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New chiral Ni^{II} complexes of Schiff's bases of glycine and alanine for efficient asymmetric synthesis of α-amino acids

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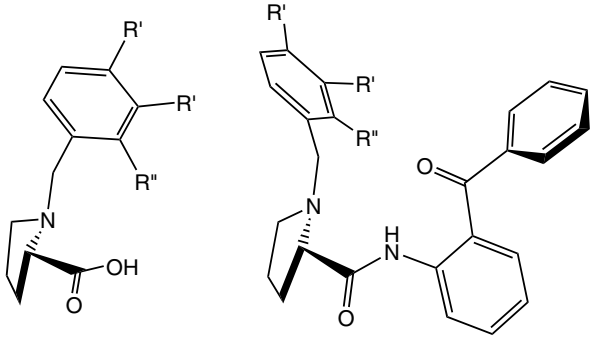
Abstract—New modified chiral auxiliaries (*S*)-*N*-(2-benzoylphenyl)-1-(2-chlorobenzyl)pyrrolidine-2-carboxamide (2-CBPB) and (*S*)-*N*-(2-benzoylphenyl)-1-(3,4-dimethylbenzyl)pyrrolidine-2-carboxamide (3,4-DMBPB) and their Ni^{II} complexes of Schiff's base with glycine and alanine have been synthesized and tested in asymmetric C-alkylation and aldol condensation reactions of amino acid moieties. The tests proved that both new auxiliaries were efficient with the ee's of the final amino acids as high as 98% even in case of α-methyl-α-amino acid synthesis.

1. Introduction

Asymmetric synthesis of non-proteinogenic amino acids, using chiral auxiliaries and catalysts, is an important domain of modern organic and bioorganic chemistry.[1] In particular, the use of enantiomerically enriched amino acids labeled with short living isotopes for PET (positron emission tomography) diagnostics is increasing dramatically.[2] For PET application, the costs and availability of the chiral auxiliaries are of minor importance, as compared to the rate and asymmetric efficiency of the reactions they promote. In this connection, the quest for new chiral auxiliaries and catalysts, ensuring highly selective and fast asymmetric synthesis of amino acids, remains urgent and novel chiral auxiliaries are being created[3] and novel catalysts for asymmetric amino acid synthesis designed.[4]

Among the different types of synthetic approaches to enantiomerically pure amino acids,[1] the use of (*S*)-2-[(*N*-benzylprolyl)amino]benzophenone (BPB, see Chart 1) was shown to be highly efficient for the preparation of both proteinogenic and non-proteinogenic α-amino acids,[5] including those employed for the synthesis of PET radiotracers.[2b,d] The latter application was particularly effective due to the simplicity of the experimental procedures and short period (few minutes) of the alkylation reactions.[2b,d]



1a R'=H, R"=Cl
1b R'=Me, R"=H

2-CBPB **2a** R'=H, R"=Cl
3,4-DMBPB **2b** R'=Me, R"=H
3,4-DCBPB **2c** R'=Cl, R"=H
BPB **2d** R'=H, R"=H

Chart 1.

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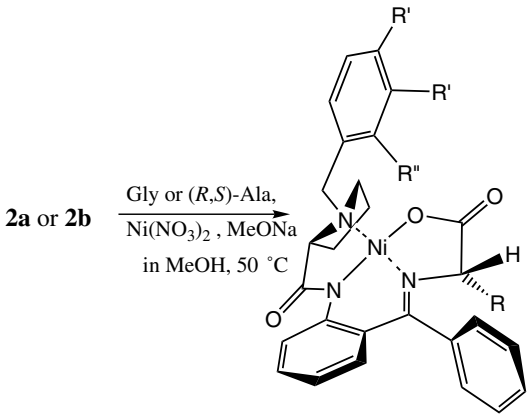
Unfortunately, use of BPB has some shortcomings, including low ee (85%) of the products in the case of α-methyl-α-amino acid synthesis.[5] Earlier attempts at improving the performance of BPB through substitution of the benzyl group of the chiral auxiliary with naphthylmethyl,[6] 2,4,6-trimethylbenzyl,[7] and 3,4 dichlorobenzyl groups led to only partial success.[8] For example, in the case of the naphthylmethyl derivative the complexes derived from the auxiliary were too poorly soluble in organic solvents to find any practical applications.[6] In the case of 2,4,6-trimethylbenzyl derivatives, the stereoselectivity of amino acid synthesis was low (41–66%).[7] High stereoselectivity and an increase in reaction rate were registered with chiral auxiliary (*S*)-*N*-(2-benzoylphenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-carboxamide (3,4-DCBPB) (ee of isolated amino acids were on average 93%).[8] However, it was unclear if the electron-withdrawing power of the substituents or their steric effects were responsible for the observed increase in the stereoselectivities of the reactions. In addition, the chiral auxiliary was too active and bis-alkylation of the glycine moiety of the complex became a problem. It seemed reasonable to proceed by the synthesis and testing of new chiral auxiliaries modified by the introduction of fewer electron withdrawing Cl-substituents positioned for a possible interaction with the central metal ion of the complex. Another avenue of study could follow the success of 3,4-DCBPB by the introduction of the same number of electron donating Me-groups of similar size and to compare the efficiency of the chiral auxiliaries with that of the parent BPB or/and 3,4-DCBPB.

2. Results and discussion

The condensation of the corresponding *N*-benzylprolines, **1a** and **1b** with *o*-aminobenzophenone, similar to earlier outlined procedures[5,8] gave two novel auxiliaries, (*S*)-*N*-(2-benzoylphenyl)-1-(2-chlorobenzyl)pyrrolidine-2-carboxamide (2-CBPB), **2a**, and (*S*)-*N*-(2-benzoylphenyl)-1-(3,4-dimethylbenzyl)pyrrolidine-2-carboxamide (3,4-DMBPB), **2b** (see Chart 1). Their Schiff's base Ni^{II} complexes with glycines **3a** and **3b** and alanines **4a** and **4b** were synthesized, employing routine procedures (see Scheme 1 and Experimental).[5,8]



3a R=H, R'=H, R"=Cl **4a** R=Me, R'=H, R"=Cl
3b R=H, R'=Me, R"=H **4b** R=Me, R'=Me, R"=H
3c R=H, R'=Cl, R"=H **4c** R=Me, R'=Cl, R"=H
3d R=H, R'=H, R"=H **4d** R=Me, R'=H, R"=H

Scheme 1.

The structures of the synthesized compounds were confirmed by the usual analytical methods. The molecular structure and absolute configurations of **4a** and **4b** (the predominant diastereoisomers) were also determined by X-ray structural analyses (see Fig. 1). As expected, the configuration of the complexes was found to be (*S*,*S*)-**4a** and (*S*,*S*)-**4b**. There are two conformers of **4b** found in its crystal structure. One had an Me-group of the *N*-benzyl substituent positioned over Ni-atom (*endo*-conformation) and another with the Me-group turned away from the Ni-atom (*exo*-conformation).

^{1}H NMR spectra of the complex indicated the presence of the two equilibrating conformers in solution at a ratio 4:1, the major conformer having an *exo*-conformation. Both crystal structure and solution ^{1}H NMR spectra of **4a**, conversely, showed no evidence of such an equilibrium, with only the *endo*-conformer found in crystal structure.

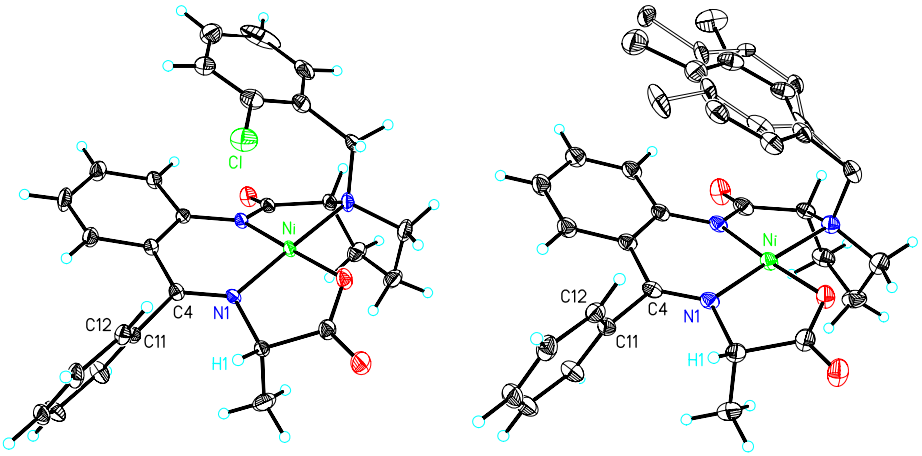


Figure 1. ORTEP structures of **4a** (Ni^{II}-2-CBPB-(*S*)-Ala) and *exo*- and *endo*-conformers of **4b** (Ni^{II}-3,4-DMBPB-(*S*)-Ala) based on X-ray analysis.

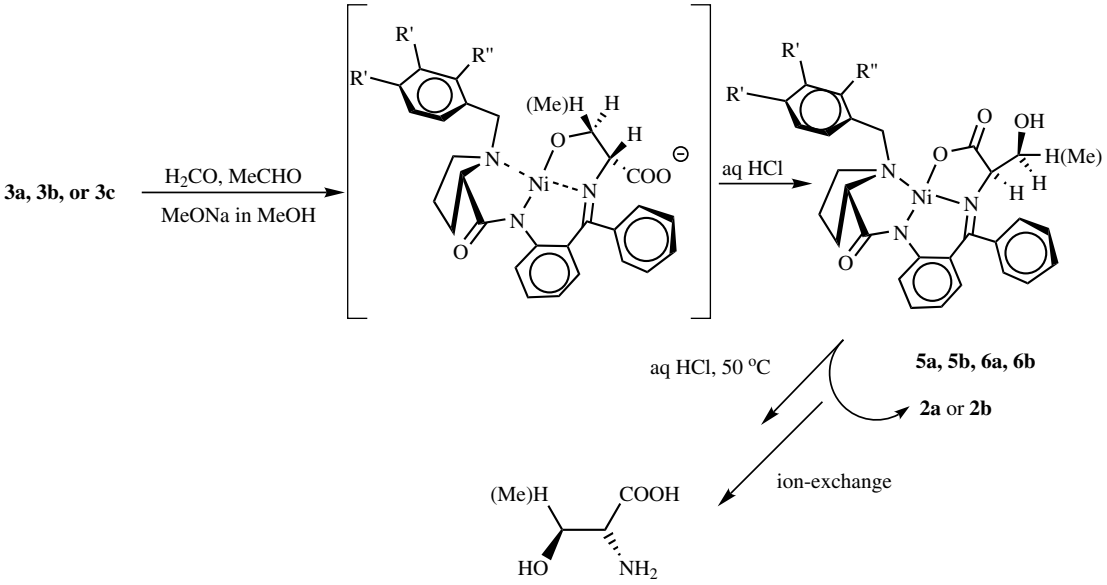
The aldol condensations of **3a** and **3b** with formaldehyde and acetaldehyde were carried out under strongly basic conditions (see Scheme 2), as described earlier.[5,9] The configurations of serine and threonine formed were invariably (*R*) in full agreement with the mechanism of the reaction, including substitution of the carboxyl group by the ionized hydroxyl group in the coordination plane of the Ni(II) ion.[5,9]

Chiral auxiliaries **2a** and **2b** were recovered from the reaction mixture after its decomposition with aq HCl with 90% yield.

As can be seen from the data collected in Table 1, the enantioselectivities of the aldol condensation reactions were very high with no bis-addition products being formed in the formaldehyde condensation reaction (Table 1, runs 1, 3, 5, and 7).

Almost diastereoisomerically pure threonine was formed in the cases of all chiral auxiliaries (Table 1, runs 2 and 4). Evidently, both novel chiral auxiliaries compare favorably with both 3,4-DCBPB and BPB in the same set of reactions (Table 1, runs 1–4 and 5–8). There was a steady increase in ee of (*R*)-serine from 90% in case of BPB (run 7) to 97% in case of 3,4-DMBPB (run 3) and to 99% in case of 2-CBPB (run 1). The same tendency was observed for the synthesis of (*R*)-threonine with a steady increase of ee from 86% to 92%, and 96.6% in the sequence BPB, **2d**, 3,4-DCBPB, **2c**, 3,4-DMBPB, **2b**, and 2-CBPB, **2a**, auxiliaries (runs 8, 6, 4, and 2). The best chiral auxiliary in terms of the asymmetric induction reaction was 2-CBPB (runs 1 and 2). The efficiency of 3,4-DMBPB was similar to that of 3,4-DCPBP.

Alkylation of **3a**, **3b**, **4a**, and **4b** with alkyl bromides was conducted in a mixture of DMF or CH_3CN with finely ground NaOH or K_2CO_3 at room temperature or at 45–50 °C (Scheme 3). The best results were obtained for a DMF/NaOH mixture. The alkylation reaction was monitored by TLC (SiO_2, $CHCl_3/CH_3COOC_2H_5$, 1:3)

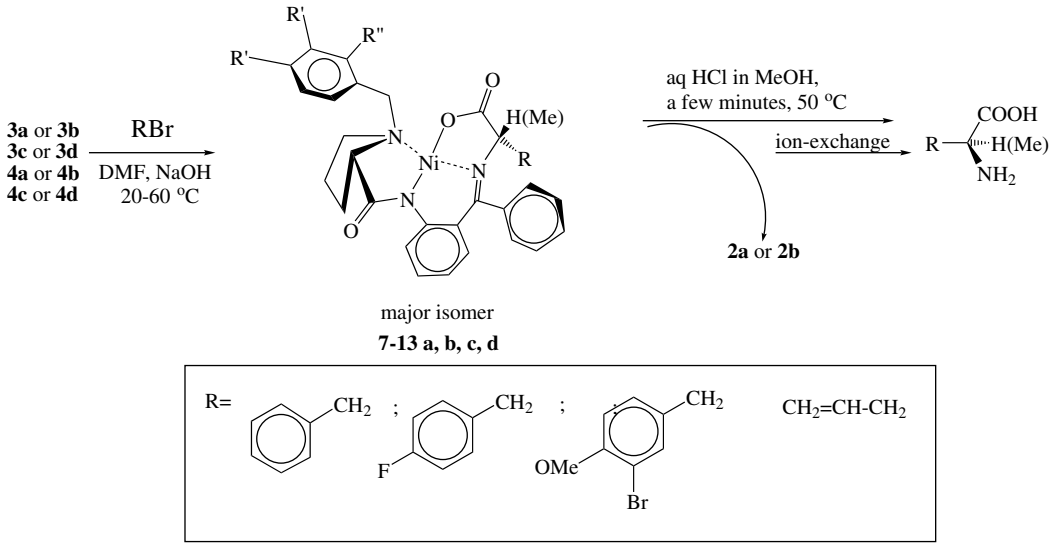


Scheme 2.

Table 1. Asymmetric aldol condensation of **3a** and **3b** with formaldehyde and acetaldehyde[a,b]

Run	Initial complex	Aldehyde	Duration (min)	Product	Chemical yield (%)	ee (%)[b]
1	**3a**	$(CH_2O)_n$	90	(*R*)-Ser	72	99.0
2	**3a**	CH_3CHO	120	(*R*)-Thr[c]	65	96.6
3	**3b**	$(CH_2O)_n$	120	(*R*)-Ser	65	97.4
4	**3b**	CH_3CHO	120	(*R*)-Thr[c]	47	92.4
5	**3c**	$(CH_2O)_n$	30	(*R*)-Ser	80	94.8
6	**3c**	CH_3CHO	240	(*R*)-Thr[c]	75	92.2
7[d]	**3d**	$(CH_2O)_n$	180	(*R*)-Ser	90	90.0
8[d]	**3d**	CH_3CHO	240	(*R*)-Thr[c]	82	86.0

[a] The experiments were conducted in 4.7 M CH_3ONa solution in CH_3OH at ambient temperatures.
[b] Enantiomeric excesses (ee) were determined by chiral GLC analysis of the amino acids recovered after decomposition of the mixture of diastereomeric complexes.
[c] Less than 2% of *allo*-isomer was formed.
[d] Literature[9] data.



Scheme 3.

and ^{1}H NMR, following the disappearance of traces of the initial complexes and establishment of a thermodynamic equilibrium between the diastereomers of the alkylation products (in the case of the initial **3a** and **3b**). The ratio of (*S*,*S*)- and (*S*,*R*)-diastereomers was determined by chiral GLC analysis of the amino acids recovered after decomposition of the mixture of complexes and/or ^{1}H NMR analysis of the reaction mixture. Invariably the (*S*,*S*)-diastereoisomers of the alkylation products were predominantly formed in the cases of both **3** and **4**. The major isomers were separated by chromatography, and their absolute configuration assigned based on their CD or ORD curves[9,11,14] and additionally verified by chiral GLC analysis of the amino acids after the decomposition of complexes and isolation of the amino acids. As in the case of aldol condensation, the initial chiral auxiliaries **2a** and **2b** were easily regenerated (90% yield) without any loss of their enantiomeric purity.

Table 2. Alkylation of complexes **3a** and **3b** with alkyl bromides[a,b]

Run	Initial complex	Alkylating agent (RBr)	Chemical yield (%)	ee (%)
1	**3a**	$C_6H_5CH_2Br$	76	96.4
2	**3a**	4-F–$C_6H_4CH_2Br$	77.9	97.6
3	**3a**	3-Br–4-OCH_3–$C_6H_3CH_2Br$	78	94.3
4	**3a**	CH_2═CH─CH_2Br	74	96.0
5	**3b**	$C_6H_5CH_2Br$	78	93.0
6	**3b**	4-F–$C_6H_4CH_2Br$	74.2	95.0
7	**3b**	3-Br–4-OCH_3–$C_6H_3CH_2Br$	72	93.0
8	**3b**	CH_2═CH─CH_2Br	73	92.3
9[b]	**3c**	$C_6H_4CH_2Br$	71	97.0
10[c]	**3d**	$C_6H_4CH_2Br$	86	90.0

[a] Alkylation of complexes by alkyl bromides was performed in DMF/NaOH for 10 min at an ambient temperature and in all the cases gave the (*S*)-configuration of the amino acids as the predominant product.
[b] Literature[8] data.
[c] Literature[5] data.

Table 2 summarizes the alkylation data of **3a** and **3b** (runs 1–8) and some literature data on alkylation of **3c** and **3d** (runs 9 and 10). The chiral auxiliary 2-CBPB, **2a**, was the best performing one in the series of **2a**, **2b**, **2c**, and **2d**, as runs 1–10 (Table 2) testified with the ee of the final product lying in 96–98% range (runs 1–4). The chiral auxiliary 3,4-DMBPB, **2b**, was less efficient than **2a** with the final ee, lying in the range 92–96% (runs 5–8). Still both novel auxiliaries proved better asymmetric inducing agents than original BPB, **2d**, with only 90% ee in case of benzyl bromide alkylation of **3d** (run 10). Although alkylation of **3c** (run 9) gave better results (ee 97%) than that of **3b** (run 5), the difference was too small and most likely 3,4-DMBPB was almost as efficient as 3,4-DCBPB.

As the final amino acid moieties of the products contain labile α-protons, epimerization of the amino acid moieties under the experimental conditions occurs and on equilibrium between (*S*,*R*)- and (*S*,*S*)-isomers became established. Thus, the ee of the recovered amino acids both in the aldol condensation reactions (Table 1) and the alkylation reactions (Table 2) reflected the position of thermodynamic equilibrium of the diastereoisomeric complexes (*S*,*R*)/(*S*,*S*).

Table 3 summarizes the data on the alkylation of alanine derivatives of complex **4** series. The data reflects the kinetic stereoselectivity of alkylations, as the final α-methyl-α-amino acid moiety lacks the labile α-proton and no epimerization of the final Ni-complexes was possible under the basic experimental conditions.

Evidently, the kinetic diastereoselectivity of alkylation was greater in the case of **4a** (runs 1–3), than in cases of **4b**, **4c**, and **4d** (runs 4–10), being in all cases greater than 93% even at 50 °C. The unmodified BPB was inefficient in the reaction with the alkylation of **4d**, giving only 80% ee of the final amino acid (run 10). When comparing auxiliaries 3,4-DCBPB, **2c**, and 3,4-DMBPB, **2b**,

Table 3. Asymmetric synthesis of α-amino acids via alkylation of **4a** and **4b** with alkyl bromides[a]

Run	Initial complex	Alkylating agent	Duration (min)	Chemical yield (%)	ee (%)
1	**4a**	$C_6H_5CH_2Br$	60 (10)	73.6	94.0 (93.4)
2	**4a**	4-F–$C_6H_4CH_2Br$	120 (20)	79.3	99.6 (98.3)
3	**4a**	3-Br–4-OCH_3–$C_6H_3CH_2Br$	224 (60)	69.7	99.0 (98.0)
4	**4a**	CH_2=CH–CH_2Br	120 (25)	75.6	99.0 (99. 8)
5	**4b**	$C_6H_5CH_2Br$	180 (90)	76.2	83.0 (94.0)
6	**4b**	4-F–$C_6H_4CH_2Br$	120 (90)	75	80.3 (83.4)
7	**4b**	3-Br–4-OCH_3–$C_6H_3CH_2Br$	120 (45)	71.9	97.6 (96.6)
8	**4b**	CH_2=CH–CH_2Br	140 (60)	77	91.5 (97.0)
9	**4c**	4-F–$C_6H_4CH_2Br$	120 (30)	78	91.32 (88.0)
10[b]	**4d**	$C_6H_5CH_2Br$	60	90	80.0

[a] Alkylation of complexes by alkyl bromides was performed in DMF/NaOH (or KOH) at an ambient temperature (or at 45–50 °C in brackets).
[b] Literature[5] data.

we found that **2c** was a better chiral inducing agent (runs 6 and 9) in the kinetically controlled reactions.

Thus, in both thermodynamically controlled set of reactions (Tables 1 and 2) and kinetically controlled ones, 2-CBPB, **2a**, proved to be the most efficient chiral auxiliary. To rationalize the observation, the crystal structures of **4a** and **4b** (Fig. 1), and **4c**[8] were compared. A salient feature of the structures is the difference in the series of C6–C5–C4–N angles formed by the phenyl substituents at C=N bond with the plane of the bond. The torsion angle is varied in the following order: **4c**, 84°; **4b**, 81.7°; and **4a**, 70°. The most significant consequence of the greater deviation of the angle from a 90° value in **4a**, as compared with other complexes, would be the inevitable increase in the shielding of the *re*-side of the amino acid carbanion in the transition state of the alkylation. This would lead to much greater kinetic diastereoselectivity of alkylation in case of **4a**, leading to a greater ratio of (*S*,*S*)/(*S*,*R*)-diastereoisomers, as compared to other complexes.

Such conformational changes in the case of **4a** can be a result of a significant repulsive interaction of the Ph-group at C=N bond in **4a** with Cl-atom of *N*-benzyl substituent of the proline moiety of the complex. The distance of the Cl-substituent from the Ni central ion is 3.149 Å, which is less than the sum of their Van-der-Waals radius. The short distance may be a sign of a kind of attractive interaction, existing between the Cl- and Ni-centers. Another indirect proof of the existence of such a Cl–Ni interaction came from molecular mechanics calculations. Simple calculation (MM2 force field in HyperChem Lite 2.0 program) indicated that if no attractive interaction between Cl- and Ni-atoms was introduced into it, both *endo*- and *exo*-conformations would have similar energies—43.80 and 43.97 kcal/mol correspondingly. Similar calculation for **4b** and **4c** showed more significant differences between the conformers: 46.11 and 46.79 kcal/mol (in cause of **4b**) and 41.49 and 42.23 kcal/mol (in cause of **4c**) for *endo*- and *exo*-isomers accordingly. This result correlated with the X-ray data on disordering rate of complexes **4b** (30:70) and **4c** (20:80)[8] in crystals. Two conformer was also detected in case of **4b** (see Fig. 1) with a double set of ^{1}H NMR resonances of the complex in solution. In fact, a single set of resonances was detected for **4a**, as well as only one structure found in a crystal of **4a**. Thus, it can be energetically more favorable to decrease the torsion angle of the Ph-group at C=N bond than to move Cl-atom from its position over Ni-atom, overcoming the hypothetical Ni–Cl attraction.

The eventual consequence of such attraction should be in much greater rigidity of the structure of **4a**, as compared to other complexes. The (*S*,*S*)-isomers, resulting from the alkylation of **3a** (Table 2) should have all the features of **4a**. Isomers of (*S*,*R*)-configuration with the alkyl group of the amino acid moieties pointed towards the tilted Ph-substituent at C=N bond and Cl-substituent of *N*-benzyl moiety should be most effected with their energy greatly increased. Thus, an increase in the thermodynamic diastereoselectivity in the case of **3a** alkylation, as compared to the alkylation of **3b**, **3c**, **3d** (Table 2), can be rationalized.

The results of aldol condensations (Table 1) can also be perceived in the same way. In this case, it was the COO^- group that pointed towards the Cl-substituent in the (*S*,*S*)-isomers, making them relatively unstable relative to the (*S*,*R*)-ones (see Scheme 1).

All the complexes synthesized and their precursors have been isolated and characterized by physicochemical methods of analysis—^{1}H NMR, element analysis, and polarimetric measuring.

3. Conclusion

Thus, in this work a new and promising chiral auxiliary 2-CBPB **2a** was elaborated for use in highly stereoselective asymmetric synthesis of a broad range of amino acids.

4. Experimental

The amino acids were purchased from 'Reanal' (Hungary); silica gel L-40/100 'Chemapol' (Praha, Czech Republic), $CHCl_3$, $(CH_3CO)_2O$, CH_3COOH, $(CH_3)_2CO$, CH_3CN, *i*-PrOH, CH_3OH, NaOH, and ROH from

'Reakhim' (Russia); 2-chlorobenzylchloride, 3,4-dimethylbenzylchloride, 3,4-dichlorobenzylchloride, benzylchloride, and 2-aminobenzophenon from 'Aldrich'. All used solvents were freshly distilled. The enantiomeric GLC analysis of the amino acids as the *N*-trifluoroacetyl derivatives of their isopropyl esters was performed using a 'ChiralsilVal' type chiral phase on quartz capillary columns (40 m × 0.23 mm) with 0.12 μm film thickness at column temperature 125 °C using helium as the carrier gas. The ^{1}H NMR spectra were recorded on a 'Mercury-300 Varian' (300 MHz) in DMSO-d_6/CCl_4: 1:3 (unless otherwise indicated). The optical rotations were measured on 'Perkin Elmer-341' polarimeter, in a 5 cm thermostated cell with an accuracy of 0.1%.

Complexes **3c**,**d** and **4c**,**d** were synthesized in accordance with known procedures.[8,10]

4.1. The synthesis of *N*-benzylprolines was carried out by using a previously developed methodology[8]

2-Chlorobenzyl chloride and 3,4-dimethylbenzyl chloride are added to the mixture at 0 °C.

4.1.1. (*S*)-*N*-(2-Chlorobenzyl)proline 1a. Yield: 95%. Anal. Calcd for $C_{12}H_{14}O_2NCl$ (239.698): C, 60.13; H, 5.89; N, 5.84. Found: C, 60.35; H, 5.56; N, 5.92. Mp 160–162 °C. $[\alpha]_D^{20} = -21.0$ (*c* 1.0, EtOH); ^{1}H NMR: δ 1.90–2.14 (3H, m, β-, 2γ-H Pro); 2.33 (1H, m, β-H Pro); 2.91 (1H, dt, δ-H Pro, $^2J = 9.8$ Hz, $^3J = 8.1$ Hz); 3.26 (1H, dt, δ-H Pro, $^2J = 9.8$ Hz, $^3J = 6.0$ Hz); 3.91 (1H, dd, α-H Pro, $^3J = 8.8$ Hz, $^3J = 6.4$ Hz); 4.22 (1H, d, NCH_2Ar, $^2J = 13.9$ Hz); 4.40 (1H, d, NCH_2Ar, $^2J = 13.9$ Hz); 7.26–7.39 (3H, m, Ar); 7.78 (1H, dd, Ar, $^3J = 6.8$ Hz, $^4J = 2.6$ Hz).

4.1.2. (*S*)-*N*-(3,4-Dimethylbenzyl)proline 1b. Yield: 74%. Anal. Calcd for $C_{14}H_{19}O_2N$ (233.306): C, 72.07; H, 8.21; N, 6.00. Found: C, 72.10; H, 8.26; N, 6.04. Mp 182–185 °C. $[\alpha]_D^{20} = -25.6$ (*c* 1.0, EtOH). ^{1}H NMR: δ 1.70–2.15 (4H, m, 2β-, 2γ-H Pro); 2.23 (3H, s, Me); 2.24 (3H, s, Me); 2.40 (1H, m, δ-H Pro); 2.95 (1H, ddd, δ-H Pro, $^2J = 9.1$ Hz, $^3J = 7.0$ Hz, $^3J = 4.1$ Hz); 3.21 (1H, dd, α-H Pro, $^3J = 8.7$ Hz, $^3J = 5.6$ Hz); 3.45 (1H, d, NCH_2Ar, $^2J = 12.8$ Hz); 3.94 (1H, d, NCH_2Ar, $^2J = 12.8$ Hz); 6.99 (2H, m, Ar); 7.05 (1H, s, Ar).

4.2. Synthesis of chiral auxiliaries 2a and 2b

Chiral auxiliaries **2a** and **2b** were synthesized in the form of hydrochlorides by a previously designed method.[8] After adding all components, the reaction mixture is stirred at room temperature for 15 h.

4.2.1. (*S*)-*N*-(2-Benzoylphenyl)-1-(2-chlorobenzyl)pyrrolidine-2-carboxamide hydrochloride 2a. Yield: 72%. Anal. Calcd for $C_{25}H_{23}ClN_2O_2$·HCl (455.376): C, 65.94; H, 5.31; N, 6.15. Found: C, 65.91; H, 5.15; N, 6.14. Mp 203–205 °C. $[\alpha]_D^{20} = -40.2$ (*c* 1.0, MeOH). ^{1}H NMR: δ 1.60 (1H, m, β-H Pro); 1.84 (1H, m, γ-H Pro); 2.03 (1H, m, γ-H Pro); 2.43 (1H, m, β-H Pro); 4.27–4.90 (5H, m, α-, 2δ-H Pro, NCH_2Ar); 7.20–7.59 (9H, m, Ar); 7.46 (2H, t, Ar, $^3J = 7.5$ Hz); 7.78 (2H, d, Ar, $^3J = 7.5$ Hz); 9.78 (1H, br, NH); 12.15 (1H, br, HCl).

4.2.2. (*S*)-*N*-(2-Benzoylphenyl)-1-(3,4-dimethylbenzyl)-pyrrolidine-2-carboxamide hydrochloride 2b. Yield: 40%. Anal. Calcd for $C_{27}H_{28}O_2N_2$·HCl (448.984): C, 72.23; H, 6.51; N, 6.24. Found: C, 72.10; H, 6.28; N, 6.19. Mp 230–235 °C. $[\alpha]_D^{20} = -38.5$ (*c* 1.0, MeOH). ^{1}H NMR: δ 1.76 (1H, m, β-H Pro); 2.00 (1H, m, β-H Pro); 2.21 (3H, s, Me); 2.24 (3H, s, Me); 3.20–3.38 (2H, m, 2γ-H Pro); 4.14–4.5 (4H, m, 2δ-H Pro, NCH_2Ar); 4.72 (1H, m, α-H Pro); 7.02–7.56 (10H, m, Ar); 7.77 (2H, d, Ar, $^3J = 7.6$ Hz); 9.72 (1H, br, NH);12.11 (1H, br, HCl).

4.3. The synthesis of complexes 3a,b and 4a,b were carried out according to the described method[9–11]

4.3.1. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-glycinato-*N*,*N*′,*N*″,*O*}-nickel(II) 3a. Yield: 85%. Anal. Calcd for $C_{27}H_{24}N_3NiO_3Cl$ (532.644): C, 60.88; H, 4.54; N, 7.89. Found: C, 60.85; H, 4.58; N, 7.88. Mp 186–188 °C. $[\alpha]_D^{20} = +2364$ (*c* 0.05, $CHCl_3$). ^{1}H NMR: δ 2.09–2.19 (2H, m, β-, γ-H Pro); 2.54 (1H, m, γ-H Pro); 2.77 (1H, m, β-H Pro); 3.43 (1H, m, δ-H Pro); 3.52 (1H, dd, α-H Pro, $^3J = 10.9$ Hz, $^3J = 6.1$ Hz); 3.64 (1H, m, δ-H Pro); 3.69 (1H, d, CH_2 Gly, $^2J = 20.0$ Hz); 3.77 (1H, d, CH_2 Gly, $^2J = 20.0$ Hz); 4.00 (1H, d, NCH_2Ar, $^2J = 12.9$ Hz); 4.56 (1H, d, NCH_2Ar, $^2J = 12.9$ Hz); 6.73 (1H, t, Ar, $^3J = 7.6$ Hz); 6.83 (1H, dd, Ar, $^3J = 8.2$ Hz, $^4J = 1.8$ Hz); 6.98 (1H, br, Ar); 7.15 (1H, d, Ar, $^3J = 7.2$ Hz); 7.21 (1H, ddd, Ar, $^3J = 8.6$ Hz, $^3J = 6.8$ Hz, $^4J = 2.0$ Hz); 7.27 (1H, dd, Ar, $^3J = 7.6$ Hz, $^4J = 1.8$ Hz); 7.36 (1H, m, Ar, $^3J = 7.5$ Hz, $^4J = 1.4$ Hz); 7.43 (1H, dd, Ar, $^3J = 8.1$ Hz, $^4J = 1.4$ Hz); 7.48–7.56 (3H, m, Ar); 8.18 (1H, dd, Ar, $^3J = 8.8$ Hz, $^4J = 1.0$ Hz); 8.29 (1H, dd, Ar, $^3J = 7.6$ Hz, $^4J = 1.8$ Hz).

4.3.2. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-glycinato-*N*,*N*′,*N*″,*O*}-nickel(II) 3b. Yield: 75%. Anal. Calcd for $C_{29}H_{29}N_3NiO_3$ (526.252): C, 66.19; H, 5.55; N, 7.98. Found: C, 66.25; H, 5.44; N, 8.00. Mp 176–178 °C. $[\alpha]_D^{20} = +1513$ (*c* 0.05, $CHCl_3$). ^{1}H NMR: δ 2.05–2.24 (2H, m, 2β-H Pro); 2.10 (3H, s, Me); 2.18 (3H, s, Me); 2.36–2.47 (2H, m, 2γ-H Pro); 3.25–3.41 (2H, m, α-, δ-H Pro); 3.50 (1H, d, CH_2 Gly, $^2J = 20.0$ Hz); 3.51 (1H, d, NCH_2Ar, $^2J = 12.3$ Hz); 3.57 (1H, m, δ-H Pro); 3.63 (1H, d, CH_2 Gly, $^2J = 20.0$ Hz); 4.32 (1H, d, NCH_2Ar, $^2J = 12.9$ Hz); 6.60 (1H, ddd, Ar, $^3J = 8.2$ Hz, $^3J = 6.8$ Hz, $^4J = 1.3$ Hz); 6.69 (1H, dd, Ar, $^3J = 8.2$ Hz, $^4J = 1.8$ Hz); 7.05–7.11 (2H, m, Ar); 7.11 (1H, d, Ar, $^3J = 7.5$ Hz); 7.23 (1H, d, Ar, $^3J = 7.5$ Hz); 7.50–7.62 (3H, m, Ar); 7.76 (1H, dd, Ar, $^3J = 7.5$ Hz, $^4J = 1.9$ Hz); 8.13 (1H, dd, Ar, $^3J = 8.9$ Hz, $^4J = 1.3$ Hz); 8.31 (1H, d, Ar, $^4J = 1.9$ Hz).

^{1}H NMR spectrum of the minor conformer (*endo*-conformer) differs from that of the major conformer by the chemical shift of the methylene protons of the *N*-benzylproline moiety: 3.92 (1H, d, NCH_2Ar, $^2J = 13.1$ Hz); 4.60 (1H, d, NCH_2Ar, $^2J = 13.1$ Hz).

4.3.3. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-alaninato-*N*,*N*′,*N*″,*O*}-nickel(II) 4a. Yield: 92%. Anal. Calcd for $C_{28}H_{26}ClN_3NiO_3$ (546.671): C, 61.52; H, 4.79; N, 7.69. Found: C, 61.59; H, 4.81; N, 7.61. Mp 324–326 °C. $[\alpha]_D^{20} = +2574$ (*c* 0.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.58 (3H, d, CH_3-Ala, $^3J = 7.0$ Hz); 2.09 (1H, m, γ-H Pro); 2.26 (1H, m, β-H Pro); 2.64 (1H, m, β-H Pro); 2.94 (1H, m, γ-H Pro); 3.51 (1H, dd, δ-H Pro, $^3J = 10.4$ Hz, $^3J = 6.1$ Hz); 3.57 (1H, dd, α-H Pro, $^3J = 11.0$ Hz, $^3J = 6.1$ Hz); 3.72 (1H, m, δ-H Pro); 3.90 (1H, q, α-H Ala, $^3J = 7.0$ Hz); 3.85 (1H, d, N*CH*$_2$Ar, $^2J = 12.9$ Hz); 4.50 (1H, d, N*CH*$_2$Ar, $^2J = 12.9$ Hz); 6.64–6.72 (2H, m, Ar); 6.96 (1H, d, Ar, $^3J = 7.3$ Hz); 7.25–7.38 (3H, m, Ar); 7.11–7.22 (2H, m, Ar); 7.43–7.54 (3H, m, Ar); 8.00 (1H, d, Ar, $^3J = 8.6$ Hz); 8.22 (1H, d, Ar, $^3J = 7.5$ Hz).

4.3.4. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 4b. Yield: 80%. Anal. Calcd for $C_{30}H_{31}N_3NiO_3$ (540.279): C, 66.69; H, 5.78; N, 7.78. Found: C, 66.76; H, 5.79; N, 7.71. Mp 315–317 °C (decomp.). $[\alpha]_D^{20} = +2562$ (*c* 0.05, $CHCl_3$). ^{1}H NMR: δ 1.50 (3H, d, CH_3-Ala, $^3J = 7.1$ Hz); 1.90 (3H, s, Me); 2.00 (3H, s, Me); 2.01 (1H, m, γ-H Pro); 2.17 (1H, m, β-H Pro); 2.51 (1H, m, β-H Pro); 2.97 (1H, m, γ-H Pro); 3.21 (1H, d, N*CH*$_2$Ar, $^2J = 12.3$ Hz); 3.37 (1H, dd, α-H Pro, $^3J = 11.1$ Hz, $^3J = 5.8$ Hz); 3.38 (1H, m, δ-H Pro); 3.63 (1H, m, δ-H Pro); 3.74 (1H, q, α-H Ala, $^3J = 7.1$ Hz); 4.19 (1H, d, N*CH*$_2$Ar, $^2J = 12.3$ Hz); 6.49–6.59 (2H, m, Ar); 6.86–7.02 (3H, m, Ar); 7.18 (1H, dt, Ar, $^3J = 6.8$ Hz, $^4J = 2.0$ Hz); 7.36–7.52 (3H, m, Ar); 7.59 (1H, dd, Ar, $^3J = 7.1$ Hz; $^4J = 1.9$ Hz); 7.81 (1H, d, Ar, $^3J = 8.6$ Hz); 8.40 (1H, d, Ar, $^4J = 1.5$ Hz).

^{1}H NMR spectrum of the minor conformer (*endo*-conformer) differs from that of the major conformer by the chemical shift of the methyl protons of the alanine moiety and the methylene protons of *N*-benzylproline moiety: δ 1.49 (3H, d, CH_3-Ala, $^3J = 7.1$ Hz); 3.50 (1H, d, N*CH*$_2$Ar, $^2J = 13.1$ Hz); 4.46 (1H, d, N*CH*$_2$Ar, $^2J = 13.1$ Hz).

4.4. Aldol condensation of 3a,b complexes

This was done in accordance with a literature method.[10,11] (*R*)-serine **5a** and **5b** complexes were crystallized from heptane/acetone mixture (1:1) while (*R*)-threonine complexes **6a** and **6b** from the mixture of heptane/acetone/methanol (1:1:1).

4.4.1. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*R*)-serinato-*N*,*N*′,*N*″,*O*}-nickel(II) 5a. Yield: 4.0 g (7.2 mmol) 72%. Anal. Calcd for $C_{28}H_{26}ClN_3NiO_4$ (561.097): C, 59.77; H, 4.66; N, 7.47. Found: C, 59.82; H, 4.70; N, 7.50. Mp 215–217 °C. $[\alpha]_D^{20} = -2235$ (*c* 0.05, $CHCl_3$). ^{1}H NMR: δ 2.01 (1H, m, β-H Pro); 2.15 and 2.22 (2H, m, γ-H Pro); 2.43 (2H, m, δ-H, β-H Pro); 3.14 (1H, d, α-H Ser, $^3J = 7.4$ Hz); 3.31 (1H, m, δ-H Pro); 3.55 (2H, m, 2β-H Ser); 3.85 (1H, d, N*CH*$_2$Ar, $^2J = 13.4$ Hz); 4.38 (1H, dd, α-H Pro, $^3J = 9.1$ Hz, $^3J = 4.4$ Hz); 4.55 (1H, d, N*CH*$_2$Ar, $^2J = 13.4$ Hz); 5.51 (1H, t, OH); 6.64 (1H, ddd, Ar, $^3J = 8.4$ Hz, $^3J = 6.9$ Hz, $^4J = 1.4$ Hz); 6.71 (1H, dd, Ar, $^3J = 8.4$ Hz, $^4J = 1.6$ Hz); 7.19 (1H, ddd, Ar, $^3J = 8.6$ Hz, $^3J = 6.9$ Hz, $^4J = 1.6$ Hz); 7.25 (1H, m, Ar); 7.40–7.60 (7H, m, Ar); 8.42 (1H, dd, Ar, $^3J = 8.6$ Hz, $^4J = 1.2$ Hz); 9.82 (1H, dd, Ar, $^3J = 7.8$ Hz, $^4J = 1.6$ Hz).

4.4.2. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*R*)-serinato-*N*,*N*′,*N*″,*O*}nickel(II) 5b. Yield: 3.6 g (6.5 mmol) 65%. Anal. Calcd for $C_{30}H_{31}N_3NiO_4$ (555.167): C, 64.77; H, 5.62; N, 7.55. Found: C, 64.81; H, 5.64; N, 7.52. Mp 248–250 °C. $[\alpha]_D^{20} = -1984$ (*c* 0.05, $CHCl_3$). ^{1}H NMR: δ 1.84 (1H, m, β-H Pro); 1.89 (3H, s, Me); 2.05 (2H, m, β-, γ-H Pro); 2.15 (3H, s, Me); 2.05 (2H, m, δ-, γ-H Pro); 3.13 (1H, d, α-H Ser, $^3J = 7.2$ Hz); 3.19 (1H, m, δ-H Pro); 3.74 (2H, m, 2β-H Ser); 3.95 (1H, m, α-H Pro); 4.15, 4.65 (AB 2H, N*CH*$_2$Ar, $^2J = 13.0$ Hz); 5.22 (1H, t, OH); 6.66 (1H, ddd, Ar, $^3J = 8.4$ Hz, $^3J = 6.9$ Hz, $^4J = 1.4$ Hz); 6.74 (1H, dd, Ar, $^3J = 8.3$ Hz, $^4J = 1.8$ Hz); 7.18–7.22 (4H, m, Ar); 7.37–7.48 (4H, m, Ar); 7.83 (1H, dd, Ar, $^3J = 7.7$ Hz, $^4J = 1.8$ Hz); 8.54 (1H, d, Ar, $^3J = 8.7$ Hz).

4.4.3. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*R*)-threoninato-*N*,*N*′,*N*″,*O*}nickel(II) 6a. Yield: 65%. Anal. Calcd for $C_{29}H_{28}ClN_3NiO_4$ (576.697): C, 60.40; H, 4.89; N, 7.29. Found: C, 60.60; H, 4.78; N, 7.21. Mp 89–91 °C. $[\alpha]_D^{20} = -679.3$ (*c* 0.05, $CHCl_3$). ^{1}H NMR: δ 1.13 (3H, d, CH_3-Thr, $^3J = 6.2$ Hz); 1.93 (1H, m, β-H Pro); 2.05–2.23 (2H, m, β-, γ-H Pro); 2.48 (1H, m, γ-H Pro); 2.74 (1H, ddd, δ-H Pro, $^2J = 11.5$ Hz, $^3J = 8.5$ Hz, $^3J = 6.4$ Hz); 3.42 (1H, d, α-H Thr, $^3J = 7.2$ Hz); 3.47 (1H, dd, α-H Pro, $^3J = 9.1$ Hz, $^3J = 4.6$ Hz); 4.06 (1H, d, N*CH*$_2$Ar, $^2J = 14.1$ Hz); 4.10–4.21 (2H, m, δ-H Pro, β-H Thr); 4.67 (1H, d, N*CH*$_2$Ar, $^2J = 14.1$ Hz); 5.14 (1H, d, OH, $^3J = 6.4$ Hz); 6.68 (1H, ddd, Ar, $^3J = 8.3$ Hz, $^3J = 6.9$ Hz, $^4J = 1.3$ Hz); 6.78 (1H, dd, Ar, $^3J = 8.3$ Hz, $^4J = 1.8$ Hz); 7.19 (1H, ddd, Ar, $^3J = 8.8$ Hz, $^3J = 6.9$ Hz, $^4J = 1.8$ Hz); 7.27 (1H, m, Ar); 7.33 (1H, m, Ar); 7.41–7.64 (6H, m, Ar); 8.52 (1H, dd, Ar, $^3J = 8.8$ Hz, $^4J = 1.0$ Hz); 9.25 (1H, dd, Ar, $^3J = 7.7$ Hz, $^4J = 1.6$ Hz).

4.4.4. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*R*)-threoninato-*N*,*N*′,*N*″,*O*}nickel(II) 6b. Yield: 47%. Anal. Calcd for $C_{31}H_{33}N_3NiO_4$ (570.305): C, 65.29; H, 5.83; N, 7.87. Found: C, 65.60; H, 5.85; N, 8.00. Mp 165–167 °C. $[\alpha]_D^{20} = -1104.0$ (*c* 0.05, $CHCl_3$). ^{1}H NMR: δ 1.20 (3H, d, CH_3-Thr, $^3J = 6.2$ Hz); 1.86 (1H, m, β-H Pro); 1.97–2.15 (2H, m, β-H, γ-H Pro); 2.41 (1H, m, γ-H Pro); 2.32 (3H, s, Me); 2.34 (3H, s, Me); 2.68 (1H, m, δ-H Pro); 3.42 (1H, d, α-H Thr, $^3J = 7.2$ Hz); 3.55 (1H, dd, δ-H Pro, $^3J = 9.1$ Hz, $^3J = 4.0$ Hz); 3.63 (1H, d, N*CH*$_2$Ar, $^2J = 13.0$ Hz); 4.15 (1H, ddq, β-H Thr, $^3J = 7.2$ Hz, $^3J = 6.4$ Hz, $^3J = 6.2$ Hz); 4.26 (1H, m, α-H Pro); 4.49 (1H, d, N*CH*$_2$Ar, $^2J = 13.0$ Hz); 5.05 (1H, d, OH); 6.66 (1H, t, Ar, $^3J = 7.5$ Hz); 6.74 (1H, dd, Ar, $^3J = 8.3$ Hz, $^4J = 1.8$ Hz); 7.16 (1H, ddd, Ar,

$^3J = 8.7$ Hz, $^3J = 6.8$ Hz, $^4J = 1.8$ Hz); 7.21–7.32 (3H, m, Ar); 7.46–7.53 (3H, m, Ar); 7.60 (1H, br, Ar); 7.75 (1H, dd, Ar, $^3J = 7.7$ Hz, $^4J = 1.8$ Hz); 8.51 (1H, d, Ar, $^3J = 8.7$ Hz).

4.5. General method of alkylation of 3a–d and 4a–d complexes by alkylbromides

To the DMF solution of complex **3a**–**d** or **4a**–**d** under an argon atmosphere an alkylating agent and finely ground solid NaOH were added. The reaction mixture was stirred under argon at either room temperature or at 45–50 °C. The course of reaction was monitored by TCL (SiO_2, AcOEt/$CHCl_3$, 4:1) by following the disappearance of initial complexes. Upon completion of the reaction, the mixture was neutralized by AcOH and diluted in H_2O. The precipitate of the mixture of diastereomer complexes was filtered and washed with water. A small part of the mixture (~0.5 g) was separated by column chromatography (20 × 30 cm, SiO_2, AcOEt/$CHCl_3$, 4:1) and the structure and absolute configuration of the pure major diastereomer of complexes [**7**–**14**(**a**–**d**)] was established by spectroscopic methods. The ratio of diastereomers (ee or de) was determined by using chiral GLC analysis of the amino acid mixture isolated after the decomposition of the mixture of diastereomeric complexes (without chromatographic purification).

4.5.1. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-phenylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) 7a. To 3 g (5.63 mmol) of **3a** in 20 ml DMF were added 0.67 ml (5.63 mmol) $C_6H_5CH_2Br$ and 0.067 g (16.89 mmol) of NaOH. Major diastereomeric complex **7a** (second fraction) was isolated with a yield of 76%. Anal. Calcd for $C_{34}H_{30}ClN_3NiO_3$ (622.767): C, 65.57; H, 4.86; N, 6.75. Found: C, 65.51; H, 4.82; N, 6.71. Mp 100–102 °C. $[\alpha]_D^{20} = +1996$ (*c* 0.2, CH_3OH). ^{1}H NMR: δ 1.65 (1H, m, β-H Pro); 1.81 (1H, m, γ-H Pro); 2.25 (2H, m, β-, γ-H Pro); 2.40 (1H, m, δ-H Pro); 2.74 and 2.88 (2H, AB part of ABX system CH*CH*$_2$Ph, $J_{AB} = 13.5$ Hz, $J_{AX} = 5.5$ Hz, $J_{BX} = 4.1$ Hz); 2.96 (1H, dd, α-H Pro, $^3J = 10.9$ Hz, $^3J = 6.2$ Hz); 3.31 (1H, dd, δ-H Pro, $^3J = 5.6$ Hz, $^3J = 3.5$ Hz); 3.72 and 4.21 (2H, AB, N*CH*$_2$Ar, $J_{AB} = 12.5$ Hz); 3.93 (1H, X part of ABX system α-H Phe); 6.62 (1H, d, Ar, $^3J = 4.2$ Hz); 7.01–7.18 (5H, m, Ar); 7.21–7.41 (4H, m, Ar); 7.43–7.71 (6H, m, Ar); 8.03 (1H, d, Ar, $^3J = 8.6$ Hz); 8.21 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.2. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-phenylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) 7b. To 3 g (5.7 mmol) of **3b** in 20 ml DMF were added 0.67 ml (5.7 mmol) $C_6H_5CH_2Br$ and 0.41 g (10.4 mmol) of NaOH. Major diastereomeric complex **7b** (second fraction) was isolated with yield of 78%. Anal. Calcd for $C_{36}H_{35}N_3NiO_3$: C, 70.15; H, 5.72; N, 6.82. Found: C, 70.12; H, 5.75; N, 6.85. Mp 129–130 °C. $[\alpha]_D^{20} = +2085$ (*c* 0.06, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.65 (1H, m, β-H Pro); 1.82 (1H, m, γ-H Pro); 1.94 (3H, s, CH_3); 2.12 (3H, s, CH_3); 2.2 (3H, m, β-, γ-, δ-H Pro); 2.78 and 2.9 (2H, AB part of ABX system CH*CH*$_2$Ph, $J_{AB} = 13.4$ Hz, $J_{AX} = 5.4$ Hz, $J_{BX} = 4.0$ Hz); 3.01 (1H, m, δ-H Pro); 3.21 and 4.18 (2H, AB, N*CH*$_2$Ar, $J_{AB} = 12.6$ Hz); 3.22 (1H, m, α-H Pro); 4.04 (1H, X part of ABX system, α-H Phe); 6.58 (1H, dd, $^3J = 8.3$ Hz, $^4J = 1.8$ Hz); 6.98–7.22 (7H, m, Ar); 7.38–7.61 (7H, m, Ar); 8.02 (1H, dd, Ar, $^3J = 8.3$ Hz, $^4J = 1.0$ Hz); 8.42 (1H, d, Ar, $^4J = 1.8$ Hz).

4.5.3. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-(4-fluorophenyl)-alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 8a. To 3 g (5.63 mmol) of **3a** in 20 ml DMF were added 0.7 ml (5.63 mmol) 4-F–$C_6H_4CH_2Br$ and 0.56 g (14.07 mmol) of NaOH. Major diastereomeric complex **8a** (second fraction) was isolated with a yield of 77.9%. Anal. Calcd for $C_{34}H_{29}ClFN_3NiO_3$ (640.757): C, 63.73; H, 4.56; N, 6.56. Found: C, 63.78; H, 4.51; N, 6.61. Mp 115–117 °C. $[\alpha]_D^{20} = +1618$ (*c* 0.03, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 1.65 (1H, m, β-H Pro); 1.81 (1H, m, γ-H Pro); 2.21–2.41 (3H, m, β-, γ-, δ-H Pro); 2.42 and 3.21 (2H, AB part of ABX system CH*CH*$_2$Ph, $J_{AB} = 13.5$ Hz, $J_{AX} = 5.8$ Hz, $J_{BX} = 4.4$ Hz); 2.96 (1H, m, δ-H Pro); 3.22 and 4.18 (2H, AB, N*CH*$_2$Ar, $J_{AB} = 12.7$ Hz); 3.32 (m, 1H, α-H Pro); 3.91 (1H, X part of ABX system, α-H Phe); 6.52 (1H, d, Ar, $^3J = 4.4$ Hz); 7.02–7.21 (5H, m, Ar); 7.33 (3H, m, Ar); 7.45–7.71 (6H, m, Ar); 8.01 (1H, d, Ar, $^3J = 8.6$ Hz), 8.33 (1H, d, Ar, $^4J = 1.9$ Hz).

4.5.4. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-(4-fluorophenyl)-alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 8b. To 3 g (5.7 mmol) of **3b** in 20 ml DMF were added 0.71 ml (5.7 mmol) 4-F–$C_6H_4CH_2Br$ and 0.57 g (14.2 mmol) of NaOH. Major diastereomeric complex **8b** (second fraction) was isolated with a yield of 74.2%. Anal. Calcd for $C_{36}H_{34}FN_3NiO_3$ (634.365): C, 68.16; H, 5.40; N, 6.62. Found: C, 68.11; H, 5.44; N, 6.59. Mp 127–129 °C. $[\alpha]_D^{20} = +1802$ (*c* 0.03, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 1.64 (1H, m, β-H Pro); 1.81 (1H, m, γ-H Pro); 1.95 (3H, s, Me); 2.22 (3H, s, Me); 2.25–2.45 (3H, m, β-, γ-, δ-H Pro); 3.71 (1H, m, δ-H Pro); 2.45 and 3.32 (2H, AB part of ABX system CH*CH*$_2$Ph, $J_{AB} = 13.7$ Hz, $J_{AX} = 5.5$ Hz, $J_{BX} = 4.7$ Hz); 3.42 (1H, m, α-H Pro); 3.63 and 4.18 (2H, AB, N*CH*$_2$Ar, $J_{AB} = 12.6$ Hz); 3.95 (1H, X part of ABX system, α-H Phe); 6.51 (1H, dd, $^3J = 8.6$ Hz, $^4J = 2.0$ Hz); 7.01–7.32 (6H, m, Ar); 7.38–7.61 (7H, m, Ar); 8.02 (1H, dd, $^3J = 8.6$ Hz, $^4J = 1.8$ Hz); 8.43 (1H, d, $^4J = 1.8$ Hz).

4.5.5. (*S*)-{({2-[1-(3,4-Dichlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-(4-fluorophenyl)-alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 8c. To 3 g (5.29 mmol) of **3c** in 20 ml DMF were added 0.65 ml (5.29 mmol) 4-F–$C_6H_4CH_2Br$ and 0.52 g (13.22 mmol) of NaOH. Major diastereomeric complex **8c** (second fraction) was isolated with yield of 74.8%. Anal. Calcd for $C_{34}H_{28}Cl_2FN_3NiO_3$ (675.202): C, 60.48; H, 4.18; N, 6.22. Found: C, 60.18; H, 4.20; N, 6.25. Mp 111–113 °C. $[\alpha]_D^{20} = +2083$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.67 (1H, m, β-H Pro); 1.82 (1H, m, γ-H Pro); 2.15–2.37 (3H, m, β-, γ-, δ-H Pro); 2.32 and 3.41 (2H, AB part of ABX system, CH*CH*$_2$Ph, $J_{AB} = 13.3$ Hz, $J_{AX} = 5.5$ Hz, $J_{BX} = 4.6$ Hz); 2.71 (1H,

m, δ-H Pro); 2.95 (1H, m, α-H Pro); 3.11 and 4.29 (2H, AB, NCH_2Ar, $J_{AB} = 12.5$ Hz); 4.35 (1H, X part of ABX system, α-H Phe); 6.67 (2H, m, Ar); 7.00 (1H, d, Ar, $^3J = 7.6$ Hz); 7.17–7.22 (5H, m, Ar); 7.35–7.40 (6H, m, Ar); 8.03 (1H, d, Ar, $^3J = 8.6$ Hz); 8.98 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.6. (*S*)-{({2-[1-Benzylpyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-(4-fluorophenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 8d. To 3 g (6.03 mmol) of **3d** in 20 ml DMF were added 0.75 ml (6.03 mmol) 4-F–$C_6H_4CH_2Br$ and 0.60 g (15.05 mmol) of NaOH. Major diastereomeric complex **8d** (second fraction) was isolated with yield of 71.2%. Anal. Calcd for $C_{34}H_{30}FN_3NiO_3$ (605.312): C, 67.35; H, 4.99; N, 6.93. Found: C, 67.15; H, 4.97; N, 6.95. Mp 125–127 °C. $[\alpha]_D^{20} = +2163$ (*c* 0.049, MeOH). ^{1}H NMR: δ 1.71 (1H, m, β-H Pro); 1.88 (1H, m, γ-H Pro); 2.21–2.51 (3H, m, β-, γ-, δ-H Pro); 2.78 and 3.02 (2H, AB part of ABX system, CHCH_2Ph, $J_{AB} = 13.4$ Hz, $J_{AX} = 5.2$ Hz, $J_{BX} = 4.4$ Hz); 2.91 (1H, m, δ-H Pro); 3.32 (1H, m, α-H Pro); 3.52 and 4.16 (2H, AB, NCH_2Ar, $J_{AB} = 12.7$ Hz); 4.12 (1H, X part of ABX, α-H Phe); 6.61 (2H, m, Ar); 7.17–7.22 (7H, m, Ar); 7.31–7.38 (7H, m, Ar); 8.05 (1H, d, Ar, $^3J = 8.6$ Hz); 8.31 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.7. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-(3-bromo-4-methoxyphenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 9a. To 3 g (5.63 mmol) of **3a** in 20 ml DMF were added 1.57 g (5.63 mmol) 3-Br–4-CH_3O–$C_6H_3CH_2Br$ and 0.67 g (16.89 mmol) of NaOH. Major diastereomeric complex **9a** (second fraction) was isolated with yield of 78%. Anal. Calcd for $C_{35}H_{31}BrClN_3NiO_4$ (731.689): C, 57.45; H, 4.27; N, 5.74. Found: C, 57.39; H, 4.29; N, 5.72. Mp 118–120 °C. $[\alpha]_D^{20} = +1718$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.83 (1H, m, β-H Pro); 1.98 (1H, m, γ-H Pro); 2.41–2.60 (3H, m, β-, γ-, δ-H Pro); 2.79 and 3.00 (2H, AB part of ABX system, CHCH_2Ph, $J_{AB} = 13.4$ Hz, $J_{AX} = 5.6$ Hz, $J_{BX} = 4.2$ Hz); 3.21 (1H, ddd, δ-H Pro, $^2J = 11.3$ Hz, $^3J = 6.6$ Hz, $^3J = 4.4$ Hz); 3.42 (1H, dd, α-H Pro, $^3J = 9.1$ Hz, $^3J = 4.4$ Hz); 3.76 and 4.36 (2H, AB, NCH_2Ar, $J_{AB} = 12.6$ Hz); 3.91 (3H, s, OMe); 4.21 (1H, X part of ABX, α-H Phe); 6.61 (2H, m, Ar); 6.84 (3H, m, Ar); 7.18 (2H, m, Ar); 7.39 (4H, m, Ar); 7.42–7.58 (3H, m, Ar); 8.12 (1H, d, Ar, $^3J = 8.8$ Hz); 8.22 (1H, d, Ar, $^4J = 1.6$ Hz).

4.5.8. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-(3-bromo-4-methoxyphenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 9b. To 3 g (5.7 mmol) of **3a** in 20 ml DMF were added 1.59 g (5.7 mmol) 3-Br–4-CH_3O–$C_6H_3CH_2Br$ and 0.57 g (14.20 mmol) of NaOH. Major diastereomeric complex **9b** (third fraction) was isolated with yield of 72%. Anal. Calcd for $C_{37}H_{36}BrN_3NiO_4$ (725.297): C, 61.27; H, 5.00; N, 5.79. Found: C, 61.21; H, 4.97; N, 5.75. Mp 100–102 °C. $[\alpha]_D^{20} = +1173$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.85 (1H, m, β-H Pro); 1.95 (1H, m, γ-H Pro); 2.01 (3H, s, Me); 2.10 (3H, s, Me); 2.12–2.62 (3H, m, β-, γ-, δ-H Pro); 2.82 and 3.33 (2H, AB part of ABX system, CHCH_2Ph, $J_{AB} = 13.6$ Hz, $J_{AX} = 5.7$ Hz, $J_{BX} = 4.1$ Hz); 3.00 (1H, m, δ-H Pro); 3.52 (1H, m, α-H Pro); 3.91 (3H, s, OMe); 3.71 and 4.32 (2H, AB, NCH_2Ar, $J_{AB} = 12.7$ Hz); 4.46 (1H, X part of ABX system, α-H Phe); 6.61 (2H, d, Ar, $J = 4.2$ Hz); 6.82 (2H, m, Ar); 7.10–7.24 (4H, m, Ar); 7.38 (m, 3H, Ar); 7.51–7.55 (2H, m, Ar); 8.10 (1H, d, Ar, $J = 8.4$ Hz); 8.82 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.9. (*S*)-{({2-[1-(3,4-Dichlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-3-(3-bromo-4-methoxyphenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 9c. To 3 g (5.29 mmol) of **3c** in 20 ml DMF were added 1.48 g (5.29 mmol) 3-Br–4-CH_3O–$C_6H_3CH_2Br$ and 0.52 g (13.22 mmol) of NaOH. Major diastereomeric complex **9c** (second fraction) was isolated with yield of 71.6%. Anal. Calcd for $C_{35}H_{30}BrCl_2N_3NiO_4$ (766.134): C, 54.87; H, 3.95; N, 5.48. Found: C, 54.75; H, 3.99; N, 5.46. Mp 107–109 °C. $[\alpha]_D^{20} = +1823$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.75 (1H, m, β-H Pro); 1.92 (1H, m, γ-H Pro); 2.22–2.49 (3H, m, β-, γ-, δ-H Pro); 2.68 and 2.92 (2H, AB part of ABX system, CHCH_2Ph, $J_{AB} = 13.9$ Hz, $J_{AX} = 5.9$ Hz, $J_{BX} = 4.1$ Hz); 3.08 and 4.11 (2H, AB, NCH_2Ar, $^2J = 12.5$ Hz); 3.16 (1H, m, δ-H Pro); 3.17 (1H, dd, α-H Pro, $^3J = 9.9$ Hz, $^3J = 6.9$ Hz); 3.83 (3H, s, OMe); 4.16 (1H, X part of ABX system, α-H Phe); 6.61 (2H, d, Ar, $J = 4.2$ Hz); 6.79 (1H, d, Ar, $^3J = 7.6$ Hz); 6.84 (1H, d, Ar, $^3J = 8.3$ Hz); 6.95 (1H, dd, Ar, $^3J = 8.3$ Hz, $^4J = 2.1$ Hz); 7.11 (1H, dt, Ar, $^3J = 8.7$ Hz, $^3J = 4.4$ Hz); 7.24 (1H, d, Ar, $^3J = 8.1$ Hz); 7.26 (1H, m, Ar); 7.38 (3H, m, Ar); 7.49 (1H, m, Ar); 7.58 (1H, dd, Ar, $^3J = 8.2$ Hz, $^4J = 2.1$ Hz); 8.10 (1H, d, Ar, $^3J = 8.7$ Hz); 8.82 (1H, d, Ar, $^4J = 2.1$ Hz).

4.5.10. (*S*)-{({2-[1-Benzylpyrrolidine-2-carboxamide]-phenyl}phenylmethylene)-(*S*)-3-(3-bromo-4-methoxyphenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 9d. To 3 g (6.02 mmol) of **3d** in 20 ml DMF were added 1.69 g (6.02 mmol) 3-Br–4-CH_3O–$C_6H_3CH_2Br$ and 0.6 g (15.05 mmol) of NaOH. Major diastereomeric complex **9d** (second fraction) was isolated with a yield of 40%. Anal. Calcd for $C_{35}H_{32}BrN_3NiO_4$ (697.244): C, 60.29; H, 4.63; N, 6.03. Found: C, 60.27; H, 4.68; N, 6.05. Mp 123–125 °C. $[\alpha]_D^{20} = +1976$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.65 (1H, m, β-H Pro); 1.92 (1H, m, γ-H Pro); 2.21–2.40 (3H, m, β-, γ-, δ-H Pro); 3.11 and 3.5 (2H, AB part of ABX system, CHCH_2Ph, $J_{AB} = 13.9$ Hz, $J_{AX} = 5.9$ Hz, $J_{BX} = 4.1$ Hz); 3.43 (1H, m, δ-H Pro); 3.55 (1H, m, α-H Pro); 3.58 and 4.25 (2H, AB, NCH_2Ar, $J_{AB} = 12.5$ Hz); 4.25 (3H, s, OMe); 5.3 (1H, X part of ABX system, α-H Phe); 6.58 (2H, m, Ar); 7.02–7.13 (5H, m, Ar); 7.15–7.20 (4H, m, Ar); 7.35–7.42 (4H, m, Ar); 8.02 (1H, d, Ar, $^3J = 8.6$ Hz); 8.23 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.11. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-allylglycinato-*N*,*N*′,*N*″,*O*}nickel(II) 10a. To 3 g (5.63 mmol) of **3a** in 20 ml DMF were added 1.48 ml (5.63 mmol) CH_2═CH─CH_2Br and 0.67 g (16.89 mmol) of NaOH. Major diastereomeric complex **10a** (second fraction) was isolated with a yield of 74%. Anal. Calcd for $C_{30}H_{28}ClN_3NiO_3$ (572.708): C, 62.92; H, 4.93; N, 7.34. Found: C, 62.82; H, 4.91; N, 7.31. Mp 156–158 °C. $[\alpha]_D^{20} = +2096$ (*c* 0.03, MeOH). ^{1}H NMR: δ 2.15 (2H, m, β-, γ-H Pro);

2.38 and 2.42 (2H, ddt, CH_2—CH=CH_2, $J = 14.2$ Hz, $J = 8.6$ Hz, $J = 1.2$ Hz); 2.51 (2H, m, β-, γ-H Pro); 3.24 (1H, m, δ-H Pro); 3.48 (2H, m, γ-, α-H Pro); 3.56 and 4.17 (2H, AB, NCH_2Ar, $J_{AB} = 12.7$ Hz); 3.78 (1H, m, α-H Allyl-Gly); 5.10 and 5.45 (2H, dd, CH_2—CH=CH_2, $J = 17.1$ Hz, $J = 10.3$ Hz); 6.58 (1H, m, CH_2—CH=CH_2); 7.05 (2H, m, Ar); 7.38–7.50 (5H, m, Ar); 7.92 (4H, m, Ar); 8.20 (1H, dd, Ar, $^3J = 8.7$ Hz, $^4J = 1.6$ Hz); 8.80 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.12. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide|phenyl}phenylmethylene)-(*S*)-2-allylglycinato-*N*,*N*′,*N*″,*O*}nickel(II) 10b. To 3 g (5.7 mmol) of **3b** in 20 ml DMF were added 0.49 ml (5.7 mmol) CH_2=CH—CH_2Br and 0.68 g (17.1 mmol) of NaOH. Major diastereomeric complex **10b** (second fraction) was isolated with yield of 73%. Anal. Calcd for $C_{32}H_{33}N_3NiO_3$ (566.316): C, 67.87; H, 5.87; N, 7.42. Found: C, 67.81; H, 5.90; N, 7.45. Mp 258–260 °C. $[\alpha]_D^{20} = +2656$ (*c* 0.03, MeOH). ^{1}H NMR: δ 1.96 (1H, m, β-H Pro); 1.99 (3H, s, Me); 2.12 (3H, s, Me); 2.33 (1H, m, γ-H Pro); 2.24 and 2.38 (2H, ddt, CH_2—CH=CH_2, $J = 13.8$ Hz, $J = 7.2$ Hz, $J = 1.2$ Hz); 2.62 (3H, m, β-, γ-, δ-H Pro); 3.22–3.50 (2H, m, α-, δ-H Pro); 3.41 and 4.22 (AB, 2H, NCH_2Ar, $J_{AB} = 12.9$ Hz); 3.52 (1H, m, α-H, Allyl-Gly); 5.25 (2H, dd, CH_2—CH=CH_2, $J_{trans} = 17$ Hz, $J_{cis} = 9.0$ Hz, $J_{hem} = 1.0$ Hz); 6.41 (1H, m, CH_2—CH=CH_2); 6.55 (2H, m, Ar); 7.28–7.42 (4H, m, Ar); 7.86 (4H, m, Ar); 8.19 (1H, dd, Ar, $^3J = 8.4$ Hz, $^4J = 1.6$ Hz); 8.63 (1H, d, Ar, $^4J = 1.4$ Hz).

4.5.13. (*S*)-{({2-[1-(3,4-Chlorobenzyl)pyrrolidine-2-carboxamide|phenyl}phenylmethylene)-(*S*)-2-allylglycinato-*N*,*N*′,*N*″,*O*}nickel(II) 10c. To 3 g (5.29 mmol) of **3c** in 20 ml DMF were added 0.45 ml (5.29 mmol) CH_2=CH—CH_2Br and 0.63 g (15.8 mmol) of NaOH. Major diastereomeric complex **10c** (second fraction) was isolated with a yield of 73.4%. Anal. Calcd for $C_{30}H_{27}Cl_2N_3NiO_3$ (607.153): C, 59.35; H, 4.48; N, 6.92. Found: C, 59.11; H, 4.51; N, 6.89. Mp 235–237 °C. $[\alpha]_D^{20} = +1756$ (*c* 0.03, MeOH). ^{1}H NMR: δ 1.95–2.21 (5H, m, 2β-, 2γ-, δ-H Pro); 2.35 and 2.44 (2H, ddt, CH_2—CH=CH_2, $J = 14.2$ Hz, $J = 7.6$ Hz, $J = 1.5$ Hz); 3.25 (1H, m, δ-H Pro); 3.39 (1H, m, α-H Pro); 3.45 (1H, m, α-H, Allyl-Gly); 3.47 and 4.22 (2H, AB, NCH_2Ar, $J_{AB} = 12.9$ Hz); 5.42 (2H, dd, CH_2—CH=CH_2, $J_{trans} = 14.0$ Hz, $J_{cis} = 9.0$ Hz, $J_{hem} = 1.0$ Hz); 6.42 (1H, m, CH_2—CH=CH_2); 6.42 (2H, m, Ar); 7.23–7.55 (4H, m, Ar); 7.87 (4H, m, Ar); 8.08 (1H, dd, Ar, $^3J = 8.7$ Hz, $^4J = 1.6$ Hz); 8.24 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.14. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide|phenyl}phenylmethylene)-(*S*)-2-methyl-3-phenylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) 11a. To 3 g (5.48 mmol) of **4a** in 20 ml DMF were added 1.62 ml (13.7 mmol) $C_6H_5CH_2Br$ and 0.65 g (16.44 mmol) of NaOH. Major diastereomeric complex **11a** (second fraction) was isolated with a yield of 73.6%. Anal. Calcd for $C_{35}H_{32}ClN_3NiO_3$ (636.793): C, 66.01; H, 5.07; N, 6.60. Found: C, 65.91; H, 5.02; N, 6.56. Mp 218–220 °C. $[\alpha]_D^{20} = +2426$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.0 (3H, s, CH_3); 1.65 (1H, m, β-H Pro); 1.88 (1H, m, γ-H Pro); 2.09 (1H, m, β-H Pro); 2.22 (2H, m, γ-, δ-H Pro); 3.0 (3H, m, δ-H Pro, C–CH_2–Ph); 3.30 (1H, dd, α-H Pro, $^3J = 9.5$ Hz, $^3J = 7.5$ Hz); 3.70 and 4.22 (2H, AB, NCH_2Ar, $J_{AB} = 12.7$ Hz); 6.56 (2H, m, Ar); 7.02 (2H, m, Ar); 7.18–7.57 (12H, m, Ar); 8.00 (1H, dd, Ar, $^3J = 8.6$ Hz, $^4J = 1.2$ Hz); 8.18 (1H, dd, Ar, $^3J = 7.8$ Hz, $^4J = 1.6$ Hz).

4.5.15. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide|phenyl}phenylmethylene)-(*S*)-2-methyl-3-phenylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) 11b. To 3 g (5.55 mmol) of **4b** in 20 ml DMF were added 1.65 ml (13.87 mmol) $C_6H_5CH_2Br$ and 0.66 g (16.65 mmol) of NaOH. Major diastereomeric complex **11b** (second fraction) was isolated with a yield of 76.2%. Anal. Calcd for $C_{37}H_{37}N_3NiO_3$ (630.401): C, 70.49; H, 5.92; N, 6.67. Found: C, 70.46; H, 5.94; N, 6.64. Mp 118–120 °C. $[\alpha]_D^{20} = +2405$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.0 (3H, s, CH_3); 1.62 (1H, m, β-H Pro); 1.88 (1H, m, γ-H Pro); 1.98 (1H, m, γ-H Pro); 2.15 (1H, m, β-H Pro); 2.00 (3H, s, Me); 2.15 (3H, s, Me); 2.22 (1H, m, δ-H Pro); 2.98 (1H, m, δ-H Pro); 3.00–3.08 (2H, AB, C–CH_2–Ph, $J_{AB} = 13.7$ Hz); 3.22 (1H, m, α-H Pro); 3.36 and 4.18 (2H, AB, NCH_2Ar, $J_{AB} = 12.6$ Hz); 6.51 (2H, m, Ar); 7.02 (3H, m, Ar); 7.33–7.61 (10H, m, Ar); 7.98 (1H, dd, Ar, $^3J = 8.8$ Hz, $^4J = 1.6$ Hz); 8.20 (1H, d, Ar, $^4J = 1.6$ Hz).

4.5.16. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide|phenyl}phenylmethylene)-(*S*)-2-methyl-3-(4-fluorophenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 12a. To 3 g (5.48 mmol) of **4a** in 20 ml DMF were added 2.73 ml (21.95 mmol) 4-F–$C_6H_4CH_2Br$ and 1.09 g (27.4 mmol) of NaOH. Major diastereomeric complex **12a** (second fraction) was isolated with a yield of 79.3%. Anal. Calcd for $C_{35}H_{31}ClFN_3NiO_3$ (654.784): C, 64.20; H, 4.77; N, 6.42. Found: C, 64.01; H, 4.74; N, 6.38. Mp 122–124 °C. $[\alpha]_D^{20} = +2230$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.16 (3H, s, CH_3); 1.69 (1H, m, β-H Pro); 1.85 (1H, m, γ-H Pro); 2.15–2.43 (3H, m, β-, γ-, δ-H Pro); 2.27 (2H, d, C–CH_2–Ph, $^2J = 13.9$ Hz); 3.18 (1H, m, δ-H Pro); 3.31 (1H, m, α-H Pro); 3.42 and 4.18 (2H, AB, NCH_2Ar, $J_{AB} = 12.8$ Hz); 6.3 (2H, m, Ar); 7.11 (3H, m, Ar); 7.18–7.57 (10H, m, Ar); 8.03 (1H, dd, Ar, $^3J = 8.6$ Hz, $^4J = 1.6$ Hz); 8.19 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.17. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide|phenyl}phenylmethylene)-(*S*)-2-methyl-3-(4-fluorophenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 12b. To 3 g (5.55 mmol) of **4b** in 20 ml DMF were added 2.76 ml (22.21 mmol) 4-F–$C_6H_4CH_2Br$ and 1.11 g (27.25 mmol) of NaOH. Major diastereomeric complex **12b** (second fraction) was isolated with yield of 75%. Anal. Calcd for $C_{37}H_{36}FN_3NiO_3$ (648.392): C, 68.54; H, 5.60; N, 6.48. Found: C, 68.33; H, 5.52; N, 6.43. Mp 129–131 °C. $[\alpha]_D^{20} = +2020$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.22 (3H, s, CH_3); 1.74 (1H, m, β-H Pro); 1.95 (1H, m, γ-H Pro); 2.15 (3H, s, Me); 2.33 (3H, s, Me); 2.18–2.45 (3H, m, β-, γ-, δ-H Pro); 2.31 (2H, d, C–CH_2–Ph, $^2J = 14.2$ Hz); 2.96 (1H, m, δ-H Pro); 3.01 and 4.42 (2H, AB, NCH_2Ar, $J_{AB} = 12.9$ Hz); 3.42 (1H, m, α-H Pro); 6.51 (2H, m, Ar); 7.22–7.57 (12H, m, Ar);

8.00 (1H, dd, Ar, $^3J = 8.6$ Hz, $^4J = 1.8$ Hz); 8.52 (1H, dd, Ar, $^3J = 8.4$ Hz, $^4J = 1.6$ Hz).

4.5.18. (*S*)-{({2-[1-(3,4-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-methyl-3-(4-fluorophenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 12c. To 3 g (5.16 mmol) of **4c** in 20 ml DMF were added 2.57 ml (20.64 mmol) 4-F–$C_6H_4CH_2Br$ and 1.19 g (29.92 mmol) of NaOH. Major diastereomeric complex **12c** (second fraction) was isolated with a yield of 78%. Anal. Calcd for $C_{35}H_{30}Cl_2FN_3NiO_3$ (689.229): C, 60.99; H, 4.39; N, 6.10. Found: C, 60.75; H, 4.42; N, 6.11. Mp 129–130 °C. $[\alpha]_D^{20} = +1976$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.18 (3H, s, CH_3); 1.71 (1H, m, β-H Pro); 1.82 (1H, m, γ-H Pro); 2.21–2.42 (3H, m, β-, γ-, δ-H Pro); 3.12 (2H, d, C–CH_2–Ph, $^2J = 13.8$ Hz); 3.21 (2H, m, α-, δ-H Pro); 3.33 and 4.18 (2H, AB, NCH_2Ar, $J_{AB} = 12.9$ Hz); 6.65 (2H, m, Ar); 6.98 (1H, d, Ar, $^3J = 7.6$ Hz); 7.17–7.22 (5H, m, Ar); 7.35–7.40 (6H, m, Ar); 8.03 (1H, d, Ar, $^3J = 8.6$ Hz); 8.98 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.19. (*S*)-{({2-[1-Benzylpyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-methyl-3-(4-fluorophenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 12d. To 3 g (5.85 mmol) of **4d** in 20 ml DMF were added 1.82 ml (14.64 mmol) 4-F–$C_6H_4CH_2Br$ and 0.7 g (17.55 mmol) of NaOH. Major diastereomeric complex **12d** (second fraction) was isolated with a yield of 72%. Anal. Calcd for $C_{35}H_{32}FN_3NiO_3$ (620.339): C, 67.77; H, 5.20; N, 6.77. Found: C, 67.51; H, 5.22; N, 6.73. Mp 115–117 °C. $[\alpha]_D^{20} = +1745$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.17 (3H, s, CH_3); 1.70 (1H, m, β-H Pro); 1.82 (1H, m, γ-H Pro); 2.11–2.51 (3H, m, β-, γ-, δ-H Pro); 2.29 (2H, d, C–CH_2–Ph, $^2J = 14.1$ Hz); 3.11 (1H, m, δ-H Pro); 3.25 (1H, m, α-H Pro); 3.42 and 4.22 (2H, AB, NCH_2Ar, $J_{AB} = 12.6$ Hz); 6.58 (2H, m, Ar); 7.01–7.25 (5H, m, Ar); 7.28–7.55 (9H, m, Ar); 8.01 (1H, d, Ar, $^3J = 8.6$ Hz); 8.32 (1H,d, Ar, $^4J = 2.0$ Hz).

4.5.20. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-methyl-3-(3-bromo-4-methoxyphenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 13a. To 3 g (5.48 mmol) of **4a** in 20 ml DMF were added 4.6 g (16.46 mmol) 3-Br–4-CH_3O–$C_6H_3CH_2Br$ and 1.05 g (26.3 mmol) of NaOH. Major diastereomeric complex **13a** (second fraction) was isolated with a yield of 69.7%. Anal. Calcd for $C_{36}H_{33}BrClN_3NiO_4$ (745.715): C, 57.98; H, 4.39; N, 5.63. Found: C, 57.81; H, 4.35; N, 5.61. Mp 244–246 °C (decomp.). $[\alpha]_D^{20} = +2000$ (*c* 0.0227, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 1.12 (3H, s, CH_3); 1.74 (1H, m, β-H Pro); 1.85 (1H, m, γ-H Pro); 2.38 (3H, m, β-, γ-, δ-H Pro); 2.25 (2H, d, C–CH_2–Ph, $^2J = 13.8$ Hz); 3.21 (1H, m, δ-H Pro); 3.32 (1H, m, α-H Pro); 3.86 and 4.21 (AB, 2H, NCH_2Ar, $J_{AB} = 12.6$ Hz); 3.90 (3H, s, OMe); 6.63 (2H, m, Ar); 6.98 (2H, m, Ar); 7.01–7.60 (11H, m, Ar); 8.11 (1H, d, Ar, $^3J = 8.6$ Hz).

4.5.21. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-methyl-3-(3-bromo-4-methoxyphenyl)alaninato-*N*,*N*′,*N*″,*O*}-nickel-(II) 13b. To 3 g (5.5 mmol) of **4b** in 20 ml DMF were added 4.66 g (16.65 mmol) 3-Br–4-CH_3O–$C_6H_3CH_2Br$ and 1.11 g (27.75 mmol) of NaOH. Major diastereomeric complex **13b** (second fraction) was isolated with a yield of 71.9%. Anal. Calcd for $C_{38}H_{38}BrN_3NiO_4$ (739.323): C, 61.73; H, 5.18; N, 5.68. Found: C, 61.52; H, 5.22; N, 5.66. Mp 139–141 °C. $[\alpha]_D^{20} = +2163$ (*c* 0.049, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, s, CH_3); 1.62 (1H, m, β-H Pro); 1.88 (1H, m, γ-H Pro); 2.11 (3H, s, Me); 2.20 (3H, s, Me); 2.21–2.52 (3H, m, β-, γ-, δ-H Pro); 2.27 (2H, d, C–CH_2–Ph, $^2J = 14.3$ Hz); 3.51 (1H, m, δ-H Pro); 3.81 (1H, m, α-H Pro); 3.90 and 4.22 (2H, AB, NCH_2Ar, $J_{AB} = 12.6$ Hz); 3.95 (3H, s, OMe); 6.61 (1H, dd, Ar, $^3J = 8.3$ Hz, $^4J = 1.8$ Hz); 6.98 (3H, m, Ar); 7.21–7.68 (9H, m, Ar); 8.08 (1H, d, Ar, $^3J = 8.6$ Hz); 8.45 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.22. (*S*)-{({2-[1-(3,4-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-methyl-3-(3-bromo-4-methoxyphenyl)alaninato-*N*,*N*′,*N*″,*O*}-nickel(II) 13c. To 3 g (5.16 mmol) of **4c** in 20 ml DMF were added 4.33 g (15.48 mmol) 3-Br–4-CH_3O–$C_6H_3CH_2Br$ and 1.03 g (25.8 mmol) of NaOH. Major diastereomeric complex **13c** (second fraction) was isolated with yield of 75.5%. Anal. Calcd for $C_{36}H_{32}BrCl_2N_3NiO_4$ (780.16): C, 55.42; H, 4.13; N, 5.39. Found: C, 55.38; H, 4.17; N, 5.35. Mp 115–117 °C. $[\alpha]_D^{20} = +1243$ (*c* 0.03, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.16 (3H, s, CH_3); 1.75 (1H, m, β-H Pro); 1.89 (1H, m, γ-H Pro); 2.38 (3H, m, β-, γ-, δ-H Pro); 2.26 (2H, d, C–CH_2–Ph, $^2J = 14.0$ Hz); 3.52 (1H, m, δ-H Pro); 3.75 (1H, dd, α-H Pro, $^3J = 8.8$ Hz, $^3J = 4.6$ Hz); 3.90 (3H, s, OMe); 3.92 and 4.19 (2H, AB, NCH_2Ar, $J_{AB} = 12.7$ Hz); 6.61 (1H, d, Ar, $^3J = 4.4$ Hz); 7.02 (3H, m, Ar); 7.22–7.61 (9H, m, Ar); 8.16 (1H, d, Ar, $^3J = 8.6$ Hz); 9.01 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.23. (*S*)-{({2-[1-Benzylpyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-methyl-3-(3-bromo-4-methoxyphenyl)alaninato-*N*,*N*′,*N*″,*O*}nickel(II) 13d. To 3 g (5.85 mmol) of **4d** in 20 ml DMF were added 4.09 g (14.6 mmol) 3-Br–4-CH_3O–$C_6H_3CH_2Br$ and 0.7 g (17.55 mmol) of NaOH. Major diastereomeric complex **13d** (second fraction) was isolated with yield of 40%. Anal. Calcd for $C_{36}H_{34}BrN_3NiO_4$ (711.27): C, 60.79; H, 4.82; N, 5.91. Found: C, 60.76; H, 4.85; N, 5.94. Mp 123–125 °C. $[\alpha]_D^{20} = +1465$ (*c* 0.087, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.13 (3H, s, CH_3); 1.72 (1H, m, β-H Pro); 1.92 (1H, m, γ-H Pro); 2.21–2.52 (3H, m, β-, γ-, δ-H Pro); 2.25 (2H, d, C–CH_2–Ph, $^2J = 14.1$ Hz); 3.12 (1H, m, δ-H Pro); 3.37 (1H, m, α-H Pro); 3.81 and 4.15 (2H, AB, NCH_2Ar, $J_{AB} = 12.5$ Hz); 3.91 (3H, s, OMe); 6.6 (1H, d, Ar, $^3J = 8.4$ Hz); 6.99 (1H, dd, Ar, $^3J = 8.6$ Hz, $^4J = 2.0$ Hz); 7.13–7.25 (6H, m, Ar); 7.36–7.49 (7H, m, Ar); 8.03 (1H, d, Ar, $^3J = 8.7$ Hz); 8.20 (1H, d, Ar, $^4J = 2.0$ Hz).

4.5.24. (*S*)-{({2-[1-(2-Chlorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-allylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) 14a. To 3 g (5.48 mmol) of **4a** in 20 ml DMF were added 1.18 ml (13.7 mmol) CH_2═CH—CH_2Br and 0.65 g (16.44 mmol) of NaOH. Major diastereomeric complex **14a** (second fraction) was isolated with a yield of 75.6%. Anal. Calcd for $C_{31}H_{30}ClN_3NiO_3$ (586.735): C, 63.46; H, 5.15; N, 7.16. Found:

C, 63.42; H, 5.11; N, 7.12. Mp 315–317 °C. $[\alpha]_D^{20} = +1562$ (c 0.03, MeOH). ^{1}H NMR: δ 1.12 (3H, s, Me); 2.09 (2H, m, β-, γ-Pro); 2.36 (1H, ddt, CH_2—CH=CH_2, $^2J = 14.2$ Hz, $^3J = 7.6$ Hz, $J = 1.4$ Hz); 2.44 (1H, ddt, CH_2—CH=CH_2, $^2J = 14.2$ Hz, $^3J = 6.9$ Hz, $J = 1.4$ Hz); 2.50 (2H, m, β-, γ-Pro); 2.54 (1H, m, δ-Pro); 3.24 (1H, m, δ-H Pro); 3.51 (1H, m, α-H Pro), 3.52 and 4.18 (2H, AB, NCH_2Ar, $J_{AB} = 12.7$ Hz); 5.16 (1H, d, —CH=CH_2, $J = 17.0$ Hz); 5.31 (1H, d, —CH=CH_2, $J = 10.3$ Hz); 6.42 (1H, m, CH_2—CH= CH_2); 6.61 (3H, m, Ar); 7.13 (2H, m, Ar); 7.19–7.61 (6H, m, Ar); 8.02 (1H, d, Ar, $^3J = 8.8$ Hz); 8.68 (1H, d, Ar, $^4J = 2.2$ Hz).

4.5.25. (*S*)-{({2-[1-(3,4-Dimethylbenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-2-allylalaninato-*N*,*N*′,*N*″,*O*}nickel(II) 14b. To 3 g (5.55 mmol) of **4b** in 20 ml DMF were added 1.2 ml (13.88 mmol) CH_2=CH—CH_2Br and 0.66 g (16.65 mmol) of NaOH. Major diastereomeric complex **14b** (second fraction) was isolated with a yield of 77%. Anal. Calcd for $C_{33}H_{35}N_3NiO_3$ (580.343): C, 68.30; H, 6.08; N, 7.24. Found: C, 67.95; H, 6.04; N, 7.21. Mp 120–122 °C. $[\alpha]_D^{20} = +2823$ (c 0.03, MeOH). ^{1}H NMR: δ 1.15 (3H, s, α-Me); 2.11 and 2.22 (6H, s, Me); 2.14 (2H, m, β-, γ-H Pro); 2.35 (1H, ddt, CH_2—CH=CH_2, $J = 14.2$ Hz, $J = 7.6$ Hz, $J = 1.5$ Hz); 2.42 (3H, m, β-, γ-, δ-H Pro); 2.45 (1H, ddt, CH_2—CH=CH_2, $J = 14.2$ Hz, $J = 7.6$ Hz, $J = 1.2$ Hz); 2.82 (1H, m, δ-H Pro); 3.32 (1H, m, α-H Pro); 3.52 and 4.22 (2H, AB, NCH_2Ar, $J_{AB} = 12.8$ Hz); 5.34 (1H, d, CH_2—CH=CH_2, $J = 17.2$ Hz); 5.43 (1H, d, CH_2—CH=CH_2, $J = 9.8$ Hz); 6.42 (1H, m, CH_2—CH=CH_2); 6.62 (3H, m, Ar); 6.98–7.22 (4H, m, Ar); 7.33–7.56 (3H, m, Ar); 7.98 (1H, d, Ar, $^3J = 8.6$ Hz); 8.40 (1H, d, Ar, $^4J = 2.0$ Hz).

4.6. X-ray diffraction study of complexes 4a and 4b

Data were collected on a Syntex $P2_1$ four-circle automated diffractometer (λ(MoK$_\alpha$)-radiation, graphite monochromator, $\theta/2\theta$ scan mode) for **4a** and a Bruker SMART 1000 CCD diffractometer (λ(MoK$_\alpha$)-radiation, graphite monochromator, ω and φ scan mode) for **4b** and corrected for Lorentz and polarization effects and for absorption (for **4b**)[12] (for details see Table 4). The structures were determined by direct methods and by full-matrix least squares refinement with anisotropic thermal parameters for non-hydrogen atoms. In the crystal **4b**, the dimethylphenyl fragment is disordered over two sites related by the rotation on 180° around the C(22)–C(23) bond, with the occupancies 0.7:0.3. The absolute structures of **4a** and **4b** were objectively determined by the refinement of Flack parameters, which have become equal 0.00(3) and 0.00(1), respectively. The hydrogen atoms were placed in calculated positions and refined in riding model with fixed thermal parameters ($U_{iso}(H) = 1.5U_{eq}(C)$ for the CH_3-groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for the other groups). All calculations were carried out by use the SHELXTL PLUS (PC Version 5.10) program package.[13] Crystallographic data for **4a** and **4b** have been deposited with the Cambridge Crystallographic Data Center. CCDC Nos. 285986 and 285985 subsequently. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

Table 4. Crystallographic data for **4a** and **4b**

	Compound	
	4a	**4b**
Empirical formula	$C_{28}H_{26}N_3O_3ClNi$	$C_{30}H_{31}N_3O_3Ni$
fw	546.68	540.29
T (K)	173(2)	105(2)
Crystal size (mm)	$0.30 \times 0.30 \times 0.20$	$0.30 \times 0.24 \times 0.21$
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	9.3354(19)	9.3420(7)
b (Å)	10.033(2)	10.5929(8)
c (Å)	25.919(5)	26.297(2)
V (Å^3)	2427.6(8)	2602.3(3)
Z	4	4
d_c (g cm^{-3})	1.496	1.379
F(000)	1136	1136
μ (mm^{-1})	0.946	0.782
$2\theta_{max}$ (deg)	58	56
Index range	$0 \leqslant h \leqslant 12$	$-12 \leqslant h \leqslant 12$
	$0 \leqslant k \leqslant 13$	$-13 \leqslant k \leqslant 14$
	$0 \leqslant l \leqslant 35$	$-34 \leqslant l \leqslant 34$
No. of rflns collected	3632	26,535
No. of unique rflns	3632	6269
No. of rflns with $I > 2\sigma(I)$	3265	5581
Data/restraints/parameters	3632/6/325	6269/14/406
$R1$; $wR2$ ($I > 2\sigma(I)$)	0.0604; 0.1540	0.0319; 0.0663
$R1$; $wR2$ (all data)	0.0704; 0.1678	0.0387; 0.0690
GOF on F^2	1.027	1.038
Absolute structure parameter	0.00(3)	0.00(1)
T_{min}; T_{max}	—	0.799; 0.853

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