Rigid Alicyclic Molecules from Bicyclo[2.2.1]hept-2-enes (= 8,9,10-Trinorbornenes) and 1,4-Dipyridin-2-ylphthalazines as Stereoselective Coupling Agents

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For the preparation of rigid polycyclic molecules from 8,9,10-trinorbornenes (= bicyclo[2.2.1]hept-2-enes), 1,4-dipyridin-2-ylphthalazines were used. Cycloaddition reactions with trinorbornenes gave coupled products in a stereoselective manner. In these reactions, the phthalazines delivered a new bicyclo[2.2.2] moiety at the junction of two trinorbornene units, which could bear appropriate functional groups (*Schemes 4* and *5*). The crystal structure of a key cycloadduct, *i.e.*, of **18** was also determined (*Fig. 2*). Relative reactivities for a series of phthalazines (*Fig. 3*) were estimated by density-functional-theory (DFT) calculations at the B3LYP/6-31G* level (*Table*). The calculations indicated an increase of reactivity when the aromaticity of the phthalazine moiety is decreased. Finally, experimentally observed stereoselectivities of the phthalazine reactions with trinorbornenes were readily predicted by DFT calculations (*Fig. 4*).

Introduction. – A particularly effective way of linking two 8,9,10-trinorbornenes (= bicyclo[2.2.1]hept-2-enes) [1] involves the coupling of fused trinorbornenes with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole [2]. The oxadiazole coupling delivers a new 7-oxabicyclo[2.2.1] moiety at a junction of two trinorbornene units (see **A**, *Fig. 1*). Another coupling method employs 1,2,4-triazine chemistry to effect the linking process. Here, the intermediate aza-1,3-diene formed in the reaction of the bicyclo[2.2.1]alkene with 1,2,4-triazine is not isolated, but is coupled *in situ* with a second equiv. of the bicyclo[2.2.1]alkene to afford a rigid, aza-bridged polycyclic product. The 1,2,4-triazine coupling protocol affords a new design element, namely, the ability to introduce an effector (in the case of phenanthroline-fused 1,2,4-triazine, this is a bidentate ligand), which is at right angles to the long axis of the polytrinorbornene rod or curve in the coupled product (see **B**, *Fig. 1*). Similar geometrical arrangements were obtained by treatment of trinorbornene polycycles with 3,6-disubstituted-1,2,4,5-tetrazines (*s*-tetrazines). When conducted in the presence of Et_3N, these reagents yield stable solutions of 4,5-dihydropyridazines. The latter can serve as 1,3-diene for the coupling

with another bicyclo[2.2.1]alkene under high pressure, to efficiently produce symmetrical and unsymmetrical polycyclic products (see **C**, *Fig. 1*) [3]. In these synthetic protocols, reactions of the triazine and tetrazine produce at the junction a bicyclo[2.2.2] moiety which slightly alters the overall curvature of the polytrinorbornane products [4]. It is important to note that coupling reagents in three synthetic protocols undergo *Diels–Alder*/elimination/*Diels–Alder* reactions [5] in a highly stereoselective manner. While oxadiazole and 1,2,4-triazine coupling reagents are synthetically more feasible for the preparation of symmetric polytrinorbornanes, *s*-tetrazines are more versatile and enable the synthesis of symmetrical as well as nonsymmetrical products.

The development of coupling reagents for the introduction of novel architectural elements into polytrinorbornanes is an ongoing part of our research. For our forthcoming studies of functionalized polytrinorbornanes, it is desirable that these cycloaddition reagents possess functionalities attached at specific positions. These functionalities could be incorporated in the course of the cycloaddition coupling process at required geometrical position within a product of the general structure **D** (*Fig. 1*). A literature search revealed that reports on the synthesis of polycyclic compounds made of alternate bicyclo[2.2.1] and bicyclo[2.2.2] units are scarce, and none of them has a bicyclo[2.2.2] moiety fused to an aromatic ring and attached effectors [6]. We found pyridazine [7] and phthalazine derivatives [8] are the best candidates for obtaining polycycles with structures of type **D**. The most remarkable example of a phthalazine coupling reaction was reported by *Komatsu* and co-workers, in which two fullerene molecules produce a symmetrical 2:1 product joined by a benzobicyclo[2.2.2] unit, under mechanochemical conditions [9]. With the requirement of C_{2v}-symmetry of the final products, phthalazine reagents were chosen.

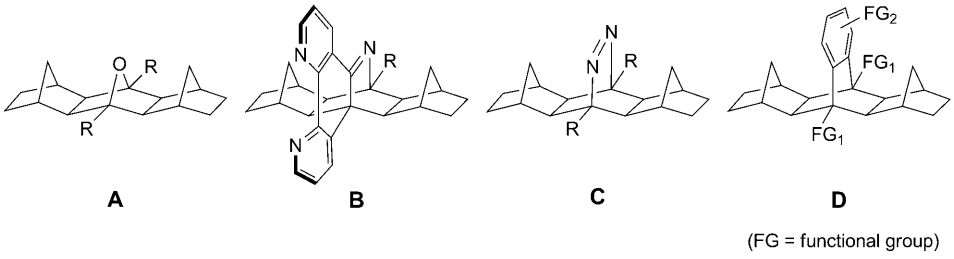


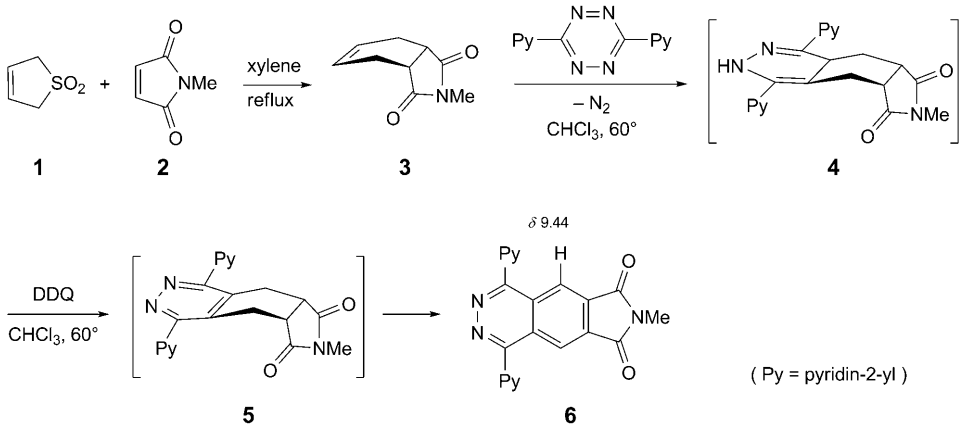
Fig. 1. *Design elements delivered by coupling reagents in polytrinorbornanes*

Here, we report preliminary results of our study on the use of phthalazines in trinorbornene coupling protocols. We aimed to ascertain the synthetic feasibility of phthalazines to act as novel coupling reagents for bicyclo[2.2.1]alkenes. In particular, we addressed the following issues: *i*) the cycloaddition reactivity of phthalazines towards trinorbornenes and heterotrinorbornenes; *ii*) the substitution patterns that are required to increase their reactivity; *iii*) the stereoselectivity of these reactions.

Results and Discussion. – *Syntheses.* The method which was previously used to synthesize 1,4-dipyridin-2-ylphthalazine-6,7-dicarboximide (**6**) [10] by 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) oxidation of the corresponding 7-oxatrinorbornene precursor proved to be unsatisfactory for the production of sufficient

amounts of **6**. Other reagents ($PhI(OAc)_2$, $TiCl_4/LiAlH_4$, $BF_3 \cdot Et_2O$, DBU/LiI, $HClO_4$, and $SnCl_4$) which are used to aromatize the 7-oxatrinorbornene moiety also failed. Finally, we developed a new and simplified synthetic method, by which useful quantities of **6** could be prepared (*Scheme 1*): First adduct **3** was prepared by heating sulfone **1** and *N*-methylmaleimide (**2**) in xylene. Subsequent addition of 3,6-dipyridin-2-yl-*s*-tetrazine followed by aromatization of **4** with DDQ in $CHCl_3$ yielded **6**. The most characteristic indicative ^{1}H-NMR chemical shift of **6** is that of the aromatic H-atoms of the central ring, which appear as a *s* at δ 9.44.

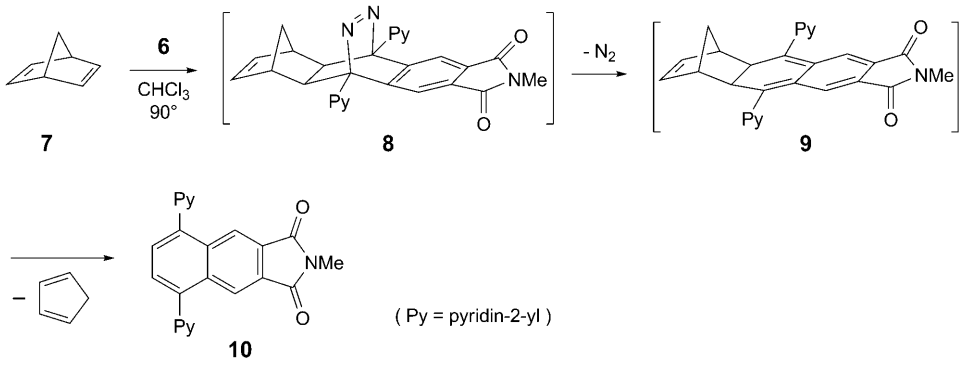
Scheme 1. *Synthetic Route to* **6**



1 **2** **3** **4** **5** **6**

The heterodiene **6** was subjected to a series of cycloaddition reactions with trinorbornen-type dienophiles. Firstly, phthalazine derivative **6** reacted with trinorbornadiene **7** on heating in $CHCl_3$ (90°, sealed tube) to form naphthalene derivative **10** (*Scheme 2*). The formation of product **10** was rationalized by the formation of an intermediate cycloadduct **8**, which spontaneously loses N_2 and subsequently cyclopentadiene in a cycloreversion process [11].

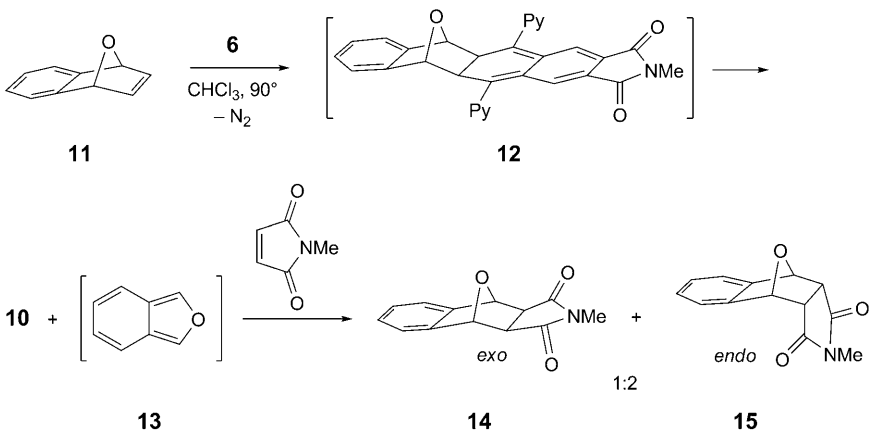
Scheme 2. *Reaction of* **6** *with Trinorbornadiene*



7 **8** **9** **10**

Phthalazine derivative **6** reacted with 7-oxabenzotrinorbornadiene in an analogous cycloaddition/cycloreversion manner [12] (*Scheme 3*). By thermal fragmentation of the initially formed adduct **12**, isobenzofuran **13** was obtained and trapped *in situ* with *N*-methylmaleimide, yielding *exo*- and *endo*-adducts **14** and **15** in a 1:2 ratio. When the reactions shown in *Schemes 2* and *3* were performed at lower temperatures (room temp.) to suppress the cycloreversion process, the obtained mixtures of products contained significant amounts of unreacted starting materials.

Scheme 3. *Reaction of* **6** *with 7-Oxabenzotrinorbornadiene*

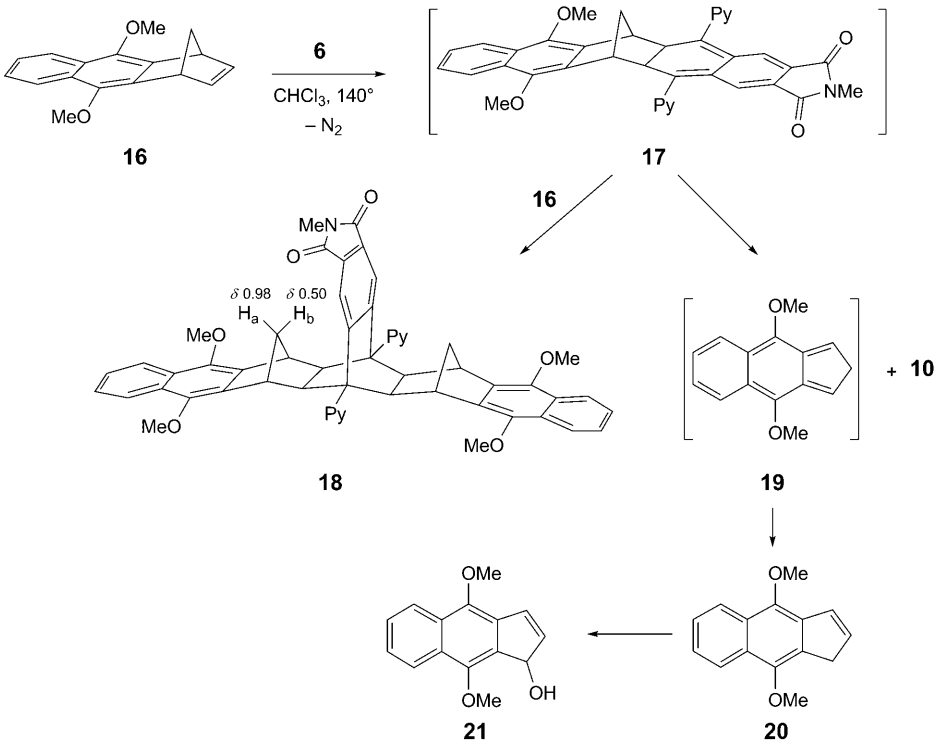


For the less reactive dienophiles, elevated temperatures were required. The reaction of phthalazine derivative **6** with alkene **16** takes place at 140° in $CHCl_3$ (high-pressure vessel) to give the 1:1 cycloadduct **17**, which was not isolated or detected spectroscopically, since it reacted further to form the 2:1 adduct **18** (32% yield; *Scheme 4*). The structure of the new product was deduced from its ^{1}H-NMR data and unequivocally established by single-crystal X-ray-analysis (*Fig. 2*). The most diagnostic ^{1}H-NMR chemical shifts of adduct **18** are those of the CH_2 H_a- and H_b-atoms facing the aromatic rings [13]. These H-atoms are shielded especially by the central aromatic ring, thus appearing at higher field (δ 0.50 and 0.98, resp.). A similar ^{1}H-NMR shielding of CH_2 H-atoms was observed earlier in our work on the 3,6-dipyridin-2-yl-*s*-tetrazine, 1,3-diazaanthracene (= benzo[*g*]quinazoline), and anthracene adducts with trinorbornenes [14].

It was found that the intermediate adduct **17**, under these reaction conditions, also underwent thermal fragmentation with loss of naphthalene-2,3-dicarboximide **10** (isolated in 6% yield), to afford the 2*H*-benz[*f*]indene intermediate **19**. However, this reactive species was not isolated or observed spectroscopically but deduced on the basis of the isolation of the rearranged more stable 1*H*-benz[*f*]indene **20** (3%), together with small amounts of the hydroxylated derivative **21** (3%). Our attempts to establish the existence of **19** by *in situ* trapping with *N*-methylmaleimide were unsuccessful (at 140°).

To study the influence of the imide substitution in phthalazine-6,7-dicarboximide **6** with respect to its cycloaddition reactivity, the corresponding 6,7-unsubstituted phthalazine **24** was prepared by reaction of *in situ* generated benzyne (**23**) with 3,6-

Scheme 4. *Reaction of* **6** *with* **16**



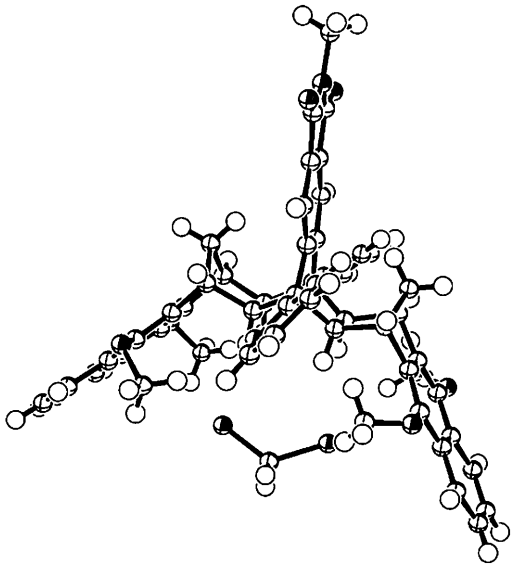
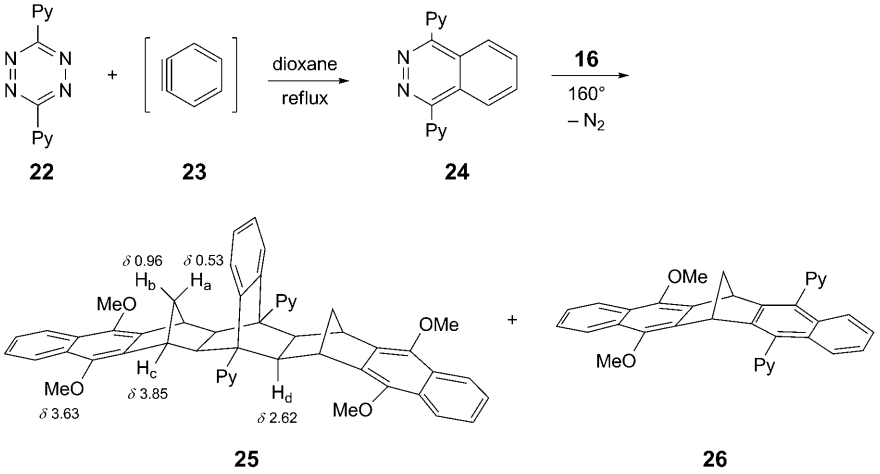


Fig. 2. *Crystal structure of adduct* **18** (40% probability thermal ellipsoids)

dipyridin-2-yl-*s*-tetrazine (**22**; *Scheme 5*). Phthalazine **24** reacted with bicyclo[2.2.1]alkene **16** in a similar manner as **6** to produce the 2:1 adduct **25** (26% yield). The aromatized 1:1 intermediate **26** was also detected. Analogously to **18**, the structure of cycloadduct **25** was established by ^{1}H-NMR spectroscopy, in particular, by the chemical shifts of the CH_2 H_a- and H_b-atoms (δ 0.53 and 0.96, resp.).

Scheme 5. *Reaction of* **16** *with* **24**

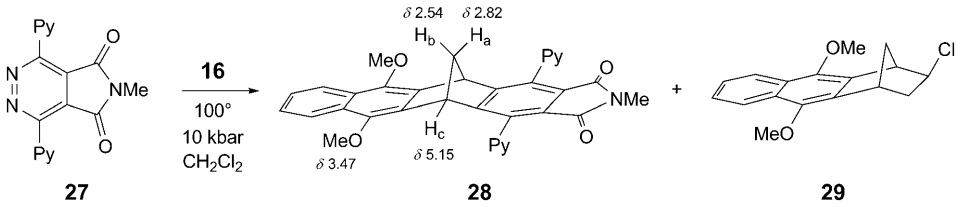


Coupling reactions of unsubstituted phthalazine (see below, **37** in *Fig. 3.*) were less successful due to lower reactivity of unsubstituted phthalazine. Reaction of the latter with **16** gave no product, even under high-pressure conditions (8 kbar, 100–120°, 2 d, CH_2Cl_2). The only detectable product was chlorinated **29** (see below, *Scheme 6*), while phthalazine decomposes under these reaction conditions. When the reaction of phthalazine and trinorbornene was conducted under high-pressure conditions (8 kbar, 100°, 1 d, CH_2Cl_2), an inseparable mixture of products was obtained, containing mostly decomposition products of phthalazine.

Cycloaddition reactivity was further diminished when a benzene ring was removed from phthalazine-6,7-dicarboximide **6** to obtain 3,6-dipyridin-2-ylpyridazin-4,5-dicarboximide **27**. When similar reaction conditions as for **24** were employed, **27** did not react with alkene **16** or 7-oxabenzotrinorbornadiene **11**. Experiments conducted thermally within a temperature range of 140–180° (overnight) did not give adducts. Further temperature increase caused decomposition of **27**.

Finally, pyridazine derivative **27** reacted with alkene **16** under high pressure (10 kbar, 100°, 2 d, CH_2Cl_2). Two products were obtained, oxidized 1:1 adduct **28** (18%) as well as chlorinated product **29** (18%) (*Scheme 6*). Characteristic chemical shifts in the ^{1}H-NMR spectrum of **28** possess again the CH_2 H-atoms, and the bridgehead H-atoms H_c (δ 5.15), being deshielded by the magnetic cone of pyridine rings (in alkene **16** these H-atoms occur at (δ 4.34). Similarly, the MeO groups are shielded by the pyridine substituents appearing at higher magnetic field (δ 3.47 (**28**) *vs.* 4.00 (**16**)).

Scheme 6. *Reaction of* **16** *with* **27**

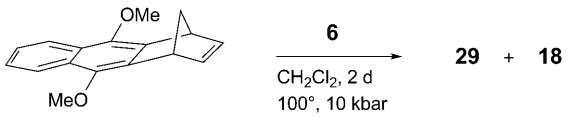


27 **28** **29**

Furthermore, isomeric adducts of isobenzofuran with 7-oxabenzonorbornadiene **11** were obtained in a 1:10 ratio by reaction of pyridazine derivative **27** with **11** (10 kbar, 100°). These results show that **27** has the lowest reactivity amongst the heterodienes investigated in this study. Its incapacity to form 2:1 cycloadducts with bicyclo[2.2.1]alkenes rules out the use of **27** as coupling reagent.

To increase yields and prevent the undesired thermal fragmentation, the reaction of **6** with **16** was conducted under high pressure but at lower temperature. Under these reaction conditions (100°, CH_2Cl_2, 10 kbar, 2 d), alongside with product **18** (35%), again the chlorinated product **29** was formed in significant amount (10%) (*Scheme 7*). High-pressure reactions of **16** with phthalazine derivative **24** and pyridazine derivative **27** also gave **29** (10 and 18% yield, resp.). It was presumed that, under high pressure/high temperature conditions, phthalazine derivatives **6** and **24** as well as pyridazine derivative **27** act as a base; there is a Cl radical formed that adds to the C=C bond. When these phthalazines were replaced by organic bases such as Et_3N, pyridine, or quinoline (or when just CH_2Cl_2 solvent was used), the chlorinated product was not detected. These data suggest that the −N=N− element present in the phthalazine moiety is required for this reaction to proceed. The addition of a radical scavenger (benzoquinone) helped to effectively suppress the formation of **29**, therefore indicating that a radical mechanism is involved. Concomitantly, the yields of cycloadducts **18** and **25** were increased to 48 and 46%, respectively.

Scheme 7. *Reaction of* **6** *with* **16** *under High Pressure*



16

Crystal-Structure Determination. The crystal-structure analysis shows that in the structure of **18**, two naphthalene rings are positioned at an interplanar angle of 75.1° (divergent aromatic-walls orientation) and a top-of-wall separation distance of 13.4 Å (*Fig. 2*), closely resembling structural features of the previously published U-shaped cavity of polytrinorbornane structures [15].

The most interesting feature of the crystal structure of adduct **18** is that a CH_2Cl_2 molecule is incorporated within the cavity, thus acting as a 'molecular tweezers'. CH_2Cl_2 is positioned in the centre of the cavity, where the plane defined by Cl−C−Cl is perpendicular to the planes defined by the naphthalene rings. There is an almost

symmetrical orientation of the guest molecule within the cavity, having the shortest contact distances between Cl-atoms and aromatic C-atoms of 3.56 and 3.71 Å. All four MeO groups of the host system are pointing inwards, forming, together with two 2-pyridinyl substituents, an almost bowl-shaped cavity, which is large enough to accommodate small guest molecules. These structural features indicate a possibility for molecular recognition, as earlier observed for related polycyclic systems by *Klärner* and co-workers [16] and *Stoddart* and co-workers [17].

Computational Study. The reactivity of a series of phthalazines shown in *Fig. 3* was investigated computationally. The FMO analysis revealed that all the studied *Diels–Alder* cycloadditions of heteroaromatic dienes are inverse-electron-demand reactions, where $HOMO_{(trinorbornadiene)}-LUMO_{(diene)}$ are dominant orbital interactions [18]. The highest reactivities were predicted for heterodienes possessing the smallest FMO gaps: **41** (2.69 eV), **34** (3.13 eV), and **38** (3.13 eV).

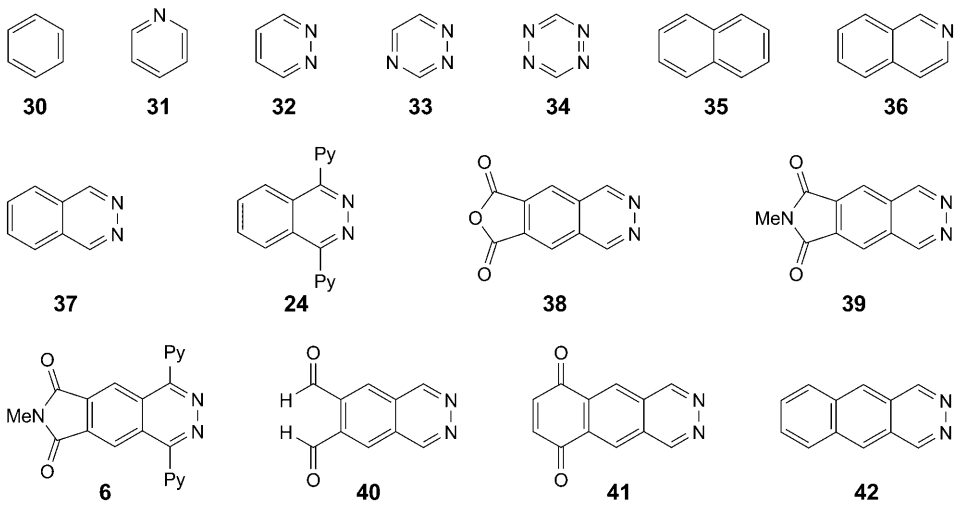


Fig. 3. *Computationally studied heterodienes*

More realistic results for reactivities of the studied phthalazines could be obtained by estimation of activation energies, performing transition-state (TS) calculations [19]. The results for cycloadditions with ethylene and bicyclo[2.2.1]alkenes are collected in the *Table*. The calculated transition states speak for a concerted, synchronous cycloaddition mechanism. The relative reactivities of phthalazines in model cycloaddition reaction with ethylene are similar to the predictions obtained from the FMO analysis of reactants in the ground state. However, the relative order of reactivity of phthalazines is slightly changed, when reactions with trinorbornenes were calculated. In these cases, more realistic systems (which are closer to the experiments) take into account the steric situation around the trinorbornene π-bond. The lowest activation energies were found for reactions of dienes **34** and **6** (12.88 and 17.60 kcal mol^{-1}, resp.). TS Calculations also reveal that the introduction of more N-atoms in the heterocycles makes these dienes more reactive, as shown by their relative order: **34** > **33** > **32** > **31** > **30** and **37** > **36** > **35**. We assume that introduction of more N-atoms in the aromatic ring

decreases the aromaticity of these heteroaromatic rings, thus making them more reactive. From the synthetic point of view, more interesting are the predictions of the influence of various substituents on the reactivity of the phthalazine moiety. These indications are important for the molecular design of phthalazine coupling reagents possessing desired functionalities. Firstly, it was predicted that the attachment of an anhydride (or imide) ring to the 6,7-positions of the phthalazine ring system increases its reactivity: **38** > **39** > **37**. Similarly, the incorporation of the phthalazine moiety into a larger aromatic anthracene-like system to form benzo[*g*]phthalazine-6,9-dione (**41**) and benzo[*g*]phthalazine (**42**) increases the reactivity: **41** > **42** > **37**. Although anthracenes are known to react exclusively across their 9,10-positions, the activation energies for reactions of **41** and **42** across the 5,10-positions (corresponding to the 9,10-positions) are predicted to be much larger than for the 1,4-ring position (30.63 and 27.78 kcal mol^{-1}, resp.). The introduction of aldehyde functionalities in **40** is also beneficial for an activation-barrier lowering. Finally, TS calculations reveal that the incorporation of pyridin-2-yl substituents at the 1,4-positions of phthalazine also decrease the activation barrier, mainly due to the electron-donating effects of the aromatic ring. The predicted relative reactivities are: **6** > **39** > **24** > **37**.

A comparison of the activation energies for reactions of phthalazines **38**, **39**, and **6** with trinorbornenes shows that introduction of a 7-oxa bridge in the trinorbornene moiety lowers the activation energy for the preferred diene approach. Furthermore, introduction of the second C=C bond in 7-oxatrinorbornene further decreases the activation energy, while trinorbornene and trinorbornadiene have almost identical activation energies. The reactivity diminishes in the following order: 7-oxatrinorbornadiene > 7-oxatrinorbornene > trinorbornene > trinorbornadiene.

Table. *B3LYP/6-31G* Activation Energies* (E_{act} [kcal mol^{-1}]) *for* the *Cycloaddition Reaction of Some Dienophiles to Dienes* **6**, **24**, *and* **30**–**42** (*Fig. 3*)

	CH_2=CH_2								
		exo,exo	*exo,endo*	*exo,exo*	*exo,endo*	*exo,exo*	*exo,endo*	*exo,exo*	*exo,endo*
30	40.6	42.52							
31	33.7	35.73	35.43						
32	27.9	29.79	28.97						
33	20.5	21.69	21.23						
34	13.2	12.88							
35	33.8	36.30	35.99						
36	28.2	29.12	29.93						
37	24.9	26.74	26.33						
38	21.6	22.88	21.97	23.02	21.65	24.18	22.55	17.54	20.31
39	22.9	24.62	23.73	20.59	23.74	25.83	24.28	19.36	21.89
6	24.3	19.75	17.60	14.48	15.59	20.21	17.72	12.61	13.84
40	21.9	27.45	21.89						
41	22.7	22.99	24.12						
42	24.1	24.49	25.89						
24	23.8	24.37	26.59						

For the formation of 1:1 trinorbornene adducts, just a slight preference was found for most of the studied diene–dienophile pairs. The small energy difference for the linear/bent approach of diene to trinorbornenes indicates that mixtures of two isomers may be formed[1]). Since the facile elimination of N_2 from initially formed 1:1 adducts leads to the formation of the planar 1,3-diene system, the knowledge of stereoselectivities has no relevance for the stereochemical outcome for the final 2:1 coupled adducts.

Experimentally observed stereoselectivities of the phthalazine reactions with trinorbornenes are readily predicted by density-functional-theory (DFT) calculations. As a model, reaction of trinorbornadiene with phthalazine derivative **38** was calculated. The final stereochemical outcome is determined in the last cycloaddition step, when trinorbornadiene approaches the 1:1 intermediate. There are eight possible approaches, as shown in *Fig. 4*. Four modes of dienophile approaches are from the bottom (*endo*) face of the intermediate (→ **TS1**–**TS4**) (defined with respect to the trinorbornene moiety of the intermediate), and four approaches are from the top (*exo*) face (→ **TS5**–**TS8**). The B3LYP/6-31G* calculations clearly indicate that the dienophile (trinorbornadiene) approach from the *endo* face of the diene is energetically preferred over the *exo* approach (by more than 8 kcal mol^{-1}). Out of four modes of trinorbornadiene addition from the *exo* face, the severe steric congestions prevented the calculation convergence in the cases of **TS6** and **TS8**.

Cycloaddition on the *endo*-face of trinorbornene is preferred over the *exo* face for all trinorbornadiene approaches depicted in *Fig. 4*. These predictions are in good accordance with previously published experimental and theoretical results on trinorbornene π-facial selectivity [20]. Accordingly, **TS2** and **TS4** have a higher activation energy than **TS1** and **TS3** (E_a [kcal mol^{-1}] 19.56 (**TS2**) 20.34 (**TS4**), 14.34 (**TS1**), and 16.88 (**TS3**)). The lowest activation energy was calculated for **TS1**, which leads to the formation of the symmetrical product (*Fig. 5*). This value is almost identical to the activation energy calculated for the model reaction of ethylene with 2,3-dihydronaphthalene, which is the part of structure of the intermediate 1:1 diene (14.4 kcal mol^{-1}). This result indicates that the incorporation of the 2,3-dihydronaphthalene fragment in the polycyclic structure does not significantly change its reactivity. On the other hand, the activation energy calculated for the ethylene reaction with *o*-quinodimethane (= 5,6-bis(methylene)cyclohexa-1,3-diene; 7.9 kcal mol^{-1}), reveals that the imposed ring strain in the polycyclic 1:1 intermediate diene significantly diminishes the reactivity of *o*-quinodimethane.

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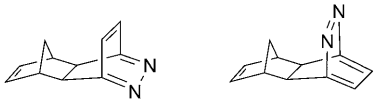
[1]) *exo*,*exo*-Orientation has the N-atoms positioned at the molecule terminus, producing linear products, while *exo*,*endo*-orientation has the N-atoms positioned close to the CH_2 bridge of the trinorbornene fragment, giving bent products.



exo,exo *exo,endo*

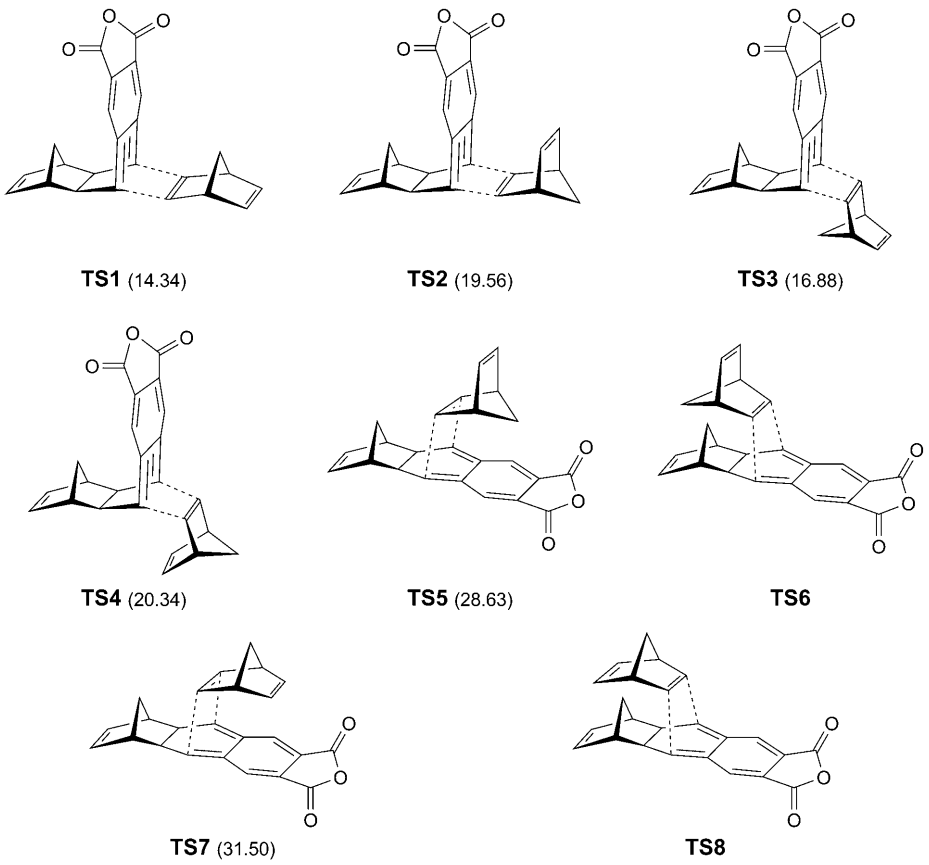


Fig. 4. *Addition modes for the reaction of trinorbornadiene and* **38**. Activation energies ([kcal mol^{-1}]) are given in parentheses

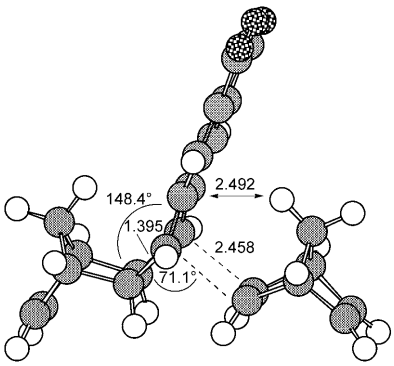


Fig. 5. *B3LYP Optimized structure of* **TS1**

Conclusions. – Phthalazines are shown to act as coupling reagents for the formation of polytrinorbornenes, delivering new design elements for alicyclic products. Cyclo-

addition reactions of 1,4-dipyridin-2-ylphthalazines with trinorbornenes give coupled products in a highly stereoselective manner. In these reactions, phthalazines deliver a new bicyclo[2.2.2] moiety at the junction of two trinorbornene units, which possess appropriate effectors. The crystal structure of a key cycloadduct was also determined, confirming the structural assignments obtained from spectroscopy. Moreover, the relative reactivities of a series of phthalazines were estimated by DFT calculations at the B3LYP/6-31G* level. Transition-state calculations indicated the increase of reactivity by a decrease of aromaticity of the phthalazine moiety. Experimentally observed stereoselectivities of the phthalazine reactions with trinorbornenes were readily predicted by DFT calculations.

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Experimental Part

1. *General.* ^{1}H- and ^{13}C-NMR Spectra: δ in ppm, J in Hz. HR-MS: in m/z.

2. *7-Methyl-1,4-dipyridin-2-yl-6*H*-pyrrolo[3,4-g]phthalazine-6,8(7*H*)-dione* (**6**). *Method A* [10]: Yield 63%.

Method B: A soln. of finely ground *N*-methylmaleimide (=1-methyl-1*H*-pyrrol-2,5-dione; 1.00 g, 9.01 mmol) and 2,5-dihydrothiophene 1,1-dioxide (1.80 g, 15.25 mmol) in xylene (2 ml) was refluxed for 1 h. Two more batches of 2,5-dihydrothiophene 1,1-dioxide (1.80 g, 15.25 mmol) were added within the next hour. The mixture was cooled to r.t. and diluted with xylene (2 ml), and petroleum ether (PE) was added until the soln. became turbid. Cooling at $-18°$ produced crystals which were collected by filtration: 0.85 g (57%) of *3a,4,7,7a-tetrahydro-2-methyl-2*H*-isoindole-1,3-dione* (**3**). M.p. 127–128°. ^{1}H-NMR ($CDCl_3$): 2.19–2.28 (*m*, 2 H, CH_2); 2.57–2.66 (*m*, 2 H, CH_2); 2.97 (*s*, Me); 3.08–3.11 (*m*, 2 CH); 5.86–5.94 (*m*, 2 C=CH). ^{13}C-NMR ($CDCl_3$): 23.5 (CH); 24.9 (Me); 39.1 (CH_2); 127.8 (HC=CH); 180.2 (C=O). HR-MS: 167.0950 ($C_9H_{13}NO_2^+$; calc. 167.0946).

One equiv. of 3,6-dipyridin-2-yl-1,2,4,5-tetrazine (143 mg, 0.61 mmol) was added to a soln. of **3** (100 mg, 0.61 mmol) in $CHCl_3$ (2 ml) and heated overnight at 60° in a high-pressure tube. To this soln., DDQ (681 mg, 3.00 mmol) was added and heated at 60° for 2 h in the high-pressure tube. Then, the mixture was washed with H_2O and dried ($MgSO_4$), and the solvent evaporated. The resultant solid was treated with cold MeOH, and the product collected by filtration: **6** (103 mg, 46%). Yellow solid. M.p. 307–308°. ^{1}H-NMR ($CDCl_3$): 3.30 (*s*, Me); 7.54 (*ddd*, J = 7.3, 4.9, 1.1, 2 H, H–C(4) of py); 8.02 (*dt*, J = 8.6, 1.8, 2 H, H–C(6) of py); 8.39 (*td*, J = 7.5, 0.8, 2 H, H–C(5) of py); 8.89 (*d*, J = 4.6, 2 H, H–C(3) of py); 9.44 (*s*, H–C(5) and H–C(9) of Ar). ^{13}C-NMR ($CDCl_3$): 25.0 (Me); 124.5; 124.9; 126.2; 129.0; 133.3; 137.9; 149.6; 155.5; 157.2; 167.2 (C=O). HR-MS: 367.1061 ($C_{21}H_{13}N_5O_2^+$; calc. 367.1069).

3. *(6β,6aα,7α,7aα,8β,15β,15aα,16α,16aα,17β)-6,6a,7,7a,8,15,15a,16,16a,17-Decahydro-5,9,14,18-tetramethoxy-23-methyl-7,16-dipyridin-2-yl-23*H*-7,16[5′,6′]-*endo*-isoindolo-6,17:8,15-dimethanoheptacene-22,24-dione* (**18**), *2-Methyl-5,8-dipyridin-2-yl-1*H*-benz[*f*]isoindole-1,3(*2H*)-dione* (**10**), *4,9-Dimethoxy-1*H*-benz[*f*]indene* (**20**), and *4,9-Dimethoxy-1*H*-benz[*f*]inden-1-ol* (**21**). *Method A:* A soln. of phthalazine derivative **6** (50 mg, 0.136 mmol) and alkene **16** (200 mg, 0.794 mmol, excess) in $CHCl_3$ (3 ml) was heated at 140° overnight in a sealed glass tube. Upon cooling, the solvent was evaporated, and the mixture subjected to radial chromatography (PE/AcOEt 10:1, then gradient up to AcOEt): **20**, **21**, **16**, **18**, and **10** (in order of elution).

Data of **10**: 3 mg (6%). M.p. 291–293°. ^{1}H-NMR ($CDCl_3$): 3.22 (*s*, Me); 7.44 (*ddd*, J = 6.1, 4.9, 1.1, 2 H, H–C(4) of py); 7.62 (*td*, J = 7.7, 1.8, 2 H, H–C(5) of py); 7.86 (*s*, 2 H, H–C(6) of py); 7.91 (*td*, J = 7.7, 18, 2 H of Ar); 8.61 (*qd*, J = 4.9, 0.9, 2 H, H–C(3) of py); 8.65 (*s*, 2 H of Ar). ^{13}C-NMR ($CDCl_3$): 24.8 (Me); 123.2; 123.6; 125.5; 128.5; 130.3; 134.4; 137.4; 141.9; 150.4; 158.3 (C=O). HR-MS: 341.1169 ($C_{21}H_{15}N_3O_2^+$; calc. 341.1164).

Data of **18**: 37 mg (32%). M.p. 295–297°. ^{1}H-NMR ($CDCl_3$): 0.50 (*d*, J = 10.4, 2 H, CH_2); 0.98 (*d*, J = 10.4, 2 H, CH_2); 2.63 (*s*, 4 *endo*-CH); 3.21 (*s*, MeN); 3.63 (*s*, 4 MeO); 3.89 (*s*, 4 bridge CH); 7.36 (*dd*,

$J = 6.2, 3.1$, 4 H of Ar); 7.46 (*t*, $J = 5.8$, 2 H, H–C(4) of py); 7.96 (*dd*, $J = 6.2, 3.1$, 4 H of Ar); 8.03–8.07 (*m*, 4 H, H–C(5,6) of py); 8.43 (*s*, 2 H of Ar); 9.03 (*d*, $J = 4.6$, 2 H, H–C(3) of py). ^{13}C-NMR ($CDCl_3$): 29.2 (MeN); 41.4 (CH_2); 44.4 (CH); 53.4 (CH); 53.8 (CH); 61.3 (MeO); 122.3; 122.4; 124.2; 125.6; 128.3; 130.3; 136.1; 137.3; 143.8; 144.3; 148.6; 149.3; 161.0; 169.5 (C=O). HR-MS: 843.3301 ($C_{55}H_{45}N_3O_6^+$; calc. 843.3308).

Data of **20**: 1 mg (3%). M.p. 198–199°. ^{1}H-NMR ($CDCl_3$): 3.65 (*t*, $J = 2.2$, CH_2); 3.99 (*s*, 1 Me); 4.07 (*s*, 1 Me); 6.57 (*td*, $J = 5.8, 2.2$, 1 =CH); 7.16 (*td*, $J = 5.8, 2.2$, 1 =CH); 7.47–7.52 (*m*, 2 H of Ar); 8.15–8.19 (*m*, 2 H of Ar). ^{13}C-NMR ($CDCl_3$): 36.9 (CH_2); 60.8 (Me); 62.8 (Me); 122.4; 122.5; 125.4; 125.7; 125.8; 127.6; 129.0; 129.9; 134.5. HR-MS: 242.0949 ($C_{15}H_{14}O_3^+$; calc. 242.0943).

Data of **21**: 1 mg (3%). M.p. 211–213°. ^{1}H-NMR ($CDCl_3$): 4.05 (*s*, 1 MeO); 4.25 (*s*, 1 MeO); 5.09 (*s*, 1 CH); 5.72 (*dd*, $J = 5.5, 1.3$, 1 =CH); 6.91 (*dd*, $J = 6.9, 3.3$, 1 =CH); 7.52–7.56 (*m*, 2 H of Ar); 8.19–8.24 (*m*, 2 H of Ar). ^{13}C-NMR ($CDCl_3$): 48.9 (CH); 61.5 (Me); 62.8 (Me); 110.0; 111.3; 122.4; 122.9; 125.7; 125.9; 128.8; 133.5; 133.9; 136.6; 148.0; 148.1; 148.6. HR-MS: 226.0989 ($C_{15}H_{14}O_2^+$; calc. 226.0994).

Method B. For the reaction of **6** with **16** under high pressure, a soln. of **6** (30 mg, 0.106 mmol), **16** (100 mg, 0.396 mmol; excess), and benzoquinone (0.396 mmol) in CH_2Cl_2 (1 ml) was pressurized at 10 kbar and heated at 100° for 2 d. The solvent was evaporated, and the mixture subjected to radial chromatography (PE/AcOEt 20:1, then gradient up to AcOEt): **18** (43 mg, 48%).

Synthesis of **10**: According to *Method B*, phthalazine derivative **6** (55 mg, 0.149 mmol) and trinorbornadiene **7** (300 mg, excess) in $CHCl_3$ (10 ml) was heated in a sealed glass tube at 90° overnight. The solvent was evaporated and the residue subjected to radial chromatography (PE/AcOEt 5:1, then gradient up to AcOEt): **10** (19 mg, 37%).

4. *(1*RS*,2*SR*,4*RS*)-2-Chloro-1,2,3,4-tetrahydro-9,10-dimethoxy-1,4-methanoanthracene* (**29**). *Method A:* A soln. of phthalazine derivative **6** (30 mg, 0.106 mmol) and **16** (100 mg, 0.396 mmol, excess) in CH_2Cl_2 (1 ml) was pressurized at 10 kbar and heated at 100° for 2 d. The solvent was evaporated and the mixture subjected to radial chromatography (PE/AcOEt 20:1, then gradient up to AcOEt): **18** (34 mg, 35%) and **29** (31 mg, 27%). **29**: a yellow oil. ^{1}H-NMR ($CDCl_3$): 2.00 (*qd*, $J = 9.5, 1.8$, 1 H, CH_2); 2.20 (*dd*, $J = 6.9, 1.8$, 1 CH); 2.25 (*t*, $J = 3.5$, 1 CH); 2.33 (*d*, $J = 9.5$, 1 H, CH_2); 3.82–3.83 (*m*, 1 CH); 3.93 (*s*, 1 bridge CH); 3.97 (*s*, 1 Me); 4.02 (*s*, 1 Me); 4.06 (*ddd*, $J = 6.9, 1.8, 0.5$, 1 bridge CH); 7.46–7.49 (*m*, 2 H of Ar); 8.07–8.10 (*m*, 2 H of Ar). ^{13}C-NMR ($CDCl_3$): 40.9 (CH); 41.1 (CH_2); 45.8 (CH_2); 50.4 (Me); 51.4 (Me); 59.6 (CH); 62.3 (CH); 122.5, 122.6, 125.8, 126.2, 128.5, 128.7, 130.5, 134.9, 144.7, 146.3. HR-MS: 288.0913 ($C_{17}H_{17}ClO_2^+$; calc. 288.0917).

Method B: A mixture of phthalazine **24** (7 mg, 0.019 mmol) and alkene **16** (10 mg, 0.038 mmol) in CH_2Cl_2 (1 ml) was pressurized at 10 kbar and heated at 100° for 2 d. The solvent was evaporated, and the mixture subjected to radial chromatography (PE/AcOEt 20:1, then gradient up to AcOEt): **25** (2 mg, 14%) and **29** as a yellow oil (3 mg, 10%).

5. *1,4-Dipyridin-2-ylphthalazine* (**24**). Solns. of anthranilic acid (1.161 g, 8.48 mmol) in dioxane (10 ml) and isoamyl nitrite (= nitrous acid 3-methylbutyl ester; 1.651 g, 13.99 mmol) in dioxane (6 ml) were added dropwise and simultaneously to a refluxing soln. of 3,6-dipyridin-2-yl-1,2,4,5-tetrazine (2.0 g, 8.48 mmol) in dioxane (15 ml) over 20 min. The resulting soln. was refluxed for 3 h, and then the solvent evaporated. The obtained black oil was separated by flash column chromatography (PE/AcOEt 25:1, then gradient up to AcOEt, MeOH, and acetone). The MeOH fraction afforded purified product. Recrystallization from AcOEt gave **24** (700 mg, 29%). Yellow solid. M.p. 163–165°. ^{1}H-NMR ($CDCl_3$): 7.49 (*dd*, $J = 7.5, 4.9$, 2 H, H–C(4) of py); 7.91 (*dd*, $J = 6.4, 3.1$, 2 H of Ar); 7.97–8.02 (*m*, 4 H of Ar, H–C(6) of py); 8.28 (*d*, $J = 7.9$, 2 H, H–C(5) of py); 8.84 (*dd*, $J = 5.8, 3.3$, 2 H, H–C(3) of py). ^{13}C-NMR ($CDCl_3$): 124.4; 126.1; 127.4; 132.6; 137.6; 149.1; 151.4; 156.4; 157.2. HR-MS: 284.1088 ($C_{18}H_{12}N_4^+$; calc. 284.1062).

6. *(6β,6aα,7α,7aα,8β,15β,15aα,16α,16aα,17β)-6,6a,7,7a,8,15,15a,16,16a,17-Decahydro-5,9,14,18-tetramethoxy-7,16-dipyridin-2-yl-7,16[1′,2′]benzeno-6,17:8,15-dimethanoheptacene* (**25**) *and 6,13-Dihydro-7,12-dimethoxy-5,14-dipyridin-2-yl-6,13-methanopentacene* (**26**). *Method A:* A soln. of phthalazine **24** (60 mg, 0.211 mmol) and alkene **16** (200 mg, 0.794 mmol, excess) in $CHCl_3$ (10 ml) was heated in a sealed glass tube at 140° overnight. The solvent was evaporated, and the residue subjected to radial chromatography (PE/AcOEt 5:1, then gradient up to AcOEt): **25** and **26** (in order of elution).

Data of **25**: 41 mg (26%). M.p. 297–298°. ^{1}H-NMR ($CDCl_3$): 0.52 (*d*, *J* = 9.9, 2 H, CH_2); 0.96 (*d*, *J* = 9.9, 2 H, CH_2); 2.62 (*s*, 4 *endo*-CH); 3.63 (*s*, 4 MeO); 3.85 (*s*, 4 bridge CH); 7.36 (*dd*, *J* = 7.5, 3.3, 4 H of Ar); 7.37 (*d*, *J* = 3.8, 2 H of Ar); 7.38 (*ddd*, *J* = 7.7, 4.2, 0.9, 2 H, H–C(4) of py); 7.87 (*dd*, *J* = 5.8, 3.3, 2 H, H–C(6) of py); 7.99 (*dd*, *J* = 5.9, 3.8, 4 H of Ar); 8.04 (*d*, *J* = 3.8, 2 H, H–C(5) of py); 8.11 (*d*, *J* = 8.2, 2 H of Ar); 8.96 (*dd*, *J* = 4.9, 0.7, 2 H, H–C(3) of py). ^{13}C-NMR ($CDCl_3$): 41.3 (CH_2); 44.5 (CH); 52.4 (Me); 52.7 (CH); 61.2 (CH); 121.9; 122.4; 125.0; 125.3; 126.9; 127.1; 128.3; 136.4; 137.2; 140.7; 143.6; 149.0. HR-MS: 760.3309 ($C_{52}H_{44}N_2O_4^+$; calc. 760.3301).

Data of **26** (from crude product): ^{1}H-NMR ($CDCl_3$): 1.75 (*d*, *J* = 9.8, 1 H, CH_2); 2.05 (*d*, *J* = 9.8, 1 H, CH_2); 3.28 (*s*, 2 CH); 3.72 (*s*, 2 MeO); 7.36 (*dd*, *J* = 5.8, 3.1, 2 H, H–C(4) of py); 7.44–7.45 (*m*, 4 H of Ar); 7.84–7.85 (*m*, 4 H of Ar); 7.96 (*dd*, *J* = 5.8, 3.1, 2 H, H–C(6) of py); 8.09 (*dt*, *J* = 7.3, 1.8, 2 H, H–C(5) of py); 8.78 (*d*, *J* = 3.9, 2 H, H–C(3) of py). HR-MS: 506.1987 ($C_{35}H_{26}N_2O_2^+$; calc. 506.1994).

Method B: A mixture of **24** (7 mg, 0.019 mmol), **16** (10 mg, 0.038 mmol), and benzoquinone (0.050 mmol) in CH_2Cl_2 (1 ml) was pressurized at 10 kbar and heated at 100° for 2 d. The solvent was evaporated, and the mixture subjected to radial chromatography (PE/AcOEt 20:1, then gradient up to AcOEt): **25** (7 mg, 46%).

7. *5,12-Dihydro-6,11-dimethoxy-2-methyl-4,13-dipyridin-2-yl-5,12-dimethano-1*H-*anthra[2,3-*f*]isoindole-1,3(2*H*)-dione* (**28**). A soln. of alkene **16** (100 mg, 0.397 mmol) and pyridazine derivative **27** (30 mg, 0.095 mmol) in CH_2Cl_2 (2 ml) was heated at 100° and 10 kbar for 2 d. Radial chromatography (PE/AcOEt 20:1, then gradient up to AcOEt) afforded in this order chlorinated product **29** (5 mg, 18%) and **28** (9 mg, 18%). **28**: M.p. 138–140°. ^{1}H-NMR ($CDCl_3$): 2.54 (*td*, *J* = 8.9, 1.6, 1 H, CH_2); 2.81 (*td*, *J* = 8.9, 1,6, 1 H, CH_2); 3.00 (*s*, MeN); 3.47 (*s*, 2 MeO); 5.15 (*s*, 2 CH); 7.40 (*dd*, *J* = 6.2, 3.5, 2 H of Ar); 7.46 (*ddd*, *J* = 7.7, 4.9, 1.1, 2 H, H–C(4) of py); 7.64 (*td*, *J* = 7.7, 1.1, 2 H, H–C(6) of py); 7.88 (*dt*, *J* = 7.7, 1.8, 2 H, H–C(5) of py); 7.94 (*dd*, *J* = 6.2, 3.3, 2 H of Ar); 8.87 (*qd*, *J* = 4.9, 1.1, 2 H, H–C(3) of py). ^{13}C-NMR ($CDCl_3$): 30.1 (MeN); 47.0 (CH_2); 61.7 (MeO); 63.8 (CH); 122.6; 123.6; 126.3; 127.1; 127.3; 133.3; 133.4; 136.1; 144.5; 149.8; 153.3; 156.7; 168.3 (C=O). HR-MS: 539.1851 ($C_{34}H_{25}N_3O_4^+$; calc. 539.1845).

8. *Crystallographic Data and Structure Refinement for* **18**[2]). Empirical formula $C_{56}H_{47}Cl_2N_3O_6$; M_r 928.87; temp. 100(2) K; wavelength 0.71073 Å; crystal system: monoclinic; space group *C*2/*c*; unit cell dimensions: $a = 31.264(3)$, $b = 17.9558(17)$, $c = 20.0201(19)$ Å; $\alpha = 90$, $\beta = 119.469(2)$, $\gamma = 90°$; $V = 9784.5(16)$ Å^3; $Z = 8$; density (calc.) = 1.261 Mg/m^3; absorption coefficient 0.187 mm^{-1}; $F(000)$ 3888; crystal size: $0.46 \times 0.10 \times 0.06$ mm^3; θ range for data collection 2.02 to 25.00°; index ranges: $-30 \le h \le 37$, $-21 \le k \le 21$, $-23 \le l \le 13$; reflections collected 25163; independent reflections 8616 (R(int) = 0.0516); completeness to $\theta = 25.00°$, 99.9%; absorption correction: empirical (SADABS); max. and min. transmission 0.9889 and 0.9190, resp.; refinement method: full-matrix least-squares on F^2; data, restraints, and parameters 8616, 36, and 646, resp.; goodness-of-fit on F^2 1.024; final R indices ($I > 2\sigma(I)$) $R_1 = 0.0657$; $wR_2 = 0.1530$; R indices (all data): $R_1 = 0.1172$, $wR_2 = 0.1682$; largest diff. peak and hole 0.699 and -0.251 eÅ^{-3}.

9. *Computational Details.* All geometrical optimizations were carried out by the B3LYP hybrid functional DFT method [21] (*Becke*'s 3 parameter functional with the nonlocal correlation provided by the expression of *Lee et al.*) employing the 6-31G* basis set, within the Gaussian03 suite of programs [22], implemented on a dual core *Opteron-240* personal computer under the Linux operating system. Harmonic vibration frequencies were calculated for all localized stationary structures to verify whether they are minima or transition states.

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[2]) CCDC-652555 contains the supplementary crystallographic data of **18**. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the *Cambridge Christallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

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