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C_2-Symmetric hemiaminal ethers and diamines: new ligands for copper-catalyzed desymmetrization of *meso*-1,2-diols and asymmetric Henry reactions

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ABSTRACT

The synthesis of novel, enantiomerically pure C_2-symmetrical hemiaminal ethers and diamines containing piperazine core is presented. The key steps of the synthesis involve the dimerization of an in situ generated α-amino aldehyde into the corresponding cyclic bis-hemiaminal, followed by dehydration in the presence of a base to give a 7-oxa-2,5-diaza-bicyclo[2.2.1]heptane derivative, which can be regarded as a bicyclic bis-hemiaminal inner ether. These compounds represent a new class of molecule, with a structure unambiguously established for the first time. Finally, sodium triacetoxy-borohydride reduction gave the corresponding diamines. Both classes of compounds, new diamines and hemiaminal ethers, were shown to be good ligands for the copper(II)-catalyzed desymmetrization of *meso*-diols (up to 87% ee) and Henry reactions (up to 84% ee).

1. Introduction

Chiral bis-tertiary diamines, both natural and synthetic, are widely used in catalytic asymmetric synthesis as organocatalysts[1a] or ligands[1b] in catalytic processes based on metal complexes. They have been successfully applied in diverse asymmetric processes, for example, Henry reactions,[2] desymmetrization of *meso*-diols,[3] deprotonations,[4] oxidative couplings,[5] cyclopropanations,[6] and many others. The rapid development of this field over the past two decades has created a rapidly growing need for new chiral amines. Due to a very limited number of readily available natural compounds that are able to catalyze stereoselective reactions, many research groups have concentrated on the design and synthesis of novel diamine ligands.

From the large number of reported bis-tertiary diamines, the derivatives of piperazine have been shown to be very effective chiral inducers[3c,7a–j] (Fig. 1). Furthermore, a facile synthesis of diamines of this class can provide a vast array of compounds containing two stereogenic centers within the piperazine ring C_2-symmetrical **1**–**4**,[3c,7b,e,j] four centers **6**[7c] or only one center **8**, and **9**.[7a] Alternatively, the asymmetric center can also be positioned at the nitrogen substituent **5** and **7**.[7f–i]

Herein we report the synthesis of novel C_2-symmetrical diamines that contain a piperazine core and their application in the copper-catalyzed desymmetrization of *meso*-1,2-diols and asymmetric Henry reaction.

2. Results and discussion

2.1. Synthesis of C_2-symmetrical diamines

As part of a current project aimed at the synthesis of isoquinoline alkaloids, we have developed a stereoselective method for the preparation of enantiomerically pure dihydroxy-hexahydro-pyrrolo-iso-quinolines with a quaternary carbon stereocenter, starting from L-tartaric acid.[8a,b] Further studies have shown that diols of type **10** undergo sodium periodate glycolic cleavage to give a diastereomeric mixture of cyclic hemiacetals **11**[8c] (Scheme 1). We have shown, using phenyl derivative **11a** as an example, that base hydrolysis of the nitrogen substituent in the product of glycolic cleavage led to the intermediary α-aminoaldehyde **12a**. The latter readily dimerized, probably via hemiaminal **13a**, and afforded the hemiaminal inner ether **14a**.

It is well known that both *N*-formyl[9a] and nonenolizable α-amino aldehydes[9b–e] undergo facile dimerization to give the cyclic hemiaminals, which contain a piperazine skeleton. The formation of an amino aldehyde dimer of a different structure is very rare.[10] On the basis of the above literature reports and available spectroscopic data, the structure of isolated **14a** was initially incorrectly identified as a C_2-symmetrical hemiaminal **13a**.[8c] However, because of the inconsistent elementary analysis of the amino aldehyde dimer, we performed a single crystal X-ray diffraction analysis.[11]

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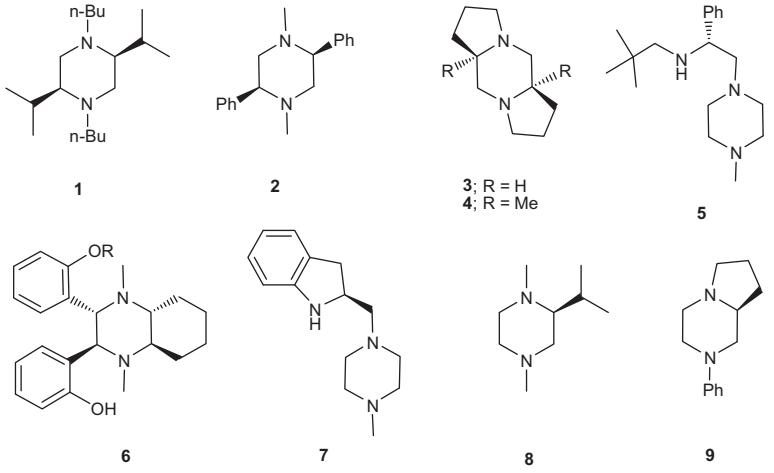
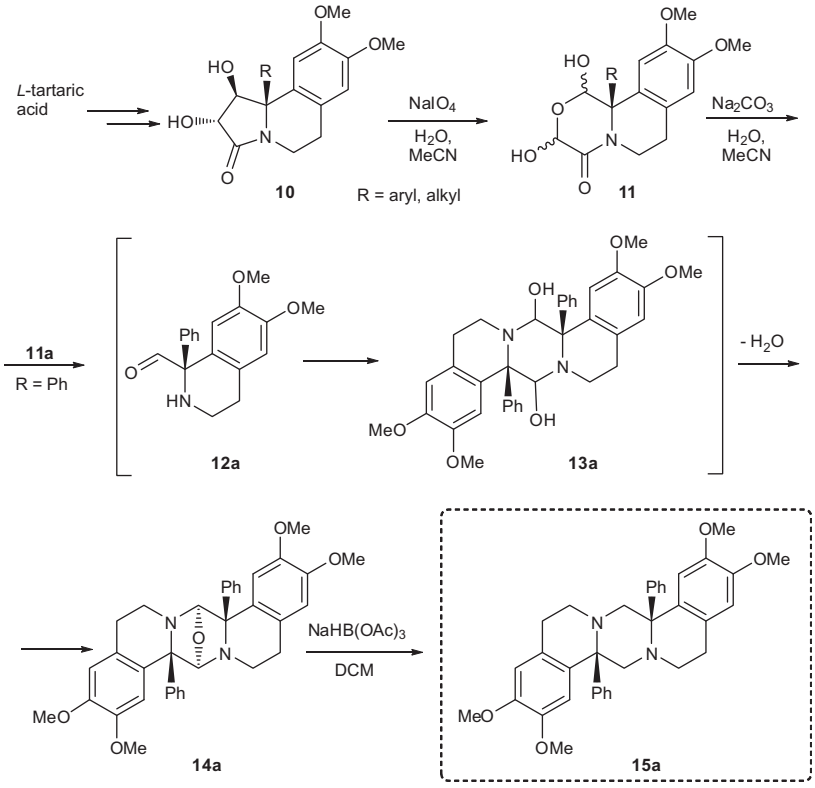


Figure 1. Tertiary diamines containing the piperazine skeleton.



Scheme 1. Previous work: synthesis of C_2-symmetrical hemiaminal ether **14a**.

The analysis showed that dimer **14a** had a unique structure of a bis-hemiaminal inner ether (Fig. 2). A thorough search of the literature revealed a single report of the synthesis of cyclic bis-hemiaminal ether derivatives. In 1960 Ogloblin[12] described the preparation of compounds of this type by thermal or base induced dehydration of α-amino aldehyde dimers. However, the author did not provide any spectroscopic data, and the proposed structure was postulated exclusively on the basis of elementary analysis.

Therefore, the herein reported 7-oxa-2,5-diaza-bicyclo[2.2.1] heptane derivative **14a** that can be described as a bicyclic bis-hemiaminal inner ether (Fig. 3), represents a new class of molecules, whose structure was unambiguously established for the first time.

Inspired by this observation, we realized that the reduction of a hemiaminal ether of type **14** could potentially open up a novel approach to C_2-symmetrical diamines with a piperazine core. The sodium triacetoxy-borohydride reduction of **14a** gave an enantiomerically pure diamine **15a** in excellent yield (93%) (Scheme 1).

In order to assess the scope of this new methodology, we prepared several derivatives of general structure **14** and **15**, varying the substituent at the bridged quaternary carbon atom (cf. Scheme 2). The synthesis of 10b-substituted hexahydropyrrolo[2,1-*a*]isoquinolines was carried out by applying our optimized procedure.[8b] The addition of a Grignard reagent to imide **16**, derived from L-tartaric acid, followed by acetylation and the $BF_3{\cdot}Et_2O$ induced cyclization furnished a diastereomeric mixture of C-10b epimers **17b**,**c**,**e** [(*S*),(*R*)] in good overall yields and with respectable diastereoselectivity [(*S*),(*R*) = 17–22:1]. Cyclization of 10b-benzyl derivatives **17d** was less stereoselective [(*S*),(*R*) = 6:1], and, in addition, the main product was accompanied by

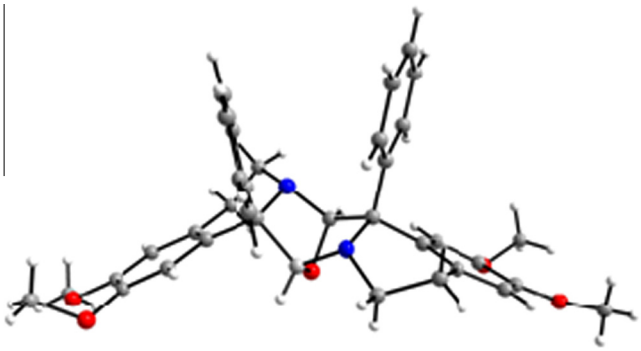


Figure 2. View of **14a**, as determined by single crystal X-ray crystallography.

hexahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepine **18**, which was isolated in approximately 8% yield as a single stereoisomer. The configuration at the newly generated stereocenters was not established. The enantiomerically pure hexahydro-pyrrolo[2,1-*a*]isoquinolines were isolated either via single crystallization **17b**,**c** or via flash chromatography **17d** or as a monopivalate **19e**.[13]

The proton NMR spectrum derived $J_{1,2}$ values for **17b**–**d** and **19e** were in a range of 6.9–8.4 Hz (Table 1), which according to our semi-empirical rule,[8b] confirmed that all compounds possessed a 10b(*S*) configuration.

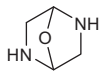


Figure 3. 7-Oxa-2,5-diaza-bicyclo[2.2.1]heptane.

Table 1
The $J_{1,2}$ value of isolated enantiomerically pure 10b-substituted hexahydro-pyrrolo[2,1-*a*]iso-quinolin-3-ones

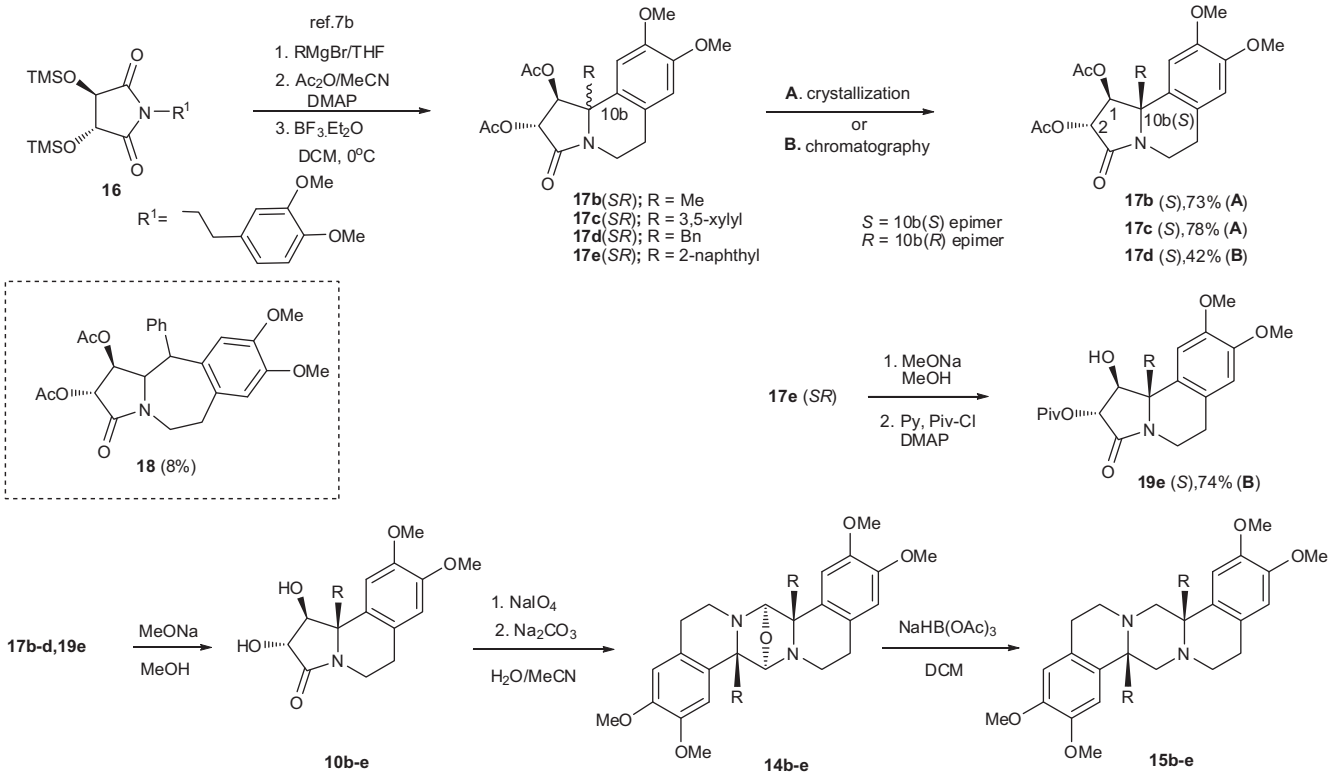
C-10b	$J_{1,2}$ (Hz)				
	17a[a]	**17b**[a]	**17c**	**17d**	**19e**
(*S*)	6,8	7,9	6,9	8,4	8,3
(*R*)	2,7	0	—	0	4,1

[a] Previously reported.[8b]

The alkaline deprotection of hydroxy groups for the parent compounds **17b**–**d** and **19e** led to diols **10b**–**e**. The glycolic cleavage using sodium periodate followed by sodium carbonate hydrolysis yielded aminal ethers **14b**–**e**. Compounds **14** and **14e** were isolated by flash chromatography. The unstable **14b** and **14d**, because of their rapid decomposition on silica gel, were used in the following step without any purification. Finally, the reduction of bis-hemiaminal ethers **14b**–**e** with sodium triacetoxy-borohydride provided C_2-symmetrical diamines **15b**–**e**.

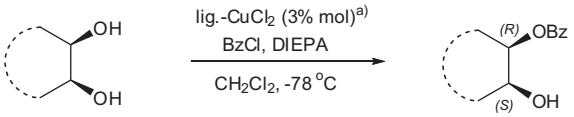
2.2. Cu-catalyzed asymmetric acylation of *meso*-diols using ligands of types 14 and 15

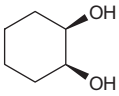
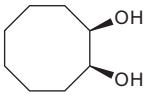
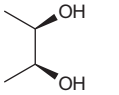
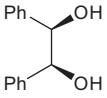
In order to evaluate the catalytic efficiency of the new ligands, we selected the asymmetric acylation of *meso*-diols[3] as a model reaction. Benzoylation of several cyclic and acyclic *meso*-1,2-diols **20**–**23**, catalyzed by 3 mol % of $CuCl_2$–diamines **15a**–**e** complexes, was carried out following Nakamura's procedure.[3c] Acylation with complexes of diamines with aryl substituents at the bridged quaternary carbon atom **15a**, **15c**, and **15e** provided the corresponding monobenzoates with moderate to high enantioselectivity (ee 41–87%; Table 2). The methyl- and benzyl analogues **15d** and **15e** showed very low levels of stereoselectivity for substrate **23** (ee 3–9%).



Scheme 2. Current work: synthesis of a new C_2-symmetrical hemiaminal ether **14b**–**d** and diamines **15b**–**d**.

Table 2
Asymmetric benzoylation of *meso*-diols catalyzed by $CuCl_2$ complexes with diamines **15a–e** and hemiaminal ethers **14a** and **14c**[a]



meso-Diol	No	15a		15b		15c		15d		15e		14a		14c	
		Yield[b] (%)	ee[c] (%)	Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)
	**20**	63	60	—	—	25	53	—	—	47	56	62	60	68	44
	**21**	78	48	95	rac.	66	41	54	rac.	84	56	78	48	82	31
	**22**	78	72	—	—	77	66	—	—	65	74	69	86	79	82
	**23**	56	74	73	9	93	87	44	3	66	75	56	34	52	30

[a] Reaction condition: *meso*-diol (0.5 mmol), $CuCl_2$·Lig. complex (0.015 mmol, 3 mol %), BzCl (1.2 mmol), DIEPA (1 mmol), CH_2Cl_2 (5,2 mL), −78 °C, 1–3 days.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpack AS-H column.

When diol **21** was used, only racemic mixtures of monoesters were isolated. These results indicated that the high stereo selectivity of this reaction is linked to the presence of a ligand with a bulky aryl substituent at the bridged quaternary carbon atom.

Recently, Wolf et al. proposed new C_2-symmetric bis-1,3-oxazolidine ligands and their application in metal based asymmetric catalysis.[14] Since a 1,3-oxazolidine can be regarded as a cyclic hemiaminal ether derived from an aldehyde or ketone, we anticipated that our new bis-hemiaminal ether **14** could also be applied for the desymmetrization of *meso*-diols. We found that the complexes of bis-hemiaminal ethers **14a**,**c** with $CuCl_2$ efficiently catalyzed the benzoylation reaction and furnished the corresponding monoesters in good yields.

The enantiomeric excess found for the products was either similar to that obtained by applying analogous diamines (diols **20** and **21**), or was substantially higher (for **22**), or was much lower (for **23**, cf. Table 1). We assume that these results can be attributed to the differences in size of the ligand cavity in which the copper cation is coordinated by two nitrogen atoms.

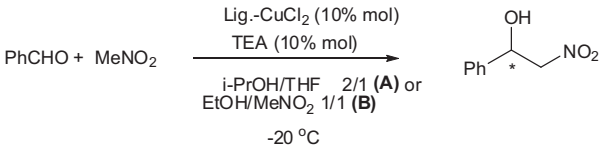
In comparison to diamines, the cavity in the respective bis-hemiaminal inner ether should be considerably narrower due to the presence of an oxygen bridge (see Fig. 2). This may explain the higher stereoselectivity observed for small diol **23**, which can more deeply penetrate into the chiral cavity compared to the bulky diphenyl analogue **24**. In all desymmetrization experiments, the main enantiomer of the monoester had the same configuration: (1*R*,2*S*) for the diols **21**, **22**, and **24** and (2*R*,3*S*) for diol **23**.

2.3. Cu-catalyzed asymmetric Henry reactions using ligands of type 14 and 15

Chiral diamine–copper complexes are widely utilized in asymmetric Henry reactions, a useful carbon–carbon bond forming process.[2] Since our C_2-symmetric diamines were shown to be promising ligands for the asymmetric acylation of *meso*-diols, it appeared logical to test them in the Henry reaction as well. The results of a model reaction between benzaldehyde and nitromethane catalyzed by complexes of anhydrous copper(II) chloride with the new ligands (10 mol % each) are listed in Table 3. All reactions were performed at −20 °C with 10 mol % of triethylamine as a base. The solvent of choice for the nitroaldol reaction is typically an alcohol such as methanol,[2a] ethanol,[2b] or iso-propanol,[2f] but sometimes THF[2e] or a mixture of solvents was used.[2d]

Due to the limited alcohol solubility of the complexes generated in dichloromethane, the test reactions were carried out either in 2-propanol/THF or in ethanol/nitromethane mixtures. Nitroaldol reactions, conducted in the presence of copper complexes with diamines **15a**, **15c**, and **15e**, furnished the corresponding β-nitroalcohol in good chemical yield and with high enantioselectivity (ee

Table 3
Asymmetric Henry reaction catalyzed by the $CuCl_2$ complexes with diamines **15a–e** and hemiaminal ether **14c**[a]



Ligand	Solvent[b]	Time (days)	Yield[c] (%)	ee[d] (%)	Configuration
15a	**A**	3	72	82	(*S*)
15b	**B**	5	28	62	(*R*)
15c	**A**	4	66	81	(*S*)
15e	**A**	3	73	85	(*S*)
14c	**B**	4	45	22	(*S*)

[a] Reaction condition: $CuCl_2$·Lig. (complex generated in DCM, 0.05 mmol, 10 mol %), beznaldehyde (0.5 mmol), solvent **A** or **B**.
[b] 2 mL, nitrometane (5 mmol, only when solvent **A** was used), TEA (0.05 mmol, 10 mol%), −20 °C. **A**: *i*-PrOH/THF 2:1, **B**: EtOH/$MeNO_2$ 1:1.
[c] Isolated yield.
[d] Determined by chiral HPLC using an OD-H Chiralpack column.

81–85%). The (*S*)-configured products were preferentially formed in all cases. For ligand **15b** with a methyl group instead of an aryl at the stereogenic center, the reaction rate was considerably slower and the reaction predominantly gave the (*R*)-enantiomer with an enantiomeric excess of 62%. In contrast to diamines **15a–c** and **15e**, the bis-hemiaminal ether **14c** showed a relatively low enantioselectivity (ee 22%) and a low reaction rate at the same time.

3. Conclusion

In conclusion, we have reported on the preparation of new C_2-symmetrical bis-hemiaminal ethers and diamine ligands, starting from L-tartaric acid. The unique structure of the bis-hemiaminal inner ether moiety was unambiguously documented for the first time. The catalytic effectiveness of both types of ligands was evaluated in the copper catalyzed asymmetric acylation of *meso*-diols (ee up to 87%) and Henry reactions (ee up to 85%). Further applications of these new ligands in asymmetric catalysis are currently under investigation.

4. Experimental

4.1. General information

NMR spectra were recorded in $CDCl_3$ at room temperature (except where indicated otherwise) using a Bruker AVANCE 500 or Varian VNMR500 spectrometer. Chemical shifts are quoted in parts per million relative to TMS for ^1H and $CDCl_3$ for ^{13}C NMR. Coupling constants *J* are reported in Hertz (Hz). IR spectra were obtained using a FTIR Jasco 6200 or FTIR Spectrum 2000 Perkin Elmer and reported in reciprocal centimeters (cm^{-1}). Optical rotations were measured at 23 °C with a JASCO P2000 digital polarimeter. Mass spectra were recorded using an AMD-604 Intectra GmbH or a Mariner Perseptive Biosystem mass spectrometer. X-ray analysis was performed on Bruker AXSAPEX diffractometer. Thin-layer chromatography was carried out on precoated silica gel (Merck Kieselgel 60 F254, 0.2 mm layer thickness). Visualization of the developed chromatogram was performed by UV absorbance and cerium molybdate water solution. Flash column chromatography was performed using Merck Kieselgel (230–400 mesh). All air and moisture sensitive reactions were carried out under an argon atmosphere in flame-dried glassware using anhydrous solvents. Most reagents were obtained from commercial suppliers and were used without further purification, unless noted. THF was distilled from Na and benzophenone, dichloromethane and toluene were distilled from CaH_2.

4.2. Preparation of the 10b-substituted hexahydro-pyrrolo[2,1-*a*]isoquinolines 17a–e

Compounds **17a**(*S*) and **17b**(*S*) were synthesized as previously reported.[8b] The same procedure[8b] was applied for the preparation of **17c–e**. The overall chemical yield from imide **16** is given below for each product separately.

4.2.1. (1*S*,2*R*,10*bS*)-10b-(3,5-Dimethylphenyl)-8,9-dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-1,2-diyl diacetate 17c(*S*)

Imide **16** (9.10 g, 26.4 mmol) was used. Isolated from the crude reaction mixture of 10b epimers via crystallization from EtOH; yield: 7.54 g, 78%; colorless crystals; mp 213–215 °C; $[\alpha]_D^{23} = -70.7$ (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2940, 1752, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 7.13 (s, 1H), 6.91 (m, 1H), 6.64 (s, 1H), 6.63 (m, 2H), 5.96 (d, 1H, *J* = 6.9 Hz), 5.72 (d, 1H, *J* = 6.9 Hz), 3.92 (s, 3H), 3.88 (s, 3H), 3.82 (m, 1H), 3.46 (m, 1H), 2.79 (m, 1H), 2.50 (m, 1H), 2.26 (2s, 6H), 2.13 (s, 3H), 1.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 170.2, 169.9, 166.2, 148.6, 147.7, 138.3, 137.8, 131.4, 129.7, 126.7, 125.1, 111.6, 109.3, 78.3, 74.6, 67.8, 56.3, 55.9, 37.7, 26.2, 21.5, 20.7, 20.7; MS (ES, HR) *m*/*z*: (M+Na^+), calcd for $C_{26}H_{29}NO_7Na$: 490.1836. Found: 490.1855. Anal. Calcd for: C, 66.80; H, 6.25; N, 3.00; Found: C, 66.77; H, 6.52; N, 2.98.

4.2.2. (1*S*,2*R*,10*bS*)-10b-Benzyl-8,9-dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-1,2-diyl diacetate 17d(*S*)

Imide **16** (0.879 g, 2.0 mmol) was used. Isolated from the crude reaction mixture of 10b epimers via flash chromatography, (MTBE/hexane, 7:3 v/v) yield: 0.382 g, 42%; colorless crystals; mp 188–189 °C (AcOEt); $[\alpha]_D^{23}$ = +111.5 (*c* 0.4, CH_2Cl_2); IR (CH_2Cl_2): 2939, 1753, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 7.25 (m, 3H), 7.07 (m, 2H), 6.72 (s, 1H), 6.55 (s, 1H), 5.44 (d, 1H, *J* = 8.4 Hz), 5.05 (d, 1H, *J* = 8.4 Hz), 4.29 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.33 (2d, 2H, *J* = 14.1 Hz), 2.85 (m, 1H), 2.65 (m, 1H), 2.55 (m, 1H), 2.29 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 170.3, 169.5, 165.3, 148.7, 148.3, 135.0, 130.7, 129.8, 128.5, 127.5, 125.2, 111.8, 107.5, 80.2, 73.7, 62.9, 56.0, 55.9, 42.5, 35.2, 27.8, 21.0, 20.6; MS (ES, HR) *m*/*z*: (M+Na^+) calcd for $C_{25}H_{27}NO_7Na$: 476.1680; Found: 476.1695. Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09; Found: C, 66.23; H, 5.90; N, 3.15.

4.2.3. (1*S*,2*R*,10b*R*)-10b-Benzyl-8,9-dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-1,2-diyl diacetate 17d(*R*)

Isolated from the crude reaction mixture of 10b epimers via flash chromatography, (MTBE/hexane 7:3 v/v) yield: 66 mg, 7%. Colorless crystals; mp 128–131 °C (MeOH), $[\alpha]_D^{23} = -47.6$ (*c* 0.56, CH_2Cl_2); IR (CH_2Cl_2): 2940, 1754, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 7.21 (m, 3H), 6.87 (m, 2H), 6.52 (s, 1H), 6.49 (s, 1H), 5.66 (s, 1H), 5.14 (s, 1H), 4.14 (m, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.43 (d, 1H, *J* = 13.5 Hz), 3.20 (d, 1H, *J* = 13.5 Hz), 2.72 (m, 1H), 2.43 (m, 1H), 2.28 (m, 1H), 2.16 (s, 3H), 1.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 169.4, 169.1, 167.1, 148.0, 147.2, 134.9, 130.5, 128.4, 127.3, 127.2, 125.1, 111.3, 109.6, 75.6, 74.6, 68.6, 55.9, 55.7, 47.1, 36.3, 28.2, 20.7, 20.5; MS (ES, HR) *m*/*z*: (M+Na^+) calcd for $C_{25}H_{27}NO_7Na$: 476.1680; Found: 476.1703. Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09; Found: C, 65.34; H, 5.92; N, 3.07.

4.2.4. (1*S*,2*R*)-8,9-Dimethoxy-3-oxo-11-phenyl-2,3,5,6,11,11a-hexahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepine-1,2-diyl diacetate 18

Isolated from the crude reaction mixture via flash chromatography, (MTBE/hexane 7:3 v/v) yield: 75 mg, 8% oil; ^1H NMR ($CDCl_3$, 500 MHz): 7.28 (m, 2H), 7.20 (m, 1H), 7.09 (m, 2H), 6.84–6.88 (m, 2H), 6.21 (dd, 1H, *J* = 4.4, 2.1 Hz), 5.99 (d, 1H, *J* = 2.1 Hz); 5.35 (d, 1H, *J* = 4.4 Hz), 3.89–3.85 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.94 (m, 3H), 2.16 (s, 3H), 1,61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 169.8, 169.7, 167.4, 149.1, 148.0, 135.6, 134.5, 130.4, 128.3, 128.0, 126.7, 120.8, 112.2, 111.5, 106.7, 74.4, 71.5, 55.9, 55.9, 42.3, 32.2, 20.5, 20.0; MS (ES, HR) *m*/*z*: (M+Na^+) calcd for $C_{25}H_{27}NO_7Na$: 476.1680; Found: 476.1683.

4.2.5. 10b-Epimeric mixture of (1*S*,2*R*)-8,9-dimethoxy-10b-(naphthalen-2-yl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]-isoquinoline-1,2-diyl diacetate 17e(*S*) and 17(*R*)

Imide **16** (4.84 g, 11.0 mmol) was used. Flash chromatography, (AcOEt/hexane 4:6 v/v). Yield 4.85 g, 90%. Selected data were taken from the chromatographically inseparable mixture of C-10b epimers **17e**(*S*):**17e**(*R*) = 16:1.

17e(*S*): ^1H NMR ($CDCl_3$, 500 MHz): 7.73–7.83 (m, 3H), 7.49 (m, 3H), 7.17–7.19 (m, 2H), 6.65 (s, 1H), 6.07 (d, 1H, *J* = 6.8 Hz), 5.80 (d, 1H, *J* = 6.8 Hz), 3.93 (s, 3H), 3.88 (s, 3H), 3.82–3.89 (m, 1H),

3.47 (m, 1H), 2.81 (m, 1H), 2.47 (m, 1H), 2.13 (s, 3H), 1.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 170.2, 169.9, 166.2, 148.7, 136.0, 132.7, 130.9, 128.3, 128.0, 127.4, 126.7, 126.7, 126.6, 126.5, 125.2, 111.6, 109.1, 78.5, 74.7, 67.9, 56.2, 55.9, 37.7, 26.2, 20.7, 20.7.

17e(*R*): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.11 (t, *J* = 2.8 Hz, 1H), 4.24 (m, 1H), 3.02 (m, 1H), 2.65 (m, 1H), 2.02 (s, 3H), 1.93 (s, 3H).

4.2.6. Preparation of 10b(*S*) and 10b(*R*) epimers (1*S*,2*R*)-1-hydroxy-8,9-dimethoxy-10b-(naphthalen-2-yl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-2-yl pivalate 19e(*S*) and 19e(*R*)

A mixture of **17e**(*S*) and **17e**(*R*) (16:1, respectively) (4.03 g, 8.24 mmol), was deacetylated applying our procedure.[8b] The crude diols obtained were dissolved in pyridine (40 mL), after which DMAP (100 mg, 0.824 mmol) was added and the solution was cooled to 0 °C. To the intensively stirred resulting solution, pivavolyl chloride (2.02 mL, 16.47 mmol) was added dropwise. The mixture was stirred at this temperature for 15 min. then temperature was brought to room temperature and stirring was continued until the disappearance of substrate ~1.5 h (TLC control). The mixture was poured into water (80 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The collected extracts were washed with 0.5 M HCl/water (3 × 100 mL) and brine, then dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography (AcOEt/hexane 4:6 v/v) to give enantiomerically pure derivatives **19e**(*S*) and **19e**(*R*).

19e(*S*): Yield: 3,142 g, 78%; colorless crystals; mp 116–118 °C (AcOEt/hexane); $[\alpha]_D^{23} = -130.4$ (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2937, 1737, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.80 (m, 3H), 7.60 (m, 1H), 7.49 (m, 2H), 7.42 (s, 1H), 7.32 (m, 1H), 6.65 (s, 1H), 5.44 (d, 1H, *J* = 8.3 Hz) 4.72 (d, 1H, *J* = 8.3 Hz), 4.02 (s, 3H), 3.89 (s, 3H), 3.79 (m, 1H), 3.64 (m, 1H), 2.79 (m, 1H), 2.53 (m, 1H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 179.7, 166.5, 148.6, 147.9, 135.4, 132.8, 137.7, 132.1, 128.3, 128.2, 127.5, 126.7, 126.6, 126.4, 125.4, 111.2, 108.9, 80.3, 77.3, 67.3, 56.4, 55.9, 38.9, 37.9, 27.1, 26.2 ; MS (EI, HR) *m*/*z*: (M^+) calcd for $C_{29}H_{31}NO_6$: 489.2151; Found: 489.2164. Anal. Calcd for $C_{29}H_{31}NO_6$: C, 71.15; H, 6.38; N, 2.86; Found: C, 71.24; H, 6.53; N, 2.72.

19e(*R*): Yield: 78 mg, 2%; oil; IR (CH_2Cl_2): 2959, 2928, 2855, 1737, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 7.80 (m, 2H), 7.73 (m, 1H), 7.63 (m, 1H), 7.48 (m, 3H), 6.67 (s, 1H), 5.13 (d, 1H, *J* = 4.1 Hz), 4.72 (d, 1H, *J* = 4.1 Hz), 4.14 (m, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.29 (m, 1H), 2.98 (m, 1H), 2.59 (m, 1H), 1.06 (s, 9H); MS (EI, HR) *m*/*z*: (M^+) calcd for $C_{29}H_{31}NO_6$: 489.2151; Found: 489.2136.

4.3. Preparation of the bicyclic bis-hemiaminal inner ethers 14a–e

1,2-Dihydroxy-hexahydro-pyrrolo-isoquinolines **10a–e** were obtained from the corresponding enantiomerically pure diacetates **17a–d** and *mono*-pivaloylate **19e** applying our procedure[8b] and used in the following step without further purification. Crude diols **10a–e** were subjected to glycolic cleavage with sodium periodate using our procedure.[8c] Compounds **14a–e** were synthesized applying our modified procedure.[8c]

General procedure: A crude diastereomeric mixture of hemiacetals **11** (obtained in two steps from 5 mmol of respective acetate **17**) was dissolved in acetonitrile (55 mL) and sodium carbonate (22 mmol, 55 mL of 0.4 M Na_2CO_3/H_2O) was added in one portion. The mixture was stirred gently at room temperature until the starting material was completely consumed, as judged by TLC analysis (5–7 days). The solution was concentrated to half of its initial volume (approx.), and then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude products **14a**, **14c**, and **14e** were purified on silica gel and/or by crystallization. Due to the rapid decomposition on silica gel, compounds **14b** and **14d** were used in the following step without any purification. The overall chemical yield from **17a–d** or **19e** is given.

4.3.1. (8*R*,8a*S*,16*R*,16a*S*)-2,3,10,11-Tetramethoxy-8a,16a-diphenyl-5,6,8,8a,13,14,16,16a-octahydro-8,16-epoxypyrazino[2,1-*a*:5,4-*a*′]diisoquinoline 14a

Acetate **17a** (2.15 g, 5.0 mmol) was used. Isolated via flash chromatography (CH_2Cl_2/hexane/AcOEt 65:20:15 v/v). Yield: 0.705 g, 49%; colorless crystals; mp 264–266 °C (AcOEt); $[\alpha]_D^{23} = +193.9$ (*c* 1.2, CH_2Cl_2); IR (CH_2Cl_2): 2937, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 2.46 (m, 2H), 2.88 (m, 2H), 3.36 (m, 4H), 3.78 (s, 12H), 5.39 (s, 2H), 6.51(s, 2H), 6.93 (s, 2H), 7.03 (m, 10H); ^{13}C NMR: 27.5, 49.0, 55.7, 56.2, 73.9, 104.0, 109.9, 111.4, 125.1, 126.7, 127.8, 130.1, 131.1, 144.7, 147.3, 147.4; MS (ES, HR) *m*/*z*: ($M+H^+$) calcd for $C_{36}H_{37}N_2O_5$: 577.2697. Found: 577.2719; Anal. Calcd for $C_{36}H_{36}N_2O_5$: C, 74.98; H, 6.29; N, 4.86. Found: C, 75.02; H, 6.34; N, 4.69.

4.3.2. (8*R*,8a*S*,16*R*,16a*S*)-8a,16a-Bis(3,5-dimethylphenyl)-2,3,10,11-tetramethoxy-5,6,8,8a,13,14,16,16a-octahydro-8,16-epoxypyrazino[2,1-*a*:5,4-*a*′]diisoquinoline 14c

Acetate **17c** (2.33 g, 5.0 mmol) was used. Isolated via flash chromatography (AcOEt/hexane, 4:6 v/v). Yield: 0.745 g, 47%; semisolid; $[\alpha]_D^{23} = +113.1$ (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3687, 2996, 2938, 1607, 1512 cm^{-1}; ^{1}H NMR (CDCl3, 500 MHz): 7.01 (s, 2H), 6.68 (m, 6H), 6.50 (s, 2H), 3,81 (s, 6H), 3,78 (s, 6H), 3.38 (m, 2H), 3.26 (m, 2H), 2.82 (m, 2H), 2.44 (m, 2H), 2.14 (s, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz): 147.3, 147.3, 144.6, 135.6, 131.5, 130.2, 127.0, 126.0, 111.4, 109.9, 103.7, 73.9, 56.2, 55.8, 49.1, 27.6, 21.4; MS (ES, HR) *m*/*z*: ($M+H^+$) calcd for $C_{40}H_{45}N_2O_5$: 633.3323. Found: 633.3333.

4.3.3. (8*R*,8a*S*,16*R*,16a*S*)-2,3,10,11-tetramethoxy-8a,16a-di(naphthalen-2-yl)-5,6,8,8a,13,14,16,16a-octahydro-8,16-epoxypyrazino[2,1-*a*:5,4-*a*′]diisoquinoline 14e

Pivaloate **19e** (1.26 g, 2.59 mmol) was used. Isolated via flash chromatography (CH_2Cl_2/hexane/AcOEt 2:2:1 v/v). Yield: 0.440 g, 50%; semisolid; $[\alpha]_D^{23} = +46.2$ (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3684, 2938, 1734, 1608, 1513 cm^{-1}; ^{1}H NMR (CDCl3, 500 MHz): 7.63 (m, 2H), 7.47 (m, 2H), 7.30–7.25 (m, 4H), 7.21 (m, 2H), 7.09–7.06 (m, 4H), 6.89 (m, 2H), 6.52 (s, 2H), 5.59 (s, 2H), 3.80 (s, 6H), 3.77 (s, 6H), 3.50 (m, 2H), 3.36 (m, 2H), 2.87 (m, 2H), 2.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 147.5, 147.5, 141.9, 132.8, 131.5, 131.0, 130.3, 127.8, 126.8, 126.7, 126.3, 125.8, 125.0, 124.9, 111.5, 109.9, 103.8, 74.2, 56.3, 55.8, 49.4, 27.7; MS (ES, HR) *m*/*z*: ($M+Na^+$) calcd for $C_{44}H_{40}N_2O_5Na$: 699.2829. Found: 699.2827.

4.4. Preparation of diamines 15a–e

General procedure: A mixture of DCM (15 mL) and acetic acid (7 mL) was cooled to 0 °C, and during intensive stirring $NaBH_4$ (8.7 mmol, 328 mg) was added portionwise (~10 min). Into the resulting solution, hemiaminal ether **14** (1.25 mmol) dissolved in DCM (10 mL) was added dropwise. The reaction mixture was allowed to warm to rt, and stirring was continued until the disappearance of the substrate (~30 min, TLC control). The solution was cooled to ~−5 °C, and during intensive stirring, NaOH (aq) (15 mL 30%) was carefully added. The resulting mixture was extracted with DCM (3 × 30 mL). The collected extracts were washed with water (2 × 30 mL) and brine, then dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography.

4.4.1. (8a*S*,16a*S*)-2,3,10,11-Tetramethoxy-8a,16a-diphenyl-5,6,8,8a,13,14,16,16a-octahydropyrazino[2,1-*a*:5,4-*a*′]diisoquinoline 15a

Compound **14a** (0.722 g, 1.25 mmol) was used (MTBE/hexane/$NH_{3/aq}$ 50:50:0.5 v/v/v). Yield: 0.654 g, 93%; semisolid; $[\alpha]_D^{23} = +107.3$ (*c* 0.55, CH_2Cl_2); IR (CH_2Cl_2): 3002, 2937, 2850, 1608, 1513 cm^{-1}; ^1H NMR (toluene-d_8, 80 °C, 500 MHz): 7.67 (m, 4H), 7.18 (m, 4H), 7.06 (m, 2H), 6.77 (s, 2H), 6.42 (s, 2H), 3.55 (s, 6H), 3.52 (s, 6H), 3.46 and 3.40 (2d, 4H, *J* = 13.4 Hz), 3.07 (m, 2H), 2.80 (m, 2H), 2.67 (m, 2H), 2.46 (m, 2H); ^{13}C NMR (toluene-d_8, 80 °C, 125 MHz): 149.9, 149.0, 148.1, 132.8, 129.3, 128.1, 126.8, 115.5, 114.6, 63.0, 57.0, 56.2, 55.7, 47.4, 27.0; MS (EI, HR) *m*/*z*: (M+) calcd for $C_{36}H_{38}N_2O_4$: 562.2832; Found: 562.2845.

4.4.2. (8a*S*,16a*S*)-2,3,10,11-Tetramethoxy-8a,16a-dimethyl-5,6,8,8a,13,14,16,16a-octahydropyrazino[2,1-*a*:5,4-*a*′]diisoquinoline 15b

(MTBE/MeOH/$NH_{3/aq}$ 95:5:0.2 v/v/v). Yield: 0.169 g, 29%; semisolid; $[\alpha]_D^{23} = +206.2$ (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2962, 2937, 2834, 1610, 1511 cm^{-1}; ^1H NMR (toluene-d_8, 90 °C, 500 MHz): 6.72 (s, 2H), 6.35 (s, 2H), 3.63 (s, 6H), 3.49 (s, 6H), 3.25 (m, 2H), 3.01–2.90 (2d, 4H, *J* = 11.6 Hz), 2.78 (m, 2H), 2.68 (m, 2H), 2.27 (m, 2H), 1.47(s, 6H); ^{13}C NMR (toluene-d_8, 90 °C, 125 MHz): 149.5, 149.4, 135.4, 127.6, 114.8, 112.4, 58.6, 57.2, 57.0, 56.3, 46.5, 26.5, 24,0; MS (ES, HR) *m*/*z*: (M+H^+) calcd for $C_{26}H_{35}N_2O_4$: 439.2591; Found: 439.2599.

4.4.3. (8a*S*,16a*S*)-8a,16a-Bis(3,5-dimethylphenyl)-2,3,10,11-tetramethoxy-5,6,8,8a,13,14,16,16a-octahydropyrazino[2,1-*a*:5,4-*a*′] diisoquinoline 15c

Compound **14c**(*S*) (0.506 g, 0.8 mmol) was used (MTBE/hexane/$NH_{3/aq}$ 40:60:0.5 v/v/v). Yield: 426, 86%; semisolid; $[\alpha]_D^{23} = +83.8$ (*c* 0.5, CH_2Cl_2); IR (CH_2Cl_2): 2928, 1514 cm^{-1}; ^1H NMR (toluene-d_8, 80 °C, 500 MHz): 7.39 (s, 4H), 6.82 (s, 2H), 6.76 (m, 2H), 6.40 (s, 2H), 3.55 (s, 6H), 3.48 (s, 6H), 3.45–3.38 (2d, 4H, *J* = 13.3 Hz), 3.12 (m, 2H), 2.78 (m, 2H), 2.68 (m, 2H), 2.45 (m, 2H), 2.22 (s, 12H); ^{13}C NMR (toluene-d_8, 80 °C, 125 MHz): 149.8, 148.9, 148.0, 137.5, 137.9, 137.0, 133.2, 128.4, 128.2, 127.6, 115.5, 114.5, 62.9, 57.0, 56.2, 56.0, 47.2, 27.0, 21.7; MS (ES, HR) *m*/*z*: (M+H^+) calcd for $C_{40}H_{47}N_2O_4$: 619.3530; Found: 619.3523.

4.4.4. (8a*S*,16a*S*)-8a,16a-Dibenzyl-2,3,10,11-tetramethoxy-5,6,8,8a,13,14,16,16a-octahydropyrazino[2,1-*a*:5,4-*a*′]diisoquinoline 15d

Compound **17d**(*S*) (0.315 g, 0.695 mmol) was used (AcOEt/hexane 30:70 v/v). Yield: 35 mg; 17%; viscous oil; $[\alpha]_D^{23} = +134.4$ (*c* 0.735, CH_2Cl_2); IR (CH_2Cl_2): 2934, 1513 cm^{-1}; ^1H NMR (toluene-d_8, 80 °C, 500 MHz): 7.11–7.02 (m, 10H), 6.34 (s, 2H), 6.18 (s, 2H), 3.46 (s, 6H), 3.42 (d, 2H, *J* = 13.0 Hz), 3.42 (s, 6H), 3.32 (m, 2H), 3.14 (d, 2H, *J* = 11.8 Hz), 3.01 (d, 2H, *J* = 13.0 Hz), 2.95 (d, 2H, *J* = 11.8 Hz), 2.70 (m, 4H), 2.26 (m, 2H); MS (ES, HR) *m*/*z*: (M+H^+) calcd for $C_{38}H_{43}N_2O_4$: 591.3217; Found: 591.3224.

4.4.5. (8a*S*,16a*S*)-2,3,10,11-Tetramethoxy-8a,16a-di(naphthalen-2-yl)-5,6,8,8a,13,14,16,16a-octahydro-pyrazino[2,1-*a*:5,4-*a*′]diisoquinoline 15e

Compound **14e**(*S*) (0.335 g, 0.495 mmol) was used (MTBE/hexane/$NH_{3/aq}$ 50:50:0.5 v/v/v). Yield: 0.279 g; 90%; semisolid, $[\alpha]_D^{23} = +76.9$ (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3688, 2937, 1609, 1513 cm^{-1}; ^1H NMR (toluene-d_8, 60 °C, 500 MHz): 8.12 (s, 2H), 7.78 (m, 2H), 7.63 (m, 2H), 7.55 (m, 2H), 7.52 (m, 2H), 7.20 (m, 4H), 6.83 (s, 2H), 6.45 (s, 2H), 3.53 (m, 4H), 3.52 (s, 6H), 3.51 (s, 6H), 3.11 (m, 2H), 2.88 (m, 2H), 2.70 (m, 2H), 2.51 (m, 2H); ^{13}C NMR (toluene-d_8, 60 °C, 125 MHz): 150.0, 149.1, 145.6, 134.0, 133.4, 132.6, 128.7, 128.6, 127.9, 127.8, 127.5, 125.9, 125.9, 115.5, 114.6, 63.1, 57.0, 56.2, 55.4, 47.5, 25.8; MS (ES, HR) *m*/*z*: (M+H^+) calcd for $C_{44}H_{43}N_2O_4$: 663.3217; Found: 663.3190.

4.5. General procedure for the asymmetric acylation of *meso*-1,2-diols catalyzed by $CuCl_2$ complexes with ligands 14 and 15

The asymmetric benzoylation of *meso*-diols was carried out by following the reported procedure.[3c]

Ligand **14** or **15** (0.016 mmol) and $CuCl_2$ (2.0 mg, 0.015 mmol) were stirred in DCM (2.4 mL) until complete dissolution of copper salt (4–24 h). A green solution of the generated complex was added to a solution of *meso*-1,2-diol (0.5 mmol) in DCM (4.0 mL) and the mixture was cooled to −78 °C. Next, diisopropylethylamine (170 μL, 1.0 mmol) and benzoyl chloride (0.26 mL, 2.4 mmol) were added. The reaction mixture was stirred until the 1,2-diol was consumed (TLC control), after which the mixture was quenched by the addition of 0.1 M aqueous citric acid. The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed sequentially with 0.1 M aqueous citric acid, water, and brine, dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 9:1–7:3) to give the desired monobenzoate.

The analytical and spectroscopic data of the obtained monobenzoate were found to be in agreement with the reported data.[3c] The enantiomeric excess was determined by HPLC methods using DAICEL Chiralpack AS-H column, as described by Nakamura.[3c] The absolute configuration of compounds **5** was assigned by comparison of the retention times in HPLC with the literature data.[3c]

4.6. General procedure for the asymmetric Henry reaction catalyzed by $CuCl_2$ complexes with ligands 14 and 15

A complex of $CuCl_2$ (6.7 mg, 0.05 mmol) with ligand **14** or **15** (0.05 mmol) was generated as described above. The obtained clear green solution was evaporated in vacuo, the residue was dissolved in 2 mL of an appropriate solvent **A** or **B** (**A**: *i*-PrOH/THF 2:1, **B**: EtOH/$MeNO_2$ 1:1) cooled to −20 °C, and nitromethane was added (271 μL, 5 mmol, only when solvent **A** was used). Next triethylamine (0.05 mmol, 50 μL of 1 M TEA/*i*-PrOH) and benzaldehyde (0.5 mmol, 51 μL) were added. The reaction mixture was stirred until the benzaldehyde was consumed (TLC control), then the mixture was quenched by the addition of 2 mL of saturated ammonium chloride, stirred for 2 min, poured into water (5 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. Flash chromatography purification (*n*-hexane/ethyl acetate, 9:1) gave the known β-nitroalcohol.[2a]

The enantiomeric excess was determined by HPLC methods using a DAICEL Chiralpack OD-H column as described by Maheswaran.[2a] The absolute configuration of the major enantiomer was assigned by comparison with the literature-known retention times on chiral HPLC.[2a]

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