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A route to 1,2-diols by enantioselective organocatalytic α-oxidation with molecular oxygen

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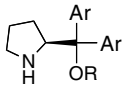
Abstract—A route to 1,2-diols by the direct organocatalytic enantioselective α-oxidation of aldehydes using molecular oxygen is presented. Protected commercially available chiral pyrrolidines catalyze the asymmetric α-oxidation of aldehydes with singlet molecular oxygen with high enantioselectivity to furnish the corresponding diols after in situ reduction in high yield with up to 98% ee. Electrophilic singlet molecular oxygen was photo or chemically generated ('dark' $^1O_2$).

Optically active 1,2-diols are common in numerous important natural products and synthetic pharmaceuticals.[1] This has led to the development of diastereoselective and enantioselective routes for their synthesis, among them, the Sharpless asymmetric dihydroxylation of olefins with osmium tetraoxide is one of the most often used.[2] Moreover, several indirect methods exist for their preparation.[3] Enzymatic resolution has also been employed as a key step for their synthesis.[4] Most of these preparations, however, require multiple manipulations, and no direct method from the corresponding aldehyde is available. For these reasons, the development of new methodologies for the direct catalytic enantioselective α-hydroxylation of aldehydes has become an intriguing target in organic synthesis. In this context, Momiyama and Yamamoto have reported an excellent catalytic asymmetric nitroso-aldol reaction between preformed tin enolates and nitrosobenzene in the presence of a catalytic amount of a BINAP–AgOTf complex.[5] Organocatalysis is a rapidly developing area of research in organic chemistry.[6] Most recently, amino acids and their derivatives were reported to catalyze α-oxidation reactions with nitrosobenzene as the oxygen source to give α-aminoxylated aldehydes and ketones.[7] Furthermore, we recently demonstrated that amino acids catalyze the biomimetic, asymmetric, aerobic α-oxidation of aldehydes with moderate enantioselectivity.[8]

Molecular oxygen or air is considered a 'green oxidant' and is used in modern oxidation methods.[9,10] Molecular oxygen can be transferred between its more reactive singlet state ($^1O_2$) and its non-excited triplet state ($^3O_2$).[11] In this context, chemists have utilized photo or chemically generated molecular $^1O_2$ as an oxygen source for several synthetic transformations.[12] Based on our research interest in the development of organocatalytic asymmetric reactions[13] and our previous research experience in catalytic C–O bond formation with aldehydes,[7h,8] we envisioned a 'green' oxidation route for the asymmetric construction of 1,2-diols based on chiral amine-catalyzed enantioselective α-oxygenation of aldehydes with $^1O_2$ followed by in situ reduction of the corresponding α-hydroxyaldehyde. We envisioned that the employment of a bulky chiral pyrrolidine derivative as the catalyst would enable shielding of one of the faces of the catalytically generated chiral enamine and consequently give high levels of asymmetric induction (Scheme 1).

Herein, we report a simple route to 1,2-diols by direct organocatalytic enantioselective α-oxidation of



1a: R = H; Ar = Ph
1b: R = TMS, Ar = Ph
1c: R = TMS, Ar = 2-Naphthyl
1d: R = TMS, Ar = 3,5-CF_3-C_6H_3

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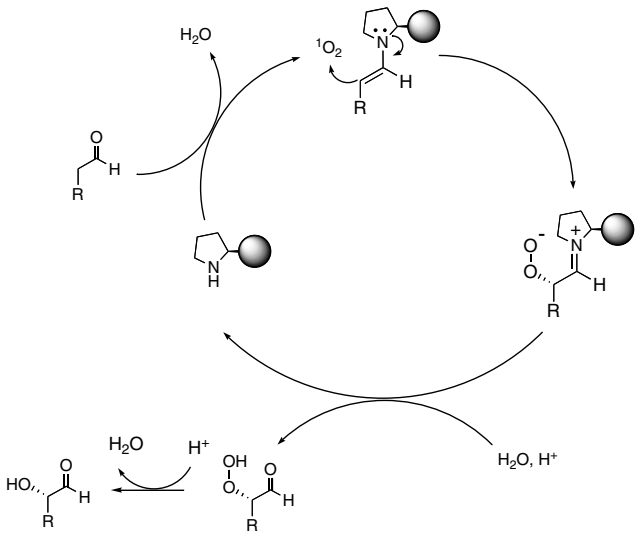


Scheme 1. Direct organocatalytic asymmetric α-oxidations of aldehydes with $^1O_2$.

aldehydes with molecular oxygen, which after in situ reduction provides the corresponding diols with up to 98% ee.

We initially decided to investigate the commercially available diphenyl-2-pyrrolidinemethanol (**1a**, diphenylprolinol), which has been developed by Corey and co-workers, as a catalyst.[14]

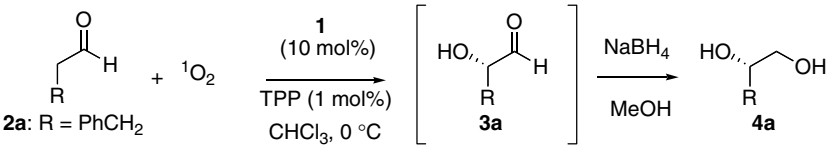
Hence, 3-phenylpropionaldehyde **2a** (0.5 mmol) was added to a scintillation vial containing $CHCl_3$ (2 mL), **1a** (10 mol %) and tetraphenylporphine (TPP) (1 mol %) at 0 °C. A continuous flow of O_2 or air was bubbled through the vial and the reaction exposed to visible light from two 250 W high-pressure sodium lamps (Table 1, entry 1). After 4 h of stirring and maintaining the temperature at 0 °C, the light was switched off and the reaction diluted with MeOH (2 mL) followed by in situ reduction of the α-hydroxy aldehyde **3a** with excess $NaBH_4$ to give the crude diol **4a**, which was purified by silica-gel column chromatography. Diacetylation of the pure diol **4a** gave the corresponding diacetate in trace amounts with 24% ee. Thus, the reaction exhibited poor reactivity and low enantioselectivity. Nevertheless, we decided to continue our study and investigate the possibility of utilizing TMS protected diarylprolinols (**1b–d**)[15] as the catalysts (Table 1).

To our delight, TMS protection of diphenylprolinol **1a** had a remarkable effect on the reactivity and enantioselectivity of the reaction. That is, the organocatalyst **1b** catalyzed the asymmetric formation of **3a** in 43% yield with 90% ee within 5 h. Increasing, the bulk of the aryl groups on the catalyst **1** from phenyl to 2-naphthyl (catalyst **1c**) slightly increased the enantioselectivity of the reaction and diol **4a** was isolated in moderate yield with 92% ee. The chiral diarylprolinol **1d** was the most efficient catalyst and gave diol **4a** in 50% yield with 70% ee. The order of asymmetric induction by the protected diaryprolinols was as follows **1c** > **1b** > **1d**. Catalyst **1b** was selected for further studies, since it gave a high asymmetric induction and can be prepared from commercially available **1a** in one-step. Thus, the chiral amine **1b** catalyzed asymmetric α-oxidation of heptanal **2b** with molecular oxygen was investigated in different solvents (Table 2). The solvent screen was performed at low conversion (<50%, 0.5–2.5 h), since ice had to be added manually in order to maintain the desired temperature.

The protected diphenylprolinol **1b** catalyzed the reaction with moderate to high enantioselectivity under all the conditions tested. For instance, the reactions in $CHCl_3$ and MeOH gave 1,2-diol **4b** with 80 and 81% ee's, respectively, after in situ reduction of **3b**. Aubry, Alsters and co-workers have reported an excellent way of chemically generating singlet molecular oxygen ('dark' $^1O_2$) by using $La(NO_2) \times 6H_2O$ as the catalyst and H_2O_2.[16] Hence, the organocatalytic α-oxygenation reactions were also performed with 'dark' $^1O_2$ and catalyst **1b** (10 mol %) to give the corresponding diol **4b** in 23% and 26% yields with 80% and 72% ee, respectively (entries 2 and 4). These results represent the first direct catalytic asymmetric reactions with 'dark' $^1O_2$. We next performed the organocatalytic asymmetric α-oxidation of aldehydes with a set of different aldehydes **2** (Table 3).[17]

The protected diphenyl prolinol **1b** catalyzed α-oxygenation reactions were efficient and highly enantioselective and furnished aldehydes **4a–f** in high yields with 74–98%

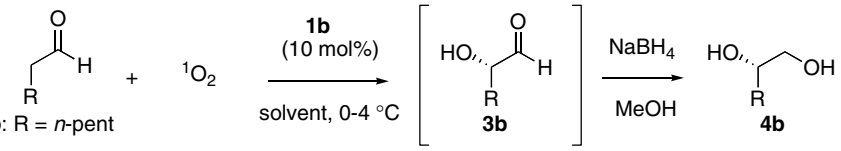
Table 1. Catalyst screen



Entry	Catalyst	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	4	Trace	24
2	**1b**	5	43	90
3	**1c**	5	38	92
4	**1d**	4	50	70

[a] Isolated yield of pure diacetylated **4a**.
[b] Ee as determined by chiral-phase HPLC analyses.

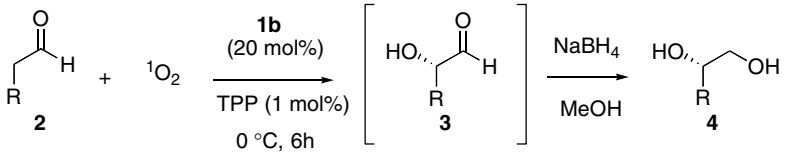
Table 2. Solvent screen



Entry	Solvent	Conditions	Time (h)	Yield[a] (%)	ee[b]
1	$CHCl_3$	A	2	28	80
2	$CHCl_3$	B	20	23	80
3	MeOH	A	0.5	10	81
4	MeOH	B	20	26	72
5	CCl_4	A	1.1	15	76
6	DMF	A	2.5	43	67
7	DMSO	A	1	34	54
8	*t*-BuOH–H_2O	A	1	12	70
9		A	1	6	57

A: The singlet oxygen was generated by TPP (1 mol %) and two 250-W high-pressure sodium lamps in $CHCl_3$. B: The singlet oxygen was catalytically generated from H_2O_2 by La^{III} according to Ref. 16 in MeOH (1 mL) at room temperature.
[a] Isolated yield of pure diacetylated **4b**.
[b] Ee as determined by chiral-phase GC analyses.

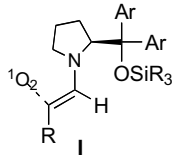
Table 3. Chiral amine **1b** catalyzed asymmetric α-oxidations of aldehydes **2** with $^1O_2$



Entry	Aldehyde	R	Prod.	Yield[a] (%)	ee[b] (%)
1	**2a**	Bn	**4a**	70	87
2	**2a**	Bn	**4a**	50[c]	90[c]
3	**2b**	*n*-Pent	**4b**	67	75
4	**2c**	4-$NO_2C_6H_4CH_2$	**4c**	64	98
5	**2d**	4-$ClC_6H_4CH_2$	**4d**	71	98
6	**2e**	4-$BrC_6H_4CH_2$	**4e**	68	98
7	**2f**	*n*-Butyl	**4f**	76	74

[a] Isolated yield of pure diacetylated **4a**.
[b] Ee as determined by chiral-phase HPLC or GC analyses.
[c] 10 mol % catalyst.

ee. In particular, the reactions with aldehydes **2c–e** proceed with excellent enantioselectivity and gave the corresponding aldehydes **4c–e** with 98% ee. The dependence of the enantioselectivity of the reaction was also investigated as a function of the optical purity of the catalyst **1b** (Fig. 1). No non-linear effects were observed. The absolute stereochemistry of the 1,2-diols **4** was (2*S*) as established by comparison with literature and chiral-phase HPLC analysis.[3a,7,8] Based on the absolute stereochemistry of the (2*S*)-1,2-diols, we propose intermediate **I** to account for the stereochemical outcome of the protected diarylprolinol **1b–d** catalyzed α-oxidation reaction of aldehydes with molecular oxygen. The high enantioselectivity of the α-oxygenation reaction can be explained by an efficient shielding of the *Si*-face of the chiral enamine and stabilization of the *trans*-configuration of the chiral enamine. Thus, the chiral enamine attacks the $^1O_2$ from its *Re*-face.



The remarkable change of reactivity by TMS protection of the diarylprolinol **1a** was explained by prevention of aminal formation with the substrate or product and the increased hydrophobicity of the corresponding diarylprolinol **1b**, which improves the rate of enamine formation with aldehydes **2**. The organocatalytic α-oxidations with 'dark' $^1O_2$ confirmed that this was the electrophile and not $^3O_2$. Furthermore, no product was observed in the amine **1** catalyzed α-oxidation reactions with molecular oxygen without addition of TPP sensitizer.

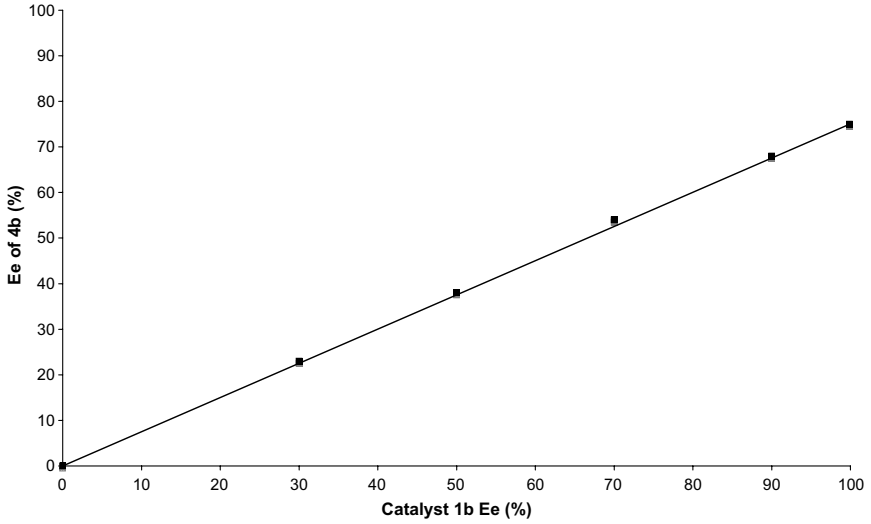


Figure 1. Relationship between the enantiomeric excess of (*S*)-**1b** and that of the newly formed aldiol **4b** (■).

In summary, we report a simple route to 1,2-diols by organocatalytic enantioselective α-oxidation with molecular oxygen. Protected diaryl prolinols catalyzed the reaction with excellent enantioselectivity and the corresponding 1,2-diols were isolated in high yields with up to 98% ee. The electrophile was photo or chemically generated $^1O_2$. In fact, the organocatalytic transformations represent the first examples of direct catalytic asymmetric reactions with 'dark' $^1O_2$. The methodology presented herein demonstrates that commercially available non-toxic catalysts can catalyze highly enantioselective α-oxidations of aldehydes with the 'green oxidant' molecular oxygen.

Acknowledgements

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16. Nardello, V.; Barbillat, J.; Marko, J.; Witte, P. T.; Alsters, P. L.; Aubry, J.-M. *Chem. Eur. J.* **2003**, *9*, 435, Typical experimental procedure for the direct catalytic α-oxidation of aldehydes with 'dark' $^1O_2$. To a scintillation vial containing a catalytic amount of **1b** (10 mol %), heptanal **2b** (0.5 mmol), $La(NO_2)_3{\cdot}6H_2O$ (4 mol %), NaOH (5M, 5 mL) in $CHCl_3$ or MeOH (1 mL) was added H_2O_2 (4.8 mmol) at room temperature. After 16 h of vigorous stirring, the reaction was quenched by in situ reduction with $NaBH_4$ at 0 °C to afford the corresponding optically active crude diol **4**. The pure diol **4** was obtained by silica-gel column chromatoghraphy (toluene/EtOAc mixtures). Next, the diol **4** was converted to the corresponding diacetylated product and the enantiomeric excess was determined by chiral-phase GC analyses.
17. Typical experimental procedure for the direct catalytic α-oxidation of aldehydes with molecular oxygen. To a scintillation vial containing tetraphenylporphine (TPP) (1 mol %) and a catalytic amount of **1b** (20 mol %) in $CHCl_3$ (2 mL) was added aldehyde **2** (0.5 mmol). The reaction was initiated and performed by bubbling a continuous flow of molecular oxygen for 6 h in the presence of visible light from two 250-W high-pressure sodium lamps at 0 °C. The reaction was quenched by in situ reduction with $NaBH_4$ at 0 °C to afford the corresponding optically active crude diol **4**. The pure diol **4** was obtained by silica-gel column chromatography (toluene/EtOAc mixtures). Next, the diol **4** was converted to the corresponding diacetylated product and the enantiomeric excess was determined by chiral-phase GC or HPLC analyses. *(2S)-3-Phenyl-propane-1,2-diol* **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.85$ (br s, 2H, O*H*), 2.78 (m, 2H, PhCH_2CH), 3.54 (m, 1H, CH_2OH), 3.70 (m, 1H, CH_2OH), 3.95 (m, 1H, C*H*OH), 7.24 (m, 3H, Ar*H*), 7.33 (m, 2H, Ar*H*); ^{13}C NMR (300 MHz, $CDCl_3$): 40.0, 66.3, 73.3, 126.9, 128.9, 129.6, 137.9; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 98:2, flow rate 0.5 mL/min, $\lambda = 242$ nm): major isomer: $t_R = 53.08$ min; minor isomer: $t_R = 47.61$ min; $[\alpha]_D$ −29.0 (*c* 1.2, EtOH), lit. (−35.4 (*c* 1.00, EtOH)) (Sone, H.; Shibata, T.; Fujita, T.; Ojika, M.; Yamada, K. *J. Am. Chem. Soc.* **1996**, *118*, 1874.).
(2S)-3-Phenyl-propane-1,2-diol diacetate: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.02$ (s, 3H), 2.07 (s, 3H), 2.93 (m, 2H), 4.02 (dd, $J = 6.3$, 12.1 Hz, 1H), 4.23 (dd, $J = 3.5$, 11.8 Hz, 1H), 5.28 (m, 1H), 7.19–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$); $\delta = 21.0$, 21.3, 37.3, 64.5, 72.3, 127.1, 128.8, 129.5, 136.5, 170.6, 171.0; Chiral-phase HPLC (Daicel Chiralpak AS, isohexanes/*i*-PrOH 99.5:0.5, flow rate 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_R = 31.02$ min; minor isomer: $t_R = 35.82$ min.
(2S)-Heptane-1,2-diol diacetate: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.77$ (m, 3H), 1.20 (m, 6H), 1.46 (m, 2H), 1.94 (s, 3H), 1.96 (s, 3H), 4.00 (dd, $J = 6.8$, 11.9 Hz, 1H), 4.11 (dd, $J = 3.3$, 11.9 Hz, 1H), 4.92–4.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 20.6, 21.0, 22.3, 24.7, 30.5, 31.4, 65.0, 71.5, 170.5, 171.0; Chiral-phase GC: (CP-Chirasil-Dex CB); $T_{inj} = 250$ °C, $T_{det} = 275$ °C, flow = 1.8 mL/min, $T_i = 80$ °C (9 min), up to 120 °C (6 min) rate 20 °C/min, $T_f = 200$ °C, rate 80 °C/min (5 min), retention times, $t_{maj} = 17.1$ min, $t_{min} = 16.9$ min.
(2S)-3-(4-Nitrophenyl)-propane-1,2-diol diacetate: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.00$ (s, 3H), 2.07 (s, 3H), 2.88–3.01 (m, 2H), 4.03 (dd, $J = 5.8$, 11.9 Hz, 1H), 4.24 (dd, $J = 3.7$, 11.9 Hz, 1H), 5.25–5.31 (m, 1H), 7.37 (d, $J = 8.7$ Hz, 2H), 8.15 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl3); $\delta = 20.9$, 21.1, 37.1, 64.3, 71.4, 124.0, 130.4, 144.4, 147.3, 170.3, 171.0; Chiral-phase HPLC (Daicel Chiralpak ODH, isohexanes/*i*-PrOH 98.0:2.0, flow rate 0.5 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 39.6$ min; minor isomer: $t_R = 46.1$ min.