Dynamic Resolution of α-Bromo-α-Alkyl Esters Using *N*-Methyl Pseudoephedrine as a Chiral Auxiliary: Asymmetric Syntheses of α-Amino Acid Derivatives

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Abstract: *N*-Methyl pseudoephedrine mediated dynamic resolution of α-bromo-α-alkyl esters in nucleophilic substitution reaction has been investigated. Best results are obtained when α-bromo-α-alkyl esters **1**, **4** and **5** are allowed to equilibrate before the addition of nucleophile. This simple epimerization-substitution sequence provides a practical protocol for asymmetric syntheses of α-amino acid derivatives **2**, **7** and **8** up to 98:2 enantiomeric ratio.

Key words: asymmetric synthesis, chiral auxiliaries, amino acids, kinetic resolution, nucleophiles

For asymmetric syntheses of α-heteroatom substituted carboxylic acids by nucleophilic substitution, dynamic resolution of α-halo esters or α-halo amides having a chiral auxiliary has been recently recognized as an effective synthetic method.[1] For the effective dynamic resolution, there must be a fast epimerization of the diastereomers with respect to their rate of substitution with the nucleophile. Two limiting pathways can be envisaged for the asymmetric nucleophilic substitutions. In one pathway, α-halo stereogenic center undergoes rapid epimerization and one of the two diastereomers reacts preferentially under the reaction condition. This is a case of dynamic kinetic resolution, in which the stereoselectivity is determined by the difference in the diastereomeric transition state energies for the reaction with the nucleophiles. In a different pathway, the stereoselectivity of the reaction is determined by the ratio of the diastereomers that is established before the substitution. This is termed dynamic thermodynamic resolution[2] because the ratio of diastereomer is thermodynamically controlled and the stereoselectivity of the reaction is not determined by the difference in the rates of substitutions. Here we wish to report nucleophilic substitution reactions of α-halo esters for asymmetric syntheses of α-amino acid derivatives in which two different pathways participate in reinforcing the asymmetric induction.

Initial studies on dynamic resolution of α-methyl-α-bromo ester were carried out with (*S*,*S*)-*N*-methyl pseudoephedrine as a chiral auxiliary.[3] When (*S*,*S*)-*N*-methyl pseudoephedrine and racemic α-bromopropionic acid were treated with DCC and DMAP to prepare α-methyl-α-bromo ester (α*RS*)-**1**, the diastereomeric ratio (dr) of **1** obtained after flash chromatography was about 65:35 dr. We found that two diastereomers were interconverting at room temp. in various solvents, favoring α*S*-epimer.[4,5] Treatment of (α*RS*)-**1** (α*S*:α*R* = 67:33) with benzylamine (1.2 equiv) as a nucleophile in CH_3CN for 4 h (>96% conversion) and subsequent removal of chiral auxiliary provided the amino acid derivatives **2** in 80% yield with 92:8 enantiomeric ratio (er) and *R*-enantiomer as a major enantiomer as shown in Table 1 (entry 1).[5] In the presence of Et_3N (1.2 equiv), the substitution reaction provided, after methanolysis, *(R)*-**2** in 83% yield with an improved er of 95:5 (entry 2).[6] The observed ers and yields in entries 1 and 2 suggest that α-bromo stereogenic center is configurationally labile with respect to the rate of substitution with benzylamine and (α*RS*)-**1** can be dynamically resolved under the reaction conditions. When tetrabutylammonium bromide (TBAB, 0.2 equiv) was added to the reaction, (*R*)-**2** was obtained with 91:9 er (entry 3). In the presence of both Et_3N and TBAB, the reaction gave (*R*)-**2** in 82% yield with 93:7 er (entry 4).[6] Based on the observed tendency of epimerization to favor (α*S*)-**1** that is a precursor of (*R*)-**2**, it seemed possible that the stereoselectivity of the reaction would improve if sufficient time for epimerization was allowed. If the two diastereomers equilibrate to the thermodynamic ratio before the addition of nucleophile, the higher asymmetric induction could be obtained than in the substitution with **1** of lower drs.[7] Consistent with our hypotheses, the er of product **2** was increased to 98:2 when benzylamine was added after 1.5 h epimerization in the presence of Et_3N as shown in Table 1 (entry 5).

In an effort to understand how different reaction conditions affect the stereoselectivity, we have monitored the reaction by ^1H NMR. When (α*RS*)-**1** of 53:47 dr (α*R*:α*S*) was treated with Et_3N in CH_3CN at room temp., the mixture equilibrated to a ratio of 3:97 (α*R*:α*S*) within 1.5 h and the ratio maintained during the course of reaction. After benzylamine was added to the thermodynamically equilibrated mixture, the substitution was completed within 4 h (>96% conversion) and provided (α*R*)-**3** with 98:2 dr with inversion of configuration as anticipated for S_N2 reaction. The observed results indicate that the addition of Et_3N accelerated the epimerization of (α*RS*)-**1**, not much affecting the rate of substitution with benzylamine.[4] Therefore, the enhanced er of **2** in entry 2 could be explained by the fast-

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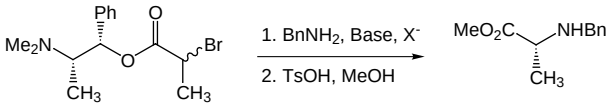
Table 1 Effects of Base and X

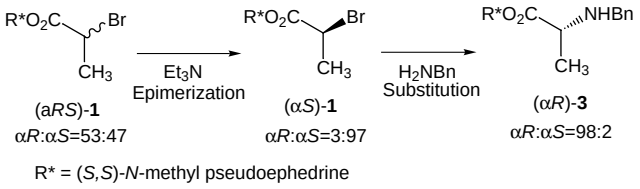


(α*RS*)-**1** (*R*)-**2**

Entry	Base	X⁻	Yield (%)[a]	Er (*R*:*S*)[b]
1	–	–	80	92:8
2	Et_3N	–	83	95:5
3	–	TBAB	71	91:9
4	Et_3N	TBAB	82	93:7
5[c]	**Et_3N**	–	**86**	**98:2**

[a] All substitution reactions were carried out at rt for 4 h in CH_3CN with (α*RS*)-**1** of 67:33 dr.
[b] The ers of **2** are determined by CSP-HPLC (Chiralcel-OD) with hexane and 2-propanol as solvent.
[c] The nucleophile was added after 1.5 h epimerization in the presence of Et_3N.

er equilibrium to the thermodynamic ratio of (α*S*)-**1** than in entry 1 (Table 1). We have also made the qualitative observation that the diastereomeric ratio of (α*R*)-**3** in Figure reflects the diastereomeric ratio of equilibrated (α*S*)-**1**. These preliminary results implied that the primary pathway of the asymmetric induction is a dynamic thermodynamic resolution in which the product ratio is determined by the thermodynamic ratio between (α*S*)-**1** and (α*R*)-**1** diastereomers, but a contribution from a dynamic kinetic resolution cannot be discounted.[7]

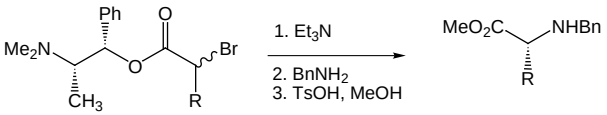


Figure

The scope of this methodology was investigated with three different α-bromo esters **4**–**6** as shown in Table 2. When α-ethyl-α-bromo ester **4** (60:40 dr) was treated with benzylamine and Et_3N for 18 h, subsequent methanolysis provided the corresponding amino acid derivatives (*R*)-**7** in 84% yield with 78:22 er (entry 1).[8] Encouraged by the high asymmetric induction using the epimerization-substitution protocol in the reaction of α-methyl-α-bromo ester **1**, we treated **4** (60:40 dr) with Et_3N in CH_3CN for 24 h for an epimerization, which provided the equilibrated mixture **4** with a thermodynamic ratio of 88:12. Even with the slower rate of epimerization and the lower thermodynamic ratio of **4**, the substitution with benzylamine for 24 h provided, after methanolysis, the highly enantioenriched amino acid derivative (*R*)-**7** with a 98:2 er (entry 2).

This epimerization-substitution protocol is also practical for the asymmetric syntheses of α-butyl-α-amino acid derivative (*R*)-**8** with 97:3 er from α-butyl-α-bromo ester **5** as shown in entry 4.[8] On the other hand, the diastereomeric ratio (65:35) of α-*iso*-propyl-α-bromo ester **6** remained invariant upon treatment with Et_3N for 24 h in CH_3CN and α-*iso*-propyl substituent almost completely halted the substitution reaction, probably due to steric effect (entry 5). Limited results indicate that the size and nature of the alkyl group attached to the reacting center affect the rate of both epimerization and substitution, which could also alter the pathway of asymmetric induction. The dependency of product ratio on the dr of α-bromo ester and the significant enhancement of product ratio compared to thermodynamic ratio of α-bromo ester suggest that the ers of (*R*)-**7** and (*R*)-**8** reflect not only the difference in population of two diastereomers but the difference in rates of substitution, induced by a dynamic thermodynamic and kinetic resolution.[7]

Table 2 Effect of Alkyl Groups



4 (R=CH_2CH_3)
5 (R=$CH_2CH_2CH_2CH_3$)
6 (R=$CH(CH_3)_2$)

7 (R=CH_2CH_3)
8 (R=$CH_2CH_2CH_2CH_3$)
9 (R=$CH(CH_3)_2$)

Entry	R	Epimerization[a]	Yield (%)[b]	Er (*R*:*S*)[c]
1	ethyl	0 h, 60:40	84	78:22
2	ethyl	24 h, 88:12	85	98:2
3	*n*-butyl	2 h, 61:39	85	76:24
4	*n*-butyl	24 h, 85:15	86	97:3
5	*iso*-propyl	24 h, 65:35	–	–

[a] Time for epimerization with Et_3N and dr (α*S*:α*R*) before the addition of nucleophile are shown.
[b] All reactions were carried out at r.t. in CH_3CN.
[c] The ers of **7** and **8** are determined by CSP-HPLC (Chiralcel-OD) with hexane and 2-propanol as solvents.

In summary, we have developed an efficient chiral auxiliary mediated method for the asymmetric syntheses of α-amino acid derivatives via dynamic resolution of α-bromo esters. The simple epimerization-substitution protocol[9] in obtaining highly enantioenriched amino acid derivatives that are suitably protected for further synthetic elaboration suggests further development of this methodology. Current work is aimed at understanding mechanistic details of these processes and applying this methodology to other nucleophiles.

Acknowledgement

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(2) This term was used by Prof. Peter Beak and coworkers for their mechanistic studies of electrophilic asymmetric substitution reaction: Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(3) (*S*,*S*)-*N*-Methyl pseudoephedrine is commercially available and can also be easily prepared by *N*-methylation of (*S*,*S*)-pseudoephedrine with MeI and NaH.

(4) When a solution of **1** (α*S*:α*R* = 67:33) in CH_3CN was stirred for 1.5 h, spontaneous epimerization provided **1** with a ratio of 80:20 (α*S*:α*R*).

(5) The absolute configurations of (α*S*)-**1** was assigned by comparison to the ^1H NMR of authentic diastereomer prepared from commercially available (*S*)-α-bromo-propionic acid. The absolute configuration of (*R*)-**2** was assigned by comparison of CSP-HPLC retention time with authentic material prepared from (*R*)-alanine.

(6) It has been proposed by several examples that the epimerization of α-halo ester and α-halo amide can be promoted by a base via keto-enol tautomerism and/or by a halide source via nucleophilic displacement of the bromide ion.[1]

(7) (a) For a quantitative analysis of the reactions of two interconverting diastereomeric species that lead to different products by a Curtin–Hammett–Winstein–Holness principle, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (b) For cases in which the stereoselectivity of the product reflects the thermodynamic ratios of diastereomeric intermediates, see: Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 3479. (c) Also see: Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718.

(8) The absolute configuration of (*R*)-**7** was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*R*)-2-aminobutyric acid. The absolute configuration of (*R*)-**8** was assigned by analogy to the formation of (*R*)-**2** and (*R*)-**7**.

(9) **General procedure for the asymmetric synthesis of methyl-*N*-benzyl alaninate [(*R*)-2]:** To a solution of (α*RS*)-**1** (α*S*:α*R* = 60:40) in CH_3CN (ca. 0.1 M) at r.t. was added Et_3N (1.2 equiv). The resulting reaction mixture was stirred at r.t. for 1.5 h, and then benzylamine (1.2 equiv) was added. After 4 h, the mixture was filtered and the solvent evaporated. The crude mixture and *p*-toluenesulfonic acid (0.1 equiv) in methanol were refluxed for 24 h. The solvent was evaporated and the crude material was purified by column chromatography to give methyl-*N*-benzyl alaninate [(*R*)-**2**]. From 100 mg of **1**, 53 mg (86% isolated yield) of **2** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) 7.32–7.23 (m, 5 H), 3.80 (d, *J* = 12.8 Hz, 1 H), 3.72 (s, 3 H), 3.67 (d, *J* = 12.8 Hz, 1 H), 3.39 (q, *J* = 7.0 Hz, 1 H), 1.85 (br, 1 H), 1.32 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.6, 140.1, 128.8, 128.6, 127.5, 56.3, 52.4, 52.2, 19.5. The enantiomeric ratio of **2** was determined to be 98:2 in favor of the *R* enantiomer by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from (*R*)-alanine. [Chiralcel OD column; 10% 2-propanol in hexane; 0.9 mL/min; the *R*-enantiomer(major) had a retention time of 6.0 min, and the *S*-enantiomer(minor) had a retention time of 5.4 min].