Stereoselective Hydrogenation of Simple Ketones Catalyzed by Ruthenium(II) Complexes

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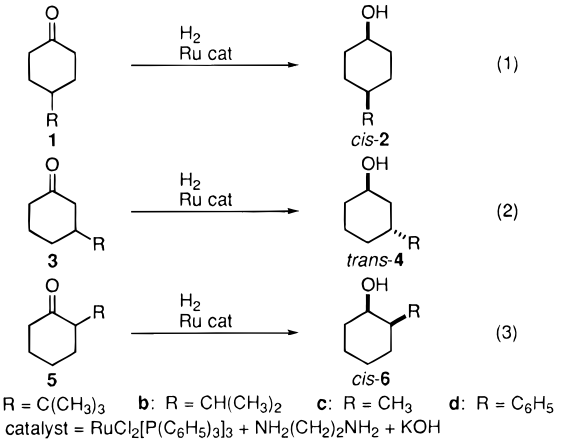
Diastereoselective reduction of ketones to secondary alcohols is a major subject of organic synthesis.[1] This important transformation has mainly been accomplished by stoichiometric metal hydride reagents.[2] Although a wide range of stereoselective reducing agents are available, each reagent has a limited scope due to the inherent chemical property as well as the difficulty in structural modification. Development of stereoselective *hydrogenation* catalyzed by transition metal-based molecular complexes is ardently desired because of the higher structural permutability of the catalyst, in addition to a series of practical benefits.[3,4] Here, we present some examples of highly diastereoselective hydrogenation of ketones catalyzed by a Ru(II)−phosphine−1,2-diamine combined system,[5,6] which can easily be perturbed by electronic and steric effects (bulkiness and chirality). The synthetic utility is further enhanced by the application of dynamic kinetic discrimination[7] of configurationally labile diastereomeric, epimeric, and enantiomeric ketones.

A Ru(II) catalyst in situ formed from $RuCl_2$(phosphine)$_n$, a 1,2-diamine, and KOH in a 1:1:2 molar ratio[5,6] effects facile hydrogenation of various ketones in 2-propanol with a high substrate/catalyst molar ratio (S/C) in 1−8 atm of H_2 at room temperature to give the corresponding alcohols in a near quantitative yield. We first tested steric requirements of the standard $P(C_6H_5)_3$−$NH_2(CH_2)_2$-NH_2 combined system. Hydrogenation of 4-*tert*-butylcyclohexanone (**1a**), a conformationally anchored substrate, with S/C = 500, or even 10 000 on a 30-g scale, occurred preferentially from the less crowded equatorial direction to give a 98.4:1.6 mixture of *cis*-4-*tert*-butylcyclohexanol (*cis*-**2a**) and its trans isomer (eq 1).[8] As expected, the stereoselectivity of the hydrogenation of other 4-substituted cyclohexanones is controlled basically by the population of the equatorial and axial conformers,[9] leading to a predominance of the cis alcohols (Table 1). Hydrogenation of 3-methylcyclohexanone (**3c**) afforded quantitatively *trans*-**4c** and the cis isomer with a 96:4 diastereoselectivity (eq 2). In a similar manner, 2-alkylcyclohexanones (**5**) were hydrogenated to afford predominantly *cis*-**6** over the trans isomers (eq 3). The diastereoselectivity, observed with **5**, is higher than the equilibrium ratio of the equatorial and axial conformers. Perhaps this is due to the repulsive interaction between the axial α-substituent and incoming Ru hydride species which prevents trans alcohol formation. 2-Methylcyclopentanone gave the cis alcohol with a diastereoselection as high as 99:1 (100%). Bicyclo[2.2.1]heptan-2-one produced a 99:1 mixture of the endo and exo alcohols.



Reaction of the 1-phenylethyl ketones **7a** and **7b**, conformationally flexible standards, showed a high Cram selectivity[10,11] to give *syn*-**8a**,**b** and *anti*-**8a**,**b** in a 98:2 and 93:7 ratio, respectively, in >96% isolated yield (eq 4). Overall, the degrees of the kinetic diastereoface discrimination observed with the standard Ru catalyst system are well compared with those accomplished by stoichiometric reduction using Selectride reagents.[2]

This catalyst system is characterized by the high tunability of the stereochemical and electronic properties

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(1) Selected reviews: (a) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567−607. (b) El-Khawaga, A. M.; Hoffmann, H. M. R. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21d, pp 3967−3987. (c) Davis, A. P. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21d, pp 3988−4048. (d) Krohn, K. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21d, pp 4099−4142. See also: (e) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378−6385. (f) Barden, M. C.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 5963−5965.

(2) Selectride reagents: (a) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159−7161. (b) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383−3384.

(3) Reviews on stereoselective hydrogenation: (a) Rylander, P. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979; Chapter 6. (b) Harada, K.; Munegumi, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 139−158.

(4) Examples of other catalytic stereoselective methods. Transfer hydrogenation: (a) Henbest, H. B.; Mitchell, T. R. B. *J. Chem. Soc. C* **1970**, 785−791. (b) Konishi, K.; Aida, T.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 816−820. Hydrosilylation: (c) Ojima, I.; Nihonyanagi, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3722. (d) Semmelhack, M. F.; Misra, R. N. *J. Org. Chem.* **1982**, *47*, 2469−2471. (e) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5405−5415. Hydrostannation: (f) Quintard, J.-P.; Pereyre, M. *Bull. Soc. Chim. Fr.* **1972**, 1950−1955.

(5) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675−2676.

(6) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417−10418.

(7) (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144−152. (b) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931−2932. (c) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−55.

(8) (a) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411−2428. (b) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53−95. (c) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449−462. (d) Franck, R. W. In *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York, 1995; Chapter 5.

(9) (a) Krohn, K. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Bracht, J., Friedrichsen, W., Krohn, K., Kropf, H., Maher-Detweiler, M., Margaretha, P., Messinger, P., Ohloff, G., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1984; Vol. 6/1b, pp 289−431. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 731−737.

(10) Reviews: (a) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Part A, Chapter 5. (b) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; Chapter 11.

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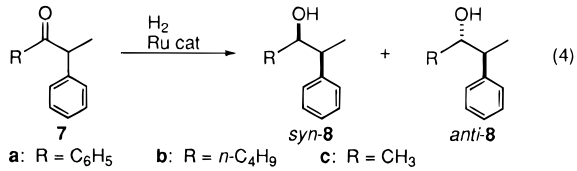
Table 1. Diastereoselective Hydrogenation of Cyclohexanones[a]

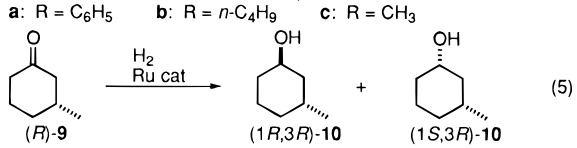
ketone		alcohol	
formula	$-\Delta G°$, kcal/mol (ratio)[b]	% yield[c]	cis:trans[c]
1a	7.62 (100:0)	>99 (96)	98.4:1.6
1c	1.76 (95:5)	97	92:8
1d	2.66 (99:1)	>99 (96)	96:4
3c	1.18 (88:12)	100	4:96
5b	0.63 (74:26)	>99 (95)[d]	>99.8:0.2
5c	2.16 (97:3)	95[e]	98:2

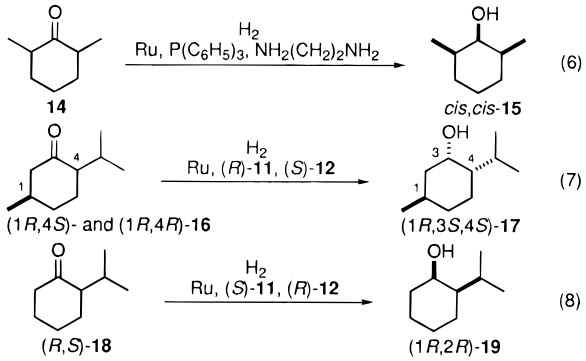
[a] A 5 mmol-scale reaction in 2-propanol. [Ketone] = 0.8−1.0 M, 4 atm of H_2, 28 °C, 1 h. Substrate: $RuCl_2[P(C_6H_5)_3]_3$: $NH_2(CH_2)_2NH_2$:KOH = 500:1:1:2. [b] Free energy difference between the axial and equatorial conformation estimated by *ab initio* MO calculation at the MP2/6-31G* level using the Gaussian 94 program.[14] The equatorial:axial ratio is given in parentheses. [c] Determined by GC. Isolated yield is given in parentheses. [d] Reaction for 9 h. [e] Reaction for 2.5 h.

through structural modification of the phosphine and diamine ligands. The reactive species generated in this hydrogenation system behaves as a "bulky hydride" as seen in eqs 1−4, but the extent of the diastereoselectivity is also significantly affected by the electronic properties of the phosphine ligands.[12] Typically, the Cram selectivity in the hydrogenation of 3-phenyl-2-butanone (**7c**) forming *syn*-**8c** and *anti*-**8c** varied from 96:4 to 95:5, 86:14, and 78:22 with the Ru catalysts possessing $P(C_6H_4$-p-$OCH_3)_3$, $P(C_6H_4$-p-$CH_3)_3$, $P(C_6H_5)_3$, or $P(C_6H_4$-p-$F)_3$ ligands in tandem with $NH_2(CH_2)_2NH_2$ (S/C = 500, 4 atm, 28 °C). The phosphine and diamine ligands can be chirally modified. Thus, hydrogenation of (*R*)-3-methylcyclohexanone [(*R*)-**9**] with a Ru complex modified by (*S*)-BINAP [(*S*)-**11**] and (*S*,*S*)-1,2-diphenylethylenediamine [(*S*)-**12**][5,6] (S/C = 500, 4 atm, 28 °C) formed a 97:3 mixture of the trans and cis alcohols, (1*R*,3*R*)-**10** and (1*S*,3*R*)-**10**, respectively (eq 5). The replacement of the diphosphine and diamine ligands to (*R*)-**11** and (*S*)-1,1-bis(*p*-methoxyphenyl)-2-isopropylethylenediamine [(*S*)-**13**] in turn gave a slightly cis-enriched mixture, (1*R*,3*R*)-**10**:(1*S*,3*R*)-**10** = 44:56.

When a configurationally labile α-substituted ketone is used, asymmetric transformation via in situ stereomutation is possible.[7] Thanks to the smooth reaction in an alkali-containing 2-propanol, the dynamic kinetic resolution method allows the diastereo- and enantioselective synthesis of chiral alcohols having contiguous stereogenic centers. 2,6-Dimethylcyclohexanone (**14**) is in a rapid equilibrium between the cis and trans isomers in 2-propanol containing KOH [diequatorial:equatorial,axial:diaxial ratio = 92:8:0 (experiment)[13] or 97:3:0 (*ab initio* calculation)[14]], where *trans*-**14** is expected to be rather unreactive because of the presence of an axially oriented methyl substituent at the α position. In







fact, hydrogenation of **14** in the presence of a $RuCl_2$-$[P(C_6H_5)_3]_3$−$NH_2(CH_2)_2NH_2$ catalyst at 4 atm for 8 h[15] gave *cis*,*cis*-**15** with 98.7% selectivity together with the cis,trans (0.2%, much less than the equilibrium population of *trans*-**14**) and trans,trans (1.1%) isomers (100% combined yield) (eq 6). When enantiomerically pure (−)-menthone [(1*R*,4*S*)-**16**] equilibrating with isomenthone, a 4*R* epimer of **16**, was subjected to hydrogenation with an achiral $RuCl_2[P(C_6H_5)_3]_3$−$NH_2(CH_2)_2NH_2$ catalyst system at 8 atm for 9 h,[15] a 93.7:6.1:0.2 mixture of (+)-neomenthol [(1*R*,3*S*,4*S*)-**17**] and the 1*R*,3*R*,4*R* and 1*R*,3*R*,4*S* stereoisomers was obtained (eq 7). However, with a chiral (*R*)-**11**−(*S*)-**12** combined system,[15] (1*R*,3*S*,4*S*)-**17** was formed exclusively.

Finally, hydrogenation of racemic 2-isopropylcyclohexanone [(*R*,*S*)-**18**] in the presence of a $RuCl_2$[(*S*)-**11**]-$(dmf)_n$−(*R*)-**12** combined catalyst[5,6] at 4 atm for 11 h[15] afforded quantitatively a 99.8:0.2 mixture of the cis alcohol, (1*R*,2*R*)-**19** (93% ee), and the trans, 1*R*,2*S* isomer (28% ee) (eq 8).[16] Computer-aided analysis[7c] of the reaction showing an inherent 1*R*,2*R*:1*S*,2*S*:1*R*,2*S*:1*S*,2*R* selectivity of 97.26:2.57:0.10:0.07 indicates that, under such conditions,[15] (*R*)-**18** is hydrogenated 36 times faster than (*S*)-**18**. The slow-reacting *S* substrate undergoes in situ stereochemical inversion 47 times faster than it is hydrogenated. The extent of the substrate-based asymmetric induction in favor of the cis isomer is calculated to be 192 and the catalyst-controlled asymmetric induction (*R**/*S**) to be 7.2.

Supporting Information Available: Hydrogention procedures and analytical data of the hydrogenation products (7 pages).

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(11) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. (b) Anh, N. T. *Fortschr. Chem. Forsch.* **1980**, *88*, 145−162. (c) Houk, K. N.; Wu, Y. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH: Weinheim, 1987; pp 247−260.

(12) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313−348.

(13) Rickborn, B. *J. Am. Chem. Soc.* **1962**, *84*, 2414−2417.

(14) Gaussian 94, Revision B.1: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.

(15) A 5 mmol-scale reaction. [Ketone] = 0.8 M, ketone:Ru:diamine:KOH = 500:1:1:20, 28 °C.

(16) Atomic coordinates for (1*R*,2*R*)- and (1*S*,2*R*)-2-isopropylcyclohexyl (*R*)-*N*-[1′-(1-naphthyl)ethyl]carbamate have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.