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Dynamic Kinetic Resolution by Stereospecific Amination Utilizing 2-Oxoimidazolidine-4-carboxylate as a Novel Chiral Auxiliary

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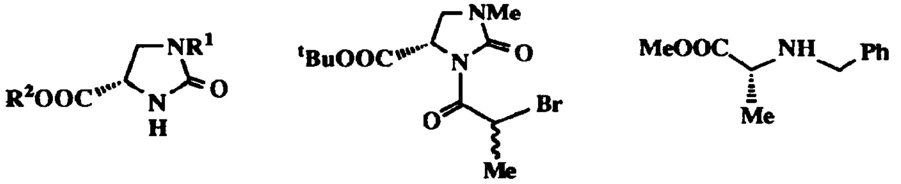
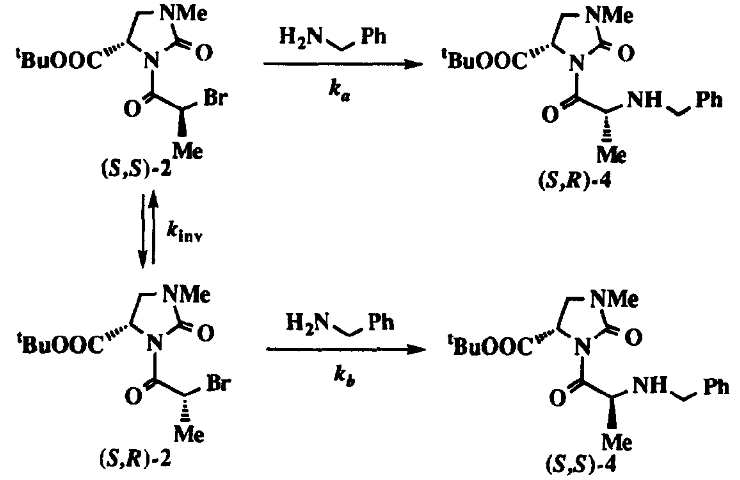
Abstract: A novel type of dynamic kinetic resolution by stereospecific amination was exploited utilizing 2-oxoimidazolidine-4-carboxylate **1** as a chiral auxiliary. The reaction of *tert*-butyl (4*S*)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate (**2**) with benzylamine in HMPA in the presence of K_2CO_3 or Et_3N at 25°C predominantly afforded *tert*-butyl (4*S*)-1-methyl-3-((2*R*)-2-benzylaminopropionyl)-2-oxoimidazolidine-4-carboxylate ((*S*,*R*)-**4**) in nearly quantitative yield.

Recently we reported a new category of kinetic resolution by stereospecific amination using 2-oxoimidazolidine-4-carboxylate **1** as a novel chiral auxiliary, which is applied to the asymmetric synthesis of optically active *N*-alkyl-α-amino acids.[1] For instance, the reaction of a diastereomeric mixture of *tert*-butyl (4*S*)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate (**2**) with 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*)-**4**) in an excellent yield, while (*S*,*R*)-**2** was recovered almost quantitatively. Compound (*S*,*R*)-**4** was easily converted to optically active methyl *N*-benzyl-D-alaninate (**3**) by removing the chiral auxiliary with NaOMe.



1 **2** **3**

Figure 1



Scheme 1

However, in this resolution, the expected product can be obtained at most in 50% yield. On the other hand, if the diastereoisomers, (*S,S*)-**2** and (*S,R*)-**2**, easily epimerize at the α position of bromo substituent under the reaction condition and both k_{inv}/k_a and k_a/k_b [2] values are high enough as shown in Scheme 1, (*S,R*)-**4** is expected to be obtained in 100% yield in theory.[3] This type of the asymmetric transformation, dynamic kinetic resolution,[4] in which the rapid interconversion between the substrates during reaction is incorporated with conventional kinetic resolution, has recently received much attention as an efficient stereoselective transformation process. The efficient kinetic resolution in our previous study prompted us to investigate dynamic kinetic resolution.

First, each epimerization rate of (*S,S*)-**2** and (*S,R*)-**2** was checked periodically by HPLC in the presence of K_2CO_3 in a solvent at 25°C (Figure 2). In consequence, no epimerization was observed in both compounds using CH_2Cl_2 or tetrahydrofuran (THF) as a solvent, while they epimerized in a polar solvent such as *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and hexamethylphosphoramide (HMPA). Especially, extremely rapid epimerization was observed in HMPA. A similar tendency was observed by using Et_3N as a base instead of K_2CO_3.

Then, a reaction of **2** with benzylamine was examined under several conditions (Table 1). All reactions afforded (*S,R*)-**4** predominantly, but their stereoselectivity was greatly affected by a solvent (Run 1-3). The most excellent result was observed by using HMPA (Run 3), which corresponded with that of the above epimerization study. Next, the base effect on stereoselectivity was examined in HMPA at 25°C. The use of Et_3N afforded almost quantitative yield of (*S,R*)-**4** (Run 4). The reaction using 2 equimolar amounts of benzylamine without additional base resulted in a little inferior stereoselectivity (Run 7).

Besides, when each isolated product, (*S,R*)- or (*S,S*)-**4**, was stirred in HMPA in the presence of K_2CO_3 and benzylamine at 25°C for 24 hr, they were recovered without any epimerization. From these results, it was apparent that the effective dynamic kinetic resolution was performed in accordance with our presumption.

Further, D-alanine derivative (**3**) was isolated in 82% overall yield from bromo derivative (**2**) by the removal of the chiral auxiliary by the procedure reported by us.[1]

Figure 2. Epimerization of (*S,S*)- and (*S,R*)-2 in the Presence of K_2CO_3

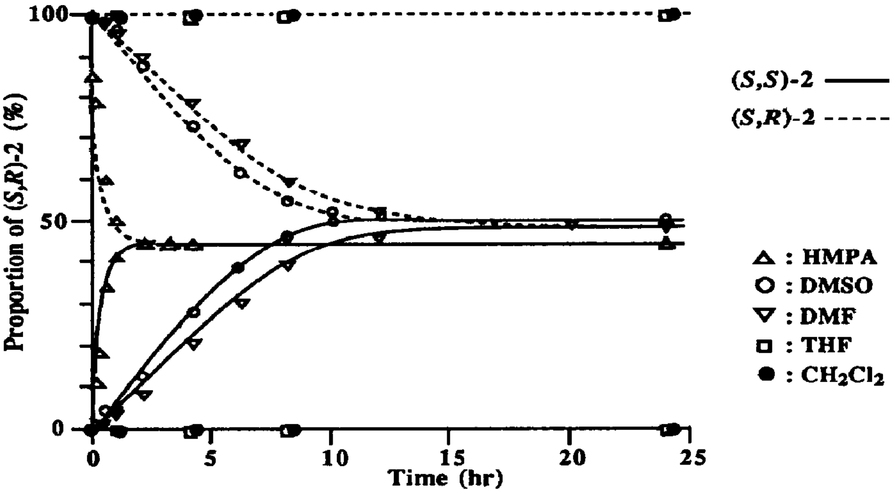


Table 1. Dynamic Kinetic Resolution of Bromo Derivative (2)

Run[a]	Benzylamine(eq.)	Base[b]	Solvent	Yield(%)[c]	(*S,R*) : (*S,S*)[d]
1	1.0	K_2CO_3	DMF	97	78 : 22
2	1.0	K_2CO_3	DMSO	94	82 : 18
3	1.0	K_2CO_3	HMPA	98	93 : 7
4	1.0	Et_3N	HMPA	96	94 : 6
5	1.0	DBU[e]	HMPA	90	90 : 10
6	1.0	——	HMPA	47[f]	93 : 7
7	2.0	——	HMPA	97	89 : 11

[a] The reaction was carried out in a 1 *M* solution of 2 at 25°C for 14 hr. [b] 1 molar equivalent. [c] Isolated yield. [d] Determined by HPLC analysis. [e] 1,8-Diazabicyclo[5.4.0]undec-7-ene. [f] Starting material was recovered in 36% yield.

In summary, a new category of dynamic kinetic resolution which provides a facile access to a range of optically pure α-amino acid synthons has been developed. Efforts to further expand the utility of this methodology are under investigation in this laboratory.

Acknowledgement

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