ORGANIC LETTERS

2004
Vol. 6, No. 20
3577–3580

Efficient Heterogeneous Oxidation of Alkylarenes with Molecular Oxygen

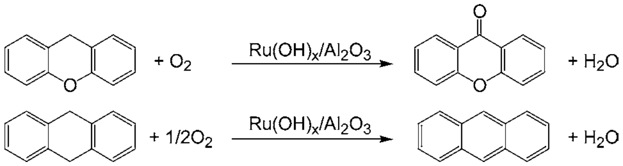
Keigo Kamata,[†] Jun Kasai,[‡] Kazuya Yamaguchi,[†, ‡] and Noritaka Mizuno*,[†, ‡]

Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, 4-1-8 Honcho, Kawaguchi, Saitama, 332-0012, Japan, and Department of Applied Chemistry, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8656, Japan

tmizuno@mail.ecc.u-tokyo.ac.jp

Received July 27, 2004

ABSTRACT



$Ru(OH)_x/Al_2O_3$ efficiently catalyzes the heterogeneous aerobic oxygenation or oxidative dehydrogenation of alkylarenes to give the corresponding oxygenated or dehydrogenated products. Catalyst/product separation is very easy, and the recovered catalyst is reusable with retention of the high catalytic performance.

The oxidation of alkylarenes has received much attention. For example, it has been reported that the polyacene derivatives can be applied to organic semiconductors and transistors[1] and that dehydrogenation of the corresponding alkylarenes is one of the most reliable candidates for the synthesis of polyacene derivatives among various synthetic procedures.[2] Since dehydrogenation of alkylarenes typically requires stoichiometric oxidation reagents and/or relatively forced reaction conditions,[3] alternative efficient procedures, i.e., catalytic aerobic oxidation systems, have been desired.[4] The development of the catalytic oxygenation of alkylarenes with molecular oxygen is also technologically and environmentally important. Although numerous catalytic systems using nitrous oxide,[5] sulfoxide,[6] and molecular oxygen in combination with reducing agents[7] or radical initiators[8] have been reported, there are only a few examples of such liquid-phase oxidation with molecular oxygen as the sole oxidant.[9] In addition, the use of solid or supported catalysts is more desirable because of their easy isolation from the products and recycling.[10] In these contexts, it is desirable to develop the heterogeneously catalyzed aerobic oxidation of alkylarenes with high turnover numbers under mild reaction conditions. We report in this paper the efficient heterogeneous aerobic oxygenation and oxidative dehydrogenation of alkylarenes catalyzed by $Ru(OH)_x/Al_2O_3$.

[†] Japan Science and Technology Agency.

[‡] The University of Tokyo.

(1) (a) Schön, J. H.; Kloc, Ch.; Bucher, E.; Batlogg, B. *Nature* **2000**, *403*, 408. (b) Dimitrakopoulos, C. D.; Purushothaman, S.; Kymissis, J.; Callegari, A.; Shaw, J. M. *Science* **1999**, *283*, 822. (c) Afzali, A.; Dimitrakopoulos, C. D.; Breen, T. L. *J. Am. Chem. Soc.* **2002**, *124*, 8812.

(2) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.

(3) (a) Nagano, T.; Yokoohji, K.; Hirobe, M. *Tetrahedron Lett.* **1984**, *25*, 965. (b) Wang, K.; Mayer, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 1470. (c) Lockwood, M. A.; Blubaugh, T. J.; Collier, A. M.; Lovell, S.; Mayer, J. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 225. (d) Takahashi, T.; Kitamura, M.; Shen, B.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 12876.

(4) (a) Tanaka, H.; Ikeno, T.; Yamada, T. *Synlett* **2003**, 576. (b) Nakamichi, N.; Kawabata, H.; Hayashi, M. *J. Org. Chem.* **2003**, *68*, 8272.

(5) (a) Ben-Daniel, R.; Neumann, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 92. (b) Hashimoto, K.; Tanaka, H.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2002**, 582.

(6) Khenkin, A. M.; Neumann, R. *J. Am. Chem. Soc.* **2002**, *124*, 4198.

(7) Maikap, G. C.; Guhathakurta, D.; Iqbal, J. *Synlett* **1995**, 189.

(8) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. *J. Org. Chem.* **1995**, *60*, 3934.

(9) (a) Khenkin, A. M.; Weiner, L.; Wang, Y.; Neumann, R. *J. Am. Chem. Soc.* **2001**, *123*, 8531. (b) Feldman, D.; Rabinovitz, M. *J. Org. Chem.* **1988**, *53*, 3779. (c) Matsushita, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **1999**, 265. (d) Holliday, R. L.; Jong, B. Y. M.; Kolis, J. W. *J. Supercrit. Fluids* **1998**, *12*, 255.

(10) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: London, 1998. (b) Sheldon, R. A. *Green Chem.* **2000**, *2*, G1. (c) Anastas, P. T.; Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11.

10.1021/ol0485363 CCC: $27.50

Table 1. Oxidation of Xanthene and 9,10-Dihydroanthracene with Molecular Oxygen by Various Catalysts[a]

		xanthene		9,10-dihydroanthracene	
entry	catalyst	conversion (%)	selectivity[b] (%)	conversion (%)	selectivity[c] (%)
1	$Ru(OH)_x/Al_2O_3$	>99	>99	>99	93
2	$Ru(OH)_3 \cdot nH_2O$	<1		37	92
3	RuO_2	<1		9	99
4	$RuCl_2(PPh_3)_3$	<1		<1	
5	$RuCl_2(DMSO)_4$	<1		58	90
6	$RuCl_2(bpy)_2$	<1		<1	
7	$RuCl_3 \cdot nH_2O$	<1		4	98
8	$[Ru_3O(OAc)_6(H_2O)_3](OAc)$	<1		<1	
9	K_2RuCl_6	<1		15	96
10	nPr_4NRuO_4	38	>99	9	82
11[d]	Al_2O_3	<1		<1	
12[d]	Al_2O_3 treated with NaOH	<1		<1	
13[e]	$Ru(OH)_3 \cdot nH_2O + Al_2O_3$	6	>99	6	54
14[e]	$RuCl_3 \cdot nH_2O + Al_2O_3$	3	>99	<1	
15[f]	$Pd(OH)_x/Al_2O_3$	2	>99	5	84
16[f]	$Rh(OH)_x/Al_2O_3$	2	>99	6	19
17[f]	$Pt(OH)_x/Al_2O_3$	1	>99	21	79
18[f]	$V(OH)_x/Al_2O_3$	<1		11	97
19[f]	$Fe(OH)_x/Al_2O_3$	<1		<1	
20[f]	$Cu(OH)_x/Al_2O_3$	2	>99	2	19

[a] Reaction conditions for xanthene: xanthene (1 mmol), catalyst (Ru: 2 mol %), $PhCF_3$ (6 mL), 373 K, 2 h, under 1 atm of molecular oxygen. Reaction conditions for 9,10-dihydroanthracene: 9,10-Dihydroanthracene (1 mmol), catalyst (Ru: 2 mol %), *p*-xylene (6 mL), 403 K, 4 h, under 1 atm of molecular oxygen. Conversion and selectivity were determined by GC with an internal standard. [b] Selectivity for xanthen-9-one. [c] Selectivity for anthracene. Anthraquinone and anthrone were formed as byproducts in some cases. [d] 80 mg. [e] Mixture of Ru catalyst (2 mol %) and Al_2O_3 (80 mg) was used. [f] Catalyst (metal: 2 mol %).

First, the catalytic activity for the oxidation of xanthene and 9,10-dihydroanthracene with 1 atm of molecular oxygen as the sole oxidant was compared with those of various catalysts (Table 1).[11] No oxidation proceeded in the presence of Al_2O_3 or Al_2O_3 treated with NaOH. The catalytic activity of $Ru(OH)_x/Al_2O_3$ was higher than those of other heterogeneous ruthenium catalysts such as $Ru(OH)_3 \cdot nH_2O$, RuO_2, and zerovalent Ru clusters and homogeneous ruthenium complexes. Under the same conditions, other supported transition metal hydroxide catalysts of Pd, Rh, Pt, V, Fe, and Cu were much less active. The catalytic activities of $Ru(OH)_3 \cdot nH_2O$ and Al_2O_3 or $RuCl_3 \cdot nH_2O$ and Al_2O_3 were lower than that obtained with $Ru(OH)_x/Al_2O_3$. The oxidation of xanthene in nonpolar *p*-xylene, trifluorotoluene, chlorobenzene, and toluene for 1 h gave xanthen-9-one yields of 80, 78, 77, and 72%, respectively, under the conditions in Table 1. The polar 1,4-dioxane, *N,N*-dimethylformamide, acetonitrile, and acetic acid were poor solvents.

When the oxidation of xanthene was carried out at 373 K in trifluorotoluene, a quantitative yield of xanthen-9-one was obtained after 2 h. After the oxidation, the $Ru(OH)_x/Al_2O_3$ could be easily separated from the reaction mixture by simple filtration. It was confirmed by inductively coupled plasma combined with atomic emission spectroscopy (detection limit of 7 ppb) that no ruthenium was present in the filtrate after the separation of the catalyst. Then, the filtrate was evaporated in vacuo, and the crude product was purified by recrystallization to give analytically pure white crystals of xanthen-9-one (92% isolated yield). Interestingly, the oxidation of xanthene was completely stopped by the removal of $Ru(OH)_x/Al_2O_3$ from the reaction solution (Figure S1, Supporting Information). A first-order dependence of the initial rate on the amount of $Ru(OH)_x/Al_2O_3$ (0.5−2.0 mol %, Figure S3, Supporting Information) was observed. These results indicate that any ruthenium species that leached into the reaction solution was not an active homogeneous catalyst and that the observed catalysis was truly heterogeneous in nature.[12] Further, recovered $Ru(OH)_x/Al_2O_3$ after the oxidation was recyclable, and both the reaction rate and selectivity toward oxygenation and dehydrogenation were retained (entries 2 and 13 in Table 2).

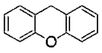
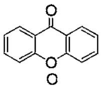
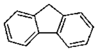
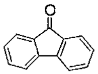
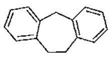
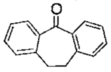
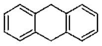
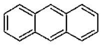
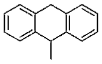
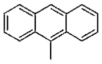
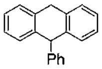
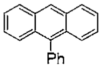
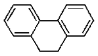
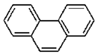
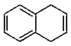
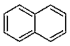
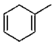
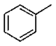
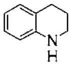
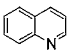
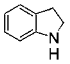
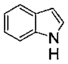
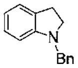
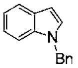
The scope of the present $Ru(OH)_x/Al_2O_3$ catalyst system toward various kinds of alkylarene derivatives was examined. The results are summarized in Table 2. In the present system, monoactivated substrates such as toluene and xylene could not be oxidized. In the case of substrates with only one benzylic methylene group such as xanthene and fluorene,

---

(11) **Typical Procedure for Oxidation.** Into a glass vial were successively placed $Ru(OH)_x/Al_2O_3$ (2 mol % Ru), xanthene (1 mmol), and $PhCF_3$ (6 mL). The reaction mixture was stirred at 373 K under 1 atm of molecular oxygen. The products were confirmed by GC analysis in combination with mass and ^1H and ^{13}C NMR spectroscopy, and the conversion and product selectivity were periodically determined by GC analysis during the oxidation. After the reaction was finished, the spent catalyst was separated by filtration, washed with a large amount of acetone, and dried in vacuo prior to being recycled.

(12) Sheldon, R. A.; Wallau, M.; Arends, I. W. C. E.; Schuchardt, U. *Acc. Chem. Res.* **1998**, *31*, 485.

Table 2. Oxidation of Various Alkylarene Derivatives with Molecular Oxygen Catalyzed by $Ru(OH)_x/Al_2O_3$[a]

entry	substrate	conditions	time(h)	conv.(%)	product	select.(%)
1 2[b]		A A	2 2	>99(92) 97		>99 >99
3		B	4	93(92)		>99
4		B	5	98		88[c]
5		C	4	>99(88)		93[d]
6		B	1.5	86(71)		92[e]
7		C	7	85		82[f]
8		B	4	82(79)		>99
9		C	8	89(81)		>99
10		A	4	99		>99
11		A	7	95(91)		>99
12 13[b]		A A	2 2	>99(90) >99		>99 >99
14		A	5	97(88)		98

[a] Reaction conditions A: substrate (1 mmol), $Ru(OH)_x/Al_2O_3$ (2 mol %), $PhCF_3$ (6 mL), 373 K, under 1 atm of molecular oxygen. Reaction conditions B: substrate (1 mmol), $Ru(OH)_x/Al_2O_3$ (5 mol %), *o*-dichlorobenzene (6 mL), 443 K, under 1 atm of molecular oxygen. Reaction conditions C: Substrate (1 mmol), $Ru(OH)_x/Al_2O_3$ (2 mol %), *p*-xylene (6 mL), 403 K, under 1 atm of molecular oxygen. Conversion and selectivity were determined by GC with an internal standard. Carbon balance for each reaction was greater than 95%. Values in parentheses are isoleted yields. [b] These experiments used a recycled catalyst. The reaction conditions were the same as those for the first runs with a fresh catalyst. The initial rates for the recycled runs were the same as that for the first run with a fresh catalyst. [c] 5*H*-Dibenzo[*a*,*d*]cyclohepten-5-one was formed (12% selectivity). [d] Anthraquinone (5% selectivity) and anthrone (2% selectivity) were formed. [e] 10-Methylanthrone was formed (8% selectivity). [f] 10-Phenylanthrone was formed (18% selectivity).

oxygenation at the benzylic position proceeded selectively to give the corresponding diaryl ketones in excellent yields (entries 1 and 3). Larger scale oxidation of xanthene (20 mmol scale, Ru: 0.1 mol %) showed a turnover frequency (TOF) of 278 h^{-1}, a turnover number (TON) of 921, and a yield of 92%. These values are the highest among those reported for oxygenation of alkylarenes using 1 atm of molecular oxygen so far: $H_5PV_2Mo_{10}O_{40}$ (TOF 3.2 h^{-1}, TON 58 for xanthene),[9a] *N*-hydroxyphthalimide (TOF 0.5 h^{-1}, TON 10 for xanthene),[8] $Bu_4NHSO_4/NaOH$ (TOF 8.5 h^{-1}, TON 5 for xanthene),[9b] Ru−Co−Al−CO_3 hydrotalcite (TOF 4.5 h^{-1}, TON 9 for xanthene),[9c] Co Shiff base complex/2-methylpropanal (TOF 0.5 h^{-1}, TON 10 for fluorene).[7] 9,10-Dihydroanthracene derivatives were smoothly converted to the corresponding anthracenes together with small amounts of the ketones (entries 5−7). Not only benzylic C−H bonds but also allylic C−H bonds were also efficiently dehydrogenated to afford the corresponding aromatized products (entries 9 and 10). Heterocyclic amines, 1,2,3,4-tetrahydroquinoline, and indoline gave the corresponding dehydrogenated products (entries 11 and 12). Remarkably, the N-protected indoline of *N*-benzylindoline was dehydrogenated to *N*-benzylindole with protection of benzyl group (entry 14).

The rates of alcohol oxidations were much faster than those of the oxidation of alkylarenes to the ketones. For example, the oxidation rate of fluoren-9-ol to fluoren-9-one at 403 K was 8.23 mM min^{-1} and was 20 times faster than that of fluorene to fluoren-9-one. When the reaction of 9-hydroxy-9,10-dihydroanthracene was carried out under reaction conditions C in Table 2, 9-hydroxy-9,10-dihydroanthracene was quantitatively converted within 10 min, and anthracene, anthrone, and anthraquinone were obtained in 91, 7, and 2% yields, respectively.[13] Al_2O_3 could also efficiently catalyze the dehydration of 9-hydroxy-9,10-dihydroanthracene to give 99% yield of anthracene as the sole product under the same reaction conditions,[13] suggesting that the dehydration may mainly be promoted by the Al_2O_3 support. Further, it was confirmed that $Ru(OH)_x/Al_2O_3$ did not catalyze the oxidation of anthracene to anthrone and anthraquinone. These facts suggest that alcohols are formed as intermediate products that are rapidly dehydrogenated or dehydrated to the corresponding oxygenated or dehydrogenated products, respectively, in the present alkylarene oxidation.

The reaction rates and selectivities for the oxidation of xanthene and 9,10-dihydroanthracene were not affected by the addition of radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (2 mol % with respect to the substrate). In addition, the skeletal isomerization of cyclopropyl and cyclobutyl rings did not take place under the present conditions.[14] These facts show that free radical intermediates are not involved in the present oxidation. The competitive oxidation of alkylarenes of xanthene, 9,10-dihydroanthracene, fluorene, triphenylmethane, and diphenylmethane was carried out. When the relative rates were plotted against the heterolytic C−H bond energy, the homolytic C−H bond energy, ionization potential, and pK_a (Figure 1 and Figure S2, Supporting Information), a fairly good correlation was observed between relative rates versus the heterolytic C−H bond energy, suggesting that the formation of carbocation-type transition state via the hydride abstraction is involved in the present oxidation.

Here, we propose the possible mechanism for the $Ru(OH)_x/Al_2O_3$-catalyzed oxidation of alkylarenes in Scheme 1. This catalytic oxidation can be divided into three steps: Initially, the reaction of ruthenium hydroxide species **I** with an alkylarene proceeds to form ruthenium hydride species **II** and the intermediate alcohol (step 1). The hydride species then reacts with molecular oxygen (step 2). The reoxidation of the hydride species likely proceeds through the insertion

---

[13] Under anaerobic conditions, the dehydration of 9-hydroxy-9,10-dihydroanthracene to anthracene proceeded with the same rate as that in the presence of molecular oxygen.

[14] (a) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4538. (b) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1480. (c) Yamaguchi, K.; Mizuno, N. *Chem. Eur. J.* **2003**, *41*, 4353.

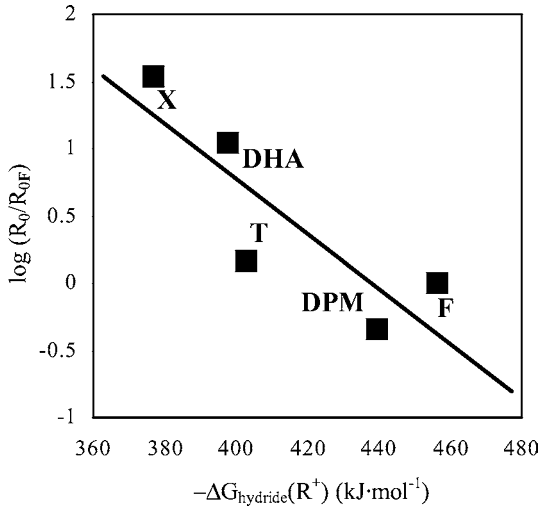
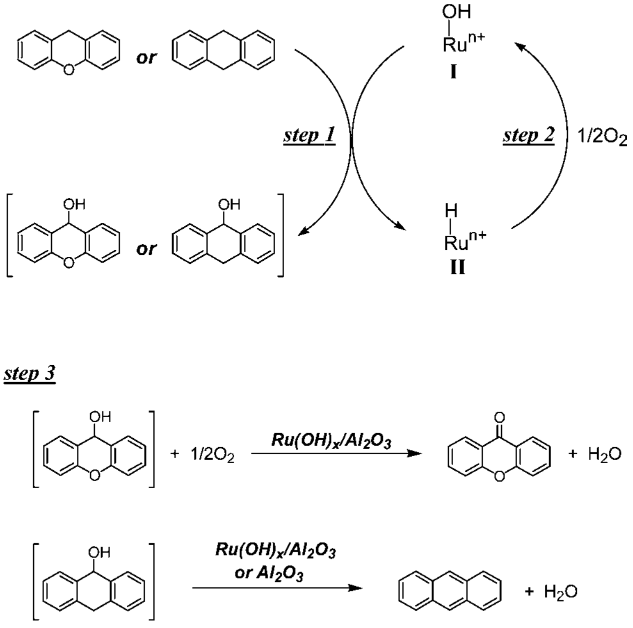


Figure 1. Relative rates for the competitive oxidations of alkylarenes, xanthene (**X**), 9,10-dihydroanthracene (**DHA**), triphenylmethane (**T**), diphenylmethane (**DPM**), and fluorene (**F**) as a function of heterolytic bond energy. $-\Delta G_{\text{hydride}}(\text{R}^+)$ is the free energy of R−H heterolytic bond disassociation: $\text{R}-\text{H} \rightarrow \text{R}^+ + \text{H}^-$.

of molecular oxygen into the hydride species.[14] In the case of alkylarenes with one methylene group such as xanthene, the oxidation of the intermediate alcohols proceeds to afford the corresponding ketones by $\text{Ru(OH)}_x/\text{Al}_2\text{O}_3$ (step 3). For other substrates such as 9,10-dihydroanthracene, the dehydration of the intermediate alcohols takes place, giving the corresponding dehydrogenated products (step 3). It was confirmed that the amounts of molecular oxygen consumed was equivalent to that of the xanthen-9-one produced for the oxidation of xanthene and that half that of anthracene produced for the oxidation of 9,10-dihydroanthracene. The formation of water for the oxidation of xanthene and 9,10-dihydroanthracene with molecular oxygen was monitored, and the respective amounts of water formed were the same as those of the oxidation products of xanthen-9-one and anthracene. These facts regarding the reaction stoichiometry support the above oxidation mechanism by $\text{Ru(OH)}_x/\text{Al}_2\text{O}_3$.

The initial rate (R_0) of the xanthene oxidation was almost independent of PO_2 (>0.5 atm, Figure S4, Supporting Information), while the dependence of R_0 on the concentration of xanthene (0.017−0.30 M, Figure S5, Supporting Information) was positive (0.5 th). These dependences show that the reoxidation (step 2) proceeds smoothly and is not a rate-limiting step. A kinetic isotope effect (k_H/k_D) of 5.3 ± 0.2 for the oxidation of fluorene and fluorene-d_{10} at 403 K supports that the above C−H bond cleavage (step 1) is a rate-limiting step (Supporting Information, Figure S6).[6,9a]

Scheme 1. Possible Reaction Mechanism



In conclusion, the present $\text{Ru(OH)}_x/\text{Al}_2\text{O}_3$ catalyst can act as an efficient heterogeneous catalyst for the oxidation of alkylarene derivatives using molecular oxygen as the sole oxidant. The oxidation of various alkylarenes can be performed with high conversion and selectivity, giving the corresponding oxygenated or dehydrogenated products. Catalyst/product separation is very easy, and the recovered catalyst is reusable with retention of the high catalytic performance.

Acknowledgment. This work was supported by the Core Research for Evolutional Science and Technology (CREST) program of the Japan Science and Technology Corporation (JST) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Science, Sports and Technology of Japan.

Supporting Information Available: Experimental Section and Figures S1−S6. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0485363