Catalytic Asymmetric Synthesis of *O*-Acetylcyanohydrins from Potassium Cyanide, Acetic Anhydride, and Aldehydes, Promoted by Chiral Salen Complexes of Titanium(IV) and Vanadium(V)

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Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

The utility of the chiral $[Ti(\mu\text{-}O)(salen)]_2$ complexes (*R*)- and (*S*)-**1** (H_2salen was prepared from (*R,R*)- or (*S,S*)-cyclohexane-1,2-diamine and 3,5-di(*tert*-butyl)-2-hydroxybenzaldehyde) as catalysts for the asymmetric addition of KCN and Ac_2O to aldehydes to produce *O*-acetylcyanohydrins was investigated. It was shown that the complexes were active at a substrate/catalyst ratio of 100:1 and produced the *O*-protected cyanohydrins with ee in the range of 60–92% at $-40°$. Other complexes, $[Ti_2(AcO)_2(\mu\text{-}O)(salen)_2]$ ((*R*)-**4**) and $[Ti(CF_3COO)_2(salen)]$ ((*R*)-**5**), were prepared from (*R*)-**1** by treatment with different amounts of Ac_2O and $(CF_3CO)_2O$, and their catalytic activities were tested under the same conditions. The efficiency of (*R*)-**4** was found to be even greater than that of (*R*)-**1**, whereas (*R*)-**5** was inactive. The synthesis of the corresponding salen complexes of V^{IV} and V^{V}, [V(O)(salen)] ((*R*)-**2**) and $[V(O)(salen)(H_2O)]$ $[S(O)_3OEt]$ ((*R*)-**3**), was elaborated, and their X-ray crystal structures were determined. The efficiency of (*R*)-**3** was sufficient to produce *O*-acetyl derivatives of aromatic cyanohydrins with ee in the range of 80–91% at $-40°$.

Introduction. – As enantiomerically pure cyanohydrins are versatile intermediates in organic synthesis, many synthetic approaches to their syntheses are being vigorously pursued [1]. The catalytic ways of making this class of compounds rely upon the asymmetric addition of a cyanide source to the carbonyl group of aldehydes, as catalyzed by enzymes [2] or purely chemical chiral catalysts [3]. Enantiomerically enriched *O*-protected cyanohydrins are customarily made by the reaction of aldehydes with Me_3SiCN usually catalyzed by chiral *Lewis* acids [1]. We recently reported an efficient catalysis of this reaction by the chiral binuclear $[Ti^{IV}(salen)]$ complex **1** (*Fig. 1*), active at a ratio of substrate/catalyst as high as 1000:1 and promoting the addition at room temperature with ee in the range of 80–92% [4]. Very efficient catalysts based on bifunctional complexes of Al^{III} and Ti^{IV} have also been developed by *Shibasaki* and co-workers, giving *O*-(trimethylsilyl) derivatives of cyanohydrins with ee as high as 90–99% at $-42°$ [5].

Unfortunately, Me_3SiCN is an expensive material, and HCN is extremely toxic. Evidently, there is a need to find cheaper and safer initial materials for the synthesis of enantiomerically pure *O*-protected cyanohydrins. This paper reports the asymmetric synthesis of *O*-acetylcyanohydrins by the reaction of KCN, acetic anhydride (Ac_2O),

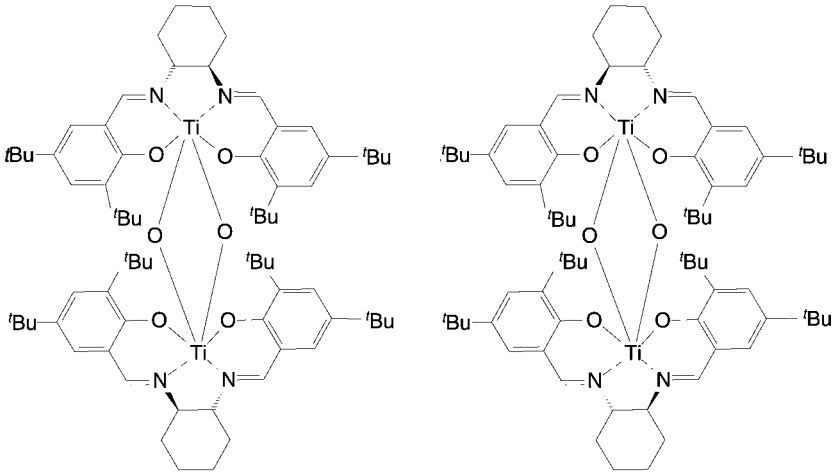
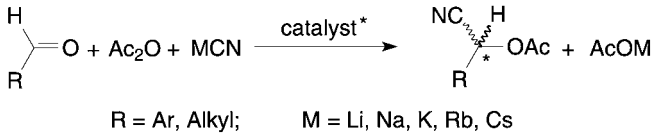


Fig. 1. *Chiral dinuclear [Ti^{IV}(salen)] catalysts* **1**

and aldehydes catalyzed by complexes **1** (*Scheme 1*) and the analogously built V^{IV} and V^{V} complexes (*R*)-**2** and (*R*)-**3**, respectively. A preliminary report of some of these results was published earlier [6].

Scheme 1. *Synthesis of Chiral* O*-Acetylcyanohydrins Promoted by Salen-Type Chiral Complexes*



Results and Discussion. – Initial experiments revealed that the combination of KCN, benzaldehyde, and Ac_2O (added as the last ingredient) in the presence of 1 mol-% of catalysts (*R*)- or (*S*)-**1** produced enantiomerically enriched *O*-acetylcyanohydrins of (*S*)- or (*R*)-configuration, respectively. The transformation showed good reproducibility and the absence of any side reactions.

The reaction was strongly dependent on the nature of the cyanide counterion. The best results of the model reaction, according to *Scheme 1* (dihydrocinnamaldehyde, alkali-metal cyanide, Ac_2O, CH_2Cl_2, $-42°$, 8 h under vigorous stirring in the presence of (*S*)-**1**), were obtained with KCN, and the range of enantiomer purity of the resulting (*R*)-*O*-acetylcyanohydrin was as follows: KCN (82% ee) > RbCN (76% ee) > NaCN (56% ee) > CsCN (54% ee) > LiCN (4% ee). The addition of 1 equiv. of Bu_4NBr to the mixture resulted in the formation of completely racemic product.

The reaction of benzaldehyde and KCN catalyzed by (*R*)-**1**, according to *Scheme 1*, was also solvent-dependent and gave, at $-20°$ after 8 h of stirring, (*S*)-*O*-acetylmandelonitrile (=α-(acetyloxy)benzeneacetonitrile) with the following ee: 1,2-dichloro-

ethane (90%) ≥ CH_2Cl_2 (88%) > toluene (78%) > CCl_4 (72%) > hexane (58%). The ee of the reaction was found to increase significantly from 74% at 20° to 88% at −20°, whilst further decrease of the temperature to −42° did not produce any significant increase in the ee of the final product (see *Table 1*, *Entry 1*). For other aldehydes, the trend was the same, and further decrease of the temperature to −78° generally resulted in diminished ee of the product (see *Table 1*, *Entries 1*, *3*, and *4*), with the exception of 2-fluorobenzaldehyde (*Entry 5*).

Table 1. *Influence of Temperature on the ee of (*R*)-*O*-Acetylcyanohydrins Obtained by the Addition of KCN and Ac_2O to Aldehydes, Promoted by Complex (*S*)-***1***[a])*

Entry	Aldehyde	ee [%]				
		20°[b])	−20°[c])	−30°[d])	−42°[e])	−78°[f])
1	PhCHO	74	88	88	89	85
2	$PhCH_2CH_2CHO$	49	–	80	82	–
3	4-$CF_3C_6H_4CHO$	60	–	–	76	54
4	4-FC_6H_4CHO	65	–	–	90	84
5	2-FC_6H_4CHO	45	–	–	86	88

[a]) 1 mol-% of catalyst (*S*)-**1** was employed, and all reactions were carried out in CH_2Cl_2. [b]) Stirring for 4 h (conversion of aldehyde >90%). [c]) Stirring for 10 h (conversion of aldehyde *ca.* 40%). [d]) Stirring for 10 h (conversion of aldehyde *ca.* 30%). [e]) Stirring for 10 h (conversion of aldehyde 20%). [f]) Stirring for 2 d (conversion of aldehyde *ca.* 30%).

Fast and efficient stirring was very important for obtaining good chemical yields during the reaction, but above a certain rotation speed (280 rotations/min), any further increase in the rate of stirring had no effect on the chemical yield. The curves shown in *Fig. 2*, describing the consumption of benzaldehyde at 20° in CH_2Cl_2 in the presence of KCN, Ac_2O, and (*R*)- or (*S*)-**1** (1 mol-%), were obtained in the stirring-speed-independent range and surprisingly testified to the first-order kinetic behavior of the reaction. Generally, without any additives, the reaction was sluggish even at room temperature, as the data of *Fig. 2* illustrate.

The addition of acids generally and AcOH in particular decreased the rate of the reaction even further, whereas replacement of KCN with HCN as well as addition of HCN (100 mol-% with respect to KCN) to the reaction mixture led to a dramatic loss of optical purity (0% ee and 29% ee, resp.). Use of AcCl or $(CF_3CO)_2O$ in place of Ac_2O was unsuccessful, with no *O*-protected cyanohydrins detected in the reaction media. However, the reaction is not limited to Ac_2O as use of propanoic anhydride with benzaldehyde gave *O*-propanoylmandelonitrile in 99% yield and 92% ee under optimized conditions. An attempt to use AcCN in place of KCN/Ac_2O failed, as no *O*-acetyl derivative of mandelonitrile was found in the reaction mixture under the standard reaction conditions.

Fortunately, some additives greatly accelerated the chemical reaction. We tested H_2O, organic and mineral acids, N-bases, thiols, thiourea, CS_2, Ph_4BNa, mineral carbonates, surfactants, phosphines, and phosphine oxides for this purpose, but the most successful proved to be the use of 1*H*-imidazole (10 mol-% rel. to benzaldehyde), ^{t}BuOH, or H_2O. The mixture of H_2O/^{t}BuOH (10 and 100 mol-% rel. to benzaldehyde, resp.) added to the reaction mixture greatly improved the performance of the system as

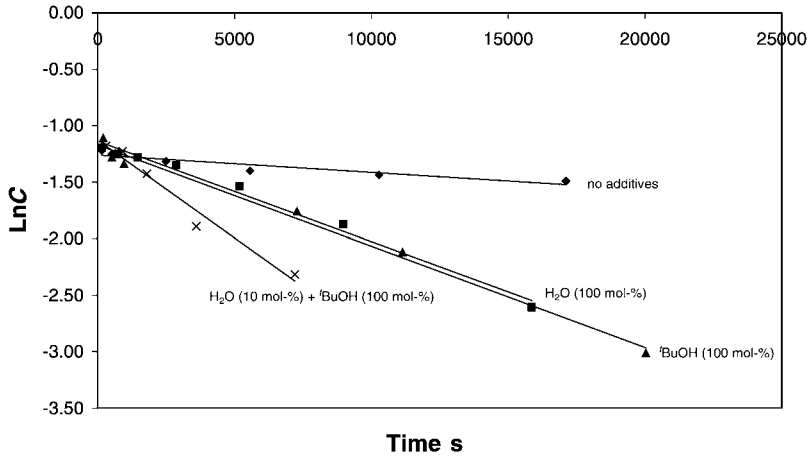


Fig. 2. *Dependence of benzaldehyde consumption on time for the reaction of benzaldehyde* ($C = 0.38$M) *with KCN, Ac_2O* (mol ratio benzaldehyde/KCN/Ac_2O 1:4:4), *promoted by 1 mol-% of* **1** *in CH_2Cl_2 influenced by some additives at* $-42°$

the data of *Fig. 2* illustrate. *Table 2* summarizes the results of asymmetric synthesis of different *O*-acetylcyanohydrins, promoted by **1** under the optimal conditions found for the reaction with benzaldehyde as substrate. As can be seen from the data, aromatic aldehydes proved to be much better substrates than aliphatic aldehydes, and acetophenone was not a substrate for the reaction.

Earlier, we reported efficient catalysis by the vanadium complex (*R*)-**2** of the addition of Me_3SiCN to aldehydes [7]. It might have been assumed that (*R*)-**2** could

Table 2. *Enantioselective Synthesis of* O-*Acetylcyanohydrins, According to* Scheme 1, *Promoted by Catalysts* (R)- *or* (S)-**1**[a])

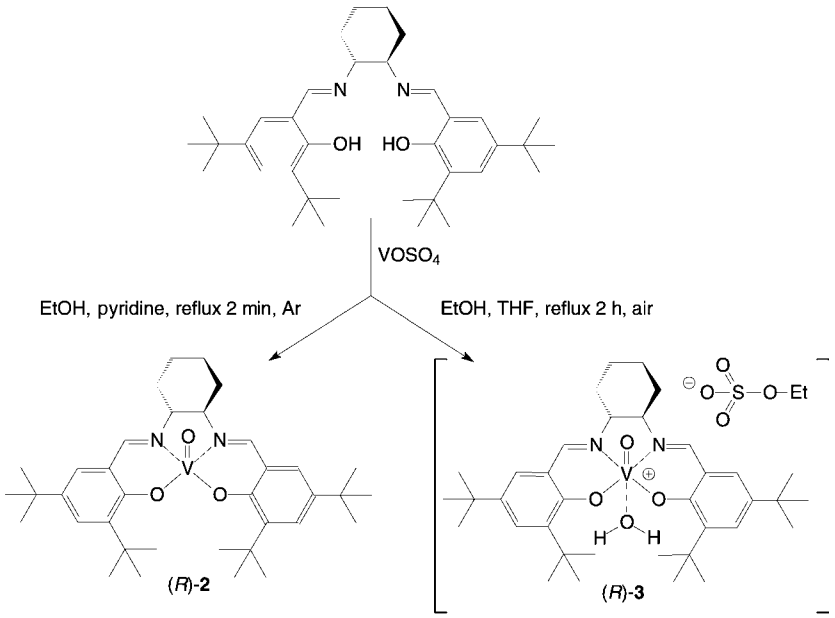
Aldehyde	(*R*)-**1**		(*S*)-**1**	
	Yield [%][b])	ee [%][c]) (configuration)	Yield [%][b])	ee [%][c]) (configuration)
PhCHO	93	90 (*S*)	92[d])	89 (*R*)
4-$MeOC_6H_4CHO$	–	–	74	93 (*R*)
3-$MeOC_6H_4CHO$	–	–	99	93 (*R*)
3-$PhOC_6H_4CHO$	99	90 (*S*)	99	89 (*R*)
4-FC_6H_4CHO	98	92 (*S*)	99	93 (*R*)
2-FC_6H_4CHO	87	85 (*S*)	86	82 (*R*)
3-FC_6H_4CHO	–	–	99	89 (*R*)
2-ClC_6H_4CHO	87	86 (*S*)	89[d])	88 (*R*)
$PhCH_2CH_2CHO$	80	84 (*S*)	79[d])	82 (*R*)
Me_2CHCHO	64	69 (*S*)	62[d])	72 (*R*)
Me_3CCHO	40	62 (*S*)	40[d])	60 (*R*)
PhCOMe	no reaction		no reaction	

[a]) Reaction conditions: mol ratio aldehyde ($C = 0.37-0.4$M)/KCN/Ac_2O 1:4:4, promoted by 1 mol-% of **1** at $-42°$, CH_2Cl_2/^{t}BuOH/H_2O 2500:10:1, stirring for 10 h. [b]) Yield of *O*-acetylcyanohydrin as determined by NMR, adding an internal standard to the evaporated reaction mixture, unless indicated otherwise. [c]) Determined by chiral GLC. [d]) Yield of isolated product.

also catalyze the synthesis of enantiomerically enriched *O*-acetylcyanohydrins. In addition, it was of interest to learn if similarly constructed complexes of V^V could be involved in the catalytic cycle. Therefore, the V^{IV} and V^V complexes (*R*)-**2** and (*R*)-**3**, respectively, were prepared from the same initial material (*Scheme 2*), the only difference being the use of an inert-gas atmosphere in case of (*R*)-**2** and the necessary presence of an oxidizing agent, O_2, in case of (*R*)-**3** (the enantiomeric complexes can be obtained in the same manner). The solid-state structures of (*R*)-**2** and (*R*)-**3** were determined by X-ray analysis (*Figs. 2* and *3*). Both complexes are monomeric with a central V=O moiety and the distorted planar chiral salen ligand occupying the four coordination sites of the central metal. The remaining positive charge of the central V^V atom of (*R*)-**3** is neutralized by an ethyl sulfonate anion (presumably formed *in situ* from the vanadyl sulfate and EtOH) that is not coordinated to the metal. Instead, a H_2O molecule occupies the remaining vacant coordination position at the metal in (*R*)-**3**, whereas in (*R*)-**2**, the position is taken by one toluene solvent molecule sandwiched between two molecules of the V^{IV} complex.

Under the experimental conditions of the addition of KCN and Ac_2O to benzaldehyde catalyzed by (*R*)-**1** (without any additives), the corresponding V^{IV} and V^V complexes showed different catalytic behavior. In spite of its efficiency in promotion of the addition of Me_3SiCN to aldehydes, (*R*)-**2** was not a very efficient catalyst compared to the Ti^{IV} complex in the addition of KCN to aldehydes. On the other hand, V^V-derived (*R*)-**3** proved to be catalytically active, converting aldehydes into the corresponding *O*-acetylcyanohydrins in the presence of KCN and Ac_2O at low temperatures. As expected, (*R*)-**3** converted aldehydes into (*S*)-cyanohydrins, and its

Scheme 2. *Synthesis of Salen Complexes of V^{IV} and V^V*



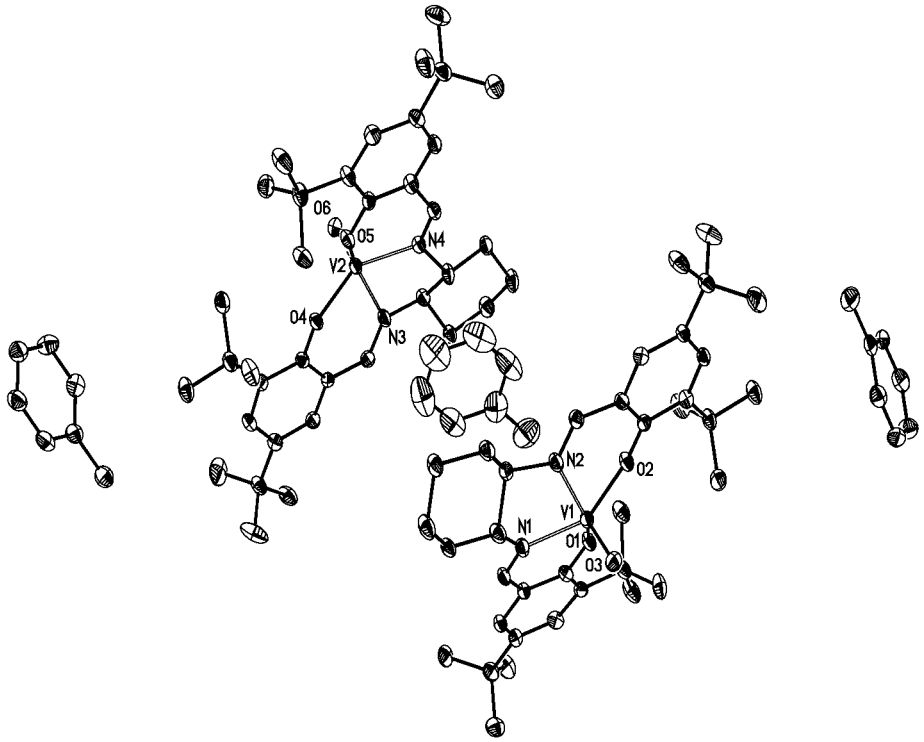


Fig. 3. *Molecular structure of (*R*)-***2*** with 30% probability ellipsoids of anisotropic displacements.* The two independent molecules and three solvate toluene molecules are shown.

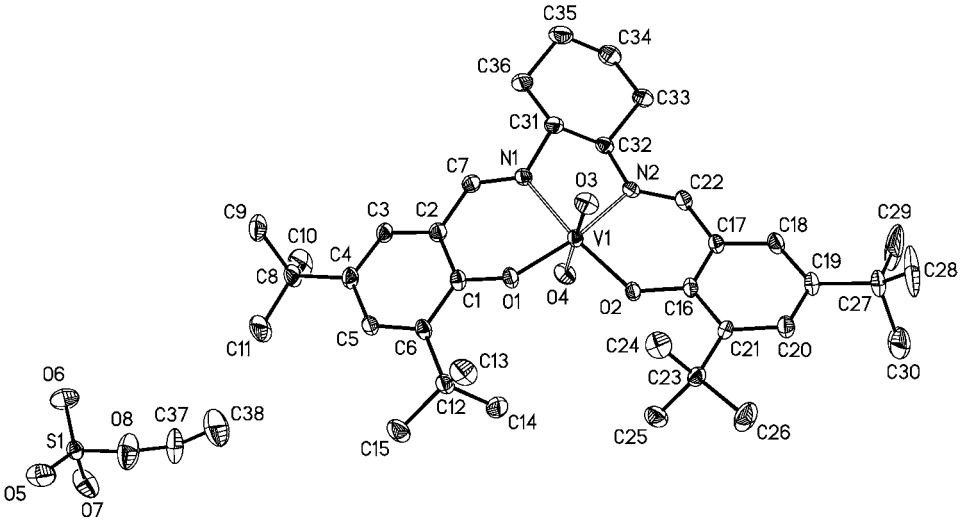


Fig. 4. *Crystal structure of salt (*R*)-***3*** (*one of the two independent structures are illustrated*) with 50% probability ellipsoids of anisotropic displacements.* The solvate toluene molecule is not shown.

enantiomer furnished (*R*)-cyanohydrins. *Table 3* summarizes the results of syntheses catalyzed by (*R*)-**3**. Although we have no experimental data related to the mechanism of V^{V} catalysis, some similarity with the Ti^{IV} catalyst can be assumed, as the sense of chirality and the magnitude of asymmetric induction were almost the same in both (*R*)-**1** and (*R*)-**3** cases.

Table 3. *Addition of KCN/Ac_2O to RCHO in the Presence of V^{V} Catalyst (*R*)-***3***[a])*

Aldehyde	ee of (*S*)-*O*-Acetylcyanohydrin[b])	Yield [%]
PhCHO	90.3[c])	87.2[c])
3-$MeOC_6H_4CHO$	84.88	97 (NMR)
2-ClC_6H_4CHO	77.62	99 (NMR)

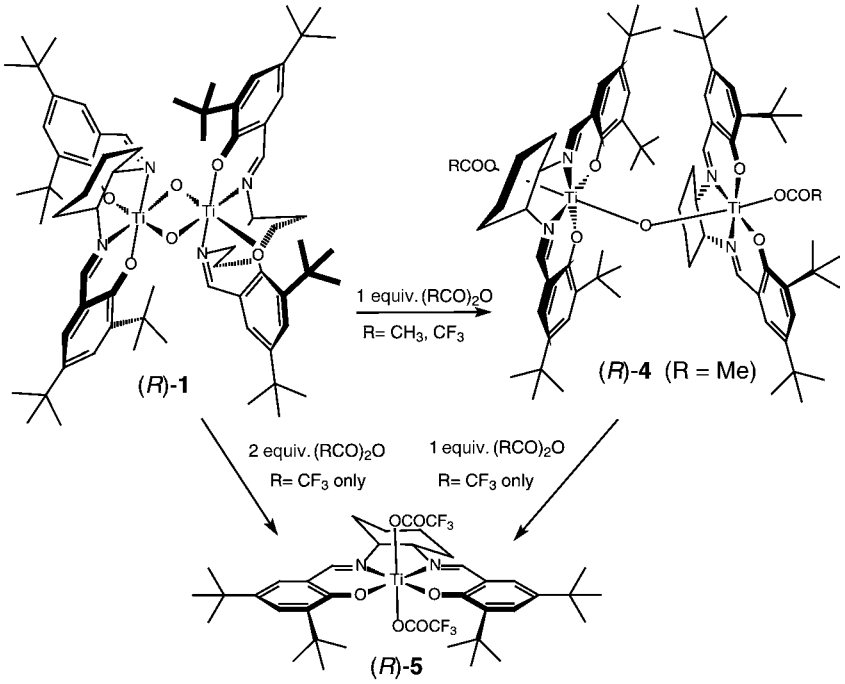
[a]) Conditions: concentration of aldehydes 0.4–1.2M (mol ratio aldehyde/KCN/Ac_2O 1:4:4), promoted by 1 mol-% of (*R*)-**3** in CH_2Cl_2/*t*BuOH/H_2O 2500:10:1), 10 h, stirring at $-42°$. [b]) Determined by chiral GLC. [c]) On a 4–6 g scale experiment.

The key step of the formation of the C–CN bond is most likely similar for both Me_3SiCN addition and KCN/Ac_2O addition catalyzed by (*R*)-**1** and (*S*)-**1**, as the almost identical ee and sense of chirality testify (*cf.* data of [4a,b] and the data of *Table 2*). The key feature of the mechanism, suggested by us earlier [4b], is the formation of an intermediate chiral Ti-cyanide-metalloacetal complex where the cyanide ion attacks the aldehyde carbonyl C-atom intramolecularly with the formation of a Ti-coordinated cyanohydrin. According to this mechanism, the O-atom or O-atoms, bridging two Ti^{IV} ions of the salen complexes, play the most important role in the scheme.

The controlled interaction of 1 equiv. of Ac_2O with (*R*)-**1** gave the corresponding mono-bridged dinuclear [$Ti_2(AcO)_2(salen)_2(\mu\text{-O})$] ((*R*)-**4**; *Scheme 3*), the solid-state structure of which was established by X-ray-analysis (see *Fig. 5*). Any attempts to obtain diacetato complex [$Ti(AcO)_2(salen)$] by the interaction of (*R*)-**4** with another equiv. of Ac_2O resulted in failure, and even further, after heating (*R*)-**4** in Ac_2O, only the initial mono-bridged complex and some decomposition products were detected. In accordance with the mechanism, complex (*R*)-**4** was an even more efficient catalyst than (*R*)-**1**, catalyzing the formation of (*S*)-*O*-acetylmandelonitrile with an ee of 70% and $k_{obs} = 0.021\ s^{-1}$ at room temperature, as compared to an ee of 74% and $k_{obs} = 0.01\ s^{-1}$ obtained under identical conditions without any additives in the case of (*R*)-**1**. The [$Ti(CF_3COO)_2(salen)$] complex (*R*)-**5** could also be easily prepared by treatment of (*R*)-**1** with $(CF_3CO)_2O$ and was found to be catalytically inactive in the Me_3SiCN addition and only marginally active in the KCN/Ac_2O addition. Furthermore, addition of benzaldehyde to (*R*)-**4** before addition of KCN was necessary for the catalysis to be observed. If KCN was added first to (*R*)-**4**, no catalytic reaction was detected. Thus, the presented data serve to support the suggestion that the O-bridged dinuclear complexes and metalloacetal formation serve to generate the real catalyst of the cyanation reaction. The underlying reason for the failure to apply $(CF_3CO)_2O$ or AcCl in the reaction could be traced to the complete breaking of the O-bridges in the catalysts by the too active acylating agents.

The breaking of the Ti-O bond of the coordinated cyanohydrin by interaction with Ac_2O or ROH may be the rate-limiting stage. The latter feature of the mechanism can

Scheme 3. *Interaction of* (R)-**1** *with* Ac_2O *and* $(CF_3CO)_2O$



explain why 1*H*-imidazole, H_2O, or ^{t}BuOH catalyzed the reaction. The free cyanohydrins formed in this way undergo easy acylation without racemization, as control experiments indicated.

Conclusions. – We have developed a very efficient procedure to prepare enantiomerically enriched *O*-protected cyanohydrins in very good chemical yields and with high ee values, starting with inexpensive and non-volatile starting materials. The scale-up of the procedure to 200 g of aldehydes can be easily brought about.

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Supplementary data is available from the author: Tables of atom coordinates, bond lengths and angles, and anisotropic displacement parameters for (*R*)-**2**, (*R*)-**3**, and (*R*)-**4**.

Experimental Part

1. *General.* CH_2Cl_2 was distilled over CaH_2. Ac_2O was distilled from the commercial product (99%). Commercial KCN (98%) was thoroughly powdered and stored *in vacuo* over P_2O_5. Aliphatic and aromatic aldehydes were purified by usual methods. Chiral ligands were prepared by refluxing (1*R*,2*R*)- or (1*S*,2*S*)-cyclohexane-1,2-diamine with 3,5-di(*tert*-butyl)salicylaldehyde. Chiral GC: *DP-TFA-γ-CD*, fused-silica capillary column (32 m × 0.2 mm), He as the carrier gas. $[\alpha]_D$: *Optical-Activity-Ltd.-Polar-2001* or *Perkin-Elmer*

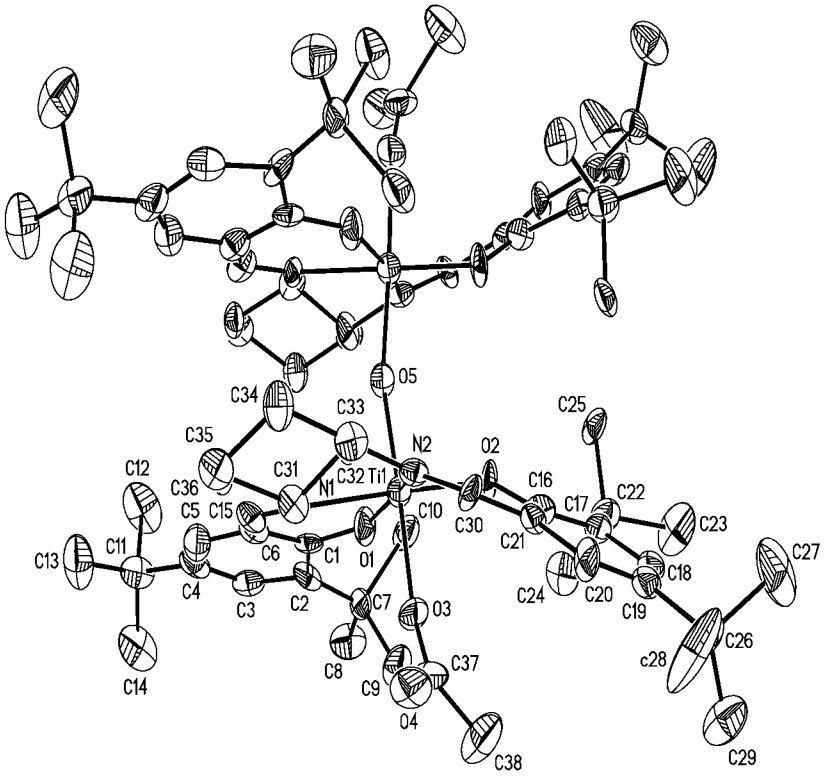

Fig. 5. *Molecular structure of (*R*)-***4*** with 50% probability ellipsoids of anisotropic displacements*

241 polarimeter; *c* in g/100 ml. IR Spectra (in cm^{-1}): *Nicolet Magna-750-FT* spectrometer, resolution of 2 cm^{-1}, 0.06-mm KBr cell; solvent spectra were subtracted from soln. spectra with the OMNIC *Nicolet* program. ^{1}H-NMR Spectra: *Bruker AM250* (250 MHz), *Bruker Avance* digital (360 MHz), or *Bruker AMX-400* spectrometer (400 MHz); at 293 K in $CDCl_2$ or CD_2Cl_2; referenced internally either to $SiMe_4$ or to the residual solvent peak, δ reported in ppm downfield of $SiMe_4$. ^{13}C-NMR Spectra: *Bruker Avance* digital spectrometer (90 MHz). Elemental analyses were performed within the Chemistry Department of INEOS (*Carlo-Erba 1106* or *1108* analyser).

2. *Kinetic Experiments.* Kinetic experiments for the addition of Ac_2O/KCN to benzaldehyde in the presence of catalysts were carried out at $20 \pm 0.5°$ and $-42 \pm 0.5°$. Standard solns. (0.02 mol/l) of complexes **1** and **3** were prepared in dry CH_2Cl_2. A sample of these solns. was injected in due order into a soln. of benzaldehyde (0.2 ml, 2 mmol), Ac_2O (0.36 ml, 4 mmol), and KCN (0.4 g, 6 mmol) in an appropriate volume of CH_2Cl_2 (the total volume of the reaction mixture was 5 ml). The initial ($t = 0$) absorption of the benzaldehyde soln. at 246 nm in CH_2Cl_2 was determined from a soln. containing just the appropriate concentration of benzaldehyde and catalyst, without Ac_2O. Samples were taken at appropriate intervals as the reaction progressed, and subjected to centrifugation. Of each purified sample, 10 µl were immediately diluted with 5 ml of dry CH_2Cl_2 and then analyzed by UV spectrophotometry at maximum benzaldehyde absorption (246 nm in CH_2Cl_2). The absorption data were used to determine the concentration of benzaldehyde.

3. *[Ti^{IV}(salen)] Complexes (*R*)- or (*S*)-***1***.* The [$TiCl_2$(salen)] (H_2salen is the *Schiff* base derived from (1*R*,2*R*)- or (1*S*,2*S*)-cyclohexane-1,2-diamine and 3,5-di(*tert*-butyl)salicylaldehyde) complex was prepared according to [4a]. To a soln. of this complex (2 g, 3 mmol) in CH_2Cl_2 (150 ml) was added pH 7 phosphate buffer (200 ml; prepared by dissolving $Na_2HPO_4 \cdot 12H_2O$ (4.4 g) and $NaH_2PO_4 \cdot 2H_2O$ (1.2 g) in H_2O (200 ml)). The mixture was vigorously stirred at 20–25° for 1 h until the soln. turned orange. The aq. layer was removed and a

fresh portion of the phosphate buffer (200 ml) was then added to the org. layer. The mixture was vigorously stirred for 30 min until the soln. turned yellow. The org. layer was then washed with H_2O, dried (Na_2SO_4), and evaporated and the resulting yellow residue dried at 1 Torr: (*R*)- or (*S*)-**1** (1.3 g, 71%). (*R*)-**1**: M.p. 315° (dec.). $[\alpha]_D^{25} = -267$ ($c = 0.01$, $CHCl_3$). IR (CH_2Cl_2): 2962*s*, 2865*m*, 1625*s*, 1555*m*, 687*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.04 (*s*, 9 H); 1.22 (*s*, 9 H); 1.31 (*s*, 9 H); 1.40 (*s*, 9 H); 2.5–2.6 (*m*, 4 H); 4.0–4.1 (*m*, 2 H); 6.95 (*s*, 1 H); 7.05 (*s*, 1 H); 7.23 (*s*, 1 H); 7.42 (*s*, 1 H); 7.75 (*s*, 1 H); 8.15 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.6; 24.9; 28.1; 29.7; 30.1; 31.5; 31.7; 34.1; 35.0; 35.7; 65.7; 69.8; 121.0; 125.8; 127.5; 128.0; 128.5; 137.6; 138.0; 139.1; 139.4; 157.1; 161.3. Anal. calc. for $C_{72}H_{104}N_4O_6Ti_2$: C 71.04, H 8.61, N 4.60, Ti 7.87; found: C 71.03, H 8.80, N 4.46, Ti 7.91.

4. *[V^{IV}(salen)] Complex* (R)-**2**. The solns. of (1*R*,2*R*)-*N*,*N*′-bis[3,5-di(*tert*-butyl)salicylidene]cyclohexane-1,2-diamine (1.0 g, 1.8 mmol) in pyridine (4 ml) and of vanadyl sulfate hydrate (0.55 g, 2.0 mmol) in hot EtOH (40 ml) were mixed under Ar and refluxed for 2–3 min until a crystalline solid began to precipitate. The mixture was allowed to cool to r.t., and light-green crystals were collected by filtration after 3 h, washed thoroughly with EtOH, and dried *in vacuo:* 1.01 g (90.3%) of pure (*R*)-**2**. $[\alpha]_D^{25} = -442$ ($c = 0.01$, $CHCl_3$). IR (KBr): 1615*s*, 984*w*. Anal. calc. for $C_{36}H_{52}N_2O_3V$: C 70.68; H 8.57; N 4.58; V 8.33; found: C 70.65; H 8.51; N 4.57; V 8.31.

Data of (*S*)-**2**: $[\alpha]_D^{25} = +467$ ($c = 0.01$, $CHCl_3$).

5. *[V^V(salen)] Complex* (R)-**3**. The solns. of (1*R*,2*R*)-*N*,*N*′-bis[3,5-di(*tert*-butyl)salicyliden]cyclohexane-1,2-diamine (1.0 g, 1.8 mmol) in THF (20 ml) and of vanadyl sulfate hydrate (0.55 g, 2.0 mmol) in hot EtOH (32 ml) were mixed and stirred under reflux for 2 h in air. Then the solvent was evaporated and the residue dissolved in CH_2Cl_2 and submitted to column chromatography (SiO_2, CH_2Cl_2, then AcOEt/MeOH 2:1): 0.6 g (53%) of (*R*)-**3**. Dark-green crystalline solid that can be recrystallized from benzene/CH_2Cl_2. $[\alpha]_D^{25} = -914$ ($c = 0.01$, $CHCl_3$). IR (KBr): 1618*s*, 1250*w*, 965*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.83 (*t*, $J = 7.2$, 3 H); 1.33 (*s*, 18 H); 1.49 (*s*, 18 H); 1.7–2.2 (*m*, 8 H); 3.41 (*q*, $J = 7.2$, 2 H); 3.81 (*m*, 1 H); 4.26 (*m*, 1 H); 7.49 (*s*, 1 H); 7.52 (*s*, 1 H); 7.68 (*s*, 1 H); 7.73 (*s*, 1 H); 8.53 (*s*, 1 H); 8.73 (*s*, 1 H). Anal. calc. for $C_{38}H_{59}N_2O_7SV \cdot H_2O$: C 60.30, H 8.12, N 3.70, S 4.24; found: C 60.45, H 8.12, N 3.62, S 4.30.

6. *[$Ti_2(AcO)_2(\mu\text{-}O)(salen)_2$] Complex (R)*-**4**. To a soln. of (*R*)-**1** (0.243 g, 0.0002 mol) in hexane (10 ml), Ac_2O (0.038 ml, 0.0004 mol) was added, and the mixture was stirred for 12 h. The precipitated solid was then filtered off and washed with benzene: 0.205 g (77.7%) of nearly pure (*R*)-**4** that was further purified by recrystallization from benzene/CH_2Cl_2. $[\alpha]_D^{25} = -178$ ($c = 0.05$, $CHCl_3$). IR (KBr): 1629*s*, 707*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (*s*, 9 H); 1.32 (*s*, 9 H); 1.35 (*s*, 9 H); 1.44 (*s*, 9 H); 1.25–3.25 (*m*, 16 H); 3.45 (*m*, 1 H); 4.18 (*m*, 1 H); 7.15 (*s*, 1 H); 7.20 (*s*, 1 H); 7.42 (*s*, 1 H); 7.52 (*s*, 1 H); 7.99 (*s*, 1 H); 8.10 (*s*, 1 H). Anal. calc. for $C_{76}H_{110}N_4O_9Ti_2 \cdot H_2O$: C 68.25, H 8.44, N 4.19; found: C 68.01; H 8.43 N 4.09.

7. *Attempted Synthesis of [Ti(AcO)$_2$(salen)] Complex*. A soln. of (*R*)-**1** (24.4 mg, 0.00002 mol) in Ac_2O (7 ml, 0.074 mol) was stirred for 12 h. The resulting soln. was evaporated and the residue examined by ^{1}H-NMR: spectrum identical to those of (*R*)-**4**.

8. *[Ti(CF_3COO)$_2$(salen)] Complex* (R)-**5**. To a soln. of (*R*)-**1** (0.243 g, 0.0002 mol) in CH_2Cl_2 (5 ml), $(CF_3CO)_2O$ (0.115 ml, 0.00081 mol) was added, and the mixture was stirred for 12 h. The resulting mixture was filtered, and the filtrate was evaporated: 0.314 g (96%) of nearly pure (*R*)-**5**. $[\alpha]_D^{25} = -25$ ($c = 0.05$, $CHCl_3$). IR (KBr): 1629*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.34 (*s*, 9 H); 1.49 (*s*, 9 H); 1.22–2.05 (*m*, 6 H); 2.13 (*m*, 2 H); 2.63 (*m*, 2 H); 4.02 (*m*, 2 H); 7.35 (*m*, 1 arom. H); 7.62 (*m*, 1 arom. H); 8.38 (*s*, 2 CH=N). Anal. calc. for $C_{40}H_{52}F_6N_2O_6Ti$: C 58.68, H 6.40, N 3.42; found: C 58.65, H 6.75, N 3.11.

Under the same conditions, but with 0.00042 mol (0.059 ml) of $(CF_3CO)_2O$, complex *[$Ti_2(CF_3COO)_2(\mu\text{-}O)(salen)_2$]* was obtained. $[\alpha]_D^{25} = -124$ ($c = 0.05$, $CHCl_3$). IR (KBr): 1629*s*, 707*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.08 (*s*, 18 H); 1.32 (*s*, 18 H); 1.36 (*s*, 18 H); 1.40 (*s*, 18 H); 1.2–1.4 (*m*, 8 H); 1.66 (*m*, 4 H); 2.00 (*m*, 2 H); 2.40 (*m*, 2 H); 3.81 (*m*, 2 CH–N=); 3.41 (*m*, 2 CH–N=); 7.21 (*m*, 2 arom. H); 7.26 (*m*, 2 arom. H); 7.50 (*m*, 2 arom. H); 7.56 (*m*, 2 arom. H); 8.12 (*s*, 2 CH=N); 8.19 (*s*, 2 CH=N). Anal. calc. for $C_{76}H_{104}F_6N_4O_9Ti_2 \cdot 3\ CF_3COOH$: C 55.66, H 6.09, N 3.17; found: C 55.18, H 5.51, N 3.08.

9. *Addition of KCN/Ac_2O to Aldehydes Catalyzed by* **1**: *General Procedure:* The experiment with (*S*)-**1** is described as example: A stirred mixture of KCN (12.37 g, 0.19 mol), (*S*)-**1** (0.487 g, $4 \cdot 10^{-4}$ mol), ^{t}BuOH (3.7 g, 4.8 ml, $5.0 \cdot 10^{-2}$ mol), and 2-chlorobenzaldehyde (6.68 g, 5.35 ml, $4.75 \cdot 10^{-2}$ mol) in dry CH_2Cl_2 (120 ml) was cooled to −42°, and Ac_2O (19.4 g, 17.9 ml, 0.19 mol) was then added in one portion. The mixture was stirred for 7 h at −42°. Solid salts were filtered and washed thoroughly with CH_2Cl_2. To remove the catalyst, the filtrate was passed through a silica-gel pad (10 mm × 50 mm) eluting with CH_2Cl_2. The solvent was evaporated, and the resulting yellowish residue distilled *in vacuo:* 8.87 g (88.6%) of *(R)-(2-chlorophenyl)(cyano)methyl acetate*. B.p. 127–130° /0.2 Torr. ee 88.3%. $[\alpha]_D^{25} = +27$ ($c = 1$, $CHCl_3$). $[n]_D^{25} = 1.5189$. ^{1}H-NMR (200 MHz, $CDCl_3$,): 2.15 (*s*, 3 H); 6.66 (*s*, 1 H); 7.32–7.70 (*m*, 4 H). Anal. calc. for $C_{10}H_8ClNO_2$: C 57.30, H 3.85, Cl 16.91, N 6.68; found C 56.93, H 3.83, Cl 17.03, N 6.69.

10. *Addition of KCN/Propanoic Anhydride to Benzaldehyde Catalyzed by* **1**. To a stirred mixture of KCN (2.54 g, 39.21 mmol) and catalyst **1** (0.119 g, 0.098 mmol) in dry CH_2Cl_2 (20 ml) cooled to $-90°$, *t*BuOH (0.98 ml, 10.3 mmol), followed by H_2O (0.1 ml, 4.4 mmol), benzaldehyde (0.95 ml, 9.8 mmol), and propanoic anhydride (5.08 ml, 39.2 mmol) were added. The mixture was warmed to $-40°$ and stirred for 48 h. The mixture was filtered, the solid washed thoroughly with CH_2Cl_2, and the filtrate passed through a silica-gel pad (10 mm × 50 mm) eluting with CH_2Cl_2 to remove the catalyst. The solvent was evaporated and the residue purified by flash chromatography (AcOEt/hexane 1:5): 1.83 g (99%) of *(*S*)-cyano(phenyl)methyl propanoate*. ee 92%. $[\alpha]_D^{25} = -5.09$ ($c = 1.08$, $CHCl_3$). IR (neat): 2987*m*, 1756*s*. ^{1}H-NMR ($CDCl_3$): 1.20 (*t*, $J = 7.5$, *Me*CH_2); 2.3–2.6 (*m*, MeCH_2); 6.45 (1 *s*, CHCN); 7.4–7.6 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 7.70; 26.70; 62.13; 115.65; 127.16; 128.59; 129.69; 131.29; 170.67. EI-MS: 189 (15, $[M+H]^+$), 133 (30), 116 (34), 57 (100).

11. *Addition of KCN/Ac$_2$O to Benzaldehydes Promoted by Catalyst (*R*)-***3***: General Procedure.* To a stirred mixture of KCN (12.37 g, 190 mmol), *t*BuOH (3.7 g, 4.8 ml, 50 mmol), and benzaldehyde (5.21 g, 5 ml, 47.5 mmol) in CH_2Cl_2 (50 ml), H_2O (0.5 ml, 31 mmol) was added. The mixture was then cooled to $-42°$ (MeCN/CO_2) and (*R*)-**3** (0.35 g, 0.475 mmol) in CH_2Cl_2 (20 ml) was added, followed by Ac_2O (11.41 g, 10.55 ml, 190 mmol) in one portion. The mixture was vigorously stirred for 10 h at $-42°$. Solid salts were then filtered and washed thoroughly with CH_2Cl_2. To remove the catalyst, the mixture was filtered through a silica-gel pad (10 mm × 50 mm) eluting with CH_2Cl_2. The solvent was evaporated and the resulting light green residue fractionated *in vacuo:* 7.5 g (87.2%) of *cyano(phenyl)methyl acetate*. B.p. 95–97°/0.2 Torr. ee 90.3% (*S*).

12. *X-Ray Crystal-Structure Determination*. The details of crystal-data collection and structure-refinement parameters for compounds (*R*)-**2**, (*R*)-**3**, and (*R*)-**4** are listed in *Table 4*. The structures were solved by the direct methods and refined by the full-matrix least-squares technique on F^2 with anisotropic approximations for non-

Table 4. *Crystallographic Data for Compounds (*R*)-***2***, (*R*)-***3***, and (*R*)-***4***

	(*R*)-**2**	(*R*)-**3**	(*R*)-**4**
Empirical formula	$C_{36}H_{52}N_2O_3V \cdot 1.5\ C_7H_8$	$[C_{36}H_{54}N_2O_4V]^+\ [C_2H_5O_4S]^- \cdot 0.5\ C_7H_8$	$C_{76}H_{110}N_4O_9Ti_2 \cdot H_2O$
M_r	749.94	800.94	1337.50
Crystal size [mm]	0.2 × 0.1 × 0.05	0.5 × 0.3 × 0.2	0.3 × 0.2 × 0.1
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1$	$P1$	$C2$
a [Å]	13.039(2)	8.826(2)	14.656(3)
b [Å]	12.525(2)	16.220(3)	31.261(6)
c [Å]	26.445(5)	16.494(3)	16.180(3)
α [°]	90	108.43(3)	90
β [°]	99.331(4)	91.55(3)	91.48(3)
γ [°]	90	95.10(3)	90
V [Å^3]	4261.9(14)	2227.5(8)	7411(3)
Z	4	2	4
d_c [Mg/m^3]	1.169	1.194	1.199
Diffractometer	*SMART CCD 1000*	*Siemens P3*	*Syntex P2$_1$*
Radiation, λ [Å]	MoK_α, 0.71073	MoK_α, 0.71073	MoK_α, 0.71073
μ [mm^{-1}]	0.273	0.319	0.274
T [K]	120	293	163
Scan mode	ω and φ	$\theta/2\theta$	$\theta/2\theta$
θ_{max} [°]	27	25	25
Absorption correction	semi-empirical	none	none
T_{min}, T_{max}	0.7568, 0.9281	–	–
Reflections collected	41462	9259	6970
Independent reflections	18506	8348	6744
Reflections with $I > 2\sigma(I)$	11325	7131	5048
Refined parameters	946	966	857
R_1	0.0561	0.0497	0.0765
wR_2	0.1412	0.1324	0.2070
Flack parameter	0.00(2)	0.00(2)	0.01(5)
S	0.900	1.029	1.033

H-atoms. The crystals of (*R*)-**2** and (*R*)-**3** contain 1.5 and 0.5 solvate toluene molecules, respectively. The crystal of (*R*)-**4** contains two solvate H_2O molecules. Both the molecules of (*R*)-**4** and molecules of solvate H_2O occupy special positions on the two-fold (C_2) axis. Two of the eight *tert*-butyl groups of molecules of (*R*)-**4** are disordered over two sites by turning by 60° around $C_{alk}-C_{ar}$ bond with occupancies 0.7:0.3 and 0.85:0.15, respectively, for two independent molecules. Positions of all H-atoms of (*R*)-**2**, (*R*)-**3**, and (*R*)-**4** were geometrically calculated and refined isotropically in the riding model with fixed displacement parameters ($U_{iso}(H) = 1.5U_{eq}(C)$ for the Me groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for the other groups). The absolute configurations were objectively determined by the refined *Flack* parameters. All calculations were carried out by means of the SHELXTL (PC Version 5.10) program [8]. The crystallographic information files have been deposited at the *Cambridge Crystallographic Data Centre (CCDC)*, No 186928, 186929, and 186930. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

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