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Palladium-catalyzed oxidation of cyclohexanones to conjugated enones using molecular oxygen

Makoto Tokunaga,*,† Saki Harada, Tetsuo Iwasawa, Yasushi Obora and Yasushi Tsuji*,‡

Catalysis Research Center and Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 001-0021, Japan
CREST, Japan Science and Technology Agency (JST), Japan

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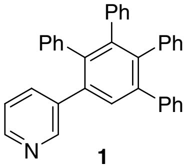
Abstract—Oxidation of cyclohexanones into conjugated enones with molecular oxygen as oxidant was achieved by palladium catalysts. A catalyst system consists of 1 mol % $Pd(OCOCF_3)_2$ and 5,5′-dimethyl-2,2′-bipyridine accomplished maximum 84% yield for the oxidation of cyclohexanone and 51–78% yields for 4-substituted-cyclohexanones.

Aerobic oxidation of organic molecules is a fundamental and important transformation from the viewpoint of environmentally benign synthesis.[1] There is an increasing demand for replacing stoichiometric oxidants with more clean chemicals such as molecular oxygen and hydrogen peroxide.[2] In this context, we have developed a Pd-catalyzed air-oxidation of alcohols[1g] and Cu- and Brønsted acid-catalyzed oxidative C=C bond cleavage using molecular oxygen.[1b,d] In the alcohol oxidation,[1g] a remarkable steric effect of 2,3,4,5-tetraphenylphenyl substituent[3] was observed.[1c,g] A pyridine ligand bearing this group at *meta*-position (**1**) successfully suppresses the zero valent Pd oligomerization and deactivation.[1c]



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With regard to catalytic oxidation of ketones into conjugated enones with molecular oxygen, only a few reports have been made.[4] Since this transformation is very important in organic synthesis, many stoichiometric methods have been developed over the years, employing selenium reagents,[5] hypervalent iodine reagents,[6] and others.[7] Another popular method is the Pd-catalyzed aerobic oxidation of silylenol ethers.[8] However, direct oxidation of parent ketones using Pd-catalysts suffered from the deactivation of the catalysts and resulted in poor yields.[4,9] For example, in the oxidation of cyclohexanone, two catalyst systems $PdCl(NO_2)(MeCN)_2$–$Ag(OSO_2CF_3)$ and $Pd(OCOCF_3)_2$–$P(p\text{-}CH_3C_6H_4)_3$ realized only small turnover numbers of 11[4d] and 5.9,[4b] respectively. In these reports, only the turnover numbers were presented, but they are corresponding to 27% and 1.9% chemical yields, respectively. In this Letter we describe a new and active Pd-catalyst system for oxidation of ketones into conjugated enones with molecular oxygen, which realizes 84% chemical yield for cyclohexenone.

The oxidation of cyclohexanone with various Pd precursors and ligands was examined. Typically, 1 mol % $Pd(OCOCF_3)_2$ was used as a Pd source under 1 atm oxygen atmosphere at 100 °C (Table 1). Although phosphine ligands have been used in the previous studies, pyridine ligands were found to be more efficient in this reaction. The monodentate pyridine ligand **1**, which exhibited excellent performance in the alcohol oxidation,[1h] was not so effective, although **1** gave better yield than the unsubstituted pyridine (entries 1 and 2) (Scheme 1).

Strongly coordinating DMAP prevented Pd black formation but also inhibited the reaction (entry 3). Bipyridine

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[*] Corresponding authors. Tel./fax: +81 92 642 7528 (M.T.); tel.: +81 75 383 2515; fax: +81 75 383 2514 (Y.T.); e-mail addresses: mtok.scc@mbox.nc.kyushu-u.ac.jp; ytsuji@scl.kyoto-u.ac.jp

[†] Present address: Department of Chemistry, Graduate School of Science, Kyushu University, Fukuoka, 812-8581, Japan.

[‡] Present address: Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Kyoto, 615-8510, Japan.

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Table 1. Pd-catalyzed oxidation of **2a** into **3a** with atmospheric oxygen[a]

Entry	Ligand	Solvent	Yield of **3a**[b] (%)	Yield of **4a**[b] (%)
1	Pyridine[c]	Toluene	17	0
2	**1**[c]	Toluene	24	2
3	DMAP[d,c]	Toluene	Trace	0
4	**5a**	Toluene	19	0
5	**5a**	Chlorobenzene	24	1
6	**5b**	Toluene	25	0
7	**5b**	Chlorobenzene	46	4
8[e]	**5b**	Chlorobenzene	70 (84)[f]	2 (4)[f]
9	**5c**	Toluene	11	2
10	**5d**	Chlorobenzene	27	2
11	**5e**	Chlorobenzene	10	3
12	**5f**	Chlorobenzene	2	0
13	**5g**	Chlorobenzene	11	0
14	**6**	Chlorobenzene	42	2
15[e]	**6**	Chlorobenzene	3	0
16	**7**	Chlorobenzene	13	0
17	**8**	Chlorobenzene	29	1

[a] A mixture of **2a** (1 mmol), $Pd(OCOCF_3)_2$ (0.01 mmol), ligand (0.01 mmol), and solvent (0.9 mL) was stirred at 100 °C for 24 h under 1 atm O_2.[10]

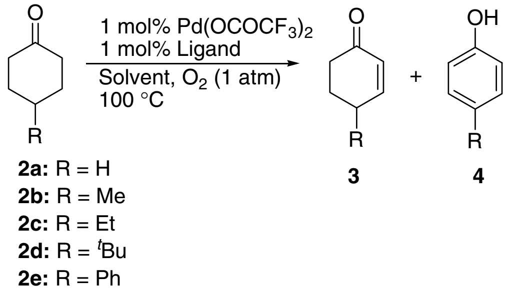
[b] GC yield.[11]

[c] 8 mol % (0.08 mmol) ligand was used.

[d] DMAP: 4-(dimethylamino)pyridine.

[e] Molecular sieves 4 Å (100 mg) was added.

[f] For 48 h.



Scheme 1. Pd-catalyzed oxidation of **2** into **3** with atmospheric oxygen.

ligands (**5**) and structurally related ligands provided favorable results in terms of catalyst lifetime and activity (entries 4–17) (Fig. 1). Particularly, 5,5′-dimethyl-2,2′-bipyridine **5b** exhibited highest performance. Using 1 equiv of **5b** as ligand to Pd, yield of **3** was improved to 46% by the use of chlorobenzene as solvent and 70% in the presence of molecular sieves 4 Å (entries 7 and 8). The catalyst was still active under the condition and 84% yield was obtained with prolonged reaction time (48 h, entry 8). Amount of the molecular sieves affected the reaction; the highest yield was obtained in entry 8. Gradual decrease of yield was observed with a larger or a lesser amount of the molecular sieves. The addition of molecular sieves was not always favorable, and lower activity was observed when 2,2′-biquinoline **6** was employed as ligand (entry 15). Other Pd precursors such as $Pd(OAc)_2$ showed slightly lower activity but almost no reaction occurred when $PdCl_2(PhCN)_2$ was used. The addition of basic salts, such as NaOAc, K_2CO_3, and NaO^{t}Bu, decreased the activity.

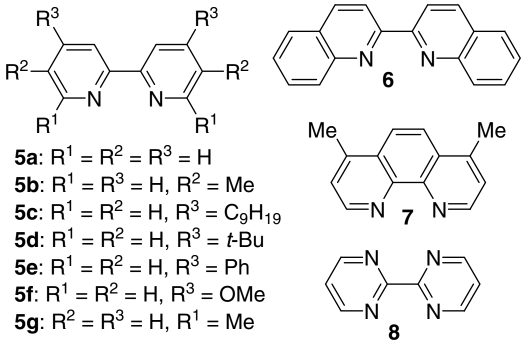


Figure 1. Pyridine ligands used in this study.

Next we examined the oxidation of various ketones under the optimized condition using ligand **5b** (Table 2). Substituted cyclohexanones at the 4-position (**2b**–**e**) gave good yields (51–78%) of the products (**3b**–**e**) (entries 1–4). The selectivity for the enone formation was generally high, the product yields were near to the substrate conversions in all cases. Thus only trace amount of corresponding phenols **4b**–**e** were formed. A bulky substituent did not decrease the yield (entry 3, 78% yield for **2d**: R = ^{t}Bu:).

On the other hand, substituent at the 2- or 3-position of cyclohexanone decreased the yield of enones (<20%). For example, 19% yield for 76 h with 2-*t*-butylcyclohexanone, 9% yield for 54 h with 3,5-dimethylcyclohexanone, and trace yield for 24 h with, α- and β- tetralone were observed. Other cyclic substrates also showed low reactivity. Among them, the highest yield (26%) was obtained with cyclopentanone. Acyclic substrates such as 4-phenyl-2-butanone and nonyl phenyl ketone also resulted in low yield (<20% for 24 h).

Although a precise mechanism of the present reaction is unclear, ketonic substrates would react with Pd in a similar manner to the previous report.[4b–d] Thus probably the reaction include the formation of palladium *C*-enolate followed by β-H elimination to give Pd^0 species. During the course of the reoxidation of Pd, aggregation and deactivation of the catalyst takes place. The bipyridine

Table 2. $Pd(OCOCF_3)_2$/**5b**-catalyzed oxidation of **2b**–**d** with atmospheric oxygen[a]

Entry	Substrate	Time (h)	Yield of **3a**[b] (%)
1	**2b**	24	53
		96	72
2	**2c**	24	55
		48	69
		95	78
3	**2d**	20	53
		44	78
4	**2e**	20	47
		48	51

[a] A mixture of **2** (1 mmol), $Pd(OCOCF_3)_2$ (0.01 mmol), **5b** (0.01 mmol), molecular sieves 4 Å (100 mg), and chlorobenzene (0.9 mL) was stirred at 100 °C under 1 atm O_2.

[b] GC yield.[11,12]

ligands may stabilize Pd active species and prevent their aggregation to extend the catalyst lifetime.

In conclusion, we have achieved catalytic transformation of cyclohexanone derivatives into corresponding enones up to 84% yield with molecular oxygen as oxidant.

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9. Under the reaction condition, facile formation of phosphine oxides was observed.
10. Typical procedure for Pd-catalyzed oxidation of cyclohexanone (Table 1, entry 8). A dry 20-mL Schlenk flask was charged with molecular sieves 4 Å (100 mg, powder, activated, 5 μm, Aldrich), then heated at 200 °C for 5 min under reduced pressure. After cooled to room temperature, $Pd(OCOCF_3)_2$ (3.3 mg, 0.010 mmol), 5,5′-dimethyl-2,2′-bipyridine (1.8 mg, 0.010 mmol) and chlorobenzene (0.9 mL) were introduced under Ar atmosphere, then stirred at 60 °C for 15 min. To this were added cyclohexanone (98.1 mg, 1.00 mmol) and tridecane (internal standard, 37.8 mg, 0.205 mmol) at room temperature, then the flask was purged with 1 atm O_2. The mixture was stirred at 100 °C for 48 h, and the yield of the product was determined by GC analysis.
11. GC analysis was performed by Agilent GC 6850 equipped with Agilent HP-1 column (length 30 m, 0.32 mm I.D.). Commercially unavailable authentic samples of enones were synthesized by literature procedure.[12]
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