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An efficient and simple Morita–Baylis–Hillman reaction based on the *N*-methylpyrrolidine–$Ba(OH)_2$ catalytic system

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ABSTRACT

By using of precise catalytic amount of *N*-methylpyrrolidine (5 mol %) and $Ba(OH)_2$ (1.5 mol %) in H_2O/CH_3OH 5/1 or CH_3OH/CH_2Cl_2 3/1 solvent mixtures at T=0 °C a Morita–Baylis–Hillman derivatives could be obtained in good to excellent yield from 2-cyclopenten-1-one, 2-cyclohexen-1-one and formaldehyde and diverse aryl aldehydes after suitable reaction time.

1. Introduction

The Morita–Baylis–Hillman reaction (MBH) has been recognized as important coupling protocol between the electrophiles and activated alkenes promoted generally by nucleophilic catalysts.[1,2] Enormous scientific efforts have been made to develop a number of effective promoters and physical methods enlarging the substrate scope.[3] The striking challenges to find the optimal catalysts and conditions for MBH reaction with cyclic enones have motivated many remarkable investigations.[4–7]

The MBH reaction allowed an atom economy and a formation of chemospecific functional groups in closeness to the α-alkylene-β-hydroxyl product. Newly the popularity of MBH protocol was growing due to a broad range of reaction scope, cost-effective starting materials and a facility to be applied on complex synthetic routes exploring the reactivity of formed allylic alcohols.[8] The modern development of asymmetric and aza-MBH reactions was investigated the stereoselective C–C bond formation under mild conditions with a main array of alkenes and imines, tosylimines, α-ketoesters, fluoroesters, and π-deficient olefins in addition to aldehydes.[3e,9–11] Recently the intrinsic mechanism of MBH reaction was disclosed successfully.[12–15] The new frontiers for the evolution of forward methodologies for multicomponent reactions and rationalized syntheses of important natural and medicinal products become more discernible.[16]

Our motivation to investigate the classical MBH reaction with cyclic enones becomes from the requirement of a large amount of the 2-(hydroxymethyl)-2-cyclopenten-1-one, key starting material for the synthesis of particular medicinal compounds with carbocyclic ring.[17] The simple but demanding reaction between 2-cyclopenten-1-one and aqueous HCHO could offer rapidly direct access to 2-(hydroxymethyl)-derivative in aqueous media. The application of this MBH protocol increases even under difficult synthetic circumstances and a high yield of MBH hydroxymethyl derivative is a prerequisite for feasible and successful realization of various total synthetic routes.[18,19] The particular industrial scale-up processes for a preparation of important drugs, such as sampatrilat claimed for a simple, economical, efficient and environmentally clean catalytic system promoting a formation of 2-(hydroxymethyl)-enone derivatives.[20] In fact the reported MBH methods based on the different catalysts reveal a number of deficiencies, for example: a low yield and or long reaction time[21–24] or use of hazardous and expensive catalysts such as the phosphine derivatives and others.[25,26] The historical background call attention to the important unsolved problems correlated with MBH reaction between activated cyclic enones and formaldehyde. Here we described the development of capable, low-costing, and environmentally friendly methodology for the MBH reaction with activated

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alkenes as a 2-cyclopent-1-one and 2-cyclohexen-1-one and 36% aqueous solution of HCHO.

2. Result and discussion

2.1. Screening of various additives for promoters

Initially we selected more of 50 inorganic and organic environmentally clean and available compounds (Lewis acids and bases, nucleophilic amines, cinchona derivatives, etc.) that could act as efficient and unexplored promoters of the MBH reaction between 2-cyclopenten-1-one (**1**) and 36% aqueous solution of HCHO. The DMSO was used as polar aprotic medium exploring its property to accelerate the MBH reaction by stabilization of the ionic transition states.[12,27] The additives were tested by TLC studies and the obtained yield of 2-(hydroxymethyl)-2-cyclopenten-1-one (**2**) with every single one additive was calculated from following HPLC analysis. All results are listed on the Table S1 of Supplementary data (SD). The best ones are shown on the Table 1.

Table 1
Selected promoters of studied MBH reaction[a] (TLC and HPLC analysis)

Entry	Additive	Time (h)	Yield[b] (%) of **2**
1	NMP	25 h	21.3
2	Li_2CO_3	17 days	7.6
3	$Ba(OH)_2$[c]	0.5 h	6.2[d]
4	CH_3ONa[e]	48 h	6.0

[a] Reaction conditions: 2-cyclopenten-1-one (**1**) (10.5 μL, 0.12 mmol), 36% aqueous HCHO (11 μL, 0.144 mmol), additive (30 mol %) in 0.25 mL of DMSO, T=25 °C.
[b] Based on HPLC analysis.
[c] Solvent $CH_3OH/CHCl_3$, 3/1.
[d] Precipitate formation.
[e] T=25–40 °C.

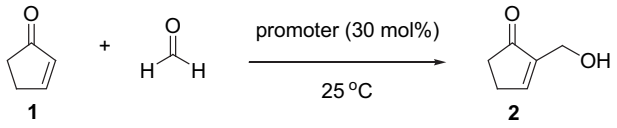
Table 1 provided the vital initial information: from all tested additives an NMP (*N*-methylpyrrolidine) revealed superior promoter's activity of studied MBH reaction and furnished the product **2** in 21.3% yield (entry 1). Li_2CO_3 was inefficient as promoter (entry 2) while the reaction with $Ba(OH)_2$ ran faster but in fact a precipitate formation at the beginning of the reaction (half hour) apparently suppressed an increase of yield of **2** with the time (entry 3). The additive CH_3ONa which is a known catalyst for MBH reaction in CH_3OH[4e] was ineffective in our experimental conditions. We decided to carry on the studies with NMP and $Ba(OH)_2$ as potential promoters of investigated MBH reaction.

2.2. Tuning of a solvent and a mole equivalent of 36% aqueous HCHO

Then a type of solvent and amount of 36% HCHO used on the MBH reaction, promoted by each of two selected previously additives, were investigated. The total data of realized experiments is given on the Table S2 of SD while the selected ones are presented on Table 2.

The MBH reaction was performed in three different solvents namely CH_3OH, H_2O, and DMSO, keeping the amount of promoters at 30 mol %. CH_3OH and H_2O were selected for the reaction solvents taken into account their properties. A protic media (H_2O) could help to reduce the barrier for the proton transfer and accelerate the reaction moreover the hydrogen-bond donors as a H_2O and CH_3OH activate the reaction allowing the proton-transfer step from the α-position to the alkoxide of intermediate.[12,14,27] After a comparison of evolution of yields of **2** and $\mathbf{1^R}$ (unconverted substrate) depicted on Table 2 (entries 2, 5 and 6) with (entry 4), H_2O and CH_3OH were selected as solvents of choice in studied reaction

Table 2
Initial optimization of the reaction conditions[a]



1 **2**

Entry	Promoter	Solvent	36% HCHO (mol equiv)	Time	Yield[b] (%)	
					2	$\mathbf{1^R}$
1[c]	$Ba(OH)_2$[c]	CH_3OH	1.2	20 min	24	3.4
2	NMP	CH_3OH	1.2	15 h	41	38
3	NMP	CH_3OH	5	4 h	31.4	11.5
4	NMP	DMSO	1.2	4 h	2.8	38
5	NMP	H_2O	1.2	40 min	23.4	14.6
6	NMP	H_2O	1.2	3 h	25	13.8

$\mathbf{1^R}$ Unconverted substrate.
[a] Reaction conditions: see footnote ([a]) of Table 1.
[b] Calculated from HPLC analysis.
[c] Precipitate formation.

conditions. The inferior yields of **2** and $\mathbf{1^R}$ were observed when 5 mol equiv of 36% HCHO were used (compare entries 3 and 2). These results could due to the formation of side products created by the excess of formaldehyde. The optimal enone/formaldehyde ratio for production of **2** was 1:1.2 mol equiv. The precipitate formation in water was observed on the reactions with 30 mol % $Ba(OH)_2$ (see Table S2 of SD). The reaction with promoter NMP was faster in water (entries 5 and 6) than in CH_3OH (entry 2) although the yield of $\mathbf{1^R}$ found on the reaction mixture after 40 min or 3 h was lower than this after 15 h (entry 2). We understand that NMP at 30 mol % in water might promote also other non MBH reaction pathways and a substrate **1** was spent on the formation of side products.

The experimental data at this point of investigation revealed an increment of yield of **2** (from 21% to 41%) in protic media (H_2O, CH_3OH) using the following MBH reaction conditions: 1.2 mol equiv of 36% HCHO, 30 mol % of promoter, at T=25 °C and reaction time from 20 min to 15 h.

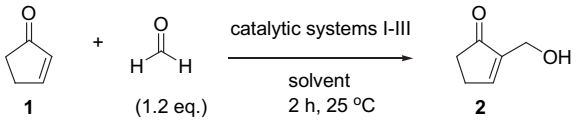
2.3. Fine tuning of the catalytic system

With these results in the hands we investigated how the quantity of promoter influenced the modification of yield of **2** and $\mathbf{1^R}$ testing the mixtures of NMP and $Ba(OH)_2$ in H_2O/CH_3OH 5/1, H_2O/CH_3OH 1/3, H_2O/CH_3OH 1/1, and respectively in each solvent alone. The MBH reaction was carried out at T=25 °C for 2 h varying a mol % of promoter (s) on an individual system or a promoter alone. To each reaction mixture was added a reaction rate accelerator NaI[28] in different concentrations. Full data of the experimental results is listed on Table S3, SD while the selected ones are presented on Table 3 to help the discussion. After a careful examination of the obtained data at this point of studies, we accomplished the following conclusions:

The best yield of **2** was attained in H_2O/CH_3OH 5/1 reaction medium (see Table 3, entries 1–3). The promoter system NMP/$Ba(OH)_2$, 5/1.5 mol %, (**III**) was a superior (entry 3) achieving 65% yield of **2** with 26.4% of $\mathbf{1^R}$ for 2 h reaction time. The substrate **1** was almost completely spent only on the MBH derivative formation. The catalytic amount of $Ba(OH)_2$ in system **III** was optimal. For example a promoting MBH reaction system NMP/$Ba(OH)_2$ 5/3 mol % attained only 51% yield of **2** (entry 5). Most likely $Ba(OH)_2$ acted as a base and/or a nucleophile.[29]

Apparently, the system NMP/NaI/$Ba(OH)_2$ 50/22/3 mol %, (**I**), (entry 1) was able to get 70% yield of **2** nevertheless almost 20% of initial substrate amount was depleted and only 10% of $\mathbf{1^R}$ was found in the reaction mixture after 2 h reaction time. A precipitate was observed on the reactions with system **I** in all solvent mixtures or

Table 3
Final fine tuning of the studied catalytic systems: promoters and additive (mol %) in varied solvent mixtures proportions[a]



Entry	Catalytic system	NMP	NaI	$Ba(OH)_2$	Yield[b] (%)	
					2	$\mathbf{1^R}$
H_2O/CH_3OH 5/1						
1[c]	**I**	50	22	3	70	10
2	**II**	5	5	1.5	69	17.5
3	**III**	**5**	—	1.5	65	26.4
4		5	—	—	64	24
5		5	—	3	51	12
H_2O/CH_3OH 1/3						
6	**II**	5	5	1.5	49	18
7	**III**	5	—	1.5	46.4	17
8[c]	**I**	50	22	3	41	13
H_2O/CH_3OH 1/1						
9	**II**	5	5	1.5	52	24.6
10[c]	**I**	50	22	3	40	11
H_2O						
11	**III**	5	—	1.5	21.5	24.1
12	**II**	5	5	1.5	14.6	15.3
13[c]	**I**	50	22	3	9.5	12.5

[a] See footnote ([a]) of Table 1, 2 h reaction time at T=25 °C.
[b] Determined by HPLC analysis.
[c] Precipitate formation.

solvents alone. The system NMP/NaI/$Ba(OH)_2$ 5/5/1.5 mol %, (**II**), (entry 2) showed better than the system **III** performance with 69% yield of **2** but about 14% of the total substrate amount was employed in the formation of side products. And finally, the additive NaI does not induce significant acceleration of the reaction or (and) enhance of yield of **2**.

2.4. Preparative synthetic studies

Three promising values of the yield of **2** in solvent mixture H_2O/CH_3OH, 5/1: (70%) using system **I**, (69%) with system **II** and (65%) attained by system **III** were achieved by the presented above HPLC optimization of studied MBH reaction. The following step was to employ preparative synthetic studies using these three catalytic system and others for comparison in order to validate or discard some of provided by HPLC results.

Full data of all fulfilled independently preparative syntheses of **2** at different substrate scales' employing the catalytic system **I**, **II**, and **III** and others was presented on Table 4.

The best isolated yield of **2** at T=25 °C was 67%, using system **III** (Table 4 entry 6). Next the MBH reaction was carried out at T=0 °C to validate the temperature control on a formation of **2** under our reaction conditions. In the initial synthetic experiment we isolated 88% yield of **2** after 5 h reaction time (entry 8). The fine tuning of the reaction time was done by carefully performed HPLC studies of six individual samples provided from separated MBH reactions carried out at diverse times at T=0 °C. The correlation of calculated from HPLC yields of **2** and $\mathbf{1^R}$ in function of reaction time is presented on Fig. 1 showing a non linear relationship with max of yield of **2** at 8 h.

During the described HPLC improvement of the reaction conditions we observed the formation of unknown side products under MBH conditions (see Fig. S5, SD). There are seen two anonymous peaks at 7.98 (7.47) and 9.63 (9.35) min. Their intensities at T=25 °C are stronger than these at T=0 °C. In fact, the last temperature

Table 4
Preparative syntheses of **2**[a]

Entry	Catalytic system or individual promoter (mol %)	**1**, g (mmol)	Time (h)	T °C	Isolated yield (%) of **2**
1	**I**	0.20 (2.4)	2	25	50[b,c]
2	**I**	0.20 (2.4)	16	25	48[b,c]
3	**II**	0.30 (3.6)	9	25	57[b]
4	**II**	0.20 (2.4)	2	25	63[b]
5	**III**	0.20 (2.4)	2	25	53[b]
6	**III**	0.40 (4.8)	6	25	67[b]
7	**III**	0.30 (3.6)	18	25	59[b]
8	**III**	0.20 (2.4)	5	0	88[b]
9	**III**	0.20 (2.4)	6	0	93[d]
10	**III**	0.60 (7.3)	8	0	94[d,e]
11	**III**	0.20 (2.4)	10	0	90[d]
12	**III**	1.00 (12.0)	8	0	94[d,f]
13	**III**	3.00 (36.5)	8	0	93[g](90)[d]
14	**III**	5.00 (60.9)	9	0	91[g](88)[d]
15	**III**	10.00 (121.8)	8.5	0	90[g](87)[d]
16[h]	NMP (30)	0.30 (3.6)	15	25	49[b]
17[h]	NMP (30)	0.20 (2.4)	10 days	25	42[b]
18	NMP (5)	0.20 (2.4)	2	25	49[b]
19	NMP (5), $Ba(OH)_2$ (0.75)	0.20 (2.4)	2.5	25	61[b]

[a] Unchanged reaction conditions were: 1.2 mol equiv of 36% HCHO and H_2O/CH_3OH, 5/1 as solvent.
[b] Isolated yield after chromatographic purification.
[c] Precipitate formation.
[d] Isolated yield without using chromatography.
[e] The degree of purity determined by ^1H NMR and ^{13}C NMR spectra and HPLC chromatography(see Fig. 2).
[f] Using formaldehyde aqueous solution, containing precipitate of para-formaldehyde, **2** was isolated in 86% yield.
[g] Overall yield (see procedure C, Experimental section).
[h] CH_3OH as solvent was used.

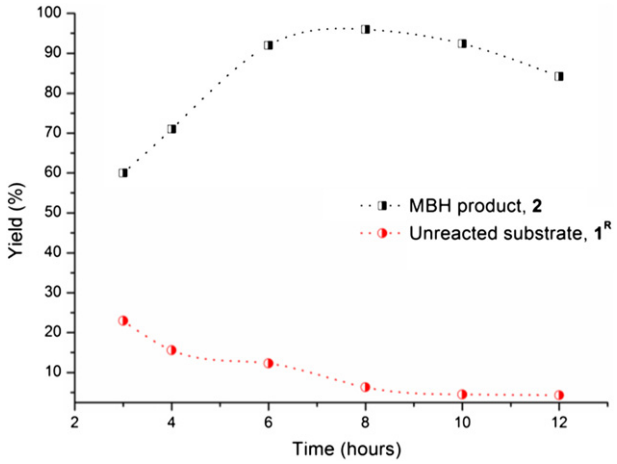


Fig. 1. Correlation between yield (%) of **2**, $\mathbf{1^R}$ and a time of reaction at T=0 °C (HPLC data).

suppressed a formation of side products thus increases the possibility of realization of MBH reaction pathway.

The isolated yield of **2** with 6 h reaction time was 93% and respectively 94% at 8 h, without using chromatographic purification (Table 4, entries 9 and 10) and (Fig. 2).

A number of preparative synthetic experiments in substrate scale 0.60–10.00 g (7.3–121.8 mmol) with catalytic system **III** were performed exploring optimized from HPLC studies data (8 h reaction time and T=0 °C) and the obtained results are presented on Table 4 (entries 10, 12–15). About 100% conversation of **1** were observed using different scales. For our gratefulness the investigated MBH reaction exhibited very good reproducibility when **1** was employed in gram scale. A principal amount of **2** (87–94%)

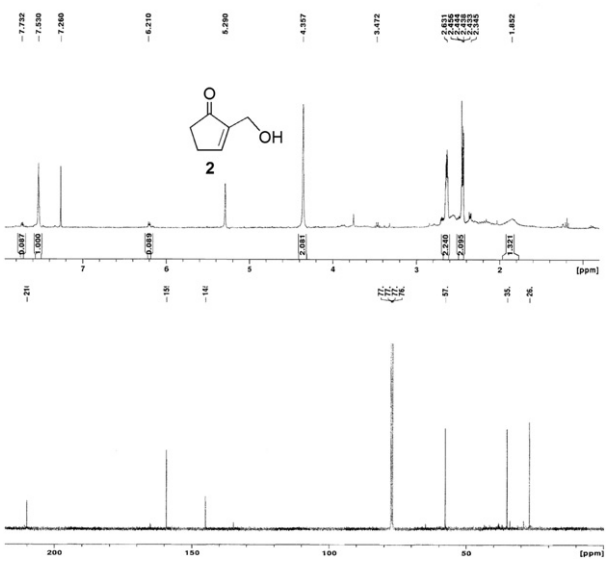


Fig. 2. Typical ^{1}H and ^{13}C NMR spectra of **2** obtained devoid of chromatographic purification (Table 4, entry 9–15).

was achieved devoid of chromatography (entries 12–15), see also Fig. 2. The purification of remaining after extraction aqueous layers furnished about 3% of MBH adduct (see Procedure 3 of Experimental part). The new miscellaneous catalytic system **III** in our experimental MBH conditions took the equal reaction time (8–9 h) to transform 0.60 g or 10.00 g of substrate to MBH adduct and also could work well with relatively uncertain formaldehyde concentration (see Table 4, entry 12, footnote [(f)]). Truly the cooperative catalytic system **III** in our adjusted MBH conditions demonstrated robustness on the preparative synthetic experiments in large scale.

The better results reached at T=0 °C might due to the higher efficiency of catalytic system **III** as catalyst of desirable MBH reaction at this temperature range in detriment to other reaction pathways. Leahy et al. observed enormous acceleration of MBH reaction with methyl acrylate and different aldehydes at T=0 °C using DABCO or Bu_3P catalysts.[30] The phenomenon was explained with the existence of different populations of purported intermediates enolate species at room temperature and T=0 °C.

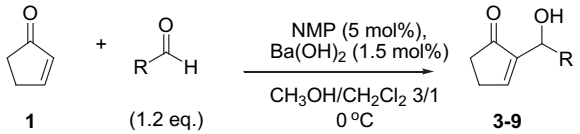
At the best of our knowledge only two methods reported the similar yields of an MBH adduct obtained on the reaction between **1** and 36% HCHO: 86% for 17 days, using 5 mol % imidazole[22] and 97% for 1 h employing 5 mol % Me_2PhP[25] as catalysts.

The verification of a reproducibility of the reported methods in our conditions and the results of these experiments together with a data from the literature are presented on (Table S4, SD). The reaction with a phosphine catalyst was shown a good reproducibility however this type of catalyst has an intrinsic chemical instability (it's difficult to manipulate and maintain) and is harmful. Due to the last reason the scope of its application in a total synthesis of medicinal drugs is very limited and required the use of chromatography thus increasing the anticipated high cost of this catalyst in scale-up processes.

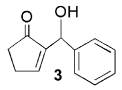
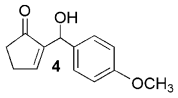
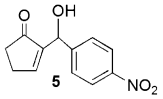
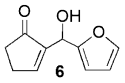
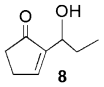
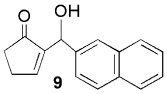
2.5. Preparative synthesis of aryl MBH derivatives

The optimal catalytic system **III** in H_2O/CH_3OH, 5/1, worked very well under MBH conditions with **1** and 36% HCHO. Besides the catalytic system **III** was developed and attuned for the preparation of the important building block **2**, we explored the possibility to apply this methodology to aryl and alkyl aldehydes (Table 5). All details and the comparison of our results with reported methods are listed on Table S5, SD. The reaction scope of catalytic system **III** included also

Table 5
MBH reaction of cyclopentenone **1** with representative aryl and alkyl aldehydes



1 (1.2 eq.) **3-9**

Entry	BH product	Time (h)	Yield (%)
1	 **3**	9	73
2	 **4**	50	83
3	 **5**	4	65
4	 **6**	18	85
5	 **7**	2[a]	46
6	 **8**	6	40
7	 **9**	14[a]	67

[a] T=25 °C.

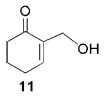
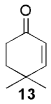
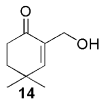
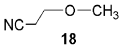
less active than HCHO electrophiles, such as aryl aldehydes even in CH_3OH/CH_2Cl_2 3/1 solvent mixture. The achieved yields with the different types of aldehydes are similar to the best reported on the literature. However some important differences were observed. For instance, system **III** exhibited the selective behavior under employed working reaction conditions with *p*-nitrobenzaldehyde, *p*-methoxybenzaldehyde, and 2-furylaldehyde (Table 5, entries 2–4). The MBH derivative of *p*-nitrobenzaldehyde (**5**) was attained in 65% yield which was a bit lower compared with the reported ones (Table S5 of SD). Contrary, the *p*-methoxybenzaldehyde containing the electron-donating group reacted slowly but **4** was furnished in 83% as a sole product (Table 5, entry 2). The 2-furylaldehyde reacted relatively fast with **1** at T=0 °C (18 h, Table 5, entry 4) and the obtained good yield of **6** (85%) could be compared with the best reported using imidazole as catalyst (84%), obtained for longer reaction time (70 h)[24] also see Table S5, SD. Interestingly, with the hindered 2-naphthylaldehyde after 14 h at T=25 °C from the reaction mixture was isolated the MBH product **9** in 67% yield, (Table 5, entry 7) and also unconverted substrate in 24% yield. The catalytic system **III** was fairly efficient with the aliphatic aldehydes providing **7** and **8** in 46% and 40% yields, respectively (Table 5, entries 6 and 7 and Table S5, SD) for comparison.

2.6. MBH reaction with other cyclic enones

The preparative synthetic experiments with selected cyclic enones were carried out in the solvent mixture H_2O/CH_3OH 5/1

to determine the substrate scope of optimum catalytic system **III**. The system **III** promoted satisfactorily MBH reaction with **10** and at T=0 °C and **11** was produced at 89% yield (Table 6, entry 1A) well-matching with a number of reported results (see Table S6 of SD).

Table 6
MBH reaction with different cyclic enones and acyclic Michael receptors and formaldehyde, using NMP/$Ba(OH)_2$ mixed catalytic system[a]

Entry	Substrate	Catalytic system (mol %)	Time (h)	Products	Isolated yield (%)	
					11, **14**	Recovered substrate
1A[a]	 **10**	**III**	24	 **11**	89[c]	—
1B[a]		**III**	16	11	73	—
2	 **12**	NMP (15), $Ba(OH)_2$ (7.5)	12	—	—	80
3A[b]	 **13**	NMP (15), $Ba(OH)_2$ (7.5)	30	 **14**	42	15
3B[b]		NMP (30), $Ba(OH)_2$ (3)	30	14	36	17
4A	 **15**	**III**	15	—	—	—[d]
4B	 **15**	**III**	7	 **18**	98	—
5	 **16**	**III**	72	—	—	100
6	 **17**	**III**	8	—	—	100

[a] Reaction conditions: 36% aqueous HCHO (1.5 mol equiv), H_2O/CH_3OH 5/1, T=25 °C.
[b] Aqueous HCHO (2.0 mol equiv, 36%).
[c] T=0 °C.
[d] Decomposition of the substrate.

The 4,4-dimethyl-2-cyclohexen-1-one (**13**) reacted slowly with 2 mol equiv HCHO and **14** was isolated in 42% yield. Luo et al. also reported moderate yields (17–37%) of aryl derivatives of **13**.[4e] Other researcher group has been investigated the MBH reaction with 5,5-dimethyl-2-cyclohexen-1-one and HCHO employing DMAP and SDS as co-catalytic system. They attained fairly good (53–63%) yield of MBH derivative.[31] Both groups imputed a sluggishness of the reaction and reached yields of MBH derivatives to the relatively hindered structure of cyclic alkenes.

The MBH reaction did not work with 3-methyl-2-cyclopenten-1-one (**12**) and 1.5 equiv HCHO employing the catalytic system NMP/$Ba(OH)_2$ (Table 6, entry 2). This absence of reactivity was in line with the reported data observed for 2-cyclohexen-1-one analogs.[21] The lack of a formation of MBH product derived from **12** indicated that the MBH pathway was interrupted by steric effect at β-position of 3-methyl-2-cyclopenten-1-one. Thus the nucleophilic tertiary amine catalyst (NMP) could not undergo a 1–4 addition as a first step of MBH reaction.[12–14]

2.7. MBH reaction with acyclic Michael acceptors

We studied also the MBH reaction between activated acyclic alkenes, such as acrylonitrile (**15**), ethylacrylate (**16**), and methyl vinyl ketone (**17**) and 36% HCHO under catalytic action of system **III** in H_2O/CH_3OH, 5/1 and CH_3OH/CH_2Cl_2 3/1 (see details in Table 6, entries 4–6).

The MBH products of **15**, **16**, and **17** were not observed. Compound **15** underwent 1–4 addition in CH_3OH/CH_2Cl_2 (3/1) originating 98% yield of respective 3-methoxypropanenitrile (**18**) (entry 4B).

The experiments with activated acyclic alkenes identified **III** as a specific catalytic system for MBH reaction involving cyclic enones. However this type of limitation of the substrate catalytic scope corresponding to the acyclic alkenes was observed also for the catalytic mixed system DMAP/TMEDA/MgI_2.[7] In this context our catalytic system might address the longstanding problem of addition to acyclic enones and enoates. Recently have been published some work in this field.[32]

3. Conclusions

The classical MBH reaction involving aqueous 36% HCHO and a number of cyclic enones was explored. The discovery and fine tuning of the new miscellaneous catalytic system NMP/$Ba(OH)_2$ 5/1.5 mol % (**III**) was supported by detailed analytic HPLC and preparative synthesis studies. The efficiency of the novel system is strongly dependent of a precise catalysts loading, solvents media, the temperature and the reaction time. The system **III** promotes very efficiently MBH reaction with 2-cyclopenten-1-one (**1**) and 36% HCHO at T=0 °C in H_2O/CH_3OH 5/1 solvent mixture in range 0.20–10.00 g of **1** and 2-(hydroxymethyl)-2-cyclopent-1-one (**2**) was isolated in 90–94% total yield. The catalytic system **III** promotes well the MBH reaction with other cyclic enones, such as 2-cyclohexen-1-one and some low reactive aryl aldehydes.

The resourceful, cost-effective and environmentally sustainable synthetic methodology for the preparation of MBH hydroxymethyl adducts of cyclic enones exploring a new mixed catalytic system NMP/$Ba(OH)_2$ was described. The methodology could consist of benefit for the synthetic organic chemists[37] to be applied on the total syntheses of pharmaceutical drugs and biologically active natural compounds.

In our present work we are studied the asymmetric functionalization of 2-hydroxymethyl cyclopentenone derivative (**2**), which is a key step of the synthesis of important pharmacologically active molecules.

4. Experimental

4.1. General remarks

Dichloromethane (CH_2Cl_2), ethyl ether (Et_2O), and methanol (CH_3OH) were freshly distilled prior to use. Ethyl acetate (EtOAc) was distilled over potassium carbonate. The water used for HPLC studies was a Mili-Q grade and the acetonitrile was HPLC grade. The preparative thin layer chromatography plates were prepared with silica gel 60 GF_{254} Merck (Ref. 1.07730.1000) while the flash chromatography were carried out on silica gel 60 M purchased from MN (Ref. 815381). Reaction mixtures were analyzed by TLC using ALUGRAM® SIL G/UV254 from MN (Ref. 818133, silica gel 60), and visualization of TLC spots was effected using UV and ninhydrine (2,2-dihydroxyindane-1,3-dione) or phosphomolybdic acid (PMA) solutions. The additives used on TLC and HPLC scanning studies were purchased from Aldrich, Merck and Fluka and used without further purification. The 36% aqueous solution of HCHO with methanol as stabilizer was purchased from Fluka and Merck. The 2-cyclopenten-1-one and 2-cyclohexen-1-one were obtained from

Aldrich and Alfa Aesar while 4,4-dimethyl-2-cyclohexen-1-one, *N*-methylpyrrolidine, $Ba(OH)_2.8H_2O$, 4-nitrobenzaldehyde, furan-2-carbaldehyde, 2-naphthylaldehyde, and propionaldehyde were purchased from Aldrich. Acetaldehyde was obtained from Merck and used as received. The benzaldehyde, 4-methoxybenzaldehyde, 2-furylaldehyde, acrylonitrile, ethylacrylate, and methyl vinyl ketone, were obtained from Aldrich and used after purification by distillation under vacuum. NMR spectra were recorded in a Bruker AMX 400 using $CDCl_3$ as a solvent. All coupling constants are expressed in Hz. The HPLC studies were done on the Shimadzu Prominence system apparatus using the C_{18} Kromasil 100 5 μm column, 250×4.6 mm and 5% of CH_3CN in Mili-Q water to mobile phase. The SPD-20A UV–vIS detector was used with sensitivity to the limit (Noise level 0.5×10(-5) AU), wide linearity (2.5AU), and Wavelength range: 190–700 nm.

4.2. General procedure for the MBH reaction by TLC screening (Table 1 and Table S1, SD)

The MBH reactions were performed on the home-made carousel reaction station apparatus in respective size reaction-flasks using 0.12 mmol (10 mg, 10.5 μL) of 2-cyclopenten-1-one (**1**) and 0.14 mmol (11 μL) of aqueous formaldehyde in 0.250 mL of different solvents. For every one reaction a 30 mol % catalytic amount of each respective additive was employed. The vials were emerged in oil bath with controlled temperature. The reaction time varied from minutes to 2–3 h or more as the major amount of substrate was disappeared and the formation of the MBH product was considerable, observed by TLC using the mixture of EtOAc/hexane 9/1 as eluent.

4.3. General procedure for the MBH reaction by HPLC screening (Tables 1 and 2, Tables S2 and S3, SD)

Those experiments were performed on the basis of prior TLC screening. Then from each reaction were taken 10 μL of reaction solution and dissolved in 1 mL H_2O (Mili-Q)/acetonitrile, 95/5. From these solutions 20 μL were injected on the Shimadzu Prominence system apparatus with the C_{18} Kromasil 100 5 μm column, 250×4.6 mm and 5% of CH_3CN in water as a mobile phase was used. The detection of the analyzed samples took place at 206 nm. The flow rate employed was 0.7 mL/min. In these experimental conditions the retention time (t_R) observed for the MBH product (**2**) was between 17 and 18.5 min and respective one for the 2-cyclopenten-1-one (**1**) was between 23 and 24.5 min depending of the column equilibrium and temperature. The column temperature was room temperature (approximately 25 °C). To obtain the reproductive results before HPLC analysis daily was done 'black' flush with the used working solvent gradient. The daily work was slighter than 10 h and at a finish of the work the column was cleaned with used as eluent solvent gradient of Mili-Q water and acetonitrile. The time between each injection was 10–15 min. The routine sample calculations were based on the comparison of peak areas of MBH product and 2-cyclopenten-1-one, with external standard peak area from previously obtained calibration curves at equal working conditions. Six samples with the concentration from 0.0036 to 0.0001 mg of the 2-cyclopent-1-one **1** were used while the samples for the BH product **2** were seven with the concentration between 0.005 and 0.0003 mg. Each calibration curve was obtained based of the ratio area of respective peak and concentration on the sample.

4.4. General procedures for the preparative synthetic MBH reaction between 2-cyclopenten-1-one (1) and 36% aqueous solution of HCHO (Table 4). Spectral data for (2)

Procedure A (Table 4, entries 1–7): To a mixture of $Ba(OH)_2$ (0.023 g, 1.5 mol %) and *N*-methylpyrrolidine (25.5 μL, 5 mol %) in 5/1 mixture of H_2O/CH_3OH (9 mL) were added sequentially 36% aqueous solution of HCHO (0.460 mL, 6 mmol) and 2-cyclopenten-1-one (**1**) (0.410 mL, 4.9 mmol) (entry 6). The resultant mixture was stirred at T=25 °C (water bath). Upon completion of 6 h reaction time the reaction was quenched with 1 N HCl until pH 3. To the mixture was added NaCl (10 g) and stirred about half hour. Then aqueous layer was extracted four times with $EtOAc/CH_2Cl_2$ (1/1). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel preparative TLC eluted with (1/1) mixtures of $EtOAc/CH_2Cl_2$ or Et_2O/CH_2Cl_2. The organic extracts containing the desired product **2** were concentrated carefully under reduced pressure.

Procedure B (Table 4, entries 9–15): To a mixture of $Ba(OH)_2$ (0.0114 g, 1.5 mol %) and *N*-methylpyrrolidine (12.5 μL, 5 mol %) in 5 mL of H_2O/CH_3OH (5/1) were added sequentially 36% aqueous solution of HCHO (0.220 mL, 2.88 mmol) and 2-cyclopenten-1-one (**1**) (0.200 mL, 2.4 mmol). The resulting mixture was stirred at T=0 °C. After 8 h, (Table 4, entry 9) the reaction was quenched with 1 N HCl until pH 3. To the reaction mixture was added $NaHCO_3$ until pH about 7 and then was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the desired product **2** as crystals.

Procedure C (Table 4, entries 13–15). To a mixture of $Ba(OH)_2$ (0.580 g, 1.5 mol %) and *N*-methylpyrrolidine (0.633 mL, 5 mol %) in 250 mL of H_2O/CH_3OH (5/1) were added sequentially 36% aqueous solution of HCHO (11.70 mL, 152.2 mmol) and 2-cyclopenten-1-one (**1**) (10.10 mL, 121.8 mmol) (entry 15). The resulting mixture was stirred at T=0 °C. When the TLC silica gel analysis (eluent EtOAc/hexane, 9/1) indicated the lack of the spot of **1** (after 8.5 h) the reaction mixture was quenched with 1 N HCl until pH 3. The $NaHCO_3$ was added until pH about 7 to neutralize the acid excess and then the aqueous reaction mixture was extracted with CH_2Cl_2 and after that with CH_2Cl_2/Et_2O (1/1). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the desired product **2** (11.83 g, 87% yield) as translucent crystals. The remaining aqueous layer was checked by TLC, which indicated the presence of trace of **2** together with small more polar spot. The aqueous part was evaporated under reduced pressure to slurry residue. The residue was dissolved in 1 mL of EtOAc and purified by thin layer chromatography using CH_2Cl_2/Et_2O/EtOAc, 2/1/1 as eluent. The organic extracts containing the desired product **2** were concentrated under reduced pressure to white crystalline powder (0.41 g, 3% yield). The total yield of **2** was 90%, 12.24 g.

*4.4.1. Known compound 2-(hydroxymethyl)-2-cyclopenten-1-one (**2**).* $C_6H_8O_2$, translucent crystals. Yields: 25 °C (365 mg, 67%) 0 °C (254 mg, 93%). The BH product **2** was obtained in very comparable yield (770 mg, 94%) when **1** was employed in 600 mg (entry 9) and (12.24 g, 90%) from 10.00 g of **1** (entry 15). R_f=0.36 (silica, AcOEt/hexane, 9/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.16 (br, 1H), 2.44–2.46 (m, 2H), 2.62–2.65 (m, 2H), 4.36–4.37 (d, J=4.0 Hz, 2H), 7.52–7.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 26.86, 35.01, 57.57, 144.91, 159.05, 209.98. NMR spectral properties were consistent with those previously reported.[22,25]

4.5. General procedure for the preparative synthetic MBH reaction between 2-cyclopenten-1-one (1) and representative aryl and alkyl aldehydes (Table 5). Spectral data for known compounds (3–9)

To a mixtures of $Ba(OH)_2$ (0.0057 g, 1.5 mol %) and *N*-methylpyrrolidine (6.2 μL, 5 mol %) in 2.5 mL of CH_3OH/CH_2Cl_2 (3/1) or H_2O/CH_3OH (5/1) were added 1.46 mmol of RCHO (R=phenyl,

4-methoxyphenyl, 4-nitrophenyl, 2-furanyl, 2-naphthyl, 1-ethyl and 1-propyl) and 2-cyclopenten-1-one **1** (0.100 mL, 1.2 mmol). The resulting mixtures were stirred at T=0° or 25 °C (water bath). Upon completion of the time indicated in the Table 5, the reactions were quenched with minimum quantity of 1 N HCl. To the mixtures was added $NaHCO_3$ until pH about 7 and they were concentrated under reduced pressure to slurry residues. The residues were purified by silica gel column or preparative thin layer chromatography using 2/1 to 1/1 mixtures of EtOAc/hexane, or Et_2O/CH_2Cl_2 (depending of the aldehyde employed). The combined organic layers with the presence of the desired BH derivative (tested by silica TLC using the particular mixtures of eluents) were concentrated under reduced pressure to solids. The respective known compounds were dried under vacuum and characterized by ^1H and ^{13}C spectral analysis.

*4.5.1. Known compound 2-(hydroxyphenylmethyl)-2-cyclopenten-1-one (**3**).* $C_{12}H_{12}O_2$, pale yellow solid, yields: 25 °C: (160 mg, 70%); 0 °C: (167 mg, 73%). R_f=0.31 (silica, EtOAc/hexane, 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.43–2.45 (m, 2H), 2.57 (m, 2H), 3.56–3.57 (d, J=4.0 Hz, 1H), 5.54 (s, 1H), 7.26–7.38 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 26.73, 35.32, 69.86, 126.42, 127.93, 128.57, 141.41, 147.80, 159.59, 209.77. ^{13}C NMR spectral properties were consistent with those previously reported.[4e,24,25,33,34]

*4.5.2. Known compound 2-[hydroxy(4-methoxyphenyl)methyl]-2-cyclopenten-1-one (**4**).* $C_{13}H_{14}O_3$, colorless yellow crystalline solid, yields: 25 °C: (151 mg, 57%); 0 °C: (220 mg, 83%). R_f=0.25 (silica, EtOAc/hexane, 1/1). ^1H NMR ($CDCl_{33}$, 400 MHz): δ_H 2.41–2.43 (m, 2H), 2.57 (s, 2H), 3.46 (br, 1H), 3.78 (s, 3H), 5.47 (s, 1H), 6.85–6.87 (d, J=8.0 Hz, 2H), 7.23–7.29 (m, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 26.67, 35.35, 55.34, 69.52, 113.84, 127.74, 133. 66,148. 05, 159.28, 209.69. NMR spectral properties were consistent with those previously reported.[4e,24,33,34]

*4.5.3. Known compound (**5**) 2-[hydroxy(4-nitrophenyl)methyl]-2-cyclopenten-1-one.* $C_{12}H_{11}NO_4$, slightly yellow crystalline solid, Yields: 25 °C: (173 mg, 61%); 0 °C: (184 mg, 65%). R_f=0.44 (silica, EtOAc/hexane, 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.46–2.48 (m, 2H), 2.61–2.63 (m, 2H), 3.72 (br, 1H), 5.66 (s, 1H), 7.30–7.30 (m, 1H), 7.56–7.58 (d, J=8.0 Hz, 2H), 8.18–8.19 (d, J=4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 26.96, 35.26, 69.06, 123.84, 127.21, 146.81, 147.57, 148.65, 160.06, 209.47. NMR spectral properties were consistent with those previously reported.[4e,33–35]

*4.5.4. Known compound 2-[1-hydroxy(2-furyl)methyl]-2-cyclopenten-1-one (**6**).* $C_{10}H_{10}O_3$, yellow solid, yields: 25 °C: (167 mg, 77%); 0 °C: (184.5 mg, 85%). R_f=0.28 (silica, EtOAc/hexane, 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.47–2.50 (m, 2H), 2.65 (m, 2H), 3.45–3.46, (d, J=4.0 Hz, 1H), 5.58 (s, 1H), 6.28–6.29 (d, J=4.0 Hz, 1H), 6.33–6.34 (d, J=4.0 Hz, 1H), 7.38 (m, 1H), 7.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 26.92, 35.21, 64.01, 107.48, 110.52, 142.63, 144.84, 153.82, 160.27, 209.38.[25]

*4.5.5. Known compound 2-(1-hydroxyethyl)-2-cyclopenten-1-one (**7**).* $C_7H_{10}O_2$, white solid, Yields: 25 °C: (68 mg, 46%); 0 °C: (61 mg, 40%). R_f=0.38 (silica, EtOAc/CH_2Cl_2, 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.39–1.41 (d, J=8 Hz, 3H), 1.61, (s, 1H), 2.44–2.46 (m, 2H), 2.60–2.63 (m, 2H), 4.63–4.64 (q, 1H), 7.44–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 21.60, 26.67, 35.37, 63.87, 149.03, 157.36, 210.77. NMR spectral properties were consistent with those previously reported.[36]

*4.5.6. Known compound 2-(1-hydroxypropyl)-2-cyclopenten-1-one (**8**).* $C_8H_{12}O_2$ white solid, yield 25 °C: (65 mg, 38%) 0 °C: (68 mg, 40%). R_f=0.41 (silica, EtOAc/CH_2Cl_2, 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.92–0.99 (m, 3H), 1.64–1.70 (m, 2H), 1.72–1.75 (m, 2H), 2.16 (m, 2H), 2.43 (s, 1H), 4.36 (s, 1H), 7.44–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 9.88, 26.72, 2858, 35.37, 69.25, 147.61, 158.21, 158.21, 210.38. NMR spectral properties were consistent with those previously reported.[4c]

*4.5.7. Known compound 2-[(hydroxy(naphthalen-1-yl)methyl)]-2-cyclopent-1-one (**9**).* $C_{16}H_{14}O_2$ colorless crystalline oil, yields: 25 °C: (207 mg, 67%). R_f=0.725 (silica, Et_2O/CH_2Cl_2 1/1). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ_H 2.41–2.46 (m, 2H, $C^3HC^4H_2C^5$), 2.49–2.56 (m, br 2H, $C^4C^5H_2C{=}O$), 3.68–3.69 (d, J=4 Hz, 1H, C^2CHOH), 5.72 (s, 1H, C^2CHOH), 7.271–7.276(t, 1H, $C^2C^3HC^4H_2$), 7.46–7.48 (d, J=8 Hz, 3H,β C*H*, Ar), 7.81–7.93 (m, 4H, α C*H*, Ar); ^{13}C NMR ($CDCl_3$, 400 MHz, TMS): δ_C 26.78, ($C^3HC^4H_2C^5$), 35.34 ($C^4H_2C^5H_2C{=}O$), 69.99 (C^2CHOH), 124.46, 125.24, 126.13, 126.30 (β Ar *C*H), 127.77, 128.17, 128.39 (α Ar *C*H), 133.14, 133.34, 138.80 (Ar *C*), 147.74 ($C{=}OC^2CH_2$), 159.79 ($C^2C^3HC^4H_2$), 209.79 (C=O). Spectral data are assigned based of 2D HMQC and 2D COSY NMR studies. NMR spectral properties were consistent with those previously reported.[7]

4.6. General procedure for the preparative synthetic MBH reaction between 2-cyclohexen-1-one (10) and 36% aqueous solution of HCHO (Table 6, entry 1A,B). Spectral data for known compound (11)

To the mixtures of $Ba(OH)_2$ (0.0050 g, 1.5 mol %) and *N*-methylpyrrolidine (5.5 μL, 5 mol %) in 2.5 mL of H_2O/CH_3OH (5/1) were added sequentially 36% aqueous solution of HCHO (0.120 mL, 1.56 mmol) and 2-cyclohexen-1-one (**10**) (0.102 mL, 1.04 mmol). The resulting mixtures were stirred at T=0 °C and 25 °C (water bath). Upon completion of 16 h at T=25 °C and 24 h at T=0 °C the reactions were quenched with 1 N HCl until pH 3. To the mixtures was added $NaHCO_3$ until pH about 7 and was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel column chromatography using EtOAc/hexane, 1/1 and Et_2O/CH_2Cl_2 1/1 as eluents. The organic layers that include the desired derivative **11** were concentrated under reduced pressure to solids.

*4.6.1. Known compound 2-(hydroxymethyl)-2-cyclohexen-1-one (**11**).* $C_7H_{10}O_2$ white powder, yields: 25 °C: (0.096 mg, 73%) and respectively 0 °C: (118 mg, 89%). R_f=0.28 (EtOAc/hexane, 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.97–2.03 (m, 2H), 2.37–2.41, (m, 4H), 2.41–2.44, (t, 1H), 4.22–4.24, (d, J=8.0 Hz, 2H), 6.92–6.94, (t, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 22.81, 25.72, 38.31, 62.17, 138.35, 147.10, 200.78. NMR spectral properties were consistent with those previously reported.[21,25,34]

4.7. General procedure for the preparative synthetic MBH reaction between 4,4-dimethyl-2-cyclohexen-1-one (13) and 36% aqueous solution of HCHO (Table 6, entry 3A,B). Spectral data for (14)

To the mixtures of $Ba(OH)_2$ (0.0033 g, 3 mol % or 0.0082 g, 7.5 mol %) and *N*-methylpyrrolidine (25.1 μL, 30 mol % or 12.5 μL, 15 mol %) in 2.5 mL H_2O/CH_3OH (5/1) were added sequentially 36% aqueous solution of HCHO (0.123 mL, 1.61 mmol) and 4,4-dimethyl-2-cyclohexen-1-one (**13**) (0.109 mL, 0.805 mmol). The resulting mixtures were stirred at T=25 °C (water bath) and upon completing 30 h the reactions were quenched with 5 mL of brine. The mixtures were extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel column or preparative thin layer chromatography using as eluent gradient EtOAc/hexane, (2/1 to 1/1). The organic layers that include the

desired derivative **14** were concentrated under reduced pressure to solids.

*4.7.1. Known compound (**14**): 2-(hydroxymethyl)-4,4-dimethyl-2-cyclohexen-1-one, $C_9H_{14}O_2$.* White powder. Yields: (52 mg, 42%, entry 3A) and (44 mg, 36%, entry 3B). R_f=0.72 (EtOAc/hexane, 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.17 (s, 6H), 1.84–1.87, (t, 2H), 2.47–2.50, (m, 2H), 4.20–4.21, (d, J=4.0 Hz, 2H), 6.58, (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C 22.89, 33.02, 34.75, 36.06, 62.48, 133.73, 156.18, 201.03. NMR spectral properties were consistent with those previously reported.[31]

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Supplementary data

Full experimental data of a fine optimization of the reaction conditions including TLC and HPLC details for a formation of product **2** and representative chromatograms, complete list of preparative synthetic experimental results and comparison with reported examples, copies of ^{1}H and ^{13}C NMR spectra of all isolated MBH derivatives. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.020. These data include MOL files and InChiKeys of the most important compounds described in this article.

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