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.\(^1\)\(^d\)\(^4\) 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)-3\(a\) from the axially chiral dibromide (S)-4\(a\) (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 1  Asymmetric amination of β-keto esters

Scheme 2  Projected synthesis of Ranirestat

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Quaternary Phosphonium Salts (S)-3a and (S)-3b; Phosphonium Salt 3b; Typical Procedure
A mixture of (S)-4b (0.490 g, 0.567 mmol, 1 equiv) and dibutylphosphine (as a 0.12 M solution in Et2O, 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 CH3Cl2–MeOH, 50:1, 20:1, 10:1 as eluent) afforded (S)-3b as a white solid; yield: 0.527 g (99%); [α]D27 = –26.78 (c = 0.50, CHCl3).

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

1H NMR (400 MHz, CDCl3): δ = 8.07 – 7.99 (m, 10 H), 7.66 (t, J = 7.6 Hz, 2 H), 7.45 – 7.41 (m, 4 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).

13C NMR (100 MHz, CDCl3): δ = 141.4, 136.4, 136.4, 136.3, 136.3, 133.1, 133.0 (q, J = 35 Hz), 133.0, 132.1 – 132.0 (m, 129.8 Br), 128.8, 128.6, 128.6, 126.5, 123.0 (q, J = 274 Hz), 122.9, 122.9, 122.8, 122.8, 122.6 – 122.5 (m, 23.9 (d, J = 5 Hz), 23.7 (d, J = 10 Hz), 22.3 (d, J = 48 Hz), 19.4 (dd, J = 5, 41 Hz), 13.4 (d, J = 2 Hz).

1P NMR (160 MHz, CDCl3): δ = 51.2.

HRMS (ESI-TOF): m/z calcd for C46H38F12P+: 849.2514 ([M – Br]⁺); found: 849.2506.

Phosphonium Salt (S)-3a

Yield: 99%, [α]D27 = –38.05 (c = 0.50, CHCl3).

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

1H NMR (400 MHz, CDCl3): δ = 8.06 (s, 2 H), 8.06 (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).

13C NMR (100 MHz, CDCl3): δ = 130.9, 133.9, 133.9, 132.6, 136.0, 136.0, 133.3, 133.2, 131.5, 131.4, 130.1, 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 = 17 Hz), 23.3 (d, J = 4 Hz), 21.6 (d, J = 4 Hz), 17.8 (d, J = 41 Hz), 13.2.

1P NMR (160 MHz, CDCl3): δ = 50.4.


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 K2HPO4 (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 4 h, quenched with aq sat. NH4Cl (10 mL) and extracted with Et2O (3 × 10 mL). The combined organic layers were dried (Na2SO4) and concentrated. Purification of the residue by column chromatography on silica gel with hexane–EtOAc (5:1) gave the desired product 6 as a colorless oil; yield: 37.0 mg (99%); [α]D22 +91.88 (c = 0.91, CHCl3); 91% ee.

HPLC Analysis: Daicel Chiralpak AD-H, hexane–EtOH (9:1), flow rate: 1.0 mL/min, λ = 254 nm, 6:1 min (minor) and 8.4 min (major).

HRMS (ESI-TOF): m/z calcd for C43H38F12P2O2Na+: 826.2341 ([M + Na]⁺); found: 826.2337.

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. 1H, 13C and 31P 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.
Table 1  Asymmetric Amination of β-Keto Esters and β-Diketone with Chiral Phase-Transfer Catalyst (S)-3b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Base (equiv)</th>
<th>Conditions (°C, h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>1</td>
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<td>77</td>
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<td>89</td>
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<tr>
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<td>83</td>
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<tr>
<td>6</td>
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<tr>
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<td>88</td>
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</table>

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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References
