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Asymmetric Three-Component Strecker Reactions Catalyzed by *trans*-4-Hydroxy-L-proline-Derived *N,N′*-Dioxides

Yuehong Wen,[a] Bo Gao,[a] Yingzi Fu,[a] Shunxi Dong,[a] Xiaohua Liu,[a] and Xiaoming Feng*[a, b]

Abstract: Novel *trans*-4-hydroxy-L-proline-derived *N,N′*-dioxides have been developed and used as efficient organocatalysts for the one-pot three-component Strecker reaction with an aldehyde, (1,1-diphenyl)methylamine, and TMSCN. Both aromatic and aliphatic aldehydes were found to be suitable substrates. The corresponding α-amino nitriles were obtained in high yields with up to 95% *ee* (*ee* = enantiomeric excess) under mild conditions. Optically pure products could be obtained after a single recrystallization. The catalyst can be easily prepared from *trans*-4-hydroxy-L-proline and a diamine in three steps. Based on the experimental results and the observed absolute configurations of the products, a possible transition state has been proposed to explain the origin of the asymmetric induction.

Keywords: amino acids · asymmetric catalysis · dioxides · multicomponent reactions · Strecker reactions

Introduction

As a result of the significance and the ever-increasing demand for the α-amino acids in chemistry and biology, the development of efficient methods for their preparation has attracted considerable attention.[1] The Strecker reaction, which was first reported in 1850, represents one of the simplest and most economical methods.[2] In particular, the asymmetric catalytic Strecker reaction is a highly useful and desirable strategy. In recent years, considerable effort has been devoted towards the development of catalytic asymmetric Strecker reactions.[3] Efficient catalysts are chiral metal complexes,[4] such as Al, Ti, Zr, and lanthanide compounds, and chiral metal-free compounds[5] that contain guanidines, ureas and thioureas, bis(*N*-oxides), ammonium salts, Brønsted acids, bisformamides, and *N*-galactosyl aldimines. Among those reports, Kobayashi described the first asymmetric three-component Strecker reaction catalyzed by a chiral zirconium catalyst.[4k,l] Until recently, only two examples of organocatalytic protocols had been reported by List[5f] and Feng[5s]. Since multicomponent reactions have many advantages, such as simplified procedures, mild reaction conditions, high atom economy, and environmental friendliness, the development of new catalysts for a direct access to the Strecker products by starting from an aldehyde, amine, and a cyanide donor is still the research focus and target in this field.[3a]

Chiral *N*-oxide, as a ligand or an organocatalyst, has been shown to be highly efficient in many asymmetric procedures.[6] Two main types of *N*-oxide have been developed, which are tertiary amine-derived *N*-oxides and pyridine *N*-oxides. The pyridine (or quinoline-type) *N*-oxides are very popular and successful catalysts of this class; however, the tertiary amine-derived *N*-oxides are being increasingly concentrated on. Recently, Hoveyda and Snapper reported the L-proline based mono-*N*-oxides[7] and Feng developed the amino acid derived *N,N′*-dioxides.[8] Herein, we wish to report a novel *trans*-4-hydroxy-L-proline-based *N,N′*-dioxide and its application in the catalytic asymmetric one-pot three-component Strecker reaction.

Our strategy is to design a framework of amino acid derived *N,N′*-dioxides (Scheme 1) that combine both the Lewis base (*N*-oxide) and amide moieties, which can act as a bifunctional organocatalyst in the Strecker reaction. The two molecular amino acids are connected together by a carbon

[a] Y. Wen, B. Gao, Dr. Y. Fu, S. Dong, Dr. X. Liu, Prof. Dr. X. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education, College of Chemistry
Sichuan University, Chengdu 610064 (China)
Fax: (+86) 28-8541-8249
E-mail: xmfeng@scu.edu.cn

[b] Prof. Dr. X. Feng
State Key Laboratory of Oral Diseases
Sichuan University, Chengdu 610041 (China)

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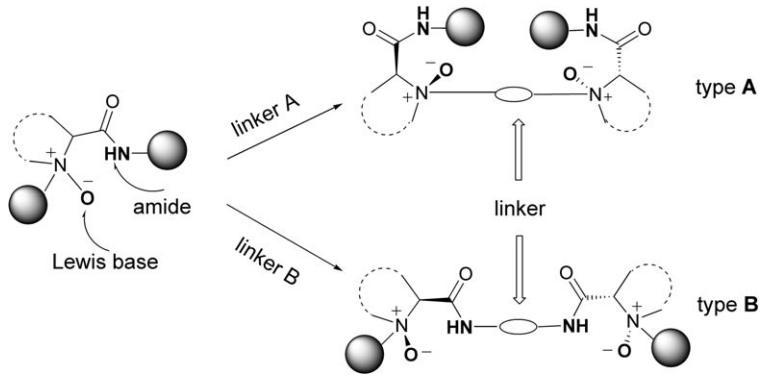
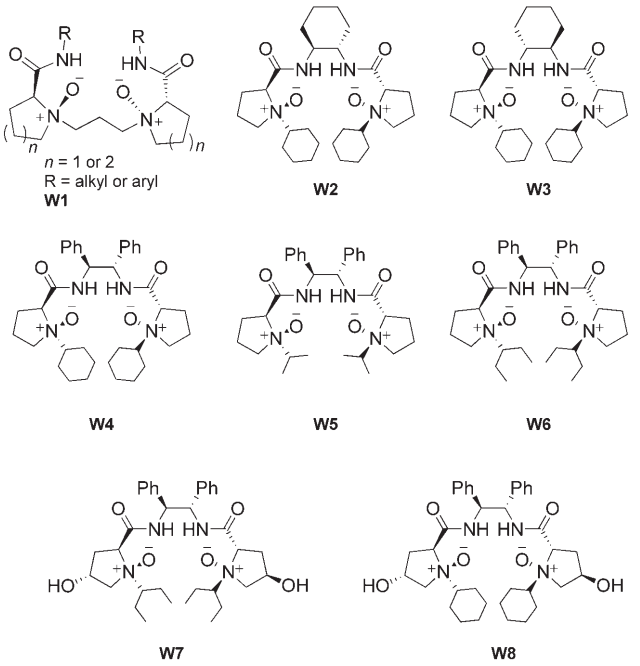


Scheme 1. The design of *N,N′*-dioxides.

chain at the N termini (type **A**) or by a diamine at the acid section (type **B**). Type **A** *N,N′*-dioxides have exhibited their function in many reactions in our previous studies,[5l,m,8] whereas type **B** *N,N′*-dioxides coordinated with indium(III) have been used primarily for the asymmetric ring opening of *meso*-epoxides with aromatic amines.[9]

Results and Discussion

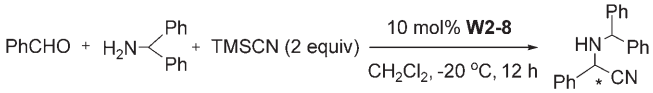
The N-substituted α-amino nitriles, in particular, those with an *N*-benzhydryl substituent, can be converted into the corresponding α-amino acids in one step without loss of enantiomeric excess.[4f,10] In our previous study, a stoichiometric amount of the chiral quinoline *N*-oxide was applied to promote the Strecker reaction between *N*-benzhydrylimines and trimethylsilyl cyanide (TMSCN).[5k] Inspired by this research, we presumed that the amino acid based *N,N′*-dioxides, which contained both the *N*-oxide and amide moieties, might be more efficient in the Strecker reaction. So the **W1** *N,N′*-dioxides were chosen as the organocatalysts for the initial tests of the one-pot three-component Strecker reaction with benzaldehyde, (1,1-diphenyl)methylamine, and TMSCN. Indeed, high reactivity was observed although the enantioselectivity was not satisfactory.[11]



The **W1** *N,N′*-dioxides used were prepared by the coupling of two amino acid units at the N termini, the backbone of which may not be beneficial for good enantioselectivity in this system. Because an amino acid has two reactive functional groups, it is logical to devise a new class of catalyst in which two prolines are connected at the C termini by a diamine. Synthesis of the new backbone of the *N,N′*-dioxides is much easier requiring only three steps: 1) reductive amination, 2) isobutyl chlorocarbonate assisted coupling, and 3) directed amine oxidation.

A series of novel *N,N′*-dioxides was prepared and examined (Table 1). Catalyst **W2** provided the product with

Table 1. Survey of *N,N′*-dioxides **W2–8** in the asymmetric one-pot, three-component Strecker reaction.[a]



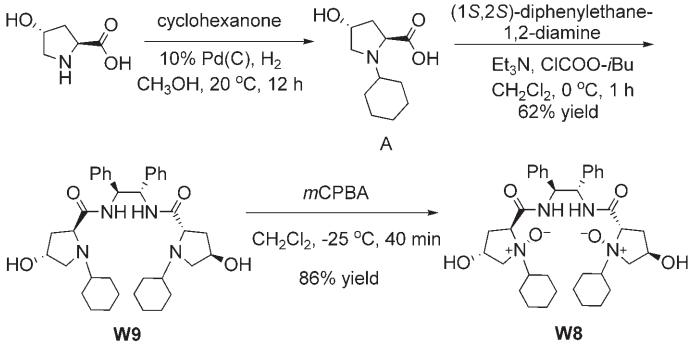
Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**W2**	94	14
2	**W3**	88	0
3	**W4**	98	60
4	**W5**	97	59
5	**W6**	98	60
6	**W7**	98	80
7	**W8**	98	82
8[d]	**W8**	87	72

[a] Reagents and conditions: After stirring the mixture of benzaldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) in CH_2Cl_2 (1.0 mL) for 2 h at 25 °C, the catalyst was added. Then TMSCN (0.4 mmol) was added at −20 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak AD-H), and the absolute configuration was established as *S* by comparison with the literature.[4f,5s] [d] The preformed imine was used as the substrate.

14% *ee* (*ee* = enantiomeric excess); however, **W3** gave only racemic product (Table 1, entries 1 and 2). It might be that the (*S,S*)-diamine possessed a better conformation to match L-proline than the (*R,R*)-diamine. When replacing the (1*S*,2*S*)-cyclohexane-1,2-diamine with (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine, much better enantioselectivity was obtained (entry 3). By changing the substituents at the N termini of the pyrrole ring, similar results were obtained with the isopropyl and 3-pentyl groups (entries 4 and 5). However, further enlargement or reduction of the ring size of the cyclohexyl substituent led to worse enantioselectivity, with

40% *ee* provided by a cycloheptyl or cyclopentyl group.[12] Encouragingly, 98% yield and 82% *ee* were gained by replacing the L-proline with *trans*-4-hydroxy-L-proline (entry 7); the reason for this might be that the hydroxy group adjusted the steric environment slightly, which was more favorable for high enantioselectivity. *N,N′*-Dioxides **W7** and **W8** were the optimal catalysts (entries 6 and 7). The synthesis of **W8** was easier than that of **W7** in the reductive amination step, so **W8** was chosen as the final catalyst. The preformed imine was also used as the substrate with catalyst **W8** (entry 8); however, the results were not as good as those of the in-situ-generated imine. This showed that the water released during the condensation of benzaldehyde and (1,1-diphenyl)methylamine was important for the reaction.

As mentioned above, one of the advantages of this protocol was that the catalyst **W8** can be prepared in three steps in good yield from commercially available optically pure *trans*-4-hydroxy-L-proline and (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (Scheme 2).[7,9] In the first step, compound **A**

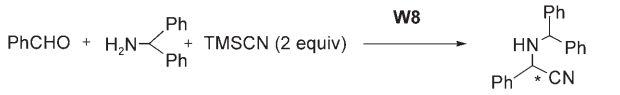


Scheme 2. Synthesis of the chiral catalyst **W8** from *trans*-4-hydroxy-L-proline.

was obtained in nearly quantitative yield by reductive amination in the presence of cyclohexanone; followed by formation of amide **W9**, the reaction of which was completed in 1 h (62% yield); **W8** was generated as a single diastereomer in 86% isolated yield.

With the optimized catalyst **W8** in hand, the reaction conditions were explored. The solvent showed an important impact on reactivity and selectivity. The ethereal solvents such as Et_2O gave low yield and moderate enantioselectivity (Table 2, entry 1). Toluene, CH_2ClCH_2Cl, and $CHCl_3$ provided good yields, but the enantioselectivities were notably diminished (entries 2, 3, and 4). When protic solvents like CH_3OH were used, high yields but racemic products were afforded (entry 6). CH_2Cl_2 was the best solvent for the three-component Strecker reaction (entry 5). The catalyst loading and substrate concentration effects were investigated next (entries 7–10). On decreasing the catalyst loading from 10 to 5 mol%, the *ee* value was maintained (entry 7). The enantioselectivity was reduced when the catalyst loading was increased to 20 mol% (entry 8).[13] The substrate concentration has little effect on reactivity and enantioselectivity in the range from 0.4 to 0.13 M (entries 9 and 10). The temperature effects were also examined (entries 11–13). On decreasing the temperature from −20 to −45 °C, the *ee* value increased to 90% *ee* (entry 12); however, a further decrease led to very low yield and enantioselectivity (entry 13). Other parameters were also checked, such as the effect of additives and the ratio of the three components, but the results were not further improved. Therefore, the optimal reaction conditions were selected as: 0.2 mmol of benzaldehyde, 0.2 mmol of (1,1-diphenyl)-methylamine, 10 mol% of **W8**, and 0.4 mmol of TMSCN in 0.5 mL of CH_2Cl_2 at −45 °C.

Table 2. Optimization of reaction conditions for the asymmetric one-pot, three-component Strecker reaction.[a]

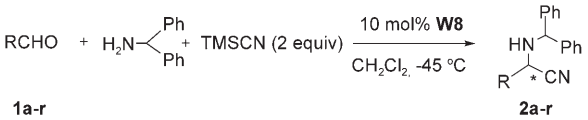


Entry	Solvent	Cat. [mol%]	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Et_2O	10	−20	20	25	60
2	$PhCH_3$	10	−20	22	90	45
3	$CHCl_3$	10	−20	10	98	42
4	$(CH_2Cl)_2$	10	−20	14	98	28
5	CH_2Cl_2	10	−20	12	98	82
6	CH_3OH	10	−20	10	99	0
7	CH_2Cl_2	5	−20	10	90	81
8	CH_2Cl_2	20	−20	7	98	60
9[d]	CH_2Cl_2	10	−20	8	98	81
10[e]	CH_2Cl_2	10	−20	12	93	82
11[d]	CH_2Cl_2	10	0	5	99	75
12[d]	CH_2Cl_2	10	−45	36	93	90
13[d]	CH_2Cl_2	10	−78	80	53	34

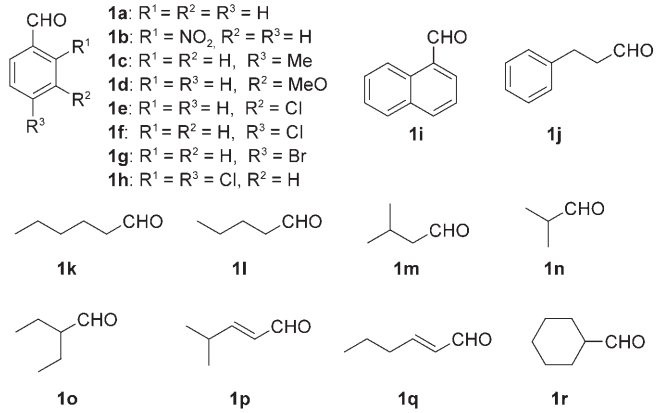
[a] Reagents and conditions: After stirring the mixture of benzaldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) in solvent (1.0 mL) for 2 h at 25 °C, the catalyst **W8** was added. Then TMSCN (0.4 mmol) was added at reaction temperature. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak AD-H). [d] 0.5 mL CH_2Cl_2 was used. [e] 1.5 mL CH_2Cl_2 was used.

Under the optimal conditions, the substrate generality was examined, and the results are listed in Table 3. Both the aromatic and aliphatic aldehydes were found to be suitable substrates for the asymmetric three-component Strecker reaction. For the aromatic aldehydes, high yields (up to 98%) and good enantioselectivities (up to 91% *ee*, up to 99% *ee* after a single recrystallization) were achieved (Table 3, entries 1–9). In general, the aromatic ring with electron-donating substituents exhibited higher reactivity (entries 3 and 4), whereas the electron-withdrawing substituents showed better enantioselectivities (entries 5–8). A low yield of 68% was obtained for 2-nitrobenzaldehyde (entry 2), which was presumably caused by the steric effect of the *ortho*-nitro substituent. 2,4-Dichlorobenzaldehyde provided the product with 89% *ee* (entry 8), whereas 96% yield and 91% *ee* were obtained with 1-naphthaldehyde (entry 9). A poor *ee* value was obtained for the heterocyclic aldehyde of furfural.[15] For the aliphatic and α,β-unsaturated aldehydes, the catalytic system was also very efficient (up to 99% yield and 95% *ee*; entries 10–18). Branched aldehydes represented very good substrates (entries 13–15), for example, the best

Table 3. Scope of the asymmetric one-pot, three-component Strecker reaction.[a]



1a-r 2a-r



Entry	1a–r	2a–r	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	**2a**	36	93	90 (99)[d] (*S*)[e]
2[f]	**1b**	**2b**	80	68	81
3	**1c**	**2c**	36	98	80 (99) (*S*)
4	**1d**	**2d**	40	95	80 (*S*)
5	**1e**	**2e**	72	90	84 (*S*)
6	**1f**	**2f**	72	95	87 (99) (*S*)
7	**1g**	**2g**	60	94	87 (99)
8[f]	**1h**	**2h**	60	82	89
9	**1i**	**2i**	36	96	91 (99) (*S*)
10	**1j**	**2j**	36	98	83
11	**1k**	**2k**	30	96	81
12	**1l**	**2l**	36	60	80
13[g]	**1m**	**2m**	36	95	90
14	**1n**	**2n**	30	98	87
15	**1o**	**2o**	36	86	95
16	**1p**	**2p**	36	93	80
17	**1q**	**2q**	40	87	72
18	**1r**	**2r**	32	99	84

[a] Reagents and conditions: After stirring the mixture of aldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) in CH_2Cl_2 (0.5 mL) for 2 h at 25 °C, the catalyst **W8** was added. Then TMSCN (0.4 mmol) was added at −45 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak AD-H or AS-H). [d] After a single recrystallization. [e] The absolute configuration was established as *S* by comparison with the literature.[4e,f,5k,s,14] [f] The reaction was carried out at −20 °C. [g] 15 mol% **W8** was used.

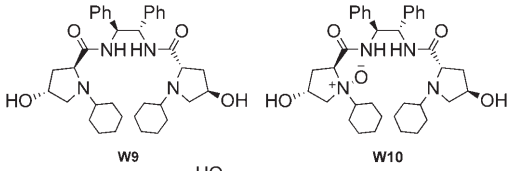
enantioselectivity was obtained with 2-ethylbutanal (entry 15). In the case of the most challenging α-unbranched aldehydes, slightly lower enantioselectivities were observed (entries 11 and 12). A high yield and good *ee* value were also given by a cyclic aldehyde (entry 18). Accordingly, a larger substrate scope, better enantioselectivities, and the opposite *S* isomers were achieved with these *N,N′*-dioxides compared with our previously reported bisformamide catalysts.[5s]

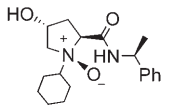
To elucidate the mechanism of the *trans*-4-hydroxy-L-proline-based *N,N′*-dioxide-catalyzed one-pot three-component Strecker reaction, a series of control experiments were designed and performed (Table 4). To determine if the TMSCN and *N*-oxide took part in the enantioselectivity-determining step, other cyanide sources and the precursor **W9**

Table 4. Control experiment for the mechanistic study.[a]

Entry	Cyanide source	Cat. [10 mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	AcCN	**W8**	40	78	0
2	TMSCN	**W9**	15	86	0
3	TMSCN	**W10**	15	96	4
4	TMSCN	**W11**	15	93	0
5	TMSCN	**W8**	8	98	81

[a] Reagents and conditions: After stirring the mixture of benzaldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) in CH_2Cl_2 (0.5 mL) for 2 h at 25 °C, the catalyst was added. Then TMSCN (0.4 mmol) was added at −20 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak AD-H). [d] The reaction was carried out at −45 °C.

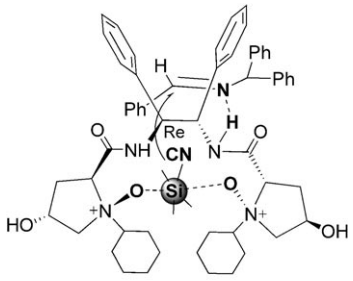




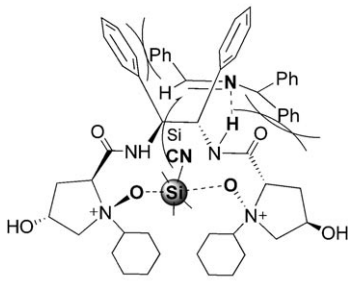
of the *N,N′*-dioxides were examined (Table 4, entries 1 and 2). The results indicated that the cooperation of the silicon-containing cyanide source and the *N*-oxide was essential for catalytic efficiency. Both the diamine-derived and the (*S*)-phenylethylamine-derived mono-*N*-oxides, **W10** and **W11,** respectively, provided racemic products (entries 3 and 4), which showed that the presence of two *N*-oxides together in one molecule was also a requirement for asymmetric induction. According to the above phenomena and the previous studies on *N,N′*-dioxides[7,8,9,16] and cyanosilylation,[5k–m,s] a possible transition state was proposed as illustrated in Figure 1. The two *N*-oxides coordinated to silicon at the same time to form a hypervalent silicate species whereby a fixed chiral pocket was created; meanwhile, the in-situ-generated imine was activated by a hydrogen bond between the nitrogen of the imine and the hydrogen of the amide. The *Re* face is much more accessible than the *Si* face, as increased repulsion between the phenyl groups of the imine and diamine occurs in **TS2**. Hence, the *S* product was smoothly produced according to favorable **TS1**. However, the real mechanism and the function of the hydroxy groups are unclear and are being studied.

Conclusion

trans-4-Hydroxy-L-proline-based *N,N′*-dioxides have been developed to catalyze the one-pot, three-component Streck-



TS1 favorable



TS2 disfavorable

Figure 1. Proposed transition states **TS1** and **TS2**.

er reaction with an aldehyde, (1,1-diphenyl)methylamine, and TMSCN. The novel organocatalyst is efficient for a broad variety of aromatic and aliphatic aldehyde substrates, leading to the corresponding products in excellent enantioselectivities (up to 95% *ee*). The catalyst is easily prepared from *trans*-4-hydroxy-L-proline. A possible transition state (**TS1**) has been proposed to explain the origin of asymmetric induction. Further investigations are focused on the exploration of related catalyst libraries, the detailed mechanism, and extension of the reaction scope.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO on commercial apparatus. TMS served as internal standard ($\delta = 0$ ppm) for ^{1}H NMR and $CDCl_3$ was used as internal standard ($\delta =$ 77.0 ppm) for ^{13}C NMR; the coupling constants *J* are given in Hz. Chemical shifts are reported in ppm with the solvent reference as the internal standard ($CHCl_3$: $\delta = 7.26$ ppm). HPLC analysis was performed on a chiral column (Daicel Chiralpak AD-H or AS-H column). Optical rotations were reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, in solvent). HRMS were recorded on a commercial apparatus (ESI or ES Source). Melting points were measured on an electrothermal digital melting point apparatus. Unless otherwise indicated, all materials were obtained from commercial sources, and used as purchased without dehydration, except for aldehydes, which were distilled before use. Solvents for reactions were dried and distilled prior to use according to the standard methods.

Typical procedure for the preparation of catalyst W8: Palladium on carbon (10% by wt, dry, 0.12 g) was suspended in methanol (10 mL) in a dry 50 mL flask, which was flushed with N_2. *trans*-4-Hydroxy-L-proline (1.31 g, 10 mmol) and cyclohexanone (1.2 mL, 11 mmol) were added to this suspension. The flask was charged with H_2 and was kept under a balloon of H_2 for 12 h. At this time, the reaction was purged with N_2 and filtered through Celite. Removal of the methanol under reduced pressure led to the unpurified acid (2.09 g, 98% unpurified yield).

Isobutyl chlorocarbonate (0.27 mL, 2.05 mmol) and Et_3N (0.3 mL, 2.2 mmol) were added to a solution of the unpurified acid (437 mg, 2.05 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 20 min, (1*S*,2*S*)-diphenylethane-1,2-diamine (212 mg, 1 mmol) was added and the mixture was allowed to stir at room temperature for 1 h. The solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated to give a crude product. The crude product was purified by silica gel chromatography (CH_3OH/ethyl acetate 1:20) to give the pure amide **W9** (374 mg, 62% yield). M.p. 114–116 °C; $[\alpha]_D^{10} = -55.9$ (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.29$ (d, *J* = 7.6 Hz, 2H), 7.28–7.19 (m, 6H), 7.08–7.06 (m, 4H), 5.33 (d, *J* = 6.8 Hz, 2H), 4.11 (dd, *J* = 9.6, 5.2 Hz, 2H), 3.54 (dd, *J* = 9.2, 5.2 Hz, 2H), 3.17 (dd, *J* = 9.6, 5.2 Hz, 2H), 2.62 (dd, *J* = 9.6, 6.0 Hz, 2H), 2.32 (s, 2H), 2.12–1.65 (m, 16H), 1.28–1.13 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.0$, 138.9, 128.4, 127.6, 127.0, 70.2, 62.8, 60.8, 57.2, 55.6, 39.7, 32.6, 28.0, 26.0, 25.9, 25.4 ppm; HRMS (ESI): *m*/*z* calcd for $C_{36}H_{51}N_4O_4$: 603.3910 $[M+H]^+$; found: 603.3910.

*m*CPBA (*m*CPBA = 3-chloroperbenzoic acid) (278 mg, 1.36 mmol) was added to a solution of the amide **W9** (374 mg, 0.62 mmol) in CH_2Cl_2 (20 mL) at −20 °C. The mixture was allowed to stir at −20 °C for 40 min. Then, the reaction was warmed to room temperature and purified by silica-gel chromatography (ethyl acetate/CH_3OH 3:1, 2:1, and 1:1) to give pure **W8** as a white solid (338 mg, 86%). M.p. 156–159 °C; $[\alpha]_D^{10} = -28.0$ (*c* = 0.1 in CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.47$, 11.01, 9.44 (s, d, d, *J* = 6.6, 9.0 Hz, 2H), 7.41–7.27 (m, 10H), 5.64 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.53 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.80 (d, *J* = 5.6 Hz, 1H), 4.56 (d, *J* = 8.0 Hz, 1H), 4.31–4.28 (m, 1H), 4.10–4.06 (m, 1H), 3.83 (dd, 10.8, 5.2 Hz, 1H), 3.74–3.68 (m, 2H), 3.55–3.35 (m, 5H), 3.24–3.20 (m, 3H), 2.82–2.74 (m, 3H), 2.40–2.05 (m, 6H), 1.92–0.91 ppm (m, 12H); ^{13}C NMR (100 MHz, [D_6]DMSO): $\delta = 169.0$, 168.9, 168.7, 141.1, 140.9, 140.0, 128.4, 128.35, 128.2, 127.6, 127.5, 127.2, 127.1, 79.0, 75.1, 74.5, 72.5, 70.8, 70.6, 70.0, 68.9, 66.6, 60.7, 57.5, 49.1, 31.8, 27.1, 26.6, 25.2, 19.3, 14.3 ppm; HRMS (ESI): *m*/*z* calcd for $C_{36}H_{51}N_4O_6$: 635.3809 $[M+H]^+$; found: 635.3809.

L-Proline-based *N,N′*-dioxides W2:[9] White solid; $[\alpha]_D^{25} = -16.4$ (*c* = 0.39 in CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 11.42$ (brs, 2H), 3.90 (m, 2H), 3.69 (m, 2H), 3.42–3.35 (m, 4H), 3.33–3.24 (m, 2H), 2.56–2.54 (m, 2H), 2.45–2.35 (m, 7H), 2.18 (m, 4H), 2.04–2.01 (m, 2H), 1.94–1.81 (m, 8H), 1.69–1.67 (m, 2H), 1.51–1.34 (m, 9H), 1.15–1.12 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.6$, 77.2, 74.8, 71.8, 64.5, 49.5, 30.9, 28.8, 28.4, 27.8 (27.82), 27.8 (27.75), 25.3, 25.2 (25.25), 25.2 (25.19), 22.4, 19.9 ppm.

L-Proline-based *N,N′*-dioxides W3:[9] Hygrometric white foam; $[\alpha]_D^{25} = -30.5$ (*c* = 0.44 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.91$ (d, *J* = 7.2 Hz, 2H), 3.78 (m, 2H), 3.64–3.59 (m, 2H), 3.44–3.40 (m, 2H), 3.26–3.21 (m, 2H), 3.10–3.04 (m, 2H), 2.40–2.35 (m, 9H), 2.17–2.08 (m, 2H), 1.99–1.96 (m, 2H), 1.90–1.87 (m, 8H), 1.71–1.62 (m, 6H), 1.59–1.52 (m, 3H), 1.36–1.31 (m, 4H), 1.15–1.11 ppm (m, 2H).

L-Proline-based *N,N′*-dioxides W4:[9] White solid; m.p. 134–136 °C; $[\alpha]_D^{25} = -48.7$ (*c* = 1.41 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.81$ (d, *J* = 5.6 Hz, 2H) 7.46–7.44 (m, 4H), 7.38–7.34 (m, 5H), 7.33–7.22 (m, 2H), 5.44–5.42 (m, 2H), 3.60–3.55 (m, 2H), 3.47–3.42 (m, 2H), 3.22–3.11 (m, 3H), 2.73–2.66 (m, 4H), 2.50 (m, 2H), 2.40–2.38 (m, 3H), 2.17–2.14 (m, 2H), 1.92–1.90 (m, 2H), 1.82–1.79 (m, 3H), 1.73–1.71 (m, 2H), 1.67–1.61 (m, 2H), 1.55–1.54 (m, 2H), 1.40–1.31 (m, 2H), 1.01–0.96 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.8$, 139.7, 128.5, 127.2, 126.5, 75.2, 72.3, 65.3, 58.0, 28.4, 27.4, 26.6, 25.1, 24.9, 24.7, 19.8 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{36}H_{51}N_4O_4$: 603.3910 $[M+H]^+$; found: 603.3910.

L-Proline-based *N,N′*-dioxides W5: White solid; m.p. 148–149 °C; $[\alpha]_D^{10} = -63.0$ (*c* = 0.10 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.87$ (d, *J* = 6.8 Hz, 2H), 7.48–7.44 (m, 4H), 7.36–7.28 (m, 4H), 7.24–7.20 (m, 2H), 5.67–5.65 (m, 2H), 3.62–3.57 (m, 2H), 3.29–3.25 (m, 2H), 3.25–3.14 (m, 2H), 2.78–2.64 (m, 4H), 2.46–2.36 (m, 4H), 1.92–1.88 (m, 2H), 1.23 (dd, *J* = 6.0, 3.6 Hz, 6H), 1.02 ppm (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.0$, 139.5, 128.4, 127.0, 126.5, 72.1, 66.3, 62.1, 56.8, 28.1, 19.7, 17.7 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{30}H_{43}N_4O_4$ 523.3279 $[M+H]^+$; found: 523.3268.

L-Proline-based *N,N'*-dioxides W6: White solid; m.p. 132–134 °C; $[\alpha]_D^{10} = -51.0$ ($c = 0.10$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 11.92 (d, $J =$ 6.0 Hz, 2H), 7.43–7.41 (m, 4H), 7.35–7.31 (m, 4H), 7.24–7.20 (m, 2H), 5.61 (d, $J = 7.2$ Hz, 2H), 3.66–3.62 (m, 2H), 3.40–3.35 (m, 2H), 3.22–3.19 (m, 2H), 2.65–2.61 (m, 4H), 2.60–2.10 (m, 4H), 2.09–1.87 (m, 4H), 1.52–1.38 (m, 6H), 0.92 (t, $J = 7.2$ Hz, 6H), 0.74 ppm (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.3, 139.6, 128.5, 127.1, 126.5, 78.1, 72.2, 64.2, 57.0, 28.1, 22.1, 21.9, 19.9, 11.9, 11.1 ppm; HRMS (ESI) m/z calcd for $C_{34}H_{51}N_4O_4$: 579.3910 $[M+H]^+$; found: 579.3910.

***trans*-4-Hydroxy-L-proline-based *N,N'*-dioxides W7**: White solid; m.p. 126–128 °C; $[\alpha]_D^{10} = -18.9$ ($c = 0.12$ in CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): 11.56, 10.78, 9.46 (s, s, d, $J = 9.6$ Hz, 2H), 7.48–7.27 (m, 10H), 5.86 (dd, $J = 9.6$,4.0 Hz, 1H), 5.70 (dd, $J = 10.0$, 4.4 Hz, 1H), 4.80 (d, $J =$ 6.0 Hz, 1H), 4.60 (d, $J = 7.2$ Hz, 1H), 4.24 (t, $J = 6.0$ Hz, 1H), 3.86 (dd, $J = 10.8$, 5.2 Hz, 1H), 3.80–3.60 (m, 2H), 3.42 (d, $J = 10.8$ Hz, 2H), 3.18–3.06 (m, 4H), 2.35–2.18 (m, 4H), 1.87–1.83 (m, 2H), 1.50–1.40 (m, 6H), 1.03–0.67 ppm (m, 12H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): 168.8, 168.0, 167.8, 140.5, 140.2, 139.4, 128.0, 127.8, 127.2, 127.0, 126.7, 126.66, 79.0, 78.2, 77.4, 73.3, 72.2, 69.9, 69.3, 66.2, 56.2, 55.0, 48.6, 38.3, 22.1, 21.7, 21.6, 12.3, 11.1, 10.0 ppm; HRMS (ESI): m/z: calcd for $C_{36}H_{51}N_4O_4$: 611.3809 $[M+H]^+$; found: 611.3808.

***trans*-4-Hydroxy-L-proline-based mono-*N*-oxide W10**: White solid; m.p. 120–122 °C; $[\alpha]_D^{10} = -42.0$ ($c = 0.11$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 11.29 (s, 1H), 8.03 (s, 1H), 7.22–7.14 (m, 10H), 5.32–5.23 (m, 2H), 4.63 (s, 1H), 4.25–4.24 (m, 1H), 3.67–3.64 (m, 2H), 3.52–3.45 (m, 4H), 3.30–3.20 (m, 1H), 3.11 (s, 1H), 2.25–1.32 (m, 10H), 1.30–0.84 ppm (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): 175.6, 168.3, 138.9, 138.5, 128.7, 128.5, 128.3, 127.7, 127.5, 126.5, 126.4, 75.4, 72.6, 71.7, 71.1, 69.5, 66.8, 63.0, 61.8, 61.2, 57.9, 57.3, 56.1, 39.2, 31.6, 29.7, 28.5, 27.5, 26.8, 25.6, 25.4, 25.0, 24.8, 19.3, 13.9 ppm; HRMS (ESI): m/z: calcd for $C_{36}H_{51}N_4O_5$: 619.3859 $[M+H]^+$; found: 619.3858.

***trans*-4-Hydroxy-L-proline-based mono-*N*-oxide W11**: White solid; m.p. 62–64 °C; $[\alpha]_D^{10} = -83.7$ ($c = 0.14$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.17$ (m, 1H), 7.29–7.23 (m, 4H), 7.20–7.15 (m, 1H), 5.03–5.00 (m, 1H), 4.70–4.68 (m, 1H), 4.02 (dd, $J = 12.0$, 6.4 Hz, 1H), 3.56 (dd, $J = 11.6$, 6.8 Hz, 1H), 3.41–3.39 (m, 1H), 3.19 (dd, $J = 11.6$, 4.8 Hz, 1H), 2.93–2.90 (m, 1H), 2.78–2.76 (m, 1H), 2.26 (dd, $J = 13.2$,6.4 Hz, 1H), 2.16–2.13 (m, 1H), 1.89–1.86 (m, 1H), 1.70–1.63 (m, 2H), 1.51–1.49 (m, 1H), 1.42 (d, $J = 6.8$ Hz, 3H), 1.31–0.86 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.4, 143.3, 128.5, 127.2, 126.3, 75.8, 73.8, 70.9, 67.0, 48.5, 39.2, 27.5, 27.4, 25.3, 25.1, 25.0, 22.0 ppm; HRMS (ESI): m/z: calcd for $C_{19}H_{29}N_2O_3$: 333.2178 $[M+H]^+$; found: 333.2179.

General procedure for the catalytic asymmetric one-pot, three-component Strecker reaction: Benzaldehyde (21 μL, 0.2 mmol) and (1,1-diphenyl)methylamine (36 μL, 0.2 mmol) were combined in a dry test tube. Then 0.2 mL CH_2Cl_2 was added to the mixture and the reaction solution was stirred at 25 °C for 2 h. After that, catalyst **W8** (10 mol %) and CH_2Cl_2 (0.3 mL) were added. The test tube was cooled to −20 °C, TMSCN (54 μL, 0.4 mmol) was added, and the mixture was stirred for 8 h at −20 °C. The crude material was purified by flash chromatography on silica gel (Et_2O/light petroleum ether 1:60) to afford the product **2a** in 81 % *ee* as determined by chiral HPLC analysis (Chiralpak AD-H).

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