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

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Supporting Information Placeholder

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 cyclopentanolic 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 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 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

Scheme 1. Hemilabile P,S-ligands used in the asymmetric intermolecular Pauson-Khand reaction.

Scheme 2. PKR reaction between norbornadiene and terminal alkynes catalyzed by P,S-Co2-alkyne complexes.
Inspired by this report, we envisaged the feasibility of an asymmetric catalytic system bearing an aminophosphane 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, and was ideally suited for this purpose since it could be further derivatized to yield a novel family of C_3 symmetric bis-phosphate ligands with a bulky tert-butyl group on one of the phosphorous atoms. Here we report on the synthesis of the ThaxPHOS family of ligands and how the use of these ligands in the asymmetric intermolecular Co-catalyzed PKR provides unprecedented levels of selectivity.

Scheme 3. Synthesis of the ThaxPHOS family of ligands.

![Scheme 3 Image]


![Scheme 4 Image]

Oxazaphospholidine 1 can be synthesized in a single step by condensation with either (+) or (−)-cis-1-amino-2-indanol with tert-BuPCl₂ and protection with borane. From 1, lithium-amide formation with one equivalent of BuLi and reaction with several diaryl and dialkyl chlorophosphanes leads to the borane mono-protected bis-phosphanes 2a-e (Scheme 3). Borane protection was found 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. Finally, we resolved that the most effective way to bind the ligand and the Co₂(CO)₆ moiety was with the intermediary of an alkylene moiety to generate a pre-catalyst. Thus, deprotection of the borane group with 1,4-diazabicyclo[2.2.2]octane (DABCO) and in situ complexation with μ-HCCOTMS)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, complex 3d could not be isolated because it decomposed during the treatment with TBAF. The bridged structure of the ThaxPHOS pre-catalyst complexes was confirmed by X-ray crystallography of 3b (See 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 oxo-cyclopentenone with 54% yield but with no enantioselectivity (Table 1, entry 1). However, when we switched to 1-hexyne, significant levels of enantio-meric excess were revealed (Table 1, entries 2 to 4). Here, the use of catalyst 3b containing a bis(p-CF₃C₆H₄)phosphane group led to the PKR product with 40% ee. The breakthrough came when the alkene 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, allowed to increase the yield to 75% 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 disopropylphosphane 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).

Table 1. Catalytic intermolecular PKR with norbornadiene.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>R</th>
<th>conditions[b]</th>
<th>yield [%][b]</th>
<th>ee [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Ph</td>
<td>atm, 100 ºC, toluene</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>nBu</td>
<td>1 bar, 100 ºC, toluene</td>
<td>54</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>nBu</td>
<td>atm, 100 ºC, toluene</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>3c</td>
<td>nBu</td>
<td>atm, 85 ºC, toluene</td>
<td>97</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>TMS</td>
<td>atm, 100 ºC, toluene</td>
<td>39</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>TMS</td>
<td>1 bar, 130 ºC, toluene</td>
<td>77</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>3a</td>
<td>TMS</td>
<td>2 bar, 130 ºC, toluene</td>
<td>51</td>
<td>86</td>
</tr>
<tr>
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<td>3a</td>
<td>TMS</td>
<td>1 bar, 100 ºC, DME</td>
<td>38</td>
<td>93</td>
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<tr>
<td>9</td>
<td>3a</td>
<td>TMS</td>
<td>2 bar, 160 ºC, diglyme</td>
<td>30</td>
<td>86</td>
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<tr>
<td>10</td>
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<td>TMS</td>
<td>1 bar, 120 ºC, toluene</td>
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<td>87</td>
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<tr>
<td>11</td>
<td>3e</td>
<td>TMS</td>
<td>1 bar, 120 ºC, toluene</td>
<td>10</td>
<td>1</td>
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<td>1 bar, 120 ºC, toluene</td>
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<tr>
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<td>SiMe₃Ph</td>
<td>1 bar, 120 ºC, toluene</td>
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<td>14</td>
<td>3a</td>
<td>SiMe₃Bn</td>
<td>1 bar, 120 ºC, toluene</td>
<td>42</td>
<td>90</td>
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</table>

[b]Reactions were run in a glass pressure tube at the designated CO pressure (atm = atmospheric CO pressure). [c]Yields refer to isolated product after flash chromatography. [d]Enantiomeric excess was determined by either chiral GC or HPLC.

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 centred our attention on the initial alkyne exchange process. Reaction of pre-catalyst 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 4,11 the subsequent coordination of the TMSA takes place with high stereorecontrol.

Scheme 5. Alkyne exchange experiment with complex 3a under catalytic conditions.

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;12 the corresponding solid state structure is shown in Figure 1. As described previously for similar complexes, the bridged diphosphane ligand and the alkyne-TMS substituent are placed in 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).

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.

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

Scheme 6. Stoichiometric PKR of a mixture of complexes TMS-3a/TMS-3a’.

With all this information in hand, the following catalytic cycle is proposed (Scheme 7). PKR of pre-catalyst I with NBD provides 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 favoured (see 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-PNSO ligand system and the absolute configuration of the products obtained, we assume that coordination of the olefin takes place at the pro-R cobalt centre.16 The pseudo-axial carbon monoxide of the pro-R cobalt centre 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.

Scheme 7. Proposed catalytic cycle.
In summary, we have described the synthesis of a novel P-
stereogenic diphasphane ligand system called ThaxPHOS. The use
of these ligands in the Co-catalysed intermolecular PKR has
led to the development of the first catalytic system with useful
levels of selectivity. Our results demonstrate that some Co-di-
phosphate 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 synthons that has been used in the asym-
metric synthesis of bioactive compounds.34e

ASSOCIATED CONTENT

Supporting Information

Ligand exchange experiments between different ThaxPHOS lig-
ands and of TMSA-Co(CO)6, experimental procedures, compound
characterization data and spectra for all new compounds. CIF files
for complexes 3b and TMS-3d. This material is available free of

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(11) To our knowledge the only example of isolated bridged diphas-
phane-Co(CO)5 complex is the one reported by Hong and co-workers,

(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,
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(13) Pure TMS-3d was synthesized by ligand exchange reaction of
TMSA-Co(CO)5 with 2d in the presence of DABCO.

(14) Ligand exchange reaction between different ThaxPHOS ligands
and of TMSA-Co(CO)5 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 4a depicted in Scheme 7 derives from the ma-
nor intermediate 3J; this hypothesis has not been proven. Although
unlikely, productive olefin coordination could also occur at the minor
isomer 3K. The lowest energy pathway will ultimately determine the
stereocchemical outcome of the reaction.

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