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Chiral Bisformamides as Effective Organocatalysts for the Asymmetric One-Pot, Three-Component Strecker Reaction

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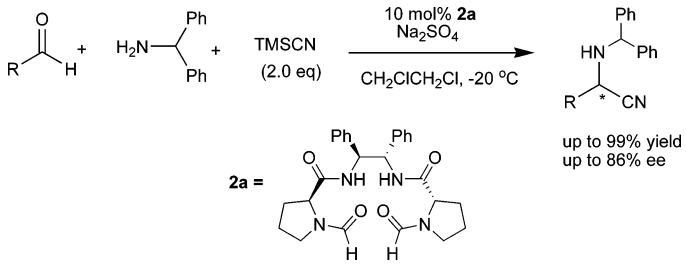

C_2-symmetric chiral bisformamides have been shown to catalyze the asymmetric one-pot, three-component Strecker reaction, which produced the α-amino nitriles in excellent yields (up to 99%) with good enantioselectivities (up to 86% ee). Optically pure products could be obtained after a single recrystallization. A possible transition state (**TS 1**) has been proposed to explain the origin of asymmetric inductivity and reactivity according to the geometry of catalyst **2a** optimized at the B3LYP/6-31G(d) level and the absolute configuration of product **4a**.

Introduction

The Strecker reaction is one of the most attractive methods for the synthesis of α-amino acids and their derivatives.[1] In recent years, considerable effort has been devoted toward the development of asymmetric Strecker reactions.[2] Several chiral metal complexes including Al, Ti, Zr, and lanthanide have been identified for this transformation.[3] Effective metal-free catalysts have been developed employing chiral guanidines, ureas and thioureas, bis(*N*-oxides), ammonium salts, and Brønsted acids.[4] Nevertheless, only very recently has a single example of organocatalytic asymmetric three-component Strecker reaction been reported by List et al.[4f] A one-pot multicomponent reaction has many advantages such as its simplified procedure, mild reaction condition, high atom economy, and environmental friendliness. Herein, we wish to report another kind of organocatalyst, C_2-symmetric chiral bisformamides, for the asymmetric one-pot, three-component Strecker reaction.

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Since *N*,*N*-dimethylformamide (DMF) proved to be an effective Lewis base catalyst for some important reactions,[5] the rational design and synthesis of new chiral DMF analogues for enantioselective synthesis have become the focus of attention.[6] However, to the best of our knowledge, the chiral formamide-based catalysts were restricted to allylation and hydrosilylation reactions. In this context, chiral formamides have been applied to the one-pot, three-component Strecker reaction for the first time, and delivered good yields and enantioselectivities.

Results and Discussion

Allyltrichlorosilane and trichlorosilane can be activated by chiral formamides through formyl coordination to silicon.[6d,j] Our earlier studies on bifunctional catalysis indicated that imines could be activated through hydrogen bonding.[4l,m] Inspired by those studies, we presumed that *N*-formyl-(L)-proline amides, which contained both the formyl and amide moieties, might have the ability to catalyze the asymmetric Strecker reaction. Therefore, the one-pot Strecker reaction starting from benzaldehyde, (1,1-diphenyl)methylamine, and TMSCN was chosen as the model reaction to verify our strategy. At the outset, the monoformamide catalyst **1e** derived from L-proline and (*S*)-1-phenylethanamine was tested. Encouragingly, 96% yield and 44% ee were obtained employing 20 mol % **1e**. Then, a series of monoformamides **1a**−**g** were prepared and the influence of the substituent *R* on the catalytic behavior was studied (Table 1). Among the aliphatic amide substituents, **1e** was optimal producing the products with 44% ee (Table 1, entry 5). Bulky substituents, like the cyclohexyl, *tert*-butyl, and adamantyl groups, gave slightly lower enantioselectivities (Table 1, entries 1−3). The phenyl substituent also resulted in a good enantioselectivity of 46% ee (Table 1, entry 6). Introducing bulky substituents onto the phenyl ring resulted in a much lower ee value (Table 1, entry 7).

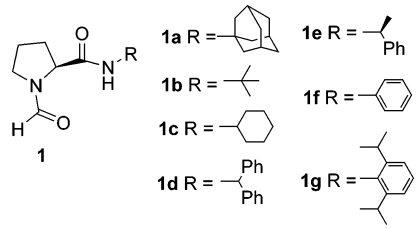


FIGURE 1. Structure of monoformamides.

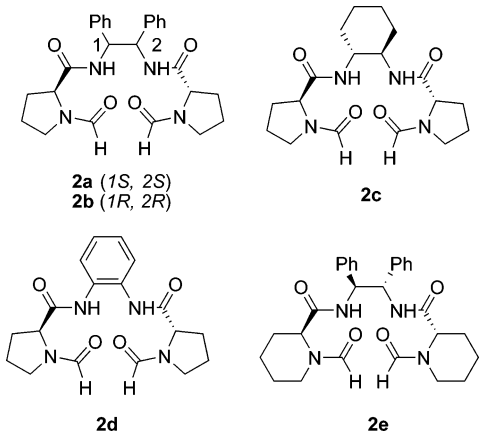
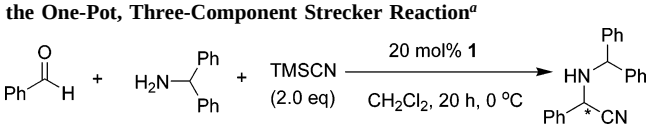


FIGURE 2. Structure of bisformamides.

TABLE 1. Survey of Chiral Monoformamide Catalysts 1a−g on the One-Pot, Three-Component Strecker Reaction[a]



entry	catalyst	yield[b] (%)	ee[c] (%)
1	**1a**	92	35
2	**1b**	99	32
3	**1c**	99	38
4	**1d**	99	20
5	**1e**	96	44
6	**1f**	99	46
7	**1g**	93	11

[a] Reaction condition: benzaldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) were stirred for 1 h at rt before catalyst **1** was added. Then TMSCN (0.4 mmol) was added at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel AD-H column.

On the basis of the above studies, we confirmed that formamides derived from the amino acid and amine could catalyze the addition of TMSCN to in situ generated imines. We speculated that an additional formyl and the changed chiral environment of C_2-symmetric bisformamides might be more advantageous. Therefore, a set of bisformamides **2a**−**e** were synthesized (Figure 2) and tested (Table 2) which were first developed and applied to allylation of aldimines with allyltrichlorosilane by Tsogoeva et al.[6k] Indeed, the reactivity (Table 2, entries 1−5) and enantioselectivity (Table 2, entries 1 and

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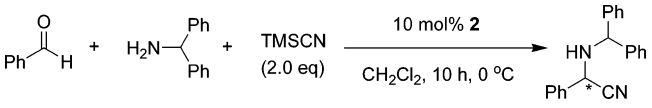
TABLE 2. Survey of Chiral Bisformamide Catalysts 2a−e on the One-Pot, Three-Component Strecker Reaction[a]



entry	catalyst	yield[b] (%)	ee[c] (%)
1	**2a**	99	61
2	**2b**	97	12
3	**2c**	90	17
4	**2d**	97	34
5	**2e**	97	51

[a] Reaction condition: benzaldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) were stirred for 1 h at rt before catalyst **2** was added. Then TMSCN (0.4 mmol) was added at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel AD-H column.

TABLE 3. Solvent Effect for the One-Pot, Three-Component Strecker Reaction[a]

entry	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	THF	20	8	7
2	Et_2O	20	37	0
3	$PhCH_3$	20	99	39
4	CH_2Cl_2	10	94	69
5	CH_2ClCH_2Cl	10	99	75
6	$CHCl_3$	7	99	58
7	CH_3OH	7	99	0

[a] Reaction condition: benzaldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) were stirred for 1 h at rt before catalyst **2a** was added. Then TMSCN (0.4 mmol) was added at −20 °C. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel AD-H column.

5) were greatly promoted by bisformamides compared with monoformamides. Catalyst **2a** produced the product with 61% ee and 99% yield within 10 h (Table 2, entry 1). Any replacement of the 1,2-diphenylethane-1,2-diamine or L-proline led to reduced enantioselectivities (Table 2, entries 3−5). The match between the chiral centers of diamine and proline was very important for catalytic efficiency. The best results were observed in the reactions with catalyst **2a**, while only 12% ee was found with **2b** (Table 2, entry 1 vs 2).

Accordingly, optimization of the reaction conditions was investigated by using **2a** as the catalyst of choice. Solvent screening showed that CH_2ClCH_2Cl was the best, with the results of 99% yield and 75% ee (Table 3, entry 5). The ethereal solvents such as THF and Et_2O gave low yields and nearly racemic products (Table 3, entries 1 and 2). Toluene provided good yields, but the enantioselectivity was notably diminished (Table 3, entry 3). CH_2Cl_2 and $CHCl_3$ were also good solvents for reactivity and enantioselectivity (Table 3, entries 4 and 6). When protic solvents like CH_3OH were used, high yields but no enantioselectivities were afforded (Table 3, entry 7).

We next observed the catalyst loading and temperature effect (Table 4). Decreasing of the catalyst loading from 10 to 5 mol %, the ee value was reduced from 75% to 66% (Table 4, entry 2 vs entry 1). Unfortunately, the enantioselectivity was not notablely improved when increasing the catalyst loading to 20 and 30 mol % (Table 4, entries 3 and 4). So 10 mol % **2a** was determined to be the optimal catalyst loading. The best results were found at −20 °C (Table 4, entry 2). Higher or lower temperatures were not beneficial for the ee value (Table 4, entries 5 and 6).

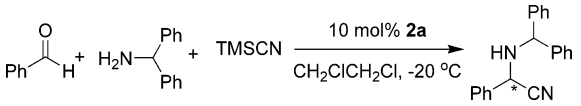
The ratio of the three components and the effect of the substrate concentration were also checked (Table 5). When the

TABLE 4. The Catalyst Loading and Temperature Effect[a]

entry	catalyst loading (mol %)	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	5	−20	10	98	66
2	10	−20	10	99	75
3	20	−20	10	99	78
4	30	−20	10	99	77
5	10	0	7	99	72
6	10	−45	16	85	55

[a] Reaction condition: benzaldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) were stirred together for 1 h at rt before catalyst **2a** was added. Then TMSCN (0.4 mmol) was added at −20, 0, or −45 °C. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel AD-H column.

TABLE 5. Effect of the Molar Ratios and the Concentration[a]



entry	ratio (PhCHO:amine:TMSCN)	concn of PhCHO (M)	yield[b] (%)	ee[c] (%)
1	1:1:1.5	0.2	99	63
2	1:1:2	0.2	99	75
3	1:1:3	0.2	99	73
4	1:1.5:2	0.2	99	75
5	1:1:2	0.4	99	75
6	1:1:2	1	99	65
7	1:1:2	0.13	97	62

[a] Reaction condition: benzaldehyde (0.2 mmol) and (1,1-diphenyl)methylamine (0.2 mmol) were stirred together for 1 h at rt before catalyst was added. Then TMSCN (0.4 mmol) was added at −20 °C and reacted for 10−14 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel AD-H column.

molar ratio of PhCHO, amine, and TMSCN was 1:1:2, 99% yield and 75% ee were obtained (Table 5, entry 2). By decreasing TMSCN to 1.5 equiv, the enantioselectivity was reduced to 63% ee (Table 5, entry 1). Increasing TMSCN to 3 equiv led to a small reduction of the ee value (Table 5, entry 3). The yield and enantioselectivity were unchanged while varying the amount of (1,1-diphenyl)methylamine (Table 5, entry 4 vs entry 2). When the concentration of benzaldehyde was diminished from 0.2 to 0.13 M, the enantioselectivity was decreased remarkably (Table 5, entry 7 vs entry 2). The same yield and ee value were produced with 0.4 M of PhCHO (Table 5, entry 5 vs entry 2). However, when further enhancing the concentration of benzaldehyde to 1 M, only 65% ee was observed (Table 5, entry 6). Thereafter, 0.2 M of PHCHO was chosen to test other conditions.

To improve the enantioselectivity, some common drying agents, such as $MgSO_4$, Na_2SO_4, and 3, 4, and 5 Å MS, were examined. The best results (81% ee and 99% yield) were obtained when using anhydrous Na_2SO_4. The optimal conditions were 0.2 mmol of benzaldehyde, 0.2 mmol of (1,1-diphenyl)-methylamine, 100 mg of Na_2SO_4, 10 mol % of **2a**, 0.4 mmol of TMSCN, 1 mL of CH_2ClCH_2Cl and −20 °C.

With the optimal conditions, the scope of this three-component reaction with different aldehydes was explored and the results were summarized in Table 6. Good to high yields (up to 99%) and good enantioselectivities (up to 86% ee; single recrystallization, up to 99% ee) were achieved. The substrates with para-substituted aromatic rings provided adducts in high enantioselectivities (Table 6, entries 2, 5, 7, 10, and 11). A slightly lower enantioselectivity was obtained for the ortho- or

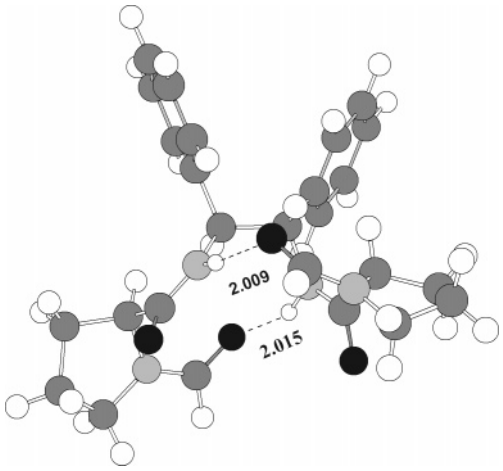


FIGURE 3. Optimized geometry of catalyst **2a** at the B3LYP/6-31G-(d) level.

meta-substituted aldehydes (Table 6, entries 4, 6, 8, and 9). The halogen-substituted aromatic aldehydes produced the corresponding α-amino nitriles with moderate to high yields and good enantioselectivities (Table 6, entries 7−10), but the reactivity was not as good as that of alkyl- or alkoxyl-substituted aromatic aldehydes. A 75% yield and 81% ee were given by 2-naphthaldehyde (Table 6, entry 12). Pivaldehyde also gave good results (Table 6, entry 13). The heterocyclic aldehyde furfural gave high yield but moderate enantioselectivity (Table 6, entry 14). Moreover, the Strecker adducts were important precursors, which could be conveniently hydrolyzed to α-amino acids with no loss of optical purity.[3d,f,g,8]

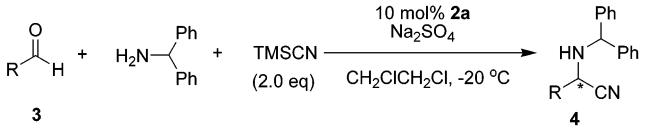
Mechanistic Consideration

The geometry of catalyst **2a** was optimized at the B3LYP/6-31G(d) level (Figure 3) with use of the Gaussian 03 program package. The distances between the O on the formyl group and the H of amide were 2.009 and 2.015 Å, which indicated two hydrogen bonds exist in **2a**. The modeling calculation also showed that the two phenyl rings of the diamine moiety are bent forward and backward, and the two pyrrole units are bent upward and downward, respectively. According to the observed absolute configuration of product **4a** (Table 6, entry1) and the optimized geometry of catalyst **2a**, a possible transition state (Figure 4, **TS 1**) has been proposed. In situ generated imine is activated by hydrogen bond via the nitrogen of imine coordinating to the hydrogen of amide,[4l,m] while TMSCN is activated by two oxygens in another pyrrole unit coordinated to silicon.[6d,j] The *Si* face attack is much more accessible than the *Re* face, as the increased repulsion between the phenyl group of the imine and the pyrrole unit occurs in **TS 2**.

Conclusion

C_2-symmetric bisformamide has been applied to catalyze the one-pot, three-component Strecker reaction in good enantioselectivities (up to 86% ee; single recrystallization, up to 99% ee) with high yields (up to 99%) for a range of aldehydes. This catalysis utilizes inexpensive chemicals and can be carried out under simple and mild conditions. It is the first example that chiral DMF analogues have been used in asymmetric cyanosilylation of imine. A possible transition state **TS 1** has been proposed according to the geometry of catalyst **2a** optimized at the B3LYP/6-31G(d) level and the absolute configuration of product **4a**. Further investigations are underway in our laboratory, including exploration of a relative catalyst library, detailed mechanisms, extended substrate scope, and enhancement of enantioselectivity.

TABLE 6. Scope of the Enantioselective One-Pot, Three-Component Strecker Reaction[a]



entry	RCHO (**3**)	time (h)	yield[b] (%)	ee[c] (%)
1	R = phenyl (**3a**)	10	99	81 (*R*)[d]
2	R = 4-methylphenyl (**3b**)	10	98	84 (>99)[e]
3	R = 2-methylphenyl (**3c**)	10	99	80 (*R*)
4	R = 3-methylphenyl (**3d**)	10	97	76
5	R = 4-methoxyphenyl (**3e**)	10	96	85
6	R = 3-methoxyphenyl (**3f**)	14	97	76
7	R = 4-chlorophenyl (**3g**)	50	98	83
8	R = 3-chlorophenyl (**3h**)	60	74	73
9	R = 2-chlorophenyl (**3i**)	50	81	75 (*R*)
10	R = 4-bromophenyl (**3j**)	60	85	86 (>99)
11	R = 4-phenylphenyl (**3k**)	14	94	86
12	R = 2-naphthyl (**3*l***)	50	75	81 (*R*)
13	R = *tert*-butyl (**3m**)	14	92	73
14	R = 2-furyl (**3n**)	14	94	43

[a] Reaction condition: Na_2SO_4 (100 mg), aldehyde (0.2 mmol), and (1,1-diphenyl)methylamine (0.2 mmol) were stirred together for 1 h at rt before catalyst **2a** was added. Then TMSCN (0.4 mmol) was added at −20 °C. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel AD-H column. [d] The absolute configuration was established as *R* by comparison of the literature (see refs 3d, 4k, and 7). [e] After single recrystallization.

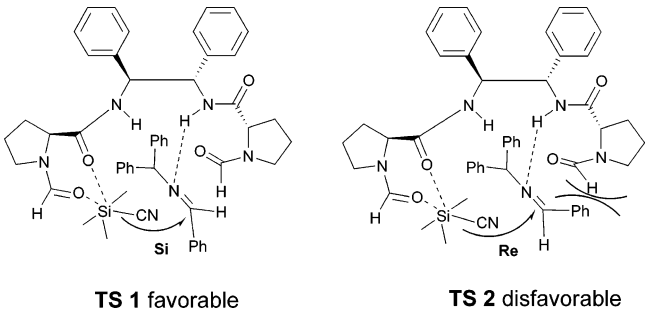


FIGURE 4. Proposed transition states.

Experimental Section

Typical Experimental Procedure for the Preparation of Catalyst 2a.[6c,e,9] To a solution of Boc L-proline (1.34 g, 6.2 mmol) in CH_2Cl_2 were added Et_3N (1.1 mL) and *sec*-butylcarbonochloridate (0.82 mL, 6.2 mmol) at 0 °C. After 15 min, (*1S*,*2S*)-1,2-diphenylethane-1,2-diamine (637 mg, 3 mmol) was added directly. Then the reaction mixture was stirred at room temperature for 3 h. The solution was washed with 1 M $KHSO_4$ (40 mL), saturated $NaHCO_3$ (40 mL), and brine (20 mL) and dried over anhydrous

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Na_2SO_4. After removal of solvents under reduced pressure, CH_2Cl_2 (20 mL) and TFA (6 mL) were added. The mixture was concentrated under reduced pressure after 1 h. The residue was dissolved in CH_2Cl_2 and the resulting solution was cooled to 0 °C. The pH was adjusted to 10 with 2 M NaOH. The product was extracted with CH_2Cl_2 (3 × 30 mL) and the filtrate was concentrated under reduced pressure. The residue was dissolved in formic acid (6 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (4 mL) was added and the mixture was allowed to stir at room temperature overnight. After removal of solvents under reduced pressure, the residue was purified though column chromatography on silica gel to give **2a** as a white solid in 80% yield: $[\alpha]^{20}_D$ −136.0 (*c* 0.20, $CHCl_3$); mp 132−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26−2.17 (m, 8H), 3.51−3.57 (m, 4H), 4.10−4.62 (m, 2H), 5.11−5.13 (m, 2H), 7.01−7.06 (m, 4H), 7.15−7.17 (m, 6H), 7.68−8.21 (m, 2H), 8.22 and 8.25 (2 × s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 162.4, 138.5, 128.3, 127.2, 127.0, 58.3, 58.2, 46.9, 44.2, 30.3, 27.7, 24.1, 24.0, 22.9, 21.1 ppm. HRMS (FT-ICRMS) exact mass calcd for $[C_{26}H_{30}N_4O_4 + H]^+$ requires *m*/*z* 463.2345, found 463.2346.

General Procedure for the Chiral Formamide (2a)-Catalyzed One-Pot, Three-Component Strecker Reaction. Benzaldehyde (21 μL, 0.2 mmol), (1,1-diphenyl)methylamine (36 μL, 0.2 mmol), and Na_2SO_4 (100 mg) were combined in a dry test tube. Then 0.2 mL of CH_2ClCH_2Cl was added to the mixture and the reaction solution was stirred at rt for 1 h. After that, catalyst **2a** (10 mol %) and CH_2ClCH_2Cl (0.8 mL) were added. The test tube was cooled to −20 °C. Then TMSCN (54 μL, 0.4 mmol) was added, and the mixture was stirred for 10 h at −20 °C. The crude material was purified by flash chromatography on silica gel (Et_2O/light petroleum ether, 1:60 v/v) to afford the product in 99% yield as a white solid. The chromatographed material was determined to be of 81% ee by chiral HPLC analysis [Chiralpak AD-H, 80:20 *n*- hexane/*i*PrOH, 1.0 mL/min, t_R(major) = 6.769 min, t_R(minor) = 12.999 min]; mp 94−96 °C. $[\alpha]^{20}_D$ 75.0 (*c* 0.10 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.20 (m, 15 H), 5.25 (s, 1 H), 4.60 (d, J = 12.4 Hz, 1 H), 2.14 (d, J = 12.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 141.0, 134.9, 129.03, 129.00, 128.98, 128.8, 127.9, 127.7, 127.4, 127.2, 127.1, 118.7, 65.6, 52.4 ppm.

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Supporting Information Available: Experimental procedures and structural proofs for catalysts and racemates, ^{1}H NMR, ^{13}C NMR spectra, and HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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