

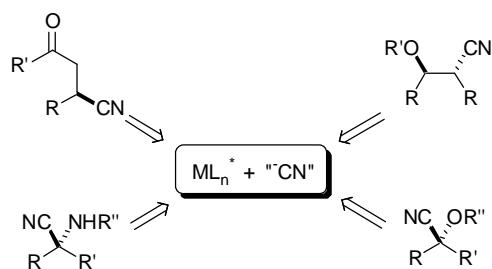
Metal-Catalyzed Enantioselective C-C Bond Constructions Employing $^- \text{CN}$ as a Nucleophile

David A. Nicewicz

Department of Chemistry, University of North Carolina, Chapel Hill, NC 27599-3290

dnnice@email.unc.edu

ABSTRACT



As a C-based nucleophile, $^- \text{CN}$ offers an attractive and mild alternative to traditional C-nucleophiles such as organomagnesium, organolithium, and organocuprate reagents. Metal-catalyzed enantioselective Strecker reactions, cyanosilylation of aldehydes and ketones, meso epoxide ring opening, and conjugate addition pathways are highlighted, as well as pertinent mechanistic details.

Since the discovery that hydrogen cyanide reacts with imines to furnish cyanoamines (the Strecker reaction; *circa* 1850),¹ the utility of $^- \text{CN}$ as a mild C-nucleophile has been demonstrated. Cyanide is, in many ways, an ideal C-based nucleophile due to its tolerance of varied functionality (esters, amides, olefins), its mild basicity, and its availability in different forms (hydrogen cyanide, metal salts, trimethylsilylcyanide, cyanoformates, or acetone cyanohydrin). Reaction pathways common to traditional C-nucleophiles (organomagnesium, organolithium, organocopper reagents) may also be accessed with $^- \text{CN}$: simple 1,2-addition, Michael reactions, epoxide ring opening, and substitution of alkyl halides are a few parallel examples. In contrast to $^- \text{CN}$, typical C-based nucleophiles can be pyrophoric, strongly basic, and incompatible with sensitive functionality present in a given substrate. Admittedly, the use of any cyanide reagent does pose a risk; however, such risks may be minimized by cautious manipulation of reactions in a well ventilated fume hood. Adducts from $^- \text{CN}$ addition may be further elaborated to

yield natural and unnatural amino acids, β -lactams, diamines, and innumerable other chiral building blocks.

With the advent of modern asymmetric catalysis, many cyanation reactions have been rendered enantioselective. Although effective organocatalytic methods of asymmetric $^- \text{CN}$ delivery are available, only chiral metal-catalyzed methods will be highlighted in this review. This is not meant to understate the effectiveness of organocatalytic methods which can, in some instances, provide complementary methods for identical cyanation reactions.

The Strecker reaction is arguably one of the simplest methods for α -amino acid synthesis available to the organic chemist.² Abbreviated enantioselective routes to structurally varied natural and unnatural α -amino acids are in high demand for a myriad of applications. Hoveyda and Snapper have met this challenge by employing modular peptide ligands (**3**) for the asymmetric Ti-catalyzed Strecker reaction (Scheme 1).^{3,4}

(2) For a review on the enantioselective Strecker reaction see: Gröger, H. *Chem. Rev.* **2003**, *103*, 2795.

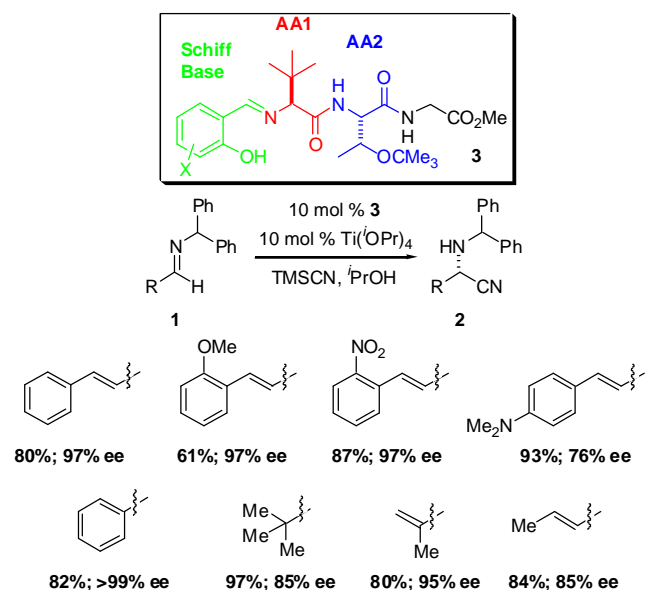
(3) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284.

(4) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657.

(1) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.

In a successful approach frequently used by the Hoveyda-Snapper groups,^{5,6} the optimal catalyst system was identified by systematic variation of the AA1, AA2, and Schiff base residues of the peptide ligand **3**, as well as the metal employed. The highest enantioselectivities were observed in all cases when the metal = Ti(O*i*Pr)₄, AA1 = *t*-Leu and AA2 = Thr(*t*-Bu); however, the optimal Schiff base was substrate dependent (X = 1-naphth, 3,5-dibromo, 5-OMe, or 3,5-dichloro).⁷ This is arguably one of the most effective metal-catalyzed asymmetric Strecker systems based on the scope of the aldimines tolerated (aromatic, aliphatic, and α,β -unsaturated imines). Mechanistic studies revealed several intriguing attributes of this system: 1) the stereochemical identity of the AA2 moiety of **3** is vital both to reactivity and selectivity (when R = Ph for **1** and AA2 = (*R*)-Thr(*t*-Bu) for **3**, only 10% conversion and <10% ee was observed after 18 h); 2) if the terminal amide of **3** was replaced with an ester, the initial reaction rate was decreased (2.3 times slower over the first 90 min); 3) the reaction rate was first order with respect to the catalyst. Based on the aforementioned observations, Hoveyda and Snapper propose that the carbonyl of AA2 likely participates in ⁻CN delivery by Lewis base activation of HCN formed *in situ*. This mode of cooperative Lewis acid-Lewis base activation is further supported by similar observations in other nucleophilic ⁻CN additions discussed later in this review.

Scheme 1. Hoveyda-Snapper Asymmetric Strecker System



Aldehydes and ketones give rise to ⁻CN addition products analogous to the Strecker reaction. Metal-

(5) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **1996**, *35*, 1668.

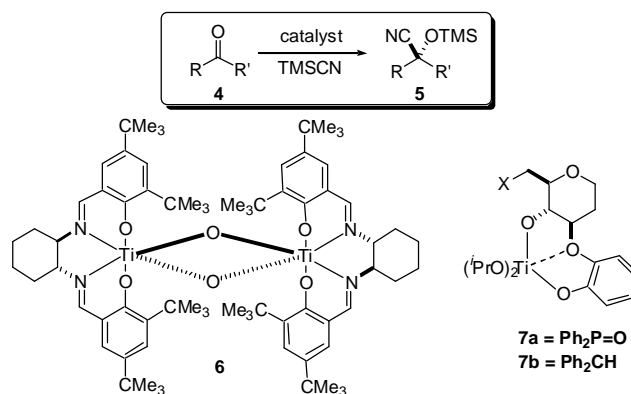
(6) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **1997**, *36*, 1704.

(7) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594.

catalyzed formation of optically active cyanohydrins (**5**; R = H) has perhaps been the most extensively studied ⁻CN addition manifold.⁸ Despite this attention, there are only a handful of catalyst systems which are particularly selective over a broad range of electrophiles with high turnover (TN = 10; Scheme 2).

While exploring the use of chiral (salen)TiCl₂ complexes in the TMSCN⁹ addition to aldehydes, Belokon and North occasionally noted inconsistent results.¹⁰ Upon further investigation, it was determined that water played a vital role with respect to reactivity and enantioselectivity. Under strictly anhydrous conditions (0.007% H₂O) (salen)TiCl₂ complexes yielded only moderate selectivities (40-62% ee) in the cyanosilylation of benzaldehyde. Conversely, when the (salen)TiCl₂ catalysts were pretreated with 1 equiv of water and 2 equiv of NEt₃, high levels of enantioinduction were observed (80-86% ee). This observation led to the isolation and X-ray structure determination of **6**. When employed in conjunction with TMSCN in as little as 0.1 mol %, the air-stable (salen)Ti-oxo dimer (**6**) furnished a variety of aliphatic and aromatic cyanohydrins (**5**; R' = H) in moderate (52-66% ee) to excellent (50-92% ee) selectivities, respectively.¹¹

Scheme 2. Enantioselective Cyanosilylation of Aldehydes and Ketones



Shibasaki and co-workers have developed a complex based on a *D*-glucal scaffold (**7**, Scheme 2) that is effective for the asymmetric cyanosilylation of ketones.¹² When X = Ph₂P=O, **7a** (10 mol %) efficiently catalyzed asymmetric TMSCN addition to a range of aryl-alkyl (69-92% ee),

(8) For a pertinent review see: North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147.

(9) Evans, D. A.; Truesdale, L. K.; L., C. G. *Chem. Comm.* **1973**, *9*, 55.

(10) Belokon, Y. N.; Cavada-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khurstalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tassinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968.

(11) Cyanofornates used as alternative cyanation source for aldehydes: (a) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3636. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021.

(12) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412.

vinyl-alkyl (91% ee), and alkyl-alkyl (76-90% ee) ketones in good to excellent yields at -50 to -20 °C. Both Shibasaki and Belokon propose, based on mechanistic experiments, that ^-CN delivery is an intramolecular process assisted by Ti in the Belokon-North system^{13,14} and the Lewis-basic diphenylphosphine oxide moiety in the Shibasaki system (Figure 1). The necessity of the pendant diphenylphosphine oxide functionality was demonstrated; when X = Ph₂CH (**7b**), cyanation occurs only at ambient temperature over long periods of time (80 h) with little or no enantioinduction (2% ee for acetophenone; cf. 92% ee when X = Ph₂P=O). Since Belokon and North note that **6** catalyzes the cyanosilylation of ketones with only moderate levels of reactivity and selectivity (1 d to 2 weeks; 30-70% ee), the Shibasaki catalyst provides a complementary approach to the ketone-cyanation problem.

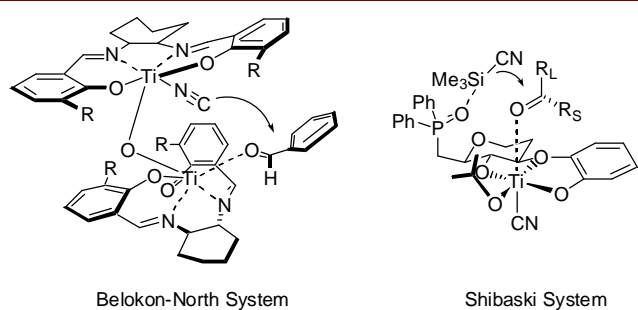


Figure 1. Transition State Proposals

Alternatives to metal-catalyzed enantioselective cyanation of C=O and C=N double bonds are available. Jacobsen has published a series of reports on the cyanation of aldimines and ketimines via chiral urea and thiourea Schiff base catalysts.¹⁵ An organocatalytic alternative to ketone cyanation was recently reported by Deng involving modified cinchona alkaloid catalysts.¹⁶ These systems provide complimentary methods to their aforementioned metal-catalyzed counterparts.

Meso epoxides can provide chiral building blocks bearing secondary alcohols after enantiodifferentiation by a nucleophile. Jacobsen has shown that azides,¹⁷ thiols,¹⁸ and benzoic acid¹⁹ can discriminate between the two enantiotopic carbon atoms of a meso epoxide with the aid

of a chiral (salen)metal catalyst. More recently, the Jacobsen group has demonstrated the ability of TMSCN to effect the asymmetric ring opening of meso epoxides to furnish optically active protected secondary cyano alcohols in the presence of a YbCl₃/pybox (**10**) catalyst system (Scheme 3).²⁰

When screening a series of lanthanide trichloride/pybox catalyst systems, it was observed that an increase in lanthanide atomic number led to an amplification in the optical activity of **9**. This periodic trend is rationalized on the basis that asymmetry is more effectively transferred from the pybox framework given a smaller atomic nucleus (assuming the mechanism remains constant for all lanthanide metals). With YbCl₃ as the optimum catalyst, the reaction gave high levels of stereoinduction for several meso epoxides, but the ligand framework was substrate dependent (R' = Ph or *t*-Bu).

Scheme 3. Asymmetric Ring Opening of Meso Epoxides

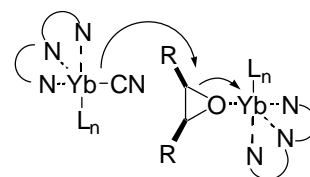
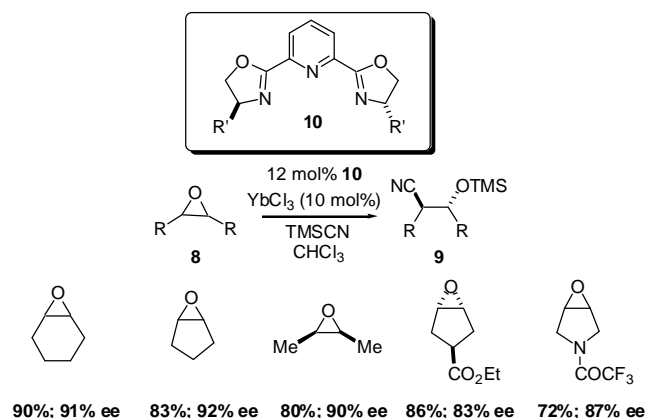


Figure 2. Bimetallic Transition State Proposal

A plot of % ee of **9** vs. % ee of **10** revealed a substantial positive nonlinear effect. This seems to suggest a bimetallic mechanism reminiscent of the hydrolytic kinetic resolution of racemic terminal epoxides (Figure 2).²¹ Further kinetic

(13) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron* **2001**, *57*, 771.

(14) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; Larichev, V. S.; Lokshin, B. V.; Moscalenko, M. A.; North, M.; Orizu, C.; Peregudov, A. S.; Timofeeva, G. I. *Eur. J. Org. Chem.* **2000**, 2655.

(15) (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (c) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279. (d) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

(16) (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (b) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900.

(17) Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197.

(18) Wu, M. H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252.

(19) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.

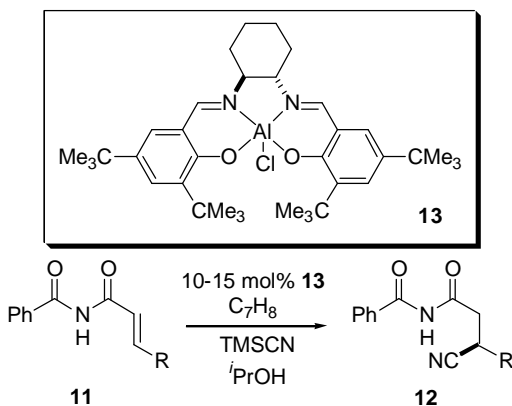
(20) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.

(21) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

studies were also in agreement with a second order catalyst rate dependence.

Perhaps the most understudied mode of enantioselective ^-CN delivery is conjugate addition to α,β -unsaturated carbonyl compounds. The first report of a catalytic enantioselective 1,4-addition of ^-CN was only recently disclosed using α,β -unsaturated imides (**11**) as the conjugate acceptors (Scheme 4).²² Conjugate adducts **12** can provide access to α -substituted- β -amino acids and β -substituted- γ -aminobutyric acids.

Scheme 4. Asymmetric Conjugate Addition



R	Yield (%)	ee (%)
Me	92	98
Et	95	97
<i>n</i> Pr	90	97
<i>i</i> Pr	91	94
<i>t</i> Bu	93	96
(CH ₂) ₃ CHCH ₂	96	95
<i>t</i> Bu	90	97
CH ₂ OBn	70	87

Salen complex **13** catalyzes conjugate addition of ^-CN to a variety of α,β -unsaturated imides (**11**). The salen framework was chosen based its previous success in catalyzing 1,4-addition of HN₃ to **11**.²³ Conjugate addition proved to be highly enantioselective for a range of electrophiles. Unsaturation present in the R group (e.g. aryl, vinyl, alkynyl) is the only substitution pattern not tolerated in the reaction. Despite this, the reaction is indiscriminate of sterics (R ranges from Me to *t*Bu) while maintaining identical levels of enantioinduction. A second order rate dependence on **13** seems to be operational, as evidenced by

kinetic studies. Also noted is the possible formation of an (salen)Al-CN species, observed by spectroscopic studies.

In all cases mentioned herein, a dual mode of activation for ^-CN delivery seems to be a necessity. Whether intramolecular as in the Hoveyda and Shibasaki examples or intermolecular as in the Jacobsen systems, some form of higher-order catalyst pre-organization remains essential for elevated levels of reactivity and enantiocontrol in cyanation reaction manifolds. This information may prove valuable for the development of novel cyanation reaction pathways and discovery of new enantioselective catalysts. Interest in the utility of ^-CN as a C-based nucleophile seems to have been renewed by the inception of modern asymmetric catalysis.

(22) Sammis, G. M.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2003**, *125*, 4442.

(23) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959.