Enantioselective Synthesis of 3,4-Dihydropyran-2-ones by Chiral Quaternary Ammonium Phenoxide-catalyzed Tandem Michael Addition and Lactonization

Takashi Tozawa, Yoshinobu Yamane, and Teruaki Mukaiyama*
Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003
Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641

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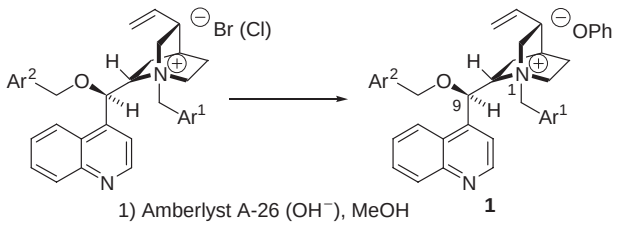
Chiral quaternary ammonium phenoxides derived from cinchona alkaloids were easily synthesized and were effectively employed in the tandem Michael addition and lactonization between α,β-unsaturated ketones and a silyl enolate derived from phenyl isobutyrate, and optically active 3,4-dihydropyran-2-ones were afforded in high yields with high enantiomeric excesses.

It was recently reported from our laboratory that a convenient one-pot preparation of 3,4-dihydropyran-2-ones was achieved by Michael addition and successive lactonization between various α,β-unsaturated ketones and silyl enolates derived from phenyl carboxylates in the presence of a catalytic amount of tetrabutylammonium phenoxide.[1] In this reaction, a phenoxy group contained in the silyl enolate behaves as an effective leaving group to facilitate intramolecular cyclization of in situ formed Michael-adduct, and the liberated phenoxide ion works also as a Lewis base catalyst to activate the silyl enolate. In order to further demonstrate the synthetic utility and versatility of the phenoxide ion-catalyzed tandem Michael addition and lactonization, enantioselective synthesis of 3,4-dihydropyran-2-one derivatives by using chiral quaternary ammonium phenoxides was planned. Chiral quaternary ammonium halides have been widely employed as catalysts in synthetically useful stereoselective carbon–carbon bond forming reactions and many excellent catalytic asymmetric reactions have been developed in accordance with the advancement of new effective catalysts.[2] However, usefulness of the chiral quaternary ammonium phenoxides in synthetic reactions has not been fully investigated yet.[3] In this communication, we would like to report on the use of chiral quaternary ammonium phenoxides in the catalytic tandem Michael addition and lactonization between α,β-unsaturated ketones and a silyl enolate derived from phenyl isobutyrate to form optically active 3,4-dihydropyran-2-one derivatives.

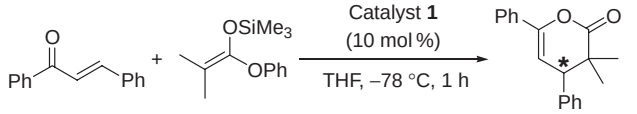
In the first place, cinchonidine, a commercially available and inexpensive reagent, was chosen as a chiral source since the quaternary ammonium halides derived from cinchona alkaloids have proved to be effective as chiral phase-transfer catalysts.[2] As shown in Scheme 1, cinchonidine-derived chiral quaternary ammonium phenoxides **1** were prepared from the quaternary ammonium halides,[3] which were first transformed into the corresponding quaternary ammonium hydroxides by an anion exchange using Amberlyst A-26 (OH^-) in methanol, and then the ammonium hydroxide intermediates were treated with phenol (1.0 equiv.). The resulted mixture was co-evaporated with benzene three times, and crystallization of the residue from diethyl ether afforded pale yellow solids, which were collected by filtration and dried under reduced pressure to give the *N*,*O*-diarylmethylated cinchonidinium phenoxides **1**.[4]



Scheme 1.

Next, reaction of chalcone **2a** with trimethylsilyl (TMS) enolate **3** was carried out in THF at −78 °C for 1 h in the presence of 10 mol % of chiral quaternary ammonium phenoxides **1** (Table 1). For the initial screening of the catalysts, effects of

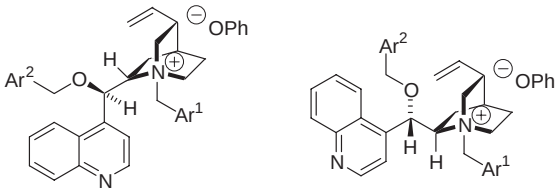
Table 1. Effects of catalysts



2a **3** (1.6 equiv.) (+)-**5a**

Entry	Catalyst	Yield[a]/%	% ee[b]
1	**1a**: Ar^1 = Ph, Ar^2 = Ph	96	2
2	**1b**: Ar^1 = 4-CF_3-C_6H_4, Ar^2 = Ph	99	4
3	**1c**: Ar^1 = 3,5-(*t*-Bu)$_2$-C_6H_3, Ar^2 = Ph	96	12
4	**1d**: Ar^1 = 1-Naphthyl, Ar^2 = Ph	93	16
5	**1e**: Ar^1 = 2-Naphthyl, Ar^2 = Ph	96	27
6	**1f**: Ar^1 = 9-Anthracenyl, Ar^2 = Ph	94	78
7[c,d]	**1f**: Ar^1 = 9-Anthracenyl, Ar^2 = Ph	12	76
8	**1g**: Ar^1 = 9-Anthracenyl, Ar^2 = 4-Me-C_6H_4	89	77
9	**1h**: Ar^1 = 9-Anthracenyl, Ar^2 = 4-MeO-C_6H_4	87	64
10	**1i**: Ar^1 = 9-Anthracenyl, Ar^2 = 4-Cl-C_6H_4	95	81
11	**1j**: Ar^1 = 9-Anthracenyl, Ar^2 = 4-NO_2-C_6H_4	96	88
12	**1k**: Ar^1 = 9-Anthracenyl, Ar^2 = 3,5-$(CF_3)_2$-C_6H_3	98	89
13[c]	**1k**: Ar^1 = 9-Anthracenyl, Ar^2 = 3,5-$(CF_3)_2$-C_6H_3	98	90
14	**1l**: Ar^1 = 9-Anthracenyl, Ar^2 = 3,5-$(CF_3)_2$-C_6H_3	96	85[e]

[a]Isolated yield. [b]Enantiomeric excess of **5a** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol as a solvent. [c]Catalyst (5 mol %) was used. [d]Reaction was carried out 6 h. [e]Opposite enantiomer (−)-**5a** was obtained.

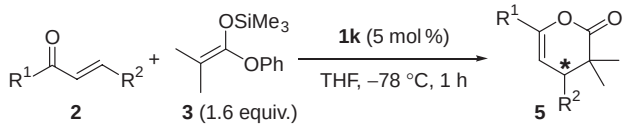


the N(1)-arylmethyl substituents (Ar^1) were examined (Entries 1–7). When the catalyst **1a** having a simple phenyl group was used, the reaction proceeded smoothly to afford the desired 3,4-dihydropyran-2-one **5a** in 96% yield, but the enantioselectivity of the product was very poor (only 2% ee) (Entry 1). Introduction of bulky substituents such as a 3,5-di-*tert*-butylphenyl group (**1c**), a 1-naphthyl group (**1d**), or a 2-naphthyl group (**1e**) to Ar^1 enhanced the enantioselectivities slightly (Entries 3–5). When the catalyst **1f** having more sterically-hindered 9-anthracenylmethyl group[3,5] at the quinuclidine nitrogen atom was employed, the enantiomeric excess of **5a** increased up to 78% ee (Entry 6). In order to further improve the enantioselectivity of this reaction, effects of the C(9)*O*-arylmethyl substituents (Ar^2) were examined next (Entries 8–13). Use of the catalysts having electron-donating substituents such as a 4-methylphenyl group (**1g**) or a 4-methoxyphenyl group (**1h**) led to a slight decrease in the enantioselectivities of **5a** (Entries 8 and 9). On the other hand, use of the catalysts having electron-withdrawing substituents such as a 4-chlorophenyl group (**1i**) or a 4-nitrophenyl group (**1j**) increased the enantioselectivities slightly (Entries 10 and 11). Further structural modification of Ar^2 by introducing a strongly electron-withdrawing 3,5-bis(trifluoromethyl)phenyl group (**1k**) improved not only the enantioselectivity but also the catalytic activity, and **5a** was obtained in 98% yield with 90% ee even when the amount of the catalyst was reduced to 5 mol % (Entry 13). It was also found that the opposite enantiomer of the 3,4-dihydropyran-2-one was accessible if the pseudoenantiomeric cinchonine-derived catalyst **1l** was used (Entry 14).

Then, reactions of TMS enolate **3** with various α,β-unsaturated ketones **2** were tried by using 5 mol % of cinchonidine-derived catalyst **1k** [Ar^1 = 9-anthracenyl, Ar^2 = 3,5-bis(trifluoromethyl)phenyl][6] in THF at −78 °C (Table 2).[7] In most cases, the reactions proceeded smoothly to provide the corresponding 3,4-dihydropyran-2-ones **5** in high yields with high enantiomeric excesses.

Thus, a new and efficient method for the synthesis of optically active 3,4-dihydropyran-2-one derivatives was established by the tandem Michael addition and lactonization between α,β-unsaturated ketones and a silyl enolate derived from phenyl isobutyrate in the presence of a catalytic amount of cinchona alkaloid-derived chiral quaternary ammonium phenoxides. Further investigation on this type of asymmetric reactions is now in progress.

Table 2. Enantioselective synthesis of 3,4-dihydropyran-2-ones by using cinchonidine-derived catalyst **1k**



2 **3** (1.6 equiv.) **5**

Entry	R^1	R^2	Yield[a]/%	% ee[b]	$[\alpha]_D$[c]
1	Ph	Ph	98	90	+182
2	Ph	4-F-C_6H_4	98	84[d]	+150
3	4-F-C_6H_4	Ph	94	82[d]	+149
4	Ph	4-MeO-C_6H_4	98	96	+153
5	4-MeO-C_6H_4	Ph	98	95[d]	+157
6	4-MeO-C_6H_4	4-Br-C_6H_4	95	88	+107
7	4-Br-C_6H_4	4-MeO-C_6H_4	98	89	+109
8	Ph	Me	86	95	+64
9	Ph	*i*-Pr	98	93	+138

[a]Isolated yield. [b]Enantiomeric excess of **5** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol as a solvent. [c]c = 1.00, $CHCl_3$. [d]Enantiomeric excess of **5** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel AD-H) with hexane/2-propanol as a solvent.

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References and Notes

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4 Catalyst **1k** was obtained as a quaternary ammonium phenoxide–phenol complex [$R_4N^+ \cdot C_6H_5O^- \cdot C_6H_5OH$],[8] which was assigned by ^{1}H NMR analysis and elemental analysis.
5 B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595.
6 Preparation of cinchonidine-derived catalyst **1k** is shown in the following (Scheme 1 and Table 1, Entry 13): To a stirred solution of *N*-(9-anthracenylmethyl)-*O*-[3,5-bis(trifluoromethyl)benzyl]cinchonidinium bromide[9] (1.0 g, 1.26 mmol) in methanol (10 mL) was added ion-exchange resin Amberlyst A-26 (OH^-) (1.0 g) at room temperature. The mixture was stirred for 10 h at the same temperature, filtered, and washed with methanol. To the filtrate was added phenol (119 mg, 1.26 mmol) and the resulted mixture was co-evaporated with benzene three times. Crystallization of the residue from diethyl ether afforded a pale yellow solid, which was collected by filtration and dried under reduced pressure to form **1k**[4] (0.49 g). This reagent can be handled in the air and stored in a sealed bottle without decomposition for over one month at room temperature. $[\alpha]_D^{29} = -97.2$ (c 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, CD_3OD) δ 9.02 (d, J = 4.3 Hz, 1H), 8.88 (s, 1H), 8.64 (d, J = 9.2 Hz, 1H), 8.56–8.51 (m, 1H), 8.31–7.89 (m, 11H), 7.79 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.15 (br s, 1H), 7.00 (t, J = 7.3 Hz, 4H), 6.65 (d, J = 7.3 Hz, 4H), 6.54 (t, J = 7.3 Hz, 2H), 6.45 (d, J = 13.8 Hz, 1H), 5.85 (d, J = 13.8 Hz, 1H), 5.73–5.59 (m, 1H), 5.24 (d, J = 12.4 Hz, 1H), 5.12 (d, J = 12.4 Hz, 1H), 5.01–4.90 (m, 2H), 4.50–4.29 (m, 2H), 3.71–3.60 (m, 1H), 3.21 (t, J = 11.6 Hz, 1H), 2.98–2.84 (m, 1H), 2.70–2.59 (m, 1H), 2.44–2.36 (m, 1H), 2.20–2.08 (m, 1H), 2.00–1.97 (m, 1H), 1.79–1.58 (m, 2H); Anal. Calcd for $C_{49}H_{42}F_6N_2O_2 \cdot C_6H_5OH$: C, 73.48; H, 5.38; N, 3.12%. Found: C, 73.42; H, 5.45; N, 3.06%.
7 Typical experimental procedure for the preparation of **5** is shown in the following (Table 2, Entry 1): To a stirred solution of **1k** (13.5 mg, 0.015 mmol) in THF (1.0 mL) were successively added a solution of chalcone **2a** (62.5 mg, 0.3 mmol) in THF (1.4 mL) and a solution of TMS enolate **3** (113 mg, 0.48 mmol) in THF (0.6 mL) at −78 °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 to give the corresponding **5a** (82.0 mg, 98%, 90% ee). $[\alpha]_D^{25} = +182.3$ (c 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, J = 5.4 Hz, 2H), 7.39–7.14 (m, 8H), 5.93 (d, J = 5.4 Hz, 1H), 3.49 (d, J = 5.4 Hz, 1H), 1.43 (s, 3H), 1.04 (s, 3H). The enantiomeric excess was determined by HPLC analysis using a DAICEL Chiralcel OD-H, hexane/2-propanol = 50/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 9.6 min (minor) and 11.2 min (major).
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9 *N*-(9-anthracenylmethyl)-*O*-[3,5-bis(trifluoromethyl)benzyl]cinchonidinium bromide was prepared according to the reported procedure (see Ref. 3).

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