Substrate-induced Kinetic Resolution of Racemic Biphosphines *in situ* for Homogeneous Catalysis

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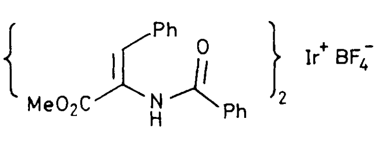
Reaction between the resolved iridium enamide complex (+)-(**3**) or (−)-(**3**) and chiral biphosphines is highly enantioselective and permits their *in situ* resolution for asymmetric catalysis; the structure of (+)-(**3**) has been confirmed by *X*-ray crystallography.

Iridium dehydroamino ester complexes have proved useful in mechanistic studies of asymmetric hydrogenation.[1] The *X*-ray crystal structure of precursor (**1**) revealed that individual cations are homochiral, although the unit cell contains both enantiomeric forms. This observation afforded the possibility for optical resolution which has now been realised.

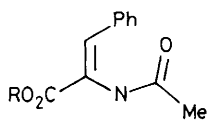
The (*R*)-menthyl[†] ester (−)-(**2**) was prepared by a modification of the literature procedure,[2] $[\alpha]_D^{20} = -45.3°$ (*c* 1.0, $CHCl_3$). It reacted readily with $[Ir(C_2H_4)_2Cl]_2$[3] under previously described conditions[1] to give a mixture of diastereoisomers (+)-(**3**) and (−)-(**4**) in *ca.* 1:2 ratio, based on their vinylic C–H signals at δ 5.89 and 5.61 respectively. They interconvert very slowly at 20 °C in $CDCl_3$ or $(CD_3)_2CO$. When the mixture was dissolved in acetone and hexane added to the point of turbidity, well formed orange crystals were deposited over the course of a few days. Redissolution of a portion demonstrated that pure (+)-(**3**) (>100:1 by ^1H n.m.r.), $[\alpha]_D^{20} = +344.5°$ (*c* 1.0, $CHCl_3$) had crystallised out, and the absolute configuration was defined by *X*-ray analysis[‡] (Figure 1) which indicates that C_α-*re* of the alkene is bound to iridium. There are two independent disymmetric molecules in the unit cell which differ in the torsion angles about CH–Ph and O–menthyl bonds. The basic structural features resemble those of methyl ester (**1**). Co-ordination of the double-bond is skewed, such that the enamide carbon assumes near-coplanarity with the adjacent N–C=O moiety, as observed in related cases.[1,4] An analogous sequence was effected with the corresponding (*S*)-menthyl ester (+)-(**2**) leading to (−)-(**3**), which is the enantiomer of complex (+)-(**3**), in analytically pure state, $[\alpha]_D^{20} = -350.3°$ (*c* 1.0, $CHCl_3$).

[†] (*R*)- and (*S*)-menthyl are the radicals formed by loss of the 1-hydroxy group of (1*R*,2*S*,5*R*)-(−)- and (1*S*,2*R*,5*S*)-(+)-2-isopropyl-5-methylcyclohexan-1-ol, respectively.

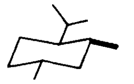
[‡] *Crystal data* for (+)-(**3**). $C_{42}H_{56}BF_4N_2O_6$, $M = 939.9$, triclinic, space group $P1$, $a = 13.288(3)$, $b = 13.372(5)$, $c = 15.982(4)$ Å, $\alpha = 78.38(2)$, $\beta = 77.80(2)$, $\gamma = 61.13(2)°$, $U = 2.414(1)$ Å^3, $Z = 2$, $\mu(\text{Mo-}K_\alpha) = 28.1$ cm^{-1}, $R = 0.044$ ($R_w = 0.047$) for 6931 observed reflections [$I/\sigma(I) > 3.0$]; anisotropic temperature factors for Ir, N, O, F. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1986.



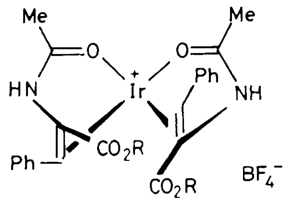
(1)



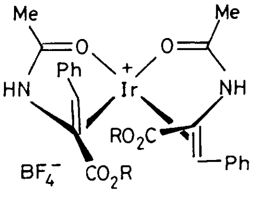
(−)-(2) R =



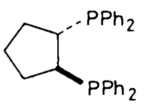
(+)-(2) R =



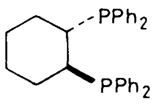
(−)-(3) R = (S)-Menthyl
(−)-(4) R = (R)-Menthyl



(+)-(3) R = (R)-Menthyl
(+)-(4) R = (S)-Menthyl



rac-(5)



rac-(6)

Table 1. Reaction products from chiral biphosphines and (+)-(3) or its enantiomer (−)-(3).[a]

Initial iridium complex	Biphosphine	δ/p.p.m.; J/Hz; (θ/°C); solvent	Isomer
(+)-(3)	(S,S)-Chiraphos	45.7, 26.6; 26; −70; CH_2Cl_2	Stable, C_α *re*
(−)-(3)	,, ,,	54.7; 30.0; br; 0; CH_2Cl_2	Metastable, C_α *si*
(−)-(3)	,, ,,	46.4, 27.1; 26; 25; CH_2Cl_2	Stable, C_α *re*
(+)-(3)	(R,R)-Dipamp	37.1, 23.6; small; 0; CH_2Cl_2	Metastable, C_α *re*
(+)-(3)	,, ,,	45.6, 24.8; small; 0; CH_2Cl_2	Stable, C_α *si*
(+)-(3)	(R,R)-Diop	−2.5, −17.0; 20; 10; MeOH	Stable, C_α *re*
(−)-(3)	,, ,,	−1.4, −22.3; 22; 5; MeOH	Metastable, C_α *si*
(−)-(3)	,, ,,	−2.6, −16.5; 20; 10; MeOH	Stable, C_α *re*

[a] (S,S)-Chiraphos and (R,R)-diop give the (R)-amino acid on Rh-catalysed asymmetric hydrogenation of dehydroamino acids; (R,R)-dipamp gives the (S)-amino acid.§

(S,S)-Chiraphos§ reacts rapidly with iridium complex (+)-(3) in CH_2Cl_2 at −70 °C with displacement of one mole of dehydroamino ester. The reaction of (S,S)-chiraphos with its

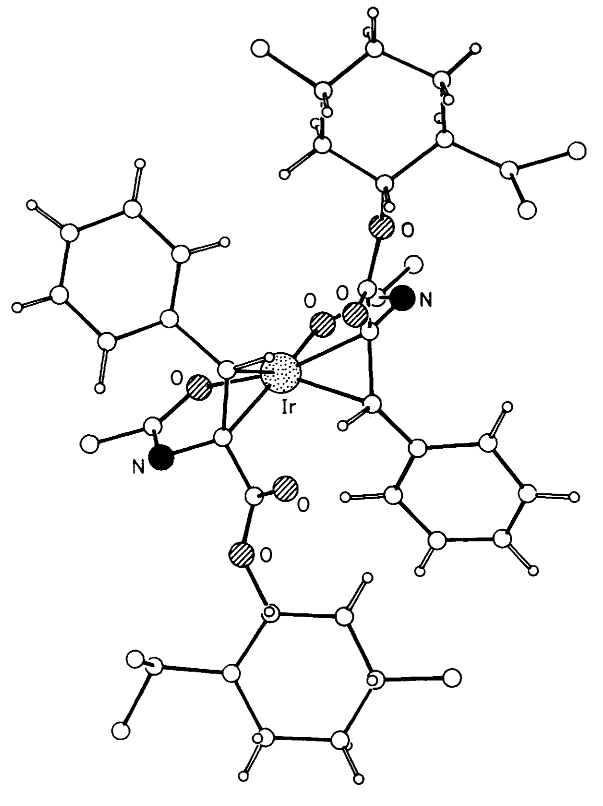
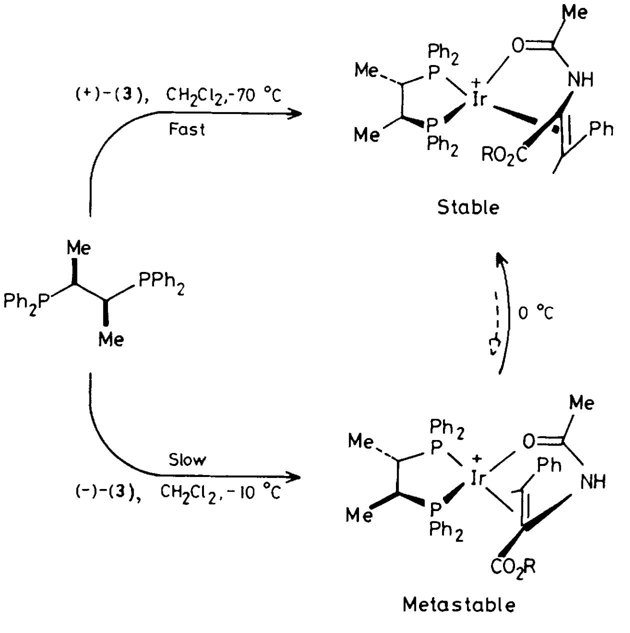


Figure 1. View of one of the cations of (+)-(3). Principal bond-lengths and angles: Ir–O(1) 2.065(11), 2.084(13); Ir–O(2) 1.991(12), 1.974(11); Ir–C_α(1) 2.109(13), 2.122(17); Ir–C_α(2) 2.119(16), 2.111(13); Ir–C_β(1) 2.129(11), 2.121(14); Ir–C_β(2) 2.123(12), 2.121(17).



Scheme 1

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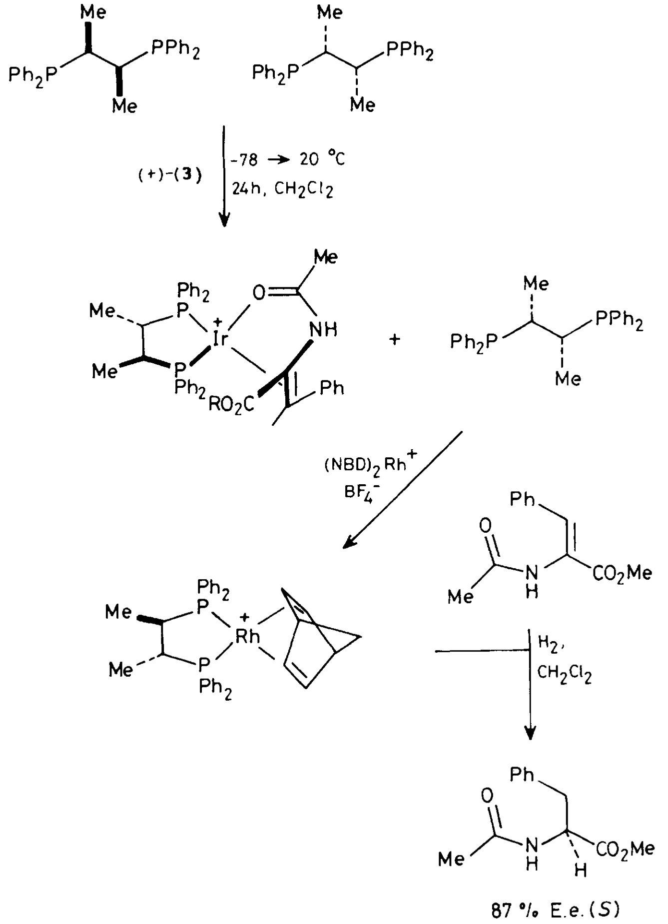
§ Abbreviations used: chiraphos = (S,S)-2,3-bis(diphenylphosphino)butane (see ref. 5); diop = 2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane; dipamp = (R,R)-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane.



Scheme 2

enantiomer (−)-(**3**) is orders of magnitude slower and the sample requires warming to −10 °C to observe significant changes in the ^{31}P n.m.r. spectrum. The first-formed product is unstable and isomerises cleanly at 0 °C. These transformations are in full accord with the pathway of Scheme 1, and the reactivity of other chiral biphosphines in similar experiments is outlined in Table 1.

The significance of these results derives from the fact that the absolute configuration of the iridium enamide complex is defined in each case. Since rhodium and iridium complexes are isostructural,[1] it implies that the metastable diastereoisomer always carries the flux of catalysis in asymmetric hydrogenation, since C_α-*re* co-ordination leads to the (*S*)-product and C_α-*si* co-ordination leads to the (*R*)-product. This has been established for the first two ligands but the generality is now extended to the 7-ring chelate complexes formed by diop.§[6,7]

The observations suggested a simple procedure for phosphine resolution. Thus *rac*-chiraphos [prepared as for the (*S*,*S*)-enantiomer[5]] (2 equiv.) was mixed with complex (+)-(**3**) (1.2 equiv.) in CH_2Cl_2 at −70 °C, held at −55 °C for 30 min and then at −20 °C for 24 h. To the resulting scarlet solution was added bisbicyclo[2.2.1]heptadienerhodium tetrafluoroborate $[(NBD)_2Rh^+BF_4^-]$ (0.8 equiv.) at −20 °C and then methyl (*Z*)-α-acetamidocinnamate (50—100 equiv.). The solution was stirred in a H_2 atmosphere under ambient conditions until reaction was complete. The product of hydrogenation was isolated and its enantiomeric purity determined by n.m.r. {tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), CO_2*Me*} and shown to be 87% (*S*) (Scheme 2). An experiment under identical conditions employing (−)-(**3**) gave the (*R*)-product in 89.5% enantiomeric excess (e.e). When authentic (*S*,*S*)-chiraphos was employed as the catalyst in CH_2Cl_2, the product was of (*R*)-configuration, in 90% e.e. In separate experiments it was demonstrated that the iridium enamide complex did not turn over to hydrogenated product on the time-scale of catalysis.

These results indicate that the phosphine remaining after the kinetic resolution procedure is essentially optically pure. Further the readily available[8] racemic biphosphine (**5**), reacting under these conditions gave the (*S*)-hydrogenation product in 90% e.e. starting with complex (+)-(**3**), and the (*R*)-hydrogenation product in 91% e.e. starting with (−)-(**3**). To illustrate the procedure with a previously unresolved biphosphine, *rac-trans*-1,2-bis(diphenylphosphino)cyclohexane,[9] (**6**), m.p. 149—152 °C was synthesised from epoxycyclohexane.[10] This reacted much less rapidly with the (*R*)-menthyl ester complex (+)-(**3**) and 1.6 equiv. of the latter were required for optimum results. When the resolution procedure was conducted over 48 h at −20 °C and hydrogenation as described above, the optical yields were 81% (*S*) starting from (+)-(**3**) and 79% (*R*) starting from (−)-(**3**).

This method has potential in the evaluation of chiral ligands where the racemate is readily synthesised, but resolution difficult,[11] and although the examples quoted related to asymmetric hydrogen it has wider application.

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