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Design and synthesis of (*S*)- and (*R*)-α-(phenyl)-ethylamine-derived NH-type ligands and their application for the chemical resolution of α-amino acids†

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This work presents the first chemical approach for the resolution of α-amino acids offering the following advantages: (1) The specially designed resolving reagent is derived from α-(phenyl)ethylamine, the most inexpensive chiral auxiliary, which can be recycled and reused, rendering the cost structure of the complete process very attractive; (2) the time-efficient two-step process can be conducted under operationally convenient conditions with virtually quantitative yields; and (3) the process can readily be adapted to large-scale use.

Introduction

α-Amino acids (α-AAs) represent an exceptional class of compounds critically involved in virtually all areas of life-related research and the health-care industries. Many generations of organic chemists have contributed to the development of synthetic methodology for the preparation of α-AAs and their derivatives, in particular peptides and peptidomimetics.[1] The wealth of methodology developed to date for the synthesis of α-AAs displays a remarkable degree of creative ingenuity, allowing the preparation of tailor-made[2] α-AAs of virtually any structural or functional complexity.[3,4] However, issues of practicality and cost of the target α-AAs have been largely ignored in the academic research, rendering many of the chemical routes prohibitively expensive for large-scale preparation of α-AAs.[5] As a result, less complicated and more cost-efficient enzyme-based methodology forms the basis of the current α-AAs industry.[6] Considering the growing importance of tailor-made α-AAs in the *de novo* design of peptides, peptidomimetics and pharmaceuticals,[7] the issue of cost-efficiency has become a key factor in the assessment of new synthetic methods. The advantage of enzymatic separation and fermentation over chemical methods is that they can be conducted under operationally convenient conditions, rendering the resultant product much less expensive. For the chemical methods the development of robust and uncomplicated methods has remained a major challenge. A number of research groups are currently focused on the development of reaction methods that avoid air- or moisture-sensitive reagents, specially purified solvents or extremely low temperatures.[8]

For quite some time we have been interested in the chemistry of Ni(II) complexes of glycine Schiff bases and their general application for the asymmetric synthesis of α-amino acids. Over the years this area has attracted the interest of a number of research groups[9] and new generations of structurally varied Ni(II) complexes have been developed[10] (Fig. 1).

The major motivation for studying the chemistry of Ni(II)-complexes of glycine Schiff bases is that their transformation to higher amino acids can be conducted under operationally convenient conditions. For example, the (*S*)- or (*R*)-proline-derived complex **1**[11] can be converted to a variety of α-amino acids *via* alkyl halide alkylation,[12] aldol,[13] Michael[9c,14] or Mannich[15] reactions using commercial grade solvents and at ambient temperatures. Achiral picolinic acid-derived complex **2**[16] can be used for the advanced synthesis of α,α-dialkyl-substituted quaternary AAs[17] or for asymmetric transformations under PTC conditions[18] and Michael addition reactions.[19] Since complex **2** has very limited solubility in common organic solvents, a new type of achiral Ni(II) complex **3** was developed.[20] The solubility of complex **3** derivatives in virtually any solvent can be tailored simply by choice of the R′ groups on the amino moiety. Complexes **3** have been successfully used

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†Electronic supplementary information (ESI) available: Crystallographic data of **14a**, HPLC analyses and copies of NMR spectra. CCDC 993563. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00669k

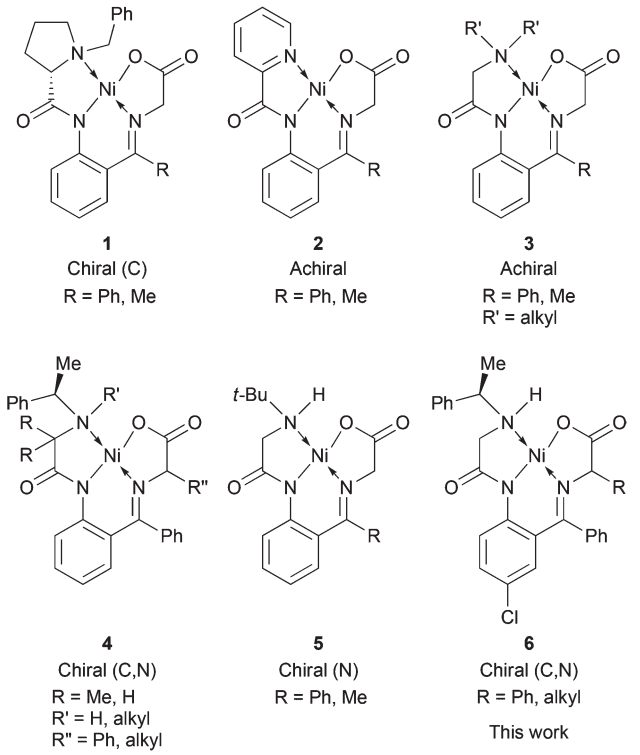


Fig. 1 Structural variety of Ni(II) complexes of glycine Schiff bases.

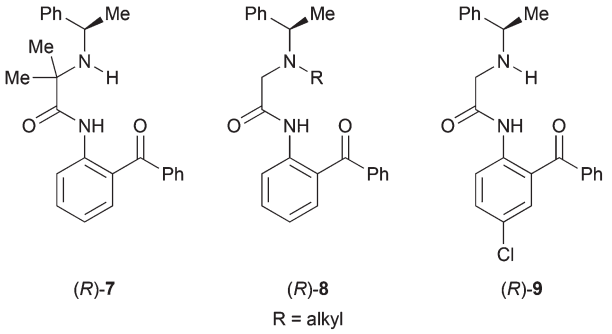


Fig. 2 Three types of α-(phenyl)ethylamine-derived ligands **7**–**9**.

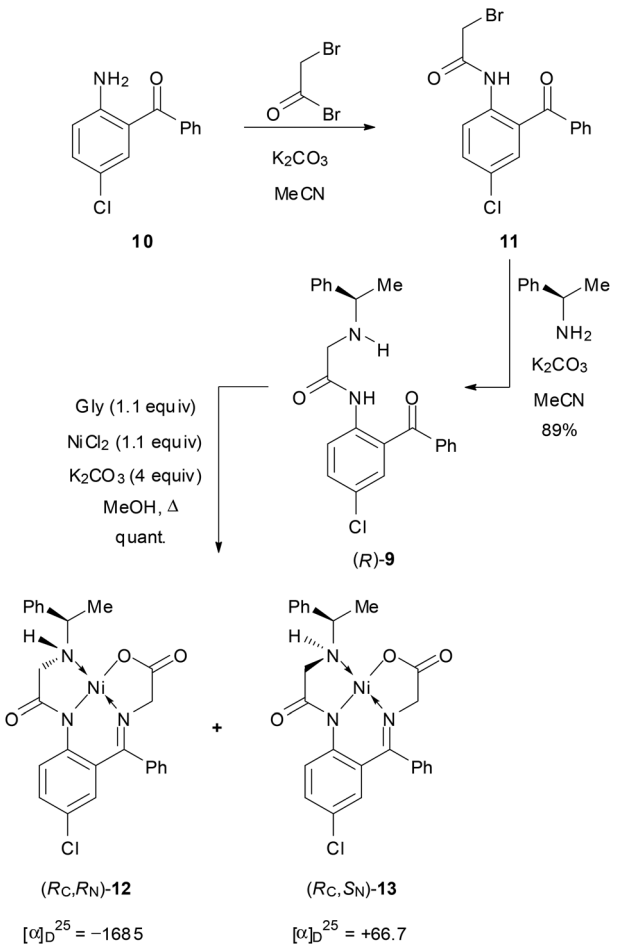
for bis-alkylations[21] as well as asymmetric Michael addition reactions.[22] Recently, using the modular design[23] first developed for the preparation of complexes **3**, a new family of chiral derivatives, **4**, has been introduced[24] and successfully used for deracemization[25] and (*S*)-to-(*R*) interconversion[26] of α-AAs. The most recent development in this area has been the study of diastereoselectivity in alkylation and Michael addition reactions of NH-type complexes **5** and their *N*-adamantyl analogs.[27] Each type of the complexes **1**–**5** has both advantageous features and limitations, leaving room for further improvements in reactivity and the stereochemical outcome of their synthetic application. In the present study, we explore structurally new NH-type complexes **6** possessing a relatively simple, non-rigid framework of three chelated rings and demonstrate their application for resolution of α-AAs, including the biologically highly valuable 2′,6′-dimethyltyrosine (DMT).

Results and discussion

During our previous studies,[24–26] we designed ligands **7** (Fig. 2), derived from one of the most inexpensive chiral auxiliaries, α-(phenyl)ethylamine.[28] While ligands **7** were quite successful for the deracemization of α-AAs, they have two serious shortcomings: their low-yield synthesis and slow rates of formation of complexes **4** (R = Me; R′ = H). These problems clearly rendered ligands **7** inefficient for the preparation of target α-AAs on the gram scale. Another type of previously reported α-(phenyl)ethylamine-derived ligands **8** are less sterically bulky at the glycine moiety and possess a tertiary amine moiety.[29] It was found that the alkyl group R on the nitrogen in **8** led to problems in the formation of complexes **4** (R = H; R′ = Me, Et, *n*-Pr) and to the overall inefficiency of ligands **8**. It should also be noted that combination of the steric features of **7** with a tertiary amine moiety, as in ligands of type **8**, failed entirely to form the corresponding Ni(II) complexes with α-AAs. Analysis of these and other[24–26,29] data obtained for the synthesis and reactivity of ligands **7** and **8** clearly suggested that the steric bulk at the glycine moiety, as in **7**, as well as on the amino group, as in **8**, were detrimental to the required reactivity of compounds **7** and **8**. We therefore envisioned the design of a simple NH-type version **9**, possessing an unsubstituted glycine moiety and a secondary amino group.

Synthesis of ligand (*R*)-**9** was accomplished using the sequence of reactions illustrated in Scheme 1. Focusing on our work on the cost structure, we chose to use 2-amino-5-chlorobenzophenone **10** as the starting compound, since it is about one-fifth of the cost of the non-chlorinated analog. Reaction of chloro-benzophenone **10** with bromoacetyl bromide gave amide **11**, which was further reacted with (*R*)-α-(phenyl)ethylamine[30] to give the target ligand (*R*)-**9**.

Optimization of the reaction conditions of ligand (*R*)-**9** with glycine and $NiCl_2$ revealed that the corresponding diastereomeric Ni(II) complexes (R_C,R_N)-**12** and (R_C,S_N)-**13** could be obtained in quantitative yield in less than an hour using just 10% excess of glycine and $NiCl_2$. These results are in sharp contrast to the reactivity of ligands **7** and **8**, which required a five-fold excess of the reagents and about 24 h reaction time.[24–26,29] The exceptional reactivity of ligand **9** is clearly the result of its simple structure and the absence of any steric obstruction in its complexation with Ni(II). On the other hand, the lack of steric hindrance results in poor control of the nitrogen stereochemistry by the (*R*)-α-(phenyl)ethylamine residue, giving rise to diastereomeric products (R_C,R_N)-**12** and (R_C,S_N)-**13** in a 54 : 46 ratio, determined by HPLC analysis. Bearing in mind that the goal of the present study was the chemical resolution of α-AAs, the low diastereoselectivity observed was quite acceptable. The nitrogen stereogenic center in compounds (R_C,R_N)-**12** and (R_C,S_N)-**13** is configurationally stable,



Scheme 1 Synthesis of ligand **9** and glycine Schiff base complexes **12** and **13**.

allowing their isolation in diastereomerically pure form by column chromatography.

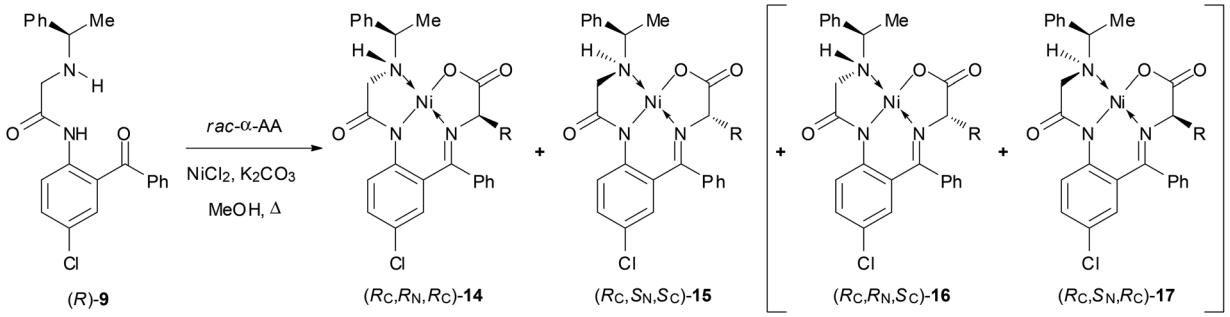
Assignment of the absolute configuration of (R_C,R_N)-**12** and (R_C,S_N)-**13** was based on their chiroptical properties. Thus, the diastereomer **12** with (R_C,R_N) configuration had very high optical rotation, $[\alpha]_D^{25}$ = −1685, whereas product **13**, of (R_C,S_N) stereochemistry, showed low rotation ($[\alpha]_D^{25}$ = +66.7). A similar trend of optical rotation was previously observed for a series of analogous complexes derived from ligands **8** (R = Me, Et, *n*-Pr), the structures of which were determined by X-ray analysis.[29]

With these preliminary results obtained for glycine Schiff base complexes **12** and **13**, we next investigated the reactions of ligand (*R*)-**9** with a range of racemic α-AAs (Table 1). It was expected that complexation of ligand (*R*)-**9** with higher α-AAs might result in the formation of up to four diastereomeric products, due to the presence of two epimerizable stereogenic centers: the α-carbon of the amino acid residue and the nitrogen of the ligand. As can be seen from Table 1, in all the cases studied two major diastereomers (R_C,R_N,R_C)-**14** and (R_C,S_N,S_C)-**15** were obtained, along with two other minor complexes (R_C,R_N,S_C)-**16** and (R_C,S_N,R_C)-**17**. Absolute configuration of the complex (R_C,R_N,R_C)-**14a**, containing a phenylalanine residue, was determined by X-ray analysis (Fig. 3). Based on the similarity of the chiroptical properties and spectral data, the remainder of products **14b–g** were assigned (R_C,R_N,R_C) stereochemistry. In particular, all the complexes **14a–g** showed high negative optical rotation (Table 1), indicating α-(*R*)-absolute configuration of the corresponding amino acid residue. On the other hand, the second major diastereomers (R_C,S_N,S_C)-**15a–g** showed similarly high positive optical rotation, confirming the α-(*S*) absolute configuration of the corresponding amino acids.[24–26] Furthermore, one can also see a clear trend in the chemical shifts of the Me group of the α-(phenyl)ethylamine moiety in the diastereomers (R_C,R_N,R_C)-**14** and (R_C,S_N,S_C)-**15**. As can be seen from the crystallographic structure of **14a** (Fig. 3), the Me group of the α-(phenyl)ethylamine moiety is located under and in close proximity to the Ni(II) atom, which noticeably deshields it.[31] Hence, in all cases studied the resonance of the Me group in diastereomers (R_C,R_N,R_C)-**14a–g** appeared downfield in comparison to that of diastereomers (R_C,S_N,S_C)-**15a–g**.

The absolute configuration of the minor diastereomers (R_C,R_N,S_C)-**16** and (R_C,S_N,R_C)-**17** can also be deduced from their optical rotation (α-carbon stereogenic center) and the chemical shift of the Me groups (*N*-stereogenic center). However, an indisputable determination of their stereochemistry can be achieved by synthesis of the minor diastereomers (R_C,R_N,S_C)-**16** and (R_C,S_N,R_C)-**17** from major products (R_C,R_N,R_C)-**14** and (R_C,S_N,S_C)-**15**, and by comparison of the properties of the compounds obtained, (R_C,R_N,S_C)-**16** and (R_C,S_N,R_C)-**17**, with those prepared directly by the reaction of ligand (*R*)-**9** with amino acids. As discussed above, the stereogenic nitrogen in complexes of this type is configurationally stable in the solid state or in solutions of the complexes in nonpolar solvents ($CHCl_3$, CH_2Cl_2). However, in protic polar solvents NH complexes undergo ready epimerization at the *N*-stereogenic center. For example, one of the major diastereomers (R_C,R_N,R_C)-**14g** was heated at 50 °C in the mixture MeOH–CH_2Cl_2, and the reaction was followed by HPLC at different reaction times. Thermodynamic equilibrium, as a 92 : 8 mixture of epimers (R_C,R_N,R_C)-**14g** and (R_C,S_N,R_C)-**17g**, was reached after 2 h (Scheme 2).

Considering the data presented in Table 1, one may conclude that in all the cases studied, regardless of the structure of the amino acid side-chain, the two major diastereomers (R_C, R_N,R_C)-**14** and (R_C,S_N,S_C)-**15** are formed in close to a 1/1 ratio. Both diastereomers **14** and **15** have relative *trans*-disposition of the amino acid side-chain and the *N*-α-(phenyl)ethyl group, rendering them more thermodynamically stable than the minor diastereomers (R_C,R_N,S_C)-**16** and (R_C,S_N,R_C)-**17**, which possess these groups in the sterically unfavorable *cis*-position. Considering the stereochemistry of all four diastereomers, (R_C, R_N,R_C)-**14**, (R_C,S_N,S_C)-**15** (major), (R_C,R_N,S_C)-**16** and (R_C,S_N,R_C)-**17** (minor), one can suggest that for the purpose of chemical resolution diastereomers (R_C,R_N,R_C)-**14** and (R_C,S_N,R_C)-**17** can be grouped together, as they contain the target amino acid of the same α-(*R*) absolute configuration. Similarly, diastereomers (R_C,S_N,S_C)-**15** and (R_C,R_N,S_C)-**16** also can be combined for isolation of the corresponding α-(*S*)-AAs. From this standpoint, it

Table 1 Reactions of ligand (*R*)-**9** with α-AAs



Entry	AA	R	Product	Ratio **14** : **15**[a]	Yield[b] (%)	$[\alpha]_D^{25}$	δ_{Me} (ppm)
1	Phe	Bn	(R_C,R_N,R_C)-**14a**	54 : 46	97	−2239	1.91
			(R_C,S_N,S_C)-**15a**			+2750	1.73
2	Phg	Ph	(R_C,R_N,R_C)-**14b**	56 : 44	93	−1969	2.05
			(R_C,S_N,S_C)-**15b**			+2494	1.95
3	Ala	Me	(R_C,R_N,R_C)-**14c**	53 : 47	95	−3075	2.04
			(R_C,S_N,S_C)-**15c**			+2669	1.95
4	Val	i-Pr	(R_C,R_N,R_C)-**14d**	55 : 45	94	−2638	1.98
			(R_C,S_N,S_C)-**15d**			+2900	1.86
5	Leu	i-Bu	(R_C,R_N,R_C)-**14e**	56 : 44	94	−2126	1.99
			(R_C,S_N,S_C)-**15e**			+2893	1.90
6	Tyr	4-OH-$C_6H_4CH_2$	(R_C,R_N,R_C)-**14f**	52 : 48	97	−2841	1.85
			(R_C,S_N,S_C)-**15f**			+2539	1.62
7	DMT	4-OH-2,6-di-Me-$C_6H_4CH_2$	(R_C,R_N,R_C)-**14g**	51 : 49	99	−1291	2.01
			(R_C,S_N,S_C)-**15g**			+1853	1.80

[a] Measured by HPLC analysis of the crude reaction mixtures. Up to 15% of isomers **16** and **17** was also detected (see Experimental part for details). [b] Overall isolated yield of pure products.

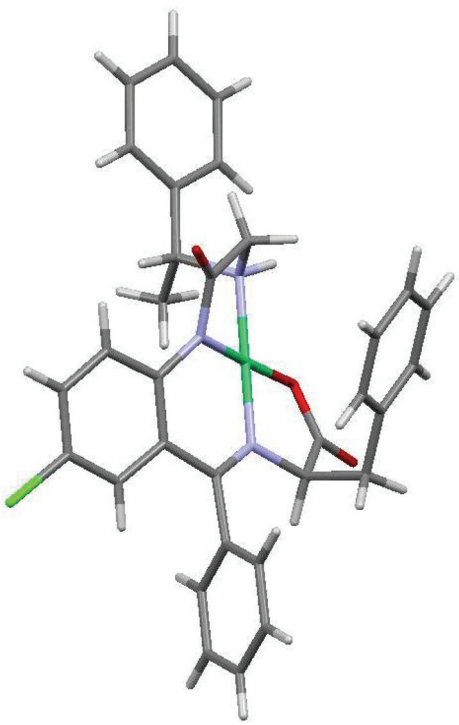
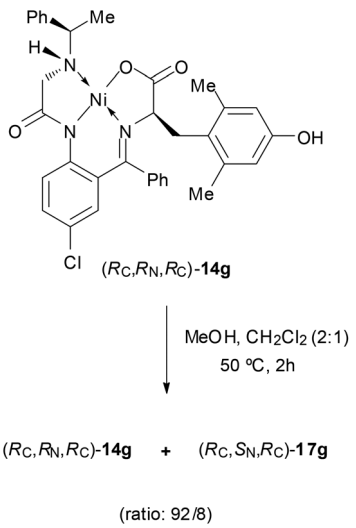


Fig. 3 Crystallographic structure of (R_C,R_N,R_C)-**14a**.



Scheme 2 Epimerization of the major product (R_C,R_N,R_C)-**14g** to the minor diastereomer (R_C,S_N,R_C)-**17g**.

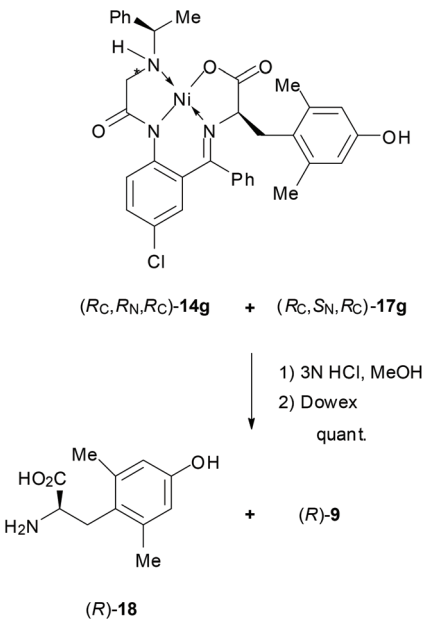
should be emphasized that in all the cases listed in Table 1 the diastereomeric complexes **14a–g**–**17a–g** were obtained in excellent yield, in every case well above 90%, using only a 10% excess of the racemic amino acid and $NiCl_2$. However, the

most important advantage of complexes **14a–g–17a–g** is that both the major and minor products have significantly different R_fs, simplifying their separation and isolation in diastereomerically pure form. The minor diastereomers usually follow the corresponding major product, and could therefore be similarly grouped for separation of (*S*)- and (*R*)-α-AAs. Importantly, the observed difference in the R_fs is not influenced by the AA side-chain and is thus a broad-spectrum property, suggesting some degree of generality in resolution.

With these results in hand, we were in position to explore the final goal of this work, which was to demonstrate a practical application of ligand (*R*)-**9** for the resolution of α-AAs. As an example we selected 2′,6′-dimethyltyrosine (DMT), for the following reasons: firstly, DMT is a very important tailor-made amino acid critically involved in the *de novo* design of various synthetic peptides, in particular opioid receptor agonists and antagonists,[32] and secondly, while racemic DMT is relatively inexpensive, the cost of pure (*R*)- and (*S*)-enantiomers of DMT is high, partly because asymmetric synthesis of DMT requires protection and deprotection of the phenolic group.[33] With this in mind, direct resolution of unprotected racemic DMT might provide a competitive alternative approach for preparation of enantiomerically pure DMT.

To this end, we carried out reaction of ligand (*R*)-**9** with racemic DMT on the gram scale. Gratifyingly, on this scale we observed virtually complete conversion of ligand (*R*)-**9**, and reaction products **14g–17g** were obtained in quantitative yield. Diastereomers **14**, **17** and **15**, **16** were readily separated by column chromatography and disassembled under standard conditions (MeOH–HCl).[29] Starting from the mixture of (R_C,R_N,R_C)-**14** and (R_C,S_N,R_C)-**17**, free amino acid (*R*)-**18** (Scheme 3) was isolated in quantitative yield, along with the starting ligand (*R*)-**9**, which could conveniently be recycled. The same procedure was performed on the mixture of (R_C,S_N, S_C)-**15** and (R_C,R_N,S_C)-**16**, giving rise to the (*S*)-enantiomer **18** of DMT in addition to the ligand (*R*)-**9**. Starting from racemic DMT, the overall yield of the (*R*)- and (*S*)-enantiomers **18** was 48 and 36%, respectively.

Finally, we felt it necessary to provide an example of preparation of diastereomerically pure complexes **14g** or **15g** without recourse to column chromatography, confirming the scalability of this method for large-scale synthesis of the target amino acids. The reaction of ligand **9** with racemic 2′,6′-dimethyltyrosine (DMT) was conducted on the 97.5 g scale, resulting in 147 g (93%) of diastereomers **14–17g**. Without purification, the resultant mixture was dissolved in $CHCl_3$ and treated with Et_2O to precipitate the major product (R_C,R_N,R_C)-**14g** in diastereomerically pure form (45.9 g, 31%). After disassembly of product **14g** under the usual hydrolytic conditions, the target (*R*)-2′,6′-dimethyltyrosine (DMT) (*R*)-**18** was obtained in enantiomerically pure form.



Scheme 3 Disassembly of complexes **14** and **17** and isolation of free (*R*)-DMT.

Conclusions

The chemistry described in this study represents the first chemical approach to the resolution of α-AAs. We have demonstrated that the resolving reagent, the specially designed ligand (*R*)-**9**, reacts with racemic α-AAs in virtually quantitative yield, giving rise to two major and two minor diastereomeric products. Complexes (R_C,R_N,R_C)-**14** and (R_C,S_N,R_C)-**17** containing α-(*R*) amino acids, and (R_C,S_N,S_C)-**15** and (R_C,R_N,S_C)-**16** having amino acids of α-(*S*) configuration, can be disassembled to furnish the target free amino acids, together with the recovery and recycling of the resolving reagent (*R*)-**9**.

The approach presented offers the advantages that it is based on an inexpensive source of chirality, α-(phenyl)ethylamine, and that all the reactions are operationally convenient and give virtually quantitative yield. Whereas asymmetric synthesis and enzymatic resolution require certain technical expertise and are procedurally intricate, the chemical resolution described is convenient, reliable and reproducible, particularly when both enantiomers of the target α-AA are required.

Experimental

General methods

All reagents and solvents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on precoated silica gel plates, and visualization was carried out using UV light. Flash column chromatography was performed with the solvents indicated on silica gel (particle size 0.040–0.063 mm). ^{1}H and ^{13}C spectra were recorded on a 300 MHz Brüker instrument. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (J) are given in hertz (Hz). The

letters m, s, d, t, q and br stand for multiplet, singlet, doublet, triplet, quartet and broad, respectively. High-resolution mass spectra (HRMS) were recorded using an UPLC/Q-TOF MS system in the ESI mode.

Synthesis of (*R*)-*N*-(2-benzoyl-4-chlorophenyl)-2-((1-phenylethyl)amino)acetamide (9). To a mixture of **11**[34] (1 equiv.), K_2CO_3 (4 equiv.) and MeCN (12 mL/1 g of **11**) was added (*R*)-α-(phenyl)ethylamine (1.1 equiv.). The reaction mixture was stirred 6 h at room temperature and monitored by TLC. The insoluble salts were filtered off and washed with EtOAc, and the filtrate was concentrated under reduced pressure. Hexane was added to the residue to form a precipitate, which was filtered and dried at 60 °C to give the title compound. Yield: 88.8%. $[\alpha]_D^{25} = -33.8$ (c = 1.604, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.56 (s, 1H), 8.65 (d, J = 9.3 Hz, 1H), 7.86–7.81 (m, 2H), 7.68 (tt, J = 7.4, 1.3 Hz, 1H), 7.62–7.48 (m, 4H), 7.40–7.35 (m, 2H), 7.32–7.21 (m, 3H), 3.83 (q, J = 6.5 Hz, 1H), 3.37 (d, J = 17.5 Hz, 1H), 3.29 (d, J = 17.5 Hz, 1H), 2.00 (br, 1H), 1.49 (d, J = 6.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 171.6, 144.2, 137.7, 137.6, 133.1, 133.0, 131.7, 130.1, 128.5, 127.3, 127.3, 126.7, 126.3, 123.0, 58.5, 51.2, 23.7.

HRMS: calc. for $C_{23}H_{22}ClN_2O_2$ $[M + H]^+$ 393.1370, found 393.1373.

General procedure for preparation of Ni(II) complexes by reaction of ligand 9 with amino acids

To a mixture of **9** (1 equiv.), $NiCl_2$ (1.1 equiv.), the corresponding amino acid (1.1 equiv.) and MeOH (30 mL/1 g of **9**) K_2CO_3 (4 equiv.) were added and the reaction mixture was stirred under reflux. The progress of the reaction was monitored by TLC and, upon completion (consumption of **9**), the reaction mixture was poured into cooled water. The target product was filtered off and washed with H_2O. The filtered precipitate was dried at 60 °C to give the corresponding Ni(II) complex.

Ni(II) complexes of the Schiff's base of 9 and glycine, (12) and (13). From 1 g (2.55 mmol) of **9**, 1.29 g of a 54 : 46 mixture of **12** and **13** was obtained (yield: quantitative). Part of the mixture was subjected to column chromatography to isolate diastereomerically pure products **12** (45 mg) and **13** (46 mg) for full analytical characterization.

*Data for **12**.* R_f: 0.29 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25} = -1685$ (c = 0.048, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 9.2 Hz, 1H), 7.57–7.43 (m, 3H), 7.40–7.10 (m, 7H), 6.93–6.80 (m, 1H), 6.75 (d, J = 2.5 Hz, 1H), 4.02–3.89 (m, 1H), 3.83 (dd, J = 16.8, 6.7 Hz, 1H), 3.72 (d, J = 20.6 Hz, 1H), 3.65 (d, J = 20.6 Hz, 1H), 3.44 (dd, J = 8.6, 7.3 Hz, 1H), 2.99 (d, J = 16.8 Hz, 1H), 2.09 (d, J = 6.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 177.4, 171.0, 141.3, 138.6, 133.9, 132.2, 132.1, 130.1, 129.6, 129.1, 128.8, 128.2, 127.4, 127.0, 126.1, 125.9, 125.8, 125.6, 61.8, 60.9, 52.3, 22.5.

HRMS: calc. for $C_{25}H_{23}ClN_3NiO_3$ $[M + H]^+$ 506.0781, found 506.0778.

*Data for **13**.* R_f: 0.16 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25} = +66.7$ (c = 0.048, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 9.2 Hz, 1H), 7.67–7.37 (m, 5H), 7.32–7.07 (m, 5H), 6.95–6.82 (m, 1H), 6.73 (d, J = 2.5 Hz, 1H), 4.05 (qd, J = 6.9, 5.7 Hz, 1H), 3.88–3.76 (m, 1H), 3.67 (s, 2H), 3.52 (dd, J = 17.3, 7.9 Hz, 1H), 3.09 (d, J = 18.5 Hz, 1H), 2.03 (d, J = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 177.9, 170.9, 141.4, 137.8, 133.9, 132.2, 132.0, 130.1, 130.0, 129.7, 128.9, 128.8, 128.3, 126.7, 126.1, 125.7, 125.6, 60.9, 59.8, 51.0, 18.0.

HRMS: calc. for $C_{25}H_{23}ClN_3NiO_3$ $[M + H]^+$ 506.0781, found 506.0771.

Ni(II) complexes of the Schiff's base of 9 and DL-phenylalanine (14a) and (15a). From 500 mg (1.27 mmol) of **9**, 736 mg of a 47 : 41 : 12 mixture of three diastereomers was obtained (yield: 96.9%). A part of the mixture was subjected to column chromatography to isolate diastereomerically pure products **14a** (121 mg) and **15a** (131 mg) for full analytical characterization.

*Data for **14a**.* R_f: 0.41 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25} = -2239$ (c = 0.050, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 9.1 Hz, 1H), 7.58–7.38 (m, 6H), 7.35–7.11 (m, 9H), 7.02 (d, J = 6.9 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 4.30–4.22 (m, 1H), 3.64–3.46 (m, 1H), 3.08 (dd, J = 16.3, 6.4 Hz, 1H), 3.01 (dd, J = 13.6, 2.6 Hz, 1H), 2.63 (d, J = 16.3 Hz, 1H), 2.60–2.53 (m, 1H), 2.06–1.97 (m, 1H), 1.91 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 175.8, 169.5, 141.4, 138.2, 135.7, 133.0, 132.3, 132.2, 131.0, 130.3, 129.4, 129.2, 129.0, 128.6, 128.2, 127.6, 127.1, 125.5, 124.9, 71.0, 61.1, 52.0, 39.0, 22.2.

HRMS: calc. for $C_{32}H_{29}ClN_3NiO_3$ $[M + H]^+$ 596.1251, found 596.1255.

*Data for **15a**.* R_f: 0.25 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25} = +2750$ (c = 0.047, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 9.0 Hz, 1H), 7.58–7.41 (m, 7H), 7.35 (d, J = 6.5 Hz, 2H), 7.28–7.15 (m, 5H), 7.10 (dd, J = 9.2, 2.5 Hz, 1H), 7.01 (d, J = 6.9 Hz, 1H), 6.64 (s, 1H), 4.24 (s, 1H), 3.66 (q, J = 6.9 Hz, 1H), 3.10–2.88 (m, 2H), 2.78 (d, J = 17.2 Hz, 1H), 2.60 (dd, J = 13.6, 5.5 Hz, 1H), 2.05 (br, 1H), 1.73 (d, J = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 177.0, 169.3, 141.4, 137.7, 136.1, 133.0, 132.3, 132.1, 131.5, 130.5, 129.5, 129.3, 128.9, 128.9, 128.6, 128.1, 127.7, 127.6, 127.3, 125.5, 125.0, 71.7, 60.2, 51.6, 39.4, 18.1.

HRMS: calc. for $C_{32}H_{29}ClN_3NiO_3$ $[M + H]^+$ 596.1251, found 596.1256.

Ni(II) complexes of the Schiff's base of 9 and L-phenylglycine (14b) and (15b). From 500 mg (1.27 mmol) of **9**, 691 mg of a 48 : 38 : 8 : 6 mixture of four diastereomers was obtained (yield: 93.1%). A part of the mixture was subjected to column chromatography to isolate diastereomerically pure products **14b** (106 mg) and **15b** (93 mg) for full analytical characterization.

*Data for **14b**.* R_f: 0.52 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25} = -1969$ (c = 0.056, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 9.2 Hz, 1H), 7.57–7.40 (m, 5H), 7.36–7.22 (m, 5H), 7.20–7.11 (m, 4H), 6.95 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 5.94 (d, J = 7.8 Hz, 1H), 4.78 (s, 1H), 3.99–3.84 (m, 2H), 3.43 (dd, J = 8.0, 7.3 Hz, 1H), 3.02 (d, J = 16.8 Hz, 1H), 2.05 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 177.6, 171.6, 141.5, 138.5, 137.8, 133.5, 132.3, 132.1, 129.7, 129.0, 128.7, 128.6, 128.6, 128.1, 128.0, 127.9, 127.6, 127.4, 126.9, 126.0, 125.6, 125.1, 74.0, 61.2, 51.9, 21.8.

HRMS: calc. for $C_{31}H_{27}ClN_3NiO_3$ $[M + H]^+$ 582.1094, found 582.1097.

*Data for **15b**.* R_f: 0.34 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25}$ = +2494 (c = 0.031, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 7.0 Hz, 2H), 7.60 (dd, J = 6.3, 3.1 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.36–7.17 (m, 8H), 7.10 (dd, J = 9.2, 2.6 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 6.59 (d, J = 2.6 Hz, 1H), 5.95 (d, J = 7.8 Hz, 1H), 4.74 (s, 1H), 3.95 (qd, J = 7.0, 2.5 Hz, 1H), 3.64 (dd, J = 7.7, 2.1 Hz, 1H), 3.54 (dd, J = 17.0, 7.9 Hz, 1H), 3.03 (d, J = 16.9 Hz, 1H), 1.95 (d, J = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 178.5, 171.5, 141.5, 138.1, 138.0, 133.5, 132.2, 132.0, 129.7, 128.8, 128.6, 128.6, 128.3, 127.7, 127.3, 126.8, 126.0, 125.4, 125.2, 74.1, 61.1, 52.4, 18.8.

HRMS: calc. for $C_{31}H_{27}ClN_3NiO_3$ $[M + H]^+$ 582.1094, found 582.1097.

Ni(II) complexes of the Schiff's base of 9 and DL-alanine (14c) and (15c). From 500 mg (1.27 mmol) of **9**, 629 mg of a 48 : 42 : 7 : 3 mixture of four diastereomers was obtained (yield: 94.9%), Part of the mixture was subjected to column chromatography to isolate diastereomerically pure products **14c** (43 mg) and **15c** (22 mg) for full analytical characterization.

*Data for **14c**.* R_f: 0.42 (CH_2Cl_2–acetone, 1 : 1). $[\alpha]_D^{25}$ = −3075 (c = 0.050, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 9.2 Hz, 1H), 7.53–7.40 (m, 3H), 7.39–7.21 (m, 6H), 7.16 (dd, J = 9.2, 2.6 Hz, 1H), 6.89 (d, J = 7.1 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 4.08–3.74 (m, 3H), 3.25 (dd, J = 8.9, 6.8 Hz, 1H), 3.01 (d, J = 16.7 Hz, 1H), 2.04 (d, J = 6.9 Hz, 3H), 1.45 (d, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 177.2, 169.8, 141.2, 138.7, 132.9, 132.2, 130.2, 129.3, 129.1, 128.8, 128.7, 128.1, 127.9, 127.7, 127.4, 126.9, 125.6, 125.1, 65.9, 61.3, 52.2, 22.2, 21.2.

HRMS: calc. for $C_{26}H_{25}ClN_3NiO_3$ $[M + H]^+$ 520.0938, found 520.0949.

*Data for **15c**.* R_f: 0.24 (CH_2Cl_2–acetone, 1 : 1). $[\alpha]_D^{25}$ = +2669 (c = 0.050, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 9.2 Hz, 1H), 7.58 (d, J = 7.0 Hz, 2H), 7.54–7.36 (m, 3H), 7.34–7.20 (m, 4H), 7.11 (dd, J = 9.2, 2.6 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 4.03 (qd, J = 6.9, 2.6 Hz, 1H), 3.90 (q, J = 7.1 Hz, 1H), 3.72 (dd, J = 17.2, 8.0 Hz, 1H), 3.32 (d, J = 6.9 Hz, 1H), 3.12 (d, J = 17.5 Hz, 1H), 1.95 (d, J = 7.1 Hz, 3H), 1.44 (d, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 178.5, 169.8, 141.3, 137.9, 133.0, 132.2, 132.1, 130.2, 129.3, 129.1, 128.8, 128.7, 128.2, 128.0, 127.7, 127.0, 125.4, 125.0, 60.0, 51.5, 29.2, 21.3, 18.3.

HRMS: calc. for $C_{26}H_{25}ClN_3NiO_3$ $[M + H]^+$ 520.0938, found 520.0947.

Ni(II) complexes of the Schiff's base of 9 and DL-valine (14d) and (15d). From 500 mg (1.27 mmol) of **9**, 654 mg of a 50 : 41 : 7 : 2 mixture of four diastereomers was obtained (yield: 93.7%). A part of the mixture was subjected to column chromatography to isolate diastereomerically pure products **14d** (97 mg) and **15d** (74 mg) for full analytical characterization.

*Data for **14d**.* R_f: 0.45 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25}$ = −2638 (c = 0.048, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 9.2 Hz, 1H), 7.52–7.38 (m, 5H), 7.32–7.18 (m, 4H), 7.14 (dd, J = 9.2, 2.5 Hz, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 3.98 (dd, J = 16.8, 6.5 Hz, 1H), 3.91–3.74 (m, 2H), 3.63 (dd, J = 8.2, 6.9 Hz, 1H), 3.01 (d, J = 16.8 Hz, 1H), 2.00 (d, J = 6.2 Hz, 3H), 1.97 (d, J = 6.3 Hz, 3H), 1.79–1.61 (m, 1H), 0.76 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 176.7, 169.6, 141.4, 138.5, 133.1, 132.3, 132.2, 130.1, 129.2, 129.1, 128.7, 128.5, 128.0, 127.5, 127.1, 125.5, 124.8, 74.8, 61.2, 52.3, 34.2, 22.0, 19.7, 18.2.

HRMS: calc. for $C_{28}H_{29}ClN_3NiO_3$ $[M + H]^+$ 548.1251, found 548.1253.

*Data for **15d**.* R_f: 0.30 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25}$ = +2900 (c = 0.021, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 9.2 Hz, 1H), 7.72 (d, J = 7.0 Hz, 2H), 7.51–7.38 (m, 3H), 7.28–7.14 (m, 4H), 7.07 (dd, J = 9.2, 2.6 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 3.94–3.69 (m, 4H), 3.12 (d, J = 16.5 Hz, 1H), 1.98 (d, J = 6.8 Hz, 3H), 1.86 (d, J = 7.0 Hz, 3H), 1.77–1.65 (m, 1H), 0.75 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 177.6, 169.5, 141.3, 138.0, 133.1, 132.2, 132.1, 130.1, 129.2, 129.1, 128.8, 128.5, 128.3, 128.0, 127.1, 125.4, 124.8, 75.0, 61.3, 52.8, 34.2, 19.8, 18.7, 18.3.

HRMS: calc. for $C_{28}H_{29}ClN_3NiO_3$ $[M + H]^+$ 548.1251, found 548.1255.

Ni(II) complexes of the Schiff's base of 9 and DL-leucine (14e) and (15e). From 500 mg (1.27 mmol) of **9**, 670 mg of a 51 : 40 : 7 : 2 mixture of four diastereomers was obtained (yield: 93.6%). A part of the mixture was subjected to column chromatography to isolate diastereomerically pure products **14e** (91 mg) and **15e** (77 mg) for full analytical characterization.

*Data for **14e**.* R_f: 0.57 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25}$ = −2126 (c = 0.049, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 9.2 Hz, 1H), 7.54–7.33 (m, 5H), 7.33–7.17 (m, 4H), 7.13 (dd, J = 9.2, 2.5 Hz, 1H), 6.86 (d, J = 6.9 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 3.95 (dd, J = 16.7, 6.6 Hz, 1H), 3.90–3.80 (m, 2H), 3.42 (t, J = 7.6 Hz, 1H), 3.01 (d, J = 16.8 Hz, 1H), 2.28 (ddd, J = 12.1, 10.3, 3.4 Hz, 1H), 1.99 (d, J = 6.9 Hz, 3H), 1.85 (br, 1H), 1.31–1.18 (m, 1H), 0.82 (d, J = 6.7 Hz, 3H), 0.38 (d, J = 6.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 176.7, 169.2, 141.2, 138.6, 133.0, 132.3, 130.3, 129.2, 129.0, 128.8, 128.5, 128.3,

127.9, 127.3, 125.7, 125.0, 68.4, 61.6, 52.4, 45.2, 24.3, 23.7, 22.4, 20.6.

HRMS: calc. for $C_{29}H_{31}ClN_3NiO_3$ $[M + H]^+$ 562.1407, found 562.1414.

Data for ***15e****.* R_f: 0.39 (CH_2Cl_2–acetone, 2 : 1). $[\alpha]_D^{25}$ = +2893 (c = 0.051, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 9.2 Hz, 1H), 7.67 (d, J = 7.0 Hz, 2H), 7.54–7.35 (m, 3H), 7.31–7.13 (m, 4H), 7.07 (dd, J = 9.2, 2.6 Hz, 1H), 6.86 (d, J = 6.8 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 3.95–3.65 (m, 4H), 3.08 (d, J = 17.1 Hz, 1H), 2.32 (ddd, J = 12.1, 10.9, 3.4 Hz, 1H), 1.90 (d, J = 6.9 Hz, 3H), 1.78 (br, 1H), 1.28–1.11 (m, 1H), 0.82 (d, J = 6.7 Hz, 3H), 0.34 (t, J = 13.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 178.0, 169.0, 141.2, 137.9, 133.0, 132.1, 130.2, 129.2, 129.2, 128.9, 128.8, 128.4, 128.1, 127.9, 127.3, 125.4, 124.9, 68.7, 60.8, 52.1, 45.3, 24.4, 23.8, 20.6, 18.4.

HRMS: calc. for $C_{29}H_{31}ClN_3NiO_3$ $[M + H]^+$ 562.1407, found 562.1415.

Ni(II) complexes of the Schiff's base of 9 and DL-tyrosine (14f) and (15f). From 500 mg (1.27 mmol) of **9**, 759 mg of a 49 : 46 : 5 mixture of three diastereomers was obtained (yield: 97.3%). A part of the mixture was subjected to column chromatography to isolate diastereomerically pure products **14f** (110 mg) and **15f** (100 mg) for full analytical characterization.

Data for ***14f****.* R_f: 0.44 (CH_2Cl_2–acetone, 1 : 1). $[\alpha]_D^{25}$ = −2841 (c = 0.027, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (br, 1H), 8.11 (d, J = 9.1 Hz, 1H), 7.58–7.42 (m, 3H), 7.31–7.08 (m, 9H), 7.02 (d, J = 6.9 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 2.5 Hz, 1H), 4.27–4.11 (m, 1H), 3.70–3.51 (m, 1H), 3.27 (dd, J = 16.7, 6.4 Hz, 1H), 2.90 (dd, J = 13.7, 2.3 Hz, 1H), 2.70 (d, J = 16.7 Hz, 1H), 2.58–2.46 (m, 2H), 1.85 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 176.5, 169.7, 156.6, 141.0, 138.1, 133.1, 132.5, 132.4, 132.3, 130.6, 129.6, 129.4, 129.2, 128.9, 128.5, 127.7, 127.3, 127.2, 126.8, 126.2, 125.1, 115.8, 71.4, 61.3, 51.9, 38.4, 22.1.

HRMS: calc. for $C_{32}H_{29}ClN_3NiO_4$ $[M + H]^+$ 612.1200, found 612.1194.

Data for ***15f****.* R_f: 0.24 (CH_2Cl_2–acetone, 1 : 1). $[\alpha]_D^{25}$ = +2539 (c = 0.028, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (br, 1H), 7.80–7.58 (m, 3H), 7.58–7.37 (m, 3H), 7.29–6.89 (m, 10H), 6.59 (d, J = 2.4 Hz, 1H), 4.25–4.09 (m, 1H), 3.47–3.16 (m, 2H), 2.94 (d, J = 11.8 Hz, 1H), 2.82 (d, J = 17.1 Hz, 1H), 2.71 (d, J = 6.5 Hz, 1H), 2.50 (dd, J = 13.6, 5.7 Hz, 1H), 1.62 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 177.5, 169.3, 156.6, 140.9, 137.7, 132.9, 132.6, 132.2, 132.1, 130.6, 129.5, 129.4, 129.0, 128.9, 128.4, 128.3, 127.6, 127.3, 127.1, 125.9, 125.1, 115.6, 71.8, 60.8, 52.2, 38.5, 18.5.

HRMS: calc. for $C_{32}H_{29}ClN_3NiO_4$ $[M + H]^+$ 612.1200, found 612.1204.

Ni(II) complexes of the Schiff's base of 9 and DL-2′,6′-dimethyltyrosine (14g) and (15g). From 2 g (4.33 mmol) of **9**, 2.74 g of a 48 : 45 : 4 : 3 mixture of four diastereomers was obtained (yield: 98.9%). A part of the mixture was subjected to column chromatography to isolate diastereomerically pure products **14g** (1.11 g) and **15g** (887 mg) for full analytical characterization.

Data for ***14g****.* R_f: 0.40 (CH_2Cl_2–acetone, 4 : 1). $[\alpha]_D^{25}$ = −1290.8 (c = 0.026, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 9.2 Hz, 1H), 7.45–7.33 (m, 4H), 7.30–7.17 (m, 5H), 7.14 (dd, J = 9.2, 2.5 Hz, 1H), 6.54 (s, 1H), 6.52 (d, J = 2.5 Hz, 1H), 6.22 (s, 2H), 6.10 (d, J = 7.0 Hz, 1H), 4.21 (dd, J = 8.7, 5.8 Hz, 1H), 3.97 (dd, J = 16.6, 6.4 Hz, 1H), 3.85–3.70 (m, 1H), 3.67–3.53 (m, 1H), 3.34 (dd, J = 14.5, 5.8 Hz, 1H), 3.04–3.00 (m, 1H), 3.03 (d, J = 16.7 Hz, 1H), 2.01 (d, J = 6.9 Hz, 3H), 1.93 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 176.7, 170.0, 155.2, 141.0, 139.2, 138.4, 132.8, 132.4, 129.9, 129.2, 129.1, 128.7, 128.7, 128.5, 128.2, 127.4, 127.3, 125.8, 124.9, 123.2, 115.4, 69.9, 61.2, 52.3, 36.2, 21.9, 19.9.

HRMS: calc. for $C_{34}H_{33}ClN_3NiO_4$ $[M + H]^+$ 640.1513, found 640.1511.

Data for ***15g****.* R_f: 0.20 (CH_2Cl_2–acetone, 4 : 1). $[\alpha]_D^{25}$ = +1852.5 (c = 0.052, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.43–7.33 (m, 2H), 7.27–7.08 (m, 6H), 7.02 (dd, J = 9.2, 2.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.24 (s, 2H), 6.10 (br, 1H), 4.18 (t, J = 7.0 Hz, 1H), 3.86–3.50 (m, 4H), 3.31 (dd, J = 14.3, 5.6 Hz, 1H), 3.07 (d, J = 17.0 Hz, 1H), 1.93 (s, 6H), 1.80 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 177.8, 169.8, 155.3, 140.9, 139.5, 138.0, 132.5, 132.5, 132.2, 129.9, 129.2, 128.8, 128.7, 128.4, 128.1, 127.4, 125.7, 124.8, 123.4, 115.4, 70.1, 61.2, 53.0, 35.9, 20.0, 18.7.

HRMS: calc. for $C_{34}H_{33}ClN_3NiO_4$ $[M + H]^+$ 640.1513, found 640.1512.

Synthesis of 2′,6′-dimethyltyrosine (DMT) (18). A mixture of **14g** and **17g** (0.5 g, 0.780 mmol) was suspended in MeOH (15 mL). 1N HCl (6 equiv.) was added and the reaction was stirred at 50 °C for 4 h. The reaction mixture was cooled to ambient temperature and then concentrated *in vacuo*. To the residue, CH_2Cl_2 (3 mL) and 28% NH_4OH (4 mL) were added, and the mixture evaporated again. To the residue CH_2Cl_2 (30 mL) and water (30 mL) were added. The aqueous layer was extracted twice with dichloromethane (15 mL). The organic layer was washed with a small amount of water, and then brine, and dried over Na_2SO_4; it was then evaporated to give compound **9** (>99% yield, 99.0% purity by HPLC). The combined water layers were concentrated to give a pale blue material (380 mg). The residue was dissolved in EtOH–H_2O and applied to a SK-1B (cation-exchange resin) column (30 mL). The column was washed with water until the eluent gave a neutral pH. The column was then washed with 8% NH_4OH and 28% NH_4OH–H_2O–MeOH as a 1 : 2 : 1 solution. The eluted fractions were collected and concentrated *in vacuo* to give (−)-**18** as a white solid. Yield: 95.3%. >98% ee. $[\alpha]_D^{25}$ = −75.8 (c = 0.4, AcOH).

Data for ***18****.* ^{1}H NMR (D_2O) δ 2.30 (s, 6H), 3.04 (dd, 1H, J = 14.5, 8.0 Hz), 3.27 (dd, 1H, J = 14.5, 8.0 Hz), 3.82 (t, 1H, J = 8.0 Hz), 6.66 (s, 2H).

A similar procedure was adopted for the synthesis of (+)-**18**, starting from a mixture of **15g** and **16g**. Yield: 75.1%. >98% ee. $[\alpha]_D^{25}$ = +76.9 (*c* = 0.4, AcOH).

Large-scale synthesis of (*R*)-2′,6′-dimethyltyrosine (DMT) (*R*)-18. To a mixture of **9** (97.5 g, 0.25 mol), $NiCl_2$ (35.4 g, 0.27 mol) and racemic 2′,6′-dimethyltyrosine (DMT) (57.1 g, 0.27 mol) in MeOH (1 L) was added K_2CO_3 (137 g, 0.99 mol), and the reaction mixture was stirred under reflux for 2 h. The reaction mixture was then poured into cooled water (1 L), and the target product was filtered off and washed with water. The filtered precipitate was dried at 60 °C to give 147 g (93%) of a mixture of Ni-complexes **14g–17g**. The resultant mixture was dissolved in $CHCl_3$ and diethyl ether was slowly added under stirring until the solution became cloudy due to a precipitate forming. Stirring was continued at ambient temperature (5 h) and then at −5 °C (24 h). The precipitate was filtered and washed three times with $CHCl_3$–Et_2O (1/1 by volume) to obtain 45.9 (31%) of diastereomerically pure (R_C,R_N,R_C)-**14g**. The product was disassembled as described above, giving (*R*)-2′,6′-dimethyltyrosine (DMT) (*R*)-**18**.

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