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Enantioselective Trimethylsilylcyanation of Aldehydes

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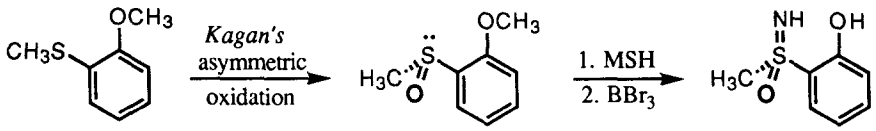
Abstract: A chiral titanium reagent derived from optically active sulfoximine (*R*)-**3** and Ti(O-*i*-Pr)$_4$ promotes the asymmetric addition of trimethylsilylcyanide to aldehydes affording cyanohydrins in high yields with good enantioselectivities (up to 91% ee).

We recently reported on the use of optically active sulfoximines in the catalyzed enantioselective reduction of ketones[1] and the asymmetric diethylzinc addition to aldehydes[2] and chalcones.[3] We now describe a chiral sulfoximine/titanium reagent for enantioselective cyanohydrin formation.[4]

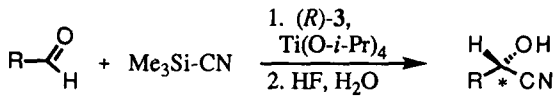
Optically active sulfoximine (*R*)-**3** was obtained as a colorless solid by enantioselective sulfur oxidation of (2-methoxyphenyl)methylsulfide (**1**) using *Kagan*'s method,[5] followed by sequential stereospecific imination of the resulting sulfoxide (*R*)-**2** with *O*-mesitylenesulfonylhydroxylamine (MSH),[6] and demethylation with BBr_3. Both enantiomers of **3** are available by this reaction sequence.



1 (*R*)-**2** (*R*)-**3**

Treatment of (*R*)-**3** with 1 equiv of Ti(O-*i*-Pr)$_4$ in dichloromethane gave a yellow solution containing a catalytically active species for the asymmetric addition of trimethylsilylcyanide to benzaldehyde.[7,8] However, catalyst reactivity and enantioselectivity were low. Thus, use of 20 mol% of catalyst afforded (*S*)-mandelonitrile after 20h at -45°C in only 28% yield with 44% *ee*. Stirring for a longer period of time gave a higher product yield, but the enantiomeric excess was significantly lower (60h at -45°C: 79% yield, 23% *ee*). This decrease in enantioselectivity was interpreted as indication for the formation of several active species during the reaction, each of which mediated the Me_3SiCN addition at different rates and with different enantiomeric excesses.[9] In accord with this assumption, a remarkable increase in selectivity was observed when larger quantities of chiral titanium reagent were used. Thus, in the presence of stoichiometric amounts of Ti(O-*i*-Pr)$_4$ and 1.1 equiv of sulfoximine (*R*)-**3**, trimethylsilylcyanation of benzaldehyde at -50°C, followed

by acidic cleavage of the trimethylsilyl group (5% aqueous solution of HF) gave (*S*)-mandelonitrile in 72% yield with 91% *ee* (Table). After the reaction (*R*)-**3** was easily recovered (70-90%).



Attempts to increase the asymmetric induction by varying the concentration (0.2 - 1 M) or lowering the reaction temperature to -65°C did not result in significant changes of *ee*. The reaction time had no influence on the optical yield.

Trimethylsilylcyanation of several aldehydes was investigated using the conditions which had been optimized for the Me_3SiCN addition to benzaldehyde.[10] As summarized in the Table, a variety of aldehydes including substituted aromatic, aliphatic, and α,β-unsaturated aldehydes were silylcyanated with good enantiocontrol. In the aromatic series, steric hinderance at the *ortho* position lowered the asymmetric induction (entry 1 versus entries 3 and 4). Aliphatic aldehydes, such as *n*-hexanal (entry 5), and α-branched cyclohexane carboxaldehyde (entry 6) were silylcyanated equally well (89% *ee*). Further substitution at the α position (pivaldehyde) lowered the enantiomeric excess (81% *ee*). The cyanohydrin of (*E*)-cinnamaldehyde was obtained with 79% *ee*. In all cases, sulfoximine (*R*)-**3** afforded cyanohydrins with (*S*)-configuration, as determined by comparison of the optical rotation values with those reported in the literature. The enantiomeric excesses were determined by ^{19}F NMR, GC, or HPLC analysis of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic esters (MTPA esters).[11]

Table. Enantiomeric excesses resulting from asymmetric trimethylsilylcyanation of aldehydes using (*R*)-**3**/$Ti(O\text{-}i\text{-}Pr)_4$ and TMSCN

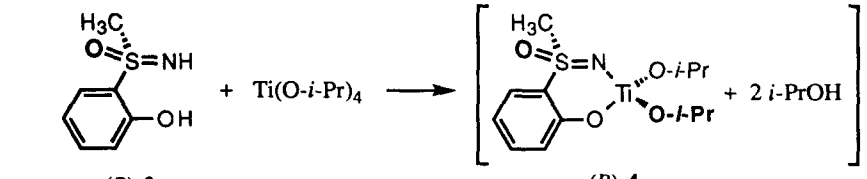
Entry	Aldehyde	% Yield [a]	% Ee [b]	Config[c]
1	benzaldehyde	72 (96)	91	(*S*)
2	4-methoxybenzaldehyde	60	87	(*S*)
3	2-methoxybenzaldehyde	72 (92)	74	(*S*)
4	1-naphthaldehyde	92 (97)	76	(*S*)
5	*n*-hexanal	64	89	(*S*)
6	cyclohexane carboxaldehyde	70 (97)	89	(*S*)
7	pivaldehyde	70	81	(*S*)
8	(*E*)-cinnamaldehyde	63	79	(*S*)

[a] Isolated as cyanohydrins by column chromatography; conversion in parentheses (determ. by ^1H NMR). [b] Ee determ. by GC analysis of the corresponding MTPA esters (Durabond DB-5, 0.3 mm x 30 m) except entries 2-4 and 8 [HPLC analysis of the MTPA esters (Nucleosil 100-5)]. [c] Absolute configurations determined by comparison of optical rotations with literature values.

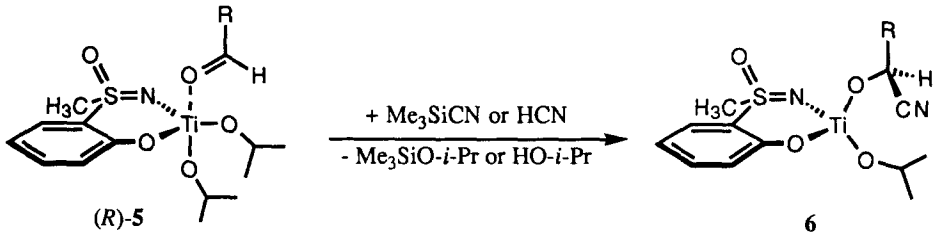
Commonly, enzymes[4b] or cyclodipeptides[12] are the catalysts of choice for enantioselective hydrocyanation of aldehydes with *hydrogen cyanide*. Reports on the use of organometallic reagents for this

transformation are still rare.[13,14] We therefore tested the effectiveness of our sulfoximine/titanium-system in the HCN addition to benzaldehyde. Smooth cyanohydrin formation ocurred even at -50°C, and after 16h the product was isolated in 89% yield with an 82:18 *S/R* enantiomer ratio.

The result of the enantioselective HCN addition is also relevant to the aldehyde/Me_3SiCN system. When equimolar amounts of sulfoximine (*R*)-**3** and $Ti(O\text{-}i\text{-}Pr)_4$ were mixed in $CDCl_3$ at ambient temperature ^1H and ^{13}C NMR spectroscopy revealed the formation of new species.[15] Presumably, two titanium alkoxides have been exchanged generating a chiral titanium-containing compound of type **4**. Two equivalents of isopropanol are liberated by this reaction. If the alcohol is involved in the reaction pathway, it can either interact with **4** forming a dynamic associate, or it can react with Me_3SiCN to generate HCN. The latter should therefore also be considered as a cyanide source, and good enantiocontrol in hydrocyanation with HCN is desirable. In the subsequent reaction pathway, (*R*)-**4** serves as a chiral Lewis acid and coordination of the aldehyde at the less hindered β face of **4** is followed by *re* side cyanation in **5** and loss of alkoxide to give **6**.[16,17]



(*R*)-**3** (*R*)-**4**



(*R*)-**5** **6**

In this sequence, predominant formation of the *(S)*-cyanohydrin is a result of two subsequent stereocontrolled events: 1. selective complexation of the aldehyde to the β face of the titanium reagent and 2. enantioselective cyanide addition to the activated aldehyde carbonyl.

Under the current reaction conditions, the species which controls the stereochemical outcome is regenerated inefficiently and catalyst turnover is blocked. Further research is therefore focussing on the development of modified procedures which lead to improved enantioselectivities and to effective *catalytic* systems for asymmetric cyanohydrin formation.

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10. **Typical Procedure.** To a stirred solution of (*R*)-**3** (235 mg, 1.375 mmol) in dichloromethane (3 ml) was added titanium tetraisopropoxide (0.365 ml, 1.250 mmol). After stirring the resulting yellow solution at ambient temperature for 1h, the mixture was cooled to -50°C. The aldehyde (1.250 mmol) was added dropwise followed by trimethylsilylcyanide (0.315 ml, 250 mg, 2.520 mmol). Stirring was continued at this temperature for 20-24h. The reaction mixture was then quenched with an aqueous solution of HF (5%, 2 ml) and stirred vigorously for 30 min at ambient temperature. After neutralization with $NaHCO_3$ the mixture was extracted dichloromethane (5 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. The residue was column chromatographed (silica gel; eluent: hexane - *tert*-butylmethyl ether), affording (*S*)-cyanohydrins. The enantiomeric excesses of the products were determined by ^{19}F NMR, GC, or HPLC analysis of the corresponding MTPA esters (Table). Sulfoximine (*R*)-**3** was recovered in 70-90% yield by elution of the chromatography column with *tert*-butylmethyl ether.
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14. *Corey* and *Wang* discuss the involvement of a 'chiral cyanide donor' derived from a bisoxazoline and HCN in a Mg-catalyzed trimethylsilylcyanation.[8b] Use of HCN as the only cyanide source gave low enantioselectivities.
15. Under these conditions broad signals were observed. Sharper resonances resulted from 2:1 mixtures of (*R*)-**3** and $Ti(O\text{-}i\text{-}Pr)_4$. This composition, however, was catalytically inactive.
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