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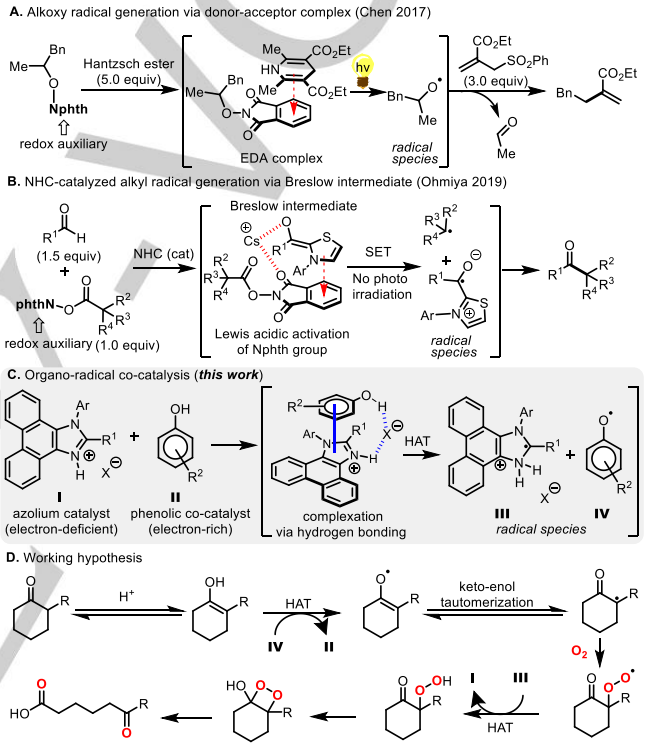
# Azolium/hydroquinone organo-radical co-catalysis: Aerobic C–C-bond cleavage in ketones

Yuya Nakatsuji, [a] Yusuke Kobayashi,*[b] Sakyo Masuda,[a] and Yoshiji Takemoto*[a]

**Abstract:** Organo-radical catalysts have recently attracted great interest, and the development of this field can be expected to broaden the applications of organocatalysis. Herein, we report the first example of a radical-generating system that does not require any photoirradiation, radical initiators, or preactivated substrates. The oxidative C–C-bond cleavage of 2-substituted cyclohexanones was achieved using an azolium salt and a hydroquinone as co-catalysts. A catalytic mechanism is proposed based on the results of diffusion-ordered spectroscopy and cyclic voltammetry measurements, as well as computational studies.

Organocatalysis has undergone substantial developments in the past few decades,[1-5] especially in terms of operational simplicity, reduction of toxicity, and minimization of the environmental impact. In this context, a wide variety of organocatalysts have been reported, which includes hydrogen-bond donors,[1] nucleophilic catalysts,[2] peptide catalysts,[3] and phase-transfer catalysts.[4] Most organocatalyzed reactions proceed via the activation of the LUMO of an electrophile and/or the HOMO of a nucleophile. Moreover, organocatalyzed reactions often suffer from substrate limitations and hence restrictions on the types of reactions accessible.[5] Organo-radical catalysis has recently attracted great attention as it enables otherwise inaccessible reactions,[6] albeit that only limited classes of organocatalytic systems have been reported to date,[7-10] including organo-photoredox catalysts,[7] thiyl radical catalysis,[8] and oxyl radical catalysis.[9] These systems often require a radical initiator and/or photo-irradiation to generate the radical species. We envisioned that the development of a novel methodology for the generation of radical species via the combination use of two different catalysts could promote the development of radical catalysis and further expand the utility of organocatalysis.

Electron-donor–acceptor (EDA) complex[10-12] is one of the most powerful strategies to generate radical species under relatively mild conditions using radical auxiliaries and photo-irradiation, which has led to unique radical cross-coupling reactions (Scheme 1A).[12a] Nagao and Ohmiya have reported that a Breslow intermediate,[13] generated from aldehydes and an *N*-heterocyclic carbene (NHC) catalyst, can undergo single-electron transfer (SET) with *N*-(acyloxy)phthalimides via Lewis acidic acitivation of Nphth group without photo-irradiation[13f] to form an NHC-derived persistent ketyl radical and a transient alkyl radical that enable a useful radical cross-coupling (Scheme 1B).




**Scheme 1.** Previous work and schematic illustration of the organo-radical co-catalytic strategy in this work.

Inspired by these pioneering studies, we envisaged that our previously reported azolium salts (**I**)[14] could effectively form a complex via hydrogen bonding and undergo HAT with electron-rich planar π-conjugated systems such as those in phenolic compounds (**II**), and that these compounds could thus be used as co-catalysts to generate azolium-derived radical (**III**) and phenoxyl radical (**IV**) species (Scheme 1C). We planned to use these radical species for the transformation of α,α-disubstituted ketones (**1**) via an enol radical intermediate (Scheme 1D). As phenoxyl radicals are typically unlikely to abstract a hydrogen atom from a C–H bond ($BDE_{C\text{-}H}$ ≈ 104.9 kcal·mol$^{-1}$) or aliphatic hydroxyl group ($BDE_{O\text{-}H}$ ≈ 104.6 kcal·mol$^{-1}$), we hypothesized that the azolium co-catalyst would promote the enolization of ketones, and that the enol form ($BDE_{O\text{-}H}$ ≈ 88.3 kcal·mol$^{-1}$) could undergo hydrogen-atom transfer (HAT) with the phenoxyl radical ($BDE_{O\text{-}H}$ ≤ 91.0 kcal·mol$^{-1}$) to form an enol radical.[15] Subsequent trapping with molecular oxygen would form a peroxyl radical

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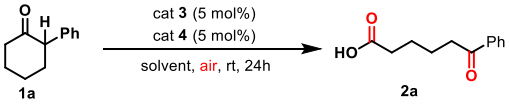
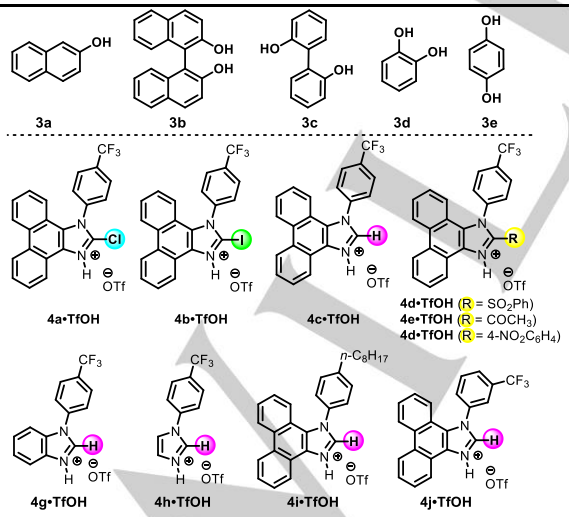
intermediate, causing C–C bond cleavage via 1,2-dioxetanes[16] to give a keto-carboxylic acid under concomitant regeneration of catalysts **I** and **II**.

Herein, we report the first example of a radical co-catalytic system generated by simply mixing two different organocatalysts. The relationship between the catalyst structure and radical generation was investigated using diffusion ordered spectroscopy (DOSY), cyclic voltammetry (CV), and computational studies.

**Table 1.** Optimization of the catalysts and reaction condition.




| entry | cat **3** | cat **4** | solvent | additive | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | **3a** | **4a·TfOH** | DCM | none | 6 |
| 2 | **3b** | **4a·TfOH** | DCM | none | 54 |
| 3 | **3c** | **4a·TfOH** | DCM | none | 17 |
| 4 | **3d** | **4a·TfOH** | DCM | none | 42 |
| 5 | **3e** | **4a·TfOH** | DCM | none | 57 |
| 6 | **3e** | **4b·TfOH** | DCM | none | 62 |
| 7 | **3e** | **4c·TfOH** | DCM | none | 77 |
| 8 | **3e** | **4d·TfOH** | DCM | none | 75 |
| 9 | **3e** | **4e·TfOH** | DCM | none | 75 |
| 10 | **3e** | **4f·TfOH** | DCM | none | 76 |
| 11 | **3e** | **4g·TfOH** | DCM | none | 39 |
| 12 | **3e** | **4h·TfOH** | DCM | none | 0 |
| 13 | **3e** | **4i·TfOH** | DCM | none | 0 (58)[b] |
| 14 | **3e** | **4j·TfOH** | DCM | none | 0 (45)[b] |
| 15 | **3e** | **4c** | DCM | none | 0 |
| 16 | **3e** | **4c·TfOH** | THF | none | 10 |
| 17 | **3e** | **4c·TfOH** | $MeNO_2$ | none | 31 |
| 18 | **3e** | **4c·TfOH** | toluene | none | 82 |
| 19 | **3e** | **4c·TfOH** | PhCl | none | **92 (93)**[c] |
| 20 | **3e** | none | PhCl | none | 0 |
| 21 | none | **4c·TfOH** | PhCl | none | 0 |
| 22 | **3e** | **4c·TfOH** | PhCl | TEMPO[d] | 0 |
| 23 | **3e** | **4c·TfOH** | PhCl | in the dark | 92 |
| 24 | none | none | PhCl | RB[e] | 0 |
| 25[f] | none | none | PhCl | DBPO | 0 |
| 26[f] | none | none | PhCl | AIBN | 0 |




[a] NMR yields; internal standard: dimethylsulfone. [b] The reaction was performed at 70 °C. [c] Isolated yields. [d] 1.0 equiv of TEMPO was used. [e] The reaction was performed under 1 atm of $O_2$. [f] 10 mol% of additive was used. TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl; RB = rose bengal; DBPO = di-*tert*-butyl peroxide; AIBN = azobis(isobutyronitrile).

As a starting point, we examined the oxidative C–C-bond cleavage[17] of 2-phenylcyclohexanone (**1a**) at ambient temperature in air (Table 1). Various phenol and naphthol derivatives were employed as electron donors to reduce the azolium-based electron acceptor (**4a·TfOH**)[14b] (entries 1–5). To our delight, when 2-naphthol (**3a**) was used as an electron donor, the C–C cleavage product **2a** was obtained as a single product, albeit in low yield (entry 1). Unlike in previous related reactions,[16] the α-hydroxylated product was not detected. Interestingly, the use of 1,1′-bi-2-naphthol (**3b**) drastically improved the yield of the desired product (entry 2), although bis-phenol (**3c**) clearly suppressed the yield (entry 3). Catechol (**3d**) and hydroquinone (HQ, **3e**) were found to be effective co-catalysts, and gave the desired product in 42% and 57%, respectively (entries 4 and 5). Thus, the more inexpensive and readily available **3e** was chosen as the co-catalyst. Next, we investigated the electron acceptor (entries 6–15). The 2-iodoimidazolium catalyst **4b·TfOH** showed similar reactivity to the 2-chloro derivative **4a·TfOH** (entry 6). Interestingly, an azolium-based catalyst without a halogen atom at the C2 position (**4c·TfOH**) showed higher reactivity in this reaction, and **2a** was obtained in 77% yield (entry 7).[18] Moreover, the azolium salts **4d·TfOH**–**4f·TfOH**, which bear other substituents at the C2 position, furnished **2a** in 75–76% yield (entries 8–10). Among the electron acceptors screened, we selected **4c·TfOH** as the optimal co-catalyst based on its synthetic advantages, given that it can be readily synthesized in two steps from inexpensive commercial reagents.[14b] The expanded π-scaffold of the azolium salts seems to be important, as the use of benzimidazolium salt **4g·TfOH** furnished **2a** in lower yield, while imidazolium salt **4h·TfOH** did not afford the desired product at all (entries 11 and 12). We then examined the effect of the substituents on the aromatic ring at the *N*1 position (entries 13, 14). When the trifluoromethyl group was replaced with an *n*-octyl group (**4i·TfOH**), the reaction did not occur, and **1a** was fully recovered (entry 13). Surprisingly, the catalyst with a *meta*-trifluoromethyl phenyl group (**4j·TfOH**) did not promote the reaction at room temperature (entry 14). These results, as well as an additional catalyst screening[19] (Table S1 and Figure S1) suggest that the substituents play an important role in enhancing the complexation with the co-catalysts and/or the reduction of the azolium salt (*vide infra*). The non-protonated catalyst **4c** did not induce any reaction (entry 15), implying that the electron-deficiency of the catalyst is of crucial importance. Amongst the solvents investigated, non-polar solvents such as toluene and chlorobenzene afforded better results (entries 16–19). Based on the solubility of the catalysts, chlorobenzene was chosen as the optimal solvent for subsequent experiments (entry 19). Next, we performed a series of control experiments (entries 20–26). The use of HQ or **4c·TfOH** alone did not promote the reaction (entries 20–21), suggesting that both catalysts are necessary to generate radical species to react with molecular oxygen. When 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was added, the reaction was completely inhibited (entry 22). The reaction proceeded in the dark (entry 23), and the use of rose bengal as a photosensitizer instead of the catalysts did not give the desired product even under an atmosphere of pure oxygen (entry 24), clearly indicating that the substrate reacts with triplet oxygen through a radical mechanism. Notably, radical initiators such as di-*tert*-butyl peroxide (DBPO) and azobis(isobutyronitrile) (AIBN) (*cf.* Table

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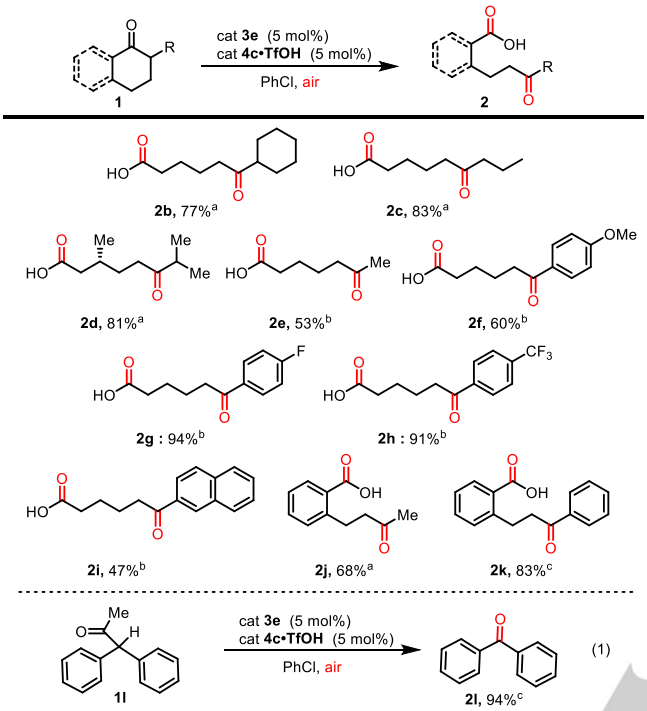
S2)[18] did not afford any product (entries 25 and 26). These results imply that **3e** or **4c·TfOH** function as radical catalysts rather than radical initiators.[20]




a) The reaction was conducted at 50 °C for 24 h. b) The reaction was conducted at 60 °C for 48 h. c) The reaction was conducted at 50 °C for 48 h.

**Figure 1.** Substrate scope

With the optimized conditions in hand, we then investigated the substrate scope of the oxidative C–C bond cleavage reaction (Figure 1). 2-Alkyl-substituted cyclohexanones (**1b–d**; R = *c*-hex, *n*-Pr, *i*-Pr) gave the corresponding 6-oxo-carboxylic acids (**2b**–**d**) in 77–83% yield, although heating at 50 °C was needed for the reaction to proceed at a reasonable rate. 2-Methylcyclohexanone (**1e**, R = Me) was fully consumed under the applied reaction conditions, and 6-oxoheptanoic acid (**2e**) was obtained in 53% yield.[21] We next investigated the reaction of several different 2-arylcyclohexanones (**1f–i**) in order to evaluate the electronic effect of the substituent at the C2 position. The oxidative C–C-bond cleavage of 2-(*p*-methoxyphenyl)cyclohexanone (**1f**, R = 4-$MeOC_6H_4$) required high temperature to afford the corresponding product. Interestingly, the reactions of 2-arylcyclohexanes that bear electron-deficient arenes (**1g**, **1h**) or a naphthyl group (**1i**) also required heating. Notably, the products with electron-withdrawing groups (**2g** and **2h**) were obtained in excellent yield, presumably due to the absence of undesired SET between the electron-deficient aromatic ring of the catalyst and the substrates/products. α-Substituted tetralones (**1j–k**; R = Me, Ph) are also good substrates for the oxidative C–C-bond cleavage reaction, affording the corresponding products (**2j** and **2k**) in good yield. The acyclic substrate 1,1-diphenylacetone (**1l**) afforded benzophenone (**2l**) in excellent yield.

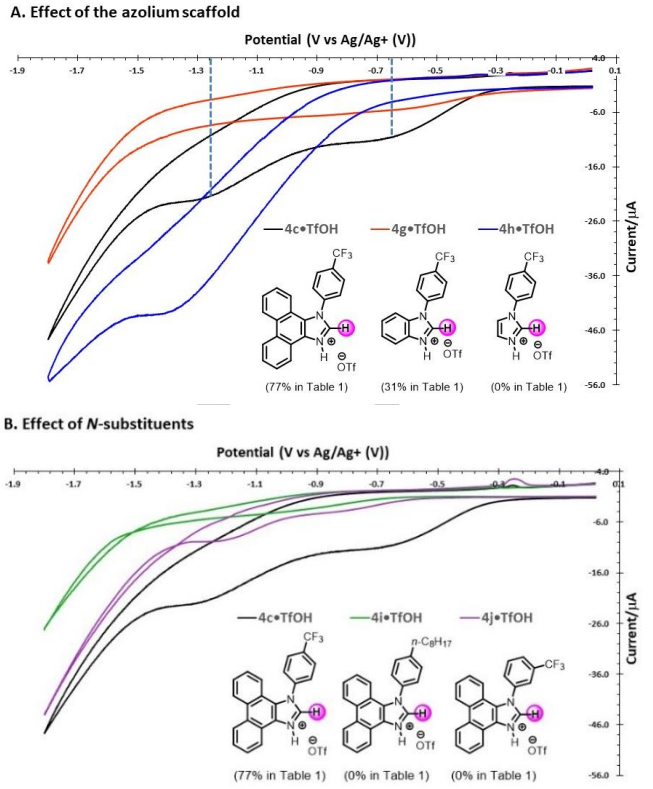



**Figure 2.** Cyclic voltammograms of solutions of the catalysts in $CH_2Cl_2$ + [(*n*-Bu)$_4$N][$BF_4$] 0.02 M (carbon electrode; Φ = 3 mm; scan rate: 100 mV $s^{-1}$; *E* vs $Ag/Ag^+$) **A**. Effect of the azolium scaffold **B**. Effect of the *N*-substituents.

To gain information concerning the SET between the catalysts, we conducted cyclic voltammetry (CV) measurements and evaluated the effect of the substituents on the reduction potential of the catalysts (Figure 2).[22,23] The CV of the best catalyst (**4c·TfOH**) showed an irreversible peak corresponding to a single-electron reduction at E = ca. –0.7 V vs $Ag/Ag^+$ (current peak: ca. –10 μA) and a second irreversible peak at E = ca. –1.3 V vs $Ag/Ag^+$ (Figure 2A; black line). In contrast, the CV of the benzimidazolium salt **4g·TfOH** showed a single irreversible peak at almost the same reduction potential (E = ca. –0.5 V) with a lower current peak (ca. –5 μA) and a second peak was not observed (Figure 2A, orange line). This result suggests that the reduction of **4c·TfOH** is faster than that of **4g·TfOH**, and that the radical species generated from **4c·TfOH** are more stable than those of **4g·TfOH**. The imidazolium salt **4h·TfOH** showed a lower reductive potential (E = ca. –1.4 V) (Figure 2A; blue line). This result suggests that the expanded π-scaffold of **4c·TfOH** and **4g·TfOH** is important for improving the susceptibility toward oxidation of the catalysts, which explains the higher reactivity of **4c·TfOH** and **4g·TfOH** in solution compared to that of **4h·TfOH**. In addition, the non-protonated catalyst precursor **4c** showed a lower reductive potential (E = ca. –1.5 V) (Figure S2), indicating that the protonation of azole **4c** is important in order to modify its electronic properties to allow it to accept a single electron from electron donor **3**. Next, we measured the CVs of **4i·TfOH** and **4j·TfOH**, which carry different substituents on the *N*-aryl group at the *N1*-position (Figure 2B). **4i·TfOH** showed a lower reductive

potential (E = ca. –0.9 V) and current peak (ca. –3 μA) (Figure 2B; green line), implying that the electron-withdrawing group is important to improve the susceptibility toward the reduction of the azolium catalyst. The CV curve of the catalyst with a *meta*-$CF_3$ group (**4j·TfOH**) was similar to that of **4c·TfOH** (Figure 2B, purple line), but its reductive potential and current peak were lower than those of **4c·TfOH**. Natural bond orbital (NBO) analyses clearly suggested the interaction between the lowest unoccupied molecular orbitals (LUMO) of **4c·TfOH** and the highest occupied molecular orbitals (HOMO) of HQ in the **4c·TfOH/**HQ complex (Figure S9-S11), and the interaction would promote the SET from HQ to **4c·TfOH**.

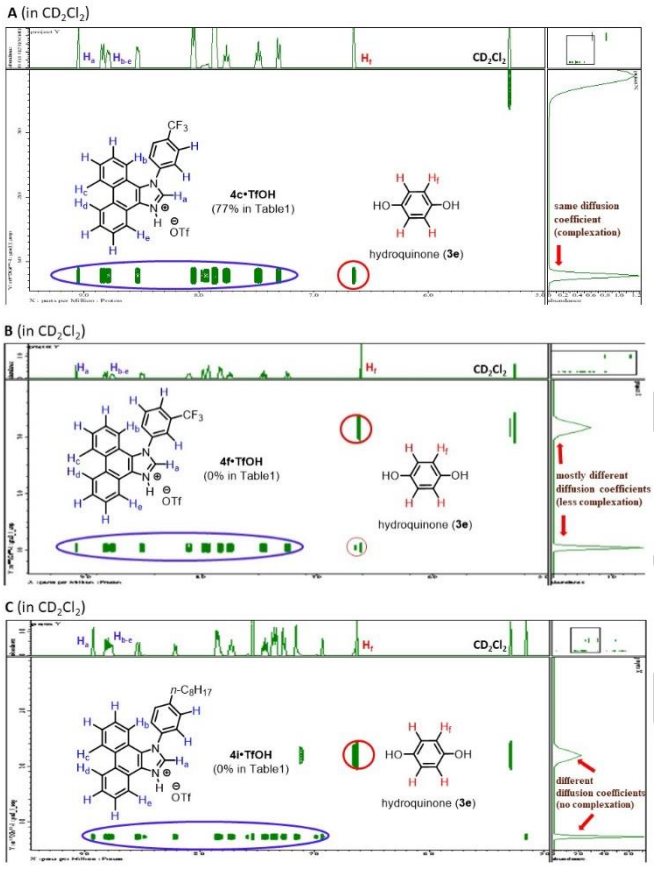



**Figure 3.** DOSY experiments: A) **3e** and **4c·TfOH** (1:1, 0.012 M) in $CD_2Cl_2$; B) **3e** and **4f·TfOH** (1:1, 0.012 M) in $CD_2Cl_2$; C) **3e** and **4i·TfOH** (1:1, 0.012 M) in $CD_2Cl_2$.

Finally, diffusion-ordered spectroscopy (DOSY) NMR measurements[24,25] of catalysts **3** and **4** (1:1, 0.012 M) were recorded in $CD_2Cl_2$ in order to gain further information regarding the complexation between the catalysts (Figure 3). A solution of **4c·TfOH** and HQ (**3e**) showed that the peaks corresponding to each compound exhibit the same diffusion coefficient (Figure 3A), which strongly suggests their complexation in solution. In sharp contrast, the components of inactive catalyst combinations, such as **4i·TfOH/**HQ and **4j·TfOH/**HQ, showed different diffusion coefficients (Figure 4B, 4C), indicating less or no complexation in solution. Such complexation would greatly increase the probability of **4c·TfOH** to undergo SET with **3e** (Scheme 1c).[26]

In conclusion, we have developed a radical co-catalytic system that consists of an azolium salt and hydroquinone. Detailed mechanistic studies revealed that the scaffold as well as the *N*-substituent of the best catalyst (**4c·TfOH**) play important roles in the context of complex formation and electron transfer from the donor. In addition, the triflic acid moiety was found to trigger the generation of radical species from the complex in our catalytic system. This report thus offers a new method to generate radical species via the combination use of two different organocatalysts; notably, unlike in the case of electron-donor–acceptor (EDA) complexes, photo-activation is not required. We are convinced that this report represents a milestone on the road to maturation of organo-radical catalysis, which is still in its infancy.

## Experimental Section

To a stirred solution of 2-phenylcyclohexanone **1a** (30.0 mg 0.172 mmol) in chlorobenzene (1.0 mL), were added hydroquinone (1.0 mg, 5 mol %) and **4c·TfOH** (4.4 mg, 5 mol %), respectively, and the reaction mixture was stirred at ambient temperature for 24 h under aerobic condition. After water was added to the mixture, the resulting mixture were extracted with $CHCl_3$ three times, and the combined organic layer was concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (Fuji Silysia COOH silica gel) or preparative thin layer chromatography to afford the desired product **2a** (33.0 mg, 93%).

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**Keywords:** radical catalysis • EDA complex • azolium salt • organocatalysis

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[18] In our previous report on the direct glycosylation of amides, halogenated catalysts gave exceptionally better results than non-substituted ones: see ref. 14.

[19] For details, see the Supporting Information.

[20] Possible reaction mechanisms are discussed in the Supporting Information (Figure S8).

[21] We could not observe any byproducts, and the somewhat lower yield could be due to an ineffective extraction step.

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[26] An alternative mechanism for the aerobic C–C-bond cleavage (Figure S13) are described in the Supporting Information.

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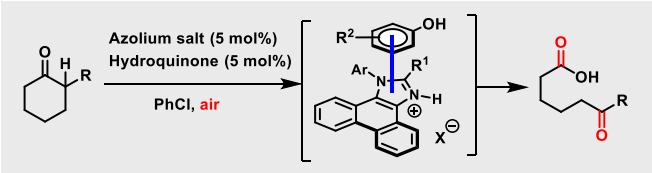


*Yuya Nakatsuji, Yusuke Kobayashi, Sakyo Masuda, and Yoshiji Takemoto**

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**Azolium/hydroquinone organo-radical co-catalysis: Aerobic C–C-bond cleavage in ketones**

A new method for the generation of radical species that does not require photoirradiation, radical initiators, or preactivated substrates is reported. The combination use of an azolium salt and hydroquinone (HQ) generated an efficient catalytic system for the aerobic C–C-bond cleavage of 2-substituted ketones. A reaction mechanism is proposed based on the results of diffusion-ordered spectroscopy (DOSY) and CV measurements, as well as computational studies.