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Micellar promiscuity: an expeditious approach to Morita–Baylis–Hillman reaction

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ABSTRACT

An accelerated and efficient method for Morita–Baylis–Hillman (MBH) reaction in aqueous cationic micellar solution under ambient conditions has been developed. The present method holds promise for future use of cyclic and acylic MBH-adducts of general utility in total synthesis of natural products in a robust fashion.

The Morita–Baylis–Hillman (MBH) reaction is a carbon–carbon sigma bond-formation reaction between activated alkenes and carbon electrophiles in a tandem Michael–Aldol sequence.[1] The reaction, catalysed by tertiary amines or tertiary phosphanes provides rapid access to polyfunctionalized synthons under relatively mild conditions.[2] The products of this reaction continue to lure synthetic organic chemists for rapid access of versatile substrates for the synthesis of natural products,[3] heterocycles[4] and drugs.[5] In recent past, the reaction has drawn increasing attention owing to its selectivity (chemo-, regio-, diastereo-, enantio-) and atom-economical efficiency for the generation of structurally variegated scaffolds. Despite its promise in generating a diverse range of β-hydroxy-α-methylene compounds, the reaction typically suffers from sluggish reaction rates that vary from days to weeks.[6] Various efforts have been made to find effective catalysts and optimal experimental conditions to circumvent the sluggish nature of the reaction and to improve its overall efficiency. Most of the strategies involve the use of organic bases like DABCO,[7] DMAP,[8] imidazole,[9] DBU,[10] etc., use of strong Lewis acids ($TiCl_4$, Et_2Al)[11] or even physical methods such as high pressure[12] and microwave irradiation.[13] But, a general solution with a high degree of substrate tolerance is still lacking and desperately needed. Recently, an interesting approach on cyclic enones by a bicyclic imidazolyl alcohol in the presence of phase transfer additives is reported.[14a] Besides, a nonionic surfactant Triton X-100 was employed to generate acyclic MBH adducts in a relatively efficient manner,[14b] though, it was not effective during our study for cyclic adducts. On the other hand, there are reports in which MBH adducts of cyclic and acyclic enones can be promoted by mild cooperative catalysis of trialkylphosphanes with hydrogen bond donors such as phenols in anhydrous THF.[15] Mechanistically, it is believed that the *p*-nitrophenol (a weak Brønsted acid) in the co-catalysed systems stabilizes the enolate intermediate in the conjugate addition step through its hydrogen-bonding with the enolate, driving the reaction forward and accelerating the reaction rate.[15b]

We have been engaged in recent past in targeting the total synthesis of complex natural products from cyclic and acylic MBH adducts.[16] We also suffered with the sluggish reaction rates and low yields during our efforts despite testing most of the conditions expected to accelerate the rates. We felt the dire need of an efficient strategy of general utility in accessing a diverse range of MBH adducts. In light of the preceding discussion, we hypothesized to stabilize the enolate intermediate in the conjugate addition step of MBH reaction through self-organized aggregates such as aqueous micellar structures instead of intermolecular hydrogen bonding with weak Brønsted acids (Fig. 1).

Interestingly, micellar media bind the otherwise insoluble organic substrates by incorporating their hydrophobic part in the micellar interior and exposing their polar part at the water-micelle interface and hence offer an alternative to traditional methods of accomplishing organic transformations. The intrinsic solubilization ability of micelles provides a discrete reaction site at the microheterogeneous interface by bringing the reacting molecules in close proximity. Hence, the local interfacial concentrations of reactants

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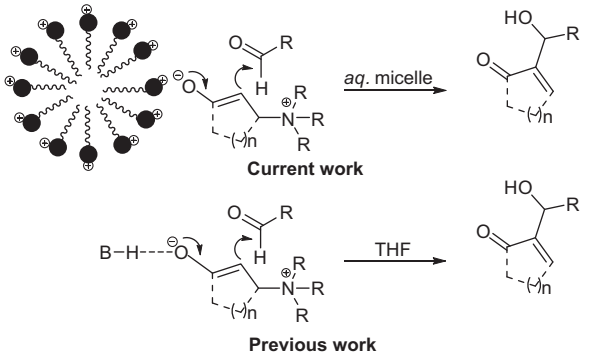


Figure 1. Schematic representation of catalysis in MBH reaction.

get enhanced compared to their stoichiometric concentration. The energy of activation is therefore, lowered presumably due to increased collisions between such interfacially concentrated reactants.[17]

During our venture on total synthesis programme starting from MBH adducts, we herein, disclose our efforts towards the establishment of an efficient protocol for MBH reaction in micellar media. We developed an interesting method of general utility to access a diverse range of MBH adducts on cationic micellar media under ambient conditions. Initially, we screened a range of cationic and anionic surfactants including SDS (**1**), SDBS (**2**), sodium cholate (**3**), CTAB (**4**) and penanediyl-1,5-bis(dimethylcetylammoniumbromide), 16-5-16 (**5**) along with two phase transfer additives TEAB (**6**) and TBAB (**7**) for the purpose (Fig. 2). Initially, it was observed that the surfactants **1**–**5** enhanced the reaction kinetics to some extent, especially with **1**, **2**, **4** and **5**, the results were on better side. Encouraged with these observations, we further investigated **1**, **2**, **4** and **5** at, below and above critical micellar concentration-CMC (concentration above which a surfactant leads to the formation of self aggregates). To our delight, it was observed that the surfactant **4** and **5** at or above CMC had a dramatic enhancement in both reaction rates as well as yields of the reactions. Contrary to this, the two phase transfer additives **6** and **7**, did not have any appreciable effect on the reaction rates. From the initial screening of surfactants and delightful results with **4** and **5** we ventured to explore the role of **4** in this reaction for further optimization of conditions while varying the organocatalyst.

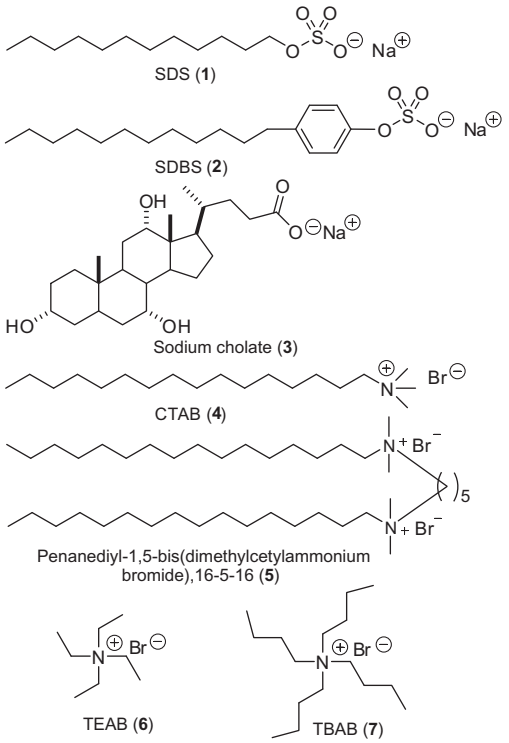


Figure 2. Structure of cationic and anionic micellar structures.

During our initial study, we tested the reaction of acrylonitrile with 2-nitrobenzaldehyde in water as solvent and **4** as a surfactant (at or above CMC), and varied the bases such as DABCO, DBU, DMAP, imidazole and Ph_3P (Table 1). From the results, it was interesting to note that the base DABCO under micellar conditions accelerated the reaction rates and reaction efficiency remarkably while DMAP only accelerated the reaction kinetics. DABCO/**4**-condition was found to be the best in terms of kinetics and yields compared to controlled reaction in which only DABCO was used.

On the other hand, in case of cyclic enones which are weak Michael acceptors and are generally less reactive towards MBH reaction, it was observed that the reaction between the cyclohexen-2-one (**11b**) and 2-nitrobenzaldehyde (**8e**) was highly efficient and accelerated in DMAP/**4** condition compared to other bases like DABCO, DBU and imidazole. DMAP/**4** condition resulted into the formation of MBH-product (**12e**) between **11b** and **8e** in 95% in 6 h compared to bare DMAP, 69% yield in 21 h (Table 2).

Having the reaction conditions optimized and based on these observations, we synthesized an array of MBH adducts from acyclic and cyclic enones under the established conditions. In our study, we studied the MBH reaction of acrylonitrile with a range of aromatic aldehydes (**8a**–**8h**) having both electron donating and electron withdrawing group/s. It was observed that in a controlled condition, that is, without micellar media, all the reactions took longer reaction time (especially those with electron donating groups) with relatively low yields compared to reactions in micellar media. Among the four surfactants (**1**, **2**, **4** and **5**), the reactions proceeded better in **4** and **5** followed by **1** and **2**, respectively (Table 3). It is clear from the results that the protocol works equally good for aliphatic aldehydes like formaldehyde (**8i**), pentanal (**8j**) and heptanal (**8k**).[18] It is to be mentioned that the protocol also works effectively with other enones like acrylates in addition to acrylonitrile. Since our proposed hypothesis is working, we believe that the self-organized micellar aggregates are playing a role in the

Table 1
Results of MBH adduct of acrylonitrile with 2-nitrobenzaldehyde with various organic bases in the presence of **4** as micellar media

S. no.	Base/CTAB	Reaction time (h)	Yield[a] (%)
1	DABCO	5.0	72
2	DABCO/**4**	0.7	95
3	DBU/**4**	4.0	10
4	DMAP/**4**	1.2	40
5	Imidazole/**4**	No reaction	—
6	Ph_3P/**4**	No reaction	—

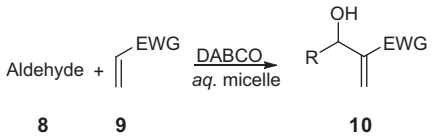
[a] Yields reported are isolated yields.

Table 2
Results of MBH adduct of cyclohexenone with 2-nitrobenzaldehyde with various organic bases in the presence of **4** as micellar media

S. no.	Base/CTAB	Reaction time (h)	Yield[a] (%)
1	DMAP	21	69
2	DMAP/**4**	6.0	95
3	DBU/**4**	10	20
4	Imidazole/**4**	10	82
5	DABCO/**4**	No reaction	—

[a] Yields reported are isolated yields.

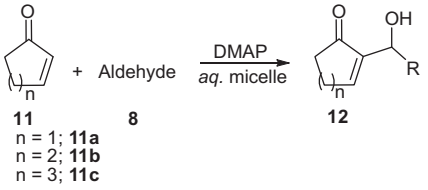
Table 3
Results of MBH adducts of acyclic alkenes with various aldehydes with and without aqueous micelles **1**, **2**, **4** and **5**



S. no.	Aldehyde	EWG	MBH adduct[a]	Reaction without micelle; time, h (yield %)[b]	Reaction with **1**; time, h (yield %)	Reaction with **2**; time, h (yield %)	Reaction with **4**; time, h (yield %)	Reaction with **5**; time, h (yield %)
1	4-ClPh (**8a**)	–CN	**10a**	25 (65)	7.0 (79)	8.0 (72)	5.5 (89)	4.0 (91)
2	4-BrPh (**8b**)	–CN	**10b**	27 (62)	6.0 (81)	8.0 (68)	5.0 (92)	4.0 (92)
3	4-MeOPh (**8c**)	–CN	**10c**	74 (59)	33 (73)	36 (64)	30 (82)	19 (83)
4	3-MeOPh (**8d**)	–CN	**10d**	62 (59)	30 (70)	33 (65)	18 (89)	13 (89)
5	2-NO_2Ph (**8e**)	–CN	**10e**	5.0 (72)	1.2 (82)	2.4 (79)	0.7 (95)	0.4 (95)
6	4-NO_2Ph (**8f**)	–CN	**10f**	6.0 (70)	1.3 (79)	2.6 (76)	0.9 (93)	0.5 (94)
7	2,4-di NO_2Ph (**8g**)	–CN	**10g**	4.0 (70)	1.2 (86)	1.3 (78)	0.6 (93)	0.3 (93)
8	4-MePh (**8h**)	–CN	**10h**	23 (61)	7.5 (77)	8.0 (69)	3.5 (89)	3.0 (89)
9	Formalin soln. (**8i**)	–CN	**10i**	6.0 (70)	4.0 (80)	NT[c]	2.0 (95)	1.2 (95)
10	Pentanal (**8j**)	–CN	**10j**	9.0 (65)	5.0 (70)	NT	2.2 (91)	2.0 (91)
11	Heptanal (**8k**)	–CN	**10k**	12 (71)	6.0 (75)	NT	3 0 (87)	2.2(87)
12	**8a**	$–CO_2Et$	**10l**	21 (65)	6.2 (80)	NT	5.0 (89)	3.6 (90)
13	**8e**	$–CO_2Et$	**10m**	4.0 (75)	2.0 (80)	NT	0.6 (95)	0.3 (95)

[a] General reaction conditions: **8** (1.0 mmol), acrylonitrile (1.0 mmol), DABCO (0.1 mmol), micelle (CMC concentration), water (2 mL).
[b] Yields reported are isolated yields.
[c] NT = not tested.

Table 4
Results of MBH adducts of cyclic enones with various aldehydes with and without aqueous micelle **4** and **5**



S No	Cyclic enone	Aldehyde	MBH adduct[a]	Reaction without micelle time, h (yield %)[b]	Reaction with **4**; time, h (yield %)	Reaction with **5**; time, h (yield %)
1	**11a**	**8c**	**12a**	23 (65)	6.5 (83)	5.0 (83)
2	**11a**	**8e**	**12b**	19 (70)	5.0 (90)	3.3 (89)
3	**11a**	**8i**	**12c**	9.0 (73)	1.2 (95)	0.8 (92)
4	**11b**	**8c**	**12d**	29 (65)	9.0 (87)	6.0 (87)
5	**11b**	**8e**	**12e**	21 (69)	6.0 (95)	4.6 (89)
6	**11b**	**8i**	**12f**	24 (70)	1.5 (98)	1.0 (95)
7	**11b**	**8j**	**12g**	27 (60)	2.3 (92)	2.0 (92)
8	**11c**	**8c**	**12h**	61 (47)	23 (85)	16 (88)
9	**11c**	**8e**	**12i**	36 (58)	7.5 (85)	5.0 (82)
10	**11c**	**8i**	**12j**	36 (30)	4.0 (90)	2.8 (90)

[a] General reaction conditions: **8** (1.0 mmol), cyclic enone (1.0 mmol), DMAP (0.1 mmol), micelle (CMC concentration), water (2 mL).
[b] Yields reported are isolated yields.

stability of the enolate intermediate in the conjugate addition step of the reaction which is also supported by the fact that the reactions are much faster in cationic micellar aggregates than in anionic media.

In the case of cyclic enones, since the reaction works better when DMAP is used as the base, we synthesized the MBH adducts of **11a**, **11b** and **11c** under the established conditions using **4** and **5**. We were delighted to observe that the reactions work smoothly in all the three enones with various aldehydes (Table 4). It is to be noted that the MBH adduct, **12j**, derived from **11c** and **8i** was a pain in the neck in our earlier efforts.[16c] We were delighted to obtain this adduct **12j**, in just 4.0 and 2.8 h (yield, 90%) using **4** and **5**, respectively, compared to the reaction without micellar media in 36 h (yield, 20–30%). Besides, the protocol also works equally good for aromatic aldehydes having electron donating or electron withdrawing group/s attached.

In summary, we have developed an efficient and accelerated MBH reaction system in an aqueous cationic micellar media for acyclic conjugated alkenes and cyclic enones using **4** and **5**. The present method is a general strategy that holds promise for future use of MBH-adducts in total synthesis of natural products in an expeditious and green fashion. Efforts are also underway to investigate the detailed mechanism of this acceleration and to develop an enantio-selective variant of the reaction in a chiral micellar media.

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18. In a typical reaction procedure, a mixture of **11c** (110 mg, 1.0 mmol) and aqueous 37% solution **8i** (2.0 mmol) was added to an aqueous solution of **4** (at or above CMC; 2 mL). To this mixture, DMAP (12.2 mg, 0.1 mmol) was added and the reaction was stirred at ambient temperature till its completion, monitored by TLC. The crude reaction mixture was diluted with water and extracted with ethylacetate to yield the pure MBH adduct. Spectral data of representative compounds; compound **12j**: IR: 3433, 3056, 1653, 1263, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.80 (m, 4H), 2.47 (q, 2H, J = 8.0 Hz), 2.63 (m, 2H), 2.90 (br s, –OH), 4.23 (s, 2H), 6.77 (t, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz): δ 21.4, 25.2, 27.9, 43.0, 64.8, 141.7, 144.9, 205.6; ESI-MS, 163.18 [M+Na]; compound **10e**: IR: 3054, 2306, 1527, 1266, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.31 (br s, –OH); 6.03 (s, 1H), 6.13 (s, 1H), 6.16 (s, 1H); 7.57 (t, 1H, J = 7.5 Hz), 7.75 (t, 1H, J = 7.5 Hz), 7.86 (d, 1H, J = 7.6 Hz), 8.05 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz): δ 67.5, 114.6, 122.6, 123.5, 127.5, 128.2, 130.6, 132.6, 146.1, 151.7; ESI-MS, 227.06 [M+Na].