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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 4115–4117

Dynamic kinetic resolution of α-chloro esters in asymmetric nucleophilic substitution using diacetone-D-glucose as a chiral auxiliary

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Received 17 March 2005; revised 30 March 2005; accepted 1 April 2005
Available online 22 April 2005

Abstract—Diacetone-D-glucose mediated dynamic kinetic resolution of α-chloro-α-aryl esters in nucleophilic substitution reactions has been investigated. Reactions of various amine nucleophiles in the presence of TBAI and DIEA can provide the substitution products **2**–**10** up to 97% yield and 97:3 dr. This simple procedure with easy removal of the chiral auxiliary provides a practical protocol for asymmetric syntheses of α-amino acid derivatives up to 97:3 er.

Chiral auxiliary mediated dynamic resolution of α-halo esters or α-halo amides has been recently recognized as an effective synthetic method for asymmetric syntheses of α-heteroatom substituted carboxylic acid derivatives.[1,2] Although many existing chiral auxiliaries can achieve a useful level of diastereoselection in the dynamic resolution process, it is still desirable to find effective chiral auxiliaries for achieving practical asymmetric nucleophilic substitution. Carbohydrates are readily available inexpensive natural products in which numerous functional groups and stereogenic centers are present in a molecule. A number of carbohydrate based templates have been used as chiral auxiliaries for various stereoselective reactions.[3] Herein, we report first successful example of carbohydrate mediated dynamic resolution of α-halo esters in nucleophilic substitution for asymmetric syntheses of α-amino acid derivatives.[4]

Initial studies on dynamic resolution of α-phenyl-α-chloro ester were carried out with diacetone-D-glucose as a chiral auxiliary. Treatment of diacetone-D-glucose with racemic α-chloro-α-phenylacetyl chloride in the presence of Et_3N provided α-chloro-α-phenyl ester (α*RS*)-**1** in 80% yield with 55:45 diastereomeric ratio (dr). When the two diastereomeric mixtures of (α*RS*)-**1** were treated with benzylamine ($BnNH_2$, 1.5 equiv), tetrabutylammonium iodide (TBAI, 1.0 equiv), and diisopropylethylamine (DIEA, 1.0 equiv) in CH_2Cl_2 at room temperature for 12 h, the amino acid derivative **2** was produced in 86% yield with 96:4 diastereomeric ratio (dr, α*S*:α*R*) as shown in Table 1 (entry 1).[5] The observed dr and yield suggest that α-chloro 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 condition. Most of the solvents explored gave similar selectivities. As shown in entries 2–5, the substitution product **2** was obtained with 97:3 dr in $CHCl_3$, 97:3 dr in ether, 96:4 dr in THF and 96:4 dr in hexane. However, the selectivity was reduced in CH_3CN (entry 6) and the reaction was very slow in toluene. The faster reaction at 50 °C gave the product with slightly lower stereoselectivity (93:7 dr) compared to the reaction at rt. Similar stereoselectivity was observed in the substitution at 0 °C (entries 7 and 8). In the absence of TBAI, the reaction of α-chloro ester **1** gave the substitution product **2** with almost the same stereoselectivity (entry 9). However, the rate of the substitution is substantially decreased compared to the reactions with TBAI and require longer reaction time (70 h) to obtain moderate yield (54% yield). In addition, in the absence of both TBAI and DIEA, the reaction did not produce product **2**, and most of the starting material was recovered (entry 10). The results in entries 9 and 10 pointed to the importance of the presence of iodide ion and base for sufficient rate acceleration. When **1** with 88:12 dr was treated with

Keywords: Dynamic kinetic resolution; Asymmetric syntheses; Nucleophilic substitution; Carbohydrate; Chiral auxiliary.
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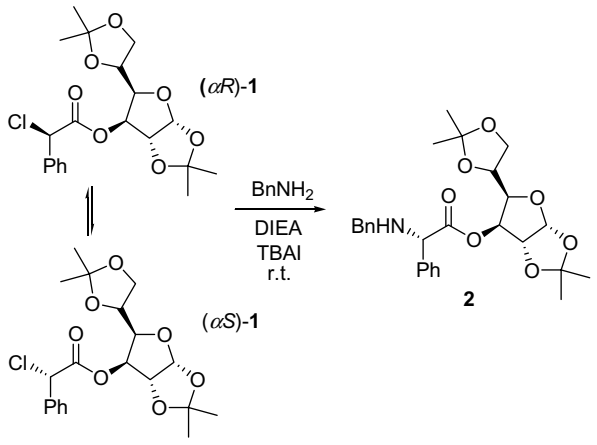
doi:10.1016/j.tetlet.2005.04.003

Table 1. Dynamic kinetic resolution of α-chloro ester **1** in nucleophilic substitution



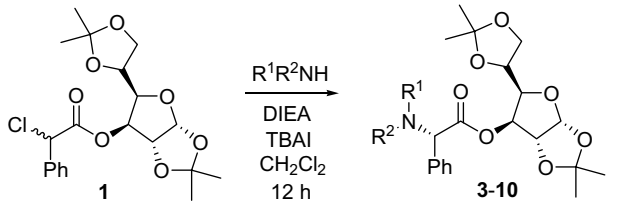
Entry	Dr of S.M.	Condition	Yield[a] (%)	Dr (αS:αR)[b]
1	55:45	CH_2Cl_2	86	96:4
2	55:45	$CHCl_3$	53	97:3
3	55:45	Ether	51	97:3
4	55:45	THF	72	96:4
5	55:45	*n*-Hexane,	70	96:4
6	55:45	CH_3CN	96	90:10
7[c]	55:45	50 °C	76	93:7
8[c]	55:45	0 °C	92	97:3
9[c]	55:45	No TBAI	54	95:5
10[c]	55:45	No TBAI, No DIEA	N.R.	—
11	88:12[d]	CH_2Cl_2	83	96:4
12	30:70[d]	CH_2Cl_2	85	95:5

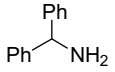
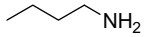
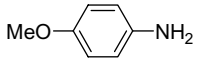
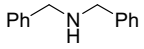
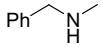
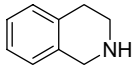
[a] Isolated yields.
[b] The drs are determined by ^1H NMR of reaction mixture.
[c] The reactions were carried out in CH_2Cl_2.
[d] The mixtures are prepared by column chromatography with fractional collection.

benzylamine in the presence of TBAI and DIEA, the reaction gave product **2** with 96:4 dr as shown in entry 11. Also, almost the same dr of **2** was observed in the reaction of **1** with reversed diastereomeric enrichment of 30:70 dr (entry 12). Thus, the dr of product **2** is not dependent on the starting ratio of two epimers of **1**. These preliminary results indicate that the epimerization promoted by TBAI and DIEA is sufficiently fast with respect to the rate of substitution and the primary pathway of the asymmetric induction is a dynamic kinetic resolution.

With the identification of diacetone-D-glucose as an appropriate stereocontrolling element for dynamic kinetic resolution of α-chloro-α-phenyl acetate, we set out to examine the scope of this methodology with eight different amine nucleophiles as shown in Table 2. We were pleased to observe that this methodology is efficient for a variety of primary amine, secondary amine, and cyclic amine nucleophiles, affording amino acid derivatives **3**–**10** in 97–48% isolated yields with high stereoselectivities as shown in entries 1–8. Limited results indicate that the size and nucleophilicity of amines may have relatively little effect on stereoselectivity, but that it significantly affected the yield.

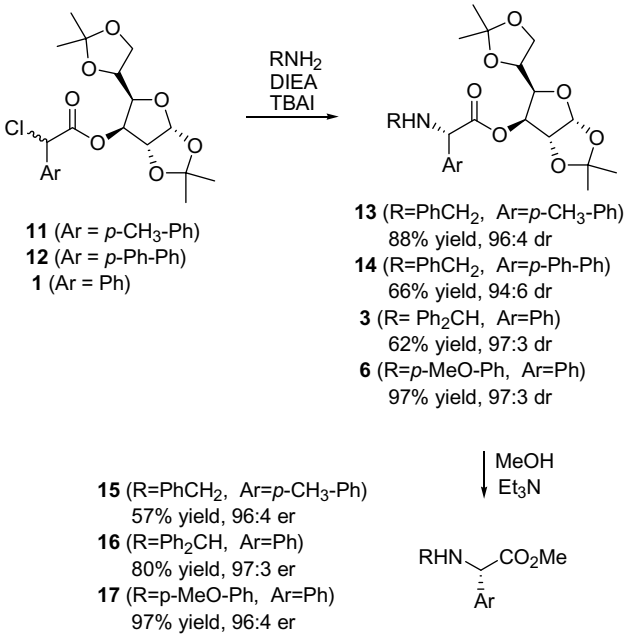
Table 2. Reactions with various amine nucleophiles



Entry	R^1R^2NH	Yield[a] (%)	Dr (αS:αR)[b]
1		62 (**3**)	97:3
2		75 (**4**)	95:5
3		48 (**5**)	95:5
4		97 (**6**)	97:3
5		61 (**7**)	94:6
6		82 (**8**)	96:4
7		73 (**9**)	93:7
8		96 (**10**)	97:3

[a] Isolated yields.
[b] The drs are determined by ^1H NMR of reaction mixture.

As an extension of the above DKR, same sequences were applied to two different α-chloro-α-aryl esters as shown in Scheme 1. Treatment of α-*p*-methylphenyl α-chloro acetate **11** with benzylamine, TBAI, and DIEA gave the substitution product **13** in 88% yield with



Scheme 1.

96:4 dr. Also, the reactions of α-*p*-phenylphenyl α-chloro acetate **12** took place with high stereoselectivity, affording **14** in 66% yield with 94:6 dr. The removal of the diacetone-D-glucose chiral auxiliary was readily achieved by the treatment of esters **3**, **6**, and **13** in methanol with Et_3N at room temperature for 2–3 days. The basic methanolysis furnished arylglycine methyl esters **15**, **16**, and **17** in 98–57% yields without racemization within experimental error.[6]

We have presented a novel and practical approach for the asymmetric syntheses of unnatural α-amino acid derivatives via dynamic kinetic resolution of α-chloro esters using carbohydrate as a chiral auxiliary. The simple protocol with mild conditions and the easy removal of chiral auxiliary suggests further development of this methodology. Further applications of this methodology to various α-alkyl substituents and nucleophiles are currently under investigation.

Acknowledgements

This work was supported by Korea Research Foundation Grant (KRF 2003-041-C00191).

References and notes

1. For reviews on dynamic resolution of α-halo esters, see: (a) Valenrod, Y.; Myung, J.; Ben, R. N. *Tetrahedron Lett.* **2004**, *45*, 2545; (b) Nam, J.; Lee, S.-k.; Park, Y. S. *Tetrahedron* **2003**, *59*, 2397; (c) Nam, J.; Lee, S.-k.; Kim, K. Y.; Park, Y. S. *Tetrahedron Lett.* **2002**, *43*, 8253; (d) Lee, S.-k.; Nam, J.; Park, Y. S. *Synlett* **2002**, 790; (e) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700.
2. For reviews on dynamic resolution of α-halo amides, see: (a) Chang, J.-y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Park, Y. S. *Tetrahedron* **2005**, *61*, 2743; (b) Nam, J.; Chang, J.-y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Jang, S.; Park, Y. S. *Tetrahedron* **2004**, *60*, 6311; (c) Nam, J.; Chang, J.-y.; Hahm, K.-S.; Park, Y. S. *Tetrahedron Lett.* **2003**, *44*, 7727; (d) 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; (e) Lee, S.-k; Lee, S. Y.; Park, Y. S. *Synlett* **2001**, 1941; (f) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. *J. Org. Chem.* **1997**, *62*, 5830; (g) Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry* **1995**, *6*, 469.
3. (a) Huang, L.-L.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2005**, *70*, 529; (b) Knauer, S.; Kunz, H. *Tetrahedron: Asymmetry* **2005**, *16*, 529; (c) Chung, C. W. Y.; Toy, P. H. *Tetrahedron: Asymmetry* **2004**, *15*, 387; (d) Totani, K.; Takao, K.; Tadano, K. *Synlett* **2004**, 2066; (e) Chéry, F.; Desroses, M.; Tatibouët, A.; Lucchi, O. D.; Rollin, P. *Tetrahedron* **2003**, *59*, 4563; (f) Yu, H.; Ballard, C. E.; Boyle, P. D.; Wang, B. *Tetrahedron* **2002**, *58*, 7663; (g) Enholm, E. J.; Cottone, J. S.; Allais, F. *Org. Lett.* **2001**, *3*, 145; (h) Totani, K.; Nagatsuka, T.; Yamaguchi, S.; Takao, K. *J. Org. Chem.* **2001**, *66*, 5965; (i) Bach, T.; Höfer, F. *J. Org. Chem.* **2001**, *66*, 3427; (j) Khiar, N.; Alcudia, F.; Espartero, J.-L.; Rodriguez, L.; Fernández, I. *J. Am. Chem. Soc.* **2000**, *122*, 7598; (k) Huang, G.; Hollingsworth, R. I. *Tetrahedron Lett.* **1999**, *40*, 581; (l) Yoshida, T.; Chika, J.; Takei, H. *Tetrahedron Lett.* **1998**, *39*, 4305; (m) Hultin, P.; Earle, M. A.; Sudharshan, M. *Tetrahedron* **1997**, *53*, 14823; (n) Chiappe, C.; Moro, G. L.; Munforte, P. *Tetrahedron: Asymmetry* **1997**, *8*, 2311; (o) Angibaud, P.; Chaumette, J. L.; Desmurs, J. R.; Duhamel, L.; Plé, G.; Valnot, J. Y.; Duhamel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1919.
4. In Ref. 1e, Ben and Durst previously reported that D-glucose diacetonide mediated nucleophilic substitution of α-ethyl-α-bromo acetate in the presence of tetrahexylammonium iodide and Et_3N gave a substitution product with low diastereoselectivity (2:1).
5. The absolute configurations of (α*S*)-**2** and (α*S*)-**6** were determined after the removal of chiral auxiliary by comparison of the CSP-HPLC retention time with authentic products prepared from L-phenylglycine.
6. Experimental procedure for the asymmetric preparation of *N*-*p*-methoxyphenyl (*S*)-phenylglycine methyl ester (**17**): To a solution of (α*RS*)-**1** in CH_2Cl_2 (ca. 0.1 M) at room temperature was added DIEA (1.0 equiv), TBAI (1.0 equiv), and a nucleophile (*p*-anisidine, 1.5 equiv). After the resulting reaction mixture was stirred at room temperature for 12 h, the solvent was evaporated and the crude material was purified by column chromatography to give **6** in 97% yield with 97:3 dr. The dr was determined by ^1H NMR integration of α-hydrogens of two diastereomers. ^1H NMR ($CDCl_3$, 400 MHz) 7.49–7.32 (m, 5H), 6.73 (d, $J = 7.0$ Hz, 2H), 6.56 (d, $J = 7.0$ Hz, 2H), 5.40 (d, $J = 3.6$ Hz, 1H), 5.29 (d, $J = 2.9$ Hz, 1H), 5.08 (s, 1H), 4.22–3.88 (m, 5H), 3.70 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.3, 153.2, 140.5, 137.6, 129.4, 129.0, 127.6, 115.3, 115.2, 112.8, 109.9, 105.4, 83.1, 80.1, 72.8, 67.8, 62.4, 56.1, 27.3, 27.1, 26.5, 25.6. For removal of chiral auxiliary, the mixture of **6** and Et_3N (15 equiv) in methanol (0.03 M) was stirred for 2 days. The solvent was evaporated and the crude material was purified by column chromatography to give (*S*)-**17** in 98% yield. ^1H NMR ($CDCl_3$, 400 MHz) 7.48–7.25 (m, 5H), 6.69 (d, $J = 8.9$ Hz, 2H), 6.52 (d, $J = 8.9$ Hz, 2H), 5.00 (s, 1H), 4.67 (br s, 1H), 3.72 (s, 3H), 3.67 (s, 3H). The spectral data of **17** were identical to those of the authentic material reported previously.[7] The enantiomeric ratio of **17** was determined to be 96:4 in favor of the *S*-enantiomer by CSP-HPLC using racemic material as a standard (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min; The *S*-enantiomer (major) had a retention time of 18.6 min, and the *R*-enantiomer (minor) had a retention time of 17.7 min.).
7. Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574.