



Iridium(I)-catalyzed hydrogen peroxide oxidation of hydroxamic acids and hetero Diels–Alder reaction of the acyl nitroso intermediates with cyclopentadiene

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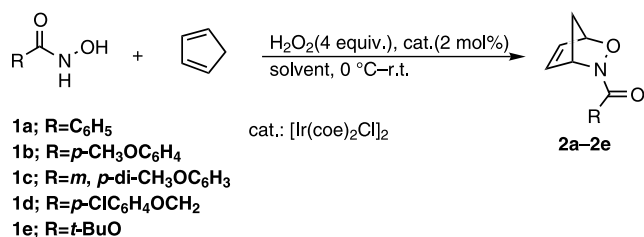
Abstract— $[\text{Ir}(\text{I})(\text{coe})_2\text{Cl}]_2$ (2 mol%)—catalyzed hydrogen peroxide oxidation of hydroxamic acids in the presence of cyclopentadiene gave the corresponding cycloadducts up to 97% yield. With a catalyst loading of 0.05 mol%, a maximum TON was attained to 740. © 2002 Elsevier Science Ltd. All rights reserved.

The synthesis of nitroso intermediates is of vital interest from both an organic synthesis and biochemistry point of view. Because this can be widely applicable to achieve many multi-functionalized molecules of natural products and also the nitroso intermediate can be formed in biological systems.¹ Nitroso intermediates are commonly obtained from the oxidation of hydroxylamine derivatives using organic and inorganic oxidants with the subsequent formation of an undesirable side product of 1 equiv.² In the choice of oxidant, hydrogen peroxide gets the top priority since water is the only side product after the oxidation process.³ In this regard, we have previously reported one of the highly efficient method for the synthesis of nitroso intermediates via Ru(II)(pybox-dh)(pydic)-catalyzed hydrogen peroxide oxidation of hydroxamic acids and its consequent het-

ero Diels–Alder reaction with cyclopentadiene.⁴ During the course of our continuous research, we were searching to find out other new catalytic systems which can be effective to the above mentioned type of oxidation process (Scheme 1). Here, we report a novel Ir(I) based method for the synthesis of nitroso intermediates via hydrogen peroxide oxidation of hydroxamic acids and its subsequent hetero Diels–Alder reaction with cyclopentadiene.

The results are summarized in Table 1. Initially we have selected a number of metallic systems (Table 1, entries 1–4). Among the tested metallic systems only $[\text{Ir}(\text{cod})\text{Cl}]_2$ (cod=cyclooctadiene) and CuI have responded moderately (entries 3 and 4).⁵ Owing to the solubility of CuI, we focus on Ir(I) catalyst. Since tautomerism of hydroxamic acids is well known, the effects of bases were also examined for this catalytic oxidation system.⁶ In the presence of catalytic or stoichiometric amounts of some bases with $[\text{Ir}(\text{cod})\text{Cl}]_2$, slight increases of cycloadduct were observed (entries 5–10).

On the other hand, $[\text{Ir}(\text{coe})_2\text{Cl}]_2$ (coe=cyclooctene) gave the highest yield without any additives (entry 11).^{5d,7} The optimized condition of both solvent and reaction temperature was briefly surveyed. The yield of cycloadduct varied with different solvent systems. Entries 11–16 shows the yields of the reaction of hydrogen peroxide oxidation of benzohydroxamic acid in the presence of cyclopentadiene in various solvent medium.



Scheme 1.

Keywords: nitroso intermediate; hydrogen peroxide; iridium catalyst; hetero Diels–Alder reaction; 1,2-oxazine.

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Table 1. Transition metal catalyzed hydrogen peroxide oxidation of hydroxamic acids and its hetero Diels-Alder reactions^a

Entry	Hydroxamic acid	Cat.	Solvent	Additive (equiv.)	2a yield (%) ^b
1	1a	Co(acac) ₂	THF	–	18
2	1a	[Rh(OAc) ₂] ₂	THF	–	19
3	1a	CuI	THF	–	60
4	1a	[Ir(cod)Cl] ₂	THF	–	51
5	1a	[Ir(cod)Cl] ₂	THF	KOH (0.3)	74
6	1a	[Ir(cod)Cl] ₂	THF	Triethylamine (1.0)	70
7	1a	[Ir(cod)Cl] ₂	THF	Diisopropylamine (1.0)	53
8	1a	[Ir(cod)Cl] ₂	THF	<i>N</i> -Methylmorpholine (1.0)	64
9	1a	[Ir(cod)Cl] ₂	THF	Morpholine (1.0)	13
10	1a	[Ir(cod)Cl] ₂	THF	Pyridine (1.0)	25
11	1a	[Ir(coe) ₂ Cl] ₂	THF	–	97
12	1a	[Ir(coe) ₂ Cl] ₂	CH ₃ OH	–	60
13	1a	[Ir(coe) ₂ Cl] ₂	CH ₂ Cl ₂	–	86
14	1a	[Ir(coe) ₂ Cl] ₂	1,4-Dioxane	–	82
15	1a	[Ir(coe) ₂ Cl] ₂	DMF	–	90
16	1a	[Ir(coe) ₂ Cl] ₂	H ₂ O	–	19
17	1b	[Ir(coe) ₂ Cl] ₂	THF	–	94
18	1c	[Ir(coe) ₂ Cl] ₂	THF	–	80
19	1d	[Ir(coe) ₂ Cl] ₂	THF	–	60
20	1e	[Ir(coe) ₂ Cl] ₂	THF	–	92

^a Hydroxamic acid (0.15 mmol), catalyst (0.003 mmol), H₂O₂ (0.60 mmol), and cyclopentadiene (0.75 mmol) at 0°C to room temperature.

^b Isolated yields.

Uniquely, benzohydroxamic acid **1a** gave the corresponding cycloadduct with a high yield in THF solvent system rather than CH₃OH and water, and it was found that THF solvent and 0°C to room temperature was the best condition for this reaction. As [Ir(coe)₂Cl]₂ is very soluble in DMF, CH₂Cl₂ and 1,4-dioxane, these solvents can also be used for the oxidation system.

Entries 17–20 summarize the products and yields of the reactions of hydrogen peroxide oxidation of various hydroxamic acids in presence of cyclopentadiene. The catalyst loading was up to 0.05 mol% to give the corresponding cycloadduct in 37% yield with TON [turnover number = product(mol)/catalyst(mol)] = 740. Acyl nitroso intermediates can be efficiently generated from hydroxamic acids with [Ir(coe)₂Cl]₂ and hydrogen peroxide in THF. The nitroso intermediates formed by the iridium catalyst and hydrogen peroxide smoothly reacted with the diene to produce the corresponding cycloadducts, 1,2-oxazines in high yield. Furthermore, other dienes such as cyclohexadiene and α -terpinene were also found to react with **1a** to give the corresponding cycloadducts in 90 and 87% yield respectively along with 9:1 regio isomer for the later.

In conclusion, [Ir(coe)₂Cl]₂-catalyzed hydrogen peroxide oxidation system works much better than any other transition metal complex-catalyzed oxidation methods. To the best of our knowledge, so far, there is no report on the use of homogeneous catalyst containing iridium and hydrogen peroxide. This system can be applied for another mild oxidation process such as quinone synthesis from phenol derivatives, which are being carried out. The mechanism of the present oxidation of hydroxamic acids is still unclear. In spite of that, this iridium-catalyzed hydrogen peroxide oxidation system can be used

for the synthesis of highly functionalized molecules since the hydrogen peroxide is environmentally sound and a cost effective oxidant.

General procedure is as follows (Table 1, entry 11): To a solution of hydroxamic acid (20.6 mg, 0.15 mmol) in THF (1.0 mL) was added a solid of [Ir(coe)₂Cl]₂ (2.7 mg, 0.003 mmol) at 0°C followed by addition of freshly distilled cyclopentadiene (61 μ L, 0.75 mmol) and hydrogen peroxide (31%, 68 μ L, 0.60 mmol). The resulting yellowish green mixture was stirred for 20 h at room temperature. The organic phase was extracted with CH₂Cl₂, and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to give hetero Diels–Alder cycloadduct (29.4 mg) in 97% isolated yield.⁸

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