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Ru(II)-catalyzed [2 + 2 + 2] cycloaddition of 1,2-bis(propiolyl)benzenes with monoalkynes leading to substituted anthraquinones†

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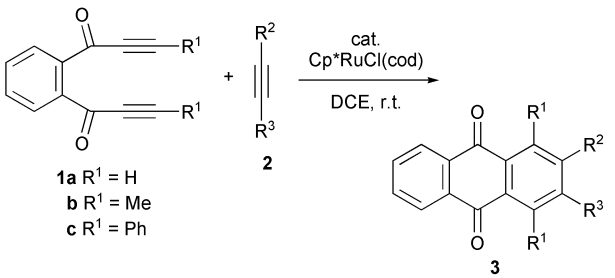
[2 + 2 + 2] cycloadditions of 1,2-bis(propiolyl)benzenes with monoalkynes were effectively catalysed by Cp*RuCl(cod) under mild conditions to give substituted anthraquinones in moderate to high yields.

The transition-metal mediated [2 + 2 + 2] cycloaddition[1] of a 1,2-bis(propiolyl)benzene **1** with a monoalkyne is a convergent and straightforward route to substituted anthraquinone frameworks (Scheme 1). Such a potentially useful anthraquinone annulation was first realized by means of the reaction of isolated naphthoquinone-fused rhodacyclopentadiene complexes with monoalkynes,[2] and direct coupling of diketodiyne **1c** and monoalkynes was independently achieved using highly toxic $Ni(CO)_4$ in large excess.[3] From the viewpoint of environmental safety, an alternative *catalytic* protocol is, however, highly desirable. In this context, some research groups reported catalytic versions of anthraquinone annulations. Müller and Meier *et al.* extended their own works to a catalytic protocol utilizing 5–25 mol% $Ni(PPh_3)_2(CO)_2$ as a precatalyst at 60–130 °C.[4] Thereafter, Vollhardt's group applied their $CpCo(CO)_2$-catalyzed method to two diketodiyne substrates to result in low yields of around 20%.[5] More recently, McDonald and co-workers reported the cycloaddition of a diketodiyne **1b** with alkynylglycals using 20 mol% $ClRh(PPh_3)_3$ in refluxing EtOH, in which interesting *C*-arylglycosides were obtained in 35–58% yields.[6] These existing examples, however, have some disadvantages which need to be improved: (1) sub-stoichiometric amounts of precatalysts (20–33 mol%) or reaction temperatures above 60 °C are required, (2) the diyne substrate was almost completely confined to the internal diketodiynes **1b** and **1c**, and (3) the product yields were not higher than 80%.

We have previously revealed that a ruthenium(II) complex, Cp*RuCl(cod) (Cp* = pentamethylcyclopentadienyl, cod = 1,5-cyclooctadiene), catalysed the cycloaddition of 1,6-diynes with monoalkynes at ambient temperature to chemo- and regioselectively give bicyclic benzene derivatives in good yields.[7] To extend the ruthenium catalysis, we investigated the ruthenium-catalysed cycloaddition of 1,2-bis(propiolyl)benzene derivatives **1** as diyne components. Initially, a terminal diketodiyne substrate **1a** was reacted with 1-hexyne **2a** (2 equiv.) in the presence of 1 mol% Cp*RuCl(cod) in 1,2-dichloroethane (DCE) at room temperature. After stirring the solution for 4 h, complete consumption of **1a** was observed by TLC analysis. Concentration of the reaction mixture followed by silica gel column chromatography afforded the desired anthraquinone **3aa** in 71% yield (Scheme 1). The cycloaddition completed for 1.5 h with increased amounts of both the catalyst (2 mol%) and **2a** (4 equiv.), and the yield was improved to 90% (Table 1, run 1).‡ The present ruthenium catalysis proved compatible with various functional groups on the monoalkyne components. In a similar manner to run 1, propargyl methyl ether **2b**, 5-chloro-1-pentyne **2c**, methyl 5-hexynoate **2d**, and *N*-propargyl phthalimide **2e** gave anthraquinones possessing a functionalised side chain in high yields (runs 2–5). Interestingly, the reaction rate was increased for the latter two monoalkynes, indicating that coordination of the ester or imide carbonyl groups to the ruthenium centre facilitated the cycloaddition. On the other hand, the ruthenium catalysis is quite sensitive to the steric bulk of the monoalkyne components. Sterically demanding *tert*-butylacetylene **2f** reacted more slowly than the above monoalkynes **2a–e** (run 6). Consequently, the yield of the expected quinone **3af** is moderate probably due to the competitive dimerization of **1a**. Phenylacetylene **2g** also exhibited low reactivity, requiring an increased catalyst loading of 5 mol% to ensure the complete conversion of **1a** (run 7). In striking contrast, upon stirring with the 2 mol% precatalyst under an acetylene atmosphere, **1a** was efficiently converted into **3ah** within 0.5 h in 92% yield (run 8).

In addition to the above terminal monoalkynes, internal alkynes can be employed for our protocol, although relatively higher catalyst loadings are required. The reaction of **1a** with 3-hexyne **2i** for 20 h gave rise to a disubstituted anthraquinone **3ai** in 33% yield (run 9). Such a low yield was again ascribed to the competitive dimerization of **1a**. An internal diketodiyne **1b** possessing methyl substituents at both alkyne termini was



Scheme 1

Table 1 Ruthenium-catalysed cycloadditions of **1** and monoalkynes

Run	R^1	R^2	R^3	Catalyst (mol%)	Time	Yield[a] (%)
1	H	H	*n*-Bu	2	1.5 h	**3aa** 90
2	H	H	CH_2OMe	1	3 h	**3ab** 84
3	H	H	$(CH_2)_3Cl$	2	1 h	**3ac** 81
4	H	H	$(CH_2)_3CO_2Me$	2	0.5 h	**3ad** 84
5	H	H	$CH_2NPhthal$[b]	1	10 min	**3ae** 76
6	H	H	*t*-Bu	2	6 h	**3af** 65
7	H	H	Ph	5	3 h	**3ag** 65
8	H	H	H[c]	2	0.5 h	**3ah** 92
9	H	Et	Et	5	20 h	**3ai** 33
10	Me	Et	Et	10	4 h	**3bi** 66
11	Me	H	*n*-Bu	10	20 h	**3ba** 80
12	Me	Ph	Ph	5	1 h	**3bj** 90

[a] Isolated yields. [b] NPhthal = phthalimide. [c] 1 atm.

† Electronic supplementary information (ESI) available: experimental procedures and analytical data. See http://www.rsc.org/suppdata/cc/b3/b301762a/

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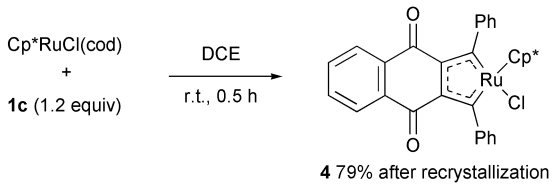
expected to be less prone to self-dimerization. Actually, upon reacting with **2i** in the presence of the 10 mol% precatalyst, **1b** afforded the desired tetrasubstituted anthraquinone **3bi** in an improved yield of 66% (run 10). The terminal alkyne **2a**, also reacted with **1b** without difficulty to furnish a trisubstituted product **3ba** in 80% yield (run 11). As already described, phenyl acetylene **2g** was found less reactive compared to other terminal monoalkynes, but, surprisingly, diphenylacetylene **2j** reacted with **1b** with less precatalyst and a shorter reaction time to afford **3bj** in excellent yield (run 12). The reason for such a striking difference in reactivity between **2g** and **2j** is not clear at this stage.

The phenyl terminal groups on a diyne component gave a deteriorative effect on the cycloaddition ability. No cycloadduct was obtained from the reaction of **1c** with both diphenyl acetylene and acetylene. As previously proposed for the ruthenium-catalyzed cycloaddition of 1,6-diynes and monoalkynes, the present anthraquinone annulation probably proceeds *via* bicyclic ruthenacycle intermediate.[7,8] If this is the case, the terminal phenyl groups on the diketodiyne might stabilize the ruthenium–carbon bonds and thus reduce the reactivity of the expected ruthenacycle **4**. In good agreement with these analyses, **4** was formed by simply stirring the solution of Cp*RuCl(cod) and a slight excess of **1c** in DCE at room temperature for 0.5 h. Recrystallization from $CHCl_3$/ether afforded **4**·$CHCl_3$ in 79% yield as single crystals (Scheme 2). The obtained single crystal was further submitted to X-ray diffraction study.§



Scheme 2

As shown in Fig. 1, **4** has the expected naphthoquinone-fused ruthenacyclic framework. The ruthenacycle core structure is very similar to the precedent ruthenacyclopentatriene complexes **I**[9] and **II**[10] formed from two phenyl acetylene molecules and CpRuBr(cod) or Cp*RuCl(cod). The Ru–C1 and Ru–C4

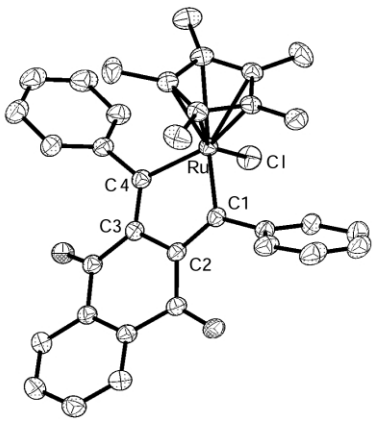
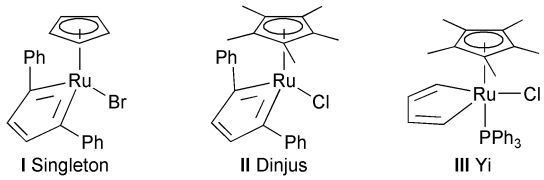


Fig. 1 ORTEP diagram of **4**. Ellipsoids are shown at the 50% probability level. All hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (°): Ru–Cl 2.3279(6), Ru–C1 1.990(2), Ru–C4 2.009(2), C1–C2 1.395(3), C2–C3 1.430(3), C3–C4 1.400(3); Ru–C1–C2 118.08(15), Ru–C4–C3 117.18(15), C1–Ru–C4 78.43(8), C1–C2–C3 113.11(19), C2–C3–C4 113.11(19).

bond distances [1.990(2) and 2.009(2) Å] are intermediate between those of the ruthenacyclopentatriene complexes [**I**: 1.942(6), **II**: 1.969(4) Å] and a ruthenacyclopentadiene(phosphine) complex **III**[11] [2.059(5) and 2.092(4) Å], indicative of these bonds having partial double bond character. Actually, the ^{13}C NMR spectrum (75 MHz, $CDCl_3$) showed the characteristic carbene resonance of C1 and C4 at δ 263.89 ppm. The length of the C2–C3 bond incorporated with the naphthoquinone ring is also longer than those in **I** and **II** [1.430 *vs*. 1.377(12) or 1.37(1) Å]. The isolated **4** never gave a cycloadduct upon exposure with acetylene, diphenylacetylene, and dimethyl acetylenedicarboxylate.



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Notes and references

‡ *Typical procedure—Synthesis of* **3aa**: To a degassed solution of Cp*RuCl(cod) (2.4 mg, 0.006 mmol) and 1-hexyne (98.7 mg, 1.2 mmol) in 1,2-dichloroethane (1 mL) was added a degassed solution of 1,2-bis(propiolyl)benzene **1a** (55.4 mg, 0.30 mmol) in 1,2-dichloroethane (4 mL) by a syringe for 20 min under Ar at room temperature. The solution was stirred for 1.5 h, and concentrated *in vacuo*. The residue was purified by silica gel flush column chromatography (hexane–AcOEt 25 : 1) to afford **3aa** (72.3 mg, 90%) as colorless solids.

§ *Crystallographic data*: Intensity data were collected at 173 K on a Bruker SMART APEX diffractometer with Mo-Kα radiation (0.71073 Å) and graphite monochromator. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 (SHELXTL). **4**·$CHCl_3$ [$C_{35}H_{30}Cl_4O_2Ru$, M_w = 725.46]; space group $P2_1/n$, monoclinic; a = 11.6335(6), b = 18.8471(10), c = 15.0128(8) Å, β = 111.8490(10)°, V = 3055.2(3) Å^3; Z = 4, D_{calc} = 1.577 g cm^{-3}; 23271 total reflections were measured of which 8153 were independent [R(int) = 0.0236]; final R_1 = 0.0380, wR_2 = 0.1072 [$I > 2\sigma(I)$], and GOF = 1.060 (for all data, R_1 = 0.0427, wR_2 = 0.1103). CCDC reference number 203734. See http://www.rsc.org/suppdata/cc/b3/b301762a/ for crystallographic data in CIF or other electronic format.

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