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1,2-Diphenylethylenediamine linked chiral Ti(IV) complex—a new entry to the highly enantioselective silylcyanation of aliphatic and aromatic aldehydes†

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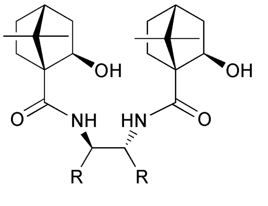
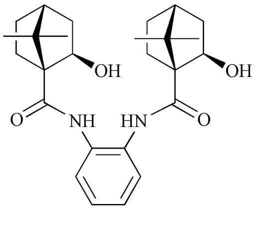
Highly enantioselective silylcyanation of aliphatic and aromatic aldehydes was achieved by using a 1,2-diphenylethylenediamine linked chiral Ti(IV) complex as the catalyst.

Enantiomerically pure cyanohydrins are versatile intermediates[1,2] useful in the synthesis of a variety of natural and non-natural biologically active molecules owing to their potential for selective transformations given by the presence of a single asymmetric center bearing two reactive functionalities. Several efficient enzymatic[2–8] and chemical methods[2,9] have been developed for the preparation of chiral cyanohydrins and enantioselective addition of trimethylsilyl cyanide to aldehydes catalysed by chiral metal complexes is amongst the most successful approaches. Despite this, need exists for new chiral catalysts as most of the catalysts used for this purpose are either unstable or difficult to prepare, and sometimes cannot be easily recovered. Our earlier efforts in this area have led to the development of a chiral Ti(IV) catalyst with dihydroxy-*trans*-1,2-diamide **1** as the constituent which has promoted the enantioselective addition of trimethylsilyl cyanide to aromatic aldehydes in 94–97% ee and to aliphatic aldehydes in 87–97% ee.[10] We have now addressed enantioselective silylcyanation using a new chiral catalyst, Ti(O^{i}Pr)$_4$–diamide **2a**, that efficiently promotes the addition of trimethylsilyl cyanide to both aromatic and aliphatic aldehydes with excellent enantioselectivity.

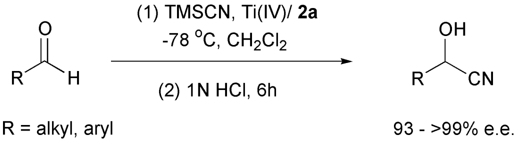


1 R, R = -(CH$_2$)$_4$-
2a R = Ph

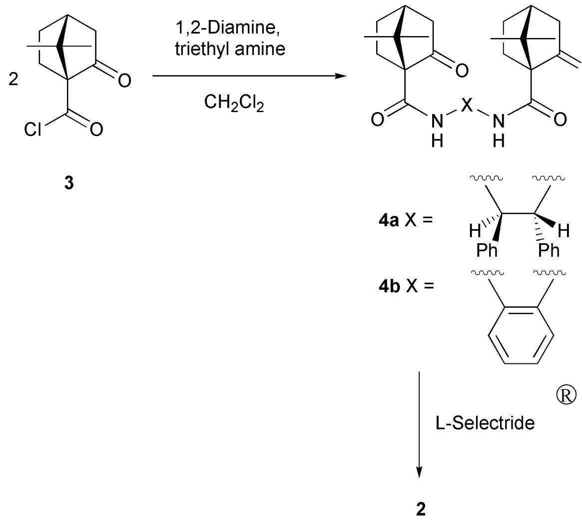


2b

It is envisioned that, replacement of the cyclohexane ring with two vicinal phenyl groups in the chiral diamide moiety of **1** would result in a more gainful catalyst which can provide greater facial selectivity in the silylcyanation of the aldehydes. A relatively bulky phenyl group would increase the energy difference between the two diastereomeric transition structure orientations thereby enhancing the enantioselectivity. Chiral compound **2a** with the desired structural and stereochemical features was prepared starting from (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine. This diamine was submitted to condensation with (1*S*)-(+)-ketopinic acid chloride **3**[11] in dichloromethane in the presence of triethylamine to furnish diketoamide **4a** (Scheme 1). Subsequent reduction of **4a** using L-selectride® in THF at −78 °C for 1 h and then at room temperature for 2 h gave **2a** with the hydroxy group in the *exo* position.[12] In conjunction with Ti(O^{i}Pr)$_4$, chiral diamide **2a** was shown to effect the enantioselective addition of trimethylsilyl cyanide to aldehydes **5** with a high degree of selectivity (Table 1).



Optimum results were obtained when the reaction was carried out at −78 °C in dichloromethane using the complex prepared from 16.5 mol% of **2a** and 15 mol% of Ti(O^{i}Pr)$_4$ in the presence of 4 Å molecular sieves.[9a,13] Under these conditions, the desired cyanohydrin was isolated in high yield and the enantioselective induction achieved in both aromatic (>93% *S*) and aliphatic aldehydes (>97% *S*) was quite high after the hydrolysis (1 N



Scheme 1

Table 1 Enantioselective trimethylsilylcyanation of aldehydes using catalyst **2a**–Ti(O^{i}Pr)$_4$ in combination with TMSCN[a]

Run	Aldehyde	Yield (%)	Ee (%)
1	Benzaldehyde **5a**	87	93
2	Cyclohexane carbaldehyde **5b**	90	>99
3	Valeraldehyde **5c**	92	97
4	2-Methylbenzaldehyde **5d**	80[b]	94
5	3-Phenoxybenzaldehyde **5e**	78[b]	95
6	4-Methoxybenzaldehyde **5f**	72[b]	99
7	2-Naphthaldehyde **5g**	78[b]	99
8	(*E*)-Cinnamaldehyde **5h**	74[b]	97
9	3-Phenylpropionaldehyde **5i**	73[b]	97

[a] Determined by HPLC with chiracel OD column by converting into TBDMS ether for run 1 and as acetyl esters for runs 2–9. Absolute configuration was determined as *S* by the comparison of rotation with literature value[5]. [b] Percent conversions.

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b1/b107867d/

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HCl, rt 6 h) of the initial addition product. At the same time, the chiral diamide **2a** was recovered in high yield. This compares favorably with other earlier reported organometallic processes used for such purpose. There is a pronounced enhancement of enantioselectivity in the reactions of aliphatic aldehydes when compared to our previously reported method.[10]

To ascertain the effect of the chirality of the diamide moiety of **2a** on the extent of enantioselectivity, compound **2b** lacking chirality in the diamide function was prepared from 1,2-phenylenediamine following the procedure used for **2a** and employed as a constituent of catalyst in the silylcyanation of benzaldehyde. As expected, the enantioselectivity was significantly low with a maximum of 61% ee under optimum reaction conditions when the reaction was carried out at −78 °C in dichloromethane using the complex prepared from 16.5 mol% of **2b** and 15 mol% of $Ti(O^iPr)_4$ in the presence of 4 Å molecular sieves. Apparently chirality in the diamide moiety is facilitating the higher enantioselectivity.

In conclusion, a new and efficient catalyst for enantioselective silylcyanation of aromatic and aliphatic aldehydes with excellent selectivity has been developed. The high degree of enantioselectivity coupled with the high stability and recovery rate of chiral component **2a** of the catalyst constitutes the major improvement on existing methods.

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