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A new fluorous/organic amphiphilic ether solvent, F-626: execution of fluorous and high temperature classical reactions with convenient biphase workup to separate product from high boiling solvent

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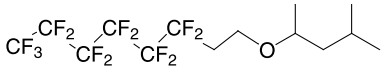
Abstract—A new fluorous/organic amphiphilic ether solvent, 1*H*,1*H*,2*H*,2*H*-perfluorooctyl 1,3-dimethylbutyl ether (F-626), is introduced. The basic properties of F-626, especially the partition coefficients with organic solvents/FC-72 (perfluorohexane), were investigated. F-626 was easy to remove by fluorous biphase treatment. Using F-626 as a solvent, LAH reduction, catalytic hydrogenation, and fluorous reductive radical reactions were successful. Classical high temperature reactions up to 200°C, such as the Vilsmeier formylation, the Wolff–Kishner reduction, and the Diels–Alder reaction, were also examined in F-626. The yields of the products in F-626 were almost comparable with those conducted in common organic solvents, which prove that F-626 has the potential to be an easily recyclable high boiling solvent.

1. Introduction

The rapid evolution of fluorous chemistry[1,2] requires amphiphilic solvents, which can dissolve both organic and fluorous reagents. The amphiphilic solvents have at least three advantages. First, fluorous compounds, which are sometimes difficult to dissolve in common organic solvents, can be treated in the solvent. Second, it is easy to remove the solvent by a fluorous/organic biphase procedure. Third, generally, the removed solvent can be reused without further purification because of low partition coefficients for general organic compounds to a fluorous phase. In addition to these advantages, many reactions with gases could be performed in the solvent because of high solubilities of gases in fluorous solvents. Unfortunately, however, with the exception of the case of BTF (benzotrifluoride) (**1**),[3] development of organic-fluorous amphiphilic solvents have lagged largely behind in the rapid conceptual advance of fluorous synthesis.

BTF (benzotrifluoride)
1



F-626 (1H,1H,2H,2H-perfluorooctyl 1,3-dimethylbutyl ether)
2

Herein, we report that a new fluorous ether solvent, F-626, 1*H*,1*H*,2*H*,2*H*-perfluorooctyl-1,3-dimethylbutyl ether (**2**), is a useful amphiphilic solvent, which is easily removable from the reaction mixture by fluorous/organic biphase workup.[4] It should be noted that we named **2** as F-626 for short, where there are six fluorous carbons and two-carbon spacer group, and a six-carbon alkyl part. There are many synthetic procedures that have to be carried out in high boiling point solvents. However, the use of such solvents as chlorobenzene and xylene requires tedious evaporation procedure to remove the solvents. Water-soluble solvents like diethylene glycol and *N*,*N*-dimethylformamide (DMF) are also used as high boiling solvents. To remove these solvents, aqueous/organic biphase workup is used conveniently, but to recover the solvents from the aqueous layer is not necessarily convenient. In this work, we tested an organic/fluorous hybrid ether F-626 as a solvent for selected organic reactions, and found that F-626 can be used as an ether-type solvent for typical metal hydride reductions and as an amphiphilic solvent in fluorous

Keywords: amphiphilic solvent; fluorous ether; biphase treatment; high-temperature reaction; fluorous tin hydride; carbonylation; Vilsmeier formylation; Wolff–Kishner reduction; Diels–Alder reaction.
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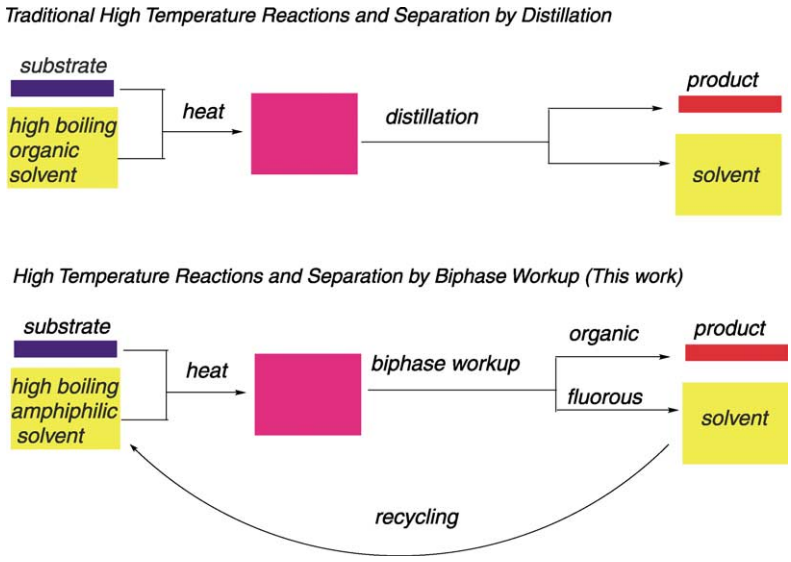


Scheme 1. Concepts of high temperature reactions using a fluorous/organic amphiphilic solvent.

reductive radical reactions. High temperature reactions up to 200°C, which include the Vilsmeier formylation, the Wolff–Kishner reduction, and the Diels–Alder reaction, can also be conducted with F-626 as a solvent. The removal of this amphiphilic solvent can be easily conducted by fluorous/organic biphase workup (Scheme 1). All these reactions are rather classical synthetic methods. However, they are still valuable not only for laboratory uses but also for commercial uses. We confirmed that F-626, recovered readily from the fluorous phase, can be subjected to reuse.

2. Results and discussions

2.1. Basic properties of F-626

F-626 is a colorless, clear, slightly viscous liquid with a boiling point of 214°C at 760 Torr, 80°C at 9 Torr, a density of 1.354 g/cm^3 (20°C), an index of refraction of 1.3418 (20°C), and a viscosity of 3.55 cp (20°C).[5] It does not freeze even at −78°C and transforms to glassy state at −110°C. F-626 is miscible with common organic solvents, such as hexane, benzene, chloroform, ether, acetone, ethyl acetate, and ethanol, but hardly soluble in water. At the outset of this study, the approximate partition coefficients associated with biphasic treatment were determined. We used the same procedure as reported by Curran et al.[6] The results are summarized in Table 1 with those of BTF for comparison. It shows that the majority of F-626 is distributed in the FC-72 (perfluorohexanes) phase except for the case when chloroform and ethyl acetate are used, whereas BTF is preferentially distributed in the organic solvents. Alcohols provide better results and acetonitrile may be the best solvent to remove F-626 from reaction mixture with biphasic treatment in case that the products can be dissolved in this solvent.

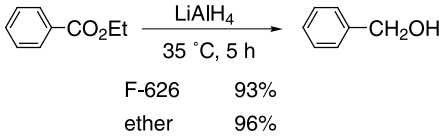
Table 1. Partition coefficient of F-626 and BTF between FC-72 with organic solvent

Solvent	Organic solvent/FC-72	
	F-626[a]	BTF[b]
MeCN	1/7.3	1/0.13
MeOH	1/3.8	1/0.21
EtOH	1/3.6	1/0.18
C_6H_6	1/1.6	1/0.18
CH_2Cl_2	1/1.3	1/0.16
Acetone	1/1.1	1/0.08
AcOEt	1/0.85	1/0.13
$CHCl_3$	1/0.85	1/0.16

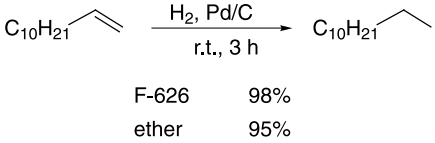
All rations were confirmed at 20°C as described in Section 4.
[a] Determined by gravimetric method.
[b] Determined by GLC.

2.2. LAH reduction and catalytic hydrogenation in F-626

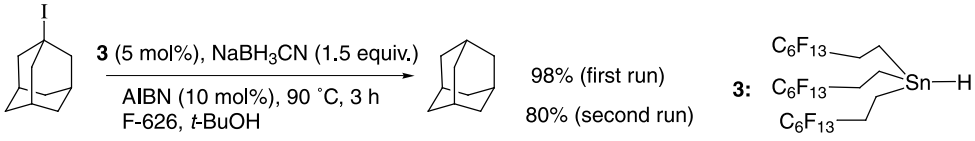
Reduction of ethyl benzoate with lithium aluminum hydride in F-626 at 35°C (5 h) afforded 93% yield of benzyl alcohol (Scheme 2). On the other hand, 1-dodecene was hydrogenated in the presence of Pd/C catalyst at room temperature for 3 h in 98% yield (Scheme 3). These results show that the yields and the reaction times in F-626 are comparable to those conducted in ether solvent. After fluorous/organic biphase workup using benzene and FC-72, more than 90% of F-626 was recovered from the fluorous phase.



Scheme 2.



Scheme 3.



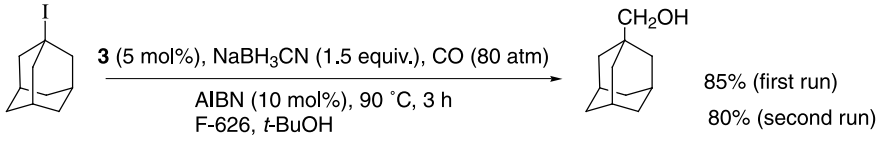
Scheme 4.

2.3. Fluorous reductive radical reactions in F-626

To determine if F-626 could indeed function as an amphiphilic solvent in fluorous reactions or not, we tested a fluorous reductive radical reaction using a fluorous tin hydride **3**[6,7] in F-626. Thus, 1-iodoadamantane was treated with sodium cyanoborohydride (1.5 molar equiv.) in the presence of 5 mol% of **3** and 10 mol% of α,α′-azobisisobutyronitrile in F-626 at 90°C for 3 h. After the reaction, we carried out triphasic treatment (H_2O/CH_2Cl_2/FC-72) of the reaction mixture. From the organic phase, the reduction product, adamantane was isolated in 98% yield (Scheme 4). On the other hand, **3** and F-626 were recovered from the fluorous phase almost quantitatively. Furthermore, the recovered F-626 solution containing **3**, when subjected to the same conditions, gave 80% of the product. The result clearly shows that a fluorous catalyst system can be reused conveniently in F-626. We also tried a fluorous radical carbonylation in F-626 (Scheme 5).[8] The reaction described above was carried out in the presence of pressurized carbon monoxide and gave the corresponding hydroxymethylation product, 1-adamantylmethanol in 85% yield. Again, the recovered F-626 solution containing **3** was successfully used for the second run experiment.

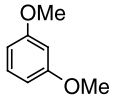
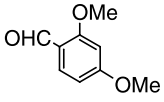
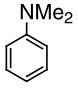
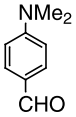
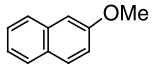
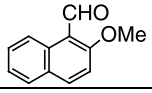
2.4. Vilsmeier formylation in F-626

The Vilsmeier reaction[9] that uses DMF or *N*-methylformanilide as a formyl source is one of the most useful formylation methods available for aromatic compounds. It is often carried out at temperatures higher than 100°C, using such high boiling solvent as *o*-dichlorobenzene, which is inert under the reaction conditions. We examined the Vilsmeier reaction using F-626 as a solvent. Thus, when *m*-dimethoxybenzene was treated with *N*-methylformanilide and phosphorus oxychloride in F-626 at 100°C for 1 h, the mixture became heterogeneous at the initial stage of the reaction and then homogeneous with a dark color at the temperature. After 20 min, the reaction mixture began to separate into two layers, a colorless upper layer and a reddish brown lower layer. The upper layer was found to be F-626 (purity: >96% analyzed by GLC). After 1 h, the reaction mixture was cooled and the upper layer was separated off. The lower layer was diluted with benzene, washed with water to free it from the phosphorus residues, and washed with FC-72 three times to remove remaining F-626. After removing the solvent in vacuo, the residue was purified by column chromatography on silica gel, which gave the formylation product, 2,4-dimethoxybenzaldehyde, in 83% yield. From the upper layer, F-626 was recovered in 93%, and additional 4% of the solvent was obtained from the FC-72 solution. *N*,*N*-Dimethylaniline and 2-methoxynaphthalene afforded 64% of 4-(dimethylamino)benzaldehyde and 58% of 2-methoxynaphthalene-1-carbaldehyde, respectively. As shown in Table 2, the yields obtained in F-626 are comparable with those in *o*-dichlorobenzene under similar conditions.



Scheme 5.

Table 2. The Vilsmeier formulation in F-626 and *o*-dichlorobenzene

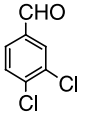
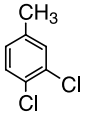
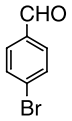
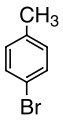
Substrate	Product	Yield (%)[a]		Recovery of F-626 (%)
		F-626	*o*-Dichlorobenzene	
		83	60	97
		64	49	96
		58[b]	70[b]	92

Reaction conditions (unless otherwise mentioned): solvent 1 mL, temp. 100°C, reaction time 1 h, substrate 1 mmol, *N*-methylformanilide 1.3 mmol, phosphorus oxychloride 1.3 mmol.

[a] Isolated yield by column chromatography.

[b] Reaction time 6 h.

Table 3. The Wolff–Kishner reduction in F-626 and diethylene glycol

Substrate	Product	Yield (%)[a]		Recovery of F-626 (%)
		F-626	Diethylene glycol	
		89	89	–[b]
		76	70	93
		37	91	–[b]

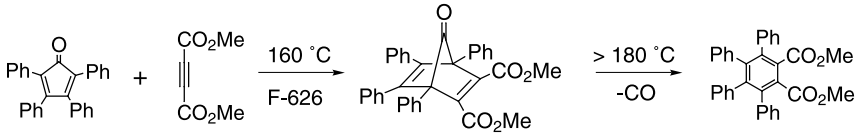
Reaction conditions (unless otherwise mentioned): solvent 2 mL, temp. 110°C for 2 h then 200°C for 6 h, substrate 2.5 mmol, KOH 5 mmol, $N_2H_4{\cdot}H_2O$ 1 mL.
[a] Isolated yield by column chromatography.
[b] Not determined.

2.5. Wolff–Kishner reduction in F-626

The Wolff–Kishner reduction[10] is a well-known reduction method for the conversion of carbonyl to methylene, which is usually carried out in the presence of potassium hydroxide and hydrazine in ethylene glycol or diethylene glycol under reflux. We examined the Wolff–Kishner reduction of aromatic aldehydes and ketones in F-626 at 200°C for 6 h. Results are summarized in Table 3. Again, to remove high boiling F-626, a fluorous/organic biphase workup was successfully carried out. From the organic layers moderate to good yields of reduced products were obtained. Aldehydes gave satisfactory results, whereas yield of α-tetralone was modest. This is presumably due to a lower solubility of the hydrazone intermediates derived from the ketones, in F-626 than in diethylene glycol.

2.6. Diels–Alder reaction in F-626

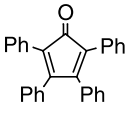
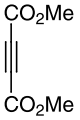
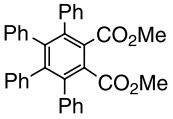
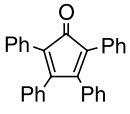
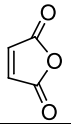
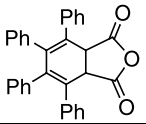
Although the Diels–Alder reaction[11] is of very broad scope, the reaction often needs high temperatures. We have chosen the reaction between tetraphenylcyclopentadienone (**4**) and dimethyl acetylenedicarboxylate (**5**) as a model of Diels–Alder reaction in F-626. Typically, this Diels–Alder reaction occurs at 160°C to afford bicyclic compound **6**, which subsequently undergoes thermal decomposition above 180°C with loss of carbon monoxide giving a benzene derivative **7** (Scheme 6). Thus, a mixture of **4** and **5** in F-626 was heated to reflux. The reaction was completed in 10 min, and the Diels–Alder annulation followed by elimination of carbon monoxide occurred. The product was separated as crystals. Then, the crystals were washed with benzene, and afforded dimethyl tetraphenylphthalate in 76% yield.



4 **5** **6** **7**

Scheme 6.

Table 4. The Diels–Alder reaction in F-626 and *o*-dichlorobenzene

Substrate		Product	Yield (%)[a]		Recovery of F-626 (%)
			F-626	*o*-Dichlorobenzene	
			76	80	95
			93	95	93

Reaction conditions: solvent 3 mL, diene 1.3 mmol, dienophile 1.3 mmol, reaction time 10 min under reflux.
[a] Isolated yield by filtration.

Similarly, the dienone **4** was treated with maleic anhydride to give 93% yield of tetraphenyldihydrophthalic anhydride. By comparison with the reaction in *o*-dichlorobenzene, the yields are about the same (Table 4). We also tried to recover F-626 from the filtrate by washing it with FC-72 and found that 93–95% of the solvent was recovered.

3. Conclusions

The results obtained here suggest that F-626 has the potential to be a useful and easy to remove high boiling solvent (up to 200°C). It can be considered as a replacement for *o*-dichlorobenzene, tetrachloroethane, and diethylene glycols. We also confirmed that F-626 can be used as an amphiphilic solvent for some fluorous and non-fluorous reactions.

4. Experimental

4.1. General

All melting points are uncorrected. IR data were obtained with a HORIBA FT-700 spectrophotometer. ^{1}H and ^{13}C NMR were obtained with a JEOL ECP-500 spectrometer with tetramethylsilane used as an internal standard. High-resonance mass spectral data were measured on a JEOL SX-102A spectrometer. Silica gel (Daisogel IR-60) was used in column chromatography. All the products prepared in this study are known compounds, and their structures were identified by the comparison of their spectra with those of authentic samples.

4.1.1. Preparation of F-626.[5] To a flask equipped with a stirrer, a thermometer, a hydrogen inlet attachment, a Dean–Stark trap, were added 1*H*,1*H*,2*H*,2*H*-perfluorooctanol (54.6 g, 150 mmol), 4-methyl-2-pentanone (30.0 g, 300 mmol), and 5% of palladium on carbon (4.36 g). The reaction mixture was heated at 105°C for 8 h under a stream of hydrogen (180 mL/min). During the reaction, water trapped in Dean–Stark apparatus was separated. After cooling, the catalyst was filtered off and excess 4-methyl-2-pentanone was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (∅ 80 mm×300 mm) with hexane/ethyl acetate (20:1) as eluent. The oily product was distillated under reduced pressure to give 61.9 g of F-626 (92%): IR (neat) 2962 (CH_2), 1369 (CF_3), 1242 (CF_2), 1145 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (d, J=6.6 Hz, 6H, CH_3 terminal), 1.12 (d, J=6.3 Hz, 3H, CH_3), 1.17 (m, 1H, CHCH_2CH), 1.44 (m, 1H, CHCH_2CH), 1.70 (m, 1H, CH_3CHCH_3), 2.36 (m, 2H, CH_2CF_2), 3.48 (m, 1H, OCH_2), 3.61 (m, 1H, OCH_2), and 3.76 (m, 1H, OCH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.60, 22.44, 22.92, 24.59, 32.00 (t, J=21.1 Hz), 46.13, 60.07, 74.42, 108.50 (m), 110.84 (m), 113.38 (m), 115.67 (m), 118.28 (m), and 120.90 (m); HRMS (CI) calcd for $C_{14}H_{17}OF_{13}$ 449.1151 $[M+H]^+$, found: 449.1178.

4.1.2. Determination of partition coefficients of F-626. Partition coefficients were determined according to the procedure reported by the Curran group.[6] To a biphasic mixture of organic solvent (3 mL) and FC-72 (3 mL), F-626 (300 mg) was added, and stirred vigorously for 10 min. After standing for 5 min, the two layers were separated and evaporated to dryness, then weighed. Partition coefficients of BTF were estimated by the same procedure for as F-626, but GLC analysis was used instead of gravimetry.

4.1.3. Reduction of ethyl benzoate with lithium aluminum hydride in F-626. To a suspension of lithium aluminum hydride (80 mg, 2.1 mmol) in F-626 (2 mL), a solution of ethyl benzoate (318 mg, 2.0 mmol) in F-626 (1 mL) was added with stirring at 0°C. After addition, the reaction mixture was warmed to 35°C and stirred for 5 h. The reaction mixture was cooled 0°C again, and H_2O (2 mL) was added. The inorganic salt precipitated was filtered off and washed with benzene. The benzene solution was washed with FC-72 (5 mL) for three times, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (∅ 8 mm×50 mm) with hexane/ethyl acetate (2:1) to afford 200 mg of benzyl alcohol (93%). From the FC-72 solution, 1.27 g (94%) of F-626 was recovered. When ether was used as a solvent, the same workup was undertaken without washing the ether solution with FC-72, which gave a 96% yield of the product.

4.1.4. Catalytic hydrogenation in F-626. A mixture of 5% of palladium on carbon (3 mg) and 1-dodecane (337 mg, 2 mmol) in F-626 (3 mL) were stirred under the atmospheric pressure of hydrogen at room temperature. After 3 h, the catalyst was filtered off and washed with benzene. The filtrate was washed with FC-72 (5 mL) for three times and concentrated in vacuo. The residue was purified by column chromatography on silica gel (∅ 8 mm×50 mm) with hexane to give 330 mg of dodecane (98%). From the FC-72 solution, 3.75 g (92%) of F-626 was recovered. When ether was used as a solvent, the same procedure was carried out without washing the filtrate with FC-72, which afforded a 95% yield of the hydrocarbon.

4.1.5. Reduction of 1-iodoadamantane with fluorous tin hydride. A mixture of 1-iodoadamantane (262 mg, 1.0 mmol), fluorous tin hydride 3 (68 mg, 0.05 mmol), sodium cyanoborohydride (94 mg, 1.5 mmol), and α,α'-azobisisobutyronitrile (17 mg, 0.1 mmol), in F-626 (1 mL) and *t*-butyl alcohol (1 mL) was stirred at 90°C for 3 h under nitrogen. After cooling, the mixture was diluted with CH_2Cl_2 (20 mL), washed twice with H_2O and three times with FC-72. The CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (∅ 8 mm×40 mm) with hexane/ethyl acetate (4:1) to afford 98% yield of adamantane (134 mg). In addition, the FC-72 solution was dried and concentrated. The resulting residue (1.45 g) was submitted to reuse in the same reaction, which gave 108 mg of the product (80%).

4.1.6. Radical carbonylation of 1-iodoadamantane with fluorous tin hydride. 1-Iodoadamantane (262 mg, 1.0 mmol), fluorous tin hydride **3** (68 mg, 0.05 mmol), sodium cyanoborohydride (94 mg, 1.5 mmol), α,α'-azobisisobutyronitrile (17 mg, 0.1 mmol), F-626 (1 mL), and *t*-butyl alcohol (1 mL) were placed in a stainless steel autoclave

equipped with an inserted glass liner. The autoclave was pressurized with 80 atm of CO and stirred for 3 h at 90°C. After cooling, the mixture was diluted with CH_2Cl_2 (20 mL), washed twice with H_2O and three times with FC-72. The CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (∅ 8 mm×40 mm) with hexane/ethyl acetate (2:1) to afford 1-adamantylmethanol (142 mg, 85%). The second run which reused the F-626 solution of **3** gave 133 mg (80%) of the product.

4.1.7. Typical procedure for the Vilsmeier formylation. Phosphorus oxychloride (1.3 mmol) was added to a mixture of aromatic compound (1 mmol), *N*-methylformanilide (1. 3 mmol) in F-626 (1 mL). The reaction mixture was heated at 100°C for 1 h. After cooling, the upper layer was decanted, and the residue was diluted with benzene (10 mL), washed with twice of H_2O and three times of FC-72. The solution was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (∅ 8 mm×40 mm) with benzene to give the formylation product. When *o*-dichlorobenzne was used as a solvent, the same procedure was carried out without decantation and washing the benzene solution with FC-72.

4.1.8. Typical procedure for the Wolff–Kishner reduction. To a mixture of carbonyl compound (2.5 mmol) and powder of potassium hydroxide (5 mmol) in F-626 (2 mL), hydrazine monohydrate (1 mL) was added and heated at 120°C for 2 h. The reaction mixture was refluxed for 6 h. After cooling, the reaction mixture was diluted with benzene (10 mL), washed with twice of H_2O and three times of FC-72. The solution was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (∅ 8 mm×40 mm) with benzene to give the reduction product. When diethylene glycol was used as a solvent, the same treatment was undertaken without washing with FC-72.

4.1.9. Typical procedure for the Diels–Alder reaction. An equimolar mixture of diene (1.3 mmol) and dienophile (1.3 mmol) in solvent (3 mL) was refluxed until the red color of the solution disappeared (about 10 min). The separated crystals were collected by filtration, washed with benzene (30 mL), and dried in vacuo. Dimethyl 3,4,5,6-tetraphenylphthlate: white needles, mp 258–260°C (lit. 256–257°C)[12]; 3,4,5,6-tetraphenyl-1,2-dihydro-*o*-phthalic anhydride: white needles, mp 252–254°C (lit. 255°C).[11c]

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