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Facile Synthesis of Isochromanones and Isoquinolones by $AuCl_3$ Catalyzed Cascade Triggered by an Internal Nucleophile

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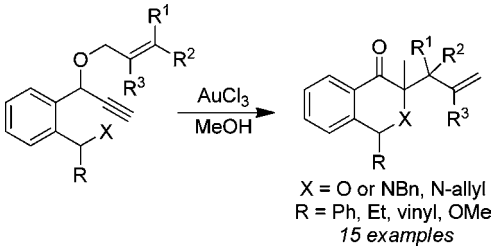
ABSTRACT



Synthesis of isochromanones and isoquinolones comprising a quaternary center with high diastereoselectivity was realized via a $AuCl_3$ catalyzed tandem intramolecular *exo-dig* heterocyclization/enol isomerization/Claisen rearrangement sequence in excellent yields. The reaction is general and amenable for the synthesis of structurally diverse analogues.

The advent of gold catalysis in organic synthesis has seen a virtual rush in recent years in developing synthetic strategies based on gold complexes. A variety of gold catalysts with a number of substrates that include a combination of alkene, alkyne, and heteroatoms leading to the evolution of diverse reactions for the construction of carbo- and heterocyclic compounds were developed.[1] Claisen rearrangement [in general 3,3-sigmatropic rearrangements], a reaction that has a profound impact in organic synthesis,[2] was also a subject of investigation with gold catalysts. Dean Toste's group disclosed the first successful gold catalyzed Claisen rearrangement of vinyl propargyl ethers for the synthesis of homoallenic alcohols.[3] Similarly, 3,3-sigmatropic rearrangement of allenyl vinyl ethers was also reported by the Kraft and Xu groups.[4] Herein we report a novel strategy, hitherto unexplored, involving a combination of tandem *exo-dig* heterocylization–enol isomerization–Claisen rearrangement triggered by an internal nucleophile to yield isochromanones and isoquinolones (Figure 1), which were important scaffolds present in a number of natural products.

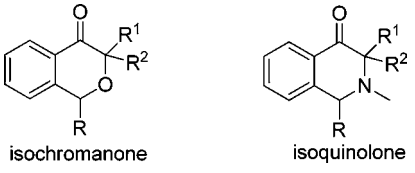


Figure 1. Isochromanone and isoquinolone.

(1) For selected reviews on gold-catalyzed cyclizations, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Corma, A.; Leyva-Perez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (e) Huang, H.; Zhou, Y.; Liu, H. *Beilstein J. Org. Chem.* **2011**, *7*, 897. (f) Nũñez, E. J.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326.

(2) (a) Claisen, L. *Ber.* **1912**, *45*, 3157. (b) For a review on Claisen rearrangement see: Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.

(3) (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978. (b) Mauleõn, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 4513. (c) Horino, Y.; Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 11364. (d) For theoretical treatment of gold mediated Claisen rearrangement, see: Vidhani, D. V.; Cran, J. W.; Krafft, M. E.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2013**, *78*, 2059.

(4) (a) Krafft, M. E.; Hallal, K. M.; Vidhani, D. V.; Cran, J. W. *Org. Biomol. Chem.* **2011**, *9*, 7535. (b) Wei, H.; Wang, Y.; Yue, B.; Xu, P.-F. *Adv. Synth. Catal.* **2010**, *352*, 2450.

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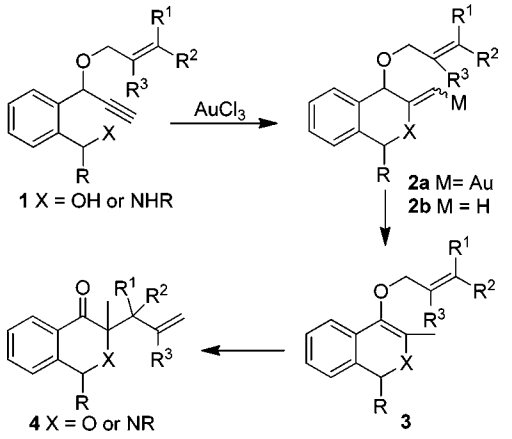
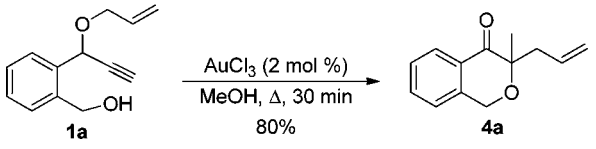
Our strategy for the synthesis of isochromanones and isoquinolones is depicted in Scheme 1. We anticipated that the propargyl-allyl ethers of type **1** should undergo $AuCl_3$ catalyzed intramolecular nucleophilic *exo-dig* heterocyclization reaction, leading to the intermediate vinyl gold complex **2a** which on protodeauration should form the exocyclic enol ether **2b**. Double bond isomerization of **2b** should afford the enol ether **3**, which is appropriately arranged to undergo the Claisen rearrangement, resulting in the product isochromanones or isoquinolones.

Scheme 1. Retrosynthesis for Isochromanones and Isoquinolones Involving Gold Mediated Tandem Process



With this hypothesis, at the outset, propargyl allyl ether **1a** was prepared from phthalyl alcohol (see Supporting Information for preparation) and was subjected to the reaction with a catalytic amount (2 mol %) of $AuCl_3$ in MeOH. We were pleased to find that the expected isochromanone **4a** was formed in 80% yield (Scheme 2).

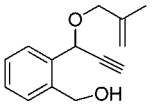
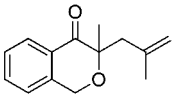
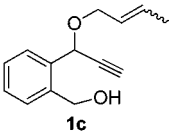
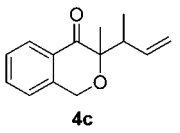
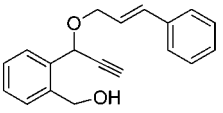
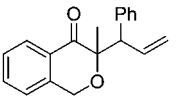
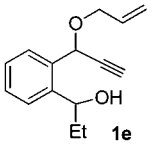
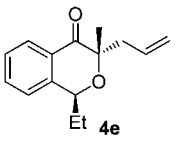
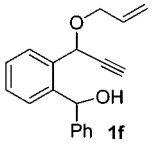
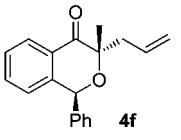
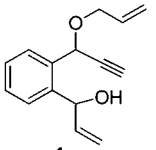
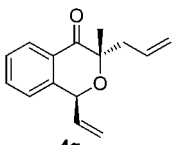
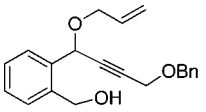
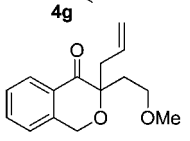
Scheme 2. Formation of the Isochromanones **4a** from **1a**



The reaction was found to be general, and a series of allyl ethers underwent an efficient tandem sequence to yield the product isochromanones in excellent yields. As evident from Table 1, reaction of the crotyl propargyl ether **1c** afforded the product isochromanone **4c** (*dr* 92:8) (entry 2, Table 1) in 89% yield.[5] Similarly, the cinnamyl propargyl ether **1d** also rendered the product isochromanone **4d** (*dr* 92:8) in 90% yield (entry 3, Table 1). Substrates **1e**

(5) Commercially available crotylbromide which is a scalemic mixture of *E*/*Z* isomers was employed to prepare the propargyl-crotylether **1c**. No efforts were made to determine the relative/absolute stereochemistry of the major diastereomer obtained in the reaction.

Table 1. Synthesis of Isochromanones **4a**–**h** by $AuCl_3$ Catalyzed Reaction of Allyl Propargyl Ethers **1a**–**h**[a]

entry	substrate	product	yield
1	 **1b**	 **4b**	86%
2	 **1c**	 **4c**	89%
3	 **1d**	 **4d**	90%
4[b]	 **1e**	 **4e**	95%
5[c,d]	 **1f**	 **4f**	91%
6[b]	 **1g**	 **4g**	92%
7	 **1h**	 **4h**	60%

[a] All reactions were performed with 2 mol % $AuCl_3$ in refluxing MeOH. [b] Reaction was performed with a scalemic mixture of diastereomers. [c] Major diastereomer was shown in the product (**4e** *dr* 83:17; **4f** *dr* 88:12; **4g** *dr* 77:23). [d] Relative stereochemsitry of the product **4f** was established by X-ray crystal structure determination.[7]

and **1f** comprising a secondary alcohol group [possessing alkyl and aryl substitution at the benzylic position] also underwent the facile tandem sequence to yield the product isochromanones **4e** and **4f** in 95% and 91% yield respectively (entries 4–5, Table 1).[6] The relative stereochemistry at both stereocenters of the product was assigned by X-ray crystal structure determination of one of the isochromanones **4f**.[7] The presence of a vinyl group α to the hydroxy group did not alter the outcome of the reaction, and the

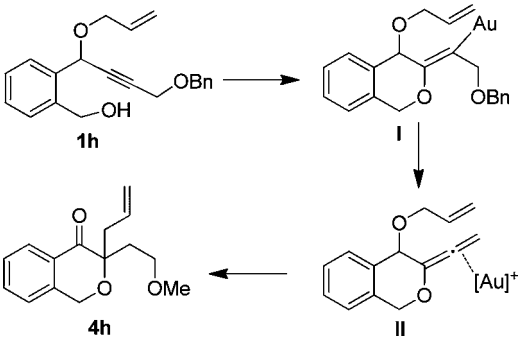
(6) The diastereomeric ratio was estimated with the aid of ^1H NMR within detectable limits.

(7) Crystallographic data were deposited with The Cambridge Crystallographic Data Centre. CCDC No. 932987. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

tandem sequence proceeded smoothly to yield the isochromanone **4g** in 92% yield. The formation of carbocycles from the enyne-ene cyclizations[8] that are normally dominant under gold catalysis was not observed in this reaction.

The reaction with the allyl propargyl ether **1h** comprising a benzyloxymethyl substitution on the alkyne did undergo the tandem reaction to yield the product isochromanone **4h**, transforming the benzyl ether to the corresponding methyl ether (entry 7, Table 1). This transformation, perhaps, proceeds through the elimination of the benzyl ether after the initial formation of the vinylgold complex (**I**) leading to an allene intermediate (**II**) which undergoes subsequent enol isomerization–Claisen rearrangement and addition of MeOH affording the product **4h** (Scheme 3).[9]

Scheme 3. Proposed Pathway for the Formation of **4h** from **1h**

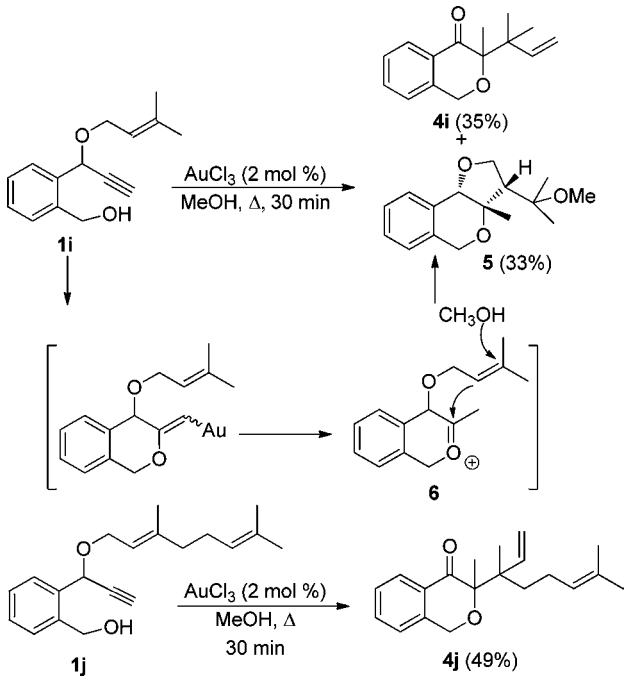


It was intriguing to find that the reaction of the prenyl propargyl ether **1i** with 2 mol % $AuCl_3$ afforded the product isochromanone **4i** in 35% yield along with the fused tetrahydrofuran **5** in 33% yield. Formation of the tetrahydrofuran **5** can be explained by the pathway involving trapping of the oxo-carbonium **6** resulting from the initial protodeauration, with an electron-rich nucleophilic double bond (Scheme 4).

To explore this pathway further, the reaction of the geranyl ether **1j** under similar reaction conditions was performed with the expectation of a cascade capture of the formed oxo-carbonium ion. However, treatment of **1j** with 2 mol % $AuCl_3$ in MeOH furnished the rearranged product **4j** (*dr* 83:17) in 49% yield along with an unidentifiable mixture of products.

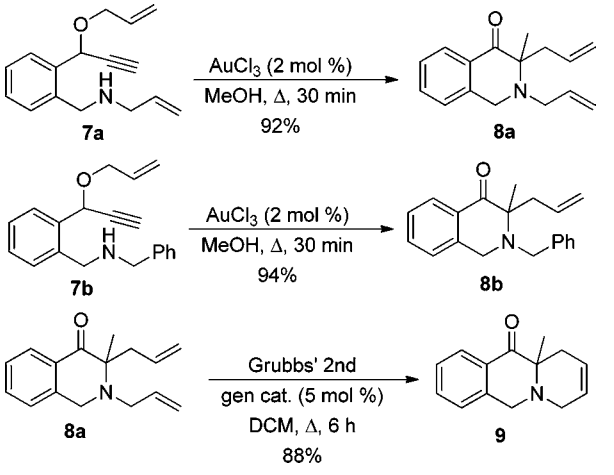
After successfully optimizing the conditions for the synthesis of the isochromanones, we turned our attention to the synthesis of corresponding amine analogues, the isoquinolones. The amine substrates **7a**–**b** required were synthesized from the alcohol **1a** (see Supporting Information

Scheme 4. Reaction of **1i** and **1j** with Catalytic $AuCl_3$ in MeOH



for synthesis). Reaction of the amines **7a**–**b** with 2 mol % of $AuCl_3$ proceeded in a facile manner to yield the isoquinolones **8a**–**b** in excellent yields. One of the formed isoquinolones **8a** was transformed to the tricyclic isoquinolonoindolizidine **9** utilizing ring closing metathesis in excellent yield (Scheme 5).

Scheme 5. Formation of the Isoquinolones **8a**–**8b** from **7a**–**7b**

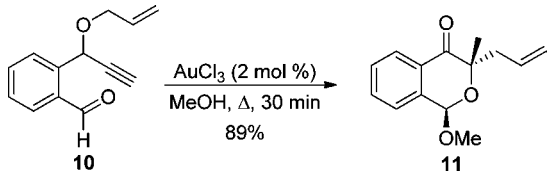


We also investigated the use of an aldehyde instead of the alcohol/amine as an internal nucleophile in the above cascade reaction. Accordingly, aldehyde **10** (prepared by oxidation of the alcohol **1a**) was subjected to the reaction with catalytic $AuCl_3$ in MeOH. We were pleased to find that the isochromanone **11** was formed in 89% yield (Scheme 6).

(8) (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (b) For a review on gold and platinum catalysis of enyne cycloisomerization, see: Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271.

(9) For a related reaction process with propargyl alcohols, see: (a) Ghebreghiorgis, T.; Biannic, B.; Kirk, B. H.; Ess, D. H.; Aponick, A. *J. Am. Chem. Soc.* **2012**, *134*, 16307. (b) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121. We thank one of the reviewers for suggesting this alternate mechanism instead of a transetherification reaction.

Scheme 6. Formation of the Isochromanone **11** from the Aldehyde **10**

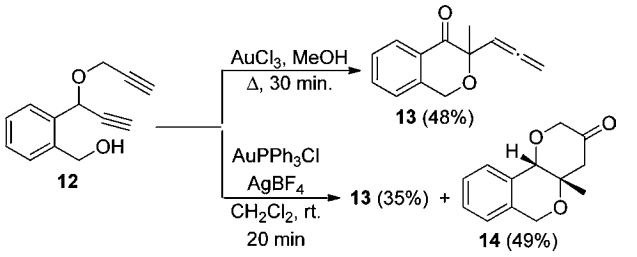


After the successful tandem sequence with the allyl propargyl ethers, we focused our attention on the reaction of analogous *bis*-propargyl ether under similar conditions. This investigation would be interesting because the acetylene functionality can act as a nucleophile in the reaction leading to carbocylic structures, while the cascade reactions described above will lead to the formation of the allene. Numerous examples of diyne cyclizations to carbocyclic compounds by gold catalysis[10] were known in the literature, while gold mediated transetherification[11] and aromatization of *bis*-propargyl ethers[12] were also reported with similar substrates.

Accordingly, treatment of the *bis*-propargyl ether **12** with 2 mol % $AuCl_3$ in MeOH furnished the allene **13** in 48% yield (60% based on the recovered starting compound). It was contemplated that a more electrophilic gold complex such as $AuPPh_3Cl/AgBF_4$ might enhance the allene formation in the reaction. However, treatment of the *bis*-propargyl ether **12** with $AuPPh_3Cl/AgBF_4$ led to the formation of the allene **13** in 35% yield along with the unexpected formation of the tricylic ketone **14** as a single diastereomer in 49% yield (Scheme 7).[13] The structure of the ketone **14** was further confirmed by X-ray crystal structure analysis (Figure 2).[14]

In conclusion, facile synthesis of isochromanones and isoquinolones possessing quaternary centers involving a three-reaction cascade from easily accessible precursors

Scheme 7. Reaction of the *Bis*-propargyl Ether **12** with Catalytic $AuCl_3$



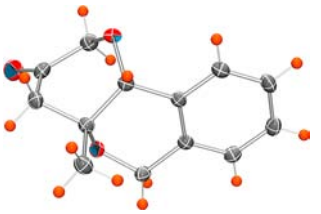


Figure 2. X-ray crystal structure of compound **14**.

was presented. This was the first synthesis of isochromanones and isoquinolones involving gold catalysis. Application of this strategy was demonstrated in the synthesis of isochromanones comprising allene substitution. Further application of this strategy in the synthesis of bioactive natural products is underway.

Acknowledgment. This paper is dedicated with warmth and respect to Prof. Goverdhan Mehta FNA, FRS, National Research Professor, University of Hyderabad, India, on the occasion of his 70th birthday. We thank the Department of Science and Technology (DST), New Delhi for funding of this project. K.R.P. is Swarnajayanthi fellow of DST. C.N. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for a research fellowship. We thank Prof. T. N. Gururow and Mr. K. Durgaprasad for their help in X-ray crystal structure determination of compounds **4f** and **14**.

Supporting Information Available. Full experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(10) (a) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (b) Rao, W.; Koh, M. J.; Kothandaraman, P.; Chan, W. H. *J. Am. Chem. Soc.* **2012**, *134*, 10811.

(11) Georgy, M.; Boucard, V.; Campagne, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

(12) (a) Lian, J.-J.; Chen, P.-C.; Lin, Y.-P.; Ting, H.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 11372. (b) Lian, J.-J.; Liu, R.-S. *Chem. Commun.* **2007**, 1337.

(13) At this stage the mechanism for the formation of the tricylic ketone **14** is unclear. Further investigations are underway to unravel the exact sequence of events leading to **14**.

(14) Crystallographic data were deposited with The Cambridge Crystallographic Data Centre. CCDC No. 930207. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.