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Dynamic resolution of α-halo carboxylic acid derivatives in asymmetric nucleophilic substitution using chiral auxiliaries

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Dedicated in memory of Professor Chi Sun Hahn

ABSTRACT

Recent results on the chiral auxiliary-mediated dynamic resolution of α-halo acid derivatives in nucleophilic substitution have been outlined and classified into two major mechanistic categories, dynamic thermodynamic resolution (DTR) and dynamic kinetic resolution (DKR). Asymmetric nucleophilic substitution of α-halo acid derivatives with various nitrogen, oxygen, sulfur, and carbon nucleophiles is widely used for the stereoselective preparation of α-substituted carboxylic acids.

Contents

1. Introduction

α-Halo carboxylic acids are synthetically useful intermediates that can be converted into a broad range of valuable structural motifs. As one example, the stereospecific nucleophilic substitution (S_N2) reaction of enantiomerically pure α-halo acid derivatives with various nitrogen, oxygen, sulfur, and carbon nucleophiles is widely used for the preparation of enantioenriched α-substituted carboxylic acids.[1] Whereas the value of these transformations is great, the nucleophilic substitution seems to lack a generality in application since the enantiomerically pure α-halo acids are generally obtained from a limited number of natural L-amino acids.[2] Alternatively, the dynamic resolution of α-halo acid in nucleophilic substitutions can allow easy access to a wide range of enantioenriched α-substituted carboxylic acid derivatives. A variety of α-halo acids are easily obtained from the α-halogenation of carboxylic acids in racemic form and the configurational lability of the α-halo carbon center can be readily induced by a halide ion or a base.[3] In recent years, many successful results on the chiral auxiliary-mediated dynamic resolution of α-halo carboxylic acid derivatives have been reported as an effective asymmetric synthetic method for α-substituted-carboxylic acid derivatives as shown in Scheme 1. Herein, an overview of the recent advances in chiral auxiliary-mediated dynamic resolution of α-halo acid derivatives is reported and its broad applicability demonstrated.

Dynamic resolution over the course of an asymmetric nucleophilic substitution of α-halo carboxylic acid derivative **1** involves an epimerization or a substitution that favors one diastereomer over the other as shown in Scheme 2. When two diastereomers of **1** have significantly different thermodynamic stabilities or activation energies in the substitution, the reaction of α-halo carboxylic acid derivative **1** can provide highly diastereoenriched product **2**. If the thermodynamic control of a diastereomeric ratio (dr) of (α*S*)-**1** and (α*R*)-**1** is possible, a dynamic thermodynamic resolution (DTR) may be developed.[4] Furthermore, one of the two diastereomers of

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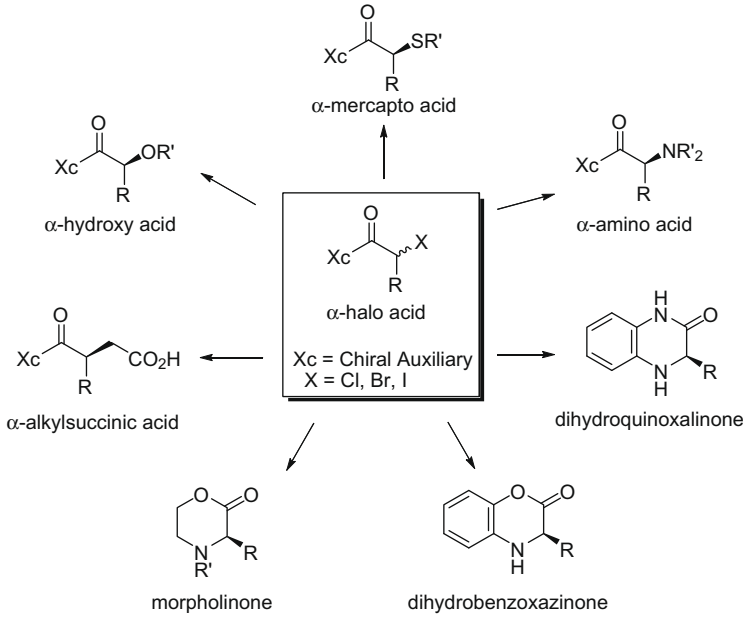
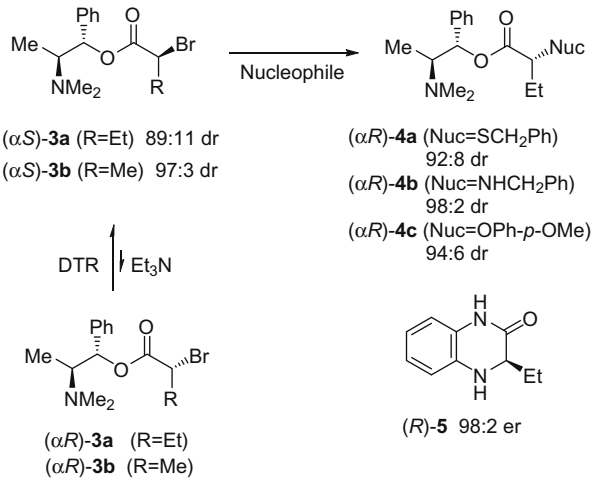


Scheme 1. Asymmetric nucleophilic substitutions of α-halo carboxylic acid.

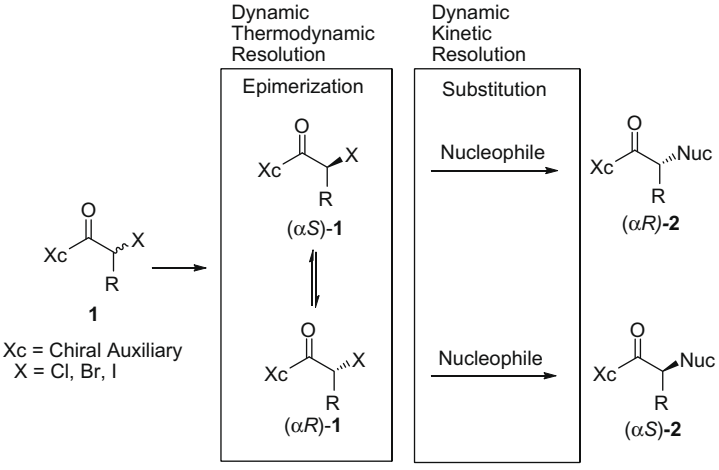
1 can crystallize selectively from solution by the thermodynamics of phase equilibrium.[5] It is the control of the diastereomeric populations that makes DTR different from dynamic kinetic resolution (DKR), in which the stereoselectivity is determined by the difference in the diastereomeric transition state energies for the substitution with a nucleophile.[6] Herein, various promising examples of the dynamic resolution of α-halo acid derivatives have been tentatively allotted according to the two major mechanistic categories mentioned above. If possible, a mechanistic rationale for the observed stereoselectivity will be outlined.[7]

2. Dynamic thermodynamic resolution (DTR)

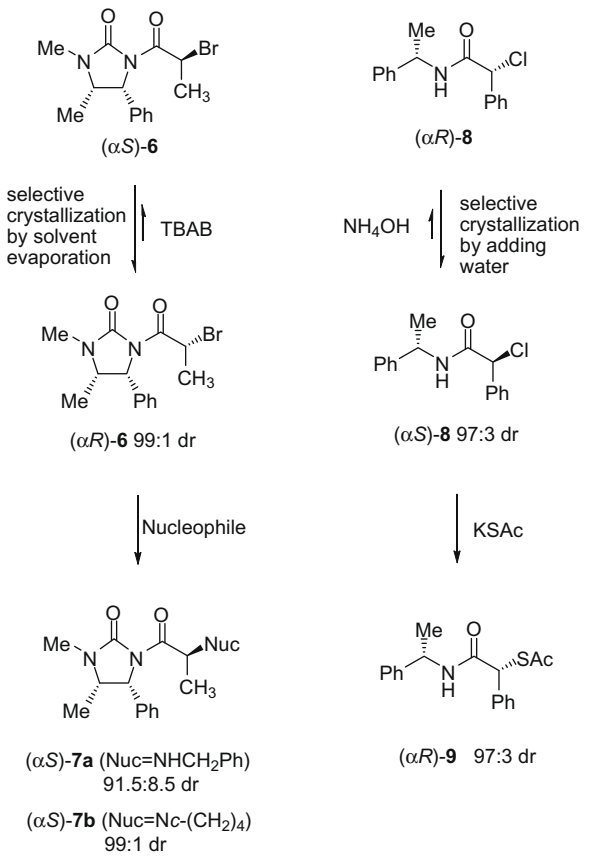
One limiting pathway which can account for the observed stereoselectivity in the nucleophilic substitution of α-halo acid derivatives is dynamic thermodynamic resolution. In this pathway the stereoselectivity is determined primarily by the diastereomeric ratio of (α*S*)-**1** and (α*R*)-**1** that is established before the substitution; however in some cases the relative rates of substitution may affect the product ratios. As shown in Schemes 3–5, a chiral



Scheme 3.

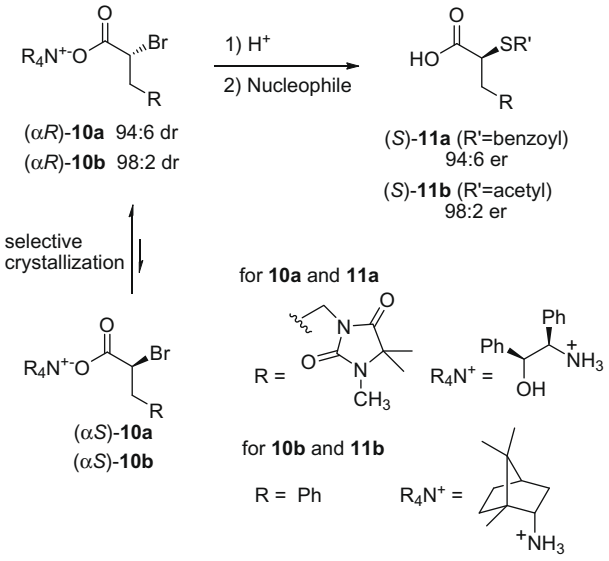


Scheme 2. Dynamic resolution of α-halo acid derivatives using a chiral auxiliary.



Scheme 4.

alcohol and various amines have been used as a chiral auxiliary for the dynamic thermodynamic resolution of α-halo acid derivatives (α*RS*)-**3**, **6**, **8,** and **10**.



Scheme 5.

2.1. DTR of α-halo esters

Several examples of (*S,S*)-*N*-methylpseudoephedrine-mediated dynamic thermodynamic resolution of α-bromo esters have recently been reported.[8] Treatment of *N*-methylpseudoephedrine α-bromo ester **3a** (58:42 dr) with benzyl thiol and Et_3N at room temperature produced α-benzylthio-substituted ester **4a** in 70% yield with 76:24 dr. However, when **3a** was equilibrated with Et_3N at room temperature before treatment with benzyl thiol, the thermodynamic equilibrium of two epimers provided an 89:11 ratio favoring the thermodynamically more stable (α*S*)-**3a** as shown in Scheme 3. Subsequent treatment of the equilibrated mixture with benzyl thiol gave (α*R*)-**4a** with a ratio of 92:8 dr. In the separate epimerization process the thermodynamically less stable (α*R*)-**3a** is converted into more stable (α*S*)-**3a**, which reacts with benzyl thiol in the subsequent substitution to give (α*R*)-**4a** with an inversion of configuration. The dependency of the product ratios on the dr of α-bromo ester **3a** implies that the epimerization is not fast with respect to the rate of substitution.[8a]

With benzylamine as the nucleophile, the stepwise epimerization–substitution protocol gave the α-benzylamino-substituted ester **4b** with a dr of 98:2. The slow substitution of the amino group presumably provides time for the epimerization, resulting in an enhanced selectivity.[8b] In a substitution with sodium *p*-methoxyphenoxide, however, the relatively fast substitution at room temperature gives α-anisyloxy-substituted ester **4c** with 89:11 dr, which is the same as the ratio of the equilibrated **3a**. It has been found that the α-bromo ester **3a** is configurationally stable at 0 °C and (α*S*)-**3a** reacts with the nucleophile faster than (α*R*)-**3a**. With 0.9 equiv of sodium *p*-methoxyphenoxide for incomplete conversion, the kinetic resolution in substitution at 0 °C gave product **4c** in 69% yield with an enhanced ratio of 94:6.[8c,d] When 1,2-phenylenediamine was used as a nucleophile, the slow substitution was completed after 24 h and spontaneous intramolecular amide formation furnished 3-ethyl dihydroquinoxalinone (*R*)-**5** in 71% yield with 98:2 enantiomeric ratio (er).[8e] In addition, a much higher diastereomeric ratio (97:3 dr) was obtained in the treatment of propionate (α*RS*)-**3b** with Et_3N in CH_3CN at room temperature for 1.5 h. Molecular mechanics calculations showed the considerable energy difference between (α*S*)-**3b** and (α*R*)-**3b** as shown in Figure 1. The energy difference of about 4.9 kcal/mol is fully consistent with the 97:3 ratio of the equilibrated mixture of **3b**.

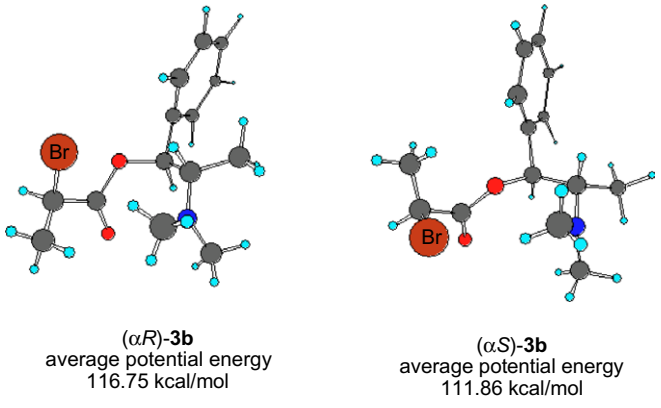


Figure 1. Lowest energy conformations of (α*R*)-**3b** and (α*S*)-**3b**.[9]

2.2. DTR of α-halo amides and imides

The dynamic resolution of α-halo acid derivatives via the formation of a more stable diastereomeric species is not limited to soluble diastereomeric species. When two diastereomers have different solubilities, the precipitation as solids would result in the conversion of the more soluble diastereomer to the less soluble one to be isolated as a highly enantioenriched α-halo acid derivatives. Caddick and Jenkins reported the crystallization-induced dynamic resolution (CIDR)

of α-bromoacyl imidazolidinone **6** through epimerization at the halogenated stereogenic center promoted by bromide ion exchange.[10] When an equimolecular mixture of two diastereomers was subjected to the equilibrating conditions and solvent allowed to evaporate slowly, the (α*R*)-**6** was isolated as the major product (99:1 dr) in 91% yield. The configurational lability of α-bromo center can be readily induced using tetrabutylammonium bromide (TBAB), and epimerization is not spontaneous in the absence of TBAB. When (α*R*)-**6** was treated with benzylamine or pyrrolidine in the absence of TBAB, the substitutions gave the substituted products (α*S*)-**7a** and (α*S*)-**7b** in 86–96% yields with 91.5:8.5 dr and 99:1 dr, respectively.

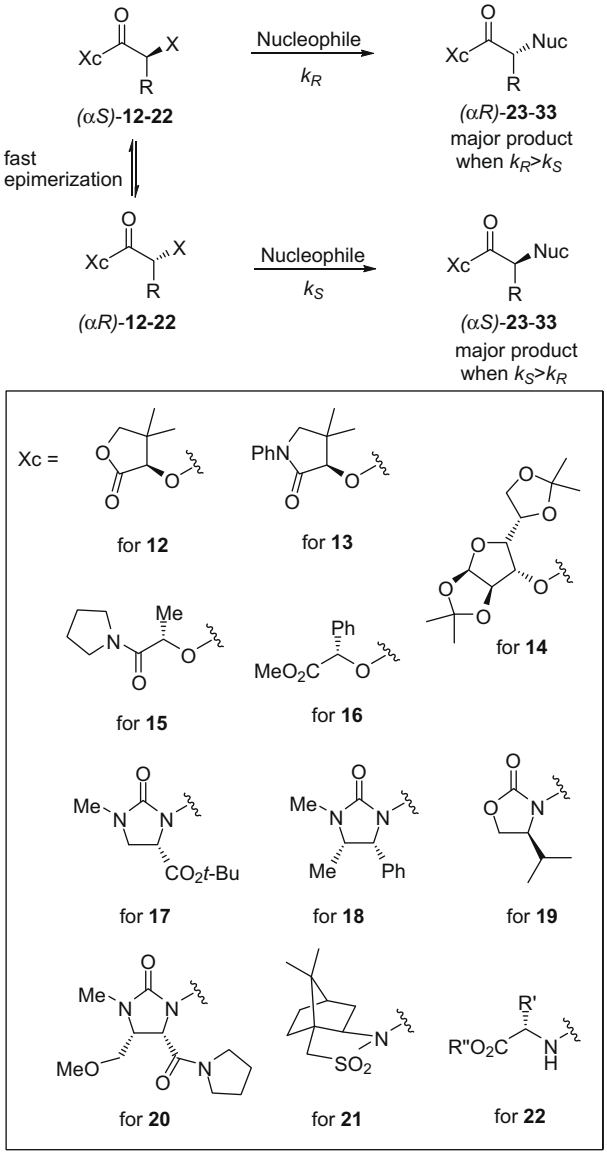
In contrast to the selective crystallization of **6** using the slow solvent evaporation, the highly stereoselective CIDR of *N*-(*S*)-(1-phenylethyl)-α-chloro-α-aryl acetamide **8** has been achieved by taking advantage of the substantially different solubilities of the two diastereomers of **8** in water.[11a] The epimerization at the α-chloro center is promoted by a base (NH_3) and (α*S*)-**8** selectively crystallizes from aqueous ammonia solution. It has been found that both amount of NH_4OH and epimerization time significantly affect the equilibrium, and that slow addition of NH_4OH in portions is necessary for high selectivities.[11b] Conversion of **8** to optically active α-mercapto carboxylic acid derivatives **9** has been accomplished by the epimerization free sequences with potassium thioacetate as shown in Scheme 4.

2.3. DTR of α-halo acid salts

Recently two research papers have been reported on novel synthetic routes to enantiomerically enriched chiral α-bromo-substituted carboxylic acids by CIDR of their diastereomeric salts with chiral amine as shown in Scheme 5. Kiau et al. found that treatment of a racemic α-bromo acid with (1*R*,2*S*)-2-amino-1,2-diphenylethanol in the presence of catalytic amounts of TBAB at 55 °C for 24 h produced diastereomerically enriched salt **10a** with a 94:6 (α*R*:α*S*) ratio in 90% yield.[12] Also, with (*R*)-bornylamine as a chiral amine, the diastereomerically enriched salt (α*R*)-**10b** (98:2 dr) was obtained in 76% yield with acetonitrile as a solvent and tetraethylammonium bromide (TEAB) as the bromide ion source.[13] Researchers have found that 48 h of stirring at 50–60 °C is necessary to reach 98:2 dr. When no bromide was added, the reaction gave much lower drs under similar conditions. After the diastereoenriched salts were treated with an acid, the enantioenriched α-bromo acids were isolated and treated with sulfur nucleophiles to give (*S*)-**11a** and (*S*)-**11b**, respectively. Enantioenriched α-benzoylthio-substituted acid (*S*)-**11a** (94:6 er) was obtained with thiobenzoic acid and K_2CO_3 via inversion of stereochemistry in 94% yield. Next, the substitution with KSAc produced an enantioenriched α-acetylthio-substituted acid (*S*)-**11b** in 90% yield with 98:2 er. In both cases, the recrystallization of α-thio-substituted acids further increased the er to >99:1.

3. Dynamic kinetic resolution (DKR)

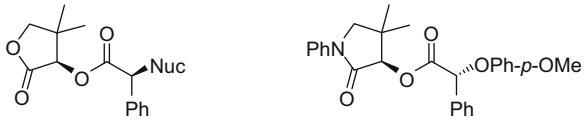
The other limiting pathway which can account for the observed stereoselectivity in asymmetric nucleophilic substitution of α-halo acid derivatives is dynamic kinetic resolution. In this pathway, the α-halo stereogenic center undergoes rapid epimerization between (α*S*)-epimer and (α*R*)-epimer and one of the two epimers reacts with a nucleophile preferentially under the reaction conditions. As shown in Scheme 6, a variety of chiral alcohols and amines have been used as chiral auxiliaries for the dynamic kinetic resolution of α-halo esters and amides (α*RS*)-**12**–**22**.



Scheme 6. DKR of α-halo acid derivatives using a chiral auxiliary.

3.1. DKR of α-halo esters

In 1993 Durst et al. discovered the dynamic kinetic resolution (DKR) of α-bromo esters containing (*R*)-pantolactone as a chiral auxiliary.[14] When α-bromo ester **12** was treated with a nucleophile and TBAI in THF, the resulting α-heteroatom-substituted acid derivatives were formed with high stereoselectivities. The (α*R*)-**12** diastereomer reacted faster with a nucleophile than the (α*S*)-**12** diastereomer and the halide served to promote epimerization. Treatment of α-bromoester (α*RS*)-**12** (R = Ph) with dibenzylamine in the presence of tetrahexylammonium iodide and Et_3N provided the substitution product (α*S*)-**23a** in 70% yield and 98:2 dr.[14a,b] When a sodium aryloxide was used as an oxygen nucleophile, the reaction of (α*RS*)-**12** (R = Ph) at 0 °C provided the α-aryloxy acid derivative (α*S*)-**23b** in 70% yield with 95:5 dr.[14c] In addition, Camps et al. used (*R*)-3-hydroxy-4,4,-dimethyl-1-phenyl-2-pyrrolidinone as the chiral auxiliary for the asymmetric syntheses of α-hydroxy acid derivatives.[15] The reactions of α-bromo ester (α*RS*)-**13** (R = Ph) with *p*-methoxyphenoxide and TBAI provided (α*R*)-α-aryloxy acid derivative **24** with 97:3 dr as shown in Scheme 7. In contrast to the reaction of (*R*)-pantolactone-derived ester **12**, (α*S*)-**13** reacts with the nucleophile faster to provide the (α*R*)-product rather than the (α*S*)-product.

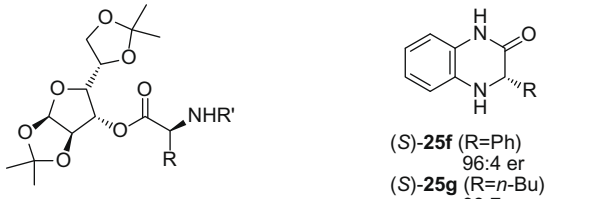


(αS)-**23a** (Nuc=NBn_2) 98:2 dr
(αS)-**23b** (Nuc=OPh-*p*-OMe) 95:5 dr

(αR)-**24** 97:3 dr

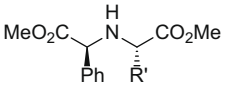
Scheme 7.

Diacetone-D-glucose-mediated dynamic kinetic resolution of α-halo esters has been recently reported as an efficient method for the asymmetric synthesis of α-amino acid derivatives as shown in Scheme 8.[16] Reactions of α-halo ester **14** with various amine nucleophiles in the presence of TBAI and diisopropylethylamine (DIEA) can provide α-amino acid derivatives **25a**–**25e** in up to 97:3 dr.[16a,b] When 1,2-phenylenediamine was used as a nucleophile, the substitution and spontaneous intramolecular amide formation furnished 3-alkyl dihydroquinoxalinone (*S*)-**25f** and (*S*)-**25g** with 96:4 er and 93:7 er, respectively.[16c] Also, the synthetic methodology is efficient for the asymmetric syntheses of 1,1′-iminodicarboxylic acid derivatives. Treatments of α-bromo ester **14** with L-alanine and L-leucine methyl ester hydrochloride, TBAI, and DIEA in CH_2Cl_2 and subsequent removal of the chiral auxiliary provided **25h** and **25i** with 99:1 dr and 98:2 dr, respectively.



(αS)-**25a** (R'=$PhCH_2$, R=*p*-CH_3-Ph) 96:4 dr
(αS)-**25b** (R'=Ph_2CH, R=Ph) 97:3 dr
(αS)-**25c** (R'=*p*-MeO-Ph, R=Ph) 97:3 dr
(αS)-**25d** (R'=*p*-MeO-Ph, R=Me) 91:9 dr
(αS)-**25e** (R'=*p*-MeO-Ph, R=*n*-Bu) 97:3 dr

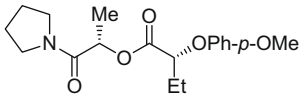
(*S*)-**25f** (R=Ph) 96:4 er
(*S*)-**25g** (R=*n*-Bu) 93:7 er



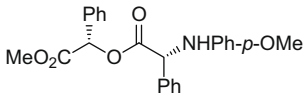
(αS)-**25h** (R'=Me) 99:1 dr
(αS)-**25i** (R'=*i*-Bu) 98:2 dr

Scheme 8.

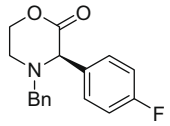
Devine et al. have reported a DKR for the preparation of α-aryloxy carboxylic acids using an (*S*)-lactamide auxiliary.[17a] When α-iodo ester **15** (R = Et) was treated with preformed lithium *p*-anisyloxide in THF at room temperature, α-aryloxy ester **26a** was obtained in 87% yield with 98:2 dr, as shown in Scheme 9. As a practical application, the methodology had been used for the asymmetric syntheses of (*S*)-tomoxetine, (*S*)-fluoxetine and (*S*)-nisoxetine.[17b] In addition, an extension of the methodology incorporating an amine as a nucleophile has led to the asymmetric synthesis of 1,4-oxazin-2-one **26b**, which is a key intermediate in the synthesis of aprepitant, a potent human NK-1 receptor antagonist.[17c] The analogous substrates using ethyl lactate, dibenzyl lactamide, and dimethyl lactamide as chiral auxiliaries were found to react sluggishly and with diminished selectivities, while the piperidine, piperazine, and morpholine-containing lactamides gave comparable selectivities.[17d,e] Furthermore, (*S*)-methyl mandelate has been utilized as an effective and convenient chiral auxiliary for the DKR of α-bromo esters in nucleophilic substitution with various aryl amines.[18] When α-bromo ester **16** (R = Ph) was treated with 1,2-phenylenediamine or 2-aminophenol in the presence of TBAI, DIEA in CH_3CN, the spontaneous removal of the chiral auxiliary provided 3-phenyl dihydroquinoxalinone (*R*)-**27b** and dihydrobenzoxazinone (*R*)-**27c** with 97:3 er and 91:9 er, respectively.



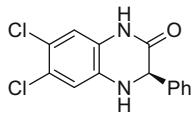
(αR)-**26a** 98:2 dr



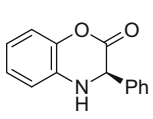
(αR)-**27a** 96:4 dr



(*R*)-**26b** 95.5:4.5 er



(*R*)-**27b** 97:3 er

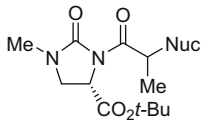


(*R*)-**27c** 91:9 er

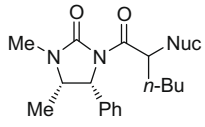
Scheme 9.

3.2. DKR of α-halo amides and imides

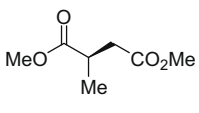
Nunami et al. introduced *t*-butyl (*4S*)-1-methyl 2-oxoimidazolidin-4-carboxylate-mediated DKR of α-bromo amides.[19] High levels of stereocontrol were observed in the nucleophilic substitutions carried out on an epimeric mixture of (α*RS*)-**17** in polar solvents under the conditions of base-catalyzed epimerization. DKR of (α*RS*)-**17** (R = Me) with benzylamine and Et_3N in HMPA gave (α*R*)-**28a** as the major product with 94:6 dr.[19a–c] When potassium phthalimide was used as a nucleophile, the reaction in HMPA gave (α*S*)-**28b** in 70% yield with 97:3 dr.[19d] With the selection of two different nitrogen nucleophiles, both enantiomers of the amino acid derivative can be obtained using the same chiral auxiliary. Furthermore, highly stereoselective carbon–carbon bond formation was accomplished by DKR of α-bromo amide (α*RS*)-**17** with a malonate anion. Treatment of (α*RS*)-**17** (R = Me) with 3 equiv of sodium malonate at 25 °C provided the α-alkyl-substituted amide (α*R*)-**28c** in 82% yield with 94:6 dr.[19e] The alkylated products were further converted to chiral α-alkylsuccinic acid derivatives **28d** and chiral β-amino acid derivatives (see Scheme 10).



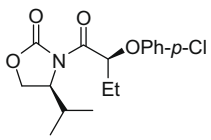
(αR)-**28a** (Nuc=NHBn) 94:6 dr
(αS)-**28b** (Nuc=*N*-phthaloyl) 97:3 dr
(αR)-**28c** (Nuc=$CH(CO_2Bn)_2$) 94:6 dr



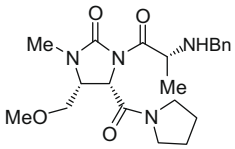
(αR)-**29a** (Nuc=Nc-$(CH_2)_5$) >99:1 dr
(αS)-**29b** (Nuc=$CH(CO_2Me)_2$) 76:24 dr
(αR)-**29c** (Nuc=SPh) 66:32 dr



(αR)-**28d**



(αR)-**30** 85:15 dr



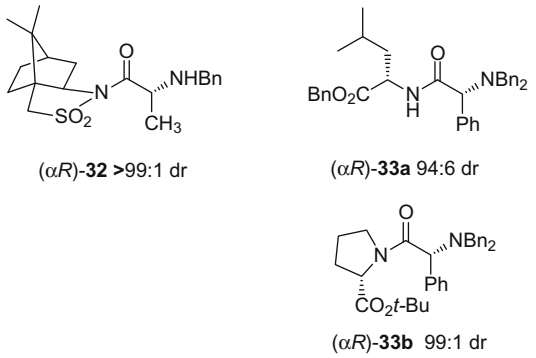
(αR)-**31** >99:1 dr

Scheme 10.

Caddick et al. have reported the DKR of α-haloacyl-imidazolidinones with a large variety of nitrogen, sulfur and carbon nucleo-

philes.[20] It has been found that the metallated nucleophiles preferentially reacted via the (αR)-**18** epimer, while the H-bonding amine nucleophiles reacted via the (αS)-**18** epimer. When α-bromo amide (αRS)-**18** (R = *n*-Bu) was treated with piperidine and TBAI in THF, (αR)-**29a** was obtained in 94% yield with >99:1 dr. In the reaction with sodium dimethyl malonate, however, the substitution gave (αS)-**29b** in 83% yield with 76:24 dr and poor selectivities were observed with rapidly reacting sulfur nucleophiles. In the reaction of (αRS)-**19** using (*S*)-4-isopropyl-1,3-oxazolidin-2-one as the chiral auxiliary, moderate stereoselectivity (85:15 dr) of (αR)-**30** was obtained with sodium 4-chlorophenoxide.[21] Based on a theoretical rationalization of the results with α-bromo amides **17**, **18** and **19**, a new efficient imidazolidinone chiral auxiliary for DKR was proposed.[22] The substitution of a new chiral auxiliary-derived (αRS)-**20** with benzylamine in the presence of TBAI and Et_3N provided (αR)-**31** in 92% yield with >99.9:0.1 dr.

Ward et al. have reported a highly efficient DKR of a α-bromo amide using Oppolzer's chiral camphorsultam.[23] When a diastereomeric mixture of (αRS)-**21** (R = Me) was treated with dibenzylamine in refluxing acetonitrile or Me_2SO, (αR)-**32** was formed as the single diastereomer in quantitative yield as shown in Scheme 11. In the nucleophilic substitution of α-halo amide **22** derived from L-amino acid, the chiral information from the L-amino acid precursor is efficiently transferred to the new C–N bond formation at α-halo center.[24] The substitution of (αRS)-**22** (R = Ph, R′ = *i*-Bu, R″ = Bn) with dibenzylamine in the presence of TBAI, DIEA produced dipeptide analogue (αR)-**33a** in 68% yield with 94:6 dr.[24a,b] Under the same conditions, the reaction of L-proline-derived α-bromo amide provided dipeptide analogue (αR)-**33b** with 99:1 dr. Also, the application of this methodology to stereoselective preparations of di-, tri-, and tetrapeptide analogues containing *N*-carboxyalkyl, *N*-aminoalkyl, and *N*-hydroxyalkyl groups is demonstrated.[24c,d]



Scheme 11.

A series of reactions has been carried out to differentiate the mechanistic pathways of dynamic resolution in nucleophilic substitution of (αRS)-**22**. When two epimeric mixtures of **22** (R = Ph, R′ = *i*-Bu, R″ = Bn) with 57:43 dr and 78:22 dr, respectively, were allowed to reach thermodynamic equilibrium in the presence of TBAI and DIEA, the dr of recovered **22** was determined to be 52:48 in both cases. These results indicate that α-bromo amide **22** is configurationally labile under the reaction condition and the thermodynamic stabilities of the two epimers are almost the same, ruling out DTR as a primary pathway. Furthermore, the dipeptide analogue (αR)-**33a** was produced with 94:6 dr in both reactions of α-bromo amide **22** with 72:28 dr and **22** with reversed diastereomeric enrichment of 30:70 dr under the same condition. Thus, the dr of product **33a** is independent of the starting dr of **22** but would depend on the difference in the diastereomeric transition state energies. These results suggest that the epimerization of **22** is sufficiently fast with respect to the rate of substitution and the primary pathway is a dynamic kinetic resolution. The transition state energies of the substitution of both leucine methyl esters (αR)-**22** and (αS)-**22** with dibenzylamine have been calculated and the results of the calculations using semi-empirical methods are depicted in Figure 2.[24b] The transition state (αS)-**22-TS** has the lower enthalpy value and the energy difference of about 3.0 kcal/mol between the transition state structures (αR)-**22-TS** and (αS)-**22-TS** is in accordance with the high stereoselectivity of the dynamic kinetic resolution process. It has been proposed that (αS)-**22** is the faster reacting diastereomer due to the formation of an intermolecular hydrogen bond that facilitates the delivery of the dibenzylamine nucleophile.

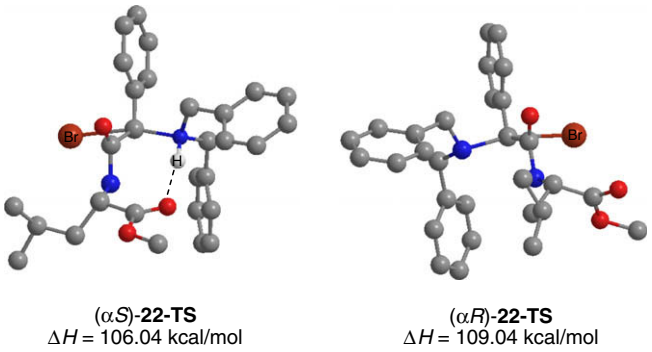
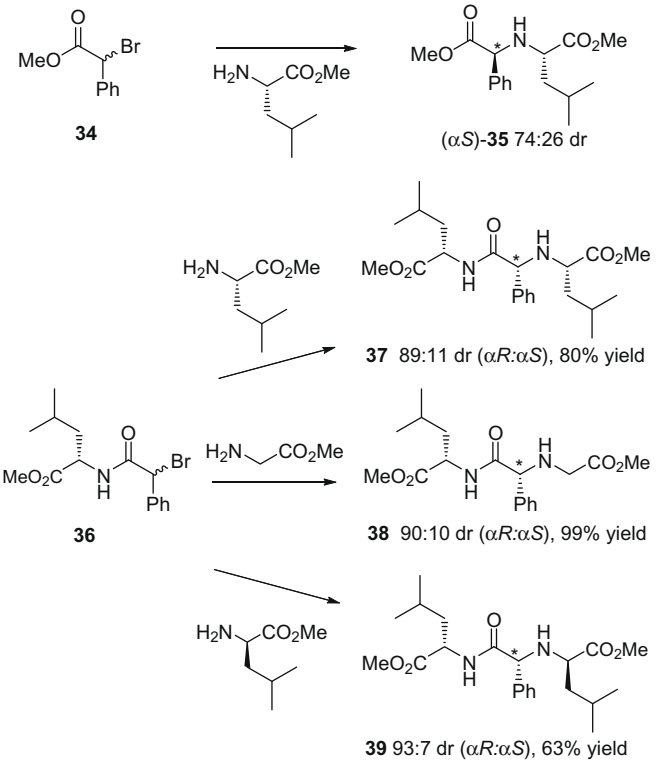


Figure 2. Transition state structures for the reactions of (αS)-**22** and (αR)-**22**.[24b]

In the reaction of racemic α-halo ester **34** with a chiral nucleophile, the chiral information of the nucleophile can be transferred to the new C–N bond formation. When the racemic α-bromo methyl ester **34** was treated with L-leucine methyl ester at room temperature, the iminodiacetate **35** was produced with a selectivity of 74:26 dr (αS:αR). As shown in Scheme 12, analogous



Scheme 12.

reactions of *N*-(α-bromo-α-phenylacetyl)-L-leucine methyl ester (α*RS*)-**36** with L-leucine, D-leucine, and glycine methyl ester nucleophiles afforded *N*-carboxyalkyl dipeptide analogues **37**, **38,** and **39 in** up to 93:7 dr.[24e] In the reactions of (α*RS*)-**36**, the stereochemistry of the major products was dominated by the chiral auxiliary and not by the incoming chiral nucleophile. α-Bromo amide **36** has experienced matching with D-leucine nucleophile to afford tripeptide analogue **39** with 93:7 dr and mismatching with L-leucine nucleophile to afford tripeptide analogue **37** with 89:11 dr. The results appear to agree with the observed stereochemical outcome of the reaction of racemic α-halo ester **34**. In brief, dynamic resolution of L-amino acid-derived α-halo amide **22** provides a highly efficient asymmetric synthetic method not only for the incorporation of unnatural amino acids into peptides, but also for various N-terminal functionalization of peptides.

4. Conclusion

There is some esthetic as well as practical appeal in utilizing a dynamic resolution of α-halo acids for an asymmetric transformation. Recent results demonstrate that the chiral auxiliary-controlled dynamic resolution of α-halo acid derivatives is a powerful approach for the asymmetric syntheses of various α-substituted carboxylic acids. The ability of nitrogen, sulfur, oxygen, and carbon nucleophiles to undergo nucleophilic substitution with α-halo acid derivatives clearly extends the utility of this methodology. Dynamic thermodynamic resolution of α-halo acid derivatives has been recognized but has been much less utilized than DKR of α-halo acid derivatives, while in some cases significant improvement in stereoselectivity can be achieved through the separation of epimerization and substitution steps of dynamic resolution. As we have seen, the possibilities created by this dynamic resolution have attracted a considerable amount of interest from both synthetic and mechanistic viewpoints. Dynamic resolution of α-halo acid derivatives will continue to be developed for further interesting and useful applications.

Acknowledgments

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7. When chiral auxiliary bound α-halo acid derivative **1** was prepared from racemic α-halo carboxylic acid, we might expect to obtain a 1:1 diastereomeric mixture of **1**. In some cases, however, the formation of anything other than a 1:1 mixture of diastereomers is observed, which can be explained by dynamic resolution in the ester or amide bond formation reaction. Also, the in situ preparation of a ketene from α-halo acid halides and its asymmetric reaction with a chiral auxiliary can afford α-halo esters or amides with high stereoselectivities: Boschi, F.; Camps, P.; Comes-Franchini, M.; Muñoz-Torrero, D.; Ricci, A.; Sánchez, L. *Tetrahedron: Asymmetry* **2005**, *16*, 3739; (b) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2004**, *15*, 593; (c) Ammazzalorso, A.; Amoroso, R.; Bettoni, G.; De Filippis, B. *Chirality* **2001**, *13*, 102; (d) Amoroso, R.; Bettoni, G.; Tricca, M. L. *Synlett* **1998**, 363; (e) Durst, T.; Koh, K. *Tetrahedron Lett.* **1992**, *33*, 6799.
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