Formal (4+1) Cycloaddition of Methylene cyclopropanes with 7-Aryl-1,3,5-cyclohepta trienes by Triple Gold(I) Catalysis**

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Abstract: 7-Aryl-1,3,5-cyclohepta trienes react intermolecularly with methylene cyclopropanes in a triple gold(I)-catalyzed reaction to form cyclopentenes. The same formal (4+1) cycloaddition occurs with cyclobutenes. Other precursors of gold(I) carbenes can also be used as the C1 component of the cycloaddition.

Carbenes have been widely used as one-carbon synthon in organic synthesis, particularly in the context of cyclopropanation reactions.[1] However, only a few (4+1) cycloadditions[2] have been reported mainly with Fischer alkoxy- (alkenyl)cyclobutene complexes[3] and dialkoxycarbenes.[2,4] To the best of our knowledge, there is no report on the (4+1) cycloaddition of aryl carbenes with 1,3-dienes, probably because of the known propensity of carbenes to give cyclopropanation products with 1,3-dienes.[5] We postulated that due to their high strain and unique electronic properties, cyclobutenes[6] could be used as synthetic equivalents of 1,3-dienes for the development of a formal (4+1) cycloaddition with metal carbenes.

We have recently found that 7-substituted 1,3,5-cyclohepta trienes 1 undergo gold(I)-catalyzed retro-Buchner reaction to form carbones 2 (Scheme 1).[7] Herein, we report a novel and potentially general formal (4+1) cycloaddition by reaction of 1 with methylene cyclopropanes 3[9] or cyclobutenes 4 to form cyclopentenes 5. In this transformation, methylene cyclopropanes 3 undergo an isomerization to form cyclobutenes 4 similar to that catalyzed by platinum or palladium.[9] Therefore, in the reaction between 1 and 3, gold(I) plays a triple catalytic role, isomerizing 3 into 4 and, in parallel, generating gold(I) carbenes 2 from 1, which cyclopropane the cyclobutenes. Finally, gold(I) cleaves the internal C–C bond of the resulting bicyclo[2.1.0]pentanes to form the cyclopentenes. This reaction can be viewed as an insertion of one carbon into a double bond, a process that has only been achieved in rare cases with dihalocarbenes.[8,9]

Methylene cyclopropanes (MCPs) 3 can be readily prepared in one step by the Wittig olefination of carbonyl compounds with commercially available 3-bromo-triphenylphosphonium bromide. We first examined the reaction of phenylmethylene cyclopropane (3a) with 7-naphthyl-cyclohepta-1,3,5-triene (1a) in the presence of gold(I) complexes (Table 1). Using cationic [(JohnPhos)Au(MeCN)]SbF 6 (A) in 1,2-dichloroethane at 120 °C, disubstituted cyclopentene 5a was isolated in 76% yield (Table 1, entry 1). Other phosphine or N-heterocyclic carbene gold(I) complexes B–E gave lower yields (entries 2–5), whereas complexes F and G failed to promote this transformation, presumably due to their instability at the temperature required for the retro-Buchner reaction. The reaction also failed with silver(I), copper(II), and platinum(II) catalysts (entries 8–10).

7-Aryl-cyclohepta-1,3,5-trienes containing groups with different electronic and steric effects at the ortho, meta, or para positions reacted with MCPs 3a–h to yield the (4+1) cycloadducts 5b–m (Table 2). The (4+1) cycloaddition proceeds satisfactorily with MCP bearing arenes with fluoro-, chloro-, and bromo-substituents. However, the reaction with o-bromophenylmethylene cyclopropane (3f) led to cycloadduct 5k in lower yield. The structure of 5k was confirmed by X-ray diffraction (Figure 1).[11] To demonstrate the synthetic utility of this method, cyclopentene 5l was prepared on a 500 mg scale using only 1 mol% gold catalyst A in 51% yield after purification by column chromatography. Alkylmethylene cyclopropanes also reacted to give (4+1) cycloaddition products, although in this case the reactions led to mixtures of regioisomers 5n–p/p'.

Substrate 3l reacted intramolecularly using catalyst E to form 2,3-dihydro-1H-cyclopenta[l]phenanthrene (5q') by iso-

Scheme 1. New strategy for the formal (4+1) cycloaddition.
merization of the initially formed adduct 5q (Scheme 2). In addition, polyarene fragments can be obtained by photo-chemical cyclization. Thus, compound 5f can be transformed into a cyclopenta derivative of benzo[g]chrysene (6) by a one pot photo-induced isomerization/oxidative Mallory cyclization.[13]

Tetrasubstituted MCP 3m reacted with 1a to give only the product of cyclopropanation 7 (Scheme 3 and Figure 1), whose structure was confirmed by X-ray diffraction (Figure 1).[12] Given that 3m does not undergo ring-expansion, the isolation of spiro derivative 7 strongly suggests that the cyclopropanation of MCP is not the initial step in the formal (4+1) cycloaddition and that cyclobutenes are likely intermediates in this transformation.

To confirm the hypothesis that cyclobutenes are intermediates in the (4+1) reaction of MCP, we performed the reaction of 1a with cyclobutene 4a, which was isolated from the reaction mixture of 1a and 3g. Under identical conditions, cycloadduct 5l was isolated in 77% yield. Trisubstituted cyclobutenes[14] also took part in the (4+1) cycloaddition reaction to afford cyclopentenes 5r–z (Table 3).

Cyclobutenes also react with intermediate gold(I) carbene generated by 1,2-acyloxy migration of propargylic acetates[15] under mild conditions with catalyst E to give two separable isomers 5aa–ac and 5′aa–ac in good overall yields (Scheme 4). By performing the reaction at room temperature at only 60% conversion, bicyclo[2.1.0]pentane 10a[16] could be isolated and then transformed cleanly into 5aa at 40°C in the presence of gold(I) catalyst. The gold(I) carbene generated from phenyl diazomethane[17–20] reacted similarly at room temperature with cyclobutene 4c to form the desired formal (4+1) product 5ad, along with 10b.[21] This bicyclo[2.1.0]pentane was converted quantitatively into cyclopentene 5ad by warming at 60°C in the presence of gold complex A.

Table 1: Gold(I)-catalyzed reaction of 7-(1-naphtyl)-1,3,5-cycloheptatriene (1a) with phenylmethylene cyclopropane (3a).[a]

| Entry | Catalyst | Yield [%][b] |
|-------|----------|--------------|
| 1     | A        | 81 (76)      |
| 2     | B        | 25           |
| 3     | C        | 28           |
| 4     | D        | < 5          |
| 5     | E        | 47           |
| 6     | F        | –[c]         |
| 7     | G        | –[c]         |
| 8     | H        | –[c]         |
| 9     | I        | –[c]         |
| 10    | J        | –[c]         |

[a] Reaction at 120°C (0.2 m in 1,2-dichloroethane), 2 equiv of 3a, catalyst (5 mol%), 2 h. [b] Yields determined by 1H NMR spectroscopy using 1,4-diacetylbenzene as internal standard. [c] Yield of isolated product.

Table 2: Scope of the formal (4+1) cycloaddition between cycloheptatrienes 1 and methylenecyclopropanes 3.[a]

| Entry | Catalyst | Yield [%][b] | Ar | R |
|-------|----------|--------------|----|---|
| 1     | A        | 53           | Ph | H |
| 2     | B        | 65           | PhO| H |
| 3     | C        | 81           | Cl | H |
| 4     | D        | 60           | Cl | H |
| 5     | E        | 51           | Cl | H |
| 6     | F        | 58           | Ph | H |
| 7     | G        | 64           | Ph | H |
| 8     | H        | 63           | Ph | H |
| 9     | I        | 80           | Br | H |
| 10    | J        | 82           | Br | H |

[a] Reaction at 120°C, 0.2 m in 1,2-dichloroethane, 2 equiv of 3a–k, catalyst A (5 mol%), 2 h. Yields are for isolated products. [b] Reaction time = 3 h. 3-Alkyl-3-arylcyclopent-1-enes 5n–p were also obtained as minor regioisomers.
To shed additional light on the reaction mechanism, we performed the reaction of cycloheptatriene 1a with MCP [D1]-3a in the presence of catalyst A (Scheme 5). In this experiment, [D 1]-5a was obtained with the deuterium label transferred completely to C-3.

According to all experimental data, we propose a mechanism for this formal (4+1) cycloaddition of cycloheptatrienes 1 and MCP in which gold(I) plays a triple role (Scheme 6). In the first catalytic cycle, h2-MCP-gold(I) complex I undergoes ring expansion to form intermediate II, which gives h2-cyclobutene-gold(I) complex III. Associative ligand exchange with the 7-aryl-1,3,5-cycloheptatriene, followed by retro-Buchner reaction then leads to the highly reactive gold(I) carbene 2, which reacts with cyclobutene 4 to form bicyclo[2.1.0]pentane-gold(I) complex IV. Cyclopropane opening by gold(I) forms the tertiary carbocation V, which leads to complex VI by a final 1,2-H shift. The cyclopropanation of 4 by 2, followed by electrophilic cleavage probably follows a pathway similar to that occurring in the gas phase for the cyclopropanation/retro-cyclopropanation of enol ethers with gold(I) carbenes. Formation of cyclopentenes from bicyclo[2.1.0]pentanes, the presumed intermediates of these reactions, has been mechanistically examined in a few cases using RhI, ZnI, and other catalysts.22,23,24 Formation of regioisomeric 3-alkyl-3-arylcyclopent-1-enes

Table 3: Scope of the formal (4+1) cycloaddition between cycloheptatrienes 1 and cyclobutenes 4.

| Ar                  | R1   | R2   | Yield |
|---------------------|------|------|-------|
| Ph                  | Br   | R    | 77%   |
| Ph                  | Br   | R    | 73%   |
| Ph                  | R    | R    | 63%   |
| Ph                  | R    | R    | 64%   |
| Ph                  | R    | R    | 66%   |
| Ph                  | R    | R    | 68%   |
| Ph                  | R    | R    | 75%   |
| Ph                  | R    | R    | 82%   |
| Ph                  | R    | R    | 83%   |
| Ph                  | R    | R    | 84%   |
| Ph                  | R    | R    | 85%   |
| Ph                  | R    | R    | 86%   |
| Ph                  | R    | R    | 87%   |
| Ph                  | R    | R    | 88%   |
| Ph                  | R    | R    | 89%   |

[a] Reaction at 120 °C, 0.2 m in 1,2-dichloroethane, 2 equiv of 4a-g, catalyst A (5 mol %), 3 h. Yields are for isolated adducts. [b] Cyclobutene 4a was isolated from the reaction mixture of 1a and 3g. [c] 2 Equiv of 7-(4-chlorophenyl)cyclohepta-1,3,5-triene were used.
together with 5n-p in the reaction of alkyl-substituted MCP can be explained by the competitive migration of the aryl group in intermediates V.

In summary, we have developed a synthesis of substituted cyclopentenes by a formal (4+1) cycladdition from methylencyclopropanes or cyclobutenes with gold(I) carbenes generated under catalytic conditions by retro-Buchner reaction of 1,3,5-cycloheptatrienes or by other methods. Further work on the application of this cycladdition in synthesis is underway.

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We also screened some donor–acceptor diazo derivatives, such as methyl-2-diazo-2-phenylacetate, but only homo-coupling product of the diazo compound was observed.

The reaction of phenyl diazomethane with cyclobutene 4c in the presence of copper thiophene-2-carboxylate or [Ag-(MeCN)2]SbF6 (5 mol %, CH2Cl2, 23 °C, 1.5 h) gave 10b and its endo diastereoisomer in 47% (6:1 ratio) and 43% (3:1 ratio) yield, respectively. No cyclopentene 5ad was formed with these catalysts under these conditions.

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