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Chiral cyclopentadiene-mediated approach to enantioselective heterobimetallic Pauson–Khand reactions

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Abstract

When the dicobalt(hexacarbonyl) complex of *N*-(2-butynoyl)-4,4-dimethyloxazolidinone (**1**) is treated with chiral cyclopentadienyl (tricarbonyl)molybdenum anions, pairs of diastereomeric heterobimetallic (Co–Mo) complexes are obtained. In one instance, the two diastereomers have been separated by chromatography and they have been reacted with norbornadiene; each diastereomer leads with virtually complete stereocontrol to a single enantiomer of the *endo* Pauson–Khand cycloadduct **5**.

Keywords: Alkynes; Asymmetric synthesis; Chiral cyclopentadienes; Cobalt; Molybdenum; Pauson–Khand reactions

1. Introduction

The transition metal-induced carbonylative cocyclization of an alkyne and an alkene, first disclosed by Pauson and Khand three decades ago [1], has emerged as a most valuable and efficient method for the synthesis of cyclopentenone derivatives [2]. In the original version of this reaction, the dicobalt(hexacarbonyl) complexes of alkynes were heated in the presence of olefins to give a 2-cyclopentenone in a single step; in addition to cobalt, other transition metals were later shown to promote the same transformation (Pauson–Khand type reactions) [3]. In particular, Mukai and Hanaoka reported in 1992 that the bis[(cyclopentadienyl)molybdenum(dicarbonyl)] complexes of alkynes, as well as the corresponding tungsten compounds, were suitable substrates for the intermolecular Pauson–Khand reaction [4]. Some years later, Rutherford and Christie [5] found that the heterobimetallic Co–Mo alkyne complexes obtained by replacing a cobalt(tricarbonyl) group with an isoelectronic (cyclopentadienyl)molybdenum(dicarbonyl) fragment were also active in Pauson–Khand type reactions. By using menthyl propargyl ether as the starting alkyne, this replacement led to a pair of diastereomeric complexes that after chromatographic separation could be used as starting materials for stereocontrolled Pauson–Khand reactions, following a strategy previously developed by Chung et al. [6] with phosphite-substituted dicobalt alkyne complexes. Recently, we have found that the introduction of a (cyclopentadienyl)molybdenum(dicarbonyl) moiety can change drastically the reactivity of alkyne dinuclear complexes [7]. Thus, while the standard Pauson–Khand reaction of norbornadiene with the dicobalt(hexacarbonyl) complex of *N*-(2-butynoyl)-4,4-dimethyl-1,3-oxazolidin-2-one (**1**) leads to a mixture of the regioisomeric adducts **2** and **3** with the usual *exo* stereochemistry [8], the heterobimetallic (Co–Mo) complex **4** affords as a major product an *endo*-fused adduct **5** with complete regioselectivity (Scheme 1). The corresponding (Co–W) complex **6** exhibits a similar behaviour [9].

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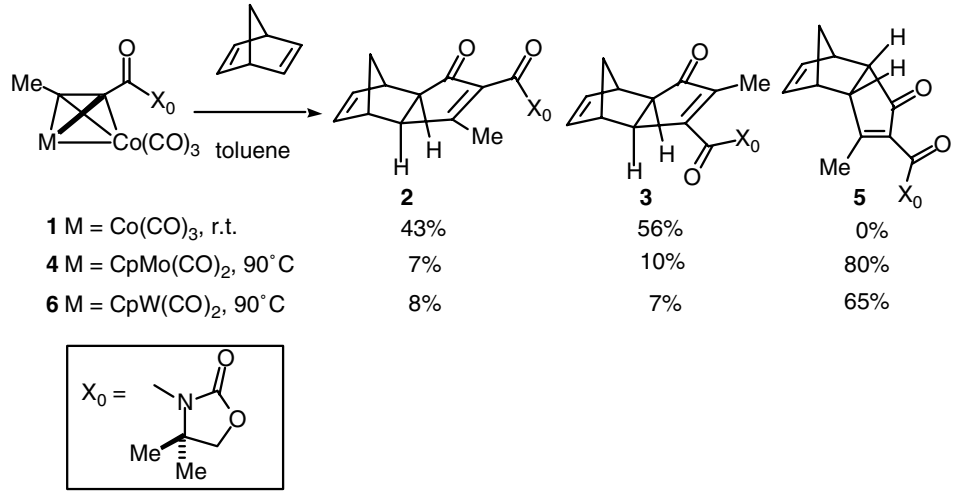


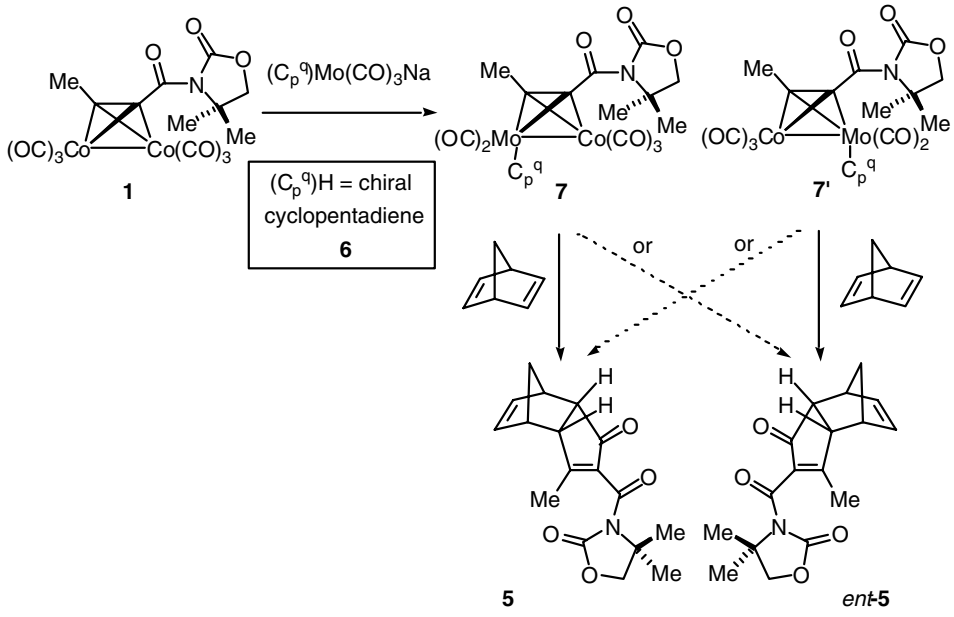
Scheme 1. Intermolecular Pauson–Khand reactions of homo- (Co–Co) and heterobimetallic (Co–Mo, Co–W) complexes.

The use of chiral oxazolidinones results in the formation of diastereomeric pairs of heterobimetallic complexes, and the Pauson–Khand reaction of each diastereomer preferentially affords a different diastereomer of the *endo* adduct [7,9]. This suggests that the chirality of the tetrahedral C_2CoMo (or W) core controls the stereoselectivity of the Pauson–Khand cyclization; moreover, by removal of the chiral oxazolidinone moiety, enantiomerically enriched adducts could be obtained. We thought however that a more straightforward approach *that would lead directly to the enantioselective formation of product* **5** would be highly desirable. The asymmetrization of achiral alkyne-dicobalt(hexacarbonyl) complexes by the substitution of a CO ligand by an enantiopure chiral phosphine is one of the few successful strategies that have evolved in the development of enantioselective intermolecular Pauson–Khand reactions [10]. In a similar way, we envisaged that by using enantiopure cyclopentadienyl ligands **6** on molybdenum, the achiral complex **1** would be converted into a pair of diastereomeric heterobimetallic complexes (**7**, **7′**), and that the Pauson–Khand reaction of each one of these would lead to the preferential formation of a single enantiomer of compound **5** (Scheme 2). We wish to report here our initial results on the experimental implementation of this concept.

2. Results and discussion

In order to ensure the formation of a single molybdenum(tricarbonyl)anion, the chiral cyclopentadienyl ligand in 2 should preferentially have homotopic faces (either due to the presence of a C_2-axis of symmetry or to the free rotation of a single bond connecting the cyclopentadiene ring and a chiral substituent); if, on the other hand, the two faces of the cyclopentadienyl ring are diastereotopic, one of them should be more sterically hindered than the other [11]. Bearing these considerations in mind, we selected a set of known chiral cyclopentadienes **6** (Fig. 1) and we proceeded to test them in the reaction shown in Scheme 2. In general, the requisite (cyclopentadienyl)molybdenum(tricarbonyl) anions were obtained from the corresponding cyclopentadienes by reaction with equimolar amounts of sodium hydride and with molybdenum(hexacarbonyl) (2 equiv.) in refluxing tetrahydrofuran for 14 h [12]. The formation of the complex anion was checked in several instances at this point by adding an excess of methyl iodide and maintaining the reflux for 1 h. After chromatographic purification, the stable, neutral (cyclopentadienyl)methylmolybdenum(tricarbonyl) complexes were isolated and characterised spectroscopically. In order to obtain the heterobimetallic complexes **7**, the solution of the complex anion generated in this way was cooled at room temperature, treated with a solution of the dicobalt complex **1** (0.5 equiv.) in anhydrous tetrahydrofuran and heated again to reflux until the reaction was complete (typically 1.5–5 h). After chromatographic purification, the heterobimetallic complexes **7** (either as diastereomer mixtures or as separated stereoisomers) were dissolved in toluene, treated with an excess of norbornadiene and heated for 3–14 h at 90 °C. The enantiomeric purity of the resulting *endo* Pauson–Khand adduct **5** was checked by HPLC (Chiralcel OD column). The results obtained are summarised in Table 1.

We studied first the behaviour of the camphor-derived cyclopentadiene **6a**, a compound that has been shown to exhibit a high π-facial preference for endo complexation [13]. When **1** was reacted with the (cyclopentadienyl)molybdenum(tricarbonyl) anion derived from **6a**, a nearly equimolecular mixture of two diastereomeric heterobimetallic complexes was obtained in moderate yield (56%) [17]. Since these compounds could



Scheme 2. Enantioselective heterobimetallic intermolecular Pauson–Khand reaction mediated by chiral cyclopentadienyl ligands.

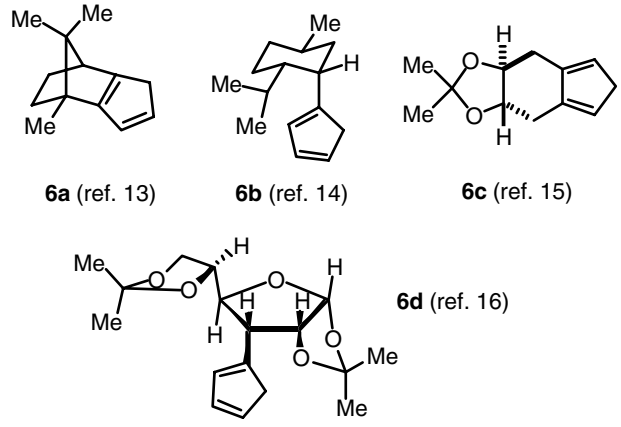


Fig. 1. Chiral cyclopentadienes used in the present study.

not be separated by column chromatography, the mixture was directly submitted to Pauson–Khand cocyclization with norbornadiene; the expected *endo* adduct **5** was obtained in racemic form (entry 1 of Table 1). Somewhat more satisfactory results were obtained when the menthol-derived cyclopentadiene **6b** [14] was used (entry 2); although the formation of the heterobimetallic complexes **7b** took place with greater diastereoselectivity (2:1 dr), the two diastereomers were again not separable by chromatography. In this case, the Pauson–Khand reaction of the mixture afforded the desired product **5** in 21% ee, but with a disappointingly low yield (23%). Much better yields (both for the formation of the heterobimetallic complexes and for the Pauson–Khand cyclization) were obtained with the C_2-symmetric cyclopentadiene **6c** [15] (entry 3). Again, however, the pair of diastereomeric complexes corresponding to **7c** could not be separated, and **5** was produced with a very low ee. Finally, we were pleased to find that the two heterobimetallic complexes derived from **6d** (readily accessible from D-acetone glucose) [16] could be separated by careful column chromatography, and that the

Table 1
Enantioselective heterobimetallic Pauson–Khand reaction of complexes **7a**–**7d** with norbornadiene (2)[a]

Entry	Chiral cyclopentadiene	Heterobimetallic complex (% yield[b], dr[c])	% yield[b] of adduct **5**	% ee[d] of adduct **5**
1	**6a**	**7a** (56, 1.1:1)	40	0
2	**6b**	**7b** (53, 2:1)	23	21
3	**6c**	**7c** (75, 1:1)	84	12
4	**6d**	**7d** (53, 1.3:1)[e]	75[f]	100[f]
5	–	–	60[g]	$\geqslant -95$[g]

[a] Reaction conditions: 10 equivs. norbornadiene, toluene, 90 °C, 3–14 h.
[b] After chromatographic purification on silica gel.
[c] By ^{13}C NMR.
[d] By HPLC (Chiralcel OD column, 90:10 hexane:IPA, 0.5 ml/min, t_R 28.7 min, 40.2 min).
[e] The two diastereomers could be separated by chromatography.
[f] From the major diastereomer of **7d**.
[g] From the minor diastereomer of **7d**.

Pauson–Khand reaction of each diastereomer led to the highly enantioselective formation of each one of the two enantiomers of the *endo*-adduct **5** (entries 4 and 5, respectively) [18].

Although there is still ample room for improvement in this approach, we feel that the present results are highly significant in that they constitute the first example of an asymmetric heterobimetallic Pauson–Khand reaction mediated by a chiral cyclopentadienyl ligand bonded to molybdenum.

Acknowledgements

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[18] *Experimental procedures for the preparation and for the Pauson–Khand reaction of **7d**. (a) Preparation of the chiral, heterobimetallic complex **7d***: To an stirred suspension of sodium hydride (43 mg, 1.8 mmol) in anhydrous THF (15 ml), under Ar, a solution of the chiral cyclopentadiene **6d** (0.50 g, 1.6 mmol) in THF (5 ml) was added dropwise. After stirring for 1 h at r.t., molybdenum(hexacarbonyl) (0.41 g, 2.54 mmol) was added in one portion, and the resulting mixture was heated to reflux for 14 h. After cooling to r.t., a solution of the complex **1** (0.80 mmol) in dry THF (10 ml) was added dropwise, and the reaction mixture was heated to reflux. After 3 h of stirring, TLC analysis revealed that the red spot corresponding to the starting complex **1** had been replaced by two more polar, brown spots corresponding to the two diastereomers of **7d**. Elimination of the solvent under vacuum afforded 0.350 g (53% yield) of **7d**, as a, ca. 1.3:1 diastereomer mixture (by ^{13}C NMR). *Spectral data for* **7d** *(diastereomer mixture):* IR (NaCl): ν = 2987, 2929, 2055, 2005, 1947, 1779, 1727, 1650, 1453, 1372, 1312, 1254, 1216, 1167, 1073, 1019, 845 cm^{-1}. ^{13}C NMR (75 MHz, C_6D_6): δ (ppm) 23.2 (CH_3), 23.9 (CH_3), 24.1 (CH_3), 24.2 (CH_3), 25.2 (CH_3), 25.3 (CH_3), 25.5 (CH_3), 26.1 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 30.2 (CH_3), 47.3 (CH), 47.5 (CH), 61.2 (Cq), 61.4 (Cq), 66.8 (CH_2), 67.2 (CH_2), 74.8 (CH_2), 75.0 (CH_2), 77.60 (CH), 77.65 (CH), 83.0 (CH), 83.2 (CH), 84.8 (CH), 84.9 (CH), 91.1 (Cp-CH), 94.2 (2Cp-CH), 94.8 (Cp-CH), 95.4 (Cp-CH), 95.8 (Cp-CH), 96.0 (Cp-CH), 96.8 (Cp-CH), 104.9 (CH), 105.4 (CH), 107.7 (Cq), 109.7 (Cq), 112.0 (Cq), 112.7 (Cq), 112.9 (Cq), 113.5 (Cq), 200-206 (CO-Cq, br), 224.8 (CO-Cq), 224.9 (CO-Cq), 226.2 (CO-Cq), 228.3 (CO-Cq). The above diastereomer mixture was submitted to chromatographic purification (silica gel, C_6H_{14}–EtOAc mixtures of increasing polarity). In this way, 10 mg of the less polar, major diastereomer of **7d**, 290 mg of diastereomer mixture and 20 mg of the more polar, minor diastereomer of **7d** could be isolated. Without further characterization, the two fractions corresponding to the pure diastereomers were submitted to Pauson–Khand cyclization. *(b) Pauson–Khand reaction*: The major diastereomer of **7d** (20 mg, 0.03 mmol) was dissolved in dry toluene (4 ml), and norbornadiene (18 μl, 0.30 mmol) was added via syringe. The resulting mixture was stirred at 90 °C, under N_2 atmosphere, for 3 h. Elimination of the solvent under reduced pressure followed by purification by column chromatography (silica gel, C_6H_{14}–EtOAc mixtures of increasing polarity) afforded 6.0 mg (75% yield) of the enantiomerically pure (HPLC) *endo*-fused adduct **5** [7]. In a similar way, the minor diastereomer of **7d** (10 mg, 0.015 mmol) gave the opposite enantiomer of **5** (2.4 mg, 60% yield) in, ca. 95% optical purity. *Conditions for the HPLC determination of the enantiomeric purity of 5*: Chiralcel-OD column, 90% C_6H_{14}-10% isopropyl alcohol,Φ = 0.5 ml min^{-1},T = 25 °C, λ = 220 nm, $t_{R(enantiomer\ 1)}$ = 28.7 min, $t_{R(enantiomer\ 2)}$ = 40.2 min..