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Electrophilic reactivity and π-complexation studies in 1,8-naphthylene-bridged [3.2]paracyclophane with a cyclobutane calliper

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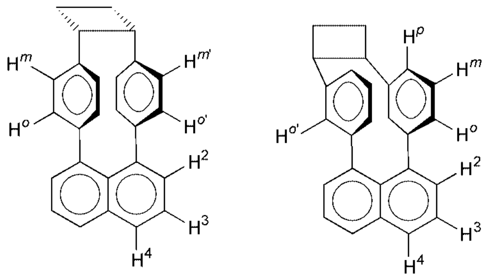
The 1,8-naphthylene-bridged [3.2]paracyclophane **1**, a novel *syn*-paracyclophane which is further rigidified *via* a cyclobutane calliper, reacts with 2.2 equivalents of Br_2 in CCl_4 in the dark to give the symmetrical dibromo derivative **2**. Bromination with excess Br_2 (6 equiv.) leads to further bromination at the 4-position of the naphthalene ring to give the tribromide **3**. In contrast to [2.2]paracyclophane and naphthalene, compound **1** does not produce a persistent π-complex with NO^+. Reaction of **1** with AgOTf results in cycloreversion to form a silver-complexed divinyl derivative **4** which could be decomplexed with excess 18-crown-6 to form **5**. With tetracobalt dodecacarbonyl a metal π-complex on the exterior of the cyclophane unit was formed (**6**) with the cyclobutane ring remaining intact. NMR spectral features of the resulting products are examined. AM1 minimizations were used as a guide to structures and relative energies. The nitration, benzoylation, benzylation and ethylation of **1** were also studied.

Introduction

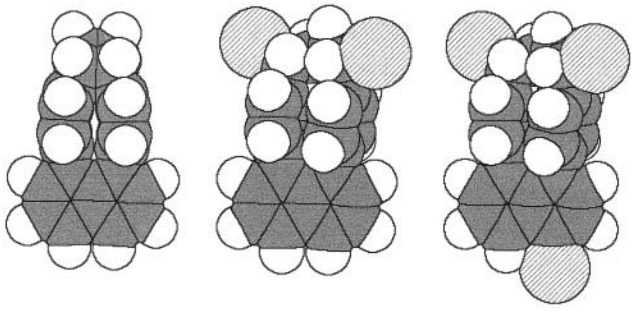
Inter- and intramolecular photochemical [2 + 2]cycloaddition reactions of suitable arylvinyl building blocks have proved to be versatile methods for the synthesis of various cyclophanes with the *syn*-configuration of π-decks, whereby the cofacial arrangements of arene phenyl or biphenyl rings are enforced *via* a *cis*-disubstituted cyclobutane (CB) calliper.[1,2] Extension of this approach led to the synthesis of paddlanes and crownopaddlanes.[3,4]

The intramolecular [2 + 2]photocycloaddition approach was used to synthesize 1,8-naphthalene (NP)-bridged para- and metacyclophanes **1** and **1a** (Fig. 1).[2] 1,8-Diarylnaphthalenes and their fluorinated derivatives have attracted recent attention as probes of polar interactions in stacked π-systems.[5,6] In relation to our interest in π–π interactions in cyclophanes and cyclophane arenium ions and in continuation of studies of electrophilic chemistry of fluorinated cyclophanes, janusenes and sterically crowded stilbenes,[7–11] we report here on bromination and metal π-complexation along with a survey of other electrophilic reactions as a means to compare the reactivity of **1** with regular cyclophanes (or annulenes). The results indicate that the chemistry of **1** is dominated by the reactivity of the CB ring which provides a driving force for relief of steric strain.



1 **1a**

Fig. 1 Compounds **1** and **1a**.



1 2 3

Fig. 2 AM1-minimized structures of **1**, **2** and **3**.

Results and discussion

The AM1-minimized structure of [3.2]paracyclophane **1** is shown in Fig. 2. The closest Ph–Ph distances are the corresponding *ipso–ipso* positions (2.71 Å on the CB side and 2.91 Å on the NP side). The distances between corresponding cofacial decks are: *ortho–ortho* 3.16/3.07 Å and *meta–meta* 3.07/2.96 Å. Thus the *vis-á-vis* rings are held in a rigid cofacial arrangement well within van der Waals distance. The 500 MHz ^1H NMR spectrum of **1** (Chart 1) shows two sets of aromatic resonances with the protons of cofacial rings significantly shielded relative to the naphthalene (NP) protons. Interestingly, whereas the H^o/H^m pairs appear nearly chemical shift equivalent in $CDCl_3$, they gave rise to two resolved doublets in THF-d_8 or in acetone-d_6–CS_2 (1 : 1), allowing more detailed NOE measurements. Thus NOE enhancements were observed between the cyclobutane C*H* protons (δ 4.28) and the doublet of doublets at δ 6.29 and between the CB methylene protons (δ 2.59) and H^m resonance at δ 6.70. Irradiation of the H^2 proton (δ 7.61) gave a NOE effect for both H^o and $H^{o'}$ pairs (at δ 6.54 and 6.64 in acetone-d_6–CS_2 solvent). Detailed assignments of the proton and carbon resonances are gathered in Chart 1. Because of the cooperative reactivity of the π-systems in smaller [*m.n*]-paracyclophanes[12] and in janusene,[8,13] it was anticipated that

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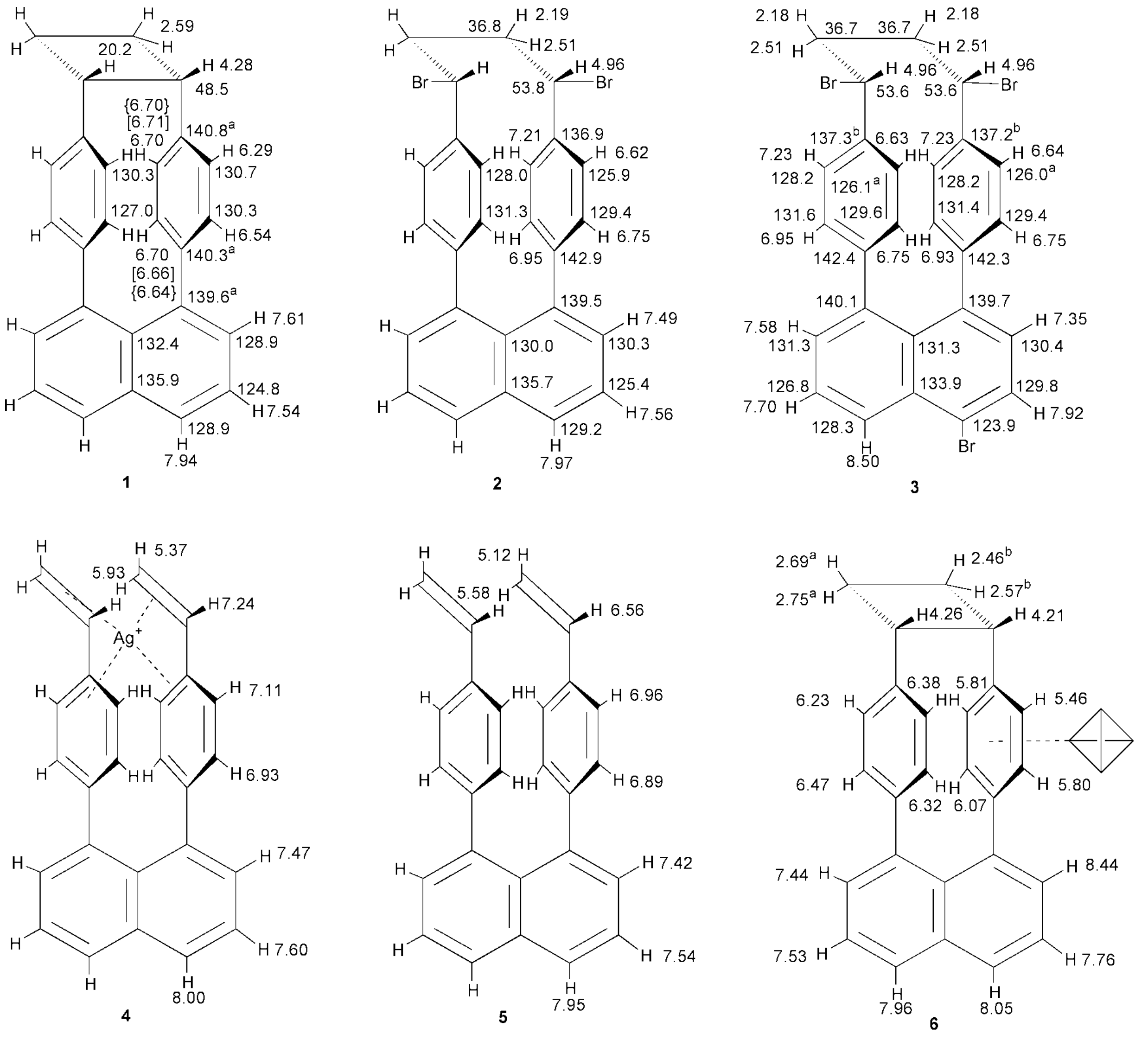

1 **2** **3** **4** **5** **6**

a, b: Interchangeable. [ ] : δ^1H in THF-d_8 solvent. { } : δ^1H in acetone-d_6-CS_2 (1:1) solvent.

Chart 1 ^{1}H and ^{13}C NMR data for **1**–**6** (assignments were assisted by H/H COSY, C/H HETCOR (and COLOC) and *via* NOED spectra as appropriate).

electrophilic substitution at a facial ring should be facile, although steric factors could override this preference. AM1-calculated protonation energies for **1** suggested that the arenium ion of attack at the *para* position (NP ring) should be most favored. Based on the relative arenium ion energies, nitration was also predicted to occur preferentially at the NP ring.

With 1,8-diphenylnaphthalene, π-complexation with $Cr(CO)_3$ occurs on the exterior of the cofacial rings.[14] Exterior complexation was also observed for [2.2.2]paracyclophane in reaction with $Co_4(CO)_{12}$.[15] We began our investigation with bromination and nitration using mild reagents *i.e.* NBS–DMF and copper nitrate–acetic anhydride, which are suitable for mild and selective monobromination and mononitration of dimethyldihydropyrene and its benzannelated derivatives.[16,17] Surprisingly, these reactions led to recovery of intact **1**. In an attempt to introduce nitro groups, nitration of **1** was studied with HNO_3–HOAc and with NO_2^+ BF_4^- in CD_3CN. In both cases **1** was recovered intact when only one equivalent of the reagent was used. In excess reagent, along with unreacted **1** a complex mixture of nitrated products was formed which could not be separated. In subsequent studies, benzoylation (PhCOOTf),[18] benzylation (with *in situ* formed $PhCH_2OTf$)[19] and ethylation with EtOTf[19] were carried out under acid free conditions by employing the bulky base 4-methyl-2,6-di-*tert*-butylpyridine to prevent CB-ring opening. No products due to benzoylation, benzylation or ethylation could be identified and unreacted **1** was recovered along with some high molecular weight (polymeric) material.

Returning to bromination, **1** was allowed to react with 2.2 equivalents of Br_2 in CCl_4 in the dark. This led to clean formation of the dibromo compound by *syn*-bromination of the cyclobutane ring resulting in the ring-opened [4.3]paracyclophane **2**. Bromination of **1** with 6 equivalents of bromine under the same set of conditions led to clean formation of the tribromo compound **3** along with minor amounts of **2** (Fig. 3). The AM1-minimized structures of **2** and **3** are included in Fig. 2. AM1 minimization suggested that further bromination of **2** at the 2- and 4-positions (observed) would produce tribromides with almost identical energies. The tribromide formed by bromination at the 3-position was computed to be more stable by about 2.5 kcal mol^{-1}. Structures of **2** and **3** were secured by NMR analysis (Chart 1) after repeated purification in addition to HRMS for both and microanalysis for **3**. Attempts to obtain suitable crystals for X-ray analysis proved unsuccessful. A notable feature in the ^{1}H NMR spectra is that shielding of cofacial protons has diminished in the more flexible [4.3]cyclophanes. In **2**, NOE enhancement was observed between C*H*Br (at δ 4.96) and the doublet of doublets at δ 6.64 (no NOE with δ 7.21); similarly, in **3** NOE was only observed between C*H*Br (at δ 4.96) and the doublet of doublets at δ 6.64, thus allowing specific assignments of the H^m and $H^{m'}$ protons in the cofacial rings.

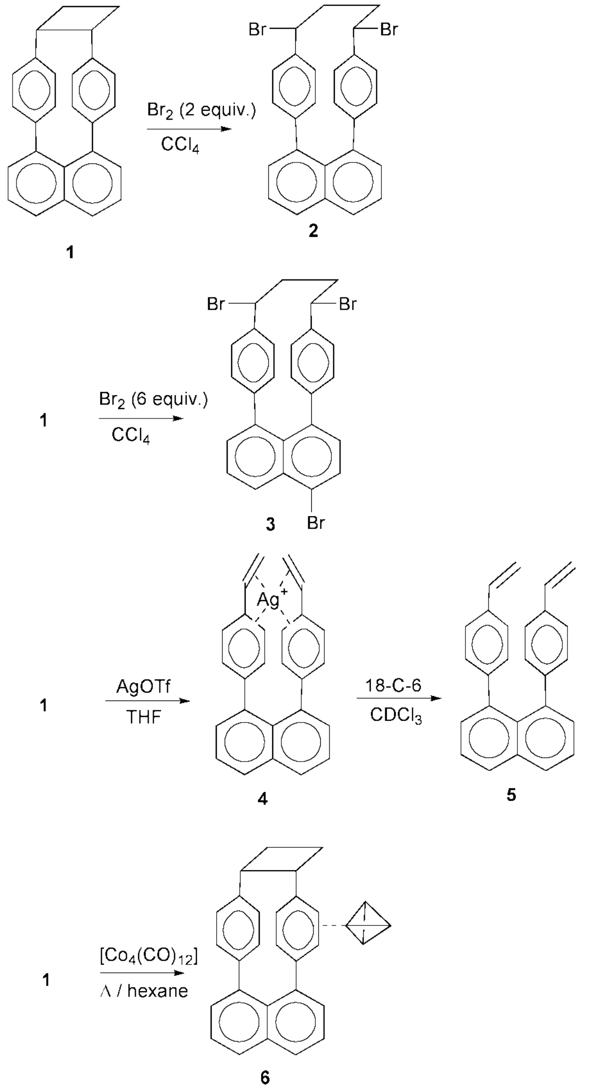

Fig. 3 Summary of reactions of **1**.

For both **2** and **3** NOE enhancement was detected between CB methylene protons (at δ 2.51) and H^m/H$^{m'}$ protons (at δ 7.21 and 7.23 respectively). In addition, for **2** a NOE effect was detected between H^2 protons (at δ 7.49) and the H^o/H$^{o'}$ resonances in the cofacial rings. A more complete assessment becomes possible *via* **3** because of the non-equivalence of the NP protons. Here, a NOE was detected between δ 7.35 and both δ 6.75/6.93 and between δ 7.58 and δ 6.75/6.95. These observations clearly reflect the parallel nature of the cyclophane decks.

π-Complexation studies (Fig. 3 and Chart 1)

Nitrosonium cation has been shown to complex with [2.2]paracyclophane[20] and with naphthalene[21] to give π-complexes of arene–NO$^+$ type. In contrast, reaction of **1** with NO$^+$ BF$_4^-$ at dry ice–acetone temperature in SO$_2$–CD$_2$Cl$_2$ or at −50 °C in CD$_3$CN–CD$_2$Cl$_2$ did not result in cationic π-complex formation; instead, polymeric materials were obtained.

Silver triflate has been shown to complex to the exterior of deltaphane and [2.2.2]paracyclophane.[22,23] With the aim of preparing a **1**·Ag$^+$ OTf$^-$ complex, cyclophane **1** was reacted with AgOTf (1.5 equiv.) in dry THF at room temperature. After removal of THF the residue was dissolved in CDCl$_3$ and examined directly by NMR. Appearance of vinylic protons at δ 5.93 and 5.37 and benzylic protons at δ 7.24 and a symmetrical structure are consistent with a silver ion-assisted [2 + 2]cycloreversion[24] to form a silver-complexed divinyl-derivative **4** in about 85% yield (for NMR assignments see Chart 1). Additional support for the formation of **4** comes from a control experiment where excess 18-crown-6 was added to **4**, prepared in an independent reaction, which resulted in decomplexation to give **5**. The identity of **5** was confirmed by comparison of its ^{1}H and ^{13}C NMR spectra with those of an authentic sample. Based on the Δδ ^{1}H values it can be concluded that Ag$^+$ interacts most strongly with the vinyl groups and the *meta* positions of the cofacial rings (H^m/H$^{m\prime}$), suggesting that it is not a deep-cavity complex. This is also borne out by AM1 and MM+ calculations.

Cyclophane **1** reacts with excess Co$_4$(CO)$_{12}$ in refluxing hexane to form the mono-cluster complex **6** as a gray solid after chromatographic purification. Complexation to the exterior of one of the cofacial rings leads to nonequivalence of all protons in **1** and to significant upfield shift of the π-complexed ring protons (Chart 1). The induced upfield shift in the *vis-á-vis* ring is taken as evidence for transannular π–π interaction in the complex. It appears that shifting of π-electron density to cobalt is compensated *via* charge delocalization into the naphthalene moiety where the Δδ values show proportional deshielding effects. Relative assignments of the H^2/H^4 protons in the NP ring were made based on the magnitude of vicinal couplings in comparison to **1**. Assuming this is correct, then increased deshielding in H^2 must stem from steric factors imposed by the bulky Co$_4$(CO)$_9$ group.

In summary, the results obtained with bromination and Ag$^+$ complexation clearly point to chemistry at the CB ring and to relief of steric strain as an important driving force in **1**. So far, the cobalt complex **6** represents the only example where the skeleton remains intact. In the electrophilic reactions survey, lack of reactivity in benzylation, benzoylation and ethylation seems unusual as does attempted nitration with mild nitrating agents which normally react with reactive arenes and annulenes.

Experimental

Compound **5** (precursor to **1**), was synthesized from 1,8-bis-(*p*-bromophenyl)naphthalene as described in ref. 2. Cyclophane **1** was prepared by a [2 + 2]photocycloaddition reaction according to Nishimura *et al.*[2] Silver triflate (Aldrich), ethyl triflate (Aldrich) and tetracobalt dodecacarbonyl (Strem) were high purity samples which were used as received. Benzoyl triflate was prepared from benzoyl chloride and AgOTf in dry dichloroethane according to Effenberger *et al.*[18] Benzyl triflate was prepared *in situ* from benzyl chloride and AgOTf.[19]

NMR spectra were recorded on a Varian INOVA 500 MHz instrument using a 5 mm broad-band probe. AM1 calculations and energy minimizations were performed using standard methods as implemented in the Hyperchem 5 package (Hypercube Inc, 1999). Global minima were confirmed by using initial structures with different twist angles between cofacial phenyl rings and the NP ring.

Bromination reactions

Synthesis of 2. A solution of Br$_2$ (7.0×10^{-3} mL, 1.3×10^{-4} mol) in CCl$_4$ (3 mL) was added dropwise to a solution of **1** (20.0 mg, 6.0×10^{-5} mol) in CCl$_4$ (4 mL) at room temperature in the dark. After stirring for 3 h at r.t. the reaction was quenched by addition of a solution of NaHSO$_3$. The mixture was extracted with CH$_2$Cl$_2$, washed with aqueous NaHCO$_3$ and with water and the organic extract was dried over Na$_2$SO$_4$. After removal of solvent, the residue was purified by column chromatography (hexane–CH$_2$Cl$_2$ 3 : 1). Further purification was achieved by GPC. HRMS Calcd: 489.9932; Observed: 489.9945.

Synthesis of 3. A solution of Br$_2$ (20×10^{-3} mL, 3.9×10^{-4} mol) in CCl$_4$ (1 mL) was added to a solution of **1** (20.0 mg, 6.02×10^{-5} mol) in CCl$_4$ (10 mL) at room temperature in the dark. After 16 h stirring at r.t. the reaction was quenched and the product was isolated and purified as described above. HRMS Calcd: 567.9037; Observed: 567.9038. Elemental analysis: C (Calcd: 54.68; Observed: 54.78); H (Calcd: 3.35; Observed: 3.40).

Reaction of 1 with silver triflate (→4)

To a mixture of cyclophane **1** (20.4 mg, 6.15×10^{-5} mol) and AgOTf (23.7 mg, 9.22×10^{-5} mol) was added dry THF (20 mL) and the mixture was stirred under an argon atmosphere at r.t. for 1.5 h. The solvent was removed, the residue was extracted with $CDCl_3$ (~0.8 mL) and examined directly by NMR.

Decomplexation of 4 (→5)

To a solution of **4** in $CDCl_3$ solvent (obtained as described above) was added a solution of 18-crown-6 in 0.15 mL $CDCl_3$. The crown:cyclophane ratio was *ca.* 37 (from ^{1}H NMR integrals). Decomplexation was monitored by NMR. Since the process was slow, additional 18-crown-6 (2.9 mg, in 0.15 mL $CDCl_3$) was added until the crown:cyclophane ratio reached 58.

Synthesis of 6

To a mixture of cyclophane **1** (15.7 mg, 4.70×10^{-5} mol) and $Co_4(CO)_{12}$ (269 mg, 4.70×10^{-4} mol) was added dry hexane (40 mL). The mixture was refluxed for 6 h with efficient stirring under an argon atmosphere. It was then cooled, the solvent was removed under vacuum and the solid residue was chromatographed on silica gel using dry hexane–CH_2Cl_2 (3 : 1) to give a dark-green solid (10 mg, 25%) which was studied directly by NMR.

Survey of electrophilic reactions

(a) NBS–DMF bromination. A solution of NBS (10.7 mg, 6.02×10^{-5} mol) in dry DMF (1.8 mL) was added to a solution of **1** (20.0 mg, 6.02×10^{-5} mol) in dry DMF (5.4 mL) and the mixture was stirred at r.t. for 24 h, after which it was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water (three times), dried (sodium sulfate) and the solvent was removed under reduced pressure. The ^{1}H NMR spectrum of the residue dissolved in $CDCl_3$ showed intact **1**.

(b) Nitration with $Cu(NO_3)_2$–HOAc. Solid $Cu(NO_3)_2$ (14.1 mg, 7.52×10^{-5} mol) was added to a solution of **1** (20.6 mg, 6.16×10^{-5} mol) in HOAc (15 mL) at 0 °C. After 2 h the solution was poured into ice–water and extracted with CH_2Cl_2. NMR analysis of the organic residue after work-up indicated only intact **1**.

(c) Nitration with HNO_3–HOAc. Conc. HNO_3 (2.5×10^{-3} mL, 5.6×10^{-5} mol) was added to a solution of **1** (20 mg, 6.02×10^{-5} mol) in HOAc (10 mL) at r.t. and the mixture was stirred for 20 h. Following standard work-up the organic extract was examined by ^{1}H NMR which showed it to be mostly unreacted **1**. A similar reaction using excess HNO_3 gave a complex mixture which did not contain the desired nitro-**1**.

(d) Nitration with $NO_2^+ BF_4^-$ in CD_3CN. To the cyclophane **1** (20 mg, 6.02×10^{-5} mmol) was added a solution of $NO_2^+ BF_4^-$ (8 mg, 6.02×10^{-5} mol) in CD_3CN (0.4 mL) at 0 °C. After stirring for 50 min the reaction mixture was assayed by ^{1}H NMR which corresponded to >90% intact **1**. As in the case of excess HNO_3–HOAc, employing excess $NO_2^+ BF_4^-$ in CD_3CN solvent resulted in a complex mixture (NMR) which could not be separated.

(e) Reaction with EtOTf–hindered base. To a solution of **1** (11.3 mg, 3.4×10^{-5} mol) and 2,6-di-*tert*-butyl-4-methylpyridine (15.8 mg, 7.7×10^{-5} mol) in dry dichloroethane (DCE) (3 mL) was added EtOTf (10.7 mg, 7.7×10^{-5} mol) in DCE (1 mL). The mixture was stirred for 3 h at r.t., DCE was removed under reduced pressure and the residue was dissolved in $CDCl_3$ and examined by NMR showing intact **1**.

In a control experiment the base was allowed to react with EtOTf in refluxing DCE for 3 h without the cyclophane. Since no ethylation of the hindered pyridine could be induced, the reaction of **1** with EtOTf–hindered base was continued under DCE reflux. Again no ethylation of **1** could be observed. The ^{1}H NMR spectrum gave evidence for the formation of small amounts of pyridinium triflate probably due to TfOH formation *via* decomposition of EtOTf.

(f) Reaction with benzyl triflate–base. To a solution of **1** (19.0 mg, 5.7×10^{-5} mol) in dry CH_2Cl_2 (6 mL) was added in sequence the hindered base (11 mg, 5.36×10^{-5} mmol), benzyl chloride (6.02×10^{-5} mmol) in dry CH_2Cl_2 (3.2 mL) and AgOTf (14 mg, 5.45×10^{-5} mol) under a nitrogen atmosphere. The mixture was stirred for 2 h at r.t., filtered and the solvent was removed under vacuum. The ^{1}H NMR spectrum of the organic extract was consistent with mostly intact **1** together with *ca.* 15% products due to decomposition/side reactions not corresponding to the desired benzyl-**1**.

(g) Reaction with benzoyl triflate. Benzoyl triflate (16.8 mg, 6.6×10^{-5} mol)[18] was allowed to react with cyclophane **1** (20 mg, 6.0×10^{-5} mol) in DCE solvent at r.t. under a nitrogen atmosphere. After 12 h stirring, the solvent was removed under vacuum and the residue was checked by ^{1}H NMR which indicated >85% of the mixture to be intact **1** (the remaining mixture gave rise to very broad features suggesting decomposition/polymer formation).

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