

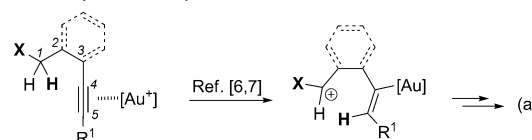
Gold-Catalyzed Functionalization of Unactivated C(sp³)–H Bonds by Hydride Transfer Facilitated by Alkynylspirocyclopropanes**

José Barluenga,* Rita Sigüeiro, Rubén Vicente, Alfredo Ballesteros,* Miguel Tomás, and Miguel A. Rodríguez

Transition-metal-catalyzed coupling reactions involving unactivated C(sp³)–H bonds constitute one of the most active research areas in both industry and academia.^[1,2] In particular, the development of methods that enable C–C bond formations through the selective cleavage of ubiquitous C(sp³)–H bonds is highly desirable as it allows for new retrosynthetic disconnections, thus minimizing the number of steps and the generation of waste.^[2] A major drawback of this transformation lies in the control of the selectivity. In general, selective functionalizations are achieved by the assistance of directing groups that bring the catalyst closer to the desired C–H bond.^[3] Alternatively, good control of the selectivity has been reported by the intramolecular thermal or Lewis acid catalyzed 1,5-hydride transfer reaction (HT).^[4] In contrast to hydride transfer to electron-poor alkenes,^[5] the use of electronically unbiased alkynes as acceptor partners requires the assistance of platinum^[6] or gold^[7] catalysts.^[8] Thus, a variety of gold- or platinum-catalyzed cleavages of C(sp³)–H bonds through intramolecular HT to alkynes have been described recently by the groups of Sames, Gagosz, and others. As a carbocation is initially generated, this strategy has been limited to C(sp³)–H bonds bearing a stabilizing functionality at the α position (OR, NR₂, aryl; Scheme 1 a). Considering this limitation, hydride transfer to alkynes from aliphatic, nonbenzylic, positions constitutes a challenging transformation.

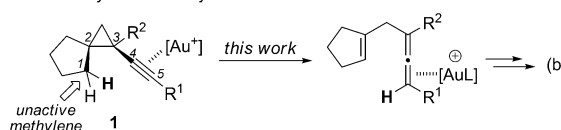
As part of our research into the synthesis and reactivity of alkynylcyclopropane derivatives,^[9,10] we have recently reported the synthesis of spiro[2.4]heptane derivatives **1** whose particular structure makes them amenable for use in investigations of new metal-catalyzed processes.^[11] These compounds have severe geometrical restrictions that place an inactive methylene group close to the alkyne moiety. We

Electronically facilitated hydride transfer



X = O, NR or R (when H is benzylic)

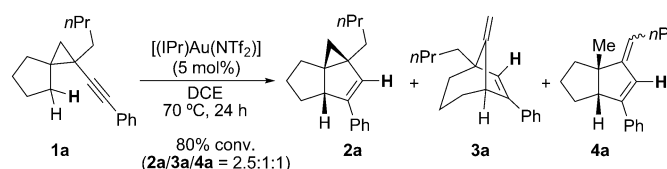
Structurally facilitated hydride transfer



Scheme 1. Complementary approaches to gold-promoted hydride transfer from C(sp³)–H bonds to alkynes.

hypothesized that this restricted geometry might facilitate the 1,5-hydride transfer to a metal-activated alkyne (Scheme 1 b).^[11] Herein, we disclose a new gold-catalyzed hydride transfer from an unactivated C(sp³)–H bond to an alkyne, and the subsequent selective cyclizations.

Initially, we studied the reactivity of spirane **1a** in the presence of various gold catalysts. We were pleased to find that a high conversion of **1a** was achieved when using cationic gold complex [(IPr)Au(NTf₂)] in 1,2-dichloroethane (70 °C, 24 h; Scheme 2), thus yielding a mixture of compounds **2–4a** (80% conv., **2a/3a/4a** = 2.5:1:1).^[12]



Scheme 2. Gold-catalyzed HT cyclizations of alkynylcyclopropane **1a**. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolium, DCE = 1,2-dichloroethane.

These transformations are noteworthy because they involve a selective cleavage of an unactivated C(sp³)–H bond, which together with the formation and cleavage of unactivated C–C bonds results in the formation of the final products. Further screening of the reaction conditions to achieve higher selectivity was undertaken using [(IPr)Au(NTf₂)] as catalyst. Shorter reaction times increased the amount of **2a**, although lower conversion was achieved. Interestingly, the use of microwave irradiation proved advantageous, as tricycles **2** could be prepared exclusively in moderate to good yields when irradiating spiranes **1** in the

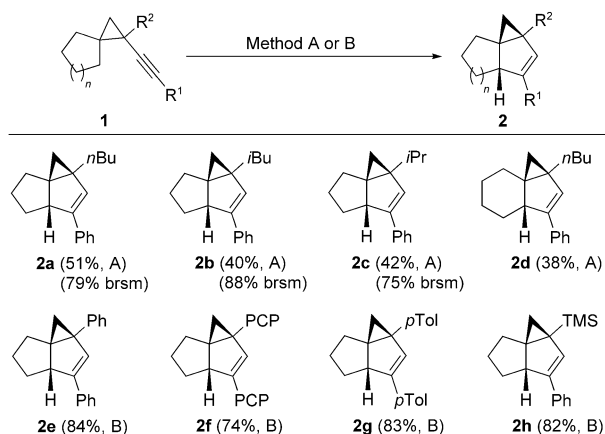
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presence of $[(\text{IPr})\text{Au}(\text{NTf}_2)]$ in DCE for 1 hour at 90 °C (Scheme 3). Under these reaction conditions, spiro[2,5]heptanes **1** ($n=1$) bearing various alkyl chains ($\text{R}^2 = n\text{Bu}$, $i\text{Bu}$, and $i\text{Pr}$) afforded the corresponding tricycles **2a–c** in moderate yields. In the same way, spiro[2,5]octane **1** ($n=2$) was also converted into the corresponding tricycle **2d**.

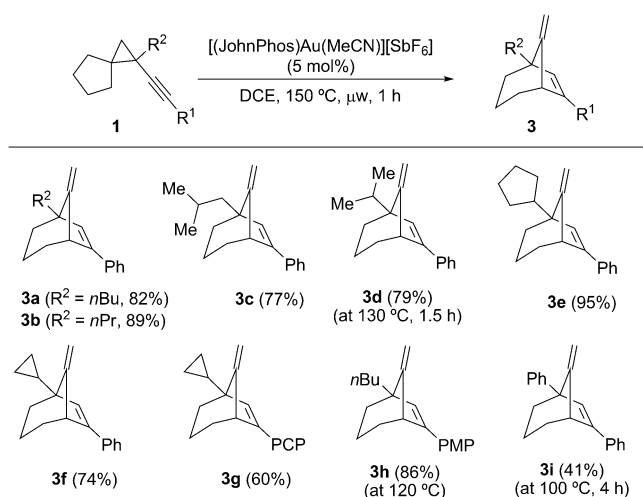


Scheme 3. Synthesis of tricycles **2** from alkynylcyclopropanes **1**. Method A: $[(\text{IPr})\text{Au}(\text{NTf}_2)]$ (5.0 mol%), DCE, 90 °C, μW , 1 h; method B: $[(\text{JohnPhos})\text{Au}(\text{MeCN})][\text{SbF}_6]$ (5.0 mol%), DCE, 70 °C, 1.5–8 h. The yields of the isolated product are in parenthesis. brsm = based on recovered starting material, PCP = 4- ClC_6H_4 .

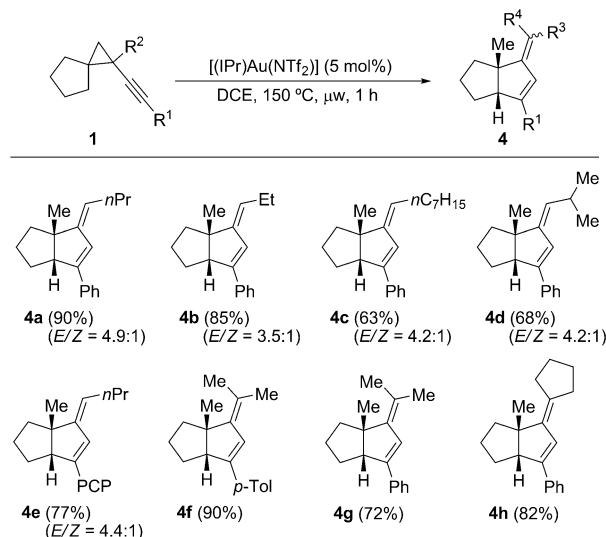
Although these reaction conditions were also amenable for the transformation of aryl- and trimethylsilyl-substituted substrates **1** ($\text{R}^2 = \text{Ar}$, TMS) into compounds **2e–h**, better efficiency was achieved using $[(\text{JohnPhos})\text{Au}(\text{MeCN})][\text{SbF}_6]$ as the catalyst under thermal conditions (DCE, 70 °C, 1.5–8 h).^[13]

Next, the beneficial effects of microwave irradiation allowed us to establish a selective route toward bicyclo[3.2.1]octenes **3** (Scheme 4). In this case, irradiation in DCE at 150 °C in the presence of $[(\text{JohnPhos})\text{Au}(\text{MeCN})][\text{SbF}_6]$ led, after 1 hour, to cycloadducts **3** in generally high yields. As depicted, alkynylcyclopropanes **1** bearing a linear alkyl chain at substituent R^2 were efficiently converted into bicycles **3a–c**.^[13,14] Likewise, compounds bearing secondary alkyl substituents such as $i\text{Pr}$ (**3d**) or c -pentyl (**3e**) were obtained in good yields. Notably, an additional cyclopropyl moiety was tolerated and remained unchanged in the final product (**3f–g**). As before, the use of electron-poor and electron-rich arenes ($\text{R}^1 = \text{PCP}$ or PMP), gave **3g–h** with similar efficacy. Moreover, alkynylcyclopropane **1i** bearing two phenyl substituents was converted into compound **3i**, albeit in relatively lower yield.^[15]

Finally, the transformation of compounds **1** ($\text{R}^2 = \text{alkyl}$) into pentalene derivatives **4** could be selectively accomplished by microwave heating in DCE at 150 °C (1 h) using $[(\text{IPr})\text{Au}(\text{NTf}_2)]$ as catalyst (Scheme 5). Thus, we were able to prepare several bicycles **4a–e** from substrates **1** bearing a primary alkyl substituent, either linear ($\text{R}^2 = n\text{Pr}$, $n\text{Bu}$, $n\text{C}_8\text{H}_{17}$) or branched ($\text{R}^2 = s\text{Bu}$), in good yields (63–90%) and with moderate E selectivity ($E/Z = 4:1$). The use of cyclopropanes **1** bearing a secondary alkyl substituent ($\text{R}^2 = i\text{Pr}$, c -pent) gave



Scheme 4. Synthesis of bicycles **3** from alkynylcyclopropanes **1**. The yields of the isolated product are in parenthesis. PMP = 4- MeOC_6H_4 .

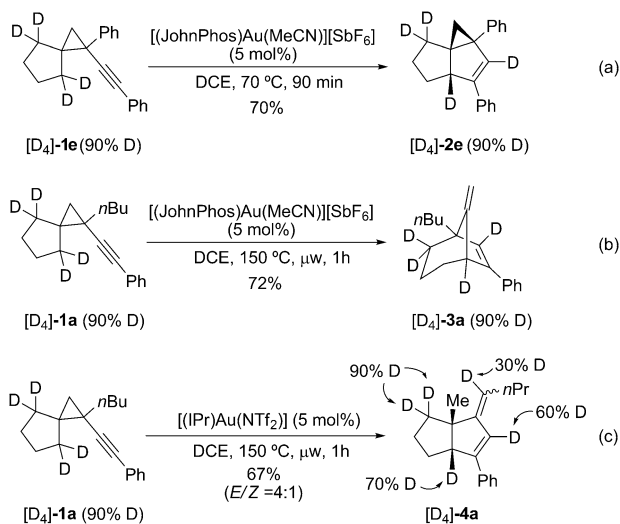


Scheme 5. Synthesis of pentalenes **4** from alkynylcyclopropanes **1**. The yields of the isolated product are in parenthesis. E/Z ratio was determined by ^1H NMR spectroscopy.

rise to compounds **4f–h** (72–90% yield) featuring a fully substituted exocyclic double bond.^[13,14]

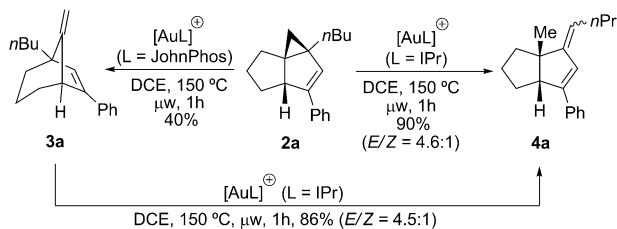
To gain an insight into the mechanism of these transformations we carried out a variety of experiments. To provide experimental support for a hydride-transfer mechanism, we subjected deuterium-labeled compounds $[\text{D}_4]\text{-1e}$ and $[\text{D}_4]\text{-1a}$ to cyclization conditions, which gave rise to $[\text{D}_4]\text{-2e}$ and $[\text{D}_4]\text{-3a}$, respectively, without loss of the deuterium label (Scheme 6a and b). The conversion of $[\text{D}_4]\text{-1a}$ into $[\text{D}_4]\text{-4a}$ took place with deuterium scrambling probably as a result of D/H shifts within the dienyl moiety as well as partial loss of the deuterium label (Scheme 6c).

We suspected that tricycles **2**, obtained selectively only under mild reaction conditions, might be a precursor to compounds **3** and **4**, but that the formation of which would require notably stronger reaction conditions. Indeed, **2a** was



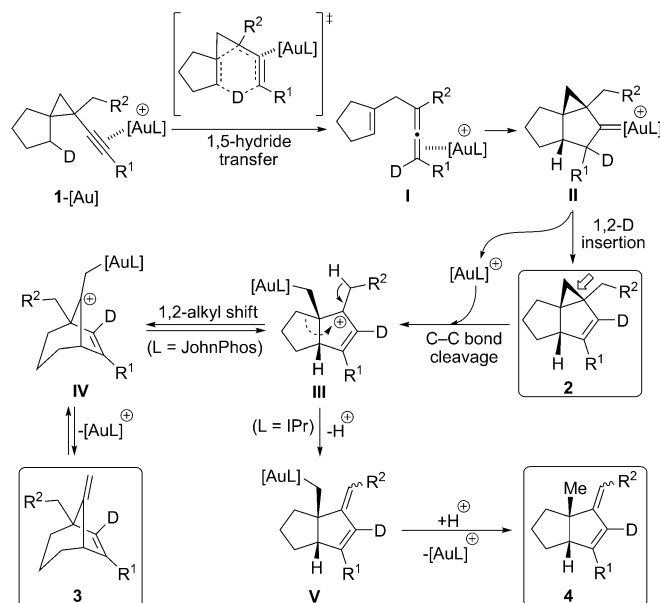
Scheme 6. Deuterium-labeling experiments.

converted into the corresponding bicycles **3a**^[16] and **4a** under microwave irradiation in the presence of [(JohnPhos)Au(MeCN)][SbF₆] and [(IPr)Au(NTf₂)], respectively (Scheme 7). Furthermore, we observed that **3a** gave **4a** almost quantitatively when treated with the [(IPr)Au(NTf₂)] catalyst (Scheme 7). The latter transformation might deserve further attention as it involves an unprecedented gold-catalyzed rearrangement of a 1,4-diene.^[17]



Scheme 7. Gold-catalyzed conversion of **2a** into **3a** and **4a**, and **3a** into **4a**.

Based on these experiments, we propose a tentative mechanism for these transformations (Scheme 8). The gold-to-alkyne coordination would trigger the 1,5-hydride transfer with concomitant cyclopropane ring cleavage.^[18] The generated 1,4-enallenyl gold intermediate **I** might then undergo a cyclization via species **II** to afford tricycle **2**.^[19] Support for the proposed mechanism was gained by computational studies, as a transition state involving the H atom migration was found.^[20,21] The subjection of **2** to harsher reaction conditions leads to **3** and **4** probably through the common intermediate **III** formed by regioselective gold-catalyzed cyclopropane C–C bond cleavage.^[22] A pinacol-type rearrangement would explain the formation of **3** from **III**. Thus, the 1,2-alkyl migration, giving intermediate **IV**, would be followed by metal elimination.^[23] On the contrary, deprotonation of **III**, giving intermediate **V**, and a subsequent



Scheme 8. Proposed mechanism.

protodemetalation would provide the pentalene **4**. Without further evidence, it is reasonable to assume that **IV** and **III** are the intermediates for the conversion of **3** into **4**.^[24]

In summary, we have reported the manifold reactivity of readily available alkynylcyclopropanes **1** that bear a spirane core. This study led us to discover an unprecedented gold-catalyzed 1,5-hydride transfer that involves an unactivated C(sp³)–H bond and an electronically neutral alkyne.^[25] Interestingly, the diverse fate of the resulting cationic gold species (C–C bond formation and bond cleavage of the unactivated species) can be efficiently controlled under microwave irradiation by simply selecting the appropriate catalyst (either [(JohnPhos)Au(MeCN)][SbF₆] or [(IPr)Au(NTf₂)] and reaction temperature. Thus, a range of cyclic structures, for example, pentalene derivatives **2** and **4**,^[26] and bicycles **3**,^[27] can be accessed with complete selectivity.^[28] Remarkably, it is herein shown that a spirane structure containing a cyclopropane ring can facilitate the intramolecular hydride transfer between unactivated donor and acceptor components. These results may open the way to study other hydride acceptor groups as well as to ascertain whether the spirane structure is essential or simpler alkynylcyclopropanes might also be employed.

Experimental Section

Representative procedure (**2a**, Scheme 3): [(IPr)Au(NTf₂)] (17 mg, 0.02 mmol, 5.0 mol %) was added to a solution of alkynylcyclopropane **1a** (100 mg, 0.424 mmol) in DCE (4.2 mL, 0.1 M) under argon in a microwave vial. The vessel was sealed with a septum cap, placed into the microwave cavity, and irradiated to maintain the reaction mixture at 90 °C during 1 h. Then, the vial was cooled down to room temperature and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on silica

gel (*n*-pentane) to afford **2a** (51 mg, 51 %, 79 % based on recovered starting material) as a colourless oil.

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