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A practical synthesis of (*S*)-oxybutynin

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Abstract—(*S*)-Oxybutynin, an important drug acting as muscarinic receptor antagonist, was practically synthesized using catalytic enantioselective cyanosilylation of cyclohexyl phenyl ketone (**6a**) as a key step. Cyanohydrin **7a** with 94% ee was obtained with 1 mol% of Gd-**5** catalyst. The key α-hydroxy carboxylic acid **8** was synthesized from **7a** in an enantiomerically pure form without column chromatography. Other cycloalkyl phenyl ketones, except cyclopentyl phenyl ketone (**6e-H**) gave products with high enantioselectivity. The enantioselectivity of the reaction of **6e** was dramatically improved using α-deuterium substituted **6e-D**. The dramatic deuterium effect provides an important insight into the competitive reaction pathway.

1. Introduction

Oxybutynin (Ditropan, **1**) is a widely utilized muscarinic receptor antagonist for the treatment of urinary urgency, frequency, and incontinence.[1] A number of derivatives have been synthesized mainly by modifying the ester (or the amide) part and the cycloalkyl part (for examples, see Fig. 1).[2] Some of these analogues have improved M_3-receptor subtype selectivity and thus the side effects caused by antagonizing other subtypes, such as M_1- and M_2-receptors are minimized. A structurally common feature of oxybutynin and related compounds is the chiral tertiary α-hydroxy carbonyl moiety. Although oxybutynin is currently prescribed in a racemic form, the (*S*)-enantiomer is proposed to have an improved therapeutic profile. Therefore, there is a high demand for the development of an efficient enantioselective synthetic route. Previously reported methods utilized diastereoselective reactions that require a stoichiometric amount of chiral auxiliary or a chiral starting material to construct the chiral stereocenter of **1**.[3] We describe the first practical catalytic enantioselective synthesis of the key synthetic intermediate **8**, utilizing catalytic cyanosilylation of the ketone as a key step.

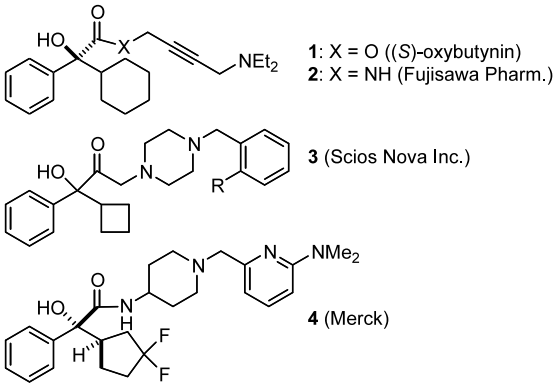

Figure 1. Oxybutynin and analogues.

2. Catalytic enantioselective synthesis of (*S*)-oxybutynin

We recently developed an (*S*)-selective catalytic cyanosilylation of ketones[4,5] using a chiral gadolinium (Gd) complex prepared from $Gd(O^iPr)_3$[6] and the D-glucose-derived chiral ligand **5** in a 1:2 ratio. We applied this reaction to the synthesis of the chiral tertiary α-hydroxy acid core of (*S*)-oxybutynin. Although the reaction produces ketone cyanohydrins in high enantioselectivity from a range of ketones, substrate **6a** for the oxybutynin synthesis is an extremely challenging ketone. In general, to achieve high enantioselectivity in a nucleophilic addition to carbonyl compounds, the chiral catalyst needs to differentiate two lone pairs of the carbonyl oxygen atom for the coordination to the Lewis acid metal of the chiral catalyst. In the case of ketone **6a**, however, differences in the steric demand of

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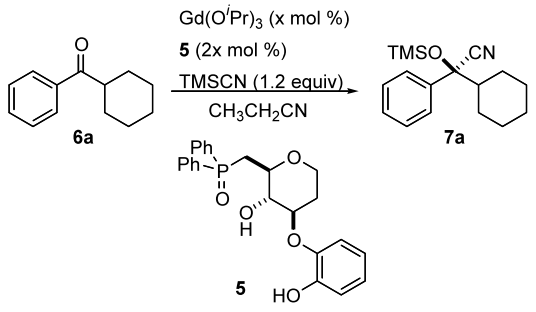
these lone pairs are not sufficient because these lone pairs are *cis* to sterically similar phenyl or cyclohexyl groups.[7]

Despite the expected difficulties, we were pleased to find that the reaction proceeded at −60°C for 21 h in the presence of 5 mol% of Gd-catalyst, giving the desired (*S*)-**7a** in 96% yield with 95% ee (Table 1, entry 1, catalyst concentration = 0.075 M, ketone concentration = 1.5 M).[8,9] Lowering the catalyst loading to 1 mol%, however, resulted in a sluggish reaction at −60°C, giving the product in 39% with 64% ee (9 days, catalyst concentration = 0.015 M, ketone concentration = 1.5 M). Increasing the reaction temperature to −40°C and using a higher concentration, the reaction proceeded to completion to give the product in 99% yield with 85% ee (entry 3, catalyst concentration = 0.075 M, ketone concentration = 7.5 M). We hypothesized that the decrease in enantioselectivity with the lower catalyst amount was due in part to the initial heat generation when a large amount of substrate ketone was added in one portion as a powder at the last stage to a mixture of the catalyst and TMSCN to start the reaction.[10] Therefore, we first added the substrate ketone to the catalyst, then cooled the reaction temperature to −40°C, addition of the solvent, and slowly added the TMSCN (over 15 min). Using this procedure improved the results and the product was obtained with 94% ee (entry 4). The reaction and purification procedures are practical and we performed the reaction on a 100 g-scale (see Section 5 for details). After the usual aqueous work-up, the crude oil was purified through short-pad silica gel column chromatography (Scheme 1). Pure **7a** was obtained with AcOEt/hexane (1/20) elution, followed by MeOH/$CHCl_3$ (1/15) elution to obtain the ligand-containing fraction (a mixture of ligand **5** and the silylated ligand). The pure ligand **5** was recovered in 98% yield after acidic desilylation (1 M HCl aq. in THF) and recrystallization.

Table 1. Catalytic enantioselective cyanosilylation of **6a**



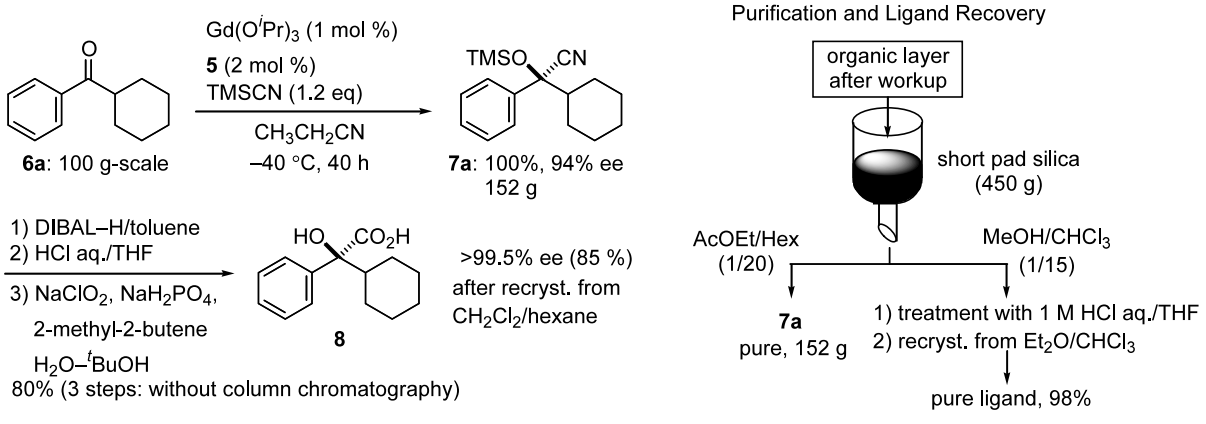
Entry	Cat. (*x* mol%)	Temp. (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	5	−60	21	96	95
2	5	−40	1.5	99	91
3	1	−40	50	99	85
4[c]	1	−40	40	100	94

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.
[c] The ketone was added prior to TMSCN (see Section 5 for details). In other entries, ketones were added at the last stage.

Having established a practical method for the catalytic enantioselective cyanosilylation of the ketone, the next task was to convert the cyanide to the carboxylic acid. The conversion was initially problematic, however, probably due to steric hindrance. Acidic hydrolysis or alcoholysis gave ketone **6a** predominantly through the elimination of HCN. Basic hydrolysis after conversion to the THP-protected cyanohydrin resulted in no reaction. Therefore, we investigated the reduction–oxidation procedure (Scheme 1). Careful reduction of **7a** with DIBAL-H in toluene, desilylation with 4 N HCl aq. in THF, followed by oxidation with $NaClO_2$ gave the known α-hydroxy carboxylic acid **8** in 80% overall yield (3 steps). Chemically pure **8** was obtained through a base/acid aqueous work-up without silica gel column chromatography. Recrystallization from CH_2Cl_2/hexane gave an enantiomerically pure intermediate for oxybutynin synthesis.[11]

3. Catalytic enantioselective cyanosilylation of other aryl cycloalkyl ketones

The unusually high enantiodifferentiation ability of the catalyst on the apparently difficult substrate led us to study the applicability of the catalytic enantioselective



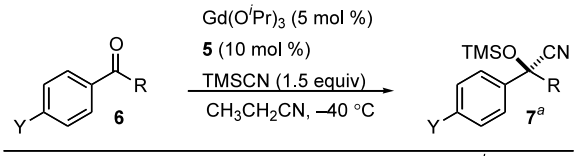
Scheme 1. Practical catalytic enantioselective synthesis of (*S*)-oxybutynin key intermediate.

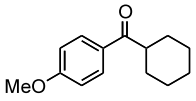
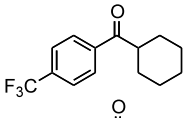
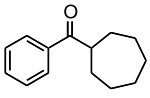
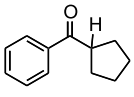
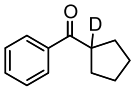
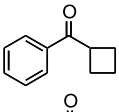
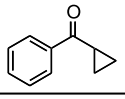
cyanosilylation to other aryl cycloalkyl ketones. As shown in Table 2, high to excellent enantioselectivity was obtained except in the case of cyclopentyl phenyl ketone (**6e-H**). Products obtained with high enantioselectivity should be very useful for synthesizing new chiral oxybutynin analogues.

The sharp contrast in the enantiomeric excess of **7e-H** (Table 2, entry 4) and products from other cycloalkyl phenyl ketones is intriguing from a mechanistic point of view. The results could not be explained from the ground state structure difference between **6e-H** and other ketones, based on the comparison of the most stable conformation of these substrates.[12] The reactivity–enantioselectivity relationship of phenyl ketones with no substituent on the aromatic rings (**6a** and **6d–g**), indicated a general trend in that high enantioselectivity was obtained when the reactions proceeded smoothly (Table 1, entry 2 and Table 2, entries 3–6). Thus, we initially hypothesized that the difference in enantioselectivity might be due to the extent of the microscopic reversibility of the reaction (Scheme 2, hypothesis 1). As we clarified in the previous paper,[4] the active nucleophile of this catalytic enantioselective reaction is a gadolinium cyanide of the chiral complex containing Gd and **5** in a 2:3 ratio (Gd-**5**). Once the gadolinium cyanide reacted with a ketone, the initial product should be a gadolinium alkoxide **9** of the corresponding ketone cyanohydrin, which would be quite labile to the retro-reaction. If the equilibrium in this first step is significantly faster than the second silylation step, the microscopic reversibility of the enantiodetermining step should diminish the enantioselectivity.[13] Based on the hypothesis, we added a mixture of free cyanohydrin **10** and TMSCN to the catalyst precursor **11**, and observed the enantiomeric excess changes. The silylation kinetics for each free cyanohydrins (**10a**, **10e-H**, and **10g**), however, was extremely fast (<5 min for completion) even at –40°C,[14] and enantiomeric excess did not change in any cases starting from enantiomerically enriched or racemic cyanohydrins (Scheme 2). Thus, hypothesis 1 was unequivocally excluded.

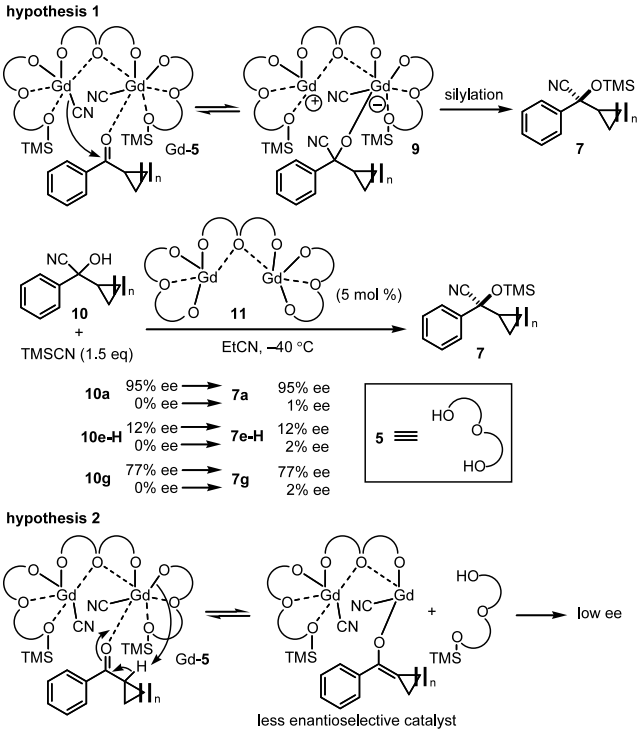
Therefore, we next focused on the alternative hypothesis in which the asymmetric catalyst might act as a Brønsted base to deprotonate the starting ketones (Scheme 2, hypothesis 2). This competitive pathway might cause a ligand exchange to produce a less enantioselective catalyst. Based on the hypothesis, we planned to utilize a deuterium kinetic isotope effect to prevent the undesired deprotonation.[15] As we expected, the reaction using **6e-D** proceeded rapidly and the product was obtained with 95% ee (Table 2, entry 5 versus entry 4). As far as we notice, this is the first example of a dramatic advantage using an isotope effect in catalytic enantioselective reactions. The results also provide a very important insight into the reaction

Table 2. Catalytic enantioselective cyanosilylation of aryl cycloalkyl ketones



entry	ketone		time (h)	yield (%)[b]	ee (%)[c]
1		**6b**	22	99	94
2		**6c**	1	96	83
3		**6d**	5	99	94
4		**6e-H**	64	87	22
5		**6e-D**[d]	1	99	95
6		**6f**	2	99	97
7		**6g**	48	97	82

[a] The absolute configuration of the product was temporarily assigned based on the analogy to **7a**.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 85%-**D**.



Scheme 2. Two hypotheses on the low reactivity and enantioselectivity of cyclopentyl phenyl ketone.

mechanism, in which the Brønsted basicity of the Gd-**5** can cause undesired decomposition of the highly enantioselective catalytic species. Studies toward development of a new enantioselective catalyst for cyanosilylation of ketones that eliminates the Brønsted basicity and demonstrates a further broad substrate generality are currently under investigation.

4. Conclusion

We developed a practical synthetic route of an important pharmaceutical, (*S*)-oxybutynin. The chiral center of the core tertiary α-hydroxy carboxylic acid was constructed by the catalytic enantioselective cyanosilylation of ketones using 1 mol% of Gd-**5** complex. These procedures are suitable for large-scale synthesis with minimal silica gel column chromatography purification. We believe that the methodology described herein should be practically useful for a process-type supply of (*S*)-oxybutynin. Furthermore, a dramatic deuterium isotope effect on the reaction kinetics and enantioselectivity in the case of ketone **6e** suggested that the ketone deprotonation might become a possible competitive pathway in some ketones.

5. Experimental

5.1. 100 g-scale cyanosilylation of 6a

$Gd(O^iPr)_3$ (5.31 mmol, 0.2 M stock solution in THF) in THF (26.6 mL) was added to a solution of chiral ligand **5** (4.51 g, 10.6 mmol) in THF (106 mL) in an ice bath and the mixture was stirred for 30 min at 45°C. After cooling to room temperature, THF was evaporated and the residue was dried for 6 h under vacuum (5 mmHg). To this catalyst powder, ketone **6a** (100 g, 0.531 mol) was added. Propionitrile (71 mL) and TMSCN (85 mL, 0.637 mol) were successively added at −40°C, and the mixture was stirred for 40 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 satd. NaCl aq. and dried over Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified through short pad SiO_2 column chromatography (450 g: AcOEt/hexane = 1/20) to give pure **7a** as a colorless oil (152 g, 100% yield). The enantiomeric excess of **7a** was determined by chiral HPLC after conversion to **8** [DAICEL CHIRALPAK AS, hexane/2-propanol/TFA = 95/5/0.1, 1.0 mL/min, t_R 7.3 (minor) and 10.6 min (major)]. The ligand and the silylated ligand were eluted from the column with $CHCl_3$/MeOH = 15/1, treated with HCl aq. in THF, extracted, and purified by recrystallization to recover pure ligand **5** in 98% yield.

Acknowledgements

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8. The absolute configuration of **7a** was determined to be (*S*) after conversion to carboxylic acid **8** and by a comparison of the optical rotation with the reported value (Ref. 3a). This is the same enantioselectivity as with other previously studied simple ketones such as acetophenone, suggesting that the catalyst recognizes the cyclohexyl group as a smaller group than the phenyl.
9. The (*R*)-selective titanium complex could not promote the reaction from **6a** at low temperature. The reaction proceeded at room temperature and (*R*)-**7a** was obtained in 96% yield with only 7% ee (36 h). For the (*R*)-selective catalytic cyanosilylation of ketones, see: Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413.
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12. Molecular modeling studies indicated that **6e** contains similar conformation and electronic character with other ketones.
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excluded based on the experiments described in the text. The related mechanism was proposed in Deng's catalytic enantioselective cyanosilylation of ketones (Ref. 5a).

14. In the absence of the catalyst precursor **11**, the silylation of the ketone cyanohydrins with TMSCN was very sluggish.
15. For the use of an isotope effect in organic synthesis to prevent the undesired deprotonation, see: (a) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett*. **2002**, *43*, 5605–5606; (b) Vedejs, E.; Little, J. *J. Am. Chem. Soc*. **2002**, *124*, 748–749.