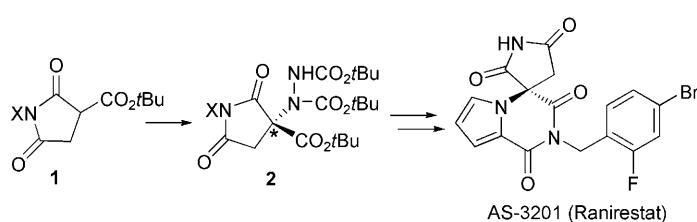


Binaphthyl-Modified Quaternary Phosphonium Salts as Chiral Phase-Transfer Catalysts: Asymmetric Amination of β -Keto Esters**

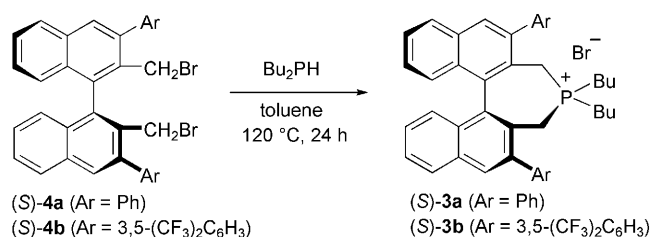
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In contrast to the broad synthetic utility of chiral quaternary tetraalkylammonium salts in asymmetric phase-transfer catalysis,^[1,2] chiral quaternary tetraalkylphosphonium salts have not been regarded as reliable phase-transfer catalysts due to 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.^[4] In this context, we are interested in using certain chiral quaternary phosphonium salts in asymmetric phase-transfer catalysis. Here we report their application in asymmetric amination of β -keto esters.^[5,6] Such an asymmetric transformation of cyclic five-membered β -keto ester **1** is valuable for preparing key intermediate **2** for asymmetric synthesis of aldose reductase inhibitor AS-3201 (Ranirestat), as shown in Scheme 1.^[7]



Scheme 1. Synthesis of Ranirestat from β -keto ester **1**.

We employed a binaphthyl structure as a basic chiral unit and first prepared C_2 -symmetric chiral quaternary tetraalkylphosphonium bromide (**S**)-**3a** from axially chiral dibromide (**S**)-**4a** (Scheme 2). Asymmetric phase-transfer amination of *tert*-butyl 1-oxo-2-indanecarboxylate (**5**) with 1 mol % of (**S**)-**3a** and di-*tert*-butyl azodicarboxylate (1.2 equiv) in toluene under basic conditions (K_2CO_3 or K_2HPO_4) at 0 °C resulted in moderate induction (0–64 % *ee*) and a quantitative yield of **6** (Table 1, entries 1 and 2). Replacing the phenyl group of



Scheme 2. Synthesis of chiral quaternary tetraalkylphosphonium bromides from axially chiral dibromides.

catalyst (**S**)-**3a** by a 3,5-bis(trifluoromethyl)phenyl group as in (**S**)-**3b** brought a moderate increase in enantiomeric excess (Table 1, entries 3–6), and use of an excess of K_2HPO_4 further enhanced the enantioselectivity (Table 1, entry 7). An enantiomeric excess of more than 90 % *ee* was finally attained by using 3 mol % of catalyst (**S**)-**3b** (Table 1, entries 9 and 10).

With the optimal reaction conditions at hand, we studied the generality of the asymmetric amination of several five-

Table 1: Asymmetric amination of β -keto ester **5** with chiral phase transfer catalyst (**S**)-**3**.^[a]

Entry	Catalyst (mol %)	Base (equiv)	Conditions [°C, h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	(S)- 3a (1)	K_2CO_3 (1)	0, 0.5	99	0
2	(S)- 3a (1)	K_2HPO_4 (1)	0, 24	99	64
3	(S)- 3b (1)	K_2CO_3 (1)	0, 0.5	99	7
4	(S)- 3b (1)	K_2CO_3 (1)	–20, 0.5	99	–20
5	(S)- 3b (1)	K_2HPO_4 (1)	0, 20	80	70
6	(S)- 3b (1)	K_2HPO_4 (1)	–20, 40	86	73
7	(S)- 3b (1)	K_2HPO_4 (5)	–20, 16	99	87
8	(S)- 3b (1)	K_2HPO_4 (5)	–40, 24	99	68
9	(S)- 3b (3)	K_2HPO_4 (1)	–20, 14	99	91
10	(S)- 3b (3)	K_2HPO_4 (5)	–20, 10	99	90

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of di-*tert*-butyl azodicarboxylate in the presence of 1–3 mol % of (**S**)-**3** and base in toluene under the given reaction conditions. [b] Yield of isolated product. [c] Enantiopurity of the products was determined by HPLC analysis on a chiral column (DAICEL Chiralcel OD-H or AD-H) with hexane/2-propanol or hexane/ethanol as solvent.

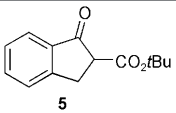
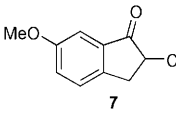
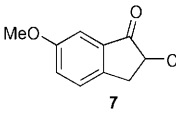
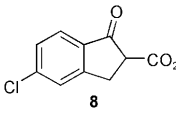
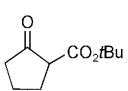
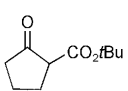
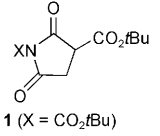
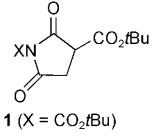
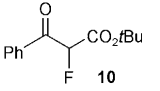
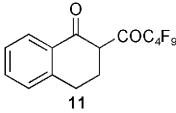
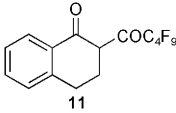
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membered cyclic β -keto esters under the influence of chiral quaternary tetraalkylphosphonium bromide (**S**)-**3b** (Table 2). The enantioselectivity was found to be relatively insensitive to the electronic effects of substituents on the aromatic ring of

Table 2: Asymmetric amination of β -keto esters and a β -diketone with chiral phase-transfer catalyst (**S**)-**3b**.^[a]

Entry	Substrate	Base (equiv)	Conditions [°C, h]	Yield [%] ^[b]	ee [%] ^[c]
1		K ₂ HPO ₄ (1)	−20, 14	99	91
2		K ₂ HPO ₄ (5)	−40, 70	97	90
3		K ₂ CO ₃ (1)	−40, 5	99	77
4		K ₂ HPO ₄ (1)	−20, 22	99	89
5		K ₂ HPO ₄ (1)	−20, 40	42	83
6		K ₂ HPO ₄ (5)	−20, 10	99	85
7		K ₂ HPO ₄ (5)	−40, 16	99	95
8		K ₂ CO ₃ (1)	−20, 2	99	90
9		K ₂ CO ₃ (1)	−40, 2	99	92
10		K ₂ HPO ₄ (1)	−20, 40	99	92
11		K ₂ HPO ₄ (5)	−20, 18	99	90
12		K ₂ HPO ₄ (5)	−20, 84 ^[d]	99	73
13		K ₂ HPO ₄ (5)	−20, 84 ^[e]	55	87
14		K ₂ HPO 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] Yield of isolated product. [c] Enantiopurity of the products was determined by HPLC analysis on a chiral column (DAICEL Chiralcel OD-H or AD-H) with hexane/2-propanol or hexane/ethanol as solvent. [d] 5 mol % of (**S**)-**3b** and 10 equiv of azodicarboxylate were used. [e] 5 equiv of azodicarboxylate were used.

tert-butyl indanecarboxylate **5** (Table 2, entries 1–4). In general, use of K₂CO₃ lowered the enantioselectivity. Notably, optically active amination product **2** (X = CO₂*t*Bu) derived from β -keto ester **1** (X = CO₂*t*Bu) is a key intermediate for aldose reductase inhibitor AS-3201 (Table 2, entries 10 and 11).^[7] Asymmetric amination of functionalized acyclic β -keto ester **10** and six-membered cyclic β -diketone **11** appears feasible (Table 2, entries 12–14).

The absolute structure of catalyst (**S**)-**3b** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).^[8] The absolute configuration of amination product

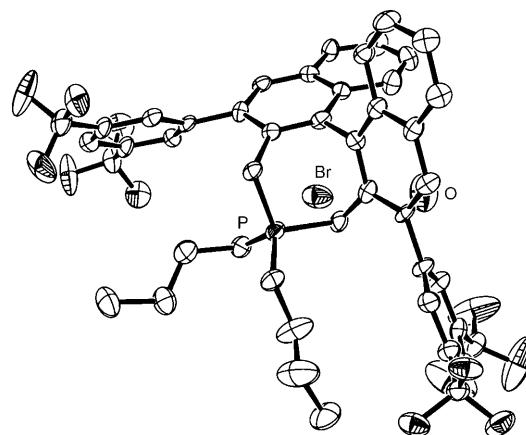
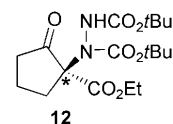


Figure 1. ORTEP diagram of catalyst (**S**)-**3b**.

12, which was prepared by asymmetric amination of ethyl 2-oxo-1-cyclopentanecarboxylate with di-*tert*-butyl azodicarboxylate in the presence of 3 mol % of (**S**)-**3b**,^[9] was firmly determined to be *S* by comparison with the optical rotation of the reported compound.^[10]

In conclusion, we have designed a new chiral quaternary tetraalkylphosphonium bromide as phase-transfer catalyst for asymmetric amination of cyclic β -keto esters and β -diketones. To the best of our knowledge, this is the first successful use of a chiral quaternary tetraalkylphosphonium bromide as phase-transfer catalyst in asymmetric synthesis.



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