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Electrophilic carbon transfer in gold catalysis: synthesis of substituted chromones

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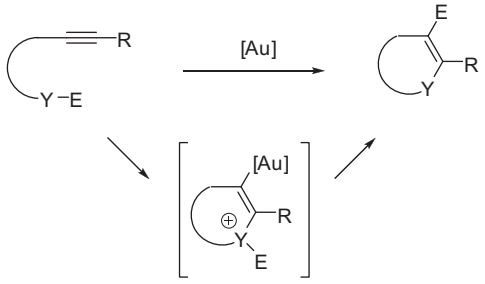
ABSTRACT

Using easily accessible aromatic alkoxy-arylalkynones, we have investigated the gold-catalyzed intramolecular addition of ethers to alkynes, to give easy access to various substituted chromones. This reaction involves the transfer of the ether substituent via a carbodemetallation process. We also noticed a competing isomerization of several starting materials for which we propose a second gold catalyzed mechanism.

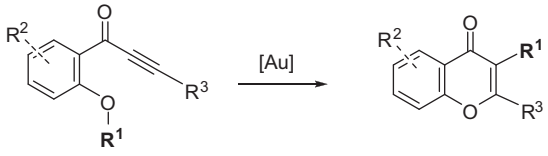
1. Introduction

Over the past few years, transition metal-catalyzed reactions have gained great importance as synthetic methods in heterocyclic chemistry. Thus, gold-catalyzed addition of heteroatoms across carbon–carbon unsaturated bonds -providing key structures of natural products and organic materials- has attracted significant interest.[1] In a large number of gold-catalyzed reactions, the catalytic cycle is completed by trapping of a vinyl–gold intermediate with a proton, so-called protodemetallation. Recently, several groups have disclosed that such intermediates can also be captured by other electrophiles[2] or used in carbon–carbon cross-coupling strategies via transmetallation.[3] In this context, one approach consists of replacing the proton on the heteroatom (Y) responsible for the cyclization process by another electrophilic group (E). Then the reaction proceeds through a [1,3] shift of the migrating group (Scheme 1).

The aim of the present work was to investigate the utility of gold catalysts for the activation of alkynes toward the intramolecular addition of ethers followed by carbodemetallation for the synthesis of substituted chromone derivatives with potential biological activities.[4] The use of an alkoxy group instead of hydroxyl allows a carbon transfer during the catalytic heterocyclization (Scheme 2).



Scheme 1. Electrophilic transfer in heterocyclization.



Scheme 2. Gold catalyzed synthesis of chromones.

2. Results and discussion

The initial model for the optimization of this reaction was allyloxyphenylpropynone **1** that was easily prepared in two steps from the commercially available 2-(allyloxy)benzaldehyde.[5] In our initial attempts, in accordance with previous results,[6] we used triphenylphosphine gold chloride (PPh_3AuCl, 10 mol %) associated

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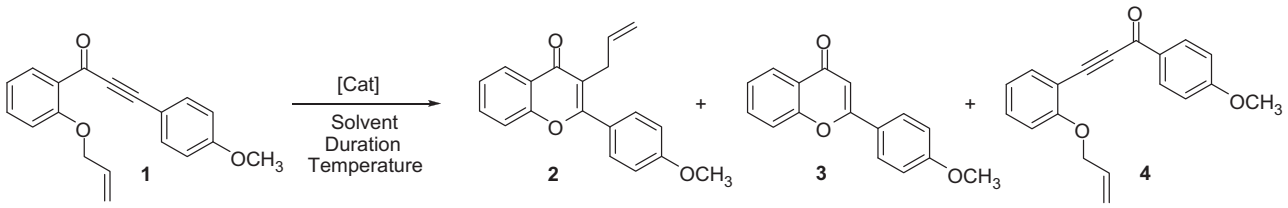


Scheme 3. Reaction observed from **1**.

Table 1
Influence of the catalytic system on the formation of compound **2**

Entry	Conditions	Yield[a] (%)			
		1	**2**	**3**	**4**
1	$PPh_3AuCl/AgOTf$, 0.5 h, 50 °C	0	43	20	36
2	$PPh_3AuCl/AgBF_4$, 0.5 h, 50 °C	0	45	20	21
3	$PPh_3AuCl/AgSbF_6$, 0.5 h, 50 °C	0	57	0	20
4	$PPh_3AuCl/ AgSbF_6$, 0.5 h, rt	0	52	15	27
5	PPh3AuCl/ $AgSbF_6$, 1 h, 50 °C	0	57	0	15
6	PPh_3AuCl, 0.5 h, 50 °C	100	0	0	0
7	$AgSbF_6$, 0.5 h, 50 °C	100	0	0	0

[a] Estimated by ^1H NMR using 1,4-dinitrobenzene as internal reference.

to a silver co-catalyst (AgOTf, 10 mol %) in 1,2-dichloroethane (DCE) for 3 h. The first experiments were carried out at room temperature in the presence of molecular sieves (4 Å) to limit a possible harmful role of water. These conditions allowed a complete conversion of the starting material but a low yield of compound **2** (23%) was obtained (Scheme 3). Starting with this model, we varied the catalytic system, duration and temperature. In most cases, besides the expected chromone, two major compounds were identified: the chromone **3—**resulting from a simple protodeauration- and the isomeric ketone **4** of the starting material. This isomerization reaction is likely to be related to the Meyer–Schuster rearrangement.[7] The ratio of these compounds could be evaluated by ^1H NMR analysis of the crude material.

The influence of the catalytic system was studied and the results are presented in Table 1. In each case, the reaction was conducted in DCE. Some differences could be noted in the formation of the expected compound **2** with various silver sources (entries 1–3) with a slightly better conversion with $AgSbF_6$ as a co-catalyst. At room temperature (entry 4), the expected compound **2** was obtained together with the chromone **3**.

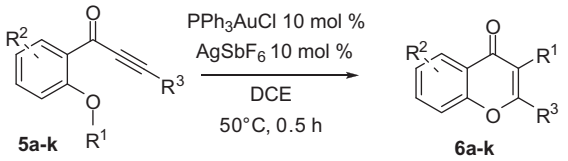
A complementary study concerning the time of reaction (entry 5) exhibited product distribution differences. After 1 h, **3** disappeared from the reaction medium and compound **4** with a better stability remained visible (from 25% to 15% compared to the internal standard). The expected chromone **2** was present in a constant amount of 57%. Complementary studies on solvents prompted us to use DCE that was clearly found more efficient than dichloromethane, chlorobenzene or acetonitrile.

In order to investigate the role of water, three reactions were carried out in the presence or absence of molecular sieves and with the addition of 20 equiv of water in DCE. Comparable results showed no obvious role of water in the reaction. Variation in the percentage of the catalytic system (1 and 5 mol %) only delayed the accomplishment of this reaction (8 h and 15 min, respectively). The absence of reaction with PPh_3AuCl or $AgSbF_6$ attested the role of the co-catalyst (entries 6–7).

With these results in hand, we decided to investigate the scope of the reaction on various analogous substrates. The compounds **5a–k** were prepared either from salicylaldehydes or salicylic acids.[5] Salicylaldehydes were *O*-alkylated and reacted with ethynyl-lithium salts to give the corresponding secondary alcohols. These latter were then oxidized to give the final ketones **5a**, **5c–d**, **5f–k**. Salicylic acids were converted into their Weinreb amides and were reacted with ethynyl-lithium salts to yield **5b** and **5e**. The alkynones **5a–k** were then reacted under 'standard conditions'.[8] The results are presented in Table 2.

In most cases, the expected compounds **6a–k** were obtained in modest isolated yields.[9] In many cases incomplete transfer of the R^1 group was observed. In the case of compound **5g**, **7** (Fig. 1) was obtained at the sole product (27%). A competing isomerization of starting material was also observed and sometimes impaired the chromone formation. Thus, **8** and **9** (Fig. 1) were the unique compounds isolated in 65% and 48% yields, respectively, from **5j** and **5k**. In the case of the reaction of **5e**, possessing an electron-rich aromatic ring at the R^3 position, in addition to the loss of R^1 group, we also observed the presence of **10a** and **10b** (8% and 12% isolated yield, respectively).

Table 2
Results obtained from compounds **5a–k** to **6a–k**



	R^1	R^2	R^3	Product	Yield[a] (%)		R^1	R^2	R^3	Product	Yield[a] (%)
5a	Ph-CH_2–	3-MeO-	*n-Pr-*	**6a**	45	**5g**	4-MeO-Bn-	H-	*n-Pr-*	**6g**	0[b]
5b	Ph-CH_2–	H-	*n*-Pr-	**6b**	31	**5h**	Allyl-	H-	Ph-	**6h**	38
5c	Ph-CH_2–	3,5-Br-	*n*-Pr-	**6c**	40	**5i**	Allyl-	H-	H-	**6i**	35
5d	Ph-CH_2–	3-Allyl-	*n*-Pr-	**6d**	38	**5j**	Et-	H-	*n*-Pr-	**6j**	0[c]
5e	Ph-CH_2–	H-	4-MeOPh-	**6e**	25	**5k**	Et-	H-	Ph-	**6k**	0[d]
5f	4-Cl-Bn–	H-	*n*-Pr-	**6f**	40						

[a] Isolated yield.
[b] Only compound **7** was isolated (27%).
[c] Isomer **8** was isolated (65%).
[d] Isomer **9** was isolated (48%).

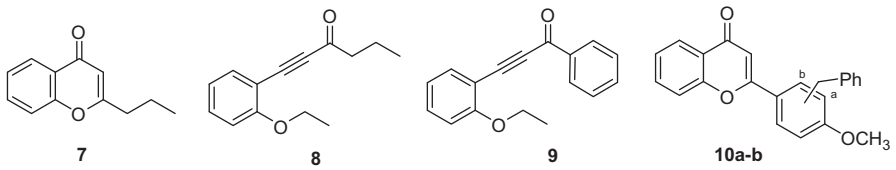
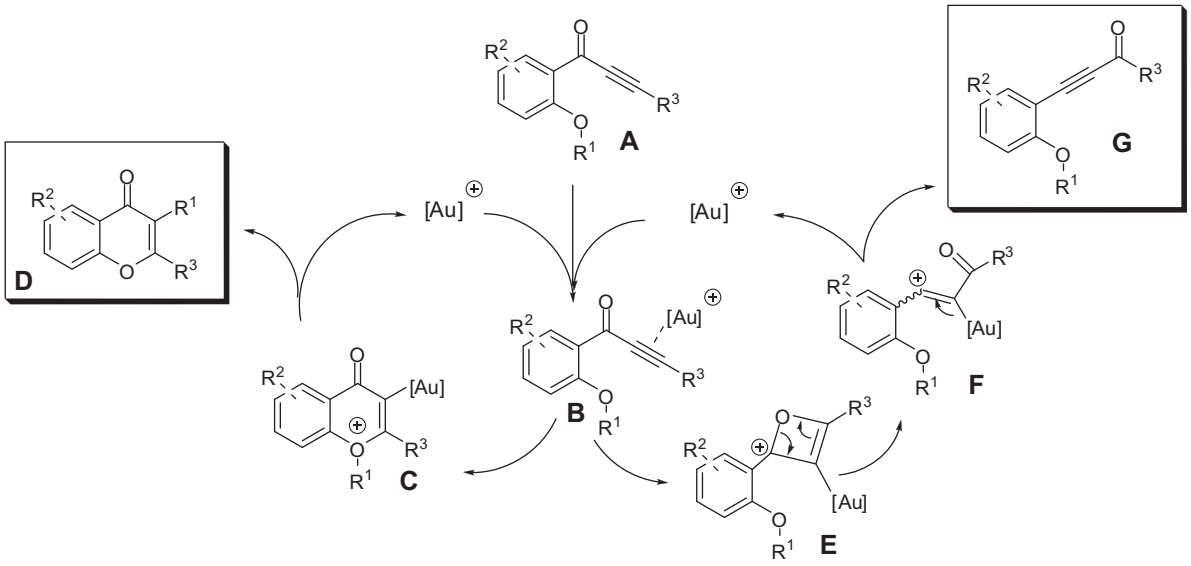


Figure 1. Structures of compounds **7**, **8**, **9**, **10a** and **10b**.

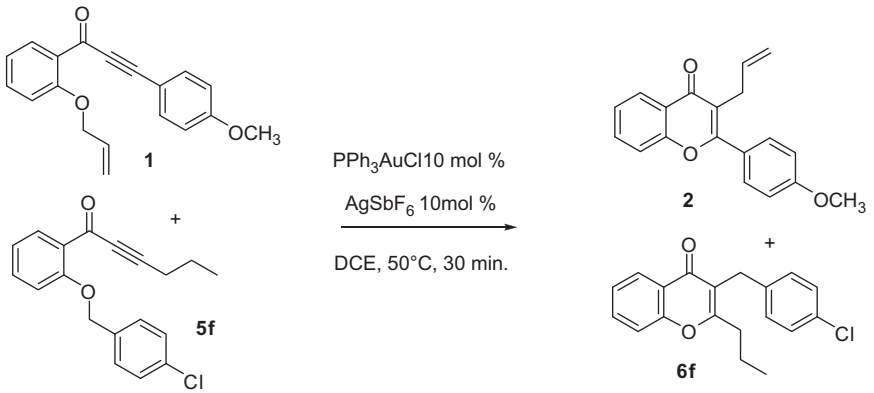
We propose catalytic cycles for these reactions (Scheme 4). The 'normal reaction'—resulting in a chromone formation—could proceed through a gold activation of the alkyne bond of the starting material **A**. Attack of the oxygen lone pair of **B** to the activated alkyne can lead to the cyclic intermediate **C**. After the transfer of the R^1 substituent, gold(I) and cyclization product **D** are liberated. In this reaction, the nature of the [1,3] migration has not been clearly elucidated to date. The intramolecular nature of the rearrangement was examined by the reaction of two mixed starting materials, alkynones **1** and **5f** (Scheme 5).

After 30 min under the standard experimental conditions, no traces of possible 'cross-reaction' could be detected. We only isolated the expected products **2** and **6f** in usual yields together with the usual by-products obtained in the individualized reactions. Yet, when the reaction was performed in the presence of phenylethanol in order to trap the carbocation intermediate—as studied by Asao[10]—traces of the corresponding ether could be obtained. Furthermore, the little isolation of **10b** ([1,4] transfer) suggests a carbocation mechanism in this process instead of a [1,3] sigmatropic rearrangement, as suggested by Yamamoto and co-workers[11] in a study of chirality transfer in a gold-catalyzed formation of benzothiophenes. Finally, it seems that transfer of the carbon group is governed by proximity effect, given that **10b** is favored over **10a** despite the activating electronic effect of the methoxy group.

The unexpected isomerization of several starting materials was also noticed and was especially favored when R^1 was an alkyl group. We propose the formation of an oxetenium intermediate **E** that could explain the formation of isomerization product **G**. Such an intermediate has been previously proposed by Yamamoto and coworkers for the gold-catalyzed intramolecular carbocyclization of alkynyl ketones[12] and by Bégué and Malissard in the $AgSbF_6$-promoted dehalogenation of α-bromoketones to form β,γ-unsaturated



Scheme 4. Proposed catalytic cycles for the synthesis of substituted chromones versus isomerization.



Scheme 5. Reaction observed for a mixture of **1** and **5f**.

enones.[13] To the best of our knowledge, no similar isomerization reactions of alkynyl ketones have been reported to date.

In conclusion, we have developed a new gold catalyzed reaction proceeding via activation of an alkyne group toward the intramolecular addition of an ether functionality, followed by carbodemetallation to give a substituted chromone derivative. Further investigation of mechanistic details in the isomerization reaction should render this reaction quite attractive in synthesis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.018.

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5. For the syntheses of compounds **1**, **5a–i**, see Supplementary materials.
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8. *Representative synthesis of chromone* ***2***: To a solution of alkynone **1** (0.1 mmol) in 1,2-dichlorethane under argon were added PPh_3AuCl (0.01 mmol) then $AgSbF_6$ (0.01 mmol). The suspension was stirred and heated at 50 °C for 30 min under argon. After filtration over celite and concentration under vacuum, compound **2** was purified using a flash chromatography. ^{1}H NMR 300 ($CDCl_3$): δ_H 3.34 (dt, J = 1.75 Hz, J = 5.60 Hz, 2H), 3.89 (s, 3H), 5.07 (m, 2H), 6.09 (m, 1H), 7.03 (m, 2H), 7.42 (m, 2H), 7.66 (m, 3H), 8.25 (dd, J = 7.95 Hz, J = 1.40 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ_C 30.2, 55.4, 113.8, 115.3, 117.8, 118.8, 122.8, 124.7, 125.6, 126.0, 130.2, 133.3, 136.2, 156.1, 161.2, 162.3, 178.1. HRMS (EI): Calcd for $C_{19}H_{16}O_3Na$: 315.0997. Found 315.0994, (57%).
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