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Convenient One-Pot Synthesis of 2,2-Bis-(4-hydroxyphenyl)-cyclopentanone

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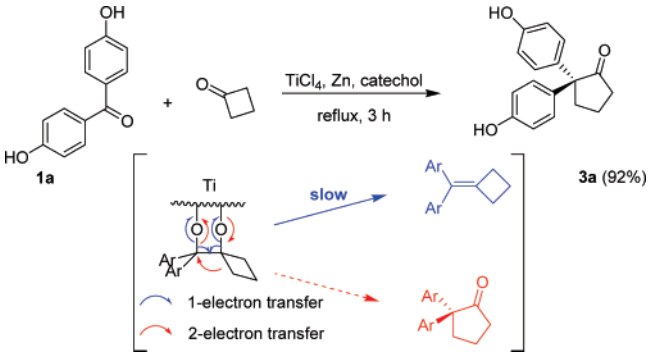
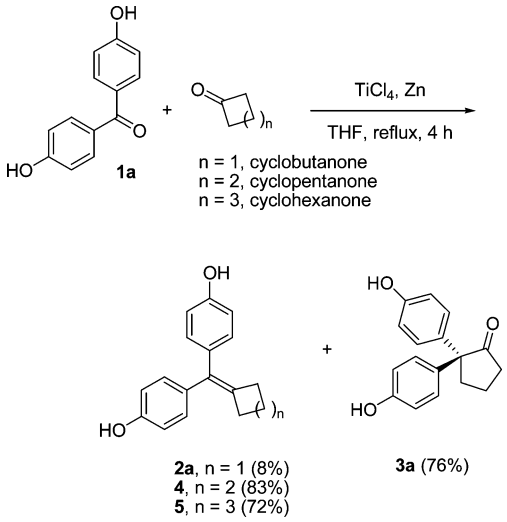


2,2-Bis-(4-hydroxyphenyl)-cyclopentanone (**3a**) was unexpectedly obtained in 76% yield from a reductive coupling reaction of 4,4′-dihydroxybenzophenone (**1a**) and cyclobutanone with $TiCl_4$ and Zn. Further optimization showed that catechol as an external ligand and a hydroxy group on benzophenone facilitated the generation of a quinonemethide (intermediate II) that is involved in the pinacol-type rearrangement of intermediate I to give the rearranged product.

The McMurry reaction is a powerful tool to synthesize alkene compounds via reductive dimerization of ketones in the presence of low-valent titanium activated by several reducing reagents such as $LiAlH_4$, $LiBH_4$, Zn, and Mg.[1] While performing McMurry reactions with several cyclic ketones and 4,4′-dihydroxybenzophenone using titanium(0) generated by zinc from titanium tetrachloride (Mukaiyama method),[2] a protocol that gave us good yields of the expected alkene products with cyclopentanone and cyclohexanone, we interestingly isolated only 8% of the expected olefinic product **2a** from the reaction with cyclobutanone, an unexpected material **3a** being obtained as the major product (76%) (Scheme 1). This unexpected major

SCHEME 1



product was identified as a 2,2-bis-(4-hydroxyphenyl)-cyclopentanone (**3a**) by analysis of its ^1H and ^{13}C NMR and mass spectra.

As far as we are aware, this interesting side reaction has heretofore not been reported. It is also of note that this 2,2-diarylcyclopentanone **3a** is an analogue of 2,2-diphenylcyclopentanone (**6**), a synthetically important precursor of 2,2-diarylcyclopentanol (**7**, Figure 1), a chiral auxiliary[3] that is used in various stereoselective syntheses: [4 + 2] cycloadditions,[4] tandem inter-[4 + 2]/intra-[3 + 2] cycloadditions,[5] and hydrogenations of β-acetoamidocrotonates.[6] Although phenolic hydroxyl groups are present in compound **3a**, the analogue of compound **7** that could be produced from it might also be useful as a chiral auxiliary, or these hydroxyl groups could be masked or removed. Synthetic methods to obtain sterically bulky α,α-diaryl substituted cyclopentanones have been investigated by several groups.[7] We performed a number of experiments to elucidate the mechanistic basis for the dramatic change in formation of olefinic products (**2a**, **4**, and **5**) versus 2,2-diarylcyclopentanone **3a** with differing cyclic ketone ring sizes.

It is generally recognized that McMurry-type carbonyl coupling reactions between arylcarbonyl and alkylcarbonyl compounds proceed by a two-step mechanism. Generation of a stabilized dianion derived from the diaryl ketone[8] is followed by nucleophilic addition of this species to the alkyl ketone to form a pinacol complex with titanium (step 1, Figure 2).[9] This pinacol intermediate is quite stable and may undergo one-

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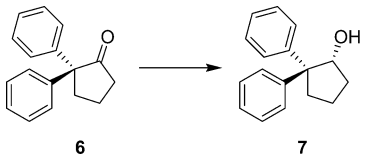


FIGURE 1. (*R*)-2,2-Diarylcyclopentanol (**7**), chiral auxiliary, and its precursor.

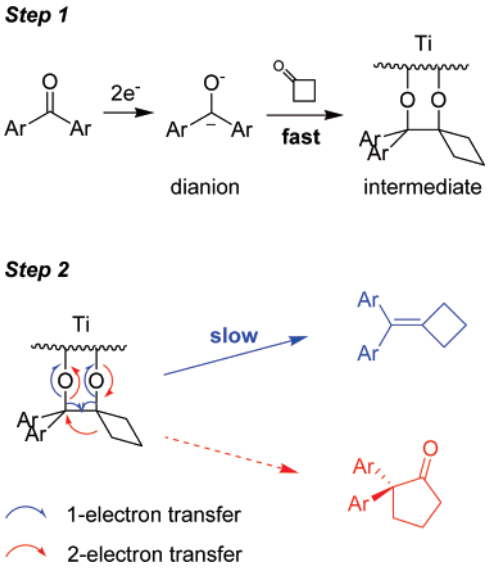


FIGURE 2. Classical mechanism of reductive coupling reaction and proposed two-electron transfer rearrangement.

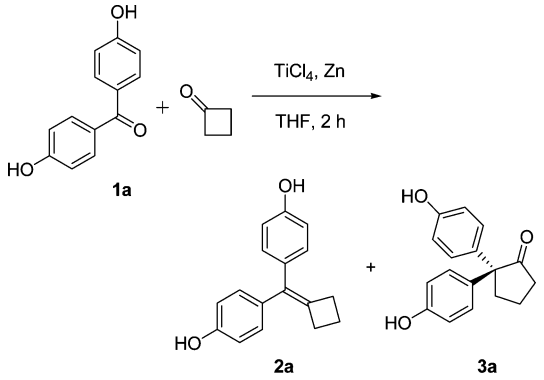
electron transfer deoxygenation to form the expected McMurry coupling alkene product, diarylmethylenecyclobutane (step 2 with blue arrows, Figure 2). In our case, however, it appears that a two-electron transfer reaction resulting in a pinacol-type rearrangement is the preferred mode of reaction because of the cyclobutane ring strain (step 2 with red arrows, Figure 2).

While most McMurry reactions have been homo couplings with a single ketone, our unexpected product was obtained by unsymmetrical reductive carbonyl addition with mixed carbonyl compounds.[8] Therefore, the effect of differing amounts of cyclobutanone (1.0, 1.5, and 2.0 equiv) was examined to obtain an optimal yield of unsymmetrical reductive coupling products. As shown in Table 1, 1 molar equiv of cyclobutanone was sufficient to obtain a good yield of products. Total product yields (**2a** + **3a**), however, did increase with additional equivalents of cyclobutanone.

Further reactions examined two different titanium reducing agents, magnesium and zinc, which form complexes with titanium after reducing titanium(IV) to titanium(0), as well as three derivatives of benzophenone (4,4′-dihydroxybenzophenone (**1a**), originally studied, 4-hydroxy-4′-methoxy-benzophenone (**1b**), and 4,4′-dimethoxybenzophenone (**1c**)), to determine how the course of the reaction was influenced by the presence of the para-hydroxyl groups. In addition, catechol was employed to see whether an external ligand of the titanium complex would affect the rearrangement.[9]

Initially, the coupling reaction of 4,4′-dimethoxybenzophenone (note, not 4,4′-dihydroxybenzophenone) and cyclobutanone

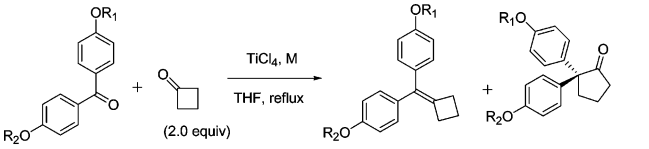
TABLE 1. Product Ratios in the McMurry Reaction of 4,4′-Dihydroxybenzophenone and Various Equivalents of Cyclobutanone[a]



entry	Equiv of cyclobutanone	yield (%)[b] **2a**	**3a**	**2a** + **3a**
1	1.0	11	64	75
2	1.5	12	69	81
3	2.0	10	76	86

[a] Reactions were carried out in a 1.0 mmol scale, and the reaction time indicated was after the addition of ketones in THF. [b] Isolated yield, based on **1a**.

TABLE 2. Rearrangement Reactions in McMurry Reactions of Different 4-Substituted Benzophenones and Cyclobutanone under Various Conditions[a]



1a, R_1 = H, R_2 = H
1b, R_1 = H, R_2 = CH_3
1c, R_1 = CH_3, R_2= CH_3

2a, R_1 = H, R_2 = H
2b, R_1 = H, R_2 = CH_3
2c, R_1 = CH_3, R_2= CH_3

3a, R_1 = H, R_2 = H
3b, R_1 = H, R_2 = CH_3
3c, R_1 = CH_3, R_2= CH_3

entry	R_1	R_2	reagent (M)	time (h)	additive (3 equiv)	yield (%)[b] **2a**−**c**	**3a**−**c**
1[c]	Me	Me	$Mg/HgCl_2$	4	−	13	trace
2[c]	Me	Me	$Mg/HgCl_2$	20	−	87	trace
3	H	H	$Mg/HgCl_2$	4	−	18	74
4	Me	Me	$Mg/HgCl_2$	4	catechol	32	Me
5	Me	Me	Zn	3	−	34	49
6	Me	H	Zn	2	−	18	57[c]
7	H	H	Zn	2	−	10	76
8[d]	Me	Me	Zn	2	catechol	5	66
9	H	H	Zn	3	catechol	−	92

[a] Reactions were carried out in a 1.0 mmol scale with a molar ratio of benzophenone (1.0 equiv), cyclobutanone (2.0 equiv), $TiCl_4$ (3.1 equiv), Zn (6.2 equiv), and Mg (6.2 equiv). [b] Isolated yields based on benzophenone. [c] Enantiomeric mixture. [d] Reactions were performed in duplicate, and the yields, which were similar, were averaged.

was performed in the presence of a low-valent titanium (LVT) complex formed by the reduction of $TiCl_4$ with magnesium, according to a published method.[10] This LVT complex was relatively unreactive, and little reaction took place by 4 h (Table 2, entry 1). After 20 h, however, the olefinic compound **2c** was obtained in 87% yield (Table 2, entry 2). With the original ketone, 4,4′-dihydroxybenzophenone, this LVT gave the typical

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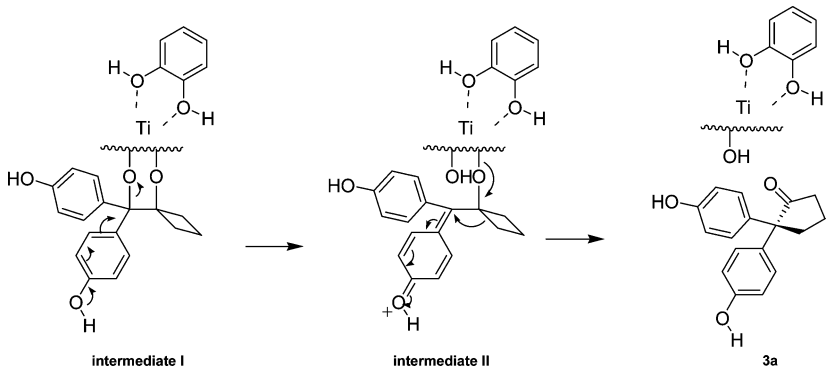

FIGURE 3. Proposed mechanism for the pinacol-type rearrangement.

ratios of alkene (**2a**) and cyclic ketone (**3a**) (Table 2, entry 3) as shown in Table 1. When titanium(IV) chloride was reduced by zinc (Table 2, entry 5), the LVT complex that formed appeared to be more reactive; the reaction time was shortened, and product ratios were altered, so by 3 h, both the alkene **2c** (34%) and the ring expanded ketone **3c** (49%) were produced from the dimethoxybenzophenone. Considering the outer shell electrons of Zn versus Mg, Zn(II), being 3d-block metal, is relatively rich in electrons. Thus, the titanium−zinc complex might be less tightly bound to the pinacol at intermediate (Figure 2), with the result that with this metal there is an increasing chance of rearrangement via the two-electron transfer mechanism shown in Figure 1.

To elucidate effects of the functional groups of starting materials, 4,4′-dihydroxybenzophenone (**1a**), 4-hydroxy-4′-methoxybenzophenone (**1b**), and 4,4′-dimethoxybenzophenone (**1c**) were used to compare the yields of the olefinic coupling products (**2a**−**c**) versus the rearranged cyclopentanone products (**3a**−**c**). In the reaction using LVT reduced by zinc, yields of cyclopentanones (**3c**, **3b**, and **3a**) gradually increased to 49, 56, and 76%, respectively, as the number of hydroxy groups increased in the order **1c**, **1b**, to **1a** (Table 2, entries 5−7). As additional examples, when reactions were performed with the LVT formed by reduction with magnesium, the same trend was observed, with the yields of the rearrangement cyclopentanone products, **3c** and **3a**, increasing from trace to 74%, respectively, as hydroxy groups replace methoxy groups (Table 2, entries 2 and 3). Other substituted or unsubstituted benzophenones were investigated (4-nitrobenzophenone, benzophenone, and 4-fluorobenzophenone), but they failed to produce the corresponding 2,2-diarylcyclopentanones, even in minor amounts. These observations led us to consider that the pinacol-type rearrangement might be occurring by an initial deoxygenation or 1,6-elimination step that could lead to the formation of a stable para-quinonemethide (intermediate II, Figure 3). This deoxygenation would also be facilitated by the relatively weak benzyl−oxygen bond.[11]

Because the reactivity or oxidation state of the LVT complex can be influenced by steric and electronic factors,[9,12] the possibility of chelation of the LVT complex by the hydroxy groups of benzophenone was examined by adding catechol to reaction media as an additional external ligand (Figure 3). We thought that external chelation of the LVT by catechol might assist in the rearrangement leading to the 2,2-diarylcyclopentanones (**3a**−**c**). Chelation of the LVT complex with catechol was performed for 30 min at room temperature after reduction of Ti(IV) by Mg or Zn. When the color of the reaction mixture turned to dark red, the ketones were added.

In the presence of catechol, the rearrangement reaction was, indeed, facilitated, so that even with the less reactive 4,4′-dimethoxybenzophenone, the 2,2-bis-(4-methoxyphenyl)-cyclopentanone rearrangement product **3c** was produced in 31% yield with the Mg−LVT complex (Table 2, entry 4) and in 66% yield with the Zn−LVT complex (Table 2, entry 8). The effect of catechol can be appreciated by noting the increment in the yields of **3c** of 31% (compare entry 2 with entry 4 in Table 2) and 17% (compare entry 5 with entry 8 in Table 2) that occurs with the addition of this chelator under both conditions. With the original ketone, 4,4′-dihydroxybenzophenone, catechol addition also boosted the yield of the rearrangement product, 2,2-bis-(4-hydroxyphenyl)-cyclopentanone (**3a**), from 76% (Table 2, entry 7) to 92% (Table 2, entry 9). Thus, this interesting product can be produced in one step, by the reaction of 4,4′-dihydroxybenzophenone and cyclobutanone upon treatment of titanium(IV) chloride with Zn and catechol (Table 2, entry 9).

In summary, we have developed a one-pot synthesis of 2,2-bis-(4-hydroxyphenyl)-cyclopentanone (**3a**) by coupling in situ a pinacol-type rearrangement with a McMurry reaction with LVT. Through several reactions performed to elucidate the mechanism of this transformation, we identified that the ring strain of cyclobutane, as well as other factors (such as hydroxy or methoxyl groups on the benzophenone and external catechol) presumed to generate a quinonemethide intermediate, facilitate this rearrangement (Figure 3). This is the first report of a one-pot synthesis of 2,2-diarylcyclopentanones and an investigation of factors that modulate the balance of product formation between diarylcyclopentanone and diarylmethylenecyclobutane in this McMurry reaction.

Experimental Section

General Procedure of McMurry Reaction: Titanium Tetrachloride with Mg/$HgCl_2$. A two-necked round-bottomed flask fitted with a reflux condenser was flame dried under vacuum, and Mg (150 mg, 6.2 mmol) and $HgCl_2$ (14 mg, 50 μmol) were added. After additional drying under high vacuum (0.5 mmHg) for 30−60 min, the flask was charged with argon. THF (5 mL) was added, and the resulting mixture was stirred at room temperature for 15 min. The turbid solution was removed by syringe, and the metal species was washed 2 times with additional portions of THF (5 mL × 2). THF (10−15 mL) was added, and the mixture was cooled

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to −10 °C. $TiCl_4$ (581 mg, 3.1 mmol) was slowly added dropwise, and the reaction mixture showed yellow fumes and turned green. After removal of the cooling bath, the reaction mixture was refluxed for 2 h. (In those experiments to investigate the affect of additional chelation, catechol was added at this point and stirred for 30 min at r oom temperature). Diarylketone (1.0 mmol) and 2 equiv of cyclobutanone (2.0 mmol) dissolved in THF (5−10 mL) were added slowly, and the mixture was refluxed for the time noted. After cooling down, the reaction mixture was slowly poured into saturated aqueous $NaHCO_3$ (150 mL), and Et_2O (100 mL) was added with stirring. The mixture was filtered through Celite, and the ether layer was decanted. The aqueous layer was extracted with additional Et_2O or EtOAc. The combined ether extracts were dried over Na_2SO_4 and evaporated. Flash column chromatography (EtOAc/hexane) was performed to obtain each product.

General Procedure of McMurry Reaction: Titanium Tetrachloride with Zn. A two-necked round-bottomed flask fitted with a reflux condenser was flame dried under vacuum, and Zn powder (405 mg, 6.2 mmol) was added. After additional drying under high vacuum (0.5 mmHg) for 30−60 min, the flask was charged with argon. THF (10−15 mL) was added, and the mixture was cooled to −10 °C. $TiCl_4$ (581 mg, 3.1 mmol) was slowly added dropwise, and the reaction mixture showed yellow fumes and turned green. The rest of the procedure is same as the one stated previously.

Bis-(4-hydroxyphenyl)-methylenecyclobutane (2a). White solid; ^{1}H NMR (400 MHz, acetone-d_6) δ 6.97 (d, J = 8.8 Hz, 4H), 6.76 (d, J = 8.8 Hz, 4H), 2.86 (t, J = 8.0 Hz, 4H), 1.99 (quintet, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 156.6, 137.7, 133.4, 133.1, 130.7, 115.6, 32.5, 17.7; MS (EI) m/z 252 (M^+, 100), 223, 107. HRMS (EI) m/z calcd for $C_{17}H_{16}O_2$, 252.1150; found, 252.1152. Registry No.: 66422−-09-1.

1-(4-Hydroxyphenyl)-1-(4-methoxyphenyl)methylenecyclobutane (2b). Off-white solid; mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 2.87 (t, J = 8.0 Hz, 4H), 2.01 (quintet, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 153.9, 138.8, 133.48, 133.45, 131.8, 130.1, 129.9, 114.9, 113.4, 55.2, 32.1, 17.3; IR (KBr): 3357, 2951, 1606, 1508, 1452, 1234, 1174, 1037, 837 cm^{-1}; MS (EI) m/z 266 (M^+, 100), 238, 167. HRMS (EI) m/z calcd for $C_{18}H_{18}O_2$, 266.1307; found, 266.1308.

Bis-(4-methoxyphenyl)-methylenecyclobutane (2c). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.8 Hz, 4H), 6.84 (d, J = 8.8 Hz, 4H), 3.81 (s, 6H), 2.91 (t, J = 8.0 Hz, 4H), 2.04 (quintet, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 138.8, 133.4, 131.8, 129.9, 113.4, 55.2, 32.1, 17.3. MS (EI) m/z 280 (M^+, 100), 249, 165, 121. Registry No.: 5289−-37-2.

2,2-Bis-(4-hydroxyphenyl)-cyclopentanone (3a). Off-white solid; mp 139−140 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.04 (d, J = 8.8 Hz, 4H), 6.75(d, J = 8.8 Hz, 4H), 2.63 (t, J = 6.8 Hz, 2H), 2.36 (t, J = 7.6 Hz, 2H), 1.87 (quintet, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 217.9, 156.7, 134.5, 130.0, 115.7, 61.6, 39.0, 38.3, 19.4; IR (KBr): 3347, 1709, 1611, 1594, 1513, 1237, 1178, 836 cm^{-1}; MS (EI) m/z 268 (M^+), 240, 212 (100), 197. HRMS (EI) m/z calcd for $C_{17}H_{16}O_3$, 268.1099; found, 268.1097.

2-(4-Hydroxyphenyl)-2-(4-methoxyphenyl)-cyclopentanone (3b). Off-white solid; mp 109−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 6.73 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H), 2.63 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 7.6 Hz, 2H), 1.91 (quintet, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.8, 158.1, 154.7, 134.1, 133.6, 129.14, 129.04, 115.3, 113.7, 61.4, 55.2, 38.30, 37.99, 18.7; IR (KBr): 3364. 1702, 1610, 1513, 1438, 1255, 1182, 836 cm^{-1}; MS (EI) m/z 282 (M^+), 254, 226 (100), 211. HRMS (EI) m/z cacld for $C_{18}H_{18}O_3$, 282.1256; found, 282.1258.

2,2-Bis-(4-methoxyphenyl)-cyclopentanone (3c). Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 9.2 Hz, 2H), 6.85 (d, J = 9.2 Hz, 2H), 3.78 (s, 3H), 2.66 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 1.93 (quintet, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.2, 158.2, 134.1, 129.0, 113.6, 61.1, 55.1, 38.2, 37.9, 18.7; MS (EI) m/z 296 (M^+), 268, 240 (100), 209, 164. Registry No.: 5383−-22-2.

Bis-(4-hydroxyphenyl)-methylenecyclopentane (4). White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.90 (d, J = 8.4 Hz, 4H), 6.66 (d, J = 8.4 Hz, 4H), 2.26 (bt, J = 6.4 Hz, 4H), 1.60 (bt, J = 6.4 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.4, 139.9, 134.2, 132.2, 129.9, 114.7, 32.7, 26.5; MS (EI) m/z 266 (M^+, 100), 223, 168, 141, 115. Registry No.: 66422−-10-4.

Bis-(4-hydroxyphenyl)-methylenecyclohexanone (5). White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (d, J = 8.4 Hz, 4H), 6.66 (d, J = 8.8 Hz, 4H), 2.10−2.21 (m, 4H), 1.42−1.60 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.6, 136.3, 133.9, 133.7, 130.4, 114.7, 31.9, 28.2, 26.3; MS (EI) m/z 280 (M^+), 199 (100), 107. Registry No.: 5189−-40-2.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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