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Enantioselective Synthesis of α-Amino Nitriles from *N*-Benzhydryl Imines and HCN with a Chiral Bicyclic Guanidine as Catalyst

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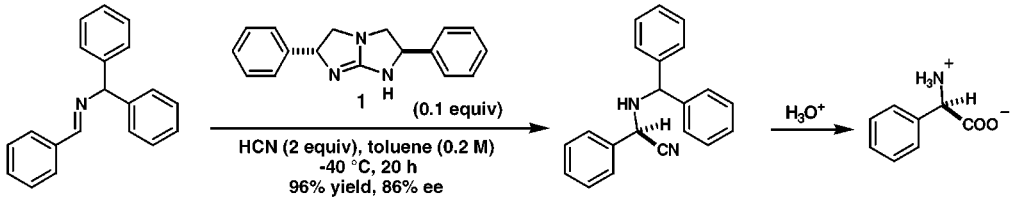
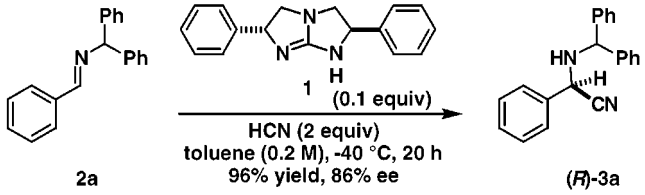
ABSTRACT



A novel catalytic enantioselective Strecker synthesis of chiral α-amino nitriles and α-amino acids is described and analyzed with regard to the possible mechanistic basis for stereoselectivity. Key features of the enantioselective process include (1) the use of the chiral bicyclic guanidine 1 as catalyst and (2) the use of the *N*-benzhydryl substituent on the imine substrate.

The classical Strecker synthesis of racemic α-amino acids starting from aldehydes and ammonium cyanide (or equivalent) is one of the simplest and most economical methods of production.[1] Consequently, enantioselective versions of this process, which could lead to the practical production of a wide range of (*R*)- or (*S*)-α-amino acids, have been of great interest. Recently, several enantioselective catalysts for the Strecker synthesis have been identified, including a chiral (Salen)Al^{III} complex,[2a] a multifunctional salicylaldimine,[2b] a Zr^{IV}BINOL complex,[2c] and a guanidine-bearing diketopiperazine.[2d] In this paper we describe a novel catalytic enantioselective Strecker reaction which utilizes the readily available chiral C_2-symmetric guanidine **1** as a bifunctional catalyst for the addition of HCN to achiral *N*-benzhydrylimines (**2**), as outlined in Scheme 1 for the specific case of the benzaldehyde imine.

Scheme 1



The reaction of imine **2a**[3] with HCN in the presence of 10 mol % of **1**[4] (synthesized as outlined in Scheme 3) in

(1) (a) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(2) (a) Sigman M. S.; Jacobsen E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (c) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3186. (d) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4910.

(3) *N*-Benzhydrylimines were prepared by combining the aldehyde and *N*-benzhydrylamine (5 mmol each) in benzene (5 mL) at 23 °C, removing solvent in vacuo, filtering a benzene solution of the residue through activated silica gel (0.2 g), and concentrating to the pure imines.

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toluene at −40 °C over 20 h occurred cleanly to form the (*R*)-amino nitrile **3a** in 96% yield and with 93:7 *R*/*S* selectivity (86% ee). This reaction is quite general for *N*-benzhydrylimines of aromatic aldehydes as shown by the results which are collected in Table 1. The yields given in Table 1 refer to isolated pure α-amino nitrile.[5] The guanidine catalyst **1** was easily separated from the crude reaction mixture by extraction with oxalic acid and recovered for reuse.[5] The amino nitriles **3** upon heating at reflux with 6 N HCl underwent benzhydryl cleavage and CN → COOH conversion to form cleanly the corresponding (*R*)-arylglycines,[2d] the absolute configurations of which were determined by measurement of optical rotation. Enantiomeric ratios were evaluated by HPLC analysis using chiral columns.[5] It is important to note that in the absence of catalyst **1** there was no reaction between HCN and the aldimines **2** in toluene at 10 °C or below and that *N*-methyl-**1** is entirely inactive as a catalyst.

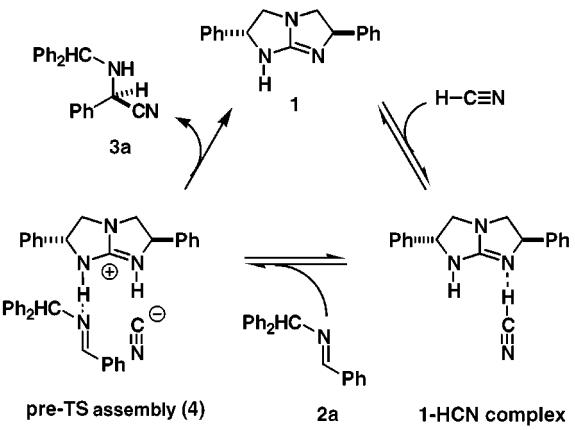
Table 1. Conversion of ArCH=NCH(C_6H_5)$_2$ (**2**) to ArCH(CN)NHCH(C_6H_5)$_2$ (**3**) by Reaction with HCN in the Presence of 10 mol % of **1**

2a−**j**	Ar =	*T*(°C)	*t* (h)	% yield	% ee	**3a**−**j**
a	Ph	−40	20	96	86	(*R*)-**3a**
a	Ph	−20	8	99	82	(*R*)-**3a**
b	*p*-tolyl	−40	20	96	80	(*R*)-**3b**
c	3,5-xylyl	−40	16	96	79	(*R*)-**3c**
d	*o*-tolyl	−20	12	88	50	**3d**
e	4-*t*-Bu-Ph	−40	72	80	85	**3e**
f	4-TBSO-Ph	−40	38	98	88	(*R*)-**3f**
g	4-MeO-Ph	−40	28	99	84	(*R*)-**3g**
h	4-F-Ph	−40	23	97	86	(*R*)-**3h**
i	4-Cl-Ph	−20	20	88	81	(*R*)-**3i**
j	1-naphthyl	−20	12	90	76	(*R*)-**3j**

The *N*-benzhydryl subunit of the aldimine substrates **2** is critical to the realization of good enantioselectivity. *N*-Benzyl- or *N*-(9′-fluorenyl) aldimine analogs of **2** underwent reaction with HCN in the presence of 10 mol % of **1** in toluene at −10 to −20 °C to afford Strecker products of poor (0−25%) enantiomeric purity. The *N*-(2,3:6,7-dibenzocycloheptadienyl) analog of **2a** afforded amino nitrile of 77% ee which is definitely below that with **2a** itself. Similarly, the placement of *para* substituents on the benzhydryl group of **2a** resulted in products of somewhat reduced enantiomeric excess (*p*-Me, OMe, Cl, and CF_3: 78, 70, 68, and 59% ee, respectively, for the analogs of **3a**).

The catalytic action of the bicyclic guanidine **1** can be understood simply in terms of the mechanism for the conversion of **2a** to **3a** which is outlined in Scheme 2. In the first step of the cycle, HCN hydrogen bonds to the catalyst **1**, generating a guanidinium cyanide complex which can serve as a hydrogen bond donor to the aldimine **2a** forming the pre-transition-state termolecular assembly shown (**4**). Finally, attack by cyanide ion within the ion pair on the hydrogen-bond-activated aldimine affords the Strecker product (*R*)-**3a**. It is likely that the last step is rate-limiting since hydrogen bond making and breaking are normally relatively fast. It is also relevant that no kinetic H/D isotope effect on the reaction rate was detected in experiments which compared the velocity of the catalytic Strecker reaction with DCN and HCN.

Scheme 2



The catalytic cycle which is summarized in Scheme 2 provides insights with regard to the origin of enantioselectivity for the conversion of **2** to **3** in the presence of catalyst **1** and HCN. Modeling of the imine **2a** hydrogen bonded to the guanidinium in pre-transition-state assembly **4** indicates the possibility of a three-dimensional arrangement depicted in Figure 1 where the cyanide is positioned to attack the *re* face of the imine carbon, a trajectory that leads to the predominating enantiomer (*R*)-**3a**. A proximal phenyl group of the catalyst can undergo π-stacking with one of the benzhydryl phenyls, while the *si* face of the imine carbon is blocked by the other phenyl of the benzhydryl group. At the same time the aryl π-conjugated to the imine of **2a** is accommodated in a vacant quadrant of the guanidine face and can experience van der Waals attractions with the guanidine core and distal phenyl edge of catalyst **1**. Rotation of imine **2a** by 180° about the H−N bond to expose the *si* face to attack removes the van der Waals attractions and

(4) (3*R*,7*R*)-3,7-Diphenyl-1,4,6-triazabicyclo[3.3.0]oct-4-ene (**1**): colorless solid, mp 159−160 °C; R_f 0.28 (1:10:90 NH_4OH/MeOH/CH_2Cl_2); $[\alpha]^{23}_D$ +23.8 (*c* 0.58, $CHCl_3$); IR (thin film) 1452, 1492, 1674, 2829, 2926, 3027, 3058, 3106, 3156, 3205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 4 H, *J* = 7.0 Hz), 7.32 (t, 4 H, *J* = 7.1 Hz), 7.25 (t, 2 H, *J* = 2.5 Hz), 6.37 (bs, 1 H), 5.17 (t, 2 H, *J* = 6.5 Hz), 3.50 (t, 2 H, *J* = 7.8 Hz), 3.03 (dd, 2 H, *J* = 6.3, 7.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 143.0, 128.5, 127.4, 126.4, 68.0, 57.2 ppm; CIMS 278(30) [M + NH_4^+], 264(100) [M + H^+].

(5) To a clear solution (0.2 M) of aldimine (0.18 mmol) and guanidine **1** (0.018 mmol) in toluene under N_2 was added liquid HCN (0.36 mmol) via a precooled 50-μL gastight syringe. Upon consumption of starting material as indicated by TLC analysis, the reaction mixture was concentrated in vacuo, acidified by addition of oxalic acid (0.018 mmol) in water (5 mL), and extracted with ether (3 × 15 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give amino nitrile **3** that could be further purified by silica gel chromatography (1% ethyl acetate−hexanes). Basification with 1 N NaOH of the oxalic acid wash and extraction with ethyl acetate and concentration allows recovery of **1** (80−90% yield). Enantioselectivity was analyzed by chiral HPLC with Chiralpak AD, Chiralpak AS or Chiralcel OJ columns with 2-propanol−hexanes as eluent.

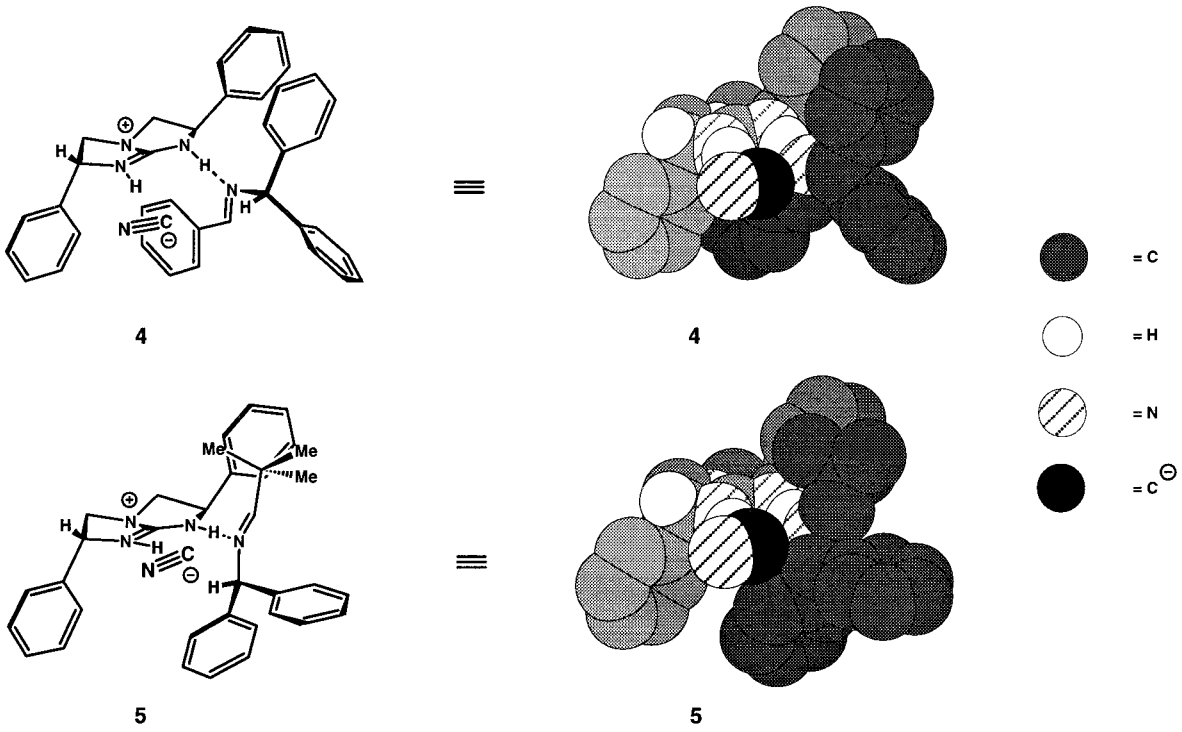


Figure 1. Pre-transition-state assemblies for the Strecker reactions of *N*-benzhydryl benzaldimine (**4**) and *N*-benzhydryl pivalaldimine (**5**).

introduces steric repulsion between the π-conjugated aldimine aryl and the proximal phenyl of catalyst **1**.

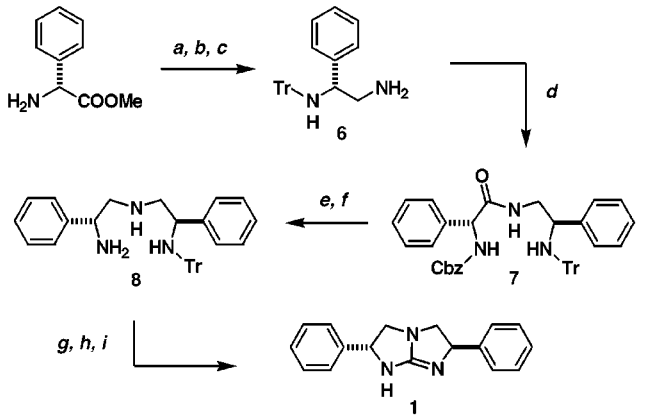
This working hypothesis receives support from studies of the Strecker reaction between HCN, catalyst **1**, and the enantiomeric imines from benzaldehyde and (*S*)-1-phenethylamine and (*R*)-1-phenethylamine. The former affords the Strecker product (toluene, −20 °C, 12 h) with the (*R*) configuration α to cyano with 93.5:6.5 *R*/*S* diastereoselectivity, whereas the latter gives under the same conditions the Strecker product with only 58:42 *R*/*S* diastereoselectivity. Only in the pre-transition-state assembly derived from the former can the two phenyl groups of the imine interact with the catalyst in a manner similar to that shown in **4** in Figure 1. The deleterious effects of replacing benzhydryl in **2a** by *N*-benzyl or *N*-(9′-fluorenyl) (see above) are also consistent with the three-dimensional model of the pre-transition-state assembly shown in Figure 1. Finally, it should be noted that the use of the bis-cyclohexyl (dodecahydro) analog[6] of catalyst **1** instead of **1** leads to conversion of **2a** to **3a** with only 56% enantiomeric excess.

The use of Schiff bases of benzhydrylamine with aliphatic aldehydes in the Strecker process catalyzed by **1** also resulted in efficient formation of α-amino nitriles. Thus with aldimines from pivalaldehyde, cyclohexanecarboxaldehyde, and *n*-heptanal, (*S*)-Strecker products were formed (toluene, −40 °C, 22 h) in ∼95% yield with ee values of 84, 76, and 63%, respectively. In terms of a mechanistic model, the (*S*) selectivity for aliphatic imines suggests a pre-transition-state assembly **5** where the aldimine alkyl group contacts the proximal phenyl of the catalyst and one benzhydryl phenyl occupies a vacant quadrant of the guanidine face, as shown in Figure 1. The inversion of product configuration from *R* for aromatic imines to *S* for aliphatic imines indicates that alkyl groups incur steric repulsions in the vacant quadrant of guanidine **1** where an imine aryl or a benzhydryl phenyl gains van der Waals attractions.

The bicyclic guanidine **1**[4] was prepared from (*R*)-phenylglycine by a route paralleling that previously utilized for the synthesis of the bis-cyclohexyl (dodecahydro) analog (Scheme 3).[6] Methyl (*R*)-phenylglycinate was converted to the trityl-protected diamine **6** by amide formation in ammonia-saturated methanol (23 °C, 24 h), tritylation (TrCl, TEA), and lithium aluminum hydride reduction in ether at reflux (79% yield for three steps). Coupling of **6** to (*R*)-*N*-(benzyloxylcarbonyl)phenylglycine (dicyclohexylcarbodiimide, 1-hydroxybenzotriazole) yielded amide **7** (77% yield) which was transformed to triamine **8** by carbamate hydrogenolysis and amide reduction with sodium bis(2-methoxyethoxy)aluminum dihydride (76% yield). Treatment of **8** with thiophosgene and aqueous sodium carbonate effected ring closure between NH_2 and the proximal NH to form the corresponding thiourea (95% yield) that was *S*-methylated with iodomethane to generate the *S*-methylisothiouronium iodide. When this compound was heated in DMF at 100 °C guanidine **1** was formed (55% yield after basic workup and silica gel chromatography). The three-dimensional structure of the benzoate salt of **1** was determined by X-ray crystal-

(6) Corey, E. J.; Ohtani, M. *Tetrahedron. Lett.* **1989**, *30*, 5227.

Scheme 3



[a] NH_3, MeOH, 23 °C, 24 h, 86%. [b] TrCl (1 equiv), TEA, CH_2Cl_2, 23 °C, 1 h, 97%. [c] $LiAlH_4$, Et_2O, reflux, 35 h, 95%. [d] (*R*)-Cbz-phenylglycine, DCC, HOBt, THF, 0 °C, 8 h, 77%. [e] H_2,10% Pd/C, 1:1 THF/MeOH, 23 °C, 6 h. [f] Red-Al (5 equiv), PhH, reflux, 2.5 h, 76%. [g] Thiophosgene (1.05 equiv), Na_2CO_3, 1:1 CH_2Cl_2/H_2O, 0 °C, 15 min, 95%. [h] MeI (3 equiv), MeOH, 50 °C. [i] DMF,100 °C, 2 h, 55% for two steps.

lographic analysis. The nitrogen at the 5/5 fusion (N-1) is 12−15° pyramidalized from planar sp^2, the N−C−N angle involving the other two nitrogens is 131°, and the benzoate ion is doubly hydrogen bonded with the guanidinium ion.[7]

(7) X-ray data for **1**·PhCOOH is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.: $C_{24}H_{24}N_3O_2$; orthorhombic; *P*2(1)2(1)2(1); a = 8.7909(3) Å; b = 10.4417(4) Å; c = 22.3969(3) Å; $\alpha = \beta = \gamma = 90°$; Z = 6; T = 213 K; *R*1[$I > 2\sigma(I)$] = 0.0416.

Despite this distorted solid-state conformation, ^{1}H NMR spectra in $CDCl_3$ at 23 °C are consistent with time averaged C_2-symmetry for bicycle **1**.

In summary, bicyclic guanidine **1** is shown to be an effective catalyst for the asymmetric synthesis of α-amino nitriles and α-amino acids, providing the first clear demonstration of a highly enantioselective catalyst for which the guanidine functionality is alone sufficient for activity. The mechanism proposed herein suggests a cause for the efficacy of the Strecker catalyst described by Lipton et al.,[2d] a guanidine-bearing diketopiperazine, and provides a model for developing new enantioselective methods with guanidine catalysts. The mechanistic explanations of enantioselectivity implied in Figure 1 depend on van der Waals attractive interactions involving nonpolar groups as a source of three-dimensional ordering in the transition state for reaction. Thus, the examples described herein add to a small but growing list of enantioselective processes thought to involve such interactions.[8]

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Supporting Information Available: Full experimental procedures for synthesis and X-ray crystallographic analysis of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See for example: (a) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.