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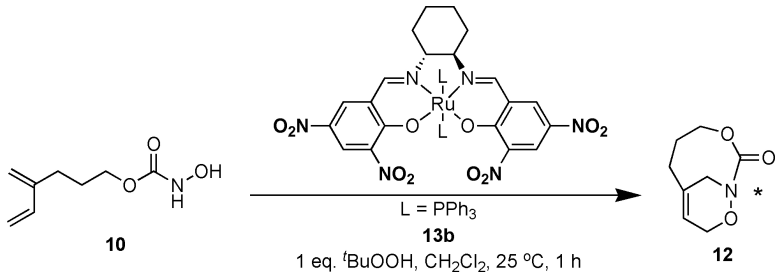

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Dual Function Catalysts. Dehydrogenation and Asymmetric Intramolecular Diels−Alder Cycloaddition of *N*-Hydroxy Formate Esters and Hydroxamic Acids: Evidence for a Ruthenium−Acylnitroso Intermediate

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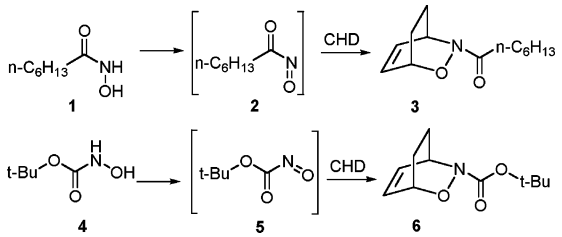
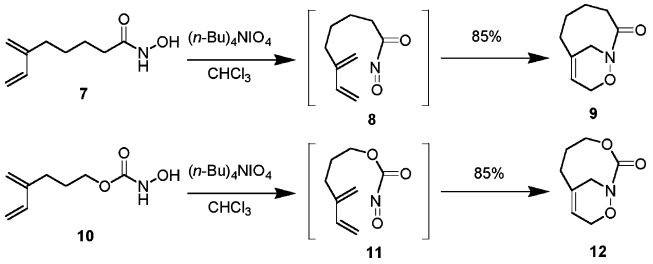
Significant progress has been made in the design of asymmetric catalysts for the Diels−Alder reaction.[1] In all cases that we are aware of, cycloaddition occurs upon treatment of a stable Diels−Alder precursor with a chiral Lewis acid catalyst. There are, however, many important Diels−Alder precursors that are not stable entities but rather are reactive intermediates that are generated in situ in the presence of a diene trap. Inducing asymmetry in these cycloadditions presents an interesting challenge. We report a dual function catalyst that serves to generate the reactive Diels−Alder precursor as well as to induce asymmetry in the subsequent cycloaddition step. This represents the first example of a strategy of this type and extends the potential utility of these important reactions. The results establish mechanistic support for formation of a complex between the reactive Diels−Alder intermediate and the catalyst.

Cycloadditions of aryl and acyl nitroso groups have played a key role in heterocycle synthesis.[2] More recently, asymmetric variants of these reactions have received attention. For example, Yamamoto reported an asymmetric catalyst for the Diels−Alder cycloaddition of 2-methyl-5-nitroso pyridine with dienes.[3] The acyl nitroso group (i.e., **2**), on the other hand, is a reactive intermediate. It is generated in situ and has a relatively short lifetime in the presence of dienes.[4] Miller[5] and others[6] have developed stoichiometric asymmetric cycloadditions of acyl nitroso derivatives by incorporating a chiral auxiliary in the acyl nitroso precursor.

Regarding efforts to develop catalysts for these reactions, the recent work of Whiting[7] and Iwasa[8] are noteworthy. In particular, the Whiting group reported that complexes of ruthenium(II) catalyze the oxidation of *tert*-butyl-*N*-hydroxy formate (**4**) to the corresponding nitroso formate **5** using *tert*-butyl hydroperoxide (TBHP) as the stoichiometric oxidant.[7] Reactions run in the presence of cyclohexadiene (CHD) resulted in moderate yield of cycloadduct **6**. Although an asymmetric ruthenium−salen catalyst was also found to be an effective oxidation catalyst, products of the bimolecular Diels−Alder reaction with CHD as the diene trap were, in all cases, racemic.[9] A very low enantiomeric excess was noted with PROPHOS. The experiment raises an intriguing question; is it feasible to develop a catalyst that functions both as an oxidant and as an effective asymmetric catalyst for the subsequent cycloaddition reaction? The expectation of asymmetry is predicated on the assumption that following oxidation, the cycloaddition takes place while the acyl nitroso intermediate remains associated with the spent ruthenium oxidation catalyst.



If one could adopt the ruthenium-catalyzed oxidation protocol, the *intramolecular* version of the cycloaddition might have a higher probability to take place while the intermediate is still in the coordination sphere of the ruthenium. To examine the influence of intramolecularity, several type 2 Diels−Alder precursors were synthesized.[10,11] Both hydroxamic acid **7** and *N*-hydroxy formate ester **10** undergo intramolecular Diels−Alder cycloaddition upon oxidation with stoichiometric tetrabutylammonium periodate. Importantly, the enantiomers of the racemic products, cycloadducts **9** and **12**, could be separated by chiral HPLC.



To evaluate the performance of ruthenium catalysts, chiral salen ligands based on (+)-1,2-diaminocyclohexane were prepared and converted to their Ru(II) complexes upon treatment with $RuCl_2(PPh_3)_3$.[12] A standard protocol was used to assess catalyst performance. The procedure involves treatment of 1 equiv of hydroxamic acid (or *N*-hydroxy formate ester) with 1 equiv of TBHP in the presence of 0.1 mol % of ruthenium catalyst in CH_2Cl_2. The reaction was allowed to proceed for 1 h at room temperature. Bimolecular reactions with precursors **1** and **4** were run in the presence of 1 M CHD. The rate of background oxidation was less than 4% after 1 h in all cases.

Consistent with the report by Whiting, *O*-*tert*-butyl-*N*-hydroxy formate (**4**) is oxidized by **13a** to yield (racemic) CHD cycloadduct **6** (74% yield). The intramolecular *N*-hydroxy formate ester precursor **10** was also oxidized by **13a** to give cycloadduct **12** in 64% yield. Importantly, chiral HPLC indicated a slight enantiomeric excess (9% ee) in the cycloadduct. Although the magnitude of the enrichment was quite low, the result has important mechanistic implications. For any level of asymmetric induction to occur, some component of the cycloaddition of the acyl nitroso intermediate **11** must have taken place within the coordination sphere of the chiral ruthenium catalyst. It has been proposed that reaction of **13a** with TBHP results in formation of the active oxidant, a Ru(IV) oxo species **14**.[7] The preceding results permit refinement of this mechanism (Scheme 1). Dehydrogenation of **10** by **14** produces a geminate pair comprised of the spent oxidant, the Ru(II) byproduct, and the nitroso formate intermediate **11** (complex **15** in Scheme 1). Some fraction of the Diels−Alder cycloaddition takes place within complex **15** prior to the dissociation and/or reoxidation of the ruthenium by TBHP. The stability and lifetime of complex **15**, therefore, is critical for the asymmetric Diels−Alder reaction.

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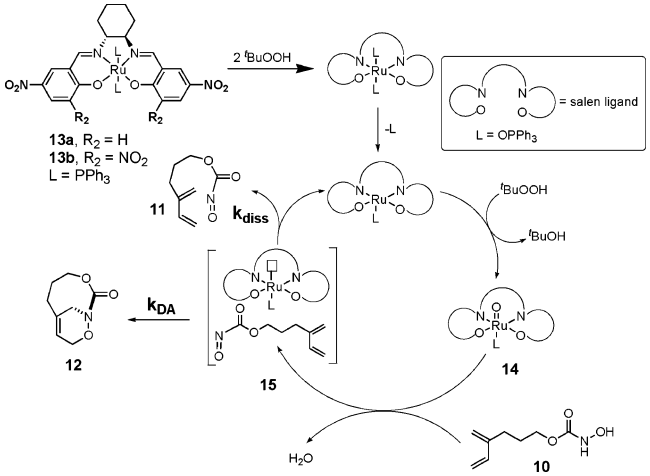
Scheme 1. Proposed Mechanism for the Asymmetric Formation of Oxazinolactam **12**



A more Lewis acidic catalyst could produce a stronger oxidant and perhaps stabilize complex **15**. Indeed, improved yields and higher enantiomeric excesses were found with electron-withdrawing substituents at positions R_1 and R_2 in **13**. (Supporting Information). The most effective substitution pattern was the dinitro derivative **13b** (R_1, R_2 = NO_2). This complex is a competent catalyst both for the oxidation of hydroxamic acid **1** (48% yield of cycloadduct **3** with 1 M CHD) as well as for the oxidation of hydroxamic acid **7** (66% yield of cycloadduct **9**). More importantly, the dinitro catalyst **13b** delivers cycloadduct **12** in 43% ee.

The enantioselectivity highlights the importance of intramolecularity for asymmetric induction; the *bimolecular* reaction of **4** (1 M CHD) with catalyst **13b** resulted in only 9% ee.

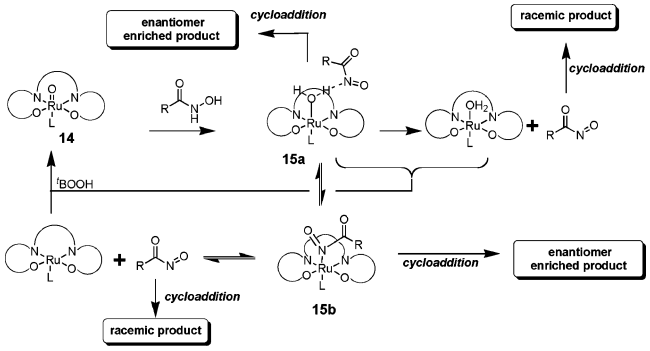
Possible explanations for the modest enantioselectivity include breakdown of complex **15** prior to cycloaddition by dissociation of the acyl nitroso intermediate or reoxidation by TBHP to **14** and/or cycloaddition within the complex with an intrinsically low enantioselectivity. Focusing on the competing reoxidation step, we note that the lifetime of **15** is dependent on the rate of reoxidation, a bimolecular reaction. Suppression of this bimolecular reaction might be achieved by decreasing the overall concentration.

Incremental dilution to 7.2×10^{-2} M showed increase in chemical yield up to 82%. A parallel trend in enantioselectivity was observed with decreasing concentration. The optimum formation of cycloadduct **12** was achieved at 7.2×10^{-2} M. These conditions also resulted in improved enantioselectivity (71%). The enantioselectivity was further enhanced (75% ee) by lowering the temperature to 15 °C. Continued decrease in reaction concentration resulted in reduced yield.

Further refinement of the mechanism is now warranted (Scheme 2). Ru(IV) oxo complexes are known dehydrogenation reagents.[13,14] Hydrogen transfer is expected to produce a Ru(II) hydrate.[15] The Ru hydrate can bind the nitroso formate intermediate by a hydrogen bond (**15a**) or it can undergo ligand replacement to produce **15b**. (The H-bonded complex would be the first intermediate in the ligand exchange.)[16] There is ample precedent for facile exchange at Ru(II) centers[16] as well as for Ru(II) nitroso complexes.[17] Coordination of the acyl formate in **15a** and/or **15b** is expected to catalyze the Diels−Alder cycloaddition in light of recent experimental evidence regarding the acceleration of α-acetoxynitroso cycloadditions by Lewis acids.[18] Cycloaddition from either intermediate (**15a**,**b**) could account for the observed asymmetry (Scheme 2).

The low (or no) enantioselectivity for the *intermolecular* reaction is consistent with the proposal since the Diels−Alder step involves

Scheme 2. Proposed Mechanism for the Dehydrogenation and Cycloaddition of *N*-Hydroxy Formate Esters



a bimolecular cycloaddition that would be competitive with the bimolecular reoxidation of Ru(II).

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Supporting Information Available: Experimental information, including the preparation of compounds **3**, **6**, **7**, **9**, **10**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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