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ORIGINAL ARTICLE

Diastereoselective Michael reaction of chiral nickel(II) glycinate with nitroalkenes for asymmetric synthesis of β-substituted α,γ-diaminobutyric acid derivatives in water

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Abstract We have developed the first operationally simple and environmentally benign protocol for the aqueous asymmetric Michael addition reaction of chiral nickel(II) glycinate with nitroalkenes. The reactions proceeded smoothly in the presence of TBAB (tetrabutyl ammonium bromide) in neat water at room temperature and provided good yields of β-substituted α,γ-diaminobutyric acid derivatives with excellent diastereoselectivities.

Keywords Michael reaction · Nickel(II) glycinate · Asymmetric synthesis · Diaminobutyric acids

Introduction

Organic reactions in aqueous media are receiving considerable attention in modern chemistry because of their substantial environmental and economic advantages over conventional reactions in organic solvents (Herrerias et al. 2007; Li 2005). As a reaction medium, water has attracted the interest of both academia and industry because of its useful properties such as safety, nontoxicity, inflammability, low cost, and environmental friendliness (Li and Chen 2006; Lindstrom 2002). Indeed, water is preferred over toxic organic solvents as a solvent in industrial procedures (Walsh et al. 2007). In this regard, the development of asymmetric Michael reactions in water has been intensively pursued (Giorgi et al. 2005; Vishnumaya and Singh 2007).

Chiral β-substituted α,γ-diaminobutyric acid derivatives are found in many biologically active compounds, and chiral auxiliaries/ligands are used in asymmetric reactions (Bellis et al. 2006; Dose et al. 2008; Lam et al. 2008; Tsai et al. 2007). Chiral α,γ-diaminobutyric acids are frequently found in various bioactive compounds, such as HA-966 (Cervo et al. 2004), L-687414 (Hargreaves et al. 1993), polymyxin B (Urban et al. 2011), and synthetic inhibitors (Belliotti et al. 2005; Field et al. 2007) (Fig. 1). Catalytic diastereoselective synthesis of these chiral building blocks mainly relies on asymmetric Michael addition reactions. Indeed, several examples of such reactions using chiral auxiliaries have been reported (Caputo et al. 2006; Huang et al. 2009; Yan et al. 2006). However, all these reactions were performed in organic solvents. In this report, we have focused on nickel(II) glycinate, which is important for asymmetric synthesis of chiral amino acids (Belokon et al. 1985; Cai et al. 2004; Soloshonok et al. 2001; Taylor et al. 2004; Wang et al. 2008). While significant progress has been made in the use of chiral nickel(II) glycinate in asymmetric synthesis of enantiopure amino acids, the development of diastereoselective Michael reactions using nickel(II) glycinate has proven to be a challenging task (Cai et al. 2001; Soloshonok et al. 2000, 2001). To the best of our knowledge, the application of nickel(II) glycinate for Michael reactions in water has not been described to date. In this study, we report the efficient synthesis of optically active β-substituted α,γ-diaminobutyric acid derivatives using asymmetric Michael addition reactions of chiral nickel(II) glycinate with nitroalkenes (Lu et al. 2006; Luo et al. 2009; Tsubogo et al. 2009; Zhu et al. 2009) in water;

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in this process, the carbon–carbon bond and two stereogenic centers are efficiently created in a single reaction with a high control of the relative and absolute stereochemistry (Scheme 1).

Results and discussion

Our initial efforts were focused on establishing the optimal conditions for the asymmetric Michael addition (Table 1). Gratifyingly, in an initial screening of a set of phase-transfer catalysts, TBAB (tetrabutyl ammonium bromide) was found to be the best promoter (Table 1, entry 4). A survey of the available bases revealed that sodium hydroxide (NaOH) was the optimal base for the asymmetric Michael reaction; the reaction with NaOH proceeded efficiently to provide a good yield giving the adduct **3a** with an excellent de value (99%) and a good *syn*:*anti* value (88:12). Similar results were obtained when the catalyst loading was lowered to 0.5 equiv. (Table 1, entry 5). Under the same conditions, other bases such as potassium hydroxide (KOH), potassium *tert*-butoxide (*t*BuOK), and sodium carbonate (Na_2CO_3) provided lower yields and diastereoselectivities (Table 1, entries 6–8). Further optimization revealed that good yields and excellent diastereoselectivities were achieved when the reaction was performed at various temperatures from 5 to 60°C using NaOH as the base and TBAB as the phase-transfer catalyst (Table 1, entries 9 and 10). However, while higher temperature (60°C) accelerated the reaction, it had a detrimental effect on the diastereoselectivity. From the viewpoint of practical application, we chose NaOH as a base, TBAB as a phase-transfer catalyst, and water as a solvent to probe the generality of the Michael addition process at ambient temperature (Table 1, entry 4). Single X-ray crystal structure analysis revealed that the major product was the *syn* diastereomer (Fig. 2).

We then investigated the scope of the asymmetric Michael addition reactions using these optimized reaction conditions (Table 2). The new methodology provided a facile approach to obtain a range of highly functionalized chiral adducts **3** with the generation of two new stereogenic centers with high diastereoselectivity. The reaction system was inert to the steric effect. The three regioisomeric nitroalkenes **2** effectively participated in the Michael reactions while providing equally high levels of yield and selectivity (Table 2, entries 1–4). In general, functionalized aryl nitroalkenes are excellent substrates for the reaction, regardless of the electronic effect. Nitroalkenes with either electron-withdrawing or electron-donating groups at the *para* position were good substrates (Table 2, entries 5–7). 4-Bromo- and 2,4-dichloro-substituted substrates also reacted well under these conditions and showed high diastereoselectivities (Table 2, entries 8 and 9). The process could also be applied to heterocyclic compounds (Table 2, entries 10–12). The less reactive aliphatic substrates also

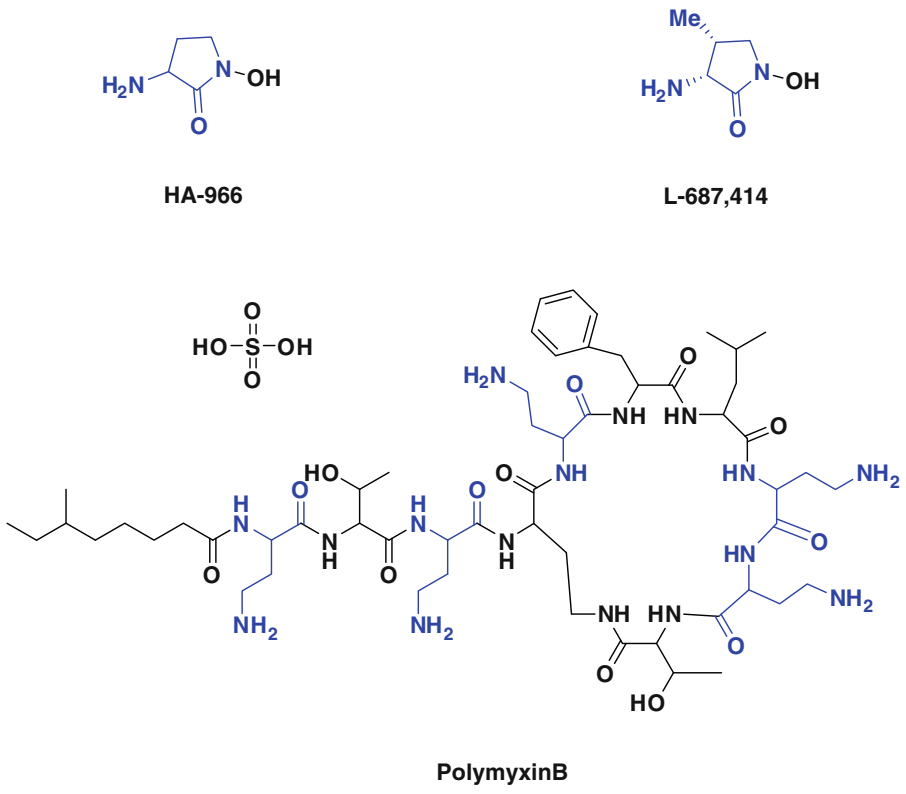


Fig. 1 Structures of some biologically important compounds containing α,γ-diaminobutyric acid motif

Scheme 1 Asymmetric Michael reactions of a chiral nickel(II) glycinate and nitroalkenes

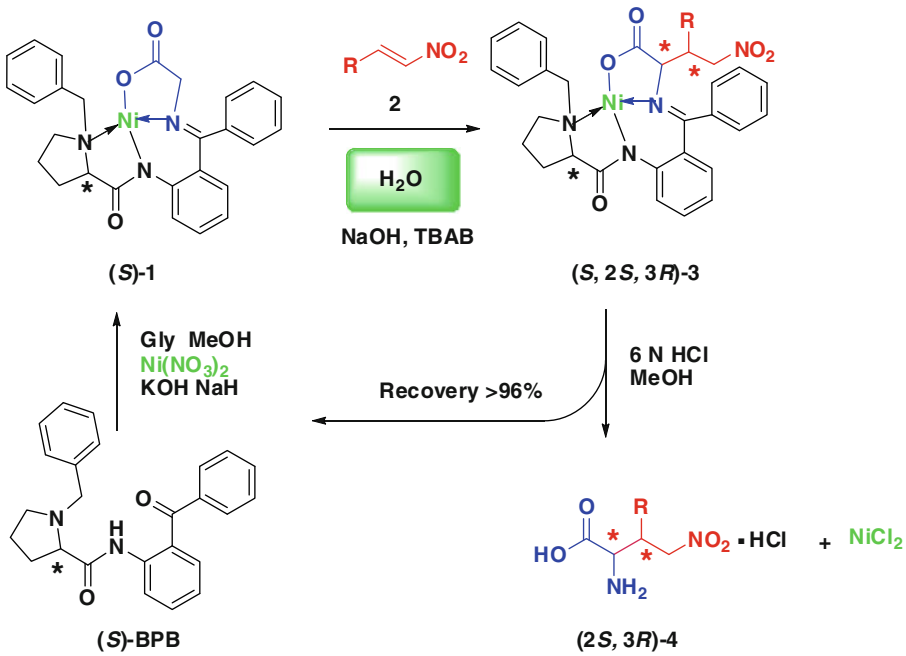
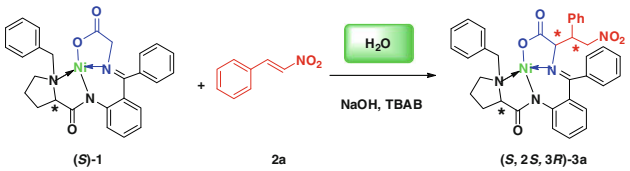


Table 1 Optimization of the reaction conditions



Entry	Base	PTC	Temp (°C)	Yield (%)[a]	*syn*:*anti*[b]	de (%)[c]
1	NaOH	–	23	0	–	–
2	NaOH	TEBA	23	60	65:35	43
3	NaOH	TEAB	23	53	64:36	56
4	NaOH	TBAB	23	68	88:12	>99
5[d]	NaOH	TBAB	23	64	86:14	>99
6	KOH	TBAB	23	69	82:18	90
7	*t*BuOK	TBAB	23	62	78:22	83
8	Na_2CO_3	TBAB	23	54	74:26	86
9	NaOH	TBAB	60	72	68:32	90
10	NaOH	TBAB	5	70	87:13	>99

Reactions were run with 0.20 mmol of (*S*)-**1**, 0.21 mmol of **2a** in 10 mL of water with 0.24 mmol base and 0.20 mmol PTC for 24 h

[a] Yield of the major products after silica gel column chromatography

[b] Determined by HPLC analysis

[c] Determined by chiral HPLC analysis (see Supporting Information for details)

[d] 0.5 equiv. catalyst was used

engaged in the reaction with good to high de values, although they provided low yields (Table 2, entries 13–15).

The chiral ligand BPB (Scheme 2) can be easily recovered quantitatively and reused after a simple procedure. The decomposition of compound (*S*,2*S*,3*R*)-**3a** under standard conditions by heating a suspension of (*S*,2*S*,3*R*)-**3a** in methanol/6 N HCl afforded a 96% yield of the target amino acid (2*S*,3*R*)-2-amino-4-nitro-3-phenylbutanoic acid (2*S*,3*R*)-**4a**, and (*S*)-BPB was recovered quantitatively with enantioselectivity >99% (Scheme 2). The optically active (2*S*,3*R*)-2-amino-4-nitro-3-phenylbutanoic acid (2*S*,3*R*)-**4a** can be easily reduced to obtain a high yield of the corresponding (2*S*,3*R*)-2,4-diamino-3-phenylbutanoic acid (2*S*,3*R*)-**5a** (Scheme 3).

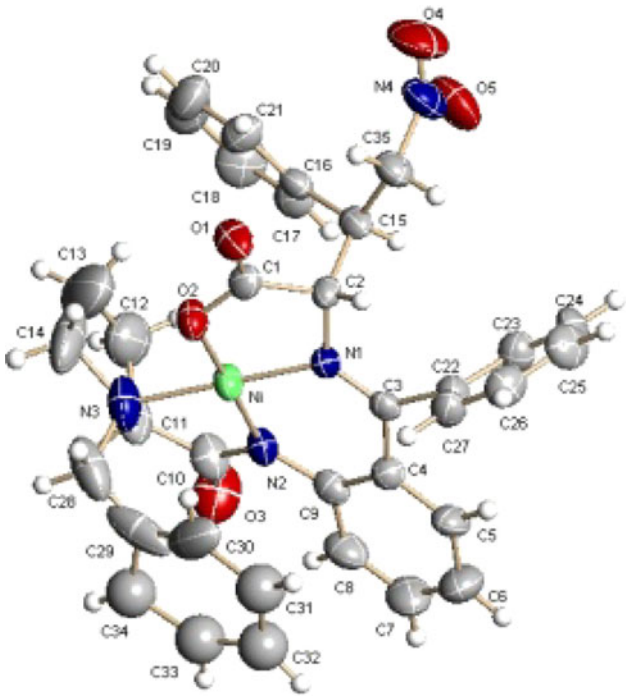
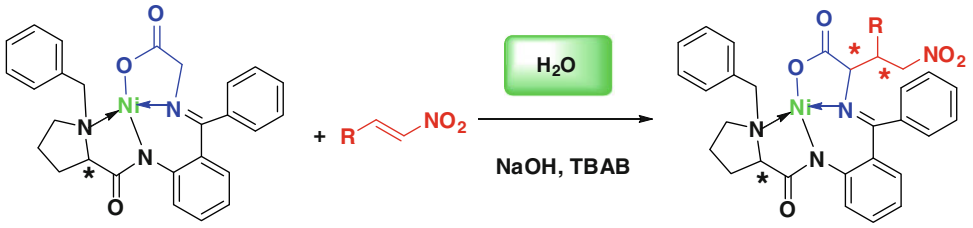


Fig. 2 The crystal structure of (*S*,2*S*,3*R*)-**3a** by X-ray analysis

Table 2 Asymmetric Michael reactions of chiral nickel(II) glycinate (*S*)-1 with nitroalkenes 2



(*S*)-1 2 (*S*, 2*S*, 3*R*)-3

Entry	Product	*R*	Yield (%)[a]	*syn*:*anti*[b]	de (%)[c]
1	(*S*,2*S*,3*R*)-**3a**	Ph	68	88:12	>99
2	(*S*,2*S*,3*R*)-**3b**	2-Cl–C_6H_4	71	85:15	97
3	(*S*,2*S*,3*R*)-**3c**	3-Cl–C_6H_4	66	83:17	>99
4	(*S*,2*S*,3*R*)-**3d**	4-Cl–C_6H_4	70	85:15	97
5	(*S*,2*S*,3*R*)-**3e**	4-Me–C_6H_4	72	82:18	97
6	(*S*,2*S*,3*R*)-**3f**	4-OMe–C_6H_4	73	80:20	98
7	(*S*,2*S*,3*R*)-**3g**	4-NO_2–C_6H_4	72	81:19	94
8	(*S*,2*S*,3*R*)-**3h**	4-Br–C_6H_4	76	83:17	97
9	(*S*,2*S*,3*R*)-**3i**	2,4-Cl_2–C_6H_4	79	80:20	98
10	(*S*,2*S*,3*R*)-**3j**	2-furyl	68	75:25	>99
11	(*S*,2*S*,3*R*)-**3k**	5-me-2-thiophenyl	65	81:19	99
12	(*S*,2*S*,3*R*)-**3l**	2-naphthyl	70	79:21	77
13	(*S*,2*S*,3*R*)-**3m**	Cy	57	82:18	98
14	(*S*,2*S*,3*R*)-**3n**	*i*-Pr	59	83:17	97
15	(*S*,2*S*,3*R*)-**3o**	*t*-Bu	46	80:20	96

Reactions were run with 0.20 mmol of (*S*)-**1**, 0.21 mmol of **2** in 10 mL of water with 0.24 mmol NaOH, and 0.20 mmol TBAB for 24 h under ambient conditions

[a] Yield of the major products after silica gel column chromatography

[b] Determined by HPLC analysis

[c] Determined by chiral HPLC analysis (see Supporting Information for details)

Conclusion

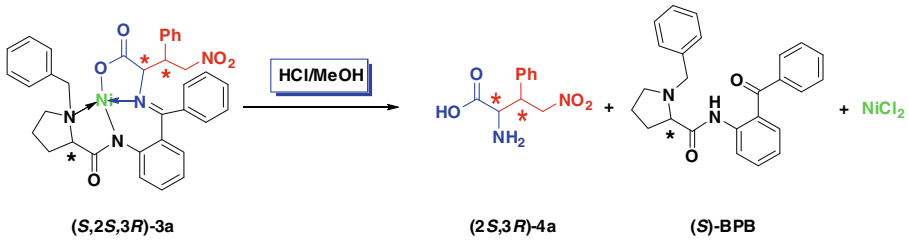
In conclusion, we have established the first asymmetric Michael addition reaction of chiral nickel(II) glycinate with nitroalkenes in pure water. This transformation, which results in the formation of carbon–carbon bond and two stereogenic centers, enables the facile synthesis of good yields of highly functionalized chiral β-substituted α,γ-diaminobutyric acid derivatives with excellent diastereoselectivities. The reactions were efficient when performed with electron-deficient, electron-rich, and sterically hindered nitroalkenes and provide functionalized Michael products with excellent diastereoselectivities. A broad range of aryl-, heteroaryl-, and alkyl-derived nitroalkenes can be employed under operationally simple and safe conditions. The absolute configuration of one product was determined. Further studies will focus on the mechanistic aspects and further applications of other chiral nickel(II) complexes in important carbon–carbon bond-forming reactions in water.

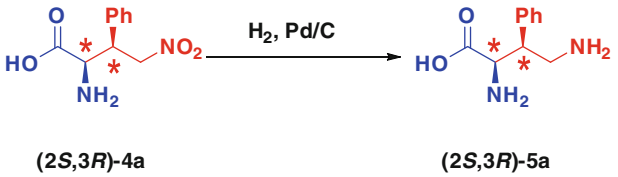
Experimental

The reagents (chemicals) were purchased from commercial sources, and used without further purification. Petroleum ether = PE. Analytical thin layer chromatography TLC used HSGF 254 (0.15–0.20 mm thickness). All products were characterized by their NMR and MS spectra. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 300 MHz instrument. Chemical shifts were reported downfield from TMS. LR- and HRMS were measured on a Finnigan MAT-95, LCQ-DECA spectrometer. Optical rotations were reported as follows: $[\alpha]_D^{22}$ (ca. g/100 mL, solvent).

Analytical HPLC was carried out using the Dionex ASI-100 automated sampler, Chiralpak IA column; loading loop:

Scheme 2 Decomposition of Ni(II) complex **3a** to release amino acid and recovery of the ligand (*S*)-BPB





Scheme 3 Hydrogenation of **4a** to afford the target amino acid **5a**

5 μL; eluent: isocratic mixture *n*-hexane-*i*-PrOH (60:40); flow rate 1 mL/min, $\lambda = 220$ nm; unless otherwise stated.

General procedure for the synthesis of (*S*,2*S*,3*R*)-**3a**

The Ni(II) complex of glycine **1** (100 mg, 0.201 mmol) was dissolved in water (10 mL). The nitrostyrene **2a** (31 mg, 0.211 mmol), NaOH (9.64 mg, 0.241 mmol), and TBAB (6.80 mg, 0.201 mmol) were added under ambient conditions. The reaction mixture was then stirred at room temperature for 24 h. The crude reaction mixture was concentrated, and then extracted with ethyl acetate (three times). The combined organic layers were dried with Na_2SO_4, concentrated and purified by flash column chromatography (petroleum ether/ethyl acetate) to give (*S*,2*S*,3*R*)-**3a** as a red solid.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-phenyl buranoic acid Schiff base complex **3a**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 68%; mp 109–111°C; $[\alpha]_D^{22} = +1{,}761$ (ca. 0.24 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, $J = 8.4$ Hz, 1H), 7.97 (d, $J = 7.2$ Hz, 2H), 7.63–7.54 (m, 6H), 7.37–7.29 (m, 5H), 7.20–7.15 (m, 3H), 6.75–6.67 (m, 2H), 4.93–4.85 (m, 1H), 4.41–4.29 (m, 2H), 4.18 (d, $J = 12.6$ Hz, 1H), 3.56–3.53 (m, 1H), 3.41 (d, $J = 12.3$ Hz, 1H), 3.23 (t, $J = 12.3$ Hz, 1H), 2.89–2.81 (m, 1H), 2.24–2.12 (m, 2H), 1.95–1.78 (m, 2H), 1.50–1.44 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 176.5, 272.5, 143.5, 134.8, 133.9, 133.7, 133.1, 132.9, 131.9, 131.2, 130.4, 130.0, 129.9, 129.6, 129.5, 129.4, 129.1, 128.9, 128.8, 127.9, 126.8, 125.8, 123.6, 120.9, 75.4, 71.8, 68.2, 59.4, 54.9, 47.1, 31.3, 23.7 ppm; IR (KBr) 702, 752, 1,165, 1,256, 1,338, 1,439, 1,554, 1,583, 1,641, 1,668 (C=N), 2,922, 3,431 cm^{-1}; MS (ESI, *m/z*): 647 $[M + H]^+$; HRMS (ESI) calcd for $C_{35}H_{32}N_4NaNiO_5$ $[M + Na]^+$ 669.1624, found 669.1620; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{major} = 16.924$ min, de > 99%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-(2-chlorophenyl) buranoic acid Schiff base complex **3b**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 71%; mp 98–100°C; $[\alpha]_D^{22} = +1{,}324$ (ca. 0.48 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, $J = 8.7$ Hz, 1H), 7.93 (d, $J = 7.5$ Hz, 2H), 7.70–7.44 (m, 8H), 7.32–7.29 (m, 3H), 7.21–7.16 (m, 2H), 6.76–6.66 (m, 2H), 4.93–4.86 (m, 1H), 4.38–4.32 (m, 1H), 4.24–4.04 (m, 3H), 3.28–3.22 (m, 1H), 2.77–2.72 (m, 1H), 2.27–2.17 (m, 3H), 1.90–1.83 (m, 1H), 1.28–1.23 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 176.6, 173.2, 1,423.3, 136.6, 133.8, 133.0, 132.9, 131.4, 130.4, 130.2, 129.9, 129.6, 129.4, 128.8, 128.7, 128.1, 127.4, 126.8, 125.5, 123.2, 120.6, 75.9, 71.9, 70.5, 63.4, 56.9, 42.2, 30.8, 22.8 ppm; IR (KBr) 704, 752, 1,165, 1,256, 1,336, 1,439, 1,552, 1,585, 1,641, 1,672 (C=N), 2,852, 2,924, 3,433 cm^{-1}; MS (ESI, *m/z*): 681 $[M + H]^+$; HRMS (ESI) calcd for $C_{35}H_{31}ClN_4NaNiO_5$ $[M + Na]^+$ 703.1234, found 703.1226. HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 7.658$ min, $t_{major} = 19.521$ min, de = 97%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-(3-chlorophenyl) buranoic acid Schiff base complex **3c**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 66%; mp 98–100°C; $[\alpha]_D^{22} = +1{,}486$ (ca. 0.42 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, $J = 8.7$ Hz, 1H), 8.06 (d, $J = 6.9$ Hz, 2H), 7.51–7.48 (m, 2H), 7.34–7.29 (m, 3H), 7.20–7.06 (m, 5H), 6.95–6.94 (m, 1H), 6.66–6.61 (m, 1H), 6.55–6.54 (m, 1H), 6.43 (s, 1H), 6.17 (d, $J = 7.5$ Hz, 1H), 4.92 (d, $J = 10.8$ Hz, 1H), 4.78–4.73 (m, 1H), 4.38 (d, $J = 12.6$ Hz, 1H), 4.17 (d, $J = 6.9$ Hz, 1H), 3.64–3.49 (m, 5H), 2.95–2.91 (m, 1H), 2.71–2.64 (m, 1H), 2.33–2.29 (m, 1H), 2.19–2.12 (m, 1H) ppm; ^{13}C NMR

(100 MHz, $CDCl_3$) δ 180.3, 176.8, 172.5, 143.2, 134.6, 133.8, 133.1, 132.9, 131.4, 131.3, 130.3, 129.4, 128.9, 128.8, 128.7, 128.3, 127.8, 126.7, 125.6, 123.2, 120.7, 75.9, 71.4, 70.3, 63.6, 60.4, 57.2, 46.4, 30.6, 22.9, 21.0, 14.1 ppm; IR (KBr) 702, 754, 1,165, 1,256, 1,338, 1,439, 1,554, 1,641, 1,680 (C=N), 2,850, 2,922, 3,433 cm^{-1}; MS (ESI, *m/z*): 681 $[M + H]^+$; HRMS (ESI) calcd for $C_{35}H_{31}ClN_4NaNiO_5$ $[M + Na]^+$ 703.1234, found 703.1232. HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{major} = 9.844$ min, de > 99%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-(4-chlorophenyl) buranoic acid Schiff base complex **3d**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 70%; mp 105–107°C; $[\alpha]_D^{22} = +1{,}197$ (ca. 0.36 g/100 mL, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, $J = 6.6$ Hz, 1H), 7.98 (d, $J = 5.4$ Hz, 2H), 7.64–7.42 (m, 6H), 7.19–7.17 (m, 4H), 6.76–6.69 (m, 2H), 4.91–4.85 (m, 1H), 4.34–4.19 (m, 3H), 3.57–3.44 (m, 2H), 3.27 (t, $J = 7.2$ Hz, 1H), 2.98–2.94 (m, 1H), 2.29–2.14 (m, 3H), 1.99–1.93 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 176.7, 172.4, 143.1, 134.5, 133.7, 133.6, 133.1, 132.8, 131.4, 130.2, 129.4, 128.9, 128.7, 128.6, 127.7, 126.6, 125.5, 123.1, 120.6, 75.8, 70.4, 70.3, 63.6, 60.3, 57.2, 46.3, 30.5, 22.9, 20.9, 14.1 ppm; IR (KBr) 702, 1,165, 1,256, 1,338, 1,439, 1,553, 1,583, 1,643, 1,670 (C=N), 2,924, 3,433 cm^{-1}; MS (ESI, *m/z*): 681 $[M + H]^+$; HRMS (ESI) calcd for $C_{35}H_{31}ClN_4NaNiO_5$ $[M + Na]^+$ 703.1234, found 703.1229; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 7.878$ min, $t_{major} = 14.463$ min, de = 97%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-*p*-tolyl buranoic acid Schiff base complex **3e**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 72%; mp 121–123°C; $[\alpha]_D^{22} = +1{,}595$ (ca. 0.34 g/100 mL, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, $J = 7.2$ Hz, 1H), 7.97 (d, $J = 5.1$ Hz, 2H), 7.63–7.60 (m, 3H), 7.36–7.28 (m, 5H), 7.25–7.15 (m, 5H), 6.74–6.67 (m, 2H), 4.89–4.83 (m, 1H), 4.40–4.35 (m, 1H), 4.26 (d, $J = 2.7$ Hz, 1H), 4.20 (d, $J = 9.3$ Hz, 1H), 3.54–3.51 (m, 1H), 3.41 (d, $J = 9.3$ Hz, 1H), 3.24 (t, $J = 5.7$ Hz, 1H), 2.93–2.87 (m, 1H), 2.44 (s, 3H), 2.25–2.21 (m, 1H), 2.13–2.07 (m, 1H), 1.98–1.95 (m, 2H) 1.51–1.45 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 176.9, 172.4, 143.2, 138.8, 133.9, 133.8, 133.2, 132.9, 131.5, 130.3, 130.1, 129.5, 129.3, 128.8, 128.7, 127.9, 126.7, 125.7, 123.2, 120.7, 76.0, 71.5, 70.4, 63.7, 57.3, 46.2, 30.5, 22.7, 21.2 ppm; IR (KBr) 704, 1,165, 1,256, 1,338, 1,439, 1,552, 1,585, 1,641, 1,672 (C=N), 2,922, 3,431 cm^{-1}; MS (ESI, *m/z*): 661 $[M + H]^+$; HRMS (ESI) calcd for $C_{36}H_{34}N_4NaNiO_5$ $[M + Na]^+$ 683.1780, found 683.1764; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 8.417$ min, $t_{major} = 17.224$ min, de = 97%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-(4-methoxyphenyl) buranoic acid Schiff base complex **3f**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 73%; mp 116–118°C; $[\alpha]_D^{22} = +1{,}684$ (ca. 0.43 g/100 mL, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, $J = 8.4$ Hz, 1H), 7.99 (d, $J = 7.2$ Hz, 2H), 7.63–7.61 (m, 3H), 7.32–7.28 (m, 3H), 7.18–7.06 (m, 6H), 6.76–6.70 (m, 3H), 4.91–4.84 (m, 1H), 4.35–4.18 (m, 4H), 3.86 (s, 3H), 3.56–3.51 (m, 1H), 3.44–3.40 (m, 1H), 3.29–3.23 (m, 1H), 2.98–2.91 (m, 1H), 2.21–2.14 (m, 2H) 2.00–1.93 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 176.8, 172.3, 160.2, 143.1, 133.8, 133.7, 133.2, 131.4, 130.4, 130.2, 129.4, 128.8, 12.87, 127.8, 126.7, 126.1, 125.6, 123.2, 120.6, 114.7, 76.0, 71.5, 70.4, 63.7, 57.4, 55.3, 53.4, 45.9, 30.5, 22.8 ppm; IR (KBr) 704, 754, 1,165, 1,256, 1,338, 1,439, 1,514. 1,552, 1,583, 1,641, 1,670 (C=N), 2,929, 3,435 cm^{-1}; MS (ESI, *m/z*): 677 $[M + H]^+$; HRMS (ESI) calcd for $C_{36}H_{34}N_4NaNiO_6$ $[M + Na]^+$ 699.1730, found 699.1732; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 9.086$ min, $t_{major} = 17.865$ min, de = 98%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-(4-nitrophenyl) buranoic acid Schiff base complex **3g**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 72%; mp 148–150°C; $[\alpha]_D^{22} = +1{,}529$ (ca. 0.48 g/100 mL, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, $J = 8.1$ Hz, 2H), 8.30 (d, $J = 9.0$ Hz, 1H), 7.96 (d, $J = 6.6$ Hz, 2H), 7.65–7.56 (m, 5H), 7.31–7.27 (m, 4H), 7.36–7.31 (m, 3H), 7.21–7.14 (m, 3H), 6.77–6.70 (m, 2H), 5.04–4.96 (m, 1H), 4.30–4.16 (m, 3H), 3.71–3.67 (m, 1H), 3.49–3.40 (m, 1H), 3.29–3.23 (m, 1H), 2.88–2.83 (m, 1H), 2.24–2.18 (m, 2H), 1.71–1.68 (m, 1H), 1.53–1.49 (m, 1H), 1.26 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 176.3, 173.2, 148.6, 143.3, 141.9, 133.9, 133.7, 133.4, 133.0, 131.4, 130.5, 129.7, 129.6, 128.9, 128.8, 127.7, 126.6, 125.3, 124.4, 123.4, 120.9, 94.2, 75.4, 70.2, 63.7, 57.2, 46.4, 30.6, 29.7, 22.7 ppm; IR (KBr) 704, 754, 856, 1,165, 1,256, 1,346, 1,439, 1,522, 1,556, 1,645, 1,672 (C=N), 2,924, 3,435 cm^{-1}; MS (ESI, *m/z*): 692 $[M + H]^+$; HRMS (ESI) calcd for $C_{35}H_{31}N_5NaNiO_7$ $[M + Na]^+$ 714.1475, found

714.1497; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 9.925$ min, $t_{major} = 19.109$ min, de = 94%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-(4-bromophenyl) buranoic acid Schiff base complex **3h**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 76%; mp 104–106°C; $[\alpha]_D^{22} = +1{,}456$ (ca. 0.52 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, $J = 8.7$ Hz, 1H), 7.99 (d, $J = 7.2$ Hz, 2H), 7.71–7.61 (m, 5H), 7.31–7.27 (m, 4H), 7.23–7.15 (m, 5H), 6.72–6.69 (m, 2H), 4.92–4.84 (m, 1H), 4.30–4.24 (m, 2H), 4.20–4.16 (m, 1H), 3.47–3.42 (m, 2H), 3.38–3.30 (m, 1H), 3.27 (t, $J = 7.8$ Hz, 1H), 2.93–2.88 (m, 1H), 2.32–2.27 (m, 1H), 2.19–2.14 (m, 1H), 2.04–1.96 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 176.2, 171.1, 148.6, 142.0, 133.9, 133.7, 133.4, 133.1, 131.3, 130.9, 130.5, 129.7, 129.6, 128.9, 128.8, 127.7, 126.6, 125.3, 124.3, 120.9, 75.4, 71.1, 70.2, 63.8, 60.3, 57.2, 46.4, 30.6, 29.6, 22.7, 20.9, 14.1, 13.7 ppm; IR (KBr) 704, 754, 856, 1,165, 1,256, 1,346, 1,439, 1,522, 1,556, 1,645, 1,672 (C=N), 2,924, 3,435 cm^{-1}; MS (ESI, *m/z*): 727 $[M + H]^+$; HRMS (ESI) calcd for $C_{35}H_{31}BrN_4NaNiO_5$ $[M + Na]^+$ 749.1350, found 749.1345; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 9.29$ min, $t_{major} = 18.177$ min, de = 97%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-(2,4-dichlorophenyl) buranoic acid Schiff base complex **3i**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 79%; mp 88–90°C; $[\alpha]_D^{22} = +1{,}124$ (ca. 0.38 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, $J = 7.2$ Hz, 1H), 7.97 (d, $J = 5.1$ Hz, 2H), 7.63–7.60 (m, 3H), 7.36–7.28 (m, 5H), 7.25–7.15 (m, 5H), 6.74–6.67 (m, 2H), 4.89–4.83 (m, 1H), 4.40–4.35 (m, 1H), 4.26 (d, $J = 2.7$ Hz, 1H), 4.20 (d, $J = 9.3$ Hz, 1H), 3.54–3.51 (m, 1H), 3.41 (d, $J = 9.3$ Hz, 1H), 3.24 (t, $J = 5.7$ Hz, 1H), 2.93–2.87 (m, 1H), 2.44 (s, 3H), 2.25–2.21 (m, 1H), 2.13–2.07 (m, 1H), 1.98–1.95 (m, 2H) 1.51–1.45 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 176.9, 172.4, 143.2, 138.8, 133.9, 133.8, 133.2, 132.9, 131.5, 130.3, 130.1, 129.5, 129.3, 128.8, 128.7, 127.9, 126.7, 125.7, 123.2, 120.7, 76.0, 71.5, 70.4, 63.7, 57.3, 46.2, 30.5, 22.7, 21.2 ppm; IR (KBr) 704, 1,165, 1,256, 1,338, 1,439, 1,552, 1,585, 1,641, 1,672 (C=N), 2,922, 3,431 cm^{-1}; MS (ESI, *m/z*): 715 $[M + H]^+$; HRMS (ESI) calcd for $C_{35}H_{30}Cl_2N_4NaNiO_5$ $[M + Na]^+$ 737.0844, found 737.0856; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 7.506$ min, $t_{major} = 20.102$ min, de = 98%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-furan-2-yl buranoic acid Schiff base complex **3j**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 68%; mp 93–95°C; $[\alpha]_D^{22} = +1{,}632$ (ca. 0.36 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, $J = 8.7$ Hz, 1H), 7.97 (d, $J = 7.2$ Hz, 2H), 7.65–7.56 (m, 4H), 7.33–7.31 (m, 3H), 7.21–7.14 (m, 3H), 6.71–6.62 (m, 3H), 6.52–6.51 (m, 1H), 4.80–4.72 (m, 1H), 4.43–4.21 (m, 3H), 3.80–3.73 (m, 1H), 3.58–3.53 (m, 1H), 3.35–3.18 (m, 2H), 2.55–2.17 (m, 4H), 2.03–1.97 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 176.7, 172.8, 162.5, 148.9, 143.5, 143.1, 133.8, 133.7, 132.9, 132.8, 131.5, 130.3, 129.4, 129.3, 128.8, 128.7, 127.9, 126.5, 125.7, 123.3, 120.6, 111.3, 109.7, 74.4, 70.3, 63.5, 56.9, 39.7, 36.4, 31.4, 22.9 ppm; IR (KBr) 704, 752, 1,165, 1,256, 1,338, 1,439, 1,556, 1,639, 1,672 (C=N), 2,852, 2,922, 3,435 cm^{-1}; MS (ESI, *m/z*): 637 $[M + H]^+$; HRMS (ESI) calcd for $C_{33}H_{30}N_4NiO_6$ $[M + Na]^+$ 659.1417, found 659.1422; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{major} = 16.928$ min, de > 99%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-(5-methythiophene-3-yl) buranoic acid Schiff base complex **3k**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 65%; mp 95–97°C; $[\alpha]_D^{22} = +1{,}643$ (ca. 0.29 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, $J = 6.3$ Hz, 1H), 7.98 (d, $J = 5.4$ Hz, 1H), 7.61–7.60 (m, 3H), 7.33–7.29 (m, 3H), 7.21–7.14 (m, 4H), 6.94–6.87 (m, 2H), 6.73–6.67 (m, 2H), 4.85–4.79 (m, 1H), 4.34–4.25 (m, 3H), 4.15–4.06 (m, 4H), 3.77–3.73 (m, 1H), 3.54–3.51 (m, 1H), 3.32–3.28 (m, 1H), 3.16–3.10 (m, 1H), 2.55 (s, 3H), 1.41–1.37(m,1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 176.5, 172.3, 142.9, 140.4, 133.6, 133.4, 133.2, 133.0, 132.5, 131.2, 130.6, 130.0, 129.2, 128.6, 128.5, 128.4, 127.5, 126.8, 126.3, 125.9, 125.5, 123.0, 120.3, 76.1, 70.9, 70.2, 65.2, 63.9, 63.4, 60.0, 56.9, 41.2, 30.3, 22.4, 20.7, 18.8, 15.1, 13.9 ppm; IR (KBr) 704, 752, 1,165, 1,256, 1,338, 1,377, 1,439, 1,552, 1,581, 1,641, 1,668 (C=N), 2,922, 2,956, 3,060, 3,435 cm^{-1}; MS (ESI, *m/z*): 667 $[M + H]^+$; HRMS (ESI) calcd for $C_{34}H_{32}N_4NaNiO_5S$ $[M + Na]^+$ 689.1345, found 689.1332; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{major} = 13.860$ min, de > 99%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-naphthalen-2-yl buranoic acid Schiff base complex **3l**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 70%; mp

100–102°C; $[\alpha]_D^{22} = +1{,}573$ (ca. 0.28 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, $J = 8.4$ Hz, 1H), 8.03–7.76 (m, 7H), 7.64–7.55 (m, 7H), 7.42–7.35 (m, 4H), 7.19–7.09 (m, 3H), 6.77–6.67 (m, 2H), 5.06–4.99 (m, 1H), 4.54–4.47 (m, 1H), 4.35–4.34 (m, 1H), 4.15–3.96 (m, 3H), 3.77–3.71 (m, 1H), 3.26–3.22 (m, 1H), 3.05 (t, $J = 9.0$ Hz, 1H), 2.54–2.46 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 176.5, 172.2, 143.0, 133.6, 133.5, 133.4, 133.1, 132.6, 131.8, 131.1, 130.7, 130.1, 129.8, 129.5, 129.3, 128.7, 128.5, 128.4, 128.2, 128.1, 127.6, 127.4, 126.6, 125.4, 123.0, 120.4, 75.6, 70.0, 63.5, 57.3, 46.3, 29.9, 20.8, 13.9 ppm; IR (KBr) 704, 752, 1,165, 1,256, 1,338, 1,439, 1,552, 1,641, 1,668 (C=N), 2,922, 3,057, 3,435 cm^{-1}; MS (ESI, *m/z*): 697 $[M + H]^+$; HRMS (ESI) calcd for $C_{39}H_{34}N_4NaNiO_5$ $[M + Na]^+$ 719.1780, found 719.1791; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 9.167$ min, $t_{major} = 18.461$ min, de = 77%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-cyclohexyl buranoic acid Schiff base complex **3m**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 57%; mp 102–104°C; $[\alpha]_D^{22} = +1{,}357$ (ca. 0.40 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, $J = 6.6$ Hz, 1H), 8. 03 (d, $J = 5.1$ Hz, 1H), 7.56–7.49 (m, 3H), 7.34–7.30 (m, 2H), 7.26–7.23 (m, 1H), 7.18–7.14 (m, 2H), 6.90 (d, $J = 6.3$ Hz, 1H), 6.68–6.59 (m, 2H), 4.73 (br, 2H), 4.62–4.56 (m, 1H), 4.39 (d, $J = 9.3$ Hz, 1H), 4.25–4.20 (m, 1H), 4.13 (m, 1H), 3.64–3.47 (m, 4H), 3.28–3.20 (m, 2H), 2.89–2.81 (m, 1H), 2.58–2.52 (m, 1H), 2.43–2.37 (m, 1H), 2.21–2.03 (m, 2H), 1.54–1.44 (m, 3H), 1.24–1.14 (m, 3H), 0.93–0.91 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 177.9, 172.9, 142.8, 133.9, 133.7, 133.2, 132.8, 131.5, 130.2, 129.3, 129.2, 128.9, 128.8, 127.9, 126.6, 125.9, 123.0, 120.7, 73.4, 70.6, 69.1, 63.7, 57.1, 46.3, 36.3, 33.6, 30.9 27.6, 26.8, 26.4, 25.9, 23.8 ppm; IR (KBr) 704, 752, 1,165, 1,256, 1,336, 1,439, 1,551, 1,643, 1,672 (C=N), 2,854, 2,926, 3,442 cm^{-1}; MS (ESI, *m/z*): 653 $[M + H]^+$; HRMS (ESI) calcd for $C_{35}H_{38}N_4NaNiO_5$ $[M + Na]^+$ 675.2093, found 675.2094; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 8.74$ min, $t_{major} = 24.082$ min, de = 98%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-isopropyl buranoic acid Schiff base complex **3n**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 59%; mp 100–102°C; $[\alpha]_D^{22} = +1{,}572$ (ca. 0.42 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, $J = 6.3$ Hz, 1H), 8.06 (d, $J = 5.4$ Hz, 2H), 7.57–7.49 (m, 3H), 7.35–7.33 (m, 2H), 7.22–7.12 (m, 4H), 6.89–6.85 (m, 2H), 4.71–4.66 (m, 1H), 4.41 (d, $J = 9.6$ Hz, 1H), 4.26–4.11 (m, 4H), 3.37–3.29 (m, 3H), 2.81–2.77 (m, 1H), 2.57–2.48 (m, 1H), 2.41–2.36 (m, 1H), 2.14–2.09 (m, 2H), 1.45 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 177.8, 172.7, 142.7, 133.8, 132.8, 131.5, 130.3, 129.3, 128.9, 127.6, 126.7, 126.2, 123.2, 120.8, 114.7, 72.2, 70.4, 69.2, 65.4, 63.7, 57.1, 52.3, 45.9, 30.8, 28.4, 26.3, 23.9, 23.3, 17.2 ppm; IR (KBr) 700, 756, 1,165, 1,259, 1,440, 1,551, 1,639, 1,674 (C=N), 2,962, 3,415 cm^{-1}; MS (ESI, *m/z*): 613 $[M + H]^+$; HRMS (ESI) calcd for $C_{32}H_{34}N_4NaNiO_5$ $[M + Na]^+$ 635.1780 found 635.1765; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 8.19$ min, $t_{major} = 17.216$ min, de = 97%.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-4-nitro-3-tetrtbutoxyl buranoic acid Schiff base complex **3o**

Obtained as a red solid by flash column chromatography (petroleum ether/ethyl acetate 1:1), yield 46%; mp 98–100°C; $[\alpha]_D^{22} = +1{,}386$ (ca. 0.43 g/100 mL, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, $J = 9.0$ Hz, 1H), 8.04 (d, $J = 7.5$ Hz, 2H), 7.56–7.54 (m, 3H), 7.34–7.30 (m, 3H), 7.17–7.12 (m, 2H), 6.96–6.94 (m, 1H), 6.67–6.54 (m, 2H), 4.92–4.85 (m, 1H), 4.45–4.41 (m, 1H), 4.37–4.23 (m, 1H), 3.64–3.47 (m, 5H), 3.26–3.25 (m, 1H), 2.81–2.74 (m, 1H) 2.59–2.53 (m, 1H), 2.46–2.42 (m, 1H) 1.56 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 178.1, 171.0, 167.2, 165.7, 162.3, 162.2, 159.8, 142.4, 142.2, 140.1, 133.4, 133.1, 132.9, 132.6, 132.1, 131.3, 129.5, 128.6, 128.3, 127.5, 127.3, 126.6, 126.3, 126.0, 125.4, 123.2, 120.4, 117.3, 111.7, 70.3, 69.6, 64.1, 62.9, 60.9, 57.1, 32.9, 30.2, 22.9, 14.0 ppm; IR (KBr) 704, 752, 1,165, 1,256, 1,338, 1,375, 1,439, 1,470, 1,554, 1,586, 1,643, 1,670 (C=N), 2,924, 3,433 cm^{-1}; MS (ESI, *m/z*): 627 $[M + H]^+$; HRMS (ESI) calcd for $C_{33}H_{36}N_4NaNiO_5$ $[M + Na]^+$ 649.1937, found 649.1252; HPLC (Chiralpak IA, *i*-propanol/*n*-hexane = 40/60, flow rate 1.0 mL/min, $\lambda = 220$ nm), $t_{minor} = 10.422$ min, $t_{major} = 20.165$ min, de = 96%.

Procedure for the synthesis of (2*S*,3*R*)-**4a**

The crystallized complex (*S*,2*S*,3*R*)-**3a** (1 g, 1.5 mmol) was decomposed by refluxing a suspension in a mixture of aqueous 6 N HCl (1 mL) and MeOH (15 mL) for 30 min, until the red color of the solution disappeared, as described previously. The reaction was cooled to room temperature and then evaporated to dryness. Water (20 mL) was added to the residue to form a clear solution, and this solution was then separated by column chromatography on C_{18}-reversed phase (230–400 mesh) silica gel. Pure water as an eluent

was employed to remove the green $NiCl_2$ and excess HCl; MeOH/Water (1/1) was then used to obtain optically pure product (2*S*,3*R*)-**4a** (323 mg, 96%). The ligand BPB that decomposed from (*S*,2*S*,3*R*)-**3a** was recovered by MeOH eluent (571 mg, 96%), and the column chromatography was washed with 100 mL MeOH, for further use.

(2*S*,3*R*)-2-Amino-4-nitro-3-phenylbutanoic acid **4a**

Obtained as a white solid by flash column chromatography (MeOH/water 1:1), yield 96%; mp 248–250°C; $[\alpha]_D^{22} = +3.2$ (ca. 0.34 g/100 mL, 6 N HCl); ^{1}H NMR (300 MHz, D_2O) δ 7.42–7.39 (m, 3H), 7.32–7.29 (m, 2H), 5.18 (d, $J = 10.8$ Hz, 1H), 4.56–4.41 (m, 2H), 4.15–4.11 (m, 1H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 169.1, 131.8, 129.7, 129.5, 128.4, 128.2, 75.8, 54.3, 43.4 ppm; IR (KBr) 706, 1,335, 1,381, 1,404, 1,498, 1,551, 1,614, 2,953, 3,246, 3,427 cm^{-1}; MS (ESI, *m/z*): 225 $[M + H]^+$; HRMS (ESI) calcd for $C_{10}H_{11}N_2O_4$ $[M\text{-}H]^+$ 223.0719, found 223.0720.

Procedure for the synthesis of (2*S*,3*R*)-**5a**

In a hydrogenation flask was placed compound (2*S*,3*R*)-**4a** (200 mg, 0.893 mmol) and methanol (10 mL) before the addition of Pd/C. The resulting mixture was pressurized to hydrogen and mechanically stirred at room temperature for 4 h. The reaction mixture was filtered and the filtrate was concentrated in a rotary evaporator to afford the crude product. The crude residue was purified by column chromatography on C_{18}-reversed phase (230–400 mesh) silica gel (water/methanol = 11/9) to give **5a** as a white solid in 90% yield, and the column chromatography was washed with 100 mL of methanol for further use.

(2*S*,3*R*)-2-Amino-4-nitro-3-phenylbutanoic acid **5a**

Obtained as a white solid by flash column chromatography (MeOH/water 1:1), yield 90%; mp 242–244°C; $[\alpha]_D^{22} = +11.1$ (ca. 0.48 g/100 mL, 6 N HCl); ^{1}H NMR (300 MHz, D_2O) δ 7.42–7.31 (m, 5H), 5.29–5.16 (m, 1H), 4.55–4.54 (m, 2H), 4.17–4.11 (m, 1H), ppm; ^{13}C NMR (100 MHz, D_2O) δ 169.1, 131.8, 129.7, 129.5, 129.4, 129.3, 129.2, 129.1, 128.9, 128.4, 128.0, 75.6, 75.4, 55.1, 54.2, 47.0, 43.3 ppm; MS (ESI, *m/z*): 195 $[M + H]^+$; HRMS (ESI) calcd for $C_{10}H_{15}N_2O_2$ $[M + H]^+$ 195.1128, found 195.1129.

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