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2-Oxoimidazolidine-4-carboxylate as a Novel Chiral Auxiliary for Kinetic Resolution

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Abstract: A kinetic resolution by stereospecific amination using 2-oxoimidazolidine-4-carboxylate as a novel chiral auxiliary was investigated. The reaction of *tert*-butyl (4*S*)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate (**5**) with an equimolar benzylamine in CH_2Cl_2 proceeded stereospecifically to afford *tert*-butyl (4*S*)-1-methyl-3-((2*R*)-2-benzylaminopropionyl)-2-oxoimidazolidine-4-carboxylate ((*S*,*R*)-**6**) in a good yield, while (*S*,*R*)-**5** was recovered quantitatively.

During recent years kinetic resolution has received much attention as one of the efficient methods for the synthesis of optically active compounds.[1] Although various attempts on kinetic resolution have been accomplished, no report which involves direct nucleophilic substitution by amine has appeared so far.

In the series of our synthetic studies on angiotensin converting enzyme (ACE) inhibitors, the conformational analysis using X-ray, NMR and molecular modeling of our inhibitor elucidated that (4*S*)-1-methyl-2-oxo-imidazolidine-4-carboxylic acid moiety restricted the amide bond at the 3-position exclusively to the *trans* geometry as shown in Figure 1.[2] In addition to the restriction ability, compound **1**, which is facilely prepared

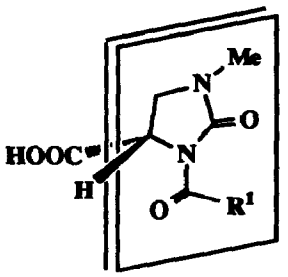
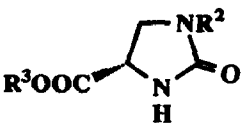
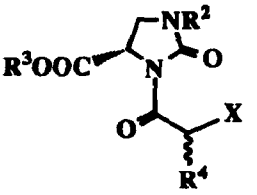


Figure 1



1



X : Leaving group

2

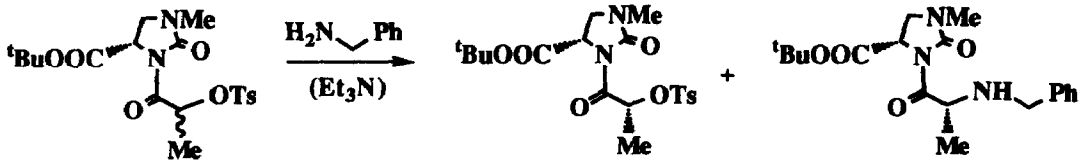
Figure 2

from L-asparagine,[3] inherently has an asymmetric carbon, functional groups and a planar 2-oxoimidazolidine ring. These structural characteristics prompted us to exploit **1** as a novel chiral auxiliary for the asymmetric synthesis.

Thus, we designed the bimolecular substitution reaction of (4*S*)-3-acyl-1-alkyl-2-oxoimidazolidine-4-carboxylate (**2**) having a racemic leaving group on the exocyclic acyl moiety with a primary amine. In this case, according to the steric and/or electronic effects of the auxiliary, the reaction rate was expected to be different between each diastereoisomer resulting in an effective kinetic resolution. Furthermore, since the acyl moiety attached to this auxiliary was supposed to be scissile under a mild basic condition, the present methodology was expected to provide a facile access to a range of optically pure α-amino acid synthons.

First, the reaction of *tert*-butyl (4*S*)-1-methyl-3-(2-tosyloxypropionyl)-2-oxoimidazolidine-4-carboxylate (**3**) [4] with benzylamine was examined. When an equimolar mixture of the diastereoisomers was treated with benzylamine in the presence or absence of Et_3N in several solvents, a kinetic resolution was observed as expected (Table 1). However, even when CH_2Cl_2 was used as a solvent, (*S*,*R*)-**4** of 62-82% de was obtained in 27-52% yield, and (*S*,*R*)-**3** of 76% de was recovered at the highest (Run 8). These results indicated that tosyloxy group was not good enough as a leaving group to realize an ideal kinetic resolution.

Table 1. Kinetic Resolution of Tosyloxy Derivatives (3)



3 (*S*,*R*)-**3** (*S*,*R*)-**4**

Run	Benzylamine (eq.)	Et_3N (eq.)	Solvent	Temp. (°C)	Time (hr)	(*S*,*R*)-3 Yield[a] (%)	(*S*,*R*)-3 de%[b]	(*S*,*R*)-4 Yield[a] (%)	(*S*,*R*)-4 de%[b]
1	1	—	DMSO	r.t.	144	44	34	46	34
2	0.5	0.5	DMSO	50	36	48	32	39	42
3	1	1	DMSO	50	36	15	70	70	16
4[c]	1	—	THF	r.t.	144	48	24	30	76
5	1	—	CH_2Cl_2	r.t.	144	64	30	27	82
6	1	—	CH_2Cl_2	reflux	48	54	48	37	72
7	1	1	CH_2Cl_2	reflux	24	60	40	33	80
8	1	1	CH_2Cl_2	reflux	48	38	76	52	62

[a] Isolated yield. [b] Determined by HPLC analysis.
[c] (*R*)-*N*-Benzyl-2-tosyloxypropionamide of 70% ee was isolated in 15% yield.

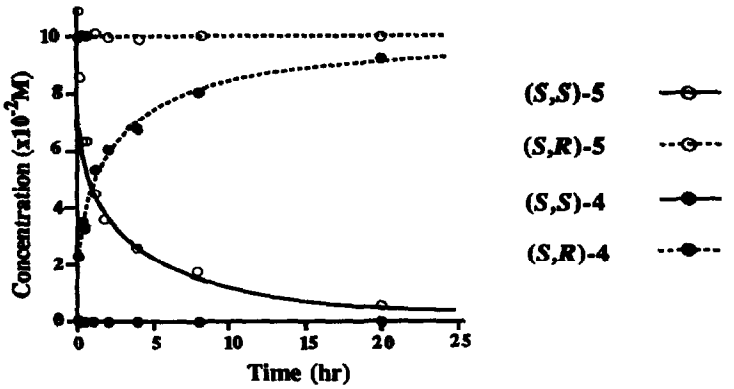
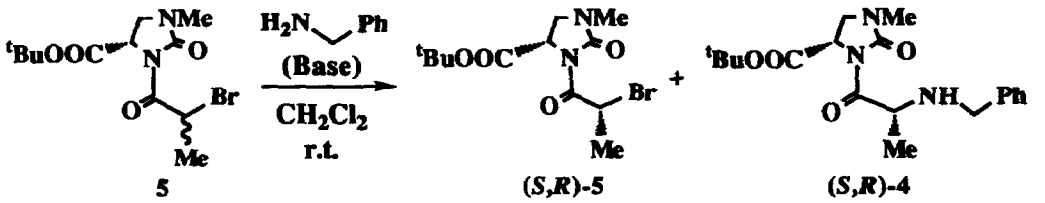


Figure 3. Conversion of 5 into 4

Table 2. Kinetic Resolution of Bromo Derivatives (5)



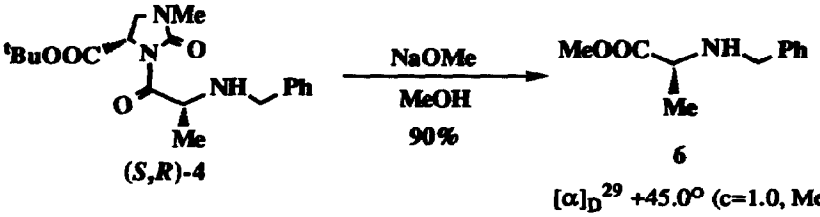
Run	Benzylamine (eq.)	Base (eq.)	Time (hr)	(S,R)-5 Yield[a] (%)	(S,R)-5 de%[b]	(S,R)-4 Yield[a] (%)	(S,R)-4 de%[b]
1	0.5	—	144	71	34	24	>99
2	0.5	K_2CO_3 (0.5)	120	50	88	42	96
3	0.5	Et_3N (0.5)	120	52	72	40	96
4	1	—	40	49	96	48	94
5	1	K_2CO_3 (1)	24	41	96	55	73

[a] Isolated yield. [b] Determined by HPLC analysis.

Then, the reaction was examined using *tert*-butyl (4*S*)-3-(2-bromopropionyl)-1-methyl-2-oxoimidazolidine-4-carboxylate (**5**)[3] as a substrate. Namely, a mixture of diastereoisomers was allowed to react with 1 equivalent of benzylamine in CH_2Cl_2 at room temperature and checked periodically by HPLC as shown in Figure 3. This result apparently showed that (*S*,*R*)-**5** [5] scarcely reacted with benzylamine under this condition and (*S*,*R*)-**4** increased with accompanied by decrease of (*S*,*S*)-**5** [5]. After 40 hours, aqueous work-up followed by column chromatography on silica gel gave (*S*,*R*)-**4** of 94% de in 48% yield and (*S*,*R*)-**5** of 96% de was recovered almost quantitatively (Run 4 in Table 2). The effective kinetic resolution was also performed using 0.5 equivalent of

benzylamine with 0.5 equivalent of Et_3N or K_2CO_3 (Run 2, 3).

Finaly, in order to remove the chiral auxiliary, (*S,R*)-**4** was treated with 1 equivalent of NaOMe in MeOH for 2 hours at room temperature. In consequence, optically pure methyl *N*-benzyl-D-alaninate (**6**) was isolated in 90% yield. The absolute configuration of **6** was confirmed by comparison of its optical rotation value with that in the literature.[6]



$[\alpha]_D^{29}$ +45.0° (c=1.0, MeOH)

(Lit.[6] $[\alpha]_D^{21}$ -41.0° for the antipode of **6**)

Scheme 1

In summary, a new category of kinetic resolution which is applied to the preparation of α-alkyl-α-amino acids has been developed. Efforts to further expand the utility of this methodology are under investigation in this laboratory.

Acknowledgment

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References and Notes

1. a) H. B. Kagan and J. C. Fiaud, *Topics in Stereochemistry*, eds. E. L. Eliel and S. H. Wilen, 1988, vol. 18, p. 249. b) C.-S. Chen and C. J. Sih, *Angew. Chem., Int. Ed. Engl.*, **1989**, *28*, 695. c) M. Hayashi, H. Miwata and N. Oguni, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1167. d) A. Guy, J. Doussot, R. Garreau and A. Godefroy-Falguieres, *Tetrahedron Asymmetry*, **1992**, *3*, 247. e) M. S. VanNieuwenhze and K. B. Sharpless, *J. Am. Chem. Soc.*, **1993**, *115*, 7864.
2. R. Shimizu, K. Nunami, H. Kubota, A. Kinumaki and K. Matsumoto, *Peptide Chemistry 1992*, ed. N. Yanaihara, 1993, p. 227.
3. K. Hayashi, K. Nunami, J. Kato, N. Yoneda, M. Kubo, T. Ochiai and R. Ishida, *J. Med. Chem.*, **1989**, *32*, 289.
4. a) H. Kubota, K. Nunami, M. Yamagishi, S. Nishimoto and K. Hayashi, *Chem. Pharm. Bull.*, **1991**, *39*, 1374. b) H. Kubota, K. Nunami, K. Hayashi, Y. Hashimoto, N. Ogiku, Y. Matsuoka and R. Ishida, *Chem. Pharm. Bull.*, **1992**, *40*, 1619.
5. The optically pure (*S,S*)-**5** and (*S,R*)-**5** were isolated by column chromatography on silica gel from a mixture of diastereoisomers, and their absolute configurations were established by X-ray analysis.
6. L. Szilagyi and Z. Gyorgydeak, *J. Am. Chem. Soc.*, **1979**, *101*, 427.

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