Homogeneous Catalysis

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# Rapid Access to Chroman-3-ones through Gold-Catalyzed Oxidation of Propargyl Aryl Ethers**

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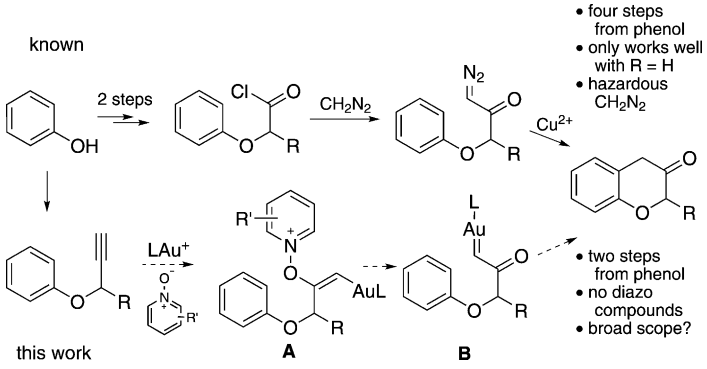
Chroman-3-one is an important structural motif and its derivatives have served as key intermediates in the total synthesis of natural products such as miroestrol,[1] (+)-myristinin A,[2] and afzelechin,[3] as well as in accessing a range of bioactive chromans for managing various diseases including hypertension,[4] HIV,[3] sexual dysfunction,[5] and melanoma.[6] In their 1991 review,[7] Danan and Kirkiacharian concluded that there was a lack of efficient synthetic methods for this structure. Since then, little progress[8] has been made. To date, the 20 year old statement still remains largely true. Invariably, these compounds are prepared through multistep routes[7,9] from basic chemicals. For example, a typical route starts from basic condensation of salicylaldehyde with acrylonitrile to form 2*H*-chromene-3-carbonitrile under refluxing conditions with subsequent basic hydrolysis, acidification, formation of acyl azide, Curtius rearrangement, and acidic hydrolysis of the resulting vinyl isocyanate.[1,9–10] While the overall yield could be as high as 60%,[1] the step[11] and atom[12] economy is low. An alternative approach using toxic α-diazo-α′-phenoxy acetones still requires four steps starting from phenols (Scheme 1),[13] and no application of this method has been reported in the literature because of its limited scope[14] and the clear drawback associated with using dangerous diazomethane. Herein, we report an efficient synthesis of chroman-3-ones through gold-catalyzed oxidation of propargyl aryl ethers, which in turn can be easily prepared in one step from readily available phenols.




***Scheme 1.*** Access to chroman-3-ones via metal carbene intermediates?

We have in the past two years developed several gold-catalyzed intermolecular oxidations of alkynes using pyridine/quinoline N-oxides as oxidants.[15] The common intermediates generated in these reactions were most likely α-oxo gold carbenes, which appeared to be highly reactive and underwent facile O–H,[15b,c] N–H,[15a] or 1,2 C–H insertions[15d] or reaction with nitriles en route to oxazoles.[15e] Several recent reports from other research groups also corroborated the intermediacy of gold carbenes.[16] Since metal carbenes in general can be generated through dediazotization,[17] this strategy permits replacement of the toxic, potentially explosive, and sometimes difficult-to-access α-diazo ketones with benign and readily available alkynes in gold carbene chemistry.[18] In the context of chroman-3-one synthesis, we envisioned that this strategy would allow replacement of α-diazo-α′-phenoxy acetones with readily available propargyl aryl ethers (Scheme 1), thereby establishing a succinct, safe, and potentially highly efficient route to this class of heterocycles.

At the outset, 4-*tert*-butylphenyl propargyl ether (**1a**) was chosen as the substrate for optimization of the reaction conditions. Some of the results are listed in Table 1. When either $Ph_3PAuNTf_2$[19] (entry 1) or the more electrophilic phosphite-coordinated **L1**$AuNTf_2$[20] [**L1** = tris(2,4-di-*tert*-butylphenyl)phosphite; entry 2] was employed as the catalyst and 2,6-dibromopyridine *N*-oxide as the oxidant, both reactions were sluggish, and the desired chroman-3-one **2a** was formed in less than 10% yield.

In our previous work on azetidine-3-one synthesis,[15a] we noticed that gold catalysts based on biphenylphosphine ligands[21] were increasingly effective as the biphenyl moiety became bulkier and BrettPhosAu$NTf_2$ was the optimal catalyst. To our delight, the same trend was observed with this reaction (compare entries 3–5, Table 1), and the chroman-3-one **2a** was formed in 65% yield (NMR) in only 0.5 hours with BrettPhosAu$NTf_2$ as the catalyst (entry 5). In seeking to additionally improve this reaction, we tried $Me_4t$BuXPhosAu$NTf_2$.[22] To our delight, the yield was improved to 78% (entry 6). Single-crystal X-ray diffraction studies established the structure of this effective catalyst (Figure 1). In comparison with BrettPhosAu$NTf_2$ (Figure 1),[15a] the Au1-P1-C2 angle is smaller by 5.52°, and the distance between Au1 and C1′ is shorter by 0.265 Å, thus suggesting that $Me_4t$BuXPhos presses the Au center more towards the shielding 2,4,6-triisopropylphenyl group[23] and thereby increases the steric crowding of the metal center. This

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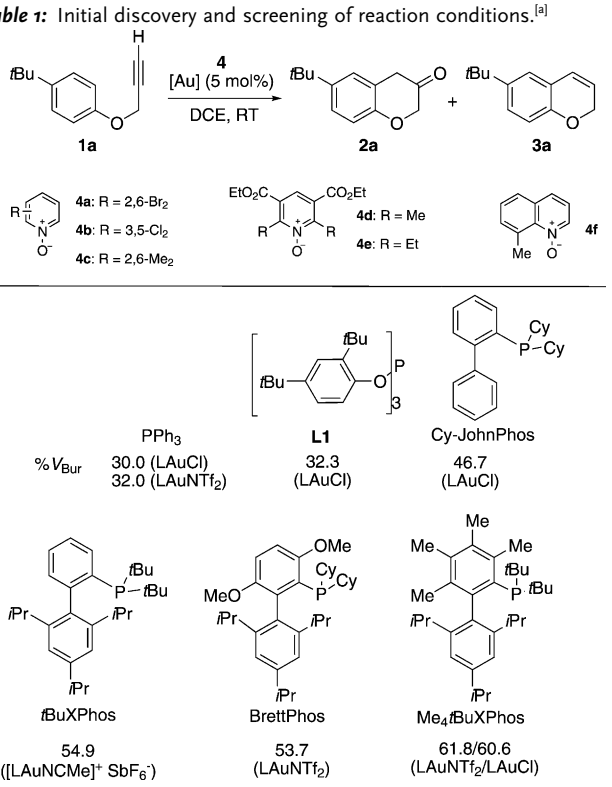
***Table 1:*** Initial discovery and screening of reaction conditions.[a]




| Entry | Catalyst | 4 | *t* [h] | Unreacted **1a** [%][b] | Yield [%][b] **2a** | **3a**[c] |
|---|---|---|---|---|---|---|
| 1 | $Ph_3PAuNTf_2$ | **4a** | 16 | 41 | 6 | – (66) |
| 2 | **L1**$AuNTf_2$ | **4a** | 16 | 58 | 7 | – (73) |
| 3 | Cy-JohnPhos$AuNTf_2$ | **4a** | 16 | 17 | 9 | 2 (64) |
| 4 | *t*BuXPhos$AuNTf_2$ | **4a** | 16 | – | 27 | 4 (76) |
| 5 | BrettPhos$AuNTf_2$ | **4a** | 0.5 | – | 65 | 4 (87) |
| 6 | $Me_4$*t*BuXPhos$AuNTf_2$ | **4a** | 0.5 | – | 78 | 8 (79) |
| 7 | $Me_4$*t*BuXPhos$AuNTf_2$ | **4b** | 15 | 18 | 38 | < 2 |
| 8 | $Me_4$*t*BuXPhos$AuNTf_2$ | **4c** | 15 | 39 | 29 | 8 |
| 9 | $Me_4$*t*BuXPhos$AuNTf_2$ | **4f** | 15 | 10 | 45 | 5 |
| 10 | $Me_4$*t*BuXPhos$AuNTf_2$ | **4d** | 1 | 6 | 76 | ca. 2 |
| 11 | $Me_4$*t*BuXPhos$AuNTf_2$ | **4d**[d] | 1 | – | 84[f] | ca. 2 |
| 12 | $Me_4$*t*BuXPhos$AuNTf_2$ | **4e**[e] | 1 | – | 87 | ca. 2 |

[a] [**1a**] = 0.05 M, and 1.1 equiv of the oxidant **4**. [b] Estimated by $^1$H NMR spectroscopy using diethyl phthalate as the internal reference. [c] Yield in parentheses is that for a reaction run without the oxidant, and the reaction time was 1 h except for reactions with BrettPhos$AuNTf_2$ (15 min) and $Me_4$*t*BuXPhos$AuNTf_2$ (25 min). [d] 1.3 equivalents. [e] 1.2 equivalents. [f] Yield of isolated product: 82%. DCE = 1,2-dichloroethane. The $\%V_{Bur}$ values were calculated by SambVca[24a] using ligand coordinates from the X-ray structure of the gold complex indicated within the parentheses.

crowding is reflected by its $\%V_{Bur}$ value[24,25] (61.8 based on the X-ray structure of its $AuNTf_2$ complex and 60.6 on its AuCl complex[22c]), which is significantly higher than that of BrettPhos[26] (53.7 $\%V_{Bur}$ based on the X-ray structure of its $AuNTf_2$ complex[15a]). In fact, $Me_4$*t*BuXPhos has a higher $\%V_{Bur}$ value than any of the $Au^I$ ligands investigated by Clavier and Nolan.[25] This bulky ligand likely prevents the corresponding gold carbene **B** (Scheme 1) from deleterious intermolecular side reactions as the carbene center is sterically shielded, and thereby leads to increased efficiency.

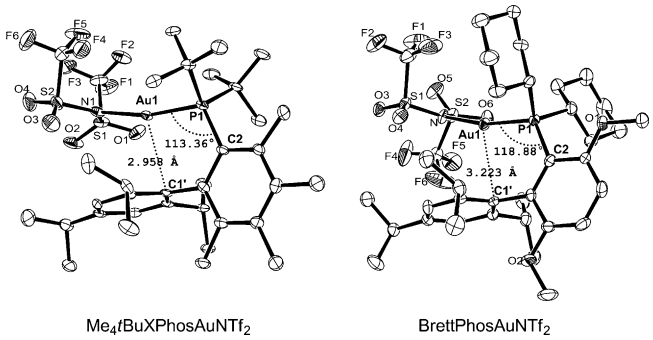
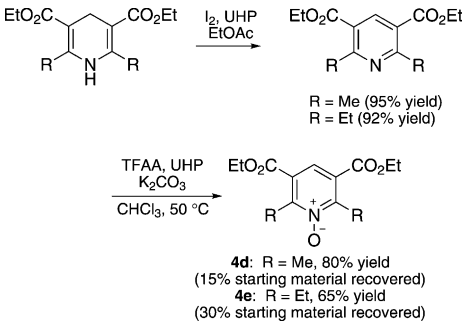



***Figure 1.*** Ortep ellipsoid drawing of complexes $Me_4$*t*BuXPhos$AuNTf_2$[29] and BrettPhos$AuNTf_2$[15a] are shown at 50% probability. The hydrogen atoms have been omitted for clarity.

Notably, Barriault and co-workers[22c] recently reported that $[Me_4$*t*BuXPhosAuNCMe$]^+SbF_6^-$ is the best catalyst for promoting 6-*endo-dig* cyclizations selectively over typically favored 5-*exo-dig* ones.

In these reactions, only small amounts of the benzopyran **3a** were formed through a competitive gold-catalyzed 6-*endo-dig* cyclization. However, in the absence of the oxidant **4a**, this cyclization was facile and generally efficient in the presence of a range of gold catalysts (see yields in parenthesis in entries 1–6, Table 1).[27] These results suggested that the N-oxide, besides being the oxidant, played the requisite role of retarding this side reaction, most likely as a result of its coordination to the gold catalyst.

Other oxidants that we previously used[15] did not improve the reaction (entries 7–9, Table 1). However, it was clear that hindered and electron-deficient N-oxides fared better. Consequently, we prepared the pyridine *N*-oxides **4d** and **4e** by double oxidation of the corresponding Hantzsch esters (Scheme 2), which can be easily prepared.[28] To the best of our knowledge, these hindered and electron-deficient N-oxides have never been used as oxidants before. Gratifyingly, with 1.3 equivalents of **4d**, the reaction yield was improved to 84% (entry 11); a better yield was obtained with the even more hindered **4e** (entry 12).

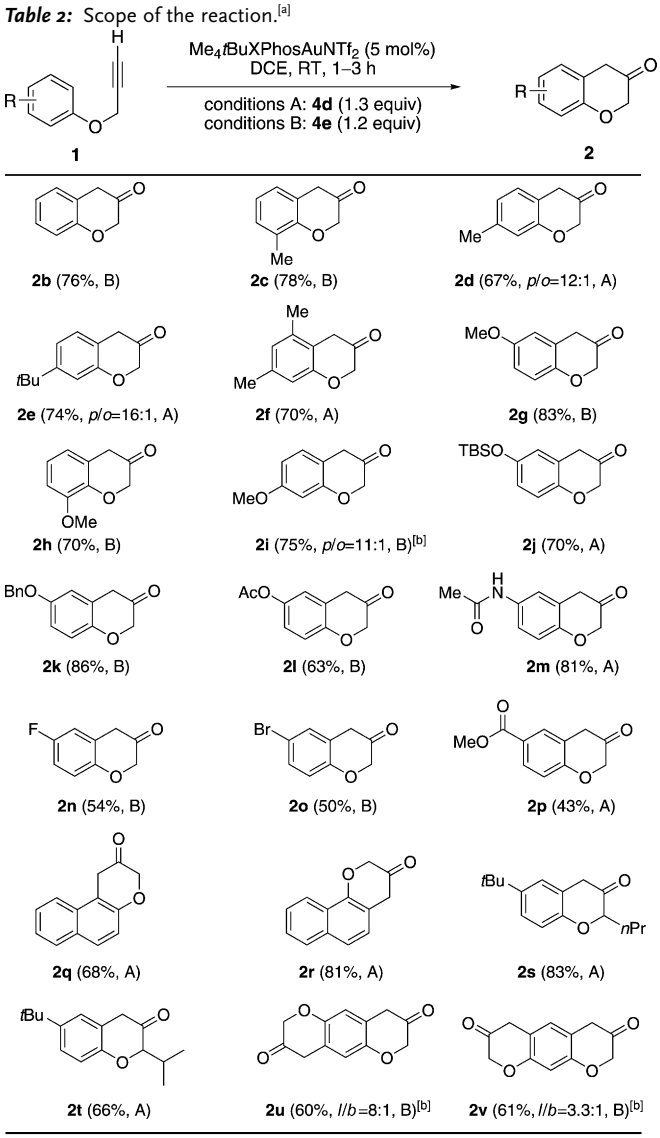



***Scheme 2.*** Synthesis of the pyridine *N*-oxides **4d** and **4e**. TFAA = trifluoroacetic anhydride, UHP = urea hydrogen peroxide.

With $Me_4$*t*BuXPhos$AuNTf_2$ as the catalyst and **4d** or **4e** as the oxidant, we explored the reaction scope (Table 2). For the parent phenyl propargyl ether, the unsubstituted chroman-3-

***Table 2:*** Scope of the reaction.[a]




[a] The reactions were run in a vial without exclusion of air and moisture, and the substrate concentration was 0.05 M. Yields of isolated products are reported. [b] The reaction was run at 0 °C. Bn = benzyl, TBS = *tert*-butyldimethylsilyl. *l*/*b* = linear/bent.

one **2b** was obtained in 76% yield. An *ortho*-methyl substitution on the benzene ring was inconsequential (**2c**). The cyclization in the case of a *meta*-methyl group (**2d**) was highly regioselective, thus favoring the position *para* to the methyl group; an even higher regioselectivity was achieved with a *tert*-butyl-substituted substrate (**2e**). A second methyl substitution on the benzene ring did not affect the reaction yield much (**2f**). Substrates with methoxy substituents at different positions on the ring reacted smoothly, thus affording corresponding products in good yields (**2g–i**). Importantly, the regioselectivity in the case of a *meta*-methoxy group (**2i**) could be improved to 11:1 when the reaction was run at 0 °C. Notably, these chroman-3-ones, that is **2g–i**, were previously prepared from more costly methoxy-substituted salicylaldehydes following the aforementioned multistep sequence, and the overall yields were mostly less than 41 %.[9] The functional group tolerance of this chemistry is good as substrates with a TBS ether (**2j**), a benzyl ether (**2k**), an acetate (**2l**), and a secondary amide (**2m**) all reacted well. With electron-withdrawing groups including halides (**2n**,**o**) and methoxycarbonyl (**2p**), the reactions were less efficient albeit still useful considering the short sequences. This chemistry also worked well with naphthalene substrates (**2q**,**r**), showing excellent regioselectivities.

Aliphatic substitutions at the propargyl position, including the sterically demanding isopropyl group, were readily tolerated (**2s**,**t**). Notably, the diazo ketone approach could not afford this type of 2-alkyl-substituted product cleanly becasue of a major side reaction leading to norcaradiene side products.[14] In the case of a phenyl group at the propargylic position, the yield was low (< 40 %), and was likely due to the sensitivity of the substrate in the presence of the Lewis acidic gold complex. With the bis(ether) substrate derived from *p*-hydroquinone, double oxidative cyclization occurred smoothly to afford the linear tricycle **2u** selectively in a respectable yield. A similar reaction was achieved with the substrate derived from resorcinol although the regioselectivity was moderate (**2v**).

In summary, we have developed a one-step synthesis of chroman-3-ones from readily available propargyl aryl ethers. In comparing our method with literature protocols, this gold oxidation approach is step-economic and efficient, and should facilitate research involving this versatile heterocycle. A new gold catalyst, $Me_4$*t*BuXPhosAuNTf$_2$, was prepared and fully characterized. Its hindered nature is revealed by X-ray diffraction studies. This study as well as the work of Barriault and co-workers suggests that cationic gold complexes based on $Me_4$*t*BuXPhos can be uniquely effective and should be included in the ligand repertoire of practitioners interested in gold catalysis. In addition, two easily accessible pyridine *N*-oxides derived from Hantzsch esters were and shown to be highly effective oxidants; they should help facilitate the development of gold-catalyzed alkyne oxidation reactions, which promise excellent step economy and synthetic efficiency.

## *Experimental Section*

General procedure: Pyridine *N*-oxide **4d** (0.65 mmol, 1.3 equiv) or **4e** (0.6 mmol, 1.2 equiv), and $Me_4$*t*BuXPhosAuNTf$_2$ (0.025 mmol, 5 mol %) were added sequentially to a solution of the propargyl aryl ethers **1** (0.50 mmol) in DCE (10 mL. 0.05 M) at room temperature. The resulting reaction mixture was stirred at RT, and the progress of the reaction was monitored by TLC. The reaction typically took 1–3 h. Upon completion, the mixture was concentrated and the residue was purified by silica gel flash chromatography (eluent: hexanes/ethyl acetate) to afford the desired products **2**.

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[29] CCDC 860147 ($Me_4tBuXPhosAuNTf_2$) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

  