Regio- and Stereoselective Cross-aldol Reactions *via* Dialkylboryl Triflates

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New borylating reagents, (Bu_2BOTf and 9-BBNOTf), were prepared in high yields. The triflates reacted with enolizable ketones in the presence of tertiary amines to generate selectively one of the regioisomers of vinyloxyboranes by the choice of the reagents (the dialkylboryl triflates and tertiary amines) under mild reaction conditions. Vinyloxyboranes thus generated showed remarkable reactivity toward aldehydes to give only one regioisomer of the corresponding cross-aldols in good yields. High stereoselectivity was also observed in these reactions.

Recently, attention is focussed on the cross-aldol reaction, a most useful means of organic synthesis, and various efficient intermediates such as enolates and their equivalents have been worked out.[1] Nevertheless, the methods so far reported are not generally feasible because of difficulties in regio- and stereoselective generation of the enolates from one of carbonyl compounds.

Vinyloxyboranes react easily with various carbonyl compounds to give corresponding β-hydroxy ketones and β-hydroxy esters under mild conditions.[2] Despite the synthetic use of vinyloxyboranes, no general and convenient methods for the direct formation of these key intermediates from ketones was reported until 1976.[3]

We prepared dialkylboryl triflates, a new class of borylation reagents, from borane derivatives and trifluoromethanesulfonic acid. The triflates (trifluoromethanesulfonates) react smoothly with various ketones in the presence of tertiary amines, giving the corresponding vinyloxyboranes. The reactions using these enolates represent new regioselective cross-aldol reactions under mild conditions.[3] In this paper, we wish to report on the extension of our works.

Results and Discussion

Design and Synthesis of Dialkylboryl Triflates. We prepared a new borylation reagent which has potential utility for the formation of vinyloxyboranes with enolizable ketones under mild conditions. Dialkylboryl carboxylates, derivatives of dialkylboric acids, were reported to be easily formed by the reaction of trialkylboranes with carboxylic acids.[4] This promoted us to prepare dialkylboryl triflate which has a better leaving group than dialkylboryl carboxylate by the reaction of equimolar amount of borane derivatives and trifluoromethanesulfonic acid.

$Bu_3B + TfOH \longrightarrow Bu_2BOTf$ 84%

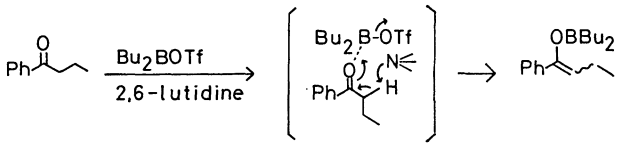
9-BBN + TfOH ⟶ 9-BBNOTf 85%

(9-Borabicyclo[3,3,1]nonane)

Scheme 1.

The reactions proceeded quite smoothly at room temperature, the corresponding dialkylboryl triflates being isolated in high yields by distillation.[5] We attempted to prepare anologous compounds by the combined use of borane derivatives or trialkylaluminum and various sulfonic acids (*e.g.* Bu_3B–$MeSO_3H$, Bu_3B–TsOH, Bu_3B–FSO_3H, Et_3B–TfOH, catecholborane–TfOH, 2,3-dimethylboracyclopentane–TfOH, Et_3Al–TfOH, *i*-Bu_3Al–TfOH). However, the desired boron and aluminum compounds were too unstable to be isolated in pure form for the generation of enolates.

Formation of Vinyloxyboranes from Ketones. 1-Pheny-1-butanone was treated with dibutylboryl triflate in the presence of 2,6-lutidine at room temperature. The NMR spectrum of the reaction mixture showed a signal at δ 5.4 assigned to a vinyl proton of dibutyl (1-phenyl-1-butenyloxy)borane, indicating that tertiary amine promotes the condensation reaction between ketones and dibutylboryl triflate and acts as the proton accepter (Scheme 2).



Scheme 2.

This is the first example for the formation of enolate from ketone by the combined use of Lewis acid and Lewis base.

The vinyloxyborane thus generated in situ was allowed to react with 3-phenylpropanal at room temperature for the formation of the cross-aldol (**1**) (Table 1).

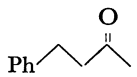
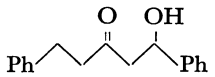
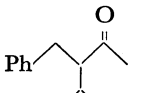
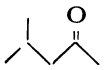
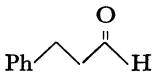
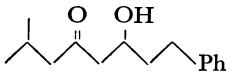
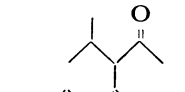
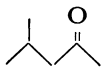
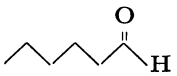
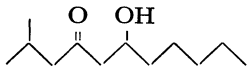
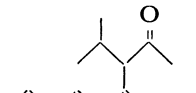
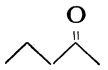
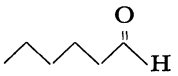
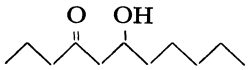
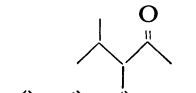
Table 1. Effects of amines and solvents on the yield of 1,5-diphenyl-2-ethyl-3-hydroxy-1-pentanone[a]

Amine	Solvent	Yield of **1**/%
2,6-Lutidine	Hexane	83
	Diethyl ether	77
	Tetrachloromethane	70
N,*N*-Diisopropylethylamine	Hexane	74
Tributylamine	Hexane	65
Protonsponge	Hexane	38

a) The reactions were carried out at room temperature overnight.

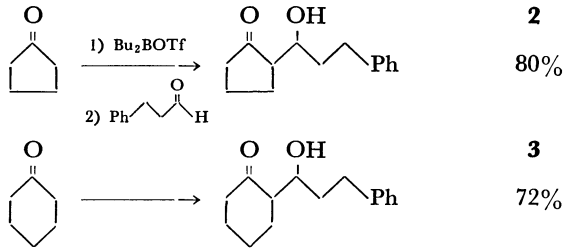
The combined use of 2,6-lutidine and hexane afforded the corresponding aldol in the highest yield. The reaction conditions were applied to the reactions of cyclic ketones such as cyclopentanone or cyclohexanone with 3-phenylpropanal. However, no corresponding cross-aldols could be obtained in satisfactory yield, presumably because of the self-aldol type reactions of starting ketones. In order to avoid such undesirable side reactions, preparation of the vinyloxyboranes and

Table 2. Synthesis of aldols using dibutylboryl triflate from ketones and aldehydes

	Ketone	Aldehyde	Product (Yield/%)	
4		PhCHO	 (84)	 (≈0)
5			 (82)	 (≈0)
6			 (70)	 (≈0)
7			 (65)	 (≈0)

the subsequent reaction with aldehydes were carried out at lower temperature (−78 °C).

This gave better results in the formation of the cross-aldols (Scheme 3).



Scheme 3.

Regioselectivity. In order to examine the regioselection of the new method, methyl ketones were allowed to react with aldehydes using dibutylboryl triflate under similar conditions. The results are given in Table 2.

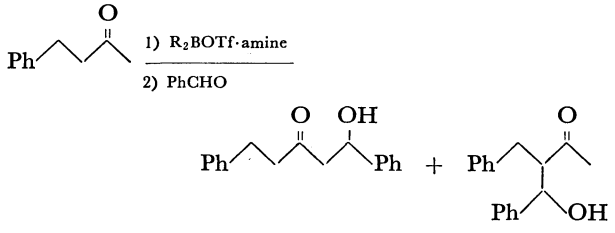
Only one of the regioisomers of cross-aldols was product without being accompanied by detectable amount of the other regioisomers. The results are interpreted by considering vinyloxyboranes to be generated through kinetically controlled steps.

The regioselectivity was examined by changing the combination of the triflates and amines in the reaction of 4-phenyl-2-butanone with benzaldehyde in ether at −78 °C (Table 3).

The results show that the ratio (**A**/**B**) of regioisomers great depends on the properties of the triflates and amines employed. The use of 9-BBNOTf and 2,6-lutidine afforded a remarkably high ratio (**A**/**B**=12/88) in contrast with the ratio of Bu_2BOTf and *N*,*N*-diisopropylethylamine (**A**/**B**=100/0).

Tertiary amines employed in the borylation also affected the yield and selectivity of the produced aldol greatly (Table 4).

Table 3. Ratios of regioisomers of the cross-aldol (**8**) by the combination of triflates and amines[a)]



Triflate	Amine	Ratio(**8A**:**8B**)
Bu_2BOTf	*N*,*N*-Diisopropylethylamine	100: 0
	2,6-Lutidine	69:31
9-BBNOTf	*N*,*N*-Diisopropylethylamine	38:62
	2,6-Lutidine	12:88

a) The reaction time for the generation of vinyloxyborane was 15 min and for the subsequent reaction with benzaldehyde 3 h at −78 °C.

Table 4. Ratio of regioisomers by the combination of 9-BBNOTf and amine[a)]

Amine	Temp/°C	Yield/%	Ratio(**8A**:**8B**)
2,6-Lutidine	−78	70	12:88
	−50	44	18:82
Tributylamine	−78	72	19:81
N,*N*-Diisopropylethylamine	−78	73	38:62
2,5-Lutidine	−78	34	56:44
Pyridine	−78	30	36:64

a) Reaction conditions the same as those in Table 3.

It was confirmed that the use of 2,6-lutidine at −78 °C gives a satisfactory yield and the highest ratio. For the formation of vinyloxyborane, the ef-

Table 5. The effect of time on the ratios of the regioisomers by the use of 9-BBNOTf at −78 °C[a)]

Time/h	Yield/%	Ratio(**8A**:**8B**)
0.25	70	12:88
2	80	6:94
3	90	2:98
4	92	1:99
16	96	0:100

a) Reaction conditions the same as those in Table 3.

fect of reaction time was studied in the same reaction (Table 5).

The synthetic yield and selectivity increased with increase in reaction time, complete reverse of selectivity being achieved in a different way from the case in which dibutylboryl triflate was used under kinetic controlled conditions. This revealed the fact that the vinyloxyborane kinetically formed isomerizes easily to the other more stable isomer. No such complete isomerization has been reported, though kinetically controlled enolates or enol ethers isomerize to thermodynamically stable ones in the presence of proton donor till two isomers equilibrate.[6)]

The method using 9-BBNOTf with 2,6-lutidine was applied to the reactions of other methyl ketones with various carbonyl compounds (Table 6).

The procedure provides an efficient method for the preparation of one regioisomer of cross-aldols from thermodynamically stable enolates of methyl ketones.

Stereoselectivity. The aldol reaction was subjected to kinetic stereoselection, with (*Z*)-enolate giving predominantly the erythro aldol, and (*E*)-enolate leading preferentially to threo isomer.[7)] This suggests that high stereoselection takes place in the present aldol reaction, since the key intermediate, vinyloxyborane, might be generated stereoselectively under suitable conditions. Thus, the reaction of 3-pentanone with benzaldehyde was taken as a model for examining selectivity. The results obtained under various conditions are summarized in Table 7.

It is apparent that reaction temperature is the most important factor to affect the selectivity. The reaction at lower temperature (−78 °C) gave rise to a remarkably high stereoselection (erythro/threo=96:4), and a fairly good selection at room temperature. The high selectivity of the reaction is explained by assuming that the initial generation of vinyloxyborane and subsequent reaction with benzaldehyde proceed in stereoselective manner at low temperature (Scheme 4).

Attempted Reactions of Vinyloxyboranes to Some Electrophiles.

The reactivity of vinyloxyboranes generated from

Table 6. Synthesis of aldols by the use of 9-BBNOTf from ketones and carbonyl compounds

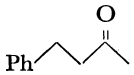
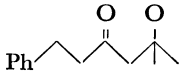
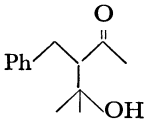
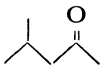
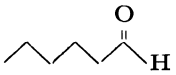
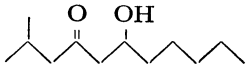
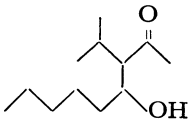
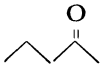
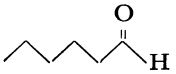
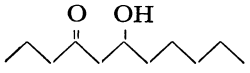
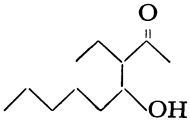
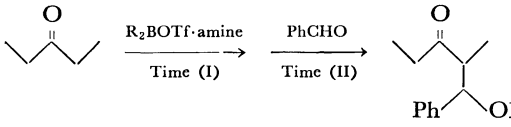
	Ketone	Carbonyl compounds	Product (Yield/%)	
9			 (≈0)	 (63)
10			 (≈0)	 (67)
11			 (≈0)	 (78)

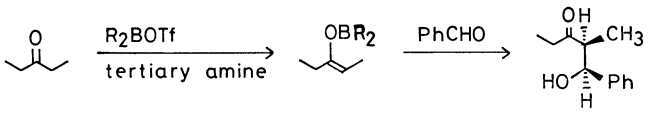
Table 7. Effect of the triflates and amines on the ratios of the stereoisomers



(**12**)

R_2BOTf	Amine	Solvent	Temp	Time (I)	Time (II)	Yield/%	e : t [a)]
Bu_2BOTf		Hexane	r.t.	1 min	overnight	60	70:30
9-BBNOTf		Hexane	r.t.	1 min	overnight	49	75:25
Bu_2BOTf	Et_3N	Ether	−78 °C	15 min	3 min	92	96: 4
9-BBNOTf		Ether	−78 °C	16 h	3 min	79	96: 4

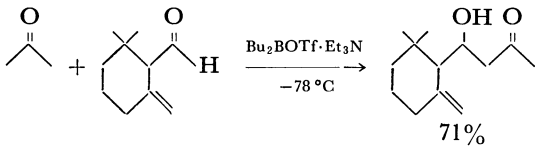
a) The ratios (erythro:threo) were determined on the basis of their NMR spectra.



Scheme 4.

3-pentanone was examined for various electrophiles such as ethyl acetate, acetic anhydride, acetal, 1-phenyl-1-propanone and benzyl bromide. The electrophiles were recovered nearly quantitatively when the reactions were carried out by the two methods (Tables 2 and 6). The utility of the present procedure in the preparation of vinyloxyboranes is shown clearly in the difference of reactivity toward aldehydes and other electrophiles.

The reaction with γ-cyclocitral was achieved in 71% yield without any isomerization of the vinyl group (Scheme 5).[8]



Scheme 5.

In this case, use of alkali metal enolates or titanium tetrachloride with silyl enol ether of acetone on an acid or base sensitive double bond of γ-cyclocitral was unsatisfactory, the desired product not being obtained in satisfactory yield. The present methods might provide the mildest conditions among the procedures so far employed.

Summary. Various directed cross-aldols with high regio- and stereoselectivities were prepared in good yields starting from ketones with aldehydes by using dialkylboryl triflates and tertiary amines.

Experimental

Materials. Tributylborane was prepared from boron trifluoride etherate and butylmagnesium bromide in dry ether under argon. 9-BBN was prepared from borane–THF complex and 1,5-cyclooctadiene in dry THF under argon. Commercially available trifluoromethanesulfonic acid was distilled under argon before use.

Dibutylboryl Triflate.[5] Trifluoromethanesulfonic acid (12.51 g, 83.3 mmol) was added to tributylborane (15.16 g, 83.3 mmol) at room temperature under argon. After being stirred for 3 h, the reaction mixture was distilled *in vacuo* under argon. Bp 37 °C/0.12 mmHg, 19.15 g (84%). IR (CCl_4): 1405, 1380, 1320, 1200, 1150 cm^{-1}.

9-BBN Triflate. Trifluoromethanesulfonic acid (18.75 g, 125 mmol) was added to 9-BBN (15.33 g, 127 mmol) in hexane (100 ml) under argon. After being stirred overnight, the reaction mixture was concentrated and distilled *in vacuo* under argon. Bp 38 °C/0.03 mmHg, 28.84 g (85%). IR (CCl_4): 1400, 1240, 1080 cm^{-1}.

Reaction of 1-Phenyl-1-butanone with 3-Phenylpropanal Using Dibutylboryl Triflate (1). To a hexane solution (2 ml) of dibutylboryl triflate (0.253 g, 0.92 mmol) and 2,6-lutidine (0.099 g, 0.92 mmol) was added a hexane solution (1 ml) of 1-phenyl-1-butanone (0.137 g, 0.92 mmol) under argon at room temperature. After stirring for 10 min, a hexane solution (1 ml) of 3-phenylpropanal (0.124 g, 0.92 mmol) was added at room temperature and the reaction mixture was allowed to stand overnight. The mixture was added to phosphate buffer (pH 7.0) and extracted with ether. After removal of ether, the mixture was treated with 30% H_2O_2 (1 ml) in MeOH (3 ml) for 2 h and water was added. The mixture was concentrated *in vacuo* in order to remove most of the methanol and extracted with ether. The ethereal layer was washed with a 5% solution of $NaHCO_3$ and a saturated solution of NaCl, and dried over Na_2SO_4, the solvent being removed. The crude oil was purified by preparative TLC to give 1,5-diphenyl-2-ethyl-3-hydroxy-1-pentanone (0.233 g, 83%).

IR (neat); 1670 cm^{-1}: NMR (CCl_4) δ 7.20—8.10 (broad, 5H), 7.10 (s, 5H), 3.91 (m, 1H), 3.50 (m, 2H), 2.40—3.10 (broad, 2H), 1.40—2.10 (broad, 4H), 0.81 (t, 3H, J=6 Hz). The other reactions given in Table 1 were carried out according to the same procedure.

Reaction of 2-Methyl-4-pentanone with 3-Phenylpropanal Using Dibutylboryl Triflate (5). To an ether solution (1.5 ml) of dibutylboryl triflate (0.301 g, 1.1 mmol) and *N,N*-diisopropylethylamine (0.142 g, 1.1 mmol) was added dropwise an ether solution (1.5 ml) of 2-methyl-4-pentanone (0.100 g, 1.0 mmol) at −78 °C under argon. After being stirred for 30 min, an ether solution (1.5 ml) of 3-phenylpropanal (0.134 g, 1.0 mmol) was added at that temperature. The reaction mixture was allowed to stand for 1 h, then added to phosphate buffer (pH 7.0) at room temperature and extracted with ether. After removal of ether, the crude oil was treated as described above and purified by TLC to give 6-hydroxy-2-methyl-8-phenyl-4-octanone (0.192 g, 82%). IR (neat); 1695 cm^{-1}: NMR (CCl_4); δ 7.11 (s, 5H), 4.00 (m, 1H), 3.05 (broad, s, 1H), 2.06—2.92 (m, 6H), 1.70—2.00 (m, 3H), 0.86 (d, 6H), J=7 Hz.

The other reactions **2**, **3**, **4**, **6**, and **7** (Scheme 2 and Table 2), were carried out according to the same procedure (triethylamine was used as proton accepter in Reactions **4**, **6**, and **7** instead of *N,N*-diisopropylethylamine.), the physical and analytical data being given in Table 8. Absence of the regioisomers was determined by NMR or GLC (10% QF_1 at 130 °C).

Examination of Regioselectivity. Reaction of 4-Phenyl-2-butanone with Benzaldehyde (8). All the reactions (Tables, 3, 4, and 5) were carried out as follows: To a mixture of dialkylboryl triflate (2.00 mmol) and tertiary amine (2.00 mmol) in a solvent (3 ml) was added a solution (1.5 ml) of 4-phenyl-2-butanone (2.00 mmol) under argon. A solution (2 ml) of benzaldehyde (2.00 mmol) was added to the above mixture and allowed to stand for 3 h. The reaction mixture was added into phosphate buffer of pH 7.0 (5.0 ml), methanol (10 ml) and 30% H_2O_2 (5 ml) at 0 °C. After 15 min, the mixture was concentrated *in vacuo* in order to remove most of the methanol, extracted with dichloromethane and dried over $MgSO_4$, the solvent being then removed. The crude oil was purified by TLC, the regioisomers ((**8A**) and (**8B**)) being separated.

Reaction of 4-Phenyl-2-butanone with Benzaldehyde Using 9-BBN Triflate (8). To a solution of 9-BBN triflate (0.551 g, 2.04 mmol) and 2,6-lutidine (0.218 g, 2.04 mmol) in ether (6 ml) was added a solution of 4-phenyl-2-butanone (0.302 g, 2.04 mmol) in ether (3 ml) at −78 °C under argon. After the mixture had been stirred for 4 h, benzaldehyde (0.216 g, 2.04 mmol) in ether (3 ml) was added at the same temperature. The reaction mixture was left to stand for 3 h and worked up as described above. The resulting crude oil was purified by TLC to give 1-hydroxy-1,5-diphenyl-3-pentanone (**8A**) (0.006 g, 1%) and 3-benzyl-4-hydroxy 4-phenyl-2-butanone (**8B**) (0.476 g, 92%. (**8A**): IR (neat);

Table 8. Physical and analytical data for the products

Product	IR(C=O) ν/cm^{-1}	NMR (CCl_4), δ	Found(Calcd), % C	H
2	1725	7.12(s, 5H), 3.38—4.12(m, 1H), 3.60—4.12 (broad, 1H), 1.20—2.87 (broad, 11H)	76.67 (77.03)	8.46 (8.31)
3	1700	7.00(s, 5H), 3.95—4.20(broad, 1H), 3.20—3.72(m, 1H), 1.20—3.20 (broad, 13H)	77.42 (77.55)	8.79 (8.68)
4	1700	7.17(s, 5H), 7.08(s, 5H), 4.98(t, 1H), J=7.5 Hz, 3.24—3.64(broad s, 1H), 2.25—3.12(m, 6H)	80.12 (80.28)	7.54 (7.13)
6	1700	3.50—4.06(m, 1H), 3.00—3.50(broad, 1H), 2.38(t, 2H), J=7 Hz, 2.43(d, 2H), J=6 Hz	71.84 (71.94)	12.23 (12.09)
7	1700	3.61—4.21(m, 1H), 3.03—3.35(broad, 1H), 2.42(d, 2H), J=6 Hz, 2.30(t, 2H), J=6 Hz, 0.63—1.78(broad, 16H)	70.81 (70.92)	12.04 (11.90)
9	1700	7.14(s, 5H), 2.60—3.11(broad, 4H), 1.24(s, 6H)		
10	1700	3.53—4.07(broad, 1H), 3.00—3.53(broad, 1H), 2.31—2.90(m, 1H), 2.13(s, 3H), 0.60—1.73(m, 18H)	71.79 (71.94)	12.40 (12.09)
11	1700	3.40—4.30(m, 1H), 3.09—3.52(broad, 1H), 2.23—2.77 (m, 1H), 2.10(s, 3H), 0.60—1.97(m, 16H)	71.16 (70.92)	12.08 (11.90)

1700 cm^{-1}: NMR; 7.17 (s, 5H), 7.08 (s, 5H), 4.98 (t, 1H), J=7.5 Hz, 3.24—3.64 (broad s, 1H), 2.25—3.12 (m, 6H). Found; C, 80.12; H, 7.54%. Calcd for $C_{17}H_{18}O_2$; C, 80.28; H 7.13%. (**8B**): IR (neat); 1700 cm^{-1}: NMR (CCl_4); 7.22 (s, 5H), 7.05 (s, 5H), 4.63 (d, 0.96 H, J=5 Hz), 4.53 (d, 0.04 H, J=8 Hz), 3.70—4.20 (broad, 1H), 2.60—3.42 (broad, 3H), 1.73 (s, 0.12 H), 1.34 (s, 2.88 H). Found: C 80.12; H 7.50%. Calcd for $C_{17}H_{18}O_2$; C 80.28; H 7.13%. Reactions **9**, **10**, and **11**, listed (Table 6) were carried out according to the same procedure. Physical and analytical data are given in Table 8. Absence of the regioisomers was determined by GLC (QF$_1$, 130 °C).

*Examination of Stereoselectivity. Reaction of 3-Pentanone with Benzaldehyde (**12**).* The reactions were carried out by the same procedure as described in 2 mmol scale. IR (neat); 1695 cm^{-1}: NMR (CCl_4); 7.13 (s, 5H), 4.81 (d, 0.70—0.96 H), J=6 Hz, 4.55 (d, 0.04—0.30 H), J=9 Hz, 3.50—3.85 (broad, 1H), 1.78—2.95 (m, 3H), 0.60—1.10 (m, 6H). Found; C, 74.50; H 8.88%. Calcd for $C_{12}H_{16}O_2$; C 74.97; H 8.39%.

References

1) Reviews: a) A. T. Nielsen and W. H. Houlihan, *Org. React.*, **16**, 1 (1968); b) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp. 629—682; c) M. E. Jung, *Tetrahedron*, **32**, 3 (1976); d) J. d'Angelo, *ibid.*, **32**, 2979 (1976); e) T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **16**, 817 (1977). Recent papers: H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973); T. Mukaiyama, T. Sato, S. Suzuki, T. Inoue, and H. Nakamura, *Chem. Lett.*, **1976**, 95; I. Kuwajima, T. Sato, M. Arai, and N. Minami, *Tetrahedron Lett.*, **1976**, 1817; R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **99**, 1265 (1977); K. Maruoka, S. Hashimoto, Y. Kitagawa, H. H. Yamamoto, and H. Nozaki, *ibid.*, **99**, 7705 (1977); I. Kuwajima, T. Inoue, and T. Sato, *Tetrahedron Lett.*, **1978**, 4887; and references cited there in.

2) T. Mukaiyama, K. Inomata, and M. Muraki, *Bull. Chem. Soc. Jpn.*, **46**, 1807 (1973).

3) T. Mukaiyama and T. Inoue, *Chem. Lett.*, **1976**, 559; T. Inoue, T. Uchimaru and T. Mukaiyama, *ibid.*, **1977**, 153.

4) E. Negishi, *J. Chem. Ed.*, **52**, 159 (1975).

5) The reactions may proceed through a radical chain path, since they do not ccur in the absence of oxygen and can be initiated by the injection of air.

6) Ref. 1 b), pp. 546—570; H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

7) J.-E. Dubois and M. Dubois, *Tetrahedron Lett.*, **1967**, 4215; J.-E. Dubois and P. Fellmann, *C. R. Acad. Sci.*, **274**, 1307 (1972); *Tetrahedron Lett.*, **1975**, 1225; W. Fenzl and R. Köster, *Liebigs Ann. Chem.*, **1975**, 1322.

8) T. Mukaiyama, K. Saigo and O. Takazawa, *Chem. Lett.*, **1976**, 1033.