

**Synthetic Methods**

# Gold-Catalyzed [2+2+1] Cycloaddition of 1,6-Diyne Carbonates and Esters with Aldehydes to 4-(Cyclohexa-1,3-dienyl)-1,3-dioxolanes

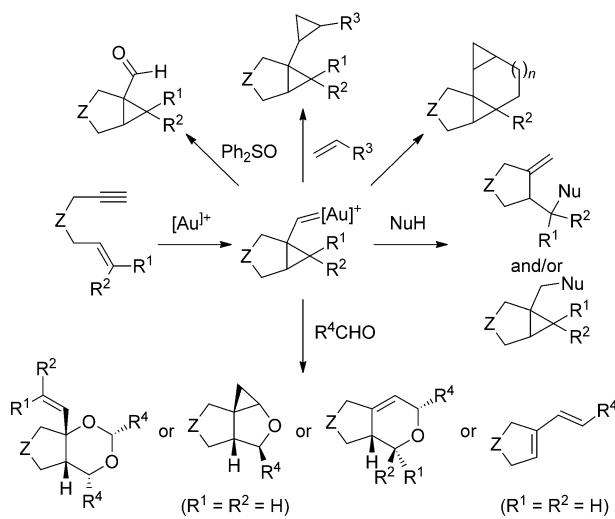
Weidong Rao and Philip Wai Hong Chan\*<sup>[a]</sup>

**Abstract:** A synthetic method to stereoselectively prepare 4-(cyclohexa-1,3-dienyl)-1,3-dioxolanes in good to excellent yields by gold(I)-catalyzed [2+2+1] cycloaddition of 1,6-diyne carbonates and esters with aldehydes is described. The cascade process involves 1,2-acyloxy migration followed by cyclopropenation and cycloreversion. This leads to an un-

precedented [2+2+1] cycloaddition of the resulting alkenyl-gold carbenoid species, examples of which are extremely rare, with two aldehyde molecules at catalyst loadings as low as 1 mol %. The usefulness of this cycloisomerization chemistry was further demonstrated by the transformation of one example to the corresponding phenol.

## Introduction

Over the last decade, gold-catalyzed alkyne cycloisomerizations involving an *in situ* generated gold carbenoid species have become an important addition to the synthetic chemist's toolbox for the assembly of architecturally challenging compounds.<sup>[1–16]</sup> An illustrative example of this has been the number of impressive works describing the construction of various synthetically valuable products from cyclopropane-substituted gold carbenoid intermediates derived from 1,*n*-enyne (Scheme 1).<sup>[2–7]</sup> In the case of transformations with an aldehyde or ketone as the nucleophile, this has provided an expedient approach to oxaheterocyclic compounds.<sup>[6,7]</sup> Included in this has been an intramolecular variant of the reaction applied to the synthesis of the natural products englerin A and B.<sup>[7]</sup> However, the analogous cycloadditions of an *in situ* formed alkenyl-gold carbenoid adduct, resulting from [2,3]-sigmatropic rearrangement of a propargylic carbonate or ester, with a carbonyl compound is not known.<sup>[8]</sup> This is surprising given that the presence of a vinyl instead of a cyclopropane moiety in the putative organogold intermediate might be expected to exhibit different modes of reactivity and thus the possibility of access to a wider scope of cycloisomerization products. In this context and as part of an ongoing program examining the utility of gold catalysis in heterocyclic synthesis,<sup>[9]</sup> we were drawn to examining the Au<sup>I</sup>-catalyzed cycloisomerization chemistry of 1,6-diyne carbonates and esters **1** in the presence of an aldehyde



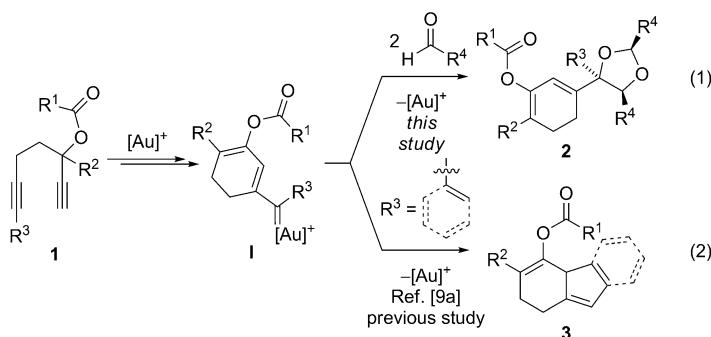
**Scheme 1.** Exploiting the reactivity of *in situ* formed cyclopropylgold carbenoid species.

[Scheme 2, Eq. (1)].<sup>[10,11]</sup> In doing so, we report herein our discovery that the resultant putative gold carbenoid species **I** formed *in situ* was susceptible to an unprecedented [2+2+1] cycloaddition with aldehydes. This provided an expedient and chemoselective route to 4-(cyclohexa-1,3-dienyl)-1,3-dioxolanes **2**, a key building block in organic synthesis, in good to excellent yields. To our knowledge, this type of dipolar cycloaddition had been previously only achieved by Rh<sup>II,III</sup>-, Cu<sup>I</sup>- or Cu<sup>II</sup>-catalyzed reactions of  $\alpha$ -diazo esters with aldehydes.<sup>[17,18]</sup> Moreover, supported by experimental evidence and ONIOM-(QM:QM') [ONIOM(QM:QM')=our own *n*-layered integrated molecular orbital and molecular mechanics(quantum mechanics:quantum mechanics')] calculations, the present gold carbenoid intermediate approach has only been documented once before in which it was shown to undergo Nazarov cyclization

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**Scheme 2.** Cycloisomerizations of 1,6-diyne carbonates and esters involving an in situ formed gold carbenoid species.<sup>[2–7]</sup>

to give 2,4a-dihydro-1*H*-fluorenes **3** [Scheme 2, Eq. (2)].<sup>[9a, 12]</sup> Prior to this and the present work, there have been only three other examples describing the posited migration of a gold carbenoid moiety to an alkyne to form a second alkynylgold carbenoid species.<sup>[13]</sup> Additionally, there has been only one reported instance of this type of reactivity in which [2+2+2] cycloaddition of 1,6-enynes ( $Z=C(\text{CO}_2\text{Me})_2$  in Scheme 1) with two molecules of the aldehyde that was demonstrated to afford 1,3-dioxanes in low to good yields.<sup>[6b]</sup>

## Results and Discussion

Table 1 summarizes our efforts to establish the reaction conditions for the gold-catalyzed cycloaddition of 1,6-diyne ester **1a** with *n*-heptanal.<sup>[19]</sup> This initially revealed that treating 1 equivalent of the starting ester and aldehyde (5 equiv) with 5 mol % of NHC-Au<sup>l</sup> (NHC=N-heterocyclic carbene) complex **A** as the catalyst and 4 Å molecular sieves (MS) in dichloromethane at room temperature for 30 min gave **2a** as a single diastereomer along with **3a** in 62 and 8% yield, respectively (entry 1). The structure and stereochemistry of the 1,3-cyclohexadiene adduct was confirmed by NMR analysis and X-ray crystal structure determination of a closely related analogue (vide infra).<sup>[20]</sup> Our studies subsequently showed an increase in the amount of the *n*-heptanal from five to ten equivalents resulted in an increase in product yield from 62 to 68% (entry 2). By lowering the reaction temperature from room temperature to 0 °C, a further increase in product yield from 68 to 72% yield was observed (entry 3). In contrast, an inspection of entries 4–11 in Table 1 showed that repeating the reaction with other gold(I) and gold(III) complexes in place of **A** was found to be markedly less effective. The analogous reactions with the NHC-gold(I) complexes **B**, **C**, and **D** as catalyst gave the product in lower yields or as a mixture with the tricyclic adduct (entries 4–6).<sup>[21]</sup> A similar outcome was found when NHC-gold(I) complex **A** was replaced with the Au<sup>l</sup> phosphine complexes **E** and **F**, and Au<sup>III</sup>

complex **G** as catalyst (entries 7, 8, and 11). No reaction was detected in control experiments catalyzed by Ph<sub>3</sub>PAuNTf<sub>2</sub> or AuCl based on TLC and <sup>1</sup>H NMR analysis of the crude mixtures (entries 9 and 10). Likewise, control reactions with PtCl<sub>2</sub> or AgSbF<sub>6</sub> as the catalyst were found to lead to the recovery of the substrate in near quantitative yield (entries 12 and 13). On the basis of the above results, reaction of **1a** with *n*-heptanal (10 equiv) in the presence of 5 mol % of NHC-Au<sup>l</sup> complex **A** and 4 Å MS in dichloromethane at 0 °C for 30 min was deemed to provide the optimum conditions.

To define the scope of the present procedure, we next turned our attention to the reactions of a variety of 1,6-diyne carbonates and esters and aldehydes (Table 2). These experiments showed that with of NHC-Au<sup>l</sup> complex **A** as catalyst, the reaction conditions proved to be

**Table 1.** Optimization of the reaction conditions.<sup>[a]</sup>

| Catalyst               | Reaction Time [h]                   | Yield [%] <sup>[b]</sup> |
|------------------------|-------------------------------------|--------------------------|
| <b>1<sup>[c]</sup></b> | <b>2a</b>                           | <b>3a</b>                |
| 2                      | 0.5                                 | 68                       |
| 3 <sup>[d]</sup>       | 0.5                                 | 72                       |
| 4                      | 20                                  | 23                       |
| 5                      | 2                                   | 61                       |
| 6                      | 20                                  | 55                       |
| 7                      | 0.5                                 | 11                       |
| 8                      | 24                                  | 19                       |
| 9                      | Ph <sub>3</sub> PAuNTf <sub>2</sub> | — <sup>[e]</sup>         |
| 10                     | AuCl                                | — <sup>[e]</sup>         |
| 11                     | <b>G</b>                            | 7                        |
| 12                     | PtCl <sub>2</sub>                   | — <sup>[e]</sup>         |
| 13                     | AgSbF <sub>6</sub>                  | — <sup>[e]</sup>         |

[a] All reactions were performed with 0.2 mmol of **1a** and 2 mmol of *n*-heptanal in the presence of 5 mol % of catalyst and 4 Å MS (100 mg) at room temperature. PNB = *p*-nitrobenzyl. [b] Isolated yield. [c] Reaction performed with 5 equiv of *n*-heptanal.

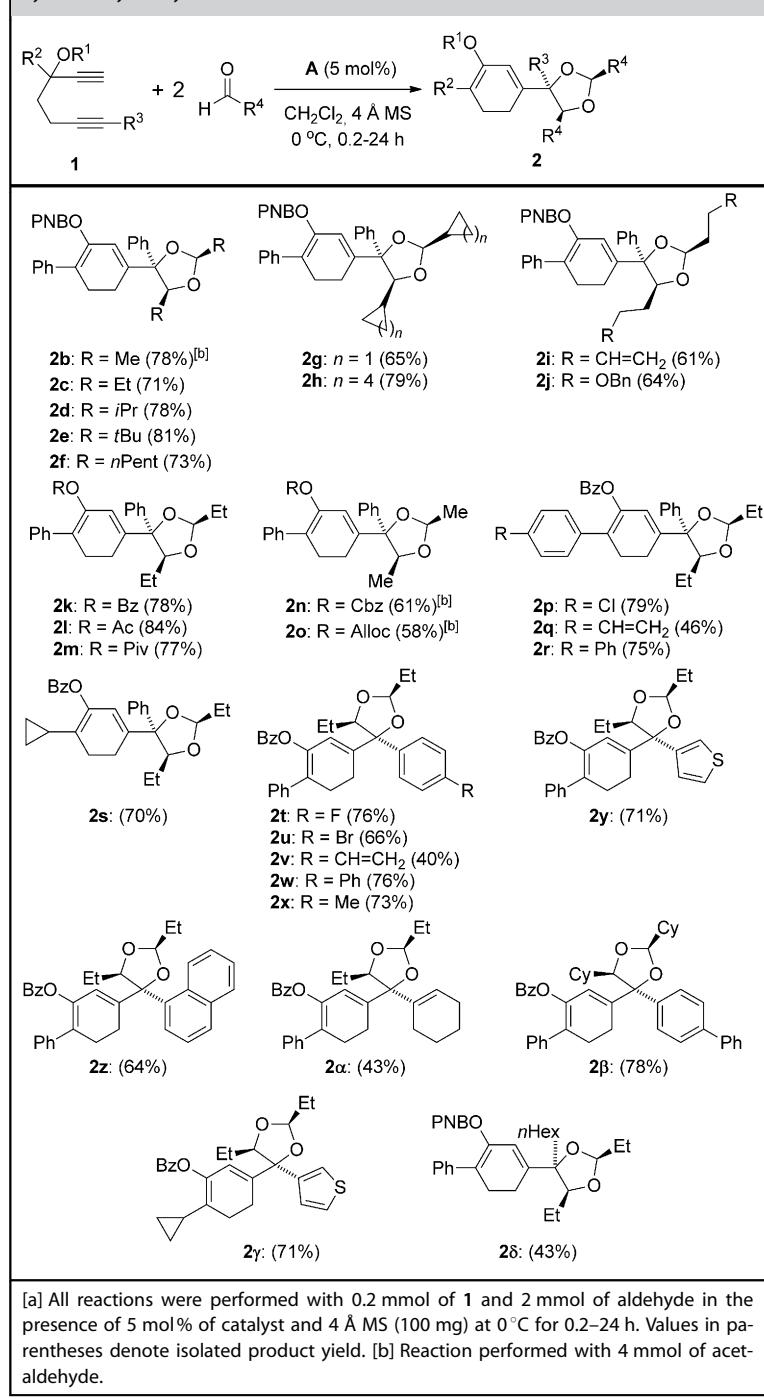
[d] Reaction performed at 0 °C. [e] No reaction detected based on TLC and <sup>1</sup>H NMR analysis of the crude reaction mixture.

general with a variety of substituted 4-(cyclohexa-1,3-dienyl)-1,3-dioxolanes afforded in 40–84% yield from [2+2+1] cycloaddition of the corresponding substrates **1a–t** and aldehydes. Reactions of **1a** with acetaldehyde, propionaldehyde, isobutyraldehyde, pivalaldehyde and *n*-hexanal were found to proceed well and furnish **2b–f** in 71–81% yield. The [2+2+1] cycloaddition of **1a** with aldehydes with a pendant carbocyclic (cyclopropanal and cyclohexanal) or alkene (4-pentenal) or ether (4-(benzyloxy)butanal) group were found to well tolerated under

the reaction conditions to give **2g–j** in 61–79% yield. The diastereosemantics and structure of **2g** was also confirmed by X-ray crystallography (Figure 1).<sup>[20]</sup> The presence of a Bz (**1b**), Ac (**1c**), Piv (**1d**), Cbz (**1e**), and Alloc (**1f**) instead of a PNB migrating group was found to have little influence on the course of the reaction, with [2+2+1] cycloaddition of these substrates with either acetaldehyde or propionaldehyde providing **2k–o** in 58–84% yield. Similarly, reactions of starting 1,6-diyne esters containing other aryl motifs or a cyclopropane, cyclohexene, *n*-hexane or thiophene group at the alkyne or benzoate carbon center (**1g–t**) with propionaldehyde or cyclohexanal were found to give the corresponding 1,3-dioxolanes **2p–2s** in 40–79% yield. In all the above transformations, the cycloisomerization process was additionally shown to occur in a highly selective manner with the [2+2+1] cycloadduct being obtained as a single diastereo- and regioisomer. Other than a number of unknown byproducts, no cyclopropane adducts that could be obtained from cyclopropanation of the putative gold carbenoid species in substrates containing an alkene moiety, as in **1i**, **o**, **q**, **v**, and **α**, were detected by <sup>1</sup>H NMR measurement of the crude reaction mixtures.<sup>[4]</sup> Likewise, no oxacyclic side-products resulting from participation of the organogold intermediate in [3+2] cycloaddition with an aldehyde were observed by <sup>1</sup>H NMR analysis of the crude reaction mixtures. This was further corroborated by obtaining **2l** as the only cyclic adduct in 77% yield (1.5 g) on repeating the large-scale [2+2+1] cycloaddition of **1c** (1.4 g) with propionaldehyde in the presence of 1 mol % of **A** under the conditions described in Scheme 3.

A speculative mechanism for the present Au<sup>I</sup>-catalyzed [2+2+1] cycloaddition of 1,6-diyne carbonates and esters with aldehydes is illustrated in Scheme 4. This could initially involve coordination of the ester-alkyne moiety of **1** by the Au<sup>I</sup> catalyst to afford the gold(I)-activated complex **II**.<sup>[8]</sup> As a consequence, this triggers the *syn* 1,2-acyloxy migration process to give the 1,3-dioxin-1-ium species **III**, which undergoes cycloreversion to form the gold carbenoid intermediate **IV**. Further reaction of this newly formed organogold complex with the remaining alkyne moiety followed by activation of the ensuing cyclopropene compound **V** by the Lewis acidic catalyst might then furnish the gold(I)-coordinated species **VI**.<sup>[15]</sup> Electrophilic ring opening of the cyclopropene motif in this bicyclic adduct would provide the second gold carbenoid intermediate **I** and its gold-stabilized allylic cation resonance form **I'**.<sup>[9a,13]</sup> Subsequent [2+2+1] cycloaddition of this metallocarbenoid species with two molecules of the aldehyde would lead to the regeneration of the gold(I) catalyst and formation of **2**. The observed product stereochemistry could be due to the cycloaddition occurring via the transition state conformation shown in Scheme 4 so as to minimize the possibility of un-

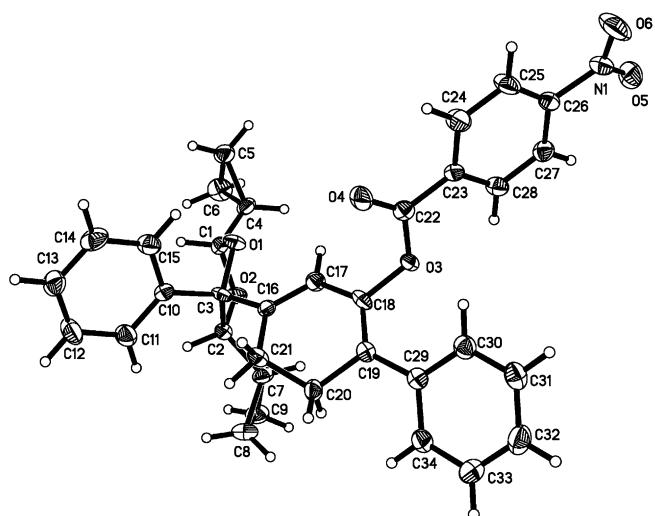
**Table 2.** [2+2+1] Cycloaddition of 1,6-diyne carbonates and esters **1b–t** with aldehydes catalyzed by **A**.<sup>[a]</sup>



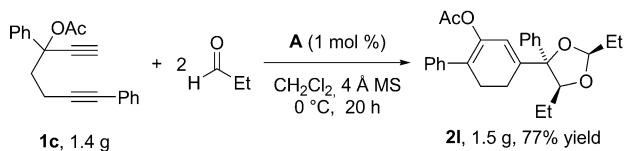
**Table 2. [2+2+1] Cycloaddition of 1,6-diyne carbonates and esters **1b–t** with aldehydes catalyzed by **A**.<sup>[a]</sup>**

| Substrate <b>1</b>                 | Aldehyde        | Product <b>2</b> | Yield (%) |
|------------------------------------|-----------------|------------------|-----------|
| <b>1b</b> : R = Me                 | Acet aldehyde   | <b>2b</b>        | 78%       |
| <b>1c</b> : R = Et                 | Acet aldehyde   | <b>2c</b>        | 71%       |
| <b>1d</b> : R = iPr                | Acet aldehyde   | <b>2d</b>        | 78%       |
| <b>1e</b> : R = tBu                | Acet aldehyde   | <b>2e</b>        | 81%       |
| <b>1f</b> : R = nPent              | Acet aldehyde   | <b>2f</b>        | 73%       |
| <b>1g</b> : R = Bz                 | Propionaldehyde | <b>2g</b>        | 65%       |
| <b>1h</b> : R = Bz                 | Propionaldehyde | <b>2h</b>        | 79%       |
| <b>1i</b> : R = CH=CH <sub>2</sub> | Propionaldehyde | <b>2i</b>        | 61%       |
| <b>1j</b> : R = OBn                | Propionaldehyde | <b>2j</b>        | 64%       |
| <b>1k</b> : R = Bz                 | Cyclohexanal    | <b>2k</b>        | 78%       |
| <b>1l</b> : R = Ac                 | Cyclohexanal    | <b>2l</b>        | 84%       |
| <b>1m</b> : R = Piv                | Cyclohexanal    | <b>2m</b>        | 77%       |
| <b>1n</b> : R = Cbz                | Propionaldehyde | <b>2n</b>        | 61%       |
| <b>1o</b> : R = Alloc              | Propionaldehyde | <b>2o</b>        | 58%       |
| <b>1p</b> : R = Cl                 | Propionaldehyde | <b>2p</b>        | 79%       |
| <b>1q</b> : R = CH=CH <sub>2</sub> | Propionaldehyde | <b>2q</b>        | 46%       |
| <b>1r</b> : R = Ph                 | Propionaldehyde | <b>2r</b>        | 75%       |
| <b>1s</b> : R = F                  | Propionaldehyde | <b>2s</b>        | 70%       |
| <b>1t</b> : R = Br                 | Propionaldehyde | <b>2t</b>        | 76%       |
| <b>1u</b> : R = CH=CH <sub>2</sub> | Propionaldehyde | <b>2u</b>        | 66%       |
| <b>1v</b> : R = Ph                 | Propionaldehyde | <b>2v</b>        | 40%       |
| <b>1w</b> : R = Me                 | Propionaldehyde | <b>2w</b>        | 76%       |
| <b>1x</b> : R = Me                 | Propionaldehyde | <b>2x</b>        | 73%       |
| <b>1y</b> : Cy                     | Propionaldehyde | <b>2y</b>        | 71%       |
| <b>1z</b> : Cy                     | Propionaldehyde | <b>2z</b>        | 64%       |
| <b>1α</b> : Cy                     | Propionaldehyde | <b>2α</b>        | 43%       |
| <b>1β</b> : Cy                     | Propionaldehyde | <b>2β</b>        | 78%       |
| <b>1γ</b> : Cy                     | Propionaldehyde | <b>2γ</b>        | 71%       |
| <b>1δ</b> : nHex                   | Propionaldehyde | <b>2δ</b>        | 43%       |

[a] All reactions were performed with 0.2 mmol of **1** and 2 mmol of aldehyde in the presence of 5 mol % of catalyst and 4 Å MS (100 mg) at 0 °C for 0.2–24 h. Values in parentheses denote isolated product yield. [b] Reaction performed with 4 mmol of acetaldehyde.



**Figure 1.** ORTEP drawing of **2g** with thermal ellipsoids at 50% probability levels<sup>[20]</sup>



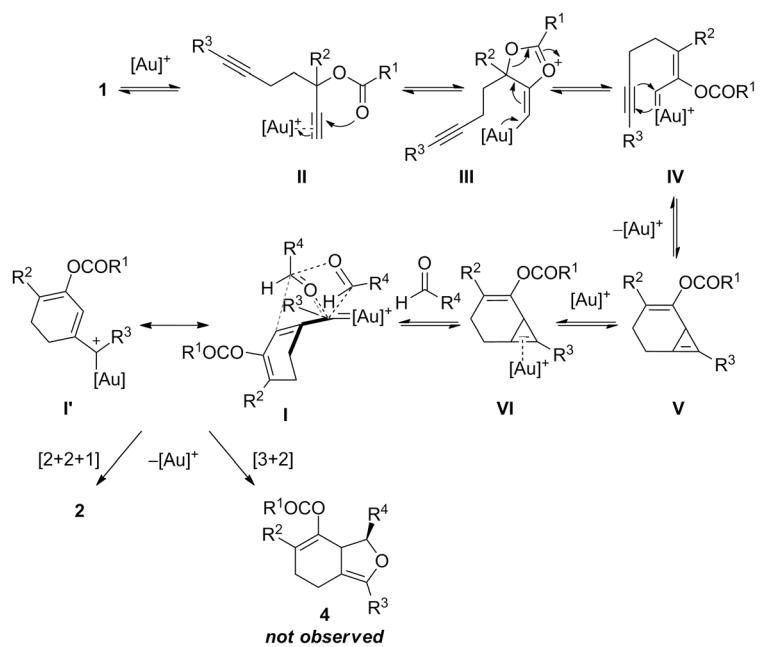
**Scheme 3.** Large-scale [2+2+1] cycloaddition of **1c** with propionaldehyde catalyzed by **A**.

favorable steric interactions between the R<sup>3</sup> and R<sup>4</sup> groups of the substrates.<sup>[17,18]</sup> The formation of the product as a single diastereomer along with the absence of the tetrahydroisobenzofuran adduct 4 resulting from a competitive [3+2] cycloaddition, as depicted in Scheme 4, suggests the 1,3-dioxolane ring forming process might also occur in a concerted manner.

In this work, the conversion of the 1,3-cyclohexadiene to the phenol was also examined (Scheme 5). Subjecting a dichloromethane solution containing **2I** to 1.5 equivalents of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for 4 h was found to afford the phenyl acetate **5I** in 96% yield. Further exposure of this aromatic compound to  $K_2CO_3$  in methanol at room temperature for 2 h followed by  $FeCl_3$  (10 mol %) in dichloroethane at  $80^\circ C$  for 2 h then furnished **6I** in 83% yield. In view of the synthetic utility of phenols as building blocks in organic synthesis, the present method also provides a new route to this important member of the benzoid family of compounds.<sup>[16,22]</sup>

## Conclusion

In summary, we have developed an efficient chemo- and dia stereoselective gold-catalyzed synthetic route to 4-(cyclohexa-1,3-dienyl)-1,3-dioxolanes from [2+2+1] cycloaddition of 1,6-diyne carbonates and esters with aldehydes. The approach offers a potential scale-up strategy at a catalyst loading as low as 1 mol% to the synthetically useful 1,3-cyclohexadiene motif containing an equally valuable 1,3-dioxolane ring system, as demonstrated by one example in an excellent yield. Added to this, the utility of this chemistry was illustrated by the conversion of one adduct to the corresponding phenol, another useful building block in organic synthesis. Efforts exploring the scope and synthetic applications of the present reaction are currently underway and will be reported in due course.



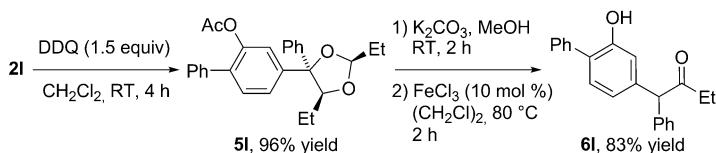
**Scheme 4.** Proposed mechanism for the [2+2+1] cycloaddition of 1,6-diyne carbonates and esters with aldehydes catalyzed by A. The possibility of a competing [3+2] cycloaddition pathway is represented by the grey dotted lines.

## Experimental Section

To a solution of the 1,6-diyne carbonate or ester 1 (0.2 mmol), aldehyde (2 mmol) and 4 Å MS (100 mg) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was added gold(I) complex A (10  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (1 mL) under an argon atmosphere at 0 °C. The reaction mixture was stirred at 0 °C for a further 0.2–24 h and monitored by TLC analysis until completion. The solution was filtered through Celite, washed with  $\text{CH}_2\text{Cl}_2$  (5 mL), concentrated under reduced pressure and purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc/ $\text{CH}_2\text{Cl}_2$  = 50:1:1) to give the 4-(cyclohexa-1,3-dienyl)-1,3-dioxolane product 2.

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Scheme 5. Conversion of **2l** to **6l**.

Yongxin Li of this Division for the X-ray crystallographic data reported in this work.

**Keywords:** aldehydes • cycloaddition • gold • homogenous catalysis • propargylic compounds

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