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Synthetic Approach to Multifunctional Planar Chiral Carba-paracyclophane and its Stereochemical Properties

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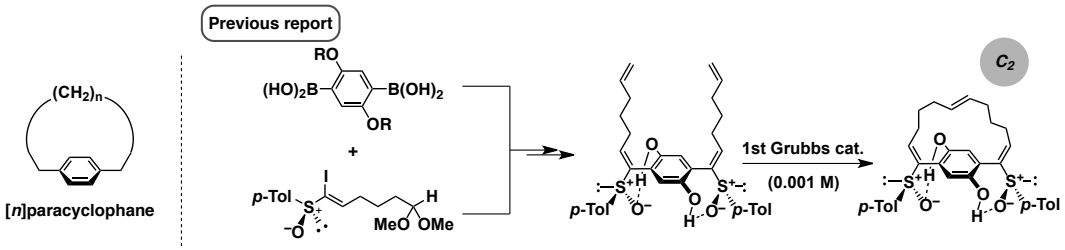
1. Introduction

Planar-chiral cyclophanes constitute a unique class of a macrocyclic molecules, consisting of an aromatic ring and an aliphatic ansa-chain. Intrigued by their unique structures as well as potential utility as a chiral platform in asymmetric catalysis or material science, this class of compounds have captured interests of many scientists. The most distinct characteristic of cyclophanes is potential chiroptical property, *i.e.* planar stereochemisty, which arises from restricted rotation around the central benzene unit. However, synthetic accesses to chiral cyclophanes remain challenges owing to difficulties in constructing the strained macrocyclic skeleton as well as controlling its stereochemistry.

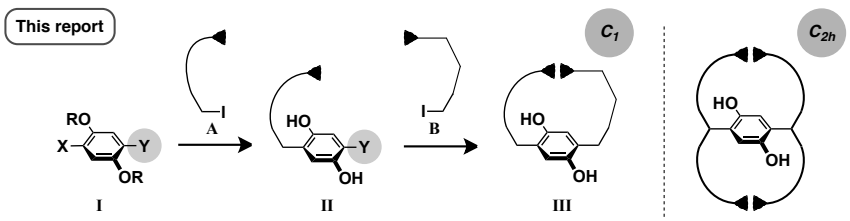
Recently, our laboratory have reported the stereoselective synthesis of C_2-symmetric planar chiral carba-paracyclophanes. A key for control of the planar chirality is construction of the dual α-sulfinyl styrene system, which forms hydrogen bondings between phenols and sulfinyl oxygens juxtaposing two side chains on the same side of the benzene plane. These features fulfilled a stereoselective access to C_2-symmetric planar chiral paracyclophanes by ring-closing olefin metathesis.



Although this stereocontrolled strategy is straightforward and efficient for consturcting a chiral paracyclophane system, there are following drawbacks; 1) C_2 symmetrical paracyclophanes can only be accessible, 2) poor variation of functional groups, in particular, in the side chain makes the approach narrow window. Herein, a new synthetic approach to planar chiral unsymmetric carba-paracyclophanes is discussed.

Scheme 1 outlines this study. The author envisioned that the stepwise conjugation of two distinct side chains **A** and **B** with the benzene unit **I** would give rise to the unsymmetrized compound **III** (**I**→**II**→**III**). Therefore, desymmetrized benzene unit **I** was set as a key starting material.

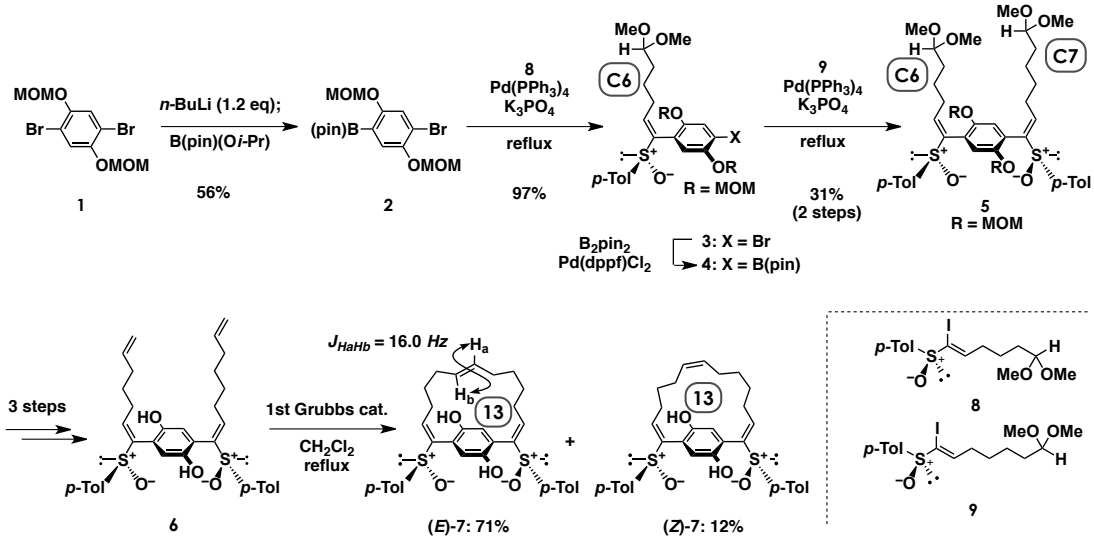
Besides, to expand synthetic utility, stereochemical properties and further functionalization of cyclophane derivatives as well as synthesis of double-strand carba-paracyclophane were also investigated.



Scheme 1

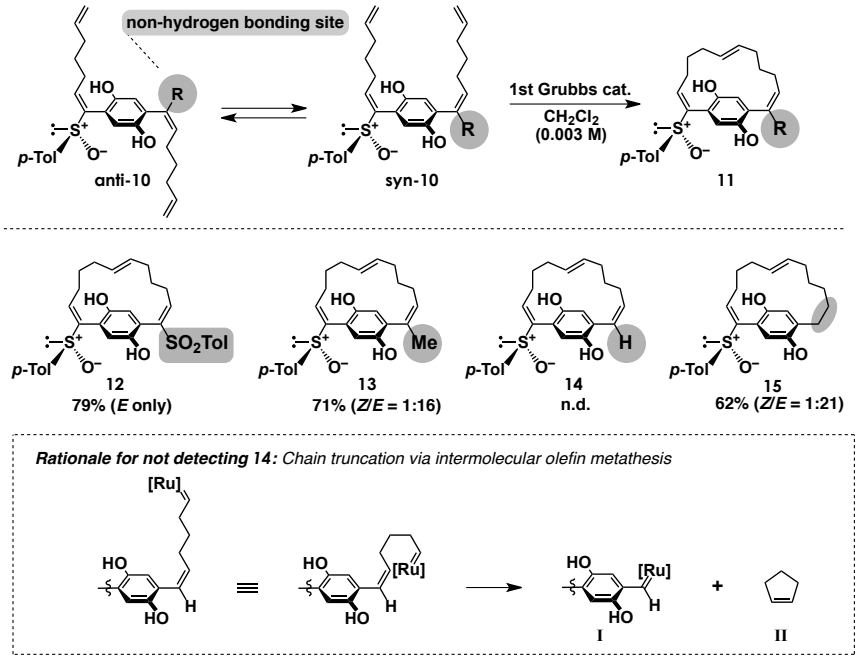
2. Stepwise coupling of side chains toward the unsymmetric planar chiral carba-[*n*]paracyclophanes

At first, odd-numbered paracyclophane **7** was targeted, because its ring size (n = 13) would only be accessible from unsymmetrized cyclization precursor, such as **6**. Thus, successive reactions, involving Suzuki coupling and Miyaura borylation, allowed installation of two distinct side chains, **8** and **9**, into **2**, giving **5** in 31% yield (3 steps). Following the three-step sequence led to the cyclization precursor **6**. Ring-closing metathesis of **6** was performed in refluxing CH_2Cl_2 with 1st generation of Grubbs catalyst under dilute conditions (0.003 M), giving the cyclization products, **(*E*)-7** and **(*Z*)-7**, in 71% and 12% yield, respectively. The stereochemistry of the newly formed C=C bond in the major product was verified by observing ^{1}H-NMR with a large coupling constant (16.0 Hz), between vinylic protons.



Scheme 2

With stepwise-coupling protocols succeeded, further applicability of this method was studied. Firstly, the simple substrate **10** with no substituent at vinyl positions (R = H) was tested. However, no formation of the cyclization product was observed. It can be explained by disfavored conformation **I** of the cyclization precursor. Indeed, the vinyl side chain preferably adopts a planar conformation to the benzene unit, gaining stabilization energy by conjugation. On the contrary, the substituted substrates, e.g. having methyl or sulfonyl groups at vinylic positions, become favorable in conformation **II** since the side chains orients perpendicular to the benzene ring owing to ^{1,3}A strain between the substituent R and the phenol. Thus, reaction of methyl or sulfonyl derivative preceded well to give the corresponding unsymmetric cyclophane, e.g. **12** or **13**, as a sole isomer. Notably, cyclization of the saturated derivative also worked well, thereby giving the planar chiral cyclophane **15** in 62% yield.



Scheme 3

3. The functionalization and synthesis of double-strand carba-paracyclophanes

Having various unsymmetric paracyclophanes, the sulfinyl function, substituted on side chains would become a pivotal functionality for further transformation. In this context, sulfoxide-metal exchange was examined. Thus, upon treatment of **16** with *t*-BuLi in the presense of TMEDA, the resulting dilithio-species was affected 1-formylpiperidine, giving dialdehyde **18** in 71% yield. Subsequently, Wittig reaction was conducted with phosphonium salt **19** and KHMDS, allowing elongation with aliphatic chains. The reaction gave a mixture of two olefinic stereoisomers with a 87:13 ratio, of which stereochemistries were determined by ^{1}H-NMR. The major product proved to be *Z*, *Z* isomer (J_{cis} = 11.8 Hz and 11.8 Hz), while *Z*, *E* stereochemistry of the minor isomer was confirmed by observing coupling constants (J_{cis} = 11.8 Hz and J_{trans} = 15.4 Hz). The key ring-closing olefin metathesis of the mixture was attained by using 1st generation Grubbs catalyst, giving double-strand paracyclophane **21** as an inseparable mixture (90% yield). All unsaturated bonds in **21** were reduced by the hydrogenation under high pressure (30 bar) to give **22** in 91 % yield. Diagnostic NOE correlations between benzylic proton and an aryl methines indicated its *trans* relationship to alkoxy groups. Interestingly, the molecular symmetry group of the molecule was changed after hydrogenation from C_2 to C_{2h} converting from chiral to achiral compound. Indeed, the planar chirality was lost at this stage. Finally, removal of the MEM groups by Lewis acids ($CeCl_3$•H_2O, NaI in MeCN) gave hydroquinone **23** in 79% yield.

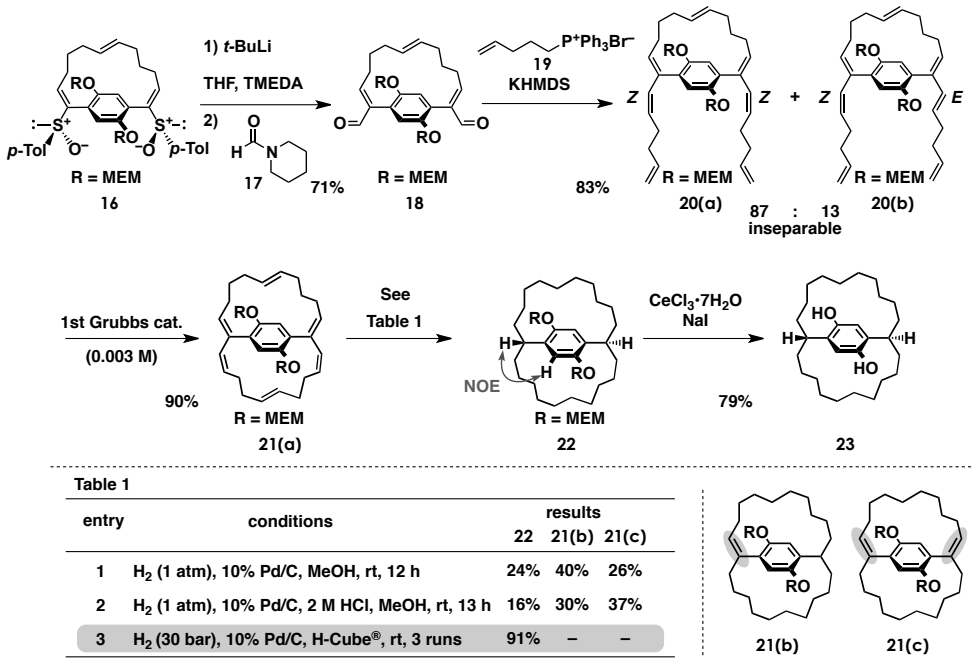


Table 1

entry	conditions	results 22	21(b)	21(c)
1	H_2 (1 atm), 10% Pd/C, MeOH, rt, 12 h	24%	40%	26%
2	H_2 (1 atm), 10% Pd/C, 2 M HCl, MeOH, rt, 13 h	16%	30%	37%
3	H_2 (30 bar), 10% Pd/C, H-Cube®, rt, 3 runs	91%	–	–

Scheme 4

In conclusion, planar chiral unsymmetric paracyclophanes adorned with various functional groups were synthesized by the stepwise-coupling procedure. Moreover, double-strand paracyclophane could be accessed from sulfinylated paracyclophane derivative through the halogen-metal exchange and carbon-chain elongation followed by cyclization. Transfer of chiral elements during the conversion is worth mentioning. The stereochemical information of central chirality on the sulfur atom could reflect to that of newly constructed planar chirality, which was finally converted to C_{2h} symmetric scaffold. Further approaches to more functionalized paracyclophanes are in progress.