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Asymmetric Hydrocyanation of Hydrazones Catalyzed by Lanthanide–PYBOX Complexes

John M. Keith[†] and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

jacobsen@chemistry.harvard.edu

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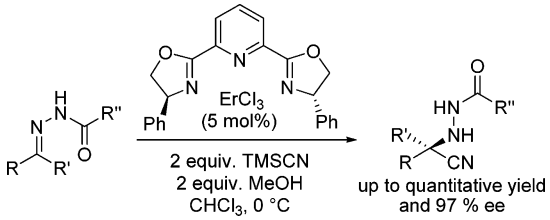
ABSTRACT



The asymmetric addition of HCN to hydrazones is catalyzed in high yield and good-to-excellent enantioselectivity by the easily prepared (PhPYBOX)$ErCl_3$ complex. This constitutes the first example of asymmetric catalytic hydrocyanation of hydrazones.

Hydrocyanation of carbonyl derivatives affords straightforward access to chiral difunctional compounds with considerable synthetic utility, thanks in large part to the possibility of effecting high-yielding hydrolysis, reduction, or alkylation reactions of the nitrile group. Accordingly, substantial effort has been directed over the past few years toward the development of effective catalysts for enantioselective reactions of HCN, with notable successes achieved particularly in additions to aldehydes, ketones, and imines.[1] We turned our attention recently to the possible use of hydrazones as substrates for asymmetric hydrocyanation reactions, motivated in part by the increased air and hydrolytic stability of these electrophiles relative to imines, their ease of preparation, and their usually high degree of crystallinity.[2] More important, the availability of asymmetric hydrazone cyanation methodology could enable practical access to α-hydrazino acids and related chiral bulding blocks with proven utility. For example, hydrazino acids, which can be viewed as aza-analogues of β-amino acids, have been studied as inhibitors of certain amino acid-metabolizing enzymes.[3] Recently, hydrazino acid-derived peptides have been predicted to fold into defined secondary structures, including conformationally unique helices,[4] thus making them attractive components for protein design and interesting potential surrogates for peptidic chemotherapeutic agents.

Existing routes to enantioenriched hydrazino acids rely generally on elaboration of amino acid derivatives[5,6] or on trapping of enolate derivatives with azodicarboxylates.[7] In

[†] Current address: Johnson & Johnson Pharmaceutical Research & Development, L.L.C., La Jolla, CA.

(1) For reviews, see: (a) Mori, A.; Inoue, S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York; 1999, Chapter 28. (b) Vachal, P.; Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York; 2003, Chapter 28.

(2) For recent examples of enantioselective additions to hydrazones, see: (a) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura M. *J. Am. Chem. Soc.* **2003**, *125*, 6610−6611. (b) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640−5641. (c) Kobayashi, S.; Shimizu, H.; Yamashita, Y.; Ishitani, H.; Kobayashi, J. *J. Am. Chem. Soc.* **2002**, *124*, 13678−13679.

(3) (a) Munier, R. L.; Bompeix, G. *C. R. Acad. Sci., Ser.* **1985**, *300*, 203−206. (b) Brand, L. M.; Harper, A. E. *Biochemistry* **1976**, *15*, 1814−1821. (c) Tanase, S.; Guirard, B. M.; Snell, E. E. *J. Biol. Chem.* **1985**, *260*, 6738−6746. (d) Yamada, R.-H.; Wakabayashi, Y.; Iwashima, A.; Hasegawa, T. *Biochim. Biophys. Acta* **1985**, *831*, 82−88.

(4) Günther, R.; Hofmann, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 247−255.

(5) Bonnet, D.; Samson, F.; Rommens, C.; Gras-Masse, H.; Melnyk, O. *J. Peptide Res.* **1999**, *54*, 270−278.

(6) Viret, J.; Gabard, J.; Collet, A. *Tetrahedron* **1987**, *43*, 891−894.

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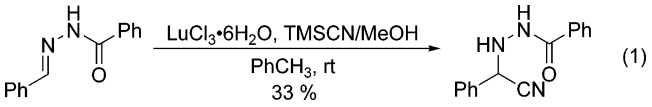
contrast, approaches involving catalytic hydrocyanation of hydrazone derivatives have received relatively little attention. Uncatalyzed addition of HCN to hydrazones can be effected under solvent-free conditions or in alcoholic solution.[8] Phase-transfer-catalyzed addition of cyanide to ketohydrazones has been described, although enantioselective variants have not been disclosed.[9] More recently, Kobayashi reported the addition of HCN to hydrazones catalyzed by achiral hafnium trifluoromethane sulfonate complexes.[10]

A survey of catalyst systems known to promote hydrocyanation reactions afforded a promising lead result in the use of $LuCl_3$ [11] with moderate levels of reactivity obtained using an *N*-benzoyl-protected hydrazone as a substrate (eq 1).[12]



(1)

Prompted by recent successes obtained in asymmetric hydrocyanation of aldehydes and epoxides using (PYBOX)-lanthanide complexes,[13] we carried out a systematic screen of $LnCl_3$ complexes in the presence of the (*S*)-*i*-PrPYBOX ligand. An interesting trend was observed (Figure 1), with

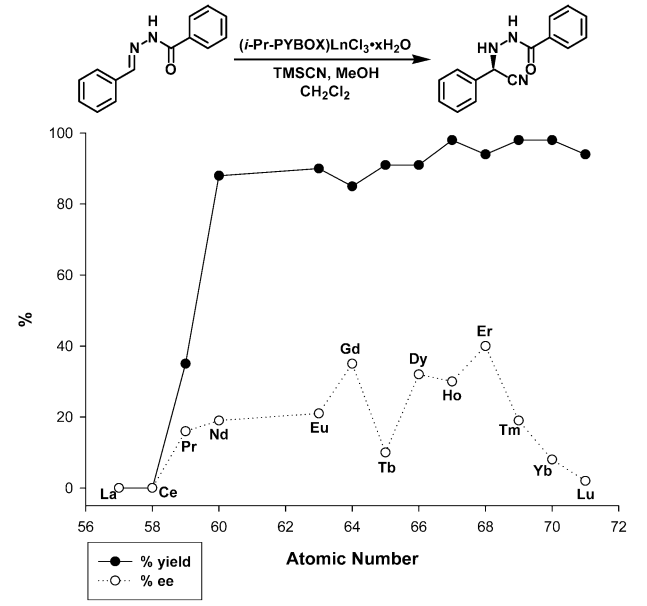
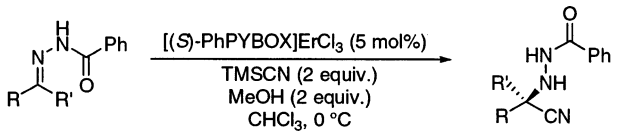
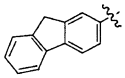
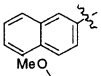
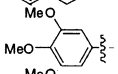
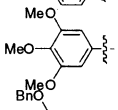
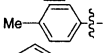
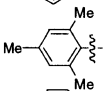
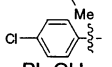


Figure 1. Lanthanide screen.

the yield of the product improving with increasing atomic number; the ee followed a similar, albeit less regular trend, reaching a maximum value with erbium and then decreasing sharply with metals of higher atomic number.

Table 1. Enantioselective Hydrocyanation of Hydrazones



entry	R	R'	time (days)	yield (%)[a]	ee (%)[b]
1	Me_2N-	H	3	85	97
2	BnO-	H	2	92	93
3	Ph	H	2	96	90
4		H	2	quant.	90.5 (>98)
5		H	3	93	88
6		H	3	90	85
7		H	3	87	80
8		H	2	90	83
9		H	2	96	79
10		H	2	98	80 (94)
11		H	2	99	76
12		H	3	89	76
13		H	3	94	84
14	Ph_2CH	H	2	98	69 (83)
15	*t*-Bu	H	2	98	66
16	$PhCH_2$	H	2	99	31
17	Ph	Me	4	92	44[c]

[a] Isolated yield. [b] Ee of crude product. Values in parentheses are those obtained after recrystallization. Stereochemical assignments were made by analogy with that of the 4-bromophenyl derivative (Table 2, entry 1). [c] Absolute stereochemistry not assigned.

Upon further optimization of the reaction conditions, it was found that hydrazone hydrocyanation could be performed at 0 °C in freshly purified chloroform[14] (0.25−0.10 M) using TMSCN and methanol[15] and 5 mol % [(*S*)-PhPYBOX]$ErCl_3$ [16] to give excellent yield of the adducts in 2−3 days (Table 1). A range of *N*-benzoyl-protected hydrazone derivatives underwent efficient reaction under these conditions. Best results were obtained with aromatic hydrazones (entries 1−13), with electron-rich substrates affording

(7) (a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394−6395. (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395−6397. (c) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397−6399.

(8) Ziegler, F. E.; Wender, P. A. *J. Org. Chem.* **1977**, *42*, 2001−2003.

(9) Chiba, T.; Okimoto, M. *Synthesis* **1990**, 209−211.

(10) Manabe, K.; Oyamada, H.; Sugita, K.; Kobayashi, S. *J. Org. Chem.* **1999**, *64*, 8054−8057.

(11) Lanthanum triflates and alkoxides were found to be ineffective catalysts, inducing only low substrate conversion.

(12) Only *N*-benzoyl, *N*-2-furanoyl, and *N*-2-thiophenoyl hydrazones displayed any reactivity under these reaction conditions, with both *N*-2-furanoyl and *N*-2-thiophenoyl derivatives undergoing hydrocyanation to very low conversion. Other hydrazones examined included *N*-tosyl, *N*-nosyl, *N*-formyl, *N*-acetyl, *N*-octoyl, *N*-phenylacetyl, *N*-phenyl, *N*-2,4-dinitrophenyl, and *N*-Boc derivatives.

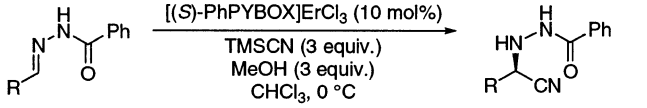
highest ees (entries 1 and 2). Aliphatic substrates also underwent reaction in high yield, albeit with significantly diminished enantioselectivity (entries 14−16).

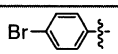
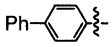
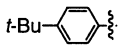
Electron-deficient substrates displayed very poor reactivity under the standard conditions. Substrates bearing strongly electron-withdrawing aromatic substituents (e.g., CF_3, NO_2, CO_2Et, CH═NNHCOPh) proved to be completely unreactive, whereas those bearing weakly withdrawing substituents (Cl and Br) reacted slowly but with high enatioselectivity. In the case of *m*- and *p*-bromo-substituted derivatives, complete conversion to the HCN adduct could be accomplished by using elevated catalyst loadings (10 mol %) and 3 equiv of TMSCN/MeOH (Table 2). The diminished reactivity of these substrates relative to their electron-rich counterparts suggests that complexation of the hydrazone to the Lewis acidic catalyst may be rate-limiting in these addition processes.

Other substrates displaying low reactivity are listed in Table 2. With the *p*-biphenyl derivatives, as with brominated substrates, simply increasing catalyst and cyanide loadings resulted in excellent yields (entry 3). However, other substrates failed to go to complete conversion even after 4 days under these conditions.

All of the hydrocyanation adducts obtained in this study were found to be solids at room temperature, raising the possibility of enhancing product enantiopurity through recrystallization. This proved to be possible with several selected substrates (Table 1, entries 4, 10, and 14, and Table 2, entries 1 and 2). X-ray structural determination of the 4-bromophenyl hydrocyanation adduct (Table 2, entry 1) permitted unambiguous assignment of absolute stereochemistry. In this manner, it was determined that the (*S*,*S*)-PhPYBOX ligand affords products of *R*-configuration.

Table 2. Enantioselective Hydrocyanation of Slowly Reacting Hydrazone Derivatives



entry	R	R'	time (days)	yield (%)[a]	ee (%)[a,b]
1		Ph	3	quant [31]	93 [91] (95)
2		Ph	3	98 [48]	90 [92] (94)
3		Ph	2	quant [24]	77 [83]
4		Ph	4	69	70
5	Ph	2-furyl	4	42 [17]	55 [65]
6	Ph	2-thienyl	4	50 [15]	33 [47]

[a] Values in brackets are those obtained using 5 mol % catalyst. [b] Ee values in parentheses are those obtained after recrystallization. The stereochemical assignment of entry 1 was made by X-ray crystallography, and all others were made by analogy.

In summary, we have developed the first catalytic asymmetric hydrocyanation of hydrazones to give stable, crystalline acyl hydrazino nitriles in excellent yield and good-to-excellent ee. Further efforts are being directed toward exploring the scope and mechanism of lanthanide−PYBOX-catalyzed cyanation reactions.

Acknowledgment. Financial support for this project has been provided by the NIH (GM59316) and through a postdoctoral fellowship to J.M.K. from AstraZeneca. We thank Dr. Richard Staples for carrying out the crystallographic studies.

Supporting Information Available: Experimental procedures for catalyst preparation and synthesis, isolation, and characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035844C

(13) (a) Aspinall, H. C.; Greeves, N.; Smith, P. M. *Tetrahedron Lett.* **1999**, *40*, 1763−1766. (b) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004.

(14) Aged chloroform, which can contain chlorine and HCl, induced hydrazone oxidation to afford several products, one of which was identified as 2,5-diphenyl-1,3,4-oxadiazole. Interestingly, treatment of a hydrazone with DDQ gives an identical product ratio as aged chloroform.

(15) Combination of MeOH and TMSCN afforded better conversions and ees than TMSCN alone or preformed HCN.

(16) Ligand:$ErCl_3$ ratios of 1.2−2.0 may be employed with no effect on ee or yield, although catalysts prepared with 2 equiv of ligand display better solubility.