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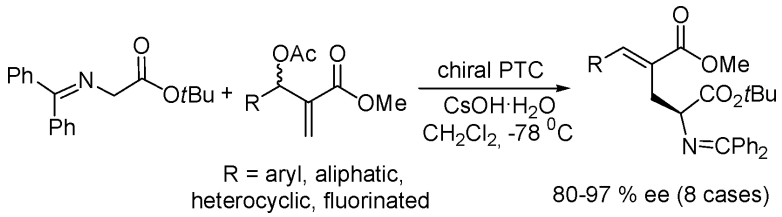

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Catalytic Enantioselective Synthesis of Glutamic Acid Derivatives via Tandem Conjugate Addition−Elimination of Activated Allylic Acetates under Chiral PTC Conditions

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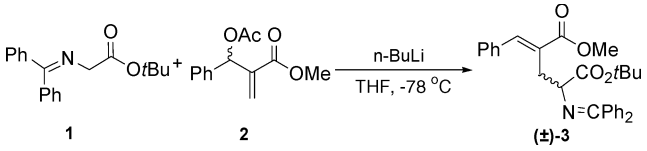
Glutamic acid is the main excitatory amino acid in the central nervous system. The design of ligands for the various types of glutamate receptors as potential therapeutic agents has attracted the attention of numerous groups.[1] 4-Substituted glutamate analogues, such as 4-substituted alkylidene glutamic acids, have been the targets of several synthetic and pharmacological studies.[2]

The enantioselective synthesis of α-amino acid derivatives employing chiral phase-transfer catalysts (PTC) represents an important synthetic advancement.[3] Enantioselective reactions of the Schiff bases of amino esters, using PTC conditions catalyzed by quaternized *Cinchona* alkaloids by O'Donnell,[4] Corey,[5] Lygo,[6] and related systems by others,[7] have been used to obtain a variety of amino acid products with impressive levels of enantioselection using simple procedures. However, to the best of our knowledge, there have been no reports on the tandem conjugate addition−elimination[8,9] under phase-transfer conditions for the enantioselective preparation of amino acids.[10] Herein we report a new, general, and practical method for the preparation of 4-alkylidenyl glutamic acids via tandem conjugate addition−elimination under PTC.

Targets for initial studies, which focused on standardizing the reaction conditions and determining the scope of the methodology, were the racemic glutamate derivatives **3** (Scheme 1).

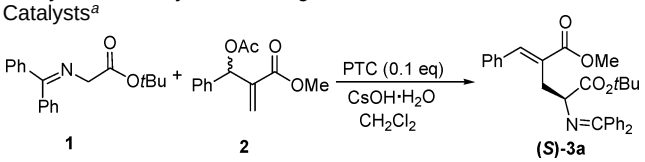
Scheme 1. Synthesis of the 4-Alkylidenyl Glutamic Acid Derivatives



Reaction of the lithium enolate of the benzophenone imine of glycine *tert*-butyl ester (**1**) with allylic acetates **2**, prepared via vinylalumination[11] or Baylis−Hillman reaction,[9] in THF at −78 °C for 1.5−4.5 h, gave the racemic products **3**.[12] A variety of types of allylic acetates, including aromatic, aliphatic, heterocyclic, and fluoroaromatic, smoothly undergo the tandem conjugate addition−elimination (see Supporting Information). It is noteworthy that, with allylic acetates that are not activated with an ester group at the 2-position, palladium catalysis is required in similar reactions.[13]

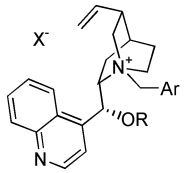
We then investigated the enantioselective version of the tandem conjugate addition−elimination to prepare optically active 4-alkylidenyl glutamates **3** using chiral PTC. Catalysts derived from the *Cinchona* alkaloids were chosen because of their demonstrated applicability in phase-transfer catalysis and their facile preparation from inexpensive and available sources.[3−6] The reaction of **1** with **2a** using *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**4a**) as the PTC ($CsOH·H_2O$, CH_2Cl_2, −78 °C) gave the model product (*S*)-**3a** in 92% yield and 92% ee (Table 1 and Figure 1).

Table 1. Enantioselective Alkylation of the Benzophenone Imine of Glycine *tert*-Butyl Ester Using Various Phase-Transfer Catalysts[a]



entry	catalyst	temp, °C	time, h	yield, %[b]	ee, %[c]
1	**4a**	−78	30	92	92
2	**4b**	25	24	72	60
3	**4c**	−78	36	78	86
4	**4d**	−78	36	82	85
5	**4e**	−78	36	78	84

[a] The reaction was conducted with the benzophenone imine of glycine *tert*-butyl ester **1** (1 mmol), allylic acetate **2** (1 mmol), $CsOH·H_2O$ (10 equiv), and PTC (10 mol %) in CH_2Cl_2 for the given time. [b] Isolated yield. [c] The enantiopurity of model product (*S*)-**3a** was determined by chiral HPLC analysis of the product using a (*S*,*S*)-Whelk-O1 column (Regis Technologies) with hexane:2-propanol as the solvent system; the resolution of the enantiomers was confirmed by analysis of racemic glutamate (**3a**); see Supporting Information.



4a Ar = 9-anthracenyl, R = allyl, X = Br
4b Ar = 9-anthracenyl, R=H, X=Cl
4c Ar = 2-naphthyl, R = allyl, X = Br
4d Ar = 1-naphthyl, R = allyl, X = Br
4e Ar = phenyl, R = allyl, X = Br

Figure 1. Structure of the phase-transfer catalysts.

Use of homogeneous reaction conditions (catalyst **4a**, Schwesinger base BEMP, CH_2Cl_2, −78 °C, 24 h)[4c,d] afforded (*S*)-**3a** in 90% yield and 79% ee. Similarly, liquid−liquid PTC (**4b**, 50% KOH, PhMe, 25 °C, 24 h)[6a] also gave poorer results. Variation in the *N*-alkyl group on the quinuclidine core of the quaternary ammonium salt (**4c**−**4e**) also resulted in decreased yields and enantioselectivities (Table 1). As expected from literature reports, the anthracenylmethyl-derived catalyst (**4a**) gave the best enantioselectivity (92% ee) and yield. *N*-Benzyl cinchonidinium bromide (**4e**) was the least effective catalyst of those studied (84% ee), while the 2- and 1-naphthylmethyl-derived catalysts (**4c** and **4d**, respectively) gave intermediate results.

A number of optically active 4-alkylidene glutamates were prepared using the optimized conditions developed for the model phenyl-substituted product **3a** using **4a** as the PTC (Table 2). Product **3b**, derived from the electron-poor allylic acetate **2b**, gave

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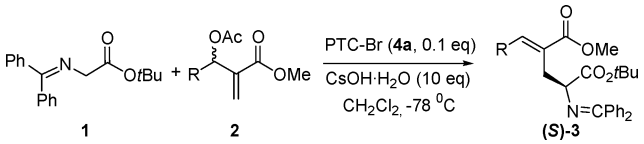
Table 2. Enantioselective Synthesis of 4-Alkylidenyl Glutamic Acid Derivatives under Phase-Transfer Conditions[a]



1 2 (*S*)-3

entry	allyl acetate	R	time, h	glutamic acid derivative	yield, %[b]	ee, %[c]
1	**2a**	Ph	30	(*S*)-**3a**	92	92
2	**2b**	4-NO_2−Ph	48	(*S*)-**3b**	72	97
3	**2c**	4-MeO−Ph	48	(*S*)-**3c**	63	89
4	**2d**	2-thienyl	48	(*S*)-**3d**	90	86
5	**2e**	2-pyridinyl	34	(*S*)-**3e**	72	82
6	**2f**	2,6-F_2Ph	48	(*S*)-**3f**	68	80
7	**2g**	^{n}Pr	34	(*S*)-**3g**	82	82
8	**2h**	^{t}Bu	40	(*S*)-**3h**	63	85

[a] The reaction was conducted with the benzophenone imine of glycine *tert*-butyl ester **1** (1 mmol), allylic acetate **2** (1 mmol), $CsOH·H_2O$ (10 equiv), and **4a** (10 mol %) in CH_2Cl_2 for the given time. [b] Isolated yield. [c] Enantiopurities of the products (*S*)-**3** were determined by chiral HPLC analysis of the product using a (*S,S*)-Whelk-O1 column (Regis Technologies) with hexane:2-propanol as the solvent system; in each case, the resolution of the enantiomers was confirmed by analysis of racemic glutamates (**3**); see Supporting Information.

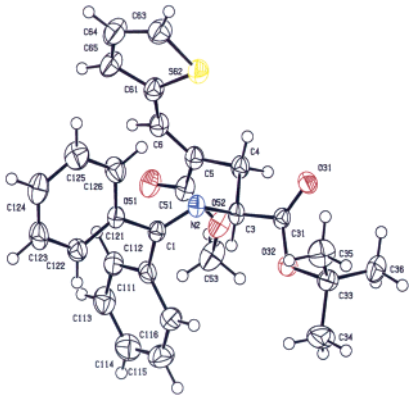


Figure 2. X-ray crystal structure of glutamate product (*S*)-**3d**.

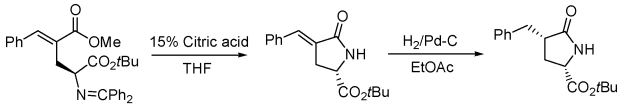
the highest enantioselectivity (97% ee, entry 2), while the deactivated electron-rich allylic acetate **2c** gave a lower % ee of product **3c** (89% ee, entry 3). In the case of heterocyclic, fluoroaromatic, and aliphatic allylic acetates, slightly lower enantioselectivities (80−86%) were obtained.

The structure of product **3d**, including the *E*-double bond geometry, was elucidated by spectroscopic and X-ray crystallographic techniques (Figure 2). The absolute configuration (2*S*) of the stereogenic center resulting from the enantioselective alkylation was assigned by analogy with earlier studies, which have shown that 2*S* products result when cinchonidine-derived catalysts are used in the PTC alkylation.[3−6,7f] This assignment was confirmed by conversion of (*S*)-**3d** to the known 4-oxo glutamic acid via the dihydroxylation−periodate cleavage of the double bond, followed by hydrolysis[14] (see Supporting Information).

The utility of this process was demonstrated by transforming a representative 4-alkylidene glutamate (*S*)-**3a** into 4-oxo glutamates and 4-substituted pyroglutamates (Scheme 2), which can be readily converted to 4-substituted glutamic acids[15] (see Supporting Information).

In conclusion, we have presented a new, general, and practical procedure for the asymmetric synthesis of 4-alkylidenyl glutamic acid derivatives, which is based on the catalytic enantioselective tandem conjugate addition−elimination of the Schiff base of glycine *tert*-butyl ester with activated allylic acetates under phase-transfer conditions. The simple procedure and high enantioselectivity of the process offer a practical route to these important targets.

Scheme 2. Synthesis of 4-Substituted Pyroglutamates



(*S*)-3a (*S*)-4 (2*S*,4*S*)-5

Acknowledgment. Dedicated to the memory of Professor Herbert C. Brown.We gratefully acknowledge the National Institutes of Health (GM 28193) for support of this research.

Supporting Information Available: Experimental details, spectral data, and X-ray crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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