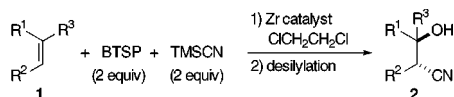# Novel Multiaction of Zr Catalyst: One-Pot Synthesis of β-Cyanohydrins from Olefins

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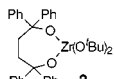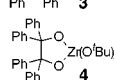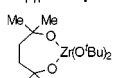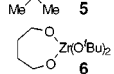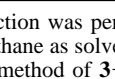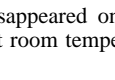*Tokyo 113-0033, Japan*

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Improving the efficiency of organic syntheses, including minimizing the energy cost and chemical waste, is a major goal in synthetic chemistry. To this regard, performing multistep bond-formation and/or bond-cleavage in one pot is an attractive strategy.[1] Therefore, we are interested in developing catalytic tandem reactions, in which one catalyst promotes each step of sequential reactions.[2] Significant contribution has been achieved by using late transition metal catalysts.[3] On the other hand, we have recently reported the one-pot process to synthesize *trans*-β-acetoxy alcohols from olefins in the presence of bis(trimethylsilyl) peroxide (BTSP) and TMSOAc, promoted by a catalytic amount of $Zr(O^iPr)_4$.[4] In this reaction, the Zr catalyst promotes the epoxidation step[5] and the epoxide-opening step. We planned to extend this chemistry to a more valuable carbon−carbon bond-forming reaction, using TMSCN as the nucleophile. In this work, the first one-pot *trans*-β-cyanohydrin synthesis with broad substrate scope is reported. From mechanistic studies, it seems that the Zr catalyst plays a multiple role being an oxidant, a Lewis acid, and a nucleophile, in a tandem reaction process.

We first found extremely sluggish β-cyanohydrin formation, when the best reaction conditions of acetoxy alcohol synthesis were applied, using TMSCN instead of TMSOAc. From cyclohexene **1b**, the corresponding cyanohydrin **2b** was obtained in 33% yield at room temperature for 30 days (CH_2Cl_2 as solvent) in the presence of $Zr(O^iPr)_4$ (10 mol %), BTSP (2 mol equiv), and TMSCN (2 mol equiv). Preliminary optimization of the reaction conditions such as solvent, concentration, and reaction temperature resulted in a synthetically acceptable reaction time and chemical yield, using 20 mol % of $Zr(O^iPr)_4$ (Table 1, entry 2). Systematical survey of the Zr source[6] revealed an intriguing relationship between the steric bulkiness of the ligand of Zr and the reaction rate (Table 1, entry 1−4). The catalyst containing the bulkiest tertiary alkoxide ligand (**3**) showed the shortest reaction time for the complete consumption of the starting material (entry 4). We assumed that this tendency should stem from the more facile ligand exchange (for example, from O^tBu to CN) in the case of Zr catalyst with bulkier alkoxide ligand. Efficient ligand exchange should be the key for promoting the two completely different steps (epoxidation and epoxide-opening). Therefore, we attempted to observe the effect of additives which should coordinate to Zr and facilitate the ligand exchange. Moreover, we expected that the Lewis base should enhance the

Table 1. One-Pot Synthesis of **2b** from Cyclohexene **1b**[a]

entry	Zr catalyst (mol %)[b]	additive (mol %)	time/h[c]	yield/%[d]
1	$Zr(O^nBu)_4$ (20)	–	84	62
2	$Zr(O^iPr)_4$ (20)	–	63	63
3	$Zr(O^tBu)_4$ (20)	–	38	63
4	**3** (20)	–	15	68
5	**3** (20)	Ph_3PO (20)	1.5	94
6[e]	**3** (5)	Ph_3PO (5)	12	95
7	**4** (20)	Ph_3PO (20)	1.5	92
8	**5** (20)	Ph_3PO (20)	17	84
9	**6** (20)	Ph_3PO (20)	24	78

[a] The reaction was performed with 2 equiv of BTSP and TMSCN in dichloroethane as solvent at 50 °C unless otherwise noted. [b] For the preparation method of **3**−**6**, see ref 13. [c] The reaction was quenched when **1b** disappeared on NMR. [d] Isolated yield. [e] The reaction was conducted at room temperature.

nucleophilicity of the zirconium cyanide. Among the additives screened,[7] it was found that the reaction became much faster and cleaner in the presence of 20 mol % of Ph_3PO and the product was obtained in 94% yield in 1.5 h (entry 5).[8] Surprisingly, in the presence of 40 mol % of Ph_3PO, the reaction did not proceed at all, indicating that the Lewis acidity of Zr would also play an important part. The ring size of the diol ligand is not important for the activity of the catalyst and only the steric factor seemed to have a dominant role (entry 7−9). Finally, we have found that even in the presence of 5 mol % of catalyst **3**, **2b** was obtained in 95% yield at room temperature for 12 h (entry 6).

Next we investigated the generality of this one-pot β-cyanohydrin synthesis. As shown in Table 2, cyanohydrin **2d** could be obtained in good yield even from much less reactive cyclooctene **1d** (entry 4).[9] The ester group is also tolerated and the product was obtained in completely stereoselective manner (entry 5). It is noteworthy that the reaction of **1e** catalyzed by $Zr(O^tBu)_4$ in the absence of Ph_3PO resulted in the formation of many side products. The reaction was successfully applied to **1f** which could be prone to aromatize due to the oxidative conditions (entry 6). The regioselectivity of **1j** and **1k** was perfect (entry 10, 11), although in the case of **1k**, trans isomer was contaminated with cis isomer.[10] The regioselectivity of sterically unsymmetrical olefins was moderate only in one case (entry 12), but perfect in other cases (entry 13−15).[11] In all these cases, the major isomer was derived from the attack of cyanide at the less hindered carbon center.[12] Thus, this one-pot β-cyanohydrin synthesis is general to a wide variety of olefins with synthetically useful selectivities.[13]

To get preliminary insight into the reaction mechanism, several

(1) (a) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2000; p 39. (b) Hall, N. *Science* **1994**, *266*, 32−34.

(2) Another interesting tandem system composed of multi (two) artificial catalysts in one pot was reported recently: Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220−10221.

(3) For example, see: de Meijere, A.; Bräse, S. In *Perspectives in Organopalladium Chemistry for the XXI Century*; Tsuji, J., Ed.; Elsevier: 1999; p 88.

(4) Sakurada, I.; Yamasaki, S.; Göttlich, R.; Iida, T.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 1245−1246.

(5) (a) Irie, R.; Hosoya, N.; Katsuki, T. *Synlett* **1994**, 255−256. (b) Yudin, A. K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 11536−11537.

(6) Other metals such as Ti or Sn were completely ineffective.

(7) Other additives: Bu_3PO, 57% (6.5 h); HMPA, 75% (3.5 h); DMSO, 62% (6.5 h); pyridine oxide, 82% (15 h).

(8) For an example of ligand-accelerated catalysis, see: Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968−1970.

(9) Even the epoxide opening reaction by cyanide from cyclooctene oxide is unprecedented.

(10) The trans/cis selectivity was higher with use of Ph_3AsO than with use of Ph_3PO (trans/cis = 2.6/1) as additive in the case of **1k**.

(11) In other cases than entry 14, no advantage was observed with Hf catalyst.

(12) In the absence of Ph_3PO, **1o** gave the primary alcohol derived from the internal attack of the cyanide as the major product.

(13) Representative procedure (Table 2, entry 2): To a mixture of the diol (0.025 mmol) and Ph_3PO (0.025 mmol) in dichloroethane (0.43 mL) was added $Zr(O^tBu)_4$ (0.025 mmol) at 0 °C and the whole mixture was stirred for 10 min. To the resulting clear solution were added BTSP (213 μL, 1 mmol), TMSCN (133 μL, 1 mmol), and **1b** (0.5 mmol) to start the reaction.
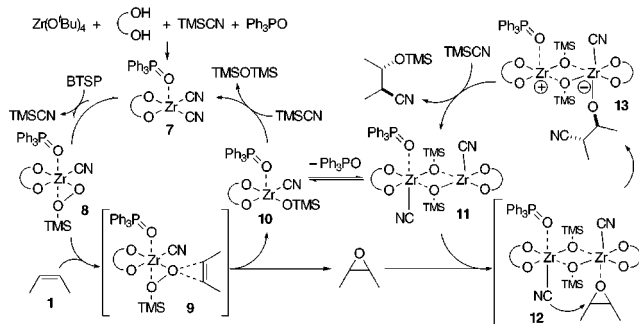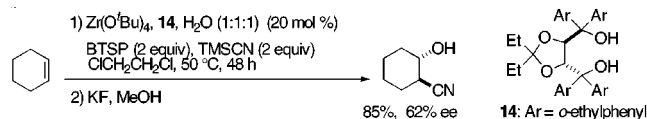
Table 2. One-Pot Synthesis of β-Cyanohydrins **2** from Olefins **1** Promoted by **3**−Ph₃PO (1:1) Complex[a]

entry	Olefin	Product	catalyst (mol %)	temp (°C)	time (h)	yield (%)
1	**1a**	(n = 1) **2a**	5	r.t.	5	87
2	**1b**	(n = 2) **2b**	5	r.t.	12	95
3	**1c**	(n = 3) **2c**	5	50	5	96
4	**1d**	(n = 4) **2d**	10	50	59	82 [b]
5	MeO₂C... **1e**	MeO₂C... **2e**	10	50	4	100
6	**1f**	**2f**	5	r.t.	24	90
7	ArO₂S−N **1g** (Ar = 2,4,6-triisopropylphenyl)	ArO₂S−N **2g**	10	50	7	91
8	**1h**	**2h**	10	50	10	86
9	**1i**	**2i**	10	50	59	63 [c]
10	**1j**	**2j**	10	50	1	78
11	**1k** (Ns = p-nitrobenzenesulfonyl)	**2k** **2k'**	20	r.t.	60	53 [c,d] (48 + 5)
12	**1l**	**2l** **2l'**	10	50	24	55 [e] (41 +14)
13	**1m**	**2m**	10	r.t.	48	75
14	**1n**	**2n**	10	50	12	94 [f]
15	Ph **1o**	Ph **2o**	5	r.t.	12	76

[a] For the representative procedure, see ref 13. [b] 4 equiv of TMSCN were used. [c] 4 equiv of TMSCN and BTSP were used. [d] Ph₃AsO was used instead of Ph₃PO. [e] 10 mol % of Zr(O^{t}Bu)₄ and 20 mol % of the diol were used. [f] Hf(O^{i}Pr)₄ was used instead of Zr(O^{t}Bu)₄.

techniques were used. First, we found that this one-pot reaction proceeded stepwise. The intermediate epoxide was observed tracing the reaction of **1a**, **1d**, and **1i** by ¹H NMR. Second, TMSCN was necessary to promote the epoxidation step. Thus, in the absence of TMSCN, no reaction took place from cyclohexene **1b**, BTSP, and Zr(O^{t}Bu)₄. However, **2b** was obtained adding TMSCN to this mixture. On the contrary, BTSP was not necessary for the epoxide-opening step. Cyclohexene oxide reacted with TMSCN in the presence of 20 mol % of Zr(O^{t}Bu)₄, and **2b** was obtained in 65% yield at 50 °C for 1.5 h. Therefore, cyanide should be incorporated in the catalyst. Further evidence of the catalyst structure was obtained from NMR studies. After addition of Ph₃PO (1 equiv) to the mixture of Zr(O^{t}Bu)₄ and the diol (1 equiv), the peaks corresponding to Ph₃PO showed large downfield shift (³¹P NMR: $\Delta\delta = 8.3$ ppm). After further addition of TMSCN (4 equiv) to this mixture, the signals corresponding to 4 equiv of TMSO^{t}Bu and 2 equiv of HCN emerged, indicating the generation of zirconium dialkoxy dicyanide coordinated by Ph₃PO (**7**) as shown in Scheme 1. The third bit of information was obtained from kinetic studies. The initial reaction rates of the epoxidation of **1b** and the epoxide opening of cycloheptene oxide were studied, varying the concentration of **3**.[14] Very interestingly, the reaction rate of the epoxidation step showed a first-order and that of the epoxide opening a second-order dependency on the catalyst concentration. These results indicated

Scheme 1. Working Model for the Catalytic Cycle

Scheme 2

1) Zr(O^{t}Bu)₄, **14**, H₂O (1:1:1) (20 mol %)
BTSP (2 equiv), TMSCN (2 equiv)
ClCH₂CH₂Cl, 50 °C, 48 h
2) KF, MeOH
85%, 62% ee
14: Ar = o-ethylphenyl

that the catalyst(s) should change the mode of action in one pot, promoting the epoxidation step in the single metal-centered mechanism and the epoxide-opening step in the binuclear metal-centered mechanism. Considering the precedent studies concerning the reaction mechanism of the Ti-catalyzed epoxidation[15] and Yb-catalyzed epoxide opening by cyanide,[16] we proposed a working hypothesis for this novel reaction (Scheme 1). Addition of BTSP to the precatalyst **7** may give **8** by ligand exchange from cyanide to trimethylsilyl peroxide.[17] The olefin might then attack the peroxide activated by bidentate coordination to Zr center (**9**), thus giving the epoxide as the initial product and **10**. From **10**, ligand exchange by TMSCN would regenerate **7** with the formation of disiloxane. On the other hand, partial dissociation of Ph₃PO might generate a binuclear catalyst **11** possessing a vacant site on Zr. The epoxide, generated by the first catalytic cycle, would be activated coordinating to this Lewis acidic Zr. The cyanide transfer from the adjacent Zr cyanide (**12**) followed by silylation by TMSCN would give the silylated β-cyanohydrin.[18] This reaction mechanism is consistent with the reaction rate dependency on the catalyst observed by the kinetic studies. Therefore, the Zr catalyst works as an oxidant, a Lewis acid, and a nucleophile. This multiaction of the Zr catalyst should be the key factor for the success of this one-pot process.

Preliminary application to the catalytic asymmetric reaction was performed using TADDOL derivative **14** as the chiral ligand (Scheme 2).[19] Although the enantioselectivity is still not satisfactory, this result demonstrates the possibility for the one-pot synthesis of chiral β-cyanohydrins[16,20] from olefins.

In conclusion, we have accomplished the general one-pot synthesis of β-cyanohydrins from olefins promoted by Zr catalyst. Further optimization of the enantioselective reaction is ongoing.

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

(14) Since the reaction rate of the epoxide opening of cyclohexene oxide was too fast, we used cycloheptene oxide as the substrate for the kinetic studies of the second step. See Supporting Information for more details.

(15) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106−113.

(16) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004.

(17) Consistent with the precedent case of Ti-catalyzed epoxidation, NMR signals corresponding to **8** could not be observed due to the predominant preference of **7** vs **8**.

(18) This reaction mechanism may also explain the adverse effect of the excess additive Ph₃PO.

(19) The ee was lower in the absence of H₂O. The positive effect of H₂O would stem from the formation of μ-oxo complex, which would make the entry to the enantioselective binuclear transition state **12** more favorable. In the presence of Ph₃PO, the product was almost racemic.

(20) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704−1707.