Pergamon

Tetrahedron Letters 41 (2000) 7457–7460

TETRAHEDRON LETTERS

The asymmetric addition of trimethylsilylcyanide to aldehydes catalysed by anionic chiral nucleophiles. Part 2

Ian P. Holmes and Henri B. Kagan*

Laboratoire de Synthèse Asymétrique, associé au CNRS, ICMO, Université Paris-Sud, 91405 Orsay, France

Received 21 July 2000; accepted 24 July 2000

Abstract

Studies have been carried out on the addition of trimethylsilylcyanide to aldehydes using highly active chiral lithium phenolate catalysts. The screening of a number of chiral phenolates has resulted in a system which gives the TMS ethers of cyanohydrins in excellent chemical yields with enantiomeric excesses of up to 97%.

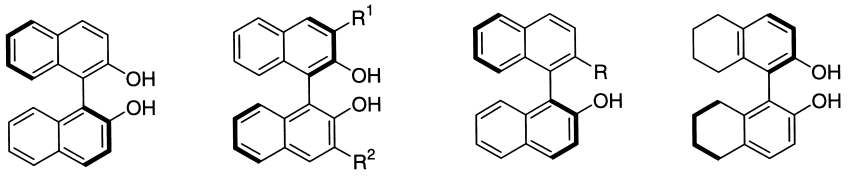
Keywords: asymmetric addition; trimethylsilylcyanide; aldehydes; chiral nucleophiles; hypervalent silicon.

In our previous communication we detailed studies on the addition of trimethylsilylcyanide (TMSCN) to aldehydes catalysed by the monolithium salt of (*S*)-(−)-1,1′-bi-2-naphthol **1** (*S*)-(−)-BINOL).[1] These reactions are believed to proceed through hypervalent silicon intermediates.[2,3] In order to investigate the possibility of obtaining higher enantioselectivities for the transfer of the cyanide group, the addition of TMSCN to aldehydes catalysed by lithium salts of other chiral phenols and related compounds has been studied.

Initially several analogues of BINOL **1** were screened (Fig. 1).[4–10] These compounds were tested for activity using benzaldehyde as a model aldehyde under the conditions that were found to be optimal for BINOL (Scheme 1).[1] Results were disappointing. Whilst all compounds showed excellent catalytic activity, giving high yields of the desired TMS ether of 2-hydroxy-2-phenylacetonitrile **10**, the enantioselectivity never exceeded 5%.

* Corresponding author. Fax: 33 1 69 15 46 80; e-mail: kagan@icmo.u-psud.fr

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01276-4



1 [4]

2 $R^1=R^2=Me$ [5]

3 $R^1=R^2=C(Ph)_2OH$ [6]

4 $R=OSiMe_3$ [7]

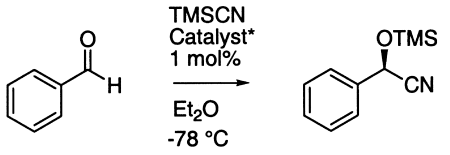
5 R=OMe [8]

6 R=OBn [8]

7 R=H [9]

8 [10]

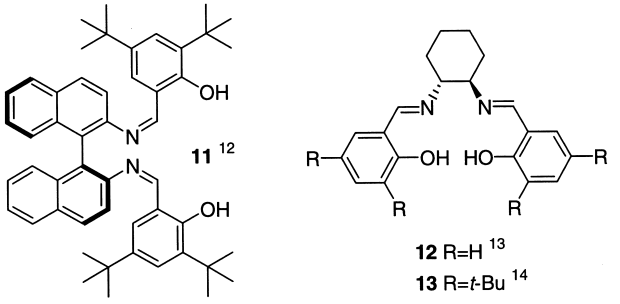
Figure 1.



9 **10**

Scheme 1.

Thus, a range of chiral phenols derived from Schiff's bases were investigated (Fig. 2).[11–14] Testing these compounds using the same conditions described above we were pleased to obtain TMS ether **10** in an isolated chemical yield of 94%, with 70% ee[15] (configuration *R*)[16] using the monolithium salt of (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine **13** (*R*,*R*)-(−)-SALEN). The closely related compounds **11** and **12** gave poor enantioselectivity. With these results in hand optimal conditions for the reaction catalysed by **13** were investigated.



11 [12]

12 R=H [13]

13 R=*t*-Bu [14]

Figure 2.

Firstly, the effect of catalyst loading was studied at room temperature. Thus, benzaldehyde **9** was treated with the mono lithium salt of **13** in a range of solvents, with varying catalyst loadings. As a general trend, as for BINOL, in all the solvents studied, (THF, ether, toluene and dichloromethane) starting from a catalyst loading of 30 mol% decreasing the amount of catalyst led to an increase in the rate of reaction to an optimal value of 1 mol%. Using 1 mol% of catalyst a rapid and exothermic reaction yielded, essentially quantitatively, the racemic TMS cyanohydrin **10** on completion of the addition of TMSCN. The (*R*,*R*)-(−)-SALEN was recovered unchanged from the reaction mixture.

It was observed that as the temperature of reaction was lowered the enantioselectivity improved. The choice of solvent was found to strongly influence the degree of enantioselectivity, the rate and the yield of the reaction. Poor results were obtained with all solvents other than ether that were investigated: toluene (96% yield, 0% ee), dichloromethane (95% yield, 0% ee) and THF (96% yield, 0% ee). The mono lithium salt of (*R*,*R*)-SALEN was found to be superior to the dilithium salt, as already noted for BINOL catalysed TMSCN additions.[1] Again the dilithium salt was shown to be a good catalyst for the reaction, a nearly identical chemical yield was obtained, though the enantioselectivity was severely reduced (18% ee). Changing the cation to Na, K or Mg gave a good catalyst, but cyanohydrin **10** was isolated as a racemic mixture.

Finally, the effects of concentration were investigated. Here, a marked difference was found between the SALEN and BINOL systems. The SALEN system proved to be quite tolerant of dilution, whereas the BINOL system rapidly lost enantioselectivity. Optimum conditions found were concentrations of 0.28 M for SALEN compared with 1.18 M for BINOL. Under these optimised conditions **10** was obtained in 98% yield with an ee of 86%.

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 the results obtained is presented below (Table 1).

Table 1
Asymmetric TMSCN addition to aldehydes catalysed by the monolithium salt of (*R*,*R*)-SALEN **13**

Entry	Starting aldehyde[17]	% Isolated yield[a]	% ee[b]	Abs. config.[16]	Rxn time
1	Benzaldehyde	98	86	*R*	15 min
2	*p*-Tolualdehyde	96	93	*R*	45 min
3	*m*-Tolualdehyde	88	97	*R*	20 min
4	*o*-Tolualdehyde	96	45	*R*	40 min
5	*p*-Anisaldehyde	93	2	*R*	11 days
6	*m*-Anisaldehyde	96	77	*R*	45 min
7	*o*-Anisaldehyde	86	6	*R*	9 days
8	*o*-Anisaldehyde	96	40	*R*	[c]
9	*p*-Chlorobenzaldehyde	85	64	*R*	4 h
10	*p*-CF_3 benzaldehyde	88	0	–	2 h 20 min
11	2-Naphthaldehyde	64	6	*S*	2 h
12	4-Ethylbenzaldehyde	99	61	*R*	2 h
13	4-Isopropylbenzaldehyde	99	82	*R*	40 min
14	4-*t*-Butylbenzaldehyde	99	53	*R*	1 h 20 min

[a] TMS cyanohydrins were purified by column chromatography on silica gel.[18]

[b] Enantiomeric excess were determined by HPLC analysis[15] of either the *O*-TMS cyanohydrin (entries 1–5 and 8–10) or *O*-acetyl cyanohydrin derivatives (entries 1–7 and 11–14).

[c] The reaction medium was stirred at −78°C for 3 h, then allowed to warm slowly to room temperature, concentration of aldehyde 0.39 M.

It should be noted that the ee values obtained are strongly dependent on the aldehyde used, i.e. the nature of the substrate strongly influences the reaction. Furthermore, studies have revealed that the reaction mechanism is complex and probably differs from that occurring for BINOL.

To conclude, we have formed a number of highly enantiomerically enriched cyanohydrins in up to 97% ee. The enantioselectivity and rate of reactions are very substrate specific. Investigations are currently underway to try to discover the nature of the reaction mechanism and to check the applicability of such catalyst systems in the asymmetric transfer of other groups to aldehydes and ketones.

Acknowledgements

We acknowledge the EU INCO-COPERNICUS scheme (Contract Number IC15 CT96-722) for financial support and for a postdoctoral fellowship to one of us (I.P.H.). We also thank the CNRS, Université Paris-Sud and the Institut Universitaire de France for additional funding. We also wish to acknowledge Professor Y. Belokon and F. Lagasse for useful discussions.

References

1. Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett*. **2000**, *41*, 7453–7456.
2. Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev*. **1993**, *93*, 1371–1448.
3. Holmes, R. R. *Chem. Rev*. **1996**, *96*, 927–950.
4. Cai, D.; Hughes, D. L.; Verhoeven, T. L.; Reider, P. J. *Tetrahedron Lett*. **1995**, *36*, 7991–7994.
5. Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett*. **1992**, *33*, 2253–2256.
6. Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc*. **1994**, *116*, 1561–1562.
7. Formed by the reaction of (*S*)-(−)-BINOL with TMSCN in ether at room temperature.
8. Takahashi, M.; Ogasawara, K. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3125–3130.
9. Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293–4302.
10. Sugimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 649–655.
11. Hosoya, N.; Hatayama, A.; Irie, R.; Sasaki, H.; Katsuki, T. *Tetrahedron* **1994**, *50*, 4311–4322.
12. Bernardo, K.; Leppard, S.; Robert, A.; Commengues, G.; Dahan, F.; Meunier, B. *Inorg. Chem*. **1996**, *35*, 387–396.
13. Casella, L.; Gullotti, M. *J. Am. Chem. Soc*. **1983**, *105*, 803–809.
14. Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem*. **1994**, *59*, 1939–1942.
15. The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column.
16. Absolute configurations were determined by optical rotation, see: (a) Yang, W.; Fang, J. M. *J. Org. Chem*. **1998**, *63*, 1356–1359; (b) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tassinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc*. **1999**, *121*, 3968–3973; (c) Hwang, C.; Hwang, D.; Uang, B. *J. Org. Chem*. **1998**, *63*, 6762–6763 and references cited therein.
17. All aldehydes used were distilled and stored under argon.
18. All data obtained was in accordance with literature values.[16a–c]