

Complex Chromene Derivatives through a Silver-Catalysed Cascade Reaction of Simple *o*-Alkynylsalicylaldehydes and Alkenes

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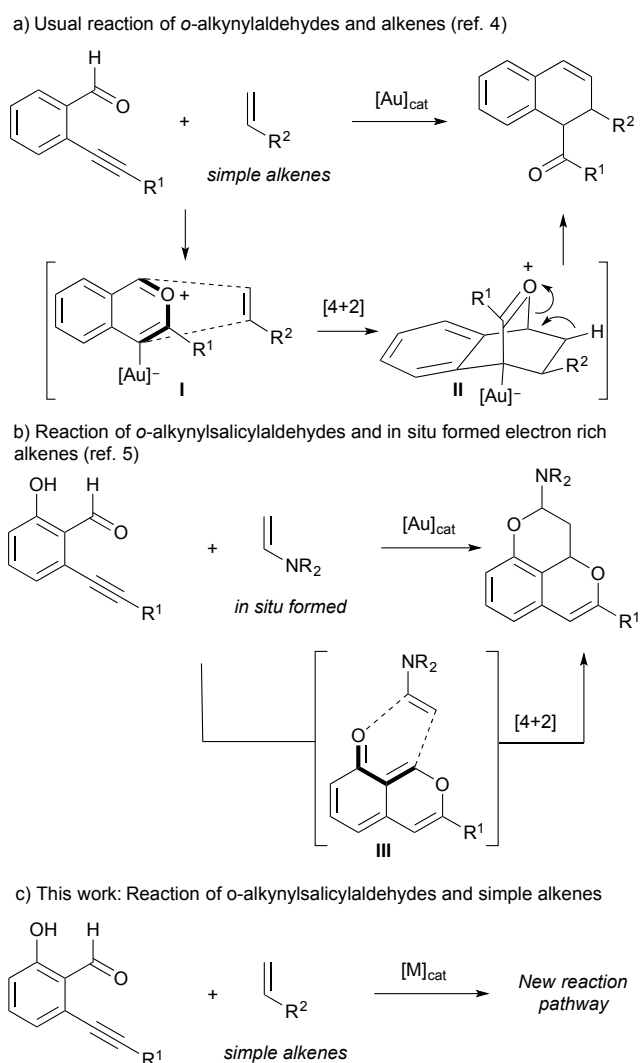
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The silver-catalysed reaction of simple *ortho*-alkynylsalicylaldehydes and alkenes gives complex benzo[*de*]chromenyl ketones through an unusual cascade process where the starting *ortho*-alkynylsalicylaldehyde behaves as a bis-diene derivative that participates in two different formal [4+2]-cycloaddition reactions.

ortho-Alkynylbenzaldehydes have become valuable reagents for the synthesis of a wide range of interesting complex molecules.^{1–3} In this context, the reaction of *ortho*-alkynylbenzaldehydes with alkenes under gold-catalytic conditions usually leads to the formation of dihydronaphthalene derivatives (Scheme 1a).⁴ This reaction proceeds through the formation of an isochromenylium intermediate I that participates in a subsequent [4+2]-cycloaddition reaction with the alkene to form intermediate II. This intermediate evolves to the final product by a ring-opening reaction followed by a formal protodemetalation process. Recently, we have found that *ortho*-alkynylbenzaldehydes derived from salicylaldehyde (*ortho*-alkynylsalicylaldehydes) react with *in situ* formed alkenes (enamine derivatives) to form pyrano[2,3,4-*de*]chromenes (Scheme 1b).⁵ This reaction proceeds through a mechanism alternative to that above commented for conventional *ortho*-alkynylbenzaldehydes and implies the formation of an isochromanone intermediate III that acts as the heterodiene counterpart in a subsequent formal [4+2] cycloaddition reaction.⁶ In this context, we became interested in exploring the reactivity of *ortho*-alkynylsalicylaldehydes with simple alkenes (Scheme 1c). More precisely, we wanted to know the way this particular type of *ortho*-alkynylbenzaldehydes behaved in the presence of alkenes not necessarily *in situ* formed. We were curious to know if dihydronaphthalene derivatives, coming from a conventional route (Scheme 1a), or

pyrano[2,3,4-*de*]chromenes, derived from our recently found new route (Scheme 1b), would be obtained. However, as it will be shown, unanticipated results were observed.



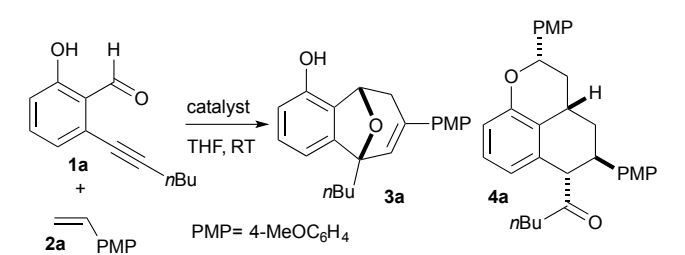
Scheme 1. Reactivity of *ortho*-alkynylbenzaldehydes and alkenes.

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We started our investigation by studying the model reaction shown in Table 1 where *ortho*-alkynylsalicylaldehyde **1a** and 4-methoxystyrene **2a** were chosen as starting materials. In our initial experiments we used different gold catalysts. With this type of catalysts we were expecting the formation of dihydronaphthalene or pyrano[2,3,4-*de*]chromene derivatives (Scheme 1). Surprisingly, we were not able to identify the formation of these compounds in any of our attempts. In fact, the formation of a complex mixture of unidentified products was observed when the reaction was performed with cationic gold(I) complexes or gold(III) chloride (Table 1, entries 1-3). No improvements were observed by the addition of typical protic acids or bases as co-catalysts.

Table 1. Initial experiments. Screening of catalysts.^a



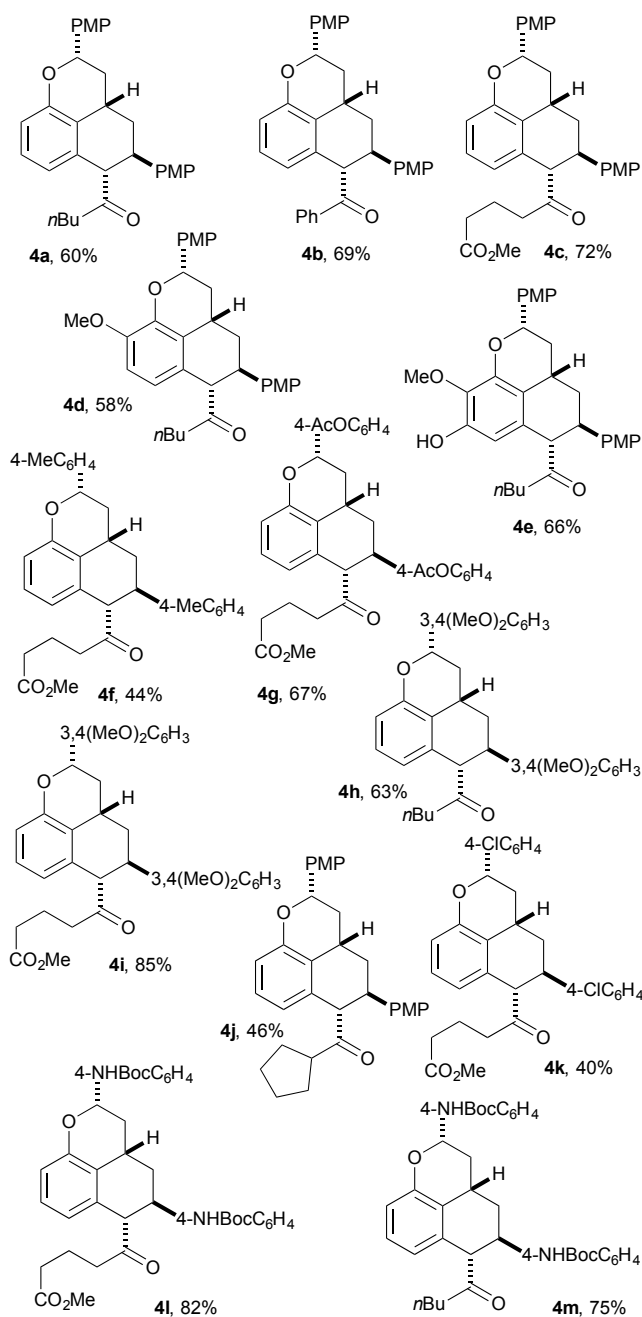
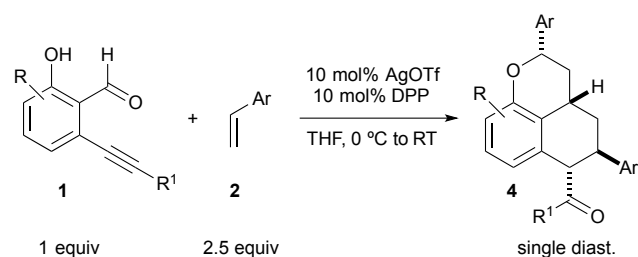
Ent	Catalyst	Products	Yield (%) ^b
1	AuCl(Ph ₃ P) / AgOTf	- ^{c,d}	-
2	AuNTf ₂ (JohnPhos)	- ^{c,d}	-
3	AuCl ₃	- ^{c,d}	-
4	Pd(OAc) ₂	- ^{c,d}	-
5	PtCl ₂	3a	83
6	PtCl ₄	3a	80
7	AgOTf	4a	20
8	AgOTf / DPP ^e	4a	60
9	AgOTf / BEMP ^f	- ^c	-
10	DPP	- ^g	-

^a The reactions were performed by adding the catalyst (5 mol%) to a solution of **1a** (1 equiv) and **2a** (2.5 equiv) at 0 °C and then allowing the reaction to stir at room temperature for 8-12 hours. ^b Isolated yield based on **1a**. ^c Mixture of undefined products. ^d No improvements were observed by the addition of typical protic acids or bases as co-catalysts. ^e 10 mol% of DPP [(PhO)₂PO₂H] was added along with the silver catalyst. ^f 10 mol% of BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine) was added along with the silver catalyst. ^g Reaction performed only with 10 mol% of DPP [(PhO)₂PO₂H]. The starting materials were recovered unreacted after 12 hours at room temperature.

In view of these negative results observed under gold catalytic conditions, we tried the reaction with other π -acid catalysts. However, similar disappointed results were observed with the palladium(II) catalyst, Pd(OAc)₂ (Table 1, entry 4). When the reaction was performed with platinum(II or IV) catalysts (PtCl₂ or PtCl₄) we observed the clean formation of the 5,9-epoxybenzo[7]annulene derivative **3a** (Table 1, entries 5,6). It should be noted that formation of products similar to **3a** has been observed by other authors in reactions performed with typical *ortho*-alkynylbenzaldehydes.⁷ This means that under

platinum-catalysed conditions our *ortho*-alkynylsalicylaldehyde **1a** did not show any differential reactivity if compared with conventional *ortho*-alkynylbenzaldehydes. But, an unexpected result was observed when silver triflate was used as catalyst and formation of the benzo[*de*]chromenyl ketone derivative **4a** was detected (Table 1, entry 7). It should be noted that the silver-catalysed reaction of conventional *ortho*-alkynylbenzaldehydes with styrene derivatives had been previously reported to give cyclopropane derivatives.⁸ However, as shown in Table 1 (entry 7) when *ortho*-alkynylsalicylaldehyde **1a** was used, we did not observe the formation of such cyclopropane derivative and instead, the benzo[*de*]chromenyl ketone derivative **4a** was isolated in low yield (20%). Some remarkable features of this reaction should be noted. Thus, a relatively complex product with an interesting architecture was formed from two very simple starting materials in a process where four new bonds, a formal migration of the oxygen of the initial aldehyde functionality and the incorporation of two units of the styrene had occurred. The stereoselectivity of the process was also noteworthy as four new stereocentres were selectively formed. The interest of accessing molecules such as **4a**, a chromene derivative, should also be remarked upon at this point. In fact, chromenes are considered privileged structural motifs. Their interesting biological activity and extensive pharmacological applications has resulted in a renewed interest about the development of new methods to get this type of molecules.⁹ For these reasons, we tried to optimize the above commented initial result and we found that the yield could be improved when the reaction was performed in the presence of 10 mol% of diphenyl hydrogen phosphate [DPP, (PhO)₂PO₂H]. Under these conditions, compound **4a** could be isolated in 60% yield (Table 1, entry 8). On the contrary, the presence of a non-coordinating base (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine; BEMP) completely inhibited the process (Table 1, entry 9). As expected, DPP alone was not able to promote any reaction (Table 1, entry 10).

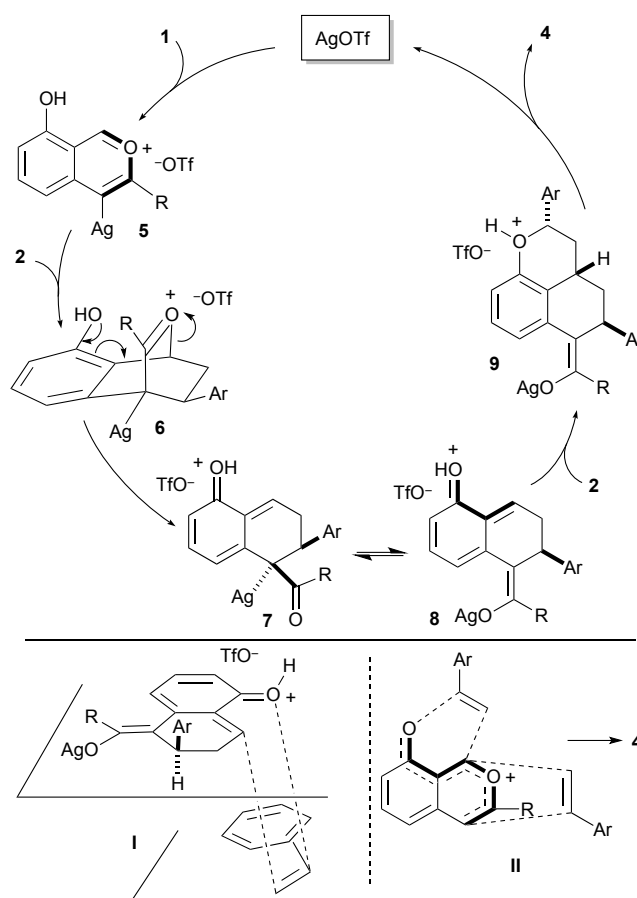
With optimal reaction conditions in hand, we next studied the scope of this new silver-catalysed reaction. As summarized in Scheme 2, the catalytic process could be successfully applied to a variety of *ortho*-alkynylsalicylaldehydes **1** and styrene derivatives **2**. Both, aliphatic and aromatic substituents were allowed at the terminal position of the alkyne of **1** (R¹). However, a lower yield was observed for compound **4j** containing a relatively bulky cyclopentyl substituent. *ortho*-Alkynylsalicylaldehydes **1**, which are substituted at the aromatic ring (R), are also appropriate substrates for this reaction (**4d,e**). Regarding the styrene derivative, the reaction seems to work better when the arene is decorated with electron-donating groups. Finally, the reaction did not provide the expected products **4** for styrene derivatives containing electron-withdrawing groups at the aromatic ring. Remarkably, the reaction was totally diastereoselective and thus, a single diastereoisomer was isolated in all cases.



Scheme 2. Scope of the reaction of synthesis of benzo[de]chromenyl ketone derivatives **4**.

A plausible mechanism for the formation of products **4** is shown in Scheme 3. First, we propose a typical

cycloisomerization of the *ortho*-alkynylsalicylaldehyde **1** to give the isochromenylium **5**. This type of intermediates is known to react with alkenes through a formal [4+2] cycloaddition reaction to produce the new intermediate **6** that evolves through a ring opening process to give **7**. This ketone may be in equilibrium with silver enolate **8** in which an activated heterodiene (shown in bold) can be distinguished. A new formal [4+2] cycloaddition reaction between this diene and alkene **2** delivers the tricyclic intermediate **9**. Protodemetalation of the later regenerates the silver catalyst and affords an enol derivative that is the direct precursor of the final ketone **4**. The enhanced yield observed when the reactions are performed in the presence of diphenyl hydrogen phosphate (DPP) could be explained considering that this protic acid favours the final protodemetalation step improving the global catalyst efficiency.



Scheme 3. Mechanistic proposal.

The stereochemistry observed in the final products **4** can be understood attending to the formal cycloaddition between the heterodiene **8** and the styrene derivative **2**. Thus, in order to avoid steric hindrance, it is supposed that the styrene **2** approach the diene **8** from the opposite face where the aromatic substituent (Ar) is placed and following an *endo*-trajectory (see I in the bottom part of Scheme 3). This

approach would justify the stereochemistry observed in three of the four stereocentres of **4**. The final stereocentre is generated when the enol derived from **9** is converted into the final ketone **4**. This transformation should occur in such a way that the more stable isomer, where the ketone and the vicinal aryl group are disposed in a *trans*-disposition, is formed. In fact, this is the relative stereochemistry observed in the final product **4**. Interestingly, considering the global transformation, the very simple *ortho*-alkynylsalicylaldehydes **1** could be formally considered as “bis-diene equivalents” that participate in two different [4+2] cycloaddition (see **II** in Scheme 3).¹⁰

In summary, we have found a new mode of reactivity of *ortho*-alkynylsalicylaldehydes and we have discovered that these simple molecules can be selectively transformed into complex benzo[*de*]chromenyl ketones through a silver-catalysed reaction with styrenes. These results further demonstrate the very rich and atypical reactivity of *ortho*-alkynylsalicylaldehydes. Indeed, in this work we show that this simple molecule may behave as an unusual bis-diene equivalent that participates in two consecutive formal [4+2] cycloaddition processes. The interest of the molecules obtained by the new reaction here described (chromene derivatives) in the context of medicinal chemistry should also be remarked. In this sense, our reaction offers a straightforward method to get complex products that are otherwise difficult to reach. The potential applicability of the reaction to identify new drug candidates is being considered.

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Silver triflate catalyses a complex transformation of simple *ortho*-alkynylsalicylaldehydes and alkenes to give benzo[*de*]chromenyl ketones in a process that involves two formal [4+2]-cyclization reactions.

