Enantioselectivity

# Chemical Kinetic Resolution of Unprotected β-Substituted β-Amino Acids Using Recyclable Chiral Ligands**

Shengbin Zhou, Jiang Wang, Xia Chen, José Luis Aceña, Vadim A. Soloshonok, and Hong Liu**

Abstract: The first chemical method for resolution of N,C-unprotected β-amino acids was developed through enantioselective formation and disassembly of nickel(II) complexes under operationally convenient conditions. The specially designed chiral ligands are inexpensive and can be quantitatively recycled along with isolation of the target β-substituted-β-amino acids in good yields and excellent enantioselectivity. The method features a broad synthetic generality including β-aryl, β-heteroaryl, and β-alkyl-derived β-amino acids. The procedure is easily scaled up, and was used for the synthetically and economically advanced preparation of the anti-diabetic drug sitagliptin.

The β-amino acids (β-AAs) and their derivatives make up one of the fastest-growing sectors of the health related chemical industry. Besides some established applications of β-AAs as building blocks for numerous drugs, β-lactam antibiotics, potent derivatives of naturally occurring Taxol and dolastatins, β-AAs-based peptides and peptidomimetics[1] have emerged in the recent decade as field having pharmaceutical significance. Consequently, the preparation of β-AAs in enantiomerically pure form has been a focal point of synthetic organic chemistry, thereby leading to many truly ingenious synthetic approaches.[2] Considering the subject from the standpoint of practicality, it might be a general consensus that resolution of racemic β-AAs (rac-β-AAs) of
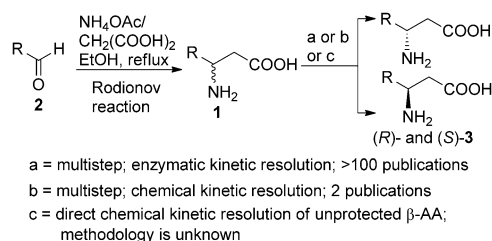
Scheme 1. Enzymatic versus chemical resolution of rac-β-AAs.

type **1** (Scheme 1) is the most economically feasible solution for large-scale preparation of enantiomerically pure β-AAs.

The major attractive argument of this approach is that rac-β-AAs of type **1** are exceptionally inexpensive by using the Rodionov reaction,[3] thus allowing preparation of virtually any type of β-monosubstituted β-AA.[4] The enzymatic resolution of rac-β-AAs[5] has been perfected during the last decades, thus resulting in optimized and highly efficient procedures.[5,6] In contrast, the possibility of a chemical resolution of rac-β-AAs has been completely overlooked. Thus, there are only two reports dealing with the purely chemical kinetic resolution of rac-β-AAs,[7] thus showing this subject to be the least explored area of β-AA chemistry. Furthermore, these two literature approaches require preparation of sterically constrained cyclic derivatives such as oxazinones[7a] or N-acyl-β-lactams,[7b] which can be enantioselectively opened under kinetic conditions. Besides the multistep character of these methods, they also suffer incomplete enantioselectivity and lead to overall low effectiveness as compared with enzymatic approaches.

Herein we present a novel method for the chemical kinetic resolution of N,C-unprotected rac-β-AAs. The process consists of a very simple reaction between unprotected rac-β-AAs and a specially designed chiral tridentate ligand, which reacts in a highly selective manner with stereochemically matching to the enantiomer of the starting β-AA. All reactions are conducted under operationally convenient conditions featuring excellent chemical yields and stereoselectivity. We demonstrate truly broad generality of this methodology for various β-substituted-β-AAs and its application for advanced synthesis of the anti-diabetic drug sitagliptin.[8]

Motivated by the recent success of the chemical kinetic resolution/deracemization of α-amino acids (α-AAs)[9] through Schiff-base formation between unprotected α-AAs and the ligands **4**[10] and **5**[11] (Figure 1), we first tried a straightforward application of **4** and **5** for the resolution

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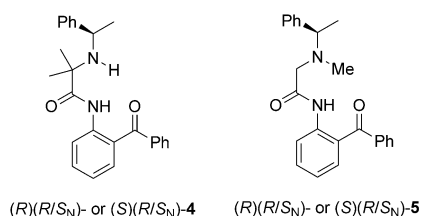Alameda Urquijo 36-5, Plaza Bizkaia, 48011 Bilbao (Spain)

Figure 1. Tridentate ligand successfully used for chemical resolution of α-AAs.

of β-AAs. Interestingly, the reactions of racemic β-phenyl-β-alanine [(*rac*)-**6a**; Table 1] with either **4** or **5** did not give even a trace of the desired nickel(II) complex products. Then, taking into account that the corresponding nickel(II) complex

Table 1: Optimization of chiral ligand.[a]

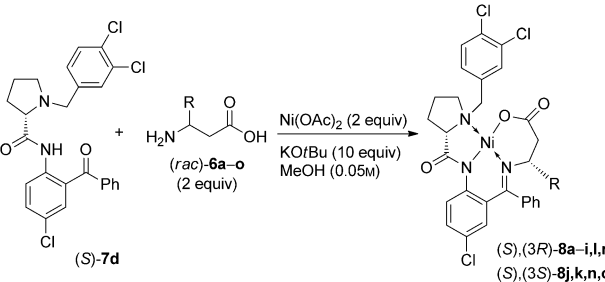| Entry	(*S*)-**7**	R^1, R^2	**8/9**	Base	Yield [%][b]	d.r.[c]
1[d]	(*S*)-**7a**	H, H	**8aa/9aa**	NaOH	trace	–
2	(*S*)-**7a**	H, H	**8aa/9aa**	NaOH	15	–
3	(*S*)-**7a**	H, H	**8aa/9aa**	NaH	60	89:11
4	(*S*)-**7b**	Cl, H	**8ab/9ab**	NaH	98	92:8
5	(*S*)-**7c**	H, Cl	**8ac/9ac**	NaH	60	94:6
6	(*S*)-**7d**	Cl, Cl	**8a/9a**	NaH	98	96:4
7	(*S*)-**7d**	Cl, Cl	**8a/9a**	KO*t*Bu	95	97:3

[a] Reaction conditions: (*S*)-**7** (0.2 mmol), *rac*-3-amino-3-phenylpropanoic acid **6a** (0.4 mmol), anhydrous Ni(OAc)$_2$ (0.4 mmol), and base (2 mmol) were refluxed in methanol (4 mL) for 8–10 h. [b] Combined yield of the isolated crude reaction mixture of **8/9**. Yield is based on ligands **7a–d**. [c] Determined by ^{1}H NMR and LC/MS analyses of the crude reaction mixture of **8/9**. [d] Ni(NO$_3$)$_2$·6H$_2$O as the source of Ni^{II} ions.

can be prepared from achiral unsubstituted β-alanine and ligands of type (*S*)-**7**,[12] we conducted the reaction of the compound (*S*)-**7a** with (*rac*)-**6a** under the standard reaction conditions: heating a methanol solution of the ligand (*S*)-**7a**, (*rac*)-**6a**, Ni(NO$_3$)$_2$·6H$_2$O, and NaOH.[13] In this case, we observed the formation of colored nickel(II) complex products, however, in only trace amounts (Table 1, entry 1). After extensive experimentation, we found that the presence of H$_2$O in the reaction mixture had a detrimental effect on the reaction progress. Thus, the first significant breakthrough in this study was made with application of anhydrous Ni(OAc)$_2$ as the source of nickel(II) ions (entry 2). Further optimization of the reaction conditions was made by using NaH as a base. In this case, the target diastereomeric nickel(II) complexes of

β-phenyl-β-alanine, (*S*),(*3R*)-**8aa** and (*S*),(*3S*)-**9aa**, were obtained in 60% yield and in a ratio of 89:11 (entry 3).

These results were quite encouraging, as they established that direct chemical resolution of unprotected β-AAs by a simple reaction with (*S*)-**7a** is possible. However, for this method to be of practical significance further improvement of the stereochemical outcome was clearly necessary. After numerous attempts to modify both the reaction conditions and the structural features of (*S*)-**7**, we found that the presence of the chlorine atom in the position *para* to the amino group on the benzophenone moiety [(*S*)-**7b**; for preparation of all ligands (*S*)-**7a–d**, see the Supporting Information[13]] allowed a noticeable improvement of both the chemical yield of (*S*),(*3R*)-**8ab** and (*S*),(*3S*)-**9ab**, and the enantioselectivity of the nickel(II) complexes formed (entry 4). Another important result was observed with modification of the phenyl ring of the N-benzyl group. We discovered that introduction of chlorine atoms at the *p*- and *m*-positions (**7c**) had a beneficial effect on the enantioselectivity. As shown in entry 5 of Table 1, the products (*S*),(*3R*)-**8ac** and (*S*),(*3S*)-**9ac** were obtained in a ratio of 94:6. In contrast, the yields of (*S*),(*3R*)-**8ac** and (*S*),(*3S*)-**9ac** were quite low, and similar to those obtained using (*S*)-**7a** (entry 5 versus 3). Eventually, we designed a new ligand, (*S*)-**7d**, thus combining the substitutions on both the benzophenone as well as *N*-benzyl moieties. Hence, the reaction of (*rac*)-**6a** with the trichlorosubstituted ligand (*S*)-**7d** gave the long sought after result, that is, preparation of the major product (*S*)(*3R*)-**8a** in 98% yield with a d.r. value of 96:4 (entry 6). Additional experiments were conducted to further optimize the reaction conditions and revealed that NaH, as a base, can be substituted with KO*t*Bu (entry 7). In this case, the reaction yield was a bit lower, whereas the stereoselectivity was slightly improved. The complexes (*S*),(*3R*)-**8a** and (*S*),(*3S*)-**9a** were isolated in diastereomerically pure form and their structure as well as the absolute configuration of the major product (*S*),(*3R*)-**8a** was determined by X-ray analysis[14] (see the Supporting Information). Accordingly, the minor diastereomer **9a** was assigned a (*S*)(*3S*) configuration.

Having established the optimized reaction conditions and structure of the chiral ligand, our next goal was to explore the generality of (*S*)-**7d** for reactivity and enantioselectivity in reactions with various β-AAs. All reactions presented in Table 2 were conducted under the standard reaction conditions (see the footnote) to evaluate the effect of the β-AA structure on the stereochemical outcome.[15] First we studied the effect of electronic properties of the substituents. As shown in entries 1–6, the β-aryl-substituted β-amino propanoic acids (*rac*)-**6a–f**, bearing electron-withdrawing as well as electron-donating groups, all gave the products with excellent yields and diastereoselectivity. The chemical yields were in the 87–97% range and the diastereomeric ratios were greater than 97:3. Furthermore, the reaction could be extended to the sterically bulky 2-naphthyl **6g** and heterocyclic β-amino acids **6h,i**. Also, in these cases the stereochemical outcome was exceptionally good (entries 7–9). Of greater importance were the reactions of the β-alkyl-containing β-AAs **6j–o** (entries 10–16). Gratifyingly, the reactions proceeded quite smoothly and with excellent stereoselectiv-

Table 2: Investigation of substrate scope.[a]

Entry	R (**6**)	**8**	Yield [%][b]	d.r.[c]
1	Ph (**6a**)	(*S*),(3*R*)-**8a**	95	97:3
2	4-MeOC$_6$H$_4$ (**6b**)	(*S*),(3*R*)-**8b**	87	98:2
3	4-FC$_6$H$_4$ (**6c**)	(*S*)(3*R*)-**8c**	90	97:3
4	4-ClC$_6$H$_4$ (**6d**)	(*S*)(3*R*)-**8d**	97	97:3
5	4-BrC$_6$H$_4$ (**6e**)	(*S*),(3*R*)-**8e**	91	97:3
6	4-MeC$_6$H$_4$ (**6f**)	(*S*),(3*R*)-**8f**	92	97:3
7	2-naphthyl (**6g**)	(*S*)(3*R*)-**8g**	95	98:2
8	3-pyridyl (**6h**)	(*S*),(3*R*)-**8h**	50	99:1
9	2-thienyl (**6i**)	(*S*),(3*R*)-**8i**	80	99:1
10	methyl (**6j**)	(*S*),(3*S*)-**8j**	75	97:3
11	*n*-butyl (**6k**)	(*S*),(3*S*)-**8k**	63	99:1
12	isopropyl (**6l**)	(*S*),(3*R*)-**8l**	45	98:2
13	cyclohexyl (**6m**)	(*S*),(3*R*)-**8m**	42	99:1
14	benzyl (**6n**)	(*S*),(3*S*)-**8n**	76	98:2
15	2,4,5-F$_3$C$_6$H$_2$CH$_2$ (**6o**)	(*S*),(3*S*)-**8o**	56	97:3
16[d]	2,4,5-F$_3$C$_6$H$_2$CH$_2$ (**6o**)	(*R*),(3*R*)-**8o**	68	98:2

[a] Reaction conditions: (*S*)-**7** (0.2 mmol), *rac*-β-AA **6** (0.4 mmol), anhydrous Ni(OAc)$_2$ (0.4 mmol), and KO*t*Bu (2 mmol) were refluxed in methanol (4 mL) for 10–16 h. [b] Combined yield of the isolated crude reaction mixture of **8/9**. [c] Determined by LC/MS analysis of the crude reaction mixture of **8/9**. [d] Large-scale synthesis using the *R*-configured ligand **7d**; reaction time of 3 h.

ity. Notably, the aliphatic series of the major products (*S*),(*3S*)-**8j,k,n,o** have the same relative stereochemistry as in the case of aromatic β-AAs, however, their absolute configuration at the amino acid stereogenic carbon center is *S* as a consequence of the CIP priority rules.[16] The chemical yields were generally lower when compared with those of the aromatic series, thus indicating that the reaction conditions might need some additional optimization. Most likely the difference is the nucleophilic properties of the amino group, in aromatic and aliphatic series, which plays the important role in the in situ Schiff base formation. Still, the straight alkyl chain substituted β-AAs **6j,k,n,o** such as methyl, *n*-butyl, and benzyl can give corresponding nickel(II) complexes with reasonably good yield and, most importantly, excellent diastereoselectivity (entries 10, 11, and 14–16). Moreover, the sterically demanding β-AAs containing an isopropyl (**6l**) and cyclohexyl group (**6m**), did not give any complications and provided the major products (*S*),(*3R*)-**8l,m** with excellent diastereoselectivity (entries 12 and 13). The benzyl-and trifluorobenzyl-substituted β-amino acids **6n,o** were successfully resolved with satisfactory yields and excellent selectivity (entries 14–16). These results were of particular significance for the final goal of this study: preparative large-scale synthesis of 3-amino-4-(2,4,5-trifluorophenyl)butanoic acid for advanced preparation of the anti-diabetic drug sitagliptin.

According to the observed stereochemical outcome, use of the (*S*)-**7d** gives preference for the reactions with *S* enantiomers of the aliphatic β-AAs **6j,k,n,o**. Accordingly, for preparation of the target amino acids having an *R* configuration at the β-position, in particular, 3-amino-4-(2,4,5-trifluorophenyl)butanoic acid (**6o**), the *R*-configured **7d** must be used. To this end, starting form *R* proline we prepared the new ligand (*R*)-**7d** (for preparation, see the Supporting Information) and studied its reaction with (*rac*)-**6o**. Quite interestingly, we observed that on a relatively large scale the reaction was completed in about 3 hours and both the chemical yield and diastereoselectivity were noticeably improved (Table 2, entry 16 versus 15). These results were particularly gratifying, as they provide factual support for the preparative objective of this methodology. The product (*R*)(3*R*)-**8o** was disassembled under the usual conditions,[17] that is, heating a solution of (*R*)(3*R*)-**8o** in EtOH with 3 N HCl,[18] and the target (*R*)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid [(*R*)-Boc-**6o**] was isolated in a N-Boc-protected form in good overall yield (77%; Scheme 2). Notably, the chiral ligand (*R*)-**7d** was recycled in virtually quantitative yield and can be reused again for the resolution of this or other β-AAs. Starting with thus prepared fluorinated (*R*)-Boc-**6o** we used the literature procedure[19] for condensation with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-
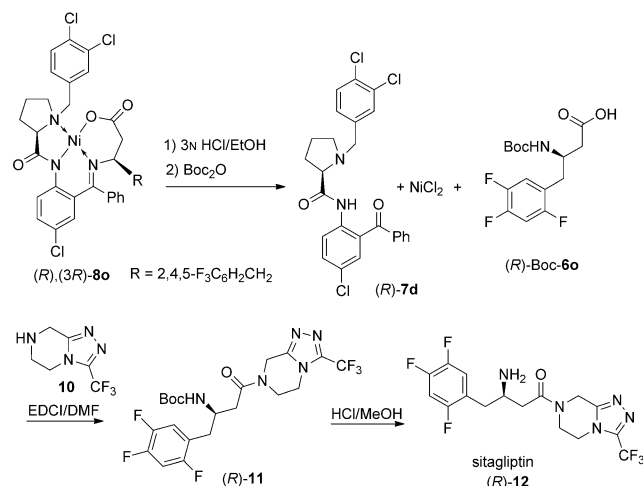
Scheme 2. Preparation of target amino acid and synthesis of the anti-diabetic drug sitagliptin. Boc = *tert*-butoxycarbonyl.

1,2,4-triazolo[4,3-a]pyrazine (**10**), thus giving rise to the intermediate product (*R*)-**11**. The final step, deprotection of (*R*)-**11**, afforded the target drug sitagliptin (*R*)-**12** with greater than 99% *ee*.

To conclude, we have developed an advanced chemical resolution method for the preparation of β-AAs in enantiomerically pure form with the following advantages and breakthroughs: The presented approach is the first of its kind as it can be used on N,C-unprotected β-AAs and includes only two reaction steps, in situ enantioselective formation of the nickel(II) complexes of β-AA Schiff bases with subse-

quent disassembly, thus furnishing the target enantiomerically pure β-AAs. The whole process can be conducted under operationally convenient conditions without recourse to inert atmosphere, controlled low temperature, or specially purified reagents and solvents. The process features good-to-excellent chemical yields and virtually complete stereoselectivity (up to >99:1). This method shows broad synthetic generality as various β-aryl-, β-heteroaryl-, and β-alkyl-containing β-amino acids could be efficiently resolved to enantiomerically pure form. The newly designed chiral ligands (*S*)- and (*R*)-**7d** are inexpensive and can be quantitatively recycled and reused. The method can be reliably reproduced on a large scale, with even better performance, and was used for preparation of the anti-diabetic drug (*R*)-sitagliptin in enantiomerically pure form. Overall, the work presented herein is the first chemical method for preparation of enantiomerically pure β-AAs and can rival the supremacy of the enzymatic methods for economical efficiency and practicality.

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