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

Benito Alcaide, a,* Pedro Almendros, b,* Alejandro Escobar, a Fernando Herrera, a and Amparo Luna a

a Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica I, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid
b Instituto de Química Orgánica General, IQOG-CSIC, Consejo Superior de Investigaciones Científicas, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

E-mail: alunac@quim.ucm.es

1. ABSTRACT

A methodology for the direct preparation of dihydrocyclopenta[b]indoles from indole-tethered α-hydroxacyclates 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

* Corresponding author. Tel.: (+34) 91-3944314; fax: (+34) 91-3944103; e-mail: alcaideb@quim.ucm.es (B. Alcaide)
* Corresponding author. Tel.: (+34) 91-5618806; fax: (+34) 91-5644853; e-mail: Palmendros@iqog.csic.es (P. Almendros)
Novel BH adducts 1b, 1c, 2a, and 2b were prepared using the above standard procedure with slight modifications.

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 AuCl₃ as the most suitable promoter. AuCl and Gagosz’ catalyst [(Ph₃P)AuNTf₂] 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 AuCl₃ 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 AuCl₃, providing a handle for subsequent orthogonal reactivity.
Due to the fact that the C3-position of an indole is the most reactive site for electrophilic functionalization,\textsuperscript{7} carbocyclization of indole-tethered alkenes to the C2 indole position is considerably less studied and is mainly restricted to 1,2-dienes.\textsuperscript{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\textsubscript{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\textsubscript{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)Cl₂. This step deliberates AuCl₃ and water.

![Scheme 4](image)

**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


