STUDIES ON CHIRALITY TRANSFER THROUGH HYDROGEN BONDING IN STRECKER REACTION : THE CASE FOR AMINO ACIDS

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ABSTRACT: As direct precursors of α -amino acids, α-amino nitrile derivatives have prompted several research groups to develop new routes or improve existing ones to optimize the conditions involved in their synthesis. Efforts have primarily focused on a stereoselectivity and low catalyst loading. Here we report our preliminary results describing the use of simple, low-cost chiral carboxylic acids and α- amino acids as potential catalysts in the hydrocyanation reaction.

Key words: α-amino acids, stereoselectivity, chiral, carboxylic acids, hydrocyanation

RESUME: S'agissant de précurseurs direct aux α-acides amines, les dérivés d'α- amino-nitrile ont suscité l'intérêt de plusieurs groupes de recherche afin de développer de nouvelles voies, ou améliorer les routes existantes, pour optimiser les conditions favorables à leur synthèse. L'intérêt s'est focalisé principalement sur la stéréosélectivité et les faibles ajouts en catalyseurs. Nous présentons dans ce travail nos résultats préliminaires décrivant l'utilisation d'acides carboxyliques chiraux simples et bon marché, de même que celle des acides aminés comme catalyseurs potentiels dans la réaction d'hydro-cyanation de Strecker.

Mots clés: α- acides aminés, stéréosélectivité, acides carboxyliques, hydrocyanation

INTRODUCTION

Several reports described the use of either metallic or non-metallic catalysis in Strecker reactions to generate enantiopure α-amino nitrile derivatives, which are readily transformed to enantiopure α-amino acids. Lipton and coworkers[1a] reported that a dipeptide obtained from S-phenylglycine and L-arginine exhibited excellent catalytic seteroselective induction >99%ee, however the scope was limited and reproducibility was problematic[1b]. C_2–Symmetric bicyclic guanidine has been employed by Corey and coworkers[2] as a catalyst to achieve up to 86%ee. Hoveyda and coworkers[3,4] used a tripeptide modified Schiff base as a ligand for titanium based catalysis. In this instance, the appropriate amount of additives is crucial to obtaining up to 99%ee. Jacobsen and coworkers[5] have screened a variety of salen complexes and reported high enantioselectivity. In the same context, Kobayashi [6] used Zirconium BINOL complexes as catalysts to convert aldimines to amino-nitriles in good yields with high enantioselectivity. Shibasaki and coworkers[7] described an asymmetric approach in the Strecker reaction based on chiral lanthanide – β-hydroxyphosphine oxide complex. Aryl and alkyl ketoimine underwent the hydrocyanation with good yields and enantioselectivity[8]. A more recent report from Khan's group[9] highlighted, for the first time the use of chiral alkaloids as organocatalyst in Strecker reaction.

RESULTS AND DISCUSSION

In this report, we describe our efforts to identify simple, low cost organic catalysts for this transformation. Specifically, we theorized that an appropriate hydrogen bonding network should allow simple chiral organic to induce stereoselectivity in the hydrocyanation reaction of imines.

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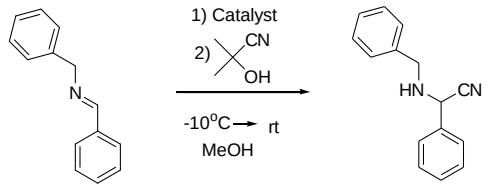
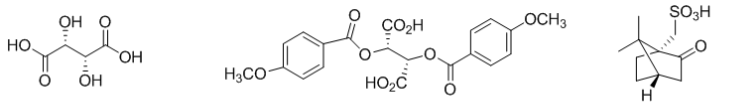
Investigations commenced with acetone cyanohydrin as the hydrocyanating agent due its ease of handling and low toxicity. An initial screen of the imine generated from benzaldehyde and benzyl amine (**1**) was undertaken with stoichiometric chiral acids to determine the feasibility of the approach for simple imines (Scheme 1). The rate of conversion and the enantiomeric excess of the product were determined by ^{1}H NMR and optical rotation respectively (Table 1). No reaction was observed when tartaric acid was used, however camphor sulfonic acid and di-*p*-toluoyl tartaric acid afforded the product with low yield and no significant enatiomeric excess.



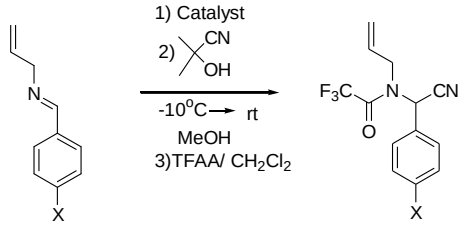
Scheme 1

Table I

Entry	Catalyst	%Conversion (Rxn time)	%ee [α]
1	No catalyst	100 (2h)	racemic
2	Di-p-Toluoyl Tartaric acid	40 (20h)	<5
3	L- Camphorsulfonic acid	30 (2d)	<5
4	Tartaric acid	NR	-



Theorizing that the imine substituent would modulate interactions with the catalyst, the *N*-allyl derivative was explored (Scheme 2). In order to compare the optical rotation of **4** to the literature value, the α-amino nitrile obtained was acetylated by reaction of trifluoroacetic anhydride. Unfortunately, no selectivity was observed (Table 2).



Scheme 2

Table II

Entry	Catalyst	% Conversion (Rxn time)	%ee [α]
1 (X= H)	No catalyst	100 (5h)	racemic
2 (X= H)	Di-p-Toluoyl Tartaric acid	40 (20h)	<5
3 (X= H)	Tartaric acid	>90 (2d)	<5
4 (X= OCH_3)	Di-p-Toluoyl Tartaric acid	30 (20h)	<2

Examination of the molecular model of the imine complexed with tartaric acid (A, Figure 1) reveals that numerous conformational isomers are available to the acid-bound substrate. It is therefore unlikely that one face of the imine would be selectively blocked explaining the low observed selectivity. In the light of these results, we envisioned that greater rigidity and selective shielding could be engineered into the system by means of a two-point binding interaction. Since we desired to use simple, readily available catalysts, the design process commenced with α–amino acids. Using molecular modeling, the *meta*-position of an N-phenyl group was found to position a potential hydrogen bonding group with the correct separation and orientation to complement an α–amino acid (B, Figure 1). AM1 calculations[10] of both complexes in Figure 1 showed that complex II is more stable due to the presence of two hydrogen bonds. The complexation energy was evaluated by substracting the total energy of the minimized individual structures from the total energy obtained for the complex. The two-point binding also rigidified the complex creating a scenario where one face of the imine can be blocked from attack of HCN, which would give rise to a stereoselective process.

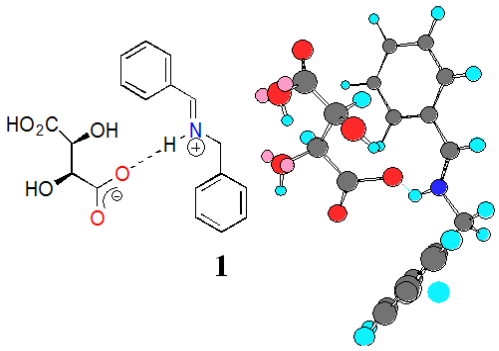


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Figure 1A (complex I)

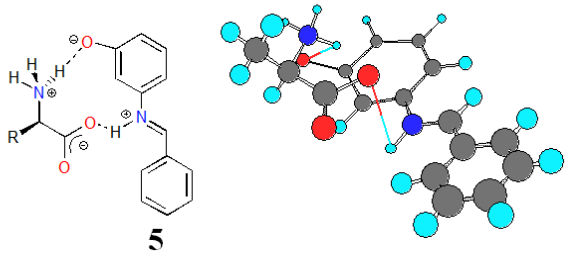

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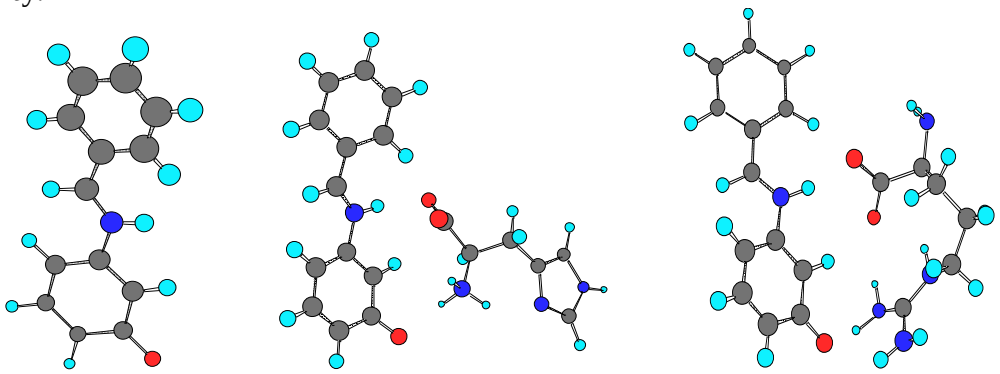
Figure 1B (complex II)

3-(Benzylideneamino)phenol **5** was synthesized by treating 3-hydroxyaniline with benzaldehyde in MeOH or EtOH in the presence of magnesium sulfate as water absorbent. It is worth noting that a protic solvent was essential to obtain this imine. Our attempts to use benzene, toluene with a Dean Stark trap or with $MgSO_4$ were unsuccessful and a brick colored solid was obtained that could not be identified.[11]

The background reaction of acetone cyanohydrin with imine **5** was conducted in methanol at room temperature and monitored by ^1H NMR spectroscopy, which showed complete disappearance of the peak at 8.4 ppm after 50 hrs. The product is sufficiently stable to be fully characterized and to undergo HPLC analysis. A direct assay of the product enantioselectivity was obtained via chiral stationary phase HPLC without any need for derivatization of the obtained amino nitrile product **6** (Scheme 3).

Table 3 summarizes the results from the hydrocyanation of **5** with a series of amino acids catalysts. A strong rate acceleration was observed when arginine (entry 7) was used in methanol; the reaction reached completion in less than 90 min. However, this rate increase was accompanied by a loss of selectivity. Similarly, L-histidine showed rate acceleration when the reaction was conducted in methanol (entry 10). An encourageing level of enantioselectivity (27% ee) was observed with L-histidine in toluene despite the poor solubility of the catalyst, which negatively affected the rate of the reaction (Entry 11). AM1 calculations performed on both complexes imine **5** -L-histidine and imine **5**-L-arginine provided heats of formation of 16.7 kcal/mol and –34.9 kcal/mol, respectively. These data explain the difference in the reaction rates observed in the presence of the corresponding amino acids (Figure 2). Furthermore the models reveal that neither

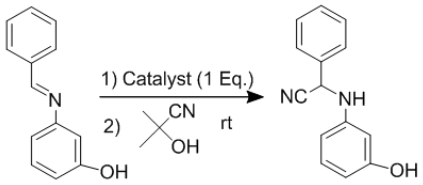
face of the iminium is highly blocked by the catalyst in line with the low observed enantioselectivity.



Relative reaction rate (k_{rel})	1	2	30

Figure 2

Additional unnatural amino acids with greater hydrophobicity and rigidity were investigated in order to increase the solubility and decrease the number of potential conformers (Table 3, entries 17-20). However, no significant enhancement of enantioselectivity was observed. The best selectivity in this series was obtained with tetrahydroisoquinoline carboxylic acid (20 %ee) in MeOH. The reaction rate decreased considerably when the reaction was performed in toluene due to the low solubility of the carboxylic acid.



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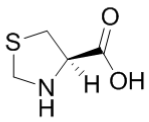
Scheme 3

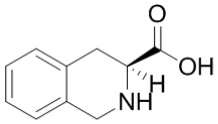
Table III

Entry	Catalyst	Solvent	% Conversion (Rxn time)	%ee
1	No catalyst	CH_3OH	100 (50h)	racemic
2	L-Proline	CH_3OH	100 (5d)	14
3	L-Proline	$PhCH_3$	82 (3d)	10
4	L-terLeucine	CH_3OH	100 (20h)	<2
5	L-Isoleucine	CH_3OH	100 (3d)	<2
6	L- PhenylGlycine	CH_2Cl_2	80 (5d)	4
7	L-Arginine	CH_3OH	100 (90 min)	< 2
8	L-Arginine	CH_3OH (-10°C)	100 (4h)	5
9	L-Arginine	$PhCH_3$	75 (3d)	6
10	L-Histidine	CH_3OH	100 (28h)	5
11	L-Histidine	$PhCH_3$	45 (3d)	27
12	L-Histidine (10%mol.)	$PhCH_3$	40 (3d)	10
13	L-Histidine	CH_2Cl_2	NR	-
14	N-Benzyl- L-Histidine	CH_3OH	100 (18h)	6
15	N-Benzyl- L-Histidine	$CHCl_3$	80 (3d)	20

Entry (continuation)	Catalyst	Solvent	% Conversion (Rxn time)	%ee
16	N-Benzyl- L-Histidine	CF_3CH_2OH	70 (4d)	5
17	L-Tetrahydroisoquinoline carboxylic acid	CH_3OH	100 (40h)	20
18	L-Tetrahydroisoquinoline carboxylic acid	$PhCH_3$	100 (4d)	12
19	L-Tetrahydroisoquinoline carboxylic acid	CH_2Cl_2	NR	-
20	L-Thiazolidine carboxylic acid	CH_3OH	100 (3d)	9



L-Thiazolidine carboxylic acid



L-Tetrahydroisoquinoline carboxylic acid

In summary, the use of simple α-amino acids in stochiometric or catalytic amounts in the Strecker reaction did not induce stereoselectivity despite enhancing reactivity. Thus, the results do support that complexation and activation occurs in a two-point manner with α–amino acids and imine **5**. In addition, the criteria for a selective catalyst are now apparent: 1) solubilizing groups need to be incorporated into the catalysts to allow the reactions to be conducted in hydrophobic solvents that promote the hydrogen bonding complexation between the substrate and the catalyst and 2) either the positioning group on the substrate needs to be moved to allow more effective blocking of one stereoface of the imine or a more elaborate amino acid side chain is needed that utilizes additional secondary interaction (e.g., π–π stacking) to block one stereoface of the imine.

Experimental section

Melting points were determined in unsealed capillary tubes and are uncorrected. NMR spectra were recorded at 20-25 °C at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solution and chemical shifts are reported in ppm relative to trimethylsilane. Mass spectra were recorded using electron impact. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}) and visualization was accomplished with UV light. Flash column chromatography on silica gel was performed with Merck Kiesegel 60. Enantiomeric excess was determined by chiral HPLC analysis using a Daicel OD column.

3- (Benzylidene- amino) phenol (5)

To a mixture of 3-hydroxyaniline (1.09 g, 10 mmol) and $MgSO_4$ (500 mg) in MeOH (15 mL), 1.0 eq (1 mL, 10 mmol) of benzaldehyde is added. The reaction mixture is allowed to stir until all the benzaldehyde is consumed, as indicated by ^{1}HNMR. The solution is then filtered off and the filtrate is concentrated under vacuum to yield yellowish oil, which was triturated with ether to afford **5** as a white solid in 30%Yield. Mp 186-190^{o}C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.1 (s, 1H), 7.7-7.6 (m, 2H), 7.3-7.2 (m, 3H), 7.1-7.0 (m, 1H), 6.6-6.5 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 154.3, 137.3 132.6, 131.0, 130.7, 129.8, 114.3, 113.0, 108.9, 108.6, 106.8, 103.9).

2-Phenyl-2-N (3-hydroxyphenyl) amino acetonitrile (6)

A mixture of imine **5** (0.125 mmol, 24.6 mg) and 1 equivalent of catalyst is allowed to stir at room temperature for 15 min under atmosphere of N_2. Acetone cyanohydrin (3eq. 34.35 μL) is added via syringe. When the reaction reached completion as judged by ^{1}H NMR, the mixture is washed with water and

extracted with dichloromethane. After drying over $MgSO_4$ the solution is concentrated and the residue chromatographed with Hexane/ EtOAc: 5/1.

mp (racemic): 25-28°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, 6.2 Hz, 2H), 7.48-7.43 (m, 3H), 7.11(t, J = 8 .0 Hz, 1H), 6.36 (dt, J = 2.0 Hz, J = 8.3 Hz), 6.28 (m, 1H), 5.39 (d, J= 8.2 Hz, 1H), 5.2 (bs, 1H), 4.03 (d, J = 7.9 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$)δ 156.7, 146.2, 133.7, 130,6, 129.6, 129.4, 127.3, 118.0, 107.3, 106.8, 101.2, 50.1.

Chiral HPLC (OD): 70:30 hexanes: iPrOH, 1 mL/min; $t_R(1)$ = 14.85 min, $t_R(2)$ = 23.58 min.

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