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Copper(II)-Catalyzed Room Temperature Aerobic Oxidation of Hydroxamic Acids and Hydrazides to Acyl-Nitroso and Azo Intermediates, and Their Diels–Alder Trapping

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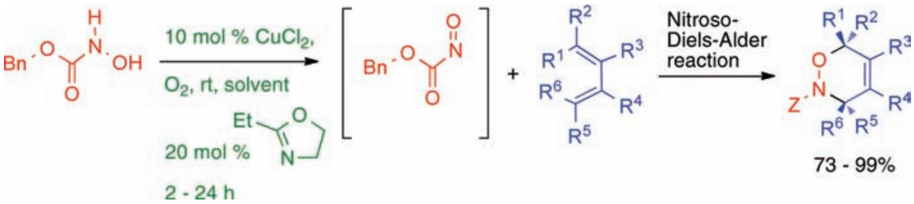
ABSTRACT



CuCl$_2$, in the presence of a 2-ethyl-2-oxazoline ligand, is an effective catalyst for the room temperature, aerobic oxidation of hydroxamic acids and hydrazides, to acyl-nitroso and azo dienophiles respectively, which are efficiently trapped *in situ* via both inter- and intramolecular hetero-Diels–Alder reactions with dienes. Both inter- and intramolecular variants of the Diels–Alder reaction are suitable under the reaction conditions using a variety of solvents. Under the same conditions, an acyl hydrazide was also oxidized to give an acyl-azo dienophile which was trapped intramolecularly by a diene.

Nitroso dienophiles are known to undergo [4 + 2] cycloaddition reactions with conjugated dienes[1] to provide heteroatom Diels–Alder adducts. These cycloadducts are valuable synthetic intermediates for natural product synthesis and have been used to synthesize novel oxazine derivatives, possessing new biological properties.[2,3] However, electron-rich nitroso compounds are not particularly reactive. They readily dimerize[1] and are known to form unreactive complexes with Lewis acids.[5] Far more useful for the Diels–Alder reaction are nitroso species bearing electron-withdrawing groups.[2e,f] In particular, the highly reactive, unstable acyl-nitroso compounds have found the greatest utility.[4]

The formation of acyl-nitroso dienophiles is generally carried out *in situ* in the presence of the diene to trap the unstable species.[6] The oxidation of hydroxamic acids has been achieved using periodates, DMSO-based oxidants, and lead(IV) reagents.[7] Recent advances involve more atom-economic and less toxic, metal-catalyzed oxidations involving peroxides.[8] Peroxides, however, are still not ideal reagents because yields are substrate, oxidant, and catalyst dependent.[8d] There is a need, therefore, to develop new, clean, green, mild, and general *in situ* hydroxamic acid oxidation reactions. Herein, we report such a process using catalytic Cu(II) in air.

Following mechanistic studies on the oxidation of hydroxamic acids catalyzed by various metals, and the

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in situ formation of Cu(II)-based catalyst systems in the presence of aryl-nitroso species,[9] we began to explore the potential for developing a hydroxamic acid oxidation procedure which did not involve peroxides or other strong oxidants. Indeed, from the point of view of developing an environmetally benign oxidation process, an aerobic oxidation was highly attractive. Among potential oxidative systems that could be employed for such a process, we examined various palladium(II) systems with ligands that included thioureas, oxazolines, and phosphines, together with co-oxidants such as copper(II) salts because related systems have been employed for other oxidative transformations.[10] These were screened for the *in situ* oxidation of the *Z*-protected hydroxamic acid **1** to derive the corresponding acyl-nitroso species **2**. Formation of intermediate acylnitroso compound **2** was initially followed by trapping with cyclohexaadiene **3b** to give cycloadduct **4b** to screen potential catalytic systems. Preliminary results were encouraging; however, more detailed studies revealed that the palladium(II) salts were not involved, and indeed, it was in fact the copper(II) salt alone which was acting as a catalytic oxidant in air, *i.e.* as outlined in eq 1 (Table 1). Examination of different copper(II) salts (i.e., $CuCl_2$, $CuBr_2$, CuI_2) and loadings, with different ligands (includng tetramethylthiourea, 2-ethyl-2-oxazoline and mixed ligand systems[10]), showed that $CuCl_2$ (10 mol %), in the presence of 2-ethyl-2-oxazoline (20 mol %), in air at RT in various solvents (*vide infra*) including $CHCl_3$ (eq 1) gave essentially quantitative conversion of hydroxamic acid **1** to the cycloadduct **4b**, which was isolated in 86% yield after recrystallization. Cycloadduct **4b** gave single crystals suitable for X-ray structure analysis (see Supporting Information (SI)).

Further studies with a variety of dienes (Table 1) revealed that the Cu(II)-catalyzed, room temperature aerobic oxidation reaction was indeed a general and useful process in the solvent $CHCl_3$. Although reaction times vary from 3 (Table 1, entry 2) to 24 h (Table 1, entries 3 and 5–7), the isolated yields were universally high, representing a substantial improvement upon our previous preferred oxidation systems.[8b,d] For example, the formation of the DMA adduct is readily achieved in 24 h in 86% yield after recrystallization (Table 1, entry 6), contrasting with a previous best reaction yield of 36% in 96 h using a ruthenium-salen + TBHP oxidation system.[8b] Crystals of cycloadduct **4f** suitable for single-crystal X-ray diffraction were grown (see SI). Cycloadduct **4g** was also isolated in a substantially improved yield of 74%, compared with 16% using an iron catalyst.[8d] For dienes which are capable of undergoing both Diels–Alder addition and ene-reactions, the overall yields were also high and we were able to ascertain accurately the ratio of cycloaddtion to ene product. Thus, in the case of 2,3-dimethylbuta-1,3-diene **3c**, reaction with acyl-nitroso species **2** resulted in a 75% combined yield of an inseparable mixture of products **4c** and **5c** in a ratio of 3:1. (Table 1, entry 3). Similarly, when isoprene **3e** was employed (Table 1, entry 5), the 9:1 ratio of Diels–Alder to ene products obtained was reasonable, with a 2:1 ratio of regioisomeric Diels–Alder adducts **4e** and **4e′** being produced. This shows that the slightly more electron-rich end of the diene prefers to react at the nitroso nitrogen atom rather than at oxygen.

Despite the success of the reactions shown in Table 1, development of a more environmentally benign oxidation process led to an examination of different solvent systems for the reaction. Thus, a solvent screen was performed with 2,3-dimethylbutadiene **3c** employed as the trapping diene (Table 2). The effects of solvent upon the rate, yield, and ratio of competing nitroso-Diels–Alder cycloaddition and ene reactions were studied.[14]

The reaction was carried out in a range of solvents (Table 2), with universally high yields being obtained (80 to 89%). All of the reactions carried out in $CHCl_3$ were then repeated in the preferable, inexpensive solvent MeOH, as the reaction proceeded at the highest rate in this solvent (Table 2, entry 1). Significant effects on both the rate of reaction and the product distribution as a function of solvent polarity were observed. For example, the reaction shown in eq 2 was approximately 70 times

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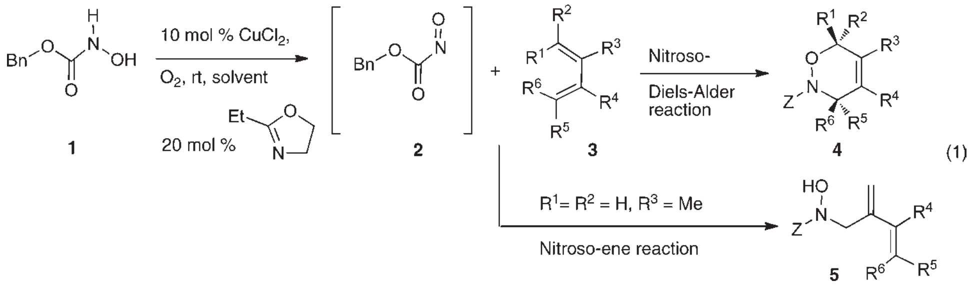
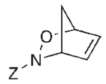
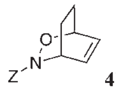
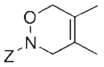
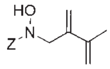
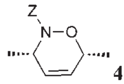
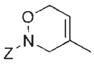
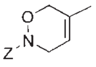
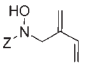
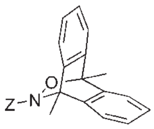
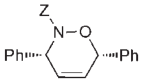
Table 1. Products and Isolated Yields for the *in Situ* *Z*-Nitroso Dienophile Generation and Diels–Alder Trapping



(1)

entry	diene **3**	nitroso-Diels-Alder products **4** and ene-adducts **5**	solvent			
			CHCl$_3$		MeOH	
			time (h)	yield **4** / %[a] (crude ratio of **4**:**5**)	time (h)	yield **4** / %[a] (ratio **4**:**5**)
1	cyclopenta-diene **3a**	 **4a**	4	99[b]	3	97[b]
2	cyclohexa-1,3-diene **3b**	 **4b**	3	86[c]	3	92[c]
3	2,3-dimethyl-buta-1,3-diene **3c**	 **4c**  **5c**	24	75 (7:1)	2	85 (5:1)
4	hexa-2,4-diene **3d**	 **4d**	5	83[c]	2	97[c]
5	2-methyl-buta-1,3-diene **3e**	 **4e**  **4e'**  **5e**	24	73[d] ratio **4e**:**4e'** = 2:1 (9:1)	8	79[d] ratio **4e**:**4e'** = 2:1 (8.5:1)
6	9,10-dimethyl-anthracene **3f**	 **4f**	24	86[b]	10	88[b]
7	1,4-diphenyl-buta-1,3-diene **3g**	 **4g**	24	74	18	79[e]

[a] Typical procedure: MeOH (5 mL), diene (0.75 mmol), CuCl$_2$ (0.06 mmol), 2-ethyl-2-oxazoline (0.12 mmol), *N*-(benzyloxycarbonyl)hydroxylamine (0.63 mmol), stirred at rt in air. At completion, the solvent evaporated and the product was purified by silica gel chromatography. Isolated yields quoted after purification (see Supporting Information). [b] See ref 11. [c] See ref 12. [d] See ref 13. [e] Isolated with 10% benzyl methyl carbonate derived from **1** by methanolysis.

slower in acetronitrile (Table 2, entry 3) than in MeOH (Table 2, entry 1), yet the ratio of Diels–Alder adduct **4c** to ene adduct **5c** increased from 5:1 in MeOH to 25:1 in MeCN. The origin of this effect is unclear, as is the increased **4c**:**5c** ratio observed in MTBE, *i*PrOH, 2-MeTHF, and toluene (Table 2, entries 2, 6–8).

As shown in Table 1, isolated yields of cycloadducts **3** when the reactions were carried out in MeOH were even greater than when run in CHCl$_3$. The reactions were generally either moderately or considerably faster, reinforcing the general utility of MeOH as the solvent. Interestingly, the DMA adduct **4f** (Table 1, entry 6) was isolated with a small amount (10%) benzyl methyl carbonate. Hydroxamic acid **1** is stable in MeOH, suggesting that intermediate **2** is indeed unstable, as discussed elsewhere,[4] and is a source of HNO in hydroxylic solvents. An intramolecular variant of the decomposition of **2** has been used deliberately to generate HNO.[15]

Having developed an efficient aerobic oxidation of hydroxamic acid **1** with subsequent intermolecular trapping with different dienes (Table 1), this method was applied to intramolecular analogues, as outlined in eq 3.

To our gratification, *in situ* oxidations of hydroxamic acids **6a** and **6b** both proceeded smoothly. The intramolecular diene efficiently intercepted the intermediate acylnitroso species to provide bridged bicyclic cycloadducts **7a** and **7b**, respectively, in high yields (eq 3).

The success of the intramolecular nitroso Diels–Alder reactions also led us to examine the corresponding

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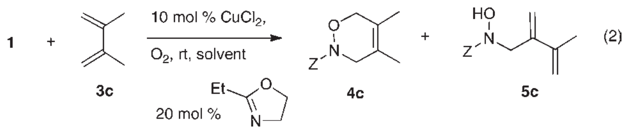
Table 2. Solvent Effects for the RT Oxidation of **1** and Trapping with **3c**

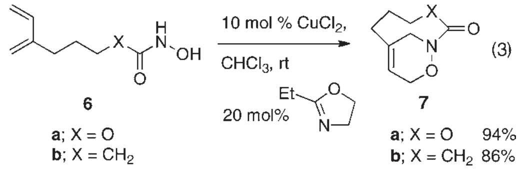


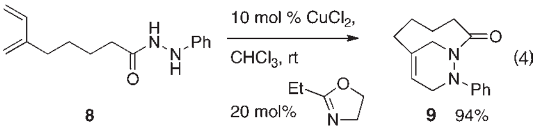
entry	solvent	time (h)	ratio **4c**:**5c**	yield (%)[a]
1	MeOH	2	5:1	85
2	MTBE	20	15:1	85
3	MeCN	144	25:1	80
4	EtOH	7	4:1	83
5	EtOAc	7	4:1	81
6	*i*PrOH	48	13:1	89
7	2-MeTHF	20	12:1	88
8	toluene	4	12:1	82
9	MeOH/toluene, 1:4	3	5:1	82
10	$CHCl_3$	3	7:1	75

[a] Isolated yields after purification (see Supporting Information).

acyl-hydrazide system **8** (eq 4). Exposure to the aerobic oxidation conditions again caused efficient oxidation, followed by trapping of the azo dienophile by the diene, providing acyl-azo cycloadduct **9** in 94% yield. Therefore, this novel oxidation system is also useful for the *in situ* formation of highly reactive acyl-azo compounds.[16]

In summary, we have developed a particularly efficient, mild, and more environmentally benign *in situ* process for the oxidation of hydroxamic acids to acyl-nitroso derivatives based on Cu(II) catalysis. Although aerobic oxidation probably involving Cu(II) catalysis has been used for oxidative processes previously,[17] this is the first such application for *in situ* acyl-nitroso and azo formation. These reactive intermediates are readily trapped under the reaction conditions, both inter- and intramolecularly, to provide the corresponding cycloadducts in good yields. In addition, we observed interesting solvent effects on the rate as well as the regio- and chemoselectivity of the reaction. The same conditions also provide acyl-azo derivatives *in situ* via the oxidation of acyl-hydrazide compounds.





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Supporting Information Available. Experimental details and characterization data for new compounds; X-ray crystallographic data for **4b** and **4f** in CIF format (CCDC-820904 and 820905, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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