



# A mild oxidation method of hydroxamic acids: efficient trapping of acyl nitroso intermediates

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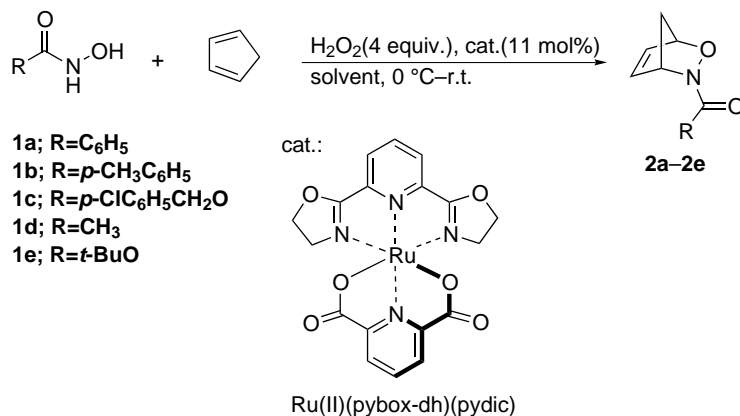
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**Abstract**—Ruthenium(II)-pyridine-2,6-dicarboxylate (pydic) of 2,6-bis(oxazolanyl)pyridine (pybox-dh) complex catalyzed the hydrogen peroxide oxidation of hydroxamic acid in the presence of cyclopentadiene to give acyl nitroso cycloadducts in 74–99% yield. © 2001 Elsevier Science Ltd. All rights reserved.

Nitroso intermediates play an important role in organic chemistry since highly functionalized molecules such as pyrrolidines, amino alcohols and aza sugars are easily available from nitroso compounds by hetero Diels–Alder reaction.<sup>1</sup> The prominent utility of nitroso intermediate is that the synthesis of 1,4-amino alcohols as building blocks for total synthesis of natural products.<sup>2</sup> Although recent studies on the synthesis of 1,4-amino alcohols are still focused and increasing the utility of nitroso intermediates, the synthetic method of nitroso intermediates are limited. In general, the nitroso intermediates are obtained from the oxidation of hydroxyl amine derivatives using organic and inorganic oxidants such as periodate salts,<sup>3</sup> hypochlorite,<sup>4</sup> PCC,<sup>5</sup> NMO–nitrite oxides<sup>6</sup> and Swern–Moffat method.<sup>7</sup> With usually accompany with the corresponding undesired side

products at the equivalent. In this context, we report here the synthesis of nitroso intermediates via the ruthenium-catalyzed hydrogen peroxide oxidation of hydroxamic acid and its subsequent hetero Diels–Alder reaction with cyclopentadiene (Scheme 1).

We have chosen hydrogen peroxide or O<sub>2</sub> as an oxidant, because water is the only side product after the oxidation process.<sup>8</sup> Initially, we tried Marko's procedure for the preparation of nitroso intermediates from hydroxamic acids, where we used TPAP (tetra-isopropylammonium perruthenate)–O<sub>2</sub> system, since the method for the oxidation of alcohols seems to be applied.<sup>8b</sup> Table 1 summarizes the products and yields of the reaction of hydrogen peroxide oxidation of various hydroxamic acids in the presence of cyclopentadi-



## Scheme 1.

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

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**Table 1.** Ruthenium-catalyzed hydrogen peroxide oxidation of hydroxamic acids

Entry	Hydroxamic acids	Catalyst	Oxidant	Solvent	Cycloadduct	Yield (%) <sup>a</sup>
1	<b>1a</b>	–	H <sub>2</sub> O <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	<b>2a</b>	0
2	<b>1a</b>	TPAP <sup>b</sup>	O <sub>2</sub> <sup>c</sup>	CH <sub>2</sub> Cl <sub>2</sub>	<b>2a</b>	33
3	<b>1a</b>	TPAP <sup>b</sup>	H <sub>2</sub> O <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	<b>2a</b>	39
4	<b>1a</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	CH <sub>3</sub> OH–H <sub>2</sub> O <sup>d</sup>	<b>2a</b>	90
5	<b>1a</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	THF	<b>2a</b>	90
6	<b>1b</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	CH <sub>3</sub> OH–H <sub>2</sub> O <sup>d</sup>	<b>2b</b>	91
7	<b>1b</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	THF	<b>2b</b>	92
8	<b>1c</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	CH <sub>3</sub> OH–H <sub>2</sub> O <sup>d</sup>	<b>2c</b>	74
9	<b>1c</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	THF	<b>2c</b>	76
10	<b>1d</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	CH <sub>3</sub> OH–H <sub>2</sub> O <sup>d</sup>	<b>2d</b>	81
11	<b>1d</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	THF	<b>2d</b>	84
12	<b>1e</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	CH <sub>3</sub> OH–H <sub>2</sub> O <sup>d</sup>	<b>2e</b>	99
13	<b>1e</b>	Ru(II)(pybox-dh)(pydic)	H <sub>2</sub> O <sub>2</sub>	THF	<b>2e</b>	99

<sup>a</sup> Isolated yield.<sup>b</sup> Tetrapropylammoniumperruthenate.<sup>c</sup> 1 atm.<sup>d</sup> 1/1 v/v.

ene. The transient nitroso intermediate was subsequently trapped with the diene to give the corresponding 1,2-oxazine **2** in 33% yield (entry 2). The TPAP–H<sub>2</sub>O<sub>2</sub> system also gave the same level of the yield (entry 3).

On the other hand, acyl nitroso intermediates can be efficiently generated by the mild oxidation of hydroxamic acid with Ru(pybox-dh)(pydic) (11 mol%) and hydrogen peroxide (4 equiv.) in both CH<sub>3</sub>OH–H<sub>2</sub>O and THF (entries 4 and 5). The ruthenium catalyst was synthesized from the same procedure as we reported before.<sup>9</sup> The optimized condition on solvent system and reaction temperature were briefly surveyed and polar solvent at 0°C to room temperature was the best for this reaction because of the solubility of hydroxamic acids and stability of cyclopentadiene. The nitroso intermediate, formed by the ruthenium catalyst with hydrogen peroxide, smoothly reacted with the diene to produce the corresponding cycloadducts 1,2-oxazines **2** in high yields (entries 6–11). Even in 1 mol% catalyst loading, the reaction efficiently proceeded in high yield (91%). Especially, *t*-butoxycarbonyl hydroxamic acid **1e** gave the corresponding cycloadduct in a quantitative yield (entries 12 and 13). THF, THF–H<sub>2</sub>O or CH<sub>3</sub>OH–H<sub>2</sub>O proved to be relatively good solvents system for the preparation of nitroso intermediate as well as for the hetero Diels–Alder reactions. To best of our knowledge, this ruthenium(II) (pybox)(pydic) system of the pre-catalyst works much better than any other oxidation method reported in previous literature. Furthermore, the double bond of the cycloadducts and hydroxyl group of the solvent system have no effect during the reaction time. The mechanism for the present oxidation of hydroxamic acids is still unclear. However, this ruthenium catalyzed hydrogen peroxide oxidation condition can be used for the synthesis of highly functionalized molecules since the hydrogen peroxide is low cost and safety oxidant. We are also applying this method for intramolecular nitroso hetero Diels–Alder reactions.

*Typical experimental procedure:* To a solution of hydroxamic acid **1a** (24.1 mg, 0.176 mmol) in THF (2.0 mL) was added a solid ruthenium(II)(pybox-dh)(pydic) (10.0 mg, 0.0194 mmol) at 0°C followed by addition of 30% H<sub>2</sub>O<sub>2</sub> (0.077 mL, 0.70 mmol) and freshly distilled cyclopentadiene (0.072 mL, 0.88 mmol) in one portion. The resulting dark blue mixture was stirred at room temperature. After 2 h, TLC showed no starting material was present. The product was extracted with ether, dried over Na<sub>2</sub>SO<sub>4</sub> and purified by flash column chromatography on silica gel (hexane:EtOAc=1:3 v/v) to give the cycloadduct **2a** (31.8 mg) in 90% isolated yield.<sup>10</sup>

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