Asymmetric Synthesis

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Reactions of Iminium Ions with Michael Acceptors through a Morita–Baylis–Hillman-Type Reaction: Enantiocontrol and Applications in Synthesis**

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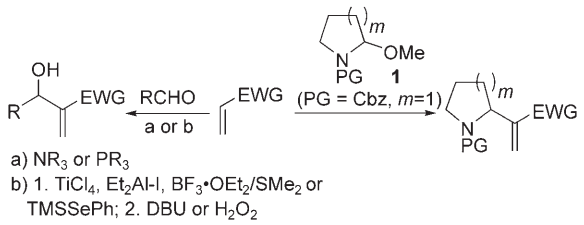
α-Functionalization of alkenes activated by electron-withdrawing groups (EWGs) encompass an important C–C bond-forming strategy in organic synthesis, and can be realized in one of three ways: a) metal-catalyzed functionalization of α-halogeno[1] or α-metallo substrates;[2] b) a vinylogous enolization, α-alkylation, and isomerization sequence;[3] or c) nucleophilic catalysis: the Rauhut–Currier and Morita–Baylis–Hillman (MBH) reactions.[4] The MBH transformation (Scheme 1),[5] which is traditionally effected by catalytic



Scheme 1. The Morita–Baylis–Hillman reaction and our proposed study. Cbz = benzyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMS = trimethylsilyl, PG = protecting group.

amounts of a tertiary amine or phosphine and uses an aldehyde as the terminal electrophile, has become more recently a powerful synthetic tool with the increased scope in Michael acceptors (for example, vinyl sulfones[6a] and acrylamides[6]) and electrophiles (for example, halides,[7a,b] epoxides,[7c] allyl carbonates,[7d] acetals,[7e–h] and aryl cation equivalents[7i]). A class of electrophile that has received little attention is N-acyl iminium ions[8] which would lead to biologically important and highly functionalized β′-amido-α,β-unsaturated carbonyl compounds.[9] Herein, we describe our success in employing this class of substrates and also in rendering the reaction asymmetric.

Initial investigations focused on the pyrrolidine **1** (PG = Cbz, $m = 1$; Scheme 1) and reaction conditions in which a combination of a Lewis acid (to form the iminium ion electrophile) and a weak Lewis base (to form the enolate nucleophile) were used.[10] The standard Lewis bases for the MBH reaction (phosphines and amines) were ineffective with $BF_3{\cdot}OEt_2$: use of PPh_3 resulted in a stable phosphine–iminium ion adduct[11] presumably because of the poor leaving group ability of the phosphine,[12] and pyridine caused dimerization of the pyrrolidine presumably through base-promoted enamine formation and subsequent attack on a second iminium ion.[13] In contrast, sulfides proved effective: treatment of a solution of pyrrolidine **1** and methyl vinyl ketone (MVK) with $BF_3{\cdot}OEt_2$ and SMe_2,[10a] followed by treatment of the resultant crude mixture with DBU, resulted in the isolation of the MBH-type adduct **2a** in 30% yield. Other Lewis acid/Lewis base combinations were then investigated, namely $TiCl_4$,[10c,14] $TiCl_4/SMe_2$,[10b,15] Et_2Al-I,[16] and TMSOTf/SMe_2.[7f,g] The latter combination was found to be optimum and provided adducts **2a**–**m**; in good to excellent yield (Table 1). With these conditions, the scope of the alkene was exceptionally broad and encompassed enones, both acyclic (entry 1) and cyclic (entries 2 and 3), enals including acrolein (entries 4 and 5), and *S*-ethyl propenethiolate[17] (entry 6). Methyl acrylate (entry 7) was only moderately successful since the dimerization of pyrrolidine **1** was again observed as a competing process.

The scope of the N,O-acetal was also explored (Table 1). The piperidine analogue of **1** gave adducts in good to excellent yield (entries 8 and 9). With this substrate, the temperature had to be maintained below −60 °C since dimerization of the N,O-acetal was extremely facile at higher temperatures.[13] The Boc (entries 10 and 11) and tosyl analogues (entries 12 and 13) of **1** also gave good to excellent yields of adducts.

We then chose to apply this methodology to the synthesis of the necine base (+)-heliotridine (Scheme 2).[18] Pyrrolidine **3** was prepared from (*S*)-malic acid using the procedure of Speckamp and co-workers.[19] Although the employment of the above methodologies failed to provide MBH-type adduct **4**, it was found that treatment of a solution of **3** and methyl acrylate in CH_3CN with the combination of TMSOTf, $BF_3{\cdot}OEt_2$[20] and SMe_2 gave the required adduct **4** in 85% yield, albeit as a mixture of diastereomers in favor of the *trans*

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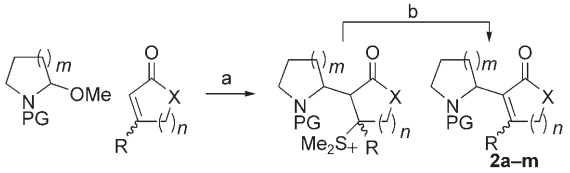
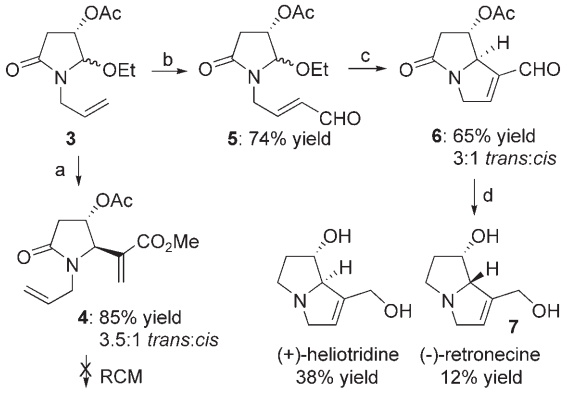
Table 1: Synthesis of MBH-type adducts **2a–m**.



Entry	PG	*m*	*n*	R	X	Product	Yield [%]
1	Cbz	1	0	H	CH_3	**2a**	95
2	Cbz	1	1	H	CH_2	**2b**	96
3	Cbz	1	2	H	CH_2	**2c**	96
4	Cbz	1	0	H	H	**2d**[c]	85
5	Cbz	1	0	CH_3	H	**2e**[c,d]	94
6	Cbz	1	0	H	SEt	**2f**	90
7	Cbz	1	0	H	OMe	**2g**[e]	51
8	Cbz	2	1	H	CH_2	**2h**[f]	90
9	Cbz	2	2	H	CH_2	**2i**[f]	75
10	Boc	1	1	H	CH_2	**2j**	69
11	Boc	1	2	H	CH_2	**2k**	60
12	Ts	1	0	H	CH_3	**2l**[g]	90
13	Ts	1	0	H	SEt	**2m**[g]	90

[a] Alkene (2.0 equiv), TMSOTf (2.5 equiv), SMe_2 (1.5 equiv), CH_2Cl_2, −78 °C to −20 °C, 3 h; sat. aq $NaHCO_3$ quench. [b] DBU (1.5 equiv), CH_2Cl_2, RT, 10 min. [c] Treatment with DBU was not required. [d] *E*/*Z* 5:1 [e] Reaction was carried out at −20 °C for 16 h; pyrrolidine dimerization was a competing pathway. [f] Temperature was kept below −60 °C. [g] Reaction mixture was warmed slowly from −78 °C to RT. Boc = *tert*-butoxycarbonyl, Tf = trifluoromethanesulfonyl, Ts = tosyl = toluene-4-sulfonyl.

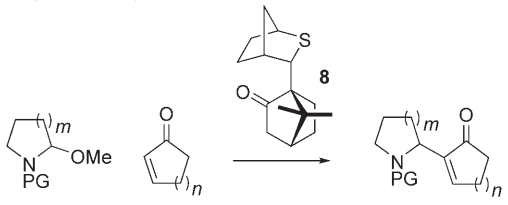


Scheme 2. Synthesis of (+)-heliotridine. a) **3** (1 equiv), methyl acrylate (3.0 equiv), TMSOTf (3.0 equiv), $BF_3{\cdot}OEt_2$ (3.0 equiv), SMe_2 (3.0 equiv), CH_3CN, RT, 24 h; b) acrolein (3.0 equiv), Grubbs–Hoveyda cat. (2×5 mol%), CH_2Cl_2, RT, 12 h; c) TMSOTf (3.0 equiv), $BF_3{\cdot}OEt_2$ (3.0 equiv), SMe_2 (3.0 equiv), CH_3CN, RT, 3 h; d) $LiAlH_4$ (7.0 equiv), THF, reflux, 1 h.

isomer. However, all attempts to bring about ring-closing metathesis (RCM) of diene **4** failed, with isomerization of the allyl moiety to the enamide the only transformation observed.[21] An alternative route to the necine base was then devised in which metathesis precedes the MBH-type reaction. Cross-metathesis of **3** with acrolein was achieved using the Grubbs–Hoveyda catalyst, and subsequent MBH-type ring closure was effected using the conditions developed for the acyclic transformation.[8] Ultimately, bicyclic aldehyde **6** was isolated as an inseparable mixture of epimers. Multisite reduction to the requisite oxidation state was achieved by heating a solution of **6** in THF with $LiAlH_4$ to reflux to give (+)-heliotridine in 38% yield. The unnatural isomer (−)-retronecine (**7**) was also isolated in 12% yield. Whilst the structure of the natural product is relatively simple, its synthesis has prompted us to develop alternative reaction conditions for more demanding substrates, and the problems encountered with the RCM step clearly demonstrate the superiority of the MBH ring closure in this context.

To render the reaction asymmetric, enantiomerically pure chiral sulfide was used in place of SMe_2 (Table 2). Using the camphor sulfonic acid derivative, sulfide **8**, which was

Table 2: Asymmetric synthesis of MBH adducts.[a]



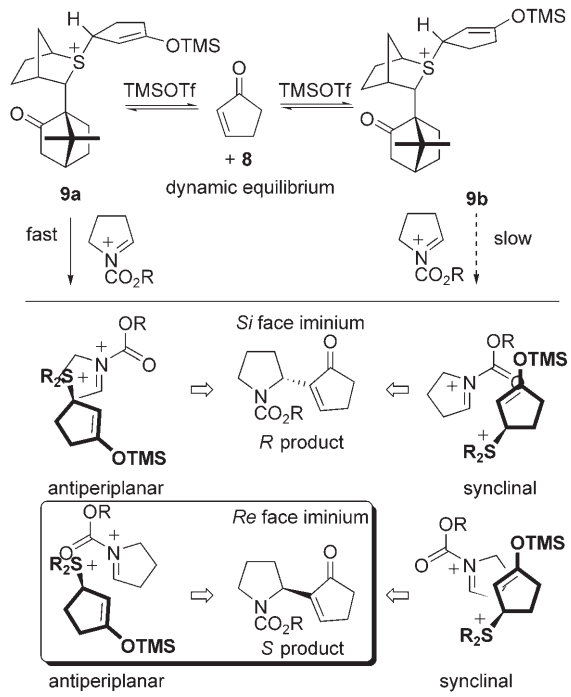
Entry	PG	*m*	*n*	Product (*R*/*S*)	Yield [%]	*ee* [%]
1	Cbz	1	1	**2b** (*S*)	69	82
2	Cbz	1	2	**2c** (*S*)	86	80
3	Boc	1	1	**2j** (*S*)	75	88
4	Boc	1	2	**2k** (*S*)	90	88
5	Cbz	2	1	**2h** (*S*)	88	94
6	Cbz	2	2	**2i** (*S*)	49	98

[a] Alkene (2.0 equiv), sulfide **8** (1.5 equiv), TMSOTf (2.5 equiv), CH_2Cl_2, < −60 °C, 5 h.

designed and synthesized within our research group for use in chemistry based on sulfonium ylides,[22] gave adducts in good yield and with high *ee* values (Table 2, entries 3 and 4). Sulfide **8**, was easily recoverable (> 90% yield) by column chromatography of the crude mixtures.

It was found that piperidine-based rather than pyrrolidine-based N,O-acetals (Table 2, entries 5 and 6 versus 1 and 2), and Boc rather than Cbz carbamate (Table 2, entries 3 and 4 versus 1 and 2) provided MBH-type adducts with improved *ee* values. When the acyclic enone MVK was employed, the corresponding adduct **2a** was obtained with a low *ee* value (8%). The absolute stereochemistry of **2k** was determined to be *S* by synthesis, crystallization, and X-ray analysis of the camphor sulfonamide derivative; the remaining adducts were assigned by analogy.

The origin of the high asymmetric induction is intriguing. Low-temperature NMR studies of a solution of cyclohexenone, sulfide **8**, and TMSOTf in CD_2Cl_2 at −90 °C revealed a mixture of diastereomeric β-sulfonium silyl enol ethers **9a** and **9b** in an unassigned ratio of 2:1 as the predominant species (Scheme 3).[23] On warming the mixture to −10 °C in increments of 20 °C, the equilibrium shifted in favor of starting material **8**;[24] at −30 °C only starting material was detected. On recooling to −90 °C, the 2:1 mixture of β-sulfonium silyl enol ethers was formed again. This reveals that the silyl enol ethers **9a** and **9b** are formed reversibly and, at the reaction temperature, are in dynamic equilibrium with the



Scheme 3. Model proposed to explain the origin of the enantioselectivity.

starting material. Thus, enantioselectivity is not determined at the stage of formation of the β-sulfonium silyl enol ethers. The origin of the enantioselectivity must therefore result from a dynamic kinetic transformation of β-sulfonium silyl enol ether **9a**,**b**, in which either the major or minor isomer reacts faster, thereby allowing the remaining diastereomer to revert to starting material for repartitioning. Focusing on one of two scenarios in which **9a** reacts faster, it could be envisioned to approach the iminium ion in several ways (Scheme 3).

The synclinal approaches can be tentatively discounted since altering the size of the silyl moiety from trimethylsilyl to triisopropylsilyl had little impact on the *ee* value. Of the two remaining antiperiplanar approaches, attack on the *Si* face of the iminium ion would be disfavored because of nonbonding interactions between the two rings. This suggests that **9a** should favor attack on the *Re* face of the iminium ion, thereby leading to the *S* enantiomer of the product as observed. This analysis still leaves open the question of why one diastereomer (**9a**/**9b**) is more reactive than the other, and this aspect is under further study.

To conclude, we have developed a novel methodology which allows a very broad range of readily available Michael acceptors, including acrolein and acrylates, to couple with readily available iminium ions (masked as N,O-acetals) in both an inter- and intramolecular MBH-type reaction to give densely functionalized heterocycles. The process has been rendered asymmetric and high enantioselectivity has been achieved with cyclic enones. Finally, the usefulness of the methodology has been exemplified in a short synthesis of (+)-heliotridine.

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[14] When the reaction was carried out at −78 °C (2 equiv of $TiCl_4$ and MVK, and subsequent treatment with DBU), the MBH adduct was not produced and the starting material, N,O-acetal **1**, along with the hydroxy aminal derivative were recovered. This result is intriguing since Goodman and co-workers have demonstrated that the generation of the required β-chloro titanium enolate is facile at this temperature (see Ref. [10a]). It is possible that at −78 °C, N,O-acetal **1** is converted into its kinetically stable α-chloro derivative, which only becomes unstable with respect to an iminium ion at higher temperatures, namely −20 °C. When the reaction was carried out at −20 °C, the MBH adduct was isolated in 67 % yield. Attempts to expand the scope of the alkene beyond MVK were unsuccessful.
[15] This combination gave similar results as produced with $TiCl_4$ alone.
[16] The reagent Et_2Al-I, which is suitably active to allow generation of the β-iodo enolate of methyl acrylate (see Ref. [10d]), did not lead to the required adduct **2g**; the delivery of the ethyl rather than the enolate ligand to the iminium ion was the only process observed.
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[23] See the Supporting Information for ^{1}H NMR spectra of the low-temperature experiments.
[24] The high sensitivity of K_{eq} to temperature suggests an entropy ($T\Delta S$) and enthalpy (ΔH) term which are of a similar order of magnitude.

