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A New Chiral Catalyst for the Enantioselective Strecker Synthesis of α-Amino Acids

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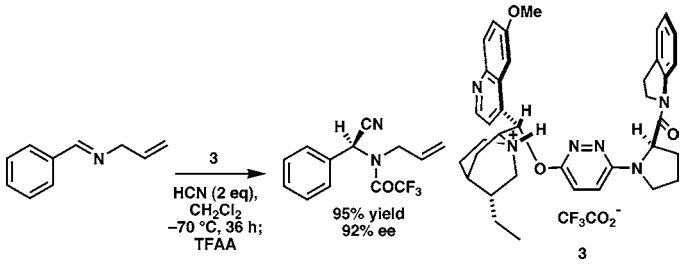
ABSTRACT



The chiral ammonium salt 3 is demonstrated to be an effective catalyst for the highly enantioselective Strecker reaction of *N*-allylbenzaldimines with hydrogen cyanide in CH_2Cl_2 solution.

The Strecker hydrocyanation of aldehydes[1] to α-amino nitriles provides a short and practical route to (±)-α-amino acids. For this reason there have been numerous attempts to develop enantioselective versions of this reaction in recent years.[2] A variety of chirally coordinated Lewis acids have been studied with Al,[3] Ti,[4] Zr,[5] and lanthanide[6] metal centers. A number of metal-free chiral carbogenic catalysts have also been described, including diketopiperazines,[7] C_2-symmetric bicyclic guanidines,[8] ureas or thioureas,[9] and bis-*N*-oxides.[10] We report herein the successful development of yet another type of catalyst for the enantioselective process, a chiral ammonium salt that possesses an activating site and a binding pocket for *N*-allyl aldimines as substrates.

The starting point for the development of the new catalyst for the enantioselective Strecker reaction was the successful design and demonstration of catalyst **1** for the enantioselective dihydroxylation of olefins by OsO_4.[11] This design was based on extensive mechanistic studies[12−16] of the basis for enantioselection in the cinchona alkaloid-promoted dihydroxylation reaction.[17,18] The use of catalyst **1** with OsO_4 led to the highly enantioselective dihydroxylation of a varied

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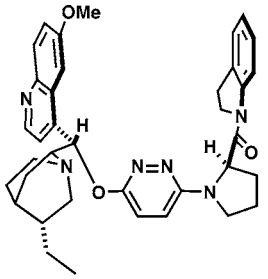
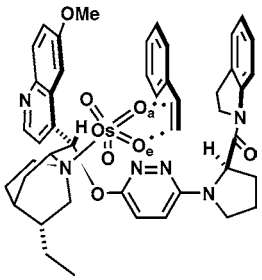
series of olefins to form 1,2-diols with the absolute configurations predicted by the mechanistic model, for example **2** with styrene as substrate.



1



2

The logic behind the application of catalyst **1** to the enantioselective Strecker reaction derived from the idea that the U-shaped binding pocket in the conjugate acid of **1**, the chiral ammonium salt **3**, could be used to hold the aldehyde-derived part of an aldimine that was activated by hydrogen bonding to the protonated quinuclidine moiety of **3** as shown in Figure 1 for the *N*-allylimine of benzaldehyde as substrate.

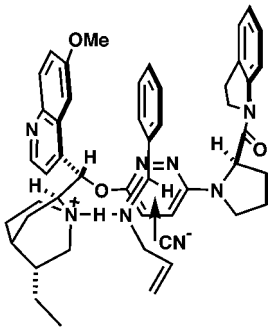
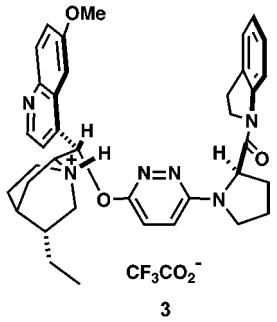


Figure 1. Proposed pre-transition-state assembly for the catalytic hydrocyanation of *N*-allylbenzaldimine.

Attack by cyanide ion on the carbon of the hydrogen-bonded imine would lead to an α-amino nitrile, the Strecker product. Three-dimensional molecular modeling of the pre-transition-state assembly shown in Figure 1 reveals that cyanide should attach to the *re* face of the aldimine carbon to produce the (*S*)-α-amino nitrile.



3

Reaction of **1**[11] with trifluoroacetic acid generated a stable crystalline salt that functioned very well as a catalyst for the Strecker reaction of HCN with a series of *N*-allylbenzaldimines.[19] In the case of the parent *N*-allylbenzalimine, hydrocyanation occurred smoothly with 2 equiv of hydrogen cyanide and 10 mol % catalyst **3** in CH_2Cl_2 solution at −70 °C for 36 h to give the corresponding (*S*)-α-amino nitrile in 95% yield and 92% enantiomeric excess after column chromatography on silica gel, which also afforded recovered reagent **1** with ca. 90% efficiency. The enantioselective Strecker reaction was also carried out with several other benzaldimines with excellent results, as summarized in Table 1.[20,21] Enantioselectivities were determined by HPLC or GC analysis of the *N*-trifluoroacetyl derivatives of the α-amino nitriles using chiral columns, and absolute configurations (*S*

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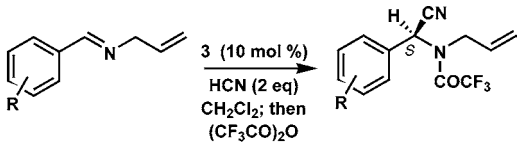
(19) Pure *N*-allylimines were prepared by combining the corresponding aldehyde, magnesium sulfate, and allylamine in benzene at room temperature, removing solvent and distilling in vacuo. The imines were stored at −20 °C (freezer) until use.

(20) For **3**: $[\alpha]_{22}^{D} = -66$ (*c* 1.0, $CHCl_3$). Mp: > 150 °C. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 13.61 (s, 1 H), 8.68 (d, *J* = 4 Hz, 1 H), 8.09 (t, *J* = 5 Hz, 2 H), 7.64 (s, 1 H), 7.46 (dd, *J* = 10, 2 Hz, 1 H), 7.41 (d, *J* = 5 Hz, 1 H), 7.37 (s, 2 H), 7.19 (d, *J* = 7 Hz, 1 H), 7.12 (t, *J* = 7 Hz, 1 H), 7.00 (m, 2 H), 6.83 (d, *J* = 10 Hz, 2 H), 4.78 (d, *J* = 9 Hz, 1 H), 4.30 (m, 1 H), 4.04 (s, 3 H), 3.99 (m, 1 H), 3.69 (m, 1 H), 3.58−3.48 (m, 4 H), 3.39 (m, 1 H), 3.30 (m, 1 H), 3.20 (m, 2 H), 2.65 (t, *J* = 9 Hz, 1 H), 2.29 (m, 1 H), 2.19 (m, 1 H), 2.08 (m, 3 H), 1.91 (m, 3 H), 1.75 (m, 4 H), 1.38 (m, 1 H), 1.01 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (CD_2Cl_2, 400 Hz): δ 170.61, 162.67, 162.33, 159.86, 155.55, 145.43, 143.50, 131.51, 127.37, 126.83, 124.63, 123.73, 118.83, 118.10, 117.80, 100.76, 71.98, 59.73, 58.89, 56.98, 49.75, 49.52, 48.03, 47.70, 35.22, 30.02, 28.38, 25.48, 24.98, 24.11, 23.80, 18.98, 11.50 ppm. ^{19}F NMR (CD_2Cl_2, 400 Hz): −76.06 ppm. FTIR (cm^{-1}, film): 1660, 1461, 1415, 1187, 1129, 983, 825, 756. HRMS calcd for $[C_{37}H_{43}N_6O_3 + H^+]$, 619.3396; found, 619.3386.

(21) ***CAUTION:*** *HCN is highly toxic and must be kept in a well-ventilated hood and handled with protective gloves.* General procedure for the asymmetric Strecker reaction: To a clear solution of aldimine (0.2 mmol) and catalyst **3** (21 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) under nitrogen was added liquid HCN (0.015 mL, 0.4 mmol by precooled syringe; or TMSCN (0.056 mL, 0.4 mmol) followed by 2-PrOH (0.03 mL, 0.4 mmol)). The resulting homogeneous solution was kept at −70 °C until all of the aldimine had been consumed as monitored by TLC analysis (16−48 h). The reaction mixture was treated with TFAA and flushed with a stream of N_2 that was passed through bleach to remove HCN and then concentrated under vacuum. The residue was taken up in a minimum amount of dichloromethane and purified by silica gel column chromatography to give the product (elution with 1−5% ethyl acetate in hexanes) and the recovered chiral reagent **1** (80−95%, eluted with 95:5 EtOAc−Et_3N). Enantiomeric excess was determined by GC or HPLC analysis of the *N*-trifluoroacetyl α-amino nitriles using a chiral column as described in ref 9.

Table 1. Enantioselective Strecker Reactions Catalyzed by the Chiral Ammonium Trifluoroacetate **3**



Ar	time (h)	yield (%)	ee (%)
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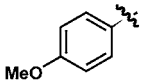
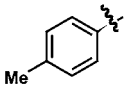
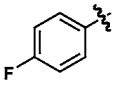
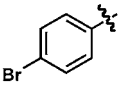
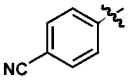
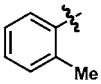
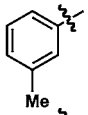
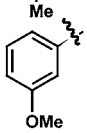
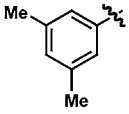
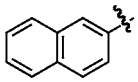
	36	95	90
	36	94	87
	24	96	89
	40	88	85
	24	92	80
	40	86	89
	40	98	>99
	40	96	>99
	48	88	90
	40	95	79

in all cases) were established by measurement of optical rotation and comparison with literature data.[9] The formation of (*S*)-configured Strecker products accords with the mechanistic rationale/pre-transition-state assembly shown in Figure 1. The aromatic ring of the substrate and the N^+-H-N hydrogen bond hold the iminium linkage just above the pyridazine linker, which blocks the rear face of the C=N function. Attack by CN^- on the C=N carbon must therefore occur at the face opposite the pyridazine ring (*re* face). The binding pocket that holds the aromatic part of the aldimine is thought to consist of the dihydroindole and quinoline rings (approximately 7.5 Å apart in almost parallel planes) and the N_2 part of the pyridazine linker. It is possible that the nucleophile is not free CN^- but a complex of hydrogen cyanide and trifluoroacetate ion. In this regard, it is noteworthy that although the free quinuclidine **1** catalyzes the addition of HCN (2 equiv) to *N*-allylbenzalimine, the enantiomeric excess of the Strecker product is lower (by 10%) than with **3** as a catalyst under identical conditions.

Allyl was found to be preferable to benzyl as the N-protecting group of the aldimine since enantioselectivities were generally higher. On the other hand, the *N*-benzyhydryl aldimine analogues afforded Strecker products with much lower ees (30−35%), a result that is readily understood as a consequence of steric repulsion between benzyhydryl and the quinuclidine moiety of the catalyst **3**. Another interesting observation was that the use of toluene as the solvent rather than CH_2Cl_2 led to much lower ees of Strecker product. Although this detrimental solvent effect at first sight seems surprising in view of the fact that toluene is traditionally the solvent of choice for enantioselective Strecker reactions, it may be due to the ability of toluene to compete with the aldimine substrate for the U-shaped binding pocket. Aliphatic aldehydes, especially those with bulky groups attached to formyl undergo Strecker reactions in the presence of **3**, but with poor enantioselectivity, as expected from the mechanistic model.

There are several advantages to the enantioselective Strecker process described herein: (1) catalysts **1** and **3** are readily prepared and stable and (2) are easily and efficiently recovered for reuse, (3) the experimental procedure is both convenient and simple, and (4) catalyst **3** produces the natural (*S*)-form of the α-amino acid. Although the mechanistic model summarized by the pre-transition-state assembly in Figure 1 is supported by the results of this investigation, it remains a working hypothesis and further studies are required to confirm it. The model is of special interest because it represents one of only a small group of enantioselective reactions that are thought to depend on an enzymelike interaction between the substrate and a binding pocket within the catalyst.

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