Highly Efficient C-H Hydroxylation of Carbonyl Compounds with Oxygen under Mild Conditions

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检查:　　蔡先锋
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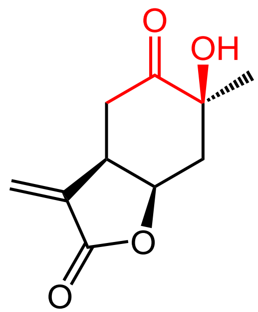
Peking University

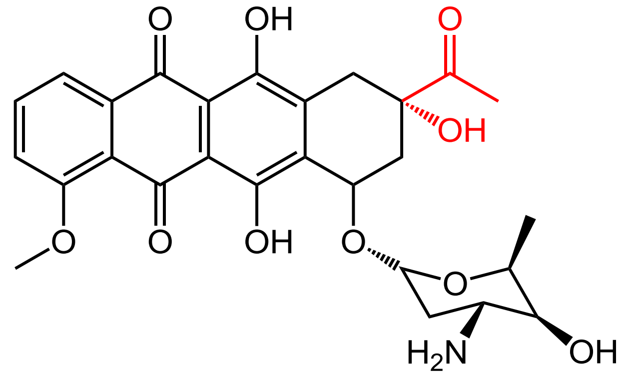
Jiao, N. *et al.*
Angew. Chem. Int. Ed. **2014**, *53,* 548-552.

Contents

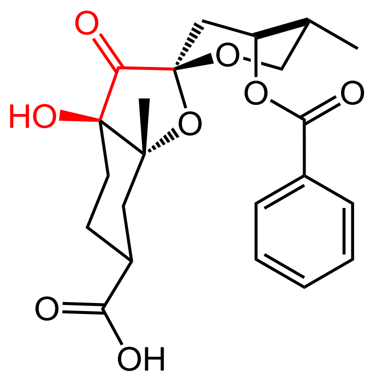
Introduction



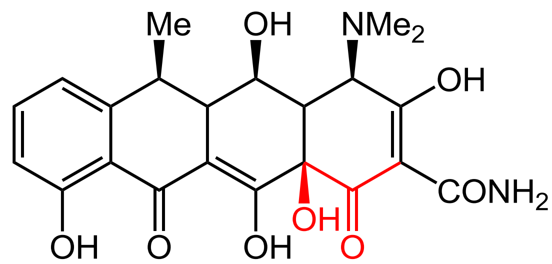
Paeonilactone B



Daunorubicin

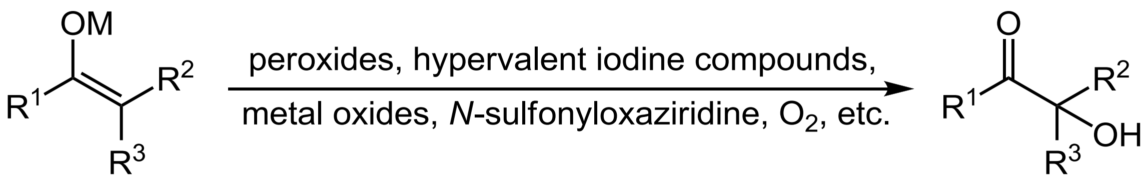


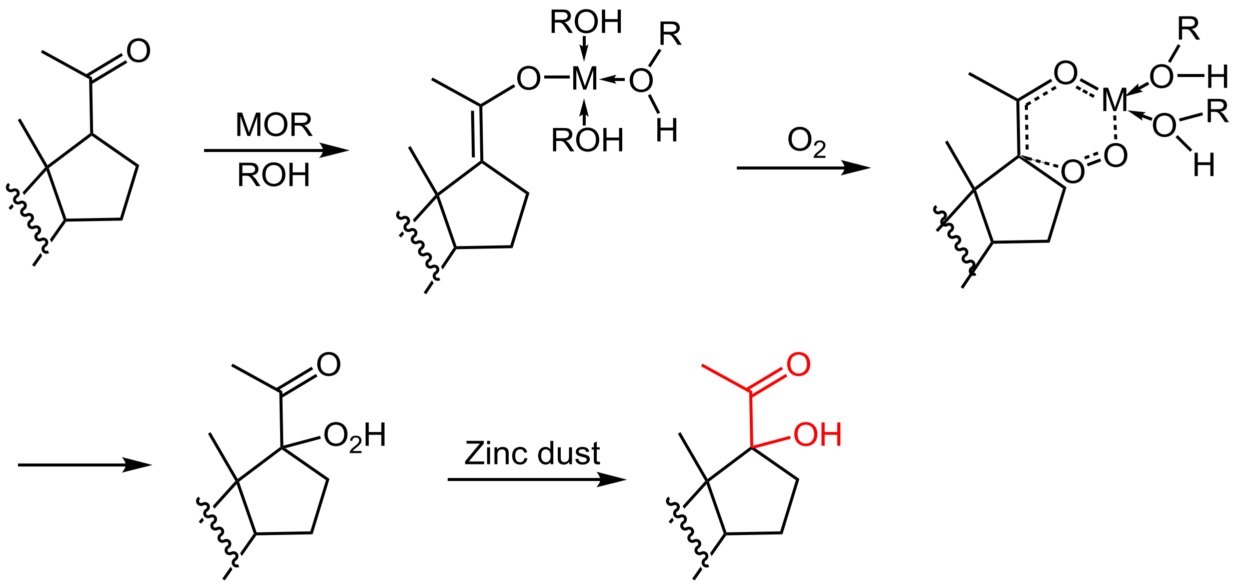
Phyllaemblic acid



Doxycycline

Oxidation of enolates or silyl enol ethers

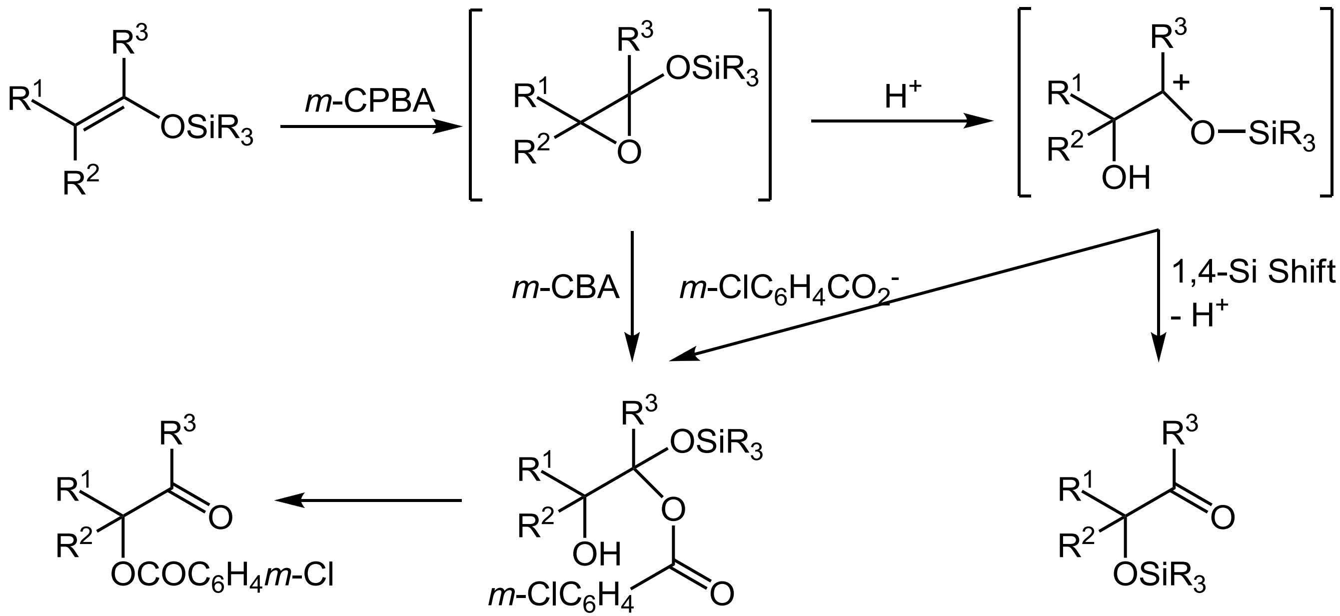




Templeton, J. F. *et al. J. Chem. Soc.* **1962**, 1578.

Oxidation of enolates or silyl enol ethers

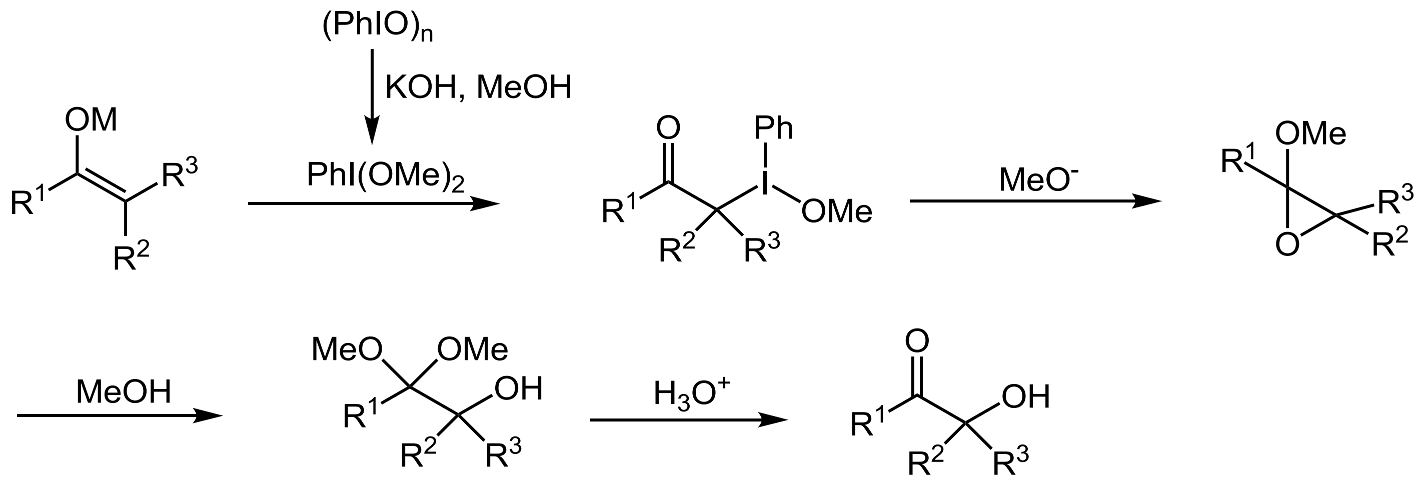
Peroxy Reagent as Oxidant and Oxygen Source (Rubottom Oxidation)

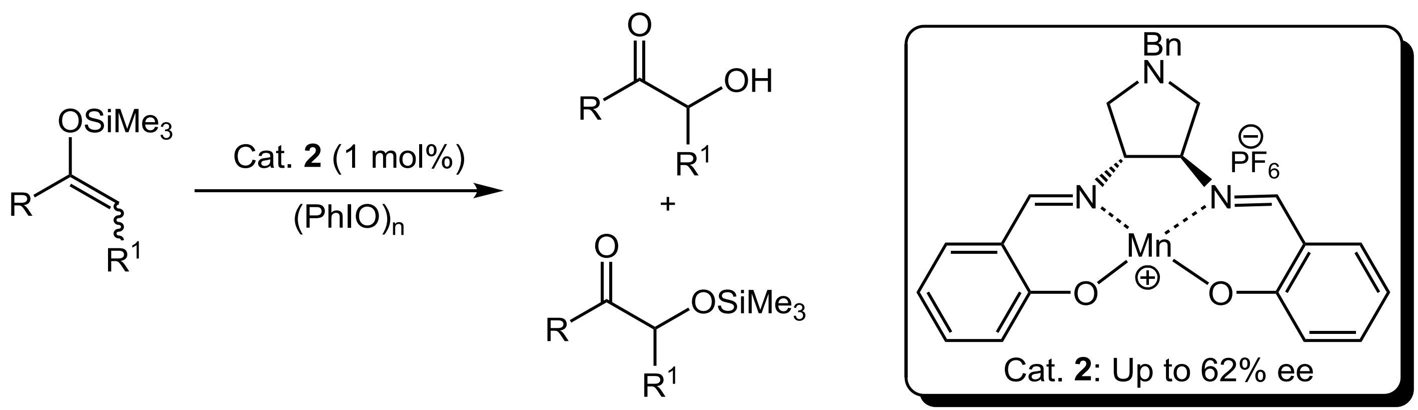


Rubottom, G. M. *et al. Tetrahedron Lett.* **1974**, 4319.

Oxidation of enolates or silyl enol ethers

Hypervalent Iodine Reagents as Oxidant

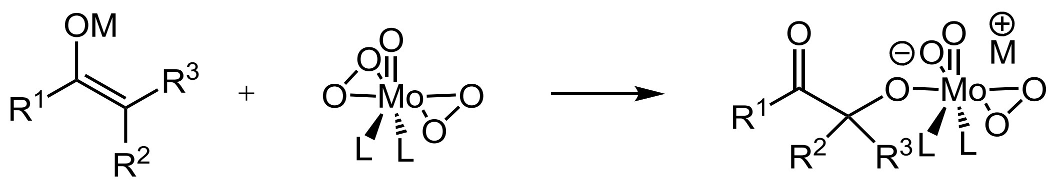




Thornton, E. R. *et al. J. Chem. Soc., Chem. Commun.* **1992**, 172.

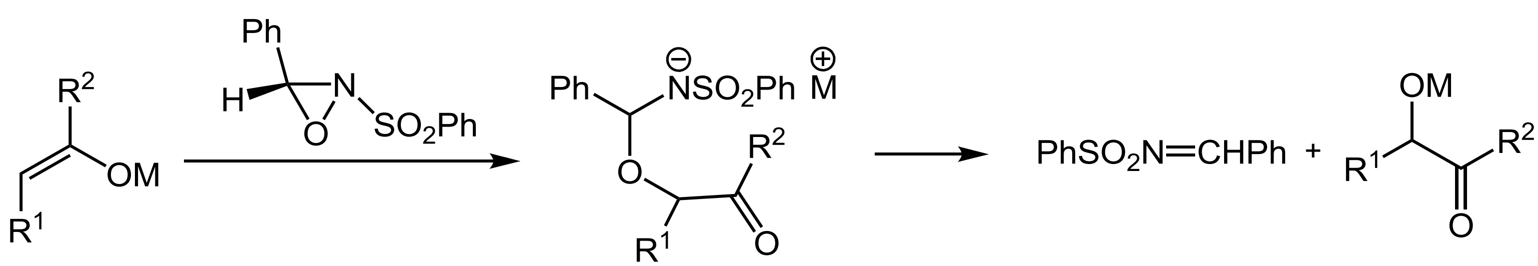
Oxidation of enolates or silyl enol ethers

Metal Oxides and Related Reagent As Oxidant and Oxygen Source



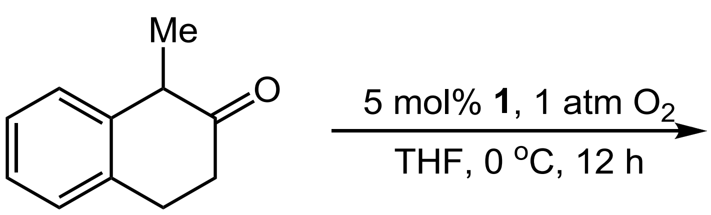
Vedejs, E. *et al. J. Org. Chem.* **1978**, *43*, 188

N-Sulfonyloxaziridines As Oxygen Source



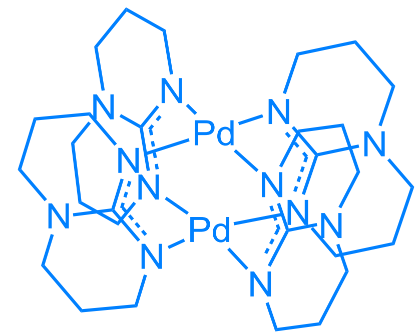
Davis, F. A. *et al. J. Am. Chem. Soc.* **1990**, *112*, 6679

Pd-catalyzed hydroxylation



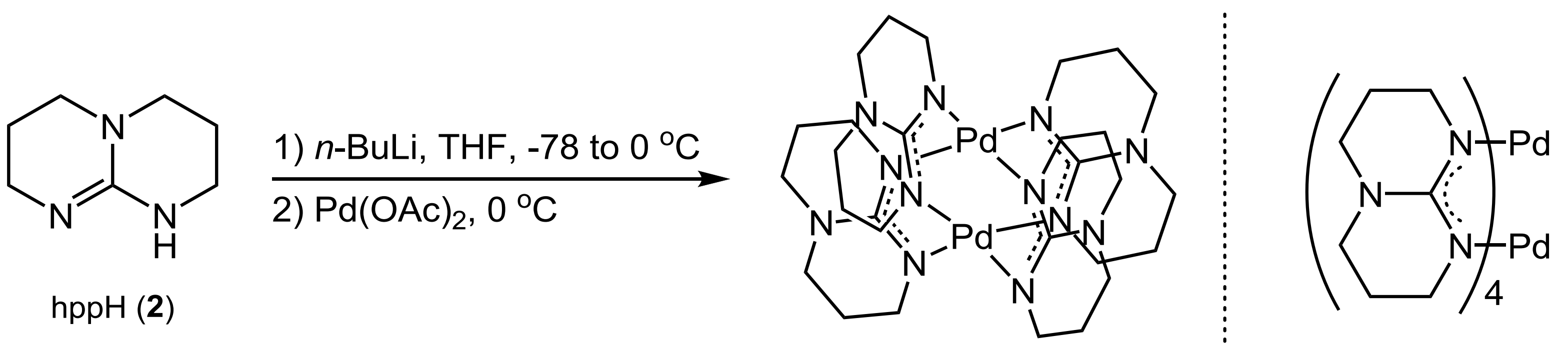
3

4, 77%



Pd_2hpp_4 (**1**)

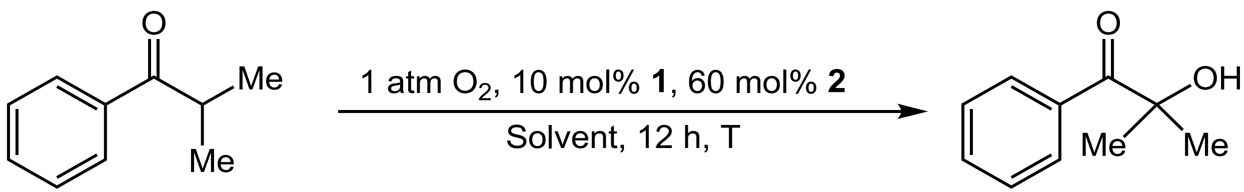
Synthesis of Pd Catalyst 1



hppH (**2**)

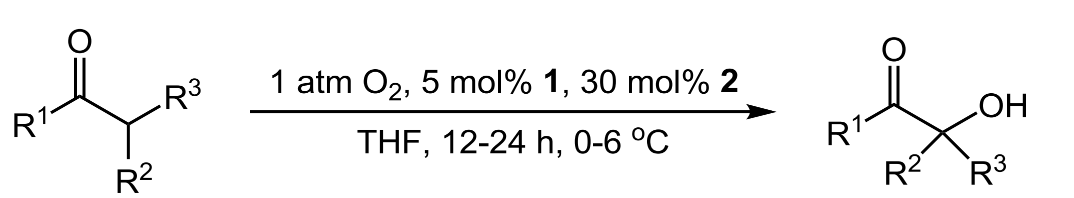
Ritter, T. *et al. J. Am. Chem. Soc.* **2011**, *133*, 1760.

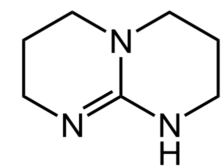
Pd-catalyzed hydroxylation



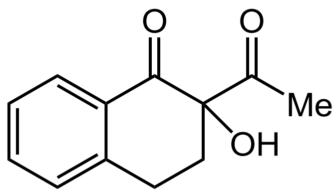
Entry	T (°C)	Solvent	*Con.* (%)
1	50	C_6D_6	0
2	23	C_6D_6	60
3	6	C_6D_6	80
4	-78	C_6D_6	0
5	6	Benzene	60
6	6	Toluene	82
7	**6**	**THF**	**82**
8	6	Ether	72
9	6	Nitromethane	0
10	6	Acetone	< 5
11	6	Ethyl actate	68
12	6	Dioxane	53
13	6	Acetonitrile	52

Pd-catalyzed hydroxylation

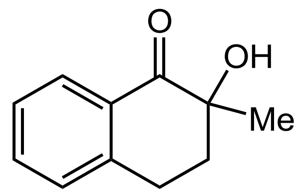




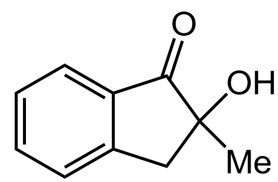
2



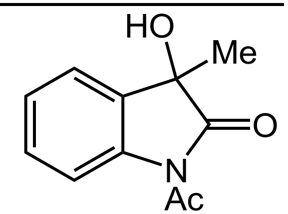
5, 96% [a,b]



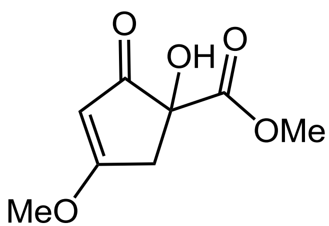
6, 94% [b]



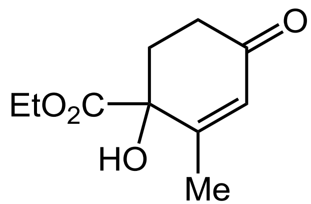
7, 88%



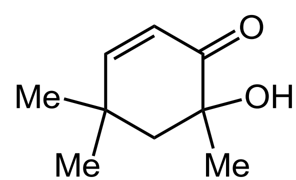
8, 70%



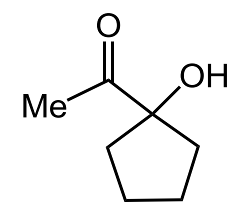
9, Kjellmanianone, 97% [b]



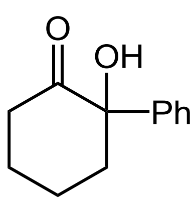
10, 90% [b]



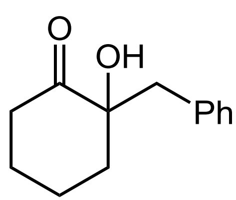
11, 70%



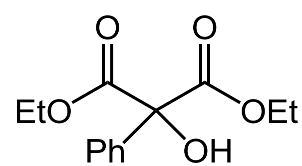
12, 60% [c]



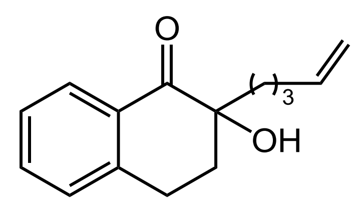
13, 70%



14, 68% [c]



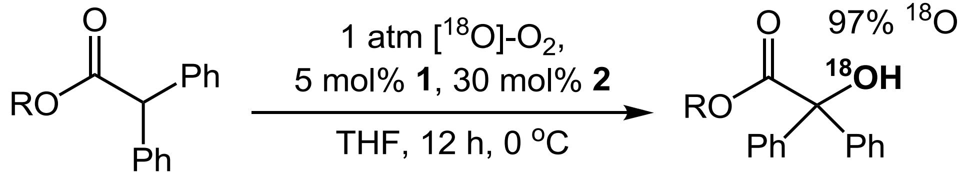
15, 97%

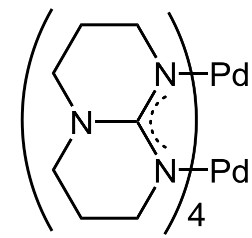


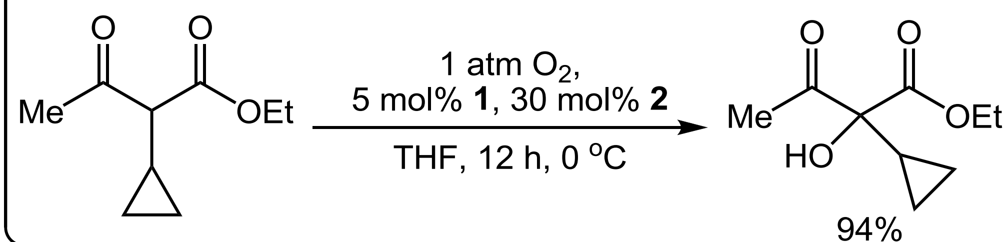
16, 71%

[a] A total of 2.5 mol % of **1** was used. [b] No **2** was added. [c] A total of 10 mol % of **1**, and 60 mol % of **2** were used

Pd-catalyzed hydroxylation

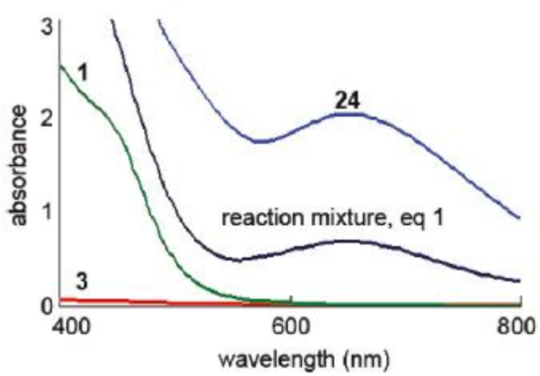


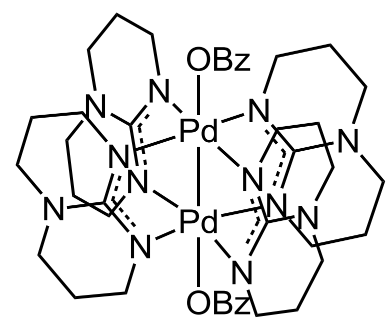




- Both oxygen atoms from O_2 were incorporated
- No hydroperoxide was observed
- $HCPh_3$ was not oxidized

In situ UV-vis spectroscopy of reaction intermediate and dinulear Pd(III) benzoate complex **24**

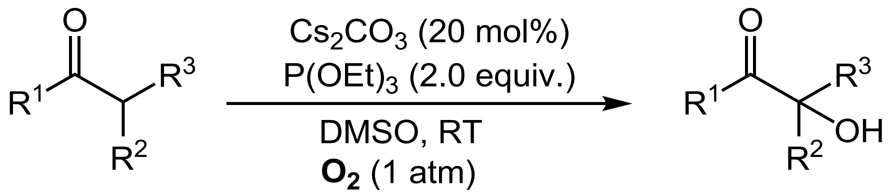




$Pd_2hpp_4(OBz)_2$ (**24**)

Pd(III)-Pd(III), X-ray;
Pd-Pd bond length: 2.40 Å

Transition-metal-free hydroxylation



- Transition-metal-free
- Ligand-free
- Environmental friendly and Pratical

OH, so simple!

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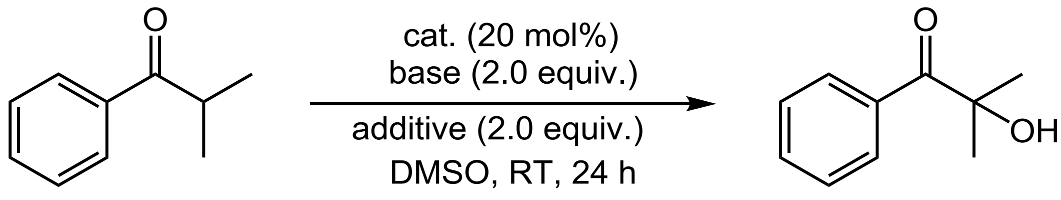
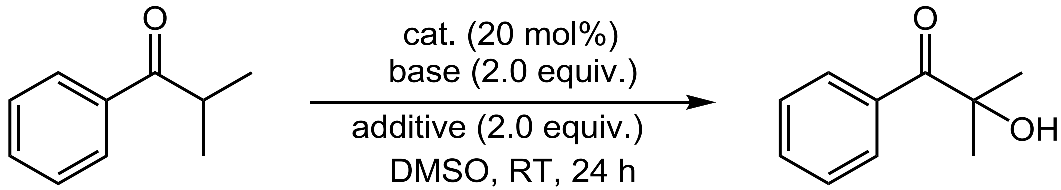
Transition-metal-free hydroxylation



1a **2a**

Entry [a]	Catalyst	Base	Additive	Yield [%] [b]
1	$CuBr_2$	Cs_2CO_3	--	5
2	$CuBr_2$	Cs_2CO_3	$P(OEt)_3$	91 (87)
3	**Cs_2CO_3**	**--**	**$P(OEt)_3$**	**91 (87)**
4	K_2CO_3	--	$P(OEt)_3$	0
5	Na_2CO_3	--	$P(OEt)_3$	0
6	CsOAc	--	$P(OEt)_3$	0
7	$CsNO_3$	--	$P(OEt)_3$	0
8	CsOH	--	$P(OEt)_3$	trace
9	Cs_2CO_3	--	PPh_3	78 (74)
10	Cs_2CO_3	--	$Na_2S_2O_3$	trace
11	--	--	$P(OEt)_3$	0

Transition-metal-free hydroxylation

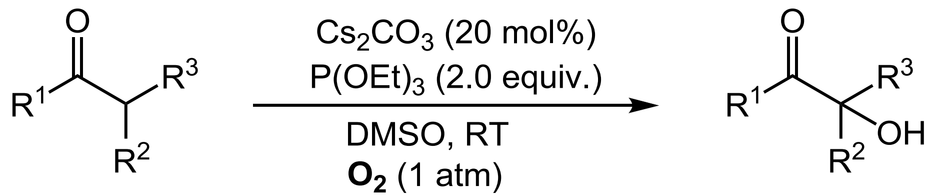


1a 2a

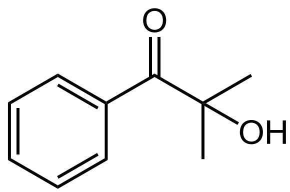
Entry [a]	Catalyst	Base	Additive	Yield [%] [b]
12	Cs_2CO_3	--	--	trace
13 [c]	Cs_2CO_3	--	$P(OEt)_3$	76 (73)
14 [d]	Cs_2CO_3	--	$P(OEt)_3$	0
15 [e]	Cs_2CO_3	--	$P(OEt)_3$	79 (75)

[a] Reaction condition: 1a (0.5 mmol), catalyst (0.1 mmol), base (1.0 mmol), additive (1.0 mmol), DMSO (2 mL); the mixture was stirred at room temperature under O_2 (1 atm) for 24 h. [b] The yield was determined by GC with biphenyl as an internal standard. The value in parentheses is the yield of the isolated products. [c] The reaction was carried out in air (1 atm) for 48 h. [d] The reaction was carried out under Ar (1 atm). [e] The reaction was carried out in the dark.

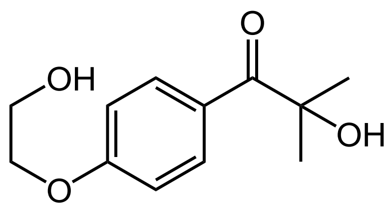
Transition-metal-free hydroxylation



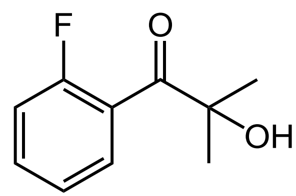
1a-1l → **2a-2l**



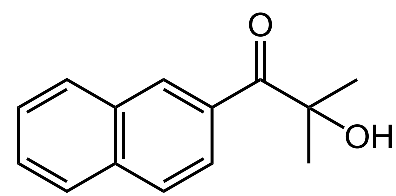
2a, 87%



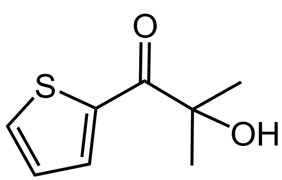
2b, 75%



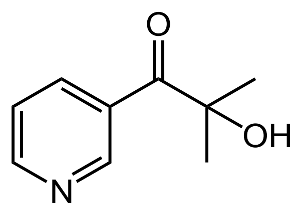
2c, 84%



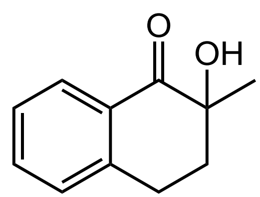
2d, 82%



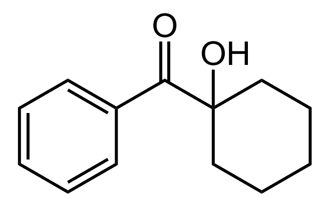
2e, 75%



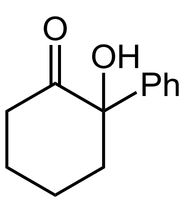
2f, 70%



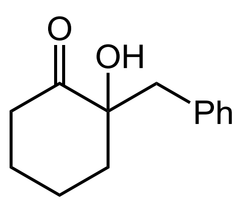
2g, 99%



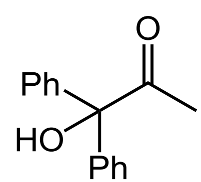
2h, 60% [a]
96% [a,b]



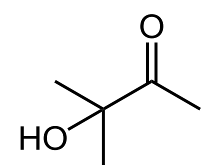
2i, 93%



2j, 50%



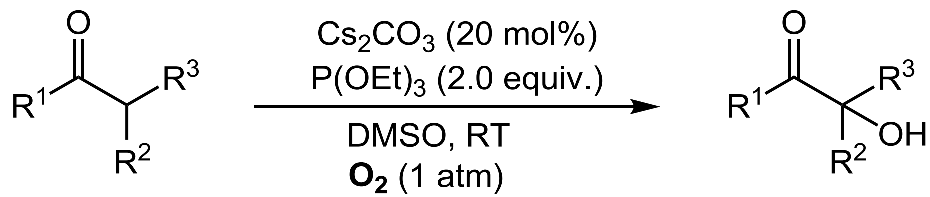
2k, 53%



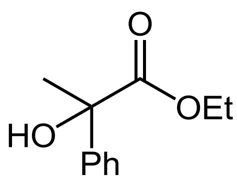
2l, 80% [c]

[a] Reaction time: 72 h. [b] The reaction was carried out with 1.0 equiv of Cs_2CO_3. [c] The yield was determined by ^{1}H NMR spectroscopy

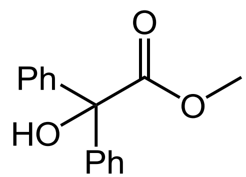
Transition-metal-free hydroxylation



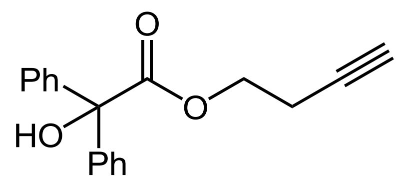
1m-1x **2m-2x**



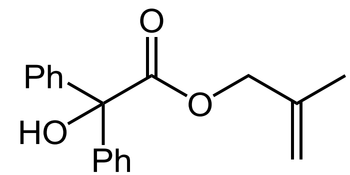
2m, 89%



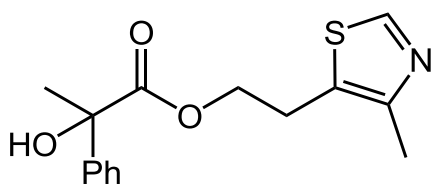
2n, 88%



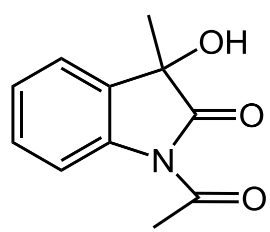
2o, 81%



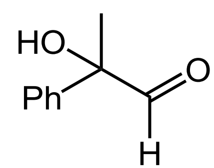
2p, 84%



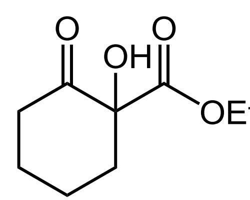
2q, 85%



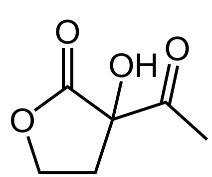
2r, 59%



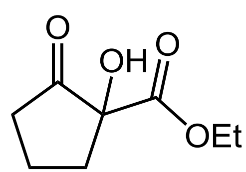
2s, 31% [a]



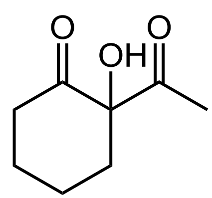
2t, 67%



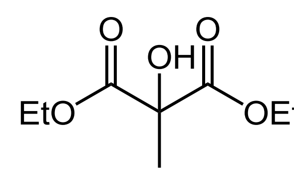
2u, 70%



2v, 52%



2w, 64%

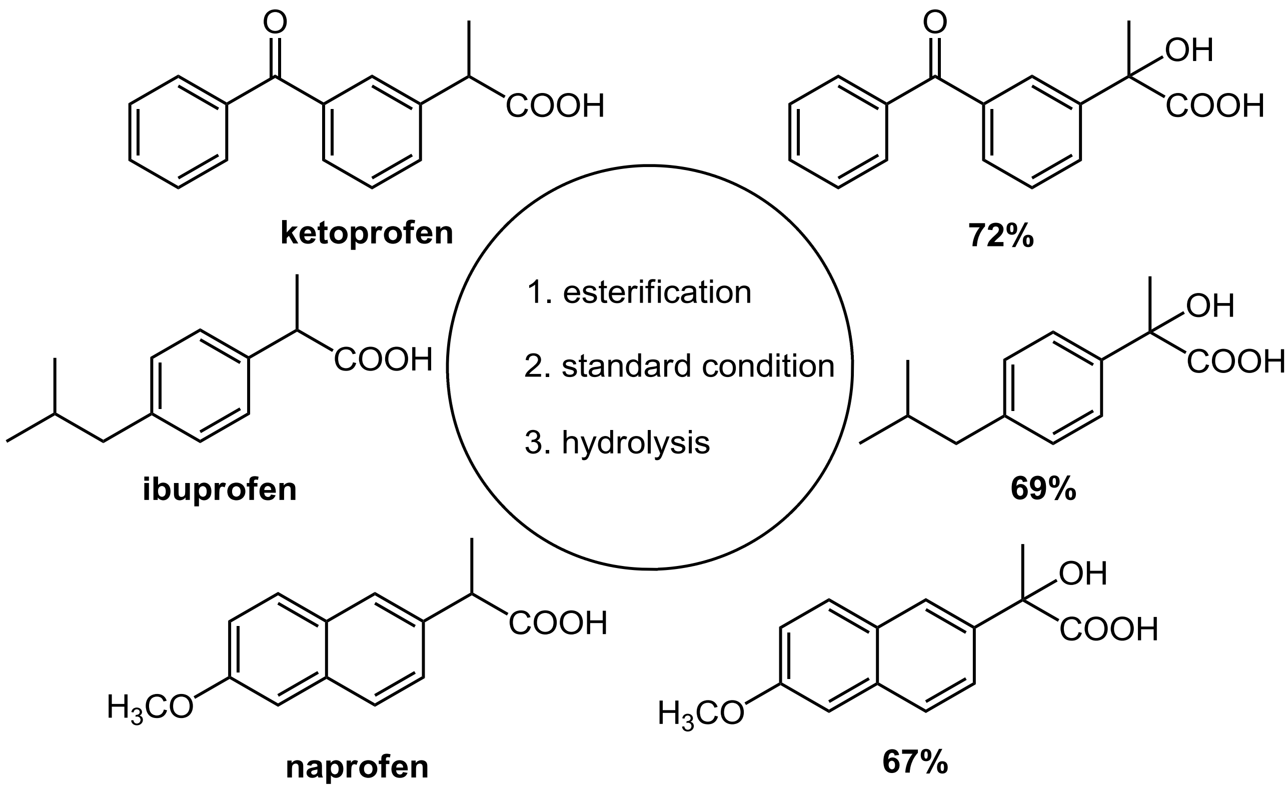


2x, 73%

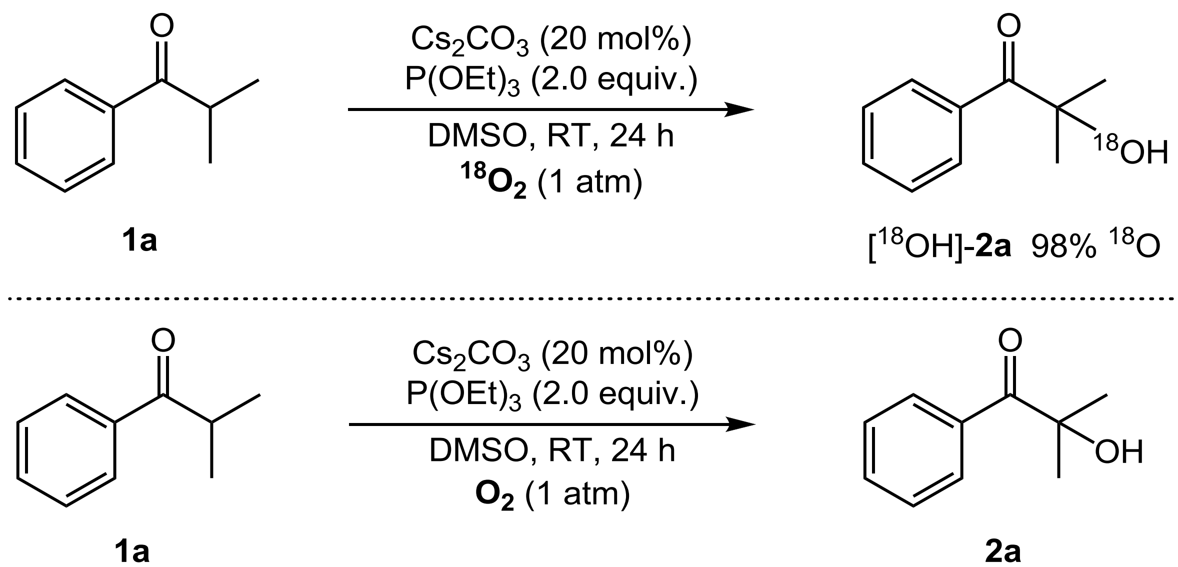
[a] Morpholine (1.0 equiv) was added

Transition-metal-free hydroxylation

Drug diversification

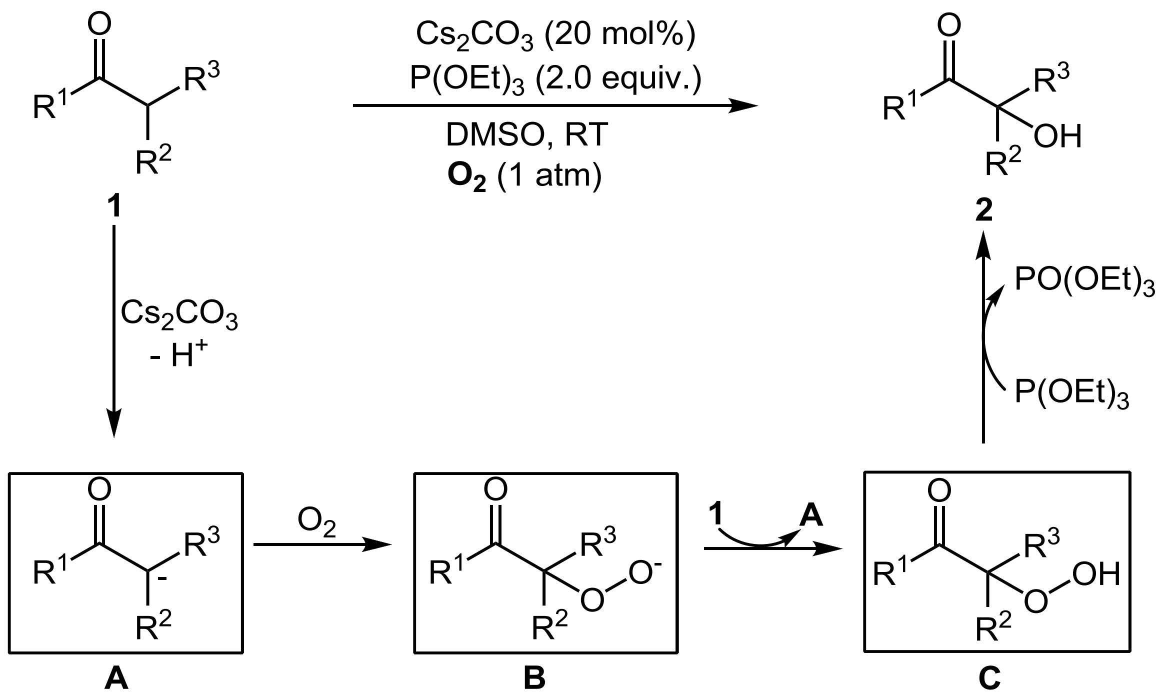


Transition-metal-free hydroxylation

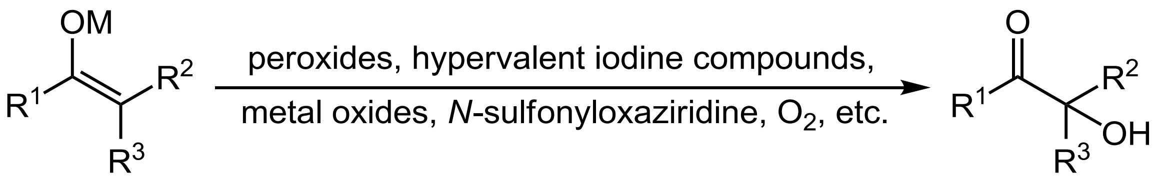


- 88% yield of **2a** in the presence of TEMPO
- 86% yield of **2a** in the presence of 1,1-diphenylethylene
- 81% yield of **2a** in the presence of DABCO

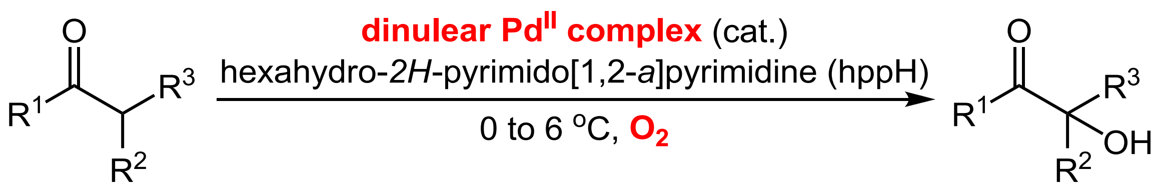
Transition-metal-free hydroxylation



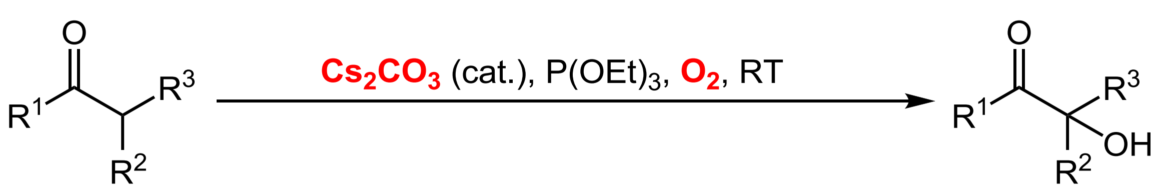
Summary



Templeton, J. F. and Rubottom, G. M. etc



Ritter, T.



Jiao, N.

Tertiary α-hydroxycarbonyl groups are ubiquitous structural motifs in organic chemistry. They serve as valuable building blocks and are present in many biologically active compounds and synthetic drugs, such as paeonilactone B, daunorubicin, phyllaemblic acid, and doxycycline. Furthermore, they have been widely used as efficient photoinitiators for ultraviolet-light-cured coatings in the coating industry for the surface protection of various materials. Therefore, the preparation of tertiary a-hydroxycarbonyl compounds has received considerable attention. In the past decades, oxidation of the corresponding enolates or silyl enol ethers with peroxides, hypervalent iodine compounds, metal oxides, *N*-sulfonyloxaziridines, oxygen, and other oxidants has been described.

The use of molecular oxygen as an oxidant and oxygenatom source for oxygen incorporation in organic synthesis has attracted considerable attention owing to its inexpensive, abundant, and environmentally benign nature.

Although a significant number of transition-metal-catalyzed C-H hydroxylation reactions have been developed, practical and efficient C-H hydroxylation reactions with molecular oxygen as the oxidant and oxygen source are still desirable. Whereas previous autoxidation and metal-mediated aerobic oxidative hydroxylation reactions of carbonyl compounds had shown limited scope in terms of possible substrates, a milestone was set by Ritter and co-workers in the form of a transformation catalyzed by a bimetallic palladium complex with O_2 as the oxidant and oxygen source as the first practical, efficient, and general approach based on aerobic C-H hydroxylation for the synthesis of tertiary α-hydroxycarbonyl compounds. Despite the significance of the reaction, it is not without disadvantages: The expensive and complex Pd catalyst used has to be completely removed from the product, especially in the synthesis of pharmaceutical compounds. Therefore, a practical and efficient method for the direct C-H hydroxylation of carbonyl compounds with molecular oxygen under mild conditions is still required.

In summary, we have demonstrated a Cs_2CO_3-initiated α-hydroxylation of carbonyl compounds to give tertiary α-hydroxycarbonyl compounds, which are highly valued chemicals and widely used in the chemical and pharmaceutical industries. The reaction is not only applicable to ketones, but also to esters, amides, aldehydes, and β-dicarbonyl compounds. Notably, molecular oxygen or air, the most environmentally friendly oxidant, was employed at a pressure of 1 atmosphere at room temperature without any transitionmetal catalysts. Studies to elucidate the detailed mechanism and synthetic applications of this efficient and practical hydroxylation are under way in our laboratory.