

Asymmetric Intermolecular Cobalt-Catalyzed Pauson–Khand Reaction Using a P-Stereogenic Bis-phosphane

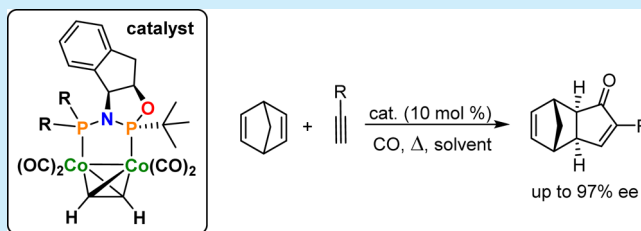
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S Supporting Information

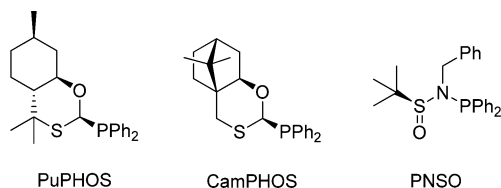
ABSTRACT: The asymmetric intermolecular and catalytic Pauson–Khand reaction has remained an elusive goal since Khand and Pauson discovered this transformation. Using a novel family of P-stereogenic phosphanes, we developed the first catalytic system with useful levels of enantioselection for the reaction of norbornadiene and trimethylsilylacetylene. The results demonstrate that Co–bisphosphane systems are sufficiently reactive and that they lead to high selectivity in the intermolecular process.



The Pauson–Khand reaction (PKR), disclosed in 1973, has become a textbook method for the synthesis cyclopentanic compounds.¹ The intramolecular PKR has been widely used in the syntheses of highly complex polycyclic compounds.² Although the intermolecular process has the great advantage of being able to rapidly assemble simple building blocks (alkyne, alkene, and CO) into valuable cyclopentenones, it has been less exploited in synthesis. Nevertheless, our group and others have reported several total syntheses of biologically active compounds using the intermolecular PKR as a key step, thus showing its value in synthesis.³ While several effective catalytic systems have been developed for the asymmetric intramolecular PKR, this goal remains elusive for the intermolecular process.^{4,5}

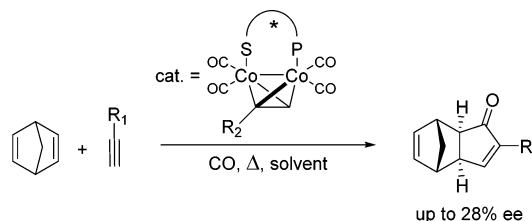
Over the past two decades, we have developed several Co₂–ligand systems (e.g., PuPHOS, CamPHOS, and PNSO) that provide excellent selectivity (up to 99% ee) in the enantioselective stoichiometric intermolecular PKR (Scheme 1).⁶

Scheme 1. Hemilabile P,S-Ligands Used in the Asymmetric Intermolecular Pauson–Khand Reaction



However, when these ligands are applied to the catalytic reaction, the selectivity drops dramatically. The Co-catalyzed PKR between norbornadiene (NBD) and a bulky propiolamide using CamPHOS ligand provides the corresponding PKR product in only 28% ee (Scheme 2).⁷ We attributed this lack of selectivity to the hemilabile nature of these ligands, which were

Scheme 2. PKR Reaction between Norbornadiene and Terminal Alkynes Catalyzed by P,S-Co₂–Alkyne Complexes



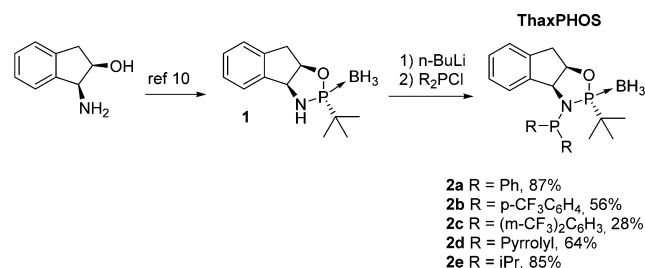
unable to maintain the original bridged disposition on the Co₂–alkyne core under the required CO atmosphere.

Chiral bis-phosphanes do not have this limitation; however, they have barely been explored in this process because double-phosphane substitution in Co₂ complexes usually results in impaired reactivity.⁸ One of the few exceptions is the report of Gimbert and co-workers in which the stoichiometric PKR of a binol-derived bisamidophosphinite–Co₂–alkyne complex with norbornene proceeded in excellent yield, although with poor selectivity (17% ee) (Scheme 2).⁹

Inspired by this report, we envisaged the feasibility of an asymmetric catalytic system bearing an aminodiphosphane ligand. The challenge was to improve the stereocontrol without reducing the reactivity. In this respect, a ligand system with a large steric bias was required. We considered oxazaphospholidine **1** (Scheme 3), which we had previously developed in the context of P-stereogenic phosphane synthesis,¹⁰ was ideally suited for this purpose since it could be further derivatized to yield a novel family of C₁-symmetric bis-phosphane ligands with a bulky *tert*-butyl group on one of the phosphorus atoms. Here, we report on the synthesis of the ThaxPHOS family of ligands and how the use

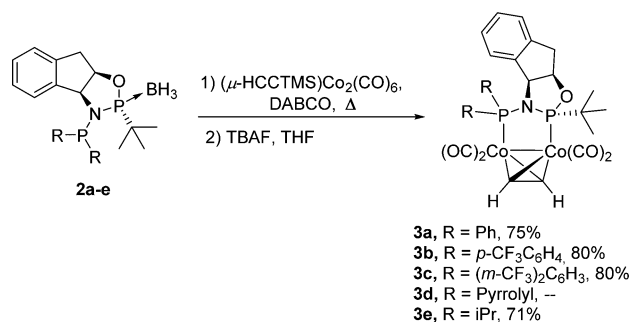
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Scheme 3. Synthesis of the ThaxPHOS Family of Ligands



of these ligands in the asymmetric intermolecular Co-catalyzed PKR provides unprecedented levels of selectivity.

Oxazaphospholidine **1** can be synthesized in a single step by condensation with either (+)- or (–)-*cis*-1-amino-2-indanol with *t*-BuPCl₂ and protection with borane.¹⁰ From **1**, lithium amide formation with 1 equiv of BuLi and reaction with several diaryl- and dialkylchlorophosphanes leads to the borane-monoprotected bis-phosphanes **2a–e** (Scheme 3). Borane protection was found to be unnecessary since the isolation of pure **2a–e** was achieved by direct crystallization from MeOH. With these ligands in hand, we sought to prepare a suitable cobalt–phosphane complex to use as catalyst in the intermolecular PKR. The preparation of the corresponding Co₂(CO)₆–ThaxPHOS complexes was unsuccessful because of the low stability of such compounds.¹¹ Finally, we resolved that the most effective way to bind the ligand and the Co₂(CO)₈ moiety was with the intermediacy of an alkyne moiety to generate a precatalyst. Thus, deprotection of the borane group with 1,4-diazabicyclo[2.2.2]octane (DABCO) and in situ complexation with (μ-HCCTMS)Co₂(CO)₆ at 85 °C provided a mixture of diastereomeric cobalt complexes. These compounds were then treated with tetrabutylammonium fluoride (TBAF) to yield the acetylene complexes **3a**, **3b**, **3c**, and **3e** as single isomers (Scheme 4). Although the initial complexation of **2d** proceeded smoothly,

Scheme 4. Synthesis of ThaxPHOS–Co–Alkyne Catalysts^a

^aYields correspond to complexation and removal of the TMS group.

complex **3d** could not be isolated because it decomposed during the treatment with TBAF. The bridged structure of the ThaxPHOS precatalyst complexes was confirmed by X-ray crystallography of **3b** (see the Supporting Information).

We next examined the catalytic intermolecular PKR between norbornadiene and various terminal alkynes using complexes **3a–e** as catalysts (Table 1). Reaction of phenylacetylene provided the corresponding *exo*-cyclopentenone with 54% yield but with no enantioselectivity (Table 1, entry 1). However, when we switched to 1-hexyne, significant levels of enantiomeric excess were revealed (Table 1, entries 2–4). Here, the use of

Table 1. Catalytic Intermolecular PKR with Norbornadiene

entry	catalyst	R	conditions ^a	yield ^b (%)	ee ^c (%)
1	3a	Ph	atm, 100 °C, toluene	54	2
2	3a	nBu	1 bar, 100 °C, toluene	54	3
3	3b	nBu	atm, 100 °C, toluene	53	40
4	3c	nBu	atm, 85 °C, toluene	97	28
5	3a	TMS	atm, 100 °C, toluene	39	97
6	3a	TMS	1 bar, 130 °C, toluene	77	89
7	3a	TMS	2 bar, 130 °C, toluene	51	86
8	3a	TMS	1 bar, 100 °C, DME	38	93
9	3a	TMS	2 bar, 160 °C, diglyme	30	86
10	3b	TMS	1 bar, 120 °C, toluene	25	87
11	3e	TMS	1 bar, 120 °C, toluene	10	1
12	3a	SiMe ₂ Ph	1 bar, 120 °C, toluene	40	48
13	3b	SiMe ₂ Ph	1 bar, 120 °C, toluene	32	72
14	3a	SiMe ₂ Bn	1 bar, 120 °C, toluene	42	90

^aReactions were run in a glass pressure tube at the designated CO pressure (atm = atmospheric CO pressure). ^bYields refer to isolated product after flash chromatography. ^cEnantiomeric excess was determined by either chiral GC or HPLC.

catalyst **3b** containing a bis(*p*-CF₃C₆H₄)phosphane group led to the PKR product with 40% ee. The breakthrough came when the alkyne partner was switched to trimethylsilylacetylene (TMSA). Under atmospheric CO pressure (balloon), using **3a** as a catalyst, the corresponding PKR adduct was obtained in 39% yield but with an unprecedented 97% ee (Table 1, entry 5). Increasing the temperature and the CO pressure to 130 °C and 1 bar, respectively, led to an increased yield of 77% accompanied by a slight decline in selectivity (Table 1, entry 6). A further increase in the CO pressure (2 bar) slowed the reaction down, and after 24 h only a 51% yield of the product was achieved (Table 1, entry 7). Changing the toluene for a coordinating solvent (DME) or switching to a higher boiling point solvent (diglyme) to run the catalytic PKR at higher temperatures did not improve the results (Table 1, entries 8 and 9). The use of complex **3e** with a diisopropylphosphane group completely inhibited the reactivity (Table 1, entry 11). Finally, we demonstrated that other trialkylsilyl-substituted acetylenes also provided elevated selectivity (Table 1, entries 13 and 14).

In an attempt to clarify the underlying mechanism and to reveal the origin of the high selectivity encountered, we examined the different catalytic events and the intermediates involved. We first centered our attention on the initial alkyne exchange process. Reaction of precatalyst **3a** with NBD and TMSA under atmospheric CO pressure (balloon) at the reduced temperature of 80 °C afforded the corresponding acetylene PKR adduct **4** and a mixture of diastereomeric complexes **TMS-3a** and **TMS-3a'** (Scheme 5). These complexes, with the opposite orientation of the TMS substituent, were obtained in a 12:1 diastereomeric ratio. This experiment revealed that under the catalytic reaction conditions, after the initial PKR affording **4**,¹² the subsequent coordination of the TMSA takes place with high stereocontrol.

We next addressed the structural elucidation of **TMS-3a** by X-ray diffraction studies; however, crystallization of this intermediate complex was elusive. Finally, suitable single crystals of the corresponding analogue **TMS-3d** were grown;¹³ the corresponding solid-state structure is shown in Figure 1. As

Scheme 5. Alkyne-Exchange Experiment with Complex 3a under Catalytic Conditions

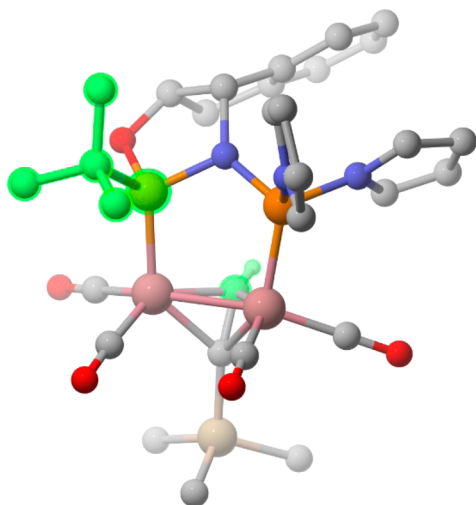
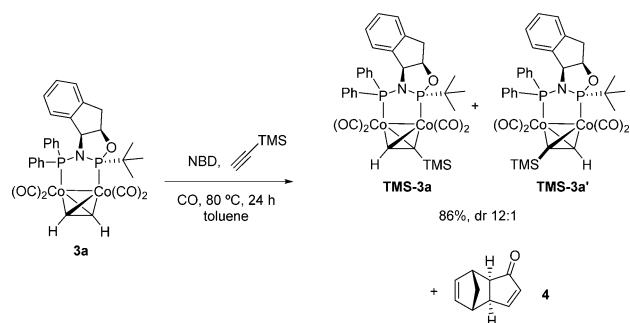
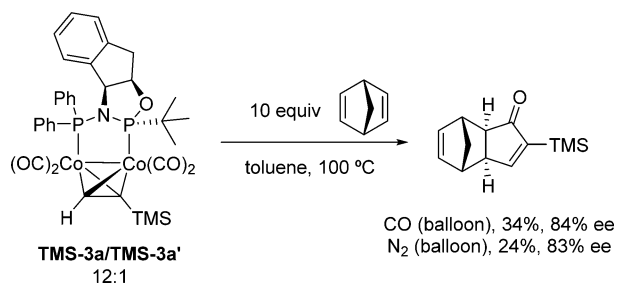


Figure 1. X-ray structure of the major complex TMS-3d. The phosphane *tert*-butyl group and the alkyne–methyne fragments are highlighted in green.

described previously for similar complexes, the bridged diphosphane ligand and the alkyne–TMS substituent are placed in an *anti*-arrangement.^{6a,b} The origin of the selectivity in the alkyne ligand exchange is found in the steric bias caused by the bulky *tert*-butyl group. Thus, in the major diastereomer, the *tert*-butyl fragment is placed eclipsed with a CO ligand, away from the alkyne–methyne moiety (Figure 1).

Finally, we tested the stoichiometric reaction of a mixture of TMS-3a/TMS-3a' (12:1) in the presence of an excess of NBD in toluene (Scheme 6). The reaction provided the PKR as the major reaction product in 84 and 83% ee depending on whether the reaction was performed under CO or nitrogen atmosphere.

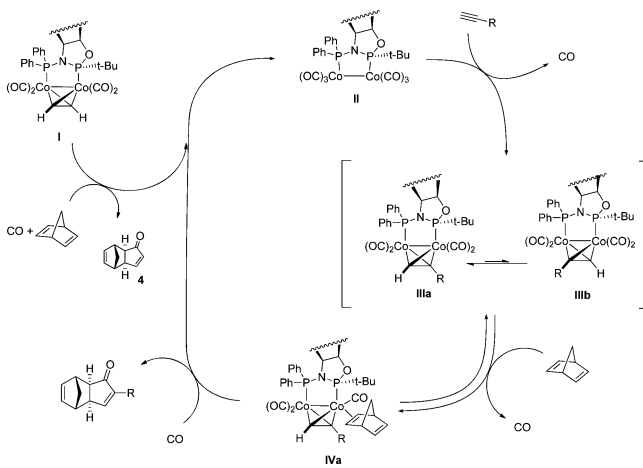
Scheme 6. Stoichiometric PKR of a Mixture of Complexes TMS-3a/TMS-3a'



These findings thus confirm that TMS-3a/TMS-3a' are catalytically significant intermediates.

With all this information in hand, the following catalytic cycle is proposed (Scheme 7). PKR of precatalyst I with NBD provides

Scheme 7. Proposed Catalytic Cycle



an equimolar amount of enone 4 and generates intermediate complex II. Ligand exchange of II with the terminal alkyne produces a mixture of diastereomeric alkyne complexes IIIa/IIIb. Intermediates IIIa and IIIb are in equilibrium in the reaction conditions, IIIa being the complex most favored (see the Supporting Information).¹⁴ Stereoselective formation of complex IIIa over IIIb appears to be essential for the final outcome of the reaction. From this point, CO → NBD ligand exchange leads to complex IVa.¹⁵ By analogy with the previous dicobalt–PN(SO) ligand system and the absolute configuration of the products obtained, we assume that coordination of the olefin takes place at the pro-*R* cobalt atom.¹⁶ The pseudo-axial carbon monoxide of the pro-*R* cobalt center is the less crowded of the CO ligands since it is eclipsed to the –O– fragment of the oxazaphospholidine ring (Figure 1). Finally, alkene insertion in IVa will give rise to the corresponding PKR product and regenerate the active intermediate II. We believe that the diphosphane ligand remains firmly attached to the dicobalt cluster in a bridged-mode throughout the catalytic cycle and that it does not act as a hemilabile ligand. We consider that the unprecedented selectivity observed for this process and the absence of monophosphane complexes support this hypothesis.

In summary, we have described the synthesis of a novel P-stereogenic diphosphane ligand system called ThaxPHOS. The use of these ligands in the Co-catalyzed intermolecular PKR has led to the development of the first catalytic system with useful levels of selectivity. Our results demonstrate that some Co–diphosphane complexes are sufficiently reactive in intermolecular PKR to provide high yields and enantioselectivities. Although the challenge remains to develop catalysts with greater activity and a wider reaction scope, it is worth noting that the TMS-substituted cyclopentenone obtained in the present study is a general cyclopentenone synthon that has been used in the asymmetric synthesis of bioactive compounds.^{3d,e}

■ ASSOCIATED CONTENT

Supporting Information

Ligand-exchange experiments between different ThaxPHOS ligands and of TMSA–Co₂(CO)₆, experimental procedures,

compound characterization data, and spectra for all new compounds. X-ray data for complexes **3b** and **TMS-3d** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to the memory of Professor Peter L. Pauson (1925–2013).

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- (12) Compound **4** was detected by TLC and could not be isolated due to its high volatility. For the preparation of **4**, see: Iqbal, M.; Duffy, P.; Evans, P.; Cloughley, G.; Allan, B.; Lledó, A.; Verdaguer, X.; Riera, A. *Org. Biomol. Chem.* **2008**, 6, 4649–4661.
- (13) Pure **TMS-3d** was synthesized by ligand-exchange reaction of TMSA–Co₂(CO)₆ with **2d** in the presence of DABCO.
- (14) Ligand-exchange reaction between different ThaxPHOS ligands and of TMSA–Co₂(CO)₆ has been studied. It has been found that higher temperatures increase the selectivity of the reaction. See the Supporting Information for more details.
- (15) Olefin complex **IVa** depicted in Scheme 7 derives from the major intermediate **IIIa**; this hypothesis has not been proven. Although unlikely, productive olefin coordination could also occur at the minor isomer **IIIb**. The lowest energy pathway will ultimately determine the stereochemical outcome of the reaction.
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