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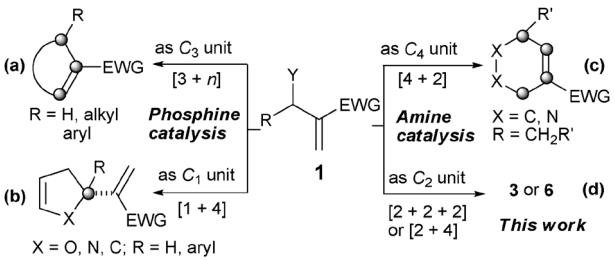
Distinct reactivity of Morita–Baylis–Hillman acetates as a novel C_2 component in amine-catalyzed [2 + 2 + 2] and [2 + 4] annulations†

Rongshun Chen,[a] Silong Xu,*[b] Liyi Wang,[a] Yuhai Tang[b] and Zhengjie He*[a]

Amine-catalyzed [2 + 2 + 2] and [2 + 4] annulations of Morita–Baylis–Hillman (MBH) acetates with cyano activated alkenes and 1,3-azadienes have been developed to provide cyclohexanes and tetrahydropyridines. In the annulations, MBH acetates serve as a novel C_2 component with an inactive homoallylic methyl involved in the bond formation.

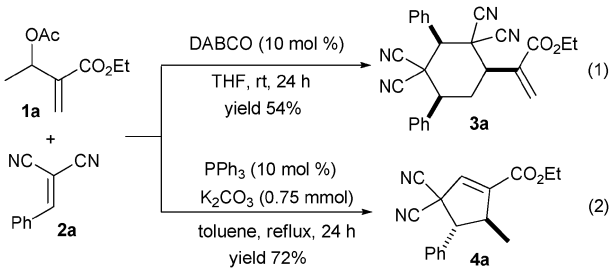
Lewis base catalysis[1] using phosphines and amines as catalysts has emerged as a powerful tool to facilitate chemical transformation. Intensive investigations into this area have predominantly focused on a group of prevailing substrates including electron-deficient allenes.[2] Recently, a class of so-called modified allylic derivatives **1** (Y = OAc, OBoc, halo, *etc.*; EWG = ester, acyl, *etc.*), which could be conveniently prepared from Morita–Baylis–Hillman (MBH) adducts,[3] have been proven to be attractive and versatile substrates in many important Lewis base catalyzed annulation reactions (Scheme 1).[4–6] The pioneering and extensive studies by Lu and others have disclosed that MBH allylic derivatives **1** could be used as a C_3 unit in a series of inter- or intramolecular phosphine-catalyzed [3 + *n*] annulations (*n* = 2, 3, 4, 6)[4] to build various ring structures (Scheme 1, path a). The latest reports by Zhang, Huang, Shi, and He also illustrated that, in the catalysis of tertiary phosphines, **1** could serve as a C_1 unit to produce rings like dihydrofurans, pyrrolines and cyclopentenes in a [1 + 4] cyclization fashion (Scheme 1, path b).[5] Interestingly, in the catalysis of amine Lewis bases, MBH derivatives **1** may undertake distinct annulation modes. Very recently, we have successfully developed an amine-catalyzed [4 + 2] annulation of MBH derivatives **1** with a variety of electron-deficient alkenes and diazenes, in which the allylic derivatives **1** act as a C_4 unit (Scheme 1, path c).[6] As part of our continuous



Scheme 1 Divergent annulation modes of MBH allylic derivatives **1** in phosphine and amine catalysis.

efforts on further exploring divergent catalysis between amines and phosphines, we herein report another amine-catalyzed new annulation mode of MBH allylic compounds **1** as a C_2 unit in [2 + 2 + 2] and [2 + 4] annulations (Scheme 1, path d).[7]

Our initial investigation showed that DABCO-catalyzed reaction of MBH acetate **1a** (0.5 mmol) with doubly activated olefin benzylidenemalononitrile **2a** (0.5 mmol) produced a novel [2 + 2 + 2] annulation[8] product **3a** in 54% yield as a single diastereomer {Scheme 2, eqn (1) DABCO = 1,4-diazabicyclo[2.2.2]octane}. Formation of **3a** accordingly illustrated an interesting annulation mode of the MBH allylic derivatives **1** as a C_2 unit, in which the inactive homoallylic methyl of the MBH acetate **1a** was involved in the C–C bond formation, while the electrophilic alkene subunit remained intact. It is also noteworthy that the above [2 + 2 + 2] annulation represents divergent catalysis between amines and phosphines, since the MBH acetate **1a** and alkene **2a** only



Scheme 2 Distinct annulation modes between **1a** and **2a**.

[a] *The State Key Laboratory of Elemento-Organic Chemistry and Department of Chemistry, Nankai University, Tianjin 300071, P.R. China. E-mail: zhengjiehe@nankai.edu.cn*

[b] *Department of Chemistry, School of Science, Xi'an Jiaotong University, Xi'an 710049, P.R. China. E-mail: silongxu@mail.xjtu.edu.cn*

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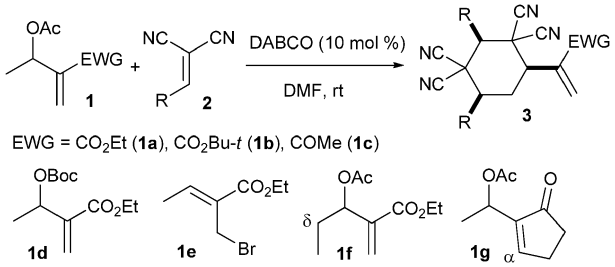
Table 1 DABCO-catalyzed [2 + 2 + 2] annulation between **1** and **2**[a]



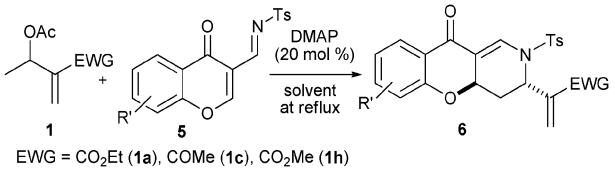
Entry	1	R in 2	Time (h)	Yield[b] (%)
1	**1a**	C_6H_5 (**2a**)	12	**3a**, 93
2	**1a**	2-Cl-C_6H_4 (**2b**)	24	**3b**, 77
3	**1a**	3-Cl-C_6H_4 (**2c**)	36	**3c**, 87
4	**1a**	4-Cl-C_6H_4 (**2d**)	7	**3d**, 88
5	**1a**	2-Br-C_6H_4 (**2e**)	8	**3e**, 54
6	**1a**	3-Br-C_6H_4 (**2f**)	36	**3f**, 88
7	**1a**	3-F-C_6H_4 (**2g**)	12	**3g**, 77
8	**1a**	4-F-C_6H_4 (**2h**)	16	**3h**, 84
9	**1a**	4-CH_3-C_6H_4 (**2i**)	12	**3i**, 78
10	**1a**	2-OCH_3-C_6H_4 (**2j**)	20	**3j**, 69
11	**1a**	3-OCH_3-C_6H_4 (**2k**)	48	**3k**, 84
12	**1a**	4-OCH_3-C_6H_4 (**2l**)	12	**3l**, 40
13[c]	**1a**	2-CF_3-C_6H_4 (**2m**)	48	**3m**, 73
14[c]	**1a**	4-CF_3-C_6H_4 (**2n**)	36	**3n**, 95
15[c]	**1a**	4-NO_2-C_6H_4 (**2o**)	12	**3o**, 84
16	**1a**	2-Thienyl (**2p**)	24	**3p**, 40
17	**1a**	3-Pyridyl (**2q**)	20	**3q**, 56
18	**1a**	C_2H_5 (**2r**)	48	/
19	**1b**	C_6H_5 (**2a**)	24	**3r**, 99
20	**1c**	C_6H_5 (**2a**)	24	**3s**, 99
21	**1d**	C_6H_5 (**2a**)	24	**3a**, 72
22[d]	**1e**	C_6H_5 (**2a**)	24	**3a**, 65
23	**1f**	C_6H_5 (**2a**)	48	/
24	**1g**	C_6H_5 (**2a**)	48	/

[a] Typical conditions: under a N_2 atmosphere, to a stirred solution of **1** (0.3 to 0.5 mmol) and **2** (0.5 mmol) in DMF (3 mL) DABCO (0.05 mmol) was added and the resulting mixture was stirred at rt. [b] Isolated yield based on **2**. [c] Solvent THF was used. [d] K_2CO_3 (0.5 mmol) was added.

underwent the known [3 + 2] annulation[4b] in the catalysis of PPh_3 {Scheme 2, eqn (2)}.

Under optimized conditions as shown in Table 1 {for details, see ESI†}, we further studied the substrate scope of the amine-catalyzed [2 + 2 + 2] annulation (Table 1). A variety of arylmethylidenemalononitriles **2** were tested with **1a**. Phenyl-substituted methylidenemalononitriles **2** bearing a halogen (Cl, Br, F) or an electron-donating substituent at the phenyl ring worked well, providing the annulation products **3** in good to excellent yields (entries 2–12). For these arylmethylidenemalononitriles **2** bearing electron-withdrawing groups, their cyclizations with **1a** were better conducted in THF, readily furnishing the annulation products in good yields (entries 13–15). Heteroaryl substituted methylidenemalononitriles **2** were also effective candidates to give the corresponding products **3** in moderate yields (entries 16 and 17). However, aliphatic propylidenemalononitrile **2r** bearing acidic methylene was ineffective, only producing a complex mixture (entry 18). Several structurally similar MBH allylic derivatives **1** were also tested in the annulation reaction with representative **2a**. The analogues of MBH acetate **1a** with varied electron-withdrawing groups (EWG) such as a bulky *tert*-butoxycarbonyl (**1b**) or an acetyl (**1c**) all behaved similarly, delivering

Table 2 DMAP-catalyzed [2 + 4] annulation between **1** and **5**[a]



Entry	1	R′ in 5	Solvent	Yield[b] (%)
1	**1c**	H (**5a**)	$CHCl_3$	**6a**, 79
2	**1c**	6-Cl (**5b**)	$CHCl_3$	**6b**, 77
3	**1c**	6-Br (**5c**)	$CHCl_3$	**6c**, 71
4	**1c**	6-CH_3 (**5d**)	$CHCl_3$	**6d**, 76
5	**1c**	6,7-Benzo (**5e**)	$CHCl_3$	**6e**, 97
6[c]	**1c**	H (**5f**)	$CHCl_3$	**6f**, 75
7[d]	**1a**	H (**5a**)	THF	**6g**, 46
8[d]	**1a**	6-Br (**5c**)	THF	**6h**, 33
9[d]	**1h**	H (**5a**)	THF	**6i**, 47
10[d]	**1h**	6-Br (**5c**)	THF	**6j**, 46

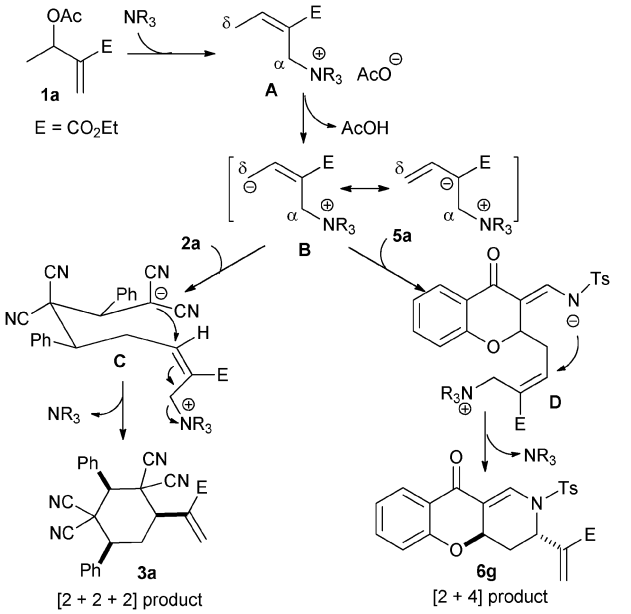
[a] Typical conditions: a mixture of MBH acetate **1** (0.3 mmol), azadiene **5** (0.2 mmol), and DMAP (0.04 mmol) in solvent (2.0 mL) was refluxed for 24 h. [b] Isolated yield based on **5**. [c] **5f** refers to 3-(*N*-phenylsulfonyliminomethyl)chromone. [d] MBH acetates **1** (0.4 mmol) were used.

products **3** in excellent yields (entries 19 and 20). Other allylic derivatives like *tert*-butyl carbonate **1d** and bromide **1e** also possessed similar reactivity and smoothly produced **3a** in satisfactory yields (entries 21 and 22). In the case of bromide **1e**, an inorganic base K_2CO_3 was needed to facilitate the reaction.[9] However, structural modification of the MBH allylic derivatives **1** at the δ- or α-carbon was found to significantly affect their reactivity as a C_2 unit. MBH acetates **1f** and **1g** both failed to afford the corresponding [2 + 2 + 2] products with **2a** (entries 23 and 24).

Based upon the above [2 + 2 + 2] annulation, we reasoned that MBH acetates **1** might be also used as a feasible C_2 unit in amine-catalyzed [2 + 4] annulations. To our delight, electrophilic azadienes such as 3-(*N*-tosyliminomethyl)chromones **5** emerged as competent partners of the [2 + 4] annulation. Using DMAP (20 mol%) as the catalyst and in refluxing chloroform (DMAP = 4-dimethylaminopyridine, for a condition survey, see ESI†), the [2 + 4] annulation of MBH acetate **1c** and a series of substituted 3-(*N*-tosyliminomethyl)chromones **5** proceeded smoothly, delivering chroman-fused tetrahydropyridine products **6** in good to excellent yields with exclusive *trans* diastereoselectivity (Table 2, entries 1–6). The ester group-activated allylic acetates **1a** and **1h** appeared less reactive and their DMAP-catalyzed [2 + 4] annulations with representative 3-(*N*-tosyliminomethyl)chromones **5** were better carried out in refluxing THF to generate the corresponding products **6** in modest yields (entries 7–10).

It is noteworthy that all annulation products **3** and **6** were obtained as a single diastereomer. Their structures and stereochemistry were well identified using ^1H and ^{13}C NMR, COSY, HSQC, NOESY, HRMS, and X-ray crystallographic analysis of **3a** and **6a** (for details, see ESI†).

Based on our latest report and others' work,[6,10] a plausible mechanism is depicted in Scheme 3 to rationalize the amine-catalyzed [2 + 2 + 2] and [2 + 4] annulations of MBH acetate **1a**. Initially, nucleophilic attack of the catalyst amine at the MBH acetate **1a** generates ammonium acetate **A** *via* an S_N2' pathway. Since the N-atom lacks the suitable ability to stabilize its *N*-ylide



Scheme 3 A proposed mechanism.

intermediate,[10] with the aid of the *in situ* generated acetate anion as a base, deprotonation of intermediate **A** takes place regioselectively at its δ-carbon rather than at its α-carbon, leading to a resonance-stabilized intermediate **B**. Theoretically, the putative intermediate **B** could be fairly stabilized by the electron-withdrawing ester group. When exposed to a doubly activated olefin **2a**, intermediate **B** is entrapped by a tandem double Michael addition process to generate intermediate **C**. Through a more stable six-membered chair-like transition state, intermediate **C** undergoes a 6-*exo-trig* ring closure *via* a S_N2' pathway to accomplish the stereoselective formation of [2 + 2 + 2] product **3a** and release of the catalyst amine. In another scenario, when reactive intermediate **B** is exposed to azadiene **5a**, 1,4-conjugate addition leads to intermediate **D**, which subsequently undergoes a 6-*exo-trig* cyclization *via* the S_N2' pathway to generate the [2 + 4] annulation product **6g** (Scheme 3). At the current stage, another possible Diels–Alder pathway of the [2 + 4] annulation could not be completely ruled out: product **6g** could be generated from a Diels–Alder cycloaddition of the azadiene **5a** with 2-carboethoxy-1,3-diene which results from elimination of the amine of intermediate **B**.[6] However, the *trans* stereochemistry of product **6g** points to an unfavored *exo* Diels–Alder pathway.[11]

In conclusion, we have developed new amine-catalyzed [2 + 2 + 2] and [2 + 4] annulation reactions of MBH acetates **1** with activated alkenes and azadienes, respectively, which provide facile access to cyclohexanes and tetrahydropyridines in good yields and exclusive diastereoselectivity. These reactions unveiled an expedient annulation mode of the versatile allylic derivatives **1** as a C_2 unit in the Lewis base catalysis, in which the inactive homoallylic methyl of the MBH acetates **1** is directly involved in the C–C bond formation. Together with the annulation mode as a C_4 unit disclosed recently by us,[6] the divergent amine-catalyzed annulation mode as a C_2 unit complements well the intensely studied phosphine-induced annulation modes as C_3 and C_1 units.[4,5] As two pillars of the organic Lewis base catalyst, divergent catalysis between amines and phosphines has recently aroused considerable interest.[12] We believe that our findings in this study may further intrigue the research interest in this area.

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