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Synthesis, Fe(II)-induced degradation, and antimalarial activities of 1,5-diaryl-6,7-dioxabicyclo[3.2.2]nonanes: direct evidence for nucleophilic *O*-1,2-aryl shifts

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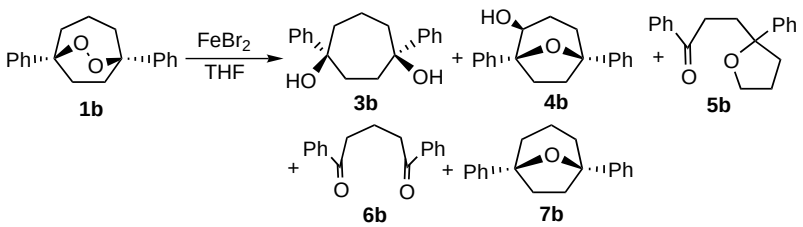
Abstract—1,5-Diaryl-6,7-dioxabicyclo[3.2.2]nonanes **1a–d** (**1a**: Ar = *p*-FC_6H_4, **1b**: Ar = Ph, **1c**: Ar = *p*-MeC_6H_4, **1d**: Ar = *p*-$MeOC_6H_4$) were prepared by a modified method of photo-electron transfer oxygenation, and the reactions of **1** with $FeBr_2$ were investigated under various conditions. The Fe(II)-induced degradation of **1** afforded various rearrangement products and fragmentation products through competitive single electron transfer (SET) and Lewis acid pathways. Direct evidence for the *O*-1,2-aryl shift was obtained by the isolation of rearrangement products, 1-aryloxy-5-aryl-8-oxabicyclo[3.2.1]octanes **8**. The degradation mechanism was proposed and the in vitro antimalarial activities were also evaluated.

The discovery of non-alkaloidal antimalarial endoperoxides such as artemisinin and related compounds has stimulated synthetic and mechanistic studies on antimalarial cyclic peroxides.[1–14] In particular, considerable efforts have been devoted to mechanistic studies for the Fe(II)-induced degradation of cyclic peroxides to clarify potent antimalarial intermediates.[15–17] Posner reported that structurally simple and easily prepared 1,5-diaryl-6,7-dioxabicyclo[3.2.2]nonanes **1b** (Ar = Ph) and **1d** (Ar = *p*-$MeOC_6H_4$) are potent antimalarials.[6,7] They also demonstrated that the reaction of 1,5-diphenyl-substituted cyclic peroxide **1b** with $FeBr_2$ afforded various fragmentation products (**3b**, **6b**, and **7b**) and rearrangement products (**4b** and **5b**) (Scheme 1).[6,7] However, they later reported that the structural assignment of **1b** was incorrect.[7] These results have prompted us to investigate the synthesis of variously substituted **1a–d**, the reactions with $FeBr_2$, and the antimalarial activities since we have been studying the effects of aromatic substituents on the reactivities of the oxyl radical species generated from arylated cyclic peroxides.[18–20] Herein we wish to report our preliminary but novel results for the improved synthesis of **1a–d**, Fe(II)-induced degradation of **1a–d** involving direct evidence for nucleophilic *O*-1,2-aryl shifts,[20] and their antimalarial activities.

As for the synthesis of **1b–d**, Takahashi reported that 9,10-dicyanoanthracene (DCA)-sensitized photo-electron transfer (PET) oxygenation of the corresponding



Scheme 1.

Keywords: 1,5-diaryl-6,7-dioxabicyclo[3.2.2]nonanes; cyclic peroxides; $FeBr_2$; rearrangement; fragmentation; *O*-1,2-aryl shift; reaction mechanism; antimalarial activity.

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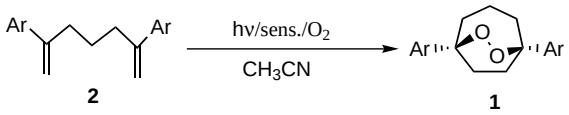
2,6-diaryl-1,6-heptadienes **2b–d** afforded **1b–d** in 0% (11%: in the presence of $Mg(ClO_4)_2$), 37, 98% yields, respectively.[21,22] In order to improve the isolation procedures and the yields of **1a–c**, we modified the above method by using 2,4,6-triphenylpyrylium tetrafluoroborate ($TPPBF_4$) as a sensitizer since $TPPBF_4$ has a stronger oxidizing power than DCA and can be easily separated from the reaction mixtures by column or TLC separation. As summarized in Scheme 2 and Table 1, $TPPBF_4$-sensitized PET oxygenation of **2a–c** afforded the corresponding **1a–c** in reasonable yields (33–58%).[†] While

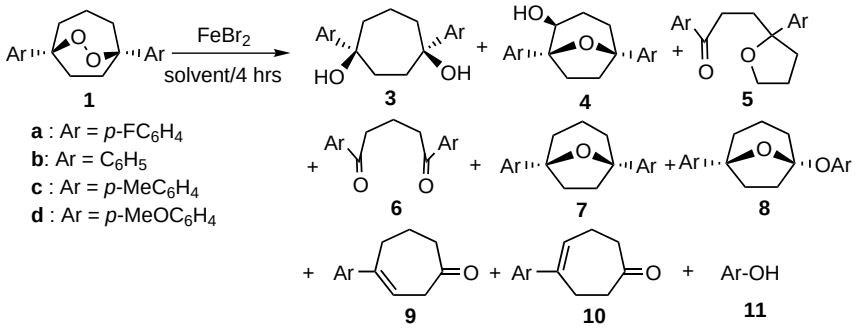


a : Ar = *p*-FC_6H_4
b: Ar = C_6H_5
c : Ar = *p*-MeC_6H_4
d : Ar = *p*-$MeOC_6H_4$

Scheme 2.

the DCA-sensitized PET oxygenation of **2d** produced **1d** in good yield (87%) as reported in the literature,[21,22] the $TPPBF_4$-sensitized PET oxygenation of **2d** resulted in the decomposition of **1d.** These results indicate that the choice of a suitable sensitizer is essential for the PET oxygenation of **2**. Thus, $TPPBF_4$ is suitable for the less electron-donating substrates such as **2a–c** whereas DCA is suitable for the more electron-donating substrate such as **2d**.

In order to clarify the reactivities of the oxyl radical species generated from **1a–d**, the reactions of **1a–d** with $FeBr_2$ were performed (Scheme 3). When 1,5-di(*p*-fluorophenyl)-substituted cyclic peroxide **1a** (0.2 mmol) was treated with 1 equiv. of $FeBr_2$ in dry THF (10 ml) under nitrogen (4 h), 2-hydroxy-1,5-di(*p*-fluorophenyl)-8-oxabicyclo[3.2.1]octane **4a** (15%), 1-(*p*-fluorophenyl)-3-(2-(*p*-fluorophenyl)tetrahydrofuran-2-yl)propan-1-one **5a** (22%), 1,5-di(*p*-fluorophenyl)-pentan-1,5-dione **6a** (12%), and 1,5-di(*p*-fluorophenyl)-8-oxabicyclo-[3.2.1]octane **7a** (33%) were obtained (run 1 in Table 2).[‡]



a : Ar = *p*-FC_6H_4
b: Ar = C_6H_5
c : Ar = *p*-MeC_6H_4
d : Ar = *p*-$MeOC_6H_4$

Scheme 3.

[†] A typical experimental procedure is as follows: An oxygen-purged acetonitrile (50 ml) solution of **2** (0.50 mmol) and sensitizer ($TPPBF_4$: 0.05 mmol; DCA: 0.0125 mmol) was selectively irradiated (λ>360 nm) with a 2 kW Xe lamp. The resulting reaction mixture was concentrated and the residue was separated by TLC (CH_2Cl_2–*n*-hexane) to afford products. The cyclic peroxides **1a–d** were characterized by their spectral data and also confirmed by the comparison with reported spectral data.[21,22]

Selected data for **1d**: mp 185–186°C (CH_3CN); IR (KBr, cm^{-1}) 3080, 3040, 3020, 2990, 2960, 2940, 2880, 1615, 1587, 1518; ^1H NMR (200 MHz, $CDCl_3$) δ 1.78–2.50 (m, 10H), 3.79 (s, 6H), 6.82–6.92 (m, 4H), 7.30–7.42 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.28 (t, 1C), 29.36 (t, 2C), 40.44 (t, 2C), 55.25 (q, 2C), 82.48 (s, 2C), 113.53 (d, 4C), 125.75 (d, 4C), 138.54 (s, 2C), 158.56 (s, 2C). Anal. calcd C, 74.19; H, 7.25; requires C, 74.09; H, 7.11; MS (EI) 340 (M^+, 12%), 135 (100%).

[‡] A typical experimental procedure is as follows: To a solution of **1** (0.2 mmol) in dry THF or dry CH_2Cl_2 (10 ml) was added $FeBr_2$ (0.2 mmol). The mixture was stirred at 23–25°C under a nitrogen atmosphere for 4 h. The mixture was passed through silica gel short column and eluted with CH_2Cl_2 to remove inorganic iron compounds. The eluent was concentrated and the residue was separated by TLC (CH_2Cl_2–*n*-hexane) to afford products. All products were characterized by their spectral data.

Selected data for **4c**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3600–3300 (O–H), 3075, 3020, 2975, 2945, 2900, 1518, 1475, 1450, 1385, 1360, 1300, 1260; ^1H NMR (200 MHz, $CDCl_3$) δ 1.76–2.42 (m, 9H), 2.35 (s, 3H), 2.36 (s, 3H), 3.80–3.91 (m, 1H), 7.14–7.24 (m, 4H), 7.35–7.47 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.09 (q, 2C), 25.96 (t, 1C), 33.25 (t, 1C), 35.67 (t, 1C), 36.39 (t, 1C), 70.35 (d, 1C), 84.59 (s, 1C), 86.36 (s, 1C), 124.36 (d, 2C), 124.77 (d, 2C), 128.81 (d, 2C), 128.99 (d, 2C), 136.31 (s, 1C), 136.52 (s, 1C), 140.68 (s, 1C), 143.48 (s, 1C).

Selected data for **5d**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3050, 3020, 2970, 2950, 2930, 2890, 2850, 1675 (C=O), 1603, 1580, 1512; ^1H NMR (200 MHz, $CDCl_3$) δ 1.70–2.36 (m, 6H), 2.47–2.67 (m, 1H), 2.95–3.14 (m, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 3.89–4.01 (m, 2H), 6.82–6.92 (m, 4H), 7.26–7.35 (m, 2H), 7.78–7.88 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.56 (t, 1C), 33.61 (t, 1C), 36.38 (t, 1C), 39.36 (t, 1C), 55.18 (q, 1C), 55.36 (q, 1C), 67.60 (t, 1C), 85.84 (s, 1C), 113.41 (d, 2C), 113.45 (d, 2C), 126.29 (d, 2C), 129.99 (s, 1C), 130.20 (d, 2C), 138.06 (s, 1C), 158.09 (s, 1C), 163.14 (s, 1C), 199.03 (s, 1C).

Selected data for **7d**: mp 126–127.5°C (CH_3OH); IR (KBr, cm^{-1}) 3080, 3050, 2960, 2930, 2880, 2850, 1618, 1587, 1513; ^1H NMR (200 MHz, $CDCl_3$) δ 1.62–2.12 (m, 8H), 2.25–2.40 (m, 2H), 3.80 (s, 6H), 6.84–6.93 (m, 4H), 7.37–7.47 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.34 (t, 1C), 37.20 (t, 2C), 37.71 (t, 2C), 55.24 (q, 2C), 83.83 (s, 2C), 113.34 (d, 4C), 125.66 (d, 4C), 139.79 (s, 2C), 158.10 (s, 2C). Anal. calcd C, 77.48; H, 7.67; requires C, 77.75; H, 7.46; MS (EI) 324 (M^+, 13%), 135 (100%).

Selected data for **8d**: mp 109–110°C (CH_3OH); IR (KBr, cm^{-1}) 3050, 3020, 2980, 2960, 2930, 2890, 2860, 1618, 1590, 1521, 1510; ^1H NMR (200 MHz, $CDCl_3$) δ 1.52–2.28 (m, 10H), 3.76 (s, 3H), 3.80 (s, 3H), 6.75–6.92 (m, 4H), 7.13–7.24 (m, 2H), 7.28–7.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.60 (t, 1C), 32.44 (t, 1C), 34.07 (t, 1C), 34.90 (t, 1C), 37.53 (t, 1C), 55.22 (q, 1C), 55.46 (q, 1C), 84.19 (s, 1C), 109.51 (s, 1C), 113.40 (d, 2C), 113.92 (d, 2C), 123.31 (d, 2C), 125.37 (d, 2C), 138.96 (s, 1C), 147.95 (s, 1C), 155.64 (s, 1C), 158.21 (s, 1C). Anal. calcd C, 74.02; H, 7.12; requires C, 74.09; H, 7.11; MS (EI) 340 (M^+, 21%), 217 (100%).

Selected data for the mixture of **9d** and **10d**: pale yellow oil; IR (neat, cm^{-1}) 3050, 2960, 2950, 2920, 2850, 1702 (C=O), 1608, 1573, 1512; ^1H NMR (200 MHz, $CDCl_3$) for **9d**: δ 2.02–2.20 (m, 2H), 2.60–2.85 (m, 4H), 3.32 (d, 2H, J=6.3 Hz), 3.81 (s, 3H), 5.79 (t, 1H, J=6.3 Hz), 6.82–6.92 (m, 2H), 7.22–7.33 (m, 2H); ^1H NMR (200 MHz, $CDCl_3$) for **10d**: δ 2.43–2.56 (m, 2H), 2.60–2.85 (m, 6H), 3.81 (s, 3H), 6.03 (t, 1H, J=5.8 Hz), 6.82–6.92 (m, 2H), 7.22–7.33 (m, 2H).

Table 1. PET oxygenation of 2,6-diaryl-1,6-heptadienes **2**[a]

Run	Substrate	Sensitizer[b]	Irradiation time (min)	Yield of **1** (%)[c]
1	**2a**	$TPPBF_4$	50	33
2	**2b**	$TPPBF_4$	65	44
3	**2c**	$TPPBF_4$	20	58
4	**2d**	DCA	15	87

[a] **2** = 0.5 mmol; CH_3CN = 50 ml; irradiated by a 2 kW Xe lamp (λ>360 nm).
[b] $TPPBF_4$ = 0.05 mmol; DCA = 0.0125 mmol.
[c] Isolated yield by silica gel TLC.

No diol **3a** was obtained.[6] When **1b** and **1c** were treated with $FeBr_2$, similar product distributions were observed (runs 2 and 3). Interestingly, a new type of product, 1-(*p*-methoxyphenyl)oxy-5-(*p*-methoxyphenyl)-8-oxabicyclo[3.2.1]octane **8d** (11%) was obtained besides **4d**–**7d** when 1,5-di(*p*-methoxyphenyl)-substituted **1d** was treated with $FeBr_2$ (run 4). On the other hand, **8a**–**c** (11%, 8%, 86%) were produced from **1a**–**c**, respectively in the reactions of **1a**–**c** with $FeBr_2$ in dry CH_2Cl_2 (runs 5–7). On the contrary, 4-(*p*-methoxyphenyl)cyclohept-3-en-1-one **9d** and 4-(*p*-methoxyphenyl)cyclohept-4-en-1-one **10d** (**9d**+**10d** = 74%) were newly produced accompanied with *p*-methoxyphenol **11d** (65%) when **1d** was treated with $FeBr_2$ in dry CH_2Cl_2 (run 8). Interestingly, a catalytic amount of $FeBr_2$ (0.5 equiv.) also promoted the O–O bond cleavage reactions of **1b** and **1d** (runs 9 and 10). A control experiment in CH_2Cl_2 demonstrated that **8d** was decomposed by a catalytic amount of $FeBr_2$ to afford **9d**, **10d**, and **11d** quantitatively (Lewis acid-catalyzed fragmentation).[20] Addition of an electron-donating compound such as 1,2,4,5-tetramethoxybenzene (TMB) slightly suppressed the fragmentation of **8d** (run 11).

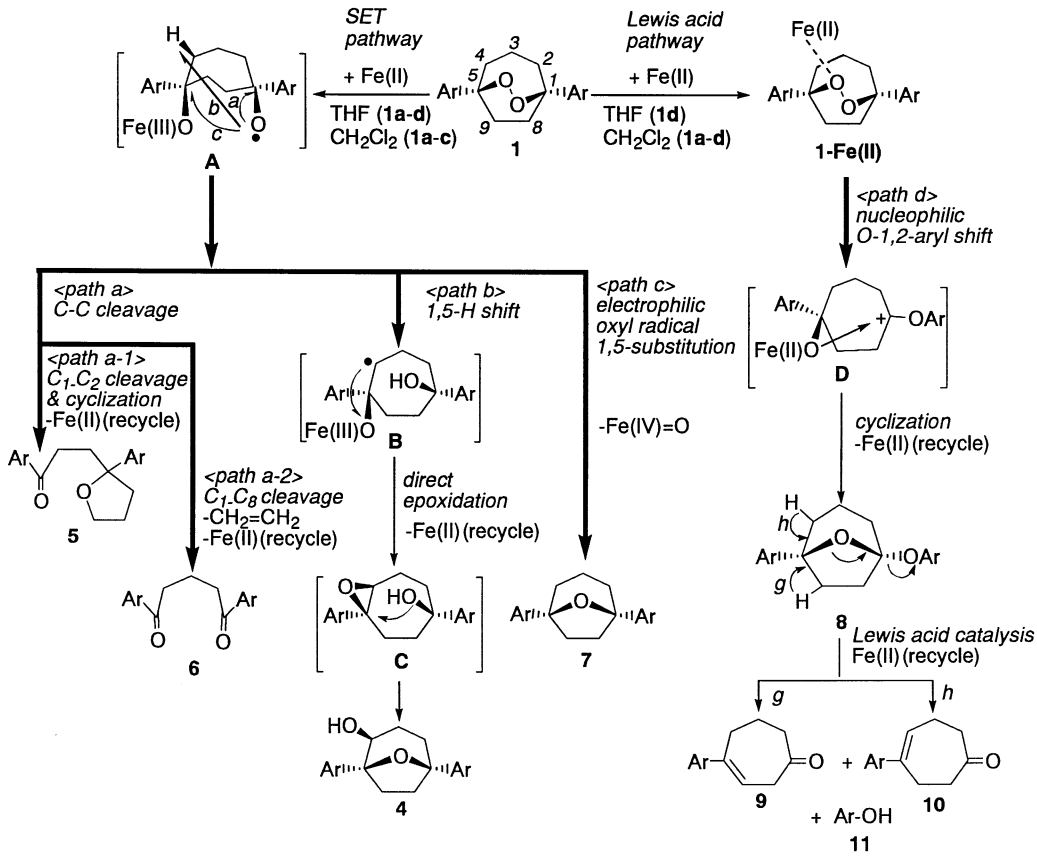
On the basis of the above results, we propose a plausible mechanism as shown in Scheme 4. Both in THF and CH_2Cl_2, the mono-oxyl radical intermediate **A** is generated by single electron transfer (SET) from Fe(II) to **1**.[6,7,20,23] Four different pathways are plausible for the product formation from **A**. The first and the second pathways are the formation of **5** (path a-1: C_1–C_2 cleavage) and **6** (path a-2: C_1–C_8 cleavage) through C–C bond cleavage. The third is the formation of the intermediate **B** through a 1,5-hydrogen shift followed by direct epoxidation to afford the intermediate **C** (path b), which finally rearranges to **4** through an intramolecular nucleophilic cyclization. The fourth is the formation of deoxygenated product **7** through an electrophilic oxyl radical 1,5-substitution accompanied with elimination of the Fe(IV)=O species (path c).[20] In CH_2Cl_2, Fe(II) also acts as a Lewis acid that generates the complex of **1** with Fe(II) (**1-Fe(II)**). **1-Fe(II)** undergoes a nucleophilic *O*-1,2-aryl shift to generate the intermediate **D** (path d),[20] which is promoted by electron-donating substituents (*p*-An>*p*-Tol>Ph=*p*-FC_6H_4: runs 5–9). The intermediate **D** undergoes cyclization to afford the rearrangement product **8** which is direct evidence for the nucleophilic *O*-1,2-aryl shift. In the presence of the Fe(II) species (Lewis acid), **8d** easily undergoes fragmentation to afford **9d**, **10d**, and **11d**. Thus, the products **4**–**7** are produced through the SET pathway while **8**–**11** are produced through the Lewis acid pathway. THF and TMB are considered to act as a weak Lewis base, interfering with the Lewis acid pathway and/or promoting the SET pathway.

The in vitro antimalarial activities of **1a**–**d** against *P. falciparum* and cytotoxicities against FM-3A cells were tested to clarify the relationship between the antimalarial activities and the effects of the aromatic substituents of **1** (Table 3).[12] The EC_{50} values of **1a**–**d** against *P. falciparum* were in the range from 2.5×10^{-7} to 9.0×10^{-8} M and the selectivities were fairly high (60–300), regardless of their aromatic substituents. In particular, **1b**–**d** can be promising lead compounds for the synthesis of new antimalarial drugs. Notably, fluoro-substi-

Table 2. Reactions of 1,5-diaryl-6,7-dioxabicyclo[3.2.2]nonanes **1** with $FeBr_2$[a]

Run	Substrate	Solvent	Additive	Yields (%)[b]							
				3	**4**	**5**	**6**	**7**	**8**	**9**+**10** (**9**:**10**)[c]	**11**
1	**1a**	THF	None	0	15	22	12	33	0	0	0
2	**1b**	THF	None	0	14	24	13	42	0	0	0
3	**1c**	THF	None	0	19	27	28	34	0	0	0
4	**1d**	THF	None	0	12	22	17	31	11	0	0
5	**1a**	CH_2Cl_2	None	0	11	29	30	10	11	0	0
6	**1b**	CH_2Cl_2	None	0	9	29	29	2	8	0	0
7	**1c**	CH_2Cl_2	None	0	0	8	6	0	86	0	0
8	**1d**	CH_2Cl_2	None	0	0	0	0	0	0	74 (44:56)	65
9	**1b**	CH_2Cl_2	None[d]	0	9	28	27	1	13	0	0
10	**1d**	CH_2Cl_2	None[d]	0	0	0	0	0	0	84 (54:46)	78
11	**1d**	CH_2Cl_2	TMB[e]	0	0	0	0	3	10	72 (54:46)	77

[a] **1** = 0.2 mmol, $FeBr_2$ = 0.2 mmol, solvent = 10 ml, at 23–25°C.
[b] Isolated yield by silica gel TLC.
[c] Determined by ^1H NMR.
[d] $FeBr_2$ = 0.1 mmol.
[e] In the presence of 1,2,4,5-tetramethoxybenzene (0.2 mmol).



Scheme 4.

Table 3. In vitro antimalarial activities of **1** against *P. falciparum* (FCR-3 strain) and cytotoxicities against FM3A cells[a]

Substrate	EC_{50} (M)		Selectivity[b]
	P. falciparum	FM3A	
1a	2.5×10^{-7}	1.5×10^{-5}	60
1b	9.0×10^{-8}	2.7×10^{-5}	>300
	(8.9×10^{-8})[c]	(59%)[d]	
1c	1.6×10^{-7}	1.6×10^{-5}	>100
		(59%)[d]	
1d	1.6×10^{-7}	1.6×10^{-5}	>100
	(6.2×10^{-8})[c]	(83%)[d]	
Artemisinin	7.8×10^{-9}	1.0×10^{-5}	1280
Chloroquine	1.8×10^{-8}	3.2×10^{-5}	1780

[a] Ref. 12.
[b] Selectivity = cytotoxicity/antimalarial activity.
[c] IC_{50} values against *P. falciparum* (NF54 strain), Ref. 6.
[d] Growth percent at the concentration indicated.

tuted **1a** did not enhance the activity or the selectivity although Posner reported such a fluorine atom effect for 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes.[9] Similar antimalarial activities of **1a–d** indicate that there is no significant relationship between the antimalarial activities and the effects of the aromatic substituents of **1a–d**.

In conclusion, we have improved the synthesis of **1a–c** by using the $TPPBF_4$-induced PET oxygenation. We have found the direct evidence (isolation of **8**) for the nucleophilic *O*-1,2-aryl shifts in the Fe(II)-induced degradation of **1**. Furthermore, we have disclosed that Fe(II) acts not only as a SET donor but also as a Lewis acid in the Fe(II)-induced O–O bond cleavage of cyclic peroxides. We are conducting further studies on the Fe(II)-induced degradation of arylated cyclic peroxides to substantiate the generality of the reaction and the relationship between the reaction intermediates and the antimalarial activities.

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