Phase-Transfer Catalysis

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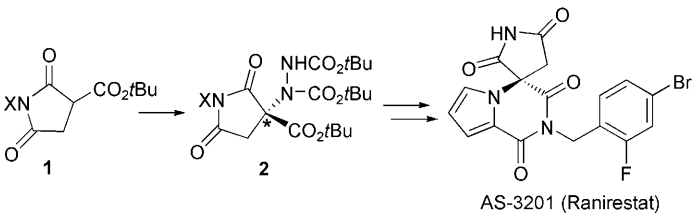
Binaphthyl-Modified Quaternary Phosphonium Salts as Chiral Phase-Transfer Catalysts: Asymmetric Amination of β-Keto Esters**

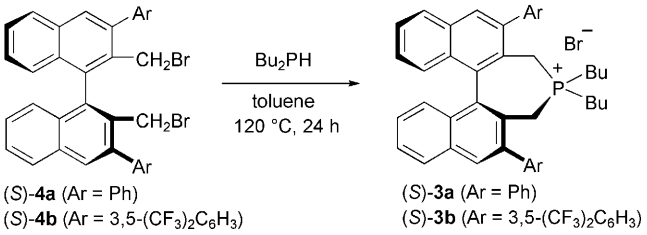
*Rongjun He, Xisheng Wang, Takuya Hashimoto, and Keiji Maruoka**

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

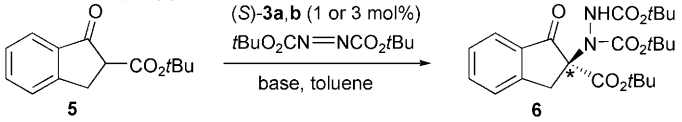


Scheme 2. Synthesis of chiral quaternary tetraalkylphosphonium bromides from axially chiral dibromides.

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]	*ee* [%][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.

[*] Dr. R. He, X. Wang, T. Hashimoto, Prof. Dr. K. Maruoka
Department of Chemistry
Graduate School of Science
Kyoto University
Sakyo, Kyoto, 606-8502, (Japan)
Fax: (+81) 75-753-4041
E-mail: maruoka@kuchem.kyoto-u.ac.jp

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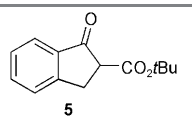
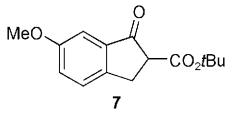
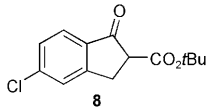
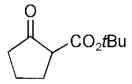
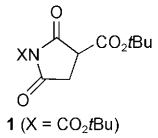
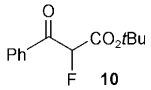
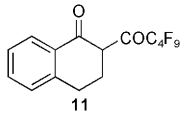
membered cyclic β-keto esters under the influence of chiral quaternary tetraalkylphosphonium bromide (*S*)-**3b** (Table 2). The enantioselectivity was found to be relatively insensitive to the electronic effects of substituents on the aromatic ring of

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	 **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_2tBu)	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] 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 K_2CO_3 lowered the enantioselectivity. Notably, optically active amination product **2** (X = CO_2tBu) derived from β-keto ester **1** (X = CO_2tBu) 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

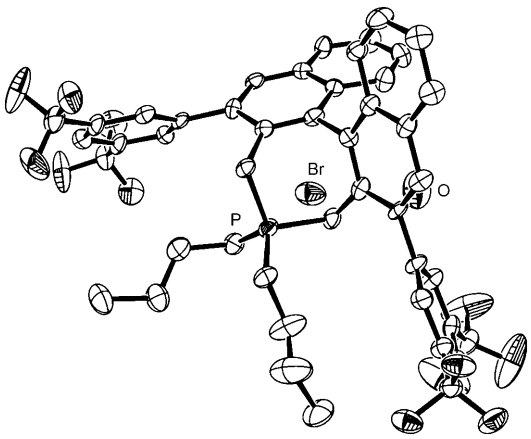
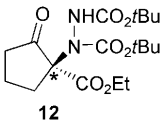


Figure 1. ORTEP diagram of catalyst (*S*)-**3b**.

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]


12

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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[8] CCDC-685327 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] Reaction conditions: di-*tert*-butyl azodicarboxylate (1.2 equiv) and K_2HPO_4 (5 equiv) in the presence of 3 mol% of (*S*)-**3b** in toluene at −20 °C for 6 h (99% yield, 73% *ee*).

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