A New Entry to Enantioselective Synthesis of α-Methylene-β-hydroxy Ketones by the Chalcogeno-Baylis–Hillman Reaction

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Chiral hydroxy chalcogenides in the presence of $TiCl_4$ achieved the asymmetric version of the chalcogeno-Baylis–Hillman reaction. The reaction proceeded under atmospheric pressure for 1 h. 10-Methylthioisoborneol (9) achieved the best enantioselectivity. A methoxy derivative 10 of 10-methylthioisoborneol resulted in lower selectivity than that obtained by 10-methylthioisoborneol (9). A hydroxyl group is required to perform good asymmetric induction. The asymmetric chalcogeno-Baylis–Hillman reaction with a C_2 symmetric bidentate ligand–$TiCl_4$ complex was also examined. Diol ligands gave the adduct in low to good yields with low or no enantiomeric excess. The adduct was also obtained in low to high yields with low or no enantiomeric excess using bisoxazoline ligands.

Key words chalcogeno-Baylis–Hillman reaction; asymmetric induction; 10-methylthioisoborneol; C_2 symmetric ligand; titanium(IV) chloride

A carbon–carbon bond forming reaction with activated alkenes and aldehydes provides allylic alcohols bearing a new stereocenter which are regarded as useful building blocks in organic synthesis.[1—3] The coupling reaction catalyzed by a tertiary compound of the group 15 element is referred to as the Baylis–Hillman reaction. There are few reports on enantioselective versions due to difficulty of asymmetric induction in the Baylis–Hillman reaction.[1—3] Chiral tertiary amine catalysts have required very high pressure and given adducts with low to moderate enantiomeric excess (ee).[4,5] Leahy and co-workers reported excellent stereoselective Baylis–Hillman reaction using Oppolzer's sultam as a chiral auxiliary.[6] Recently Soai and co-workers have developed chiral bis-phosphine catalysts for the enantioselective Baylis–Hillman reaction; however, the reaction has needed long reaction time and has given unsatisfactory yields and ee.[7] More recently, highly enantioselective Baylis–Hillman reaction has been achieved with a chiral hydroxy pyrrolizidine catalyst in the presence of $NaBF_4$ or $NaBPh_4$.[8] Thus, investigation of asymmetric Baylis–Hillman reaction is still an attractive subject.

We recently developed the chalcogeno-Baylis–Hillman reaction catalyzed by chalcogenides in the presence of Lewis acids.[9,10] This reaction proceeds very smoothly under atmospheric pressure. We more recently reported the enantioselective chalcogeno-Baylis–Hillman reaction using a chiral hydroxy chalcogenide–$TiCl_4$ complex under atmospheric pressure.[11] The use of a Lewis acid has showed a new concept in the asymmetric variation of the Baylis–Hillman reaction. In this paper we describe the enantioselective synthesis of α-methylene-β-hydroxy ketones by the chalcogeno-Baylis–Hillman reaction with a chiral hydroxy chalcogenide–$TiCl_4$ or a C_2 symmetric bidentate ligand–$TiCl_4$ complex.

Results and Discussion

p-Nitrobenzaldehyde **1** and methyl vinyl ketone **2** were treated with 0.1 eq of various chiral hydroxy chalcogenides in the presence of 1 eq of $TiCl_4$ in CH_2Cl_2 at −20 °C for 1 h under atmospheric pressure (Chart 1). Most of the hydroxy chalcogenides **4**—**8** and an amino chalcogenide **12** gave adduct **3** in excellent yields (93—99%) without ee. Adduct **3** obtained by (1*S*)-10-methylthioisoborneol **9**[12] exhibited only 2% ee (Table 1, entry 1). Formation of a titanium alkoxide complex between $TiCl_4$ and a hydroxy chalcogenide might inhibit the occurrence of effective enantioselectivity. Therefore, we examined a reaction with a methoxy derivative **10**[13] which can form a weaker complex with $TiCl_4$ than that of the corresponding alcohol **9**. The adduct **3** was obtained in excellent yield; however, the ee was only 1% (entry 2). Next, we carried out reactions using 1 eq of hydroxy chalcogenides at −20 °C for 1 h under atmospheric pressure. In the cases of conformationally flexible substrates **4**—**7**, adduct **3** was obtained in moderate yields with low ee (entries 3—6). The reduced Lewis acidity of $TiCl_4$ by formation of a titanium alkoxide with a hydroxy chalcogenide would decrease the yields of **3**. The use of a conformationally rigid hydroxy sulfide, 10-benzylthioisobornenol **8**,[12] provided **3** in 41% yield with 15% ee (entry 7). 10-Methylthioisoborneol **9** provided **3** in 27% yield with 44% ee (entry 8). Methoxy derivative **10** gave **3** in moderate yield with slight ee (entry 9). Formation of a titanium alkoxide between a chiral hydroxy sulfide and $TiCl_4$ would be necessary for effective asymmetric induction. Another isoborneol derivative **11**[14] improved the yield of **3** up to 44% but with low ee (entry 10). Good enantioselectivity (72% ee) was achieved when a reaction using methylthioisoborneol **9** was carried out at −70 °C for 1 h (entry 13). Prolonged reaction time at −73 °C improved the yield to 17% without significant lowering of ee (entry 14). The yield of **3** was not improved by the use of 1.5 eq of **9** and $TiCl_4$ (entry 15). Adduct **3** was obtained in 26% yield with 71% ee from a reaction with 6 eq of enone **2** at −78 °C for 1 h (entry 16). Enantioselectivity decreased to only 14% ee when 2 eq of $TiCl_4$ was used (entry 17). Absolute configuration of the adduct **3** was determined according to the literature.[4]

We treated adduct **3** with 0.3 eq of $TiCl_4$ in CH_2Cl_2 at −20 °C for 44 h to confirm whether epimerization of **3** proceeds under reaction conditions (Chart 2). Adduct **3** was recovered in 69% yield without racemization, and an allyl chloride **13** was isolated in 21% yield as a sole by-product.

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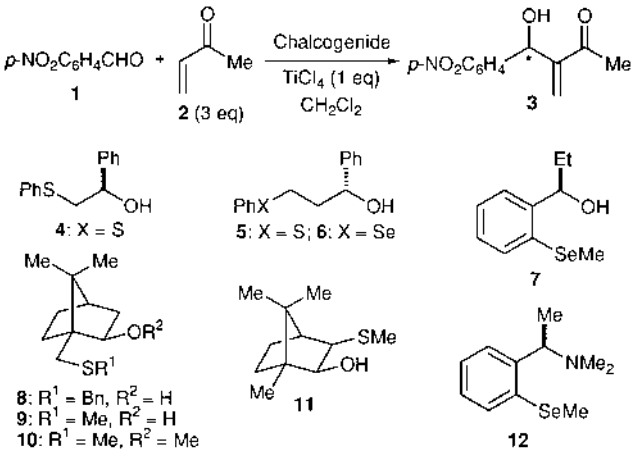


Chart 1`

Table 1. The Asymmetric Chalcogeno-Baylis–Hillman Reaction with Chiral Hydroxy Chalcogenides

Entry	Chalcogenide (eq)	Temp. (°C)	Time (h)	% Yield[a]	% ee[b] (config.)[c]
1	**9** (0.1)	−20	1	95	2 (*R*)
2	**10** (0.1)	−20	1	97	1 (*R*)
3	**4** (1.0)	−20	1	34	<1
4	**5** (1.0)	−20	1	49	3 (*S*)
5	**6** (1.0)	−20	1	44	3 (*S*)
6	**7** (1.0)	−20	1	26	1 (*S*)
7	**8** (1.0)	−20	1	41	15 (*R*)
8	**9** (1.0)	−20	1	27	44 (*R*)
9	**10** (1.0)	−20	1	48	4 (*R*)
10	**11** (1.0)	−20	1	44	8 (*S*)
11	**12** (1.0)	−20	1	37	—
12	**8** (1.0)	−74	45	22	31 (*R*)
13	**9** (1.0)	−70	1	10	72 (*R*)
14	**9** (1.0)	−73	24	17	69 (*R*)
15[d]	**9** (1.5)	−78	18	15	70 (*R*)
16[e]	**9** (1.0)	−78	1	26	71 (*R*)
17[f]	**9** (1.0)	−78	1	43	14 (*R*)

a) Isolated yield based on *p*-nitrobenzaldehyde (**1**). *b*) Calculated by HPLC analysis using DAICEL CHIRALCEL OD-RH (H_2O/CH_3CN=4/1, flow rate=0.45 ml/min). *c*) Absolute configuration was determined according to ref 4. *d*) 1.5 eq of $TiCl_4$ was used. *e*) 6 eq of enone **2** was used based on **1**. *f*) 2 eq of $TiCl_4$ was used.

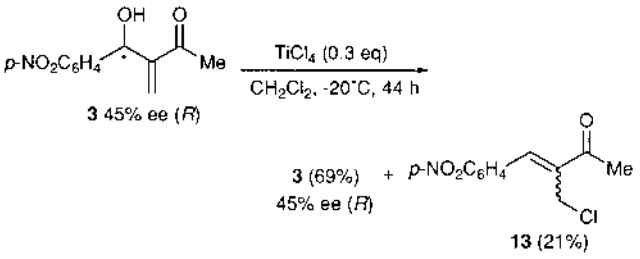


Chart 2

We examined reactions of some aldehydes and methyl vinyl ketone **2** with 1 eq of methylthioisoborneol **9** and $TiCl_4$ in CH_2Cl_2 at −78 °C for 1 h under atmospheric pressure (Chart 3, Table 2). The enantioselectivity was very sensitive to the substituents of aldehydes. 3-Phenylpropionaldehyde, an aliphatic aldehyde, gave adduct **18** in 43% yield with 74% ee (entry 5). Reactions of cyclohexen-2-one and cyclopenten-2-one gave no coupling product because of steric hindrance

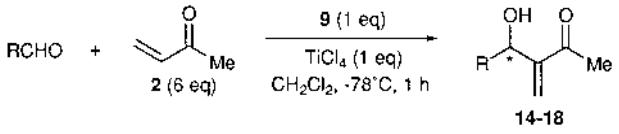


Chart 3

Table 2. Reactions of Various Aldehydes and Methyl Vinyl Ketone (**2**)

Entry	Aldehyde (RCHO)	Product (% yield)[a]	% ee
1	*p*-$CF_3C_6H_4CHO$	**14** (25)	8[b]
2	*p*-ClC_6H_4CHO	**15** (22)	40[b]
3	3-Pyridyl-CHO	**16** (31)	29[b]
4	4-Pyridyl-CHO	**17** (35)	14[b]
5	$PhCH_2CH_2CHO$	**18** (43)	74[c]

a) Isolated yield based on an aldehyde. *b*) Calculated by HPLC analysis using DAICEL CHIRALCEL OD-RH. *c*) Calculated by HPLC analysis using DAICEL CHIRALCEL OJ-R.

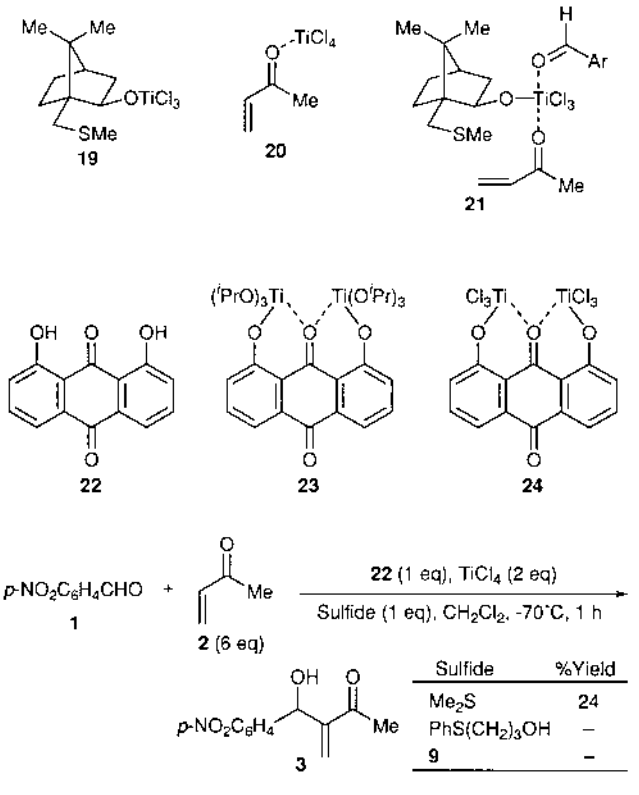


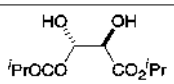
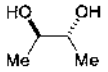
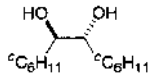
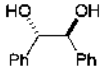
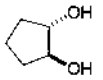
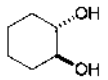
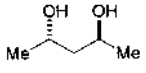
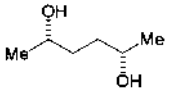
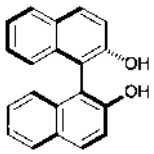
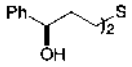
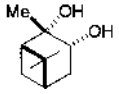
Chart 4

of β-substituents.

The use of 2 eq of $TiCl_4$ improved the yield of adduct **3**, but the enantioselectivity was dramatically decreased (compare entry 13 in Table 1 with entry 17). An alkoxy titanium **19** is formed from the corresponding chiral alcohol and 1 eq of $TiCl_4$, and extra $TiCl_4$ would activate methyl vinyl ketone (complex **20**). This separate complex formation would decrease the enantioselectivity. High enantioselectivity would be achieved through a four-component complex **21** among $TiCl_4$, 10-methylthioisoborneol, methyl vinyl ketone and an aldehyde.

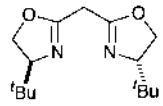
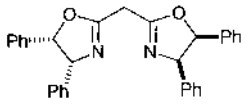
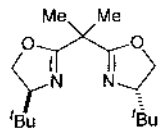
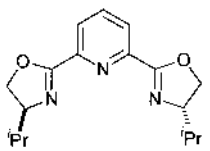
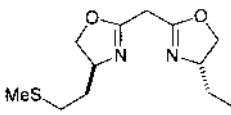
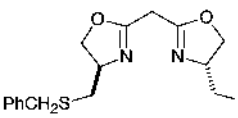
Recently, Maruoka and co-workers reported activation of carbonyl compounds with bidentate titanium Lewis acid **23** which can be easily prepared *in situ* from commercial-

Table 3. Examination of Diol Ligands[a)]

Entry	Diol		3 (% yield)[b)]	% ee[c)] (config.)[d)]
1[e)]		**25** 2*R*,3*R*	28	4 (*S*)
2		**26** 2*R*,3*R*	17	5 (*R*)
3		**27** 1*R*,2*R*	25	2 (*R*)
4		**28** 1*S*,2*S*	21	7 (*S*)
5		**29** 1*S*,2*S*	33	1 (*S*)
6		**30** 1*S*,2*S*	8	1 (*S*)
7		**31** 2*S*,4*S*	10	—
8		**32** 2*S*,5*S*	16	2 (*S*)
9		**33** *S*	69	4 (*S*)
10[f)]		**34** *R*,*R*	22	1 (*S*)
11		**35** 1*S*,2*S*,3*R*,5*S*	46	4 (*S*)

a) Conditions: *p*-nitrobenzaldehyde (**1**) (1 eq), methyl vinyl ketone (**2**) (3 eq), Me_2S (0.1 eq), diol (1 eq), $TiCl_4$ (1 eq), CH_2Cl_2, −20 °C, 1 h. *b*) Isolated yield based on *p*-nitrobenzaldehyde (**1**). *c*) Calculated by HPLC analysis using DAICEL CHIRALCEL OD-RH (H_2O/CH_3CN=4/1, flow rate=0.45 ml/min). *d*) Absolute configuration was determined according to ref 4. *e*) 1 eq of methyl vinyl ketone (**2**) was used based on *p*-nitrobenzaldehyde (**1**). *f*) The reaction was carried out with 1 eq of dihydroxy sulfide **34** and 2 eq of $TiCl_4$ without Me_2S at −70 °C.

Table 4. Examination of Bisoxazoline Ligands[a)]

Entry	Oxazoline		3 (% yield)[b)]	% ee[c)] (config.)[d)]
1		**36** 4*S*	29	1 (*S*)
2[e)]			—	—
3		**37** 4*R*, 5*S*	24	1 (*R*)
4[e)]			—	—
5		**38** 4*S*	90	6 (*R*)
6		**39** 4*S*	80	—
7[f)]		**40** 4*S*	18	—
8[f)]		**41** 4*S*	49	2 (*S*)

a) Conditions: *p*-nitrobenzaldehyde (**1**) (1 eq), methyl vinyl ketone (**2**) (3 eq), Me_2S (1 eq), oxazoline (1 eq), $TiCl_4$ (2 eq), CH_2Cl_2, −20 °C, 1 h. *b*) Isolated yield based on *p*-nitrobenzaldehyde (**1**). *c*) Calculated by HPLC analysis using DAICEL CHIRALCEL OD-RH (H_2O/CH_3CN=4/1, flow rate=−0.45 ml/min). *d*) Absolute configuration was determined according to ref 4. *e*) 1 eq of $TiCl_4$ was used based on *p*-nitrobenzaldehyde (**1**). *f*) The reaction was carried out without Me_2S.

ly available 1,8-dihydroxyanthraquinone **22** and $Ti(O^iPr)_4$.[15)] This prompted us to use bidentate titanium complex **24** for promotion of the chalcogeno-Baylis–Hillman reaction. First, we examined a reaction of *p*-nitrobenzaldehyde **1** and 6 eq of methyl vinyl ketone **2** in the presence of 1 eq of **22**, 2 eq of $TiCl_4$ and 1 eq of Me_2S (Chart 4) in CH_2Cl_2 at −7 °C for 1 h. Adduct **3** was given in 24% yield comparable to that of entry 16 in Table 1. Therefore, we next carried out a reaction with 3-phenylthiopropanol or **9** as a hydroxy sulfide,however, no adduct **3** was isolated from the reactions. Titanium complex **24** was ineffective for the chalcogeno-Baylis–Hillman reaction using a hydroxy sulfide.

C_2 Symmetric diols[16,17)] including diisopropyl tartarate[18,19)] and bisoxazolines[20—22)] are versatile ligands for enantioselective synthesis, because they construct effective asymmetric space with metals. We examined C_2 symmetric diol ligands for enantioselective reactions of *p*-nitrobenzaldehyde **1** and 3 eq of methyl vinyl ketone **2** in the presence of 1 eq of $TiCl_4$ and 0.1 eq of Me_2S in CH_2Cl_2 at −20 °C for 1 h (Table 3). Adduct **3** was obtained in low to good yields with no or low ee. The best enantioselectivity was obtained using hydrobenzoin **28**, however, in only 7% ee (entry 4). Binaphthol **33** gave adduct **3** in 69% yield but with 4% ee (entry 9). Dihydroxy sulfide **34** with 2 eq of $TiCl_4$ provided adduct **3** in 22% yield but with low ee (entry 10). Pinanediol **35** was also examined for an asymmetric reaction to give adduct **3** in 46% yield with 4% ee (entry 11).

Next, we examined C_2 symmetric bisoxazoline ligands in reactions of *p*-nitrobenzaldehyde **1** and 3 eq of methyl vinyl ketone **2** in the presence of 2 eq of $TiCl_4$ and 1 eq of Me_2S in CH_2Cl_2 at −20 °C for 1 h (Table 4). Bisoxazolines **36** and **37** provided adduct **3** in low yields with only slight ee (entries 1 and 3). The use of 1 eq of $TiCl_4$ gave no adduct **3** in reactions with bisoxazolines **36** and **37** (entries 2 and 4). Adduct **3** was obtained in high yield with 6% ee using bisoxazoline ligand **38** (entry 5). Bisoxazoline ligand **39** gave adduct **3** in good yield without ee (entry 6). Bifunctional oxazoline ligands **40**, **41**[23)] bearing sulfide groups in the molecules were examined for the asymmetric chalcogeno-Baylis–Hillman reaction. Oxazoline **40** provided adduct **3** in 18% yield without ee (entry 7). The use of another oxazoline **41** gave adduct **3** in 49%

yield with 2% ee (entry 8).

In conclusion, an asymmetric C–C bond formation between aldehydes and activated alkenes was achieved by the chalcogeno-Baylis–Hillman reaction using a chiral hydroxy chalcogenide-$TiCl_4$ to give adducts in low to good yields with low to moderate ee. The enantioselectivity was sensitive to substituents of aldehydes. This reaction serves as a novel method for enantioselective synthesis of α-methylene-β-hydroxy ketones. A complex of $TiCl_4$ and a C_2 symmetric bidentate ligand constructed the asymmetric space although the enantioselectivity was very low. This low selectivity is due to poor stereocommunication among the chiral space of the titanium complex, an enone and an aldehyde. Modeling and synthesis of efficient C_2 symmetric bidentate ligands are currently in progress.

Experimental

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 flash column chromatography or Kieselgel 60 PF_{254} containing gypsum (Merck) for preparative TLC. Chiral HPLC analyses were performed on a JASCO chromatography system (PU-986, UV-970) with monitoring of the 254 nm, and their data were recorded with a System Instruments integrator (Chromatocorder 21). Chiral chalcogenides **8**,[12] **9**,[12] **10**,[13] **11**[14] and bisoxazoline ligands **40**, **41**[23] were prepared according to the literature. Chiral ligands **25**—**39** are commercially available from Aldrich Chemical Co., Inc.

Synthesis of Hydroxy Sulfides 4—6. General Procedure To a stirred suspension of NaH (60% in paraffin oil, 440 mg, 11 mmol) in DMF (25 ml) was added thiophenol (660 mg, 6 mmol) in DMF (2 ml) followed by a commercial chiral hydroxy chloride (5 mmol) in DMF (2—5 ml) at 0 °C. The mixture was stirred overnight at room temperature, and cold water (25 ml) was added to it. The whole was extracted with toluene (25 ml×3), and the extracts were washed twice with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified with flash column chromatography eluting with EtOAc–hexane (1 : 10—1 : 5, v/v).

(*R*)-1-Phenyl-2-phenylthioethanol (**4**)[24]: 94% ee, chiral HPLC analysis: DAICEL CHIRALCEL OD, hexane/isopropanol=40/1, flow rate=0.6 ml/min, (*S*)-**4**: 48 min, (*R*)-**4**: 51 min.

(*R*)-1-Phenyl-3-phenylthiopropanol (**5**): 100% ee, chiral HPLC analysis: DAICEL CHIRALCEL OD, hexane/isopropanol=40/1, flow rate=0.6 ml/min, (*R*)-**5**: 66 min, (*S*)-**5**: 70 min. White powder (hexane), mp 58—60 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.94—2.02 (1H, m, 2-H), 2.06—2.15 (2H, m, 2-H, OH), 2.99 (2H, t, J=7 Hz, 3-H), 4.86 (1H, m, 1-H), 7.16 (1H, t, J=8 Hz, ArH), 7.24—7.35 (9H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 30.0 (t), 38.1 (t), 73.1 (d), 125.8 (d), 126.0 (d), 127.7 (d), 128.6 (d), 128.9 (d), 129.2 (d), 136.2 (s), 144.0 (s). MS *m/z* (rel. int. %): 244 (M^+, 53), 133 (100). IR (KBr) cm^{-1}: 3275 (OH). *Anal.* Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60. Found: C, 73.63; H, 6.63.

(*R*)-1-Phenyl-3-phenylselenopropanol (**6**): PhSeNa (6 mmol, prepared from $(PhSe)_2$ and $NaBH_4$ in 5 ml of EtOH) in DMF (15 ml) was used instead of PhSNa in DMF. 100% ee, chiral HPLC analysis: DAICEL CHIRALCEL OD, hexane/isopropanol=40/1, flow rate=0.6 ml/min, (*R*)-**6**: 61 min, (*S*)-**6**: 67 min. White powder (hexane), mp 54 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.99 (1H, br s, OH), 1.99—2.09, 2.13—2.22 (each 1H, m, 2-H), 2.97 (2H, t, J=7 Hz, 3-H), 4.83 (1H, m, 1-H), 7.22—7.35 (8H, m, ArH), 7.46—7.48 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 23.8 (t), 39.0 (t), 73.8 (d), 125.8 (d), 126.8 (d), 127.7 (d), 128.5 (d), 129.1 (d), 130.0 (s), 132.5 (d), 144.0 (s). MS *m/z* (rel. int. %): 292 (M^+, 65), 134 (100). IR (KBr) cm^{-1}: 3250 (OH). *Anal.* Calcd for $C_{15}H_{16}OSe$: C, 61.86; H, 5.54. Found: C, 61.84; H, 5.52.

Synthesis of Selenides 7 and 12. General Procedure To a stirred solution of (*R*,*R*)-bis[*o*-(1-hydroxypropyl)phenyl]diselenide[25] (680 mg, 1.6 mmol) in EtOH (10 ml) was added $NaBH_4$ (90 mg, 2.4 mmol) in portions followed by MeI (0.2 ml, 3.4 mmol) at 0 °C. After 30 min, the reaction mixture was evaporated under reduced pressure. Water was added to the residue, and the whole was extracted with EtOAc. The extracts were washed twice with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified with flash column chromatography eluting with ether–hexane (1 : 10, v/v) to give selenide **7** (575 mg, 79%).

(*R*)-*o*-(1-Hydroxypropyl)phenyl methyl selenide (**7**): Chiral HPLC analysis: DAICEL CHIRALCEL OD-RH, H_2O/CH_3CN=3/1, flow rate=0.4 ml/min, (*R*)-**7**: 25 min. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz, Me), 1.71—1.80 (2H, m, CH_2), 2.30 (3H, s, SeMe), 2.38 (1H, br s, OH), 4.95 (1H, br t, J=6 Hz, 1-H), 7.17, 7.19 (each 1H, dt, J=2, 8 Hz, ArH), 7.36, 7.42 (each 1H, dd, J=2, 8 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 7.6 (q), 10.2 (q), 30.9 (t), 74.1 (d), 125.9 (d), 126.4 (d), 127.9 (d), 130.2 (d), 130.5 (s), 144.7 (s). MS *m/z* (rel. int. %): 230 (M^+, 69), 201 (100). IR (NaCl) cm^{-1}: 3375 (OH). *Anal.* Calcd for $C_{10}H_{14}OSe$: C, 52.41; H, 6.16. Found: C, 52.13; H, 6.16.

(*R*)-*o*-[1-(Dimethylamino)ethyl]phenyl methyl selenide (**12**): Prepared from (*R*,*R*)-bis[*o*-[1-(dimethylamino)ethyl]phenyl] diselenide.[26] 100% ee, chiral HPLC analysis: DAICEL CHIRALCEL OD, hexane, flow rate=0.25 ml/min, (*S*)-**12**: 58 min, (*R*)-**12**: 64 min. 82%, light yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=7 Hz, Me), 2.19 (6H, s, NMe_2), 2.23 (3H, s, SeMe), 3.65 (1H, q, J=7 Hz, CH), 7.15—7.18 (2H, m, ArH), 7.32—7.35 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 6.9 (q), 15.9 (q), 41.9 (q), 63.2 (d), 125.5 (d), 126.6 (d), 127.2 (d), 128.8 (d), 133.5 (s), 144.5 (s). MS *m/z* (rel. int. %): 243 (M^+, 23), 228 (100). IR (NaCl) cm^{-1}: 3000, 2845, 2795, 1465, 960, 745. *Anal.* Calcd for $C_{11}H_{17}NOSe$: C, 54.55; H, 7.07; N, 5.78. Found: C, 54.76; H, 7.20; N, 5.58.

Synthesis of Dihydroxy Sulfide 34 To a stirred solution of $Na_2S\cdot 9H_2O$ (600 mg, 2.5 mmol) in DMF–H_2O (20 ml—4 ml) was added a commercial chiral chloride (5 mmol) in DMF (2 ml) at room temperature under argon. After stirring 1—3 d, water (30 ml) was added to the reaction mixture, and the whole was extracted with toluene (20 ml×3). The extracts were washed twice with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified with flash column chromatography eluting with EtOAc–hexane (1 : 5, v/v).

(*R*,*R*)-Bis(3-hydroxy-3-phenylpropyl) sulfide: Chiral HPLC analysis: DAICEL CHIRALCEL OD, hexane/isopropanol=25/1, flow rate=0.6 ml/min, (*R*,*R*)-isomer: 22 min. 51%, white powder (hexane), mp 56—58 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.91—1.98, 2.00—2.09 (each 2H, m, 2-H), 2.30 (2H, br s, OH), 2.61 (4H, t, J=7.3 Hz, 1-H), 4.80—4.83 (2H, m, 3-H), 7.25—7.36 (10H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 28.4 (t), 38.3 (t), 73.3 (d), 125.8 (d), 127.7 (d), 128.5 (d), 144.1 (s). MS *m/z* (rel. int. %): 286 (M^+, 2), 133 (100). IR (KBr) cm^{-1}: 3200 (OH). *Anal.* Calcd for $C_{18}H_{22}O_2S$: C, 71.49; H, 7.33. Found: C, 71.20; H, 7.41.

The Chalcogeno-Baylis–Hillman Reaction with Chiral Hydroxy Chalcogenides. General Procedure To a stirred solution of a hydroxy chalcogenide (0.5 mmol) in dry CH_2Cl_2 (4 ml) at −20 °C was added dropwise $TiCl_4$ (55 μl, 0.5 mmol), and the solution was stirred for 5 min. *p*-Nitrobenzaldehyde (**1**) (75 mg, 0.5 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise for a few minutes, and after stirring for several min, methyl vinyl ketone (**2**) (125 μl, 1.5 mmol) was added dropwise to the mixture at −20 °C. The mixture was stirred at the same temperature for 1 h, and the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC eluting with EtOAc–hexane (1 : 2, v/v). Reaction conditions and yields are summarized in Tables 1 and 2.

3-[1-Hydroxy-1-(4-nitrophenyl)methyl]-3-buten-2-one (**3**):[10] Chiral HPLC analysis: DAICEL CHIRALCEL OD-RH, H_2O/CH_3CN=4/1, flow rate=0.45 ml/min, (*R*)-**3**: 43 min, (*S*)-**3**: 49 min. Absolute configuration was determined according to the literature.[4]

3-[1-Hydroxy-1-(4-trifluoromethylphenyl)methyl]-3-buten-2-one (**14**): Chiral HPLC analysis: DAICEL CHIRALCEL OD-RH, H_2O/CH_3CN=4/1, flow rate=0.45 ml/min, the first fraction: 63 min, the second fraction: 68 min. Light yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s, 1-H), 3.34 (1H, br s, OH), 5.64 (1H, br s, benzylic H), 6.00, 6.23 (each 1H, s, 4-H), 7.48, 7.58 (each 2H, d, J=7.8 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 26.4 (q), 72.4 (t), 123.1 (s, $^1J_{CF}$=272 Hz), 125.4 (s, $^3J_{CF}$=4 Hz), 126.8 (d), 127.3 (t), 129.9 (s, $^2J_{CF}$=33 Hz), 145.6 (s), 149.5 (s), 200.2 (s). MS *m/z* (rel. int. %): 244 (M^+, 13), 175 (100). IR (NaCl) cm^{-1}: 3400 (OH), 1660 (C=O), 1110 (CF_3). *Anal.* Calcd for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 58.85; H, 4.69.

3-[1-(4-Chlorophenyl)methyl-1-hydroxy]-3-buten-2-one (**15**)[27]: Chiral HPLC analysis: DAICEL CHIRALCEL OD-RH, H_2O/CH_3CN=4/1, flow rate=0.45 ml/min, the first fraction: 68 min, the second fraction: 73 min.

3-[1-Hydroxy-1-(3-pyridyl)methyl]-3-buten-2-one (**16**): Chiral HPLC

analysis: DAICEL CHIRALCEL OD-RH, $H_2O/CH_3CN=20/1$, flow rate= 0.45 ml/min, the first fraction: 34 min, the second fraction: 39 min. Colorless solid (CH_2Cl_2–hexane), mp 74.5—76 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, 1-H), 3.64 (1H, br s, OH), 5.65 (1H, s, benzylic H), 6.08, 6.25 (each 1H, s, 4-H), 7.27 (1H, dd, J=4.5, 8 Hz, ArH), 7.72 (1H, d, J=8 Hz, ArH), 8.48 (1H, dd, J=1.5, 4.5 Hz, ArH), 8.54 (1H, d, J=1.5 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 26.3 (q), 70.7 (d), 123.3 (d), 127.0 (t), 134.3 (d), 137.3 (s), 148.3 (d), 148.8 (d), 149.4 (s), 199.9 (s). FAB-MS *m/z* (rel. int. %): 178 (M^+, 51), 154 (100). IR (KBr) cm^{-1}: 3380 (OH), 1700 (C=O). FAB-HRMS Calcd for $C_{10}H_{11}NO_2$+H: 178.0868. Found: 178.0871. *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.28; H, 6.29; N, 7.81.

3-[1-Hydroxy-1-(4-pyridyl)methyl]-3-buten-2-one (**17**): Chiral HPLC analysis: DAICEL CHIRALCEL OD-RH, $H_2O/CH_3CN=20/1$, flow rate= 0.2 ml/min, the first fraction: 102 min, the second fraction: 111 min. Yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s, 1-H), 3.49 (1H, br s, OH), 5.57 (1H, s, benzylic H), 6.02, 6.25 (each 1H, s, 4-H), 7.30, 8.55 (each 2H, d, J=5.9 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 26.3 (q), 71.5 (d), 121.4 (d), 127.5 (t), 149.1 (s), 149.6 (d), 151.2 (s), 199.9 (s). FAB-MS *m/z* (rel. int. %): 178 (M^++1, 100). IR (NaCl) cm^{-1}: 3250 (OH), 1715 (C=O). FAB-HRMS Calcd for $C_{10}H_{11}NO_2$+H: 178.0868. Found: 178.0871.

3-[1-Hydroxy-3-phenylpropyl]-3-buten-2-one (**18**)[27]: Chiral HPLC analysis: DAICEL CHIRALCEL OJ-R, $H_2O/CH_3CN=7/1$, flow rate=0.9 ml/min, the first fraction: 130 min, the second fraction: 139 min.

Reaction of Adduct 3 with $TiCl_4$ To a stirred solution of adduct **3** (13 mg, 0.059 mmol, 45% ee) in CH_2Cl_2 (2 ml) at −20 °C was added $TiCl_4$ (2 ml, 0.018 mmol), and the solution was stirred for 44 h at the same temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC eluting with EtOAc–hexane (1 : 2, v/v) to give recovered **3** [9 mg (69%, 45% ee)] and chloride **13** [3 mg (21%)].

3-Chloromethyl-4-(4-nitrophenyl)-4-buten-2-one (**13**): Light yellow prisms (EtOAc–hexane), mp 127—128.5 °C. ^{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, 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). MS *m/z* (rel. int. %): 239 (M^+, 13), 222 (100). IR (KBr) cm^{-1}: 1665 (C=O), 1335 and 1500 (NO_2). *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.

Reactions with 1,8-Dihydroxyanthraquinone–Titanium Complex. General Procedure To a stirred solution of dihydroxyanthraquinone **22** (120 mg, 0.5 mmol) in dry CH_2Cl_2 (18 ml) was added dropwise $TiCl_4$ (110 μl, 1 mmol) at room temperature, and the solution was stirred for 1 h. The solution was cooled to −70 °C, and *p*-nitrobenzaldehyde (**1**) (75 mg, 0.5 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise for a few minutes, and after stirring for several minutes, methyl vinyl ketone (**2**) (250 μl, 3 mmol) was added dropwise to the mixture. Me_2S (37 μl, 0.5 mmol) was added, and the mixture was stirred at −70 °C for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC eluting with EtOAc–hexane (1 : 2, v/v). Yields are summarized in Chart 4.

Reactions with Dihydroxy Sulfide To a stirred solution of dihydroxy sulfide **34** (72 mg, 0.25 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise $TiCl_4$ (55 μl, 0.5 mmol) at −20 °C. *p*-Nitrobenzaldehyde (**1**) (75 mg, 0.5 mmol) in dry CH_2Cl_2 (1 ml) was added dropwise for a few minutes, and after stirring for several minutes, methyl vinyl ketone (**2**) (63 μl, 0.75 mmol) was added dropwise to the mixture. After 1 h at −20 °C, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC eluting with EtOAc–hexane (1 : 2, v/v).

The Asymmetric Chalcogeno-Baylis–Hillman Reaction with Diol Ligands. General Procedure To a stirred solution of $TiCl_4$ (55 μl, 0.5 mmol) in dry CH_2Cl_2 (2 ml) at −20 °C was added dropwise a diol (0.5 mmol) in dry CH_2Cl_2 (2 ml), and the solution was stirred for 5 min. *p*-Nitrobenzaldehyde (**1**) (75 mg, 0.5 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise for a few minutes, and after stirring for several minutes, methyl vinyl ketone (**2**) (126 μl, 1.5 mmol) was added dropwise at −20 °C. Me_2S (4 μl, 0.05 mmol) was added to the mixture, and the whole was stirred at −20 °C for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with ethyl acetate–hexane (1 : 2, v/v) to give adduct **3**. Yields are summarized in Table 3.

The Asymmetric Chalcogeno-Baylis–Hillman Reaction with Bisoxazoline Ligands 36—39. General Procedure To a stirred solution of $TiCl_4$ (110 μl, 1 mmol) in dry CH_2Cl_2 (2 ml) at −20 °C was added dropwise a bisoxazoline (0.5 mmol) in dry CH_2Cl_2 (2 ml), and the solution was stirred for 5 min. *p*-Nitrobenzaldehyde (**1**) (75 mg, 0.5 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise for a few minutes, and after stirring for several minutes, methyl vinyl ketone (**2**) (126 μl, 1.5 mmol) was added dropwise at −20 °C. Me_2S (37 μl, 0.5 mmol) was added to the mixture, and the whole was stirred at −20 °C for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with ethyl acetate–hexane (1 : 2, v/v) to give adduct **3**. Yields are summarized in Table 4.

The Asymmetric Chalcogeno-Baylis–Hillman Reaction with Bifunctional Oxazoline Ligands 40 and 41. General Procedure To a stirred solution of an oxazoline (0.5 mmol) in dry CH_2Cl_2 (2 ml) at −20 °C was added dropwise $TiCl_4$ (55 μl, 0.5 mmol), and the solution was stirred for 5 min. *p*-Nitrobenzaldehyde (**1**) (38 mg, 0.25 mmol) in dry CH_2Cl_2 (1 ml) was added dropwise for a few minutes, and after stirring for several minutes, methyl vinyl ketone (2) (63 μl, 0.75 mmol) was added dropwise at −20 °C. After stirring at the same temperature for 1 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 ml). The inorganic precipitates were removed by filtration through CeliteTM, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with ethyl acetate–hexane (1 : 2, v/v) to give adduct 3. Yields are summarized in Table 4.

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