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Studies toward practical synthesis of (20*S*)-camptothecin family through catalytic enantioselective cyanosilylation of ketones: improved catalyst efficiency by ligand-tuning

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Abstract—Enantioselective catalyst efficiency for the synthesis of the camptothecin family was improved through ligand-tuning. Key intermediates of two convergent syntheses of camptothecin (Curran's intermediate and Corey's intermediate) were obtained in up to 10 g scale through the catalytic enantioselective cyanosilylation of ketones.

1. Introduction

Camptothecin (Fig. 1, **1**), a pentacyclic alkaloid isolated from *Camptotheca acuminata* by Wall and co-workers in 1966, is a promising anti-cancer agent, especially for the treatment of solid tumors.[1] A mechanism of action of **1** is to interfere with the unwinding of supercoiled DNA by the cellular enzyme topoisomerase I.[2] Accumulated data on the structure–activity relationship of **1** indicates that, in general, substitution on C, D, and E rings is not well tolerated; however, substituents on A and B rings, especially at C7, C9, and C10, often have good biologic activity and improved physical or pharmacologic activity. Two analogs, topotecan (**2**) and irinotecan (**3**), are currently commercial antitumor agents. Therefore, efficient synthesis of this important group of anti-cancer agents (the camptothecin family) is currently under intensive investigation.[3]

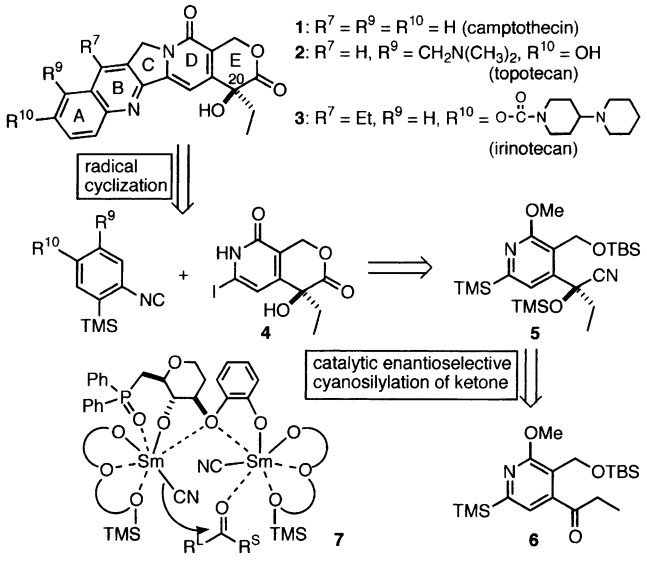

Figure 1.

For synthesis of various camptothecin analogs containing substituents on the A and B rings, the convergent synthetic route reported previously, in which AB rings and DE rings are connected at the later stage through radical cyclization, is very advantageous.[3a] This synthetic route utilizes chiral α-hydroxy lactone **4** as a key intermediate. We recently reported a catalytic enantioselective synthesis of **4** through the cyanosilylation of ketone **6** promoted by the (*S*)-selective catalyst prepared from chiral ligand **8** and Sm in a ratio of 1:1.8.[4] Based on mechanistic studies, we determined the structure of the active catalyst as 2:3 complex **7**, and proposed a working model of the transition state, in which one of the Sm-metals acts as a Lewis acid to activate the ketone substrate, while the other Sm-cyanide acts as a nucleophile. The reaction should proceed through an intramolecular cyanide transfer to the activated ketone. Although the reaction is generally applied to a range of

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substrates, the enantioselectivity and catalyst loading in the case of ketone **6** was not satisfactory, especially for a practical supply of intermediate **4** (see below). Therefore, we attempted to improve the catalyst efficiency by ligand tuning. For this purpose, the new synthetic route of ligands described in the previous paper was essential for surveying a wide variety of catechol moieties.[5] Here we report that the catalyst derived from ligand **13** is a significantly improved catalyst for camptothecin synthesis through intermediate **4** (Curran's route), in terms of enantioselectivity and catalyst loading. Moreover, we describe that the catalytic enantioselective cyanosilylation is also applicable to another convergent camptothecin synthesis (Corey's route).

2. Catalytic enantioselective synthesis of Curran's intermediate

Using 5 mol% of Sm-catalyst prepared in a ratio of Sm: **8** = 1:1.8, (*S*)-**5** was obtained in 98% yield with 84% ee (Table 1, entry 1). The enantioselectivity became lower, when the catalyst loading was decreased to 2 mol%, giving cyanohydrin **5** with 82% ee (Table 1, entry 2). Therefore, we attempted to improve the catalyst efficiency by introducing an electron-withdrawing group on the catechol moiety. This modification should increase the Lewis acidity of the catalyst, which was expected to produce a beneficial effect. We first tried the catalyst derived from ligand **9** (Fig. 2), because **9** was a better ligand than **8** for the (*R*)-selective catalytic enantioselective cyanosilylation promoted by the Ti-complex.[6] In the case of the Sm-complex, however, both catalyst activity and enantioselectivity were much lower than the original catalyst (entry 3). Molecular modeling studies indicated that the adverse effect of the benzoyl group was attributed to its bulkiness, especially the effective thickness (bulkiness perpendicular to the aryl plane) of the catechol moiety. Because the space around Sm of the 2:3 complex **7** seemed fairly congested, the bulky catechol moiety should hinder the access of sterically demanding ketone **6** to the metal center. Consequently, the reaction might be mainly promoted by less enantioselective catalytic species other than **7**.[7,8] Consistent with this rationalization, a catalyst prepared from ligand **10**, containing tetrachlorocatechol, gave slightly better enantiomeric excess than that from **9** (entry 4), reflecting the reduced effective thickness of the catechol moiety. On the other hand, a catalyst prepared from **11** gave comparable results (entry 5) with the original catalyst, indicating that the in-plane size of the catechol moiety is not very influential on the enantioselectivity.

Based on these observations, we designed ligand **12**, containing difluorocatechol. The size of the difluorocatechol moiety should be very similar to the original

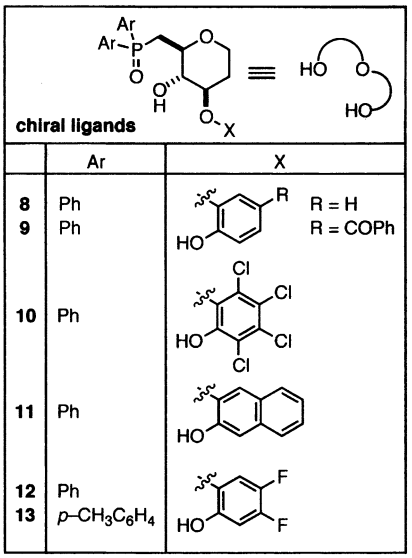
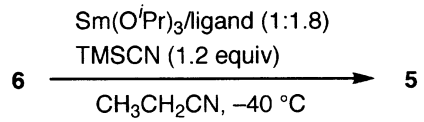


Figure 2.

Table 1. Catalytic enantioselective cyanosilylation of ketone **6**: synthesis of Curran's intermediate



Entry	Ligand	Cat. (mol%)	Time (h)	Yield (%)[c]	ee (%)[d]
1[a]	**8**	5	18	98	84
2	**8**	2	44	100	82
3	**9**	5	96	100	38
4	**10**	5	65	90	42
5	**11**	5	16	94	83
6	**12**	5	14	100	91
7	**12**	2	38	95	83
8	**13**	5	12	94	90
9	**13**	2	19	95	89
10[b]	**13**	2	36	93	90

[a] Reported in Ref. 4.
[b] CH_3CH_2CN:CH_3CN = 1:1 was used as solvent.
[c] Isolated yield.
[d] Determined by HPLC after conversion to **14**.

catechol moiety, because the atomic radius of a fluorine atom is only slightly larger than a hydrogen atom. Furthermore, the high electron-withdrawing ability of the fluorine atom should increase the Lewis acidity of the center metal and stabilize the metal complex. As expected, the catalyst prepared from **12** gave a higher enantioselectivity (91% ee with 5 mol% of catalyst, entry 6) than the original catalyst prepared from ligand **8**. The reaction promoted by 2 mol% of catalyst from **12**, however, gave product **5** with a reduced 83% ee (entry 7). We hypothesized that this dependency of the enantioselectivity on the catalyst loading might be attributed to the competitive less enantioselective pathway. Therefore, to stabilize and increase the population of the desired 2:3 complex, we attempted to increase the Lewis basicity by introducing an electron-donating substituent on the aromatic group of the phosphine oxide. Although the role of the phosphine oxide in the (*S*)-selective lanthanide complex is not completely clear, it should stabilize the desired 2:3 complex, possibly by coordinating to one of the Sm atoms (see **7**).[9] Thus, we designed ligand **13** containing di-(*p*-tolyl)phosphine oxide and a difluorocatechol moiety. Using 5 mol% of catalyst prepared from **13**, cyanohydrin **5** was obtained in 90% ee. Fortunately, enantiomeric excess remained at 89% even using 2 mol% of catalyst. Using an acetonitrile and propionitrile (1:1) mixture,[10] **5** was obtained with 90% ee. The reaction was successfully conducted on a 10 g scale, clearly indicating the practicality of the reaction.

Conversion of cyanohydrin **5** to key intermediate **4** and recrystallization from MeOH/$CHCl_3$ gave enantiomerically pure **4** (Scheme 1).

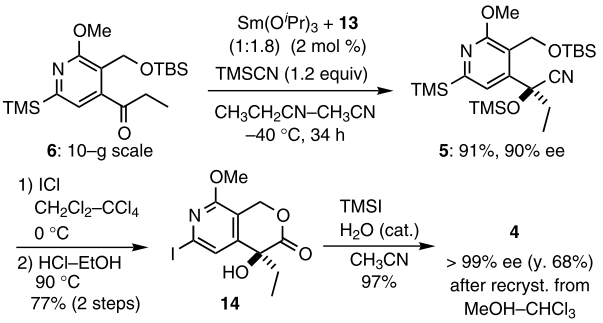
3. Catalytic enantioselective synthesis of Corey's intermediate

To demonstrate the usefulness of the catalytic enantioselective cyanosilylation of ketones, we applied the reaction to another convergent synthesis[11] of camptothecin, previously reported by Corey.[12] We first developed a convenient and reproducible route for the synthesis of ketone **22** (Scheme 2), modifying the original synthetic route. Results of catalytic enantioselective cyanosilylation of **22** using three selected ligands (**8**, **12**, and **13**) are summarized in Scheme 2. In this case, the Gd-catalyst gave better results than the Sm-catalyst,[13] and cyanohydrin **23** was obtained with up to 94% ee using 2 mol% of catalysts.[14] From **23**, enantiomerically pure Corey's intermediate **26** was obtained in high overall yield as follows. Reduction of the cyanide with DIBAH followed by acid deprotection of TBS group gave lactol **24**, which was then oxidized to lactone **25**.[15] Enantiomerically pure **25** was obtained by recrystallization from $CHCl_3$/Et_2O/hexane mixture. Methoxycarbonylation of the *tert*-alcohol through a lithium alkoxide gave enantiomerically pure **26**.

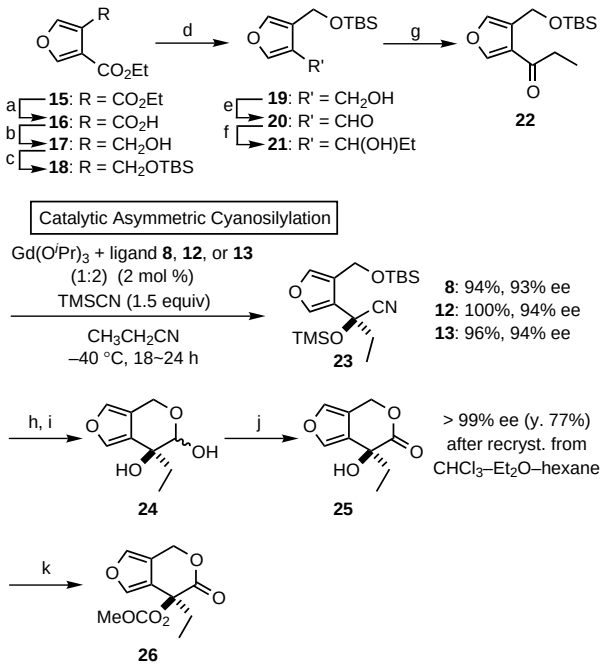
In summary, we developed an improved catalyst for the key enantioselective cyanosilylation in camptothecin synthesis. The enantiomerically pure intermediates of two typical convergent synthetic routes of the camptothecin family are available in up to 10 g scale. The results clearly demonstrate that electronic-tuning of both the catechol moiety and the phosphine oxide moiety are very important for achieving the high catalyst-turnover and enantioselectivity. Further studies toward practical synthesis of the camptothecin family are now in progress.

4. Experimental

Cyanosilylation of 6 to 5 (Curran's route): $Sm(O^iPr)_3$ (0.600 mmol, 0.2 M stock solution in THF) in THF (3.0 mL) was added to a solution of chiral ligand **13**



Scheme 1. Catalytic enantioselective synthesis of Curran's intermediate.



Scheme 2. Catalytic enantioselective synthesis of Corey's intermediate. *Reagents and conditions*: (a) NaOH (1 equiv.), MeOH, 79%; (b) ^{i}BuOCOCl, Et_3N, THF; $NaBH_4$, H_2O, 84%; (c) TBSCl, imidazole, DMF, 100%; (d) DIBAH, CH_2Cl_2, 99%; (e) MnO_2, CH_2Cl_2; (f) EtMgBr, THF, 66% (two steps); (g) Dess–Martin periodinane, CH_2Cl_2, 98%. (h) DIBAH, toluene; (i) $TsOH{\cdot}H_2O$, THF–H_2O, 89%; (j) NIS, TBAI, CH_2Cl_2, 85%; (k) BuLi; MeOCOCl, THF, 76%.

(528 mg, 1.08 mmol) in THF (12 mL) in an ice bath and the mixture was stirred for 30 min at 45°C. Cooling to room temperature, THF was evaporated and the residue was dried for 1.5 h under vacuum (5 mmHg). Dissolving the residue in propionitrile (5 mL) and acetonitrile (5 mL) mixture, TMSCN (4.8 mL, 36.0 mmol) was added at −40°C. After 20 min, a solution of **6** (11.5 g, 30.0 mmol) in propionitrile (5 mL) and acetonitrile (5 mL) mixture was added slowly over 30 min and the mixture was stirred for 34 h at −40°C. H_2O was added to quench the reaction (caution: HCN is generated.), and the product and the ligand were extracted with AcOEt. The combined organic layer was washed with sat. NaCl aq. and dried over Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified by SiO_2 column chromatography (hexane/Et_2O = 400/1 to 200/1) to give pure **5** as colorless oil (13.2 g, 91% yield). Enantiomeric excess of **5** was determined by chiral HPLC after conversion to **14** (DAICEL CHIRALPAK AS, hexane/2-propanol = 20/1, 1.0 mL min^{-1}, t_R 19.6 (minor) and 23.3 min (major)). The ligand and the silylated ligand were eluted from the column with MeOH/$CHCl_3$, treated with HCl aq. in THF, extracted, and purified by SiO_2 column chromatography to recover pure ligand **13** in >90% yield.

Cyanosilylation of 22 to 23 (Corey's route): $Gd(O^iPr)_3$ (0.015 mmol, 0.2 M stock solution in THF) in THF (75 μL) was added to a solution of chiral ligand **13** (15 mg, 0.030 mmol) in THF (0.3 mL) in an ice bath and the mixture was stirred for 30 min at 45°C. Cooling to room temperature, THF was evaporated and the residue was dried for 1.5 h under vacuum (5 mmHg). Dissolving the residue in propionitrile (0.25 mL), TMSCN (0.15 mL, 1.13 mmol) was added at −40°C. After 20 min, a propionitrile solution (0.38 mL) of **22** (0.201 g, 0.75 mmol) was added and the mixture was stirred for 24 h at −40°C. Workup as described above and purification by column chromatography gave **23** as colorless oil (96% yield). Enantiomeric excess was determined after conversion to the corresponding benzoylamido alcohol (1. LAH, THF; 2. BzCl, Et_3N; 3. TBAF) by chiral HPLC (DAICEL CHIRALCEL OJ-H, hexane/2-propanol = 9/1, 1.0 mL min^{-1}, t_R 16.0 (minor) and 18.7 min (major)).

Acknowledgements

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7. The adverse effect of the benzoyl group was less significant in the case of a simple substrate such as acetophenone, which gave the corresponding cyanohydrin in 80% yield with 74% ee (1 mol% of catalyst, −40°C, 60 h). The catalyst (1 mol%) derived from **8** gave the product in 93% yield with 92% ee. The phenyl ketone of the ligand was intact under the reaction conditions based on TLC and ^1H NMR analysis.
8. The enantioselectivity was quite sensitive to the reaction conditions (Sm/ligand ratio, concentration, and/or reaction temperature), which indicated the existence of competitive reaction pathways promoted by several catalytic species other than the highly enantioselective 2:3 complex.
9. This hypothesis is based on structural studies of the control catalyst prepared from the ligand containing a diphenylmethyl group instead of a phosphine oxide. See Ref. 4 for details.
10. Preliminary studies on solvent effects indicated that enantioselectivity was improved as the solvent polarity increased. We could not use 100% acetonitrile, however, because the starting ketone **6** was not soluble in acetonitrile.
11. We use the term 'convergent' for synthetic routes through coupling of AB rings and DE rings (or their equivalents) at the final stage, because these approaches should be advantageous for finding efficient camptothecin analogs. In this context, Wani and Wall's synthesis (Wani, M. C.; Ronman, P. E.; Lindley, J. T.; Wall, M. E. *J. Med. Chem.* **1980**, *23*, 554–560) and Commins' synthesis (Ref. 3b) are also convergent.
12. Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140–2141 In this first synthesis of naturally occurring (20*S*)-camptothecin, an optically pure synthetic intermediate was obtained through optical resolution. A drawback of their synthesis is the low yield of the final step.
13. For example, the Sm-catalyst (5 mol%) derived from ligand **8** gave **23** in 96% yield with 81% ee (−40°C, 20 h).
14. The advantages of fluorinated ligands **12** and **13** were not significant in this case, possibly because the substrate size of **22** is not so large and **22** could easily access the catalytic center of the 2:3 complex. Thus, the contribution of the competitive pathway promoted by undesired catalytic species is not important.
15. Direct acid hydrolysis of **23** to **25** was not successful.