Binaphthyl-Modified Quaternary Phosphonium Salts as Chiral Phase Transfer Catalysts: Application to Asymmetric Amination of β-Keto Esters

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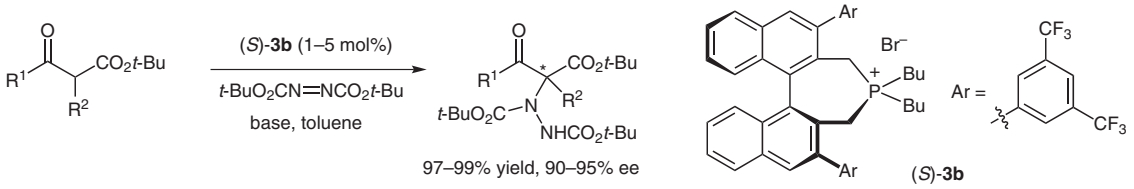
Abstract: A chiral quaternary tetraalkylphosphonium salt has been successfully utilized for the first time as a phase-transfer catalyst for asymmetric amination of β-keto esters in high yield with high ee. Asymmetric amination of a cyclic five-membered β-keto ester is a valuable method for preparing a key intermediate for asymmetric synthesis of aldose reductase inhibitor AS-3201 (Ranirestat).

Key words: amination, asymmetric synthesis, phase-transfer catalysis, phosphonium salts



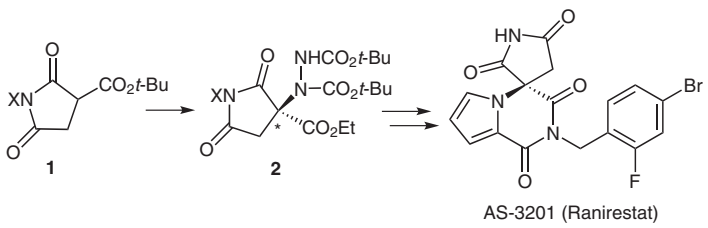
Scheme 1 Asymmetric amination of β-keto esters

Introduction

In contrast to the broad synthetic utility of chiral quaternary tetraalkylammonium salts in asymmetric phase-transfer catalysis,[1,2] chiral quaternary tetraalkylphosphonium salts have not been regarded as reliable phase-transfer catalysts due to the facile formation of the corresponding ylides (Wittig reagents) under basic conditions.[3] Indeed, catalytic asymmetric synthesis utilizing chiral quaternary tetraalkylphosphonium salts as phase-transfer catalysts remains poorly studied, and only a few special examples have been reported so far with limited success.[1d,4] In this context, we were interested in the possibility of using certain chiral quaternary phosphonium salts in asymmetric phase-transfer catalysis. Here we wish to report a first example on this subject by the successful application to asymmetric amination of β-keto esters.[5,6] Such an asymmetric transformation of cyclic five-membered β-keto ester **1** is quite valuable to prepare a key intermediate **2** for asymmetric synthesis of aldose reductase inhibitor AS-3201 (Ranirestat) as shown in Scheme 2.[7]

We employed a binaphthyl structure as a basic chiral unit and first prepared the C_2-symmetric chiral quaternary tetraalkylphosphonium bromide of type (*S*)-**3a** from the axially chiral dibromide (*S*)-**4a** (Scheme 3).

The potential of the catalyst was evaluated in the asymmetric phase-transfer amination of *tert*-butyl 1-oxo-2-indanecarboxylate (**5**) using di-*tert*-butyl azodicarboxylate (1.2 equiv) in toluene under basic conditions, giving the corresponding amination product **6** (Scheme 4).



Scheme 2 Projected synthesis of Ranirestat

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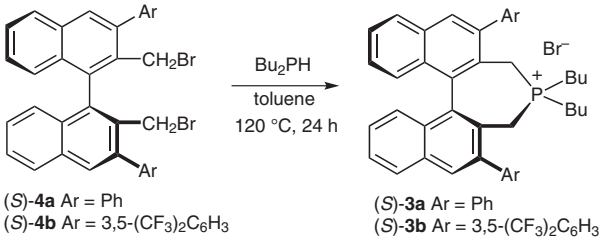
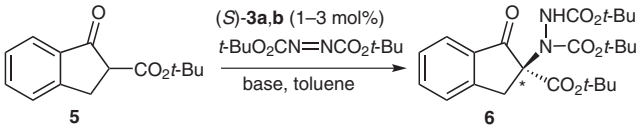


Scheme 3 Synthesis of chiral quaternary phosphonium salts



Scheme 4

Scope and Limitations

After some preliminary experiments, an enantiomeric excess of more than 90% ee was attained by using 1 equivalent of β-keto ester and 1.2 equivalents of di-*tert*-butyl azodicarboxylate in the presence of 3 mol% of catalyst (*S*)-**3b** and 1 equivalent of K_2HPO_4 at –20 °C in toluene.

With the optimal reaction conditions at hand, we further studied the generality of the asymmetric amination of several five-membered cyclic β-keto esters under the influence of chiral quaternary tetraalkylphosphonium bromide (*S*)-**3b** as shown in Scheme 1 and Table 1. Electronic effect on the aromatic moiety in *tert*-butyl indanecarboxylate **5** was found to be not so sensitive on the enantioselectivity (entries 1–4). In general, use of K_2CO_3 lowered the enantioselectivity. Notably, optically active amination product **2** (X = CO_2t-Bu) derived from β-keto ester **1** (X = CO_2t-Bu) is a key intermediate for aldose reductase inhibitor AS-3201 (entries 10 and 11).[7] Asymmetric amination of functionalized acyclic β-keto ester **10** and six-membered cyclic β-diketone **11** appears feasible (entries 12–14).

In conclusion, we have succeeded in designing a new, chiral quaternary tetraalkylphosphonium bromide as phase-transfer catalyst to realize the asymmetric amination of cyclic β-keto esters and β-diketones. To the best of our knowledge, this is the first successful example employing chiral quaternary tetraalkylphosphonium bromide as a reliable phase-transfer catalyst in asymmetric synthesis.

Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8200A spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were measured on a Jeol JNM-FX400 NMR instrument. High-performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel CHIRALPAK AD-H, or OD-H, 4.6 mm × 25 mm column. High-resolution mass spectra (HRMS) were performed on a Bruker micrOTOF focus–KR. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter. All simple chemicals were purchased and used as received.

Quaternary Phosphonium Salts (*S*)-3a and (*S*)-3b; Phosphonium Salt 3b; Typical Procedure

A mixture of (*S*)-**4b**[8] (0.490 g, 0.567 mmol, 1 equiv) and dibutylphosphine[9] (as a 0.12 M solution in Et_2O, 15 mL, 1.701 mmol, 3 equiv) in toluene (15 mL) was heated at 120 °C for 24 h under argon, and then concentrated under vacuum. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 1:1, then CH_2Cl_2–MeOH, 50:1, 20:1, 10:1 as eluent) afforded (*S*)-**3b** as a white solid; yield: 0.527 g (99%); $[\alpha]_D^{27}$ –26.78 (*c* = 0.50, $CHCl_3$).

IR (ATR): 2963, 2934, 2876, 2359, 2330, 1468, 1371, 1321, 1279, 1175, 1134, 897, 847, 750, 710, 681 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.99 (m, 10 H), 7.66 (t, *J* = 7.6 Hz, 2 H), 7.45–7.41 (m, 2 H), 7.12 (d, *J* = 8.8 Hz, 2 H), 4.17 (dd, *J* = 10.0, 15.6 Hz, 2 H), 3.25 (t, *J* = 16.0 Hz, 2 H), 2.52 (q, *J* = 12.7 Hz, 2 H), 2.04 (q, *J* = 12.1 Hz, 2 H), 1.26–1.13 (m, 4 H), 0.98–0.92 (m, 2 H), 0.74–0.70 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 136.4, 136.4, 136.3, 136.3, 133.1, 133.0 (q, $J_{C\text{-}F}$ = 35 Hz), 133.0, 132.1–132.0 (m), 129.8 (br), 128.8, 128.6, 128.3, 126.5, 123.0 (q, $J_{C\text{-}F}$ = 274 Hz), 122.9, 122.9, 122.8, 122.8, 122.6–122.5 (m), 23.9 (d, $J_{C\text{-}P}$ = 5 Hz), 23.7 (d, $J_{C\text{-}P}$ = 10 Hz), 22.3 (d, $J_{C\text{-}P}$ = 48 Hz), 19.4 (dd, $J_{C\text{-}P}$ = 5, 41 Hz), 13.4 (d, $J_{C\text{-}P}$ = 2 Hz).

^{31}P NMR (160 MHz, $CDCl_3$): δ = 51.2.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{46}H_{38}F_{12}P^+$: 849.2514 ([M – Br]$^+$); found: 849.2506.

Phosphonium Salt (*S*)-3a

Yield: 99%; $[\alpha]_D^{27}$ –38.05 (*c* = 0.50, $CHCl_3$).

IR (ATR): 3055, 2959, 2928, 2872, 1493, 1464, 1449, 1400, 1248, 1229, 897, 746, 704, 658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 2 H), 8.00 (d, *J* = 8.4 Hz, 2 H), 7.60–7.54 (m, 10 H), 7.51–7.44 (m, 2 H), 7.36–7.32 (m, 2 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 4.30 (dd, *J* = 9.6, 15.6 Hz, 2 H), 3.00 (t, *J* = 16.0 Hz, 2 H), 2.37 (q, *J* = 13.3 Hz, 2 H), 1.55 (dq, *J* = 4.0, 13.7 Hz, 2 H), 1.20–1.06 (m, 4 H), 0.96–0.84 (m, 2 H), 0.68 (t, *J* = 7.6 Hz, 6 H), 0.31–0.25 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 139.3, 139.2, 136.0, 136.0, 133.3, 133.2, 131.5, 131.4, 131.0, 130.9, 129.9, 129.5, 128.5, 128.5, 128.2, 127.5, 127.5, 127.5, 126.6, 126.6, 123.5, 123.4, 23.8 (d, $J_{C\text{-}P}$ = 17 Hz), 23.3 (d, $J_{C\text{-}P}$ = 4 Hz), 21.6 (d, $J_{C\text{-}P}$ = 48 Hz), 17.8 (d, $J_{C\text{-}P}$ = 41 Hz), 13.2.

^{31}P NMR (160 MHz, $CDCl_3$): δ = 50.4.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{42}H_{42}P^+$: 577.3019 ([M – Br]$^+$); found: 577.3026.

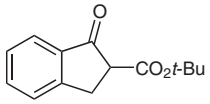
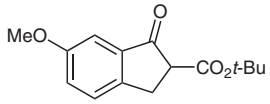
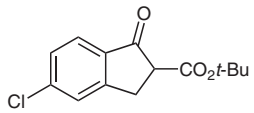
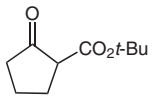
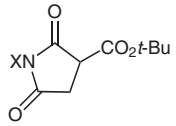
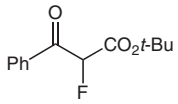
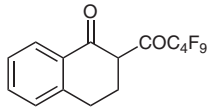
Asymmetric Amination of β-Keto Esters; Compound 6; Typical Procedure

A mixture of substrate **5** (17.4 mg, 0.075 mmol), (*S*)-**3b** (2.1 mg, 3 mol%) and K_2HPO_4 (13.0 mg, 0.075 mmol) in toluene (1 mL) was cooled to –20 °C, to which was added di-*tert*-butyl azodicarboxylate (20.7 mg, 0.09 mmol). The mixture was stirred vigorously at the same temperature for 14 h, quenched with aq sat. NH_4Cl (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography on silica gel with hexane–EtOAc (5:1) as eluent afforded **6** as a colorless oil; yield: 37.0 mg (99%); $[\alpha]_D^{22}$ +91.88 (*c* = 0.91, $CHCl_3$); 91% ee.

HPLC Analysis: Daicel Chiralpak AD-H, hexane–EtOH (9:1), flow rate: 1.0 mL/min, λ = 254 nm, t_R: 6.1 min (minor) and 8.4 min (major).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{24}H_{34}N_2O_7$ + Na^+: 485.2258 ([M + Na]$^+$); found: 485.2264.

Table 1 Asymmetric Amination of β-Keto Esters and β-Diketone with Chiral Phase-Transfer Catalyst (*S*)-**3b**[a]

Entry	Substrate	Base (equiv)	Conditions (°C, h)	Yield (%)[b]	ee (%)[c]
1	 **5**	K_2HPO_4 (1)	–20, 14	99	91
2	 **7**	K_2HPO_4 (5)	–40, 70	97	90
3		K_2CO_3 (1)	–40, 5	99	77
4	 **8**	K_2HPO_4 (1)	–20, 22	99	89
5	 **9**	K_2HPO_4 (1)	–20, 40	42	83
6		K_2HPO_4 (5)	–20, 10	99	85
7		K_2HPO_4 (5)	–40, 16	99	95
8		K_2CO_3 (1)	–20, 2	99	90
9		K_2CO_3 (1)	–40, 2	99	92
10	 **1** (X = CO_2t-Bu)	K_2HPO_4 (1)	–20, 40	99	92
11		K_2HPO_4 (5)	–20, 18	99	90
12	 **10**	K_2HPO_4 (5)	–20, 84[d]	99	73
13	 **11**	K_2HPO_4 (5)	–20, 84[e]	55	87
14		K_2HPO_4 (5)	–20, 96[d]	75	88

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of di-*tert*-butyl azodicarboxylate in the presence of 3 mol% of (*S*)-**3b** and base in toluene under the given reaction conditions.
[b] Isolated yield.
[c] Enantiopurity of the products was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H or AD-H) with hexane–*i*-PrOH or hexane–EtOH as solvent.
[d] Use of 5 mol% of (*S*)-**3b** and 10 equiv of azodicarboxylate.
[e] Use of 5 equiv of azodicarboxylate.

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