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Highly Diastereoselective Pauson-Khand Reactions of a Stable, Internally Chelated, Dicobalt Pentacarbonyl Complex of a Chiral Acetylene Thioether

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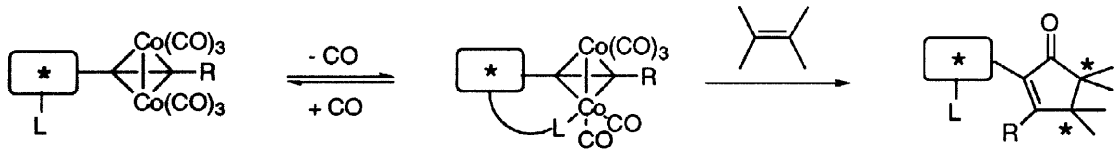
Abstract. The hexacarbonyl dicobalt complex of the acetylene thioether derived from (2*R*)-*exo*-10-(methylthio)-2-bornanethiol has been prepared in good yield. This compound affords a stable internally chelated pentacarbonyl complex either by thermal or oxidative decarbonylation. Optimal conditions for the highly diastereoselective reaction of the chelated species have been developed.

The Pauson-Khand (PK) reaction has become over the years one of the most reliable methodologies for cyclopentenone synthesis,[1] as evidenced by its use as the key step in the syntheses of many natural products. It is thus not surprising that increasing efforts are being devoted to the development of practical enantioselective versions of the reaction.[2-6] Leaving apart the recent report by Buchwald[2] on an enantioselective catalytic intramolecular PK type reaction mediated by titanium, two main approaches have been followed to induce asymmetry in the archetypal, cobalt-mediated process: The use of chiral auxiliaries directly bound to either of the reacting fragments[3-5] and the intermediate generation of complexes possessing a disymmetric C_2Co_2 core.[6] In spite of the conceptual appeal inherent to the second approach, only the first one has found wide application, mainly due to practical reasons.

Inspired by the work of Krafft on the directed PK reaction,[7] we introduced some years ago a new concept in stereocontrolled PK reactions which combines the main advantages of the two aforementioned approaches: The use of a chiral auxiliary with chelating capability[8] which could allow an efficient transfer of chirality to the C_2Co_2 core, as represented in Figure 1.



Chirality transfer to cobalt *Chirality transfer to cyclopentenone*

Figure 1

Our first candidate to put these ideas into work was (10-methylthioisobornyloxy)acetylene **1a**. Working with the dicobalt hexacarbonyl complex of this alkyne (**2a**) , we could observe the establishment of an equilibrium with a presumed pentacarbonyl complex (**3a**) and we could also study the diastereoselective reactions thereof[8a] (Scheme 1).

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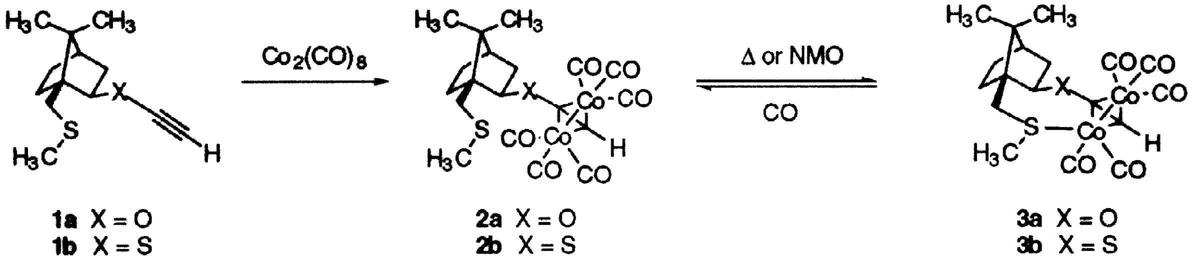


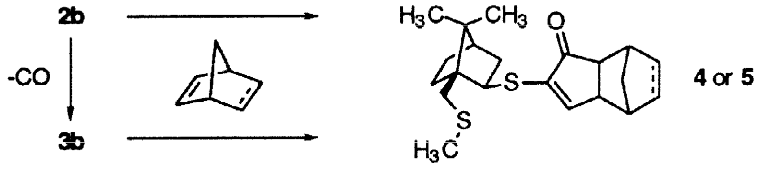
Scheme 1

Complex **3a** exhibited only a moderate stability, readily decomposing into **2a** and paramagnetic products, and this fact prevented its isolation and full characterisation. We reasoned that replacement of oxygen with sulphur in our chiral auxiliary could have two advantages: the easier preparation of the hexacarbonyl dicobalt complex[4d] and an enhancement of the stability of the chelated complex since the longer C-S bonds would diminish the strain of the ring formed by chelation. To test this idea, however, the synthesis of the designed auxiliary was first required; this goal has been recently achieved.[9] We wish to report here the generation and isolation of the internally chelated dicobalt pentacarbonyl complex **3b**, as well as its reactivity with strained alkenes.

The starting acetylene thioether **1b** was prepared from (2*R*)-*exo*-10-(methylthio)-2-bornanethiol **4**[9] according to our previously published procedure[4d] in 64% overall yield or, more conveniently, by the method of A.E. Greene[10] in 71% yield. The corresponding dicobalt hexacarbonyl complex **2b**, in turn, was prepared in 92% yield under standard conditions. In full agreement with our expectations, the chelated pentacarbonyl complex **3b** was readily formed under thermal (55°C, 1h, N_2 stream) or oxidative (≥3 equiv. NMO, CH_2Cl_2, r.t., 0.5 h) conditions, and could be isolated in essentially pure form as a red-brown oil by column chromatography. It is worth noting that both complexes **2b** and **3b** proved to be much more stable than their oxygenated analogues. This stability allowed their chromatographic purification and spectroscopic characterisation. Although two diastereomeric pentacarbonyl complexes can be formed by chelation of the methylthio group to each one of the two diastereotopic cobalt atoms, in the ^1H and ^{13}C NMR spectra of **3b** only one set of signals corresponding to one stereoisomer was observed. A detailed spectroscopic study of the pentacarbonyl complex **3b** will be given in the full paper.

Although both studied methods for the generation of **3b** are almost equivalent in terms of yield (thermal: 89%; NMO: 83%), we have observed that under oxidative conditions the prepared samples of **3b** are completely free of **2b**. As we will see, this fact can be of some concern in reactivity studies.

To analyse the effect of chelation on diastereoselectivity, we next studied the reactions of **2b/3b** with norbornadiene and norbornene (Scheme 2) under a variety of experimental conditions. The results are summarised in Table 1.



Scheme 2

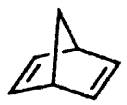
As a control experiment we first performed (entry 1) the PK reaction of the hexacarbonyl complex **2b** with norbornadiene under CO at 0 °C. Under these conditions, designed to inhibit the formation of **3b**, the reaction takes place very slowly and with poor diastereoselectivity. To study the corresponding reaction of **3b**, we first employed the classical Schreiber's conditions[11] involving the use of 6 equivalents of NMO in dichloromethane (entries 2 and 3). Quite disappointingly, we observed no improvement in the diastereoselectivity in the reaction at 0°C and, even more surprisingly, the diastereoselectivity was completely lost when the reaction was conducted at -20°C, in sharp contrast with the behaviour of **3a**.[8a]

By controlling the formation of **3b** by TLC, we could realise that 3 equivalents of NMO are enough for the complete conversion of **2b**, and this observation guided the development of reaction conditions D (entry 6), which provided the tricyclic ketone **4** in good yield and excellent diastereoselectivity (95:5). Clearly, the presence of excess NMO in the reaction medium has a deleterious effect on diastereoselectivity.

The alternative, purely thermal procedure for the generation of **3b** (Conditions C) has the advantage of do not requiring the use of any added chemical; however, **3b** obtained in this way is always accompanied by a few percent of **2b**. A comparison of the results of entries 4 and 6 shows that this contamination is negative for diastereoselectivity; moreover, the effect of lowering the reaction temperature in order to inhibit the reaction of the present impurity (entry 5) does not represent any significant improvement.

With the less reactive norbornene, similar reactions involved longer reaction times and took place with lower diastereoselectivity (compare entries 4/8 and 6/9). Again, the optimal diastereoselectivity was recorded under conditions D.

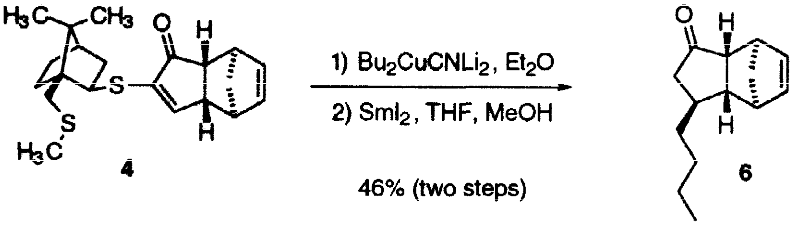
Table 1 Pauson-Khand reactions of **2b**/**3b** with strained alkenes.

Entry	**Alkene**	**Reaction conditions**[a]	**Product**	**Yield [%]**	**d.r.**
1		A, 0°C, 552 h	**4**	31	67 : 33[b]
2		B, 0°C, 24 h	**4**	64	68 : 32[b]
3		B, -20°C, 60 h	**4**	67	52 : 48[b]
4		C, 0°C, 24 h	**4**	52	92 : 8[b]
5		C, -20°C, 144 h	**4**	53	93 : 7[b]
6		D, -10°C, 72 h	**4**	65	**95 : 5**[b]
7		B, 0°C, 48 h	**5**	66	37 : 63[c]
8		C, 0°C, 48 h	**5**	45	82 : 18[c]
9		D, -10°C, 120 h	**5**	66	86 : 14[c]

[a] **Conditions A**: Stirring the dicobalt hexacarbonyl complex **2b** and the olefin (10 eq.) in hexane under CO at the specified temperature. **Conditions B**: Generation of the pentacarbonyl complex **3b** by addition of excess NMO (6 eq.) to a solution of **2b** in methylene chloride, followed by addition of the olefin (10 eq.) at the specified temperature. **Conditions C**: Generation of the pentacarbonyl complex **3b** by heating the solution of **2b** in hexane at 55°C followed by cooling and addition of the olefin (10 eq.) at the specified temperature. **Conditions D**: Generation of the pentacarbonyl complex **3b** by addition of NMO (3 eq.) to a solution of **2b** in methylene chloride and removal of the excess of NMO by filtration through Al_2O_3, followed by addition of the olefin (10 eq.) at the specified temperature. [b] HPLC (Nucleosil C18, $MeOH/H_2O$ 80:20). [c] By ^{13}C and ^{1}H NMR.

The absolute configuration and a convenient procedure for the elaboration of the major diastereomer of cycloadduct **4** is shown in Scheme 3. A two step sequence of conjugate addition with $Bu_2CuCNLi_2$ followed by SmI_2 mediated cleavage[12] of the alkylthio group afforded the bicyclic cyclopentanone **(-)-6** of known absolute configuration, [8b,c] in good yield and complete diastereoselectivity. We have previously shown[4d,8] that these tricyclic ketones are convenient precursors of enantiopure 4-alkylcyclopentenones via retro-Diels-Alder methodologies[13]

In summary, we have designed and isolated an stable, internally chelated dicobalt pentacarbonyl complex of an acetylene thioether and we have studied its highly diastereoselective Pauson-Khand reactions with strained olefins. The exceptional stability of the chelated complex **3b** should facilitate a complete NMR structural study as well as kinetic studies that could shed light on the detailed mechanism of the PK reaction. Work along these lines is in progress in our laboratories and will be reported in due term.



Scheme 3

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