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Practical synthesis of chiral ligands for catalytic enantioselective cyanosilylation of ketones

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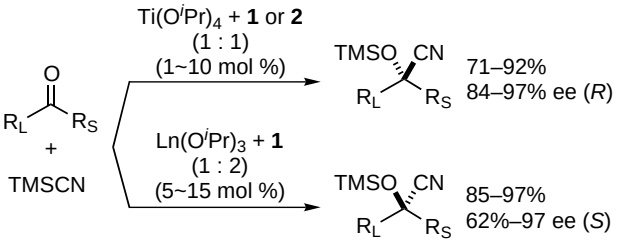
Abstract—A practical and more environmentally benign synthetic route of chiral ligands that are useful for catalytic enantioselective cyanosilylation of ketones is described. A key step is the regioselective S_N2 reaction to cyclic sulfate **12** with catechol derivatives. A range of chiral ligands containing electronically tuned catechols has become available by this new route.

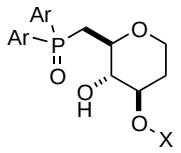
1. Introduction

We recently developed a catalytic enantioselective cyanosilylation of ketones that affords chiral tertiary cyanohydrins from a wide range of ketone substrates.[1,2] Both (*R*)- and (*S*)-cyanohydrins can be synthesized with generally high enantioselectivity by catalysts prepared from chiral ligand **1**: **1**-Ti (1:1) complex is (*R*)-selective and **1**-Ln (Gd or Sm) (2:3) complex is (*S*)-selective (Scheme 1). The synthetic importance of chiral tertiary alcohols as building blocks for various pharmaceutically significant compounds (e.g. camptothecin, fostriecin, oxybutynin, pyruvate dehydrogenase kinase inhibitor, etc.)[3] illustrates that **1** is an extremely useful chiral ligand.

1 was previously synthesized in high overall yield from commercially available tri-*O*-acetyl-D-glucal (**7**).[4] A key step was the introduction of the catechol moiety (X in Scheme 1) by an aromatic substitution of the arene–chromium complex.[5] Use of a stoichiometric amount of chromium, however, is environmentally problematic, especially in a large-scale synthesis. Furthermore, tuning the catechol moiety of **1** was very difficult using this synthetic route, because arene–chromium complexes containing electron-deficient aromatic groups are generally difficult to prepare. Introducing an electron-withdrawing group on the catechol moiety, however, is an attractive approach for improving the catalyst efficiency, because it increases the Lewis acidity of the metal. For example, benzoyl-containing ligand **2** synthesized by a laborious route produced significantly better results in reactions promoted by a Ti-complex.[1b]



chiral ligands



	Ar	X
1	Ph	R_1, R_2 = H
2	Ph	R_1 = COPh, R_2 = H
3	Ph	R_1, R_2 = F
4	*p*-$CH_3C_6H_4$	R_1, R_2 = F
5	Ph	
6	Ph	

Scheme 1.

Keywords: chiral ligand; catalytic enantioselective reaction; cyanosilylation; ketones; practical synthesis; cyclic sulfate; ligand-tuning.

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Herein, we report a new and practical synthetic route of chiral ligands that is more suitable for large-scale synthesis (Scheme 2). The direct introduction of electron-deficient catechols allows for a facile synthesis of electronically tuned chiral ligands (**2**–**6**).

2. Practical synthetic route of chiral ligands

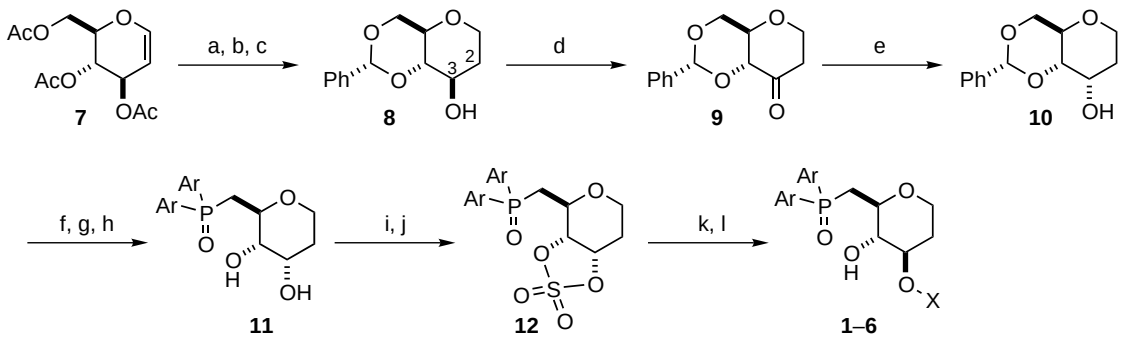
We attempted to introduce the key catechol via a regioselective S_N2 attack of catechol derivatives to cyclic sulfate **12**. To do so required inversion of the 3-OH group of the D-glucose derivative **8** to the D-allose derivative **10**. Although there are several reports on the synthesis of **10**,[6] none of them were satisfactory for our purpose. Therefore, we planned to develop an original method to synthesize **10** through an oxidation-stereoselective reduction sequence from **8**. Previous reports using related ketones indicated that the reduction with $NaBH_4$ should proceed mainly via an equatorial hydride attack to give the desired α-OH.[7]

Precursor ketone **9** was synthesized via Swern oxidation of **8**,[8] which was readily obtained from commercially available **7** through three steps. Reduction of **9** with $NaBH_4$ in MeOH, however, resulted in low stereoselectivity (**8**:**10** = 1.5:1) and undesired **8** was obtained as the major isomer.[9] After several attempts, reduction with L-selectride gave the desired **10** with complete selectivity in 93% yield from **8** (two steps).[10] It is advantageous, especially for a large scale synthesis, that column chromatography was not necessary through **7**–**10**, and all the purifications could be performed by recrystallization.[11] Deprotection of the benzylidene acetal, selective tosylation of the primary alcohol, and introduction of the phosphine oxide gave **11**.[12] The key cyclic sulfate **12** was synthesized following the reported procedure.[13] From **12**, a variety of catechol moieties were introduced in an S_N2 manner with complete regioselectivity at the less hindered position (C-3).[14] Deprotection of the methyl ether[15] gave chiral ligands **1**–**6** [total 12 steps from **7** for **1**, **2**, **3**, **5**, and **6**. **1**: 17% yield (10 steps in 44% yield, previously). **2**: 17% yield (13 steps in 10% yield, previously). **3**: 19% yield. **4**: 14% yield (total 15 steps). **5**: 17% yield. **6**: 25% yield.]. Ligands **3**–**6** cannot be synthesized by the former route using arene–chromium complexes.

In conclusion, we developed a practical and environmentally more benign (i.e. no chromium) synthetic route of chiral ligands that are very useful for catalytic enantioselective cyanosilylation of ketones. This synthetic route made it possible to readily prepare an array of chiral ligands containing different catechol moieties. The advantages of these new ligands will be discussed in a following paper.

3. Experimental

General procedure for the inversion of 3-OH (8–10): DMSO (0.21 mL, 2.96 mmol) was added dropwise to a solution of $(COCl)_2$ (0.13 mL, 1.49 mmol) in CH_2Cl_2 (5 mL) at −78°C. After 15 min, **8** (278 mg, 1.18 mmol) in CH_2Cl_2 (2 mL) was added dropwise for 10 min, and the resulting suspension was stirred at the same temperature for 1 h. Then, Et_3N (0.85 mL, 6.10 mmol) was added at −78°C and the dry ice–acetone bath was removed to allow the reaction temperature to reach room temperature. After 30 min, H_2O was added and the product was extracted with $CHCl_3$. Evaporation of the organic solvent gave crude ketone **9**, which can be used for the next step without purification. L-Selectride (1.0 mol L^{-1} in THF, 467 μL, 0.47 mmol) was added to a solution of ketone **9** (0.44 mmol) in THF (4 mL) at −78°C. After 50 min, 30% H_2O_2 aq. (0.32 mL) was added at the same temperature and the mixture was stirred at 4°C for 20 min. The mixture was then slowly poured into sat. $Na_2S_2O_3$ aq. and the aqueous layer was



Scheme 2. *Reagents and conditions*: (a) Pd/C, H_2, MeOH, rt; (b) NaOMe (0.25 equiv.), MeOH, rt; (c) $PhCH(OMe)_2$ (1.2 equiv.), *p*-TsOH·H_2O (0.3 equiv.), toluene, reflux, 57% (three steps); (d) DMSO (2.5 equiv.), $(COCl)_2$ (1.3 equiv.), Et_3N (5 equiv.), CH_2Cl_2, −78°C to rt; (e) L-Selectride (1.03 equiv.), THF, −78°C, 93% (two steps); (f) Pd/C, H_2, MeOH–AcOH (1:1), rt, 92%; (g) TsCl (1.1 equiv.), pyridine, 78%; (h) Ph_2PK (2.5 equiv.), THF, 0°C; H_2O_2, 94% (Ar = Ph), [Ar = *p*-$CH_3C_6H_4$: MOMCl (2.5 equiv.), $^iPr_2NEt$ (3 equiv.), CH_2Cl_2, reflux, 72%; Ar_2PLi (2 equiv.), THF, 0°C; H_2O_2; cat. HCl aq.–MeOH, reflux, 85% (three steps)]; (i) $SOCl_2$ (1.2 equiv.), CH_2Cl_2; (j) $RuCl_3·3H_2O$ (1 mol%), $NaIO_4$ (1.5 equiv.), CCl_4–CH_3CN–H_2O, 90% (Ar = Ph), 98% (Ar = *p*-$CH_3C_6H_4$) (two steps); (k) catechol derivatives (1.3 equiv.), K_2CO_3 (2 equiv.), DMF; 20% H_2SO_4 aq., $Et_2O/CHCl_3$, 65–86% (two steps); (l) EtSH, $AlCl_3$, CH_2Cl_2, 82–100% (two steps).

extracted with Et_2O. The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation and purification by SiO_2 column chromatography (eluent: AcOEt/hexane = 1/2) gave pure **10** in 93% yield as white powder. In a large scale synthesis, the crude product was purified by recrystallization (AcOEt–hexane).

General procedure for the introduction of the phosphine oxide (11): A solution of the tosylate (8.57 g, 28.3 mmol) in THF (30 mL) was added to a commercially available Ph_2PK solution in THF (0.5 M, 142 mL, 71.0 mmol) over 10 min in an ice bath. After stirring for 30 min at the same temperature, sat. NH_4Cl aq. was added, followed by the addition of 30% H_2O_2 aq. (16 mL) under vigorous stirring. The mixture was then poured slowly into sat. $Na_2S_2O_3$ aq. in an ice bath. Evaporation of THF, extraction of the aqueous layer with $CHCl_3$, and concentration gave a crude oil that was purified by SiO_2 column chromatography (eluent: MeOH/$CHCl_3$ = 1/30). The resulting solid was recrystallized from $CHCl_3$–Et_2O to give white powder in 94% yield. The corresponding diol containing di-(*p*-tolyl)phosphine oxide was synthesized from the MOM protected tosylate in a similar way using (*p*-tolyl)$_2$PLi prepared following the reported procedure.[16]

General procedure for the cyclic sulfate synthesis (12): $SOCl_2$ (0.27 mL, 3.70 mmol) was added to a solution of diol **11** (1.03 g, 3.10 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred for 30 min at room temperature. Then, the reaction mixture was concentrated, followed by co-evaporation with toluene two times. The resulting crude cyclic sulfite was dissolved in a CCl_4 (15 mL)/CH_3CN (15 mL)/H_2O (30 mL), and $NaIO_4$ (994 mg, 4.65 mmol) and $RuCl_3 \cdot nH_2O$ (7.3 mg, 1 mol%) were added in an ice bath. After stirring vigorously for 1 h, H_2O was added and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with sat. NaCl aq., followed by stirring with ^{i}PrOH (5 mL) at room temperature for 1 h. Drying with Na_2SO_4, filtration through celite, and concentration gave a crude powder, which was recrystallized from AcOEt–Et_2O to give **12** as fine needles (1.10 g, 90%).

General procedure for the S_N2 reaction by catechol derivatives: K_2CO_3 (1.32 g, 9.56 mmol) and guaiacol (0.68 mL, 6.21 mmol) were added to a solution of **12** (1.86 g, 4.78 mmol) in DMF (10 mL) and the mixture was stirred for 14 h at room temperature. After **12** had disappeared on TLC, 20% H_2SO_4 aq. (100 mL) and Et_2O (50 mL)–$CHCl_3$ (50 mL) were added and the mixture was vigorously stirred for 12 h. The aqueous layer was extracted with $CHCl_3$ and the combined organic layer was washed with H_2O and sat. NaCl aq. Drying over Na_2SO_4, followed by concentration, gave a crude oil that was purified by SiO_2 column chromatography (eluent: AcOEt/hexane = 1/1 to 100/0). The methylated ligand was obtained as a white solid (65%).

4. Selected spectral data of new ligands

3: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 (dddd, J = 5.1, 12.9, 12.9, 12.9 Hz, 1H), 2.09 (m, 1H), 2.67 (ddd, J = 9.7, 15.0, 15.0 Hz, 1H), 2.85 (ddd, J = 2.5, 9.7, 15.0 Hz, 1H), 3.24 (ddd, J = 1.8, 12.3, 12.9 Hz, 1H), 3.33 (m, 1H), 3.50 (ddd, J = 5.1, 8.6, 12.9 Hz, 1H), 3.69 (brt, J = 8.6 Hz, 1H), 3.91 (m, 1H), 6.77 (ddd, J = 8.2, 10.7, 19.8 Hz, 1H), 7.53 (m, 6H), 7.76 (m, 4H), 7.85 (s, 1H), 9.16 (d, J = 1.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.56, 36.04 (d, J = 69 Hz), 65.39, 74.70 (d, J = 3 Hz), 75.93, 85.57, 105.58 (d, J = 21 Hz), 110.93 (d, J = 18 Hz), 129.03 (d, J = 12 Hz), 129.07 (d, J = 12 Hz), 130.20 (d, J = 101 Hz), 130.71 (d, J = 10 Hz), 131.17 (d, J = 10 Hz), 131.62 (d, J = 100 Hz), 132.58 (d, J = 4 Hz), 132.61 (d, J = 3 Hz), 141.14 (dd, J = 3, 7 Hz), 142.60 (dd, J = 14, 239 Hz), 146.58 (dd, J = 3, 10 Hz), 147.37 (dd, J = 13, 243 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 33.3.

4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93 (dddd, J = 5.2, 12.8, 12.8, 12.8 Hz, 1H), 2.08 (m, 1H), 2.40 (s, 3H), 2.41 (s, 3H), 2.63 (ddd, J = 10.1, 15.3, 15.3 Hz, 1H), 2.79 (ddd, J = 2.8, 9.8, 15.3 Hz, 1H), 3.23 (ddd, J = 2.1, 11.9, 12.8 Hz, 1H), 3.30 (m, 1H), 3.49 (ddd, J = 5.2, 8.9, 11.3 Hz, 1H), 3.67 (brt, J = 8.9 Hz), 3.91 (m, 1H), 6.74 (dd, J = 7.9, 11.6 Hz, 1H), 6.78 (dd, J = 8.3, 10.7 Hz, 1H), 7.29 (dd, J = 2.8, 8.3 Hz, 2H), 7.32 (dd, J = 2.8, 8.3 Hz, 2H), 7.58 (dd, J = 8.3, 11.9 Hz, 2H), 7.62 (dd, J = 8.3, 11.9 Hz, 2H), 7.97 (s, 1H), 9.24 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.71, 21.73, 31.55, 36.42 (d, J = 69 Hz), 65.38, 74.72 (d, J = 3 Hz), 76.01, 85.66, 105.58 (d, J = 22 Hz), 110.99 (d, J = 20 Hz), 126.80 (d, J = 103 Hz), 128.36 (d, J = 108 Hz), 129.74 (d, J = 12 Hz), 129.83 (d, J = 13 Hz), 130.71 (d, J = 10 Hz), 131.19 (d, J = 9 Hz), 141.17 (dd, J = 3, 8 Hz), 142.55 (dd, J = 14, 239 Hz), 143.19 (d, J = 2 Hz), 143.20 (d, J = 2 Hz), 146.67 (dd, J = 2, 10 Hz), 147.38 (dd, J = 13, 243 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 33.7.

5: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (dddd, J = 4.9, 12.8, 12.8, 12.8 Hz, 1H), 2.23 (m, 1H), 2.73 (ddd, J = 9.5, 15.0, 15.0 Hz, 1H), 2.84 (ddd, J = 3.1, 9.5, 15.0 Hz, 1H), 3.24 (ddd, J = 1.9, 12.2, 12.8 Hz, 1H), 3.39 (m, 1H), 3.71 (ddd, J = 4.9, 8.9, 11.0 Hz, 1H), 3.79 (t like, J = 8.9 Hz, 1H), 3.91 (m, 1H), 7.25 (brt, J = 7.0 Hz, 1H), 7.30 (s, 1H), 7.33 (brt, J = 7.0 Hz, 1H), 7.36 (s, 1H), 7.5–7.66 (m, 8H), 7.77 (m, 4H), 8.98 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.42, 35.95 (d, J = 69 Hz), 65.49, 74.82 (d, J = 4 Hz), 76.05, 84.16, 111.55, 117.54, 123.41, 125.10, 126.32, 126.86, 128.36, 128.98 (d, J = 12 Hz), 129.01 (d, J = 12 Hz), 130.60 (d, J = 101 Hz), 130.78 (d, J = 10 Hz), 131.23 (d, J = 9 Hz), 131.97 (d, J = 103 Hz), 132.04, 132.44 (d, J = 2 Hz), 146.88, 149.15. ^{31}P NMR (202 MHz, $CDCl_3$) δ 33.3.

6: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (dddd, J = 4.9, 12.5, 12.5, 12.5 Hz, 1H), 2.26 (m, 1H), 2.69 (ddd, J = 10.1, 15.3, 15.3 Hz, 1H), 2.85 (m, 1H), 3.21 (brt, J = 12.5 Hz, 1H), 3.36 (m, 1H), 3.70 (ddd, J = 4.9, 8.9, 11.3 Hz, 1H), 3.81 (t like, 8.9 Hz, 1H), 3.90 (m, 1H), 7.49–7.63 (m, 6H), 7.72 (dd, J = 7.3, 12.2 Hz, 2H), 7.78 (dd, J = 7.3, 11.9 Hz, 2H), 8.47 (s, 1H), 10.9 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.93, 36.02 (d, J = 69 Hz),

65.39, 74.85 (d, $J=3$ Hz), 75.67, 87.03, 120.58, 121.92, 126.81, 128.73, 129.06 (d, $J=11$ Hz), 129.10 (d, $J=12$ Hz), 129.90 (d, $J=101$ Hz), 130.62 (d, $J=10$ Hz), 131.20 (d, $J=10$ Hz), 131.57 (d, $J=100$ Hz), 132.65 (d, $J=3$ Hz), 142.78, 147.77. ^{31}P NMR (202 MHz, $CDCl_3$) δ 33.4.

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