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Organocatalytic Enantio-, Atrop-, and Diastereoselective Macrocyclization of Quinone Methides

Ting Yao[1], Chang Yuan[2], Xiaoyu Wang[1], Hongxuan Zhai[1] & Changgui Zhao[1]*

[1]*Key Laboratory of Radiopharmaceuticals, Ministry of Education, College of Chemistry, Beijing Normal University, Beijing 100875,* [2]*Key Laboratories of Theoretical and Computational Photochemistry, Ministry of Education, Beijing Normal University, Beijing 100875*

**Corresponding author: cgzhao@bnu.edu.cn*

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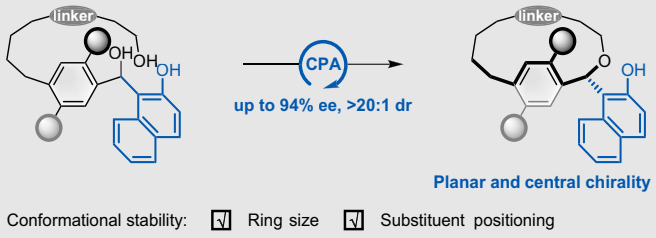
Although installation of a substituent on the ansa chain has been employed to modulate conformational stability and pharmacological properties in cyclophane systems, the detailed relationship between structure and occurrence of planar chirality remains underexplored. Herein, we report the first chiral phosphoric acid-catalyzed enantio-, atrop-, and diastereoselective macrocyclization of quinone methides with alcohols, achieving stereoselective control over the central and planar chiralities. A unique naphthol auxiliary group facilitated macrocyclization and control of the stereoselectivity. A variety of Type III planar-chiral [n]paracyclophanes containing a previously challenging accessible chiral ansa chain were synthesized. Thermal epimerization studies revealed that incorporation of a benzylic substituent on the ansa bridge significantly enhanced conformational stability in Type III [n]paracyclophane, thereby allowing two-atom elongation of the ansa chain while maintaining planar chirality within these constrained macrocyclic frameworks.



Keywords: **cyclophanes, macrocyclization, Brønsted acid, asymmetric catalysis, planar chirality**

Introduction

Cyclophanes are widely found in numerous natural products,[1–3] and are known to be privileged scaffolds in supramolecular chemistry,[4] asymmetric catalysis,[5] and drug discovery.[6] Considering that conformationally stable cyclophanes are critical for enhancing the biological activities of pharmaceuticals,[7–9] the catalytic enantioselective syntheses of planar-chiral cyclophanes and unlocking their structure–conformational stability relationships have recently attracted increasing attention (Scheme 1a).[10,11] In this context, the late-stage atroposelective functionalization of cyclophanes, which strategically installs bulky substituents on benzene rings, has emerged as a robust strategy to access planar-chiral cyclophanes with enhanced conformational stability and precise stereocontrol.[12–19] In addition, catalytic enantioselective macrocyclization of preorganized linear precursors is also an attractive method for constructing planar-chiral cyclophanes.[20–26] More recently, our group pioneered a

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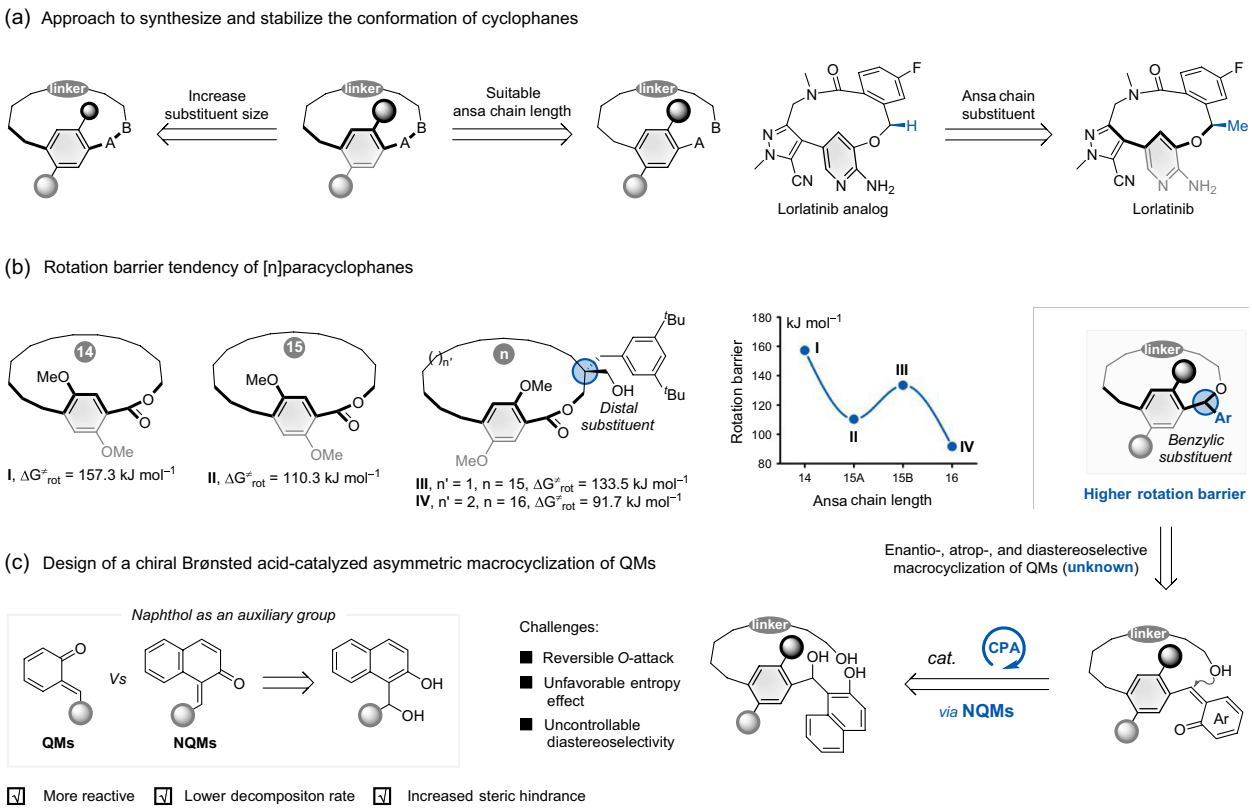

Scheme 1 | *Overview of planar-chiral cyclophanes and the design of an enantio-, atrop-, and diastereoselective macrocyclization protocol of NQMs. In the scheme, the white number in the gray circle represents the ansa chain length.*

cooperative *N*-heterocyclic carbene/chiral phosphoric acid (CPA) dual-catalytic approach that enables enantioselective desymmetrizing macrolactonization, thereby establishing a modular route to stereochemically challenging Type III [n]paracyclophanes.[27] Remarkably, although the introduction of a distal all-carbon stereogenic center within the ansa bridge confers exceptional conformational rigidity to [15]paracyclophane (Scheme 1b, $\Delta G^{\neq}_{rot}$ = 133.5 kJ mol^{-1}), its 16-membered homolog unexpectedly pronounced conformational lability (Scheme 1b, $\Delta G^{\neq}_{rot}$ = 91.7 kJ mol^{-1}), definitively establishing the dual dependency on (1) macrocyclic ring-size[28] and (2) ansa-bridge substituent position[27] for preserving planar chirality in strained [n]paracyclophane systems. To further optimize the conformational stability of these macrocyclic atropisomers, we hypothesized that installation of a sterically demanding moiety at the benzylic position would effectively amplify the torsional barrier associated with benzene ring rotation.

Retrosynthetically, the nucleophilic attack of alcohols on intramolecular quinone methides (QMs) could provide a novel approach for the synthesis of benzylic-substituted Type III [n]paracyclophanes (Scheme 1c). However, the macrocyclization of QMs using alcohols is expected to be limited by several difficulties: (1) despite the well-established asymmetric transformation of QMs,[29–34] the majority of previous reports have focused on the assembly of central and axial chirality,[35–49] and the synthesis of planar-chiral cyclophanes via the asymmetric macrocyclization of QMs remains essentially underexplored; (2) the weak nucleophilicity of alcohols and the good leaving-group ability of alkoxides render these reactions reversible and challenging in the context of stereoselective control;[50] (3) macrocyclization is sensitive to substrate conformational effects that can result in highly variable and unpredictable reaction efficiencies;[51,52] and (4) organocatalytic enantio-, atrop-, and diastereoselective macrocyclization is rare, and diastereoselective control is challenging.[53–55]

Thus, to achieve the macrocyclization of QMs with intramolecular alcohols, it was rationalized that a suitable auxiliary group for the formation of a QM intermediate species is essential to inhibit decomposition of the QM precursor and facilitate the nucleophilic addition reaction. As a subtype of QMs, naphthoquinone methides (NQMs) are more reactive species,[56–58] and previous reports have suggested reduced degrees of decomposition for NQM precursors.[51,59] Furthermore, the steric hindrance associated with NQMs should result in high enantioselectivity and diastereoselectivity

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(Scheme 1c).[51,60–63] Considering the above points along with our continuous interest in the asymmetric syntheses of planar-chiral cyclophanes,[27,28,64–67] the current study focuses on the first chiral Brønsted acid-catalyzed enantio-, atrop-, and diastereoselective macrocyclization reaction between alcohols and NQMs. More specifically, bulky CPAs and 2-naphthol auxiliary groups are employed in the macrocyclization reaction to produce a wide range of planar-chiral macrocycles containing previously less-accessible chiral ansa chains.

Experimental Methods

General procedure for organocatalytic enantio-, atrop-, and diastereoselective macrocyclization: To a 50 mL flask equipped with a magnetic stirring bar was added substrates **1a**–**1f** and **S-4**-**S-33** (0.10 mmol, 1.0 equiv), CPA **C8** (9.9 mg, 0.01 mmol, 0.1 equiv), and 3 Å molecular sieves (MS) (100 mg) under N_2 atmosphere. After that, dry toluene (20.0 mL) was added to the reaction mixture at 25 °C and stirred for 36 h. The precipitate was filtered and washed with toluene, and Na_2CO_3 (10 mg) was added to the above solution. The solvent was evaporated, and the crude residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate (PE/EA) = 70:1, *v*/*v*) affording the planar-chiral cyclophanes. For further details, see Supporting Information.

Results and Discussion

The study was commenced using naphthol-derived benzylic alcohol **1a** as a precursor to generate the NQM species for the macrocyclization reaction. Notably, the reaction mixture was highly diluted (5 mM) to prevent the oligomerization of **1a**. As shown in Scheme 2a, using 3 Å MS as an additive and toluene as a solvent, a number of CPA catalysts were investigated. Generally, BINOL-derived CPA catalysts bearing bulky 3,3′-substituents afforded higher enantioselectivities (entries 1–7). H_8-BINOL-based CPA **C8** bearing 3,3′-(2,4,6-$(Cy)_3$-C_6H_2) produced planar-chiral macrocycle **2a** in an acceptable yield (48%) and an excellent stereoselectivity [92% enantiomeric excess (ee), >20:1 diastereomeric ratio (dr), entry 8]. However, spiroindane-based catalysts **C10** and **C11** failed to catalyze the reaction, probably because of their low acidities (entries 10–11).[50] In addition, a low ee was observed when the reaction was conducted using phosphoric trifylamides **C12** and **C13** as catalysts (entries 12–13). Changing the additive to 4 Å MS or $MgSO_4$ led to a slightly reduced enantioselectivity (entries 14–15), and solvent optimization experiments indicated that tetrahydrofuran (THF) and ethyl acetate inhibited the reaction, presumably due to their competitive binding to the CPA catalyst (entries 16–17).[50,58] Similarly, macrocyclization did not proceed upon lowering the temperature to 0 °C (entry 20). The absolute configuration of **2a** was determined by X-ray crystallography [Cambridge Crystallographic Data Centre (CCDC) 2422998].

Thermal stability studies revealed no detectable epimerization of (S_p, *S*)-**2a** under heating conditions [dimethyl sulfoxide (DMSO)-d_6, 110 °C, 48 h], as rigorously validated by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy analysis (Scheme 2b). These results establish a definitive structure-conformational stability relationship, demonstrating that the benzylic-positioned ansa-bridge substituent significantly increases the rotational barrier in type III [15]paracyclophane.[27]

Notably, when QM precursors were employed, relatively fast precursor decomposition was observed, affording the corresponding macrocycles in low yields (Scheme 2c, **2b–2f**). In addition, the corresponding dimer **3** of **2b** was identified by X-ray crystallography (CCDC 2422997, for details, see the Supporting Information). Moreover, the significantly decreased enantioselectivities observed for products **2d**–**2f** revealed the role of NQM steric hindrance in imparting enantioselective control on the reaction. Based on these results, it was confirmed that the naphthol auxiliary group facilitates the macrocyclization reaction.

With the optimized conditions in hand (entry 8, Table 1), the scope of the macrocyclization reaction was investigated (Table 1). More specifically, substituted 2-naphthol, bearing a bromo group at the C3, C4, C6, or C7 position, was considered to be a suitable substrate for generating NQM species via intramolecular nucleophilic addition, affording the corresponding [15]paracyclophanes in high stereoselectivities (**4**–**6**, **10**). The C6 methyl-substituted substrate gave a slightly decreased diastereoselectivity (**7**), while the phenyl- and 3-thiophenyl substituents were well tolerated (**8** and **9**). Moreover, the reaction of C7 methyl-substituted 2-naphthol proceeded smoothly to yield macrocycle **11** in a 31% yield with a 91% ee and a 16:1 dr. In addition, different 2,5-dialkoxyl groups were evaluated on the benzene ring, and it was found that the C5 benzyloxy-substituted substrate afforded high ee and dr values (**12**). Additionally, upon changing the substituent on the C2 hydroxyl group from methyl to benzyl, 2-methylnaphthalene, 3,5-dimethylbenzyl, 4-methylbenzyl, 4-fluorobenzyl, 3-chlorobenzyl, and 3,3-dimethylbutyl groups, the corresponding cyclophanes were obtained in excellent stereoselectivities (**13**–**17** and **19**–**20**). However, the 4-chlorobenzyl substituent afforded the corresponding product with a low diastereoselectivity (**18**, 4:1 dr).

The reaction scope was further evaluated by varying the composition and length of the ansa chain. More specifically, alkyl chains bearing ether groups were amenable to the reaction, yielding the corresponding cyclophanes in high stereoselectivities (**21**–**23**). In addition, reducing the alkyl chain length to 12–13 atoms produced

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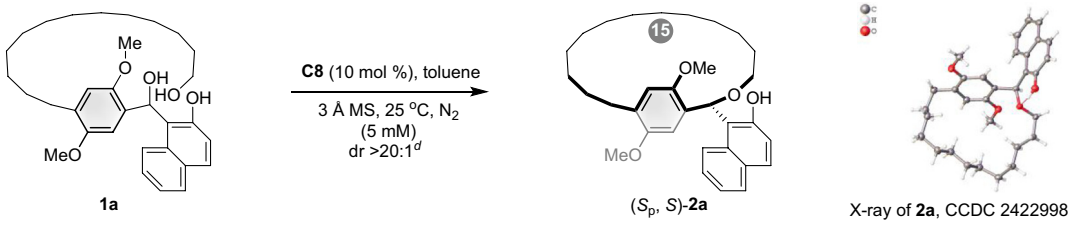
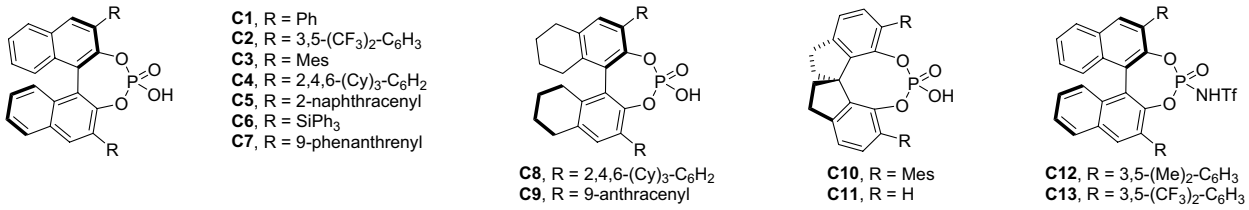
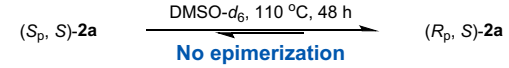




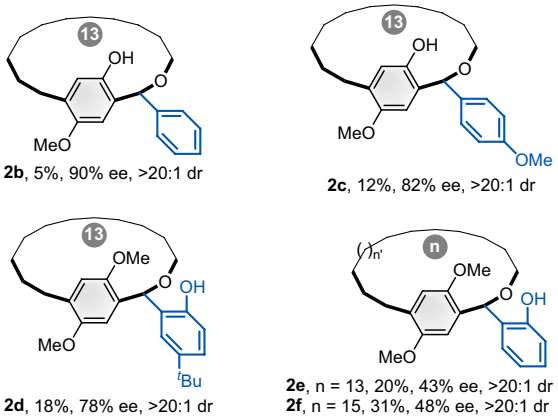
(a) Screening of CPA catalyst, additive and solvent

Entry [a]	Variation from above conditions	2a [yield[b], ee[c], %]
1	**C1**	45, 5
2	**C2**	43, 7
3	**C3**	49, 47
4	**C4**	30, 90
5	**C5**	38, 25
6	**C6**	33, 79
7	**C7**	40, 40
8	Standard conditions	48, 92
9	**C9**	33, 20
10	**C10**	N.R.
11	**C11**	N.R.
12	**C12**	45, 25
13	**C13**	33, 6
14	4 Å MS as additive	45, 86
15	$MgSO_4$ as additive	39, 83
16	THF as solvent	N.R.
17	Ethyl acetate as solvent	N.R.
18	Xylene as solvent	48, 91
19	PhCl as solvent	38, 89
20	0 °C	N.R.

(b) Thermodynamic experiments of **2a**



(c) Macrocyclization of QMs



Scheme 2 | *Optimization of reaction conditions and thermodynamic experiments of **2a**. [a]Reaction conditions: **1a** (0.1 mmol), **CPA** (0.01 mmol, 10 mol %), additive (100 mg), solvent (20.0 mL), 25 °C, nitrogen atmosphere, 36 h. [b]Isolated yield. [c]The ee value was determined by high performance liquid chromatography (HPLC) analysis of the chiral stationary phase. [d]The dr value was determined by ^{1}H NMR spectroscopy. N.R., no reaction; THF, tetrahydrofuran; BINOL, 1,1′-bi-2,2′-naphthol.*

cyclophanes **24** and **25** in low yields but with high stereoselectivities. The corresponding oligomer was observed as a reaction by-product. The substrate containing a 14-membered chain delivered planar-chiral macrocycles **26** and **27** in moderate yields with high ee and dr values. Furthermore, conformationally stable [16]- and [17]paracyclophanes **28**–**32** were obtained in high stereoselectivities. Further extending the alkyl chain length afforded [18]paracyclophane **33** in a low dr (2:1). This observed erosion in diastereoselectivity could be attributed to decreased conformational stability, which presumably facilitated rapid epimerization of the planar chirality.

The conformational stability of the cyclophane benzene ring is crucial in determining the biological activity of the corresponding pharmaceutical.[7–9] To further gain insights into the structure-stability correlation in Type III [n]paracyclophanes, specifically probing the size-dependent conformational stability, thermal epimerization studies were conducted on [16]- and [17]paracyclophanes derivatives. Notably, no epimerization of **28** was observed by ^{1}H NMR spectroscopy after heating in DMSO-d_6 at 110 °C for 48 h (for details, see the Supporting Information). A similar stabilizing effect was observed for [17]paracyclophane **31**.[a] While previous

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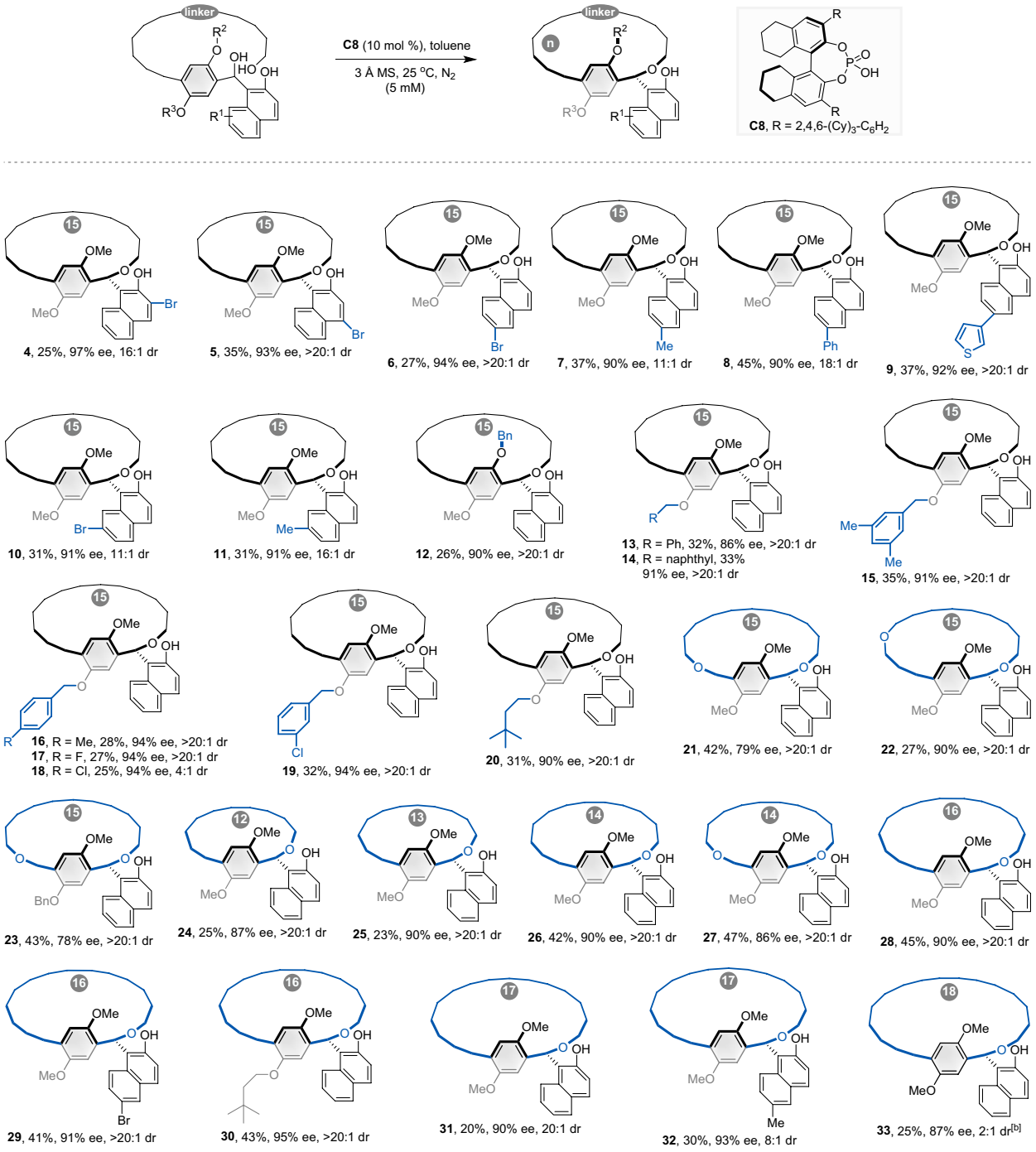
Table 1 | *Scope of the Substrates*[a]



[a] Reaction conditions: A mixture of the substrate (0.1 mmol), 3 Å MS (100 mg), and **C8** (10 mol%) in toluene (20.0 mL) was stirred at 25 °C under nitrogen atmosphere for 36 h. The dr value was determined by ^{1}H NMR spectroscopy.
[b] 87% ee for the major and minor isomers.

reports have established the conformational instability of [16]paracyclophane bearing a distal 2,5-dimethoxy substituent on the ansa bridge and the absence of planar chirality in its 17-membered homolog,[28] our variable-temperature thermodynamic analyses reveal that naphthyl installation at the benzylic position enables two-atom extension of the ansa bridge while maintaining the stereochemical integrity of planar chirality in these constrained macrocyclic systems.

To elucidate the reaction mechanism and determine the origin of the low reaction yield, a series of control experiments were proposed (Scheme 3). Initially, the reaction of substrate **1g** was performed, which contains a methyl-protected naphthol hydroxyl group. No

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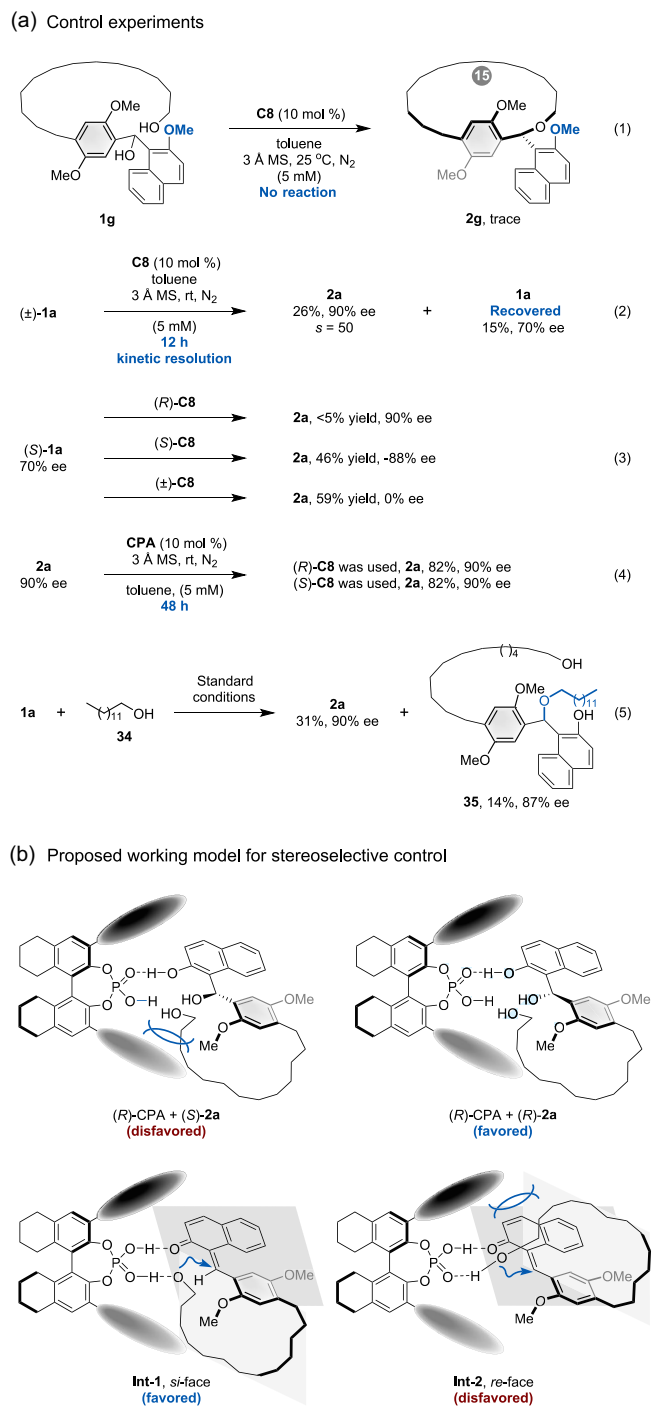
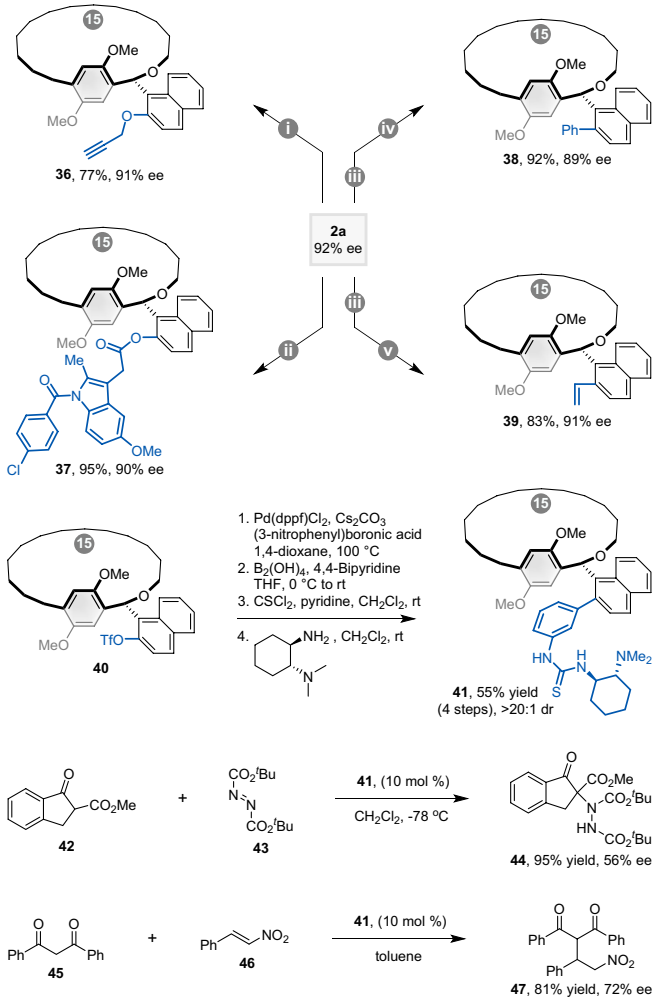


Scheme 3 | *Control experiments and proposed working model for achieving stereoselective control.*



Scheme 4 | *Synthetic transformation and applications. Reaction conditions: (i) propargyl bromide, K_2CO_3, MeCN, 90 °C, 4 h. (ii) Indomethacin, $(COCl)_2$, dimethylformamide, CH_2Cl_2, 25 °C, 1 h. Then Et_3N, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, rt, 2 h. (iii) Tf_2O, Et_3N, DMAP, THF, –78 °C, 30 min. (iv) Phenylboronic acid, Pd(dppf)Cl_2, Cs_2CO_3, 1,4-dioxane, 110 °C, 8 h. (v) Potassium vinyltrifluoroborate, Pd(OAc)$_2$, xPhos, Cs_2CO_3, 1,4-dioxane, 110 °C, 8 h.*

macrocyclization was observed under the standard reaction conditions, suggesting the key role of the free hydroxyl group (Scheme 3a, equation 1). This supports the hypothesis that the reaction proceeds via the NQM intermediate pathway, as the NQM species cannot be formed without a hydroxyl group.[58,62] Furthermore, the reaction of **1a** was performed under standard conditions for 12 h, affording **2a** in 26% yield and a 90% ee. Unreacted **1a** was recovered in a 15% yield and a 70% ee. This observation was consistent with the kinetic resolution process (Scheme 3a, equation 2, *s* = 50). Subsequently, the recovered (*S*)-**1a** was subjected to further reaction using (*R*)-**C8** as the catalyst, and product **2a** was obtained in a <5% yield with a 90% ee (Scheme 3a, equation 3). In contrast, the reaction of (*S*)-**1a** with (*S*)-**C8** gave the opposite configuration of product **2a** in a 46% yield, while the racemic **C8** catalyst resulted in a 0% ee. These results indicate that the stereochemistry of the product was dependent on the absolute configuration of the catalyst, regardless of the stereochemistry of **1a**. The above control experiments further support the NQM intermediate

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reaction pathway and exclude the S_N2 pathway from the macrocyclization process. Macrocycle **2a** remained configurationally stable under standard conditions for 48 h (Scheme 3a, equation 4), and remarkably, no stereochemical erosion was observed when **2a** was exposed to (*S*)-**C8**. These results suggest that the intramolecular conjugate addition of an alcohol moiety to the NQM intermediate may be irreversible, which differs from the intermolecular *O*-attack on QM species.[50]

In the kinetic resolution process, decomposition of the unmatched substrate (*S*)-**1a** was observed in the presence of (*R*)-**C8** (Scheme 3a, equation 3). Moreover, the relatively low yields achieved in the reactions of (*S*)-**1a** with the (*S*)-**C8** and racemic **C8** catalysts indicated that the highly dilute macrocyclization reaction conditions inhibited *O*-addition to the NQM intermediate. Competitive intra- and intermolecular reactions were conducted by the addition of 1-tridecanol **34** during the macrocyclization of **1a** under standard conditions (Scheme 3a, equation 5). As a result, the corresponding intermolecular *O*-attack by-product **35** was obtained in 14% yield with 87% ee. Taken together, decomposition of the substrate and oligomerization of the NQM intermediate may account for the low reaction efficiency of this macrocyclization process.

Subsequently, a possible stereochemical model was proposed based on control experiments (Scheme 3b). More specifically, the dehydration of (*R*)-**1a** in the presence of (*R*)-**C8** favors the formation of an NQM intermediate, whereas the unmatched substrate (*S*)-**1a** decomposes under the same conditions. Nucleophilic addition from the *si*-face then proceeds with minimal steric hindrance, yielding a planar-chiral cyclophane in a high stereoselectivity (**Int-1**). In contrast, significant steric hindrance between the ansa chain and the catalyst backbone in **Int-2** prevents *re*-face attack from the alcohol onto the NQM species.

To illustrate the synthetic utility of this protocol, derivatization of the planar-chiral cyclophane **2a** was performed (Scheme 4). More specifically, propargylation of the 2-naphthol hydroxyl group of **2a** yielded **36** without any loss of stereoselectivity, while the use of an esterified substrate proceeded smoothly to afford indomethacin-derived cyclophane **37**. Furthermore, the triflation of **2a** followed by separate Suzuki–Miyaura cross-coupling reactions with phenylboronic acid and potassium vinyltrifluoroborate provided the corresponding cyclophanes **38** and **39** in high yields without any loss of enantioselectivity.

Lastly, thiourea bifunctional catalyst **41** was synthesized via Suzuki cross-coupling of triflate **40** with (3-nitrophenyl)boronic acid, followed by nitro group reduction to the corresponding amine, and subsequent treatment with thiophosgene ($CSCl_2$) and chiral (*1R,2R*)-*N,N′*-dimethylcyclohexane-1,2-diamine. Although cyclophane-derived bifunctional organocatalyst **41** demonstrated moderate enantioselectivity (56% ee) in the catalytic asymmetric Michael addition of β-ketoester **42** to *di-tert*-butyl azodicarboxylate **43**, it offers a potential solution for improved catalyst design. Notably, when applied to the Michael addition of 1,3-diphenylpropane-1,3-dione **44** to (2-nitrovinyl)benzene **46**, the thiourea-based catalyst **41** proved more effective, yielding **47** with enhanced enantioselectivity (72% ee).

Conclusion

In summary, this study reports the first Brønsted acid-catalyzed enantio-, atrop-, and diastereoselective macrocyclization between an alcohol and a QM moiety. The high enantioselectivity and diastereoselectivity were achieved through a bulky CPA catalyst in combination with a sterically hindered 2-naphthol auxiliary group. Control experiments revealed that the reaction proceeded via an NQM intermediate, and that kinetic resolution was responsible for the generation of these species. Notably, decomposition of mismatched substrates under the reaction conditions limited the efficiency of the intramolecular macrocyclization. Despite this challenge, the developed protocol enabled the successful synthesis of diverse Type III planar-chiral [n]paracyclophanes. Further thermal epimerization studies demonstrated that introducing a naphthyl group at the benzylic position allowed for two-atom extension of the ansa chain while preserving planar chirality. These results highlight a dual dependence on (1) macrocyclic ring size and (2) ansa-bridge substituent positioning for conformational stability in these strained macrocyclic systems.

Footnote

[a] The decomposition of **31** was observed after heating in DMSO-d_6 at 130 °C for 3 h.

Supporting Information

Supporting Information is available and included free of charge. It consists of additional experimental details, materials, methods, and analytical data (PDF). The X-ray crystallographic coordinates for structures reported in this study have been deposited at the CCDC, under deposition numbers CCDC 2422998 (for **2a**) and CCDC 2422997 (for **3**). These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/data_request/cif.

Conflict of Interest

There is no conflict of interest to report.

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