Diastereo- and Enantioselective Tandem Michael Addition and Lactonization Catalyzed by Chiral Quaternary Ammonium Phenoxide: Stereoselective Synthesis of the Two Enantiomers by Using a Single Chiral Source

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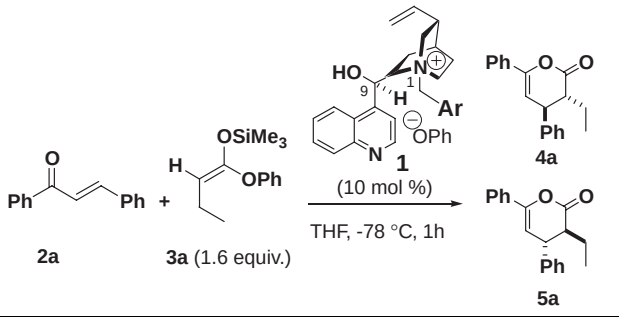
Diastereo- and enantio-selective synthesis of 3,4-dihydropyran-2-ones from various silyl enolates and α,β-unsaturated ketones were successfully carried out by using cinchonidine-derived quaternary ammonium phenoxide. In this reaction, a synthesis of the two enantiomers was achieved by an appropriate choice of a substituent on the bridgehead nitrogen of cinchonidine.

Recently, it was reported that high diastereo- and enantioselective synthesis of 3,4-dihydropyran-2-ones was achieved via successive reactions of Michael addition and lactonization in the presence of a catalytic amount of the chiral quaternary ammonium phenoxide derived from cinchonidine.[1] In this reaction, the cinchonidine-derived chiral catalyst functioned in reverse enantiofacial selectivity when a substituent on the bridgehead nitrogen atom was changed. Now we would like to show that the two enantiomers were successfully synthesized by using a single chiral source, that is, quarternary ammonium phenoxide.

In the first place, reaction of chalcone **2a** with trimethylsilyl (TMS) enolate **3a** was carried out in THF at -78 °C for 1 h in the presence of 10 mol % of chiral quaternary ammonium phenoxides **1**[2] (Table 1). When the catalyst **1a** having a simple phenyl group was used, Michael addition and successive lactonization reactions proceeded smoothly to afford the corresponding 3,4-dihydropyran-2-one **4a** in 91% yield with high anti-selectivity (anti/syn = 89:11)[3] while the enantioselectivity of the major anti isomer turned out to be poor (23% ee) (Entry 1). Next, it was observed that the use of a catalyst **1b** having 2,6-difluorophenyl group enhanced both diastereo- and enantio-selectivities (anti/syn = 96:4, anti = 64% ee) (Entry 2). On the other hand, their enantioselectivities considerably decreased against **1b** (Entries 3–5) when substituents such as 3,5-di-*tert*-butylphenyl (**1c**), 3,5-bis(trifluoromethyl)phenyl (**1d**), and 3,5-diphenylphenyl groups (**1e**) were introduced. It is particularly interesting that the use of a catalyst having bulky substituents on the nitrogen atom of cinchonidine, **1f** (Ar = 3,5-bis(3,5-di-*tert*-butylphenyl)-phenyl or **1g** (Ar = 3,5-bis[3,5-bis(trifluoromethyl)phenyl]-phenyl) showed to give the opposite enantioselectivity to the result obtain when **1b** was employed: that is, 3,4-dihydropyran-2-one **5a** in 78 and 92% yields with diastereo- and enantioselectivities (anti/syn = 78:22 and 75:25, anti = 51% ee and 31% ee) (Entries 6 and 8). In addition, enantioselectivities were observed to increase up to 70% ee and 83% ee when the reactions were carried out in CH_2Cl_2 (Entries 7 and 9).

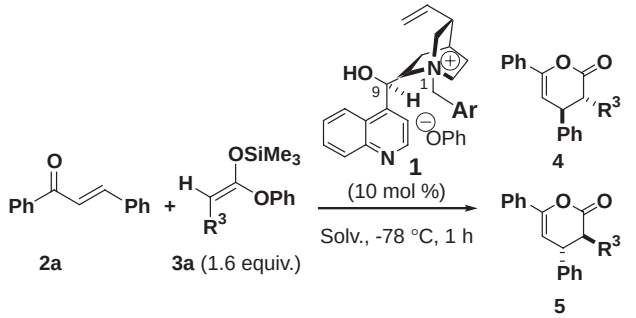
Table 1. Effect of catalysts



Entry	Catalyst	Product	Yield[a](%) (anti/syn)[b]	% ee[c]
1	**1a**: Ar = Ph	**4a**	91 (89:11)	23
2	**1b**: Ar = 2,6-$F_2C_6H_3$	**4a**	94 (96:4)	64
3	**1c**: Ar = 3,5-(*t*-Bu)$_2C_6H_3$	**4a**	99 (87:13)	12
4	**1d**: Ar = 3,5-$(CF_3)_2C_6H_3$	**4a**	91 (>99:1)	13
5	**1e**: Ar = 3,5-$(Ph)_2C_6H_3$	**4a**	99 (90:10)	45
6	**1f**: Ar = 3,5-[3,5-(*t*-Bu)$_2C_6H_3$]$_2C_6H_3$	**5a**	78 (78:22)	51
7[d]	**1f**: Ar = 3,5-[3,5-(*t*-Bu)$_2C_6H_3$]$_2C_6H_3$	**5a**	99 (87:13)	70
8	**1g**: Ar = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$	**5a**	92 (75:25)	31
9[d]	**1g**: Ar = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$	**5a**	99 (93:7)	83

[a]Isolated yield. [b]Diastereomeric ratio was determined by ^{1}H NMR analysis. [c]Enantiomeric excess of major *anti*-**4a**, **5a** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (volume ratio = 50:1) as a solvent. [d]Reaction was carried out in CH_2Cl_2.

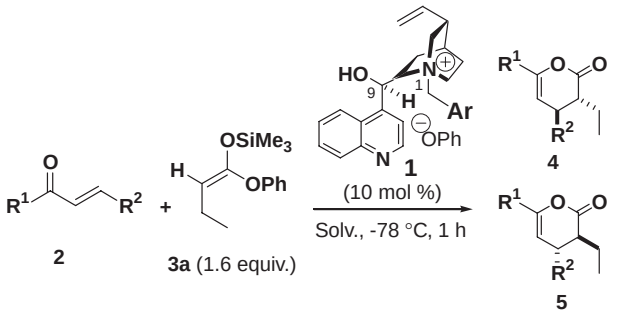
Table 2. Reactions of chalcone **2a** with various silyl enolates **3** in the presence of cinconidine-derived catalysts **1b** and **1g**



Entry	Sily enolate	Catalyst	Product	Yield[a](%) (anti/syn)[b]	% ee[c]
1[d]	**3b**: R^3 = Me	**1b**: Ar = 2,6-$F_2C_6H_3$	**4b**	91 (92:8)	42
2[e]	**3b**: R^3 = Me	**1g**: Ar = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$	**5b**	92 (89:11)	95
3[d]	**3c**: R^3 = *i*-Pr	**1b**: Ar = 2,6-$F_2C_6H_3$	**4c**	77 (>99:1)	75
4[e]	**3c**: R^3 = *i*-Pr	**1g**: Ar = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$	**5c**	99 (>99:1)	74

[a]Isolated yield. [b]Diastereomeric ratio was determined by ^{1}H NMR analysis. [c]Enantiomeric excess of major *anti*-**4**,**5** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H or Chiralpak AD-H) with hexane/2-propanol (volume ratio = 50:1) as a solvent. [d]Reaction was carried out in THF. [e]Reaction was carried out in CH_2Cl_2.

Table 3. Diastereo- and enantioselective synthesis of 3,4-dihydropyran-2-ones by using catalysts **1b** or **1g**



Entry	R^1	R^2	Catalyst	Product	Yield[a](%) (anti/syn)[b]	% ee[c]
1[d]	Ph	4-MeO–C_6H_4	**1b**: Ar = 2,6-$F_2C_6H_3$	**4d**	99 (>99:1)	58
2[d]	4-MeO–C_6H_4	Ph		**4e**	97 (97:3)	62
3[d]	Ph	4-F–C_6H_4		**4f**	97 (97:3)	57
4[d]	4-F–C_6H_4	Ph		**4g**	95 (91:9)	34
5[d]	Ph	Me		**4h**	99 (97:3)	29
6[d]	Ph	*i*-Pr		**4i**	99 (86:14)	11
7[e]	Ph	4-MeO–C_6H_4	**1g**: Ar = 3,5-[3,5-$(CF_3)_2$–C_6H_3]$_2C_6H_3$	**5d**	99 (97:3)	92
8[e]	4-MeO–C_6H_4	Ph		**5e**	99 (97:3)	90
9[e]	Ph	4-F–C_6H_4		**5f**	99 (90:10)	71
10[e]	4-F–C_6H_4	Ph		**5g**	87 (85:15)	72
11[e]	Ph	Me		**5h**	99 (>99:1)	81
12[e]	Ph	*i*-Pr		**5i**	99 (>99:1)	69

[a]Isolated yield. [b]Diastereomeric ratio was determined by ^{1}H NMR analysis. [c]Enantiomeric excess of major *anti*-**4**,**5** was determined by HPLC analysis using a chiralcolumn (DAICEL Chiralcel OD-H or Chiralpak AS-H) with hexane/2-propanol (volume ratio = 50:1) as a solvent. [d]Reaction was carried out in THF. [e]Reaction was carried out in CH_2Cl_2.

Next, the effect of alkyl substituents (R^3) contained in TMS enolates was examined (Table 2). When the catalyst **1b** was used in THF, the use of sterically hindered TMS enolates **3c** (R^3 = *i*-Pr) enhanced the enantioselectivity (*anti*-**4c** = 75% ee) (Entry 3). On the other hand, the enantiomeric excess of *anti*-**5b** increased up to 95% ee when less hindered TMS enolate **3b** (R^3 = Me) was used in CH_2Cl_2 in the presence of a catalyst **1g** (Entry 2). It was consequently found that the alkyl substituents (R^3) contained in TMS enolates played important roles in controlling enantioselectivities of this asymmetric reaction. Actually, the enantioselecivity was improved by using TMS enolates with more bulky R^3 substituents in the presence of a catalyst **1b**. Furthermore, the enantioselectivity in the case of using a catalyst **1g** was enhanced with less hindered TMS enolate.

Then, reactions of TMS enolate **3a** with various α,β-unsaturated ketones **2** were tried in the presence of 10 mol % cinconidine-derived catalysts **1b** or **1g** in THF or in CH_2Cl_2 at $-78\,^\circ$C for 1 h (Table 3).[4] The enantioselectivities decreased concerning when alkyl-substituted α,β-unsaturated ketones **2** was used in the presence of a catalyst **1b** (Entries 5 and 6). On the other hand, it increased when a catalyst **1g** was used in the reaction with α,β-unsaturated ketones **2** having an electron-donating substitutent such as a 4-methoxyphenyl group (Entries 7 and 8).

Thus, the chiral catalysts functioned in reverse enantiofacial selectivities through examining the effect of substituents on the bridgehead nitrogen of cinchonidine in Michael addition and lactonization between silyl enolates and α,β-unsaturated ketones. Further investigation to explain the reaction mechanism is now in progress.

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References and Notes

1 a) T. Tozawa, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 56. b) T. Tozawa, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 360.

2 For the preparation and X-ray crystallographic analysis of quaternary ammonium *p*-nitrophenoxide, see: E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414.

3 Structural assignment of diastereomeric 3,4-dihydropyran-2-ones was based on the ^{1}H NMR chemical shift of the characteristic vinyl proton, which resonates at a lower magnetic field in the cis isomer than in the trans isomer. see: T. Tozawa, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 514.

4 Typical experimental procedure for the preparation of **5** is shown in the following (Table 3, Entry 7): To a stirred solution of **1g** (27.1 mg, 0.03 mmol) in CH_2Cl_2 (0.6 mL) were successively added a solution of 4-methoxychalcone (71.5 mg, 0.3 mmol) in CH_2Cl_2 (0.8 mL) and a solution of TMS enolate **3a** (113.3 mg, 0.48 mmol) at $-78\,^\circ$C. After the mixture was stirred for 1 h at the same temperature, it was quenched with 1 M HCl (aq) and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by preparative TLC (hexane/EtOAc = 5/1) to give *anti*-3,4-dihydropyran-2-one (**5d**) (92.0 mg, 99%, 92% ee) as a coloress oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68–7.65 (m, 2H), 7.40–7.36 (m, 3H), 7.15 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 5.83 (d, J = 4.6 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, J = 7.2 Hz, 4.6 Hz, 1H), 2.70 (dd, J = 12.9 Hz, 7.2 Hz, 1H), 1.77–1.67 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H). The enantiomeric excess was determined by HPLC analysis using DAICEL Chiralcel OD-H, hexane/2-propanol = 50/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 15.1 min (major) and 17.3 min (minor).

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