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Generation of Acylnitroso Dienophiles: A Study of Metal Catalysis

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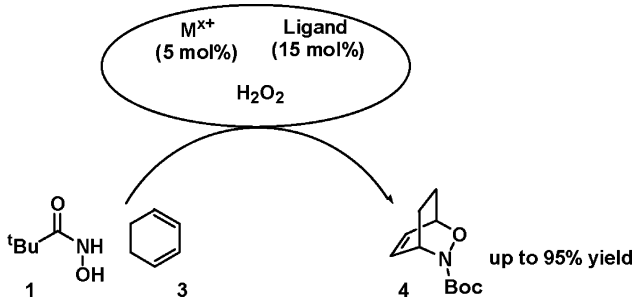
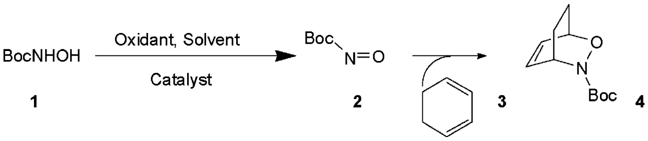
Received November 13, 2006



Four novel metal/amine catalysts efficiently converted Boc-NHOH to its acylnitroso species at 5 mol % catalyst loading. These reactions allowed the preparation of polyfunctional hetero Diels−Alder adducts in high yield and from truly commercially available materials.

Acylnitroso compounds have been widely used since the 1940s as efficient hetero dienophiles in [4 + 2]-cycloaddition reactions with conjugated dienes.[1,2] In general, the acyl nitroso components are obtained from the oxidation of hydroxamic acids using organic and inorganic oxidants including periodate salts,[3] hypochlorite,[4] PCC,[5] NMO-nitrile oxides,[6] and the Swern−Moffat method.[7] As a part of our ongoing research on the generation of chemical diversity, we became interested in the generation of acylnitroso species. Our approach to the development of diversity oriented syntheses is based on the generation of building blocks that contain multiple functionalities that could be selectively reacted (polyfunctional scaffolds).[8−11] We hypothesized that a reagent containing a number of functionalities *m*, which could be selectively reacted in a number of *n* directions, will generate diversity in $D = (mn)$ directions. We identified cycloadduct **4** (Scheme 1) as an example of a polyfunctional scaffold, which contains four contiguous chemo-differentiable functionalities.

SCHEME 1. Generation of Polyfunctional Scaffold 4



In this respect, the [4 + 2] cycloaddition of acylnitroso dienophile **2** to a diene **3** is an ideal transformation to initiate structural divergence. Additionally, hydroxamic acid **1** and dienes like **3** are commercially available. We reasoned that if **4** could be prepared from a mild oxidation of 1 equiv of **1** and 1 equiv of **3**, then the hetero Diels−Alder reaction could be run in tandem with other transformations involving the functionalities formed in **4**. For this reason, we focused our attention to metal catalyzed oxidations of **1**, as metals were often involved in the transformation of alkenes bearing proximal heteroatom functionalities.[12,13] In the choice of the oxidant, hydrogen peroxide was selected since water was the only side product formed. A literature survey revealed that $\mathrm{Ru^{II}}$[14,15] and $\mathrm{Cu^{I}}$[16,17] were reported as catalysts for the oxidation of hydroxamic acid **1**. In particular, Iwasa et al. reported the oxidation of **1** using hydrogen peroxide as the oxidant.[14] This method exploited a preformed $\mathrm{Ru^{II}}$(pybox-dh)(pydic) catalyst that was employed at 1 mol % loading. However, Iwasa's catalyst was soluble only in mixtures of methanol/water or THF,[14] and this poor solubility profile was not ideal for the development of tandem catalyses. Nicholas and co-workers reported that $\mathrm{Cu^{I}}$ salts catalyzed the oxidation of **1** to **2** with hydrogen peroxide as the oxidant: 15 mol % CuCl was necessary to convert **1** to **2**; the reaction occurred in 7 h and required an excess of the diene component to ensure a high yield of cycloadduct **4**.[16] In a related work, $\mathrm{Cu^{I}}$ and $\mathrm{Cu^{II}}$ salts were described as catalysts for the oxidation of phenylhydroxylamine to PhNO, which was subsequently trapped with a diene.[18] This process required high temperatures and long reaction times and gave a cycloadduct related to **4** in low yield and contaminated by several side products. Whiting et al. reported a few $\mathrm{Ru^{II}}$ complexes as catalysts for the oxidation of **1** to **2** using ^{t}BuOOH as an oxidant.[15] A $\mathrm{Ru^{II}}$ salen complex was described to be active at 0.1 mol % loading. The preparation of the $\mathrm{Ru^{II}}$ salen catalyst required two steps of synthesis. To

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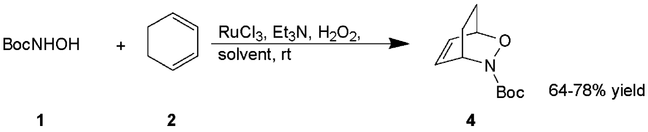
10.1021/jo062334y CCC: $37.00

SCHEME 2. Generation of Adduct 4 with Metal/Amine Catalyst Ru^{III}/NEt_3



find a metal catalyzed oxidation of **1** to **2** based on truly commercially available sources, we decided to screen a number of metal salts. Considering that ligands have repeatedly influenced the reactivity of the metal catalyst (ligand accelerated catalysis),[19] we carried out the screening in the presence of ligands, which could also facilitate the solubility of the catalyst. In a test experiment, we used $RuCl_3$ and NEt_3. We were delighted to observe that the metal/amine couple Ru^{III}/NEt_3 showed a remarkable catalytic activity (Scheme 2 and Table 1).

When Boc-NHOH was reacted with hydrogen peroxide in the presence of sub-stoichiometric amounts of $RuCl_3$ and Et_3N, cycloadduct **4** was obtained in good isolated yield (Scheme 2), showing that Ru^{III} is an efficient catalyst for this reaction. When neither Ru^{III} nor Et_3N was present, no reaction had occurred (Table 1, entries 1 and 2). However, with just 5 mol % Ru^{III} catalyst, cycloadduct **4** was obtained in 64−78% isolated yield (Table 1, entries 4−6). The reaction proceeded equally well in a variety of solvents including DCM, THF, and CH_3CN, and complete conversion of **1** was typically observed in 20−30 min. Importantly, the crude reaction mixture contained only adduct **4**, as evidenced by ^1H NMR.[20]

We then turned our attention to other potentially useful metal/amine catalysts, with commercially available CuCl and $CuCl_2$ being an obvious choice. We also included in this study $FeCl_3$ and $NiCl_2$, as Fe^{III} and Ni^{II} were repeatedly reported as good catalysts for the oxidation of amines[21] or alkenes[22] using H_2O_2. Ethanol amine, ethylene diamine, and triethylamine were selected as the ligands considering that enantiopure amino alcohols, diamines, and tertiary amines are easy to obtain. These choices were placed in an experimental setup in which equimolar amounts of **1** and **2** were reacted with H_2O_2 in the presence of 5 mol % metal salt and 15 mol % ligand. As a solvent was needed, we selected THF and DCM. We were interested in comparing the catalytic efficiency of the metal/amine catalyst in solvents able (THF) or unable (DCM) to participate in metal ligation.

These studies revealed three novel and efficient catalysts for the generation of acylnitroso species that work under a set of mild reaction conditions (Table 2). The reactions were very simple to set up and did not require either controlled atmosphere or controlled temperature. A mixture of the required metal salt and ligand was usually premixed prior to the addition of the diene. We noticed that to ensure high yields and fast reaction rates, the sequence of addition of the reagents was crucial. Particularly, it was important to add the oxidant as the last component. The data collected (Table 2) pointed out the following facts: (a) faster reaction rates were observed in DCM versus THF in the presence of a ligand. (b) Cu^I, Cu^{II}, and Fe^{III} showed a high level of activity even in the absence of a ligand (Table 2, entries 1, 7, 8, 13, and 14); this is in line with the previous reports,[16−18] although our procedure worked well using a reduced catalyst loading and a 1:1 ratio of hydroxamic acid/diene. (c) The reaction proceeded also in the absence of ligand, which was due to the ability of THF to act as a ligand, although the role of *N*-Boc hydroxylamine as a ligand could not be ruled out. (d) In the absence of the ligand, the reactions of Cu^I and Cu^{II} were faster in THF as compared to DCM, but this was reverted in the presence of the ligand (Table 2, entries 1 and 2 and 3 and 4 or entries 7 and 8 and 9 and 10). (e) Amino alcohols were the best ligands for Cu^{II} and Cu^I, to which they imparted a significant acceleration (Table 2, entries 1 and 3 or 7 and 9); experiments run using several enantiopure aminoalcohols gave racemic **4**, suggesting that the nitroso species was released from

TABLE 1. Yield of Adduct 4 Obtained Using Catalytic Amounts of Ru^{III}

entry	% Ru^{III}	amine	solvent	% of **4**[a]
1		Et_3N	DCM	
2	10		DCM	9
3	10	Et_3N	DCM	71[b]
4	5	Et_3N	DCM	76[b]
5	5	Et_3N	THF	74[b]
6	5	Et_3N	CH_3CN	78[b]
7	1	Et_3N	DCM	34

[a] Isolated yields after chromatography. [b] ^1H NMR of the crude reaction mixture showed a complete conversion of **1** and the presence of adduct **4** as the only product.

TABLE 2. Yields of 4 Obtained Using a Metal/Amine Catalyst

entry	metal	amine	solvent	time (min)[a]	% yields of **4**[b,c]
1	CuCl		DCM	390	76
2	CuCl		THF	300	95
3	CuCl	$HOCH_2CH_2NH_2$	DCM	30	83
4	CuCl	$HOCH_2CH_2NH_2$	THF	180	95
5	CuCl	NEt_3	DCM	720	80
6	CuCl	$H_2NCH_2CH_2NH_2$	DCM	300	32
7	$CuCl_2$		DCM	255	58
8	$CuCl_2$		THF	45	94
9	$CuCl_2$	$HOCH_2CH_2NH_2$	DCM	20	84
10	$CuCl_2$	$HOCH_2CH_2NH_2$	THF	30	95
11	$CuCl_2$	NEt_3	DCM	120	77
12	$CuCl_2$	$H_2NCH_2CH_2NH_2$	DCM	180	27
13	$FeCl_3$		DCM	30	48
14	$FeCl_3$		THF	30	95
15	$FeCl_3$	$HOCH_2CH_2NH_2$	DCM	35	62
16	$FeCl_3$	$HOCH_2CH_2NH_2$	THF	1800	89
17	$FeCl_3$	NEt_3	DCM	30	69
18	$FeCl_3$	$H_2NCH_2CH_2NH_2$	DCM	20	76
19	$NiCl_2$		DCM	5760	52
20	$NiCl_2$		THF	11520	78
21	$NiCl_2$	$HOCH_2CH_2NH_2$	DCM	1080	71
22	$NiCl_2$	$HOCH_2CH_2NH_2$	THF	10080	71
23	$NiCl_2$	NEt_3	DCM	4560	81
24	$NiCl_2$	$H_2NCH_2CH_2NH_2$	DCM	4680	60

[a] Time required to observe complete conversion of **1**. [b] Isolated yield after column chromatography. [c] ^1H NMR of the crude reaction mixture showed a complete conversion of **1** and the presence of adduct **4** as the only product.

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(20) A typical ^1H NMR of the crude reaction mixture is included in the Supporting Information.

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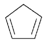
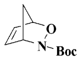
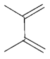
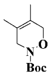
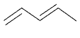
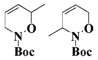
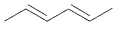
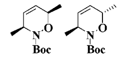
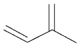
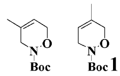
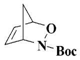
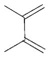
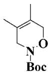
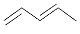
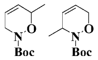
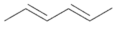
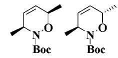
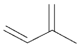
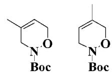
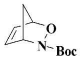
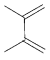
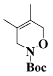
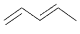
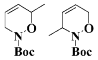
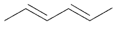
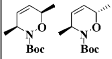
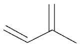
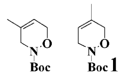
TABLE 3. $\mathrm{Cu^{I}}$, $\mathrm{Cu^{II}}$, or $\mathrm{Fe^{III}}$ Catalyzed Hetero Diels−Alder Reactions of Dienes 5, 7, 9, 11, and 13

Entry	Catalyst	Diene	Product	Yield^{a}	Time (m)
1	$\mathrm{Cu^{I}/HOCH_2CH_2NH_2}$	 **5**	 **6**	63	20
2	$\mathrm{Cu^{I}/HOCH_2CH_2NH_2}$	 **7**	 **8**	74	30
3	$\mathrm{Cu^{I}/HOCH_2CH_2NH_2}$	 **9**	 **10a/b**	70^{b}	30
4	$\mathrm{Cu^{I}/HOCH_2CH_2NH_2}$	 **11**	 **12a/b**	64^{c}	30
5	$\mathrm{Cu^{I}/HOCH_2CH_2NH_2}$	 **13**	 **14a/b**	58^{d}	30
6	$\mathrm{Cu^{II}/HOCH_2CH_2NH_2}$	 **5**	 **6**	64	20
7	$\mathrm{Cu^{II}/HOCH_2CH_2NH_2}$	 **7**	 **8**	70	30
8	$\mathrm{Cu^{II}/HOCH_2CH_2NH_2}$	 **9**	 **10a/b**	54^{b}	30
9	$\mathrm{Cu^{II}/HOCH_2CH_2NH_2}$	 **11**	 **12a/b**	70^{c}	30
10	$\mathrm{Cu^{II.}/HOCH_2CH_2NH_2}$	 **13**	 **14a/b**	65^{d}	30
11	$\mathrm{Fe^{III}/H_2NCH_2CH_2NH_2}$	 **5**	 **6**	78	20
12	$\mathrm{Fe^{III}/H_2NCH_2CH_2NH_2}$	 **7**	 **8**	76	30
13	$\mathrm{Fe^{III}/H_2NCH_2CH_2NH_2}$	 **9**	 **10a/b**	54^{b}	30
14	$\mathrm{Fe^{III}/H_2NCH_2CH_2NH_2}$	 **11**	 **12a/b**	58^{c}	30
15	$\mathrm{Fe^{III}/H_2NCH_2CH_2NH_2}$	 **13**	 **14a/b**	64^{d}	30

[a] Isolated yields after chromatography. [b] Obtained as a 1:1.6 mixture of regioisomers. [c] Obtained as a 1:3 mixture of diastereoisomers. [d] Obtained as a 1:1 mixture of regioisomers.

SCHEME 3. Hetero Diels−Alder Reaction of Dienes 5, 7, 9, 11, and 13 Using a $\mathrm{Cu^{I}}$, $\mathrm{Cu^{II}}$, and $\mathrm{Fe^{III}}$ Catalyst

$$\underset{\mathbf{1}}{\text{BocNHOH}} \quad + \quad \underset{\mathbf{5,7,9,11,13}}{\text{Diene}} \xrightarrow[\mathrm{H_2O_2}\text{, DCM, rt}]{\text{Metal (5 mol\%), Ligand (15 mol\%),}} \underset{\mathbf{6,8,10,12,14}}{\text{Adduct}}$$

the metal after oxidation; this is in line with the observation reported by Whiting[15a] using chiral $\mathrm{Ru^{II}}$ salen catalysts. (f) Although $\mathrm{Ni^{II}}$ catalyzed reactions gave a high yield of **4**, these reactions appeared to be significantly slower. Having established four new methodologies for the generation of **4**, we explored the scope of the reaction by using different dienes (Scheme 3and Table 3). Both cyclic and acyclic dienes gave the corresponding adducts in good yields (Table 3). Complete conversion of **1** was typically observed in 20−30 min.

In conclusion, we have developed four novel methodologies for the generation of nitroso dienophiles. These reactions were practical and executable from truly commercially starting materials and afforded synthetically useful products in good to excellent yields. As compared with existing methodologies, these procedures afforded cycloadducts in similar yields, employing reagents in a 1:1 ratio and a reduced catalyst loading.[16−18] Remarkably, the crude reaction mixture showed the hetero Diels−Alder adduct as the only compound present: this renders the reactions described herein as ideal for the development of tandem processes. Considering the rich catalytic chemistry of $\mathrm{Ru^{III}}$, $\mathrm{Cu^{I}}$, $\mathrm{Cu^{II}}$, and $\mathrm{Fe^{III}}$, this could be easily envisaged.

Experimental Section

General Procedure for the Experiments Described in Table 1. To a solution of BocNHOH (200 mg, 1.5 mmol) in an opportune solvent (2.5 mL), were added $RuCl_3$ (for entry 6, 15 mg, 0.05 equiv) and triethylamine (for entry 6, 23 mg, 0.15 equiv). Cyclohexadiene (120 mg, 1.0 equiv) was added to the resulting solution, and the reaction mixture was stirred for 10 min before H_2O_2 (30%) (0.84 mL, 7 equiv) was added dropwise. The reaction was quenched by the addition of water (5 mL) when the starting material disappeared. The crude product was extracted with DCM (2 × 20 mL), the organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude material was purified by flash chromatography on silica gel using petroleum ether (40−60 °C)/ethyl acetate (3:1) as the eluent.

General Procedure for the Experiments Described in Table 2. To a solution of BocNHOH (200 mg, 1.5 mmol) in an opportune solvent (2.5 mL) were added a metal salt (0.05 equiv) and an opportune amine (0.15 equiv). Cyclohexadiene (120 mg, 1.0 equiv) was added to the resulting solution, and the reaction mixture was stirred for 10 min before H_2O_2 (30%) (0.84 mL, 7 equiv) was added dropwise. The reaction was quenched by the addition of water (5 mL) when the starting material disappeared. The crude product was extracted with DCM (2 × 20 mL), the organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude material was purified by flash chromatography on silica gel using petroleum ether (40−60 °C)/ethyl acetate (3:1).

General Procedure for the Experiments Described in Table 3. To a solution of BocNHOH (200 mg, 1.5 mmol) in dichloromethane (2.5 mL) were added a metal salt (0.05 equiv) and an opportune amine (0.15 equiv). A diene (1.0 equiv) was added to the resulting solution, and the reaction mixture was stirred for 10 min before H_2O_2 (30%) (0.84 mL, 7 equiv) was added dropwise. The reaction was quenched by the addition of water (5 mL) when the starting material disappeared. The crude product was extracted with DCM (2 × 20 mL), the organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude material was purified by flash chromatography on silica gel using petroleum ether (40−60 °C)/ethyl acetate (3:1).

Acknowledgment. We acknowledge the Irish Research Council for Science, Engineering, and Technology (IRCSET) for a grant to S.B. and PTRLI cycle III for a grant to M.F.A.A.

Supporting Information Available: General experimental procedures; spectroscopic characterization of **4**, **6**, **8**, **10a**/**b**, **12a**/**b**, and **14a**/**b**; ^{1}H NMR of compounds **4**, **6**, **8**, **10a**/**b**, **12a**/**b**, and **14a**/**b**; ^{1}H NMR of the crude reaction mixture of entry 4 (Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

JO062334Y