Organometallic reactions in aqueous media — Bismuth-mediated crossed aldol type reactions[1]

Yoon Joo Lee and Tak Hang Chan

Abstract: Bismuth metal, upon activation by zinc fluoride, can effect the crossed aldol reaction between α-bromocarbonyl compounds and aldehydes in aqueous media. The reaction was found to be regiospecific and syn-diastereoselective.

Key words: bismuth, zinc fluoride, aldol reaction, regioselectivity, aqueous media.

Résumé : En milieu acide, le bismuth métallique activé par le fluorure de zinc rend possible la réaction aldolique croisée entre des composés α-bromocarbonylés et des aldéhydes. On a observé que la réaction est régiospécifique et syn-diastéréosélective.

Mots clés : bismuth, fluorure de zinc, réaction aldolique, régiosélectivité, milieu aqueux.

[Traduit par la Rédaction]

Introduction

The aldol reaction has played an important role in organic synthesis for the formation of carbon–carbon bonds, providing β-hydroxycarbonyl compounds. However, under the classical aldol reaction conditions involving basic aqueous media, side products, such as regioisomers, dimers, polymers, self-condensation products, and α,β-unsaturated carbonyl compounds, are invariably formed as well. The formation of these side products is often attributed to the fact that the aldol reaction is an equilibrium process (1). To circumvent this problem, useful modifications of the classical aldol reaction, particularly using Lewis-acid-promoted reactions of enol silyl or tin ethers with carbonyl compounds, have been developed (2). In general, these methods employ organic solvents as reaction media. Recently, there has been considerable interest in conducting organic reactions in aqueous media (3) because of the need to reduce volatile organic solvents as a burden to the environment. In 1990 and subsequently, we reported on the possibility of conducting metal-mediated crossed aldol type reactions in aqueous media, using zinc, tin, and indium (4). The yields of the crossed aldol products were modest. In 1997, Shen et al. (5) reported using bismuth to mediate the crossed aldol type reactions in aqueous media. In the presence of bismuth(III) chloride and metallic aluminum, α-bromocarbonyl compounds **1** were found to react with various aldehydes **2** in water under a nitrogen atmosphere at 60 °C to afford the corresponding β-hydroxycarbonyl compounds **3** in good yields together with the dehalogenated products **4** (Scheme 1).

Very recently, J. Zhang and Y. Zhang (6) demonstrated that a bimetallic system of bismuth(III) chloride and samarium could mediate similar crossed aldol type reactions of α-bromoacetophenone with a variety of aldehydes in a mixture of THF and H_2O. Because of our continuing interest in this area, we have examined the bismuth-mediated reaction with the following objectives in mind: (1) use bismuth metal directly in place of the reduction of bismuth chloride for the crossed aldol reaction; (2) extend the reaction to aliphatic acyclic ketones since most reported examples of α-halocarbonyl compounds **1** have been limited to arylketones; and (3) examine the regioselection of the reaction.

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Results

Study of different fluoride salts as promoters

In general, mechanically atomized metals are less reactive than metals chemically prepared by the reduction of metal salts with alkali metals or other reducing agents (7). The low reactivity of the bismuth metal powder may result from the insufficient removal of metal oxide layers from the metal surface and the low surface area of the metal particles. Thus, it is obvious that activation of the bismuth metal is needed for the reaction to proceed. Previous reports from our research group have shown that fluoride salts are quite effective in activating metals, such as aluminum (8) and antimony (9), to mediate organometallic reactions in aqueous media. More recently, we found that ammonium hydrogen fluoride (NH_4HF_2) could efficiently activate commercially available bismuth metal to reduce α-halocarbonyl compounds **1** to the corresponding dehalogenated products **4** in excellent yields (10). The reaction is presumed to proceed through the intermediacy of a bismuth enolate **5** (X = Br or F, Scheme 2). We were able to demonstrate that starting with 2-bromoisobutyrophenone (**1a**, R^1 = Ph, R^2 = R^3 = Me) and benzaldehyde in the presence of bismuth and NH_4HF_2, the crossed aldol product **3a** (R^1 = R^4 = Ph, R^2 = R^3 = Me) was obtained. The reaction was carried out in water as the reaction medium. However, reduction was a serious side reaction giving product **4a** in 44% yield, substantially lowering the yield of the aldol product **3a** to 56%.

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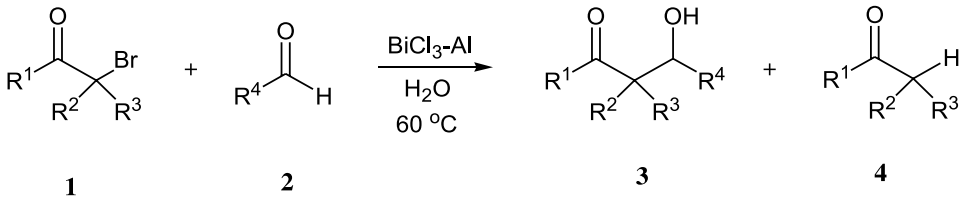
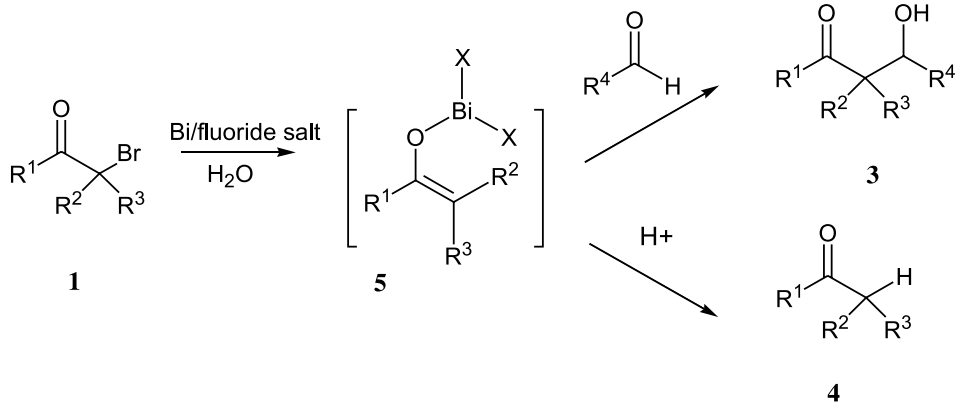
Scheme 1.



1 **2** **3** **4**

Scheme 2.



1 **5** **3** **4**

Table 1. Screening of promoters for the bismuth-mediated crossed aldol type reaction of 2-bromoisobutyrophenone with benzaldehyde in aqueous media.[a]

Entry	Promoter	Time (h)	Unreacted **1a** (%)[b]	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	KF	24	100	0	0
2	CaF_2	24	100	0	0
3	AlF_3	24	100	0	0
4	NH_4F	24	40	53	7
5	NH_4HF_2	12	0	82 (78[c])	18
6	Bu_4NF	24	100	0	0
7	TlF_4	18	0	75	25
8	VF_4	16	0	50	50
9	CrF_3	18	0	75	25
10	MnF_2	24	99	Trace	Trace
11	FeF_2	24	84	15	Trace
12	CoF_2	24	89	10	Trace
13	NiF_2	24	87	12	Trace
14	CuF_2	12	0	58	42
15	ZnF_2	12	0	95 (90[c])	5
16	$ZnCl_2$	24	100	0	0

[a]Ratio of **1a**:benzaldehyde:Bi:promoter = 1 : 1.1 : 1.5 : 1.5 mmol and 1 mL of D_2O.
[b]Determined by ^1H NMR of the crude product.
[c]Isolated yield.

In this reaction, the use of ammonium hydrogen fluoride was found to be necessary since neither the crossed aldol type reaction nor the reduction proceeded with bismuth alone. In an attempt to search for a more effective promoter for bismuth metal activation, a wide range of fluoride salts was screened using the reaction of compound **1a** with benzaldehyde as a model reaction (Scheme 2), and the results are shown in Table 1.

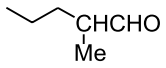
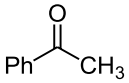
Table 2. Screening of solvents for the bismuth-mediated crossed aldol type reaction of 2-bromoisobutyrophenone with benzaldehyde in the presence of ZnF_2.[a]

Entry	Solvent	Time (h)	Unreacted **1a** (%)[b]	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	Neat	24	78	21	Trace
2	H_2O	12	0	85 (81[c])	15
3	D_2O	12	0	95 (90[c])	5
4	EtOH	24	100	0	0
5	H_2O–THF (1:1)	24	0	77	23
6	THF	24	100	0	0

[a]Ratio of **1a**:benzaldehyde:Bi:ZnF_2 = 1 : l.l : 1.2 : 1.2 mmol and 1 mL of solvent
[b]Determined by ^1H NMR of the crude product.
[c]Isolated yield.

As can be seen from Table 1, the main group metal fluorides (KF, CaF_2, and AlF_3) could not activate bismuth to mediate the reaction in D_2O (entries 1–3). Most of the transition metal fluorides tested were found to be inefficient in activating bismuth leading to unsatisfactory yields of the aldol product (entries 7–14). However, the reactions with TiF_4, VF_4, CrF_3, and CuF_2, which are not commonly used reagents in organic synthesis, afforded the corresponding aldol adducts in moderate yields. In the case of zinc fluoride, the aldol addition product was obtained predominantly along with a minimal amount of the reduction product (entry 15). Fluoride anion seemed to have a special activating effect as $ZnCl_2$ was ineffective (entry 16). Several different solvents were also screened using the same model reaction at room temperature with ZnF_2. The results are summarized in Table 2. Hardly any desired product was observed when ethanol or THF was employed as the solvent (entries 4 and

Table 3. Bismuth-mediated crossed aldol type reactions of 2-bromoisobutyrophenone with various aldehydes and ketones in the presence of ZnF_2 in aqueous media.[a]

Entry	Electrophile	Time (h)	Unreacted **1a** (%)[b]	Yield of **3** (%)[b]	Yield of **4** (%)[b]
1	PhCHO	12	0	95 (90[c]) (**3a**)	5
2	*p*-CH_3PhCHO	24	10	80 (66[c]) (**3b**)	10
3	*p*-CH_3OPhCHO	24	98	Trace (**3c**)	Trace
4	*p*-ClPhCHO	16	26	69 (91[c]) (**3d**)	5
5	*p*-CNPhCHO	16	19	80 (98[c]) (**3e**)	Trace
6	*n*-C_5H_{11}CHO	12	0	53 (35[c]) (**3f**)	47
7	$Ph(CH_2)_2CHO$	12	20	67 (56[c]) (**3g**)	13
8		12	7	0	93
9		20	10	0	90

[a]Ratio of **1a**:aldehyde:Bi:ZnF_2 = 1 : 1.1 : 1.2 : 1.2 mmol and 1 mL of D_2O.
[b]Determined by ^1H NMR of the crude product.
[c]Isolated yield based on reacted **1a**.

6). In a mixture of water and THF (1:1), the reduction product was formed to a significant extent as well (entry 5). Aqueous media, water, or deuterium oxide, proved to be the most suitable solvents for this bismuth-mediated crossed aldol type reaction (entries 2 and 3).

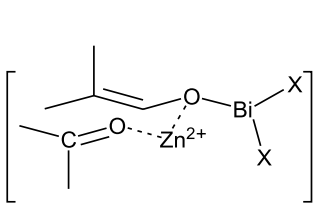
Scope of the bismuth-mediated aqueous crossed aldol type reaction

The bismuth-mediated aqueous crossed aldol type reactions of compound **1a** with a variety of aldehydes were surveyed (Table 3). In general, both aromatic and aliphatic aldehydes reacted smoothly with compound **1a** to provide the corresponding aldol products **3** in moderate to high yields. The exception appeared to be *p*-methoxybenzaldehyde (entry 3). The presence of the methoxy group seemed to have interfered with the activation process since unreacted **1a** could be recovered. On the other hand, for α-branched aldehydes or ketones (entries 8 and 9), compound **1a** was transformed efficiently to the presumed enolate and was protonated faster than the aldol condensation.

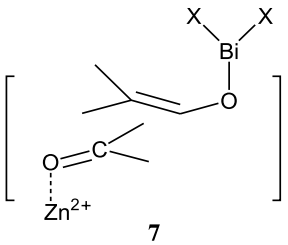
The generality of the reaction was also explored with various α-bromocarbonyl compounds using benzaldehyde under similar reaction conditions. The results are summarized in Table 4. Aromatic α-bromoketones generally reacted better to provide the corresponding β-hydroxyketones in higher yields (entries 1–3) in comparison with aliphatic α-bromoketones (entries 4 and 5). The reactions of α-bromocarboxylic acids with benzaldehyde resulted in the formation of the corresponding reduction products as the major product (entries 6 and 7).

Discussions

The ability of zinc fluoride to promote the crossed aldol reaction can be attributed to two factors. First, the fluoride anion may activate the metal for chemical reactions in aqueous media. Many metals, though considered to be reactive based on their ionization potentials, may be inert in aqueous media because of the easy formation of insoluble metal oxide on the metal surface. Aluminum metal is a good example. It has a first ionization potential (5.984 eV) which is much lower than that of magnesium (7.646 eV) and is expected to be a reactive metal. On the other hand, aluminum is resistant to water because it readily forms a layer of insoluble Al_2O_3 and this prevents the metal from further reaction. It has been reported that trace amounts of fluoride anion in water dramatically increased the corrosion of aluminum metal (11). This effect is attributed to the reaction of fluoride ion with Al_2O_3 to form various water soluble fluoroaluminates (12). Bismuth metal may be activated by fluoride salts in a similar manner in that fluorobismuthates can be prepared from Bi_2O_3 and fluorides (13). The second factor is that the zinc ion must also play a role. Recently, Chan and co-workers (14) and others (15) have found that zinc fluoride acts as an effective Lewis acid in aqueous media by the coordination of the zinc cation with the carbonyl function. In the crossed aldol reaction, the bismuth enolate **5** may react with the Zn^{2+}- coordinated aldehyde in either the cyclic chair transition state (**6**) (16) or the extended *antiperiplanar* transition state (**7**) (17).



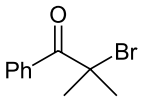
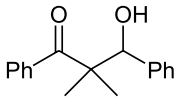
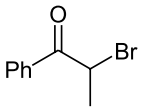
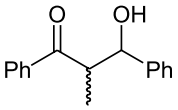
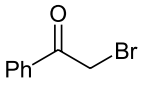
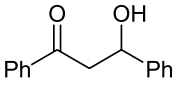
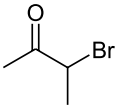
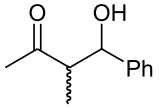
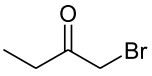
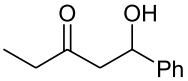
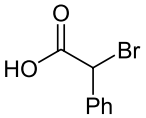
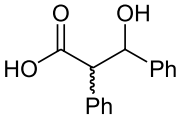
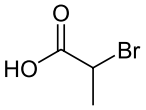
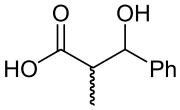
6



7

By comparing the products derived from 3-bromobutan-2-one (Table 4, entry 4) and 1-bromobutan-2-one (Table 4, entry 5), it is possible to conclude that the reaction is regiospecific. The two regioisomeric bismuth enolates (**8** and **9**) must have been generated separately. Reactions of the enolates with benzaldehyde led to different isomeric aldol

Table 4. Bismuth-mediated crossed aldol type reactions of α-bromocarbonyl compounds with benzaldehyde in the presence of ZnF_2 in aqueous media.

Entry	Compound **1**	Product **3**		Isolated yield of **3** (syn:anti)(%)[a]	% Yield of **4**[a]
1			**3a**	90[b]	5
2			**3h**	98[b] (55:45)	Trace
3			**3i**	55[c]	43
4			**3j**	50[d] (73:27)	43
			**3k**	12[d]	88
6			**3l**	22[a,e] (64:36)	78
7			**3m**	0[a,f]	100

[a]Determined by ^{1}H NMR of the crude product.
[b]Ratio of **1**:aldehyde:Bi:ZnF_2 = 1 : 1.1 : 1.2 : 1.2 mmol / 12 h.
[c]Ratio of **1**:aldehyde:Bi:ZnF_2 = 1 : 2 : 2 : 2 mmol / 40 h.
[d]Ratio of **1**:aldehyde:Bi:ZnF_2 = 1 : 2 : 3 : 2 mmol / 40 h.
[e]Ratio of **1**:aldehyde:Bi:ZnF_2 = 1 : 1.1 : 1.5 : 1.5 mmol / 6 h.
[f]Ratio of **1**:aldehyde:Bi:ZnF_2 = 1 : 1.1 : 1 : 2 mmol / 24 h.

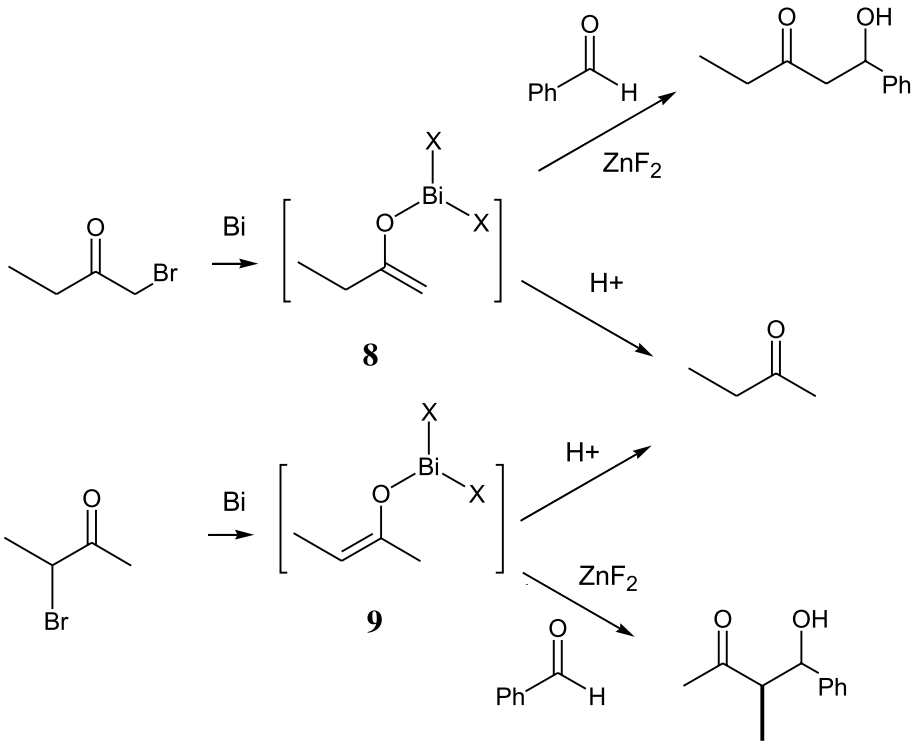
products. Furthermore, protonation of the enolates to give butan-2-one must not be reversible, otherwise both enolates would have been regenerated in the reaction mixture, which would have led to a mixture of regioisomers in both reactions (Scheme 3).

In the three examples where diastereomeric aldol products were formed, the syn-isomer was formed preferentially over the anti-isomer (Table 4, entries 2, 4, and 6). Using the condensation of 3-bromobutan-2-one as the example (entry 4), the syn/anti ratio was found to be 73:27. The preferred formation of the syn-isomer is usually explained by one of the following two (or more) possibilities: (1) in the formation of the bismuth enolate, *E*-**9** was formed preferentially, which then reacted with benzaldehyde via the extended antiperiplanar transition state **7** to give the syn- product; or (2) the *Z*-**9** bismuth enolate was formed preferentially, and it reacted with benzaldehyde via the cyclic chair transition state **6**. While there is insufficient experimental evidence to prefer one explanation over the other in the present reaction, similar stereochemical preference was observed in the bismuth-mediated coupling of crotyl bromide with aldehydes, and the acyclic transition state explanation similar to **7** was invoked (18).

Conclusion

The bismuth-mediated aqueous crossed aldol type reaction was investigated. The study showed that bismuth activated by several fluoride salts could mediate the aldol addition reaction of α-bromocarbonyl compounds with aldehydes in aqueous media. Zinc fluoride was found to be the promoter of choice. The scope of this bismuth-mediated aqueous crossed aldol type reaction was examined and the reaction was found to be regiospecific and diastereoselective.

Scheme 3.



Experimental

General information

Chemicals were purchased from Aldrich or the Alfa Aesar Chemical Company. All the aldehydes were purified by distillation or column chromatography prior to use. Thin layer chromatography was performed on plastic plates precoated with silica gel (60 F_{254}), which were developed using a mixture of hexane and ethyl acetate as an eluent. Analytes were visualized by UV light or by dipping the plate into a developing agent (a solution of ammonium molybdate and ceric sulfate in dilute sulfuric acid) and heating with a heat gun. Column chromatography was performed on 230–400 mesh silica gel.

Melting points were determined using a Gallenkamp apparatus and were uncorrected. Infrared spectra were recorded on an Avatar 360 FT-IR spectrometer and reported in cm^{-1}. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury 300 or 400 MHz spectrometer or a Varian Unity 500 MHz spectrometer at ambient temperature. Chemical shifts (δ) were reported in parts per million (ppm) and referenced to $CDCl_3$ at δ 7.25 ppm for ^1H and δ 77.00 ppm for ^{13}C. The multiplicity of each signal was indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), and m (multiplet). Coupling constants (*J*) were reported in Hz. The syn and anti configurations of **3h**, **3j**, and **3m** were assigned on the basis that the coupling constants of the methyl-bearing methine proton and the hydroxyl-bearing methine proton have greater values for anti- than for syn-isomers (19). Mass spectra were recorded on a Kratos MS25RFA mass spectrometer or on a HP 5980A GC–MS.

General procedure for bismuth-mediated aqueous crossed aldol type reaction

To a mixture of 2-bromoisobutyrophenone (1 mmol), an aldehyde (1.1 mmol), bismuth powder (1.2 mmol), and ZnF_2 (1.2 mmol) was added D_2O (1 mL). The reaction mixture was vigorously stirred at room temperature for the indicated time in Table 3 (12–24 h). Additional distilled water (10 mL) was added in the reaction mixture, and the product was extracted with diethyl ether (3 × 30 mL). The combined organic layer was dried over anhyd Na_2SO_4 and filtered. After the evaporation of solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel using 5% ethyl acetate in hexane as an eluent to give the corresponding pure aldol addition product.

3-Hydroxy-2,2-dimethyl-1,3-diphenyl-1-propanone (3a) (20)

White solid, mp 105–107 °C. IR ($CHCl_3$) (cm^{-1}): 3475 (O-H), 1672 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.58–7.54 (m, 2H), 7.48–7.25 (m, 8H), 5.15 (d, *J* = 3.5 Hz, 1H), 2.92 (d, *J* = 4.0 Hz, 1H), 1.27 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 211.59, 140.04, 139.51, 130.37, 127.86, 127.81, 127.64, 127.58, 126.98, 78.82, 52.52, 24.34, 19.70.

3-Hydroxy-2,2-dimethyl-3-(4-methylphenyl)-1-phenyl-1-propanone (3b) (20)

White solid, mp 83.5–85.0 °C. IR ($CHCl_3$) (cm^{-1}): 3490 (O-H), 1673 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.58–7.55 (m, 2H), 7.47–7.42 (m, 1H), 7.40–7.36 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.10 (s, 1H), 2.94 (br s, 1H), 2.36 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.62, 139.59, 137.19, 137.06,

130.30, 128.30, 127.83, 127.68, 126.98, 78.67, 52.54, 24.34, 21.21, 19.62.

3-(4-Cyanophenyl)-3-hydroxy-2,2-dimethyl-1-phenyl-1-propanone (3e)

Colorless oil. IR ($CHCl_3$) (cm^{-1}): 3477 (O-H), 2229 (C≡N), 1673 (C=O).; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.55–7.49 (m, 4H), 7.43–7.31 (m, 5H), 5.13 (d, J = 3.3 Hz, 1H), 3.72 (d, J = 3.8 Hz, 1H), 1.17 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.73, 145.52, 138.80, 131.30, 130.75, 128.54, 127.95, 127.03, 118.58, 111.18, 77.93, 52.38, 24.03, 19.63. MS (CI, NH_3) *m/z*: 280 (M + H^+, 5), 148 (51), 130 (48), 105 (100), 77 (13). HR-MS (FAB) for $C_{18}H_{17}NO_2$ + H^+ calcd.: 280.1337; found: 280.1338.

3-(4-Chlorophenyl)-3-hydroxy-2,2-dimethyl-1-phenyl-1-propanone (3d)

White solid, mp 57–59 °C. IR ($CHCl_3$) (cm^{-1}): 3475 (O-H), 1673 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.54–7.50 (m, 2H), 7.44–7.39 (m, 1H), 7.36–7.32 (m, 2H), 7.26–7.19 (m, 4H), 5.04 (s, 1H), 3.61 (br s, 1H), 1.18 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.25, 139.17, 138.53, 133.15, 130.46, 129.07, 127.83, 127.65, 126.96, 77.95, 52.36, 24.10, 19.53.

3-Hydroxy-2,2-dimethyl-1-phenyl-1-octanone (3f)

Colorless oil. IR ($CHCl_3$) (cm^{-1}): 3489 (O-H), 1671 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.61–7.58 (m, 2H), 7.44–7.40 (m, 1H), 7.37–7.33 (m, 2H), 3.85 (dd, J = 10.0, 2.1 Hz, 1H), 2.69 (br s, 1H), 1.61–1.14 (m, 14H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.75, 139.01, 130.52, 127.80, 127.19, 76.96, 52.11, 31.75, 31.59, 26.48, 22.89, 22.64, 21.20, 14.09. MS (FAB) *m/z*: 249 (M + H^+, 15), 231 (7), 149 (27), 131 (30), 105 (100), 77 (16). HR-MS (FAB) for $C_{16}H_{24}O_2$ + H^+ calcd.: 249.1855; found: 249.1855.

3-Hydroxy-2,2-dimethyl-1,5-diphenyl-1-pentanone (3g) (21)

Colorless oil. IR ($CHCl_3$) (cm^{-1}): 3489 (O-H), 1669 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.63–7.60 (m, 2H), 7.48–7.44 (m, 1H), 7.41–7.36 (m, 2H), 7.31–7.27 (m, 2H), 7.22–7.18 (m, 3H), 3.91 (dd, J = 10.4, 2.4 Hz, 1H), 3.02–2.95 (m, 1H), 2.77 (br d, J = 5.7 Hz, 1H), 2.71–2.63 (m, 1H), 1.85–1.71 (m, 2H), 1.34 (d, J = 2.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.72, 141.86, 138.73, 130.80, 128.32, 128.22, 127.95, 127.32, 125.68, 76.57, 51.93, 33.57, 33.06, 23.18, 21.24.

3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (3h) (22)

syn-*Isomer*

White solid, mp 71–73 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.96–7.92 (m, 2H), 7.62–7.56 (m, 1H), 7.50–7.23 (m, 7H), 5.25 (d, J = 2.6 Hz, 1H), 3.71 (qd, J = 7.3, 3.2 Hz, 1H), 3.69 (br s, 1H), 1.21 (d, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.53, 141.63, 135.46, 133.47, 128.67, 128.36, 128.13, 127.19, 125.91, 73.03, 47.03, 11.24.

anti-*Isomer*

Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99–7.95 (m, 2H), 7.59–7.53 (m, 1H), 7.49–7.25 (m, 7H), 4.99 (d, J = 8.1 Hz, 1H), 3.84 (quint, J = 7.3 Hz, 1H), 3.09 (br s, 1H), 1.07 (d, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.63, 142.00, 136.54, 133.15, 128.50, 128.30, 127.77, 126.58, 76.68, 47.96, 15.76.

3-Hydroxy-1,3-diphenyl-1-propanone (3i) (23)

Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.97–7.93 (m, 2H), 7.61–7.55 (m, 1H), 7.48–7.27 (m, 7H), 5.35 (dd, J = 7.7, 4.4 Hz, 1H), 3.73 (br s, 1H), 3.39–3.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.74, 142.77, 136.29, 133.41, 128.46, 128.33, 127.95, 127.43, 125.56, 69.86, 47.34.

4-Hydroxy-3-methyl-4-phenyl-2-butanone (3j) (24)

syn-*Isomer*

Colorless oil. IR ($CHCl_3$) (cm^{-1}): 3443 (O-H), 1703 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.21 (m, 5H), 5.05 (d, J = 4.1 Hz, 1H), 3.25 (br s, 1H), 2.82 (qd, J = 7.1, 4.1 Hz, 1H), 2.11 (s, 3H), 1.08 (d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.20, 141.54, 128.04, 127.14, 125.69, 72.96, 53.20, 29.43, 10.29.

anti-*Isomer*

Colorless oil. IR ($CHCl_3$) (cm^{-1}): 3431 (O-H), 1705 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.25 (m, 5H), 4.72 (d, J = 8.8 Hz, 1H), 3.02 (br s, 1H), 2.92 (quint, J = 7.2 Hz, 1H), 2.22 (s, 3H), 0.92 (d, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.19, 141.67, 128.32, 127.83, 126.46, 76.44, 53.66, 30.12, 14.21.

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