The Enantioselective Chalcogeno-Baylis-Hillman Reaction Using a Chiral Hydroxy Chalcogenide-$TiCl_4$ Complex

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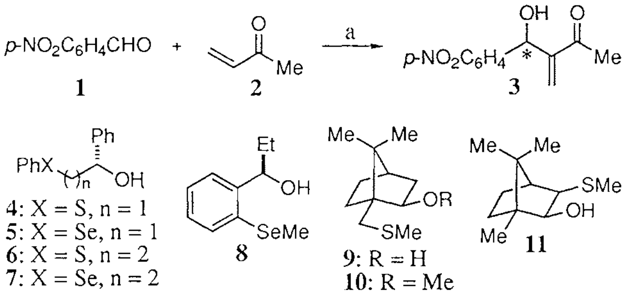
The enantioselective chalcogeno-Baylis-Hillman reaction was investigated by the use of chiral hydroxy chalcogenides in the presence of $TiCl_4$ under atmospheric pressure. The best result was obtained with 10-methylthioisobornenol as a chiral hydroxy chalcogenide.

The Baylis-Hillman reaction is well-known as a coupling reaction of activated alkenes with aldehydes catalyzed by a tertiary compound of the group 15 element, and serves as useful building blocks bearing a stereocenter in organic synthesis.[1] Therefore, the investigation of an asymmetric variation of the Baylis-Hillman reaction is a challenging problem. However, there are few reports on asymmetric Baylis-Hillman reaction.[1] The enantioselective Baylis-Hillman reaction catalyzed by chiral tertiary amines has required very high pressure and given adducts with low to moderate enantiomeric excess (ee).[2,3] Recently, Leahy and co-workers reported an excellent diastereoselective Baylis-Hillman reaction using Oppolzer's sultam as a chiral auxiliary.[4] More recently, Soai and co-workers have developed an enantioselective Baylis-Hillman reaction catalyzed by chiral bis-phosphines, which, however, has required long reaction time and has given moderate yields and ee.[5] A highly enantioselective Baylis-Hillman reaction has been achieved with a chiral hydroxy pyrrolizidine catalyst in the presence of $NaBF_4$ or $NaBPh_4$.[6] Thus, investigation of an asymmetric Baylis-Hillman reaction is still an interesting subject.

We have recently reported the first Baylis-Hillman reaction catalyzed by sulfides or selenides, the group 16 element compounds, in the presence of Lewis acids and referred to as the chalcogeno-Baylis-Hillman reaction.[7] The chalcogeno-Baylis-Hillman reaction proceeds very smoothly under atmospheric pressure, and the use of Lewis acids would present a new concept in the asymmetric Baylis-Hillman reaction. A hydroxy chalcogenide would form a four-component complex with an enone, an aldehyde and $TiCl_4$ which would enable asymmetric induction in the chalcogeno-Baylis-Hillman reaction. In this communication we describe the first enantioselective chalcogeno-Baylis-Hillman reaction using a chiral hydroxy chalcogenide-$TiCl_4$ complex under atmospheric pressure.



a) aldehyde **1** (1 equiv.), enone **2** (3 equiv.), chalcogenide, $TiCl_4$ (1 equiv.), CH_2Cl_2

Scheme 1.

Table 1. The asymmetric chalcogeno-Baylis-Hillman reaction

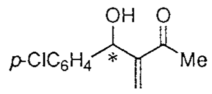
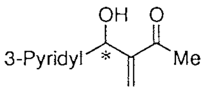
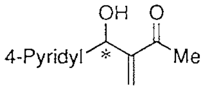
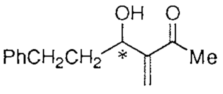
Entry	Chalcogenide (equiv.)	Temp. (°C)	Time (h)	Yield/%^{a}	Ee/%^{b} (Config.)^c
1	**9** (0.1)	-20	1	95	2 (*R*)
2	**10** (0.1)	-20	1	97	1 (*R*)
3	**4** (1.0)	-20	1	34	< 1
4	**6** (1.0)	-20	1	49	3 (*S*)
5	**7** (1.0)	-20	1	44	3 (*S*)
6	**8** (1.0)	-20	1	26	1 (*S*)
7	**9** (1.0)	-20	1	27	44 (*R*)
8	**11** (1.0)	-20	1	44	8 (*S*)
9	**9** (1.0)	-70	1	10	72 (*R*)
10	**9** (1.0)	-73	24	17	69 (*R*)
11^d	**9** (1.0)	-78	1	26	71 (*R*)

^{a}Isolated yield based on p-nitrobenzaldehyde. ^{b}Calculated by HPLC analysis using DAICEL CHIRALCEL OD-RH (H_2O/CH_3CN = 80/20, flow rate = 0.45 cm^3/min). ^{c}Absolute configuration was determined according to ref 2. ^{d}6 equiv. of enone **2** was used based on **1**.

The enantioselective chalcogeno-Baylis-Hillman reaction between p-nitrobenzaldehyde **1** and methyl vinyl ketone **2** was examined by a catalytic amount of various chiral hydroxy chalcogenides in the presence of 1 equiv. of $TiCl_4$ in CH_2Cl_2 at -20 °C for 1 h under atmospheric pressure (Scheme 1).[8] Most of the reactions with hydroxy chalcogenides **4**-**7**[9] and **8**,[10] gave adduct **3** in excellent yields (93–99%), albeit, without enantiomeric excess. The use of (1*S*)-10-methylthioisobornenol **9**[11] gave the best result but in only 2% ee[2] (entry 1 in Table 1). Formation of a titanium alkoxide complex between $TiCl_4$ and a hydroxy chalcogenide would inhibit the catalytic cycle of the alcohol. Therefore, we examined the reaction with methoxy derivative **10** 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% with the use of the catalyst **10** (entry 2). Next, we carried out reactions using 1 equiv of hydroxy chalcogenides at -20 °C for 1 h under atmospheric pressure. In the cases of conformationally flexible substrates **4** and **6**-**8**, 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 adduct **3**. The use of a conformationally rigid hydroxy sulfide, 10-methylthioisobornenol **9**, provided adduct **3** in 44% ee (entry 7). The enantioselectivity is comparable to those of the reported results using chiral tertiary amines under high pressure[2,3] and chiral bis-phosphine under atmospheric pressure.[4] Another isoborneol derivative **11**[12] improved the yield of adduct **3** up to 44% but with lower ee (entry 8). Good enantioselectivity (72% ee) was achieved when a reaction using methylthioisobornenol **9** was carried out at -70 °C for 1 h (entry 9). Prolonged reaction time at -73 °C improved the yield to 17% without significant lowering of ee (entry 10). The use of 6 equiv. of enone **2** at -78 °C for even 1 h gave adduct **3** in 26% yield with 71% ee (entry 11).

Reactions of various aldehydes and methyl vinyl ketone **2** were examined with 1 equiv. of methylthioisobornenol **9** and $TiCl_4$ in CH_2Cl_2 at -78 °C for 1 h under atmospheric pressure (Table 2). The enantioselectivity was very sensitive to the substituents of the aldehydes. 3-Phenylpropionaldehyde, an aliphatic aldehyde, gave adduct **15** in moderate yield with good ee (entry 5).

Table 2. Reactions of aldehydes and methyl vinyl ketone[a]

Entry	Product	Yield/%[b]	Ee/%
1	 **12**	22	40[c]
2	 **13**	31	29[c]
3	 **14**	35	14[c]
4	 **15**	43	74[d]

[a]Reactions were carried out with the use of aldehyde (1 equiv.), methyl vinyl ketone (6 equiv.), $TiCl_4$ (1 equiv.) and chalcogenide 9 (1 equiv.) in CH_2Cl_2 at -78 °C for 1 h under atmospheric pressure. [b]Isolated yield based on aldehyde. [c]Calculated by HPLC analysis using DAICEL CHIRALCEL OD-RH. [d]Calculated by HPLC analysis using DAICEL CHIRALCEL OJ-R.

In conclusion, the chalcogeno-Baylis-Hillman reaction using chiral hydroxy chalcogenides-$TiCl_4$ would offer a novel methodology for the asymmetric C-C bond formation between aldehydes and activated alkenes.

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8 Typical procedure for the asymmetric chalcogeno-Baylis-Hillman reaction: To a stirred solution of a hydroxy chalcogenide (0.5 mmol) in dry CH_2Cl_2 (4 cm^3) at -20 °C was added dropwise $TiCl_4$ (55 μdm^3, 0.5 mmol), and the solution was stirred for 5 min. *p*-Nitrobenzaldehyde (75 mg, 0.5 mmol) in dry CH_2Cl_2 (2 cm^3) was added dropwise for a few min, and after stirring for several min, methyl vinyl ketone (126 μdm^3, 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 cm^3). The inorganic precipitates were removed by filtration through Celite^{TM}, 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**.

9 Hydroxy chalcogenides **4-7** were prepared from the corresponding commercially available chiral chloro alcohols and PhSNa (prepared from PhSH and NaH) or PhSeNa (prepared from $(PhSe)_2$ and $NaBH_4$ in EtOH) in DMF.

10 Hydroxy selenide **8** was prepared from sodium *o*-(1-hydroxypropyl)phenyl selenide (prepared from (*R*,*R*)-bis[*o*-(1-hydroxypropyl)phenyl] diselenide[13] and $NaBH_4$ in EtOH) and MeI in DMF.

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