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The asymmetric addition of trimethylsilyl cyanide to ketones catalysed by a bimetallic, chiral (salen)titanium complex

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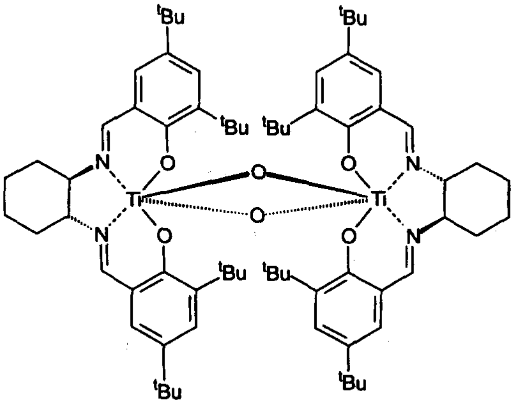
Abstract

The use of a bimetallic titanium salen complex as a catalyst for the asymmetric addition of trimethylsilylcyanide to ketones is reported. The cyanohydrin trimethylsilyl ethers are obtained with enantiomeric excesses of up to 72% from reactions carried out at room temperature and atmospheric pressure employing 0.5 mol% of the catalyst. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric synthesis; catalysis; cyanohydrins; ketones; salen; titanium.



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Cyanohydrins are highly versatile synthetic intermediates and can easily be converted into a wide variety of important synthetic intermediates including α-hydroxy acids, α-amino acids, and β-amino

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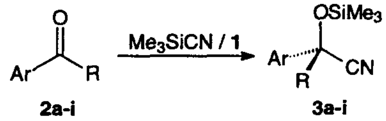
alcohols.[1] In view of their importance, there is currently considerable interest in the asymmetric synthesis of cyanohydrins, especially by methods that utilize a chiral catalyst.[2] A number of catalysts for the asymmetric addition of cyanide to aldehydes have been reported, including enzymes,[1,2] synthetic peptides,[2] and chiral transition metal complexes.[2] Whilst impressive enantiomeric excesses have been obtained in some of these reactions, the only previous reports of the asymmetric addition of cyanide to ketones have utilized oxynitrilase enzymes[3] which gave chemical yields >15% only for methyl or ethyl ketones, or have employed high pressure (0.8 Gpa) to induce the titanium catalysed reaction between acetophenone and trimethylsilyl cyanide.[4] In recent publications[5] we have shown that chiral (salen)titanium(IV) complexes are effective catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes.[6,7] This work culminated in the discovery of the bimetallic catalyst **1**, 0.1 mol% of which was found to induce the asymmetric addition of trimethylsilyl cyanide to a range of aldehydes in less than 1 h at ambient temperature, giving the corresponding (*S*)-cyanohydrin silyl ethers with 80–90% enantiomeric excess. In this communication, we show that catalyst **1** is also the first transition metal based catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones at atmospheric pressure.

Treatment of acetophenone **2a** with 1.1 equivalents of trimethylsilyl cyanide and 0.1 mol% of catalyst **1** in dichloromethane at ambient temperature resulted in the formation of the corresponding cyanohydrin silyl ether **3a** as shown in Scheme 1. However, this reaction was very slow, 38% reaction occurring after 1 day at ambient temperature to produce compound **3a** with an enantiomeric excess of 70%. To improve the reaction rate, the amount of catalyst used in the reaction was increased and as shown in Table 1, it was possible to obtain complete reaction after 1 day by using 1 mol% of the catalyst. However, the enantiomeric excess of product **3a** was found to decrease as the amount of catalyst used was increased, an effect which is consistent with earlier results using aldehyde substrates.[5] The optimum amount of catalyst was found to be 0.5 mol%, although under these conditions the reaction is still much slower than for the corresponding reaction using aldehydes as substrates. Comparison of the sign of the specific rotation of the cyanohydrin derived from compound **3a** with that reported in the literature[3] showed that the major enantiomer had the (*S*)-configuration, which is consistent with the stereochemistry observed for the reaction using aldehydes as substrates.[5]



a) R = Me; Ar = Ph
b) R = Et; Ar = Ph
c) R = ^{i}Pr; Ar = Ph
d) R = ^{t}Bu; Ar = Ph
e) R = Me; Ar = 4-MeC_6H_4
f) R = Me; Ar = 2-$MeOC_6H_4$
g) R = Me; Ar = 3-$MeOC_6H_4$
h) R = Me; Ar = 4-$MeOC_6H_4$
i) R = Me; Ar = 4-$F_3CC_6H_4$

Scheme 1.

Other aromatic-aliphatic ketones (**2b,e–i**) were also found to be converted into the corresponding cyanohydrin silyl ethers (**3b,e–i**) (the optimum substrate to catalyst ratio again generally being 200:1 as shown in Table 1) provided that the alkyl group was not too large. No reaction occurred with compounds **2c** and **2d** and compound **2b** gave a significantly lower enantiomeric excess than ketone **2a**. Both of these effects are probably due to the increased size of the alkyl group in **2b–d**, which both hinders the approach of the cyanide moiety and decreases the difference in activation energy for reaction of cyanide with the two enantiotopic faces of the ketone. Attempts to use aliphatic ketones (2-butanone or 3,3-dimethyl-2-butanone) in this reaction were unsuccessful even with 1 mol% of the catalyst. It is notable that there is no significant variation of enantiomeric excess with the electronic properties of the ketone,

Table 1
Addition of trimethylsilyl cyanide to ketones (ArCOR)

	Ar	R	1 (mol%)	Time	yield (%)	ee$^+$ (%)
2a	Ph	Me	0.1	1 day	38	70
2a	Ph	Me	0.5	1 day	93	66
2a	Ph	Me	1.0	1 day	100	62
2b	Ph	Et	0.1	2 weeks	41	32
2b	Ph	Et	0.5	4 days	64	32
2b	Ph	Et	1.0	4 days	100	30
2c	Ph	^{i}Pr	0.5	no reaction		
2d	Ph	^{t}Bu	0.5	no reaction		
2e	4-MeC$_6$H$_4$	Me	0.1	4 days	100	52
2e	4-MeC$_6$H$_4$	Me	0.5	1 day	100	66
2f	2-MeOC$_6$H$_4$	Me	0.1	4 days	27	64
2f	2-MeOC$_6$H$_4$	Me	0.5	2 days	100	72
2g	3-MeOC$_6$H$_4$	Me	0.1	4 days	82	54
2g	3-MeOC$_6$H$_4$	Me	0.5	1 day	100	56
2h	4-MeOC$_6$H$_4$	Me	0.1	4 days	54	54
2h	4-MeOC$_6$H$_4$	Me	0.5	1 day	100	60
2i	4-F$_3$CC$_6$H$_4$	Me	0.1	4 days	78	60
2i	4-F$_3$CC$_6$H$_4$	Me	0.5	1 day	100	56

+ Determined by chiral gas chromatography of compounds **3**. Chiral GC was carried out on a DP-TFA-γ-CD, fused silica capillary column (32m x 0.2mm) using helium as the carrier gas (flow rate 1.6 ml / min). In all cases, the injector and detector temperatures were 230°C. An isothermal column temperature between 105 and 130°C was used.

thus ketones **2a,e,h,i** all gave cyanohydrin silyl ethers with enantiomeric excesses of 60–66%. This is in contrast with the results reported for the cyanohydrins derived from aromatic aldehydes using catalyst **1** and related catalysts[5] where electron-withdrawing groups on the aromatic ring were found to give very low enantiomeric excesses, and suggests that the low enantiomeric excesses observed in those cases were due to racemization during the conversion of the cyanohydrins to their Mosher esters.

In conclusion, complex **1** has been shown to be the first transition metal based catalyst for the asymmetric addition of trimethylsilyl cyanide to aromatic–aliphatic ketones at atmospheric pressure. The catalyst is compatible with both electron-rich and electron-deficient aromatic ketones, and the enantiomeric excess of the product is primarily determined by the difference in size between the aromatic and aliphatic substituents attached to the ketone carbonyl.

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