

The Direct and Enantioselective Organocatalytic α -Oxidation of Aldehydes

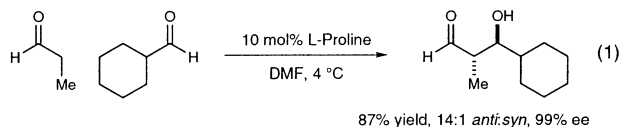
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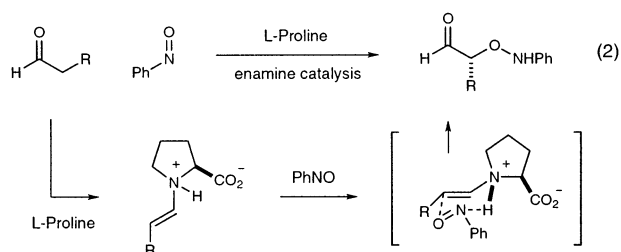
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Abundant among natural isolates and highly versatile as a functional intermediate, the α -oxycarbonyl synthon remains an important structural target for the development of new enantioselective technologies. At the present time, however, catalytic oxidation approaches to this asymmetric motif have relied exclusively upon the use of preformed enolates or enolate equivalents.¹ As part of a program aimed at developing broadly useful organic catalysts for asymmetric synthesis,² we recently reported the first direct proline-catalyzed cross-aldol reaction of aldehydes (eq 1).³ In this communication we advance this enamine catalysis concept to describe a highly enantioselective protocol for the α -oxidation of aldehydes. To our knowledge, this study represents the first example of a *direct* catalytic α -carbonyl oxidation that can be accomplished with high levels of asymmetric induction.

Proline Catalyzed Cross Aldol Addition



Organocatalyzed Direct α -Oxyamination



Yamamoto and co-workers recently disclosed a conceptually novel approach to the enantioselective oxidation of tin enolates using nitrosobenzene⁴ as an electrophilic source of oxygen in the presence of various BINAP-AgX catalysts.⁵ On the basis of these studies, as well as the recent elegant work by List,⁶ we were prompted to consider the direct, proline-catalyzed α -oxyamination of aldehydes with nitrosobenzene (eq 2).⁷ While Yamamoto has shown that uncatalyzed reactions of silyl ketene acetals with nitrosobenzene lead exclusively to *N*-selective nucleophilic addition,⁸ we hypothesized that the enhanced Brønsted basicity of the nitrogen atom should partition the addition toward the desired, *O*-addition manifold. Direct formation of highly versatile aldehyde products without preactivation via an enol derivative is attractive from operational, atom-⁹ and step-economy standpoints. Moreover, the facile conversion to terminal 1,2-diols represents an alternative and practical solution to the long-standing question of asymmetric terminal olefin dihydroxylation.¹⁰

Our initial studies revealed that the proposed organocatalytic α -oxyamination is indeed facile at room temperature and can be accomplished using a variety of reaction conditions (Table 1). While

variation of solvents has a pronounced effect on reaction rate (cf. entries 1 and 2 vs entries 8 and 9), excellent levels of enantioselection were observed for a diverse range of dielectric media. Notably, suppression of the homodimerization aldol³ and the α -amination pathway was accomplished by using CHCl_3 to provide the desired α -oxyaldehyde in 78% yield and 96% ee. As might be expected, improved selectivities were observed at lower temperature (4 °C), thus defining the optimal conditions to investigate the scope of this new transformation.

Table 1. Effect of Solvent on the Asymmetric α -Oxyamination

entry	solvent	% yield ^a	% ee ^b
1	dioxane	8	97
2	EtOAc	18	95
3	THF	24	97
4	DMSO	35	94
5	DMF	46	97
6	NMP	50	98
7	CH_3CN	67	96
8	PhH	67	97
9	CHCl_3	78	96

^a Isolated yield at arbitrary 15-min time point. The α -oxyaldehyde product was found to be oligomeric in solution. Yields were calculated after conversion to the corresponding primary alcohol. ^b Enantiomeric excess determined by chiral HPLC analysis (Chiralcel AD).

The effect of catalyst loading on reaction efficiency was next evaluated (Table 2). Remarkably, catalyst loadings as low as 0.5 mol % can be utilized without significant loss in enantiocontrol (entry 5, 94% ee). In terms of operational convenience, the use of 2 mol % L-proline ensures high levels of reaction efficiency and enantioselectivity while maintaining expedient reaction times (entry 3, 2 mol % L-proline, 88% yield, 97% ee, 2 h).

Table 2. Effect of Catalyst Loading on Organocatalyzed Oxidation

entry	mol % L-proline	time	% yield ^a	% ee ^b
1	10	20 min	88	97
2	5	45 min	86	97
3	2	2 h	88	97
4	1	8 h	83	97
5	0.5	18 h	68	94

^a Yields based upon isolation of the corresponding primary alcohol. ^b Determined by chiral HPLC analysis (Chiralcel AD).

Experiments that probe the scope of the aldehyde substrate are summarized in Table 3. Considerable variation in the steric demand of the aldehyde component ($\text{R} = \text{Me}, \text{Bu}, i\text{-Pr}, \text{Ph}$, entries 1–3

and 6) is possible without loss in efficiency or enantiocontrol (60–88% yield, 97–99% ee). Notably, these mild reaction conditions allow the use of electron-rich π -systems which are typically prone to oxidative degradation. For example, enamine oxidation to access enantio-enriched α -oxyaldehydes can be selectively accomplished with substrates that incorporate olefinic or indolic functionality (entries 4 and 8; $\geq 80\%$ yield, $\geq 98\%$ ee).

Table 3. Enantioselective α -Oxyamination: Substrate Scope

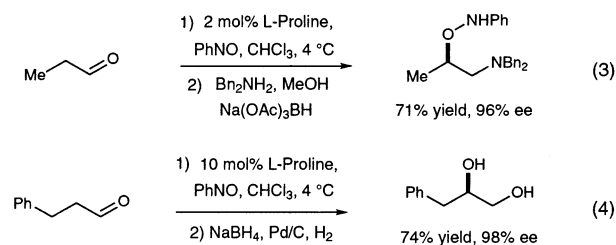
entry	R	Product	% yield ^a	% ee ^b
1	Me		88	97 ^c
2	<i>n</i> -Bu		79	98
3	<i>i</i> -Pr		85	99
4	CH ₂ CH=CH ₂		80	99 ^d
5	CH ₂ Ph		95	97 ^d
6	Ph		60	99
7	(CH ₂) ₃ OTIPS		76	98
8	CH ₂ -(3'- <i>N</i> -methyl-indole)		83 ^e	98

^a Yields based upon isolation of the corresponding primary alcohol.

^b Enantiomeric excess determined by chiral HPLC analysis (Chiracel AD).
^c Using 2 mol % L-proline. ^d Using 10 mol % L-proline. ^e Yield determined by NMR analysis.

The α -oxyaldehyde products are oligomeric in solution and were most conveniently isolated as the corresponding primary alcohols. Nonetheless, these oligomeric aldehydes smoothly undergo reactions typical of aldehydes. For example, treatment of the unpurified oxyamination product with dibenzylamine and sodium triacetoxyborohydride provides 1,2-amino alcohols in high yield and with excellent enantioselectivity (eq 3). Furthermore, a convenient one-

pot procedure highlights the utility of this organocatalytic protocol as a dihydroxylation surrogate. Specifically, reduction of the oxyamination product with NaBH₄, followed by N–O bond hydrogenolysis provides the corresponding terminal diol in 74% yield and 98% ee (eq 4). With respect to operational convenience, it should be noted that all reactions performed in this study were conducted in an aerobic atmosphere with wet solvents.



In summary, we have described the first direct, enantioselective α -oxyamination of aldehydes. Further efforts to evaluate the scope of this and related processes are underway. A full account of these studies will be forthcoming.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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