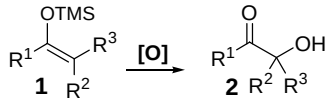
CATALYTIC, ENANTIOSELECTIVE α-HYROXLATION OF CARBONYL COMPOUNDS USING NITROSO BENZENE

Reported by JohnMark Derryberry October 28, 2004

INTRODUCTION

α-Hydroxy aldehydes and ketones are synthetically important chiral building blocks for the synthesis of many natural products.[1] The most common methods for the enantioselective formation of α-oxy carbonyl compounds include selective oxidation of a hydroxyl group of a terminal diol,[2] the ozonolysis of an allylic alcohol,[3] sequential diazotization and hydrolysis of amino acids,[4] alkylations of hydroxy acetalaldehydes using chiral hydrazones,[5] benzoin condensation,[6] enzymatic resolution of racemates,[7] and a host of biocatalytic syntheses.[8] Additionally, α-hydroxy ketones are accessible via the oxygenation of enolates (Scheme 1).[9] This process is illustrated in the Rubottom reaction,[10] in which a silyl enol ether is epoxidized and subsequently hydrolyzed to afford an α-hydroxy ketone **2**.

Scheme 1. Oxygenation of a Silyl Enol Ether



Enantioselective oxidizing agents used with preformed enolates include fructose derived dioxiranes,[11] (salen)manganese(III) complexes,[12] and *N*-sulfonyloxaziridines.[13]

Recently, nitrosobenzene was found to be an enolate oxidant in the presence of catalytic amounts of a Lewis acid.[14] This represents a departure from normal reactivity observed with nitrosobenzene[15] wherein, the nitrogen acts as an electrophilic site instead of the oxygen.[15] The nitrogen is also the more reactive heteroatom for nucleophilic attack of electrophiles.[15] The nitrogen's duality of function can be observed in reductions, oxidations, nitroso ene reactions,[15] hetero Diels-Alder reactions[16] and nitrosobenzene metal complexation reactions.[17]

The oxidation of enolates with nitrosobenzene is a particularly useful transformation. Comparing all of the methods for the formation of enantiomerically enriched α-hydroxyl carbonyl compounds, the use of nitrosobenzene offers a number of advantages; including, short reaction times, high yields, mild reaction conditions, and excellent chemical- and enantioselectivity through the use of BINOL-derived silver complexes and proline as chiral catalysts. This review focuses on the recent development and understanding of nitrosobenzene-mediated, asymmetric, α-hydroxylation of aldehydes and ketones.

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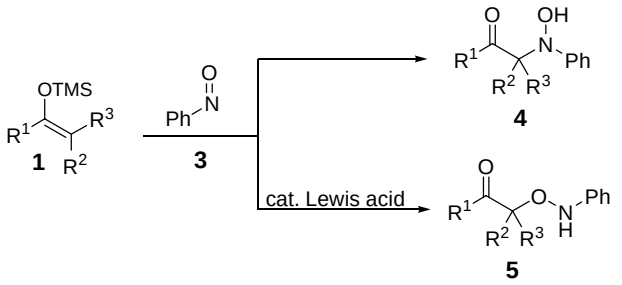
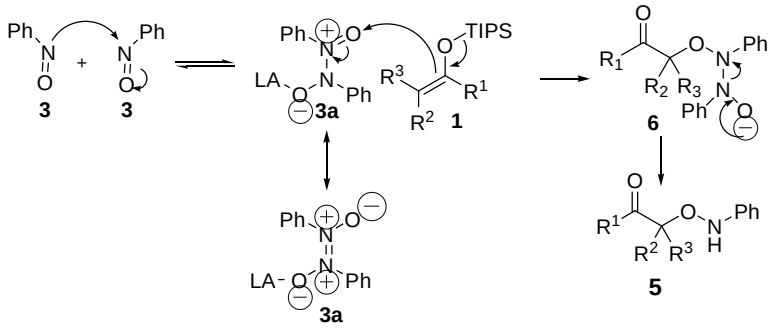
LEWIS ACID-CATALYZED α-HYDROXYLATION OF KETONES

In 1983, Sasaki and coworkers reported the reaction of various silyl enol ethers **1** with nitrosobenzene (**3**) to yield α-hydroxyamino carbonyl compounds, **4**.[18] Yamamoto and coworkers discovered that the chemoselectivity of enolate addition could be altered to generate α-oxy ketones **5** with the addition of Lewis acid catalysts (Scheme 2).[15] The authors observed that the green solution of a silyl enol ether and nitrosobenzene became colorless upon the addition of a Lewis acid. Subsequent ReactIR studies revealed the disappearance of an absorbance peak at 1505 cm^{-1} inversely proportional to the appearance of an absorbance at 1264 cm^{-1}. These absorbences correspond to the monomer **3** and trans dimer **3a** of nitrosobenzene. Yamamoto suggests that *O*-selectivity arises from reaction of the homodimer of nitrosobenzene **3a** (Scheme 3). This Lewis-assisted dimerization generates an electrophile that can subsequently undergo attack by the silyl enol ether **1**. Triethylsilyl triflate affords the highest *O*-selectivity (Scheme 4).

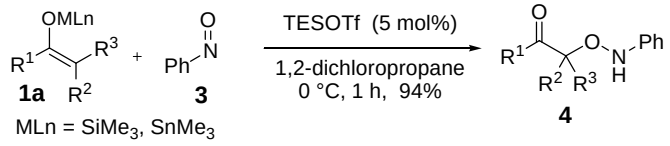
Scheme 2. Formation of Aminoxy and Hydroxy Ketones



Scheme 3. Lewis Acid-catalyzed Mechanism

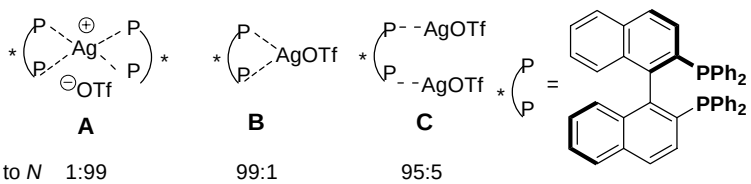


Scheme 4. Formation of a-Hydroxy Ketones



Yamamoto then investigated an enantioselective variant of the reaction.[19] The combination of a silver(I) salt and (*R*)-BINAP provides the α-aminoxy ketone in high enantiomeric purity. Of the silver(I) salts surveyed, the reactions with AgOTf and $AgClO_4$ show the highest regio- and enantioselectivity. Depending upon the silver salt employed and the ratio of silver salt to (*R*)-BINAP ligand three possible Lewis acid complexes are formed (Chart 1). X-ray crystallographic analysis of the silver complexes confirmed the structure of complexes **A**, **B** and **C**. These three complexes show different reaction selectivities. Complex **A** is

Chart 1. Silver (R)- BINAP Complexes



	A	B	C
O to *N*	1:99	99:1	95:5
er	51:49	>99:1	55:45

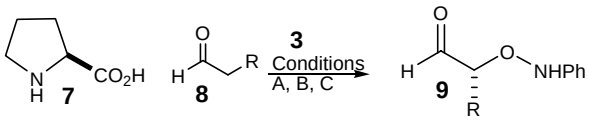
found to be *N*-selective forming product **4**, whereas **B** and **C** are both *O*-selective affording product **4**. Complex **B** proves to give the highest enantioselectivity for α-oxy ketone formation. Complex **A** is apparently too congested to assist in the dimerization of nitrosobenzene and its reactivity therefore mimics a reaction without Lewis acid assistance, thus leading to *N*-selective reactions. Similarly, Yamamoto suggests that complex **C** would have difficulty in properly transferring the chirality of (*R*)-BINAP to the α-oxygenation. The reaction was then applied to the silyl and stannyl enol ethers of various cyclic ketones. While the stannyl enol ether afforded increased reactivity, the toxic nature of tin is an undesirable attribute of the oxygenation reaction.

PROLINE-CATALYZED α-HYDROXLATIONS

α-Hydroxylation of Aldehydes

The oxygenation of enolates with nitrosobenzene is a successful and useful reaction. However, the oxygenation requires preformed enolates. An ideal solution would be the construction of a catalyst able to form an enolate in situ as well as transmit enantioselectivity. One example involves the formation of an enamine via the amino acid proline. Interest in the use of proline for asymmetric catalysis has been renewed.[20] As early as 1971, two groups independently developed an asymmetric, intramolecular aldol addition catalyzed by proline. This reaction later became known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction.[21] Current work utilizes proline as an asymmetric catalyst for a variety of reactions; including, aldol reactions, Michael reactions, Mannich reactions, α-chlorinations, α-aminations and intramolecular α-alkylations.[22] Following the reports of α-oxygenation utilizing nitrosobenzene by Yamamoto, three groups independently developed a proline-catalyzed oxygenation of aldehydes with nitrosobenzene. The reaction protocols employed by MacMillan,[23] Zhong[24] and Hayashi[25] vary, but all show excellent enantioselectivity albeit on a narrow substrate scope (Table 1). The temperature ranged from -20 °C to room temperature and with catalyst loadings from 5% to 30%. MacMillan showed that a catalyst loading as

Table 1. α-Hydroxylation of Aldehydes Using Proline (7)



Key: (a) **7** 5 mol %, **8** 1.2 equiv, $CHCl_3$, 4°C, 4 h
(b) **7** 20 mol %, **8** 2-3 equiv, DMSO, rt, 10-20 min
(c) **7** 30 mol %, **8** 3 equiv, CH_3CN, -20 °C, 24 h

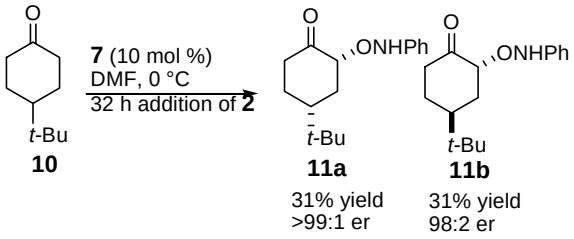
entry	R	method	% yield	er
1	Me	A	88	99:1
2	Me	B	60	99:1
3	Me	C	>99	99:1
4	Et	C	87	>99:1
5	*n*-Pr	C	81	98:2
6	*i*-Pr	A	85	>99:1
7	*n*-Bu	A	79	99:1
8	Ph	C	62	>99:1
9	Bn	A	95	99:1
10	Bn	B	86	99:1
11	Bn	C	70	>99:1
12	$(CH_2)_3OTIPS$	A	76	99:1
13	$(CH_2)_2CH=CH_2$	B	73	>99:1
14	CH_2OBn	B	54	>99:1
15	$(CH_2)_4NHBoc$	B	61	97:3

A = MacMillan
B = Zhong
C = Hayashi

low as 0.5% could be employed without significant loss in yield or enantioselectivity. Furthermore, MacMillan also showed that carrying out the reaction at 4 °C suppresses self-aldol condensation.[26] Hayashi attempted to account for the discrepancy between the groups in yield, solvents, temperature and reaction time. Hayashi and coworkers have been unable to duplicate Zhong's results at room temperature or MacMillan's low catalyst loading without a significant drop in yield.[27] However, the enantiomeric ratios do remain excellent. The scope of the reaction, exhibited in Table 1, shows that the reaction is reproducible, as in the case of propanal. Also, a variety of functional groups are tolerant to the reaction conditions and the reaction is not impeded by steric bulk.

α-Hydroxylation of Ketones

Scheme 5. Asymmetric Desymmetrization



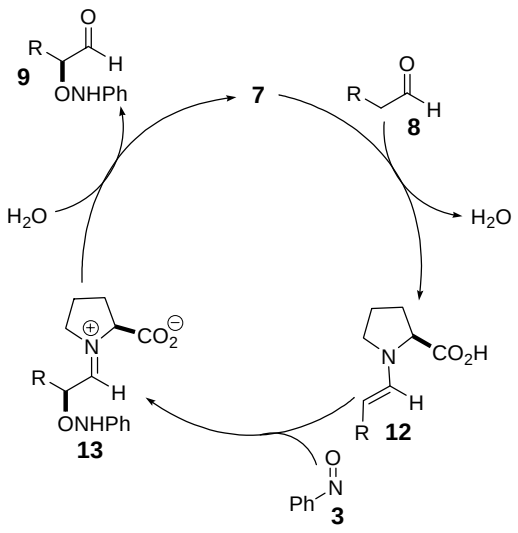
In contemporaneous reports, Hayashi[28] and Cordova[29] extended the α-hydroxylation method to ketones. Ketones present a formidable challenge, because the regioselectivity of enamine formation is difficult to control.[28] However, symmetrical ketones such as cyclohexanone afford high yields and enantioselectivities. In general, these reactions are performed at 0 °C, because ketone enamines are less reactive. Also, it is necessary to add the nitrosobenzene slowly by syringe pump to suppress the homodimerization of nitrosobenzene and α,α'dioxygenation of ketones.[28] Achiral ketone **10** undergoes desymmetrization to afford equivalent amounts of the two possible diastereomers of the product (Scheme 5).[27] Cordova demonstrated that acyclic methyl ketones tend to form some *N*-functionalized product (**4**).[29] The scope of the α-oxygenation of ketones is narrow because of the necessity for symmetric nonchiral substrates; otherwise, a mixture of diastereomers is formed. The class of nonsymmetric ketone substrates is limited to methyl ketones, which favor enamine formation to the more substituted side.[27] For these reasons aldehydes are the more advantageous substrate of proline-catalyzed α-oxygenations.

MECHANISTIC STUDIES ON PROLINE-CATALYZED α-HYDROXLATIONS

Initial Studies

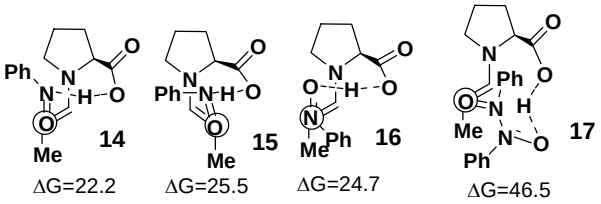
On the basis of previous proposals for the aldol reaction catalyzed by proline, a modified catalytic cycle is suggested (Scheme 6). Condensation of proline (**7**) with aldehyde **8** provides E-enamine **12,** which subsequently reacts with nitrosobenzene monomer forming iminium ion **13.** Finally, hydrolysis of **13** provides the desired α-oxyaldehyde **9** and regenerates the proline catalyst **7**.

Scheme 6. Proposed Catalyic Cycle



Several transition state structures for the addition of nitrosobenzene to the enamine have been proposed.[23,24,27] Houk and coworkers sought to clarify the discrepancies through computational calculations (Chart **2**).[30] Transition state **12** in which nitrosobenzene is directed to si facial attack is the most favorable transition state. Transition state **15** features a syn relationship of the carboxylic acid and *E*-enamine. Transition state **15** is 3.3 kcal less favorable than transition state **14**. The calculations predict an enantiomeric ratio of 99:1. This has been experimentally verified as transition state **14** leads to the observed major enantiomer for propanal and transition state **15** leads to the minor enantiomer in an enantiomeric ratio roughly equivalent (Table **1**). Also, in the case of proline catalysis, *N*-selective addition (**16**) is found to be 2.6 kcal/mol less favorable than *O*-selective addition (**14**). However, in the absence of the carboxylic acid moiety of proline to act as a Brøsted acid cocatalyst the selectivity reverses with *N*-selective addition being 3.7 kcal/mol more favorable than *O*-selective addition. Lastly, oxygenation with nitrosobenzene dimer **2a** is 24.3 kcal/mol less favorable than the reaction with the monomer (**17**).

Chart 2. TS Structures From DFT Calculations (kcal/mol)



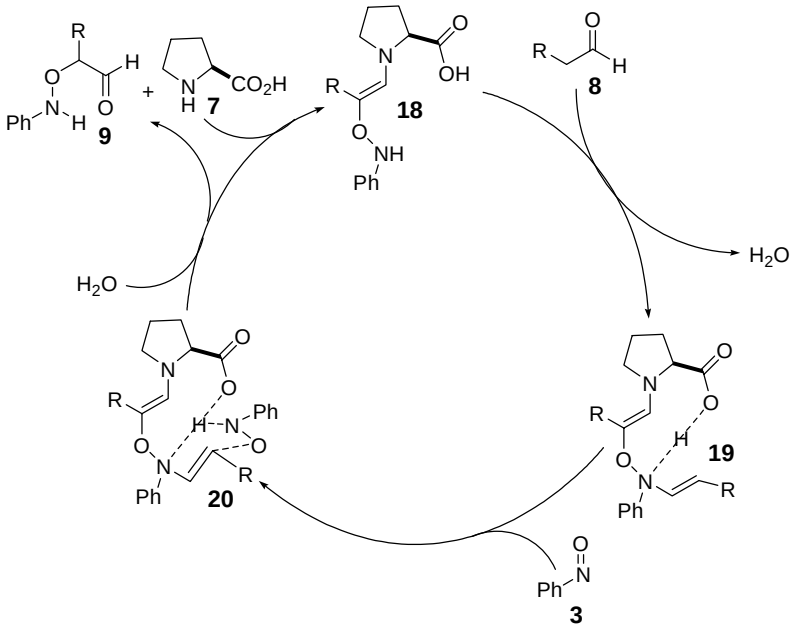
Asymmetric Autocatalysis and Non-linear Effects

Asymmetric autocatalysis is a phenomenon in which chiral reaction product serves as a catalyst to produce more of itself.[31] A well-known example is the Soai reaction, in which an achiral pyrimidine-based aldehyde reacts with diisopropylzinc to produce an enantioenriched product.[31] This

reaction exhibits asymmetric nonlinear effects, when the enantiomeric ratio of product in a reaction deviates from a linear correlation to the enantiomeric ratio of chiral directing influences.

Autocatalytic effects are not observed in the proline-catalyzed of α-oxygenation of carbonyl compounds.[32] The enantiomeric composition of the α-oxy ketone product is linearly proportional to the enantiomeric composition of proline in DMSO. However, Blackmond and coworkers saw evidence for potential nonlinear effects. The interest arose from the reported reaction rates, which are higher for this process in comparison to other recent aminocatalytic reactions. Blackmond examined these reactions using microcalorimetry (Figure 1).[33] In the diagram the black dots indicate microfluctuations in the reaction heat flow, which has been shown to be directly proportional to reaction rate. The gray line is an estimated representation of percent conversion at the given time of the reaction. The diagram in Figure 1 shows a slow increase in reaction rate in the first reaction. Following the addition of extra equivalents of aldehyde and nitrosobenzene to the reaction vessel, the second reaction proceeds at an initial rate near the peak rate of the first reaction. This suggests the presence of a catalytic species generated in the first reaction that is still present at the onset of the second reaction. Implementation of the reaction with a proline racemate affords enantiomerically amplified products.

Scheme 7. Proposed Catalytic Cycle



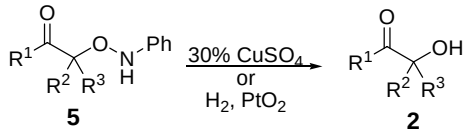
Blackmond proposes a mechanism to account for the increase of rate and selectivity through the course of the reaction (Scheme 5). In this mechanism, proline condenses with α-oxyaldehye **9** to form enamine (**18**). The nitrogen α to the oxygen would theoretically be more nucleophilic by virtue of the alpha effect.[34] The proposed transition state **20** demonstrates the potential for the carboxylic acid to act as a Brønsted acid cocatalyst. Subsequent hydrolysis affords oxyaldehyde product **9** and enamine catalyst **18**. While not universally accepted, the mechanism offers a unique interpretation of data.

APPLICATIONS

Transformations of α-Oxy Aldehydes and Ketones

The synthetic utility of the oxygenation by nitrosobenzene relies on the ready cleavage of the N-O bond in the product, which provides access to synthetically useful α-hydroxy aldehydes and ketones (**2**). Cleavage can be accomplished via a hydrogenation reaction using Adams' catalyst, or platinum dioxide, under an atmosphere of hydrogen.[24] A newly developed method for this cleavage is the mild transamination reaction with a catalytic amount of $CuSO_4$ in methanol.[14b] Both reactions proceed in high yields without loss in enantioselectivity. Additional applications of α-oxy aldehydes and ketones include synthesis of chiral building blocks for natural product synthesis and utilization of the α-aminoxy carbonyl compounds as precursors for olefination reactions and the formation of diols.[24]

Scheme 8. Cleavage of the N-O bond



5 **2**

CONCLUSION

The formation of α-hydroxyl carbonyl compounds has been achieved through the oxygenation of enol ethers and enamines with nitrosobenzene. The use of silver(I) BINAP complexes as well as proline enable the reaction to be catalytic and enantioselective. The reactions display many attractive features in comparison to other methods, including excellent enantioselectivity and mild reaction conditions. Although the substrate scope is currently limited to aldehydes and select ketones, the reaction exhibits potential for extension into other molecular frameworks; for example aryl ketones, tertiary ketones and ketones in which enamine formation would be selective. Future catalysts modeled after the proline design will be required to mimic the acidic behavior for similar reactivity.

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