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Thiourea-Catalyzed Enantioselective Cyanosilylation of Ketones

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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-Spengler8 reactions.9 Application of achiral urea and thiourea derivatives to carbonyl activation reactions was demonstrated in seminal work by Curran¹⁰ 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 Wheareas 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 ions¹⁷ 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 CF3CH2OH 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



Figure 1. Thiourea catalysts.

Table 1. Optimization Studies^a

	Ű	catal	yst (10 mol	%) IM	SOLCN	
F	Ph Me +	IMSCN solv	vent, additiv	re F	h Me	
			temp	time	conv	ee
catalyst	solvent	additive	(°C)	(h)	(%) ^b	(%) ^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 ₃ CH ₂ OH ^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 CF₃CH₂OH were used.

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

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 1,2addition 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 CF₃CH₂OH (20 mol %) within 2 h in 96% ee and 93% ee, respectively. As an indication of the possible

by 3d^a 3d (5 mol%) TMSQ CN TMSCN R¹ R² CF₃CH₂OH, CH₂Cl₂ R¹ R² -78°C ketone yield $(\%)^{l}$ $ee(\%)^c$ entry time (h) R = Me24 96 97 2 24 95 95 R = Et3 97 $\mathbf{R} = i - \mathbf{P} \mathbf{I}$ 24 86 4^{*d*} 96 98 R = o - Me36 5 R = p-Me 36 97 96 6 97 R = m-OMe 12 97 R = p-OMe 93 95 7 48 8 94 R = p - Br12 93 9 91 95 36 10 12 98 97 48 81 97 12 48 88 98 13^e 48 87 97 96 14 12 94 R = Me15 R = n-Bu12 97 93 16 48 95 89 17 12 97 95 18 48 97 91

Table 2. Enantioselective Cyanosilylation of Ketones Catalyzed

^{*a*} Reactions were carried out on a 1.0 mmol scale with 2.2 equiv of TMSCN and 1.0 equiv of CF₃CH₂OH in 2.0 mL of CH₂Cl₂. ^{*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 CF₃CH₂OH.

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 sp²-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.

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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.

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