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Kinetics and Mechanism of Aziridine Synthesis from Ketoxime with Lithium Aluminum Hydride[1)]

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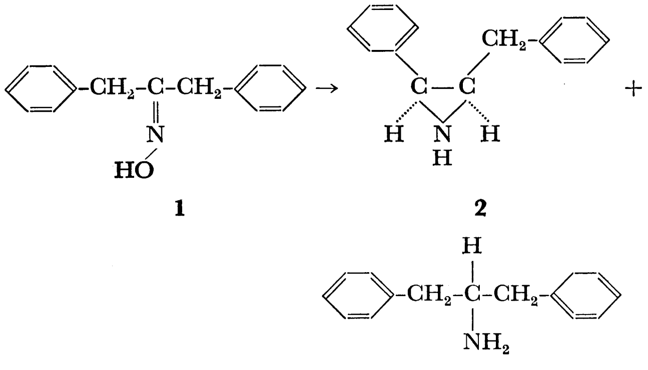
The stoichiometry and rate of the reaction of dibenzyl ketoxime (**1**) with lithium aluminum hydride in tetrahydrofuran leading to *cis*-2-benzyl-3-phenylaziridine (**2**, 92%) and 2-amino-1,3-diphenylpropane (**3**, 8%) were determined by gas meter and vpc. It was found that the aziridine formation proceeds with an immediate evolution of 1 mole of hydrogen followed by a slow liberation of a second mole of hydrogen and an accommodation of 1 equiv. of hydride into the molecule. Also, the formation has an induction period and there is a catalytic acceleration effect by the concurrently-formed minor product **3**. Combination of the previously-reported results and the present findings leads us to propose a mechanism by which an aluminum derivative rapidly obtained on addition of **1** to the solution of lithium aluminum hydride undergoes slow hydrogen elimination to afford an azirine intermediate, followed by reduction to the aziridine. Making use of the catalytic effect discovered, the reaction rate and yield of aziridine were increased by the addition to the reaction mixture of an amine, particularly a secondary amine such as *n*-butylmethylamine.

Although the principal products from the reductions of ketoximes with lithium aluminum hydride (LAH) had been reported to be the corresponding primary amines,[2)] we observed some years ago that the reactions of certain aryl ketoximes and bridged benzocyclene oximes mainly yielded the aziridine derivatives.[3)] Since then, this reaction has been considerably developed as a simple and convenient method for aziridine synthesis.[4−6)] During this development, some characteristic features of the reaction have been revealed. First, the reaction produces only *cis* aziridine. For example, dibenzyl ketoxime (**1**) leads to *cis*-2-benzyl-3-phenylaziridine. Secondly, aziridine ring-closure takes place on the side syn to the oxime configuration preferably to the side anti to it.[7)] This is entirely different from the Neber rearrangement, which has been reported to proceed independently of oxime configuration.[8)] Thirdly, aziridine ring-closure at a benzylic position is favored over that at an aliphatic position.[6,7)] Fourthly, when lithium aluminum deuteride (LAD) is used, one deuterium atom is incorporated into the carbon originally carrying the oximino function, but not at all into other carbons.[3,4d,6)] Fifthly, no aziridine is formed from *N*-(α-methylphenethyl)hydroxylamine so that it is very unlikely that the reaction proceeds through a hydroxylamine intermediate.[9)] With these findings in mind, we undertook a kinetic investigation in order to get further insight into the mechanism of this reaction and also to improve the reaction from a synthetic viewpoint.

Results and Discussion

As reported earlier,[4 ,5)] dibenzyl ketoxime (**1**) undergoes the reaction affording *cis*-2-benzyl-3-phenylaziridine (**1**) and 2-amino-1,3-diphenylpropane (**3**) in the isolated yields of 71—78% and about 8%, respectively. The present procedure was essentially the same as that reported, but it involved the use of a reaction mixture of LAH (0.25 M, 1.00 M in hydride) and **1** (0.167 M) in tetrahydrofuran.[10)] When reaction was complete, the mixture was treated with water to destroy the excess hydride and analyzed by vpc, showing the formation of **2** in 92% yield and **3** in 8% yield.



1 **2** **3**

The rate and stoichiometry were determined by measurement of evolving hydrogen with a gas meter and the results obtained are presented in Table 1 and Fig. 1. It is noted that about 1 mol (the amount actually found was 1.13 mol) of hydrogen is evolved very rapidly on mixing **1** with the LAH solution, the reaction then proceeding with slow evolution of a second

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1) Presented in part at the 19th Organic Reaction Mechanism Symposium of the Chemical Society of Japan in Yamagata, Oct., 1968.

2) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, New York, N. Y. (1956).

3) K. Kitahonoki, K. Kotera, Y. Matsukawa, S. Miyazaki, T. Okada, H. Takahashi, and Y. Takano, *Tetrahedron Lett.*, **1965**, 1059.

4) a) K. Kotera, M. Motomura, S. Miyazaki, T. Okada, and Y. Matsukawa, *Tetrahedron*, **24**, 1727 (1968). b) K. Kotera, S. Miyazaki, H. Takahashi, T. Okada, and K. Kitahonoki, *ibid.*, **24**, 3681 (1968). c) K. Kitahonoki, Y. Takano, and H. Takahashi, *ibid.*, **24** 4605 (1968). d) K. Kotera, Y. Matsukawa, H. Takahashi, T. Okada, and K. Kitahonoki, *ibid.*, **24**, 6177 (1968).

5) K. Kotera and K. Kitahonoki, "Organic Syntheses," Vol. 48, p. 20 (1968).

6) K. Kotera and K. Kitahonoki, *Organic Preparations and Procedures*, **1**, 305 (1969).

7) K. Kotera, T. Okada, and S. Miyazaki, *Tetrahedron Lett.*, **1967**, 841; *Tetrahedron*, **24**, 5677 (1968).

8) H. O. House and W. F. Berkowitz, *J. Org. Chem.*, **28**, 307, 2271 (1963).

9) Footnote 26 in Ref. 5.

10) It is convenient to discuss the utilization of the reagent in terms of moles of hydride consumed per mole of compound.

Table 1. Kinetic analysis by gas meter[a)]

Reaction time hr	Hydrogen evolved	Hydride consumed	Hydride utilized for reduction
0	1.13	1.21	0.08
0.5	1.14	1.27	0.13
1.0	1.19	1.51	0.32
3.0	1.75	2.53	0.78
6.0	2.10	3.17	1.07
12.0	2.12	3.36	1.24

a) Units: mol for hydrogen and mol equiv for hydride.

1 mol of hydrogen (in total, 2.12 mol were evolved before cessation of reaction). At appropriate time intervals, the reaction mixture was hydrolyzed by addition of dilute sulfuric acid and the hydrogen evolved was determined to calculate the hydride consumed; this is shown in the second column of Table 1. The difference between the hydride consumed and the hydrogen evolved corresponds to the hydride taken up by the molecule of **1** for reduction; this is 1.24 mol equiv. at 100% reaction. It has been reported that the reduction of cyclohexanone oxime to cyclohexylamine requires 4 equiv of hydride, 2 for reaction and 2 for hydrogen evolution, and also that the reaction proceeds with a rapid evolution of 1 equiv. of hydrogen followed by a slow utilization of 2 equiv. of hydride for reduction and slow liberation of a second mole of hydrogen.[11)] In this connection, 100% formation of aziridine would require, after an immediate evolution of 1 mol of hydrogen, a slow utilization of 1 equiv of hydride for reduction and a slow liberation of a second mole of hydrogen. It is obvious that the first step in both the reactions with **1** and cyclohexanone oxime is the formation of an O–Al bond, as evidenced by the immediate evolution of hydrogen corresponding to the active hydrogen on the oxime function.[2,12)] If an aziridine is then formed as the only product, since the molecular formula is equal to that of an imine, the stoichiometry will involve utilization of 1 equiv. of hydride for reduction and the liberation of a second mole of hydrogen. Therefore, the stoichiometric difference between the formation of amine and that of aziridine will be indicated by the amount of hydride utilized for reduction; 2 equiv. or 1 equiv. In this connection, the results in Table 1 (1.24 mol equiv were utilized at the completion of reaction) are understood if one considers the formation of a mixture consisting of mostly **2** with a minor amount of **3**.

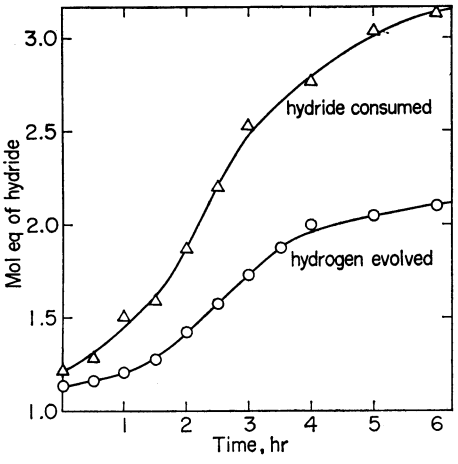


Fig. 1. Kinetic analysis by gas meter. At $t=0$, [**1**]=0.167 M and [LAH]=0.25 M in THF; reaction temp., 25°C.

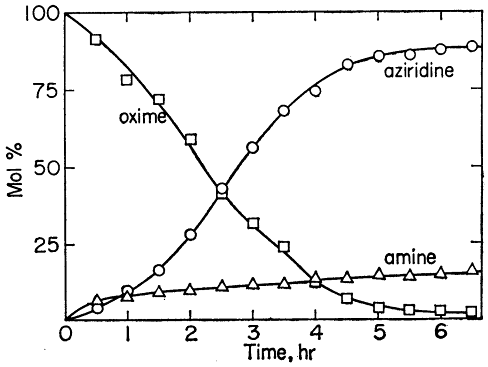


Fig. 2. Kinetic analysis by vapor phase chromatography. At $t=0$, [**1**]=0.167 M and [LAH]=0.25 M in THF; reaction temp., 26°C.

The results obtained by monitoring the reactant and products by vpc are shown in Fig. 2. Of note are the existence of an induction period in the reaction and the close resemblance between the curve for the slow evolution of hydrogen in Fig. 1 and that for the production of aziridine in Fig. 2. The vpc data were analyzed in our laboratory[13)] by a Melcom EA-7410 analog computer and it was found possible to accommodate the data by the following kinetic equations. An important implication of these equations

$$\text{Oxime} + \text{LAH} \xrightarrow{\text{very fast}} I_1 + H_2$$

$$I_1 \xrightarrow{k_1} \text{Amine} \qquad I_1\text{: Intermediate}$$

$$I_1 \xrightarrow{k_2\, C_{\text{Amine}}} \text{Aziridine}$$

is that the amine formed by k_1 has a catalytic acceleration effect upon the formation of aziridine with

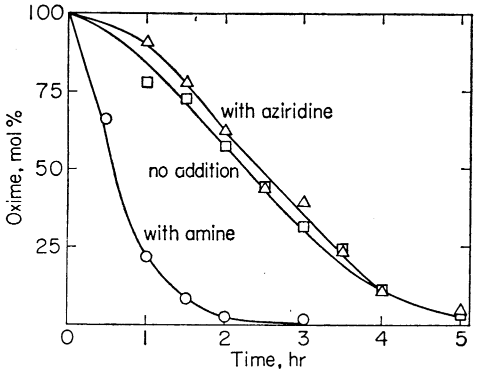


Fig. 3. Demonstration of catalytic effect by the amine. At $t=0$, [1]=0.167 M and [LAH]=0.34 M in THF; reaction temp., 26°C. The concentrations of **2** and **3** added were 0.167 M.

[11)] H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966).

[12)] W. T. Borden, *ibid.*, **90**, 2197 (1968).

[13)] We thank Dr. T. Takahashi and Mr. M. Shudo for the aid.

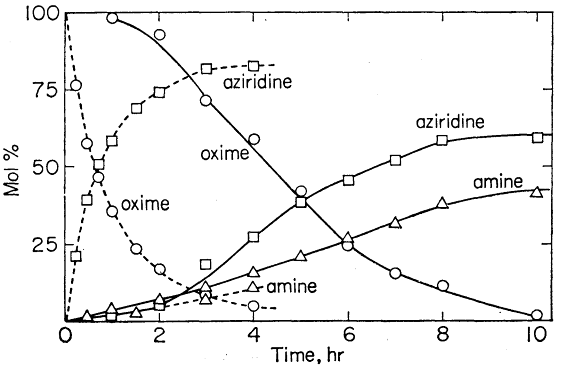
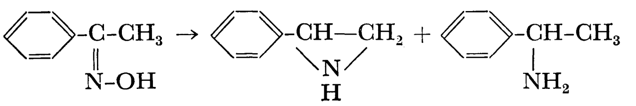


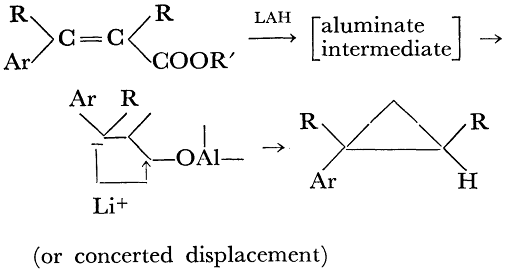
Fig. 4. Reaction of acetophenone oxime; solid lines for results without addition of n-butylmethylamine, dotted lines for those with addition. At $t=0$, [oxime] = 0.167 M and [LAH] = 0.30 M in THF; reaction temp., 40°C.

the rate coefficient k_2 C_{Amine}. Indeed, it was confirmed that addition of **3** to the reaction mixture enhances the reaction rate and shortens the induction period though the addition of **2** has no effect; these experiments are shown in Fig. 3.

Similar experiments were carried out for the reaction of *anti*-acetophenone oxime.[14] Figure 4 shows the results monitored by vpc. Again, treatment by the computer yielded equations of the same type as the above and suggested a positive catalytic effect by the by-product amine. The yield of 2-phenylaziridine was raised to 80% by addition of an amine, n-butylmethylamine, although it had been reported as 60% without the addition.



In the reaction with **1**, variation of the concentration of LAH did not affect the reaction rate or the aziridine yield. Therefore, the transition state in the rate-determining step must be of an intramolecular nature. Transformation of certain α,β-unsaturated carboxylic acids or esters into the corresponding cyclopropanes by reduction with LAH may be a related reaction. The ring-closing steps in these reactions have been suggested as intramolecular nucleophilic displacement reactions.[17,18]



(or concerted displacement)

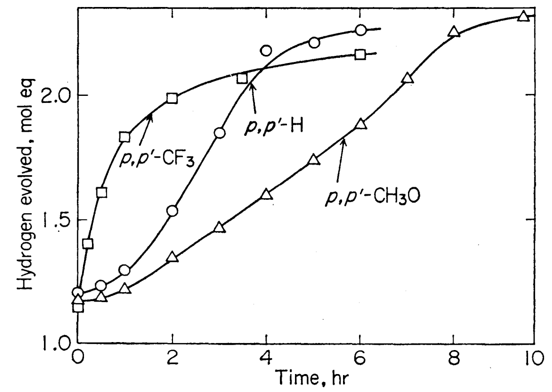
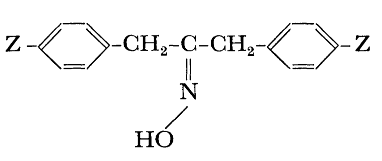


Fig. 5. Substituent effects. At $t=0$, [oxime] = 0.167 M and [LAH] = 0.25 M in THF; reaction temp., 26°C.

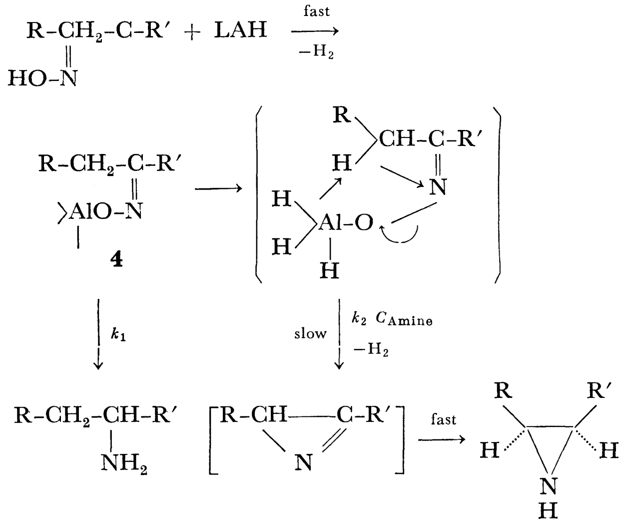
Studies of substituent effects were carried out with p,p'-di-(trifluoromethyl) and p,p'-dimethoxyl derivatives of **1** and the results obtained are shown in Fig. 5.



$Z = CH_3O,\ CF_3$

Shortening of the induction period and enhancement of the rate are noted with introduction of the electron-withdrawing trifluoromethyl substituents and a rate decrease is noted with that of the electron-donating methoxy substituents. Therefore, increasing capability of the proton α to the aryl group for elimination increases the overall rate.

On the basis of the present data and previous findings (see Introduction) we propose that the aziridine formation proceeds by the rapid formation of an aluminate intermediate **4** on addition of the oxime to the LAH solution, followed by a concerted intramolecular displacement to give an azirine and, finally, saturation to the aziridine. This may be depicted as follows.



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[14] The anti configuration has been reported by Karabatsos and Taller.[15] We have determined by NMR that the aluminate of this oxime has the same configuration and no alternation of it at the reaction temperature.[16]

[15] G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3347 (1968).

[16] We thank Mr. Y. Terui for this determination.

[17] M. J. Jorgenson and A. W. Friend, *J. Amer. Chem. Soc.*, **87**, 1815 (1965).

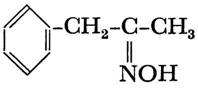
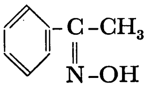
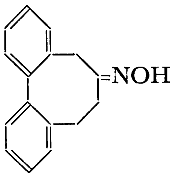
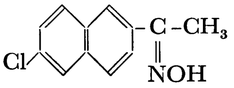
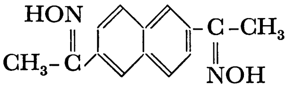
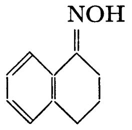
[18] R. Y. Uyeda and D. J. Cram, *J. Org. Chem.*, **30**, 2083 (1965)

Table 2. Solvent effect

Solvent	Product, %		Half life, hr	pK_a of conjugated acid[a]
	Amine	Aziridine		
Tetrahydrofuran	13	86	2.3	−2.08
2-Methyltetrahydrofuran	23	68	3.3	−2.65
Tetrahydropyran	21	71	3.0	−2.79
Dimethoxyethane	9	86	3.5	−3.27(−2.97)
Diethyl ether	70	25	4.5	−3.59

a) E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, **84**, 1684 (1962).

Table 3. Effects of added *n*-butylmethylamine[a]

Ketoxime	With addition		Without addition	
	Aziridine, %	Amine, %	Aziridine, %	Amine, %
	75	15	30	60
	82	11	57	47
	50	20	12	60
	51		10	
	30		2	
	60	35	20	75

a) One mol of the amine was added per mol of lithium aluminum hydride.

The by-product amine is considered to activate one of the aluminate hydrogens in **4** thereby facilitating proton elimination. Reduction of the azirine with LAH will take place from a sterically less hindered side resulting in the *cis* aziridine.[2–6,19] Since according to the proposed mechanism hydrogen is incorporated in the steps from the azirine to the aziridine and from **4** to the amine, the results obtained with LAD (Introduction)[3,4d,6] are reasonably accommodated.

Solvent Effects. Various solvents were tested in the reaction with **1**. Yields of products and half-lives of the reaction were as shown in Table 2. Relatively high yields of **2** were found in solvents having high solvation ability such as tetrahydrofuran and dimethoxyethane, while a low yield was found in ether, which has a low solvation ability.

Influence of Added Amine on Yield. Several kinds of amine were added to the reaction mixture to improve the reaction; the results obtained are shown in Fig. 6. Of the amines tested, secondary *n*-butylmethylamine gave the best result. Reactions with

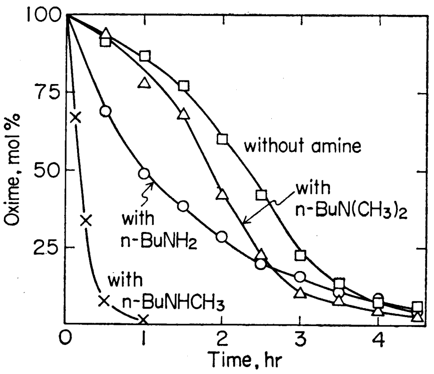


Fig. 6. Catalytic effects by various amines. At $t=0$, [**1**]=0.167 M, [LAH]=0.70 M, and [amine catalyst]=0.30 M in THF; reaction temp., 26°C.

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[19] A Hassner and W. Fowlen, *J. Amer. Chem. Soc.*, **90**, 2869 (1968).

and without added *n*-butylmethylamine were carried out with the oximes listed in Table 3. It is clearly seen that the addition increases the yield of aziridine and decreases the yield of amine; with benzylmethyl ketoxime, for example, aziridine increases from 30% to 75% and amine decreases from 60% to 15%.

None of the experimental results so far obtained are inconsistent with the above-proposed mechanism.

Experimental

Materials. Purification of lithium aluminum hydride was carried out by the method of Davis *et al.*[20] Forty grams of LAH purchased from Metal Hydrides Inc. was added to 500 ml of anhydrous ether, refluxed for several days under argon atmosphere, and filtered. The filtrate was concentrated to a volume of 50 ml under reduced argon atmosphere, mixed with anhydrous benzene which had been distilled over LAH, and stored for several hours in an ice bath to deposit 23 g of prismatic crystals. LAH thus purified was completely soluble in THF. Commercially available THF was refluxed for three days over LAH under argon atmosphere and distilled. Two further distillations over LAH then provided THF suitable for the present use.

Dibenzyl Ketoxime. A solution of 50 g of dibenzyl ketone (Tokyo Kasei, GR. grade) in 100 ml of pyridine was added to a solution of 10 g of hydroxylamine hydrochloride in 30 ml of water and 30 ml of alcohol. After being stirred for 2 hr at room temperature, the reaction mixture was poured into water and extracted with ether. The ether layer was washed with dilute hydrochloric acid, dilute sodium carbonate, and water, and dried over sodium sulfate. Evaporation of the solvent followed by recrystallization from a mixture of hexane and ether yielded 50 g of dibenzyl ketoxime, mp 123—124°C.

Vapor Phase Chromatography. Concentrations of the reactants and reaction temperatures in the reactions analyzed by vpc are indicated in the captions of the figures. The analyses were carried out on a Hitachi gaschromato Model K-53 equipped with a hydrogen flame ionization detector using a 1 m×3 mm stainless steel column.

Procedure-A: A column packed with 4% KF-54 on 60—80 mesh Chromosorb W was used for analysis of **1**, **2**, and **3**; benzyl *p*-methylbenzyl ether was used as an internal reference. The retention times of benzyl *p*-methylbenzyl ether, **3**, **2**, and **1** were 6.8, 9.0, 13.0, and 16.5 min, respectively, at 170°C with 1.0 kg/cm^2 of N_2.

Procedure-B: A column packed with 10% KF-54 on 80—100 mesh Chromosorb W was used for analysis of acetophenone oxime, 2-phenylaziridine, and 1-phenylethylamine, using pentamethyl benzene as an internal reference. The retention times of the amine, the aziridine, pentamethylbenzene, and the oxime were 7.0, 16.2, 26.0, and 41.3 min, respectively, at 70°C with 1.4 kg/cm^2 of N_2.

Kinetic Analysis by Gas Meter. Hydrogen Evolved. A 100 ml three-necked flask equipped with a magnetic stirrer was kept in a constant temperature bath. A glass tube connected one neck of the flask to a trap which was kept at −50°C in a dry ice-acetone bath, and an exit to the trap was connected to a buret adjusted by a water level. The flask was flushed with argon and stoppered with a gum cap. When the water level of buret became constant, 15.0 ml of the LAH solution was injected into the flask through the gum cap, then the oxime solution was added over a period of 2 min under stirring. A control experiment was performed by addition of the reaction solvent containing no oxime to the LAH solution. Concentrations of the reactants and reaction temperatures are shown in the captions of the figures. Hydrogen evolved was measured at appropriate time intervals with the buret.

Hydride Consumed. A known volume of the reaction mixture was injected through the gum cap and decomposed by 5% sulfuric acid with ice-water cooling. Hydrogen liberated was measured with the buret. Subtraction of the amount of hydrogen thus-liberated at a given reaction time from the amount liberated at zero reaction time corresponds to the amount of hydride consumed.

We are indebted to Dr. K. Kitahonoki for his encouragement.

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[20] W. D. Davis, L. S. Mason, and G. Stegeman, *J. Amer. Chem. Soc.*, **71**, 2775 (1949).