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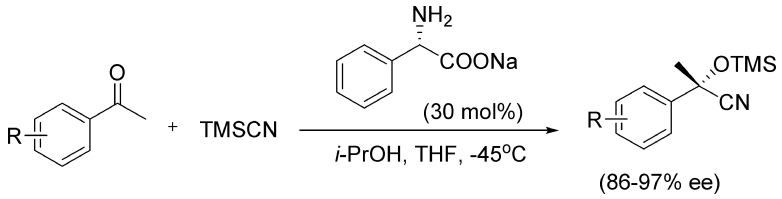
J. Am. Chem. Soc., **2005**, 127 (35), 12224-12225• DOI: 10.1021/ja052629d • Publication Date (Web): 13 August 2005



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Catalytic Asymmetric Cyanosilylation of Ketones by a Chiral Amino Acid Salt

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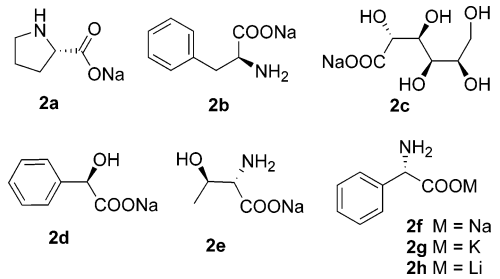
Received April 22, 2005; E-mail: xmfeng@scu.edu.cn

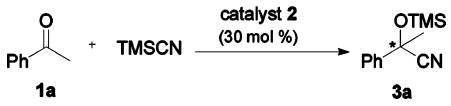
Homochiral cyanohydrins are of synthetic interest as they may be elaborated into a number of key multifunctional intermediates.[1] There have been intense research activities in enantioselective synthesis of cyanohydrins from aldehydes, ketones, and acetals in recent years.[2] The resultant reactions mainly employed catalysts such as enzymes, cyclic dipeptides, and transition metal complexes. But the asymmetric cyanation of ketones has been historically considered as problematic. At present, the majority of chiral catalysts used for this goal are chiral ligands attached to metals such as Al,[3] Ti,[4] and La,[5] basic cinchona alkaloid catalysts,[6] chiral oxazaborolidinium ions,[7] and thiourea catalysts.[8] In these contexts, a new methodology emerged from the study of interesting findings by Shibasaki and our group in which the oxygen atom of the phosphine oxide and *N*-oxide coordinated to the silicon atom of TMSCN to activate TMSCN. Meanwhile, some important observations have been made regarding the effect of heterogeneous catalysts on the synthesis of racemic cyanohydrins, such as solid acid and base catalysts,[9] diamino-functionalized mesoporous polymers,[10] and the inorganic/organic salts catalysts used in our early work.[11] It was of particular interest to us to explore this approach via the development of a catalytic asymmetric cyanation of ketones with readily accessible amino acid salts, in light of the abundance of chiral amino acids.

Herein, we described the first example of chiral organic salts as catalysts for asymmetric cyanosilylation of ketones. Our initial catalyst screening revealed that L-phenylglycine sodium salt **2f** was an effective catalyst and led to product formation in 44% ee. L-Proline has been widely used as an organocatalyst in many reactions,[12] with its sodium salt giving a racemic product, however. Both the primary amine moiety and the metal carboxylate moiety of catalyst **2f** were essential for the catalytic activity and asymmetric induction. Lithium and potassium salts of L-phenylglycine were less effective than the sodium salt in that the products were both racemic. The crucial role of the primary amino group of **2f** was evident upon comparison of the amine substituent on the catalyst (see Supporting Information for details).



Optimization of other reaction parameters led to further improvements in enantioselectivity with catalyst **2f**. The best result was obtained when 30 mol % catalyst loading was used. The solvent study indicated that THF afforded the best overall result, with 54% ee (Table 1, entries 6 and 9). Moreover, some key features associated with the use of L-phenylglycine sodium salt are noteworthy. When the catalyst was stirred with TMSCN in THF for 1 h at 30 °C before acetophenone was added, the enantioselectivity was greatly improved from 54% to 80% ee at −20 °C and up to 94% ee at −45 °C (entries 9−12). Interestingly, a small amount of water contained in the catalyst **2f** was crucial to retain enantioselectivity, and any attempt to remove water from the catalyst gave bad results. Moreover, introduction of ^{i}PrOH greatly promoted cyanosilylation rates, with complete acetophenone conversion within 24 h at −45 °C without loss of enantioselectivity (Table 1, entry 13) (see Supporting Information for details).

Table 1. Optimization Studies[a]



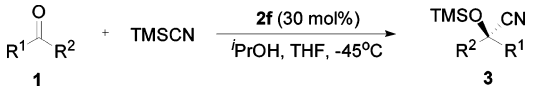
entry	catalyst	solvent	temp (°C)	yield[e] (%)	ee[f] (%)
1	**2a**	Et_2O	−20	94	4
2	**2b**	Et_2O	−20	92	4
3	**2c**	Et_2O	−20	98	11
4	**2d**	Et_2O	−20	15	14[g]
5	**2e**	Et_2O	−20	65	32
6	**2f**	Et_2O	−20	45	44
7	**2g**	Et_2O	−20	71	7[g]
8	**2h**	Et_2O	−20	98	2
9	**2f**	THF	−20	50	54
10	**2f**[b]	THF	−20	70	80
11	**2f**[b,c]	THF	−20	68	82
12	**2f**[b,c]	THF	−45	64	94
13	**2f**[b,d]	THF	−45	96	94

[a] Reactions were carried out on a 0.5 mmol scale with 1.2 equiv of TMSCN in 1.0 mL of solvent, unless noted otherwise. [b] The catalyst was stirred with 1.2 equiv of TMSCN in THF for 1 h at 30 °C before acetophenone was added. [c] The catalyst was prepared in situ. [d] 1.5 equiv of TMSCN and 0.5 equiv of ^{i}PrOH were used. [e] Isolated yield. [f] Determined by GC analysis. [g] The absolute configuration of the major product was *S*, assigned by comparing GC with the literature, and the others were *R*[4b] (see Supporting Information for details).

The scope of L-phenylglycine sodium salt **2f**-catalyzed enantioselective cyanosilylation was explored using a variety of ketones. Table 2 summarizes the most significant results obtained under optimized conditions. In most cases, useful reaction rates were obtained. Most of the aromatic, heterocyclic ketones were converted into the corresponding cyanohydrin trimethylsilyl ethers with high enantioselectivities (90−97% ee). When *trans*-cinnamophenone was subjected to our reaction condition, only the 1,2-addition product was afforded in 96% isolated yield and 97% ee (Table 2, entry 9). The aliphatic and α,β-saturated ketones gave moderate ee values (entries 11, 12). L-Phenglycine could be easily and efficiently recovered for reuse by simple filtration and acidic treatment after the reaction (ca. 94% recovery yield of L-phenylglycine).

10.1021/ja052629d CCC: $30.25

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

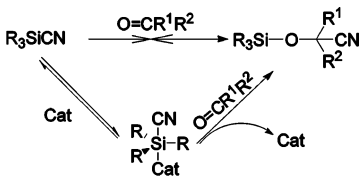


1 3

entry	ketone **1**	time (h)	yield[b] (%)	ee[c] (%)
1	acetophenone **1a**	24	96	94 [d]
2	4′-methoxyacetophenone **1b**	54	81	92
3	4′-methylacetophenone **1c**	54	75	97
4	4′-fluoroacetophenone **1d**	27	90	92
5	4′-chloroacetophenone **1e**	40	83	90
6	3′-chloroacetophenone **1f**	54	80	96
7	2′-fluoroacetophenone **1g**	36	77	90
8	2-acetylthiophene **1h**	54 (66)[e]	84 (58)[e]	86 (92)[e]
9	*trans*-4-phenyl-3-buten-2-one **1i**	27	96	97
10	*β*-acetonaphthone **1j**	27	90	96
11	benzylacetone **1k**	20	97	81
12	3-methylbutanone **1l**	20	92	55

[a] All reactions were carried out according to experimental procedure of Method D (see Supporting Information for details). [b] Isolated yield. [c] Determined by chiral GC or HPLC. [d] Absolute configuration of the major product was *R* by comparison with the literature.[4b] [e] The reaction was performed by Method C (see Supporting Information for details).

Scheme 1. Activation of Organosilicons by Nucleophilic Catalysts



Nucleophilic substitution at silicon in R_3SiX compounds can be activated by nucleophiles (e.g., RCO_2^-, RO^-, *N*-oxide, HMPA),[13,14] which are good coordinating agents for Si, and proceeds via the formation of hypervalent silicon intermediates with penta- or hexacoordination states. Studies have been carried out on the cyanosilylation of aldehydes using active chiral lithium phenolate catalyst[15] based on the hypervalent silicon intermediates. We considered hypervalent silicate formed from the interaction between the carboxylate ion of **2f** and TMSCN to be an active cyanation intermediate, since the nucleophilicity of the cyano group is enhanced by electron donation from the hypervalent silicon (Scheme 1). This silicon intermediate readily reacts with a carbonyl compound, followed by the immediate silylation to give the corresponding product. Support for this idea was obtained by a few simple NMR experiments (see Supporting Information for details). The spectral changes are consistent with use of Ph_3PO[16b] and *N*-oxides,[16c] and also strongly indicate that the environment around the silicon atoms of some TMSCN species is changed in the presence of L-phenylglycine sodium salt; the possible formation of hypervalent silicate species is suggested. Further characterization of catalyst coordination geometries through spectroscopic and computational model studies is underway.

In summary, we have developed a highly enantioselective cyanosilylation of ketones promoted by a simple chiral amino acid salt. The reaction is mechanistically interesting as the first chiral organic salt approach which differed from the known enzyme- and transition metal-based methods. Additional notable features of the reaction are the utilization of commercially available and fully recyclable catalysts and employment of simple and convenient experimental procedure. These features should render the reaction a catalytic entry for the other asymmetric creation of quaternary stereocenters. Further efforts will be devoted to search for effective systems that tolerate a broad range of ketones with higher yield and enantioselectivity.

Acknowledgment. We thank the National Natural Science Foundation of China (Nos. 20225206, 20390055, and 20372050), the Ministry of Education of China (No. 104209 and others), and Sichuan University (No. 2004CF07) for financial support.

Supporting Information Available: Experimental procedures and spectral and analytical data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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