Direct α-Hydroxylation of Ketones Catalyzed by Organic–Inorganic Hybrid Polymer

Takayoshi Arai,[1] Toru Sato,[2] Hiroshi Noguchi,[2] Hirofumi Kanoh,[1]
Katsumi Kaneko,[1] and Akira Yanagisawa*[1]
[1]*Department of Chemistry, Faculty of Science, Chiba University, Inage 263-8522*
[2]*Graduate School of Science and Technology, Chiba University, Inage 263-8522*

(Received June 27, 2006; CL-060723; E-mail: ayanagi@faculty.chiba-u.jp)

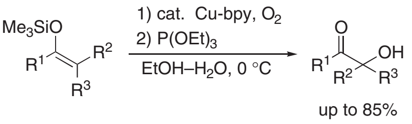
Direct α-hydroxylation of ketones using molecular oxygen was accomplished by organic–inorganic hybrid polymers. A newly prepared Cu-piperazine hybrid polymer was tolerant to the basic conditions, and with employment of lithium hydroxide smoothly catalyzed the α-hydroxylation of ketones. In the present catalytic process not only tetralone derivatives, but also acyclic ketones were converted to the α-hydroxy ketones in good yield.

α-Hydroxy carbonyls are valuable building blocks in organic synthesis and impressive structural motifs in a variety of biologically active natural products. The biological importance of the α-hydroxy carbonyl functionality has inspired the development of a number of catalytic processes.[1] Among the various useful processes, the oxidation of a carbon center adjacent to carbonyls is a beneficial route to prepare the fascinating functionality, and the ultimate oxidant would be the molecular oxygen from the viewpoint of the promotion of sustainable chemistry.[2]

In the course of our recent effort to apply the organic–inorganic hybrid polymer directed toward organic synthesis, we have succeeded in the catalytic synthesis of α-hydroxy ketones using the molecular oxygen as the oxidant.[3] Thus, in the previous report, the hybrid polymer "$\{[Cu(bpy)(BF_4)_2(H_2O)_2](bpy)\}_n$ (bpy = 4,4′-bipyridine)"[4] abbreviated as "Cu-bpy" shows activity to provide the α-hydroxy ketones from the trimethylsilyl enolates (Scheme 1).[5,6]

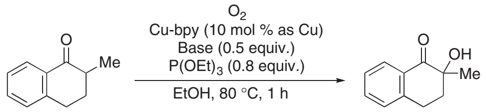
Although the Cu-bpy catalyst showed remarkable catalytic activity, one drawback is the requirement of preformation of the silyl enolate of the ketones before enforcing the target reaction. One apparent way to solve this problem is the use of carbonyl compounds directly. We report herein that the direct molecular oxygen derived α-hydroxylation of ketones using the organic–inorganic hybrid polymers under the basic conditions.

Toward the development of direct α-hydroxylation of ketones, initially, we screened various bases to generate the enolate in situ. The results are summarized in Table 1. Among the bases tested, lithium hydroxide monohydrate smoothly promoted the reaction of 2-methyl-1-tetralone (**1**) to give α-hydroxy ketone **2** in 82% yield in 1 h (Entry 5).[7] The use of amine bases resulted in lower chemical conversions (Entries 2 and 3).



Scheme 1. Organic–inorganic hybrid polymer catalyzed synthesis of α-hydroxy ketones from the trimethylsilyl enolates.

Table 1. Direct α-hydroxylation of ketone **1** under basic conditions



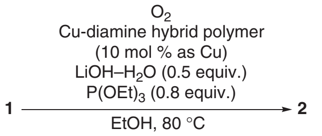
1 **2**

Entry	Base	Yield/%
1	—	no reaction
2	piperazine	no reaction
3	DBU	31
4	NaOH	7
5	LiOH–H_2O	82

Though we succeeded in the first direct α-hydroxylation using the hybrid polymer, it was revealed that the Cu-bpy catalyst was dissolved in the reaction media under the basic conditions. This makes the recovery and reuse of catalyst difficult. More seriously, the catalytic activity dramatically declined after dissolving. For example, the reaction using sodium hydroxide was completely disrupted within 1 h under the reaction conditions. To overcome the problem, we decided to prepare new organic–inorganic hybrid polymers in structural variation of the ligand framework. With the analogous method for the preparation of the Cu-bpy complex, a series of hybrid polymers were prepared, and the catalytic activities were examined as summarized in Table 2.

To our delight, the hybrid polymer derived from piperazine (Cu-piperazine) showed remarkable catalytic activity to provide α-hydroxy ketone **2** in 79% yield, and the complex did not dissolve in EtOH under the basic conditions (Entry 4).[8] After the reaction completed, the catalyst was recovered in 81% yield by centrifugation. The survived catalytic activity was confirmed

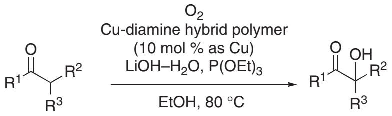
Table 2. A series of hybrid polymers and the catalyst activities[a]

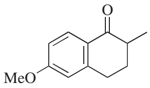
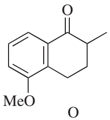
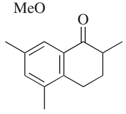
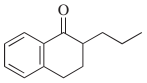
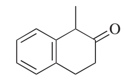
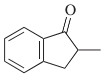
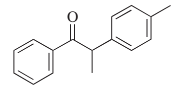
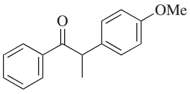


Entry	Diamine	Yield/%	Solubility
1	pyrazine	no reaction	soluble
2	*p*-phenylenediamine	67	insoluble
3	*p*-xylylenediamine	68	insoluble
4	piperazine	79	insoluble
5	DABCO	65	insoluble

[a]Catalyst amount was calculated as the similar structure to $\{[Cu(bpy)(BF_4)_2(H_2O)_2](bpy)\}_n$ (bpy = 4,4′-bipyridine).

Table 3. Cu-piperazine-catalyzed direct α-hydroxylation of ketones



Entry	Substrate	Cu-bpy[a]		Cu-piperazine[b,c]	
		Time/h	Yield/%	Time/h	Yield/%
1	**1**	14.5	84	14.5	77
2		9	65	9	76
3		9	60	9	72
4		9	74	9	60
5		11	2	18	53
6		12	67	12	71
7		13	71	13	79
8		15.5	33	15.5	67
9		15.5	49	15.5	56

[a] $LiOH–H_2O$ (0.5 equiv.) and $P(OEt)_3$ (0.8 equiv.) were used. [b] $LiOH–H_2O$ (0.3 equiv.) and $P(OEt)_3$ (0.8 equiv.) were used. [c] Catalyst amount was calculated as similar structure to $\{[Cu(bpy)(BF_4)_2(H_2O)_2](bpy)\}_n$ (bpy = 4,4′-bipyridine).

in the second use in the promotion of the reaction (68% yield).

Encouraged by the success of the Cu-piperazine-catalyzed synthesis of α-hydroxy ketone, the synthetic procedure was optimized. The amount of LiOH could be reduced to 0.3 equiv. for obtaining the synthetically useful chemical yield (**2**: 77% for 14.5 h). Under the optimized conditions, the generality of the new direct method was examined in Table 3.

Various advantages were realized in the correlation of the catalytic activity with that obtained by using the original Cu-bpy catalyst. In the reaction of a sterically hindered substrate such as 2-propyl-1-tetralone (Entry 5), which shows relatively lower reactivity, the Cu-piperazine complex catalyzed the α-hydroxylation in 53% yield, despite the fact that the Cu-bpy was hard to promote the reaction (only 2%). In the reaction of 1-methyl-2-tetralone, only the tertiary carbon center adjacent to the carbonyl group was oxidized at 80 °C (Entry 6). Not only the cyclic ketones, but also acyclic ketones were transformed to the corresponding α-hydroxy ketones, and the chemical yields were higher than those obtained using Cu-bpy (Entries 8 and 9). In the reaction of 2-benzylcyclohexan-1-one, only 2-benzyl-2-hydroxycyclohexan-1-one was obtained in 13% under the current conditions. This fact suggests that the selective reaction was performed from the thermodynamic enolate.[9]

In conclusion, we have disclosed the direct α-hydroxylation of ketones using molecular oxygen. The newly prepared Cu-piperazine complex is durable against the strong base, and the reaction proceeds smoothly with the coexistence of lithium hydroxide.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government, and by grants from the Graduate School of Science and Technology, and Venture Business Laboratory, Chiba University.

References and Notes

1 Recent reviews of the synthesis of α-hydroxy ketones: A. B. Jones, in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, Pergamon, Oxford, **1991**, Vol. 7, p. 151.

2 Recent progress in the synthesis of α-hydroxy kenones: a) H. Yamamoto, M. Tsuda, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **1997**, *62*, 7174. b) A. Solladié-Cavallo, P. Lupattelli, L. Jierry, P. Bovicelli, F. Angeli, R. Antonioletti, A. Klein, *Tetrahedron Lett.* **2003**, *44*, 6523. c) H. Sundén, M. Engqvist, J. Casas, I. Ibrahem, A. Córdova, *Angew. Chem., Int. Ed.* **2004**, *43*, 6532.

3 T. Arai, H. Takasugi, T. Sato, H. Noguchi, H. Kanoh, K. Kaneko, A. Yanagisawa, *Chem. Lett.* **2005**, *34*, 1590.

4 a) S. Ohnishi, T. Ohmori, T. Ohkubo, H. Noguchi, L. Di, Y. Hanzawa, H. Kanoh, K. Kaneko, *Appl. Surf. Sci.* **2002**, *196*, 81. b) D. Li, K. Kaneko, *Chem. Phys. Lett.* **2001**, *335*, 50. c) A. J. Blake, S. J. Hill, P. Hubberstey, W.-S. Li, *J. Chem. Soc., Dalton Trans.* **1997**, 913.

5 Remarkable metal-catalyzed synthesis of α-hydroxy ketones from the silyl enolates: a) T. V. Lee, J. Toczek, *Tetrahedron Lett.* **1982**, *23*, 2917. b) T. Takai, T. Yamada, O. Rhode, T. Mukaiyama, *Chem. Lett.* **1991**, 281.

6 Selected examples of the applications of organic–inorganic hybrid polymer to organic synthesis: a) C. Bianchini, E. Farnetti, M. Graziani, J. Kaspar, F. Vizza, *J. Am. Chem. Soc.* **1993**, *115*, 1753. b) M. Fujita, Y. J. Kwon, S. Washizu, K. Ogura, *J. Am. Chem. Soc.* **1994**, *116*, 1151. c) J. S. Seo, D. Whang, H. Lee, S. I. Jun, J. Oh, Y. J. Jeon, K. Kim, *Nature* **2000**, *404*, 982. d) S. Takizawa, H. Somei, D. Jayaprakash, H. Sasai, *Angew. Chem., Int. Ed.* **2003**, *42*, 5711. e) R. Dorta, L. Shimon, D. Milstein, *J. Organomet. Chem.* **2004**, *689*, 751. f) X. Wang, K. Ding, *J. Am. Chem. Soc.* **2004**, *126*, 10524. g) H. Guo, X. Wang, K. Ding, *Tetrahedron Lett.* **2004**, *45*, 2009. h) Y. Liang, Q. Jing, X. Li. L. Shi, K. Ding, *J. Am. Chem. Soc.* **2005**, *127*, 7694. i) S.-H. Cho, B. Ma, S. T. Nguyen, J. T. Hupp, T. E. Albrecht-Schmitt, *Chem. Commun.* **2006**, 2563.

7 Though the aerobic oxidation of metal enolates has been reported,[1] α-hydroxylation of **1** does not proceed without use of Cu-bpy catalyst.

8 Preparation of Cu-piperazine catalyst: To the solution of $Cu(BF_4)_2–6H_2O$ (237 mg, 1 mmol) in H_2O (25 mL) was added piperazine (172 mg, 2 mmol). After standing 17 days, the resulting insoluble residue was collected by centrifugation (3000 rpm), and dried under reduced pressure to give the Cu-piperazine complex (144 mg, ca. 35% yield as similar structure to $\{[Cu(bpy)(BF_4)_2(H_2O)_2](bpy)\}_n$).

9 The catalysis using Cu-bpy for the kinetic trimethylsilyl enolate of 2-benzylcyclohexanone provided 2-benzyl-6-hydroxycyclohexan-1-one in ca. 3% yield under the reaction conditions similar to those reported in Ref. 3, while 2-benzyl-2-hydroxycyclohexan-1-one was not obtained at all.