Achiral and α-Amino Acid Derived Dicationic Imidazoliophanes

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Abstract: Achiral and chiral imidazoliophanes were prepared by N-alkylation of chiral imidazole derivatives featuring an α-amino acid motif and subsequent double quarternization of the imidazole N3-position of the corresponding precyclophanes. Eight new optically pure imidazoliophanes were synthesized in good yields, whereas the molecular structure of one achiral analogue was confirmed by X-ray analysis.

Key words: cyclophanes, imidazoliophanes, amino acids, chiral pool, ligands

Annular α-amino-derived macrocycles steadily attract considerable attention of organic chemists due to their biological, catalytic and binding activities.[1] Furthermore, their structures represent tempting synthetic challenges. Among others, heterocyclic compounds incorporating an imidazole nucleus and diverse imidazole-based systems are investigated for their unique properties such as acid-base character, imidazole tautomerism, hydrogen bonding, coordination properties, or aromaticity.[2] Thus, imidazole-containing compounds have found wide applications as ionic liquids,[3] biologically active substances,[4] nitrogen ligands,[5] carbenes,[6] or π-conjugated scaffolds.[7] However, the most widely known naturally occurring imidazole derivative is certainly the essential α-amino acid – histidine. In general terms, application of the α-amino acids as enantiopure synthetic precursors for such systems seems to be advantageous because of their readily availability and low cost.[8] Thus, combination of the imidazole nucleus with an α-amino acid residue brings into the molecule chiral information and such optically active molecules have found application in asymmetric synthesis and chiral recognition.

Inspired by the molecule of histidine, we have recently reported the synthesis of optically active α-amino acid derivatives **1** (Figure 1).[9] The synthesis of **1** started from the corresponding α-amino acids, their stepwise transformation into the α-bromo ketones, and subsequent condensation with formamidine to afford target imidazoles **1**. More recently, we have used the Cbz-protected amines **2** as starting compounds for the construction of ligands **3** via Negishi and Suzuki–Miyaura cross-coupling reactions (Figure 1).[10] Thus, the amines **1/2** proved to be useful optically active precursors for further syntheses, which prompted us to report herein the synthesis of achiral and α-amino acid derived N-(di)substituted imidazoles **4/5** and **6** as well as imidazoliophanes **7–10**.

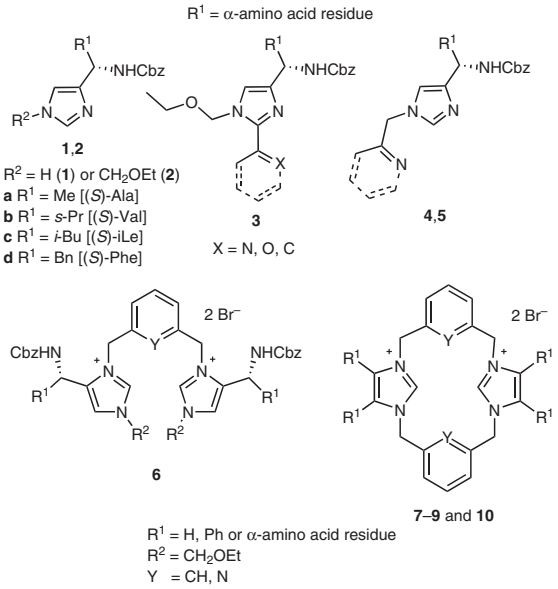

Figure 1 Recently synthesized α-amino acid-derived imidazoles **1–3** and newly proposed 1-substituted imidazoles **4/5** and 1,3-disubstituted imidazoles **6**, **7–9**, and **10**

Whereas the imidazole derivatives **1–3** and **4/5** are uncharged, 1,3-disubstituted (bridged) imidazoles **6** and **7–10** are dicationic. Although a variety of chiral cyclophanes with different structures and properties have already been reported,[11] imidazoliophanes featuring α-amino acid residues similar to **10** are quite rare.[12] However, (benz)imidazoliophanes have found wide application as model structures for anion recognition,[13] as antibacterially active substances,[14] and in particular, for N-heterocyclic carbenes with unique metal coordination abilities.[15]

The first attempted synthesis of imidazoles **4/5** started from imidazole **1b** derived from (*S*)-valine and 2-(bromomethyl)pyridine as an alkylating agent (Scheme 1). As expected, the reaction carried out in an acetonitrile/NaOH system[16] afforded two regioisomers **4b** and **5b** in a ratio of 3:1 and 74% overall yield. This is in contrast to our previous observations,[10] resulting in the ethoxymethylation of imidazoles **1** affording 1:1 mixture of both regioisomers

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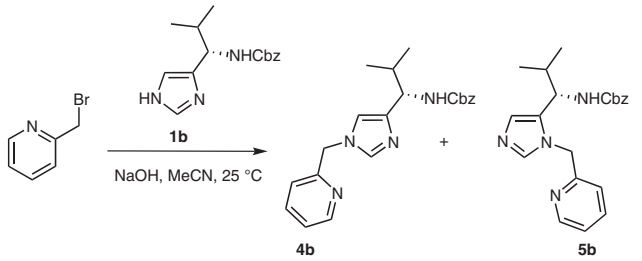
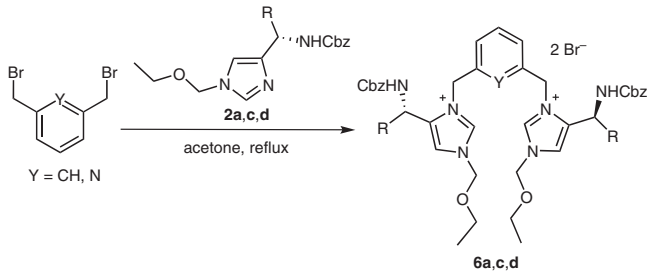


Scheme 1 The first attempted synthesis of N-substituted imidazole **4/5**

2. However, both regioisomers **4b/5b** could be separated by two consecutive chromatographic separations.

Delighted with such smooth reaction course, the second alkylation of imidazole was attempted at the N3 position. Thus, the quarternization of imidazoles **2** with either 1,3-bis(bromomethyl)benzene or 2,6-bis(bromomethyl)pyridine, carried out in acetone at reflux,[15f] afforded three 1,3-disubstituted dicationic imidazoles **6** in 51–67% yields (Scheme 2, Table 1).

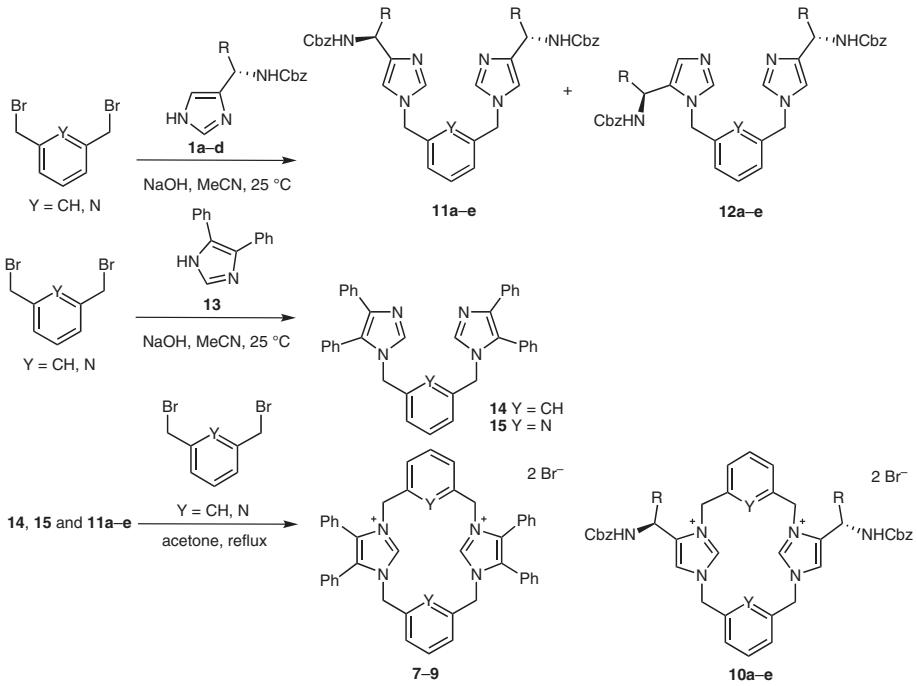


Scheme 2 Synthesis of 1,3-disubstituted imidazoles **6**

Table 1 Pincer type ligands **6**

Product	Starting imidazole	R	Y	Reaction time (days)	Yield (%)
6a	**2a**	Me/(*S*)-Ala	CH	6	67
6c	**2c**	*i*-Bu/(*S*)-Leu	N	7	51
6d	**2d**	Bn/(*S*)-Phe	N	7	59

With verified N-alkylation and subsequent quarternization of imidazoles **1** and **2** in this way, the synthesis of precyclophanes **11**, **12**, **14**, **15**, and imidazoliophanes **7–10** was conducted. The synthesis of precyclophanes **11**, **12,** **14**, and **15** started from chiral 4(5)-substituted imidazoles **1a–d** or the commercially available 4,5-diphenylimidazole (**13**). The N-alkylation of these imidazoles with either 1,3-bis(bromomethyl)benzene or 2,6-bis(bromomethyl)pyridine in a similar ways as for **4/5** afforded the desired precyclophanes in 61–92% yields. Since the starting chiral 4(5)-substituted imidazoles **1a–d** exhibit 1*H*-imidazole tautomerism, three different regioisomeric products are possible. However, the formation of only two of the three possible regioisomers was observed. The less sterically hindered regioisomers **11a–e** with 1,4-disubstituted imidazoles were isolated as the major products. A mixture of both regioisomers **11** (1,4-disubstituted) and **12** (1,4- and 1,5-disubstituted) could be separated by two consecutive column separations. Similar to **4b/5b**, the regioisomers **11/12** were isolated in approximate ratios of 3:1 (**a–c**) and 2:1 (**d**,**e**). It should be noted that the N-alkylation using THF instead of MeCN afforded generally lower yields (e.g., 43% conversion for **11a/12a**). Only the symmetric chiral precyclophanes **11a–d** along with achiral **14** and **15** were further used for the construction of



Scheme 3 The synthesis of precyclophanes **11**,**12/14**,**15** and imidazoliophanes **7–9/10**

Table 2 Precyclophanes **11**,**12/14**,**15** and Imidazoliophanes **7**–**9/10**

Product	Starting material	R	Y	Time (h)	Conversion (%)	Yields of **11/12** (%)
11a/12a	**1a**	Me/(*S*)-Ala	N	16	83[a]	58/19[b]
11b/12b	**1b**	*i*-Pr/(*S*)-Val	N	20	86[a]	62/22[b]
11c/12c	**1c**	*i*-Bu/(*S*)-Leu	N	20	73[a]	52/16[b]
11d/12d	**1d**	Bn/(*S*)-Phe	N	20	93[a]	55/32[b]
11e/12e	**1e**	Me/(*S*)-Ala	CH	72	94[a]	61/31[b]
14	**13**	–	CH	20	65	–
15	**13**	–	N	20	61	–
7	**14**	–	CH/CH	192	95	–
8	**14**	–	CH/N	120	84	–
9	**15**	–	N/N	48	88	–
10a	**11a**	Me/(*S*)-Ala	N/N	96	92	–
10b	**11b**	*i*-Pr/(*S*)-Val	N/N	192	82	–
10c	**11c**	*i*-Bu/(*S*)-Leu	N/N	96	85	–
10d	**11d**	Bn/(*S*)-Phe	N/N	144	98	–
10e	**11e**	Me/(*S*)-Ala	CH/CH	168	76	–

[a] Isolated mixture of regioisomers **11** and **12** (after first column chromatography).
[b] Isolated yields for pure regioisomers **11/12** (after second column chromatography).

the target imidazoliophanes. The quarternization reaction, carried out in anhydrous acetone at reflux (4–8 days), afforded the target imidazoliophanes **7**–**9** and **10** as pure white precipitates in 76–98% yields (Scheme 3, Table 2).

The assigned molecular structures of all the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy employing ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC, and HMBC methods. The 2D NMR analyses showed, in particular, interactions between the imidazole C4 and C5 and the adjacent CH and CH_2 groups (see Supporting Information). The prepared compounds also provided satisfactory elemental analyses and ESI-MS spectra. In addition, slow evaporation of a methanol solution of cyclophane **9** at 20 °C afforded crystals suitable for X-ray analysis. The ORTEP plots in Figure 2 confirmed the molecular structure and spatial arrangement of **9**. There are two symmetry independent molecules with C_i site symmetry. They show the same conformation with the exception of the phenyl

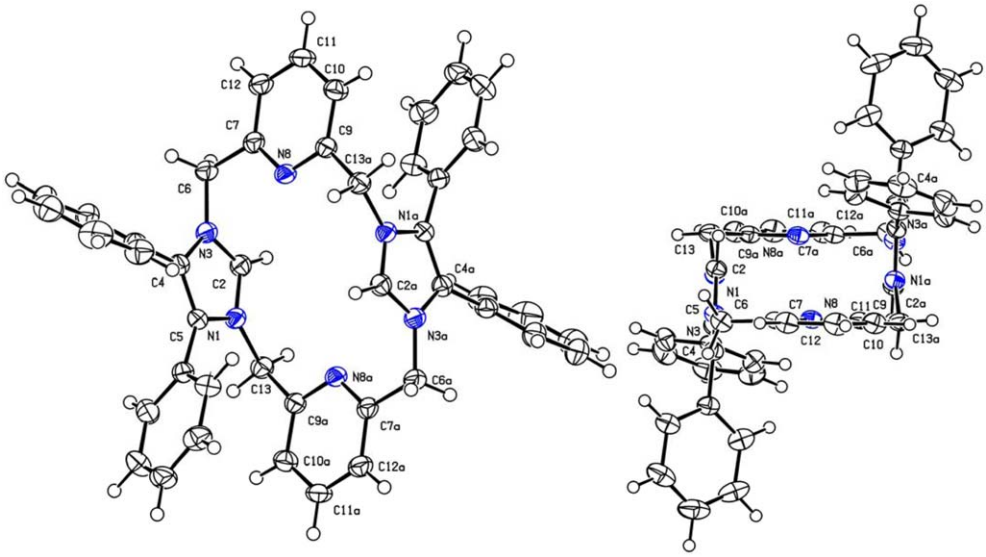


Figure 2 ORTEP drawing showing one of the two symmetry independent molecules in the crystal structure of **9** (left: upper view, right: side view) at 223 K. Ellipsoids are shown at 50% probability level. Solvent molecules (MeOH) and anions (Br^-) were omitted for clarity.

ring at C5, which differ by 40° in the torsion angle of the two ring planes. In general, imidazoliophanes in solution have been observed previously to exhibit interconversion between *syn* and *anti* conformations of the bridged imidazole moiety.[17] Although the measured ^{1}H NMR spectra of our cyclophanes showed an averaged signal for all the CH_2 groups adjacent to the imidazole, the crystal structure revealed the presence of only the *anti* conformation with the reversed parallel imidazole units and nearly vertically oriented bridging pyridine moieties.

In conclusion, the N-alkylation and subsequent quarternization of either achiral or α-amino acid-derived imidazoles have been reported. Following such synthetically simple methodology, pincer type ligands **6** and **11**,**12**/**14**,**15** (precyclophanes) as well as imidazoliophanes **7**–**9** and **10** were constructed. Overall, eight new optically pure imidazoliophanes were synthesized in good yields and the molecular structure of **9** was also confirmed by X-ray analysis.

Column chromatography was carried out with silica gel 60 (particle size 0.040–0.063 mm, 230-400 mesh; Merck) and commercially available solvents. TLC was conducted on aluminum sheets coated with silica gel 60 F_{254} obtained from Merck, with visualization by UV lamp (254 or 360 nm). Melting points (mp) were measured on a Büchi B-540 melting point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 360/500 MHz and 90/125 MHz, respectively, with Bruker AMX 360 or Bruker Avance 500 instruments at 25 °C. Chemical shifts are reported in ppm relative to TMS. Residual solvent signals in the ^{1}H and ^{13}C NMR spectra were used as an internal reference ($CDCl_3$: δ = 7.25 and 77.23, CD_3OD: δ = 3.31 and 49.15). Coupling constants (*J*) are given in Hz. The phenyl, pyridine, imidazole, and imidazolium protons and carbons are marked as Ar, Py, Im, and Im, respectively. Additional NMR techniques such as ^{13}C-APT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBC, and ^{1}H-^{13}C HMQC were used for regular signal assignment. Occasionally, ^{1}H and ^{13}C NMR spectra showed broad signals or two set of signals without estimated spin-spin interactions as a result of hindered rotation in carbamate function. In CD_3OD solution, a rapid H–D exchange of C2-H of the imidazole was observed for the target imidazoliophanes. Optical rotation values were measured on a Perkin–Elmer 341 instrument, concentration *c* is given in g/100 mL MeOH. The enantiomeric purity was verified by measuring ^{1}H NMR spectra with (*R*)-Mosher acid. The mass spectra were measured on a LC-MS Micromass Quattro Micro API (Waters) instrument with a direct input (ESI+, 0.5 mL stream MeOH, mass range 200–1100; Da and MassLynx software were used). Reagents and solvents were purchased from Aldrich or Penta and used without further purification. Anhyd acetone was freshly prepared prior to use. Starting imidazoles **1a–d** and **2** were synthesized according to the literature.[9,10]For the experimental details and characterization of compounds **4a**, **5b**, **6a**, **c**, **d**, **12a–e**, **14**, **15**, crystal data of **9**,[18] and representative NMR spectra, see Supporting Information.

Precyclophanes 11a–e; General Procedure

To a solution of imidazole **1a–d** (1.05 mmol) in MeCN (5 mL) was added 25% aq NaOH (0.5 mL) and the reaction mixture was stirred for 20 min. 1,3-Bis(bromomethyl)benzene or 2,6-bis(bromomethyl)pyridine (0.5 mmol) was added at once and the solution was stirred at 25 °C for the indicated time until TLC showed that the reaction was complete. The solvent was evaporated in vacuo, H_2O (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by two consecutive column chromatographic separations. The first separation (R_{f1}) afforded a pure mixture of both regioisomers that were separated on a second column (R_{f2}).

2,6-Bis{[4-(1-(1*S*)-benzyloxycarbonylaminoethyl)-1*H*-imidazol-1-yl]methyl}pyridine (11a)

The title compound was synthesized from **1a** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 172 mg (58%); yellowish oil; R_{f1} = 0.40 (silica gel; hexane–EtOAc–MeOH–NH_4OH, 3:5:1:0.1); R_{f2} = 0.36 (silica gel; acetone–MeOH, 10:1), $[\alpha]_D^{22}$ –13.6 (*c* 0.5, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (6 H, d, *J* = 6.7 Hz, 2 × C*H*$_3$CH), 4.81–4.84 (2 H, m, 2 × C*H*NH), 5.00–5.08 (8 H, m, 2 × C*H*$_2$Ph and 2 × C*H*$_2$Py), 5.80–5.86 (2 H, m, 2 × CHN*H*), 6.75 (2 H, 2 s, 2 × 5-H$_{im}$), 6.88 (2 H, d, *J* = 6.6 Hz, Py), 7.23–7.31 (10 H, m, Ar), 7.44 (2 H, s, 2 × 2-H$_{im}$), 7.58 (2 H, t, *J* = 7.7 Hz, Py).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (2 × *C*H$_3$CH), 45.2 (2 × CH), 52.2 (2 × Py*C*H$_2$), 66.5 (2 × Ph*C*H$_2$), 115.5 and 115.5 (2 × 5-C$_{im}$), 120.6 (2 × Py), 128.0 (Ar), 128.1 (Ar), 128.5 (Ar), 136.8 (Ar), 137.5 (2 × 2-C$_{im}$), 138.5 and 138.6 (Py), 144.6 (2 × 4-C$_{im}$), 155.9 (2 × Py), 155.0 and 156.1 (2 × C=O).

MS (ESI): *m*/*z* = 594 $(M)^+$, 616 $(M + Na)^+$.

Anal. Calcd for $C_{33}H_{35}N_7O_4$: C, 66.76; H, 5.94; N, 16.52. Found: C, 66.45; H, 6.06; N, 16.21.

2,6-Bis{[4-(1-(1*S*)-benzyloxycarbonylamino-2-methylpropyl)-1*H*-imidazol-1-yl]methyl}pyridine (11b)

The title compound was synthesized from **1b** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 201 mg (62%); pale yellow oil; R_{f1} = 0.42 (silica gel; hexane–EtOAc–MeOH–NH_4OH, 3:5:1:0.1); R_{f2} = 0.12 (silica gel; acetone–hexane, 2:1); $[\alpha]_D^{22}$ –27.6 (*c* 0.5, MeOH).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.81 [6 H, d, *J* = 6.4 Hz, (C*H*$_3$)$_2$CH], 0.92 [6 H, d, *J* = 6.4 Hz, (C*H*$_3$)$_2$CH], 2.09–2.13 [2 H, m, (CH$_3$)$_2$C*H*], 4.45–4.49 (2 H, m, 2 × C*H*NH), 4.99–5.08 (8 H, m, 2 × C*H*$_2$Py and 2 × C*H*$_2$Ph), 5.97 (2 H, d, *J* = 8.7 Hz, 2 × CHN*H*), 6.76 (2 H, s, 2 × 5-H$_{im}$), 6.82 (2 H, d, *J* = 7.4 Hz, Py), 7.25–7.29 (10 H, m, Ar), 7.48 (2 H, s, 2 × 2-H$_{im}$), 7.57 (1 H, t, *J* = 7.5 Hz, Py).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 18.8 [(*C*H$_3$)$_2$CH], 19.4 [(*C*H$_3$)$_2$CH], 33.0 [2 × (CH$_3$)$_2$*C*H], 52.3 (Py*C*H$_2$), 55.1 (2 × CH), 66.7 (2 × Ph*C*H$_2$), 116.6 (2 × 5-C$_{im}$), 120.4 (2 × Py), 128.0 (Ar), 128.0 (Ar), 128.6 (Ar), 136.9 (Ar), 137.5 (2 × 2-C$_{im}$), 138.7 (Py), 142.4 (2 × 4-C$_{im}$), 156.2 (2 × Py), 156.4 (2 × C=O).

MS (ESI): *m*/*z* = 650 $(M)^+$, 672 $(M + Na)^+$.

Anal Calcd for $C_{37}H_{43}N_7O_4$: C, 68.39; H, 6.67; N, 15.09. Found: C, 67.94; H, 7.11; N, 14.47.

2,6-Bis{[4-(1-(1*S*)-benzyloxycarbonylamino-3-methylbutyl)-1*H*-imidazol-1-yl]methyl}pyridine (11c)

The title compound was synthesized from **1c** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 176 mg (52%); pale yellow oil; R_{f1} = 0.33 (silica gel; hexane–EtOAc–MeOH–NH_4OH, 3:5:1:0.1); R_{f2} = 0.76 (silica gel; acetone–MeOH, 10:1); $[\alpha]_D^{22}$ –30.8 (*c* 0.5, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89–0.91 [12 H, m, 2 × (C*H*$_3$)$_2$CH], 1.54–1.56 [2 H, m, 2 × (CH$_3$)$_2$C*H*], 1.68–1.70 [4 H, m, 2 × (CH$_3$)$_2$CHC*H*$_2$], 4.74–4.79 (2 H, m, 2 × C*H*NH), 5.03 (4 H, ABq, *J* = 16.2 Hz, 2 × C*H*$_2$Py), 5.04–5.06 (4 H, m, 2 × C*H*$_2$Ph), 5.89 (2 H, d, *J* = 8.4 Hz, CHN*H*), 6.66 (2 H, s, 5-H$_{im}$), 6.83 (2 H, d, *J* = 7.6 Hz, Py), 7.25–7.28 (10 H, m, Ar), 7.45 (2 H, s, 2-H$_{im}$), 7.57–7.59 (1 H, m, Py).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5 [$(CH_3)_2CH$], 22.7 [$(CH_3)_2CH$], 24.9 [2 × $(CH_3)_2CH$], 44.7 [2 × $(CH_3)_2CHCH_2$], 47.6 (2 × CHNH), 52.2 (2 × PyCH_2), 66.5 (2 × PhCH_2), 116.0 (2 × 5-C_{im}), 120.5 (2 × Py), 127.5 (Ar), 128.1 (Ar), 128.5 (Ar), 136.8 (Ar), 137.7 (2 × 2-C_{im}), 138.6 (Py), 143.8 (2 × 4-C_{im}), 156.0 (2 × Py), 156.2 (2 × C=O).

MS (ESI): *m*/*z* = 678 $(M)^+$, 701 $(M + Na)^+$.

Anal. Calcd for $C_{39}H_{47}N_7O_4$: C, 69.10; H, 6.99; N, 14.46. Found: C, 68.68; H, 7.09; N, 14.07.

2,6-Bis{[4-(1-(1*S*)-benzyloxycarbonylamino-2-phenylethyl)-1*H*-imidazol-1-yl]methyl}pyridine (11d)

The title compound was synthesized from **1d** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 205 mg (55%); white solid; R_{f1} = 0.47 (silica gel; hexane–EtOAc–MeOH–NH_4OH, 3:5:1:0.1); R_{f2} = 0.59 (silica gel; acetone–MeOH, 10:1); mp 75–77 °C; $[\alpha]_D^{22}$ –29.4 (*c* 0.5, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.11–3.17 (2 H, m, PhCH_2CH), 3.23–3.28 (2 H, m, PhCH_2CH), 4.93–4.98 (6 H, m, 2 × PhCH_2CO and 2 × C*H*NH), 5.07 (4 H, ABq, *J* = 12.3 Hz, 2 × CH_2Py), 6.44 (2 H, d, *J* = 7.5 Hz, 2 × CHN*H*), 6.49 (2 H, s, 2 × 5-H_{im}), 6.55 (2 H, d, *J* = 7.5 Hz, Py), 7.03–7.07 (4 H, m, Ar), 7.10–7.14 (6 H, m, Ar), 7.23–7.27 (10 H, m, Ar), 7.42 (2 H, s, 2 × 2-H_{im}), 7.46 (1 H, t, *J* = 7.8 Hz, Py).

^{13}C NMR (125 MHz, CD_3OD): δ = 30.8 (2 × PhCH_2CH), 52.6 (2 × *C*HNH), 52.9 (2 × CH_2Py), 67.3 (2 × PhCH_2O), 118.2 (2 × 5-C_{im}), 121.9 (2 × Py), 127.4 (Ar), 128.7 (Ar), 128.9 (Ar), 129.3 (Ar), 129.5 (Ar), 130.6 (Ar), 138.4 (Ar), 139.0 (2 × 2-C_{im}), 139.7 (Ar), 139.9 (Py), 143.8 (2 × 4-C_{im}), 157.6 (2 × Py), 158.0 (2 × C=O).

MS (ESI): *m*/*z* = 746 $(M)^+$, 769 $(M + Na)^+$.

Anal. Calcd for $C_{45}H_{43}N_7O_4$: C, 72.46; H, 5.81; N, 13.15. Found: C, 72.57; H, 5.90; N, 13.29.

1,3-Bis[4-(1-(1*S*)-benzyloxycarbonylaminoethyl)-1*H*-imidazol-1-yl]benzene (11e)

The title compound was synthesized from **1a** and 1,3-bis(bromomethyl)benzene following the general procedure; yield: 181 mg (61%); pale yellow oil; R_{f1} = 0.38 (silica gel; hexane–EtOAc–MeOH–NH_4OH, 3:5:1:0.1); R_{f2} = 0.08 (silica gel; acetone–hexane, 2:1); $[\alpha]_D^{22}$ –15.6 (*c* 0.5, MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (6 H, d, *J* = 5.5 Hz, 2 × CH_3CH), 4.82–4.85 (2 H, m, 2 × C*H*NH), 4.90–4.91 (4 H, m, 2 × CH_2N_{im}), 5.04 (4 H, ABq, *J* = 12.1 Hz, 2 × CH_2Ph), 6.12 (2 H, d, *J* = 8.1 Hz, 2 × CHN*H*), 6.69 (2 H, s, 2 × 5-H_{im}), 6.79 (1 H, d, *J* = 11.2 Hz, Ar), 7.03 (2 H, d, *J* = 7.1 Hz, Ar), 7.23–7.28 (11 H, m, Ar), 7.39 (2 H, s, 2 × 2-H_{im}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4 (2 × CH_3CH), 45.0 (2 × CH), 50.2 (2 × $N_{im}CH_2$), 66.2 (2 × PhCH_2), 115.0 (2 × 5-C_{im}), 125.9 (Ar), 127.0 (Ar), 127.8 (Ar), 127.9 (Ar), 128.3 (Ar), 129.5 (Ar), 136.6 (Ar), 137.0 (Ar), 137.1 (2 × 2-C_{im}), 144.5 (2 × 4-C_{im}), 155.7 (C=O).

MS (ESI): *m*/*z* = 593 $(M)^+$, 616 $(M + Na)^+$.

Anal. Calcd for $C_{34}H_{36}N_6O_4$: C, 68.90; H, 6.12; N, 14.18. Found: C, 68.52; H, 6.53; N, 13.78.

Imidazoliophanes 7–9 and 10a–e; General Procedure

To a solution of precyclophane (0.5 mmol) in anhyd acetone (15 mL) was added 1,3-bis(bromomethyl)benzene or 2,6-bis(bromomethyl)pyridine (0.5 mmol) at once and the reaction mixture was heated at reflux under argon atmosphere for the indicated time. After completion of the reaction as monitored on TLC (silica gel, hexane–EtOAc–MeOH–NH_4OH, 3:5:1:0.1), the imidazoliophane was collected by filtration, thoroughly washed with EtOAc–hexane (3:1), and dried in vacuo.

Imidazoliophane 7

The title compound was synthesized from precyclophane **14** and 1,3-bis(bromomethyl)benzene following the general procedure; yield: 382 mg (95%); white solid; mp 290 °C (dec.).

^{1}H NMR (360 MHz, CD_3OD–D_2O): δ = 5.86 (8 H, s, 4 × CH_2N), 6.90 (4 H, d, *J* = 7.7 Hz, Ar), 7.13 (2 H, t, *J* = 7.5 Hz, Ar), 7.20 (8 H, d, *J* = 7.1 Hz, Ar), 7.36 (8 H, t, *J* = 7.8 Hz, Ar), 7.46 (4 H, t, *J* = 7.5 Hz, Ar), 7.52 (2 H, s, Ar), 9.80 (2 H, s, 2 × 2-H_{im}).

^{13}C NMR (90 MHz, CD_3OD–D_2O): δ = 52.2 (4 × *C*H_2N), 126.1 (Ar), 126.7 (Ar), 130.3 (Ar), 130.4 (Ar), 130.7 (Ar), 131.9 (Ar), 132.4 (Ar), 134.4 (Ar), 136.9 (Ar); one signal is missing.

MS (ESI): *m*/*z* = 725/727 (1:1) $(M–Br)^+$, 645 $(M – 2\ Br + 1)^+$, 323.2 $(M – 2\ Br)^{2+}$.

Anal. Calcd for $C_{46}H_{38}Br_2N_4$: C, 68.49; H, 4.75; Br, 19.81; N, 6.95. Found: C, 68.45; H, 4.98; Br, 19.64; N, 6.93.

Imidazoliophane 8

The title compound was synthesized from precyclophane **14** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 338 mg (84%); white solid; mp 290 °C (dec.).

^{1}H NMR (500 MHz, CD_3OD–D_2O): δ = 5.42–5.63 (8 H, m, 4 × CH_2N), 6.87 (1 H, s, Ar), 6.93 (2 H, d, *J* = 7.3 Hz, Ar), 7.01 (2 H, d, *J* = 7.6 Hz, Ar), 7.04–7.08 (6 H, m, Ar), 9.13 (3 H, t, *J* = 7.1 Hz, Ar), 7.25–7.32 (9 H, m, Ar), 7.40–7.44 (3 H, m, Ar), 7.59 (1 H, t, *J* = 7.3 Hz, Ar), 9.70 (2 H, s, 2 × 2-H_{im}).

^{13}C NMR (90 MHz, CD_3OD–D_2O): δ = 51.9 (2 × CH_2N), 53.2 (2 × CH_2N), 123.8 (Ar), 124.6 (Ar), 125.6 (Ar), 125.8 (Ar), 129.2 (Ar), 130.2 (Ar), 130.7 (Ar), 131.8 (Ar), 131.8 (Ar), 132.1 (Ar), 133.6 (Ar), 133.7 (Ar), 134.2 (Ar), 132.3 (Ar), 136.8 (Ar), 138.8 (Ar), 139.6 (Py), 154.4 (Py).

MS (ESI): *m*/*z* = 726/728 (1:1) $(M – Br)^+$, 646 $(M – 2\ Br + 1)^+$, 323.6 $(M – 2\ Br)^{2+}$.

Anal. Calcd for $C_{45}H_{37}Br_2N_5$: C, 66.92; H, 4.62; Br, 19.79; N, 8.67. Found: C, 67.11; H, 4.77; Br, 19.43; N, 8.69.

Imidazoliophane 9

The title compound was synthesized from precyclophane **15** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 355 mg (88%); white solid; mp 290 °C (dec.).

^{1}H NMR (360 MHz, CD_3OD–D_2O): δ = 5.62 (8 H, s, 4 × CH_2N), 7.07–7.14 (12 H, m, Ar), 7.31 (8 H, t, *J* = 7.7 Hz, Ar), 7.44 (4 H, t, *J* = 7.4 Hz, Ar), 7.59 (2 H, t, *J* = 7.7 Hz, Ar), 9.55 (2 H, s, 2 × 2-H_{im}).

^{13}C NMR (90 MHz, CD_3OD–D_2O): δ = 52.9 (4 × CH_2N), 123.8 (Ar), 126.0 (Ar), 130.1 (Ar), 131.7 (Ar), 131.7 (Ar), 133.6 (Ar), 139.3 (Ar), 139.6 (Ar), 154.3 (Py).

MS (ESI): *m*/*z* = 727/729 (1:1) $(M – Br)^+$, 647 $(M – 2\ Br + 1)^+$, 323.9 $(M – 2\ Br)^{2+}$.

Anal. Calcd for $C_{44}H_{36}Br_2N_6$: C, 65.36; H, 4.49; Br, 19.76; N, 10.39. Found: C, 65.32; H, 4.73; Br, 19.74; N, 10.21.

Imidazoliophane 10a

The title compound was synthesized from precyclophane **11a** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 394 mg (92%); white solid; mp 154–157 °C; $[\alpha]_D^{22}$ –9.6 (*c* 1, MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ = 1.41 (3 H, d, *J* = 6.9 Hz, CH_3CH), 1.44 (3 H, d, *J* = 6.9 Hz, CH_3CH), 4.70–4.71 (1 H, q, *J* = 6.8 Hz, C*H*NH), 4.78–4.79 (1 H, q, *J* = 6.8 Hz, C*H*NH), 4.97–4.99 (4 H, m, CH_2Ph), 5.49–5.57 (8 H, m, 4 × CH_2Py), 7.25–7.36 (10 H, m, Ar), 7.44 (2 H, t, *J* = 7.5 Hz, Py), 7.59 (2 H, s, 2 × 5-H_{im}),

7.62–7.65 (2 H, m, Py), 7.74–7.89 (1 H, m, Py), 7.97 (1 H, t, J = 7.7 Hz, Py), 9.04 (2 H, s, 2 × 2-H_{im}).

^{13}C NMR (90 MHz, CD_3OD): δ = 20.1 (2 × CH_3CH), 42.6 and 42.7 (2 × CHNH), 52.3 (2 × PyCH_2), 54.5 (2 × PyCH_2), 67.8 (2 × PhCH_2), 122.0 and 122.1 (2 × 5-C_{im}), 124.1 (2 × Py), 124.5 (2 × Py), 129.0 and 129.1 (Ar), 129.3 (Ar), 129.7 (Ar), 138.2 and 138.5 (Ar), 139.5 and 139.6 (2 × 4-C_{im}), 140.1 and 141.1 (2 × 2-C_{im}), 140.3 and 140.3 (2 × Py), 154.2 (2 × Py), 154.5 and 154.6 (2 × Py), 157.5 (2 × C=O).

MS (ESI): m/z = 777–779 (1:1) (M – Br)$^+$, 697 (M – 2 Br + 1)$^+$, 349.3 (M – 2 Br)$^{2+}$.

Anal. Calcd for $C_{40}H_{42}Br_2N_8O_4$: C, 55.95; H, 4.93; Br, 18.61; N, 13.05. Found: C, 55.59; H, 5.15; Br, 18.24; N, 12.57.

Imidazoliophane 10b

The title compound was synthesized from precyclophane **11b** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 374 mg (82%); mp 147–151 °C; $[\alpha]_D^{22}$ –10.5 (c 1, MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ = 0.53 [3 H, d, J = 5.8 Hz, (CH_3)$_2$CH], 0.69 [3 H, d, J = 5.6 Hz, (CH_3)$_2$CH], 0.88–0.92 [6 H, m, (CH_3)$_2$CH], 2.01–2.06 [2 H, m, (CH_3)$_2$CH], 4.29–4.32 (2 H, m, 2 × CHNH), 5.00–5.06 (4 H, m, 2 × CH_2Ph), 5.50–5.67 (8 H, m, 4 × CH_2Py), 7.32–7.36 (10 H, m, Ar), 7.53 (1 H, s, 5-H_{im}), 7.59–7.60 (2 H, m, Py), 7.64–7.65 (2 H, m, Py and 5-H_{im}), 7.70–7.78 (1 H, m, Py), 7.57 (1 H, t, J = 7.0 Hz, Py), 9.04 (2 H, s, 2 × 2-H_{im}).

^{13}C NMR (90 MHz, CD_3OD): δ = 19.0 and 19.1 [(CH_3)$_2$CH], 20.5 and 20.6 [(CH_3)$_2$CH], 32.9 and 33.0 [2 × (CH_3)$_2$CH], 52.4 and 52.5 (2 × PyCH_2), 52.9 (2 × CH), 54.4 and 54.6 (2 × PyCH_2), 68.0 (2 × PhCH_2), 122.0 and 122.5 (2 × 5-C_{im}), 124.5 (2 × Py), 124.7 (2 × Py), 129.0 (Ar), 129.4 (Ar), 129.7 (Ar), 137.6 and 138.0 (Ar), 139.0 and 139.1 (2 × 4-C_{im}), 140.3 (2 × 2-C_{im}), 140.5 (2 × Py), 154.3 (2 × Py), 154.4 (2 × Py), 154.5 (2 × Py), 158.3 and 158.4 (2 × C=O).

MS (ESI): m/z = 833/835 (1:1) (M – Br)$^+$, 753 (M – 2 Br + 1)$^+$, 377.1 (M – 2 Br)$^{2+}$.

Anal. Calcd for $C_{44}H_{50}Br_2N_8O_4$: C, 57.77; H, 5.51; Br, 17.47; N, 12.25. Found: C, 57.40; H, 5.43; Br, 17.15; N, 11.67.

Imidazoliophane 10c

The title compound was synthesized from precyclophane **11c** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 399 mg (85%); white solid; mp 125–128 °C; $[\alpha]_D^{22}$ –28.5 (c 1, MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ = 0.78–0.91 [12 H, m, 2 × (CH_3)$_2$CH], 1.54–1.58 [4 H, m, 2 × (CH_3)$_2$CHCH_2], 2.02–2.06 [2 H, m, 2 × (CH_3)$_2$CH], 4.67–4.70 (2 H, m, 2 × CHNH), 4.92–5.02 (4 H, m, 2 × CH_2Ph), 5.53–5.64 (8 H, m, 8 × CH_2Py), 7.30–7.38 (12 H, m, Ar and Py), 7.53–7.70 (4 H, m, Py and 2 × 5-H_{im}), 7.78–7.99 (2 H, m, Py), 9.03 (2 H, s, 2 × 2-H_{im}).

^{13}C NMR (125 MHz, CD_3OD): δ = 21.8 and 23.4 [2 × (CH_3)$_2$CH], 25.8 [2 × (CH_3)$_2$CH], 43.4 [2 × (CH_3)$_2$CHCH_2], 44.9 (2 × CHNH), 52.4 (2 × PyCH_2), 54.6 (2 × PyCH_2), 67.8 (2 × PhCH_2), 121.8 and 122.2 (2 × 5-C_{im}), 124.2 (2 × Py), 124.5 and 124.6 (2 × Py), 128.9 (Ar), 129.3 (Ar), 129.7 (Ar), 138.1 and 138.3 (Ar), 139.3 (2 × 4-C_{im}), 140.1 (2 × 2-C_{im}), 140.4 (2 × Py), 154.2 (2 × Py), 154.3 and 154.5 (2 × Py), 158.0 (2 × C=O).

MS (ESI): m/z = 861/863 (1:1) (M – Br)$^+$, 781 (M – 2 Br + 1)$^+$, 391.3 (M – 2 Br)$^{2+}$.

Anal. Calcd for $C_{46}H_{54}Br_2N_8O_4$: C, 58.60; H, 5.77; Br, 16.95; N, 11.89. Found: C, 58.44; H, 5.98; Br, 16.67; N, 11.57.

Imidazoliophane 10d

The title compound was synthesized from precyclophane **11d** and 2,6-bis(bromomethyl)pyridine following the general procedure; yield: 494 mg (98%); mp 148–151 °C; $[\alpha]_D^{22}$ –44.0 (c 0.1, MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ = 3.06–3.11 (4 H, m, 2 × PhCH_2CH), 4.83 (4 H, ABq, J = 12.5 Hz, 2 × PhCH_2CO), 4.91–4.95 (2 H, m, 2 × CHNH), 5.38 (4 H, ABq, J = 16.5 Hz, 2 × CH_2^aPy), 5.50–5.56 (4 H, m, CH_2^bPy), 7.07–7.10 (4 H, m, Ar), 7.13–7.16 (4 H, m, Ar), 7.18–7.21 (6 H, m, Ar), 7.26–7.28 (6 H, m, Ar), 7.46 (2 H, d, J = 6.3 Hz, Py), 7.65 (2 H, d, J = 7.3 Hz, Py), 7.8 (2 H, s, 2 × 5-H_{im}), 7.85 (1 H, t, J = 7.6 Hz, Py), 8.0 (1 H, t, J = 7.5 Hz, Py), 8.87 (2 H, s, 2 × 2-H_{im}).

^{13}C NMR (125 MHz, CD_3OD): δ = 40.5 (2 × PhCH_2CH), 48.4 (2 × CHNH), 52.3 (2 × CH_2Py^a), 54.6 (2 × CH_2Py^b), 67.7 (2 × PhCH_2CO), 122.3 and 122.6 (2 × 5-C_{im}), 124.2 (2 × Py), 124.5 (2 × Py), 128.2 (Ar), 128.8 (Ar), 129.2 (Ar), 129.5 (Ar), 129.6 (Ar), 129.7 (Ar), 130.6 (Ar), 137.4 (2 × 4-C_{im}), 137.9 (Ar), 138.0 (Ar), 140.2 (2 × 2-C_{im}), 140.5 (2 × Py), 154.0 (2 × Py), 154.5 (2 × Py), 157.8 (2 × C=O).

MS (ESI): m/z = 929/931 (1:1) (M – Br)$^+$, 849 (M – 2 Br + 1)$^+$, 425.2 (M – 2 Br)$^{2+}$.

Anal. Calcd for $C_{52}H_{50}Br_2N_8O_4$: C, 61.79; H, 4.99; Br, 15.81; N, 11.09. Found: C, 61.44; H, 5.36; Br, 15.52; N, 10.71.

Imidazoliophane 10e

The title compound was synthesized from precyclophane **11e** and 1,3-bis(bromomethyl)benzene following the general procedure; yield: 325 mg (76%); white solid; mp 160–170 °C; $[\alpha]_D^{22}$ –5.7 (c 0.5, MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ = 1.37 (3 H, d, J = 6.7 Hz, CH_3CH), 1.45 (3 H, d, J = 6.8 Hz, CH_3CH), 4.70–4.73 (1 H, q, J = 7.0 Hz, CHNH), 4.78–4.82 (1 H, q, J = 6.9 Hz, CHNH), 4.90–5.00 (4 H, m, 2 × CH_2Ph), 5.37–5.50 (8 H, m, 4 × CH_2Ph), 6.63–6.66 (1 H, m, Ph), 7.06–7.08 (1 H, m, Ph), 7.26–7.30 (10 H, m, Ar), 7.39–7.43 (3 H, m, Ph), 7.50–7.54 (1 H, m, Ph), 7.57–7.60 (2 H, m, Ph), 7.68 (1 H, s, 5-H_{im}), 7.71 (1 H, s, 5-H_{im}), 9.32 (1 H, s, 2-H_{im}), 9.40 (1 H, s, 2-H_{im}).

^{13}C NMR (125 MHz, CD_3OD): δ = 19.9 and 20.0 (2 × CH_3CH), 42.6 (2 × CHNH), 51.5 (2 × PhCH_2), 53.7 (2 × PhCH_2), 67.8 (2 × PhCH_2), 122.4 (2 × 5-C_{im}), 124.7 and 125.0 (2 × Ph), 126.5 and 126.6 (2 × Ph), 128.8 (Ar), 129.2 (Ar), 129.7 (Ar), 129.8 (Ar), 129.9 (Ar), 130.6 (Ar), 130.9 (Ar), 131.2 (Ar), 136.2 and 136.5 (Ar), 137.4 (Ar), 138.1 and 138.2 (Ar), 139.0 and 139.1 (2 × 2-C_{im}), 157.5 (2 × C=O).

MS (ESI): m/z = 775/777 (1:1) [M$^+$ – Br].

Anal. Calcd for $C_{42}H_{44}Br_2N_6O_4$: C, 58.89; H, 5.18; Br, 18.66; N, 9.81. Found: C, 58.61; H, 5.36; Br, 18.32; N, 9.66.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(18) CCDC 757647 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033, E-mail: deposit@ccdc.cam.ac.uk].