Enantioselective Reduction of Ketones on Sterically-controlled Lanthanoid(III) Complexes

Hisashi Okawa,* Tsutomu Katsuki, Michio Nakamura, Naohisa Kumagai, Yuko Shuin, Teruo Shinmyozu, and Sigeo Kida

Department of Chemistry, Faculty of Science, Kyushu University, Hakozaki, Higashiku, Fukuoka 812, Japan

Sterically controlled lanthanoid complexes, *fac*-Λ-tris{4-(*l*-menthyloxy)-1-(*p*-tolyl)butane-1,3-dionato}lanthanoid(III), functioned as Lewis acid catalysts for enantioselective reduction of ketones (acetophenone, octan-2-one, butan-2-one) with $NaBH_4$ in cyclohexane.

Configuration-controls of labile metal complexes are of importance owing to the development of new stereoselective reactions using these sterically controlled complexes. Our strategy for configuration-controls of metal complexes is to take advantage of noncovalent interligand interactions occurring within a complex.[1] We have shown[1b] that tris{4-*l*-menthyloxy)-1-(*p*-tolyl)butane-1,3-dionato}metal(III) [M(*l*-moba-Me)$_3$] prefers the *fac*-Λ configuration of possible diastereoisomers by such intramolecular noncovalent interactions, attractive dispersion forces occurring between aliphatic CH groups and aromatic π-systems (Figure 1; R = Me). Of particular interest are the lanthanoid complexes, which are co-ordinatively unsaturated (six-ordination) and can incorporate substrates to achieve a co-ordination number larger than six. Thus, those sterically controlled complexes are expected to offer a chiral arena available for asymmetric reactions. Here we report enantioselective reduction of ketones on [Ln(*l*-moba-Me)$_3$] (Ln = La, Pr, Gd, Er) (Figure 1).

A mixture of [Ln(*l*-moba-Me)$_3$], the ketone substrate, and powdered $NaBH_4$ in dry cyclohexane was stirred at ambient temperature for five days. Unchanged $NaBH_4$ was filtered off, and the reduced alcohol and the unchanged ketone were separated from the reaction mixture.† The yields (conversion %) of alcohols were evaluated by ^{1}H n.m.r. spectroscopy, and the absolute configuration of the preferred enantiomer was determined by specific rotation. Enantiomeric purities of the alcohols were determined by the 400 MHz ^{1}H n.m.r. spectra for the corresponding acetate esters,‡ using tris[3-(heptafluoropropyl)hydroxymethylene-(+)-camphorato]-europium(III) as a shift reagent.

In the preliminary experiments each run was carried out in the molar ratio [host]:[substrate]:[reducing agent] = 1:1:1.5, using the La, Pr, Gd, or Er complex as the complex, acetophenone as substrate, and $NaBH_4$ or $NaBH(OMe)_3$ as reducing agent. Results are given in Table 1. $NaBH_4$ alone could not reduce ketones to alcohols in cyclohexane. In the presence of a host complex, on the other hand, the reduction proceeded in tolerable yields to give 1-phenylethanol. Evidently, the host complexes functioned as Lewis acid catalysts to form host–substrate adducts prior to the reduction. The formation constants of these host–substrate adducts were not determined. The preferred enantiomer of 1-phenylethanol was always *S*,[2] irrespective of the host complex used. When $NaBH(OMe)_3$ was used as the reducing agent, the

† Steam-distillation for acetophenone or octan-2-one and water-extraction for butan-2-one as the substrate.

‡ The esterification was carried out in quantitative yield by the reaction of the alcohol and acetyl chloride in the presence of 4-dimethylaminopyridine in benzene.

Table 1. Enantioselective reductions of ketones on chiral lanthanoid complexes.[a]

Complex	Substrate[b]	Reducing agent	Ratio[c]	Conversion %[d]	$[\alpha]_D$[e]	(*S*)/(*R*)[f]
None	A	$NaBH_4$	1:1:1.5	0		
La	A	$NaBH_4$	1:1:1.5	52	−11.7°	71/29
Pr	A	$NaBH_4$	1:1:1.5	44	−12.5°	63/37
Pr	A	$NaBH(OMe)_3$	1:1:1.5	28	—[g]	—[g]
Gd	A	$NaBH_4$	1:1:1.5	56	−20.9°	89/11
Gd	A	$NaBH(OMe)_3$	1:1:1.5	32	—[g]	—[g]
Er	A	$NaBH_4$	1:1:1.5	41	−12.1°	72/28
Gd	A	$NaBH_4$	1:1:5	64	−22.8°	92/8
Gd	A	$NaBH_4$	1:1:10	62	−22.5°	92/8
Gd	A	$NaBH_4$	1:10:50	4.5	−18.5°	85/15
Gd	O	$NaBH_4$	1:1:5	65	−3.4°	29/71
Gd	B	$NaBH_4$	1:1:5	68	−1.9°	42/58

[a] *Conditions*: in cyclohexane, 5 days at ambient temp. [b] Substrate: A = acetophenone, B = butan-2-one, O = octan-2-one. [c] [complex]:[substrate]:[reducing agent]. [d] Based on the substrate. [e] In CH_2Cl_2, corrected for contaminated ketone. [f] Determined by 400 MHz n.m.r. for acetate esters. [g] Obscured by contamination with methanol.

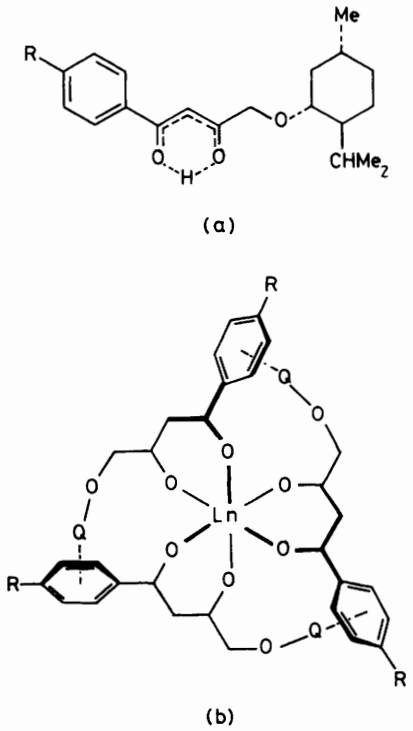

Figure 1. (a) Structure of H(*l*-moba-Me) (R = Me); (b) schematical representation of intramolecular noncovalent interaction in 1:3 lanthanoid complexes (Q = *l*-menthyl, the laevorotatory stereoisomer).

product was contaminated with significant amounts of methanol.

More detailed experiments were made using the Gd complex as a host complex. The results are included in Table 1. In reactions in the molar ratio [host]:[substrate]:[$NaBH_4$] = 1:1:5, both the conversion % and the enantioselectivity were improved significantly. However, further increase of $NaBH_4$ (1:1:10) did not improve the selectivity. In the reaction with the molar ratio of 1:10:50, the conversion % did not exceed 10%. All these facts suggest that the reaction is stoicheiometric but not catalytic. However, the host complex could be recovered in good yield (>90%) and used for another run, after recrystallization from absolute ethanol.

When octan-2-one or butan-2-one was the substrate, the (*R*)-alcohol[3] was obtained preferentially in each case. Thus, the enantioselectivity in the reduction of ketones is reversed by the change of the substrate from acetophenone (aromatic ketone) to octan-2-one and butan-2-one (aliphatic ketones). For the enantioselective reduction of prochiral ketones a wide variety of asymmetric reducing agents have been developed.[4] The method described here is of less practical use. However, the present result illustrates a promising approach for molecular design of functionally significant metal complexes based on noncovalent interligand interactions.

This work was supported by a Grant-in-Aid for Scientific Research (No. 62430011) from the Ministry of Education, Japan.

Received, 8th August 1988; Com. 8/03237H

References

1 (a) M. Nakamura, H. Ōkawa, T. Ito, M. Kato, and S. Kida, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 583 and references therein; (b) H. Ōkawa, H. Tokunaga, T. Katsuki, M. Koikawa, and S. Kida, *Inorg. Chem.*, 1988, **27**, 4373.

2 (*S*)-1-Phenylethanol: $[\alpha]_D$ −27.75; S. Mitsui and Y. Kudo, *Tetrahedron*, 1967, **23**, 4271.

3 (*S*)-Octan-2-ol: $[\alpha]_D$ +9.47°; S. J. Cristol, B. Franzus, and A. Shadan, *J. Am. Chem. Soc.*, 1955, **77**, 2512. (*R*)-butan-2-ol: $[\alpha]_D$ −13.5°; P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, 1951, **73**, 41.

4 For example: H. C. Brown, W. S. Park, B. T. Cho, and P. V. J. Ramachandran, *J. Org. Chem.*, 1987, **52**, 5406, and references therein; H. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, and H. Takaya, and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 629.