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When cobalt-mediated [2 + 2 + 2] cycloaddition reaction dares go astray: synthesis of unprecedented cobalt(III)-complexes†

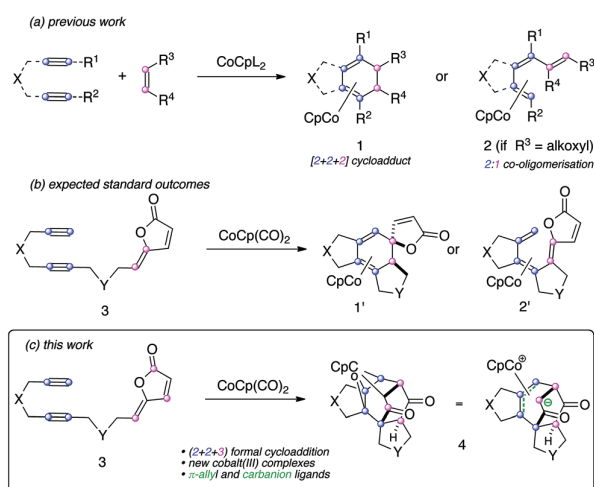
Marion Delorme,^a Alexander Punter,^a Raquel Oliveira,^b Corinne Aubert,^c Yannick Carissan,^a Jean-Luc Parrain,^a Muriel Amatore,^{*a} Paola Nava^{id} ^{*a} and Laurent Commeiras^{id} ^{*a}

In sharp contrast with the standard [2 + 2 + 2] cycloaddition reaction of diyne/ene, cobalt-mediated cycloadditions with γ -alkylidenebutenolide led to unprecedented cobalt(III) polycyclic complexes. A plausible mechanism supported by a computational study based on an unusual fragmentation of the butenolide moiety was postulated to account for this original reaction.

The transition metal-catalyzed [2 + 2 + 2] cycloaddition reaction is well established as one of the most elegant methods for the rapid construction of functionalised aromatic and hetero-aromatic polycyclic compounds, as well as 1,3-cyclohexadiene derivatives. Since the original report of a metal-mediated [2 + 2 + 2] cycloaddition reaction of acetylene derivatives,¹ many groups have demonstrated the significance of this reaction through the use of various transition metal complexes, mainly from group 8–10 elements (Ir, Ru, Ni, Fe, Co, Rh, Nb the most employed).² Among all the available catalysts, CpCoL₂ complexes (L = CO, PR₃, alkenes) have been frequently employed as an active source of “CpCo”. Such systems have proved their efficiency (i) for the co-cyclisation of alkynes with alkenes to give cyclohexadiene products **1** in their complexed form,^{2a} (ii) for the linear 2 : 1 co-oligomerisation³ of alkynes with acyclic enol ethers (R³ = alkoxyl) to give 1-alkoxy-1,3,5-triene derivatives **2** (Scheme 1a). It is worth noting that the use of cyclic enol ethers such as 2,3-dihydrofuran produced unconjugated 1,3,6-trienes³ whereas benzofuran derivatives led to the formation of the corresponding CpCo-complexed cyclohexadienes.⁴ Herein, we report the development of a cobalt-

mediated polycyclisation reaction with the original enediynes **3** bearing an alkylidenebutenolide moiety. Compared to “classic” alkenes as well as “classic” enol ethers, alkylidenebutenolides display a unique *exo*-cyclic double bond.

This double bond, which was never been used as 2 π partner in intra- or intermolecular [2 + 2 + 2] cycloaddition reactions, could have two distinct electronic properties due to the cyclic enol acetate and γ,δ -unsaturated lactone moieties. This specificity would account for the unusual reactivity (Scheme 1b and c). The main features of the present work include (i) formal (2 + 2 + 3) cycloaddition reaction, (ii) unprecedented formation of cobalt(III) complexes **4** featuring both π -allyl and carbanion ligands (highlighted in green in Scheme 1c) and (iii) high levels of regio- and diastereoselectivities. These cobalt(III) complexes rearranged in acidic conditions to give bicyclo[3.3.1] non-3-en-2-one scaffolds found in polyprenylated acylphloroglucinol natural products. Furthermore, a mechanism pathway, supported by a computational approach, based on



Scheme 1 Outcomes of cobalt(I)-mediated process.

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† Electronic supplementary information (ESI) available: Synthesis procedures, ¹H and ¹³C NMR spectra of each compound and computational studies. CCDC 1853760, 1853762, 1853766 and 1853778. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9dt03311d

unusual fragmentation of the butenolide moiety was also postulated.

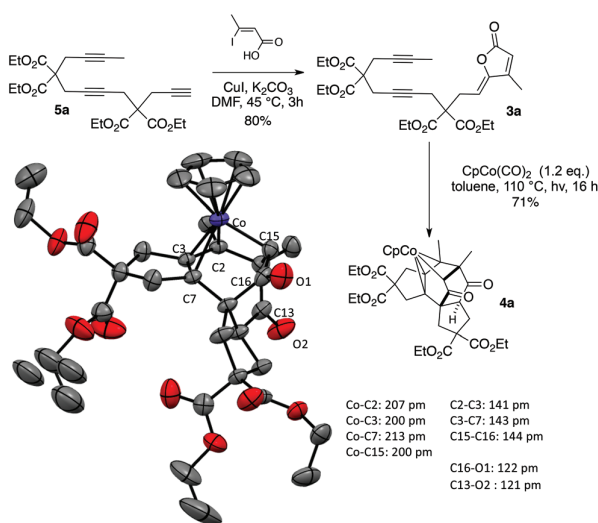
The study set out with the ene-1,6-diyne model **3a** (Scheme 2). This benchmark substrate, featuring two *gem*-bis-ethylester tethers, was prepared from the known triyne **5a**,⁵ via a palladium-free Sonogashira coupling/oxacyclisation sequence developed in our group.⁶ When diyne **3a** was exposed to a stoichiometric amount of CpCo(CO)₂ in toluene at 110 °C under irradiation, we did not observe the formation of the expected γ -spiro- γ -lactone **1a'** or 1,3,5-triene **2a'**. Interestingly however, an unforeseen tetracyclic cobalt complex **4a** has been isolated in 71% yield, as the sole diastereomer. Satisfyingly, the structure of **4a** was established without ambiguity thanks to an X-ray diffraction analysis.⁷ This cobalt(III) complex exhibits a bicyclo[3.2.2]nonane-6,8-dione core, in which the cobalt center is bound to the cyclopentadienyl anion, to the π -allyl moiety and to the carbanion in alpha position of a ketone. NMR (¹H, ¹³C and ⁵⁹Co) and UV-Vis spectroscopies as well as electrochemical studies complete the characterisation of complex **4a** (see the ESI†). Although the formation of the two five-membered rings could be expected in such a process, the conversion of the γ -alkylidenebutenolide backbone to a cyclohexa-1,3-dione pattern is unusual. This surprising result encouraged us to evaluate the potential influence of other cobalt sources, solvent or temperature. One other air-stable cobalt complex, activated only by heating (without irradiation) was tested. In these conditions, the use of CpCo(CO)dmfu⁸ (1 equiv. of complex in the toluene at 110 °C for 16 hours) gave rise to **4a** in 42% yield and with a conversion rate of 43%. An additional irradiation allowed an increase in the conversion rate (80%) as well the yield (54%). Because the CpCo(CO)₂ complex with a thermal (110 °C in toluene) and photochemical activation (CO dissociation) gave better results for obtaining the polycyclic complex **4a**, two other attempts in

which we varied the nature of solvent were next investigated. Firstly, in *o*-xylene at 140 °C under irradiation, the product **4a** was isolated in 28% yield. Many colored residues were obtained allowing us to evoke possible and important product degradation under these conditions. In addition, the activation of the CpCo(CO)₂ complex without irradiation is made possible by heating the mixture to 170 °C in *n*-decane. Unfortunately, only traces of the expected product **4a** were observed, despite the total disappearance of the starting material. These two results further support that the starting material and/or the product could be degraded at high temperature. Finally, the best conditions for the synthesis of **4a** request a stoichiometric amount of CpCo(CO)₂ in toluene at 110 °C under irradiation. With optimal conditions in hand, we further explored the versatility of this reaction for the synthesis of some tetracyclic cobalt(III) complexes by varying the nature and length of the two tethers (X and Y) along with the nature of the R¹ and R² substituents on the alkyne moiety and the γ -alkylidenebutenolide backbone, respectively (Scheme 3).

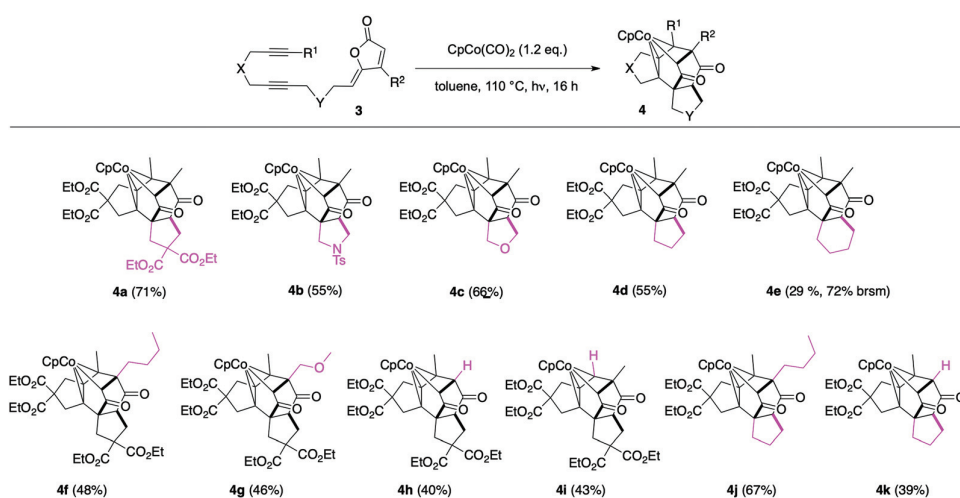
The nature of the tether Y was investigated first. In general, the desired products were obtained with similar efficiency and satisfactory yields. When Y = NTs, O or CH₂, the complexes **4b**,⁹ **4c** and **4d**¹⁰ were obtained at a yield of 55, 66 and 55%, respectively. Not surprisingly, when the reaction was conducted with an enediyne **5e** possessing an all carbon six-membered tether (Y = CH₂CH₂), the conversion rate was found to be lower (40%) even after a prolonged reaction time (24 h) and complex **4e** was isolated in a 29% yield (72% based on recovery starting material, brsm). We then turned our attention to the γ -alkylidenebutenolide pattern. Several substituents, such as hydrogen, *n*-butyl and CH₂OMe, are well tolerated, giving the desired cobalt(III) complexes **4f–h** in satisfactory yields. When R² is a phenyl group, and despite the complete consumption of the starting material, only products resulting from degradation were detected in the crude reaction mixture. In addition, changing the methyl group to a hydrogen atom on the alkyne part (R¹ = H) did not affect the efficiency of the reaction. To complete our study, we altered both the nature of the Y tether and R² group. Remarkably, the reaction proceeded smoothly giving the corresponding diketones **4j–k**.

We then investigated the potential of cobalt(III) complexes towards demetallation (Scheme 4). While reductive demetallation (Zn in DCE) was unsuccessful, protodemetallation reaction of **4a** (HCl 4 M in dioxane) gave a single product **6a** arising from a rearrangement of the bicyclo[3.2.2]nonane-6,8-dione core to 5-hydroxybicyclo[3.3.1]non-3-en-2-one in 55% yield. Similar results were also obtained when X = NTs (complex **4b**), giving polycyclic enone **6b** that, to our delight, led to crystals suitable for X-ray diffraction studies.¹¹ This rearrangement opens new opportunities to access bicyclo[3.3.1]non-3-en-2-one core of natural products from the family of polyprenylated acylphloroglucinol PPAP.¹²

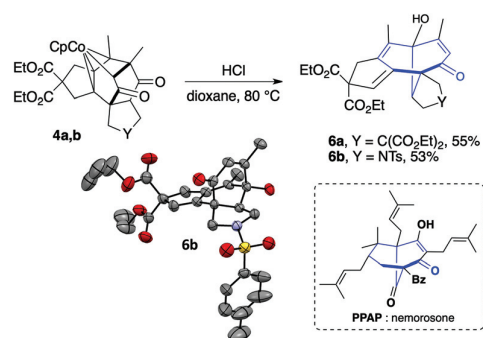
A preliminary computational study allows us to propose a possible mechanism that accounts for the formation of the polycyclic Co(III) complexes from a simplified model of **4d**, where X = C(CO₂Me)₂ (Fig. 1). It was previously shown that the



Scheme 2 Cobalt(II)-mediated synthesis and crystallographically-derived molecular structure of polycyclic cobalt(III) complex **4a**.



Scheme 3 Cobalt(I)-mediated synthesis of polycyclic cobalt(III) complexes.



Scheme 4 Demetallation and rearrangement of the cobalt(III) complexes **4a,b**.

two carbonyl ligands' substitution by two acetylenic units on CpCo is dissociative, and leads to **I**.³ The initial dissociation of the CO ligand leads to a complex in its triplet state. This was experimentally¹³ and theoretically¹⁴ studied by Bengali *et al.* and by Siegbahn respectively. From here, an inter-system-crossing is necessary to reach **I**, which is in a singlet state, as extensively studied.^{3,15,16}

Reported energies are Gibbs energies ($T = 110\text{ °C}$) relative to **I**. Structures were optimized and frequencies were computed at the BP86-D3/def2-TZVP level,¹⁷ following Kozłowski *et al.*¹⁸ Solvent effects were included by performing single-point energy calculations with the COSMO continuum solvent model.¹⁹ The first step, which requires an activation energy of 6.0 kcal mol^{-1} is the oxidative coupling of **I** to obtain **II**. The

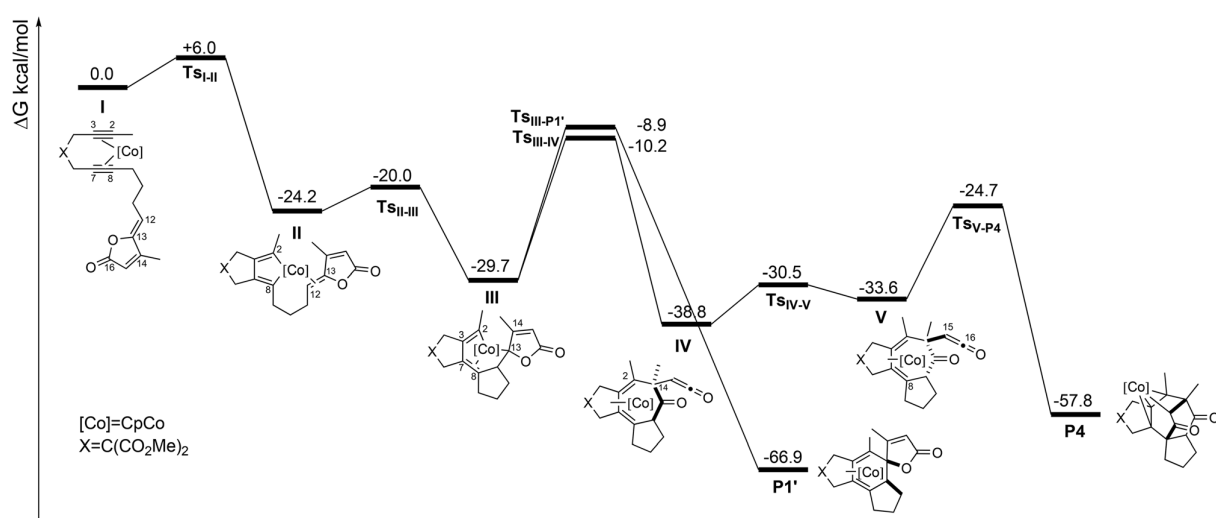


Fig. 1 Computed ΔG profile ($T = 110\text{ °C}$, kcal mol^{-1}). Computational level: BP86-D3/def2-TZVP, solvent effects by the COSMO model.

exo-cyclic double bond (C12–C13) binds to the cobalt metal center in **II** with a $-24.2 \text{ kcal mol}^{-1}$ stabilisation energy. Similar reactivities were already reported in an intermolecular fashion.^{3,15,16} In these reports, once the cobaltacyclopentadiene is formed, the triplet potential energy surface is reached. The following coordination of the 2π partner leads to a singlet intermediate, which would be analogous to **II** in our intramolecular approach. In both these inter- and intramolecular pathways, the mechanism proceeds from the coordinated singlet intermediate.²⁰ The presence of the five-membered link that joins C8 to C12 imposes a constraint in the approach of the double bond to the metal, resulting in a low-energy demanding closure of the C8–C12 σ -bond to give **III** with a barrier of $4.2 \text{ kcal mol}^{-1}$. From intermediate **III**, the next step is the formation of the C2–C14 bond, with a computed barrier of $19.4 \text{ kcal mol}^{-1}$ to give the β -oxo-ketene intermediate **IV**, which is 10 kcal mol^{-1} more stable than **III**. The formation of the C2–C14 bond triggers a concomitant reorganization of the electronic system: the Co–C13 bond breaks and, more interestingly, so does the lactone moiety in **III**. It is worth noting that the formation of the C2–C13 bond, which would lead to the normally expected spiro-like product **P1'**, is kinetically slightly disfavored with a barrier computed at $20.8 \text{ kcal mol}^{-1}$. Once **IV** is reached, the reaction proceeds to **P4** with no further energetic obstacles, *via* a two-step mechanism. Firstly, a conformational change around the ketone is necessary, leading to **V**. This latter is slightly endothermic (by $5.2 \text{ kcal mol}^{-1}$) and requires an activation Gibbs energy of $8.3 \text{ kcal mol}^{-1}$. Secondly, a final transition state (with a barrier of $8.9 \text{ kcal mol}^{-1}$) leads to the formation of both Co–C15 and C8–C16 bonds, giving the final product **P4** in an irreversible manner. A concerted mechanism was also explored to connect directly **II** to **IV**, nevertheless the transition state was located at $+1.4 \text{ kcal mol}^{-1}$ with respect to **I**, which corresponds to a $25.6 \text{ kcal mol}^{-1}$ barrier, higher than the ones associated to **Ts_{II-III}** and **Ts_{III-IV}**.

In summary, the Co-mediated cycloaddition reactions of enediynes bearing a γ -alkylidenebutenolide provided unexpected outcomes. A Co(I)-mediated formal (2 + 2 + 3) cycloaddition was observed leading to original cobalt(III) complexes possessing a bicyclo[3.2.2]nonane-6,8-dione backbone. A plausible mechanism supported by a computational study based on an unusual fragmentation of the butenolide moiety was postulated to account for this original reaction.

Furthermore the cobalt(III) complexes rearranged in acidic conditions to give bicyclo[3.3.1]non-3-en-2-one scaffolds found in polyprenylated acylphloroglucinol natural products. The increasing complexity associated with a perfect diastereoselectivity makes this cobalt-mediated process particularly attractive and opens new possibilities. Experimental and computational studies on related Co-mediated cycloadditions are ongoing in our laboratories.

Conflicts of interest

There are no conflicts to declare.

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