Journal of Organometallic Chemistry, 370 (1989) 203–221
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 09703

Preparation of optically active peralkyldiphosphines and their use, as the rhodium(I) complex, in the asymmetric catalytic hydrogenation of ketones

Kazuhide Tani *, Kenichi Suwa, Eiji Tanigawa, Tomokazu Ise, Tsuneaki Yamagata, Yoshitaka Tatsuno, and Sei Otsuka

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, Japan 560

(Received December 13th, 1988)

Abstract

Two types of the optically active peralkyldiphosphine, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(dialkylphosphino)butane (Rdiop **3**) and *N*-(*N'*-substituted carbamoyl)-4-dicyclohexylphosphino-2-dicyclohexylphosphinomethylpyrrolidine (R-Cycapp **8**), have been prepared by various synthetic methods. Rhodium(I) complexes of **3** and **8** showed high catalytic activity for hydrogenation of various kinds of prochiral ketones, which were reduced smoothly to the corresponding optically active hydroxy compounds, under hydrogen at atmospheric pressure and ambient temperature. The neutral rhodium(I) complexes (diphosphine-Rh^N) hydrogenated α-ketoamides and α-ketopantolactone in fairly high optical yields (66–77%ee). In the hydrogenation of *N*-(α-ketoacyl)-α-amino esters, the Cydiop-Rh^N catalyst showed a marked contrast to the diop-Rh^N system; in the hydrogenation of the methyl ester of *N*-(phenylglyoxyl)-(*S*)-α-phenylalanine, 72%de was attained with little double asymmetric induction by the chiral center in the substrate.

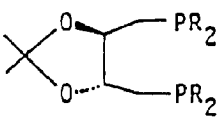
Introduction

Although preparation of optically active hydroxy compounds by catalytic asymmetric hydrogenation of ketones is an important unit process in organic synthesis, there are only a limited number of reports on the catalytic asymmetric hydrogenation of ketones compared to that of olefins [1]. One principal reason seems to be that few efficient catalysts are available; although the chiral rhodium(I) diphosphine complexes used for the asymmetric hydrogenation of ketones are similar to those used for olefin hydrogenation, rates for ketone hydrogenation are generally much slower than those for olefins. Virtually all the ligands used for olefin hydrogenation

0022-328X/89/$03.50

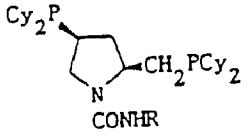
have two phosphines that have two aryl groups. We found recently that rhodium(I) complexes having a highly basic peralkyldiphosphine ligand show high catalytic activity for hydrogenation of ketones and various kinds of ketones and aldehydes can be reduced smoothly to give the corresponding hydroxy compounds under very mild conditions, i.e., of hydrogen at atmospheric pressure and room temperature [2]. Further, we have reported briefly on the preparation of optically active peralkyldiphosphines and the asymmetric hydrogenation of ketones with their rhodium(I) complexes [3].

Here we present the details of the studies on the preparation of optically active peralkyldiphosphines and the outcome of the asymmetric hydrogenation of several prochiral ketone substrates with their rhodium(I) complex catalysts. The optically active peralkyldiphosphines we have prepared are of two types; 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(dialkylphosphino)butane (Rdiop **3**), alkyl analogues of a conventional ligand, diop (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) [4], and *N*-(*N'*-substituted carbamoyl)-4-dicyclohexylphosphino-2-dicyclohexylphosphinomethylpyrrolidine (R-Cycapp **8**), cyclohexyl analogues of a pyrrolidine diphosphine, R-capp (*N*-(*N'*-substituted carbamoyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine) [5]. Their parent diphosphines are known to be efficient ligands for asymmetric olefin hydrogenation. Excellent results were recently obtained for the asymmetric hydrogenation of functionalized ketones catalyzed by Ru-binap systems [6]. It has also been reported that rhodium catalysts having a chiral pyrrolidinediphosphine, developed on the basis of our concept, show good results for asymmetric hydrogenation of α-ketopantolactone, α-keto esters, or α-keto acetals [7]. However, fairly forcing conditions are required to obtain practical reaction rates. Since the chiral peralkyldiphosphines, **3** and **8**, cannot be made by the conventional methods used for synthesis of ordinary chiral diphosphines having diarylphosphino groups, we think that our synthetic



(-)-Rdiop (3)

R=Et, ^{i}Pr, Cy



(-)-R-Cycapp (8)

R=Ph, ^{t}Bu, Cy

methods supply some general routes to peralkyl chiral diphosphines.Thus we think that it is worthwhile to describe in detail the preparation of these optically active peralkyldiphosphines.

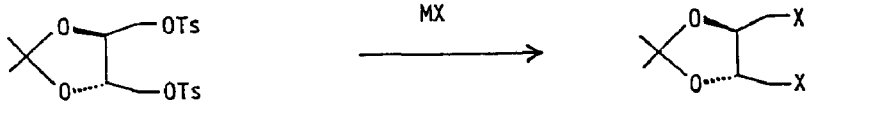
Generally, as the catalyst precursors for the asymmetric hydrogenation of ketone substrates, the neutral rhodium(I) complex catalysts (diphosphine-Rh^{N}), prepared in situ from the reaction of $[Rh(olefin)_2Cl]_2$ with 2 moles of diphosphine, were found to be much more effective than the corresponding cationic complexes, [Rh(diene)(diphosphine)]$^{+}X^{-}$ (diphosphine-Rh^{+}). Of the various ketone substrates subjected to the present chiral peralkyldiphosphine-rhodium(I) catalyst systems, α-ketoamides, *N*-(α-ketoacyl)-α-amino esters, and α-ketopantolactone were reduced to the corresponding optically active hydroxy compounds in fairly good optical yields (66–77% optical yields).

Results and discussion

Preparation of alkyl analogues of diop [(−)-Rdiop (3)]

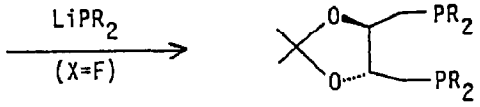
The conventional method used for the preparation of diop, namely the nucleophilic substitution of the ditosylate **1** with alkali metal phosphide, cannot be applied to the synthesis of the alkyl analogues of diop, Rdiop (**3**). The reaction of **1** with alkali metal dialkylphosphide produced only intractable substances. Since the peralkyldiphosphines, $R_2P(CH_2)_nPR_2$ (n = 3,4) can be prepared by replacement of the halides $X(CH_2)_nX$ with R_2PLi [8], the reactions of the dihalides (**2a–2c**) with R_2PLi were examined under various conditions. However, the reactions gave mainly diphosphanes, R_2PPR_2, and unidentifiable products, with only a very small amount of the desired diphosphine **3** being formed. To our surprise, **3** could be isolated in substantial yields from the reaction of the difluoride **2d** with R_2PLi.

The key substance, (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-difluorobutane (**2d**), was obtained in 63% yield by heating the ditosylate **1** with an excess of anhydrous potassium fluoride under vacuum (130 °C/11–12 Torr) in absolute diethylene glycol. The reaction product was collected in a reservoir by direct distillation from the reaction flask. The reaction of the difluoride **2d** with R_2PLi proceeded smoothly at ambient temperature in dioxane or dioxane-THF mixture to give the expected, optically active peralkyldiphosphines **3**, as an air-sensitive colorless liquid [(−)-Etdiop (**3a**) and (−)-^{i}Prdiop (**3b**)] or as a solid [(−)-Cydiop (**3c**)] in practical yields. These air-sensitive peralkyldiphosphines can be purified by vacuum distillation or by recrystallization and can be characterized spectroscopically. More conveniently, however, the purification can be carried out by recrystallization of their air-stable solid CS_2 adduct, especially in the case of (−)-Cydiop. The free diphosphine is readily and quantitatively recovered from the CS_2 adduct by simple heating under reflux in EtOH in a slow stream of nitrogen. Thus the air-sensitive diphosphine Cydiop can be conveniently stored in a bottle as the air-stable CS_2



(1) (2)

a X=I ; b X=Br
c X=Cl; d X=F



(3)

a R=Et [(-)-Etdiop]
b R=^{i}Pr [(-)-^{i}Prdiop]
c R=Cy [(-)-Cydiop]

Scheme 1

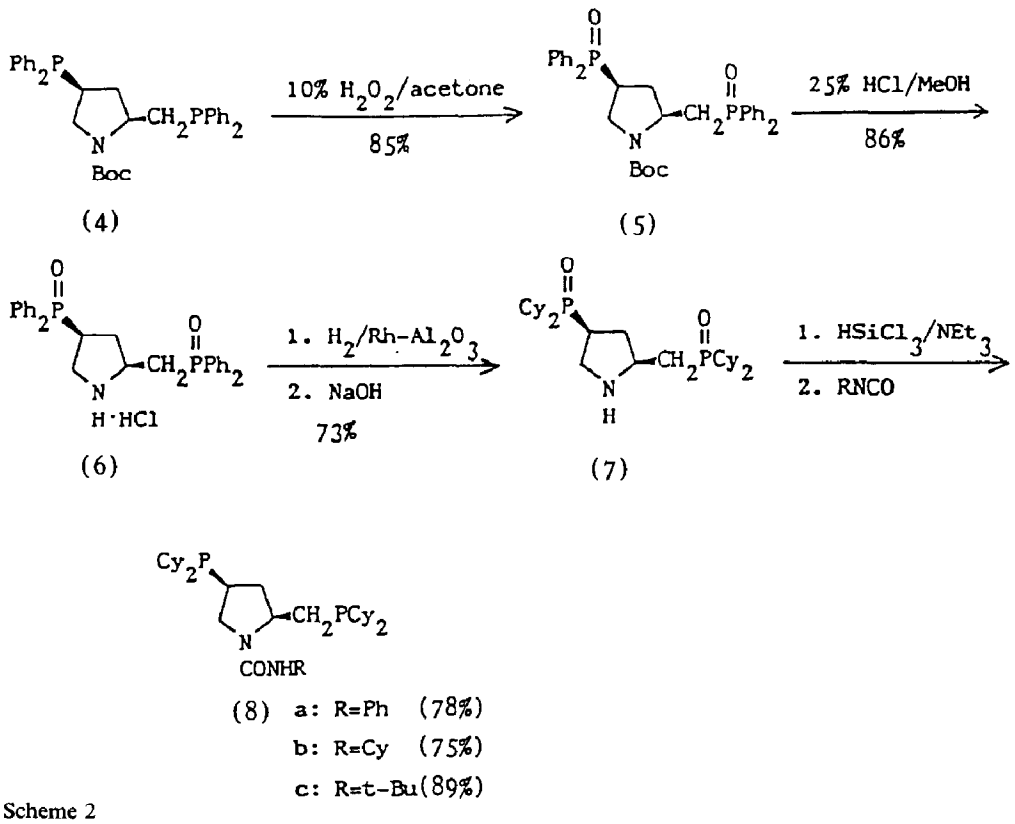
adduct, and freed from CS_2 immediately before use. (+)-Cydiop can be similarly prepared starting from (−)-tartaric acid.

All these Rdiops form the corresponding cationic rhodium(I) complexes [Rh(Rdiop)(diene)]X (diene = nbd (norbornadiene), cod (1,5-cyclooctadiene); X = ClO_4, BF_4] by a conventional method, but the nbd complexes gave the well characterized, more crystallizable products.

*Preparation of cyclohexyl analogues of R-capp [R-Cycapp(**8a–8c**)]*

As another type of peralkyl chiral diphosphine we have chosen the pyrrolidine-containing diphosphines, (2*S*,4*S*)-*N*-(*N'*-substituted carbamoyl)-4-dicyclohexylphosphino-2-dicyclohexylphosphinomethylpyrrolidine [R-Cycapp (**8**)], because usual chiral diphosphines containing a pyrrolidine ring, such as bppm [(2*S*,4*S*)-*N*-(t-butoxycarbonyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine] (**4**) [9a] or R-capp [(2*S*,4*S*)-*N*-(*N'*-substituted carbamoyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine] [5], are known to show often excellent asymmetric inductions of more than 90%ee for the asymmetric hydrogenation of olefins, i.e. dehydroamino acid derivatives. For the preparation of optically active peralkyldiphosphines having dicyclohexylphosphino groups such as Cydiop, another synthetic method is possible. Because many optically active diphosphines carry diphenylphosphino groups, dicyclohexylphosphine analogues should be accessible by reduction of the benzene rings of ordinary chiral diphosphines. This methodology was applied in the synthesis of cyclohexyl analogues of R-capp (Scheme 2). Attempts to convert the pyrrolidine diphosphines (bppm or R-capp) into the cyclohexyl analogue by direct hydrogenation of the diphenylphosphino groups failed even under rigorous conditions. Reduction of the phenyl group in diphosphines to the cyclohexyl group was first accomplished after the diphenylphosphino group had been converted into the diphenylphosphinyl group. Oxidation of bppm (**4**) proceeded smoothly with 10% hydrogen peroxide in ice-cooled acetone to give the corresponding P,P'-dioxide (**5**). Removal of the t-butoxycarbonyl (Boc) group from **5** by 25% methanolic hydrogen chloride at 0 °C gave the bis(diphenylphosphinyl)compound (**6**), which was hydrogenated to give the cyclohexyl analogue. The hydrogenation was slow and Rh–Al_2O_3 was found to be the most satisfactory catalyst. The bis(diphenylphosphinyl) compound, **6**, was reduced in methanol with hydrogen (130 kg/cm^{-2}) at 150 °C for 2 d over 5% Rh–Al_2O_3. After neutralization and recrystallization from $CHCl_3$–Et_2O the bis(dicyclohexylphosphinyl) compound (**7**) was isolated as colorless crystals containing 2 moles of solvating chloroform. Reduction of the phosphine oxide was achieved with $HSiCl_3$–NEt_3 in acetonitrile at reflux under nitrogen for 2 h, followed by treatment with 25% NaOH. The resulting oily product, *N*-unsubstituted diphosphine, without prior purification, was transformed into the crystalline product **8** by reaction with the appropriate isocyanate in CH_2Cl_2 at room temperature. The desired peralkyl chiral diphosphines (**8a–8c**) were isolated in good yields as colorless crystals after recrystallization from ethanol. These diphosphines are easily crystallized and fairly air-stable in the solid state. That there are only two singlet $^{31}P\{^1H\}$ NMR signals for each diphosphine indicates that the diphosphines (**8a–8c**) are optically pure and that no racemization occurred during the transformation.

An analogous method has also successfully been applied in the preparation of Cydiop **3c** and (*S*,*S*)-2,3-bis(dicyclohexylphosphino)butane [10]. Thus the method-



Scheme 2

ology described here is a widely applicable method for the preparation of chiral peralkylphosphines.

Asymmetric hydrogenation of prochiral ketones

In addition to the cationic complexes, diphosphine-Rh^+, we also examined the neutral complexes, diphosphine-Rh^N as catalyst precursors. In contrast to the usual rhodium-diphosphine complexes, the rhodium complexes of the present chiral peralkyldiphosphines showed high catalytic activity for the hydrogenation of ketones. This is expected from the previous results with achiral peralkyldiphosphine-rhodium(I) complexes [2]; various kinds of ketone substrates were hydrogenated under mild conditions (1 atm H_2 at room temperature).

The results of asymmetric hydrogenation of ketone substrates with rhodium(I)-Rdiop complexes are listed in Table 1. All hydrogenations were carried out under hydrogen at atmospheric pressure. Simple ketones, α-keto acids, α-keto esters, α-keto lactones, and α-keto amides underwent smooth hydrogenation to give the corresponding hydroxy compounds. The catalytic activity of the cationic complexes in the hydrogenation of simple ketones is markedly different from that of the neutral complexes; acetophenone was smoothly hydrogenated in the presence of the cationic complexes but the rate in the presence of the neutral catalysts was much lower under the mild conditions used. The other substrates examined, all α-functionalized ketones, were easily hydrogenated by both types of complexes. The asymmetric induction in these hydrogenations was not high, except for the α-keto

Table 1

Asymmetric hydrogenation of prochiral ketones with Rdiop-Rh [a]

Entry	Substrate	Catalyst [b]	Solvent	$t_{1/2}$ [c] (min)	%ee [d] (config.)
1	PhCOMe	(−)-Etdiop-Rh^+	MeOH	58	0
2	PhCOMe	(−)-^{i}Prdiop-Rh^+	MeOH	51	4(*S*)
3	PhCOMe	(−)-Cydiop-Rh^+	MeOH	41	6(*S*)
4	PhCOMe	(−)-^{i}Prdiop-Rh^N	MeOH	(59%/24 h)	11(*R*)
5	$MeCOCO_2Me$	(−)-^{i}Prdiop-Rh^+	MeOH	34	7(*R*)
6	$MeCOCO_2Me$	(−)-^{i}Prdiop-Rh^N	THF	27	32(*R*)
7	$PhCOCO_2Et$	(−)-Cydiop-Rh^+	MeOH	7	7(*S*)
8	$PhCOCO_2Et$	(−)-Cydiop-Rh^N	THF	24	10(*R*)
9	$PhCOCO_2H$	(−)-Cydiop-Rh^N	C_6H_6	(100%/27 h) [f]	17(*R*)
10	$PhCOCO_2H$	(−)-Cydiop-Rh^N [e]	$EtOH/C_6H_6$ (2:1 v/v)	(100%/7 h)	20(*S*)
11	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-^{i}Prdiop-Rh^+	EtOH	11	7(*S*)
12	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-^{i}Prdiop-Rh^N	C_6H_6	16	54(*R*)
13	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-Cydiop-Rh^N	C_6H_6	21	45(*R*)
14	$PhCOCONHCH_2Ph$	(−)-^{i}Prdiop-Rh^+	EtOH	46	31(*S*)
15	$PhCOCONHCH_2Ph$	(−)-Cydiop-Rh^+	EtOH	19	64(*S*)
16	$PhCOCONHCH_2Ph$	(−)-Cydiop-Rh^N	THF	5	77(*S*)
17	$PhCOCONHCH_2Ph$	(+)-Cydiop-Rh^N	THF	4.5	76(*R*)
18	$PhCOCONHCH_2Ph$	(−)-Cydiop-Rh^N [e]	$EtOH/C_6H_6$ (2:1 v/v)	(75%/1 h)	67(*S*)

[a] Reaction conditions: [Rh] 2.5 m*M*, [substrate] 0.5 *M*, 1 atm H_2, 25 °C. [b] Diphosphine-Rh^+ = $[Rh(diphosphine)(nbd)]ClO_4$; diphosphine-$Rh^N$ = $[Rh(C_2H_4)_2Cl]_2$ + 2 diphosphine. [c] Time required for 50% conversion. The value in the parentheses shows time required to achieve the given conversion. [d] Enantiomeric excesses were calculated on the basis of the following values for the pure enantiomers, (*S*)-1-phenylethanol: $[\alpha]_D^{25}$ +43.6° (neat) [11], (*S*)-methyl lactate: $[\alpha]_D^{20}$ −8.25° (neat) [12], (*S*)-ethyl mandelate: $[\alpha]_D^{25}$ +136.6° (*c* 3.74, $CHCl_3$) [13], (*R*)-mandelic acid: $[\alpha]_D^{20}$ −156.9° (*c* 2, H_2O) [14], (*R*)-pantolactone: $[\alpha]_D^{25}$ −50.7° (*c* 2.05, H_2O) [15], (*S*)-*N*-benzyl mandelamide: $[\alpha]_D^{26}$ +79.9° (*c* 1.09, $CHCl_3$): see Experimental. [e] Two equivalents of triethylamine with respect to the rhodium complex were added. The reaction was run with [Rh] 5 m*M* at 40 °C. [f] The reaction was run at 40 °C.

amide. Further general trends observed with these catalysts are: (i) the catalytic activity with varying alkyl groups of Rdiop increases slightly in the order Et < ^{i}Pr < Cy, (ii) the most bulky alkyl group, i.e., cyclohexyl, is the most effective for asymmetric induction, (iii) the neutral complexes are more effective for asymmetric induction than the corresponding cationic complexes, and in some cases, the major hydroxy compound enantiomer produced was reversed depending on the nature of the complex catalyst, i.e., by use of (−)-Rdiop ligands, (*S*)-products were obtained with the cationic complexes, whereas (*R*)-products were obtained with the neutral complexes (entries 2 vs. 4; 7 vs. 8; 11 vs. 12).

In the hydrogenation of phenylglyoxylic acid the addition of triethylamine caused a reversal in the enantiomeric ratio (entries 9 and 10). The α-keto amide is a specific substrate. The hydrogenation of *N*-benzylphenylglyoxylamide with (−)-Cydiop complexes gave the corresponding (*S*)-hydroxy amide in much higher optical yields (> 65%ee) regardless of the nature of the catalyst (cationic, neutral, with or without added amine) (entries 15, 16, and 18). The highest optical yield was 77%ee. In this case the neutral complexes are more active than the cationic ones.The α-keto amide probably coordinates firmly to rhodium as a bidentate chelate and

Table 2

Asymmetric hydrogenation of prochiral ketones with R-Cycapp-Rh [a]

Entry	Substrate	Catalyst [b]	Solvent	$t_{1/2}$ [c] (min)	%ee [d] (Config.)
1	$PhCOCONHCH_2Ph$	(−)-Ph-Cycapp-Rh^N	THF	19	35(*R*)
2	$PhCOCONHCH_2Ph$	(−)-Cy-Cycapp-Rh^N	THF	20	41(*R*)
3	$PhCOCONHCH_2Ph$	(−)-Cy-Cycapp-Rh^N	THF	(94%/18 h) [e]	48(*R*)
4	$PhCOCONHCH_2Ph$	(−)-^{t}Bu-Cycapp-Rh^N	THF	25	47(*R*)
5	$PhCOCONHCH_2Ph$	(−)-^{t}Bu-Cycapp-Rh^+	THF/EtOH (1:1)	28 [f]	15(*S*)
6	$PhCOCONHCH_2Ph$	(−)-bppm-Rh^N	THF	(23%/15 h)	49(*S*)
7	$PhCOCONH^tBu$	(−)-^{t}Bu-Cycapp-Rh^N	THF	18	11(*R*)
8	PhCOCONHPh	(−)-^{t}Bu-Cycapp-Rh^N	THF	15	$[\alpha]_D^{22}$ −6.8° (*c* 2.36, acetone)
9	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-Ph-Cycapp-Rh^N	THF	26	41(*S*)
10	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-Cy-Cycapp-Rh^N	THF	23	50(*S*)
11	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-^{t}Bu-Cycapp-Rh^N	THF	16	62(*S*)
12	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-^{t}Bu-Cycapp-Rh^N	C_6H_6	20	66(*S*)
13	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-Ph-Cycapp-Rh^+	EtOH	(26%/20 h)	10(*R*)
14	$\overline{C(CH_3)_2CH_2OCOCO}$	(−)-^{t}Bu-Cycapp-Rh^+	EtOH	(55%/42 h)	10(*R*)
15	$MeCOCO_2Me$	(−)-Ph-Cycapp-Rh^N	THF	(76%/18 h)	28(*S*)
16	$MeCOCH_2CO_2Me$	(−)-Ph-Cycapp-Rh^N	THF	(79%/16 h)	2(*S*)
17	PhCOCOOH	(−)-Cy-Cycapp-Rh^N	THF	(60%/10 h)	15(*R*)
18	PhCOCOPh	(−)-^{t}Bu-Cycapp-Rh^N	C_6H_6	(81%/54 min) [g]	25(*S*)
19	$PhCOCH_2NMe_2$	(−)-^{t}Bu-Cycapp-Rh^N	C_6H_6	(100%/14 h) [h]	20(*S*)
20	$PhCOCH_2NMe_2 \cdot HCl$	(−)-Ph-Cycapp-Rh^+	THF/MeOH (1:1)	(100%/22 h) [h,i]	14(*S*)

[a] For reaction conditions, see footnote *a* of Table 1, otherwise noted. [b] diphosphine-Rh^N = $[Rh(C_8H_{14})_2Cl]_2$ + 2.2 diphosphine; diphosphine-Rh^+ = $[Rh(nbd)_2]ClO_4$ + 1.1 diphosphine. [c] Time required for 50% conversion. The value in parentheses shows time required to achieve the given conversion. [d] Enantiomeric excesses were calculated on the basis of the optical rotations for the pure enantiomers; (*S*)-*N*-t-butyl mandelamide $[\alpha]_D^{18}$ +58.5° (*c* 0.55, MeOH) (see Experimental), (*S*)-methyl 3-hydroxybutyrate: $[\alpha]_D^{23}$ +33.3° (*c* 1.00, $CHCl_3$) [16], (*R*)-benzoin: $[\alpha]_D^{11}$ −118.5° (*c* 1.1467, acetone) [17], (*R*)-2-dimethylamino-1-phenylethanol: $[\alpha]_D^{31}$ +65.2° (*c* 5.95, EtOH) [18]. See also footnote *d* of Table 1. [e] Reaction was run at −25 °C. [f] [substrate] = 0.25 *M*, [Rh] = 1.25 m*M*. [g] Reaction was stopped after ca. 1 equiv. of hydrogen with respect to the substrate had been absorbed and the conversion was determined by HPLC. The isolated yield of pure benzoin was 64% on the basis of the substrate. [h] Reaction with 5 atm H_2. [i] [substrate] = 0.15 *M*, [Rh] = 1.64 m*M*.

thus becomes a suitable substrate for asymmetric hydrogenation of ketones. This correlates well with the fact that an enamide is a good substrate for asymmetric hydrogenation of an olefin.

Some representative results of the asymmetric hydrogenation of ketones with rhodium complexes of R-Cycapp are listed in Table 2. The present catalyst systems can also hydrogenate various kinds of ketones under mild conditions (1–5 atm H_2, 35 °C) and with the neutral complexes being the more effective for the asymmetric induction. In general the neutral and the cationic complexes are almost equally efficient in asymmetric induction in the asymmetric hydrogenation of olefins, i.e. α-aminoacrylic acid derivatives. The hydrogenation of α-keto amide, PhCO-

$CONHCH_2Ph$, proceeds at a satisfactory rate even at low temperature ($-25°C$) under 1 atm H_2, and a slight enhancement of the optical yield was observed. Our chiral peralkyl diphosphines containing a pyrrolidine ring (**8**), though less effective for the hydrogenation of the α-keto amide, were found to be more effective than the Rdiop-rhodium system described above for the asymmetric hydrogenation of α-ketopantolactone and a maximum optical yield of 66%ee has been achieved with the neutral catalyst, **8c**-Rh^N. The *N*-substituent of the carbamoyl group of the phosphine **8** directs chiral recognition; the %ee generally decreases in the order, $^tBu > Cy > Ph$. A marked difference in the hydrogenation of $PhCOCONHCH_2Ph$ between R-Cycapp **8** and bppm **4** is present. As expected, **8** are more active catalysts than **4**. Moreover, the (*R*)-product was obtained when (*S*,*S*)-R-Cycapp-Rh^N was used as the catalyst, but the (*S*)-product resulted when (*S*,*S*)-bppm-Rh^N was used; both (*S*,*S*)-R-Cycapp **8** and (*S*,*S*)-bppm **4** have the same chiral pyrrolidine moiety (compare entries 1–4 and 6 in Table 2). Such reversal in product configuration as a result of converting the diphenylphosphino groups of a chiral diphosphine into dicyclohexylphosphino groups is also observed in the hydrogenation of α-ketopantolactone in the presence of R-Cycapp or the tetracyclohexyl analogue of bppm. (*R*)-Pantolactone was obtained with (*S*,*S*)-bppm [19], but (*S*)-pantolactone was obtained with (*S*,*S*)-R-Cycapp (entries 7–10 in Table 2) or with the tetracyclohexyl analogue of bppm [7b]. The reason for this is not clearly understood at present, but one plausible explanation could be the difference in mechanism between the two types of catalyst system.

In the hydrogenation of benzil, a marked difference between the cationic and the neutral catalyst was observed; the hydrogenation proceeded much faster in the presence of the cationic complex but the neutral catalyst showed much better chiral recognition. When the reaction was stopped after ca. one equivalent of hydrogen with respect to the substrate had been consumed, the optical yield of the main product, benzoin, was 25%ee (*S*) with (−)-^{t}Bu-Cycapp-Rh^N (entry 18) but only 0.3%ee (*R*) with (−)-Cy-Cycapp-Rh^N. If the reaction was allowed to proceed until hydrogen uptake had ceased (14 h), hydrobenzoin (*meso*: *dl* = 38 : 62) was the sole product in the presence of the cationic complex, whereas a mixture of benzoin (36%) and hydrobenzoin (64%; *meso*: *dl* = 84 : 16) was obtained in the presence of the neutral complex. The difference in mechanism between the two catalyst systems is probably responsible for the disparate outcomes [2b].

As our catalyst systems, especially that of Cydiop-Rh, were found to be efficient catalyst systems for asymmetric hydrogenation of α-keto amides, we have examined the asymmetric hydrogenation of *N*-(α-ketoacyl)-α-amino esters (**9**) giving the *N*-(α-hydroxyacyl)-α-amino esters (**10**) (eq. 1). Representative results are summarized in Table 3. Interestingly our results are in shapr contrast with those for the

$$\underset{(S)}{\overset{R^2}{\underset{|}{\underset{|}{R^1COCONHCHCO_2Me}}}} \xrightarrow[H_2(1\ atm),\ 20°C]{\text{diphosphine-}Rh^{N,+}} \underset{*}{\overset{OH}{\underset{|}{\underset{|}{R^1CHCONHCHCO_2Me}}}} \qquad (1)$$

(9) $\qquad$ $\overset{R^2}{\underset{(S)}{|}}$ **(10)**

a: $R^1 = Ph$; $R^2 = CH_2Ph$; b: $R^1 = Ph$; $R^2 = Me$;

c: $R^1 = Me$; $R^2 = CH_2Ph$

Table 3

Asymmetric hydrogenation of *N*-(α-ketoacyl)-α-amino esters [a]

Entry	Substrate	Catalyst [b]	Conversion (%)	(*R*,*S*)/(*S*,*S*) [c]	%de
1	CH_2Ph	(−)-Cydiop-Rh^N	100	14/86	72
2	|	(+)-Cydiop-Rh^N	100	84/16	68
3	PhCOCONHCHCO$_2$Me (**9a**)	(−)-Cydiop-Rh^+	78	41/59	18
4	(*S*)	dipb-Rh^+	60	48/52	4
5	Me	(−)-Cydiop-Rh^N	100	17/83	66
6	|	(+)-Cydiop-Rh^N	100	82/18	64
7	PhCOCONHCHCO$_2$Me (**9b**)	dipb-Rh^+	57	53/47	6
	(*S*)				
8	CH_2Ph	(−)-Cydiop-Rh^N	80	27/73	46
9	|	(+)-Cydiop-Rh^N	72	74/26	48
10	MeCOCONHCHCO$_2$Me (**9c**)	dipb-Rh^+	33	53/47	6
	(*S*)				

[a] Reactions were run with [Rh] = 2.5 m*M*, [substrate] = 0.5 *M* under 1 atm of H_2 at 25 °C for 20 h in MeOH (for cationic catalysts) or in THF (for neutral catalysts). [b] Diphosphine-Rh^N = $[Rh(C_2H_4)_2Cl]_2$ +2 diphosphine; diphosphine-Rh^+ = [Rh(diphosphine)(nbd)]ClO_4; dipb = $^iPr_2P(CH_2)_4P^iPr_2$. [c] Determined by ^{19}F NMR spectroscopy of the trifluoroacetate (for **10b**) or by HPLC (for **10a, 10c**).

diop-rhodium(I) system as obtained by Ojima et al. [20]. They reported that the asymmetric hydrogenation of **9** in the presence of the diop-rhodium(I) complexes required a high pressure of H_2 (50 atm) and resulted only in simple asymmetric induction owing to the chiral center of the substrate. Fairly high optical induction in the asymmetric reduction of **9** was first achieved by asymmetric hydrosilylation. The hydrogenation of *N*-(α-ketoacyl)-α-amino esters with Cydiop-rhodium catalyst proceeded smoothly even under an atmospheric pressure of hydrogen at ambient temperature. For the asymmetric hydrogenation of **9**, the neutral complex, Cydiop-Rh^N, was again much more effective compared with the cationic complex, Cydiop-Rh^+, both in catalytic activity and in chiral recognition. The highest optical induction of 72%de has been attained with Cydiop-Rh^N complex catalyst for the hydrogenation of **9a** and almost no double asymmetric inductions due to the inherent chiral center of the substrates was observed, because (+)- and (−)-Cydiop complex gave almost the same optical induction in the opposite directions. In contrast to the hydrogenation in the presence of the usual phosphine-rhodium(I) complex system, that little double induction occurred during hydrogenation of **9** in the presence of peralkyldiphosphine-rhodium(I) catalyst systems was also confirmed for the hydrogenation with an achiral catalyst, dipb-Rh^+ (dipb = 1,4-bis(diisopropylphosphino)butane). Although this marked difference between Cydiop-, and diop-rhodium complexes cannot be explained at present, it probably arises from a change in the mechanism in both cases.

Experimental

The preparations of diphosphine ligands and their metal complexes were carried out under pure nitrogen. ^1H NMR (100 MHz), $^{13}C\{^1H\}$ NMR (25 MHz), and

$^{31}P\{^1H\}$ NMR (40.5 MHz) spectra were recorded on a JEOL FX-100 instrument. ^1H NMR (60 MHz) and ^{19}F NMR (56 MHz) were recorded on a JEOL JNM-C-60 HL instrument. Tetramethylsilane (^1H and ^{13}C NMR), 5% phosphoric acid in methanol-d_4 (^{31}P NMR), and C_6F_6 (^{19}F NMR) were used as standards. Downfield shifts relative to the standards were taken as positive. IR spectra were run with a Hitachi 295 infrared spectrophotometer. Optical rotations were measured on a Jasco polarimeter DIP-SL. GLC and HPLC analyses were performed on a Shimadzu GC-6A (Apiezon GL, Triiton X-305 and PEG 20M) and on a Waters Model 6000A solvent delivery system with UV and IR detectors (column: LiChrosorb SI 10, 5 mm ∅ × 250 mm; eluent: hexane/ethyl acetate = 1 : 1).

Materials. Transition metal complexes, $[Rh(nbd)Cl]_2$ [21], $[Rh(C_2H_4)_2Cl]_2$ [22], $[Rh(C_8H_{14})_2Cl]_2$ [23], $[Rh(nbd)_2]ClO_4$ [24], $[Rh(dipb)(nbd)]ClO_4$ [2b], (−)-(2*S*,3*S*)- and (+)-(2*R*,3*R*)-2,3-*O*-isopropylidene-1,4-ditosylbutane (**1**) [25], (−)-(2*R*,3*R*)-2,3-*O*-isopropylidene-1,4-diiodobutane (**2a**) [25], diethylphosphine [26], diisopropylphosphine [27], dicyclohexylphosphine [28], and (−)-(*S*,*S*)-bppm (**4**) [9] were prepared by published procedures. *N*-Benzylphenylglyoxylamide [2b], α-ketopantolactone [19c,29], and α-dimethylaminoacetophenone [30] were also prepared by procedures described previously. Acetophenone, benzil, methyl pyruvate, methyl acetoacetate, phenylglyoxylic acid, ethyl phenylglyoxylate, and (*S*)- and (*RS*)-mandelic acid were of reagent grade and distilled under nitrogen or recrystallized before use. *p*-Toluenesulfonic acid salts of α-amino esters were supplied by Hamari Chemical Co. Ltd..

(+)-(2R,3R)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-dibromobutane (2b)

Similar to the method described for the preparation of the diiodide (**2a**) [25], the dibromide (**2b**) was prepared in 88% yield as a colorless oil by refluxing the ditosylate (−)-**1** (19.4 g, 41.2 mmol) and LiBr (17.9 g, 205 mmol) in anhydrous acetone (60 ml) for 15 h; b.p. 75–77 °C/3 Torr, $[\alpha]_D^{22}$ +8.40° (*c* 9.55, $CHCl_3$). Anal. Found: C, 29.25; H, 4.18; Br, 55.77. $C_7H_{12}O_2Br_2$ calcd.: C, 29.19; H, 4.20; Br, 55.49%. ^1H NMR ($CDCl_3$): δ 1.54(s, 6H, $C(CH_3)_2$), 3.60 (m, 4H, CH_2Br), 4.20 ppm (m, 2H, CH).

(+)-(2R,3R)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-dichlorobutane (2c)

The dichloride **2c** was similarly prepared from the ditosylate **1** and LiCl. A mixture of (−)-**1** (16.4 g, 34.9 mmol) and LiCl (7.40 g, 175 mmol) were stirred at 110 °C in anhydrous DMF until almost all the solid materials had dissolved. After the reaction mixture had been cooled to room temperature, ether (120 ml) and water (400 ml) were added and the organic phase was separated. The extract was washed with water (100 ml) and dried over $CaCl_2$. After removal of the solvent, the residue was distilled to give the pure product as a colorless liquid (6.1 g, 88%); b.p. 47–48 °C/3 Torr, $[\alpha]_D^{22}$ +13.4° (*c* 3.45, $CHCl_3$). Anal. Found: C, 42.04; H, 6.10; Cl, 35.64. $C_7H_{12}O_2Cl_2$ calcd.: C, 42.23; H, 6.08; Cl, 35.62%. ^1H NMR ($CDCl_3$): δ 1.37 (s, 6H, $CH(CH_3)_2$), 3.63 (m, 4H, CH_2Cl), 4.07 ppm (m, 2H, CHO).

(+)-(2R,3R)- and (−)-2S,3S)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-difluorobutane [(+)- and (−)-2d]

The difluoride was similarly prepared from the ditosylate **1** and KF. A mixture of (−)-**1** (25.0 g, 53.0 mmol) and anhydrous KF (12.9 g, 222 mmol) in anhydrous

ethylene glycol (52 ml) was placed in a 200 ml round-bottomed flask equipped with a magnetic stirrer bar and a side arm was connected to a Liebig's condenser, a reservoir, and to a vacuum system. The reaction mixture was stirred in an oil bath at 130 °C under reduced pressure (11–12 Torr) during about 4 h until all the volatile materials had distilled off. Ether (120 ml) and water (400 ml) were added to the distillate and the organic phase was separated off. The extract was washed with water (100 ml) and dried over $MgSO_4$. After removal of the solvent, the residue was distilled to give the pure product (+)-**2d** as a colorless liquid (5.5 g, 63%); b.p. 56–57 °C/16 Torr, $[\alpha]_D^{19}$ +23.5° (*c* 1.64, $CHCl_3$).Anal. Found: C, 50.78; H, 7.42. $C_7H_{12}O_2F_2$ calcd.: C, 50.60; H, 7.28%. ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 6H, $C(CH_3)_2$), 4.13 (m, 2H, $CHCH_2F$), 4.50 ppm (dd, J_{HH} 3.5 Hz, J_{HF} 49 Hz, 4H, CH_2F). ^{19}F NMR ($CDCl_3$): δ −68.0 ppm (dt, $^2J_{HF}$ 49 Hz, $^3J_{HF}$ 21 Hz). IR (neat): 1250, 1215, 1165, 1115, 1005, 985, 845 cm^{-1}.

Similarly, (−)-(2*S*,3*S*)-**2d** was prepared from (+)-(2*R*,3*R*)-**1** and KF. $[\alpha]_D^{22}$ −20.7° (*c* 2.90, $CHCl_3$).

Lithium dialkylphosphide

Dialkylphosphine was treated with a slight excess of butyllithium in hexane under reflux for 2 h. After cooling to room temperature, colorless ($LiPEt_2$) to pale yellow (LiP^iPr_2, $LiPCy_2$) precipitates of the resulting lithium dialkylphosphide were isolated by filtration. The residues were washed with hexane and dried in vacuo. The lithium dialkylphosphides were obtained in almost quantitative yields, and were used for the preparation of the peralkyl diphosphines (**3a–3c**) without further purification.

(−)-(2R,3R)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diethylphosphino)butane [(−)-Etdiop ***3a****]*

To a suspension of lithium diethylphosphide (5.65 g, 58.9 mmol) in dioxane (170 ml) was added a solution of the difluoride (+)-**2d** (3.34 g, 20.1 mmol) in dioxane (5 ml) at room temperature and the resulting suspension was stirred at that temperature. The gradual dissolution of the lithium phosphide was slightly exothermic. After 22 h a small amount of water was added and the solvents were removed in vacuo. The oily residue was stirred with a mixture of ether (75 ml) and water (35 ml). The organic phase was separated and the aqueous layer was extracted with 20 ml of ether. The combined ethereal solution was dried over Na_2SO_4. Ether was removed under reduced pressure and the residue was distilled in vacuo to give the diphosphine (**3a**) as a pale green oil (5.1 g, 83%); b.p. 90–91 °C/0.001 Torr, $[\alpha]_D^{20}$ −25.5° (*c* 6.63, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.06 (dt, $^3J_{PH}$ 14 Hz, $^3J_{HH}$ 5 Hz, 12 H, PCH_2CH_3), 1.38 (s, 6H, $C(CH_3)_2$), 1.42 (m, 8H, PCH_2CH_3), 1.70 (m, 4H, $CHCH_2P$), 3.86 ppm (m, 2H, $CHCH_2$). $^{31}P\{^1H\}$ NMR (5% THF-d_8/THF): δ −27.85 ppm (s).

The diphosphine was converted into the air-stable disulfide by treatment with elemental sulfur in benzene at room temperature and the disulfide was precipitated by addition of hexane. The disulfide was obtained as colorless needles after recrystallization from benzene-hexane (1 : 2); m.p. 136–137 °C, $[\alpha]_D^{20}$ −30.6° (*c* 1.59, $CHCl_3$). Anal. Found: C, 48.39; H, 8.52. $C_{15}H_{32}O_2P_2S_2$ calcd.: C, 48.64; H, 8.71%. ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.22 (m, 12H, PCH_2CH_3), 1.40 (s, 6H, $C(CH_3)_2$), 2.0 (m, 12H, $CHCH_2P(CH_2CH_3)_2$), 4.3 ppm (m, 2H, $CHCH_2P$).

*(−)-(2R,3R)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diisopropylphosphino)butane [(−)-^{i}Prdiop **3b**]*

To a stirred suspension of lithium diisopropylphosphide, which had been prepared from diisopropylphosphine (6.10 g, 160 mmol), in dioxane (150 ml) was added a THF solution (75 ml) of the difluoride (+)-**2d** (3.58 g, 21.5 mmol) at room temperature. After the suspension had been stirred overnight at room temperature, ca. 5 ml of water was cautiously added and the solvents were removed in vacuo. The residue was dissolved in a mixture of ether (80 ml) and water (40 ml). The ethereal layer was separated and the aqueous layer was further extracted with 35 ml of ether. The combined extracts were dried over Na_2SO_4 and distilled in vacuo to give the diphosphine (**3b**) as a pale yellow oil (2.61 g, 34%); b.p. 125–130°C/0.001 Torr, $[\alpha]_D^{20}$ −31.0° (*c* 2.97, C_6H_6).

We attempted to convert the diphosphine into the air-stable disulfide as described above, but failed to isolate a pure sample that gave satisfactory elemental analyses. However the ^{1}H NMR data for the crude disulfide were consistent with the expected structure. ^{1}H NMR ($CDCl_3$): δ 1.3 (m, 24H, $PCH(CH_3)_2$), 1.37 (s, 6H, $C(CH_3)_2$), 2.10 (m, 8H, CH_2PCH), 4.23 ppm (br m, 2H, $CHCH_2P$).

*(−)-(2R,3R)- and (+)-(2S,3S)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(dicyclohexylphosphino)butane [(−)- and (+)-Cydiop **3c**]*

To a stirred suspension of lithium dicyclohexylphosphide (6.4 g, 31 mmol) in dioxane (130 ml) was gradually added the difluoride (+)-**2d** (1.91 g, 11.5 mmol) and the reaction mixture was stirred at 35°C for 42 h. After addition of 1 ml of methanol the solvents were removed in vacuo to give colorless semi-solids. The residue was treated with a mixture of ether (70 ml), saturated aqueous ammonium chloride (15 ml) and water (20 ml). The ethereal layer was separated and the aqueous layer was extracted with 30 ml of ether. The combined ethereal solution was dried over Na_2SO_4. Evaporation of the ether gave colorless semi-solids, which were converted into a CS_2 adduct by mixing with 150 ml of CS_2 in ethanol (150 ml). The solid CS_2 adduct was separated and recrystallized from hot EtOH to give the pure product as reddish brown needles (5.71 g, 74%); m.p. 92–93°C (dec). Anal. Found: C, 58.67; H, 8.32. $C_{33}H_{56}O_2P_2S_4$ calcd.: C, 58.72; H, 8.36%. IR (nujol): 1530, 1260, 1212, 1100, 1040 cm^{-1}.

Pure (−)-Cydiop [(−)-**3c**] was quantitatively isolated as colorless crystals from a suspension of (−)-Cydiop · $2CS_2$ that had been heated in EtOH under reflux, in a slow stream of N_2 until the initially red suspension changed to a colorless solution and the EtOH had been removed in vacuo; m.p. 90–92°C, $[\alpha]_D^{20}$ −24.1° (*c* 0.97, C_6H_6). ^{1}H NMR ($CDCl_3$): δ 1.24 and 1.80 (br, 48H, $CHCH_2P(C_6H_{11})_2$), 1.42 (s, 6H, $C(CH_3)_2$), 3.81 ppm (m, 2H, $OCHCH_2P$). $^{31}P\{^1H\}$ NMR (5% THF-d_8/THF): δ −13.58 ppm (s). IR (nujol): 1260, 1210, 1200, 1100, 1032 cm^{-1}.

The antipode (+)-(2*S*,3*S*)-Cydiop was similarly prepared from (−)-**2d** and $LiPCy_2$. $[\alpha]_D^{22}$ + 24.3° (*c* 1.03, C_6H_6).

[Rh{(−)-Cydiop}(nbd)]ClO_4

A suspension of (−)-Cydiop · $2CS_2$ (650 mg, 0.97 mmol) in ethanol (10 ml) was heated under reflux in a slow stream of nitrogen until a colorless solution was obtained (ca. 10 min). Evaporation of the solvent in vacuo gave the colorless solids of the free diphosphine (−)-Cydiop. The diphosphine was converted into [Rh{(−)-

Cydiop}(nbd)]ClO_4 by a standard method [24]. To a suspension of $[Rh(nbd)Cl]_2$ (225 mg, 0.49 mmol) in acetone (9 ml) was added solid $AgClO_4$ (210 mg, 1 mmol) and the reaction mixture was stirred at room temperature for 1 h. The resulting yellow solution was filtered from the precipitated AgCl and the colorless solids were washed with 2 ml of acetone. To this combined filtrate was added a solution of the (−)-Cydiop, obtained as described above, in warm acetone (10 ml). The mixture immediately turned red. After 1 h at room temperature, the red solution was concentrated to ca. 5 ml in vacuo. Ether (ca. 35 ml) was added slowly and, after the mixture had been allowed to stand overnight at room temperature, orange crystals of [Rh{(−)-Cydiop}(nbd)]ClO_4 were collected. One more crystallization from acetone (6 ml) and ether (30 ml) gave the analytically pure product (680 mg, 86%); m.p. (in a sealed capillary under nitrogen) 183°C (dec.). The analytical and spectral data have been published elsewhere [3a].

Similarly prepared were: [Rh{(−)-Etdiop}(nbd)]ClO_4, red crystals (acetone-ether), m.p. 145°C (dec), yield 69%; [Rh{(−)-^{i}Prdiop}(nbd)]ClO_4, red crystals (acetone-ether), m.p. 124°C (dec), yield 72%.

(2S,3S)-N-(t-Butoxycarbonyl)-4-diphenylphosphinyl-2-diphenylphosphinylmethylpyrrolidine (5)

To an acetone solution (160 ml) of (−)-bppm **4** (15.6 g, 28.2 mmol) was slowly added 10% hydrogen peroxide (28.5 g) under ice-cooling. After the reaction mixture had been stirred at room temperature for a further 1 h, acetone was removed in vacuo. The heterogeneous residue was extracted with chloroform. The extract was washed with water and then with brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuo and recrystallization of the residue from THF-ether gave the pure dioxide (**5**) as colorless crystals (9.8 g, 59%); m.p. 227–230°C, $[\alpha]_D^{20}$ −12.6° (*c* 1.18, C_6H_6). Anal. Found: C, 69.63; H, 6.41; N, 2.27. $C_{34}H_{37}NO_4P_2$ calcd.: C, 69.73; H, 6.37; N, 2.39%. IR (KBr tablet): 1685, 1470, 1175, 1120, 1100, 740, 720, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.39 (s, 9H, ^{t}Bu), 2.3–4.2 (m, 8H, $CH + CH_2$), 7.4–7.8 ppm (m, 20H, *arom.*).

(2S,4S)-4-Diphenylphosphinyl-2-diphenylphosphinylmethylpyrrolidine HCl salt (6)

The diphosphine dioxide **5** (13 g, 22.2 mmol) was dissolved in methanol (300 ml) and then 24% HCl/MeOH (117 ml) was added with stirring at room temperature. After being stirred at room temperature for a further 40 min, the solvent was removed in vacuo. Recrystallization of the viscous residue from EtOH gave the HCl salt **6** as colorless crystals (9.9 g, 86.3%), m.p. 263–266°C. $[\alpha]_D^{23}$ +5.9° (*c* 2.69, CH_3OH). Anal. Found: C, 66.17; H, 5.88; N, 2.66; Cl, 6.80. $C_{29}H_{30}ClNO_2P_2$ calcd.: C, 66.73; H, 5.79; N, 2.68; Cl, 6.79%. IR (KBr tablet): 3050–2500 br, 1585, 1170, 1120, 1100, 745, 725, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.5–3.7 (m, 10H), 7.3–7.8 ppm (m, 20H, *Ph*).

(2S,3S)-4-Dicyclohexylphosphinyl-2-dicyclohexylphosphinylmethylpyrrolidine (7)

The hydrochloric acid salt of the diphosphine dioxide **6** (2.5 g, 4.8 mmol), 5% Rh/Al_2O_3 (2.0 g), and methanol (40 ml) were placed in a 100 ml-autoclave and hydrogenated at 150°C and 130 kg/cm^{-2} for 2 d. The catalyst was filtered off and the pale brown filtrate was evaporated to dryness.The resulting pale brown solid was dissolved in $CHCl_3$, neutralized by shaking with sodium hydroxide solution,

washed with brine, and dried over $MgSO_4$. After removal of the solvent, the resulting crude product was recrystallized from $CHCl_3$-ether to give the bis(dicyclohexylphosphinyl) compound **7** as colorless crystals solvated with 2 moles of $CHCl_3$ (2.6 g, 73%); m.p. 215–215.5 °C, $[\alpha]_D^{20}$ −11.4° (*c* 2.3, C_6H_6). Anal. Found: C, 50.28; H, 7.49; N, 1.91; Cl, 28.25. $C_{29}H_{53}NO_2P_2 \cdot 2CHCl_3$ calcd.: C, 49.75; H, 7.41; N, 1.87; Cl, 28.42%. IR (KBr tablet): 3260 (NH), 1150, 1035, 1015 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (br m), 1.85 (br m), 2.3 (br m), 3.3 ppm (br m). ^{31}P NMR (5% $CDCl_3/CHCl_3$): δ 52.7(s), 49.8 ppm (s). Mass (*m/e*): 509(M^+), 426(M − Cy), 296(M − $POCy_2$), 83(Cy).

(2S,4S)-N-(N′-Phenylcarbamoyl)-4-dicyclohexylphosphino-2-dicyclohexylphosphinomethylpyrrolidine (Ph-Cycapp ***8a****)*

The bis(dicyclohexylphosphinyl) compound **7** (1.0 g), was stirred under reflux for 2 h with triethylamine (2.8 ml) and trichlorosilane (2.0 ml) in 10 ml of acetonitrile. After 25% aq. NaOH had been added cautiously with ice-cooling, the acetonitrile was removed in vacuo. The residue was extracted with toluene and dried over Na_2SO_4. After removal of the solvent the resulting oily residue was dissolved in 10 ml of CH_2Cl_2 and was stirred with 0.44 ml of PhNCO at room temperature for 2 h. Evaporation of the solvent and recrystallization of the pale yellow solid residue from EtOH gave pure **8a** as colorless needles (0.91 g, 78%); m.p. 212–212.5 °C (in a vacuum sealed capillary). $[\alpha]_D^{20}$ −30.4° (*c* 0.68, C_6H_6). Anal. Found: C, 71.51; H, 9.71; N, 4.61. $C_{36}H_{58}N_2OP_2$ calcd.: C, 72.45; H, 9.79; N, 4.69%. IR (nujol): 3300 (NH), 1645 (CO), 1600, 1535 (amide), 1250, 1070, 1020, 750, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 (br m), 1.7 (br m), 2.3 (m), 3.2 (m), 4.0 (m), 6.8–7.5 ppm (m, Ph). ^{31}P NMR (5% $CDCl_3/CHCl_3$): δ 6.9(s), −11.1 ppm (s). Mass (*m/e*): 596 (M^+), 513 (M − Cy), 504 (M − NHPh).

(2S,4S)-N-(N′-Cyclohexylcarbamoyl)-4-dicyclohexylphosphino-2-dicyclohexylphosphinomethylpyrrolidine (Cy-Cycapp ***8b****)*

The *N′*-cyclohexyl substituted analogue (**8b**) was similarly prepared as colorless crystals (EtOH) in 75% yield from **7** and CyNCO; m.p. 192.5–195 °C (in a vacuum sealed capillary). $[\alpha]_D^{21}$ −13.9 (*c* 0.96, C_6H_6). Anal. Found: C, 71.48; H, 10.58; N, 4.58. $C_{36}H_{64}N_2OP_2$ calcd.: C, 71.72; H, 10.69; N, 4.64%. IR (nujol): 3260 (NH), 1615 (CO), 1540 (amide), 1260, 1080, 1020 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 (br m), 1.7 (br m), 2.2 (m), 3.1 (m), 3.8 (m), 4.3 ppm (m). ^{31}P NMR (5% $CDCl_3/CHCl_3$): δ 5.6 (s), −11.6 ppm (s). Mass (*m/e*): 603 ($M^+ + 1$), 602 (M^+), 519 (M − Cy), 504 (M − NHCy).

(2S,4S)-N-(N′-t-Butylcarbamoyl)-4-dicyclohexylphosphino-2-dicyclohexylphosphinomethylpyrrolidine (ᵗBu-Cycapp ***8c****)*

The *N′*-t-butyl substituted analogue **8c** was similarly prepared as colorless crystals (EtOH) in 89% yield from **7** and ᵗBuNCO; m.p. 165–166 °C (in a vacuum sealed capillary). $[\alpha]_D^{21}$ −13.3° (*c* 1.62, C_6H_6). Anal. Found: C, 69.23; H, 10.63; N, 4.70. $C_{34}H_{62}N_2OP_2$ calcd.: C, 70.79; H, 10.83; N, 4.85%. IR (nujol): 3290 (NH), 1625 (CO), 1530 (amide), 1350, 1325, 1210 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 (br m), 1.34 (s, ᵗBu), 1.7 (br m), 2.1 (m), 3.0 (m), 3.8 (m), 4.2 ppm (m). ^{31}P NMR (5% $CDCl_3/CHCl_3$): δ 6.4 (s), −12.3 ppm (s). Mass (*m/e*): 576 (M^+).

N-t-Butylphenylglyoxylamide

Ethyl phenylglyoxylate (6.2 ml, 39 mmol) and t-butylamine (18 ml, 0.17 mol) were dissolved in ethanol (10 ml) and heated at 50 °C for 2 d in a sealed glass ampoule. After being cooled to room temperature the ampoule was opened and the solvent was removed in vacuo. The resulting viscous residue was triturated with hexane and the solid was collected. Recrystallization of the crude product from benzene gave the pure α-keto amide as colorless crystals containing one mole of solvating water (3.7 g, 46%); m.p. 175 °C. Anal. Found: C, 64.47; H, 7.61; N, 6.27. $C_{12}H_{15}O_2N \cdot H_2O$ calcd.: C, 64.55; H, 7.67; N, 6.27%. IR (nujol): 3010 (NH), 1670 (CO), 1560 (amide), 660 cm^{-1} (NH).

N-Phenylphenylglyoxylamide

To an ice-cooled solution of phenylglyoxylic acid (2.0 g, 13 mmol) in chloroform (35 ml) was added aniline (1.2 ml, 13 mmol) and dicyclohexylcarbodiimide (2.7 g, 13 mmol) with stirring and the resulting pale yellow suspension was stirred for a further 2 h at that temperature. After removal of the solvent in vacuo, dicyclohexylurea was precipitated by addition of ethyl acetate and filtered off. The filtrate was washed successively with 10% citric acid, water, 4% sodium bicarbonate, and water, and then dried over Na_2SO_4. After removal of the solvent the crude product was recrystallized from pentane to give the pure α-keto amide as colorless crystals (1.55 g, 52%); m.p. 65–67.5 °C. Anal. Found: C, 74.87; H, 5.00; N, 6.42. $C_{14}H_{11}O_2N$ calcd.: C, 74.65; H, 4.92; N, 6.22%. IR (KBr tablet): 3320 (NH), 1660 (CO), 1600, 1540 (amide), 1065, 750, 690 cm^{-1}.

(S)-N-Benzylmandelamide

(*S*)-Mandelic acid (1.91 g, 12.6 mmol; 98.4%ee) was converted into the acetonide by a published procedure [31]. To an ice-cooled suspension of the acetonide in methanol (10 ml) was added benzylamine (1.62 g, 15.1 mmol) and the reaction mixture was stirred at room temperature. The resulting oily material was separated and crystallized from benzene to give the crude product. Further recrystallization of the crude product from acetone during one week gave the pure product as colorless crystals (1.2 g, 39%); m.p. 137–138 °C, $[\alpha]_D^{26}$ +78.6° (*c* 1.09, $CHCl_3$). Calculated maximum rotation should be +79.9° ($CHCl_3$). Anal. Found: C, 74.88; H, 6.22; N, 5.81. $C_{15}H_{15}NO_2$ calcd.: C, 74.67; H, 6.27; N, 5.81%. IR (KBr tablet): 3500–2600 br, 1620, 1500, 1450, 1090, 1065, 755, 725, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.60 (d, *J* 3 Hz, 1H, O*H*), 4.45 (d, *J* 6 Hz, 2H, CH_2), 5.07 (d, *J* 3 Hz, 1H, C*H*), 6.5 (br, 1H, N*H*), 7.28 (s, 5H, *Ph*), 7.39 ppm (s, 5H, *Ph*).

(S)-N-t-Butylmandelamide

The optically active α-hydroxyamide was similarly prepared in 43.4% yield from the acetonide of (*S*)-mandelic acid (1.0 g, 5.55 mmol) and t-butylamine (1.5 ml, 14.2 mmol); m.p. 140–142 °C. $[\alpha]_D^{18}$ +57.6° (*c* 0.545, MeOH). Calculated maximum rotation should be +58.5° (MeOH). IR (KBr): 3450 (NH), 3030–2520, 1640, 1570, 1380, 1350, 1185, 1080, 1060, 740, 700 cm^{-1}. ^1H NMR (CD_3OD): δ 1.32 (s, 9H, ^{t}*Bu*), 4.9 (m, C*H*), 7.2–7.6 ppm (m, 5H, *Ph*).

*N-(Phenylglyoxyl)-(S)-α-phenylalanine methyl ester (**9a**)*

The *N*-(α-ketoacyl)amino ester was prepared by the method described by I. Ojima et al. [20]. Phenylglyoxyl chloride, prepared from phenylglyoxylic acid (3.26

g, 21.7 mmol) and 1,1-dichloromethyl methyl ether (1.97 ml, 21.7 mmol) by a procedure previously described [32], and the *p*-toluenesulfonic acid salt of (*S*)-α-phenylalanine methyl ester (7.64 g, 21.7 mmol) were dissolved in dichloromethane (30 ml). To this solution was added *N*-methyl morpholine (6.1 ml, 154 mmol) with ice-cooling and the resulting reaction mixture was stirred at room temperature. After the starting materials had been consumed (TLC), the reaction mixture was washed with water, dried over $MgSO_4$, and evaporated to dryness in vacuo. The resulting brown residue was purified on a silica gel column (eluent: hexane/ethyl acetate) to give the pure *N*-(α-ketoacyl)amino ester **9a** as a pale orange oil (4.9 g, 72%). IR (neat): 3325, 1750, 1670, 1595, 1510, 1270, 1240, 1210, 1170, 1050, 740, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.16 (m, 2H, CH_2Ph), 3.70 (s, 3H, CH_3), 4.95 (mt, 1H, CH), 7.0–8.3 ppm (m, 11H, *Ph* + NH).

*N-(Phenylglyoxyl)-(S)-α-alanine methyl ester (**9b**)*

The *N*-(α-ketoacyl)amino ester (**9b**) was similarly prepared in 53% yield from phenylglyoxyl chloride and the *p*-toluenesulfonic acid salt of (*S*)-α-alanine as an orange oil. IR (neat): 3325, 1750, 1670, 1595, 1520, 1270, 1200, 1180, 1050, 750, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.53 (d, *J* 7.5 Hz, 3H, CH_3CH), 3.75 (s, 3H, CH_3), 4.67 (quintet, *J* 7.56 Hz, 1H, CH), 7.2–8.4 ppm (m, 6H, *Ph* + NH).

*N-(Pyruvoyl)-(S)-α-phenylalanine methyl ester (**9c**)*

The *N*-(α-ketoacyl)amino ester (**9c**) was similarly prepared in 60% yield as a pale yellow oil from pyruvoyl chloride [31] and the *p*-toluenesulfonic acid salt of (*S*)-α-phenylalanine methyl ester. IR (neat): 3350, 1750, 1690, 1510, 1370, 1350, 1240, 1165, 1045, 745, 705 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 3.10 (d, *J* 6.0 Hz, 2H, CH_2Ph), 3.65 (s, 3H, CH_3O), 4.78 (m, 1H, CH), 6.9–7.5 ppm (6H, *Ph* + NH).

*N-((S)- and (R,S)-Mandelyl)-(S)-α-phenylalanine methyl ester [(S,S)-**10a** and (RS,S)-**10a**]*

(*S*)-Mandelic acid (200 mg, 1.31 mmol), the *p*-toluenesulfonic acid salt of (*S*)-phenylalanine methyl ester (450 mg, 1.31 mmol), *N*-methylmorpholine (0.15 ml, 1.31 mmol), and 1-oxybenzotriazole (360 mg, 2.62 mmol) were dissolved in THF (10 ml). To this solution was added dicyclohexylcarbodiimide (300 mg, 1.44 mmol) at 0 °C and the reaction mixture was stirred at that temperature for 1 h. The reaction mixture was stirred at room temperature for an additional few hours until the starting material had been consumed (TLC). After removal of the solvent the condensed residue was dissolved in ethyl acetate and washed successively with saturated aq. $NaHCO_3$, 10% citric acid, aq. $NaHCO_3$, and water, and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave the title compound (*S,S*)-**10a** as a colorless solid (300 mg, 73%). IR (nujol): 3480 (OH), 3350 (NH), 1740, 1720, 1660, 1500, 1295, 1055, 760, 735, 715, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.0 (m, 2H, CH_2Ph), 3.63 (s, 3H, CH_3), 3.95 (br, 1H, CH), 4.5–5.0 (m, 2H, OH + CH), 6.5–7.6 ppm (m, 11H, *Ph* + NH).

The diastereomeric mixture (*RS,S*)-**10a** was similarly prepared from (*RS*)-mandelic acid and the *p*-toluenesulfonic acid salt of (*S*)-α-phenylalanine methyl ester.

The following *N*-(α-hydroxyacyl)amino esters were also prepared by a similar procedure.

*N-((S)- and (RS)-Mandelyl)-(S)-α-alanine methyl ester [(S,S)- and (RS,S)-**10b**)]*; ^{1}H NMR ($CDCl_3$): δ 1.35 (d, *J* 7 Hz, 3H, CH_3CH), 3.67 (s, 3H, CH_3O), 4.0 (br, 1H, O*H*), 4.50 (quintet, *J* 7 Hz, 1H, $CHCH_3$), 4.98 (s, 1H, C*H*OH), 7.1 (br, 1H, N*H*), 7.35 ppm (s, 5H, *Ph*).

*N-((S)- and (RS)-lactoyl)-(S)-phenylalanine methyl ester [(S,S)- and (RS,S)-**10c**)]*; IR (neat): 3400 br, 1750, 1660, 1530, 1240 br, 1130, 1050, 750, 705 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.80 (d, *J* 7 Hz, 3H, CH_3CH), 3.1 (m, 2H, CH_2Ph), 3.3 (br, 1H, O*H*), 3.68 (s, CH_3O), 4.15 (m, 1H, $CHCH_2$), 4.6–5.1 (m, 1H, C*H*OH), 6.9–7.5 ppm (m, 6H, N*H* + *Ph*).

Asymmetric hydrogenation

Master solutions (25 m*M*) of the catalyst precursor were prepared in a Schlenk tube by dissolving [Rh(diphosphine)(nbd)]ClO_4 or $[Rh(nbd)_2]ClO_4$ and 1.1 equiv. of diphosphine (for the cationic catalyst) or $[Rh(C_8H_{14})_2Cl]_2$ or $[Rh(C_2H_4)_2Cl]_2$ and 2.2 equiv. of diphosphine (for the neutral catalysts) in an appropriate solvent under nitrogen, and stored in a refrigerator. In a 50 ml Schlenk flask having a three-way stop cock, and a magnetic stirrer bar, were placed a substrate (1.25 mmol) and a solvent (2.25 ml) under nitrogen. The nitrogen atmosphere was replaced with hydrogen by a freeze-thaw method (three times) and the reaction vessel was connected to a hydrogen gas burette, and immersed in a thermostatted bath. After the system had been left to equilibrate with stirring for 10 min, 0.25 ml of the catalyst solution, as prepared above, was injected into the reaction flask through a rubber septum and hydrogen uptake was monitored with a gas burette. After hydrogen uptake had ceased, the conversion was checked by GLC or HPLC. The reaction products were purified by column chromatography (silica gel, eluent: a 1 : 1 mixture of ethyl acetate and hexane) or by distillation (Kugelrohr) and then subjected to analysis. The reaction rates were compared with the time required for 50% of the hydrogen uptake to attain 100% conversion. When the reaction was slow, it was stopped after an appropriate length of time and the conversion was determined.

In the case of the hydrogenation of benzil, the reaction was stopped when the hydrogen uptake amounted to 30 ml (ca. 1.2 mmol) and benzoin was separated on a silica gel column (eluent: benzene/ethyl acetate, 10 : 1).

For the asymmetric hydrogenation of *N*-(α-ketoacyl)amino esters, the reaction was stopped after 20 h. The solvent was removed in vacuo and then the catalyst was removed through a short silica gel column (eluent: ethyl acetate). The conversion and the diastereomeric excess were determined by HPLC (for **10a** and **10c**). In both cases the (*R*,*S*)-isomer eluted first, followed by the (*S*,*S*)-isomer.

*Determination of the diastereomeric excess of **10b***

As the two diastereomers of **10b** could not be separated well on HPLC, the samples were converted into the trifluoroacetates and the diastereomeric excess was determined by ^{19}F NMR. The purified sample of *N*-mandelyl-(*S*)-α-alanine methyl ester **10b** (114 mg, 0.714 mmol), prepared by hydrogenation of **9b** with the (−)-Cydiop-Rh^N complex (Table 3, entry 8), and trifluoroacetic anhydride (0.12 ml, 0.714 mmol) were dissolved in dichloromethane (5 ml) and cooled in an ice-bath. Then *N*-methylmorpholine (0.12 ml, 1.1 mmol) was slowly added, and the reaction mixture was stirred at room temperature until the starting materials had been

consumed (TLC). The resulting solution was washed with brine and dried over Na_2SO_4. After removal of the solvent the residue was purified on a silica gel column to give the trifluoroacetate of **10c** as a colorless solid. ^1H NMR ($CDCl_3$): δ 1.45 (d, J 6 Hz, 3H, CH_3CH), 3.76 (s, 3H, OCH_3), 4.6 (m, 1H, $CHCH_3$), 6.18 (s, 1H, CHPh), 6.6 (br, 1H, NH), 7.43 ppm (s, 5H, *Ph*). ^{31}F NMR data for the mixture of the trifluoroacetate (50 mg) and Eu(fod)$_3$ (40 mg) in $CDCl_3$ (4 ml) showed two well-separated singlet signals attributable to the CF_3 groups of the two diastereomers [(R,S), a lower field signal, and (S,S), an upper field one] in a ratio of 17 : 83. Thus the diastereomeric excess was estimated to be 66%.

Acknowledgment

This work was partly supported by a Grant-in-Aid from the Ministry of Education, Japan (No. 59550595).

References

1 K.E. Koenig, in J.D. Morrison (Ed.), Asymmetric Synthesis, Academic Press, Orlando, 1985, Vol. 5, p. 71 and references therein.
2 (a) K. Tani, K. Suwa, E. Tanigawa, T. Yoshida, T. Okano, and Sei Otsuka, Chem. Lett., (1982) 261; (b) K. Tani, E. Tanigawa, Y. Tatsuno, and Sei Otsuka, J. Organomet. Chem., 279 (1985) 87.
3 (a) K. Tani, K. Suwa, T. Yamagata, and Sei Otsuka, Chem. Lett., (1982) 265; (b) K. Tani, K. Suwa, and Sei Otsuka, ACS Symposium Series, 185 (1982) 283; (c) K. Tani, T. Ise, Y. Tatsuno, and T. Saito, J. Chem. Soc., Chem. Commun., (1984) 1641; (d) K. Tani, E. Tanigawa, Y. Tatsuno, and Sei Otsuka, Chem. Lett., (1986) 737.
4 H.B. Kagan and T.-P. Dang, J. Am. Chem. Soc., 94 (1972) 6429.
5 I. Ojima and N. Yoda, Tetrahedron Lett., 21 (1980) 1051.
6 (a) R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, and S. Akutagawa, J. Am. Chem. Soc., 109 (1987) 5856; (b) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, and R. Noyori, J. Am. Chem. Soc., 110 (1988) 629.
7 (a) H. Takahashi, M. Hattori, M. Chiba, T. Morimoto, and K. Achiwa, Tetrahedron Lett., 27 (1986) 4477; (b) T. Morimoto, H. Takahashi, K. Fujii, M. Chiba, and K. Achiwa, Chem. Lett., (1986) 2061; (c) H. Takahashi, T. Morimoto, and K. Achiwa, Chem. Lett., (1987) 855; (d) H. Takahashi and H. Achiwa, Chem. Lett., (1987) 1921.
8 K. Issleib and D.-W. Müller, Chem. Ber., 92 (1959) 3175.
9 (a) K. Achiwa, J. Am. Chem. Soc., 98 (1976) 8265; (b) G.L. Baker, S.J. Fritschel, J.R. Stille, and J.K. Stille, J. Org. Chem., 46 (1981) 2954.
10 K. Yamamoto and S.-U. Rehman, Chem. Lett., (1984) 1603.
11 E.L. Eliel, J. Am. Chem. Soc., 71 (1949) 3970.
12 T. Purdie and J.C. Irvine, J. Chem. Soc., (1899) 483. G.W. Clough, J. Chem. Soc., 113 (1918) 531.
13 W.A. Bonner and C.D. Hurd, J. Am. Chem. Soc., 73 (1951) 4290.
14 R.H.F. Manske and T.B. Johnson, J. Am. Chem. Soc., 51 (1929) 1906.
15 E.T. Stiller, S.A. Harris, J. Finkelstein, J.C. Kresztesy, and K. Folkers, J. Am. Chem. Soc., 62 (1940) 1785.
16 R.U. Lemieux and J. Giguere, Can. J. Chem., 29 (1951) 678.
17 I.V. Hopper and F.J. Wilson, J. Chem. Soc., (1928) 2483.
18 S. Ose and Y. Yoshimura, Yakugaku Zasshi, 77 (1957) 730.
19 (a) K. Achiwa, T. Kogure, and I. Ojima, Tetrahedron Lett., (1977) 4431; (b) K. Achiwa, T. Kogure, and I. Ojima, Chem. Lett., (1978) 297; (c) I. Ojima and T. Kogure, J. Organomet. Chem., 198 (1980) 239.
20 I. Ojima, T. Tanaka, and T. Kogure, Chem. Lett., (1981) 823.
21 E.W. Abel, M.A. Bennett, and G. Wilkinson, J. Chem. Soc., (1959) 3138.
22 R. Cramer, Inorg. Chem., 1 (1962) 722.
23 A. van der Ent and A.L. Onderdelinden, Inorg. Synth., 14 (1973) 92.

24 M.D. Fryzuk and B. Bosnich, J. Am. Chem. Soc., 99 (1977) 6262.
25 L.J. Rubin, H.A. Lardy, and H.O.L. Fischer, J. Am. Chem. Soc., 74 (1952) 425.
26 K. Issleib and A. Tzschach, Chem. Ber., 92 (1959) 1118.
27 K. Issleib and F. Krech, J. Organomet. Chem., 13 (1968) 283.
28 K. Issleib and A. Tzschach, Chem. Ber., 92 (1959) 1118.
29 (a) C. Broquet and M.J. Bedin, C.R. Acad. Ser. (C), 262 (1966) 1891. (b) P.F. Kruse, N. Geurkink, and K.L. Grist, J. Am. Chem. Soc., 76 (1954) 5796.
30 (a) R.L. Letsinger and R. Collat, J. Am. Chem. Soc., 74 (1952) 621. (b) A.K. Samaddar, S.K. Konar, and D. Nasipuri, J. Chem. Soc., Perkin Trans. I, (1983) 1449.
31 L.F. Audrieth and M. Sveda, Org. Synth. Col. Vol. III, (1955) 536.
32 (a) H.C.J. Ottenheijm and M.W. Tijhuis, Org. Synth., 61 (1983) 1. (b) H.C.J. Ottenheijm and J.H.M. de Man, Synthesis, (1975) 163.