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Catalytic enantioselective cyanosilylation of ketones: improvement of enantioselectivity and catalyst turn-over by ligand tuning

Yoshitaka Hamashima, Motomu Kanai and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract—Sterical and electronical tuning of the bifunctional catalyst **1** afforded the improved catalyst **2**, which promoted the cyanosilylation of ketones with higher enantioselectivity as well as with improved catalyst turn-over with a factor of up to 10. Thus, chiral quaternary α-hydroxynitriles were obtained with excellent ee (up to 94% ee) using 1 mol% of **2** in the case of aryl ketones and 2.5 mol% of **2** in the case of aliphatic ketones.

We have recently disclosed the first general catalytic enantioselective cyanosilylation of ketones promoted by the novel bifunctional catalyst **1**.[1,2] Chiral quaternary α-hydroxynitriles were obtained with excellent selectivities from a wide variety of ketones. From mechanistic studies, we proposed the working model for the transition state as shown in Fig. 1: the Lewis acid (Ti) and the Lewis base (phosphine oxide) activate the ketone and TMSCN, respectively, at defined positions.[3] However, there still remained 'difficult substrates' that gave only good to moderate ee. For example, 2-heptanone **8a** and 1-indanone **8b** gave the corresponding products with 76 and 69% ee, respectively. Relatively high catalyst loading (10 mol%) was also necessary to promote the reaction efficiently. During the course of our pursuit for truly practical asymmetric catalysts, we planned to improve these points by tuning the ligand structure. Herein, we report the new catalyst **2** containing a benzoyl substituent on the catechol moiety, which is a greatly improved catalyst in terms of enantioselectivity, substrate scope and catalyst turn-over.

For the highly enantioselective dual activation pathway to take place, it is essential that the ketone coordinates to Ti at the position *syn* to the phosphine oxide (site A, Fig. 1). The catechol moiety at C-3 should differentiate the coordination sites A and B, sterically shielding site B. We expected that introducing a bulky group to this catechol moiety should hinder site B more effectively, making the desired coordination of the ketone at site A more favored. Furthermore, if the substituent X is an electron-withdrawing group, the Ti–phenoxide bond should become stronger, thus giving rise to the more stable catalyst complex, which should be advantageous

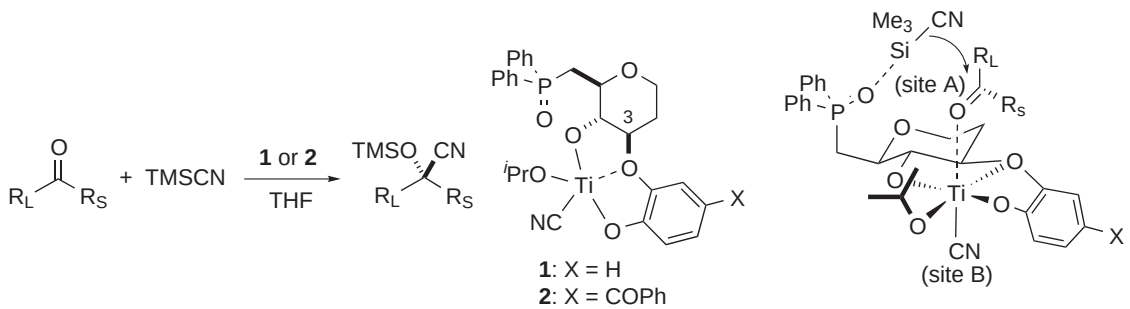

Figure 1. Working transition state model.

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

* Corresponding author.

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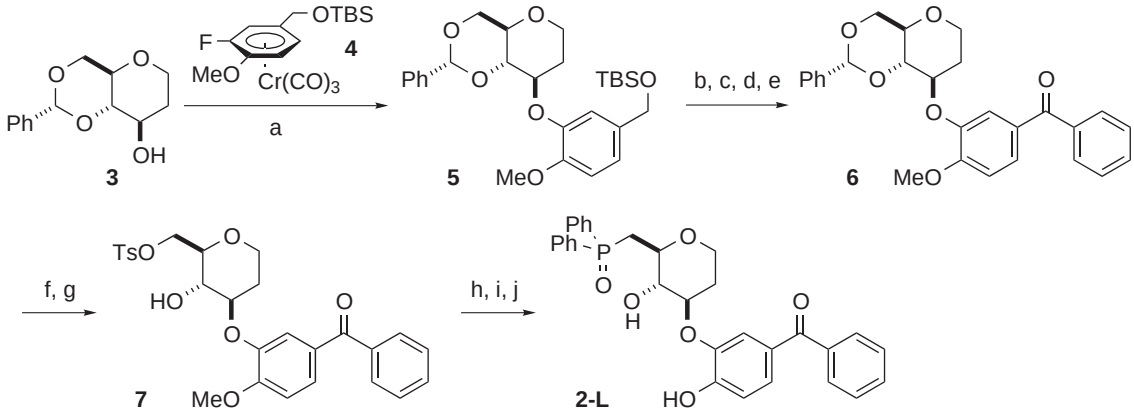


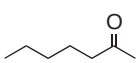
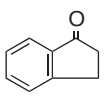
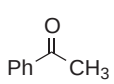
Scheme 1. Reagents and conditions: (a) **4**, NaH, THF; I_2, 84%; (b) TBAF, THF, 99%; (c) PDC, 4 Å MS, CH_2Cl_2, 94%; (d) PhMgBr, THF, 95%; (e) PDC, 4 Å MS, CH_2Cl_2, 88%; (f) $TsOH \cdot H_2O$, MeOH, 97%; (g) TsCl, py, 83%; (h) Ph_2PK (2.2 equiv.), THF; (i) H_2O_2, MeOH–H_2O, 40% (two steps); (j) LiI, DMF, 150°C, 80%.

for a minimized catalyst loading. From these steric and electronic reasons, we decided to introduce a benzoyl group at the *para*-position of the phenoxide (**2-L**). The new ligand **2-L** was synthesized as shown in Scheme 1.[4]

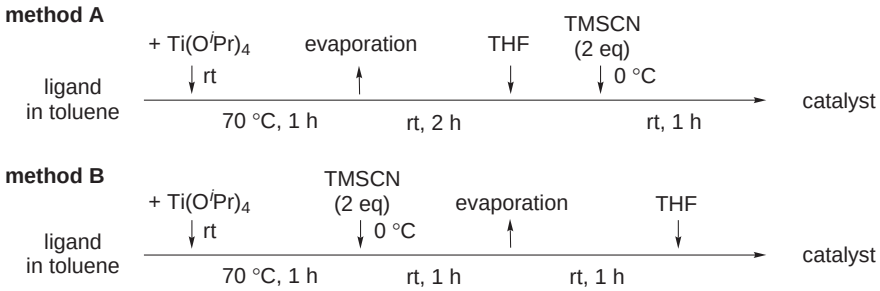
We first assessed the ability of **2** by the reaction of 2-heptanone **8a**, 1-indanone **8b** and acetophenone **8c**, using 10 mol% of **2** (Table 1). As we expected, the enantioselectivity for all the ketones was significantly improved, and for **8c** an ee of 97% could be obtained (entry 7). Next, we investigated the use of a reduced catalyst loading. When the new catalyst **2** was employed, the catalyst loading could be reduced to 2.5 mol% without affecting the reaction time, chemical yield and enantioselectivity (entries 8 and 9).[5] However, when 1 mol% of **2** was used, the reaction became slower and the product was obtained in only 52% yield after even 88 h (entry 10). It was found that the reactivity of the catalyst was improved to a synthetically acceptable range, slightly modifying the preparation method of the catalyst (Scheme 2, method B).[6] Thus, even when 1 mol% of **2** was used, the reaction proceeded at –20°C for 88 h to give the product in 92% yield with 94% ee (entry 11). Under the same conditions, 1 mol% of catalyst **1** gave the product only in 31% yield with 84% ee even after 130 h (entry 6). Therefore, the new catalyst **2** has shown an improved enantioselectivity, as well as an improved catalyst turn-over with a factor of 10.

With the optimized reaction conditions in hand, we investigated the generality of this improved catalytic asymmetric cyanosilylation of ketones. As shown in Table 2, the cyanohydrins were obtained in good to excellent yields with excellent ee using 1 mol% of **2** in the case of aryl ketones and 2.5 mol% of **2** in the case of aliphatic ketones.[7] The absolute configuration of the products can be explained by the working model depicted in Fig. 1: Ti and the phosphine oxide activate the ketone and TMSCN, respectively, which defines the

Table 1. Catalytic asymmetric cyanosilylation of ketones: comparison of **1** and **2**

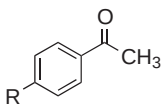
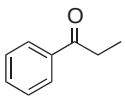
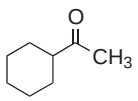
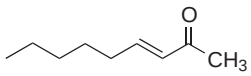
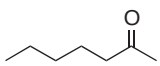
entry	ketone	catalyst (mol %) (method[a])	temp (°C)	time (h)	yield (%)	ee (%)
1	 **8a**	**1** (10) (A)	-50	36	88	76
2		**2** (10) (A)	-50	44	71	86
3	 **8b**	**1** (10) (A)	-40	96	72	69
4		**2** (10) (A)	-40	96	90	84
5	 **8c**	**1** (10) (A)	-30	36	85	92
6		**1** (1) (B)	-20	130	31	84
7		**2** (10) (A)	-30	44	76	97
8		**2** (5) (A)	-30	44	84	95
9		**2** (2.5) (A)	-30	48	84	96
10		**2** (1) (A)	-20	88	52	94
11		**2** (1) (B)	-20	88	92	94

[a] For the preparation method of the catalyst, see Scheme 2.



Scheme 2. Two methods for catalyst preparation.

Table 2. Catalytic enantioselective cyanosilylation of various ketones by **2**

entry	ketone		**2** (mol %) (method[a])	temp/°C	time/h	yield/%	ee/%
1		R = H **8c**	1 (B)	-20	88	92	94
2		R = Cl **8d**	1 (B)	-25	92	72	90
3		**8e**	1 (B)	-10	92	90	92
4		**8f**	2.5 (A)	-30	70	91	93
5		**8g**	2.5 (A)	-30	92	72	90
6		**8a**	2.5 (A)	-45	92	80	82

[a] For the preparation method of the catalyst, see Scheme 2.

sense of entry of TMSCN to the ketone. The beneficial effect of the benzoyl substituent of **2** could be attributed to steric, as well as electronic, factors. Shielding the coordination site B sterically, the position of the ketone should be defined at site A (Fig. 1). Furthermore, electronically stabilizing the Ti complex, the catalyst **2** should be more stable than **1**, thus making it possible to use lower catalyst loading.

In conclusion, we have succeeded in improving the enantioselectivity, generality of the substrates and catalyst turn-over, developing the new tuned catalyst **2** containing a benzoyl group at the catechol moiety. This contribution clearly demonstrated that a general and practical asymmetric catalyst for the cyanosilylation of ketones should be accessible by thorough tuning of **2**. Studies toward this goal including the determination of the catalyst structure, as well as the application to the catalytic asymmetric synthesis of lead compounds for drugs are in progress.

Acknowledgements

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References

1. Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413.
2. For other examples using chemical catalyst, see; Belokon', Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147–8150 and references cited therein.
3. Enantioselective Lewis acid–Lewis base bifunctional catalysts have been applied to a variety of reactions:

Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641–2642; Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 2405–2409; Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 1650–1652; Takamura, M.; Funabashi, K.; Kanai, M. Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328.

4. Spectroscopic data for **2-L**: ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.94 (m, 1H), 2.16 (m, 1H), 2.72 (ddd, $J=9.45$, 15.0, 15.0 Hz, 1H), 2.84 (ddd, $J=3.35$, 9.45, 15.3 Hz, 1H), 3.23 (m, 1H), 3.38 (ddd, $J=3.05$, 9.15, 16.5 Hz, 1H), 3.60 (ddd, $J=5.20$, 8.90, 11.3 Hz, 1H), 3.74 (dd, $J=8.90$, 9.20 Hz, 1H), 3.89 (m, 1H), 6.98 (d, $J=8.25$ Hz, 1H), 7.43–7.80 (m, 18H), 9.73 (s, 1H): ^{13}C NMR (125.65 MHz, $CDCl_3$); δ 31.5, 36.0 (d, $J=68.2$ Hz), 65.3, 74.7, 75.8, 84.8, 116.5, 123.8, 128.0, 128.7, 128.8, 128.8, 128.9, 129.0, 129.0, 129.6, 130.0, 130.5, 130.6, 130.8, 130.9, 131.0, 131.2, 131.7, 132.1, 132.3, 138.3, 145.7, 154.8, 195.1: ^{31}P NMR (202.35 MHz, $CDCl_3$); δ 34.5: $[\alpha]_D^{27}$ +13.2 ($c=2.34$, $CHCl_3$).
5. The concentration of the catalyst was adjusted to 0.3 M when 2.5–10 mol% of the catalyst was used. When 1 mol% of catalyst was used, however, it was necessary to reduce the concentration of the catalyst to 0.2 M, since TMSCN (mp 11–12°C) froze out from THF solution. Lower concentration of the catalyst and reagents should be the reason for the slower reaction rate when 1 mol% of catalyst was used (Table 1, entries 6, 10 and 11).
6. However, the catalyst prepared by method B showed higher reaction rate only in the case of aryl ketones. In the case of aliphatic ketones, the catalyst prepared by method A was more reactive. For example, in the case of 2-heptanone **8a**, catalyst **2** (10 mol%) prepared by method B afforded the product in only 14% yield with 81% ee under the same conditions as entry 2 of Table 1. Elucidation of the structural differences between the catalysts depending on the preparation method is currently under investigation.
7. Representative procedure. (a) Using catalyst preparation method A: $Ti(O^iPr)_4$ (11 μL, 0.0372 mmol) and **2-L** (20 mg, 0.0378 mmol) were mixed in toluene (0.3 mL), and the mixture was stirred at 70°C for 1 h. After removing toluene under reduced pressure, the resulting yellow solid was dried in vacuo for 1 h. The residue was dissolved in THF (0.2 mL) and treated with TMSCN (10 μL, 0.0744 mmol) at rt for 1 h. To this solution cyclohexylmethylketone **8f** (200 μL, 1.49 mmol) was added at −30°C, followed by the addition of TMSCN (300 μL, 2.23 mmol). After 70 h, pyridine (0.1 mL) and water (1.0 mL) were successively added for quenching. Usual workup and purification by silica gel column chromatography afforded the corresponding product (90%, 93% ee) as a colorless oil; (b) using catalyst preparation method B: $Ti(O^iPr)_4$ (11 μL, 0.0372 mmol) and **2-L** (20 mg, 0.0378 mmol) were mixed in toluene (0.3 mL), and the mixture was stirred at 70°C for 1 h. Then, TMSCN (10 μL, 0.0744 mmol) was added at 0°C. After stirring at rt for 1 h, toluene was evaporated under reduced pressure. The residue was further dried in vacuo for 1 h. The resulting yellow solid was dissolved in THF (0.2 mL). To this solution, acetophenone **8c** (434 μL, 3.72 mmol) and TMSCN (740 μL, 5.58 mmol) were successively added at −20°C. After 88 h, the reaction was quenched. Further purification was performed by silica gel column chromatography to give the product (92%, 94% ee) as a colorless oil. For determination of ee and the absolute configuration of the products, see Ref. 1.