Chalcogenide–Lewis Acid Mediated Tandem Michael Aldol Reaction − an Alternative to the Morita–Baylis–Hillman Reaction and a New Development

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A tandem Michael aldol reaction mediated by a chalcogenide and Lewis acid was developed in three different types. Reactions of electron-deficient alkenes with aldehydes or α-keto esters in the presence of a sulfide and $TiCl_4$ gave α-chloromethyl aldols. Reactions of chalcogenide–enones with carbonyl compounds gave α-(α-hydroxyalkyl)enones (Morita–Baylis–Hillman adducts) after the work-up of the reaction mixture with triethylamine. The intramolecular Michael aldol reactions of *N*-enoylthioamides with aldehydes in the presence of BF_3Et_2O produced tricyclic compounds bearing a bridgehead bound to four heteroatoms and induced four stereocenters in one step, three of which were consecutive.

I. Introduction

A tandem reaction, or so-called domino reaction, not only constructs more than two new bonds by one chemical operation but also omits the perplexing protection and deprotection steps and shortens the processes and operations.

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The Morita–Baylis–Hillman (MBH) reaction[1] is a typical example of a sequential C–C-bond-formation reaction and consists of tandem Michael aldol–retro-Michael reactions. This reaction, catalyzed by *tert*-amines or *tert*-phosphanes, produces polyfunctional α-(α-hydroxyalkyl)-α,β-unsaturated carbonyl compounds from electron-deficient alkenes and aldehydes and therefore is widely used in organic synthesis. However, the big drawback of this reaction is that it is very slow under mild reaction conditions. In order to overcome this drawback, a variety of alternatives, such as changes in the catalysts, irradiation with microwaves, or reactions under high pressure, have been examined.[1]

We found that vinyl selenonium salts reacted with nucleophiles to give the apparent substitution products with reten-

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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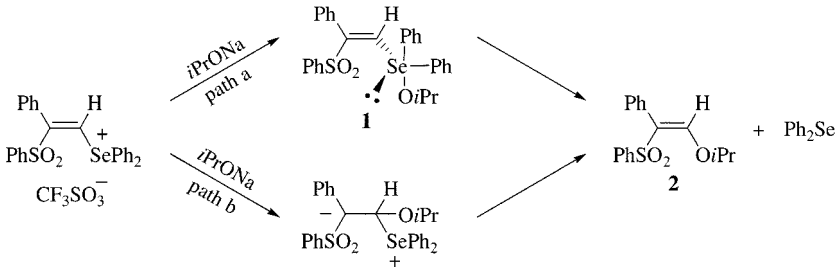
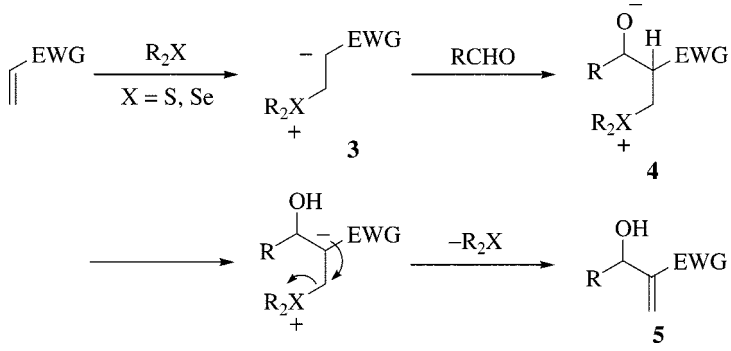


Scheme 1. Reaction mechanism of a vinyl selenonium salt with a nucleophile



Scheme 2. Anticipated reaction of an electron-deficient alkene with an aldehyde in the presence of a chalcogenide

tion of configuration. The reaction mechanism can be explained by the two pathways shown in Scheme 1, in which the reaction with isopropoxide is depicted as an example.[2,3]

Path a involves the formation of the selenurane intermediate **1** followed by ligand coupling between the alkoxy group and the alkenyl carbon.[2,3] Path b proceeds along an alternative route, whereby the Michael addition of an alkoxide to the β-carbon in the vinyl selenonio moiety forms betaine, and the subsequent elimination of a selenide leads to vinyl sulfone **2** with retention of configuration.[3] If the reverse reaction of path b proceeds in the presence of an aldehyde, the reaction shown in Scheme 2 might occur.

A chalcogenide adds to an electron-deficient alkene and forms betaine **3**, which reacts with an aldehyde to afford a zwitterion intermediate **4**. The alkoxide moiety of **4** intermolecularly abstracts the proton α to an electron-withdrawing group and brings about β-elimination. We can obtain an allyl alcohol **5** from this reaction, which is a chalcogenide version of the MBH reaction (the chalcogeno MBH reaction).

II. Chalcogenide–$TiCl_4$-Mediated Tandem Michael Aldol Reaction

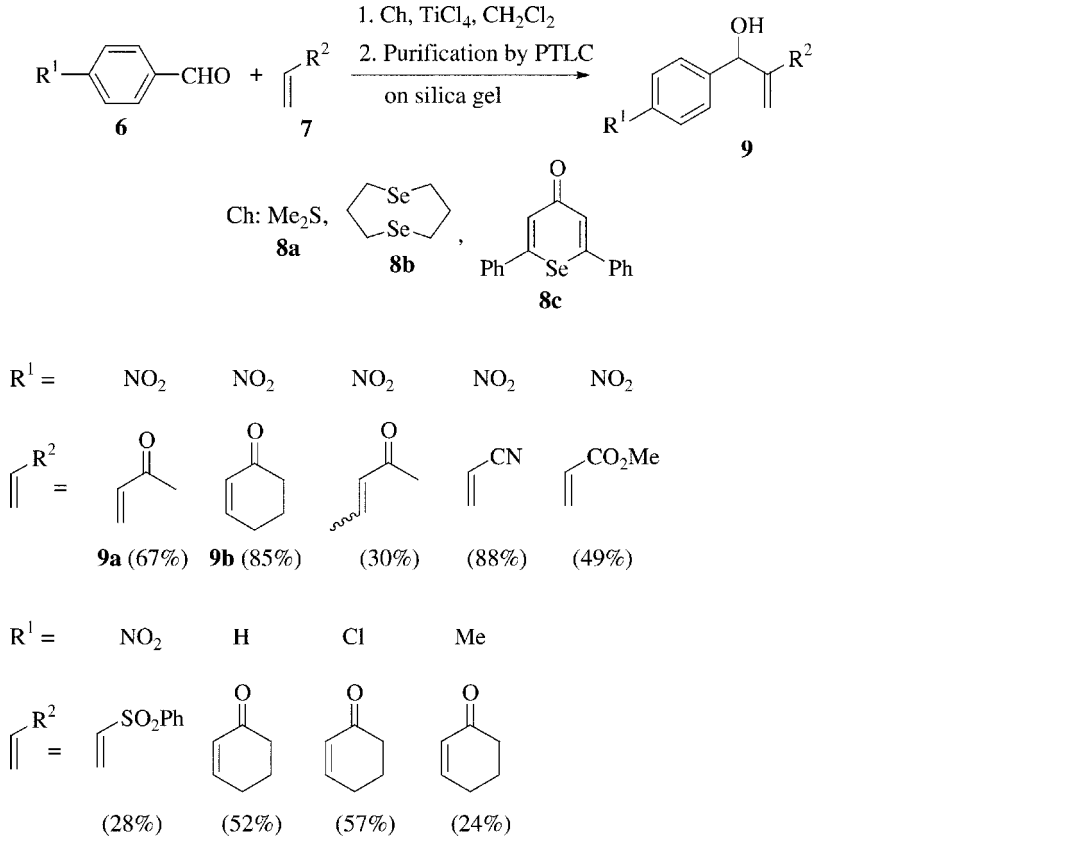
We conducted reactions of various electron-deficient alkenes **7** with *p*-nitrobenzaldehyde (**6a**) using a chalcogenide **8** and $TiCl_4$ and obtained the MBH adducts **9** shown in Scheme 3 after purification of the raw products by preparative TLC (PTLC) on silica gel.[4]

Shortly afterwards, when we purified the product from the reaction of **6a** with methyl vinyl ketone **7a** by column chromatography on silica gel, we happened to get chloromethyl aldol **10a** in 95 % yield as a mixture of two diastereoisomers in the ratio *syn*/*anti* = 3:1 (Scheme 4).[5]

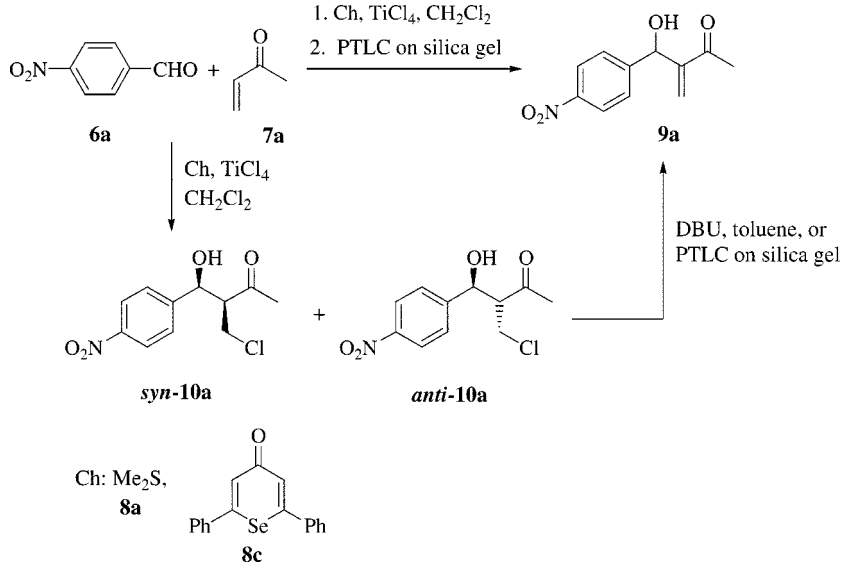
In order to clarify that different products were obtained with different purification procedures, chloride **10a** was submitted to PTLC on silica gel, and dehydrochlorination took place to afford α-methylene aldol **9a**. The chloride **10a** was also transformed into the α-methylene aldol **9a** upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

From the findings described above, we may conclude that chalcogenides did not add to an electron-deficient alkene, but that a chlorine atom derived from $TiCl_4$ worked as a Michael donor in the chalcogenide–$TiCl_4$-mediated reaction of the alkenes with aldehydes. This reaction is a tandem Michael aldol reaction and proceeds rapidly. The product, α-chloromethyl aldol, can be transformed to the MBH product by PTLC treatment on silica gel or with a base. Therefore, this reaction can be used as an alternative to the MBH reaction.

Usually, the tandem Michael aldol reaction should be distinguished from the MBH reaction, in which the stoichiometric quantity of a nucleophile is used, and a process to remove the group added by the Michael addition is sepa-



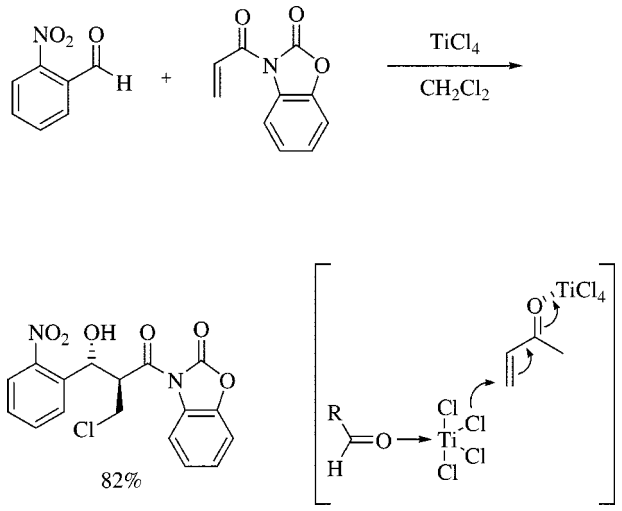
Scheme 3. Tandem Michael aldol reaction of various alkenes with aromatic aldehydes



Scheme 4. Formation of α-chloromethyl aldol

rately conducted.[6,7] However, the chalcogenide–Lewis acid mediated reactions of cyclohexenone or cyclopentenone produced the MBH adducts with no work-up with a base[4,5] (see transformation of **14** into **15** in Scheme 6), and reactions with other enones gave the MBH products after work-up with a base. Therefore, this reaction, newly developed by us, can be used in a way similar to the MBH reaction and can be called a "chalcogeno MBH reaction" when it gives the MBH adduct by shaking of the reaction mixture with a base such as triethylamine in a separating funnel.

Many Michael aldol reactions in the presence of a Lewis acid have been reported. Li et al.[8] studied the reactions mediated by only $TiCl_4$ that plays a double role as an activator of the enone and a reagent providing the chloride ion (Scheme 5), and then developed them for reactions in the presence of Et_2AlI.



Scheme 5. $TiCl_4$-mediated reaction of an electron-deficient alkene with an aldehyde

Oshima's group[9] examined the precise reactions supported by $TiCl_4$–ammonium salt. In many papers, Shi et al.[10] reported on the tandem Michael aldol reaction and the MBH reaction. Recently, various kinds of Lewis acids and Michael donors have been used for the tandem Michael aldol reactions of electron-deficient alkenes with aldehydes.[11]

Aldol products form complexes with $TiCl_4$ in the chalcogenide–$TiCl_4$-mediated reaction of alkenes with aldehydes, and the reaction requires more than one equivalent of a Lewis acid. A catalytic amount of a chalcogenide (0.1 equiv.) is sufficient for the reaction. It is noteworthy and surprising that the reaction with a chalcogenide and a Lewis acid was dramatically accelerated in comparison with the MBH reaction catalyzed by amines because the use of an amine and a Lewis acid[12] had decelerated the reactions owing to the formation of a complex. The reactions overcame the drawback of the slow rate of the MBH reaction.

The chalcogenides shown in Figure 1 were used, and eight-membered heterocycles possessing two chalcogen atoms at the 1,5-positions worked effectively because the intermediary onium ion was stabilized by the transannular interaction between the chalcogen atoms, forming a hypervalent bond.[4b] Selenopyran-4-one, thiopyran-4-one and their 4-thione congeners formed the stable 6π cations by coordination of a Lewis acid at the 4-carbonyl or thiocarbonyl group and were also efficient catalysts.[13]

Aromatic and aliphatic aldehydes were reactive.[4b] α-Keto esters could be used as carbonyl compounds.[14] Acyclic and alicyclic enones were very reactive, but acrylonitriles and acrylates were less reactive than enones. Thioesters[15] were quite active in the reactions and therefore can be used for the synthesis of acrylic acid derivatives instead of acrylates (see Scheme 9). Alkynyl ketones and acetylenic acid esters[16] underwent this reaction and gave the β-halo-substituted MBH products (see Scheme 12).

Lewis acids which catalyze the reaction are $AlCl_3$, BBr_3, BCl_3 and $TiCl_4$. $TiCl_4$ produces especially excellent results.[4b,16] When BBr_3, BCl_3 and their adducts with dimethyl sulfide were used as Lewis acids, and the reaction mixture was worked up with water, dehydration took place, and allyl halides **11** were produced in good yields.[17] Reaction of cyclohexenone as an alkene gave *o*-benzylphenol **12** (33 %) and half-acetal **13** (38 %). A mechanism for the formation of **12** and **13** is shown in Scheme 6. This abnormal reaction takes place for the following reasons. The 3-halo-2-(α-hydroxybenzyl)cyclohexanone **14** which is initially formed can readily undergo dehydrohalogenation in situ to form 2-(α-hydroxybenzyl)cyclohexenone **15**.[5] Dehydration of MBH adduct **15** forms cross-conjugated dienone **16**, which causes a [1,5]-hydrogen shift and aromatization to afford *o*-benzylphenol **12**. Enolization of **15** followed by Michael addition to cyclohexenone gives 4-(cyclohexanon-3-yl)cyclohexen-3-one **17**, which is transformed to phenol **18** in a similar manner to **15**.

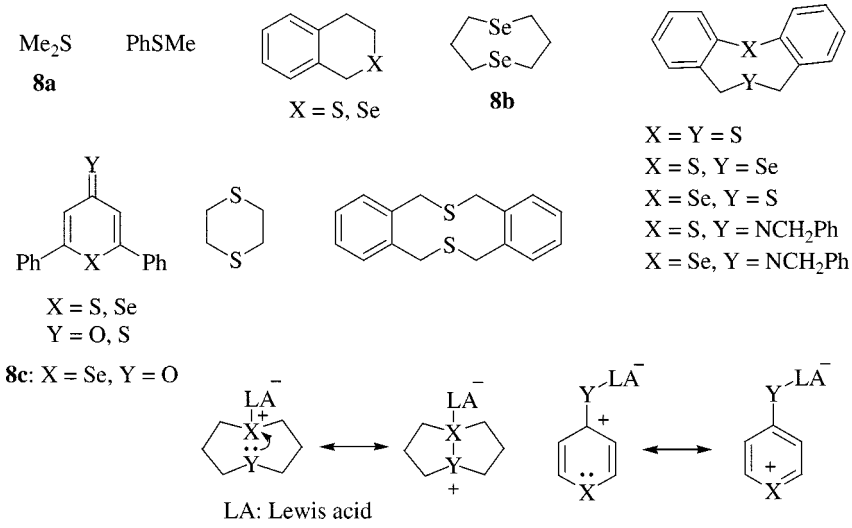
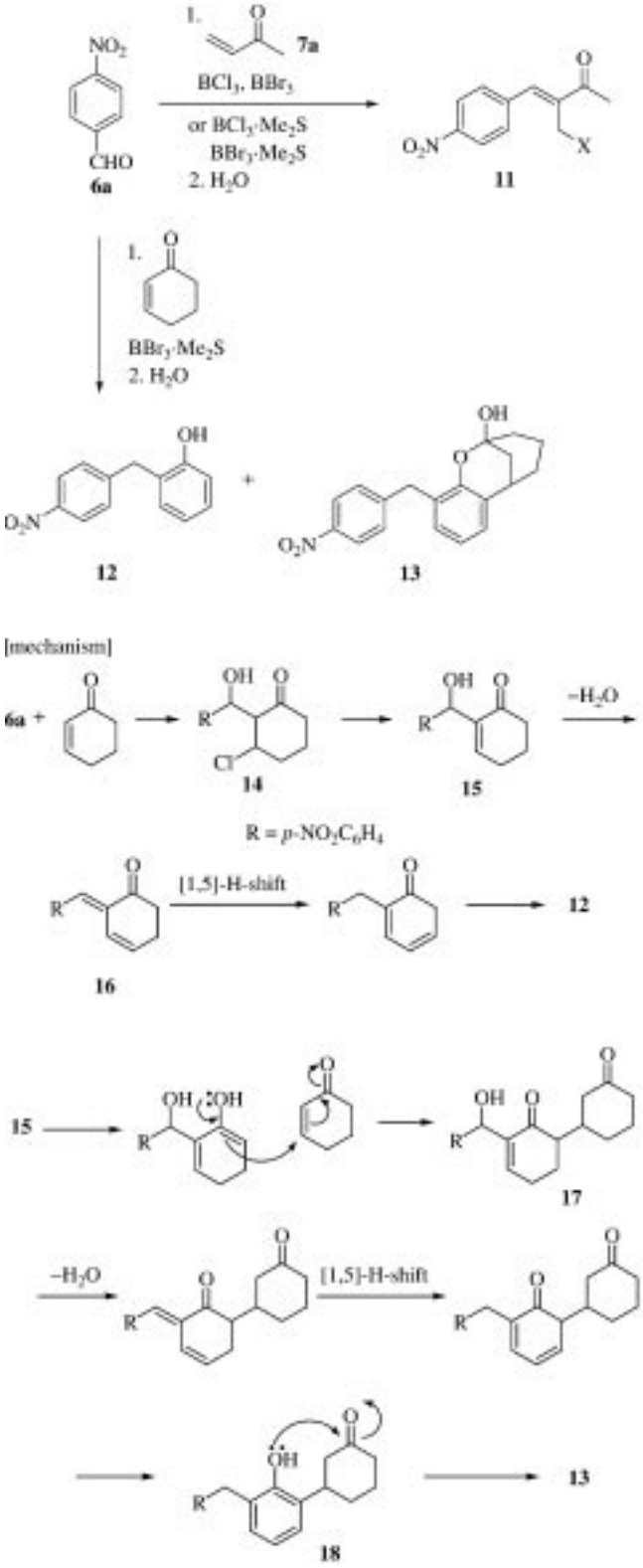


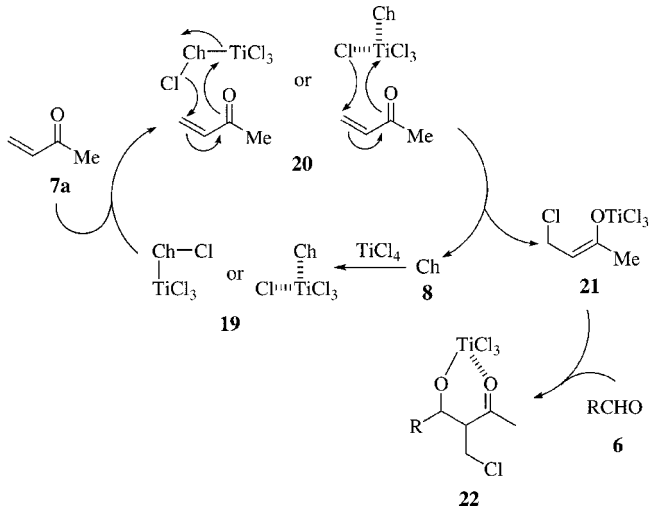
Figure 1. Chalcogenide catalysts



Scheme 6. Reactions of cyclohexenone with butenone, mediated by boron halides

Batra et al.[18] obtained similar products from the reaction of cyclohexenone with 5-isooxazolecarboxaldehyde after our results were reported.

We conducted various experiments to confirm the pathway for the formation of α-chloromethyl aldol **10** and then proposed the mechanism shown in Scheme 7.[5]



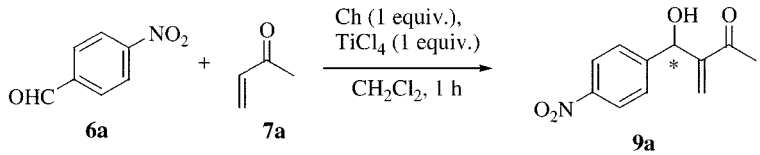
Scheme 7. Mechanism for the formation of α-chloromethyl aldols

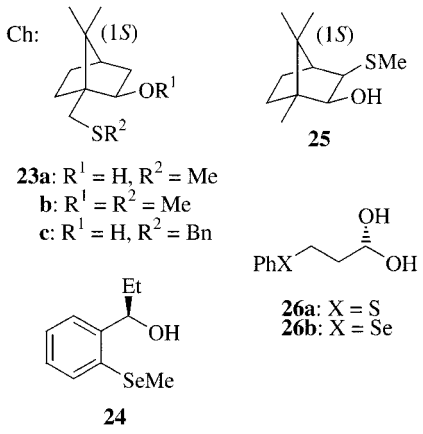
Chalcogenide **8** coordinates with $TiCl_4$ and assists it in releasing a chlorine atom. The exact structure of the $TiCl_4$–chalcogenide complex **19** cannot be determined, but complex **19** reacts with enone **7a** via the cyclic transition state **20**. The chlorine atom nucleophilically attacks the positively charged β-carbon of the enone. A (*Z*)-titanium enolate **21** is predominantly formed, and chalcogenide **8** is regenerated. The titanium enolate **21** then reacts with aldehyde **6**, and chloromethyl aldol **22** is produced. Trichlorotitanium enolate **21** has high Lewis acidity, and the chelated cyclic transition states can more feasibly predict the diastereoselectivity than open-chain transition states.[5]

The MBH reaction gives a chiral allyl alcohol, and asymmetric synthesis by the MBH reaction has been studied widely.[1g,1j] Reactions inducing high enantioselectivity have been reported.[19] We conducted the catalytic asymmetric reactions using 0.1 equivalent of various bifunctional catalysts containing chalcogenide and alcohol, ether or amine groups **23**–**26** at –20 °C.[20] In all cases, chemical yields were very high, but optical yields were very low. Therefore, the amount of catalyst **23a** was increased to one equivalent and 44 % of enantiomeric excess was induced, but the chemical yield was low (Table 1, Entry 1). The highest optical yield was obtained from the reaction of enone **7a** (6 equiv.) and aldehyde **6a** (1 equiv.) in the presence of (1*S*)-10-methylthioisoborneol (**23a**) (1 equiv.) at –78 °C for 1 h (Entry 8).

The merits of our reaction are that it proceeds quickly and that reactions which do not occur under MBH reaction conditions progress smoothly. Basavaiah et al.[14] conducted reactions of aromatic α-keto esters with alkyl vinyl ketones catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) for 8 days. They recovered more than 60 % of the unreacted keto ester and obtained the desired product in less than 10 % yield. When they applied our method to this reaction, they obtained the desired products in 40–70 % yields (Scheme 8).

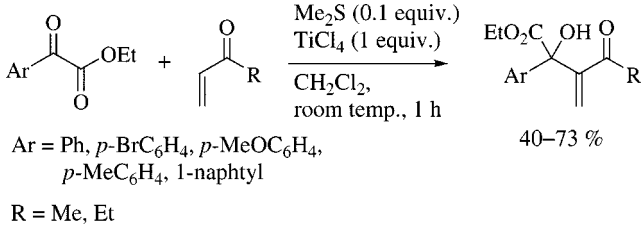
Table 1. Asymmetric reaction of enone **7a** with aldehyde **6a** catalyzed by a chiral chalcogenide





Entry	Ch	**9a** (yield [%])	% *ee* (config.)[a]
1	**23a**	27	44 (*R*)
2	**23b**	41	6 (*R*)
3	**23c**	41	15 (*R*)
4	**24**	26	1 (*S*)
5	**25**	44	8 (*S*)
6	**26a**	49	3 (*S*)
7	**26b**	44	3 (*S*)
8	**23a**	26	71 (*R*)

[a] *ee* was calculated by HPLC analysis using DAICEL CHIRALCEL OD-RH.



Scheme 8. Reaction of enones with α-keto esters

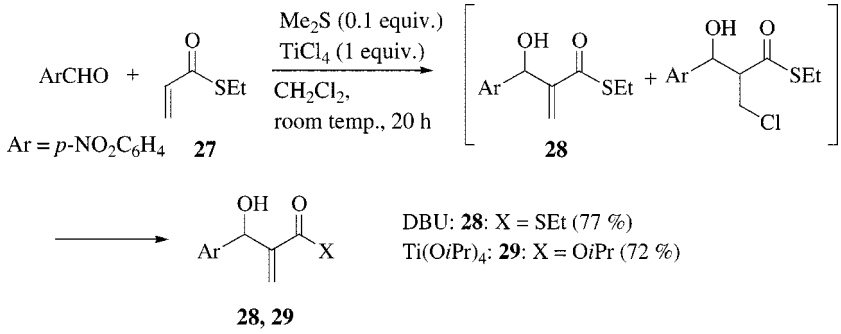
When the reaction of *S*-ethyl thioacrylate **27** with aldehyde **6a** was conducted in the presence of a DABCO catalyst, product **28** was obtained in 0–15 %. A reaction mediated by Me_2S–$TiCl_4$ gave **28** (77 %) or **29** (72 %) after treatment of the raw product with DBU or Ti(O*i*Pr)$_4$, respectively (Scheme 9).[15]

Bauer et al.[21] examined the asymmetric reaction of a chiral glyoxylate, but this reaction did not proceed under the MBH reaction conditions. The reaction supported by Me_2S–$TiCl_4$ produced the MBH adduct in 78 % chemical yield and more than 95 % *de* (Scheme 10).

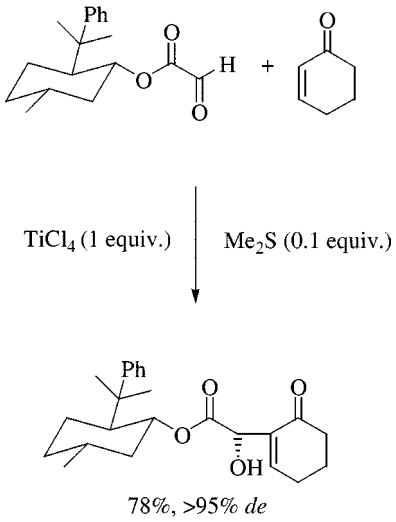
Shaw et al.[22] succeeded in the elongation of the functionalized side chains of acyclic sugar derivatives, shown in Scheme 11. DABCO did not work as an amine catalyst, but Me_2S–$TiCl_4$ was effective for this reaction.

Recently, Verkade et al.[23] found that bicyclic proazaphosphatrane sulfide acted as an efficient catalyst for the chalcogeno MBH reaction. This catalyst was used with $TiCl_4$, and the MBH reaction was complete within 30 minutes. Reactions of β-substituted enones, acrylates and acrylonitrile gave the MBH adducts in high yields. Reactions using this catalytic system did not afford the α-chloromethyl aldols but only MBH adducts which were different from those found by Li[8] and us.[4,5,15]

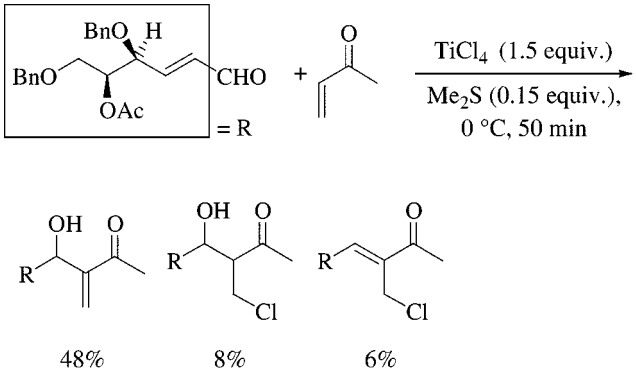
In the MBH reaction, an elimination (retro-Michael) reaction is required in the final step, and therefore a hydrogen α to the electron-withdrawing group is necessary to com-



Scheme 9. Reaction of thioacrylates with aromatic aldehydes



Scheme 10. Asymmetric reaction of cyclohexenone with glyoxylate

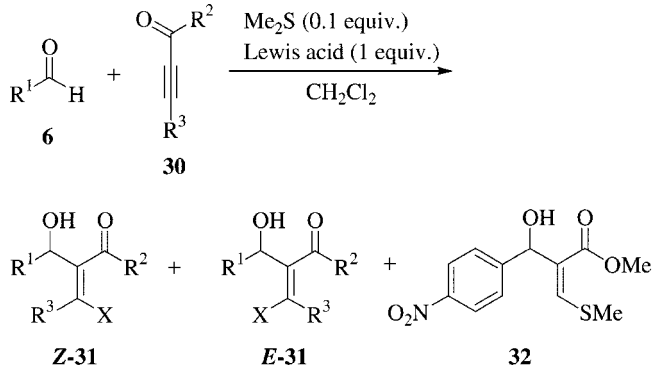


Scheme 11. Reaction of enone with functionalized acroleins

plete the reaction. In other words, only alkenes with an α-hydrogen can be used for the MBH reaction. In contrast, since our reaction forms α-chloromethyl aldol derivatives, the α-hydrogen of the alkenes is not necessary, and our reaction is applicable to alkynes.

Reactions of 3-butyn-2-one (**30**, R^2 = Me) with aromatic aldehydes proceeded smoothly and gave (*E*)-β-chloro-α-(α-hydroxybenzyl)enones **31** (R^2 = Me) in high yields (Scheme 12).[16] On the other hand, reactions of methyl propiolate (**30**, R^2 = OMe) provided 3-chloro-2-(α-hydroxybenzyl)acrylates (**31**, R^2 = OMe) in 36–75 % yields as a mixture of geometrical isomers (*E*/*Z* = 1:1.6–1:7). When a chalcogenide catalyst was not used, the isomer ratios were changed in the case of 3-butyn-2-one, and no product was formed in the reactions of methyl propiolate.[8c,16] These findings indicate that a chalcogenide plays an important role in the reaction of the electron-deficient alkynes. Vinyl sulfide **32**, formed by the Michael addition of Me_2S **8a**, was obtained in 8 % yield from the reaction of (**30**, R^2 = OMe) by using Me_2S–$TiBr_4$.[16b]

The selectivity of geometrical isomers is explained on the basis of a mechanism via the titanium allenolates proposed by Kishi et al. (Scheme 13).[24] A chlorine atom of $TiCl_4$ undergoes the Michael addition to the β-carbon of an elec-

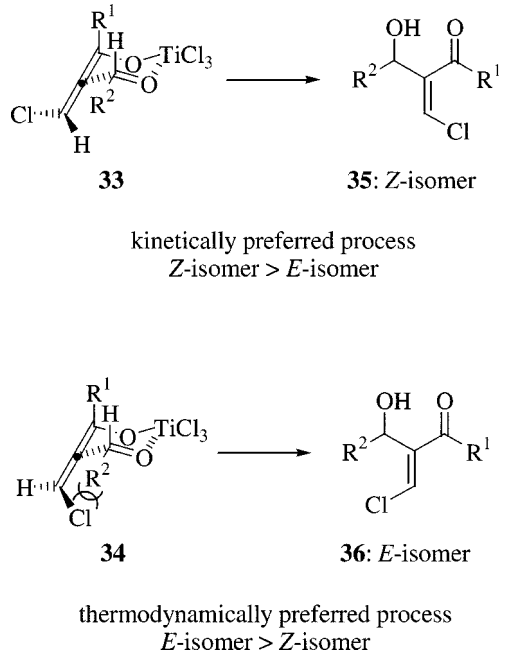


R^2 = Me: Me_2S–$TiCl_4$, room temp.–0 °C, 1 h, **31** (X = Cl, 73–89 %, *E*/*Z* = 20:1–*E* only)
$TiCl_4$, 0 °C, 2 h, **31** (X = Cl, 84 %, *E*/*Z* = 1:1)
$TiBr_4$, 0 °C, 2 h, **31** (X = Br, 49 %, *E* only)

R^2 = OMe: Me_2S–$TiCl_4$, 0 °C, 2 h, **31** (X = Cl, 25–75 %, *E*/*Z* = 1:3–1:7)
$TiCl_4$ or $TiBr_4$, **31** (not obtained)

Scheme 12. Reaction of electron-deficient alkynes with aldehydes

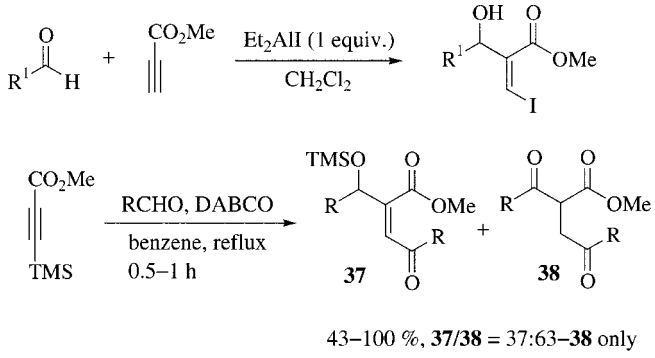
tron-deficient alkyne via the cyclic transition state and forms titanium allenolates. The allenolates react with an aldehyde via cyclic transition state **33** or **34**. In transition state **33**, there is scarcely any steric repulsion between the β-hydrogen of the allenolate and the substituent R^2 of the aldehyde, whereas transition state **34** causes steric hindrance between the chlorine atom of the allenolate and the R^2 group of the aldehyde. Therefore, **33** is more stable than **34**, and the reaction proceeds via **33** under the kinetic control conditions to form *Z*-isomer **35** predominantly. On the other



Scheme 13. Selectivity of geometrical isomers

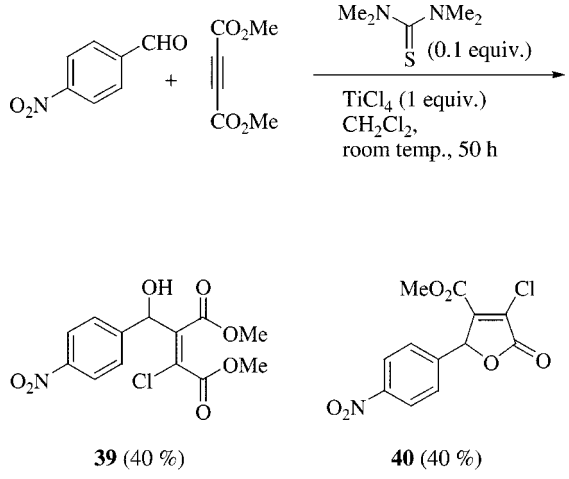
hand, *E*-isomer **36** is thermodynamically more stable than *Z*-isomer **35** and is preferably afforded in a thermodynamically controlled reaction.

Li et al.[8c] reported the reactions of alkynyl ketones with aldehydes in the presence of only $TiCl_4$. At almost the same time, we reported the reactions mediated by Me_2S–$TiCl_4$.[16] However, the reaction of acetylenic esters did not go well, and Li's group[8,8h] developed the improved method using Et_2AlI, as shown in Scheme 14. Recently, Nemoto et al.[25] observed an interesting reaction of methyl 3-(trimethylsilyl) propiolate with aldehydes catalyzed by DABCO.



Scheme 14. Reaction of acetylenic esters with aldehydes

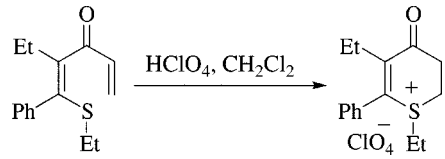
Reaction of dimethyl acetylenedicarboxylate with *p*-nitrobenzaldehyde (**6a**) afforded dimethyl maleate derivative **39** and 5-oxo-2,5-dihydrofuran-3-carboxylate **40** (Scheme 15). Tetramethylthiourea was a good catalyst for this reaction.[16b]



Scheme 15. Reaction of dimethyl acetylenedicarboxylate with an aldehyde

III. Tandem Michael Aldol Reaction of Chalcogenide–Enones with Carbonyl Compounds

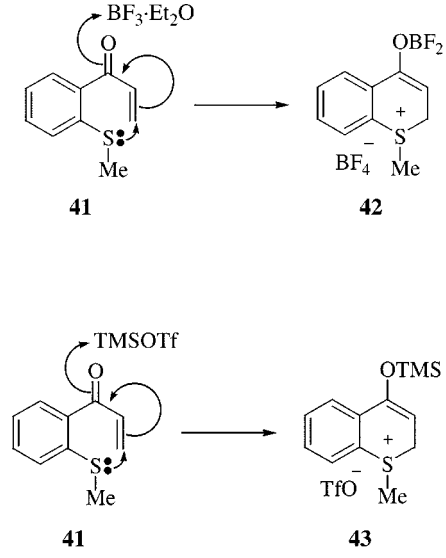
We considered whether chalcogenides added to electron-deficient alkenes and the tandem Michael aldol reaction proceeded as we had originally expected. Vinyl sulfide **32** was formed, though the yield was low, as shown in Scheme 12.[16b] 1-Ethyl-4-oxo-2,3-dihydrothiopyranium perchlorate was formed on treatment of 1-(ethylsulfanyl) pentane-1,3-dien-3-one with perchloric acid (Scheme 16).[26]



Scheme 16. Cyclization of sulfide–enone

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 very low nucleophilicity.

We first carried out the intramolecular Michael addition of 1-[2-(methylsulfanyl)phenyl]propenone (**41**) in the presence of BF_3Et_2O (Scheme 17).

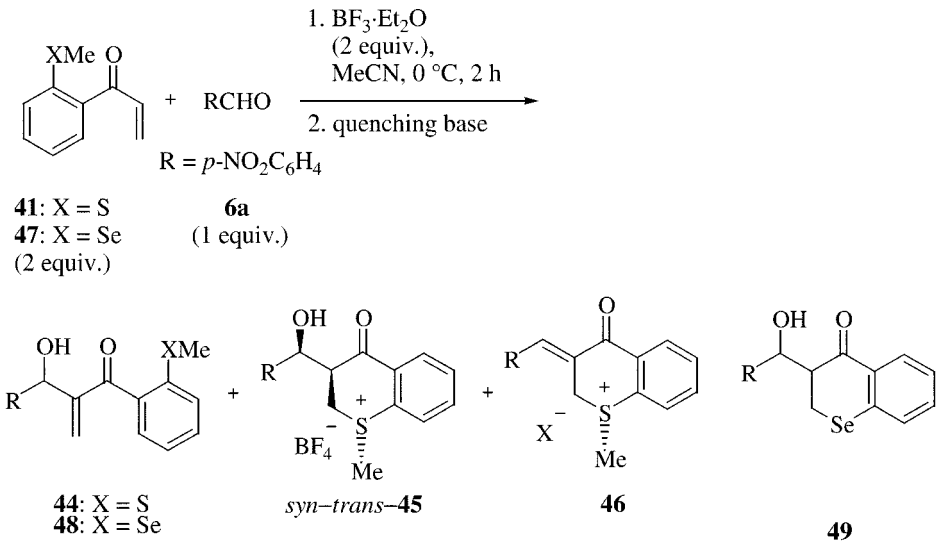


Scheme 17. Reaction of sulfide–enone with Lewis acids

The ^1H NMR spectrum showed signals due to boron enolate **42** at δ = 3.90 (dd, J = 5.0 and 18.0 Hz, 1 H; 2-H), 4.39 (dd, J = 2.0 and 18.0 Hz, 1 H; 2-H), 5.27 (dd, J = 2.0 and 5.0 Hz, 1 H; 3-H) ppm, which agreed closely with the corresponding trimethylsilyl (TMS) enol ether **43**.[27] This finding suggested that the reaction of **41** with aldehyde **6a** would proceed. Reaction conditions were examined in the presence of Lewis acids such as TiF_4, BF_3Et_2O, $Yb(TfO)_3$, and $Sc(TfO)_3$ (Table 2).

The quenching method influenced the products. Treatment of the reaction mixture with saturated $NaHCO_3$ gave the MBH adduct **44** (15 %) and the sulfonium salt *syn*-*trans*-**45** (26 %), the stereostructure of which was determined by comparison with an authentic sample, whereas treatment with triethylamine afforded **44** (75 %) only.[27b] The reaction in the presence of $Sc(TfO)_3$ produced dehydrated sulfonium salt **46** as a byproduct. Reaction of selenide–enone **47** formed selenochromanone **49** together with **48**.

Table 2. Reaction of chalcogenide–enones with aldehydes



Entry	Chalcogenide–enone	Quenching base	Products (yield [%])
1	**41**	satd. aq. $NaHCO_3$	**44** (45), **45** (26)
2	**41**	satd. aq. $NaHCO_3$[a]	**44** (52)
3	**41**	Et_3N (2 equiv.)	**44** (75)
4	**47**	Et_3N (2 equiv.)	**48** (75), **49** (16) (*syn*/*anti* = 95:5)

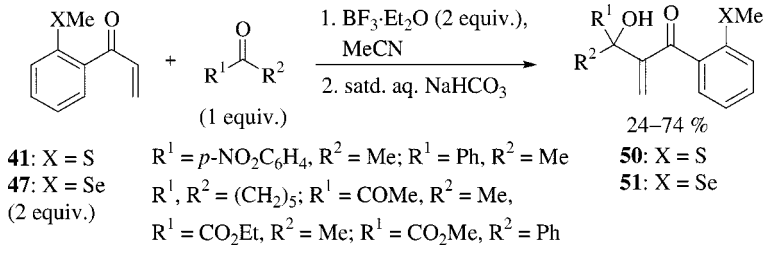
[a] The reaction mixture was poured into an excess of an $NaHCO_3$ solution.

The use of carbonyl compounds in the MBH reaction is restricted. Ketones, except for trifluoromethyl derivatives, reacted with electron-deficient alkenes only under high pressure.[28] No reports on the reactions of enolizable α-diketones have been published. The reaction of α-keto esters progressed only when there was a good match between an electron-deficient alkene and a Lewis acid.[14a,29] It was shown from the findings mentioned above that the boron enolate was an intermediate of the BF_3-mediated intramolecular Michael reaction. Furthermore, it is known that boron enolates react with carbonyl compounds under mild reaction conditions.[30] Therefore, we next examined the reactions of **41** and **47** with various carbonyl compounds.

Reactions of acetophenone derivatives and cyclohexanone at 0 °C for 30 min gave products **50** and **51** in low to moderate yields (Scheme 18).

The easily enolizable α-diketones and α-keto esters reacted with **41** and **47** to afford the products in low to high yields.[31] These results were not satisfactory, but these are the first examples of the MBH-type reactions of α-dicarbonyl compounds which are enolizable under mild conditions.

If chalcogenide–ynones react with aldehydes in the presence of BF_3Et_2O, 3-(hydroxymethyl)chalcogenochromen-4-one derivatives can be synthesized. This reaction involves the 6-*endo*-*dig* cyclization and is interesting from the view-

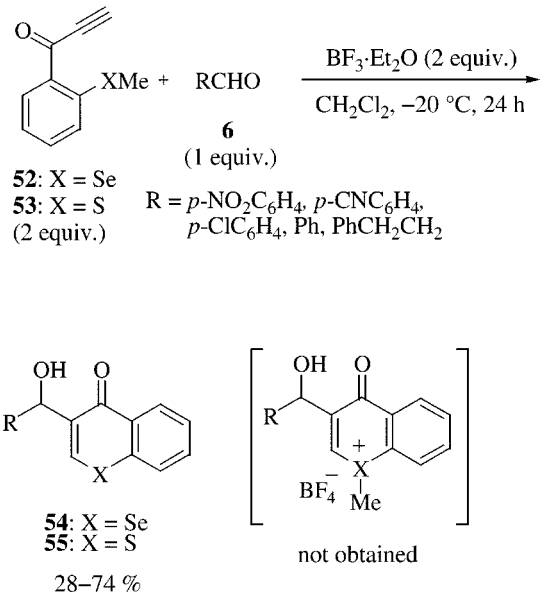


Scheme 18. Reaction of chalcogenide–enones with ketones

point of the Baldwin rule. Cyclization of 1-(hydroxyaryl)-3-phenylpropynones proceeded in the 6-*endo-dig* or the 5-*exo-dig* manner depending upon the reaction conditions,[32] whereas the selenium analogues selectively cyclized in the 6-*endo-dig* manner under the basic conditions.[33] Reactions of chalcogenide–ynone **52** or **53** with aldehydes occurred in 6-*endo-dig* fashion to give 3-(hydroxymethyl)chalcogenochromen-4-one **54** or **55** (Scheme 19).[34]

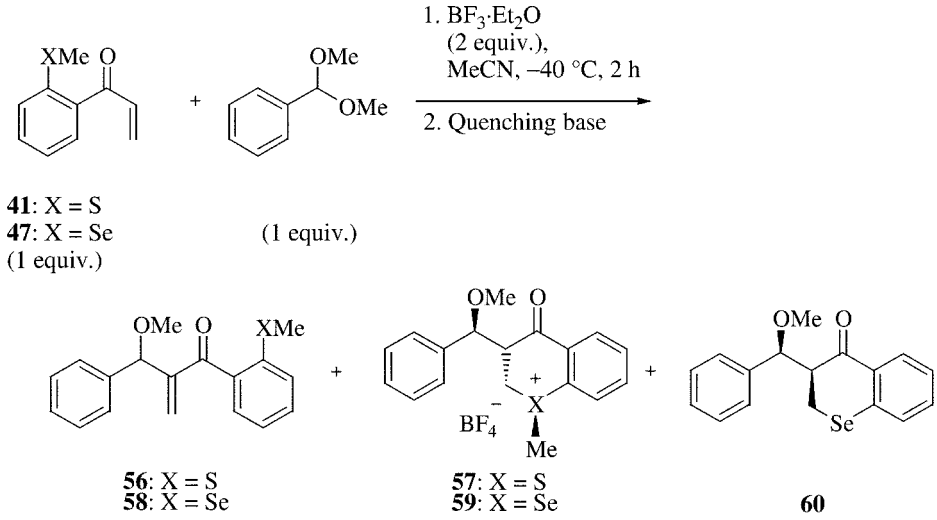
No chalcogenonium salt was obtained because the coordination of a boron Lewis acid with an aldol moiety decreased the electron density of the chalcogenopyran ring and demethylation of the onium salt would easily have occurred. This method is convenient for the synthesis of 2-unsubstituted 3-(hydroxymethyl)chalcogenochromen-4-one derivatives because 2-unsubstituted chromenone has ring-opened on treatment with lithium diisopropylamide.[35,36] Recently, Basavaiah et al.[37] synthesized 2-unsubstituted 3-(hydroxymethyl)chromen-4-ones from chromenone in the presence of Me_3N in methanol, but benzaldehyde and aliphatic aldehydes did not give the products.

Acetals function as electrophiles on treatment with a Lewis acid,[38] and Noyori et al.[39] first reported the α-alkoxyalkylation of α,β-unsaturated ketones with acetals or ortho esters in the presence of TMSOTf. Shortly afterwards, variations of this method were reported by some groups.[40–42] If acetals instead of aldehydes are used for the chalcogeno MBH reaction, BF_3Et_2O works for the formation of both enolate–onium salts and α-alkoxy carbocations, and α-alkoxyalkylation of enones can be accomplished. Reaction of benzaldehyde dimethyl acetal at



Scheme 19. Reaction of chalcogenide–ynones with aldehydes

Table 3. Reaction of chalcogenide–enones with an acetal



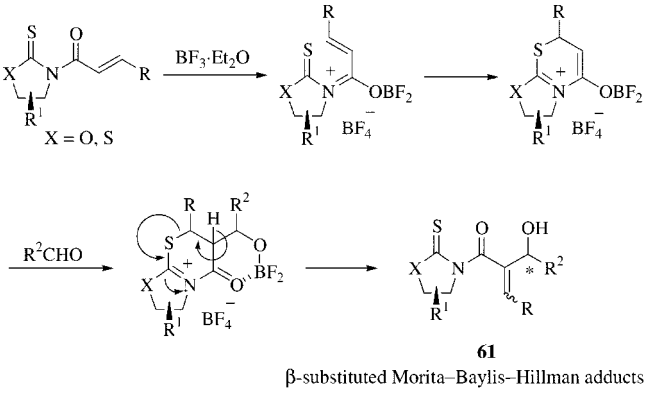
Entry	Chalcogenide–enone	Solvent	Quenching base	Products (yield [%])
1	**41**	MeCN	Et_3N (2 equiv.)	**56** (78)
2	**41**	MeCN	satd. aq. $NaHCO_3$	**56** (43), **57** (40)
3	**47**	MeCN	Et_3N (2 equiv.)	**58** (79), **60** (5)
4	**47**	MeCN	satd. aq. $NaHCO_3$	**58** (36), **59** (51)

–40 °C for 2 h gave the MBH adduct **56** (78 %) or **58** (79 %) after work-up of the reaction mixture with Et_3N and onium salt **57** (40 %) or **59** (51 %) together with **56** or **58**, respectively, after work-up with saturated $NaHCO_3$ (Table 3).[43] Stereostructures of **57** and **59** were determined by X-ray crystallography and ^1H- and ^{13}C NMR spectroscopy. Cyclic acetal, 2-phenyl-1,3-dioxolane and methyl orthoformate can be applied to this reaction.

Recently, Goodman et al.[44] reported an intermolecular chalcogeno MBH reaction mediated by chalcogenide and a Lewis acid, as we had anticipated. They used 1.2 equivalents of chiral tetrahydrothiophenes and BF_3Et_2O instead of $TiCl_4$ and worked up the reaction mixture with triethylamine. These reaction conditions[44] were different from ours.[4] This reaction was applicable to enones, and the optical yields were moderate.

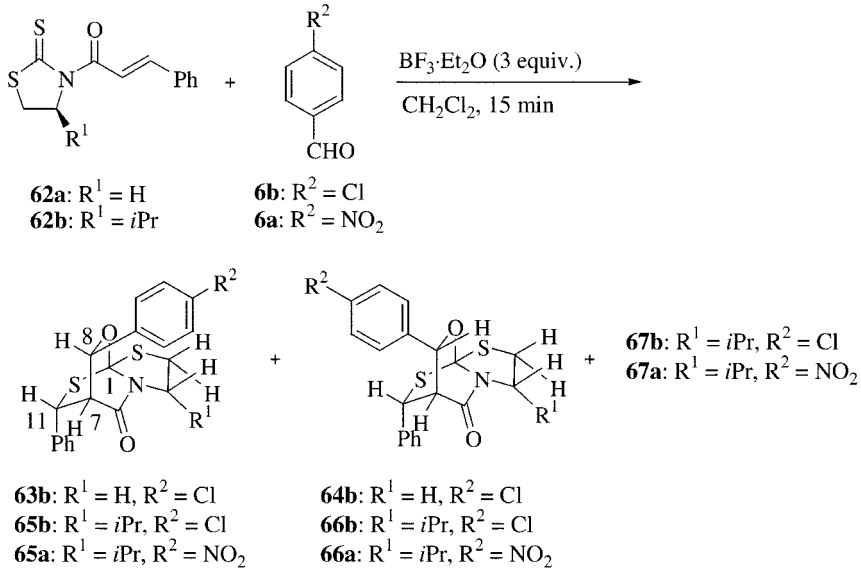
IV. Tandem Michael Aldol Reaction of *N*-Enoylthioamides with Aldehydes

As mentioned above, we have demonstrated that a chalcogenide group brought about intramolecular Michael addition to an enone moiety,[27] and a thiocarbonyl compound such as thiopyran-4-thione[13] or tetramethylthiourea[16b] catalyzed the tandem Michael aldol reaction. On the basis of these findings, a novel reaction involving the Michael addition of the thione to the intramolecular enone moiety and the formation of the boron enolate was anticipated to



Scheme 20. Anticipated MBH reaction of enone–thioamides with aldehydes

Table 4. Reaction of enone–thioamides with aldehydes

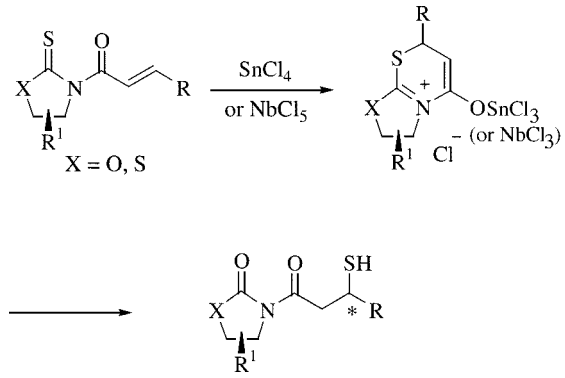


Entry	Enone (equiv.)	Aldehyde (equiv.)	Temp.	Products (yield [%])
1	**62a** (2)	**1e** (1)	room temp.	**63b** (58), **64b** (31)
2	**62b** (2)	**1e** (1)	0 °C	**65b** (54), **66b** (28), **67b** (4)
3	**62b** (2)	**1a** (1)	0 °C	**65a** (43), **66a** (41), **67a** (4)

[a] Minor products **67a** and **67b** have the same molecular weights and composition formulas, $C_{22}H_{22}N_2O_4S_2$ and $C_{22}H_{22}ClNO_2S_2$, as **65a**, **65b** and **66a**, **66b**, respectively, but the amounts of **67a** and **67b** are so small that their stereostructures could not yet be determined.

occur, as shown in Scheme 20. If this reaction goes well, we can synthesize a β-substituted MBH product **61**, which is difficult to prepare by the MBH reaction.

When we use chiral 1,3-oxazolidine-[45] or 1,3-thiazolidine-2-thione derivatives[46] as chiral auxiliaries, an asymmetric tandem Michael aldol reaction can be developed, and optically active products can be obtained. Palomo et al.[47] separately reported the sulfur-transfer reaction of chiral *N*-enoyl cyclic thioamides in which thioamide underwent an asymmetric Michael addition to the intramolecular enone moiety (Scheme 21). In their early report, $SnCl_4$ was most effective,[47a] but later the Lewis acid was changed into $NbCl_5$[47b] or BF_3Et_2O.[47c]

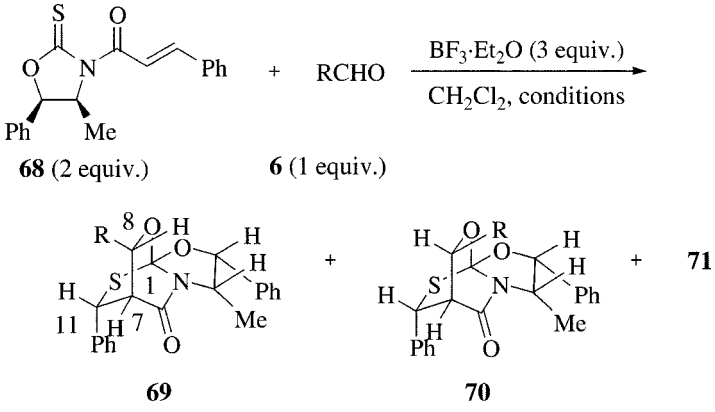


Scheme 21. Sulfur-transfer reaction of thioamides

The reaction conditions were examined in the reaction of *N*-cinnamoyl-1,3-thiazolidine-2-thione **62a** with *p*-chlorobenzaldehyde (**6b**) (Table 4); the highest yield was obtained by using 3 equivalents of BF_3Et_2O, 2 equivalents of **62a** and 1 equivalent of **6b**.[48]

The structure of a major product **65b** obtained from the reaction of a chiral (4*S*)-4-isopropylthiazollidine-2-thione **62b** and aldehyde **6b** was determined to be a tricyclic adduct with 1*R*, 7*R*, 8*S* and 11*R* configurations on the basis of the 4*S*-absolute configuration by X-ray crystallography. From this analysis, it was determined that the product was not an MBH adduct but a tricyclic compound with a bridgehead

Table 5. Asymmetric reaction of enone–thioamide with aldehydes



Entry	Aldehyde **6**	Conditions	Yield [%][a]	**69**:**70**:**71**[b]
1	R = *p*-$NO_2C_6H_4$	–78 °C, 25 h	27	100:0:0
2	R = *p*-$NO_2C_6H_4$	–40 °C, 5 h	77	94:6:0
3	R = *p*-$NO_2C_6H_4$	–40 °C, 24 h	93	95:5:0
4	R = *m*-$NO_2C_6H_4$	–40 °C, 24 h	85	95:5:0
5	R = *p*-ClC_6H_4	–40 °C, 24 h	71	86:7:7
6	R = C_6H_5	0 °C, 1 h	67	71:0:29
7	R = *p*-MeC_6H_4	0 °C, 1 h	59	92:0:8

[a] Mixture of diastereoisomers. [b] HRMS data indicate that products **70** and **71** have the same molecular formulas as product **69**, but their stereostructures could not yet be determined because of the small amount.

carbon bound with four heteroatoms (Figure 2), which would be formed by the nucleophilic cyclization of the alkoxide ion of the aldol moiety to the iminium carbon of the intermediate.

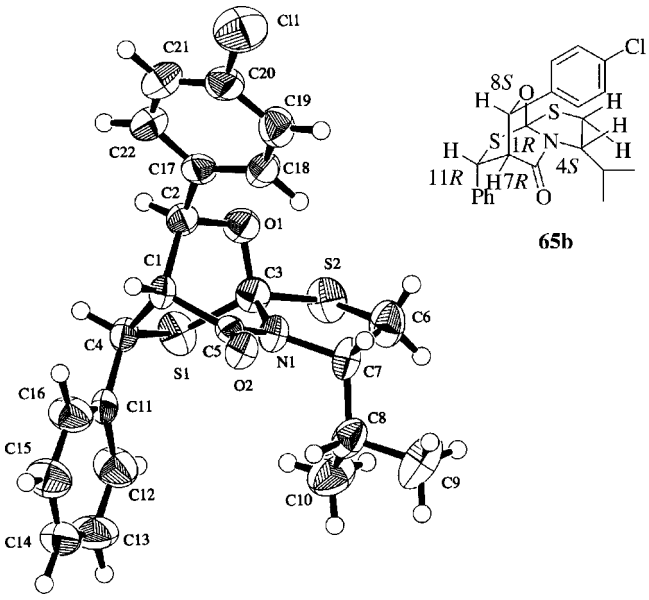


Figure 2. ORTEP drawing of tricyclic compound **65b**

This reaction induced four stereocenters at the same time. After investigation of the chiral auxiliary, (4*S*,5*R*)-4-methyl-5-phenyloxazoline-2-thione gave the best diastereoselectivity. Reactions of the *N*-cinnamoyl-thioamide **68** with aromatic aldehydes afforded tricyclic compounds **69** in moderate to good optical yields, but reactions with aliphatic aldehydes did not give satisfactory yields (Table 5).

Reactions giving high optical yields for all kinds of aldehydes and transformation of the tricyclic products to other optically active compounds are under investigation. Our next task is the application of these reactions to the synthesis of pharmacologically active compounds and useful chiral compounds.

Acknowledgments

The work reported here would not have been possible without the excellent efforts made by our coworkers and students, whose names appear in the references. The authors thank the Ministry of Education, Science, Sports and Culture of Japan, and the Japanese Society for the Promotion of Science for financial support of this research.

[1] This reaction is commonly called the Baylis–Hillman reaction. However, Morita[1a,1b] reported the *tert*-phosphane-catalyzed reactions of electron-deficient alkenes with aldehydes four years earlier than Baylis and Hillman.[1c] This has been pointed out by Drewes[1d] and Ciganek.[1f] Therefore, the Baylis–Hillman reaction should be referred to as the Morita–Baylis–Hillman reaction. a) K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815; b) K. Morita, *Japan Patent* 68 03,364 (1968) [*Chem. Abstr.* **1968**, *69*, 58828s]; c) A. B. Baylis, M. E. D. Hillman, *Ger. Offen.* 2,155,113 (1972) [*Chem. Abstr.* **1972**, *77*, 34174q]. Reviews for the Morita–Baylis–Hillman reaction: d) S. E. Drewes, G. H. P. Roos, *Tetrahedron* **1988**, *44*, 4653–4670; e) D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001–8062; f) E. Ciganek, *Org. React.* **1997**, *51*, 201–350; g) P. Langer, *Angew. Chem. Int. Ed.* **2000**, *39*, 3049–3052; h) Y. Iwabuchi, S. Hatakeyama, *J. Syn. Org. Chem. Jpn.* **2002**, *60*, 2–16; i) J. N. Kim, K. Y. Lee, *Curr. Org. Chem.* **2002**, *6*, 627–645; j) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–891.

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