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Asymmetric Pauson–Khand reaction with chiral, electron-deficient mono- and bis-phosphine ligands

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Abstract—The intermolecular Pauson–Khand reaction between norbornene and dicobalt carbonyl complexes of phenylacetylene substituted with chiral phosphorus ligands has been investigated. High yields ($\geqslant$ 98%) and enantiomeric excesses of up to 56% have been observed.
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The Pauson–Khand reaction, which unites an alkyne, an alkene, and carbon monoxide through the agency of dicobalt octacarbonyl, is an effective method for constructing cyclopentenones.[1] Over the 30-year period since its discovery in 1973, significant insight has been gained into the mechanism of this intriguing reaction and its usefulness has been broadened through the discovery of promoters and catalytic techniques.[2]

Effort has also been expended toward developing an asymmetric variant of this reaction,[3] principally through the use of a chiral auxiliary attached to the alkyne or alkene substrate,[4] and by replacing a carbonyl ligand in the complex with a chiral phosphine ligand.[5] This latter approach has to date proven considerably more successful in the intramolecular than intermolecular version of this and similar reactions.[6] The first intermolecular enantioselective approach was disclosed in 1988 by Pauson and co-workers, who used the chiral unidentate phosphine Glyphos®.[5a] Improvements in this approach were later reported,[5b–e] but still the two diastereomers had to be separated prior to cyclization with the olefin.

In an effort to overcome this major drawback, a few years ago we undertook a study of bidentate bridging ligands with the goal of ultimately being able to generate unique chiral complexes that would be effective in the asymmetric Pauson–Khand reaction.[7] Pauson and co-workers[8] had reported in 1988 that achiral bis(diphenylphosphino)methane (dppm) had a markedly deleterious effect on the cyclization of the phenylacetylene–dicobalt complex with norbornene (24% yield vs 60% yield without dppm);[9] we felt, however, that diphosphine complexes could be made more reactive through modification of the electronic properties of the phosphine substituents. In 1999, we were able to demonstrate[7] that electron-deficient diphosphinoamine ligands did indeed lead to vastly improved yields in this reaction (up to 98%). These novel ligands, relative to common phosphine ligands, facilitate the first step of the Pauson–Khand reaction by rendering the carbon monoxides more labile by virtue of the increase in the backbonding from cobalt to phosphorus and, at the same time, protect the intermediate dicobalt–alkyne complex against oxidation and clusterization pathways.

The second phase of this program has focused on the use of chiral electron-deficient ligands in the intermolecular Pauson–Khand reaction.[10] The simplest way to introduce chirality in the diphosphinoamines, a priori, is by placing a chiral substituent on nitrogen. In preliminary work, it was found that the diphosphinoamine ligand **1a** could be readily prepared from 1-phenylethylamine and chlorodiphenylphosphine[11] and then through reaction with **2** transformed into the bridged complex **3a**;[12] in the presence of norbornene, **3a** afforded cyclopentenone **4** with a small, but encouraging, enantiomeric excess (16% ee, 57% yield) (Scheme 1).[13]

Since electron-withdrawing substituents on phosphorus could be expected not only to improve the yield as before, but in addition to increase the asymmetric

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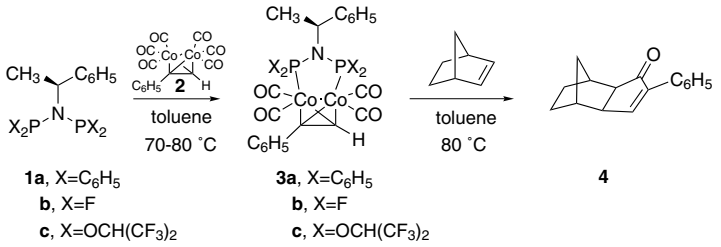


Scheme 1.

induction in the reaction by bringing the chiral ligand nearer to the diastereotopic cobalts through a shortening of the Co–P bonds, the derivatives **1b**,**c** were next prepared.[14] The corresponding chiral complexes **3b**,**c**, formed in 40–45% yield, on exposure to norbornene in warm toluene produced the expected cyclopentenone **4** in 90% and 99% yield, respectively, but, surprisingly, devoid of enantiomeric excess (Scheme 1).

Given that asymmetric induction depends on the ligand's ability to provide a chiral environment close to the reaction center and that the distance of the chiral center on the amine is significant in the complexes **3**, induction in **3a** must occur through transmission, that is, through the spatial orientation imposed on the phenyl groups on phosphorus.[15] Hence, the small fluoro and the mobile hexafluoroisopropoxy[16] substituents should be, and are, ineffective. Merely increasing the size of the amine cannot provide a workable solution to this problem: bulky amines in reaction with PCl_3 tend to give cyclodiphosphazanes[17] and with chlorodiphenylphosphine rearranged products[18] and, in fact, all reactions directed toward diphosphinoamine formation from 1-(2,6-dichlorophenyl)ethylamine and 2-amino-3,3-dimethylbutane did indeed fail.

Placing the chiral groups on phosphorus, thereby bringing the chiral and the reactive centers into closer proximity, was also investigated. The Pauson–Khand reaction of complex **7**, prepared as shown in Scheme 2,[19] with norbornene gave cyclopentenone **4** in 83% yield, but unfortunately with only 17% ee, again a high yield but low enantiomeric excess.[20]

The difficulties encountered in this bridging-ligand approach led us to consider an attractive alternative: complexation of each of the cobalts with identical chiral *mono*phosphine ligands. This approach, as that above, effectively obviates the necessity of a high degree of Co discrimination in the complexation.

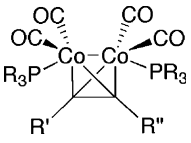
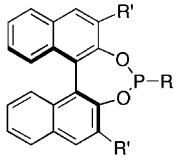


Figure 1.

It has long been known that two ligands can be introduced into acetylene–dicobalt hexacarbonyl complexes and these ligands occupy the two axial positions[21] (Fig. 1). In a recent example, Pericas and co-workers prepared a phenylacetylene–dicobalt tetracarbonyl complex in which achiral tripyrrolylphosphines were in the axial positions.[22] Significantly, they also reported an 85% yield in the reaction with norbornene, showing that the beneficial effect of electron-deficient substituents in diphosphinoamines, which we had previously observed, is also found with the monophosphine ligands. The chiral ligands we chose to investigate were the readily

Table 1. BINOL phosphoramidite and phosphite derivatives



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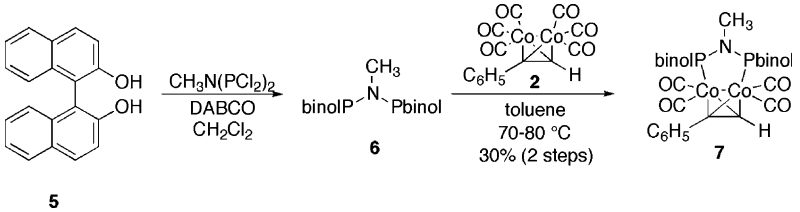
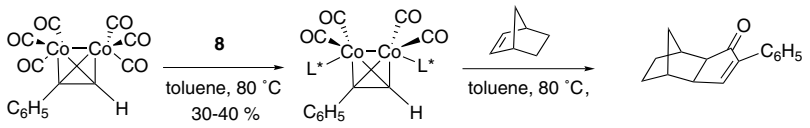
	R	R′	Ref.
8a	OC_6H_5	H	25
8b	$OCH(CF_3)_2$	H	26
8c	$N(CH_3)_2$	H	27
8d	$N(i\text{-}C_3H_7)_2$	H	27
8e	$N(C_2H_5)_2$	H	27
8f	$N(C_2H_5)_2$	CH_3	This work
8g	$N(C_2H_5)_2$	C_6H_5	This work



Scheme 2.



	yield (%)	ee (%)
9a	65	24
9b	75	36
9c	75	13
9d	60	21
9e	70	38
9f	40	30
9g	30	16

Scheme 3.

prepared BINOL phosphoramidite and phosphite derivatives **8a**–**g** (Table 1).[23,24]

These chiral, unidentate ligands could be introduced into the axial positions of the phenylacetylene–dicobalt hexacarbonyl complex in moderate (nonoptimized) yields. On warming in toluene solution in the presence of excess norbornene for 12 h, these new complexes provided cycloadduct **4** in generally good yield and with the indicated enantiomeric excess (Scheme 3).

While the yields are roughly comparable to those obtained with the bis-phosphine ligands, in several cases the induction is significantly better, particularly with the phosphoramidite **8e**. Disappointingly, *ortho* substitution in this ligand (**8f**,**g**) did not yield an improved enantiomeric excess, but this is in line with results obtained by Feringa and co-workers in the conjugate addition of diethylzinc in the presence of chiral copper complexes.[27] A significant improvement with ligand **8e** was observed, however, on lowering the reaction temperature to 60 °C and replacing the toluene with DME: 56% ee, 60% yield.[28,29] Although the reaction time is considerably lengthened under these conditions (96 h vs 12 h), this represents the best result reported to date (previously[10]<10% ee, 29% yield) for the intermolecular Pauson–Khand reaction using chiral ligands without separation of diastereomers.

In conclusion, chiral monophosphine ligands at each of the axial positions in the acetylene–dicobalt complex appear to be generally more effective in the asymmetric intermolecular Pauson–Khand reaction than chiral bisphosphine ligands that bridge the two cobalts in equatorial positions. The level of enantioselectivity reached with the chiral phosphoramidites encourages further research on this approach to asymmetric induction in this important reaction.

Acknowledgements

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14. Ligands **1b** and **1c** were prepared from *N,N*-bis(dichlorophosphino)-1-phenylethylamine (1-phenylethylamine, PCl_3, C_2H_5N, ether) by using SbF_3 in refluxing methylcyclohexane (35%, two steps) and $(CF_3)_2CHOH$ and C_2H_5N in refluxing ether (40%, two steps), respectively.
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