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A versatile and efficient approach to enantiomerically pure monodentate and bidentate P-chiral phosphines

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Abstract

Enantiomerically pure (*R*)-methylphenylvinylphosphine and the P-chiral diphosphine ligands (5*R*,7*R*)-, (5*R*,7*S*)- and (5*S*,7*R*)-[5-(methylphenylphosphino)-2,3-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene] were stereospecifically obtained in high yields from the chiral palladium template controlled Diels–Alder reaction between (±)-methylphenylphosphine and 3,4-dimethylphenylphosphole.

1. Introduction

Enantiomerically pure phosphines containing resolved stereogenic phosphorus centers are not available from the natural pool of chirons. To date, most P-chiral phosphines are obtained from tedious multistep synthesis or by resolution. However, the growing demand for these compounds in various fields such as catalysis, pharmaceuticals and many other chemical industries has led to an intense search for a more facile and efficient approach to these optically active materials.[1] Recently, we found that several bidentate P-chiral phosphines can be prepared by asymmetric template syntheses.[2] In this paper, we describe a flexible approach that utilizes the desirable features of asymmetric synthesis and kinetic resolution for the synthesis of selected diastereomers and enantiomers of monodentate and bidentate P-chiral phosphines.

2. Results and discussion

When coordinating to platinum group metal ions, dimethylphenylphosphole (DMPP) is activated as a cyclic diene and is able to react, in a controllable manner, with dienophiles adopting either an intramolecular *exo*-cycloaddition pathway or via an intermolecular *endo*-cycloaddition mechanism.[3] It

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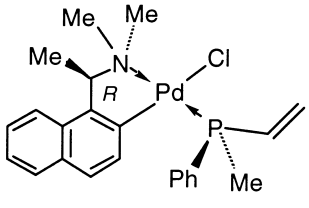
has been established that when DMPP is coordinated to the perchlorato complex (−)-**1**, chiral *exo*-cycloadducts are always obtained.[4] As illustrated in Scheme 1, when the chiral template was treated with precisely two equivalents of (±)-methylphenylvinylphosphine in dichloromethane at 0°C for 4 h, the *exo*-diastereomer (+)-**2** was obtained stereospecifically.[5] The 202 MHz ^{31}P NMR spectrum of the crude reaction product in $CDCl_3$ showed a pair of doublets at δ 116.2 and 44.2 (J_{pp}=41.9 Hz) for the cycloadduct together with a singlet at δ −31.0 for the excess dienophile. No other ^{31}P NMR signal was recorded in the spectrum. The cycloadduct and excess dienophile were separated by silica column chromatography, initially using hexane as the eluent to isolate the excess phosphine and subsequently using acetone to isolate the product complex. Thus, enantiomerically pure (+)-**2** was obtained as a white powder in 80% yield, $[\alpha]_D$ +3.8 (*c* 0.5, CH_2Cl_2). Chemoselective removal of the naphthylamine auxiliary from (+)-**2** was achieved by treatment of the complex with concentrated HCl. The resulting dichloro complex (+)-**3** was obtained as beige prisms in 85% yield, $[\alpha]_D$ +97.6 (*c* 0.5, CH_2Cl_2). The absolute stereochemistry of (+)-**3** has been confirmed by X-ray crystallography: the configurations at P_5 and P_7 are (*R*) and (*S*), respectively.[5] Evidently, it was the (*S*)-enantiomer of the methylphenylvinylphosphine that underwent the coupling reaction to yield (+)-**2**. Since other possible diastereomeric complexes were not formed, the (*R*)-enantiomer of methylphenylvinylphosphine was, ipso facto, discriminated from the cycloaddition reaction. Furthermore, NMR spectroscopy established that the recovered (*R*)-enantiomer of methylphenylvinylphosphine (87%), with $[\alpha]_D$ +8.2 (*c* 0.5, CH_2Cl_2), is enantiomerically pure. In these NMR determinations, the recovered monodentate phosphine ligand was coordinated to the di-μ-chloro dipalladium complex containing the *ortho*-metallated form of the (*R*)-naphthylamine auxiliary,[6] and complex **8** was obtained regiospecifically.[7,8] Prior to crystallization, the 202 MHz ^{31}P NMR spectrum of crude **8** in $CDCl_3$ showed a sole sharp singlet at δ 17.1. On the other hand, when the recovered phosphine was coordinated to the di-μ-chloro dipalladium complex containing the (*S*)-naphthylamine auxiliary, a new sharp singlet was detected at δ 17.2 in the ^{31}P NMR spectrum and, significantly, no signal was detected at δ 17.1. When the recovered dienophile was coordinated to the dipalladium complex containing the racemic form of the naphthylamine auxiliary, as expected, two sharp singlets of ca. equal intensities were recorded at δ 17.1 and δ 17.2 for the diastereomeric complexes **8** and **9**, respectively. It should be noted that the stereoselectivity of the Diels–Alder reaction is sensitive to the reaction temperature. When conducted at 30°C, the cycloaddition reaction produced a 6:1 mixture of (+)-**2** and (−)-**5** and the enantiomeric excess of the recovered (*R*)-enantiomer of methylphenylvinylphosphine was also affected accordingly. At 0°C and below, the kinetic resolution occurs stereospecifically.



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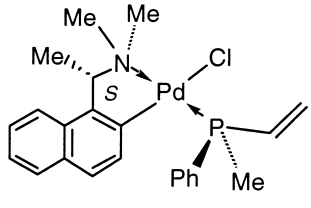

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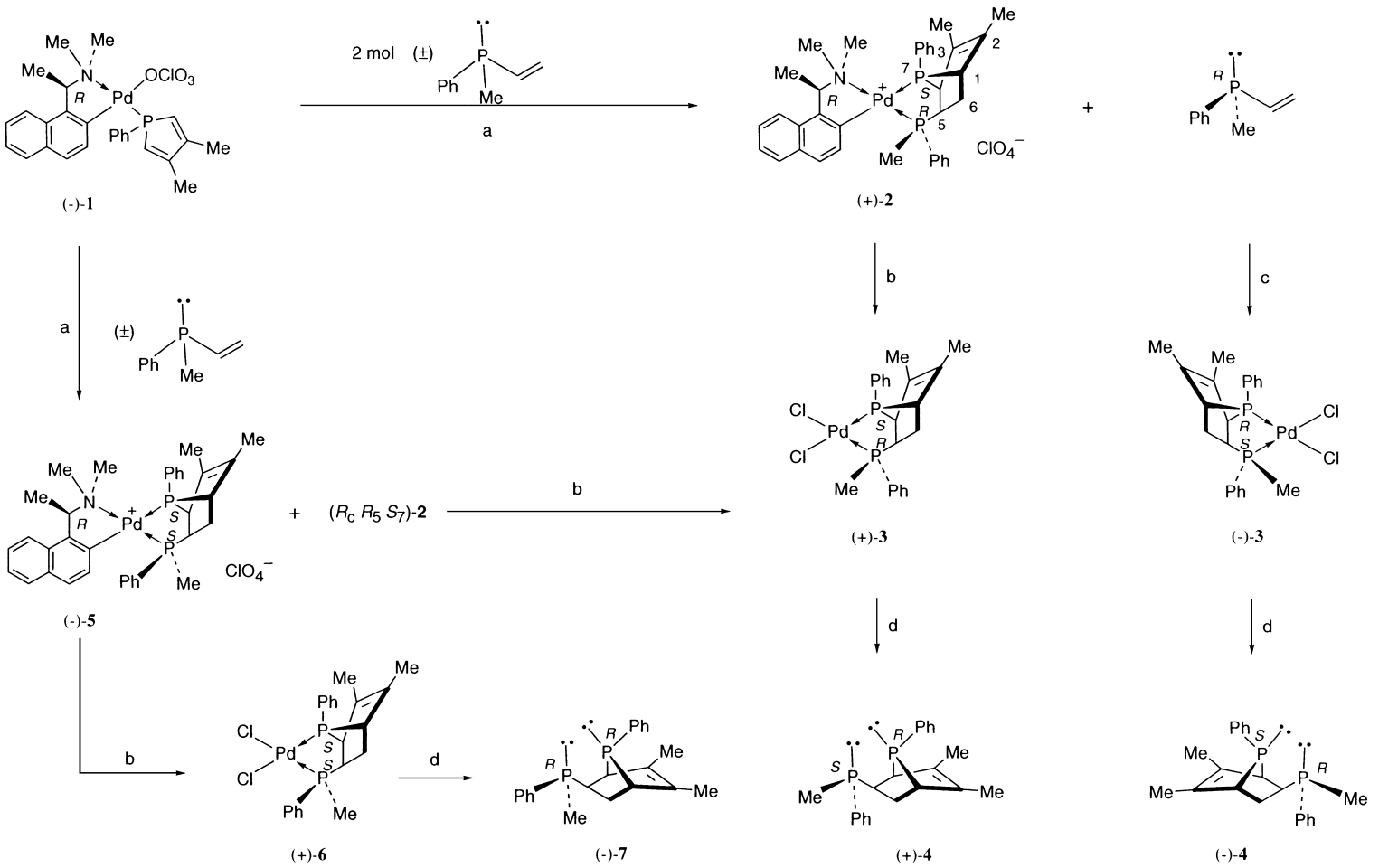
It was noted that, in addition to the cycloaddition reaction and the kinetic resolution operation, a ligand redistribution process was also involved in the chiral template-assisted synthesis of (+)-**2**. Due to the distinct electronic directing effects originating from the σ-donating nitrogen and π-accepting aromatic carbon atom of the *ortho*-metallated naphthylamine ring, the phosphorus donor atom in methylphenylvinylphosphine is expected to take up the template site *trans* to the NMe_2 group, since it is a softer donor than its counterpart, DMPP.[9] Furthermore, it has been well established that the prochiral N–Me groups in the chiral auxiliary are locked into the stereochemically non-equivalent axial and equatorial positions.[10] The adoption of the (*R*)-configuration at P_7 in the cycloadduct avoided any



Scheme 1. (a) In CH_2Cl_2; (b) dissolved in acetone then HCl; (c) $[PdCl_2(CH_3CN)_2]$, 0.5 equiv. then $[PdCl_2(DMPP)_2]$, 0.5 equiv. in CH_2Cl_2; (d) KCN

severe inter-chelate repulsion between the P_7-phenyl substituent and the sterically protruding equatorially deposed N–Me group. On the other hand, the (*R*)- rather than (*S*)-stereochemistry observed at C_5 in the cycloaddition product complex was probably due to the intra-chelate steric congestion that would otherwise be present between the proximal P_5-phenyl group and the *exo*-proton at C_6.

Interestingly, when activated by $PdCl_2$, the recovered (*R*)-methylphenylvinylphosphine reacts stereospecifically with DMPP to give (−)-**3** in a quantitative yield, $[\alpha]_D$ −97.2 (*c* 0.5, CH_2Cl_2). It was noted that (−)-**3** was the enantiomeric form of the dichloro cycloadduct which was obtained via the chiral template-assisted reaction. The ^{31}P NMR spectrum of crude (−)-**3** in $CDCl_3$ showed signals identical to that recorded for (+)-**3** and, more importantly, signals due to the other possible diastereomer, (+)-**6**, were not detected. In the absence of an external auxiliary, it was clear that the (S_5,R_7) rather than the (S_5,S_7) stereochemistry observed in this palladium chloride-activated cycloaddition reaction was, indeed, due merely to the intra-chelate strain that would otherwise be present between the P_5-phenyl group and the *exo*-proton at C_6.

When (−)-**1** was reacted with a stoichiometric quantity of (±)-methylphenylvinylphosphine at room temperature for 2 h and then treated with concentrated HCl, as expected, a 1:1 mixture of (+)-**3** and the new diastereomer (+)-**6** was obtained. In contrast to their non-separable intermediates (+)-**2** and (−)-**5**, the diastereomeric dichloro complexes could be efficiently separated via fractional crystallization. Thus, (+)-**6** was isolated as pale yellow prisms from CH_2Cl_2−Et_2O in 90% yield, $[\alpha]_D$ +11.2 (*c* 0.5, CH_2Cl_2). The ^{31}P NMR spectrum of (+)-**6** in CD_2Cl_2 showed a pair of doublets at δ 126.4 and 32.5 (J_{pp}=3.7 Hz). The absolute stereochemistry of the third diastereomer (+)-**6** has been confirmed by X-ray crystallography.[5] In this synthesis, the more soluble diastereomer (+)-**3** was isolated in 70% yield from $CHCl_3$−Et_2O. It is worth noting that the inversion energies of free tertiary phosphines are relatively low and thus the interconversion or racemization of enantiomers may occur at higher temperatures.[11] Indeed, when this stoichiometric cycloaddition reaction was carried out at 100°C in chlorobenzene for 0.5 h and then treated with concentrated HCl, an expected 3:1 diastereomeric mixture of (+)-**3** and (+)-**6** was obtained in practically quantitative yields. The 3:1 ratio remained unchanged when further heated at a higher temperature. The results illustrate that, firstly, the chiral (*R*)-naphthylamine auxiliary is able to control the stereospecific formation of the (S_7)-chiral center, even at elevated temperatures; and secondly, it is possible to enhance the formation of (+)-**3** despite using a stoichiometric quantity of the racemic dienophile. This high temperature racemization approach, however, is less efficient than the low temperature kinetic resolution process described earlier.

The above syntheses demonstrate that (*R*)-methylphenylvinylphosphine and three out of the four possible stereoisomers of the dichloro complexes can be obtained in a strategic manner using (−)-**1** as the common starting material. However, the fourth isomer (−)-**6** could not be obtained directly from (−)-**1**. This stereoisomer needed to be prepared by parallel synthetic approaches using the equally accessible (+)-**1** as the starting material.[4] It was noted that, in addition to (−)-**6**, two more diastereomers, (+)-**3** and (−)-**3**, as well as the monodentate ligand (*S*)-methylphenylvinylphosphine could be obtained from (−)-**1**. Individual treatments of the four stereoisomeric dichloro complexes with aqueous potassium cyanide liberated the corresponding enantiomerically pure P-chiral diphosphines in quantitative yields. Thus, we have demonstrated the ability of template synthesis of stereoisomeric P-chiral diphosphines with simultaneous resolutions of the methylphenylvinylphosphine. It should be reiterated that the resolution of P-chiral phosphines is rather tedious and inefficient.[1] Our approach offers these enantiomerically pure ligands within several hours and with the preferred chiralities. We are currently exploring how this methodology can be utilized in the synthesis of other stereochemically demanding functionalized ligands.

3. Experimental

Reactions involving air-sensitive compounds were performed under a positive pressure of purified nitrogen. Proton NMR spectra were recorded at 500.14 MHz and ^{31}P spectra at 202.46 MHz on a Bruker AMX500 NMR spectrometer. Optical rotations were measured on specified solutions in a 1 dm cell at 25°C with a Perkin–Elmer model 341 polarimeter. Elemental analyses were performed by the Microanalytical Laboratory of the Department of Chemistry at the National University of Singapore. The chiral templates (−)-**1** were obtained as previously described.[3,4] Spectroscopic data for diastereomeric complexes (+)-**2**, (+)-**3**, (−)-**5** and (+)-**6** have been reported elsewhere.[5]

Asymmetric Diels–Alder reactions: in general, the cycloaddition reaction involving the kinetic resolution process was carried out according to the following experimental procedure. A solution of (−)-**1** (1.64 g, 2.70 mmol) in CH_2Cl_2 (30 mL) was added dropwise into a stirring solution of (±)-methylphenylvinylphosphine (0.81 g, 5.39 mmol) in CH_2Cl_2 (30 mL) at 0°C. The reaction mixture was then stirred at 0°C for 4 h. After removal of solvent, the product was purified by silica gel chromatography giving (*R*)-methylphenylvinylphosphine (0.34 g, 87%) and (+)-**2** (1.60 g, 80%). The naphthylamine auxiliary was generally removed chemoselectively from the template complex **2** by heating a solution of the complex (2 mmol) in acetone (20 mL) in the presence of concentrated HCl (2 mL) for 2 h. Liberation of the free diphosphine ligand (+)-**4** was achieved by adding a solution of KCN (10 mmol) in H_2O (10 mL) to a rapidly stirred solution of a stereochemically pure isomer of (+)-**3** (2 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was then stirred at room temperature for 5 min. After the usual workup the corresponding free diphosphine was obtained as a colorless oil in 95–100% yield. (+)-**4**: $[\alpha]_D$ +42.4 (*c* 0.5, CH_2Cl_2), ^{31}P NMR ($CDCl_3$) δ −22.8 (d, J_{pp}=66.6 Hz, P_5), 91.4 (d, J_{pp}=66.6 Hz, P_7). (−)-**7**: $[\alpha]_D$ −22.6 (*c* 0.5, CH_2Cl_2), ^{31}P NMR ($CDCl_3$) δ −22.6 (d, J_{pp}=70.2 Hz, P_5), 91.2 (d, J_{pp}=70.2 Hz, P_7). (−)-**4**: $[\alpha]_D$ +41.1 (*c* 0.5, CH_2Cl_2), (+)-**7**: $[\alpha]_D$ +22.3 (*c* 0.5, CH_2Cl_2), ^{31}P NMR spectra identical to that recorded for (+)-**4** and (−)-**7**, respectively. (*R*)-Methylphenylvinylphosphine: $[\alpha]_D$ +8.2 (*c* 0.5, CH_2Cl_2), ^{31}P NMR ($CDCl_3$) δ −31.0 (s).

Acknowledgements

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