Oxidations

Direct Amino Acid Catalyzed Asymmetric α Oxidation of Ketones with Molecular Oxygen**

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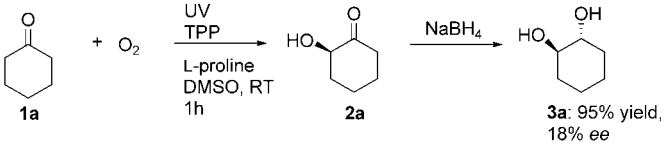
Molecular oxygen is fundamental for the existence of complex multicellular life on earth. The initially very small amounts of molecular oxygen is believed to have been formed around 4 billion years ago by the decomposition of CO_2 and water promoted by UV irradiation from the sun.[1] Molecular oxygen can be transferred between its more reactive singlet state ($^1O_2$) and its non-excited triplet state ($^3O_2$).[2] Singlet molecular oxygen ($^1O_2$) plays a significant role in several biochemical processes. For example, it is involved in the development of different diseases and biochemical oxidations.[3,4] Furthermore, chemists have utilized photo- or chemically generated molecular $^1O_2$ as an oxygen source for several synthetic transformations.[1,5] For example, it is used in the formation of allylic hydroperoxides (analogous to the "ene" reaction) and to generate cyclic peroxides (analogous to a Diels–Alder-type reaction). There is a demand in today's society for the development of sustainable chemistry from renewable resources.[6] The content of molecular oxygen in air is 21%, which allows its use in oxidation reactions. Thus, molecular oxygen is one of the ultimate oxidants for oxidation of organic molecules and the development of sustainable chemistry.

Asymmetric reactions that are catalyzed by small organic molecules have received increased attention in recent years.[7] Among several transformations, amine-catalyzed asymmetric epoxidations with dioxirane have been reported.[8] The employment of non-toxic, small organic molecules has the potential for allowing environmentally benign reaction conditions. Based on our previous investigations of organic reactions that are mediated by metal-free organic molecules,[9] we became interested in whether an amino acid would allow the catalytic incorporation of molecular oxygen into ketones [Eq. (1)].[10–11] Moreover, this potential amino acid catalyzed transformation may warrant investigation as a prebiotic pathway for the synthesis of α-hydroxyketones, which are the building blocks of sugars.[12] Herein, we report the unprecedented direct amino acid catalyzed asymmetric incorporation of singlet molecular oxygen into ketones. This α oxidation of ketones with molecular oxygen or air furnished α-hydroxyketones and diols.

(1)

In an initial experiment, cyclohexanone **1a** (1 mmol) was added to a vial containing dimethyl sulfoxide (DMSO) (1 mL), L-proline (20 mol%) and tetraphenylporphine (TPP) (1 mol%). A continuous flow of O_2 or air was bubbled through the vial and the reaction was exposed to visible light from a 250-W high-pressure sodium lamp (Scheme 1). To our



Scheme 1. Amino acid catalyzed asymmetric α oxidation of cyclohexanone to give **2a** and in situ reduction to diol **3a**.

delight, complete conversion had occurred after one hour, and the reaction was quenched by aqueous workup. The crude ketone **2a** existed as a mixture of dimeric and oligomeric products. The crude product mixture was purified by silica-gel column chromatography to yield α-hydroxyketone **2a** with 18% *ee*.[13,14] We also performed the reaction with in situ reduction of α-hydroxyketone **2a** with $NaBH_4$ to afford the corresponding optically active *trans*- and *cis*-diols **3a** (*trans*/*cis* = 3:1) in 95% combined yield after silica-gel column chromatography. The enantiomeric excess of the pure *trans*-**3a** diol was determined by chiral-phase GC analyses to be 18% *ee*.

Next, we screened several natural amino acids and their derivatives for their potential in catalyzing the introduction of $^1O_2$ at the α position of **1a** and to improve the stereoselectivity of the reaction (Table 1). We found that several of the amino acids investigated catalyzed the α oxidations with molecular $^1O_2$ with high efficiency and chemoselectivity. The simple amino acids alanine and valine mediated the reaction with the highest stereoselectivity. In fact, this is the first case in which an acyclic amino acid provides higher asymmetric induction than proline and its derivatives in organic solvents. In previously reported direct organocatalytic intermolecular transformations, the catalyst required a cyclic five-membered ring to allow high efficiency and enantioselectivity.[7] However, a higher enantioselectivity was obtained with L-α-methylproline than with L-proline (increase from 18 to 48% *ee* for **2a**). Thus, the presence of a methyl group at the α position of proline significantly increased the stereoselectivity. In contrast, this effect was not observed when comparing valine with α-methylvaline. The asymmetric α oxygenation reactions that were catalyzed by a D-amino acid afforded the opposite enantiomer of **2a** to that obtained in the reactions catalyzed by the corresponding L-amino acid, without affecting the asymmetric induction. Furthermore, amino alcohols, dipeptides, amino acids with amide and amine functionalities, and synthetic amino acid derivatives catalyzed the direct asymmetric introduction of molecular oxygen into

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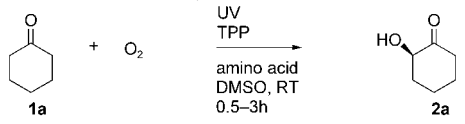
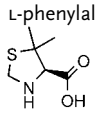
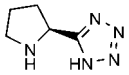
Table 1: Direct amino acid-catalyzed introduction of $^1O_2$ to **1a**.[a]



Entry	Amino acid	Product	Yield [%][b]	*ee* [%][c]
1	L-alanine	*ent*-**2a**	93	56
2	D-alanine	**2a**	88	57
3	L-valine	*ent*-**2a**	78	49
4	D-valine	**2a**	77	48
5	L-proline	**2a**	95	18
6	D-proline	*ent*-**2a**	93	16
7	L-hydroxyproline	**2a**	88	11
8	L-α-methylproline	**2a**	20	48
9	L-α-methylvaline	*ent*-**2a**	15	6
10	L-α-phenylglycine	*ent*-**2a**	70	20
11	L-phenylalanine	*ent*-**2a**	89	38
12	D-α-phenylglycine	**2a**	71	21
13	L-threonine	*ent*-**2a**	20	10
14	L-phenylalinol	*ent*-**2a**	67	< 2
15		**2a**	62	11
16	glycine	**2a**	85	–
17	ethanolamine	**2a**	81	–
18		**2a**	97	< 5

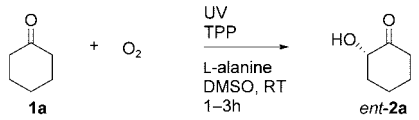
[a] See experimental section. [b] Yields of isolated product after column chromatography on silica gel of the pure **3a** furnished after reduction of **2a**. [c] Determined by chiral-phase GC analyses. The racemic product derived by glycine catalysis was used as reference material. The absolute configuration was determined by comparison with commercially available diols and literature data.

ketones with a similar efficiency to that of the amino acids. However, the amino acid catalysts were superior to the amino alcohols with regards to stereoselectivity. It should be noted that the direct introduction of $^1O_2$ into ketones was also readily catalyzed by glycine and ethanolamine, providing a novel inexpensive entry to α-oxygenated compounds.

We also performed a solvent screen of the L-alanine-catalyzed asymmetric incorporation of molecular oxygen into **1a** in different solvents (Table 2). Direct L-alanine-catalyzed asymmetric α oxidations with $^1O_2$ proceeded smoothly in DMSO, *N*-methylpyrrolidinone (NMP), and *N*,*N*-dimethylformamide (DMF). In contrast, L-alanine only furnished trace amount of product in MeOH, trifluoroethanol (TFE), and $CHCl_3$. Hence, the best selectivity and efficiency is obtained in the more polar aprotic solvents. We did not observe any significant temperature dependence of the stereoselectivity in DMSO. Furthermore, the reactions were also efficient in aqueous media with air as the molecular oxygen source, which could allow the development of environmentally benign reaction conditions.

Next, we investigated the amino acid catalyzed asymmetric α oxidations with molecular oxygen of various ketones (Table 3). The direct amino acid catalyzed asymmetric α-oxygenation reactions progressed with excellent chemoselectivity and furnished the corresponding α-oxygenated adducts *ent*-**2a** and **2b–e** with good enantioselectivity. For example,

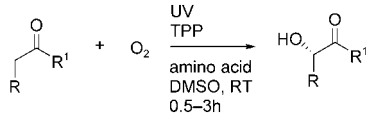
Table 2: Solvent screen of the L-alanine-catalyzed incorporation of $^1O_2$ to ketones.[a]

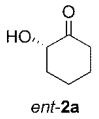
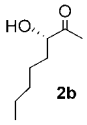
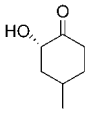
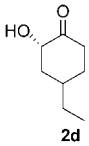
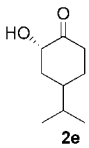


Entry	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	MeOH	RT	traces	n.d.
2	DMSO	40	79	55
3	DMSO	RT	93	56
4	DMSO	0→RT	80	48
5	DMSO[d]	RT	82[d]	56[d]
6	NMP	RT	86	48
7	DMF	RT	82	49
8	TFE	RT	traces	n.d.
9	phosphate buffer[e]	RT	80[e]	18[e]
10	H_2O[e]	RT	77[e]	19[e]
11	$CHCl_3$	RT	traces	n.d.

[a] See experimental section. [b] Yields of isolated product after column chromatography on silica gel of the pure *ent*-**3a** furnished after reduction of *ent*-**2a**. [c] Determined by chiral-phase GC analyses. [d] Reaction performed with air as the O_2 source. [e] Protoporphine (1 mol%) was used as the sensitizer and DMSO (40% *v*/*v*).

Table 3: Direct catalytic asymmetric incorporation of molecular oxygen to ketones.[a]

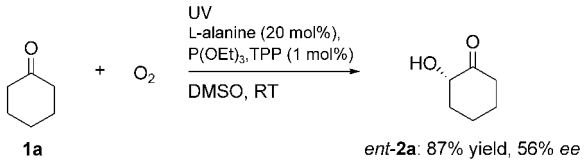


Entry	Product	Amino acid	Yield [%][b]	*ee* [%][c]
1	 *ent*-**2a**	L-alanine	93	56
2	 **2b**	L-valine	50	28
3	 **2c**	L-valine	75	69
4		L-alanine	67	72
5	 **2d**	L-alanine	61[d]	60
6	 **2e**	L-alanine	58[d]	52

[a] See experimental section. [b] Yields of isolated products after column chromatography on silica gel of the diol **3**. [c] Determined by chiral-phase GC analyses. The racemic products were derived by glycine or D-, L-proline catalysis and were used as reference materials. [d] Reaction performed in NMP.

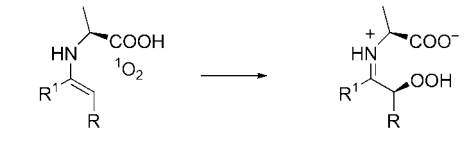
L-alanine catalyzed the formation of **2c** in 67% yield with 72% *ee*. Furthermore, the amino acid catalyzed reactions with linear acyclic ketones progressed with excellent regioselectivity, and molecular oxygen was asymmetrically incorporated at the most substituted side of the ketone. Moreover, the reactions were readily scaled up and performed on the gram scale. The amino acids were also able to catalyze the asymmetric incorporation of molecular oxygen into unmodified aldehydes.[15] For example, L-α-methylproline furnished (*R*)-2-hydroxy-3-phenylpropanal with 65% *ee*. The direct amino acid catalyzed α oxygenation with molecular $^1O_2$ may be considered as a new, simple, metal-free entry into the synthesis of α-hydroxyketones and diols.

We also tested the amino acid-catalyzed α-oxidations of unmodified ketones with molecular $^3O_2$ as the electrophile in the presence of triethylphosphite.[16] The reactions with molecular $^3O_2$ did not provide the α-hydroxyketone adducts **2** or the diol **3**. Thus, molecular $^1O_2$ is the more reactive electrophile and not $^3O_2$. Moreover, no products were formed in the absence of the amino acid catalysts. We also investigated the possibility of background oxidation by α-hydroperoxide ketone intermediates or another peroxide intermediate that potentially could influence the enantioselectivity of the reaction.[13–14] However, the use of excess (5 equiv) H_2O_2, NaClO, *m*-chloroperbenzoic acid (MCPBA), or oxone as the oxidants for cyclohexanone (1 mmol) in the presence of a catalytic amount of L-proline or L-alanine (20 mol%) in DMSO only provided trace amounts of the diol **3a** after in situ reduction with $NaBH_4$. Furthermore, the L-alanine-catalyzed α oxygenation with $^1O_2$ in the presence of triethylphosphite furnished *ent*-**2a** in 87% yield with 56% *ee*, which is the same *ee* value of *ent*-**2a** obtained without the addition of phosphite (Scheme 2).

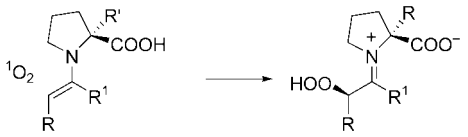


Scheme 2. Direct L-alanine-catalyzed introduction of molecular $^1O_2$ to **1a** in the presence of triethylphosphite.

These results indicated that the potential background oxidation by peroxide intermediates was not significant under the set reaction conditions. We were also able to rule out a 1,2-cycloaddition between $^1O_2$ and the catalytic chiral enamine to form a dioxetane intermediate, as no cleavage products from such an intermediate was detected. The stereochemical outcome of the reaction was determined by optical rotation and chiral-phase GC analyses of **2a** and *trans*-**3a**, which revealed that acyclic L-amino acids provided (2*S*)-α-hydroxycyclohexanone *ent*-**2a** and (1*S*, 2*S*)-*trans*-cyclohexane-1,2-diol (*ent*-**3a**). In contrast, L-proline and its derivatives furnished (2*R*)-α-hydroxycyclohexanone (**2a**). The reaction plausibly proceeds through a catalytic enamine mechanism [Eq. (2) and (3)]. Hence, the tentative (2*S*)-α-hydroperoxide intermediate is formed through proton abstraction by molecular $^1O_2$ from the carboxy group of the acyclic L-amino acids,[14] which provides the sterochemical information, together with addition to the *Re* face of the amino acid derived enamine to furnish (2*S*)-α-hydroxyketone [Eq. (2)]. In the case of α oxygenation mediated by a cyclic L-amino acid, the addition of $^1O_2$ occurs at the *Si* face of the enamine to provide the (2*R*)-α-hydroxyketone [Eq. (3)].



(2)



(3)

R' = H, Me

We also established that natural amino acids catalyze the asymmetric incorporation of molecular oxygen into ketones in aqueous buffer. For example, L-alanine catalyzed the direct asymmetric synthesis of *ent*-**2a** in phosphate buffer at 37 °C. Moreover, the amino acids mediated the direct catalytic asymmetric α oxidations in air with the sun as the light source. Hence, terrestrial and extraterrestrial amino acids were able to catalyze the introduction of molecular oxygen under prebiotic conditions to form α-hydroxyketones. In fact, the amino acids were able to catalyze the α oxidation of acetone with $^1O_2$ to furnish hydroxyacetone and dihydroxyacetone, which are the building blocks and donors in amino acid catalyzed asymmetric synthesis of sugars under prebiotic conditions.[12a,17] Thus, the amino acid catalyzed introduction of molecular oxygen may plausibly have served as the first step in their homochirality transfer of their asymmetry to polyhydroxylated compounds, even in the presence of small amounts of oxygen.[12]

In conclusion, we have disclosed the unprecedented ability of amino acids to catalyze the direct asymmetric incorporation of singlet molecular oxygen into ketones. The smallest amino acids alanine and valine catalyzed the transformation with the highest stereoselectivity. The direct catalytic α oxygenations are a novel, inexpensive, operationally simple, and environmentally benign entry to the preparation of α-hydroxyketones and diols. All materials in this process stem from renewable sources, thus allowing a highly sustainable catalytic process. Readily available amino acids allow catalytic asymmetric oxidations with molecular oxygen or air, which has previously been considered to be in the domains of enzymes and chiral transition-metal complexes.

Experimental Section

Typical experimental procedure (Table 1, entry 1): Cyclohexanone (1 mmol) was added to a vial containing TPP (1 mol%) and a catalytic amount of L-alanine (20 mol%) in DMSO (1 mL). A

continuous flow of O_2 or air was bubbled through the vial, and the reaction was exposed to visible light by a 250-W high-pressure sodium lamp. After 1 hour, complete conversion had occurred, and the reaction was quenched either by the addition of brine followed by extraction with EtOAc to furnish α-hydroxyketone *ent*-**2a** or by in situ reduction with $NaBH_4$ to afford the corresponding optically active crude diol *ent*-**3a** (*trans*/*cis* 3:1). The crude *ent*-**2a** existed as an oligomeric mixture that, upon standing, formed the dimer, which was isolated by silica-gel column chromatography (EtOAc/pentane 1:20) with 56% *ee* (determined by chiral-phase GC-analysis). GC: (CP-Chirasil-Dex CB); $T_{inj} = 250\,^{\circ}C$, $T_{det} = 275\,^{\circ}C$, flow = 1.8 mL min^{-1}, $t_i = 60\,^{\circ}C$ (9 min), rate = 85 °C min^{-1}, $t_f = 200\,^{\circ}C$ (5 min); retention times of **2a**: $t_{maj} = 10.64$ min, $t_{min} = 10.66$ min. The *trans*-**3a** and *cis*-**3a** diols were isolated by silica-gel column chromatography (EtOAc/pentane 1:1) in a combined yield of 92% with 56% *ee* of the pure *trans*-**3a** diol (determined by GC analyses). (1*S*, 2*S*)-*trans*-cyclohexane-1,2-diol: $[\alpha]_D = +21$ ($c = 0.2$, $CHCl_3$); GC: (CP-Chirasil-Dex CB); $T_{inj} = 250\,^{\circ}C$, $T_{det} = 275\,^{\circ}C$, flow = 1.8 mL min^{-1}, $t_i = 90\,^{\circ}C$ (2 min), $t_f = 110\,^{\circ}C$, rate = 0.3 °C min^{-1}; retention times of acetylated compound: $t_{maj} = 9.75$ min, $t_{min=}$9.61 min.

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[1] a) H. D. Holland, *The Chemistry of the Atmosphere and Oceans*, Wiley, New York, **1978**; b) J. F. Kasting, T. P. Ackerman, *Science* **1986**, *234*, 1383; c) J. H. Carver, *Nature* **1981**, *292*, 136; d) K. Plankensteiner, H. Reiner, B. Schranz, B. M. Rode, *Angew. Chem.* **2004**, *116*, 1922; *Angew. Chem. Int. Ed.* **2004**, *43*, 1886.

[2] a) C. S. Foote, *Acc. Chem. Res.* **1968**, *1*, 104; b) C. Schweitzer, R. Schmidt, *Chem. Rev.* **2003**, *103*, 1685.

[3] a) B. Halliwell, M. C. John, *Free Radical in Biology and Medicine*, 2nd ed., Clarwndon, Oxford, **1982**; b) N. I. Krinsky in *Biological roles of singlet oxygen*, *Vol. 40* (Ed.: H. H. Wasserman), Academic Press, New York, **1979**, pp. 597–641.

[4] a) B. Samuelsson, *J. Am. Chem. Soc.* **1965**, *87*, 3011; b) P. Wentworth, Jr., L. H. Jones, A. D. Wentworth, X. Zhu, N. A. Larsen, I. A. Wilson, X. Xu, W. A. Goddard III, K. D. Janda, A. Eschenmoser, R. A. Lerner, *Science* **2001**, *293*, 1806.

[5] a) For an example in total synthesis see: K. C. Nicolaou, Z. Yang, G.-q. Shi, J. L. Gunzner, K. A. Agrios, P. Gärtner, *Nature* **1998**, *392*, 264; b) For diasteroselective photooxygenations, see: M. Prein, W. Adam, *Angew. Chem.* **1996**, *108*, 519; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 477.

[6] M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem.* **2002**, *114*, 402; *Angew. Chem. Int. Ed.* **2002**, *41*, 414.

[7] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; b) B. List, *Tetrahedron* **2002**, *58*, 5573; c) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481; d) R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005; *Angew. Chem. Int. Ed.* **2003**, *42*, 975.

[8] a) L. Bohe, G. Hanquet, M. Lusinchi, X. Lusinchi, *Tetrahedron Lett.* **1993**, *34*, 7271; b) M. F. A. Adamo, V. K. Aggarwal, M. A. Sage, *J. Am. Chem. Soc.* **2000**, *122*, 8317; c) A. Armstrong, *Angew. Chem.* **2004**, *116*, 1484; *Angew. Chem. Int. Ed.* **2004**, *43*, 1460, and references therein.

[9] a) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109; b) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673; c) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1937; d) A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 3949; e) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; f) A. Córdova, *Synlett* **2003**, 1651, and references therein.

[10] For proline-catalyzed α-aminooxylation reactions reported by other groups, see: a) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; c) M. Y. Hayashi, J. Yamaguchi, T. Sumaiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112; d) M. Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293; for the use of proline derivatives as catalysts, see: N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374, and reference [9b].

[11] For examples of proline-catalyzed α aminations, see: a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; b) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656.

[12] a) S. Pizarello, A. L. Weber, *Science* **2004**, *303*, 1151; b) L. E. Orgel, *Science* **2000**, *290*, 1306.

[13] In addition to the α oxidation of **1a**, the DMSO was also oxidized to the corresponding dimethyl sulfone at prolonged reaction times.

[14] We were only able to isolate the α-hydroxyketone adducts and not a potential α-hydroperoxide intermediate. Hence, we believe that the α-hydroperoxide intermediate is rapidly converted into the α-hydroxyketone product.

[15] A. Córdova, H. Sundén, M. Engqvist, I. Ibrahem, J. Casas, *J. Am. Chem. Soc.* **2004**, *126*, 8914.

[16] a) E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc.* **1975**, *97*, 6908; b) E. F. J. de Vries, L. Ploeg, M. Colao, J. Brussee, A. van der-Gen, *Tetrahedron: Asymmetry* **1995**, *6*, 1123.

[17] A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, *24*, 3024. For a Zn–amino acid mediated sugar synthesis under prebiotic conditions, see: J. Kofoed, M. Machuqueiro, J.-L. Reymond, T. Darbre, *Chem. Commun.* **2004**, *26*, 1540.

