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# Chiral bispyridylamide metal complexes as catalysts for the enantioselective addition of TMSCN to aldehydes

Oscar Belda [a,*], Sophie Duquesne [a], Andreas Fischer [b], Christina Moberg [a,*]

[a] Department of Chemistry, Organic Chemistry, KTH, Teknikringen 36 Plan 6, SE-100 44 Stockholm, Sweden
[b] Department of Chemistry, Inorganic Chemistry, KTH, SE-100 44, Stockholm, Sweden

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**Abstract**

The use of (1*R*,2*R*)-*N*,*N*′-bis(2-pyridinecarboxyamido)-1,2-diphenylethane metal complexes as catalysts for the enantioselective addition of trimethylsilyl cyanide to aldehydes is described. Enantioselectivities up to 70% ee were obtained with a Ti(IV) catalyst. Complexes with Zr(IV), Sc(III), Yb(III) and Cu(II) afforded less selective catalysts. For the Zr(IV) complex, a rate and selectivity enhancement was observed when adding 0.5 equiv. of water with respect to the catalyst. Studies of the metal complexes involved in the reaction were carried out by means of $^1$H NMR spectroscopy. A Zr complex was shown by X-ray crystallography to exhibit distorted octahedral coordination, with the four nitrogen atoms of the doubly deprotonated ligand essentially in one plane.


*Keywords:* Pyridylamide; Asymmetric catalysis; Cyanohydrins; Lewis acid

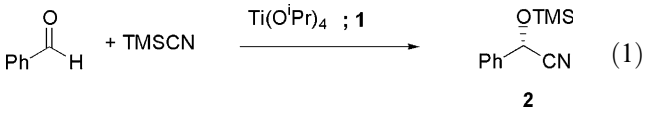
## 1. Introduction

The asymmetric addition of cyanide to carbonyl groups is a topic of major interest because the resulting enantiomerically enriched cyanohydrins can be transformed into synthetically versatile building blocks without loss of the optical purity [1]. Enzymatic methods, chiral Lewis bases and chiral Lewis acids have been used to induce asymmetry in the reaction [2]. Tetradentate salen ligands [3,4] have been much studied in this reaction, and they have become the basis of some of the most efficient and versatile asymmetric catalysts for the synthesis of cyanohydrins by means of asymmetric Lewis acid catalysis. Our group has studied the use of another type of tetradentate ligands, bispyridylamides, in asymmetric catalysis and showed that complexes of bispyridylamide **1** (Fig. 1) with group IV metal alkoxides, catalyzed the ring opening of cyclohexene oxide with good enantioselection [5].

Herein, we describe the use and achievements of diverse ligand **1**–metal complexes in the enantioselective addition of cyanide to aldehydes.

## 2. Results and discussion

In order to determine the best conditions for the reaction, we used benzaldehyde as model substrate and $Ti(O^iPr)_4$ as the Lewis acid (Eq. (1)). As for the cyanating reagent, we employed trimethylsilyl cyanide (TMSCN), a widely used source of cyanide in reactions affording silylated cyanohydrins [6,7]



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* Corresponding authors. Tel.: +4687908128; fax: +4687912333.
*E-mail address:* belda@kth.se (O. Belda).

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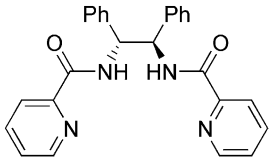


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Fig. 1. Structure of bispyridylamide **1**.

First we examined the effect of the solvent on the reaction outcome when using 5 mol% of the catalyst with respect to benzaldehyde (Table 1) and found that methylene chloride was a better solvent for the reaction than THF, EtOAc and toluene, affording the product in almost quantitative yield and with 60% ee after 4 h reaction time. In dry acetonitrile, almost complete conversion was obtained after already 1 h and the product displayed also in this reaction 60% ee. When THF or acetonitrile was used as solvent, the addition of $CH_2Cl_2$ was needed in order to dissolve the ligand.

Next, the influence on the reaction of the amount of catalyst relative to benzaldehyde, the metal to ligand ratio and the concentration of benzaldehyde at the start of the reaction ($[PhCHO]_0$) was explored. Dichloromethane was used as solvent, in order to keep the system as anhydrous as possible (Table 2).

Table 1
Effect of the solvent on the reaction[a] (Eq. (1))

| Entry | Solvent | *t* (h) | Yield (%)[b] | ee (%) |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 4 | >95 | 60 |
| 2 | THF:$CH_2Cl_2$ 4:1 | 1 | 15 | 4 (*R*) |
| 3 | EtOAc | 1 | 16 | 28 |
| 4 | $CH_3CN$:$CH_2Cl_2$ 5:1 | 1 | 93 | 60 |
| 5 | Toluene | 1 | 11 | 2 |

[a] Reactions were carried out with 5 mol% of $Ti(O^iPr)_4$ and **1** and initial concentration of PhCHO = 1 M.
[b] GC yields.

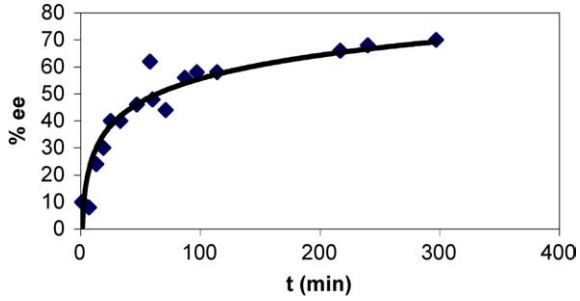



Fig. 2. Variation of the ee with time.

While changes in the metal to ligand ratio had no significant effect (entries 1–4), both the relative amount of catalyst and the initial concentration of benzaldehyde had a clear effect on the outcome of the reaction. With 1–2.5% mmol of catalyst with respect to benzaldehyde and an initial concentration of benzaldehyde between 5 and 10 M, trimethylsilyl protected mandelonitrile **2** was obtained in high yield and with 70% ee (entries 5 and 6). Dilution of the reaction mixture had a negative effect on the enantioselectivity, but yields were still high (entries 7–9).

Cooling the reaction mixture to 0 °C did not improve the ee of the cyanohydrin and performing the reaction at 100 °C in a microwave cavity afforded 91% yield of the product with merely 34% ee.

In the course of this optimization, we observed that the enantiomeric excess increased with time (Fig. 2). A possible explanation to this effect might be that a catalyst exhibiting higher enantioselectivity may be formed from the enantiomerically enriched product.

To test this hypothesis, a small amount of TMS-protected mandelonitrile (**2**) with 70% ee was added together with the catalyst and the reagents in the beginning of the reaction. However, this had no noticeable effect on the enantioselectivity (Table 3, entry 1). Neither was any effect observed when 70% ee mandelonitrile was added instead (entry 2).

Table 2
Effect of the amount of $Ti(O^iPr)_4$ and **1** relative to benzaldehyde and the concentration of benzaldehyde in the beginning of the reaction (Eq. (1))

| Entry | mol% $Ti(^iPrO)_4$ | mol% **1** | $[PhCHO]_0$ (M) | Yield (%)[a] | ee (%) |
|---|---|---|---|---|---|
| 1 | 5 | 5 | 1 | >95 | 60 |
| 2 | 10 | 10 | 1 | >95 | 60 |
| 3 | 10 | 5 | 1 | 90 | 60 |
| 4 | 5 | 10 | 1 | >95 | 60 |
| 5 | 1 | 1 | 10 | >95 (86)[b] | 70 |
| 6 | 2.5 | 2.5 | 5 | >95 | 70 |
| 7 | 2.5 | 2.5 | 0.5 | >95 | 66 |
| 8 | 2.5 | 2.5 | 0.33 | >95 | 63 |
| 9 | 2.5 | 2.5 | 0.25 | >95 | 57 |

[a] Determined by GC.
[b] Isolated yield.

Table 3
Influence of addition of **2** on the reaction[a] (Eq. (1))

| Entry | mol% Added **2** | Yield (%)[c] | ee (%) |
|---|---|---|---|
| 1 | 2.16 | >95 | 60 (*S*) |
| 2 | 1.64[b] | >95 | 60 (*S*) |

[a] Reactions were carried out with 5 mol% of $Ti(O^iPr)_4$ and **1** and 70% ee **2** as additive.
[b] Deprotected alcohol from **2**.
[c] GC yield.

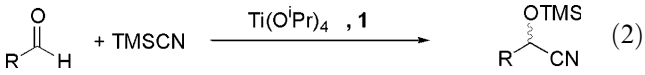
A second hypothesis was formulated on the supposition that a more enantioselective catalyst might form as a result of the decrease in concentration of benzaldehyde during the reaction. To test this assumption we performed the reaction by slowly adding the substrate, benzaldehyde, to the reaction mixture in such a way that the concentration of benzaldehyde was essentially constant during the reaction. The enantiomeric excess of the product obtained in this way was the same as when the reaction was run under the standard conditions, however.

It has been observed in similar systems, that slow diffusion of water into the reaction mixture resulted in an increase of the ee of the product with time, due to the formation of a dimeric Ti complex with *O*-bridges that was more active and selective in the reaction than the initial monomeric complex [8]. We added small amounts of water to the reaction mixture but the product **2** was then obtained with lower ee (30% ee with 0.5% water, and 0% ee with 1.2% water).

At this point, we decided to study the complexes that were involved in the reaction by NMR spectroscopy to see whether the increase in ee with time was caused by slow formation of different catalytic species. When mixing one equivalent of ligand **1** with one equivalent of $Ti(O^iPr)_4$ no reaction occurred. In order to form a Ti(IV) complex with ligand **1**, TMSCN needed to be present, as evidenced by these studies. Indeed, TMSCN reacted with $Ti(O^iPr)_4$, as shown by the disappearance of the $^1H$ NMR signals for the isopropyl groups of $Ti(O^iPr)_4$ at $\delta$ 1.23 (doublet) and 4.47 ppm (heptet) and the appearance of new signals at $\delta$ 1.03 (doublet) and 3.88 ppm (heptet) as well as new $^{13}C$ NMR signals at $\delta$ 26.2 and 65.1 ppm, replacing the initial signals at $\delta$ 26.9 and 76.6 ppm. The complex obtained reacted further with **1** to give a mixture of complexes: all $^1H$ NMR signals from the ligand disappeared and a new set of signals appeared. Particularly significant are the new low field signals at $\delta$ 9.99 and 9.81 ppm (ratio 100:17), indicative of complex formation. When these preformed complexes were used for the cyanation reaction instead of the in situ formed complexes, the final enantiomeric excess of the product was again 70%. Attempts to isolate the complexes by crystallization were unsuccessful.

It has been shown in similar systems, that bimetallic species, in which Ti activates both TMSCN and the aldehyde, are present in the catalytic cycle. The proposed key step is the intramolecular transfer of cyanide to the coordinated aldehyde [9]. A similar mechanism, with dual activation of the nucleophile and the electrophile, may be operating for our catalyst as well, even though conclusive evidence cannot be drawn from the NMR data only.

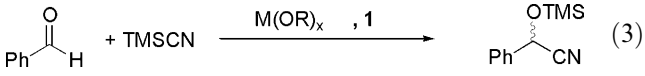
When using the catalytic system for other aldehydes than benzaldehyde (Eq. (2)), the respective products were generally obtained with lower enantioselectivity and reaction times were in the same range or longer (Table 4).



(2)

*Para*-substituted benzaldehydes with an electron-donating group (MeO–) were more reactive and gave the product with higher enantioselectivity than those having an electron-withdrawing group ($F_3C$–) (16 vs. 66 h, and 47 vs. 11% ee, entries 2 and 3). This unexpected reactivity was similar to that previously found by North et al. [8]. With a bromine in the *ortho* position a reaction time of 25 h was required for the reaction to go to completion and the product was obtained with 24% ee. Aliphatic aldehydes, such as valeraldehyde (entry 5), exhibited a reactivity similar to that of benzaldehyde and the product had 41% ee. For the more sterically hindered pivalaldehyde (entry 6), the reactivity was similar, but the enantiomeric excess of the resulting cyanohydrin was only 12%. In contrast to the results obtained when using aldehydes as substrates, acetophenone required a reaction time of 119 h and the enantiomeric excess of the product was very low (entry 7).

Next, we turned our attention to other metal alkoxides that could form efficient catalysts for the reaction using **1** as a ligand (Eq. (3)). A first screening was made using the best conditions found for Ti (Table 5)



(3)

Table 4
Cyanation of other carbonyl compounds (Eq. (2))[a]

| Entry | R | *t* (h) | Yield (%)[b] | ee (%) |
|---|---|---|---|---|
| 1 | Ph | 6 | >95 | 70 |
| 2 | 4-MeOPh | 16 | >95 | 47 |
| 3 | 4-$F_3$CPh | 66 | >95 | 11 |
| 4 | 2-BrPh | 25 | >95 | 24 |
| 5 | $C_4H_9$ | 5 | >95 | 41 |
| 6 | $^t$Bu | 5 | >95 | 12 |
| 7 | Acetophenone | 119 | >95 | 8 |

[a] Reactions were carried out in $CH_2Cl_2$ with 1% $Ti(O^iPr)_4$ and **1** at room temperature.
[b] GC yield.

Table 5
Screening of various metals together with ligand **1** as catalysts for the cyanide addition to benzaldehyde (Eq. (3))[a]

| $M(OR)_x$ | mol % | *t* (h) | Yield (%)[b] | ee (%) |
|---|---|---|---|---|
| $Zr(O^tBu)_4$ | 1 | 23 | 78 | 3 |
| $Zr(O^tBu)_4$ | 10 | 4 | 91 | 26 |
| $Sc(O^iPr)_3$ | 1 | 3 | >95 | 2 |
| $Yb(O^iPr)_3$ | 1 | 16 | >95 | 8 |
| $Cu(OAc)_2$ | 1 | 3 | 10 | 0 |

[a] Reactions were carried out in $CH_2Cl_2$ at room temperature.
[b] GC-yield.

All metal complexes catalyzed the reaction, with the exception of the Cu(II) complex [10], but very low or no asymmetric induction was observed. Despite these disappointing results, we decided to optimize the reaction conditions for Zr. We had previously found that addition of a small amount of a secondary amine was crucial for the reactivity and enantioselectivity induced by the catalyst in the ring opening of cyclohexene oxide with trimethylsilyl azide [5]. Adding a small amount of pyrrolidine to the reaction mixture did not improve the reactivity or enantioselectivity of the catalyst (Table 6) for the addition of TMSCN to benzaldehyde catalyzed by **1** and $Zr(O^tBu)_4$, however. On the other hand, addition of 0.5 equiv. of $H_2O$ proved to increase both the reactivity and enantioselectivity. This effect has previously been observed in the asymmetric aldol reaction catalyzed by Zr–binol complexes [11]. The reason for the improvement in reactivity and enantioselectivity seemed to be the formation of a more active symmetric dimeric or oligomeric catalyst containing oxygen bridges.

By heating an equimolar mixture of $Zr(^tBuO)_4$ and **1** in benzene, a complex could be crystallized. The X-ray structure showed a monomeric Zr complex with a distorted octahedral coordination, in which the two pyridine nitrogen atoms and the two deprotonated amide nitrogen atoms were almost coplanar and the two alkoxide groups above and below the plane, respectively ($O_3$–Zr–$O_4$ = 124.1°, Table 7) (Fig. 3). This mode of coordination is typical for the deprotonated ligands [12]. It is interesting to note that the C–O–Zr angles are close to linear, 169.7° and 174.1°, indicating multiple bonding of the alkoxide groups [13].

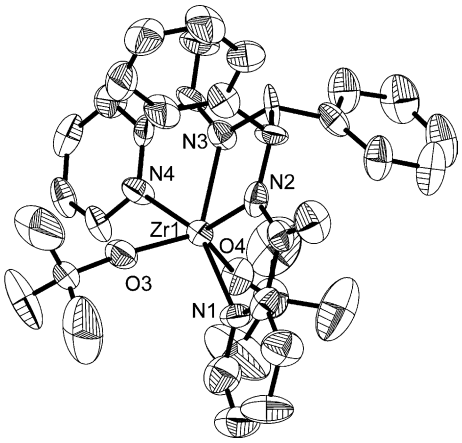



Fig. 3. X-ray structure of [$Zr(O^tBu)_2$(1*R*,2*R*)-*N*,*N*′-bis(2-pyridinecarboxyamido)-1,2-diphenylethane].

Table 7
Selected bond lengths (pm) and bond angles (°) for Zr complex with ligand **1**

| Bond lengths | | Bond angles | |
|---|---|---|---|
| Zr1–O3 | 192.4(8) | O3–Zr1–O4 | 124.1(3) |
| Zr1–O4 | 192.2(7) | O4–Zr1–N3 | 105.7(4) |
| Zr1–N1 | 234(1) | O3–Zr1–N3 | 118.8(3) |
| Zr1–N2 | 220.7(8) | O4–Zr1–N2 | 120.6(3) |
| Zr1–N3 | 220.6(9) | O3–Zr1–N2 | 70.6(3) |
| Zr1–N4 | 236.5(8) | O3–Zr1–N1 | 84.3(3) |
| | | N3–Zr1–N1 | 138.1(3) |
| | | N2–Zr1–N1 | 69.5(3) |
| | | O4–Zr1–N4 | 82.9(3) |
| | | O3–Zr1–N4 | 82.9(3) |
| | | N3–Zr1–N4 | 69.2(3) |
| | | N2–Zr1–N4 | 137.7(3) |
| | | N1–Zr1–N4 | 152.4(3) |

The conformation of the ligand, with pseudo-axial orientation of the phenyl rings, was found to be similar to that of the previously described Cu(II) complex [10].

In the presence of TMSCN, benzaldehyde and water, a mixture of complexes formed, as shown by NMR spectroscopy. One of these, with e.g., a doublet at 10.12 ppm originating from an amide proton, was identical to a dimeric complex previously observed in the

Table 6
Screening of additives

| Entry | mol% **1** | mol% $Zr(^tBuO)_4$ | Remarks | *t* (h) | Yield (%)[a] | ee (%) |
|---|---|---|---|---|---|---|
| 1 | 1 | 1 | – | 23 | 78 | 3 |
| 2 | 10 | 10 | – | 4 | 91 | 26 |
| 3 | 10 | 10 | 1 mol% $C_4H_8NH$ | 5 | >95 | 26 |
| 4 | 10 | 10 | 1 mol% $H_2O$ | 3 | >95 | 29 |
| 5 | 10 | 10 | 5 mol% $H_2O$ | 2 | >95 | 56 |
| 6 | 10 | 10 | 10 mol% $H_2O$ | 2 | >95 | 7 |

[a] GC yield.

ring opening of epoxides with trimethylsilyl azide [5]. Whether activation of both the nucleophile and the carbonyl group took place using the Zr catalyst is not clear. Attempts to isolate dimeric or oligomeric Zr complex of **1** by crystallization were unsuccessful.

## 3. Conclusions

A study of the asymmetric addition of TMSCN to aldehydes catalyzed by metal alkoxides and (1*R*,2*R*)-*N*,*N*′-bis(2-pyridinecarboxyamido)-1,2-diphenylethane as ligand was carried out. The products were obtained in good yields but with modest enantioselectivity (11–70% ee).

Ti and Zr alkoxide complexes with bispyridylamide **1** as ligand were prepared and studied by NMR spectroscopy and X-ray crystallography. When the catalyst was formed from $Ti(O^iPr)_4$ and ligand **1**, evidence for dimeric or oligomeric species was obtained. From $Zr(O^tBu)_4$ and **1**, a monomeric complex was isolated and characterized in the solid state as well as in solution. The active catalyst was, however, composed of dimeric or oligomeric complexes which were formed more efficiently when adding a small amount of water.

Further applications of **1** in asymmetric catalyzed reactions are under study.

## 4. Experimental

### 4.1. General

Benzaldehyde and $Ti(O^iPr)_4$ were distilled and stored under Ar. $Zr(O^tBu)_4$, $Sc(O^iPr)_3$ and $Yb(O^iPr)_3$ (Strem) were stored in a drybox and used as received. All solvents were carefully dried according to standard procedures before use and handled under $N_2$. All catalytic reactions were run in dried glassware under a dry Ar atmosphere using standard techniques. Yields were determined by GC using naphthalene as external standard unless otherwise noted. The enantiomeric excess of the cyanohydrins was determined by GC on a Chiraldex G-TA 30 m×0.25 mm column.

### 4.2. Preparation of (1R,2R)-N,N′-bis(2-pyridinecarboxamide)-1,2-diphenylethane (1)

A suspension of picolinic acid (0.59 g, 4.76 mmol) and 1,1′-carbonyldiimidazole (CDI) (0.92 g, 5.70 mmol) in THF (5 mL) was heated to 50 °C for 1 h (evolution of gas was observed). Then (1*R*,2*R*)-1,2-diphenyldiaminoethane (0.50 g, 2.38 mmol) was added at once at 50 °C and the mixture stirred vigorously at room temperature (formation of a precipitate). The mixture was then extracted ($CH_2Cl_2/H_2O$) and the combined organic extracts dried ($Na_2SO_4$). Evaporation of the solvent afforded a solid that was recrystallized from EtOH to give the pure product as white needles. Yield: 0.81 g, 80%. Spectroscopic data were in agreement with that published previously for the compound [10].

### 4.3. General procedure for the addition of TMSCN to benzaldehyde catalyzed by Ti

TMSCN (0.39 mL, 2.95 mmol) and benzaldehyde (0.25 mL, 2.46 mmol) were added to a solution of **1** (10.5 mg, 0.025 mmol) and $Ti(O^iPr)_4$ (7.5 μL, 0.025 mmol) in $CH_2Cl_2$ (0.5 mL) and the reaction was monitored by GC. The reaction mixture was diluted with $Et_2O$ and the product purified by column chromatography on $SiO_2$ using $Et_2O$ as eluent. Spectroscopic data of the product were identical to that previously reported in the literature [14]. The absolute configuration was assigned by means of optical rotation [15].

### 4.4. General procedure for the addition of TMSCN to benzaldehyde catalyzed by Zr with $H_2O$ as additive

TMSCN (95 μL, 0.71 mmol) and benzaldehyde (60 μL, 0.59 mmol) were added to a solution of **1** (25 mg, 0.059 mmol) and $Zr(O^tBu)_4$ (23 μL, 0.059 mmol) in a 0.06 M solution of $H_2O$ in $CH_2Cl_2$ (0.5 mL, 0,03 mmol $H_2O$) and the reaction was monitored by GC.

## 5. X-ray crystallography

### 5.1. Structural analysis of 1–Zr(O$^t$Bu)$_2$

Crystals of **1**–$Zr(O^tBu)_2$ were prepared as follows: $Zr(O^tBu)_4$ (25 μL, 0.064 mmol) was added to a suspension of ligand **1** (22.5 mg, 0.054 mmol) in dry benzene (0.5 mL) at 70 °C under an Ar atmosphere. The resulting solution was cooled to room temperature over a period of 5 h. The resulting hygroscopic crystals were sealed into capillaries in a nitrogen-filled glove box. Diffraction data were collected at 297 K on a Bruker-Nonius Kappa CCD diffractometer. The structures were solved using Direct Methods [SHELXS97] [16] and refined on $F^2$ with anisotropic thermal parameters for all non-H atoms [SHELXL97] [17]. H atoms were refined on calculated positions using a riding model. Crystal data for **1**–$Zr(O^tBu)_2$: sum formula $C_{34}H_{36}N_4O_4Zr$, cell constants $a=9.1450(13)$, $b=10.291(2)$, $c=34.450(5)$ Å, $V=3242.1(9)$ Å$^3$, $Z=4$, $\rho_{calc}=1.344$ g/cm$^3$, orthorhombic, space group $P2_12_12_1$ (No. 19), $T=297$ K, radiation Mo Kα, $\lambda=0.71073$ Å, absorption coefficient 0.381 mm$^{-1}$, $\theta$ range $4.5°<\theta<20.8°$, number of measured reflections 10214, number of unique reflections 3312, $R_{int}=0.0857$, number of refined parameters 388, residuals $R_1=0.0662$ (2649 reflections with $I>2\sigma(I)$)

$wR_2 = 0.142$ (all reflections), goodness-of-fit 1.166, flack parameter $x = -0.07(10)$, difference electron density peak/hole 0.65/−0.36.

## 6. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 237475 for **1**–$Zr(O^tBu)_2$. These data can be obtained free of charge via The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/conts/retrieving.html).

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[7] We realized that the quality of the TMSCN used was very important for the outcome of the reaction. When dark-coloured TMSCN from Lancaster was used the reaction times were longer, the products were obtained in low ee:s (10–46% ee) and the reproducibility was low. On the other hand, when we used TMSCN from Acros or Aldrich, the reproducibility was high whereas the ee:s of the products varied slightly between two different batches of the reagent supplied by Acros (batch 1 afforded the product **2** in 70% ee and batch 2 in 60% ee under the best conditions found). No significant differences were observed in the $^1H$ NMR spectra of the reagent from the different suppliers. The reagent from Lancaster and batch 1 from Acros were both dark-colored liquids, whereas the reagent from batch 2 Acros and Aldrich were colorless liquids. Since Fe–CN complexes are dark-colored, we decided to analyze by ICP whether any Fe was present in the various reagents and found that the reagents did not contain Fe above 0.08 ppm. We decided to use TMSCN from Aldrich kept under $N_2$, and the experiments were run several times in order to verify their reproducibility.
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