Crystallization Induced Dynamic Resolution and Nucleophilic Substitutions of *N*-(*S*)-(1-Phenylethyl)-α-chloro-α-phenyl Acetamide for the Preparation of *N*-Carboxyalkylated Flavone

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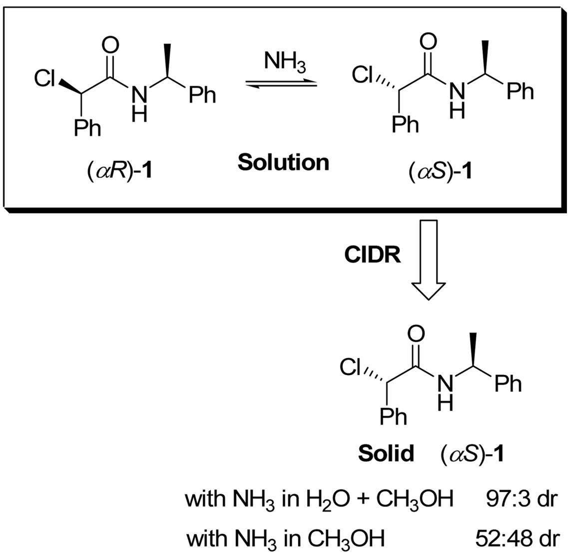
Chiral auxiliary mediated dynamic resolution of α-halo carboxylic acid derivatives in nucleophilic substitution has been recognized as an effective asymmetric synthetic method in recent years, and several attractive strategies have been discovered.[1-3] Since α-haloacyl compounds are easily obtained in racemic form and configurational lability of them is readily induced by halide sources, base or polar solvents, dynamic resolution in nucleophilic substitutions at α-halo carbon center can allow easy access to a wide range of enantioenriched α-heteroatom substituted carboxylic acid derivatives. We previously reported a crystallization induced dynamic resolution (CIDR) method for the preparation of optically active α-chloro carbonyl functionality.[3a] One of two diastereomeric species of *N*-(*S*)-(1-phenylethyl)-α-chloro-α-aryl acetamides selectively crystallizes from aqueous ammonia solution controlled by the thermodynamics of phase equilibrium as shown in Scheme 1. Here we wish to report recent results on the efficient CIDR and the nucleophilic substitutions of acetamide **1**. The stereospecific nucleophilic substitution with potassium thioacetate can provide a novel thiol chiral auxiliary **5** for dynamic resolution of α-bromo carboxylic acid derivatives in the nucleophilic substitution.



Scheme 1

Initial studies to develop the CIDR process have focused on finding more effective solvent system. In order to understand the role of water in the selective crystallization, we have performed a CIDR process in the absence of water. When the solution of α-chloro-α-phenyl acetamide (αRS)-**1** and NH_3 in MeOH was allowed to slowly evaporate, the complete evaporation of MeOH provided **1** as a white solid with 52:48 diastereomeric ratio (dr) as shown in Scheme 1. The low selectivity indicates that water is crucial for an efficient CIDR, reducing the solubility of (αS)-**1** selectively. On the basis of these observations, we set out to find appropriate water and methanol solvent system in which α-chloro acetamide (αS)-**1** can be selectively precipitated while simultaneously, two epimers of **1** equilibrate in the presence of NH_3 base.

We therefore investigated several CIDR protocols to establish if there was a relationship between the amount of NH_4OH used and diastereomeric excess (de) of **1** as illustrated in Figure 1. We have closely monitored the progress of the reactions in terms of % de by NMR analysis of crude reaction mixture of **1** (100 mg) in 2 mL of MeOH with various amount of NH_4OH. The results shown in Figure 1(a) clearly indicate that a direct relationship between the amount of NH_4OH added and de of **1**. As the amount of NH_4OH added increases, the final de of **1** is improved. However, the addition of 8 mL of NH_4OH did not provide better de of **1**. Figure 1(b) presents the effect of slow addition of NH_4OH on the CIDR process. Better results in de of **1** were obtained when the additional 4 mL of NH_4OH was added in four equal portions every 12 h. (condition D, --●--) The CIDR system was further optimized by the use of 1 mL of MeOH, to shorten the required time for the phase equilibration. (condition E, –■–) Under this condition it is just a matter of time before thermodynamic equilibration is reached, producing (αS)-**1** with 94% de. The plots show that the amount of MeOH is not crucial for final de of the product.

After a simple evaporation of NH_4OH, (αS)-**1** could be obtained as a white solid in quantitative yield and (αS)-**1** is configurationally stable in the absence of NH_4OH. As an application of the CIDR method to the asymmetric preparation of α-heteroatom substituted carboxylic acid derivatives, we have carried out substitution reactions of α-chloro acetamide (αS)-**1** with various heteroatom nucleophiles as

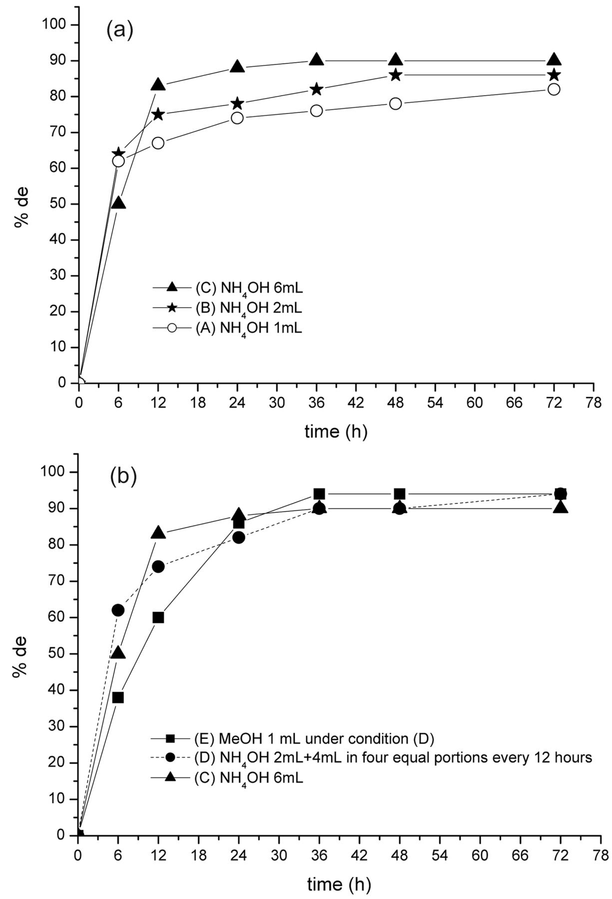
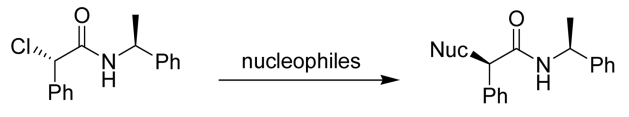
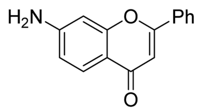
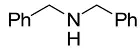
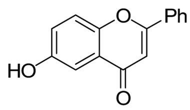
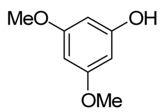


Figure 1. Relationship between the amount of NH_4OH used and de of **1** (100 mg in 2 mL of MeOH). The CIDR condition E used 1 mL of MeOH for the dissolution of **1**.

Table 1. Nucleophilic substitutions of (*aS*)-**1** with various nucleophiles



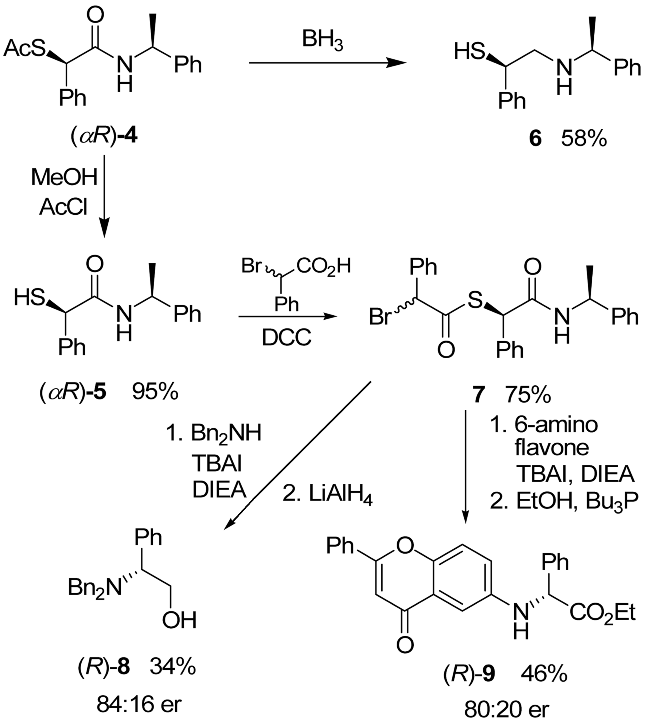
Entry	Dr of **1**	Nucleophile	Condition	Yield[a] (%)	Dr[b]
1	97:3		TBAI, DIEA, CH_2Cl_2, rt	N.R.	–
2	97:3		TBAI, DIEA, CH_2Cl_2, rt	N.R.	–
3	97:3		Cs_2CO_3, CH_3CN, rt	66 (**2**)	53:47
4	97:3		Cs_2CO_3, CH_3CN, rt	57 (**3**)	52:48
5	97:3	KSAc	MeOH, rt	80 (**4**)	97:3
6	50:50	KSAc	MeOH, rt	82 (**4**)	51:49

[a]Isolated yields. [b]Drs were determined by ^{1}H-NMR.

shown in Table 1. The reactions with amine nucleophiles did not produce the substitution product in the presence of tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIEA). (entries 1 and 2) On the other hand, when (αS)-**1** (97:3 dr) was treated with 6-hydroxyflavone and 3,5-dimethoxyphenol in the presence of Cs_2CO_3 (or NaH), the alkoxide nucleophiles provided the substituted products **2** and **3** in 66% and 57% yields, respectively. In both cases, however, the dr of products is almost 1:1. The results in entries 3 and 4 can be taken to suggest that (αS)-**1** and/or the substitution products are configurationally labile under strongly basic conditions. As shown in entry 5, treatment of (αS)-**1** (97:3 dr) with potassium thioacetate (KSAc) in MeOH at rt for 24 h gave a α-acetylthio carboxylic acid derivative (αR)-**4**. We were pleased to observe that no epimerization was observed during the substitution reaction as judged by ^{1}H NMR on the crude reaction mixture (97:3 dr). After column chromatography of crude reaction mixture, optically pure α-acetylthio substituted product (αR)-**4** was obtained in 80% yield. Also, the result in entry 6 can rule out the possibility of dynamic resolution of (αRS)-**1** in nucleophilic substitution with KSAc.

Despite the significance of optically active α-mercapto carboxylic acids in organic synthesis, only a few methods have been reported for asymmetric syntheses of α-mercapto carboxylic acid derivatives.[4] As shown in Scheme 2, we successfully accomplished the conversion of optically pure α-chloro carbonyl functionality to α-mercapto carbonyl functionality by the epimerization free sequences. Deacylation of (αR)-**4** with acetyl chloride in MeOH produced (αR)-**5** in 95% yield without any detectable epimerization as judged by ^{1}H NMR. In addition, the reduction of **4** using an excess amount of BH_3-THF (5 equiv) in THF provided the expected β-amino thiol **6** in 58% yield.[5] We then examined the capability of thiol (αR)-**5** as a chiral auxiliary in nuleophilic substitution of α-bromo carboxylic acid derivatives with amine nucleophiles. The treatment of α-bromo thioester **7** with dibenzylamine (1.2 equiv) in the presence of TBAI and DIEA in CH_2Cl_2 at room temperature provided the substitution product in 61% yield. Subsequent reductive removal of the chiral auxiliary using $LiAlH_4$ in THF furnished the enantioenriched β-amino alcohol (R)-**8** in 55% yield with 84:16 enantiomeric ratio (er).[6]

Flavones are plant products with many biological and pharmacological activities. A number of *O*-alkylated and *N*-alkylated flavones have recently been prepared to improve their biochemical and pharmacological properties of naturally occurring flavones.[7] In our continuing investigation on the stereoselective preparation of alkylated flavonoids and their activity studies,[8] we have attempted to prepare *N*-carboxyalkylated flavones by the chiral auxiliary **5** mediated dynamic resolution of α-bromo thioester **7**. As shown in Scheme 2, treatment of α-bromo thioester **7** with 6-aminoflavone (1.2 equiv) in the presence of TBAI and DIEA for 24 h provided



Scheme 2

the substitution product in 70% yield. Subsequent removal of the chiral auxiliary with EtOH and Bu_3P gave *L*-phenylglycine-flavone conjugate (*R*)-**9** in 66% yield with 80:20 er.

We conclude that CIDR of *N*-(*S*)-(1-phenylethyl)-α-chloro-α-phenyl acetamide **1** is effectively promoted by addition of NH_4OH. It has been found that slow addition of NH_4OH in portions gave better selectivities than the addition at once. Stereospecific nucleophilic substitution of **1** with a thio nucleophile (KSAc) and subsequent deacylation can provide thiol **5**, which can be used as a chiral auxiliary for the preparation of enantioenriched β-amino alcohol **8** and *N*-alkylated flavone **9** by the nucleophilic substitutions of **7**. Further studies to extend the scope of the methodology for the preparation of various *N*-carboxyalkylated flavones are underway.

Experimental

Crystallization induced dynamic resolution of *N*-(*S*)-(1-phenylethyl)-α-chloro-α-phenyl acetamides ((*αRS*)-1). To a solution of (*αRS*)-**1** (100 mg, 0.36 mmol) in MeOH (1 mL) at rt was added 2 mL of NH_4OH. The resulting reaction mixture was stirred at r.t. for 2 days, adding 4 mL of NH_4OH in four equal portions every 12 hours. Simple evaporation of reaction mixture gave (*αS*)-**1** as a white solid in quantitative yield. The dr of **1** was determined to be 97:3 by ^{1}H NMR using the integration of α-chloromethine protons. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49-7.24 (m, 10H), 6.98 (br, 1H), 5.11 (m, 1H), 1.52 (d, *J* = 6.8 Hz, 3H).

General procedure for the preparation of 2 and 3. To a solution of α-chloroacetamide **1** (1.5 equiv) in CH_3CN (0.1 M) at rt was added a hydroxy nucleophile (1.0 equiv) and Cs_2CO_3 (1.0 equiv). After the resulting reaction mixture was stirred at rt for 24 h, the mixture was quenched with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with EtOAc twice and the combined extracts were washed with brine. The solvent was evaporated and the crude material was purified by column chromatography.

***N*-(*S*)-(1-Phenylethyl)-α-(6-flavonoxy)-α-phenyl acetamide (2).** 66% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.81-7.18 (m, 18H), 6.68 (d, *J* = 5.5 Hz, 1H), 5.73, 5.69 (s, 1H, two peaks), 5.16 (m, 1H), 1.50 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 178.2, 168.7, 163.8, 154.4, 152.5, 143.2, 136.4, 132.1, 129.4, 129.2, 129.1, 129.0, 127.8, 127.3, 126.7, 126.6, 126.5, 125.1, 124.0, 120.2, 110.3, 107.1, 81.2, 49.1, 22.1.

***N*-(*S*)-(1-Phenylethyl)-α-(3,5-dimethoxyphenoxy)-α-phenyl acetamide (3).** 57% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.54-7.18 (m, 10H), 6.87 (d, *J* = 7.5 Hz, 1H), 6.13-6.09 (m, 3H), 5.53, 5.50 (s, 1H, two peaks), 5.10 (m, 1H), 3.75, 3.66 (s, 3H, two peaks), 1.48, 1.45 (d, *J* = 7.1 Hz, 3H, two peaks); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.3, 162.0, 159.0, 143.2, 136.8, 129.1, 129.0, 127.8, 127.0, 126.5, 95.2, 95.0, 94.7, 80.9, 55.8, 49.0, 22.2.

Preparation of *N*-(*S*)-(1-phenylethyl)-α-acetylthio-α-phenyl acetamide ((*αR*)-4). To a solution of (*αS*)-**1** (139 mg, 0.51 mmol, 97:3 dr) in 3 mL of MeOH was added potassium thioacetate (KSAc, 1.2 equiv) under a nitrogen atmosphere. The resulting material was stirred for 24 h at r.t. followed by regular extractive work up and column chromatography to give α-acetylthio substituted product (127 mg, > 99:1 dr determined by ^{1}H NMR and HPLC) as a colorless oil in 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37-7.14 (m, 10H), 6.41 (d, *J* = 7.5 Hz, 1H), 5.23 (s, 1H), 5.07 (m, 1H), 2.32 (s, 3H), 1.44 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 195.4, 168.5, 143.1, 136.2, 129.3, 129.0, 128.99, 128.7, 127.7, 126.4, 52.6, 49.8, 30.5, 22.0.

Preparation of *N*-(*S*)-(1-phenylethyl)-α-mercapto-α-phenyl acetamide ((*αR*)-5). Deacylation of **4** (120 mg) was carried out with acetyl chloride (1 mL) in MeOH (3 mL) at r.t. for 12 h to produce (*αR*)-**5** in 95% yield (> 99:1 dr determined by ^{1}H NMR and HPLC, compared with a sample of (*αRS*)-**5**) ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36-7.22 (m, 10H), 6.62 (d, *J* = 6.4 Hz, 1H), 5.10 (m, 1H), 4.68 (d, *J* = 6.2 Hz, 1H), 2.57 (d, *J* = 6.2 Hz, 1H), 1.48 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.8, 143.1, 139.4, 129.6, 129.3, 129.0, 128.6, 127.9, 126.4, 49.9, 48.4, 22.2.

Preparation of 2-((*S*)-1-phenylethylamino)-1-(*S*)-phenylethanethiol (6). To a solution of **4** in THF (0.5 M) was added BH_3-THF (1.0 *M*, 5.0 equiv), and the mixture was refluxed for 12 h. The reaction was quenched by adding MeOH (0.5 mL) under ice-water cooling, and the solvents were evaporated. Aqueous 5%-HCl (2 mL) was added to the residue, and the mixture was refluxed for 1 hour. The reaction mixture was basified with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (5 mL $\times$ 3). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated to provide the crude product that was purified by column chromatography on silica gel. 58% yield;

^{1}H NMR ($CDCl_3$, 400 MHz) 7.35-7.18 (m, 10H), 4.03 (t, *J* = 7.2 Hz, 1H), 3.79 (q, *J* = 6.6 Hz, 1H), 2.88 (m, 2H), 1.80 (br, 2H), 1.32 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 145.7, 142.8, 129.1, 128.9, 127.9, 127.6, 127.4, 126.9, 58.4, 55.9, 44.6, 24.8.

Preparation of *N*-(*S*)-(1-phenylethyl)-α-(bromophenylacetylthio)-α-(*R*)-phenyl acetamide (7). Acetamide **5** (1.0 equiv), racemic α-bromo phenylacetic acid (1.0 equiv), DCC (1.0 equiv), Et_3N (2.2 equiv) and DMAP (0.2 equiv) were dissolved in CH_2Cl_2 and stirred at room temperature for 3 h. The precipitate was filtered off and the organic phase was washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated to provide the crude product that was purified by column chromatography on silica gel in 75% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.34-7.12 (m, 15H), 6.48, 6.46 (d, *J* = 8.1 Hz, 1H, two peaks), 5.49 (s, 1H), 5.18, 5.16 (s, 1H, two peaks), 5.03 (m, 1H), 1.41, 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 194.2, 167.7, 143.0, 135.5, 135.1, 130.0, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 127.8, 126.4, 54.4, 54.0, 49.9, 22.0.

Preparation of (*R*)-2-*N,N*-dibenzylamino-2-phenylethanol (8): To a solution of α-bromo thioester **7** in CH_2Cl_2 (*ca*. 0.1 M) were added DIEA (1.0 equiv), TBAI (1.0 equiv) and dibenzylamine (1.2 equiv). After the resulting reaction mixture was stirred at rt for 20 h, the solvent was evaporated and the crude material was purified by column chromatography to give the product in 61% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.35-7.17 (m, 25H), 6.50 (d, *J* = 7.8 Hz, 1H), 5.19 (s, 1H), 5.13 (m, 1H), 4.40 (s, 1H), 1.51 (d, *J* = 6.9 Hz, 3H). After the addition of $LiAlH_4$ (1.5 equiv) to the substitution in THF, the mixture was stirred at rt for 3 h and then quenched with EtOAc and 0.1 M-HCl solution. Extractive workup and column chromatography gave (*R*)-**8** in 55% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.44-7.25 (m, 15H), 4.14 (dd, *J* = 10.6, 10.6 Hz, 1H), 3.96-3.90 (m, 3H), 3.62 (m, 1H), 3.15 (d, *J* = 13.4 Hz, 1H), 3.01 (br, 1H). The enantiomeric ratio of **8** was determined to be 84:16 in favor of the *R* enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min): 12.7 min (*R*), 19.4 min (*S*).

Preparation of ethyl (*R*)-2-[(4-oxo-2-phenyl-4*H*-chromem-6-yl)amino]phenyl acetate (9). To a solution of α-bromo thioester **7** in CH_2Cl_2 (*ca*. 0.1 M) were added DIEA (1.0 equiv), TBAI (1.0 equiv) and 6-aminoflavone (1.2 equiv). After the resulting reaction mixture was stirred at rt for 20 h, the solvent was evaporated and the crude material was purified by column chromatography to give the product in 70% yield.

^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.85 (m, 2H), 7.51-6.99 (m, 21H), 6.71 (s, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 5.24 (d, *J* = 5.3 Hz, 1H), 5.01 (m, 1H), 5.16 (s, 1H), 5.03 (m, 1H), 4.94 (d, *J* = 5.3 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 3H). The mixture of the substituted product and Bu_3P (0.1 equiv) in ethanol was stirred for 24 h. The solvent was evaporated and purified by column chromatography to give **9** in 66% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.86 (m, 2H), 7.53-7.22 (m, 10H), 7.00 (m, 1H), 6.72 (s, 1H), 5.23 (d, *J* = 6.6 Hz, 1H), 5.19 (d, *J* = 6.6 Hz, 1H), 4.20 (m, 2H), 1.24 (t, *J* = 9.6 Hz, 3H).[8d] The enantiomeric ratio of **9** was determined to be 80:20 in favor of the *R* enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min): 101 min (*R*), 94 min (*S*).

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