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The Chalcogeno-Baylis-Hillman Reaction: A New Preparation of Allylic Alcohols from Aldehydes and Electron-deficient Alkenes

Tadashi Kataoka,* Tetsuo Iwama, Shin-ichiro Tsujiyama, Tatsunori Iwamura and Shin-ichi Watanabe

Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5-chome, Gifu 502-8585, Japan

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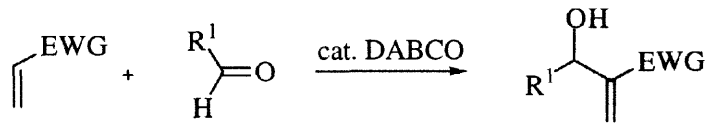
Abstract: The chalcogeno-Baylis-Hillman reaction catalyzed by sulfides and selenides, the group 16 element compounds, in the presence of Lewis acids was developed. The reactions proceeded smoothly by the use of 1 equiv of $TiCl_4$ to give the coupling products in moderate to good yields. Bis-chalcogenides and related compounds were investigated as a catalyst, and 1,5-diselenocyclooctane gave the best result owing to stabilization of a cationic intermediate by the transannular interaction.

INTRODUCTION

The Baylis-Hillman reaction is a useful method for C-C bond formation utilizing activated alkenes and aldehydes (Scheme 1).[1] A tertiary compound of the group 15 element is required as a catalyst, and 1,4-diazabicyclo[2.2.2]octane (DABCO) is the most popular one. Some tertiary phosphine catalysts have been also reported.[2] Although the Baylis-Hillman reaction serves as useful building blocks in organic synthesis, the reaction rate is generally very slow.[1] Much attention has been paid to accelerating the reactions,[2c,3-8] and there have been some examples activated with Lewis acids. Aggarwal and co-workers have reported that lanthanides and group 3 metal triflates accelerated the Baylis-Hillman reaction using DABCO; however, formation of an amine-Lewis acid complex decelerated the reaction in the cases of $TiCl_4$ and $BF_3 \cdot Et_2O$.[6] A phosphine catalyst and triethylaluminum promoted the Baylis-Hillman reaction owing to activation of an aldehyde by coordination with the Lewis acid.[2d] Recently, Leahy and co-workers have investigated the asymmetric Baylis-Hillman reaction using DABCO by the use of Oppolzer's sultam.[9] More recently, Soai and co-workers have reported the enantioselective Baylis-Hillman reaction with chiral phosphine catalysts.[2e] There are no reports concerning catalysts other than the group 15 element compounds. We have recently developed the first chalcogeno-Baylis-Hillman reaction catalyzed by sulfides and selenides, the group 16 element compounds, in the presence of Lewis acids,[10] and here we wish to describe extensive study on the preliminary result.

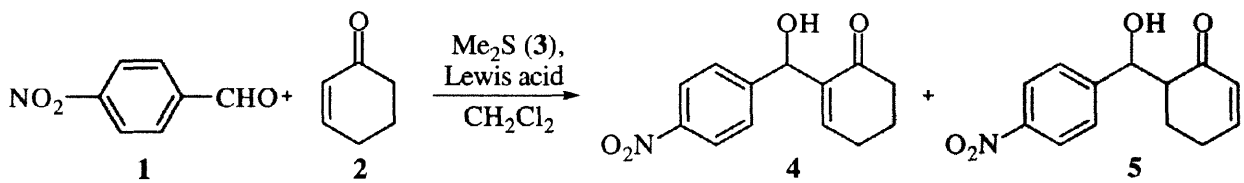


Scheme 1

PII: S0040-4020(98)00708-X

RESULTS AND DISCUSSION

First, we examined reactions of *p*-nitrobenzaldehyde **1** and 3 equiv of 2-cyclohexen-1-one **2** by the use of dimethyl sulfide **3** in CH_2Cl_2 (Scheme 2, Table 1). A reaction of the compounds **1** and **2** with 1 equiv of the sulfide **3** at room temperature for 5 days gave no coupling product **4** (entry 1). 0.1 Equiv of $TiCl_4$ was added to the mixture of **1**, **2** and 1 equiv of **3** in order to enhance the reactivity of the enone towards the Michael addition of the sulfide, and the Baylis-Hillman product **4** was obtained in 17% yield at room temperature for 1 h (entry 2). The yield of **4** was improved up to 62% by the use of 1 equiv of $TiCl_4$ (entry 3). Therefore, we examined the reaction with a catalytic amount of **3** (0.1 equiv) in the presence of 1 equiv of $TiCl_4$, and the adduct **4** was given in 60% yield (entry 4). The adduct **4** was also obtained in 58% yield under refluxing in CH_2Cl_2 for 10 min (entry 5). The results revealed that dimethyl sulfide **3** smoothly catalyzed the Baylis-Hillman reaction in the presence of 1 equiv of $TiCl_4$. It is noteworthy that the reaction using a sulfide and a Lewis acid is dramatically accelerated in comparison with reactions utilizing amine catalysts.[1] It is also interesting that 1 equiv of $TiCl_4$ is necessary for the smooth reactions in contrast to the fact that the use of DABCO and $TiCl_4$ decelerated the reaction owing to formation of a deactivated amine-Lewis acid complex.[6] The β-substituted active alkenes which had been used were only methyl crotonate, crotononitrile and crotonaldehyde.[1a] Our results are the first examples for the Baylis-Hillman reaction utilizing a β-substituted enone. Next, we examined several Lewis acids under standard conditions (1 equiv of Lewis acid, 0.1 equiv of **3** in CH_2Cl_2 at room temperature for 1 h (Table 1)). The yields of the adduct **4** increased with increasing Lewis acidity in the cases of aluminum Lewis acids (entries 6-8). The use of $HfCl_4$ gave the Baylis-Hillman adduct **4** in 15% yield together with the aldol-type adduct **5** in 5% yield (entry 9). The aldol-type adduct **5** was obtained as the sole product in 47% yield by the use of $Hf(OTf)_4$ (entry 10). Reactions with other Lewis acids,



1 **2** **4** **5**

Scheme 2

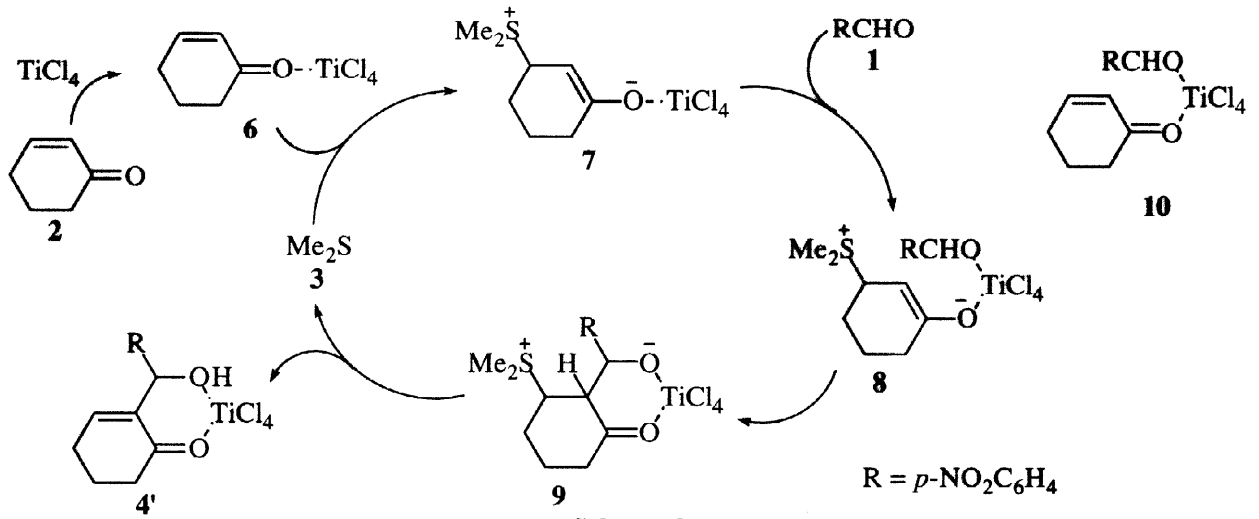
Table 1. Chalcogeno-Baylis-Hillman Reaction Catalyzed by Me_2S in the Presence of Lewis Acids.[a]

Entry	Me_2S (equiv)	Lewis acid (equiv)	Temp.	Time	**4** (%yield)[b]	**5** (%yield)[b]
1	1	–	r.t.	5 d	–	–
2	1	$TiCl_4$ (0.1)	r.t.	1 h	17	–
3	1	$TiCl_4$ (1)	r.t.	1 h	62	–
4	0.1	$TiCl_4$ (1)	r.t.	1 h	60	–
5	0.1	$TiCl_4$ (1)	reflux	10 min	58	–
6	0.1	$AlCl_3$ (1)	r.t.	1 h	30	–
7	0.1	$EtAlCl_2$ (1)	r.t.	1 h	13	–
8	0.1	Et_2AlCl (1)	r.t.	1 h	11	–
9	0.1	$HfCl_4$ (1)	r.t.	1 h	15	5
10	0.1	$Hf(OTf)_4$ (1)	r.t	1 h	–	47

[a] 3 equiv of enone **2** was used based on aldehyde **1**. The use of $BF_3{\cdot}Et_2O$, $SnCl_4$, $ScCl_3$, $Sc(OTf)_3$, $LaCl_3$, $La(OTf)_3$, $SmCl_3$, $Sm(OTf)_3$, $LuCl_3$, $Lu(OTf)_3$, $YbCl_3$, $Yb(OTf)_3$ and $Mg(ClO_4)_2$ in CH_2Cl_2 or CH_3CN gave no coupling products. [b] Isolated yield based on aldehyde **1**.

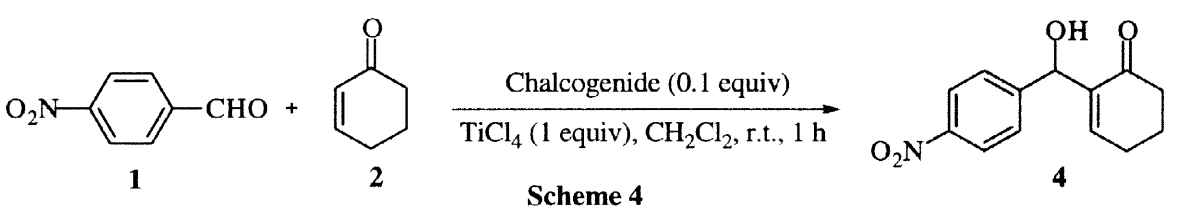
BF_3•Et_2O, $SnCl_4$, $ScCl_4$, $Sc(OTf)_3$, $LaCl_3$, $La(OTf)_3$, $SmCl_3$, $Sm(OTf)_3$, $LuCl_3$, $Lu(OTf)_3$, $YbCl_3$, $Yb(OTf)_3$ and $Mg(ClO_4)_2$, in CH_2Cl_2 and MeCN gave no coupling products **4** and **5**. The use of $TiCl_4$ gave the best result.

A plausible mechanism is shown in Scheme 3. Addition of methyl sulfide **3** to the enone **2** is allowed by coordination with $TiCl_4$ *via* a complex **6** to generate the enolate intermediate **7**. The aldehyde **1** is activated by coordination with $TiCl_4$ (a complex **8**), and the aldol reaction proceeds to give the adduct **9**. The adduct **9** provides a Baylis-Hillman product-$TiCl_4$ complex **4'** by β-eliminating methyl sulfide **3**. A stoichiometric amount of $TiCl_4$ is necessary for a smooth reaction because $TiCl_4$ forms the stable complex **4'** and can not activate another molecule of **2** so as to react with the sulfide **3**. The reaction may proceed *via* a complex **10**.



Scheme 3

Chalcogenide catalysts **11**, **12**,[11] **13**,[12] **14**, **15**,[13] **16**,[14] **17**,[15] **18**, **19**,[16] **20**[15] and **21** were examined in the presence of 1 equiv of $TiCl_4$ in CH_2Cl_2 at room temperature for 1 h (Scheme 4, Table 2). A reaction with thioanisole **11** provided the adduct **4** in 67% yield (entry 2). Cyclic mono chalcogenides **12** and **13** gave better results than dimethyl sulfide **3** (entry 1) to provide **4** in 71% and 70% yields, respectively. The Michael addition step of the chalcogenide to the enone may be promoted by the high electron-releasing ability of the chalcogenide, and we selected bis-chalcogenides **14-19** and related chalcogenides **20,21**. They are expected to stabilize a cation species by transannular interaction of a chalcogen and a heteroatom (intermediates **22,23**).[17] Some chalcogenides **16,17,18,20** gave better results than mono chalcogenides **12** and **13**, and others **14,15,19,21** gave similar results. The best result was obtained by the use of bis-selenide **16**, probably due to the transannular interaction (entry 7). In the cases of aromatic chalcogenides **15,17-21**, steric interactions, for example between *peri*-hydrogens of the aromatic rings and an enone, would prevent the Michael addition step, and quantitative analyses of the reactions are very difficult at present. Chalcogenide catalysts were recoverable without significant loss although some were decomposed with prolonged reaction time.



Scheme 4

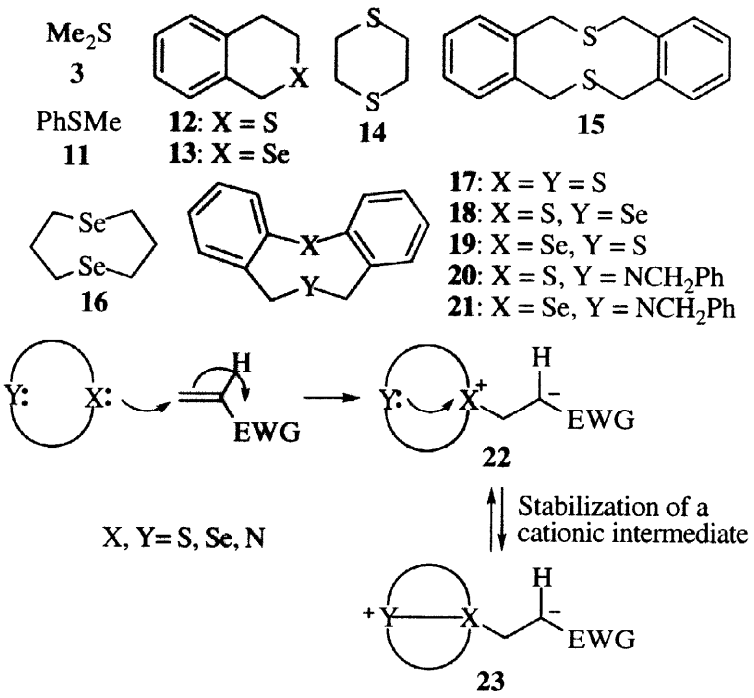
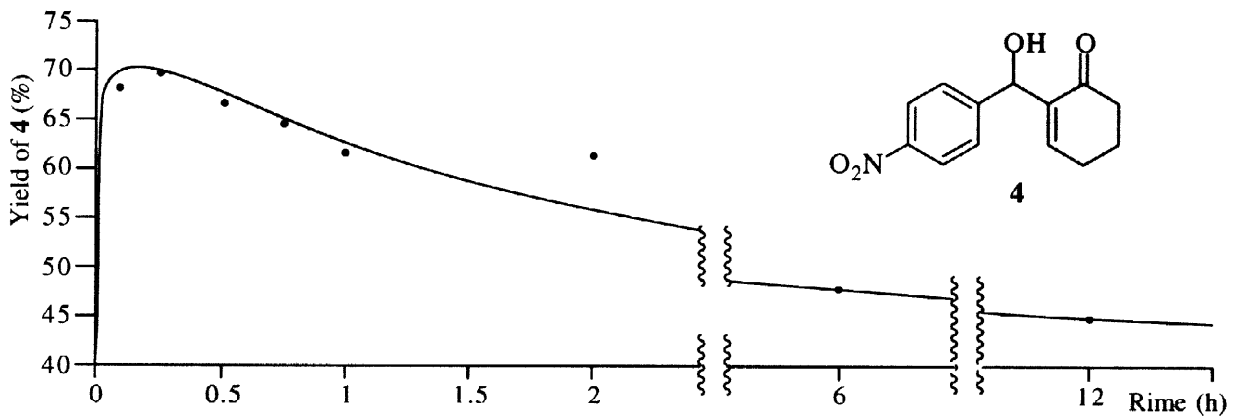


Table 2. Investigation of Chalcogenide Catalyst in the Presence of $TiCl_4$.

Entry	Chalcogenide	4 (%yield)[a]
1[b]	3	60
2	11	67
3	12	71
4	13	70
5	14	69
6	15	71
7	16	85
8	17	74
9	18	78
10	19	71
11	20	76
12	21	69

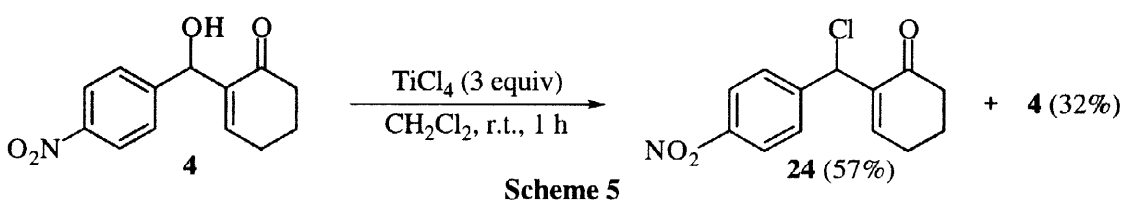
3 equiv of enone **2** was used based on aldehyde **1**. [a] Isolated yield based on aldehyde **1**. [b] The result appeares as entry 4 in Table 1.

We studied the time course of the yield of Baylis-Hillman adduct **4** in the reactions of *p*-nitrobenzaldehyde **1** and 3 equiv of 2-cyclohexenone **2** catalyzed by Me_2S (0.1 equiv)-$TiCl_4$ (1 equiv) in CH_2Cl_2 at room temperature (Fig. 1). Surprisingly, the reaction completed after even 15 min, and the yield of **4** gradually decreased with prolonged reaction time. The adduct **4** was decomposed by $TiCl_4$ in the reaction system. In fact, treatment of **4** with 3 equiv of $TiCl_4$ in CH_2Cl_2 at room temperature for 1 h provided chloride **24** in 57% yield together with the recovered **4** in 32% yield (Scheme 5).[18]



Conditions: 3 equiv of 2-cyclohexenone **2**, 0.1 equiv of Me_2S, 1 equiv of $TiCl_4$, CH_2Cl_2, r.t.

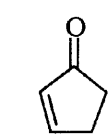
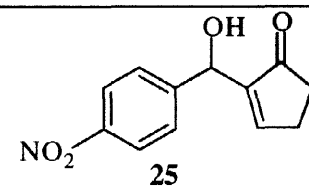
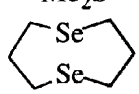
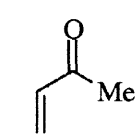
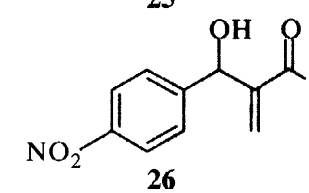
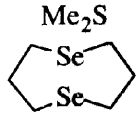
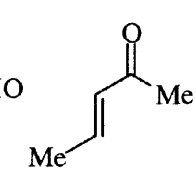
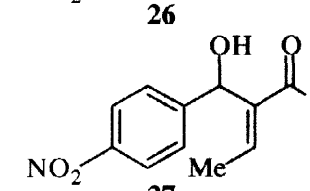
Fig. 1 Time Course of the Yield of Adduct **4** in Chalcogeno-Baylis-Hillman Reaction Catalysed by Me_2S-$TiCl_4$ System.



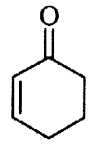
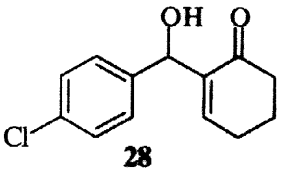
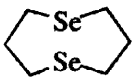
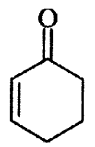
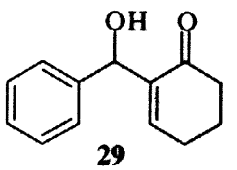
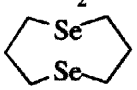
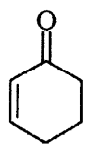
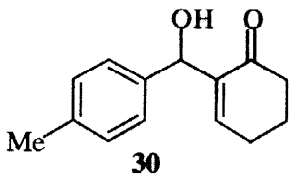
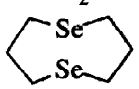
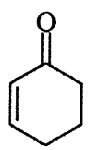
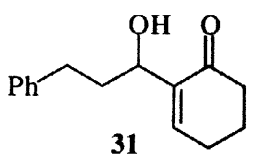
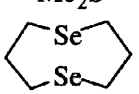
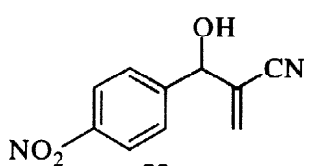
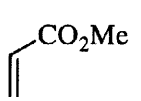
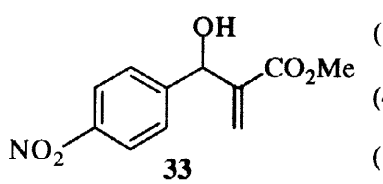
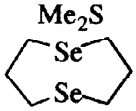
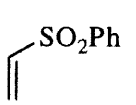
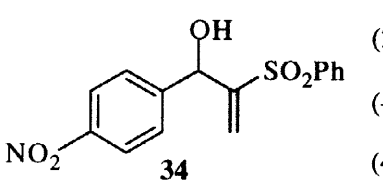
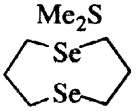
Scheme 5

Some aldehydes and activated alkenes were subjected to the chalcogeno-Baylis-Hillman reaction by the use of 0.1 equiv of Me_2S **3** or bis-selenide **16** in the presence of 1 equiv of $TiCl_4$ in CH_2Cl_2 (Table 3).[18] Reactions of *p*-nitrobenzaldehyde with cyclopentenone catalyzed by Me_2S gave a coupling product **25** in 68% yield (entry 1). Methyl vinyl ketone, acyclic enone, also provided the adduct **26** in good yield together with a small amount of a 2:1 adduct **35** (entry 3). The use of the bis-selenide slightly improved the yield of **25** and **26** (entries 2,4). Reactions of (*E*)-3-penten-2-one were slow and complicated compared with those of the other enones, and a Baylis-Hillman adduct **27** was given in low yields together with an aldol product **36** (entries 5,6). The stereochemistry of **27** was determined as (*E*) by NOE technique (see experimental section). In reactions of cyclohexenone and aromatic aldehydes with Me_2S, the yields of the adducts **4,28,29,30** were reduced with decreasing the electrophilicities of the aldehydes (entry 4 in Table 1, entries 7,9,11 in Table 3, respectively). The yields of **28-30** were improved to the extent of 11-27% by the use of the bis-selenide (entries 8,10,12). The adduct **31** was obtained in 42% yield from the reaction of an aliphatic aldehyde and cyclohexenone catalyzed by Me_2S under reflux in CH_2Cl_2 for 10 min (entry 13). The use of the bis-selenide **16** provided the adduct **31** in 55% yield (entry 14). A reaction of acrylonitrile and *p*-nitrobenzaldehyde using Me_2S gave the adduct **32** in high yield under reflux in CH_2Cl_2 for 24 h (entry 15). Methyl acrylate and phenyl vinyl sulfone were less reactive than enones, and reactions with *p*-nitrobenzaldehyde catalyzed by 0.1 equiv of Me_2S provided adducts **33** and **34** in 35% and 28% yields, respectively, even for 50 h at room temperature (entries 16,19). In the cases of methyl acrylate the use of 1 equiv of Me_2S shortened the reaction time, and the yields of **33** were improved (entries 17) although reactions of phenyl vinyl sulfone using 1 equiv of chalcogenides gave trace amounts of the Baylis-Hillman adduct **34** (entries 20,21). In the reactions of methyl acrylate with 1 equiv of Me_2S, the reaction mixtures rapidly solidified by addition of $TiCl_4$, and the yields of **32** were reduced with prolonged reaction time (for example, 34% for 30 min and 21% for 1 h). Decomposition of bis-selenide **16** was observed when 1 equiv of **16** was used (entries 18,21). Phenyl vinyl sulfoxide and diethyl vinylphosphonate were unreactive under conditions using 0.1-1 equiv of Me_2S **3** or bis-selenide **16** in the presence of 1 equiv of $TiCl_4$ in CH_2Cl_2 at room temperature for 1-36 h, and no Baylis-Hillman adducts could be isolated.

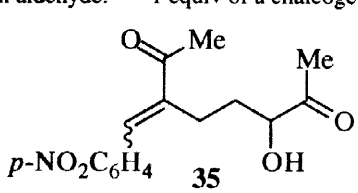
Table 3. Reactions of Some Aldehydes and Activated Alkenes in the Presence of $TiCl_4$.

Entry	Chalcogenide	Aldehyde	Alkene	Conditions	Product (%yield)[a]
1	Me_2S			r.t., 1 h	 (68)
2		*p*-$NO_2C_6H_4CHO$		r.t., 1 h	(70)
					25
3	Me_2S			r.t., 1 h	 (63)[b]
4		*p*-$NO_2C_6H_4CHO$		r.t., 1 h	(67)[c]
					26
5	Me_2S			r.t., 6 h	 (30)[d]
6		*p*-$NO_2C_6H_4CHO$		r.t., 6 h	(29)[e]
					27

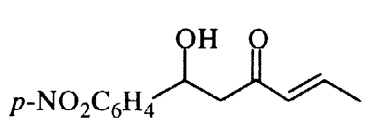
continued

7	Me_2S			r.t., 1 h		(43)
8		p-ClC_6H_4CHO		r.t., 1 h		(57)
					28	
9	Me_2S			r.t., 1 h		(25)
10		PhCHO		r.t., 1 h		(52)
					29	
11	Me_2S			r.t., 1 h		(13)
12		p-MeC_6H_4CHO		r.t., 1 h		(24)
					30	
13	Me_2S			reflux, 10 min		(42)
14		$PhCH_2CH_2CHO$		reflux, 10 min		(55)
					31	
15	Me_2S	p-$NO_2C_6H_4CHO$		reflux, 24 h		(88)
					32	
16	Me_2S			r.t., 50 h		(35)
17[f]	Me_2S	p-$NO_2C_6H_4CHO$		r.t., 2 min		(49)
18[f]				r.t., 2 min		(14)
					33	
19	Me_2S			r.t., 50 h		(28)
20[f]	Me_2S	p-$NO_2C_6H_4CHO$		r.t., 1 h		(–)
21[f]				r.t., 1 h		(4)
					34	

Conditions: 1 equiv of an aldehyde, 3 equiv of an activated alkene, 0.1 equiv of a chalcogenide, 1 equiv of $TiCl_4$, CH_2Cl_2. [a] Isolated yield based on an aldehyde. [b] A small amount of **35** was obtained. [c] Compound **35** was obtained in 11% yield based on an aldehyde. [d] Compound **36** was obtained in 15% yield based on an aldehyde. [e] Compound **36** was obtained in 20% yield based on an aldehyde. [f] 1 equiv of a chalcogenide was used.



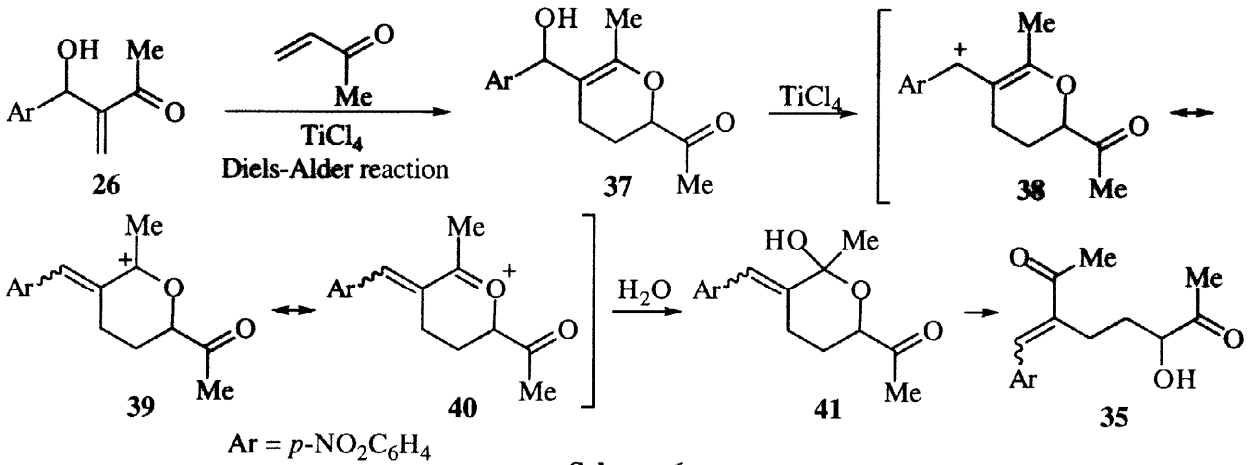
35



36

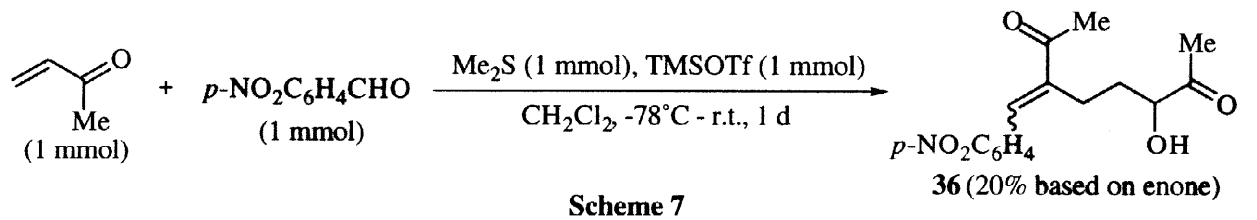
The 2:1 adduct **35** would be formed as follows: the Baylis-Hillman adduct **26** undergoes the Lewis acid-promoted Diels-Alder reaction with another methyl vinyl ketone molecule to give cycloadduct **37**.[19,20] A reaction of **37** and $TiCl_4$ generates a benzylic cation intermediate **38**. A hemiketal **41** is formed from another

cationic intermediate **39**, which is stabilized by the contribution of an oxonium ion structure **40**. The diketone **35** is given by ring-opening of the hemiketal **41**.



Scheme 6

The 2:1 adduct **35** was also obtained in 20% yield based on the enone from a reaction of methyl vinyl ketone and *p*-nitrobenzaldehyde with 1 equiv of TMSOTf in the presence of 1 equiv of Me_2S at -78°C - room temperature in CH_2Cl_2 (Scheme 7).



Scheme 7

SUMMARY

The chalcogeno-Baylis-Hillman reaction was investigated by the use of chalcogenides as catalysts in the presence of Lewis acids. The reaction was applied to activated alkenes such as enones including β-substituted derivatives, acrylonitrile, methyl acrylate, phenyl vinyl sulfone and phenyl vinylsulfonate. Diethyl vinylphosphonate and phenyl vinyl sulfoxide were inactive to the chalcogeno-Baylis-Hillman reaction. 1,5-Diselenooctane gave the best result as a catalyst due to the transannular interaction between the selenium atoms. $TiCl_4$ was the best Lewis acid, and 1 equiv of $TiCl_4$ was necessary for smooth reactions. Further development of the chalcogeno-Baylis-Hillman reaction is now 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) or JEOL EX-90 (90 MHz) spectrometer with tetramethylsilane as an internal standard. The *J* values are given in Hz. ^{13}C-NMR spectra and NOE were obtained on a JEOL EX-400 spectrometer with chloroform-d as an internal standard.

Mass spectra (EI and FAB) were recorded on a JEOL JMS-D 300 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 either BW-127ZH (Fuji Silysia) for column chromatography or Kieselgel 60 PF_{254} containing gypsum (Merck) for TLC.

Synthesis of Chalcogenide 18

To a mixture of selenium powder (790 mg, 10 mmol) and $NaBH_4$ (946 mg, 25 mmol) was added dropwise EtOH (40 cm^3) at 0°C under argon. After stirring for 1 h at room temperature, the solution of Na_2Se was diluted with EtOH (960 cm^3) and bis(2-bromomethylphenyl) sulfide[15] (3.721 g, 10 mmol) in THF (20 cm^3) was added to it over 30 min. The mixture was stirred for 17 h and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 cm^3), washed with water (40 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with acetone–hexane (1:30, v/v) to give 720 mg (25%) of **18**.

10*H*,12*H*-Dibenzo[c,f][1,5]selenathiocin (18) Light yellow prisms (from $CHCl_3$-hexane), mp 116-118°C (Found: C, 57.54; H, 4.16. $C_{14}H_{12}SSe$ requires C, 57.73; H, 4.15%); ^1H NMR ($CDCl_3$) δ: 3.81 and 5.14 (each 2 H, d, *J* 13, benzylic H), 7.09-7.22 (6 H, m, ArH) and 7.81 (2 H, d, *J* 7.8, ArH); ^{13}C NMR ($CDCl_3$) δ: 30.8 (t), 127.8 (d), 129.2 (d), 130.3 (d), 136.3 (s), 137.6 (d) and 147.7 (s); MS (EI) *m/z* (rel. int. %): 292 (100, M^+), 211 (80) and 178 (79); IR (KBr) ν_{max}/cm^{-1} 755 (Ar).

Synthesis of Chalcogenide 21

To a solution of bis(2-bromomethylphenyl) selenide[16] (3.738 g, 8.9 mmol) in $CHCl_3$ (70 cm^3) was added dropwise a solution of benzylamine (1 cm^3, 9.2 mmol) and Et_3N (3.7 cm^3, 27 mmol) in $CHCl_3$ (10 cm^3) and the mixture was refluxed for 10 h. After cooling, the reaction mixture was washed with water (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with acetone–hexane (1:100, v/v) to give 931 mg (29%) of **21**.

6-Benzyl-6,7-dihydro-5*H*-dibenzo[b,g][1,5]selenazocine (21) Yellow *oil* (Found: 365.0676 $C_{21}H_{19}NSe$ requires 365.0682); ^1H NMR ($CDCl_3$) δ: 3.48 (2 H, s, CH_2), 4.13 (4 H, br s, 5- and 7-H), 7.03 (2 H, d, *J* 7, ArH), 7.36 (9 H, m, ArH) and 7.66 (2 H, d, *J* 7, ArH); ^{13}C NMR ($CDCl_3$) δ: 56.3 (very broad), 126.9 (d), 127.6 (d), 127.9 (d), 128.3 (d), 128.6 (d), 132.3 (d), 135.1 (s) and 139.3 (s), two aromatic carbons are overlapped); MS (EI) *m/z* (rel. int. %): 365 (36, M^+), 363 (18) and 91 (100); IR (NaCl) ν_{max}/cm^{-1} 755 (Ar).

The Chalcogeno-Baylis-Hillman Reaction in the Presence of Lewis Acids

Typical procedure. To a stirred solution of *p*-nitrobenzaldehyde (151 mg, 1 mmol), 2-cyclohexen-1-one (0.29 cm^3, 3 mmol) and methyl sulfide (7 μdm^3, 0.1 mmol) in CH_2Cl_2 (2 cm^3) was added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1 cm^3, 1 mmol) or $TiCl_4$ (0.11 cm^3, 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) and saturated aqueous $NaHCO_3$ (2 cm^3). The precipitate of inorganic material was removed by filtration through celite, and the filtrate was extracted with CH_2Cl_2 (20 cm^3 x 2). The extracts were dried ($MgSO_4$) and 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 an adduct. Reaction conditions and yields are summarized in Tables 1-3.

2-[1-Hydroxy-1-(4-nitrophenyl)methyl]-2-cyclohexen-1-one (4) Light yellow prisms (from EtOAc-hexane), mp 87-89°C (Found: C, 62.87; H, 5.35; N, 5.48. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.30; N, 5.67%); ^{1}H NMR ($CDCl_3$) δ: 1.99-2.04 (2 H, m, 5-H), 2.42-2.47 (4 H, m, 4- and 6-H), 3.67 (1 H, d, *J* 5, OH), 5.62 (1 H, d, *J* 5, benzylic H), 6.86 (1 H, t, *J* 4, olefinic H), 7.54 and 8.17 (each 2 H, d, *J* 8, ArH); ^{13}C NMR ($CDCl_3$) δ: 22.3 (t), 25.7 (t), 38.3 (t), 71.7 (d), 123.4 (d), 127.1 (d), 140.2 (s), 147.2 (s), 148.1 (d), 149.4 (s), 199.9(s); MS (EI) *m/z* (rel. int. %): 247 (7, M^+), 230 (100); IR (KBr) ν_{max}/cm^{-1} 3430 (OH), 1660 (C=O), 1510 and 1340 (NO_2).

6-[1-Hydroxy-1-(4-nitrophenyl)methyl]-2-cyclohexen-1-one (5) Light yellow prisms (from EtOAc-hexane), mp 157.5-161.0°C (Found: 247.0852. $C_{13}H_{13}NO_4$ requires 247.0844); ^{1}H NMR ($CDCl_3$) δ: 1.49-1.67 (2 H, m, 5-H), 2.30-2.35 (2 H, m, 4-H), 2.53-2.60 (1 H, m, 6-H), 4.90 (1 H, d, *J* 1.5, OH), 4.98 (1 H, dd, *J* 1.5 and 9, benzylic H), 6.10 (1 H, ddd, *J* 10, 3 and 1.5, 2-H), 7.03-7.07 (1 H, m, 3-H), 7.55 and 8.23 (each 2 H, d, *J* 9, ArH); ^{13}C NMR ($CDCl_3$) δ: 25.3 (t), 25.7 (t), 52.5 (d), 74.7 (d), 123.6 (d), 128.0 (d), 129.6 (d), 147.7 (s), 148.2 (s), 151.8 (d), 202.7 (s); MS (EI) *m/z* (rel. int. %): 247 (3, M^+), 96 (100); IR (KBr) ν_{max}/cm^{-1} 3490 (OH), 1655 (C=O), 1510 and 1345 (NO_2).

2-[1-Hydroxy-1-(4-nitrophenyl)methyl]-2-cyclopenten-1-one (25) Light yellow prisms (from $CHCl_3$), mp 136.5-138.5°C (Found: C, 61.47; H, 4.75; N, 6.02. $C_{12}H_{11}NO_4$ requires C, 61.56; H, 4.74; N, 5.98%); ^{1}H NMR ($CDCl_3$) δ: 2.48-2.49 (2 H, m, CH_2), 2.63 (2 H, br s, CH_2), 3.66(1 H, d, *J* 4, OH), 5.68 (1 H, d, *J* 3, benzylic H), 7.31 (1 H, br s, olefinic H), 7.59 and 8.21 (each 2 H, d, *J* 9, ArH); ^{13}C NMR ($CDCl_3$) δ: 26.9 (t), 35.2 (t), 69.0 (d), 123.8 (d), 127.1 (d), 146.7 (s), 147.5 (s), 148.6 (s), 159.8(d), 209.3 (s); MS (EI) *m/z* (rel. int. %): 233 (100, M^+); IR (KBr) ν_{max}/cm^{-1} 3340 (OH), 1690 (C=O), 1515 and 1345 (NO_2).

3-[1-Hydroxy-1-(4-nitrophenyl)methyl]-3-buten-2-one (26) Light yellow prisms (from EtOAc-Hexane), mp 82-83°C (Found: C, 59.56; H, 4.95; N, 6.34. $C_{11}H_{11}NO_4$ requires C, 59.73; H, 5.01; N, 6.33%); ^{1}H NMR ($CDCl_3$) δ: 2.36 (3 H, s, CH_3), 3.37 (1 H, d, *J* 5.9, OH), 5.68 (1 H, d, *J* 5.9, benzylic H), 6.05 and 6.27 (each 1 H, s, olefinic H), 7.55 and 8.19 (each 2 H, d, *J* 8.8, ArH); ^{13}C NMR ($CDCl_3$) δ: 26.1 (q), 71.5 (d), 123.3 (d), 127.2 (d), 127.5 (t), 147.1 (s), 149.0 (s), 149.1 (s), 199.8 (s); MS (EI) *m/z* (rel. int. %): 221 (3%, M^+), 204 (100); IR (KBr) ν_{max}/cm^{-1} 3480 (OH), 1655 (C=O), 1520 and 1345 (NO_2).

3-Hydroxy-6-(4-nitrobenzylidene)octane-2,7-dione (35) Yellow oil (Found: 292.1187. $C_{15}H_{17}NO_5$ + H requires 292.1185); ^{1}H NMR ($CDCl_3$) δ: 1.74-1.83 and 2.00-2.07 (each 1 H, m, 4-H), 2.28 and 2.50 (each 3 H, s, CH_3 x 2), 2.45-2.52 (1 H, m, 5-H), 2.64 (1 H, dt, *J* 5 and 12, 5-H), 3.64 (1 H, d, *J* 4, OH), 4.23 (1 H, dt, *J* 7 and 4, 3-H), 7.53 (1 H, s, olefinic H), 7.62 and 8.28 (each 2 H, d, *J* 9, ArH); ^{13}C NMR ($CDCl_3$) δ: 21.7 (t), 25.1 (q), 26.0 (q), 32.3 (t), 76.5 (d), 123.9 (d), 130.1 (d), 138.0 (d), 141.6 (s), 143.9 (s), 147.5 (s), 199.6 (s), 209.4 (s); MS (FAB) *m/z* (rel. int. %): 292 (11, M^++1); IR (NaCl) ν_{max}/cm^{-1} 3475 (OH), 1715 (aliphatic C=O), 1665 (unsaturated C=O), 1510 and 1350 (NO_2).

(*E*)-3-[1-Hydroxy-1-(4-nitrophenyl)methyl]-3-penten-2-one (27) Colorless prisms (from CH_2Cl_2-Hexane), mp 99-101°C (Found: 236.0914. $C_{12}H_{13}NO_4$ + H requires 236.0923); ^{1}H NMR ($CDCl_3$) δ: 2.09 (3 H, d, *J* 7.3, 5-H), 2.32 (3 H, s, 1-H), 4.45 (1 H, d, *J* 8.7, OH), 5.75 (1 H, d, *J* 8.7, benzylic H), 7.08 (1 H, q, *J* 7.3, 4-H), 7.50 and 8.16 (each 2 H, d, *J* 8.8, ArH); ^{13}C NMR ($CDCl_3$) δ: 14.8 (q), 26.2 (q), 69.3 (d), 123.5 (d), 126.0 (d), 141.8 (s), 142.9 (d), 146.9 (s), 150.6 (s), 201.5 (s); MS (FAB) *m/z* (rel. int. %): 236 (17%, M^++1), 154 (100); IR (KBr) ν_{max}/cm^{-1} 3360 (OH), 1630 (C=O), 1510 and 1340 (NO_2). 7% of NOE was observed between 5-methyl and benzylic methine groups.

1-Hydroxy-1-(4-nitrophenyl)-4-hexen-3-one (36) Yellow oil (Found: 235.0840. $C_{12}H_{13}NO_4$ requires 235.0845); ^{1}H NMR ($CDCl_3$) δ: 1.92 (3 H, dd, *J* 2 and 6.8, 6-H), 2.92 (1 H, dd, *J* 9 and 18, 2-H), 2.98 (1 H, dd, *J* 3 and 18, 2-H), 3.88 (1 H, d, *J* 3, OH), 5.30 (1 H, dt, *J* 9 and 3, 1-H), 6.15 (1 H, dq, *J* 16 and 2, 4-H), 6.92 (1 H, dq, *J* 16 and 6.8, 5-H), 7.56 and 8.21 (each 2 H, d, *J* 8.8, ArH); ^{13}C NMR ($CDCl_3$) δ: 18.4 (q), 47.6 (t), 69.2 (d), 123.7 (d), 126.5 (d), 131.8 (d), 145.2 (d), 147.3 (s), 150.2 (s), 199.5 (s); MS (EI) *m/z* (rel. int. %): 235 (14%, M^+), 69 (100); IR (NaCl) ν_{max}/cm^{-1} 3450 (OH), 1660 (C=O), 1515 and 1345 (NO_2).

2-[1-Hydroxy-1-(4-chlorophenyl)methyl]-2-cyclohexen-1-one (28) Yellow oil (Found: 236.0598. $C_{13}H_{13}ClO_2$ requires 236.0604); ^{1}H NMR ($CDCl_3$) δ: 1.99 (2 H, quintet, *J* 6 and 8, 5-H), 2.37-2.45 (4 H, m, 4- and 6-H), 3.53 (1 H, d, *J* 5, OH), 5.51 (1 H, d, *J* 5, benzylic H), 6.75 (1 H, t, *J* 4, olefinic H), 7.29 (4 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ: 22.4 (t), 25.7 (t), 38.5 (t), 71.8 (d), 127.8 (d), 128.4 (d), 133.1 (s), 140.2 (s), 140.7 (s), 147.4 (d), 200.3 (s); MS (EI) *m/z* (rel. int. %): 236 (56, M^+), 235 (100), 201 (97); IR (NaCl) ν_{max}/cm^{-1} 3420 (OH), 1665 (C=O).

2-(1-Hydroxy-1-phenylmethyl)-2-cyclohexen-1-one (29) Light yellow oil (Found: 202.0999. $C_{13}H_{14}O_2$ requires 202.0994); ^{1}H NMR ($CDCl_3$) δ: 1.99 (2 H, quintet, *J* 6 and 8, 5-H), 2.38-2.46 (4 H, m, 4- and 6-H), 3.48 (1 H, d, *J* 5, OH), 5.55 (1 H, d, *J* 4, benzylic H), 6.74 (1 H, t, *J* 4, olefinic H), 7.26-7.35 (5 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ: 22.8 (t), 26.0 (t), 38.8 (t), 72.8 (d), 126.7 (d), 127.7 (d), 128.6 (d), 141.4 (s), 142.0 (s), 147.6 (d), 200.7 (s); MS (EI) *m/z* (rel. int. %): 202 (79, M^+), 201 (100); IR (NaCl) ν_{max}/cm^{-1} 3430 (OH), 1665 (C=O).

2-[1-Hydroxy-1-(4-tolyl)methyl]-2-cyclohexen-1-one (30) Yellow oil (Found: 217.1230. $C_{14}H_{16}O_2$ + H requires 217.1228); ^{1}H NMR ($CDCl_3$) δ: 2.00 (2 H, quintet, *J* 6, 5-H), 2.34 (3 H, s, CH_3), 2.37-2.47 (4 H, m, 4- and 6-H), 3.37 (1 H, d, *J* 5, OH), 5.52 (1 H, d, *J* 5, benzylic H), 6.74 (1 H, t, *J* 4, olefinic H), 7.15 and 7.24 (each 2 H, d, *J* 8, ArH); ^{13}C NMR ($CDCl_3$) δ: 21.1 (q), 22.5 (t), 25.7 (t), 38.6 (t), 72.5 (d), 126.4 (d), 129.0 (d), 137.1 (s), 138.7 (s), 141.1 (s), 147.2 (d), 200.5 (s); MS (FAB) *m/z* (rel. int. %): 217 (10, M^++1), 199 (74); IR(NaCl) ν_{max}/cm^{-1} 3430 (OH), 1670 (C=O).

2-(1-Hydroxy-3-phenylpropyl)-2-cyclohexen-1-one (31) Light yellow oil (Found: 230.1312. $C_{15}H_{18}O_2$ requires 230.1307); ^{1}H NMR ($CDCl_3$) δ: 1.89-2.03 (4 H, m), 2.36-2.43 (4 H, m, 4- and 6-H), 2.62-2.69 and 2.77-2.85 (each 1H, m, $ArCH_2$), 3.04 (1 H, d, *J* 7, OH), 4.32 (1 H, dt, *J* 7 and 5, C*H*-OH), 6.85 (1 H, t, *J* 4, olefinic H), 7.15-7.29 (5 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ: 22.5 (t), 25.6 (t), 32.2 (t), 37.6 (t), 38.6 (t), 71.1 (d), 125.8 (d), 128.3 (d), 128.4 (d), 140.6 (s), 141.8 (s), 146.0 (d), 200.7 (s); MS (EI) *m/z* (rel. int. %): 230 (5, M^+), 212 (100); IR (NaCl) ν_{max}/cm^{-1} 3440 (OH), 1660 (C=O).

2-[1-Hydroxy-1-(4-nitrophenyl)methyl]acrylonitrile (32) Colorless prisms (from EtOAc-hexane), mp 72-74°C (Found: C, 58.59; H, 3.94; N, 13.63. $C_{10}H_8N_2O_3$ requires C, 58.82; H, 3.95; N, 13.72%); ^{1}H NMR ($CDCl_3$) δ: 3.53 (1 H, s, OH), 5.45 (1 H, s, benzylic H), 6.10 and 6.18 (each 1 H, s, olefinic H), 7.60 and 8.22 (each 2 H, d, *J* 8.5, ArH); ^{13}C NMR ($CDCl_3$) δ: 73.1 (d), 116.3 (s), 123.9 (d), 125.3 (s), 127.3 (d), 131.1 (t), 146.2 (s), 147.9 (s); MS (EI) *m/z* (rel. int. %): 204 (8, M^+), 152 (100); IR (KBr) ν_{max}/cm^{-1} 3480 (OH), 2230 (CN), 1505 and 1340 (NO_2).

Methyl 2-[1-hydroxy-1-(4-nitrophenyl)methyl]acrylate (33) Light yellow oil (Found: C, 55.37; H, 4.78; N, 5.85. $C_{11}H_{11}NO_5$ requires C, 55.70; H, 4.67; N, 5.91%); ^{1}H NMR ($CDCl_3$) δ: 3.34 (1 H, d, *J* 6, OH), 3.75 (3 H, s, CH_3), 5.64 (1 H, d, *J* 6, benzylic H), 5.88 and 6.40 (each 1 H, s, olefinic H), 7.58 and 8.21 (each 2 H, d, *J* 8.5, ArH); ^{13}C NMR ($CDCl_3$) δ: 52.1 (q), 72.4 (d), 123.5 (d), 127.1 (t), 127.3

(d), 141.0 (s), 147.3 (s), 148.7 (s), 166.3 (s); MS (EI) *m/z* (rel. int. %): 237 (30%, M^+), 150 (100); IR (NaCl) ν_{max}/cm^{-1} 3490 (OH), 1715 (C=O),1520 and 1350 (NO_2).

1-(4-Nitrophenyl)-2-phenylsulfonyl-2-propen-1-ol (34) Light yellow solid (from EtOAc-Hexane), mp 116-118°C (Found: C, 56.46; H, 4.16; N, 4.13. $C_{15}H_{13}NO_5S$ requires C, 56.42; H, 4.10; N, 4.39%); ^1H NMR ($CDCl_3$) δ: 3.32 (1 H, d, *J* 3.9, OH), 5.66 (1 H, d, *J* 3.9, benzylic H), 5.91 and 6.56 (each 1 H, s, olefinic H), 7.35 and 8.07 (each 2 H, d, *J* 8.5, ArH), 7.47 (2 H, t, *J* 8, ArH), 7.61 (1 H, t, *J* 8, ArH), 7.75 (2 H, d, *J* 8, ArH); ^{13}C NMR ($CDCl_3$) δ: 70.5 (d), 123.5 (d), 127.5 (d), 127.8 (t), 128.0 (d), 129.2 (d), 133.9 (d), 138.7 (s), 146.0 (s), 147.6 (s), 152.1 (s); MS (EI) *m/z* (rel. int. %): 319 (2%, M^+), 143 (100); IR (KBr) ν_{max}/cm^{-1} 3490 (OH), 1520 and 1345 (NO_2), 1285 and 1130 (SO_2).

Reaction of Baylis-Hillman Product 4 with $TiCl_4$

To a stirred solution of adduct **4** (156 mg, 0.63 mmol) in CH_2Cl_2 (3 cm^3) was added $TiCl_4$ (0.2 cm^3, 1.9 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) and saturated aqueous $NaHCO_3$ (2 cm^3). The precipitate of inorganic material was removed by filtration through celite, and the filtrate was extracted with CH_2Cl_2 (20 cm^3 x 2). The extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with ethyl acetate–hexane (1:3, v/v) to give 50 mg (32%) of the starting material and 98 mg (64%) of a chloride **24**.

2-[1-Chloro-1-(4-nitrophenyl)methyl]-2-cyclohexen-1-one (24) Colorless needles (from EtOAc-Hexane), mp 107-108.5°C (Found: C, 58.81; H, 4.62; N, 5.26. $C_{13}H_{12}ClNO_3$ requires C, 58.76; H, 4.55; N, 5.27%); ^1H NMR ($CDCl_3$) δ: 1.98-2.08 (2 H, m, 5-H), 2.39-2.53 (4 H, m, 4- and 6-H), 6.11 (1 H, s, benzylic H), 7.29 (1 H, t, *J* 4, olefinic H), 7.57 and 8.19 (each 2 H, d, *J* 8.5, ArH); ^{13}C NMR ($CDCl_3$) δ: 22.3 (t), 26.0 (t), 38.1 (t), 56.6 (d), 123.7 (d), 128.4 (d), 138.5 (s), 147.1 (s), 147.4 (s), 149.1 (d), 196.3 (s); MS (EI) *m/z* (rel. int. %): 265 (20%, M^+), 248 (100); IR (KBr) ν_{max}/cm^{-1} 1660 (C=O), 1520 and 1350 (NO_2).

The Chalcogeno-Baylis-Hillman reaction with TMSOTf

To a solution of methyl vinyl ketone (70 mg, 1 mmol) and dimethyl sulfide (63 mg, 1 mmol) in CH_2Cl_2 (3 cm^3) was added TMSOTf (222 mg, 1 mmol) at -78°C. After stirring for 1 h, *p*-nitrobenzaldehyde (151 mg, 1 mmol) in CH_2Cl_2 (1 cm^3) was added to it at -78°C and the whole was stirred at room temperature for 1 d. Water (5 cm^3) and saturated aqueous $NaHCO_3$ (2 cm^3) were added and the organic layer was separated. The water layer was extracted with CH_2Cl_2 (20 cm^3 x 2). The organic layer and extracts were combined, dried ($MgSO_4$) and 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 29 mg (20%) of a 2:1 adduct **35**.

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