Vanadium-catalyzed Asymmetric Transcyanation of Aliphatic Aldehydes with Acetone Cyanohydrin

Junko Takaki, Hiromichi Egami, Kazuhiro Matsumoto, Bunnai Saito, and Tsutomu Katsuki*
Department of Chemistry, Faculty of Science, Graduate School, Kyushu University, 33 Hakozaki, Higashi-ku, Fukuoka 812-8581

(Received February 27, 2008; CL-080220; E-mail: katsuscc@mbox.nc.kyushu-u.ac.jp)

The vanadium(V)(salalen) complex prepared in situ from the corresponding vanadium(IV) complex **4** under aerobic conditions was found to be an excellent catalyst for asymmetric transcyanation of aliphatic aldehydes with acetone cyanohydrin as the cyanide source, showing high enantioselectivity of 91–95% ee.

Asymmetric cyanation of carbonyl functionalities is one of the most direct and efficient methods for preparing optically active cyanohydrins and a large number of highly enantioselective methods have been developed.[1,2] Although the utility of those reactions is associated with many factors, it largely depends on the cyanide source used. Hydrogen cyanide is inexpensive and the most atom-efficient but it is a highly toxic gas and requires a special care to use. Today, trimethylsilyl cyanide (TMSCN) is widely used as the source because its use gives the corresponding trimethylsilyl ether that does not undergo reverse cyanation. However, it is expensive, volatile, and still difficult to handle. Hence, the use of other cyanide sources such as cyanoformate,[3,4] acyl cyanide,[4] cyanophosphonate,[5] and potassium cyanide[3,6] has been examined. In 2000, Maruoka et al. reported another approach, an enantioselective Meerwein–Ponndorf–Verley type transcyanation using a commercially available and manageable acetone cyanohydrin as the cyanide source.[7] Though requiring relatively high catalyst loading and low reaction temperatures, this approach has an advantage of providing a non-protected cyanohydrin. The potential of this approach prompted us to examine the cyanation using an cationic oxovanadium(V)(salen) complex as the catalyst and we found that the reaction proceeded in the presence of an appropriate amine base with moderate to high enantioselectivity.[8] A μ-oxo vanadium complex of cis-β configuration had been proposed to participate in asymmetric cyanation with a vanadium(salen)/TMSCN system by North et al.[9] The mechanistic study of our method also infers the participation of a vanadium complex of cis-β configuration.[8] On the other hand, in parallel with this study, we discovered that chiral cis-β metal(salalen) complexes exhibited versatile and potent asymmetric catalysis.[10,11] Therefore, we were intrigued by vanadium(salalen) complexes as catalysts for asymmetric transcyanation using acetone cyanohydrin.

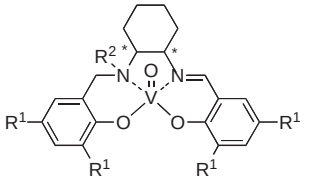
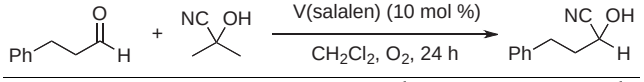


Figure 1. Oxovanadium(IV)(salalen) complexes **1**–**4**.

We prepared oxovanadium(IV)(salalen) complexes **1**–**4** according to the known procedure with a slight modification (Figure 1)[11a,12] and examined cyanation of 3-phenylpropanal with acetone cyanohydrin in dichloromethane (Table 1). The reaction was first conducted with complex **1** as a catalyst at room temperature under a nitrogen atmosphere. The reaction was rather slow, and the enantioselectivity and yield were poorly reproducible (Entry 1). Since oxovanadium(V)(salen) complexes are more efficient catalysts for asymmetric transcyanation than the corresponding oxovanadium(IV)(salen) complexes[8] and an oxovanadium(IV) complex is oxidized to the corresponding oxovanadium(V) species by molecular oxygen,[6,13] we considered that the catalytically poor oxovanadium(IV) complex **1** was partly oxidized by contaminating oxygen to a more reactive oxovanadium(V) species. Therefore, complex **1** was exposed prior to the reaction with oxygen for 1 h at room temperature and used for the cyanation in an oxygen atmosphere. As expected, the reaction proceeded smoothly, though the enantioselectivity was low (Entry 2).[14] However, lowering the reaction temperature to 0 °C remarkably improved the enantioselectivity to 81% ee, without reducing the yield (Entry 3).[15] We speculated that this cyanation was reversible at room temperature, but the reverse reaction was significantly suppressed at 0 °C. Indeed, the exposure of the cyanohydrin of 81% ee to the reaction

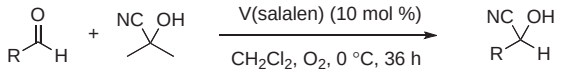
Table 1. Asymmetric cyanation of 3-phenylpropanal with oxovanadium complexes **1**–**4**[a]



Entry	Complex	T/°C	Yield/%[b]	ee/%[c]	Config.[d]
1[e]	**1**	rt	20–80	2–42	*R*
2	**1**	rt	>99	11	*R*
3	**1**	0	>99	81	*R*
4	**1**	−15	38	86	*R*
5	**2**	0	>99	87	*S*
6	**3**	0	37	89	*S*
7	**4**	0	74	93	*S*
8[f]	**4**	0	>99	92	*S*
9[g]	**4**	0	99[h]	91	*S*

[a]Complexes were exposed prior to the reaction to oxygen for 1 h at rt and the reaction was carried out on a 0.2 mmol scale, unless otherwise mentioned. [b]Determined by ^{1}H NMR (400 MHz) analysis. [c]Determined by the reported method (ref. 8). [d]Determined by comparison of the optical rotations with the literature value. [e]Complex **1** was used without pretreatment with oxygen and the reaction was carried out under nitrogen. [f]Reaction time was 36 h. [g]Carried out on a gram scale for 36 h. [h]Isolated yield.

Table 2. Asymmetric cyanation of various aldehydes with complex **4**[a]



Entry	R	Yield/%[b]	ee/%	Config.
1	n-C_7H_{15}	83	94[c]	—
2	c-C_6H_{11}	>99	94[c]	S[d]
3	c-C_5H_9	75	95[c]	—
4	t-Bu	92	94[e]	S[d]
5	i-Bu	66	94[c]	S[d]
6	t-BuPh$_2$SiO(CH$_2$)$_5$	>99	94[f]	—
7	Ph	44–61	25–39[c]	—

[a]The reaction was carried out on a 0.2 mmol scale. [b]Determined by ^{1}H NMR (400 MHz) analysis. [c]Determined by GC analysis (SUPELCO BETA-DEX-325) after conversion to the corresponding acetate. [d]Determined by comparison of the optical rotation with the literature value. [e]Determined by the reported method (ref. 8). [f]Determined by HPLC analysis (Daicel CHIRALPAK IB) after conversion to the corresponding acetate.

conditions, with the exception of 3-phenylpropanal, at room temperature, diminished the ee to 25% after 22 h. In addition, the formation of a trace amount of 3-phenylpropanal was detected by ^{1}H NMR analysis. These results indicated that the poor reproducibility observed in the initial attempt arose from not only the partial oxidation of complex **1**, but also the reversibility of the reaction at the room temperature. Further lowering the temperature to $-15\,^\circ$C significantly diminished the rate of the reaction, though the enantioselectivity was slightly improved (Entry 4). To examine the effect of the *N*-alkyl group and the aromatic substituents, we carried out the cyanation with complex **2** bearing *t*-hexyl groups and complex **3** bearing an *N*-ethyl group as the precatalyst at $0\,^\circ$C (Entries 5 and 6). We found that enantioselectivity was improved in both cases. Eventually, enantioselectivity as high as 93% ee was achieved with complex **4** (Entry 7), though the yield was moderate. Ultimately, a satisfactory yield was obtained with a negligible reduction of enantioselectivity by extending the reaction time (Entry 8). It is noteworthy that this reaction could be carried out on a gram scale with almost equal enantioselectivity of 91% (Entry 9).[16]

We investigated the scope of the asymmetric cyanation using complex **4** as the precatalyst (Table 2). Various aliphatic aldehydes were converted to the cyanohydrins with high enantioselectivity, together with good yields, irrespective of the presence or absence of the α-substituent(s) (Entries 1–6). On the other hand, the reaction of benzaldehyde was unproductive due to the rapid reverse reaction (Entry 7).[8]

In conclusion, we were able to determine that oxovanadium(IV)(salalen) complex **4** carrying a chiral nitrogen atom adjacent to the metal center is an efficient precatalyst for the asymmetric transcyanation with acetone cyanohydrin, though the substrate scope is limited to various aliphatic aldehydes. The present study clearly demonstrated the potential of transcyanation as the method for preparing nonprotected cyanohydrins. Further study is underway in our laboratory.

Financial support (Specially Promoted Research no. 18002011) from a Grant-in-Aid for Scientific Research from MEXT, Japan, is gratefully acknowledged. H. E., K. M., and B. S. are grateful for a JSPS Research Fellowships for Young Scientists.

References and Notes

1 a) A. Mori, S. Inoue, in *Comprehensive Asymmetric Catalysis*, ed. by E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer, Berlin, **1999**, Vol. 2, p. 983. b) F. Effenberger, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555. c) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649.
2 For recent reviews on asymmetric cyanohydrin synthesis, see: a) M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147. b) J. Brunel, I. Holmes, *Angew. Chem., Int. Ed.* **2004**, *43*, 2752, and references therein.
3 a) J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem., Int. Ed.* **2002**, *41*, 3636. b) J. Casas, A. Baeza, J. M. Sansano, C. Nájera, J. M. Saá, *Tetrahedron: Asymmetry* **2003**, *14*, 197. c) Y. N. Belokon', A. J. Blacker, L. A. Clutterbuck, M. North, *Org. Lett.* **2003**, *5*, 4505. d) Y. N. Belokon', A. J. Blacker, P. Carta, L. A. Clutterbuck, M. North, *Tetrahedron* **2004**, *60*, 10433. e) N. Yamagiwa, J. Tian, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 3413. f) Y. N. Belokon', W. Clegg, R. W. Harrington, E. Ishibashi, H. Nomura, M. North, *Tetrahedron* **2007**, *63*, 9724.
4 a) S. Lundgren, E. Wingstrand, M. Penhoat, C. Moberg, *J. Am. Chem. Soc.* **2005**, *127*, 11592. b) A. Baeza, C. Nájera, J. M. Sansano, J. M. Saá, *Tetrahedron: Asymmetry* **2005**, *16*, 2385.
5 A. Baeza, J. Casas, C. Nájera, J. M. Sansano, J. M. Saá, *Angew. Chem., Int. Ed.* **2003**, *42*, 3143.
6 Y. N. Belokon', P. Carta, A. V. Gutnov, V. Maleev, M. A. Moskalenko, L. V. Yashkina, N. S. Ikonnikov, N. V. Voskoboev, V. N. Khrustalev, M. North, *Helv. Chim. Acta* **2002**, *85*, 3301.
7 a) T. Ooi, K. Takaya, T. Miura, K. Maruoka, *Synlett* **2000**, 69. b) T. Ooi, T. Miura, K. Takaya, H. Ichikawa, K. Maruoka, *Tetrahedron* **2001**, *57*, 867.
8 A. Watanabe, K. Matsumoto, Y. Shimada, T. Katsuki, *Tetrahedron Lett.* **2004**, *45*, 6229.
9 Y. N. Belokon', M. North, T. Parsons, *Org. Lett.* **2000**, *2*, 1617.
10 Salalen ligand is half-reduced salen ligand; A. Yeori, S. Gendler, S. Groysman, I. Goldberg, M. Kol, *Inorg. Chem. Commun.* **2004**, *7*, 280.
11 a) B. Saito, T. Katsuki, *Angew. Chem., Int. Ed.* **2005**, *44*, 4600. b) K. Matsumoto, Y. Sawada, B. Saito, K. Sakai, T. Katsuki, *Angew. Chem., Int. Ed.* **2005**, *44*, 4935. c) B. Saito, H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2007**, *129*, 1978. d) Y. Sawada, K. Matsumoto, T. Katsuki, *Angew. Chem., Int. Ed.* **2007**, *46*, 4559. e) T. Yamaguchi, K. Matsumoto, B. Saito, T. Katsuki, *Angew. Chem., Int. Ed.* **2007**, *46*, 4729. f) H. Fujita, T. Uchida, R. Irie, T. Katsuki, *Chem. Lett.* **2007**, *36*, 1092. g) A. Berkessel, M. Brandenburg, E. Leitterstorf, J. Frey, J. Lex, M. Schäfer, *Adv. Synth. Catal.* **2007**, *349*, 2385.
12 H. Egami, H. Shimizu, T. Katsuki, *Tetrahedron Lett.* **2005**, *46*, 783.
13 Y. N. Belokon', V. I. Maleev, M. North, D. L. Usanov, *Chem. Commun.* **2006**, 4614.
14 Ambient air can be used instead of molecular oxygen: when **4** was exposed to air for 1 h, the same enantioselectivity was observed, albeit with a diminished yield (82%).
15 The reaction of 3-phenylpropanal with the salen counterpart of **1** did not proceed under the same conditions.
16 Complex **4** (0.562 g, 0.75 mmol) was dissolved in CH_2Cl_2 (37 mL) and stirred under oxygen balloon for 1 h at room temperature. After the balloon was detached, hydrocinnamaldehyde (0.98 mL, 7.5 mmol) was added and cooled to $0\,^\circ$C, and freshly distilled acetone cyanohydrin (2.0 mL, 22 mmol) was added. The solution was stirred for 36 h. The reaction was quenched by 1 M HCl and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were evaporated in vacuo and the residue was chromatographed on silica gel to give the corresponding cyanohydrin in 99% yield.

Published on the web (Advance View) March 29, 2008; doi:10.1246/cl.2008.502