Highly Stereoselective Hydrogen Transfer from Alcohols to Carbonyl Compounds Catalysed by Aluminium Porphyrins

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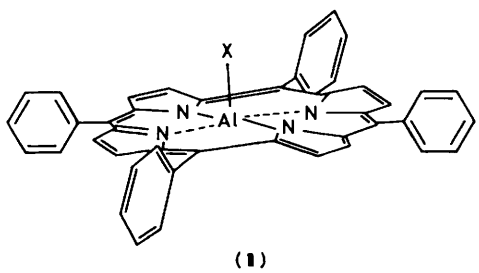
Aluminium porphyrins, such as chloroaluminium porphyrin, catalyse a novel hydrogen transfer process in the reduction of aldehydes or ketones with alcohols, and the reactions eventually proceed with very high stereoselectivities.

To investigate enzymatic redox transformation of organic substrates by heme-containing oxygenases such as cytochrome P-450, numerous attempts have been made to exploit synthetic metalloporphyrins as artificial metalloenzymes capable of effectively catalysing alkane hydroxylations and/or alkene epoxidations under mild conditions.[1] In these reactions, the processes of oxygen transfer from the oxygen sources to the substrates possibly take place *via* active oxometalloporphyrins as the oxidizing intermediates. Very high stereoselectivities have been observed in some cases, attributed to the steric effect of the large, rigid, macrocyclic porphyrin ligands around the active metal centres.[2] Here we report a novel highly stereoselective hydrogen transfer process catalysed by a metalloporphyrin, developed in the Meerwein–Ponndorf–Verley(MPV)-type reduction[3] of aldehydes or ketones with alcohols using the aluminium porphyrin (TPP)AlX (**1**) (TPP = 5,10,15,20-tetraphenylporphinato) as catalyst.

A typical example is the reaction of cyclohexanone with propan-2-ol in the presence of (TPP)AlCl (**1**; X = Cl)[4] (Table 1, run 4). To (TPP)AlCl (0.5 mmol) in a 50 cm^3 round-bottom flask equipped with a three way stopcock under dry nitrogen, was added cyclohexanone (5 equiv.) followed by chloroform (2.5 cm^3), and the mixture was stirred vigorously at room temperature for a few minutes. To the resulting bluish–purple, homogeneous solution was added propan-2-ol (2.5 mmol) and stirring was continued at 30 °C. The reaction system gradually turned greenish–purple and heterogeneous over a period of 30 min. G.c. analysis of the reaction mixture after 3 h showed two new peaks, which were identified as cyclohexanol and acetone from the retention times, g.c.–mass spec.. and/or ^1H n.m.r. analyses. The conversion into cyclohexanol, as determined by g.c., was 80%, which corresponds to a turnover number (*n*) with respect to (TPP)AlCl [*i.e.*, product per mol (TPP)AlCl] of 4.0. Thus, the catalytic reduction of cyclohexanone to cyclohexanol takes place at the expense of the oxidation of propan-2-ol to acetone.

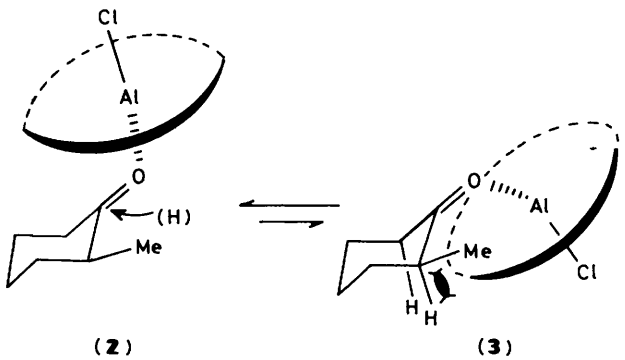


(**1**)

Table 1. Reaction of carbonyl compounds (aldehydes and ketones) with alcohols in the presence of (TPP)AlX (**1**) as catalyst.[a]

Run	Carbonyl compound	Alcohol	Catalyst	Temp/ °C	Time/h	Conversion[b] %	ratio of product[b]
1	hexanal	2-PrOH	(**1**; X = Cl)	30	3	84	
2	PhCHO	2-PrOH	(**1**; X = Cl)	30	3	40	
3	PhCHO	2-PrOH	(**1**; X = 2-PrO)			6	
4	cyclohexanone	2-PrOH	(**1**; X = Cl)	30	3	80	
5	cyclohexanone	(−)-Borneol	(**1**; X = Cl)			84	
6	cyclohexanone	$PhCH_2OH$	(**1**; X = Cl)			6	
7	cyclohexanone	Bu^tOH	(**1**; X = Cl)			0	
8	2-methylcyclohexanone	2-PrOH	(**1**; X = Cl)	0	3	90	7:93
9	2-methylcyclohexanone	2-PrOH	(**1**; X = Cl)	30	1.5	85	8:92
10a	2-methylcyclohexanone	(±)-Isoborneol	(**1**; X = Cl)	30	0.3	93	93:7
10b	2-methylcyclohexanone	(±)-Isoborneol			1	~100	84:16
10c	2-methylcyclohexanone	(±)-Isoborneol			2	~100	66:34
10d	2-methylcyclohexanone	(±)-Isoborneol			3	~100	50:50
10e	2-methylcyclohexanone	(±)-Isoborneol			4	~100	30:70
10f	2-methylcyclohexanone	(±)-Isoborneol			5	~100	5:95
11	2-methylcyclohexanone	2-PrOH	$Al(2\text{-}PrO)_3$	0	3	8	54:46
12	2-methylcyclohexanone	2-PrOH	$Al(2\text{-}PrO)_3$	30	3	55	55:45
13	2-methylcyclohexanone	2-PrOH	(**1**; X = 2-PrO)	30	3	6	54:46
14	3-methylcyclohexanone	2-PrOH	(**1**; X = Cl)	0	3	94	82:18
15	4-methylcyclohexanone	2-PrOH	(**1**; X = Cl)	0	3	90	12:88
16	4-methylcyclohexanone	(±)-Isoborneol	(**1**; X = Cl)	30	3	100	7:93
17	4-t-butylcyclohexanone	2-PrOH	(**1**; X = Cl)	0	3	74	14:86

[a] $[Carbonyl]_o:[Alcohol]_o:[Cat]_o$ 2.5:2.5:0.5 mmol, in $CHCl_3$ (2.5 ml) under N_2. [b] By g.c.



Scheme 1

The present catalytic system is also applicable to various aldehydes. For example, hexanal and benzaldehyde were reduced by propan-2-ol to hexan-1-ol and benzyl alcohol, respectively, with 88 (n = 4.4) and 43% conversion (n = 2.2) [$CHCl_3$, 30 °C, 3 h (run 1 and 2)]. (1*S*)-(−)-borneol, a secondary alcohol, was also effective for reduction of cyclohexanone in the presence of (TPP)AlCl, affording cyclohexanol in 88% yield (n = 4.4) (run 5). Similarly, use of a primary alcohol such as benzyl alcohol coupled with (TPP)AlCl brought about the reduction of cyclohexanone, although very slowly (run 6). On the other hand, use of t-butyl alcohol, with no carbinol hydrogen, combined with (TPP)AlCl, resulted in no reduction of cyclohexanone under the same conditions (run 7). Thus, (TPP)AlCl successfully catalysed the reduction of aldehydes or ketones with alcohols under mild conditions, when the catalytic transfer of the carbinol hydrogen to the carbonyl group was involved.

With respect to the stereochemical course of this hydrogen transfer process, it is noteworthy that reductions of monosubstituted cyclohexanones by the (TPP)AlCl–alcohol systems proceeded with high diastereoselectivities (runs 8—17). A typical example is the reduction of 2-methylcyclohexanone (2MCHXN) with propan-2-ol(2-PrOH) catalysed by (TPP)AlCl {$[2MCHXN]_o:[2\text{-}PrOH]_o:[(TPP)AlCl]_o$ 5:5:1; 0 °C, 3 h}, which gave an isomeric mixture of 2-methylcyclohexanols (90% conversion) with the *cis*:*trans* ratio of 7:93 (run 8). Similarly, 4-methylcyclohexanone was reduced quantitatively by (±)-isoborneol in the presence of (TPP)AlCl at 30 °C for 3 h to give the *trans* isomer predominantly (*cis*:*trans* 7:93) (run 16).

In sharp contrast, the reduction of 2-methylcyclohexanone with propan-2-ol using aluminium tris(2-propoxide) [$Al(2\text{-}PrO)_3$], a representative catalyst for the MPV reaction (0 °C, 3 h) gave an isomeric mixture of the reduced product in only 8% conversion with very low diastereoselectivity (*cis*:*trans* 46:54) (run 11). More detailed investigations demonstrated that in the (TPP)AlCl-catalysed reaction the observed *cis*:*trans* ratio is time dependent owing to the concomitant epimerization of the reduced products. This is particularly illustrated by the reduction of 2-methylcyclohexanone with (±)-isoborneol catalysed by (TPP)AlCl at 30 °C, which, after 0.3 h, gave the isomeric mixture of 2-methylcyclohexanols in 93% conversion with a very high preference for the *cis* isomer (*cis*:*trans* 93:7) (run 10a). However, the observed isomer ratio gradually changed with time to furnish a *cis*:*trans* ratio of 5:95 after 5 h, although the starting ketone had been consumed almost completely within the first hour (run 10b—f). Under similar conditions, a highly *trans*-selective epimerization was observed upon addition of (TPP)AlCl to a mixture of isomeric 2-methylcyclohexanone and 2-methylcyclohexanol (*cis*:*trans* 54:46; $[alcohol]_o:[ketone]_o:[(TPP)AlCl]_o$ 5:1:1) and the *cis*:*trans* ratio rapidly changed to 11:89 after 0.3 h, and 7:93 after 2 h, respectively. On the

other hand, the attempted epimerization of 2-methylcyclohexanol (*cis* : *trans* 27 : 73) by $Al(2\text{-}PrO)_3$ under similar conditions took place without any particular stereoselectivity, giving a final *cis* : *trans* ratio of 35 : 65. Thus, in the reaction using (TPP)AlCl as catalyst, not only the reduction of the carbonyl group by alcohol (hydrogen transfer process), but also the epimerization of the reduced products, took place stereoselectively, owing to the pronounced steric effect of the bulky porphyrin ligand.

As a catalyst for the reduction of carbonyl compounds with alcohol, $(TPP)AlOCHMe_2$ (**1**; X = 2-PrO)[5]† was found to be very much inferior to (TPP)AlCl in terms of both catalytic activity and stereoselectivity (run 3 and 13).† The notable catalytic function of (TPP)AlCl can be ascribed to its highly oxygenophilic nature due to the inherent Lewis acidity of the central halogenoaluminium atom.‡ In fact, the ^1H n.m.r. signals of acetophenone, when mixed with (TPP)AlCl (0.6 equiv.) in $CDCl_3$ at 27 °C, exhibited appreciable upfield shifts upon co-ordination to the central aluminium atom owing to the shielding effect of the porphyrin ring.§¶ Similar upfield shifts were observed for propan-2-ol in a 1 : 5 mixture with (TPP)AlCl, ‖ but the spectrum was different from that in $(TPP)AlOCHMe_2$. Thus, in the present reduction system catalysed by (TPP)AlCl, the carbonyl group of the substrates is activated by the co-ordination to (TPP)AlCl, leading to facile hydrogen transfer from the alcohol. In the case of the reduction of 2-methylcyclohexanone, the co-ordination of the carbonyl group to (TPP)AlCl is considered to result in the preferential formation of complex (**2**) rather than the alternative (**3**) (Scheme 1), because of the absence of steric repulsion between the 2,6-axial hydrogens of the cyclohexane ring and the porphyrin disk. Consequently, hydrogen transfer to the carbonyl group preferably takes place from the sterically less hindered equatorial side of (**2**), resulting in the predominant formation of *cis*-2-methylcyclohexanol.

In contrast to biological redox processes which proceed *via* oxygen transfer reactions mediated by heme-containing enzymes, the novel redox process reported herein involves a hydrogen transfer reaction. Chloroaluminum prophyrin, being a bulky catalyst, gives rise to the activation of carbonyl group, leading to the unprecedented high stereoselectivities in the reduction of cyclic ketones.

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† $(TPP)AlOCHMe_2$ was prepared by the reaction of (TPP)AlMe with propan-2-ol[5]. For $(TPP)AlOCHMe_2$, ^1H n.m.r. in $CDCl_3$: δ −1.92 (Me).

‡ Strong Lewis acids such as $AlCl_3$ or $BF_3{\cdot}OEt_2$ brought about no reduction under similar conditions.

§ For acetophenone, in $CDCl_3$, δ 2.60 (Me); for acetophenone–(TPP)AlCl (1.6 : 1), in $CDCl_3$ δ 2.44 (br., Me).

¶ Similar co-ordinative activation of carbonyl compounds by aluminium porphyrins was observed in the reaction of δ-valerolactone with (porphinato)aluminium alkoxide.[6]

‖ For propan-2-ol in $CDCl_3$: δ 1.03 (Me) and 3.82 (CH); for propan-2-ol–(TPP)AlCl (5 : 1) in $CDCl_3$: δ 0.48 (br., Me) and 2.78 (br., CH).

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