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The asymmetric addition of trimethylsilylcyanide to aldehydes catalysed by anionic chiral nucleophiles. Part 1

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Abstract

Trimethylsilylcyanide has been added to a number of aldehydes using a highly active chiral catalyst. This procedure gives the TMS ethers of the corresponding cyanohydrins in excellent chemical yields with enantiomeric excesses of up to 59%. The reaction is believed to occur through hypervalent silicon intermediates.

Keywords: asymmetric addition; trimethylsilylcyanide; aldehydes; chiral nucleophiles; hypervalent silicon.

In recent years reactions generating hypervalent silicon intermediates[1,2] have found widespread application in catalytic asymmetric synthesis.[3–8] Recent work from our laboratories focused on the asymmetric catalytic reduction of ketones using hypervalent silicon hydrides.[8] These were generated in situ by the addition of trialkoxysilanes to the mono lithium salt of (*R*)-(+)-1,1′-bi-2-naphthol[9] ((*R*)-(+)-BINOL). In order to investigate the possibility of the enantioselective transfer of other groups from hypervalent silicon intermediates, generated from readily available trialkylsilanes, we have studied the addition of trimethylsilylcyanide (TMSCN) to aldehydes catalysed by the mono lithium salt of *S*-(−)-BINOL.

Recently, the chiral Lewis acid mediated addition of TMSCN to aldehydes and ketones has received much attention. Catalysts based on a number of metal systems have been investigated,[10] though by far the most studied area is that of Ti(IV) complexes.[10–12] To date, we believe there have been no examples of chiral nucleophile catalysed additions of TMSCN to aldehydes or ketones.

For our strategy to work, we required the formation of a pentavalent silicon complex **1**, which could act as a Lewis acid and coordinate a carbonyl group as in **2**. Enantioselective transfer of cyanide could then occur giving **3**, followed by elimination to give the desired TMS cyanohydrin **4** and regeneration of the catalyst (Scheme 1). Two potential problems are highlighted in Scheme

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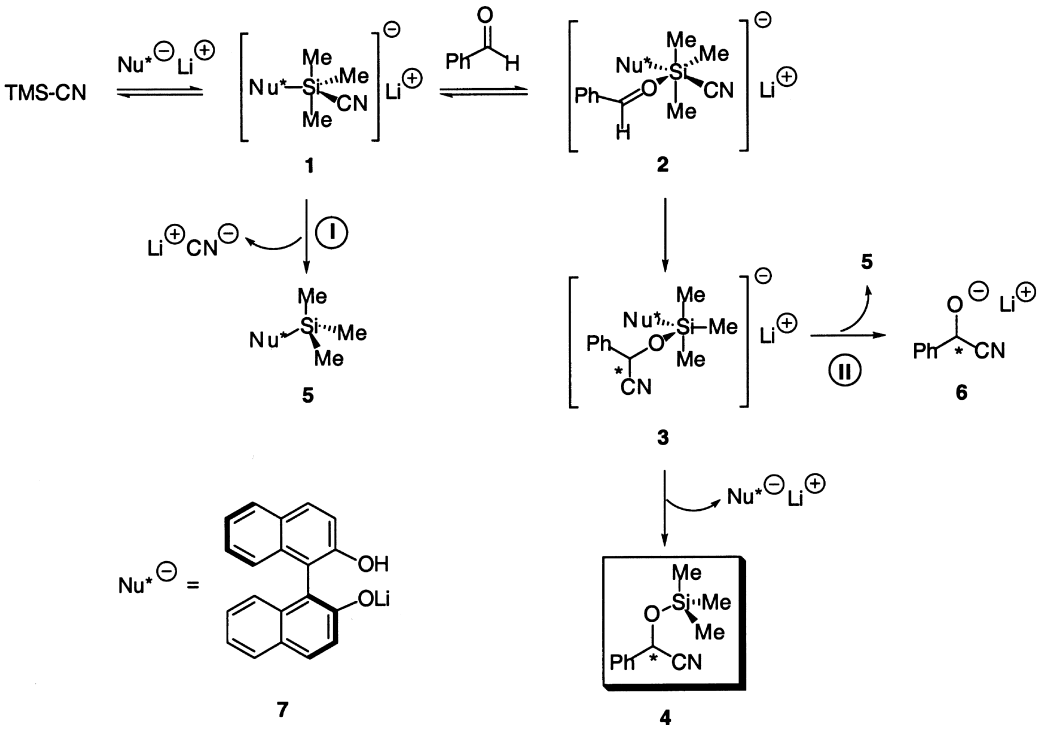
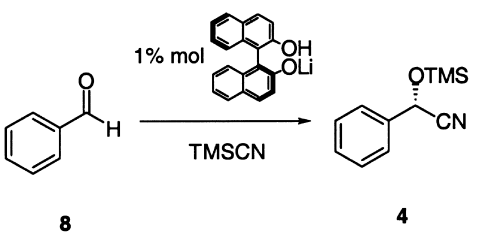
1. The first (pathway I) is the rapid ionisation of the TMSCN by the catalyst to give silylated compound **5** and a cyanide ion. The cyanide ion can act as a non-enantioselective carrier in the catalytic cycle.[13] Secondly, after the enantioselective transfer of cyanide the resulting complex **3** can collapse to eliminate the alkoxide formed **6** instead of the catalyst (pathway II). This gives silylated compound **5** and hence poisoning of the catalyst. The alkoxide **6** can also competitively act as a carrier in the catalytic cycle and despite being enantiomerically enriched it was not envisaged that it would lead to good enantioselectivity as alkoxides of cyanohydrins are known to be configurationally unstable (cf. the benzoin condensation). We hoped both these potential problems could be overcome by our choice of catalyst.



Scheme 1.

Thus, benzaldehyde was treated at room temperature with the mono lithium salt of (*S*)-(−)-BINOL **7** (Scheme 2), in a range of solvents, with varying catalyst loadings. As a general trend in all the solvents studied, (THF, ether, toluene, hexane and dichloromethane) starting from a catalyst loading of 30 mol% decreasing the amount of catalyst led to an increase in the rate of



Scheme 2.

reaction to an optimal value of 1 mol%. Under stoichiometric conditions only silylation of the catalyst was observed. Using 1 mol% of catalyst a rapid and exothermic reaction yielded, essentially quantitatively, racemic TMS cyanohydrin **4** on completion of the addition of TMSCN. The catalyst was recovered as its bis TMS adduct.

The enantioselectivity improved as the temperature of reaction was lowered. The choice of solvent was found to strongly influence the degree of enantioselectivity, the rate and the yield of the reaction. In all the solvent systems investigated the same major enantiomer was formed with *S* configuration. From these initial studies we were delighted to obtain the TMS ether of 2-hydroxy-2-phenylacetonitrile **4** in an isolated chemical yield of 96%, with 56% ee[14] (configuration *S*)[15] from a reaction carried out at −78°C in ether.[16–18] Varying results were obtained with other solvents: toluene (94% yield, 47% ee), dichloromethane (96% yield, 30% ee), THF (98% yield, 0% ee) and hexane (67% yield, 0% ee). From this point onwards ether was used as the solvent of choice. The mono lithio salt of BINOL was superior to the dilithio salt, as already noted in ketone reductions with trialkoxysilanes.[8] Though the dilithio salt was shown to be a good catalyst for the reaction, an identical chemical yield was obtained, the enantioselectivity was markedly reduced (38% ee). Changing the cation to Na, K or Mg gave a good catalyst, but cyanohydrin **4** was isolated as a racemic mixture.

With these results in hand, the addition of TMSCN to other aldehydes was studied using the optimal reaction conditions for benzaldehyde detailed above. A summary of results obtained is presented below (Table 1).

Table 1
Asymmetric TMSCN addition to aldehydes catalysed by the monolithium salt of (*S*)-BINOL

Entry	Starting aldehyde	% Isolated yield[a]	% ee[b]	Abs. config.[15]	Rxn time
1	Benzaldehyde	96	56	*S*	5 min
2	*p*-Tolualdehyde	95	59	*S*	15 min
3	*m*-Tolualdehyde	93	55	*S*	40 min
4	*o*-Tolualdehyde	99	5	*S*	40 min
5	*p*-Anisaldehyde	95	54	*S*	67.5 h
6	*m*-Anisaldehyde	89	52	*S*	30 min
7	*o*-Anisaldehyde	92	47	*S*	7.5 h
8	*p*-Nitrobenzaldehyde	Decomposition			
9	*p*-Chlorobenzaldehyde	38	43	*S*	2 h
10	*p*-CF_3 benzaldehyde	73	0	–	<5 min
11	2-Naphthaldehyde	93	6	*S*	24 h
12	Cinnamaldehyde	95	8	*S*	3.5 h
13	Hexanal	82	9	*S*	<5 min
14	Cyclohexylcarboxaldehyde	94	30	*S*	20 min
15	Pivalaldehyde	62	26	*S*	5 min

[a] TMS cyanohydrins were purified by chromatography on silica gel.
[b] Enantiomeric excess were determined either by HPLC analysis[14] of the *O*-TMS cyanohydrin (entries 1–4, 7, 9, 10 and 12), *O*-acetyl cyanohydrin (entries 1–3, 5, 6 and 11) or *O*-benzoyl cyanohydrin (entry 13) derivatives or by optical purity (entries 13–15).

To conclude, we have formed a number of enantiomerically enriched cyanohydrins, using a simple reaction catalysed by an easily prepared lithium phenolate. The reaction is believed to proceed through hypervalent silicon intermediates, work is on going to elucidate the mechanism.

Moreover, from these preliminary results, we were able to develop the concept of chiral lithio phenolates as catalysts to give a second generation system which has allowed a substantial increase in enantioselectivity (see accompanying paper).

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14. The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column.
15. Absolute configurations were determined by optical rotation.
16. *n*-Butyl lithium (1.5 M; 16 μL, 0.024 mmol) was added dropwise to a stirred solution of (*S*)-(−)-BINOL (6.9 mg, 0.024 mmol) in ether (2 mL) at room temperature under argon. The mixture was stirred for 5 min then benzaldehyde[17] (0.25 g, 0.24 mL, 2.4 mmol) was added and the reaction cooled to −78°C. Trimethylsilylcyanide **CAUTION** (0.23 g, 0.32 mL, 2.4 mmol) was added over 10 s and after stirring for 5 min the reaction was diluted with water (10 mL) and ethyl acetate (10 mL). The organic phase was separated, washed with water (10 mL), dried ($MgSO_4$) and evaporated to give the crude product which was chromatographed (90:10 pentane:ethyl acetate) to give **4**[18] as a colourless oil (0.46 g, 96%).
17. All aldehydes used were distilled and stored under argon. The reaction was found to be extremely sensitive to impurities e.g. the inclusion of 1 mol% of benzoic acid resulted in a racemic product.
18. All data obtained was in accordance with literature values.[10–12]