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Synthesis and Structure of *N,N′*-Diaryl Derivatives of *trans*-1,2-Diaminocyclohexane*

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Synthesis of *N,N′*-diaryl derivatives of *trans*-1,2-diaminocyclohexane (DACH) by palladium-catalyzed aromatic nucleophilic substitution reactions is described. The conformation of the *N*-acetylated *N,N′*-diaryl derivatives of DACH has been studied by the computational, circular dichroism and X-ray diffraction methods. Reversal of the relative orientation of the *N*-aryl residues due to *N*-acetylation has been established.

Key words: *trans*-1,2-diaminocyclohexane, palladium, *N*-arylation, conformation, circular dichroism

trans-1,2-Diaminocyclohexane (DACH, **1**) is one of the few examples of chiral vicinal diamines available commercially. It is a C_2-symmetric rigid molecule, having two equatorial C–N bonds in a chair cyclohexane skeleton. The N–C*–C*–N dihedral angle is negative for the *R,R* configuration (*M* helicity). These structural parameters of DACH and its availability in both enantiomeric forms have made DACH derivatives attractive bidentate ligands for chiral catalysts. The most common chiral ligands are the bis-Schiff base derivatives for asymmetric epoxidation (AE) or asymmetric epoxide ring opening (ARO) [1], whereas the bis-(2-diphenylphosphinebenzamide) derivatives (Trost's ligands) are used as chiral ligands for asymmetric allylic alkylations (AAA) [2]. Unlike imine [3] or imide [4] type derivatives, the *N*-aryl derivatives of DACH received little attention. Only recently Frost and Mendonça [5] prepared and tested *N*-aryl derivatives of DACH as chiral ligands for transfer hydrogenation reactions. *N,N′*-Bis-(4-nitrophenyl)-*trans*-1,2-diaminocyclohexane was found to exhibit high β-hyperpolarizability in the crystal, a property of potential use in nonlinear optics [6].

The palladium catalyzed amination of aryl halides and triflates has been shown to be a simple and general method for the formation of aromatic carbon-nitrogen bonds. This method was developed independently by Buchwald [7] and Hartwig [8] in 1995, and nowadays it has found many applications for the synthesis of aniline derivatives, indole alkaloids, pharmaceuticals, ligands, organic components and so on [9]. Al-

* Dedicated to Prof. M. Szafran on the occasion of his 70th birthday.
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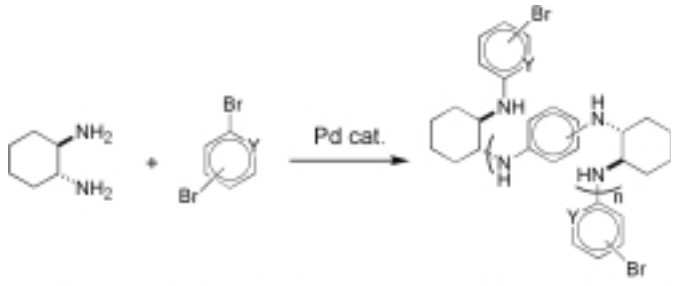
though coupling of either diamine and aryl halide [10] or amine and aryl dihalide [11] is known, the reaction between chiral diamine and aryl dihalide has not been yet investigated.

RESULTS AND DISCUSSION

We decided to obtain *N,N′*-diaryl derivatives of DACH, using 1,4- and 1,3-dibromobenzene (**2**, **3**) and 2,6-dibromopyridine (**4**, Scheme 1). The aim of this work was not only the synthesis of simple *N,N′*-diaryl derivatives of DACH, but also the preparation of more complex derivatives, as depicted in Scheme 1. No less important were structural investigations of the relative orientation of the *N*-aryl residues and the effect of *N*-acetylation on the substituents conformation.

Scheme 1



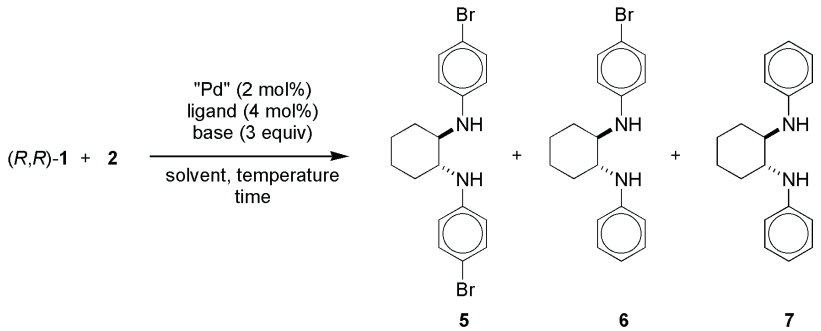
1

2: 4-Br, Y = CH
3: 3-Br, Y = CH
4: 6-Br, Y = N

5: 4-Br, Y = CH, n = 0
8a: 3-Br, Y = CH, n = 0
8b: 3-Br, Y = CH, n = 1
9a: 6-Br, Y = N, n = 0
9b: 6-Br, Y = N, n = 1

Because there are no data in the literature on the reaction of diamines with dihaloarenes, we decided to find initially the optimal conditions for coupling of (*R*,*R*)-**1** and **2**. We tested different combinations of the ligand, base, solvent and the palladium source, as well as the influence of the temperature and the reaction time on the yield of the products (Scheme 2).

Scheme 2



5 **6** **7**

Table 1. Yields of products of the reaction between DACH and 1,4-dibromobenzene under different conditions.

Entry	"Pd"	Ligand	Base	Solvent	Temp. [°]	Time [h]	Yield [%]		
							5	**6**	**7**
1	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	xylene	140	24	35	12	20
2	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	xylene	140	36	22	14	42
3	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	xylene	140	48	2	25	40
4	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	xylene	140	72	–	10	54
5	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	xylene	110	10	21	2	–
6	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	toluene	110	20	39	14	–
7	$Pd_2(dba)_3$	BINAP	NaO-*t*-Bu	toluene	80	36	–	–	–
8	$Pd_2(dba)_3$	PPh_3	NaO-*t*-Bu	toluene	110	24	–	–	–
9	$Pd_2(dba)_3$	P(*o*-tolyl)$_3$	NaO-*t*-Bu	toluene	110	24	5	–	–
10	$Pd_2(PPh_3)_4$	PPh_3	NaO-*t*-Bu	toluene	110	24	trace	–	–
11	$Pd_2(PPh_3)_4$	P(*o*-tolyl)$_3$	NaO-*t*-Bu	toluene	110	36	4	–	–
12	$Pd_2(dba)_3$	PPh_3	NaOH	toluene	110	36	–	–	–
13	$Pd_2(dba)_3$	PPh_3	NaOH	toluene	110	36	–	–	–
14	$Pd_2(dba)_3$	BINAP	K_2CO_3	THF	60	96	–	–	–
15	$Pd_2(dba)_3$	BINAP	NaOH	DMF	150	36	12	3	–
16	$PdCl_2$	BINAP	NaO-*t*-Bu	xylene	140	48	–	–	–
17	$PdCl_2$	PPh_3	NaO-*t*-Bu	xylene	140	48	–	–	–
18	$PdCl_2$	P(*o*-tolyl)$_3$	NaO-*t*-Bu	xylene	140	48	–	–	–

The experimental procedure involved heating a mixture of (*R*,*R*)-**1** (1.2 equiv.), **2** (2 equiv.), the base (3 equiv.), the ligand (0.04 equiv.) and the palladium source (0.02 equiv. relative to the aryl halide) under argon atmosphere. The typical concentration of **1** was 0.2 mol dm^{-3}. The results are summarized in Table 1.

Along with the main product **5**, the side-products **6** and **7**, resulting from the partial reduction of the starting aryl dibromide or the product **5**, were formed in variable amounts in these reactions. These side-products were readily separated from **5** by column chromatography on silica gel. It follows from the experimental data, that the choice of ligand type and palladium source is critical to the success of the reaction. The most effective catalyst was $Pd_2(dba)_3$/BINAP (Entry 1, Table 1). The ratios of the products also depend on the temperature and reaction time. The *N*-arylation reaction required the temperatures above 80 ºC and the use of sodium *tert*-butoxide as a base (Entries 1–6, Table 1). Using higher-boiling solvents (xylene, DMF) did not improve yield of **5** (Entries 1–4 and 15, Table 1). Long reaction time increased the yield of the products of reductive dehalogenation **6** and **7** (Entries 2–4, Table 1). Monodentate ligands such as PPh_3 and P(*o*-tolyl)$_3$ were found to be inefficient (Entries 8-13, 17 and 18, Table 1). Increasing the quantity of the catalyst from 2 mol% Pd to 4 mol% Pd allowed shortening the reaction time from 24 to 16 hours, this also suppressed the formation of the side products **6** and **7** (see Table 2, Entries 1 and 7). Higher loads of the catalyst caused enrichment of the reaction mixture with the products of reduction (Entries 2–5, Table 2).

Table 2. Yields of products of the reaction between DACH and 1,4-dibromobenzene with different combinations of the reaction time and catalyst amount.[a]

Entry	$Pd_2(dba)_3$ [mol%]	BINAP [mol%]	Time [h]	Yield [%]		
				5	**6**	**7**
1	2	4	24	42	12	4
2	4	8	24	48	13	11
3	6	12	24	40	18	11
4	8	16	24	32	26	14
5	10	20	24	19	21	29
6	4	8	12	32	3	–
7	4	8	16	56	8	–

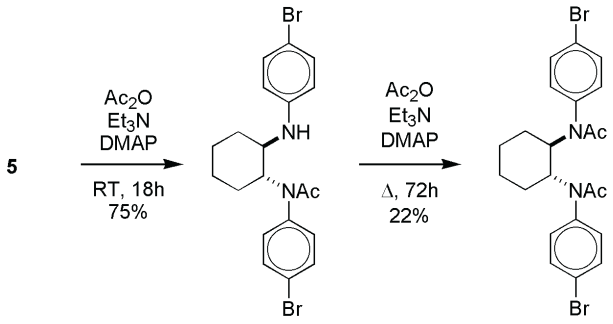
[a]Other reaction conditions: DACH (1.2 mmol), **2** (2.0 mmol), NaO-*t*-Bu (3.0 mmol), toluene, temp. 105–110℃ (oil bath).

Although the yield of *N*-arylation reaction was moderate, the use of the optimal procedure (Entry 7, Table 2) gave access to *N,N′*-diaryl derivatives **8a** and **9a**, when (*R*,*R*)-**1** was reacted with **3** or **4** (Scheme 1). As the side products compounds **8b** and **9b** of the general structure Ar-DACH-Ar-DACH-Ar were obtained. Change of the diamine-dihalide ratio (0.8 : 1) and higher load of the catalyst (6 mol% Pd) provided

higher yields of the products **8b** (42%) and **9b** (39%). Interestingly, all attempts to convert **1** and **2** into more complex product than *N,N′*-diarylated diamine **5** were unsuccessful. Apparently, the amino group in the *para* position to the bromine atom, strongly deactivated substrate **5** to further amine arylation reactions. On the other hand, the amino group in the *meta* position, as in products **8a** and **9a**, had little effect on further arylation reactions, allowing to prepare products **8b** and **9b**.

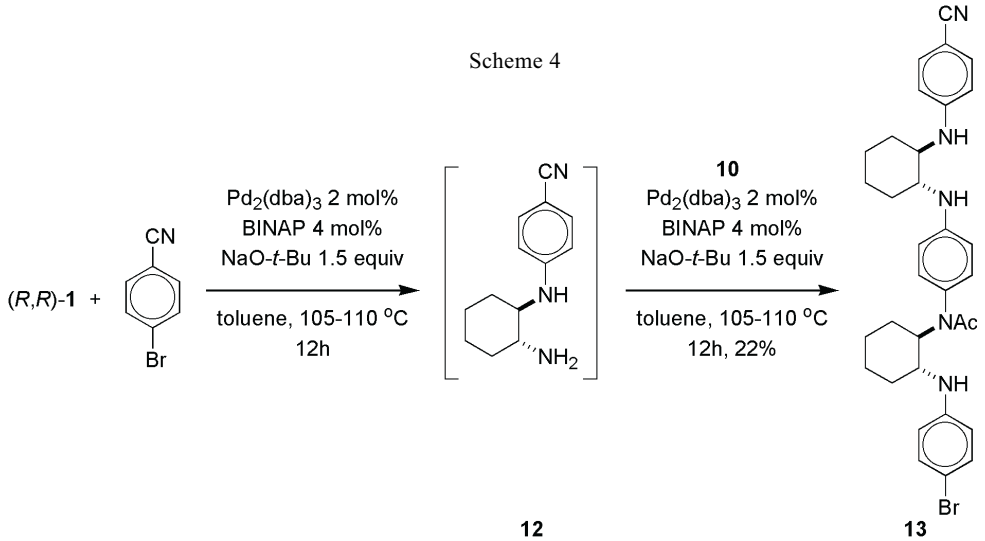
N,N′-Diaryl derivative **5** could be further derivatized by the action of acetic anhydride–triethylamine–DMAP at ambient temperature (Scheme 3).

Scheme 3



Under these conditions only *N*-monoacetyl product **10** was obtained. Introduction of the second acetyl group required prolongated heating of **10** with acetic anhydride-triethylamine-DMAP. Yield of the *N,N′*-diacetylated product **11** was low, apparently due to the high energy of the tetrahedral transitions state of the amine addition to the carbonyl group. With the use of the *N*-monoacetyl product **10**, we could obtain selectively the unsymmetrical derivative **13** (Scheme 4).

Scheme 4



The reaction was carried out in two steps. In the first step, mono-*N*-arylated intermediate **12** was obtained as a product of coupling between (*R*,*R*)-**1** and 4-bromobenzonitrile. In the following step, second amino group of the *in situ* formed **12** was arylated with **10**. Unfortunately, the yield of the product **13** was low, prohibiting further prolongation of the chain by additional amine arylation reactions.

The structure and CD spectra of *N,N'*-diaryl derivatives of DACH were alredy discussed [12]. Here we will concentrate on the effect of mono- and diacetylation of **5** (products **10** and **11**). The CD spectra of **5**, **10** and **11** (Figure 1) show the change of the sign and the magnitude of the Cotton effects.

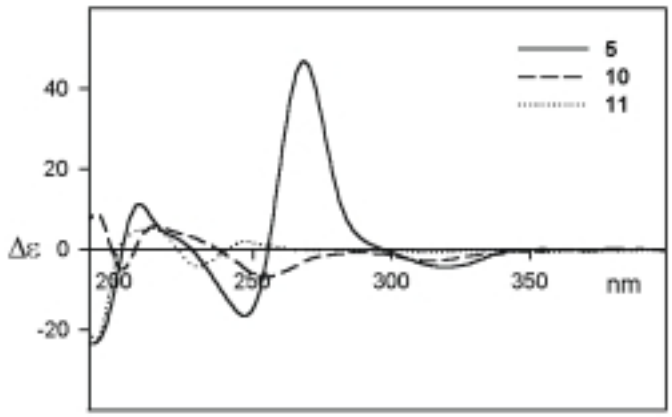


Figure 1. CD spectra of diamine **5** and its *N*-acetylated derivatives **10** and **11**.

In order to correlate the change of the CD spectra with the change of conformation we calculated the electronic transitions of the model amines: *N*-methyl-4-bromoaniline and *N*-acetyl-*N*-methyl-4-bromoaniline by the CIS/6-31+g(d) method and compared the results with the experimental electronic absorption spectra of **5** and **11**, respectively (Figure 2). Prior to computing the electronic transitions the geometries of the model amines were optimized at the b3lyp/6-31g(d) level of theory. The structures obtained were of C_1 symmetry, due to the pyramidalization of the nitrogen atom or non-perpendicular arrangement the acetamido group relative to the aryl ring (the torsion angle C_{ar}–C_{ar}–N–C(O) was 109°). According to the computational results the most intense electronic transitions within the bands at *ca*. 250 nm and 200 nm in the chromophoric fragment of **5** were polarized nearly parallel to the long axis of the chromophore.

Knowledge of the directions of the electronic dipole transition moments, determined by the computations, made possible assignment of the preferred conformations of diamine **5** as well as of the acetylated derivatives **10** and **11**. Strong positive Cotton effect observed in the case of **5** is predicted for the positive helicity of the chromophoric system (**A**, Scheme 5).

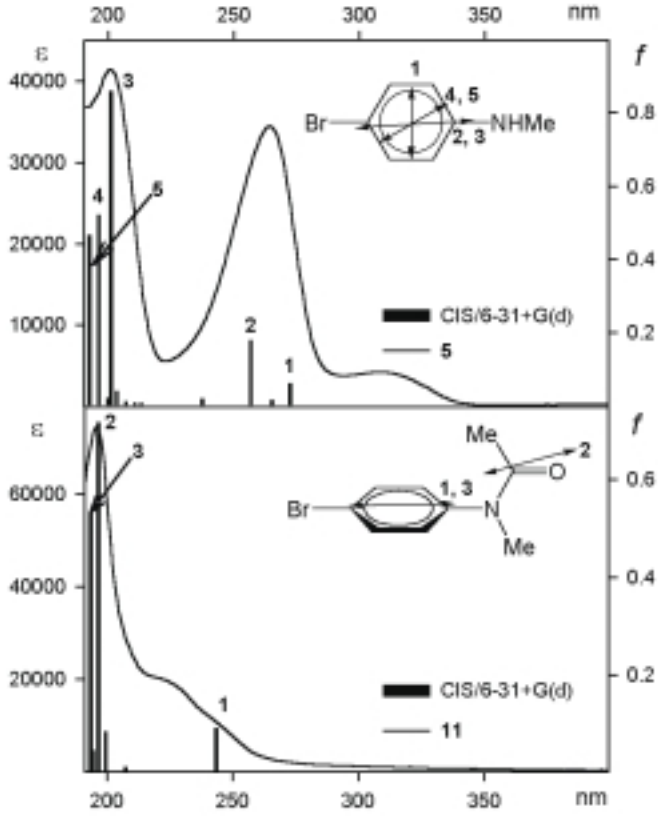
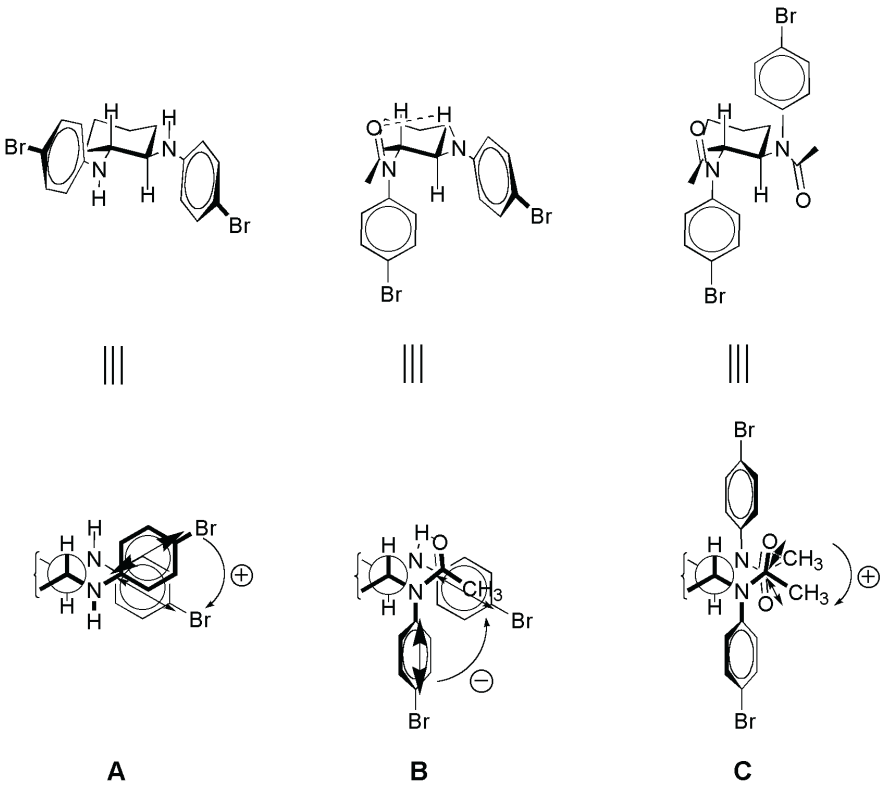


Figure 2. Measured UV spectra (solid line) of **5** and **11** and calculated electronic transitions (vertical bars) of *N*-methyl-4-bromoaniline and *N*-acetyl-*N*-methyl-4-bromoaniline. Energies of the electronic transitions were multiplied by a factor 1.208 to account for electron correlation.

N-Acetylated diamine **10** can exist in a number of conformations, differing in amide *Z* or *E* configuration and the orientation of the aryl substituent relative to the vicinal C*–H bond. With the PM3 semiempirical method we optimized the structures of conformers of **10**. Out of the total number of eighth conformers of **10**, the one having the lowest energy is stabilized by the intramolecular hydrogen bond C=O···H–N. For this conformer the predicted sign of the Cotton effect is negative, in good agreement with the experimental data (**B**, Scheme 5). Measured CD spectrum of **10** shows a negative Cotton effect at 253 nm and a positive one at 215 nm.

We also determined the structure of **10** by the X-ray diffraction method. Selected bond lengths and bond angles for **10** are given in Table 3. Figure 3 shows a perspective view of the molecule with the atom numbering scheme. The overall X-ray determined structure of **10**, shown in Figure 3, resembles the computed one, as in Scheme 5 (**B**).

Scheme 5



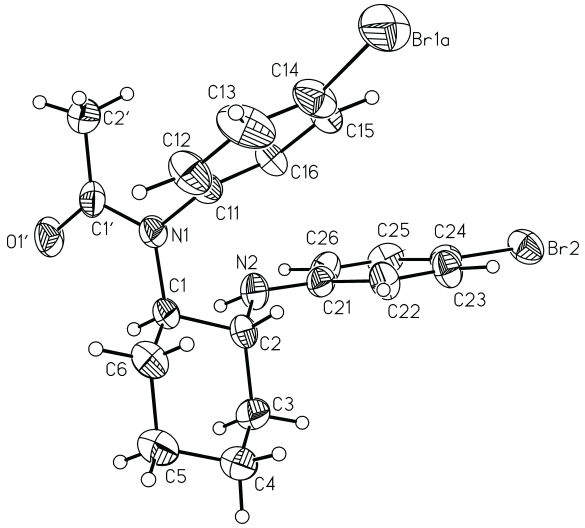


Figure 3. X-ray determined structure of **10**.

Table 3. Selected geometric parameters (Å, deg) for **10** with e.s.d.'s in parentheses.

C1–N1	1.473(5)	C2–N2	1.459(5)
N1–C1′	1.365(5)	N1–C11	1.453(5)
C1′–O1′	1.216(4)	C1′–C2′	1.488(5)
C14–Br1A	1.923(7)	C14–Br1B	1.908(7)
N2–C21	1.385(5)	N2–H2A	0.86(4)
C24–Br2	1.907(4)		
C1′–N1–C11	122.6(3)	C1′–N1–C1	120.0(3)
C11–N1–C1	117.2(4)	O1′–C1′–N1	120.8(4)
O1′–C1′–C2′	121.7(4)	C21–N2–C2	122.0(4)
C1–C2–C3–C4	–53.4(5)	C2–C3–C4–C5	55.0(5)
C3–C4–C5–C6	–55.7(6)	C4–C5–C6–C1	57.6(6)
C2–C1–C6–C5	–56.3(5)	C6–C1–C2–C3	53.2(5)
N1–C1–C2–N2	–54.1(5)	C6–C1–C2–N2	178.9(4)
N1–C1–C2–C3	–179.8(4)	N2–C2–C3–C4	–178.2(3)
N1–C1–C6–C5	175.9(4)	C6–C1–N1–C1′	–107.5(5)
C2–C1–N1–C1′	126.1(4)	C6–C1–N1–C11	68.2(5)
C2–C1–N1–C11	–58.3(5)	C11–N1–C1′–O1′	–174.0(4)
C1–N1–C1′–O1′	1.4(6)	C11–N1–C1′–C2′	7.4(6)
C1–N1–C1′–C2′	–177.2(4)	C1′–N1–C11–C16	–95.4(5)
C1–N1–C11–C16	89.1(5)	C1′–N1–C11–C12	82.5(5)
C1–N1–C11–C12	–93.0(5)		
C3–C2–N2–C21	–74.3(5)	C1–C2–N2–C21	160.8(4)
C2–N2–C21–C22	–26.0(6)	C2–N2–C21–C26	157.0(4)
C14···C11···C21···C24	–13.0(3)	H1–C1–N1–C1′	8(3)
H2–C2–N2–H2A	–173(4)		

As expected, the cyclohexane ring adopts a chair conformation and both amino-substituents are in the equatorial orientations (see Table 3). Consequently, both hydrogen atoms, at C1 and at C2, are in the axial positions. The mutual orientation of all fragments within the amine substituents results in an interplay between electronic and steric factors in the molecule. Although some conformational freedom towards rotation around the C1–N1, N1–C11, C2–N2 and N2–C21 bonds exists, the axial orientation of H1 and H2A in the cyclohexane ring is substantial for the overall conformation. The hydrogen atoms H2 and H(N2) are in *trans* orientation (the torsion angle H2–C2–N2–H2A equals to 176(4)°). The situation is different with the N1 atom. The acetamide group assumes *E* configuration, as it is frequently the case with tertiary amides [13]. The torsion angle H1–C1–N1–C1′ equals to 7(3)°; this brings the amide O1′ oxygen into attractive interaction with the H1 atom. In consequence, both phenyl rings are oriented on one side of the cyclohexane ring; the torsion angle C14···C11···C21···C24 equals –13.0(3)°.

The orientation of both phenyl groups in relation to the cyclohexane ring is different. The angle between the amino group (N2, H2A, C2, C21) and the phenyl ring C21…C24 is 24.6(3)° whereas the angle between the amino group (N1, C1′, C11, C1) and the phenyl ring C11…C14 is 85.8(2)°. In consequence, bond lengths N–C(Ph) are also differentiated: 1.385(5) Å and 1.453(5) Å for N2–C21 and N1–C11, respectively. The large difference in the bond lengths is caused by the resonance of the N2 lone pair with the aromatic π-electron system and the lack of the resonance between the N1 lone pair and the phenyl ring C11…C14. On the other hand, the bond length N1–C1′ 1.365(5) Å is the result of resonance within the amide group.

The crystal packing of **10** is determined mainly by weak intermolecular hydrogen bonds between the amine and amide groups (N–H···O=C) and by a number of weak C–H···Br interactions (Table 4).

Table 4. Hydrogen bond data.

D–H...A	D–H	H...A	D···A	D–H···A
N2–H2A...O1′ [i]	0.86(4)	2.39(4)	3.193(5)	157(4)
C3–H3A...Br2[ii]	0.97	3.10	3.861(4)	136
N2–H2A...Br2[iii]	0.86(4)	3.36(4)	3.864(4)	120(3)
C4–H4A...Br1B[iv]	0.97	2.94	3.825(7)	152
C22–H22...Br1A[iv]	0.96	2.99	3.932(8)	168
C22–H22...Br1B[iv]	0.96	3.06	3.975(8)	160

Symmetry transformations used to generate equivalent atoms:
[i] –x + 2, y – 1/2, –z + 1
[ii] x + 1, y, z
[iii] –x + 1, y + 1/2, –z + 1
[iv] –x + 1, y – 1/2, –z

The case of **11** is more complicated. The Cotton effects, having the highest rotatory strengths, were found at 213 nm ($\Delta\varepsilon$ = +5) and 193 nm ($\Delta\varepsilon$ = –22). According to the computational results at the b3lyp/6-31+g(d,p)//b3lyp/3-21g(d) level of theory, the lowest-energy conformer of **11** (**C**, Scheme 5) is characterized by parallel directions of the electric dipole transition moments in the aryl fragments, hence there are no exciton Cotton effects due to the transitions within the aromatic chromophore. Instead, the exciton-like Cotton effects at 213 and 193 nm correspond to the positive helicity of the allowed transitions of the acetamide chromophores [14].

In conclusion, we described a convenient method of synthesis of *N,N′*-diaryl derivatives of DACH, based on the Pd-catalyzed coupling of the diamine and the aryl dihalide. *N*-Acetylation of diamine **5** resulted in products **10** and **11**, having different conformational arrangement of the aromatic chromophores, as determined by the computational, circular dichroism and X-ray data.

EXPERIMENTAL

General. All reactions were carried out in dry, freshly distilled and degassed solvents under argon atmosphere. Reagents were commercial materials (Sigma-Aldrich, Strem). Column chromatography was performed on silica gel (Merck 60). NMR spectra were recorded with a Varian Gemini 300 spectrometer. Mass spectra were recorded with an AMD 402 mass spectrometer. CD and UV spectra were measured on a JASCO J-810 spectrapolarimeter in acetonitrile solutions. IR spectra (KBr pellets) were measured using a Brucker instrument. All calculations were carried out with Gaussian 98 suite of programs [15].

Crystal structure determination. Diffraction data were collected on a KUMA KM4CCD diffractometer [16] using graphite-monochromated MoK_α radiation (λ = 0.71073 Å). The data collection was performed in six separate runs in order to cover the symmetry-independent part of the reciprocal space. The ω-scan was used with the step of 0.75°, two reference frames were measured after every 50 frames, they did not show any systematical changes neither in the peak position nor in their intensities. Total of 782 frames was collected. The unit-cell parameters were determined by least-squares treatment of the setting angles of 3224 highest-intensity reflections, chosen from the whole experiment. The Lorentz and polarization corrections were applied [17] as well as the absorption correction [18]. Relevant crystallographic data, together with data collection and structure refinement details, are listed in Table 4. The structure was solved by direct methods with SHELXS-97 program [19], and refined by full-matrix least-squares on F^2, using SHELXL-97 [20]. Scattering factors incorporated in SHELXL97 were used. The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized, with $w^{-1} = [\sigma^2(F_o)^2 + 0.001P^2]$ ($P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$). Non-hydrogen atoms were refined anisotropically, H1, H2 and H2A hydrogen atoms were refined isotropically, all other hydrogen atoms were located geometrically and were refined as the "riding model" with their isotropic displacement parameters set at 1.2 times (1.3 times for methyl group) U_{eq} of appropriate carrier non-hydrogen atom. One of bromine atoms was found to be disordered over two positions with s.o.f. of 0.5. Both alternative atoms were succesfully refined with anisotropic displacement parameters.

CCDC-211549 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk.).

Table 5. Crystal data and structure refinement for **10**.

Empirical formula	$C_{20}H_{22}Br_2N_2O$
Formula weight	466.22
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.0296(7) Å
	b = 8.8329(8) Å
	c = 12.5427(10) Å
	β = 93.110(6)°
Volume	998.90(14) Å^3
Z	2
Density (calculated)	1.550 Mg/m^3
Absorption coefficient	4.068 mm^{-1}
F(000)	468
Crystal size	0.5 × 0.3 × 0.1 mm^3

Table 5 (continuation)

Theta range for data collection	3.23 to 29.80°
Index ranges	–12 <= h <= 12, –12 <= k <= 6, –16 <= l <=17
Reflections collected	9733
Independent reflections	3424 [R(int) = 0.0670]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3424/1/247
Goodness-of-fit on F^2	0.908
Final R indices [I> 2sigma(I)]	R1 = 0.0344, wR2 = 0.0522
R indices (all data)	R1 = 0.0892, wR2 = 0.0588
Absolute structure parameter	0.003(9)
Largest diff. peak and hole	0.309 and –0.396 e · Å^{-3}

Pd-catalyzed coupling of *trans*-(1*R*,2*R*)-1,2-diaminocyclohexane with aryl dibromides. General procedure. An oven-dried flask equipped with a stirbar was purged with argon, charged with (±)-BINAP (50 mg, 0.08 mmol) and $Pd_2(dba)_3$ (36 mg, 0.04 mmol) and capped with a rubber septum. The flask was purged with argon, and anhydrous toluene (2 mL) was added *via* syringe. The mixture was heated to 80°C with stirring for 30 minutes. After cooling to room temperature, the septum was removed and NaO-*t*-Bu (288 mg, 3.0 mmol) was added in one portion. The flask was capped with the rubber septum and then it was purged with argon. The solution of DACH (137 mg, 1.2 mmol) and aryl dibromide (2 mmol) in 3 mL of anhydrous toluene was added. The mixture was heated with stirring for 16 hours at 105–110°C (oil bath) under argon atmosphere. The mixture was allowed to cool to room temperature, diluted with diethyl ether (20 mL), filtered through the Celite pad and concentrated *in vacuo*. Crude product was then purified by column chromatography (25% dichloromethane in hexane).

***trans*-(1*R*,2*R*)-*N,N'*-Di-(4-bromophenyl)-1,2-diaminocyclohexane (5)**: solidified oil; 56% yield; ^{1}H NMR ($CDCl_3$) δ 1.05–1.15 (m, 2H), 1.20–1.30 (m, 2H), 1.80 (m, 2H), 2.28 (d, J = 13.46 Hz, 2H), 3.13 (m, 2H), 3.80 (br, 2H), 6.47 (d, J = 8.79 Hz, 4H), 7.23 (d, J = 9.06 Hz, 4H); HREIMS *m/z* 423.99545, cacld. for $C_{18}H_{20}N_2Br_2$ 423.99728; UV ε (nm) 4600 (307), 35400 (264), 46300 (200); CD $\Delta\varepsilon$ (nm) –4 (319), +50 (268), –18 (248), 14 (208), –25 (194).

***trans*-(1*R*,2*R*)-*N,N'*-Di-(3-bromophenyl)-1,2-diaminocyclohexane (8a)**: solidified oil; 45% yield; ^{1}H NMR ($CDCl_3$) δ 1.05–1.15 (m, 2H), 1.20–1.25 (m, 2H), 1.80 (m, 2H), 2.28 (d, J = 11.26 Hz, 2H), 3.13 (m, 2H), 3.80 (br, 2H), 6.48 (dd, J = 8.17, 0.84 Hz, 2H), 6.73 (m, 2H), 7.79 (d, J = 8.62 Hz, 2H), 7.00 (t, J = 7.96 Hz, 2H); HREIMS *m/z* 423.99548, calcd. for $C_{18}H_{20}N_2Br_2$ 423.99728; UV ε (nm) 5000 (306), 26800 (260), 45400 (209); CD $\Delta\varepsilon$ (nm) –7 (313), +45 (263), –11 (245), +17 (217), –37 (203).

***trans*-(1*R*,2*R*)-*N,N'*-Di-(6-bromo-2-pyridyl)-1,2-diaminocyclohexane (9a)**: oil; 48% yield; ^{1}H NMR ($CDCl_3$) δ 1.35–1.50 (m, 4H), 1.80 (m, 2H), 2.18 (d, J = 11.26 Hz, 2H), 3.74 (m, 2H), 5.30 (br, 2H), 6.19 (br, 2H), 6.60 (d, J = 7.83 Hz, 2H), 7.11 (t, J = 7.83 Hz, 2H); HRFABMS (NBA matrix) *m/z* 426.99541 (M+H), calcd. for $C_{16}H_{19}N_4Br_2$426.99561; UV ε (nm) 10000 (311), 25100 (252); CD $\Delta\varepsilon$ (nm) +6 (309), +21 (258), –2.5 (238), +22 (201).

Compounds 8b and 9b were obtained according to a general procedure described above, with the following modification: (±)-BINAP (75 mg, 0.12 mmol), $Pd_2(dba)_3$ (55 mg, 0.06 mmol), NaO-*t*-Bu (480 mg, 5.0 mmol) DACH (273 mg, 2.4 mmol) and aryl dihalide (3 mmol) were used in these reactions.

Compound 8b: solidified oil; 42% yield; ^{1}H NMR ($CDCl_3$) δ 1.19–1.23 (m, 4H), 1.74 (m, 4H), 1.78 (m, 4H), 2.30 (m, 4H), 3.12 (m, 4H), 3.62 (br, 2H), 3.91 (br, 2H), 5.83 (s, 1H), 6.02 (dd, J = 7.96, 2.20 Hz, 2H), 6.50 (dq, J = 7.83, 2.47, 2.20, 0.82 Hz, 2H), 6.73 (s, 2H), 6.80 (dq, J = 7.83, 1.92, 0.82 Hz, 2H), 7.01 (td, J = 7.96, 1.10 Hz); ^{13}C NMR ($CDCl_3$) δ 24.5, 24.6, 32.3, 32.7, 57.0, 57.2, 98.6, 103.3, 112.2, 115.6, 120.1, 123.3, 130.3, 130.5, 148.7, 149.1; HRFABMS (NBA matrix) *m/z* 613.13334 (M+H), calcd. for $C_{30}H_{36}N_4Br_2$ 613.13196; UV ε (nm) 10600 (307), 41700 (256), 41500 (230), 57600 (209); CD $\Delta\varepsilon$ (nm) –6 (317), +56 (259), +17 (227), –45 (209).

Compound 9b: solidified oil; 39% yield; ^{1}H NMR ($CDCl_3$) δ 1.26–1.55 (m, 8H), 1.74 (m, 4H), 2.20–2.27 (m, 4H), 3.56–3.74 (m, 4H), 4.60 (br, 2H), 5.56 (br, 2H), 5.60 (d, J = 7.96 Hz, 2H), 6.02 (d, J = 8.24 Hz, 2H), 6.60 (d, J = 7.42 Hz, 2H), 7.04 (t, J = 7.42 Hz, 3H); HRFABMS (NBA matrix) *m/z* 616.11942 (M+H), calcd. for $C_{27}H_{34}N_7Br_2$ 616.12219; UV ε (nm) 17100 (309), 28000 (250), 29700 (197); CD $\Delta\varepsilon$ (νμ) +17 (311), □4 (248), +9 (204).

Compound 13: An oven-dried flask equipped with a stirbar was purged with argon, charged with (±)-BINAP (3.1 mg, 0.005 mmol) and $Pd_2(dba)_3$ (2.2 mg, 0.0025 mmol) and capped with a rubber septum. The flask was purged with argon, and anhydrous toluene (1.5 mL) was added *via* syringe. The mixture was heated to 80°C with stirring for 30 minutes. After cooling to room temperature, the septum was removed and NaO-*t*-Bu (72 mg, 0.75 mmol) was added in one portion. The flask was capped with the rubber septum and then was purged with argon. The solution of DACH (68 mg, 0.6 mmol) and 4-bromobenzonitrile (91 mg, 0.5 mmol) in 2 mL of anhydrous toluene was added. The mixture was heated with stirring for 12 hours at 105–110°C (oil bath) under argon atmosphere. After cooling to room temperature, the septum was removed and (±)-BINAP (3.1 mg, 0.005 mmol), $Pd_2(dba)_3$ (2.2 mg, 0.0025 mmol) and NaO-*t*-Bu (72 mg, 0.75 mmol) were added in one portion. The flask was capped with the rubber septum and then was purged with argon. The solution of **10** (279 mg, 0.6 mmol) in 2 mL of anhydrous toluene was added. The mixture was heated with stirring for additional 12 hours at 105–110°C (oil bath) under argon atmosphere. The mixture was allowed to cool to room temperature, diluted with diethyl ether (10 mL), filtered through the Celite pad and concentrated *in vacuo*. Crude product was then purified by column chromatography (50% dichloromethane in hexane); oil; 22% yield; ^{1}H NMR ($CDCl_3$) δ 1.02–1.83 (m, 19H), 2.20–2.40 (m, 4H), 2.95 (br, 1H), 3.20–3.30 (m, 2H), 3.62 (br, 1H), 4.75 (br, 1H), 6.47 (br, 2H), 6.57 (d, J = 8.51 Hz, 2H), 6.77 (br, 2H), 6.89 (br, 2H), 7.26 (m, 2H), 7.38 (d, J = 8.79 Hz, 2H); HREIMS *m/z* 601.22636, calcd. for $C_{33}H_{38}N_5OBr$ 601.22394; UV ε (nm) 30300 (289), 36900 (262), 65700 (198); CD $\Delta\varepsilon$ (nm) –10 (320), +27 (285), –32 (265), –8 (230), +19 (203).

***trans*-(1*R*,2*R*)-*N*-Acetyl-*N,N′*-di-(4-bromophenyl)-1,2-diaminocyclohexane (10)**: To a solution of **5** (211 mg, 0.5 mmol), triethylamine (0.5 mL) and DMAP (10 mg) in dichloromethane (2 mL), acetic anhydride (2 mL) was added dropwise at 0°C with stirring. The mixture was allowed to warm to room temperature and stirred overnight. Water (5 mL) was added and the mixture was stirred additionally for 2 hours. After separation of the organic layer, the aqueous layer were extracted twice with dichloromethane (5 mL). The organic layers were collected and washed twice with brine, $NaHCO_3$ and water, dried over magnesium sulphate and evaporated to dryness. The crude product was purified by flash chromatography (10% AcOEt in dichloromethane); white solid; 61% yield after crystallization (diethyl ether–hexane); m.p. 104–6, 175–7°C; ^{1}H NMR ($CDCl_3$) δ 1.05–1.90 (m, 10H), 2.28 (d, J = 13.46 Hz, 1H), 2.99 (m, 1H), 4.77 (m, 1H), 6.41 (d, J = 6.87 Hz, 2H), 6.83 (br, 1H), 6.97 (br, 1H), 7.24 (d, J = 6.87 Hz, 2H), 7.46 (br, 1H), 7.52 (br, 1H); HREIMS *m/z* found 466.00923, calcd. for $C_{20}H_{22}N_2OBr_2$ 466.00862; UV ε (nm) 2800 (309), 21200 (259), 62200 (196); CD $\Delta\varepsilon$ (nm) –6 (315), –7 (253), +6 (215), –5 (203), +9 (193).

***trans*-(1*R*,2*R*)-*N,N′*-Diacetyl-*N,N′*-di-(4-bromophenyl)-1,2-diaminocyclohexane (11)**: A solution of **10** (93 mg, 0.2 mmol), triethylamine (0.5 mL) and DMAP (5 mg) in acetic anhydride (2 mL) was heated at 80°C with stirring for 72 hours. The mixture was allowed to cool to room temperature and water (5 mL) was added. The mixture was stirred additionally for 2 hours. After separation of the organic layer, the aqueous layer were extracted twice with dichloromethane (5 mL). The organic layers were collected and washed twice with brine, $NaHCO_3$ and water, dried over magnesium sulphate and evaporated to dryness. The crude product was purified by flash chromatography (10% AcOEt in dichloromethane); oil; 15% yield; ^{1}H NMR ($CDCl_3$) δ 1.11–1.28 (m, 4H), 1.61 (br, 2H), 1.78 (s, 6H), 1.85 (m, 2H), 4.16 (br, 2H), 6.95 (br, 2H), 7.45 (br, 2H), 7.56–7.62 (m, 4H); UV ε (nm) 74600 (196); CD $\Delta\varepsilon$ (nm) +2 (247), –4 (230), +5 (213), –22 (193).

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