Air Oxidation of 2-Aryl-1-tetralones in Basic, Neutral, and Acidic Media: An Unprecedented Oxidative Aryl Migration to 2-Aryloxy-1-naphthols under Acidic Condition

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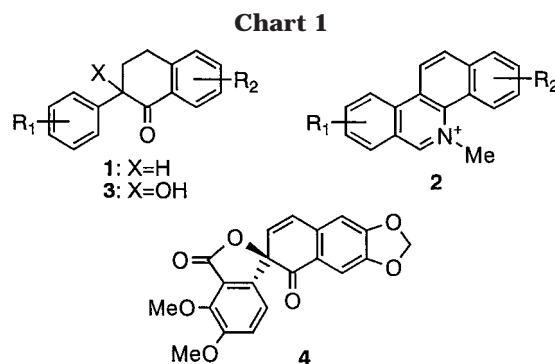
Introduction

2-Aryl-1-tetralones **1** are key intermediates in the synthetic scheme of benzophenanthridine bases **2** developed by us.[1] A corresponding 2-aryl-2-hydroxytetralone **3** also acts as a synthetic precursor for arnottin II (**4**)[2], a spirolactone compound biogenetically related to the benzophenanthridine bases (Chart 1). It is well-known that the α-position of carbonyl groups in aldehydes or ketones can be easily oxidized with molecular oxygen (O₂) under strongly basic conditions to give the corresponding α-hydroxycarbonyl compounds.[3] Thus, basic air oxidation of 2-aryl-1-tetralones **1** gave expected 2-hydroxytetralones **3** (route A in Scheme 1). However, benzoic acid derivatives **5** were obtained as oxidation products when **1** was treated with neutral triethylamine trihydrofluoride complex (Et₃N·3HF)[4] (route B in Scheme 1). On the other hand, heating **1** in benzene or toluene in the presence of *p*-toluenesulfonic acid (TsOH) unexpectedly afforded arylmigrated 2-aryloxy-1-naphthols **6** as main products, together with aromatized products of 2-aryl-1-naphthols **7** and benzoic acids **5** (route C in Scheme 1). In this paper we present not only the product distribution dependent upon the conditions used (basic, neutral, and acidic conditions) in air oxidation of 2-aryl-1-tetralones **1** but also the unprecedented production of 2-aryloxy-1-naphthols **6** through oxidative aryl migration under acidic condition.

Results and Discussion

Air Oxidation under Basic and Neutral Media. In the synthetic study of arnottin II (**4**)[2] it was found that a 2-benzofuranyl-1-tetralone (**1a**)[1,5] in DMF could be easily oxidized by air in the presence of sodium hydride (NaH) to produce the corresponding 2-hydroxy derivative **3a** in 79% yield. Reexamination of this basic air oxidation resulted in improving the yield (91%) (run 1 in Table 1). It is known that a fluoride anion derived from the
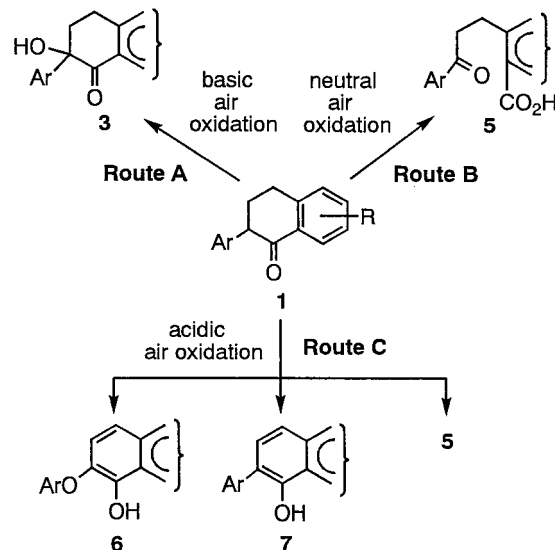
[†] Faculty of Pharmaceutical Sciences.
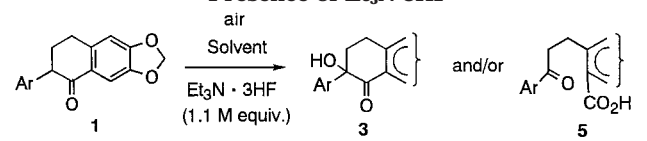[‡] Chemical Analysis Center.
(1) Ishii, H.; Ishikawa, T.; Takeda, S.; Suzuki, M.; Harayama, T. *Chem. Pharm. Bull.* **1992**, *40*, 2002−2006 and references therein.
(2) Ishikawa, T.; Murota, M.; Watanabe, T.; Harayama, T.; Ishii, H. *Tetrahedron Lett.* **1995**, *36*, 4269−4271.
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Chart 1

Scheme 1

Table 1. Basic Air Oxidation of a 2-Aryl-1-tetralones 1

run	1 (Ar)	bases (M equiv.)	time (h)	3[a] (%)
1	**1a**	NaH (1.5)	2.5	91
2	**1a**	TBAF (1.3)	1.0	83
3	**1b**	NaH (1.5)	1.2	78
4	**1b**	TBAF (1.1)	0.5	71

[a] Isolated, but not optimized yields.

corresponding salts such as cesium fluoride (CsF)[6] or tetrabutylammonium fluoride (TBAF)[7] acts as a base. Thus, the same oxidation product **3a** was obtained when TBAF (run 2 in Table 1) was used as a base in place of NaH.[8] These conditions were also applicable to the production of a 2-hydroxytetralone (**3b**) from a trimethoxy tetralone (**1b**)[9] (runs 3 and 4 in Table 1).

On the other hand, Et₃N·3HF is known as a noncorrosive and neutral equivalent of HF.[4] Next, our attention
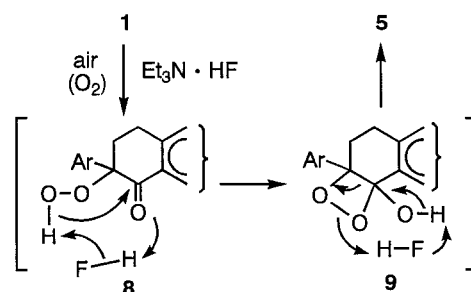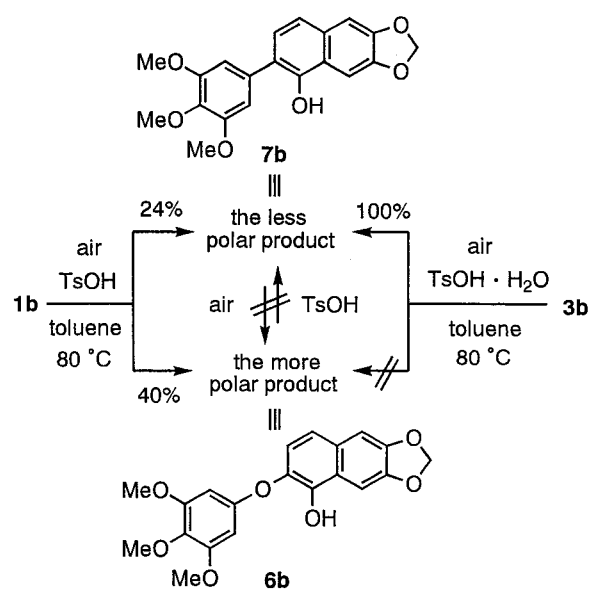
Table 2. Air Oxidation of 2-Aryl-1-tetralones 1 in the Presence of Et₃N·3HF

run	1 (Ar)	Sol[a]	(EtO)₃P (M equiv.)	temp. (°C)	time (h)	products[b] (%) 3	products[b] (%) 5
1	**1b** (MeO, MeO, MeO)	DMF	–	70	27	–	62
2	**1c** (iPrO, MeO)	DMF	–	60	50	–	71
3		DMF	2.0	60	48	NR[c]	
4		THF	–	reflux	24	46	8

a Solvent. *b* Isolated, but not optimized yields. *c* No reaction.

was paid to this complex as an alternative fluoride base (Table 2). Treatment of a trimethoxy tetralone (**1b**) in DMF with Et₃N·3HF at 70 °C afforded a benzoic acid derivative (**5b**) as a sole product (62% yield) produced through oxidative cleavage between the C_1-C_2 bond (run 1 in Table 2). A similar cleaved product (**5c**) was also given in 71% yield when an isopropoxy tetralone (**1c**)[10] was treated under the same condition (run 2 in Table 2). However, the co-presence of triethyl phosphite [(EtO)₃P] resulted in complete recovery of the starting **1c** (run 3 in Table 2).[11] The use of THF in place of DMF as a solvent led to the formation of a 2-hydroxytetralone (**3c**) along with the cleaved product **5c** (run 4 in Table 2). The oxidative cleavage observed here could be reasonably explained by the HF-mediated ring-opening of a hydroxy-endoperoxide intermediate (**9**), which is yielded by attack of HF to an α-hydroperoxyketone (**8**), as shown in Scheme 2 (also see paths C and D in Scheme 5).

Air Oxidation Under Acidic Medium. Finally acidic air oxidation was investigated for comparison. Heating a trimethoxy tetralone (**1b**) in toluene at 80 °C in the presence of a catalytic amount (0.3 M equiv) of an anhydrous TsOH afforded two weakly acidic products showing close R_f values in TLC (ethyl acetate: hexane 4:1), which were not convertible to each other under the same condition used. The less polar product was isolated as colorless needles, mp 211−213 °C, whereas the more polar one as colorless prisms, mp 185−187 °C, in 24 and 40% yields, respectively (see Supporting Information). The former product was determined to be a 2-aryl-1-

(6) For example, see: Clark, J. H.; Holland, H. L.; Miller, J. M. *Tetrahedron Lett.* **1976**, 3361−3364. We have also observed the effectivity of CsF as a base in some organic reactions: Ishikawa, T.; Mizutani, A.; Miwa, C.; Oku, Y.; Komano, N.; Takami, A.; Watanabe, T. *Heterocycles* **1997**, *45*, 2261−2272. Ishikawa, T.; Oku, Y.; Kotake, K.-I.; Ishii, H. *J. Org. Chem.* **1996**, *61*, 6484−6485. Ishikawa, T.; Nagai, K.; Ohkubo, N.; Ishii, H. *Heterocycles* **1994**, *39*, 371−380. Ishii, H.; Ishikawa, T.; Takeda, S.; Ueki, S.; Suzuki, M. *Chem. Pharm. Bull.* **1992**, *40*, 1148−1153.
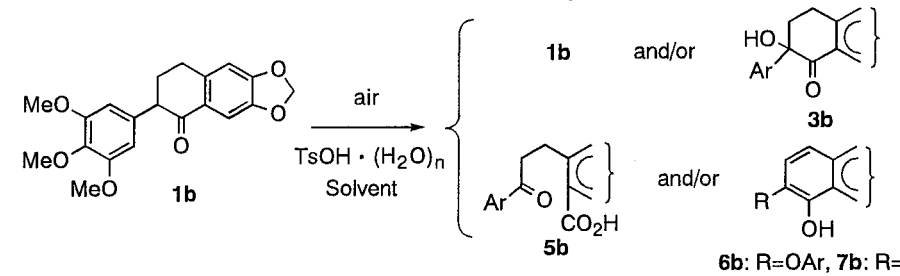
(7) For example, see: Kuwajima, I.; Murofushi, T.; Nakamura, E. *Synthesis* **1976**, 602−604.

(8) We have examined basic air-oxidation using various weak bases including CsF. The results will be reported elsewhere.

(9) Ishii, H.; Kawanabe, E.; Harada, K.-I.; Deushi, T.; Ueda, E.; Watanabe, T.; Ichikawa, Y.-I.; Sakamoto, M.; Ishida, T.; Takahashi, T.; Nakajima, K.; Ishikawa, T. *Chem. Pharm. Bull.* **1983**, *31*, 3039−3055.

(10) Ishii, H.; Chen, I.-S.; Masuda, T.; Morita, K.; Ishikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2415−2420.

(11) Although trialkyl phosphites are often used for the in situ reductive cleavage of the O−O bond in a hydroperoxy function, (EtO)₃P acted as an O₂ scavenger under this condition.

Scheme 2

Scheme 3

naphthol (**7b**) by the spectral data in addition to the chemical evidence that it was quantitatively given by treatment of a 2-hydroxy-1-tetralone (**3b**), easily derived from **1b** by basic air oxidation, with a hydrated TsOH (TsOH·H₂O).

On the other hand, the MS and the elemental analysis of **6b** showed that it corresponded to a further oxidized product [m/z 370 (M⁺, $C_{20}H_{18}O_7$)] carrying one more oxygen atom than **7b** ($C_{20}H_{18}O_6$). A hydroxy absorption band (3420 cm⁻¹) was shown in the IR spectrum but no carbonyl absorption. No aliphatic protons except methoxy and methylenedioxy functions were observed in the ¹H NMR spectrum. Instead, a pair of doublets due to aromatic protons with ortho coupling ($J = 8.8$ Hz) was newly born at δ 6.99 and 7.20. These data allowed us to deduce it as a 2-aryloxy-1-naphthol **6b** (Scheme 3). However, there are no reports on an aerobic oxidation of the α-position of a carbonyl group under acidic conditions to our knowledge. Thus, we finally established the aryl-migrated structure of **6b** by X-ray analysis (see Supporting Information).

Next we examined in detail the TsOH-induced air oxidation of a trimethoxy tetralone (**1b**) under various conditions using ¹H NMR spectra (Table 3). Although the reaction under the condition described above (at 80 °C in toluene) gave **6b** and **7b**, a benzoic acid (**5b**) was found to be additionally produced. The products ratio of them was estimated to be **6b:7b:5b** = 48:26:26 (run 1 in Table 3). Either the use of TsOH·H₂O in benzene (run 2 in Table 3) or the reaction in the dark (run 3 in Table 3) led to nearly same results as run 1, indicating that the

Table 3. Examination of the Oxidation of a Trimethoxy Tetralone (1b) under Acidic Conditions

run	TsOH · (H₂O)ₙ (0.3 M equiv.)	Sol[a]	temp. (°C)	time (h)	Ar[b]	light	additive	products ratio[c]				
								1b	3b	5b	6b	7b
1	n=0	toluene	80	22	-[d]	+[e]	-	0	0	26	48	26
2	n=1	benzene	80	24	-[d]	+[e]		0	0	20	60	20
3	n=0	benzene	80	22	-[d]	-	-	0	0	23	59	18
4	n=0	benzene	80	22	+	+[e]	-	100	0	0	0	0
5	n=1	benzene	80	22	-[d]	+[e]	(MeO)₃P	84	0	8	8	0
6	n=0	toluene	130	22	-[d]	+[e]	-	100	0	0	0	0
7	n=0	toluene	130	22	-[d]	-	-	97	0	0	2	1
8[f]	n=1	benzene	rt	120	-[d]	+[e]	-	5	68	12	7	5
9	n=1	benzene	rt	120	-[d]	-	-	7	69	14	7	3

[a] Solvent. [b] Argon. [c] The products ratio was determined by ¹H NMR. [d] The reaction was done in an open flask without any degassed treatment. [e] The reaction was carried out using pyrex glass without protection of light. [f] 4-Hydroxy-3-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-naphthoquinone was additionally formed in 3% yield (the spectral data in Supporting Information).

oxidation profile was not affected by H₂O, light, or solvent. On the other hand, the oxidation was greatly suppressed either under strictly anaerobic condition (argon-bubbling during the reaction) (run 4 in Table 3) or in the presence of trimethyl phosphite [(MeO)₃P][11] (run 5 in Table 3). These facts strongly suggested the participation of O₂. Interestingly, although the reaction under reflux (at 130 °C in toluene) resulted in complete recovery of the starting material (runs 6 and 7 in Table 3), a 2-hydroxytetralone (3b) was given as a main product when the reaction was carried out at room temperature (rt) for a long time (120 h) (runs 8 and 9 in Table 3), indicating that the reaction temperature controls the reaction course. Although it is reported that the solubility of O₂ to benzene increases as temperature is higher in a range of 10−60 °C,[12] heating at 130 °C without additional supply of O₂ may cause the low concentration of O₂ in the reaction mixture.

A corresponding 2-aryloxy-1-naphthol (6a) was also found to be formed by treatment of a benzofuranyl tetralone (1a) under the similar condition described in run 2 in Table 3. However, no rearrangement was observed in the case of 2-phenyl-1-tetralone (1d),[13] instead a benzoic acid derivative (5d)[14] was obtained as a sole product (see Supporting Information) (Scheme 4). Thus, substituents on the 2-aryl group in 1 should be responsible for the oxidative aryl migration.

A longer reaction time (120 h) was needed for the acidic air oxidation of 2-phenyl-1-tetralone (1d) than for that

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(13) Stille, J. K.; Newsome, R. A. *J. Org. Chem.* **1961**, *26*, 1375−1379.
(14) Hauser, C. R.; Swamer, F. W.; Ringler, B. I. *J. Am. Chem. Soc.* **1948**, *70*, 4023−4026.

Scheme 4
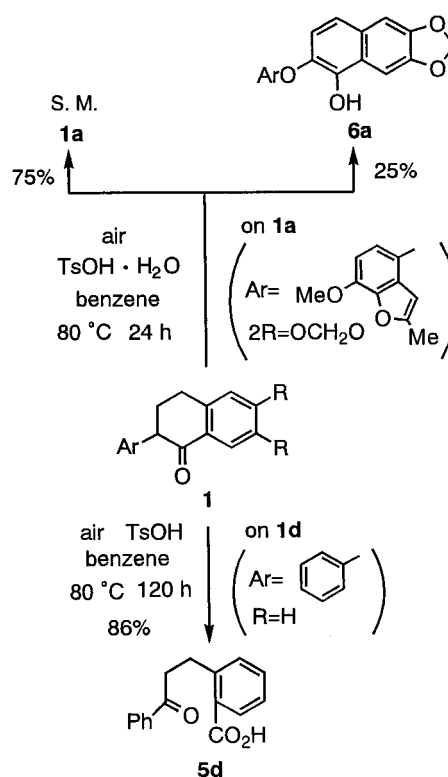
of the trimethoxy tetralone 1b (ca. 24 h). It had been reported that the aromatic protons on 3,4,5-trimethoxytoluene were easily exchanged with deuterium under acidic conditions.[15] We also observed the complete disappearance of the aromatic protons on the 3,4,5-trimethoxyphenyl ring when the ¹H NMR spectrum of 1b was

Scheme 5
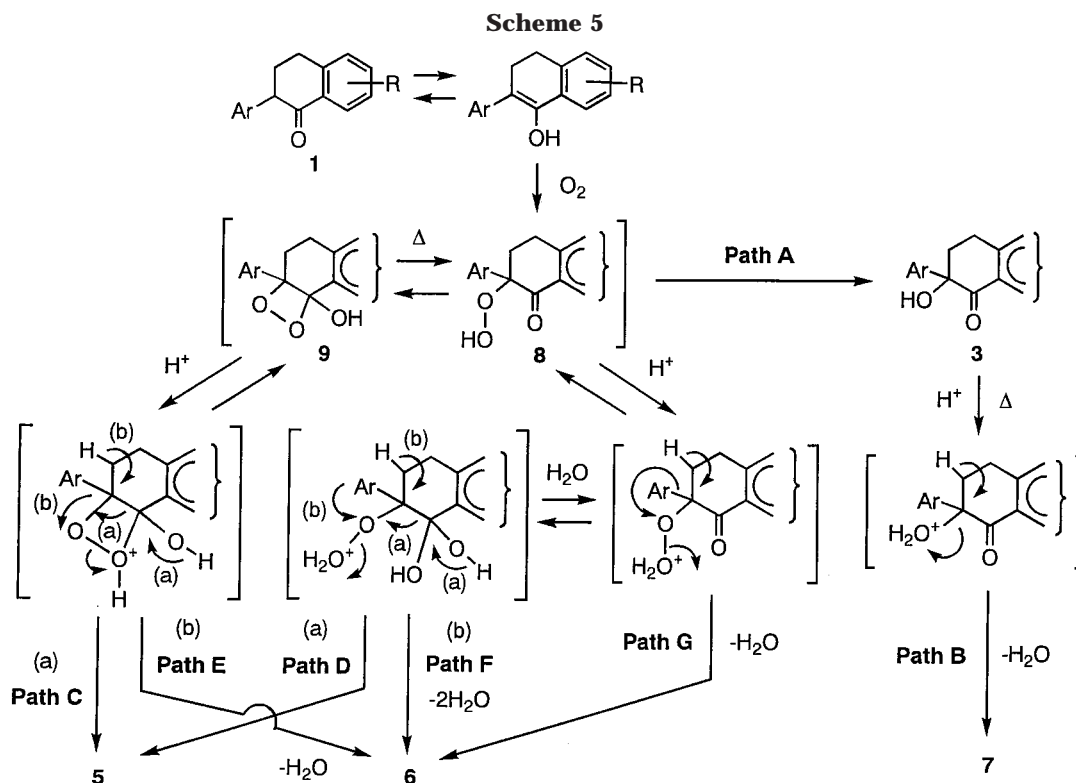
measured in CF_3COOD. This fact suggests that an electron-rich 3,4,5-trimethoxyphenyl substituent can be protonated even with TsOH and acts as an electron-deficient group under the acidic condition. Acidic air oxidation of 2-aryl-1-tetralones would be initiated by action of O_2 to their enol forms present (see Scheme 5). The ratio of keto and enol tautomers is influenced by the acidity of the 2-proton and it is expected that the presence of more acidic proton increases the relative concentration of the enol form. Thus, the electron poorness of the protonated trimethoxyphenyl group in **1b** under acidic conditions causes to increase the acidity of the 2-proton, resulting in leading to easier oxidation than in the case of 2-phenyl-1-tetralone (**1d**).

Proposed Mechanism for the Acidic Air Oxidation. Experimental facts on the acidic air oxidation described above are summarized as follows: (i) O_2 in air causes oxidation, (ii) strictly anhydrous condition was not needed for the oxidation, (iii) the oxidation is not affected by light, (iv) the reaction temperature is crucial for the products distribution, that is, α-hydroxylation occurs at room temperature; oxidative aryl migration mainly at ca. 80 °C; no reaction at 130 °C, and (v) an electron-rich aryl substituent is necessary for the migration at 80 °C. On the basis of these we proposed a plausible mechanism for the acidic air oxidation of 2-aryl-1-tetralones **1** (Scheme 5).[16]

The enols of **1** produced under the acidic condition are reacted with O_2 to give α-hydroperoxytetralones **8**. At lower temperature hydroxytetralones **3** are slowly produced as main products by reduction of the hydroperoxy function in **8** (path A in Scheme 5). The hydroxytetralones **3** are further changed into 2-aryl-1-naphthols **7** after

protonation through dehydration followed by aromatization, when the reaction is effected at higher temperature (at 80 °C) (path B in Scheme 5). The hydroperoxytetralones **8** must be in equilibration to hydroxyendoperoxides **9** at the higher temperature and they were easily protonated. Benzoic acid derivatives **5** could be given by the C_1–C_2 bond cleavage of either the endoperoxide ring[17] (path C in Scheme 5) or hydrated hydroperoxy derivatives (path D in Scheme 5).[18] Furthermore, in the case of electron-rich tetralones the 2-aryl group in three possible intermediates can migrate to an adjacent oxygen atom with dehydration through Baeyer–Villiger-type rearrangement, giving 2-aryloxy-1-naphthols **6** after aromatization (paths E, F, and G in Scheme 5).

Conclusion

As mentioned above we observed that 2-aryl-1-tetralones **1** were susceptible to air to give different oxidation products dependent upon the reaction media used. In general carbonyl compounds are stable to air under acidic conditions, although a hydrogen bromide-catalyzed oxygenation of hydrocarbons in a gaseous phase[19] had been reported. Therefore it would be interesting that TsOH is able to promote the air oxidation of 2-aryl-1-tetralones **1** under a relatively mild condition. Furthermore, it should be noted here that oxidative aryl migration is a main path in this case.

(15) Banijamali, A. R.; Charalambous, A.; Van der Schyf, C. J.; Makriyannis, A. *J. Labeled Compd. Radiopharm.* **1987**, *24*, 1479–1482.

(16) To simplify the discussion, additional pathways and intermediates, arising from hydration of the ketone carbonyls of **3** and **8**, are excluded from the proposed mechanism in Scheme 5.

(17) It is known that endoperoxides generate light during their concerted decomposition under basic conditions. Although no chemical luminescence was observed in our reactions, we supposed the pathway through endoperoxides **9** as a possible route because of different acidic condition used in our case.

(18) Ogata et al. reported the acyclic mechanism such as path D in Scheme 5 for the alkaline decomposition of α-hydroperoxy ketones as a main path, but alternative cyclic one such as path C in Scheme 5 was also suggested by other group (Sawaki, Y.; Ogata, Y. *J. Am. Chem. Soc.* **1975**, *97*, 6983–6989 and references therein).

(19) Rust, F. F.; Vaughan, W. E. *Ind. Eng. Chem.* **1949**, *41*, 2595–2597.

The industrial preparation of phenol from cumene has been well established as a cumene method,[20] in which a final step is a Baeyer–Villiger-type rearrangement of cumene hydroperoxide triggered by acid. The oxidative aryl migration in the acidic air oxidation of 2-aryl-1-tetralones **1** to 2-aryloxy-1-naphthols **6** observed here can be basically classified into the category of cumene hydroperoxide rearrangement. However, a key intermediate hydroperoxide for the rearrangement in cumene method has been prepared by an aerobic oxidation of a benzylic position in the presence of a radical initiator such as light. Thus, to our knowledge this is the first example of oxidative aryl migration[21] in the acidic air oxidation of ketonic compounds without any initiators.

Experimental Section

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with tetramethylsilane as the internal reference. Columns for chromatography contained silica gel 60 (70–230 mesh ASTM; Merck), and TLC proceeded on silica gel GF$_{254}$ (Merck). All solvents were distilled over drying agent before use. THF was distilled under Ar from the sodium-benzophenone ketyl. TBAF was prepared from tetrabutylammonium hydroxide by the reported method.[7]

Basic Air Oxidation. General Procedure. (a) With NaH. To a solution of the tetralone **1** in DMF (0.017 g/mL for **1a**; 0.058 g/mL for **1b**) was added NaH (dispersion in mineral oil, 1.5 M equiv), and the whole was stirred at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over K$_2$CO$_3$, and evaporated to dryness in vacuo to give the 2-hydroxytetralone **3** after recrystallization.

(b) With TBAF. A solution of the tetralone **1** (0.14 mmol) in DMF (2.5 mL) was added to the base (1.2–1.3 M equiv), and the whole was stirred at room temperature under Ar atmosphere. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over MgSO$_4$, and evaporated to dryness in vacuo. The residue was recrystallized to afford **3**.

Air Oxidation with Et$_3$N·3HF. General Procedure. To a solution of the tetralones **1b** or **1c** (0.14–0.28 mmol) in THF or DMF (0.5–2 mL) was added Et$_3$N·3HF (1.1 M equiv), and the whole was heated at the temperature cited in Table 2. The same workup as in the basic oxidation followed by purification by preparative TLC gave **3** and/or **5**.

Air Oxidation with TsOH or TsOH·H$_2$O. General Procedure. To a solution of TsOH·H$_2$O (0.3 M equiv) in benzene (20 mL) or anhydrous TsOH [prepared from TsOH·H$_2$O (0.3 M equiv) in benzene or toluene (20 mL) by refluxing for 1 h in Dean–Stark apparatus] was added the tetralone **1** (1.00 mmol), and the whole was stirred at the temperature cited in Table 3. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over MgSO$_4$, and evaporated to dryness in vacuo. The residue was purified with column chromatography using hexane–AcOEt (2:1) as eluent.

Supporting Information Available: Full spectroscopic and analytical data for compounds **3a**–**c**, **5b**–**d**, **6a**,**b**, **7b**, and the naphthoquinone in the footnote of Table 3 and X-ray structure report for compound **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Schlecht, M. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, pp 815–836.