Gold-catalyzed cyclization of Baylis–Hillman adducts Derived from formyl-indoles

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1. ABSTRACT

A methodology for the direct preparation of dihydrocyclopenta[*b*]indoles from indole-tethered α-hydroxacrylates under gold catalysis has been developed. The newly formed five-membered ring arises from a selective indole hydroarylation followed by dehydration.

2. INTRODUCTION

The use of gold salts has gained a lot of attention in the recent times because of their powerful soft Lewis acidic nature. Such a property allows gold catalysts to activate unsaturated functionalities such as alkynes, alkenes, and allenes, to create C–C bonds under extremely mild conditions.[1] On the other hand, Baylis–Hillman (BH) adducts are usually flexible and multifunctional products which can be easily transformed in a huge number of derivatives.[2] However, although many efforts have been made in these fields, the gold-catalyzed reactions using BH adducts derived from formyl-indoles as substrates constitute an unexplored field of noble metal catalysis. In connection with our current research interest in metal-catalyzed reactions,[3] we wish to report now details of the cyclization of indole-tethered BH adducts to cyclopenta[b]indoles,[4] which is carried out using gold catalysis.

3. RESULTS AND DISCUSSION

Starting substrates, BH adducts **1a–c**, **2a**, and **2b** (Figure 1) required for our study were prepared through a DABCO-catalyzed reaction from methyl acrylate and the appropriate indole-carbaldehydes.[5] Indole-linked acrylate **1a** was synthesized according to a literature procedure.[6]

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Novel BH adducts **1b**, **1c**, **2a**, and **2b** were prepared using the above standard procedure with slight modifications.

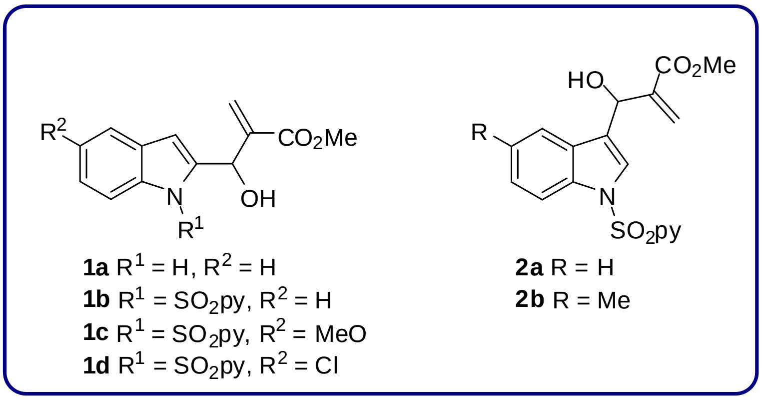
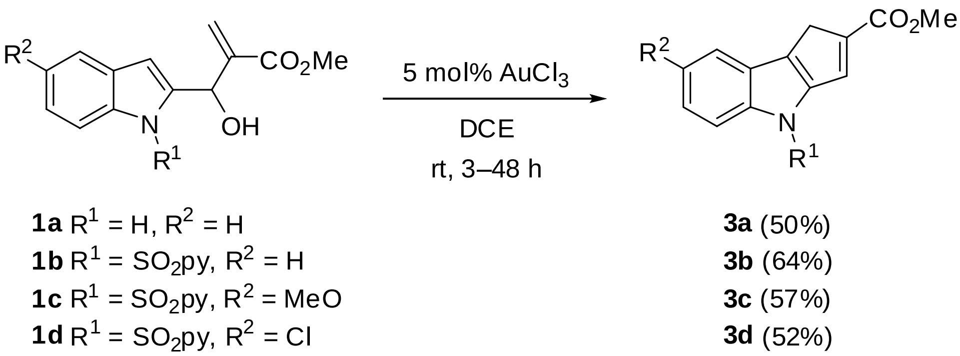


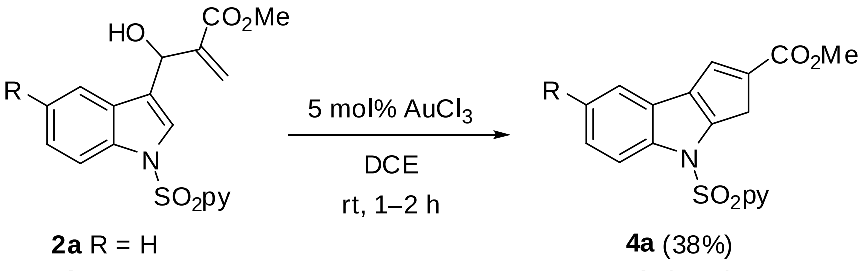
Figure 1. Structures of cyclization precursors, Baylis–Hillman adducts **1a–c**, **2a**, and **2b**. SO_2py = (2-pyridyl)sulfonyl.

Initially, we started to evaluate the cyclization reaction by employing BH adduct **1a** as model substrate. NH-Indole-tethered α-hydroxacrylate **1a** has diverse reactive sites, at which at least three different transformations (*C*-cyclization versus *O*-cyclization versus *N*-cyclization) can take place. Our catalyst screening led to the identification of $AuCl_3$ as the most suitable promoter. AuCl and Gagosz' catalyst [(Ph3P)$AuNTf_2$] were less effective for the tricycle formation. Our solvent screening led to the identification of 1,2-dichloroethane (DCE) as the most suitable solvent. It was found that $AuCl_3$ is an effective reagent for the room temperature carbocyclization of indole-linked acrylate **1a** to afford the cyclopentene-fused indole **3a** in 40% yield in a totally selective fashion. Nicely, using deactivated silica gel during purification resulted in an increased 50% yield for adduct **3a** (Scheme 1). Similarly, 1,4-dihydrocyclopenta[b]indoles **3b–d** were selectively obtained in the presence of the gold salt (Scheme 1). The placement of a chlorine atom or a methoxy group at C5 position of the indole ring was tolerated in the presence of $AuCl_3$, providing a handle for subsequent orthogonal reactivity.



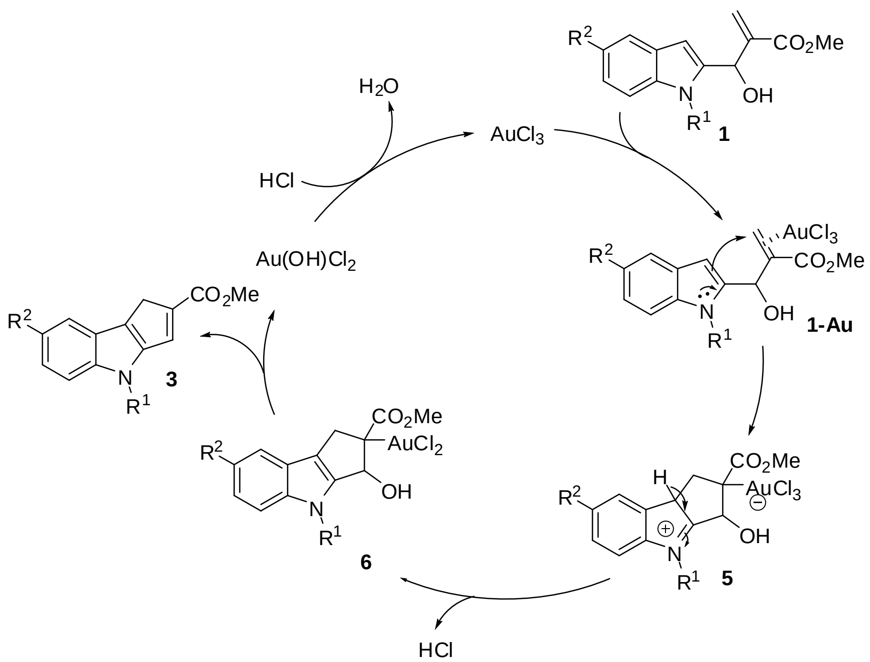
Scheme 1. Controlled intramolecular gold-catalyzed C3-hydroarylation of alkenyl-tethered indoles **1a–d**.

Due to the fact that the C3-position of an indole is the most reactive site for electrophilic functionalization,[7] carbocyclization of indole-tethered alkenes to the C2 indole position is considerably less studied and is mainly restricted to 1,2-dienes.[8] Fortunately, the gold-catalyzed reaction of indole-tethered α-hydroxacrylates **2** was also successful. As shown in Scheme 2, under gold(III) catalysis, the C3–C2 annulation products **4** were obtained, but in modest yields.



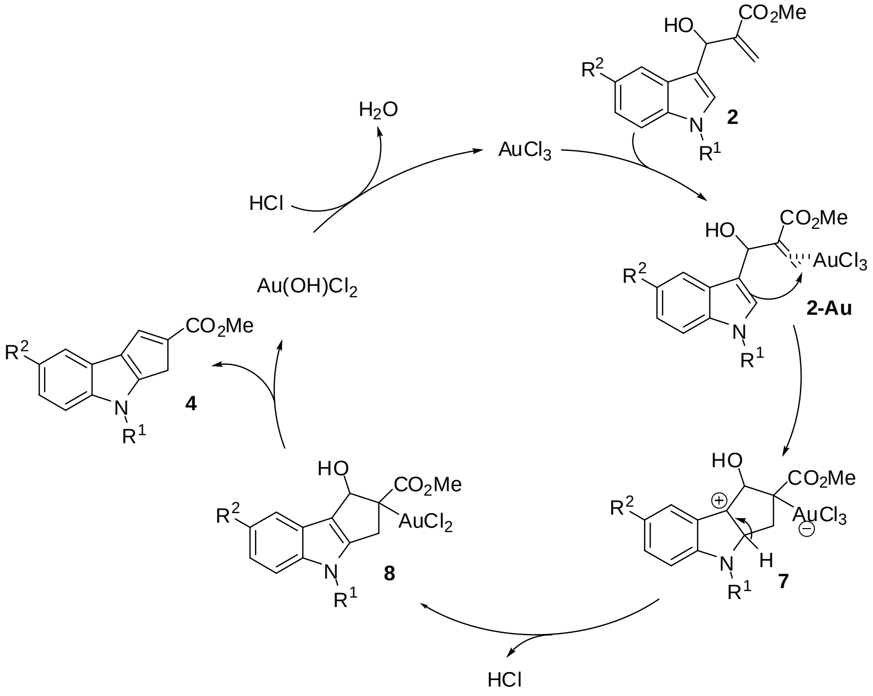
Scheme 2. Controlled intramolecular gold-catalyzed C2-hydroarylation of alkenyl-tethered indoles **2a** and **2b**.

Scheme 4 describes a putative mechanism for generating 1,4-dihydrocyclopenta[*b*]indoles **3** from the carbocyclization of indole-C2-tethered α-hydroxacrylates **1**. Initially, $AuCl_3$ coordinates to the alkenic double bond of BH adducts **1** to produce **1-Au**. The chemo- and regioselective 5-endo hydroarylation reaction of the thus generated gold complexes gives zwitterionic intermediates **5**. Attack at the 3-position of the indole occurs as a result of the stability of the iminium species **5**. The loss of HCl in zwitterion **5** furnishes neutral species **6**, which after loss of hydroxygold(III) chloride yields adducts **3**. Protonolysis of $Au(OH)Cl_2$ releases water and eventually reforms the Au(III) catalytic species (Scheme 3).



Scheme 3. Mechanistic explanation for the gold-catalyzed synthesis of 1,4-dihydrocyclopenta[*b*]indole-2-carboxylates **3**.

Our proposed mechanism for the gold-catalyzed generation of 3,4-dihydrocyclopenta[*b*]indole-2-carboxylates **4** is shown in Scheme 4. It is assumed that the mechanism starts with the coordination of the gold salt to the alkenic double bond of BH adducts **2** to give the corresponding complex **2-Au**. Then the 5-endo-trig carbocyclization towards the terminal alkene carbon takes place with formation of zwitterion **7**. This is followed by loss of HCl to produce neutral species **8**. The required fused cyclopentenes **4** are generated from **8** by dehydroxyauration. The subsequent regeneration of the gold catalyst is facilitated by the action of HCl over Au(OH)Cl_2. This step deliberates $AuCl_3$ and water.



Scheme 4. Mechanistic explanation for the gold-catalyzed synthesis of 3,4-dihydrocyclopenta[*b*]indole-2-carboxylates **4**.

4. CONCLUSIONS

In conclusion, we have developed a convenient methodology for the gold-catalyzed direct synthesis of dihydrocyclopenta[*b*]indoles from Baylis–Hillman adducts derived from formyl-indoles. A conceivable mechanism for the achievement of cyclopentene-fused indoles may imply a selective indole hydroarylation followed by dehydration.

5. REFERENCES

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