Diastereoselectivity

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# Chemical Dynamic Kinetic Resolution and *S*/*R* Interconversion of Unprotected α-Amino Acids**

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***Abstract:*** *Reported herein is the first purely chemical method for the dynamic kinetic resolution (DKR) of unprotected racemic α-amino acids (α-AAs), a method which can rival the economic efficiency of the enzymatic reactions. The DKR reaction principle can be readily applied for S/R interconversions of α-AAs, the methodological versatility of which is unmatched by biocatalytic approaches. The presented process features a virtually complete stereochemical outcome, fully recyclable source of chirality, and operationally simple and convenient reaction conditions, thus allowing its ready scalability. A quite unique and novel mode of the thermodynamic control over the stereochemical outcome, including an exciting interplay between axial, helical, and central elements of chirality is proposed.*

**D**ynamic kinetic resolution (DKR) of racemates is unarguably the most economical approach for large-scale production of α-amino acids (α-AAs).[1] From the methodological standpoint, this field is entirely dominated by the enzymatic approaches, while chemical methods play a rather ornamental role. Thus, despite the intellectual brilliance and reaction ingenuity, synthetic processes[2,3] are still prohibitively expensive.[4] In contrast, the enzymatic route enjoys operationally convenient conditions,[5] inexpensive reagents, and overall attractive cost-structure.[6] Furthermore, the development of the directed evolution of enzymes,[7] providing an access to even more efficient biocatalysts, sets yet higher economical standards, which seems unfeasible for synthetic approaches.

Herein we report the first purely chemical method for DKR of unprotected racemic α-AAs, a method which can rival convenience, generality, and overall economic efficiency of the biocatalytic approaches. Moreover, we show that the same reaction principle can be readily applied for α-*S*/*R* interconversion of α-AAs, the methodological versatility of which is unmatched by enzymatic reactions. The process disclosed herein features a virtually complete stereochemical outcome, fully recyclable source of chirality, and operationally simple and convenient reaction conditions. Furthermore, we demonstrate unproblematic scalability of this process and discuss the quite unique and novel mode of the thermodynamic control over the stereochemical outcome.

The DKR of unprotected α-AAs is a considerably underdeveloped area of chemistry, as compared to that of protected, specially derivatized α-AAs.[2,3] There are only two literature methods based on the application of the chiral ligands **1**[3f–g,8] and **2**[9] (Figure 1). While these compounds can be useful for some types of α-AAs their application is quite limited because of the lack of substrate generality and incomplete stereochemical outcome necessitating separation of diastereomeric derivatives.

Consistent with our interest in the development of asymmetric methods for the preparation of tailor-made[10] α-AAs,[11,12] we have been actively working on a modular approach[13] to the design of chiral ligands of type **2** (Figure 1).

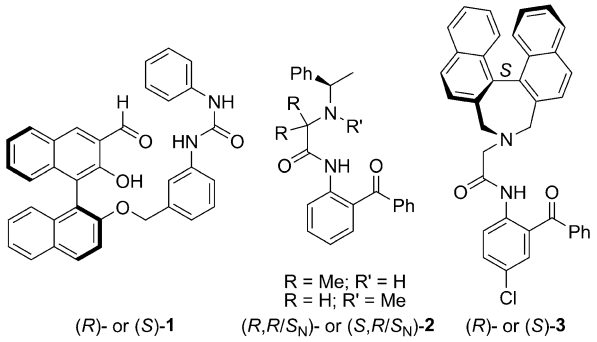


***Figure 1.*** Known **1**, **2**, and the new ligands **3** for DKR of unprotected α-AAs (only one enantiomer depicted for each compound).

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One of the problems we faced was a presence of the stereogenic nitrogen atom in **2**, thus increasing the number of possible stereoisomeric products. A critical conceptual breakthrough came with realization that the application of chiral $C_2$-symmetric amines might significantly simplify the overall stereochemical background. In contrast, the ligands of this type are novel and their stereochemical performance is unknown. After extensive experimentation using various $C_2$-symmetric secondary amines we identified the ligand **3**, derived from bis(naphthyl) amine,[14] which can be prepared in both *S*- and *R*-enantiomeric forms on a large scale (see the Supporting Information). Optimization of the reaction conditions for **3** with racemic α-AAs has been systematically studied, including various bases, solvents, reaction temperature, and time as well as stoichiometry of all starting materials involved. The optimized reaction conditions and representative examples are summarized in Table 1.

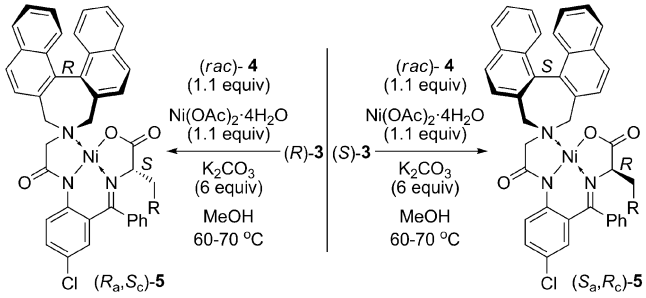
As an illustrative example to discuss the reaction progress and the stereochemical outcome, we selected one of the polyfunctional α-AAs, tryptophan (**4a**; Table 1, entry 1). Using HPLC analysis we monitored the reaction as a function of time. As one can see from Figure S1 in the Supporting Information, the chiral ligand (*S*)-**3** reacted notably faster with the *R* enantiomer of **4a**, thus rendering the diastereomer ($S_a$,$R_c$)-**5a**[15] as the kinetically favored product. Over the time the relative amounts of the diastereomer ($S_a$,$R_c$)-**5a** steadily increased while that of ($S_a$,$S_c$)-**5a** was proportionally decreased, thus suggesting that ($S_a$,$R_c$)-**5a** is also thermodynamically preferred. Final thermodynamic control was achieved after nearly 4 hours, thus affording ($S_a$,$R_c$)-**5a** as virtually a single reaction product which was isolated in 95% yield (entry 1). The ($S_a$,$R_c$)-**5a**/($S_a$,$S_c$)-**5a** ratio was 99.445:0.380 (see the Supporting Information) and did not change over time (up to 24 h). We can reasonably assume that the transformation of ($S_a$,$S_c$)-**5a** into the more thermodynamically stable ($S_a$,$R_c$)-**5a** is an epimerization process occurring by base-catalyzed formation of the corresponding intermediate enolate.[16]

Other aromatic (*rac*)-AAs such as Phe (**4b**; Table 1, entry 2) and Tyr (**4c**; entry 3) also easily reacted with (*S*)-**3**, thus giving rise to the thermodynamically controlled ($S_a$,$R_c$)-configured products **5b** and **5c**, respectively, in excellent yield and diastereomeric purity. Next, we demonstrated the use of (*S*)-**3** for the DKR of a series of racemic ω-functionalized amino acids such as methionine (**4d**; entry 4), glutamine (**4e**; entry 5), glutamic acid (**4f**; entry 6), and lysine (**4g**; entry 7). Interestingly, in these cases the thermodynamic control was noticeably faster, possibly suggesting some substituent effect of the side-chain ω-functional groups on the intermediate enolate formation rate. Importantly, the stereochemical outcome in this series was consistently excellent, thus allowing isolation of the resultant products ($S_a$,$R_c$)-**5d–g** in both chemical yields and diastereomeric excesses well above 90%. To complete this part of the study, three racemic aliphatic AAs, leucine (**4h**; entry 8), alanine (**4i**; entry 9) and valine (**4j**; entry 10) were tested. Similar to the aromatic series, the thermodynamic control was achieved in about 24 hours and the expected diastereomers ($S_a$,$R_c$)-**5h–j** were obtained virtually as the sole reaction products in excellent chemical yields.

As one may assume, use of the (*R*)-**3** might lead to the formation of the corresponding thermodynamically controlled diastereomeric products **5** having the $R_a$,$S_c$ absolute configuration. To confirm this assumption experimentally, we performed the reactions of (*R*)-**3** with three (*rac*)-AAs (**4c**,**d**,**i**) representing different structural types used in the study with (*S*)-**3**. While quite expected, we were pleased to see a flawless reproducibility of the data previously obtained for preparation of ($S_a$,$R_c$)-configured products (Table 1, entry 11 versus 3; entry 12 versus 4; entry 13 versus 9).

To conclude this part of the study, we would like to emphasize that very efficient DKR of racemic amino acids was achieved using the ligands (*S*)- or (*R*)-**3**, the (*rac*)-AAs **4a–j**, and $Ni(OAc)_2$ in nearly stoichiometric ratios. The choice to use excess (1.1 equiv) (*rac*)-AA **4** relative to the chiral ligand **3** is based on the fact that in most cases the former is much less expensive than the latter. However, in some exceptional cases when a rare (*rac*)-AA is difficult to obtain, **3** can be used in 10 mol% excess, thus affording the optimal stereochemical outcome. This option was demonstrated using (*S*)-**3** and (*rac*)-**4b** (Table 1, entry 14). Furthermore, the process is conducted under operationally convenient conditions and can be easily scaled up. To demonstrate this advantageous feature, we performed the DKR of (*rac*)-**4b** on a 10 gram scale using (*S*)-**3**. As shown in entry 15 in Table 1, full thermodynamic control was accomplished under 22 hours

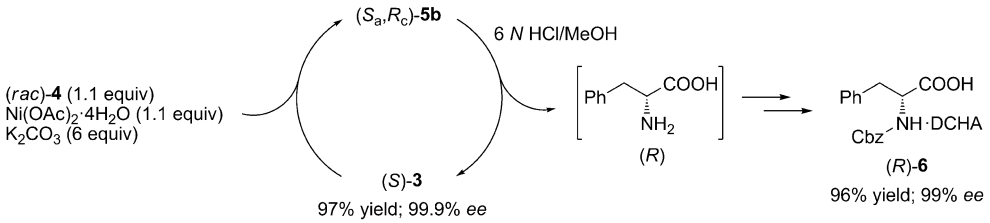
***Table 1:*** Reaction of ligands (*S*)- and (*R*)-**3** with racemic α-AAs.




| Entry | 3 | *rac*-AA 4 | Yield [%] | (*S*,*R*)/(*S*,*S*)[a] | *t* [h] |
|---|---|---|---|---|---|
| 1 | (*S*)-**3** | Trp (**4a**) | 95 | >97:3 | 24 |
| 2 | (*S*)-**3** | Phe (**4b**) | 94 | >97:3 | 24 |
| 3 | (*S*)-**3** | Tyr (**4c**) | 99 | >97:3 | 24 |
| 4 | (*S*)-**3** | Met (**4d**) | 97 | >97:3 | 3 |
| 5 | (*S*)-**3** | Gln (**4e**) | 92 | >96:4 | 3 |
| 6 | (*S*)-**3** | Glu (**4f**) | 92 | >96:4[b] | 10 |
| 7 | (*S*)-**3** | Lys (**4g**) | 91 | >96:4[c] | 4 |
| 8 | (*S*)-**3** | Leu (**4h**) | 94 | >96:4 | 24 |
| 9 | (*S*)-**3** | Ala (**4i**) | 97 | >97:3 | 24 |
| 10 | (*S*)-**3** | Val (**4j**) | 93 | >97:3 | 24 |
| 11 | (*R*)-**3** | Tyr (**4c**) | 98 | >97:3[d] | 24 |
| 12 | (*R*)-**3** | Met (**4d**) | 98 | >97:3[d] | 5 |
| 13 | (*R*)-**3** | Ala (**4i**) | 96 | >97:3[d] | 24 |
| 14 | (*S*)-**3** | Phe (**4b**) | 95 | >97:3 | 24[e] |
| 15 | (*S*)-**3** | Phe (**4b**) | 94 | >97:3 | 22[f] |

[a] Ratio was based on reverse-phase HPLC analysis. [b] Ratio was determined on the basis of $^1$H NMR analysis. [c] Ratio was determined on that of the free AA after disassembly. [d] (*R*,*S*)/(*R*,*R*) ratio. [e] The ligand (*S*)-**3** was used in 10 mol% excess. [f] Large-scale (10 g) reaction.




***Scheme 1.*** Disassembly of ($S_a$,$R_c$)-**5b**: isolation of the target AA (*R*)-**6**, recycling, and reuse of the chiral ligand (*S*)-**3**.

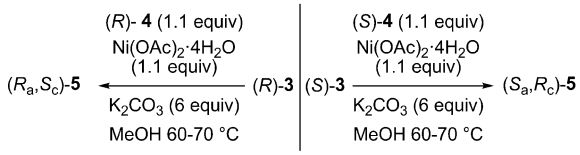
and the product ($S_a$,$R_c$)-**5b** was isolated in 94% yield. Without any additional purification, the resultant ($S_a$,$R_c$)-**5b** was subjected to the disassembly procedure presented in Scheme 1.

The disassembly procedure is also conducted under operationally convenient reaction conditions, thus affording the target (*R*)-**6**, which was isolated in good chemical yield. Furthermore, (*S*)-**3**, can be easily recycled in nearly quantitative yield. Control of enantiomeric purity (99.9% *ee*) of the recovered (*S*)-**3** confirmed our assumption that the axial chirality of (*S*)-**3** would not be stereochemically compromised. Thus recovered (*S*)-**3** was reused for repetitive DKR of other (*rac*)-α-AAs.

With these results in hand, we focused on the second part of our study: *S*/*R* interconversion of α-AAs. As one can assume, the chemistry and thermodynamic preference for the stereochemical outcome discovered in the DKR study should be the same for the targeted *S*/*R* interconversion process. Thus, to transform the *S* enantiomers into *R*-configured α-AAs one would need to use the (*S*)-**3** ligand, and correspondingly the preparation of *S*-configured α-AAs from *R* enantiomers might require (*R*)-**3**. As illustrative example, once again, we selected **4a** (Table 2, entry 1). The reaction of (*S*)-**4a** with (*S*)-**3** was monitored by HPLC analysis and the data obtained are presented in Figure S2 in the Supporting Information.

The ligand (*S*)-**3** readily reacted with (*S*)-Trp [(*S*)-**4a**], thus giving rise to the kinetic product ($S_a$,$S_c$)-**5a** which was a major product in the initial stages of the process. For example, after 5 minutes the ratio between diastereomers ($S_a$,$S_c$)-**5a** and ($S_a$,$R_c$)-**5a** was about 97:3. However, the base-catalyzed epimerization of ($S_a$,$S_c$)-**5a** to ($S_a$,$R_c$)-**5a** was observed at relatively high rate, thus giving rise to almost equal amounts of the diastereomers ($S_a$,$S_c$)-**5a** and ($S_a$,$R_c$)-**5a** at about 1.5 hours into the reaction time. Complete thermodynamic control was achieved after 24 hours as the kinetic diastereomer ($S_a$,$S_c$)-**5a** had almost completely disappeared. The product ($S_a$,$R_c$)-**5a**, containing (*R*)-**4a**, was isolated as a single diastereomer with excellent chemical yield.

***Table 2:*** *S*/*R* interconversion of α-AAs using ligands (*S*)- and (*R*)-**3**.




| Entry | 3 | 4 | Yield [%] | (*S*,*R*)/(*S*,*S*) or (*R*,*S*)/(*R*,*R*)[a] | *t* [h] |
|---|---|---|---|---|---|
| 1 | (*S*)-**3** | (*S*)-Trp [(*S*)-**4a**] | 96 | >97:3 (*S*,*R*) | 24 |
| 2 | (*S*)-**3** | (*S*)-Phe [(*S*)-**4b**] | 93 | >97:3 (*S*,*R*) | 24 |
| 3 | (*S*)-**3** | (*S*)-Tyr [(*S*)-**4c**] | 97 | >97:3 (*S*,*R*) | 24 |
| 4 | (*R*)-**3** | (*R*)-Met [(*R*)-**4d**] | 97 | >97:3 (*R*,*S*) | 3 |
| 5 | (*R*)-**3** | (*R*)-Gln [(*R*)-**4e**] | 93 | >96:4 (*R*,*S*) | 3 |
| 6 | (*R*)-**3** | (*R*)-Val [(*R*)-**4j**] | 92 | >97:3 (*R*,*S*) | 24 |

[a] Ratio was based on reverse-phase HPLC analysis.

Reaction of (*S*)-**3** with two other aromatic α-AAs (*S*)-phenylalanine [(*S*)-**4b**; Table 2, entry 2] and (*S*)-tyrosine [(*S*)-**4c**; entry 3] gave quite similar results, thus allowing very convenient preparation of the target unnatural *R* enantiomers of **4b** and **4c** from the very inexpensive *S*-configured starting α-AAs. The opposite, *R*- to *S*-enantiomer transformation was demonstrated using (*R*)-**3** and the α-AAs (*R*)-**4d**,**e**,**j**, representing ω-functionalized as well as aliphatic α-AAs. As follows from entries 4–6 in Table 2, the *R* into *S* conversion proceeds smoothly, thus affording the target ($R_a$,$S_c$)-**5** complexes in excellent chemical yields and diastereoselectivity.

Taking advantage of the high crystallinity of ($S_a$,$R_c$)-**5a** we performed an X-ray analysis. The crystallographic structure (see Figure S3 in the Supporting Information) has at least two remarkable features. First, the position of (*S*)-bis(naphthylamine) chiral auxiliary is quite remote from the α-AA residue and seems irrelevant in controlling the configuration of the tryptophan α-stereogenic center. Second, while the three nitrogen atoms and one oxygen atom coordinated to nickel(II) are found in the same plane, the chelate rings around the nickel(II) are extremely puckered out of plane. Consequently, the crystallographic analysis did not give us direct answers as to what the mode of asymmetric induction of the chiral auxiliary on the configuration of the α-AA moiety was. However, more detailed structural analysis pointed us to the puckered arrangement of the chelate rings. Thus, viewing the structure as shown in Figure S3, allows one to notice that the ring A is clearly above the nickel(II) plane with the torsion angle of Ni-sp$^3$N-sp$^3$C-C(O)N being −39.02°. Furthermore, the adjacent chelate B ring is below the plane with a torsion angle [Ni-N(C=N)-sp$^2$C-sp$^2$C] of 22.77°. Finally, the ring C, bearing the α-AA side chain, is above the plane with a torsion angle [Ni-N(C=N)-sp$^3$C-sp$^2$C] of −31.83°. We were pleased to find that this arrangement of the chelate rings constitutes a helical chirality of *S* absolute configuration. As a result of this chelate ring puckering, the benzophenone phenyl ring is located underneath of the α-AA stereogenic carbon atom, thus forcing the α-AA side chain to point in the opposite direction. Thus, based on this analysis, we can suggest that the *S* configuration of **3** generates the *S*-helical chirality of the chelate rings, which in turn, controls the *R*-absolute configuration of the α-AA moiety. This mode of asymmetric induction is rather unique to this type of nickel(II) complexes and is obviously novel.

To conclude, we have developed the first purely chemical method for DKR of unprotected racemic α-AAs. This approach can be readily extended for α-*S*/*R* interconversion of α-AAs, thus underscoring its methodological versatility and synthetic flexibility. The process presented here features substrate generality, a virtually complete stereochemical outcome, fully recyclable source of chirality, and operationally simple and convenient reaction conditions, thus allowing its application on a relatively large scale.

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