The chalcogeno-Baylis–Hillman reaction: the first examples catalysed by chalcogenides in the presence of Lewis acids

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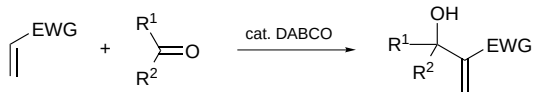
The chalcogeno-Baylis–Hillman reaction catalysed by sulfides and selenides, the group 16 element compounds, in the presence of Lewis acids gave coupling products in moderate to good yield even after only 1 h at room temperature.

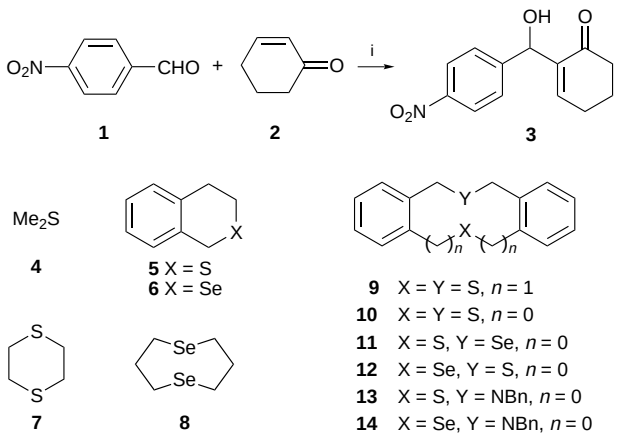
The coupling of activated alkenes with aldehydes or ketones is referred to as the Baylis–Hillman reaction (Scheme 1).[1] The reaction requires a compound containing a tertiary group 15 element as a catalyst. Generally tertiary amines are utilised as catalysts, and 1,4-diazabicyclo[2.2.2]octane (DABCO) is the most popular. There are some known examples which utilise tertiary phosphine catalysts.[2] Although the Baylis–Hillman reaction provides useful building blocks for organic synthesis,[1] it has a number of disadvantages. The main drawback is the slow reaction rate, and much attention has been paid to accelerating such reactions.[2c,3–8] Recently, Aggarwal *et al.* reported that lanthanides and group 3 metal triflates accelerate the Baylis–Hillman reaction, and that standard Lewis acids such as $TiCl_4$ and $BF_3{\cdot}Et_2O$ decelerate the reaction due to formation of an amine–Lewis acid complex.[6] Imagawa *et al.* described the Baylis–Hillman reaction promoted by a phosphine catalyst and Et_2AlCl due to activation of the aldehyde by coordination with the Lewis acid.[9] Therefore, we aimed to develop new catalysts other than those containing group 15 elements. We report here a preliminary study on the first chalcogeno-Baylis–Hillman reaction catalysed by sulfides and selenides, compounds containing group 16 elements, in the presence of Lewis acids.



Scheme 1

We examined the reaction of *p*-nitrobenzaldehyde **1** and 3 equiv. of cyclohex-2-en-1-one **2** in the presence of chalcogenides **4**, **5**,[10] **6**,[11] **7**, **8**,[12] **9**,[13] **10**,[14] **11**,† **12**,[15] **13**[14] and **14**‡ in CH_2Cl_2 at room temperature for 1 h (Scheme 2, Table 1).§ First, **4** was used in order to confirm the possibility of sulfide catalysts for the Baylis–Hillman reaction. A mixture of compounds **1** and **2** was treated with 1 equiv. of the sulfide **4** at room temperature for 4 days, and no coupling product **3** was obtained (entry 1). For the purpose of enhancing the reactivity of the enone towards the Michael addition of the sulfide, 0.1 equiv. of $TiCl_4$ was used and the Baylis–Hillman product **3** was produced in 17% yield (entry 2). Therefore, we examined the reaction with a catalytic amount of **4** (0.1 equiv.) in the presence of 1 equiv. of $TiCl_4$ and obtained the adduct **3** in 60% yield (entry 3). The reaction time was reduced to 10 min in refluxing CH_2Cl_2 (entry 4). It is significant that the reaction rate was dramatically accelerated in comparison to reactions utilising amine catalysts. Generally, it takes a few days or more to complete reactions catalysed by tertiary amines.[1] In addition it is also noteworthy that 1 equiv. of $TiCl_4$ is necessary for smooth reaction even though deceleration of the reaction has been observed when using an amine catalyst and $TiCl_4$ because of the formation of a deactivated amine–Lewis acid complex.[6]

A plausible mechanism is shown in Scheme 3. Activation of enone **2** by coordination with $TiCl_4$ allows addition of methyl sulfide **4** to complex **I** to generate an enolate intermediate **II**. The aldol reaction of the enolate **II** and aldehyde **1** gives an adduct **III**, which provides a Baylis–Hillman product–$TiCl_4$ complex **3′** *via* β-elimination and regeneration of methyl sulfide **4**. Formation of the complex **3′** requires a stoichiometric amount of $TiCl_4$ for a smooth reaction. Next, we examined several Lewis acids under standard conditions. The use of $BF_3{\cdot}Et_2O$ and $SnCl_4$ gave no coupling product (entries 5 and 6). The yields of the adduct **3** increased with increasing Lewis acidity in the cases

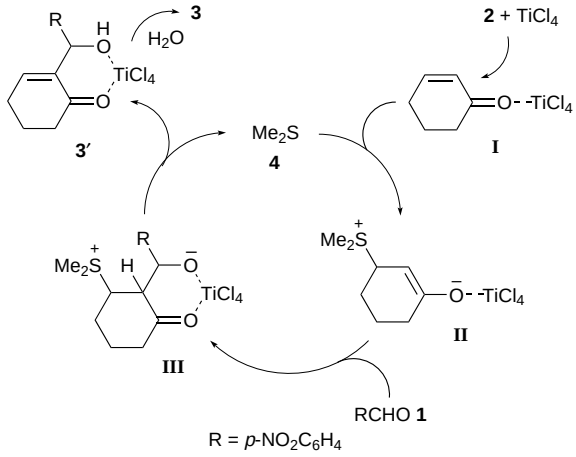


Scheme 2 *Reagents and conditions*: i, **1** (1 equiv.), **2** (3 equiv.), chalcogenide, Lewis acid, CH_2Cl_2, room temp., 1 h

Table 1 Chalcogeno-Baylis–Hillman reaction in the presence of Lewis acids[a]

Entry	Chalcogenide (equiv.)	Lewis acid (equiv.)	**3** (% yield)[b]
1[c]	**4** (1)	—	—
2	**4** (1)	$TiCl_4$ (0.1)	17
3	**4** (0.1)	$TiCl_4$ (1)	60
4[d]	**4** (0.1)	$TiCl_4$ (1)	58
5	**4** (0.1)	$BF_3{\cdot}Et_2O$ (1)	—
6	**4** (0.1)	$SnCl_4$ (1)	—
7	**4** (0.1)	$AlCl_3$ (1)	30
8	**4** (0.1)	$EtAlCl_2$ (1)	13
9	**4** (0.1)	Et_2AlCl (1)	11
10	**5** (0.1)	$TiCl_4$ (1)	71
11	**6** (0.1)	$TiCl_4$ (1)	70
12	**7** (0.1)	$TiCl_4$ (1)	69
13	**8** (0.1)	$TiCl_4$ (1)	85
14	**9** (0.1)	$TiCl_4$ (1)	71
15	**10** (0.1)	$TiCl_4$ (1)	74
16	**11** (0.1)	$TiCl_4$ (1)	78
17	**12** (0.1)	$TiCl_4$ (1)	71
18	**13** (0.1)	$TiCl_4$ (1)	76
19	**14** (0.1)	$TiCl_4$ (1)	69

[a] 3 equiv. of enone **2** was used against aldehyde **1**. Reactions were carried out in CH_2Cl_2 at room temperature for 1 h. [b] Isolated yield based on aldehyde **1**. [c] The reaction was carried out at room temperature for 4 d. [d] The reaction was carried out in refluxing CH_2Cl_2 for 10 min.



Scheme 3

Table 2 Reactions of some enones and aldehydes catalysed by Me_2S–$TiCl_4$[a]

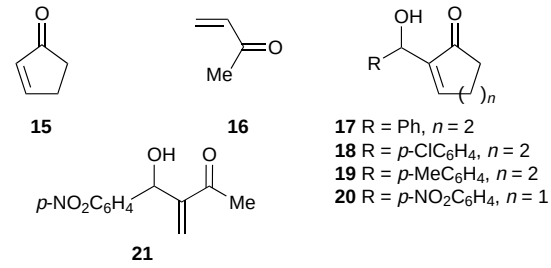
Entry	Aldehyde	Enone	Product (% yield)[b]
1	PhCHO	**2**	**17** (25)
2	*p*-ClC_6H_4CHO	**2**	**18** (43)
3	*p*-MeC_6H_4CHO	**2**	**19** (13)
4	*p*-$NO_2C_6H_4CHO$	**15**	**20** (68)
5	*p*-$NO_2C_6H_4CHO$	**16**	**21** (63)

[a] Conditions: 1 equiv. of aldehyde, 3 equiv. of enone, 0.1 equiv. of Me_2S, 1 equiv. of $TiCl_4$, CH_2Cl_2, room temp., 1 h. [b] Isolated yield based on the aldehyde.

of aluminium Lewis acids (entries 7–9). The best result was obtained when using $TiCl_4$. Chalcogenide catalysts **5**–**14** were examined in the presence of 1 equiv. of $TiCl_4$. Cyclic monochalcogenides **5** and **6** catalysed the chalcogeno-Baylis–Hillman reaction to provide the adduct **3** in 71 and 70% yield, respectively. We considered that the electron-releasing ability of the chalcogenide might promote the Michael addition step, and selected bis-chalcogenides **7**–**12** and related chalcogenides **13** and **14** are expected to donate electrons to a cationic species by transannular interaction of a chalcogen and a heteroatom.[16] Some (**8**, **10**, **11** and **13**) gave better results than monochalcogenides **5** and **6**, and others (**7**, **9**, **12** and **14**) gave similar results. The best result was obtained using bis-selenide **8**, probably due to transannular interaction (entry 13). In the cases of aromatic chalcogenides **9**–**14** steric interaction, for example between *peri*-hydrogens of the aromatic rings and the enone, may prevent the Michael addition step.

Various aldehydes and enones were applied to the chalcogeno-Baylis–Hillman reaction under standard conditions (Table 2).§ The yields of the adducts **4**, **18**, **17** and **19** decreased with the decreasing electrophilicity of the aldehydes (entry 3 in Table 1, entries 2, 1 and 3 in Table 2, respectively). Reactions of *p*-nitrobenzaldehyde **1** with enones **15** and **16** gave coupling products **20** and **21**, respectively, in moderate yields.

Reactions of other substrates such as acrylonitrile and an aliphatic aldehyde using the Me_2S–$TiCl_4$ system resulted in low (< 24%) yields. Further examination of different combinations of chalcogenides and Lewis acids, and extension of the chalcogeno-Baylis–Hillman reaction to various substrates, is now under investigation.



Footnotes and References

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† Chalcogenide **11** was prepared by the reaction of bis(2-bromomethylphenyl) sulfide and Na_2Se (prepared from Se and $NaBH_4$ in EtOH) in EtOH by a procedure similar to that for compound **10** (ref. 14).

‡ Selenide **14** was prepared from bis(2-bromomethylphenyl) selenide (ref. 15) and benzylamine by the same procedure as for sulfide **13** (ref. 14). The *N*-methyl derivative of selenide **14** has been synthesised: H. Fujihara, H. Mima, T. Erata and N. Furukawa, *J. Chem. Soc., Chem. Commun.*, 1991, 98.

§ *Typical procedure* for the chalcogeno-Baylis–Hillman reaction: To a stirred solution of *p*-nitrobenzaldehyde (151 mg, 1 mmol), cyclohex-2-en-1-one (0.29 ml, 3 mmol) and methyl sulfide (7 μl, 0.1 mmol) in CH_2Cl_2 (2 cm^3) was added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1 ml, 1 mmol) at room temperature. The mixture was stirred for 1 h at ambient temperature, and the reaction was quenched by addition of water (5 cm^3). The precipitate of inorganic material was removed by filtration through Celite, and the filtrate was extracted with CH_2Cl_2 (20 ml × 2). The extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with ethyl acetate–hexane (1 : 1, v/v) to give 148 mg (60%) of an adduct **3**.

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