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Addition of Trifluoroborates to Oxetanyl *N,O*-Acetals: Entry into Spiro and Fused Saturated Heterocycles

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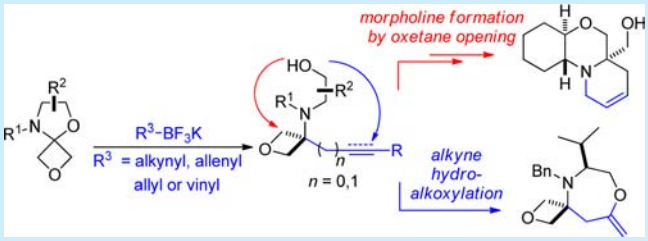
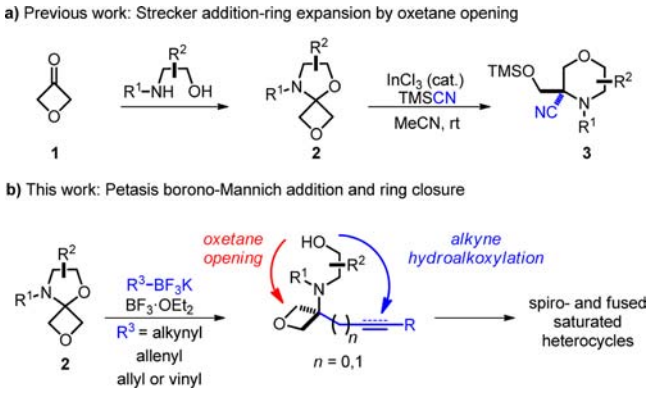
Supporting Information

ABSTRACT: *N,O*-Acetals derived from 3-oxetanone and 1,2-amino alcohols undergo addition reactions with alkynyl-, allyl-, allenyl-, and vinylpotassium trifluoroborates. The resulting products undergo cyclization by orthogonal activation of the oxetane and the alkyne to give a diverse set of spiro and fused heterocycles.



Oxetanes have recently gained increased attention in drug discovery as versatile modules, which may bestow favorable physiochemical and metabolic properties.[1] This attention has spurred the development of new synthetic methods for incorporation of the oxetane functionality in various settings as well as exploration of oxetanes as synthetic intermediates.[2] In this context, we recently reported that 3-oxetanone (**1**) derived *N,O*-acetals **2** partake in a sequence of reactions involving In(III)-catalyzed Strecker addition and ring opening to afford highly substituted morpholines **3** (Scheme 1a).[3] We envisioned

Scheme 1. Nucleophilic Addition to 3-Oxetanone-Derived *N,O*-Acetals 2



that further investigation of the reactivity of **2** could lead to the synthesis of saturated spiro and fused heterocyclic ring systems that populate novel chemical space provided the nucleophilic reactant could be expanded beyond cyanide to include other carbon nucleophiles. Herein, we describe a Lewis acid promoted addition of alkynyl, allenyl, allyl, and vinyl trifluoroborate nucleophiles to *N,O*-acetals **2** (Scheme 1b) and subsequent cyclization reactions based on oxetane opening and alkyne hydroalkoxylation.

3-Amino oxetanes display valuable properties, including attenuated amine basicity and an ethereal oxygen with pronounced affinity as a hydrogen-bond acceptor. The latter has led us to implement and study oxetanes as surrogates for carbonyls as peptidomimetics[4] and in biologically active lactams.[5] They are also increasingly found in the patent literature.[6] Commercially available 3-oxetanone serves as an important starting point for the synthesis of a wide range of substituted 3-amino oxetanes by the addition of Grignard reagents to *tert*-butanesulfinimines,[7] conjugate addition to oxetanyl-substituted nitroolefins[8] as well as other Michael acceptors,[9] and Strecker synthesis.[10] Nucleophilic addition to 3-oxetanone-derived *N,O*-acetals **2** would provide an alternative method for the synthesis of oxetane 3-amines. The pendant alcohol would also provide a handle for further functionalization and could undergo cyclization to form *N,O*-heterocycles. Given the versatility of propargylic amines as building blocks in asymmetric synthesis[11] and our long-standing interesting in alkynylation reactions,[12] we investigated the addition of alkynyl nucleophiles to **2**.

Initial attempts at aminal ring-opening reactions with metal acetylides generated in situ employing Zn(II), Cu(I), and In(III) failed to give addition products.[13] Given the latent iminium reactivity of **2**, we considered the possibility of using boronic acid derivatives as nucleophiles.[14,15] Accordingly, we examined the use of alkyne potassium trifluoroborates **4** in addition to **2**. In prospecting experiments, $BF_3{\cdot}OEt_2$ was found to effectively promote the desired alkyne addition of potassium phenylacetylene trifluoroborate **4a** to *N,O*-acetal **2b** in CH_2Cl_2 in combination with $(n\text{-Bu})_4NBr$ (10 mol %) to give adduct **5a** (Scheme 2).[16,17] Importantly, the product was obtained with the

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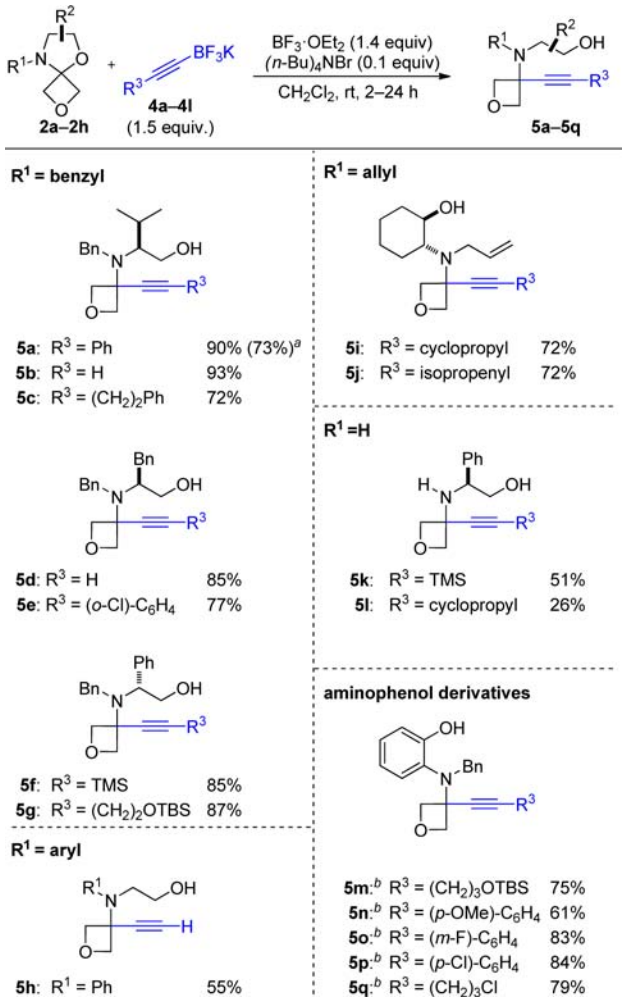
Scheme 2. Alkynylation of *N,O*-Acetals



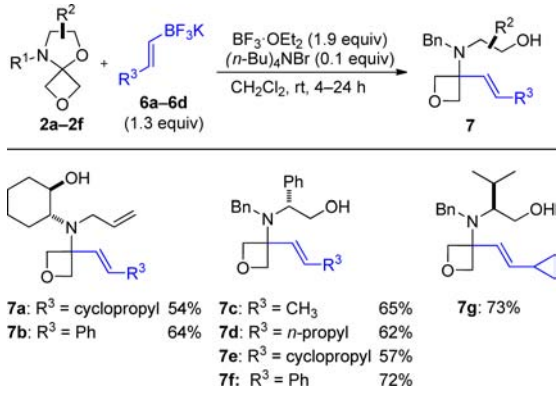
[a]Yield of one-pot reaction (conditions: *N*-benzylvalinol, 3-oxetanone (1.0 equiv), $BF_3{\cdot}OEt_2$ (10 mol %), CH_3CN, MS 3 Å, rt, 18 h, then **4a** (2 equiv), $BF_3{\cdot}OEt_2$ (1.9 equiv). [b]Reaction conducted at 0 °C with 1.0 equiv of $BF_3{\cdot}OEt_2$.

oxetane ring intact. Other conditions known to activate potassium trifluoroborates toward nucleophilic addition were found to be ineffective.[18] *N,O*-Acetal **2a** could also be generated in situ from 3-oxetanone (**1**) and the corresponding amino alcohol and subjected to the alkynylation conditions to furnish **5a** in a one-pot sequence.

We then investigated the reaction scope with respect to the alkyne, amino alcohol precursor, and protective group R^1. Potassium acetylene trifluoroborate **4b** (R^3 = H) is an effective nucleophile, giving terminal alkyne **5b** in excellent yield (93%). Trifluoroborates bearing alkyl and aryl groups gave addition products in good yield (**5c**; 72%, **5e**; 77%). Silyl groups on the nucleophile were well tolerated, giving TMS-protected alkyne **5f** and TBS ether **5g** in 85% and 87% yield, respectively. Examination of the scope of the *N,O*-acetal demonstrated compatibility with a variety of substituted amino alcohols. In addition to *N*-benzyl derivatives, anilines were also tolerated (**5h**, 55%). Alkynylation of *N*-allyl substrate **2f** provided products **5i** and **5j** in good yields (72%). *N,O*-Acetals bearing a free NH also underwent alkynylation, albeit in lower yields (**5k,l**). Aminophenol-derived substrate **2h** was particularly reactive, giving products **5m−q** in 61−84% yield in short reaction times at 0 °C.

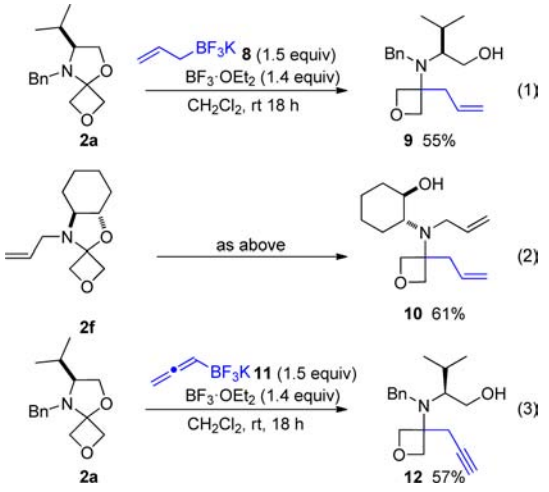
We then investigated the addition of vinylic potassium trifluoroborates to **2**. Trifluoroborates **6a−d**, bearing 2-alkyl and 2-phenyl groups, proved to be competent nucleophiles and underwent addition to **2** under similar reaction conditions (Scheme 3). Interestingly, in these cases, an excess of $BF_3{\cdot}OEt_2$ (1.9 equiv) relative to trifluoroborate **6** (1.3 equiv) was required to drive the reaction to completion.

Scheme 3. Vinylation of *N,O*-Acetals



We next considered the analogous allylation reactions of **2**, which would provide useful building blocks complementary to those the products of alkynylation and vinylation. Under similar reaction conditions, *N,O*-acetals **2a** and **2c** underwent allylation with potassium allyl trifluoroborate **8** (Scheme 4, eqs 1 and 2).[15a,18] Interestingly, potassium allenyl trifluoroborate **11**,[19] which in principle could lead to either the allenyl or propargyl product, gave exclusively the latter (Scheme 4, eq 3).[20]

Scheme 4. Allylation and Propargylation of *N,O*-Acetals



To explore the utility of the reaction products as building blocks for the synthesis of more intricate systems, we considered intramolecular cyclization of the pendant alcohols onto the two potential electrophilic sites, namely the oxetane and alkyne (Scheme 1). Ring closure by intramolecular opening of the oxetane by the alcohol would result in the formation of a morpholine ring, in analogy to our previous report.[3] Alternatively, cyclization onto the alkyne would produce oxetane-substituted *N,O*-heterocycles. In initial attempts at oxetane opening, **5b** proved to be resistant to several Brønsted and Lewis acids (TsOH, $BF_3{\cdot}OEt_2$, $In(OTf)_3$). Silylation of the alcohol

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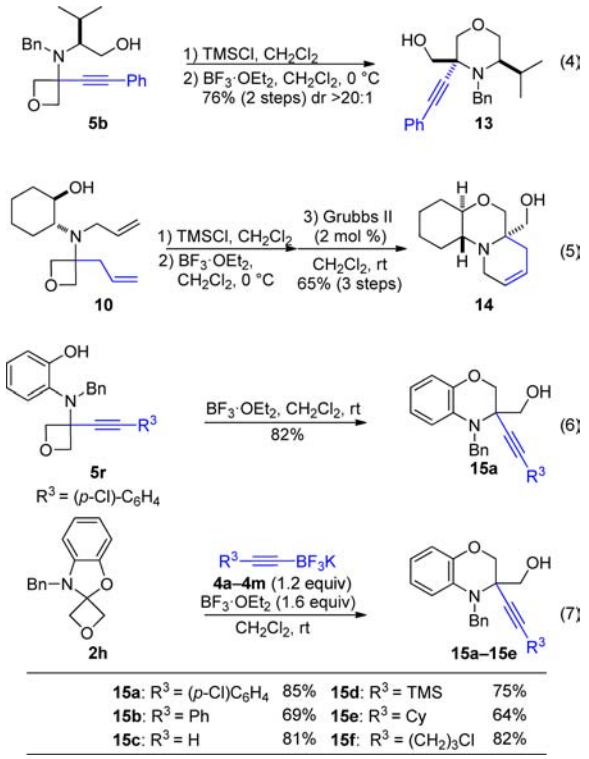
functionality resolved the problem, allowing for an efficient and highly diastereoselective oxetane opening promoted by $BF_3{\cdot}OEt_2$ to generate morpholine **13** (Scheme 5, eq 4). Allylation

Scheme 5. Synthesis of Morpholines by Ring Expansion



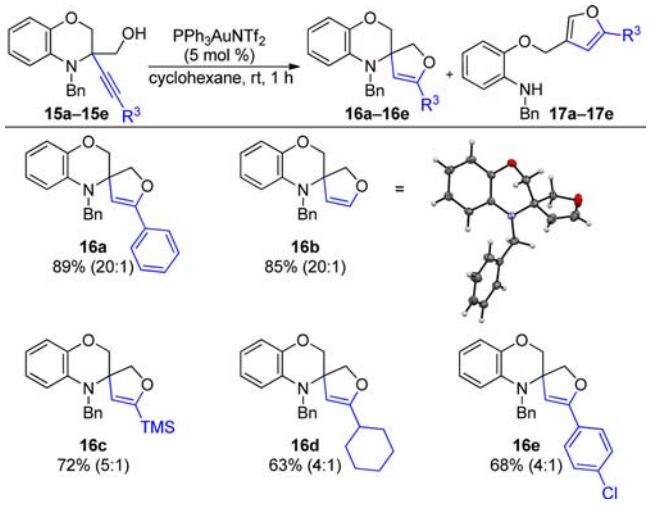
product **10** was efficiently converted to tricyclic morpholine **14** by a ring-expansion−ring-closing metathesis sequence (Scheme 5, eq 5).[21] The aminophenol derived products underwent ring opening in the presence of $BF_3{\cdot}OEt_2$ (Scheme 5, eq 6). The process could be coupled to alkynylation by simply using a slight excess of $BF_3{\cdot}OEt_2$ and extended reaction times (Scheme 5, eq 7).

We then considered the of possibility of ring closure of **15** by catalytic intramolecular alkyne hydroalkoxylation (Scheme 6).[22] Initial attempts at cyclization using Au(I) complexes resulted in predominant formation of the rearranged furan **17**.[23] However, the use of PPh_3AuNTf_2[24] in nonpolar solvents arrested the rearrangement at the desired spiro-dihydrofuran **16**, the structure of which was confirmed by X-ray crystallographic analysis.[25] The cyclization protocol was showcased with a variety of substituted alkynes as shown in Scheme 6.

We next examined cyclization of propargyl adduct **12** by intramolecular catalytic hydroalkoxylation as a means of forming medium-sized heterocycles. PPh_3AuNTf_2 served as a catalyst in the hydroalkoxylation of **12**, giving 7-*exo-dig* cyclization product **18** (Scheme 7). Products arising from oxetane opening and rearrangement were obtained as minor byproducts. The strained enol ether **18** was prone to hydration and decomposition on silica, yet it could be reduced and deprotected to give **19** in 65% yield over three steps. Given the wide distribution of heteroatom-substituted 7-membered rings in medicinal chemistry, **19** may serve as an attractive template for future development of building blocks.[26]

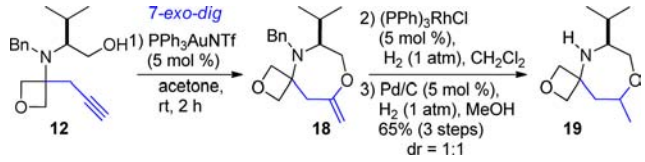
In conclusion, we have developed the addition of alkynyl-, vinyl-, allyl-, and propargylpotassium trifluoroborates to *N,O*-

Scheme 6. Au(I)-Catalyzed Hydroalkoxylation[a]



[a]Values in parentheses refer to the ratio of **16**:**17** as determined by ^1H NMR analysis of the unpurified reaction mixture.

Scheme 7. Synthesis of Oxetanyl 1,4-Oxazepane 19



acetals **2** derived from 3-oxetanone. This transformation is distinguished by several salient features, including compatibility of a wide range of bench-stable and easily accessible trifluoroborate nucleophiles[27] and the use of ketone-derived electrophiles, which have rarely been used in such reactions apart from allylations.[16c,17,28−30] The utility of the products generated was demonstrated by orthogonal activation of the alkyne and oxetane moieties in cyclization reactions, providing highly substituted morpholines and other saturated heterocycles. The application of this reaction to additional substrates is currently underway, and the results will be reported as they become available.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental data, experimental procedures, characterization, and NMR spectra of all novel compounds and X-ray data for **5q** and **16b** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01607.

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Notes

The authors declare no competing financial interest.

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