Convenient Preparation of 3,3-Diaryl-2-propen-1-ols

for Synthesis of Cibenzoline and the Analogs

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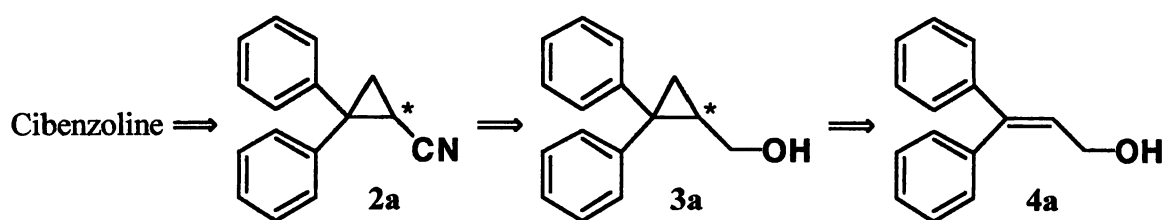
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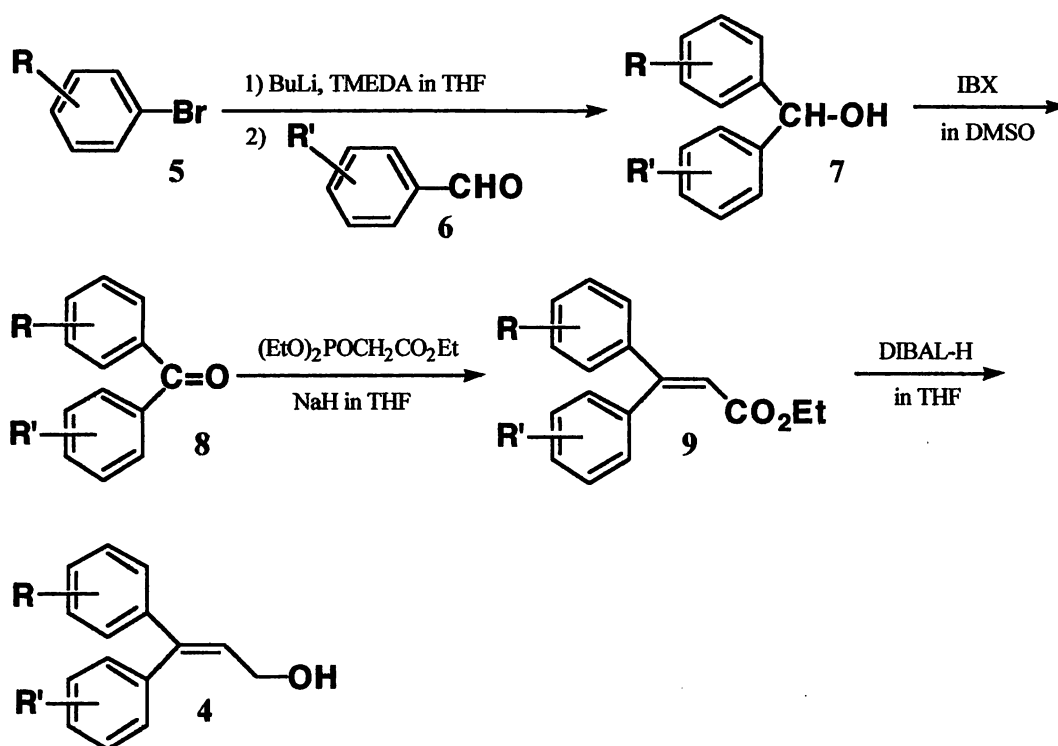*1-1 Ridai-cho, Okayama 700-0005, Japan*

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Abstract: **Various 3,3-diaryl-2-propen-1-ols (4) were synthesized from the corresponding aryl bromides (5) and arylaldehydes (6) in four steps. The yields were good to excellent in all steps. In particular, 3,3-diphenyl-2-propen-1-ol (4a) is the important starting material for synthesis of chiral cibenzoline by the catalytic enantioselective Simmon-Smith cyclopropanation using α-amino acid-derived disulfonamide, which we have recently reported. The secondary alcohols (7) were prepared from aryl bromides 5, butyllithium, and TMEDA, followed by addition of substituted benzaldehydes 6. The alcohols 7 were converted to 3,3-diaryl-2-propen-1-ols 4 by oxidation of 7 with IBX, by Horner-Wadsworth-Emmons reaction of the ketones (8) with $(EtO)_2POCH_2CO_2Et$ and sodium hydride, then by reduction of the esters (9) with DIBAL-H.**

We have recently developed α-amino acid-derived disulfonamide (1) for a catalytic enantioselective Simmons-Smith reaction[1a,1b] and alkylation.[2a] Cibenzoline is commercially an available medicine as a class I antiarrhythmic agent.[3] We will apply the catalytic enantioselective cyclopropanation using α-amino acid-derived disulfonamide to synthesis of chiral cibenzoline and the analogs, in which a key compound is 3,3-diphenyl-2-propen-1-ol (4a) as shown in Scheme 1. In this paper, we describe a convenient route for synthesis of 3,3-diaryl-2-propen-1-ols (4) from the corresponding aryl bromides (5) and arylaldehydes (6) in four steps. The outline for preparation of 3,3-diaryl-2-propen-1-ols 4 is summarized in Scheme 2.

Cibenzoline

1

Cibenzoline ⟹ 2a ⟹ 3a ⟹ 4a

Scheme 1.

5 —Br   1) BuLi, TMEDA in THF
        2) R'   —CHO
                    6
                              CH-OH   7   IBX
                                           in DMSO

8 C=O   (EtO)₂POCH₂CO₂Et
         NaH in THF   9 CO₂Et   DIBAL-H
                                              in THF

4 —OH

Scheme 2.

Initially, the various secondary alcohols (7) substituted on the aromatic rings by electron-donating or electron-withdrawing groups were prepared in 68~91% yields from the corresponding aryl bromides (5), butyllithium, and N,N,N',N'-tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF), followed by addition of the corresponding arylaldehydes (6). Even chlorinated alcohols on the aromatic rings were easily synthsized in good yields as described in entries 4 and 5. The alcohols 7 were oxidized with 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide (DMSO) to afford the corresponding substituted benzophenones 8 in 75~99% yields. The results of preparation of various benzophenone derivatives 8 are collected in Table 1.

Table 1. Preparation of Various Benzophenone Derivatives 8
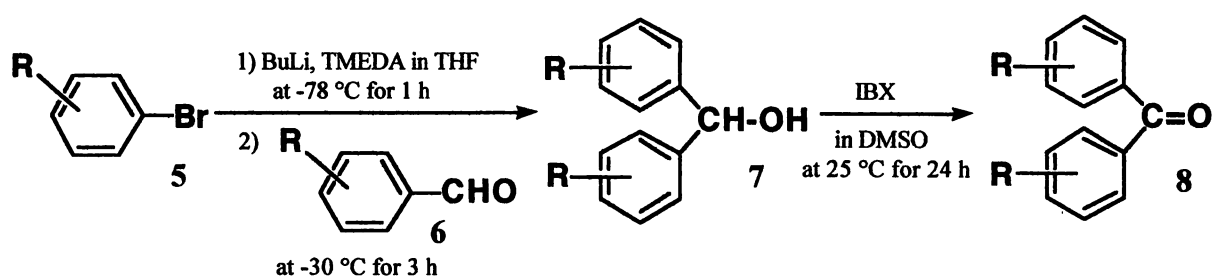
| Entry	R	7	Yield (%)[a]	8	Yield (%)[b]
1	4-MeO	7b	89	8b	96
2	3-MeO	7c	73	8c	90
3	4-Me	7d	91	8d	99
4	4-Cl	7e	86	8e	87
5	3-Cl	7f	68	8f	84
6	4-CF$_3$	7g	80	8g	75

a) All reactions were carried out with 13 mmol of an aryl bromide 5, 12 mmol of butyllithium, 13 mmol of TMEDA, and 10 mmol of an arylaldehyde 6 in 50 mL of anhydrous THF. b) All reactions were carried out with 1 equivalent of the diarylmethanol 7 and 1.2 equivalents of IBX in anhydrous DMSO.

Next, Horner-Wadsworth-Emmons reaction of benzophenone (8a) as a steric hindered ketone with $(EtO)_2POCH_2CO_2Et$ and sodium hydride was studied and the results are collected in Table 2.   When we ran the reaction of benzophenone 8a with $(EtO)_2POCH_2CO_2Et$ and sodium hydride in THF at 25 °C for 2 h, a mixture of 8a and ethyl 3,3-diphenyl-2-propenate (9a) was obtained as an inseparable solid after silica gel column chromatograpy. The mixture of 8a and 9a was reduced with 2 equivalents of diisobutylaluminum hydride (DIBAL-H) in THF at 25 °C for 3 h to afford 3,3-diphenyl-2-propen-1-ol 4a in 4% yield (entry 1).

The relationship between temparature and yield in Horner-Wadsworth-Emmons reaction was examined (entries 1~4) and the reaction at 50 °C yielded 28% (entry 3). Effect of concentration of **8a** on the yield was evaluated at 50 °C and it is noted that better yields (40% and 34 %) were afforded in higher concentration (entries 5 and 6). When DMSO was used as a co-solvent, much better yields (47% and 59%) were given with 1.2 and 1.5 equivalents of sodium hydride, respectively (entries 7 and 8). The reaction was run at 60 °C with 1.5 equivalents of sodium hydride in a 3 : 1 mixture of THF-DMSO to afford **4a** in 66% yield (entry 9).

Table 2. Preparation of 3,3-Diphenyl-2-propen-1-ol **4a** from Benzophenone **8a**[a]

| | 1) $(EtO)_2POCH_2CO_2Et$, NaH for 2 h |
| | 2) DIBAL-H in THF at 25 °C for 3 h |
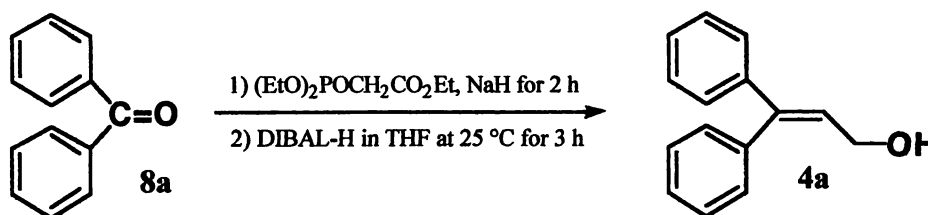
Entry	Temp. (°C)	NaH (equiv.)	Solvent (mL)	Yield (%)
1	25	1.2	THF (15)	4
2	35	1.2	THF (15)	9
3	50	1.2	THF (15)	28
4	65	1.2	THF (15)	20
5	50	1.2	THF (1.2)	40
6	50	1.5	THF (1.2)	34
7	50	1.2	THF-DMSO (1.2-0.4)	47
8	50	1.5	THF-DMSO (1.2-0.4)	59
9	60	1.5	THF-DMSO (1.2-0.4)	66

a) 1) All reactions were carried out with 3.8 mmol of benzophenone **8a**, 5.0 mmol of $(EtO)_2POCH_2CO_2Et$, and the indicated equivalents of sodium hydride in the indicated anhydrous solvents.   2) After silica gel column chromatograpy, the mixture of **8a** and ethyl 3,3-diphenyl-2-propenate **9a** was reduced with 7.6 mmol of DIBAL-H in 66 mL of anhydrous THF.

Finally, Horner-Wadsworth-Emmons reactions of various substituted benzophenones **8** on the aromatic rings by electron-donating or electron-withdrawing groups were carried out. In all cases, separation of the products were performed after reduction of the mixture of ethyl 3,3-diaryl-2-propenates **9** and the recovered ketones **8** with DIBAL-H

in THF at 25 °C for 3 h to afford 3,3-diaryl-2-propen-1-ols **4** and diarylmethanols **7** .   All results are summarized in Table 3.

Table 3. Preparation of Various 3,3-Diaryl-2-propen-1-ols **4**[a)]
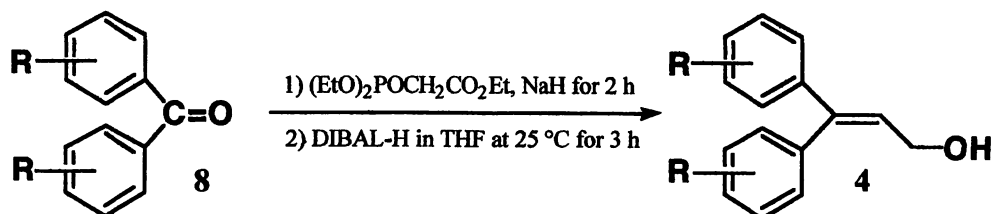
Entry	R	Temp. (°C) for 1)	Solvent (mL)	4	Yield (%)
1	H	60	THF-DMSO (0.3-0.1)	**4a**	63
2	H	100	1,4-dioxane-DMSO (0.3-0.1)	**4a**	52
3	4-MeO	100	1,4-dioxane-DMSO (0.3-0.1)	**4b**	23
4	4-Me	100	1,4-dioxane-DMSO (0.3-0.1)	**4d**	95
5	4-Cl	60	THF-DMSO (0.3-0.1)	**4e**	30
6	4-Cl	100	1,4-dioxane-DMSO (0.3-0.1)	**4e**	75
7	4-Cl	100	1,4-dioxane-DMSO (0.2-0.2)	**4e**	16
8	4-Cl	100	1,4-dioxane-DMSO (0.1-0.3)	**4e**	53
9	4-Cl	80	1,2-dimethoxyethane-DMSO (0.3-0.1)	**4e**	51
10	4-Cl	110	toluene-DMSO (0.3-0.1)	**4e**	48
11	4-Cl	60	DMSO (0.4)	**4e**	0
12	4-CF$_3$	100	1,4-dioxane-DMSO (0.3-0.1)	**4g**	38

a) 1) All reactions were carried out with 1.0 mmol of a benzophenone derivative **8**, 1.3 mmol of (EtO)$_2$POCH$_2$CO$_2$Et, and 1.5 mmol of sodium hydride at the indicated temparature for 2 h in 0.4 mL of the indicated anhydrous solvents. 2) After silica gel column chromatograpy, the mixture of **8** and the ethyl 3,3-diaryl-2-propenate **9** was reduced with 2.0 mmol of DIBAL-H in 3.3 mL of anhydrous THF at 25 °C for 3 h.

Interestingly, the reaction of benzophenone **8a** gave 63% yield in THF-DMSO (3 : 1) and 52% yield in 1,4-dioxane-DMSO (3 : 1) as shown in entries 1 and 2. On the other hand, the reaction of 4,4'-dichlorobenzophenone (**8e**) afforded 30% yield in THF-DMSO (3 : 1) and 75% yield in 1,4-dioxane-DMSO (3 : 1) as indicated in entries 5 and 6. Then 3,3-bis(4-methylphenyl)-2-propen-1-ol (**4d**) was obtained in 95% of an excellent yield. Unfortunately, Horner-

Wadsworth-Emmons reactions of methoxy- or trifluoromethyl-substituted ketones (**8b** or **8g**) on the aromatic rings yielded low (23% and 38%, respectively in entries 3 and 12).

In summary, the steric hindered 3,3-diary-2-propen-1-ols **4** were easily prepared from the corresponding benzophenone derivatives **8** in moderate to excellent yields. The substituted benzophenones **8** on the aromatic rings by electron-donating or electron-withdrawing groups were obtained from the corresponding aryl bromides **5** and arylaldehydes **6** in good to excellent yields. It is found that the yields of Horner-Wadsworth-Emmons reactions of the ketones **8** extremely depend on concentration and solvent.

We are currently working on the enantioselective Simmons-Smith cyclopropanation of these steric hindered 3,3-diaryl-2-propen-1-ols **4** with Et_2Zn and CH_2I_2 in the presence of a catalytic amount of α-amino acid-derived disulfonamide **1**. Further investigations on synthesis of cibenzoline and the analogs using 3,3-diaryl-2-propen-1-ols **4** are also in progress.

Experimental Section

^1H NMR and ^{13}C NMR spectra were measured with a JEOL JNM-GSX400 (400MHz and 100MHz, respectively). The chemical shifts are expressed in ppm downfield from tetramethylsilane, using tetramethylsilane (δ = 0) and/or residual chloroform (δ = 7.25) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. For thin layer chromatographic (TLC) analyses, Merck precoated TLC aluminum plates (silica gel 60 F254, Art 5554) were used.

Typical Procedure for Preparation of Diarylmethanols 7:

To a colorless clear solution of 2.43 g (13 mmol, 1.3 equiv.) of 4-bromoanisole (**5b**) and 1.99 mL (13 mmol, 1.3 equiv.) of TMEDA in 50 mL of anhydrous THF was added dropwise at -78 °C 7.50 mL (12 mmol, 1.2 equiv.) of a 1.59M solution of butyllithium in hexane. After stirring for 1 h at -78 °C, 1.22 mL (10 mmol, 1 equiv.) of 4-methoxybenzaldehyde (**6b**) was added dropwise at -78 °C to the colorless clear solution. The mixture was stirred for 3 h at -30 °C, quenched at the temparature with 20 mL of 2M aq. NH_4Cl, extracted with 50 mL of EtOAc, washed with 10 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 1 : 4 mixture of EtOAc and hexane to afford 2.82 g (89% yield) of bis(4-methoxyphenyl)methanol (**7b**). **7b**: ^1HNMR ($CDCl_3$) δ 2.36 (1H, brs, OH), 3.76 (6H, s, CH_3 x 2), 5.72 (1H, s, CH), 6.84, 7.25 (4H, 4H, d, d, J = 8.6, 8.6 Hz, C_6H_4 x 2). ^{13}C NMR ($CDCl_3$) δ 55.2 (CH_3 x 2), 75.3 (CH), 113.7, 127.6, 136.3, 158.8 (C_6H_4 x 2).

Bis(3-methoxyphenyl)methanol (7c): ^1HNMR ($CDCl_3$) δ 2.24 (1H, brs, OH), 3.79 (6H, s, CH_3 x 2), 5.78 (1H, d, J = 3.2 Hz, CH), 6.80, 6.95, 6.96, 7.24 (2H, 2H, 2H, 2H, d, d, s, t, J = 7.6, 7.6, 7.6 Hz, C_6H_4 x 2). ^{13}C NMR ($CDCl_3$) δ 55.2 (CH_3 x 2), 76.1 (CH), 112.0, 113.0, 118.8, 129.4, 145.2, 159.6 (C_6H_4 x 2).

Bis(4-methylphenyl)methanol (7d): ^{1}H NMR (CDCl$_3$) δ 2.16 (1H, brs, OH), 2.32 (6H, s, CH$_3$ x 2), 5.78 (1H, s, CH), 7.13, 7.25 (4H, 4H, d, d, J = 8.0, 8.0 Hz, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 21.2 (CH$_3$ x 2), 75.9 (CH), 126.4, 129.1, 137.0, 141.0 (C$_6$H$_4$ x 2).

Bis(4-chlorophenyl)methanol (7e): ^{1}H NMR (CDCl$_3$) δ 2.26 (1H, brs, OH), 5.79 (1H, s, CH), 7.26-7.32 (8H, m, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 75.0 (CH), 127.8, 128.7, 133.5, 141.7 (C$_6$H$_4$ x 2).

Bis(3-chlorophenyl)methanol (7f): ^{1}H NMR (CDCl$_3$) δ 2.32 (1H, d, J = 2.8 Hz, OH), 5.77 (1H, d, J = 2.8 Hz, CH), 7.22-7.31, 7.38 (6H, 2H, m, s, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 75.1 (CH), 124.6, 126.6, 127.9, 129.8, 134.5, 145.0 (C$_6$H$_4$ x 2).

Bis[4-(trifluoromethyl)phenyl]methanol (7g): ^{1}H NMR (CDCl$_3$) δ 2.46 (1H, brs, OH), 5.94 (1H, s, CH), 7.50, 7.61 (4H, 4H, d, d, J = 8.2, 8.2 Hz, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 75.2 (CH), 125.6, 125.6, 125.7, 126.7, 146.7 (CF$_3$ x 2, C$_6$H$_4$ x 2).

Typical Procedure for Preparation of Substituted Benzophenones 8:

To a solution of 1.71 g (7.65 mmol, 1 equiv.) of **7b** in 15 mL of anhydrous DMSO was added 2.57 g (9.17 mmol, 1.2 equiv.) of IBX After stirring for 24 h at 25 °C, the reaction mixture was diluted with 200 mL of EtOAc, washed with 20 mL of 2M aq. NaHCO$_3$, 20 mL of half brine, 10 mL of brine, and dried over MgSO$_4$. The crude product was chromatographed on silica gel with a 1 : 3 mixture of EtOAc and hexane to afford 1.63 g (96% yield) of 4,4'-dimethoxybenzophenone (**8b**). **8b:** ^{1}H NMR (CDCl$_3$) δ 3.89 (6H, s, CH$_3$ x 2), 6.96, 7.79 (4H, 4H, d, d, J = 8.8, 8.8 Hz, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 55.5 (CH$_3$ x 2), 113.4, 130.7, 132.1, 162.7 (C$_6$H$_4$ x 2), 194.3 (C=O).

3,3'-Dimethoxybenzophenone (8c): ^{1}H NMR (CDCl$_3$) δ 3.67 (6H, s, CH$_3$ x 2), 6.92, 6.99, 7.43, 7.51 (2H, 2H, 2H, 2H, d, t, t, d, J = 8.0, 7.2, 8.0, 7.6 Hz, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 55.7 (CH$_3$ x 2), 111.4, 120.3, 130.2, 130.4, 132.5, 158.2 (C$_6$H$_4$ x 2), 195.2 (C=O).

4,4'-Dimethylbenzophenone (8d): ^{1}H NMR (CDCl$_3$) δ 2.44 (6H, s, CH$_3$ x 2), 7.27, 7.70 (4H, 4H, d, d, J = 8.4, 8.4 Hz, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 21.7 (CH$_3$ x 2), 128.8, 130.1, 135.1, 142.8 (C$_6$H$_4$ x 2), 196.1 (C=O).

4,4'-Dichlorobenzophenone (8e): ^{1}H NMR (CDCl$_3$) δ 7.47, 7.73 (4H, 4H, d, d, J = 8.8, 8.8 Hz, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 128.7, 131.2, 135.4, 139.1 (C$_6$H$_4$ x 2), 194.1 (C=O).

3,3'-Dichlorobenzophenone (8f): ^{1}H NMR (CDCl$_3$) δ 7.45, 7.59, 7.65, 7.78 (2H, 2H, 2H, 2H, t, d, d, s, J = 8.0, 8.0, 8.0 Hz, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 128.0, 129.7, 129.7, 132.7, 134.7, 138.5 (C$_6$H$_4$ x 2), 193.7 (C=O).

4,4'-Bis(trifluoromethyl)benzophenone (8g): ^{1}H NMR (CDCl$_3$) δ 7.79, 7.91 (4H, 4H, d, d, J = 8.4, 8.4 Hz, C$_6$H$_4$ x 2). ^{13}C NMR (CDCl$_3$) δ 125.5, 125.6, 125.6, 130.1, 139.7 (CF$_3$ x 2, C$_6$H$_4$ x 2), 194.2 (C=O).

Typical Procedure for Preparation of 3,3-Diaryl-2-propen-1-ols 4:

To a suspension of a washed sodium hydride (1.5 mmol, 1.5 equiv.) in 0.3 mL of anhydrous THF was added dropwise at 60 °C for 40 min 260 μL (1.3 mmol, 1.3 equiv.) of (EtO)$_2$POCH$_2$CO$_2$Et. After stirring for 1 h at 25 °C, the yellow clear solution was added dropwise at 60 °C for 30 min to a solution of 182 mg (1 mmol, 1 equiv.) of benzophenone **8a** in 0.1 mL of anhydrous DMSO. The mixture was stirred for 2 h at the temparature, quenched at 0 °C

with 15 mL of sat. aq. NH_4Cl, extracted with 100 mL of EtOAc, washed with 5 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 1 : 5 mixture of EtOAc and hexane to afford 182 mg of a mixture of ethyl 3,3-diphenyl-2-propenate **9a** and benzophenone **8a**.

The solution of 182 mg of the mixture in 3.3 mL of anhydrous THF was added dropwise at -78 °C 2.11 mL (2 mmol) of a 0.95M solution of DIBAL-H in hexane. After stirring for 3 h at 25 °C, the reaction solution was quenched with 10 mL of EtOAc and 3 mL of water, and diluted with 50 mL of EtOAc. The resulted suspension was filtered and the filtrate was washed with 5 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 1 : 5 mixture of EtOAc and hexane to afford 132 mg (63% yield) of 3,3-diphenyl-2-propen-1-ol **4a**. **4a**: ^1H NMR ($CDCl_3$) δ 1.38 (1H, t, J = 6.0 Hz, OH), 4.22 (2H, dd, J = 6.0, 6.8 Hz, CH_2), 6.25 (1H, t, J = 6.8 Hz, CH), 7.16-7.40 (10H, m, C_6H_5 x 2).^{13}C NMR ($CDCl_3$) δ 60.7 (CH_2), 126.4, 127.4, 127.5, 128.1, 128.1, 128.4, 129.6, 138.9, 141.7, 144.1 (>C=CH, C_6H_5 x 2).

3,3-Bis(4-methoxyphenyl)-2-propene-1-ol (4b): ^1H NMR ($CDCl_3$) δ 1.80 (1H, brs, OH), 3.79, 3.82 (3H, 3H, s, s, CH_3 x 2), 4.19 (2H, d, J = 6.8 Hz, CH_2), 6.10 (1H, t, J = 6.8 Hz, CH), 6.81, 6.89, 7.08, 7.18 (2H, 2H, 2H, 2H, d, d, d, d, J = 8.8, 8.8, 8.8, 8.8 Hz, C_6H_4 x 2). ^{13}C NMR ($CDCl_3$) δ 55.3, 55.3 (CH_3 x 2), 60.8 (CH_2), 113.4, 113.5, 125.3, 128.8, 130.9, 131.5, 134.7, 143.4, 158.9, 159.1 (>C=CH, C_6H_4 x 2).

3,3-Bis(4-methylphenyl)-2-propene-1-ol (4d): ^1H NMR ($CDCl_3$) δ 1.40 (1H, brs, OH), 2.33, 2.38 (3H, 3H, s, s, CH_3 x 2), 4.21 (2H, d, J = 6.8 Hz, CH_2), 6.18 (1H, t, J = 6.8 Hz, CH), 7.05, 7.08, 7.15, 7.17 (2H, 2H, 2H, 2H, d, d, d, d, J = 8.0, 8.0, 8.0, 8.0 Hz, C_6H_4 x 2). ^{13}C NMR ($CDCl_3$) δ 21.2, 21.3 (CH_3 x 2), 60.8 (CH_2), 126.3, 127.5, 128.8, 129.1, 129.6, 136.1, 137.1, 137.3, 139.1, 144.1 (>C=CH, C_6H_4 x 2).

3,3-Bis(4-chlorophenyl)-2-propene-1-ol (4e): ^1H NMR ($CDCl_3$) δ 1.45 (1H, t, J = 5.0 Hz, OH), 4.20 (2H, dd, J = 5.0, 7.0 Hz, CH_2), 6.23 (1H, t, J = 7.0 Hz, CH), 7.09, 7.16, 7.26, 7.36 (2H, 2H, 2H, 2H, d, d, d, d, J = 8.4, 8.4, 8.4, 8.4 Hz, C_6H_4 x 2). ^{13}C NMR ($CDCl_3$) δ 60.5 (CH_2), 128.3, 128.4, 128.5, 128.8, 131.0, 133.7, 133.8, 136.9, 139.8, 142.0 (>C=CH, C_6H_4 x 2).

3,3-Bis[4-(trifluoromethyl)phenyl]-2-propene-1-ol (4g): ^1H NMR ($CDCl_3$) δ 1.64 (1H, brs, OH), 4.22 (2H, d, J = 6.8 Hz, CH_2), 6.38 (1H, t, J = 6.8 Hz, CH), 7.29, 7.33, 7.56, 7.66 (2H, 2H, 2H, 2H, d, d, d, d, J = 8.0, 8.0, 8.0, 8.0 Hz, C_6H_4 x 2). ^{13}C NMR ($CDCl_3$) δ 60.4 (CH_2), 125.3, 125.3, 125.4, 125.4, 125.4, 127.7, 130.0, 130.5, 141.6, 141.9, 144.4 (CF_3 x 2, >C=CH, C_6H_4 x 2).

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