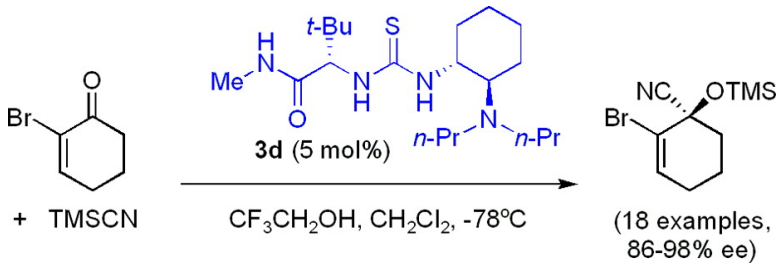
Communication

Thiourea-Catalyzed Enantioselective Cyanosilylation of Ketones

Douglas E. Fuerst, and Eric N. Jacobsen

J. Am. Chem. Soc., **2005**, 127 (25), 8964-8965• DOI: 10.1021/ja052511x • Publication Date (Web): 04 June 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 40 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 06/04/2005

Thiourea-Catalyzed Enantioselective Cyanosilylation of Ketones

Douglas E. Fuerst and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02318

Received April 18, 2005; E-mail: jacobsen@chemistry.harvard.edu

Lewis acid catalysis stands as the traditional and proven strategy for activation of carbonyl compounds toward enantioselective reactions.[1] Only recently, general acid catalysis with small-molecule hydrogen-bond donors has emerged as a promising alternative for electrophile activation in asymmetric synthesis.[2] Catalysts that function as H-bond donors exploit a mode of activation common in enzymatic pathways,[3] and may hold complementary reactivity and scope relative to metal-based systems. Our own efforts in general acid asymmetric catalysis have focused on chiral urea and thiourea derivatives (e.g. **1**, Figure 1) for activation of alkyl- or acyl-substituted imines in Strecker,[4] Mannich,[5] hydrophophonylation,[6] nitro-Mannich,[7] and acyl Pictet−Spengler[8] reactions.[9] Application of achiral urea and thiourea derivatives to carbonyl activation reactions was demonstrated in seminal work by Curran[10] and subsequent studies by Schreiner,[11] but only very recently have thiourea derivatives been applied with varying success to the asymmetric catalytic activation of carbonyl compounds.[12] We describe here a significant new example of thiourea catalysis in carbonyl 1,2-addition chemistry, in the highly enantioselective cyanosilylation of ketones and aldehydes with a new bifunctional thiourea−amine derivative.

The catalytic asymmetric cyanation of carbonyl compounds ranks among the most important and well-studied reaction classes in asymmetric catalysis, due in large part to the utility of the product cyanohydrins as precursors to α-hydroxy acids, β-amino alcohols, and other valuable chiral building blocks.[13] Whereas several outstanding catalyst systems have been identified for cyanation of aldehydes,[14] ketones present a greater challenge as a substrate class, and only recently have effective methods using chiral metal complexes,[15] cinchona alkaloids,[16] and chiral oxazaborolidinium ions[17] been devised. The known Schiff base derivative **1** displayed no measurable catalytic activity in the model cyanosilylation of acetophenone with TMSCN (Table 1). However, primary amine **2**, the immediate synthetic precursor to **1**, proved highly active and led to product formation in 25% ee. The modular nature of the thiourea derivatives allowed straightforward and systematic optimization of the catalyst structure.[18] While *tert*-leucine proved to be the optimal amino acid component, less sterically demanding amide derivatives led to improved enantioselectivities, with secondary methyl amides (catalysts **3a**−**d**) affording the best results. Replacement of the primary amine in **3a** with the corresponding *N*,*N*-dimethyl tertiary amine (**3b**) resulted in complete suppression of reactivity. However, introduction of CF_3CH_2OH for in situ generation of HCN restored catalytic activity and led to product formation in 90% ee.[19]

Optimization of other reaction parameters (e.g. solvent, temperature) led to further improvements in enantioselectivity with catalyst **3b**, albeit at the expense of reactivity (95% ee and 30% conversion at 48 h). The crucial role of the amine substituent on the catalyst was evident upon comparison of *N*,*N*-dimethyl (**3b**), *N*,*N*-diethyl (**3c**), and *N*,*N*-di-*n*-propyl (**3d**) derivatives. The more sterically demanding catalysts promoted silylcyanation with significantly increased reaction rates, with complete substrate conversion within 12 h at −78 °C.[20] Catalyst **3d** also induced measurably improved enantioselectivity (97% ee).[21]

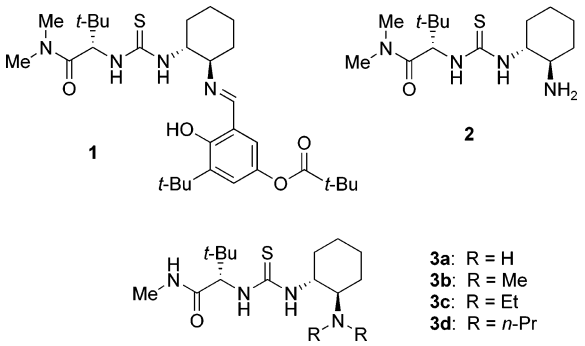
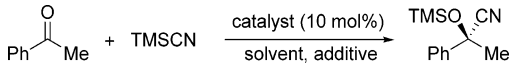


Figure 1. Thiourea catalysts.

Table 1. Optimization Studies[a]



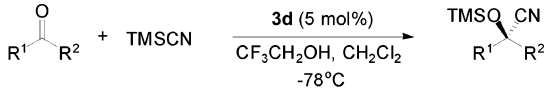
catalyst	solvent	additive	temp (°C)	time (h)	conv (%)[b]	ee (%)[c]
1	toluene		23	48	<5	
2	toluene		−40	3	100	25
3a	toluene		−40	3	100	55
3b	toluene		−40	24	0	
3b	toluene	CF_3CH_2OH[d]	−40	24	80	90
3b	CH_2Cl_2	CF_3CH_2OH[d]	−78	48	30	95
3c	CH_2Cl_2	CF_3CH_2OH[d]	−78	12	100	94
3d	CH_2Cl_2	CF_3CH_2OH[d]	−78	12	100	97

[a] Reactions were carried out on a 0.2 mmol scale with 1.3 equiv of TMSCN in 0.5 mL of solvent, unless noted otherwise. [b] Determined by GC relative to dodecane as internal standard. [c] Determined by GC analysis. [d] 2.2 equiv of TMSCN and 1.0 equiv of CF_3CH_2OH were used.

Thiourea catalyst **3d** proved to be general for the highly enantioselective cyanosilylation of a wide range of ketones (Table 2). In most cases, useful reaction rates were obtained at 5 mol % catalyst loading. Alkyl aryl ketones underwent reaction with high enantioselectivity with only slight dependence on the size of the alkyl group (entries 1−3) or the properties of the aromatic ring (entries 4−10). Heteroaromatic ketones were also excellent substrates, highlighting the tolerance of Lewis basic functionality with thiourea catalysts (entries 11−13). In addition, a range of α,β-unsaturated ketones were well-tolerated and afforded the 1,2-addition products exclusively (entries 14−17). Although **3d** was optimized for the reaction of ketones, it was also found to be an efficient catalyst for the cyanosilylation of aldehydes. Thus, benzaldehyde and *trans*-cinnamaldehyde underwent cyanosilylation with **3d** (0.05 mol %) and CF_3CH_2OH (20 mol %) within 2 h in 96% ee and 93% ee, respectively. As an indication of the possible

10.1021/ja052511x CCC: $30.25

Table 2. Enantioselective Cyanosilylation of Ketones Catalyzed by **3d**[a]



entry	ketone	time (h)	yield (%)[b]	ee (%)[c]
1	R = Me	24	96	97
2	R = Et	24	95	95
3	R = *i*-Pr	24	97	86
4[d]	R = *o*-Me	36	96	98
5	R = *p*-Me	36	97	96
6[e]	R = *m*-OMe	12	97	97
7	R = *p*-OMe	48	93	95
8	R = *p*-Br	12	94	93
9		36	91	95
10		12	98	97
11[e]		48	81	97
12[e,f]		48	88	98
13[e]		48	87	97
14	R = Me	12	94	96
15	R = *n*-Bu	12	97	93
16		48	95	89
17		12	95	97
18[e]		48	97	91

[a] Reactions were carried out on a 1.0 mmol scale with 2.2 equiv of TMSCN and 1.0 equiv of CF_3CH_2OH in 2.0 mL of CH_2Cl_2. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral GC or chiral HPLC (see Supporting Information). [d] Reaction carried out on 10 mmol scale. [e] Reaction carried out using 10 mol % catalyst. [f] Reaction carried out with 2.7 equiv of TMSCN and 1.5 equiv of CF_3CH_2OH.

practical potential of this catalyst system, the cyanosilylation of 2′-methylacetophenone was carried out on 10 mmol scale (96% yield, 98% ee) and the catalyst recovered in 96% yield by silica gel chromatography (entry 4).

High enantioselectivities have been obtained only in cyanosilylation of carbonyl substrates bearing one sp^2-hybridized substituent.[22] While the mechanism of catalysis with **3d** remains under investigation, electronic, rather than steric, differentiation of the two ketone substituents is implicated strongly as the source of asymmetric induction (compare entries 1−3 and 14−15).[23] The critical role of the Brønsted basic amine moiety in combination with the thiourea unit suggests a cooperative mechanism for **3d** involving simultaneous nucleophile and electrophile activation.[24]

Thiourea **3d** represents one of the most effective and general carbonyl cyanation catalysts identified to date. Current work is directed toward elucidating the mechanism of carbonyl activation and discovering other carbonyl addition reactions catalyzed by chiral thiourea derivatives.

Acknowledgment. This work was supported by the NIGMS through GM-43214 and P50 GM069721. We thank Mark S. Taylor for helpful discussions.

Supporting Information Available: Complete experimental procedures, characterization data, and chiral chromatographic analyses of racemic and enantiomerically enriched products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley: New York, 2000; Vols. 1 and 2. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.

(2) Reviews: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296. (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064. See also: (c) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (d) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094−12095.

(3) Reviews: (a) Shan, S.-O.; Herschlag, D. *Methods Enzymol.* **1999**, *308*, 246−276. (b) Schowen, K. B.; Limbach, H.-H.; Denisov, G. S.; Schowen, R. L. *Biochim. Biophys. Acta* **2000**, *1458*, 43−62.

(4) (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279−1281. (c) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867−890. (d) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012−10014.

(5) (a) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964−12965. (b) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 1919−1922.

(6) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102−4103.

(7) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466−468.

(8) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559.

(9) See also: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *124*, 12672−12673. (b) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625−627.

(10) (a) Curran, D. P.; Kuo, L. H. *J. Org Chem.* **1994**, *59*, 3259−3261; (b) *Tetrahedron Lett.* **1995**, *36*, 6647−6650.

(11) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217−220. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407−414.

(12) Dynamic kinetic resolution of azlactones: (a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807−811. (b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898−1900. Enantioselective Baylis−Hillman reactions: (c) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589−5592. Enantioselective arenethiol 1,4 additions to α,β-unsaturated imides: (d) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603−606. Nitromethane addition to chalcones: (e) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967−1969.

(13) For a review on the synthetic utility of cyanohydrins see: Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649−3682.

(14) For an excellent recent review on the catalytic asymmetric cyanation of aldehydes and ketones see: Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752−2778.

(15) (a) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron* **2001**, *57*, 771−779. (b) Hamashima, Y.; Kanai, M.; Shibasaki M. *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413. (c) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908−9909. (d) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009−1012. (e) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett.* **2003**, *5*, 949−952.

(16) (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195−6196. (b) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900−9901.

(17) Riu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384−5387.

(18) For a complete list of all urea and thiourea catalysts examined see the Supporting Information.

(19) The role of the alcohol additive is presumably to generate HCN as the active nucleophile in the addition reaction, as is the case in thiourea-catalyzed Strecker reactions (ref 4). For other examples of the beneficial effect of alcohol additives on cyanosilylation of carbonyls see: (a) Hayashi, M.; Matsuda, N.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3135−3140. (b) Brunel, J. M.; Legrand, O.; Buono, G. *Tetrahedron: Asymm.* **1999**, *10*, 1979−1984. (c) Reference 15d.

(20) The corresponding *N*,*N*-di-*n*-butylamine- and *N*,*N*-di-*n*-pentylamine-substituted catalysts afforded comparable conversion to **3d**, but with slightly lower enantioselectivity (95%).

(21) For the preparation of **3d**, see the Supporting Information.

(22) Dialkyl ketones are poor substrates in cyanosilylation reactions with **3d**: 2-heptanone, 11% ee; cyclohexyl methyl ketone, <5% conversion.

(23) Ketone enantioface selectivity dictated solely by electronic differentiation is well-precedented: (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153−9156. (b) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 10497−10504.

(24) The cyclohexylamine-derived analogue of **3d**, which lacks the tertiary amine group, displayed no reactivity under the standard conditions.

JA052511X