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Pd(II)-catalyzed atroposelective and enantioselective C–H olefination of [*n*]metacyclophanes

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Abstract

A Pd(II)-catalyzed C–H olefination strategy has been established for the enantioselective synthesis of [*n*]metacyclophanes. The method demonstrates excellent functional group tolerance across a series of olefins and metacyclophane precursors with varying ansa-chain lengths, achieving high stereocontrol through kinetic or dynamic kinetic resolution. Racemization experiments were conducted to investigate the relationship between molecular structure and conformational stability. Furthermore, the synthetic utility of this approach was demonstrated through gram-scale synthesis and the application of a resulting bifunctional thiourea catalyst in asymmetric Michael additions, highlighting its potential in asymmetric synthesis.

Keywords: Metacyclophanes, C–H olefination, asymmetric catalysis, palladium

1. Introduction

[*n*]Cyclophanes are molecules comprising aromatic rings bridged by alkyl chains, which are classified into ortho-, meta-, and para-subtypes according to the substitution pattern linking the arene to the ansa chain[1-4]. In meta- and paracyclophanes, the presence of sterically demanding substituents on the aromatic ring, combined with an optimally sized alkyl tether, can impart planar chirality by restricting the rotation of the arene around the bridge[5-7]. Conformationally defined metacyclophanes constitute the core structure of numerous bioactive natural products, such as complestatin[8], which exhibits inhibitory activity against HIV-1 integrase (Scheme 1A). Furthermore, optically pure metacyclophanes represent privileged scaffolds in pharmaceutical research[9-12], asymmetric catalysis[13,14], and supramolecular chemistry[15-20]. Recently, atroposelective and enantioselective synthesis of planar-chiral cyclophanes has garnered growing interest, with most efforts focusing on paracyclophanes[21-46]. In contrast, catalytic asymmetric synthesis of metacyclophanes remains less developed, primarily due to challenges associated with their conformational flexibility and significant ring strain[47-50].

In 2007, Tanaka and colleagues pioneered a rhodium-catalyzed atroposelective arene formation to afford [7]–[10]metacyclophanes in moderate yields (Scheme 1B, I)[51]. Subsequently, asymmetric macrocyclization strategies have emerged as an alternative route to metacyclophanes. In this context, Li and co-workers developed a Pd-catalyzed C–O bond-forming macrocyclization for the synthesis of enantioenriched planar-chiral metacyclophanes (Scheme 1B, II)[52]. Independently, Wang and Zhou reported N-heterocyclic carbene- or chiral phosphoric acid (CPA)-catalyzed asymmetric macrolactonizations to access indole-based metacyclophanes[13,53]. Beyond these methods, the Povarov reaction has also proven attractive for constructing such scaffolds. More recently, Li's group described a CPA-catalyzed enantioselective desymmetric Povarov reaction, coupled with oxidative aromatization, to access planar-chiral [*n*]metacyclophanes (Scheme 1B, III)[14]. In these systems, conformational stability is maintained through bulky substituents on the benzene ring and a short ansa chain. Most recently, our group reported a CPA-catalyzed asymmetric ansa chain editing strategy for the synthesis of metacyclophanes (Scheme 1B, IV)[54]. This approach leverages the combined effects of ansa chain length, substituent bulk on the arene ring, and restricted rotation of the tertiary amide bond to cooperatively stabilize the resulting conformation.

The Pd/*p*Glu-catalyzed atroposelective C–H olefination has been well established for constructing enantioenriched scaffolds[55-67]. For example, Shi and co-workers developed an elegant picolinamide-directed asymmetric C–H olefination to access axially chiral anilides[59]. This catalytic system was subsequently extended to the construction of N–aryl peptide atropisomers and axially chiral styrenes[60-62]. More recently, we employed the Pd/*p*Glu platform in the late-stage C–H functionalization of cyclophanes, providing

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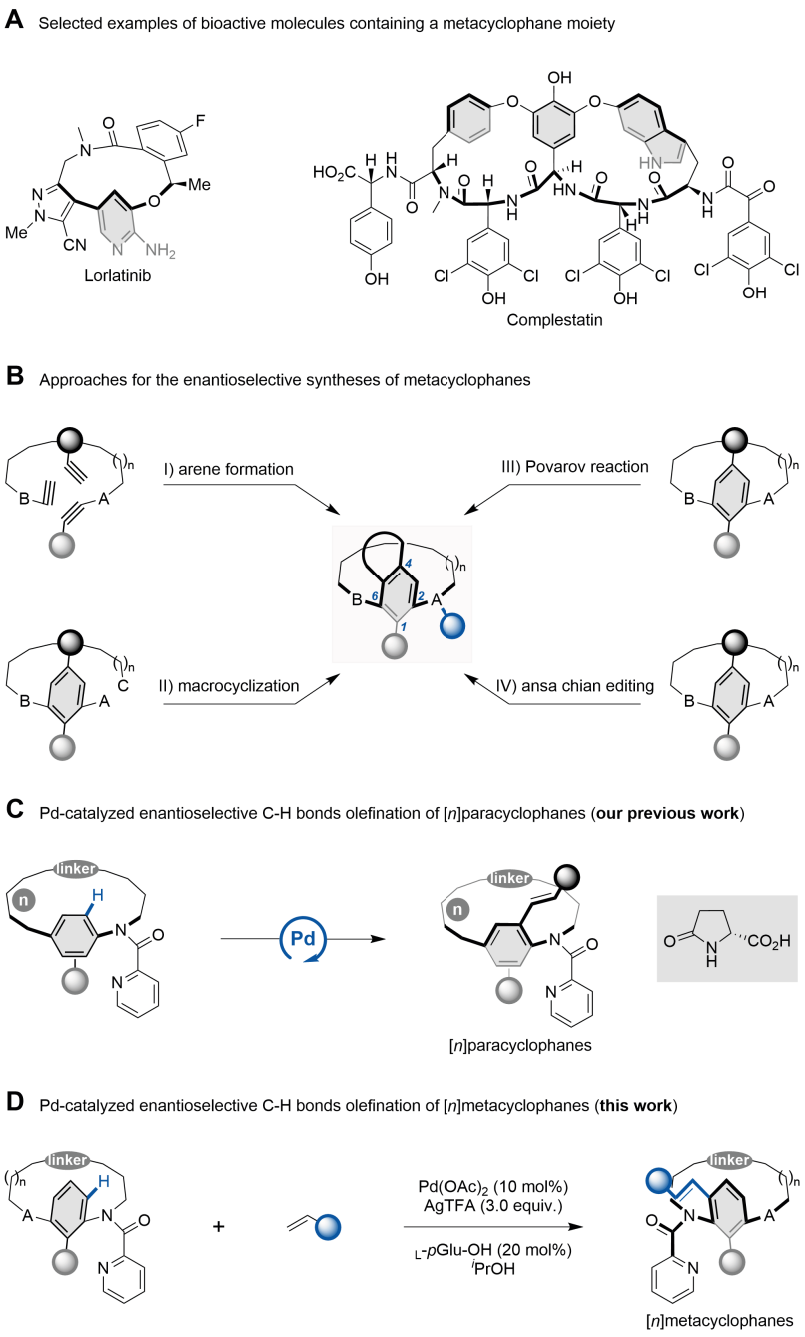
efficient access to diverse planar-chiral paracyclophanes (Scheme 1C)[40-42]. We hypothesized that the same strategy could be applicable to the atroposelective synthesis of metacyclophanes. Herein, we report a Pd-catalyzed late-stage C–H olefination of metacyclophanes enabled by a monoprotected amino acid ligand (Scheme 1D). Furthermore, our study revealed that introducing a picolinamide group onto the ansa chain offers additional conformational stabilization for the resulting metacyclophanes.



Scheme 1. Overview of metacyclophanes and design of a Pd(II)-catalyzed C–H olefination strategy for the atroposelective synthesis of [*n*]metacyclophanes. Created in ChemDraw.

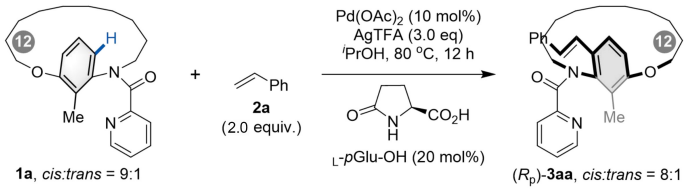
2. Experimental

Representative Synthesis of [*n*]metacyclophanes 3. A 10 mL-reaction tube equipped with a magnetic stirring bar was charged with metacyclophanes **1** (0.1 mmol, 1.0 equiv.), alkene **2** (0.2 mmol, 2.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.1 equiv.), $_L$-*p*Glu-OH (2.6 mg, 0.02 mmol, 0.2 equiv.) and AgTFA (66.3 mg, 0.3 mmol, 3.0 equiv.). The tube was sealed and ^{i}PrOH (2.0 mL) was injected into the tube via a syringe. The reaction mixture was allowed to stir at 60 °C (pre-heated metal module) under air for 12 h. Then, the reaction mixture was immediately cooled to room temperature. The solvent was evaporated and the residue was purified by alkaline alumina column chromatography (PE/EA = 2:1, *v*/*v*) affording the metacyclophanes **3**.

3. Results and Discussion

The Pd-catalyzed late-stage atroposelective C–H olefination of metacyclophane was investigated using picolinamide-derived [12]metacyclophane **1a** and styrene **2a** as model substrates. As summarized in Table 1, a series of palladium catalysts was evaluated with AgTFA (3.0 equiv.) as the oxidant, $_L$-*p*Glu-OH (20 mol%) as the chiral ligand, and ^{i}PrOH as the solvent. When $Pd(OAc)_2$ was used as the catalyst, product **3aa** was obtained in high yield with 88% ee (entry 1). Catalysts such as $Pd(PPh_3)Cl_2$, $Pd(COD)Cl_2$, and $Pd(MeCN)_2Cl_2$ also afforded excellent conversion, with ee values ranging from 69% to 71% (entries 3-4, 6). In contrast, $PdCl_2$ and $PdBr_2$ led to slightly lower reaction efficiencies (entries 2, 5). Screening of other oxidants, including Ag_2O, AgOAc, Ag_2SO_4, $AgNO_3$, and Ag_3PO_4, did not improve the reaction outcomes (entries 7-11). Further investigation of solvents revealed that protic solvents generally afforded the product in high yield and ee (entries 12-13), whereas MeCN and toluene gave **3aa** in moderate yield (entries 14-15). Although aprotic solvents such as chlorobenzene and 1,2-dimethoxyethane (DME) resulted in excellent conversion, the product was obtained with low ee (entries 16-17). Interestingly, lowering the reaction temperature led to an increase in enantiomeric excess (entries 18-19), which is attributed to the suppression of racemization of **3aa** under milder conditions. Conformational stability studies indicated a rotational barrier of 124.37 kJ·mol^{-1} for **3aa**, corresponding to a half-life of 65.2 minutes for the rotation reaction at 110 °C. Both substrate **1a** and product **3aa** exist as inseparable mixtures of *cis* and *trans* rotamers, which originate from rotation about the N–CO bond of the 2-pyridyl formyl group. ^{1}H NMR and X-ray diffraction analysis indicated that the *cis* isomer was found to be predominant[40-42,59-61].

Table 1. Optimization of the reaction conditions.

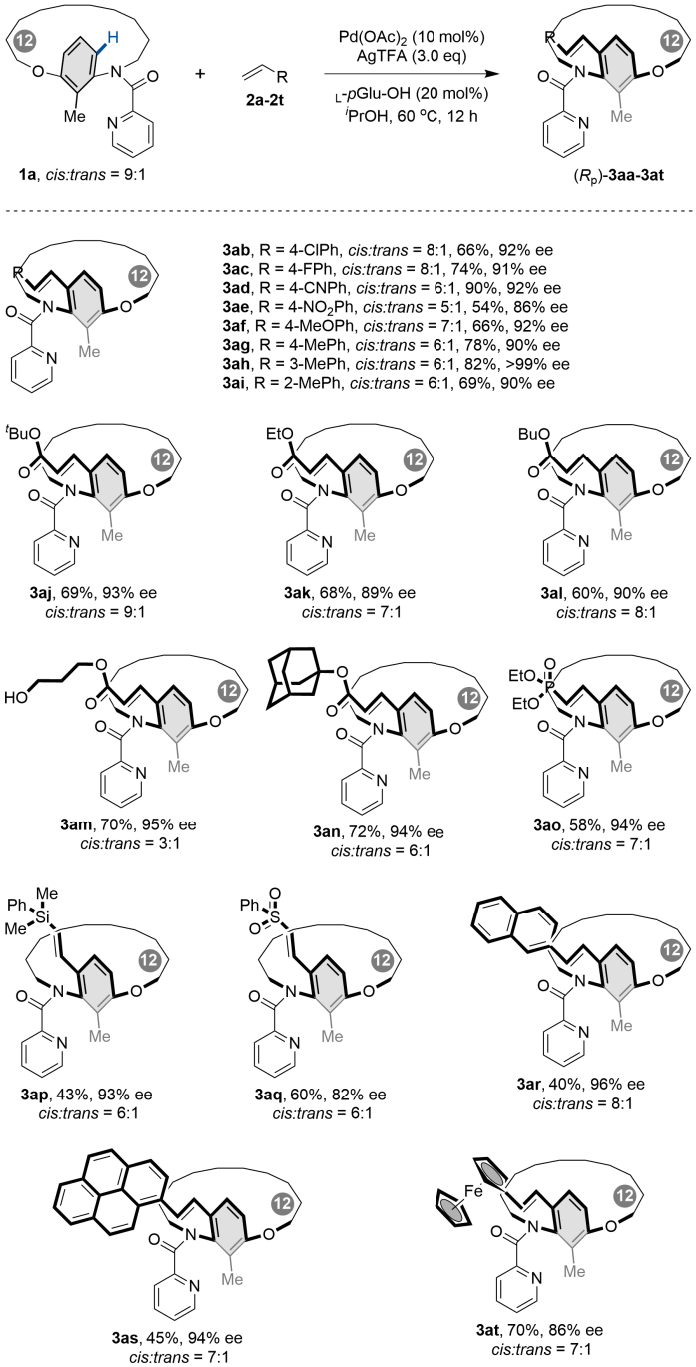


Entry[a]	Variation from above conditions	Yield (%)[b]	ee (%)[c]
1	None	99	88
2	$PdCl_2$ (10 mol%)	72	69
3	$Pd(PPh_3)Cl_2$ (10 mol%)	99	71
4	$Pd(COD)Cl_2$ (10 mol%)	99	69
5	$PdBr_2$ (10 mol%)	84	69
6	$Pd(MeCN)_2Cl_2$ (10 mol%)	99	70
7	Ag_2O (3.0 equiv.)	70	69
8	AgOAc (3.0 equiv.)	85	72
9	Ag_2SO_4 (3.0 equiv.)	68	72
10	$AgNO_3$ (3.0 equiv.)	99	84
11	Ag_3PO_4 (3.0 equiv.)	75	73
12	*t*-AmylOH as the solvent	99	82
13	TFE as the solvent	99	84
14	MeCN as the solvent	64	83
15	toluene as the solvent	64	53
16	PhCl as the solvent	99	27
17	DME as the solvent	99	56
18	70 °C	96	90
19	**60 °C**	**90 (80)[d]**	**95**

[a]: Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol, 2.0 equiv.), $Pd(OAc)_2$ (0.01 mmol, 10 mol%), $_L$-*p*Glu-OH (0.02 mmol, 20 mol%), and oxidant (0.3 mmol, 3.0 equiv.) in ^{i}PrOH (2.0 mL). The mixture was stirred at 80 °C for 12 h under air. *cis*/*trans* ratio was determined by ^{1}H NMR analysis; [b]: The yields were determined by ^{1}H NMR with

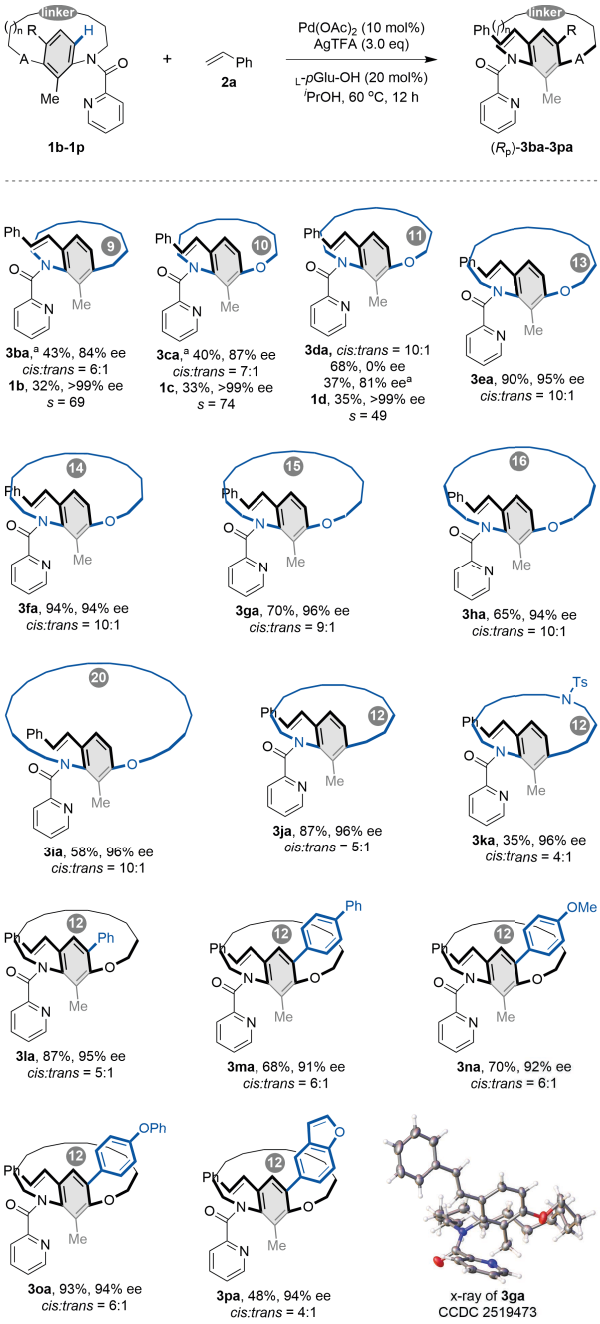
1,3,5-trimethoxybenzene (1/3 equiv.) as an internal standard; [c]: Enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase; [d]: Yield refers to isolated yield. Numbering in grey circles indicates ansa chain length. ee: enantiomeric excess; TFE: trifluoroethanol; DME: 1,2-dimethoxyethane.

After establishing the optimal reaction conditions, we evaluated the substrate scope of alkenes in the Pd-catalyzed C–H olefination for the synthesis of [*n*]metacyclophanes (Scheme 2). Substituted vinylarenes with electron-neutral, electron-donating, and electron-withdrawing groups all proved compatible (**3aa**-**3ai**), affording [12]metacyclophanes in moderate to good yields with high to excellent enantioselectivities. Notably, substitution at the 3-position of the benzene ring further improved enantiocontrol (**3ah**, > 99% ee). A range of acrylates, including sterically hindered derivatives, also reacted smoothly to deliver the corresponding products (**3aj**-**3an**) in good yields with high enantioselectivities. Moreover, substrates bearing other functional groups, such as phosphate acrylate, dimethyl(phenyl)silane, and phenyl sulfone, were also suitable, providing [12]metacyclophanes (**3ao**-**3aq**) in moderate to good yields with high enantioselectivities. Additionally, vinylarenes including 2-vinylnaphthalene, 1-vinylpyrene, and vinylferrocene were efficiently transformed into the target metacyclophanes (**3ar**-**3at**).



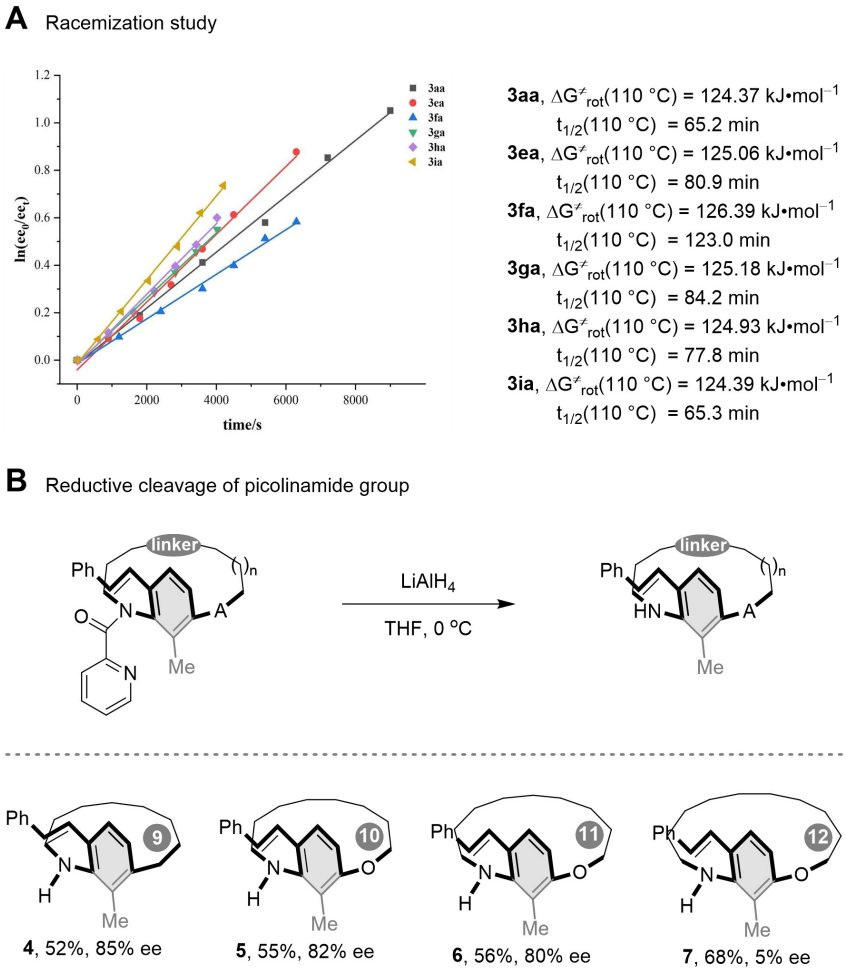
Scheme 2. Scope of alkenes. Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2** (0.2 mmol, 2.0 equiv.), $Pd(OAc)_2$ (0.01 mmol, 0.1 equiv.), L-*p*Glu-OH (0.02 mmol, 0.2 equiv.) and AgTFA (0.3 mmol, 3.0 equiv.) in ^{i}PrOH (2.0 mL) was stirred at 60 °C for 12 h under air. Created in ChemDraw.

We next examined the effect of ansa chain length and benzene ring substituents on the reaction (Scheme 3). For [9]-[11]metacyclophanes, the C–H olefination proceeded via a kinetic resolution pathway. Under standard conditions, using 2.0 equivalents of alkene **2a**, [11]metacyclophane **3da** was obtained in 68% yield with 0% ee, as both isomers were fully consumed. When the loading of **2a** was reduced to 0.5 equivalents, product **3da** was obtained in 37% yield with 81% ee, while the remaining starting material **1d** was recovered in 35% yield and > 99% ee. A similar trend was observed for the [9]-[10]metacyclophanes (**3ba**–**3ca**), which also exhibited high selectivity under kinetic resolution conditions. In contrast, the longer-chain [13]-[16]- and [20]metacyclophanes underwent dynamic kinetic resolution, furnishing the corresponding products (**3ea**–**3ia**) in moderate to high yields with high enantioselectivities. Furthermore, [12]metacyclophane comprising heteroatom variations in the ansa chain were obtained in good yields with high enantioselectivity (**3ka**). More importantly, the reaction demonstrated broad tolerance for diverse aromatic substituents at the 2-position of the benzene ring, affording products **3la**–**3pa** in synthetically useful yields and with high enantioselectivities.



Scheme 3. Scope of the ansa chain and the benzene ring substituents. Reaction conditions: **1** (0.1 mmol, 1.0 equiv.), **2a** (0.2 mmol, 2.0 equiv.), $Pd(OAc)_2$ (0.01 mmol, 0.1 equiv.), $_L$-*p*Glu-OH (0.02 mmol, 0.2 equiv.) and AgTFA (0.3 mmol, 3.0 equiv.) in ^{i}PrOH (2.0 mL) was stirred at 60 °C for 12 h under air. [a]**2a** (0.5 equiv.) was used, the reaction was performed for 8 h. Created in ChemDraw.

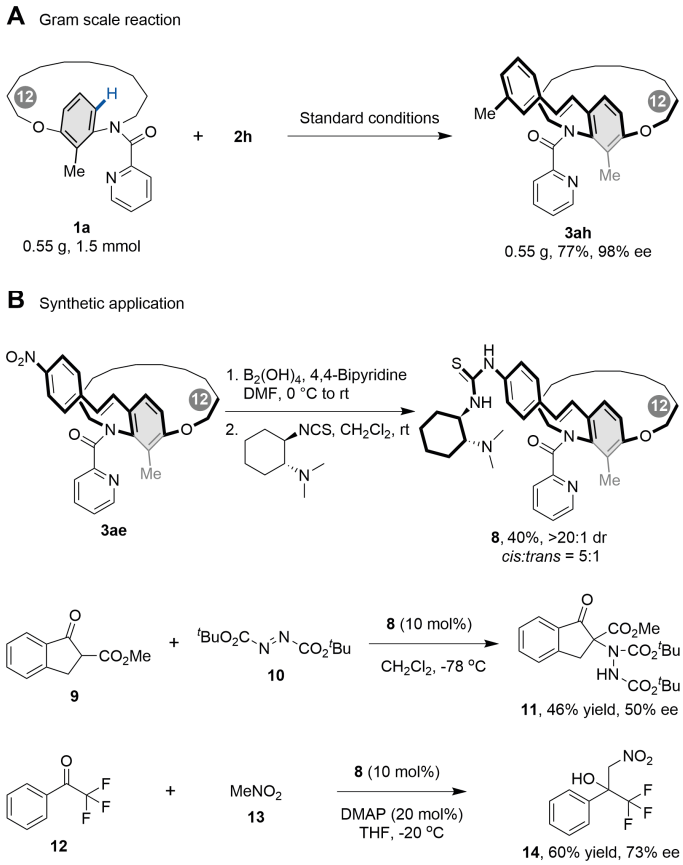
To further investigate the conformational stability of [*n*]metacyclophanes, racemization experiments were conducted on derivatives with varying ansa chain lengths (Scheme 4A). The results demonstrate that as the number of atoms in the ansa chain increased from 12 to 14 (**3aa**, **3ea** to **3fa**), the racemization energy barrier gradually rose. Additionally, the barriers for compounds **3ga**, **3ha**, and **3ia** were determined to be 125.18, 124.93, and 124.39 kJ·mol^{-1}, respectively. These observations contrast with the previously established trend[41,42,68], which suggested that increasing the length of the ansa chain reduces steric hindrance to aromatic ring rotation and thereby lowers conformational stability. Furthermore, the introduction of a picolinamide group onto the ansa chain enables concurrent rotation of the aromatic ring about both the ansa chain and the C–N axis. The overall conformational stability is governed by the combined steric hindrance arising from these two rotational modes.



Scheme 4. Investigation on the conformational stability. Created in ChemDraw.

We also performed reduction experiments to further confirm the auxiliary role of the picolinamide group in stabilizing the conformation of the metacyclophanes (Scheme 4B). Compounds **3aa**–**3da** were treated with lithium aluminium hydride ($LiAlH_4$) to afford products **4**–**7**. In the case of product **7**, derived from [12]metacyclophane, the removal of the C–N rotational hindrance meant that the 12-atom ansa chain alone could not effectively restrict rotation of the benzene ring. Consequently, enantioselective control was poor (5% ee). In contrast, when the ansa chain contained ⩽ 11 atoms, the chain itself was sufficiently short to restrict benzene-ring inversion without additional steric assistance. Thus, reduced products **4**–**6** exhibited almost no loss of enantiomeric excess, maintaining 80%–85% ee. These outcomes clearly demonstrate the auxiliary contribution of the picolinamide group around the C–N axis to conformational stability[41,42,69].

To further demonstrate the synthetic utility of this methodology, a gram-scale reaction of **1a** with **2h** was carried out (Scheme 5). The C–H olefination proceeded smoothly under the standard conditions, affording 0.55 g of metacyclophane **3ah** in 98% ee. Subsequently, compound **3ae** was transformed into a thiourea-based bifunctional catalyst. The resulting catalyst **8** was employed in the Michael addition of β-ketoester **9** to di-tert-butyl azodicarboxylate **10**, furnishing product **11** in 46% yield and 50% ee. Additionally, catalyst **8** proved effective in catalyzing the Henry reaction between trifluoromethyl acetophenone **12** and nitromethane **13**, affording the centrally chiral product **14** in 60% yield with 73% ee.



Scheme 5. Synthetic transformation and applications. Created in ChemDraw.

4. Conclusion

In summary, we have developed a Pd(II)-catalyzed enantioselective C–H olefination strategy for constructing [*n*]metacyclophanes. The protocol affords a range of metacyclophanes in high yields with excellent enantioselectivities. Studies on racemization indicate that the conformational stability of these macrocycles depends on the rotation of the aromatic ring along both the ansa chain and the C–N axis. The practicality of this approach is underscored by its scalability and the effective use of resulting products as catalysts in asymmetric transformations.

Supplementary materials

The supplementary material for this article is available at: Supplementary materials.

Declarations

Authors contribution

Tang Q, Zhao C: Conceptualization, writing-original draft, writing-review & editing, data curation, formal analysis.
Yan XE, Li J, Dong Z, Zhai H: Methodology, investigation, data curation, formal analysis.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data and materials could be obtained from the corresponding author upon request.

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