Diastereo- and Enantioselective Tandem Michael Addition and Lactonization between Silyl Enolates and α,β-Unsaturated Ketones Catalyzed by a Chiral Quaternary Ammonium Phenoxide

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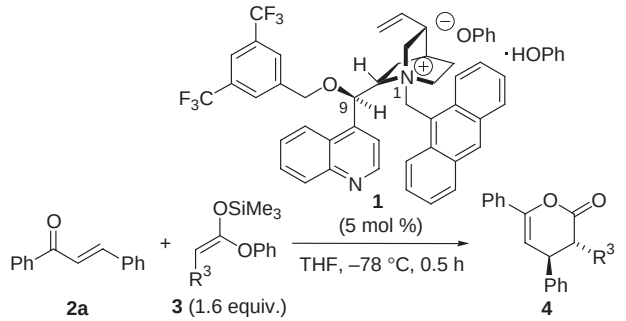
Diastereo- and enantioselective tandem Michael addition and lactonization between various silyl enolates derived from phenyl carboxylates and α,β-unsaturated ketones were successfully carried out by using an efficient organic catalyst, a cinchonidine-derived chiral quaternary ammonium phenoxide. In this asymmetric tandem reaction, the corresponding *trans*-3,4-dihydropyran-2-ones were obtained in high yields with almost complete diastereoselectivities and good to excellent enantioselectivities.

In our preceding paper, it was shown that novel types of chiral quaternary ammonium phenoxides were prepared readily from commercially available cinchona alkaloids and were thus proved to be useful new asymmetric catalysts.[1] Of the chiral quaternary ammonium phenoxides, cinchonidine-derived catalyst **1** that possessed both a sterically hindered N(1)–9-anthracenylmethyl group and a strongly electron-withdrawing C(9)–*O*-3,5-bis(trifluoromethyl)benzyl group was found extraordinarily effective for Michael addition and successive lactonization between a silyl enolate derived from phenyl isobutyrate and α,β-unsaturated ketones, which afforded optically active 3,4-dihydropyran-2-ones in high yields with high enantioselectivities.[2]

Table 1. Reactions of chalcone **2a** with various silyl enolates **3** in the presence of cinchonidine-derived catalyst **1**



2a **3** (1.6 equiv.) **4**

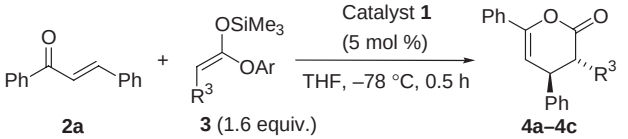
Entry	Silyl enolate[a]	Product	Yield[b]/%	*trans*/*cis*[c]	% ee[d]
1	**3a**: R^3 = Me	**4a**	91	92:8	25 (75[e])
2	**3b**: R^3 = Et	**4b**	99	99:1	67
3	**3c**: R^3 = *i*-Bu	**4c**	96	99:1	76
4	**3d**: R^3 = *i*-Pr	**4d**	99	>99:1	96
5[f,g]	**3e**: R^3 = *t*-Bu	**4e**	96	>99:1	96

[a]*E*/*Z* = >95:5. [b]Isolated yield. [c]Diastereomeric ratio was determined by ^{1}H NMR analysis. [d]Enantiomeric excess of the major *trans*-**4** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane/2-propanol (volume ratio = 50:1) as a solvent. [e]Enantiomeric excess of the minor *cis*-**4a**. [f]Catalyst (10 mol %) was used. [g]Reaction was carried out at −78 °C for 0.5 h, and then the reaction mixture was gradually warmed up to rt.

To explore further potential of this asymmetric reaction, diastereochemistry of the two newly created adjacent carbon centers was studied in detail. In this communication, we would like to report on highly diastereo- and enantioselective synthesis of 3,4-dihydropyran-2-ones by way of chiral quaternary ammonium phenoxide-catalyzed tandem Michael addition and lactonization between various silyl enolates derived from phenyl carboxylates and α,β-unsaturated ketones.

In the first place, reactions of chalcone **2a** with various (*E*)-trimethylsilyl (TMS) enolates **3a**–**3e** derived from phenyl carboxylates were tried in THF at −78 °C by using 5 mol % of cinchonidine-derived catalyst **1** to examine stereochemical behavior of the alkyl substituents (R^3) contained in TMS enolates (Table 1). When TMS enolate **3a** (R^3 = Me) derived from phenyl propionate was used, Michael addition and successive lactonization proceeded smoothly to afford the corresponding 3,4-dihydropyran-2-one **4a** in 91% yield with high *trans*-selectivity (*trans*/*cis* = 92:8)[3] although the enantioselectivity of the major *trans*-isomer turned out to be poor (25% ee) (Entry 1). Next, it was observed that the use of TMS enolate **3b** (R^3 = Et) derived from phenyl *n*-butyrate enhanced both diastereo- and enantioselectivities and the desired product **4b** was obtained quantitatively with excellent *trans*-selectivity (*trans*/*cis* = 99:1) and 67% ee (*trans*-isomer) (Entry 2). Significantly, the reactions that used more sterically-hindered TMS enolates, **3d** (R^3 = *i*-Pr) and **3e** (R^3 = *t*-Bu), produced the corresponding 3,4-dihydropyran-2-ones, **4d** and **4e**, in excellent yields with almost complete stereo-

Table 2. Effects of aryl substituents (Ar)



2a **3** (1.6 equiv.) **4a–4c**

Entry	Silyl enolate[a]		Yield[b]/%	*trans*/*cis*[c]	% ee[d]
1	**3b**: Ar = Ph	R^3 = Et	99	99:1	67
2	**3f**: Ar = 4-F-C_6H_4		99	95:5	59
3	**3g**: Ar = 4-MeO-C_6H_4		95	99:1	38
4	**3h**: Ar = 2-Naphthyl		93	98:2	55
5	**3i**: Ar = 1-Naphthyl		84	>99:1	70
6	**3j**: Ar = 2-*i*-Pr-C_6H_4		95	>99:1	76
7[e]	**3j**: Ar = 2-*i*-Pr-C_6H_4		99	>99:1	84
8	**3a**: Ar = Ph	R^3 = Me	91	92:8	25
9[e]	**3k**: Ar = 2-*i*-Pr-C_6H_4		93	98:2	57
10	**3c**: Ar = Ph	R^3 = *i*-Bu	96	99:1	76
11[e]	**3l**: Ar = 2-*i*-Pr-C_6H_4		99	>99:1	88

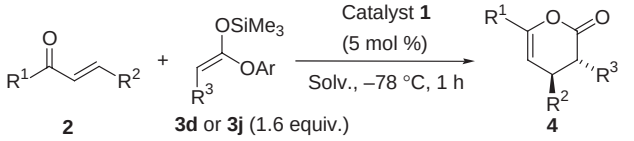
[a]*E*/*Z* = >95:5. [b]Isolated yield. [c]Diastereomeric ratio was determined by ^{1}H NMR analysis. [d]Enantiomeric excess of the major *trans*-**4** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane/2-propanol (volume ratio = 50:1) as a solvent. [e]Reaction was carried out in toluene–CH_2Cl_2 (volume ratio = 1:1).

chemical control (*trans*/*cis* = >99:1, 96% ee) (Entries 4 and 5). It was consequently revealed that the alkyl substituents (R^3) contained in TMS enolates played important roles in controlling both diastereo- and enantioselectivities of this asymmetric reaction and therefore stereoselectivities improved as bulkiness of R^3 increased.

In order to further improve stereoselectivities of the above-mentioned reactions particularly with the TMS enolates having relatively small alkyl substituents (R^3), effects of aryl substituents (Ar) contained in the TMS enolates were investigated next (Table 2). Then, for the initial screening of the TMS enolates (R^3 = Et), electronic tuning of aryl substituents was tried. The use of TMS enolates having an electron-withdrawing substituent such as a 4-fluorophenyl group (**3f**) or an electron-donating substituent such as a 4-methoxyphenyl group (**3g**) was found to cause a decrease in the enantioselectivities of the desired product **4b** (Entries 2 and 3). On the other hand, steric modification by introducing sterically hindered aryl substituents such as a 1-naphthyl group (**3i**) or a 2-isopropylphenyl group (**3j**) in place of a simple phenyl group enhanced the enantioselectivities, and *trans*-**4b** was obtained in 95% yield with 76% ee if TMS enolate **3j** (R^3 = Et, Ar = 2-*i*-Pr-C_6H_4) was used (Entry 6). In addition, the enantiomeric excess of *trans*-**4b** increased up to 84% ee when the reaction was carried out in a mixture of toluene and CH_2Cl_2 (volume ratio = 1:1) as a solvent (Entry 7). It was also found that the use of TMS enolates, **3k** (R^3 = Me, Ar = 2-*i*-Pr-C_6H_4) and **3l** (R^3 = *i*-Bu, Ar = 2-*i*-Pr-C_6H_4), improved the stereoselectivities and gave the corresponding 3,4-dihydropyran-2-ones, **4a** and **4c**, with excellent *trans*-selectivities and appreciable enantioselectivities (Entries 9 and 11).

Next, reactions of TMS enolates, **3d** (R^3 = *i*-Pr, Ar = Ph) and **3j** (R^3 = Et, Ar = 2-*i*-Pr-C_6H_4), with various α,β-unsaturated ketones **2** were tried by using 5 mol % of cinchonidine-derived catalyst **1** in THF or in toluene–CH_2Cl_2 (volume ratio = 1:1) at −78 °C (Table 3).[4] In most cases, the reactions proceeded smoothly to provide the corresponding 3,4-dihydropyran-2-ones (**4**) in high yields with almost complete *trans*-selectivities and high to excellent enantioselectivities.

Table 3. Diastereo- and enantioselective synthesis of 3,4-dihydropyran-2-ones by using cinchonidine-derived catalyst **1**



2 **3d** or **3j** (1.6 equiv.) **4**

Entry	R^1	R^2	R^3	Product	Yield[a]/% (*trans*/*cis*)[b]	% ee[c]
1[d]	Ph	4-F-C_6H_4	*i*-Pr	**4f**	98 (>99:1)	95
2[d]	4-F-C_6H_4	Ph	(**3d**)	**4g**	92 (>99:1)	94
3[d]	Ph	4-MeO-C_6H_4		**4h**	93 (>99:1)	94
4[d]	4-MeO-C_6H_4	Ph		**4i**	94 (>99:1)	97
5[d]	4-MeO-C_6H_4	4-Br-C_6H_4		**4j**	98 (>99:1)	95
6[d]	4-Br-C_6H_4	4-MeO-C_6H_4		**4k**	94 (>99:1)	92
7[e]	Ph	4-MeO-C_6H_4	Et	**4l**	95 (>99:1)	85
8[e]	4-MeO-C_6H_4	Ph	(**3j**)	**4m**	97 (>99:1)	87
9[e]	PhCH=CH	Ph		**4n**	87 (97:3)	86

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

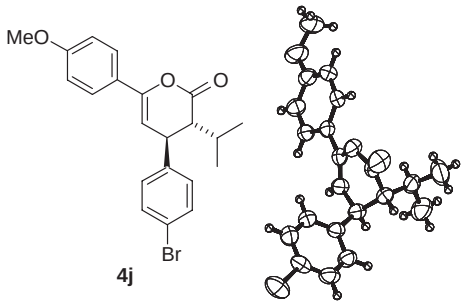


Figure 1. ORTEP drawing of compound **4j**.

Relative and absolute configurations at the two newly created adjacent carbon centers of compound **4j** were clearly identified by X-ray crystallographic analysis (Figure 1).[5]

Thus, highly efficient asymmetric tandem Michael addition and lactonization between various silyl enolates derived from phenyl carboxylates and α,β-unsaturated ketones were achieved in excellent stereochemical control by using cinchonidine-derived chiral quaternary ammonium phenoxide **1** as a catalyst. Detailed investigations on the mechanism as well as on the scope and limitations of the present asymmetric system are currently being conducted in our laboratory.

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References and Notes

1 T. Tozawa, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 56.
2 Catalyst **1** was obtained as a quaternary ammonium phenoxide–phenol complex [$R_4N^+ \cdot C_6H_5O^- \cdot C_6H_5OH$], which was assigned by ^{1}H NMR analysis and elemental analysis (see Ref. 1).
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 **4** is shown in the following (Table 1, Entry 4): To a stirred solution of **1** (13.5 mg, 0.015 mmol) in THF (0.6 mL) were successively added a solution of chalcone **2a** (62.5 mg, 0.3 mmol) in THF (0.8 mL) and a solution of TMS enolate **3d** (120 mg, 0.48 mmol) in THF (0.6 mL) at −78 °C. After the mixture was stirred for 0.5 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 to give *trans*-3,4-dihydropyran-2-one (**4d**) (87.0 mg, 99%, 96% ee). $[\alpha]_D^{21}$ = +188.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.70–7.66 (m, 2H), 7.42–7.16 (m, 8H), 5.86 (d, *J* = 5.9 Hz, 1H), 3.81 (dd, *J* = 5.9, 3.2 Hz, 1H), 2.55 (dd, *J* = 7.6, 3.2 Hz, 1H), 2.08–1.96 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 168.9, 149.8, 141.3, 132.0, 129.0, 128.9, 128.4, 127.2, 127.0, 124.5, 101.9, 54.3, 41.2, 29.1, 21.1, 20.1. The enantiomeric excess was determined by HPLC analysis using a DAICEL Chiralpak AD-H, hexane/2-propanol = 50/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 15.0 min (major) and 16.7 min (minor).
5 Compound **4j** was recrystallized from hexane/CH_2Cl_2. Crystal data: $C_{21}H_{21}BrO_3$ (FW = 401.30), orthorhombic, $P2_12_12_1$, a = 12.375(2), b = 18.007(1), c = 8.4329(9) Å, V = 1879.2(3) Å^3, Z = 4, D_{calcd} = 1.418 g cm^{-3}, T = 298 K. X-ray intensities were measured on a Rigaku AFC7R diffractometer with Cu Kα radiation (λ = 1.54178 Å), R = 0.030.

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