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Stereoselectivity in Hydrosilylative Reduction of Substituted Cyclohexanone Derivatives with Chiral Rhodium-Bis(oxazolinyl)pyridine Catalyst

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Abstract: Stereoselectivity in the reduction of substituted cyclohexanones, 4-tert-butylcycohexanone, 2-methylcycohexanone, 2-phenylcyclohexanone, and 2-methoxycarbonyl-methylcyclohexanone, was examined with chiral rhodium-bis(oxazolinyl)pyridine catalyst and diphenylsilane. 4-tert-Butylcyclohexanone gave the corresponding trans(*equatorial*)-alcohol predominantly; the ratio of the trans/cis alcohols, 67:33. Other 2-substituted cyclohexanones showed exclusive enantioselectivities for each diastereomer in terms of the kinetic resolution; e.g. from 2-phenylcyclohexanone, 99 % ee of (1S, 2R)-trans-2-phenylcyclohexanol and 96 % ee of (1S, 2S)-cis-2-phenylcyclohexanol in 92 % yield (the trans/cis ratio = 51:49).

Introduction

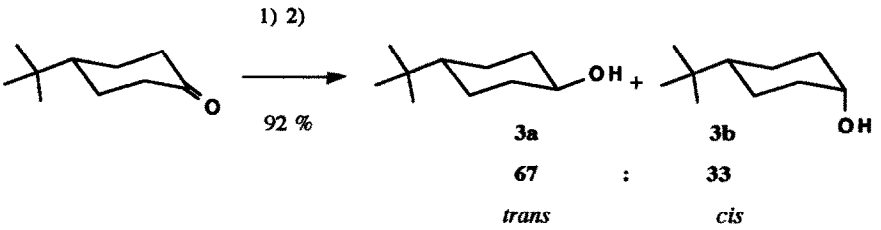
Stereoselectivity in the reduction of substituted cyclohexanone derivatives has been well studied with a variety of hydride reagents.[1] Especially, 4-tert-butylcyclohexanone is adopted as a common substrate, giving mainly the cis(*axial*)-alcohol in kinetically controlled reactions via equatorial attack by relatively hindered reducing agents, while affording the trans(*equatorial*)-alcohol via axial attack under thermodynamic conditions with less-hindered reducing agents. The selectivity by using transition-metal catalysts has been examined to show high proportions (>90%) of the cis-alcohol in transfer hydrogenation with homogeneous iridium or rhodium-phosphite catalysts[2] and in hydrogenation with heterogeneous rhodium-carbon catalysts[3]. However, the Wilkinson catalyst $RhCl(PPh_3)_3$ in the hydrosilylation with diphenylsilane decreased the proportion (30~57 %) of the cis-alcohol; the stereoselectivities of product cyclohexanol derivatives were strongly influenced by alkylsilanes and the 2-substituents of the cyclohexanone skeletons.[4]

We have developed a new chiral rhodium-bis(oxazolinyl)pyridine, Rh-pybox, catalyst for asymmetric hydrosilylation of ketones giving extremely high enantioselectivities.[5] We can assume that the real active rhodium catalyst has only one pybox ligand (**1**) as a terdentate ligand. We are, therefore, interested in examining the stereoselectivity in the hydrosilylative reduction of cyclohexanone derivatives with our efficient chiral catalyst. We report here the stereoselectivity for the reduction and discuss the stereochemical environment around the active rhodium catalyst or its transition state.

Results and discussion

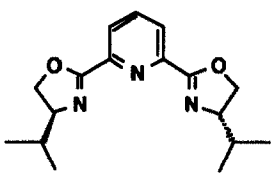
4-tert-Butylcyclohexanone was subjected to the hydrosilylative reduction with diphenylsilane (1.3 eq) and (ip-pybox)$RhCl_3$ (**2**) (1.0 mol%) in THF assisted with $AgBF_4$ (2.0 mol%) to give the corresponding silyl ether, which was then hydrolyzed to give a mixture of the trans- and cis-alcohols, (**3a**) and (**3b**), in 92 %; the ratio of **3a**:**3b** = 67:33 (Scheme 1). Since the catalytic system with the (ip-pybox)Rh catalyst and diphenylsilane showed an extremely high enantioselectivity in the hydrosilylative reduction of ketones,[5] it was expected as if the chiral circumstance around the active rhodium center should be highly congested to give the cis-alcohol (**3b**) as a major product via an equatorial attack, as usually observed with bulky reducing agents.[1] However, an axial attack was predominantly observed to give the trans-alcohol (**3a**). The ratio of the trans/cis alcohols showed a similar outcome of stereoselectivity to that with phosphine-Rh catalysts,[4] so that the transition state with the (ip-pybox)Rh catalyst should be also similar to that with the Wilkinson catalyst or chiral phosphine-rhodium catalysts via product-developing step as previously postulated.[6]

Scheme 1



1) (ip-pybox)$RhCl_3$ (**2**) (1 mol%), ip-pybox (**1**) (4 mol%), $AgBF_4$ (2 mol%), THF (2 mL), Ph_2SiH_2 (1.3 eq, 10.4 mmol), 0° C, 1 day.

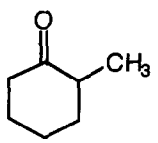
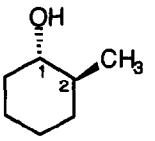
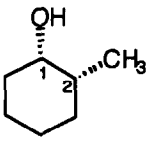
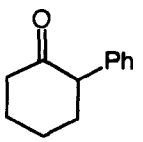
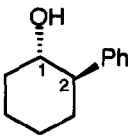
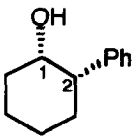
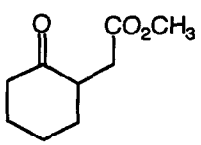
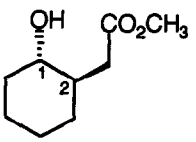
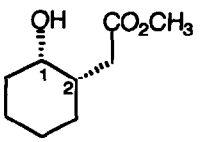
2) Then, H^+



ip-pybox (**1**)

Then we have examined the reduction of 2-substituted-cyclohexanones (Table 1). 2-Methylcyclohexanone was reduced to a mixture of trans- and cis-2-methylcyclohexanols in 88 % yield; the ratio of the trans/cis alcohols (**5a** and **5b**) = 41:59. Each alcohol showed a high enantiomeric purity in 91 % for (1S,2S)-**5a** and in 89 % for (1S,2R)- **5b**. This fact apparently indicates that the *re*/*si*-face selection by the (ip-pybox)Rh catalyst greatly predominates rather than the axial/equatorial attack (trans/cis selection).

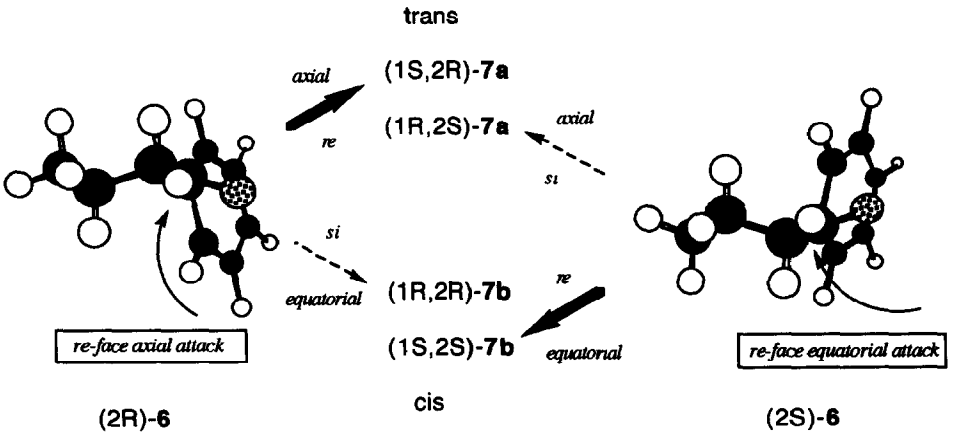
Table 1. Hydrosilylative Reduction of 2-Substituted-Cyclohexanones with (ip-pybox)Rh Catalyst and Diphenylsilane.[a]

substrate	yield[b]	ratio of trans:cis (% ee)[c]	
 **4**	88 %	 **5a** 41 : 59 (1S,2S) (91 % ee)	 **5b** (1S,2R) (89 % ee)
 **6**	92 %	 **7a** 51 : 49 (1S,2R) (99 % ee)	 **7b** (1S,2S) (96 % ee)
 **8**	76 %	 **9a** 54 : 46 (1S,2R) (95 % ee)	 **9b** (1S,2S) (92 % ee)

[a] Reaction scale; 8.0 mmol of ketones; 1.0 mol% of (ip-pybox)$RhCl_3$, 10.4 mmol of Ph_2SiH_2. [b] The yield and the ratio of the trans/cis alcohols were determined by ^1H NMR analysis of the recovered residue. [c] The values of the enantiomeric excess for **5** and **7** were determined by ^1H NMR of the corresponding MTPA esters. **9** was converted to the corresponding lactone **10** before chiral GLPC analysis. Absolute configurations were established by comparison of the sign of optical rotation with authentic compounds.

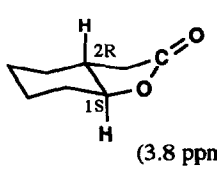
A similar result was obtained for 2-phenylcyclohexanone (**6**) giving a 51:49 mixture of the corresponding trans- and cis-alcohols (**7a** and **7b**, 92 % yield) with almost complete enantioselectivities, 99 % ee [(1S,2S)] and 96 % ee [(1S,2R)] respectively. The reduction of (2S)-**6** gave completely (1S,2R)-**7b** via an equatorial attack of the active rhodium-hydride species. While (2R)-**6** gave mainly (1S,2S)-**7a** accompanied with a trace amount of (1R,2S)-**7b** decreasing the enantioselectivity of the cis-alcohol **7b**. The conformational analysis by the molecular mechanics (MM2) shows the appropriate side views for the enantiomers of 2-phenylcyclohexanone, (2R)-**6** and (2S)-**6** (Scheme 2). The carbonyl group of (2S)-**6** has a free *re*-face and a slightly congested *si*-face comparing to those of (2R)-**6**. Therefore, we can assume that the equatorial attack to the *re*-face of (2S)-**6** is the most favorable approach for the chiral rhodium-hydride species.

Scheme 2



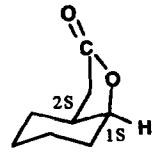
The reduction of the γ-ketoester **8** showed a similar result to produce the hydroxy compounds **9a** and **9b**, which were converted to the lactones **10a** and **10b** by treatment with p-toluenesulfonic acid in refluxing benzene to determine their enantiomeric purities by chiral gas-chromatography, respectively (Scheme 3).

Scheme 3



(3.8 ppm)

10a



(4.5 ppm)

10b

Thus we have found that stereochemical environment of the active chiral (ip-pybox)rhodium-hydride species is not so congested like as heterogeneous transition-metal catalysts for reduction of ketones exhibiting an equatorial attack. We can rather emphasize that the (ip-pybox)Rh catalyst has a steric tolerance for its axial and equatorial attack to the cyclohexanone skeletons in spite of its inherent preference for prochiral faces of ketones.

Experimental Section

General. All reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran was distilled under nitrogen from sodium. ^1H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded on a JEOL JNM-GX 270 spectrometer using tetramethylsilane as the internal reference. Optical purity was determined by Shimadz Capillary Gas Chromatograph 14A with a chiral capillary column (Astec Chiraldex G-TA ,20 m). Analytical tlc was performed on Merck (Art 5715) precoated silica gel plates (0.25 mm). Column chromatography was performed with silica gel (Merck, Art 7734). MM2 calculation and modelling were carried with Chem3D-Plus as an application by Macintosh (IIci) computer. 2-Methylcyclohexanone was commercially available. 2-Phenylcyclohexanone was synthesized from cyclohexene oxide by phenylation with PhMgBr and CuI followed by Jones oxidation. 2-Carbomethoxymethylcylcohexanone was prepared by alkylation of 1-piperidino-1-cyclohexene with methyl bromoacetate.[7]

Hydrosilylative reduction of 4-t-Butylcyclohexanone. A suspension of (ip-pybox)$RhCl_3$ (42 mg, 0.08 mmol), ip-pybox (96 mg, 0.32 mmol), and $AgBF_4$ (31 mg, 0.16 mmol) in THF (2.0 ml) was stirred at rt for 1 h. After addition of 4-t-butylcyclohexanone (1.23 g, 8.0 mmol), diphenylsilane (1.91 g, 10.4 mmol) was added at -10 °C. The mixture was stirred for 1 day at 0 °C and then treated with hydrochloric acid (1.0 *N*) at 0 °C. The product yield (92 %) and the trans/cis ratio (68:32) were determined by ^1H NMR of the recovered residue; for *H*-COH, δ 3.52 ppm for **3a** and δ 4.04 ppm for **3b**.

Asymmetric Hydrosilylation of 2-Substituted Cyclohexanones (4, 6, and 8). The procedure was similar to that above described with **4** (0.90 g, 8.0 mmol), **6** (1.39 g, 8.0 mmol), and **8** (1.36 g, 8.0 mmol); see also ref. 5. The reaction temperatures and times were -10 °C for 4 h for **4**, 0 °C for 4 h for **6**, and 0 °C for 12 h for **8**. Determination of the enantiomeric purities; the MTPA esters of **5**, 0.80 ppm (d, CH_3) for (1R,2R)-**5a**, 0.95 ppm (d, CH_3) for (1S, 2S)-**5a**, 0.81 ppm (d, CH_3) for (1R,2S)-**5b**, 0.92 (d, CH_3) for (1S, 2R)-**5b**; the MTPA esters of **7**, 3.10 ppm (OCH_3) for (1S,2R)-**7a**, 3.20 ppm (OCH_3) for (1R, 2S)-**7a**, 3.30 ppm (OCH_3) for (1S,2S)-**7b**, 3.36 (OCH_3) for (1R,2R)-**7b**. GLPC analysis of **10** was performed at 130 °C with the chiral column above described; the order of elution, (1R,2S)-**10a**, (1S,2R)-**10a**, (1R,2R)-**10b**, then (1S,2S)-**10b**. Values of optical rotation for authentic compounds; $[\alpha]_D$ = +42.9 (c = 1, MeOH) for (1S,2S)-**5a**, [8] $[\alpha]_D$ = +21.8 (neat) for (1S,2R)-**5b**,[9] $[\alpha]_D$ = +55 (c = 0.1, MeOH) for (1S,2R)-**7a**,[10] $[\alpha]_D$ = +106 (c = 0.2, MeOH) for (1S,2S)-**7b**,[10] $[\alpha]_D$ = -77.6 (c = 4.6, $CHCl_3$) for (1S,2R)-**10a**,[11] $[\alpha]_D$ = +41.9 (c = 10.3, $CHCl_3$) for (1R,2R)-**10b**. [11]

References

1 M. Hudlicky, *Reduction in Organic Chemistry*; Ellis Horwood LTD.: Chichester, 1984, p 113. M. Nogradi, *Stereoselective Synthesis*; VCH Verlagsgesellschaft: Weinheim, 1987, p 131.

2 (a) H. B. Henbest and T. R. B. Mitchell, *J. Chem. Soc. (C)*, **1970**, 785. (b) J. Kaspar, R. Spogliarich, and M. Graziani, *J. Organomet. Chem.*, **1982**, *231*, 71. (c) K. Felföldi, I. Kapocsi and M. Barók, *J. Organomet. Chem.*, **1984**, *277*, 439. (d) M. A. Bennett and T. R. B. Mithcell, *J. Organomet. Chem.*, **1985**, *295*, 223. (e) T. A. Smith and P. M. Maitlis, *J. Organomet. Chem.*, **1985**, *289*, 385.

3 S. Mitsui, H. Saito, Y. Yamashita, M. Kaminaga, and Y. Senda, *Tetrahedron*, **1973**, *29*, 1531.

4 (a) J. Ishiyama, Y. Senda, I. Shinoda, and S. Imaizumi, *Bull. Chem. Soc. Jpn.*, **1979**, *59*, 2353. (b) M. F. Semmelhack and R. N. Misra, *J. Org. Chem.*, **1982**, *47*, 2469.

5 H. Nishiyama, M. Kondo, T. Nakamura, and K. Itoh, *Organometallics*, **1991**, *10*, 500. H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, and K. Itoh, *Organometallics*, **1989**, *8*, 846.

6 I. Ojima, T. Kogure, M. Kumagai, *J. Org. Chem.*, **1977**, *42*, 1671.

7 G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **1963**, *85*, 207.

8 R. Backstrom and B. Sjoberg, *Ark. Kemi.*, **1966**, *26*, 549.

9 A. Kergomard, M.F. Renard, and H. Veschambre, *Tetrahedron Lett.*, **1978**, 5197.

10 L. Verbit and H. C. Price, *J. Am. Chem. Soc.*, **1972**, *94*, 5143.

11 W. H. Pirkle, P. E. Adams, *J. Org. Chem.*, **1980**, *45*, 4111.