DOI: 10.1002/adsc.200800739

Cyclic Enones as Substrates in the Morita–Baylis–Hillman Reaction: Surfactant Interactions, Scope and Scalability with an Emphasis on Formaldehyde

Brett D. Schwartz,[a] Achim Porzelle,[a] Kevin S. Jack,[b] Jonathan M. Faber,[a] Ian R. Gentle,[a] and Craig M. Williams[a,*]

[a] School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, 4072, Queensland, Australia
Fax: (+61)-7-3365-4299; e-mail: c.williams3@uq.edu.au
[b] Centre for Microscopy and Microanalysis, The University of Queensland, Brisbane, 4072, Queensland, Australia

Received: November 27, 2008; Published online: May 5, 2009

This paper is dedicated to Prof. Armin de Meijere on the occasion of his 70th birthday.

Abstract: Traditionally, cyclic enones and formalin are reactants notorious for displaying problematic behaviour (i.e., poor solubility and low yields) under Morita–Baylis–Hillman (MBH) reaction conditions. The body of research presented herein focuses on the use of surfactants in water as a solvent medium that offers a resolution to many of the issues associated with the MBH reaction. Reaction scope, scalability and small angle X-ray scattering have been studied to assist with the understanding of the reaction mechanism and industrial application. A comparison against known literature methods for reaction scale-up is also discussed.

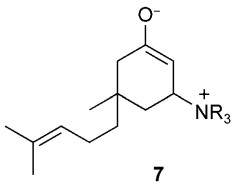
Keywords: cyclic enones; Morita–Baylis–Hillman reaction; small angle X-ray scattering (SAXS); surfactants

Introduction

The Morita–Baylis–Hillman (MBH) reaction[1] has played an important role in the construction of complex molecules, such as biological targets and natural products.[2] In fact, our own synthetic endeavours have seen the utilisation of the MBH reaction in the early stages of total synthesis campaigns, for example, azedaralide **1**[3] and 2-*O*-methylneovibsanin H **2**[4] (Scheme 1) from MBH products **3** and **4**, respectively.[5] Activities in this area quickly highlighted problems associated with the reactivity of cyclic enones and formalin under MBH conditions (e.g., conversion of cyclohexenones **5** and **6** to MBH products **3** and **4**), in particularly isolated yield and reaction scale, facets critical to resolve for future work and the greater synthetic community. Herein we report a full account[6] of our efforts to rectify problems associated with the MBH reaction of cyclic enones.

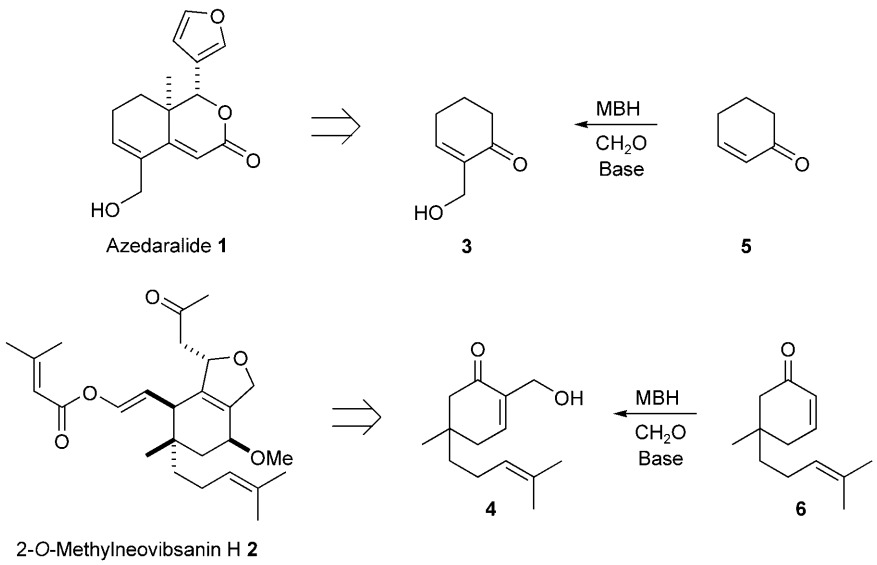
Results and Discussion

The first reaction of interest was the conversion of cyclohexenone **6** to enone **4**. Initial efforts concentrated on two protocols [that is, 1) DMAP/60 °C/5 days/68% and 2) imidazole/room temperature/17 days/93%] reported by El Gaïed,[7,8] for the conversion of 5,5-dimethylcyclohexenone to the corresponding MBH product. However, translation (and modification) of these conditions to substrate **6** gave at best yields of **4** in the range of 30%. Considering that other methods[9,10] were not superior, some thought was given to the reaction mechanism in the hope of designing an improved protocol. In the view of the zwitterionic nature of MBH reaction intermediates[11] (i.e., **7**) and



7

the lipophilic properties of cyclohexenone **6**, it was surmised that a surfactant in water may well provide the ideal reaction medium to satisfy both requirements. Water offers many environmental and eco-



Scheme 1.

nomical benefits, not to mention reactivity enhancement in some cases,[12] however, the combination with surfactants, most commonly in the form of micellar dispersions,[13] has been utilised in organic synthesis only sparingly.[14] It could, therefore, be envisaged that the lipophilic cyclohexyl ring and/or side chains [i.e., homoprenyl (**6**)] would reside in the hydrophobic region of the surfactant tail allowing the enone portion of cyclohexenone **6** to reside in the water phase. Furthermore, additional stabilisation of the reaction intermediates could be provided by the polar head group of the surfactant, whether it be anionic or cationic. In order to test this hypothesis one example each of an anionic [sodium dodecyl sulfate (SDS)], cationic [cetyltrimethylammonium bromide (CTAB)] and neutral [α-octyl-glucoside (Oct-Glc)][6,15] surfactant was investigated (Table 1).[16]

The control reaction, in the absence of any surfactant, gave only trace amounts of **4** (entry 1). Gratifyingly, however, SDS (entry 2), CTAB (entry 3) and Oct-Glc (entry 4) gave product (i.e., **4**) in 85, 39 and 70 percent yields, respectively (Table 1). A reaction scale increase indicated that both the anionic and neutral surfactants were demonstrating similar behaviour, whereas the comparison system, imidazole in sodium hydrogen carbonate solution (entries 5–8,

Table 1. Evaluating of the Baylis–Hillman reaction of **6** with formaldehyde using surfactants under various conditions.[a,b]

Entry	Base (1 equiv.)	Solvent	Surfactant (10 mol%)[c]	Yield [%][d]
1	DMAP[e]	H_2O	none	trace
2	DMAP	H_2O	SDS	85[f] (70),[g] (63)[h]
3	DMAP	H_2O	CTAB	39[f] (53)[g]
4	DMAP	H_2O	Oct-Glc	70[f] (67)[g]
5	Imidazole	1 M $NaHCO_3$[i]	none	trace
6	Imidazole	1 M $NaHCO_3$[i]	SDS	40[f]
7	Imidazole	1 M $NaHCO_3$[i]	CTAB	65[f]
8	Imidazole	1 M $NaHCO_3$[i]	Oct-Glc	55[f]

[a] See Experimental Section for representative procedure.
[b] A concentration above the critical micelle concentration (CMC), but below the point where phases other than spherical micellar may become possible, or where phase separation at the purification stage may become problematic,[17] was chosen for each surfactant.
[c] Total surfactant concentration 50 mM.
[d] Isolated yield.
[e] *N*,*N*-Dimethylaminopyridine.
[f] 40-mg scale.
[g] 100-mg scale.
[h] 1-g scale.
[i] $NaHCO_3$ (1 M)/formalin (1:1, v/v).

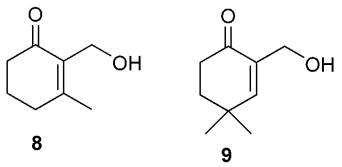


Figure 1.

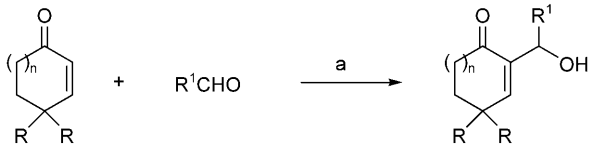
Table 1), gave yields which were generally lower and required longer reaction times. However, in this system the cationic surfactant (CTAB) afforded the best results, possibly due to a counterion exchange from bromide to hydrogen carbonate.

Considering that SDS is readily available, we applied the newly discovered conditions (i.e., SDS, water, DMAP) to cyclohexenone, 3-methylcyclohexenone and 4,4-dimethylcyclohexenone. Comparable or slightly lower yields to those reported[7,8,9,10] were observed in the case of the reaction of cyclohexenone with formaldehyde (i.e., **3**). However, the reaction rate increase was quite significant with the SDS reaction being complete in under 1 hour (65%) as compared to multiple hours or more commonly days for known literature procedures. Decreasing the amount of DMAP to 50 mol% gave a slight reduction in yield (58%) and the use of Oct-Glc (10 mol%) as the surfactant gave comparable yields (63%). No reaction (i.e., **8**)[18] was observed with 3-methylcyclohexenone. Again comparable yields of **9** were obtained with SDS (70%) and Oct-Glc (10 mol%) (68%) in the case of 4,4-dimethylcyclohexenone, although the use of imidazole instead of DMAP lowered the yield considerably (45%) (Figure 1). Cyclopentenone and cycloheptenone were completely consumed, but very little or no product formation was observed.

Although the focus of this study concentrated on formalin as the aldehyde component of the MBH reaction it was clearly beneficial to examine surfactant performance using substituted aldehydes with cyclic enones (Table 2). Other than 4-*N*,*N*-dimethylaminobenzaldehyde (entry 1), 4-methoxy- (entry 2), 4-bromo- (entry 3) and 4-nitrobenzaldehydes reacted smoothly as did cyclohexyl (entry 5) and cinnamylaldehyde (entry 6) (Table 2). It was found in some cases (entries 3 and 5), however, that isolated yields could be more than doubled if three equivalents of enone were used (Table 2).

An important aspect of the above series of evaluations was the question of performance when running the surfactant modified MBH reaction on a large scale. Two cyclic enones (i.e., cyclohexenones **5** and **6**) and two aldehydes [formaldehyde (formalin) and 4-nitrobenzaldehyde **15**] where chosen as exemplars (Table 3). It was found that the optimum conditions on a 5-g scale (entry 1, Table 3) was only a slight excess of formalin, 30 mol% DMAP, 10 mol% SDS

Table 2. Morita–Baylis–Hillman reaction of cyclic enones with various aldehydes.[a]



5 R = H, n = 1
10 R = Me, n = 1
11 R = H, n = 0

12 R^1 = 4-NMe_2-C_6H_4
13 R^1 = 4-OMe-C_6H_4
14 R^1 = 4-Br-C_6H_4
15 R^1 = 4-NO_2-C_6H_4
16 R^1 = C_6H_{11}
17 R^1 = CH=CH-C_6H_4

18 R = H, n = 1, R^1 = 4-NMe_2-C_6H_4
19 R = H, n = 1, R^1 = 4-OMe-C_6H_4
20 R = H, n = 1, R^1 = 4-Br-C_6H_4
21 R = H, n = 1, R^1 = 4-NO_2-C_6H_4
22 R = H, n = 1, R^1 = C_6H_{11}
23 R = H, n = 1, R^1 = CH=CH-C_6H_4
24 R = Me, n = 1, R^1 = CH=CH-C_6H_4
25 R = H, n = 0, R^1 = 4-NO_2-C_6H_4

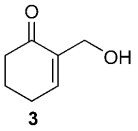
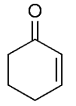
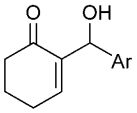
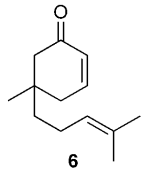
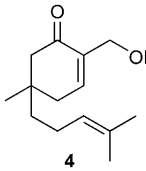
Entry	Enone	Aldehyde	Product	Yield [%][b]
1	**5**	**12**	**18**	0
2	**5**	**13**	**19**	43,[c] 20
3	**5**	**14**	**20**	71,[c,d] 27[d]
4	**5**	**15**	**21**	61,[c] 68, (69[c])[10]
5	**5**	**16**	**22**	78,[c] 31
6	**5**	**17**	**23**	73,[c] 78
7	**10**	**17**	**24**	44,[c] 39
8	**11**	**15**	**25**	65,[c] 54, 48–90[10,19]

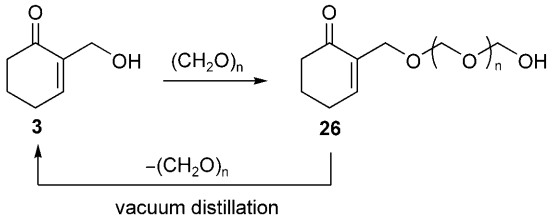
[a] Ratio enone/aldehyde (1:1.1), DMAP (1 equiv.), SDS (0.1 equiv.), water, room temperature, 16 h.
[b] Isolated yield.
[c] Enone (3 equiv.).
[d] SDS (25 mol%).

performed at 0 °C for 40 min, which gave a yield of 78%. For comparison the gold standard procedure, utilising quinuclidinol (entry 2, Table 3),[9] was investigated at the same scale, but this performed poorly giving only 28% yield. To further test our system the reaction was repeated on a 20-g scale (entry 4, Table 3), which gratifyingly afforded a slightly improved yield of 82%. If the reaction conditions were changed to imidazole THF/water (entry 3, Table 3), but the scale maintained (i.e., 20 g) the yield (48%) was significantly reduced. This procedure was further complicated by the formation of noticeable amounts of polymeric material (i.e., **26** from **3**), which was being produced due to a gross excess of formalin. This material, however, was easily converted back into product **3** *via* distillation (Scheme 2), although it should be noted that none of the polymeric material was observed in the optimum procedure (i.e., entry 1, Table 3).

In order to obtain direct evidence for the proposed mechanism, which suggests incorporation of the starting material into the surfactant micelles, small angle scattering (SAXS) measurements of mixtures of the SDS micelles and starting cyclohexenone **6**, and mixtures of SDS micelles and product cyclohexenone **4** were performed. SDS micelles alone were also studied for reference purposes.[20,21]

Table 3. Performance analysis of large-scale MBH reactions involving cyclic enones.

Entry	Cyclohexenone (amount)	Aldehyde/Base/Surfactant	Product	Yield
1	(5 g, 52 mmol)	Formaldehyde (1.4 equiv)/DMAP (30 mol%)/SDS (10 mol%); temp. 0 °C, time (40 min)		78%
2	(5 g)	Formaldehyde (5 equiv)/Quinuclidinol (1 equiv)/–; temp. r.t., time (4 h)	 **3**	28%
3	(20 g)	Formaldehyde (12 equiv)/Imidazole (1.5 equiv)/THF/Water; temp. r.t., time (24 h)		48%
4	(20 g)	Formaldehyde (1.2 equiv)/DMAP (30 mol%)/SDS (10 mol%); temp. 0 °C, time (40 mins)		82%
5	 **5**	4-Nitrobenzaldehyde (1.1 equiv)/DMAP (1 equiv)/SDS (10 mol%); temp. r.t., time (16 h)	 **21** Ar = 4-NO_2-C_6H_4	67%
6	 **6**	Formaldehyde (13 equiv)/DMAP (1.2 equiv)/SDS (10 mol%); temp. r.t., time (16 h)	 **4**	46%
7	(12 g)	Formaldehyde (13 equiv)/DMAP (1.2 equiv)/SDS (10 mol%); temp. r.t., time (16 h)		48%



Scheme 2.

Figure 2 shows the SAXS data obtained for 3 samples containing 50 mM SDS, 50 mM SDS with 50 mM of cyclohexenone **6** (starting material), and 50 mM SDS with 50 mM of **4** (i.e., reaction product), respectively. The SAXS curve obtained for the pure SDS sample is qualitatively similar to that reported by Narayanan et al. for a 70 mM SDS solution in water.[22] Their scattering curves were modelled assuming that the micelles adopt a prolate ellipsoidal shape of *ca.* 3.3×2.3 nm with a core-shell type morphology in which the electron density of the core (composed of the hydrocarbon chains) is less than that of water and that the shell (composed of the SDS head groups; 0.65 nm thick) has a greater electron density than the solvent. In addition the contributions to the SAXS from the inter-micelle interactions (i.e., the structure factor) were accounted for assuming a screened columbic interaction between the charged micelles.

In contrast with the work of Narayanan et al.,[22] the SAXS data presented for the 50 mM SDS sample

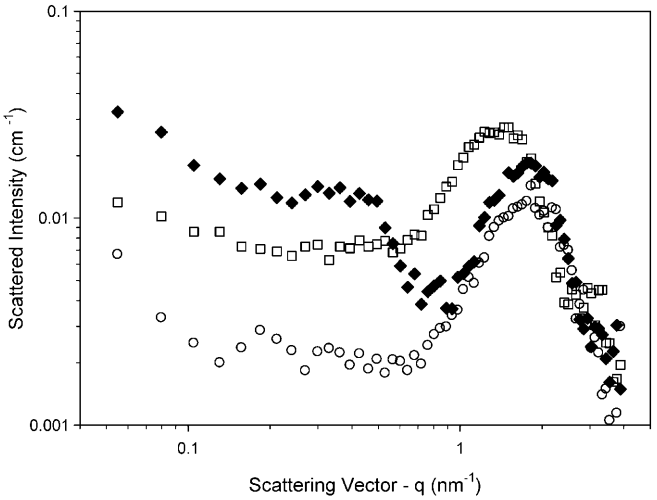


Figure 2. SAXS data measured for solutions containing 50 mM SDS (filled diamonds) and 50 mM SDS with 50 mM **6** (squares) or 50 mM **4** (circles). Data are represented as intensity as a function of scattering vector magnitude q [$q = (4\pi/\lambda)\sin\theta$, where λ is the wavelength of the incident radiation and the scattering angle is 2θ].

in this work show an additional upturn in the SAXS at $q < 0.25$ nm^{-1}, which is indicative of larger-scale aggregation, and may be due to differences in the purity of the surfactant used. Nonetheless, the position of the maxima shown in Figure 2 suggest that the mean size and shape of the micelles are similar to those reported previously and good agreement with the data can be achieved using a structural model[23] and pa-

rameters similar to those of Narayanan et al. for at $q > ca.\ 0.25\ nm^{-1}$.

From Figure 2 it can also be seen that the addition of **6** (i.e., starting enone) to an SDS solution to produce a solution containing 50 mM of each compound leads to a dramatic change in the scattering of the solution. This change shows that the addition of enone **6** leads to changes in the structural features of the SDS micelles and hence strongly suggests incorporation of **6** within the micelles. Qualitatively, the main changes observed in the SAXS, that is, the disappearance of the peak at $0.4\ nm^{-1}$ and the shift toward lower q of the maximum at $1.8\ nm^{-1}$ can be replicated by a concurrent decrease ($<10\%$) in the electron density of the shell, and an increase of *ca.* 0.3–0.5 nm^{-1} in the radius of the core, and hence an increase in the overall dimensions of the micelle.[23] Such changes are consistent with a model in which **6** is taken up into the SDS micelle and resides within both the hydrocarbon core and the shell thus leading to swelling in the volumes of both the core and shell. Presumably the cyclohexane ring of **6** resides predominantly within the shell layer and the hydrocarbon tail protrudes into the core. Moreover, the presence of the cyclohexane group of **6** within the shell layer could lead to a decrease in the electron density of the shell layer through disruption of the packing of the surfactant alkyl chains.

Finally, it can be seen that the mixture of the reaction product **4** with 50 mM SDS also leads to a significant change in the observed SAXS and hence the structure of the micelles as can be seen in Figure 2. In contrast with the changes observed upon addition of **6** the addition of **4** results in the apparent disappearance of the maximum at $0.4\ nm^{-1}$, whilst the position of the second maximum ($1.8\ nm^{-1}$) shows no significant shift in position. Qualitatively, these observations are consistent with a model for the SDS micelles in which the electron density of the shell is reduced (as above), but in which there is little change in the dimensions of the core of the micelles. Such a model can be understood by considering the relative hydrophobic/hydrophilic balance of starting material (i.e., **6**) and product (i.e., **4**). That is, the reactant (i.e., **6**) would be expected to be more hydrophobic than the product (i.e., **4**) and hence would have the potential to partition to a greater extent within the hydrophobic core of the SDS micelles. Models are currently being developed, for the SAXS of the micelles, which can account for both the observed polydispersity and the excess scattering at low q in addition to the contribution from micelles, so as to be able to quantify the changes observed in the structure of the micelles upon addition of substrate.

Conclusions

Surfactants have been found not only to increase the performance of the Morita–Baylis–Hillman reaction involving cyclic enones, but allow the reaction to be performed without the use of organic co-solvents and at room temperature with observable reaction rate increases. The present study indicates that these reactions are scalable to quantities attractive to those wishing to utilise such products as starting points in target-orientated synthesis. Small angle scattering (SAXS) measurements suggest incorporation of starting material into the surfactant micelles, supporting the proposed mechanism, although work in this area requires more extensive analysis.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded with Bruker AV300 (300.13 MHz; 75.47 MHz), AV400 (400.13 MHz; 100.62 MHz), DRX500 (500.13 MHz; 125.77 MHz), and AV750 (749.41 MHz; 188.46 MHz) spectrometers in deuteriochloroform ($CDCl_3$) or hexadeuteriobenzene (C_6D_6) unless otherwise stated. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. The GC/MS data were recorded on a Shimadzu QP5050 gas chromatograph-mass spectrometer at 70 eV, fitted with a $30\ m \times 0.25$ mm BP5 column. The standard program was set as 2 min at 100 °C, followed by a temperature increase of $16\ °C\ min^{-1}$, and left for 10 min at 250 °C. High and low resolution EI mass spectral data were obtained on a KRATOS MS 25 RFA. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. SAXS data were collected using an Anton Paar/Panalytical *SAXSess* small-angle X-ray scattering system. The instrument uses Cu-K_α radiation from a sealed X-ray tube, line collimation and a CCD detector. Samples were contained in a 1 mm silica capillary and data were collected at 20 °C. The scattering data were collected from $q = 0.05$ to $3.5\ nm^{-1}$ and were reduced to remove the contributions from the dark current of the detector, scattering of the water and empty capillary and to remove broadening due to the finite beam length. The data were further normalised to absolute intensity using water as a calibration standard.

Representative Procedure for Reactions with Formalin and DMAP (Table 1)

To a mixture of water (200 μL) and **6** (40 mg, 0.208 mmol) were added SDS (6 mg, 0.02 mmol) and DMAP (25 mg, 0.2 mmol). After stirring for 15 min. formalin (200 μL) was added and stirred for 16 h at room temperature. The mixture was then quenched with brine (1 mL) and extracted with ethyl acetate (2×3 mL). The combined organic layers were dried ($MgSO_4$) and concentrate under vacuum. Then the residue was purified by column chromatography (petro-

leum spirit/ethyl acetate, 2:1 $R_f = 0.33$) to give **4** as a colourless liquid; yield: 39 mg (85%).

Representative Procedure for Reactions with Formalin and Imidazole (Table 1)

To a mixture of 1 M $NaHCO_3$ (200 μL) and **6** (40 mg, 0.208 mmol) were added CTAB (8 mg, 0.02 mmol) and imidazole (14 mg, 0.2 mmol). After stirring for 15 min formalin (200 μL) was added and stirring continued for 16 h at room temperature. The mixture was then quenched with brine (1 mL) and extracted with ethyl acetate (2x 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrate under vacuum. The residue was purified by column chromatography (petroleum spirit/ethyl acetate, 2:1 $R_f = 0.33$) to give **4** as a colourless liquid; yield: 30 mg (65%).

2-(Hydroxymethyl)-4,4-dimethylcyclohexenone (9)

To a mixture of water (3 mL) and dimethylcyclohexenone (372 mg, 3 mmol) were added SDS (80 mg, 0.3 mmol) and DMAP (366 mg, 3 mmol). After stirring for 15 min. formalin (3 mL) was added and the mixture stirred for 45 min at room temperature. The mixture was then quenched with brine (5 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrate under vacuum. The residue was purified by column chromatography (petroleum spirit/ethyl acetate, 2:1 $R_f = 0.36$) to give 2-(hydroxymethyl)-4,4-dimethylcyclohex-2-enone (**9**) as a colourless liquid; yield: 305 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.17$ (s, 6H), 1.86 (t, 2H, $J = 6.7$ Hz), 2.48 (t, 2H, $J = 6.7$ Hz), 3.00 (br s, 1H), 4.21 (s, 2H), 6.63 (s, 1H); ^{13}C NMR: $\delta = 27.7$, 32.7, 34.5, 35.8, 61.5, 135.0, 155.8, 200.3; MS (EI): $m/z = 154$ (25) [$M^{+\cdot}$], 139 (26), 136(8), 125 (37), 121 (17), 111 (22), 97 (24), 79 (29), 69 (30), 57 (20), 55 (41), 43 (100); HR-MS: $m/z = 154.0993$, calcd. for $C_9H_{14}O_2$: 154.0994.

Representative Procedure for Reactions with Various Aldehydes in Water (Table 2)

To a mixture of water (6 mL) and cyclohex-2-enone (300 mg, 3 mmol) were added SDS (80 mg, 0.3 mmol) and DMAP (366 mg, 3 mmol). After stirring for 15 min 4-nitrobenzaldehyde (538 mg, 3.6 mmol) was added and stirring continued for 16 h at room temperature. The mixture was then quenched with brine (5 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrate under vacuum. The residue was purified by column chromatography (petroleum spirit/ethyl acetate, 2:1 $R_f = 0.36$) to give 2-[hydroxy(4-nitrophenyl)methyl]cyclohex-2-enone as a yellow syrup; yield: 500 mg (68%). Spectroscopic data for new compounds are given below.

2-[(4-Bromophenyl)hydroxymethyl]cyclohex-2-enone (20): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.93$–1.96 (m, 2H), 2.33–2.41 (m, 4H), 3.58 (br s, 1H), 5.45 (s, 1H), 6.72–6.74 (m, 1H), 7.18–7.20 (m, 2H), 7.40–7.42 (m, 2H); ^{13}C NMR: $\delta = 22.4$, 25.7, 38.4, 71.7, 121.2, 128.2, 131.3, 140.7, 140.9, 147.5, 200.2; MS (EI): $m/z = 282$ (38) [$M^{+\cdot}$], 281 (58), 280 (42) [$M^{+\cdot}$], 279 (51), 264 (2), 262 (2), 236 (2), 219 (2), 208 (13), 206 (12), 202 (15), 201 (100), 195 (3), 185 (25), 183 (23), 169 (1), 157 (12), 155 (28), 145 (15), 131 (10), 129 (10), 128 (14), 125 (13), 123 (19), 116 (16), 97 (17), 96 (40), 95 (19), 79 (11), 78 (19), 77 (61); HR-MS: $m/z = 280.0104$, calcd. for $C_{13}H_{13}BrO_2$: 280.0099 (^{79}Br).

(*E*)-2-(1-Hydroxy-3-phenylallyl)cyclohex-2-enone (23): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.95$–2.01 (m, 2H), 2.37–2.47 (m, 4H), 3.40 (br s, 1H), 5.06 (d, 1H, $J = 5.9$ Hz), 6.29 (dd, 1H, $J = 6.3$, 15.9 Hz), 6.62 (d, 1H, $J = 15.9$ Hz), 6.97 (t, 1H, $J = 4.2$ Hz), 7.19–7.37 (m, 5H); ^{13}C NMR: $\delta = 22.5$, 25.7, 38.5, 71.6, 126.5, 127.6, 128.6, 129.6, 130.6, 136.6, 140.2, 147.0, 200.3; MS (EI): $m/z = 228$ [$M^{+\cdot}$] (43), 210 (12), 200 (10), 182 (5), 172 (11), 167 (5), 153 (5), 137 (17), 131 (12), 128 (15), 124 (19), 123 (18), 115 (23), 105 (18), 104 (17), 103 (18), 96 (100), 95 (21), 91 (37), 77 (37); HR-MS: $m/z = 228.1151$, calcd. for $C_{15}H_{16}O_2$: 228.1150.

(*E*)-2-(1-Hydroxy-3-phenylallyl)-4,4-dimethylcyclohex-2-enone (24): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.17$ (s, 6H), 1.84 (t, 2H, $J = 6.7$ Hz), 2.47 (t, 2H, $J = 6.7$ Hz), 3.30 (br s, 1H), 5.00 (d, 1H, $J = 5.88$ Hz), 6.26 (dd, 1H, $J = 6.3$, 15.9 Hz), 6.60 (m, 2H), 7.38–7.19 (m, 5H); ^{13}C NMR: $\delta = 27.6$, 27.8, 32.9, 34.9, 35.6, 71.7, 126.5, 127.6, 128.5, 129.6, 130.8, 136.6, 136.8, 155.8, 200.2; MS (EI): $m/z = 256$ [$M^{+\cdot}$] (29), 223 (5), 201 (16), 200 (100), 181 (5), 172 (28), 165 (5), 158 (5), 151 (14), 137 (11), 131 (22), 124 (29), 115 (18), 109 (35), 104 (20), 91 (33), 77 (30); HR-MS: $m/z = 256.1458$, calcd. for $C_{17}H_{20}O_2$: 256.1463.

Procedure for Large-Scale Synthesis of 2-(Hydroxymethyl)cyclohex-2-enone (3)

To a mixture of water (210 mL) and cyclohex-2-enone (20 g, 0.21 mol) at 0 °C were added SDS (6.04 g, 21 mmol) and DMAP (7.62 g, 62 mmol). After stirring for 15 min. at 0 °C formalin (18.6 mL, 0.25 mol) was added portion-wise over 15 min then stirring was continued for 40 min at room temperature. The mixture was then saturated with sodium chloride and extracted with ethyl acetate (10×150 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under vacuum which afforded an oil that was purified by column chromatography (petroleum spirit/ethyl acetate, 1:2) to give 2-(hydroxymethyl)cyclohex-2-enone (**3**) as a colourless liquid; yield: 21.5 g (82%).

Acknowledgements

We thank the University of Queensland and the Australian Research Council (DP0666855) for financial support.

References

[1] a) A. B. Baylis, M. E. D. Hillman, German Patent 2,155,113, **1972**; *Chem. Abstr.* **1972**, *77*, 341174q; b) for asymmetric versions, see: P. Langer, *Angew. Chem.* **2000**, *112*, 3177–3180; *Angew. Chem. Int. Ed.* **2000**, *39*, 3049–3052.

[2] D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–891.

[3] L. A. Baker, C. M. Williams, P. V. Bernhardt, G. W. Yanik, *Tetrahedron* **2006**, *62*, 7355–7360.

[4] A. P.-J. Chen, C. M. Williams, *Org. Lett.* **2008**, *10*, 3441–3443.
[5] A variety of natural product advanced intermediates has also been construction by our group utlising the MBH reactions, see, for example: a) R. Heim, S. Wiedemann, C. M. Williams, P. V. Bernhardt, *Org. Lett.* **2005**, *7*, 1327–1329; b) D. P. Tilly, C. M. Williams, P. V. Bernhardt, *Org. Lett.* **2005**, *7*, 5155–5157; c) B. D. Schwartz, D. P. Tilly, R. Heim, S. Wiedemann, C. M. Williams, P. V. Bernhardt, *Eur. J. Org. Chem.* **2006**, 3181–3192; d) B. D. Schwartz, C. M. Williams, P. V. Bernhardt, *Beilstein J. Org. Chem.* **2008**, No. 34.
[6] An in part preliminary account has been reported, see A. Porzelle, C. M. Williams, B. D. Schwartz, I. R. Gentle, *Synlett* **2005**, 2923–2926.
[7] F. Rezgui, M. M. El Gaied, *Tetrahedron Lett.* **1998**, *39*, 5965–5966.
[8] R. Gatri, M. M. El Gaïed, *Tetrahedron Lett.* **2002**, *43*, 7835–7836.
[9] V. K. Aggarwal, D. K. Dean, A. Mereu, R. Williams, *J. Org. Chem.* **2002**, *67*, 510–514.
[10] S. Luo, P. G. Wang, J.-P. Cheng, *J. Org. Chem.* **2004**, *69*, 555–558.
[11] L. S. Santos, C. H. Pavam, W. P. Almeida, F. Coelho, M. N. Eberlin, *Angew. Chem.* **2004**, *116*, 4430–4433; *Angew. Chem. Int. Ed.* **2004**, *43*, 4330–4333.
[12] a) *Organic Syntheses in Water*, (Ed.: P. A. Grieco), Blackie Academic and Professional, London, **1998**; b) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, **1997**; c) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *435*, 746–747.
[13] a) G. T. Barnes, I. R. Gentle, *Interfacial Science: An Introduction*, Oxford University Press, Oxford, **2005**; b) J. H. Fendler, E. J. Fendler, *Catalysis in Micellar and Macromolecular Systems*, Academic Press, London, **1975**.
[14] See for example; a) K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 7202–7207, and references cited therein; b) H.-Y. Tian, H.-J. Li, Y.-J. Chen, D. Wang, C.-J. Li, *Ing. Eng. Chem. Res.* **2002**, *41*, 4523–4527, and references cited therein; c) F. Orsini, G. Sello, T. Fumagalli, *Synlett* **2006**, 1717–1719.
[15] a) A. J. J. Straathof, J. Romein, F. van Rontwijk, A. P. G. Kieboom, H. van Beekum, *Starch/Staerke* **1987**, *39*, 362–368; b) A. J. J. Straathof, H. van Beekum, A. P. G. Kieboom, *Starch/Staerke* **1988**, *40*, 229–23; c) G. M. Brown, P. Dubreuil, F. M. Ichhaporia, J. E. Desnoyers, *Can. J. Chem.* **1970**, *48*, 2525–2531.
[16] Phosphines also catalyse the MBH reaction (see, for example: F. O. Seidel, J. A. Gladysz, *Adv. Synth. Catal.* **2008**, *350*, 2443–2449 and ref.[19] below), but the current study concentrated on nitrogen and inorganic bases only.
[17] M. J. Rosen, *Surfactants and Interfacial Phenomena*, 3rd edn., John Wiley and Sons, New York, **2004**.
[18] This molecule has been obtained by our group previously in low yield, see ref.[19] in A. Porzelle, C. M. Williams, *Synthesis* **2006**, 3025–3030.
[19] For a non-aqueous comparison, see J. You, J. Xu, J. G. Verkade, *Angew. Chem.* **2003**, *115*, 5208–5210; *Angew. Chem. Int. Ed.* **2003**, *42*, 5054–5056.
[20] D. Orthaber, A. Bergmann and O. Glatter, *J. Appl. Crystallogr.* **2000**, *33*, 218–225.
[21] C. Dreiss, K. S. Jack and A. Parker, *J. Appl. Crystallogr.* **2006**, *39*, 32–38.
[22] J. Narayanan, A. S. A. Rasheed, J. R. Ballare, *J. Colloid Interface Sci.* **2008**, *328*, 67–72.
[23] S. R. Kline, *J. Appl. Crystallogr.* **2006**, *39*, 895–900.

