Pergamon

Tetrahedron Letters 41 (2000) 2405–2409

TETRAHEDRON
LETTERS

Design of a new bifunctional asymmetric catalyst from carbohydrates: application to catalytic asymmetric cyanosilylation of aldehydes and acetophenone

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Received 22 December 1999; revised 17 January 2000; accepted 21 January 2000

Abstract

A new active Lewis acid–Lewis base bifunctional asymmetric catalyst **7** was developed using carbohydrate as a scaffold and this catalyst was applied to the asymmetric cyanosilylation of aldehydes and acetophenone. The β-Ph group at the 6-position of **7** was found to be important for a high asymmetric induction (up to 80% ee) by bringing the Al and the phosphine oxide at optimum positions for a dual activation of carbonyl compounds and TMSCN.

Keywords: bifunctional asymmetric catalyst; Lewis acid; Lewis base; cyanosilylation; conformation.

We have recently succeeded in developing the new Lewis acid–Lewis base bifunctional catalyst **1**, and we could demonstrate that **1** is the most general catalyst for the asymmetric cyanosilylation of aldehydes.[1] From experimental results, such as kinetic profiles and the absolute configuration of the products, it was deduced that in the transition state, Al and the oxygen atom of the phosphine oxide work cooperatively as a Lewis acid and as a Lewis base to activate the aldehyde and TMSCN, respectively. In the course of our studies to develop a general and more reactive asymmetric catalyst based on the concept of bifunctional catalysis,[2] we anticipated that carbohydrates would be an ideal matrix providing multifunctionalities at well-defined positions. Although carbohydrates are among the most easily available chiral compounds in nature, they have barely been used as chiral scaffolds for Lewis acid catalysts.[3,4] Within this report, the design and synthesis of a new Lewis acid–Lewis base bifunctional catalyst derived from carbohydrates and its application to the cyanosilylation of aldehydes,[5] as well as a preliminary result with acetophenone,[6] are described.

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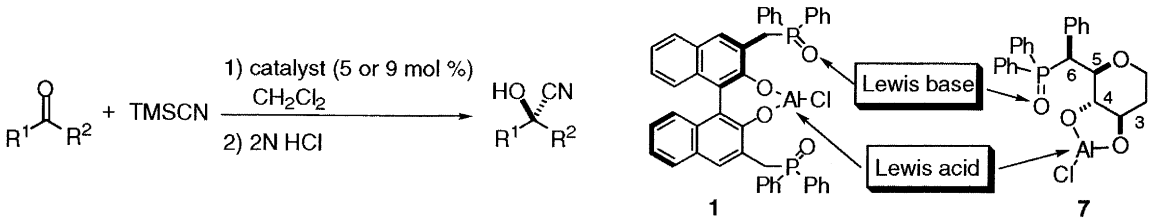
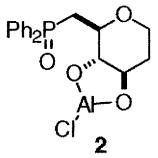
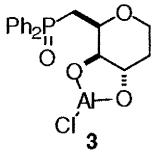
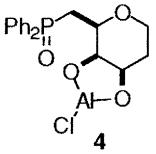
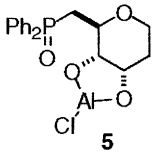
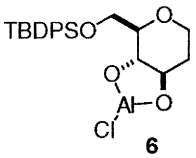
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00174-X



Our design of the asymmetric catalyst for the cyanosilylation of carbonyl compounds is as follows. The Lewis acid should be attached to the 3- and 4-OH groups forming a five-membered metal alkoxide, while the Lewis base should be connected to C-6 (see **7**). The OH groups at the 1- and 2-positions should be deleted for specifying the combination of the Lewis acid and the Lewis base moieties. From molecular modeling, it seems that the transition state via a dual activation of the carbonyl compounds and the TMSCN by the Lewis acid and the Lewis base moieties of the catalyst is readily feasible, when the Lewis base moiety is moving to an optimum position. This basic design prompted us to synthesize four possible catalysts **2**–**5** from the corresponding glycals.[7]

We first evaluated these catalysts by the reaction of TMSCN with PhCHO (**8a**). As shown in Table 1, **2** was found to be the most reactive catalyst, giving the highest ee among **2**–**5**. Although the stereochemistry of the Lewis acid moiety (3*R*,4*S* for **2** and 3*S*,4*R* for **3**) seems to have a predominant effect on the enantioselectivity, as can be seen from the reversed absolute configuration of the product by **2** (giving *S*-**9a**) and **3** (giving *R*-**9a**), the phosphine oxide appears to have some contribution.[8] This was confirmed by a low selectivity and lower activity of the control catalyst **6**, containing no Lewis base moiety. The absolute configuration of the product can be explained from a working model of a dual activation by the Lewis acid and the Lewis base. These results suggest that the designed catalyst promotes the reaction in the bifunctional manner.

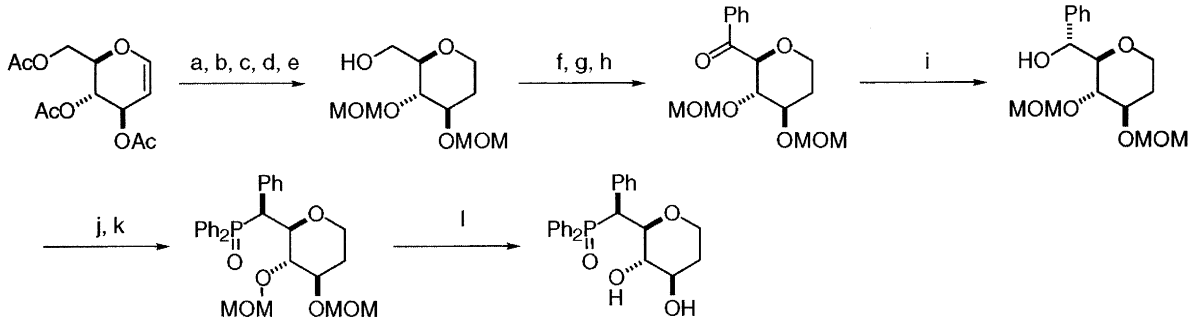
Table 1
Initial results of catalytic asymmetric cyanosilylation of PhCHO **8a** to give **9a**[a]

 **2**	 **3**	 **4**	 **5**	 **6**
99% (21 h)	100% (69 h)	96% (38 h)	84% (23 h)	87% (96 h)
46% ee (*S*)	21% ee (*R*)	45% ee (*S*)	20% ee (*S*)	5% ee (*S*)

[a] Reactions were performed using 9 mol % of the catalyst at –40 °C in CH_2Cl_2.

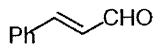
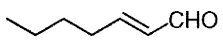
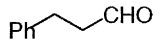
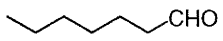
In order to improve the enantioselectivity by enhancing such a dual activation pathway, we planned to introduce a conformationally constraining group at the 6-position, to which the phosphine oxide is connected. If the substituent restricts the conformation, fixing the Lewis base moiety at an optimum position for the cooperation with the Lewis acid, the transition state of the dual activation pathway should be more stabilized, thus being more favored. Synthesizing ligands containing several kinds of substituents at the 6-position (Scheme 1)[9] we found that catalyst **7**, containing a β-phenyl group,[10] afforded improved enantioselectivity compared to the original catalyst, **2**. Thus, **7** afforded **9a** in 96% yield with 80% ee (66% ee using **2** under the same conditions) (Table 2, entry 1).[11] These results clearly show that the orientation of the Lewis base moiety constrained by the substituent at the 6-position is very important for

a high asymmetric induction. The results of the catalytic asymmetric cyanosilylation of aldehydes with catalyst **7** are shown in Table 2.[12]



Scheme 1. Reagents and conditions: (a) H_2, Pd/C, MeOH; (b) NaOMe, MeOH, 100% (two steps); (c) TBDMSCl (1.6 mol equiv.), Et_3N (1.8 mol equiv.), DMF, 70%; (d) MOMCl (4.5 mol equiv.), $^iPr_2NEt$ (5 mol equiv.), CH_2Cl_2, 75%; (e) TBAF (2 mol equiv.), THF, 88%; (f) PDC (5 mol equiv.), DMF–H_2O, 52%; (g) MeNHOMe·HCl (2 mol equiv.), EDCI (3 mol equiv.), Et_3N (2.2 mol equiv.), DMAP (0.4 mol equiv.), CH_2Cl_2, 70%; (h) PhMgBr (1.2 mol equiv.), THF, 82%; (i) $NaBH_4$ (2 mol equiv.), MeOH, 87% (+9% β-Ph); (j) MsCl (5 mol equiv.), py (10 mol equiv.), CH_2Cl_2; (k) Ph_2PK (2 mol equiv.), THF; H_2O_2, 79% (two steps); (l) Me_2AlCl (10 mol equiv.), CH_2Cl_2, 54%

Table 2
Catalytic asymmetric cyanosilylation of aldehydes by **7**[a]

entry	aldehydes		product	**7** (mol %)	h	yield (%)	ee (%)	conf.
1	PhCHO	**8a**	**9a**	9	50	96	80	*S*
2		**8b**	**9c**	5	76	82	76	*S*
3		**8c**	**9c**	5	63	97	76	–[b]
4		**8d**	**9d**	5	50	96	70	*S*
5		**8e**	**9e**	5	38	98	80	*S*

[a] Reactions were performed at –60 °C in CH_2Cl_2. See ref. 12 for the representative procedure. [b] Not determined.

The origin of the C-6 substituent effect was further investigated by molecular modeling studies (Fig. 1). It was initially anticipated that the conformer **A** would be ideal for the cooperation of the Lewis acid and the Lewis base moieties. From a conformation search by randomly generating initial structures (Monte Carlo method), the conformer **A** was found to be the most stable in both cases of R=H and Ph.[13] However, it was found that the substituent R changes the contribution of the second most stable conformer **B** by destabilizing this conformer. Thus, in the case of the catalyst **2** (R=H), the energy difference between the conformer **A** and **B** is only 0.34 kcal/mol. On the other hand, in the case of **7** (R=Ph), this value is 4.2 kcal/mol. Therefore, the population of the conformer **A** is more predominant in the case of **7** than in the case of **2**.[14,15] The absolute configuration of the products may be explained by the working model of the dual activation transition state depicted in Fig. 1.

Although the ee values are not better compared to the previous catalyst **1**,[1] several advantages are noteworthy: (1) The additive phosphine oxides such as $Bu_3P(O)$ and $MeP(O)Ph_2$ are not necessary any more for high asymmetric induction. (2) Slow addition of TMSCN is not necessary. (3) The catalytic

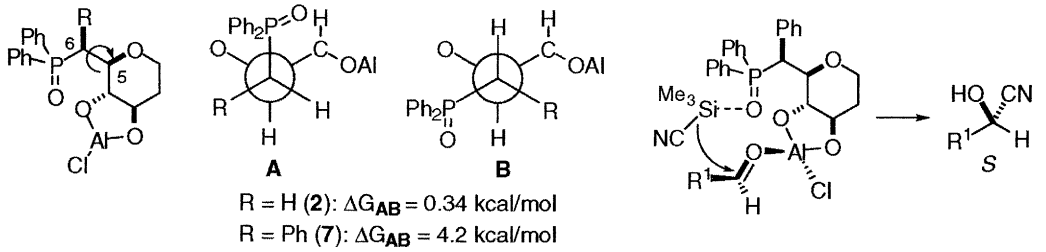


Fig. 1. Newman projection in terms of C5–C6 bond of catalysts **2** and **7** and working model of the transition state with **7**

activity of **2** and **7** is significantly higher than that of **1**, which enables lower catalyst loadings at lower reaction temperatures.

Taking advantage of the higher reactivity of **2** and **7**, we tried the catalytic asymmetric cyanosilylation of a ketone.[16] Thus, in the presence of 20 mol% of **2**, the cyanosilylation of acetophenone took place to give the product in 96% yield with 20% ee (*R*) at −10°C for 64 h.[17]

In summary, we have developed new Lewis acid–Lewis base asymmetric bifunctional catalysts using carbohydrates as scaffolds. We have shown that by restricting the conformation of the Lewis acid and the Lewis base moieties at optimum positions relative to each other for the dual activation transition state, the enantioselectivity of this type of catalyst could be optimized. Further studies for improving the enantioselectivity, especially for ketones are currently under investigation.

Acknowledgements

This work was supported by CREST and RFTF.

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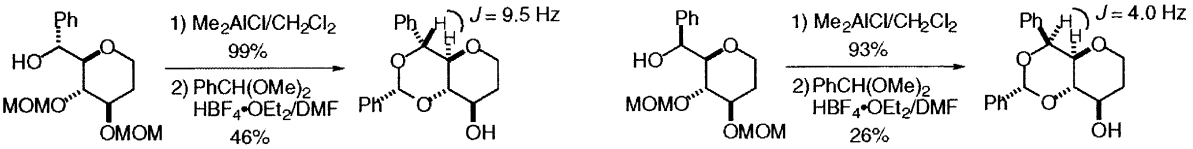
7. ^{1}H (500 MHz) and ^{31}P (202.35 MHz) NMR of the ligands of the catalysts **2**–**5**: **2** ($CDCl_3$): δ 1.65 (dddd, *J*=4.9, 12.5, 12.5, 12.5 Hz, 1H), 1.87 (m, 1H), 2.78 (m, 2H), 3.28 (m, 2H), 3.39 (m, 1H), 3.55 (ddd, *J*=5.2, 8.5, 11.6 Hz, 1H), 3.78 (m, 1H), 7.5 (m, 6H), 7.73 (m, 4H); ^{31}P; δ 37.90; **3** (CD_3OD): δ 1.36 (br dd, *J*=1.4, 14 Hz, 1H), 2.05 (dddd, *J*=3.1, 5.5, 12.8, 12.8

Hz, 1H), 2.55 (ddd, *J*=4.6, 14.3, 15.5 Hz, 1H), 2.84 (ddd, *J*=8.5, 8.5, 15.6 Hz, 1H), 3.37 (br d, *J*=3.4 Hz, 1H), 3.49 (m, 1H), 3.59 (m, 1H), 3.86 (br d, *J*=3.1 Hz, 1H), 4.14 (m, 1H), 7.58 (m, 6H), 7.78 (m, 4H); ^{31}P; δ 38.93; **4** ($CDCl_3$): δ 1.65 (m, 1H), 1.84 (dddd, *J*=4.9, 12.6, 12.6, 12.6 Hz, 1H), 2.71 (ddd, *J*=5.8, 7.9, 15.3 Hz, 1H), 2.85 (ddd, *J*=7.9, 15.3, 15.3 Hz, 1H), 3.29 (ddd, *J*=2.2, 12.2, 12.2, 1H), 3.62 (m, 2H), 3.86 (m, 2H), 7.5 (m, 6H), 7.74 (m, 4H); ^{31}P; δ 34.19; **5** ($CDCl_3$): δ 1.83 (m, 2H), 2.63 (ddd, *J*=9.5, 15.0, 15.0 Hz, 1H), 2.75 (ddd, *J*=3.1, 9.5, 15.0 Hz, 1H), 3.46 (dd, *J*=3.1, 9.2 Hz, 1H), 3.58 (m, 1H), 3.67 (ddd, *J*=3.8, 11.6, 11.6 Hz, 1H), 3.75 (ddd, *J*=3.1, 9.2, 17.0 Hz, 1H), 4.12 (dd, *J*=3.1, 5.8 Hz, 1H), 7.5 (m, 6H), 7.72 (m, 4H); ^{31}P; δ 34.23.

8. The importance of a phosphine oxide as the Lewis base was also confirmed from the fact that the catalysts containing a phosphine or an amine as the Lewis base gave rather low selectivities.
9. Spectral data of ligand **7**: ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.38 (dddd, *J*=4.9, 12.8, 12.8, 12.8 Hz, 1H), 1.73 (m, 1H), 2.93 (s, 1H), 3.29 (m, 2H), 3.51 (m, 2H), 3.81 (dd, *J*=4.0, 11.6 Hz, 1H), 4.07 (dd, *J*=2.5, 12.5 Hz), 6.67 (s, 1H), 7.25 (m, 6H), 7.53 (m, 7H), 7.94 (m, 2H): ^{31}P NMR (202.35 MHz, $CDCl_3$); δ 38.29: ^{13}C NMR (125.65 MHz, $CDCl_3$); δ 31.68, 51.53 (d, *J*=66 Hz), 65.86, 71.62, 73.51, 78.37 (d, *J*=6 Hz), 127.56, 128.26, 128.30, 128.39, 129.02, 129.11, 129.88, 130.65, 130.72, 130.97, 131.04, 131.07, 131.14, 131.46, 131.52, 131.70 (d), 131.82 (d), 132.23 (d): $[\alpha]_D^{18}$ +14.1 (*c*=0.55, $CHCl_3$).
10. The stereochemistry of the substituent was determined from the coupling constant of ^{1}H NMR as shown below.



11. Effects of other substituents: β-Me (58% ee (*S*)), α-Me (23% ee (*S*)), β-Bu (56% ee (*S*)), α-Bu (47% ee (*S*)), β-^{i}Pr (37% ee (*S*)) α-^{i}Pr (32% ee (*R*)).
12. Representative procedures: To a solution of the ligand (0.0245 mmol) in CH_2Cl_2 (0.4 mL) was added Et_2AlCl (0.0238 mmol as a 0.95 M hexane solution) at ambient temperature under Ar atmosphere. After stirring for 2 h, the reaction mixture was cooled to −78°C and the aldehyde (0.48 mmol) was added. After 30 min, TMSCN (0.58 mmol) was added in one portion and the mixture was stirred at −60°C until the starting aldehyde disappeared on TLC (SiO_2, AcOEt/hexane 1/4). Acid hydrolysis and usual workup followed by purification by silica gel column chromatography gave the corresponding cyanohydrin.
13. These calculations were done with the universal force field of Cerius 2_3.8.
14. From the Curtin–Hammet principle, the distribution of the ground state species may not be reflected on the actual reaction pathway. However, the difference between transition state energies by the dual activation pathway and the mono activation pathway by the Lewis acid seems to be not large enough to overcome the ground state distribution, since the activation of TMSCN by the phosphine oxide is not strong. For the activation ability of the phosphine oxide toward TMSCN, see Ref. 1.
15. The same consideration may explain the lower enantioselectivities by α-substituted catalysts (see Ref. 11). In these cases, the optimum conformer **A** is destabilized by the α-substituent.
16. However, the cyanosilylation of acetophenone with catalyst **1** did not proceed.
17. The ee of the TMS protected cyanohydrin was determined by chiral HPLC column (Chiralcel OJ, ^{i}PrOH/hexane 2/98, flow rate 0.5 mL/min, retention time 15 min for the *R* isomer and 16 min for the *S* isomer). The absolute configuration of the product was determined by the optical rotation of the cyanohydrin: Kilijunen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1997**, *8*, 1551–1557. Compound **7** gave the almost the same ee.