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Ultrasound in Baylis–Hillman reactions with aliphatic and aromatic aldehydes: scope and limitations

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Abstract—The utilization of ultrasound radiation in the Baylis–Hillman reaction with several aldehydes (aromatics and aliphatics) and different α,β-unsaturated reactants is described. For all aldehydes tested, the utilization of ultrasound sources augmented the reaction rate and the chemical yields. The use of ultrasound with two different catalysts (tri-*n*-butylphosphine and 1,4-diazabicyclo[2.2.2]octane [DABCO]) was also investigated. It was clearly demonstrated that DABCO is much more effective for catalyzing a Baylis–Hillman reaction under the influence of ultrasound than is tri-*n*-butylphosphine. No effect on reaction rate was observed when the concentration of DABCO was increased.

1. Introduction

In the last few years the Baylis–Hillman reaction has attracted the attention of many organic chemists,[1] because it is a simple and straightforward method to generate a new C–C σ bond. This reaction may be broadly defined as a condensation between the α-position of activated double bond (I) with carbon electrophiles containing an electron-deficient sp^2 carbon atom (II) under the influence of suitable catalysts, such as phosphines or tertiary amines, producing multifunctional molecules with high synthetic potential (Scheme 1).[1c,2,3]

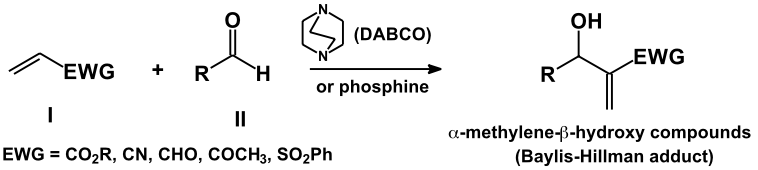
Besides the synthetic potential, the Baylis–Hillman reaction is a totally atom-efficient process, since all the carbon atoms from the reagents are incorporated in the end product, thus being an inherently green transformation.[3]

Aldehydes are the most used carbon electrophiles in this reaction. However, aromatic aldehydes are reluctant to serve as substrates for the Baylis–Hillman reaction under the usual relatively mild conditions. When aromatic aldehydes are used, under standard conditions (room temperature or solvent reflux), the major drawbacks from this reaction are its relative slowness (typically 1 to 4 weeks to be completed) associated with very low chemical yields (5–10%).

Due to the synthetic potentiality of Baylis–Hillman adducts obtained from aromatic aldehydes,[4] various modifications of the experimental protocol have been proposed, e.g. the use of microwaves,[5] salts and metals,[6] ionic liquids[7] and an aqueous medium.[8]

In a preliminary communication, we demonstrated that the use of ultrasound dramatically accelerates the rate and increases the chemical yield of the Baylis–Hillman reaction, especially when aromatic aldehydes are used as electrophile.[9] Roos et al.[10] have already reported the use of ultrasound in the Baylis–Hillman reaction. However, their attention was focused on the association of temperature with ultrasound and little attention was paid to the substrate.

In a current research program directed towards the



Scheme 1. Formation of α-methylene-β-hydroxy compounds by the Baylis–Hillman reaction.

Keywords: Baylis–Hillman reaction; α,β-unsaturated compounds; 1,4-diazabicyclo[2.2.2]octane (DABCO).
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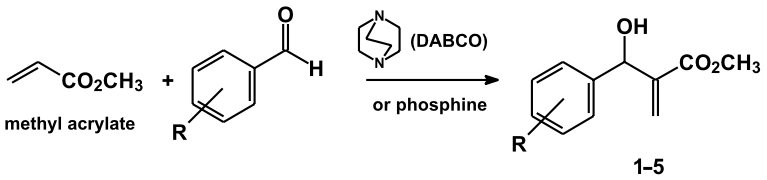
Table 1. Baylis–Hillman reaction using *n*-Bu_3P or DABCO as bases, without and with ultrasound



1–5

Entry	Aldehydes	Without ultrasound				With ultrasound[a]		
		Bases	Time (h)[b]	Product	(%)[c]	Time (h)[b]	Product	%[c]
1	R=H (Benzaldehyde)	*n*-Bu_3P	96	**1**	–	96[a]	**1**	<30[d]
		DABCO	144	**1**	25	96[b]	**1**	74
2	R=4-OCH_3 (*p*-Anisaldehyde)	*n*-Bu_3P	96	**2**	–	96	**2**	32[d]
		DABCO	240	**2**	25	96[b]	**2**	90[e]
3	R=3,4-OCH_2O- (Piperonal)	*n*-Bu_3P	504	**3**	–	504	**3**	–
		DABCO	480	**3**	30	96	**3**	73[e]
4	R=4-Cl, (*p*-Chlorobenzaldehyde)	*n*-Bu_3P	96	**4**	–	96	**4**	22[d]
		DABCO	192	**4**	74	48	**4**	87
5	R=4-NO_2 (*p*-Nitrobenzaldehyde)	*n*-Bu_3P	96	**5**	–	96[c]	**5**	40[d]
		DABCO	72	**5**	45	16	**5**	88[f]

[a] Ultrasonic source: 1000 W, 25 kHz.
[b] Time after which the composition of the reaction mixture no longer evolved.
[c] Isolated yield.
[d] Determined by GC (HP-5 column).
[e] Yield based on recovered aromatic aldehyde.
[f] With 4-nitrobenzaldehyde the solvent (methanol) was replaced by dichloromethane, because we observed the formation of a byproduct (≈30–40%) coming from the 1,4-addition of methanol to the double bond of the Baylis–Hillman adduct.

preparation of intermediates for the synthesis of natural products,[2] we needed to prepare several Baylis–Hillman adducts from aromatic and aliphatic aldehydes, on a large scale. To achieve this we studied the use of ultrasound radiation while performing these reactions. Our intention was on establishing when the utilization of this type of radiation would be more indicated.

To our surprise, a careful search of the literature revealed that there is no systematic study in situations where the use of ultrasound radiation could be advantageous.

Having these objectives in mind, we describe herein a complementary study focused on the determination of the scope and limitations of use of the ultrasound technique on the Baylis–Hillman reaction with aliphatic and aromatic aldehydes and different α,β-unsaturated reactants. In this study, the main emphasis was given to aromatic aldehydes, because they are harder to react in Baylis–Hillman than aliphatic one.

Our interest was centered on evaluating the influence of the association of different catalysts with ultrasound on the rate of the Baylis–Hillman reaction. Moreover, the influence of the substituents incorporated into the structure of the aromatic aldehydes on the rate of this reaction was also investigated. No special attention was paid in verifying the influence of the temperature associated with the use of ultrasound on the rate of the Baylis–Hillman reaction, because a study of these effects has already been published by Roos et al.[10]

2. Results and discussions

We initiated our study using only aromatic aldehydes (three different types). Our choices were based on the influence of the substituents on the electrophilicity of the carbon atom of the carbonyl group. Thus, we investigated one aldehyde without any substituents on the aromatic ring (**1**, benzaldehyde), two substituted with electron donating groups (OCH_3 and 3,4-methylenedioxy, **2** and **3**, respectively) and two substituted with electron-withdrawing groups (Cl and NO_2, **4** and **5**). Initially, the reactions were performed without the presence of ultrasound.

The literature reports the use of phosphines in the Baylis–Hillman reaction (mainly triphenyl- and tri-cyclohexyl-phoshines).[11] For all aldehydes we tested in our study we employed either tri-*n*-butylphoshine or 1,4-diazabicyclo-[2.2.2]octane (DABCO), as the catalyst. As standard experimental conditions, we established the following concentration ratio: aldehyde (1.0)/DABCO or phoshine (0.65)/methyl acrylate (1.3). All reactions were performed at room temperature. The first set of reactions (with each of the five aldehydes) was carried out with magnetic stirring. The second set (same five aldehydes) was carried out in the presence of an ultrasound source. The results are summarized in Table 1.

2.1. The ultrasound effect

Without the presence of the ultrasound radiation, only poor to moderate yields (25–74%) were obtained when DABCO was used. Moreover, the reaction times are completely unsuitable for synthetic purposes (Table 1). In addition, in all cases where tri-*n*-butylphosphine was used as catalyst, the formation of the Baylis–Hillman adducts could be only detected in very low yields (by GC/HP5 column). On the other hand, we were able to detect (by TLC and GC) a large amount of degradation products. The reaction medium immediately became dark when phosphine was added to the

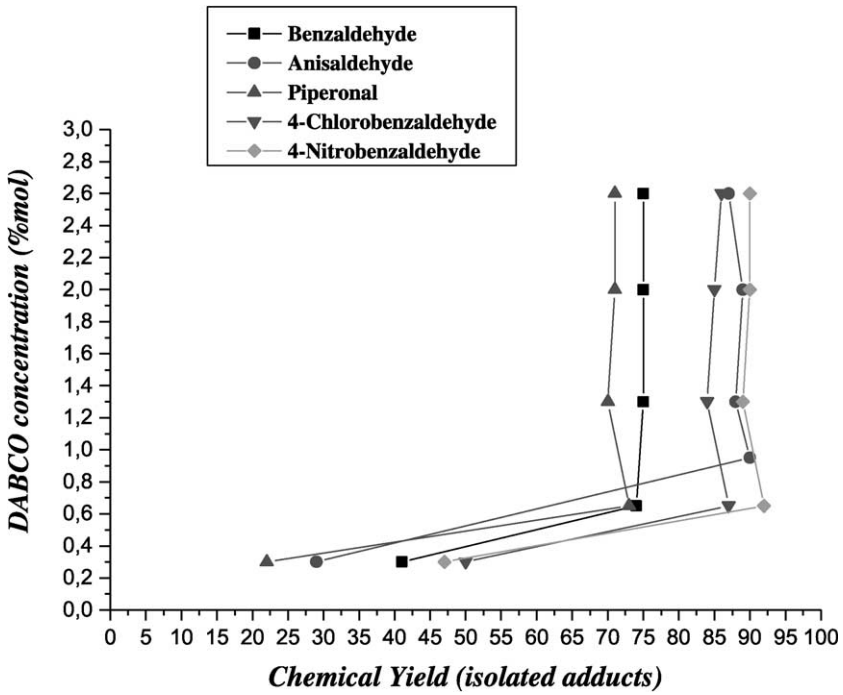


Figure 1. Chemical yield as a function of the DABCO concentration used in the Baylis–Hillman reaction in the presence of ultrasound.

aldehyde and acrylate mixture. We attempted to overcome these unexpected results by performing these reactions at low temperature (0°C), for longer times (5–10 days) or by changing the addition sequence of the reagents. Unfortunately, in all situations, the reaction worked very badly. The tendency of phosphines (especially tri-*n*-butylphoshine) to catalyze the dimerization reaction of acrylate derivatives has already been reported.[12] This dimerization tendency can probably explain the results we had.

The effect caused by ultrasound radiation in organic media is well documented.[13,14] Due to the cavitation effect, it is possible to transfer locally a huge amount of energy, which can effectively contribute to produce a dramatic acceleration of the reaction rate of several organic processes.[14] Thus, we decided to repeat these reactions under the influence of an ultrasound source, using the same experimental conditions as before. The results obtained under these conditions are also shown in Table 1.

The results clearly show that when DABCO is used, associated with ultrasound, a remarkable augmentation of the rate and of the chemical yield of the reaction is observed (Table 1). Under the influence of ultrasound radiation it was possible to obtain moderate to good yields (70–90%) of the Baylis–Hillman adducts associated with a dramatic decrease in the reaction time (all reactions were at least 50% faster). However, these observations were not duplicated with tri-*n*-butylphosphine and ultrasound radiation. For these cases, TLC and GC (HP-5 column) indicated that the reaction is very sluggish and still gives several by-products, as commented above.

Based on these data, we decided to give up the use of tri-*n*-butylphosphine, because it was not adequate for our purposes. Thus, we concentrated our attention on determining the influence of the DABCO concentration on the rate of the reaction.

To evaluate this influence, we established four different experimental conditions, in which the DABCO concentration was varied relative to the concentration of acrylate, which remained constant. In the first set of experiments, we decreased the ratio DABCO/acrylate to 0.3:1.3. In the second set, we increased the ratio to 1.3/1.3. In the third and fourth sets, the amount of DABCO was progressively increased to ratios of 2.0/1.3 and 2.6/1.3, respectively.

All reactions were carried out using ultrasound without external heating. The ultrasonic bath temperature stayed at 35–40°C. The results are plotted in Fig. 1.

In order to compare all the reactions under the same experimental conditions, we stopped the Baylis–Hillman reactions after 96 h, the only exception being the reaction with 4-nitrobenzaldehyde which was complete after 16 h (no starting material detected). This decision was based on preliminary experimental observations that, after this time, no significant increases of the chemical yields are perceived.

As can be seen in Fig. 1, augmentation of DABCO concentration had little influence on either the rate or the chemical yield of the reaction. In other words, with a ratio of 0.65:1 (DABCO/acrylate) it is possible to achieve a reasonable chemical yield for all these reactions. No effect was observed on the rate of the reaction when we increased the DABCO concentration during the reaction (starting with 0.65 and increasing the concentration ratio to 2.6, after 96 h).

From our point of view, at this stage of the work we had optimized experimental conditions. Now our interest was focused on determining for which cases the utilization of

Table 2. Use of aromatic and aliphatic aldehydes in the Baylis–Hillman reaction in the presence of an ultrasound source

Entry	Aldehydes	B–H adduct	Time without ultrasound (h)[a]	Time with ultrasound (h)	Yield without ultrasound (%)[b]	Yield with ultrasound (%)[b]
1	3-Bromobenzaldehyde	**6**	192	48	71	88
2	4-Hydroxybenzaldehyde	**7**	480	96	12	54
3	4-Trifluoromethoxybenzaldehyde	**8**	170	48	73	80
4	4-Dimethylaminobenzaldehyde	**9**	480	480	0	0
5	4-Methylsulphonylbenzaldehyde	**10**	144	60	40	70
6	3-Methoxy-4-hydroxybenzaldehyde	**11**	480	192	0	54
7	3-Methoxy-4-hydroxy-5-iodobenzaldehyde[c]	**12**	480	480	0[d]	<5[d]
8	6-Bromo-1,3-benzodioxole-5-carbaldehyde[e]	**13**	480	32	0	75
9	7-Methoxy-1,3-benzodioxole-5-carbaldehyde[f]	**14**	480	60	0	52[g]
10	3-Hydroxy-4-methoxybenzaldehyde	**15**	480	96	0	51[g]
11	3,4,5-Trimethoxybenzaldehyde	**16**	192	72	34	72
12	2-Hydroxy-3-methoxybenzaldehyde	**17**	192	96	20	67[h]
13	2-Fluorobenzaldehyde	**18**	96	16	50	100[g]
14	2-Bromobenzaldehyde	**19**	102	26	12	73[g]
15	4-Methylbenzaldehyde	**20**	196	72	15	79
16	Formaldehyde	**21**	240	120	66[i]	74
17	Acetaldehyde	**22**	168	96	88[i]	90
18	Propionaldehyde	**23**	120	72	71[i]	72
19	*n*-Butyraldehyde	**24**	168	72	85[i]	85
20	*n*-Pentanaldehyde	**25**	168	48	74[i]	82

[a] All reactions were carried out using standard conditions (see text).
[b] Isolated yield.
[c] Commercial product or prepared according the procedure described in Ref. 15.
[d] Determined by GC.
[e] Prepared according Ref. 16.
[f] See Ref. 17 for the preparation of this aldehyde from 3-methoxy-4-hydroxy-5-iodobenzaldehyde.
[g] Yield based on recovered aldehyde.
[h] A chromene derivative was produced by a S_N2' mechanism involving the participation of the phenolic hydroxyl group, see Ref. 18.
[i] See Ref. 19a–d.

ultrasound could be considered a valuable tool to accelerate the rate of the Baylis–Hillman reaction with aromatic and aliphatic aldehydes.

2.2. Generalization of the method

2.2.1. Aliphatics and substituted aromatic aldehydes. To answer these questions, various additional aldehydes (aliphatics and aromatics) were tested. For aromatic ones our preference was clearly directed to aldehydes substituted with electron donating groups, because this type of aldehyde is more resistant to undergoing the Baylis–Hillman reaction.

As expected, the presence of electron withdrawing groups on the aromatic ring accelerates the rate of the reaction, while the presence of an electron donating group causes a decrease in the rate. However, it is not clear to us which substitution pattern on the aromatic ring could be successfully used under the influence of ultrasonic radiation. The results obtained are summarized in Table 2.

For majority of the cases, ultrasound radiation increased enormously the efficiency of the reaction. For aldehydes with electron-withdrawing groups, the utilization of ultrasound certainly increases the rate of the reaction, however no substantial increase in the chemical yield was observed. Otherwise, the effect of ultrasound is more remarkable when aldehydes with electron-donating groups are used.

In most cases, we observed a considerable increase in chemical yield as well as a decrease in reaction time. For some cases (see Table 2, entries 6–10), we have dramatically altered the situation, since without ultrasound the reaction did not go at all.

Even in the presence of ultrasound radiation, some aromatic aldehydes are quite reluctant to react. The presence of an amino group on the ring changes completely the chemical profile of this reaction (entry 4). It is worth mentioning that this reaction normally is very clean. However, with this aldehyde (entry 4) the reaction is dirty and several by-products were observed by TLC and GC. Several experimental modifications were tried (use of acetonitrile as solvent instead of methanol, use of methyl acrylate as solvent, both increasing and decreasing the temperatures), however no effect on the rate of the reaction was perceived. Probably, the tertiary amine group is in competition with DABCO for the acrylate.

A similar behavior was observed when an iodine atom was conjugated with other electron donating groups (entry 7). In this case we are able to detect by gas chromatography the presence of the Baylis–Hillman adduct in the reaction medium, in approximately 5–10% yield, after 480 h. However, in general, even for aldehydes with several electron donating substituents on ring, the reaction worked quite well (entries 8–11). These results demonstrate that ultrasound accelerates the Baylis–Hillman reaction with most, but not all, aromatic aldehydes.

However, for all aliphatic aldehydes tested (entries 16–20), we observed a dramatic decrease in reaction time associated with an increase in the chemical yields of the reaction.

Table 3. Use of aromatic heterocyclic aldehydes in the Baylis–Hillman reaction in the presence of an ultrasound sources

Entry	Aldehydes	B–H adduct	Time without ultrasound (h)[a]	Yield (%) without ultrasound[b]	Time with ultrasound (h)[a]	Yield (%) with ultrasound[b]
1	2-Furancarboxaldehyde	**26**	24[c]	76	6	80
2	2-Pyridinecarboxaldehyde	**27**	16	97	4	98
3	3-Pyridinecarboxaldehyde	**28**	4[d]	<82	2	97
4	2-Thiophenecarboxaldehyde	**29**	72[d]	97	8	100
5	2-Thiazolecarboxaldehyde	**30**	1	86	0.25	92

[a] All reactions were carried out using standard conditions (see text and Section 4).
[b] Isolated yield.
[c] See Ref. 20.
[d] See Ref. 21.

2.2.2. Aromatic heterocyclic aldehydes. To evaluate the generality of this method we decided to test the use of ultrasound radiation in a Baylis–Hillman reaction using as electrophiles some aromatic heterocyclic aldehydes. Thus, 2- and 3-pyridinecarboxaldehyde, 2-thiophenebenzaldehyde, furfural and 2-thiazolecarboxaldehyde were submitted to the same experimental conditions described previously. Unfortunately, when the reactions were performed using methanol or dichloromethane as solvent, in the presence of ultrasound, we observed no significant enhancement in the chemical yield or/and in the rate of the reaction.

Aiming to circumvent these problems, we decided to remove the solvent (methanol) and perform the reactions without any additional solvent when in the presence of ultrasound. This condition has already been tested with the aromatic non-heterocyclic aldehydes, however no enhancement of the reaction parameters was observed with these substrates.

To our surprise, under this new experimental protocol, we observed an augmentation in the chemical yields and a large decrease in the reaction time in those cases where ultrasound radiation was used. The results are summarized in Table 3.

Some results are worth special comment. For all cases where heterocyclic aromatic aldehydes were used in the presence of ultrasound, we perceived a reasonable decrease in the reaction time, compared with those described in the literature. For some cases (entries 3 and 5), we also observed an increase in the chemical yield of the reaction. For one aldehyde, e.g. thiazolecarboxaldehyde (Table 3, entry 5) the reaction is complete in only 15 min, with a quite good chemical yield. Undoubtedly, the utilization of ultrasound radiation to perform the Baylis–Hillman reaction with aliphatic and aromatic aldehydes is really advantageous.

2.2.3. Other α,β-unsaturated reactants. In order to demonstrate that the utilization of ultrasound radiation was compatible with different situations, we performed some additional experiments using other α,β-unsaturated reactants commonly employed in the Baylis–Hillman reaction. We selected acrylonitrile and methyl vinyl ketone, based on two features of these compounds: they are prone to polymerize; normally their reactions require special attention; they provide synthetically interesting Baylis–Hillman adducts. In Table 4 we summarize the results obtained.

Once again, the utilization of ultrasound radiation demonstrated its usefulness. For all combinations (aromatic aldehydes and α,β-unsaturated reactants) the results obtained are quite reasonable. It was possible to shorten the reaction time and increase, or at least maintain the chemical yield. For one case (entry 1, Table 4), we observed a decrease in the reaction rate associated with a decrease in the chemical yield. This reaction was specially not clear-cut and the formation of several by-products was observed.

However, in general, when we compare the results obtained

Table 4. Use of different α,β-unsaturated compounds in the Baylis–Hillman reaction in the presence of an ultrasound sources

Entry	Aldehydes/α,β-unsaturated compounds	B–H adduct	Time without ultrasound (h)[a]	Yield without ultrasound (%)[b]	Time with ultrasound (h)[a]	Yield with ultrasound (%)[b]
1	Piperonal/acrylonitrile	**31**	48[c]	95[c]	15	78
2	4-Chlorobenzaldehyde/methyl vinylketone	**32**	192[d]	61[d]	48	60
3	4-Nitrobenzaldehyde/methyl vinyl ketone	**33**	50	54	24	73
4	2-Pyridinecarboxaldehyde/acrylonitrile	**34**	24[e]	92[e]	3/4	98
5	2-Pyridinecarboxaldehyde/methyl vinyl ketone	**35**	24[e]	81[e]	3/4	90
6	Propionaldehyde/acrylonitrile	**36**	40	81[f]	8	80
7	Propionaldehyde/methyl vinyl ketone	**37**	24	84[g]	5	82

[a] All reactions were carried out using standard conditions (see text and Section 4).
[b] Isolated yield.
[c] See Ref. 22.
[d] See Ref. 23.
[e] See Ref. 24.
[f] See Ref. 25.
[g] See Ref. 26.

with the Baylis–Hillman reaction carried out in the presence of ultrasound radiation, with those obtained without it, it is obvious that ultrasound radiation should be seriously taken into consideration while performing this type of condensation reaction.

3. Conclusion

Our results demonstrate unambiguously the great influence of ultrasound radiation on the Baylis–Hillman reaction with several substituted aromatic and aliphatic aldehydes. For most cases tested, a moderate to quite good chemical yield was obtained. Without ultrasound radiation, many of these Baylis–Hillman reactions did not work at all or required a long reaction times before observing the formation of the adduct, normally in very low yield. For most aldehydes employed, we observed a remarkable increase of the rate of the reaction accompanying the increase in the chemical yield.

It was also pointed out that the utilization of ultrasound is compatible with other α,β-unsaturated reactants normally employed in the Baylis–Hillman process as nucleophiles. Unfortunately, some aromatic aldehydes are reluctant to react even under the influence of ultrasound radiation. Finally, these results properly demonstrate that ultrasound radiation should be seriously taken in consideration, as a good alternative to perform a Baylis–Hillman reaction, specially when aromatic aldehydes are employed as electrophiles.

4. Experimental

4.1. General

The ^{1}H and ^{13}C spectra were recorded on a Varian GEMINI BB-300 at 300 and 75.4 MHz, respectively, or on an Inova instrument at 500 and 125 MHz, respectively. The mass spectra were recorded using a HP model 5988A GC/MS with a High Resolution Autospec-Micromass/EBE. IR were obtained with a Nicolet model Impact 410. Melting points were measured in open capillary tubes using an Electrothermal apparatus model 9100, and are uncorrected. Yields were determined from GC analyses on a HP6890 equipment with a flame ionization detector, using a HP-5 capillary (crosslinked 5% PH ME Siloxane, 28 m) column. Manipulations and reactions were not performed under dry atmospheres or employing dry solvents, unless otherwise specified. Purification and separations by column chromatography were performed on silica gel, using normal or flash chromatography. TLC visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. All Baylis–Hillman reactions were sonicated in an ultrasonic cleaner UNIQUE model GA 1000 (1000 W, 25 kHz). Ice was added occasionally to avoid increasing the temperature of the water bath of the ultrasonic cleaner, which was maintained between 30 and 40°C. Aromatic aldehydes were purchased from Aldrich, Acros or Lancaster and were used without previous purification.

4.2. General procedure for the preparation of Baylis–Hillman adducts 1–5, 6–20 (aromatic aldehydes) and 21–25 (aliphatic aldehydes)

A mixture of the aliphatic or aromatic aldehyde (18–20 mmol), methyl acrylate (1.3 equiv.) and DABCO (0.65 equiv.) in methanol, dichloromethane or acetonitrile (2 cm^3/mmol, indicated for each aldehyde), was sonicated for 16–120 h. In some cases where no Baylis–Hillman adduct was detected after this time, the mixture was sonicated for 504 h (the reaction time for each aldehyde has been indicated together with the spectral data). Ultrasound bath temperature was constantly monitored and kept at 30–40°C during the reaction, through ice addition or by using a refrigerated recirculator. After the reaction time, the mixture was diluted with dichloromethane (50 cm^3). The organic solution was washed with 10% aqueous HCl (2×20 cm^3), concentrated under reduced pressure and dried over $MgSO_4$. After filtration and solvent removal, the residue was filtered through a pad of silica gel (eluent indicated for each adduct).

4.2.1. (±)-Methyl 2-[hydroxy(phenyl)methyl]acrylate (1). Reaction time: 96 h, dichloromethane solvent; 74% of a colorless viscous oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 65:35); IR ν_{max}/cm^{-1} 3482, 3062, 1714, 1336 (film); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5H, aromatic), 6.33 (s, 1H), 5.83 (s, 1H), 5.55 (s, 1H), 3.71 (s, 3H), 3.14 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.9, 142.1, 141.4, 128.5, 127.9, 126.7, 126.1, 73.2, 51.9; MS (70 eV, *m/e*, %) 192 (M^+, 34), 191 (30), 160 (30), 159 (12), 132 (56), 115 (32), 105 (100), 91 (10), 79 (40), 77 (50), 55 (28). Anal. calcd for $C_{11}H_{12}O_3$: C, 68.74%; H, 6.29%. Found C, 68.69%; H, 6.30%.

4.2.2. (±)-Methyl 2-[hydroxy(4-methoxyphenyl)methyl]-acrylate (2). Reaction time: 96 h, methanol solvent; 90% of a white solid (yield based on recovered aldehyde) purified by silica gel column chromatography (eluting with hexane/ethyl acetate 80:20); mp 54–56°C; IR ν_{max}/cm^{-1} 3073, 2960, 2924, 2871, 2353, 1706, 1634, 1456, 1385, 1319, 1141, 1034, 909, 808 (film); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80–5.66 (m, 1H), 5.07–5.00 (m, 2H), 2.52 (dd, *J*=14.0, 8.4 Hz, 1H), 2.47–2.28 (m, 2H), 2.17 (dd, *J*=14.0, 8.4 Hz), 2.0–1.87 (m, 2H), 1.85–1.75 (m, 1H), 1.74–1.65 (m, 1H), 1.64–1.50 (m, 1H), 1.0 (s, 3H), 0.91 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 216.2, 135.4, 117.6, 52.3, 40.8, 38.5, 38.4, 29.1, 24.3, 18.9, 15.2; MS (70 eV, *m/e*, %) 222 (M^+, 25), 190 (16), 162 (18), 135 (100), 108 (46), 94 (20), 77 (33). Anal. calcd for $C_{12}H_{14}O_4$: C, 64.85%; H, 6.35%. Found C, 64.82%; H, 6.30%.

4.2.3. (±)-Methyl 2-[1,3-benzodioxol-5-yl(hydroxy)-methyl]acrylate (3). Reaction time: 96 h, methanol solvent; 73% yield of a white solid (yield based on recovered aldehyde) purified by silica gel column chromatography (eluting with hexane/ethyl acetate 75:25); mp 40–41°C; IR ν_{max}/cm^{-1} 3492, 3119, 1706, 1620; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (dd, *J*=1.9, 0.46 Hz, 1H), 6.84 (ddd, *J*=7.96, 1.74, 0.55 Hz, 1H), 6.77 (d, *J*=8.0 Hz, 1H), 6.3 (s, H), 5.9 (s, OCH_2O), 5.85 (m, H), 5.45 (d, CH, *J*=5 Hz), 3.7 (s, CH_3), 3.0 (d, OH, *J*=5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ

166.7, 147.7, 147.2, 141.9, 135.2, 125.9, 120.1, 108.1, 107.1, 101.0, 72.9, 51.9; MS (70 eV, *m/e*, %) 236 (M^+, 84), 204 (30), 176 (27), 151 (40), 149 (100), 93 (55), 65 (44); HRMS (M^+) calcd for $C_{12}H_{12}O_5$ 236.06847. Found 236.06849. Anal. calcd for $C_{12}H_{12}O_5$: C, 61.01%; H, 5.12%. Found C, 60.81%; H, 4.93%.

4.2.4. (±)-Methyl 2-[(4-chlorophenyl)(hydroxy)methyl]-acrylate (4). Reaction time: 48 h, methanol solvent, 87% yield of a white solid purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); mp 42°C, lit.[11] 42°C; IR ν_{max}/cm^{-1} 3512, 2992, 1724, 1634; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (s, 4H, aromatics), 6.33 (s, 1H), 5.82 (s, 1H), 5.51 (d, 1H, J=5.86 Hz, C*H*OH), 3.72 (s, 3H), 3.15 (d, J=5.89 Hz, 1H, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 116.4, 141.8, 139.9, 133.7, 128.7, 128.1, 126.4, 72.7, 52.0; MS (70 eV, *m/e*, %) 226 (M^+, 28), 194 (21), 166 (50), 137 (52), 139 (100), 77 (80), 55 (35). Anal. calcd for $C_{11}H_{11}ClO_3$: C, 58.29%; H, 4.89%. Found C, 58.27%; H, 4.88%.

4.2.5. (±)-Methyl 2-[hydroxy(4-nitrophenyl)methyl]-acrylate (5). Reaction time: 16 h, dichloromethane solvent, 88% yield of a yellow tinged solid purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); mp 73–74°C, lit.[11] 74°C; IR ν_{max}/cm^{-1} 3512, 2992, 1724, 1634; ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, J= 8.79 Hz, 2H, aromatics), 7.56 (d, J=8.79 Hz, 2H, aromatics), 6.40 (s, 1H), 5.89 (s, 1H), 5.64 (d, J=5.86 Hz, 1H, C*H*OH), 3.75 (s, 3H), 3.40 (d, J=6.34 Hz, 1H, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.6, 148.7, 147.6, 141.1, 127.48, 127.4, 123.7, 72.8, 72.7, 61.3, 52.2; MS (70 eV, *m/e*, %) 237 (M^+, 20), 220 (58), 205 (40), 177 (90), 155 (100), 131 (22), 115 (30), 104 (25), 77 (73), 55 (80). Anal. calcd for $C_{11}H_{11}NO_5$: C 55.70% H 4.67%. Found C, 55.67%; H, 4.63%.

4.2.6. (±)-Methyl 2-[(3-bromophenyl)(hydroxy)methyl]-acrylate (6). Reaction time: 72 h, methanol solvent, 88% yield of a viscous colorless oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 80:20); IR ν_{max}/cm^{-1} 3467, 3082, 3001, 2951, 1716, 1631, 1570, 1439, 1292, 1192, 1153, 1045, 960, 787; ^1H NMR (300 MHz, $CDCl_3$): δ 7.5 (t, J=1.8 Hz, 1H), 7.4 (dt, J= 1.1, 8.0 Hz, 1H), 7.3 (m, 1H), 7.2 (t, J=7.7 Hz), 6.3 (t, J= 1.1 Hz, 1H), 5.8 (t, J=1.1 Hz, 1H), 5.5 (br s, 1H), 3.7 (s, 3H), 3.2 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.3, 143,.5, 141.1, 130.7, 129.8, 129.5, 126.4, 125.1, 122.4, 72.5, 52.0; MS (70 eV, *m/e*, %) 271 (M^+, 45), 238 (25), 211 (25), 184 (60), 156 (48), 115 (100), 77 (90); HRMS (M^+) calcd for $C_{11}H_{11}BrO_3$ 269.98915. Found 269.98907.

4.2.7. (±)-Methyl 2-[hydroxy(4-hydroxyphenyl)methyl]-acrylate (7). Reaction time: 96 h, methanol solvent, 54% yield of a colorless oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 80:20); IR ν_{max}/cm^{-1} 3470, 3001, 1716, 1632; ^1H NMR (300 MHz, $CDCl_3$): δ 7.13 (d, J=8.4 Hz, 2H), 6.7 (d, J=8.4 Hz, 2H), 6.61 (br s, 1H), 5.86 (t, J=1.1 Hz, 1H), 5.48 (br s, 1H), 3.68 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 155.4, 141.6, 132.6, 128.0, 125.7, 115.3, 72.7, 52.1. Anal. calcd for $C_{11}H_{12}O_4$ C, 63.45%; H 5.81%. Found C, 63.39%; H, 5.79%.

4.2.8. (±)-Methyl 2-{hydroxy[4-(trifluoromethoxy)phenyl]-methyl}acrylate (8). Reaction time: 48 h, methanol solvent, 80% yield of a viscous colorless oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); IR ν_{max}/cm^{-1} 3467, 3039, 3005, 2958, 2908, 1712, 1631, 1508, 1442, 1273, 1227, 1181, 1045, 849; ^1H NMR (300 MHz, $CDCl_3$): δ 7.4 (d, J=8.8 Hz, 2H), 7.2 (d, J= 8.8 Hz, 2H); 6.3 (t, J=0.73 Hz, 1H), 5.8 (t, J=1.1 Hz, 1H), 5.5 (br s, 1H), 3.7 (s, 3H), 3.0 (br s, 1H, changeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.4, 148.5, 141.5, 139.8, 127.9, 126.2, 120.7, 72.5, 52.0; MS (70 eV, *m/e*, %) 276 (M^+, 18), 259 (10), 244 (18), 216 (40), 189 (100), 115 (10), 95 (12), 77 (47), 55 (20); HRMS (M^+) calcd for $C_{12}H_{11}F_3O_4$ 276.0609. Found 276.06104.

4.2.9. (±)-Methyl 2-{hydroxy[4-(methylsulfonyl)phenyl]-methyl}acrylate (10). Reaction time: 60 h, methanol solvent, 70% yield of a viscous oil-purified by silica gel column chromatography (eluting with hexane/ethyl acetate 80:20); IR ν_{max}/cm^{-1} 3494, 3020, 2954, 2927, 1712 (C=O), 1631, 1439, 1296, 1146, 1049, 980; ^1H NMR (300 MHz, $CDCl_3$): δ 7.8 (d, J=7.68 Hz, 2H, aromatics), 7.5 (d, J=8.42 Hz, 2H, aromatics), 6.3 (s, 1H), 5.9 (s, 1H), 5.6 (d, J=5.4 Hz, 1H), 3.73 (s, 3H), 3.5 (d, J=5.4 Hz, 1H, exchangeable with D_2O), 3.0 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.1, 147.5, 140.9, 139.5, 127.36, 127.3, 126.8, 72.5, 52.1, 44.4; MS (70 eV, *m/e*, %) 270 (M^+, 37), 253 (12), 238 (10), 210 (45), 183 (93), 158 (20), 157 (18), 131 (45), 130 (43), 103 (55), 77 (100), 55 (63), 52 (50); HRMS (M^+) calcd for $C_{12}H_{14}O_5S$ 270.05619. Found 270.05515.

4.2.10. (±)-Methyl 2-[hydroxy(4-hydroxy-3-methoxy-phenyl)methyl]acrylate (11). Reaction time: 96 h, methanol solvent, 54% yield of a viscous yellow tinged oil-purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); IR ν_{max}/cm^{-1} 3460, 1716, 1632; ^1H NMR (300 MHz, $CDCl_3$): δ 6.9 (s, 1H, aromatics), 6.8 (dd, J=13.9, 8.0 Hz, 2H, aromatics), 6.3 (bs, 2H, one hydrogen exchangeable with D_2O, OH phenolic), 5.85 (t, J=1.09 Hz, 1H), 3.8 (s, 3H, OCH_3), 3.7 (s, 3H, OCH_3 ester), 3.2 (bs, 1H, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 161.1, 146.5, 145.2, 142.0, 133.2, 125.8, 119.6, 114.1, 109.1, 73.0, 55.9, 51.9. Anal. calcd for $C_{12}H_{14}O_5$: C, 60.5%; H, 5.92%. Found C, 60.43%; H, 5.89%.

4.2.11. (±)-Methyl 2-[(6-bromo-1,3-benzodioxol-5-yl)-(hydroxy)methyl]acrylate (13). Reaction time: 32 h methanol solvent, 75% yield of a viscous yellow tinged oil purified by silica gel column chromatography, eluting with hexane/ethyl acetate 80:20); IR ν_{max}/cm^{-1} 3483, 2954, 2920, 2854, 1720, 1631, 1477, 1261, 1234, 1038; ^1H NMR (500 MHz, $CDCl_3$): δ 6.94 (s, 1H), 6.92 (s, 1H), 6.26 (s, 1H), 5.91 (s, 2H), 5.78 (s, 1H), 5.54 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 166.9, 147.9, 147.6, 140.6, 133.1, 126.8, 113.6, 112.6, 108.2, 101.8, 71.4, 52.1; MS (70 eV, *m/e*, %) 315 (M+2, 17), 313 (M^+, 15), 235 (87), 203 (43), 175 (24), 149 (100), 122 (81), 113 (66), 63 (60); HRMS (M^+) calcd for $C_{12}H_{11}BrO_5$ 313.97898. Found 313.97930.

4.2.12. (±)-Methyl 2-[hydroxy(7-methoxy-1,3-benzo-dioxol-5-yl)methyl]acrylate (14). Reaction time: 60 h,

methanol solvent, 52% yield of a viscous colorless oil (based on recovered aldehyde) purified by silica gel column chromatography, eluting with hexane/ethyl acetate 70:30) IR ν_{max}/cm^{-1} 3467, 3001, 2920, 1712, 1631, 1504, 1431, 1311, 1122, 1034; ^1H NMR (500 MHz, $CDCl_3$): δ 6.59 (d, J=0.78 Hz, 1H), 6.53 (d, J=1.22 Hz, 1H), 6.33 (s, 1H), 5.96 (s, 2H), 5.84 (t, J=0.78 Hz, 1H), 5.46 (br s, 1H), 3.89 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 148.8, 143.5, 141.7, 135.9, 134.7, 126.1, 106.1, 101.5, 100.8, 73.1, 56.5, 52.0. Anal. calcd for $C_{13}H_{14}O_6$: C, 58.65%; H, 5.30%. Found C, 58.60%; H, 5.27%.

4.2.13. (±)-Methyl 2-[hydroxy(3-hydroxy-4-methoxyphenyl)methyl]acrylate (15). Reaction time: 96 h, methanol solvent, 51% yield of a viscous colorless oil purified by silica gel column chromatography, (eluting hexane/ethyl acetate 70:30); IR ν_{max}/cm^{-1} 3433, 3005, 2954, 1712, 1628, 1593, 1508, 1439, 1273; ^1H NMR (300 MHz, $CDCl_3$): δ 6.90–6.78 (m, 3H), 6.31 (t, J=1.1 Hz, 1H), 5.86 (t, J=1.1 Hz, 1H), 5.46 (br s, 1H), 3.85 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.5, 146.0, 145.3, 134.4, 125.6, 118.2, 112.8, 110.3, 72.7, 55.9, 51.9; MS (70 eV, *m/e*, %) 238 (M^+, 55), 207 (20), 178 (20), 151 (100), 124 (15), 93 (28), 65 (12); HRMS (M^+) calcd for $C_{12}H_{14}O_5$ 238.0841. Found 238.0840.

4.2.14. (±)-Methyl 2-[hydroxy(3,4,5-trimethoxyphenyl)methyl]acrylate (16). Reaction time: 72 h, dichloromethane solvent, 72% yield of a viscous colorless oil purified by silica gel column chromatography eluting with hexane/ethyl acetate 70:30) IR ν_{max}/cm^{-1} 3491, 2997, 2943, 1716, 1631, 1593, 1504, 1327, 1234; ^1H NMR (300 MHz, $CDCl_3$): δ 6.58 (br s, 2H), 6.32 (t, J=1.1 Hz, 1H), 5.85 (t, J=1.1 Hz, 1H), 5.49 (br s, 1H), 3.83 (s, 6H), 3.82 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.5, 152.9, 141.6, 137.1, 136.7, 125.8, 103.4, 72.9, 60.7, 55.9, 51.9; MS (70 eV, *m/e*, %) 282 (M^+, 100), 250 (47), 222 (22), 195 (60), 169 (30), 138 (12), 113 (6); HRMS (M^+) calcd for $C_{14}H_{18}O_6$ 282.11033. Found 282.10639.

4.2.15. Methyl 8-methoxy-2*H*-chromene-3-carboxylate (17). Reaction time: 96 h, methanol solvent, 67% yield of a viscous yellow tinged oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 85:15); IR ν_{max}/cm^{-1} 2997, 2951, 2839, 1705, 1639, 1577, 1481, 1265, 1211, 1111; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39 (t, J=1.47 Hz, 1H), 6.85 (m, 3H), 6.74 (m, 1H), 5.0 (br s, 2H), 3.84 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.4, 147.4, 143.5, 133.2, 121.0, 120.5, 114.1, 64.4, 55.7, 51.6; HRMS (M^+) calcd for $C_{12}H_{12}O_4$ 220.0735. Found 220.0730.

4.2.16. (±)-Methyl 2-[(2-fluorophenyl)(hydroxy)methyl]acrylate (18). Reaction time: 16 h, methanol solvent, 100% yield of a viscous colorless oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); IR ν_{max}/cm^{-1} 3437, 2954, 1721, 1588, 1491, 1456, 1439, 1399, 1226, 1152, 1042; ^1H NMR (300 MHz, $CDCl_3$): δ 7.4 (m, 1H), 7.29 (m, 1H), 7.16 (m, 1H), 7.0 (m, 1H), 6.34 (br s, 1H), 5.88 (br s, 1H), 5.76 (m, 1H), 3.76 (s, 3H), 2.90 (br s, 1H, exchangeable with D_2O);^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.6, 161.4, 158.1, 140.5, 129.4, 129.3, 127.9, 126.3, 124.1, 124.0, 115.3, 115.0, 67.0, 52.0; HRMS (M^+) calcd for $C_{11}H_{11}FO_3$ 210.0692. Found 210.0690.

4.2.17. (±)-Methyl 2-[(2-bromophenyl)(hydroxy)methyl]acrylate (19). Reaction time: 26 h, methanol solvent, 73% yield of a viscous colorless oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); IR ν_{max}/cm^{-1} 3437, 3062, 3000, 2951, 1717, 1590, 1568, 1468, 1438, 1400, 1269, 1195, 1147, 1052, 962, 758; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, J=1.4, 8.0 Hz, 1H), 7.35 (m, 1H), 7.17 (m, 1H), 6.35 (d, J=0.74 Hz, 1H), 5.94 (br s, 1H), 5.57 (t, J=1.1 Hz, 1H), 3.78 (s, 3H), 2.95 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.7, 140.4, 139.6, 132.6, 129.1, 128.2, 127.5, 126.9, 122.9, 71.4, 52.1; HRMS (M^+) calcd for $C_{11}H_{11}BrO_3$ 269.9891. Found 269.9889.

4.2.18. (±)-Methyl 2-[hydroxy(4-methylphenyl)methyl]acrylate (20). Reaction time: 72 h, methanol solvent, 79% yield of a viscous colorless oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); IR ν_{max}/cm^{-1} 3447, 3024, 2951, 2922, 1722, 1629, 1512, 1438, 1397, 1275, 1195, 1149, 1040, 957; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J=8.0 Hz, 2H), 7.13 (d, J=8.0 Hz, 2H), 6.35 (s, 1H), 6.31 (s, 1H), 5.10 (s, 1H), 3.73 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.9, 142.2, 138.5, 137.6, 129.2, 126.6, 125.9, 73.0, 51.8, 20.9; HRMS (M^+) calcd for $C_{12}H_{14}O_3$ 206.0942. Found 206.0938.

4.2.19. (±)-Methyl 3-hydroxy-2-methylene-propanoate (21). Reaction time 120 h, no additional solvent, 74% yield of a pale yellow oil purified by distillation under reduced pressure; bp 65–70°C (1 mm Hg); IR (ν_{max}/neat) 3446, 2999, 2902, 1720, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.87 (s, 1H), 4.32 (s, 2H), 3.78 (s, 3H), 3.4–3.2 (br s, 1H, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 167, 139.5, 125.5, 62, 52; MS (70 eV, *m/e*, %) 116 (M^+, 2), 115 (2), 87 (100), 85 (75), 84 (86), 55 (65).

4.2.20. (±)-Methyl 3-hydroxy-2-methylenebutanoate (22). Reaction time: 96 h, no additional solvent, 90% yield of a yellow tinged oil purified by distillation under reduced pressure; bp 94–95°C (15 mm Hg); IR (ν_{max}/neat) 3470, 2937, 1712, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J=1.4 Hz, 1H), 5.8 (d, J=1.2 Hz, 1H), 4.75 (m, 1H), 3.73 (s, 3H), 3.0 (br d, J=3.8 Hz, 1H), 1.22 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ. Other spectral data were identical to those previously reported.[19b]

4.2.21. (±)-Methyl 3-hydroxy-2-methylene-pentanoate (23). Reaction time: 72 h, no additional solvent, 72% yield of a pale yellow oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 80:20); IR (ν_{max}/neat) 3473, 2966, 2937, 2879, 1716, 1633, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.2 (br s, 1H), 5.7 (br s, 1H), 4.3 (t, J=7 Hz, 1H), 3.8 (s, 3H), 3.4 (br s, 1H), 1.8–1.3 (m, 2H), 0.9 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.6 (C=O), 142.1, 124.6, 72.3, 51.5, 29.0, 9.8. Calcd for $C_7H_{12}O_3$ C 58.34; H 8.33%. Found C, 58.30%; H, 8.32%.

4.2.22. (±)-Methyl 3-hydroxy-2-methylene-hexanoate (24). Reaction time: 72 h, no additional solvent, 85%

yield of a pale yellow oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 80:20); IR (ν_{max}/neat) 3600, 3500, 2980, 2940, 2850, 2100, 1700, 1620, 1430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (t, J=1 Hz, 1H), 5.80 (t, J=1 Hz, 1H), 4.43 (q, J=7 Hz, 1H), 3.78 (s, 3H), 2.72 (br d, J=6.5 Hz, 1H, OH), 1.75–1.2 (m, 4H), 0.9 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.7 (C=O), 142.4, 124.6, 71.2, 60.3, 38.3, 19.0, 13.8. Calcd for $C_8H_{14}O_3$ C, 60.74%; H, 8.92%. Found C, 60.68%; H, 8.90%.

4.2.23. Methyl 3-hydroxy-2-methylene-heptanoate (25). Reaction time: 48 h, no additional solvent, 85% yield of a pale yellow oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); IR (ν_{max}/neat) 3600 (O–H), 3500, 2980, 2850, 2100, 1705 (C=O), 1620 (C=C), 1430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (t, J=1 Hz, 1H), 5.80 (t, J=1 Hz, 1H), 4.43 (t, J=6.5 Hz, 1H), 3.77 (s, 3H), 2.70 (br s, 1H, OH), 1.75–1.2 (m, 4H), 0.9 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.7, 142.4, 124.7, 71.5, 51.8, 35.9, 27.9, 22.5, 14.0. Calcd for $C_9H_{16}O_3$ C, 62.77%; H, 9.36%. Found C, 62.72%; H, 9.35%.

4.3. General procedure for preparation of Baylis–Hillman adducts 26–30 (aromatic heterocyclic aldehydes)

A mixture of the aromatic heterocyclic aldehyde (4.4–4.8 mmol), methyl acrylate (1.3 equiv.) and DABCO (0.65 equiv.) was sonicated (the reaction time for each aldehyde has been indicated together with the spectral data). Ultrasound bath temperature was constantly monitored and kept at 30–40°C during the reaction, through ice addition or by using a refrigerated recirculator. After the reaction time (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (40 mL). The organic layer was washed with distilled water (40 mL). The aqueous phase was extracted with ethyl acetate (4×40 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to furnish the Baylis–Hillman adducts. For some cases, no chromatographic purification is needed.

4.3.1. (±)-Methyl 2-[2-furyl(hydroxy)methyl]acrylate (26). Reaction time: 6 h; no additional solvent, 80% yield of a viscous oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 90:10); IR (Film) ν_{max}/cm^{-1} 3467, 3120, 3001, 2954, 2850, 1716, 1635, 1504, 1450, 1284, 1146, 1041, 952, 820, 747; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 1H), 6.36 (m. 1H), 6.30 (dd, J=3.3, 1.83 Hz, 1H), 6.23 (m, 1H), 3.70 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.3, 154, 142.2, 139.3, 126.6, 110.2, 107, 110.2, 107, 66.9, 51.9. Other spectral data were identical to those previously reported.[20]

4.3.2. (±)-Methyl 2-[hydroxy(pyridin-2-yl)methyl]acrylate (27). Reaction time: 4 h; no additional solvent, 98% yield of a yellowish viscous solid, no purification needed; mp 102–105°C, lit.[21b] 102°C; IR (KBr) ν_{max}/cm^{-1} 3418, 3125, 2959, 2850, 1712, 1605, 1564, 1441, 1417, 1341, 1290, 1225, 1191, 1141, 816; ^1H NMR (300 MHz, CD_3OD) δ 3.68 (3H, s); 5.78 (1H, s); 6.05 (1H, s); 6.36 (1H, s); 7.43 (2H, d, J=4.58 Hz); 8.45 (2H, d, J=4.58 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.3, 71.7, 123.6, 126.5, 143.8, 149.9, 154.3, 167.3; MS (70 eV, *m/e*, %) 193 (M^+, 55), 192 (35), 161 (100), 133 (94), 118 (25), 117 (23), 106 (82), 83 (45), 55 (42); HRMS (M^+) calcd for $C_{10}H_{11}NO_3$ 193.07389. Found 193.07377.

4.3.3. (±)-Methyl 2-[hydroxy(pyridin-3-yl)methyl]acrylate (28). Reaction time: 2 h; no additional solvent, 97% yield of a yellow tinged amorphous solid purified by silica gel column chromatography (eluting with hexane/ethyl acetate/methanol 60:40:0.02); mp 99–101°C; lit.[21b] 100°C; IR (KBr) ν_{max}/cm^{-1} 3422, 3125, 2954, 2850, 1716, 1629, 1593, 1439, 1330, 1297, 1150, 1061, 977; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J=1.6 Hz, 1H), 8.39 (dd, J=4.76, 1.47 Hz, 1H), 7.78 (dt, J=8.0, 1.83 Hz, 1H), 7.35 (dd, J=7.3, 5.1 Hz, 1H), 6.35 (bs, 1H), 6.11 (bs, 1H), 5.59 (s, 1H), 4.86 (bs, 1H, exchangeable with D_2O), 3.63 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.1, 149.0, 148.9, 143.8, 140.1, 136.7, 125.5, 124.9, 70.7, 52.2; HRMS (M^+) calcd for $C_{10}H_{11}NO_3$ 193.07389. Found 193.07377.

4.3.4. (±)-Methyl 2-[hydroxy(thien-2-yl)methyl]acrylate (29). Reaction time: 8 h; no additional solvent, 100% yield of a yellow tinged viscous oil, no purification needed; IR (Film) ν_{max}/cm^{-1} 3485, 3106, 2951, 2877, 1714, 1631, 1620, 1439, 1277, 1151, 1040, 990, 794; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J=1, 4 Hz, 1H), 6.95 (m, 1H), 6.92 (m, 1H), 6.34 (s, 1H), 5.97 (s, 1H), 5.76 (s, 1H), 3.48 (br s, 1H, exchangeable with D_2O), 3.73 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.2, 145.7, 141.3, 126.5, 125.7, 124.9, 124.5, 69.1, 51.9. Other spectral data were identical with those previously reported.[20]

4.3.5. (±)-Methyl 2-[hydroxy(1,3-thiazol-2-yl)methyl]-acrylate (30). Reaction time: 0.25 h; no additional solvent, 92% yield of a viscous oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 60:40). IR (Film) ν_{max}/cm^{-1} 3228, 3122, 2952, 1728, 1633, 1504, 1445, 1333, 1259, 1155, 1045, 964, 930, 818; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=1.8 Hz, 1H), 7.3 (d, J=1.8 Hz, 1H), 6.41 (bs, 1H), 6.0 (br s, 1H), 5.78 (s, 1H), 4.53 (br s, 1H, exchangeable with D_2O), 3.73 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.5, 166, 141.8, 139.4, 127.7, 119.7, 71.1, 52.1; MS (70 eV, *m/e*, %); 199 (M^+, 2), 182 (8), 167 (40), 139 (100), 123 (25), 111 (55), 86 (82), 57 (87); HRMS (M^+) calcd for $C_8H_9NO_3S$ 199.03032. Found 199.03034.

4.4. General procedure for preparation of Baylis–Hillman adducts 31–35 (methyl vinyl ketone and acrylonitrile as nucleophiles)

A mixture of the aromatic aldehyde (4–10 mmol), DABCO (0.65 equiv.) and acrylate derivative (1.3 equiv.) in methanol, dichloromethane (2 cm^3/mmol, indicated for each aldehyde) or without any additional solvent, was sonicated (the reaction time for each aldehyde has been indicated together with the spectral data). Ultrasound bath temperature was constantly monitored and kept at 30–40°C during the reaction, through ice addition or by using a refrigerated recirculator. After the reaction time (monitored by TLC),

the mixture was diluted with dichloromethane (50 cm^3). The organic solution was washed with 10% aqueous HCl (2×20 cm^3), concentrated under reduced pressure and dried over $MgSO_4$. After filtration and solvent removal, the residue was filtered through a pad of silica gel (eluent indicated for each adduct).

4.4.1. 2-[1,3-Benzodioxol-5-yl(hydroxy)methyl]acrylonitrile (31). Reaction time: 15 h, no additional solvent, 78% yield of a colorless viscous oil no purification needed; IR (Film) ν_{max}/cm^{-1} 3458, 2989, 2901, 2232, 1610, 1504, 1489, 1445, 1248, 1099, 1038, 932; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81–6.76 (m, 3H), 6.1 (d, J=1.46 Hz, 1H) 1H), 6.0 (d, J=1.47 Hz, 1H), 5.99 (s, 2H), 5.17 (s, 1H) 2.6 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 147.9, 147.8, 132.9, 129.4, 126, 120.2, 108.2, 106.7, 101.2, 73.7; MS (70 eV, %) 203 (M^+, 65), 172 (2), 151 (100), 121 (5), 93 (55), 65 (35); HRMS (M^+) calcd for $C_{11}H_9NO_3$ 203.05824. Found 203.05734.

4.4.2. (±)-[(4-Chlorophenyl)(hydroxy)methyl]buten-3-en-2-one (52). Reaction time: 48 h, dichloromethane used as solvent, 60% yield of a colorless viscous oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); IR (film) ν_{max}/cm^{-1} 3423, 1674; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 4H), 6.19 (s, 1H), 6.0 (s, 1H), 5.56 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 200, 149.6, 140.1, 133.2, 128.4, 127.8, 126.7, 71.8, 26.3; MS (70 eV, *m/e*, %) 212 (30), 210 (100), 195 (20), 175 (80), 157 (10), 139 (18), 77 (4 5); HRMS (M^+) calcd for $C_{11}H_{11}ClO_2$ 210.04476. Found 210.04474.

4.4.3. (±)-3-[Hydroxy(4-nitrophenyl)methyl]but-3-en-2-one (33). Reaction time: 24 h, dichloromethane used as solvent, 73% yield of a colorless viscous oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 70:30); IR (film) ν_{max}/cm^{-1} 3425, 1678; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J=1.83 Hz, 1H), 7.55 (d. J=1.83 Hz, 1H), 6.28 (s, 1H), 6.0 (s, 1H), 5.68 (s, 1H), 3.38 (br s, 1H, exchangeable with D_2O), 2.35 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 199.9, 149.0, 148.9, 147.1, 127.6, 127.2, 123.4, 71.8, 26.2; MS (70 eV, *m/e*, %) 221 (5), 220 (15), 204 (100), 174 (85), 131 (33), 115 (28), 77 (18); HRMS (M^+) calcd for $C_{11}H_{11}NO_4$ 221.06881. Found 221.06882.

4.4.4. (±)-2-[Hydroxy(pyridin-2-yl)methyl]acrylonitrile (34). Reaction time: 3/4 h, no additional solvent, 98% yield of a yellow amorphous solid purified by silica gel column chromatography (eluting with dichloromethane); mp 66–67°C, lit.[23] 66–67°C; IR (Film) ν_{max}/cm^{-1} 3200, 2225, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (m, 1H), 7.76 (m, 1H), 7.39 (m, 1H), 7.29 (m, 1H), 6.22 (s, 1H), 6.05 (s, 1H), 5.27 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 156, 148.5, 137.5, 130.9, 125.8, 123.7, 121.2, 116.7, 72.8. Other spectral data were identical with those previously reported.[23]

4.4.5. (±) 3-[Hydroxy(pyridin-2-yl]but-3-en-2-one (35). Reaction time: 3/4 h, no additional solvent used, 98% yield of a viscous oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate/methanol 70:20:10); IR (film) ν_{max}/cm^{-1} 3350, 1685; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J=4.6 Hz, 1H), 7.52 (td, J=1.8, 7.7 Hz, 1H), 7.30 (d, J=7.9 Hz, 1H), 7.05 (dd, J=5.0, 7.3 Hz, 1H), 6.1 (s, 1H), 6.0 (s, 1H), 5.6 (s, 1H), 4.99 (br s, 1H, exchangeable with D_2O), 2.19 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 199.3, 159.9, 149.7, 136.5, 126.4, 122.2, 121.2, 70.9, 26.1. Other spectral data were identical with those previously reported.[23]

4.4.6. (±)-2-(1-Hydroxypropyl)acrylonitrile (36). Reaction time: 8 h, no additional solvent used, 80% yield of a pale yellow oil purified by distillation under reduced pressure: bp 64–65°C (1 mm Hg); IR (film) ν_{max}/cm^{-1} 3460, 220, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (s, 2H), 4.1 (t, 1H), 3.4 (br s, 1H), 1.67 (q, 2H), 0.91 (t, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 130.3, 126.9, 117, 73, 29.1, 9.0. Other spectral data were identical with those previously reported.[25]

4.4.7. (±)-3-(1-Hydroxypropyl)but-3-en-2-one (37). Reaction time: 5 h, no additional solvent used, 82% yield of a colorless oil purified by silica gel column chromatography (eluting with hexane/ethyl acetate 90:10); IR (film) ν_{max}/cm^{-1} 3450, 1683, 1661; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 5.96 (s, 1H), 4.46 (m, 1H), 2.68 (br, s, exchangeable with D_2O), 2.17 (s, 3H), 1.67 (q, 2H), 0.97 (t, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 199.5, 145.4, 126.1, 69.9, 28.2, 26.5, 7.7. Other spectral data were identical with those previously reported.[26]

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