

Recent Developments in the Catalytic Asymmetric Cyanation of Ketimines

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In several research groups α,α -dialkylated amino acids (α,α -DAAs) are currently a subject of intense investigation from both biological^[1] and synthesis standpoints.^[2] Several desirable features of α,α -DAAs have attracted the attention of the pharmaceutical industry. Their incorporation into peptides and proteins might affect the secondary or tertiary structure and confer unusual and interesting biological properties.^[3] The quaternary center in an α,α -DAA preserves its stereochemical integrity and often imparts increased metabolic stability to the peptide. Also, many α,α -DAAs are powerful enzyme inhibitors.^[4]

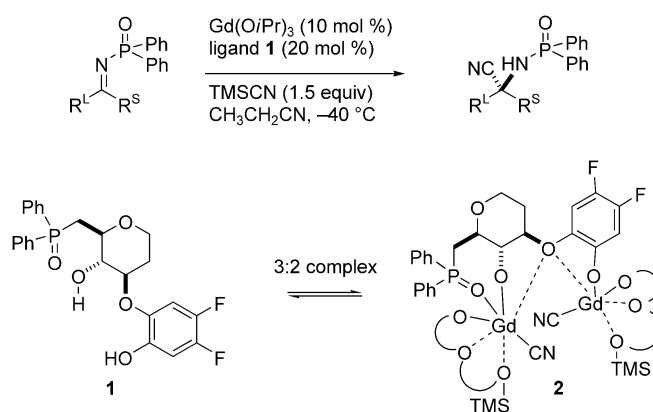
The cyanation of imines, the second step in the Strecker synthesis, offers a short route to amino acids. Efforts have recently culminated in efficient catalysts for the cyanation of aldimines affording α -amino acids of high enantiomeric purity.^[5] In principle, the same strategy could be applied to ketimines to afford α,α -DAAs. In practice, the enantiotopic faces of ketimines are not as easily discriminated as those of aldimines, but recent advances indicate that a solution is at hand.

The gadolinium complex of D-glucose-derived ligand **1** developed by Shibasaki et al. is able to effect the cyanation of *N*-diphenylphosphanoil ketimines with a high degree of enantioselectivity (Scheme 1).^[6] The reactions of methyl phenyl, methyl naphthyl,

and other aryl methyl ketimines all gave the corresponding amino nitriles in 89–98% *ee*. The real breakthrough, however, is the broad substrate generality. Prior to this report, only aryl methyl ketimines and *tert*-butyl methyl ketimine were known to undergo a highly enantioselective catalytic cyanide addition. Catalyst **2** (believed to be a 3:2 complex of ligand **1** and Gd^{3+} , see Scheme 1) effected the cyanation of the alkyl methyl ketimines **4** and **5** with moderate to good enantioselectivity

(Figure 1). Phenyl ethyl ketimine **3** was also reported to afford the corresponding amino nitrile in 85% *ee*.

Importantly, vinyl methyl ketimines **6–8**, in which the vinyl moiety is di- or trisubstituted, also gave good results. The significance of this result rests in the versatility of the alkene in further transformations. For example, simple hydrogenation of the double bond in the final amino acid provides an efficient alternative to the cyanation of the corresponding saturated alkyl methyl ket-



Scheme 1. Catalytic asymmetric cyanation of a ketimine and the proposed structure (**2**) of the cyanation catalyst Gd/**1**. TMSCN = trimethylsilyl cyanide.

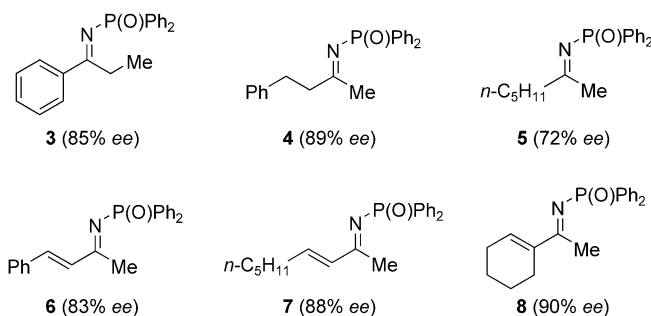
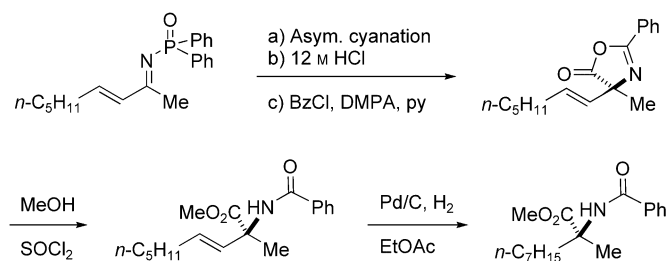


Figure 1. Ketimines that underwent cyanation with Gd/**1** to give aminonitriles.

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Scheme 2. Vinyl ketimines as equivalents of alkyl ketimines. BzCl = benzyl chloride, DMPA = 2,2-dimethoxy-2-phenylacetophenone, py = pyridine.

imine, which usually occurs with lower selectivity (Scheme 2). Moreover, dihydroxylation, electrophilic addition, metathesis, and a myriad other possible reactions will render this type of substrates very useful for the synthesis of more complex α,α -DAAs.

Although the precise mechanistic details of this reaction are not known yet, closely related complexes were used to achieve the cyanation of ketones.^[7] Mechanistic studies for the latter led the authors to propose a rationale for the enantioselectivity. Structures **9** and **10** in Figure 2 are based on their proposed structure for the cyanation of ketones.^[7a] Note that in both cases (ketones and ketimines), a ligand-to-metal ratio of 2:1 is optimum. It is therefore plausible that the structures of the active catalysts are analogous, and thus that the author's proposed transition state for the cyanation of ketones may apply to the ketimine case as well (cf. **10** in Figure 2). One notable difference, however, is the presence of the diphenylphosphonyl substituent at the imine nitrogen atom. This substituent was shown to play an

important role.^[6] It was speculated that chelation of the phosphanoyl oxygen atom to the lanthanide center was important for the enantioselectivity.

Catalyst **2** and its analogues are new members of a family of bimetallic complexes developed by the Shibasaki group. These catalysts are thought to exert their action much like enzymes by coordinating both the substrate and the reactant (in this case a nucleophile) and bringing them into proximity.^[8] Vallée and co-workers have also tested one such bimetallic complex for the asymmetric cyanation of ketimines with moderate success.^[9]

A good understanding of the reaction mechanism is necessary for the rational design of a truly better catalyst. The Jacobsen group achieved this with catalyst **12**,^[10] which was rationally derived from its predecessor **11**, itself discovered by combinatorial screening (Figure 3). Catalyst **11** gave good enantioselectivity for the cyanation of aldimines and aryl

methyl ketimines.^[11] A working model for catalyst **11** was proposed with the help of multidimensional NMR spectroscopy, high-level calculations, and kinetic experiments.^[10] It was established that the minor *Z* isomer of the ketimine was preferentially bound by the formation of hydrogen bonds between the imine nitrogen and the two urea hydrogen atoms (Figure 3). High-level calculations favored a bridged structure with two hydrogen bonds rather than rapidly equilibrating structures each having a single hydrogen bond.^[10] In addition, there was no significant conformational change induced in the catalyst upon binding of the imine.

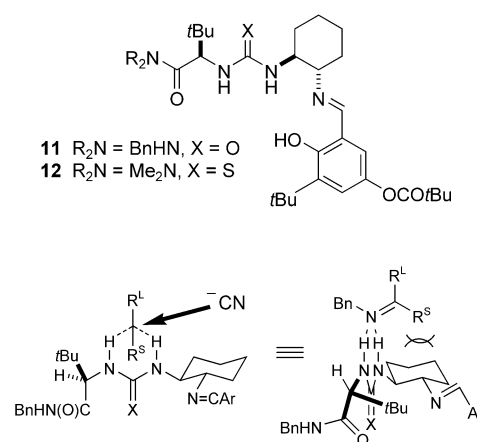


Figure 3. Catalysts **11** and **12** and their proposed mechanism of action.

The imine is oriented such that the smaller group (Me in the case of methyl ketimines) points "inside" the U-shaped catalyst. This probably explains the observation that the catalyst coordinates only *Z* imines, since *E* imines would have the larger group (R^L) pointing "inside" the catalyst's framework. Attack then takes place from the least hindered right-hand side of the complex as drawn. Conceptually, this mode of action imposes a limitation on the reactivity and selectivity achievable by this system. Because the imine's smaller substituent is pointing directly toward the catalyst, its maximum size can be determined by the available space in the catalyst's optimum conformation. Larger groups could disrupt this conformation and cause a decrease in enantioselectivity. Indeed, it was found that

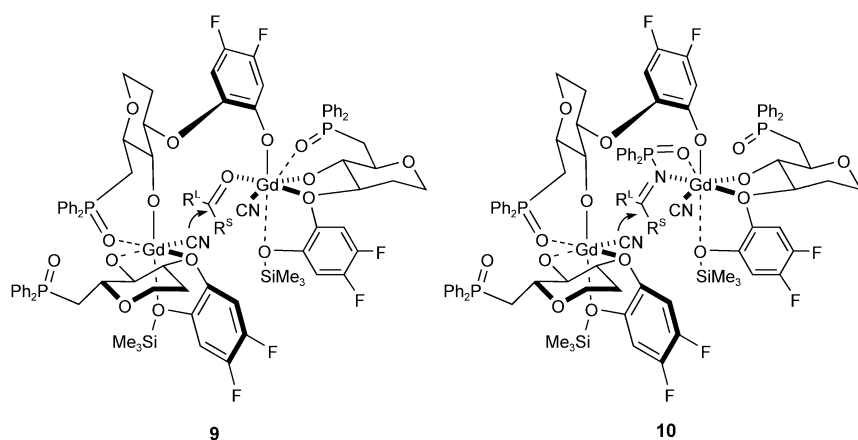


Figure 2. Proposed transition state structures for the cyanation of ketones and ketimines with **2**.

imines with large groups were poorer substrates.^[11]

The solid understanding of the mechanistic details in the case of catalyst **11** enabled the Jacobsen group to devise yet a better catalyst. They reasoned that a bulkier group on the left-hand side (the fragment derived from the amino acid) and tuning of the electronic properties of the critical urea moiety should augment the efficacy of the catalyst. The increase in observed enantioselectivities achieved with catalyst **12** was indeed remarkable and underscores the power of rational design. At the same time, rational design alone would likely not have delivered the initial key catalyst **11** as efficiently as combinatorial screening did. This combination of random screening followed by rational optimization could mark the future of catalyst design.^[12]

At present, the bulk of the results reported for catalyst **12** concerns the cyanation of aldimines. Only two ketimines were included in the study, namely *N*-benzyl *tert*-butyl methyl ketimine (86% *ee*) and *N*-(*p*-bromobenzyl) methyl phenyl ketimine (96% *ee*). Nevertheless, catalyst **12** and, particularly, catalyst **2** offer good performances in a very difficult arena. There is still room for improvement in the Strecker synthesis of α,α -DAAs besides obtaining higher enantioselectivities and achiev-

ing a broader scope. For example, the requirement for an auxiliary group on the imine implies steps to put it on (unless the amine is readily available) and selective removal at the end, which is not always straightforward. The cost and time involved in synthesizing the catalysts still impinges on the method. Chiral ligand **1** requires 12 steps starting from *D*-glucose. Catalysts **11** and **12** require only five steps to put the four fragments together, but their syntheses involve the costly chiral cyclohexyldiamine and *tert*-leucine portions. Solid-phase versions of the catalysts with similar effectiveness would render their recovery and reuse particularly easy.

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