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REACTIONS BASED ON THE ONIUM SALTS OF AZAAROMATICS

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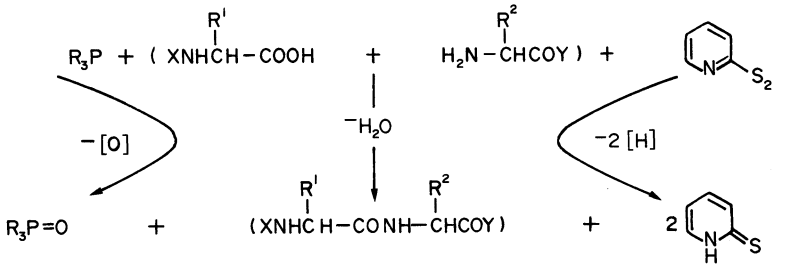
Abstract - Various kinds of compounds having active hydrogen, such as carboxylic acids, alcohols, and amides are effectively activated by the use of onium salts of azaaromatics. The condensation reactions, substitution reactions, and intramolecular dehydration reactions take place under extremely mild conditions.

A potential example of reactions which reach completion under neutral and mild conditions was demonstrated in the oxidation-reduction condensation (Ref. 1).



In these types of reactions, the utilization of the onium salts seems to be promising, since ionic character in the intermediate would result in the close proximity of reacting species around the onium salts, and thus the reaction would proceed smoothly under mild conditions. On the basis of this consideration, we have investigated the exploration of new synthetic reactions using the onium salts of azaaromatics, and it has become clear that the onium salts are effective for the activation of carboxyl and hydroxyl components in the presence of such weak bases as trialkylamines under neutralization conditions.

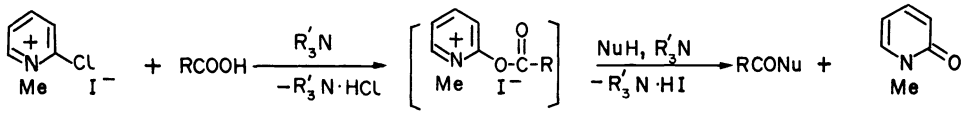
Recent advances in synthetic reactions using 2-halopyridinium, 2-fluorobenzothiazolium and 2-chlorobenzoxazolium salts will be described here under the following three headings:

I) Intermolecular Dehydration
   i) Activation of Carboxylic Acid
  ii) Activation of Hydroxylic Compound
II) Intramolecular Dehydration
III) The Preparation of Optically Active Substances

I) INTERMOLECULAR DEHYDRATION

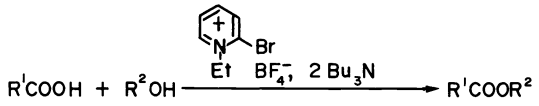
i) Activation of Carboxylic Acids

The principal consideration of these reactions is as follows: 2-Acyloxy-1-methylpyridinium iodide(2), an active acylating intermediate, would be produced easily and rapidly by a nucleophilic attack of a carboxylate ion on 2-chloro- or 2-bromo-1-methylpyridinium iodide(1), since the halogen atom at 2-position of 1 is easily replaced by the attack of nucleophiles. The intermediate(2) is in turn converted into a stable neutral molecule, i. e. the acylated products(3), 1-methyl-2-pyridone, and the ammonium salt by the attack of nucleophile in the presence of tertiary amine, a hydrogen iodide captor. Since all the reacting species are in close proximity to the central pyridinium salt, the condensation reaction should be entropically advantageous.

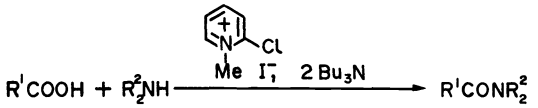


(1) (2) (3)

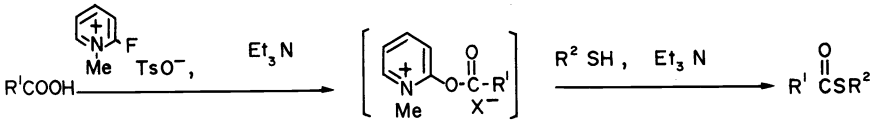
Based on these assumptions, the attempted formation of carboxylic esters from equimolar amounts of carboxylic acids and alcohols was investigated. When a mixture of carboxylic acid and alcohol was treated with 2-bromo-1-methylpyridinium tetrafluoroborate in the presence of tributylamine, the corresponding ester was formed in high yield. According to this method carboxylic acids, such as pivalic acid, trichloroacetic acid, and benzoylacetic acid, or various sterically hindered alcohols, such as t-butanol, were also successfully employed as reactants, and the corresponding carboxylic esters were produced in good yields by the equimolar reaction (Ref. 2).



When alcohols were replaced by primary or secondary amines as nucleophiles, the corresponding carboxamindes were obtained in high yields (Ref. 3). The preparation of carboxamides had been previously studied in detail by Sutherland et.al. using 2-iodopyridinium salt as a coupling agent (Ref. 4). However, using the iodo compound only modest yields were obtained. These results indicate the significant effect of the kind of halogen atom attached to 2-position, and that the introduction of chlorine or bromine atom is indispensable if favourable results are to be obtained.

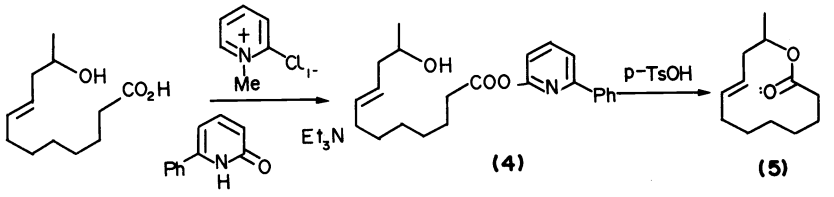


A similar procedure is not successful for the preparation of thiol esters from carboxylic acids and thiols, since competitive attack of thiols on the 2-chloropyridinium salts caused the reaction to become rather complex. However, this difficulty was overcome by use of a stepwise procedure and employment of a 2-fluoropyridinium salt. When a carboxylic acid was treated with a 2-fluoropyridinium salt and triethylamine in methylene chloride at low temperature, a 2-acyloxypyridinium salt was formed immediately, and subsequent addition of thiol afforded the corresponding thiol ester in high yield (Ref. 5).

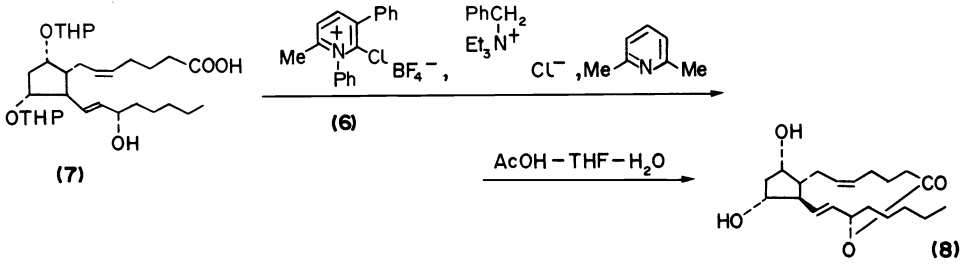


In the above mentioned reaction of carboxylic ester formation utilizing 2-halopyridinium salt, all reaction steps take place with involvement of the pyridinium salt, the condensation reaction should be favoured in term of entropy. Therefore, the macrocyclic lactone formation was investigated with the expectation that the reaction would proceed smoothly and effectively. When long chain ω-hydroxy carboxylic acids were treated with 2-chloro-1-methylpyridinium iodide and triehtylamine in refluxing acetonitrile, the corresponding macrocyclic lactones were obtained in reasonable but not satisfactory yields (Ref. 6).

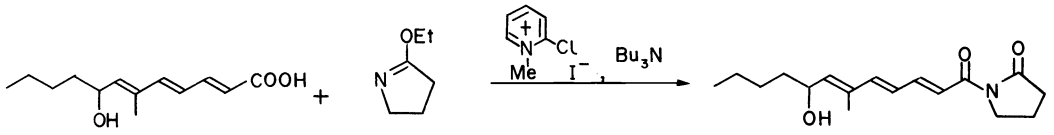
During the course of further investigation we have developed an efficient method for cyclization of long chain hydroxy acids to macrocyclic lactones via 6-phenyl-2-pyridyl esters(4) by a two-step procedure. This method was successfully applied to the syntheses of recifeiolide(5) and ricinelaidic acid lactone (Ref. 7), however, it was afraid that the use of p-TsOH in the second step for the cyclization of 6-phenyl-2-pyridyl ester would limit the application to more complex molecules. The previous method was, therefore, reexamined, and it was found that 2-chloro-6-methyl-1,3-diphenylpyridinium



tetrafluoroborate(6) is very effective for the lactonization reaction. For example, prostaglandin $F_{2\alpha}$ 9,11-bis(THP)ether(7) was converted into prostaglandin $F_{2\alpha}$ 1,15=lactone(8) in high yield by the treatment with 6, tetraalkylammonium chloride and 2,6-dimethylpyridine (Ref. 8).



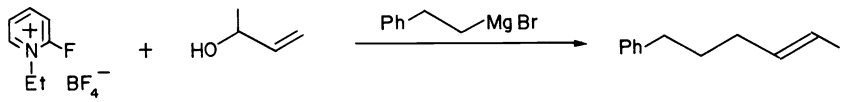
Lactim ethers can also act as nucleophiles, toward the active key intermediates, 2-acyloxypyridinium salts, and N-acyl lactams are obtained in good yield. By employing this method, dl-variotin(9), an antifungal antiobiotic, was synthesized in a rather simplified manner, that is, the reaction is carried out without protection of the hydroxyl group (Ref. 9).



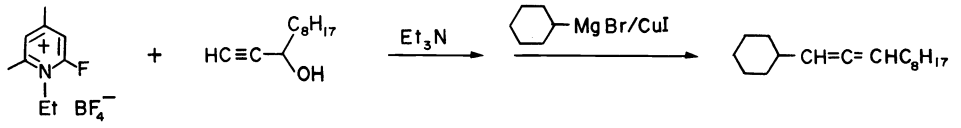
(9)

ii) Activation of Hydroxylic Compound

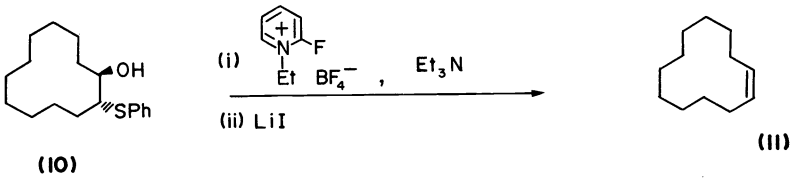
At first, the formation of 2-alkyloxypyridinium salt by the reaction of 2-chloropyridinium salt and alcohol was tried, but the introduction of an alkyloxy group into pyridinium salt could not be realized. 2-fluoropyridinium salt is more active and 2-alkyloxypyridinium salt was easily formed by the treatment of alcohol with 2-fluoropyridinium salt and tertiary amine. When 2-allyloxypyridinium salt was reacted with Grignard reagent, the corresponding cross coupling product was obtained in good yield. Primary and secondary alkylmagnesium bromide coupled with allyloxypyridinium salt at C-3 (S_N2' reaction) exclusively. On the other hand, in the case of phenylmagnesium bromide, the mode of action was dramatically changed to S_N2 reaction (C-1 carbon attack) exclusively (Ref. 10).



2-Propargyloxypyridinium salt can be also attacked by Grignard reagents at the γ-position in the presence of a catalytic amount of cuprous iodide, and the corresponding allene was obtained in high yield (Ref. 11).

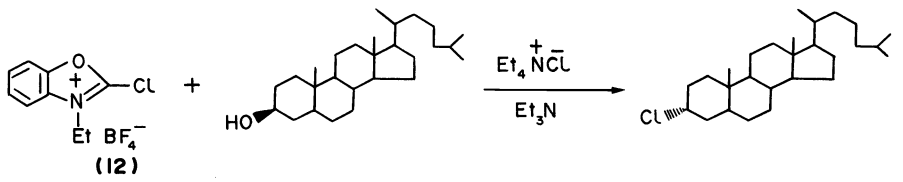


The reductive β-elimination of a β-hydroxysulfide is possible by utilizing a 2-fluoropyridinium salt. When an alkyloxypyridinium salt derived from a β-hydroxysulfide was treated with lithium iodide in refluxing acetone, the olefin was obtained in good yield. The stereospecificity of this reaction is demonstrated in the reduction of 2-phenylthiocyclododecanol. Erythro and threo(10) isomer gave exclusively trans- and cis-cyclododecene (11) respectively (Ref. 12).



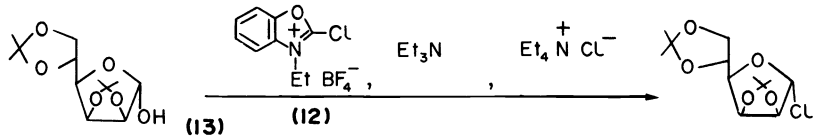
(10) (11)

2-Chlorobenzoxazoilium salt(12), which is very reactive as compared to pyridinium salt, reacted easily with alcohols in the presence of triethylamine to afford the corresponding alkyl chlorides in good yields. Further, the addition of tetraethylammonium chloride was found to give a better yield. Moreover, the reaction of 3β-cholestanol or (R)-(-)-2-octanol proceeds clearly with inversion of configuration at the reaction centre (Ref. 13).



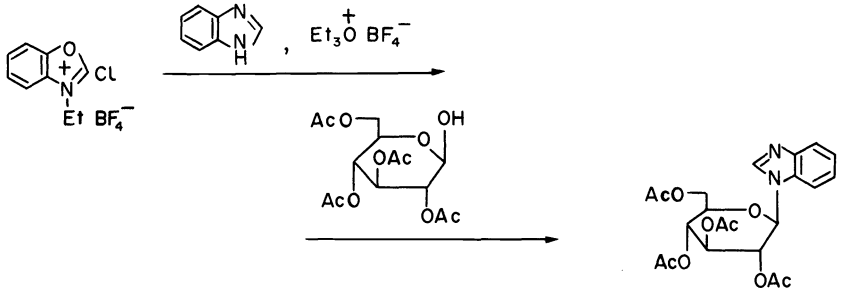
(12)

In order to examine the utility of the method, we employed two carbohydrates as substrates. When 2,3-5,6-di-O-isopropylidene-α-D-mannofuranose(13) or 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose was treated with 12 and tetraethylammonium chloride, one isomer which had the same configuration as the starting material, was exclusively obtained in excellent yield (Ref. 13).

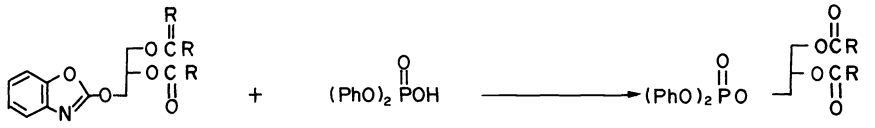


(13) (12)

The preparation of nucleosides from 1-hydroxysugars and heterocycles utilizing the benzoxazolium salt was also established; that is, nucleoside was obtained in good yield as shown in the following equation (Ref. 14).



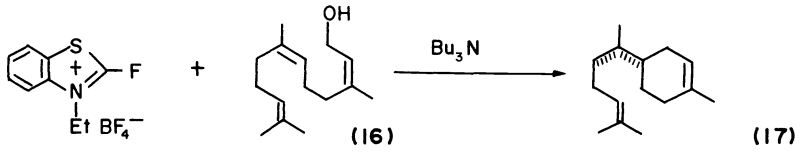
The concept of the activation of alcohols utilizing the onium salt method was further extended to the phosphorylation of alcohols involving 2-alkyloxybenzoxazoles as intermediates. When 2-alkyloxybenzoxazoles(14), easily prepared from alcohols and 2-fluorobenzoxazole, were treated with diphenyl hydrogen phosphate in refluxing benzene, the corresponding alkyl diphenyl phosphates(15) were obtained in good yields (Ref. 15).



(14) (15)

II) INTRAMOLECULAR DEHYDRATION

During the course of further investigations on the reaction of 2-fluoropyridinium salts and alcohols, 2-alkyloxypyridinium salts derived from the terpene alcohols, nerol or geraniol, were found to be unstable even at -78°C and were readily converted to hydrocarbon and 1-methyl-2-pyridone. For example, when nerol was allowed to react with 1,3-dimethyl-2-fluoropyridinium tosylate and tri-n-butylamine in methylene chloride at -40°C for 7 hr, limonene and terpinolene were produced in 82% and 15% yield, respectively. Cyclization of trans,cis-farnesol(16) using 2-fluorobenzothiazolium salt gave bisaborene(17) in 75% yield (Ref. 16).

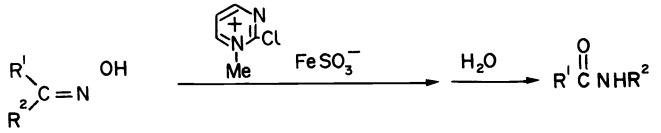


(16) (17)

The results obtained by the investigation of the cyclization of terpene alcohols suggest that the onium salts of 2-haloazaaromatics are useful reagents for rearrangement reactions or an intramolecular dehydration as well as for intermolecular reactions. Since such dehydration or rearrangement reactions have been usually carried out in an acidic medium,

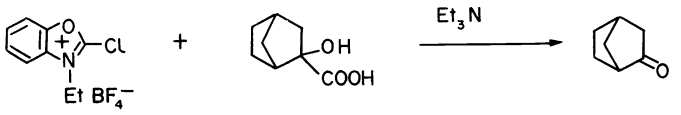
the utilization of the onium salt under weakly basic medium could cause reactions to take a different course.

When oximes are treated with 2-fluoropyridinium salt and triethylamine or with 2-chloropyrimidinium salt alone, the rearrangement smoothly proceeds at low temperature to afford the corresponding amides in high yields under mild conditions (Ref. 17).



By utilizing the onium salts of azaaromatics, various kinds of Intramolecular dehydration reactions were developed, such as nitriles from amide (Ref. 18), isocyanates from methyl thiocarbamates (Ref. 19), carbodiimides from thioureas (Ref. 20), isothiocyanates from dithiocarbamates (Ref. 20) and isocyanides from formamides (Ref. 21).

Ketone formation from α-hydroxy carboxylic acid was realized by the use of benzoxazolium salt without acid and oxidizing reagent (Ref. 22).



III) THE PREPARATION OF OPTICALLY ACTIVE SUBSTANCES

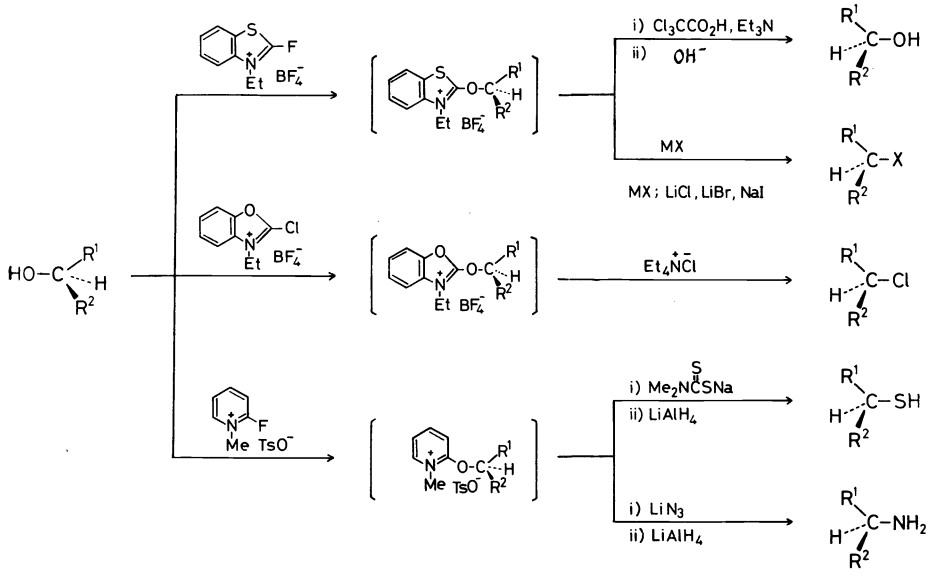
The fact that the reaction utilizing the onium salts proceeds stereospecifically with the inversion of the central carbon prompted us to examine the optical interconversion of chiral alcohols and the transformation of the alcohols into other derivatives.

Optical interconversion of enantiomeric secondary alcohols was investigated. Optically active 2-alkyloxybenzothiazolium salt, formed in situ from an optically active alcohol and 2-fluorobenzothiazolium salt, reacted in the presence of triethylamine with a strong acid such as trichloroacetic acid to yield the corresponding ester, which on facile base-catalysed hydrolysis afforded the alcohol that had the asymmetric carbon atom of opposite configuration to that of the starting alcohol (Ref. 23). Thus, this sequence makes possible the interconversion of the configurationally isomeric secondary alcohols by a simple procedure.

The above-mentioned intermediate, optically active 2-alkyloxybenzothiazolium salt, also reacts with alkali metal halides to afford the alkyl halide in high optical purity with inversion of configuration at the reaction center (Ref. 13, 24).

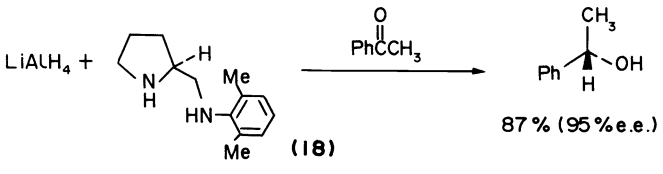
Various optically active thiols were also prepared with high stereospecificity from enantiomeric alcohols by the procedure consisting of (i) the reaction of alcohols with 1-methyl-2-fluoropyridinium tosylate to give 2-alkyloxypyridinium salts, (ii) S_N2 type reaction of the 2-alkyloxypyridinium salts with sodium N,N-dimethyldithiocarbamate, to give alkyl dithiocarbamates, and (iii) reductive cleavage to thiols (Ref. 25).

In order to prepare primary amines, various combinations of nitrogen containing nucleophiles and onium salts were examined. The combination of lithium azide and 2-fluoropyridinium salt gave favourable results for optically active amine synthesis (Ref. 26).



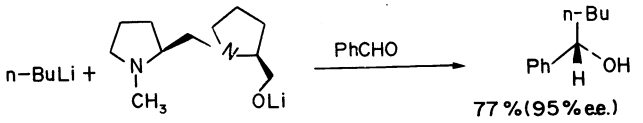
Thus various types of optically active compounds are available when an effective route to chiral secondary alcohols could be found. On the basis of this consideration we have recently investigated the asymmetric reduction and alkylation of carbonyl compounds to obtain chiral alcohols.

For the asymmetric reduction of prochiral ketones, chiral hydride reagents, prepared in situ from (S)-2-(anilinomethyl)-pyrrolidine or (S)-2-(2,6-xylidinomethyl)pyrrolidine(18) and lithium aluminium hydride, were found to be efficient. For example, acetophenone was reduced to 1-phenylethanol in 95% optical yield (Ref. 27).



(18)

Contrary to the case of asymmetric reduction of carbonyl compounds where relatively high optical yields were realized, optical yields in the asymmetric alkylation of organometallic reagents. However, pyrrolidine derivative was found to be also effective for the asymmetric alkylation of carbonyl compounds. Thus, various optically active alcohols were obtained by the asymmetric reaction of alkyl lithium with aldehydes using bis pyrrolidine derivative(19) as the chiral ligand (Ref. 28).



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REFERENCES

1. T. Mukaiyama, Angew. Chem., 88, 111 (1976); Angew. Chem. Int. Ed. Engl., 15, 94 (1976).
2. T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, Chem. Lett., 1975, 1045; K. Saigo, M. Usui, K. Kikuchi, E. Shimada, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 50, 1863 (1977).
3. E. Bald, K. Saigo, and T. Mukaiyama, Chem. Lett., 1975, 1163.
4. J. K. Sutherland and D. A. Widdowson, J. Chem. Soc., 1964, 4650.
5. Y. Watanabe, S. Shoda, and T. Mukaiyama, Chem. Lett., 1976, 741.
6. T. Mukaiyama, M. Usui, and K. Saigo, Chem. Lett., 1976, 49.
7. T. Mukaiyama, K. Narasaka, and K. Kikuchi, Chem. Lett., 1977, 441 ; K. Narasaka, M. Yamaguchi, and T. Mukaiyama, Chem. Lett., 1977, 959.
8. K. Narasaka, K. Maruyama, and T. Mukaiyama, Chem. Lett., 1978, 885.
9. A. Ishida, T. Bando, and T. Mukaiyama, Chem. Lett., 1976, 711; A. Ishida and T. Mukaiyama, ibid., 1977, 467.
10. T. Mukaiyama, M. Imaoka, and T. Izawa, Chem. Lett., 1977, 1257.
11. T. Mukaiyama and K. Kawata, Chem. Lett., 1978, 785.
12. T. Mukaiyama and M. Imaoka, Chem. Lett., 1978, 413.
13. T. Mukaiyama, S. Shoda, and Y. Watanabe, Chem Lett., 1977, 383.
14. T. Mukaiyama, S. Shoda, T. Nakatsuka, and K. Narasaka, Chem. Lett., 1978, 605.
15. Y. Watanabe and T. Mukaiyama, Chem. Lett., 1978, 349.
16. S. Kobayashi, M. Tsutsui, and T. Mukaiyama, Chem. Lett., 1976, 1137; Idem, ibid., 1977, 1169.
17. M. Shiono, Y. Echigo, and T. Mukaiyama, Chem. Lett., 1976, 1397.
18. T. Mukaiyama and Y. Echigo, unpublished results.
19. Y. Echigo, Y. Watanabe, and T. Mukaiyama, Chem. Lett., 1977, 1345
20. T. Shibanuma, M. Shiono, and T. Mukaiyama, Chem Lett., 1977, 573 ,575.
21. Y. Echigo, Y. Watanabe, and T. Mukaiyama, Chem Lett., 1977, 697.
22. T. Mukaiyama and Y. Echigo, Chem Lett., 1978, 49.
23. T. Mukaiyama and K. Hojo, Chem. Lett., 1976, 893.
24. K. Hojo and T. Mukaiyama, Chem. Lett., 1976, 619.
25. K. Hojo, H. Yoshino, and T. Mukaiyama, Chem Lett., 1977, 437.
26. K. Hojo, S. Kobayashi, K. Soai, S. Ideda, and T. Mukaiyama, Chem. Lett., 1977, 635.
27. T. Mukaiyama, M. Asami, J. Hanna, and S. Kobayashi, Chem. Lett., 1977,

783; M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 51, 1869 (1978).

28. T. Mukaiyama, K. Soai, and S. Kobayashi, Chem. Lett.,1978, 219; K. Soai, and T. Mukaiyama, ibid., 1978, 491; T. Sato, K. Soai, K. Suzuki, and T. Mukaiyama, ibid., 1978, 601.