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Dynamic Kinetic Resolution Utilizing a Chiral Auxiliary by Stereoselective SN2 Alkylation with Malonic Ester Enolate

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Abstract: Dynamic kinetic resolution by highly stereoselective carbon-carbon bond formation 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 (**1**) with sodium dimethyl malonate in HMPA at room temperature predominantly afforded *tert*-butyl (4*S*)-1-methyl-3-((2*R*)-2-methyl-3,3-bis(methoxycarbonyl)propionyl)-2-oxoimidazolidine-4-carboxylate ((*S*,*R*)-**2a**) in a good yield.

In recent years, dynamic kinetic resolution has been noticed as one of the efficient methods for asymmetric synthesis.[1] As a part of our studies on exploiting a new category of stereoselective transformation process using 2-oxoimidazolidine-4-carboxylate as a chiral auxiliary, we reported the kinetic resolution and the dynamic kinetic resolution of *tert*-butyl (4*S*)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate (**1**) with benzylamine, which led to the synthesis of optically active α-amino acid.[2] In order to extend this methodology to the synthesis of a wide variety of chiral compounds, the reaction employing other types of nucleophiles should be investigated. We wish to report here the dynamic kinetic resolution of **1** with a carbon nucleophile.

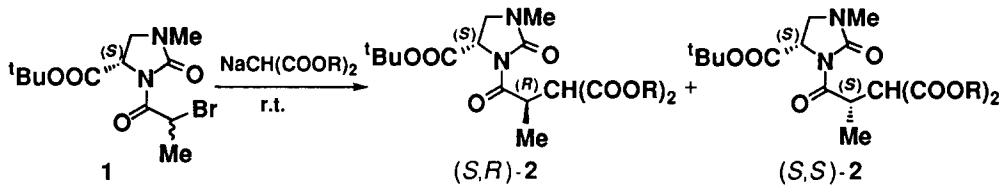
Malonic ester enolates were selected as carbon nucleophiles based on their soft nucleophilicity enough to make alkylation easily and on their appropriate basicity to cause rapid epimerization at the asymmetric carbon attached to the bromo substituent of **1**,[2b] which is essential to achieve the dynamic kinetic resolution, but not to racemize the asymmetric carbon of 2-oxoimidazolidine ring of **1**. Besides, their alkylated products were expected to be converted to chiral α-alkylsuccinic acid derivatives which have been noticed as key building blocks for the synthesis of a variety of biologically active compounds.

First, the reaction of **1** with sodium dimethyl malonate was examined in several kinds of polar solvents which accelerated epimerization of **1** in the presence of a base (Table 1, entry 1—3).[2b] All reactions afforded (*S*,*R*)-**2a** predominantly [3] as expected but the selectivity was much affected by a solvent. The best result was observed by using HMPA (entry 3). The selectivity was greatly reflected by the epimerization speed of **1**, which was higher in HMPA than in DMSO or DMF.[2b] Besides, when the isolated product **2a** was treated again with sodium dimethyl malonate at room temperature for 3h in HMPA, **2a** was recovered without any epimerization. These results apparently indicated that (*S*,*R*)-**2a** was predominantly afforded by the dynamic kinetic resolution of **1** with sodium dimethyl malonate. Next, the effect of ester moiety of malonic esters on stereoselectivity was examined. The bulkiness of the ester moieties of malonate scarcely influenced the

selectivity of the reaction (entry 4—6). On the other hand, sodium dibenzyl malonate increased the stereoselectivity affording 88% de of (*S,R*)-**2e** in 82% yield (entry 7).

In summary, highly stereoselective dynamic kinetic resolution of **1**, which was composed of the chiral auxiliary and an acyl moiety having a racemic leaving group in the α-position, with malonic ester enolates would be a new entry to the synthesis of a variety of chiral α-alkylsuccinic acid derivatives. It is noteworthy that the selectivity of the reaction was in striking contrast to that of the reaction of benzylamine with **1**.[2b] The mechanistic study and further expansion of the utility of this methodology are now under investigation in this laboratory.

Table 1. Dynamic Kinetic Resolution of Bromo Derivatives 1



1

Entry[a]	R	Solvent	Time (h)	Yield(%)[b]	Product	(*S,R*)-**2** : (*S,S*)-**2**[b]
1	Me	DMF	24	77	**2a**	68 : 32
2	Me	DMSO	3	97	**2a**	69 : 31
3	Me	HMPA[c]	3	92	**2a**	88 : 12
4	Et	HMPA	12	86	**2b**	91 : 9
5	^{i}Pr	HMPA	12	93	**2c**	90 : 10
6	^{t}Bu	HMPA	12	73	**2d**	89 : 11
7	CH_2Ph	HMPA	12	82	**2e**	94 : 6

a) The reaction was carried out with 1.0 mmol of **1** and sodium dialkyl malonate, which was freshly prepared from malonic ester and NaH in 8 ml of solvent. b) Determined by HPLC analysis. c) Hexamethylphosphoramide.

References and Notes

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3. In order to confirm the stereochemistry of the product, (*S,R*)-**2e** was converted to dimethyl 2-methylsuccinate and its optical rotation value was compared to that in the literature.[4]
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