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Resolution/Deracemization of Chiral α-Amino Acids Using Resolving Reagents with Flexible Stereogenic Centers

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Despite the dazzling potential of asymmetric synthesis,[1,2] resolution of racemates remains the most favorable approach to the large-scale preparation of enantiomerically pure compounds.[3,4] While enzymatic resolution is more economically feasible,[3] it has certain substrate limitations that require the application of a chemical approach via formation of diastereomeric derivatives. In the latter approach, application of a resolving reagent with one stereogenic center is a well-established practical technique.[5,6] On the other hand, alternative approaches that include multiple stereogenic centers in the resolving reagent remain virtually unstudied.[7] Therefore, it is totally unknown what advantage or disadvantage the application of a resolving reagent with more than one stereogenic center may have for practical resolutions. General considerations suggest that application of a resolving reagent with, for instance, two stereogenic centers will lead to two different stereochemical combinations of the corresponding diastereomeric derivatives. Thus, setting the two stereogenic centers of the resolving reagent as (*R*,*R*) or (*R*,*S*) yields diastereomeric products of the (*R*,*R*)(*R*) and (*R*,*R*)(*S*) or (*R*,*S*)(*R*) and (*R*,*S*)(*S*) configurations, respectively. In this case, the stereochemical difference in these products, and therefore the success of their separation, is predetermined by the absolute configuration of the resolving reagent and leaves no room for rational methodological choice. In particular, the alternative diastereomeric pairs, such as (*R*,*R*)(*R*) and (*R*,*S*)(*S*) or (*R*,*S*)(*R*) and (*R*,*R*)(*S*), cannot be prepared by this approach. On the other hand, these unavailable diastereomeric combinations possess an obviously greater degree of stereochemical difference and, if they can be obtained, may offer an unexpected advantage in their separations. However, to realize this potential advantage for practical separations, at least two challenges mast be addressed. First, the design of the corresponding resolving reagent must allow one of the stereogenic centers (or, in general, other elements of chirality) to be configurationally unstable. Second, to make this approach practical, upon product formation, the fixation of the configurationally unstable stereogenic center in either the (*R*) or (*S*) configuration must be totally controlled by the complete stereochemical match among all three stereogenic centers in the corresponding product, leading to the formation of only two (out of the four possible) diastereomers, of either (*R*,*R*)(*R*) and (*R*,*S*)(*S*) or (*R*,*S*)(*R*) and (*R*,*R*)(*S*) absolute configuration.

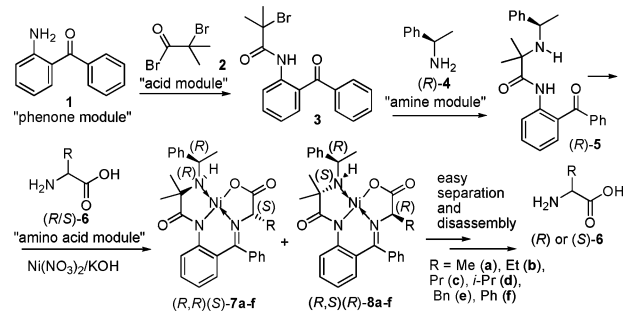
Such stereochemical design has never been realized and presents an adorable intellectual challenge. Furthermore, the exploration of this approach based on the rationally controlled combination of the three stereogenic centers in the corresponding diastereomers may be advantageous and lead to the development of a new methodology for separations of enantiomers.

Here we describe a general synthetic approach to a novel type of chiral ligand containing a configurationally stable carbon and configurationally unstable nitrogen stereogenic centers, which can be used as efficient resolving agents for chiral tailor-made[8] α-amino acids via formation and separation of the corresponding diastereomeric products.

In the course of our work on the chemistry of Ni(II) complexes of α-amino acid Schiff bases,[9] recently we reported the design and synthesis of a new generation[10] of "NH" Ni(II)-complexed Schiff bases of glycine[11] that contain configurationally unstable stereogenic nitrogen. While studying the synthetic potential of these new nucleophilic glycine equivalents in asymmetric Michael addition reactions,[12] we found that the stereochemistry of the configurationally unstable nitrogen can be completely controlled by the absolute configuration of the α-stereogenic carbon of the glutamic acid residue in the corresponding addition products. Drawing on these results, we have designed a new type of ligand containing a configurationally stable stereogenic carbon in addition to the configurationally unstable stereogenic nitrogen, with a goal of exploring the application of these ligands in the resolution of chiral α-amino acids. It should be noted that the application of configurationally unstable stereogenic nitrogen centers as additional stereocontrolling elements in dynamic chemical processes, such as catalysis, is a well-known principle.[13] On the other hand, stereochemically controlled conversion of the flexible chirality of the stereogenic nitrogen to the conformationally stable form, as required by our design, along with the added dimension of its translation into the desired physicochemical properties of an organic compound, has never been realized.

As shown in Scheme 1, chiral ligand (*R*)-**5** can easily be prepared via a simple two-step process. The initial step involves coupling

Scheme 1. Preparation of Ligand (*R*)-**5** and Assembly of the Diastereomeric Ni(II) Complexes (*R*,*R*)(*S*)-**7a**–**f** and (*R*,*S*)(*R*)-**8a**–**f**



of *o*-aminobenzophenone (**1**) with 2-bromo-2-methylpropanoyl bromide (**2**) followed by alkylation of (*R*)-1-phenylethylamine (**4**) with the intermediate bromide **3**.[14] It should be noted that the modular nature of ligands **5**, assembled using "phenone", "acid", and "amine" modules (**1**, **2**, and **4**, respectively), renders this design virtually unlimited for potential fine-tuning of the reactivity and structural and stereochemical features. Reactions of ligand (*R*)-**5** with racemic amino acids **6** were conducted under operationally

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convenient conditions at 60−70 °C in methanol in the presence of potassium hydroxide as a base and nickel nitrate as the metal source.

Analysis (^{1}H NMR, X-ray) of the reaction between ligand (*R*)-**5** and *rac*-alanine (**6a**) revealed, to our delight, that only two (**7a** and **8a**) of the four possible diastereomeric products were formed. Furthermore, the ratio of **7a** to **8a** was found to be time-dependent. Thus, at the earlier stages of the reaction, the kinetic diastereoselectivity did not favor either of the diastereomers **7a** or **8a**, resembling the racemic nature of the amino acid used. However, because of the basic reaction conditions used, the amino acid residues in **7a** and **8a** can easily be enolized, rendering the corresponding stereogenic center configurationally flexible. Consequently, the resulting system of one stable and two flexible stereogenic centers can further undergo thermodynamic control to settle the optimal balance of mutual stereochemical preferences. Thus, as the reaction progressed, the established thermodynamic control[15] strongly favored the diastereomer (*R*,*R*)(*S*)-**7a** over (*R*,*S*)(*R*)-**8a** (Table 1, entry 1). The observed stereochemical

Table 1. Reactions of Ligand (*R*)-**5** with Amino Acids (*R*/*S*)-**6** and Preparation of Diastereomeric Ni(II) Complexes (*R*,*R*)(*S*)-**7a**−**f** and (*R*,*S*)(*R*)-**8a**−**f**

entry	1	2	3	4	5	6
R	Me	Et	Pr	Bn	*i*-Pr	Ph
yield (%)	84	89	84	71	99	80
7/**8** ratio	>98/2	>98/2	>98/2	>98/2	60/40	59/41

outcome suggests that ligand (*R*)-**5** can be of multipurpose use, allowing for the separation of the enantiomers of **6a** (under kinetic control) or deracemization of *rac*-**6a** (under thermodynamic control) to the individual (*S*) form.

Similar stereochemical outcomes were observed in the reactions of ligand (*R*)-**5** with a series of α-amino acids containing a straight alkyl chain or a benzyl group (Table 1, entries 2−4). Application of this method to the family of *β*-branched amino acids was also successful, as represented by the reactions of ligand (*R*)-**5** with valine and phenylglycine (Table 1, entries 5 and 6). The thermodynamic control in these cases still favored the major diastereomers (*R*,*R*)(*S*)-**7e**,**f** over (*R*,*S*)(*R*)-**8e**,**f**, however, with a ratio of 1.5/1. On the other hand, under the same reaction conditions, α-branched quaternary amino acids did not react with (*R*)-**5**, probably because of their substantial steric bulk, which prevented the formation of the corresponding Schiff bases.[16]

According to our expectation, the diastereomers (*R*,*R*)(*S*)-**7a**−**f** and (*R*,*S*)(*R*)-**8a**−**f** showed noticeably different physicochemical properties, possibly as a result of the favorable stereochemical difference between their three stereogenic centers. Thus, the minor diastereomers (*R*,*S*)(*R*)-**8e**,**f** were found to be substantially more soluble in various organic solvents, such as acetone or even ether, significantly facilitating separation of (*R*,*R*)(*S*)-**7a**−**f** from (*R*,*S*)(*R*)-**8a**−**f**. Furthermore, the chromatographic behavior (i.e., retention factors R_f) of diastereomers (*R*,*R*)(*S*)-**7a**−**f** and (*R*,*S*)(*R*)-**8a**−**f**also differed noticeably, rendering their separation on SiO_2 quite feasible even on a large (50 g) scale. Diastereomerically pure products (*R*,*R*)(*S*)-**7a**−**f** and (*R*,*S*)(*R*)-**8a**−**f** were disassembled under the standard conditions (HCl/MeOH)[10c] to furnish the enantiomerically pure amino acids **6** along with quantitative recycling of the chiral ligand **5**.

The stereochemical assignments of (*R*,*R*)(*S*)-**7a**−**f** and (*R*,*S*)(*R*)-**8a**−**f** were made on the basis of their spectral, chiroptical, and crystallographic data. The assigned absolute configurations were confirmed by X-ray analysis of the five major (**7a**,**c**−**f**) and two minor (**8d**,**f**) diastereomers.[17]

In summary, this work has demonstrated that a previously unexplored approach to separation of enantiomers via formation of diastereomeric derivatives with three stereogenic centers has obvious practical potential and deserves further systematic study. The design reported here is based on the quite unusual application of a configurationally unstable stereogenic nitrogen, which plays a key role in setting up the complete stereochemical match between the three stereogenic centers in the corresponding products. The observed stereochemical match in the exclusive formation of only two diastereomers, (*R*,*R*)(*S*)-**7** and (*R*,*S*)(*R*)-**8**, represents the case of possibly optimal differences in stereochemistry and therefore physicochemical properties, allowing for easy separation of these diastereomeric products. Furthermore, the present design can be used for both separation of the enantiomers and deracemization of *rac*-α-amino acids. The practicality of the processes described here is due to the fact that they are very inexpensive and facile to carry out in any regular laboratory, as all of the reactions involved can be conducted under operationally convenient conditions[17] without recourse to inert atmosphere, rigorously dried/degassed solvents, or difficult-to-maintain temperatures.

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Supporting Information Available: Experimental procedures, characterization of new compounds, and crystallographic data for compounds (*R*,*R*)(*S*)-**7a**,**c**−**f** and (*R*,*S*)(*R*)-**8d**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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