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Synthesis of bis-α,α′-amino acids through diastereoselective bis-alkylations of chiral Ni(II)-complexes of glycine

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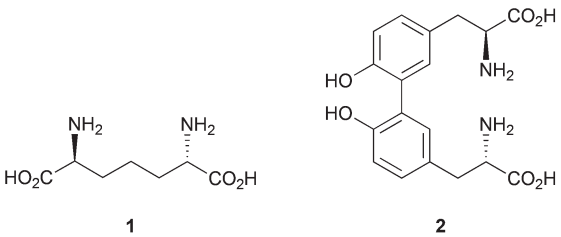
The Ni(II) complex derived from glycine Schiff base with (*S*)-*N*-(benzylprolyl)-2-aminobenzophenone can be effectively alkylated with α,ω-dibromide reagents to furnish the corresponding bis-alkylated products. This method presents a direct approach for the preparation of the corresponding bis-α,α′-amino acids with high biological importance. Heterogeneous (phase-transfer) as well as homogeneous conditions for the alkylation reactions have been investigated and the latter proved to be more efficient in terms of stereochemical outcome. In particular, alkylation of the glycine Schiff base Ni(II) complex with 1,3-dibromopropane followed by acid-catalysed hydrolysis of the resulting bis-alkylation product, allowed for the preparation of naturally occurring (2*S*,6*S*)-diaminopimelic acid in high overall yield.

Introduction

Bis-α,α′-amino acids (bis-AAs) are a class of compounds frequently found in nature as subunits of peptidic molecules. For instance, they play an important role in the structure of peptidoglycane cell walls of fungi and bacteria, and can act as cross-linking elements to allow for an efficient control of the peptide secondary structure. Representative examples of naturally occurring bis-AAs include diaminopimelic acid (**1**), a biosynthetic precursor of L-lysine in Gram-positive bacteria,[1] and dityrosine (**2**), which cross-links peptidic chains in elastin and collagen[2] (Fig. 1). In addition, bis-AAs are key structural units present in antibiotics that disrupt microbial cell wall synthesis (*e.g.* vancomycin).[3]

Due to their specific biological properties and bio-structural functions, the synthesis of bis-AAs has received significant interest. Generally, synthesis of bis-AA-containing peptides relies on late-stage couplings of suitably functionalized precursors, by means of metathesis[4] or metal-mediated cross-coupling reactions.[5] However, this frequently involves lengthy reaction sequences as well as low yields of the final coupling steps. The alternative approach is the preparation of the corresponding bis-AA subunits for its subsequent insertion into the desired peptidic chain. Consequently, many synthetic strategies leading to a variety of bis-AAs have been reported. Most of the literature methods make use of enantiomerically pure α-amino acids such as allylglycine or 3-iodotyrosine, followed by the corresponding coupling reactions.[6] In contrast, the asymmetric synthesis of the bis-AAs *via* alkylation of glycine derivatives with dihalogenated reagents has received very little attention.[7]



1 2

Fig. 1 Structures of diaminopimelic acid (**1**) and dityrosine (**2**).

Diastereoselective homologation of nucleophilic chiral glycine equivalents is the most studied method for asymmetric synthesis of α-amino acids, particularly with the aim of producing them in high scale and optical purity.[8] Extension of this methodology to the synthesis of bis-AAs would involve a bis-alkylation protocol, starting from a proper dihalogenated reagent and two equivalents of the glycine derivative. Nevertheless, this procedure has not yet been fully explored. The most notable literature examples are represented by Seebach's chiral

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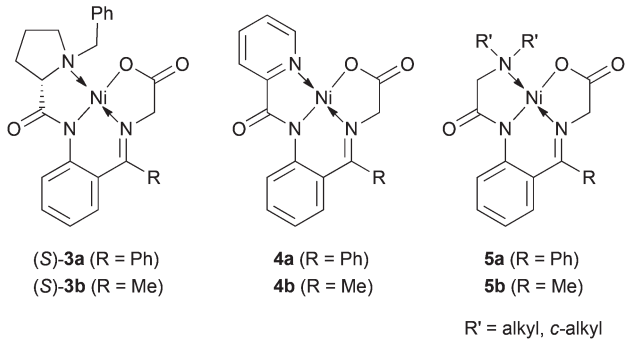


(*S*)-**3a** (R = Ph) (*S*)-**3b** (R = Me) **4a** (R = Ph) **4b** (R = Me) **5a** (R = Ph) **5b** (R = Me)

Fig. 2 Structures of Ni(II) complexes **3–5**.

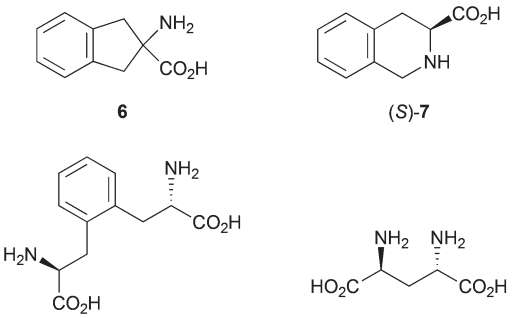


Fig. 3 Structures of mono AAs **6–7** and bis-AAs **8–9**.

oxazolidinones[9] and the asymmetric alkylations of benzophenone derived achiral glycine Schiff base using a chiral catalyst under phase-transfer conditions developed by Lygo's group.[10] These methods are generally applicable for the preparation of a wide range of bis-AAs, including aromatic and aliphatic derivatives. The only disadvantage of the literature methods is the relatively high cost of these glycine equivalents and hence the final bis-AAs, rendering these approaches of limited use for large scale preparation of the target bis-AAs. Therefore exploration of other approaches would be highly desirable to render various bis-AAs readily available for comprehensive biological and medicinal studies.

Among various nucleophilic glycine equivalents,[8] Ni(II) complex of glycine Schiff base with (*S*)-*N*-(benzylprolyl)-2-aminobenzophenone ((*S*)-BPBP) (*S*)-**3a** or acetophenone (*S*)-**3b**[11] and structurally similar derivatives **4–5**[12] (Fig. 2) possess some advantageous features such as their cost structure and operationally convenient conditions. Homologation of glycine derivatives **3–5** can be conducted at room temperature in commercial grade solvents using various types of reactions. For example, alkylation,[13] aldol,[14] Michael[15] and Mannich[16] reactions allow for the preparation of various types of amino acids in enantiomerically pure form. In particular, the alkylation reactions have been extensively studied using various primary or secondary, chiral[17] and sterically constrained alkyl halides,[18] conducted on a relatively large scale.[19] On the other hand, the application of alkyl dihalides for alkylation of derivatives **3–5** remains virtually unstudied. Among known examples are the reactions of derivatives **3a,b** with α,α′-dibromo-*o*-xylene allowing preparation of amino acids **6–8**[20] (Fig. 3). Another example is an unusual methylene dimerization of **3a** by the tetra-*n*-butylammonium bromide (TBAI) catalyzed reaction with dichloromethane leading to bis-AA **9**.[21]

Accordingly, one may agree that the reactions of glycine derivatives **3–5** with dihaloalkanes have not been sufficiently studied to disclose the practical potential of these derivatives, in particular **3a**, for the preparation of bis-AAs. Consequently, we decided to explore this area using various dihalogenated substrates, both activated (benzyl, allyl) and not activated (alkyl). Also, we envisioned to explore different types of alkylation procedures under both homogeneous and heterogeneous (phase-transfer) conditions.

Results and discussion

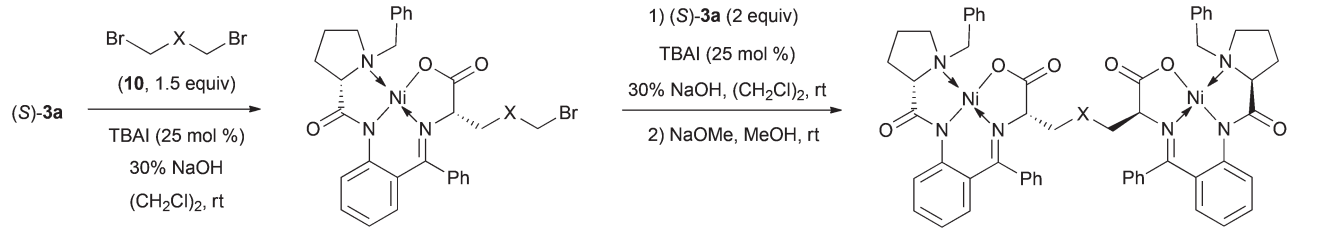
Recently, we have established an optimized reaction procedure for the monoalkylation reactions of chiral complex **3a** under phase-transfer conditions. This method consists of a two-step protocol, namely, the alkylation reaction under PTC followed by epimerization with NaOMe, under homogeneous conditions in MeOH solution, to overcome the low diastereomeric outcome of the first step.[22] The next target would be to develop a similar method for the bis-alkylation process. Accordingly, Ni(II) complex (*S*)-**3a** was reacted with 0.5 equiv. of dihalogenated reagents such as *para*- and *meta*-bis(bromomethyl)benzene (**10a** and **10b**, respectively), in a mixture of 1,2-dichloroethane–40% aqueous NaOH, and in the presence of TBAI as a phase-transfer catalyst. However, all examples studied afforded mixtures of mono- and bis-alkylation products, as determined by TLC and NMR analysis (*ca.* 30 : 70 mono- *vs.* bis-alkylation), and the conversion could not be improved even using up to 25 mol % of TBAI.†

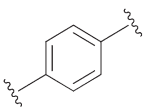
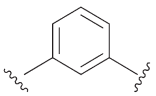
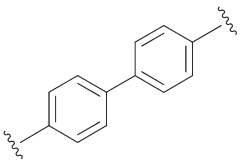
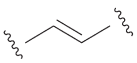
Because of the impracticality of the previous protocol, a different approach was followed (Table 1). First, alkylation of (*S*)-**3a** with an excess (1.5 equiv.) of benzylic dibromide reagents **10a–c** (entries 1–3) as well as *trans*-1,4-dibromobut-2-ene (**10d**) (entry 4) gave monoalkylated products **11** as epimeric mixtures in good yields and moderate diastereoselectivities. Although the major (*S*,*S*)-diastereomer‡ could be separated by column chromatography in some cases, the next step was best carried out with the mixtures of (*S*,*S*) and (*S*,*R*) isomers. Thus, a second alkylation of compounds **11** with another molecule of the starting Ni(II) complex (*S*)-**3a** allowed full conversion to the corresponding bis-alkylated products **12**. These compounds were obtained once again as diastereomeric mixtures which were finally treated with NaOMe to provide for complete

†The diastereoselectivity of the bis-alkylated products could not be properly determined by NMR due to the complexity of the spectra, but analysis by TLC gave approximately 75 : 25 ratio (two out of three possible isomers).

‡The (*S*) absolute configuration of the *N*-benzylproline moiety induced the resulting (*S*) stereochemistry in the newly created stereocenter of the major diastereomers as demonstrated in previous work (see ref. 13). This assignment was also supported by the chiroptical data and the distinctive NMR pattern of the major diastereomers.

Table 1 Bis-alkylations of complex (*S*)-**3a** under phase-transfer catalysis



Entry	10	X	11	dr of 11[a]	Yield of 11[b] (%)	12	dr of 12[a]	Yield of 12[b] (%)
1	**10a**		**11a**	76 : 24	92	**12a**	>97 : 3	60
2	**10b**		**11b**	83 : 17	90	**12b**	>97 : 3	58
3	**10c**		**11c**	79 : 21	98	**12c**	>97 : 3	58
4	**10d**		**11d**	86 : 14	72	**12d**	>97 : 3	70

[a] Measured by integration in the ^{1}H NMR spectra. [b] Isolated yield.

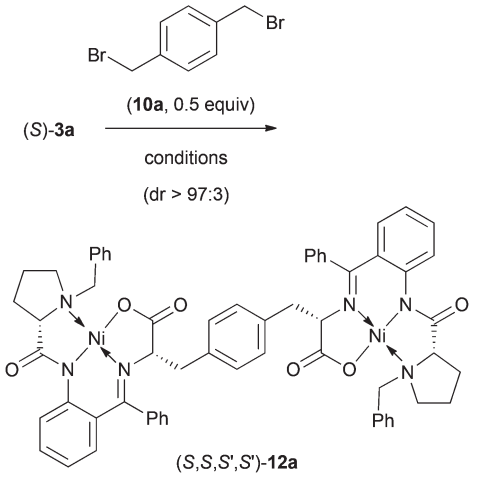
equilibration to the thermodynamically most stable diastereomer (*S*,*S*,*S*′,*S*′)-**12**. However, the full process afforded only moderate yields of compounds **12**, in contrast to our previously described reaction conditions for the monoalkylation procedure. In addition, purification of the reaction mixtures was required after every synthetic step. As we observed in our previous monoalkylation studies, these phase-transfer conditions would be less suitable for non-activated, alkyl dihalides; nevertheless, the access to aliphatic bis-AAs would be possible using allylic reagents such as **10d** followed by hydrogenation of the double bond.

In order to improve the stereochemical outcome of these bis-alkylation reactions, the use of homogeneous conditions was next investigated. Thus, a variety of bases, solvents and reaction temperatures were tested in the model reaction of Ni(II) complex (*S*)-**3a** with *para*-bis(bromomethyl)benzene (**10a**) (Table 2). Employing CH_2Cl_2 as a solvent, different bases only produced low yields of bis-alkylated product **12a** (entries 1–4). On the other hand, the use of DBU as a base in several organic solvents also led to unsatisfactory chemical yields (entries 5–8). Finally, NaOH produced the best results when the solvent was changed to MeCN and the reaction was conducted at 40 °C (entry 9), and the yield was further enhanced to 82% by heating the reaction at 60 °C (entry 10). It is worth mentioning that this bis-alkylation proceeded with excellent diastereoselectivity, as only the (*S*,*S*,*S*′,*S*′)-diastereomer of **12a** was observed within the detection limits of NMR.

After establishing this optimized protocol for the bis-alkylation of (*S*)-**3a** under homogeneous conditions, the substrate scope was next studied using different types of dibromide reagents. Thus, benzylic dibromides **10a** and **10b** provided bis-alkylated compounds **12a** and **12b**, respectively (Table 3, entries 1 and 2), in chemical yields substantially better than those previously achieved using phase-transfer conditions (Table 1, entries 1 and 2). Similarly, 2,6-disubstituted pyridine **10e** led to the corresponding bis-alkylation product **12e** albeit in somewhat lower yield (Table 3, entry 3). The method also enabled us to use non-activated alkyl dibromides, and hence the reaction of (*S*)-**3a** with 1,3-dibromopropane (**10f**) produced **12f** in similar yield to those obtained with benzylic reagents (Table 3, entry 4). Once again, bis-alkylation compounds **12a–b** and **12e–f** were obtained as single diastereomers.

As a final point, an example of free bis-AA was prepared from compound **12f**. Accordingly, the disassembly of the Ni(II) complex was carried out using standard conditions (6 N HCl, MeOH) and was followed by isolation of free (2*S*,6*S*)-diaminopimelic acid (**1**) using a cation-exchange resin (Scheme 1). The spectral features and optical rotation of (*S*,*S*)-**1** matched those of previously described data.[23]

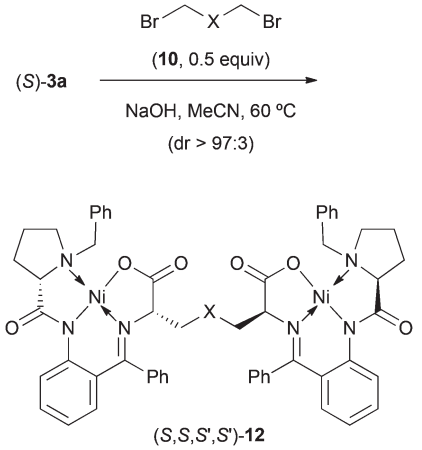
Table 2 Optimization of the bis-alkylation of complex (*S*)-**3a** under homogeneous conditions[a]

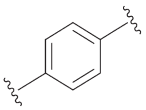
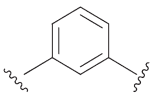
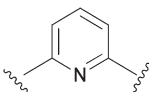
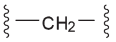


Entry	Base	Solvent	Temp. (°C)	Yield[b] (%)
1	DBU	CH_2Cl_2	23	26
2	NaH	CH_2Cl_2	23	22
3	*t*-BuOK	CH_2Cl_2	23	28
4	NaOH	CH_2Cl_2	23	35
5	DBU	MeCN	23	40
6	DBU	Acetone	23	23
7	DBU	THF	23	28
8	DBU	DMF	23	30
9	NaOH	MeCN	40	60
10	NaOH	MeCN	60	82[c]

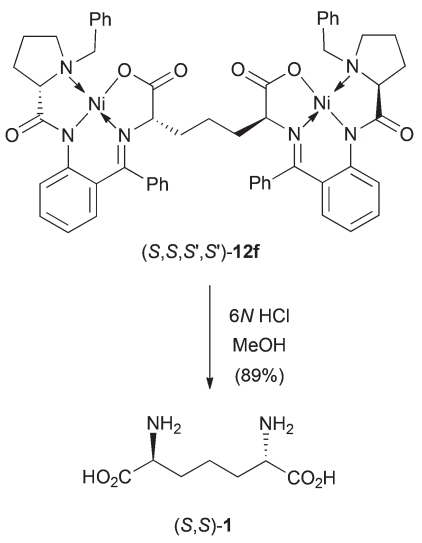
[a] Reactions were performed with 0.20 mmol of (*S*)-**3a**, 0.10 mmol of **10a** and 0.24 mmol of base in 10 mL of solvent for 2 h. [b] Conversion estimated by NMR. [c] Isolated yield.

Table 3 Bis-alkylations of complex (*S*)-**3a** under homogeneous conditions[a]



Entry	10	X	12	Yield[b] (%)
1	**10a**		**12a**	82
2	**10b**		**12b**	79
3	**10e**		**12e**	68
4	**10f**		**12f**	74

[a] Reactions were performed with 0.20 mmol of (*S*)-**3a**, 0.10 mmol of **10** and 0.24 mmol of NaOH in 10 mL of MeCN for 2 h at 60 °C. [b] Isolated yield.



Scheme 1

Conclusions

In summary, two different procedures have been studied for the diastereoselective bis-alkylation of the chiral nickel(II) complex (*S*)-**3a**. Heterogeneous, phase-transfer conditions allowed us to obtain the desired bis-alkylation products in a three-step procedure including two alkylation steps and base-catalysed equilibration of the resulting mixtures of diastereomers. However, the overall yield was not satisfactory and that led us to test also homogeneous conditions which proved to be more suitable using both activated and non-activated dibromides. The target bis-alkylation products were obtained in high yields and essentially as single diastereomers. The synthesis of final bis-AA, namely (2*S*,6*S*)-diaminopimelic acid (**1**), has been also carried out by easy disassembly of the corresponding bis-Ni(II) complex precursor.

Experimental

General methods

All reagents and solvents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on precoated silica gel plates, and visualization was carried out with UV light. Flash column chromatography was performed with the indicated solvents on silica gel (particle size 0.040–0.063 mm). ^1H and ^{13}C spectra were recorded on a

300 MHz or 400 MHz instrument. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (J) are given in hertz (Hz). The letters m, s, d, t, and br stand for multiplet, singlet, doublet, triplet, and broad, respectively. High-resolution mass spectra (HRMS) were recorded with an UPLC/Q-TOF MS system in the ESI mode.

General procedure for the monoalkylation of Ni(II) complex (*S*)-3a under PTC

30% aq. NaOH (8.0 mmol, 0.8 mL) was added to a solution of (*S*)-**3a** (100 mg, 0.20 mmol) and the corresponding dibromide **10** (0.30 mmol) in $(CH_2Cl)_2$ (0.8 mL), followed by TBAI (18 mg, 0.05 mmol). After stirring at room temperature for 1 h, the mixture was diluted with H_2O and extracted with CH_2Cl_2; the organic phases were then dried over Na_2SO_4 and concentrated at reduced pressure. Purification by column chromatography on silica (CH_2Cl_2–acetone, 5 : 1) afforded the corresponding monoalkylated product **11**.

Ni(II) complex of the Schiff's base of (*S*)-BPBP and (*S*)-2-amino-3-(4-(bromomethyl)phenyl)propanoic acid (11a). Yield: 92%. A 76 : 24 mixture of (*S*,*S*) and (*S*,*R*) diastereomers was obtained, and a pure fraction of (*S*,*S*)-**11a** was isolated for characterization purposes. $[\alpha]_D^{25}$ = +1175.0 (c = 0.020, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80–2.00 (m, 2H), 2.34–2.58 (m, 3H), 2.90 (dd, J = 13.8, 5.6 Hz, 1H), 3.12–3.21 (m, 2H), 3.33 (dd, J = 9.4, 7.0 Hz, 1H), 3.52 (d, J = 12.7 Hz, 1H), 4.29 (t, J = 5.0 Hz, 1H), 4.33 (d, J = 12.7 Hz, 1H), 4.54 (s, 2H), 6.68–6.71 (m, 2H), 6.81 (d, J = 7.6 Hz, 1H), 7.14–7.21 (m, 4H), 7.29–7.37 (m, 3H), 7.39–7.49 (m, 3H), 7.51–7.61 (m, 2 H), 8.02 (d, J = 7.0 Hz, 2H), 8.28 (d, J = 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 30.9, 33.0, 39.6, 56.9, 63.1, 70.2, 71.3, 120.6, 123.3, 126.0, 127.1, 127.8, 128.7, 128.9, 129.0, 129.5, 129.7, 130.8, 131.4, 132.4, 133.1, 133.5, 134.0, 136.2, 136.8, 142.8, 171.3, 178.3, 180.3. HRMS: calcd for $C_{35}H_{33}BrN_3NiO_3$ $[M + H]^+$ 680.1059, found 680.1050.

Ni(II) complex of the Schiff's base of (*S*)-BPBP and (*S*)-2-amino-3-(3-(bromomethyl)phenyl)propanoic acid (11b). Yield: 90%. A 83 : 17 mixture of (*S*,*S*) and (*S*,*R*) diastereomers was obtained, and a pure fraction of (*S*,*S*)-**11b** was isolated for characterization purposes. $[\alpha]_D^{25}$ = +1425.9 (c = 0.027, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74–1.88 (m, 1H), 1.95–2.05 (m, 1H), 2.30–2.58 (m, 3H), 2.93 (dd, J = 13.7, 6.0 Hz, 1H), 3.08–3.20 (m, 2H), 3.36 (t, J = 8.4 Hz, 1H), 3.49 (d, J = 12.6 Hz, 1H), 4.27 (dd, J = 5.9, 4.5 Hz, 1H), 4.31 (d, J = 12.7 Hz, 1H), 4.43 (d, J = 10.3 Hz, 1H), 4.48 (d, J = 10.3 Hz, 1H), 6.70 (d, J = 3.9 Hz, 2H), 6.89 (d, J = 7.6 Hz, 1H), 7.10–7.22 (m, 4H), 7.29–7.38 (m, 3H), 7.39–7.51 (m, 3H), 7.52–7.62 (m, 2H), 8.04 (d, J = 7.0 Hz, 2H), 8.28 (d, J = 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3, 30.6, 33.1, 39.8, 57.2, 63.2, 70.2, 71.2, 120.5, 123.3, 126.0, 127.1, 127.8, 128.1, 128.7, 128.9, 129.1, 129.8, 130.4, 131.0, 131.4, 132.4, 133.2, 133.5, 134.1, 136.4, 138.3, 142.8, 171.2, 178.3, 180.3. HRMS calcd for $C_{35}H_{33}BrN_3NiO_3$ $[M + H]^+$ 680.1059, found 680.1053.

Ni(II) complex of the Schiff's base of (*S*)-BPBP and (*S*)-2-amino-3-(4-(4′-(bromomethyl)phenyl)phenyl)propanoic acid (11c). Yield: 98%. A 79 : 21 inseparable mixture of (*S*,*S*) and (*S*,*R*) diastereomers was obtained. HRMS calcd for $C_{41}H_{37}BrN_3NiO_3$ $[M + H]^+$ 756.1372, found 756.1369.

Ni(II) complex of the Schiff's base of (*S*)-BPBP and (*S*)-*trans*-2-amino-6-bromohex-4-enoic acid (11d). Yield: 72%. An 86 : 14 inseparable mixture of (*S*,*S*) and (*S*,*R*) diastereomers was obtained. HRMS calcd for $C_{31}H_{31}BrN_3NiO_3$ $[M + H]^+$ 630.0902, found 630.0896.

General procedure for the bis-alkylation of Ni(II) complex (*S*)-3 under PTC

30% aq. NaOH (8.0 mmol, 0.8 mL) was added to a solution of (*S*)-**3a** (100 mg, 0.20 mmol) and the corresponding bromide **11** (0.10 mmol) in $(CH_2Cl)_2$ (0.8 mL), followed by TBAI (18 mg, 0.05 mmol). After stirring at room temperature for 2 h, the mixture was diluted with H_2O and extracted with CH_2Cl_2; the organic phases were then dried over Na_2SO_4 and concentrated at reduced pressure. The product was dissolved in MeOH (1 mL) and NaOMe (8 mg, 0.15 mmol) was added. Sat. aq. NH_4Cl was added after stirring at room temperature for 1.5 h. The reaction was extracted with CH_2Cl_2, and the organic phases were dried over Na_2SO_4 and concentrated at reduced pressure. Purification by column chromatography on silica (CH_2Cl_2–acetone, 1 : 2) afforded the corresponding bis-alkylated product **12**.

Bis-(Ni(II) complex of the Schiff's base of (*S*)-BPBP) and (2*S*,2′*S*)-3,3′-(1,4-phenylene)bis(2-aminopropanoic acid) (12a). Yield: 60%. Mp: 178–180 °C. $[\alpha]_D^{25}$ = +2430 (c 0.028, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94–2.00 (m, 4H), 2.15–2.19 (m, 3H), 2.72–2.77 (m, 3H), 2.91–3.02 (m, 5H), 3.20–3.24 (m, 3H), 3.42 (d, J = 12.4 Hz, 2H), 4.10 (s, 2H), 4.20 (d, J = 12.4 Hz, 2H), 6.04 (d, J = 7.2 Hz, 2H), 6.41 (d, J = 7.6 Hz, 2H), 6.51–6.55 (m, 3H), 6.92 (s, 2H), 7.07–7.15 (m, 6H), 7.28–7.33 (m, 4H), 7.43 (s, 4H), 7.52–7.53 (m, 2H), 7.96 (d, J = 7.6 Hz, 5H), 8.45 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 29.4, 30.1, 39.5, 56.8, 63.0, 69.7, 71.0, 120.1, 123.1, 124.7, 126.2, 127.0, 128.4, 128.5, 128.6, 129.3, 129.4, 129.9, 130.0, 131.1, 131.9, 132.9, 133.0, 133.3, 135.9, 142.7, 171.6, 178.0, 180.0. LRMS m/z found 1097 $[M + H]^+$. HRMS calcd for $C_{62}H_{56}N_6Ni_2O_6Na$ $[M + Na]^+$ 1119.2866, found 1119.2875.

Bis-(Ni(II) complex of the Schiff's base of (*S*)-BPBP) and (2*S*,2′*S*)-3,3′-(1,3-phenylene)bis(2-aminopropanoic acid) (12b). Yield: 58%. Mp: 190–192 °C. $[\alpha]_D^{25}$ = +2080 (c = 0.042, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90–1.97 (m, 4H), 2.13–2.18 (m, 2H), 2.71–2.77 (m, 2H), 2.94–3.02 (m, 4H), 3.19–3.24 (m, 2H), 3.39–3.49 (m, 6H), 4.09–4.22 (m, 4H), 6.03 (d, J = 7.5 Hz, 2H), 6.40 (d, J = 7.5 Hz, 2H), 6.50–6.55 (m, 2H), 6.92 (s, 1H), 7.03–7.21 (m, 7H), 7.30–7.56 (m, 12H), 7.96 (d, J = 7.2 Hz, 4H), 8.44 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 30.4, 39.7, 57.1, 63.3, 70.0, 71.3, 120.4, 123.4, 125.0, 126.5, 127.2, 128.6, 128.8, 129.7, 130.1, 130.3, 131.4, 132.2, 133.2, 133.6, 136.1, 142.9, 171.8, 178.2, 180.3. LRMS m/z found 1097 $[M + H]^+$. HRMS calcd for $C_{62}H_{56}N_6Ni_2O_6Na$ $[M + Na]^+$ 1119.2866, found 1119.2872.

Bis-(Ni(II) complex of the Schiff's base of (*S*)-BPBP) and (2*S*,2′*S*)-3,3′-((1,1′-biphenyl)-4,4′-diyl)bis(2-aminopropanoic acid) (12c). Yield: 58%. $[\alpha]_D^{25}$ = +1729.2 (*c* = 0.053, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88–2.00 (m, 2H), 2.20–2.50 (m, 8H), 2.95 (dd, *J* = 13.5, 5.2 Hz, 2H), 3.12–3.24 (m, 4H), 3.31 (t, *J* = 9.0 Hz, 2H), 3.50 (d, *J* = 12.6 Hz, 2H), 4.26–4.38 (m, 4H), 6.70 (d, *J* = 3.8 Hz, 4H), 6.92 (d, *J* = 6.8 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 4H), 7.26–7.37 (m, 10H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.54–7.62 (m, 4H), 7.67 (d, *J* = 7.6 Hz, 4H), 8.03 (d, *J* = 7.3 Hz, 4H), 8.29 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.0, 30.7, 39.5, 57.0, 63.2, 70.3, 71.4, 120.6, 123.4, 126.1, 127.2, 127.8, 128.8, 128.9, 129.1, 129.8, 131.1, 131.5, 132.4, 133.2, 133.5, 134.2, 135.1, 139.8, 142.9, 171.2, 178.5, 180.3. HRMS calcd for $C_{68}H_{61}N_6Ni_2O_6$ $[M + H]^+$ 1173.3360, found 1173.3395.

Bis-(Ni(II) complex of the Schiff's base of (*S*)-BPBP) and (2*S*,7*S*)-*trans*-2,7-diaminooct-4-enedioic acid (12d). Yield: 70%. $[\alpha]_D^{25}$ = +1816.2 (*c* = 0.037, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00–2.20 (m, 6H), 2.46–2.60 (m, 6H), 3.37–3.53 (m, 6H), 3.61 (d, *J* = 12.7 Hz, 2H), 3.98 (dd, *J* = 7.3, 3.8 Hz, 2H), 4.42 (d, *J* = 12.7 Hz, 2H), 5.95 (t, *J* = 3.9 Hz, 2H), 6.62–6.70 (m, 4H), 6.87 (d, *J* = 7.1 Hz, 2H), 7.13–7.27 (m, 6H), 7.36 (t, *J* = 7.6 Hz, 4H), 7.42–7.61 (m, 6H), 8.04 (d, *J* = 7.1 Hz, 4H), 8.21 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6, 29.2, 30.8, 37.8, 56.9, 63.0, 70.1, 120.7, 123.6, 126.2, 126.8, 127.5, 128.2, 128.8, 129.0, 129.8, 131.5, 132.2, 133.0, 133.3, 133.8, 142.4, 171.0, 178.6, 180.2. HRMS calcd for $C_{58}H_{55}N_6Ni_2O_6$ $[M + H]^+$ 1047.2890, found 1047.2911.

General procedure for the bis-alkylation of Ni(II) complex (*S*)-3a under homogeneous conditions

NaOH (9.6 mg, 0.24 mmol) was added to a solution of (*S*)-**3a** (100 mg, 0.20 mmol) and the corresponding dibromide **10** (0.10 mmol) in MeCN (10 mL) at room temperature, and then heated up to 60 °C for 2 h. The reaction was quenched by pouring the crude mixture over 30 mL of aq. sat. NH_4Cl. The suspension was extracted with EtOAc (3 times). The combined organic layers were dried with $MgSO_4$ and concentrated. Purification by column chromatography on silica (CH_2Cl_2–acetone, 1 : 2) afforded the corresponding bis-alkylated product **12**.

Bis-(Ni(II) complex of the Schiff's base of (*S*)-BPBP) and (2*S*,2′*S*)-3,3′-(1,4-phenylene)bis(2-aminopropanoic acid) (12a). Yield: 82%. Its spectral features were the same as above.

Bis-(Ni(II) complex of the Schiff's base of (*S*)-BPBP) and (2*S*,2′*S*)-3,3′-(1,3-phenylene)bis(2-aminopropanoic acid) (12b). Yield: 79%. Its spectral features were the same as above.

Bis-(Ni(II) complex of the Schiff's base of (*S*)-BPBP) and (2*S*,2′*S*)-3,3′-(pyridine-2,6-diyl)bis(2-aminopropanoic acid) (12e). Yield: 68%. Mp: 183–184 °C. $[\alpha]_D^{25}$ = +2280 (*c* 0.025, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83–1.90 (m, 3H), 2.00–2.20 (m, 7H), 2.85–2.90 (m, 2H), 2.98–3.01 (m, 2H), 3.08–3.12 (m, 2H), 3.19–3.23 (m, 2H), 3.50 (d, *J* = 12.8 Hz, 2H), 4.12–4.15 (m, 2H), 4.23 (d, *J* = 12.8 Hz, 2H), 6.35–6.37 (m, 2H), 6.49–6.51 (m, 2H), 6.59–6.93 (m, 2H), 6.91–6.95 (m, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.14–7.20 (m, 5H), 7.27–7.40 (m, 10H), 7.93 (d, *J* = 7.2 Hz, 4H), 8.43 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 30.6, 41.9, 56.7, 63.2, 70.1, 71.0, 120.1, 123.6, 125.6, 126.6, 127.4, 128.7, 128.8, 128.9, 129.3, 129.5, 131.5, 132.2, 133.1, 133.6, 134.0, 137.7, 142.9, 156.9, 172.0, 178.7, 180.0. LRMS *m*/*z* found 1098 $[M + H]^+$. HRMS calcd for $C_{61}H_{56}N_7Ni_2O_6$ $[M + H]^+$ 1098.2999, found 1098.3013.

Bis-(Ni(II) complex of the Schiff's base of (*S*)-BPBP) and (2*S*,6*S*)-2,6-diaminoheptanedioic acid (12f). Yield: 74%. Mp: 166–167 °C. $[\alpha]_D^{25}$ = +2360 (*c* 0.025, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 2H), 1.40–1.45 (m, 2H), 2.07–2.20 (m, 6H), 2.46–2.53 (m, 2H), 2.69–2.73 (m, 2H), 3.41–3.47 (m, 2H), 3.51–3.56 (m, 6H), 3.82–3.86 (m, 2H), 4.41 (d, *J* = 12.3 Hz, 2H), 6.58–6.68 (m, 4H), 6.82–6.85 (m, 2H), 7.12–7.22 (m, 6H), 7.32–7.34 (m, 8H), 7.51–7.52 (m, 2H), 8.05 (d, *J* = 7.5 Hz, 4H), 8.15 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 23.6, 30.6, 34.8, 57.1, 62.8, 69.7, 70.0, 120.3, 123.5, 126.0, 126.8, 126.9, 127.8, 128.2, 128.5, 128.9, 129.5, 131.2, 131.8, 132.8, 133.0, 133.4, 142.0, 170.0, 178.6, 180.2. LRMS *m*/*z* found 1034 $[M + H]^+$. HRMS calcd for $C_{57}H_{54}N_6Ni_2O_6Na$ $[M + Na]^+$ 1057.2709, found 1057.2712.

Synthesis of (2*S*,6*S*)-(+)-diaminopimelic acid (1)

A solution of 12f (25 mmol) in MeOH (50 mL) was added to a stirring solution of 6 N HCl in MeOH (90 mL, ratio 1 : 1, acid–MeOH) at 70 °C. Upon disappearance of the red color (about 5–10 min), the reaction mixture was evaporated in vacuum. Water (85 mL) was added and the resultant mixture was treated with an excess of concentrated NH_4OH and extracted with CH_2Cl_2. The organic extracts were dried over magnesium sulfate and evaporated in vacuum to give recovered (*S*)-BPBP (97% yield). The aqueous solution was evaporated in vacuum, dissolved in a minimum amount of water, loaded onto a Dowex-50 ion-exchange resin, and washed with H_2O followed by elution with a 10% NH_4OH solution to afford diaminopimelic acid (**1**) in 89% yield. Mp: 310–312 °C. $[\alpha]_D^{25}$ = +43.5 (*c* 1.2, 1 N HCl) (lit.[23a] data: $[\alpha]_D^{25}$ = +44.5 (*c* 0.95, 1 N HCl)). ^{1}H NMR (300 MHz, D_2O): δ 1.22–1.44 (m, 2H), 1.51–2.00 (m, 4H), 3.46–3.75 (m, 2H).

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Notes and references

1 (*a*) R. J. Cox, *Nat. Prod. Rep.*, 1996, **13**, 29–43; (*b*) R. J. Cox, A. Sutherland and J. C. Vederas, *Bioorg. Med. Chem.*, 2000, **8**, 843–871.
2 S. O. Andersen, *Biochim. Biophys. Acta*, 1964, **93**, 213–215.
3 B. K. Hubbard and C. T. Walsh, *Angew. Chem., Int. Ed.*, 2003, **42**, 730–765.

4 C. E. Schafmeister, J. Po and G. L. Verdine, *J. Am. Chem. Soc.*, 2000, **122**, 5891–5892.
5 L. Feliu and M. Planas, *Int. J. Pept. Res. Ther.*, 2005, **11**, 53–97.
6 For examples, see: (*a*) J. R. Del Valle and M. Goodman, *J. Org. Chem.*, 2004, **69**, 5946–5948; (*b*) O. Skaff, K. A. Jollife and C. A. Hutton, *J. Org. Chem.*, 2005, **70**, 7353–7363; (*c*) A. C. Tadd, K. Meinander, K. Luthman and E. A. A. Wallén, *J. Org. Chem.*, 2011, **76**, 673–675; (*d*) D. B. Kastrisnky, P. Kumar, G. A. Marriner and C. E. Barry III, *Synthesis*, 2012, 3043–3048.
7 For examples involving the asymmetric hydrogenation of an enamide precursor, see: (*a*) A. Ritzén, B. Basu, S. K. Chattopadhyay, F. Dossa and T. Frejd, *Tetrahedron: Asymmetry*, 1998, **9**, 503–512; (*b*) W. Wang, C. Xiong, J. Yang and V. J. Hruby, *Synthesis*, 2002, 94–98.
8 For reviews, see: (*a*) R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539–1560; (*b*) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013–3028; (*c*) J.-A. Ma, *Angew. Chem., Int. Ed.*, 2003, **42**, 4290–4299; (*d*) C. Nájera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584–4671; (*e*) V. A. Soloshonok and A. E. Sorochinsky, *Synthesis*, 2010, 2319–2344.
9 R. Fitzi and D. Seebach, *Tetrahedron*, 1988, **44**, 5277–5292.
10 (*a*) B. Lygo, J. Crosby and J. A. Peterson, *Tetrahedron Lett.*, 1999, **40**, 1385–1388; (*b*) B. Lygo, *Tetrahedron Lett.*, 1999, **40**, 1389–1392; (*c*) B. Lygo, J. Crosby and J. A. Peterson, *Tetrahedron*, 2001, **57**, 6447–6453.
11 (*a*) Y. N. Belokon, A. G. Bulychev, S. V. Vitt, Y. T. Struchkov, A. S. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. G. Ryzhov, L. A. Lysova, V. I. Bakhmutov and V. M. Belikov, *J. Am. Chem. Soc.*, 1985, **107**, 4252–4259; (*b*) Y. N. Belokon, V. I. Tararov, V. I. Maleev, T. F. Savel'eva and M. G. Ryzhov, *Tetrahedron: Asymmetry*, 1998, **9**, 4249–4252.
12 (*a*) H. Ueki, T. K. Ellis, C. H. Martin, T. U. Boettiger, S. B. Bolene and V. A. Soloshonok, *J. Org. Chem.*, 2003, **68**, 7104–7107; (*b*) H. Ueki, T. K. Ellis, C. H. Martin and V. A. Soloshonok, *Eur. J. Org. Chem.*, 2003, 1954–1957; (*c*) T. K. Ellis, H. Ueki and V. A. Soloshonok, *Tetrahedron Lett.*, 2005, **46**, 941–944; (*d*) V. A. Soloshonok, H. Ueki, T. K. Ellis, T. Yamada and Y. Ohfune, *Tetrahedron Lett.*, 2005, **46**, 1107–1110; (*e*) T. K. Ellis, H. Ueki, T. Yamada, Y. Ohfune and V. A. Soloshonok, *J. Org. Chem.*, 2006, **71**, 8572–8578; (*f*) V. A. Soloshonok, H. Ueki and T. K. Ellis, *Synlett*, 2009, 704–715.
13 (*a*) Y. N. Belokon, N. I. Chernoglazova, C. A. Kochetkov, N. S. Garbalinskaya and V. M. Belikov, *J. Chem. Soc., Chem. Commun.*, 1985, 171–172; (*b*) Y. N. Belokon, V. I. Bakhmutov, N. I. Chernoglazova, K. A. Kochetkov, S. V. Vitt, N. S. Garbalinskaya and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1988, 305–311; (*c*) V. P. Kukhar, Y. N. Belokon, N. Y. Svistunova, V. A. Soloshonok, A. B. Rozhenko and N. A. Kuzmina, *Synthesis*, 1993, 117–121; (*d*) V. A. Soloshonok, Y. N. Belokon, N. A. Kuzmina, V. I. Maleev, N. Y. Svistunova, V. A. Solodenko and V. P. Kukhar, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1525–1529; (*e*) Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, O. V. Larionov, S. R. Harutyunyan, S. Vyskocyl, M. North and H. B. Kagan, *Angew. Chem., Int. Ed.*, 2001, **40**, 1948–1951; (*f*) Y. N. Belokon, N. B. Bespalova, T. D. Churkina, I. Cisarova, M. G. Ezernitskaya, S. R. Harutyunyan, R. Hrdina, H. B. Kagan, P. Kocovsky, K. A. Kochetkov, O. V. Larionov, K. A. Lyssenko, M. North, M. Polasek, A. S. Peregudov, V. V. Prisyaznyuk and S. Vyskocyl, *J. Am. Chem. Soc.*, 2003, **125**, 12860–12871; (*g*) T. K. Ellis, C. H. Martin, G. M. Tsai, H. Ueki and V. A. Soloshonok, *J. Org. Chem.*, 2003, **68**, 6208–6214; (*h*) J. Wang, D. Lin, S. Zhou, X. Ding, V. A. Soloshonok and H. Liu, *J. Org. Chem.*, 2011, **76**, 684–687.
14 (*a*) V. A. Soloshonok, V. P. Kukhar, S. V. Galushko, N. Y. Svistunova, D. V. Avilov, N. A. Kuzmina, N. I. Raevski, Y. T. Struchkov, A. P. Pysarevsky and Y. N. Belokon, *J. Chem. Soc., Perkin Trans. 1*, 1993, 3143–3155; (*b*) V. A. Soloshonok, D. V. Avilov, V. P. Kukhar, V. I. Tararov, T. F. Saveleva, T. D. Churkina, N. S. Ikonnikov, K. A. Kochetkov, S. A. Orlova, A. P. Pysarevsky, Y. T. Struchkov, N. I. Raevsky and Y. N. Belokon, *Tetrahedron: Asymmetry*, 1995, **6**, 1741–1756; (*c*) V. A. Soloshonok, D. V. Avilov and V. P. Kukhar, *Tetrahedron: Asymmetry*, 1996, **7**, 1547–1550; (*d*) V. A. Soloshonok, D. V. Avilov and V. P. Kukhar, *Tetrahedron*, 1996, **52**, 12433–12442; (*e*) Y. N. Belokon, K. A. Kochetkov, N. S. Ikonnikov, T. V. Strelkova, S. R. Harutyunyan and A. S. Saghiyan, *Tetrahedron:Asymmetry*, 2001, **12**, 481–485.
15 (*a*) Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, S. A. Orlova, V. V. Smirnov and A. S. Chesnokov, *Mendeleev Commun.*, 1997, **7**, 137–138; (*b*) V. A. Soloshonok, C. Cai and V. J. Hruby, *Tetrahedron: Asymmetry*, 1999, **10**, 4265–4269; (*c*) V. A. Soloshonok, C. Cai and V. J. Hruby, *Tetrahedron Lett.*, 2000, **41**, 135–139; (*d*) V. A. Soloshonok, C. Cai and V. J. Hruby, *Tetrahedron Lett.*, 2000, **41**, 9645–9649; (*e*) V. A. Soloshonok, H. Ueki, R. Tiwari, C. Cai and V. J. Hruby, *J. Org. Chem.*, 2004, **69**, 4984–4990.
16 V. A. Soloshonok, D. V. Avilov, V. P. Kukhar, L. Van Meervelt and N. Mischenko, *Tetrahedron Lett.*, 1997, **38**, 4671–4674.
17 (*a*) V. A. Soloshonok, X. Tang, V. J. Hruby and L. Van Meervelt, *Org. Lett.*, 2001, **3**, 341–343; (*b*) V. A. Soloshonok, T. U. Boettiger and S. B. Bolene, *Synthesis*, 2008, 2594–2602.
18 (*a*) X. Tang, V. A. Soloshonok and V. J. Hruby, *Tetrahedron: Asymmetry*, 2000, **11**, 2917–2925; (*b*) V. A. Soloshonok, X. Tang and V. J. Hruby, *Tetrahedron*, 2001, **57**, 6375–6382.
19 W. Qiu, V. A. Soloshonok, C. Cai, X. Tang and V. J. Hruby, *Tetrahedron*, 2000, **56**, 2577–2582.
20 Y. N. Belokon, K. A. Kochetkov and D. A. Borkin, *Mendeleev Commun.*, 2003, **13**, 132–134.
21 (*a*) S. M. Taylor, T. Yamada, H. Ueki and V. A. Soloshonok, *Tetrahedron Lett.*, 2004, **45**, 9159–9162; (*b*) V. A. Soloshonok, T. Yamada, H. Ueki, A. M. Moore,

T. K. Cook, K. L. Arbogast, A. V. Soloshonok, C. H. Martin and Y. Ohfune, *Tetrahedron*, 2006, **62**, 6412–6419.

22 D. Houck, J. L. Aceña and V. A. Soloshonok, *Helv. Chim. Acta*, 2012, **95**, 2672–2679.

23 For previous syntheses of (2*S*,6*S*)-diaminopimelic acid, see: (*a*) R. M. Williams and C. Yuan, *J. Org. Chem.*, 1992, **57**, 6519–6527; (*b*) A. R. Jurgens, *Tetrahedron Lett.*, 1992, **33**, 4727–4730; (*c*) R. M. Williams and C. Yuan, *J. Org. Chem.*, 1994, **59**, 6190–6913; (*d*) R. C. Holcomb, S. Schow, S. Ayral-Kaloustian and D. Powell, *Tetrahedron Lett.*, 1994, **35**, 7005–7008; (*e*) Y. Gao, P. Lane-Bell and J. C. Vederas, *J. Org. Chem.*, 1998, **63**, 2133–2143; (*f*) F. A. Davis and V. Srirajan, *J. Org. Chem.*, 2000, **65**, 3248–3251; (*g*) F. Paradisi, G. Porzi, S. Rinaldi and S. Sandri, *Tetrahedron: Asymmetry*, 2000, **11**, 1259–1262; (*h*) P. N. Collier, I. Patel and R. J. K. Taylor, *Tetrahedron Lett.*, 2001, **42**, 5953–5394; (*i*) N. Hernández and V. S. Martín, *J. Org. Chem.*, 2001, **66**, 4934–4938; (*j*) E. G. Nolen, C. J. Fedorka and B. Blicher, *Synth. Commun.*, 2006, **36**, 1707–1713; (*k*) Y. Saito, Y. Yoshimura, H. Wakamatsu and H. Takahata, *Molecules*, 2013, **18**, 1162–1173. See also ref. 6*a*, *d* and 7*b*.