Strecker Reaction

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# The Catalytic Asymmetric Strecker Reaction: Ketimines Continue to Join the Fold

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asymmetric synthesis · cyanides · homogeneous catalysis · ketimines · Strecker reaction

*Dedicated to Prof. John (Seán) Corish on the occasion of his 65th birthday*

The operational simplicity, relative atom economy, and ready availability of starting materials make the Strecker synthesis a cornerstone technology for the preparation of both natural and unnatural α-amino acids today—over 150 years after Adolf Strecker first reported the synthesis of alanine by the hydrolysis of the adduct formed from the addition of ammonia and hydrogen cyanide to acetaldehyde. The addition of HCN to a preformed imine in general is often referred to as the Strecker reaction.[1] Over 100 years passed before the first asymmetric Strecker synthesis using a chiral imine formed in situ was accomplished,[2] and it was not until the mid-1990s that the development of general, enantioselective catalytic Strecker processes gathered appreciable pace.[3] Currently a surfeit of catalyst systems capable of promoting highly efficient asymmetric Strecker reactions to form chiral α-amino nitriles from aldimines are available.[3,4] The corresponding processes using ketimine substrates have proved somewhat more difficult and of narrower scope, with the first effective catalytic asymmetric system reported in 2000.[5] Ketimines are less electrophilic than their aldimine counterparts, however of importance in the context of asymmetric catalysis is their lower potential for discrimination between the enantiotopic ketimine faces by a catalyst owing to the presence of a relatively bulky alkyl moiety in place of the small aldimine hydrogen substituent. Unsurprisingly therefore, the catalytic enantioselective hydrocyanation of aliphatic ketimines (in particular those not derived from methyl ketones) is a significant challenge. Notwithstanding these difficulties, the medicinal and biological relevance of α,α-disubstituted amino acids, which are not readily available directly from the chiral pool, has provided significant impetus to the search for selective catalyst systems compatible with these substrates.[6,7] A short monologue on this topic detailing early successes appeared in 2004;[8] the objective of this Highlight is to present selected subsequent developments.

In 2003, Shibasaki and co-workers reported on a bimetallic gandolinium-based catalyst capable of promoting enantioselective Strecker reactions of *N*-diphenylphosphanoyl ketimines **1** (Scheme 1) with moderate to good enantioselectivity.[9a] The catalyst was formed in situ by mixing $Gd(OiPr)_3$ and D-glucose-derived ligand **3** in a 1:2 ratio, although the active species was postulated to be a 2:3 complex, represented by **4**. In attempting to expand the scope of these reactions to include heterocycle-substituted and cycloalkanone-derived ketimines, it was observed that the enantioselectivity of the addition reaction, which was initially poor, increased dramatically at high catalyst loadings. Speculating that the improvement was due to the excess of ligand **3** acting as a Brønsted acid capable of protodesilylation, the authors found that the addition of stoichiometric amounts of 2,6-dimethylphenol **5** led to substantial improvements in both reactivity and selectivity (Scheme 1) at −40 °C. Thus, α-amino nitriles derived from challenging cyclic, heterocycle-substituted, aliphatic-ketone-derived, and (significantly) non-methyl-ketone-derived ketimine substrates **6**–**9** could be isolated in excellent yield and enantioselectivity, and at low catalyst loadings. It was proposed that the catalytically active species in the presence of **5** is desilylated **4a** (detected by mass spectrometry upon the addition of **5** to **4**), which acts as a bifunctional catalyst which is able to coordinate the imine electrophile, deliver a bound cyanide ion to a single imine face (**A**), and subsequently protonate the resulting tetrahedral intermediate (**B**).[9b,10] The high potential utility of this reaction was underscored by its use in the enantioselective synthesis of (+)-lactacystin[11] and key chiral precursors to antifungal agents.[12] It was subsequently demonstrated that both reactivity and selectivity depended strongly on the three-dimensional organization of the ligands. For example, an attempt to crystallize the catalytically active species resulted in a complex that catalyzed the formation of the opposite product enantiomer to that afforded by a catalyst generated in situ using the same ligand with excellent enantioselectivity.[13]

Recently Rueping et al. reported that axially chiral phosphoric acid derivatives, such as **10**, that are capable of activating imines substituted with simple *N*-alkyl protecting groups could promote highly enantioselective Strecker reactions of aldimine substrates.[4g] When this methodology was applied to the corresponding ketimines, the adducts were isolated with lower but appreciable levels of enantiomeric excess (Scheme 2).[14] Although this methodology is not as selective and efficient as the benchmark thiourea catalyst systems pioneered by Jacobsen and Vachal[15] for use with

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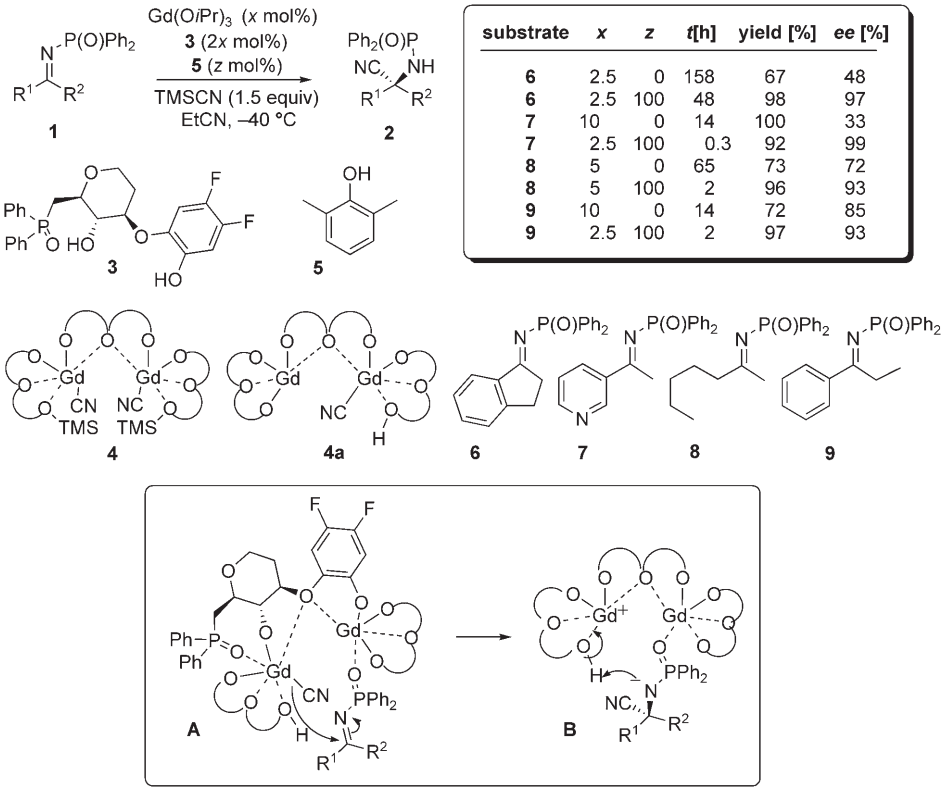
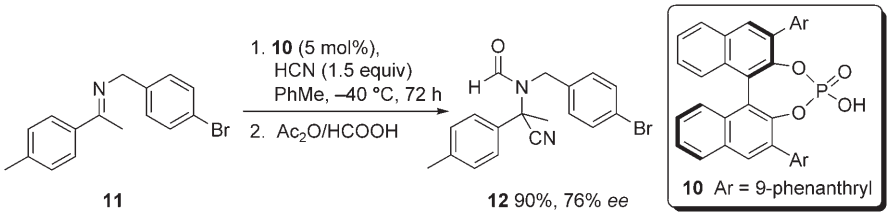



| substrate | x | z | t[h] | yield [%] | ee [%] |
|---|---|---|---|---|---|
| 6 | 2.5 | 0 | 158 | 67 | 48 |
| 6 | 2.5 | 100 | 48 | 98 | 97 |
| 7 | 10 | 0 | 14 | 100 | 33 |
| 7 | 2.5 | 100 | 0.3 | 92 | 99 |
| 8 | 5 | 0 | 65 | 73 | 72 |
| 8 | 5 | 100 | 2 | 96 | 93 |
| 9 | 10 | 0 | 14 | 72 | 85 |
| 9 | 2.5 | 100 | 2 | 97 | 93 |

***Scheme 1.*** Bimetallic catalysts for the Strecker reaction and the beneficial effects of a phenolic additive **5**. $R^1$, $R^2$ shown in substrates **6**–**9**; ligand **3** shown coordinated schematically to **4**. TMS = trimethylsilyl.

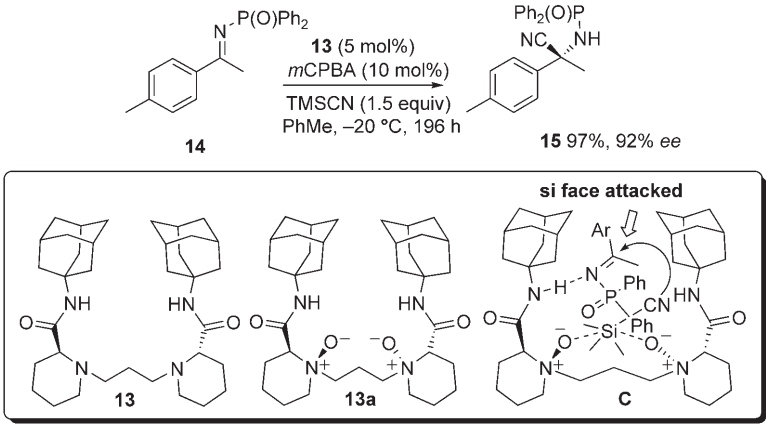



***Scheme 2.*** Chiral phosphoric acid catalysis of ketimine hydrocyanation. $Ac_2O$ = acetic anhydride.

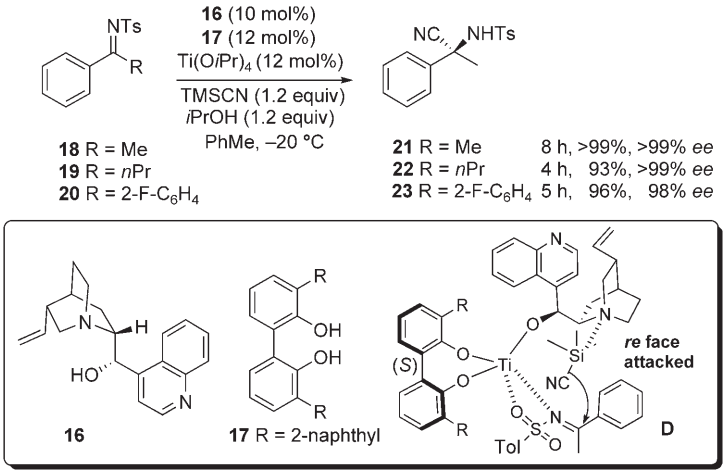
these substrates (detailed in a previous Highlight[8]), it should be pointed out that the phosphoric acid-catalyzed reactions were carried out at a higher temperature (−40 °C vs. −75 °C).

Feng et al. have recently developed chiral *N*,*N*′-dioxides for use as catalysts for the asymmetric hydrocyanation of ketimines such as **14** (Scheme 3).[16,17] The catalyst **13a** is prepared in situ by the oxidation of diamine **13** and could promote the formal[18] addition of HCN to a variety of substrates, including cyclic, heterocycle-substituted, aliphatic-ketone-derived, and non-methyl-ketone-derived ketimines. Although the products from these reactions were isolated in good to excellent levels of enantiomeric excess, catalyst efficiency and enantioselectivity is not on a par with Shibasaki's gadolinium-based system (see Scheme 1). It is noteworthy however that **13a** can be utilized at temperatures closer to ambient and the catalyst could be recovered by chromatography after reaction and reused in five iterative cycles without loss of efficiency or enantioselectivity. A selectivity model was proposed in which binding of the imine electrophile mediated by hydrogen bonding to the amide substituent occurs in such a way as to minimize steric interaction between the bulky diphenylphosphinyl and catalyst adamantyl moieties, which allows the *N*,*N*′-dioxide-activated TMSCN nucleophile to add to the electrophile's *si* face selectively (**C**, Scheme 3).

Feng et al. also very recently reported the discovery of a highly enantioselective general catalyst system compatible with both aldimine and ketimine substrates at −20 °C.[19] It was found that a binary ligand system of cinchonine (**16**) and bis(phenol) **17** together with $Ti(OiPr)_4$ in a 5:6:6 ratio could promote the highly efficient and enantioselective hydrocyanation of *N*-tosyl ketimines in the presence of TMSCN and isopropyl alcohol (Scheme 4). The catalyst system was of wide scope: both aldimines and ketimines could be transformed under almost identical reaction conditions and both yield and enantioselectivity were uniformly excellent. A variety of substrates are tolerated by the catalyst, including methyl (e.g. **18**), heterocyclic, aliphatic-ketone-derived, non-methyl-ketone-derived (e.g. **19**), and (for the first time) diaryl ketimines (e.g. **20**). Experiments involving the addition of TMSCN to substrate **18** in which **17** was replaced by (*R*)- and (*S*)-binol demonstrated that the former (*R*)-binol enantiomer afforded the product in relatively low yield and enantioselectivity




***Scheme 3.*** A Strecker reaction promoted by a recoverable *N*,*N*′-dioxide catalyst **13a**. *m*CPBA = *meta*-chloroperoxybenzoic acid.




***Scheme 4.*** A titanium-based Strecker reaction catalyst system formed in situ. For **21**, **16** (5 mol%), **17** (6 mol%), and $Ti(OiPr)_4$ (6 mol%) were used. Ts = 4-tolylsulfonyl, Tol = 4-tolyl.

(25%, 71% *ee*, *S* product configuration) whereas for the (*S*)-binol isomer, nearly identical results were obtained to those using ligand **17**. In the absence of bis(phenol) or bis(naphthol) ligands, no reaction occurred. Thus although the alkaloid is responsible for facial recognition by the catalyst formed in situ, the bis(phenol) ligand also plays a key auxiliary role. Feng and co-workers therefore proposed a preliminary model (**D**, Scheme 4) in which the substrate, the cinchona alkaloid and the bis(phenol) ligand (in the *S* configuration shown) coordinate to the titanium ion. The resultant activated imine is attacked by the Lewis-base-activated TMSCN[20] in a tuneable asymmetric environment. The facile, in situ catalyst synthesis from readily available materials, the broad substrate scope, and high adduct yield/enantiopurity possible using this methodology make it a valuable addition to the growing array of methodologies available for the catalytic asymmetric synthesis of α-substituted α-amino nitriles.

In summary, great strides have been made in towards general catalyst systems for the asymmetric hydrocyanation of ketimines in a relatively short space of time. Most of the more recently reported catalysts have been designed for use with activated *N*-phosphinyl or *N*-tosyl ketimines, which complement Jacobsen and Vachal's systems[15] for *N*-alkyl protected substrates. Although this is certainly good news for the practitioner, as always, scope for further development remains. As the field matures, catalyst systems for activated *N*-protected ketimines that are demonstrably compatible with Lewis basic and/or protic substrate functionality (e.g. secondary amides, carbamates) present in many multistep syntheses, and an enantioselective Strecker reaction involving imines formed in situ from achiral ketone substrates[21] would represent most welcome advances.

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[1] A. Strecker, *Ann. Chem. Pharm.* **1850**, *75*, 27.
[2] K. Harada, *Nature* **1963**, *200*, 1201.
[3] Recent reviews: a) H. Gröger, *Chem. Rev.* **2003**, *103*, 2795; b) T. Vilaivan, W. Bhanthumnavin, Y. Sritana-Anant, *Curr. Org. Chem.* **2005**, *9*, 1315.
[4] Post-2003 examples: a) Z. G. Jiao, X. M. Feng, B. Liu, F. X. Chen, G. L. Zhang, Y. Z. Jiang, *Eur. J. Org. Chem.* **2003**, 3818; b) W. Mansawat, W. Bhanthumnavin, T. Vilaivan, *Tetrahedron Lett.* **2003**, *44*, 3805; c) S. Nakamura, N. Sato, M. Sugimoto, T. Toru, *Tetrahedron: Asymmetry* **2004**, *15*, 1513; d) V. Banphavichit, W. Mansawat, W. Bhanthumnavin, T. Vilaivan, *Tetrahedron* **2004**, *60*, 10559; e) J. Huang, E. J. Corey, *Org. Lett.* **2004**, *6*, 5027; f) T. Ooi, Y. Uematsu, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2548; g) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; h) S. C. Pan, J. Zhou, B. List, *Angew. Chem.* **2007**, *119*, 618; *Angew. Chem. Int. Ed.* **2007**, *46*, 612; i) S. C. Pan, B. List, *Org. Lett.* **2007**, *9*, 1149.
[5] a) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; b) J. J. Byrne, M. Chavarot, P.-Y. Chavant, Y. Vallée, *Tetrahedron Lett.* **2000**, *41*, 873.
[6] Recent reviews on α,α-disubstituted amino acid synthesis: a) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569; b) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406.
[7] Recent review of asymmetric addition reactions to ketimines: O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873.
[8] C. Spino, *Angew. Chem.* **2004**, *116*, 1796; *Angew. Chem. Int. Ed.* **2004**, *43*, 1764.
[9] a) N. Kato, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2004**, *45*, 3147; b) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Pure Appl. Chem.* **2005**, *77*, 2047.
[10] Shibasaki and co-workers also demonstrated that the use of stoichiometric HCN in conjunction with catalytic amounts of TMSCN resulted in highly effective catalysis: N. Kato, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2004**, *45*, 3153.
[11] N. Fukuda, K. Sasaki, T. V. R. S. Sastry, M. Kanai, M. Shibasaki, *J. Org. Chem.* **2006**, *71*, 1220.
[12] Reaction (without additive **5**): M. Suzuki, N. Kato, M. Kanai, M. Shibasaki, *Org. Lett.* **2005**, *7*, 2527.
[13] N. Kato, T. Mita, M. Kanai, B. Therrien, M. Kawano, K. Yamaguchi, H. Danjo, Y. Sei, A. Sato, S. Furusho, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6768.
[14] M. Rueping, E. Sugiono, S. A. Moreth, *Adv. Synth. Catal.* **2007**, *349*, 759.
[15] a) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; b) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012.
[16] J. Huang, X. Liu, Y. Wen, B. Qin, X. Feng, *J. Org. Chem.* **2007**, *72*, 204.
[17] X. Huang, J. Huang, Y. Wen, X. Feng, *Adv. Synth. Catal.* **2006**, *348*, 2579.
[18] Catalyst **13a** did not catalyze the addition of HCN itself to imine substrates.
[19] J. Wang, X. Hu, J. Jiang, S. Gou, X. Huang, X. Liu, X. Feng, *Angew. Chem.* **2007**, *119*, 8620; *Angew. Chem. Int. Ed.* **2007**, *46*, 8468.
[20] A referee has pointed out that in the presence of stoichiometric amounts of isopropyl alcohol, an analogous catalysis mode involving the activation of HCN by the quinuclidine ring nitrogen could also be considered. For a discussion of the influence of protic additives see: M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 1716; *Angew. Chem. Int. Ed.* **2000**, *39*, 1650.
[21] Very recently, a non-enantioselective version of such a process has been reported using an achiral $Gd(OTf)_3$ catalyst: G. K. S. Prakash, T. Matthew, C. Panja, S. Alconcel, H. Vaghoo, C. Do, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 3703.

  