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Short communication

Cationic chiral surfactant based micelle-guided asymmetric Morita-Baylis-Hillman reaction

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ABSTRACT

Cationic chiral surfactant (*1R, 2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB) was utilized for the first time in inducing asymmetry to Morita-Baylis-Hillman reaction in aqueous medium. Proton NMR studies carried out to determine the locus of the reaction in micro-heterogeneous micellar environment, were found useful in proposing a plausible model for asymmetric induction. This work demonstrates that under such mild and non-hazardous reactions conditions, the reaction rates increase, good yields are favored and above all reasonable enantiomeric excesses are obtained.

1. Introduction

Morita-Baylis-Hillman (MBH) reaction is a powerful chemical transformation where simple starting materials are converted into highly functionalized molecular synthons in a catalytic process [1–2]. As a result this reaction has been applied to synthesis of natural products [3,4], biologically relevant heterocycles [5,6] and more importantly in synthesizing versatile chiral building blocks [7–9]. However, the reaction has traditionally suffered from low reaction rates leading to limited substrate scope, but recent developments have focused on improving rates [10–14] and changed its scope considerably. In our own efforts towards synthesizing natural products using MBH-adducts as building blocks, we also suffered with its sluggish reaction rates and lower yields [15–18]. It is important to mention that over the years many chiral catalysts have been employed to develop asymmetric versions of MBH-reaction to produce variety of chiral building blocks. The diversity of chiral catalysts tested include Lewis acids and Lewis bases, Bronsted acids, thioureas, bulky ammonium salts, ionic liquids, phosphines and many more bi-functional organocatalysts including proline [19–22].

During the endeavour to increase efficiency of chemical reactions, micellar catalysis is gaining considerable attention among scientific community owing to their efficient outcome and involvement of green protocols [23]. These micellar environments are considered to be the nano-reactors having unique features that include isolation of the substrates from bulk solvent, enhancement of organic species solubilization in water, increase the local concentration and reactivity of reagents and promote chemo- regio- & stereo-selectivities [23,24]. Keeping in view these features of micellar-guided reactions, we earlier developed an expeditious protocol for MBH-reaction that utilizes the cationic surfactant cetyltrimethylammonium bromide (CTAB) as catalyst enhancing its reaction kinetics substantially. A plausible model was proposed that explains the stabilization of enolate-intermediate in the conjugate addition step of MBH- reaction through the positive charge on the self-organized aggregates of these cationic micellar structures thereby driving the reaction faster. To further capitalize on the utility of the micelles as catalysts in MBH-reaction, we sought to develop a generalized, fast and enantioselective variant of this reaction with the use of an enantiopure cationic surfactant, (*1R,2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB) [25] which is expected to induce enantio-selectivity in addition to increase the reactions kinetics.

2. Experimental

2.1. Representative procedure for MBH reaction of 4-nitrobenzaldehyde with acrylonitrile in presence of chiral DMEB surfactant

The micellar solution was prepared by dissolving DMEB (100 mg, 0.22 mmol) in distilled water (4 mL) and the resulting solution was stirred for 20 min at room temperature. To this solution, 4-nitrobenzaldehyde (30 mg, 0.19 mmol), acrylonitrile (14 μL, 0.19 mmol) and DABCO (4 mg, 0.038 mmol) were added followed by continuous stirring till the reaction was over in 6 h. After the completion of reaction (monitored by TLC), the crude product was extracted with ethylacetate

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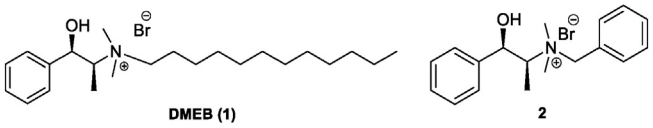
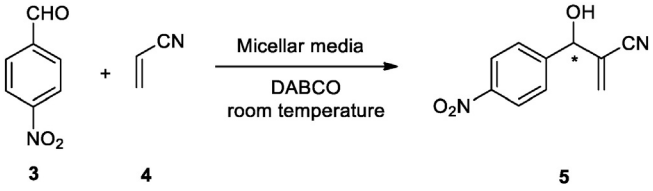


Fig. 1. Structure of ephedrinium slats, (*1R,2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide, DMEB (**1**) and (*1R, 2S*)-(−)-*N*-benzyl-*N*-methylephedrinium bromide (**2**) used in this study.



Scheme 1. MBH-reaction of 4-nitrobenzaldehyde with acrylonitrile in presence of DABCO and micellar medium.

(3 × 10 mL). The combined organic layer was dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography (60–120 mesh; eluent, 7:3 petroleum ether and ethylacetate).

3. Results and discussion

In light of the above discussion, we proposed that the chiral micellar environment could be the potential alternative strategy in carrying out the rapid asymmetric version of MBH-reaction. For this purpose, two ephedrinium based enantiopure salts were used to validate our concept. A well known and commercially available chiral surfactant, (*1R, 2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB), **1**, and its non-surfactant variant, (*1R, 2S*)-(−)-*N*-benzyl-*N*-methylephedrinium bromide, **2**, were used in this study (Fig. 1).

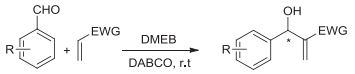
We initially attempted the reaction of 4-nitrobenzaldehyde and acrylonitrile in presence of DABCO in CTAB and proline mixture (Scheme 1). To our surprise, a marginal enantioselectivity was achieved in the MBH-adduct **5** with *ee* = 18% (entry 1, Table 1). We next utilized the chiral surfactant **1** for this reaction. In order to ensure the presence of micelles in the reaction medium we determined the critical micelle concentration (*cmc*) of DMEB in water using the surface tension method. The *cmc* of DMEB was obtained from the plot of surface tension vs logarithm of surfactant concentration and observed to be 4.11 mM. To our delight, it was observed that an aqueous micellar solution of **1** above its *cmc*, the enantiomeric excess (*ee*) of adduct **5** was enhanced upto 52% (Table 1, entry 2). In order to further confirm that the *ee* was achieved due to micellar micro-environment, the *ee* was also carried out in presence of a non-surfactant enantiopure ephedrinium salt **2**. It was interesting to observe that under these conditions, both *ee* and chemical yield of adduct **5** were poor (Table 1, entry 3).

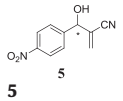
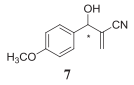
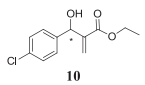
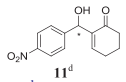
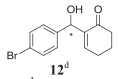
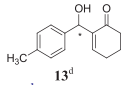
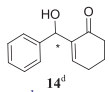
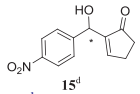
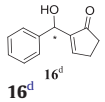
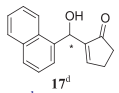
Table 1
Formation of MBH-adduct **5** under various conditions.

Entry	Conditions	Yield of 5	ee (%)
1.	CTAB + L-proline	70	18
2.	(*1R,2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide	72	52
3.	(*1R,2S*)-(−)-*N*-Benzyl-*N*-methylephedrinium bromide[a]	43	03

[a] In order to ensure the solubility of reactants under this reaction condition, THF:H_2O (1:1) were taken as the solvent for the reaction.

Table 2
Range of non-racemic MBH-adducts synthesized using DMEB as a chiral surfactant.



Entry	Product[a]	Reaction time in h	Percentage yield[b]	ee (%)
1	 **5**	6	72	56.0[c] (S)
2	 **6**	5	75	40.0[c] (S)
3	 **7**	37	70	42.0[c] (R)
4	 **8**	18	71	44.0[c] (R)
5	 **9**	15	70	44.0[c] (R)
6	 **10**	16	73	22.0[c] (R)
7	 **11**[d]	13	78	44.3[e] (S)
8	 **12**[d]	21	70	40.6[e] (S)
9	 **13**[d]	19	70	42.8[e] (R)
10	 **14**[d]	23	71	47.6[e] (R)
11	 **15**[d]	15	72	45.7[e] (R)
12	 **16**[d]	17	77	43.9[e] (R)
13	 **17**[d]	22	68	48.4[e] (R)

[a] All reactions were carried out in presence of aqueous solution of DMEB surfactant above its CMC at room temperature using DABCO as a catalyst.
[b] Yields reported are isolated yields.
[c] Enantiomeric excess (*ee*) of MBH- adducts were determined by chiral HPLC using a Chiralcel OD-H column.
[d] For the synthesis of adducts **11–17**, DMAP was used as a tertiary amine catalyst.
[e] Enantiomeric excess of adducts **11–17** were calculated from their specific rotation when compared to enantiopure adducts in literature and absolute configuration of all MBH-adducts were also assigned based on literature reports [9,26–29].

After optimizing the reaction conditions, a wide range of substrates were screened for carrying out the MBH-reaction under DMEB-micellar conditions in presence of DABCO as a catalyst. All the reactions showed a

marked enhancement in reaction kinetics as expected in cationic micellar media. It is to mention here that this MBH-reaction was carried out with a range of aldehydes (having electron withdrawing and electron donating groups) and electron deficient alkenes (including acrylonitrile, ethyl acrylate and cyclic enones), Table 2. All the reactions proceeded smoothly to deliver the corresponding MBH-adducts in descent yields with moderate to good *ee*. The *ee* of the MBH- adducts were determined either by HPLC using a Chiralcel OD-H column or based on specific rotation of known enantiopure MBH-adducts and their absolute configuration was assigned based on literature reports. It was generally observed that the *ee* of most of these MBH-adducts were on average 40% with compound **5** having the maximum *ee* of 56%. Further, it is to mention that the absolute configuration of most of the adducts were found to be *R* except adducts **5**, **6**, **11** and **12** that were found to have *S*-configuration (Table 2).

In order to understand the possible mechanism of induction of enantioselectivity in the reaction, we attempted to find the locus of the reaction in DMEB micellar environment using the NMR technique.

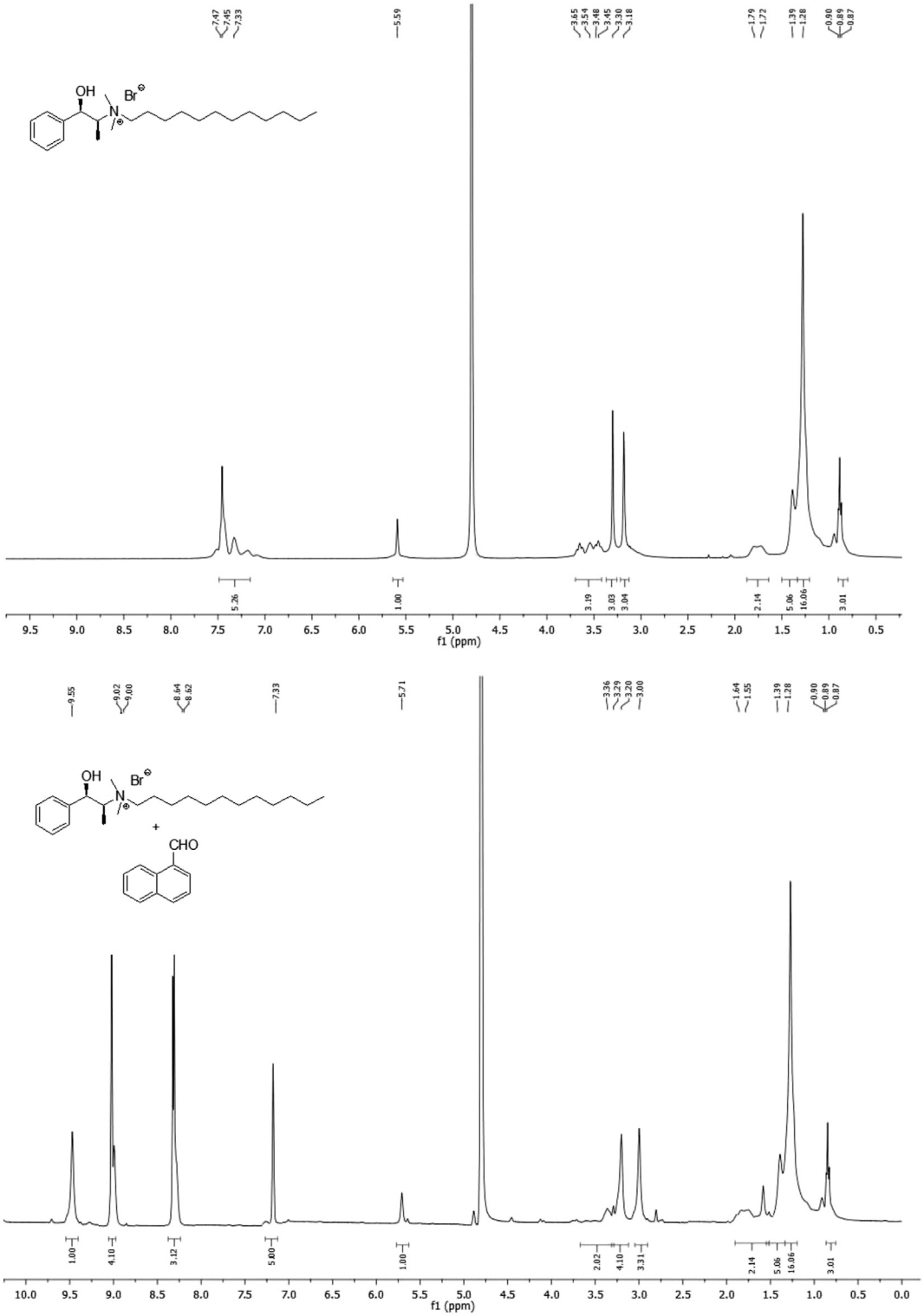


Fig. 2. Proton NMR of DMEB in D_2O (top) and proton NMR of DMEB + naphthaldehyde (1:1 ratio) in D_2O (down).

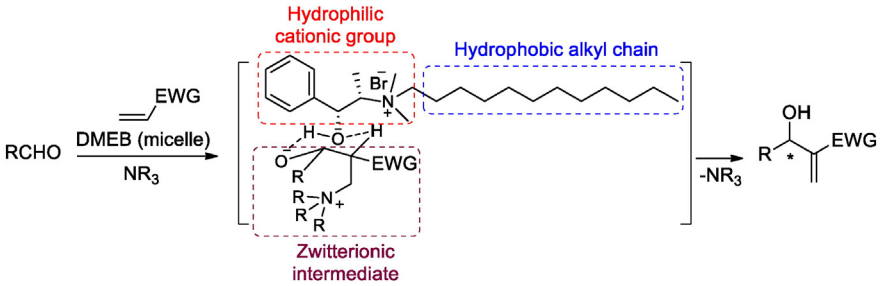


Fig. 3. Plausible explanation of the role of DMEB (**1**) in asymmetric induction in presence of tertiary amine base.

It is to note here that the interaction between catalyst, substrate and micellar aggregates could be efficiently determined by the NMR studies [30]. Examination of the change in chemical shift of the surfactant and the analyte in the solutions of increasing relative concentration provides reliable information about portions of the molecules which interact [31–33]. In this conception, we recorded the proton NMR of DMEB in D_2O in presence and absence of model substrate, naphthaldehyde (Fig. 2). Our analysis of the proton NMR spectra of DMEB and DMEB + naphthaldehyde (1:1 ratio) in D_2O indicated that there is a significant change in chemical shift of protons on ephedrinium moiety of DMEB in presence of naphthaldehyde. For example, the hydroxyl attached proton of DMEB shifted from δ 5.59 to δ 5.71 in presence of naphthaldehyde. Similarly the protons on aromatic ring δ 7.33–7.47 (multiplet) merged to δ 7.33 (singlet). These are the strong evidences that the naphthaldehyde finds itself near the polar head group of DMEB surfactant where it reacts with activated olefins to deliver the non-racemic MBH-adducts guided by the chirality of the surfactant head group.

Based on these observations and in light of the literature evidence [34,35] we finally attempted to assign the plausible enantioselective model of this reaction in DMEB environment. In presence of a DMEB micellar solution, the water insoluble compounds enter into the micellar structure. In this environment, the hydroxyl group of the micelle **1** stabilizes the zwitter-ionic intermediate generated after the Michael addition of the tertiary amine base over an activated olefin and subsequent reaction of the zwitterionic adduct with electrophile by means of hydrogen bonding interactions (Fig. 3). The stabilization of the zwitterionic intermediate in the micellar phase leads to an increase in the rate of both the electrophile addition and proton transfer steps in addition to being guided by the chirality of the ephedrinium head group of the surfactant, consequently delivering the non-racemic MBH-adducts rapidly.

4. Conclusion

In conclusion, we developed a rapid and generalized strategy in generating non-racemic MBH-adducts using chiral DMEB surfactant. Proton NMR studies suggest that the reaction occurs near the polar head group of DMEB micellar media that was helpful in predicting the plausible enantioselective model for this reaction. The outcomes of these results are expected to be useful in designing the better catalysts based on surfactants for asymmetric MBH-reaction in future studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2016.05.010.

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