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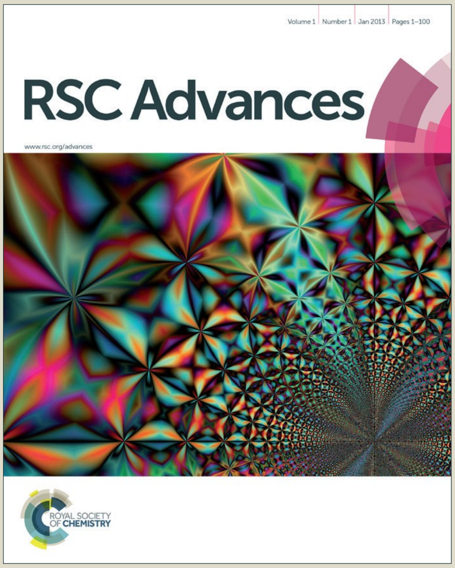

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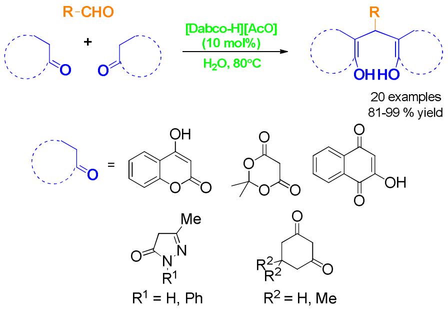
Ionic liquid [Dabco-H][AcO] as a highly efficient and recyclable catalyst for the synthesis of various bisenol derivatives via domino Knoevenagel–Michael reaction in aqueous media

Cheng Yang, Wan-Qi Su, Da-Zhen Xu*



An efficient, green and reusable catalytic system for synthesis of various bisenol derivatives is presented.

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Ionic liquid [Dabco-H][AcO] as a highly efficient and recyclable catalyst for the synthesis of various bisenol derivatives *via* domino Knoevenagel–Michael reaction in aqueous media

Cheng Yang, Wan-Qi Su, Da-Zhen Xu*

National Pesticide Engineering Research Center (Tianjin), State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, People's Republic of China

Fax: +86 22 2350 5948; E-mail: xudazhen@nankai.edu.cn

Keywords

aldehydes, aqueous medium, ionic liquid, recyclability, domino Knoevenagel−Michael reaction

Abstract

A simple and highly efficient domino Knoevenagel–Michael reaction procedure for the synthesis of a series of bisenols has been successfully developed. In the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco)-based ionic liquid catalysts, which are environmental friendly, inexpensive, and recyclable, the reaction afforded the corresponding bisenols compounds in excellent yields within short times in aqueous media. This green synthetic protocol is applicable to a wide range of aldehydes with enol compounds, including 4-hydroxycoumarin, 2,4-dihydro-3H-pyrazol-3-one, cyclohexane-1,3-dione, Meldrum's acid, 2-hydroxy-1,4-naphthoquinone (Lawsone) and their derivatives. This method is readily amenable to large-scale synthesis. The use of water as the reaction medium makes the process environmentally benign. Moreover, water is the only byproduct. The catalysts can be recycled five times without activity loss.

Introduction

Nowadays, the increasing environmental pollution and its intensive impact on living systems have attracted significant attention. It is very urgent to develop chemical processes using environmentally acceptable chemicals, solvents, catalysts, employing atom efficient procedures and reducing waste. The concept of green chemistry has been more and more deeply rooted in the people's hearts. Based on the principles of green chemistry, firstly, hazardous organic solvents should be avoid and replaced with nonpolluting alternative reaction media, particularly aqueous media.[1] Water is cheap, safe, non-toxic and readily available. To perform the organic reactions in water is one of the fundamental challenges.[2] Secondly, using low toxic and recyclable catalysts instead of transition metals, which are often toxic and difficult to dispose of properly in large quantities, is a significant part of this innovation. So, the catalysts should be with characteristics, such as high activity, selectivity and easy separation, recovery, recycling. Ionic liquids (ILs) as homogeneous catalysts, which could be easily separated from reaction mixtures for reuse, have consequently attracted significant attention as environmentally benign media for chemical processes.[3] Among the various ionic liquids, functional ionic liquids (ILs) catalysts are particularly attractive and important. They have been applied as soluble and recyclable organocatalysts in many reactions with good to excellent performance.[4-8] Thirdly, efficient procedures with high atom economy are essentials for green chemistry. The one-pot multi-component reactions (MCRs), which have emerged as a highly valuable synthetic tool in the context of modern drug discovery, could rapidly create several new bonds in a single step to give highly functionalized organic molecules.[9] Development and utilization of multi-component reactions (MCRs) are of prime important for both drug discovery and green chemistry. Therefore, people have paid increasingly attention on the development of MCRs in order to find new, efficient synthetic methodologies to afford a broad range of complexity and diversity of the molecules.[10] Finally, the purification procedure must be simply. After completion of the reaction, the desired products could be easily separated and purified without any requirement of column

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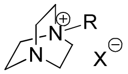
chromatographic purification. So the reaction is readily amenable to large-scale synthesis and the waste can be reduced effectively in both academic and industrial research.

Enol is an important structural component and widespread in natural compounds. In particular, the compounds of bisenols, such as biscoumarins, bis(1H-pyrazol-5-ols), bis(cyclic 1,3-diketones), bis(Meldrum's acids), bis(2-hydroxynaphthalene-1,4-diones) etc. and their derivatives, are often appeared a wide variety of pharmacologically and biologically activities. For example, biscoumarins and its derivatives showed diverse range of biological properties such as anti-HIV, antibiotic, antifungal, antibacterial, antioxidant, anticancer, and anticoagulant.[11] Bis(1H-pyrazol-5-ols), as an important class of pyrazoles which are an important class of bioactive drug target in the pharmaceutical industry,[12] have been used as anti-inflammatory, antipyretic, gastric secretion stimulatory, antidepressant, antibacterial, and antifilarial agents.[13] Bis(cyclic 1,3-diketones) and bis(Meldrum's acids), as important class of tetraketones, are key intermediates for the preparation of heterocyclic three-ring systems xanthendione and acridindione.[14] 2-Hydroxy-1,4-naphthoquinone (Lawsone), isolated from a medicinal plant Lawsonia inermis, has been used for more than 4000 years as hair dye, body paint and tattoo dye. Recently, chemists have found that lawsone and its derivatives also have a wide range of biological and pharmacological activities, including antibacterial, antioxidant, trypsin inhibitor, and anticoagulant activity.[15]

These bisenols usually synthesized through the domino Knoevenagel–Michael reactions of aldehydes with two equivalents of enol compounds in the presence of catalyst. Various procedures involving different catalysts and solvents have been reported for the synthesis of biscoumarins,[16] tetraketones (including bis(cyclic 1,3-diketones) and bis(Meldrum's acids)),[17] bis(1H-pyrazol-5-ols)[18] and bis(2-hydroxynaphthalene-1,4-diones).[19] But there is no universal procedure that could promote the domino Knoevenagel–Michael reaction to afford more than two kinds of bisenols under the same conditions. Even though, the reported catalyst systems often suffered from drawbacks like low yield, long reaction time, expensive reagents, harsh conditions, and use of expensive, toxic and unreusable catalyst. Therefore, the development of green, efficient and universal procedures for the synthesis of bisenols is crucial in terms of both synthetic technology and environmental concerns. In continuation of our interest in green chemistry and ILs catalyzed organic reactions[20], here, following the principles of green chemistry (pure water as solvent, reusable catalysts, high atom economy and easy purification), we wish to disclose a domino Knoevenagel–Michael reaction for the synthesis of various bisenols catalyzed by Dabco-base ionic liquid in nearly quantitative yields.

Results and discussion

The ionic liquid catalysts 1,4-diazabicyclo[2.2.2]octane hydroacetate ([Dabco-H][AcO]), hydrochloride ([Dabco-H]Cl), and hydrotetrafluoroborate ([Dabco-H][BF_4]), and 1-butyl-1,4-diazabicyclo[2.2.2]octanylium bromide ([Dabco-C_4]Br), chloride ([Dabco-C_4]Cl), 1-(3-hydroxypropyl)-1,4-diazabicyclo[2.2.2]octanylium chloride ([Dabco-C_3OH]Cl) and 1-(2,3-dihydroxypropyl)-1,4-diazabicyclo[2.2.2]octanylium chloride ([Dabco-DHP]Cl) were synthesized by the literature we have reported and shown in Figure 1.[20(c)]



[Dabco-H][AcO], X = AcO, R = H
[Dabco-H]Cl, X = Cl, R = H
[Dabco-H][BF_4], X = BF_4, R = H
[Dabco-C_4]Br, X = Br, R = n-Butyl
[Dabco-C_4]Cl, X = Cl, R = n-Butyl
[Dabco-C_3OH]Cl, X = Cl, R = 3-hydroxypropyl
[Dabco-DHP]Cl, X = Cl, R = 2,3-dihydroxypropyl

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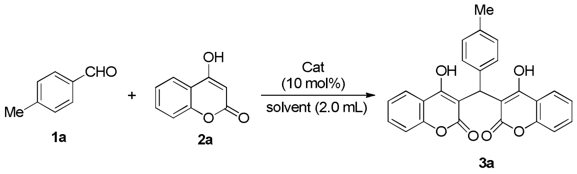
Figure 1. Structures of the Dabco-base ionic liquid catalysts.

Initially, the reaction between 4-methylbenzaldehyde (**1a)** and 4-hydroxycoumarin (**2a)** was employed as the model reaction to screen the Dabco-base ILs catalysts in ethanol as well as other common solvents in order to develop appropriate reaction conditions. As can be seen from the results summarized in Table 1, all the tested Dabco-base ILs catalysts could drive well the reaction, and afford the product **3a** with moderate to excellent yield (71-95%)(Table 1, entries 1-7). Among them, the catalyst [Dabco-H][AcO] gave **3a** with a very high yield of 95% in 3 hours at 30 ºC (Table 1, entry 1). The initial trials were very encouraging as the biscoumarin **3a** could be achieved *via* domino Knoevenagel–Michael reaction catalyzed by Dabco-base ionic liquids. Next, [Dabco-H][AcO] was used as the catalyst of choice and evaluated in different solvents. We found that when the reaction performed in the solvent containing OH group, such as ethanol, methanol and water, the target products were often formed in very high yields (95%, 92%, 96%)(Table 1, entries 1, 8 and 9). Other solvents also provided **3a** with moderate to good yields (Table 1, entries 10-12). It was very fortunate that the best results were obtained for water, which is a desirable solvent from the green chemistry viewpoint. Then we tried to raise the reaction temperature up to 50 and 80 ºC in water in the presence of 10 mol% [Dabco-H][AcO] catalyst (Table 1, entries 13-14). Finally, we found that under conditions of 80 ºC in water product **3a** could be obtained in an excellent yield of 96% within only 0.25 hour (Table 1, entry 14). It was particularly gratifying that when we decreased the catalyst loading to 5 mol% or 3 mol%, the reaction still smoothly proceeded in water to provide **3a** in good yield, just only more reaction time was needed (Table 1, entries 15 and 16). Importantly, without any catalyst only a trace of the product was observed even after 24 hours which further necessitates the use of [Dabco-H][AcO] catalyst in this transformation (Table 1, entry 17). Moreover, this simple procedure allowed easy scale-up of the reaction, and as shown in Table 1, 92% yield was obtained in the 50 mmol scale reaction (Table 1, entry 18), indicating the practicability of our protocol.

Under the optimal conditions, after completion of the reaction, the crude products were easily separated from the mixture just by filtering and no chromatographic technique was used for product purification. The ionic liquid catalysts dissolved in water which could be easily recover and directly reused in the next recycling run under the same conditions. This is an atom economic procedure, and it just produces water as waste. In addition, using water as the solvent is cheap, safe, non-toxic, readily available, and allowed the domino Knoevenagel–Michael reaction for the synthesis of bisenol derivatives to be performed in a very simple, cheap and green manner.

Table 1. Optimization of reaction conditions[a]



Entry	Cat (10 mol%)	Solvent	T (°C)	Time (h)	Yield (%)[b]
1	[Dabco-H][AcO]	C_2H_5OH	30	3	95
2	[Dabco-H]Cl	C_2H_5OH	30	4	90
3	[Dabco-H][BF_4]	C_2H_5OH	30	4	85
4	[Dabco-C_4]Br	C_2H_5OH	30	3	94
5	[Dabco-C_4]Cl	C_2H_5OH	30	4	88
6	[Dabco-C_3OH]Cl	C_2H_5OH	30	4	83
7	[Dabco-DHP]Cl	C_2H_5OH	30	4	71

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8	[Dabco-H][AcO]	CH_3OH	30	4	92
9	[Dabco-H][AcO]	H_2O	30	3	96
10	[Dabco-H][AcO]	DCE	30	4	63
11	[Dabco-H][AcO]	CH_3CN	30	4	82
12	[Dabco-H][AcO]	THF	30	4	69
13	[Dabco-H][AcO]	H_2O	50	1.5	96
14	[Dabco-H][AcO]	H_2O	80	0.25	96
15[c]	[Dabco-H][AcO]	H_2O	80	0.25	93
16[d]	[Dabco-H][AcO]	H_2O	80	0.3	90
17	---	H_2O	80	24	Trace
18[c,e]	[Dabco-H][AcO]	H_2O	80	1	92

[a] Conditions: 4-methylbenzaldehyde (**1a**, 1 mmol), 4-hydroxycoumarin (**2a**, 2 mmol), Dabco-base IL catalyst (0.1 mmol) and solvent (2 mL).

[b] Isolated yield.

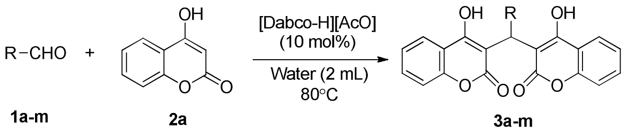
[c] 5 mol% catalyst.

[d] 3 mol% catalyst.

[e] 50 mmol scale.

With the optimal conditions in hand, we then examined the scope of various aldehydes (**1a-m**) with 4-hydroxycoumarin (**2a**) to synthesis of biscoumarins (**3a-m**) *via* domino Knoevenagel–Michael reaction catalyzed by [Dabco-H][AcO] in water under 80°C. As shown in Table 2, a large number of aromatic aldehydes with electron withdrawing groups or donating groups were all converted to the corresponding products in near quantitative yields within 15 minutes (Table 2, entries 1-10). Different subsituted aryl group has not shown much effect on the formation of final product. Similar results were obtained with the heteroaromatic aldehydes (Table 2, entries 11-12). n-Butyraldehyde as an aliphatic aldehyde was also tested in this procedure, the corresponding product was obtained in a quantitative yield (Table 2, entry 13).

Table 2. Domino Knoevenagel–Michael reaction of aromatic/heteroaromatic/aliphatic aldehydes with 4-hydroxycoumarin catalyzed by [Dabco-H][AcO][a]



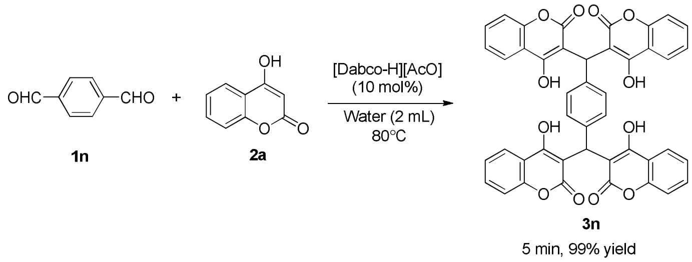
Entry	R	Product	Time (min)	Yield (%)[b]
1	4-MeC_6H_4	**3a**	15	96
2	Ph	**3b**	3	98
3	4-$MeOC_6H_4$	**3c**	3	98
4	4-ClC_6H_4	**3d**	2	99
5	4-BrC_6H_4	**3e**	2	99
6	3-BrC_6H_4	**3f**	3	98
7	2-BrC_6H_4	**3g**	3	98
8	p-$NO_2C_6H_4$	**3h**	5	99
9	2,4-$Cl_2C_6H_3$	**3i**	15	96

10	Naphthalen-2-yl	**3j**	6	99
11	Thiophen-2-yl	**3k**	8	98
12	Furan-2-yl	**3l**	10	98
13	n-Propyl	**3m**	6	99

[a] Conditions: aldehyde (**1**, 1 mmol), 4-hydroxycoumarin (**2**, 2 mmol), IL catalyst [Dabco-H][AcO] (0.1 mmol) in water (2 mL), 80°C.

[b] Isolated yield.

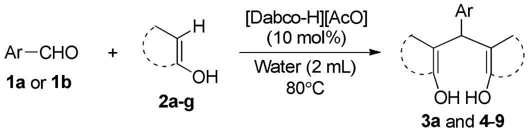
It is of interest to further extend the application of this procedure to structurally complex skeleton synthesis. Thus, we selected the reaction of terephthaldehyde with 4-hydroxycoumarin to give the Bis[bis(4-hydroxycoumarinyl)methanes] **3n** with an excellent yield of 99% in the presence of 10 mol% [Dabco-H][AcO] in aqueous medium within 5 minutes at 80 °C (Scheme 1).

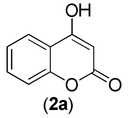
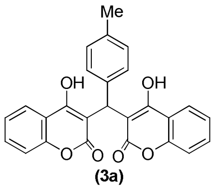


Scheme 1. Synthesis of Bis[bis(4-hydroxycoumarinyl)methanes] **3n**.

After the above success, to confirm the generality of the present approach, we then extended the method to synthesis more kinds of bisenol derivatives in aqueous media. The results are summarized in Table 3. Under the optimal reaction conditions, the substrates, such as 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one, 3-methyl-1H-pyrazol-5(4H)-one, dimedone and cyclohexane-1,3-dione, gave the corresponding products **4**-7 in quantitative yields within 1-10 minutes (Table 3, entries 2-5). Furthermore, product benzylidene-bis-(Meldrum's acid) (**8**) could be formed with an excellent yield of 93% in only 30 minutes even at room temperature (Table 3, entry 6). When 2-hydroxy-1,4-naphthoquinone was used as substrate in the reaction, a good yield of 81% (**9**) was also obtained (Table 3, entry 7).

Table 3. The reaction of aromatic aldehydes with different enols compounds[a]



Entry	Enols	Product	Time (min)	Yield (%)[b]
1	 (**2a**)	 (**3a**)	15	96

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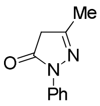
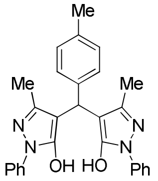
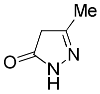
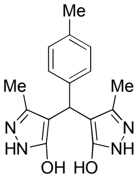
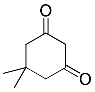
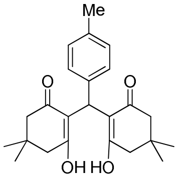
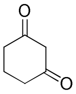
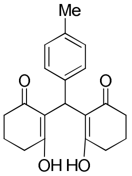
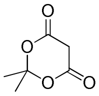
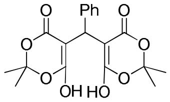
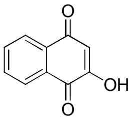
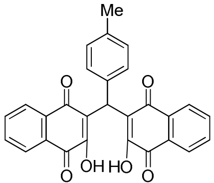
2	 (**2b**)	 **(4)**	<1	98
3	 (**2c**)	 **(5)**	5	98
4	 (**2d**)	 **(6)**	10	96
5	 (**2e**)	 **(7)**	10	98
6 ^c	 (**2f**)	 **(8)**	30	93
7^d	 (**2g**)	 **(9)**	120	81

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[a] Conditions: aromatic aldehyde (**1**, 1 mmol), enols (**2**, 2 mmol), IL catalyst [Dabco-H][AcO] (0.1 mmol) in water (2 mL), 80°C.

[b] Isolated yield.

[c] Room temperature.

[d] Ethanol-H_2O (1:1).

The reusability of the catalyst was examined for the synthesis of **3c**. After completion of the reaction, the catalyst could be easily recycled by filtering the products from the mixture. The filtrate containing the water and the IL catalyst [Dabco-H][AcO] could be directly reused for the next cycle. The crude product was purified by the crystallization technique and no column purification was followed. It was observed that this Dabco-base catalyst

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could be recovered and reused in the domino Knoevenagel–Michael reaction for five times at least. The results are presented in Figure 2.

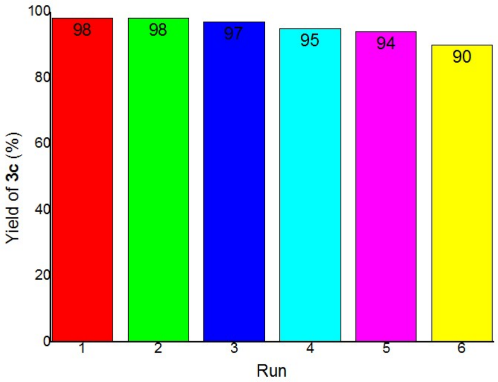
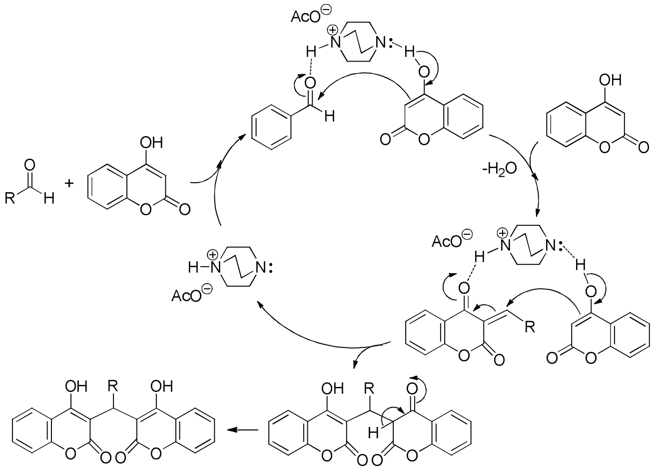


Figure 2. Recycling of the catalyst [Dabco-H][AcO] for the synthesis of **3c**.

A plausible mechanism for the formation of bisenols in the presence of [Dabco-H][AcO] is shown in Scheme 2. The process represents a typical domino reaction by double-activation. In the initiation step of the catalytic cycle, double-activation of the carbonylgroup of aldehydes and enols (4-hydroxycoumarin as example) by the catalyst ([Dabco-H][AcO]) occurred to formation of Knoevenagel intermediate. Then the catalyst may activate both the Knoevenagel intermediate and another molecule of enol to occur the Michael reaction, and take the H^+ from enol by the right N and give the H^+ attaching to left N to –C=O. Finally, a tautomerzation via H [1, 3] shift takes place to produce target product.



Scheme 2. Proposed mechanism for the synthesis of bisenols.

Conclusion

In conclusion, we have described a green and simple protocol for highly efficient synthesis of a series of bisenols using catalytic amount of efficiently reusable Dabco-base ionic liquid catalysts. Performing in aqueous media allowed these domino Knoevenagel–Michael reactions to be driven in a very simple, clean and green manner. After completion of the reaction, the desired products could be easily separated and purified without any requirement of column chromatographic purification. This procedure also offers other significant advantages including simple operation, excellent yield, short reaction time, atom economy, scaling up to multigram quantities, ease of separation and recyclability of the catalyst. To the best of our knowledge, such an efficient domino

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Knoevenagel–Michael reaction performed in water for the synthesis of a wide variety of bisenols is reported for the first time. A plausible reaction mechanism was proposed. We believe that this method will be found useful applications in the synthesis of bisenols.

Experimental

General experimental information. All chemicals were purchased from commercial suppliers and were used without further purification. Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were determined with an X-4 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer with DMSO-d_6 and $CDCl_3$ as the solvent. Chemical shifts are reported relative to TMS as internal standard. The ^{1}H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constant in hertz, and number of protons.

General procedure for the synthesis of bisenols.

A 5-mL round bottomed flask was charged with the aldehydes (**1**, 1 mmol), enols (**2**, 2 mmol), [Dabco-H][AcO] catalyst (0.1 mmol), and water 2.0 mL. Then the mixture was vigorously stirred at 80 °C. The formation of the products was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, filtered and washed with cold water. The crude products were purified by recrystallization from ethanol and no column purification was followed. After removing more water under vacuum, the catalyst [Dabco-H][AcO] left in water could be directly reused in the next recycling run under the same conditions.

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