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COMMUNICATIONS

Published on Web 08/03/2002

Structure-Based Analysis and Optimization of a Highly Enantioselective Catalyst for the Strecker Reaction

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Received June 10, 2002

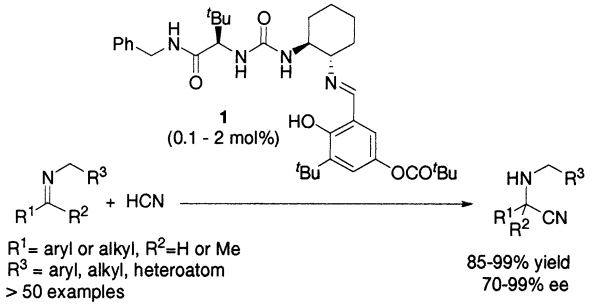
The hydrocyanation of imines (the Strecker reaction) has become one of the most intensively studied reactions in the field of asymmetric catalysis over the past several years.[1] A particularly intriguing system identified in the course of these investigations is the structurally novel metal-free catalyst **1**, which displays high enantioselectivity with extraordinary substrate scope in the hydrocyanation of aldimines and methylketoimines (Scheme 1).[2] In a compelling illustration of the potential role of combinatorial strategies for the development of new selective catalyst systems, **1** was discovered and optimized by a parallel library synthesis and screening approach without any direct understanding of how it functions. At this stage, however, gleaning insight into the mode of action of this catalyst becomes important both fundamentally (given its remarkable effectiveness) and practically (since it is likely that the full scope and utility of this class of catalysts cannot be elucidated without a solid mechanistic foundation). We report here structural and mechanistic studies that shed light on this issue and lay the foundation for rational catalyst optimization.

Despite its relatively small size (fw = 621 g/mol), catalyst **1** was found to adopt a well-defined secondary structure in solution. The ground state conformation was determined through ROESY and NOE NMR experiments in d_8-THF and d_8-dioxane solutions of **1** (Figure 1A)[3] and found to be in full accord with the calculated energy-minimized geometry.[4] The 3-D structure of **1** in solution was independent of the solvent used for the NMR study,[5] and investigation of the NMR solution structures of several related analogues of **1** revealed closely similar geometries.[6]

In an effort to ascertain the precise role of **1** in the Strecker reaction, we carried out rate studies of the hydrocyanation of a model substrate (*N*-allyl-4-methoxybenzaldimine). The transformation was found to obey Michaelis−Menten kinetics, with a first order dependence on catalyst and HCN, and saturation kinetics with respect to the imine substrate ($K_M = 0.214 \pm 0.009$ M, $k_{cat}/K_M = 3.8 \times 10^{-3}$ M^{-1} s^{-1}). This result implicates reversible formation of an imine−catalyst complex, presumably through a hydrogen bond between the imine nitrogen and an acidic proton of the catalyst. To identify the relevant proton(s), we prepared a series of analogues of **1** and evaluated them as catalysts for activity and enantioselectivity in the Strecker reaction.[7] Remarkably, only the two urea hydrogens of **1** were found to be essential for catalyst activity. Isotope shift experiments provided further unequivocal evidence that the imine substrate interacts solely with the urea hydrogens.[8]

The *N*-alkylimine substrates utilized by **1** exist as directly observable mixtures of *Z*- and *E*-stereoisomers that interconvert rapidly in solution.[10] To develop a useful understanding of the nature of the interaction between imines and **1**, it was crucial to determine which imine stereoisomer is involved in the substrate−catalyst complex. NMR titration of a solution of a representative ketoimine

Scheme 1. Asymmetric Strecker Reaction Catalyzed by **1**



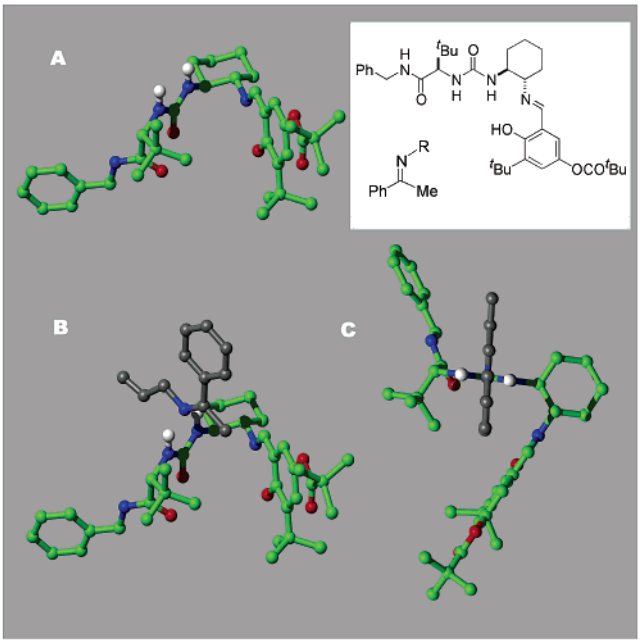


Figure 1. (A) Solution structure of catalyst **1** and (B, C) two views of the complex generated upon binding of a *Z*-imine, as determined by NMR analysis (see text). The images were generated using MOLMOL.[10] The imine employed in the NMR studies was *N*-*p*-methoxybenzyl acetophenone imine (R = *p*-methoxybenzyl). For clarity, the N-substituent R in the graphic is represented as an allyl group. The imine is shown hydrogen-bonded to both urea hydrogens in agreement with both experimental and computational data (see text).

derivative (*N*-*p*-methoxybenzyl acetophenone imine; *E*:*Z* = 20:1) with catalyst **1** resulted in a downfield shift of the *Z*-imine methyl resonance exclusively. Furthermore, a cyclic *Z*-imine, 3,4-dihydroisoquinoline, was found to be a highly competent substrate for the Strecker reaction, undergoing hydrocyanation in quantitative yield and in 89% ee.[11] The sense of absolute stereoinduction was identical to that of all other Strecker adducts derived from acyclic imines that exist predominantly as *E*-isomers. Taken together, these

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10.1021/ja027246j CCC: $22.00

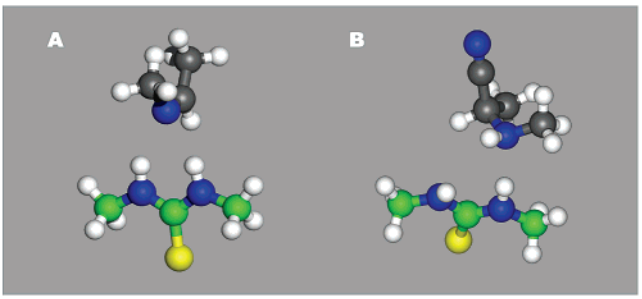


Figure 2. Calculated geometry (energy minimum) of a catalyst−imine complex (A) and a catalyst−product complex (B). All calculations were performed on a simplified relevant system: *N*,*N*′-dimethylurea or *N*,*N*′-dimethylthiourea, (*Z*)-ethylidene methylamine, and 2-(methylamino)propionitrile using Gaussian 98 (B3LYP, 6-31G(d,p) basis set.

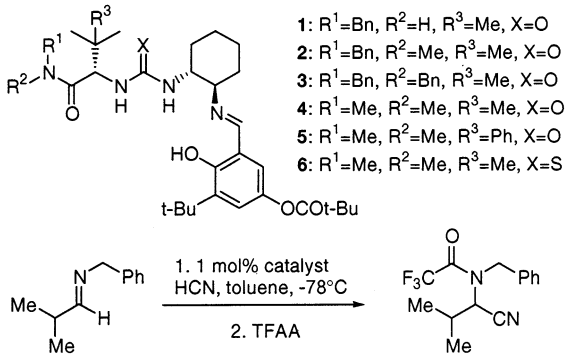
data provide compelling evidence that Strecker reactions with **1** involve binding of the imine substrate as the *Z*-isomer.

With this insight into the general features of the imine−catalyst interaction in hand, we sought to establish a detailed 3-D structure of the substrate-bound complex. Multiple NOE interactions between **1** and a variety of *Z*-imines were observable, allowing determination of the orientation of these substrates relative to the catalyst.[6] Intramolecular cross-peaks due to catalyst in the bound and free states were essentially invariant, indicating that no significant change in conformation of **1** results from binding of the imine.[12] Depictions of the structure of the complex between **1** and a *Z*-imine substrate fully consistent with all of the NOE data are shown in Figure 1B,C. The imine substrate is placed in a bridging mode between the two urea hydrogens. This structural assignment is in line with the experimental data[13] and supported by high level calculations (Gaussian 98, B3LYP level with the 6-31G(d,p) basis set)[4] on a simplified model of the bound complex. Energy minimization revealed a significant preference for a bridged structure, with imine hydrogen-bonded to both urea hydrogens simultaneously (Figure 2A).[14] In contrast, analogous calculations assign a singly hydrogen-bonded structure to the product aminonitrile−catalyst complex (Figure 2B). This establishes a plausible explanation for the basis for catalyst turnover: the bridging interaction in the catalyst−imine complex is stronger (8.5 kcal/mol for urea; 10.0 kcal/mol for thiourea) than the classical hydrogen bond in catalyst−product complex (5.0 and 6.3 kcal/mol, respectively).[15]

The structure elucidated for the catalyst−substrate complex sheds substantial light on the basis for the scope and selectivity of asymmetric Strecker reactions with **1**: (1) The large group on the imine carbon is directed away from the catalyst and into solvent (Figure 1B); this serves to explain why **1** catalyzes hydrocyanation of most aldimines with high ee, regardless of the steric and electronic properties of the substrate. (2) The small group (H for aldimines, Me for methylketoimines) is aimed directly into the catalyst; ketoimines bearing larger substituents are poor substrates for the reaction,[2c] presumably because they cannot be accommodated within the optimal geometry. (3) The *N*-substituent is also directed away from the catalyst. However, its size is restricted as a result of the requirement to access the *Z*-isomer of the imine. (4) On the basis of the observed sense of stereoinduction, addition of HCN takes place over the diaminocyclohexane portion of the catalyst (i.e., from the right-hand side in Figure 1C) and away from the amino acid/amide portion.

The last hypothesis leads to the prediction that increasing the steric properties of the amino acid/amide portion of the catalyst should lead to higher enantioselectivity in the hydrocyanation reactions. To test this notion, we prepared a series of derivatives

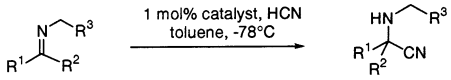
Table 1. Model-Driven Optimization of Catalyst **1**



catalyst	ee[a] (%)	catalyst	ee[a] (%)
1	80.0	**4**	95.8
2	93.5	**5**	96.6
3	93.1	**6**	97.0

[a] Determined by chiral GC analysis on γ-TA column.

Table 2. Comparison of Asymmetric Strecker Reactions of Selected Aldimines and Ketoimines Using Original Catalyst **1** and Optimized Catalyst **6**



	substrate			ee[a] of product (%)	
entry	R^1	R^2	R^3	catalyst **1**	catalyst **6**
1	*i*-Pr	H	Ph	80	97
2	*n*-Pent	H	Ph	79	96
3	*t*-Bu	Me	Ph	70	86
4	Ph	Me	*p*-BrC_6H_4	92	96
5	*t*-Bu	H	Ph	96	99.3
6	Ph	H	Ph	96	99.3

[a] Determined by GC and HPLC analyses using commercial chiral columns.

2−**6** and tested them as catalysts in the asymmetric Strecker reaction of a substrate that performed relatively poorly with catalyst **1** (80% ee, Table 1). Replacement of the secondary amide of **1** with a bulkier tertiary amide (**2**−**4**) led to significant improvements in enantioselectivity. Likewise, increasing the steric bulk of the amino acid side chain had a beneficial effect (compare **4** vs **5**). Given the critical role identified for the urea in substrate binding, we anticipated that the reaction outcome would be highly sensitive to fine tuning of its electronic properties. Indeed, replacement of the urea with a thiourea group led to a measurable improvement in enantioselectivity (compare **4** vs **6**). Thus, through this mechanism-driven optimization exercise, catalyst **6** was identified as the most enantioselective Strecker catalyst prepared to date.

The benefits of catalyst **6** relative to **1** extend over a wide range of substrates. Imines that had represented limitations for this Strecker methodology now undergo hydrocyanation with synthetically useful ee's (Table 2, entries 1−3). Substrates that performed relatively well with **1** can now be transformed with nearly perfect enantiocontrol (entries 5 and 6).

A synthetically useful chiral catalyst that had been developed by a purely empirical approach has evolved into a system amenable to rational design and improved significantly on the basis of detailed mechanistic and structural insights. The very unusual basis for substrate activation emerges as one of the most intriguing findings of this study. Further work will be directed toward elucidating the

details of the HCN addition step and toward evaluating the potential of this catalyst system for other enantioselective reactions of imines.

Acknowledgment. This work was supported by the NIH (GM-43214) and through fellowship support to P.V. from A. Bader, BMS, and Eli Lilly. The authors thank Dr. T. Kuribayashi, Dr. M. S. Sigman, and A. G. Wenzel for important background experiments and Q. Chen, Dr. K. Gademann, Dr. S. Huang, Dr. Z. Yu, and R. Ruck for valuable discussions.

Supporting Information Available: Experimental procedures and details of the structural analyses (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) The values of the intramolecular NOE cross-peak volumes and the calculated distances are provided as Supporting Information.

(4) Energy minimization was performed in Gaussian at the B3LYP level using the 3-21G* basis set. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision 5.4; Gaussian, Inc.: Pittsburgh, PA, 1998.

(5) NMR data obtained in THF and dioxane were indistinguishable. Hydrocyanations catalyzed by **1** afford essentially identical enantioselectivity in a wide range of nonprotic solvents (toluene, benzene, THF, dioxane, or hexanes).

(6) Full details provided as Supporting Information.

(7) Deletion of the secondary amide proton, the phenolic proton, and the imine functionality did not suppress catalytic activity. In contrast, alkylation of either of the urea nitrogens or replacement with a carbamate group led to dramatic loss of activity and enantioselectivity. Details are provided as Supporting Information.

(8) A solution of the catalyst in d_8-THF was split evenly into two NMR tubes; *N*-benzylpivalaldimine (*N*-(2,2-dimethylprpylidene)benzylamine) was added to the first NMR tube; to the second an identical quantity of the corresponding ^{15}N-labled imine was added. ^{1}H NMR spectra were recorded and were found to be completely superimposable ($\Delta\,\delta$ for all resonances $= <1$ Hz) with the exception of both urea hydrogens ($\Delta\,\delta = 16.1$ and 16.9 Hz). Direct through-bond coupling (N−H or N−H−N) was not observed, but this was expected given the noncovalent and rapidly exchanging nature of the interaction. For selected examples of studies involving chemical shift invoked by isotope change, see: (a) Benedict, H.; Hoelger, C.; Aquilar-Parrilla, F.; Fehlhammer, P.; Wehlan, M.; Janoschek, R.; Limbach, H. H. *J. Mol. Struct.* **1996**, *378*, 11. (b) Hansen, P. E.; Hansen, A. E.; Lycka, A.; Buvari-Barcza, A. *Acta Chim. Scand.* **1993**, *47*, 777. (c) Jameson, C. J.; Jameson, A. J.; Oppusunggu, D. *J. Chem. Phys.* **1986**, *85*, 5480.

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(10) Irradiation of resonances due to either the *E*- or *Z*-imine stereoisomers results in observable saturation of the corresponding resonances of the other isomer. For theoretical details on energy transfer experiments invoked by chemical exchange, see: (a) Sanders, J. K. M.; Hunter, B. K. *Modern NMR Spectroscopy A Guide for Chemists*; Oxford University Press: New York, 1989. (b) Alger, J. R.; Shulman, R. G. *Quart. Rev. Biophys.* **1984**, *17*, 83. (c) Sanders, J. K. M.; Merch, J. D. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *15*, 353. (d) Boyd, J.; Brindle, K. M.; Campbell, I. D.; Radda, G. K. *J. Magn. Reson.* **1984**, *60*, 149.

(11) In contrast, cyclic imines restricted to *E*-configurations (e.g., 6-phenyl-2,3,4,5-tetrahydropyridine) underwent no reaction under the same conditions, even under extended reaction times.

(12) On the basis of K_M values determined in the kinetics studies, it was calculated that >80% of **1** was bound to substrate under the conditions of the NMR experiments.

(13) In addition to NOE cross-peak data, which are consistent with the placement of imine in such an orientation, titration of solutions of **1** with *Z*-imines results in upfield shifts of the two urea protons to similar degrees. This can be ascribed either to a rapidly equilibrating structure where the imine shifts back and forth between the two urea protons or to a static, bridged structure. A strong preference for the latter is suggested by the computational studies. It must be noted, however, that such a bridging structure may not be maintained in the intermediates and transition states generated upon addition of HCN to the medium.

(14) For examples of X-ray crystal structures in which analogous interactions are observed, see: (a) Carpy, P. A.; Leger, J.-M.; Wermuth, C.-G.; Leclerc, G. *Acta Crystallogr., Sect. B* **1981**, *37*, 885. (b) Lock, C. J. L.; Pilon, P.; Lippert, B. *Acta Crystallogr., Sect. B* **1979**, *35*, 2533.

(15) All hydrogen bond energies as well as energy minimizations were calculated for the gas phase. Given the absence of solvent dependence in the asymmetric Strecker reaction noted in ref 5, this significant simplification appears justified.

JA027246J