Gold Catalysis

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Gold(I)-Catalyzed Generation of the Two Components of a Formal [4+2] Cycloaddition Reaction for the Synthesis of Tetracyclic Pyrano[2,3,4-*de*]chromenes

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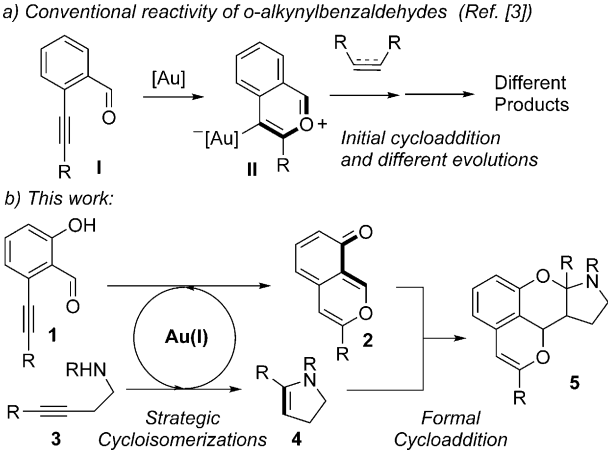
Abstract: *Ortho-Alkynylbenzaldehydes have been widely used to generate isochromenylium derivatives through gold-catalyzed cycloisomerization. These isochromenylium derivatives have been exploited as formal diene derivatives for reactions with different dienophiles. Herein, we describe the behavior of ortho-alkynylsalicylaldehydes, a particular case of ortho-alkynylbenzaldehydes. The gold-catalyzed cycloisomerization of ortho-alkynylsalicylaldehydes delivers an unusual heterodiene derivative that reacts with electron-rich alkenes through a formal [4+2] cycloaddition. In this reaction, both the diene and dienophile are generated in situ through gold-catalyzed cycloisomerization of appropriate alkynamines or alkynols. This reaction was used to synthesize complex tetracyclic pyrano[2,3,4-de]chromenes from two very simple starting materials (an ortho-alkynylsalicylaldehyde and an alkynamine or alkynol) with complete atom economy and with selective formation of bonds, cycles, and stereocenters.*



Scheme 1. The conventional reactivity of *ortho*-alkynylbenzaldehydes **I** and our proposed reaction.

The tremendous advances in the context of gold catalysis witnessed during the last decade have brought about a revolution in organic synthesis.[1] The cycloisomerization of alkyne-containing molecules is one very useful process where gold catalysts have become unbeatable. For example, the cycloisomerization of *ortho*-alkynylbenzaldehydes **I** is a powerful strategy to obtain the versatile synthetic intermediates isochromenyliums **II** (Scheme 1 a).[2] These intermediates are usually employed as the heterodiene partner in processes initiated by [4+2] cycloaddition reactions with appropriate dienophiles.[3] In this context, and following our interest in the development of new reactions based on catalytic cycloisomerization reactions,[4] we envisioned that the gold-catalyzed cycloisomerization of alkynylsalicylaldehydes **1**, a particular type of *ortho*-alkynylbenzaldehydes **I**, would deliver the isochromanone derivatives **2** (Scheme 1 b).[5] Interestingly, these compounds contain in their structures a 1,4-heterodiene moiety different from that obtained from simple *ortho*-alkynylbenzaldehydes **I** (isochromenyliums **II** are obtained from **I** but isochromanones **2** from **1**). To our knowledge, the presence of the mentioned heterodiene moiety in **2** has not been synthetically exploited. In this context, we thought that intermediates **2** could react with electron-rich alkene derivatives through a formal [4+2] cycloaddition. Our goal was not only to develop this new formal [4+2] cycloaddition reaction but also to generate both precursors, the heterodiene and the dienophile, in situ from simple reagents. We envisaged that a unique gold catalyst could promote the synchronized formation of both reagents, the dienes **2** from alkynylsalicylaldehydes **1** and the dienophiles **4** from alkynamines **3**, through cycloisomerization reactions.[6] Subsequent [4+2] cycloaddition between **2** and **4** would then deliver interesting polycyclic compounds **5** in an apparently straightforward way from very simple starting materials. It should be noted that although the in situ generation of dienes or dienophiles for subsequent cycloaddition has been reported,[7] to our knowledge, this concept of producing both reagents at the same time through the action of a single catalyst has not been fully exploited.

Our initial investigation was performed with *ortho*-alkynylsalicylaldehyde **1a** and the *N*-Boc-protected alkynamine **3a** as model substrates (Table 1). The first experiment was carried out in dichloromethane as the solvent and in the presence of the cationic gold(I) complex generated in situ from 5 mol% of $[AuCl(PPh_3)]$ and 5 mol% of AgOTf (Table 1, entry 1). Pleasingly, this reaction afforded the desired polycyclic compound **5a** in 40% yield, thus demonstrating the viability of our proposal. However, under these conditions, an equimolecular mixture of two diastereoisomers was obtained. A brief screening of solvents showed that the diastereoselectivity of the reaction could be easily improved by using toluene or tetrahydrofurane (THF) as solvents

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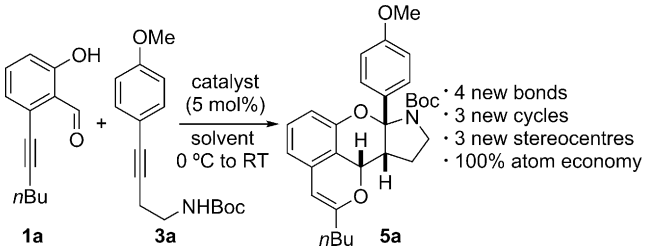
Table 1: Catalyst screening and optimization of the reaction conditions.[a]

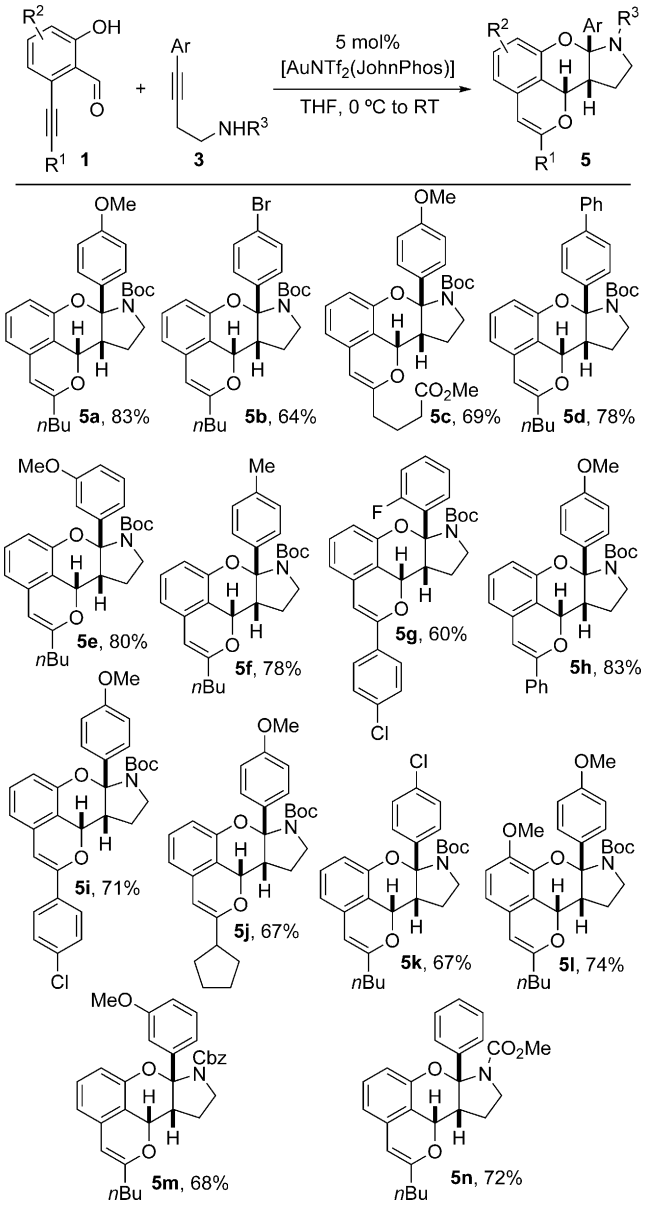


Entry	Catalyst	Solvent	Yield (d.r.)[a]
1	[AuCl(Ph$_3$P)]/ AgOTf	CH_2Cl_2	40% (1:1)
2	[AuCl(Ph$_3$P)]/ AgOTf	toluene	52% (>20:1)
3	[AuCl(Ph$_3$P)]/ AgOTf	THF	63% (>20:1)
4	[AuNTf$_2$(JohnPhos)]	THF	83% (>20:1)
5	AgOTf	THF	–
6	$PtCl_4$	THF	–

[a] The reactions were performed by adding the catalyst (5 mol%) to a solution of **1a** (1 equiv) and **3a** (1.1 equiv) at 0°C and then allowing stirring the reaction at room temperature for 6 hours. [b] Yield of isolated product based on **1a**. The diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

(Table 1, entries 2 and 3). Finally, we observed that more reliable results in terms of yield and selectivity were obtained by using the preformed cationic gold(I) catalyst [AuNTf$_2$(JohnPhos)] in THF as a solvent (Table 1, entry 4). Other typical silver- and platinum-derived catalysts used in related cycloisomerization reactions of *ortho*-alkynylbenzaldehydes did not afford positive results (Table 1, entries 5 and 6). The intricate transformation observed in this reaction should be remarked upon at this point. A complex tetracyclic compound is obtained from two simple starting materials in a process in which four new bonds, three cycles, and three stereogenic centers (one of them on a quaternary carbon atom) are formed in a selective way and without the generation of any byproducts (100% atom economy). It should also be noted that the reactivity observed with *ortho*-alkynylsalicylaldehyde **1a** is different from the conventional reactivity of *ortho*-alkynylbenzaldehydes (such as **I** in Scheme 1) and electron-rich alkenes under gold catalysis.[8]

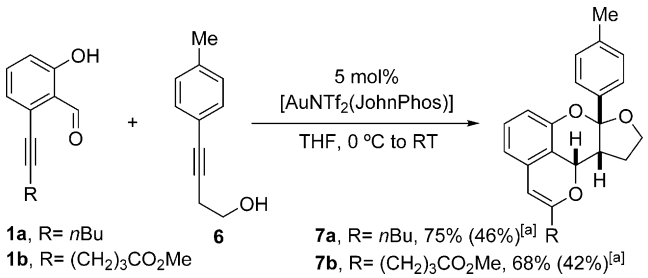
With optimal reaction conditions in hand, we next examined the scope of this new gold-catalyzed polycyclization process. As illustrated in Scheme 2, this transformation proceeds at room temperature and in good to high yield with a wide range of *ortho*-alkynylsalicylaldehydes **1** and alkynamine derivatives **3**. Specifically, the reaction seems general with respect to the substitution of aldehydes **1**, and aromatic and aliphatic substituents at the R^1 position were accepted. *ortho*-Alkynylsalicylaldehydes **1**, which are substituted at the aromatic ring (R^2), are also appropriate substrates for this reaction (**5l**). Regarding the alkynamines **3**, the reaction also seems general whenever the alkyne is substituted with an aryl group (alkyl substitution or unsubstituted alkynamines did not provide the desired products). Different protecting groups, Boc (**5a–l**), Cbz (**5m**) and CO_2Me (**5n**), on the nitrogen atom of the alkynamine derivatives **3** are accepted. Moreover, compounds **5** were formed as single diastereoisomers in all cases.



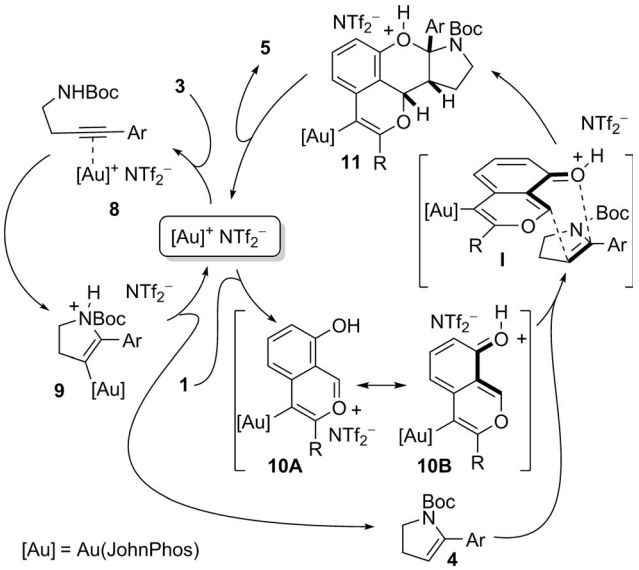
Scheme 2. Synthesis of chromeno[2,3-*b*]pyrrole derivatives **5**.

This new gold-catalyzed reaction is not limited to the use of alkynamines **3** as precursors of electron-rich alkene derivatives for coupling with the proposed heterodienes **2**. In this context, we also used the alkynol derivative **6** to generate a cyclic enol ether as the formal dienophile for the proposed cycloaddition reaction. The reaction of *ortho*-alkynylsalicylaldehydes **1a**,**b** with alkynol derivative **6** in the presence of 5 mol% of catalyst [AuNTf$_2$(JohnPhos)] in THF from 0°C to room temperature afforded the furo[2,3-*b*]pyrano[2,3,4-*de*]chromene derivatives **7a**,**b** in good yield and as single diastereoisomers (Scheme 3). Although these furan derivatives **7**, once isolated, were stable compounds, we observed some degradation under the column chromatography purification conditions.

The mechanism proposed to explain the formation of products **5** is shown in Scheme 4. The reaction is initiated by



Scheme 3. Synthesis of furo[2,3-*b*]pyrano[2,3,4-*de*]chromene derivatives **7**. [a] Yield determined by 1H-NMR using an internal standard, with the yield of isolated product after column chromatography given in parentheses.



Scheme 4. Proposed mechanism for the formation of compounds **5**.

coordination of the cationic gold complex to the triple bond of the starting alkynamine derivative **3** to form intermediate **8**. Intramolecular addition of the nitrogen atom to the external carbon of the triple bond generates **9**. Protodemetalation of the latter affords the enamine derivative **4** and releases the catalytic gold species.

The gold catalyst is also able to activate the other starting material, the *ortho*-alkynylsalicylaldehyde **1**, through coordination to the alkyne. This coordination promotes intramolecular addition of the oxygen of the aldehyde to form species **10** (Scheme 4). This intermediate may be represented as the isochromenylium **10A** or the isochromanone resonance form **10B**. The subsequent formal inverse-electron-demand [4+2] cycloaddition reaction between the activated electron-poor heterodiene shown in the isochromanone resonance form **10B** and the previously formed electron-rich enamine derivative **4** delivers the new intermediate **11**. A final protodemetalation step closes the second catalytic cycle to afford the final chromeno[2,3-*b*]pyrrole derivative **5** and regenerate the gold catalyst. The relative configuration observed at the new stereogenic centers in the final products **5** could be explained by the dienophile approaching the diene by following an *endo* trajectory as shown in **I** (*endo* refers to the orientation of the nitrogen in dienophile **4** with respect to the diene **10B**).[9] As shown, the global process could be considered a new example of self-relay one-pot catalysis because one catalyst promotes at least two mechanistically distinct reactions in a single flask.[10]

In summary, we have developed a new gold-catalyzed cascade reaction of *ortho*-alkynylsalicylaldehydes and alkynamines (or alkynols) towards functionalized tetracyclic compounds in a process in which several bonds, cycles, and stereocenters are formed in a selective way. The process is operationally simple, 100% atom-economic, and further demonstrates the ability of gold catalysts to promote complex transformations that would be otherwise difficult to accomplish. The reaction proceeds through a double cycloisomerization reaction followed by a formal [4+2] cycloaddition. Interestingly, in this reaction, the gold catalyst promotes the in situ formation of both the diene and dienophile.

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Keywords: cascade reactions · cycloaddition · gold · homogeneous catalysis · synthetic methods

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