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

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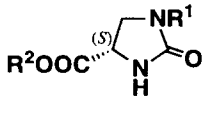
Abstract: A Highly stereoselective Gabriel reaction via dynamic kinetic resolution utilizing 2-oxoimidazolidine-4-carboxylate as a chiral auxiliary was exploited. The reaction of *tert*-butyl (4*S*)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate (**2a**) with potassium phthalimide at 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).



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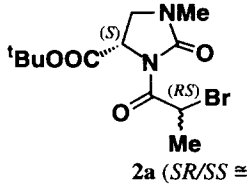
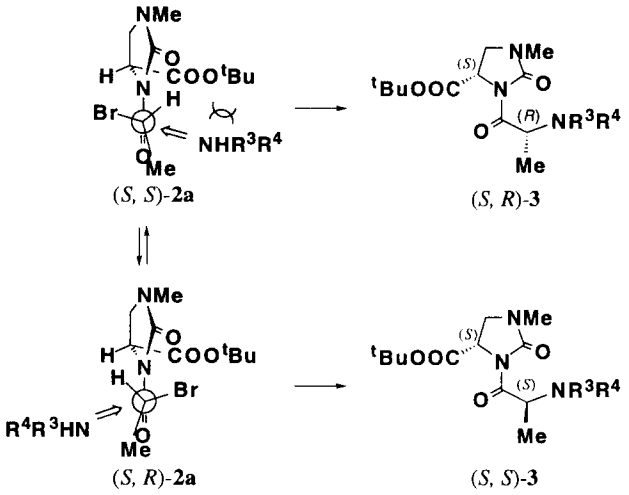


2a (*SR*/*SS* ≅ 1)



Scheme 1

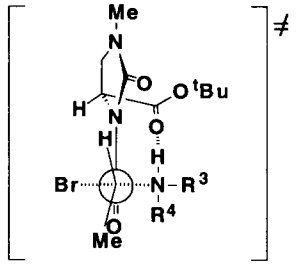
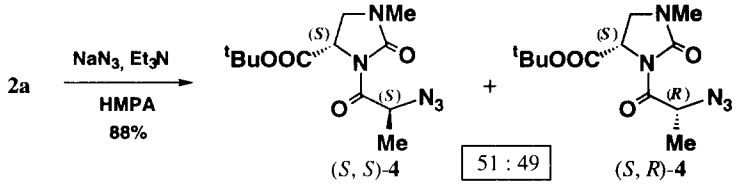


Figure 1

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.

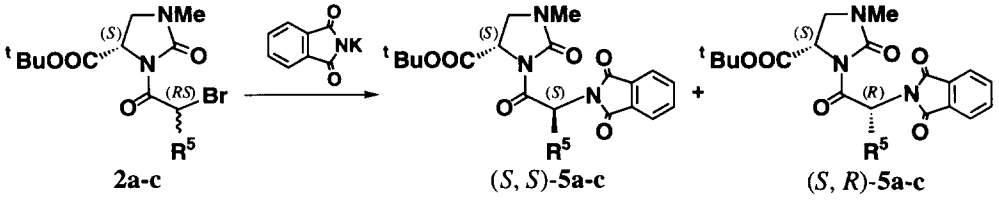


Scheme 2

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 = Et) and **2c** (R^5 = $(CH_2)_2Ph$) as substrates also proceeded stereoselectively to afford *L*-α-amino acid derivatives **5b** and **5c**, respectively (entry 6, 7).

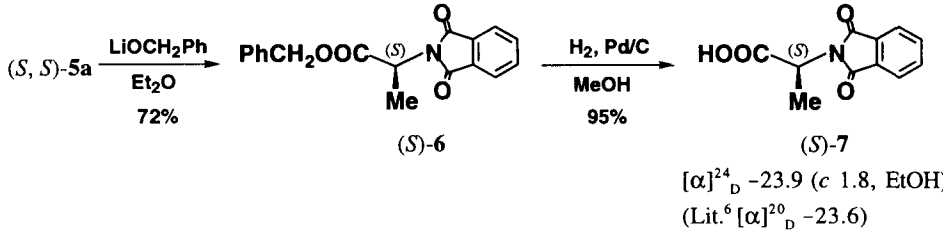
Finally, in order to remove the chiral auxiliary, (*S*,*S*)-**5a** was treated with 1 equivalent of $LiOCH_2Ph$ in Et_2O at −20°C for 30 minutes (Scheme 3).[1b] Benzyl *N*-phthaloyl-*L*-alaninate ((*S*)-**6**), being isolated in a moderate yield, was successively hydrogenated to afford *N*-phthaloyl-*L*-alanine ((*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



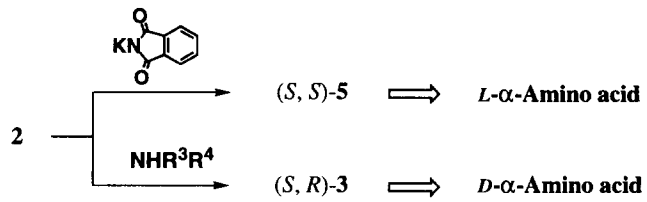
Entry[a]	R^5	Solvent	Time(h)	Product	Yield(%)[b]	(*S*,*S*)-**5** : (*S*,*R*)-**5**[c]
1	Me	DMSO	12	**5a**	90	88 : 12
2	Me	DMF	12	**5a**	85	95 : 5
3	Me	HMPA	12	**5a**	51[d]	97 : 3
4[e]	Me	HMPA	24	**5a**	70	97 : 3
5	Me	NMP	12	**5a**	90	97 : 3
6	Et	NMP	36	**5b**	74	95 : 5
7	$(CH_2)_2Ph$	NMP	36	**5c**	69	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

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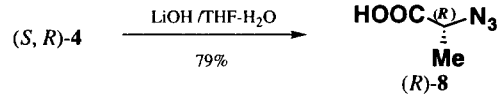
2. In order to confirm the stereochemistry of the products, the minor diastereomer was converted to azido acid ((*R*)-**8**) by treatment with lithium hydroxide in aqueous THF. Its optical rotation value ($[\alpha]^{25}_{D}$ -20.9 (*c* 1.2, $CHCl_3$)) was identical with known (2*R*)-2-azidopropionic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



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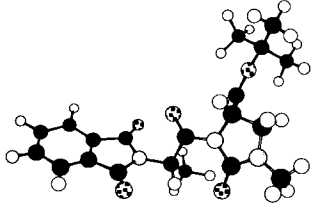
4. (*S*,*S*)-**5a** : ^{1}H-NMR ($CDCl_3$) δ 1.49 (9H, s), 1.89 (3H, d, *J* = 7.3 Hz), 2.87 (3H, s), 3.35 (1H, dd, *J* = 4.5, 9.7 Hz), 3.69 (1H, dd, *J* = 9.7, 10.3 Hz), 4.66 (1H, dd, *J* = 4.5, 10.3 Hz), 5.98 (1H, q, *J* = 7.3Hz), 7.66-7.88 (4H, m); IR (KBr) 1716 cm^{-1} ; SIMS m/z 402 (M^+ + 1), 346, 174(base).
5. 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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