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Metal-free Hydroalkoxylation-Formal [4+2] Cycloaddition Cascade for the Synthesis of Ketals

Santosh J. Gharpure*, Santosh K. Nanda, Padmaja, Yogesh G. Shelke

Abstract: A transition metal free, acid promoted cascade hydroalkoxylation-formal [4+2] cycloaddition of various alkynols with salicylaldehyde is demonstrated for the synthesis of tetrahydrofurano/pyrano-chromenes and spiroketals. In general, alkynols underwent hydroalkoxylations in an *endo-dig* manner when internal alkynes were used to furnish the heteroannular ketals, whereas terminal alkynes proceeded in an *exo-dig* fashion leading to spiroketals. The study revealed that intramolecular hydroalkoxylation of alkynols is a preferred path over a generation of oxocarbenium ion formation when coupling partner is salicylaldehyde. This metal-free transformation provides a new avenue for the stereoselective synthesis of tetrahydrofurano- and pyrano-chromenes in an expeditious manner.

Polycyclic heteroannular and spirocyclic ketal motifs are frequently encountered in structurally complex natural products, which display varied pharmacological and biological activity.[1] Xyloketal A (**1**) belonging to xyloketal family acts as potent inhibitor of acetylcholine esterase whereas alboatrin (**3**) inhibits the root growth of the host plant and causes vascular-wilt disease in alfalfa (Fig. 1).[2] Spiroketals such as paecilospirone (**4**) act as potential antimitotic agent and berkelic acid (**5**) exhibits selective activity against the ovarian cancer cell line.[3] Biological activity of these natural ketals coupled with the structural diversity has attracted attention of the synthetic chemists and plethora of strategies have been developed for their synthesis. In this context, significant progress has been made on the synthesis of cyclic ketals using transition metal catalysed *bis*-etherification *via* hydroalkoxylation of alkyne diols.[4-6] Further, precious transition metal catalyzed hydroalkoxylation of alkyne coupled with formal cycloaddition reactions such as [4+2] or [3+2] have emerged as a method of choice for the synthesis of oxygen containing heterocycles.[7-9] While many of these approaches are elegant and efficient, they require use of very costly metals such as gold and platinum along with additives, which range from metals such as silver to Brønsted acids, as well as higher reaction temperatures. Thus, a transition metal free cascade process involving alkynols for the synthesis of ketal derivatives is highly desirable. We disclose herein one such approach where a Lewis or Brønsted acid can be used not only to effect intramolecular hydroalkoxylation of an alkynol at lower temperatures but also carry out formal [4+2] cycloaddition with salicylaldehyde derivatives in a cascade manner to furnish tetrahydrofurano/pyrano-chromenes bearing tricyclic ketal frameworks in highly stereoselective manner. This general approach also gives access to spirocyclic ketals.

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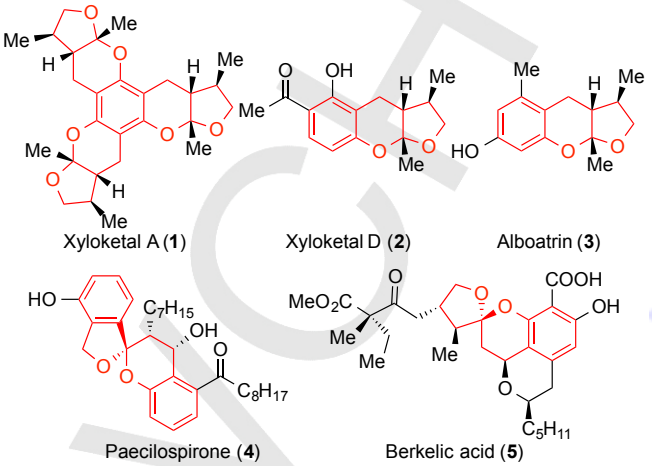
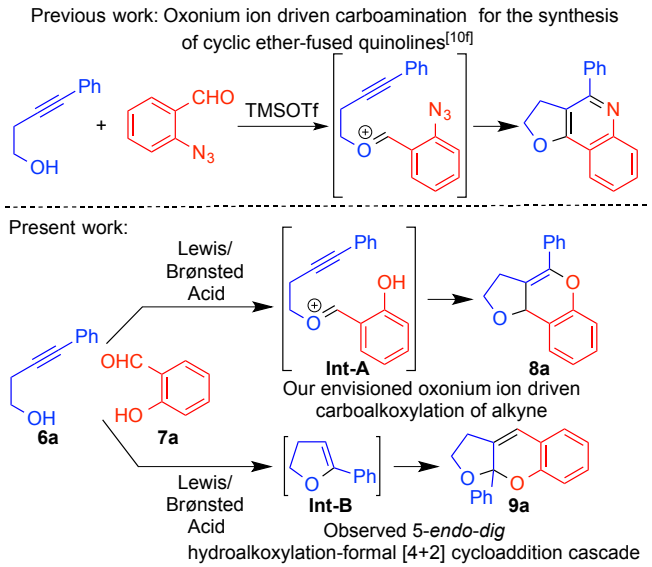


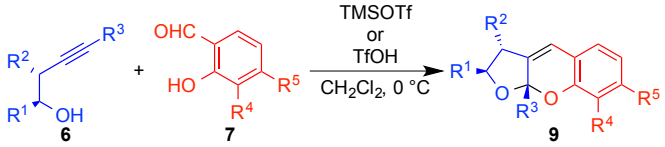
Figure 1. Natural products bearing heteroannular and spirocyclic ketal motif.

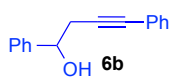
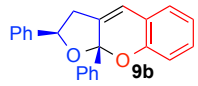
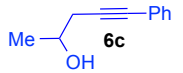
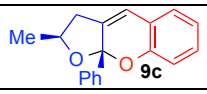
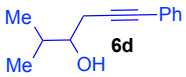
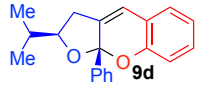
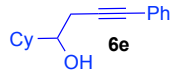
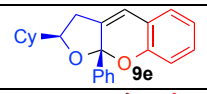
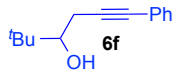
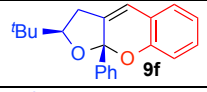
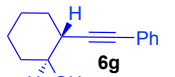
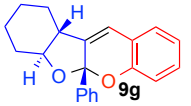
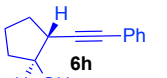
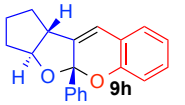
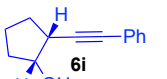
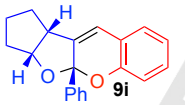
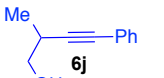
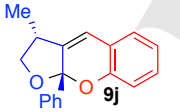
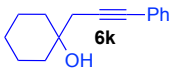
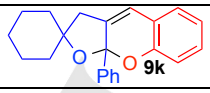
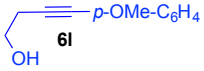
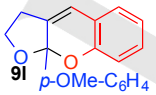
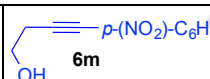
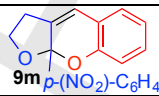
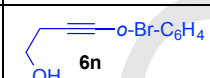
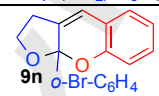
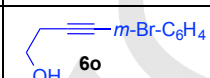
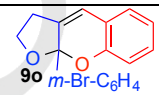
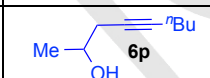
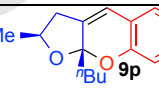
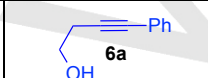
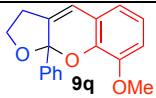
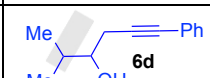
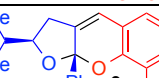
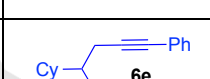
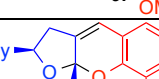
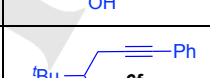
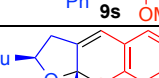
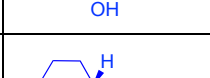
In a programme directed at developing methods for synthesis of various functionalized heterocycles,[10a-e] recently we disclosed a Lewis acid promoted oxonium ion driven carboamination of alkynes for the synthesis of cyclic ether-fused quinolines (Scheme 1).[10f] Based on this study, we envisioned that alkynol **6** on reaction with salicylaldehyde (**7**) in the presence of Lewis/ Brønsted acid would furnish oxonium ion **Int-A**, which on intramolecular formal [4+2] cycloaddition would afford cyclic ether fused-chromene derivative **8**. Interestingly, when such a reaction was attempted with alkynol **6a** and salicylaldehyde (**7a**) using TMSOTf, the ketal **9a** was formed rather than the expected cyclic ether fused-chromene derivative **8a**. This observation could be explained by initial Lewis acid mediated hydroalkoxylation leading to the intermediate **Int-B**, which upon formal [4+2] cycloaddition gave rise to ketal **9a**.[11]



Scheme 1. Proposed hydroalkoxylation-formal [4+2] cycloaddition cascade for heteroannular ketal synthesis.

Table 1. Scope of hydroalkoxylation-formal [4+2] cycloaddition cascade for the synthesis of tetrahydrofurano chromenes **9.**



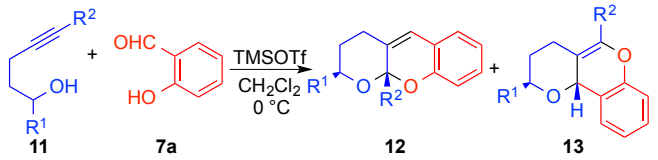
Entry	Alkynol	Product	Yield (%), dr[a]
1	 **6b**	 **9b**	98, 2:1[b] 75, 5.6:1[c]
2	 **6c**	 **9c**	83, 2:1[b]
3	 **6d**	 **9d**	95, 4:1[b] 85, 4.5:1[c]
4	 **6e**	 **9e**	86, 3.2:1[b] 82, 3.5:1[c]
5	 **6f**	 **9f**	86, 4.5:1[b] 71, 4.5:1[c]
6	 **6g**	 **9g**	76, ≥19:1[b] 71, ≥19:1[c]
7	 **6h**	 **9h**	0[d]
8	 **6i**	 **9i**	89, 2:1[b] 78, 4:1[c]
9	 **6j**	 **9j**	98, 10:1[b]
10	 **6k**	 **9k**	94[b]
11	 **6l**	 **9l** *p*-OMe-C_6H_4	56[b]
12	 **6m**	 **9m** *p*-(NO_2)-C_6H_4	45[b]
13	 **6n**	 **9n** *o*-Br-C_6H_4	98[b]
14	 **6o**	 **9o** *m*-Br-C_6H_4	92[b]
15	 **6p**	 **9p**	55, 2.5:1[b]
16	 **6a**	 **9q**	99[b]
17	 **6d**	 **9r**	88, 4:1[b] 89, 4.5:1[c]
18	 **6e**	 **9s**	89, 3.2:1[b] 78, 4.5:1[c]
19	 **6f**	 **9t**	79, 5.8:1[b] 76, 9:1[c]
20	 **6g**	**9u**	67, ≥19:1[b] 61, ≥19:1[c]
21	**6k**	**9v**	91[b]
22	**6f**	**9w**	79,10:1[b] 52,10:1[c]
23	**6g**	**9x**	60, ≥19:1[b] 60, ≥19:1[c]

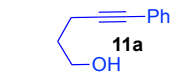
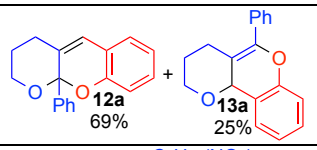
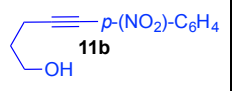
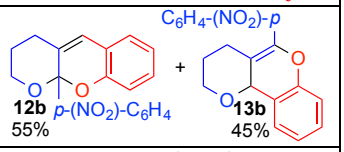
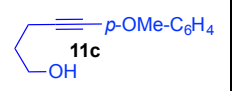
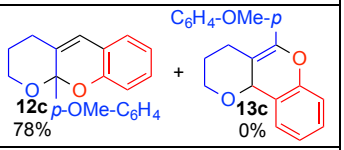
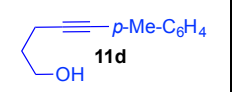
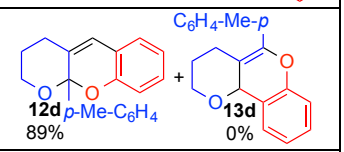
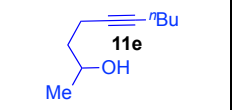
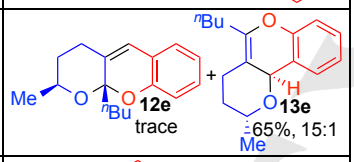
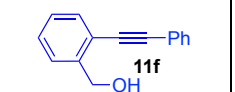
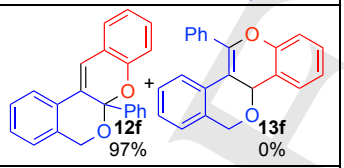
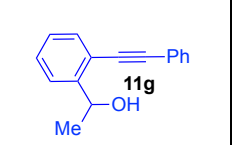
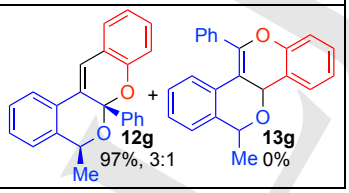
[a]In all the cases dr was obtained on crude reaction mixture by ^{1}H NMR analysis, [b]reaction was carried out with TMSOTf, [c]reaction was carried out with TfOH, [d]starting materials were recovered back.

This unusual reaction outcome prompted us to explore transition metal-free tandem hydroalkoxylation-cycloaddition reaction for the synthesis of ketal derivatives **9**.

Study of the reaction scope commenced by treatment of alkyn-1-ol **6b** with salicylaldehyde (**7a**) in the presence of TMSOTf (2 equiv.). Gratifyingly the ketal **9b** was obtained in excellent yield, albeit with moderate diastereoselectivity [Method **A**] (Table 1, entry 1). To improve diastereoselectivity, various Lewis/Brønsted acids were screened (see, supporting information). It was found that use of TfOH (2 equiv.) in CH_2Cl_2 at 0 °C resulted in formation of the ketal **9b** with improved diastereoselectivity [Method **B**]. Stereochemistry of the major diastereomer was assigned as '*cis*' based on the single crystal X-ray diffraction studies.[12] Further scope and limitation of the method was then investigated using both the methods **A** and **B**. While changing substituents on alkynol next to OH group (R^1) had little effect on the yield, the diastereoselectivity was found to improve as the substituent became bulkier. It was found that alkynol bearing *tert*-butyl group (**6f**) offered better diastereoselectivity for the formation of the corresponding chromene ketal (**9f**) than that observed for alkynols with methyl (**6c**), isopropyl (**6d**) or cyclohexyl (**6e**) group (Table 1, entry 2-5). The *trans* alkynyl cyclohexanol **6g** gave excellent diastereoselectivity for the formation of the chromene **9g**. Interestingly, when '*cis*' alkynyl cyclopentanol **6i** was used, the product ketal **9i** was obtained in excellent yield, unlike the '*trans*' alkynol **6h**, albeit with moderate

Table 2. Synthesis tetrahydropyrano chromene.

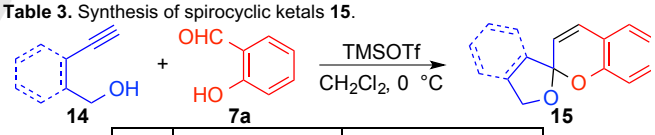


Entry	Alkynol	Product
1		
2		
3		
4		
5		
6		
7		

diastereoselectivity [Method B] (Table 1, entry 7-8). The alkynol **6j** bearing methyl substitution on second carbon gave a much better diastereoselectivity for formation of the ketal **9j** (Table 1, entry 9 *v/s* entry 2). It is pertinent to note that tertiary alcohol **6k** too was tolerated under reaction conditions employed and the spirocyclic ketal **9k** was obtained in excellent yield (Table 2, entry 10). Interestingly, both the alkynols **6l-m** having either electron donating or electron withdrawing group on the aryl ring gave lower yield of the chromene **9l** and **9m**, respectively (Table 2, entry 11-12). While competing formation of the keto alcohol **10** [4-hydroxy-1-(4-methoxyphenyl)butan-1-one] due to net hydration of alkyne was the reason for lower yield in the former case, lower stability of the vinyl cation was responsible in the latter. On the other hand, alkynols **6n-o** with bromide substituent on the aryl ring gave desired chromenes **9n-o** in near quantitative yield (Table 1, entry 13-14). The reaction of aliphatic alkynol **6p** gave the ketal **9p** in only moderate yield and diastereoselectivity (Table 1, entry 15). Salicylaldehyde derivatives bearing electron releasing substituents (**7b-c**) were also tested with different alkynols and in all the cases desired chromene derivatives **9q-x** were obtained in excellent yield (Table 1, entry 16-23). In all the cases, the stereochemistry of the major *cis*-isomer was assigned based on NOESY or NOE experiments. It was further confirmed from single crystal X-ray diffraction studies on the **9d**, **9e**, **9t** and **9u**.[12]

Synthesis of tetrahydropyrano chromene derivatives **12** was studied next. Pentyn-1-ol (**11a**) on reaction with salicylaldehyde (**7a**) furnished the tetrahydropyrano chromene **12a** as the major product along with the chromene **13a** formed by alkyne Prins type cyclization – intramolecular vinyl cation trapping cascade (Table 2, entry 1). The alkynol **11b** with aryl ring substituted with electron withdrawing NO_2 group also furnished a mixture of the chromene ketal **12b** (55%) and pyrano chromene **13b** (45%) with poor selectivity. However, alkynols **11c-d** bearing electron releasing substituents on the aryl ring led to exclusive formation of the chromene ketals **12c-d**, respectively (Table 2, entry 3-4). Interestingly, alkyl substituted alkynol **11e** upon reaction with salicylaldehyde (**7a**) furnished the pyrano chromene **13e** along with only trace of chromene ketal **12e** (Table 2, entry 5). There appears to be a delicate balance between the two possible reaction paths, *viz.* hydroalkoxylation-formal [4+2] cycloaddition *v/s* alkyne Prins type reaction-vinyl cation trapping. In the cases where vinyl cation is stabilised, former seems to dominate whereas if this intermediate is destabilised, the latter path competes. It should also be noted that the *5-endo-dig* reactions of alkynes are faster than the corresponding *6-endo-dig* cyclization and hence no such competing product formation was observed in the case of alkynols **6**. This was further corroborated by reaction of the aryl fused alkynols **11f** and **11g**, which exclusively furnished the chromene ketals **12f** and **12g**, respectively, in quantitative yield (Table 2, entry 6-7). Here, due to lower conformational flexibility of the alkynols, the intramolecular 6-*endo-dig* hydroalkoxylation was significantly faster than the competing intermolecular oxonium ion formation, which resulted in the eventual formation of the chromene ketals (*cf.* Scheme 1).

Table 3. Synthesis of spirocyclic ketals **15**.



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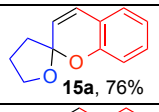
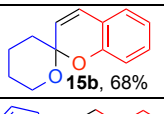
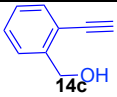
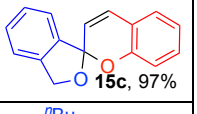
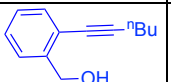
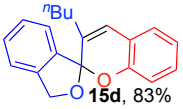
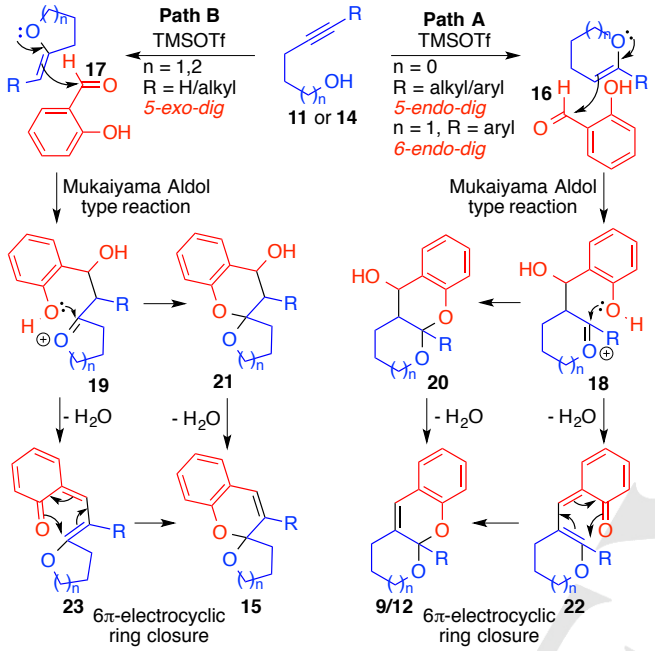
1		
2		
3		
4		

The hydroalkoxylation of alkyne-formal [4+2] cycloaddition cascade was also studied with terminal alkynols **14**. To begin with, pentyn-1-ol (**14a**) was coupled with salicylaldehyde (**7a**) using TMSOTf. Interestingly, hydroalkoxylation step proceeded in a *5-exo-dig* manner leading to the spirocyclic ketal **15a**, albeit

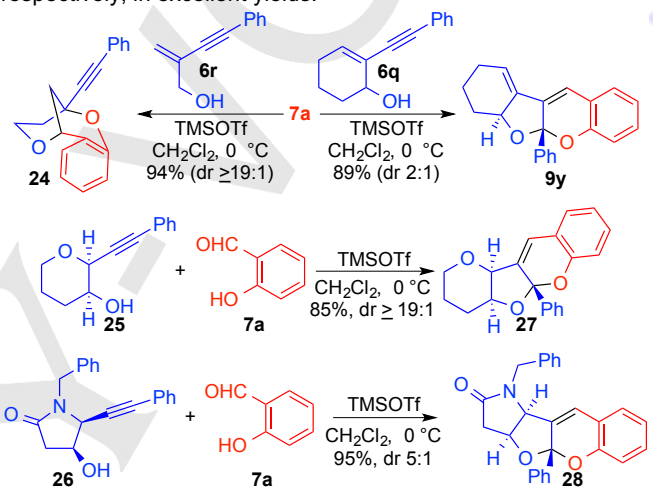
requiring longer reaction time (Table 3, entry 1). This reaction was found to be general and alkynols **14b-c** gave the spirocyclic ketals **15b-c** in good yield (Table 3, entry 2-3). Interestingly, when aliphatic alkynol **14d** was subjected to reaction with salicylaldehyde (**7a**) under optimized conditions, the spirocyclic ketal **15d** was obtained as the only detectable product (Table 3, entry 4). The structure of spirocyclic ketal **15d** was confirmed based on the NMR correlation experiments (see, supporting information for details). This strategy can be potentially used in the total synthesis of spiroketal natural products such as paecilospirone (**4**).



Scheme 2. Mechanism of formation of chromene ketals.

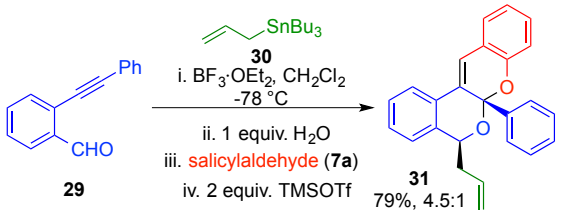
Mechanistically, diverse outcomes of the varied chromene formations starting from alkynols and salicylaldehyde derivatives **7** can be explained by two competing paths *viz.* hydroalkoxylation *v/s* oxonium ion formation (*vide supra*). Further, regioselectivity of hydroalkoxylation decides whether linearly-fused or spirocyclic chromene would form as the product (Scheme 2). When homopropargyl alcohols are used, the hydroalkoxylation proceeds in a *5-endo-dig* (rather than *4- exo-dig*) fashion (Path A). Since the *5-endo-dig* mode of hydroalkoxylation is very facile, the oxonium ion formation does not seem to compete and tetrahydrofurano chromenes **9** are formed as exclusive products. While *bis*-homopropargyl internal alkynols undergo hydroalkoxylation in *5/6-endo-dig* manner (Path A), terminal ones proceed through *5/6-exo-dig* mode (Path B). The internal alkynol with alkyl substitution on the aryl alkyne (e.g. alkynol **14d**) prefer the *5-exo-dig* cyclization, perhaps due to extra stability of benzylic vinyl cation. The vinyl ethers **16** and **17** formed by hydroalkoxylation undergo Mukaiyama aldol reaction with salicylaldehyde to form oxonium ions **18** and **19**, respectively. The oxonium ions **18** and **19** lead to chromenes **9**/**12** and **15**, either by their trapping by phenolic OH followed by water elimination or their rearrangement to dienones **22** and **23**, respectively, followed by 6-electrocyclic ring closing reaction.

During the study of substrate scope, it was envisioned that substrate like enynol **6q/6r** would be interesting as they would give an opportunity to compare reactivity of hydroalkoxylation and Prins cyclization of olefin through oxonium ion. When alkynol **6r** was subjected to reaction with salicylaldehyde (**7a**) under optimized conditions using TMSOTf, bicyclic ether **24** was obtained as exclusive product through conventional alkene Prins cyclization followed by trapping of the tertiary carbocation intermediate by phenolic OH. The alkynol **6q** on the other hand gave the ketal **9y** in good yield *via* tandem hydroalkoxylation-formal [4+2] cycloaddition process, further demonstrating that subtle conformational changes can significantly influence the reaction pathway (Scheme 3). It was envisaged that synthesis of *oxa-* or *aza*-cycle fused tetrahydrofurano chromenes would be challenging. Towards this end, the alkynols **25** and **26** were treated with salicylaldehyde (**7a**) using optimized reaction condition to furnish the products **27** (dr ≥ 19:1) and **28** (dr 5:1), respectively, in excellent yields.[13]



Scheme 3. Synthesis of bicyclic ether and cyclohexene/tetrahydropyran/ pyrrolidine-fused tetrahydrofurano chromenes.

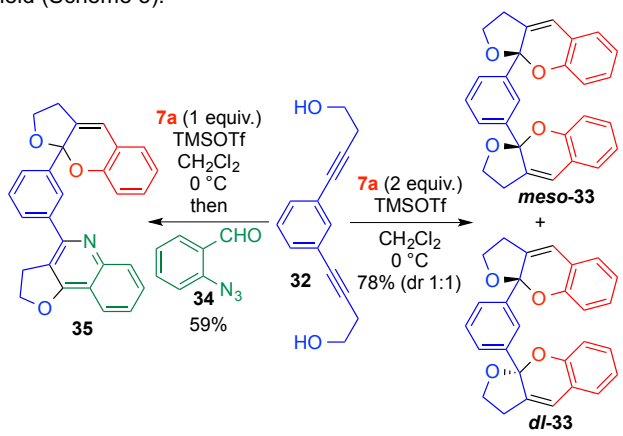
To further expedite the synthesis of tetrahydropyrano chromene derivatives, a 'one pot' protocol involving even generation of the requisite alkynol in the same flask was attempted. Alkynal **29** was subjected to allylation using allyltributylstannane (**30**) and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 followed by addition of 1 equiv. of water. Salicylaldehyde (**7a**) and TMSOTf were added sequentially to the same reaction mixture to furnish the chromene ketal **31** in excellent overall yield with moderate diastereoselectivity (Scheme 4). It is interesting to note that the reaction sequence was successful only when 1 equiv. of water was added in order to hydrolyse tin alkoxide intermediate.



Scheme 4. 'One Pot' allylation-hydroalkoxylation of alkyne-formal [4+2] cycloaddition.

Finally, to enhance the utility of our established protocol, *bis*-alkynol **32** was treated with 2 equiv. of salicylaldehyde (**7a**) to afford *bis*-chromene derivative **33** in 78% yield as a *ca.* 1:1

mixture of diastereomers. At this juncture, we thought that this strategy could be extended to a sequence involving two reaction mechanisms *viz.* hydroalkoxylation of alkyne-formal [4+2] cycloaddition as well as oxonium ion driven carboamination in a 'one pot' manner to rapidly build structural complexity. To demonstrate this concept, *bis*-alkynol **32** was reacted with 1 equiv. salicylaldehyde (**7a**) followed by azido aldehyde **34** [after starting material was consumed in the first step (TLC control)], which indeed gave the quinoline chromene derivative **35** in good yield (Scheme 5).[10f]



Scheme 5. 'One pot' synthesis of *bis*-chromene **33** and quinoline chromene derivative **35**.

In conclusion, we have demonstrated a transition metal free, Lewis/Brønsted acid catalysed cascade hydroalkoxylation-formal [4+2] cycloaddition reaction of alkyne to construct tetrahydrofurano/pyrano chromenes and spirocyclic chromene derivatives. We have shown that the stereoelectronic effects were responsible for the alkynols to participate in reaction with salicylaldehyde derivative through two competing paths *viz.* hydrolkoxylation – formal [4+2] cycloaddition v/s oxonium ion driven carboalkoxylation. The factors affecting regioselectivity of hydroalkoxylation of alkynols were studied and it was found that internal alkynes underwent *5/6-endo-dig* cyclization whereas terminal alkynols followed *5/6-exo-dig* cyclization. The method was also used for the synthesis of linearly fused heterocycles. Further, it has been shown that the reactions can be sequenced to carry out 'one pot' synthesis of chromene ketal, *bis*-chromene as well as quinoline chromene derivatives.

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Keywords: Hydroalkoxylation • Lewis/Brønsted acid catalysed reactions • Cyclic ether-fused chromenes • [4+2] cycloaddition • Linear/spirocyclic Ketal

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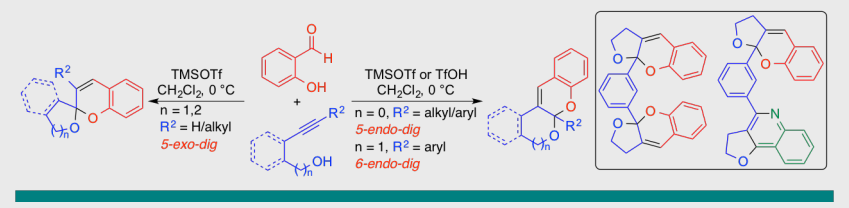

Lewis/Brønsted acid mediated stereoselective synthesis of chromene ketals is demonstrated. The cascade reaction involved transition metal free hydroalkoxylation of alkyne-formal [4+2] cycloaddition with salicylaldehyde. Complex scaffolds like *bis*-chromene, quinoline-fused chromene, core of xyloketal and paecilospirone natural products could be assembled employing this method. The study suggested that substituents on alkyne govern *exo v/s endo* mode of hydroalkoxylation of alkynols to furnish polycyclic heteroannular or spirocyclic chromene ketals.

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