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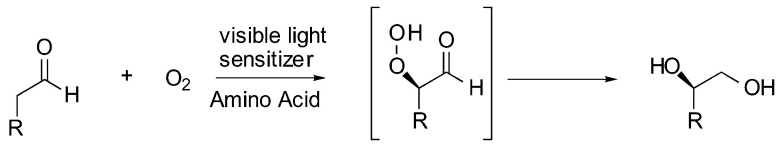

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The Direct Amino Acid-Catalyzed Asymmetric Incorporation of Molecular Oxygen to Organic Compounds

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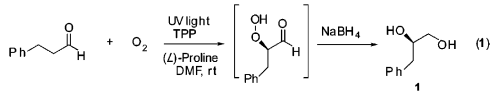
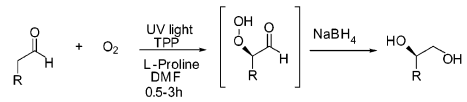
Molecular oxygen is an essential part of complex multicellular life on earth. Along with newer geochemical research, the secondary atmosphere on the earth around 4 billion years ago, was mainly formed by volcanic outgassing after hydrogen and helium had escaped the earth's weak gravitational field.[1] As ammonia and methane were too unstable under the UV irradiation of the sun, this atmosphere should predominantly have consisted of water, carbon dioxide, nitrogen, and smaller amounts of other gases including oxygen that could have formed through the decomposition of carbon dioxide and water.[1,2] Molecular oxygen can be transferred between its triplet state ($^3O_2$) and the more reactive singlet state ($^1O_2$).[3] Singlet molecular oxygen ($^1O_2$) plays a significant role in several biochemical processes. For instance, it is involved in the development of different diseases and biocatalytic oxidations.[4,5] Furthermore, chemists have utilized photo- or chemically generated molecular $^1O_2$ as an oxygen source for several synthetic transformations.[3,6] For example, it is used to generate cyclic peroxides analogous to a Diels−Alder-type reaction and in the formation of allylic hydroperoxides analogous to the "ene" reaction. Asymmetric reactions that are catalyzed by small organic molecules have received increased attention in recent years.[7] In particular, the employment of nontoxic small organic molecules have the potential for allowing development of a sustainable process from renewable resources.[8] On the basis of our previous investigations of asymmetric transformations mediated by amino acids,[9] we became interested whether a catalytically generated enamine would be able to react with molecular oxygen and form an oxygenated organic compound.[10] In addition, this potential amino acid-catalyzed transformation may warrant investigation for a prebiotic entry for the creation of α-hydroxy aldehydes, which are the building blocks of sugars.[11] Herein, we report that amino acids are able to catalyze direct asymmetric incorporation of singlet molecular oxygen to aldehydes. The unprecedented amino acid-catalyzed α-oxidations of aldehydes with molecular oxygen or air afforded terminal diols and α-hydroxy aldehydes.

In an initial catalyst screen of natural amino acids for the reaction between 3-phenyl propionaldehyde (1 mmol) and $^1O_2$, we found that several amino acids were able to mediate the asymmetric incorporation of molecular oxygen at the α-position of the aldehyde.[12] Among the amino acids tested L-proline was the most effective catalyst affording the corresponding (2*R*)-hydroxy-3-phenylpropanol **1** after in situ reduction of the α-hydroperoxide intermediate with $NaBH_4$ in 45% yield with 22% ee (eq 1).



Next, we tested proline as a catalyst for the direct asymmetric α-oxidation reaction with molecular oxygen for a variety of aldehydes (Table 1).

Table 1. Direct Catalytic Asymmetric Incorporation of $^1O_2$ to Aldehydes[a]



entry	R	temp (°C)	yield (%)[b]	er (*R*/*S*)[c]	cmpd
1	CH_2Ph	27	45	61/39	**1**
2	CH_2Ph	−5	91	74/26	**1**
3	Ph	−20	92	62/38	**2**
4	*i*-Pr	−5	95	71/29	**3**
5	*i*-Pr[d]	−5[d]	93[d]	28/69[d]	ent-**3**
6	*n*-Pent	−5	91	58/42	**4**
7	*n*-Bu	−5	92	61/39	**5**

[a] In a typical experiment, the amino acid (20 mol %) was stirred in the solvent (5 mL) for 20 min followed by addition of tetraphenylprophine (TPP) (5 mol %) and the aldehyde (1 mmol). The reaction was initiated and performed by bubbling a continuous flow of molecular oxygen or air for 0.5−3 h in the presence of visible light by a 250-W high-pressure sodium lamp. [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral-phase HPLC or GC. The racemic diols derived by D,L-proline catalysis were used as reference materials. The absolute configuration was determined by comparison with commercially available diols and/or literature data. [d] D-Proline was used as the catalyst.

The proline-catalyzed α-oxygenation reactions proceeded with excellent chemoselectivity, affording the optically active terminal diols **1**−**5** in high yield after in situ reduction with $NaBH_4$. The ee's of the diols derived by proline-catalysis were between 16 and 48%. Moreover, the reaction with a D-amino acid afforded the opposite enantiomer as compared to the same L-amino acid without affecting asymmetric induction. To improve the enantioselectivity of the α-oxygenations, a catalyst screen of different amino acid derivatives was performed.[12] The screen revealed that a methyl group at the α-position of proline significantly increased the stereoselectivity of the reaction, and L-α-methyl proline was therefore further investigated (Table 2). The L-α-methyl proline-catalyzed reactions were highly chemoselective, and all aldehydes exclusively converted to the corresponding α-oxygenated products within 1 h and afforded diols **1**−**5** in good yields with up to 66% ee (Table 2). The catalytic introduction of molecular oxygen at the α-position of unmodified aldehydes was also efficient with air as the oxygen provider. The catalyst loading could be decreased to 10 mol % without significantly affecting the efficiency of the reaction. In addition, unmodified ketones can be used as substrates. For example, L-alanine was able to mediate the synthesis of *trans*-(1*S*,2*S*)-cyclohexan-1,2-diol in 56% ee. The presence of an α-hydroperoxide intermediate was confirmed by the high yield of the diol derived from the α-oxygenation of 2-phenylacetaldehyde, since no benzaldehyde or benzyl alcohol was detected during the reaction. These results rule out a 1,2-cycloaddition between $^1O_2$ and the catalytic chiral enamine forming a dioxetane intermediate, which would have decomposed to benzaldehyde.[3a] Furthermore, we tested the proline-catalyzed α-oxidations of unmodified aldehydes with

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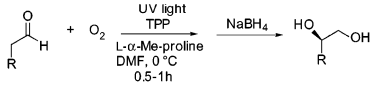
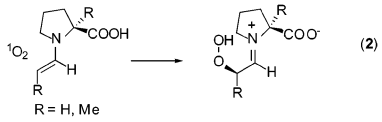
Table 2. Direct L-α-Me-proline Catalyzed Introduction of $^1O_2$[a]



entry	R	cmpd	yield (%)[b]	ee (%)[c]
1	CH_2Ph	**1**	77	66
2	CH_2Ph[d]	**1**	72[d]	66[d]
3	*i*-Pr	**3**	75	57
4	*n*-Pent	**4**	77	54
5	*n*-Bu	**5**	73	57

[a] In a typical experiment, the amino acid (20 mol %) was stirred in the DMF (1 mL) for 20 min followed by addition of tetraphenylprophine (TPP) (5 mol %) and the aldehyde (1 mmol). The reaction was initiated and performed by bubbling a continuous flow of molecular oxygen or air for 0.5−3 h in the presence of visible light by a 250-W high-pressure sodium lamp. [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral-phase HPLC or GC. [d] The reaction performed with air as the oxygen provider.

molecular $^3O_2$ as the electrophile in the presence of triethyl phosphite.[13,14] The reactions with molecular $^3O_2$ did not provide the diols. Thus, molecular $^1O_2$ was the fastest reacting electrophile and not $^3O_2$. Moreover, no diol product was formed without addition of the amino acid catalysts. The reaction plausibly proceeded via a catalytic enamine mechanism (eq 2). Hence, the (2*R*)-α-hydrogen peroxide aldehyde intermediate was formed via molecular $^1O_2$ proton abstraction of the L-amino acid carboxyl group, which provided the sterochemical information, together with addition to the *si*-face of the amino acid-derived enamine.



(2)

We also found that natural amino acids were able to catalyze the direct incorporation of molecular oxygen to aldehydes in aqueous buffer. For example, L-proline catalyzed the direct asymmetric synthesis of terminal diol **3** in phosphate buffer at room temperature. In addition, the amino acids mediated the direct catalytic asymmetric α-oxidations in open air with the sun as the light source. In a plausible prebiotic scenario, the α-hydrogen peroxide intermediate could have readily been reduced to the corresponding α-hydroxy aldehyde. In fact, α-hydroxy aldehydes are both donors and acceptors in amino acid-catalyzed asymmetric aldol reactions under prebiotic conditions to furnish sugars.[11a] Hence, the amino acid-catalyzed incorporation of molecular oxygen to aldehydes may have served as the starting point for the synthesis of polyhydroxylated compounds even in the presence of small amounts of oxygen.

In conclusion, we have revealed that natural amino acids catalyze the asymmetric incorporation of molecular oxygen to the α-position of aldehydes. The transformations are unprecedented direct catalytic asymmetric oxidations with singlet oxygen. Furthermore, the direct catalytic asymmetric α-oxygenations may be considered a metal-free entry for the preparation of optically active building blocks such as terminal diols. The α-oxygenations are inexpensive, operationally simple, and environmentally benign. All materials in this process are from renewable resources, thus allowing for a highly sustainable catalytic process. Our results demonstrate that simple amino acids can accomplish catalytic asymmetric oxidations with singlet molecular oxygen, which has previously been considered to be in the domains of enzymes and chiral transition-metal complexes.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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