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Direct organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes

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Abstract—The organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes with peroxides or sodium percarbonate is presented. Chiral pyrrolidine derivatives, proline and amino acid derived imidazolidinones mediate the asymmetric epoxidation of α,β-unsaturated aldehydes. For example, commercially available protected α,α-diphenyl-2-prolinol catalyzes the asymmetric formation of 2-epoxy-aldehydes in 81–95% conversion with up to 96:4 dr and 98% ee. The use of non-toxic catalysts, aqueous solvents and hydrogen peroxide or sodium percarbonate as the oxygen sources makes the reaction environmentally benign.

Catalytic asymmetric epoxidation is a fundamental reaction in organic synthesis.[1] The pioneering work of Katsuki and Sharpless resulted in the discovery of titanium–tartrate complexes as asymmetric epoxidation catalysts of allylic alcohols.[2] Following this seminal work Jacobsen and Katsuki independently demonstrated that chiral manganese–salen complexes were excellent catalysts for the asymmetric epoxidation of unfunctionalized olefins.[3] Catalytic asymmetric epoxidation reactions are also mediated by organic catalysts.[4] For example, epoxidations of α,β-enones are mediated by polypeptides[5] and cinchona alkaloids.[6] Moreover, Shi and Aggarwal have developed elegant methods for the epoxidations of unfunctionalized olefins catalyzed by chiral ketones[7] and pyrrolidines,[8] respectively. Furthermore, Shibasaki and co-workers have developed several chiral Lewis acid-catalyzed epoxidations of α,β-unsaturated carbonyl compounds.[9]

The direct organocatalytic asymmetric α-oxidation of aldehydes and ketones is performed with electrophilic oxidants such as nitrosobenzene,[10] iodosobenzene,[11] oxaziridines,[11] and singlet molecular oxygen.[12] In stark contrast, *tert*-butyl hydroperoxide, *m*-CPBA and hydrogen peroxide failed as oxidants for this transformation.[11] It is known that chiral amines can activate α,β-unsaturated aldehydes and ketones towards nucleophilic attack by forming iminium ions.[13] However, the direct asymmetric epoxidation of α,β-unsaturated aldehydes is a new frontier in asymmetric catalysis.[14] Based on our research program on the development of environmentally benign enantioselective oxidations,[11,12] we became interested in whether hydrogen peroxide and sodium percarbonate[15] (SPC) could be used as nucleophilic oxidants in organocatalytic asymmetric epoxidations of α,β-unsaturated aldehydes. Herein, we show that proline, several chiral pyrrolidine derivatives and imidazolidinone **11** catalyze the asymmetric epoxidation of α,β-unsaturated aldehydes with hydrogen peroxide or solid SPC as the oxidants.

In an initial catalyst screen, we tested different organocatalysts (10–30 mol %) for their ability to mediate the asymmetric epoxidation of cinnamic aldehyde **1a** (0.25 mmol) with hydrogen peroxide (50 wt %, aqueous solution, 1.2–7 equiv) in $CHCl_3$ (2 mL) (Table 1).

We found that organocatalysts **3**–**6** and **8**–**11** mediated the direct asymmetric epoxidation of **1a**. Notably, addition of 0.8 equiv of TEA enabled the use of proline and tetrazole **4** as catalysts (entries 2 and 3). For example, proline catalyzed the formation of *ent*-**2a** with 79% conversion and 36% ee.[16] Moreover, chiral proline-derived diamines such as **5** and **6** catalyzed the asymmetric epoxidation of **1a** with poor to good enantioselectivity.[17] For instance, catalyst **5** exhibited the highest asymmetric

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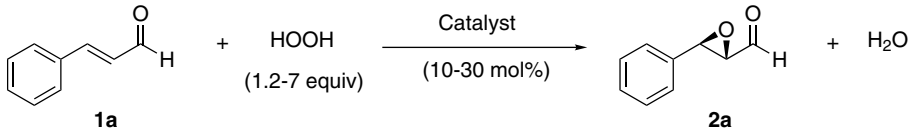
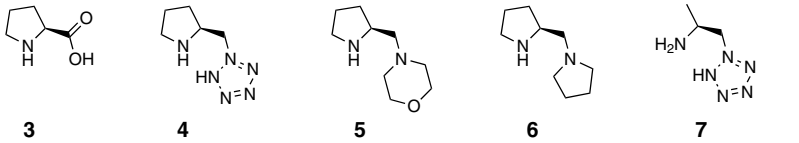
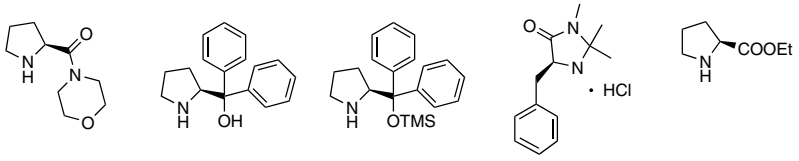
Table 1. Catalyst screen for the direct catalytic asymmetric epoxidation of **1a** with hydrogen peroxide[a]



1a **2a**



3 **4** **5** **6** **7**



8 **9** **10** **11** **12**

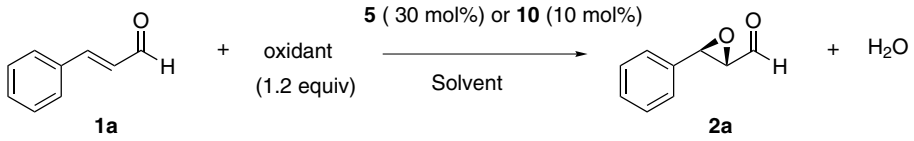
Entry	Catalyst	Time (h)	Conversion (%)[b]	dr[c]	ee (%)[c]
1	**3**[d]	24	<1	n.d.	n.d.
2	**3**[d,e]	16	79	60:40	−36
3	**4**[d,e]	16	82	74:26	−15
4	**5**[d]	22	60	53:47	66
5	**6**[d]	19	41	45:54	7
6	**7**[d]	24	<1	n.d.	n.d.
7	**8**[d]	14	85	79:21	24
8	**9**[d]	16	43	5:95	22
9	**10**[f]	2	91 (81)[g]	93:7	97
10	**11**[f,h]	3	28	48:52	12
11	**11**[f,i]	18	55	96:4	12
12	**12**[d]	16	<1	n.d.	n.d.

[a] To a stirred solution of catalyst (10-30 mol %) in $CHCl_3$ (1 mL) was added aldehyde **1a** (0.25 mmol) and H_2O_2 (0.3–1.75 mmol, 50% aqueous solution). The reaction was vigorously stirred at room temperature and monitored by chiral-phase GC analyses.
[b] Amount of formed product as determined by chiral-phase GC analyses.
[c] The dr (*trans*/*cis*) and ee were determined by chiral-phase GC analyses.
[d] 30 mol % catalyst.
[e] 0.8 equiv TEA added.
[f] 10 mol % catalyst and 1.2 equiv H_2O_2.
[g] Isolated yield of pure **2a** after silica gel column chromatography.
[h] Reaction run in H_2O/EtOH 1:1.
[i] Reaction run in dioxane.

induction and catalyzed the enantioselective epoxidation of **1a** with good conversion (60%) to furnish **2a** in a 53:47 dr (*trans*/*cis*) and with 66% ee. Moreover, we investigated diphenyl-2-pyrrolidinemethanol (**9**, diphenylprolinol), which has been developed by Corey and coworkers,[18] as a catalyst. Diphenylprolinol **9** (20 mol %) catalyzed the stereoselective epoxidation of **1a** with excellent diastereoselectivity (5:95) and low enantioselectivity (22%). The exchange of the hydroxy group in **9** to a siloxy group had a remarkable effect on the reactivity and enantioselectivity of the asymmetric epoxidation.[19] That is, the chiral pyrrolidine **10** (10 mol %) catalyzed the asymmetric epoxidation of **1a** within 2 h (91% conv.) and furnished epoxide **2a** in 81% yield in a 93:7 dr and 97% ee. Moreover, TMS protection of diphenylprolinol **9** switched the diastereoselectivity of the reaction. MacMillan's imidazolidinones such as **11** also catalyzed the direct asymmetric epoxidation of α,β-unsaturated aldehydes with high diastereoselectivity and modest enantioselectivity under our reaction conditions.[20] Encouraged by our initial results, we decided to investigate the utilization of different oxidants and reaction conditions for the direct asymmetric epoxidation of **1a** mediated by catalysts **5** and **10** (Table 2).

The proline-derived diamine **5** catalyzed the enantioselective epoxidation of **1a** with the highest asymmetric induction in $CHCl_3$. Unfortunately, decreasing the reaction temperature to −20 °C and increasing the catalyst loading did not improve the enantioselectivity (entries 2 and 3). Moreover, chiral amine **10** catalyzed the asymmetric epoxidation of α,β-unsaturated aldehyde **1a** with hydrogen peroxide, solid SPC and *tert*-butyl hydrogen peroxide as the oxidants to form **2a** with high diastereoselectivities (82:18–95:5) and excellent enantioselectivities (>95% ee). The highest diastereo and enantioselectivity for the catalyst **10**-mediated asymmetric epoxidation of **1a** was achieved at 4 °C and room temperature in $CHCl_3$ using H_2O_2 and SPC, respectively, as the oxidants. In addition, chiral

Table 2. The catalyst **5**- and **10**-mediated direct asymmetric epoxidation of **1a** mediated by catalysts **5** and **10** under different reaction conditions[a]



1a **2a**

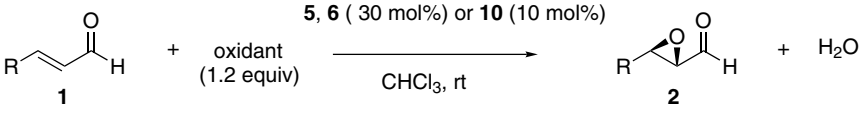
Entry	Cat.	Oxidant	Solvent	Temp (°C)	Time (h)	Conv. (%)[b]	dr[b]	ee (%)[b]
1	**5**	H_2O_2	$CHCl_3$	4	22	60	53:47	66
2	**5**[c]	H_2O_2	$CHCl_3$	−20	19	94	81:19	60
3	**5**[c]	H_2O_2	CH_2Cl_2	−20	19	97	82:18	50
4	**5**	H_2O_2	TBME	4	48	53	58:42	31
5	**5**	H_2O_2	THF	4	48	7	56:44	52
6	**10**	H_2O_2	$CHCl_3$	rt	2	91 (81)[d]	93:7	97
7	**10**	H_2O_2	$CHCl_3$	4	7	88	95:5	98
8	**10**	SPC	$CHCl_3$	rt	6	75	84:16	>95
9	**10**	*t*-BuOOH	$CHCl_3$	rt	3	84	82:18	>95
10	**10**	*m*-CPBA	$CHCl_3$	rt	16	<10	96:4	51
11	**10**	H_2O_2	CH_2Cl_2	rt	2	88	90:10	96
12	**10**	H_2O_2	Toluene	rt	2	94	91:9	97
13	**10**	H_2O_2	THF	rt	2	17	95:5	90
14	**10**	H_2O_2	EtOH	rt	2	94	87:13	92
15	**10**	H_2O_2	H_2O/*tert*-BuOH (1:1)	rt	2	84	87:13	94
16	**10**	H_2O_2	H_2O/EtOH (1:1)	rt	2	67	87:13	90

[a] To a stirred solution of catalyst **5** (30 mol %) or **10** (10 mol %) in organic solvent (2 mL) was added aldehyde **1a** (0.25 mmol) and oxidant (0.3 mmol, 1.2 equiv). The reaction was vigorously stirred at the temperature shown in the table and monitored by chiral-phase GC analyses.
[b] Determined by chiral-phase GC analyses.
[c] 60 mol % catalyst. and 7 equiv H_2O_2.
[d] Isolated yield of pure **2a** after silica gel column chromatography.

amine **10** catalyzed the direct asymmetric epoxidation of **1a** in CH_2Cl_2, toluene, THF and ethanol with excellent stereoselectivities. Notably, high enantioselectivity was obtained in aqueous media (H_2O/*tert*-BuOH 1:1 or H_2O/EtOH 1:1) where epoxide **2a** was formed with 90–94% ee. Thus, the chiral amine-catalyzed asymmetric epoxidation reaction is environmentally benign.

Next, we reacted a series of different substituted α,β-unsaturated aldehydes **1** with H_2O_2 and SPC as the oxidants in the presence of catalysts **5**, **6** and **10** (Table 3).[21] Diamines **5** and **6** catalyzed the asymmetric epoxidations of α,β-unsaturated aliphatic aldehydes **1** using hydrogen peroxide as the oxidant with high diastereoselectivity and modest enantioselectivity. To our satisfaction, TMS prolinol **10** was an excellent catalyst for the asymmetric synthesis of aliphatic and ester functionalized epoxides such as **2b–d** (91:9–96:4 dr and 91–98% ee). Moreover, TMS-prolinol **10** mediated the direct asymmetric epoxidations with excellent stereoselectivity in aqueous solvent utilizing H_2O_2 as the oxidant.

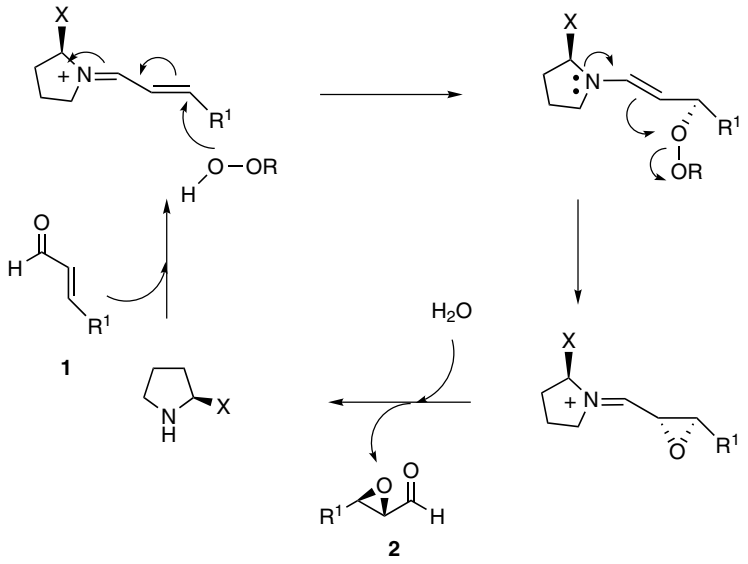
Table 3. The direct asymmetric epoxidation of α,β-unsaturated aldehydes **1** with hydrogen peroxide or SPC mediated by catalysts **5**, **6** and **10**[a]



1 **2**

Entry	Cat.	Oxidant	R	Prod.	Temp (°C)	Time (h)	Conv. (%)[b]	dr[c]	ee (%)[c]
1	**5**	H_2O_2	Ph	**2a**	4	22	60	53:47	66
2	**10**	H_2O_2	Ph	**2a**	rt	2	91 (81)[d]	93:7	97
3	**6**	H_2O_2	*n*-Propyl	**2b**	rt	20	81	84:16	6
4	**5**	H_2O_2	*n*-Propyl	**2b**	rt	20	70	81:19	14
5	**10**	H_2O_2	*n*-Propyl	**2b**	rt	2	>90	95:5	93
6	**10**	H_2O_2	*n*-Propyl	**2b**	rt	2[e]	99[e]	96:4[e]	>95[e]
7	**10**	H_2O_2	*n*-butyl	**2c**	rt	1.5	94	95:5	91
8	**10**	H_2O_2	CO_2Et	**2d**	rt	2	>90	91:9	98
9	**10**	SPC	CO_2Et	**2d**	rt	2	>90	90:10	98

[a] To a stirred solution of catalyst **5**, **6** (30 mol %) or **10** (10 mol %) in $CHCl_3$ (2 mL) was added aldehyde **1** (0.25 mmol) and oxidant (0.3 mmol, 1.2 equiv). The reaction was vigorously stirred at the temperature shown in the table and monitored by chiral-phase GC analyses.
[b] Amount of formed product as determined by chiral-phase GC analyses.
[c] Determined by chiral-phase GC analyses.
[d] Isolated yield of pure **2** after silica gel column chromatography.
[e] Reaction run in H_2O/*tert*-BuOH 1:1.



Scheme 1. The probable catalytic mechanism of the chiral pyrrolidine-catalyzed asymmetric epoxidation of α,β-unsaturated aldehydes.

We also attempted the catalytic asymmetric epoxidation of α,β-unsaturated ketones with different oxidants and **10** as the organocatalyst under our reaction conditions. However, catalyst **10** failed to furnish the desired epoxide. Instead, diphenylprolinol **9** mediated the asymmetric epoxidation of α,β-unsaturated ketones.[8c]

The mechanism of the direct organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes starts with iminium activation of the α,β-unsaturated aldehyde by the chiral pyrrolidine derivative followed by stereoselective nucleophilic conjugate attack on the β-carbon resulting in a chiral enamine derivative (Scheme 1). Next, the chiral enamine performs a nucleophilic attack on the electrophilic peroxygen, followed by hydrolysis of the resulting iminium intermediate. The reverse catalytic cycle has been observed in direct organocatalytic enantioselective tandem α-aminoxylation/Michael reactions[10i,k,l] and aza-Diels–Alder reactions[22] with α, β-unsaturated ketones, which further supports the proposed mechanism. The remarkable change of the reactivity by TMS protection of the diphenylprolinol **9** was explained by prevention of plausible aminal formation and increased hydrophobicity of the catalyst, which improves the rate of iminium formation with aldehydes **1**. In addition, the high enantioselectivity observed for the asymmetric epoxidations with catalyst **10** is plausibly due to stabilization of the configuration of the iminium ion intermediate as well as efficient shielding of the *Si*-face of the chiral iminium and enamine intermediates by the bulky aryl groups.

In summary, we have shown that proline, proline-derived chiral amines and imidazolidinone **11** catalyze the asymmetric epoxidation of α,β-unsaturated aldehydes with hydrogen peroxide or SPC. In particular, organocatalyst **10**, derived in one-step from the commercially available diphenylprolinol **9**, catalyzed the asymmetric epoxidation with excellent stereoselectivity and furnished the desired products in high efficiency with up to 96:4 dr and 98% ee. Moreover, the use of aqueous media, hydrogen peroxide and non-toxic metal-free catalysts makes this process environmentally benign.

Acknowledgement

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15. Sodium percarbonate (SPC) represents one of the most powerful oxidants available. It is particularly advantageous owing to its ease of handling and storage. See: (a) McKillop, A.; Sanderson, W. R. *Tetrahedron* **1995**, *51*, 6145; (b) Muzart, J. *Synthesis* **1995**, 1325.
16. Typical proline and tetrazole **4** catalyzed asymmetric epoxidation: To a stirred solution of proline or **4** (30 mol %) in $CHCl_3$ (2 mL) was added aldehyde **1a** (0.25 mmol), H_2O_2 (1.75 mmol, 50% aqueous solution) and TEA (0.2 mmol). The reaction was vigorously stirred at room temperature and monitored by chiral-phase GC analyses. The formation and enantiomeric excess of **2a** was determined on a Chromasil CP-Chirasil-Dex CB-column. Temperature program: 70–160 °C, rate; 10 °C/min, hold 1 min, 160–200 °C, rate; 80 °C/min, hold 5 min. t_R (min) = major enantiomer 8.04 min, minor enantiomer 8.12 min.
17. Typical catalyst **5**, **6**, **9** and **10** catalyzed asymmetric epoxidation: To a stirred solution of **4**, **5** (30 mol %), **9** (20 mol %) or **10** (10 mol %) in $CHCl_3$ (2 mL) was added aldehyde **1a** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). The reaction was vigorously stirred at room temperature and monitored by chiral-phase GC analyses. The formation and enantiomeric excess of **2a** was determined on a Chromasil CP-Chirasil-Dex CB-column. Temperature program: 70–160 °C, rate; 10 °C/min, hold 1 min, 160–200 °C, rate; 80 °C/min, hold 5 min. t_R (min) = major enantiomer 8.04 min, minor enantiomer 8.12 min. Isolation of **2a** derived by diphenylprolinol **10** catalysis by silica gel column chromatography (pentane/EtOAc 3:1) furnished (2*S*,3*R*)-3-phenyloxirane-2-carbaldehyde **2a** (81%, 30 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.20 (d, $J = 6.1$ Hz, 1H), 7.39–7.29 (m 5H), 4.17 (d, $J = 1.8$ Hz, 1H), 3.46 (dd, $J = 1.8$, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm): 196.7, 134.2, 129.2, 128.8 (2C), 125.7 (2C), 62.9, 56.6; $[\alpha]_D^{25}$ −30.1 ($c = 1.6$, $CHCl_3$) (Lit. *ent*-**2a**, $[\alpha]_D^{23}$ +14.3 ($c = 0.48$, $CHCl_3$, 94% ee)[9]).
18. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; For an excellent review see: Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.
19. The commercially available catalyst **9** (1 g, 3.95 mmol) was readily protected with TMSOTf (1.1 g, 5.1 mmol) in the presence of TEA (0.51 g, 5.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was stirred at room temperature for 17 h and quenched with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x15 mL). The combined organic extracts were stirred with $NaHCO_3$ for 15 min, dried over anhydrous Na_2SO_4 and concentrated in vacuo after filtration. Purification with silica gel column chromatography (EtOAc/pentane 1.7 → 1.3) furnished 10 as a thick oil (99%, 1.3 g). Jørgensen and co-workers have shown that TMS protection of diarylprolinols is an excellent strategy to achieve high stereoselectivity in organocatalytic α-fluorinations and α-sulfenylation of aldehydes see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794; (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703; (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.
20. Typical **11**-catalyzed asymmetric epoxidation: To a stirred solution of **11** (10 mol %) in solvent (2 mL) was added aldehyde **1a** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution). The reaction was vigorously stirred at room temperature and monitored by chiral-phase GC analyses. The formation and enantiomeric excess of **2a** was determined on a Chromasil CP-Chirasil-Dex CB-column.
21. Typical **10**-catalyzed asymmetric epoxidation of aldehydes **1**: To a stirred solution of **10** (10 mol %) in solvent (2 mL) was added aldehyde **1a** (0.25 mmol) and H_2O_2 (0.3 mmol, 50% aqueous solution) or SPC (0.38 mmol + 50 μL H_2O). The reaction was vigorously stirred at room temperature and monitored by chiral-phase GC analyses. The formation and enantiomeric excess of the desired epoxides **2** were determined on a Chromasil CP-Chirasil-Dex CB-column.
22. Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed* **2005**, *44*, 4877.