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Catalytic, Cascade Ring-Opening Benzannulations of 2,3-Dihydrofuran *O,O*- and *N,O*-Acetals

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Abstract: An $Al(OTf)_3$-catalyzed intramolecular cascade ring-opening benzannulation of 2,3-dihydrofuran *O,O*- and *N,O*-acetals is described. The cascade sequence involves the dihydrofuran ring-opening by acetal hydrolysis, an intramolecular Prins-type cyclization, and aromatization to generate an array of benzo-fused (hetero)aromatic systems in up to 95% yield. This method represents the first example of dihydrofuran acetal usage in benzannulation reactions. The approach provides excellent regiocontrol based on the choice of alkenes used to form the requisite dihydrofuran acetals.

Benzo-fused polycycles are important frameworks with broad applications in natural products synthesis, medicinal chemistry, chemical biology, and materials science (Figure 1).[1] The classical synthetic approach to access these systems involves functional group manipulation of preformed aromatic derivatives.[2] However, the aromatic products formed display limited substitution patterns. A more efficient strategy to construct these molecules is benzannulation,[3] which involves appending a benzene directly onto a pre-existing ring. Benzannulation is preferable due to the likely reduction of reaction steps and better control of regiochemical outcomes. The vast majority of benzannulation approaches involve [4+2],[4] [2+2+2],[5] [3+3],[6] and [6+4][7] cycloadditions, ring-closing metatheses,[8] Danheiser annulations,[9] transition-metal-promoted processes,[10] and base-induced rearrangements.[11] Many of these methods have serious limitations that reduce their scope and applications, including: 1) the requirement of an additional oxidation step (usually 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DDQ) to form the final aromatic ring; 2) the use of highly functionalized precursors that are challenging or not straightforward to access; and 3) the employment of highly air- or moisture-sensitive precursors. Therefore, methods involving readily-accessible, stable precursors that directly convert to the desired benzo-fused products remain an important synthetic endeavor.

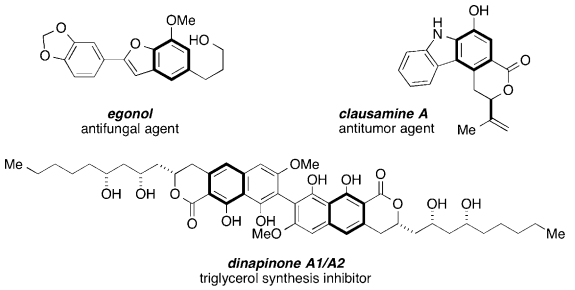
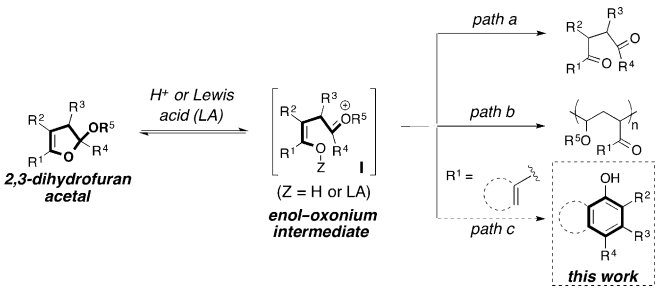


Figure 1. Representative naturally-occurring benzo-fused (hetero)aromatics.

Dihydrofuran (DHF) *O,O*-acetals have received particular attention from the synthetic community in recent years. This interest is attributed in part to the identification of bioactive natural products containing 5,5- and 5,6-fused bicyclic DHF *O,O*-acetals.[12,13] DHF acetals are readily prepared in good yields by Rh(II)-catalyzed reactions[14] of α-diazo β-ketoesters with enol ethers, or Mn^{III}-mediated reactions[15] of β-ketoesters with enol ethers.[16] DHF acetals undergo two primary types of reactions as described in the literature. First, they serve as precursors for furans following acid-promoted alcohol elimination.[17] Second, acid-promoted acetal hydrolysis results in either the substitution of the exocyclic alkoxy group (in the presence of a nucleophile) or DHF ring-opening leading to a putative enol(ate)-oxonium intermediate (Scheme 1). Based on this intermediate, 2,3-dihydrofuran acetals have been



Scheme 1. General ring-opening reactivity of 2,3-dihydrofuran (DHF) acetals.

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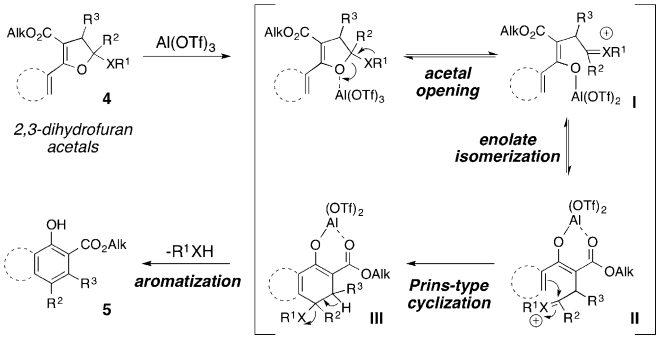
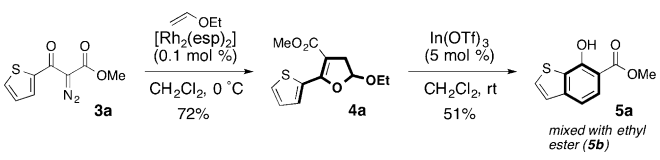
employed as a means to access 1,4-dicarbonyl compounds (Scheme 1path a),[17b,18] 2-cyclopentenones (following base-promoted intramolecular aldol condensations of the resulting 1,4-dicarbonyls),[18] or cationic ring-opening polymerizations (Scheme 1path b).[19] Beyond these examples, the use of DHF acetals as a means to access benzo-fused (hetero)aromatic compounds (Scheme 1path c) has not been reported.

Herein, we disclose an $Al(OTf)_3$-catalyzed cascade ring-opening benzannulation of 5-(hetero)aryl-2,3-dihydrofuran *O,O*- and *N,O*-acetals **4** (Scheme 2). The proposed cascade reaction involves an initial Lewis acid promoted DHF ring-opening. Upon ring-opening, the resulting alkoxonium (or iminium) intermediate **I** undergoes enolate isomerization to form the Lewis acid–enolate chelate complex **II**. Next, a Prins-type cyclization[23] occurs to form the intermediate **III**, which readily aromatizes by elimination of R^1XH (X = O or NR^4) to form the benzo-fused product.



Scheme 2. Cascade ring-opening Prins-type benzannulations of 2,3-DHF *O,O*- and *N,O*-acetals (X = O or NR^4).

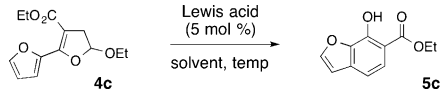
Based on a previous study, we observed that a mixture of the benzothiophenes **5a** and **5b** were generated when the 2-thienyl DHF *O,O*-acetal **4a** was treated with catalytic amounts of $In(OTf)_3$ (Scheme 3).[21] This transformation[22] equates to a formal Lewis acid catalyzed cascade benzannulation, a benzannulation class that has been underexplored. Given our established interest in the synthesis of benzo-fused compounds[23] and encouraged by this initial result, we sought to explore the ring-opening benzannulation reactions of DHF acetals as a potentially general approach to functionalized benzo-fused (hetero)aromatics.



Scheme 3. Conversion of the 2-thienyl DHF acetal **4a** to benzothiophene **5a** (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid).

In order to optimize the cascade transformation, we chose to utilize the dihydrofuran acetal **4c** as a model system. Due to the relative instability of the furan unit in the presence of certain Lewis acids (prone to ring-opening), we anticipated that successful optimization of the reaction of this substrate would bode well for a broader exploration of the substrate scope (Table 1). In contrast to the example with **4a**, $In(OTf)_3$ proved to be ineffective for the transformation of the furan **4c**, because mostly degradation was observed and an isolated yield of the desired benzofuran **5c** of only 5% was obtained (Table 1, entry 1). Degradation or poor conversions were also observed with other Lewis acids, such as $Sc(OTf)_3$, $Cu(OTf)_2$, and $Yb(OTf)_3$ (Table S1 in the Supporting Information).[24] Greater amounts of **5c** were obtained with $Ga(OTf)_3$ and $Al(OTf)_3$ (Table 1, entries 2 and 3). Performing the reaction at reflux with $Al(OTf)_3$ afforded **5c** in 35% yield (Table 1, entry 4). Changing the solvent to toluene and performing the reaction again at reflux gave a 40% yield (Table 1, entry 5). Reducing the temperature to 85 °C was found to increase the yield to 46% (Table 1, entry 6). All other attempts to further optimize the reaction (e.g., changing temperature, catalyst loading, concentration, etc.) failed to provide improved yields.[24] Therefore, the conditions used for the examination of the reaction scope were 5 mol% $Al(OTf)_3$ in toluene at 85 °C.

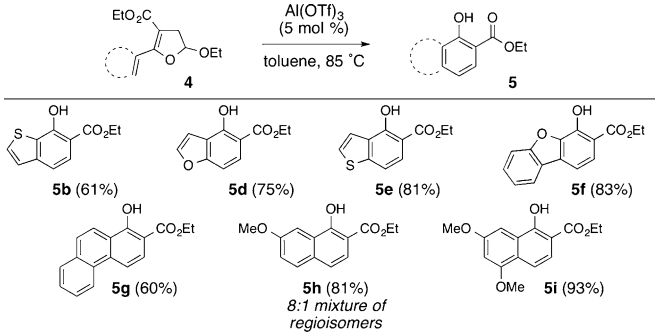
Table 1. Optimization of the cascade reaction with **4a**.



Entry[a]	Lewis acid	Solvent	T [°C]	t [h]	Yield[b] [%]
1	$In(OTf)_3$	CH_2Cl_2	23	45.0	5
2	$Ga(OTf)_3$	CH_2Cl_2	23	9.5	16
3	$Al(OTf)_3$	CH_2Cl_2	23	45.0	19
4	$Al(OTf)_3$	CH_2Cl_2	40	6.5	35
5	$Al(OTf)_3$	toluene	111	1.0	40
6	**$Al(OTf)_3$**	**toluene**	**85**	**1.0**	**46**

[a] Reaction conditions: Lewis acid (5 mol%), **4c**, and solvent (0.2 M) at the indicated temperature. [b] Isolated yield of **5c** after column chromatography.

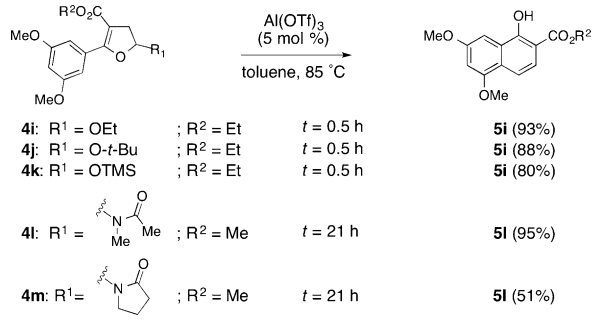
With the optimized conditions, the cascade reactions with other (hetero)aryl dihydrofuran derivatives were evaluated (Scheme 4). The 2-thienyl dihydrofuran **4b** was readily converted to the benzothiophene **5b** in 61% yield. The 3-furyl derivative **4d** provided the corresponding benzofuran **5d** in 75% yield, which is notable given that **5d** can be readily converted



Scheme 4. $Al(OTf)_3$-catalyzed cascade reactions of DHF acetals **4**.

in two steps to a range of naturally-occurring furanoflavonoids, including pongol methyl ether and millettocalyxins C.[25,26] A similar conversion of the 3-thienyl derivative **4d** to the benzothiophene **5e** was observed in 81% yield. As anticipated, the benzofuryl dihydrofuran **4f** generated the dibenzo[*b*,*d*]furan **5f** in 83% yield. The 2-naphthyl substrate **4g** afforded the phenanthrene derivative **5g** in 60% yield as the only regioisomer, whereas the 3-methoxyphenyl dihydrofuran **4h** gave a 8:1 mixture of the naphthalene **5h** and its regioisomer **5h′** in 81% yield.[24] A high yield (93%) was afforded for the cascade reaction of the 3,5-dimethoxy dihydrofuran **4i** to give the naphthalene **5i**.

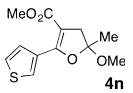
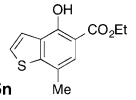
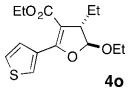
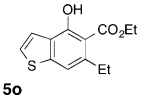
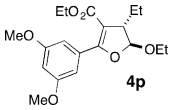
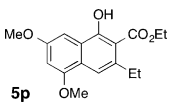
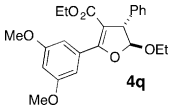
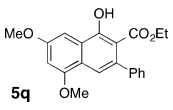
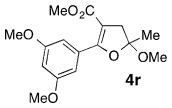
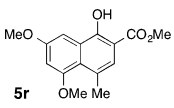
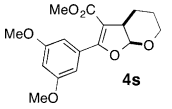
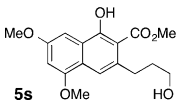
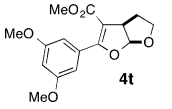
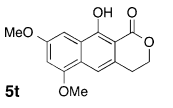
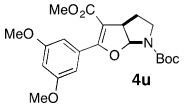
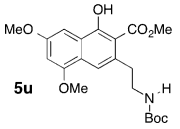
Next, the nature of the acetal group was changed to evaluate its effect on the reaction efficiency (yield and time). The results were compared to the DHF acetal **4i** (Scheme 5). Dihydrofuran *O*,*O*- and *N*,*O*-acetals **4j**–**m** were prepared and subjected to the optimized cascade conditions. When **4j** (containing a *tert*-butoxy group) was used, **5i** was obtained in 88% yield. The siloxy derivative **4k** afforded smooth conversion to **5i** in 80% yield. The methyl acetamido DHF **4l** provided **5l** with a yield (95%) comparable to **4i**, but with a longer reaction time (24 h vs. 1 h, respectively).[27] Finally, the pyrrolidin-2-one **4m** gave a modest 51% yield of **5l** with a similarly long reaction time (21 h). It is likely that additional coordination of the amide carbonyl to the Lewis acid is responsible for the elongated reaction time. Taken together, the ethyl derivative **4i** proved to be the most efficient derivative.



Scheme 5. Probing of the acetal-substituent effect.

To examine the reaction scope, tetra-substituted DHF acetals were synthesized and explored. When the 2-methoxy-2-methyl-5-thienyl DHF **4n** was subjected to the optimized conditions, none of the expected 7-methyl benzothiophene **5n** was observed and a furan derivative was formed instead (Table S2).[24] Interestingly, when the temperature was reduced to 70 °C and a drop of water was added to the reaction mixture, a 1:1.18 crude mixture of **5n**/furan was observed. After some optimization, it was found that 20 mol% $Al(OTf)_3$ in toluene with a drop of water at 70 °C provided **5n** in 80% yield (Table 2, entry 1). It is plausible that water may be promoting the formation of a dihydrofuran hemiacetal intermediate that facilitates ring-opening over the furan formation. Under these new conditions, the 3-ethyl-2-methoxy-5-thienyl DHF **4o** gave the expected 6-ethyl benzothiophene **5o** in 69% yield (entry 2). Similarly with **4p** and **4q**, the 3-ethyl and 3-phenyl naphthalenes **5p** and **5q** were formed in 88% and 79% yield, respectively. In comparison, the 2,2-*gem*-disubstituted acetal **4r** afforded the 4-methyl naphthalene **5r** in 86% yield. These examples demonstrate the general strength of the method for the strategic synthesis of regioisomeric benzo-fused systems. Since the acetal serves as the directing group for ring-opening, the placement of the substituent presumably determines the regiochemistry. Therefore, the selection of the alkene for the DHF synthesis becomes an important reaction-design component, since it could dictate the cascade product regiochemistry. To our knowledge, this level of regiocontrol is unprecedented for Lewis acid promoted benzannulations.

Table 2. Cascade reactions of tetra-substituted 2,3-DHF acetals.

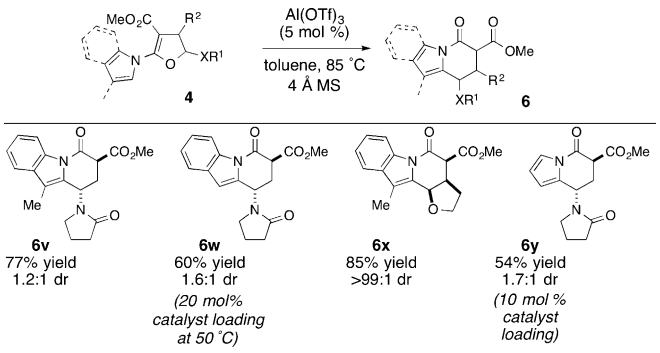
Entry[a]	4	5	*t* [h]	Yield[b] [%]
1	 **4n**	 **5n**	2.0	80
2	 **4o**	 **5o**	4.0	69
3	 **4p**	 **5p**	7.5	88
4	 **4q**	 **5q**	7.0	79
5	 **4r**	 **5r**	0.67	86
6[c]	 **4s**	 **5s**	7.5	85
7[c]	 **4t**	 **5t**	5.0	90
8[c]	 **4u**	 **5u**	19.0	17

[a] Reaction conditions: $Al(OTf)_3$ (20 mol%), **4** (1 equiv) in toluene (0.2 M) with water (1 drop), 70 °C. [b] Isolated yield after column chromatography. [c] Performed using $Al(OTf)_3$ (5 mol%) at 85 °C (no added water).

For the fused bicyclic DHF acetals (**4s**–**u**), the original reaction conditions [5 mol% $Al(OTf)_3$, 85 °C] gave better yields of the expected products. The 3a,5,6,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran **4s** gave a 85% yield of the naphthalene **5s**, which contains a pendant hydroxypropyl unit that can serve as a point for further functionalizations (Table 2, entry 6). In contrast, lactonization was observed for the 2,3,3a,6a-tetrahydrofuro[2,3-*b*]furan **4t** as the tricyclic naphthopyranone **5t** was generated in 90% yield (entry 7). This result is particularly

interesting as naphthopyranones have received tremendous attention from medicinal chemists due to the existence of a large number of naturally occurring, bioactive, and therapeutically relevant derivatives.[28] The 6-Boc-3a,5,6,6a-tetrahydro-4*H*-furo[2,3-*b*]pyrrole **4u** (a bicyclic *N*,*O*-acetal) provided only 17% yield (52%, BSRM) of naphthalene **5u** (entry 9). The low yield can be attributed to catalyst deactivation by coordination with the pendant carbamate group. Increasing the catalyst loading or the temperature did not improve the product yield.[24] Finally, attempts to access the expected benzannulated products from penta-substituted DHF acetals failed and only furan formation was observed.[24]

Based on our ongoing interest in the synthesis of indole-containing compounds,[29] a series of DHF acetals, substituted at the 5-position with the nitrogen of an indole (or pyrrole), was prepared and subjected to the initial reaction conditions (Scheme 6). In each case, only cycloisomerization was observed



Scheme 6. Reactions of 2-(1*H*-indol-1-yl) and 2-(1*H*-pyrrol-1-yl) DHF acetals (X = O or NR^3).

and the final elimination/aromatization did not take place. For example, the *N*-indole-substituted DHF *N*,*O*-acetals **4v** and **4w** gave the resulting hydropyrido[1,2-*a*]indoles **6v** and **6w** in 77% and 60% yield, respectively. Similarly, the 2-(1*H*-Indol-1-yl)-3a,4,5,6a-tetrahydrofuro[2,3-*b*]furan **4x** provided the tetracyclic 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one **6x** in 85% yield. Lastly, the corresponding 2-(1*H*-pyrrol-1-yl) DHF *N*,*O*-acetal **4y** afforded the 7,8-dihydroindolizin-5(6*H*)-one **6y** in 54% yield.

In conclusion, we have developed a powerful new strategy towards accessing functionalized benzo-fused (hetero)aromatics from DHF acetals. Our approach utilizes catalytic amounts of $Al(OTf)_3$ and provides the benzo-fused products in up to 95% yield. The approach offers excellent regiocontrol based on the choice of the alkene used to form the requisite DHF acetal. Moreover, in the cases of *N*-indolyl- or *N*-pyrrolyl-substituted DHF acetals, cycloisomerization products are obtained in good yields. This method represents a novel reactivity for DHF acetals and allows future methodologies (inter- and intramolecular) to be developed with them as versatile synthetic building blocks. Future work will involve: 1) utilizing the method to access several naturally-occurring compounds; 2) improving the product yields of the fused bicyclic *N*,*O*-acetals; and 3) accessing benzannulated products from penta-substituted DHF acetals.

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Keywords: benzannulation · domino reactions · fused-ring systems · heterocycles · ring-opening cyclizations

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Organic Synthesis

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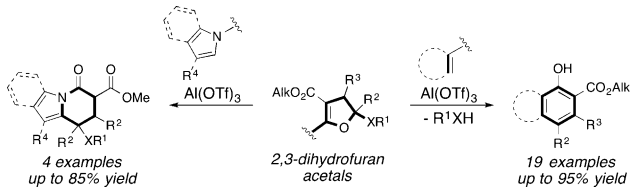
Catalytic, Cascade Ring-Opening Benzannulations of 2,3-Dihydrofuran *O,O*- and *N,O*-Acetals



An intramolecular cascade ring-opening benzannulation of 2,3-dihydrofuran (DHF) acetals is disclosed, which generates highly functionalized benzannulation products, including naphthalenes, benzofurans, benzothiophenes, and dibenzofurans. When the DHF acetal is substituted at the 5-position with 1-pyrroles or 1-indoles, the ring-opening cyclization occurs without aromatization to afford tetrahydroindolizines or hydropyrido[1,2-a]indoles, respectively.