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# Pauson–Khand reaction of 7-oxabicyclo[2.2.1] systems

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**Abstract**—The amine oxide-promoted Pauson–Khand cycloaddition of 7-oxanorbornene and norbornadiene derivatives affords easily oxa-bridged bicyclic cyclopentenones with satisfactory 60–80% yields. © 2003 Elsevier Science Ltd. All rights reserved.

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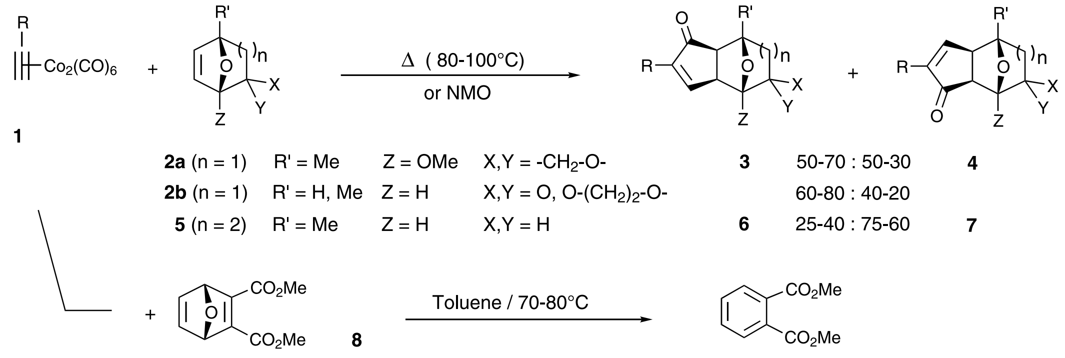
The $Co_2(CO)_8$-mediated Pauson–Khand reaction (PKR)—carbonylative co-cyclisation of an alkyne and an alkene—has emerged as one of the most versatile routes to cyclopentenones,[1] particularly in its intramolecular version which has been used for the synthesis of numerous polycyclic natural products.[2,3] Intermolecular PKR has met with less success, and is limited to strained olefins such as norbornene or norbornadiene derivatives[4] and to some olefins bearing a heteroatom.[5] Particularly, the intermolecular PKRs of carbon-bridged cycloalkenes were recently revisited by Laschat et al. from a mechanistic point of view.[6]

Unexpectedly, very few works have been devoted to oxa-bridged bicyclic alkenes as the olefinic components. Apart from some isolated results obtained with 4-methyl-1-methoxy-7-oxanorbornene **2a**,[1c,7] the only work in this area described the cycloadditions of 2-keto-7-oxanorbornene derivatives **2b** (Scheme 1).[8] This last work focused on the electronic influence of the keto group (protected or not) at the C-2 on the regiochemical control of the formation of the regioisomeric cyclopentenones **3** and **4** (**3**:**4** = 60–80:40–20). On the other hand several studies were carried out on 8-oxabicyclo[3.2.1]octenes **5** which led to reversed regioselectivities (**6**:**7** = 25–40:75–60).[9] As for 7-oxanorbornadienes, these compounds such as **8** were described to be deoxygenated to aromatic compounds under classical thermal PKR conditions.[10]

In order to gain more insight into the PKRs of oxa-bridged bicyclic alkenes, we were interested by the unexplored reactivities of 2,3-disubstituted-7-oxa-bicyclo[2.2.1] systems under the mild amine oxide-promoted cycloaddition conditions.[11] Indeed, these substrates are very prone to decomposition via an easy *retro*-Diels–Alder reaction[12] which may compete with a desired PKR. We report here our recent results in this field.



**Scheme 1.**

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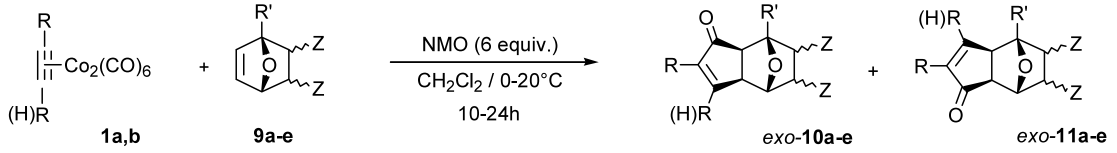
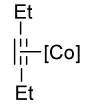
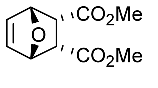
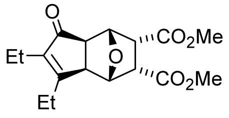
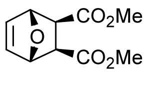
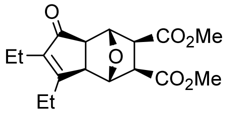
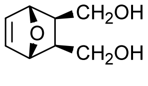
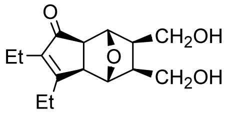
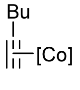
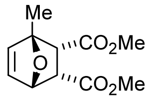
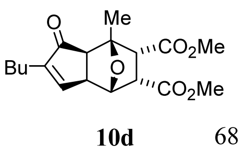
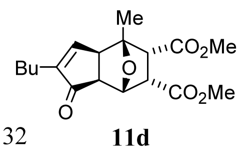
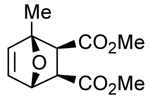
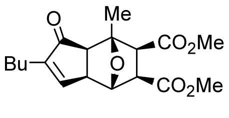
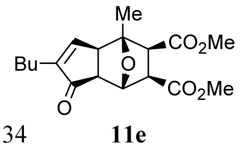
We first looked at the reactivity of 2,3-disubstituted 7-oxanorbornenes **9a**–**e**.[13] Thus, the reactions of dicobalthexacarbonyl complexes **1a**,**b** with 7-oxanorbornenes **9a**–**e** were carried out in $CH_2Cl_2$ at 0–20°C in the presence of *N*-methylmorpholine oxide (NMO, 6 equivalents with respect to complex **1**) (Table 1). The 3-hexyne-dicobalt complex **1a** reacted with symmetrical 7-oxanorbornenes *endo*-**9a** and *exo*-**9b** and gave with fairly good yields the expected *exo*-cyclopentenones **10a**–**b** (entries 1 and 3). The reactivity of 7-oxanorbornene *endo*-**9a** was also checked under thermal conditions in refluxing benzene (entry 2). The cyclopentenone **10a** was then obtained with a low 23% yield, together with the *retro*-Diels–Alder product dimethyl maleate (28%) and the recovered dicobalt complex **1a** (37%), which shows that thermal conditions are unsuitable for these substrates.

The 7-oxanorbornenic diol **9c** also reacted and gave the *exo*-cyclopentenone **10c** (entry 4). The cycloadditions of the terminal alkyne–dicobalt complex **1b** with the *endo*-**9d** and *exo*-1-methyl-7-oxanorbornene **9e** both gave a mixture of regioisomeric cyclopentenones **10d**,**e** and **11d**,**e** in a similar ratio **10**:**11** = 68:32 and 66:34, respectively, which proves that the regioselectivity is independent of the *endo* or *exo* stereochemistry of the carbomethoxy substituents at carbons C-2 and C-3 (entries 5 and 6). As already encountered with the PKRs of norbornenic compounds,[4b,6] the cycloadducts **10a**–**e** and **11d**–**e** were assigned *exo*-cyclopentenones structures, as demonstrated by the typical absence of coupling constant between the Hα and Hβ protons with the bridghead protons.[14]

We next studied the reactivity of 2,3-dicarbomethoxy-7-oxanorbornadienes **8a**,**b**[15] under similar conditions

**Table 1.** Pauson–Khand reaction of 7-oxanorbornenes **9a**–**e**[a]



| Entry | Alkyne-dicobalt complex **1a**,**b**[b] | 7-Oxanorbornene **9a-e** | Cycloadducts **10-11** | Yield (%)[c] |
|---|---|---|---|---|
| 1 |  **1a** |  **9a** |  **10a** | 68 |
| 2[d] | **1a** | **9a** | **10a** (23%) + MeO2C-CH=CH-CO2Me (28%) + **1a** (37%) | - |
| 3 | **1a** |  **9b** |  **10b** | 78 |
| 4 | **1a** |  **9c** |  **10c** | 70 |
| 5 |  **1b** |  **9d** |  **10d** 68 : 32  **11d** | 67 |
| 6 | **1b** |  **9e** |  **10e** 66 : 34  **11e** | 82 |

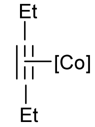
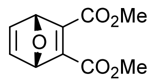
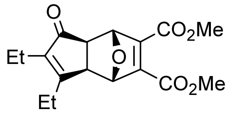
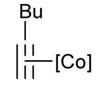
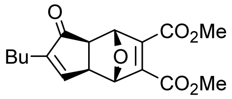
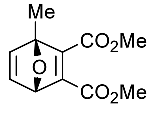
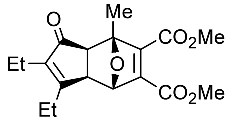
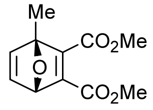
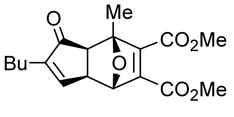
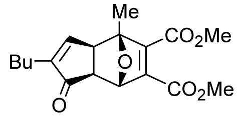
[a] Reactions were carried out in $CH_2Cl_2$ at 0-20°C (ratio **1**:**9**:NMO = 1.1:1:6.6)

[b] [Co] = $Co_2(CO)_6$.

[c] Yields of purified products after flash-chromatography.

[d] Reaction carried out without NMO in benzene at 80°C during 2h.

**Table 2.** Pauson–Khand reaction of 7-oxanorbornadienes **8a**,**b**[a]

| Entry | Alkyne-dicobalt Complex **1a**,**b**[b] | 7-Oxanorbornadiene **8a**,**b** | Products **12-13** | Yield (%)[c] |
|---|---|---|---|---|
| 1 |  <br>**1a** |  <br>**8a** |  <br>*exo*-**12a** | 59 |
| 2 |  <br>**1b** | **8a** |  <br>*exo*-**12b** | 62 |
| 3 | **1a** |  <br>**8b** |  <br>*exo*-**12c** | 81 |
| 4 | **1b** |  <br>**8b** |  <br>*exo*-**12d** 74 : 26 *exo*-**13d**<br> | 79 |

[a] Reactions were carried out in $CH_2Cl_2$ at 0-20°C (ratio **1**:**8**:NMO = 1.1:1:6.6)

[b] [Co] = $Co_2(CO)_6$.

[b] Yields of purified products after flash-chromatography.

(Table 2). The reaction of the symmetrical diene **8a** with both dicobalt complexes **1a**,**b** afforded the *exo*-cyclopentenones **12a** and **12b**, respectively (entries 1 and 2). Dicobalt complex **1a** reacted with 1-methyl-7-oxanorbornadiene **8b** and gave the *exo*-cyclopentenone **12c**; none of the regioisomeric cyclopentenone **13c** was isolated (entry 3). On the other hand, the reaction of the monosubstituted alkyne–dicobalt complex **1b** with **8b** gave a mixture 74:26 of the two regioisomeric *exo*-cyclopentenones **12d** and **13d** (entry 4).

In conclusion, we have shown that the PKRs of 7-oxanorbornene and norbornadiene derivatives, which did not seem possible under thermal conditions, are easily carried out when promoted by NMO.[16] They lead to oxa-bridged bicyclic cyclopentenones with satisfactory yields.

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13. The 7-oxanorbornenes **9a**,**b** and **9d**,**e** were prepared from furanes via $ZnBr_2$-catalyzed Diels–Alder reaction. 7-Oxanorbornenic diol **9c** was obtained from the reduction of diester **9b**.
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16. **Typical procedure** (Table 2, entry 2): 8,9-dimethoxy-carbonyl-4-butyl-10-oxatricyclo[5,2,1,$0^{2,6}$]deca-4,8-dien-3-one **12b**. A stirred solution of $Co_2(CO)_8$ (3.6 g, 10.5 mmol) in anhydrous $CH_2Cl_2$ (80 mL) under nitrogen, was treated in minutes with 1-hexyne (1.33 mL, 11.55 mmol), and the mixture was stirred for 2 h. A solution of 2,3-dicarbomethoxy-7-oxanorbornadiene **2a** (2 g, 9.51 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise. After cooling at 0°C, *N*-methylmorpholine oxide NMO (7.4 g, 63 mmol) was added in small portions. The reaction mixture was then stirred overnight at room temperature. The resulting suspension was filtered through Celite and the solvent evaporated. Flash-chromatography (silica gel, petroleum ether–ether, 6:4) afforded 1.9 g (62%) of cyclopentenone **12b** as a white solid: mp 75–76°C; IR (KBr) $\nu$ 1780, 1710 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J=7.2$ Hz, 3H), 1.29 (m, 2H), 1.43 (m, 2H), 2.15 (t, $J=7.9$ Hz, 2H), 2.67 (d, $J=5.1$ Hz, 1H), 3.12 (br.s, 1H), 3.81 (s, 6H), 4.95 (s, 1H), 5.20 (s, 1H), 7.18 (d, $J=1.3$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 205.6 (*C*=O), 162.8 (*C*=O), 162.5 (*C*=O), 154.7 (*C*=), 151.5 (*C*=), 145.4 (*C*=), 144.3 (*C*=), 82.9 (*C*H-O), 81.8 (*C*H-O), 52.8 (2×$CH_3$-O), 51.1 (*C*H), 47.2 (*C*H), 29.8 ($CH_2$), 25.1 ($CH_2$), 22.7 ($CH_2$), 14.4 ($CH_3$); HMRS (CI), calcd for $C_{17}H_{21}O_6$ $[M+H]^+$ 321.1338, found 321.1335.