Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids via Enantioselective Alkylation of Azlactones under Biphasic Conditions Using *P*-Spiro Chiral Tetraaminophosphonium Salts as a Phase-Transfer Catalyst

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Received 3 October 2008

Abstract: Highly enantioselective alkylation of azlactones derived from α-amino acids has been achieved under solid–liquid phase-transfer conditions using *P*-spiro chiral tetraaminophosphonium salt as a catalyst. The resulting alkylated azlactones can be readily converted into the corresponding α,α-disubstituted α-amino acids through simple acidic hydrolysis.

Key words: aminophosphonium salt, phase-transfer catalysis, azlactone, α,α-disubstituted α-amino acid, asymmetric synthesis

α,α-Disubstituted α-amino acids have received considerable interests in biological and medicinal chemistry mainly because the restricted conformational flexibility of their side chains, upon incorporated in peptide strands, plays a crucial role for controlling the secondary structure. This property also leads to impart an enhanced resistance against chemical and enzymatic degradations to the peptides.[1,2] Furthermore, α,α-disubstituted α-amino acids are often found in nature either in their free form or as constituents of biologically active natural products.[3] Accordingly, extensive research efforts have been devoted into the development and refinement of efficient methods for the preparation of α,α-disubstituted α-amino acids,[4–6] and a number of reliable strategies have been elaborated for the catalytic asymmetric construction of the fully substituted stereocenter.[5,6] Among them, enantioselective alkylation of Schiff bases derived from α-amino acid esters represents one of the most practical protocols, which can be conveniently performed under mild biphasic conditions in the presence of an appropriate phase-transfer catalyst such as chiral quaternary ammonium salts.[6] On the other hand, the use of oxazol-5-(4*H*)-one, namely azlactone, as a key substrate to establish quaternary carbon stereocenter in α,α-disubstituted α-amino acids is another attractive approach from atom-economical viewpoint. However, it has still remained relatively unexplored,[7,8] despite the fruitful applications of azlactone as a nucleophile for asymmetric allylic alkylation catalyzed by chiral transition-metal complexes.[9] In this communication, we wish to address this problem by demonstrating the effectiveness of asymmetric phase-transfer catalysis of our recently developed *P*-spiro chiral tetraaminophosphonium salts of type **1** (Figure 1) for achieving highly enantioselective direct alkylation of azlactones **2** under solid–liquid biphasic conditions.

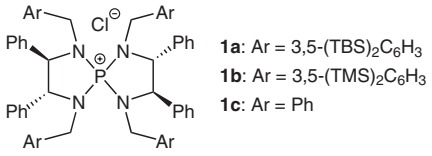


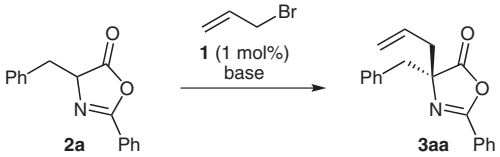
Figure 1 *P*-Spiro chiral tetraaminophosphonium chlorides

We recently succeeded in introducing a new strategy for incorporating various optically active α,α-disubstituted α-amino acid residues into the specific site of the peptide strand.[10] It is based on the **1a**-catalyzed highly stereoselective alkylation of peptide backbone at C-terminal azlactone moiety under liquid–liquid phase-transfer conditions. Although the reaction was inherently diastereoselective, stereochemical control of the newly created quaternary carbon center was mainly governed by the catalyst **1a** and the effect of the chirality of the pre-existing adjacent amino acid residue appeared to be rather marginal. This interesting observation prompted us to examine the possibility of applying **1a** to the enantioselective alkylation of simple azlactones.[11]

The initial experiment was carried out under previously optimized liquid–liquid biphasic conditions. Thus, treatment of phenylalanine-derived azlactone **2a** with allyl bromide under the influence of **1a** in cyclopentyl methyl ether (CPME)-saturated K_3PO_4 aqueous solution at 0 °C for one hour afforded the corresponding quaternization product **3aa** in 74% yield, and its enantiomeric excess was determined to be 86% ee (Table 1, entry 1). Optimization was then made by screening of base, solvent, and reaction temperature. Use of K_2CO_3 instead of K_3PO_4 as an aqueous base led to the production of **3aa** in higher chemical yield, though the enantioselectivity was unaffected (entry 2). When ground solid bases were employed, substantial rate retardation was generally observed (entries 3–6). Nevertheless, a reasonable reaction rate and a slightly higher enantioselectivity were attained by using K_3PO_4 (entry 3). Under the solid–liquid biphasic conditions, the allylation was found to be speeded up in *tert*-butyl methyl ether (TBME), while both reactivity and selectivity were decreased in toluene (entries 7 and 8). Moreover, enantioselectivity was gradually increased as the temperature was

SYNLETT 2009, No. 4, pp 0658–0660
Advanced online publication: 16.02.2009
DOI: 10.1055/s-0028-1087812; Art ID: Y01208ST

Table 1 Optimization of Reaction Parameters in Asymmetric Alkylation of Azlactone **2a** under Phase-Transfer Conditions[a]



Entry	Base	Solvent	Catalyst	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	sat. aq K_3PO_4	CPME	**1a**	0	1	74	86
2	sat. aq K_2CO_3	CPME	**1a**	0	1	94	86
3	K_3PO_4	CPME	**1a**	0	7	91	87
4	Na_2CO_3	CPME	**1a**	0	24	80	82
5	K_2CO_3	CPME	**1a**	0	20	98	87
6	Cs_2CO_3	CPME	**1a**	0	22	91	83
7	K_3PO_4	toluene	**1a**	0	15	93	81
8	K_3PO_4	TBME	**1a**	0	3	90	87
9	K_3PO_4	TBME	**1a**	–15	7	99	89
10	K_3PO_4	TBME	**1a**	–30	18	91	91
11	K_3PO_4	TBME	**1b**	–30	18	62[d]	70
12	K_3PO_4	TBME	**1c**	–30	18	22[d]	21

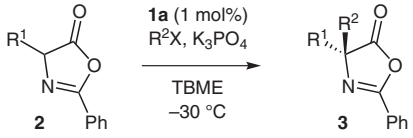
[a] Reactions were performed on a 0.1 mmol scale in 0.6 mL of organic solvent with 0.2 mL of aqueous base or 5 equiv of solid base.
[b] Isolated yield.
[c] Determined by chiral stationary phase HPLC analysis.
[d] Incomplete conversion.

lowered, and **3aa** was isolated in 91% yield with 91% ee by conducting the reaction at –30 °C (entries 9 and 10). In addition, results of the attempted reactions with sterically less demanding aminophosphonium salts **1b** and **1c** as a catalyst clearly indicate the importance of the *tert*-butyldimethylsilyl substituents of aryl moiety in order to create suitable reaction environment for inducing high reactivity and selectivity (entries 11 and 12).

The optimized reaction conditions were used for further investigating the applicability of this procedure for the synthesis of various enantiomerically enriched α,α-disubstituted α-amino acids. As listed in Table 2, construction of quaternary carbon centers having methallyl and propargyl substituents was realized in a similar manner (entries 1 and 2). Although the enantiomeric excesses were moderate, the present system can be extended to the asymmetric synthesis of α-alkylated aspartic acid and serine derivatives (entries 3 and 4). The catalytic asymmetric quaternization of leucine-derived azlactone **2b** appeared feasible and similar tendency was observed in terms of reactivity and stereoselectivity (entries 5–8).

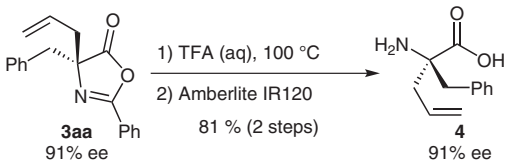
The alkylated azlactone **3** can be readily derivatized to the corresponding α-disubstituted α-amino acid without loss of stereochemical purity. For instance, exposure of azlactone **3aa** (91% ee) to aqueous trifluoroacetic acid at 100 °C facilitated the complete deprotection, and subsequent purification by ion-exchange resin (Amberlite IR120) gave free amino acid **4** in 81% overall yield (91% ee, Scheme 1).

Table 2 Current Scope of Chiral Tetraaminophosphonium Salt **1a** Catalyzed Asymmetric Alkylation of Azlactones **2**[a]



Entry	R^1 (**2**)	R^2X	Time (h)	Yield (%)[b]	ee (%)[c]	Prod. **3**
1	Bn (**2a**)	$BrCH_2C(Me)=CH_2$	18	90	90	**3ab**
2	Bn (**2a**)	$BrCH_2C{\equiv}CH$	18	85	93	**3ac**
3	Bn (**2a**)	$BrCH_2CO_2Me$	24	80	72	**3ad**
4	Bn (**2a**)	$ClCH_2OCMe$	12	63	74	**3ae**
5	CH_2i-Pr (**2b**)	$BrCH_2CH=CH_2$	16	87	83	**3ba**
6	CH_2i-Pr (**2b**)	$BrCH_2C(Me)=CH_2$	17	86	85	**3bb**
7	CH_2i-Pr (**2b**)	$BrCH_2C{\equiv}CH$	28	82	89	**3bc**
8	CH_2i-Pr (**2b**)	BrBn	16	85	72	**3bf**

[a] All reactions were performed on a 0.1 mmol scale in 0.6 mL of TBME with 5 equiv of ground K_3PO_4.
[b] Isolated yield.
[c] Determined by chiral stationary phase HPLC analysis.



Scheme 1 Deprotection of alkylated azlactone **3aa** to give α,α-disubstituted α-amino acid **4**

In conclusion, we have successfully demonstrated that *P*-spiro chiral tetraaminophosphonium salt **1a** can function as an effective catalyst for the highly enantioselective alkylation of simple azlactones under mild solid–liquid phase-transfer conditions. Further studies to improve the enantioselectivity and general applicability of this potentially practical methodology are currently under way in our laboratory.

General Procedure of the Catalytic Asymmetric Allylation of 2a under Solid–Liquid Biphasic Conditions

To a solution of catalyst **1a** (1.8 mg, 0.001 mmol, 0.01 equiv), azlactone **2a** (25.1 mg, 0.10 mmol, 1.0 equiv), and allyl bromide (10.4 μL, 0.12 mmol, 1.2 equiv) in TBME (0.6 mL) was added ground $K_3PO_4{\cdot}nH_2O$ (132.7 mg, 0.5 mmol, 5.0 equiv) with vigorous stirring at –30 °C. The reaction mixture was stirred until complete conversion of **2a** (8 h) and poured into ice-cooled H_2O. The aqueous phase

was extracted with EtOAc (3×) and the organic extracts were washed with sat. aq NaCl. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel using hexane–EtOAc (10:1) as eluent to give **3aa** (91%) as colorless paste. The ee was determined by chiral stationary phase HPLC analysis [DAICEL CHIRALCEL OD-H, hexane–2-PrOH (1000:1), flow rate = 0.5 mL/min, t_R = 39.0 (*R*) and 48.3 (*S*) min]. The absolute configuration was determined after complete deprotection. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.5 Hz, 2 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.19–7.12 (m, 5 H), 5.68 (ddt, *J* = 16.8, 9.9, 7.2 Hz, 1 H), 5.21 (dd, *J* = 16.8, 1.8 Hz, 1 H), 5.12 (dd, *J* = 9.9, 1.8 Hz, 1 H), 3.23 (d, *J* = 13.5 Hz, 1 H), 3.16 (d, *J* = 13.5 Hz, 1 H), 2.77 (dd, *J* = 13.5, 7.2 Hz, 1 H), 2.70 (d, *J* = 13.5, 7.2 Hz, 1 H).

Deprotection of Alkylated Azlactone 3aa to α,α-Disubstituted α-Amino Acid 4

A solution of **3aa** (0.09 mmol) in 90% aq TFA (1.8 mL) was stirred for 12 h at 100 °C. After cooling to r.t., the reaction mixture was concentrated, and the resulting residue was purified by ion-exchange resin (Amberlite IR120; H^+ form) according to the literature procedure.[12] Analytically pure α,α-disubstituted α-amino acid **4** was obtained in 81% yield, and its absolute configuration was determined to be *R* by comparison of optical rotation with the literature value. $[\alpha]_D^{25}$ –22.9 (*c* 1.0, H_2O) for 91% ee; lit.[13] $[\alpha]_D^{20}$ +27.3 (*c* 1.0, H_2O). ^{1}H NMR (300 MHz, CD_3OD):δ = 7.36–7.24 (m, 5 H), 5.86 (dddd, *J* = 15.9, 10.8, 8.4, 6.3 Hz, 1 H), 5.25 (d, *J* = 15.9 Hz, 1 H), 5.24 (d, *J* = 10.8 Hz, 1 H), 3.29 (d, *J* = 14.4 Hz, 1 H), 2.96 (d, *J* = 14.4 Hz, 1 H), 2.78 (dd, *J* = 14.4, 6.3 Hz, 1 H), 2.43 (dd, *J* = 14.4, 8.4 Hz, 1 H).

Acknowledgment

This work has been partially supported by the Global COE Program in Chemistry of Nagoya University, Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Naito Science & Engineering Foundation.

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