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NOVEL KINETIC RESOLUTION OF 2-DIMETHYLAMINOPROPIOPHENONE DURING ASYMMETRIC CATALYTIC HYDROSILYLATION

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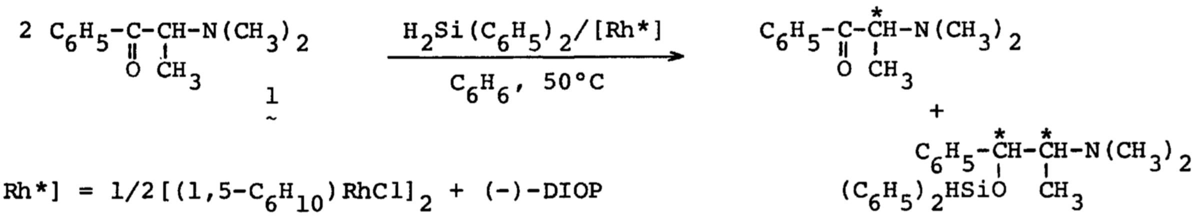
Kinetic resolution was observed when (±)-2-dimethylaminopropiophenone was allowed to react with one-half equivalent of diphenylsilane in the presence of rhodium(I)-(-)-DIOP as catalyst. The recovered amino ketone was found to be (R)-(+)-enantiomer of 23% optical purity, while asymmetrically hydrosilylated products, after hydrolysis, were (1S,2S)-(+)-pseudomethylephedrine and (1R,2S)-(-)-methylephedrine in 27% and 20% ee, respectively.

During a course of study on a chiral rhodium complex-catalyzed hydrosilylation of alkyl phenyl ketones[1], certain ω-dimethylaminoacylophenones were also examined, since anticipated attractive interactions between the amino group and the catalyst likely contribute to the asymmetric potential of the reaction.[2]

We now report a novel kinetic resolution of (±)-2-dimethylaminopropiophenone(1) during the asymmetric catalytic hydrosilylation. In this case kinetic resolution and asymmetric synthesis took place simultaneously.[3]



$$2\ C_6H_5\text{-}\underset{\substack{\parallel\\ O}}{C}\text{-}\underset{\substack{|\\ CH_3}}{CH}\text{-}N(CH_3)_2\ \ \underset{\mathbf{1}}{} \xrightarrow[C_6H_6,\ 50°C]{H_2Si(C_6H_5)_2/[Rh^*]} C_6H_5\text{-}\underset{\substack{\parallel\\ O}}{C}\text{-}\underset{\substack{|\\ CH_3}}{\overset{*}{C}H}\text{-}N(CH_3)_2 + C_6H_5\text{-}\underset{\substack{|\\ (C_6H_5)_2HSiO}}{\overset{*}{C}H}\text{-}\underset{\substack{|\\ CH_3}}{\overset{*}{C}H}\text{-}N(CH_3)_2$$

$[Rh^*] = 1/2[(1,5\text{-}C_6H_{10})RhCl]_2 + (-)\text{-DIOP}$

A mixture of (±)-1 (2.66 g, 15.0 mmol), diphenylsilane (1.38 g, 7.50 mmol), μ-dichlorobis(1,5-hexadiene)dirhodium(I) (16.5 mg, 3.75×10^{-2} mmol; 0.5 mol%), and (-)-DIOP[4] (37.4 mg, 7.50×10^{-2} mmol) dissolved in dry benzene (3 ml) was heated at 50°C for 2 days in a degassed sealed glass tube. The reaction mixture was directly distilled *in vacuo* to recover unreacted 1, bp 83°C/2 Torr, 1.59 g (9.09 mmol, 60% recovery); α^{20}_D +0.749° (neat, 0.05 dm), $\tilde{d}^{20}_4 = 1.01$; NMR (CCl_4, TMS) δ 1.15 (d, J = 6.6 Hz, CMe), 2.20 (s, NMe), 3.90 (q, J = 6.6 Hz, CH), and 7.2-8.0 ppm (m, Ph); IR (film) 1680 cm^{-1} ($\nu_{C=O}$).

Determination of enantiomeric purity of the partially active amino ketone was carried out by using a chiral NMR shift reagent: use of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) (30 mol%) caused effective enantiomeric shift differences to the dimethylamino protons, and samples, α^{20}_D +0.435° and +0.523° (neat, 0.05 dm), were found to be 13.1 and 15.6% ee, respectively. On the basis of calculated maximum rotation, $[\alpha]^{20}_{D\,max}$ +66° (neat), (R)-(+)-1 obtained here was found to be 23% optically pure.[5] This amino ketone, however, racemized slowly at ambient temperature.[6]

The distillation residue was hydrolyzed by potassium hydroxide in aqueous methanol, and the products were extracted with ether. The extract was washed, dried ($MgSO_4$), and concentrated, giving 1.0 g of an oil. Column chromatography (silica gel) by gradient elution with n-hexane-ether readily separated two diastereomers: (1*S*,2*S*)-(+)-pseudomethylephedrine, 0.531 g (50% yield on the basis of **1** consumed); $[\alpha]^{20}_{D}$ +12.95° (c 1.99, MeOH) (27% ee): lit.[7] $[\alpha]^{20}_{D\,max}$ +48.1° (MeOH); NMR (CCl_4, TMS) δ 0.70 (d, *J* = 6.4 Hz, C*Me*), 2.25 (s, N*Me*), 2.25-2.70 (m, C*H*Me), 4.05 (d, *J* = 9.6 Hz, C*H*Ph), 4.20 (s, O*H*), and 7.15 ppm (s, Ph), and (1*R*,2*S*)-(-)-methylephedrine, 0.255 g (24% yield); $[\alpha]^{20}_{D}$ -5.81° (c 1.69, MeOH) (20% ee): lit.[7] $[\alpha]^{20}_{D\,max}$ -29.0° (MeOH); NMR (CCl_4, TMS) δ 0.75 (d, *J* = 6.4 Hz, C*Me*), 2.25 (s, N*Me*), 2.40-2.60 (m, C*H*Me), 3.80 (s, O*H*), 4.75 (d, *J* = 3.8 Hz, C*H*Ph), and 7.10 ppm (s, Ph).

Of particular interest were the facts that this is the first example of chiral rhodium complex-catalyzed hydrosilylation (reduction equivalent) of (±)-amino ketone **1**, accompanying effective kinetic resolution, and that enantiomerically enriched (*S*)-(-)-**1** gave rise to preferably (1*S*,2*S*)-amino alcohol over (1*R*,2*S*)-epimer *via* hydrosilylation.[8] Thus, in the asymmetric catalysis approach to the reduction of ketones, we have always found the preferential attack of diphenylsilane on the same side of diastereotopic as well as enantiotopic faces of the three different amino ketones, ω-dimethylaminoacetophenone, (±)-2-dimethylaminopropiophenone(**1**), and 3-dimethylaminopropiophenone, as far as (-)-DIOP-rhodium complex catalyst is concerned.[2]

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References and Notes

1. T. Hayashi, K. Yamamoto, K. Kasuga, H. Omizu, and M. Kumada, J. Organometal. Chem., **113**, 127 (1976), and references cited therein.
2. K. Shinohara, T. Hayashi, S. Baba, K. Yamamoto, and M. Kumada, Presented at the 34th JCS Meeting, Abstr. 2G34 (1976).
3. J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice-Hall, Inc., (1971), pp 30-35, and p 94.
4. 2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane.
5. Similar results were obtained when equivalent amounts of amino ketone **1** and diphenylsilane (15 mmol) were employed for the chiral rhodium complex-catalyzed hydrosilylation, but the reaction was interrupted before it had reached completion (45°C, 42 h): the unconverted **1** was isolated by distillation, bp 84°C/2.5 Torr, 1.00 g (38% recovery). The optical rotation, α^{20}_{D} +0.760°(neat, 0.05 dm), indicated that the substrate was enriched in the (*R*)-isomer (23% ee).
6. K. Freudenberg and F. Nikolai, Ann., **510**, 223 (1934): Reported value, $[\alpha]_{578}$ +24.9° (neat), is thus far from optically pure one.
7. Landolt-Börnstein, Zahlenwerte und Fuktionen, Optische Konstanten, 6 Auflage, Springer Verlag, (1962), 5-683.
8. The extent of asymmetric bias between two epimers was estimated to be 33%, the direction being consistent with the "cyclic model".[3]

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