating to the work outlined in this chapter. New methodologies, synthetic approaches to

biologically relevant molecules, and theoretical explorations of benzyne cycloadditions to dipoles have been explored, highlighting a pertinent interest in the field.[33]

2.5 Experimental Section

General Information

All reactions were carried out in oven dried glassware. THF was distilled from sodium, CH_2Cl_2 and CH_3CN were distilled from CaH_2. CsF and KF were dried for one hour at 110ºC in a vacuum oven to remove any traces of moisture. TBAF, 18-crown-6, and 15-crown-5 were purchased from Aldrich and used as received. ^{1}H-, ^{13}C-, and ^{19}F-NMR were recorded on a Varian AMX400 (400, 100.59 MHz, and 200 MHz, respectively) using $CDCl_3$ as solvent unless otherwise indicated. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H and δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, dt=doublet of triplets, td=triplet of doublets, m=multiplet), coupling constants (Hz), and integration. Flash chromatography was performed on silica gel . All reactions were monitored by thin layer chromatography on Merck F-254 silica gel plates. Visualization of the TLC plates was performed with $KMnO_4$ reagent and UV (254 nm). Conversion of reactions was determined by GC-MS (GC HP6890, MS HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer by EI (70 eV) measurements.

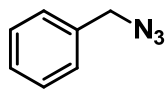
Safety

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

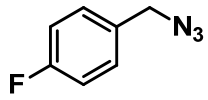
General Procedure: to a stirred solution of the corresponding bromide (1.0 eq) in a water/acetone mixture (1:4 v/v, 50 mL) was added NaN_3 (1.5 eq). The resulting suspension was stirred at room temperature for 24 h. DCM (50 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3 x 10 mL aliquots of DCM and the combined organic layers were dried over $MgSO_4$. Solvent was removed under reduced pressure, and the azide was sufficiently pure to use without further purification.

Benzyl azide



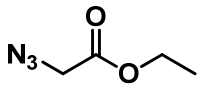
Yellow oil. From 2.5 mmol benzyl bromide, 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.43 (m, 5H), 4.35 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 135.5, 129.3, 128.3, 128.2, 54.8.

1-(Azidomethyl)-4-fluorobenzene



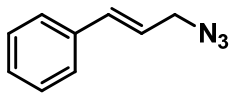
Pale yellow oil. From 2.5 mmol 1-(bromomethyl)-4-fluorobenzene, 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.39 (m, 2H), 7.00-7.11 (m, 2H), 4.30 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 162.5 (d, $J_{F\text{-}C}$= 1307 Hz), 131.4, 129.9 (d, $J_{F\text{-}C}$= 45.2 Hz), 115.7 (d, $J_{F\text{-}C}$= 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 (s, 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

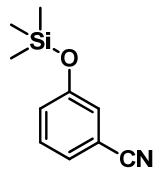


Colorless oil. From 2.5 mmol cinnamyl bromide, 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.45 (m, 5H), 6.67 (d, *J*=15.6 Hz, 1H), 6.26 (dt, *J*=16, 6.4 Hz, 1H), 3.95 (d, *J*=6.4 Hz, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 135.7, 134.5, 128.7, 128.2, 126.7, 122.4, 53.0; HRMS (EI) calcd for $C_9H_9N_3$ 159.0796, found 159.0790.

Experimental Procedures for the Preparation of Benzyne Precursors

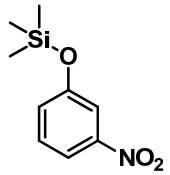
The following benzyne precursors were prepared according to literature procedure and characterized accordingly: 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**17**), 2-(trimethylsilyl)naphthalen-1-yl trifluoromethanesulfonate (**18**), and 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**28**).[20]

3-((Trimethylsilyl)oxy)benzonitrile



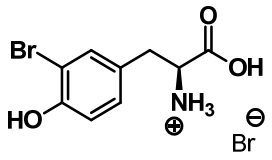
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7. 27 (m, 1H), 7.17-7.19 (m, 1H), 7.00-7.03 (m, 2H), 0.22 (s, 9H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 155.8, 130.7, 125.4, 123.5, 118.9, 113.4, 0.26.

Trimethyl(3-nitrophenoxy)silane



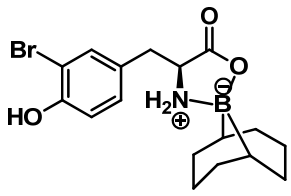
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J*=8.0 Hz, 1H), 7.60 (s, 1H), 7.33 (t, *J*=8.0 Hz, 1H), 7.11 (d, *J*=8.4 Hz, 1H), 0.26 (s, 9H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 156.2, 149.3, 130.2, 126.6, 116.6, 115.1, 0.20.

(*S*)-2-(3-Bromo-4-hydroxyphenyl)-1-carboxyethanaminium bromide (18)



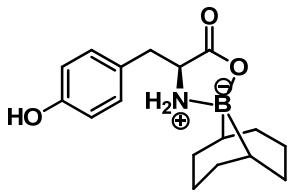
A solution of HBr in glacial acetic acid (33% w/v) was added to a vigorously stirred suspension of L-tyrosine (5.54 g, 30.6 mmol) in acetic acid (25 mL). To the resulting solution was added Br_2 (1.7 mL, 33.2 mmol) in acetic acid (12 mL) dropwise over a 3 h period. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was filtered and the white precipitate was washed with acetic acid (3 x 10 mL) and then diethyl ether (5 x 10 mL). The product was isolated as a white solid. Yield=79%.Note: to allow for dropwise addition of Br_2, a thick metal needle is required to prevent corrosion of the needle. ^{1}H NMR (400 MHz, D_2O): δ 7.34 (s, 1H), 7.04 (m, 1H), 6.74-6.85 (m, 1H), 4.12 (br s, 1H), 3.08-3.14 (m, 1H), 2.95-3.02 (m, 1H); ^{13}C NMR (100.59 MHz, D_2O): δ 171.0, 152.1, 133.7, 130.8, 129.9, 116.8, 109.8, 54.2, 34.4.

(*S*)-4'-(3-Bromo-4-hydroxybenzyl)-5'-oxospiro[bicyclo[3.3.1]nonane-9,2'-[1,3,2]oxazaborolidin]-3'-ium-11-uide (19)



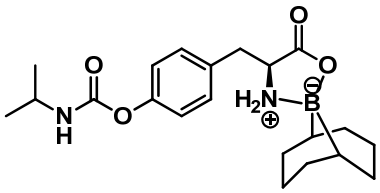
9-BBN (40.6 mL, 20.2 mmol) was added to a roundbottom flask containing 120 mL of MeOH. The resulting solution was heated to reflux for 30 min under an inert atmosphere of N_2 with the purpose of dissolving the 9-BBN. After 30 min (or once all of the 9-BBN is dissolved), **18** was added (6.00 g, 18.4 mmol) to the solution and the reaction was heated and monitored by thin layer chromatography (100% diethyl ether, R_f=0.85). Upon completion of the reaction, the solvent and excess 9-BBN were evaporated to yield the product as a white solid. Yield=85% (5.94 g). ^{1}H NMR (400 MHz, CD_3OD): δ 7.48 (s, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 6.86 (d, *J*=8.0 Hz, 1H), 6.44 (br t, *J*=8.0 Hz, 1H), 5.25 (br t, *J*=8.0 Hz, 1H), 3.92 (m, 1H), 3.16 (dd, *J*=8.0, 8.0 Hz, 1H), 2.96 (dd, *J*=8.0, 8.0 Hz, 1H), 1.34-1.90 (m, 12H), 0.54 (br s, 1H), 0.25 (br s, 1H); ^{13}C NMR (100.59 MHz, CD_3OD): δ 174.2, 153.4, 133.8**,** 129.4**,** 128.8**,** 116.3, 109.7, 56.8, 35.1, 31.5, 31.3, 31.0, 24.5, 24.0.

(*S*)-4'-(4-Hydroxybenzyl)-5'-oxospiro[bicyclo[3.3.1]nonane-9,2' [1,3,2]oxazaborolidin]-3'-ium-11-uide (25)



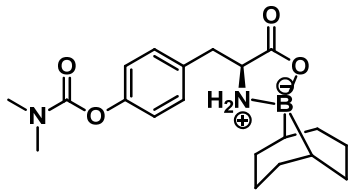
Tyrosine (1.0 g, 5.52 mmol) was dissolved in 60.0 mL of MeOH in a roundbottom flask under inert atmosphere. To this solution was added a solution of 9-BBN in THF (12.1 mL, 6.07 mmol). The reaction mixture was heated at reflux overnight, and the progress of the reaction was monitored by TLC (100% diethyl ether, R_f=0.9). After cooling the solution, the methanol was evaporated, and the resulting residue was redissolved in boiling THF and filtered. The filtrate was concentrated and triturated twice with hot diethyl ether and pentane. The resulting viscous solid was placed under vacuum overnight. Yield=71% (1.18 g). White viscous solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.13 (d, *J*=12.0 Hz, 2H), 6.77 (d, *J*=8.0 Hz, 2H), 3.93 (dd, *J*=12.0, 2.0 Hz, 1H), 3.14 (dd, *J*=8.0, 8.0 Hz, 1H), 3.04 (dd, *J*=8.0, 8.0 Hz, 1H), 1.40-1.81 (m, 12H), 0.53 (s, 1H), 0.20 (s, 1H); ^{13}C NMR (100.59 MHz, CD_3OD): δ 175.4, 156.8, 130.4, 126.5, 115.6, 56.6, 35.4, 31.4, 31.3, 31.1, 31.0, 24.5, 24.0.

(*S*)-4'-(4-((Isopropylcarbamoyl)oxy)benzyl)-5'-oxospiro[bicyclo[3.3.1]nonane-9,2'-[1,3,2]oxazaborolidin]-3'-ium-11-uide (26)



BBN-protected tyrosine (1.0 g, 3.32 mmol) was dissolved in dry DCM (20 mL). To this stirred solution was added isopropylisocyanate (423.9 mg, 4.98 mmol), followed by Et_3N (0.54 mL, 0.66 mmol). The solution was allowed to stir at room temperature overnight after which the solvent was evaporated to yield a yellow solid. The resulting solid was triturated with diethyl ether and pentane to remove any impurities. Yield=75% (0.96 g). ^{1}H NMR (400 MHz, CD_3OD): δ 7.35 (d, *J*=8.0 Hz, 2H), 7.07 (d, *J*=8.0 Hz, 2H), 3.96 (m, 1H), 3.76 (m, 1H), 3.49 (dd, *J*=8.0, 8.0 Hz, 1H), 3.00 (dd, *J*=8.0, 8.0 Hz, 1H), 1.34-1.95 (m, 12H), 1.19 (s, 6H), 0.55 (s, 1H), 0.42 (s, 1H).

(S)-4'-(4-((Dimethylcarbamoyl)oxy)benzyl)-5'-oxospiro[bicyclo[3.3.1]nonane-9,2'-[1,3,2]oxazaborolidin]-3'-ium-11-uide (30)



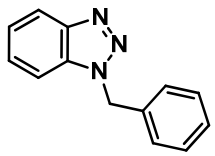
BBN-protected tyrosine (100.0 mg, 0.33 mmol) was dissolved in pyridine (5.0 mL). To this solution was added dimethyl carbamoyl chloride (0.1 mL, 1.05 mmol) and the resulting solution was heated to reflux. Progress of the reaction was monitored by thin layer chromatography (3:1 EtOAc:pentane, R_f=0.2). Upon completion, the solvent was evaporated and the crude mixture was purified by column

chromatography (5:1 EtOAc:pentane) to give the product as a white powder. Yield=57% (70.0 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.36 (d, *J*=8.0 Hz, 2H), 7.07 (d, *J*=8.0 Hz, 2H), 3.94-3.98 (m, 1H), 3.31 (dd, *J*=8.0, 8.0 Hz, 1H), 3.12 (s, 3H), 3.02 (dd, *J*=8.0, 8.0 Hz, 1H), 3.01 (s, 3H), 1.43-1.85 (m, 12H), 0.55 (s, 1H), 0.45 (s, 1H).

Experimental Procedure for the Cycloaddition of Azides and Arynes

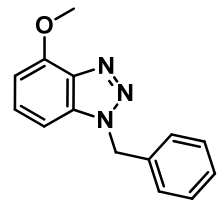
General Procedure: to a stirred solution of azide (0.60 mmol, 3.0 eq) in 3 mL of solvent in a 10 mL glass roundbottom flask was added a fluoride source (0.40 mmol, 2.0 eq) and crown ether (0.40 mmol, 2.0 eq) as stated. After 10 min of stirring at room temperature, the aryne precursor (0.20 mmol, 1.0 eq) in 1 mL of solvent was added dropwise to the reaction mixture. The roundbottom was sealed and the progress of the reaction was monitored by TLC or GC/MS. Upon completion, the reaction mixture was poured into saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography (heptane/ethyl acetate (7:1)) yielding pure products with the exception of 1-benzyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole and 1-benzyl-1*H*-naphtho[1,2-*d*][1,2,3]triazole, which could not be separated by column chromatography.

1-Benzyl-1*H*-benzo[*d*][1,2,3]triazole



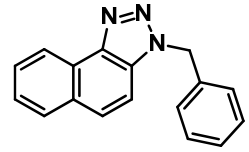
White solid: mp 114-115ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J*=8.0 Hz, 1H), 7.26-7.41 (m, 8H), 5.85 (s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 146.3, 134.7, 132.8, 129.0, 128.4, 127.6, 127.4, 123.9, 120.0, 109.7, 52.2; HRMS (EI) calcd for $C_{13}H_{11}N_3$ 209.0953, found 209.0945.

1-Benzyl-4-methoxy-1*H*-benzo[*d*][1,2,3]triazole



White solid: mp 93-94ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.27-7.33 (m, 6H), 6.90 (d, *J*=11.2 Hz, 1H), 6.65 (d, *J*=10.4 Hz, 1H), 5.81 (s, 2H), 4.11 (s, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 138.4, 134.8, 134.5, 128.7, 128.4, 128.1, 127.2, 103.1, 101.7, 56.0, 52.0; HRMS (EI) calcd for $C_{14}H_{13}N_3O$ 239.1059, found 239.1061.

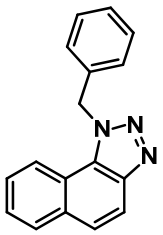
1-Benzyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole



White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, *J*=8.0 Hz, 1H), 7.94 (d, *J*=7.6 Hz, 1H), 7.71-7.74 (m, 2H), 7. 58 (t, *J*=6.4 Hz, 1H), 7.26-7.36 (m, 5H), 7.18 (s, 1H), 5.93 (s, 2H). ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 135.7, 134.8, 133.1, 130.5, 129.3, 129.0,

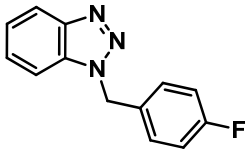
128.5, 128.2, 127.4, 127.0, 126.3, 122.3, 118.5, 109.2, 52.4. HRMS (EI) calcd for $C_{17}H_{13}N_3$ 259.1109, found 259.1115.

1-Benzyl-1*H*-naphtho[1,2-*d*][1,2,3]triazole



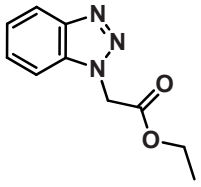
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (m, 2H), 7.71-7.74 (m, 2H), 7.51-7.54 (m, 1H), 7.26-7.36 (m, 5H), 7.16 (s, 1H) 6.28 (s, 2H). ^{13}C NMR (100.59 MHz, $CDCl_3$): δ135.7, 134.9, 133.1, 130.9, 129.3, 129.1, 128.6, 128.2, 127.4, 127.1, 126.4, 122.3, 118.1, 115.7, 54.0. HRMS (EI) calcd for $C_{17}H_{13}N_3$ 259.1109, found 259.1115.

1-(4-Fluorobenzyl)-1*H*-benzotriazole



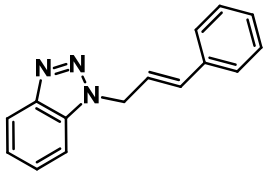
White solid: mp 92-93ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J*=9.02 Hz, 1H), 7.26-7.43 (m, 5H), 7.04 (t, *J*=8.4 Hz, 2H), 5.82(s, 2H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 162.6 (d, *J*=98.5 Hz), 146.3, 132.6, 130.5, 129.4 (d, *J*=30.4 Hz), 127.5, 123.9, 120.1, 116.0 (d, *J*=88.4), 109.4, 51.4. HRMS (EI) calcd for $C_{13}H_{10}FN_3$ 227.0859, found 227.0851.

Ethyl 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)acetate



Pale yellow solid: mp 76-78ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11(d, *J*=8.4 Hz, 1H), 7.48-7.52 (m, 2H), 7.39-7.42 (m, 1H), 5.42 (s, 2H), 4.26 (q, *J*=7.2 Hz, 2H), 1.26 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 166.6, 146.3, 133.6, 128.2, 124.4, 120.5, 109.4, 62.6, 49.3, 14.3. HRMS (EI) calcd for $C_{10}H_{11}N_3O_2$ 205.0851, found 205.0852.

1-Cinnamyl-1*H*-benzo[*d*][1,2,3]triazole



White solid: mp 72-73ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J*=11.2 Hz, 1H), 7.57 (d, 8.4 Hz, 1H), 7.45 (t, *J*=7.2 Hz, 1 H), 7.26-7.40 (m, 6H), 6.69 (d, *J*=16.0 Hz, 1H), 6.41 (dt, *J*=21.2, 8.0 Hz, 1H), 5.45 (dd, *J*=6.8, 1.6 Hz, 2H). ^{13}C NMR (100.59 MHz, $CDCl_3$): δ 146.2, 135.5, 134.4, 132.9, 128.6, 128.3, 127.3, 126.6, 123.9, 122.1, 120.0, 109.6, 50.6. HRMS (EI) calcd for $C_{15}H_{13}N_3$ 235.1109, found 235.1116.

2.6 References and Notes

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(23) Note: During our investigation, a paper in Organic Letters (F. Shi, J. Waldo, Y. Chen, R.C. Larock. *Org. Lett.*, **2008**, *10*, 2409) was published showing similar work but in the absence of crown ether. Our attempts to reproduce these results revealed that virtually no reaction was observed (with THF as solvent) or excessively long reaction times (48 h with MeCN as solvent) were needed. In contrast we found that the presence of crown ether was essential for short reaction times as shown in this chapter.
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(29) The oxazaborolidinone is stable in the presence of alkyl halides and acid halides. Can be treated with sulfur trioxide, ammonia, POCl3, PSCl3, *m*-chloroperoxybenzoic acid (*m*CPBA), monoperoxyphthalic acid magnesium salt (MMPP), Arbusov conditions (110°C, neat triethyl phosphite), as well as Finkelstein conditions (refluxing NaI, acetone). None of these conditions resulted in any cleavage of the protecting group. In cases where HCl has the potential to be released, it is necessary to add a scavenger, for instance Et3N.

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