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TANDEM REACTIONS INITIATED BY THE CONJUGATE ADDITION OF CHALCOGEN COMPOUNDS
— UTILIZATION AND SYNTHESIS OF HETEROCYCLES —

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Abstract – Alkynyl- and alkenylselenonium salts reacted with nucleophiles at the α- or β-carbon depending upon the nucleophiles. The α-attack caused the addition-elimination reaction; *i.e.,* the apparent substitution reaction and the β-attack (the conjugate addition) generated an ylide, which brought about the tandem reaction to form a variety of heterocyclic compounds. Some new reactions proceeded *via* the selenuranes formed by the attack of a nucleophile on the positively charged selenium atom.

An interesting tandem Michael-aldol reaction of enones (ynones) bearing a chalcogenide or a thioamide was developed. The reactions of the 1-[2-(methylchalcogeno)phenyl]propenones gave α-(α-hydroxyalkyl)enones (Morita-Baylis-Hillman adducts) after a work-up with Et_3N. The reactions of the 3-cinnamoyl-1,3-oxazolidine-2-thiones with aldehydes gave tricyclic compounds with a bridgehead bound to four heteroatoms. The asymmetric reactions simultaneously induced four stereocenters, three of which are contiguous. Removal of the chiral auxiliary provided 1,3-diols bearing three consecutive stereocenters.

1. INTRODUCTION

The Michael reaction is the most significant C-C bond-forming reactions and a powerful synthetic tool in organic synthesis due to the various combinations between donors and acceptors.[1] One of the properties of the Michael reaction is the formation of a stabilized carbanion at the α−position of the

electron-withdrawing group in an acceptor after the 1,4-conjugate addition. The formation of this Michael adduct followed by the next C-C bond-forming reaction is applied to useful tandem reactions such as the Michael-aldol reaction known as Robinson annulation,[2] Michael-Claisen reaction,[3] and the double Michael reaction.[4] Chalcogen compounds, such as thiolate and selenolate ions, are very useful nucleophiles for Michael reactions, and asymmetric Michael addition reactions have recently been studied intensively.[5,6] This review describes the Michael reaction of alkenes or alkynes substituted by an electron-withdrawing chalcogen group and the intramolecular Michael addition-aldol reaction of chalcogenides or thiocarbamates in which novel heterocyclic compounds are produced and the heterocyclic systems play important roles.

2. STUDIES OF ALKYNYL, ALKENYL, AND ALLENYLSELENONIUM SALTS

The Michael acceptor possesses an electron-withdrawing and resonance-stabilizing activating group, such as the carbonyl, nitrile, sulfonyl and nitro groups, which stabilizes the anionic intermediate. However, the synthesis of alkynes and alkenes bearing onium cation groups as an electron-withdrawing group and their use for Michael acceptors have been rarely reported. The 1,4-conjugate addition for an alkenyl-onium salt produced the ylide as a conjugate adduct. For example, the conjugate addition of β-formyl alkoxide to a vinylphosphonium salt followed by the intramolecular Wittig reaction produced heterocyclic compounds.[7] The utilization of alkynyl- and alkenyliodonium salts as the acceptor showed intriguing reactivity derived from the hypervalent iodan chemistry.[8] The application of these acceptors bearing sulfonio and selenonio groups as the electron-withdrawing group was a somewhat unexplored field when we began our research.[9] We were particularly interested in selenonium salts that have an unsaturated carbon-carbon bond.

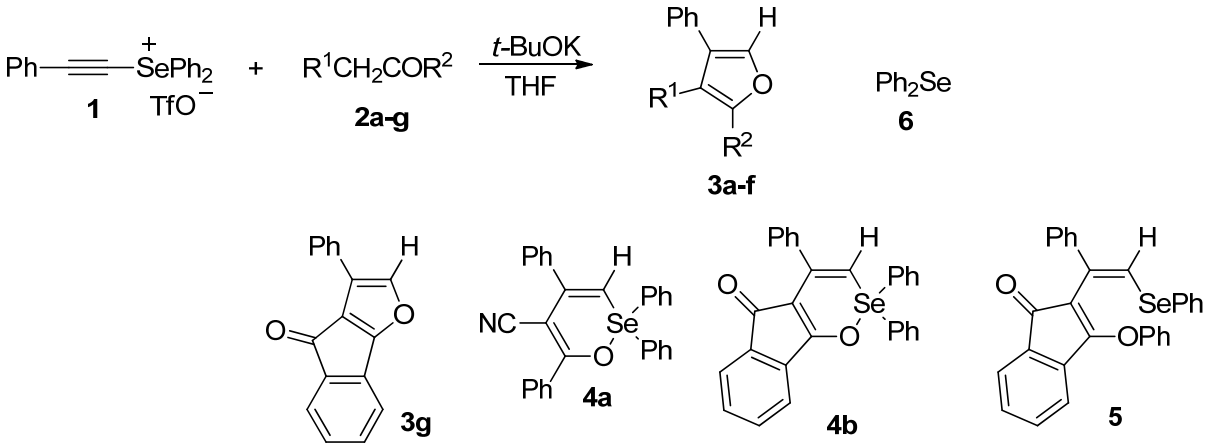
Because of these factors, we report on the synthesis of novel alkynyl, alkenyl, and allenylselenonium salts and the investigation of their reactivities as the Michael acceptor with a variety of nucleophiles. Furthermore, the novel Michael-aldol reaction discovered in the research of alkenylselenonium salts is also described.

3. THE REACTION OF ALKYNYLSELENONIUM SALTS WITH ACTIVE METHYLENE CARBANIONS[10]

We first investigated the reactions of alkynylselenonium salts, which were prepared from trimethyl(arylethynyl)silane and diaryl selenoxide in the presence of trifluoromethanesulfonic anhydride, with active methylene carbanions. The reaction of diphenyl(phenylethynyl)selenonium triflate **1** with 2,4-pentanedione **2a** and *t*-BuOK in THF gave the furan derivative **3a** (40%) and diphenyl selenide **6** (62%) (entry 1 in Table 1). The yield of this reaction was much improved when the reaction mixture

was heated to the refluxing temperature (entry 2). The reactions with other active methylene compounds (**2b-f**) under the refluxing conditions similarly gave the corresponding furan derivatives in high yields (entries 3-7). However, the reaction with 1,3-indandione **2g** afforded the furan derivative **3g** in poor yield (2%) with **6** (24%), **4b** (30%), and **5** (8%) in entry 8. In sharp contrast, the reactions with benzoylacetonitrile **2f** and 1,3-indandione **2g** at room temperature only gave the products **4a** and **4b** in yields of 70% and 39%, respectively (entries 9 and 10).

Table 1. The reactions of alkynylselenonium salt **1** with active methylene compounds

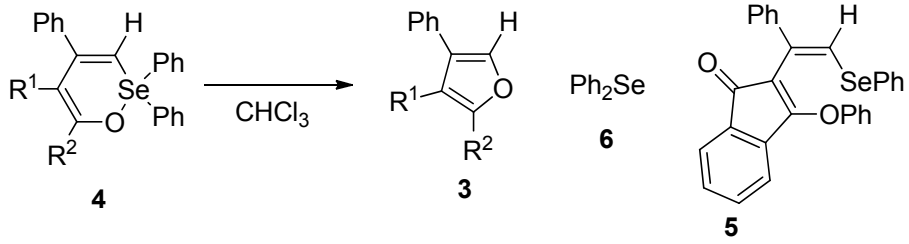


Entry	**2**	R^1	R^2	Temp.	Time	Products (%Yield)			
1	**2a**	COMe	Me	rt	1 d	**3a** (40)			**6** (62)
2	**2a**			reflux	1 h	**3a** (58)			**6** (88)
3	**2b**	COPh	Me	reflux	1 h	**3b** (80)			**6** (86)
4	**2c**	COPh	Ph	reflux	2 h	**3c** (53)			**6** (97)
5	**2d**	COOMe	Me	reflux	1 h	**3d** (83)			**6** (97)
6	**2e**	COOEt	Ph	reflux	1 h	**3e** (58)			**6** (97)
7	**2f**	CN	Ph	reflux	1 h	**3f** (63)			**6** (77)
8	**2g**	(1,3-indandione)		reflux	1 h	**3g** (2)	**4b** (30)	**5** (8)	**6** (24)
9	**2f**			rt	1 d	**4a** (70)			
10	**2g**			rt	1 d	**4b** (39)			

Based on the result of the thermal reactions of compounds **4a** and **4b** as described below, it was anticipated that these products were the reaction intermediates that form the furan derivatives **3f** and **3g** or the ring-opened coupling product **5**. Thus, we confirmed that compounds **4a** and **4b** underwent the ligand coupling reactions to form **3f**, **3g** and **6** (Table 2). When a solution of **4a** in chloroform was allowed to stand at room temperature for 3 days, the furan derivative **3f** (77%) and **6** (81%) were obtained (entry 1). The reaction was completed in 8 h under reflux in chloroform (entry 2). The reaction of **4b** slowly proceeded to give the furan derivative **3g** (13%), **6** (60%) and the ring-opened product **5** (29%) in entry 3. The crystal structure of the intermediate **4a** was more clearly established by an X-ray diffraction analysis (Figure 1). The apical-bond distance of Se-O (2.553Å) is shorter than the sum of the van der Waals radii

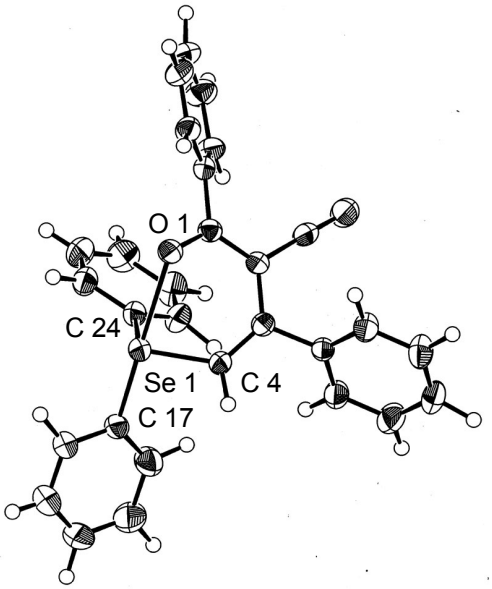
for selenium and oxygen (3.40Å). The O-Se-C_{17} bond angle of 173.5° is approximately collinear and close to those of other selenuranes.[11] The quadruple average angle of **4a** (111.3°) coincided with the mean values (ca. 112°) in the literature.[12] The configuration about the selenium atom is a slightly distorted trigonal bipyramid which consisted of two apical Se-O_1 and Se-C_{17} bonds and two equatorial Se-C_4 and Se-C_{24} bonds and a lone-pair at the third equatorial position. These structural features are consistent with a σ-selenurane structure. We isolated the first selenuranes with three carbon-selenium bonds and an oxygen-selenium bond [10-Se-4(C3O)] as the reaction intermediates.[13]

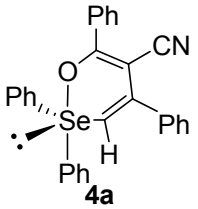
Table 2. Thermal decomposition of **4**



4 **3** **6** **5**

Entry	**4**	Temp.	Time	Products (%Yield)		
1	**4a**	rt	3 d	**3f** (77)		**6** (81)
2	**4a**	reflux	8 h	**3f** (87)		**6** (85)
3	**4b**	reflux	3 d	**3g** (13)	**5** (29)	**6** (60)



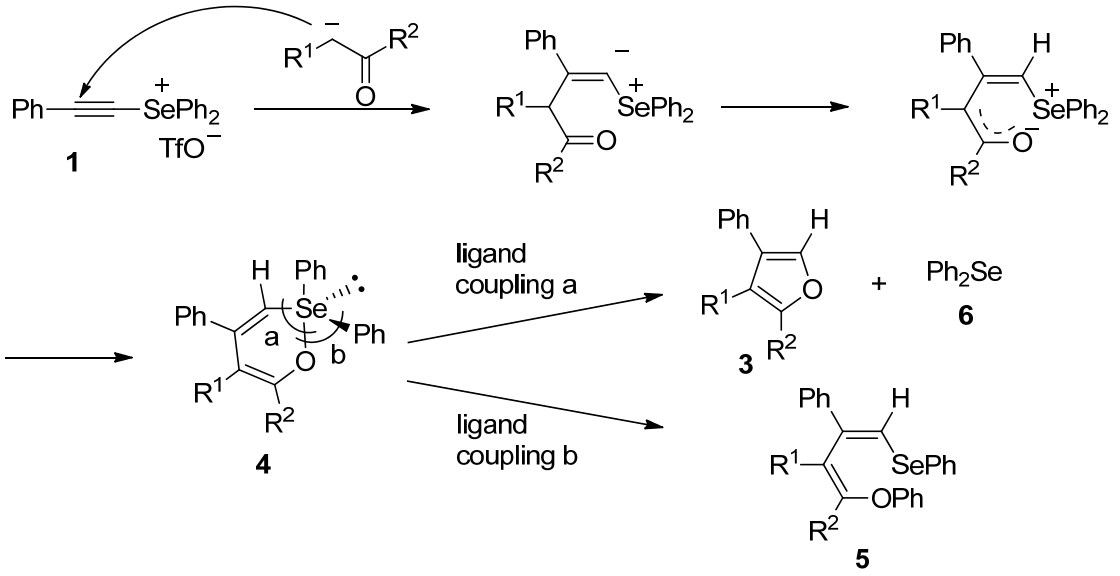


4a

Figure 1. ORTEP drawing of **4a**

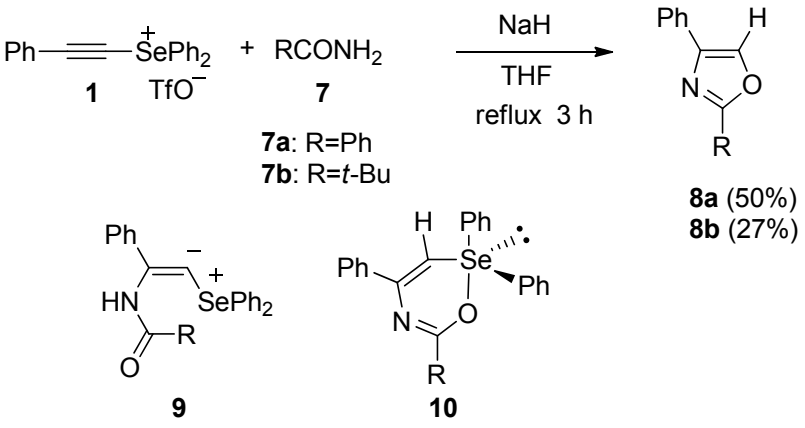
A plausible mechanism is shown in Scheme 1. The 1,4-conjugate addition of an active methylene carbanion to the alkynylselenonium salt **1** gives a selenonium ylide. Subsequent proton transfer from methine generates an enolate ion, of which the alkoxide ion attacks the selenium atom to form the

selenurane intermediate **4**. Finally, the ligand coupling reaction produced the furan **3** through *path a* cleavage or a ring-opened product **5** through *path b* cleavage.



Scheme 1. Plausible mechanism for the formation of furan derivatives

When amides **7a**, **b** were used instead of the active methylene compounds, oxazole derivatives **8a** (50%) and **8b** (27%) were obtained (Scheme 2). They would be formed by the ligand coupling reaction of the selenurane **10** through the ylide **9** in a similar manner to the formation of furans.



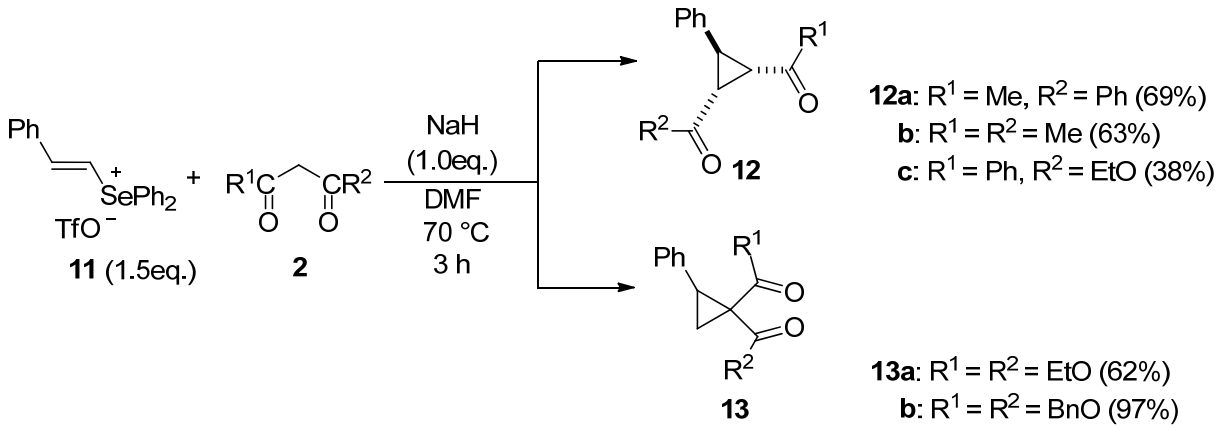
Scheme 2. The reactions of alkynylselenonium salt **1** with amide compounds

4. THE REACTION OF ALKENYLSELENONIUM SALTS WITH ACTIVE METHYLENE CARBANIONS[14]

The tandem Michael addition-cyclization route between the alkynylselenonium salts and active methylene carbanions afforded highly functionalized furan derivatives through vinylselenonium ylide intermediates that caused the intermolecular deprotonation of the active methine moiety. We were interested in the

reactivity of the alkylselenonium ylide which would be formed by the Michael addition of an active methylene carbanion to an alkenylselenonium salt instead of an alkynyl one.

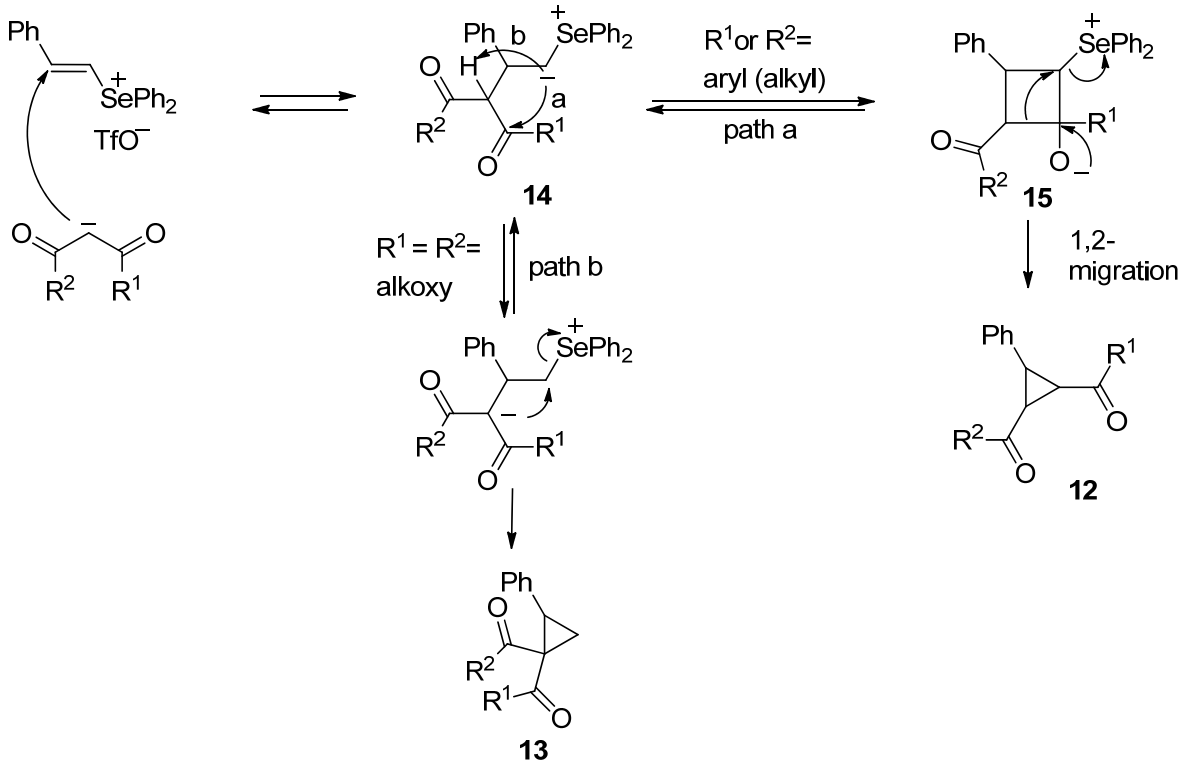
(*E*)-β-Styrylselenonium triflate **11** was prepared from (*E*)-trimethylstyrylsilane and diphenyl selenoxide in the presence of trifluoromethanesulfonic anhydride in good yield. The reactions of **11** with the active methylene carbanions were examined (Scheme 3). The reaction with a carbanion generated from benzoylacetone and sodium hydride in DMF at 70 °C for 3 hours gave the cyclopropane derivative **12a**, the relative configuration of which was determined to be (1*R**, 2*S**, 3*R**) by the NOE measurement, in 69% yield together with a (1*R**, 2*R**, 3*S**) isomer (12%) and a (1*S**, 2*S**, 3*S**) isomer (12%). Other cyclopropanes, **12b** and **c**, with *anti* relationships between the phenyl group and the other functional groups, were prepared as the main products in moderate to good yields from 2,4-pentanedione or ethyl benzoylacetate. On the other hand, the reaction with diethyl or dibenzyl malonate afforded the diethyl or dibenzyl 2-phenylcyclopropane-1,1-dicarboxylate **13a** (62%) or **13b** (97%), respectively.



Scheme 3. Cyclopropane formation from **11** and active methylene compounds

The reactions gave different cyclopropanes depending upon the substituents on the active methylene group, *i.e.*, bearing at least one ketone group or two ester groups (malonates). The interesting results can be explained by the plausible mechanism shown in Scheme 4. Selenonium ylides **14** are formed from the conjugate addition of the carbanion to the alkenylselenonium salt. When the active methylene compound possesses one or more ketone group(s), the ylide carbanion intramolecularly attacks the ketone carbonyl group to form a cyclobutane ring **15**, which is followed by the 1,2-migration of the endo carbon-carbon bond accompanied with the elimination of diphenyl selenide to form a cyclopropane derivative bearing 1,2-dicarbonyl groups (*path a*). This ring contraction reaction is similar to the semibenzylic pathway for the Favorskii rearrangement.[15] On the other hand, since the carbonyl groups of the ylide **14** with the malonate moiety are less reactive toward the ylide carbanion, deprotonation of an active methine proton preferentially occurs to form a betaine, followed by intramolecular nucleophilic substitution to give a

cyclopropane derivative bearing 1,1-diester groups (*path b*). Thus, we have found the first example of a tandem Michael-Favorskii-type process in the reactions of alkenyl-substituted onium salts with active methylene carbanions bearing at least one ketone group to produce α,β-dicarbonylcyclopropane derivatives. It is noteworthy that the formation of the cyclopropane skeleton depends on the properties of the functional groups in active methylene compounds.



Scheme 4. Plausible mechanism for cyclopropane formation

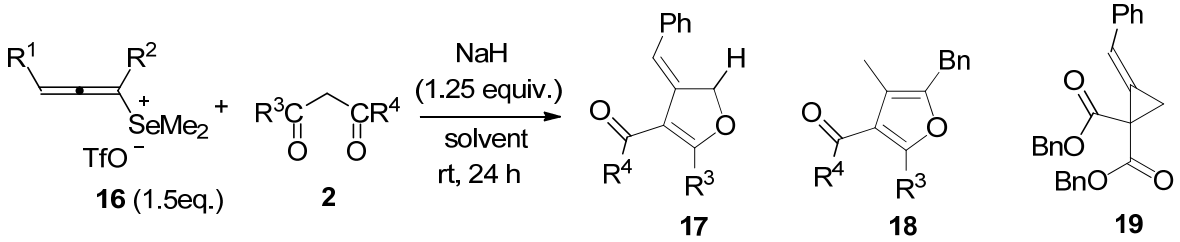
5. THE REACTION OF ALLENYLSELENONIUM SALTS WITH ACTIVE METHYLENE CARBANIONS[16]

The addition of nucleophiles to electron-deficient allene compounds is one of the most widely used construction methods in organic synthesis.[17] In spite of their interesting features, allenylselenonium salts, which have still not been synthesized, should be targeted to determine their properties.

Allenyl methyl selenides were alkylated with methyl trifluoromethanesulfonate to afford the desired selenonium salts **16a** and **16b**. Table 3 shows the reactions of the allenylselenonium salt **16** with active methylene carbanions. We first conducted the reaction of **16a** with 2,4-pentanedione **2a** in DMF (entry 1) and *t*-BuOH (entry 2) at room temperature for 3 h to afford the dihydrofuran derivative **17a** in 32% and 42%, respectively. The reaction with the ketoester **2h** in a mixture of *t*-BuOH and DMF gave **17b** in 41% yield (entry 3). On the other hand, the methylene cyclopropane derivative **19** was obtained from the reaction with dibenzyl malonate **2i** (entry 4). The structures of **17** and **19** were determined on the basis of

their spectral data. Interestingly, the reactions of **16b** gave different products from those of **16a**. The tetra-substituted furan derivative **18a** was produced in 60% yield by the reaction of **16b** with 2,4-pentanedione **2a** in the presence of sodium hydride in DMF for 24 h (entry 5). The ketoester **2h** also reacted with **16b** to afford the corresponding furan **18b** in 56% yield (entry 6). Furthermore, the reactions with the dibenzyl malonate **2i** produced the furan derivative **18c** (entry 7), differently from the reaction forming the methylenecyclopropane **19** from **16a**.

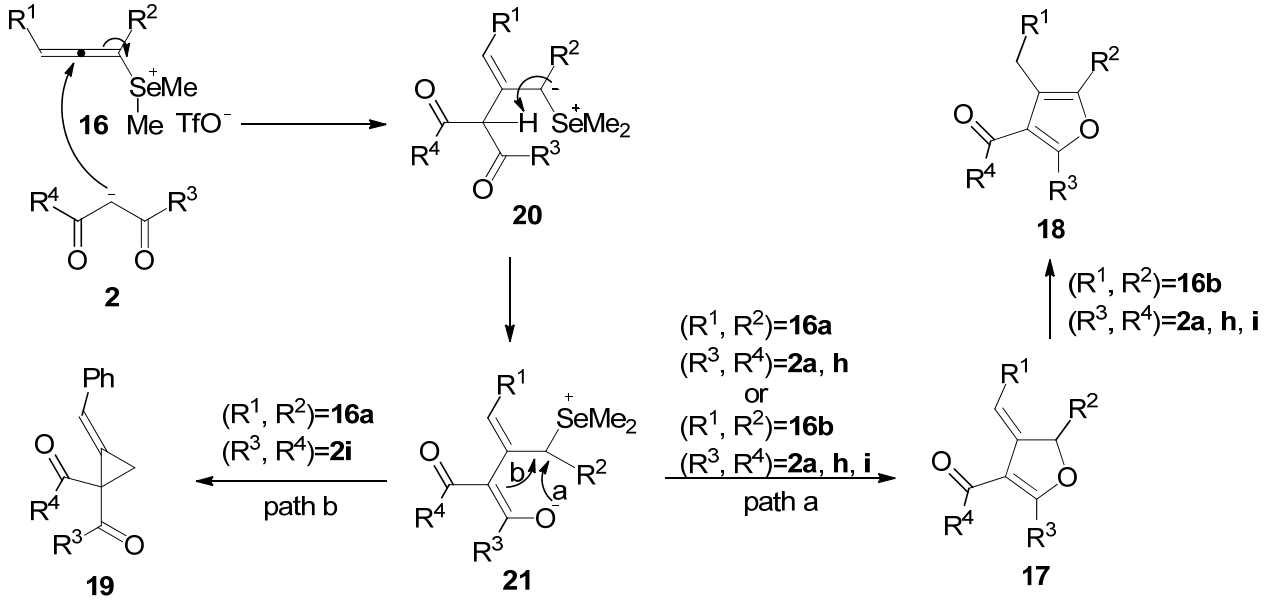
Table 3. The reactions of **16** with active methylene compounds



Entry	**16**	R^1	R^2	**2**	R^3	R^4	solvent	Products (%Yield)		
1	**16a**	Ph	H	**2a**	Me	Me	DMF	**17a** (32)		
2	**16a**			**2a**			*t*-BuOH	**17a** (42)		
3	**16a**			**2h**	Me	OEt	*t*-BuOH-DMF 3 : 1	**17b** (41)		
4	**16a**			**2i**	OBn	OBn	*t*-BuOH			**19** (50)
5	**16b**	H	Bn	**2a**			DMF		**18a** (60)	
6	**16b**			**2h**			DMF		**18b** (56)	
7	**16b**			**2i**			DMF		**18c** (47)	

The reactions of **16** with various active methylene compounds gave furan derivatives **17** and **18** except for the formation of the cyclopropane derivative **19** from **16a** and dibenzyl malonate **2i**. A plausible reaction mechanism is shown in Scheme 5. The selenonium ylides **20** are formed from the conjugate addition of an active methylene carbanion to the allenylselenonium salt **16**. Deprotonation of an active methine proton generates betaine **21**. In the case of the selenonium salt **16a**, the intramolecular nucleophilic attack of the enolate occurs to afford the dihydrofuran derivatives **17** (*path a*) when the active methylene compound possesses not less than one acyl group. On the other hand, an active methylene carbanion of the diester derivative **21** ($R^3 = R^4$ = OBn), which has greater electron density on the carbon, attacks the primary α-carbon (R^2 = H) of the selenonio group to give the methylenecyclopropane derivative **19** in spite of their ring strain (*path b*). Since carbanions attack the center carbon of the allenyl moiety in **16** from the backside of the R^1 (phenyl) group, the geometry of the phenyl group and the nucleophiles has a *trans* configuration. Meanwhile, the reactions of **16b** with active methylene carbanions proceed through *path a* regardless of the structure of the active methylene compounds. Due to the steric hindrance of the secondary α-carbon (R^2 = Bn) to the selenonio group, the nucleophilic attack of the carbanion to the

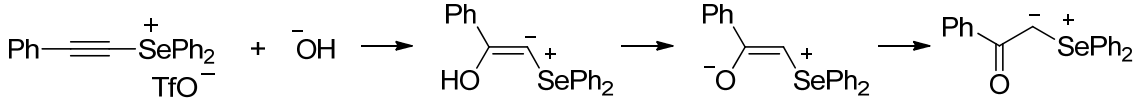
α-carbon (*path b*) is inhibited and the enolization predominantly proceeds to produce unstable dihydrofurans, which are easily transformed into the more stable furan derivatives **18** under the given reaction conditions.



Scheme 5. Plausible mechanism for the reactions of **16** with **2**

6. THE REACTION OF AN ALKYNYLSELENONIUM SALT WITH A HYDROXY NUCLEOPHILE[18]

Although some stable selenonium ylides bearing two electron-withdrawing substituents on the carbanionic center were prepared by diverse methods,[19] selenonium ylides bearing an electron-withdrawing group were generated only by the deprotonation of the corresponding selenonium salts.[20] Only a β-ketodiarylselenonium ylide stabilized by a carbonyl group was prepared but its reactivities have not been studied.[21] Based on our research on the reactivities of the diarylalkynylselenonium salts, we expected that the diarylalkynylselenonium salts would react with an hydroxide ion followed by the enol–keto tautomerization to afford a ketodiarylselenonium ylide (Scheme 6).[22] We investigated the reactions of alkynylselenonium salts with lithium hydroxide and the capture of the resulting ylides with aldehydes.

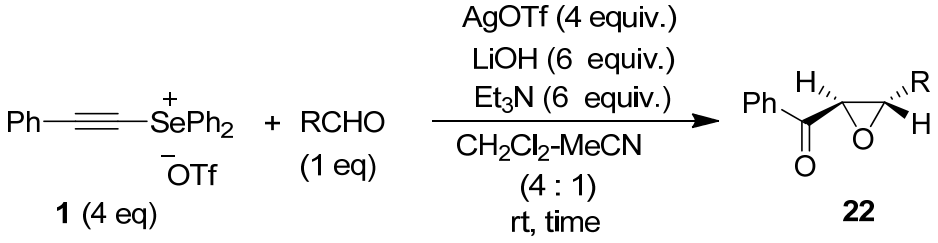


Scheme 6. Conjugate addition of hydroxide to alkynylselenonium salt

The reaction of *p*-nitrobenzaldehyde with 2 equiv. of the alkynylselenonium salt **1a** in the presence of 3 equiv. of lithium hydroxide at room temperature slowly proceeded, and *trans*-2-benzoyl-3-

(4-nitrophenyl)oxirane and diphenyl selenoxide were obtained in 17% and 17% yields, respectively, as shown in Table 4 (entry 1). The optimization of the experimental conditions clarified that the addition of silver triflate and triethylamine improved the yield of the oxirane. The best yield of **22a** was obtained when using 4 equiv. of the alkynylselenonium salt **1a** and silver triflate and 6 equiv. of triethylamine and lithium hydroxide toward the aldehyde for 12 h (entry 2). Under the same conditions, several aromatic aldehydes underwent the reactions, and good yields of the desired oxiranylketones **22** were obtained. Electron-withdrawing groups on the aromatic ring accelerated the reaction rate (entries 3-7). The reactions with aliphatic aldehydes were carried out under the same reaction conditions as those used for the aromatic aldehydes. The desired compound **22g** was obtained in 54% yield from the reaction with 3-phenylpropanal (entry 8). Additionally, isobutyraldehyde as a chain-branching aldehyde reacted with the ketoselenonium ylide to produce the oxiranyl ketone **22h** in 37% yield, and the reaction with 3-methylbutanal showed a better result, producing a 63% yield of the oxirane **22i** (entries 9 and 10). NMR analysis showed that these oxirane compounds obtained from the above reactions were only *trans*-isomers.

Table 4. The reactions of ketoselenonium ylide with RCHO

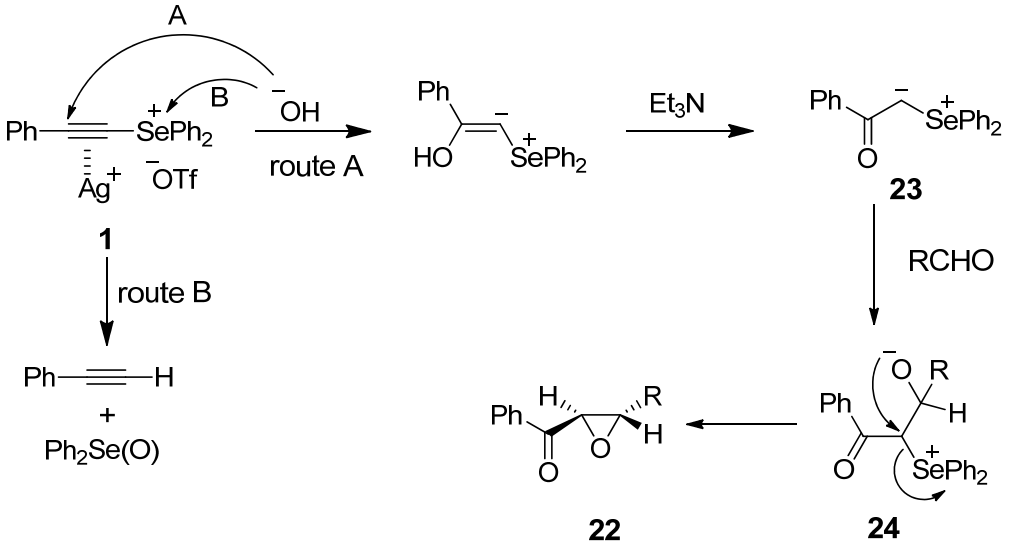


Entry	R	Time	Products (%Yield)
1[a]	*p*-$NO_2C_6H_4$	24 h	**22a** (17)[b]
2	*p*-$NO_2C_6H_4$	3.5 h	**22a** (84)
3	*o*-$NO_2C_6H_4$	1.5 h	**22b** (71)
4	*m*-$NO_2C_6H_4$	2 h	**22c** (58)
5	*p*-ClC_6H_4	12 h	**22d** (78)
6	*p*-BrC_6H_4	9 h	**22e** (55)
7	Ph	6.5 h	**22f** (40)
8	$Ph(CH_2)_2$	24 h	**22g** (54)
9	Me_2CH	overnight	**22h** (37)
10	Me_2CHCH_2	24 h	**22i** (63)

[a] **1** (2 equiv.), *p*-$NO_2C_6H_4CHO$ (1 equiv.) and LiOH (3 equiv.) were used.
[b] Diphenyl selenoxide was also obtained (17%).

On the basis of these results, we propose a plausible mechanism for the reaction of an alkynylselenonium salt with aldehydes in the presence of hydroxide, silver salt and triethylamine (Scheme 7). The triple bond

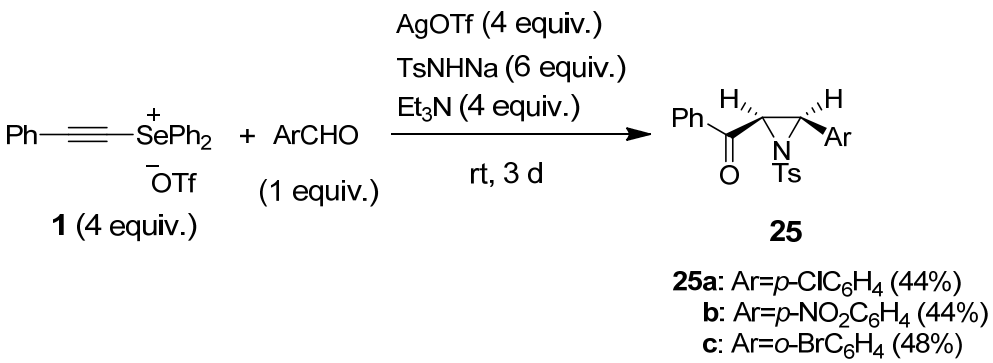
of the alkynylselenonium salt is activated by a silver cation, and a hydroxide ion attacks the β-carbon of the alkynylselenonium salt to form the vinyl ylide, which is transformed into the ketodiphenylselenonium ylide **23** by enol–keto tautomerization accelerated by triethylamine. The ylide reacts with aldehydes to give oxiranylketones together with diphenyl selenide (route A). On the other hand, diphenyl selenoxide is formed by the attack of the hydroxide on a selenonium cation without activation of a triple bond by the silver ion (route B).[23] The reason that only *trans*-oxiranes are formed can be explained by the assumption that an active methine hydrogen in the betaine intermediate is easily deprotonated by excess bases in this system and the resulting thermodynamically stable conformer cyclizes to produce the *trans*-epoxides **22**.



Scheme 7. Plausible mechanism for oxirane formation

In anticipation of the production of oxiranyl imines, *p*-toluenesulfonamide was selected as a nucleophile (Scheme 8). The reaction of the alkynylselenonium salt **1** with *p*-chlorobenzaldehyde and sodium *p*-toluenesulfonamide in the presence of triethylamine and silver trifluoromethanesulfonate was undertaken under conditions similar to those in Table 4. Unexpectedly, 2-benzoyl-3-(*p*-chlorophenyl)-1-tosylaziridine **25a**, not the oxiranyl imine was obtained in 44% yield as a single *cis*-isomer. Other aldehydes also reacted to give the tosylaziridine derivatives in moderate yields. The coupling constants of the methine protons on the aziridine ring of **25** (7–8 Hz) indicate that these isomers have a *cis* geometry. The initial step of the above reaction is presumed to be the formation of an *N*-sulfonylaldimine and a hydroxide ion from a *p*-toluenesulfonamide monosodium salt and an aromatic aldehyde. The subsequent reaction of the *N*-sulfonylaldimine with the β-ketoselenonium ylide **23**, which is generated by an alkynylselenonium salt and a hydroxide ion, would lead to producing an aziridine derivative. However, the reaction of the alkynylselenonium salt **1** with *N*-tosyl-4-nitrobenzaldimine and lithium hydroxide in the presence of triethylamine and silver trifluoromethansulfonate at room temperature for 10 h gave the oxiranylketone **22b** in 42% yield, and the desired aziridine derivative was not obtained. Recently, the

preparation of aziridines starting from ylides and imines was reported.[24] We have achieved a novel type of aziridine formation using the alkynylselenonium salt, aldehyde, and sodium *p*-toluenesulfonamide.



1 (4 equiv.)

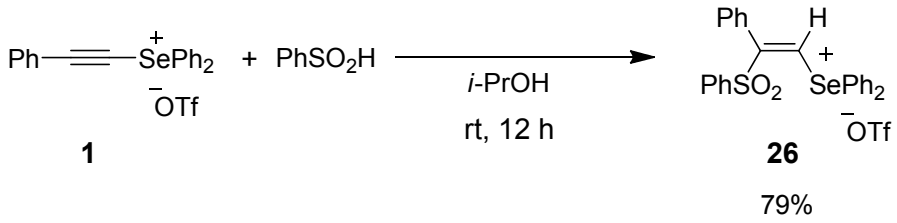
25

25a: Ar=*p*-ClC_6H_4 (44%)
b: Ar=*p*-$NO_2C_6H_4$ (44%)
c: Ar=*o*-BrC_6H_4 (48%)

Scheme 8. Reactions of alkynylselenonium salt with ArCHO and TsNHNa

7. THE REACTION OF ALKYNYLSELENONIUM SALTS WITH SULFUR NUCLEOPHILES[22d,e]

Next, the reactivities of a sulfinic acid and a thiol as soft nucleophiles toward the selenonium salt were investigated. The reaction of the alkynylselenononium salt **1** with benzenesulfinic acid in *i*-PrOH gave the (*Z*)-β-sulfonylvinylselenonium salt **26** in good yield. The stereochemistry of **26** was determined as (*Z*) by the NOE measurement (8.0%) between the vinylic proton and *ortho*-protons of the *Z*-phenyl group. This result indicated that the alkynylselenonium salt underwent the anti-addition of the Michael-type reaction of benzenesulfinic acid in a way similar to the general nucleophilic addition to alkynes (Scheme 9).



1

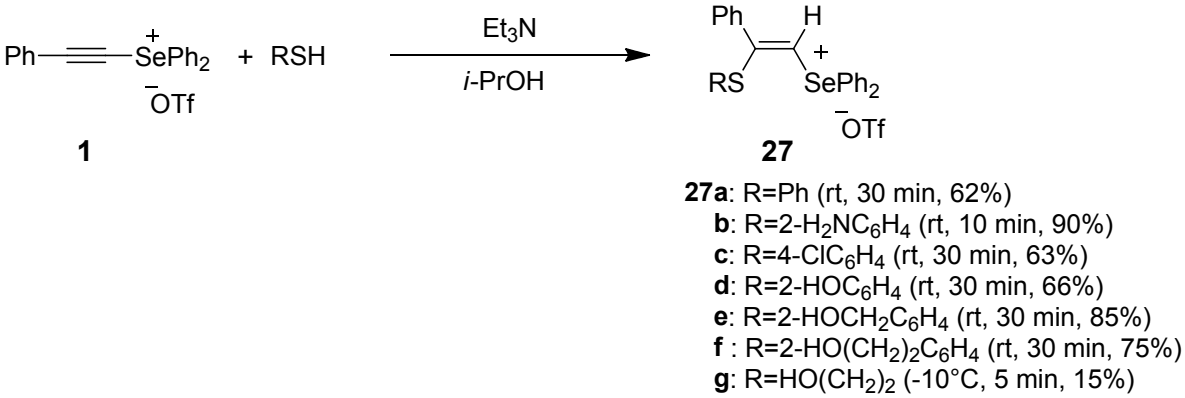
26

79%

Scheme 9. Reaction of alkynylselenonium salt with $PhSO_2H$

The reactions of diphenylalkynylselenonium triflate **1** with various thiols in *i*-PrOH at room temperature were examined (Scheme 10). The reaction with 2 equiv. of thiophenol for 24 h afforded an inseparable mixture of a conjugate adduct **27a** and unreacted starting material **1** in 10% and 20% yields, respectively. The reaction with 1.1 equiv. of thiophenol in the presence of 0.1 equiv. of triethylamine for only 30 min afforded **27a** in 62% yield. To confirm the effect of an amine, the reaction with *o*-aminothiophenol without triethylamine was carried out to afford the desired compound **27b** in 90% yield only for 10 min. The reaction with other arenethiol derivatives bearing neutral substituents, such as a chloro, hydroxy, or hydroxy alkyl group, also produced the vinylselenonium salts **27c-f** in good yields. Based on these

findings, the presence of a small amount of a weak base is very important for the preparation of the *β*-arylthioalkenylselenonium salts. The interaction between the base and a thiol group activates the nucleophilicity of the thiols. In contrast to arenethiols, the alkanethiols did not give good results. The vinylselenonium salt **27g** was generated from the reactions with 2-mercaptoethanol in only 15% yield after neutralization of the reaction mixture with aqueous $NaHCO_3$. The (*Z*) stereochemistry of **27** was determined by the NOE technique, and the results were attributable to the *anti*-addition of the thiols with the alkynyl moiety.



1 **27**

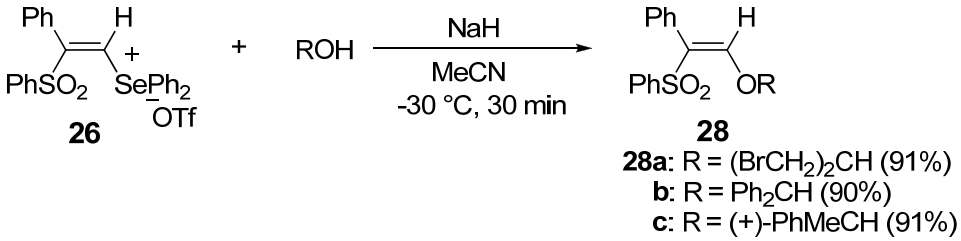
27a: R=Ph (rt, 30 min, 62%)
b: R=2-$H_2NC_6H_4$ (rt, 10 min, 90%)
c: R=4-ClC_6H_4 (rt, 30 min, 63%)
d: R=2-HOC_6H_4 (rt, 30 min, 66%)
e: R=2-$HOCH_2C_6H_4$ (rt, 30 min, 85%)
f : R=2-$HO(CH_2)_2C_6H_4$ (rt, 30 min, 75%)
g: R=$HO(CH_2)_2$ (-10°C, 5 min, 15%)

Scheme 10. Reaction of alkynylselenonium salt with thiols

8. THE REACTION OF (*Z*)-β-SULFONYLVINYLSELENONIUM SALT WITH NUCLEOPHILES[22b,e]

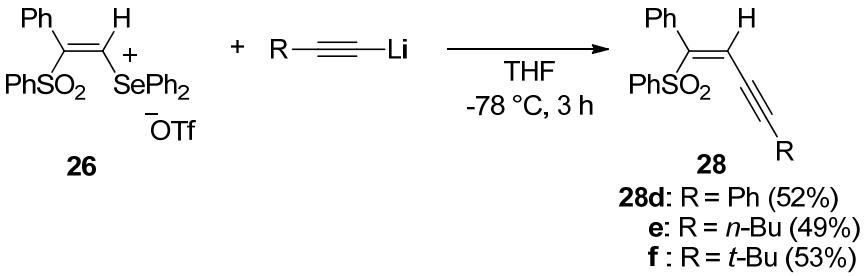
Vinyl sulfones are some of the most important building blocks in organic synthesis because of their versatility. Various synthetic methods to achieve vinyl sulfones have been developed.[25] However, there have been only a few reports on the introduction of a substituent at the β-position by manipulation of a simple vinyl sulfone.[26] We attempted to prepare β-functionalized vinyl sulfones by using the β-sulfonylvinylselenonium salts because the selenonium group is an effective leaving group.

The reactions of the β-phenylsulfonylvinylselenonium salt **26** with alkoxides in MeCN were investigated (Scheme 11). The selenonium salt smoothly reacted with 1,3-dibromo-2-propanol as an acyclic secondary alcohol in the presence of NaH at -30 °C for 30 minutes to produce the (*Z*)-β-alkoxyvinyl sulfone **28a** in 91% yield. Employment of a bulky secondary alcohol, *i.e.*, diphenyl methanol, also reacted to afford the corresponding vinyl sulfone **28b** in high yield under the same conditions. Application of this method to the chiral *O*-alkyl enol ether synthesis was achieved by the reaction with (+)-1-phenylethanol, and a chiral (*Z*)-β-alkoxyvinyl sulfone **28c** was obtained in 91% yield. The β-alkoxyvinyl sulfones **28** shown in Scheme 10 were only single geometrical isomers. The stereochemistry of compound **28a** was determined to be (*Z*) by NOE enhancement of the *ortho*-protons of the *Z*-phenyl group (7.3%) or the methine proton of the geminal 2-bromo-1-(bromomethyl)ethoxy group (18.6%) upon irradiation of the vinyl proton.



Scheme 11. Reaction of (*Z*)-β-phenylsulfonylvinylselenonium salt with alkoxides

The reactivity of alkynylides as carbanions with the vinylselenonium salts was also examined (Scheme 12). The reaction of the diphenylvinylselenonium salt **26** with 1.2 mole equivalents of lithium phenylethynylide, prepared from the reaction of phenylethyne and *n*-butyllithium in THF at -78 °C, afforded the (*Z*)-β-alkynylvinyl sulfone **28d** in 52% yield. The reactions with other alkynylides similarly produced the corresponding (*Z*)-enyne sulfone derivatives in good yields. The *Z* configuration was determined by the NOE experiment on **28f**, showing the enhancement of the *ortho*-protons of the *Z*-phenyl group (6.1%) upon irradiation of the vinyl proton.

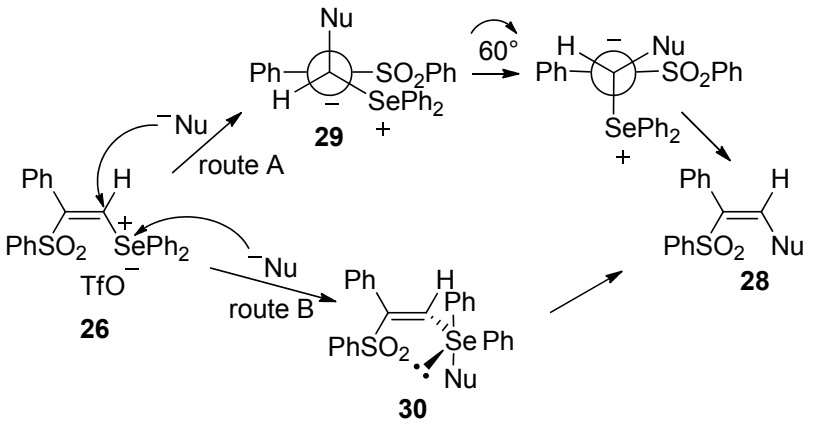


Scheme 12. Reaction of (*Z*)-β-phenylsulfonylvinylselenonium salt with acetylides

A plausible mechanism for the formation of the β-substituted (*Z*)-vinyl sulfones **28** from the reactions of the vinylselenonium salt **26** with nucleophiles is shown in Scheme 13. Route A proceeds *via* the pathway whereby the Michael-type addition of a nucleophile to the β-carbon in the vinyl sulfonyl moiety forms betaine **29** and the subsequent elimination of a selenide leads to the (*Z*)-vinyl sulfones with retention of its configuration.[27] Another pathway, route B, involves the formation of the selenurane intermediate **30**, *via* direct attack of the nucleophile on the selenium atom in the vinylselenonium salt, followed by ligand coupling between the Nu and the vinyl group of **30**.[28] Both pathways provide feasible explanations of the stereochemical outcome observed in these reactions. The attack of nucleophiles at the α position on the vinyl group in **26** was attributed to the steric hindrance around the β-carbon of **26**.[29]

9. THE REACTION OF (*Z*)-β-THIOVINYLSELENONIUM SALT WITH NUCLEOPHILES[22c,d]

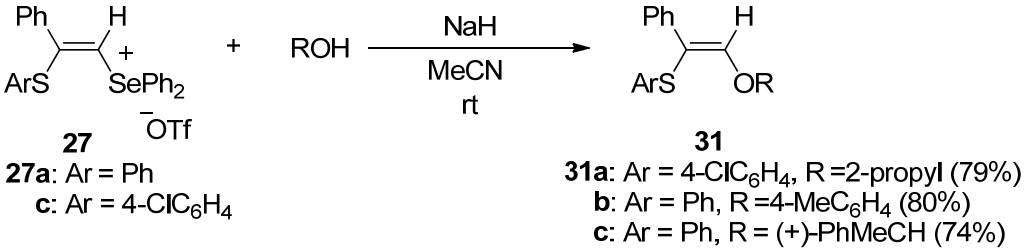
The (*Z*)-β-sulfonylalkenylselenonium salts with two kinds of electron-withdrawing groups on the double bond reacted with a variety of nuclephiles to produce (*Z*)-β-substituted vinyl sulfones (not



Scheme 13. Plausible mechanism for the reaction of **26** with nucleophiles

vinylselenonium salts) with retention of their configuration. Interestingly, if the sulfonyl group in the β-sulfonylalkenylselenonium salts is replaced by an alkylthio group, the reactivity of the β-alkylthioalkenylselenonium salts against nucleophiles will be changed, and it is anticipated that the Michael-type addition against the selenonio group would occur at only the β-carbon. On the basis of this background, we investigated the reactions of (*Z*)-β-thioalkenylselenonium salts with nucleophiles.

First, the reactivity of the alkoxide toward the β-thioalkenylselenonium salts was examined (Scheme 14). The reaction of **27c** with isopropoxide in MeCN afforded the 2-alkoxy-1-arylthioethene **31a** in 79% yield. A good result was also obtained from the reaction of **27a** in the case of the phenoxide derivative. In addition, we tried to prepare a chiral β-alkoxylvinyl sulfide from the reaction with a chiral alkoxide. The reaction of **27a** with sodium (+)-1-phenylethanolate, which was prepared from the corresponding alcohol and NaH, produced a chiral β-alkoxylvinyl sulfide **31c** in 74% yield at room temperature for 90 min. The NOE experiment of **31a** showed an enhancement of the *ortho*-protons of the *cis*-phenyl group and the methine proton of the geminal 2-propoxy group upon irradiation of the vinyl proton.

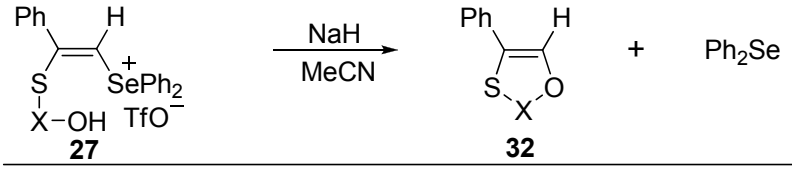


Scheme 14. Reaction of (*Z*)-β-arylthiovinylselenonium salt with alkoxides

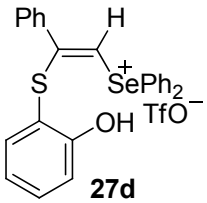
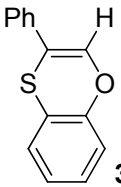
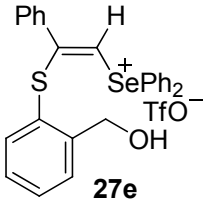
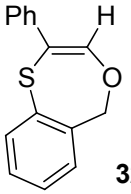
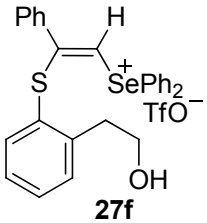
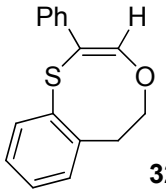
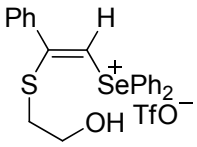
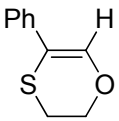
Due to the success of the reactions of the alkenylselenonium salts **27** with an alkoxide in MeCN, we decided to try the synthesis of medium-sized heterocyclic compounds containing sulfur and oxygen atoms *via* an intramolecular cyclization reaction (Table 5). The reaction of the alkenylselenonium salt **27d** with NaH in MeCN at −10 °C for 24 h produced a complex mixture, and the ring closure product **32a** was obtained in only 17% yield (entry 1). On the other hand, the reaction of the selenonium salt **27e** smoothly

proceeded to afford the desired compound, 2-phenyl-5*H*-4,1-benzoxathiepine **32b**, in 67% yield (entry 2). 2-Phenyl-5,6-dihydro-4,1-benzoxathiocine **32c** was also prepared from **27f** in 54% yield (entry 3). In contrast to the compound bearing a hydroxyphenylthio group **27d**, the compound with a hydroxyethyl side chain, **27g**, produced the cyclic product **32d** in 51% yield. The syntheses of six- and seven-membered heterocycles including sulfur and oxygen atoms have been reported;[30] however, only a few studies on the preparation of 5*H*-4,1-benzoxathiepine derivatives have been published.[31] Furthermore, there has been no report on the synthesis of 4,1-benzoxathiocine and related compounds. This new method of preparing medium-sized heterocycles containing sulfur and oxygen atoms is expected to have a wide number of applications.

Table 5. Ring closure reaction of alkenylselenonium salts **27d-g**

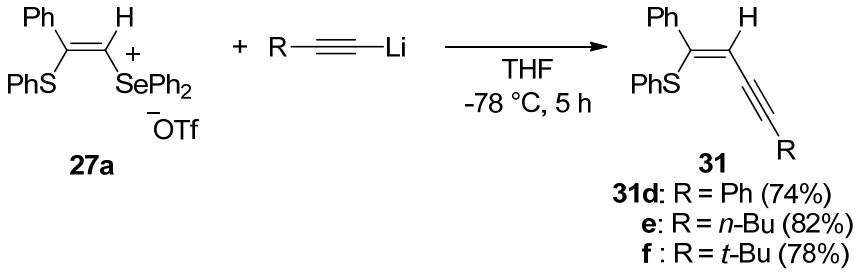


27 **32**

Entry	RPh_2Se^+	Temp.	Time	Products (%Yield)
1	 **27d**	-10 °C	24 h	 **32a** (17)
2	 **27e**	rt	3 h	 **32b** (67)
3	 **27f**	rt	20 h	 **32c** (54)
4	 **27g**	rt	3 h	 **32d** (51)

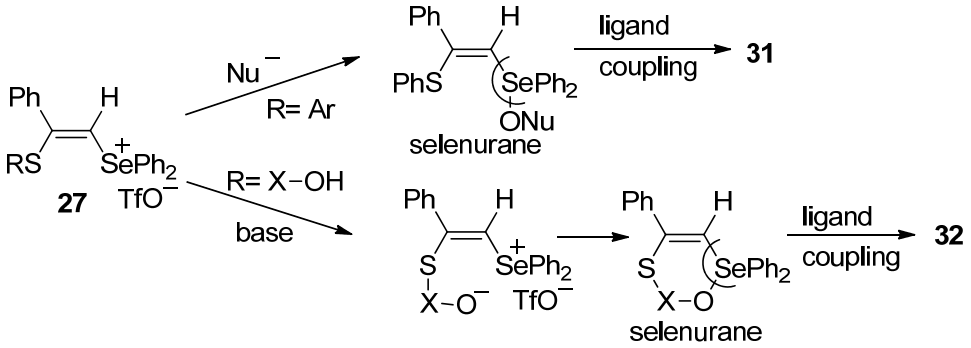
Next, the reactions of the *β*-thioalkenylselenonium salt **27a** with alkynylides were conducted (Scheme 15). The reaction of **27a** with lithium phenylethynylide produced (*Z*)-4-phenyl-1-(phenylthio)-1-buten-3-yne **31d** in 74% yield in THF at −78 °C for 5 h. The reactions with other alkynylides, such as 1-hexynylide

and 3,3-dimethyl-1-butynylide, also afforded the desired compounds under the same conditions in good yields. The structures of **31d–f** were identified by spectral data. In particular, the ^{1}H NMR spectrum of **31e** showed long-range coupling between a vinyl proton and protons of the 5-position (2 Hz). The (*Z*) stereochemistry of **31d–f** was established by observation of the NOE enhancement (10%) between the vinylic proton and *ortho*-protons of the *cis*-phenyl group in compound **31d**.



Scheme 15. Reaction of (*Z*)-β-phenylthiovinylselenonium salt with acetylides

A plausible reaction mechanism to produce (*Z*)-vinyl sulfides consists of the formation of the selenurane intermediate followed by ligand coupling between the Nu group and the alkenylcarbon with retention of the configuration (Scheme 16).

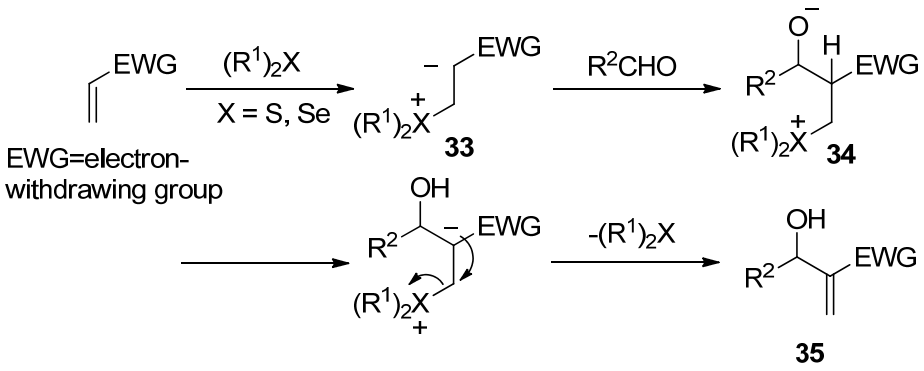


Scheme 16. Plausible mechanism for the reaction of (*Z*)-β-thiovinylselenonium salts with nucleophiles

10. REACTIONS OF ELECTRON-DEFICIENT ALKENES WITH ALDEHYDES MEDIATED BY CHALCOGENIDE-$TiCl_4$[32-35]

We discussed the reactions of vinyl selenonium salts with nucleophiles in Section 8 and showed the addition-elimination mechanism as one of their reaction processes in Scheme 13. If the reverse reaction of this mechanism, the conjugate addition of a chalcogenide to an electron-deficient alkene proceeds in the presence of an aldehyde, the reaction shown in Scheme 17 might possibly occur.

A chalcogenide adds to an electron-deficient alkene and forms betaine **33**. The betaine **33** reacts with an aldehyde to afford a zwitterionic intermediate **34**, the alkoxide moiety of which intermolecularly abstracts the proton α to an electron-withdrawing group and brings about the β-elimination to afford an allyl



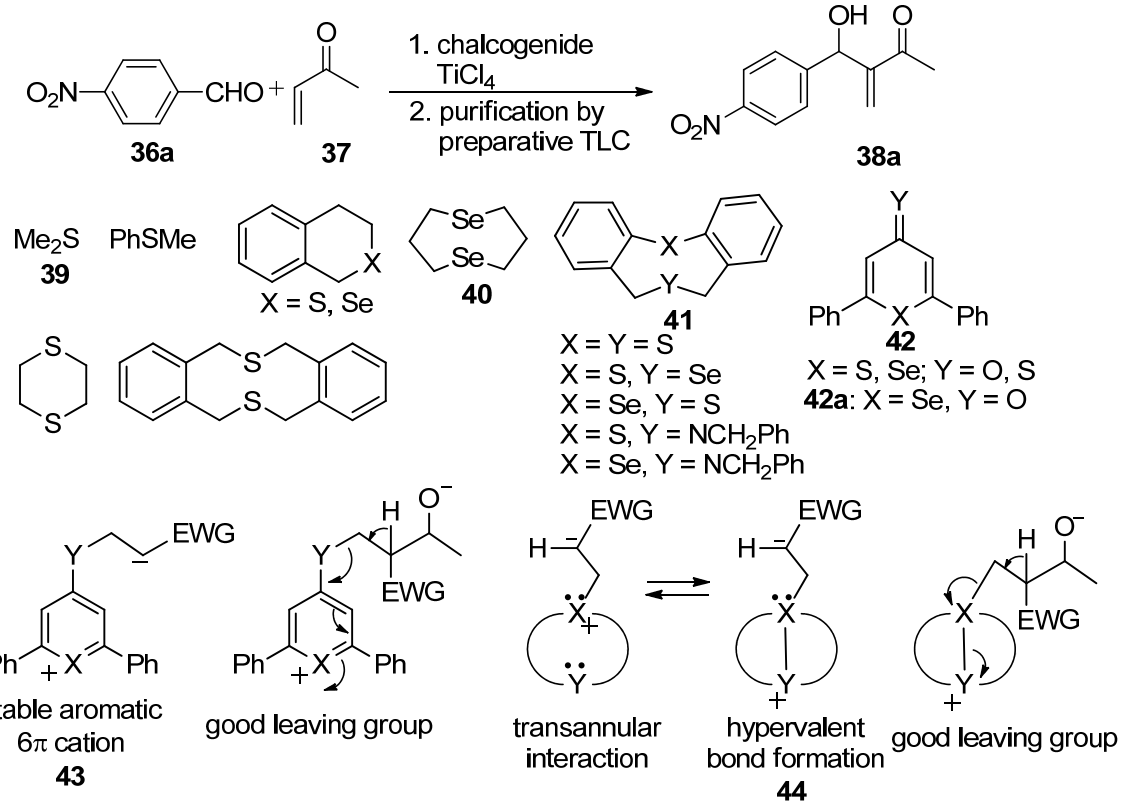
Scheme 17. Anticipated Morita-Baylis-Hillman reaction using a chalcogenide

alcohol **35**. This reaction is regarded as a chalcogenide version of the Morita-Baylis-Hillman（MBH）reaction (the chalcogeno-MBH reaction).

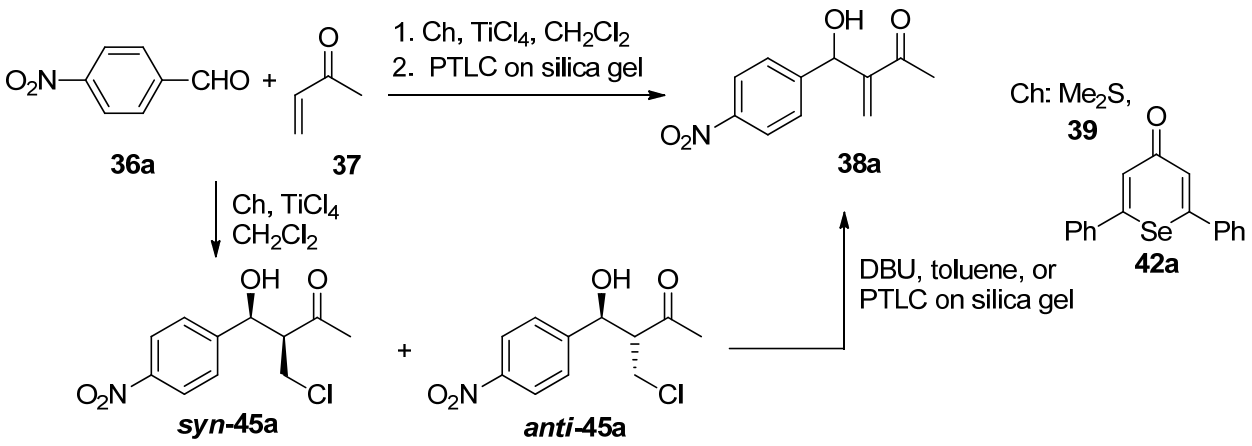
The chalcogeno-MBH reactions successfully proceeded using only a chalcogenide with a Lewis acid. The chalcogeno-MBH adducts were purified by preparative TLC on silica gel to give the desired products.[33] Various Lewis acids such as $AlCl_3$, BBr_3, BCl_3, and $TiCl_4$, were useful, and, especially, $TiCl_4$ exerted excellent effects.[33b] The chalcogenides shown in Scheme 18 were used. The 8-membered heterocycles **40** and **41** possessing two chalcogen atoms at the 1,5-positions effectively worked because the intermediary onium ion **44** was stabilized by the transannular interaction between the chalcogen atoms forming a hypervalent bond. Selenopyran-4-one, thiopyran-4-one and their 4-thione congeners **42** formed the stable 6π cations **43** by coordination of a Lewis acid at the 4-carbonyl or thiocarbonyl group and were also efficient catalysts.[34]

The reaction of but-3-en-2-one (**37**) with *p*-nitrobenzaldhyde (**36a**), shown in Scheme 19 as a typical example, afforded the MBH product **38a** in good yield. When the product was purified by column chromatography on silica gel, the *syn*- and *anti*-chloromethyl aldols **45a** were isolated.[35]

Although the results were different from the anticipated ones, in which a chalcogenide would nucleophilically attack the positively charged β-carbon of an enone, the reaction using a chalcogenide and a Lewis acid was the tandem Michael-aldol reaction from the viewpoint of the reaction mechanism (Scheme 20) and proceeded rapidly in comparison with the MBH reaction. Chalcogenide **46** coordinates with $TiCl_4$ and assists it in releasing a chloride ion. The resulting $TiCl_4$-chalcogenide complex **47**, the exact structure of which has not been determined, reacts with enone **37** *via* the cyclic transition state **48**. The stereoisomers of the chloride **45a** were easily transformed into the α-methylene-aldol **38a** upon treatment with a base or by preparative TLC on silica gel. Therefore, our newly developed reaction can be used as an alternative to the MBH reaction.[36]

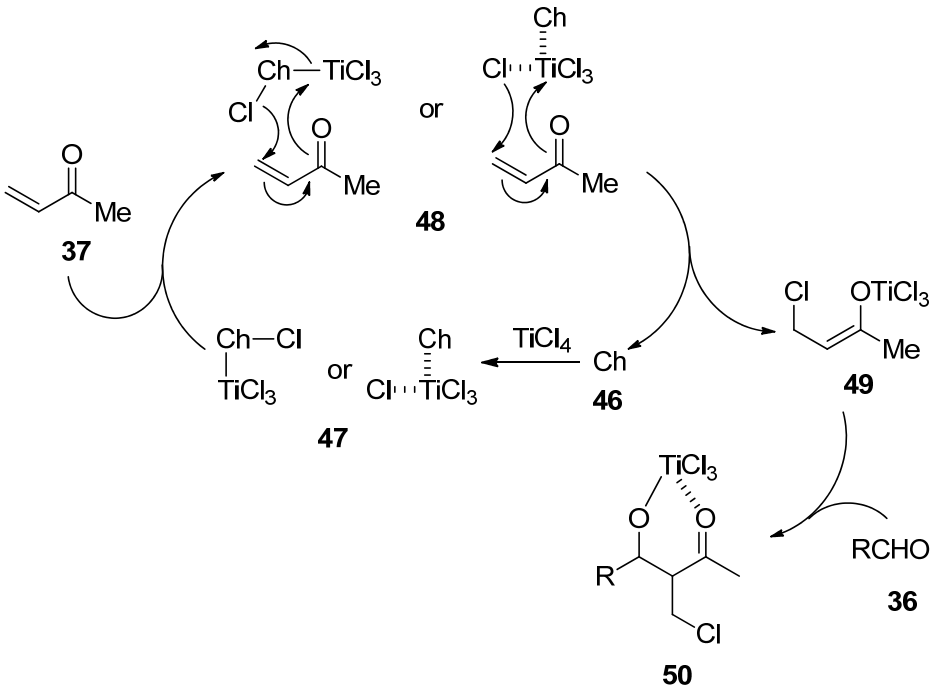


Scheme 18. Chalcogenide-$TiCl_4$-mediated reaction and chalcogenide catalysts

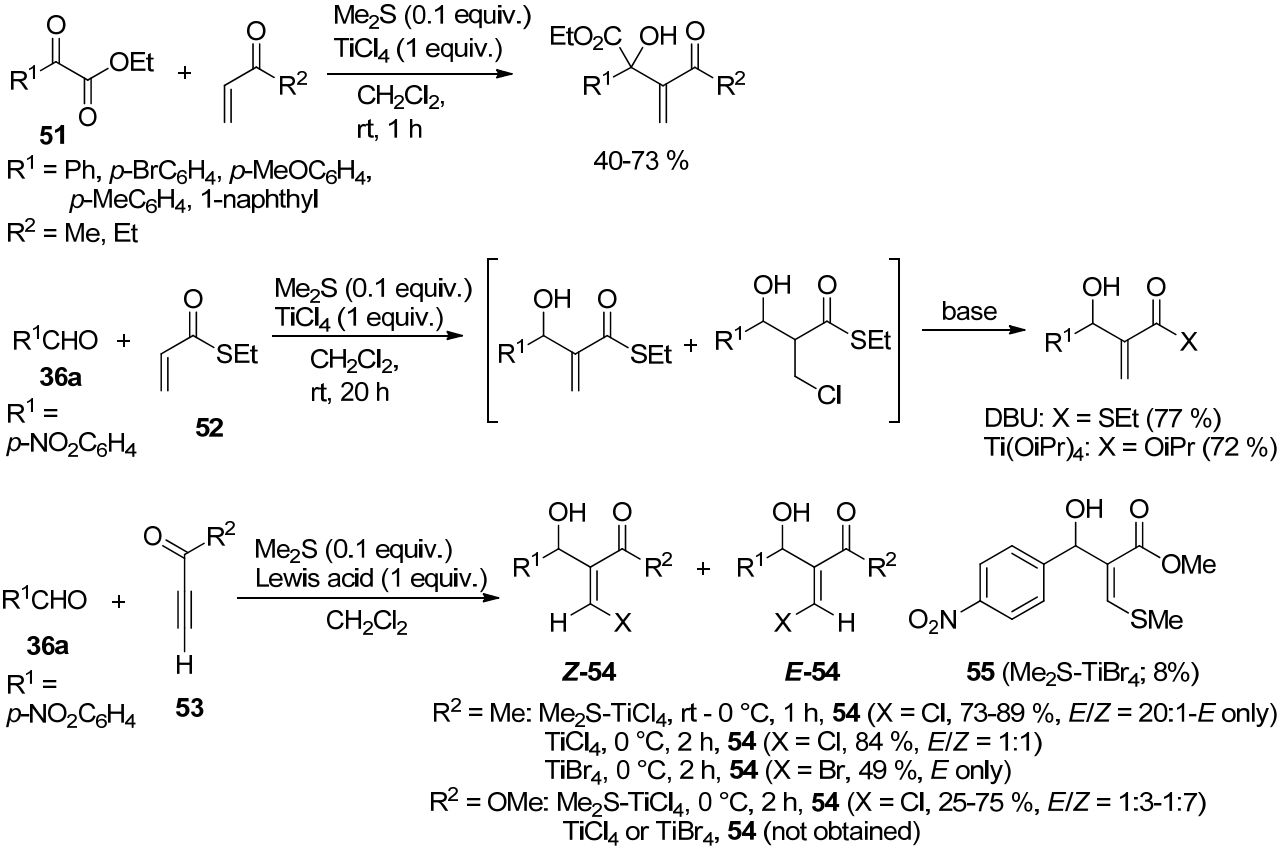


Scheme 19. Chalcogenide-$TiCl_4$-mediated tandem Michael-aldol reaction

Aromatic and aliphatic aldehydes[33b] and α-keto esters[37] **51** were reactive as carbonyl compounds for the reactions. Acyclic and alicyclic enones were very reactive as a Michael acceptor, but acrylonitrile and the acrylates were less reactive than the enones. Acrylic acid thioesters[38] **52** were quite active in the reactions and therefore, can be used for the synthesis of acrylic acid derivatives instead of the acrylates. Alkynyl ketones and acetylenic acid esters[39] **53** were applicable for this reaction and gave the β-halo-substituted MBH products **54** (Scheme 21).



Scheme 20. Mechanism for the formation of α-chloromethyl aldols

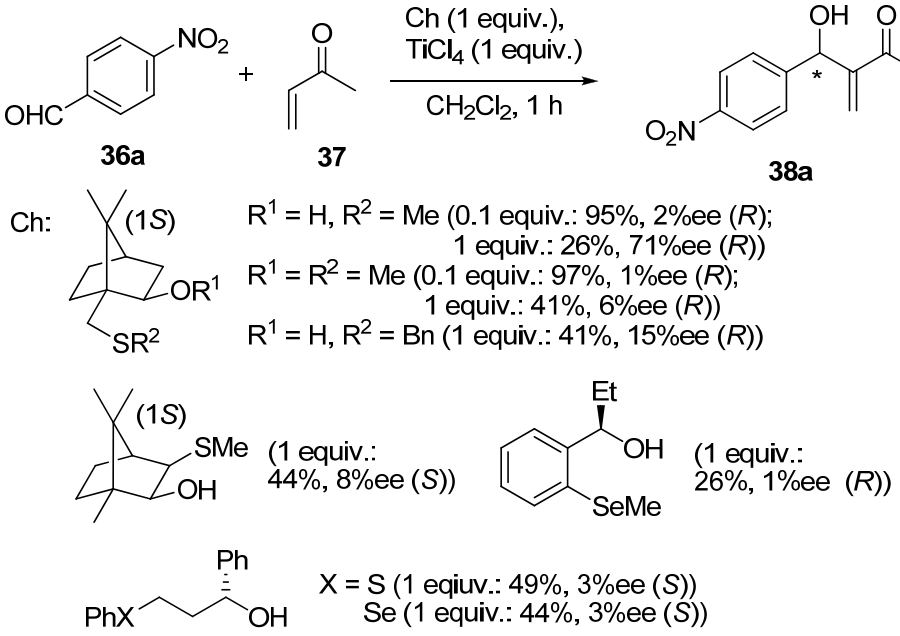


Scheme 21. Various tandem Michael-aldol reactions mediated by chalcogenide-$TiCl_4$

The Michael-aldol reactions using $TiCl_4$ have been reported one after another by the research groups of Li,[40] Ohshima,[41] and Shi.[42] Various kinds of Lewis acids and Michael donors have been used for the

tandem Michael-aldol reactions of electron-deficient alkenes with aldehydes.[43] Recently, Verkade and his co-workers found that the bicyclic proazaphosphatrane sulfide acted as an efficient catalyst for the MBH reaction.[44] This catalyst was used with $TiCl_4$ and the MBH reaction was complete within 30 minutes. The reactions of the β-substituted enones, acrylates and acrylonitrile were enabled by the catalyst to give the MBH adducts in high yields. The reactions using this catalytic system did not afford the α-chloromethyl aldols, but only the MBH adducts. This is different from the results of Li[40] and us.[33,35,38]

The MBH reaction that forms a chiral allyl alcohol and asymmetric synthesis using the MBH reaction has been thoroughly studied.[36d,g] Some reactions induced a high enantioselectivity.[45] We conducted the catalytic asymmetric reactions using 0.1 equiv. of various bifunctional catalysts containing a chalcogenide and alcohol, ether or amine group at −20 °C, as shown in Scheme 22. When 0.1 equiv. of chalcogenide was used, the chemical yields were very high, but the optical yields were very low. Good enantioselectivity (71%ee) was achieved using 1 equiv. of 10-methylsulfanylisoborneol, but the chemical yield was decreased.



Scheme 22. Asymmetric tandem Michael-aldol reaction using chiral chalcogenides

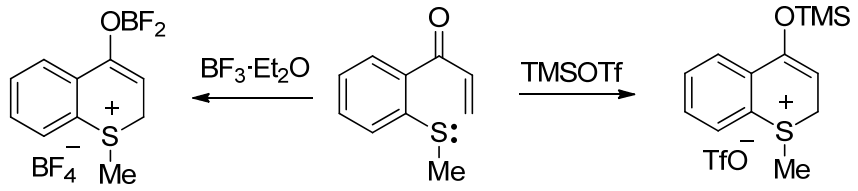
The asymmetric reaction of a chiral glyoxylate using Me_2S-$TiCl_4$ and that using a chiral sulfide-$BF_3{\cdot}Et_2O$ have been reported by Bauer[46] and Goodman,[47] respectively. Our reaction has the merits that it proceeds quickly and that the reactions of α-dicarbonyl compounds, alkynyl ketones and esters, which do not occur under the MBH reaction conditions, proceed smoothly.[37,38,46,48]

11. TANDEM MICHAEL-ALDOL REACTION OF CHALCOGENIDE-ENONES WITH CARBONYL COMPOUNDS[32,50]

The reactions of enones with aldehydes using the chalcogenide-$TiCl_4$ were the tandem Michael-aldol reaction initiated by the nucleophilic attack of a chloride ion on the electron-deficient β-carbon of enones and gave the β-chloro-α-hydroxymethyl adducts. Therefore, we returned to the starting point of this research and reconsidered the plan again that the reaction began with the Michael addition of a chalcogenide to an enone.

Vinyl sulfide **55** was formed, although the yield was low, from the reaction of *p*-nitrobenzaldehyde (**36a)** with methyl propiolate in the presence of Me_2S-$TiBr_4$, as shown in Scheme 21.[39b] Nenajdenko *et al*. reported that 1-ethyl-4-oxo-2,3-dihydrothiopyranium perchlorate was formed upon the treatment of 1-(ethylsulfanyl)pentane-1,3-dien-3-one with perchloric acid.[49]

These results indicate that sulfides work as Lewis bases and undergo the Michael reaction. We made a new plan for the tandem Michael-aldol reaction in which a key step was the intramolecular Michael addition of the chalcogenide group to the enone moiety activated by a Lewis acid whose conjugate base had a very low nucleophilicity. We first confirmed the intramolecular Michael addition of 1-[2-(methylsulfanyl)phenyl]propenone (**56**) in the presence of $BF_3{\cdot}Et_2O$ to form the cyclic sulfonio-enolate **57** by comparison of the ^{1}H-NMR spectrum of **57** with that of the TMS-enol ether **58** (Scheme 23).[50]



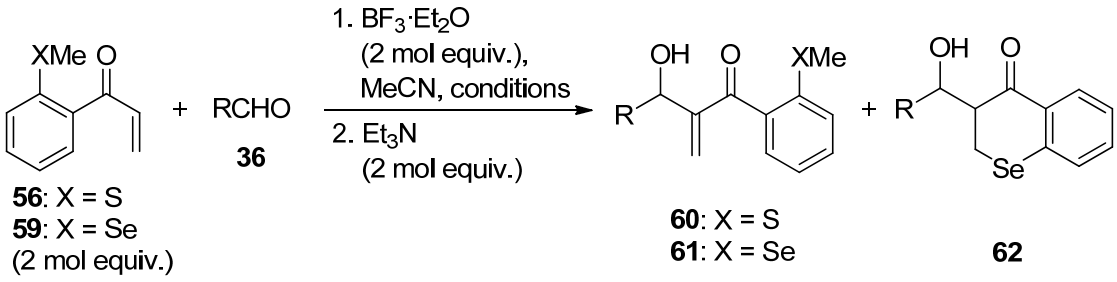
Scheme 23. Reaction of sulfide-enone with Lewis acids

The reaction conditions for the chalcogeno-enones **56** and **59** with aldehydes **36** were closely examined, and $BF_3{\cdot}Et_2O$ and triethylamine were selected as the Lewis acid and quenching base, respectively. The reactions of the sulfide-enone **56** gave MBH products **60**, but those of the seleno congener **59** afforded the selenochromanone **62** together with MBH products **61** (Table 6).

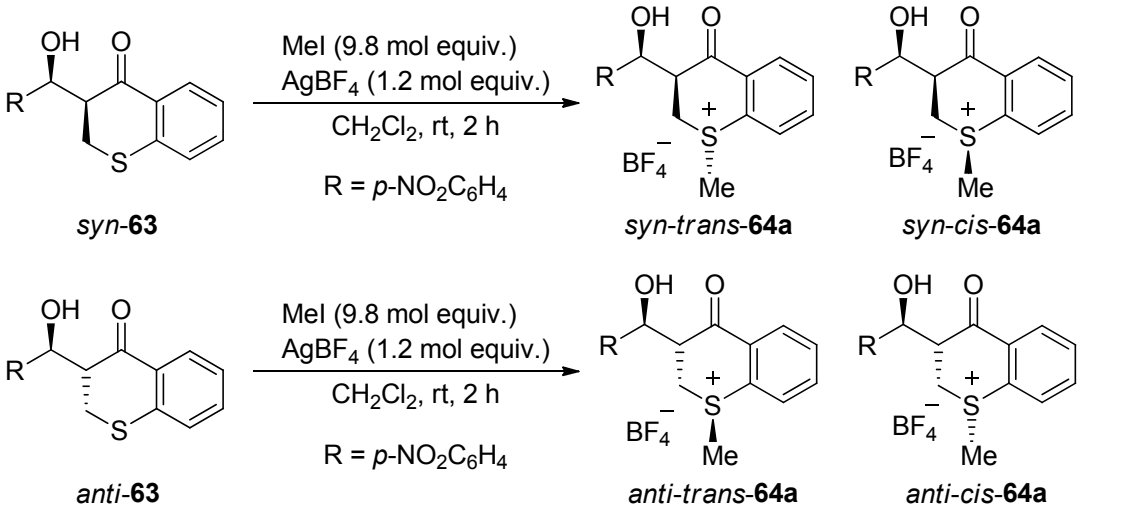
To elucidate the reaction mechanism, several experiments involving the intermediates, the sulfonium salts **64**, were conducted. Four stereoisomers of the selenonium salts **64** were synthesized by methylation of the *syn*- and *anti*-aldols **63** and their stereostructures were determined from the NOEs between the methyl group and the 3-proton (Scheme 24).

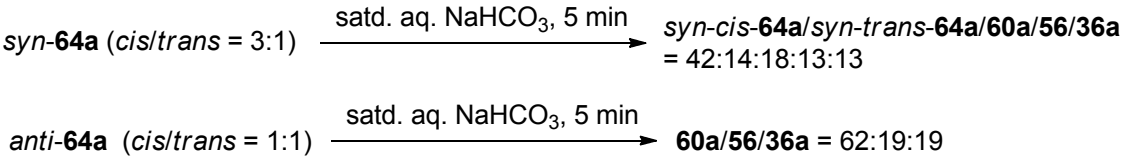
Treatment of the *syn*-sulfonium salt **64a** (*syn-cis* **64a**:*syn-trans* **64a** = 3:1) with saturated aqueous $NaHCO_3$ gave the MBH adduct **60a**, sulfonium salts **64a**, *p*-nitrobenzaldehyde (**36a**), and sulfide-enone **56**. On the other hand, treatment of the *anti*-sulfonium salts **64a** (*anti-cis* **64a**:*anti-trans* **64a** = 1:1) with

Table 6. Reaction of 1-[2-(methylchalcogeno)phenyl]propenones **56** and **59** with aldehydes **36**



Entry	Chalcogenide–enone	Aldehyde **36**	Conditions	Products (%Yield)
1	**56**	R = *p*-$NO_2C_6H_4$ (**36a**)	0 °C, 1 h	**60a** (75)
2	**56**	R = *p*-ClC_6H_4 (**36b**)	0 °C, 2 h	**60b** (73)
3	**56**	R = *p*-$CF_3C_6H_4$ (**36c**)	0 °C, 2 h	**60c** (75)
4	**56**	R = C_6H_5 (**36d**)	0 °C, 2 h then rt, 3 h	**60d** (60)
5	**56**	R = $PhCH_2CH_2$ (**36e**)	0 °C, 2 h then rt, 3 h	**60e** (70)
6	**59**	**36a**	0 °C, 2 h	**61a** (75), **62a** (16, *syn*/*anti*=95:5)
7	**59**	**36b**	0 °C, 2 h	**61b** (69), **62b** (20, *syn* only)

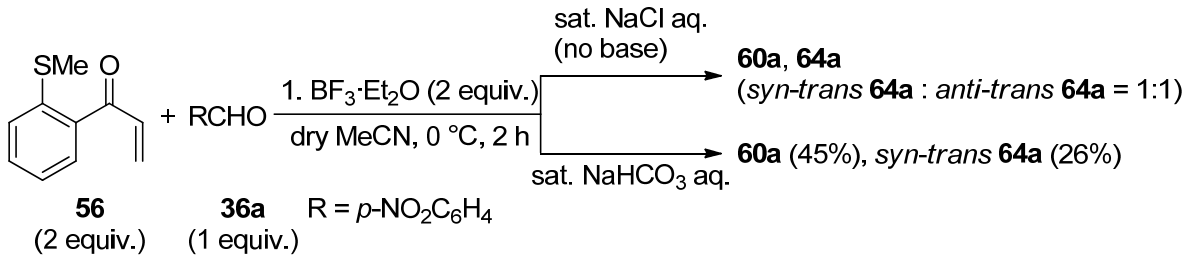




Scheme 24. Synthesis of sulfonium salts **64** and reactions with $NaHCO_3$

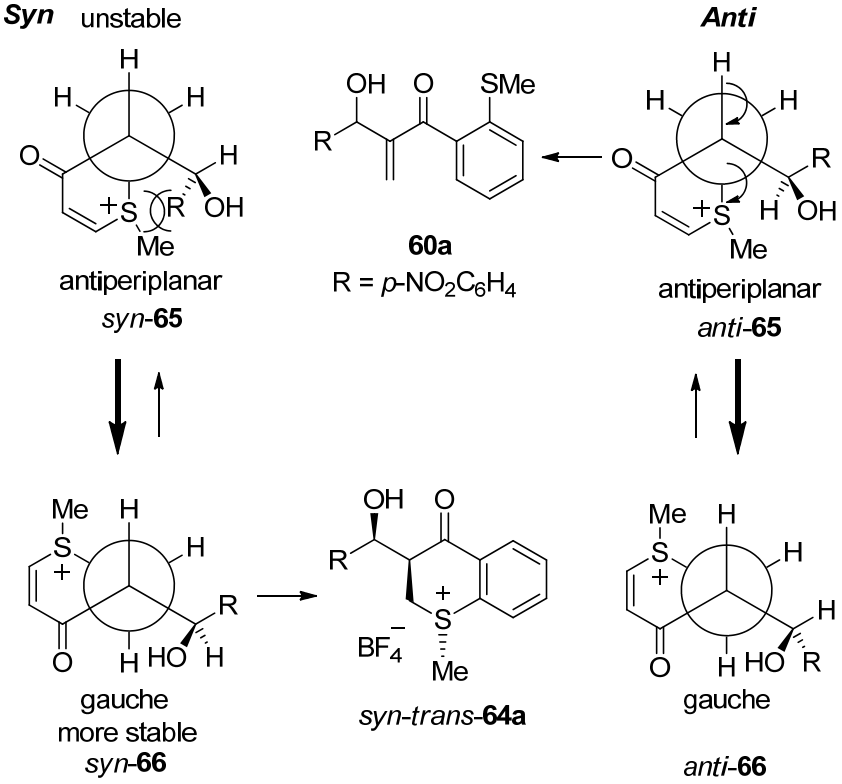
saturated aqueous $NaHCO_3$ gave the Morita-Baylis-Hillman adduct **60a**, *p*-nitrobenzaldehyde (**36a**), and sulfide-enone **56**, and the starting material **64a** was not recovered. These findings indicate that the *anti*-**64a** more easily undergoes β-elimination than the *syn*-isomer and that the retro-aldol reaction of **60a** also occurs in competition with the β-elimination upon treatment with a base.

When the reaction mixture of **56** and **36a** was worked up in different ways, the isolated sulfonium salts were different (Scheme 25).



Scheme 25. Isomer ratio of sulfonium salts **64** formed from sulfide-enone **56** and aldehyde **36a**

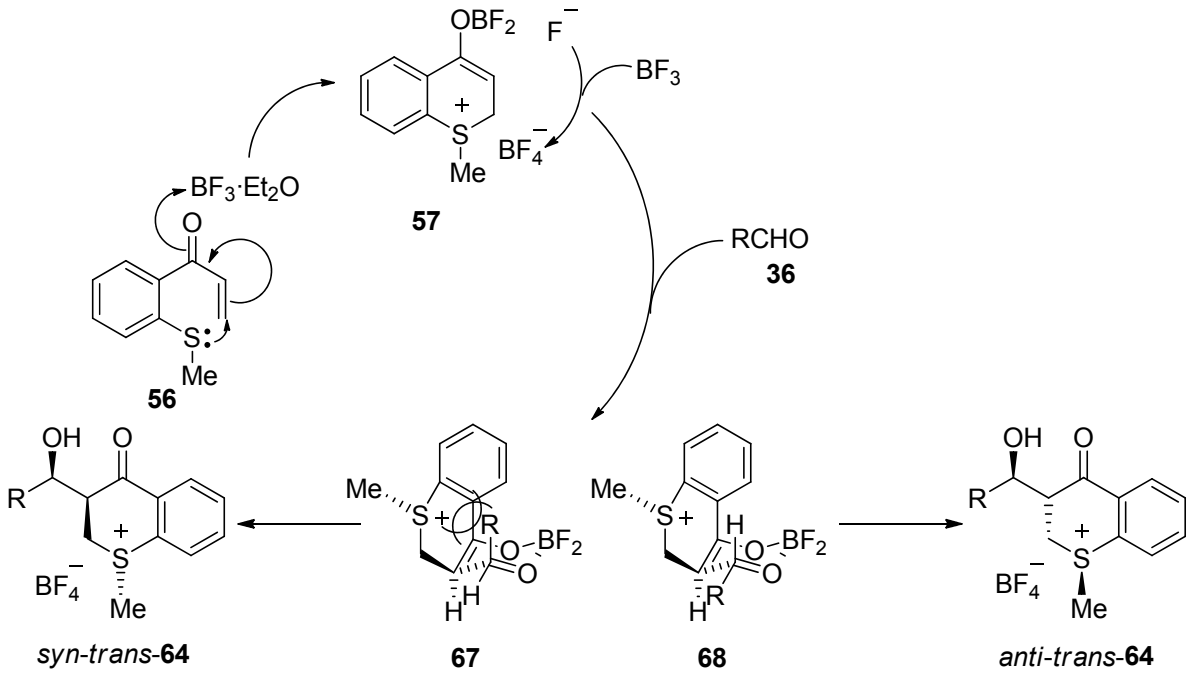
The difference in reactivity between the *syn*- and *anti*-**64** against a base is explained as shown in Scheme 26. In both isomers, the gauche conformation **66**, in which the hydroxybenzyl group is in the equatorial position, is more stable than the antiperiplanar conformation **65** with the axial hydroxybenzyl group. β-Elimination occurs *via* the antiperiplanar conformation **65**. Steric repulsion between the lone pair electrons and the benzylic hydrogen in the *anti*-**65** is much less than that between the lone pair electrons and the group R in the *syn*-**65**. Therefore, the *anti*-**65** causes the β-elimination more easily than the *syn*-**65**. This is the reason that the *anti*-**64a** was not obtained from the reaction of **56** and **36a** after working up the reaction mixture with a base.



Scheme 26. Structure and reactivity of sulfonium salt intermediates

Based on these results, a possible mechanism for the tandem Michael-aldol reaction mediated by a Lewis acid is shown in Scheme 27. The activation of the enone by BF_3·Et_2O allows a chalcogenide to add to the

β-carbon of an enone moiety. The diastereoselectivity would be induced in the reaction step of the boron-enolate **57** with the aldehyde **36**. The transition state **68** with an equatorial R group is favored over the other transition state **67** with an axial R group, and the *anti*-isomer *anti*-**64** is favorably formed. When the aldehyde **36** approaches the enolate **57**, the methyl group on the chalcogen atom takes a position opposite to the aldehyde, *i.e.*, the *trans*-configuration. The *anti-trans*-**64** undergoes β-elimination *via* the antiperiplanar *anti*-**65** on the treatment with a base to give the MBH adduct **60a**.



Scheme 27. Mechanism of intramolecular Michael-aldol reaction

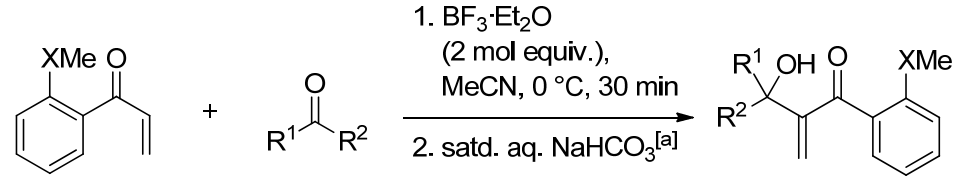
Carbonyl compounds other than aldehydes are used for the MBH reaction, but their use is limited. Ketones except for the trifluoromethyl derivatives reacted with electron-deficient alkenes only under high pressure.[51] No reports on the reactions of the enolizable α-diketones have been published. The reaction of α-keto esters progressed only in the good match of an electron-deficient alkene with a Lewis acid.[37a,52]

Boron enolate is an intermediate of the BF_3-mediated intramolecular Michael reaction from the findings reported above and generally reacts with carbonyl compounds under mild reaction conditions.[53] Therefore, we next examined the reactions of **56** and **59** with various carbonyl compounds.

The reactions of the acetophenone derivatives **69a**, **b**, and cyclohexanone (**69c**) at 0 ºC for 30 min gave products **70** and **71** in low to moderate yields (Table 7).

The α-diketones and α-keto esters reacted with **56** and **59** to afford the products **73**-**75** in low to high yields.[50b] These results were not satisfactory, but these are the first examples of the MBH-type reactions of the α-dicarbonyl compounds **72b** and **c** which are enolizable under mild conditions (Table 8).

Table 7. Reaction of chalcogenide-enones **56** and **59** with ketones **69**



56: X = S
59: X = Se
(2 mol equiv.)

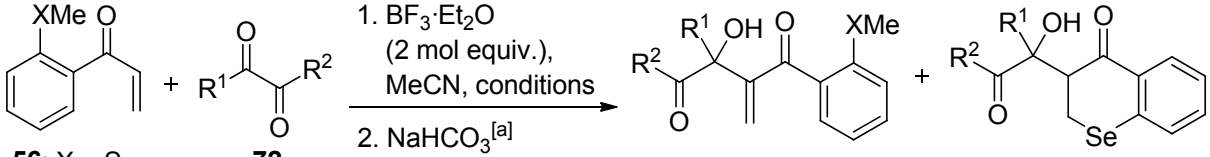
69

70: X = S
71: X = Se

Entry	Chalcogenide–enone	Ketone **69**	Product (%Yield)
1[b]	**56**	R^1 = *p*-$NO_2C_6H_4$, R^2 = Me (**69a**)	**70a** (47)
2	**59**	**69a**	**71a** (50)
3	**56**	R^1 = C_6H_5, R^2 = Me (**69b**)	**70b** (19)
4	**59**	**69b**	**71b** (26)
5	**56**	R^1 = R^2 = $(CH_2)_5$ (**69c**)	**70c** (56)
6	**59**	**69c**	**71c** (53)

[a] The reaction mixture was poured into an $NaHCO_3$ solution.
[b] Et_3N (2 mol equiv.) was used instead of an $NaHCO_3$ solution.

Table 8. Reaction of chalcogenide-enones **56** and **59** with α-dicarbonyl cmpounds **72**



56: X = S
59: X = Se
(2 mol equiv.)

72

73: X = S
74: X = Se

75

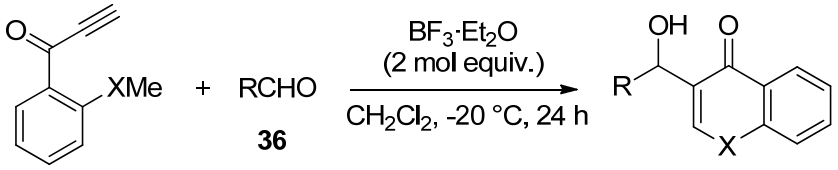
Entry	Chalcogenide–enone	α-Dicarbonyl compound **72**	Conditions	Products (%Yield)
1[b]	**56**	R^1 = R^2 = Ph (**72a**)	0 °C, 2 h	**73a** (41)
2[b]	**59**	**72a**	0 °C, 2 h	**74a** (4)
3	**56**	R^1 = R^2 = Me (**72b**)	0 °C, 1 h	**73b** (29)
4	**59**	**72b**	0 °C, 1 h	**74b** (24)
5	**56**	R^1 = Me, R^2 = OEt (**72c**)	rt, 2 h	**73c** (70)
6	**59**	**72c**	rt, 2 h	**74c** (74), **75a** (2)[c]
7	**56**	R^1 = Ph, R^2 = OMe (**72d**)	rt, 2 h	**73d** (37)
8	**59**	**72d**	rt, 2 h	**74d** (29), **75b** (6)[c]

[a] The reaction mixture was poured into an excess of an $NaHCO_3$ solution.
[b] $BF_3·Et_2O$ (3 mol equiv.) was used.
[c] Only one diastereoisomer was obtained, but the stereostructure was not determined.

If chalcogenide-ynones react with aldehydes in the presence of $BF_3·Et_2O$, the 3-(hydroxymethyl)-chalcogenochromen-4-one derivatives can be synthesized. This reaction involves the 6-*endo-dig* cyclization and is interesting from the viewpoint of the Baldwin rule. The cyclization of the 1-(hydroxyaryl)-3-phenylpropynones proceeded in a 6-*endo-dig* or a 5-*exo-dig* manner depending upon

the reaction conditions,[54] whereas the selenium analogs were selectively cyclized in a 6-*endo-dig* manner under basic conditions.[55] The reactions of the chalcogenide-ynone **76** or **77** with aldehydes occurred in a 6-*endo-dig* fashion to give the 3-(hydroxymethyl)chalcogenochromen-4-one **78** or **79**, respectively (Table 9).[56]

Table 9. Reaction of chalcogenide-ynones **76** and **77** with aldehydes **36**

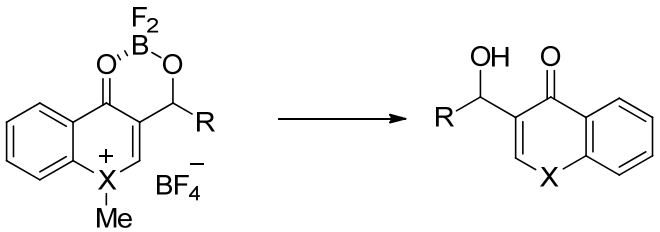


76: X = S
77: X = Se
(2 mol equiv.)

78: X = S
79: X = Se

Entry	Chalcogenide-ynone	R	Product (%Yield)
1	**76**	*p*-$NO_2C_6H_4$ (**36a**)	**78a** (56)
2	**77**		**79a** (74)
3	**76**	*p*-ClC_6H_4 (**36b**)	**78b** (28)
4	**77**		**79b** (62)
5	**76**	Ph (**36d**)	**78c** (42)
6	**77**		**79c** (56)
7	**76**	$PhCH_2CH_2$ (**36e**)	**78d** (31)
8	**77**		**79d** (58)
9	**76**	*p*-CNC_6H_4 (**36f**)	**78e** (36)
10	**77**		**79e** (65)

No chalcogenonium salt **80** was obtained because coordination of a boron Lewis acid with an aldol moiety decreased the electron density of the chalcogenopyran ring and demethylation of the onium salt would have easily occurred (Scheme 28).



80: X=S, Se

78, 79

Scheme 28. Demethylation of chalcogenonium salts

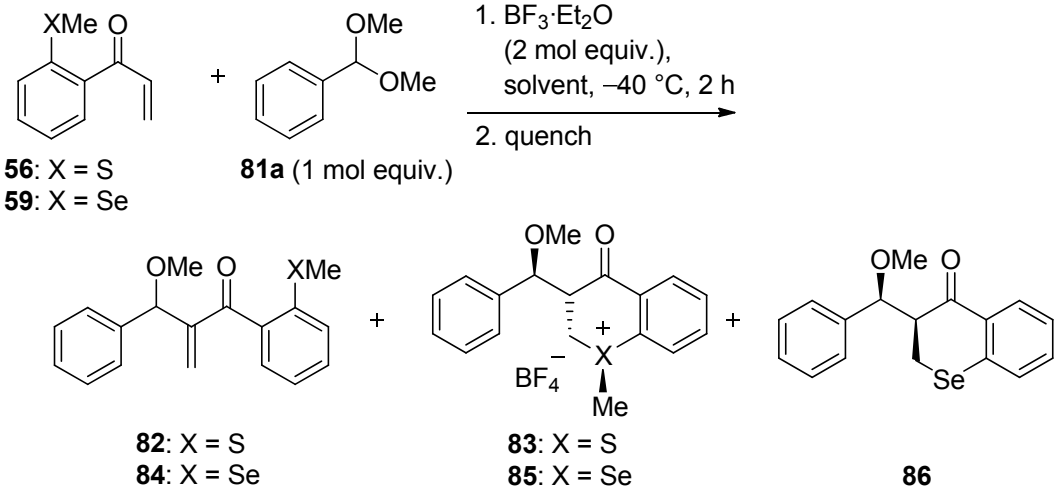
This method is convenient for the synthesis of the 2-unsubstituted 3-(hydroxymethyl)chalcogeno-chromen-4-one derivatives because the 2-unsubstituted chromenone was ring-opened, upon treatment

with lithium diisopropylamide, before alkylation of the newly formed carbanion.[57,58] Recently, Basavaiah and his co-workers synthesized the 2-unsubstituted 3-(hydroxymethyl)chromen-4-ones from chromenone using Et_3N in methanol, but benzaldehyde and aliphatic aldehydes did not produce the products.[59]

Acetals function as electrophiles upon treatment with a Lewis acid.[60] Noyori[61] and other groups[62-64] reported the α-alkoxyalkylation of α,β-unsaturated ketones with acetals or orthoesters in the presence of a silicon-Lewis acid. If acetals are used for the chalcogeno-MBH reaction instead of aldehydes, $BF_3{\cdot}Et_2O$ plays an important role in generating both the enolate-onium salts and α-alkoxy carbocations, and the α-alkoxyalkylation of the enones will be accomplished.

The reaction of benzaldehyde dimethyl acetal **81a** at −40 ºC for 2 h gave the MBH-adduct **82** (78%) or **84** (79%) after work-up of the reaction mixture with Et_3N and the onium salt **83** (40%) or **85** (51%) together with **82** or **84**, respectively, after work-up with saturated $NaHCO_3$ (Table 10).[65] The structures of **83** and **85** were determined by X-ray crystallography and ^1H- and ^{13}C-NMR spectroscopies.

Table 10. Reaction of chalcogenide-enones **56** and **59** with acetal **81a**

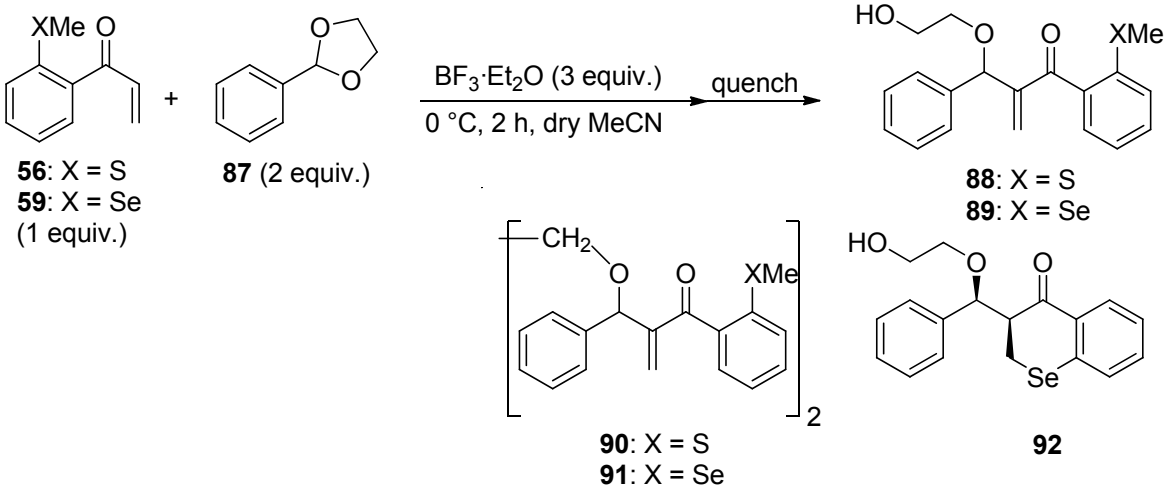


Entry	Chalcogenide-enone	Solvent	Quench	Products (%Yield)
1[a]	**56**	CH_2Cl_2	Et_3N (2 mol equiv.)	**82** (82)
2	**56**	CH_2Cl_2	Et_3N (2 mol equiv.)	**82** (79)
3[b]	**56**	CH_2Cl_2	Et_3N (2 mol equiv.)	**82** (57)
4	**56**	MeCN	Et_3N (2 mol equiv.)	**82** (78)
5	**56**	MeCN	satd. aq. $NaHCO_3$	**82** (43), **83** (40)
6	**59**	MeCN	Et_3N (2 mol equiv.)	**84** (79), **86** (5)
7	**59**	MeCN	satd. aq. $NaHCO_3$	**84** (36), **85** (51)

[a] Acetal **81a** (2 mol equiv.) was used. [b] $BF_3{\cdot}Et_2O$ (1 mol equiv.) was used.

Cyclic acetal, 2-phenyl-1,3-dioxolane and trimethyl orthoformate were applicable for this reaction (Table 11).

Table 11. Reaction of chalcogenide-enones **56** and **59** with cyclic acetal **87**



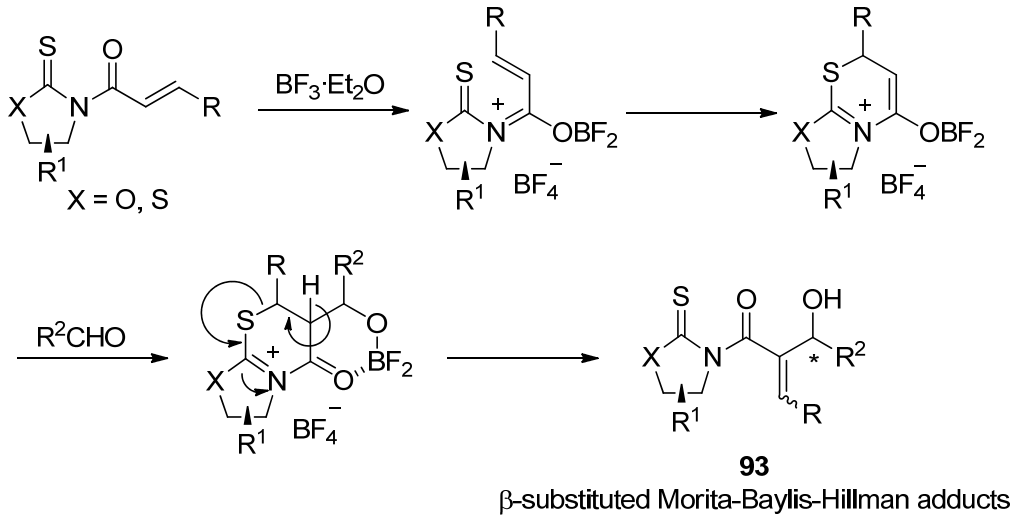
Entry	Chalcogenide-enone	Quench	Products (%Yield)
1	**56**	Et_3N (3 mol equiv.)	**88** (56), **90** (6)
2	**59**	Et_3N (3 mol equiv.)	**89** (39), **91** (19), **92** (19)
3	**56**	satd. aq. $NaHCO_3$	**88** (45)
4	**59**	satd. aq. $NaHCO_3$	**89** (45), **91** (10), **92** (7)

12. TANDEM MICHAEL-ALDOL REACTION OF *N*-ENOYLCYCLIC THIOAMIDES WITH ALDEHYDES[68,69]

As reported above, we found that a chalcogenide group caused the intramolecular Michael addition to an enone moiety[50,56,65] and that a thiocarbonyl compound, such as thiopyran-4-thione[35] or tetramethylthiourea,[39] catalyzed the tandem Michael–aldol reaction. When we started the study on the tandem Michael-aldol reaction of thioamides, the Michael addition of *N*-unsubstituted thioamides with α,β-unsaturated carbonyl compounds[66] was already well known, but that of the *N*-substituted thiocarbamates was only slightly known.

Based on our findings on the intramolecular Michael cyclization of the chalcogenide group and the catalytic action of thioamides, we studied a new tandem Michael-aldol reaction of *N*-cinnamoyl cyclic thiocarbamates with aldehydes, as shown in Scheme 29. If this reaction goes well, we can synthesize the β-substituted MBH product **93**, which is difficult to prepare by the MBH reaction.

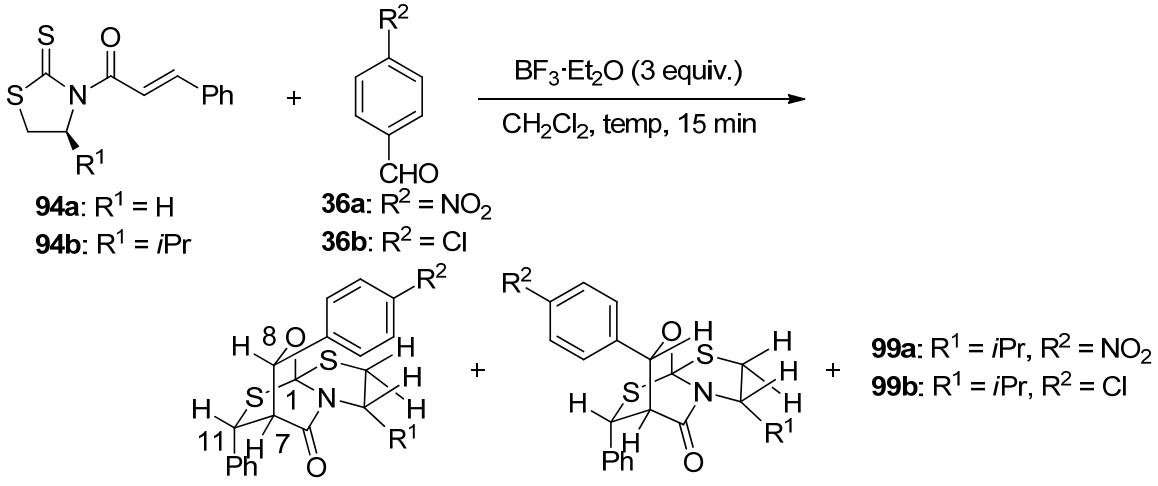
When chiral 1,3-oxazolidine- or 1,3-thiazolidine-2-thione derivatives are used as a chiral auxiliary, an asymmetric tandem Michael–aldol reaction can be developed, and optically active products can be obtained. Palomo and co-workers separately reported the sulfur transfer reaction of a chiral *N*-enoyl–cyclic moiety with a Lewis acid followed by hydrolysis of the products.[67] In their early report, $SnCl_4$ was the most effective Lewis acid, but then the Lewis acid was changed into $NbCl_5$ or $BF_3{\cdot}Et_2O$.



Scheme 29. Anticipated MBH reaction of enone-thiocarbamates with aldehydes

The reaction conditions were examined for the reaction of the *N*-cinnamoyl-1,3-thiazolidine-2-thione **94a** with *p*-chlorobenzaldehyde (**36b**) (Table 12), and the highest yield of **95** and **96** was afforded when using 3 equiv. of $BF_3{\cdot}Et_2O$, 2 equiv. of **94a** and 1 equiv. of **36b**.[68]

Table 12. Reaction conditions of *N*-cinnamoyl-1,3-thiazolidine-2-thione **94** with aldehydes **36**

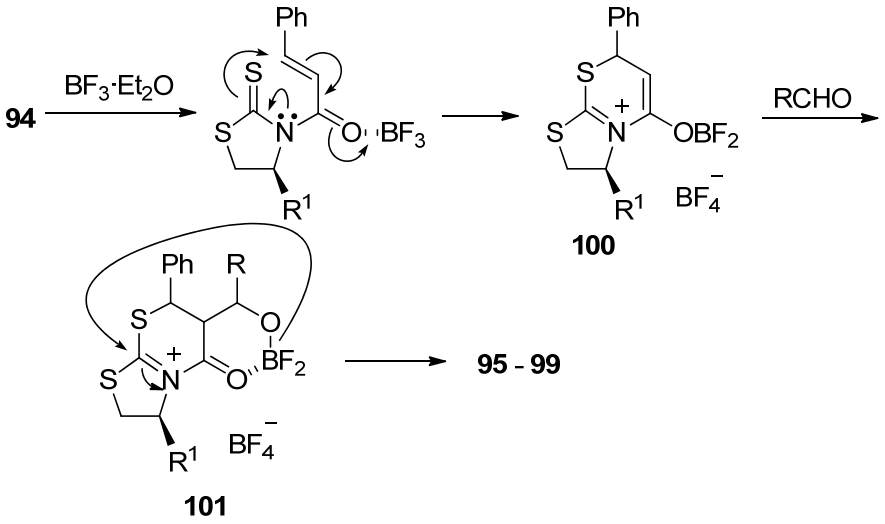


Entry	Enone (mol equiv.)	Aldehyde (mol equiv.)	Temp	Products (%Yield)
1	**94a** (2)	**36b** (1)	rt	**95** (58), **96** (31)
2[a]	**94a** (2)	**36b**(1)	rt	**95** (50), **96** (33)
3	**94a** (1)	**36b** (2)	rt	**95** (48), **96** (30)
4	**94b** (2)	**36b** (1)	0 °C	**97b** (54), **98b** (28), **99b** (4)
5	**94b** (2)	**36a** (1)	0 °C	**97a** (43), **98a** (41), **99a** (4)

[a] $BF_3{\cdot}Et_2O$ (2 equiv.) was used. [b] Compounds **99a, b** were diastereoisomers of **97** and **98** but their stereostructures were not determined because of their small amounts.

The products were not the MBH adducts, but the tricyclic compounds with a bridgehead carbon bound with four heteroatoms. This reaction induced four chiral centers in the one-step reaction.

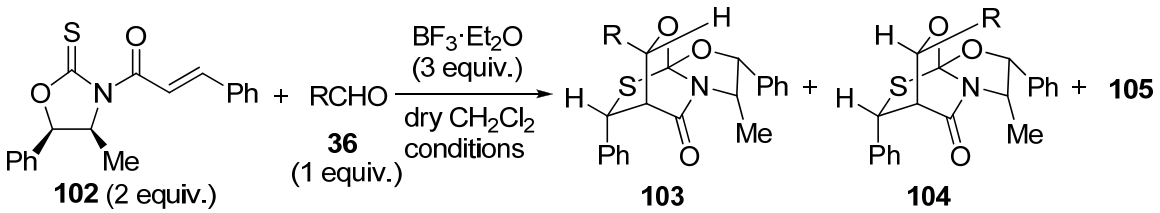
The structurally rare compounds **95-99** were formed *via* the reaction pathways shown in Scheme 30. Coordination of $BF_3 \cdot Et_2O$ with the carbonyl oxygen of the *N*-cinnamoylthiazolidinethione **94** activates the enone moiety and the intramolecular conjugate addition of the thiocarbonyl group to the enone moiety forms the boron enolate-iminium salt **100**. The aldol reaction of the boron enolate yields the aldol product **101**, the alkoxide ion of which nucleophilically attacks the iminium carbon to afford the tricyclic products **95-99**.



Scheme 30. Reaction mechanism for formation of tricyclic compounds **95-99**

After investigation of the chiral auxiliary, 4*S*-methyl-5*R*-phenyloxazoline-2-thione showed the best diastereoselectivity. The reactions of *N*-cinnamoyl thioamide **102** with aromatic aldehydes afforded tricyclic compounds **103** in moderate to good optical yields, but the reactions with aliphatic aldehydes did not give satisfactory yields (Table 13).

Table 13. Reactions of *N*-cinnamoylthiocarbamate **102** with aldehydes **36**



Entry		Conditions	Yield (%) [a]	**103** : **104** : **105**
1	*p*-$NO_2C_6H_4$ (**36a**)	-40°C, 24 h	93	95 : 5 : 0
2	*p*-ClC_6H_4 (**36b**)	-40°C, 24 h	71	86 : 7 : 7
3	C_6H_5 (**36d**)	0°C, 1 h	69	71 : 0 : 29
4	*m*-$NO_2C_6H_4$ (**36g**)	-40°C, 24 h	85	95 : 5 : 0
5	*p*-MeC_6H_4 (**36h**)	0°C, 1 h	59	92 : 0 : 8

[a] Mixture of diastereomers. [b] Compounds **105** were diastereoisomers of **103** and **104** but their stereostructures could not be determined because of their small amount.

The diastereomeric ratios were determined from the signal intensities of the ^{1}H-NMR spectra. The structure of the *m*-nitro derivative **103g** was determined to be a tricyclic adduct with 1*R*, 7*R*, 8*R* and 11*R* configurations based on the 3*R* and 4*S*-absolute configurations by X–ray crystallography (Figure 2). From this analysis, products contain three consecutive stereocenters and a chiral bridgehead carbon bound to four heteroatoms.

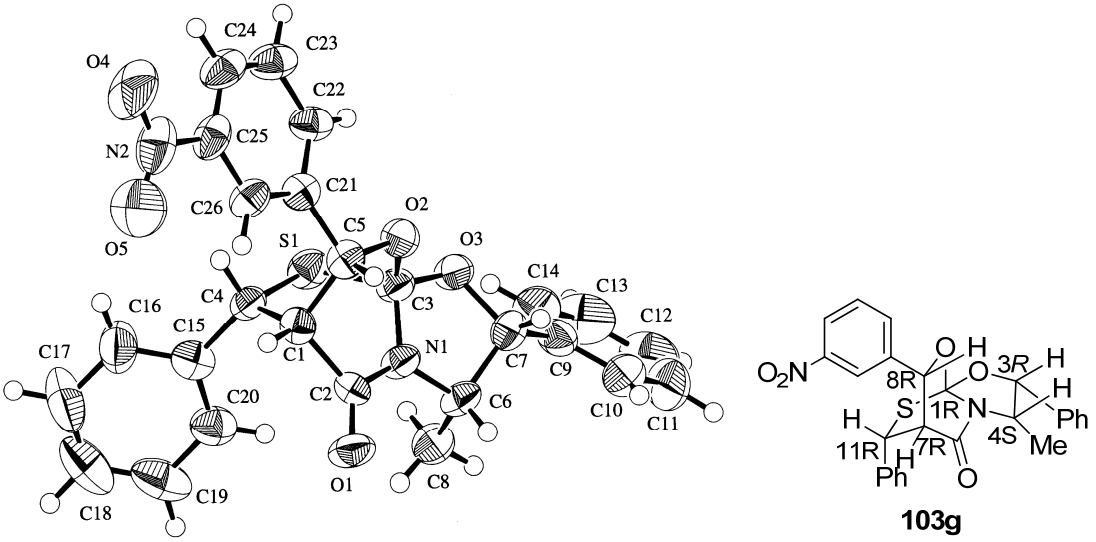
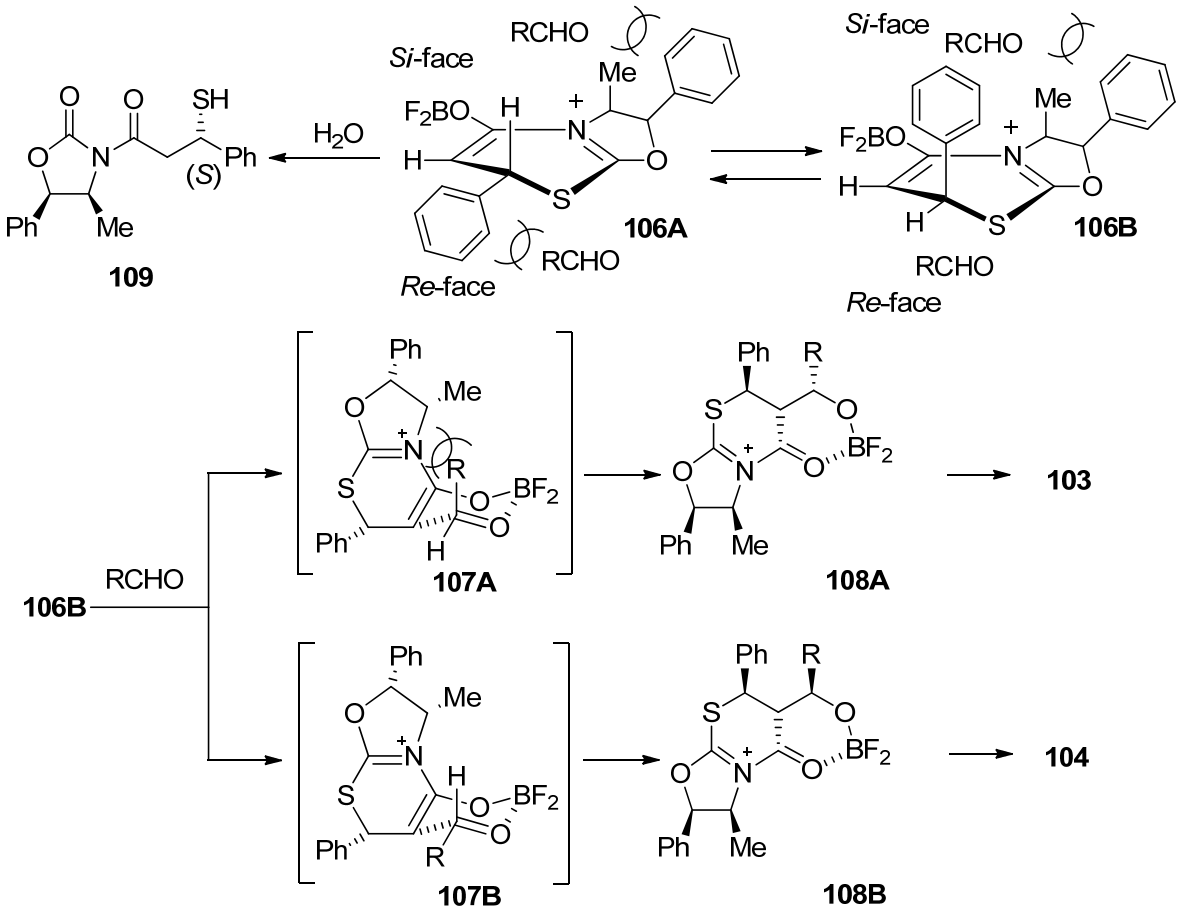


Figure 2. ORTEP drawing of **103g**

The asymmetric induction of four stereogenic centers can be explained as shown in Scheme 31. The boron enolate-iminium salt **106** consists of two diastereoisomers **106A** and **106B**, the *anti*- and *syn*-configurations between the phenyl group adjacent to the sulfur atom and the substituents of the oxazolidine ring, respectively. The approaches of an aldehyde from the *Si*- and the *Re*-faces to the boron enolate moiety in isomer **106A** are prevented by the methyl and the phenyl groups of the oxazolidine ring and the phenyl group α to the sulfur, respectively. If the reaction were to proceed *via* **106A**, the chiral carbon adjacent to the sulfur of the product should have an *S*-configuration, but they in fact had an *R*-configuration. Therefore, this pathway *via* intermediate **106A** is inappropriate. On the other hand, isomer **106B** with the *S* configuration has three substituents in the *Si*-face, and an aldehyde can easily attack the enolate carbon from the sterically relaxed *Re*-face.

Palomo and co-workers obtained β-sulfanylpropanoic acid derivatives **109** with the *S*-configuration, which is opposite to the 11*R*-configuration of **95**–**99** and **103**-**105**, from the sulfur transfer reaction of the chiral *N*-enoyl-oxazolidinethiones.[67] This reaction does not contain the subsequent aldol reaction with an aldehyde. Therefore, thiols **109** were afforded by hydrolysis of the diastereomer **106A**, which is more stable than the other **106B**.

The induction of three concecutive stereocenters in the aldol reaction of the cyclic enolate **106B** is discussed by two possible processes *via* the cyclic transition state or the acyclic one. If the reaction of

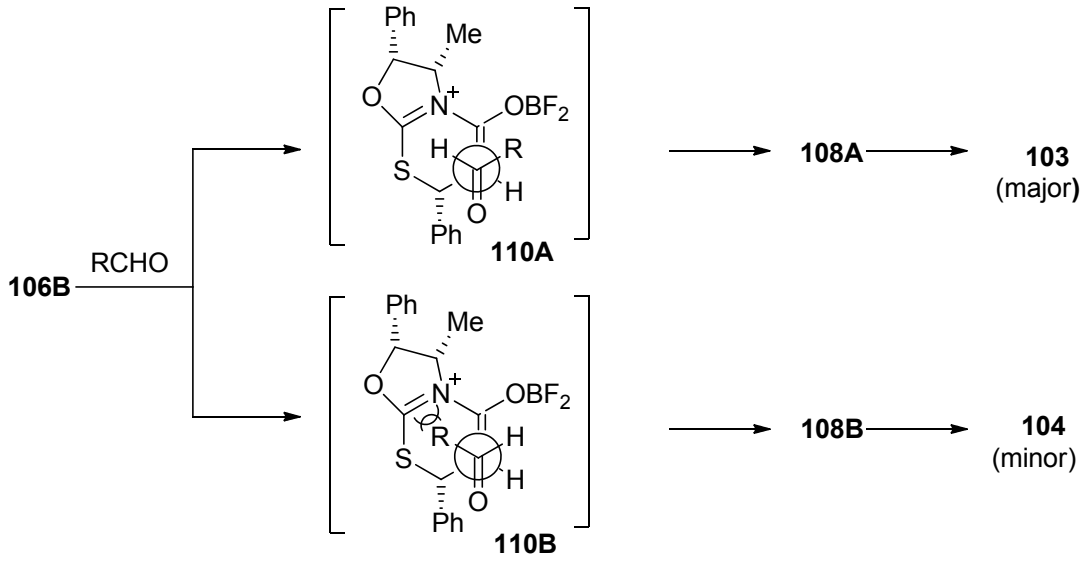


Scheme 31. Cyclic model for the asymmetric aldol reaction

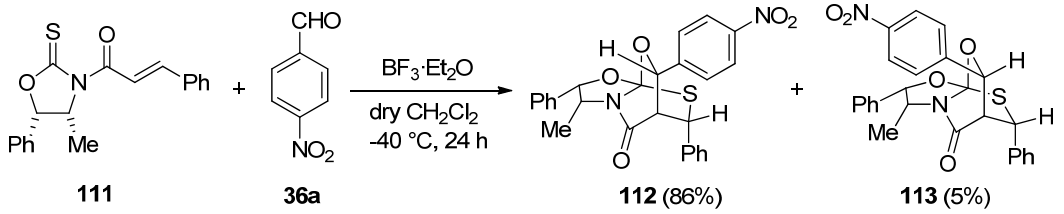
106B with an aldehyde proceeds *via* the cyclic 6-membered ring transition state, two transition states **107A** and **107B** are considered. Transition state **107B** bearing an equatorial R group is more stable than transition state **107A** bearing an axial R group. The reaction progressed *via* **107B** favorably to form the aldol product **108B**, which leads to the tricyclic product **104**. This is inconsistent with the finding that compound **104** is the minor isomer.

On the other hand, the acyclic transition states shown in Scheme 32 provide a reasonable explanation. In the acyclic transition models, stereoselection in the aldol reaction is governed by the transition state **110A** or **110B**. The transition state **110A** is more favorable than **110B**, which has a steric repulsion between the iminium moiety and the R group. The pathway *via* **110A** produces the aldol adduct **108A**, which cyclizes to product **103**, which is the major product of the reaction. Based on the discussion above, we conclude that the tandem Michael-aldol reaction of **102** with aldehydes proceeds *via* the boron-enolate-iminium salt **106B** and acyclic transition state **110A**.

4*R*-Methyl-5*S*-phenyloxazoline-2-thione **111**, an enantiomer of **102**, reacted with *p*-nitrobenzaldehyde (**36a**) to give tricyclic compounds **112** and **113**, the enantiomers of **103** and **104**, respectively (Scheme 33).

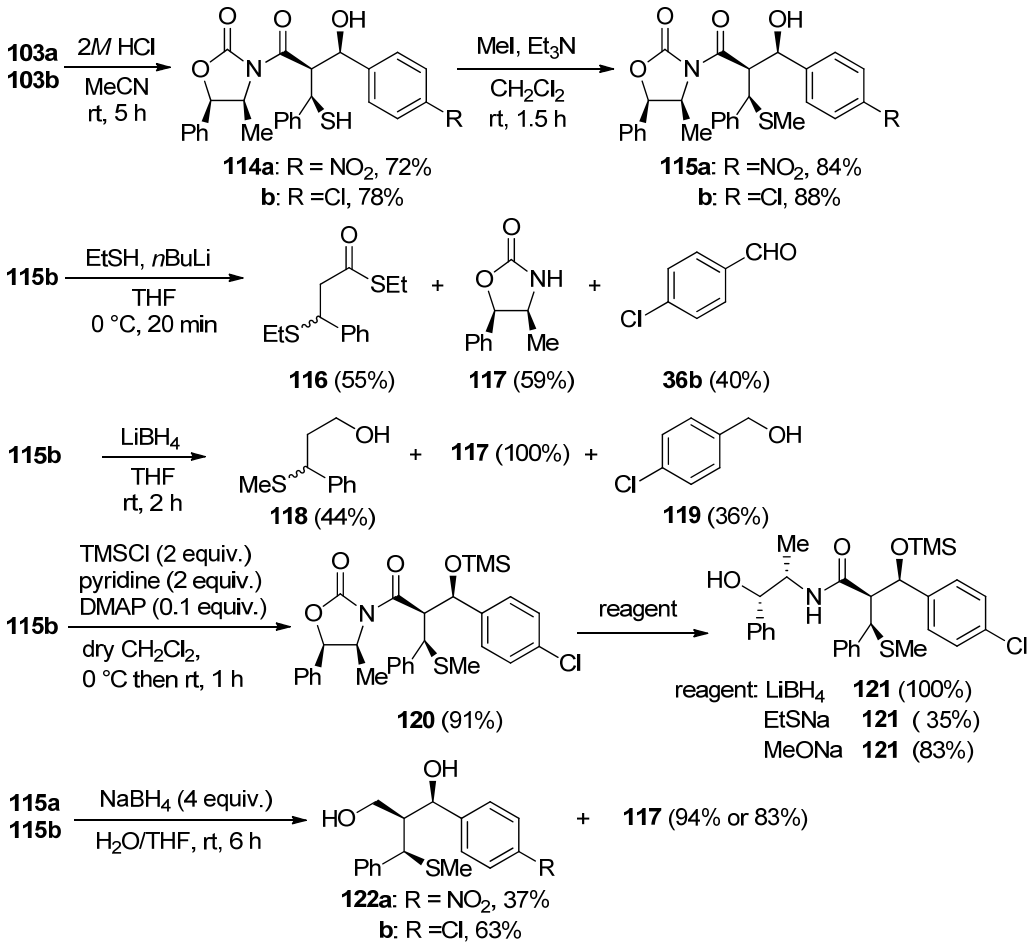


Scheme 32. Acyclic model for the asymmetric aldol reaction



Scheme 33. Asymmetric Michael-aldol reaction of enantiomer **111**

To utilize the chiral products, removal of the chiral auxiliary from the tricyclic compounds was examined as shown in Scheme 34. Tricyclic compounds were stable to alkaline hydrolysis but were hydrolyzed with 2M HCl. The acid hydrolysis of **103a**, **b** selectively cleaved the C-S bond of the six-membered ring to give *N*-(3-sulfanylpropanoyl)oxazolidines **114a** (72%) and **114b** (78%), respectively, which were converted to the *S*-methyl derivatives by methylation with MeI-Et_3N. Removal of the oxazolidinone **117** was conducted by using EtSLi or $LiBH_4$, but the retro-aldol reaction took place to give **116** and **36b** or **118** and **119**, respectively. These findings indicated that protection of the hydroxyl group is necessary to prevent compounds **115** from the retro-aldol reaction. Treatment of the trimethylsilyl ether **120** with $LiBH_4$, EtSNa, or MeONa caused the oxazolidine ring to open to give the amide **121**. Protection of the hydroxyl group inhibited the retro-aldol reaction, but the bulky trimethylsilyl group interfered with the attack of a nucleophile on the *exo*-carbonyl group. The nucleophile exclusively attacked the *endo*-carbonyl group. Therefore, returning to the original concept, various means were tried to remove the chiral auxiliary without protection of the hydroxy group of **115**, and the reductive removal of the oxazolidinone moiety using sodium borohydride in aqueous THF successfully produced propanediols **122** and the oxazolidinone **117**.

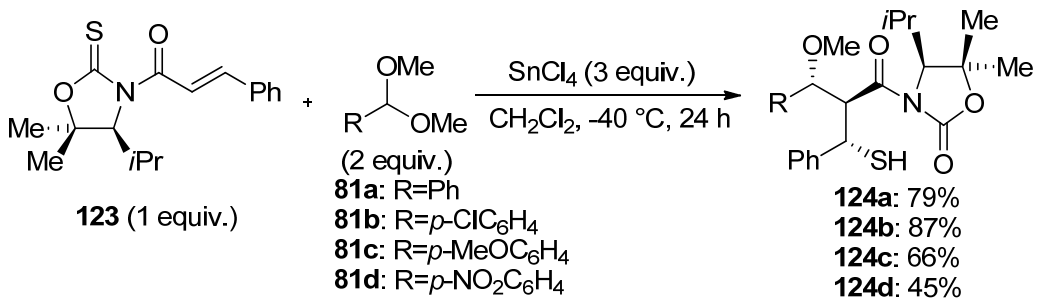


Scheme 34. Transformation of tricyclic compounds

As reported above, the tandem Michael-aldol reaction of *N*-cinnamoyl-4*S*-methyl-5*R*-phenyl-oxazolidinethione with aldehydes afforded structurally rare tricyclic compounds with a bridgehead carbon bound to four heteroatoms. If acetals are used instead of aldehydes for this reaction, the cyclization of the aldol intermediate in the final step to form the tricyclic compounds is prevented, and it is anticipated that the 3-alkoxy-2-(α-sulfanylbenzyl)propionimides **124**, which correspond to the hydrolysis-*O*-alkylation products of **114**, will be formed. We have already achieved a simple procedure for the α-alkoxyalkylation of enones *via* the tandem Michael-aldol reaction of chalcogenide-enones with acetals using $BF_3{\cdot}Et_2O$, as shown in Table 10.[65]

$SnCl_4$ as a Lewis acid promoted the reaction better than $BF_3{\cdot}Et_2O$ for the acetals. This is probably because the chloride ion generated from $SnCl_4$ would react with the iminium intermediate to give a more stable chloroamine intermediate. The reactions of *N*-cinnamoyl-4*S*-isopropyl-5,5-dimethyloxazolidine-thione (**123**) with aromatic aldehyde dimethyl acetals **81** are shown in Scheme 35.[69]

The configurations of the newly created stereogenic centers were assigned by an X-ray structural analysis of the crystalline dimer **125** (Figure 3). The absolute configuration of the benzylic position α to the sulfur



Scheme 35. Reaction of *N*-cinnamoylthioamide **123** with acetals **81**

atom of **125** is different from that of the product obtained from the reaction with aldehydes using $BF_3 \cdot Et_2O$.

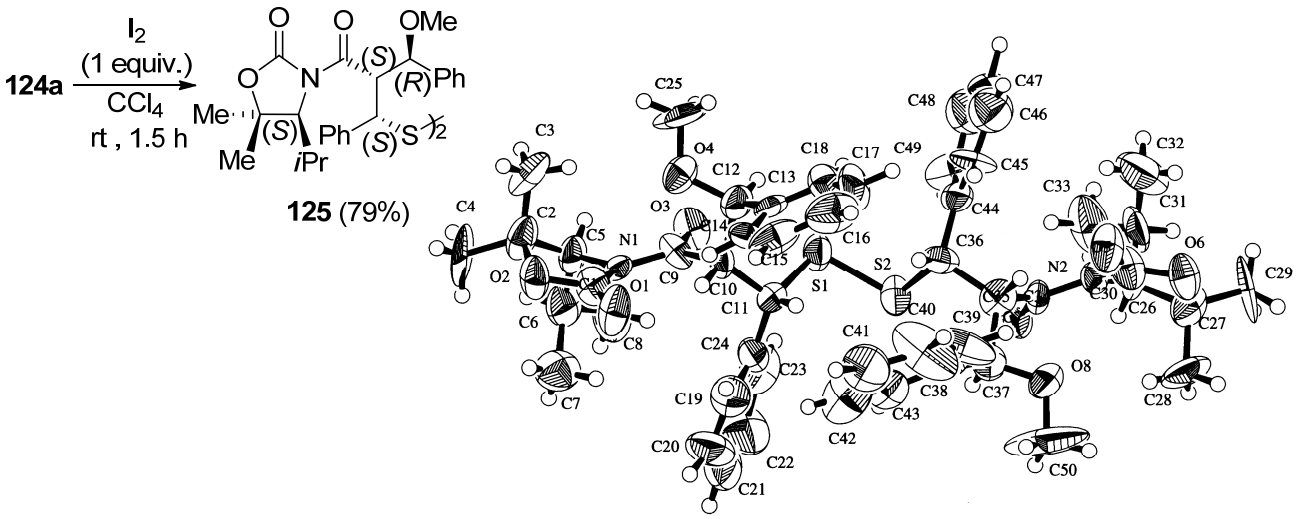
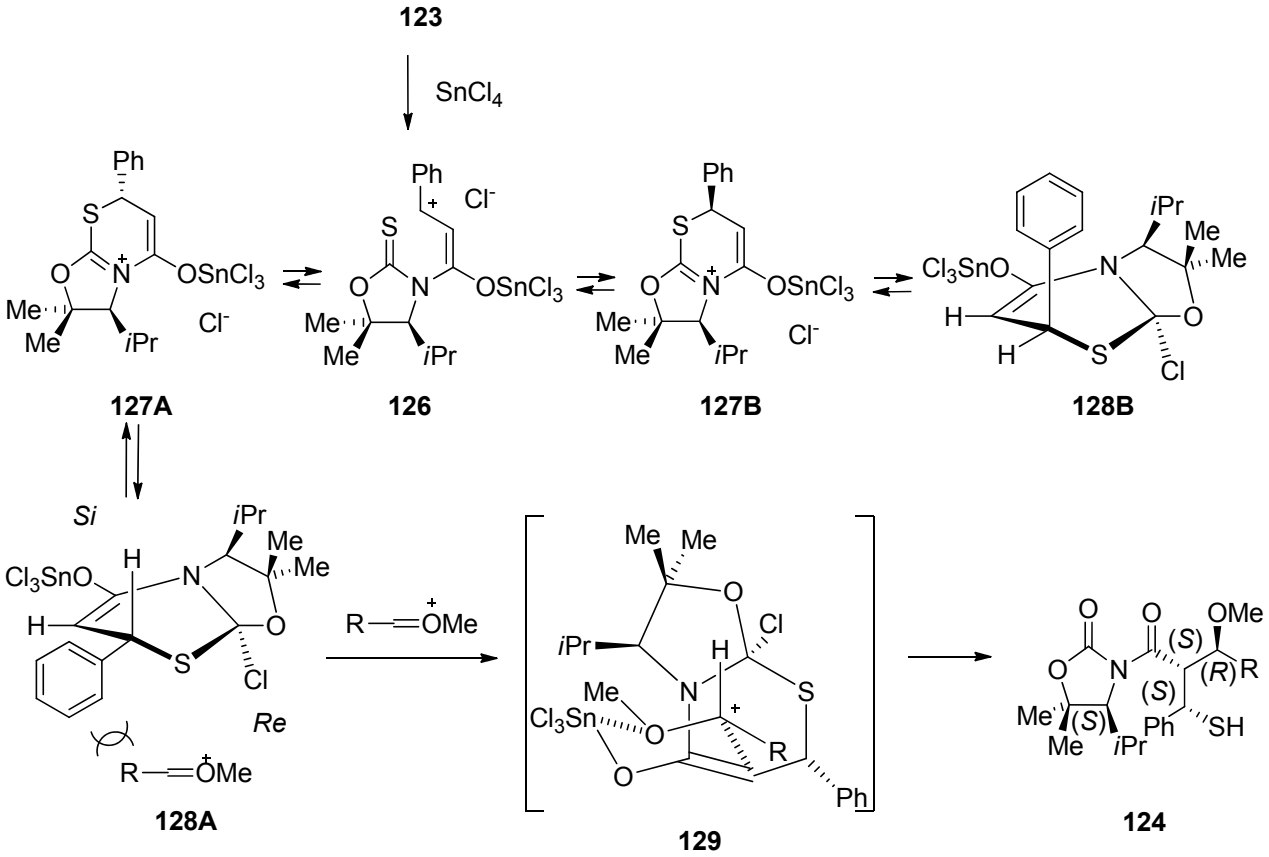


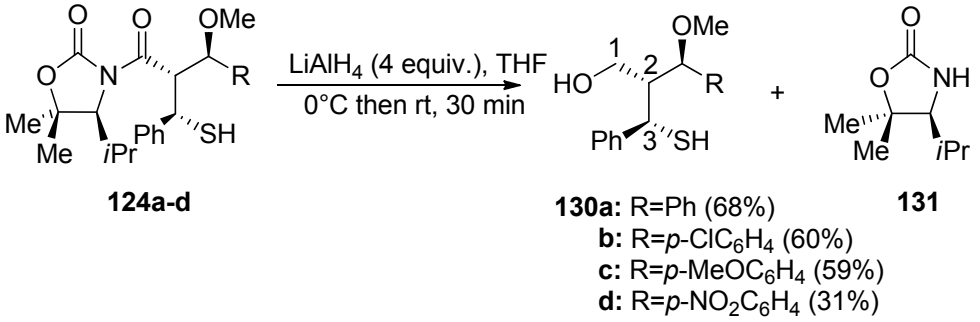
Figure 3. Stereostructure of dimer **125**

Based on this finding, a plausible reaction mechanism is shown in Scheme 36. The intramolecular Michael addition of the thioamide group of **123** to the enone moiety activated by $SnCl_4$ forms the iminium chloride **127** *via* the tin enolate **126**. The iminium chloride **127** transforms into the more stable cyclic chloroamine **128**. Since the *Si* face is sterically more crowded than the *Re* face and the $SnCl_3$ moiety occupies the opposite side of the isopropyl, methyl, and phenyl groups, the chloride anion of **127** attacks the iminium carbon from the *Re* face to form the chloroamine **128**. Steric repulsion among the phenyl, methyl, and isopropyl groups of **128B** is quite strong on the *Si* face. The chlorine atom interferes with the *Re* face attack of the methoxycarbenium ion to the enolate ion. The other isomer **128A** has a pseudoequatorial phenyl group, and this conformation relaxes the steric hindrance between the phenyl group and the isopropyl or methyl group and is more stable than **128B**. The methoxycarbenium ions can attack from the *Si* face to form the Michael-aldol product **124** *via* the cyclic transition state **129**. The phenyl group and the chloro substituent block the *Re* face approach of the carbenium ion.



Scheme 36. Reaction mechanism for the formation of **124**

We have developed the asymmetric tandem Michael−aldol reaction of *N*-cinnamoylthioamides with aldehydes and acetals. This reaction furnishes diastereomerically pure tricyclic compounds, 2-(α-hydroxybenzyl)- or 2-(α-methoxybenzyl)-3-phenyl-3-sulfanylpropionimides, which contain three contiguous chiral centers. The reductive removal of the chiral auxiliary from them provides 2-(α-methylsulfanylbenzyl)propane-1,3-diols and 2-alkoxybenzyl-3-sulfanylpropanols in good yields (Scheme 37).



Scheme 37. Removal of the chiral auxiliary **131**

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