In Situ Generation of Ruthenium–Chiral Phosphine Complexes and Their Use in Asymmetric Hydrogenation

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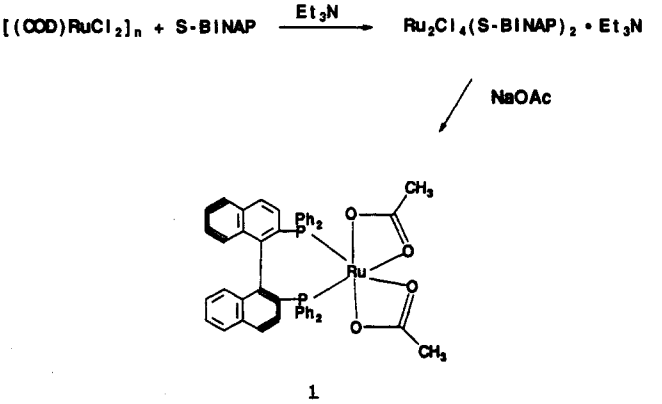
Summary: The complexes ((S)-BINAP)Ru(acac)$_2$ (4), (SKEW)Ru(acac)$_2$ (5), and (DIOP)Ru(acac)$_2$ (6) were generated by hydrogenation of a mixture of the appropriate phosphine and Ru(acac)$_3$ in methanol. Addition of 2-(4-isobutylphenyl)propenoic acid (2) to these solutions, followed by hydrogenation at about 1000 psig, afforded (S)-(+)-ibuprofen in various enantiomeric excesses (about 90% ee using complex 4). A crystal structure was obtained for complex 6.

A significant recent advance in chiral molecule synthesis involves the asymmetric hydrogenation reactions catalyzed by ((*S*)-BINAP)Ru(acetate)$_2$ (**1**).[1] The transformation of α,β-unsaturated acids to chiral acids in high conversion and high enantiomeric excess (ee) is of potential industrial importance for the production of profen-type non-steroidal antiinflammatory drugs, as demonstrated by Noyori's synthesis of (*S*)-naproxen.[2]

The optimization and mechanistic investigation[3,4] of these reactions was facilitated by the availability of **1** as a well-characterized, monomeric complex.[1] The synthesis of **1** involves a two-step procedure (Scheme I). Subsequently, reports of the in situ formation of ruthenium/(*S*)-BINAP complexes from (*S*)-BINAP and (COD)Ru(acetate)$_2$,[5] [(benzene)RuCl$_2$]$_2$,[6] or [(COD)RuCl$_2$]$_n$[7] appeared. These systems eliminate the need to synthesize and handle **1** and in two cases[6,7] begin with commercially available materials.

Our interest in (*S*)-(+)-ibuprofen (**3**) prompted a study of the asymmetric hydrogenation of 2-(4-isobutylphenyl)-propenoic acid (**2**) (Scheme II). Attempts to find a conveniently prepared catalyst for this reaction led to a method for in situ preparation of ((*S*)-BINAP)Ru(acac)$_2$ (**4**), an analog of **1**, from (*S*)-BINAP and Ru(acac)$_3$ (acac = acetylacetonate) (Scheme III).

Scheme I



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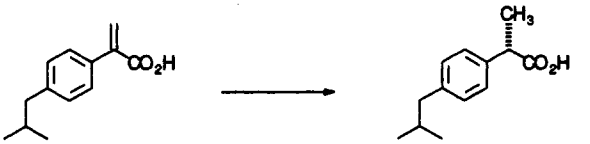
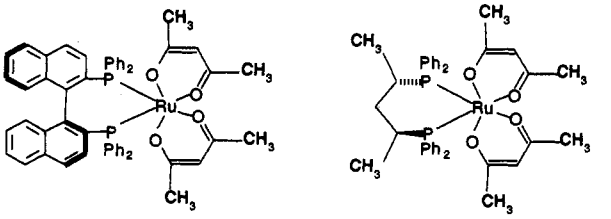
Scheme II

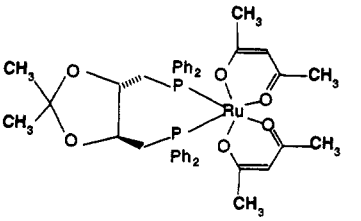


2 **3**

Scheme III



4 **5**



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Results and Discussion

A mixture of an amine salt of compound **2**, (*S*)-BINAP, Ru(acac)$_3$, and methanol, kept under 1000 psig of hydrogen for about 20 h at ambient temperature, afforded **3** in about 90% ee (Table I, entries 1–6). The structure of the ammonium cation did not effect the stereochemical outcome of the hydrogenation. Using (*S*)-BINAP, both (*R*)- and (*S*)-α-methylbenzylamine, benzylamine, and triethylamine, salts of **2** all afforded **3** in high ee. The opposite enantiomer ((*R*)-**3**) was obtained using (*R*)-BINAP, again regardless of the nature of the ammonium ion.

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Table I. Hydrogenation of 2-(4-Isobutylphenyl)propenoic Acid (2) To Give (*S*)-(+)-Ibuprofen (3)[a]

entry no.	substrate	catalyst	catalyst pretreatment	temp (°C)/ time (h)	conversn (GC area %)	% ee of 3 (config)
1	2·(*S*)-MBA[b]	Ru(acac)$_3$/(*S*)-BINAP[c]	no	24/22	100	91 (*S*)
2	2·(*R*)-MBA[d]	Ru(acac)$_3$/(*R*)-BINAP[e]	no	24/17	100	85 (*R*)
3	2·(*R*)-MBA	Ru(acac)$_3$/(*S*)-BINAP	no	24/17	94	88 (*S*)
4	2·(*S*)-MBA	Ru(acac)$_3$/(*R*)-BINAP	no	24/53	100	89 (*R*)
5	2·BZA[f]	Ru(acac)$_3$/(*S*)-BINAP	no	22/18	94	85 (*S*)
6	2·Et$_3$N[g]	Ru(acac)$_3$/(*S*)-BINAP	no	24/18	100	88 (*S*)
7	2	Ru(acac)$_3$/(*S*)-BINAP	no	24/18	100	6 (*S*)
8	2	Ru(acac)$_3$/(*S*)-BINAP	yes	23/17	100	88 (*S*)
9	2·(*S*)-MBA	((*S*)-BINAP)Ru(acetate)$_2$ (**1**)	no	24/5	100	89 (*S*)
10	2	((*S*)-BINAP)Ru(acetate)$_2$ (**1**)	no	28/7	100	90 (*S*)
11	2·(*S*)-MBA	Ru(acac)$_3$	no	24/18	100	0
12	2	Ru(acac)$_3$/(*S*)-BINAP	yes	27/18[h]	100	86 (*S*)
13	2·Et$_3$N	Ru(acac)$_3$/(*S*)-BINAP	yes	27/66[i]	32	90 (*S*)
14	2·(*S*)-MBA	RuCl$_3$·*x*H$_2$O/(*S*)-BINAP	no	24/22	100	64 (*S*)
15	2·Et$_3$N	[(COD)RuCl$_2$]$_n$/(*S*)-BINAP	no	24/18	100	85 (*S*)
16	2·(*S*)-MBA	(COD)Ru(acac)$_2$/(*S*)-BINAP	no	24/19	100	89 (*S*)
17	2	(CH$_3$CN)Ru(acac)$_2$ClO$_4$/(*S*)-BINAP	yes	22/24	100	86 (*S*)
18	2·Et$_3$N	Ru(acac)$_3$/SKEW[j]	no	22/211	94	8 (*R*)
19	2	Ru(acac)$_3$/DIOP[k]	yes	20/69	100	22 (*S*)
20	2	(SKEW)Ru(acac)$_2$ (**5**)[l]	no	24/20	100	3 (*S*)
21	2	(DIOP)Ru(acac)$_2$ (**6**)[l]	no	22/17	93	4 (*S*)
22	2	(DIOP)Ru(acac)$_2$ (**6**)[m]	no	22/19	100	6 (*S*)

[a] See Experimental Section for reaction conditions. [b] (*S*)-MBA salt of **2**; (*S*)-MBA = (*S*)-(−)-α-methylbenzylamine. [c] (*S*)-BINAP = (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [d] (*R*)-MBA salt of **2**; (*R*)-MBA = (*R*)-(+)-α-methylbenzylamine. [e] (*R*)-BINAP = (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [f] BZA salt of **2**; BZA = benzylamine. [g] Triethylamine salt of **2**. [h] Substrate:catalyst ratio 800:1; run under 2000 psig of H$_2$. [i] Substrate:catalyst ratio 38 000:1; run under 2000 psig of H$_2$. [j] SKEW = (2*S*,4*S*)-bis(diphenylphosphino)pentane. [k] DIOP = (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. [l] Mixture of diastereomers. [m] Single diastereomer.

When the free acid **2** was used, the asymmetric induction decreased significantly (entry 7). We believe that in this case the absence of an amine allows the achiral hydrogenation reaction (entry 11) to compete with the formation of catalyst **4**. Pretreatment of (*S*)-BINAP, Ru(acac)$_3$, and methanol with hydrogen, followed by introduction of acid **2**, gave **3** in high ee (entry 8). In all these cases the conversions and product ee's were the same as those obtained using preformed **1** (entries 9 and 10).

Note that reaction times and catalyst loadings were not optimized. Our standard substrate to catalyst ratio (30:1) was chosen for convenience due to the small scale of most experiments. The reaction was complete within the same time when an 800:1 substrate:catalyst ratio was used but was slower using a 38 000:1 ratio (entries 12 and 13).

Our use of a Ru(III) starting material differs from the previously reported systems, which employ Ru(II) compounds. It is reasonable to expect that Ru(III) species are reduced to Ru(II) species under the reaction conditions, by either hydrogen or the phosphine.[8] The identical reduction results obtained using either our system or preformed **1** suggests that the acac analog of **1** (compound **4**) is being formed in solution. The decrease in product ee when **2** was hydrogenated without pretreatment of the BINAP/Ru(acac)$_3$ mixture is likely due to the time required for assembly of **4** by reduction of Ru(acac)$_3$ and complexation by BINAP.

Ru(acac)$_3$ is not the only Ru compound that can form an effective system; RuCl$_3$, [(COD)RuCl$_2$]$_n$, (COD)Ru(acac)$_2$, or (CH$_3$CN)Ru(acac)$_2$ClO$_4$, mixed with (*S*)-BINAP, also catalyzed the reduction of **2** to **3** (entries 14–17).

Additional evidence for the formation of **4** was obtained from a ^{31}P NMR study. A spectrum of the solution generated by hydrogenating a mixture of BINAP and Ru(acac)$_3$ in methanol (60 °C, 2 h, 1000 psi of H$_2$) exhibited

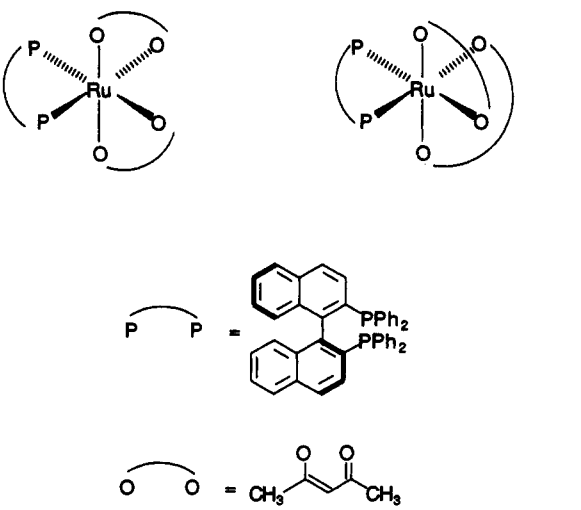

Figure 1.

two singlets of unequal intensities at 56.0 and 56.3 ppm. Each singlet probably arises from one diastereomer of complex **4** (Figure 1). These diastereomers result from enantiomeric configurations of the acac ligands.[9] Similar Ru complexes bearing achiral phosphine ligands exist as enantiomers resolvable at ambient temperature.[10] By comparison, **1** exhibits a singlet at 65.1 ppm in the ^{31}P NMR.[1] Stereospecific binding of acetate in this case was attributed by Noyori to steric interactions between the P-bound phenyl groups and the acetate ligands, leading to only one diastereomer.[1] This interaction is probably of less importance in acac binding because of its increased flexibility relative to acetate.

Since complex **1** can be generated by reaction of Ru(COD)(acetate)$_2$ and (*S*)-BINAP,[5] we attempted the analogous reaction using Ru(COD)(acac)$_2$. A ^{31}P NMR

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(9) Seddon, E. A.; Seddon, K. R. *The Chemistry of Ruthenium*; Elsevier: New York, 1984; p 352.

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spectrum of the resulting mixture was nearly identical with that described above, indicating the presence of 4. Also, by analogy to the reaction shown in Scheme I, treatment of $Ru_2Cl_4((S)\text{-BINAP})_2NEt_3$ with acetylacetone and sodium carbonate in *tert*-butyl alcohol afforded 4, again indicated by ^{31}P NMR. These NMR spectra were all identical except for the ratio of intensities of the two signals at 56.0 and 56.3 ppm. This ratio varied slightly depending on the method used to make 4 and also varied run-to-run using the same method.

We found that (bisphosphine)Ru(acac)$_2$ complexes could be synthesized from various bisphosphines and Ru(acac)$_3$. For example (SKEW)Ru(acac)$_2$ (5) and (DIOP)Ru(acac)$_2$ (6) were generated in solution using this method. These complexes, made in methanol and used as catalysts for the hydrogenation of 2, afforded 3 of low optical purity (Table I, entries 18 and 19). The poor asymmetric induction exhibited by these catalysts is presumably because of the increased flexibility of the DIOP and SKEW ligands compared to BINAP.[11] However, our synthetic method is general and allows the in situ production of these monomeric Ru complexes from a variety of bisphosphines under one set of conditions. This is not the case for Noyori's method of making complex 1, as substitution of other chelating bisphosphines for BINAP leads to diverse products.[12] Alcock reported syntheses of several chiral bisphosphine–Ru complexes by a single method.[13] Although active hydrogenation catalysts were derived from these, multiple steps and isolation of intermediates were required.

Complexes 5 and 6 behaved analogously to complex 4. That they exist as diastereomeric pairs was evident from both the ^{31}P and ^1H NMR spectra. Also, they were made by treatment of Ru(COD)(acac)$_2$ with DIOP and SKEW.

Attempts to generate crystals of complex 4 by several methods were unsuccessful. However, crystalline 5 and 6 were obtained by syntheses of the diastereomeric mixtures from Ru(COD)(acac)$_2$ in *N,N*-dimethylformamide (DMF), followed by slow evaporation of the solvent. ^{31}P and ^1H NMR spectra showed that one diastereomer was crystallized preferentially in each case, leaving the mother liquors enriched in the other diastereomer. The solids were stable in the air under ambient conditions. However, isomerization could be thermally induced. For example, heating a DMF solution of the isolated diastereomer of 6 at 145 °C for 6 h regenerated the isomeric pair.

An X-ray analysis of 6 confirmed the structure. An orange crystal of the DMF hemisolvate $RuC_{41}H_{46}P_2O_6 \cdot {}^1/_2C_3H_7NO$ is orthorhombic, space group $P2_12_12$, with $Z = 4$ and lattice constants $a = 16.6121(8)$ Å, $b = 19.932(2)$ Å, and $c = 12.3768(8)$ Å. A total of 6565 unique (4778 observed, $I > 3\sigma(I)$) intensity data were measured in $\theta/2\theta$ geometry on an Enraf-Nonius CAD4 diffractometer at 292 K. Full-matrix least-squares refinement of a structural model with 479 independent variables yielded an R_F value of 0.036. The two molecules of DMF in the unit cell are disordered about the crystallographic 2-fold axis. The absolute configuration of the Ru moiety, shown in Figure 2, was confirmed by significantly inferior refinement ($R = 0.039$) of the enantiomeric model.

When used as catalysts for the hydrogenation of 2 to 3,

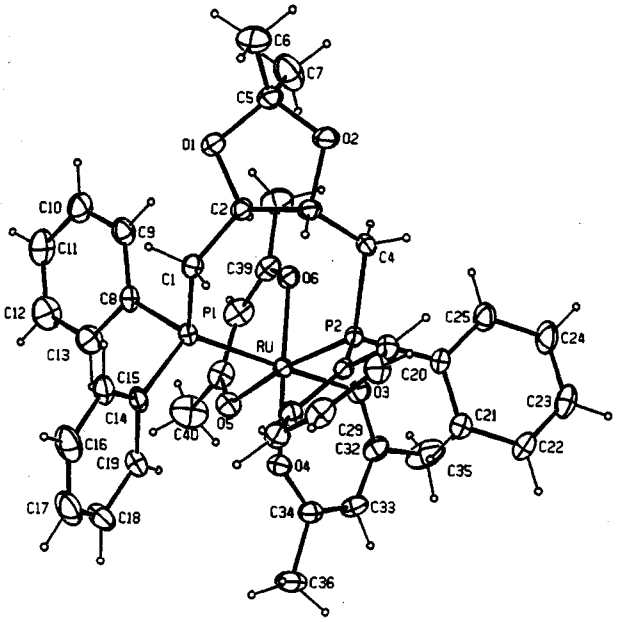

Figure 2. ORTEP drawing of (DIOP)Ru(acac)$_2$ (6).

the preformed diastereomeric pairs of 5 and 6, as well as the isolated diastereomer of 6, gave the same low asymmetric induction as the corresponding mixture of diastereomers formed in situ (Table I, entries 20–22). Due to the observed ease of isomerization in solution, it is unclear if only one of each diastereomeric pair is responsible for the asymmetric induction in the hydrogenation reaction.

Conclusions

The bis(acac)/(*S*)-BINAP complex 4 is as efficient as the bis(acetate)/(*S*)-BINAP complex 1 in enantioselective hydrogenations. However, the synthesis of (bisphosphine)Ru(acac)$_2$ complexes from bisphosphines and Ru(acac)$_3$ offers several advantages. First is the ready availability of a catalyst equivalent to 1 in asymmetric hydrogenation reactions. As pointed out by Noyori himself[6] and others,[5,7] the preparative difficulties associated with 1 are eliminated by in situ formation. This is particularly important in commercial applications. In addition, Ru(acac)$_3$ is the most stable, available, and inexpensive Ru precursor to such complexes reported to date.

Second, our method will allow rapid screening of new chiral bisphosphines for their ability to impart enantioselectivity to Ru-based acrylic acid hydrogenation catalysts. A parallel may be found in Rh-catalyzed hydrogenations of (acylamino)acrylic acids, which can utilize catalysts formed in situ.[14]

Finally, the generality of the method was demonstrated by the synthesis of complexes 4–6. The nature of the bisphosphines in these complexes varies greatly. This suggests that a wide variety of related complexes can be made in the same way.

Experimental Section

General Considerations. ^1H NMR spectra were recorded on a GE QE-300 spectrometer at 300 MHz. Chemical shifts are reported in parts per million relative to tetramethylsilane. ^{31}P

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NMR spectra were taken on a Nicolet NT-360 (146 MHz) spectrometer. Chemical shifts are reported in parts per million relative to 85% H_3PO_4. Gas chromatographic (GC) analyses were carried out using an HP 5890 Series II instrument equipped with a thermal conductivity detector and an SE-54 megabore column (15 m × 0.053 mm × 1.2 μm). Optical purities were determined on a Hewlett-Packard 1090 high-pressure liquid chromatograph (HPLC) equipped with a filter photometric detector and a chiral AGP 100-4 column from Advanced Separation Technologies. The eluent was 10% (V/V) isopropyl alcohol in water containing 0.01 M potassium dihydrogen phosphate and 0.005 M octanoic acid and adjusted to pH 7 with sodium hydroxide. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Reagents and solvents were obtained from Aldrich, Fluka, or Curtin Matheson Scientific and were used without further purification. Solvents were dried by storage over activated 3- or 4-Å molecular sieves and were deoxygenated by sparging with nitrogen for several hours. ((*S*)-BINAP)Ru(acetate)$_2$,[1] (COD)Ru(acac)$_2$,[15] and 2-(4-isobutylphenyl)propenoic acid (**2**)[16] are known compounds.

General Hydrogenation Procedure. A 100-mL Parr autoclave (Monel or Hastelloy C) was taken into a nitrogen-filled glovebox and charged with 22 mg (0.055 mmol) of ruthenium(III) acetylacetonate [Ru(acac)$_3$], 38 mg (0.061 mmol) of (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((*S*)-BINAP), 1.54 mmol of substrate, and 30 mL of methanol. The reactor was closed, removed from the glovebox, flushed (3 × 300 psig) with H_2, and then pressurized to 1000 psig with H_2. The mixture was stirred at 300–700 rpm under the indicated time/temperature conditions. The degree of conversion was determined by GC analysis, and the optical purity of the product (**3**) was determined by HPLC analysis. Reaction times were not optimized. Conditions and results are shown in Table I.

Hydrogenation of 2-(4-Isobutylphenyl)propenoic acid (2) with Catalyst Preformation. A 100-mL (Monel) Parr autoclave was taken into a nitrogen-filled glovebox and charged with 18 mg (0.045 mmol) of Ru(acac)$_3$, 26 mg (0.042 mmol) of (*S*)-BINAP, and 30 mL of methanol. The reactor was closed, removed from the glovebox, flushed (3 × 300 psig) with H_2, and then pressurized to 1000 psig with H_2. After the mixture was stirred (300 rmp) at ambient temperature for 4 h, the reactor was vented and a solution of 250 mg (1.22 mmol) of **2** in 10 mL of methanol was added. Repressurization to 1000 psig with H_2 followed by stirring at ambient temperature for 17 h afforded a product mixture containing only (*S*)-(+)-ibuprofen (**3**). HPLC indicated this was 94% *S*/6% *R* (88% ee).

((*S*)-BINAP)Ru(acac)$_2$ (4) from (*S*)-BINAP and Ru(acac)$_3$. A mixture of 0.31 g (0.50 mmol) of (*S*)-BINAP, 0.20 g (0.50 mmol) of Ru(acac)$_3$, and 30 mL of degassed methanol was kept under 1000 psig of H_2 pressure at 60 °C for 2 h. The reaction mixture was subjected to ^{31}P NMR ($CH_3OH/CDCl_3$): δ 56.3 (s), 56.0 (s).

(SKEW)Ru(acac)$_2$ (5). A mixture of 84 mg (0.21 mmol) of (COD)Ru(acac)$_2$, 100 mg (0.23 mmol) of (2*S*,4*S*)-bis(diphenylphosphino)pentane (SKEW), and 3 mL of *N*,*N*-dimethylformamide (DMF) was heated at 140–145 °C under an argon atmosphere for 33 h. A portion of the reaction mixture was concentrated in vacuo. NMR analyses indicated the presence of two isomers of **5**: ^{31}P NMR ($CDCl_3$) δ 61.0 (s), 61.8 (s).

After the remainder of the reaction mixture stood at room temperature for 17 days, a yellow-brown crystalline solid was removed by filtration and washed with hexane followed by a small amount of DMF. This was one isomer of **5**: mp 229 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.00 (dd, *J* = 12, 6.5 Hz, 6H), 1.56 (s, 6H), 1.62 (s 6H), 2.18 (m, 2H), 2.90 (m, 2H), 4.86 (s, 2H), 7.06–7.48 (m, 20H); ^{31}P NMR ($CDCl_3$) δ 60.7 (s).

(DIOP)Ru(acac)$_2$ (6). By the same method used to prepare **5**, (COD)Ru(acac)$_2$ and (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) afforded an isomeric mixture of **6**: ^{31}P NMR ($CDCl_3$) δ 44.3 (s), 45.6 (s).

From DMF was obtained one isomer of **6** as a crystalline solid: mp 238 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 6H), 1.42 (s, 6H), 1.70 (s, 6H), 2.73–3.05 (m, 4H), 4.11 (m, 2H), 4.72 (s, 2H), 7.03–7.49 (m, 20H); ^{31}P NMR ($CDCl_3$) δ 44.3.

Supplementary Material Available: For **6**, a figure showing the structure of the DMF solvate molecule and tables of positional parameters, bond distances and angles, torsion angles, and anisotropic thermal parameters (13 pages). Ordering information is given on any current masthead page.

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