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Catalytic Enantioselective Synthesis of Key Intermediates for Triazole Antifungal Agents

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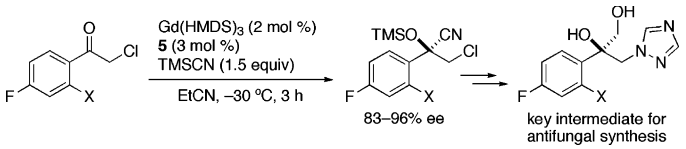
ABSTRACT



A short-step synthesis of versatile chiral building blocks for triazole antifungal agents such as ZD0870 and Sch45450 was developed via catalytic enantioselective cyanosilylation of electron-deficient ketones as the key step. High enantioselectivity was produced using a catalyst prepared from Gd(HMDS)$_3$ and ligand 5 in a 2:3 ratio. This new catalyst preparation method was superior to the previous method using Gd(O^{i}Pr)$_3$ as a metal source. A rationale for the difference is proposed on the basis of structural studies of the catalyst complexes using ESI-MS.

Systemic fungal infections can be fatal for patients with immune deficiency or suppression such as occurs in AIDS, cancer, or following organ transplants. Triazole antifungal agents (Figure 1) demonstrate great potential to treat these infectious diseases because of their broad antifungal spectrum and low toxicity.[1] Fluconazole, itraconazole, and voriconazole are clinically used representative antifungal drugs of this family, and at least several compounds are currently undergoing clinical trials. Therefore, the development of an efficient and convergent synthetic route that can be applied to large-scale synthesis of these antifungals is an important goal.

Many triazole antifungal agents share a common synthetic intermediate, **1**, containing a chiral tertiary alcohol. Previous synthesis of **1** utilized either Sharpless asymmetric dihydroxylation,[2] Sharpless asymmetric epoxidation,[3] or enzymatic transformations[4] as a key enantioinduction step. Although excellent enantioselectivity was obtained in these cases, multiple steps were required for the synthesis of substrates of the key catalytic enantioselective reactions, which decreases the total synthetic efficiency. In this communication, we describe a short synthetic route to **1** using a catalytic, enantioselective cyanosilylation of commercially available ketone **2a** as the key step. During the optimization of the key cyanosilylation reaction, we developed a new catalyst preparation protocol using Gd(HMDS)$_3$ as a metal source. The catalyst prepared through this new method produced significantly higher enantioselectivity than the previous method using Gd(O^{i}Pr)$_3$.

We developed an enantioselective cyanosilylation of ketones catalyzed by a gadolinium complex generated from Gd(O^{i}Pr)$_3$ and ligand **4** in a 1:2 ratio.[5,6] This reaction is practical and applicable to the catalytic asymmetric synthesis of key intermediates of important pharmaceuticals such as

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(1) For review, see: (a) Como, J. A.; Dismukes, W. J. *New Engl. J. Med.* **1994**, *330*, 263. (b) ZD0870: Peng, T.; Galgiani, J. N. *Antimicrob. Agents Chemother.* **1993**, *37*, 2126. (c) Sch45450: Murakami, K.; Mochizuki, H.; Boyle, F.; Wardleworth, J. M. Eur. Pat. Appl. 472392, 1992.

(2) Blundell, P.; Ganguly, A. K.; Girijiavallabhan, V. M. *Synlett* **1994**, 263.

(3) Saksena, A. K.; Girijiavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Desai, J. A.; Ganguly, A. K.; Hare, R. S.; Loebenberg, D.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2023.

(4) (a) Lovey, R. G.; Saksena, A. K.; Girijiavallabhan, V. M. *Tetrahedron Lett.* **1994**, *35*, 6047−6050. (b) Yasohara, Y.; Miyamoto, K.; Kizaki, N.; Hasegawa, J.; Ohashi, T. *Tetrahedron Lett.* **2001**, *42*, 3331.

(5) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908.

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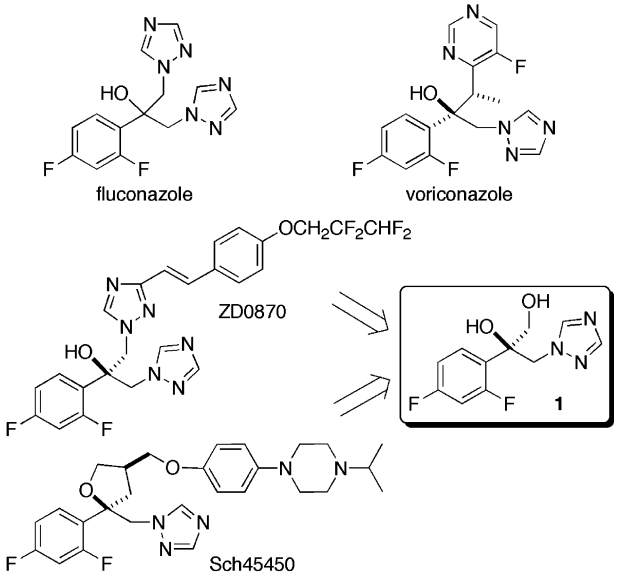


Figure 1. Examples of triazole antifungal agents.

camptothecins[7] and oxybutynin.[8] On the basis of preliminary studies of the catalyst structure using ESI-MS, the active catalyst was proposed to be a 2:3 complex **6** of gadolinium cyanides and the ligands. Because slightly higher enantioselectivity was obtained when the catalyst was prepared with a 1:2 gadolinium/ligand ratio than with a 2:3 ratio, we determined this 1:2 ratio to be optimal for simple ketones.[5] On the basis of this background, as well as the increasing demands for new triazole antifungal agents, we planned to develop an alternative synthetic route to **1** using the catalytic enantioselective cyanosilylation of ketones.

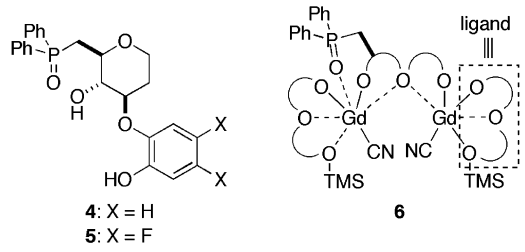
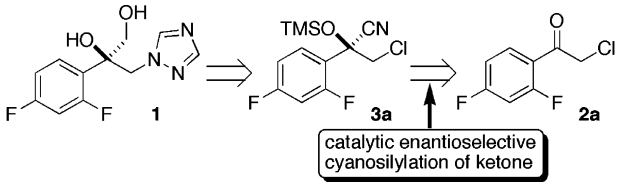


Figure 2. Chiral ligands and proposed catalyst structure for cyanosilylation of ketones.

Our synthetic plan is summarized in Scheme 1. Because our preliminary studies suggested that synthetically useful enantioinduction from the corresponding triazole-containing ketone is difficult, we selected commercially available ketone **2a** as a substrate for the key catalytic enantioselective cyanosilylation. Once **3a** is obtained with high enantioselectivity, reduction of the cyanide into the hydroxymethyl group followed by substitution of the chloride by triazole should give the versatile intermediate **1**.

Scheme 1. Synthetic Plan



On the basis of the above plan, we started our studies with optimization of the catalytic enantioselective cyanosilylation of reactive ketone **2a**. When previously optimized conditions were applied to **2a** using the catalyst derived from $Gd(O^iPr)_3$ and ligand **4** in propionitrile at −40 °C, product **3a** was obtained in good yield, but with only 24% ee (Table 1, entry 1). Using ligand **5** containing difluorocatechol, the enantioselectivity was significantly improved to 68% ee (entry 2).[9−11] Efforts to further improve the enantioselectivity through optimization of the fundamental reaction conditions (temperature, concentration, solvent, lanthanide metals, and metal/ligand ratio), ligand structure tuning, or additive effects were not successful.

Delightful results were obtained when switching the metal source from $Gd(O^iPr)_3$ to $Gd(HMDS)_3$. Thus, when the catalyst was prepared from $Gd(HMDS)_3$ and **5** in a 1:2 ratio, product **3a** was obtained with 80% ee (Table 1, entry 4).[12] Screening of the gadolinium/ligand ratio using 2 mol % catalyst at −30 °C revealed that the highest enantioselectivity was produced with $Gd(HMDS)_3$/**5** = 2:3 (entry 6), and product **3a** was obtained with a synthetically useful enan-

(6) For examples of catalytic enantioselective cyanation of ketones from other groups, see: (a) Belokon', Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett*. **1999**, *38*, 6669. (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.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc*. **1999**, *121*, 3968. (c) Belokon', Y. N.; Green, B.; Ikonnikov, N. S.; Larichev, V. S.; Lokshin, B. V.; Moscalenko, M. A.; North, M.; Orizu, C.; Peregudov, A. S.; Timofeeva, G. I. *Eur. J. Org. Chem.* **2000**, 2655. (d) Belokon', Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron* **2001**, *57*, 771. (e) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc*. **2001**, *123*, 6195. (f) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc*. **2003**, *125*, 9900. (g) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed*. **2002**, *41*, 1009. (h) Chen, F.; Feng, Z.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett*. **2003**, *5*, 949. (i) Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2004**, 129.

(7) (a) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett*. **2002**. *43*, 2923. (b) Yabu, K.; Masumoto, S.; Kanai, M.; Shibasaki, M. *Heterocycles* **2003**, *59*, 369.

(8) (a) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett*. **2002**. *43*, 8647. (b) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 10497.

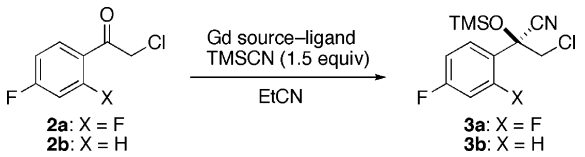
(9) Chiral ligands **4** and **5** are commercially available from Junsei Chemical Co., Ltd., Tokyo, Japan. Fax: +81-3−3270-5461.

(10) Ligands **4** and **5** produced almost comparable enantioselectivity from simple ketones (e.g., acetophenone or 2-heptanone) as a substrate. Therefore, the significant difference in enantioselectivity between **4** and **5** is specific for the electron-deficient substrate **2a**.

(11) A marked advantage of **5** to **4** was observed in the Strecker reaction of ketoimines and the conjugate addition of cyanide: (a) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2003**, *125*, 5634 (Strecker reaction). (b) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2005**, *127*, 514 (conjugate addition).

(12) Addition of a small amount of HMDS (1 equiv to gadolinium) to a catalyst solution prepared from $Gd(O^iPr)_3$ (2 mol %) did not improve the enantioselectivity, which suggested that the improvement is not due to remaining trace amount HMDS.

Table 1. Catalytic Enantioselective Cyanosilylation of Ketones for the Synthesis of Triazole Antifungals



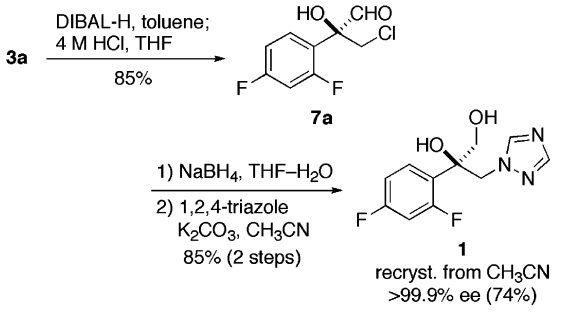
entry[a]	Gd source[b] (mol %)	ligand (mol %)	ketone	time (h)	yield[c] (%)	ee[d] (%)
1	A (5)	**4** (10)	**2a**	14	74	24
2	A (5)	**5** (10)	**2a**	3	85	68
3	A (5)	**5** (7.5)	**2a**	3	83	52
4	B (5)	**5** (10)	**2a**	3	96	80
5	B (2)	**5** (4)	**2a**	3	81	80
6	B (2)	**5** (3)	**2a**	3	93	83
7	A (2)	**5** (4)	**2b**	3	99	91
8	B (2)	**5** (3)	**2b**	3	95	96

[a] Reaction temperature was −40 °C for entries 1−4 and −30 °C for entries 5−8. [b] A = $Gd(O^iPr)_3$. B = $Gd(HMDS)_3$. [c] Isolated yield. [d] Enantiomeric excess (ee) was determined by chiral GC. See Supporting Information for details.

tioselectivity of 83% ee (entry 6).[13] This optimized catalyst preparation protocol also produced better enantioselectivity in the case of another electron-deficient ketone, **2b**, and product **3b** was obtained with 96% ee (entry 8).[14] **3b** should be a useful chiral building block for the synthesis of new antifungal triazole derivatives.[15]

Having established synthetically useful catalytic enantioselective cyanosilylation for electron-deficient ketone **2a**, conversion of **3a** to the versatile, enantiomerically pure intermediate **1** was relatively straightforward (Scheme 2).

Scheme 2. Conversion to Intermediate **1**



Reduction of the cyanide with DIBAL-H and treatment with aqueous HCl provided the hydroxyaldehyde **7a** in high yield.

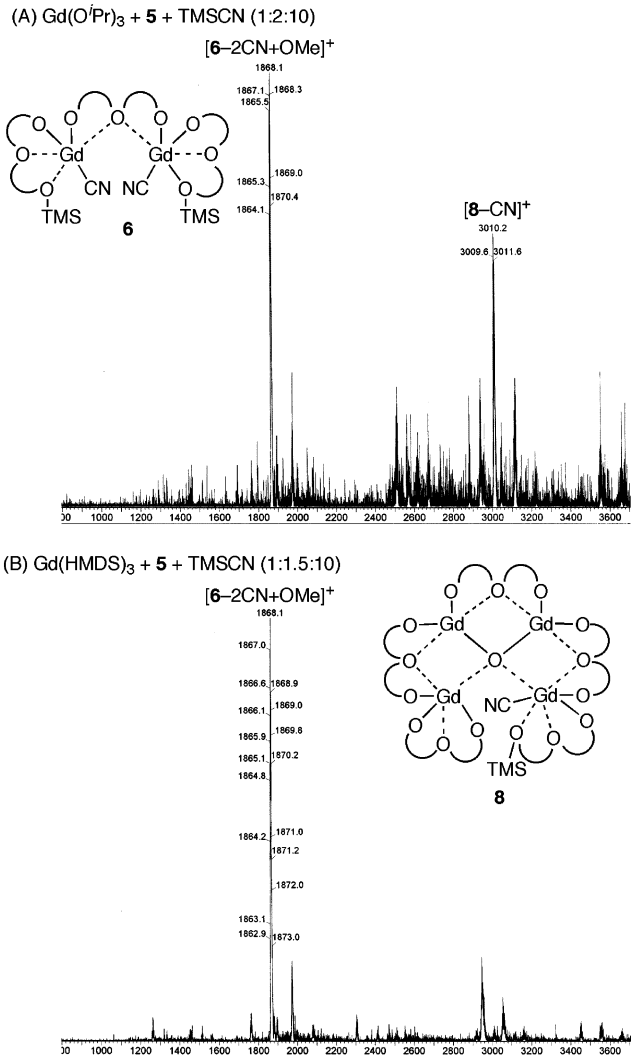


Figure 3. ESI-MS observations of the catalyst complexes.

Reduction of the aldehyde with $NaBH_4$, followed by substitution of the chloride with triazole anion, gave the target **1** with reasonable yield. Enantiomerically pure **1** was obtained through recrystallization from acetonitrile. This is the shortest catalytic enantioselective synthesis of the versatile intermediate **1** from a commercially available starting material.

To elucidate a possible origin of the enantioselectivity difference between using $Gd(O^iPr)_3$ or $Gd(HMDS)_3$ as a metal source, we studied catalyst compositions and molecular weights by ESI-MS. After $Gd(O^iPr)_3$ and **5** were mixed in a 1:2 ratio, the liberated ^{i}PrOH was evaporated under vacuum

(13) **Representative Procedure Using the Catalyst Prepared from Gd(HMDS)$_3$.** $Gd(HMDS)_3$ (0.17 M stock solution in THF, 1.3 mL, 0.22 mmol) was added to a solution of **5** (164 mg, 0.35 mmol) in THF (7 mL) in an ice bath, and the mixture was warmed to 45 °C for 30 min. After cooling to room temperature, volatiles were evaporated, and the resulting white powder was dried under vacuum (2 mmHg) at 45 °C for 3 h. Propionitrile (7 mL) was added, followed by the addition of TMSCN (2.1 mL, 15.8 mmol) at −30 °C. After 10 min, substrate ketone **2a** (2.00 g, 10.5 mmol) was added to start the reaction.

(14) In contrast to the results obtained from electron-deficient ketones **2a** and **2b**, comparably high enantioselectivity was obtained from a simple ketone (acetophenone), either using $Gd(O^iPr)_3$ or $Gd(HMDS)_3$ as a gadolinium source (95 and 96% ee, respectively, using 2.5 mol catalyst at −40 °C). The different tendency might be attributed to the susceptibility of the reactive ketones to the undesired reaction pathways promoted by the contaminating complex **8** (see text).

(15) Itoh, H.; Furukawa, Y.; Tsuda, M.; Takeshiba, H. *Bioorg. Med. Chem.* **2004**, *12*, 3561.

(ca. 2 mmHg) for 1 h. The resulting alkoxide complex was dissolved in CH_3CN, and TMSCN (10 equiv) was added to generate the active gadolinium cyanide catalyst. Two main species were observed in this solution by ESI-MS measurement (Figure 2, A); one major peak corresponded to the 2:3 complex **6** (observed MW = 1868, calcd for $[M - 2CN + OMe]^+ = 1867$), which is consistent with previous observations.[16] Another higher molecular weight peak corresponded to a μ-oxo-containing 4:5 complex **8** (observed MW = 3010, calcd = 3011).[17] On the other hand, when the active catalyst was prepared from $Gd(HMDS)_3$ and **5** in a 2:3 ratio, the peak corresponding to complex **8** was not observed (Figure 2, B).[18] On the basis of this comparison, we proposed that the difference in enantioselectivity is due to the presence of the μ-oxo 4:5 complex.[19] This complex might promote the cyanosilylation of reactive ketones such as **2a** and **2b** with lower enantioselectivity than the desired 2:3 complex. The activity of the μ-oxo 4:5 complex, however, should be lower than that of the 2:3 complex because enantioselectivity from simple ketones such as acetophenone is not affected by the gadolinium source. These results also suggested a reason the optimum metal/ligand ratio is different depending on the gadolinium source; more chiral ligand might be necessary to maximize the **6**/**8** ratio when the catalyst is prepared from $Gd(O^iPr)_3$.

In summary, the enantioselectivity of catalytic cyanosilylation of reactive ketones can be improved using a catalyst prepared from $Gd(HMDS)_3$ and difluorocatechol-containing ligand **5** in a 2:3 ratio. This finding allowed for a short, efficient enantioselective synthesis of a versatile chiral intermediate **1** for triazole antifungal agents. Preliminary studies of the catalyst compositions using ESI-MS suggested that the improvement in enantioselectivity is due to the absence of contamination by the μ-oxo 4:5 complex. This study should facilitate further structural studies of the active and enantioselective 2:3 complex. Studies are ongoing in the due course.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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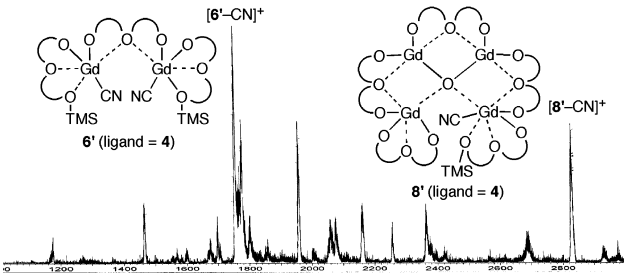
(16) ESI-MS provided valuable information about the compositions of the multimetallic chiral gadolinium complexes. See: Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett*. **2004**, *45*, 3147. See also ref 5. The methoxide ligand might come from remaining trace amounts of MeOH in the MS apparatus. Observation of the peak corresponding to the methoxide-incorporated 2:3 complex is to be considered an exception only in cases where ligand **5** was used. Using ligand **4**, the 2:3 complex **6′** (calcd for $[M - CN]^+ = 1754$) without methoxide incorporation was observed, concomitant with the μ-oxo 4:5 complex **8′** (calcd for $[M - CN]^+ = 2831$; see ESI-MS chart below).



(17) Rare earth metal isopropoxides can generate the μ-oxo complex even under strictly anhydrous conditions with liberation of diisopropyl ether at temperatures higher than the boiling point of 2-propanol. See: Bradley, D. C.; Chudzynska, H.; Frigo, D. M.; Hammond, M. E.; Hursthouse, M. B.; Mazid, M. A. *Polyhedron* **1990**, *9*, 719.

(18) Only a single peak corresponding to the 2:3 complex was observed, even when the catalyst was prepared from $Gd(HMDS)_3$ and **5** in a 1:2 ratio, which excluded the possibility that generation of the μ-oxo 4:5 complex is due to the different metal/ligand ratio.

(19) Studies to selectively generate the μ-oxo 4:5 complex and to elucidate the catalyst activity and enantioselectivity of this complex are ongoing.