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$Zr(OBu^t)_4$ As an effective promoter for the Meerwein–Ponndorf–Verley alkynylation and cyanation of aldehydes: development of new asymmetric cyanohydrin synthesis

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Abstract—$Zr(OBu^t)_4$ Can serve as an effective promoter for the Meerwein–Ponndorf–Verley alkynylation of aldehydes and also facilitate MPV type cyanide transfer to aldehyde carbonyls with commercially available acetone cyanohydrin under mild conditions. Based on this finding, a new procedure for asymmetric cyanohydrin synthesis has been developed employing (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL, **6**) as a chiral ligand. For instance, sequential treatment of CH_2Cl_2 solution of **6** (1 equiv.) with $Zr(OBu^t)_4$ (1 equiv.) and acetone cyanohydrin (2 equiv.) at room temperature for 1 h, and subsequent reaction with 3-phenylpropanal at −40°C for 7.5 h resulted in formation of the corresponding cyanohydrin **5g** [R=$Ph(CH_2)_2$] in 63% isolated yield with 85% ee. The scope and limitations of this method have been clarified with various aldehydes as substrates.

During our recent study on the development of the new Meerwein–Ponndorf–Verley (MPV) reduction system,[1] we discovered that facile alkynyl transfer [**A**] to aldehyde carbonyls can be successfully realized by the utilization of modified aluminum alkoxides (Scheme 1).[2] Although this MPV alkynylation is highly effective for the selective transformation of aldehydes into the corresponding propargyl alcohols without using organometallic reagents, the reaction heavily depends on the significant rate-acceleration provided by *o*,*o*′-biphenylenedioxy ligand on aluminum, because the intrinsic reactivity of the simple aluminum alkoxide, e.g. $Al(OC(CH_3)_2C{\equiv}CPh)_3$ was found to be exceedingly low as exemplified in Scheme 1. This situation caused us to devote further effort to the search for appropriate metal reagents of sufficient reactivity, which should expand the generality of the transformation and open it up for broad synthetic applications.[3]

First, we examined the reactivity of various metal alkoxides in the alkynylation of pentafluorobenzaldehyde. Initially, metal alkoxide (1 equiv.) was treated with propargylic alcohol **1** (4 equiv.) in CH_2Cl_2 at room temperature for 30 min and then pentafluorobenzaldehyde was added. Each reaction was monitored by TLC and the results are listed in Table 1, which unambiguously shows that most of the metal isopropoxides and/or *t*-butoxides examined here turned out to be totally ineffective. Interestingly, the desired alkynylation product **2** was obtained in 82% yield only when $Zr(OBu^t)_4$ was used as a promoter.[4,5] It should be noted that commonly used, strong Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_4$, and $SnCl_4$ were found to be unsuitable, and nearly instantaneous decomposition of the propargylic alcohol was observed. Here, we performed a ^{13}C NMR study to confirm the generation of expected zirconium alkoxide.

The original signals of alkoxy α-carbons of $Zr(OBu^t)_4$ and **1** occurred at δ 74.75 and 65.05, respectively. Upon mixing $Zr(OBu^t)_4$ and **1** in a 1:4 molar ratio in CD_2Cl_2 at room temperature, significant downfield shift of hydroxy bearing carbon of **1** was observed at δ 71.22 with concurrent appearance of the free *t*-BuOH signal at δ 68.28 and none of the original signals were detected. This result indicates the complete alcohol exchange between $Zr(OBu^t)_4$ and **1** and therefore $Zr(OC(CH_3)_2C{\equiv}CPh)_4$ must be an actual reactive species in solution, enabling facile MPV-type alkynyl transfer through a six-membered transition state like **A**.

The efficiency of $Zr(OBu^t)_4$ as a promoter was also emphasized in the MPV alkynylation of 2,2-dichlorodecanal. Thus, treatment of 2,2-dichlorodecanal with $Zr(OBu^t)_4$ and **1** (4 equiv.) in CH_2Cl_2 at room temperature for 1 h produced the acetylenic alcohol **4** in 50% isolated yield, while the use of $Al(OC(CH_3)_2C{\equiv}CPh)_3$ under otherwise identical reaction conditions gave none of the desired product **4** (Scheme 2).

We further applied the present approach to cyanation of aldehydes using acetone cyanohydrin as a cyanide source.

Keywords: cyanohydrin; alkynylation; cyanation.
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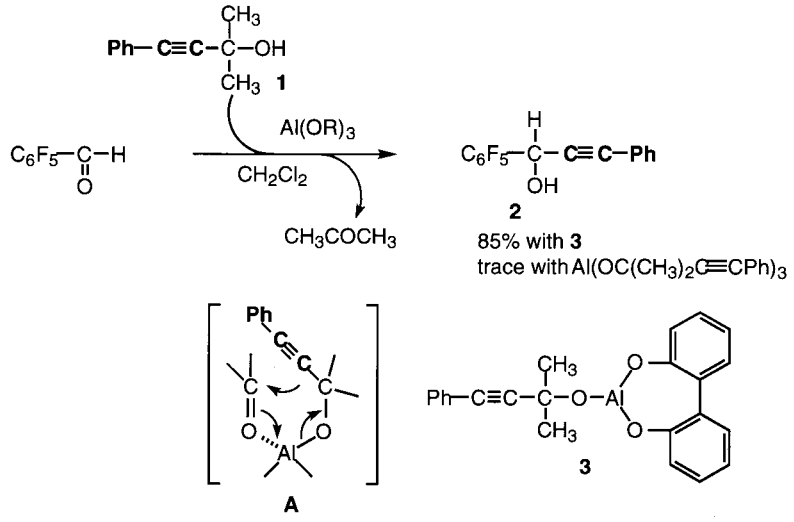


Scheme 1.

To our surprise, treatment of pentafluorobenzaldehyde with a premixed CH_2Cl_2 solution of $Zr(OBu^t)_4$ (1 equiv.) and acetone cyanohydrin (2 equiv.) at room temperature resulted in a rapid and clean formation of the corresponding cyanohydrin **5a** (R=C_6F_5) in 90% yield (entry 1 in Table 2) and comparable reactivity was also attained in the reaction with benzaldehyde (entry 2). Other selected examples summarized in Table 2 clearly demonstrate the efficiency and general applicability of the MPV cyanation: it proceeds smoothly with various aldehydes under mild reaction conditions by the use of commercially available, safe-to-handle acetone cyanohydrin as a cyanide source and the only by-product is relatively non-toxic, volatile acetone.

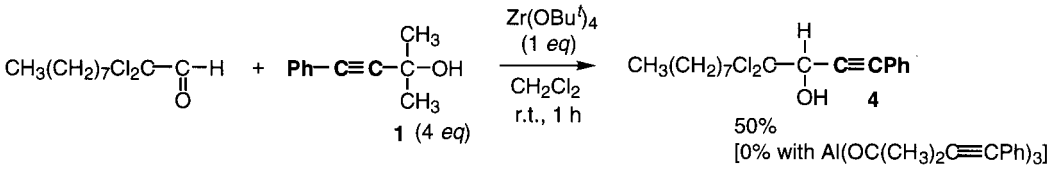
Table 1. MPV Alkynylation of C_6F_5CHO with various metal alkoxides (the reaction was carried out in CH_2Cl_2 at room temperature with 1 equiv. of metal alkoxide and 4 equiv. of **1** under indicated conditions)

Entry	Alkoxide	Time (h)	Yield (%)[a,b]
1	$Al(OPr^i)_3$	6	6
2	$Al(OBu^t)_3$	6	10
3	$Ti(OPr^i)_4$	6	n.r.
4	$TiCl_2(OPr^i)_2$	2	n.r.[c]
5	$Ti(OBu^t)_4$	9	n.r.
6	$Zr(OPr^i)_4$	6	n.r.
7	$Zr(OBu^t)_4$	0.25	82
8	$Sm(OPr^i)_3$	6	n.r.
9	$Yb(OPr^i)_3$	6	n.r.

[a] Isolated yield of **2**.
[b] n.r.=no reaction.
[c] Decomposition of **1** was mainly observed.

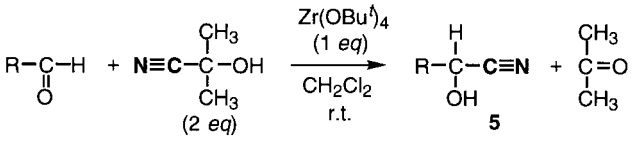
Based on this finding, we set out to investigate the asymmetric version of the MPV cyanation employing a chiral zirconium ligand,[6] which could provide a new access to optically active cyanohydrins,[7,8] versatile synthetic intermediates of various homochiral compounds such as α-hydroxy carboxylic acids, α-hydroxy aldehydes, α-hydroxy ketones, β-hydroxy amines and α-amino acid derivatives as well as other biologically important organic molecules.[9]

Optically active phenols, alcohols and amines were examined in the cyanation of 3-phenylpropanal as a model substrate under fixed reaction conditions (−20°C for 2 h). Since it is well known that ligand exchange between $Zr(OBu^t)_4$ and binaphthol derivatives enhances the Lewis acidity,[4c] we first chose (*S*)-binaphthol for our purpose with the expectation that the reaction could proceed even at lower temperature, which would be beneficial to enantiofacial control. However, sequential treatment of CH_2Cl_2 solution of (*S*)-binaphthol (1 equiv.) with $Zr(OBu^t)_4$ (1 equiv.) and acetone cyanohydrin (2 equiv.) at room temperature for 1 h, and subsequent reaction with 3-phenylpropanal at −20°C for 2 h gave rise to the corresponding cyanohydrin, 2-hydroxy-4-phenylbutanenitrile [**5g**; R=$Ph(CH_2)_2$] in only 7% isolated yield and the enantiomeric excess was determined to be 23% ee (entry 1 in Table 3). This result indicates that enhancement of Lewis acidity is not necessarily effective for this MPV-type reaction and preservation of the appropriate push-pull relay seems to be indispensable. Although employment of other commercially available, optically active diols and diamines including (*R*)-(+)-1,1,2-triphenyl-1,2-ethanediol[5c] for the cyanation gave



Scheme 2.

Table 2. $Zr(OBu^t)_4$-Promoted MPV cyanation of aldehydes (unless otherwise noted, acetone cyanohydrin (2 equiv.) was treated with $Zr(OBu^t)_4$ (1 equiv.) in CH_2Cl_2 at room temperature for 30 min, and then reacted with aldehyde under the given reaction conditions)

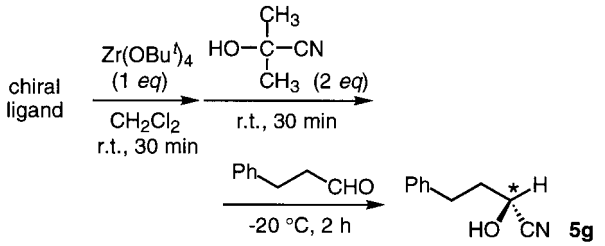


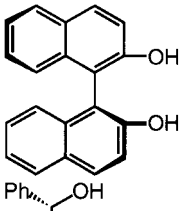
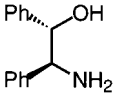
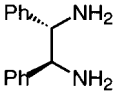
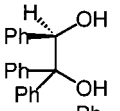
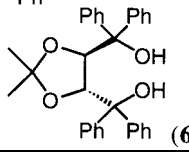
Entry	Aldehyde (R)	Reaction time (h)	Product	Yield (%)[a]
1	C_6F_5	0.1	**5a**	90
2	Ph	0.5	**5b**	93
3	*o*-Cl-C_6H_4	0.5	**5c**	76
4	*p*-NO_2-C_6H_4	0.5	**5d**	82
5	*p*-MeO-C_6H_4	5	**5e**	91
6	α-Np	2	**5f**	91
7	$Ph(CH_2)_2$	1	**5g**	96
8	$CH_3(CH_2)_6$	0.5	**5h**	91
9		0.5	**5i**	82

[a] Isolated yield.

disappointing results especially in terms of asymmetric induction as shown in Table 3, on reaction with (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL, **6**)[10] under similar conditions the enantioselectivity was greatly improved to 79% ee with satisfactory chemical yield (67%) (entry 5). With this information, our attention was focused on the optimization of the reaction condition and evaluation of the generality of the present approach. The enantioselectivity was further enhanced by performing the reaction at −40°C (entry 1 in Table 4). Use of 4 equiv. of acetone cyanohydrin led to better chemical yield (80%) with slightly diminished enantiomeric excess (80% ee) and the enantioselectivity was improved to 91% ee by lowering the reaction temperature to −78°C, for which chemical yield was sacrificed (32%) (entries 2 and 3). Consequently, we decided to examine a variety of aldehydes as substrates for this TADDOL-derived zirconium alkoxide-mediated asymmetric MPV cyanation at −40°C with 2 equiv. of acetone cyanohydrin, and the results are listed

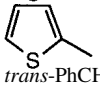
Table 3. Chiral zirconium alkoxides-promoted asymmetric MPV cyanation of 3-phenylpropionaldehyde (unless otherwise specified, the reaction was carried out with $Zr(OBu^t)_4$ (1 equiv.) and chiral ligand (1 equiv.) in CH_2Cl_2 at −20°C for 2 h)



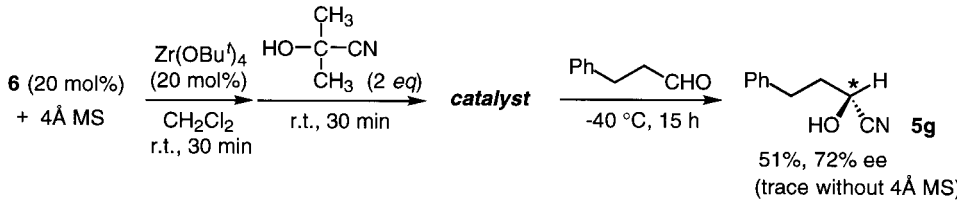
Entry	Chiral ligand	Yield (%)[a]	ee (%)[b] (config)[c]
1		7	23 (*R*)
2		93	28 (*R*)
3		51	8 (*R*)
4		11	8 (*R*)[d]
5	 (**6**)	67	79 (*R*)

[a] Isolated yield of acetate.
[b] Enantiomeric excesses were determined by GC analysis of the corresponding acetates with chiral column (GL SCIENCE CP-CHIRASIL-DEX CB).
[c] Absolute configurations were determined by comparison of optical rotations of cyanohydrins with literature values.
[d] At 0°C for 1 h.

Table 4. Chiral zirconium alkoxides-mediated asymmetric MPV cyanation of aldehydes (unless otherwise noted, **6** (1 equiv.) was sequentially treated with $Zr(OBu^t)_4$ (1 equiv.) and acetone cyanohydrin (2 equiv.) in CH_2Cl_2 at room temperature for 1 h, and then reacted with aldehyde under the given reaction conditions)

Entry	Aldehyde (R)	Condition (°C, h)	Product	Yield (%)[a]	ee (%)[b] (config)[c]
1	$Ph(CH_2)_2$	−40, 7.5	**5g**	63	85 (*R*)
2		−40, 7.5		80	80 (*R*)[d]
3		−78, 7.5		32	91 (*R*)
4	$CH_3(CH_2)_8$	−40, 5	**5j**	63	84 (*R*)
5	*c*-Hex	−40, 5	**5k**	55	79 (*R*)
6	*t*-Bu	−40, 5	**5l**	36	72 (*R*)
7	$PhCH_2$	−40, 5	**5m**	47	59 (*R*)
8	Ph	−40, 18	**5b**	45	63 (*R*)
9		−40, 18	**5i**	30	61 (*R*)
10		−40, 18	**5n**	28	54 (*R*)
11	*trans*-PhCH=CH	−40, 18	**5o**	25	29 (*R*)

[a] Isolated yield of acetate.
[b] Enantiomeric excesses were determined by GC analysis of the corresponding acetates with chiral column (GL SCIENCE CP-CHIRASIL-DEX CB).
[c] Absolute configurations were determined by comparison of optical rotations of cyanohydrins with literature values.
[d] 4 equiv. of acetone cyanohydrin was used.



Scheme 3.

in Table 4. In the asymmetric cyanation of aliphatic aldehydes, as were more substituents on the α-position of substrates, both reactivity and selectivity were gradually decreased (entries 4–6). Aromatic aldehydes were also found to be employable, giving the corresponding cyanohydrins in moderate enantioselectivities (entries 8–10). Unfortunately, the reaction with α,β-unsaturated aldehyde such as *trans*-cinnamaldehyde gave less satisfactory results (entry 11).

In the present MPV cyanation of aldehydes, the amount of chiral zirconium alkoxide is reducible to catalytic if facile alcohol exchange with acetone cyanohydrin can regenerate the catalyst and derivatize the product cyanohydrin in situ. Since the advantages of the catalytic version are quite obvious in terms of economy, large-scale preparation and isolation, we further investigated on this possibility and found that the presence of 4 Å molecular sieves played a prominent role in establishing the catalytic cycle.[8] For instance, treatment of 3-phenylpropanal with the catalyst (20 mol%), prepared with activated, powdered 4 Å molecular sieves in an otherwise similar manner, in CH_2Cl_2 at −40°C for 15 h gave rise to the cyanation product, 2-hydroxy-4-phenylbutanenitrile [**5g**; R=Ph$(CH_2)_2$] in 51% with 72% ee, whereas the cyanation without molecular sieves under otherwise identical conditions afforded only a trace amount of **5g** as illustrated in Scheme 3.[11]

1. Experimental

1.1. General

Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8200A spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-300 spectrometer and a JEOL JNM-FX400 spectrometer. Analytical gas-liquid phase chromatography (GLC) was performed on Shimadzu GC-14B instruments equipped with a flame ionization detector and a chiral capillary column of GL Science CP-CHIRASIL-DEX CB (0.25×25,000 mm) using nitrogen as carrier gas. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). Elemental analyzes were accomplished at the Center for Instrumental Analysis, Hokkaido University.

In experiments requiring dry solvents, ether was purchased from Kanto Chemical Co. Ltd as 'Dehydrated'. Methylene chloride was freshly distilled from calcium hydride, and toluene was freshly distilled from sodium metal. Pyridine was stored over KOH pellets. Zirconium tetra-*tert*-butoxide was purchased from Strem Chemicals Co. Ltd. 2,2-Dichlorodecanal[12] and (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL, **6**)[10a] were prepared according to the literature procedures. Other simple chemicals were purchased and used as such.

1.2. General procedure for Meerwein–Ponndorf–Verley (MPV) alkynylation of pentafluorobenzaldehyde with various metal alkoxides

2-Methyl-4-phenyl-3-butyn-2-ol (**1**) (0.32 g, 2 mmol) and metal alkoxide (0.5 mmol) were placed in a dry, two-neck flask with stirring bar under argon and freshly distilled CH_2Cl_2 (5 mL) was introduced, then this mixture was stirred for 30 min at room temperature. Freshly distilled pentafluorobenzaldehyde (62 μL, 0.5 mmol) was added dropwise and the reaction mixture was stirred for 0.25–9 h at room temperature. The reaction was quenched by the addition of 1N HCl and an extractive workup was performed with ether. The ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ether/hexane=1:4 as eluant) gave the alkynylation product **2**.

1.2.1. 2-Methyl-4-phenyl-3-butyn-2-ol (1).[13] This alcohol was prepared by treatment of acetone with an ether solution of lithium phenylacetylide at 0°C. ^{1}H NMR ($CDCl_3$) δ 7.39–7.46 (2H, m, Ph), 7.27–7.36 (3H, m, Ph), 2.02 (1H, s, OH), 1.62 (6H, s, $2CH_3$).

1.2.2. 1-(Pentafluorophenyl)-3-phenyl-2-propyn-1-ol (2). ^{1}H NMR ($CDCl_3$) δ 7.41–7.48 (2H, m, Ph), 7.29–7.40 (3H, m, Ph), 5.98 (1H, d, *J*=8.1 Hz, C*H*OH), 2.71 (1H, d, *J*=8.1 Hz, OH); IR (KBr) 3172, 2242, 1656, 1506, 1290, 1122, 1053, 984, 915, 756, 693 cm^{-1}. Anal. Calcd for $C_{15}H_7F_5O$: C, 60.42; H, 2.37. Found: C, 60.43; H, 2.35.

1.3. MPV Alkynylation of 2,2-dichlorodecanal with $Zr(OBu^t)_4$

To a solution of 2-methyl-4-phenyl-3-butyn-2-ol (**1**) (0.32 g, 2 mmol) in freshly distilled CH_2Cl_2 (5 mL) was added a 1 M toluene solution of $Zr(OBu^t)_4$ (0.5 mL, 0.5 mmol) at room temperature and the mixture was stirred for 30 min. Freshly distilled 2,2-dichlorodecanal (113 mg, 0.5 mmol) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of 1N HCl and an extractive workup was performed with ether. The ethereal extracts

were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane=1:5 as eluant) gave the alkynylation product **4** (82 mg, 0.25 mmol; 50% yield).

1.3.1. 4,4-Dichloro-1-phenyl-1-dodecyn-3-ol (4). ^{1}H NMR ($CDCl_3$) δ 7.44–7.53 (2H, m, Ph), 7.29–7.40 (3H, m, Ph), 4.83 (1H, d, J=8.4 Hz, C*H*OH), 2.77 (1H, d, J=8.4 Hz, OH), 2.30–2.40 (2H, m, CCl_2CH_2), 1.74 (2H, quint, J=7.8 Hz, CCl_2CCH_2), 1.18–1.46 (10H, m, $5CH_2$), 0.88 (3H, t, J=6.9 Hz, CH_3); IR (liquid film) 3423, 3034, 2926, 2855, 2237, 1598, 1491, 1466, 1445, 1379, 1236, 1069, 756, 691 cm^{-1}. Anal. Calcd for $C_{18}H_{24}Cl_2O$: C, 66.06; H, 7.39; Cl, 21.66. Found: C, 65.87; H, 7.58; Cl, 21.45.

1.4. General procedure for MPV cyanation of aldehydes

To a solution of acetone cyanohydrin (92 μL, 1 mmol) in freshly distilled CH_2Cl_2 (5 mL) was added a 1 M CH_2Cl_2 solution of $Zr(OBu^t)_4$ (0.5 mL, 0.5 mmol) at room temperature and the mixture was stirred for 30 min. Freshly distilled aldehyde (0.5 mmol) was added dropwise and the reaction mixture was stirred for 0.1–5 h at room temperature. The reaction was quenched with 1N HCl and the aqueous phase was extracted with ether. The ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ethyl acetate/hexane=1:5 as eluant) gave the cyanation products **5**.

1.4.1. 2-Hydroxy-2-(pentafluorophenyl)acetonitrile (5a).[14] ^{1}H NMR ($CDCl_3$) δ 5.83 (1H, d, J=8.4 Hz, C*H*OH), 2.97 (1H, d, J=8.4 Hz, OH); IR ($CHCl_3$) 3414, 3024, 2934, 2860, 1709, 1659, 1512, 1431, 1335, 1306, 1132, 1057, 1001, 893, 669 cm^{-1}.

1.4.2. 2-Hydroxy-2-phenylacetonitrile (5b). Described below.

1.4.3. 2-(*o*-Chlorophenyl)-2-hydroxyacetonitrile (5c).[15] ^{1}H NMR ($CDCl_3$) δ 7.70–7.85 (1H, m, Ph), 7.37–7.48 (3H, m, Ph), 5.88 (1H, d, J=6.8 Hz, C*H*OH), 2.90 (1H, d, J=6.8 Hz, OH); IR (liquid film) 3408, 3107, 2930, 2251, 1595, 1578, 1475, 1445, 1416, 1279, 1192, 1134, 1059, 1036, 941, 920, 818, 758, 729, 710 cm^{-1}.

1.4.4. 2-Hydroxy-2-(*p*-nitrophenyl)acetonitrile (5d).[16] ^{1}H NMR ($CDCl_3$) δ 8.33 (2H, d, J=8.4 Hz, Ph), 7.76 (2H, d, J=8.4 Hz, Ph), 5.71 (1H, d, J=6.4 Hz, C*H*OH), 3.04 (1H, d, J=6.4 Hz, OH); IR (KBr) 3406, 3119, 1609, 1524, 1346, 1229, 1190, 1109, 1067, 858, 808, 746, 704 cm^{-1}.

1.4.5. 2-Hydroxy-2-(*p*-methoxyphenyl)acetonitrile (5e).[17] ^{1}H NMR ($CDCl_3$) δ 7.46 (2H, d, J=8.8 Hz, Ph), 6.96 (2H, d, J=8.8 Hz, Ph), 5.49 (1H, d, J=7.2 Hz, C*H*OH), 3.84 (3H, s, CH_3), 2.54 (1H, d, J=7.2 Hz, OH); IR (liquid film) 3414, 3037, 2937, 2841, 2245, 1612, 1514, 1466, 1308, 1256, 1178, 1115, 1032, 926, 835, 770 cm^{-1}.

1.4.6. 2-Hydroxy-2-(α-naphthyl)acetonitrile (5f).[18] ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, d, J=8.4 Hz, Naph), 7.96 (1H, d, J=8.0 Hz, Naph), 7.94 (1H, δ, J=7.2 Hz, Naph), 7.85 (1H, d, J=7.2 Hz, Naph), 7.50–7.67 (3H, m, Naph), 6.20 (1H, s, C*H*OH), 2.70 (1H, br s, OH); IR (liquid film) 3414, 3055, 2924, 2250, 1601, 1512, 1396, 1358, 1267, 1242, 1167, 1086, 1024, 928, 802, 779 cm^{-1}.

1.4.7. 2-Hydroxy-4-phenylbutanenitrile (5g). Described below.

1.4.8. 2-Hydroxynonanenitrile (5h).[19] ^{1}H NMR ($CDCl_3$) δ 4.48 (1H, q, J=6.8 Hz, C*H*OH), 2.27 (1H, br s, OH), 1.85 (2H, m, CH_2COH), 1.51 (2H, m, CH_2CCOH), 1.20–1.41 (8H, m, $4CH_2$), 0.89 (3H, t, J=6.8 Hz, CH_3); IR (liquid film) 3445, 2955, 2928, 2858, 2250, 1466, 1379, 1333, 1128, 1074, 723 cm^{-1}.

1.4.9. 2-(2-Furyl)-2-hydroxyacetonitrile (5i). Described below.

1.5. General procedure for asymmetric MPV cyanation of aldehydes with TADDOL-derived zirconium alkoxide

(4*R*,5*R*)-2,2-Dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL, **6**) (233 mg, 0.5 mmol) was placed in a dry, two-neck flask with stirring bar under argon and freshly distilled CH_2Cl_2 (5 mL) was introduced. To this solution was added a 1 M CH_2Cl_2 solution of $Zr(OBu^t)_4$ (0.5 mL, 0.5 mmol) at room temperature and the mixture was stirred for 30 min. Then distilled acetone cyanohydrin (92 μL, 1.0 mmol) was added and the stirring was continued for an additional 30 min. Freshly distilled aldehyde (0.5 mmol) was slowly added dropwise at −40°C and the reaction mixture was stirred there for 5–18 h. The solution was poured into 1N HCl and an extractive workup was performed with ether. The ethereal extracts were washed with brine, dried over Na_2SO_4 and the volatiles were evaporated. After the filtration through a short silica gel column, the analytically pure cyanohydrin (**5b**, **5g**, **5i**–**5o**) was dissolved into CH_2Cl_2 and treated with pyridine (101 μL, 1.25 mmol), Ac_2O (118 μL, 1.25 mmol) and a catalytic amount of DMAP at 0°C for 30 min. The reaction was quenched by the addition of water and extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ethyl acetate/hexane=1:9 as eluant) gave the corresponding acetate. Enantiomeric excess was determined by capillary GC analysis with a chiral column (GL SCIENCE CP-CHIRASIL-DEX CB). The absolute configulation of each cyanohydrin was determined by comparison of the optical rotation with literature values.

1.5.1. 2-Hydroxy-2-phenylacetonitrile (5b).[17] ^{1}H NMR ($CDCl_3$) δ 7.40–7.59 (5H, m, Ph), 5.56 (1H, d, J=7.2 Hz, C*H*OH), 2.59 (1H, br s, OH); IR (liquid firm) 3423, 3067, 3036, 2928, 2858, 2253, 1697, 1495, 1456, 1406, 1244, 1192, 1040, 934, 820, 762, 741, 698 cm^{-1}; $[\alpha]_D^{27}$=+28.94° (*c* 1.00, $CHCl_3$); 63% ee (*R*). **Acetate of 5b:** ^{1}H NMR ($CDCl_3$) δ 7.42–7.58 (5H, m, Ph), 6.42 (1H, s, CHOAc), 2.17 (3H, s, Ac); IR (liquid film) 3069, 2953, 1755, 1458, 1373, 1217, 1026, 964, 901, 760, 698 cm^{-1}. t_R=11.4 min for (*R*)-isomer, 14.3 min for (*S*)-isomer at the column temperature of 140°C.

1.5.2. 2-Hydroxy-4-phenylbutanenitrile (5g).[17] ^{1}H NMR ($CDCl_3$) δ 7.18–7.37 (5H, m, Ph), 4.44 (1H, q, J=6.4 Hz, C*H*OH), 2.86 (2H, dt, J=3.6, 7.6 Hz, $PhCH_2$), 2.24 (1H, d, J=6.4 Hz, OH), 2.18 (2H, ddt, J=2.6, 6.4, 7.6 Hz, CH_2COH); IR (liquid film) 3441, 3028, 2929, 2862, 2245, 1717, 1605, 1497, 1456, 1304, 1072, 941, 752, 700 cm^{-1}; $[\alpha]_D^{27}$=−6.38° (c 1.03, $CHCl_3$); 85% ee (R). **Acetate of 5g:** ^{1}H NMR ($CDCl_3$) δ 7.16–7.35 (5H, m, Ph), 5.27 (1H, t, J=6.8 Hz, CHOAc), 2.84 (2H, dt, J=2.0, 8.0 Hz, $PhCH_2$), 2.24 (2H, dt, J=6.8, 8.0 Hz, CH_2COAc), 2.13 (3H, s, Ac); IR (liquid film) 3065, 3030, 2936, 2868, 1755, 1605, 1499, 1456, 1373, 1223, 1043, 752, 702 cm^{-1}. t_R=14.0 min for (R)-isomer, 15.5 min for (S)-isomer at the column temperature of 160°C.

1.5.3. 2-(2-Furyl)-2-Hydroxyacetonitrile (5i).[20] ^{1}H NMR ($CDCl_3$) δ 7.49 (1H, dd, J=0.8, 2.0 Hz, C═CHOC), 6.62 (1H, dd, J=0.8, 3.6 Hz, C*H*═CCOH), 6.43 (1H, dd, J=2.0, 3.6 Hz, CH═COC), 5.55 (1H, d, J=8.0 Hz, C*H*OH), 2.71 (1H, br s, OH); IR (liquid film) 3420, 3155, 3126, 2928, 2250, 1643, 1500, 1418, 1234, 1150, 1036, 1016, 959, 899, 881, 825, 750 cm^{-1}; $[\alpha]_D^{31}$=+23.30° (c 0.92, $CHCl_3$); 61% ee (R). **Acetate of 5i:** ^{1}H NMR ($CDCl_3$) δ 7.51 (1H, dd, J=0.8, 1.6 Hz, C═CHOC), 6.68 (1H, δ, J= 3.2 Hz, CH═CCOAc), 6.48 (1H, s, CHOAc), 6.45 (1H, dd, J=1.6, 3.2 Hz, CH═COC), 2.17 (3H, s, Ac); IR (liquid film) 3155, 3130, 2953, 1755, 1499, 1431, 1373, 1217, 1153, 1016, 918, 883, 829, 752 cm^{-1}. t_R=5.8 min for (R)-isomer, 6.5 min for (S)-isomer at the column temperature of 140°C.

1.5.4. 2-Hydroxyundecanenitrile (5j).[21] ^{1}H NMR ($CDCl_3$) δ 4.48 (1H, q, J=6.8 Hz, C*H*OH), 2.29 (1H, d, J=6.8 Hz, OH), 1.85 (2H, m, CH_2COH), 1.51 (2H, m, CH_2CCOH), 1.20–1.40 (12H, m, 6CH_2), 0.88 (3H, t, J=6.8 Hz, CH_3); IR (liquid film) 3441, 2926, 2856, 2250, 1466, 1379, 1128, 1082, 721 cm^{-1}; $[\alpha]_D^{28}$=+7.30° (c 1.09, $CHCl_3$); 84% ee (R). **Acetate of 5j:** ^{1}H NMR ($CDCl_3$) δ 5.31 (1H, t, J= 6.8 Hz, CHOAc), 2.14 (3H, s, Ac), 1.89 (2H, q, J=6.8 Hz, CH_2COAc), 1.49 (2H, m, CH_2CCOAc), 1.18–1.40 (12H, m, 6CH_2), 0.88 (3H, t, J=6.8 Hz, CH_3); IR (liquid film) 2928, 2856, 1757, 1466, 1373, 1223, 1040 cm^{-1}. t_R=13.1 min for (R)-isomer, 14.7 min for (S)-isomer at the column temperature of 160°C.

1.5.5. 2-Cyclohexyl-2-hydroxyacetonitrile (5k).[17] ^{1}H NMR ($CDCl_3$) δ 4.28 (1H, t, J=6.4 Hz, C*H*OH), 2.17 (1H, d, J=6.4 Hz, OH), 1.66–1.98 (6H, m, CH and CH_2), 1.07–1.38 (5H, m, CH_2); IR (liquid film) 3441, 2932, 2856, 2250, 1452, 1086, 1059, 1043, 970, 895 cm^{-1}; $[\alpha]_D^{27}$= +8.12° (c 0.77, $CHCl_3$); 79% ee (R). **Acetate of 5k:** ^{1}H NMR ($CDCl_3$) δ 5.18 (1H, d, J=6.4 Hz, CHOAc), 2.14 (3H, s, Ac), 1.66–1.99 (6H, m, CH and CH_2), 1.08–1.36 (5H, m, CH_2); IR (liquid film) 2934, 2858, 1755, 1452, 1373, 1225, 1144, 1074, 1038, 989, 916, 887, 770 cm^{-1}. t_R=10.5 min for (R)-isomer, 12.6 min for (S)-isomer at the column temperature of 140°C.

1.5.6. 3,3-Dimethyl-2-hydroxybutanenitrile (5l).[17] ^{1}H NMR ($CDCl_3$) δ 4.13 (1H, d, J=6.8 Hz, C*H*OH), 2.23 (1H, br s, OH), 1.09 (9H, s, 3CH_3); IR (liquid film) 3449, 2966, 2914, 2878, 2247, 1641, 1479, 1398, 1371, 1321, 1290, 1244, 1186, 1076, 1022, 949, 934, 864, 766 cm^{-1}; $[\alpha]_D^{28}$= +16.82° (c 1.17, $CHCl_3$); 72% ee (R). **Acetate of 5l:** ^{1}H NMR ($CDCl_3$) δ 5.07 (1H, s, CHOAc), 2.16 (3H, s, Ac), 1.09 (9H, s, 3CH_3); IR (liquid film) 2972, 2877, 1755, 1481, 1375, 1302, 1232, 1057, 1026, 974, 904 cm^{-1}. t_R=10.1 min for (R)-isomer, 14.9 min for (S)-isomer at the column temperature of 105°C.

1.5.7. 2-Hydroxy-3-phenylpropionenitrile (5m).[21] ^{1}H NMR ($CDCl_3$) δ 7.19–7.46 (5H, m, Ph), 4.68 (1H, q, J=6.4 Hz, C*H*OH), 3.14 (2H, d, J=6.4 Hz, $PhCH_2$), 2.28 (1H, d, J=6.4 Hz, OH); IR (liquid film) 3429, 3065, 3032, 2934, 2250, 1605, 1497, 1456, 1337, 1263, 1080, 1065, 1032, 746, 700 cm^{-1}; $[\alpha]_D^{30}$=+6.36° (c 0.94, $CHCl_3$); 59% ee (R). **Acetate of 5m:** ^{1}H NMR ($CDCl_3$) δ 7.20–7.42 (5H, m, Ph), 5.48 (1H, t, J=6.8 Hz, CHOAc), 3.19 (2H, d, J=6.8 Hz, $PhCH_2$), 2.12 (3H, s, Ac); IR (liquid film) 3067, 3034, 2939, 1755, 1605, 1499, 1456, 1437, 1373, 1225, 1036, 905, 754, 702 cm^{-1}. t_R=19.5 min for (R)-isomer, 22.5 min for (S)-isomer at the column temperature of 140°C.

1.5.8. 2-Hydroxy-2-(2-thienyl)acetonitrile (5n).[17] ^{1}H NMR ($CDCl_3$) δ 7.43 (1H, dd, J=1.2, 5.2 Hz, C═CHSC), 7.31 (1H, dt, J=1.2, 3.6 Hz, C*H*═CCOH), 7.05 (1H, dd, J=3.6, 5.2 Hz, CH═CSC), 5.74 (1H, d, J=7.6 Hz, C*H*OH), 2.76 (1H, d, J=7.6 Hz, OH); IR (liquid film) 3414, 3111, 2928, 2250, 1655, 1433, 1269, 1238, 1175, 1134, 1028, 903, 854, 712 cm^{-1}; $[\alpha]_D^{28}$=+34.07° (c 0.72, $CHCl_3$); 51% ee (R). **Acetate of 5n:** ^{1}H NMR ($CDCl_3$) δ 7.46 (1H, dd, J=1.2, 5.2 Hz, C═CHSC), 7.35 (1H, dt, J=1.2, 3.6 Hz, C*H*═CCOH), 7.05 (1H, dd, J=3.6, 5.2 Hz, CH═CSC), 6.64 (1H, s, CHOAc), 2.17 (3H, s, Ac); IR (liquid film) 3111, 2941, 1753, 1431, 1371, 1285, 1215, 1134, 1020, 945, 903, 856, 843, 716 cm^{-1}. t_R=12.0 min for (R)-isomer, 14.1 min for (S)-isomer at the column temperature of 140°C.

1.5.9. 2-Hydroxy-4-phenyl-3-(*E*)-butenenitrile (5o).[17] ^{1}H NMR ($CDCl_3$) δ 7.29–7.55 (5H, m, Ph), 6.94 (1H, d, J=16.0 Hz, PhCH═C), 6.27 (1H, dd, J=5.6, 16.0 Hz, PhC═CH), 5.17 (1H, dd, J=1.2, 5.6 Hz, C*H*OH), 2.45 (1H, br s, OH); IR ($CHCl_3$) 3358, 3028, 2926, 2253, 1655, 1493, 1450, 1416, 1300, 1088, 1072, 1024, 976, 926, 818, 695 cm^{-1}; $[\alpha]_D^{30}$=+7.90° (c 1.00, $CHCl_3$); 33% ee (R). **Acetate of 5o:** ^{1}H NMR ($CDCl_3$) δ 7.29–7.48 (5H, m, Ph), 6.98 (1H, d, J=15.2 Hz, PhCH═C), 6.20 (1H, dd, J=6.8, 15.2 Hz, PhC═CH), 6.03 (1H, dd, J=1.2, 6.8 Hz, CHOAc), 2.17 (3H, s, Ac); IR (liquid film) 3061, 3030, 2936, 1753, 1657, 1580, 1499, 1450, 1373, 1217, 1022, 968, 752, 694 cm^{-1}. t_R=10.2 min for (R)-isomer, 10.9 min for (S)-isomer at the column temperature of 180°C.

1.6. Representative procedure for catalytic asymmetric MPV cyanation of 3-phenylpropanal

(4*R*,5*R*)-2,2-Dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL, **6**) (46 mg, 0.1 mmol) was placed in a dry, two-neck flask with stirring bar and activated, powdered 4 Å molecular sieves (100 mg) under argon and freshly distilled CH_2Cl_2 (5 mL) was introduced. To this solution was added a 1 M CH_2Cl_2 solution of $Zr(OBu^t)_4$ (0.1 mL, 0.1 mmol) at room temperature and the mixture was stirred for 30 min. Then distilled acetone

cyanohydrin (92 μL, 1.0 mmol) was added and the stirring was continued for an additional 30 min. Freshly distilled 3-phenylpropanal (66 μL, 0.5 mmol) was slowly added dropwise at −40°C and the reaction mixture was stirred there for 15 h. The solution was poured into 1N HCl and extracted with ether. The ethereal extracts were washed with brine, dried over Na_2SO_4 and the volatiles were evaporated. After the filtration through a short silica gel column, the product **5g** was acetylated in a similar manner as described above to give the corresponding acetate as a colorless oil (52 mg, 0.26 mmol; 51% yield). Enantiomeric excess was determined to be 72% ee (*R*) by capillary GC analysis with a chiral column (GL SCIENCE CP-CHIRASIL-DEX CB) at the column temperature of 160°C.

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