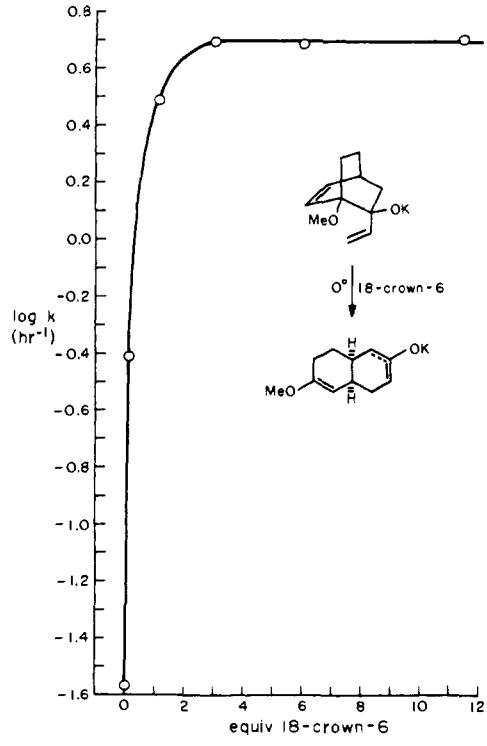
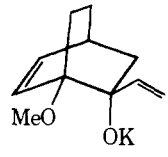


Figure 1. Effect of 18-crown-6 on the rate of rearrangement of **2a** (M = K) in THF at 0°.

conditions which **2a** (M = K) rearranges within minutes (66°, THF) the diene **7** shows no rearrangement even after heating for 24 hr.



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Both the increased yields and lower reaction temperatures encountered in these anionic oxy-Cope processes imply that these modifications should significantly improve the synthetic utility of these and related molecular rearrangements. The full scope of these modified sigmatropic processes will be reported in due course.

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health for support of this research. We would also like to express our appreciation to Professors R. G. Bergman and J. A. Berson for stimulating discussions during the course of this research.

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Reduction by a Model of NAD(P)H. Effect of Metal Ion and Stereochemistry on the Reduction of α-Keto Esters by 1,4-Dihydronicotinamide Derivatives

Sir:

Stereospecific reduction of pyruvate to D- or L-lactate by the reduced pyridine nucleotide, NADH, is catalyzed by a D- or L-lactate dehydrogenase, respectively.[1-3] To help understand the mechanism of biochemical processes,[4] we have constructed and studied a model system[5] whose reduction proceeds stereoselectively under mild conditions and which, therefore, may also be used in organic syntheses.

In this communication, we wish to report mild and stereoselective nonenzymatic reduction of esters of pyruvic acid[6] and benzoylformic acid[6,7] in the presence of magnesium perchlorate or zinc perchlorate and a 1,4-dihydronicotinamide derivative, a model of NAD(P)H. Stereoselective reduction by a model of NAD(P)H has not previously been reported. The reaction may be valuable in determining the mechanism of biochemical coenzyme-substrate interaction.

Ethyl benzoylformate in acetonitrile is not reduced by 1-benzyl-1,4-dihydronicotinamide (BNAH) alone at room temperature in the dark.[8] In the presence of an equimolar amount of magnesium perchlorate, however, ethyl benzoylformate was converted into racemic ethyl mandelate quantitatively. A mixture of 1 mmol each of ethyl benzoylformate, BNAH, and magnesium perchlorate in 15 ml of acetonitrile was allowed to react for 17 hr at room temperature; 5 ml of water was then added. The mixture was concentrated in vacuo and the residual oil was column-chromatographed on silica gel and eluted with benzene or ethanol. Recovered ethyl benzoylformate, ethyl mandelate, and 1-benzyl-3-carbamoylpyridinium perchlorate ($BNA^+ClO_4^-$) were identified from their spectra which were compared with those of authentic samples. The reaction was not affected by hydroquinone (0.5 mmol). Under the same reac-

Table I. Reduction of Ethyl Benzoylformate with 1-Benzyl-1,4-dihydronicotinamide[a]

BNAH, mmol	Metal ion,[b] mmol	Other conditions	Isolated yields, % Recovered keto ester	Isolated yields, % Ethyl mandelate
1.06	None		90	None
1.11	Mg^{2+} 1.08		6	86
1.09	Mg^{2+} 1.13	44 hr	0	100[c]
1.09	Mg^{2+} 0.11		91	2
1.11	Mg^{2+} 1.09	p-Hydroquinone (0.5 mmol)	8	81
1.11	Mg^{2+} 1.12	5% aqueous MeCN	78	7
1.09	Li^{+} 2.57		92	2
1.09	Zn^{2+}[d] 1.25		8	66

[a] These reactions were run with 1 mmol of keto ester in 15 ml of acetonitrile for 17 hr at room temperature. [b] Perchlorate. [c] Oxidized BNAH (BNA^{+}) was isolated in 90% yield. [d] Hydrated zinc perchlorate was used.

tion conditions, esters of pyruvic acid afforded the corresponding racemic lactates. Although zinc(II) perchlorate was as effective as magnesium perchlorate, lithium perchlorate was not effective, suggesting that magnesium and zinc ions play an important role in these reductions. The results are summarized in Table I.

The reaction of ethyl benzoylformate with BNAH-*4*-d_1 (85% purity) revealed that 70% of the available deuterium atoms were transferred to the carbonyl carbon of the substrate,[9] which demonstrates that these reactions involve the direct transfer of hydrogen in analogy with the in vivo reduction of carbonyl compounds.[4,5] Thus, the model reactions parallel enzymatic hydrogen transport.

It was important to determine whether or not the reductions occurred asymmetrically with these models. For this purpose, derivatives of (*R*)-(−)-*N*-α-methylbenzyl-1,4-dihydronicotinamide (**1a–c**) as chiral models for NAD(P)H were synthesized from (*R*)-(+)-α-methylbenzylamine ($[\alpha]^{24}D$ +38.2°, neat 0.1 dm) and nicotinyl chloride. The reduction of ethyl benzoylformate with **1a** ($[\alpha]^{24}D$ −173°, *c* 2.1 acetonitrile) at room temperature was quantitative and gave predominantly ethyl (*R*)-(−)-mandelate with an optical purity of 19%. Reductions with **1b** and **1c** were also quantitative and gave (*R*)-(−)-mandelates with optical purities of 18 and 11%, respectively (Table II). Furthermore, the reduction of *n*-butyl pyruvate with **1a** afforded *n*-butyl (*R*)-(+)-lactate[10] of 38% optical purity in 20% yield. The optical activity of the product was determined on the chromatographically separated material. No appreciable enhancement of optical activity was exhibited by samples that were distilled.[11]

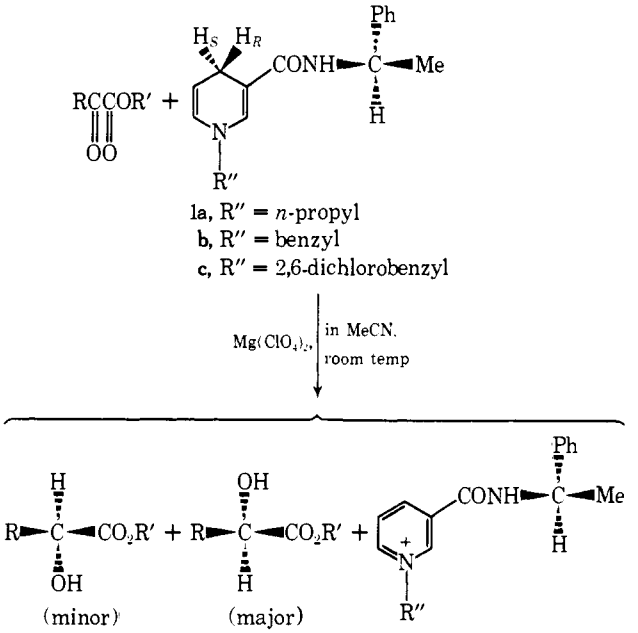
Although a detailed mechanism cannot be established at present, the role of metal ions in the model reduction of carbonyl compounds[12,13] may closely resemble their catalytic function in enzymatic systems. For example, it is known that the biological reactions with alcohol dehydrogenases, which are also NAD(P)H-dependent, require the interaction of zinc ion which is thought to coordinate with the carbonyl oxygen of the substrate and thereby reduce the electron density at the carbonyl carbon.[14] A lactate dehydrogenase (E.C. 1.1.1.27) utilizes its arginine 171 and histidine 195 to form salt bridges with a substrate.[15] The inhibitory effect of water suggests the strong coordination of magnesium ion to either dihydropyridine derivative or α-keto ester, or both.

Since BNAH itself does not induce asymmetry in the product, it is apparent that the chiral center in **1**, which is separated from the reaction center by five atoms, is respon-

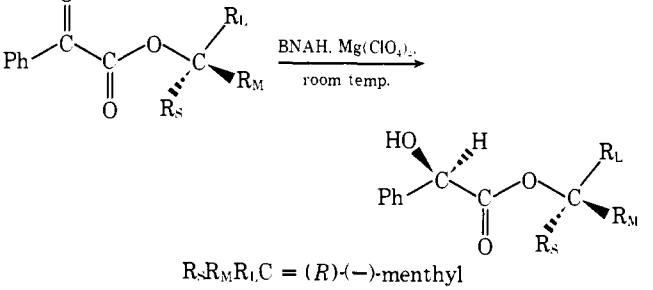
Table II. Asymmetric Reduction of Ethyl Benzoylformate with (*R*)-(−)-*N*-α-Methylbenzyl-1,4-dihydronicotinamide Derivatives[a]

Reducing reagent	$[\alpha]^{24}D$ of **1**	Ethyl mandelate obtained: $[\alpha]^{24}D$[b]	Configuration	Optical purity,[c] %
1a	−173° [d]	−20°	*R*	20[e]
1b	−74° [d, f]	−19°	*R*	18
1c	−34° [g]	−10°	*R*	11

[a] In the presence of magnesium perchlorate at room temperature for 44 hr. Yields of products are quantitative. [b] In 99.5% ethanol. [c] $[\alpha]^{24}D$ −104° is taken as rotation of pure ethyl (*R*)-(−)-mandelate: R. Roger, *J. Chem. Soc.*, 2168 (1932). [d] In acetonitrile. [e] Oxidized **1a** was isolated as the reduced form ($[\alpha]^{24}D$ −173°) in 90% yield. [f] Contaminated by small amount of the enantiomer. [g] In a mixture of benzene and methanol (1:1 v/v).



sible for the asymmetric reduction. Although it is difficult to rationalize the stereochemistry observed in the present model reaction, we have found that the reduction of (*R*)-(−)-menthyl benzoylformate with BNAH in the presence of magnesium perchlorate in acetonitrile afforded (*R*)-(−)-menthyl (*R*)-(−)-mandelate with 6% optical purity.[16] This fact suggests that the stereochemistry of the reaction can be predicted by the Prelog generalization.[17,18] Assum-



$R_SR_MR_LC$ = (*R*)-(−)-menthyl

ing the same stereochemistry (namely, the trans configuration for two carbonyl groups in α-keto esters) and the least hindered transition state[21,22] for the reaction of **1**, the molecular arrangement diagrammatically illustrated in Figure 1[23] is proposed and predicts that the pro-*R* hydrogen in **1** is transferred to the substrate; steric effects of the (*R*)-(+)-α-methylbenzylamine moiety in **1** prevent the pro-*S* hydrogen from participating in the reaction.[24] It is reported that steric interference of the adenyl group distinguishes the

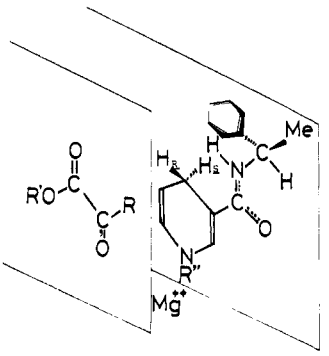


Figure 1. Schematic representation for stereochemical interpretation of the reaction.

pro-*R* hydrogen from the pro-*S* counterpart in NAD(P)H and its analog.[25] The stereochemistry of the reactions with the enantiomers of **1** as well as the effect of the prochirality of the C_4 hydrogens are currently under investigation in these laboratories.

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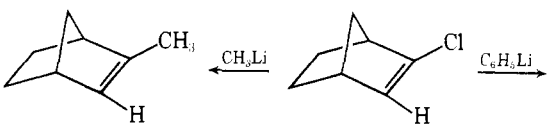
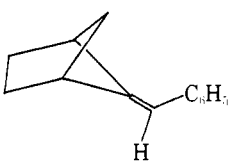
Norbornyne[1]

Sir:

The reaction of organolithium reagents with cyclic vinyl halides has been much discussed as a route to strained cycloalkynes.[2,3] Thus, it was of interest that the reactions of methyllithium and phenyllithium with 2-chlorobicyclo[2.2.1]heptene (**1**) gave 2-methylbicyclo[2.2.1]heptene (**2**)[4] and 5-benzalbicyclo[2.1.1]hexane (**3**)[5] in 73 and 62% yields, respectively. Even more surprising was the observation that optically active **1** gave optically active **2** with retention of stereochemistry.[6] These observations, in particu-



2 1



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lar those associated with the formation of **2**, rule out the intermediacy of a symmetrical intermediate in the reaction of **1** with certain organolithium reagents. The failure of **1** to react with methyllithium to form a cycloalkyne can be rationalized in terms of the large amount of strain which would occur if a triple bond were to be incorporated into the bicyclo[2.2.1]heptyl skeleton. This rationalization would appear to be justified by the difficulty observed in the generation of cyclopentyne from a variety of precursors.[2] With this background in mind, we wish to report that the reaction of **1** with *n*-butyllithium takes yet a different mechanistic pathway, which is best explained by the intermediacy of bicyclo[2.2.1]heptyne (norbornyne).

Treatment of a solution of **1** with 4–5 equiv of *n*-butyllithium in tetrahydrofuran[7] at 25° for 2 hr, followed by quenching with water, gave 80% of a 1:1.6 mixture of 3-*n*-butyltricyclo[2.2.1.$0^{2,6}$]heptane (**4**) and 2-*n*-butylbicyclo[2.2.1]heptene (**5**). In order to elucidate the mechanistic pathway from **1** to **4** and **5**, three sets of labeling experiments were carried out. In the first of these studies, the reaction mixture was quenched with deuterium oxide instead of with water. This gave an 88% yield of a 1:1.6 mixture of **4** (no deuterium incorporation) and **5**. Both mass