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Alkaline metal ion-enhanced chemiluminescence of bicyclic dioxetanes bearing a hydroxyaryl group with an '*even*' substitution pattern

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ABSTRACT

Bicyclic dioxetane **5** bearing a 3-hydroxynaphthalen-2-yl group and its analogs **14** and **15** decomposed to give light with efficiencies of only 0.002–0.005% in a tetrabutylammonium fluoride (TBAF)/THF system, which was as expected for dioxetanes with a so-called '*even*' substitution pattern. However, the chemiluminescence efficiencies (Φ^{CL}) markedly increased when these dioxetanes were decomposed with alkaline metal *t*-butoxide in THF. This enhancement of Φ^{CL} by alkaline metal ion was most likely due to the highly ordered conformation of an aromatic ring by chelate formation of the metal ion with both an oxido anion and oxygen atom of a tetrahydrofuran ring in an intermediary dioxetane like **12**. Alkaline metal ion-enhanced chemiluminescence was similarly observed for dioxetane **6** bearing a 2-hydroxyphenyl group.

Dioxetanes substituted with an oxidoaryl anion as an electron donor undergo intramolecular charge-transfer-induced decomposition (CTID) accompanied by the emission of light.[1–7] The position of the oxido anion relative to the attachment point of the dioxetane on the aryl group affects the chemiluminescence efficiency (Φ^{CL}). For instance, dioxetane **1** bearing a *m*-oxidophenyl group ('*odd*' substitution pattern) gives bright light while its *o*- or *p*-oxidophenyl analogs ('*even*' substitution pattern) give only weak light.[8,9] Such an '*odd*/*even*' relationship is also observed for dioxetanes **2** substituted with an oxidonaphthalen-2-yl group: analogs with an oxido anion at the 4-, 5-, or 7-position on the naphthalene ring ('*odd*' substitution pattern) give light far more effectively than those with an oxido anion at the 2-, 6- or 8-position ('*even*' substitution pattern) (Scheme 1).[10–14] This phenomenon of an '*odd*/*even*' relationship has also been observed for other oxidoaryl-substituted dioxetanes.[15]

On the other hand, we have very recently found that conformation of the oxidoaryl group significantly affects the efficiency of chemiluminescence for CTID of an *N*-acylamino-substituted dioxetane bearing a 6-oxidonaphthalen-1-yl group: Φ^{CL} for *anti*-**3** is 10–20 times higher than that for *syn*-**3**, though both rotamers give the same decomposition product **4** (Scheme 2).[16] This finding suggested the possibility that highly efficient chemiluminescence could be observed even with a dioxetane bearing an '*even*'-pattern oxyaryl group by controlling its stereochemistry. In this Letter, we describe how we realized this expectation by fixing the stereochemistry of the oxidoaryl group through chelation with an alkaline metal ion.

Bicyclic dioxetanes bearing a 3-hydroxynaphthalen-2-yl **5** or 2-hydroxyphenyl group **6** have very recently been found to possess a structure in which the hydroxy group shows intramolecular hydrogen bonding with an oxygen atom of the dihydrofuran ring in $CDCl_3$ solution, as illustrated in Figure 1.[17] Dioxetane **6** in a crystalline state (colorless prisms, mp 60.5–61.0 °C) was also confirmed by X-ray single crystallographic analysis to form intramolecular hydrogen bonds, as shown in Figure 2.[18] Thus, we attempted to investigate the base-induced decomposition of **5** and **6** in the presence of an alkaline metal ion, which should coordinate with both oxidoaryl anion and oxygen of the dihydrofuran ring.

When a solution of dioxetane **5** in tetrahydrofuran (THF) (1.0×10^{-4} M, 1 mL) was added to a solution of tetrabutylammonium fluoride (TBAF) in THF (1.0×10^{-2} M, 2 mL) at 25 °C, **5** decomposed accompanied by the emission of orange light. This CTID showed a maximum wavelength of chemiluminescence, λ^{CL}_{max}, at 556 nm and a decomposition rate, k^{CTID}, of 1.7×10^{-2} s^{-1}. However, the chemiluminescence efficiency, Φ^{CL}, was quite poor (2.4×10^{-5}),[19,20] and was as low as those for typical '*even*'-pattern hydroxynaphthyl dioxetanes.[10,11] After neutralization of the spent reaction mixture of **5**, keto ester **9** was isolated in high yield. The fluorescence spectrum of authentic **8** generated from **9** in TBAF/THF coincided with the chemiluminescence spectrum of **5**. These results indicate for the CTID of **5** that the emitter was an oxido anion of keto ester **8** in a singlet-excited state, which was produced by CTID of oxidonaphthyl-substituted dioxetane **7**, as illustrated in Scheme 3.

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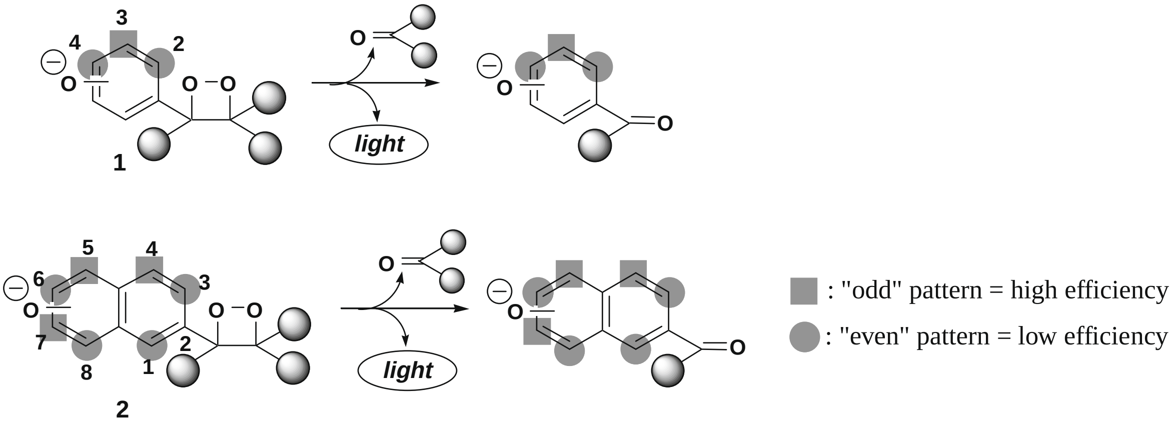
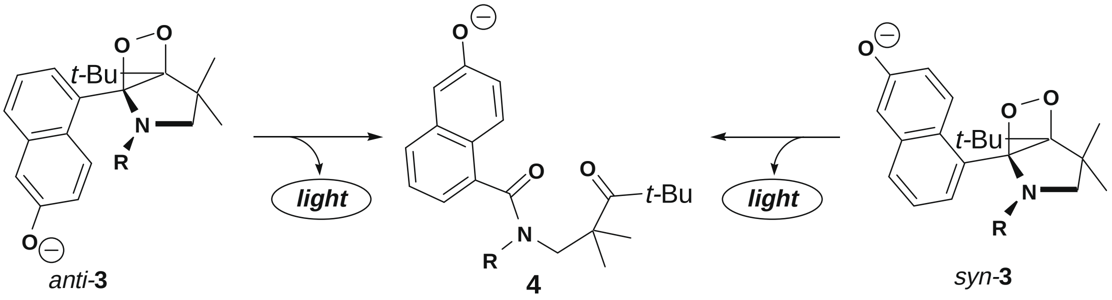


Scheme 1. 'Odd/even' relationship for chemiluminescence efficiency of oxidoaryldioxetanes.



Scheme 2. Rotamer dependent chemiluminescence for an N-substituted dioxetane.

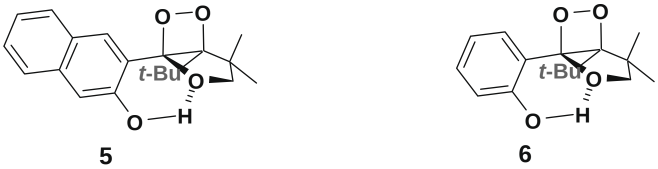


Figure 1. Intramolecular hydrogen bonding for dioxetane **5** and **6**.

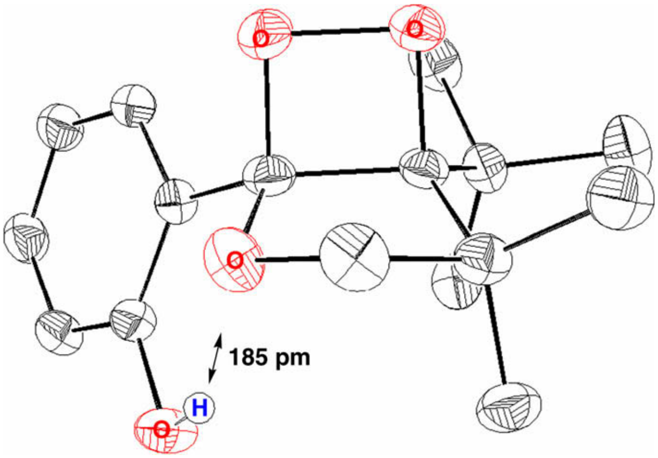
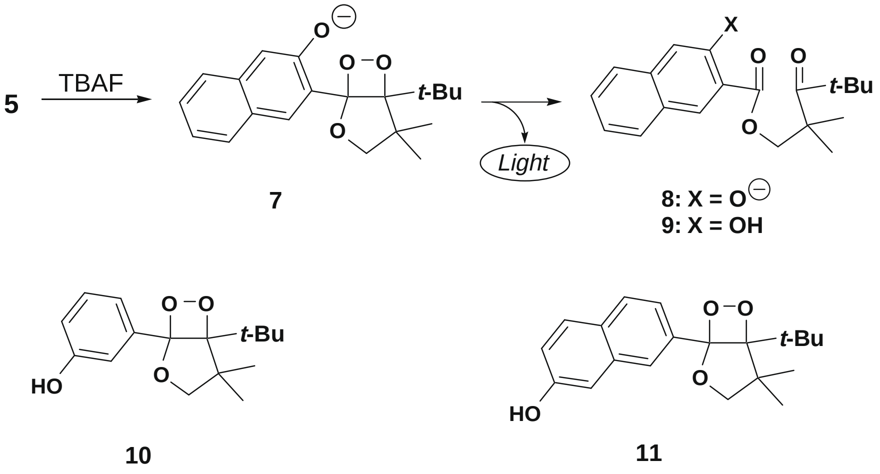


Figure 2. ORTEP view of 2-hydroxyphenyl-substituted dioxetane **6**.

On the other hand, when **5** (1.0×10^{-4} M, 1 mL) was treated with a large excess of potassium *t*-butoxide (*t*-BuOK) (1.0×10^{-2} M, 2 mL) in place of TBAF in THF, **5** decomposed with $k^{\mathrm{CTID}} = 0.11\ \mathrm{s}^{-1}$ to give intense light with $\lambda^{\mathrm{CL}}_{\mathrm{max}} = 539$ nm and $\Phi^{\mathrm{CL}} = 4.5 \times 10^{-4}$. The chemiluminescence spectrum is shown in Figure 3a together with those in the TBAF system, and *t*-BuONa and *t*-BuOLi systems (vide infra). If we compare the chemiluminescence properties of *t*-BuOK/THF to those of TBAF/THF, we see that the Φ^{CL} value was increased 19-fold, $\lambda^{\mathrm{CL}}_{\mathrm{max}}$ shifted to blue (17 nm), and k^{CTID} increased ca. sixfold. These results are summarized in Table 1.

Upon treatment with *t*-BuONa instead of *t*-BuOK in THF, dioxetane **5** decomposed slowly ($k^{\mathrm{CTID}} = 4.0 \times 10^{-2}\ \mathrm{s}^{-1}$) to emit light with $\lambda^{\mathrm{CL}}_{\mathrm{max}} = 537$ nm. As shown in Table 1, Φ^{CL} (1.5×10^{-3}) for *t*-BuONa was 63-fold greater than that in the TBAF system. Finally, we carried out the decomposition of **5** with *t*-BuOLi in THF. Lithium ion was expected to coordinate quite strongly to oxidoaryl anion in an organic solvent because of its small ionic radius, and thus we did not expect that *t*-BuOLi would function as a base for CTID. In fact, a parent dioxetane bearing a 3-hydroxyphenyl **10** decomposed sluggishly in the presence of *t*-BuOLi, though it underwent rapid TBAF-induced decomposition to give bright light ($\Phi^{\mathrm{CL}} = 0.26$) in DMSO, as reported previously.[11] However, the CTID of **5** induced by *t*-BuOLi in THF took place smoothly at 45 °C to give intense light with $\lambda^{\mathrm{CL}}_{\mathrm{max}} = 536$ nm and $k^{\mathrm{CTID}} = 4.9 \times 10^{-3}\ \mathrm{s}^{-1}$ (Fig. 3 and Table 1). Astonishingly, the Φ^{CL} (5.1×10^{-3}) was more than 200-fold greater than that in the TBAF system, and was comparable to that for naphthyl-substituted dioxetane **11** with an '*odd*'-pattern (vide infra).

The effects of alkaline metal ions on the chemiluminescent decomposition of dioxetane **5** in THF observed here can be summarized as follows. First, all chemiluminescence spectra in the presence of alkaline metal ion were shifted 17–20 nm to blue relative to the case of TBAF. This blue shift of chemiluminescence is presumably due to decrease of negative charge in emitter **13**



Scheme 3. Base-induced chemiluminescent decomposition of a dioxetane **5** and its related dioxetanes **10** and **11**.

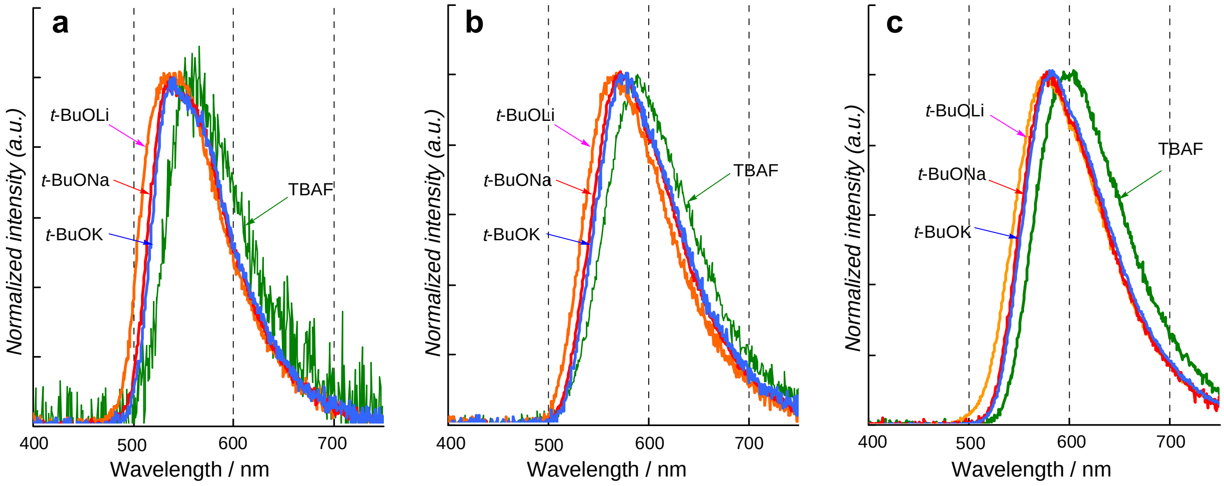


Figure 3. Base-induced chemiluminescence spectra of dioxetane **5** (a), **14** (b), and **15** (c).

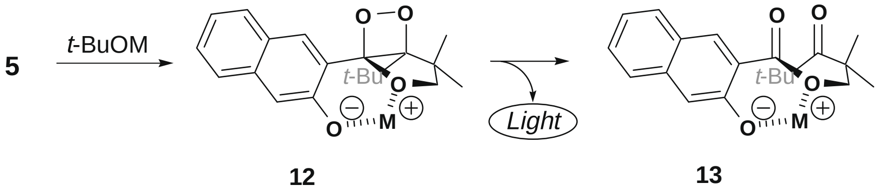
Table 1
Chemiluminescent decomposition of hydroxyaryl-substituted dioxetanes **5**, **6**, **11**, **14**, and **15** in the presence of alkaline metal ion[a]

Dioxetane	Base	$\lambda_{\max}^{\mathrm{CL}}$ (nm)	Φ^{CL}[b]	Relative Φ^{CL}	k (s^{-1})	$t_{1/2}$ (s)
5	TBAF	556	2.4×10^{-5}	1	1.7×10^{-2}	42
	t-BuOK	539	4.5×10^{-4}	19 ↑	1.1×10^{-1}	6.4
	t-BuONa	537	1.5×10^{-3}	63 ↑	4.0×10^{-2}	18
	t-BuOLi[c]	536	5.1×10^{-3}	210 ↑	4.9×10^{-3}	140
6	TBAF	427	1.8×10^{-5}	1	1.6×10^{-1}	4.3
	t-BuOK	423	1.2×10^{-4}	7 ↑	7.7×10^{-1}	0.9
	t-BuONa	423	1.6×10^{-4}	9 ↑	3.4×10^{-1}	2.0
14	TBAF	588	4.6×10^{-5}	1	6.7×10^{-2}	10
	t-BuOK	574	1.3×10^{-3}	28 ↑	3.4×10^{-1}	2.0
	t-BuONa	572	2.5×10^{-3}	55 ↑	1.5×10^{-1}	4.7
	t-BuOLi	565	3.0×10^{-3}	65 ↑	6.2×10^{-3}	110
15	TBAF	596	4.6×10^{-5}	1	4.7×10^{-1}	1.5
	t-BuOK	582	1.7×10^{-3}	37 ↑	9.3×10^{-1}	0.8
	t-BuONa	578	4.9×10^{-3}	110 ↑	3.7	0.2
	t-BuOLi	575	2.7×10^{-3}	59 ↑	2.0×10^{-1}	3.5
11	TBAF	580	2.3×10^{-2}	1	5.0×10^{-3}	140
	t-BuOK[c]	583	8.6×10^{-3}	0.4 ↓	5.9×10^{-3}	120
	t-BuONa[c]	566	1.2×10^{-2}	0.5 ↓	8.3×10^{-4}	840

[a] All reactions were carried out at 25 °C unless otherwise stated.

[b] Φ^{CL} was estimated based on the value for the chemiluminescent decomposition of 3-adamantylidene-4-(3-siloxyphenyl)-4-methoxy-1,2-dioxetane.[19]

[c] Reactions were carried out at 45 °C.



Scheme 4. Alkaline metal *t*-butoxide-induced chemiluminescent decomposition of dioxetane **5**.

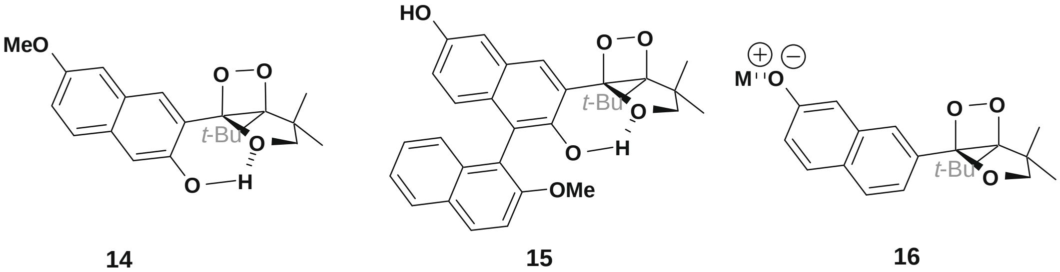


Figure 4. Dioxetane **14**, **15**, and **16**.

caused by coordination of alkaline metal ion (vide infra). Second, k^{CTID} increased in the order *t*-BuOLi < *t*-BuONa < *t*-BuOK. This order coincides with the order of the increase in ionic radius: $Li^+ < Na^+ < K^+$. This strongly suggests that alkaline metal ion coordinates to oxidonaphthyl ion of **7**, as expected, and Li^+ coordinates the most tightly among these three alkaline metal ions. As illustrated in Scheme 4, CTID of **5** proceeded most likely through a chelate form of anionic dioxetane **12** to give chelated keto ester **13** accompanied by the emission of light. Third, Φ^{CL} increased in the order TBAF ≪ *t*-BuOK ≪ *t*-BuONa ≪ *t*-BuOLi. Thus, the conformation of the oxidonaphthyl group as an electron donor relative to the dioxetane ring should affect the singlet-chemiexcitation process, and the chelate **12** with Li^+ presumably had a conformation that was the most favorable for singlet-chemiexcitation among the four base-systems described here. The increased k^{CTID}s for the *t*-BuOK and *t*-BuONa systems may also be attributed to a fixed conformation of the naphthyl group favorable for CTID.

Next, we examined whether or not *t*-BuOM (M: alkaline metal) acted to enhance the Φ^{CL} of dioxetane **6** bearing a 2-hydroxyphenyl group. The results in Table 1 show that both *t*-BuONa and *t*-BuOK were effective as expected, though the magnitude of the enhancement was not so large. On the other hand, *t*-BuOLi barely induced the decomposition of **6** even at 45 °C, in contrast to the results with **5**. This difference between **5** and **6** in the response to *t*-BuOLi is likely due to the fact that phenol is a weaker acid than 2-naphthol. Dioxetane substituted with a 3-hydroxy-7-methoxynaphthyl group **14** and dioxetane bearing a rather complex binaphthyl moiety **15** also underwent alkaline metal ion-enhanced chemiluminescent decomposition (Fig. 4). These chemiluminescence spectra are illustrated in Figure 3b and c. The chemiluminescence properties are summarized in Table 1, which shows for both dioxetanes **14** and **15** that *t*-BuOMs effectively increased k^{CTID} as well as Φ^{CL}. In addition, for binaphthyl dioxetane **15**, sodium ion was the most effective among the alkaline metal ions at enhancing Φ^{CL}.

Finally, dioxetane bearing a 7-hydroxynaphthalen-2-yl group **11** was subjected to CTID in the presence of *t*-BuOM in THF. Dioxetane **11** was selected as a representative of the '*odd*'-pattern family that emitted light effectively, but could not form a chelate with a metal ion, in contrast to **5**, **6**, **14,** and **15**. When **11** was treated with TBAF in THF, **11** decomposed to give light effectively, with $\lambda^{CL}_{max} = 580$ nm, $k^{CTID} = 5.0 \times 10^{-3}\ s^{-1}$, and $\Phi^{CL} = 2.3 \times 10^{-2}$. On the other hand, the decomposition of **11** induced by *t*-BuOLi proceeded too slowly to estimate k^{CTID} and Φ^{CL}, though λ^{CL}_{max} was barely observed at 564 nm. For both *t*-BuONa and *t*-BuOK, the chemiluminescent decomposition of **11** took place with rates sufficient to estimate Φ^{CL}s, as shown in Table 1. Based on the chemiluminescent properties of **11** in the TBAF system, the decomposition of **11** in a *t*-BuOM system has several characteristic features. In contrast to the results with **5**, **6**, **14,** and **15**, alkaline metal ions, Li^+ and Na^+, significantly decreased k^{CTID} of **11.** Alkaline metal ion decreased the Φ^{CL} of **11**, albeit moderately. The λ^{CL}_{max}s for the *t*-BuOM (M = Li or Na) system were shifted to blue, as with **5**, **14,** and **15**. The decrease in k^{CTID} and the blue shift of λ^{CL}_{max} suggest that alkaline metal ion strongly attached to an oxido anion of an intermediary dioxetane such as **16** (Fig. 4).

In conclusion, the results showed that chelation with alkaline metal ion markedly enhanced the chemiluminescence efficiency of CTID for hydroxyaryl-substituted dioxetanes with an '*even*'-pattern, for example, bicyclic dioxetanes bearing a 3-hydroxynaphthalen-2-yl group (**5**, **14**, **15**) or a 2-hydroxyphenyl group (**6**) in THF. Lithium ion was the most effective at enhancing Φ^{CL} for **5** and **14**, while sodium ion gave the best results for **15**. Chelation with sodium or potassium ion increased the decomposition rate of these dioxetanes. In contrast to these dioxetanes that were capable of forming a chelate, dioxetane bearing a 7-hydroxynaphthalen-2-yl group (**11**) was affected rather negatively by alkaline metal ions.

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18. Crystal data for **6**: $C_{16}H_{22}O_4$ ($M_r = 278.35$), colorless prism, $0.20 \times 0.20 \times 0.20$ mm, monoclinic, space group $P21/c$ (#14), $a = 12.004(8)$ Å, $b = 10.191(7)$ Å, $c = 12.30(1)$ Å, $\beta = 97.593(8)^\circ$, $V = 1491.1(23)$ Å^3, $Z = 4$, $\rho_{\text{calcd}} = 1.240$ g cm^{-3}, $T = 120$ K, $F(000) = 600.00$, reflections collected/unique 16,002/3391 ($R_{\text{int}} = 0.037$), μ(Mo Kα) = 0.88 cm^{-1}. Final R indices $R_1 = 0.034$ [$I > 2\sigma(I)$], $wR_2 = 0.083$ (all data), GOF on $F^2 = 1.001$, and residual electron density 0.16/−0.14 e Å^{-3}. CCDC deposition number: 714384.These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax(+44)1223-336-033; or deposit@ccdc.cam.au.uk).
19. All Φ^{CL}s presented here were estimated, based on the value reported for 3-adamantylidene-4-(3-siloxyphenyl)-4-methoxy-1,2-dioxetane ($\Phi^{\text{CL}} = 0.29$).[20]
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