ORGANIC LETTERS

2003
Vol. 5, No. 6
949−952

Enantioselective Cyanosilylation of Ketones by a Catalytic Double-Activation Method Employing Chiral Lewis Acid and Achiral *N*-Oxide Catalysts

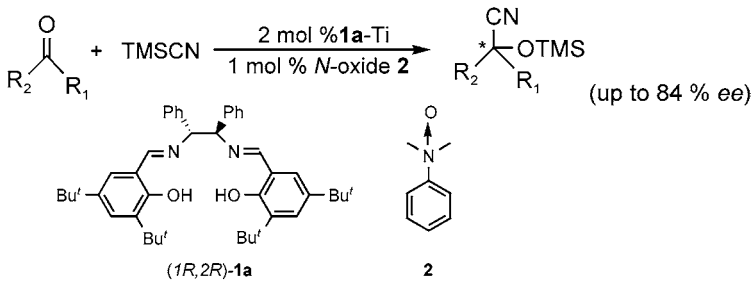
Fuxue Chen,[†] Xiaoming Feng,*[,‡] Bo Qin,[‡] Guolin Zhang,[§] and Yaozhong Jiang[†]

Sichuan Key Laboratory of Green Chemistry and Technology, College of Chemistry, Sichuan University, Chengdu 610064, China, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (CAS), Chengdu, China, and Chengdu Institute of Biology, CAS, Chengdu, China

xmfeng@pridns.scu.edu.cn

Received January 28, 2003

ABSTRACT



Enantioselective addition of TMSCN to ketones is achieved by a catalytic double-activation method using 1a–Ti(IV) complex as the Lewis acid and achiral *N*-oxide 2 as the Lewis base to activate ketones and TMSCN, respectively.

The ever-increasing demand for optically pure intermediates has driven much effort to develop and improve chiral catalyst systems by synthesizing and screening even structurally complicated discrete ligands.[1] Meanwhile, alternative approaches have also been advanced, including asymmetric activation and deactivation,[2] combinatory use of chiral or achiral additives,[3] and other techniques.[4] Herein, we present a novel scheme to develop an efficient catalyst system, in which a chiral Lewis acid and an achiral Lewis base act synergistically in a manner of double activation. The method is adapted to the enantioselective cyanosilylation of ketones.

In general, an asymmetric reaction between two or more components can proceed smoothly by either of the following methodologies: (1) less reactive electrophiles are activated

[†] Chengdu Institute of Organic Chemistry.
[‡] Sichuan University.
[§] Chengdu Institute of Biology.

(1) Pfaltz, A. In *Comprehensive Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 1, p 4.

(2) For a review, see: (a) Mikami, K.; Terada, M.; Korenaga, T.; Matrumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532. For recent examples, see: (b) Mikami, K.; Aikawa, K.; Yusa, Y.; Hatano, M. *Org. Lett.* **2002**, *4*, 91. (c) Mikami, K.; Aikawa, K.; Yusa, Y. *Org. Lett.* **2002**, *4*, 95. (d) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett.* **2002**, 1561.

(3) (a) Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570 and references therein. (b) Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carrol, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 6929 and references therein. (c) Long, J.; Hu, J. Y.; Shen, X. Q.; Ji, B. M.; Ding, K. L. *J. Am. Chem. Soc.* **2002**, *124*, 10.

(4) (a) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 3250. (b) Pandiaraju, S.; Chen, G.; Lough, A.; Yudin, A. K. *J. Am. Chem. Soc.* **2001**, *123*, 3850. (c) Reetze, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179.

10.1021/ol034158a CCC: $25.00
Published on Web 02/15/2003

by coordinating to a chiral Lewis acid, and the nucleophiles react favorably with the homogeneous electrophile/catalyst complexes to give enantiomerically enriched products (Lewis acid catalysis); or (2) less reactive nucleophiles coordinate to a chiral Lewis base, and the resulting nucleophile/Lewis base complexes react smoothly with the electrophiles to give optically active products (Lewis base-promoted reaction). When the components are too sluggish and neither methodology works effectively, a double activation approach may be the choice.[5] While a bifunctional catalyst integrates a Lewis acid and a Lewis base moiety into one molecule,[6] the double-activation method mixes the Lewis acid with the Lewis base in one flask, and they activate the electrophiles and nucleophiles, respectively.

Optically active cyanohydrins are synthetically important building blocks and chiral auxiliaries in the context of asymmetric synthesis.[7] Moreover, enantioselective construction of quaternary carboncenters via a C−C bond-forming process with keto electrophiles has gained more and more attention in recent years.[6b,8] Asymmetric addition of TMSCN (TMS = trimethylsilyl) to ketones is the most popular strategy to produce optically active cyanohydrins.

Belokon has reported a Ti-catalyzed cyanosilylation of aromatic ketones by utilizing a C_2-symmetric Schiff base as the chiral ligand.[9] Shibasaki has developed a novel bifunctional catalyst with a phosphoryl moiety to promote the addition of TMSCN to aromatic and aliphatic ketones.[10] Deng has outlined a method for cyanide addition to ketones with cyanoformate by employing Sharpless's cinchona derivatives as catalysts.[11] Most recently, Snapper has disclosed an aluminum-catalyzed enantioselective addition of TMSCN to aromatic and aliphatic ketones using recyclable peptide as the ligand.[12] Despite these advances, some pressing problems still exist such as the comparatively long route of synthesis and screening of the candidate ligands. This letter reports the development of a new double activation catalyst system and the application to the enantioselective addition of TMSCN to ketones with an easily accessible Ti−salen complex as the Lewis acid and achiral *N*-oxide as the Lewis base (Figure 1).

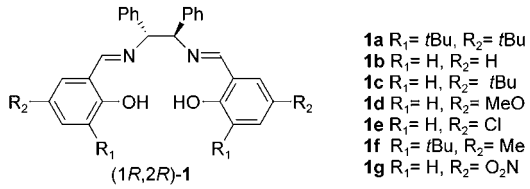


Figure 1. Chiral salen ligands evaluated in this study.

Previously, our group has reported a titanium-catalyzed asymmetric hydrocyanation of aldehydes,[13] and an *N*-oxide-promoted enantioselective Strecker reaction.[14] Also, we have disclosed a bifunctional *N*-oxide titanium-catalyzed enantioselective cyanosilylation of ketones, in which the metal titanium played the role of a Lewis acid and the N−O dipolar moiety a Lewis base to activate the keto group and TMSCN, respectively.[15] Accordingly, the Ti−salen complexes and *N*-oxides would be the catalysts for the double-activation method.

In a preliminary study, **1a**−Ti(O*i*Pr)$_4$ complex and *N*-oxide **2** are employed as the catalysts.[16] Fortunately, the product

Table 1. Addition of TMSCN to Acetophenone Catalyzed by **1a**−Ti(O*i*Pr)$_4$ and Lewis Bases[a]

entry	Lewis base	temp (°C)	yield (%)[b]	ee (%)[c]
1	**2**	0	95	67
2	HMPA	0	3	34
3	PyNO	0	0	0
4	NMNO	0	32	60
5	TMNO	0	26	65
6	**2**	−20	62	81
7	**2**	−40	30	76
8	**2**	−78	9	59
9[d]	**2**	0	25	74
10[e]	**2**	0	54	73
11[f]	**2**	0	90	74
12[g]	**2**	−20	75	84

[a] Conditions: 20 mol % **1a**−Ti(O*i*Pr)$_4$ complex, 20 mol % base, concentration of acetophenone = 0.12 M in CH_2Cl_2 (unless otherwise indicated), 84 h. [b] Isolated yield. [c] Determined by chiral GC analysis on Chirasil DEX CB. [d] **1a**−Ti(O*i*Pr)$_4$ (2 mol %), 2 mol % **2**, concentration of acetophenone = 0.12 M, 84 h. [e] **1a**−Ti(O*i*Pr)$_4$ (2 mol %), 2 mol % **2**, concentration of acetophenone 0.23 M, 84 h. [f] **1a**−Ti(O*i*Pr)$_4$ (2 mol %), 2 mol % **2**, concentration of acetophenone 0.52 M, 84 h. [g] Optimized conditions: 2 mol % **1a**-Ti(O*i*Pr)$_4$, 1 mol % **2**, concentration of acetophenone = 1.1 M, 120 h. HMPA = hexamethyl-phosphorus triamide; PyNO = pyridine *N*-oxide; NMNO = *N*-methylmorpholine *N*-oxide; TMNO = trimethylamine *N*-oxide.

is obtained in 95% yield with 67% ee after 84 h (Table 1, entry 1). With respect to reactivity and enantioselectivity,

(5) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394.
(6) For review on bifunctional catalysis, see: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (c) Hamashima, Y.; Sawasa, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641.
(7) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649.
(8) (a) For a review on catalytic enantioselective construction of quaternary carbon stereogenic centers, see: Cory, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. For recent examples, see: (b) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (c) Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239. (d) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061. (e) Garcfa, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970.
(9) (a) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147.
(10) (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412. (b) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691. (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. (d) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2923. (e) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647.
(11) Tian, S. K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195.
(12) Deng, H.; Snapper, M. P.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009.
(13) For our related reports on hydrocyanation of aldehydes catalyzed by Ti−salen complex, see: (a) Pan, W. D.; Feng, X. M.; Gong, L. Z.; Hu, W. H.; Li, Z.; Mi, A. Q.; Jiang, Y. Z. *Synlett*. **1996**, 337. (b) Jiang, Y. Z.; Gong, L. Z.; Feng, X. M.; Hu, W. H.; Pan, W. D.; Li, Z.; Mi, A. Q. *Tetrahedron* **1997**, *53*, 14327. (c) Feng, X. M.; Gong, L. Z.; Hu, W. H.; Li, Z.; Pan, W. D.; Mi, A. Q.; Jiang, Y. Z. *Chem. J. Chin. Univ.* **1998**, *19*, 1416 (in Chinese).

N-oxide **2** is preferred to other *N*-oxides and HMPA (Table 1, entries 2−5). PyNO (pyridine *N*-oxide) strongly coordinates to titanium, and no reaction occurs (Table 1, entry 3). Ligand screening reveals that **1a** has the highest capability of chiral induction among **1a**−**g**.[16] When the reaction is conducted at −20 °C, the enantioselectivity is improved to 81% ee (Table 1, entry 6). However, further decrease in the reaction temperature leads to a reduction in both enantioselectivity and reactivity (Table 1, entries 6−8). Moreover, the lower catalyst loading results in a sharp decrease in yield but a slight increase in enantioselectivity (Table 1, entry 9). Interestingly, the problem of the yield decrease caused by low catalyst loading can be solved by increasing the substrate concentration without any loss in enantioselectivity (Table 1, entries 9−11). The best ee value is recorded as 84% under the optimized molar ratio of Lewis acid to Lewis base (2:1) (Table 1, entry 12).

To broaden the applicability and the scope of the catalysts, a number of ketones were tested under the optimized conditions,[16] with the results listed in Table 2. While the

Table 2. Asymmetric Cyanosilylation of Ketones Catalyzed by **1a**−Ti(O*i*Pr)$_4$ and **2** Catalysts[a]

entry	ketone	yield (%)[b]	ee %[c]
1	$C_6H_5COCH_3$	75	84[d]
2	4-$MeC_6H_4COCH_3$	57	73
3	2-$FC_6H_4COCH_3$	80	76
4	4-$FC_6H_4COCH_3$	71	83
5	4-$ClC_6H_4COCH_3$	58	84
6	3-$ClC_6H_4COCH_3$	93	80
7	*β*-acetonaphthone	50	84[e]
8	α-tetralone	37	81
9	benzylacetone	85	84[f]
10	(*E*)-$C_6H_5CH{=}CHCOCH_3$	79	64[f]

[a] Conditions: 2 mol % **1a**−Ti(O*i*Pr)$_4$, 1 mol % **2**, substrate concentration = 1.1 M in CH_2Cl_2, − 20 °C, 120 h. [b] Isolated yield. [c] Determined by GC on Chirasil DEX CB. [d] Absolute configuration was established to be *S* by comparing the sign of optical rotation with that of literature.[10a] [e] Determined by HPLC on Chiralcel OJ. [f] Determined by HPLC on Chiralcel OD.

para-methyl and *ortho*-fluoro substituents on the aromatic ring lead to lower enantioselectivities than acetophenone (Table 2, entries 1−3), the *para*-fluoro- and chloro-substituted ketones give products of similar enantioselectivities with acetophenone (Table 2, entries 4−6). In terms of the product yield, *para*-substituted ketones are inferior to *meta*- or *ortho*-substituted ones. *β*-Acetonaphthone and α-tetralone afford products with similar enantioselectivities and reactivities (Table 2, entries 7 and 8). Different from Snapper's report,[12] the α,*β*-saturated ketone gives a higher ee value than the α,*β*-unsaturated one (Table 2, entries 9 and 10). This is in agreement with Shibasaki's result.[10a]

To identify the double activation, a series of control experiments were carried out, with the results listed in Table 3. Neither Ti(O*i*Pr)$_4$ nor the *N*-oxide **2** is sufficiently effective

Table 3. Addition of TMSCN to Acetophenone as a Control Experiment[a]

entry	Lewis acid	Lewis base	yield %[b]	ee %[c]
1	Ti(O*i*Pr)$_4$		0	
2		2	0	
3	Ti(O*i*Pr)$_4$	2	13	0
4	**1a**−Ti(O*i*Pr)$_4$		3	66
5	**1a**−Ti(O*i*Pr)$_4$	2	75	84
6[d]	**1a**−Ti(O*i*Pr)$_4$	2	31	75

[a] Conditions: 2 mol % Lewis acid, 1 mol % **2**, substrate concentration = 1.1 M in CH_2Cl_2, −20 °C, 120 h. [b] Isolated yield. [c] Determined by GC analysis on Chirasil DEX CB. [d] Catalysts were generated in situ by stirring the mixture of **1a**, **2**, and Ti(O*i*Pr)$_4$ in one flask.

to promote the addition of TMSCN to acetophenone (Table 3, entries 1 and 2). Only when these two are used together could the desired *O*-TMS cyanohydrin be found in the reaction mixture (Table 3, entry 3). While 2 mol % **1a**−Ti(O*i*Pr)$_4$ promotes the reaction in 3% yield with 66% ee (Table 3, entry 4), additional activation of TMSCN by 1 mol % *N*-oxide **2** results in a sharp increase in both isolated yield and enantioselectivity as 75% yield and 84% ee, respectively (Table 3, entry 5). These results indicate that, in this case, the chirality of the cyanohydrin is mainly homogeneously induced by the chiral Lewis acid, and the highly accelerated reaction rate is mostly due to the coordination of the *N*-oxide to TMSCN.[14a−b,17] The above discussion proves our hypothesis that this transformation could be performed via a double-activation path with Ti−salen complex as a Lewis acid and achiral *N*-oxide as a Lewis base. Nevertheless, when the Lewis acid and the Lewis base are generated together in one flask, unlike the typical procedure,[16] a much lower catalyst efficiency is recorded as 31% yield with 75% ee (Table 3, entry 6). The result again suggests that the *N*-oxide should act not as an additive[4b,3a] but as a double activation catalyst.[18] Although coordination complexes between *N*-oxides and diverse metals have been reported,[19] this observation removes Kanemasa's concern that the Lewis acid and the Lewis base might strongly bind to each other resulting in the disappearance of the catalytic capability.[5] Therefore, it can be expected that the double-activation method will have prospective

(14) On Strecker reaction, see: (a) Liu, B.; Feng, X. M.; Chen, F. X.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2001**, 1551. *N*-Oxides have been used previously to promote the reactions of other chlorosilane reagents; see: (b) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (c) Tao, B.; Lo, M. C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353. (d) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. (e) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799.

(15) (a) Shen, Y. C.; Feng, X. M.; Li, Y.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2002**, 793. (b) Shen, Y. C.; Feng, X. M.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2002**, 1353.

(16) See Supporting Information.

(17) ^{1}H NMR (400 MHz, $CDCl_3$) shows that the chemical shift of TMSCN is $\delta = 0.35$ ppm. However, after TMSCN coordinates to *N*-oxide **2**, a new signal appears at $\delta = 0.17$ ppm.

(18) The following observation also supports this conclusion using chiral *N*-oxide. The addition of TMSCN to acetophenone is achieved in 14% yield with 35% ee by using 20 mol % **1b**−Ti(O*i*Pr)$_4$ and 20 mol % (*R*)-3,3′-dimethyl-2,2′-biquinoline *N*,*N*′-dioxide[14b] at 0 °C for 84 h.

(19) For a review on *N*-oxide metal complexes, see: (a) Karayannis, N. M.; Pytlewski, L. L.; Mikulski, C. M. *Coord. Chem. Rev.* **1973**, *11*, 93. For a recent example, see: (b) Dyker, G.; Hölzer, B.; Henkel, G. *Tetrahedron: Asymmetry* **1999**, *10*, 3297.

applications and provide more alternatives in the screening for efficient catalyst systems.

In conclusion, a highly efficient catalyst system has been developed for the enantioselective cyanosilylation of ketones by a catalytic double-activation method (CDAM), in which electrophiles and nucleophiles are activated by a catalytic amount of a chiral Lewis acid (2 mol %) and an achiral Lewis base (*N*-oxide, 1 mol %), respectively. Moreover, one-step preparation of the catalyst from commercially available material, low catalyst loading, and mild reaction conditions all make this approach practical. Further mechanistic studies and other related reactions along this line are underway.

Acknowledgment. The authors thank the National Natural Science Foundation of China (No. 20225206) and the Ministry of Education, P. R. China, for financial support. The authors also thank Dr. Xiandeng Hou at Sichuan University for fruitful discussions.

Supporting Information Available: Experimental procedure and characterization for **1a**, **2**, and the cyanohydrins and chiral GC or HPLC analyses of the *O*-TMS cyanohydrins. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034158A