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Expanding the Strained Alkyne Toolbox: Generation and Utility of Oxygen-Containing Strained Alkynes

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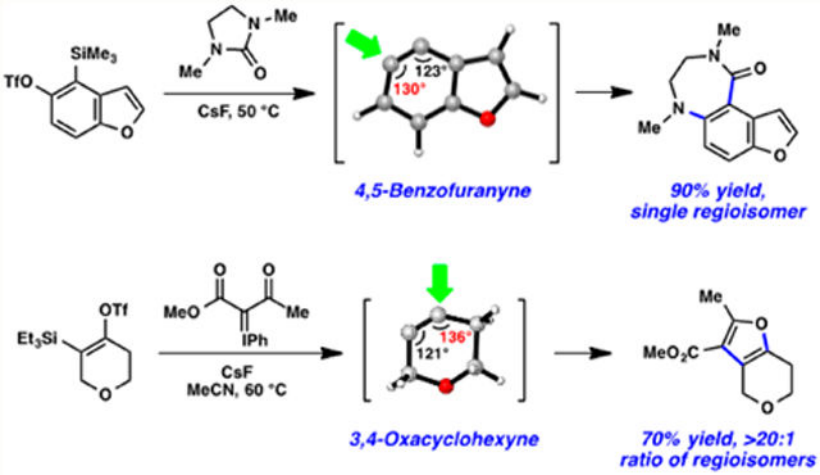
Abstract

We report synthetic methodology that permits access to two oxacyclic strained intermediates, the 4,5-benzofuranyne and the 3,4-oxacyclohexyne. In situ trapping of these intermediates affords an array of heterocyclic scaffolds by the formation of one or more new C–C or C–heteroatom bonds. Experimentally determined regioselectivities were consistent with predictions made using the distortion/interaction model and were also found to be greater compared to selectivities seen in the case of trapping experiments of the corresponding *N*-containing intermediates. These studies demonstrate the synthetic versatility of oxacyclic arynes and alkynes for the synthesis of functionalized heterocycles, while further expanding the scope of the distortion/interaction model. Moreover, these efforts underscore the value of harnessing strained heterocyclic intermediates as a unique approach to building polycyclic heteroatom-containing frameworks.

Graphical Abstract



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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01986.

Detailed experimental procedures, Cartesian coordinates and energies, as well as characterization data for all new compounds (PDF)

The authors declare no competing financial interest.

INTRODUCTION

New approaches for the synthesis of decorated heterocycles remain highly sought after because of the prevalence of heterocycles in drugs, agrochemicals, materials, and natural products.[1] One unique strategy for heterocycle construction involves the trapping of transient heterocyclic arynes or alkynes.[2] For example, pyridynes,[2m,3] indolynes,[4–6] and piperidynes[7] (e.g., **1–3**, Figure 1) can now be used as building blocks for the synthesis of functionalized heterocycles in a predictable manner using the distortion/interaction model.[8]

Whereas advances in heterocyclic aryne and alkyne chemistry have focused on nitrogen-containing reactive intermediates, the corresponding chemistry of oxacycles has remained underdeveloped. The first aryne ever proposed was the 2,3-benzofuranyne;[9] however, this structural assignment was later called into question.[2b] Subsequent contributions in the area of oxacyclic arynes are limited to scattered examples involving dehydrohalogenation of benzofuran derivatives[10] and access to the 6,7-benzofuranyne using butyllithium reagents.[11] With regard to oxacyclohexynes, even less is known, with only two studies involving metalated oxacyclohexynes in the literature.[12] Silyl triflate precursors to oxacyclic arynes or alkynes have not been synthesized previously; likewise, no general methodologies for oxacyclic aryne or alkyne trapping have been reported to date.

We reasoned that mild methodologies involving the trapping of oxacyclic arynes and alkynes through a multitude of cycloadditions would provide a new avenue for building *O*-containing compounds. Oxygenated heterocycles, such as benzofuran and pyran derivatives, are often seen in natural products and drugs.[13] Notable examples include Saprisartan (treatment of hypertension),[14] hopeafuran (antimicrobial agent),[15] artemisinin (antimalarial drug),[16] rhoeadine (sedative and antitussive),[17] and frenolicin B (kinase inhibitor).[18] Moreover, some oxygen-containing heterocycles are known bioisosteres for their nitrogen and sulfur-containting counterparts in medicinal chemistry.[19]

In the present study, we describe synthetic methodology to access two oxacyclic strained intermediates: the 4,5-benzofuranyne (**4**) and the 3,4-oxacyclohexyne (**5**) (Figure 1). In addition to establishing synthetic routes to silyl triflate precursors to **4** and **5** and using these species to build an assortment of functionalized heterocycles, we show that reliable regioselectivity predictions can be made prior to experiment using the distortion/interaction model. Selectivities are compared to those seen in the case of trapping experiments of the corresponding *N*-containing intermediates. Overall, our studies demonstrate that oxacyclic arynes and alkynes can be harnessed to efficiently construct decorated oxygen-containing heterocycles. The methodology is expected to prove useful in the synthesis of new pharmaceuticals and natural products.

RESULTS AND DISCUSSION

Prediction of Regioselectivities Based on the Distortion/Interaction Model.

An attractive aspect of using strained alkynes as synthetic building blocks is the ability to make reliable regioselectivity predictions prior to experiments using the distortion/interaction model.[8] Briefly stated, substituted arynes or cyclic alkynes are unsymmetrically

distorted in their ground state. Nucleophilic addition occurs at the terminus of the aryne (or alkyne) that is more distorted toward linearity (i.e., the site that possesses a larger internal angle). The geometry of the unsymmetrical aryne or alkyne can readily be determined by performing simple geometry optimization calculations using DFT methods. In addition to revealing the preferred site of attack by nucleophiles, these calculations can also be used to roughly assess the magnitude of regioselectivities. The greater the difference in internal angles between the two aryne (or alkyne) termini ($\Delta\theta$), the more pronounced regioselectivities are expected.

With the aim of predicting the site of nucleophilic attack on 4,5-benzofuranyne (**4**) and 3,4-oxacyclohexyne (**5**), while drawing comparisons to the corresponding *N*-containing heterocyclic alkynes **6** and **7**, we performed geometry optimizations using DFT calculations (B3LYP/6–31G(d)) (Figure 2).[20] First, we compared the optimized structures of 4,5-benzofuranyne (**4**) and 4,5-indolyne (**6**); each is distorted such that nucleophilic addition is expected to occur at C5, which is the more linear terminus. 4,5-Benzofuranyne (**4**) was found to be unsymmetrically distorted with the C5−C4 $\Delta\theta$ being 7°. In comparsion, 4,5-indolyne (**6**) is less distorted, with the C5−C4 $\Delta\theta$ being 4°.[5e,f] As the $\Delta\theta$ is greater in the case of 4,5-benzofuranyne (**4**), we predicted this species would react with greater regioselectivity compared to 4,5-indolyne (**6**). To see if this trend extended to nonaromatic strained alkynes, we compared 3,4-oxacyclohexyne (**5**) and 3,4-piperidyne **7**. For both cyclic alkynes, nucleophilic attack is preferred to occur at C4, the site further distorted toward linearity. C4−C3 $\Delta\theta$ is 15° in the case of 3,4-oxacyclohexyne (**5**), but slightly less (i.e., 12°) for 3,4-piperidyne 7.[7c] As such, we surmised that 3,4-oxacyclohexyne (**5**) would react with greater regioselectivities compared to 3,4-piperidyne **7**.

Synthesis of Silyl Triflate Precursors.

Our study relied on developing efficient syntheses of suitable precursors to 4,5-benzofuranyne (**4**) and 3,4-oxacyclohexyne (**5**). Given the well-known versatility of silyl triflate precursors to arynes,[21] we targeted silyl triflates **10** and **14** (Scheme 1). The benzofuranyne precursor was derived from 5-hydroxybenzofuran (**8**), which is commercially available or readily accessible from hydroquinone.[22] Bromination of **8** proceeded smoothly to deliver the known bromoalcohol **9**.[23] Subsequent *O*-silylation, followed by retro-Brook rearrangement and triflation, furnished silyl triflate **10** in 81% yield. 3,4-Oxacyclohexyne precursor **14** could be synthesized in four steps beginning from commercially available 4-oxotetrahydropyran **11**. α-Bromination of **11** was performed using a known two-step sequence to provide bromoketone **12**.[24] Treatment of **12** with DABCO and TESCl afforded silyl enol ether **13** in 91% yield. Finally, lithiation, retro-Brook rearrangement, and triflation delivered silyl triflate **14**.

Generation and Trapping of 4,5-Benzofuranyne.

With the silyl triflate precursors in hand, we first investigated the generation and trapping of the 4,5-benzofuranyne (**4**) with symmetrical cycloaddition partners (Table 1). Thus, silyl triflate **10** was exposed to 2-pyrone and CsF in MeCN at 50 °C; to our delight, the desired benzannulated product was obtained via a Diels–Alder/retro-Diels–Alder sequence (entry 1). We also performed trapping experiments with furan and *N*-Boc pyrrole (entries 2 and 3). In

each case, the corresponding [2.2.1]-bridged bicyclic adduct was formed in synthetically useful yields. These results not only validated that the 4,5-benzofuranyne (**4**) can be generated, but also demonstrated how this intermediate can be used to build two new C–C bonds on the benzofuran motif in an efficient manner. In the latter case, the two linkages formed are sp^2–sp^3 C–C bonds, which would be difficult to introduce by known means.

With the aim of probing regioselectivity trends and accessing functionalized benzofurans, we shifted our attention to trapping benzofuranyne **4** with nucleophiles and unsymmetrical cycloaddition partners (Table 2). We found that *p*-cresol, morpholine, and *N*-Me-aniline could be employed as trapping agents,[25] to furnish benzofuranyne adducts in good yields (entries 1–3). In all cases, the major product was indicative of nucleophilic attack occurring at C5, consistent with the prediction made by the distortion/interaction model. To access more unique scaffolds and further examine regioselectivities, we surveyed trapping agents that would allow for the appendage of seven-, six-, or five-membered heterocycles on the benzofuran motif. In situ trapping of **4** with 1,3-dimethyl-2-imidazolidinone[26] furnished the corresponding product of formal C–N bond insertion in 90% yield (entry 4). Only one constitutional isomer was observed in this case, although the subsequent trappings led to mixtures with a preference for initial bond formation also occurring at C5. The use of an amido acrylate trapping agent[27] allowed for the appendage of substituted pyridine rings to the benzofuran unit (entry 5). With regard to the formation of 5-membered rings, several trapping agents were deemed successful and could be used to forge C–C, C–O, and C–N bonds (entries 6–11).[28–33] In all cases, synthetically useful yields of substituted heterocycles were prepared with the expected regioselectivities. Thus, with access to a single new aryne precursor (i.e., **10**), one can build arrays of decorated benzofurans using this methodology.

Generation and Trapping of 3,4-Oxacyclohexyne.

Efforts were also put forth to generate and trap 3,4-oxacyclohexyne (**5**). To confirm the in situ formation of the strained alkyne, we first examined trappings with dienes to give Diels–Alder adducts (Table 3). Thus, silyl triflate **14** was treated with CsF in the presence of 3 equiv of tetracyclone in THF at 60 °C. This furnished the desired benzannulated product in quantitative yield (entry 1). Trapping with 2-pyrone delivered the expected benzannulated product (entry 2). To arrive at more complex, heterocyclic adducts, Diels–Alder trappings were performed with 2,5-dimethylfuran and *N*-Bocpyrrole. In each case, the desired [2.2.1]-bicycles, which would arguably be difficult to make by other means, were formed (entries 3 and 4).

Analogous to our studies involving the 4,5-benzofuranyne (**4**), we tested the generation and trapping of 3,4-oxacyclohexyne (**5**) with nucleophiles and unsymmetrical cycloaddition partners (Table 4). Trapping with imidazole was examined primarily as a means to probe regioselectivity (entry 1). In this case, the 4-substituted adduct was obtained in >20:1 regiochemical preference. Addition at C4 was also seen in a variety of other trapping experiments, consistent with the predictions made by the distortion/interaction model. For example, interception of **5** with methyl salicylate[34] gave two products, both indicative of the same regioselectivity trend (entry 2). We also performed the trapping with an amido acrylate species,[23] which led to the appendage of pyridine motifs, albeit with modest selectivity

(entry 3). Several efforts to annulate the oxacyclohexyne with 5-membered heterocycles were also put forth. Trapping with an iodoniun ylide[24] led to the introduction of a furan (entry 4), whereas nitrone trapping[25] gave the expected isoxazoline product (entry 5). Similarly, an azide cycloaddition[27] proceeded smoothly to give triazole-containing products (entry 6). In two additional examples, pyrazole derivatives could be obtained by trapping the oxacyclohexyne intermediate with either a sydnone[28] or diazoester[29] (entries 7 and 8). With this methodology, a variety of annulated oxacycles can be readily accessed from silyl triflate **14**, with good to excellent control of regioselectivity. It should be noted that the products obtained from these trapping studies possess significant sp^3 character. The generation of such sp^3-rich heterocyclic frameworks is an important direction in modern drug discovery.[35]

Comparison of Regioselectivities for *N*- and *O*-Containing Strained Alkynes.

As noted earlier, we predicted that the 4,5-benzofuranyne (**4**) and the 3,4-oxacyclohexyne (**5**) would react with significant regioselectivities to give nucleophilic addition preferentially at C5 and C4, respectively. These predictions were verified, as described above. Additionally, we predicted that **4** and **5** would undergo trapping with more significant regioselectivities in comparison to their *N*-containing analogues, **22** and **7**.

Table 5 shows a comparison of regioselectivities for trapping experiments of 4,5-benzofuranyne (**4**) and *N*-Me-4,5-indolyne (**22**). When *p*-cresol was used as the nucleophile (entry 1), the indolyne reacted to furnish the C5- and C4-substituted adducts in a 3.0:1 ratio. In the case of benzofuranyne **4**, a higher degree of selectivity was observed (8.5:1). Similarly, in the trapping of the arynes with benzylazide (entry 2), selectivity was greater in the case of the benzofuranyne (2.4:1 vs 6.2:1), consistent with predictions.

Similar comparisons were made between the 3,4-oxacyclohexyne (**5**) and the corresponding *N*-Cbz-protected piperidyne **7** using cycloaddition reactions (Table 6). In the case of nitrone trapping (entry 1), the piperidyne undergoes cycloaddition to give a 12.7:1 ratio of products. However, use of the oxacyclic variant gave >20:1 selectivity. Likewise, slightly higher selectivities were seen in the trapping of oxacyclohexyne **5** with benzyl azide, compared to the trapping of piperidyne **7** (entry 2). The more pronounced selectivities seen in the case of the 4,5-benzofuranyne (**4**) and the 3,4-oxacyclohexyne (**5**), compared to their nitrogen-containing counterparts, can be attributed to the greater electronegativity of oxygen. The oxygen atom has a stronger inductive effect that leads to increased distortion,[36] which in turn parlays into the more significant selectivities observed.

CONCLUSION

In summary, we have developed methodology that allows for the generation and trapping of two oxacyclic strained intermediates, the 4,5-benzofuranyne and the 3,4-oxacyclohexyne. Interception of these species by nucleophiles and cycloaddition partners provides a new means to prepare arrays of heterocyclic scaffolds by the formation of one or more new C–C or C–heteroatom bonds. The distortion/interaction model was used to make regioselectivity predictions about the preferred sites of reactivity, which were validated by experiments. Moreover, greater selectivities were seen in the trapping of the oxacyclic strained intermediates compared to the corresponding *N*-containing compounds, also consistent with

computational predictions. Our studies demonstrate that oxacyclic arynes and alkynes can be generated from silyl triflate precursors and strategically harnessed to build decorated oxygen-containing heterocycles. Given the abundance of aryne trapping reactions available in the literature, this methodology is expected to find utility in the synthesis of medicinal substances and natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(29). For the trapping of arynes with nitrones, see: Lu C; Dubrovskiy AV; Larock RC J. Org. Chem 2012, 77, 2279–2284. [PubMed: 22329405]

(30). For the trapping of arynes with azomethine imines, see: Shi F; Mancuso R; Larock RC Tetrahedron Lett. 2009, 50, 4067–4070. [PubMed: 20161257]

(31). For the trapping of arynes with azides, see: Shi F; Waldo JP; Chen Y; Larock RC Org. Lett 2008, 10, 2409–2412. [PubMed: 18476707]

(32). For the trapping of arynes with sydnones, see: Wu C; Fang Y; Larock RC; Shi F Org. Lett 2010, 12, 2234–2237. [PubMed: 20394430]

(33). For the trapping of arynes with diazoesters, see: Jin T; Yamamoto Y Angew. Chem., Int. Ed 2007, 46, 3323–3325.

(34). Zhao J; Larock RC Org. Lett 2005, 7, 4273–4275. [PubMed: 16146405]

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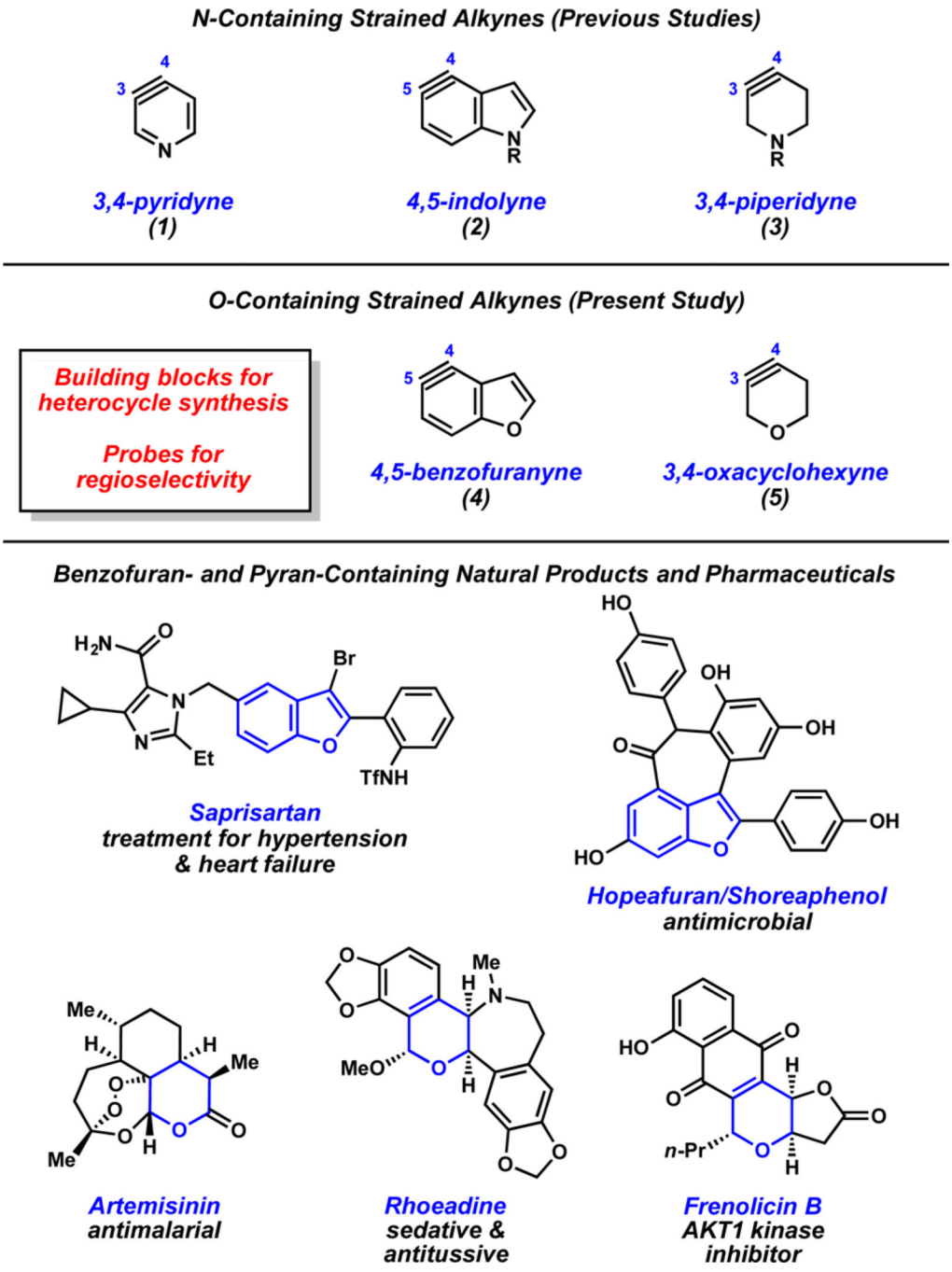


Figure 1.

Well studied *N*-containing cyclic alkynes **1–3**, *O*-containing strained alkynes **4** and **5** (present study), and representative drugs and natural products.

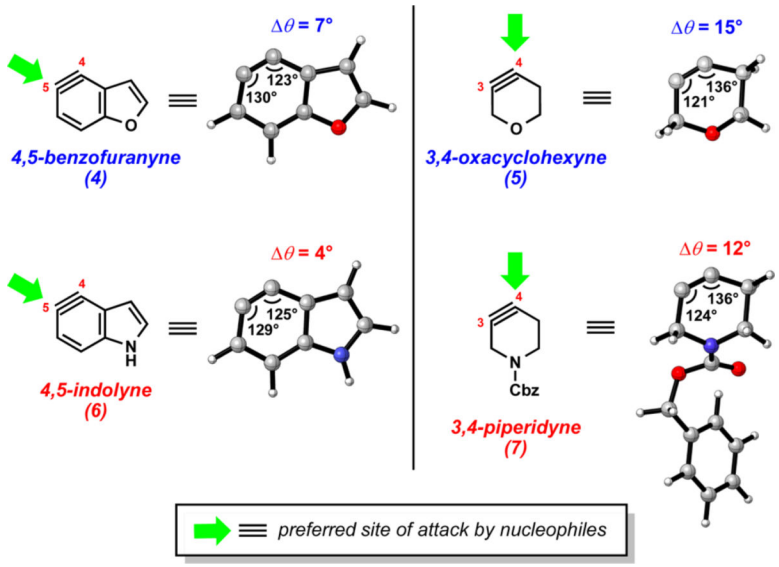
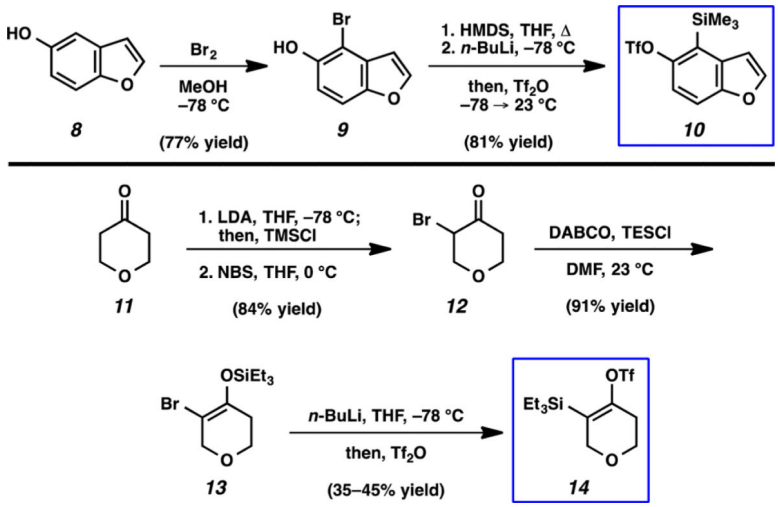


Figure 2.

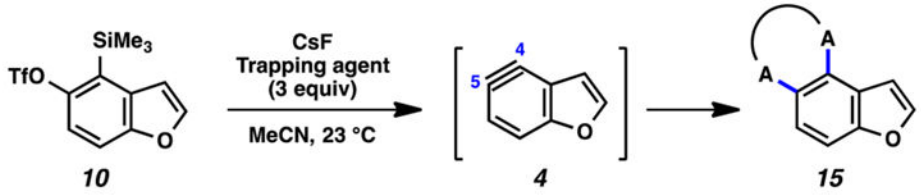
Geometry optimized structures of **4–7** obtained at the B3LYP/6–31G(d) level and predicted site of nucleophilic attack. $\Delta\theta$ represents the net distortion of the alkyne.

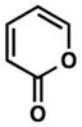
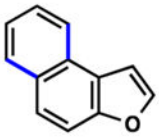
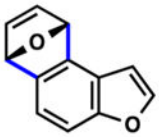
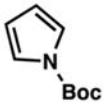


Scheme 1.
Syntheses of Silyl Triflates 10 and 14

Table 1.

Diels–Alder Cycloadditions of 4,5-Benzofuranyne (4)



Entry	Trapping agent	Product	Yield[a]
1			68%[b]
2			96%
3			75%

[a]Reported yields are the average of two experiments and are based on the amount of isolated products.

[b]Reaction performed at 50 °C.

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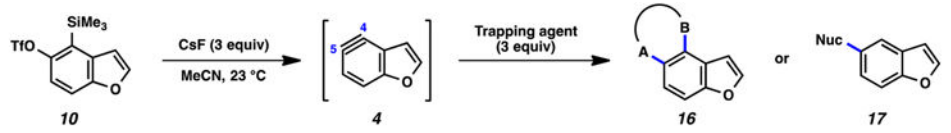
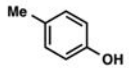
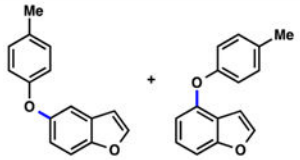
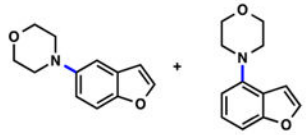
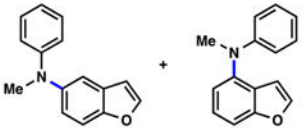
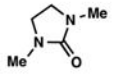
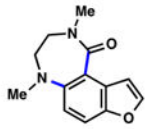
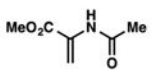
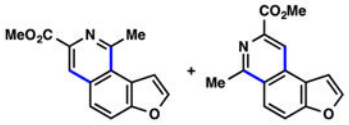
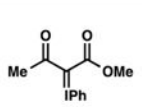
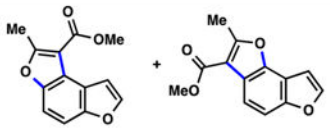
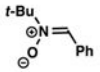
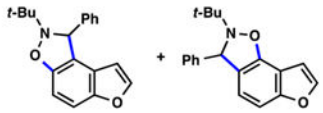
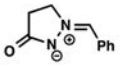
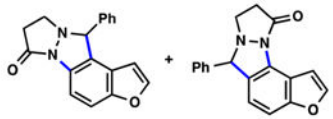
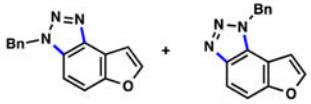
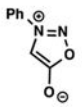
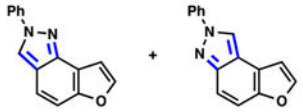
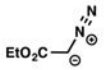
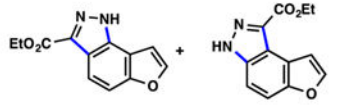
Table 2.

Reactions of Silyl Triflate 10 with Nucleophiles and Cycloaddition Partners



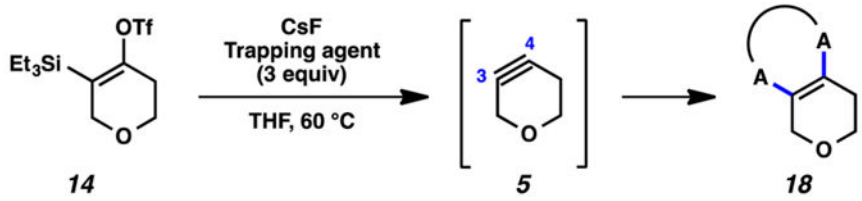
Entry	Trapping agent	Product(s)	Yield[a] (ratio)
1			73% (8.5:1)
2			78% (4.2:1)
3			83% (10:1)
4			90%[b]
5			51% (2.9:1)
6			66% (12:1)
7			82% (5.4:1)
8			64% (4.5:1)
9			71% (6.2:1)
10			85% (1.3:1)
11			65% (2.5:1)

[a]Reported yields are the average of two experiments and are based on the amount of isolated products.

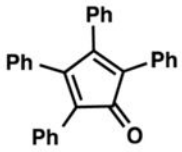
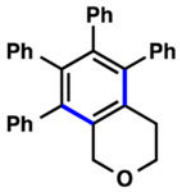
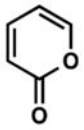
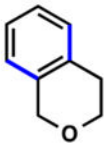
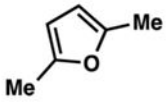
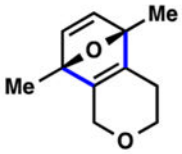
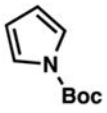
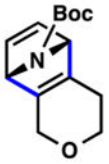
[b]Reaction performed neat with 1,3-dimethyl-2-imidazolidinone (10 equiv) at 50 °C with yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

Table 3.

Diels–Alder Cycloadditions of 3,4-Oxacyclohexyne (5)



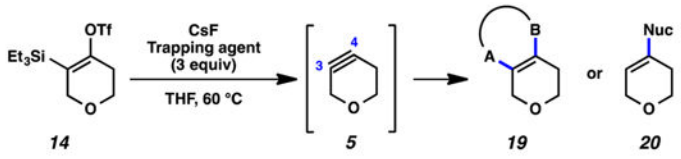
14 5 18

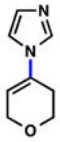
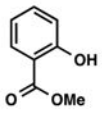
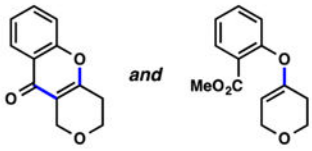
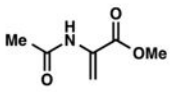
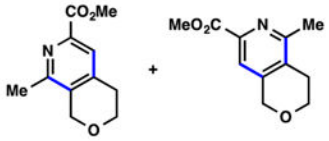
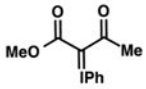
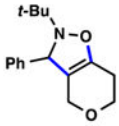
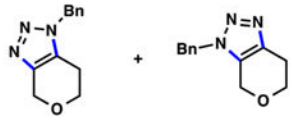
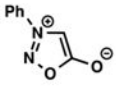
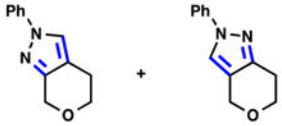
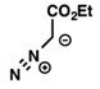
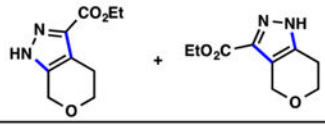
Entry	Trapping agent	Product	Yield[a]
1			100%
2			49%
3			50%
4			48%

[a]Reported yields are the average of two experiments and are based on the amount of isolated products.

Table 4.

Reactions of Silyl Triflate 14 with Nucleophiles and Cycloaddition Partners



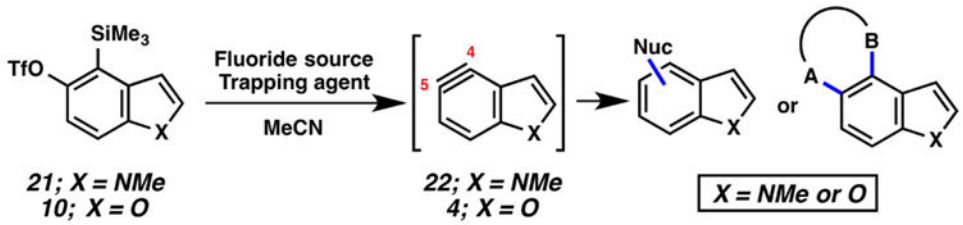
Entry	Trapping agent	Product(s)	Yield[a] (ratio)
1			59% (>20:1)
2			79% (>20:1)
3			71% (2.6:1)
4			70%[b] (>20:1)
5			73% (>20:1)
6			69% (7.2:1)
7			88% (1.5:1)
8			64% (6.1:1)

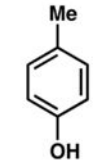
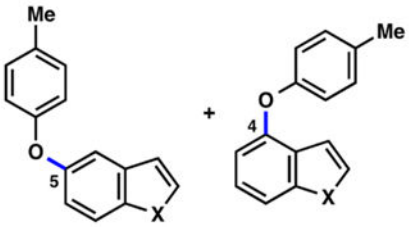
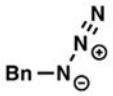
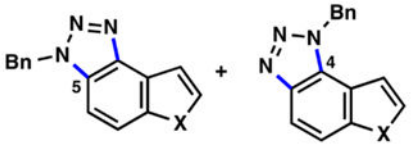
[a]Reported yields are average of two experiments and are based on the amount of isolated products.

[b]Reaction performed with MeCN as the solvent.

Table 5.

Comparison of 4,5-Indolyne and 4,5-Benzofuranyne Regioselectivities



Entry	Trapping agent	Products	Ratio (Yield) X = NMe	Ratio (Yield) X = O
1			3.0 : 1[a] (80%)	8.5 : 1[b] (73%)
2			2.4 : 1[c] (86%)	6.2 : 1[b] (71%)

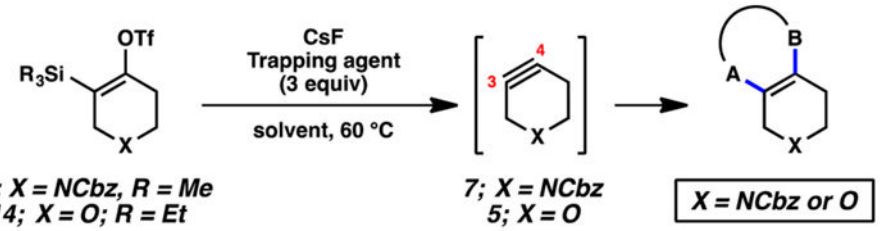
[a]Reaction performed with *p*-cresol (1.5 equiv) and CsF (3 equiv) at 50 °C.

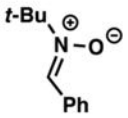
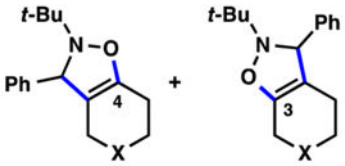
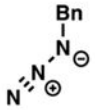
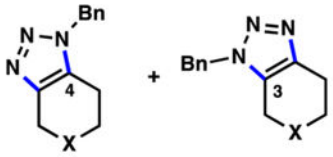
[b]Reactions performed with trapping agent (3 equiv) and CsF (3 equiv) at 23 °C.

[c]Reaction performed with benzyl azide (5 equiv) and TBAF (2 equiv) at 23 °C.

Table 6.

Comparison of Oxacyclohexyne and Piperidyne Regioselectivities



Entry	Trapping agent	Products	Ratio (Yield)[a] X = NCbz	Ratio (Yield)[b] X = O
1			12.7:1 (84%)	>20:1 (73%)
2			5.3:1 (81%)	7.2:1 (69%)

[a] Reaction performed with MeCN as the solvent.

[b] Reactions performed with THF as the solvent.