

Chiral reagents for asymmetric construction of carbon frameworks

Koichi Narasaka

Department of Chemistry, Faculty of Science, The University of Tokyo,
7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan

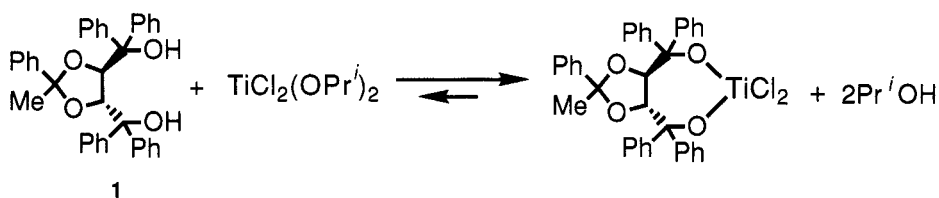
Abstract - Chiral titanium reagent prepared *in situ* by mixing dichlorodiisopropoxy titanium and a tartrate-derived chiral 1,4-diol catalyzed various carbon-carbon bond forming reactions as a chiral Lewis acid; for example, asymmetric cycloaddition reactions such as Diels-Alder reaction and [2+2] cycloaddition reaction. In the presence of the titanium catalyst and MS 4A, 3-alkenoyl-1,3-oxazolidin-2-ones reacted with various dienes to give the Diels-Alder adducts with high enantioselectivity. Hydro-naphthalene moieties of mevinic acids were synthesized by applying the catalyst to the intramolecular Diels-Alder reaction. As a β -hydroxy acrylic acid equivalent, 3-(3-borylpropenoyl)-1,3-oxazolidin-2-ones were prepared and utilized in the above asymmetric Diels-Alder reaction. The boryl group of the adducts thus produced was readily converted to hydroxyl group oxidatively. Asymmetric [2+2] cycloaddition reaction occurred by the treatment of a mixture of 3-alkenoyl-1,3-oxazolidin-2-ones and vinylic and acetylenic sulfides with the titanium catalyst. Various cyclobutanes, cyclobutenes and methylenecyclobutanes were prepared in high optical purity.

INTRODUCTION

Artificial chiral catalysts have many features that render their use in asymmetric synthesis particularly appealing. Foremost is the possibility of achieving extremely high level of enantiocontrol in a truly practical manner; chiral multiplication, ease of handling, economical advantage and applicability to broad substrates. Lewis acids, one of the most common reaction promoters in organic synthesis, catalyze a variety of carbon-carbon bond forming reactions. We, therefore, studied to develop a chiral Lewis acid with the expectation that such a catalyst will be able to be applied for certain asymmetric carbon-carbon bond forming reactions.

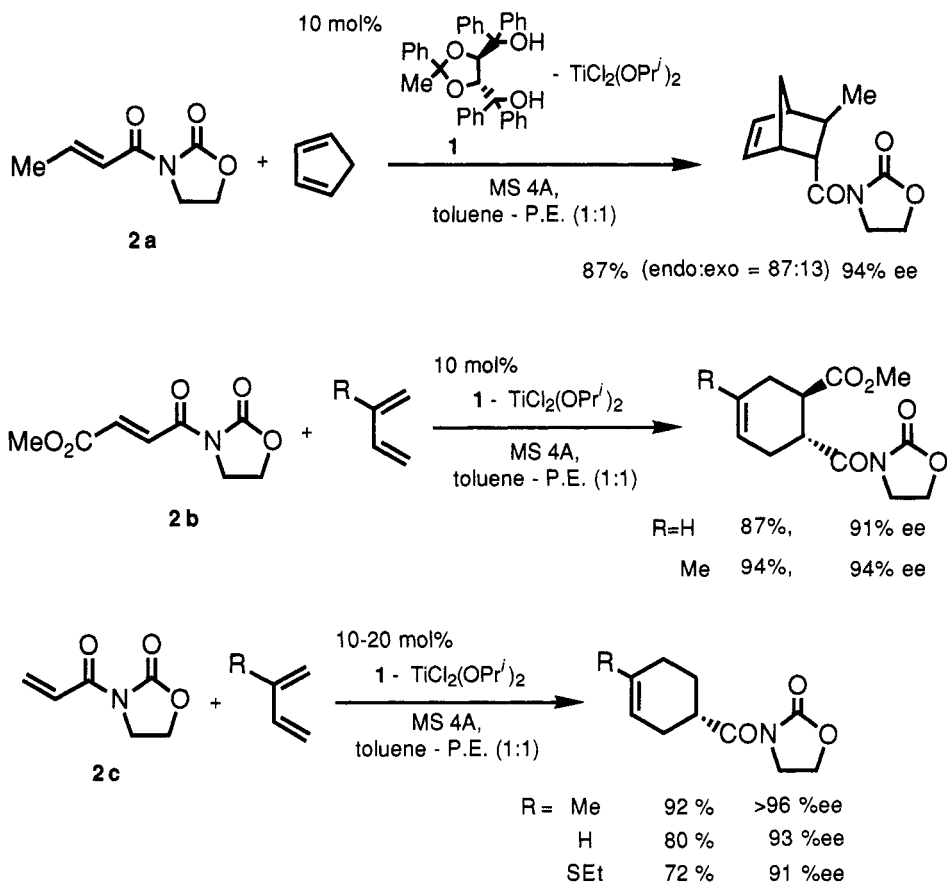
ASYMMETRIC DIELS-ALDER REACTION

By designing chiral titanium alkoxides, it was found that a chiral titanium reagent generated *in situ* from dichlorodiisopropoxytitanium ($\text{TiCl}_2(\text{OPr}^i)_2$), and a tartrate-derived chiral 1,4-diol, (2*R*,3*R*)-1,1,4,4-tetra-phenyl-2,3-*O*-(1-phenylethylidene)-1,2,3,4-butanetetrol (**1**), catalyzes some asymmetric reactions.



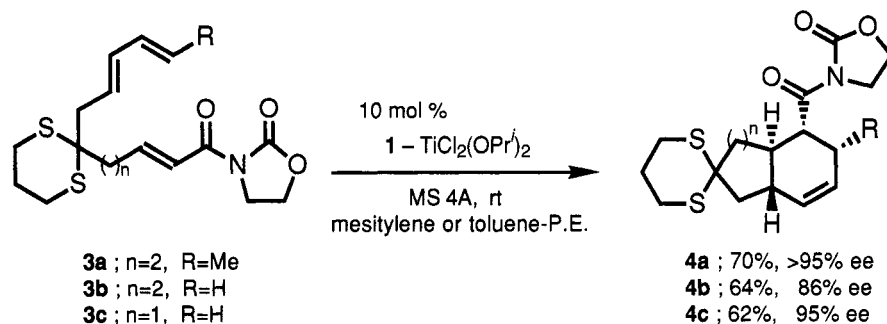
The Diels-Alder reaction (ref. 1) of 3-alkenoyl-1,3-oxazolidin-2-ones (**2**, abbreviated as oxazolidinone) and dienes proceeded by the catalytic use of the titanium reagent. The enantioselectivity was largely dependent on the solvent and a mixture of toluene and petroleum ether was found to be suitable reaction solvent. Particularly with the coexistence of MS 4A, oxazolidinone derivatives of crotonic acid **1a**, fumaric

acid **1b** and acrylic acid **1c** reacted with dienes, and various Diels-Alder adducts were prepared with high optical purity as shown in the following equations. (ref. 2)



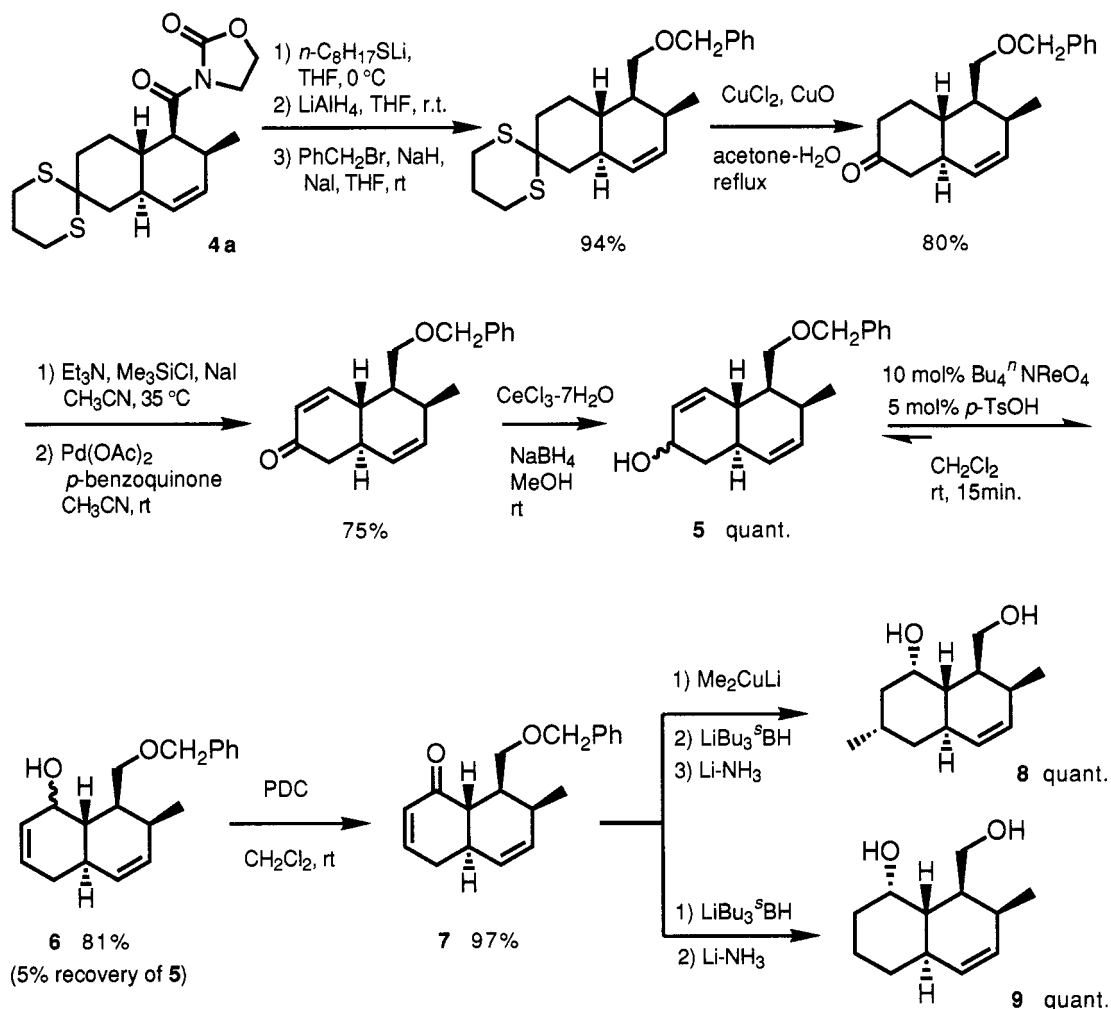
INTRAMOLECULAR ASYMMETRIC DIELS-ALDER REACTION

The intramolecular Diels-Alder reaction was also catalyzed by the titanium reagent, which affords an efficient method to the asymmetric synthesis of bicyclic compounds. That is, treatment of trienes **3** with the titanium catalyst gave hydronaphthalene and hydroindane derivatives **4** with high optical purity. (ref. 3)



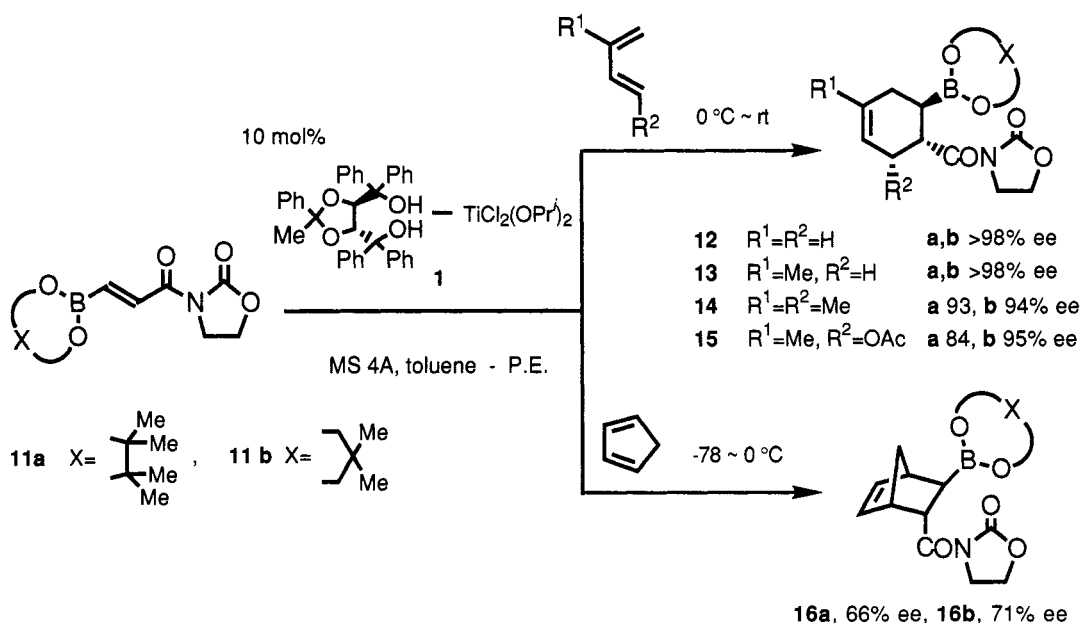
The synthesis of the hydronaphthalene moieties of mevinic acids (ref. 4) was investigated starting from the bicyclic compounds **4a** prepared by using (*S*)-1,4-diol **1** as a chiral auxiliary, which satisfies most of the stereochemistry of hydronaphthalene moieties of dihydromevinolin **8** and dihydrocompactin **9**. The stereochemistry of the remaining asymmetric center(s) was expected to be controlled by assuming an enone **7** as a common synthetic intermediate for mevinic acids.

The Diels-Alder product **4a** was transformed into the allylic alcohol **5** as shown in the following scheme, and the successive hydroxyl group transposition was accomplished by the newly developed allylic rearrangement reaction. (ref. 5) Thus, when **5** was treated with a catalytic amounts of tetrabutylammonium perchlorate and *p*-toluenesulfonic acid, the allylic rearrangement proceeded immediately to afford a mixture of both of the rearranged allylic alcohol **6** and the starting alcohol **5**. The desired isomer **6**, in which hydrogen bond formation is observed between OH and PhCH₂O groups, was obtained predominantly in 81% yield. Oxidation of **6** led to the desired common synthetic intermediate **7**. The hydronaphthalene moiety of dihydromevinolin **8** was synthesized stereoselectively by the successive treatment with methyl cuprate and Li-selectride. The reduction of the enone **7** with Li-selectride yielded the hydronaphthalene moiety of dihydrocompactin **9** as shown in the following scheme. (ref. 6)

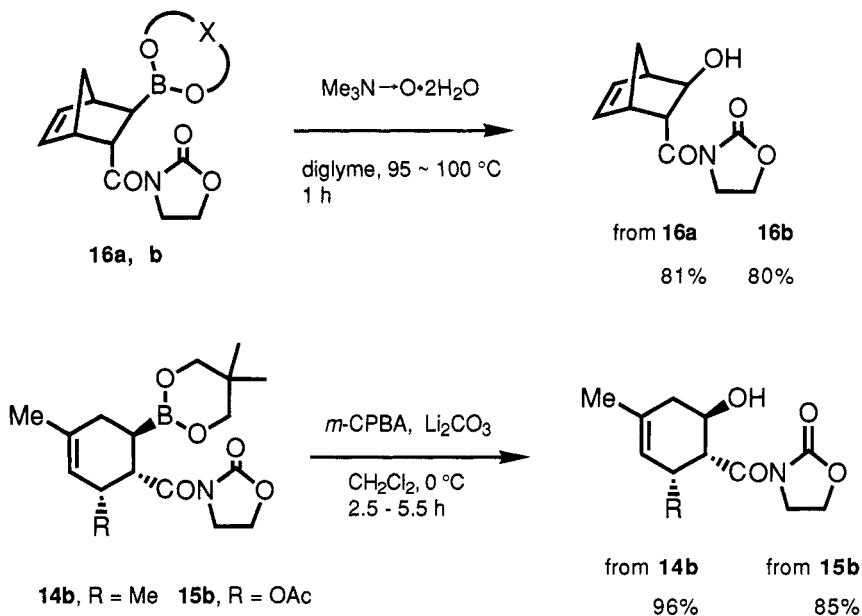


ASYMMETRIC DIELS-ALDER REACTION OF β -BORYL ACRYLOYL OXAZOLIDINONE

For the preparation of oxygen-functionalized Diels-Alder products, 3-(3-borylpropenyl)oxazolidinones **11a, b** were synthesized from 3-propioyloxazolidinone **10**. Hydroboration of **10** with diisopinocampheylborane (ref. 7), followed by treatment with excess acetaldehyde, and the successive transesterification with pinacol or 2,2-dimethyl-1,3-propanediol. The boronates **11a, b** smoothly reacted with butadiene, isoprene and 2-methyl-1,3-pentadiene in the presence of the titanium catalyst, yielding the adducts **12-14** as a single isomer in good yield with high enantioselectivity (>93% ee). The reaction of **11b** with 1-acetoxy-3-methyl-1,3-butadiene also afforded selectively the endo adduct **15b** in 71% yield with 95% ee. In the reaction with cyclopentadiene, the boronates **11** afforded the adducts **16** in high yield but with somewhat lower optical purity (66-71% ee) as compared with the acyclic dienes. (ref. 8)



The boryl groups of the Diels-Alder products were converted to hydroxyl group by the oxidation. For examples, with trimethylamine *N*-oxide dihydrate, the norbornene type adducts **16a, b** were oxidized to the desired alcohol. The oxidation of **14b** and **15b** was also carried out smoothly with *m*-chloroperbenzoic acid. Treatment of **14b** and **15b** with *m*-chloroperbenzoic acid alone gave the desired alcohol with considerable amount of the epoxides, while the reaction in the presence of lithium carbonate afforded 2-hydroxycyclohexene carboxylic acids in 96% and 85% yield, respectively, without formation of epoxides.



ASYMMETRIC [2+2] CYCLOADDITION REACTION

In addition to the asymmetric Diels-Alder reaction, the titanium catalyst found the successful application to [2+2] cycloaddition reaction. Generally [2+2] cycloaddition between two olefinic moieties is carried out under photoirradiation. However, it was found that when a mixture of ketene dimethyldithioacetal **17** and alkenoyl oxazolindiones **2** was treated with the titanium catalyst, [2+2] cycloaddition reaction proceeded smoothly under mild reaction conditions and cyclobutanes **18** were obtained as a single regioisomer in good enantioselectivity. (ref. 9)

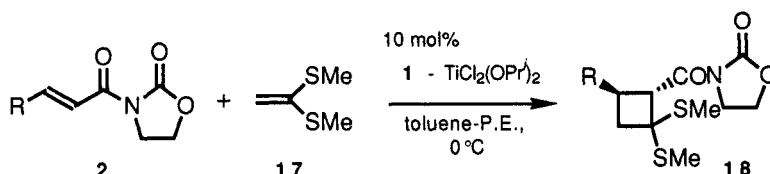
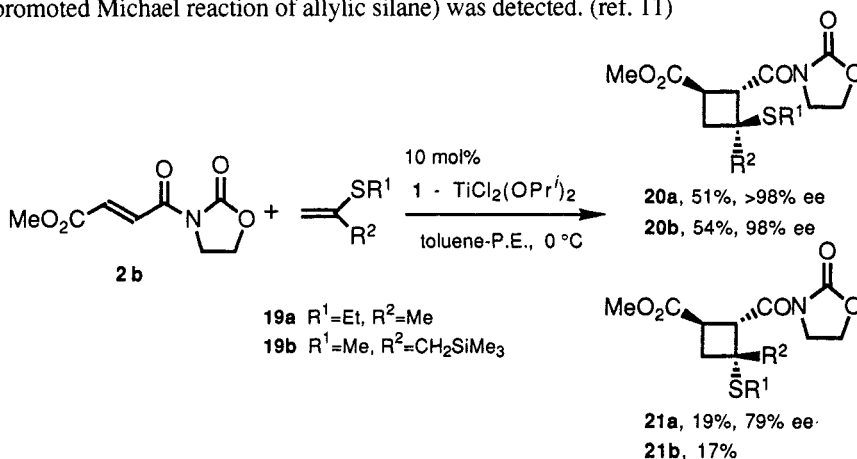


TABLE 1. Asymmetric [2+2] cycloaddition reaction of 17.

R	Time/h	Yield/%	Opt. Purity/%ee
CO ₂ Me	0.5	96	98
H	0.5	74	88
Me	109	64	80

Since Lewis acid catalyzed [2+2] cycloaddition has remained a rather unexplored area, (ref. 10) the scope and limitations of the present [2+2] cycloaddition was further investigated. In contrast with the reaction of the ketene dithioacetal, the corresponding acetal did not react with **2** under the same reaction conditions. However, various type of vinyl and acetylenic sulfides reacted with **2** in the presence of the titanium catalyst. The reactions of vinyl sulfides **19** with **2b** predominantly afforded the [2+2] cycloadducts **20a** and **21a** in 70% total yield along with a small amount (16%) of the ene product. Allylsilane-type vinyl sulfide **19b** also exclusively gave the cyclobutenes **20b** and **21b** and none of the allylation product (the Lewis acid promoted Michael reaction of allylic silane) was detected. (ref. 11)



Acetylenic sulfides are less reactive than the ketene dithioacetal, and crotonoyloxazolidinone **2a** did not react with 1-hexynyl methyl sulfide even when a mole equivalent of the catalyst was employed. Fumaric and acrylic acid derivatives **2b**, **c**, however, reacted with various acetylenic sulfides and afforded cyclobutenes **22** in almost optically pure forms.

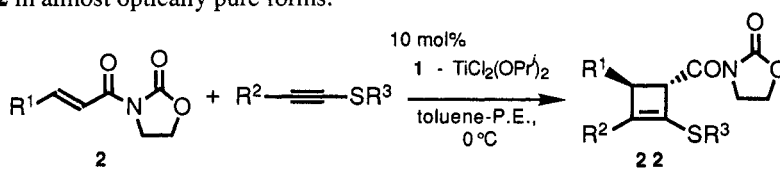


TABLE 2. Asymmetric [2+2] cycloaddition reaction of acetylenic sulfides.

R ¹	R ²	R ³	Amount of Ti /equiv.	Yield /%	Opt. Purity /%ee
CO ₂ Me	Bu ⁿ	Me	1.1	92	>98
			0.3	55	90
	Cyclohexyl	Me	1.1	90	>98
			1.1	84	>98
			0.1	83	>98
H	Bu ⁿ	Me	1.1	86	>98
			0.1	80	98
			0.3	65	>98

[2+2] Cycloaddition reactions between allenes and olefins have frequently been employed for the preparation of methylenecyclobutanes. Most of the reactions proceed with photochemical activation, and thermal reactions, including Lewis acid promoted reaction, are restricted to a rather limited number of examples. (ref. 12) By introducing an alkylthio group, it was expected that allene compounds could be utilized effectively in the [2+2] cycloaddition reaction. And, to test this, reaction of allenyl methyl sulfides **23** having an α -trimethylsilyl, trimethylstannyl, or benzyl substituent were examined. As expected, by catalytic use of the titanium reagent, the corresponding methylenecyclobutanes **24**, **25** were synthesized in good chemical yield in nearly optically pure form. (ref. 13)

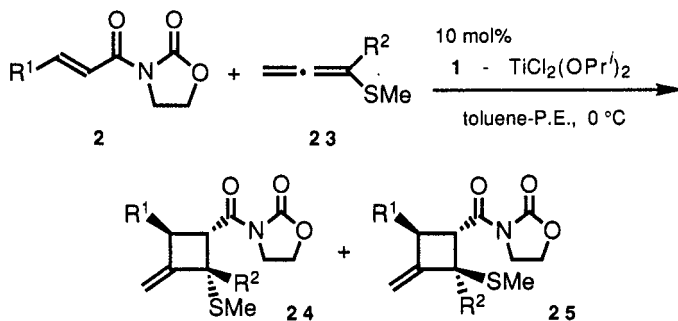
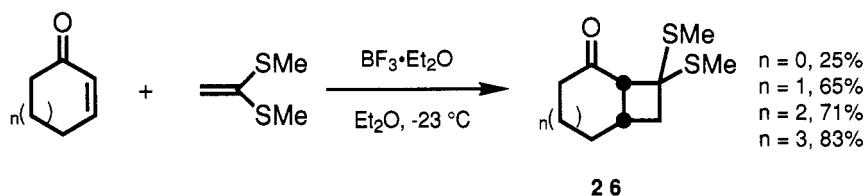


TABLE 3. Asymmetric [2+2] cycloaddition reaction of allenyl sulfides **23**.

R ¹	R ²	Yield/%		Opt. Purity/%	
		24	25	24	25
CO ₂ Me (2b)	SiMe ₃ (23a)	quant.	—	>98	—
	SnMe ₃ (23b)	93	—	96	—
	SnBu ₃	0	0		
	CH ₂ Ph (23c)	30	57	94	>98
H (2c)	SiMe ₃ (23a)	41	21	>98	—

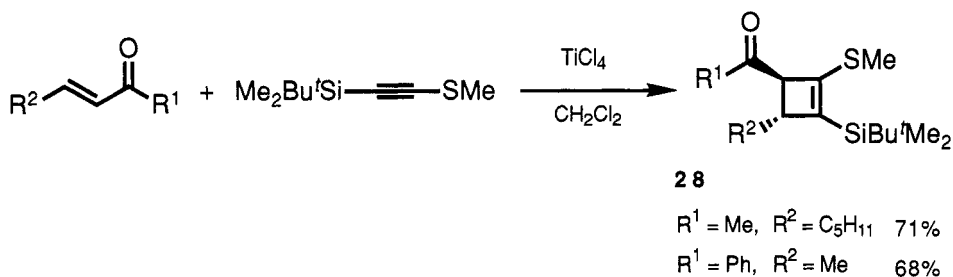
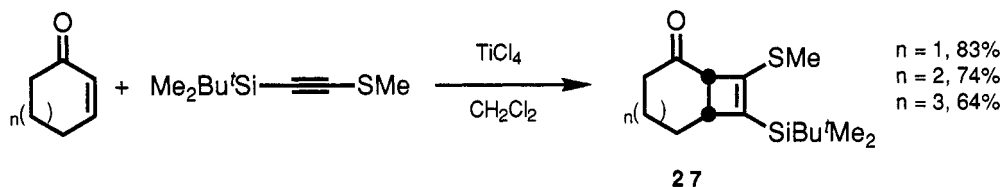
GENERILITY OF THE LEWIS ACID CATALYZED [2+2] CYCLOADDITION REACTION OF VINYLIC AND ACETYLENIC SULFIDES

As mentioned, oxazolidinone derivatives **2** are well activated by the chiral titanium for the asymmetric [2+2] cycloaddition reaction, but the titanium reagent did not promote the reaction when some electron deficient olefins were employed in place of the oxazolidinone derivatives. Accordingly, for the reaction of various electron deficient olefins with ketene dithioacetal, the choice of the suitable Lewis acid and solvent becomes essential to promote the reaction and to prevent the opening of the resulted rather unstable cyclobutanes. For the reaction of cyclic enones, the use of BF₃·OEt₂ in Et₂O is suitable to get the bicyclo[n.2.0] compounds **26**. A characteristic feature of the Lewis acid catalyzed [2+2]cycloaddition reaction appears to be in its regioselectivity. The sense of the regioselectivity is opposite to that of the photochemical reaction in which 1,1-dimethoxyethylene reacts with 2-cyclohexen-1-one to afford 7,7-dimethoxybicyclo[4.2.0]octan-2-one, whereas the 8,8-bis(methylthio) derivative **26**, n=1 was prepared selectively by the Lewis acid catalyzed reaction. (ref. 14)



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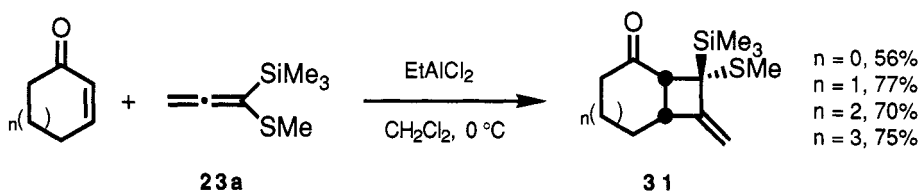
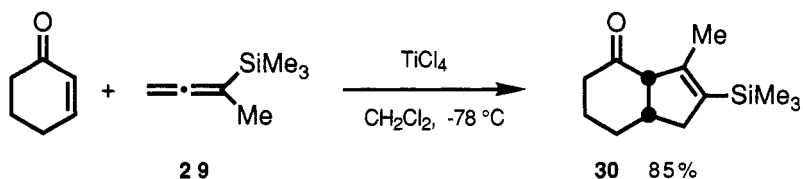
The reactions with vinyl sulfides did not exhibit the generality, but acetylenic and allenyl sulfides reacted with a wide range of electron deficient olefins. In the presence of TiCl_4 , acetylenic sulfides reacted with cyclic and acyclic olefins in dichloromethane, to give cyclobutenes **27** and **28**.



Danheiser reported that the TiCl_4 catalyzed reaction of α -methyl allenyl silane **29** and cyclohexenone gave [3+2] cycloadduct **30** with the migration of silyl group. (ref. 15) On the contrary, α -methylthio allenylsilane **23a** reacted with cycloalkenones in the presence of EtAlCl_2 , and the [2+2] cycloaddition product, methylene cyclobutenes **31** were obtained selectively. These results explain that the reaction course of allenyl compounds is well controlled by the introduction of these substituents.

Semi-empirical MO calculations (PM3, ref. 16) were performed on allene derivatives and we can quantitatively explain the effect of alkylthio and silyl substituents. 1) An α -alkyl allenyl sulfide like **23c** has a large electron population on $\text{C}\beta$ rather than on $\text{C}\gamma$, whereas a silyl substituent increases the electron population on $\text{C}\gamma$. 2) For the allenyl sulfide, the MO coefficient at $\text{C}\beta$ of the HOMO is much larger than $\text{C}\gamma$. However, in the allenyl silane **29**, the energy gap of HOMO and the next HOMO (NHOMO) is quite small and the NHOMO coefficient at $\text{C}\gamma$ is large. This suggested that both $\text{C}\beta$ and $\text{C}\gamma$ exhibit almost the same reactivity. The combination of the relative charge populations and the value of the HOMO or NHOMO coefficients, together with the steric effect of the substituents at $\text{C}\alpha$, leads to the conclusion that the reactivity of $\text{C}\beta$ is higher than that of $\text{C}\gamma$ in the allenyl sulfide **23c**, while $\text{C}\gamma$ is supposed to be more reactive in the allenyl silane **29**.

For the allene derivative **23a** having both methylthio and trimethylsilyl substituents, the effect of the alkylthio group apparently predominates over that of the silyl group, resulting in the exclusive formation of the [2+2] cycloadduct **31**.



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