5382 *Organometallics* **2003,** *22,* 5382−5384

Identification of an Asymmetric Pauson−Khand Precatalyst

Susan E. Gibson,*[†,‡] Sara E. Lewis,[†] Jennifer A. Loch,[†,‡]
Jonathan W. Steed,[†] and Matthew J. Tozer[§]

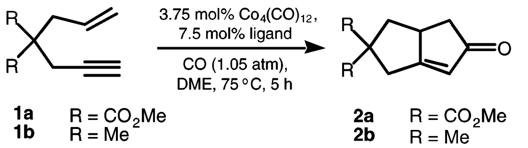
Department of Chemistry, King's College London,
Strand, London WC2R 2LS, United Kingdom, and Medivir UK, Peterhouse Technology Park,
100 Fulbourn Road, Cambridge CB1 9PT, United Kingdom

Received September 7, 2003

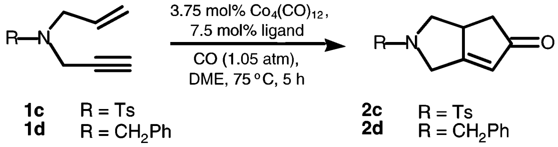
Summary: X-ray crystallographic analysis of red crystals formed on mixing octacarbonyldicobalt(0) and BINAP, combined with NMR evidence obtained from a catalytic asymmetric Pauson−Khand reaction, suggests that this complex is a precatalyst to this reaction and leads to a new hypothesis for the role of axially chiral diphosphanes in the catalytic asymmetric Pauson−Khand reaction.

The Pauson−Khand reaction (PKR), the [2 + 2 + 1] cyclocarbonylation of an alkyne and an alkene to form a cyclopentenone, is of considerable synthetic interest not only because cyclopentenones are useful building blocks for more elaborate structures but also because they are important biologically active compounds in their own right. For example, the cyclopentenone prostanoids have recently started to attract much interest, and this area of research is now providing promising candidates for, inter alia, antiinflammatory and antiviral pharmaceuticals.[1] While most applications of the PKR to date have used stoichiometric amounts of cobalt, there are now several catalytic versions of the reaction available that use a range of metals.[2] Initial exploratory attempts to introduce asymmetry into the reaction using titanium,[3] rhodium,[4] and iridium[5] catalysts have been encouraging, providing good enantioselectivities and turnover numbers.

The feasibility of an asymmetric cobalt-catalyzed PKR has been demonstrated.[6] Using octacarbonyldicobalt(0) (20 mol %) as the cobalt source, a range of chiral diphosphanes (20 mol %) were tested on standard intramolecular substrates. While very modest enantioselectivities were observed for DIOP, DuPHOS, and planar chiral ferrocene diphosphanes, high selectivities were observed with the axially chiral ligand BINAP. For example, cyclocarbonylation of enyne **1a** (eq 1) gave the product cyclopentenone **2a** in 53% yield and 90% ee in 14 h. It was proposed that the phosphorus atoms of the BINAP ligand bridge the two cobalt atoms, while cyclopentenone formation occurs with participation of both cobalt centers[6] according to the generally accepted Pauson−Khand mechanism.[7]



(1)



(2)

As a result of our interest in the cobalt-catalyzed PKR,[8] we initiated a study of its asymmetric version. After detailing our modified conditions for the cobalt-catalyzed asymmetric PKR based on axially chiral diphosphanes, we wish to report herein (a) the isolation of a hexacarbonyldicobalt(0) complex in which BINAP binds to just one of the two cobalts and (b) evidence that suggests that this complex is a precatalyst to asymmetric catalytic PKRs.

We initially examined the cyclocarbonylation of enyne **1a** in the presence of (*S*)-BINAP. Optimization of this reaction led to the use of 3.75 mol % of $Co_4(CO)_{12}$ as the cobalt source,[9] which in our hands proved more robust and reliable than $Co_2(CO)_8$, together with 7.5 mol % of (*S*)-BINAP. After $Co_4(CO)_{12}$ and (*S*)-BINAP were premixed, operating at 75 °C under 1.05 atm of carbon monoxide for 5 h gave a 70% yield of cyclopentenone **2a** and 89% ee (Table 1, entry 1). A survey of five other diphosphanes (Table 1, entries 2−6) revealed that, once again, only the ligands with axial chirality led to significant chiral induction (Table 1, entries 5 and 6). Examination of three further substrates (**1b**−**d**) using

---

* To whom correspondence should be addressed. E-mail: susan.gibson@kcl.ac.uk. Fax: +44-207-848-2810.

[†] King's College London.

[‡] Address as of Oct 1, 2003: Department of Chemistry, Imperial College London, South Kensington Campus, London SW7 2AZ, United Kingdom.

[§] Medivir UK.

(1) Roberts, S. M.; Santoro, M. G.; Sickle, E. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1735.

(2) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800.

(3) (a) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. (b) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7026.

(4) Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771.

(5) Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*, 9852.

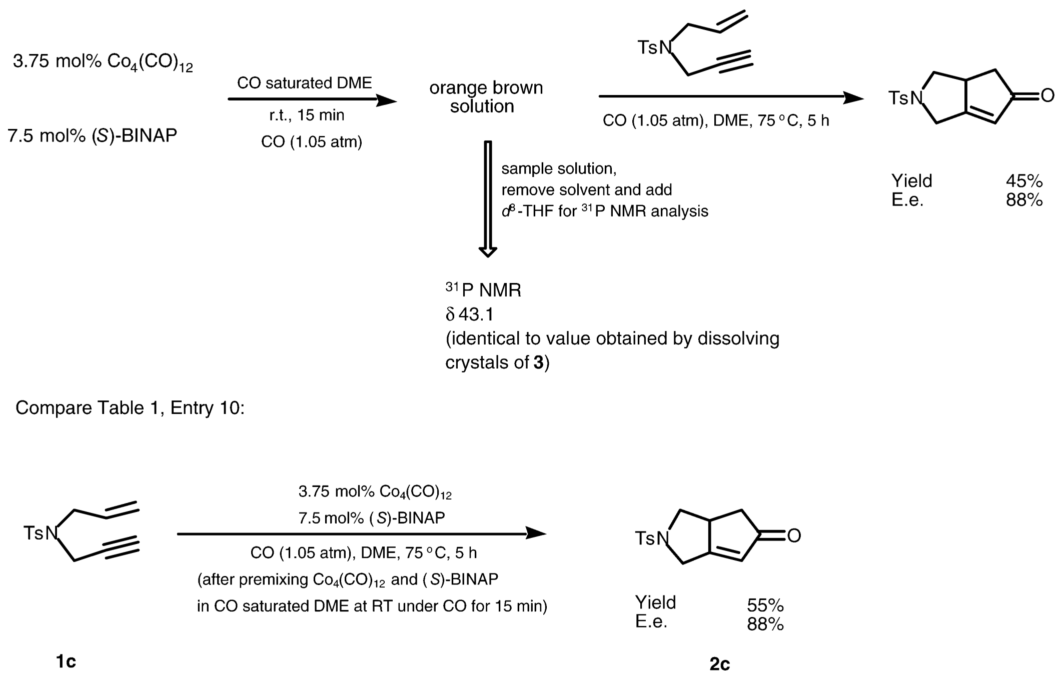
(6) (a) Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I. *Tetrahedron Lett.* **2000**, *41*, 891. (b) Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I. *Tetrahedron: Asymmetry* **2000**, *11*, 797.

(7) (a) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. (b) Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2001**, *123*, 1703.

(8) (a) Comely, A. C.; Gibson, S. E.; Stevenazzi, A.; Hales, N. J. *Tetrahedron Lett.* **2001**, *42*, 1183. (b) Gibson, S. E.; Johnstone, C.; Stevenazzi, A. *Tetrahedron* **2002**, *58*, 4937.

10.1021/om0341606 CCC: $25.00 © 2003 American Chemical Society
Publication on Web 11/20/2003

Scheme 1



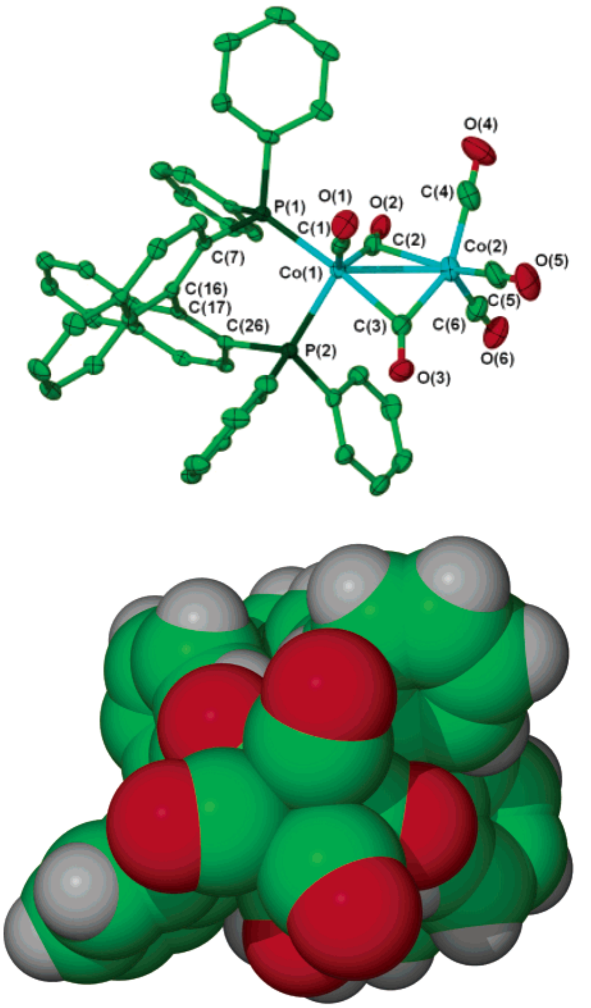


Figure 1. ORTEP drawing of complex **3** (top; hydrogen atoms are omitted for clarity) and space-filling view of complex **3** (bottom).

the three phosphanes with axial chirality led to good to excellent asymmetric induction (Table 1, entries 7–15).

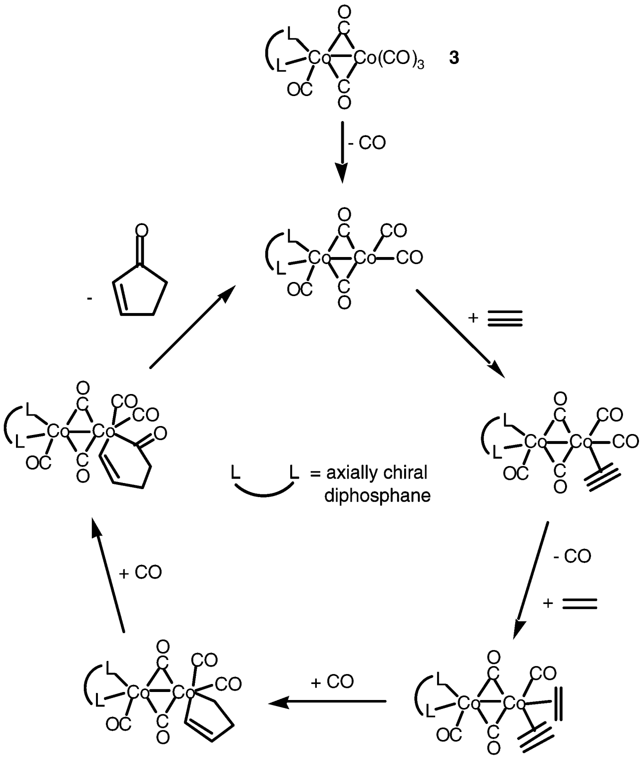
Table 1. Catalytic Pauson–Khand Reactions of Substrates 1a–d[a,b]

entry	sub-strate	ligand[c]	conversn (%)	yield (%) of **2a–d**	ee (%)[d] of **2a–d** (±)
1	**1a**	(*S*)-BINAP	100	70	89 (+)
2	**1a**	(*S*)-PHANEPHOS	100	61	5
3	**1a**	(*R*)-TROST LIGAND	100	64	2
4	**1a**	(*R*)-NORPHOS	0		
5	**1a**	(*S*)-TolBINAP	100	85	96 (+)
6	**1a**	(*R*)-HEXAPHEMP	95	75	93 (−)
7	**1b**	(*S*)-BINAP	82	59	72 (+)
8	**1b**	(*S*)-TolBINAP	81	51	82 (+)
9	**1b**	(*R*)-HEXAPHEMP	66	36	59 (−)
10	**1c**	(*S*)-BINAP	91	55	88 (+)
11	**1c**	(*S*)-TolBINAP	92	59	95 (+)
12	**1c**	(*R*)-HEXAPHEMP	89	62	80 (−)
13	**1d**	(*S*)-BINAP	88	70	92 (+)
14	**1d**	(*S*)-TolBINAP	80	58	96 (+)
15	**1d**	(*R*)-HEXAPHEMP	81	63	74 (−)

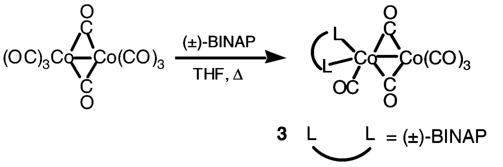
[a] All reactions were performed according to the procedure detailed here for entry 5: $Co_4(CO)_{12}$ (11 mg, 0.01875 mmol) and (*S*)-TolBINAP (25 mg, 0.0375 mmol) were dissolved in CO-saturated DME (2 cm^3) and stirred at room temperature under a CO atmosphere (1.05 atm) for 15 min. A solution of enyne **1a** (104 mg, 0.50 mmol) in CO-saturated DME (2 cm^3) was added to the above solution and heated to 75 °C for 5 h. The resulting brown solution was cooled, filtered through a short pad of Celite, and concentrated in vacuo. The brown residue was redissolved in $CDCl_3$, and the extent of the reaction was calculated from ^{1}H NMR spectroscopy (100%). Purification of the residue by flash column chromatography (SiO_2; 7:3 hexane–EtOAc) gave **2a** (106 mg, 85% yield, 96% ee). [b] All experiments were performed at least twice; on the basis of all the results, errors are estimated as conversions (±6%), yields (±6%), and ee's (±3%). [c] Abbreviations: BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; PHANEPHOS, 4,12-bis-(diphenylphosphino)[2.2]paracyclophane; TROST LIGAND, 1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl); NORPHOS, 2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene; TolBINAP, 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl; HEXAPHEMP, 6,6′-bis(diphenylphosphanyl)-2,3,4,2′,3′,4′-hexamethylbiphenyl. [d] The ee's of **2a-d** were determined by HPLC analysis using CHIRALPAK AD for **2a** and CHIRALPAK AS for **2b-d**.

To try to probe the cause of the effectiveness of the axially chiral diphosphanes in the cobalt-catalyzed PKR, we reacted octacarbonyldicobalt(0) with (±)-BINAP and discovered that, with care, a small number of dark red,

Scheme 2



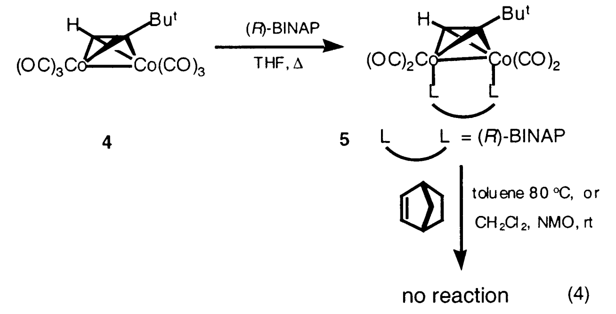
air-sensitive crystals could be obtained from its product mixture.[10] X-ray analysis[11] of the crystals revealed that BINAP is bound to just one of the two cobalt atoms (eq 3 and Figure 1). To aid identification of complex **3** in subsequent solution studies of the Pauson−Khand reaction, the ^{31}P NMR spectrum of the crystals was recorded (a single resonance at δ_P 43.1 ppm was observed).



(3)

The asymmetric catalytic Pauson−Khand experiment described in Table 1, entry 10, was then repeated, but just prior to adding substrate **1c**, a sample of the solution formed from mixing $Co_4(CO)_{12}$ and (*S*)-BINAP was removed (Scheme 1). Removal of solvent from this sample and analysis by ^{31}P NMR spectroscopy using d_8-THF as solvent gave a spectrum containing a peak at δ 43.1 (alongside peaks corresponding to (*S*)-BINAP and (*S*)-BINAP monoxide). Addition of **1c** to the remaining precatalyst solution and running the reaction exactly as described in Table 1 gave a yield of 45% and an ee of 88% (cf. Table 1, entry 10: yield 55%, ee 88%).

It is interesting to view this result against the background of observations made following a thermal ligand exchange reaction between the alkyne-containing complex **4** and BINAP (eq 4).[12] X-ray crystallographic analysis of product **5** revealed that it contained a bridging BINAP ligand. Complex **5** proved to be inert to a range of stoichiometric Pauson−Khand conditions, a situation partially attributed to a retardation of the initial decarbonylation step of the PKR resulting from the increased carbonyl back-bonding caused by the more donating phosphane substituents.



Combining the recorded inertness of **5** with our observation that BINAP can bind to one cobalt of carbonyldicobalt(0) species, together with the dramatic steric and carbonyl deactivating effects that result from this mode of binding, leads us to the working hypothesis that asymmetric cobalt-catalyzed Pauson−Khand reactions based on axially chiral diphosphanes may occur solely at the phosphane-free cobalt center with asymmetric induction arising from what may be regarded as an asymmetric cobalt-centered ligand (Scheme 2).

Acknowledgment. We thank Medivir UK for generous studentship support (to S.E.L.), ChiroTech for providing samples of (*R*)-HEXAPHEMP, and AstraZeneca and the Royal Society (Rosalind Franklin Award) for consumables support (to J.A.L.).

Supporting Information Available: Text and tables giving crystallographic details for **3**; data are also available as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

OM0341606

---

(9) (a) Krafft, M. E.; Boñaga, L. V. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3676. (b) Krafft, M. E.; Boñaga, L. V. R.; Hirosawa, C. *J. Org. Chem.* **2001**, *66*, 3004.

(10) Experimental procedure for **3**: in a Schlenk flask under nitrogen, anhydrous THF (10 mL) was added to $Co_2(CO)_8$ (50 mg, 0.15 mmol). After (±)-BINAP (93 mg, 0.15 mmol) was added, the solution was stirred for 30 min at room temperature. (On one occasion, a sample (2 mL) of the solution was removed by syringe after 15 min and the solvent of the sample was removed in vacuo. IR ($CHCl_3$, cm^{-1}): ν_{CO} 2087 (m), 2053 (s), 2011 (m), 1986 (s, br), 1891 (s, br), 1795 (m, br). ^{31}P NMR (146 MHz, THF-d_8): δ 43.1; 41.5; 25.6 and −13.8 (BINAP monoxide); −14.3 (BINAP).) Stirring was continued for an additional 30 min at 40 °C. After the mixture was cooled, nitrogen-saturated hexane (20 mL) was added and a red solid precipitated. The filtrate was removed by cannula, additional hexane (10 mL) was added, and the filtrate was removed again. The red solid was dried in vacuo. IR ($CHCl_3$, cm^{-1}): ν_{CO} 2053 (s), 1985 (s, br), 1890 (w, br), 1796 (m, br). ^{31}P NMR (162 MHz, THF-d_8): δ 43.1; 25.4 and −13.8 (BINAP monoxide). On one occasion, a small sample of **3** suitable for a single-crystal structure determination was obtained by slow diffusion of petroleum ether into a solution of **3** in CH_2Cl_2 at −20 °C. IR ($CHCl_3$, cm^{-1}): ν_{CO} 2053 (s), 1986 (s, br), 1890 (w, br), 1850 (sh), 1795 (m, br). ^{31}P NMR (146 MHz, THF-d_8): δ 43.1. All attempts to characterize by other methods were unsuccessful due to the instability of **3**.

(11) Crystal data for **3**: $C_{50}H_{32}Co_2O_6P_2 \cdot 1.5CH_2Cl_2$, $M_r = 1035.95$, red block (0.15 × 0.10 × 0.10 mm), monoclinic, space group $P2_1/n$ (No. 14), $a = 14.4575(3)$ Å, $b = 19.3414(4)$ Å, $c = 16.2073(4)$ Å, $\beta = 94.5540(10)°$, $V = 4517.71(17)$ Å^3, $Z = 4$, $D_c = 1.523$ g/cm^3, $F_{000} = 2108$, Nonius KappaCCD, Mo Kα radiation, $\lambda = 0.710\,73$ Å, $T = 120(2)$ K, $2\theta_{max} = 50.0°$, 14 623 reflections collected, 7931 unique ($R_{int} = 0.0779$), final GOF = 1.028, R1 = 0.0582, wR2 = 0.1380, R indices based on 4786 reflections with $I > 2\sigma(I)$ (refinement on F^2), 587 parameters, 0 restraints. *Lp* and absorption corrections applied, $\mu = 1.034$ mm^{-1}.

(12) Derdau, V.; Laschat, S.; Dix, I.; Jones, P. G. *Organometallics* **1999**, *18*, 3859.