ACID-CATALYZED CYCLIZATION REACTIONS OF 2,2'-BIS(DIARYLHYDROXY-
METHYL)BIPHENYLS TO 5,5,7,7-TETRAARYL-5,7-DIHYDRODIBENZO[c,e]OXEPINS
IN THE SOLID STATE
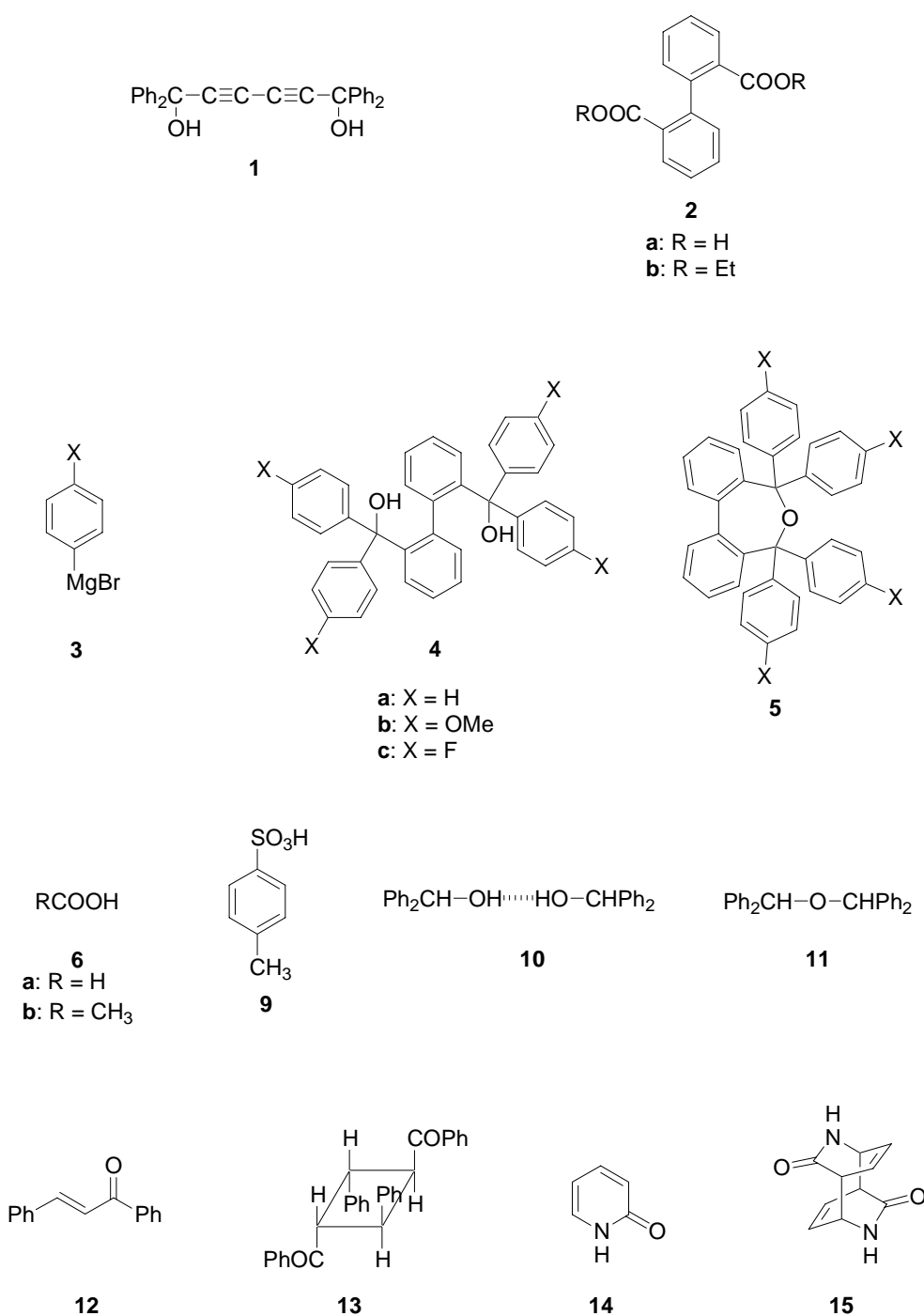
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Abstract – Heating of 2:1 inclusion crystals of 2,2'-bis(hydroxydiphenylmethyl)biphenyl and
formic acid in the solid state gave 5,5,7,7-tetraphenyl-5,7-dihydrodibenzo[c,e]oxepin in 89%
yield. When mixtures of 2,2'-bis([bis(p-methoxyphenyl)hydroxymethyl]biphenyl and
p-toluenesulfonic acid in 2:1 and 1:0.1 molar ratios were kept at room temperature for 80 min
and 12 h, respectively, 5,5,7,7-tetra(p-methoxyphenyl)-5,7-dihydrobenzo[c,e]oxepin was
obtained in quantitative yields. These are the first examples of an acid-catalyzed reaction in
the solid state.

In 1968, 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (**1**), which bearing sterically crowded tertiary hydroxy groups, was found to behave as an excellent host compound for a wide variety of guest molecules.[1] Since alcohol molecules that have sterically crowded hydroxyl groups cannot associate by themselves through formation of hydrogen bond, these molecules tend to include small molecules as guest by forming host-guest hydrogen bond.[1,2] By this idea, various host compounds which have sterically crowded hydroxyl groups have been designed.[3] 2,2'-Bis(hydroxyl-diphenylmethyl)biphenyl (**4a**), prepared by the reaction of diethyl 1,1'-diphenyl-2,2'-dicarboxylate (**2b**) and phenylmagnesium bromide (**3a**), was also found to act as a good host compound for various guests.[4] We further reported that **4a** includes carboxylic acids in the monomeric state. For example, **4a** and acryllic acid form a 2:1 inclusion complex in which the acid exists as the monomeric *s-trans* form.[5]

Recently, we found that a 2:1 inclusion complex (**7a**) of **4a** and formic acid (**6a**) gives the title oxepin derivative (**5a**) in 89% yield on heating at 80 °C for 12 h in the solid state. The data show that the etherification reaction in the solid state proceeds catalytically, since the molar amount of **6a** is just half that of **4a**. This suggests an easy molecular movement of **6a** in the cavity of inclusion crystal of **7a**. X-Ray structural study of the 2:1 inclusion complex of **4a** and acrylic acid showed that six **4a** molecules form a circle array and within this cavity three acrylic acid molecules are accommodated in the monomeric *s-trans* form.[5] Furthermore, strong disorder of the acrylic acid molecules in the cavity was observed.[5] The 2:1 complex (**7a**) of **4a** and **6a** probably has a similar crystal structure, and formic acid molecules in **7a** probably also exist as disordered monomers. Aided by this disorder, formic acid molecules can move in the inclusion cavity and catalyze the etherification reaction of **4a** to **5a** in the solid state. This is the first finding of a proton-catalyzed reaction within inclusion crystals. In contrast, 2,2'-bis[bis(p-fluorophenylhydroxymethyl)]biphenyl (**4c**), which had been

prepared from **2b** and **3c**, formed 1:1 inclusion complexes (**8a, 8b**) with formic (**6a**) and acetic acid (**6b**), but both compounds are thermally stable. It is interesting to note that the formic acid complex (**8a**) of **4c** is thermally stable, although the molar ratio of **6a** to **4c** in **8a** is double that in **7a**. The structure of **8a** and **8b** would differ from those of **7a** and **7b**. Unfortunately, however, neither **8a** nor **8b** formed crystals suitable for X-Ray analysis. The non-reactivity of **8a** probably results from electron withdrawing effects of the fluorine-substituents destabilizing formation of the carbocation generated from **4c**. However, heating **4c** in neat formic acid easily gave the oxepin **5c** in quantitative yield. The structure of **5c** was elucidated by X-Ray analysis (Figure. 1). In 2002, Golding and his co-workers first prepared the oxepin derivative (**5a**) and determined the structure by X-Ray analysis of its toluene complex.[6] However, we elucidated the structure of **5a** by X-Ray analysis of the apohost **5a** itself (Figure.2).

Ph$_2$C−C≡C−C≡C−CPh$_2$
    | |
    OH   OH

1

2

a: R = H
b: R = Et

3

4

a: X = H
b: X = OMe
c: X = F

5

RCOOH

6

a: R = H
b: R = CH$_3$

9

Ph$_2$CH−OH""""HO−CHPh$_2$

10

Ph$_2$CH−O−CHPh$_2$
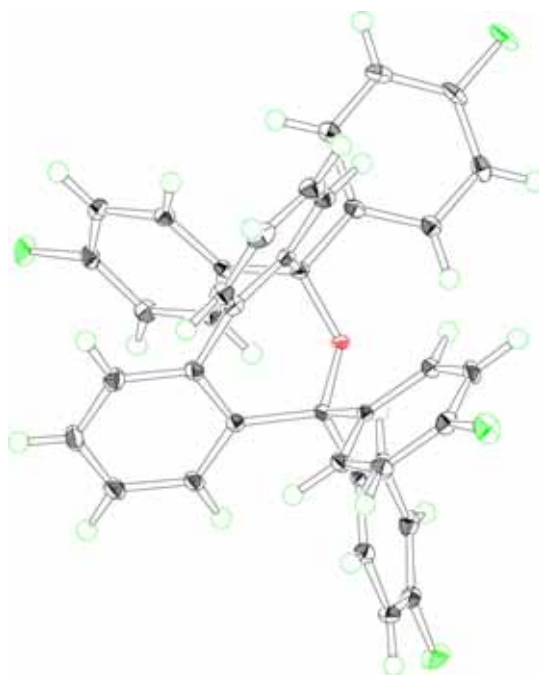
11

12

13
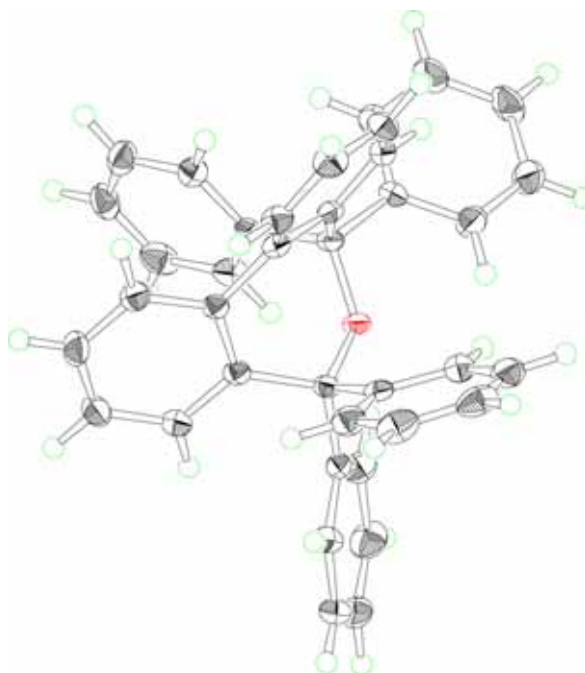
14

15

Figure 1. X-Ray structure of **5c**

Figure 2. X-Ray structure of **5a**

Nevertheless, the 2:1 inclusion complex of **4a** and acrylic acid is thermally stable below 130 °C. This is probably due to the difference in acidity between acrylic acid (*p*Ka = 4.26) and formic acid (*p*Ka = 3.55). In fact, a 2:1 inclusion complex (**7b**) of **4a** and acetic acid (**6b**) (*p*Ka = 4.56) is thermally stable (mp 261 °C) and can be prepared by recrystallization of **4a** from acetic acid in ether solution. However, preparation of the formic acid complex (**7a**) of **4a** is not easy and **4a** in neat formic acid gives **5a** immediately. Careful recrystallization of **4a** from a diluted solution of **6a** in ether gave the 2:1 complex (**7a**) as colorless needles.

In order to clarify whether the catalytic etherification of **4a** in the solid state is special to the inclusion cavity of **7a**, or not, *p*-toluenesulforic acid (**9,** *p*Ka = -6.5)-catalyzed etherification reactions of **4a** in the solid state were studied. When a mixture of powdered **4a** and **9** in a 2:1 molar ratio was heated in the solid state at 50 °C for 3 and 12 h, **5a** was obtained in 70 and 100% yields, respectively. These data clearly show that the etherification reaction proceeds catalytically. Furthermore, we found that the catalytic etherification reaction in the solid state proceeds much more efficiently for the *p*-methoxy substituted derivative (**4b**) which has been prepared by the reaction of **2b** and **3b**. For example, when a mixture of powdered **4b** and **9** in a 2:1 molar ratio was kept at room temperature for 80 min, **5b** was obtained in quantitative yield. The molar ratio of **9** to **4b** can be decreased. When a mixture of **4b** and **9** in 1:0.1molar ratio was kept at room temperature for 12 h, **5b** was also obtained in quantitative yield. These catalytic reactions were studied by continuous monitoring measurements of IR spectra in Nujol mulls. As the reaction proceeds in the 2:1 ratio of **4b** to **9**, the aromatic proton absorption of **4b** at 753 cm^{-1} decreased and finally disappeared, and new absorptions of **5b** at 768 and 744 cm^{-1} appeared and increased (Figure 3). In the case of the reaction of the 1:0.1 ratio, reaction proceeded slowly to show similar spectral change and was complete after 12 h (Figure 4).
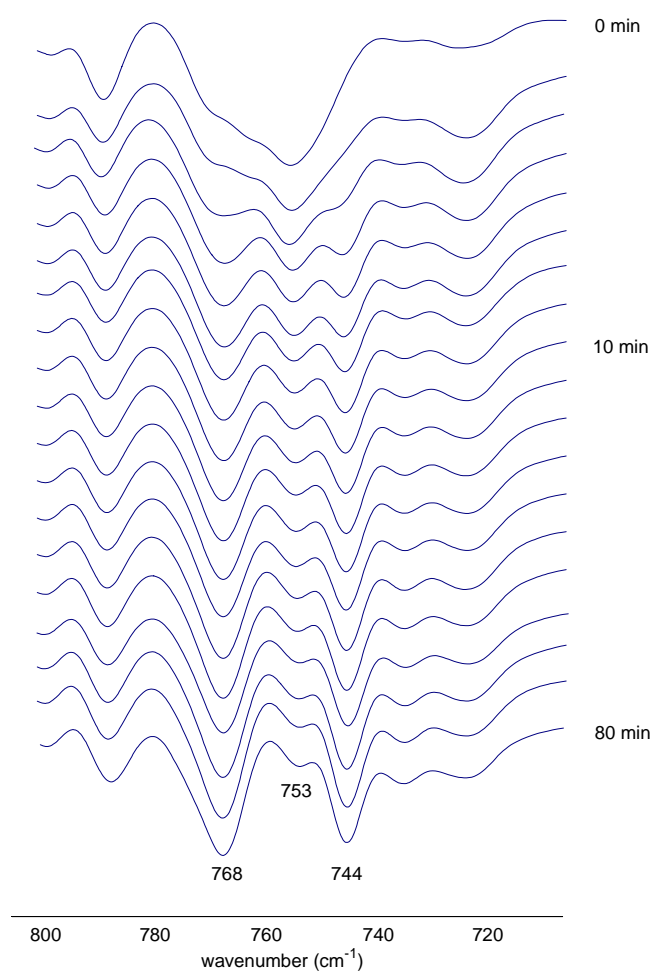

Figure 3. Monitoring by IR spectra in Nujol mulls of the *p*-toluenesulfonic acid-catalyzed etherification reaction of **4b**. The molar ratio of **4b** : **9** = 1 : 0.5 was used and the process conducted in the solid state at room temperature.
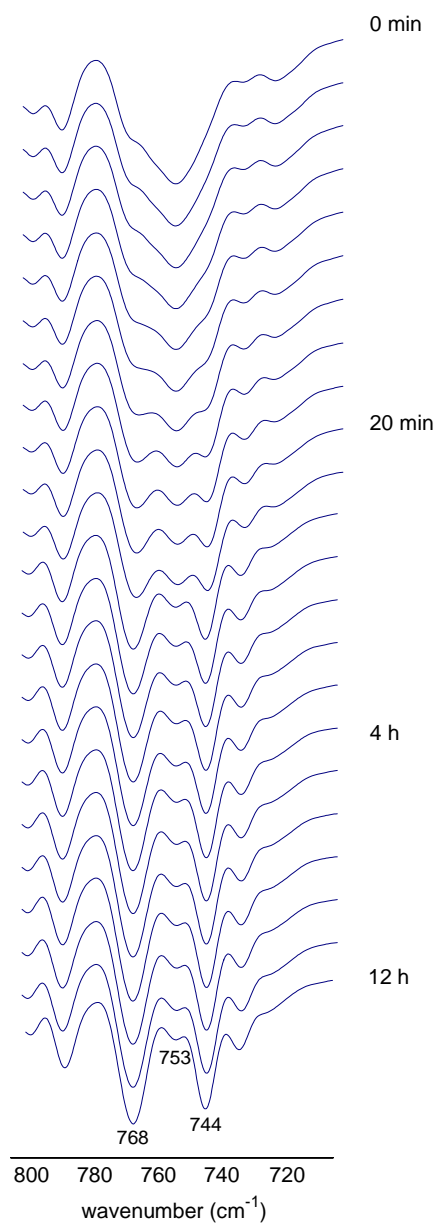
Figure 4. Monitoring by IR spectra in Nujol mulls of the *p*-toluenesulfonic acid-catalyzed etherification reaction of **4b**. The molar ratio of **4b** : **9** = 1 : 0.1 was used and the process conducted in the solid state at room temperature.

Previously, we have reported that benzhydrol (**10**) gives its ether derivative (**11**) on treatment with **9** in the solid state.[7,8] X-Ray study showed that two benzhydrol molecules are arranged as depicted in **10**, so as to form a hydrogen-bonded dimer. Therefore, solid-state intermolecular etherification reaction of **10** to **11** proceeds efficiently in the presence of **9**. Nevertheless, no acid-catalyzed reaction of **10** was observed. Finally, the etherification of **4a** and **4b** to **5a** and **5b**, respectively, in the presence of a catalytic amount of **9** is the first example of the catalyzed thermochemical reaction in the solid state, although catalytic photochemical reactions in the solid state have been reported.[9,10]
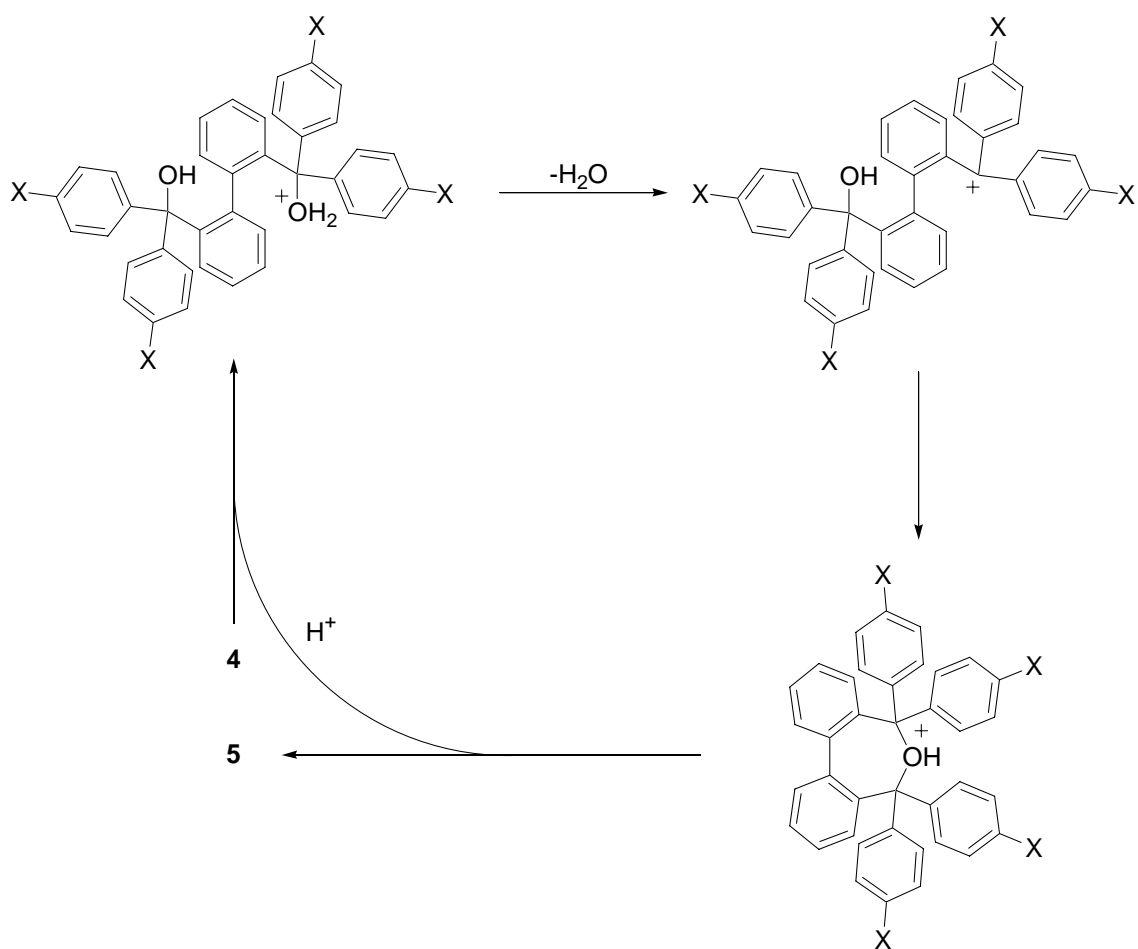
Scheme 1. Acid-catalyzed etherification reaction in the solid state.

In the acid-catalyzed etherifications reactions, a proton would move from one molecule to another in the solid state as depicted in Scheme 1. However, molecular movements of formic acid (**6a**) and *p*-toluenesulforic acid (**9**) themselves in the solid state are also possible, since the following catalytic photoreactions involving molecular movement in the solid state occur easily. Photoirradiation of a mixture of powdered host **1** and chalcone guest (**12**) in a 1:4 molar ratio under occasional grinding using a pestle and mortar gave *syn*-head-to-tail dimer (**13**) in 90% yield.[9] By mixing powdered **1** and **12** in the solid state, a 1:2 inclusion complex is formed and its irradiation gives the photodimer (**13**). On formation of **13**, the inclusion complex dissociates and **1** is liberated as the apohost. On further mixing, compound (**1**) includes excess **12** and then gives **13** upon irradiation. The data shows that the host (**1**) is used twice as a catalyst. The next example is a much simpler catalytic photodimerization reaction of 2-piridone (**14**) in the solid state. When a mixture of powdered **2a** and **14** in a 1:4 molar ratio is irradiated for 20 h in the solid state under occasional grinding, the *trans-anti*-dimer (**15**) was obtained in 81% yield.[10] However, it is not easy to clarify which the proton or the acid molecule itself (**6a** or **9**) moves in these acid-catalyzed etherification reactions in the solid state.

EXPERIMENTAL

General Procedures

^{1}H NMR spectra were measured in CDCl$_3$ at -50 °C on a JEOL Lambda-300 at 300 MHz. IR spectra were measured as Nujol mulls at room temperature on a JEOL FT/IR-460 Plus. Melting points were measured on a Stuart Scientific SMP3. Elemental analyses were performed on a Perkin-Elmer 2400 series analyzer.

X-Ray crystallography

The diffraction data were collected on a Rigaku RAXIS-IV imaging plate diffractometer with MoKα radiation (λ= 0.71070 Å) to a maximum 2θ value of 55.1° at −100 °C. The reflection data were corrected for the Lorentz-polarization effects and secondary extinction. The crystal-to-detector distance was 100.00 mm with the detector at the zero swing position. The readout was performed in the 0.100 mm pixel mode. The structure was solved by direct method and refined by the full-matrix least-squares method by using a $_{TE}X_{SAN}$ program. The non-hydrogen atoms were refined anisotropically.

Crystal and refinement data for 5a, Formula = C$_{38}$H$_{28}$O, MW = 500.64, Crystal System = monoclinic, Space group = P2$_1$/c (#14), Lattice Parameters a = 13.5671(6) Å, b = 11.4629(4) Å, c = 17.0536(9) Å, β = 89.7602(8)°, V = 2652.1(2) Å^3, Z = 4, D$_{calc}$ = 1.254 g/cm^3, number of unique reflection = 5899, R$_{int}$ = 0.0464 up to a 2θ = 55.1° , number of parameters = 465, R = 0.069, wR = 0.102, Gof = 0.91 for 3938 reflections

Crystal and refinement data for 5c, Formula = C$_{38}$H$_{24}$F$_4$O, MW = 572.60, Crystal System = orthorhombic, Space group = Pbcn(#60), Lattice Parameters a = 13.9086(2) Å, b = 10.7143(2) Å, c = 18.7150(2) Å, V = 2788.9(1) Å^3, Z = 4, D$_{calc}$ = 1.364 g/cm^3, number of unique reflection = 3193, R$_{int}$ = 0.016 up to a 2θ = 55° , number of parameters = 244, R = 0.0314, wR = 0.0859, Gof = 1.521 for 2788 reflections.

Preparation of 7a.

When a solution of **4a** (389 mg) in ether (35 mL)-**6a** (1.5 mL) was kept at rt for 24 h, **7a** (283 mg, 67%) was obtained. Anal. Calcd for C$_{38.5}$H$_{29}$O$_2$•H$_2$O: C, 82.62; H, 5.94. Found: C, 82.57; H, 6.00.

Preparation of 7b.

When a solution of **4a** (389 mg) in ether (35 mL)-**6b** (1.5 mL) was kept at rt for 24 h, **7b** (235 mg, 55%) was obtained, mp 261 °C. Anal. Calcd for C$_{39}$H$_{30}$O$_2$•H$_2$O: C, 82.66; H, 6.05. Found: C, 82.97; H, 5.90.

Preparation of 8a.

When a solution of **4c** (54.8 mg) in ether (1 mL)-**6a** (0.05 mL) was kept at rt for 24 h, **8a** (51.3 mg, 87%) was obtained, mp is not clear.

Preparation of 8b.

When a solution of **4c** (48.3 mg) in **6b** (1 mL) was kept at 120 °C for 24 h, **8b** (30.3 mg, 57%) was obtained, mp 273 °C.

Thermal reaction of 7a. **7a** (40 mg) was heated at 80 °C for 12 h and the reaction mixture was chromatographed on silica gel (hexane-AcOEt = 97:3) to give **5a** (31.7 mg, 89% yield); mp 291.5-291.7 °C. ^{1}H NMR: 6.62 (2H, d, J = 7.9 Hz), 6.79-6.97 (10H, m), 7.11-7.14 (4H, m), 7.21 (2H, t, J = 7.9 Hz), 7.32 (2H, t, J = 7.3 Hz), 7.60-7.67 (4H, m), 8.67 (2H, d, J = 7.9 Hz), Anal. Calcd for C$_{38}$H$_{28}$O: C, 91.17; H, 5.64. Found: C, 90.99; H, 5.52.

Data of 5c: mp 273.4-273.8 °C. ^{1}H NMR: 6.53-6.57 (6H, m), 6.62-6.71 (4H, m), 6.91-6.96 (4H, m), 7.11-7.19 (4H, m), 7.25-7.32 (2H, m), 7.49-7.54 (2H, m), 8.47-8.52 (2H, m), Anal. Calcd for C$_{38}$H$_{24}$OF$_4$; C, 79.71; H, 4.22. Found: C, 79.82; H, 4.38

General procedure of the *p*-toluenesulfonic acid-catalyzed cyclization reaction of 4.

A mixture of powdered **4** and **9** was reacted under the conditions described in the text and the resulting material was

washed with water to give the cyclization product **5** in the yield shown in the text. In all these experiments, commercially available *p*-toluenesulfonic acid monohydrate was used.

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