Simple and Effective Protocol for Claisen–Schmidt Condensation of Hindered Cyclic Ketones with Aromatic Aldehydes

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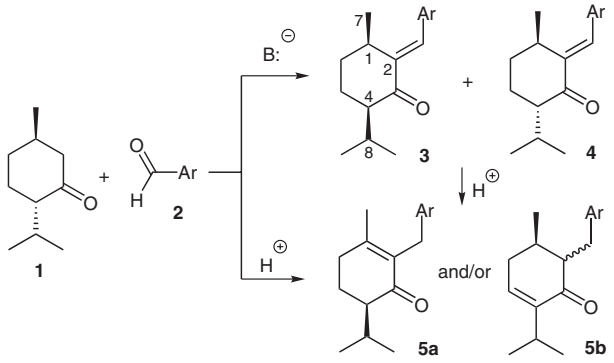
Dedicated to the memory of Professor Ludmila Yanovskaya

Abstract: A simple and effective methodology for Claisen–Schmidt condensation of (–)-menthone and other hindered cyclic ketones with aromatic aldehydes under highly basic conditions using a polar aprotic solvent and a strong base (alkali metal hydroxide or an alkoxide) is described and discussed.

Key words: aldehydes, α,β-unsaturated ketones, condensation, diastereoselectivity, super basic conditions

(–)-Menthone (**1**) has been widely used in organic synthesis as an inexpensive chiral synthon.[1] One of the ways of modifying **1** is to introduce an arylidene moiety by Claisen–Schmidt condensation with aromatic aldehydes **2** to produce chiral α,β-unsaturated ketones **3** and **4** (Scheme 1). However, a poor reactivity of **1** under common reaction conditions (alkali metal hydroxides or alkoxides in alcohol media[2]) has been found (Table 1, entries 1,2,12,14,31).[3] The use of stronger bases such as $NaNH_2$[3] or NaH[4,5] in low-polar solvents has not improved the result substantially, and moderate yields of **3a** have been obtained at best (entries 3,4).[5] The acid-catalyzed reaction is complicated due to migration of the benzylidene double bond in cyclohexane ring (compounds **5a** and **5b**, Scheme 1),[6,7] and only in rare cases has acid catalysis been reported (entry 5).[3]

These obstacles have been successfully overcome by applying the so-called super-basic media[8] (the combination of an alkali hydroxide and a polar aprotic solvent).[9] Such an approach has allowed us to synthesize a number of arylidene menthanones **3** in good yields.[10-12] These compounds have found practical application as chiral components for liquid crystal materials.[13–17] The stereochemistry of the major product of the condensation, **3** (*cis-E*,1*R*,4*R*-configuration), has been exhaustively studied by different methods[18,19] including X-ray diffraction for compounds **3h**,**3k**,**3n** and **3o**.[19] Compounds of the same configuration at C-4 as in **1**, *trans-E*,1*R*,4*S*-diastereomers **4o** and **4x** (R = 4-COOMe), have been synthesized indirectly, and their stereochemistry has been proved by X-ray crystallographic and NMR spectroscopic data.[20] The *Z*-isomers of 1*R*,4*R*-2-arylidene derivatives have been obtained by photochemical isomerization of the corresponding *E*-isomers **3** and studied by NMR and molecular simulation.[18c,d]



Scheme 1

Thus, the most pronounced differences in ^{1}H NMR spectra of diastereomeric compounds **3** and **4** were found to be the lower field chemical shifts of protons at C-4, C-6 and C-8 adjacent to the C-4 chiral center in 1*R*,4*R*-diastereomers **3** when compared to corresponding 1*R*,4*S*-diastereomers **4**. Moreover, it was shown experimentally that *trans-E*,1*R*,4*S*-diastereomers **4o**[21] and **4y** (R = 4-OH)[14b] are thermodynamically less stable than corresponding *cis*-diastereomers **3o** and **3y,** and the equilibrium mixture of **3** and **4** forms in approximately a 70:30 ratio under conditions (both basic and acidic) which allow the epimerization of **3**. In the case of *Z*-isomers of **3**, the arylidene proton is observed in the range of 6.2–6.3 ppm[18c,d] that is about 1 ppm upfield when compared to the corresponding *E*-isomers (6.9–7.2 ppm) in the ^{1}H NMR spectra.

However, the detailed synthetic procedure for compounds of type **3** and discussion on its features have hitherto been published in sources which are difficult to access.[10–12,21–23] Apparently, it sometimes results in applying the simplest and non-optimized procedure,[24,25] or even in repeated studies on the reaction optimization.[5] Applications of superbasic media to Claisen–Schmidt condensation[26,27] and to subsequent transformations of α,β-unsaturated ketones[28,29] were also reported.

Here we summarize our work on Claisen–Schmidt condensation of (–)-menthone with aromatic aldehydes promoted by hydroxides and alkoxides of alkali metals and tetrabutylammonium in polar aprotic solvents. We also extend the approach on the reactions to some other cyclic ketones and discuss the scope and limitation of the synthetic methodology proposed.

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We have failed to obtain any 2-arylidenementhanones **3** apart from 2-benzylidene derivative (**3a**) following the method described in reference 3 (acid catalysis with dry HCl, Table 1, entry 5). However, the use of the super-basic media, alkali hydroxides or alkoxides (KOH, $CsOH·H_2O$, Bu_4NOH, *t*-BuOK) in combination with polar aprotic solvents (DMSO, DMF, DMA) (Table 1) solved the problem.

Table 1 Reaction of (–)-Menthone (**1**) with Aromatic Aldehydes **2**

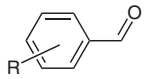
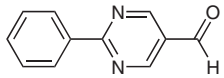
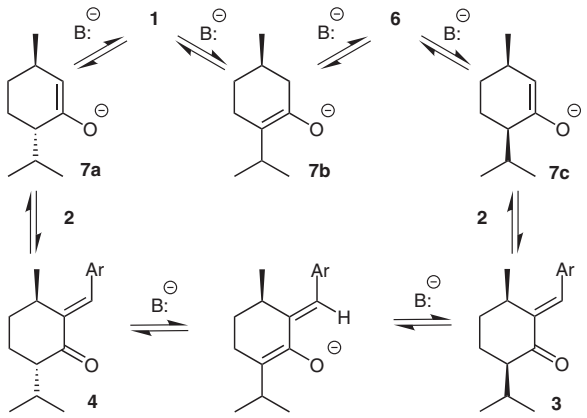
Entry	Aldehyde	Method[a]	Catalyst (equiv per **1**)	Solvent	Reaction time (h)	Product	Yield (%)
							
1	R = H, **2a**	–[5]	50% aq NaOH	H_2O	–	**3a**	10
2	**2a**	–[5]	15% NaOEt	EtOH	–	**3a**	14
3	**2a**	–[3]	$NaNH_2$ (1.0)	Et_2O	–	**3a**	18
4	**2a**	–[5]	NaH (1.0)	Et_2O	–	**3a**	32
5	**2a**	–[3]	dry HCl	neat	–	**3a**	37
6	**2a**	A	KOH (1.0)	DMSO	4	**3a**	52
7	**2a**	C	$CsOH·H_2O$ (0.25)	DMSO	16	**3a**:**4a**	84[b]
8	R = 2-F, **2b**	C	$CsOH·H_2O$ (0.25)	DMSO	16	**3b**	82
9	R = 3-F, **2c**	C	$CsOH·H_2O$ (0.20)	DMSO	24	**3c**:**4c**	70[c]
10	R = 4-F, **2d**	A	KOH (1)	DMSO	2	**3d**	49
11	**2d**	C	$CsOH·H_2O$ (0.25)	DMSO	16	**3d**	72
12	R = 4-Cl, **2e**	A	KOH (0.7)	MeOH	96	**3e**	15
13	**2e**	A	KOH (1.0)	DMSO	3	**3e**	56
14	R = 4-Br, **2f**	A	50% aq KOH (0.7)	MeOH	96	**3f**	11
15	**2f**	A	NaOH (0.5)	DMSO	3.5	**3f**	64
16	**2f**	A	KOH (0.5)	DMSO	3.5	**3f**	72
17	**2f**	A	$CsOH·H_2O$ (0.25)	DMSO	3.5	**3f**	81
18	**2f**	A	Bu_4NOH (0.11)[d]	DMSO	2	**3f**	80
19	**2f**	C	*t*-BuOK (0.1)	DMSO	2.5	**3f**	84
20	**2f**	A	KOH (0.5)	DMA	3.5	**3f**	65
21	**2f**	A	KOH (0.5)	DMF	3.5	**3f**	40
22	**2f**	A	$CsOH·H_2O$ (0.25)	DMF	3.5	**3f**	57
23	**2f**	A	Bu_4NOH (0.11)[d]	DMF	3.5	**3f**	61
24	R = 3-NO_2, **2g**	A	KOH (0.7)	DMSO	3	**3g**	–
25	**2g**	B	KOH (0.4)	3:1 DMF–MeOH	5	**3g**	47
26	R = 4-NO_2, **2h**	B	KOH (0.3)	4:1 DMSO–MeOH	3	**3h**	62
27	R = 4-CN, **2i**	A	KOH (0.36)	3:1 DMF–MeOH	3.5	**3i**	31
28		B	KOH (0.4)	4:1 DMSO–MeOH	3.5	**3j**	21
29	**2j**	C	KOH (0.4)	1:1 DMSO–MeOH	3.5	**3j**	48

Table 1 Reaction of (–)-Menthone (**1**) with Aromatic Aldehydes **2** (continued)

Entry	Aldehyde	Method[a]	Catalyst (equiv per **1**)	Solvent	Reaction time (h)	Product	Yield (%)
30	R = 4-OMe, **2k**	–[3]	$NaNH_2$ (1.0)	Et_2O		**3k**	5
31	**2k**	A	50% aq KOH (1.0)	MeOH	6	**3k**	17
32	**2k**	A	NaOH (1)	DMSO	4	**3k**	35
33	**2k**	A	KOH (1.0)	DMSO	2.5	**3k**	51
34	**2k**	A	KOH (0.9)	DMSO	24	**3k**	78
35	**2k**	A	$CsOH·H_2O$ (0.4)	DMSO	24	**3k**	46
36	R = 2-OMe, **2l**	C	$CsOH·H_2O$ (1.0)	DMSO	2.5	**3l**	74
37	R = 4-OEt, **2m**	A	KOH (1.0)	DMSO	19	**3m**	4
38	R = 4-NMe_2, **2n**	A	KOH (1.0)	DMSO	120	**3n**	15
39	R = 4-Ph, **2o**	A	KOH (0.5)	DMSO	5	**3o**	64
40	**2o**	B	KOH (0.5)	DMSO	3	**3o**	72
41	**2o**	C	$CsOH·H_2O$ (0.25)	DMSO	5	**3o**	75
	R = 4-(4-$C_nH_{2n+1}OC_6H_4$)						
42	n = 1, **2p**	A	KOH (0.5)	DMSO	5	**3p**	64
43	n = 4, **2q**	A	KOH (0.5)	DMSO	5	**3q**	18
44	**2q**	A	CsOH. H_2O (0.25)	DMSO	5	**3q**	26
45	**2q**	C	$CsOH·H_2O$ (0.25)	DMSO	5	**3q**	38
46	**2q**	C	Bu_4NOH (0.11)[d]	DMSO	5	**3q**	61
47	n = 5, **2r**	C	KOH (0.5)	DMSO	5	**3r**	38
48	**2r**	C	$CsOH·H_2O$ (0.25)	DMSO	3	**3r**	50
49	n = 7, **2s**	A	KOH (0.5)	DMSO	5	**3s**	8
50	**2s**		KOH/dibenzo-18-crown-6 (0.5)	DMSO	5	**3s**	24
51	**2s**	C	Bu_4NOH (0.11)[d]	DMSO	5	**3s**	51
52	n = 9, **2t**	A	KOH (0.5)	DMSO	5	**3t**	–
53	**2t**	C	Bu_4NOH (0.25)[d]	DMSO	5	**3t**	29
	R = 4-(4-$XC_6H_4CH_2O$)						
54	X = H, **2u**	C	KOH (0.8)	DMSO	16	**3u**	48
55	X = Me, **2v**	C	$CsOH·H_2O$ (0.25)	DMSO	2.5	**3v**	52
56	X = OMe, **2w**	C	$CsOH·H_2O$ (1.0)	DMSO	3	**3w**	13

[a] Addition of a powdered base to the mixture of reactants in an appropriate solvent at r.t. (Method A); pre-treatment of ketone solution with small KOH portion prior to dropwise addition of aldehyde solution followed by addition of the rest of the base (Method B); vacuum degassing and flushing of the mixture of reactants with argon prior to the addition of an appropriate base (Method C) or according to described in the literature. See also the experimental section.
[b] Mixture of *cis*-**3a**:*trans*-**4a** diastereomers was formed as an oil in 74:26 ratio.
[c] Mixture of *cis*-**3c**:*trans*-**4c** diastereomers formed as an oil in 77:23 ratio was further separated by HPLC.
[d] 30% aqueous solution.



Scheme 2

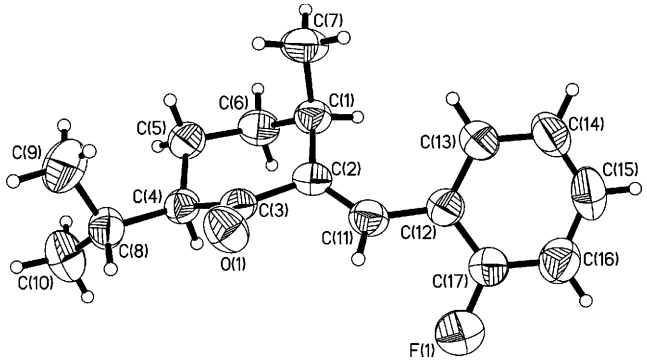


Figure 1 X-ray crystal structure of compound **3b**

The simplest reaction protocol consists in the addition of a powdered base to a mixture of reactants in an appropriate solvent at room temperature (Method A).[10] Spontaneous heating of the reaction mixture up to 45 °C occurs on addition of KOH, which often accelerates unwanted side reactions, and consequently, leads to lower yields of target compounds. It could be prevented if the base is introduced portionwise. Initially, **1** is pre-treated with small portions of KOH prior to dropwise addition of the aldehyde solution followed by the addition of the rest of the base (Method B).[11,21,23]

Moreover, it is believed that the pre-treatment of a (–)-menthone promotes its epimerization to an equilibrium mixture of **1** and its epimer (+)-isomenthone (**6**) through the enolate **7b** (Scheme 2) and, in such a way, also favors the reaction to proceed in the desirable manner.

According to HPLC data, full consumption of the aldehyde occurs in several minutes after addition of the base in the case of reactive aryl aldehydes (e.g. halogen-substituted benzaldehydes), but for 4-methoxybenzaldehyde, which has poor reactivity, it takes a minimum of four to five hours. At the beginning of the reaction, a diastereomeric mixture of **3** and **4** forms in about 75:25 ratio almost independently of the aldehyde nature (Schemes 1 and 2). In most cases, 2-arylidene derivatives **3**, being of *cis*-1*R*,4*R*-configuration, are considerably less soluble than *trans*-1*R*,4*S*-diastereomers **4**, and precipitation of **3** in the bulk usually causes the reaction mixture to thicken into a slurry. This feature is believed to be an additional factor of the stereoselectivity of the reaction towards products **3** of 4*R*-configuration. Normally, precipitation is complete in three to four hours, however, sometimes prolongation up to 24 hours is needed (entries 7–11, 33, 34). Further extension of the reaction, with or without precipitation of **3**, usually leads to the formation of essential amounts of by-products. The major ones have been identified by HPLC and ^{1}H NMR spectra as the corresponding benzoic acids and benzylic alcohols obviously arising from the Cannizzaro reaction of the starting aromatic aldehydes. An exception is the reaction of **1** with low-reactive aldehydes such as **2n** where much higher reaction times up to several days are needed to obtain reasonable yields (entry 38). If structural features of the type **3** compound do not allow precipitation, then lowering of conversion of starting materials is observed in the case of low-reactive aldehydes (entries 37,56). In the case of reactive aldehyde **2a** or **2c**, the mixture of diastereomers **3** and **4** in a ratio, similar to the equilibrium, forms after neutralization (entries 7 and 9, respectively).

Stereochemical assignment of the new products as major diastereomers **3** were made based on typical chemical shift values in their ^{1}H NMR spectra as it is shown above. Additionally, the structure of compound **3b** was proved by X-ray crystallography (Figure 1).[30]

Minor components **4a** and **4c** were isolated by preparative HPLC and assigned using NMR as well. The ^{1}H and ^{13}C spectra for diastereomeric pair **3a** and **4a** were interpreted with the aid of COSY and HSQC experiments.

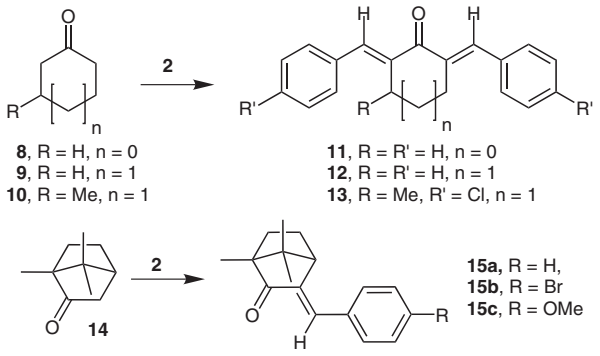
As one can see from Table 1, the yields of the products decrease in the same order as solvent basicity: DMSO > DMA > DMF[31] for each base studied (cf. entries 16,20,21 and 17,22). The amount of the base is varied depending on aromatic aldehyde reactivity amenable to the principles known for the traditional protocol.[2] Indeed, for halogen-, alkyl-, or aryl-substituted aromatic aldehydes the optimal amount of KOH lies within a range of 50–70 mol% per starting menthone and it increases up to 100 mol% for aldehydes possessing electron-donating groups, such as **2k** or **2n** (entries 33,34 and 38). In the case of aldehydes with electron-withdrawing groups **2g–j**, the basicity of the medium should be reduced both by addition of methanol and by reducing the base amount in order to prevent tarring (entries 24–29).

The influence of the alkali cation nature is illustrated in entries 10–11, 15–18, 21–23, 32–33, 40–41, 43–53 (Table 1). A smaller alkali cation (Na^+ vs. K^+, Cs^+ or Bu_4N^+) lowers the yield of the reaction. This effect manifests slightly for the reaction with quite reactive aldehydes, e.g., for **2f** (entries 15 vs. 16–18) or **2o** (entry 40 vs. 41), but becomes considerable for poor reactive ones (**2k**). In the last case, when NaOH is used, the yield of the target compound **3k** drops down to 35% (entry 32), and anisic acid is isolated as the main product of the reaction. The blank experiment (treatment of anisic aldehyde with

NaOH in DMSO) has resulted in the formation of anisic acid in 60% yield. Therefore, the use of the bases with cations smaller than K^+ is inappropriate. On the contrary, use of alkalies with cations larger than K^+, such as Cs^+ or Bu_4N^+,[12] or an alkoxide base (*t*-BuOK) essentially enhances the effectiveness of the superbasic media. This effect became apparent for the reaction of **1** with 4-biphenylcarboxaldehyde derivatives **2q–t** bearing long-chain alkyl substituents (entries 43–53). Total amount of the base can be reduced without any loss of effectiveness in these cases. Thus, the optimal amount of CsOH was found to be 25 mol%. For Bu_4NOH and *t*-BuOK it should not exceed 20 mol%, whereas the optimum is about 10 mol%. The exothermic character of the reaction, as well as yields dependent on temperature, becomes weaker when optimal amounts of CsOH, Bu_4NOH or *t*-BuOK are used in comparison to KOH. Thus, compound **3t**, completely unavailable by KOH/DMSO methodology, was obtained with a satisfactory yield (entry 53) by the use of CsOH and at 35 °C. It has also been found that maximum yield and reproducibility of the reaction are improved and the amount of side-products is reduced if the mixture of starting materials was thoroughly degassed and flushed with argon before addition of the base. The reaction was then carried out under inert atmosphere as well. This procedure (Method C) appears to be noticeably simpler than Method B. It turned out to be especially useful for the reaction of aldehydes almost insoluble in DMSO (e.g., **2q–t**) to be added to the reaction mixture dropwise in DMSO solution, as is required for Method B.

There are several limitations of the methodology proposed. Thus, all attempts to use aldehydes with highly acidic protons (4-carboxy- and 4-hydroxybenzaldehydes) in the condensation have failed, probably, due to partial neutralization of the base and, therefore, reduction of medium basicity. In the case of 4-hydroxybenzaldehyde, the lowering of the carbonyl group reactivity under basic conditions must be an additional factor of the reaction inhibition. A drastic decrease in yields was also found in attempts to use (–)-menthone in condensation reactions with several aromatic aldehydes containing long terminal alkyl or alkyloxy chains. It is clearly pronounced (see Table 1) when passing from **3k** to **3m** (entries 34 and 37) or **3v** to **3w** (entries 55 and 56) but less pronounced for the series of alkoxybiphenyl derivatives **3p–t**, cf. entries 42 and 45–48,53. Derivatives of 4-hydroxy-, 4-carboxy-, 4-amino-, and long-chain 4-alkyloxy-substituted compounds of type **3w** have been obtained indirectly.[17,32]

The applicability of the superbasic media has also been demonstrated for Claisen–Schmidt condensation of some other cyclic ketones **8–10**,**14** (Scheme 3). In the case of non-hindered cycloalkanones with both reactive α-methylene groups **8–10** formation of bis-arylidene derivatives **11–13** in DMSO proceeds even under unoptimized conditions in almost the same yields (Table 2, entries 2,3,5,7,8), and, in some cases, in less time, as compared to the traditional protocol (entries 1,3,6).[33,34] Although numerous effective methods for synthesis of bis-arylidene derivatives **11–13** have been reported recently, they often require the use of rather complex equipment and/or chemicals.[35] Therefore, even if the protocol proposed here generates some loss in yields compared to those methods, it may be considered as a simpler and cheaper alternative.



Scheme 3

Bis-arylidenecyclopentanones **11** have been shown to undergo retro-aldol reaction followed by further deep trans-

Table 2 Synthesis of Diarylidenecycloalkanones **11–13**

Entry	Ketone	Aldehyde	Method[a]	Base (equiv per ketone)	Solvent	Reaction time (h)	Product	Yield (%)	Mp (°C)
1	**8**	**2a**	–[33a]	50% aq KOH (0.7)	MeOH	24	**11**	77	189
2			A	KOH (0.8)	DMSO	0.3		79	189–190
3	**9**	**2a**	–[33b]	NaOH (0.6)	EtOH	0.5	**12**	62	116–117
4			C	CsOH (0.06)	DMSO	1.5		no reaction	–
5			A	KOH (0.7)	DMSO	0.8		62	115–116
6	**10**	**2e**	–[34]	KOH (–)	MeOH	24	**13**	73	–
7			A	KOH (0.6)	DMSO	0.8		59	150–151
8			C	KOH (0.4)	DMSO	0.14		77	150–151

[a] See footnotes in Table 1.

Table 3 Synthesis of 3-Arylidene Derivatives of Camphor

Entry	Aldehyde	Method[a]	Base (equiv per ketone)	Solvent	Reaction time (h)	Product	Yield (%)	Mp (°C)
1	**2a**	–[5]	NaOH	H_2O	6	**15a**	16	–
2		–[36b]	Na	benzene	22		50–70	97
3		–[5]	NaH	Et_2O	6		56	–
4		A	KOH (1.0)	DMSO	1.5		42	94–96
5		C	*t*-BuOK (0.35)	DMSO	3		63	95–96
6	**2f**	–[38a]	$NaNH_2$	toluene	–	**15b**	50	131[36b]
7		A	KOH (1)	DMSO	8.5		–[b]	–
8		C	CsOH (1)	DMSO	4		18[c]	–
9		C	Bu_4NOH (0.35)[a]	DMSO	72		–[d]	–
10		C	*t*-BuOK (1)	DMSO	3		18.5[e]	–
11		C	*t*-BuOK (0.35)	DMSO	3		62.6	130-131
12	**2k**	–[36c]	Na	benzene	22	**15c**	50–70	126[36b]
13		C	*t*-BuOK (0.35)	DMSO	7[f]		52.5	124–125

[a] See footnotes for Table 1.
[b] 4-Bromobenzoic acid is isolated in 16.5% yield.
[c] 1:1 Mixture of **15b** and benzoic acid is formed; yield is estimated by ^{1}H NMR spectroscopy.
[d] Mixture of 10% **2f**, 20% benzylic alcohol, 20–25% **15b** and 45–50% 4-bromobenzoic acid as is estimated by ^{1}H NMR spectroscopy.
[e] Mixture of 9% benzylic alcohol, 70–78% of **15b** and 10–20% of 4-bromobenzoic acid as it is estimated by ^{1}H NMR spectroscopy.
[f] According to HPLC, reaction was complete in 8 min.

formations in the super-basic media at elevated temperatures.[28] Nevertheless, carrying out the reaction in a KOH/DMSO mixture at milder conditions (Table 2, entry 2) produces **11a** in high yields. Moreover, no detectable amounts of side products were found in this case by HPLC analyses. Cyclohexanone (**9**) and its 3-methyl derivative **10** also appear to be not too sensitive towards super-basic media (entries 5,7,8). Moreover, a catalytic amount of the base does not promote the reaction of **9** at all (cf. entries 4 and 5).

Camphor (**14**) (Scheme 3), being a sterically hindered and low-reactive ketone, has been shown to be almost unable to react with aromatic aldehydes under the traditional protocol (see, e.g., Table 3, entry 1).[5,36,37] More effective approaches to the synthesis of 3-arylidenecamphors **15** described before are in fact variations of Haller's method,[36a] and represent two-step procedure: camphor enolization with NaH,[5] Na,[36a,c] *t*-BuOK,[36b] $NaNH_2$[38a] in a nonpolar solvent under reflux followed by the addition of an appropriate aldehyde. Haller's protocol[36a,c,38a] provides the highest yields of compounds **15** (50–70%) known to date.

As it could be seen from Table 3, the use of superbasic media produces arylidenecamphors **15** in high yields, which are comparable to the best known results (cf. entries 1–3,6,12 and 5,11,13), but carrying out the reaction as a simpler one-step procedure, in a shorter reaction time, and at a lower temperature. In these cases *t*-BuOK appears to be a more effective base than alkali hydroxides. However, the amount of *t*-BuOK should be reduced to 35% (cf. entries 10 and 11) to obtain higher yield of **15b**. Moreover, when alkali hydroxides are used (entries 4,6–8), formation of substantial amounts of the corresponding benzoic acids and benzyl alcohols were detected by NMR and HPLC, similarly to the case of using NaOH for menthone condensation (see above). This fact could be rationalized in terms of the further lowering of camphor reactivity in comparison to menthone in the Claisen–Schmidt condensation, while the rate of the Cannizzaro reaction of the aromatic aldehydes obviously remains the same.

The effectiveness of the superbasic media is believed to be clearly described in terms of the HSAB principle.[39,40] More effective solvation of soft Lewis acids (alkali cations) with softly basic solvent molecules occurs as compared to hardly basic hydroxyl anions. Consequently, these anions become more active with proton abstraction from the substrate (Scheme 2). Decrease in self-association of hydroxide anion in a polar aprotic solvent, when the cation radius increases from Na^+ to Bu_4N^+, should also be considered, which is again consistent with the HSAB principle.

Thus, it is reasonable to suppose that all elementary steps in the epimerization of **1** (see above, Scheme 2),[41] where proton abstraction occurs, are accelerated substantially in superbasic media, which provides faster accomplishment

of the equilibrium of the desired reaction (e.g., between **3** and **4**, see Scheme 2), than for any side reactions.

In conclusion, an effective protocol for Claisen–Schmidt condensation of sterically hindered ketones, such as menthone and camphor, in the superbasic media consisting of a strong base (KOH, CsOH, Bu_4NOH or *t*-BuOK) and a polar aprotic solvent (DMSO, DMF or DMA) is proposed to produce the corresponding arylidene derivatives in good to high yields. The *t*-BuOK/DMSO combination appears to be the most effective for these reactions. In the case of more reactive ketones, such as cyclopentanone and some cyclohexanones, the method proposed substantially reduces reaction times without lowering product yields.

^{1}H NMR spectra were recorded on a Bruker Avance DRX-500 (200 MHz) or Varian Mercury VX-200 (200 MHz) spectrometer. Mass spectra were recorded on a Varian 1200 L GC-MS instrument either in GC-MS mode or with the use of direct exposure probe (DEP) method with EI at 70 eV. HPLC analyses were performed using a Bischoff HPLC system equipped with Prontosil 120-5-C18H reverse-phase column (70–100 vol% MeCN–H_2O mixtures served as eluents). Elemental analyses were performed with EA-3000 analyzer (Eurovector, Italy). X-ray crystal structure analysis was made on the Xcalibur-3 diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scanning, $2\Theta_{max} = 60°$). (–)-Menthone (**1**), KOH, $CsOH·H_2O$ and Bu_4NOH (as 30% aq solution), cyclopentanone (**8**), cyclohexanone (**9**), *d*-camphor (**14**), aldehydes **2a–o** are commercially available. DMSO, DMF and DMA were dried over $MgSO_4$, vacuum-distilled and stored over molecular sieves. The following compounds were obtained as described in the literature: 3-methylcylohexanone (**10**),[42] 5-formyl-2-phenylpyrimidine (**2j**),[43] arylmethyleneoxybenzaldehydes **2v–x**.[32c] Aldehydes **2p–t** were obtained by reduction of corresponding nitriles with Ni-Al alloy[21] similarly to the methods described in the literature.[44]

Claisen–Schmidt Condensation in Super-Basic Media; General Procedures

Method A: To a solution of equimolar amounts of a ketone and an aromatic aldehyde in an appropriate solvent (see Tables 1– 3) at concentrations of 0.5–0.9 mmol/mL, was added a powdered base (for amount see Tables 1– 3) with vigorous stirring. After a short period of exothermic reaction, the mixture became red-brownish and often thickened. The resulting mixture was stirred until the reaction was complete as monitored by TLC or HPLC. In the case of well-crystallizing compounds (**3**, **11**–**13**, **15**, except **3a**, **3c**, **3d**, **3g**, **3m**), the mixture was diluted with slight excess of alcoholic AcOH, the precipitate formed was filtered, washed with alcohol, thoroughly washed with warm H_2O, then with alcohol again, and dried. The obtained crude material usually had more than 90% purity (HPLC) and could be used in further transformations without additional purification. Analytically pure sample could be obtained by crystallization from EtOH, MeCN or hexane. Otherwise, oily material formed after neutralization with aqueous acid was extracted with CH_2Cl_2 (3 × 10 mL per 1 mmol of **3**), the combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash chromatography on silica gel using CH_2Cl_2 or hexane as eluent or extracted with hot hexane via short plug of silica gel in a modified Soxhlet apparatus.

Method B: To a solution of a ketone in an appropriate solvent (see Table 1) at concentrations of 0.5–0.9 mmol/mL, was added about a third of the needed base (for total amount see Table 1) with vigorous stirring and external cooling. The mixture was stirred for 30–40 min and then aldehyde (1 equiv per menthone) was added dropwise followed by the rest of the base. The rest of the procedure was as above for Method A.

Method C: Equimolar amounts of a ketone and an aromatic aldehyde are mixed in an appropriate solvent (see Tables 1– 3) at concentrations of 0.5–0.9 mmol/mL, vacuum degassed and flushed with argon (3–5 cycles). Then a powdered base (for amount, see Tables 1– 3) was added with vigorous stirring and external cooling and the degassing procedure was repeated. Further as above for Method A.

Product Data

The identification of the following compounds described before, **3a**,**3d**,**3f**,**3g**,**3o**;[18a] **3e**,**3h**,**3i**,**3k**,**3m–o**;[18b] **3p**;[18c] **3q**,**3r**;[32] **3v** and **3w**[32c] **11**;[45] **12**;[33] **13**;[34] **15a**;[36c] **15b** and **15c**,[36b,c,38a] was made by HPLC or/and comparison of their melting points, and, in several cases, using ^{1}H NMR spectroscopy. For compound **3a**, high-resolution NMR spectra are given for comparison.[46] For all the new compounds, data confirming their structure are given below:

(3*R*,6*R*)-2-Benzylidene-6-isopropyl-3-methylcyclohexanone (3a)

An oil obtained after flash chromatography on silica gel with hexane as eluent contained 96% of mixture of diastereomers **3a** and **4a** in 74:26 ratio. The oil was diluted with MeOH (1:1) and chilled at –15 °C for 12 h. Crystals formed were collected by filtration to furnish *cis*-(3*R*,6*R*)-diastereomer **3a**; mp 49–50 °C (Lit.[3] mp 51 °C).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.43–7.37 (m, 4 H), 7.36–7.32 (m, 1 H), 6.98 (s, 1 H), 3.36 (m, 1 H, overlapped with H_2O), 2.40 (sept d, *J* = 3.4, 6.8 Hz, 1 H), 2.25 (m, 1 H), 1.88–1.76 (m, 3 H), 1.74–1.69 (m, 1 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 7.1 Hz, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.6, 18.2, 19.3, 19.9, 26.1, 29.6, 31.0, 54.9, 128.1, 128.5, 129.2, 131.4, 135.1, 144.4, 203.3.

(3*R*,6*S*)-2-Benzylidene-6-isopropyl-3-methylcyclohexanone (4a)

The mother liquor after separation of crystalline **3a** consisted of a mixture of diastereomers **3a**:**4a** in 1:1 ratio. From 6 mL of this solution, diastereomer **4a** was isolated by preparative HPLC using a mixture of MeCN–H_2O (87:13) as eluent. After evaporation of the eluate to dryness, the oil solidified; mp 46–47 °C; $[\alpha]_D^{20}$ –207 (*c* = 0.9, toluene).

IR (KBr): 3053, 2956, 2931, 2868, 1682, 1611 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.47–7.38 (m, 4 H), 7.37–7.31 (m, 1 H), 6.91 (s, 1 H), 3.36 (m, 1 H), 2.13–2.01 (m, 2 H), 1.96–1.89 (m, 2 H), 1.74–1.63 (m, 1 H), 1.40–1.31 (m, 1 H), 1.10 (d, *J* = 7.1 Hz, 3 H), 0.84 (d, *J* = 7.1 Hz, 3 H), 0.83 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.4, 20.9, 21.0, 21.2, 28.0, 28.1, 31.6, 55.2, 128.8, 129.1, 129.9, 132.4, 145.2, 206.2, 220.2.

MS: *m*/*z* (%) = 243 (16), 242 (M^+, 100), 241 (26), 227 (16), 214 (12), 200 (63), 171 (75), 144 (23), 131 (13), 129 (56), 115 (16), 91 (18).

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15; O, 6.60. Found: C, 84.56; H, 9.45.

(3*R*,6*R*)-2-(2-Fluorobenzylidene)-6-isopropyl-3-methylcyclohexanone (3b)

Mp 88–89 °C; $[\alpha]_D^{20}$ –165 (*c* 2.0, toluene).

IR (KBr): 3061, 2959, 2929, 2868, 1675, 1621 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.37 (s, 1 H), 7.09 (td, *J* = 7.8, 1.7 Hz, 1 H), 6.85 (d, *J* = 5.1, 1.7 Hz, 1 H), 6.81–6.76 (m, 2 H), 3.11–3.06 (m, 1 H), 2.62 (sept d, *J* = 3.4, 7.1 Hz, 1 H), 1.60–1.42 (m, 3

H), 1.39–1.31 (m, 1 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 7.1 Hz, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H).

^{13}C (125 MHz, C_6D_6): δ = 18.1, 19.1, 19.5, 20.4, 26.8, 30.6, 32.5, 56.1, 115.8 (d), 124.0 (d), 124.3 (d), 129.8 (d), 130.3 (d), 131.4, 147.7, 161.1 (d), 202.8.

MS: *m*/*z* (%) = 260 (M^+, 78.7), 245 (29.2), 232 (19.1), 219 (24.8), 218 (100.0), 203 (20.4), 190 (15.3), 189 (95.9), 162 (33.2), 161 (16.6), 149 (18.6), 148 (16.2), 147 (92.6), 146 (55.6), 133 (20.8), 109 (24.1).

Anal. Calcd for $C_{17}H_{21}FO$: C, 78.43; H, 8.13; Found: C, 78.13; H, 8.21.

X-ray Crystal Data

Crystals of **3b** are monoclinic. At 293 K: a = 9.570(1), b = 7.684(1), c = 10.184(1) Å, β = 95.58(1)°, V = 745.35(7) Å^3, M_r = 260.34, Z = 2, space group $P2_1$, d_{calc} = 1.160 g/cm^3, μ (MoK_α) = 0.079 mm^{-1}, $F(000)$ = 280. Intensity of 6343 reflections (3794 independent, R_{int} = 0.029) were collected. The structure was solved by direct method using SHELXTL package. Positions of hydrogen atoms were located from electron density difference maps and refined by 'riding' model with U_{iso} = nU_{eq} of non-hydrogen atom bonded with given hydrogen atom (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation using 3721 reflections was converged to wR_2 = 0.160 [R_1 = 0.057 for 2161 reflections with $F > 4\sigma(F)$, S = 0.908].

(3*R*,6*R*)-2-(3-Fluorobenzylidene)-6-isopropyl-3-methylcyclohexanone (3c) and (3*R*,6*S*)-2-(3-Fluorobenzylidene)-6-isopropyl-3-methylcyclohexanone (4c)

An oil obtained after flash chromatography on silica gel with hexane as eluent was a mixture of diastereomers **4c** and **3c** in a 27:73 ratio (according to HPLC) or in a 30:70 ratio (according to GC-MS). The mixture was separated by preparative HPLC using a mixture of MeCN–H_2O (7:13) as eluent.

3c

Oil; $[\alpha]_D^{20}$ –169 (*c* 1.2, toluene).

IR (neat): 3066, 2960, 2872, 1685, 1609, 1581 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.4 (ddd, *J* = 5.8, 8.1, 7.6 Hz, 1 H), 7.13 (d, *J* = 7.7 Hz, 1 H), 7.14–7.04 (m, 2 H), 7.11 (s, 1 H), 3.52–3.40 (m, 1 H), 2.62 (sept d, *J* = 3.3, 6.9 Hz, 1 H), 2.36–2.26 (m, 1 H), 1.99–1.83 (m, 3 H), 1.25 (d, *J* = 7.1 Hz, 3 H), 1.04 (d, *J* = 6.4 Hz, 3 H), 0.98 (d, *J* = 6.5 Hz, 3 H).

^{13}C (75 MHz, $CDCl_3$): δ = 17.7, 18.6, 19.6, 20.3, 26.5, 30.3, 31.6, 55.9, 114.9 (d), 115.8 (d), 125.2, 129.8 (d), 130.9 (d), 138.0 (d), 145.7, 162.6 (d), 204.8.

GS-MS (major component, 2nd on retention, **3c**): *m*/*z* (%) = 260 (M^+, 82.9), 245 (35.7), 219 (12.5), 218 (91.0), 203 (26.5), 190 (14.4), 189 (88.9), 175 (13.8), 162 (42.7), 161 (26.9), 159 (11.0), 149 (15.0), 147 (100.0), 146 (32.7), 133 (26.5), 123 (20.0), 109 (28.6).

Anal. Calcd for $C_{17}H_{21}FO$: C, 78.43; H, 8.13; Found: C, 78.55; H, 8.40.

4c

Oil; $[\alpha]_D^{20}$ –216 (*c* 0.9, toluene).

IR (neat): 3067, 2961, 2871, 1686, 1608, 1581 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (ddd, *J* = 5.9, 8.2, 7.5 Hz, 1 H), 7,13 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.06 (dt, *J* = 9.9, 2.4, 1.4 Hz, 1 H), 6.99 (tdd, *J* = 2.4, 8.1, 8.2, 0.9 Hz, 1 H), 6.94 (s, 1 H), 3.41–3.31 (m, 1 H), 2.18–2.07 (m, 2 H), 2.07–1.96 (m, 2 H), 1.86–1.74 (m, 1 H), 1.45–1.36 (m, 1 H), 1.17 (d, *J* = 7.1 Hz, 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H).

^{13}C (75 MHz, $CDCl_3$): δ = 19.2, 20.7, 20.8, 21.3, 27.8, 31.8, 55.7, 114.9 (d), 115.9 (d), 125.3 (d), 129.9 (d), 131.2 (d), 137.9 (d), 146.2, 162.5 (d), 207.5.

GC-MS (minor component, 1st on retention, **4c**): *m*/*z* (%) = 260 (M^+, 35.9), 245 (21.2), 219 (14.0), 218 (100.0), 217 (12.7), 203 (12.4), 190 (11.2), 189 (65.5), 162 (17.4), 161 (23.9), 148 (13.0), 147 (70.5), 146 (24.6), 133 (15.8), 109 (16.8).

Anal. Calcd for $C_{17}H_{21}FO$: C, 78.43; H, 8.13; Found: C, 78.61; H, 8.32.

(3*R*,6*R*)-6-Isopropyl-3-methyl-2-[(2-phenylpyrimidin-5-yl)methylene]cyclohexanone (3j)

Mp 131–133 °C; $[\alpha]_D^{20}$ –192 (*c* 1.2, toluene).

IR (KBr): 3049, 2956, 2868, 1682, 1603, 1574 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.79 (s, 2 H), 8.45 (m, 2 H), 7.50 (t, *J* = 6.3 Hz, 3 H), 6.99 (s, 1 H), 3.37 (m, 1 H), 2.54 (sept d, *J* = 7.0, 3.4 Hz, 1 H), 2.26 (m, 1 H), 1.99–1.87 (m, 3 H), 1.86–1.81 (m, 1 H), 1.23 (d, *J* = 7.1 Hz, 3 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9, 18.8, 19.7, 20.3, 26.6, 30.4, 32.3, 56.1, 125.1, 127.4, 128.2, 128.7, 131.0, 137.0, 148.0, 157.2, 163.3, 203.9.

MS: *m*/*z* (%) = 320 (M^+, 100.0), 306 (16.2), 305 (15.2), 292 (10.4), 279 (13.1), 278 (58.5), 277 (21.1), 263 (11.8), 250 (30.9), 249 (88.8), 222 (20.8), 221 (13.7), 207 (15.6), 105 (7.2).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.93; H, 7.49; N, 8.82.

(3*R*,6*R*)-2-(2-Methoxybenzylidene)-6-isopropyl-3-methylcyclohexanone (3l)

Mp 80–81 °C; $[\alpha]_D^{20}$ –254 (*c* 1.2, toluene).

IR (KBr): 3061, 2959, 2868, 1683, 1606 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.34 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.26 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.05 (s, 1 H) 7.04 (dd, *J* = 7.8, 0.7 Hz, 1 H), 6.98 (td, *J* = 7.6, 0.8 Hz, 1 H), 3.78 (s, 3 H), 3.21 (m, 1 H), 2.40 (sept d, *J* = 3.2, 7.0 Hz, 1 H), 2.25 (m, 1 H), 1.86–1.75 (m, 3 H), 1.71 (m, 1 H), 1.07 (d, *J* = 7.0 Hz, 3 H), 0.91 (d, *J* = 7.1 Hz, 3 H), 0.82 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.6, 18.2, 19.5, 19.9, 26.1, 29.8, 31.1, 54.8, 55.3, 111.0, 120.1, 123.7, 126.9, 128.8, 129.8, 144.1, 157.5, 203.6.

MS: *m*/*z* (%) = 272 (M^+, 5), 242 (19.4), 241 (100.0), 201 (13.1), 159 (15.4), 121 (6.1).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.29; H, 8.93.

(3*R*,6*R*)-2-[1-(4′-Heptyloxybiphenyl-4-yl)methylene]-6-isopropyl-3-methylcyclohexanone (3s)

Mp 90–91 °C; $[\alpha]_D^{20}$ –214 (*c* 1.2, toluene).

IR (KBr): 3058, 2948, 2853, 1682, 1606, 1575 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.17 (s, 1 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 4.00 (t, *J* = 6.6 Hz, 2 H), 3.49 (m, 1 H), 2.59 (sept d, *J* = 7.0, 3.2 Hz, 1 H), 2.25 (m, 1 H), 1.97–1.85 (m, 3 H), 1.85–1.77 (m, 3 H), 1.48 (quint, *J* = 7.8 Hz, 2 H), 1.41–1.30 (m, 6 H), 1.24 (d, *J* = 7 Hz, 3 H), 0.98 (d, *J* = 7 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.91 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 17.8, 18.6, 19.8, 20.4, 22.6, 26.0, 26.7, 29.0, 29.3, 30.5, 31.7, 31.7, 55.8, 68.1, 114.8, 126.5, 127.9, 130.1, 132.5, 132.6, 134.1, 140.6, 144.4, 159.0, 204.7.

MS: *m*/*z* (%) = 432 (M^+, 100.0), 431 (19.3), 390 (17.4), 361 (17.2), 334 (16.6), 263 (10.6), 221 (15.2), 207 (9.9), 183 (9.3), 181 (7.0).

Anal. Calcd for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32. Found: C, 83.19; H, 9.25.

(3*R*,6*R*)-2-[1-(4′-Nonyloxybiphenyl-4-yl)methylene]-6-isopropyl-3-methylcyclohexanone (3t)
Mp 86–87 °C; $[\alpha]_D^{20}$ –184 (*c* 1.9, toluene).

IR (KBr): 3060, 2951, 2853, 1679, 1606, 1575 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.3 Hz, 2 H), 7.54 (d, *J* = 8.3 Hz, 2 H), 7.43 (d, *J* = 8.3 Hz, 2 H), 7.17 (s, 1 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 4.00 (t, *J* = 6.6 Hz, 2 H), 3.49 (m, 1 H), 2.59 (sept d, *J* = 7.0, 3.2 Hz, 1 H), 2.25 (m, 1 H), 1.97–1.85 (m, 3 H), 1.85–1.77 (m, 3 H), 1.48 (quint, *J* = 7.8 Hz, 2 H), 1.41–1.26 (m, 10 H), 1.24 (d, *J* = 7 Hz, 3 H), 0.98 (d, *J* = 7 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.90 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 17.8, 18.7, 19.8, 20.4, 22.6, 26.0, 26.7, 29.2, 29.3, 29.4, 29.5, 30.5, 31.7, 31.9, 55.8, 68.1, 114.8, 126.5, 127.9, 130.1, 132.5, 132.6, 134.1, 140.6, 144.4, 159.0, 204.7.

MS: *m*/*z* (%) = 460 (M^+, 100.0), 459 (17.1), 418 (15.4), 389 (14.3), 362 (9.2), 347 (11.5), 333 (8.4), 306 (6.2), 292 (11.8), 263 (12.1), 241 (6.7), 236 (5.4), 235 (6.1), 222 (5.2), 221 (15.2), 207 (9.5), 183 (11.1), 181 (8.1).

Anal. Calcd for $C_{32}H_{44}O_2$: C, 83.43; H, 9.63. Found: C, 83.50; H, 9.71.

(3*R*,6*R*)-2-[4-(Phenylmethyleneoxy)benzylidene]-6-isopropyl-3-methylcyclohexanone (3u)
Mp 93–94.5 °C; $[\alpha]_D^{20}$ –225 (*c* 1.9, toluene).

IR (KBr): 1664, 1572, 1600, 1542 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.3 Hz, 2 H), 7.40 (t, *J* = 7.3 Hz, 2 H), 7.37–7.32 (m, 3 H), 7.13 (s, 1 H), 6.98 (d, *J* = 8.5 Hz, 2 H), 5.09 (s, 2 H), 3.44 (m, 1 H), 2.58 (sept d, *J* = 7.0, 3.4 Hz, 1 H), 2.23 (m, 1 H), 1.95–1.83 (m, 3 H), 1.83–1.75 (m, 1 H), 1.22 (d, *J* = 7.1 Hz, 3 H), 0.97 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.8, 18.5, 19.7, 20.3, 26.8, 30.4, 31.5, 55.6, 70.0, 114.8, 127.4, 128.0, 128.6, 128.6, 131.3, 132.8, 136.7, 142.7, 158.8, 204.6.

Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.79; H, 8.17.

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