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An efficient and rapid chalcogenide-Morita–Baylis–Hillman process promoted by TBDMSOTf and a thiolane

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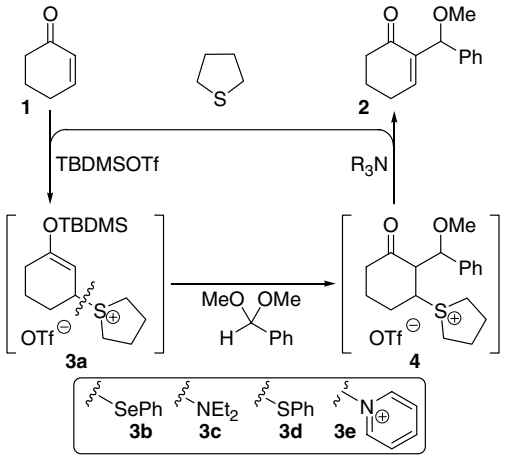
Abstract—The ability of the combination of sulfide/TBDMSOTf to promote a chalcogenide-Morita–Baylis–Hillman reaction is reported. The original Michael–Mukaiyama-retroaldol sequence took place and furnished the MBH adducts from the corresponding enones and acetals. This one step process could be performed smoothly at low temperatures (−20 to −50 °C) and is rapidly completed within a few hours.

The nucleophilic addition of an activated alkene to a carbonyl group (**1** to **2**) promoted by either an amine or a phosphine, namely the Morita–Baylis–Hillman reaction (MBH), paved the way for a steadily increasing amount of researches since its discovery.[1] A myriad of papers have been dealing with the chemistry of the obtained α-methylene-β-hydroxycarbonyl compounds as versatile,[2] and chiral synthetic intermediates.[3] In that context, Kataoka and co-workers pioneered research into the use of both a sulfide and $TiCl_4$, as promoters of the so-called chalcogenide-MBH.[4] This effective dual Lewis acid–base activation, studied by several groups,[5] leads to improved reaction rates under mild conditions.[6] This combination takes advantage of weak interactions between a hard Lewis acid and a soft chalcogenide Lewis base,[7] and can overcome the sluggishness of the processes often met under regular conditions.[8] Moreover, the use of chiral sulfides, engaged in an asymmetric process, has been envisaged and led to promising results.[9] Nevertheless, the discovery of novel and improved conditions leading to an effective MBH reaction is still an ongoing endeavour.

We would like to report herein on a domino Michael–Mukaiyama-retroaldol process,[10] promoted by the combination of TBDMSOTf/sulfide as described in Scheme 1. This system provides a formally chalcogenide-MBH reaction in which every chemical step could be studied separately.[5,11] Indeed, Noyori first demonstrated the conjugated addition of a silyl selenide to an enone (**1** to **3**), catalyzed by TMSOTf, to form a silyl enolether of type **3b**. This intermediate was then successfully engaged in the following Mukaiyama-retroaldol reactions



Scheme 1. Chalcogenide-MBH.

Keywords: Chalcogenide-Morita–Baylis–Hillman; TBDMSOTf; Sulfide; Enone; Acetal.
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with acetals (**3** to **2**).[12] Such a process was also proven by means of silyl amines (via **3c**), silyl sulfides (via **3d**) and pyridine (via **3e**).[13]

However, only one example, published by Kim and coworkers, stated the ability to carry out the three chemical steps (**1** to **2**) with sulfides and the help of both TBDMSOTf and TMSOTf.[14] Unfortunately, in the aforementioned studies, a sequential addition of reagents was usually performed after each step. Furthermore, a nucleophilic base such as DBU, or an oxidative treatment of the sulfide or selenide intermediates was required to realise the β-elimination process. We reasoned that the softness of a sulfide would facilitate the addition–elimination steps (**1** to **3** and **4** to **2**). Therefore, we undertook this study in order to allow a domino Michael–Mukaiyama-retroaldol sequence, using an enone, an acetal and a suitable amine base. In such an original single-step method, the sulfide promoter would be recycled in situ, and a catalytic and asymmetric process with chiral sulfides could be envisaged.[9]

In order to validate the chalcogenide-MBH described in Scheme 1, we simply mixed all reagents together in one pot. We also chose a sterically hindered amine such as the Hünig's base (Table 1).[15] Although a sluggish reaction took place in THF, a smooth process occurred in more polar acetonitrile (entries 1 and 2). We checked that the amine did not lead to any reaction in the absence of sulfide (entry 3). The best results were obtained in CH_2Cl_2, affording **2** with 76% yield in only 6 h at −40 °C (entry 4). So, we have in hand an original chalcogenide-MBH process, involving a single-step operation, with a resident acetal and a base,[4b] and promoted by TBDMSOTf.[16] Moreover, the cascade reactions proceed in very mild conditions.[8] We verified that the reaction did not take place at lower temperature (entry 5). At this early stage of optimisation, several observations have to be pointed out: (1) No reaction took place with benzaldehyde. More reactive acetals, as oxonium precursors, are required to react with the enol silylether **3a**.[17] (2) The base has to be the last reagent added for the success of the procedure. (3) Although the yield is not quantitative, the ^{1}H NMR spectrum of the crude product was clean after workup. (4) Almost an equal amount of the enone and the aldehyde was used. This last point is noteworthy as, in most cases, the MBH reaction requires an excess of either the aldehyde or the polymerisable enone.[2,3] We then varied the nature of the amine and found that the non-nucleophilic 2,6-lutidine gave poor yields in this reaction (entry 6). This base is likely not basic enough to promote the β-elimination step. On the other hand, by increasing the amount of Hünig's base and using a somewhat lower temperature, the yield remained similar after 6 h of reaction (entries 7 and 8). The presence of the base prevents any residual triflic acid in the reaction media, which could decompose the crude product, as we observed sometimes. Moreover, the temperature of the reaction medium is a crucial point (entry 5). We witnessed a smooth and complete transformation at −20 °C within 30 min (entry 9). This result proved the fastness of the three chemical steps and the nice compatibility of all the components (Scheme 1). The yield of **2** decreased dramatically at 0 °C (entry 10). A complete conversion was observed, but the ^{1}H spectrum of the crude product revealed a complex mixture. With this protocol in hand, we then sought a process with a catalytic amount of sulfide. Using an excess of base (entry 11) or a sterically more hindered amine (entry 12) did not furnish any turnover. Although moderate yields were obtained at −40 °C, the catalytic cycle was demonstrated with 0.2 equiv of sulfide and 1 equiv of Hünig's base (entry 13).

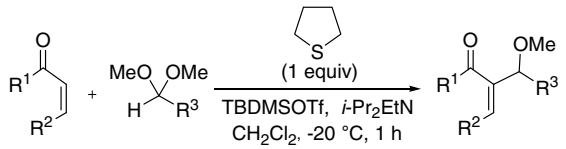
We then investigated the scope and limitations of this original chalcogenide-MBH protocol with various acetals (Table 2).[18] We firstly tested enone derivatives (entries 1–3). Both five- and six-membered rings led to smooth reactions in only 1 h at −20 °C. Even the highly polymerisable methyl vinyl ketone afforded the corresponding adduct, in a moderate yield, but without using excess of enone. The aromatic dimethylacetals bearing alkyl or halogen groups at the 4-position, turned out to be good substrates for the chalcogenide-MBH reaction with cyclohexenone (entries 4–6). Acetal acceptors displaying strongly electron-withdrawing (entries 7 and

Table 1. Optimisation of the chalcogenide-MBH reaction to give **2** according to Scheme 1[a]

Entry	R_3N (equiv)	Thiolane (equiv)	Time (h)	Solvent, T (°C)	Yield[b] (%)
1	*i*-Pr_2EtN (1)	1.1	6	THF, −40	Traces
2	*i*-Pr_2EtN (1)	1.1	6	MeCN, −40	66
3	*i*-Pr_2EtN (1)	—	6	MeCN, −40	—
4	*i*-Pr_2EtN (1)	1.1	6	CH_2Cl_2, −40	76
5	*i*-Pr_2EtN (1)	1.1	6	CH_2Cl_2, −78	—
6	2,6-Lutidine (1)	1.1	6	CH_2Cl_2, −40	37
7	*i*-Pr_2EtN (1.5)	1.1	6	CH_2Cl_2, −50	71
8	*i*-Pr_2EtN (1.5)	1.1	1	CH_2Cl_2, −50	25
9	*i*-Pr_2EtN (1.5)	1.1	0.5	CH_2Cl_2, −20	81
10	*i*-Pr_2EtN (1.5)	1.1	0.5	CH_2Cl_2, 0	37
11	*i*-Pr_2EtN (1.5)	0.2	1	CH_2Cl_2, −20	21
12	Cy_2EtN (1)	0.2	6	CH_2Cl_2, −40	Traces
13	*i*-Pr_2EtN (1)	0.2	6	CH_2Cl_2, −40	42

[a] Reaction conditions: 2-cyclohexen-1-one (0.5 mmol), $PhCH(OMe)_2$ (1.1 equiv), thiolane, TBDMSOTf (1.4 equiv), R_3N, solvent (2 mL).
[b] Isolated yield based on the cyclohexenone.

Table 2. The chalcogeno MBH reaction with various substrates[a]



Entry	Enone (R^1; R^2)	Acetal (R^3)	Yield (%)[b]
1	$(CH_2)_2$	Ph	80
2	(CH_2)	Ph	71
3	Me; H	Ph	55
4	$(CH_2)_2$	4-MeC_6H_4	66
5	$(CH_2)_2$	4-ClC_6H_4	66
6	$(CH_2)_2$	4-FC_6H_4	83
7	$(CH_2)_2$	4-$CF_3C_6H_4$	33
8	$(CH_2)_2$	4-$CF_3C_6H_4$	65[c]
9	$(CH_2)_2$	4-$MeOC_6H_4$	26
10	$(CH_2)_2$	4-$MeOC_6H_4$	39[c]
11	$(CH_2)_2$	2-MeC_6H_4	45[c]
12	$(CH_2)_2$	2-$MeOC_6H_4$	21[c]
13	$(CH_2)_2$	PhCH=CH	64[c]
14	$(CH_2)_2$	$PhCH_2CH_2$	—

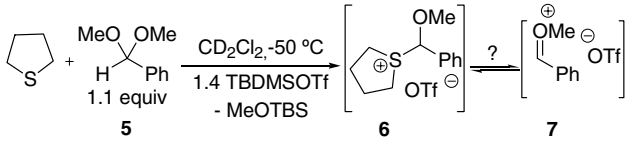
[a] Reaction conditions: enone (0.5 mmol), acetal (1.1 equiv), thiolane (1.1 equiv), TBDMSOTf (1.4 equiv), *i*-Pr_3EtN (1.5 equiv), CH_2Cl_2 (2 mL), −20 °C, 1 h.

[b] Isolated yield.

[c] This reaction has been performed at −50 °C for 6 h.

8) or donating groups (entries 9 and 10) gave better results at −50 °C. This reaction is also sensitive to steric hindrance as 2-substituted acetals tended to give lower yields (entries 11 and 12). Although a complex mixture was obtained at −20 °C, we were pleased to find that the acetal of the (*E*)-cinnamaldehyde afforded the corresponding bis-allylic ether at −50 °C (entry 13). Unfortunately, the aliphatic acetals did not undergo any chalcogenide-MBH reaction with these conditions (entry 14).

We wondered about the nature of the intermediates going on in this process. It has been shown by Kim[14] and others[19] that the dimethyl sulfonium salt of type **3a**, resulting from the addition of dimethyl sulfide to cyclohexenone in the presence of TBDMSOTf, is rapidly formed at −78 °C (Scheme 1). This salt would slowly reverse to cyclohexenone between −45 and −20 °C. In our conditions, we did not obtain any product between the silyl enolether **3a** and benzaldehyde regardless of the temperature. So, one could think that the more reactive oxonium species **7** (Scheme 2), resulting from the resident acetal and the excess of TBDMSOTf, would be involved in the Mukaiyama aldolisation step (**3a** to **4**; Scheme 1). The lack of reactivity of the hindered silylenolether **3a** would also explain the absence of reaction at −78 °C. On the other hand, a sulfide is capable to add on an acetal, in the presence of TMSOTf, to form a sulfonium of type **6** (Scheme 2).[20] To monitor the possible formation of such intermediates, we carried out the following NMR experiments. First of all, we mixed cyclohexenone (1 equiv), TBDMSOTf (1.4 equiv) and thiolane (1.1 equiv) in CD_2Cl_2 and recorded the ^1H NMR at −50 °C (solution A). Indeed, the cyclohexenone **1** was rapidly equilibrated with the corresponding sulfonium salt **3a** to afford a ratio of 39:61 (**1**:**3a**).[21] We warmed up the NMR tube and observed that only traces of the sulfonium salt **3a** remained at −20 °C. This stressed that the aldolisation step gives a rapid formation of **4** at −20 °C (vs −50 °C), and consumes intermediate **3a**, which is present at low concentration.[21] These conditions provide indeed very short reaction times (Table 2; entries 1–6). However, with more shielded or less reactive acetals (Table 2; entries 7–14), it seems desirable to have a higher concentration of the enol intermediate **3a** at −50 °C. We also mixed, in a NMR tube, the dimethylacetal of benzaldehyde and thiolane in the presence of TBDMSOTf (Scheme 2). The sulfonium salt **6** was rapidly and completely formed at −50 °C (solution B). The cyclohexenone was subsequently added to **6** in solution B. In a parallel experiment, we added the dimethyl acetal of benzaldehyde to intermediate **3a** in solution A at −50 °C. In both cases, we obtained the same NMR spectrum, which was compatible with the aldol adduct **4**. The exact interpretation of the numerous signals, likely due to a mixture of diastereoisomers, was not straightforward. Nevertheless, these experiments show that a sulfonium salt **6** could be involved either directly, or as a precursor of the oxonium **7**, in such a process.



Scheme 2. Intermediates in the chalcogenide-MBH.

In summary, we have reported on an alternative chalcogenide-Morita–Baylis–Hillman reaction requiring an equal amount of both an enone and an acetal. This process proceeds via a rapid Michael–Mukaiyama-retroaldol sequence, conveniently promoted by mixing a sulfide, TBDMSOTf in the presence of the Hünig's base. These conditions furnished the products in very mild conditions (−20 to −50 °C) and reasonably short times (30 min to 6 h). Studies are in progress to render this original process practically catalytic in sulfide and eventually asymmetric.

Acknowledgements

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