Hydrogen Transfer from Alcohols to Carbonyl Compounds Catalyzed by Aluminum Porphyrins. Stereochemical Aspects

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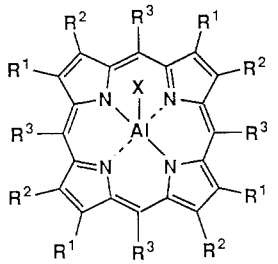
Highly diastereoselective reductions of methylcyclohexanones with alcohols such as 2-propanol, (−)-borneol, or (±)-isoborneol were brought about by using chloroaluminum porphyrins, (5,10,15,20-tetraphenylporphinato)aluminum chloride or (etioporphinato)aluminum chloride, as catalysts. When an optically active alcohol such as (−)-isoborneol was used, enantioselective reductions of prochiral ketones such as isopropyl or cyclohexyl phenyl ketone took place. ^{1}H NMR and UV–vis studies demonstrated coordination of ketone and alcohol to the central aluminum atom of the catalyst.

Introduction

The reactions of metalloporphyrins have received particular attention in relation to biochemical systems.[1] Since reactions take place as for the substrate and/or the reagent coordinated to the metal on a rigid macrocycle of porphyrin, notable stereospecificities are expected and in fact some investigations in stereochemical aspects have been made in exploiting metalloporphyrins as cytochrome P-450 model systems.[2]

We have investigated the reactions of aluminum porphyrins and found amphiphilic features, nucleophilicity of axial ligand, and Lewis acidity. Bases such as 1-methylimidazole coordinate to the central metal from the back side of the original axial group due to the Lewis acidity of aluminum atom and affect the reactivities of the axial ligand.[3] Recently, we found that aluminum porphyrins can coordinatively activate carbonyl compounds such as cyclic esters for nucleophilic attack.[4]

In a preliminary communication,[5] we have reported the novel coordinative activation of carbonyl compounds by aluminum porphyrin in the reduction of aldehydes or ketones with alcohols using the aluminum porphyrin (TPP)AlX (**1a**) (TPP:5,10,15,20-tetraphenylporphinato) as catalyst. The system of (TPP)AlCl (**1a**, X = Cl) combined with secondary alcohols such as 2-propanol and (±)-isoborneol is effective for the reduction of aldehydes and ketones under mild conditions. Although aluminum tris(2-propoxide) is a representative catalyst for the reduction of carbonyl compounds with alcohol,[6] (TPP)AlO-$CH(CH_3)_2$ (**1a**, X = $OCH(CH_3)_2$) exhibits very poor catalytic activity compared with (TPP)AlCl. Notable stereospecificity has been observed for the reduction of 2-methylcyclohexanone with the system of (TPP)AlCl coupled with (±)-isoborneol. In the present paper are described the results of a detailed investigation of diastereoselective and enantioselective reductions of various ketones with secondary alcohols using the aluminum porphyrins (TPP)AlX (**1a**) and (EtioP)AlX (**1b**) (EtioP: etioporphinato I) as catalysts, and the stereochemical course of the hydrogen-transfer process is discussed.



1a (TPP)AlX
$R^1 = R^2 = H$, $R^3 = C_6H_5$

1b (EtioP)AlX
$R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = H$

Experimental Section

Materials. All ketones were distilled over calcium hydride or anhydrous calcium sulfate under dry nitrogen. 2-Propanol was distilled over magnesium treated with iodine under a nitrogen atmosphere. (±)-Isoborneol was recrystallized from ethanol. (+)-Camphor was reduced by $LiAlH_4$ in ether to give (−)-isoborneol contaminated with 11% (+)-borneol, and the crude mixture thus obtained was subjected to esterification with *o*-nitrobenzoyl chloride/pyridine, followed by steam distillation, to give (−)-isoborneol free from (+)-borneol as distillate, which was further purified by careful sublimation to afford optically pure (−)-isoborneol (mp 209–210 °C, $[\alpha]^{25}_D$ −34.0° (*c* 5, ethanol)).[7] Commercial 2-methylcyclohexanol (cis/trans = 27/73) was distilled over anhydrous magnesium sulfate under nitrogen. 2-Methylcyclohexanol with a cis/trans isomer ratio of 54/46 was prepared by the reduction of 2-methylcyclohexanone with 2-propanol in the presence of $Al(OCH(CH_3)_2)_3$.[8] 5,10,15,20-Tetraphenylporphine ($TPPH_2$) was synthesized from pyrrole and benzaldehyde in propionic acid and recrystallized from chloroform/methanol.[9] Etioporphyrin I ($EtioPH_2$) was synthesized from *tert*-butyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate and recrystallized from chloroform/methanol.[10] Trimethylaluminum (Me_3Al) and diethylaluminum chloride (Et_2AlCl) were fractionally

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Table I. Reduction of Methylcyclohexanones with Secondary Alcohols[a]

run	cyclohexanone	alcohol	catalyst	time, h	cyclohexanol yield, %[d]	cyclohexanol cis/trans[d]
1	2-methyl	(±)-isoborneol	(TPP)AlCl	0.3	93	93/7
2				3.0	100	51/49
3				5.0	100	5/95
4[b]				0.17	47	>99/<1
5[b]				0.5	100	96/4
6[b]				3.0	100	94/6
7			(EtioP)AlCl	0.3	80	93/7
8				3.0	100	48/52
9				6.0	100	5/95
10			$Al(OCH(CH_3)_2)_3$	0.3	15	72/28
11				3.0	49	65/35
12		(−)-borneol	(TPP)AlCl	2.0	17	91/9
13				4.0	87	11/89
14				7.0	100	5/95
15[c]		2-propanol	(TPP)AlCl	0.3	52	58/42
16[c]				3.0	85	7/93
17[c]			(EtioP)AlCl	0.3	45	60/40
18[c]				3.0	78	7/93
19[c]			$Al(OCH(CH_3)_2)_3$	0.3	13	55/45
20[c]				3.0	55	55/45
21	3-methyl	(±)-isoborneol	(TPP)AlCl	1.0	64	16/84
22				6.0	100	85/15
23	4-methyl	(±)-isoborneol	(TPP)AlCl	1.0	63	83/17
24				6.0	100	7/93

[a] $[Ketone]_0/[alcohol]_0/[catalyst]_0$ = 2.5 mmol/2.5 mmol/0.5 mmol in $CHCl_3$ (4.0 mL) at 30 °C under N_2. [b] $[Ketone]_0/[alcohol]_0/[catalyst]_0$ of 2.5 mmol/20.0 mmol/0.5 mmol. [c] In 2.5 mL of $CHCl_3$. [d] Determined by GC.

distilled under reduced pressure in a nitrogen atmosphere. $Al(OCH(CH_3)_2)_3$ distilled under reduced pressure was dissolved in $CHCl_3$ and stored under nitrogen. (−)-Menthyl chloroformate, prepared by the reaction of (−)-menthol with 2 equiv of phosgene in the presence of quinoline,[11] was dissolved in benzene (1.0 M) and stored under nitrogen. All the solvents used were purified by standard procedures under nitrogen.

Preparation of Aluminum Porphyrin 1. (5,10,15,20-Tetraphenylporphinato)aluminum chloride ((TPP)AlCl, **1a** (X = Cl)) and (etioporphinato)aluminum chloride ((EtioP)AlCl, **1b** (X = Cl)) were prepared respectively by the reaction of the corresponding free-base porphyrins with 1.2 equiv of Et_2AlCl in CH_2Cl_2 at room temperature under nitrogen, followed by evaporation of the volatile fractions under reduced pressure.[12] (TPP)AlMe (**1a**, X = CH_3) was prepared by the equimolar reaction between $TPPH_2$ and Me_3Al in CH_2Cl_2 at room temperature under nitrogen.[13] $(TPP)AlOCH(CH_3)_2$ was prepared by the reaction of (TPP)AlMe (**1a**, X = CH_3) with 40 equiv of 2-propanol in CH_2Cl_2 at room temperature, followed by evaporation to dryness at 55 °C under reduced pressure.[14]

Reduction of Substituted Cyclohexanones with Alcohols Catalyzed by Aluminum Porphyrins 1a and 1b. General procedures for the reductions of substituted cyclohexanones with alcohols catalyzed by aluminum porphyrins **1a** and **1b** are represented by the following example. To a 50-mL round-bottom flask equipped with a three-way stopcock containing 0.5 mmol of (TPP)AlCl (**1a**, X = Cl) under dry nitrogen was added 2-methylcyclohexanone (2.5 mmol) by using a hypodermic syringe, and the mixture was stirred for a few minutes at room temperature. Then, a solution of (±)-isoborneol in $CHCl_3$ (2.5 mmol in 4 mL) was added, and the mixture was stirred at 30 °C. Aliquots of the reaction mixture were periodically taken out by means of a hypodermic syringe in a nitrogen stream and subjected to gas chromatographic (GC) analyses (PEG 20M, column temperature 100 °C initially, then increased at 3 °C/min) to determine the yield and the isomer ratio of 2-methylcyclohexanol produced. For isolation of 2-methylcyclohexanol from the reaction mixture, 2.5 mL of the above reaction mixture after 8 h (100% yield) was poured into hexane (10 mL), the mixture was filtered from the insoluble catalyst residue, and the filtrate was evaporated by water aspirator to leave an oily residue, which was chromatographed on silica gel with hexane/$CHCl_3$ (2/1) as eluent to give 164 mg (92% isolated yield) of an isomeric mixture of 2-methylcyclohexanol (cis/trans = 5/95) as identified by ^1H NMR and GC/MS analyses. In the case of the reduction with 2-propanol, 2.5 mL of $CHCl_3$ was used as solvent.

Reduction of Prochiral Ketones with (−)-Isoborneol Catalyzed by (TPP)AlCl (1a, X = Cl). A representative example of the reduction of prochiral ketones with (−)-isoborneol catalyzed by (TPP)AlCl (**1a**, X = Cl) is as follows. To a stirred mixture of (TPP)AlCl (0.5 mmol) and isopropyl phenyl ketone (2.0 mmol) in $CHCl_3$ (1.5 mL) was added a $CHCl_3$ solution of (−)-isoborneol (2.0 mmol/1.5 mL) under dry nitrogen, and the mixture was stirred at 55 °C. After 2 h, 0.1 mL of the reaction mixture was taken out and an aliquot was subjected to GC analysis (PEG-20M, 150 °C), by which the yield of 2-methyl-1-phenyl-1-propanol was determined to be 96%. The residue was treated at room temperature with (−)-menthyl chloroformate (1.0 M benzene solution, 5 equiv with respect to the alcohol) in the presence of pyridine to afford a diastereoisomeric mixture of (−)-menthyl 2-methyl-1-phenyl-1-propyl carbonate with a GC peak area ratio of 1:7.3, which corresponds to a 76% ee of the parent alcohol. The reaction mixture remaining was poured into hexane (10 mL), from which the insoluble catalyst residue was removed by filtration. The greenish oil, left after the evaporation of the filtrate, was chromatographed on silica gel with hexane/acetone (10/1) as eluent to afford a crude alcohol, which was subjected to preparative TLC (silica gel, hexane/ethyl acetate (9/1)) to afford 280 mg (93% isolated yield) of 1-phenyl-2-methyl-1-propanol, as identified by GC-MS and ^1H NMR analyses. $[\alpha]^{25}_D$ of the isolated alcohol, after trap-to-trap distillation, was +35.3° (*c* 5.0, ether), from which the optical purity was estimated to be 72% (*R*).[15] In excellent agreement with this, the diastereoisomer ratio of the menthyl carbonate derived from the isolated alcohol, as determined by GC analysis, was 1/6.7, which corresponds to 74% ee of the parent alcohol.

Measurements. Gas chromatographic analyses were performed with a Rascot stainless capillary column (PEG 20M, 30 m) and a flame ionization detector. ^1H NMR analyses were performed in $CDCl_3$ operating at 399.7 MHz, where the chemical shifts were determined with respect to $CHCl_3$ (δ 7.28). UV–vis spectra were recorded by using a quartz cell of 1-cm path length. Optical rotation measurements were performed on a JASCO

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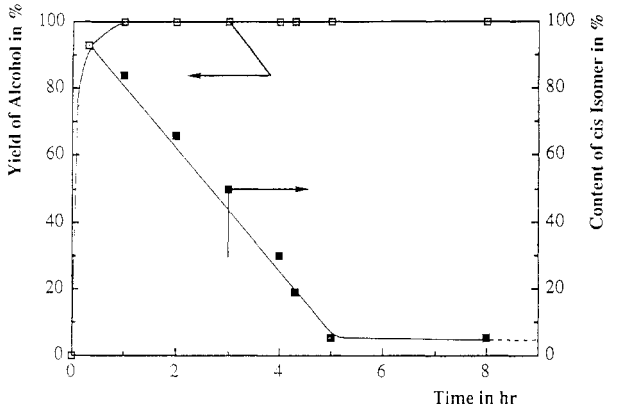

Figure 1. Reduction of 2-methylcyclohexanone with (±)-isoborneol catalyzed by (TPP)AlCl (**1**, X = Cl) in $CHCl_3$ at 30 °C. Time course of the reaction. $[2\text{-Methylcyclohexanone}]_0$ = $[(\pm)\text{-isoborneol}]_0$ = 1.0 M, $[(TPP)AlCl]_0$ = 0.2 M.

Model DIP-360 digital polarimeter.

Results and Discussion

Reduction of Substituted Cyclohexanones with Alcohols Catalyzed by Aluminum Porphyrins 1a and 1b. Reductions of monosubstituted cyclohexanones with secondary alcohols such as 2-propanol, (±)-isoborneol, and (−)-borneol were examined in $CHCl_3$ by using the aluminum porphyrins (TPP)AlCl and (EtioP)AlCl (**1a**, **1b**; X = Cl) as catalysts (Table I). The reduction of 2-methylcyclohexanone with (±)-isoborneol catalyzed by (TPP)AlCl (mole ratio 5/5/1) proceeded smoothly at 30 °C to afford 2-methylcyclohexanol and camphor quantitatively (runs 1–3), where the cis/trans isomer ratio of 2-methylcyclohexanol produced is time-dependent. As clearly illustrated in Figure 1, the cis/trans isomer ratio of the product was 93/7 in the reaction for 0.3 h (93% yield), which gradually changed with time, even after the quantitative consumption of the 2-methylcyclohexanone, to attain the constant cis/trans ratio 5/95 in 5 h. A very similar stereochemical profile was observed for the reaction catalyzed by (EtioP)AlCl (**1b**, X = Cl), where the cis/trans isomer ratio of 2-methylcyclohexanol formed in 80% yield in 0.3 h changed from 93/7 to 5/95 after 6 h, although the ketone had been completely consumed within 1 h (runs 7–9). Thus, in the reductions with (±)-isoborneol using the chloroaluminum porphyrins (TPP)AlCl and (EtioP)-AlCl as catalysts, 2-methylcyclohexanone is once reduced stereoselectively to the corresponding cis alcohol, which gradually epimerizes to the trans alcohol with also a high stereoselectivity. In sharp constrast, the attempted reduction of 2-methylcyclohexanone with (±)-isoborneol using aluminum tris(2-propoxide) ($Al(OCH(CH_3)_2)_3$), a representative catalyst for the hydrogen-transfer reaction, proceeded very slowly under similar conditions and exhibited a poor stereoselectivity throughout the reaction (runs 10 and 11).

For the reduction of 2-methylcyclohexanone catalyzed by (TPP)AlCl, use of (−)-borneol in place of (±)-isoborneol also resulted in the stereoselective formation of *cis*-2-methylcyclohexanol at the initial stage (17% yield in 0.3 h, cis isomer content 91%), where the subsequent cis-to-trans epimerization of the product also occurred to furnish the final cis/trans isomer ratio of 5/95 (runs 12–14). However, the reaction proceeded much slower than that with (±)-isoborneol. Use of 2-propanol for the reduction catalyzed by (TPP)AlCl or (EtioP)AlCl resulted in the efficient reduction of 2-methylcyclohexanone, but the cis isomer content was low even at the initial stage compared with the above two cases (runs 15–18).

Table II. Reduction of Prochiral Ketones with (−)-Isoborneol Catalyzed by (TPP)AlCl[a]

run	ketone	temp, °C	time, h	carbinol yield, %[b]	carbinol ee, %[c]
1	PhCOMe	0	2.0	57	28
2			4.0	95	28
3			8.0	98	0
4	PhCOEt	0	4.0	19	30
5			8.0	83	23
6			10.0	98	5
7	PhCOPr	0	1.5	40	30
8			4.0	93	20
9			7.0	>99	11
10	PhCO^{i}Bu	20	4.0	53	35
11			6.0	94	30
12			12.0	>99	10
13	PhCO^{i}Pr	30	4.0	42	70
14			10.0	70	76
15			30.0	>99	72
16		55	0.5	73	72
17			2.0	96	72
18	PhCO c-Hex	55	1.0	61	48
19			7.0	83	48
20	PhCO^{t}Bu	55	1.0	39	33
21			10.0	74	33
22	^{t}BuCOMe	30	6.0	28	32
23			12.0	50	32

[a] $[Ketone]_0/[(-)\text{-isoborneol}]_0/[(TPP)AlCl]_0$ = 2.0/2.0/0.5 (in mmol) in $CHCl_3$ (3.0 mL) under N_2. [b] By GC. [c] By GC as the corresponding (−)-menthyl carbonates.

The system of (±)-isoborneol coupled with (TPP)AlCl or (EtioP)AlCl was also applicable to the stereoselective reduction of other substituted cyclohexanones. Examples shown in Table I are the reductions of 3- and 4-methylcyclohexanones with the (±)-isoborneol–(TPP)AlCl system at 0 °C (runs 21–24). In both cases, the substrates were once reduced stereoselectively to the corresponding axial alcohols (*trans*-3-methylcyclohexanol, *cis*-4-methylcyclohexanol),[16] which gradually epimerized to the alcohols of opposite configuration in the subsequent stage. Thus, in the reduction of methylcyclohexanones with (±)-isoborneol catalyzed by aluminum porphyrin, the configuration of the alcohols formed at the initial stage demonstrates that the hydrogen transfer to the carbonyl group of the parent ketones preferentially occurs from the equatorial direction with respect to the cyclohexane ring.

In relation to the concomitant configurational change of the produced alcohols in the above processes, it is of interest to note that use of a large excess of (±)-isoborneol with respect to the substrate resulted in suppression of the product epimerization. An example is shown by the reduction of 2-methylcyclohexanone with the ratio $[2\text{-methylcyclohexanone})_0/[(\pm)\text{-isoborneol}]_0/[(TPP)AlCl]_0$ of 5/40/1 at 30 °C, which proceeded to afford 2-methylcyclohexanol in 47 and 100% yield in 0.17 and 0.5 h, respectively, with the cis isomer contents of >99 and 96% (runs 4 and 5). Furthermore, the high content of the cis isomer thus observed remained unchanged even upon having the reaction mixture stand for additional 2.5 h (runs 6).

Reduction of Prochiral Ketones with (−)-Isoborneol Catalyzed by (TPP)AlCl (1a, X = Cl). On the basis of the interesting results mentioned above, asymmetric reductions of prochiral ketones were attempted by using the system of (TPP)AlCl as catalyst coupled with an optically

(16) For the convenient understanding of the stereochemistry of the hydrogen transfer to methylcyclohexanones, the terms "axial" and "equatorial" are used in place of "cis" and "trans" for the denotation of the diastereoisomers of methylcyclohexanols.

active alcohol such as (−)-isoborneol in $CHCl_3$ with the ratio $[ketone]_0/[alcohol]_0/[(TPP)AlCl]_0$ of 4/4/1 (Table II). Under the conditions examined, various prochiral phenones were catalytically reduced to the corresponding alcohols in excellent yields, and the highest enantioselectivity was observed for the reduction of isopropyl phenyl ketone (2-methyl-1-phenylpropan-1-one) (runs 13–17). For example, in the reduction conducted at 30 °C for 10 h, 1-phenyl-2-methyl-1-propanol was formed in 70% yield with 76% ee (*R*) (run 13). The reduction proceeded quantitatively upon prolonged reaction, keeping the optical purity of the product unchanged (>99% yield in 30 h, 72% ee, run 15). Elevating the reaction temperature resulted in a noticeable acceleration of the reduction without decreasing the enantioselectivity; the reaction performed at 55 °C proceeded to give 1-phenyl-2-methyl-1-propanol in 96% yield in only 2 h with 72% ee (*R*) (run 17). The asymmetric reductions of other prochiral phenones (runs 1–12 and 18–21) and an aliphatic ketone such as *tert*-butyl methyl ketone (pinacolone) (runs 22 and 23) with (−)-isoborneol catalyzed by (TPP)AlCl also proceeded to give the corresponding alcohols in excellent yields with the enantiomeric excess ranging from 20 to 48%. It should be noted that all the alcohols predominantly formed with the (−)-isoborneol–(TPP)AlCl system have the *R* configuration.

In the reductions of phenyl ketones with primary alkyl groups attached to the carbonyl group (runs 1–12), the optical purity of the produced alcohols gradually decreased with time under the conditions examined. The representative example is shown by the reduction of phenyl propyl ketone with the (−)-isoborneol–(TPP)AlCl system at 30 °C, where the enantiomeric excess of the product formed in 1.5 h (40% yield) decreased from 30 to 20% (4 h, 93% yield) and 11% (7 h, >99% yield) (runs 7–9), indicating the presence of racemization.

Epimerization of Methylcyclohexanols in the Presence of (TPP)AlCl (1a, X = Cl). In the reduction of ketone with alcohol catalyzed by aluminum porphyrin, the initial stereochemistry of the carbinol carbon atom of the products eventually changes (epimerization or racemization), as described in the above sections. Similar stereochemical profiles have been observed for some hydrogen-transfer reactions reported to date, and are ascribed to the reversible nature of the reaction.[17] The reversible nature of the hydrogen transfer reaction catalyzed by aluminum porphyrin could be well demonstrated by the combination of appropriate ketones and alcohols. For example, in the presence of (TPP)AlCl (0.2 equiv) as catalyst at 30 °C, the reduction of 2-methylcyclohexanone with 2-propanol (1 equiv/1 equiv) to give 2-methylcyclohexanol and acetone proceeded to attain the plateau at 85% conversion, while the plateau was established at 15% conversion under the same conditions for the reduction of acetone with 2-methylcyclohexanol to give 2-propanol and 2-methylcyclohexanone. In connection with the reversible nature of the reaction, the addition of methylcyclohexanone (5 equiv) to the isomeric mixture of 2-methylcyclohexanol (cis/trans = 54/46) (5 equiv) in the presence of (TPP)AlCl (1 equiv) at 30 °C in $CHCl_3$ brought about the epimerization of 2-methylcyclohexanol to furnish the cis/trans isomer ratio of 10/90 in 0.5 h and the constant ratio at 7/93 after 2 h (Figure 2, i). Nearly the same trans isomer content was attained in the epimerization of 2-methylcyclohexanol with the initial cis/trans isomer ratio of 27/73 (Figure 2, ii). The epimerization of 2-methylcyclohexanol[18] in the presence of (TPP)AlCl was observed to be slow without added ketone (cis/trans isomer ratio, 54/46 initially, 25/75 in 0.5 h, and the constant ratio 7/93 after 5 h). Thus, in the hydrogen-transfer reaction with aluminum porphyrin catalyst, the epimerization of the alcohol once produced is mediated by the existing carbonyl compounds, whereupon the product undergoes re-oxidation to lose the original stereochemistry. The epimerization of 2-methylcyclohexanol (cis/trans isomer ratio: 27/73) also took place in the presence of 2-methylcyclohexanone and $Al(OCH(CH_3)_2)_3$ but with very poor stereoselectivity to attain the plateau at the cis/trans isomer ratio of 35/65 (Figure 2, iii).

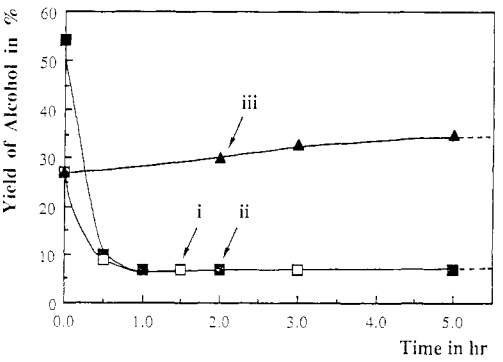

Figure 2. Epimerization of 2-methylcyclohexanol in the presence of 2-methylcyclohexanone catalyzed by (TPP)AlCl (1, X = Cl) or $Al(OCH(CH_3)_2)_3$ in $CHCl_3$ at 30 °C. $[Alcohol]_0/[ketone]_0/[catalyst]_0$ = 5/1/1 ($[alcohol]_0$ = 1.0 M). (i) $[Cis]_0/[trans]_0$ = 54/46, cat. 1 (X = Cl). (ii) $[Cis]_0/[trans]_0$ = 27/73, cat. 1 (X = Cl). (iii) $[Cis]_0/[trans]_0$ = 27/73, cat. $Al(OCH(CH_3)_2)_3$.

Coordinative Interaction between Aluminum Porphyrin and Ketones or Alcohols. We have previously reported that the Lewis acidity of (TPP)AlCl (**1a**, X = Cl) is so high that it can be coordinated by and activate the carbonyl group of cyclic esters for nucleophilic attack.[4] A similar coordinative interaction was observed by ^1H NMR for the mixture of (TPP)AlCl and a ketone such as acetophenone. In the ^1H NMR spectrum of the mixture with the mole ratio $[acetophenone]_0/[(TPP)AlCl]_0$ of 1/0.63 in $CDCl_3$ at 27 °C, all the signals due to acetophenone were observed to shift by 0.11 to 0.16 ppm upfield from those in the absence of (TPP)AlCl.[19] For example, the signal due to the methyl group, which appears in the absence of (TPP)AlCl as a sharp singlet at 2.60 ppm, was observed at 2.44 ppm with significant line broadening. Thus, acetophenone is in the proximity of (TPP)AlCl and affected by the magnetic shielding effect due to the ring current of porphyrin.

The ^1H NMR spectrum in $CDCl_3$ at 27 °C of the mixture of 2-propanol and (TPP)AlCl ($[alcohol]_0/[(TPP)AlCl]_0$ = 1/0.125) shows broadened signals assignable to CH_3, CH, and OH groups of 2-propanol (δ 0.78, 3.15, and 1.06) upfield-shifted from those in the absence of (TPP)AlCl.[19] The possibility of the ligand exchange reaction of (TPP)AlCl with 2-propanol to form $(TPP)AlOCH(CH_3)_2$ and HCl could be excluded by the comparison of the above spectrum with that of $(TPP)AlOCH(CH_3)_2$ (CH_3, δ −1.92; CH, δ −2.10) separately prepared. Thus, the upfield shifts

(17) (a) Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 1367. (b) Eliel, E. L.; Nasipuri, D. *J. Org. Chem.* **1965**, *30*, 3809. (c) Hach, V. *J. Org. Chem.* **1973**, *38*, 293.

(18) 2-Methylcyclohexanol used for the epimerization reaction was contaminated with 2-methylcyclohexanone (0.2%, as determined by GC analysis), which was unable to be removed by repeated distillations.

(19) ^1H NMR data in $CDCl_3$ at 27 °C, for acetophenone: δ 8.00 (phenyl-*o*), 7.62 (phenyl-*p*), 7.51 (phenyl-*m*), and 2.60 (CH_3). For acetophenone/(TPP)AlCl (1/0.63): δ 7.83 (phenyl-*o*), 7.56 (phenyl-*p*), 7.44 (phenyl-*m*), and 2.44 (CH_3, br). For 2-propanol: δ 1.05 (CH_3), 3.83 (CH), and 3.71 (OH). For 2-propanol/(TPP)AlCl (1/0.125): δ 0.78 (CH_3), 3.15 (CH), and 1.06 (OH).

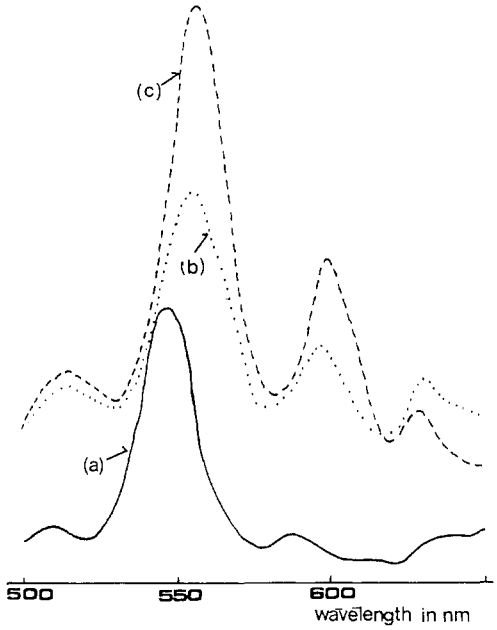

Figure 3. UV–vis spectra of (TPP)AlCl in (a) CH_2Cl_2, (b) acetone, and (c) 2-propanol under N_2 at room temperature.

for the signals of 2-propanol are also ascribed to the coordinative interaction with (TPP)AlCl.

The UV–vis spectral patterns for (TPP)AlCl in acetone and 2-propanol (Figures 3b and 3c) were both different from that in CH_2Cl_2 (Figure 3a) but similar to those for the six-coordinate complexes from 1 and Lewis bases such as 1-methylimidazole and tetraethylammonium acetate in CH_2Cl_2.[3,12] This observation and the NMR profiles mentioned above clearly demonstrate the possible coordinations of ketone and alcohol with (TPP)AlCl from the back side to generate the six-coordinate complexes. In sharp contrast, no change was observed for the NMR spectra of ketone and alcohol upon mixing with (TPP)AlOCH$(CH_3)_2$, which is much inferior to (TPP)AlCl in terms of both catalytic activity and stereoselectivity. Thus, in the reduction catalyzed by the chloroaluminum porphyrins, (TPP)AlCl and (EtioP)AlCl, the hydrogen transfer from carbinol to carbonyl group is affected by the coordinative interactions of substrates with the Lewis acidic metal center of the catalyst. The attempted reaction of cyclohexanone and 2-propanol with (TPP)AlCl in basic solvents such as tetrahydrofuran and pyridine resulted in no reduction of the substrate, probably due to the neutralization of the Lewis acidity of the catalyst by the preferential coordination of the solvent molecule.

The reduction of methylcyclohexanones with secondary alcohols catalyzed by aluminum porphyrin involves two competitive hydrogen-transfer processes, one of which leads to the reduction of methylcyclohexanones to the axial alcohols and the other results in the slow epimerization of the axial alcohols once produced to the equatorial alcohols (Table I and Figure 1). High stereoselectivities observed in both processes suggest that these two reactions proceed with a prominent steric effect of the bulky catalyst, chloroaluminum porphyrin.

Conclusion

Diastereoselective and enantioselective hydrogen-transfer reactions were observed in the reduction of ketones with alcohols by using the chloroaluminum porphyrins, (TPP)AlCl and (EtioP)AlCl, as catalysts. Coordinative interactions are present both for the ketones and alcohols with the Lewis acidic aluminum atom of the catalyst, leading to the facile hydrogen transfer under mild conditions. The reactions take place with a marked steric effect of the bulky porphyrin ligand around the metal center. Apart from the biological viewpoint, limited attempts have been reported to utilize metalloporphyrins as catalyst for synthetic reactions. The present development discloses *a potential utility of metalloporphyrins as catalysts for the steric control in organic syntheses.*

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Construction of Medium- and Large-Sized Cyclic β-Keto Esters (or Nitriles) via One-Pot Three-Carbon Ring Expansion of Carbocyclic β-Keto Esters and Its Application to the Synthesis of (−)-Muscone

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A one-pot, three-carbon ring expansion involving intramolecular aldol condensation and subsequent retro-aldol cleavage is induced by treatment of β-keto esters with potassium *tert*-butoxide in dimethyl sulfoxide to afford functionalized 8-, 9-, 10-, and 15-membered rings, respectively. The stereochemistry of intermediate **21** was established to be a cis-fused carbocyclic ring system with the methyl ketone in the cis position. The mechanism for the three-carbon ring expansion is explained by considering the dual function of the electron-withdrawing group (EWG). An iterative ring expansion was accomplished by the facile conversion of **8** to **20**. Application of this ring expansion method to the synthesis of (−)-muscone further attests to the generality of this reaction.

We recently found a one-pot, three-carbon ring expansion by treatment of carbocyclic β-keto esters with a 4-oxopentyl function at the α-position with potassium *tert*-butoxide in dimethyl sulfoxide.[1a] Medium-sized cy-

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