

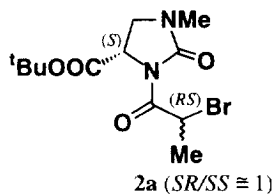
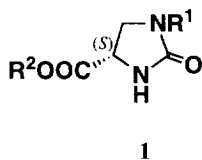
Dynamic Kinetic Resolution Utilizing 2-Oxoimidazolidine-4-carboxylate as a Chiral Auxiliary: Stereoselective Synthesis of α -Amino Acids by Gabriel Reaction

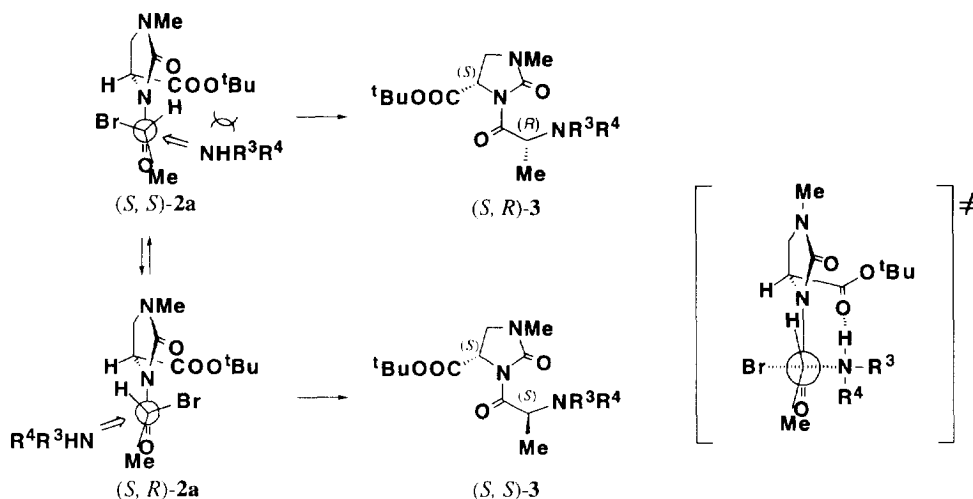
Akira Kubo, Hitoshi Kubota, Masami Takahashi, and Ken-ichi Nunami*†

Lead Optimization Research Laboratory, Tanabe Seiyaku Co., Ltd.,
 16-89, Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan.

Abstract: A Highly stereoselective Gabriel reaction via dynamic kinetic resolution utilizing 2-oxoimidazolidine-4-carboxylate as a chiral auxiliary was exploited. The reaction of *tert*-butyl (4*S*)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate (**2a**) with potassium phthalimide at room temperature predominantly afforded *tert*-butyl (4*S*)-1-methyl-3-((2*S*)-2-(phthaloylamino)propionyl)-2-oxoimidazolidine-4-carboxylate ((*S,S*)-**5a**) in a good yield which was derived to *L*-alanine derivative (**7**) by removal of the chiral auxiliary. Copyright © 1996 Elsevier Science Ltd

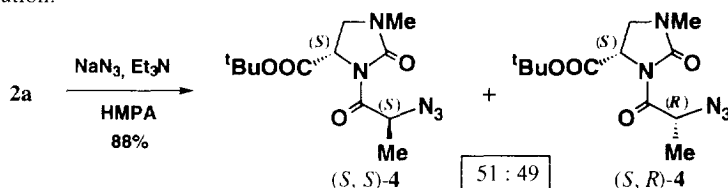
Dynamic kinetic resolution using a chiral auxiliary has recently received much attention as a new category of asymmetric synthesis.¹ As part of our studies on stereoselective nucleophilic substitution through dynamic kinetic resolution using (4*S*)-2-oxoimidazolidine-4-carboxylate (**1**) as a chiral auxiliary, we have reported the reaction of a diastereomeric mixture of *tert*-butyl (4*S*)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate (**2a**) with an amine followed by removal of the chiral auxiliary afforded *D*- α -amino acids.^{1a,b} It is noteworthy that the stereoselectivity of this reaction is in striking contrast to our initial working hypothesis^{1b} as shown in Scheme 1. Taking into account the steric hindrance of the bulky ester group, it was predicted that an amine would attack from the sterically less hindered site of (*S,R*)-**2a** resulting in the predominant formation of (*S,S*)-**3**. Primary and secondary amines, however, reacted with (*S,S*)-**2a** selectively. We speculated that the transition state in which an interaction between an amine and the ester group of (*S,S*)-**2a** accelerated the formation of (*S,R*)-**3** is responsible for the stereoselectivity of the amination (Figure 1).





On the basis of this speculation, a nitrogen nucleophile having no capability for the interaction with the ester moiety in the transition state was supposed to react with *(S,R)*-**2a** stereoselectively to afford the *L*- α -amino acid derivatives. We wish to report here the reaction of **2** with an anionic nitrogen nucleophile.

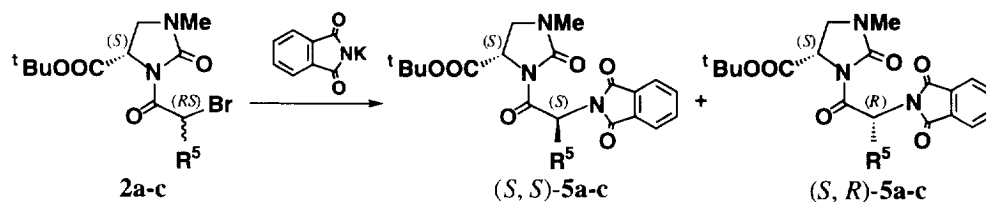
First, the reaction of **2a** with sodium azide was examined in hexamethylphosphoramide (HMPA) in the presence of triethylamine to achieve the dynamic kinetic resolution^{1a,b} (Scheme 2). The reaction afforded substituted product **4** as expected in a good yield but with a poor selectivity.² As each of *(S,S)*-**4** and *(S,R)*-**4** was elucidated not to epimerize at the asymmetric carbon attached to the azide group under the reaction conditions, it was suggested that the azide anion reacted with **2a** nonstereoselectively. This result prompted us to carry out the reaction with a more bulky nucleophile, which would induce efficient dynamic kinetic resolution.



We noticed that potassium phthalimide meets this requirement. In addition, it was expected to have enough basicity to cause rapid interconversion between *(S,S)*-**2a** and *(S,R)*-**2a** for efficient dynamic kinetic resolution without any additional base. The reaction of **2a** with potassium phthalimide was examined in several kinds of polar solvents (Table 1). In consequence all reactions afforded *(S,S)*-**5a**^{4,5} predominantly but the stereoselectivity and the yields were affected by the solvent. The best result was observed by using *N*-methyl-2-pyrrolidinone (NMP) as a solvent both in the yield and the stereoselectivity (entry 5). As the isolated products didn't epimerize under the reaction conditions, potassium phthalimide certainly reacted with *(S,R)*-**2a** selectively as predicted (Scheme 1). The reaction employing **2b** ($R^5 = \text{Et}$) and **2c** ($R^5 = (\text{CH}_2)_2\text{Ph}$) as substrates also proceeded stereoselectively to afford *L*- α -amino acid derivatives **5b** and **5c**, respectively (entry 6, 7).

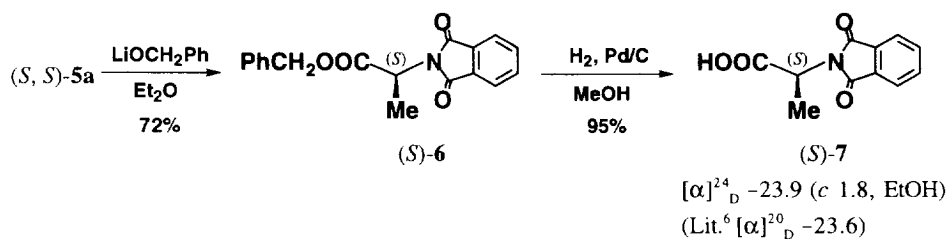
Finally, in order to remove the chiral auxiliary, (*S,S*)-**5a** was treated with 1 equivalent of LiOCH₂Ph in Et₂O at -20°C for 30 minutes (Scheme 3).^{1b} Benzyl *N*-phthaloyl-*L*-alaninate ((*S*)-**6**), being isolated in a moderate yield, was successively hydrogenated to afford *N*-phthaloyl-*L*-alanine ((*S*)-**7**). Optical purity of (*S*)-**7** was confirmed by comparison of its optical rotation value with that in the literature.⁶

Table 1. Dynamic Kinetic Resolution of Bromo Derivatives 2



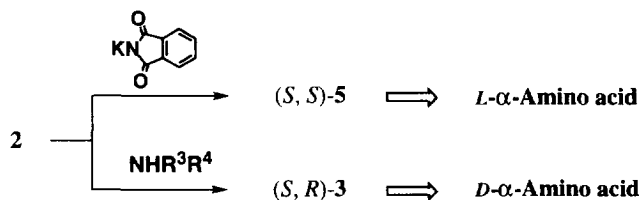
Entry ^a	R ⁵	Solvent	Time(h)	Product	Yield(%) ^b	(<i>S,S</i>)- 5 : (<i>S,R</i>)- 5 ^c
1	Me	DMSO	12	5a	90	88 : 12
2	Me	DMF	12	5a	85	95 : 5
3	Me	HMPA	12	5a	51 ^d	97 : 3
4 ^e	Me	HMPA	24	5a	70	97 : 3
5	Me	NMP	12	5a	90	97 : 3
6	Et	NMP	36	5b	74	95 : 5
7	(CH ₂) ₂ Ph	NMP	36	5c	69	96 : 4

a) The reaction was carried out with 1.0 mmol of **2** and 2 molar equivalents of potassium phthalimide in 15 ml of solvent at 25°C. b) Isolated yield. c) Determined by HPLC analysis. d) Excess amount of the reagent caused unknown side-reaction. e) 1.1 molar equivalent of potassium phthalimide was used.



Scheme 3

In summary, the stereoselective amination with potassium phthalimide by the dynamic kinetic resolution of **2**, and successive removal of the chiral auxiliary afforded *N*-phthaloyl-*L*-α-amino acid. Although the reaction of α-bromoalkanoates with phthalimide anion is a key step in the Gabriel synthesis of α-amino acids,⁷ a stereoselective one has scarcely been developed^{7b} because of the easy racemization of α-bromoalkanoates. This is the first report of the highly stereoselective Gabriel synthesis of α-amino acids by dynamic kinetic resolution. Furthermore, in combination with our previous synthetic strategy, this new Gabriel synthesis would enable the efficient synthesis of a range of *L*- and *D*-α-amino acids using the chiral auxiliary (**1**) by the selection of a nitrogen nucleophile on the basis of our working hypothesis (Scheme 4).



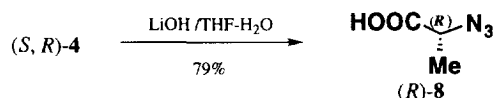
Scheme 4

Acknowledgment: We thank Dr. T. Da-te of our company for the X-ray crystallographic analysis.

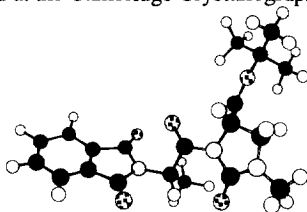
References and Notes

† Present address: R&D Planning Division, Tanabe Seiyaku Co., Ltd., 16-89, Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan.

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- In order to confirm the stereochemistry of the products, the minor diastereomer was converted to azido acid ((*R*)-**8**) by treatment with lithium hydroxide in aqueous THF. Its optical rotation value ($[\alpha]_D^{25} - 20.9$ (c 1.2, CHCl_3)) was identical with known (*2R*)-2-azidopropionic acid ($[\alpha]_D^{25} - 21.0$ (c 1.2, CHCl_3)).³



- Hoffman, R. V.; Kim, H-O. *Tetrahedron* **1992**, *48*, 3007–3020.
- (*S,S*)-**5a**: ¹H-NMR (CDCl_3) δ 1.49 (9H, s), 1.89 (3H, d, $J = 7.3$ Hz), 2.87 (3H, s), 3.35 (1H, dd, $J = 4.5, 9.7$ Hz), 3.69 (1H, dd, $J = 9.7, 10.3$ Hz), 4.66 (1H, dd, $J = 4.5, 10.3$ Hz), 5.98 (1H, q, $J = 7.3$ Hz), 7.66–7.88 (4H, m); IR (KBr) 1716 cm^{-1} ; SIMS m/z 402 ($M^+ + 1$), 346, 174(base).
- The stereochemistry of (*S,S*)-**5a** was confirmed by X-ray crystallographic analysis. Crystal data for (*S,S*)-**5a** has been deposited at the Cambridge Crystallographic Data Centre.

X-ray Structure of (*S,S*)-**5a**

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