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Reexamination of Products and the Reaction Mechanism of the Chalcogeno-Baylis–Hillman Reaction: Chalcogenide–$TiCl_4$-mediated Reactions of Electron-Deficient Alkenes with Aldehydes

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Abstract—Reactions of *p*-nitrobenzaldehyde (**4**) with methyl vinyl ketone (**5**) were conducted in the presence of $TiCl_4$ and dimethyl sulfide (**3**) or selenopyranone **6**. When the raw product was purified by column chromatography on silica gel, α-chloromethyl aldol **8** was obtained as a mixture of diastereoisomers **8a** and **8b**. In contrast, purification of the raw product by preparative TLC on silica gel gave α-methylene aldol **7**. The mechanism for the formation of α-chloromethyl aldol **8** and diasteroselection for the *syn*-isomer **8a** and *anti*-isomer **8b** are discussed.

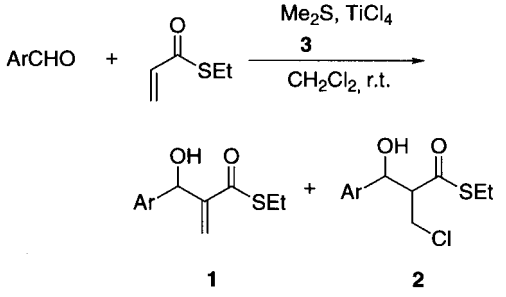
Introduction

We recently devised a new reaction, the chalcogeno-Baylis–Hillman reaction, in which a chalcogenide and $TiCl_4$ are used instead of a tertiary amine as a catalyst of the Baylis–Hillman reaction.[1] An advantage of this reaction is that it proceeds smoothly under mild conditions and is finished within an hour, thus overcoming the drawback of the slow rate of the Baylis–Hillman reaction.[2] The chalcogeno-Baylis–Hillman reaction has been applied to the reactions of α,β-unsaturated ketones, nitriles, carboxylic acid esters, and thioesters.[3,4] Enantioselective synthesis utilizing this methodology has also been studied.[5,6] A hydrogen-chloride adduct **2** was detected in the raw product from the chalcogeno-Baylis–Hillman reaction of acrylic acid thioesters by ^{1}H NMR spectroscopy[4] (Scheme 1).

On the other hand, reactions of enones with aldehydes mediated by a combination of titanium (IV) halides (TiX_4) and $(n\text{-Bu})_4NI$[7] or TiX_4 alone[8] have been studied and found to be useful for preparation of α-halomethyl aldols or α-halomethyl enones. The outcome of these studies implied that the hydrogen-chloride adducts of the Baylis–Hillman products (α-chloromethyl aldols) would also be formed from the chalcogenide–$TiCl_4$-mediated reaction of other active alkenes. We had not isolated the hydrogen-chloride adduct, but very recently were able to obtain it from the reaction of *p*-nitrobenzaldehyde (**4**) with methyl vinyl ketone (**5**) catalyzed by $TiCl_4$ and 2,6-diphenylselenopyran-4-one (**6**). Experiments were undertaken to examine the difference between the previous reactions[3,9] and the present ones. In this report we describe the formation of an α-chloromethyl aldol (a hydrogen-chloride adduct of the Baylis–Hillman product) and its formation mechanism.

Results and Discussion

In the course of our study on the chalcogenide–$TiCl_4$-mediated reaction using chalcogenopyrones, the raw product, obtained from the reaction of *p*-nitrobenzaldehyde (**4**) and methyl vinyl ketone (**5**), was purified by column chromatography instead of preparative TLC, and an



Scheme 1.

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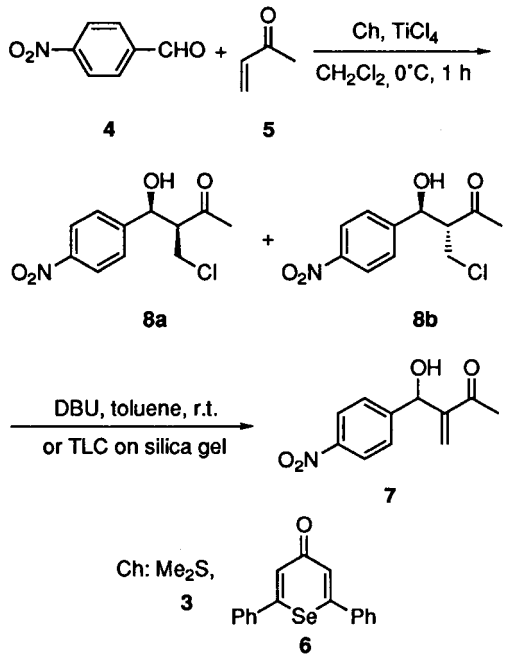
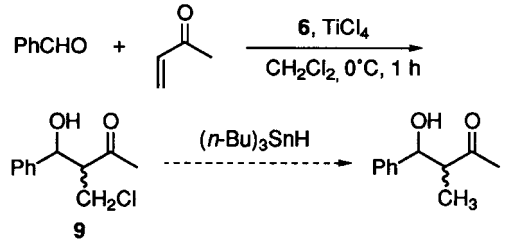


Scheme 2.

unexpected product, 3-chloromethyl-4-hydroxy-4-(*p*-nitrophenyl)butan-2-one (**8**), was afforded as a mixture of two diastereoisomers, with a ratio of **8a**:**8b**=3:1 in 95% yield. The isomer ratio did not vary with reaction times of 15 min, 1 h, and 24 h. The reaction using dimethyl sulfide (**3**) as a catalyst also gave the α-chloromethyl derivative **8**, with a ratio of **8a**:**8b**=7:1 in 74% yield (Scheme 2).

The diastereoisomers could be separated by the recycling preparative HPLC on polystyrene gel eluting with chloroform. They exhibited the following NMR spectral data. **8a**: ^{1}H NMR ($CDCl_3$) δ: 3.30 (1H, ddd, J=4, 5 and 9 Hz, 3-H), 3.67 (1H, dd, J=4 and 11 Hz, CH_2Cl), 3.89 (1H, dd, J=9 and 11 Hz, CH_2Cl), 5.11 (1H, dd, J=3 and 5 Hz, benzylic H). ^{13}C NMR ($CDCl_3$) δ: 40.8 (t, CH_2Cl), 60.3 (d, 3-C), 71.9 (d, 4-C). **8b**: ^{1}H NMR ($CDCl_3$) δ: 3.24 (1H, dt, J=5 and 7 Hz, 3-H), 3.56 (1H, dd, J=7 and 11 Hz, CH_2Cl), 3.64 (1H, dd, J=5 and 11 Hz, CH_2Cl), 5.15 (1H, t, J=6 Hz, benzylic H). ^{13}C NMR ($CDCl_3$) δ: 41.9 (t, CH_2Cl), 59.9 (d, 3-C), 72.4 (d, 4-C). The structure of the diastereoisomers of β-hydroxyketones obtained from the aldol reactions has generally been determined from the difference in the vicinal coupling constants[10] or chiral shifts using Eu(hfc)$_3$[11] in the ^{1}H NMR spectra and the difference in the chemical shifts in the ^{13}C NMR spectra.[12] However, there exist some exceptions to the above,[13] and compounds **8a** and **8b** did not show such a significant difference in their spectral data. We planned to convert the α-chloromethyl aldol into the known compound, 4-hydroxy-3-methyl-4-phenyl-2-butanone.[14] A reaction of methyl vinyl ketone (**5**) with benzaldehyde was conducted, and the diastereoisomers of α-chloromethyl aldol **9** were separated. Reductive dechlorination of **9** using tributyltin hydride was unsuccessful and gave a complex mixture (Scheme 3). Therefore, the structure of the major product **8a** was determined to be a *syn*-configuration by X-ray crystallography (Fig. 1).



Scheme 3.

This unexpected outcome prompted us to reexamine the reactions of methyl vinyl ketone (**5**) with *p*-nitrobenzaldehyde (**4**) in the presence of dimethyl sulfide (**3**) and $TiCl_4$. We obtained the same result as that obtained previously.[3,9] The only difference between these experiments was the purification method: column chromatography on silica gel or preparative TLC on silica gel. An aqueous suspension of silica gel was not basic but weakly acidic (pH 6.6), and, therefore, preparative TLC was not conducted under basic conditions. When the isolated chloromethyl derivative **8** was chromatographed on the silica gel plates, dehydrochlorination occurred during the TLC purification to give an α-methylene derivative **7**. This finding ruled out the possibility that a tiny amount of sodium hydrogen carbonate, a weak inorganic base used for easy removal of the inorganic titanium precipitate from the quenched reaction mixture (see Experimental), would cause the elimination of hydrogen chloride. A $CDCl_3$ solution of the *syn*-isomer **8a** was allowed to stand for 2 days in an NMR tube, and its ^{1}H NMR spectrum was measured. Allyl alcohol **7** and 3-chloromethyl-4-(*p*-nitrophenyl)but-4-en-2-one[6] (**10**) were detected. The (*Z*)-geometry of **10** was determined by measurement of the NOE enhancement. The *syn*-isomer **8a** isomerized to *anti*-isomer **8b**, and the isomer ratio was **8a**:**8b**=1:1 (Scheme 4).

These findings indicate that chloride **8** is very labile and readily undergoes dehydrochlorination. We have proposed the formation mechanism for α-methylene-β-hydroxy

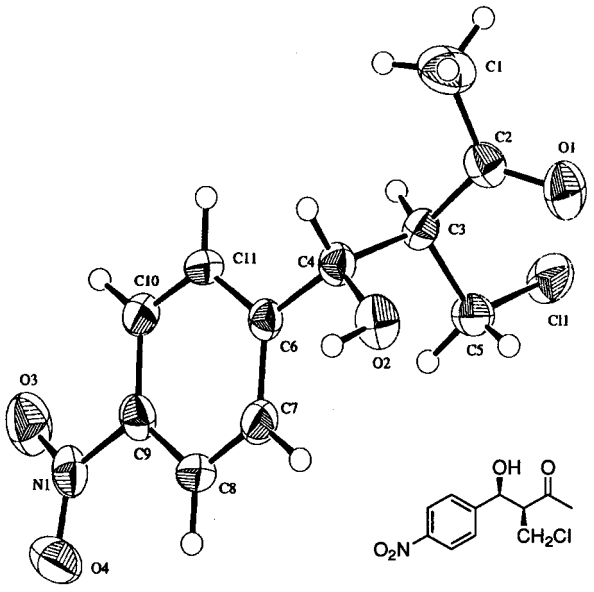
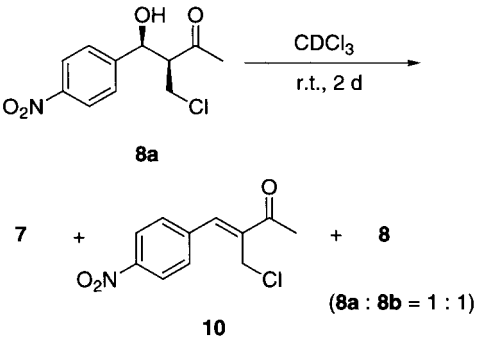


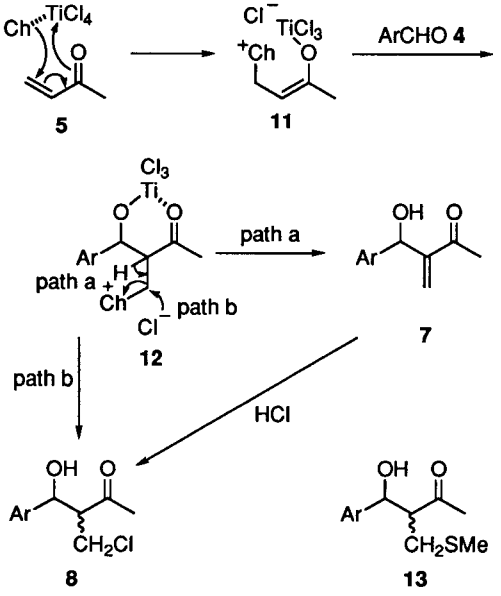
Figure 1. ORTEP drawing of **8a**.



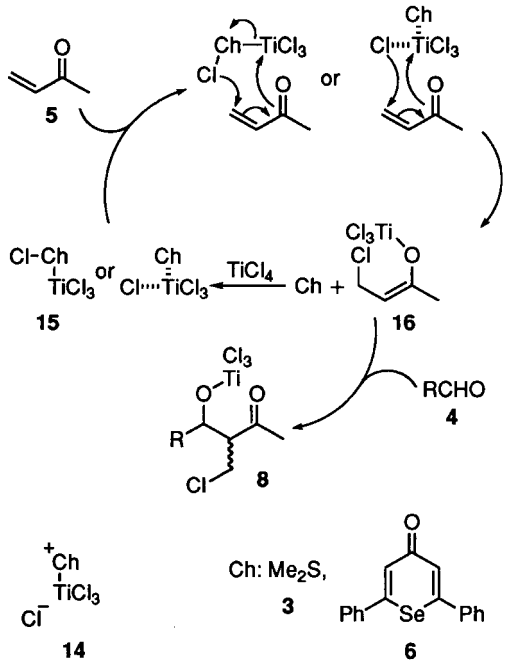
Scheme 4.

ketone **7**, but have not referred to the formation of chloride **8**.[3] Since chloride **8** was isolated by column chromatography of the raw product obtained from the reaction of aldehyde **4** and enone **5**, plausible mechanisms for the formation of **8** are discussed in Schemes 5–7. The mechanism shown in Scheme 5 involves the Michael addition of a chalcogenide.

A chalcogenide first coordinates with $TiCl_4$ to form a $TiCl_4$–chalcogenide complex, which reacts with the *s-cis* form of enone **5**, and predominantly generates titanium *Z*-enolate **11**. The reaction of the enolate **11** with an aldehyde gives an adduct **12**. Two reaction pathways can be considered for the formation of the α-chloromethyl compound **8** from the adduct **12**. The first pathway (path a) involves the formation of α-methylene-β-hydroxyketone **7** and the addition of hydrogen chloride generated in situ to **7**. In the other pathway (path b), the chloride ion attacks a carbon α to the chalcogenonio group of the aldol onium salt **12**. In order to determine which pathway is more feasible for the formation of **8**, reactions of **7** with $TiCl_4$ and/or hydrogen chloride were examined. Hydrogen chloride was bubbled into a solution of **7** in $CDCl_3$, and the reaction mixture was allowed to stand for 5 h at room temperature (Entry 1). The results are summarized in Table 1.

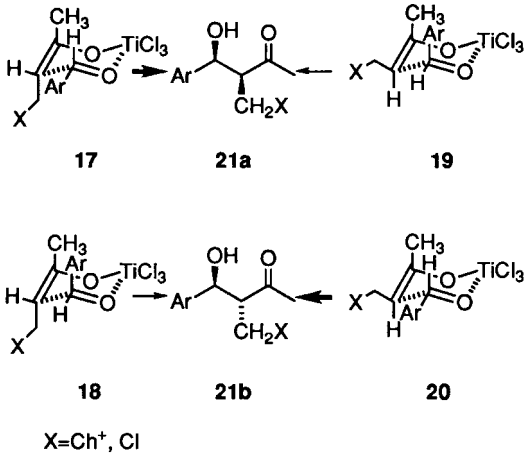


Scheme 5.



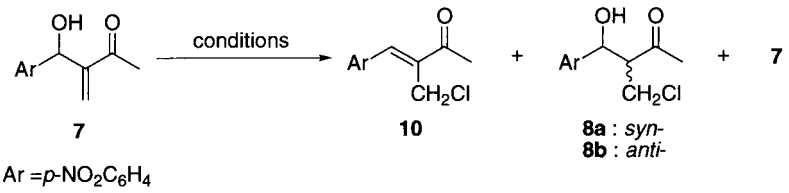
Scheme 6.

The ^1H NMR spectrum of the mixture showed signals of addition product **8** and dehydration product **10**. The ratio of the diastereoisomers was **8a**:**8b**=1:2.7. When hydrogen chloride was passed into the solution of **7** in dichloromethane in the presence of $TiCl_4$ (Entry 2), dehydration was accelerated and α-chloromethyl enone **10** was formed as a main product. Treatment of **7** with $TiCl_4$ for 10 min or 30 min gave products **8a**, **8b**, and **10**, and the diastereomer ratio was **8a**:**8b**=1:3.3 or 2.7, respectively. We conducted a reaction of sodium salt of **7** with $TiCl_4$ without evolution of hydrogen chloride; instead we obtained a complex mixture in which chlorides **8a** and **8b** were not detected (Entry 5). The isomer ratios of **8a**:**8b** in Table 1 were different from those of the product (**8a**:**8b**=3:1) obtained from the reaction of **4** and **5** mentioned above. These results indicated that the α-chloromethyl aldols **8a** and **8b** would not be formed mainly via the path a.



Scheme 7.

Table 1. Reaction of **7** with HCl and/or $TiCl_4$



Entry	Conditions	Product ratio[a] (**7**:**8a**:**8b**:**10**)
1	HCl gas, $CDCl_3$, rt, 5 h	1.8:1:2.7:0.6[b]
2	$TiCl_4$, HCl gas, CH_2Cl_2	0:1:3:70
3	$TiCl_4$, CH_2Cl_2, 0°C, 10 min	4.5:1:3.3:6.5
4	$TiCl_4$, CH_2Cl_2, 0°C, 30 min	17.4:1:2.7:18.7
5	NaH, $TiCl_4$, CH_2Cl_2, 0°C, 1 h	Complex mixture

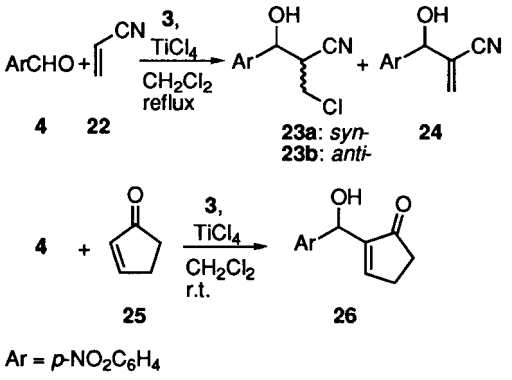
[a] The product ratio was determined from the intensities of the methyl and the chloromethyl signals of the isolated raw product in ^{1}H NMR spectrum.
[b] The reaction was conducted in $CDCl_3$ and the ^{1}H NMR spectrum was measured without isolation.

In order to detect the intermediate **11** or its enolate by NMR spectroscopy, we conducted a reaction of **5** with $TiCl_4$ in an NMR tube. ^{1}H NMR spectrum in $CDCl_3$ exhibited the signals at δ 2.79 (3H, s, Me), 6.48 (1H, t, J=5 Hz, olefinic H), 6.80 (2H, d, J=5 Hz, $CH_2^{\delta+}$), suggesting the formation of a complex of butenone **5** and $TiCl_4$, and quite rapidly changed into the absorption signals of 4-chloro-2-butanone at δ 2.24 (3H, s, Me), 2.86 (2H, t, J=6.5 Hz, CH_2CO), and 3.68 (2H, t, J=6.5 Hz, CH_2Cl). Treatment of **5** with $TiCl_4$ and dimethyl sulfide (**3**) in $CDCl_3$ formed a reddish-brown precipitate, and the ^{1}H NMR spectrum of the reaction mixture could not be measured. Although we carefully attempted the isolation of the sulfonium chloride, it was unsuccessful. The reasons why the chloride **8** was formed exclusively and α-(methylthiomethyl)aldol **13** was not detected cannot be explained by Scheme 5. Therefore, the other mechanism for the formation of the chloride **8** is shown in Scheme 6.

A chalcogenide coordinates with $TiCl_4$ and assists it in releasing a chlorine atom. Although the exact structure of the $TiCl_4$–chalcogenide complex cannot be determined, the initially-formed $TiCl_4$–chalcogenide complex or an intimate ion pair of trichlorotitanium–chalcogenonium chloride **15** reacts with enone **5** to form titanium *Z*-enolate **16** predominantly and the chalcogenide is regenerated. In this process, the chlorine atom nucleophilically attacks the positively charged β-carbon of the enone **5** mainly from the side of the titanium complex chelated with the carbonyl.[7] A pathway passing through the attack of the free chloride ion of trichlorotitanium–chalcogenonium chloride **14** on the β-carbon of enone **5** was not feasible for the explanation of the *Z*-enolate formation and the *syn*-predominant product distribution. The titanium enolate **16** thus formed reacts with an aldehyde to give an adduct **8**. Very recently, Li and his coworkers reported that the reaction proceeded by the assistance of $TiCl_4$ only.[8] This suggested that a chalcogenide was not necessary for the reaction of enone **5** with aldehyde **4**. However, their results, yielding only products with *anti*-configuration, are much different from ours, yielding predominantly the *syn*-products. Variation of the isomer ratio was observed between the reactions using dimethyl sulfide (**3**) and selenopyranone **6**. Moreover, the reactions of acrylates and acetylenic esters did not proceed using TiX_4 only,[8,15] but did proceed by assistance of a combinative TiX_4–chalcogenide promoter.[3,15] The outcome indicated that the chalcogenide played an important role in the chalcogenide–$TiCl_4$-mediated reactions of enones with aldehydes.

If the α-chloromethyl aldol **8** was formed via path b in Scheme 5 or the paths in Scheme 6, the stereoselection for the formation of **8** would be induced in the reaction step of titanium enolate **11** or **16** with aldehyde **4**.

The Zimmerman–Traxler model and the Evans model are used to explain the aldol condensation of trichlorotitanium enolates with aldehydes.[16,17] Since trichlorotitanium enolates have high Lewis acidity, chelated cyclic transition states are more feasible to predict the structure-selectivity relationships than open-chain transition states. Kuwajima et al. proposed a boat-transition state for the titanium cyclic enolate but applied a chair-transition state to the aldol reaction of titanium enolates of acyclic compounds.[16] For these reasons, the Zimmerman–Traxler model is applied for predicting *syn*-diastereoselectivity. There are four possible transition states, **17–20**, for condensation of the titanium enolate and an aldehyde (Scheme 7). For *Z*-enolates, the interaction between the methyl group and the aryl group dominates, and the transition state **17** is favored over the other transition state, **18**, leading to more of the *syn*-isomer **21a**. For *E*-enolates, the methyl-aryl group interaction favors the isomer **20** with an equatorial Ar group over the



Scheme 8.

other isomer, **19**, with an axial Ar group. The *anti*-aldol **21b** is the major product.

The *Z*-α,β-disubstituted enolates are preferred over the *E*-enolates under kinetic conditions because of the steric repulsion between the substituents.[18] In the chalcogenide–$TiCl_4$-mediated reactions *Z*-enolate **11** or **16** is predominantly formed via the process shown in Scheme 5 or Scheme 6 as mentioned above, respectively. Therefore, the reaction of enolate **11** or **16** with aldehyde **4** proceeded mainly via the transition state **17** and diastereoselectively gave the *syn*-product **21a**.

On the basis of the results obtained above, we concluded that the α-chloromethyl aldols were the products of the chalcogenide–$TiCl_4$-mediated reactions of enones with aldehydes. However, α-methylene aldols (the Baylis–Hillman products) were often formed during the chalcogenide–$TiCl_4$-mediated reactions depending upon the reaction conditions and the lability of the α-chloromethyl aldols. Reaction of acrylonitrile (**22**) with *p*-nitrobenzaldehyde (**4**) under reflux in dichloromethane gave a mixture of *syn*-, *anti*-2-chloromethyl-3-hydroxy-3-(*p*-nitrophenyl)propiononitrile (**23a**, **b**) and 2-chloromethyl-3-[1-hydroxy-1-(*p*-nitrophenyl)methyl]acrylonitrile (**24**) in a ratio of **23**:**24**=6.7:1, while reaction of cyclopentenone (**25**) at room temperature yielded only the Baylis–Hillman product (**26**) (Scheme 8).

The reaction mechanisms for formation of the α-chloromethyl aldols were discussed and propose the new ones as shown in Schemes 5 and 6. So far, we cannot decide which pathway is more suitable for the mechanism.

Experimental

General methods

Melting points were obtained with a Yanagimoto micro-melting-point apparatus and are uncorrected. IR spectra of solids (KBr) and liquids (NaCl) were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL GX-270 (270 MHz) or a JEOL EX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a JEOL EX-400 spectrometer. Mass spectra were recorded on a JEOL JMS-SX102A spectrometer with a direct-insertion probe at 70 eV. Elemental analyses of new compounds were performed by a Yanaco CHN Corder MT-5. All chromatographic isolations were accomplished with BW-350 (Fuji Silysia) for column chromatography or with Kieselgel 60 PF_{254} containing gypsum (Merck) for preparative TLC. CH_2Cl_2 was washed with water, dried over $CaCl_2$, and freshly distilled. The recycling preparative HPLC was performed by LC-918 liquid chromatography (Japan Analytical Industry Co. Ltd.) equipped with JAIGEL-1H and -2H columns (polystyrene gels).

Reaction of *p*-nitrobenzaldehyde (4) with methyl vinyl ketone (5)

(a) To a stirred solution of *p*-nitrobenzaldehyde (**4**) (76 mg, 0.5 mmol), methyl vinyl ketone (**5**) (70 mg, 1 mmol) and 2,6-diphenyl-4*H*-selenapyran-4-one[19] (**6**) (16 mg, 0.05 mmol) in dry CH_2Cl_2 (1.5 ml) were added dropwise $TiCl_4$ (55 ml, 0.5 mmol) at 0°C. The mixture was stirred at the same temperature for 1 h, and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitate was removed by filtration through Celite^{TM}, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate–hexane (1:10, v/v) to give 3-chloromethyl-4-hydroxy-4-(*p*-nitrophenyl)butan-2-one (**8**) (122 mg, 95%) as a mixture of **8a** and **8b**, with a ratio of 3:1. The diastereoisomers were separated by recycling preparative HPLC eluting with $CHCl_3$. ***syn*-Isomer 8a.** Mp 120–123°C; colorless prisms (chloroform/hexane); ^{1}H NMR ($CDCl_3$) δ: 2.19 (3H, s, CH_3), 2.96 (1H, d, J=3 Hz, OH), 3.30 (1H, ddd, J=4, 5, and 9 Hz, 3-H), 3.67 (1H, dd, J=4 and 11 Hz, CH_2Cl), 3.89 (1H, dd, J=9 and 11 Hz, CH_2Cl), 5.11 (1H, dd, J=3 and 5 Hz, benzylic H), 7.55 and 8.23 (each 2H, d, J=8 Hz, Ar H); ^{13}C NMR ($CDCl_3$) δ: 32.2 (q), 40.8 (t), 60.3 (d), 71.9 (d), 123.9 (d), 127.1 (d), 147.7 (s), 147.9 (s), 208.9 (s); IR (KBr, cm^{-1}): 3506 (OH), 1715 (C=O), 1525 and 1349 (NO_2), 701 (C–Cl); MS (FAB) *m/z* (rel. int. %): 258 (9%, M^++1), 260 (3%, M^++3). Anal. Calcd for $C_{11}H_{12}ClNO_4$: C, 51.27; H, 4.69; N, 5.44. Found: C, 51.23; H, 4.70; N, 5.38. ***anti*-Isomer 8b.** Mp 120–123° C; colorless prisms (chloroform/hexane); ^{1}H NMR ($CDCl_3$) δ: 2.22 (3H, s, CH_3), 3.24 (1H, dt, J=5 and 7 Hz, 3-H), 3.34 (1H, d, J=6 Hz, OH), 3.56 (1H, dd, J=7 and 11 Hz, CH_2Cl), 3.64 (1H, dd, J=5 and 11 Hz, CH_2Cl), 5.15 (1H, t, J=6 Hz, benzylic H), 7.55 and 8.26 (each 2H, d, J=9 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ: 32.0 (q), 41.9 (t), 59.9 (d), 72.4 (d), 124.0 (d), 127.1 (d), 147.8 (s), 148.1 (s), 209.3 (s); IR (KBr, cm^{-1}): 3458 (OH), 1715 (C=O), 1516 and 1347 (NO_2), 704 (C–Cl); MS (FAB) *m/z* (rel. int. %): 258 (9%, M^++1), 260 (3%, M^++3). Anal. Calcd for $C_{11}H_{12}ClNO_4$: C, 51.27; H, 4.69; N, 5.44. Found: C, 51.02; H, 4.73; N, 5.36.

(b) The reaction was similarly conducted on the same scale using dimethyl sulfide (**3**) (3 mg, 0.05 mmol) instead of **6**. The product **8** was obtained as a mixture of diastereoisomers, with a ratio of **8a** and **8b**=7:1 in 74% yield.

(c) The reaction was carried out in a similar way as (a), and the raw product was purified by preparative TLC on silica gel eluting with acetone–dichloromethane (1:20, v/v) to give 3-[1-hydroxy-1-(*p*-nitrophenyl)methyl]-3-buten-2-one[3] (**7**) in quantitative yield.

Conversion of 8 to 7

(a) Compound **8** (129 mg, 0.5 mmol) was dissolved in dry toluene (3 ml) and treated with DBU (114 ml, 0.75 mmol) at room temperature for 1 h. Toluene (5 ml) was added to the reaction mixture, and the whole was washed successively with 1 N aqueous HCl (5 ml) and saturated aqueous $NaHCO_3$ (2 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate–hexane (1:10, v/v) to give **7** (108 mg, 98%). The product **7** was identical to the sample obtained from the reaction.[3]

(b) Compound **8a** (128 mg, 0.5 mmol) isolated by recycling preparative HPLC eluting with $CHCl_3$ was submitted to preparative TLC on silica gel eluting with ethyl acetate–hexane (1:1, v/v) to give **7** (109 mg, 99%).

Reaction of benzaldehyde with 5

To a stirred solution of benzaldehyde (53 mg, 0.5 mmol), **5** (70 mg, 1 mmol), and **6** (16 mg, 0.05 mmol) in dry CH_2Cl_2 (1.5 ml) was added dropwise $TiCl_4$ (55 ml, 0.5 mmol) at 0°C. The mixture was stirred at the same temperature for 1 h, and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitate was removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate–hexane (1:10, v/v) to give 3-chloromethyl-4-hydroxy-4-phenylbutan-2-one (**9**) (83 mg, 78%) as a mixture of diastereoisomers, with a ratio of **9a**:**9b**=3:1. The obtained diastereoisomers were separated by recycling preparative HPLC eluting with $CHCl_3$. ***syn*-Isomer 9a.** Pale orange oil; ^{1}H NMR ($CDCl_3$) δ: 2.01 (3H, s, CH_3), 2.53 (1H, br, s, OH), 3.32 (1H, ddd, *J*=4, 7, and 10.5 Hz, 3-H), 3.78 (1H, dd, *J*=4 and 11 Hz, CH_2Cl), 3.87 (1H, dd, *J*=10.5 and 11 Hz, CH_2Cl), 4.85 (1H, d, *J*=7 Hz, benzylic H), 7.29–7.39 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ: 32.4 (q), 41.8 (t), 61.4 (d), 73.5 (d), 126.1 (d), 128.4 (d), 128.8 (d), 140.8 (s), 209.3 (s); IR (KBr, cm^{-1}): 3441 (OH), 1713 (C=O), 701 (C–Cl); MS (EI) *m/z* (rel. int. %): 212 (8%, M^+), 77 (100%). Anal. Calcd for $C_{11}H_{13}ClO_2$: C, 60.97; H, 6.16. Found: C, 61.11; H, 6.03. ***anti*-Isomer 9b.** Brown oil; ^{1}H NMR ($CDCl_3$) δ: 2.23 (3H, s, CH_3), 3.27 (1H, ddd, *J*=4.4, 7.8, and 8.3 Hz, 3-H), 3.43 (1H, dd, *J*=4.4 and 11.2 Hz, CH_2Cl), 3.58 (1H, dd, *J*=8.3 and 11.2 Hz, CH_2Cl), 3.64 (1H, dd, *J*=5 and 11 Hz, CH_2Cl), 4.92 (1H, d, *J*=7.8 Hz, benzylic H), 7.32–7.40 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ: 32.5 (q), 42.3 (t), 60.4 (d), 73.9 (d), 126.1 (d), 128.5 (d), 128.8 (d), 140.9 (s), 210.1 (s); IR (KBr, cm^{-1}): 3458 (OH), 1715 (C=O), 1516 and 1347 (NO_2); MS (EI) *m/z* (rel. int. %): 212 (8%, M^+), 107 (100%). HRMS Calcd for $C_{11}H_{12}ClNO_4$ 212.0604, found 212.0593.

Stability of 8a in $CDCl_3$

A solution of a mixture of **8a** in $CDCl_3$ was allowed to stand for 2 days at room temperature and was then submitted to ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum showed peaks of α-methylene aldol **7**, 3-chloromethyl-4-(*p*-nitrophenyl)-but-4-en-2-one[6] (**10**), **8a**, and **8b,** with a ratio of 5:6:10:10. **10:** mp 127–128.5° C; light-yellow prisms (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ: 2.55 (3H, s, 1-H), 4.38 (2H, s, CH_2), 7.71 (1H, s, 4-H), 7.75 and 8.33 (each 2H, d, *J*=8.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ: 26.0 (q), 36.8 (t), 124.0 (d), 130.2 (d), 139.6 (s), 140.1 (d), 140.4 (s), 148.0 (s), 196.6 (s); IR (KBr, cm^{-1}): 1665 (C=O), 1500 and 1335 (NO_2); MS (EI) *m/z* (rel. int. %): 239 (13%, M^+), 222 (100%). Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.04; H, 4.19; N, 5.72. The (*Z*)-configuration of **10** was determined from the NOE enhancement between 4-H and CH_3 by 7%.

Treatment of 7 with $TiCl_4$

(a) Hydrogen chloride was bubbled into a solution of **7** (110 mg, 0.5 mmol) and $TiCl_4$ (55 ml, 0.5 mmol) in dry CH_2Cl_2 (1.5 ml) at room temperature. The mixture was stirred at the same temperature for 1 h and worked up as mentioned above. The products and their ratio were listed in Entry 2 in Table 1.

(b) A solution of **7** (110 mg, 0.5 mmol) and $TiCl_4$ (55 ml, 0.5 mmol) in dry CH_2Cl_2 (1.5 ml) was stirred at 0°C for 10 min. The mixture was worked up as mentioned above. The products and their ratio were listed in Entry 3 in Table 1.

(c) A solution of **7** (110 mg, 0.5 mmol) and $TiCl_4$ (55 ml, 0.5 mmol) in dry CH_2Cl_2 (1.5 ml) was stirred at 0° C for 30 min. The mixture was worked up as mentioned above. The products and their ratio were listed in Entry 4 in Table 1.

(d) NaH (20 mg, 0.5 mmol) was added in small portions to a solution of **7** (110 mg, 0.5 mmol) in dry CH_2Cl_2 (1.5 ml) at 0°C. $TiCl_4$ (55 ml, 0.5 mmol) was added dropwise to the mixture, and the whole was stirred at the same temperature for 1 h. The mixture was worked up as mentioned above. A complex mixture was obtained, and the products could not be separated.

Addition of hydrogen chloride to 7

Hydrogen chloride was bubbled into a solution of **7** in $CDCl_3$ in an NMR tube. The mixture was allowed to stand for 5 h at room temperature and submitted to ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum showed peaks of **8a**, **8b**, **10**, and **7**, with a ratio of 1:2.7:0.6:1.8.

Product analysis of the reactions of acrylonitrile (22) and cyclopentenone (25) with *p*-nitrobenzaldehyde (4)

The chalcogeno-Baylis–Hillman reactions of acrylonitrile (**22**) and cyclopentenone (**25**) with *p*-nitrobenzaldehyde (**4**) were conducted under the same conditions in the literature.[3] The crude products were analyzed by NMR spectroscopy before purification by chromatography. The product ratio of *syn*-2-chloromethyl-3-hydroxy-3-(*p*-nitrophenyl)-propiononitrile (**23a**), the *anti*-isomer **23b** and 2-[1-hydroxy-1-(*p*-nitrophenyl)methyl]acrylonitrile (**24**) **23a**:**23b**:**24**=5.6:1.1:1 was obtained from the intensities of the peaks of benzylic protons at δ 5.29 for **23a**, δ 5.20 for **23b** and δ 5.46 for **24**. The peaks of 3-chloro-2-[1-hydroxy-1-(*p*-nitrophenyl)methyl]cyclopentanone were not observed in the ^{1}H NMR spectrum of the crude product obtained from the reaction of **25** with **4** but those of cyclopentenone **26** were observed.

X-Ray study of *syn*-3-chloromethyl-4-hydroxy-4-(*p*-nitrophenyl)butane-2-one (8a)

A colorless prismatic crystal of $C_{11}H_{12}ClNO_4$ having approximate dimensions of 0.20×0.20×0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphic monochromated Mo-Kα radiation and a 12 kW rotating anode generator.

Crystallographic data

$C_{11}H_{12}O_4NCl$, MW=257.67, orthorhombic, space group $P2_12_12_1$(#19), a=10.593 (2) Å, b=14.268 (3) Å, c=7.829 (3) Å, V=1183.3 (4) Å^3, Z=4, D_{calcd}=1.446 g/cm^3, μ(Mo-Kα)=3.25 cm^{-1}.

Data collection and processing

The data were collected at a temperature of 23±1°C using the $\omega-2\theta$ scan technique to a maximum 2θ value of 55.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.32° with a take-off angle of 6.0°. Scans of $(1.15+0.30\tan\theta)$° were made at a speed of 8.0°/min (in omega). The weak reflections ($F<10.0\sigma(F)$) were rescanned (maximum of five scans). A total of 1594 reflections was collected. The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

Structure solution and refinement

The structure was solved by direct methods[20] and expanded using Fourier techniques.[21] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 831 observed reflections and 154 variable parameters. Final R=0.037 and Rw=0.038. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.22 and −0.16 e$^-$/Å^3, respectively.

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