Pergamon

Tetrahedron Letters 39 (1998) 5807–5810

TETRAHEDRON LETTERS

Asymmetric phase-transfer alkylation catalyzed by a chiral quaternary phosphonium salt with a multiple hydrogen-bonding site

Kei Manabe

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 14 May 1998; revised 1 June 1998; accepted 5 June 1998

Abstract

A chiral phosphonium salt has been synthesized as a novel phase-transfer catalyst, and used for asymmetric benzylation of *t*-butyl 2-oxocyclopentanecarboxylate to give the corresponding product with up to 50% ee.

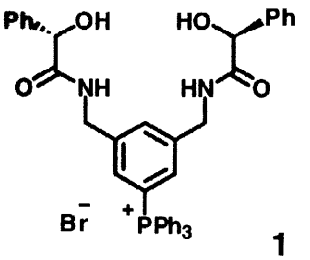
Keywords: asymmetric reactions; hydrogen bonding; phase transfer; phosphonium salts

Phase-transfer catalysis (PTC) is a very important method in synthetic organic chemistry, and has many advantages over conventional, homogeneous reaction procedures.[1-4] Although the application of chiral onium salts as catalysts to enantioselective PTC should offer attractive tools to obtain optically active compounds, there have been so far only a limited number of successful examples,[5-14] most of which use quaternary ammonium salts derived from cinchona alkaloids. In enantioselective PTC, it is essential to control the ion-pair structure composed of a chiral onium cation and a substrate anion; however, work on methodology for controlling the ion-pair structure is still in a preliminary stage. It should be desirable, therefore, to develop chiral catalysts based on a new structural concept to expand the applicability of enantioselective PTC. In the course of the research on artificial receptor molecules in this laboratory,[15] a multiple hydrogen-bonding strategy has been used for the formation of salts with well-organized geometry. The application of this strategy to the design of chiral phase-transfer catalysts would lead to a new methodology to control the ion-pair structure which affects the enantioselectivity. This paper describes the synthesis of a novel chiral phosphonium salt whose structure is designed based on a hydrogen-bonding strategy, and the application of the salt to asymmetric phase-transfer benzylation of a β-keto ester.

A chiral phosphonium salt (**1**) with two NH and two OH groups as a multiple hydrogen-bonding site was designed. This multiple hydrogen-bonding site would interact with a

0040-4039/98/$19.00
PII: S0040-4039(98)01181-2

substrate anion through hydrogen bonds and keep the anion within the asymmetric environment created by the two mandelamide units.



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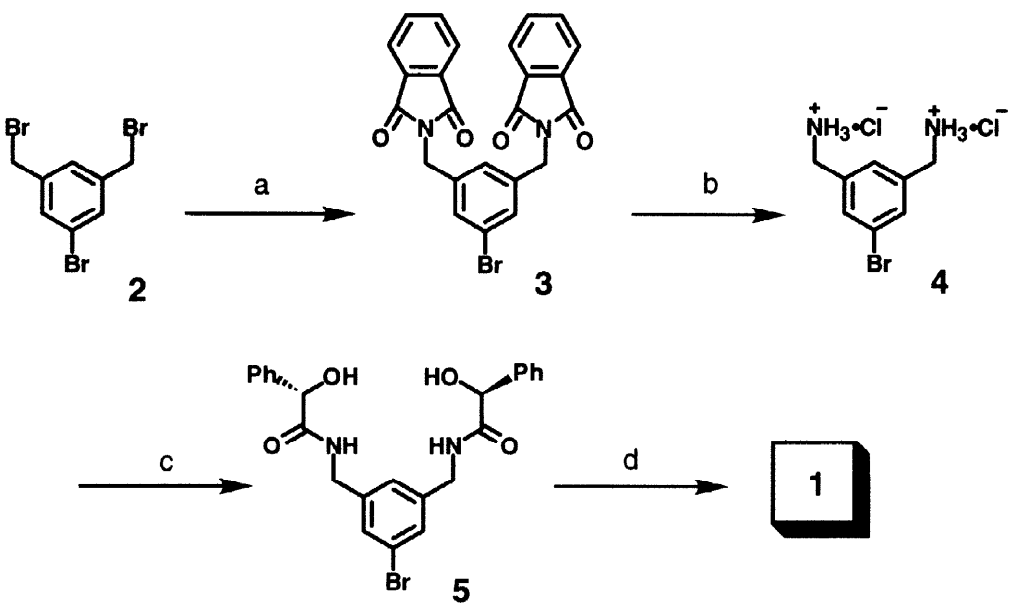
Phosphonium salt **1** was synthesized as shown below. Tribromide **2**[16] was converted to diamine hydrochloride **4** by a modified Gabriel synthesis.[17] The condensation of **4** with (*S*)-mandelic acid afforded diamide **5**, which was quaternized with triphenylphosphine in the presence of a Ni catalyst[18] to give **1**.

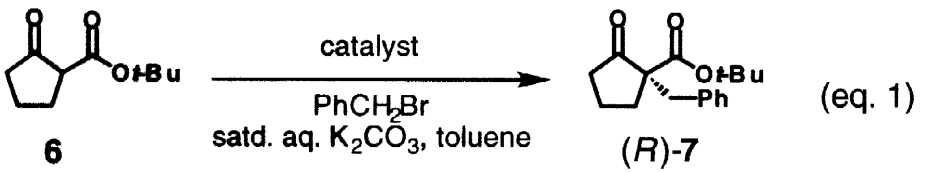
The ^{1}H NMR signal of the OH protons of diamide **5** is observed at 3.64 ppm, and that of phosphonium salt **1** at 5.05 ppm. This downfield shift of 1.41 ppm is attributable to the hydrogen bonding between the OH groups and the bromide anion of **1**. The NH protons of **1** also show a downfield shift of 1.79 ppm (6.66 ppm for **5**, 8.45 ppm for **1**), suggesting their participation in the hydrogen bonding to the bromide anion.



(a) Potassium phthalimide, hexadecyltri-*n*-butylphosphonium bromide (cat.), toluene, reflux, 80%; (b) (i) hydrazine monohydrate, EtOH, reflux; (ii) conc. HCl, MeOH, 80%; (c) (*S*)-mandelic acid, DEPC, Et_3N, DMF, rt, 77%; (d) PPh_3, $Ni(cod)_2$ (cat.), EtOH, 110 °C in a sealed tube.

Physical data for **1**: mp 118–122 °C; $[\alpha]^{27}_D$ +27.7 (c 0.448, EtOH); ^{1}H NMR ($CDCl_3$, TMS, 270 MHz) δ 4.26 (dd, J = 15.2, 5.3 Hz, 2H), 4.50 (dd, J = 15.2, 6.9 Hz, 2H), 5.05 (d, J = 5.9 Hz, 2H), 5.22 (d, J = 5.9 Hz, 2H), 7.13–7.74 (m, 24H), 7.85 (td, J = 7.6, 2.0 Hz, 3H), 7.98 (s, 1H), 8.45 (dd, J = 6.9, 5.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 42.21, 73.44, 116.40 (d, J = 89.0 Hz), 117.55 (d, J = 89.0 Hz), 126.65, 127.53, 128.09, 130.53 (d, J = 12.2 Hz), 130.84, 132.03 (d, J = 10.9 Hz), 134.34 (d, J = 9.7 Hz), 135.40, 139.96, 142.11 (d, J = 13.4 Hz), 173.80; IR (KBr) 3270, 1660, 1520, 1440, 1110 cm^{-1}; Anal. Calcd for $C_{42}H_{38}BrN_2O_4P$: C, 67.65; H, 5.14; N, 3.76. Found: C, 67.42; H, 5.25; N, 3.67.

Phosphonium salt **1** was used for benzylation of *t*-butyl 2-oxocyclopentanecarboxylate (**6**) as shown in eq. 1. Among the various bases and organic solvents tested, the combination of saturated aq. K_2CO_3 and toluene gave the best results with respect to enantioselectivity. Use of diluted aq. K_2CO_3 solutions or strong bases such as 10% NaOH resulted in a decrease of the enantioselectivity. The results under various conditions are shown in Table.



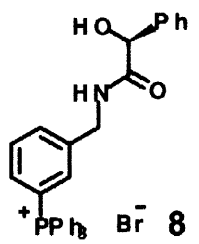
6 (*R*)-**7** (eq. 1)

Table.
Asymmetric benzylation of *t*-butyl 2-oxocyclopentanecarboxylate.

Entry	Catalyst (mol %)	Reaction temperature (°C)	Reaction time (h)	**7** Yield (%)	**7** ee(%)
1	**1** (5.0)	20	24	47	38 (*R*)
2	**1** (1.0)	20	24	43	39 (*R*)
3	**1** (0.20)	20	24	37	40 (*R*)
4	**1** (1.0)	20	168	80	38 (*R*)
5	**1** (1.0)	0	168	44	50 (*R*)
6	**8** (1.0)	20	24	63	1 (*S*)

The catalyst (**1**) accelerated the reaction, and gave **7** with 38–40% ee regardless of the amount of the catalyst used (Table, entry 1–3). Furthermore, the amount of the catalyst does not significantly affect the yields (entry 1–3). This is probably due to the very low solubility of **1** in toluene. Elongation of the reaction time from 24 h to 168 h led to an increase of the yield up to 80% with practically unchanged ee (entry 4). Finally, lowering the reaction temperature to 0 °C improved the selectivity up to 50% ee (entry 5).

As a comparison, phosphonium salt **8**, which has only one mandelamide unit, was synthesized and used, instead of **1**, for the benzylation reaction. Under the same conditions shown in eq. 1, **8** afforded the product in almost racemic form (entry 6). This result suggests that two mandelamide units of **1** are necessary to create an effective chiral environment for the substrate anion.



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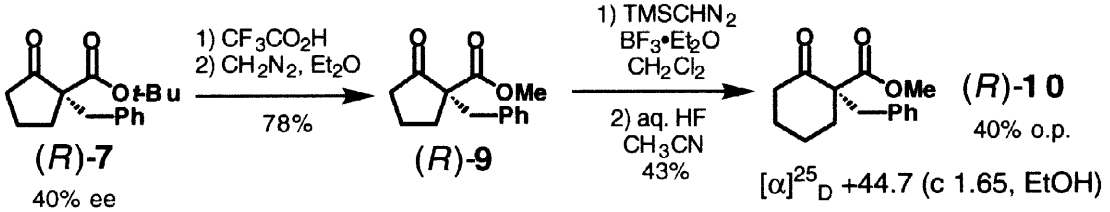
The absolute configuration of **7** was determined by its conversion[19] to the known compound **10**[20] and the comparison of the specific rotation, as shown below.



(*R*)-**7** 40% ee (*R*)-**9** (*R*)-**10** 40% o.p.

$[\alpha]^{25}_D$ +44.7 (c 1.65, EtOH)

Methyl and benzyl 2-oxocyclopentane carboxylates afforded the benzylated products with poor selectivities under the conditions same as that of Table, entry1 (80% yield, 1% ee, and 88% yield, 4% ee, respectively).

In conclusion, a phosphonium salt with a multiple hydrogen-bonding site was synthesized and used as a new phase-transfer catalyst. Although the yields and enantioselectivities still remain to be improved further, this research will contribute to the development of efficient asymmetric phase-transfer reactions.

Typical procedure for asymmetric benzylation: To a suspension of **1** (3.7 mg, 0.0050 mmol) and *t*-butyl 2-oxocyclopentanecarboxylate (92.0 mg, 0.50 mmol) in toluene (5.0 mL) was added satd. K_2CO_3 (3.0 mL) at 20 °C. After 5 min, benzyl bromide (0.090 mL, 0.76 mmol) was added, and the whole was vigorously stirred for 24 h at 20 °C. The reaction mixture was diluted with H_2O (30 mL) and satd. NaBr (10 mL), and extracted with CH_2Cl_2 (30 mL, 10 mL, 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The crude mixture was purified by silica gel column chromatography (hexanes–Et_2O 25:1) to give **7** (59.5 mg, 43%) as a colorless oil. Its ee (39% ee (*R*)) was determined by HPLC analysis (CHIRALCEL OD-H (Daicel); haxanes–2-PrOH 1000:1; flow rate: 1 mL/min; the retention time of the major isomer: 20.1 min, that of the minor isomer: 15.9 min). $[\alpha]^{25}_D$ –41.3 (c 0.606, $CHCl_3$).

Acknowledgment. The author is grateful to Professor Kenji Koga (The University of Tokyo) for helpful discussions, and to the Ministry of Education, Science, Sports, and Culture, Japan for financial support.

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