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Direct Asymmetric Intramolecular Alkylation of β-Alkoxy-α-amino Esters via Memory of Chirality

Katsuhiko Moriyama, Hiroki Sakai, and Takeo Kawabata*

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan
kawabata@scl.kyoto-u.ac.jp

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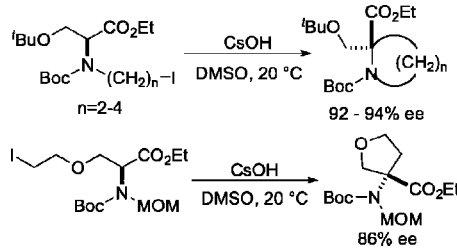
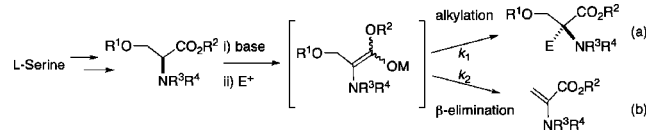
ABSTRACT



The intramolecular α-alkylation of β-alkoxy-α-amino esters derived from L-serine proceeded predominantly over β-elimination. When β-alkoxy-α-amino esters were treated with powdered CsOH in DMSO at 20 °C, α-alkoxymethyl cyclic amino esters were obtained in up to 94% ee. Optically active THF amino acids were synthesized for the first time by the present method.

α-Substituted serine derivatives are important building blocks for the synthesis of biologically active natural products such as sphingofungin-E,[1] lactacystin,[2] salinosporamide A,[3] dysibetaine,[4] kaitocephalin,[5] neooxazolomycin,[6] and so on. The most straightforward synthesis of optically active α-substituted serines might involve the α-alkylation of protected serine derivatives (Scheme 1, path a). However, this has never been achieved due to expected racemization during enolate formation and/or concomitant β-elimination[7] (Scheme

Scheme 1



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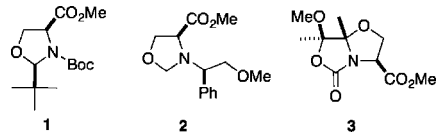
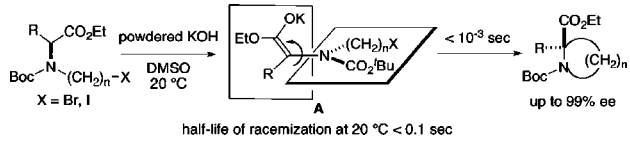
1, path b). To avoid these problems, cyclic analogues with chiral auxiliaries such as **1**−**3** have been used to prepare optically active α-substituted serine derivatives.[8] We report here the direct asymmetric synthesis of α-substituted serine derivatives by intramolecular alkylation of *β*-alkoxy-α-amino esters derived from L-serine via memory of chirality.



We have developed a direct method for the asymmetric α-alkylation of α-amino acid derivatives without the aid of external chiral sources such as chiral auxiliaries or chiral catalysts, i.e., memory of chirality.[9] The inter- and intramolecular α-alkylation of α-amino acid derivatives proceeded in up to 98% ee via axially chiral enolate intermediates, where enolate formation was performed at low temperatures such as −78 to −60 °C to maintain the enantiomeric purity of the chiral enolate.[10] Recently, we reported that asymmetric cyclization via memory of chirality could proceed with high enantioselectivity even at 20 °C when powdered KOH in DMSO was used as a base (Scheme 2).[11] The axially chiral

Scheme 2



enolate intermediate **A** with a racemization barrier of ∼15.5 kcal/mol was proposed. On the basis of this barrier, the chiral enolate was thought to undergo rapid cyclization within 10^{-3} s after its generation to give the cyclized products in 99% ee. The extremely rapid intramolecular alkylation was expected to underlie the high asymmetric induction at 20 °C because competitive racemization of the chiral enolate was minimized. The high reactivity of the enolates generated with KOH in DMSO prompted us to apply this method to the asymmetric intramolecular alkylation of *β*-alkoxy-α-amino esters. We had expected that the *β*-alkoxy enolates generated from *β*-alkoxy-α-amino esters and KOH in DMSO might undergo asymmetric cyclization predominantly over *β*-elimination due to the high rate of intramolecular alkylation (Scheme 1, $k_1 > k_2$).

We chose compounds **4** derived from L-serine as a substrate and examined the asymmetric cyclization of **4** (Table 1). Treatment of **4** with powdered KOH in DMSO at 20 °C for 60 min gave, as expected, cyclization product **6** predominantly in 97% yield (entry 2). The product resulting from *β*-elimination was not observed. Since the enantioselectivity of the cyclization was moderate (75% ee), the conditions for asymmetric cyclization of **4** were further examined. Treatment of **4** with powdered NaOH, RbOH, or CsOH in DMSO at 20 °C gave **6** in 85%, 93%, or 91% yield and in 67%, 69%, or 77% ee, respectively (entries 1, 3, and 4). While the use of powdered CsOH in DMF at −20 °C gave **6** in a slightly improved ee of 83%, this required a long reaction time and promoted *β*-elimination (11%) (entries 4 vs 5). The use of iodide **5** instead of bromide **4** increased the enantioselectivity of the asymmetric cyclization (entries 2 vs 7, 4 vs 8). Treatment of **5** with powdered CsOH in DMSO at 20 °C gave **6** in 86% ee and 84% yield (entry 8). The increase in the enantioselectivity of cyclization of the iodides could be ascribed to their increased rates of cyclization. Similar effects of leaving groups on asymmetric alkylation via memory of chirality have been reported by Carlier and co-workers.[12] The use of potassium hexamethyldisilazide (KHMDS) also gave cyclization product **6** in high yield (96%) albeit in low enantioselectivity (34% ee) (entry 6).

We next examined the effects of protective groups for the *β*-hydroxy group of serine derivatives (Table 2). Upon treatment with powdered CsOH in DMSO at 20 °C, methyl ether **7** underwent intramolecular alkylation to give α-meth-

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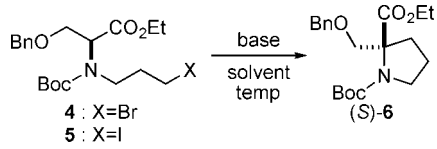
Table 1. Asymmetric Cyclization of *O*-Benzyl Serine Derivatives **4** and **5**[a]

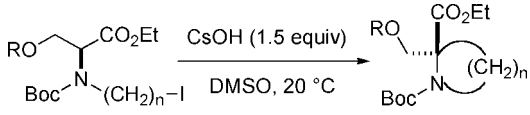


entry	substrate	X	base (mol equiv)	solvent	temp (°C)	time (min)	yield (%)	ee (%)[d]
1	**4**	Br	NaOH[b] (3.0)	DMSO	20	60	85	67
2	**4**	Br	KOH[b] (3.0)	DMSO	20	60	97	75
3	**4**	Br	RbOH[b] (1.5)	DMSO	20	20	93	69
4	**4**	Br	CsOH[b] (1.5)	DMSO	20	20	91	77
5	**4**	Br	CsOH[b] (1.5)	DMF	−20	1080	83[c]	83
6	**4**	Br	KHMDS (1.5)	THF	−78	30	96	34
7	**5**	I	KOH[b] (3.0)	DMSO	20	30	91	82
8	**5**	I	CsOH[b] (1.5)	DMSO	20	30	84	86
9	**5**	I	CsOH[b] (1.5)	1%H_2O in DMSO	20	30	88	83
10	**5**	I	CsOH[b] (1.5)	DMF	−20	420	88	81

[a] Reactions were carried out with a substrate concentration of 0.1 M. [b] Powdered metal hydroxide was used. [c] A product resulting from β-elimination was also obtained in 11% yield. [d] Ee of the corresponding *N*-benzoate determined by HPLC analysis. (*S*)-Isomer was obtained in each run. For the determination of the absolute configuration, see the Supporting Information.

oxymethyl proline **8** in 82% ee and 75% yield (entry 2). Methoxymethyl (MOM) ether **9** underwent cyclization with an efficiency similar to that of methyl ether **7** (72% yield and 82% ee, entry 3). *tert*-Butyldiphenylsilyl (TBDPS) ether **11** underwent asymmetric cyclization to give α-substituted proline **12** in 88% ee, but in only 13% yield due to the predominant β-elimination (58%) (entry 4). The use of 4-methoxybenzyl (PMB) and *tert*-butyl (^{t}Bu) ethers **13** and **15** in asymmetric cyclization gave α-substituted prolines **14** and **16** with increased enantioselectivities of 92% and 93%, respectively (entries 5 and 6). The four- and six-membered cyclization of β-alkoxy-α-amino esters was performed.

Table 2. Asymmetric Cyclization of Serine Derivatives[a]

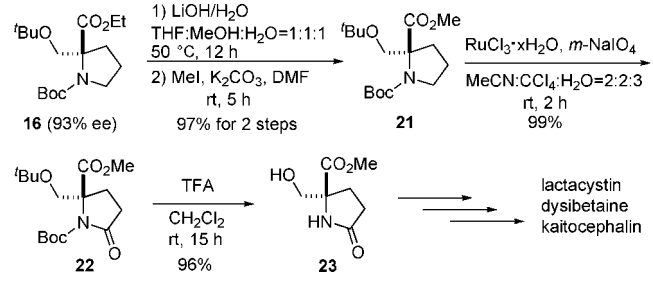


entry	substrate	R	*n*	time (min)	product	yield (%)	ee[b] (%)
1	**5**	Bn	3	60	**6**	84	86[c] (*S*)
2	**7**	Me	3	10	**8**	75	82[d] (*S*)
3	**9**	MOM	3	30	**10**	72	82[d] (*S*)
4	**11**	TBDPS	3	10	**12**	13[e]	88[d] (*S*)
5	**13**	PMB	3	30	**14**	88	92[d] (*S*)
6	**15**	^{t}Bu	3	30	**16**	89	93[d] (*S*)
7	**17**	^{t}Bu	2	20	**18**	74	92[f]
8	**19**	^{t}Bu	4	60	**20**	77	94[c]

[a] Reactions were carried out with a substrate concentration of 0.1 M. Powdered CsOH was used. [b] Ee was determined by HPLC analysis. A letter in parentheses indicates the absolute configuration. [c] Ee of the corresponding *N*-benzoate. [d] Ee of *N*-(benzoyl)-α-(hydroxymethyl)proline ethyl ester derived from the cyclization product. [e] A product resulting from β-elimination was also obtained in 58% yield. [f] Ee of ethyl *N*-(benzoyl)-α-(hydroxymethyl)azetidine-2-carboxylate derived from **18**.

Treatment of *t*-Bu ethers **17** and **19** with powdered CsOH in DMSO at 20 °C gave α-substituted azetidine **18**and

Scheme 3



α-substituted piperidine **20** in 92% or 94% ee, respectively (entries 7 and 8). The stereochemical course of the five-membered cyclization was retention in all cases (entries 1−6). α-Substituted proline **16** obtained by the present method was converted into α-hydroxymethyl pyrroglutamate **23**, a common key intermediate for the synthesis of lactacystin,[2] dysibetaine,[4] and kaitocephalin.[5] Ethyl ester **16** (93% ee) was converted into methyl ester **21** in 97% yield via hydrolysis followed by methylation of the resulting carboxylic acid. Ruthenium-promoted oxidation[13] of *N*-Boc amine **21** into amide **22** followed by removal of the Boc group gave **23** in 95% yield (Scheme 3).

The present method for the direct asymmetric intramolecular alkylation of β-alkoxy-α-amino esters was applied to the asymmetric synthesis of THF amino acids. THF amino

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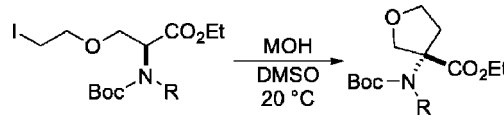
Table 3. Asymmetric Synthesis of THF Amino Acids from L-Serine[a]



entry	substrate	R	base[b] (mol equiv)	time (min)	product	yield (%)[c]	ee (%)[d]
1	**24**	MOM	KOH (3.0)	120	**25**	58 (19)	81
2	**24**	MOM	RbOH (1.5)	30	**25**	55 (23)	85
3	**24**	MOM	CsOH (1.5)	30	**25**	58 (17)	86
4	**26**	MEM	CsOH (1.5)	30	**27**	57 (20)	84

[a] Reactions were carried out with a substrate concentration of 0.1 M. [b] Powdered metal hydroxide was used. [c] Numbers in parentheses indicate the percent yield of the product resulting from β-elimination. [d] Ee of the corresponding *N*-benzoate determined by HPLC analysis.

acids are a new class of amino acids that are useful for searching conformationally restricted peptides with biological activity.[14] Racemic THF amino acids have been synthesized by Walker and co-workers via the cyclization of silyl enol ethers derived from homoserine,[15] and also by König and co-workers via the diastereoselective intramolecular aldol reaction of the sulfonium salts of methionine derivatives.[16] To the best of our knowledge, however, there has been no report on the synthesis of optically active THF amino acids. We report here the first asymmetric synthesis of THF amino acids via the direct intramolecular alkylation of serine derivatives. The precursors **24** and **26** were prepared from L-serine. The conditions for the asymmetric cyclization of **24** and **26** were examined (Table 3). Treatment of *N*-MOM derivative **24** with powdered KOH in DMSO for 120 min at 20 °C gave the desired THF amino acid with a tetrasubstituted carbon center **25** in 81% ee and 58% yield with concomitant β-elimination (19%) (entry 1). The use of powdered RbOH and CsOH instead of KOH slightly improved the enantioselectivity of the asymmetric cyclization to give **25** in 85% ee and 86% ee, respectively (entries 2 and 3). *N*-Boc-*N*-methoxyethoxymethyl (MEM) derivative **26** showed reactivity similar to that of **24** (entry 4). Treatment of **26** with powdered CsOH in DMSO at 20 °C gave THF amino acid **27** in 57% yield and 84% ee (entry 4). In the asymmetric cyclization of **24** and **26**, significant β-elimination (17−23%) was observed (entries 1−4). This suggests that intramolecular alkylation with C(α) side chains may proceed slower than that with *N* side chains.

In conclusion, we have developed a direct asymmetric intramolecular alkylation of β-alkoxy-α-amino esters. This method provides a convenient entry to optically active α-substituted serine derivatives from readily available L-serine. Optically active THF amino acids were also prepared for the first time by the present method.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformation of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedure and characterization data of componds **4**−**27** and determination of the absolute configuration of **6**, **8**, **10**, **12**, **14**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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