Stereoselective Preparation of *N*-Alkyl Dipeptide Analogues *via* Dynamic Kinetic Resolution of α-Halo Acyl Amino Esters

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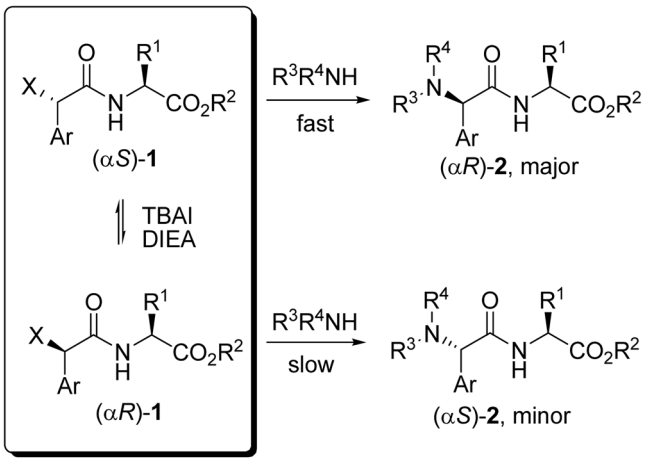
Received November 28, 2005

Key Words : Nucleophilic substitution, Asymmetric syntheses, Chiral auxiliary, Peptidomimetics, Dynamic kinetic resolution

Since configurational lability of α-halo-α-alkyl acyl compounds is readily induced by a base and/or a halide ion, chiral auxiliary mediated dynamic resolution of α-halo esters or α-halo amides in nucleophilic substitution has been recently recognized as an effective method for asymmetric syntheses.[1] Extension of this synthetic methodology to dynamic resolution of *N*-(α-haloacetyl) peptides in the stereospecific nucleophilic substitution (S_N2) could be an attractive synthetic strategy for asymmetric syntheses of peptide analogues. Recently it has been shown from our group that the chiral information of adjacent amino acid residue is efficiently transferred to the new C-N bond formation at α-halo carbon center for asymmetric syntheses of di-, tri- and tetrapeptide analogues.[2] The α-halo stereogenic center of **1** undergoes rapid epimerization in the presence of diisopropylethylamine (DIEA) and tetrabutylammonium iodide (TBAI), and (αS)-**1** reacts with the nucleophile preferentially to provide the dipeptide analogue (αR)-**2**. The mechanistic investigation showed that 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. Herein we describe our recent progress to extend the scope of the methodology to stereoselective preparation of *N*-terminal functionalized dipeptide analogues **2** with various amine nucleophiles.

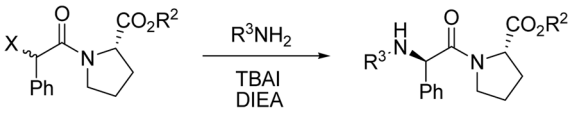


Scheme 1. Dynamic Kinetic Resolution of α-halo acetamides.

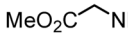
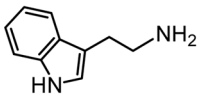
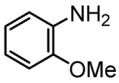
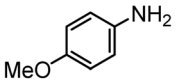
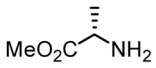
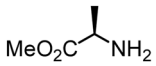
We have previously reported that the treatment of *N*-(α-bromo-α-phenylacetyl)-*L*-proline methyl ester (**3**) with benzylamine (1.2 equiv, $BnNH_2$), tetrabutylammonium iodide (1.0 equiv, TBAI) and diisopropylethylamine (1.0 equiv, DIEA) in CH_2Cl_2 at room temperature provided the dipeptide analogues **6** in 81% yield with 77 : 23 diastereomeric ratio (dr, αR : αS) as shown in Table 1, entry 1.[2c,3] Under the same reaction condition α-chloro acetamide **4** produced **7** in 68% yield with almost same selectivity as in the reaction of α-bromo acetamide **3**. (Table 1, entry 2) In the absence of TBAI, the reaction of α-chloro acetamide **4** did not produce the substitution product **7**. It is well known that TBAI might produce the α-iodo ester intermediate and can enhance the rate of the substitution and stereoselectivity.[2a] Also, We previously examined the substitution of *N*-(α-bromo-α-phenylacetyl)-*L*-proline benzyl ester (**5**) with the more sterically demanding secondary amine nucleophile, dibenzylamine (Bn_2NH) as shown in Table 2, entry 1.[2b] Dibenzylamine showed sufficient reactivity for the nucleophilic substitution to provide **17** in 90% yield and the stereoselectivity of the reaction was increased remarkably (>99 : 1 dr).[3]

We then set out to examine the scope of this methodology with various primary amines such as functionalized alkyl amines, aromatic amines, α-alkyl substituted amines and α-amino esters. With two functionalized primary alkyl amines, tryptamine and methyl glycinate, dipeptide analogues **8** and **9** were obtained with higher selectivities (96 : 4 dr and 83 : 17 dr) as shown in Table 1, entries 3-4. In the reactions with two aromatic amines which have a methoxy substituent at different positions, *o*-anisidine gave better stereoselectivity than *p*-anisidine. (entries 5 and 6) Isopropylamine also proved to be a good nucleophile to give the dipeptide analogue **12** in 45% yield with 88 : 12 dr. When two enantiomers of α-methyl benzylamine were used as nucleophiles, moderate double stereodifferentiation is observed as shown in entries 8 and 9. *N*-(α-Chloro-α-phenylacetyl)-*L*-proline benzyl ester experienced matching with (*S*)-enantiomer to afford dipeptide analogue **13** in a ratio of 86 : 14 and mismatching with (*R*)-enantiomer to provide **14** in a 79 : 21 ratio. Furthermore, we found that this tendency of stereodifferentiation was also observed in reactions of alanine methyl ester nucleophiles. (entries 10 and 11) The substitution of *N*-(α-bromo-α-phenylacetyl)-*L*-proline methyl ester with (*S*)-alanine methyl ester gave the dipeptide analogue **15** in

Table 1. Reactions of **3-5** with primary amine nucleophiles



3 (X=Br, R^2=Me)
4 (X=Cl, R^2=Bn)
5 (X=Br, R^2=Bn)

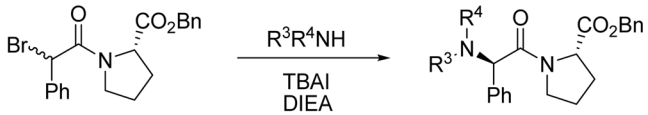
Entry[a]	X	R^2	Nucleophile	%Yield[b]	Dr[c] (αR : αS)
1	Br	Me		81 (**6**)	77:23
2	Cl	Bn		68 (**7**)	76:24
3	Br	Me		34 (**8**)	96:4
4	Br	Bn		42 (**9**)	83:17
5	Br	Bn		99 (**10**)	90:10
6	Br	Bn		99 (**11**)	74:26
7	Br	Bn		45 (**12**)	88:12
8	Cl	Bn		43 (**13**)	86:14
9	Cl	Bn		12 (**14**)	79:21
10	Br	Me		46 (**15**)	86:14
11	Br	Me		31 (**16**)	77:23

[a]Initial drs of **3-5** are approximately 50 : 50 and all reactions were carried out in CH_2Cl_2 for 24 h at rt. [b]Isolated yields. [c]The drs are determined by ^{1}H NMR of reaction mixture.

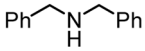
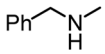
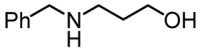
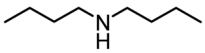
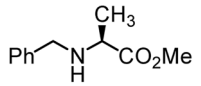
46% yield with 86 : 14 dr, while (*R*)-alanine methyl ester gave the dipeptide analogue **16** in 31% yield with 77 : 23 dr.

In addition, we were pleased to demonstrate that this methodology is also efficient for the substitution with various secondary amines, affording *N,N*-dialkyl substituted dipeptide anlogues **18-20** with high selectivities and good yields as shown in Table 2. For example, when *N*-benzyl-*N*-methyl amine was used as a nucleophile for the reaction with *N*-(α-bromo-α-phenylacetyl)-*L*-proline benzyl ester (**5**), the product **18** was formed in 84% yield with 82 : 18 dr. (entry 2) Also, treatment of **5** with 3-(benzylamino)propanol produced the substituted product **19** in 49% yield with 92 : 8 dr. (entry 3) Furthermore, we attempted the substitution reaction of **3** with dibutylamine and found that *N,N*-dibutyl product **20** was produced in 77% yield with 87 : 13 dr. (entry 4) For

Table 2. Reactions of **5** with secondary amine nucleophiles



5

Entry[a]	Nucleophile	% Yield[b]	Dr[c] (αR : αS)
1		90 (**17**)	>99:1
2		84 (**18**)	82:18
3		49 (**19**)	92:8
4		77 (**20**)	87:13
5		N.R.	-

[a]Initial dr of **5** is approximately 50 : 50 and all reactions were carried out in CH_2Cl_2 for 24 h at rt. [b]Isolated yields. [c]The drs are determined by ^{1}H NMR of reaction mixture.

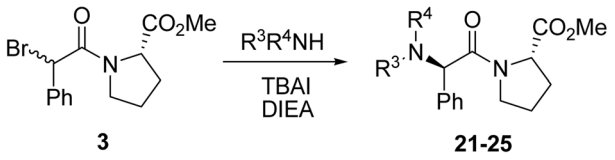
stereoselective preparation of various *N,N*-dialkyl substituted arylglycine peptide analogues, this methodology has potential advantages over *N*-alkylation of optically active arylglycine peptide analogues in simplicity and cost. The products **18-20** should serve as versatile intermediates for asymmetric construction of nonnatural peptides. However, the sterically hindered nucleophile, *N*-benzyl *L*-alanine methyl ester, did not afford the product (entry 5).

We then examined the scope of this methodology with five different cyclic secondary amine nucleophiles as shown in Table 3. The substitutions afforded the dipeptide analogues **21-25** in 98-70% isolated yields with moderate stereoselectivities. The chirality of *L*-proline is not efficiently transferred to new C-N bond formation with sterically less demanding cyclic amines such as pyrrolidine, piperidine, morpholine and 1,2,3,4-tetrahydroisoquinoline. (entries 1-4) More sterically demanding nucleophile, *L*-Leu-*L*-Pro dipeptide methyl ester gave better stereoselectivity (81 : 19 dr) as shown in entry 5.

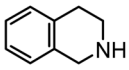
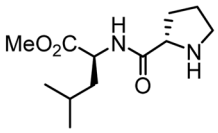
We previously reported that the treatment of *N*-(α-bromo-α-phenylacetyl)-(*L*)-leucine benzyl ester (**26**) with benzylamine ($BnNH_2$), tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIEA) in CH_2Cl_2 at room temperature afforded the dipeptide analogues **27** in 97% yield with 71 : 29 diastereomeric ratio (dr, αR : αS), while the reactions of **26** under the same condition gave the dipeptide analogue **29** in 95% yield with 93 : 7 dr (αR : αS) as shown in Table 3, entries 1 and 3.[2a] Various other nucleophiles were subjected to the above reaction conditions, and the results are summarized in Table 4. Higher level of selectivity was observed with the *L*-lysine side chain amine nucleophile, compared to the reaction with benzylamine (entry 2).

When **26** was allowed to react with *N*-methyl benzylamine

Table 3. Reactions of **3** with cyclic secondary amine nucleophiles



3 **21-25**

Entry[a]	Nucleophile	% Yield[b]	Dr[c] (αR : αS)
1		91 (**21**)	67:33
2		95 (**22**)	67:33
3		97 (**23**)	74:26
4		98 (**24**)	73:27
5		70 (**25**)	81:19

[a]Initial dr of **3** is approximately 50 : 50 and all reactions were carried out in CH_2Cl_2 for 24 h at rt. [b]Isolated yields. [c]The drs are determined by ^{1}H NMR of reaction mixture.

under the same condition used for dibenzylamine, no significant stereoselectivity was noted as shown in entry 4. Mild drops in stereoselectivity were seen with dibutylamine and 2-(benzylamino)ethanol. (entries 5 and 6) On the other hand, higher stereoselectivities were observed in the reactions with 3-(benzylamino)propanol and *N,N'*-dibenzyl 2,2'-(ethylenedioxy)diethyleneamine in good yields (entries 7 and 8).

In summary, we have shown that dynamic kinetic resolution of α-bromo and α-chloro amides in nucleophilic substitution reaction can be successfully applied towards the preparation of various *N*-terminal functionalized dipeptide analogues. The stereochemical aspects of the results showed that stereoselectivity depends critically on the structures of amine nucleophiles. This mild and practical method can be run on a multi-gram scale without any special precautions and should be applicable to stereoselective syntheses of various peptidomimetics.

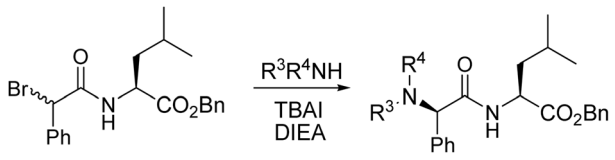
Supporting Information Available. All experimental procedures and spectroscopic data for new compounds.

Acknowledgement. This work was supported by Konkuk University in 2005.

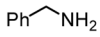
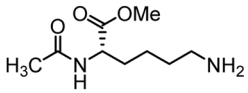
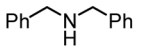
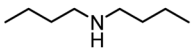
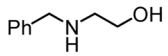
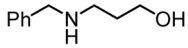
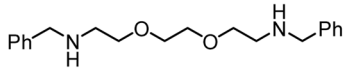
References and Notes

1. (a) Kim, H. J.; Shin, E.-k.; Chang, J.-y.; Kim, Y.; Park, Y. S. *Tetrahedron Lett.* **2005**, *46*, 4115. (b) Kiau, S.; Discordia, R. P.; Madding, G.; Okuniewicz, F. J.; Rosso, V.; Venit, J. J. *J. Org. Chem.* **2004**, *69*, 4256. (c) Valenrod, Y.; Myung, J.; Ben, R. N. *Tetrahedron Lett.* **2004**, *45*, 2545. (d) Nam, J.; Lee, S.-k.; Park, Y. S. *Tetrahedron* **2003**, *59*, 2397. (e) Nam, J.; Lee, S.-k.; Kim, K. Y.; Park, Y. S. *Tetrahedron Lett.* **2002**, *43*, 8253. (f) Lee, S.-k.; Nam, J.; Park, Y. S. *Synlett* **2002**, 790. (g) Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Santos, A. G.; Treweeke, N. R.; Weaving, R. *Tetrahedron* **2001**, *57*, 6589. (h) Lee, S.-k.; Lee, S. Y.; Park, Y. S. *Synlett* **2001**, 1941. (i) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700. (j) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. *J. Org. Chem.* **1997**, *62*, 5830. (k) Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry* **1995**, *6*, 93.
2. (a) Chang, J.-y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Park, Y. S. *Bull. Korean Chem. Soc.* **2005**, *26*, 989. (b) Chang, J.-y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Park, Y. S. *Tetrahedron* **2005**, *61*, 2743. (c) Kim, H. J.; Chang, J.-y.; Shin, E.-k.; Park, Y. S. *Bull. Korean Chem. Soc.* **2005**, *26*, 273. (d) Nam, J.; Chang, J.-y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Jang, S.; Park, Y. S. *Tetrahedron* **2004**, *60*, 6311. (e) Nam, J.; Chang, J.-Y.; Hahm, K.-S.; Park, Y. S. *Tetrahedron Lett.* **2003**, *44*, 7727.
3. The absolute configurations of **6**, **17**, **27** and **29** were assigned as αR by comparison to the ^{1}H-NMR of authentic epimers individually prepared from the coupling of *L*-proline or *L*-leucine and (*R*)-phenylglycine derivative.[2] The absolute configurations of other products reported here are provisionally assigned by analogy.

Table 4. Reactions of **26** with various amine nucleophiles



26 **27-34**

Entry[a]	Nucleophile	%Yield[b]	Dr[c] (αR : αS)
1		97 (**27**)	71:29
2		97 (**28**)	82:18
3		95 (**29**)	93:7
4		99 (**30**)	51:49
5		81 (**31**)	73:27
6		97 (**32**)	71:29
7		77 (**33**)	87:13
8		75 (**34**)	85:15

[a]Initial dr of **26** is approximately 50 : 50 and all reactions were carried out in CH_2Cl_2 for 24 h at rt. [b]Isolated yields. [c]The drs are determined by ^{1}H NMR of reaction mixture.