

A New Chiral Bidentate (P,S) Ligand for the Asymmetric Intermolecular Pauson–Khand Reaction

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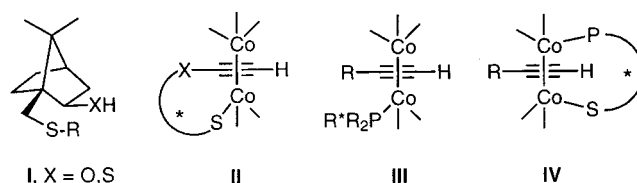
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In the past two decades the Pauson–Khand reaction (PKR)¹ has attracted much attention from the synthetic chemistry community. Although some progress has been achieved lately on the way to convert the intramolecular PKR into a catalytic enantioselective process,² the intermolecular version of the process has been left out from most of these advances.³ To turn the intermolecular PKR into an asymmetric transformation, the use of covalently bonded chiral auxiliaries,^{4,5,6} chiral ligands on cobalt,^{7,8} and chiral promoters⁹ has been explored. The use of chiral auxiliaries has been extensively investigated by our group,^{5,6} and we have introduced the extremely efficient inductors **I** (Chart 1), bearing a sulfide arm that is able to coordinate to the cobalt complex of the alkynyl derivatives as in structure **II**, thus enhancing both the reactivity and stereoselectivity of the intermolecular PKR.^{6,10}

Several phosphines have been used as chiral ligands on cobalt; however, many drawbacks hamper this methodology, i.e., low diastereoselectivity in the formation of type **III** complexes, cumbersome separation of these diastereomeric mixtures, and decreased reactivity toward the PKR.

We reasoned that a bidentate ligand, designed to form chelated structures such as **IV**, would increase, as for the covalently bonded chiral auxiliaries, both the reactivity of the complex and the

Chart 1^a



I, X = O, S

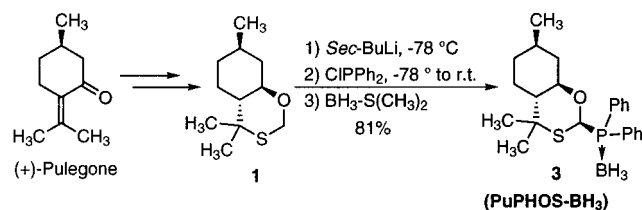
II

III

IV

^a CO ligands are omitted for clarity.

Scheme 1



diastereoselectivity of its formation. The most important step in the design of such a chiral bidentate ligand was to drive the coordination of the sulfur in the dicobalt–alkyne cluster to the cobalt atom not bonded to phosphorus. To obtain such a coordination pattern, the distance between the P and S atoms becomes crucial. A methylene link between the sulfide and the phosphine¹¹ could provide an excellent scaffold for this purpose. Since no chiral ligands bearing S and P in such close proximity could be found in the literature, we chose oxathiane **1**, which is readily accessible from natural (+)-pulegone,¹² as the starting material for our synthesis. Chlorodiphenylphosphine was first alkylated with the lithium anion of **1**, generated at low temperature by treatment with *s*-BuLi (Scheme 1). The reaction was totally stereoselective, affording the chiral phosphine **2** (PuPHOS) as a single diastereomer. The new phosphine was most conveniently isolated in its borane-protected form **3** as a shelf-stable, highly crystalline solid in 81% overall yield. The stereochemistry of the newly formed center was assumed to be the one depicted in Scheme 1, with the phosphorus substituent equatorial at C-2 of the oxathiane ring.

The free PuPHOS ligand (**2**) was conveniently generated *in situ* by simply heating in toluene the mixture of **3** with 2 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO). Generation of **2** in the presence of dicobalt hexacarbonyl complexes **4** derived from terminal alkynes smoothly led to a diastereomeric mixture of dicobalt tetracarbonyl complexes **5/6**. TLC monitoring showed that at the initial stages of the reaction both diastereomers were in an almost 1/1 ratio, as was the case with the previously described nonchelated phosphines.^{7,8} Fortunately, and according to our expectations, heating the solution for 17–18 h at 60–80 °C induced the equilibration of the diastereomers, leading to biased mixtures of complexes in excellent yields (Table 1). The observed stereoselectivity for this process mostly depended on the nature of the substituent on the alkyne. While for R = Ph no diastereoselectivity at all was detected in the complexation process (entry 1, Table 1), when the reaction was carried out with the dicobalt complexes derived from *tert*-butylacetylene and trimethylsilylacetylene, the stereoselectivity increased to 3/1 (entries 2 and 3, Table 1). The higher selectivity level in the complexation process (*dr* = 4.5/1) was reached when the complex of 2-methyl-3-butyn-2-ol was employed (entry 4, Table 1). Whereas diastereomers **5a/6a** could be separated by column

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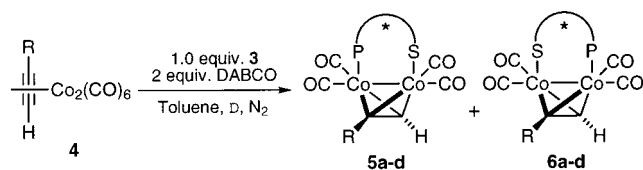
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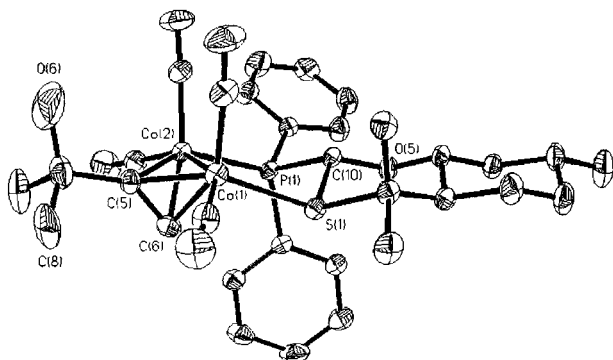
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Table 1. Thermal Reaction of PuPHOS with Alkyne–Dicobalt Hexacarbonyl Complexes

entry	R	starting complex	T (°C)	time (h)	yield (%)	dr ^a	product
1	Ph	4a^b	65	18	91	1/1	5a/6a
2	Bu ^t	4b	60	17	98	3/1	5b/6b
3	TMS	4c	80	17	91	3/1	5c/6c
4	CMe ₂ OH	4d	70	17	84	4.5/1	5d/6d

^a Established by ¹H NMR spectroscopy of the resulting mixture of complexes. ^b Starting complex **4a** was prepared in situ (Co₂(CO)₈/phenylacetylene/toluene) prior to ligand addition.

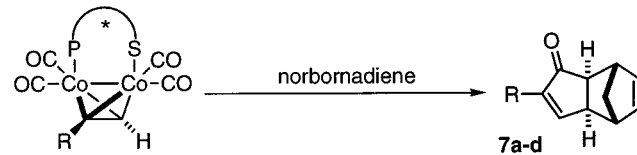
**Figure 1.** ORTEP plot of complex **5d**.

chromatography, the major diastereomers **5b**, **5c**, and **5d** were isolated by simple crystallization. This allowed for a convenient preparative-scale isolation of diastereomerically pure material. On top of that, additional isomerization of the mother liquor back to the original diastereomeric mixture could provide a second crop of crystals, affording an increased yield of the major crystalline compound. For example, in the case of complex **4c**, after a sequence of crystallization–isomerization–crystallization, a 68% yield of diastereomerically pure complex **5c** was obtained.

X-ray analysis of **5d** (Figure 1) confirmed the stereochemistry of the diphenylphosphino substituent in the ligand and showed that the sulfur and the phosphorus atoms were occupying two eclipsed pseudoequatorial coordination sites at different metal centers, anti to the dimethylcarbinol group, to avoid steric interactions.^{7c} Moreover, the sulfur atom was coordinated to the *pro-S* cobalt atom through its equatorial electron lone pair.

It is well known that mono- and diphosphino dicobalt complexes (**III**) of phenylacetylene display lower reactivity in the PKR. In sharp contrast with this, when the PuPHOS–phenylacetylene complex **5a** was reacted thermally with norbornadiene, the PKR took place in an extremely rapid and stereoselective fashion (Table 2). Within 30 min at 50 °C, the corresponding cyclopentenone (+)-**7a**¹³ was obtained in almost quantitative yield and 99% ee. Complex **5b** revealed a marked decrease in reactivity compared to its phenyl analogue **5a** and did not afford the corresponding adduct. Alternatively, complexes **5c** and **5d** provided the corresponding Pauson–Khand adducts in excellent yields. Thermal cycloaddition of **5c** at 30 °C for 3 days produced the corresponding adduct (+)-**7c**^{8,14} in high yield but moderate

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Table 2. Pauson–Khand Reaction of PuPHOS Complexes with Norbornadiene

complex	R	conditions ^a	time	yield (%)	ee ^b	product
5a	Ph	toluene/50 °C	30 min	99	99	(+)- 7a
5c	TMS	toluene/50 °C	3 d	92	57	(+)- 7c
5c	TMS	CH ₂ Cl ₂ /NMO/rt	3 d	93	97	(+)- 7c
6c	TMS	CH ₂ Cl ₂ /NMO/rt	3 d	94	95	(-)- 7c
5d	CMe ₂ OH	CH ₂ Cl ₂ /NMO/rt	4 d	98	70	(+)- 7d

^a All reactions were conducted in Schlenk flasks under nitrogen with 10 equiv of norbornadiene. ^b Enantiomeric excess (%) was determined either by HPLC (Chiracel-OD, **7a** and **7d**) or by GC (β-DEX, **7c**).

stereoselectivity (57% ee). Most gratifyingly, we could improve this result by employing *N*-methylmorpholine *N*-oxide (NMO) in CH₂Cl₂ at room temperature. Under these conditions, **5c** reacted at a similar rate but with increased selectivity (97% ee). In a similar fashion, the minor isomer **6c** yields the enantiomeric cyclopentenone (–)-**7c**, in both high yield and high enantiomeric excess (95%).

These results are in good agreement with the hypothesis that the sulfide moiety exerts a dual effect in the reaction process. The thioether being the more labile of the two coordinative bonds (Co–S/Co–P), its dissociation controls the stereochemistry of the reaction while leaving, on a precise cobalt atom, a free coordination site for the incoming alkene. Moreover, since dissociation of a hemilabile sulfide moiety is much easier than the loss of any CO ligand in the complex, the normally difficult dissociative step in the PKR is facilitated and the overall rate increased. The role of NMO¹⁵ in these processes is intriguing since it does not have a significant effect on the reaction rate but clearly increases the stereoselectivity. We have observed in related compounds that CO promotes complex epimerization, probably through the intermediacy of nonchelated species. Accordingly, NMO probably operates by preventing the presence of any free CO in the reaction medium.

In conclusion, we have prepared the new phosphine PuPHOS (**2**) and demonstrated its utility in the asymmetric Pauson–Khand reaction. PuPHOS illustrates an unprecedented multiple effect: a significant diastereoselectivity in its coordination to the prochiral dicobalt complex by thermodynamic equilibration, an increased reactivity with respect to normal phosphine-coordinated alkyne–dicobalt complexes, and efficient stereocontrol by directing the reaction to the cobalt atom where sulfur is coordinated.

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Supporting Information Available: Tables of complete X-ray crystal data, ORTEP drawings, refinement parameters, atomic coordinates, and bond distances and angles for **5d** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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