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Practical asymmetric synthesis of α-methylserine derivatives under mild phase-transfer conditions

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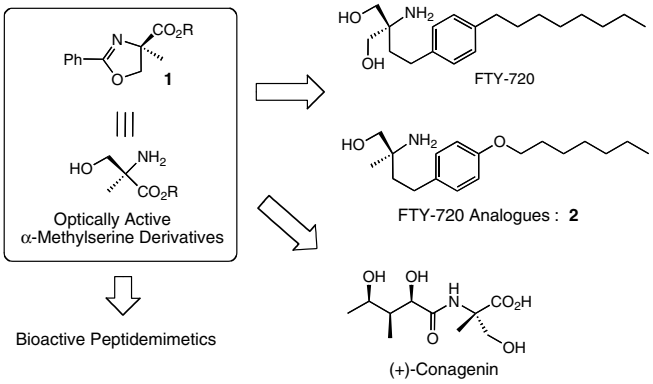
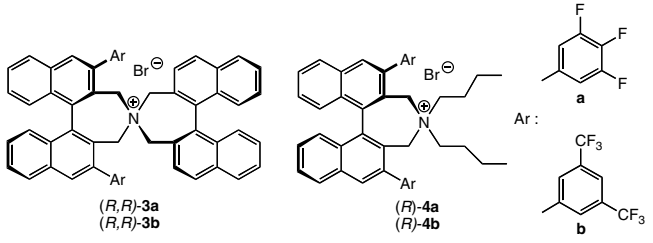
ABSTRACT

The enantioselective methylation reaction of phenyloxazoline *tert*-butyl ester **5** using (*R*)-**4b** as a catalyst under mild phase-transfer conditions provides optically active α-methylserine derivatives in moderate yields with high enantioselectivity. Other α-alkylated serine derivatives are also achievable in high yields with high enantioselectivity by using catalytic amount of (*R*)-**4b**.

In recent years, α-alkylated serines have been extensively studied for their important roles in biological and synthetic chemistry.[1] Particularly, α-methylserine derivatives are quite useful for the synthesis of bioactive natural products such as (+)-conagenin[2] and the design of bioactive peptidemimetics.[3] α-Methylserine is found to be a promising residue in the design of peptides, showing a well-defined and specific conformation.[4] Moreover, in the investigation of FTY720[5] analogues possessing immunosuppressive activity, optically active α-methylserine-derived compound **2** clearly exhibits the different bioactivity from the other enantiomer. Accordingly, the investigation of practical enantioselecitive synthetic methods for α-methylserine has been crucially important in pharmaceutical development, but only a few methods are found to be practical.[6]



Recently, Jew and Park reported asymmetric alkylation of phenyloxazoline derivatives with several efficient chiral phase-transfer catalysts to furnish α-alkylated serine derivatives with high enantioselectivity.[7,8] However, the preparation of α-methylserine derivatives, which are required for our purpose, is not described in the paper. Accordingly, we first followed reaction conditions using chiral phase-transfer catalyst (*R,R*)-**3a** for the desired methylation reaction. Attempted reaction of phenyloxazoline *tert*-butyl ester **5** with methyl iodide (5.0 equiv) in the presence of powdered KOH (5.0 equiv) and 1 mol % of (*R,R*)-**3a** in toluene at 0 °C resulted in the formation of methylation product **6a** in low yield (5%), and the enantiomeric excess of **6a** was revealed to be moderate (67% ee, entry 1 in Table 1). The use of $CsOH{\cdot}H_2O$ as base increased the chemical yield with similar enantioselectivity (entry 2). However, catalyst (*R,R*)-**3b** showed the disappointingly low enantioselectivity (entry 3).



With these preliminary results in hand, we examined the screening of binaphthyl-modified phase-transfer catalysts[9] and reaction conditions. For example, the structurally simplified catalyst (*R*)-**4a**, which was recently developed in our laboratory as powerful alkylation catalyst,[10] gave better enantiomeric excess with $CsOH{\cdot}H_2O$ (5.0 equiv) as base (entry 4). Moreover, use of 3,3′-bis(3,5-bis(trifluoromethyl)phenyl)-substituted catalyst (*R*)-**4b** (1 mol %) gave over 80% ee (entry 5).[11] At lower temperature

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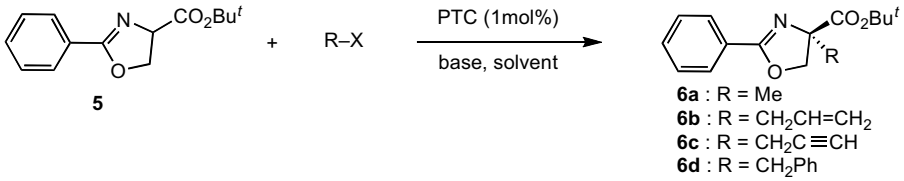
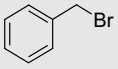
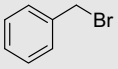
Table 1
Enantioselective alkylation of **5** with various alkyl halides using chiral PTC



Entry[a]	R–X	Catalyst	Base	Conditions (solvent, °C, h)	Product	Yield[b] (%)	ee (%)[c]
1	MeI	(*R*,*R*)-**3a**	KOH	Toluene, 0, 22	**6a**	5	67
2	MeI	(*R*,*R*)-**3a**	$CsOH·H_2O$	Toluene, 0, 22	**6a**	35	62
3	MeI	(*R*,*R*)-**3b**	$CsOH·H_2O$	Toluene, 0, 22	**6a**	20	8
4	MeI	(*R*)-**4a**	$CsOH·H_2O$	Toluene, 0, 22	**6a**	40	77
5	MeI	(*R*)-**4b**	$CsOH·H_2O$	Toluene, 0, 22	**6a**	34	81
6	MeI	(*R*)-**4b**	$CsOH·H_2O$	Toluene, −10, 22	**6a**	68 (66)[d]	86
7	MeI	(*R*)-**4b**	$CsOH·H_2O$	CPME,[e] −10, 22	**6a**	63	88
8	MeI	(*R*)-**4b**	$CsOH·H_2O$	CPME,[e] −30, 22	**6a**	55	90
9		(*R*)-**4b**	$CsOH·H_2O$	Toluene, −10, 5	**6b**	97	81
10		(*R*)-**4b**	$CsOH·H_2O$	Toluene, −10, 8	**6c**	96	94
11		(*R*)-**4b**	$CsOH·H_2O$	Toluene, −10, 8	**6d**	90	94
12		(*R*)-**4b**	$CsOH·H_2O$	Toluene, −30, 14	**6d**	87	96

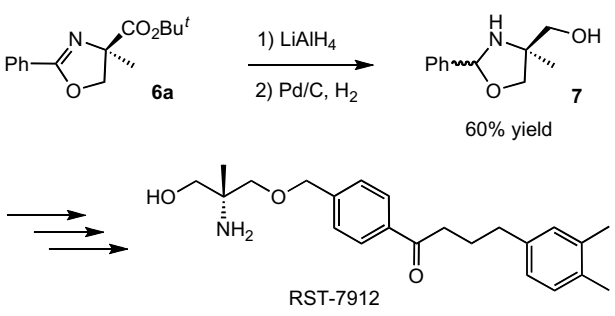
[a] The reaction was carried out with RX (5.0 equiv) and base (5.0 equiv), in the presence of catalyst in toluene or CPME (0.33 M) under the given conditions.
[b] HPLC assay yield.
[c] The ee was determined by chiral-phase HPLC analysis (Daicel Chiralcel OD-H and hexane/2-propanol as solvent).
[d] Isolated yield after column chromatography in entry 6.
[e] Use of CPME (0.15 M) as solvent.

(−10 °C), the enantioselectivity was further improved (entry 6 vs 5). Finally, the reaction using cyclopentyl methyl ether (CPME) at −30 °C afforded **6a** in 90% ee (entry 8).[12]

With the optimum reaction conditions in hand, asymmetric alkylation of phenyloxazoline *tert*-butyl ester **5** was carried out with 5.0 equiv of other alkyl halides in toluene in the presence of only 1 mol % of (*R*)-**4b** with high enantioselectivity of up to 96% ee (entries 9–12).

Reduction of **6a** with lithium aluminum hydride ($LiAlH_4$) and subsequent hydrogenation easily produced the corresponding alcohol **7**[3b] in 60% yield, which is a key intermediate for RST-7912,[13] possessing immunosuppressive activity (Scheme 1).

In summary, we have shown an efficient enantioselective synthesis of optically active α-methylserine and other α-alkylserine derivatives using the structurally simplified catalyst (*R*)-**4b** under mild phase-transfer conditions. Some α-methylserine derivatives are easily transformed into various biologically active compounds.



Scheme 1.

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