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# Synthesis of bicyclic cyclophanes with chiral cages by sixfold coupling

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**Abstract**—Coupling of (*S*)-binol with various tribromides afforded bicyclic cyclophanes by sixfold coupling. Coupling of tricarbonyl tribromide with binol gave a novel chiral cyclophane with six co-ordination sites for complexation. 

One of the most fascinating aspects of modern organic chemistry lies in the synthesis of optically active compounds.[1] Chiral compounds play an important role in the development of medicine such as modification of enzyme structures[2] and advanced materials such as liquid crystals.[3] Chiral macrocycles based on 1,1′-binaphthol were thoroughly studied by Cram[4] and enantiomeric recognition was optimized using a rational approach to host design. Although *m*-terphenyl based chiral cyclophanes incorporating binaphthol as a spacer have been recently reported from our laboratory,[5] bicyclic cyclophanes with a chiral cavity based on binol are not known. Furthermore, the synthesis of cyclophanes involving sixfold coupling is rare[6] though, Anslyn et al.[7] have recently reported such coupling. Herein, we wish to report the synthesis of novel bicyclic cyclophanes with chiral cages by sixfold coupling of tribromides and binol.

In order to check the feasibility of sixfold coupling of binol with tribromides to synthesize bicyclic cyclophane **1**, two equivalents of (*S*)-binol were treated with three equivalents of the tribromide **2**[8] in the presence of $K_2CO_3$ in acetone under high dilution conditions and at room temperature. The reaction mixture after usual work-up followed by purification over silica gel using $CHCl_3$/hexane (1:1) gave compound **3** (34%) in the forerun of elution followed by compound **4** (18%) on further elution. The $^1$H NMR spectrum of compound **3** showed two singlets at $\delta$ 4.67 and 5.12 along with aromatic protons. The $^{13}$C NMR spectrum of compound **3** showed two types of benzylic carbons at $\delta$ 29.26 and at 70.07 along with aromatic carbons. Compound **3** has a specific rotation of −52.5 (*c* 0.5, $CHCl_3$). The $^1$H NMR of cyclophane **4** showed a singlet at $\delta$ 4.46 and two doublets at $\delta$ 5.67 and at 5.98 ($J$=19.2 Hz) along with aromatic protons. The $^{13}$C NMR of cyclophane **4** showed two singlets at $\delta$ 29.67 and at 70.01 for $CH_2Br$ and $OCH_2$ carbons in addition to the aromatic carbons. Cyclophane **4** has a specific rotation of −370.0 (*c* 0.3, $CHCl_3$). The optical rotation, in general, increases enormously, if the binol group becomes more planar or conjugated.[9] The increased value of the specific rotation for the cyclophane **4** indicates that the binol group should be more planar and strained. Energy minimization calculations using the MOPAC method (PM3) also indicated the high degree of strain associated with cyclophane **1** and hence the formation of **1** is prohibited (Scheme 1).

In our attempts to synthesize cyclophanes of type **1**, the crowding around the central benzene ring has to be avoided. Hence, we decided to change to a larger spacer unit. Such a structural modification would increase the cavity size. The tribromide **2** was alkylated using *p*-hydroxybenzaldehyde in DMF in the presence of $K_2CO_3$ to give the trialdehyde **5**, which was then converted into a triol by treating with $NaBH_4$ in MeOH. Treatment of the triol with $PBr_3$ in $CH_2Cl_2$ at room temperature for 12 h gave the tribromide **6** in 62% yield. Coupling of two equivalents of the tribromide **6** with three equivalents of (*S*)-binol in the presence of $K_2CO_3$ afforded the bicyclic cyclophane **7** by sixfold coupling in 22% yield (Scheme 1).

The $^1$H NMR of the cyclophane **7** showed two doublets at $\delta$ 4.81 and at 5.01 ($J$=16.1 Hz) due to the $CH_2$

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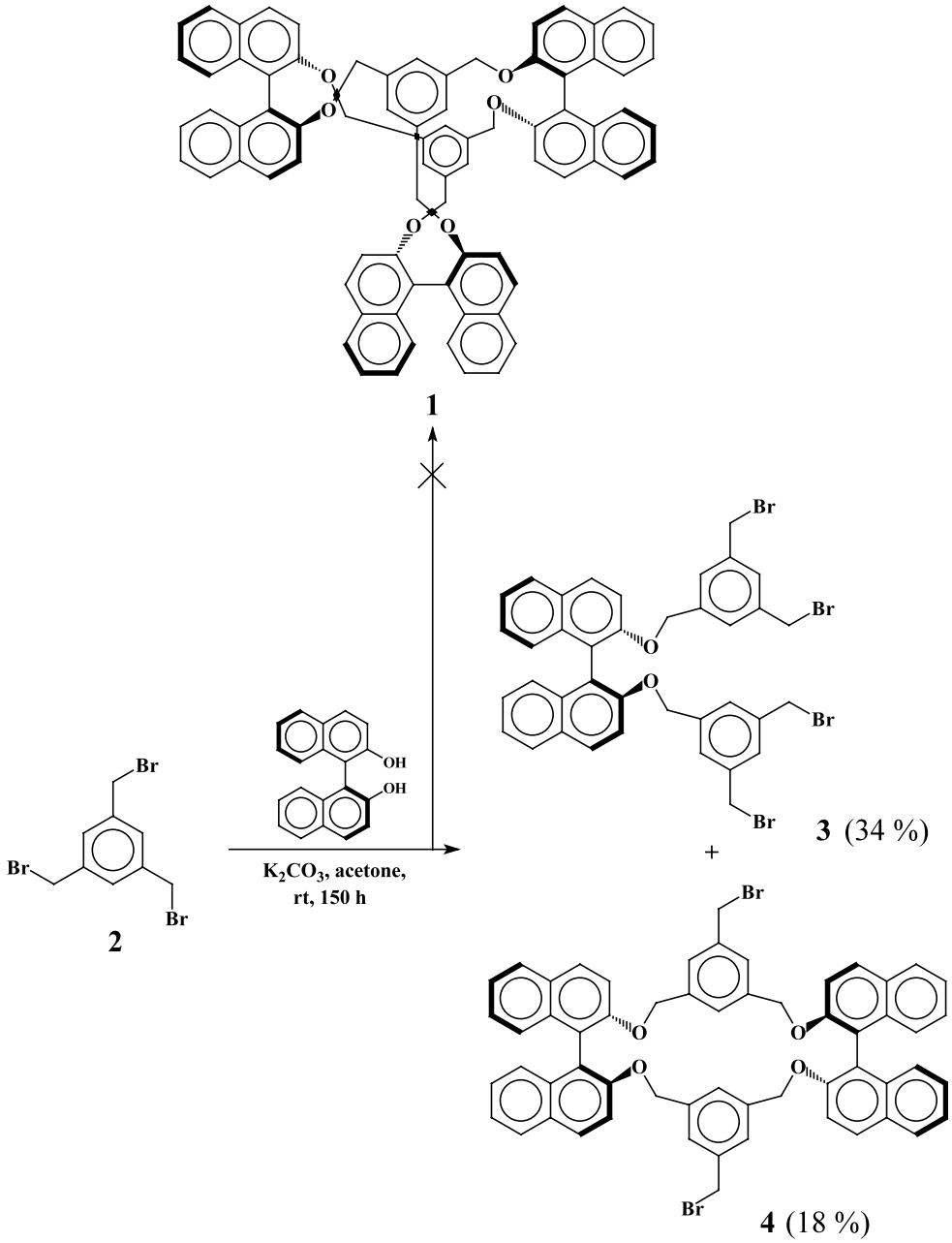
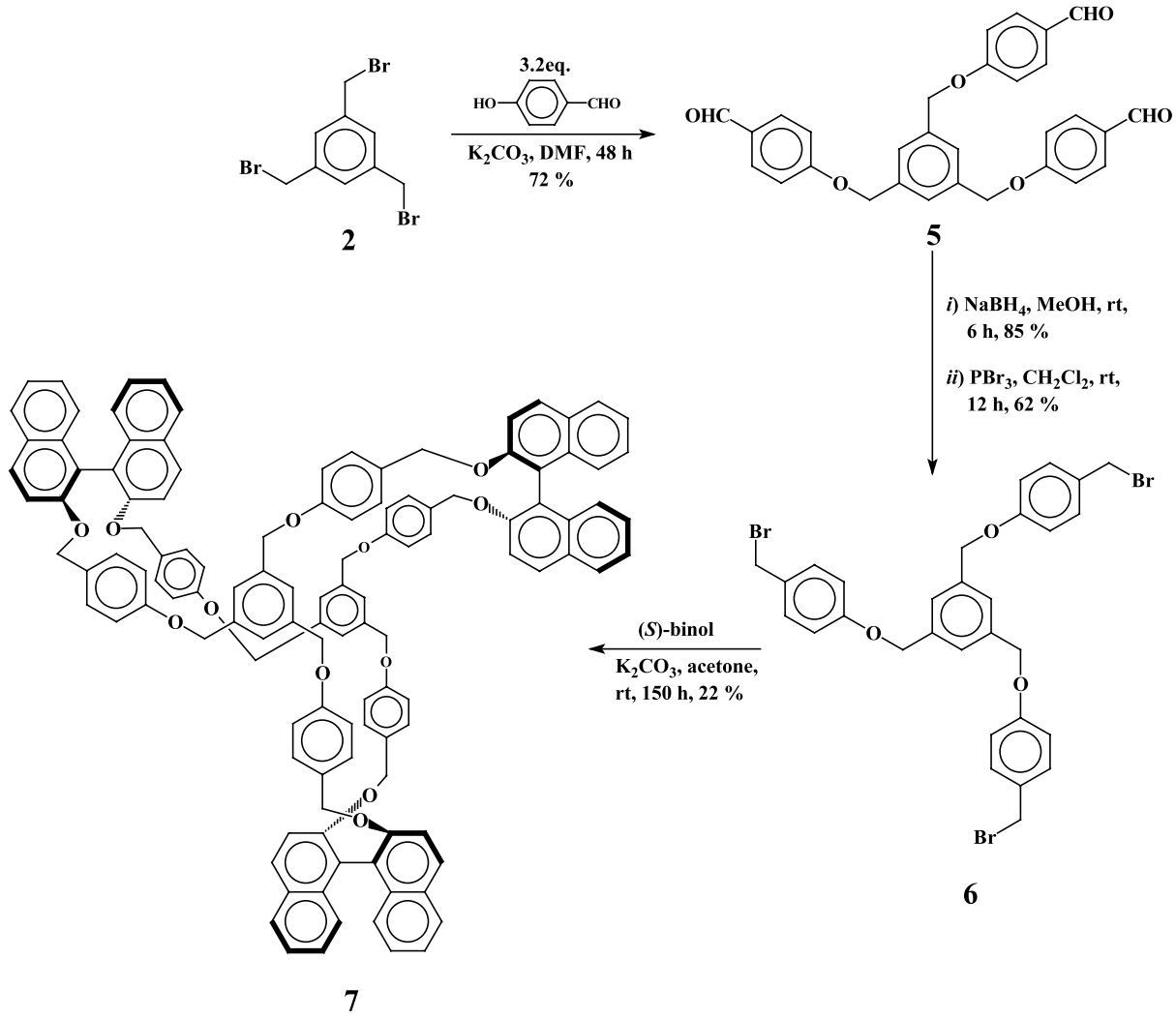



attached to binol and two doublets at $\delta$ 4.88 and 4.93 ($J=8.3$ Hz) due to the $CH_2$ of the mesitylene moiety. The $^{13}C$ NMR spectra of the cyclophane **7** showed two singlets at $\delta$ 69.35 and 70.65 for the $CH_2$ groups along with aromatic carbons. The specific rotation of the cyclophane **7** was found to be −139.16 (*c* 1.4, $CHCl_3$).

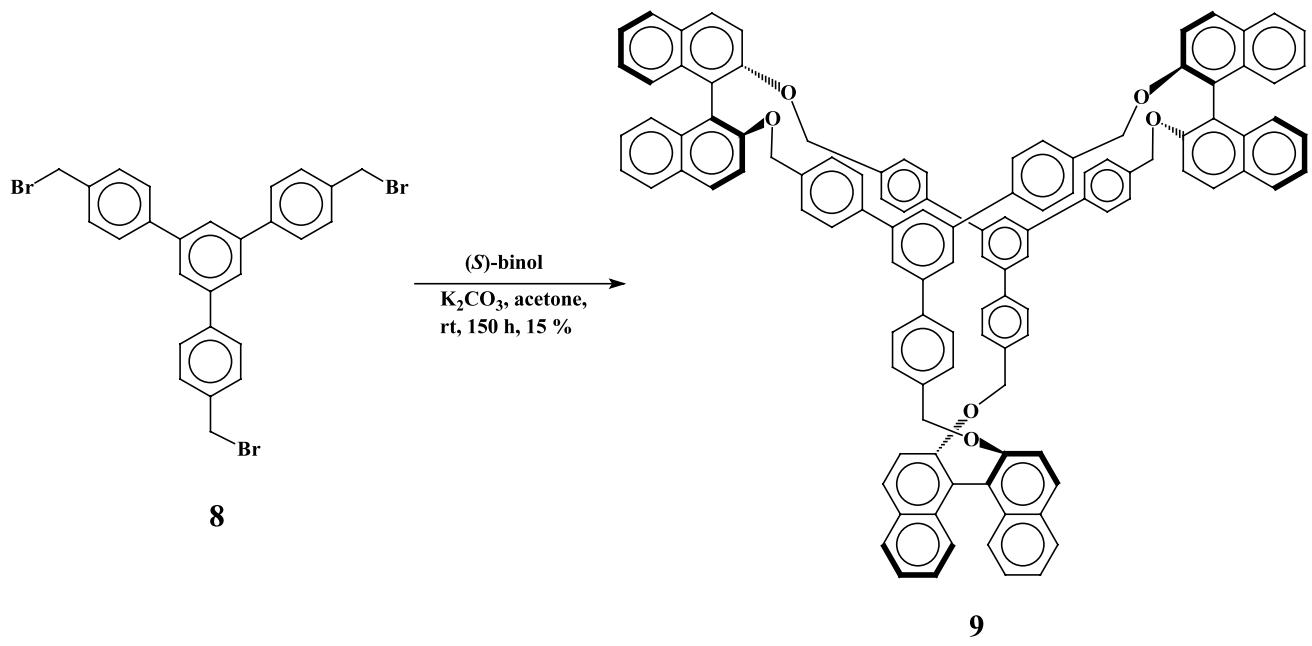
The aromatic units in a cyclophane ensure necessary rigidity to the host molecule.[10] Hence, coupling of the tribromide **8**[11] with (*S*)-binol would result in the formation of a chiral bicyclic cyclophane with a rigid and non-collapsible cavity. The tribromide **8** was treated with (*S*)-binol under high dilution conditions in acetone to furnish the cyclophane **9** in 15% yield. The cyclophane **9** shows an optical rotation of −287.50 (*c* 0.4, $CHCl_3$) and was characterized by spectroscopic and analytical data (Scheme 2).

The synthetic strategy was then directed towards the synthesis of functionalized bicyclic cyclophanes. Introduction of carbonyl groups in a cyclophane is important since they can be converted into a variety of functional groups, which will enable in understanding the complexing ability of such cyclophanes. A novel tricarbonyl tribromide **12** was obtained by the NBS bromination of triketone **11**, which was prepared by the reaction of trimesic acid chloride **10** with toluene in the presence of $AlCl_3$. Treatment of two equivalents of the tricarbonyl tribromide **12** with (*S*)-binol under high dilution conditions afforded the functionalized bicyclic cyclophane **13** in 12% yield with a specific rotation of −270.0 (*c* 0.5, $CHCl_3$) and which was characterized by spectroscopic and analytical data (Scheme 3).

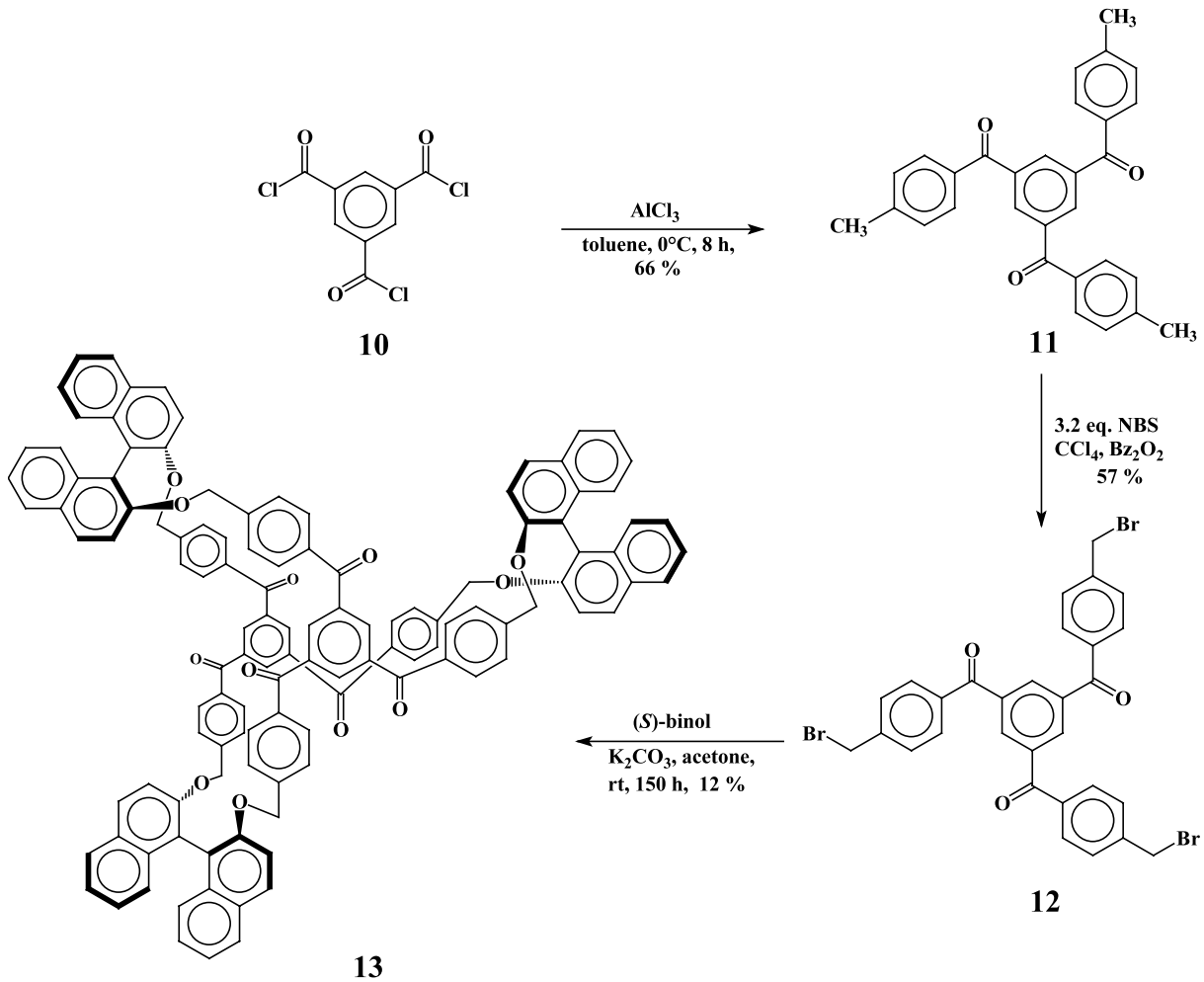
It is worthy to note that the cyclophane **7** developed a deep purple color with tetracyanoethylene (TCNE)




Scheme 1.




Scheme 2.




**Scheme 3.**

showing the formation of a charge-transfer complex. The UV–visible spectrum of the charge-transfer complex shows two absorption maxima at 416 and 398 nm. The association constant ($K_a$) was found to be 69.5 $M^{-1}$.

Reduction of cyclophane **13** with $NaBH_4$ to the corresponding alcohol and charge-transfer complexation studies of all the cyclophanes prepared with other receptors are under investigation.

## Experimental

In a typical reaction, tribromide **6** (0.72 g, 1 mmol) in acetone (1.2 L) was treated with (*S*)-1,1′-binaphthol (0.429 g, 1.5 mmol) in the presence of anhyd. $K_2CO_3$ (14.0 g, 10.1 mmol) at room temperature for 150 h, after which the reaction mixture was filtered and the filtrate evaporated to dryness. The residue obtained was extracted with $CH_2Cl_2$ (2×150 mL); washed with water (3×200 mL), aq. NaOH (25%, 2×100 mL), again with water (3×150 mL) and with brine (200 mL) and dried over anhyd. $Na_2SO_4$. Evaporation of the organic layer gave a pale yellow solid, which was chromatographed over $SiO_2$ using $CHCl_3$ to give cyclophane **7** (0.189 g, 22%); mp 186°C; $[\alpha]_D^{25}$ −139.16 (*c* 1.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 4.81 (d, 6H, $J=16.1$ Hz); 4.88 (d, 6H, $J=8.3$ Hz); 4.93 (d, 6H, $J=8.3$ Hz); 5.01 (d, 6H, $J=16.1$ Hz); 6.33 (d, 12H, $J=8.8$ Hz); 6.68 (d, 12H, $J=8.8$ Hz); 7.11 (d, 6H, $J=7.81$ Hz); 7.13–7.37 (m, 12H); 7.75–7.80 (m, 12H); 7.84 (d, 6H, $J=8.8$ Hz); 7.88 (d, 6H, $J=8.8$ Hz); $^{13}C$ NMR ($CDCl_3$, 100.4 MHz) $\delta$ 69.35, 70.65, 113.35, 114.61, 115.42, 116.41, 117.49, 120.76, 123.66, 124.74, 125.28, 126.35, 127.86, 128.61, 130.76, 134.10, 138.29, 153.89; *m*/*z* (MALDI-MS) 1722 ($M^+$); anal. calcd for $C_{120}H_{90}O_{12}$: C, 83.60; H, 5.26; Found: C, 83.44; H, 5.17%.

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