

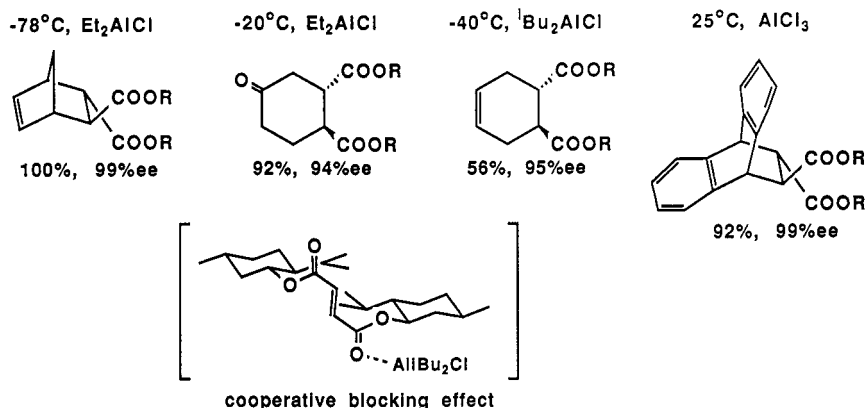
New approach for natural product synthesis using main group organometallic reagents

Hisashi Yamamoto, Keiji Maruoka, Kyoji Furuta, Yuji Naruse

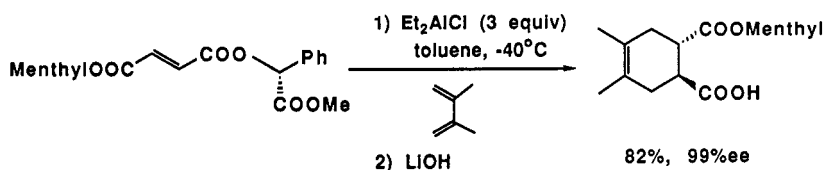
Department of Applied Chemistry, Nagoya University
Chikusa, Nagoya 464-01, Japan

Abstract - This paper will review the current state-of-art of organoaluminum- or organoboron-mediated asymmetric reactions in the natural product synthesis. The newly developed methods heavily depend on the characteristic features of main group organometallic compounds.

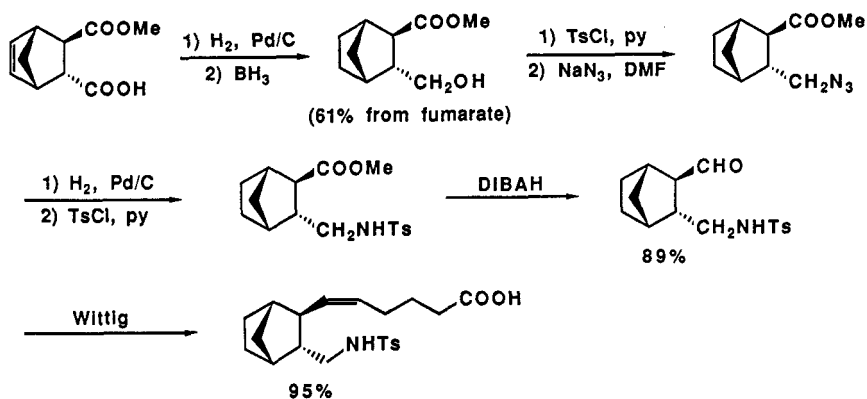
Asymmetric Diels-Alder reaction, pioneered by Walborsky (ref. 1), has been established as one of the most important tools in modern synthesis of natural products. In the study of the influence of concave-convex topological features on asymmetric Diels-Alder reactions, a number of fascinating chiral auxiliary groups were reported (ref. 2). However, readily available dimethyl fumarate appears to deserve careful reinvestigations since its primitive topological feature seems to be underestimated. Thus, the Lewis acid coordinated fumarate is considered to exist in the *s-trans* form predominantly and the two menthyl groups should cooperatively cover the re face of the molecule. A series of dienes was then subjected to Diels-Alder reaction with organoaluminum reagent at low temperature and all the attempted reaction proceeded with excellent stereoselection (ref. 3).



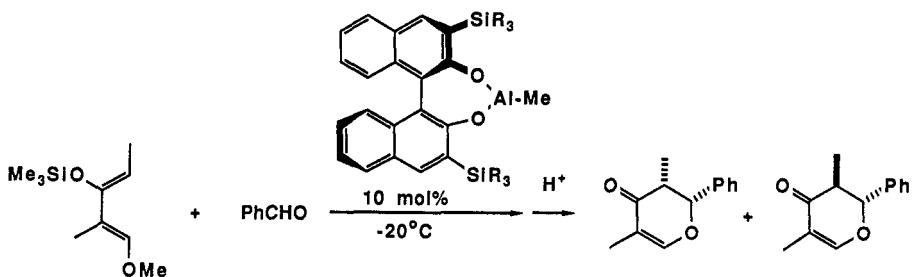
The observed rigorous selectivity in the present system can adequately prove that the concept of cooperative blocking effect is working effectively even for the unsymmetrically modified fumarates (ref. 4).



The potential of the present methodology for the synthesis of chiral cyclic molecules is demonstrated by the short synthesis of newly designed thromboxane receptor antagonist (ref. 5).

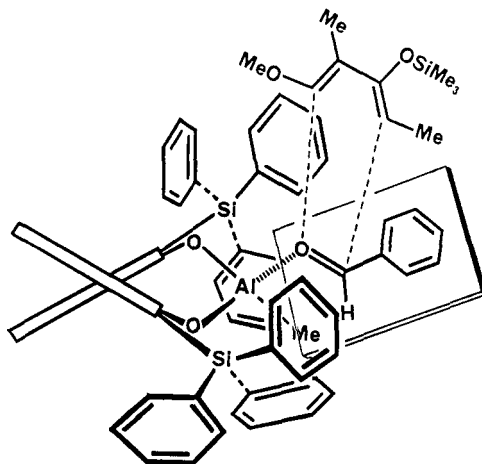


The importance of hetero-Diels-Alder reaction in natural product syntheses has been demonstrated by Danishefsky and co-workers (ref. 6). Asymmetric hetero-Diels-Alder reaction, on the other hand, has never been developed to a useful level due to the lack of the reliable catalyst. The optically pure (R)-3,3'-bis(triarylsilyl)binaphthol and trimethylaluminum afforded the new chiral aluminum catalyst which is shown to be an excellent catalyst for the present reaction (ref. 7).

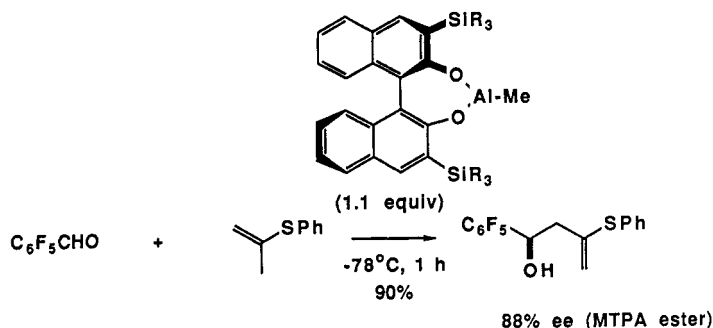


R_3	Optical Yield	cis/trans
Me_3	64% ee	1.1
$t\text{-BuMe}_2$	84% ee	2.3
Ph_3	95% ee	9.6
3,5-Xylyl $_3$	97% ee	30

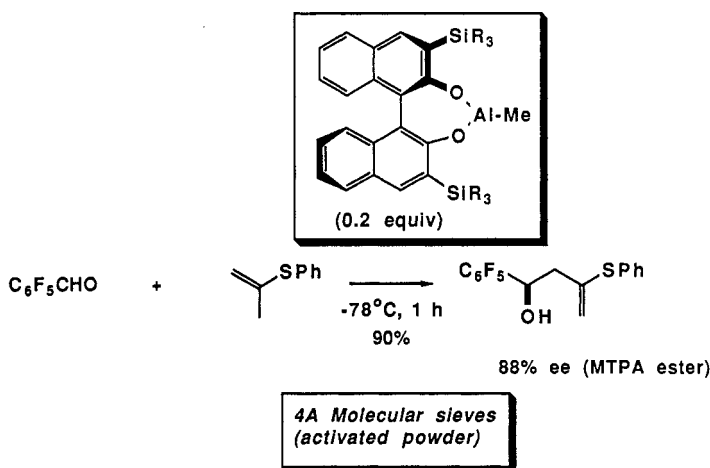
The success of the present asymmetric reaction is particularly owed to development of a new method of preparing optically active disilylbinaphthol. The chiral oxygenophilic organoaluminum catalyst bearing such sterically hindered chiral auxiliary forms a stable 1:1 complex with aldehyde, allowing the enantioselective activation of carbonyl moiety as illustrated below.



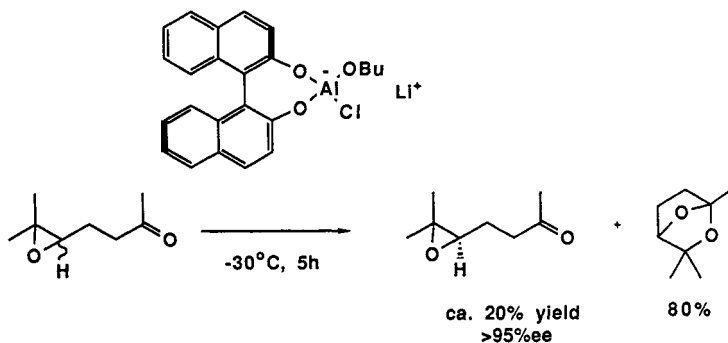
The asymmetric ene reaction of carbonyl compounds with alkenes provides a potentially valuable access to optically active homoallylic alcohols. Reported so far is only the reagent-based control of absolute stereochemistry (ref. 8). The same bulky aluminum reagent seemed to be an excellent catalyst for the asymmetric ene reaction of prochiral aldehydes and alkenes.



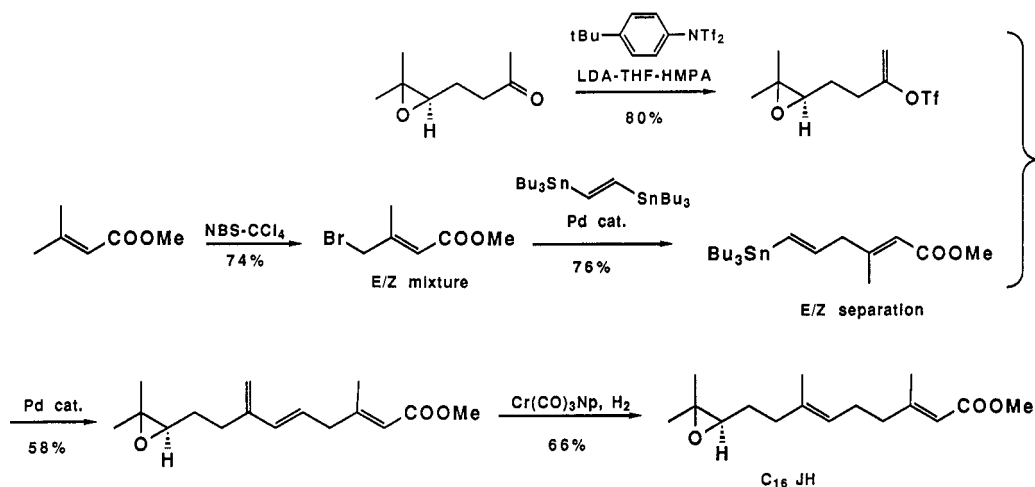
Although an attempted reaction of pentafluorobenzaldehyde and 2-(phenylthio)propene under the influence of catalytic amounts of aluminum reagent gave no appreciable results. However, 4A molecular sieves is capable of making the reaction catalytic.



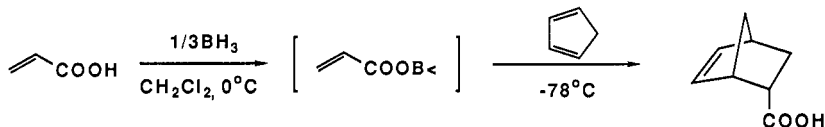
Chiral Lewis acid, which was prepared in situ from R-binaphthol, dimethylaluminum chloride, and lithium alkoxide in dichloromethane, was shown to be an effective reagent for the kinetic resolution of the keto-epoxide as shown below. The optically pure R-isomer can thus be obtained in ca. 20% yield from the readily available racemate (ref. 9).



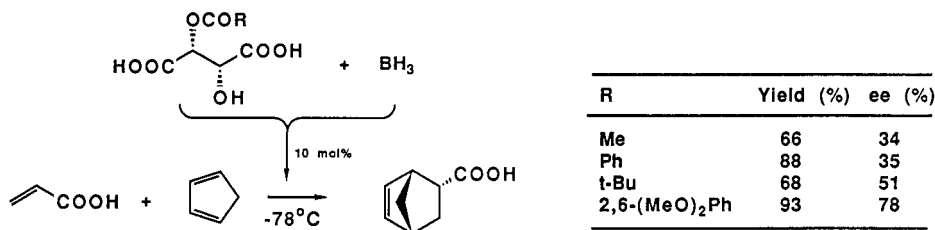
The pure epoxide was shown to be a highly useful building block in acyclic terpene synthesis. A short synthetic route to juvenile hormone is shown on p. 422 which also involves the joining of intermediate in a single flask operation to construct the sesquiterpene structure.



The rapid reaction between carboxylic acids and borane is related to the electrophilicity of borane. An acyloxyborane is recognized to be an initial intermediate (ref. 10). The carbonyl group in this molecule, which is essentially a mixed anhydride, is activated by the electronegative nature of the trivalent boron atom. Indeed, addition of 1/3 equiv of borane to the acrylic acid in dichloromethane at 0°C followed by diene at low temperature resulted in the smooth formation of Diels-Alder adduct in good yield. Further the reaction could progress satisfactory even with a catalytic amount of borane.



With the above experimental guidance, it became of interest to evaluate the inducing ability of appropriate chiral auxiliary by introducing them into the acyloxyborane intermediate. Reaction of monoacylated tartaric acid with one equiv. of borane-THF complex in dichloromethane gave a chiral catalyst. The extent of asymmetric induction largely depend on the acyl moiety of tartaric acid derivatives and results were shown below.



Acknowledgement

We would like to thank our co-workers for their enthusiasm, dedication and skill in completing these research projects. Their names are cited in the appropriate references.

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