Indium-Catalyzed Cross-Coupling Reactions between α,β-Unsaturated Carbonyl Compounds and Aromatic Aldehydes

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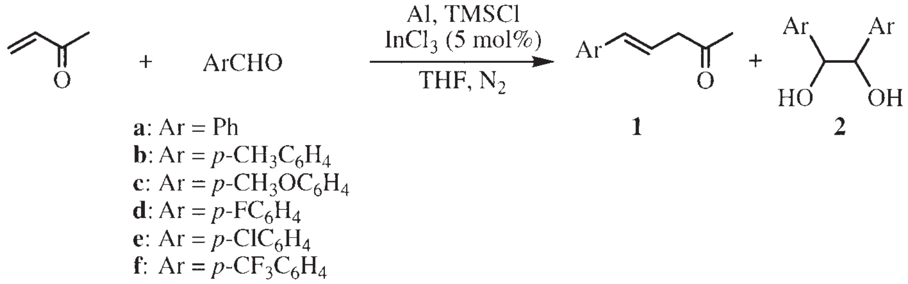
Cross-coupling reactions between α,β-unsaturated carbonyl compounds and aromatic aldehydes have been achieved in tetrahydrofuran (THF) at 25 °C under N_2 using a catalytic amount of $InCl_3$ (0.05 molar amount to the substrate) in the presence of both chlorotrimethylsilane (TMSCl) and aluminum foil (Al). These reactions provide the corresponding β,γ-unsaturated ketones in moderate yields, together with pinacol-coupling products of aldehydes as side products. Chlorides other than TMSCl and $AlCl_3$, such as LiCl, $CaCl_2$, $MgCl_2$, and $SOCl_2$, are not effective at all. Without either TMSCl or Al, no reaction proceeds even in the presence of the catalyst.

The organic chemistry of indium is of current interest from the viewpoint of organic synthesis. Many indium-mediated reactions have been reported, but the number of effective indium-catalyzed reactions is still quite limited.[1] We have recently reported some indium-catalyzed homo-coupling (pinacol-type coupling) reactions of aromatic carbonyl compounds and imines in the presence of chlorosilanes and either aluminum (Al foil) or magnesium (Mg turnings).[2] The products are the corresponding 1,2-diols or 1,2-diamines (*dl*/*meso* mixture), which are supposed to be formed by reductive dimerization of an intermediate ketyl or imino radical species. If the radical species were trapped by suitable substrates like Michael acceptors, the corresponding cross-coupled products might be produced in competition with the formation of the homo-coupling products. Actually, when the above described homo-coupling reaction of benzaldehyde was carried out in the presence of methyl vinyl ketone, the formation of a cross-coupled compound, 5-phenyl-4-penten-2-one, was observed together with those of 1,2-diphenyl-1,2-ethanediols.[3] During this work, a report[4] of similar reactions has appeared where In/$InCl_3$-mediated cross-coupling of various arenecarbaldehydes with methyl vinyl ketone afforded the corresponding β,γ-unsaturated ketones selectively in moderate to good yields. The reported reaction is conceptually the same as that of ours, but not catalytic in indium. As one of our continuing studies on In-catalyzed reactions, we report here the results of $InCl_3$-catalyzed cross-coupling reactions between α,β-unsaturated carbonyl compounds and aromatic aldehydes.

Results and Discussion

A mixture of benzaldehyde (1 molar amount) and methyl vinyl ketone (MVK; 1 molar amount) was added to a mixture of aluminum foil (Al, 4 molar amounts), chlorotrimethylsilane (TMSCl, 4 molar amounts), and a catalytic amount of $InCl_3$ (0.05 molar amount; 5 mol%) in tetrahydrofuran (THF) under a nitrogen atmosphere. The resulting mixture was stirred at 25 °C for 14 h (Method A). A cross-coupling product, 5-phenyl-4-penten-2-one (**1**), and homo-coupling products, 1,2-diphenyl-1,2-ethanediols (**2**), were obtained in 24% and 26% (*dl*/*meso* = 52/48) isolated yields, respectively (Scheme 1). However, the results were not so reproducible and the range of yields of the two products was 8–24% and 13–41%, respectively (Table 1, Entry 1). Here, the concentration of each substrate as well as the amount of TMSCl did not much affect the results (Table 1, Entries 1–3). The yield as well as the selectivity of **1** was improved by using a larger molar amount of MVK (Table 1, Entries 1, 4, and 5). Thus, with 2 molar amounts of MVK and 1 molar amount of benzaldehyde, 32% of **1** was obtained in one case with almost no by-products (Table 1, Entry 5). However, the yield of **1** decreased to 18% when 3 molar amounts of MVK and 1 molar amount of benzaldehyde were employed (Table 1, Entry 6). The presence of



Scheme 1.

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Table 1. $InCl_3$-Catalyzed Cross-Coupling between PhCHO and MVK by Method A[a]

Entry	MVK mmol	Chloride/mmol		Product yield/%[b] **1a**	 **2a**
1	1	TMSCl	4	8–24[c]	13–41[c]
2	1	TMSCl	2	17	18
3	1	TMSCl	8	24	29
4	1.5	TMSCl	4	26	16
5	2	TMSCl	4	24–32[c]	<1–7[c]
6	3	TMSCl	4	18	—[d]
7	1	$AlCl_3$	1.33	18	7

a) $InCl_3$ (0.05 mmol), Al (4 mmol), PhCHO (1 mmol), and THF (10 mL) at 25 °C for 14 h under N_2. b) Isolated yield. c) Several runs. d) Obtained as a complex mixture. The yield of **2a** is quite low.

Table 2. $InCl_3$-Catalyzed Cross-Coupling between PhCHO and MVK by Method B[a]

Entry	In species/mmol		MVK mmol	Reaction time/h	Product yield/%[b] **1a**	 **2a**
1	$InCl_3$	0.05	2	3	54–56[c]	5–18[c]
2	$InCl_3$	0.05	3	3	49	5
3	$InCl_3$	0.05	1.5	3.5	51	15
4	$InCl_3$	0.1	2	4	54	6
5	$InCl_3$	0.03	2	5.5	46	5
6	$InCl_3$	0.01	2	7	30	18
7	In powder	0.05	2	4	53	11
8	In_2O_3	0.026	2	19	17	12
9	—		2	11	0	4

a) Al (4 mmol), PhCHO (1 mmol), TMSCl (4 mmol), and THF (10 mL) at 25 °C under N_2. b) Isolated yield. c) Several runs.

Table 3. $InCl_3$-Catalyzed Cross-Coupling between PhCHO and MVK, in the Presence of Various Metal[a]

Entry	Metal, Form[b]		Reaction time/h	Product yield/%[c] **1a**	 **2a**
1	Al	F	3	54–56[d]	5–18[d]
2	Al	P	2.5	45	22
3	In	P	4	63	4
4	Zn	P	1	45	14
5	Mg	T	8	11	<25
6	Fe	P	20	—	—

a) $InCl_3$ (0.05 mmol), metal (4 mmol), PhCHO (1 mmol), MVK (2 mmol), TMSCl (4 mmol), and THF (10 mL) at 25 °C under N_2. b) F = foil, P = powder, T = turnings. c) Isolated yield. d) Several runs.

Table 4. $InCl_3$-Catalyzed Cross-Coupling between Various ArCHO and MVK, in the Presence of Al[a]

Entry	Ar	Reaction time/h	Product yield/%[c] 1	 2
1	Ph	3	**1a**, 54–56[c]	**2a**, 5–18[c]
2	*p*-$CH_3C_6H_4$	4	**1b**, 62	**2b**, 11
3	*p*-$CH_3OC_6H_4$	6	**1c**, 57	**2c**, <1
4	*p*-FC_6H_4	3.5	**1d**, 61	**2d**, 11
5	*p*-ClC_6H_4	4	**1e**, 50	**2e**, 13
6	*p*-$CF_3C_6H_4$	3.5	**1f**, 54	**2f**, 13
7	2-C_4H_3O[d]	6.5	—[e]	—[e]

a) $InCl_3$ (0.05 mmol), Al (4 mmol), ArCHO (1 mmol), MVK (2 mmol), TMSCl (4 mmol), and THF (10 mL) at 25 °C under N_2. b) Isolated yield. c) Several runs. d) Furfural. e) Obtained as a complex mixture. The yields of both **1** and **2** could not be determined.

chloride anion was indispensable in the case of $InCl_3$-catalyzed homo-coupling of aldehydes.[2] When the effect of various chlorides was examined in this cross-coupling reaction, all chlorides such as LiCl (4 molar amounts), $CaCl_2$, $MgCl_2$, and $SOCl_2$ (all, 2 molar amounts) were revealed to be ineffective, except $AlCl_3$ (1.33 molar amounts) which showed an almost identical activity to that of TMSCl (Table 1, Entry 7). In other solvents such as dioxane and diethyl ether, this cross-coupling reaction failed.

During this investigation, we noticed that the yield of **1** was affected by the order of addition of the reagents. Thus, when a mixture of benzaldehyde and MVK was added to a mixture of Al, $InCl_3$, and THF, followed by the addition of TMSCl (Method B), the yield of **1** was much improved (54–56%, Table 2, Entry 1) and the data were more reproducible than those provided by Method A. Although the exact reason for this improvement was unclear, we decided to apply Method B in subsequent investigations.

The appropriate amount of MVK to benzaldehyde (Table 2, Entries 1–3) and that of $InCl_3$ to the aldehyde (Table 2, Entries 1, 4–6) were revealed to be 2 equiv. and 0.05 equiv., respectively. Other indium catalysts were tried; In (powder) was as effective as $InCl_3$ (Table 2, Entry 7), but In_2O_3 was not effective (Table 2, Entry 8).

Other metals such as magnesium turnings and iron powder, in place of Al (foil), were not effective (Table 3, Entries 5 and 6), while aluminum powder (Table 3, Entry 2), indium powder[4] (Table 3, Entry 3), and zinc powder (Table 3, Entry 4) could be used in the same way as Al (foil) was used.

A variety of *p*-substituted aromatic aldehydes similarly afforded the corresponding expected products, **1** and **2**, irrespective of the electron-releasing or electron-withdrawing nature of the substituent (Table 4, Entries 1–6). The system could not be applied to furfural (Table 4, Entry 7).

Ethyl vinyl ketone (EVK, 1-penten-3-one), 3-penten-2-one, and 2-cyclohexen-1-one could also be employed in this cross-coupling reaction with benzaldehyde to afford the corresponding β,γ-unsaturated ketones (**3**) such as 6-phenyl-5-hexen-3-one, 3-methyl-5-phenyl-4-penten-2-one, and 2-(2-phenylethenyl)-1-cyclopentanone in moderate yields, respectively (Table 5, Entries 2–4). A substituent at the β-position of α,β-unsaturated ketones migrated to the α-position of the carbonyl groups of the corresponding β,γ-unsaturated ketones (**3**) in the latter two cases (Table 5, Entries 3 and 4; Scheme 2). Similar reactions were also investigated using indium powder in place of Al, but only EVK was reactive (Table 5, Entries 5 and 6), and other enones afforded very little **3** (Table 5, Entries 7 and 8).

As to the reaction pathway for the formation of **1**, Kang and

Table 5. $InCl_3$-Catalyzed Cross-Coupling between PhCHO and Various Enone, in the Presence of Al[a)]

Entry	Metal	Enone	Reaction time/h	Product yield/%[b)] **1a** or **3**	**2a**
1	Al	MVK	3	**1a**, 54–56[c)]	5–18[c)]
2	Al	EVK	3	**3a**, 43	11
3	Al	3-Penten-2-one	4	**3b**, 17	16
4	Al	2-Cyclohexen-1-one	4	**3c**, 37	—[d)]
5	In	MVK	4	**1a**, 63	4
6	In	EVK	4	**3a**, 24	0
7	In	3-Penten-2-one	20	**3b**, 5	0
8	In	2-Cyclohexen-1-one	20	**3c**, 3	—[d)]

a) $InCl_3$ (0.05 mmol), metal (4 mmol), PhCHO (1 mmol), enone (2 mmol), TMSCl (4 mmol), and THF (10 mL) at 25 °C for 14 h under N_2. b) Isolated yield. c) Several runs. d) Obtained as a complex mixture and unable to be determined.

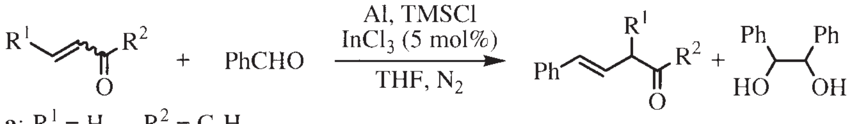
co-workers have proposed the radical cyclopropanation (Scheme 3), the cyclopropanyl proton being detected by ^{1}H NMR measurement.[4] Our results of the formation of **3b** from 3-penten-2-one and **3c** from 2-cyclohexen-1-one, where alkyl migration proceeded, support this proposal as shown in Scheme 4. Here a redox-active $InCl_3$–metal alloy ([In], metal = Al, Zn, In) is supposed to be an active indium species.[2a,b,5] This indium species causes a one-electron reduction of an α,β-unsaturated ketone to produce a ketyl radical, which might attack an aldehyde to form an intermediate species **I**. This species is intramolecularly cyclized and suffered one-electron reduction to form an α-hydroxybenzylic cyclopropanol. The cyclopropanol is protonated and dehydrated in aqueous HCl during workup procedure to afford the product β,γ-unsaturated ketone as reported.[6] The formation of pinacol-coupling product **2** may be due to the coupling of a ketyl radical partly formed from an aromatic aldehyde by an electron transfer from the $InCl_3$–metal alloy.[2a,b]

Experimental

General. The ^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM-AL300, JEOL EX-400, and JEOL GSX270 spectrometers for solutions in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts are reported in δ ppm units downfield from Me_4Si. Analytical thin-layer chromatographies (TLC) were performed with Merck silica gel 60 F-254 plates. The isolation of a pure product was carried out with column chromatography on SiO_2 (Merck 60, 230–400 mesh, Merck KGaA.).

Materials. $InCl_3$ was purchased from Aldrich and used without further purification. Aluminum foil (0.1 mm × 0.8 mm) and chlorotrimethylsilane (TMSCl) were purchased from Nacalai Tesque and used without further purification. Tetrahydrofuran (THF) was distilled from sodium diphenylketyl before use. All carbonyl compounds were commercial products and were used without further purification. The structures of 1,2-diols (**2**) were determined by comparison of spectral data with those of the authentic samples.[2] All products (**1** and **3**) except **1f** and **3c** were known compounds, the ^{1}H and ^{13}C NMR data being shown for convenience.

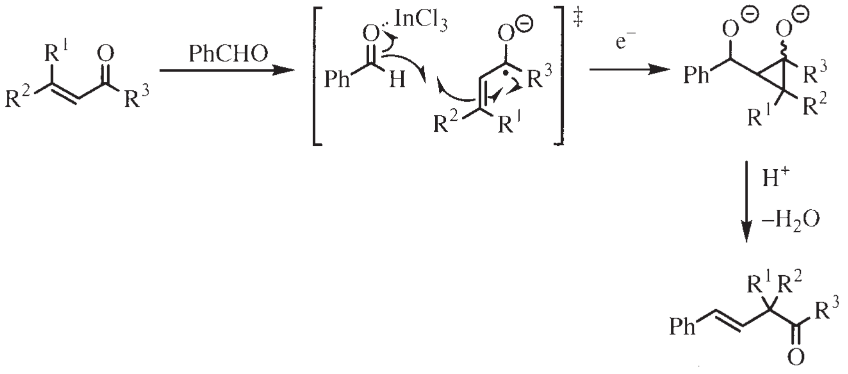
Typical Procedure for a Cross-Coupling Reaction between Methyl Vinyl Ketone with Benzaldehyde. Method A: A mixture of aluminum (0.108 g, 4 mmol), $InCl_3$ (11 mg, 0.05 mmol), chlorotrimethylsilane (0.5 mL, 4 mmol), and THF (5 mL) in a 50 mL two necked round-bottomed flask was stirred for 5 min at room temperature under N_2. To this mixture was added a solution of methyl vinyl ketone (0.071 g, 1 mmol) and benzaldehyde (0.106 g, 1 mmol) in THF (5 mL) at room temperature under N_2. The mixture was kept at room temperature with magnetic stirring for 14 h. Aqueous HCl (ca. 1 mol dm^{-3}, 10 mL) was added to the resulting mixture, which was stirred for 10 min, and the organic layer was separated. The aqueous layer was extracted by diethyl ether (20 mL × 3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL × 2), dried over $MgSO_4$, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent, hexane/ethyl acetate) to



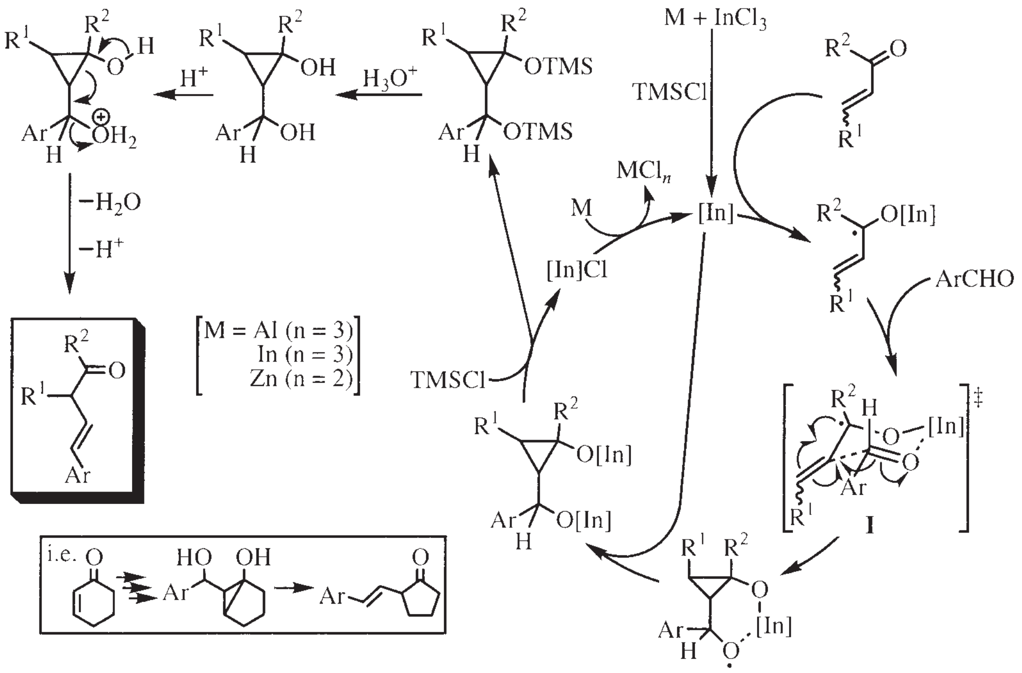
a: $R^1 = H$, $R^2 = C_2H_5$
b: $R^1 = CH_3$, $R^2 = CH_3$
c: $R^1, R^2 = (CH_2)_3$

3 **2a**

Scheme 2.



Scheme 3.



Scheme 4. Plausible reaction pathway.

give 5-phenyl-4-penten-2-one (**1**) (0.126–0.388 g, 0.079–0.242 mmol, 8–24% yield), 1,2-diphenyl-1,2-ethanediols (**2**) (0.135–0.441 g, 0.063–0.206 mmol, 13–41% yield), and a complex mixture containing benzyl alcohol and many unidentified compounds.

Typical Procedure for a Cross-Coupling Reaction between Methyl Vinyl Ketone with Benzaldehyde. Method B: In a two-necked 50 mL round-bottomed flask, equipped with a septum inlet and a three-way stopcock, were placed aluminum foil (0.108 g, 4 mmol) and $InCl_3$ (11 mg, 0.05 mmol). The system was then evacuated and flushed several times with N_2 from a N_2-filled balloon connected to the flask; THF (4 mL) and a solution of aromatic aldehyde (1 mmol) and α,β-unsaturated ketone (2 mmol) in THF (6 mL) were added and then chlorotrimethylsilane (0.5 mL, 4 mmol) was injected by a syringe. The reaction mixture was then treated as above.

5-Phenyl-4-penten-2-one (1a):[4,7–14] A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H), 3.29–3.32 (d, $J = 7.0$ Hz, 2H), 6.23–6.34 (dt, $J = 15.9$, 7.0 Hz, 1H), 6.42–6.49 (d, $J = 16.0$ Hz, 1H), 7.18–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 29.59, 47.75, 121.86, 126.24, 127.55, 128.53, 133.79, 136.81, 206.67.

5-(4-Methylphenyl)-4-penten-2-one (1b):[4,9] A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.31 (s, 3H), 3.26–3.29 (d, $J = 7.0$ Hz, 2H), 6.17–6.28 (dt, $J = 15.9$, 7.0 Hz, 1H), 6.38–6.45 (d, $J = 15.9$ Hz, 1H), 7.07–7.11 (d, $J = 7.9$ Hz, 2H), 7.23–7.26 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.01, 29.37, 47.61, 120.70, 126.01, 129.10, 133.49, 133.96, 137.19, 206.63.

5-(4-Methoxyphenyl)-4-penten-2-one (1c):[4,14] A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H), 3.26–3.30 (d, $J = 7.2$ Hz, 2H), 3.56 (s, 3H), 6.08–6.19 (dt, $J = 15.9$, 7.2 Hz, 1H), 6.36–6.43 (d, $J = 15.9$ Hz, 1H), 6.80–6.85 (d, $J = 8.8$ Hz, 2H), 7.27–7.31 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.39, 47.63, 55.11, 113.83, 119.48, 127.29, 129.56, 133.07, 159.05, 206.85.

5-(4-Fluorophenyl)-4-penten-2-one (1d):[4] A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 3.29–3.32 (d, $J = 7.0$ Hz, 2H), 6.16–6.26 (dt, $J = 15.9$, 7.0 Hz, 1H), 6.38–6.44 (d, $J = 15.9$ Hz, 1H), 6.93–7.02 (t, $J = 8.8$ Hz, 2H), 7.27–7.35 (dd, $J = 8.8$, 5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.44, 47.36, 115.12–115.41 (d, $J = 21.4$ Hz), 121.57–121.60 (d, $J = 2.4$ Hz), 127.56–127.67 (d, $J = 7.8$ Hz), 132.33, 132.92–132.96 (d, $J = 3.7$ Hz), 160.47–163.74 (d, $J = 246.6$ Hz), 206.37.

5-(4-Chlorophenyl)-4-penten-2-one (1e):[4,15] A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 3.30–3.34 (d, $J = 6.8$ Hz, 2H), 6.22–6.33 (dt, $J = 16.0$, 6.8 Hz, 1H), 6.36–6.43 (d, $J = 16.0$ Hz, 1H), 7.23–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 29.55, 47.37, 122.59, 127.35, 128.55, 132.32, 132.99, 135.26, 206.20.

5-(4-Trifluoromethylphenyl)-4-penten-2-one (1f): A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H), 3.36–3.39 (d, $J = 6.0$ Hz, 2H), 6.36–6.47 (dt, $J = 16.0$, 6.0 Hz, 1H), 6.46–6.53 (d, $J = 16.0$ Hz, 1H), 7.43–7.47 (d, $J = 8.1$ Hz, 2H), 7.53–7.57 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.76, 47.47, 122.47–133.27 (quartet, $J = 272.2$ Hz), 124.92, 125.47–125.63 (quartet, $J = 3.7$ Hz), 126.48, 128.73–130.01 (quartet, $J = 32.3$ Hz), 132.40, 140.42, 206.10. HRMS (FAB) found: 229.0843. Calcd for $C_{12}H_{12}F_3O$ (M + H^+): 229.0840.

6-Phenyl-5-hexen-3-one (3a):[4,16,17] A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.16–1.22 (t, $J = 7.3$ Hz, 3H), 2.58–2.66 (quartet, $J = 7.3$ Hz, 2H), 3.41–3.44 (d, $J = 7.0$ Hz, 2H), 6.37–6.48 (dt, $J = 16.0$, 7.0 Hz, 1H), 6.55–6.61 (d, $J = 16.0$ Hz, 1H), 7.31–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 7.64, 35.51, 46.49, 122.16, 126.15, 127.42, 128.46, 133.49, 136.86, 209.14.

3-Methyl-5-phenyl-4-penten-2-one (3b):[10,18–20] A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.25–1.29 (d, $J = 7.0$ Hz, 3H), 2.20 (s, 3H), 3.30–3.40 (dt, $J = 8.5$, 7.0 Hz, 1H), 6.12–6.21 (dd, $J = 15.8$, 8.5 Hz, 1H), 6.48–6.55 (d, $J = 15.8$ Hz, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.15, 28.16, 51.34, 126.27, 127.66, 128.61, 128.79, 132.18, 136.80, 209.37.

2-(2-Phenylethenyl)cyclopentan-1-one (3c): A pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.75–2.36 (m, 6H), 2.86–2.96 (m, 1H), 6.16–6.25 (ddd, $J = 16.1$, 6.1, 2.5 Hz, 1H), 6.41–6.48 (dd, $J = 16.1$, 1.3 Hz, 1H), 7.15–7.21 (t, $J = 7.0$ Hz, 1H), 7.23–7.30

(t, $J = 7.0$ Hz, 2H), 7.33–7.37 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.57, 29.48, 37.60, 52.27, 125.96, 126.00, 127.18, 128.27, 131.72, 136.79, 217.83. HRMS (FAB) found: 186.1039. Calcd for $C_{13}H_{14}O$ (M^+): 186.1045.

1,2-Bis(4-fluorophenyl)-1,2-ethanediol (2d) (*dl*/*meso* mixture):[21] A colorless oil or a white solid: ^{1}H NMR ($CDCl_3$) δ 1.87 (s, br, 2H), 4.64 (*dl* isomer), 4.83 (*meso* isomer) (s, 2H), 6.88–7.19 (m, 8H).

1,2-Bis[4-(trifluoromethyl)phenyl]-1,2-ethanediol (2f) (*dl*/*meso* mixture):[22] A colorless oil or a white solid: ^{1}H NMR ($CDCl_3$) δ 2.43 (s, br, 2H), 4.75 (*dl* isomer), 4.95 (*meso* isomer) (s, 2H), 7.42–7.63 (m, 8H).

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