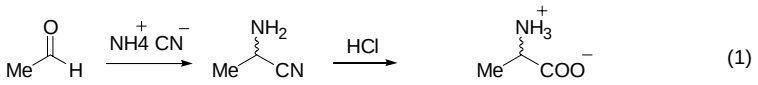
CATALYTIC ENANTIOSELECTIVE STRECKER-TYPE REACTIONS

Reported by Tommy Bui November 14, 2001

INTRODUCTION

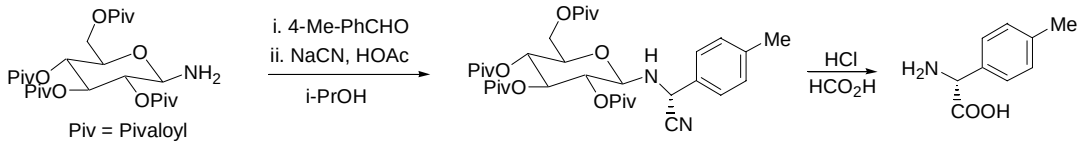
Natural and unnatural α-amino acids are important building blocks of peptides[1] and proteins.[2] They are also widely distributed in natural products and glycopeptide antibiotics.[3] An attractive, low-cost approach to these α-amino acids is the Strecker reaction, a three-component reaction of ammonia (or an amine), an aldehyde, and hydrogen cyanide (eq 1).[4] The Strecker product, an α-amino nitrile, can be hydrolyzed to afford the corresponding α-amino acid without epimerization.



(1)

Traditionally, optically pure α-amino acids can be obtained via the Strecker reaction with the use of chiral auxiliaries (Scheme 1).[5] However, the use of chiral auxiliaries requires extra steps for their introduction into the substrate and removal from the product. Moreover, these chiral auxiliaries are often expensive and difficult to recover. These limitations substantially hinder the use of this method for large-scale synthesis of α-amino acids. On the other hand, catalytic Strecker-type reactions require only a small, reusable quantity of a chiral source to achieve a comparable degree of asymmetric induction. Since the chiral source is not incorporated into the substrate, not only does this approach require fewer steps, but it is also more economical. In fact, catalytic, enantioselective-type reactions have recently become a widely used method for α-amino acid synthesis.[6]

Scheme 1. Chiral Auxiliary Approach

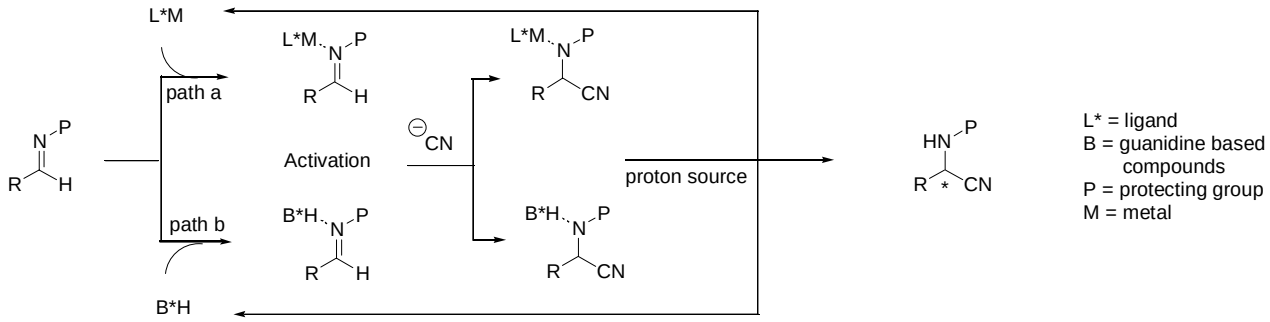


CATALYTIC, ENANTIOSELECTIVE STRECKER-TYPE REACTIONS

In general, catalytic, enantioselective Strecker-type reactions involve the addition of cyanide ion to an imine, either preformed or generated in situ from an amine and aldehyde. Catalysis is accomplished by electrophilic activation of the imine, either by a Lewis acid or via noncovalent

interactions such as hydrogen bonds (Scheme 2). In order for these processes to be catalytic, the species that is involved in the imine activation must be released after the addition of the cyanide. In some cases, an additive is needed to enhance the rate of this final step. Finally, asymmetric induction is achieved through the chiral environment provided by the catalyst. Currently, the catalysts are categorized into two general classes: metal complexes and guanidine-based compounds. The former act as Lewis acids, whereas the latter involve noncovalent activation. Highly enantiomerically enriched α-amino nitrile adducts of various imines are obtained in good yields with these two catalytic systems.

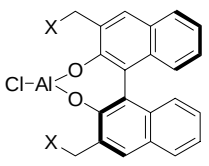
Scheme 2: Concept of Imine Activation



Bifunctional Aluminum Catalyst 1

Aluminum complex **1a** has been identified as a bifunctional catalyst because of its proposed dual activation of both the electrophile and nucleophile in the asymmetric cyanosilylation of aldehydes.[7] As a result, the use of this catalyst has been extended to the enantioselective Strecker-type reaction.[8] The addition of phenol and trimethyl silyl cyanide (TMSCN) to the fluorenyl imine **2** at – 40 ^{o}C in the presence of **1a** affords the corresponding α-amino nitrile **3** (eq 2). Good yields and enantiomeric ratios (er) were obtained with aromatic imines. α-Amino nitrile adducts of enolizable and non- enolizable aliphatic imines were also obtained in good yields, although only in moderate er.

X = $OPPh_2$ (**1a**)
X = $CHPh_2$ (**1b**)



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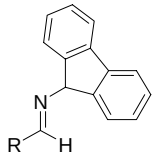
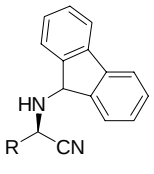


2

1a (9 mol%)
i. TMSCN (2 equiv)
ii. PhOH (20 mo%)

CH_2Cl_2, -40^{o} C, 44h



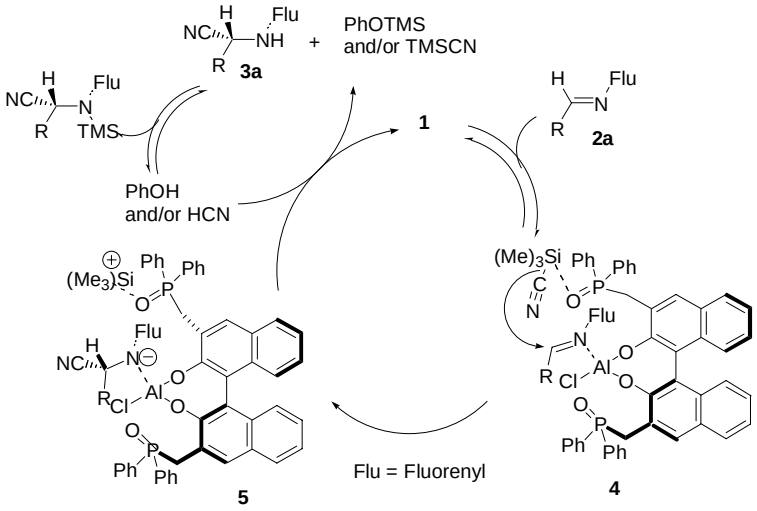
3

(2)

imines	R	product	yield (%)	er
2a	Ph	**3a**	92	98 : 2
2b	iso-Propyl	**3c**	89	86 : 14
2c	t-Butyl	**3d**	97	89 : 11

In all cases, the use of a fluorenyl group on the imines and slow addition of phenol to the reaction mixture were found to be crucial for achieving high er. The catalytic cycle (Scheme 3) involves the coordination of the imine **2a** and TMSCN to the catalyst, generating alumium-imine complex **4**. Subsequent attack of cyanide ion upon the imine produces intermediate **5,** which is protonated by PhOH and /or HCN to afford the α amino nitrile **3a**, releasing **1** back into the cycle.

Scheme 3: Catalytic Cycle



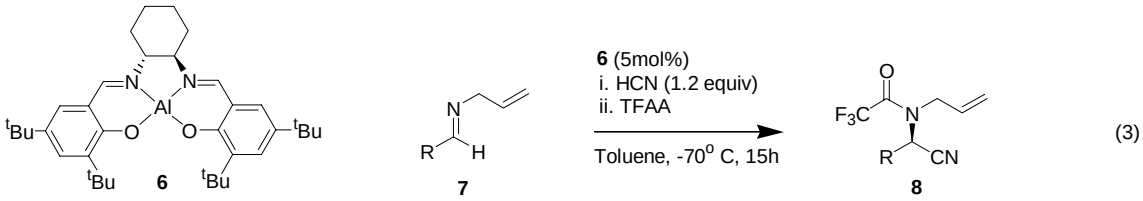
In this cycle, the author proposes that electrophilic activation of the imine **2a** is achieved by its coordination to the aluminum, while nucleophilic activation of TMSCN is accomplished by its coordination to one of the diphenyl phosphine oxides. Replacement of the diphenyl phosphine oxides by diphenyl methylenes (**1b**) provides the opposite enantiomer *S*-**3a**, with 58:42 er (100 % yield, 42h). This experimental result indicates the phophine oxides, as Lewis basic sites, are crucial for achieving high er, and it is used by the author as one of the supports, besides the absolute configuration of the product, for the mechanism proposed nucleophilic activation. However, one can argue that since the rate of catalysis of **1a** is very similar to that of **1b** (42h), it is not necessary to invoke nucleophilic activation in the former case. The drastic discrepancy in er between the two cases, however, suggests that the diphenyl phosphine oxides can act as directing groups, coordinating the TMSCN in such a way that leads to the high enantioselectivity.

Another indirect piece of evidence for the proposed mechanism is that slow addition of PhOH to TMSCN allows the generation of HCN at low concentration, so that either HCN or PhOH can act as a proton source to assist the release of the amino nitrile adduct from **5**, thus enhancing the rate of catalyst turnover. Finally, the absolute configuration of **3a** can be explained by the working model **4** (Scheme 3). The π-stacking interaction between the fluorenyl group of the imine and the naphthyl moiety of the catalyst is believed to provide stability to the transition state structure **4**. The coordination of TMSCN to one of the diphenyl phosphine oxides allows the cyanide ion to preferentially attack the *si*-face of the imine in **4**, leading to the *R* configuration of **3a**.

Chiral (Salen) Aluminum (III) Complex

Another type of chiral aluminum complex that catalyzes enantioselective addition of cyanide ion to N-allyl imines was reported by Jacobsen.[9] The aluminum catalyst **6** has been identified through

screening of a series of metal complexes.[10] α-Amino nitrile derivatives of aromatic imines are obtained in good yields and high er by treating the N-allyl imine **7** with HCN at – 70 °C in the presence of **6** (eq 3). However, the amino nitrile adducts of imines of enolizable and non-enolizable aliphatic aldehydes are obtained only in moderate yields with low er.

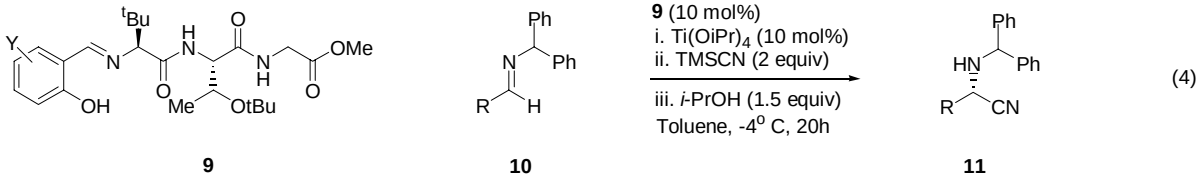


(3)

imines	R	product	yield (%)	er
7a	Ph	**8a**	91	98 : 2
7b	*p*-MeOPh	**8b**	99	97 : 3
7c	*t*-Butyl	**8c**	69	69 : 31

Titanium Tripeptide Schiff Base Complex

The combination of the Schiff base ligand **9** and titanium isopropoxide as a catalyst was identified through screening by Snapper and Hoveyda in 1999.[11] The addition of TMSCN to the imine **10** in the presence of **9** and titanium isopropoxide ($Ti(OiPr)_4$), followed by a slow addition of isopropanol (*i*-PrOH) provides the α-amino nitrile **11** (eq 4). Good yields and moderate to high er are obtained with both aromatic and non-enolizable aliphatic aldehydes.

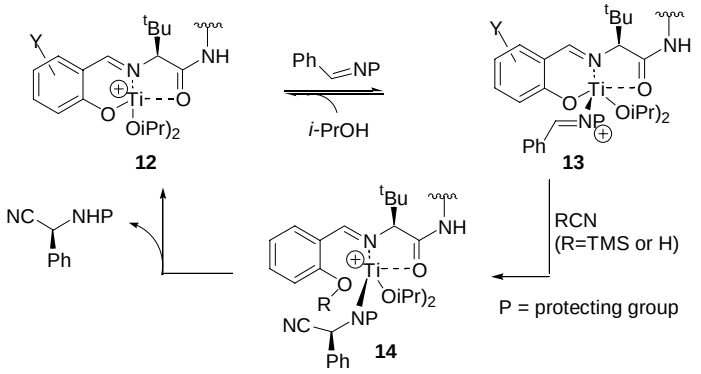


(4)

imines	R	product	Y	yield (%)	er
10a	Ph	**11a**	5-OMe	82	99 : 1
10b	*o*-MePh	**11b**	3,5-DiCl	99	97 : 3
10c	*t*-Butyl	**11c**	3,5-DiBr	97	93 : 7

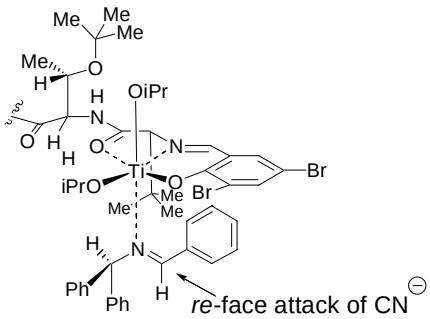
The catalytic cycle involves the generation of the catalyst active species **12** by mixing **9** with $Ti(OiPr)_4$ in a 1:1 ratio (Scheme 4). The titanium complex **12** is proposed to be the catalyst active species, although there is no direct evidence for it. Complexation of **12** with the substrate provides titanium-imine complex **13**, which undergoes nucleophilic addition of cyanide ion to give α-amino nitrile bound complex **14**. The coordination of the phenoxy to the titanium of **14** releases the α-amino nitrile adduct and regenerates the titanium catalyst **12** back into the cycle.

Scheme 4: Proposed Catalytic Cycle



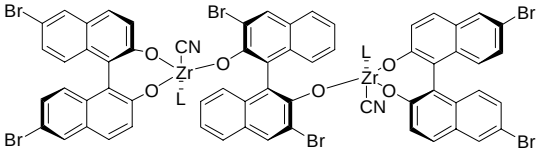
In this cycle, the catalyst turnover step involves the cleavage of the Ti-N bond in complex **14**. Again, this step is presumably facilitated by HCN, which is generated by the reaction between isopropanol and TMSCN. Since the authors do not provide a stereochemical rationale for the observed absolute configuration of the α-amino nitrile adduct, the working model **13a** (Figure 1) is proposed. According to this model, the *si*-face of the imine is blocked by the tert-butyl group α to the carbonyl group bound to the titanium. This forces cyanide ion to preferentially attack the *re*-face of the imine, leading to the *S* configuration of the amino nitrile adduct.

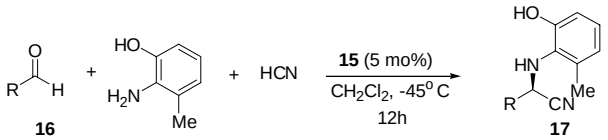
Figure 1. Stereochemistry



Chiral Zirconium Catalyst

Recently, chiral zirconium catalysts have been shown to catalyze enantioselective Mannich-type reactions.[12] Studies of ligand modification around the zirconium center[13] have led to the discovery of the zirconium catalyst **15**. The addition of a mixture of the aldehyde **16** and 2-amino-3-methyl phenol to the solution of **15** in CH_2Cl_2 produces the α-amino nitrile derivative **17** (eq 5). Excellent er and yields are obtained with aromatic and aliphatic aldehydes.[14] The mechanism of this zirconium catalyzed Strecker-type reactions is still under investigation.



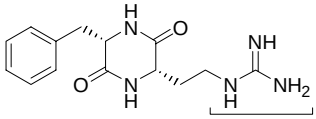


(5)

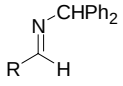
RCHO	R	product	yield (%)	er
16a	$Ph(CH_2)_2$	**17a**	85	97 : 3
16b	iso-Butyl	**17b**	99	97 : 3
16c	t-Butyl	**17c**	95	97 : 3

Guanidine-Based Catalysts:

In addtion to the metal complex catalysts, alternative catalysts have also been developed for enantioselective Strecker-type reactions. An analogue of the guanidine **18** has been shown to catalyze the asymmetric cyanation of aldehydes.[15] In 1996, Lipton first demonstrated the use of **18** in catalytic, enantioselective Strecker-type reactions.[16] α-Amino nitrile derivative **20** was obtained from benzhydryl imine **19** using 2 mol % of **18** (eq 6). Good er and yields were obtained with aromatic imines, but low er was obtained with aliphatic substrates.

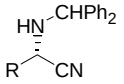


18 Guanidine side chain



19

18 (2 mol%)
HCN (2 equiv)
MeOH, -75° C

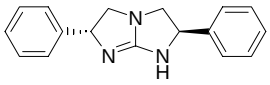


20

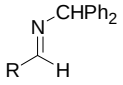
(6)

imines	R	product	yield (%)	er
19a	*p*-ClPh	**20a**	94	99 : 1
19b	*p*-MeOPh	**20b**	90	98 : 2
19c	t-Butyl	**20c**	80	59: 41

There was no mechanistic proposal at the time of discovery of this catalyst. However, a few years later, another guanidine-based catalyst for Strecker-type reactions was reported by Corey with a full mechanistic proposal.[17] α-Amino nitrile derivatives of benzhydryl imines were prepared in good yields with moderate er using catalyst **21** (eq 7). With imines of aliphatic aldehydes, the desired products were also obtained in good yields with moderate er (82:18 to 92:8). The proposed mechanism involves the formation of HCN-guanidine complex **24** (Scheme 5) via hydrogen bonding. Subsequent hydrogen bonding of benzhydryl imine **22a** and **24** generates guanidinium **25**. Cyanide addition to the activated imine provides the amino nitrile **23a** and releases the catalyst back into the cycle.

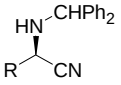


21



22

23 (10mol%)
HCN (2 equiv)
Toluene
-20° C or -40° C



23

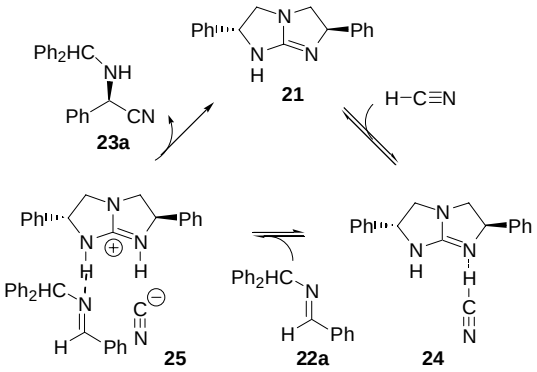
(7)

imines	R	product	yield (%)	er
22a	Ph	**23a**	96	93 : 7
22b	*p*-MeOPh	**23b**	99	92 : 8

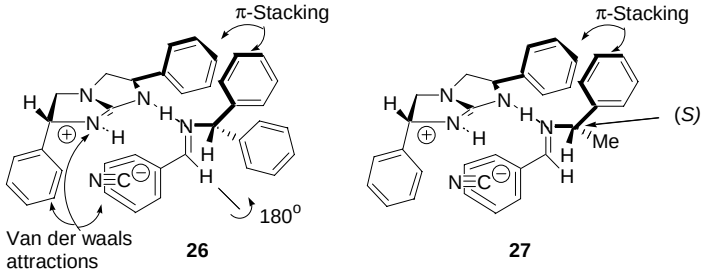
The origin of the enantioselecitivity of the catalyst **21** can be explained by the working model **26** (Scheme 6). Hydrogen bonding allows HCN, the catalyst, and the imine **22a** to be in a close proximity. The π-stacking interaction between the proximal phenyl group of **21** and one of thebenzhydryl phenyls assists positioning the imine in the orientation as shown in **26**. van der Waals attractions[18] (Scheme 6)

between the aryl π-conjugated to the imine **22a** and the guanidine core and the distal phenyl of the catalyst are invoked to explain this favorable orientation. Meanwhile, the other benzhydryl phenyl group blocks the *re*-face of the imine while leaving the *si*-face open to the attack of cyanide ion to give the *R* configuration of the product **23a**. A 180^{o} rotation of the imine **22a** about the N-H bond axis exposing the *si*-face of the imine is unfavorable due to the loss of the van der Waals attractions.

Scheme 5: Proposed Mechanism



Scheme 6: Stereochemistry



To support the stereochemical rationale above, studies of Strecker-type reactions of HCN and enantiomeric pure imines **27** from benzaldehyde and (*S*)-1-phenethylamine and (R)-1-phenethylamine have been performed. With the (*S*)-imine **27** (Scheme 6, **27**), a 94:6 R/S diastereoselectivity was obtained, while with the (*R*)-imine **27** (not shown), the R/S diastereoselectivity dropped to 58:42. These results clearly indicate that the orientation of enantiomeric pure imines **27** is similar to what is proposed in the working model **26**. Moreover, the replacement of the aryl groups of the catalyst by cyclohexyl derivatives leads to a decrease in the er of the α-amino nitrile **23a** (78:22), presumably because of the loss of π-stacking and van der Waals attractions.

SUMMARY

The catalysts discussed so far all effectively catalyze Strecker-type reactions in excellent yield with moderate to high enantioselectivity for imines of aromatic aldehydes. However, with imines derived from aliphatic aldehydes, low to moderate er are obtained. The zirconium catalyst is superior over other catalysts because it gives excellent enantioselectivity with both aromatic and aliphatic aldehydes. As for reactivity, an additive is required when TMSCN is used as a cyanide source. The Salen aluminum and the acyclic guanidine catalysts are more active than the rest (reactions at low catalyst loadings and at low temperature). The titanium catalyst is the least active.

CONCLUSION

Catalytic, enantioselective Strecker-type reactions have been shown to be a powerful method for synthesis of enantiomerically pure natural and unnatural α-amino acids from easily accessible starting materials. Metal complexes and guanidine-based catalysts efficiently catalyze these reactions to afford α-amino nitrile derivatives in good yield and in good to excellent enantioselectivity. The hydrolysis of the nitrile functionality into the corresponding carboxylic acid is performed under drastic conditions. This might give a problem with functional group compatibility in complex molecule synthesis. To fully explore the utility of catalytic, enantioselective Strecker-type reactions, a mild method for conversion of a nitrile funtionality into the corresponding carboxylic acid must be developed. The realization of these asymmetric processes on an industrial-scale will be also the next challenge for future investigations.

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