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Highly Enantioselective Synthesis of (2*S*)-α-(Hydroxymethyl)-glutamic Acid by the Catalytic Michael Addition of 2-Naphthalen-1-yl-2-oxazoline-4-carboxylic Acid *tert*-Butyl Ester

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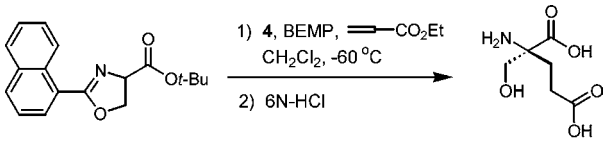
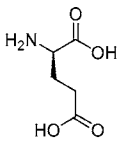
ABSTRACT

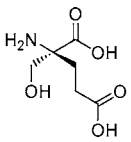


Highly enantioselective synthesis of a potent metabotropic receptor ligand, (2*S*)-α-(hydroxymethyl)-glutamic acid (2, HMG) was accomplished by the catalytic Michael addition of 2-naphthalen-1-yl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (3b), using the phosphazene base, BEMP, in CH_2Cl_2 at −60 °C in the presence of (*S*)-binaphthyl quaternary ammonium salt 4.

(*S*)-Glutamic acid (**1**) is one of the most important excitatory neurotransmitters in the mammalian central nervous system, playing a crucial role in memory and learning. **1** is also implicated in the pathogenesis of neuronal damage that causes various neuronal diseases by acting through two types of membrane receptors: inotropic (iGluR) and metabotropic (mGluR).[1,2]



1



2

To study the roles of these receptors and their modulation mechanism in the nervous system, considerable efforts have been devoted to the discovery of selective agonists and antagonists on the glutamate receptors.[3] Among the disclosed synthetic ligands so far, (2*S*)-α-(hydroxymethyl)glutamic acid (**2**) has been recognized as one of the most useful ligands; **2** is a strong antagonist of mGluR2 and a weak agonist of mGluR3, while it has no effect on the Group 1 and Group

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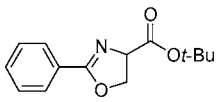
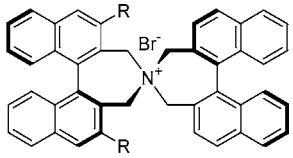
3 mGluR.[4] There have been several synthetic methods for the asymmetric synthesis of both (2*R*)- and (2*S*)-α-(hydroxymethyl)glutamic acid (HMG).[4] However, all the previous methods employed a chiral auxiliary for the chiral induction. In this letter, we report the first catalytic method for the synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid using phase-transfer catalytic Michael reaction.[5]



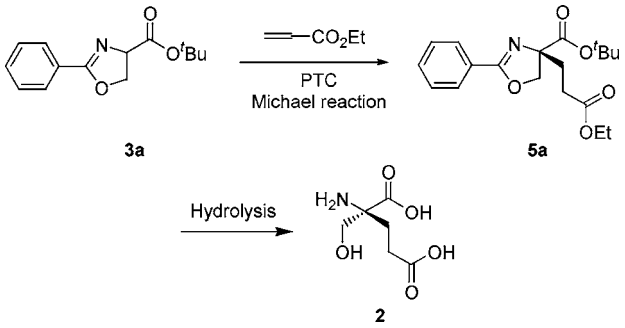
3a



4 R = 3′,4′,5′-trifluorophenyl

Recently, we reported a very efficient enantioselective synthetic method for (*S*)-α-alkylserine using the phase-transfer catalytic alkylation of 2-phenyl-2-oxazoline-4-carboxylate (**3a**)[6] in the presence of the (*S*)-binaphthyl quaternary ammonium salt **4**[7] disclosed by the Maruoka group. As part of our program for the development of practical synthetic methods for (*S*)-**2**, we attempted to use phase-transfer catalytic Michael addition of 2-phenyl-2-oxazoline-4-carboxylate (**3a**) using ethyl acrylate as an electrophile (Scheme 1). The Michael adduct **5a** could readily be converted to **2** by acidic hydrolysis.

Scheme 1. Synthetic Strategy for (2*S*)-α-(Hydroxymethyl)-glutamic Acid



3a **5a** **2**

First, the substrate **3a** was easily prepared by the coupling of ethyl benzimidate and serine *tert*-butyl ester based on the previous method (98% yield).[6] For the Michael reaction, we adapted the previous reaction conditions. The enantioselective phase-transfer catalytic Michael reaction was performed using **4** (2.5 mol %) along with **3a**, ethyl acrylate (5.0 equiv), and solid KOH (5.0 equiv) in toluene at 0 °C. It took only 10 min to afford Michael adduct **5a** in 95% chemical yield, but disappointingly the enantioselectivity was almost racemic (3% ee). We speculated that the fast reaction rate, due to the high reactivity of ethyl acrylate, might be responsible for the loss of enantioselectivity via non-PTC-mediated Michael reaction. So we attempted to reduce the reaction rate by replacing the base and solvent with aqueous 50% KOH and CH_2Cl_2, respectively. The Michael reaction under the new reaction conditions had increased but still moderate enantioselectivity (43% ee). Very recently, we reported that

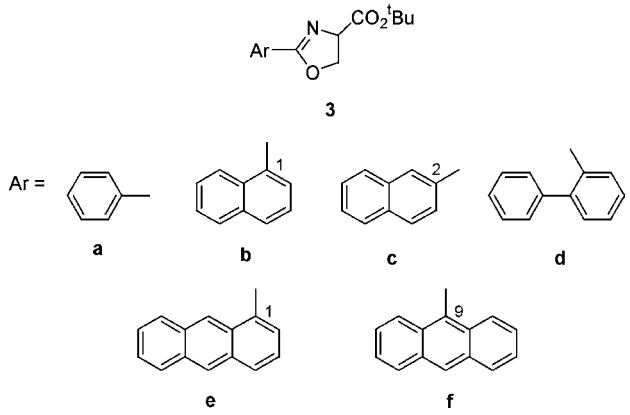


Figure 1. Oxazoline *tert*-butyl ester substrates.

the enantioselectivity of phase-transfer catalytic alkylation could be affected by the structure of aryl moiety of oxazoline-4-carboxylates.[8] Therefore, we attempted to employ various oxazoline derivatives as substrates of Michael reaction. Five oxazoline-4-carboxylates (**3b**−**f**) were prepared by a previously reported method,[8] and the phase-transfer catalytic Michael reaction was performed with 50% KOH as the base in CH_2Cl_2.

Interestingly, the enantioselectivity dramatically depended on the aryl groups (Table 1). The 1-naphthyl group (**3b**, 80% ee) and 1-anthracenyl group (**3e**, 78% ee) dramatically increased the enantioselectivity compared to phenyl group (**3a**, 43% ee), but comparable enantioselectivities were observed with 2-naphthyl group (**3c**, 39% ee) and 9-anthracenyl group (**3f**, 38% ee).

In the case of the 2-biphenyl analogue, a large loss of enantioselectivity was exhibited (**3d**, 7% ee), which is in accord with the previous results from the phase-transfer catalytic alkylation.[8] The accumulated results might suggest

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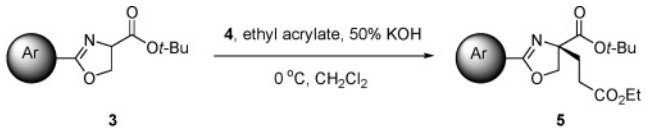
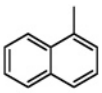
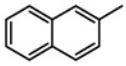
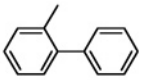
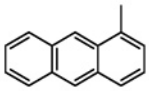
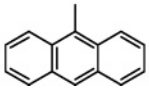
(8) Lee, Y.-j.; Lee, J.; Kim, M.-j.; Kim, T.-S.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1557.

Table 1. Enantioselective Phase-Transfer Catalytic Michael Reaction[a]

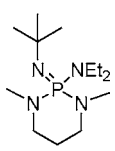


3 5

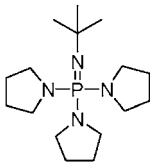
entry	substrate	Ar	time (h)	yield[b] (%)	% ee[c] (config.[d])
1	**3a**		2	95	43 (*S*)
2	**3b**		2	90	80 (*S*)
3	**3c**		2	84	39 (*S*)
4	**3d**		6	94	7 (*S*)
5	**3e**		2	81	78 (*S*)
6	**3f**		20	32	38 (*S*)

[a] Reaction was carried out with 5.0 equiv of ethyl acrylate and 5.0 equiv of 50% KOH in the presence of **4** (2.5 mol %) in methylene chloride at 0 °C. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis of **5** using a chiral column (DAICEL Chiralcel OD-H) with hexanes/2-propanol as a solvent; in this case, the enantiopurity was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] Absolute configuration was determined by comparison of the optical rotation of α-(hydroxymethyl)glutamic acid from the acidic hydrolysis of **5** with the reported value.[9]

that the aryl group plays an important role in the enantioselectivity and that the enolate of the 1-naphthyl analogue could form the most favorable ion pair intermediate with catalyst **4** in phase-transfer catalytic Michael reaction.



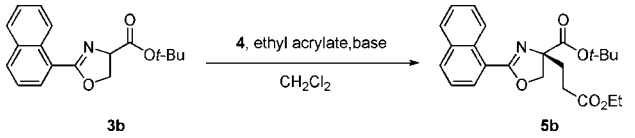
BEMP



BTPP

Next, the base and temperature conditions were optimized with the best substrate, **3b**. As shown in Table 2, solid KOH at −40 °C gave enantioselectivity comparable to that of 50% KOH at 0 °C, but solid CsOH showed quite low enantioselectivity with a long reaction time at −78 °C. Surprisingly, one of nonionic neutral phosphazene bases,[10] BEMP (97% ee), showed quite high enantioselectivity with a high

Table 2. Optimal Base Conditions for Phase-Transfer Catalytic Michael Reaction[a]



3b 5b

entry	base	temp (°C)	time (h)	yield[b] (%)	% ee[c] (configuration[d])
1	50% KOH	0	2	90	80 (*S*)
2	KOH	−40	5	77	75 (*S*)
3	CsOH	−78	20	70	36 (*S*)
4[e]	BEMP	−60	20	93	97 (*S*)
5[e]	BTPP	−60	2	90	81 (*S*)

[a] Reaction was carried out with 5.0 equiv of ethyl acrylate and 5.0 equiv of base in the presence of **4** (2.5 mol %) in methylene chloride unless mentioned otherwise. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexanes/2-propanol (volume ratio = 99:1) as a solvent. [d] Absolute configuration was determined by comparison of the optical rotation of α-(hydroxymethyl)glutamic acid from the acidic hydrolysis of **5b** with the reported value. [e] Reaction was carried out with 1.25 equiv of ethyl acrylate and 1.25 equiv of base in the presence of **4** (2.5 mol %) in methylene chloride.

chemical yield (93%) at −60 °C, but slightly lower enantioselectivity was observed by the stronger phosphazene base, BTPP (81% ee), with a 10-fold shorter reaction time. **5b** (97% ee) could be successfully hydrolyzed in 6 N HCl to give (2*S*)-α-(hydroxymethyl)-glutamic acid **2** (95%) along with 1-naphthylcarboxylic acid (98%), which could be recycled to prepare the substrate **3b**.

In conclusion, we developed the first catalytic method for the enantioselective synthesis of (2*S*)-α-(hydroxymethyl)-glutamic acid (**2**) by the catalytic Michael addition of 2-naphthalen-1-yl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (**3b**) in the presence of quarternary ammonium salt **4**. The easy preparation of substrate, the high enantioselectivity, and the very efficient procedure could make this method very practical for the industrial synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid (**2**).

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Supporting Information Available: Representative experimental procedures as well as spectroscopic characterizations of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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