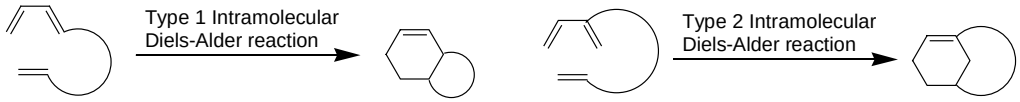
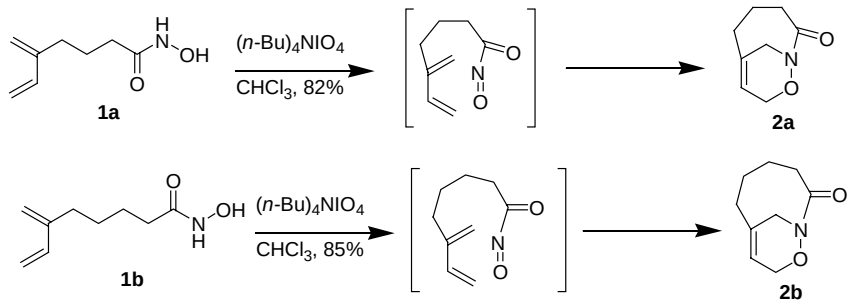
Development of Asymmetric Catalysis for the Intramolecular Acyl Nitroso Diels-Alder Reaction

Background

Diels-Alder cycloaddition reactions comprise the most important method for synthesizing six-membered rings. The intramolecular variants of these cycloadditions permit construction of polycyclic rings in a single step.[1] There are two types of intramolecular Diels-Alder reaction. The type 1 results in formation of fused ring system while the type 2 produces a bridged bicyclic structure. In the latter case the product contains a bridgehead double bond.



One reason why the Diels-Alder reaction has continued to grow in importance is the ability to incorporate heteroatoms in both diene and dienophile fragments. I am interested in the type 2 intramolecular heteroatom variants of this reaction as a means of controlling stereochemistry and regiochemistry in the cycloaddition step and for the opportunity to develop the chemistry of the novel bridgehead olefin products of these reactions. My efforts will focus on the acyl nitrso Diels-Alder reaction. Examples of this chemistry are given in the scheme below.[2]

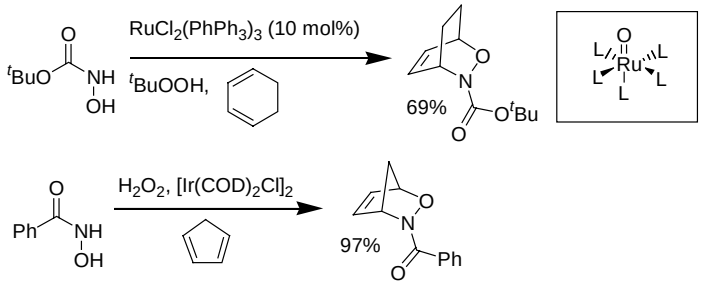


The periodate oxidation of hydroxamic acids **1a** and **1b** proceed at room temperature to generate the acyl nitroso intermediate. Cycloaddition immediately follows to give racemic crystalline bicyclic oxazinolactams **2a** and **2b**. The bridgehead oxazinolactams are masked azapines and azocines and as such, can serve as useful intermediates for medium ring heteroatom synthesis as well as for synthesis of polyfunctional acrylics. The bridgehead C=C and N-O bonds can be selectively reduced or cleaved providing stereoselective routes to medium ring lactams.

Enantiomer control in acyl nitroso cycloadditions has been achieved with varying degrees of success by incorporating chiral auxiliaries, most often carbohydrates, in the acyl nitroso precursor. This stoichiometric approach is perhaps best illustrated by the elegant work of Miller and co-workers.[3] The most efficient method of course would be asymmetric catalysis. In this proposal I outline my plans for developing asymmetric catalysts for Diels-Alder cycloaddition of acyl nitroso dienophiles.

Asymmetric catalysts for these acyl nitroso Diels-Alder reactions present fascinating challenges since the Diels-Alder precursors are not isolatable compounds, *i.e.* the dienophiles are generated *in situ* by oxidation. To induce asymmetry in these reactions the oxidation reagent should remain associated with the reactive intermediate during the subsequent cycloaddition step. This would permit development of a chiral oxidant to induce asymmetry in the cycloaddition step.

My research project will focus on developing dual function catalysts capable of both hydroxamic acid oxidation and mediation of the enantioselectivity of the subsequent acyl nitroso Diels-Alder cycloaddition. My interest in this problem was stimulated by two recent important developments in transition metal catalyzed oxidations. Whiting and co-wokers[4] reported the oxidation of t-butyl-N-hydroxy carbonate with catalytic $RhCl_2(PPH_3)_3$. t-Butyl peroxide was the stoichiometric oxidant. When the oxidation was carried out in the presence of 1,3-cyclohexadiene (CHD) the cycloadduct was obtained in 69% yield. The authors proposed a ruthenium oxo species as an intermediate. In a related report, Iwasa found that $[Ir(COD)_2Cl_2]_2$ was an efficient catalyst for the oxidation of phenyl hydroxamic acid. H_2O_2 in THF was the stoichiometric oxidant in this case.[5] The phenyl acyl nitroso intermediate was trapped in high yield by cyclopentadiene. The mechanism of this reaction is not known although it was suggested that the enol form of the hydroxamic acid may be involved. *Transition metal catalyzed generated of acyl nitroso species raise the possibility of the metal mediating subsequent cycloaddition.*

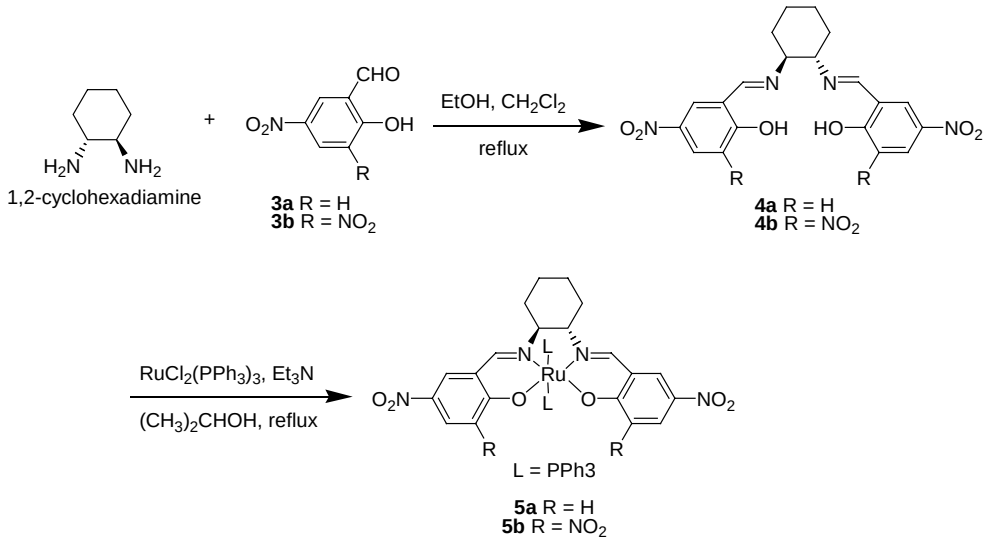


The Whiting group has examined this aspect in more detail. They have prepared a chiral salen Ru complex that, in the presence of t-BuOOH, is also an effective catalyst for oxidation. Indeed, the ligand improved the oxidation yield but the degree of asymmetric induction in the CHD adduct was negligible (<5%).

My effort to pursue this reaction is motivated by the possibility that *following oxidation by the catalyst, the acyl nitroso intermediate undergoes Diels-Alder reaction while still in the coordination sphere of the Ru. If this is true, the intramolecular variant has a far better chance f reacting prior to dissocation than the bimolecular reaction.* Indeed, the observation of asymmetry in the cycloaddition product would be evidence for such an intermediate. There are no examples of transition metal complexes of acyl nitroso compounds.

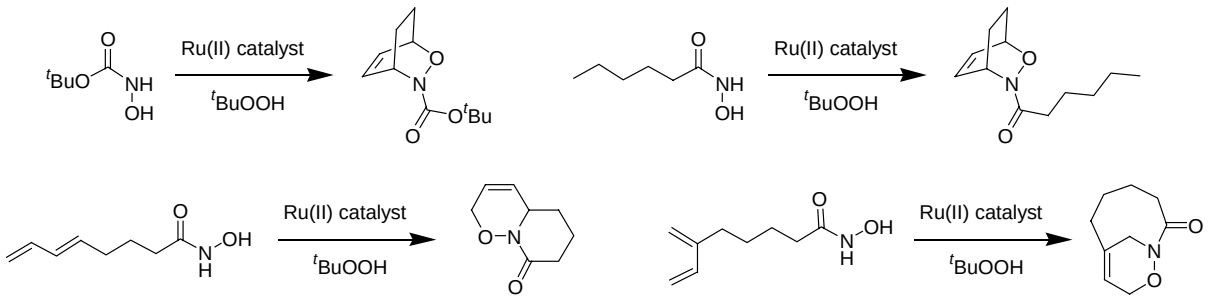
Research Plan

The first phase of this project will focus on the synthesis of a racemic mixture of two ruthenium(II) salen complexes (**5a** and **5b**). Spectroscopic characterization of the metal catalysts



will be carried out using ^{1}H, ^{13}C, and ^{31}P NMR (nuclear magnetic resonance). *Trans*-1,2-cyclohexadiamine is condensed with two equivalents of aldehydes **3a** and **3b**. Metal insertion of Schiff-base ligands **4a** and **4b** using $RuCl_2(PPh_3)_3$ can furnish complex **5a** and **5b**.
Once the racemic complexes are obtained, I will examine their catalytic efficiency to oxidize some simple hydroxamic acids following by trapping with CHD. Control studies will be carried out in the *absence* of a ruthenium catalyst to compare the rate of oxidation using only t-BOOH. The degree of product formation will be assessed by obtaining spectroscopic and/or isolated yield of the cycloaddition product.

Upon identifying the an efficient ruthenium catalyst that is versatile for oxidation of different hydroxamic acids, an *enantiomer* of the catalyst will be synthesized from (*R*, *R*)-1,2-



cyclohexadiamine. Optical rotation of the chiral salen ligand and the resulting ruthenium complex will be taken and compared with literature values. The catalyst will then be applied to the oxidation of hydroxamic acids, followed by trapping with CHD. The degree of enantiomeric excess of the cycloaddition product will be determined by measuring the ratio distribution of the *R* and *S* enantiomers by chiral HPLC separation.

Future experiments will involve separation of the enantiomers by recrystallization or derivatization of the cycloaddition product followed by chromatographic separation. The absolute stereochemistry can be determined by single crystal X-ray crystallography.

Conclusion
The ultimate goal of this project is to develop a dual function ruthenium catalyst that is efficient for oxidation of hydroxamic acids and to induce asymmetry in the subsequent cycloaddition reaction upon trapping with 1 diene. My task in the two upcoming quarters will be to synthesize both the racemic and chiral forms of the catalysts. The chemical reactivity of the catalysts in acyl nitroso Diels-Alder reaction will be examined.

TIMELINE:

Quarter 1

Week	**Activities**
#1	Order and acquisition of materials
#2-3	Synthesis and characterization of two racemic salen ligands
#4-5	Begin training in NMR, IR, and mass spectrometry
#6-8	Synthesis and characterizaion of two racemic ruthenium complexes
#9	Write a research progress report for Quarter 1.

Quarter 2

Week	**Activities**
#1-2	Examine the oxidation of ruthenium catalysts prepared from Quarter 1 using commercially available hydroxamic acids and trapping with CHD

	Purification of cycloaddition product using chromatography
#3	Establish HPLC conditions for chiral separation
#4	Being to synthesize the chiral form of the ruthenium catalyst
#5	Examine effect of chiral catalyst on simple substrates and determine enantiomeric excess.
#6-8	Synthesis of an intramolecular (Type 1 or Type 2) Diels-Alder substrate
#9	Examine effect of chiral catalyst on intramolecular substrate
	Write a research progress report for Quarter 2.

RESPONSIBILITIES:

1) Synthesis of racemic mixture of two salen ruthenium complexes. These will be used as catalysts for acyl nitroso Diels-Alder reaction. Both the salen ligands and the catalysts will be fully characterized using NMR, IR, and mass spectrometry. The degree of purity will be determined using elemental analysis.

2) Examination of oxidation reactivity of ruthenium catalyst

3) Chromatographic separation of the cycloaddition products

4) Establish HPLC conditions for separation of enantiomers

5) Measure optical rotation of chiral ruthenium catalysts

Carry out a short synthesis for preparation of an intramolecular Diels-Alder precursor.

PROPOSED BUDGET:

Item	Size	Price
Trans-1,2-Diaminocyclohexane	20 mL	$20.80
(1R,2R)-1,2-Diaminocyclohexane	2 g	$151.80
2-Hydroxy-5-nitrobenzaldehyde	5 g	$26.20
3,5-Dinitrosalcylaldehyde	5 g	$101.50
Dichlorotrs(triphenylphosphine)ruthenium(II)	5 g	$120.30
Tert-Butyl N-hydroxycarbamate	5 g	$55.80
Tert-Butyl hydroperoxide in decane	25 mL	$25.30
Silica gel	250 g	$75.00
NMR tubes	4	$60.00
Glassware		$150.00
Departmental instrumentation usage fees (NMR and MS)		$100.00
Elemental analysis service for six compounds		$102.00
Organic solvents for reaction and chromatography		$150.00
Proper Waste Disposal		$200.00
Presentation Supplies		$50
Total		**$1388.70**

References

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