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Effect of substituents on the configurational stability of the stereogenic nitrogen in metal(II) complexes of α -amino acid Schiff bases

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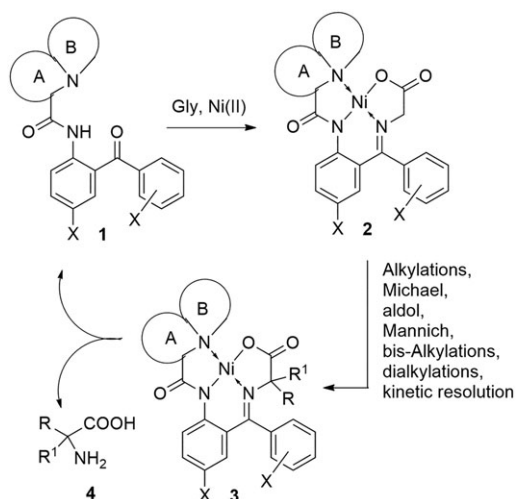
Abstract

Herein, we report a general method for quantitative measurement of the configurational stability of the stereogenic nitrogen coordinated to M (II) in the corresponding square planar complexes. This stereochemical approach is quite sensitive to steric and electronic effects of the substituents and shown to work well for Ni(II), Pd(II), and Cu(II) complexes. Structural simplicity of the compounds used, coupled with high sensitivity and reliability of experimental procedures, bodes well for application of this approach in evaluation of chemical stability and stereochemical properties of newly designed chiral ligands for general asymmetric synthesis of tailor-made amino acids.

1 | INTRODUCTION

Tailor-made amino acids (AAs),¹ are essential structural features of numerous modern pharmaceuticals.² Application of AA residues in drug design allows for fairly accurate 3-D positioning of pharmacophoric moieties and mimicking the targeted biogenic peptide–receptor interactions.³ Thus, over the past decade, about 20% of newly

introduced drugs contained at least one tailor-made AA residue.² Consequently, the development of synthetic methodology for preparation of tailor-made AAs is currently in very high demand.⁴ Following our long-standing interest in synthesis of sterically constrained⁵ and fluorine-containing AAs,⁶ we were actively contributing to the general asymmetric synthesis of α -AAs via Ni(II) complexes of AA Schiff bases (Scheme 1).⁷



SCHEME 1 General asymmetric synthesis of α -amino acids via homologation of Gly Schiff base Ni(II) complexes **2**, bearing stereochemical information on structural moieties A and/or B

As demonstrated by our and other research groups, homologation of chiral nucleophilic glycine equivalents **2** via, for example, alkylations, Michael, aldol, and Mannich addition reactions, offers a general approach to various structurally and functionally varied tailor-made AAs.⁸ Disassembly of homologation products **3** is conducted under simple acidic conditions allowing isolation of the target AAs **4** along with a complete recovery of chiral ligands **1**, as well as the Ni(II), underscoring the practicality of this methodology. Using modular approach⁹ for the design of ligands **1**, numerous glycine complexes **2** were prepared with the aim to improve the synthetic value and scalability of this methodology.⁸ However, the rational design of better performing ligands and the corresponding Ni(II) complexes of AA Schiff bases is still hindered by incomplete understanding of the effects of ligands **1** structure on the stability and reactivity of target complexes **2**. For example, as conceptually shown in Scheme 1, structural areas **A**, **B** as well as substituents X, can bear aliphatic, aromatic, electron-withdrawing/donating moieties imparting the strength of the nitrogen-nickel coordination bond, chelate rings and, therefore, the overall stability of the Ni(II) complexes of this type. Accordingly, we envisioned that the development of viable approaches for quantitative measurement of nitrogen-metal bond stability would have a profound impact on

the advancement of structural design of Ni(II) complexes **2** and their synthetic applications. Here, we report an innovative approach for experimental probing of the nitrogen-metal bond coordination energies using model compounds derived from metal(II) complexes of glycine Schiff base. The key feature of this work is the direct probing the configurational stability of stereogenic

nitrogen as a function of stereo/electronic properties of the N-ligand substituents as well as the nature coordinating metal M(II).

2 | MATERIALS AND METHODS

2.1 | General information

All commercial reagents were used without additional purification unless otherwise specified. Solvents were purified and dried according to standard methods prior to use. All experiments were monitored by thin layer chromatography (TLC) using ultraviolet (UV) light as visualizing agent. Column chromatography was performed using silica gel 60 (300-400 mesh). ¹H NMR (400 MHz) and ¹³C NMR (101 MHz) were measured on Bruker AVANCE III-400 spectrometer. Melting points are uncorrected. Values of optical rotation were measured on Rudolph Automatic Polarimeter A21101 at the wavelength of the sodium D-line (589 nm). Infrared spectra were obtained on Bruker Vector 22 in KBr pellets. HRMS were recorded on a LTQ-Orbitrap XL (ThermoFisher, Waltham, Massachusetts).

2.2 | General procedures for the reaction between o-amino-benzophenones **7** and bromoacetyl bromide

A solution of bromoacetyl bromide (46 mmol) in acetonitrile (2 mL/1 g of bromoacetyl bromide) was slowly added to a slurry of 2-aminobenzophenone (20.4 mmol) and potassium carbonate (102.2 mmol) in acetonitrile. The reaction was stirred at ambient temperature for 1 hour, and upon completion (monitored by TLC), the acetonitrile was evaporated under vacuum. Fifty milliliter of water was then added to the crude mixture and extracted with dichloromethane 50 mL for three times. The organic portions were combined and dried over anhydrous Na₂SO₄. The solvent was evaporated to give the crude product **8**, which was purified by flash chromatography.

2.3 | General procedures for preparation of **9**

To a slurry of **8** (1 equiv) and potassium carbonate (1.2 equiv) in acetonitrile was added the corresponding amine (1.1 equiv). The reaction was allowed to proceed for 2 hours at 60°C to 70°C (monitored by TLC) before the reaction mixture was concentrated under vacuum. Water was added to the viscous liquid, followed by extraction with dichloromethane. The organic portions were

combined and dried with magnesium sulfate. The solvent was evaporated to give the crude product **9**, which was purified by flash chromatography.

2.4 | General procedures for preparation of Ni(II) complex (10a-h)

An oven-dried reaction vial containing **9** (0.2 mmol), glycine (5 equiv), nickel nitrate hexahydrate (2 equiv), and K_2CO_3 was evacuated and purged with argon three times. Then, MeOH (4 mL) as solution was added via syringe at ambient temperature. Then, the reaction mixture was stirred for 8 hours at ambient temperature, and then the reaction was quenched with H_2O (5 mL). The organic layer was removed, and the aqueous layer was extracted with DCM (2×5 mL). The combined organic layers were washed with H_2O (2×10 mL) and brine (1×10 mL) and dried over anhydrous Na_2SO_4 . The solvent was evaporated to give the crude product **10**, which was purified by flash chromatography.

2.5 | General procedures for preparation of Pd(II) complex (10i)

An oven-dried reaction vial containing **9** (*N*-(2-benzoylphenyl)-2-(isopropylamino)acetamide) (0.2 mmol), glycine (5 equiv), $PdCl_2$ (2 equiv), and NaOH (7 equiv) was evacuated and purged with argon three times. Then, MeOH (4 mL) as solvent were added via syringe at ambient temperature. Then, the reaction mixture was stirred for 4 hours at $60^\circ C$ to $70^\circ C$, and then the reaction was quenched with AcOH (1 mL). The organic layer was removed, and the aqueous layer was extracted with DCM (2×5 mL). The combined organic layers were washed with H_2O (2×10 mL) and brine (1×10 mL) and dried over anhydrous Na_2SO_4 . The solvent was evaporated to give the crude product, which was purified by flash chromatography.

2.6 | General procedures for preparation of Cu(II) complex (10j)

An oven-dried reaction vial containing **9** (0.2 mmol), glycine (5 equiv), $CuSO_4 \cdot 5H_2O$ (2 equiv), and KOH (7 equiv) was evacuated and purged with argon three times. Then, MeOH (4 mL) as solvent were added via syringe at ambient temperature. Then, the reaction mixture was stirred for 8 hours at ambient temperature, and then the reaction was quenched with H_2O (5 mL). The organic layer was removed, and the aqueous layer was extracted with DCM (2×5 mL). The combined organic layers were

washed with H_2O (2×10 mL) and brine (1×10 mL) and dried over anhydrous Na_2SO_4 . The solvent was evaporated to give the crude product **10j**, which was purified by flash chromatography.

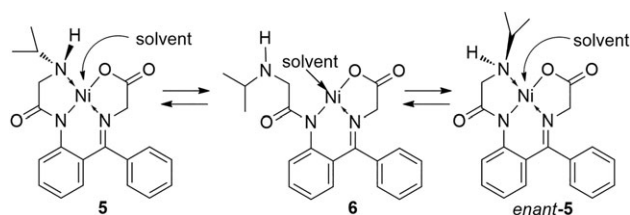
2.7 | Chiral chromatography

Analytical columns (250 x 4.6 mm, 5 microns), Chiralpak IA, IB, IC, ID, and (S,S)-Ulmo were thermostated and used to optimize the enantiomer separations, to determine ee and for dynamic chiral HPLC. Preparative columns (250 x 10 mm, 5 microns) were used to collect the enantiomers. The resulting solutions were kept in an ice bath during the separative process and below $10^\circ C$ during the evaporation.

3 | RESULTS AND DISCUSSION

Recently, we demonstrated that Ni(II)-complex **5** (Scheme 2) can be successfully used to assess its configurational stability of the stereogenic nitrogen via HPLC assisted kinetic racemization experiments.^{10a} Our preliminary studies¹⁰ served as a convincing demonstration of the viability of the chosen HPLC-based approach for working with Ni(II) complexes of AA Schiff bases. In particular, for Ni(II) complex **5**, we reported that the configurational stability of the Ni(II)-coordinated nitrogen significantly depends on the solvent used for the experiments. Thus, in strongly coordinating solvents,¹¹ such as water, acetonitrile, or alcohols, the configurational stability of the stereogenic nitrogen is rather low with the $t_{1/2}$ of racemization ranging from greater than 5 minutes to several hours. In sharp contrast, in solvents such as chloroform, ethyl acetate, or toluene, the values for racemization $t_{1/2}$ (from 6-90 years) show some remarkable, synthetically useful configurational stability.¹²

While reported in the previous work,^{10a} data provided detailed and instructive understanding of the chiral nitrogen configurational stability in relationship to the reaction solvent, the effect of substituents on the nitrogen as well as the coordinating metal remained totally unknown. Thus, drawing inspiration from the success of

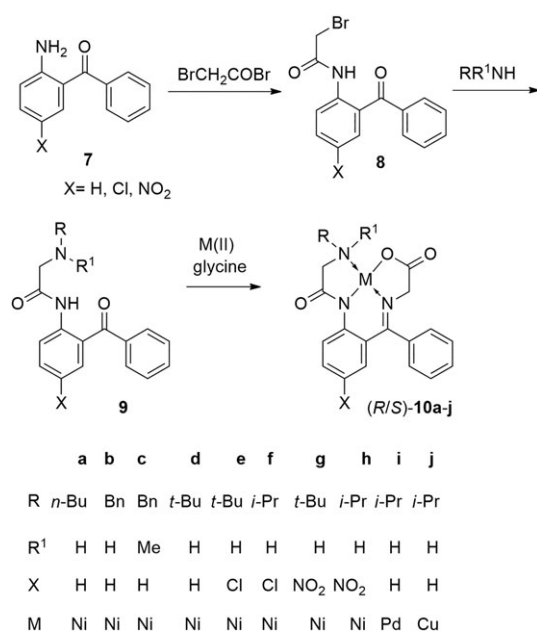


SCHEME 2 Racemization of Ni(II) complex **5**, possessing stereogenic nitrogen, via dis-coordinated intermediate **6**

the previous study,^{10a} we designed a new set of the stereochemical models presented in Scheme 3.

Synthesis of compounds **8-10a-j** was performed similar to general procedures described earlier.^{9, 10a, 13} Thus, commercially available *o*-amino-benzophenones **7** were chemo-selectively acylated using bromoacetyl bromide in acetonitrile to furnish bromo-amides **8**. Isolated and purified by column chromatography compounds **8** were reacted with the corresponding secondary or tertiary amines in the presence of Hünig's base¹² to prevent the quaternization of the amino functionality. Thus, prepared ligands **9** were heated in methanol with glycine, K₂CO₃, NaOH, or KOH (depending on the metal used), as a base, and source of M(II) ions to furnish racemic M(II) complexes of glycine Schiff bases (*R/S*)-**10a-j**. Compounds (*R/S*)-**10a-j** were purified by column chromatography and fully characterized.

The present study was initiated using available to us fully automated screening unit for chiral separation



SCHEME 3 Synthesis of ligands **9** and chiral glycine Schiff base M(II) complexes **10a-j** bearing stereogenic nitrogen

conditions (chiral stationary phases, solvents, temperature, chiroptical detection) equipped with five different columns: Pirkle-type ((*S,S*)-Ulmo), cellulose carbamates (Chiralpak IB and IC), and amylose carbamates (Chiralpak IA and ID), followed by meticulous optimization of the separation conditions for each individual compound. We decided to begin our study with **10a** (Figure 1) containing NH function and linear alkyl *N-n*-Bu group, as the simplest type of substitution on the stereogenic nitrogen. After a series of chiral chromatographic experiments, we found that reasonably good separation of enantiomers **10a** can be achieved on Chiralpak IA column with amylose carbamate stationary phase, using ethanol as an eluent. The HPLC chart of two baseline-separated enantiomers **10a**, conducted under the optimized conditions, is presented in Figure 1.

Using the optimized separation conditions, we conducted preparative separation of enantiomers **10a**. Interestingly, while enantiomers (+)- and (–)-**10a** were cleanly separated, after the solvent evaporation, the enantiomeric purity of both (+)- and (–)-**10a** was about 90% ee, clearly indicating partial racemization during the isolation procedure. Thus, using the enantiomerically enriched samples, we performed the enantiomerization (racemization) energy barriers study. An enantiomer-enriched sample was diluted in ethanol, the solution was thermostated at 22°C, and its enantiomeric excess was measured by chiral chromatography every 10 minutes for 1 hour. The first-order kinetic line for enantiomerization was drawn with an excellent correlation coefficient. The rate of enantiomerization was deduced from the slope of the first-order kinetic line and gave the following data: $k_{\text{enantiomerisation}} = 1.15 \cdot 10^{-4} \text{ s}^{-1}$ (22°C, ethanol); $\Delta G^\ddagger = 94.5 \text{ kJ/mol}$ (22°C, ethanol). These data indicated that $t_{1/2}$ racemization for enantiomers **10a** is only 50 minutes at 22°C in ethanol. In other words, the racemization occurs relatively easy at ambient temperature; yet, the configurational stability of **10a** is sufficient enough to achieve the goal of this research project. For the reference, the data reported for the *i*-propyl containing complex **5** was as follows: $k_{\text{enantiomerization}} =$

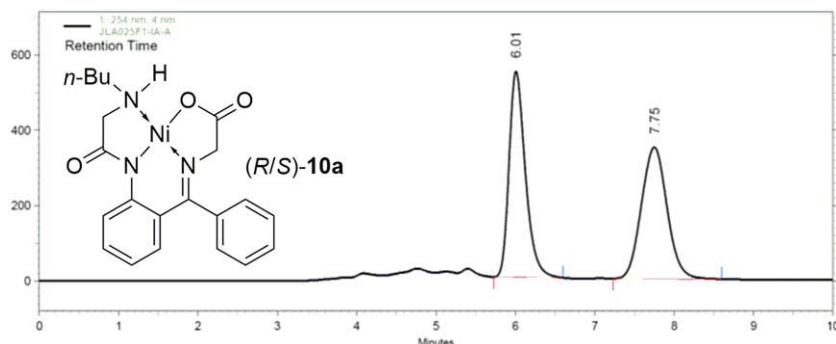


FIGURE 1 Separation of enantiomers of compound **10a** on Chiralpak IA column; ethanol, 0.8 mL/min, UV 254 nm, 25°C

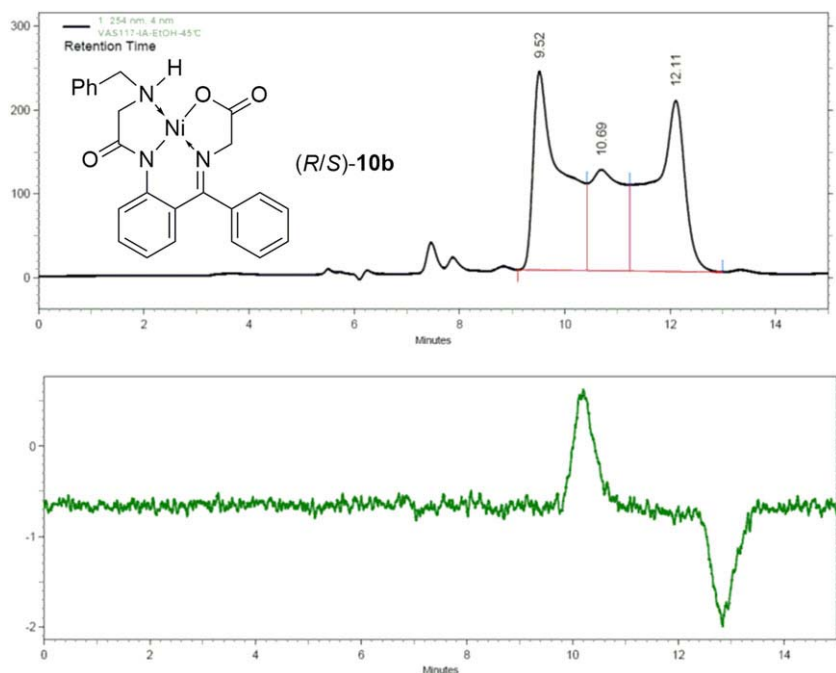


FIGURE 2 Separation of enantiomers **10b** and their on-line racemization; Chiralpak IA column; ethanol, 0.5 mL/min, ultraviolet (UV) 254 nm, and CD 390 nm, 45°C

$9.05 \cdot 10^{-6} \text{ s}^{-1}$ (22°C, ethanol) with the $\Delta G^\ddagger = 100.8$ (kJ/mol) indicated that $t_{1/2}$ racemization for enantiomers **5** is 7 hours, indicating some noticeable effect of *n*-Bu vs *i*-Pr groups on the configurational stability of the stereogenic nitrogen.

Building on this progress, we proceeded with generalization of this approach by using compound **10b** (Figure 2) containing the same NH functionally, but with the benzyl group instead of the linear alkyl substituent. We found that separation of enantiomers **10b** can also be achieved on Chiralpak IA column under the same condition as we used for separation of enantiomers of **10a** (see the Data S1).

In this case, however, the enantiomers **10b** were not isolated by preparative HPLC, as we chose to try another “online” technique to study the racemization kinetics.^{10c} Thus, the racemization was evidenced during the HPLC analysis at higher temperature, 45°C, by the occurrence of a “plateau” between both enantiomers (Figure 2). Each peak with a chiroptical sign corresponds to enantiomers that have not undergone any enantiomerization in the column and the plateau between the two peaks corresponds to molecules that have undergone one or several

enantiomerizations. According to the Trapp-Schurig's Equation¹⁴ developed for dynamic chiral HPLC, the enantiomerization barrier was calculated from chromatographic parameters, as retention times and height of the plateau. The experiments were conducted at two different temperatures and revealed the following kinetic data, at 35°C: $k_{\text{enantiomerisation}} = 4.61 \cdot 10^{-4} \text{ s}^{-1}$ (35°C, ethanol), $\Delta G^\ddagger = 95.2$ kJ/mol (35°C, ethanol); and at 45°C: $k_{\text{enantiomerisation}} = 1.07 \cdot 10^{-3} \text{ s}^{-1}$ (45°C, ethanol), $\Delta G^\ddagger = 96.2$ kJ/mol (45 °C, ethanol). Accordingly, the data recorded for enantiomers of **10b** is $t_{1/2} = 30$ minutes (25°C, ethanol), which is quite comparable with the data obtained for NH-*n*-Bu containing complex **10a**.

Another example of structural generality of this approach is presented by the example of complex **10c** (Figure 3) containing tertiary amino functionality. In this case, the best baseline separation of the enantiomers was achieved on Chiralpak ID column (Rs 1.97); see Data S1 for the HPLC charts and details.

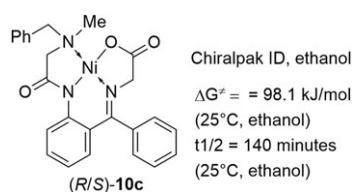


FIGURE 3 Configurational stability of complex **10c**

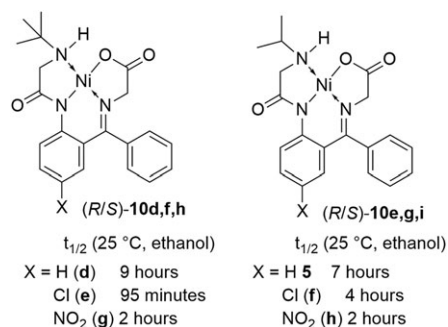


FIGURE 4 Configurational stability of complex **10**

TABLE 1 Kinetic data (in ethanol) for racemization of complexes **10d-h**

Complex	$k_{\text{enantiomerization}}$	ΔG^\ddagger	$t_{1/2}$
10d	$6.64 \cdot 10^{-6} \text{ s}^{-1}$ (22°C)	101.5 kJ/Mol (22°C)	14.5 hours (22°C)
5 (ref. 10a)	$1.62 \cdot 10^{-5} \text{ s}^{-1}$ (22°C)	99.3 kJ/Mol (22°C)	6 hours (22°C)
10e	$4.04 \cdot 10^{-5} \text{ s}^{-1}$ (22°C)	97.1 kJ/Mol (22°C)	2.4 hours (22°C)
10f	$1.63 \cdot 10^{-5} \text{ s}^{-1}$ (22°C)	99.3 kJ/Mol (22°C)	6 hours (22°C)
10 g	$2.22 \cdot 10^{-5} \text{ s}^{-1}$ (19°C)	97.5 kJ/Mol (19°C)	4.3 hours (19°C)
10 h	$2.22 \cdot 10^{-5} \text{ s}^{-1}$ (19°C)	97.5 kJ/Mol (19°C)	4.3 hours (19°C)

Enantiomers of **10c** were separated by preparative chromatography on Chiralpak ID column and remained stereochemically intact (>98% ee) during isolation and solvents evaporation, indicating some higher configurational stability, as compared with NH-*n*-Bu derivative **10a**. Indeed, the racemization and first-order kinetics experiments revealed that in this case, the $k_{\text{enantiomerisation}} = 4.11 \cdot 10^{-5} \text{ s}^{-1}$ (25°C, ethanol); $\Delta G^\ddagger = 98.1 \text{ kJ/mol}$ (25°C, ethanol). These data correspond to $t_{1/2} = 140$ minutes (25°C, ethanol), which is noticeable greater as compared with NH type complexes **10a** and **10b**.

The reason for the observed higher configurational stability of **10c** over **10a,b** can be explained by the electron-donating effect of the methyl group (vs H) and/or the overall steric bulk of the tertiary amine moiety (vs

secondary amino group). This line of considerations prompted us to study complexes **10d,e,g** bearing bulky *t*-Bu and new derivatives **10f,h** containing *i*-Pr groups (Figure 4).

Furthermore, we prepared a series of chloro- **10e,f** and nitro-derivatives **10 g,h**, bearing these substituents in the para-position to the Ni(II)-coordinated amide nitrogen (Figure 4), to briefly explore the electronic factors. For each of these five compounds **10d-h**, we optimized the chiral HPLC resolution conditions allowing for a clean baseline separation of the corresponding enantiomers. Thus, the following stationary phases were found optimal: Chiralpak ID for **10d**, Chiralpak IC for **10e,g,h**, and Chiralpak IB for **10 f**. In each case, the separation of enantiomers were successfully reproduced on preparative scale providing approximately 10 mg of the enantiomerically pure/enriched material to perform the kinetic studies. The racemization in each case was studied as described above for complexes **10a** and **10c**, following first-order kinetics experiments. The data obtained are summarized in Figure 4 and Table 1.

While the number of examples (eight complexes **10a-h** and **5**) is relatively small, one can still notice a clear trend that steric effects on the amino group have very minor effect on the stability of these Ni(II) complexes of glycine Schiff base. By contrast, the electronic effects are of a much greater role as it follows from the cases of alkyl substitution on the nitrogen as well as in the derivatives with the para-substituents on the aromatic ring. Though these trends could be anticipated on the basis of general knowledge about stability of the coordinated compounds,¹⁵ the developed method provides the previously

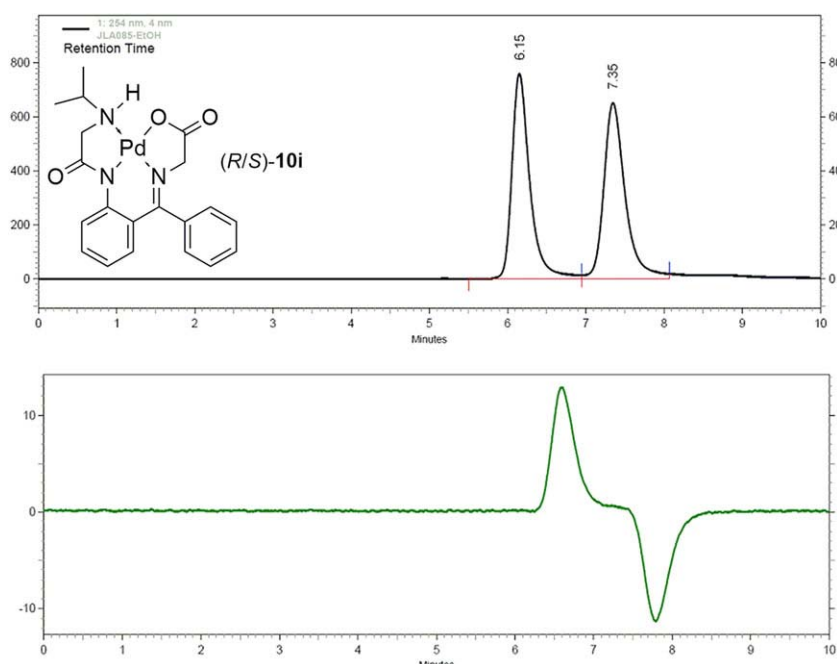
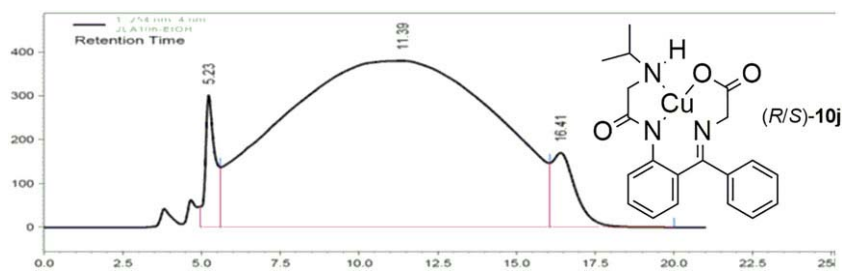
**FIGURE 5** Separation of enantiomers of complex **10i** on Chiralpak IA; (ethanol, 0.8 mL/min, UV 254 nm and CD 390 nm)

FIGURE 6 Separation of enantiomers of complex **10j** on Chiralpak IB (ethanol, 0.8 mL/min, UV 254 nm, 25°C) and the online racemization kinetics



unavailable quantitative assessment of the N—Ni(II) coordination strength.

Finally, to show the value of these stereochemical models for greater potential general applications in areas related to N-metal coordination, we decided to measure the stability of N—Pd(II) and N—Cu(II) bonds. To this end, we prepared (Scheme 3) the corresponding complexes **10i** and **10j** (Figures 5 and 6, respectively). As one can see from Figure 5, very clean baseline separation of enantiomers of **10i** was achieved on Chiralpak IA using ethanol as an eluent.

Enantiomers **10i** were also separated on the preparative scale (3 mg each) and isolated in enantiomerically pure form. Investigation of the kinetics of their racemization gave the following data: $k_{\text{enantiomerisation}} = 9.55 \cdot 10^{-6} \text{ s}^{-1}$ (25°C, ethanol); $\Delta G^\ddagger = 101.7 \text{ kJ/mol}$ (25°C, ethanol); $t_{1/2} = 10 \text{ hours}$ (25°C, ethanol). Comparison of the data obtained for the complex **10e**, containing the same ligand, we can confirm that the N—Pd(II) bond is noticeably more stable (7 vs 10 hours). While the greater stability of **10i** over **10e** can be rather expected,¹⁵ the quantitative difference was obtained for the first time in this work. By contrast, Cu(II) complex **10j** was found to be less stable, as it follows from the online racemization experiments (Figure 6). The enantiomerization of **10j** during chiral chromatography at 25°C is evidenced by the profile of the chromatogram. Most of the molecules enantiomerize during the analysis, giving a very broad central peak.

The following data: $k_{\text{enantiomerisation}} = 4.62 \cdot 10^{-3} \text{ s}^{-1}$ (25°C, ethanol); $\Delta G^\ddagger = 86.4 \text{ kJ/mol}$ (25°C, ethanol); $t_{1/2} = 1.25 \text{ minutes}$ (25°C, ethanol) indicate that Cu(II) complex **10j** is significantly less stable as compared with Ni(II) (7 hours) **10e** and Pd(II) (10 hours) **10i**. Again, while this conclusion can be anticipated,¹⁵ the quantitative difference is reported here for the first time.

4 | CONCLUSION

In conclusion, we successfully designed and realized innovative stereochemical models for quantitative measurement of the configurational stability of the stereogenic nitrogen coordinated to M(II) in the corresponding square planar complexes. These stereochemical models

are sensitive to steric as well as electronic effects and proven to work well for Ni(II), Pd(II), and Cu(II). Structural simplicity of the model compounds, coupled with high sensitivity and reliability of experimental procedures bodes well for further development and application of this approach.

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