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# Expeditious diastereoselective synthesis of medium ring heterocycle-fused chromenes *via* tandem 8/9-*endo-dig* and 8-*exo-dig* hydroalkoxylation-formal-[4 + 2] cycloaddition†

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**The first examples of highly diastereoselective tandem 8/9-*endo-dig* and 8-*exo-dig* hydroalkoxylation-formal-[4 + 2] cycloaddition are described for the synthesis of medium ring heterocycle-fused chromenes. TMS-alkynols preferred the *exo-dig* mode of hydroalkoxylation over the *endo-dig* mode leading to spiro-cyclic chromenes. The method could be used for the synthesis of linearly-fused ladder-like polyethers. A thia-heterocycle-fused chromene could be transformed into a complex bridged tricyclic ketal by a tandem carbene-insertion-[2,3]-sigmatropic shift.**

Medium ring 1,4-heterocycles are present in a wide range of biologically active natural products and bioactive molecules (Fig. 1).[1] However, access to these medium rings is often found to be difficult due to entropic and enthalpic barriers for cyclization. As a result, a very limited number of strategies have been reported for the synthesis of these motifs.[2] Hydroalkoxylation of alkynes has come to the fore as a reliable method for the synthesis of oxygen bearing heterocycles. The majority of these studies rely on transition metal catalysed processes to generate small ring cyclic ethers.[3] Surprisingly, the synthesis of medium ring heterocycles using intramolecular hydroalkoxylation of alkynes has received only a little attention. Furthermore, only scattered reports are available for the synthesis of medium ring 1,4-heterocycles.[4] To the best of our knowledge, neither 9-*endo-dig* hydroalkoxylation of alkynes nor 8/9-*endo-dig* hydroalkoxylation followed by cascade functionalization has been reported to date.[5] Structurally diverse chromenes exhibit a wide range of significant biological and pharmacological activities.[6] Interestingly, methods that provide access to chromenes bearing 1,4-heterocycles are hitherto unexplored. Hence, the development of a stereoselective method providing rapid access to these scaffolds in an efficient manner is highly desirable. Herein, we disclose the first examples of Lewis acid promoted, 8/9-*endo-dig* and 8-*exo-dig* hydroalkoxylation-formal-[4 + 2] cycloaddition of heteroatom substituted alkynols for the synthesis of 8/9-membered heterocycle-fused linear and spiro chromenes, respectively, in a highly regio- and stereoselective manner.

Our group has been engaged in developing strategies for the synthesis of 1,4-heterocycles. We have also developed a method for gaining access to cyclic ether-fused chromenes using hydroalkoxylation-formal-[4 + 2] cycloaddition.[7] In this context, we decided to explore the 8/9-*endo-dig* hydroalkoxylation-formal-[4 + 2] cycloaddition reaction cascade for the synthesis of medium ring heterocycle-fused chromenes, which is challenging. It was anticipated that in the presence of a Lewis acid, *N*/*O*/*S*-tethered alkynols **5–7** would form the corresponding cyclic enol ethers *via* the *endo-dig* mode of hydroalkoxylation, which on subsequent formal-[4 + 2] cycloaddition with salicylaldehyde derivatives **8** would give medium ring heterocycle-fused chromene derivatives **9–11**, respectively (Scheme 1).

Initially, attention was focused on studying the feasibility of the 8-*endo-dig* hydroalkoxylation-formal-[4 + 2] cycloaddition cascade for the stereoselective synthesis of 8-membered heterocycle-fused chromene derivatives. Towards this end, *N*-tethered alkynol **5a** was reacted with salicylaldehyde (**8a**) using TMSOTf as the catalyst. Interestingly, the desired 8-membered heterocycle-fused chromene **9a** was obtained as the sole product in an excellent yield (Table 1, entry 1). Alkynol **5b**

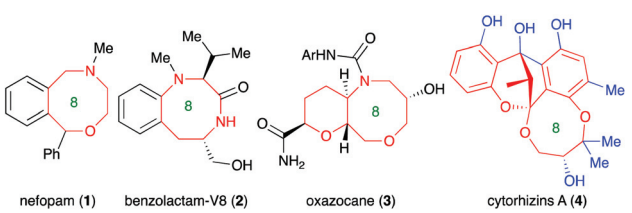


**Fig. 1** Bio-active molecules having medium ring heterocycles.

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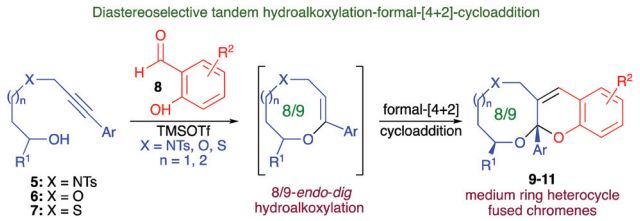
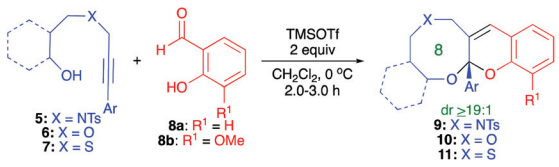
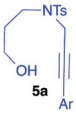
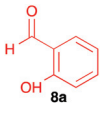
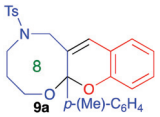
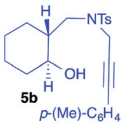
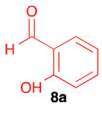
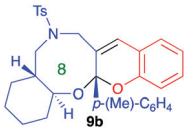
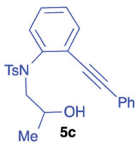
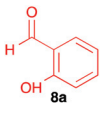
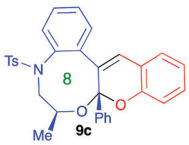
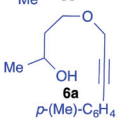
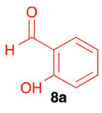
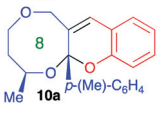
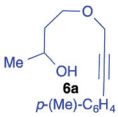
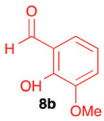
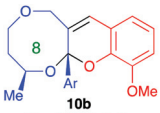
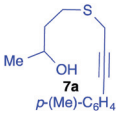
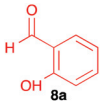
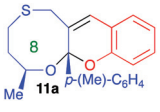
‡ Both authors contributed equally.




**Scheme 1** Proposed synthesis of medium ring heterocycle-fused chromenes.

**Table 1** Scope of the 8-*endo-dig* hydroalkoxylation-formal-[4 + 2] cycloaddition cascade

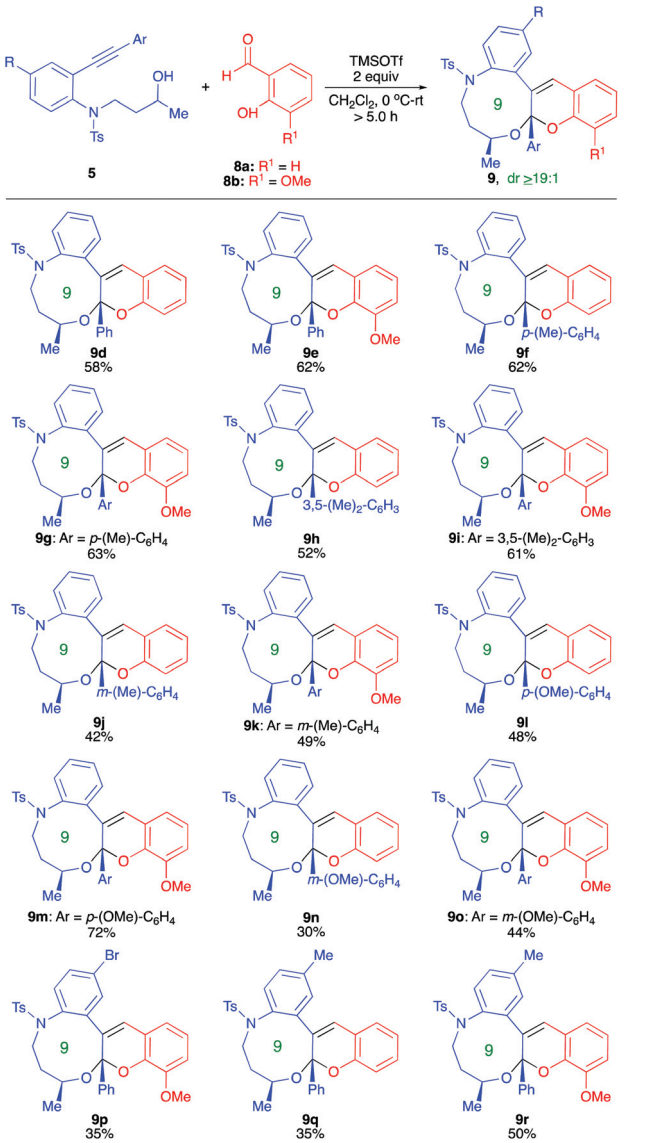



| Sr. no. | Alkynol | Aldehyde | Aldehyde | Yield[a,b] (%) |
|---|---|---|---|---|
| 1 |  **5a** |  **8a** |  **9a** *p*-(Me)-$C_6H_4$ | 82 |
| 2 |  **5b** *p*-(Me)-$C_6H_4$ |  **8a** |  **9b** *p*-(Me)-$C_6H_4$ | 71 |
| 3 |  **5c** |  **8a** |  **9c** | 95 |
| 4 |  **6a** *p*-(Me)-$C_6H_4$ |  **8a** |  **10a** *p*-(Me)-$C_6H_4$ | 66 |
| 5 |  **6a** *p*-(Me)-$C_6H_4$ |  **8b** |  **10b** Ar = *p*-(Me)-$C_6H_4$ | 66 |
| 6 |  **7a** *p*-(Me)-$C_6H_4$ |  **8a** |  **11a** *p*-(Me)-$C_6H_4$ | 85 |

[a] In all the cases, dr was determined by $^1$H NMR of the crude reaction mixture. [b] The yields correspond to isolated yields.

bearing a cyclohexyl ring furnished medium ring-fused chromene **9b** with excellent diastereoselectivity. Aniline tethered alkynol **5c** afforded 1,4-heterocycle-fused chromene **9c** with an excellent yield and diastereoselectivity (Table 1, entry 3). The structure of the chromene derivative **9c** was confirmed unambiguously by an X-ray diffraction study.[8] Furthermore, *O*/*S*-tethered alkynols **6a** and **7a**, when reacted with salicylaldehydes (**8a** and **b**), gave the corresponding medium ring 1,5-heterocycle-fused chromene derivatives **10a**, **b** and **11a**, respectively, with a good yield and diastereoselectivity (Table 1, entries 4–6).

Encouraged by these results, we decided to expand the scope of this cascade reaction to the synthesis of 9-membered ring-fused chromenes employing hitherto unknown 9-*endo-dig* hydroalkoxylation-formal-[4 + 2] cycloaddition. The alkynol **5d** was treated with salicylaldehyde (**8a**) in the presence of TMSOTf. While no reaction took place at lower temperature, prolonging the reaction time at room temperature resulted in the formation of the desired 9-membered heterocycle-fused chromene derivative **9d** with a moderate yield and excellent diastereoselectivity (Scheme 2).[9] To check the generality of the




**Scheme 2** 9-*Endo-dig* hydroalkoxylation cascade. In all the cases, dr was determined by $^1$H NMR of the crude reaction mixture. The yields correspond to isolated yields.

9-*endo-dig* hydroalkoxylation-formal-[4 + 2] cycloaddition cascade, various alkynols **5d–k** were treated with salicylaldehyde derivatives (**8a** and **b**) in the presence of TMSOTf. To our delight, in all the cases the desired 9-membered heterocycle-fused chromene derivatives **9e–r** were obtained with moderate to good yields and excellent diastereoselectivity (Scheme 2). In general, the alkynols bearing an electron releasing group on the aryl ring, which is conjugated to alkynes, were found to give higher yields. These results indicated that hydroalkoxylation of alkynes to give 9-membered rings is more difficult compared to the corresponding 8-membered rings. The structure and stereochemistry of oxazonanes **9** were established on the basis of their spectral data and further unambiguously confirmed by X-ray diffraction studies on chromene derivatives **9d–f** (Fig. 2).[8]

The hydroalkoxylation-formal-[4 + 2] cycloaddition cascade was also studied with *N*-tethered TMS-alkynes **5m** and **n**. To begin with, alkynol **5m** was coupled with salicylaldehyde **8a** using TMSOTf. Interestingly, hydroalkoxylation occurred in an 8-*exo-dig* fashion rather than in a 9-*endo-dig* manner leading to the formation of spiro-cyclic 8-membered heterocycle-fused chromenes with excellent diastereoselectivity, albeit in low yields (Scheme 3).[10] TMS-alkynol **5n** afforded spiro-cyclic chromene ketals **12b** and **c** with excellent diastereoselectivity albeit in low yields. The structures of the chromene ketals **12a** and **12c** were unambiguously confirmed by single crystal X-ray diffraction studies (Fig. 3).[8]

The divergent outcome of this cascade, whether a linearly-fused or spiro-cyclic chromene ketal would be formed, is decided at the first step of the cascade process, namely, hydroalkylation leading to the cyclic enol ethers. Once the cyclic enol ethers were formed, they would participate in formal-[4 + 2] cycloaddition with salicylaldehydes **8** to furnish the corresponding chromene ketal products. Thus, whether the alkynol will follow *8-exo-dig* or *9-endo-dig* hydroalkoxylation depends on the substituents on the alkyne that can affect the stabilization of the incipient vinyl cations **A** and **B** *en route* to cyclic enol ethers **Int C**/**D** (Scheme 4). In the case of alkynols **5d–k** (R = Ar), the presence of an aryl group provides extra stabilization to the incipient vinyl cation **A** at the benzylic position,

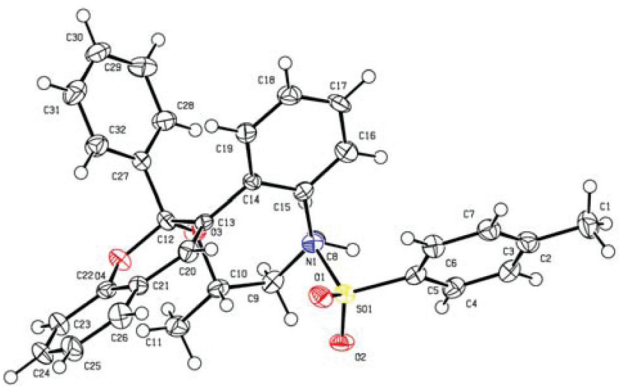
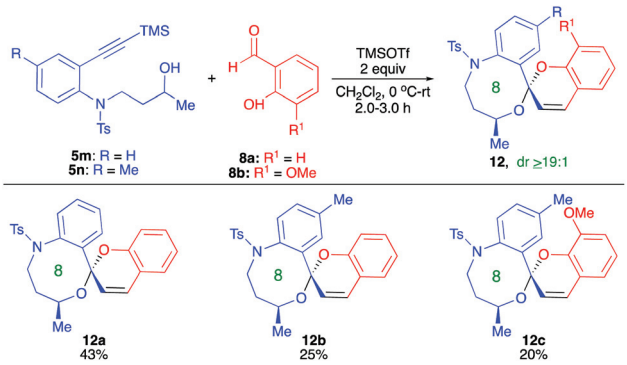


Fig. 2 ORTEP diagram of **9d**.




Scheme 3 8-*Exo-dig* hydroalkoxylation cascade. In all the cases, dr was determined by $^1$H NMR of the crude reaction mixture. The yields correspond to isolated yields.

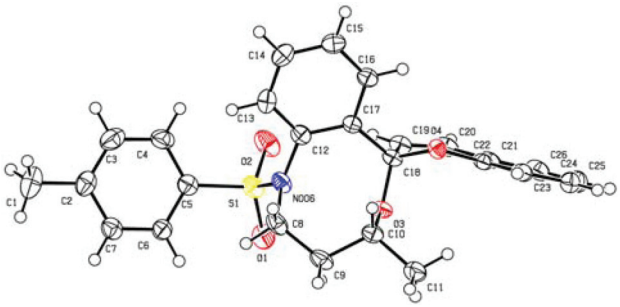
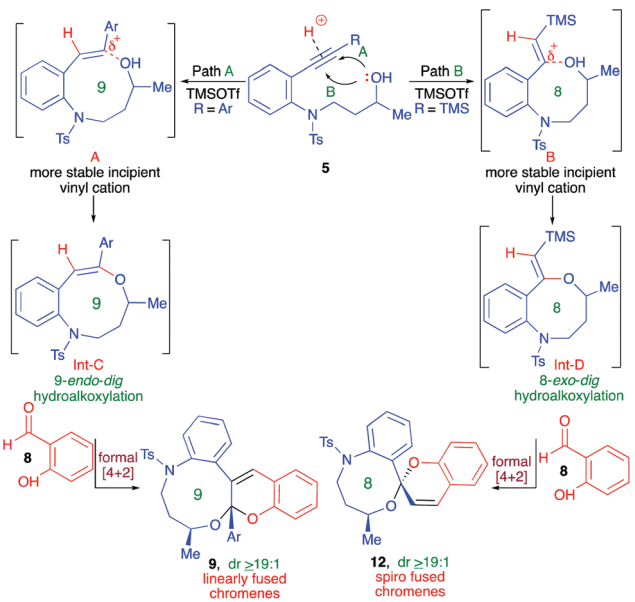


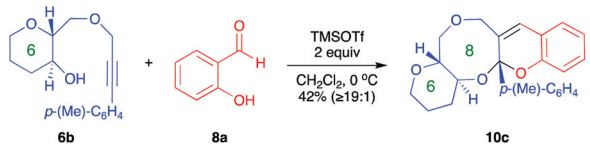
Fig. 3 ORTEP diagram of **12a**.



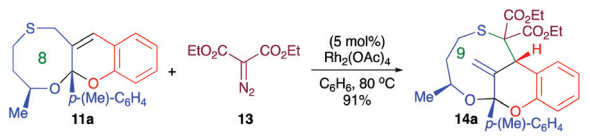

Scheme 4 Plausible reaction pathway.

thus favouring the *9-endo-dig* mode of hydroalkoxylation to give **Int C** (path A). On the other hand, in the case of alkynols **5l** and **m** (R = TMS), the incipient vinyl cation **B** at the benzylic position adjacent to the aromatic carbon is more stable; thus




**Scheme 5** Diastereoselective synthesis of linearly-fused ladder-like polyethers.




**Scheme 6** Stereoselective synthesis of medium ring bridged tricyclic ketals.

8-*exo-dig* hydroalkoxylation would be preferred leading to the formation of **Int D** (path B). These intermediates **Int-C** and **Int-D** then lead to the corresponding linearly-fused chromenes **9d–r** and spiro-cyclic chromenes **12a–c**, respectively.

Linearly-fused ladder-like polyethers are present in many bioactive natural products.[11] We envisioned that the developed cascade process can be employed to gain rapid access to this motif.

Thus, the D-glucal derived alkynol **6b** upon reaction with salicylaldehyde (**8a**) afforded ladder-like polycyclic ether-fused chromene derivative **10c** as the sole product with excellent diastereoselectivity (Scheme 5).

Finally, we decided to functionalize the obtained products to enhance the synthetic utility of the developed reaction cascade. To this end, we envisioned that generation of a bridged tricyclic ketal would be challenging. Thus, oxathiepino chromene **11a** was subjected to a reaction with diazo malonate **13** in the presence of $Rh_2(OAc)_4$ in benzene. Gratifyingly, the bridged tricyclic ketal **14a** was obtained with an excellent yield and stereoselectivity (Scheme 6). To the best of our knowledge, this is the first example of a tandem sulfonium ylid formation-[2,3]-sigmatropic shift that leads to a bridged bicyclic system.[12]

In conclusion, the Lewis acid promoted 8-*exo* and 8/9-*endo*-mode of the hydroalkoxylation-formal-[4 + 2] cycloaddition cascade was developed for the synthesis of medium ring heterocycle-fused chromenes in a highly stereoselective manner. Linearly-fused ladder-like polyethers could be successfully synthesized in a stereoselective manner using the developed hydroalkoxylation cascade. Furthermore, the product obtained was transformed into medium ring heterocycle-fused bridged tricyclic ketals *via* a tandem sulfonium ylid generation-[2,3]-sigmatropic shift.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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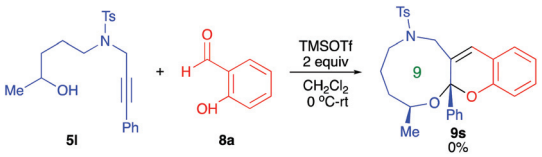
9 The aliphatic alkynol **5l** did not furnish the required chromene derivative **9s**; rather decomposition was observed. It was assumed that the lack of conformational strain could be the potential reason, which in turn made the 9-*endo-dig* hydroalkoxylation step difficult.

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