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First stereoselective pinacol coupling in the [2.2]paracyclophane series

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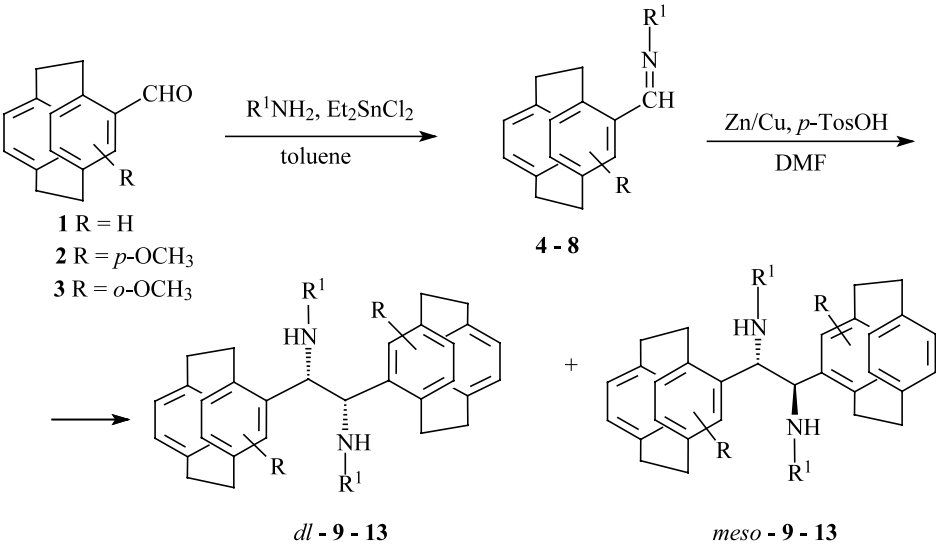
Abstract—The planar chiral *N*-arylimines of [2.2]paracyclophane undergo stereoselective pinacol coupling under the action of the Zn/Cu couple in the presence of *p*-TosOH, thus forming *N*-aryl substituted 1,2-diamines. The stereoselective formation of the asymmetric centers is governed by the planar chiral [2.2]paracyclophanyl moiety.

In the course of our continuing studies directed at the synthesis of planar chiral [2.2]paracyclophanes as ligands for asymmetric synthesis we have already reported a number of efficient methods allowing, inter alia, the preparation of optically pure *ortho*-formyl- and *ortho*-acylhydroxy[2.2]paracyclophanes and their imines, β-diketones, etc.[1] Herein we describe the first synthesis of [2.2]paracyclophane based chiral *N*-aryl substituted 1,2-diamines by stereoselective pinacol coupling of the corresponding *N*-arylimines.

For this purpose we have synthesized a number of novel racemic and enantiomerically pure Schiff bases **4**–**8** by heating aldehydes **1**–**3** with the corresponding arylamines in refluxing toluene in the presence of an Et_2SnCl_2 catalyst (Scheme 1). Aldehydes (±)- and (*R*p)-



Scheme 1.

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1, (±)- and (*R*p)-**3** were synthesized by the previously described procedures.[1–3] For the synthesis of (±)- and (*R*p)-**2** an efficient *para*-regioselective formylation of 4-methoxy[2.2]paracyclophane (similar to regioselective acylation[1]) has been carried out.

The coupling reactions of the imines were performed under conditions similar to those described for different aldehyde derivatives in the arene series.[4] DMF solutions of **4**–**8** were mixed with excess Zn/Cu couple and *p*-TosOH at 0°C and then stirred at room temperature for 24 h (Scheme 1). After workup the crude products were analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio of the product (Table 1). The diamines **9**–**13** were purified by chromatography on silica gel and characterized as diastereomeric mixtures or individual compounds by spectroscopic and chemical analyses.

The pinacol coupling of the [2.2]paracyclophane-derived imines produces diamines, bearing two planar chiral moieties and two asymmetric centers. Starting from racemic imines a mixture of six diastereomers could in principle be obtained, from which two *dl*-pairs and two *meso*-compounds have symmetry (C_2 and C_1, respectively). The coupling of the enantiomerically pure imine could give two chiral C_2-symmetrical diamines, differing in the configuration of the benzylic centers, and one unsymmetrical diastereomer.

According to the ^{1}H NMR data, the coupling of the racemic imines **4**–**8** occurs with formation of mixtures of two diastereomers either in a 1:1 ratio (Table 1, entries 1, 3, and 5) or with a noticeable excess of one diastereomer (Table 1, entries 4 and 7). No traces of the reduction product (the corresponding amine) were detected. The presence of only one half set of signals in the ^{1}H NMR spectra of diamines **9**–**13** indicate the formation of symmetrical compounds. Crystallization of **10** and **11** allowed the isolation of individual crystalline diastereomers, and their structures were determined by X-ray analysis[5] as *meso*-**10** and *meso*-**11** (major) of (*R*p,*S*,*R*,*S*p) relative configurations (Fig. 1). Next we carried out the coupling of imines (*R*p)-**4**, (*R*p)-**7** and (*R*p)-**8** (Table 1, entries 2, 6 and 8) and observed in each case the stereoselective formation of the single chiral products **9**, **12** and **13**.[6] By comparison of the ^{1}H NMR spectra the alternate products formed in the coupling of racemic **4**, **7** and **8** could be assigned as *meso*-diastereomers. The relative configuration of the diastereomerically pure **13** was determined as (*R*p,*S*,*S*,*R*p) by 2D ^{1}H NMR experiments.

Table 1. Pinacol coupling of the imines **4**–**8** with Zn/Cu couple and *p*-TosOH

Entry	R	R^1	Imine	Diamine	Isolated yield (%)	*dl*:*meso*[a] or $[\alpha]_D^{22}$
1	H	Ph	**4**	**9**	60	50:50
2	H	Ph	(*R*p)-**4**	(*R*p,*S*,*S*,*R*p)-**9**[7]	64	−15.7 (*c* 0.36, C_6H_6)
3	H	2-BrC_6H_4	**5**	**10**[5]	40	51:49
4	H	2,6-Me_2-C_6H_3	**6**	**11**[5]	67	15:85
5	*p*-OCH_3	Ph	**7**	**12**	64	50:50
6	*p*-OCH_3	Ph	(*R*p)-**7**	(*R*p,*S*,*S*,*R*p)-**12**[8]	46	+49.4 (*c* 0.23, C_6H_6)
7	*o*-OCH_3	Ph	**8**[5]	**13**	35	25:75
8	*o*-OCH_3	Ph	(*R*p)-**8**	(*R*p,*S*,*S*,*R*p)-**13**[9]	35	+28.7 (*c* 0.27, C_6H_6)

[a] Determined by ^{1}H NMR analysis of the reaction mixtures.

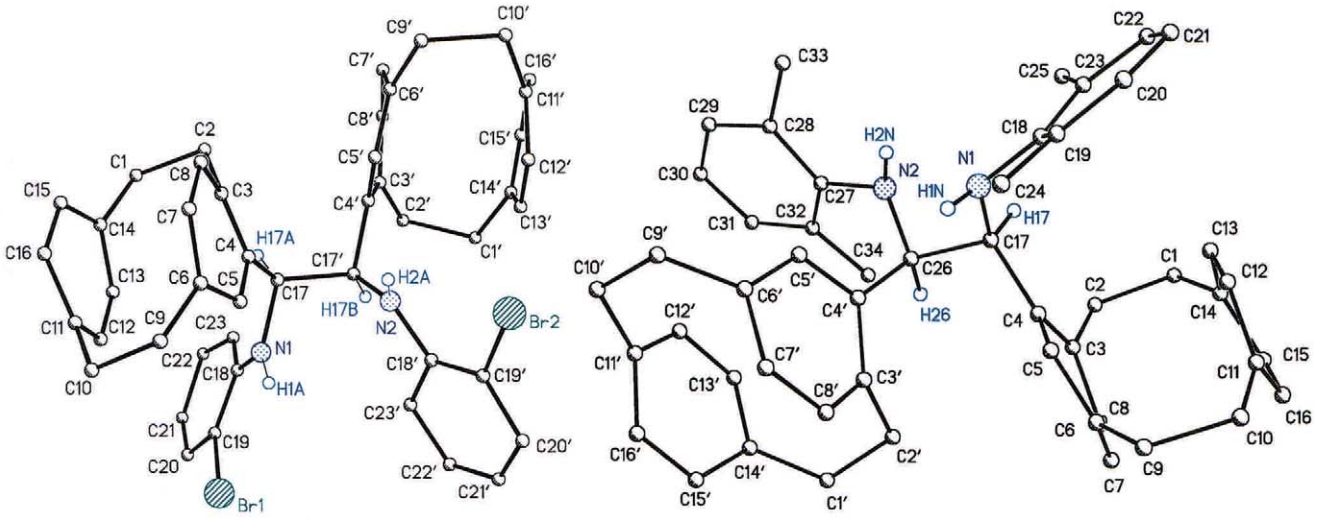

Figure 1.

Relying on the established relative configurations for *meso*-**10** and **11** and chiral **13** we assume that the planar chiral [2.2]paracyclophane moiety plays a key role in the stereochemical outcome of the reaction. Thus, if the activated imine fragment of compounds **4–7** react in *anti* conformation to the nearest ethylene bridge, the *Si*-site (for the (*R*p)-enantiomer) or *Re*-site (for the (*S*p)-enantiomer) should not be shielded by the protons of the unsubstituted [2.2]paracyclophane ring. Coupling between paracyclophanyl fragments with opposite configurations, i.e. (*R*p)- and (*S*p), should lead to the *meso*-diastereomer with (*R*p,*S*,*R*,*S*p)-configuration, which was unequivocally established for **10** and **11**, whereas the coupling of two paracyclophanyl fragments with the same absolute configuration should give rise to the (*R*p,*S*,*S*,*R*p)- or (*S*p,*R*,*R*,*S*p)-diamines. At the same time the X-ray structure of the imine **8**[5] bearing an *ortho*-substituent reveals that now the more preferable conformation of the imine fragment is the one with the *N*-Ph substituent in *syn*-orientation to the ethylene bridge, due to the repulsive interaction with the OCH_3 group. Thus, the stereochemical outcome of the coupling reaction should be opposite to that observed for the reaction of the imines **4–7**. However, for the imine **8** (and hence for the diamine **13**) the configuration of the planar chiral [2.2]paracyclophane fragment changes because of the nomenclature priority of the OCH_3 group over the imino group. Hence the coupling of paracyclophanyl fragments having opposite configurations should give (*R*p,*S*,*R*,*S*p)-**13**, whereas the coupling of two paracyclophanes with the same configurations should afford (*R*p,*S*,*S*,*R*p)-/(*S*p,*R*,*R*,*S*p)-**13**.

In conclusion, the pinacol coupling of the enantiomerically pure planar chiral *N*-aryl substituted imines of [2.2]paracyclophane occurs stereoselectively giving rise to diastereomerically pure diamines. Coupling of the racemic imines produces a mixture of the single racemic *dl*- and single *meso*-diamines. The newly synthesized chiral compounds can be regarded as potential chiral ligands in a wide range of stereoselective reactions proceeding with participation of chiral diamines.[10] The scope of the application of the pinacol coupling to the synthesis of other [2.2]paracyclophane based diamines (*N*-unsubstituted or *N*-alkyl substituted), diols and amino alcohols possessing planar and central chirality applying either the Zn–sulfonic acid system or other classical reagents (such as Sm and low valent Ti derivatives, etc.) is now in progress.

Acknowledgements

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7. **(*R*p,*S*,*S*,*R*p)-9**: Mp 125–126.5°C.—$C_{46}H_{44}N_2$ (624.87) calcd: C, 88.42; H, 7.10; N, 4.48; found: C, 88.49; H, 7.39; N, 4.04%.—^{1}H NMR (C_6D_6): $\delta = 2.30$–2.40 (m, 2H), 2.60–2.90 (m, 12H), 3.35–3.44 (m, 2H), 4.13 (d, $^3J = 9.35$ Hz, 2H, 2CH), 5.20 (d, $^3J = 9.35$ Hz, 2H, 2NH), 5.53 (s, 2H), 6.10 (d, $^3J = 7.8$ Hz, 2H), 6.24–6.53 (m, 10H), 6.88 (m, 2H), 6.98 (m, 4H), 7.30 (m, 4H).—^{13}C NMR ($CDCl_3$): $\delta = 34.19$, 34.96, 35.21 (2C), 56.62, 113.12 (2C), 117.60, 129.80 (2C), 131.05, 131.84, 132.09, 132.16, 132.23, 132.65, 134.41, 135.47, 137.28, 138.75, 139.01, 139.11, 147.74.—MS (70 eV); *m*/*z* (%): 312 (49) [M$^+$/2].
8. **(*R*p,*S*,*S*,*R*p)-12**: Mp 109.5–112°C.—$C_{48}H_{48}N_2O_2$ (684.92) calcd: C, 84.17; H, 7.06; N, 4.09; found: C, 83.97; H, 7.39; N, 3.84%.—^{1}H NMR ($CDCl_3$): $\delta = 2.15$–2.27 (m, 2H), 2.56–2.67 (m, 2H), 2.72–2.82 (m, 2H), 2.84–2.98 (m, 6H), 3.04–3.25 (m, 4H), 3.74 (s, 6H, $2OCH_3$), 3.84 (br.s, 2H, 2CH), 4.94 (br.s, 2H, 2NH), 5.32 (s, 2H), 5.60 (s, 2H), 5.99 (d, 2H), 6.25 (d, 2H), 6.36 (d, 2H), 6.65 (d, 2H), 6.78–6.87 (m, 6H), 7.28–7.36 (m, 4H).—^{13}C NMR ($CDCl_3$): 31.61, 33.35, 33.76, 34.75, 54.10, 55.85, 113.24 (2C), 117.34, 117.48, 126.08, 128.00, 128.06, 129.75 (3C), 130.58, 132.35, 132.72, 133.35, 138.07, 139.27, 139.71, 147.85, 156.41.—MS (70 eV); *m*/*z* (%): 342 (16) [M$^+$/2].
9. **(*R*p,*S*,*S*,*R*p)-13**: Mp 227.5–229°C.—$C_{48}H_{48}N_2O_2$ (684.92) calcd: C, 84.17; H, 7.06; N, 4.09; found: C, 84.27; H, 7.20; N, 4.13%.—^{1}H NMR ($CDCl_3$): $\delta = 2.45$–2.58 (m, 2H), 2.65–2.79 (m, 4H), 2.83–2.96 (m, 4H), 2.98–3.06 (m, 2H), 3.07–3.16 (m, 4H), 3.43 (s, 6H, $2OCH_3$), 4.75 (br.d, 2H, 2CH), 6.08 (d, 2H, 2NH), 6.12–6.20 (m, 4H), 6.29 (d, 2H), 6.42 (d, 2H), 6.47 (d, 2H), 6.53 (d, 2H), 6.60–6.70 (m, 6H), 7.15–7.25 (m, 4H).—^{13}C NMR ($CDCl_3$): 32.49, 34.66, 34.88, 34.96, 61.16, 61.87, 112.30 (2C), 116.01, 129.17, 129.35, 129.75 (2C), 130.70, 131.10, 131.87, 132.61, 132.83, 135.63, 138.98, 139.31, 140.76, 149.35, 159.56.—MS (70 eV); *m*/*z* (%): 342 (20) [M$^+$/2].
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