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Asymmetric Reduction with 5-Deazaflavin. III.[1] Reduction of Ethyl Benzoylformate in the Presence of Chiral Ligand

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A nonenzymatic asymmetric reduction of ethyl benzoylformate with an achiral 1,5-dihydro-5-deazaflavin derivative in chiral media was investigated as a model system for reduced nicotinamide adenine dinucleotide (phosphate)-dependent dihydrogenase. The chiral media include chiral nuclear magnetic resonance shift reagent, chiral Lewis acid, and a combination of metal ion and chiral ligand (additive). Of these reductions, a substantial asymmetric induction was observed in the presence of tris-[3-(heptafluoropropylhydroxymethylene)(+)-camphorato]europium to give ethyl mandelate possessing predominantly *S*-configuration, in an optical yield of 24 to 36%. These values are among the highest so far reported in nonenzymatic reduction of ethyl benzoylformate with a 5-deazaflavin model. The discrimination of the prochiral face of the carbonyl compound was effective even when a catalytic amount of the chiral shift reagent was employed.

Keywords 5-deazaflavin; asymmetric reduction; chiral media; ethyl benzoylformate; ethyl mandelate; chiral NMR shift reagent; europium β-diketonate

Replacement of the nitrogen atom at the N(5) position of flavin by a carbon atom gives 5-deazaflavin (pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione), and the discovery[2] of this type of naturally occurring coenzyme, such as factor 420 which functions as the low potential electron carrier in the reduction of carbon dioxide to methane, has stimulated researchers to investigate this interesting molecule in order to unveil its function in biological systems or to develop a new mimic model, for example, an organic turn-over redox catalyst.[3] In spite of the structural similarity to flavin, 5-deazaflavin can be regarded as an analogue of nicotinamide nucleotide (NAD)[4] and in fact, it is recognized that 5-deazaflavin acts as a two-electron-carrying shuttle.

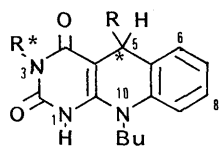
Previously, we reported the synthesis of some chiral 5-deazaflavin derivatives such as **1** or **2**, in which the asterisk indicates the position of the chiral auxiliary. These chiral 5-deazaflavins were applied to nonenzymatic asymmetric reduction as a model system for reduced nicotinamide adenine dinucleotide(phosphate) (NAD(P)H)-dependent dehydrogenase, and it has been observed that some chiral 5-deazaflavin derivatives discriminate the prochiral face of activated carbonyl compounds to some extent.[1]

In the transition state of the asymmetric reduction, the intervention of a ternary complex, consisting of 5-deazaflavin, carbonyl compound and metallic additive, was strongly suggested.[4]

In connection with the biomimetic reduction of NAD(P)H-dependent dehydrogenase, magnesium is thought to mimic the role of zinc, which is present in the enzymatic system.[5] Provided that a chiral source (chiral auxiliary) exists in the metallic additive in place of the reductant, 1,5-dihydro-5-deazaflavin, some chiral induction or transfer might be expected through the formation of the ternary complex in the transition state. Additionally, proliferation of an asymmetric induction might become feasible with a catalytic amount of the chiral additive. This system is a new type of model for an enzymatic redox reaction.

On the basis of the idea mentioned above, we investigated the asymmetric reduction of ethyl benzoylformate in the presence of a chiral additive including a metallic catalyst. Meanwhile, Zehani and Gelbard reported asymmetric reduction with a reduced nicotinamide adenine dinucleotide (NADH) model such as Hantzsch ester (**3**), catalyzed by a chiral nuclear magnetic resonance (NMR) shift reagent used as a Lewis acid, and the optical yield was moderate to high (25—55%) in this reduction.[6] The other precedents concerning chiral shift reagents as catalysts in organic synthesis include their use in the hetero Diels–Alder reaction originally reported by Danishefsky *et al.*[7]

In this paper we describe our results on asymmetric reduction of ethyl benzoylformate with an achiral 5-deazaflavin derivative in chiral media consisting of a variety of chiral metallic or nonmetallic ligands[8] (catalyst). Two 1,5-dihydro-5-deazaflavin derivatives (**4**) and (**5**), which were derived from the corresponding 5-deazaflavins, **6**[9] or



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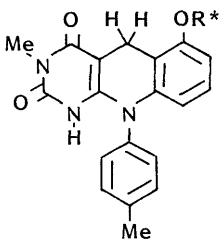

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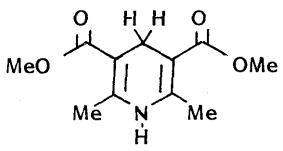

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Chart 1

This paper is dedicated to Professor Haruaki Yajima on the occasion of his retirement from Kyoto University in March 1989.

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7,[1] by reduction with sodium borohydride, were used for the present study. Of these derivatives, the latter compound (**5**)[1] has a hydroxy group at the C(6) position, close to the reaction center where (net) hydride transfer takes place. It is expected that the hydroxy group can not only enhance the reduction potential of the 1,5-dihydro derivative owing to its electron donating character, but also its chelating ability toward metal is responsible for the favorable transition state to asymmetric induction due to neighboring group participation. In most cases, the reduction was carried out in dry methylene chloride at room temperature in the dark under an atmosphere of argon for several days and the mixture was extracted with diethyl ether to give ethyl mandelate. Analyses by thin layer chromatography (TLC) or high-performance liquid chromatography (HPLC) can be applied to monitor the reaction progress. These results are summarized in Table I.

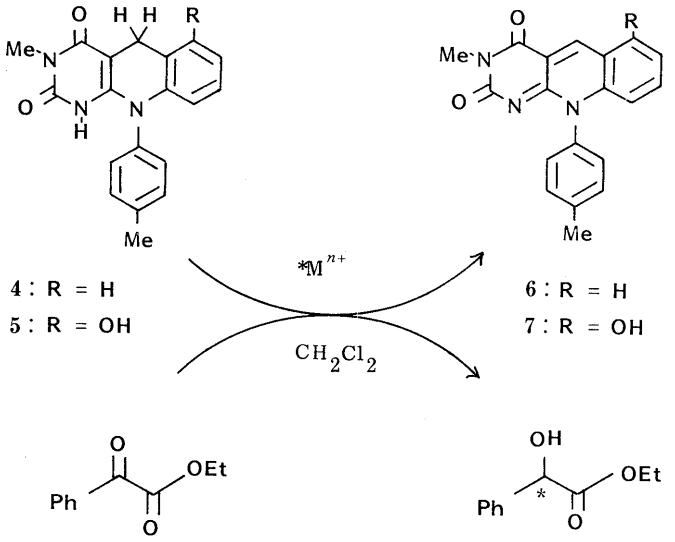


Chart 2

We previously reported that, besides magnesium ion, another metallic ion such as aluminum can catalyze the reduction as a Lewis acid.[1,4] So, aluminum, titanium and magnesium ion were used for the reduction together with a chiral additive (entries 1—3). A combination of optically active tartrate and titanium tetraisopropoxide is well-known as a basic system in the pioneering work on nonenzymatic asymmetric epoxidation of prochiral allylic alcohols developed by Sharpless *et al.*[10] However, no detectable asymmetric induction was observed in our experiment under the conditions employed. After this disappointing result, we turned our attention to the usage of a chiral aluminum compound, 1-bornyloxyaluminum dichloride, which has been successfully applied to the asymmetric Diels–Alder reaction as a chiral Lewis acid catalyst,[11] and it was found that ethyl benzoylformate was smoothly reduced under mild conditions without any asymmetric discrimination (entries 4—6).

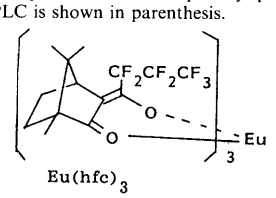
It was thought that this high reactivity is probably attributable to the inherent reducing potential of bornyloxyaluminum dichloride itself.[12] Next, a chiral nonmetallic phosphorus catalyst, (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane,[13] which is widely used as a chiral ligand for homogeneous asymmetric hydrogenation,[14] was tried (entry 7). The chiral phosphorus ligand appeared to modify the steric course of the reduction, but its precise role is obscure at present.

We have already reported our preliminary experimental result that the reduction with a catalytic amount of the achiral NMR shift reagent tris(6,6,7,7,8,8,8-heptafluoro-2-2-dimethyl-3,5-octanedionate)europium (Eu(fod)$_3$) pro-

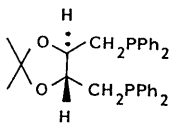
Table I. Reduction of Ethyl Benzoylformate with 1,5-Dihydro-5-deazaflavin in the Presence of Chiral Additives

Entry No.	1,5-Dihydro-5-deazaflavin R=	Additive (catalyst)	(eq)	Reaction conditions		Ethyl mandelate		
				Temp.	Time (d)	Chemical yield[a] (%)	Optical yield[b] (%)	Configuration
1	**5** OH	Ti(*O*-isoPr)$_4$ (+)-DET	(1.0) (1.0)	Room temp.	5	21	0	—
2	**5** OH	Al(*O*-isoPr)$_3$ (+)-DET	(1.0) (1.0)	Room temp.	5	20	0	—
3	**5** OH	$Mg(ClO_4)_2$ *d*-CSA	(1.0) (1.0)	Room temp.	7	10 (86)[c]	0	—
4	**4** H	(−)-BADC	(1.0)	0 °C	1	40	0	—
5	**5** OH	(−)-BADC	(1.0)	0 °C	1	11 (73)[c]	0	—
6	**5** OH	(−)-BADC	(1.0)	0 °C	1	47	0	—
7	**4** H	(−)-DIOP	(0.1)	Room temp.	6	15	6	*R*
8	**4** H	Eu(hfc)$_3$	(0.1)	Room temp.	7	7 (10)[d]	24	*S*
9	**5** OH	Eu(hfc)$_3$	(0.1)	Room temp.	7	10 (78)[c]	26	*S*
10	**5** OH	Eu(hfc)$_3$	(1.0)	Room temp.	5	14	36	*S*

a) Isolated yield. *b*) Based on the reported value of optically pure ethyl mandelate.[16] *c*) Yields based on the consumed starting ketone are shown in parentheses. *d*) Yield determined by HPLC is shown in parenthesis.



Eu(hfc)$_3$



(-)-DIOP

(-)-BADC

Eu(hfc)$_3$: tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium. (−)-DIOP: (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. (−)-BADC: (*l*-bornyloxy)aluminum dichloride. *d*-CSA: 10-*d*-camphorsulfonic acid. (+)-DET: (2*R*,3*R*)-(+)-diethyl tartrate.

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ceeded in moderate to low chemical and optical yield.[4] Chiral europium β-diketonate, $Eu(hfc)_3$, is a representative lanthanide NMR shift reagent, which is commercially available and is used extensively to evaluate optical purity.[15] Entries 8—10 show our results using $Eu(hfc)_3$ in both catalytic and stoichiometric amounts. As can be seen, the chemical yield was poor and a fair amount of the starting ketone was recovered, on the other hand, a moderate to good optical yield was obtained to afford ethyl mandelate with an excess of the (*S*)-enantiomer. This is one of the highest values in nonenzymatic reduction of ethyl benzoylformate with a 5-deazaflavin model so far reported. Optimum conditions for this reduction are under investigation. It is noteworthy that even a catalytic amount of europium chiral reagent can exert asymmetric induction comparable to that with a stoichiometric amount.

In conclusion, a combination of a metal and a chiral ligand as a chiral auxiliary is one of the most promising candidates for nonenzymatic asymmetric reduction with a 5-deazaflavin model. Mechanistic aspects of these asymmetric inductions are currently being investigated.

Experimental

Optical rotation was recorded on a JASCO DIP-360 digital polarimeter in ethanol. Preparative thin layer chromatography (p-TLC) was run on 20 × 20 cm plates with a 0.1—1.5 mm layer of Merck Silica gel PF 254 and/or GF 254. HPLC analysis was done on a Waters Associates ALC/GPC 244 instrument equipped with a μ-Porasil column (3.9 × 300 mm) in a solvent system of hexane–ethyl acetate (8 : 1). Gas liquid chromatography (GLC) was done on a Shimadzu GC-7AG with a glass column (2.0 m) packed with 3% OV-17.

Materials The 1,5-dihydro-5-deazaflavin derivatives, **4** and **5**, were obtained by the reduction of **6** (10-*p*-tolyl-3-methylpyrimido[4,5-*b*]-quinoline-2,4(3*H*,10*H*)-dione) and **7** with sodium borohydride in methanol for 10 min at room temperature. After the usual work-up, the resulting off-white crystalline 1,5-dihydro derivatives, **4** and **5**, containing re-oxidized **6** and **7** in amounts of less than 5% (from analyses of the reaction residue by HPLC and ^{1}H-NMR), were immediately used for the reduction without further purification. (−)-BADC was prepared from *l*-borneol and ethylaluminum dichloride according to the reported procedure.[11]

General Procedure for Reduction of Ethyl Benzoylformate An appropriate chiral material was added to a stirred mixture of 1 eq each of the 1,5-dihydro-5-deazaflavins, **4** and **5**, and ethyl benzoylformate in dry methylene chloride, and the mixture was stirred under the conditions specified in Table I under an atmosphere of argon in the dark. In some cases, the progress of the reaction was monitored by HPLC or GLC analysis. After the reaction, the precipitated 5-deazaflavin derivatives (oxidized form and reduced form) were filtered off and the remaining mother liquor was extracted with ether. The ether layer was washed with water, dried over magnesium sulfate and evaporated to give a residue, which was subjected to p-TLC. The purity of ethyl mandelate, thus obtained, was checked by TLC, HPLC and/or GLC. The optical purity was determined by a comparison of the specific rotation value with the reported value[16] in ethanol.

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