Chapter 4

Progress towards the Development of an Enantioselective Organocatalytic Ketone α-Oxidation

I. Introduction

α-Oxidation of Carbonyl Compounds

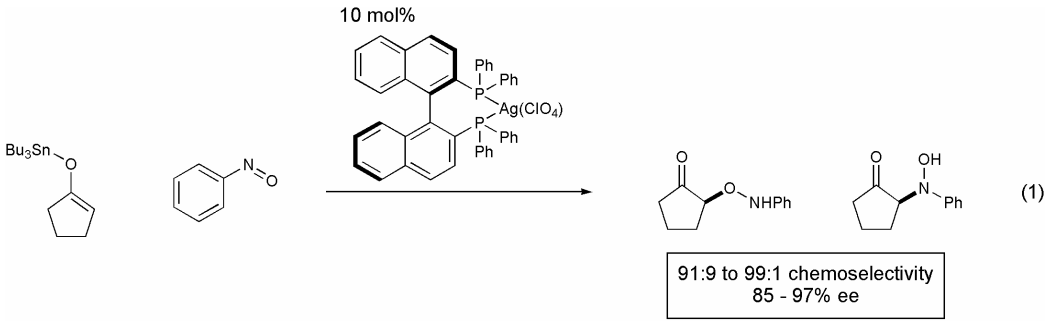
The synthesis of the α-hydroxy carbonyl structural motif is of great importance due to its prevalence in a wide variety of biologically active compounds such as sugars, antibiotics, pheromones, terpenes, and alkaloids.[1] The asymmetric construction of this structural motif is important as an end in itself, and it is useful as a directing group for the synthesis of other enantioenriched structures.[2-4]

One of the most common methods for introducing α-oxygenation to a carbonyl compound is through aprotic oxidation of the corresponding enolate[5]. These procedures typically involve the formation of an enolate from the carbonyl compound and subsequent oxidation by a molybdenum peroxo complex or *N*-solfonyloxaziridines.[6] Diastereoselective and reagent-controlled asymmetric α-oxidations based upon these two reagents have been developed by a number of groups.[1,5]

Catalytic Enantioselective α-Oxidation of Carbonyl Compounds

The development of a practical and highly selective system for asymmetric α-oxidation of carbonyl compounds is the ultimate goal of research in this field. The first report of a general enantioselective Lewis acid catalyzed α-oxidation of carbonyl

compounds was made by the Yamamoto laboratory (equation 1).[7] The oxidation of tin enolates by nitrosobenzene was catalyzed by a silver-BINAP catalyst with good yields and selectivities. This is possible because of the ambiphilic nature of the N-O double bond of nitroso compounds.[8-10] The tin enolates preferentially add to the nitroso group at the oxygen resulting in an enantioenriched α-hydroxy ketone after subsequent deprotection of the aryl hydroxy amine.



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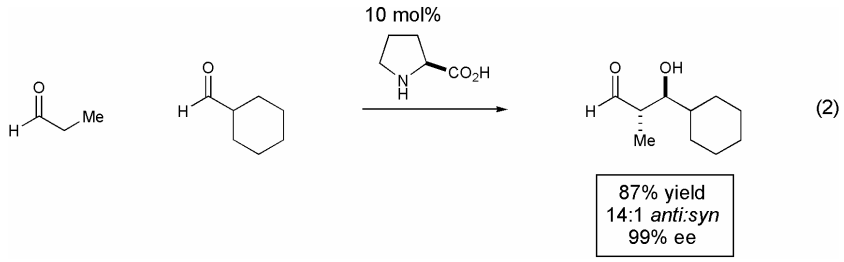
Proline Catalyzed Aldol Reactions

Research in the MacMillan lab has increased the utility of proline as a catalyst for the intermolecular aldol reaction by developing the first direct cross-aldol reaction between aldehydes (equation 2).[11] This methodology was demonstrated to be an effective procedure for coupling aldehydes of differing steric demand.



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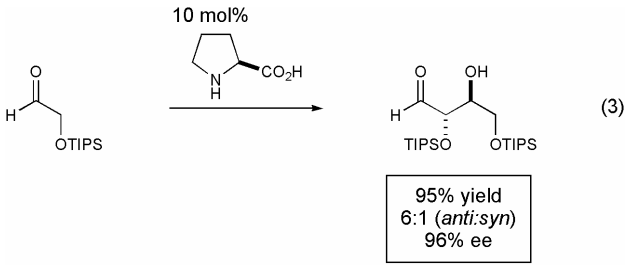

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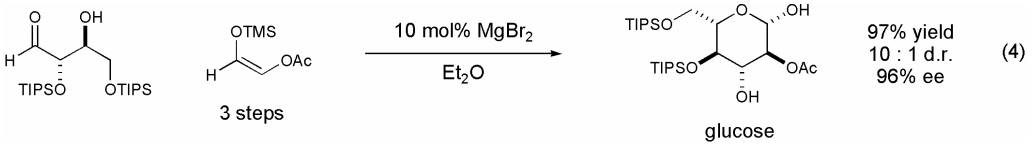
Research in the MacMillan lab has extended proline catalyzed aldol methodology to the asymmetric synthesis of highly oxygenated substrates, forming products with a high density of stereochemical information (equation 3).[12] The utility of this chemistry was demonstrated through a four-step synthesis of differentially protected hexoses (equation 4).[13]

The first report of a synthesis of a hexose from non-sugar starting materials was made by Emil Fischer in 1890.[14] Since then, there has been a great deal of research into the synthesis of monosaccharides from non-sugars, including Sharpless's elegant iterative synthesis of all eight *L*-hexoses.[15,16] The shortest synthesis of a differentially protected hexose previously reported was eight steps.[17]



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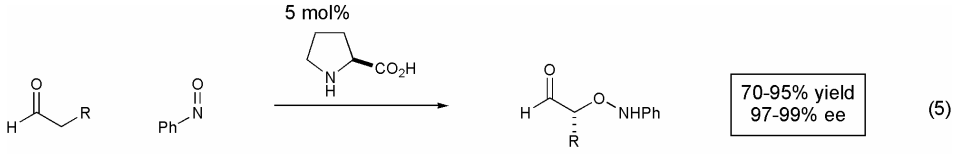
Asymmetric Organocatalytic α-Oxidation of Aldehydes

An interest in sugar synthesis led naturally to an interest in asymmetric α-oxidation chemistry. Development of the proper asymmetric α-oxidation and aldol chemistry would allow synthetic access to any monosaccharide desired from non-sugar starting materials.

The chemistry of the Yamamoto group inspired investigations into proline catalyzed α-oxidation of carbonyl compounds in the MacMillan laboratory. Under Lewis acid catalyzed conditions, latent enolate equivalents were demonstrated to preferentially add to the oxygen of nitrosobenzene.[7] Proline has been repeatedly shown to form nucleophilic enolates from carbonyl compounds, and these enolates have demonstrated the ability to participate in subsequent organic transformations.[18,19] Based on the mechanistic similarity between the Lewis acid catalyzed α-oxidation of enolates with nitrosobenzene and proline catalyzed reactions, investigations into an organocatalytic α-oxidation of carbonyl compounds were began in the MacMillan laboratory.



R = Me, *n*-Pr, *i*-Pr, allyl, Bn, Ph, $(CH_2)_3OTIPS$, CH_2-(3'-*N*-methyl-indole)

The first proline catalyzed α-oxidation of aldehydes was reported by the MacMillan laboratory (equation 5).[20] This work demonstrated a variety of structurally diverse aldehydes to be competent substrates for the proline catalyzed α-oxidation with

nitrosobenzene. Similar results were independently reported by other research groups shortly after the initial literature account.[21-23]

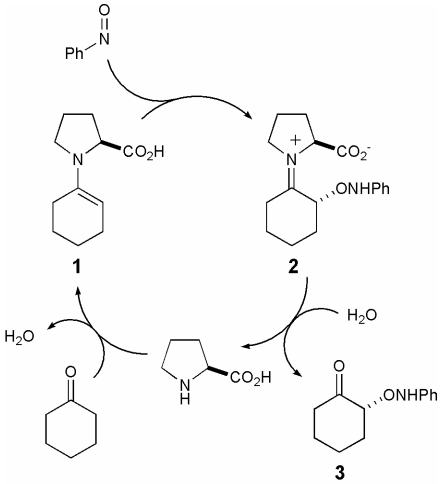
II. Results and Discussion

Initial Investigations

Initial studies in the MacMillan laboratory on the proline catalyzed α-oxidation of aldehydes had demonstrated the transformation to be possible with ketones, and it was with this knowledge that research was begun in earnest.[24]

The proposed catalytic cycle for the proline catalyzed α-oxidation of ketones with nitrosobenzene is shown in Scheme 1. Condensation of proline with a ketone and subsequent tautomerization of the iminium ion to a nucleophilic enamine results in the formation of **1**. The addition of **1** to nitrosobenzene formally oxidizes the alpha position of the carbonyl compound, and hydrolysis of the resulting iminium ion **2** regenerates the proline catalyst and frees the oxidized ketone product **3**, thereby completing the catalytic cycle.

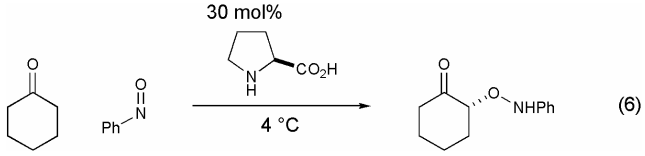
Scheme 1. Proposed proline catalyzed α-oxidation of ketones.



Concentration studies indicated that better chemical yields were possible at higher concentrations. Therefore, all initial studies were carried out at a concentration of 2.0 M relative to the limiting reagent.

Proline Catalyzed α-Oxidation of Cyclohexanone

Table 1. Effect of solvent on the proline catalyzed oxidation of cyclohexanone with nitrosobenzene.[a]



Entry	Solvent	E_T^N	% Conversion[b]	% ee[c]
1	MeOH	0.762	49	98
2	*i*-PrOH	0.546	9	93
3	CH_3NO_2	0.481	18	82
4	CH_3CN	0.460	9	99
5	DMSO	0.444	58	94
6	DMF	0.404	15	95
7	DMPU	0.352	7	94
8	CH_2Cl_2	0.309	8	96
9	$CHCl_3$	0.259	6	78
10	EtOAc	0.228	3	--
11	THF	0.207	4	--
12	Et_2O	0.117	6	--
13	Toluene	0.099	5	--

[a] All reactions performed at 2.0 M; [b] Conversion determined by ^{1}H NMR analysis; [c] Enantioselectivity determined by HPLC analysis.

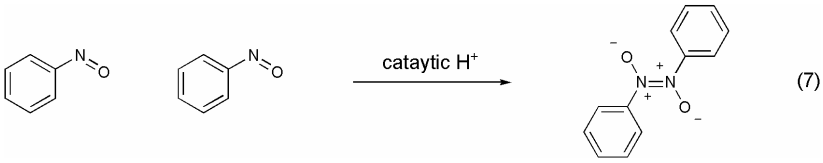
Examination of the proline-catalyzed α-oxidation of cyclohexanone was preformed in various solvents with a wide range of polarities (Table 1). This survey demonstrated that highly polar solvents like methanol and DMSO were most effective at promoting the desired oxidation reaction (Table 1, entries 1 and 5). Interestingly, other highly polar solvents were not as effective at promoting the desired transformation.

Nitromethane and DMF were noticeably better performers than other solvents studied (Table 1, entries 3 and 6), but the yields in these solvents were unsatisfactory. These results can be understood by considering the catalytic cycle proposed in Scheme 1. Those solvents most effective at promoting the formation of the nucleophilic enamine intermediate are the solvents which are most effective at promoting the oxidation reaction. DMSO and DMF are known to be effective solvents for the promotion of proline catalyzed aldol reactions, and methanol is by far the most polar solvent examined and, therefore, most able to promote the formation of enamine from iminium ion.[18] The enantioselectivity of the process appears to be quite good and relatively insensitive to solvent (78-99% ee, Table 1, entries 1-9).

The effect of temperature on the proline catalyzed oxidation of cyclohexanone in DMSO was then examined. While good yields and selectivities were observed at room temperature, the optimum temperature for the transformation was 4 °C. Yield and enantioselectivity peaked at this temperature, and reduction of temperature beyond this point only served to diminish both.

Initially, the oxidation was performed with an excess of cyclohexanone and a limiting amount of nitrosobenzene oxidant. These ratios were varied in an attempt to increase the yield of the process, and it was discovered that lower conversion occurred when excess oxidant was used. This led to the observation that a side reaction was occurring with the nitrosobenzene oxidant.

In the proline catalyzed oxidation of ketones, nitrosobenzene must exist in acidic conditions. Under these conditions, nitrosobenzene is known to dimerize (equation 7).[9,10,25] This side reaction was decreasing the overall yield of the desired transformation. Isolation of the nitrosobenzene dimer from a proline catalyzed oxidation reaction confirmed the existence of this undesired process.



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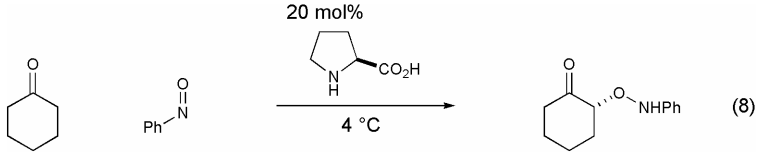
To limit the exposure of nitrosobenzene to acidic reaction conditions, an engineering solution was attempted. By adding nitrosobenzene via syringe pump to a solution of ketone and proline, the instantaneous concentration of nitrosobenzene should be low at all times during the reaction. Because the dimerization of the nitrosobenzene involves two molecules of nitrosobenzene, it is second order. The α-oxidation of ketones is only first order in nitrosobenzene. Reducing the instantaneous concentration of nitrosobenzene through syringe pump addition should therefore retard the unwanted dimerization side reaction more than the desired oxidation.

Initial studies were attempted using DMSO as the solvent, but at the optimum temperature (4 °C) syringe pump addition of a nitrosobenzene solution was not possible due to the relatively high freezing point of DMSO. Protic solvents are known to increase the rate of nitrosobenzene dimerization, so methanol was not used for further studies.[9,10,25] Subsequent investigations revealed DMF as the solvent of choice for the syringe pump additions.

As is shown in Table 2, syringe pump addition greatly increased the yield of the organocatalytic oxidation of cyclohexanone with nitrosobenzene. Slow addition of the oxidant significantly reduced the dimerization of the nitrosobenzene, thereby allowing the α-oxidation to occur in good yield.

Table 2. Reducing the rate of addition of nitrosobenzene significantly improves the organocatalytic oxidation of cyclohexanone.



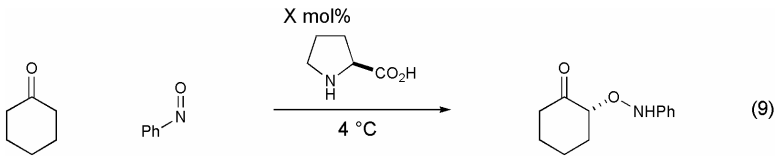
Entry	Solvent	Rate of addition of nitrosobenzene	% Converison[b]	% ee[c]
1	DMSO	Added as one portion	58	94
2	DMF	Added as one portion	31	95
3	DMSO	Syringe pump addition (4h)[d]	--	--
4	DMF	Syringe pump addition (4h)	>90	98

[a] All reactions performed at final concentration of 0.67 M; [b] Conversion determined by ^{1}H NMR analysis; [c] Enantioselectivity determined by HPLC analysis; [d] Syringe pump addition using DMSO at 4 °C was not possible due to the freezing point of the solvent.

The amount of proline catalyst required for the organocatalytic α-oxidation of cyclohexanone was examined. The oxidation appeared quite efficient when monitored by TLC. The nitrosobenzene was being consumed as quickly as it was being added to the reaction mixture, making a reduction in catalyst loading possible. This study demonstrated that 5 mol% catalyst was the ideal catalyst loading for the organocatalytic oxidation of cyclohexanone (>90% conversion, 99% ee, Table 3, entry 3). The selectivity was slightly higher than 20 mol% catalyst loading (>90% conversion, 98% ee, Table 3, entry 1) and the same as 10 mol% catalyst loading (>90% conversion, 99% ee, Table 3, entry 2). Reducing the amount of catalyst present in the reaction mixture to 2

mol% began to have deleterious effects on the conversion to product (70% conversion, 98% ee, Table 3, entry 4).

Table 3. Effect of catalyst loading on the proline catalyzed oxidation of cyclohexanone with nitrosobenzene.[a]

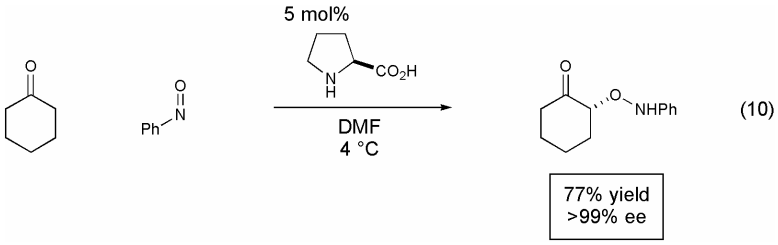


Entry	mol% proline	% Conversion[b]	% ee[c]
1	20	>90	98
2	10	>90	99
3	5	>90	99
4	2	70	98

[a] All reactions performed at a final concentration of 0.67 M in DMF; [b] Conversion determined by ^{1}H NMR analysis; [c] Enantioselectivity determined by HPLC analysis

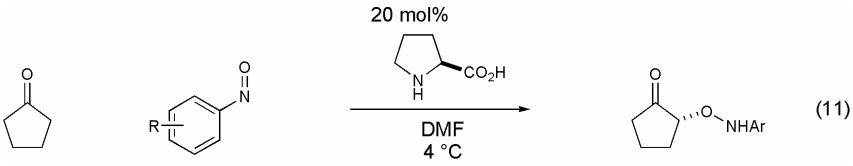
Substrate Scope

With optimized conditions for the proline catalyzed oxidation of cyclohexanone with nitrosobenzene identified, the scope of this transformation was examined. The elucidated conditions performed admirably for the organocatalytic oxidation of cyclohexanone, resulting in the isolation of oxidized product in 77% yield and >99% ee (equation 10).



Extension of this methodology to other ketones did not prove simple. Initial attempts at the organocatalytic oxidation of 3-pentanone, cyclopentanone and cycloheptanone with nitrosobenzene yielded only trace amounts of oxidized product and almost stoichiometric amounts of the nitrosobenzene dimer.

Table 4. Effect of nitrosoarene variation on the organocatalytic α-oxidation of cyclopentanone.[a]



Entry	R	% Conversion[b]	% ee[c]
1	H	<5	--
2	2-Me	<5	--
3	2-Et	18	--
4	2-(*i*-Pr)	25	69
5	2-(*t*-Bu)	0	--
6	2,6-diMe	0	--
7[d]	4-NO_2	0	--

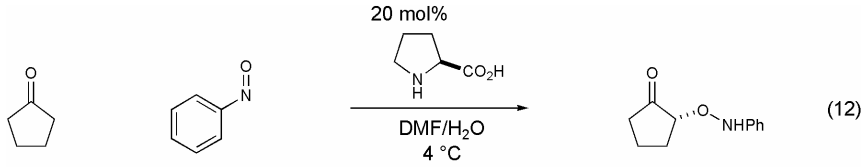
[a] All reactions performed at a final concentration of 0.67 M; nitrosoarene added via syringe pump over 4h; [b] Conversion determined by ^{1}H NMR analysis; [c] Enantioselectivity determined by HPLC analysis; [d] 4-nitronitrosobenzene added in one portion.

Variation of the nitrosoarene oxidant was examined to improve the proline catalyzed oxidation of cyclopentanone (Table 4). The steric demand of the nitrosoarene oxidant was increased in an attempt to inhibit the dimerization side reaction. This strategy did improve the yield of the α-oxidation. Only trace product was observed when nitrosobenzene and 2-nitrosotoluene were used as oxidants (Table 4, entries 1 and 2). Increasing the bulk of the 2-substituent on the nitrosobenzene ring served to increase the conversion (2-ethylnitosobenzene, 18% yield, Table 4, entry 3 and 2-isopropylnitrosobenzene, 25% yield, 69% ee, Table 4, entry 4), but once a certain steric demand is reached, both conversion to product and dimerization of the nitrosoarene halt

(Table 4, entries 5 and 6). Electron deficient nitrosobenzenes are less prone to undergo dimerization, and 4-nitronitrosobenzene is known to be particularly stable to dimerization while able to undergo other chemical transformations such as ene and Diels-Alder reactions.[25] 4-Nitronitrosobenzene was examined as an oxidant for the proline catalyzed α-oxidation of ketones, and was unreactive (Table 4, entry 7).

Tautomerization between an iminium ion and an enamine is strongly dependent on the structure of the carbonyl compound and amine involved.[26] Increasing the polarity of the reaction medium can promote enamine formation, so the effect of water on the organocatalytic α-oxidation was studied.[27] It is known that the addition of a small amount of water can have a dramatic effect on a solution's polarity and, therefore, on organocatalytic reactions (see Chapter 2, Table 3).

Table 5. Effect of added water on the proline-catalyzed α-oxidation of cyclopentanone with nitrosobenzene.[a]



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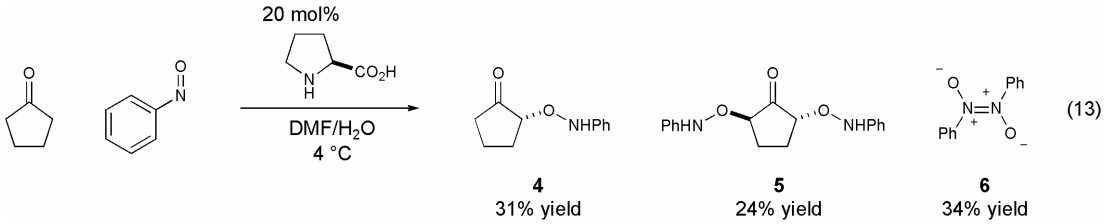
Entry	Equivalents of H_2O	% Conversion[b]
1	0	trace
2	1	68
3	2	70
4	4	80
5	6	71
6	8	53
7	10	32

[a] All reactions performed at a final concentration of 0.67 M; nitrosobenzene added via syringe pump over 8 h; [b] Conversion determined by ^{1}H NMR analysis.

As can be seen in Table 5, the addition of water to the reaction medium had a dramatic effect. When no added water is present, only trace oxidation occurs, and the

dimerization of nitrosobenzene is the dominant reaction (Table 5 entry 1). With increasing amounts of water, the conversion of the oxidation reaction increases (Table 5 entries 1-4) until the concentration of water reaches a point where the dimerization of the nitrosobenzene is again favored over oxidation of the ketone (Table 5 entries 5-7).

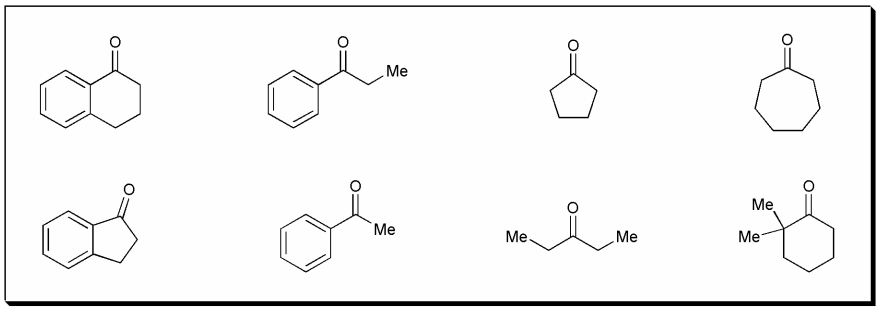
Unfortunately, the reaction conditions developed for cyclopentanone are not optimal. While the majority of nitrosobenzene is oxidizing the cyclopentanone under organocatalytic reaction conditions, dimerization is still occurring. Oxidation of the cyclopentanone is also occurring at both α-carbons (equation 13). This double oxidation (**5**) accounts for the previously observed levels of conversion (Table 5, entry 4), and results in a reduced yield of the cyclopentanone oxidation product **4**.



Limitations

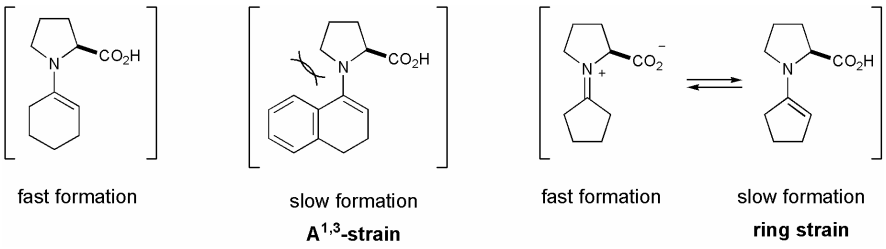
Unfortunately, most ketones studied did not prove to be competent substrates for the proline catalyzed α-oxidation (Figure 1). Of the ketones studied, only cyclohexanone produced oxidation product in reasonable yield. Aryl ketones, cyclic ketones of different sizes, acyclic ketones and sterically encumbered ketones all failed to yield oxidized products.

Figure 1. Ketones not able to participate in the proline catalyzed α-oxidation reaction.



Failure of these ketones to participate in the organocatalytic oxidation can be explained by their failure to form sufficient quantities of reactive enamine quickly (Scheme 2). Aryl ketones do not form significant amounts of enamine or iminium ions due to $A^{1,3}$-strain between the aromatic group and the substituents on the secondary amine. Cyclopentanone failed as a substrate under organocatalytic conditions because it did not form enamine quickly enough. Formation of iminium ions by proline and cyclopentanone occurs quickly and reversibly, allowing facile catalyst turnover, but the subsequent enamine formation is retarded by the ring strain inherent in the formation of a cyclopentene ring and occurs too slowly to allow an efficient α-oxidation.[28]

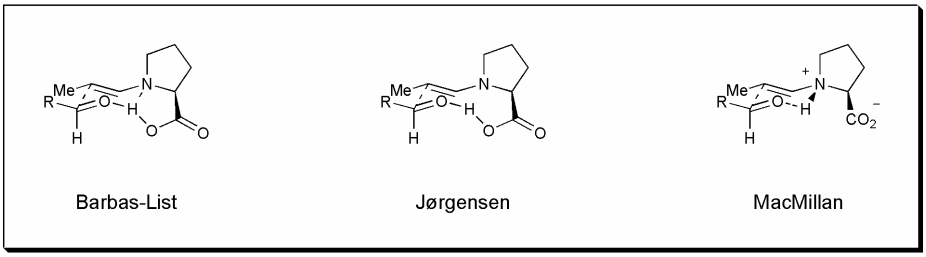
Scheme 2. Proposed rationale for substrate limitations in the organocatalytic α-oxidation reaction.



Stereochemical Rationale

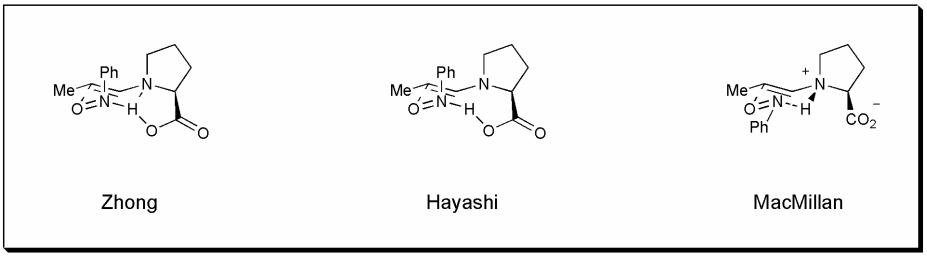
Several models have been proposed to explain the stereochemical outcome of proline catalyzed transformations (Figure 2).[11,20,21,29-31] The three models proposed in the literature correctly predict the stereochemistry resulting from a proline catalyzed aldol reaction. Computational studies appear to support the 9-membered ring transition state.[32,33] These quantum mechanical calculations suggest a pseudo-chair conformation for the closed transition state and indicate an intramolecular transfer of the hydrogen atom from the carboxylic acid of proline to the developing alkoxide in the aldol transition state. The distance between the nitrogen of the enamine and the transferring hydrogen atom was not indicative of hydrogen bonding, supporting the plausibility of a 9-membered ring transition state.

Figure 2. Proposed proline catalyzed aldol transition states.



Possible transition states for the proline catalyzed α-oxidation of aldehydes using nitrosobenzene have also been proposed (Figure 3).[20-23] All the transition states correctly predict the stereochemical course of the organocatalytic oxidation. Based on the computational studies performed on enamine aldol reactions, the 9-membered ring transition state seems most probable.[32,33]

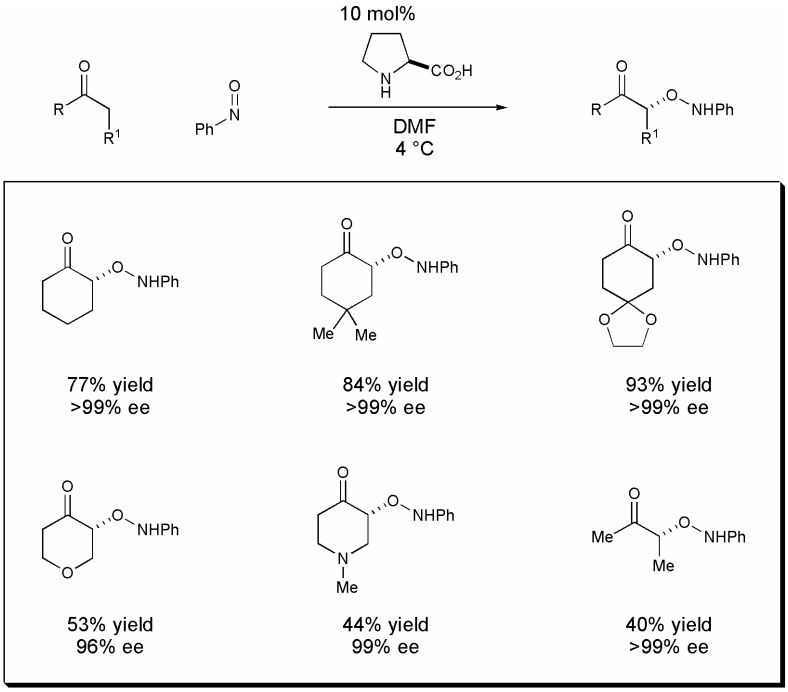
Figure 3. Proposed proline catalyzed aldehyde α-oxidation transition states.



Reports of Proline Catalyzed α-Oxidation of Ketones

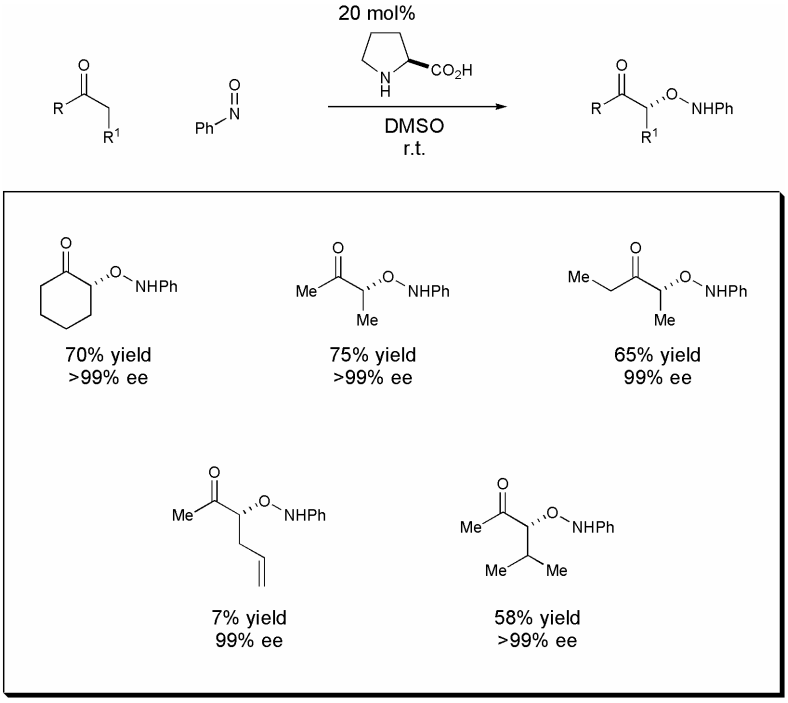
While studies aimed at extending the scope of the proline catalyzed α-oxidation beyond cyclohexanone were underway, two reports regarding this chemistry appeared.[34,35] The research outlined in this chapter is in accord with these reports.

Scheme 3. The proline catalyzed α-oxidation of ketones by the Hayashi laboratory.[35]



The Hayashi laboratory reported almost the exact same experimental conditions as elucidated in this research (DMF, 0 °C, 2 equiv. ketone, slow addition of nitrosobenzene), and found cyclohexanone and some derivatives of cyclohexanone to be competent substrates for the proline catalyzed α-oxidation reaction (Scheme 3).[35] The one alkyl ketone reported in their study only oxidized in moderate yield under forcing reaction conditions (10 equivalents ketone, r.t.).

Scheme 4. The proline catalyzed α-oxidation of ketones by the Córdova laboratory.[34]

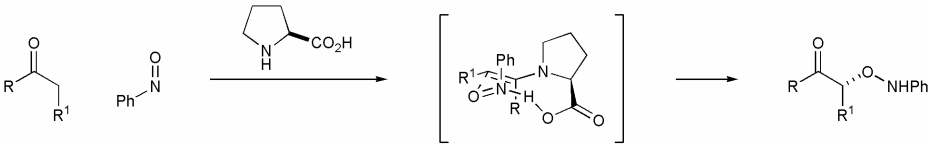


The Córdova laboratory reported different conditions for the proline-catalyzed α-oxidation of ketones than were found in this research or reported by the Hayashi laboratory (DMSO, r.t., 10 equiv. ketone, Scheme 4).[34,35] Not surprisingly, cyclohexanone oxidized with good yield and enantioselectivity under these conditions.

Asymmetric organocatalytic α-oxidation of alkyl ketones appears to be highly substrate dependent, producing enantioenriched product in variable yields (7-75% yield) but excellent enantioselectivity (99->99% ee).

Both literature reports of proline catalyzed α-oxidation of ketones propose a closed 9-membered transition state for the α-oxidation of ketones (Scheme 5).[34,35]

Scheme 5. Reported proline catalyzed ketone α-oxidation transition state.



III. Conclusion

Progress towards the development of an asymmetric, proline catalyzed α-oxidation of ketones has been described herein. Using *L*-proline, cyclohexanone can be α-oxidized in high yield and selectivity. Extension of this methodology to other ketones was not possible with acceptable yields, although all observed selectivities were high. These studies have further demonstrated the utility of proline as a general HOMO-raising catalyst, and provide a platform for the development of subsequent HOMO-raising organocatalytic methods.

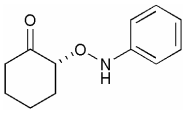
IV. Experimental Section

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[36] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still.[37] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed be fluorescence quenching, *p*-anisaldehyde stain, or $KMnO_4$ stain.

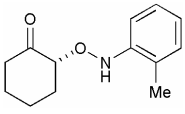
^1H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz and 75 MHz, respectively) or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported with chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) , integration, and assignment. Data for ^{13}C NMR are reported with chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 FTIR and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C, $CHCl_3$). Mass spectra were obtained from the California Institute of Technology Mass Spectrometer Facility. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254 nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

Progress of the α-oxidation was typically monitored by TLC analysis, or in cases where necessary, ^{1}H NMR analysis of the reaction *in situ* in deuterated solvent.

General procedure for the proline catalyzed α-oxidation of ketones. A 2 dram vial equipped with a magnetic stir bar was charged with the appropriate ketone (1.5 mmol), *L*-proline (5.8 mg, 0.050 mmol), and DMF (0.25 mL). The mixture was stirred at room temperature for 5 min and then cooled to 4 °C with continued stirring. A solution of nitrosobenzene (54 mg, 0.50 mmol) in DMF (0.50 mL) was slowly added to the stirring solution over 4 h. The solution was then stirred for an additional 30 min and quenched with brine (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated.



(2*R*)-2-(*N*-Phenyl-aminooxy)-cyclohexanone (equation 10). The title compound was prepared from cyclohexanone (155 μL, 1.5 mmol) according to the general procedure. The resulting residue was purified by silica gel chromatography (5% EtOAc/Hex) to yield 79 mg (77% yield, 0.38 mmol) of pure product. >99% ee. All spectra were in agreement with those previously reported.[7]



(2*R*)-2-(*N*-*ortho*-Tolylaminooxy)-cyclohexanone. A 2 dram vial equipped with a magnetic stir bar was charged with cyclohexanone (147 mg, 1.5 mmol), *L*-proline (12 mg, 0.10 mmol) and DMSO (0.25 mL). The mixture was stirred at room temperature for 5 min and then cooled to 4 °C with continued stirring. 2-Nitrosotoluene (61 mg, 0.50 mmol) was then added to the stirring solution. Upon

consumption of the nitrosotoluene (1.5 h), as judged by TLC, the reaction was then quenched with brine (5 mL) and extracted with ethyl acetate (3 x 5 mL). The resulting residue was purified by flash chromatography (5% EtOAc/Hex) to yield 63 mg (0.57 mmol, 57% yield) of pure product. 98% ee. IR (CH_2Cl_2) 2942, 2865, 1721, 1607, 1586, 1487, 1450, 1309, 1133, 1098, 1072, 888 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (br s, 1H, NH), 7.21-7.04 (m, 3H, ArH), 6.92-6.85 (m, 1H, ArH), 4.40 (ddd, *J* = 11.7, 6.1, 1.1 Hz, 1H, COCH(OR)C), 2.56-2.30 (m, 3H, cyclohexyl-H), 2.13 (s, 3H, CH_3), 2.11-1.98 (m, 2H, cyclohexyl-H), 1.89-1.58 (m, 3H, cyclohexyl-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 145.8, 130.2, 126.7, 123.5, 121.9, 114.5, 86.1, 40.9, 32.6, 27.4, 23.8, 17.0; HRMS (FAB) exact mass calcd for ($C_{13}H_{17}NO_2$) requires *m/z* 219.1259, found *m/z* 219.1252. $[\alpha]_D$ = +108.8 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 3% isopropanol in hexanes, 1 mL/min); (*S*) isomer t_r = 14.9 min and (*R*) isomer t_r = 20.9 min.

V. References

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