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STRUCTURAL REQUIREMENTS IN CHIRAL DIPHOSPHINE-RHODIUM COMPLEXES

III *. SMALL SCALE METHOD FOR FRESH PREPARATION OF CATIONIC DIOP-RHODIUM COMPLEXES AND COMPARISON WITH NEUTRAL DIOP-RHODIUM COMPLEXES

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Summary

(—)-2,3-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) was used in cationic rhodium(I)-diphosphine complexes, freshly prepared on a milligram scale, to catalyze the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid. These cationic complexes were found not to be air stable over a period of time, but when utilized after storage under argon reproducible kinetic results were noted, and the optical purity of the reduction product was found to be independent of the age of the cationic complex. The cationic rhodium(I)-DIOP complex was found to be a more reactive complex than the corresponding neutral chlororhodium(I)-DIOP complex when used in asymmetric hydrogenations, but both gave the same optical yield.

Cationic complexes of the type $[Rh(diene)\{PR^1R^2R^3\}_2]^+ \cdot X^-$ (I) (where diene = 1,5-cyclooctodiene or norbornadiene, $PR^1R^2R^3$ = triphenylphosphine, and X^- is a non-nucleophilic anion such as BF_4^-, ClO_4^-, PF_6^-, etc.) were prepared by Schrock and Osborn [2,3] and shown to be effective homogeneous procatalysts for the hydrogenation of a variety of C—C unsaturated substrates. When more basic phosphines (such as PPh_2Me, $PPhMe_2$, PMe_3) were used instead of triphenylphosphine, ketones were also readily reduced [4].

Cationic complexes I containing chiral phosphines (chiral P-atom phosphines [5—9], chiral C-atom diphosphines [10,11], or chiral P-atom diphosphines [12]) were shown to be efficient for the asymmetric hydrogenation of carbonyl groups [6—9,11], imines [11], and especially effective for C—C double bonds [5,10—12].

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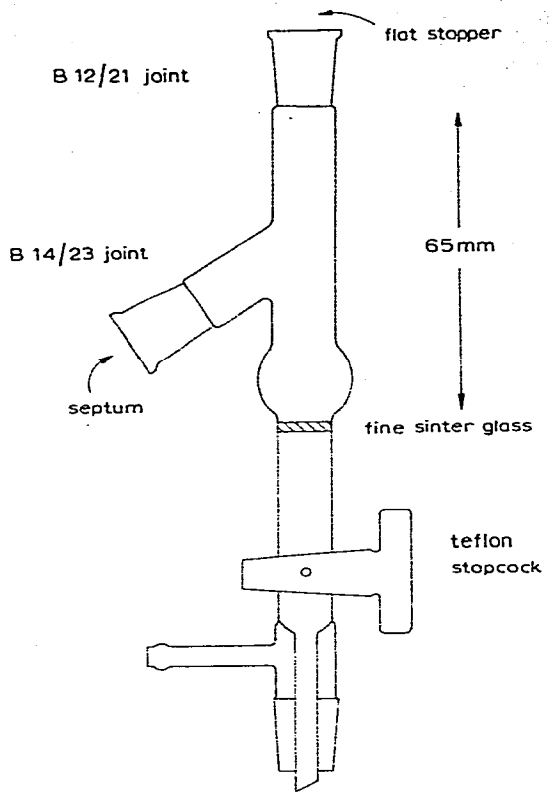


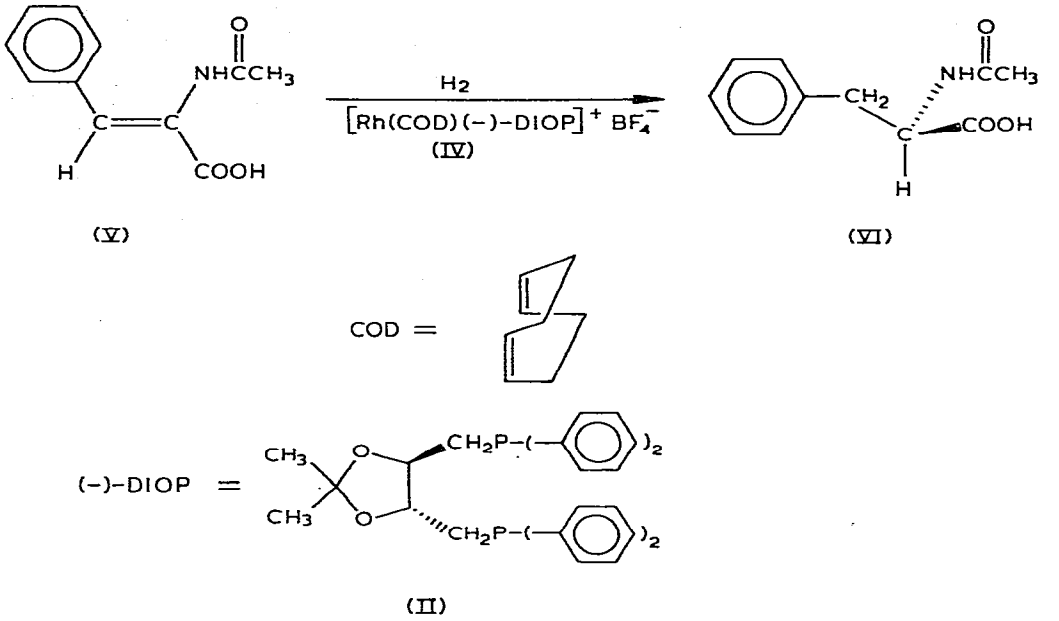
Fig. 1

Kagan's (+)- or (—)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) (II) [13] has been used to prepare both neutral [10,13] and cationic [10,11] rhodium-diphosphine complexes, which give high optical yields (80% ee) when used in asymmetric hydrogenation reactions [10,11,13]. While cationic complexes I (where $PR^1R^2R^3$ = *o*-anisylcyclohexylmethylphosphine (III)) are described as air-stable complexes [5d—f], the corresponding complexes having $2PR^1R^2R^3$ = (—)-DIOP were found to change color from orange-yellow to dirty yellow upon prolonged exposure to air, and the aged complex gave a much slower rate of reduction than the freshly-made complex [14]. In addition, Scorrano and coworkers [6,11] reported that the rates of hydrogenation with cationic complexes I (where $PR^1R^2R^3$ = chiral P-atom phosphine [6] or (—)-DIOP [11]) were irreproducible and that the optical yields of the product were strongly dependent upon the age of the complex [11].

In investigating the structural requirements in chiral rhodium-diphosphine complexes used in asymmetric hydrogenation reactions, it is desirable to have the optical yield of the reaction products reflect the structure of the components of such complexes, and to be independent of the age of the complex.

We have developed a glass micro-scale apparatus (see Fig. 1) for the preparation of [rhodium(1,5-cyclooctadiene)(—)-DIOP]$^+ \cdot BF_4^-$ (IV). This cationic complex IV was used in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid (V) [1b] to give *N*-acetylphenylalanine (VI) (see Scheme 1).

SCHEME 1



Results and discussion

As shown by Table 1, the optical yield (82% ee) of *N*-acetylphenylalanine catalyzed by the cationic complex IV is independent of the age of the complex when stored under argon. In addition, the kinetics of hydrogen uptake (for five reactions) were reasonably reproducible (7.7 ± 0.5 ml H_2 min^{-1}), when measured between the fourth and fifth minutes of the reaction. The initial rates of hydrogenation were not reproducible, and this is interpreted as aris-

TABLE 1

ASYMMETRIC HYDROGENATION OF (*Z*)-α-ACETAMIDOCINNAMIC ACID WITH [Rh(COD)(—)-DIOP]$^+ \cdot BF_4^-$ AND ClRh(—)-DIOP

	[Rh(COD)(—)-DIOP]$^+ \cdot BF_4^-$ [a]	ClRh(—)-DIOP [a]
Optical yield [b] (%) (fresh complex) [c]	81.3 [e,f]	81.9 [e,g]
Optical yield [b] (%) (aged complex) [d]	82.1 [e]	
Rate (ml H_2 min^{-1}) [h]	7.7	6.1
Conversion [i] (%)	>97	>97
Absolute configuration [e]	R	R

[a] Rh = 3.0 mmol l^{-1}; DIOP: Rh = 1.1; substrate: Rh = 100; 10 ml absolute ethanol; 1 atmos. H_2; 25°C; COD = 1,5-cyclooctadiene. [b] % enantiomeric excess; based upon at least two experiments, two determinations per experiment; precision ±1.5%. [c] Rh complex used immediately. [d] Rh complex used after 48 h storage under argon. [e] Based upon *N*-acetyl-(*S*)-phenylalanine, $[\alpha]_D^{25}$ = +46.5° (*c* 1.0, 95% EtOH), lit. +46.0° [10]. [f] Lit. 84% ee [11], based upon $[\alpha]_D^{25}$ = —51.8° (*c* 1, EtOH) for *N*-acetyl-(*R*)-phenylalanine [15]. [g] Lit. 81% ee [10], when performed in ethanol/benzene 2 : 1. [h] Measured between 4th and 5th minutes of hydrogenation; based upon five experiments; precision ±0.5 ml min^{-1}. [i] Determined by NMR and theoretical uptake of H_2.

ing from slight over- or under-pressurization in the hydrogenation apparatus due to adjustments in the heights of the reservoirs attached to the gas burettes made at the reaction start. Judging from our results, these pressure fluctuations appear to be equalized after approximately three minutes, and the kinetics for the rest of the reaction then show a decrease in hydrogen uptake in a reproducible manner.

The value of the specific rotation for the *N*-acetyl-(*S*)-phenylalanine standard (Sigma Chemicals Inc.) was found to be $[\alpha]_D^{25} = +46.5 \pm 0.5°$ (*c* 1, 95% EtOH). This value (rather than $[\alpha]_D^{25} = -51.8°$ (*c* 1, EtOH) for the (*R*)-isomer [15]) is consistent with the values determined by Kagan and coworkers [10], Knowles and coworkers [5f,12], and Clement and Porter [16]. Since these values arise from different experimental methods, the value of +46.5 ± 0.5° seems to be a reasonable value, while the —51.8° value appears to be in error *. Thus, the calculation of optical purity (% enantiomeric excess) based upon $[\alpha]_D = -43.6°$ (*c* 0.032) given by Scorrano and coworkers [11] for the hydrogenation of (*Z*)-α-acetamidocinnamic acid in ethanol using the cationic complex I (where diene = norbornadiene, $2PR^1R^2R^3$ = (—)-DIOP, and $X^- = ClO_4^-$) should be recalculated to be 94% ee (based upon the optically pure value of 46.5°, not 51.8°). This new value of 94% ee appears to be high, and perhaps is due to the experimental conditions used to obtain $[\alpha]_D$ of the reaction product. Using a concentration of 0.032 g l^{-1} would give an observed value of $\alpha_D = -0.015°$. This low observed rotation could involve a high instrument error, and can account for the difference in optical purity of our results versus those of Scorrano et al. [11].

Use by Scorrano et al. [11] of norbornadiene versus 1,5-cyclooctadiene should not affect the results, since upon formation of the hydrido complex, both dienes should undergo reduction to the saturated hydrocarbons. Use by Scorrano et al. of ClO_4^- anion versus our use of BF_4^- anion also does not appear to account for the discrepancy in results, since Knowles et al. [5b] have shown that air-stable cationic complexes I containing the chiral phosphine III and two different anions, $(C_6H_5)_4B^-$ and BF_4^-, both gave the same optical yields of the reduction products.

As seen in the table, the cationic complex IV gave the same optical yield of *N*-acetylphenylalanine as that obtained from the in situ neutral ClRh(—)-DIOP complex (VII) studied under the same conditions. However, the kinetic results show that the cationic complex appears to be more reactive than the neutral complex VII. This is even more apparent when it is considered that under the conditions used to prepare the cationic complex IV, some small amounts of rhodium may be lost when the cationic complex IV is filtered off from the mother liquor.

In conclusion, the dependence of optical yield upon age of the cationic complex, and the non-reproducibility in kinetics (at least in the experiments with (*Z*)-α-acetamidocinnamic acid) reported by Scorrano and coworkers [11] may be interpreted as arising from partial oxidation of the cationic rhodium-DIOP

* Moreover, Kagan et al. [10] reacted CH_2N_2 with *N*-acetyl-(*S*)-phenylalanine, $[\alpha]_D^{25} = +46.0°$ (*c* 1, EtOH), and (by VPC analysis using a chiral phase) showed the ester to be optically pure.

complex. Use of the micro preparation apparatus and storage under argon appears to alleviate these problems.

Experimental

The hydrogenations were carried out in a conventional glass atmospheric pressure apparatus with gas burettes modified according to suggestions by Prof. J. Manassen, Rehovot. The hydrogenation vessel (containing a rubber septum) was placed in a thermostatted bath at 25.0 ± 0.5°C. Absolute methanol was purified by distillation, and absolute ethanol purified according to Vogel [17]. All solvents were stored under argon, and re-deoxygenated via argon before use. Chloro(1,5-cyclooctadiene)rhodium(I) dimer and (—)-DIOP were purchased from Strem Chemicals Inc. and used as received. (*Z*)-α-acetamidocinnamic acid (m.p. 194—195°C) was purchased from FLUKA and used as received. Sodium tetrafluoroborate was purchased from BDH Ltd. and used as received. *N*-acetyl-(*S*)-phenylalanine was purchased from Sigma Chemicals Inc. and used as received.

Preparation of rhodium(1,5-cyclooctadiene)(—)-DIOP tetrafluoroborate and hydrogenation reaction

Rhodium(1,5-cyclooctadiene)(—)-DIOP tetrafluoroborate was prepared in the micro-scale apparatus according to a modified procedure of Schrock and Osborn [3]. In the inverted micro preparation vessel (glass filter frit upwards) under argon atmosphere, the orange neutral chlororhodium(—)-DIOP complex was prepared in situ from 7.4 mg (1.5×10^{-2} mmol) chloro(1,5-cyclooctadiene)rhodium(I) dimer and 16.5 mg (3.3×10^{-2} mmol) (—)-DIOP in 0.75 ml absolute methanol with stirring using a Conrad-type magnetic stirring button for 10 mm cuvettes (Bel—Art). Upon addition of 325 mg (3 mmol) sodium tetrafluoroborate in 1.6 ml water, the cationic complex precipitated as a yellow-orange cheesy solid. The mother liquor was slowly filtered off under argon pressure (after inverting the vessel, glass filter frit downwards), and the solid remaining inside was washed with water. After one hour of drying under argon, the solid was dissolved in 1 ml of absolute ethanol, and the orange-red solution transferred (via the sinter glass frit) under argon pressure to an empty 25 ml hydrogenation reaction vessel connected to the rest of the atmospheric hydrogenation apparatus (preflushed with argon). The micro preparation vessel was washed twice with 0.5 ml absolute ethanol each time, and the washings added to the hydrogenation reaction vessel. Under argon flow, the micro preparation vessel was disconnected from the hydrogenation vessel and a rubber septum put in its place. Prehydrogenation for ten minutes (the color of the solution changed to golden-yellow) was followed by injection through the septum via syringe of 615 mg (3 mmol) (*Z*)-α-acetamidocinnamic acid in 8 ml absolute ethanol. The color changed to red-orange and with it a rapid uptake of hydrogen gas occurred without an induction period. A color change back to golden-yellow occurred together with termination of hydrogen consumption.

In situ preparation of chlororhodium(—)-DIOP complex and hydrogenation reaction

In a 10 ml round bottom flask under argon atmosphere, the orange neutral chlororhodium(—)-DIOP complex was prepared in situ from 7.4 mg (1.5×10^{-2} mmol) chloro(1,5-cyclooctadiene)rhodium(I) dimer and 16.5 mg (3.3×10^{-2} mmol) (—)-DIOP in 4 ml absolute ethanol with magnetic stirring. The solution was transferred via syringe and injected through a septum into an empty 25 ml hydrogenation vessel connected to the rest of the atmospheric hydrogenation apparatus (preflushed with argon). Prehydrogenation for ten minutes was followed by injection through the septum via syringe of 615 mg (3 mmol) (*Z*)-α-acetamidocinnamic acid in 6 ml absolute ethanol, and rapid uptake of hydrogen gas occurred without an induction period.

Work-up of the hydrogenation product

The solutions were evaporated to dryness and a quantity removed for NMR analysis in a Varian XL-100 to determine the % conversion. The remainder of the solid residue was taken up in the minimum quantity of methanol and chromatographed on a silica-gel column (prepared in petroleum ether 40—60°C) eluted with an increasing gradient of ethyl acetate in petroleum ether 40—60° C. The rotation of the pure *N*-acetylphenylalanine fraction was determined in a Perkin—Elmer MC-141 polarimeter, at the sodium-D line, 25° C, and at a concentration of 10^{-2} g ml^{-1} in 95% ethanol.

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