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## Pd/NHC sequentially catalyzed atroposelective synthesis of planar-chiral macrocycles<sup>†</sup>

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Planar-chiral macrocycles play a pivotal role in host-guest chemistry and drug discovery. However, compared with the synthesis of other types of chiral compounds, the asymmetric construction of planar-chiral macrocycles still remains a forbidding challenge. Herein, we report a sequential palladium and N-heterocyclic carbene catalysis to build planar-chiral macrocycles. This protocol features broad scope and good functional group tolerance, and allows a rapid assembling of planar-chiral macrocycles with excellent enantioselectivities.

Planar-chiral macrocycles, as a class of atropisomers, have been widely used in asymmetric synthesis,1 materials science,2 and host-guest chemistry,3 and are also widely present in natural products.<sup>4</sup> For instance, chrysophaentin A<sup>5</sup> inhibits the activity of methicillin-resistant Staphylococcus aureus (MRSA); cylindrocyclophane A6 inhibits the activity of KB and LoVo tumor cells; and FVIIIa<sup>7</sup> promotes coagulant activity (Fig. 1A); therefore, the asymmetric preparation of planar-chiral macrocyclic skeletons has attracted sustainable attention from chemists.8 However, the enantioselective synthesis of planar-chiral macrocycles seems to have encountered difficulties. The investigative results show that only a very limited number of methods have been used to prepare optically active planar-chiral macrocycles by far. These disclosed methods are mainly divided into four categories. (i) Intramolecular macrocyclisation:9 elegant studies involve the Ru-catalyzed C-S coupling9i and the phase transfer catalyst-catalyzed S<sub>N</sub>Ar macrocycloaddition<sup>9c</sup> reported by Cai, respectively. Recently, our group disclosed the NHC-catalyzed atroposelective macrocycloaddition for the synthesis of planar-chiral indoles/pyrroles;10 (ii) intramolecular arene formation:11 the Tanaka group disclosed an enantioselective intramolecular [2 + 2 + 2] cycloaddition for the construction of macrocycles via chiral Rh-catalysis;11a (iii) modification of rings:12 Shibata and co-workers reported an asymmetric Sonogashira coupling to carry out such ring modification.<sup>12a</sup> In 2022, the Yang group reported the chiral phosphoric acid-catalyzed enantioselective electrophilic aromatic amination to deliver such macrocycles;<sup>12d</sup> (iv) intermolecular ring closure: in this context, the investigations of intermolecular ring closure are much less studied. In 2020, Collins and co-

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workers<sup>13</sup> reported the only example of biocatalytic and enantioselective intermolecular macrocyclization of diacids and diols to deliver planar-chiral macrocycles. Although the above strategies have been widely utilized to assemble enantioenriched planar-chiral macrocycles, most of the methods require pre-assembly of chains in the substrate, which significantly

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(Note: example of planar chirality construction is absent)

C. Pd/NHC sequentially catalyzed atroposelective synthesis of planar-chiral macrocycles



Fig. 1 Background and our design. (A) Representative planar-chiral macrocycle-containing molecules. (B) Asymmetric sequential catalysis. (C) Our design.

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limits the diversity of planar-chiral macrocyclic products. Therefore, the development of a catalytic methodology that enables the modular assembly of structurally diverse enantioenriched macrocycles from simple starting materials is a demanding yet highly desirable objective.

Asymmetric sequential catalysis, as an intriguing and effective strategy to promote efficient chemical synthesis, has enabled assembling valuable chiral molecules with a complex structure from readily available starting materials in a one-pot multi-step fashion of reducing time, costs, and waste generation. Therefore, it has received extensive attention from chemists and significant progress has been made.<sup>14</sup> However, it is important to note that these reports have still focused on the construction of backbones with central chirality only. The enantioselective synthesis of planar chiral compounds *via* the strategy of sequential catalysis remains yet to be explored to date (Fig. 1B).<sup>15</sup>

N-Heterocyclic carbene (NHC) asymmetric catalysis, due to its unique advantages in the field of rapid construction of complex chiral scaffolds, has achieved significant developments in recent years.<sup>16</sup> However, the development of sequential catalysis involving the NHC catalyst is still in its infancy.<sup>17</sup> Meanwhile, our laboratory is highly interested in exploring NHC catalysis for the rapid assembling of atropisomeric molecules.<sup>18</sup> Very recently, we disclosed the first NHC-catalyzed intramolecular atroposelective macrocyclization for the assembly of planar-chiral indoles/pyrroles.<sup>10</sup> Herein, we present an unprecedented intermolecular reaction of aldehydes and vinyl ethylene carbonates *via* the Pd/NHC sequential catalysis, exhibiting a wide substrate scope and good functional group tolerance, which can rapidly deliver optically pure planar-chiral macrocycles (Fig. 1C).

We chose the 6-bromovanillin derivative (1a) and phenyl vinylethylene carbonate (2a) as the model substrates, and DQ as the oxidant. The results revealed that the optimal reaction conditions are a combination of toluene as the solvent, "Bu<sub>4</sub>-NOAc as the base,  $Pd(PPh_3)_4$  as the metal catalyst, DPPP (L1) as the ligand, and NHC C1 as the organocatalyst, which provided the planar-chiral macrocycle 3a in 72% yield and with excellent enantioselectivity (Table 1, entry 1, 96% ee). NHC catalyst screening showed that the triazolium derived carbene precursors C2, C5 and C6 afforded 3a in diminished yields and with very low enantioselectivities (entries 2, 4 and 5). In addition, the carbene precursors C3 and C4 were also found to be ineffective in the reaction (entry 4). When L2 or L3 replaced L1, the yield of 3a decreased and the absence of L1 led to a little loss in yield (entries 6-8). Notably, replacing <sup>n</sup>BuN<sub>4</sub>OAc with K<sub>2</sub>CO<sub>3</sub>, KOAc or Et<sub>3</sub>N resulted in a severe decrease in the yield of 3a (entries 9– 11). The results of reactions performed in THF or CH<sub>2</sub>Cl<sub>2</sub> were inferior compared to standard conditions (toluene as solvent) (entries 12 and 13). In the absence of 4 Å MS, 3a was still obtained with excellent enantioselectivity, but the yield was partially reduced (entry 14). Additionally, increasing the reaction concentration led to a decrease in the isolated yield of product 3a (entry 15).

With optimal conditions in hand, we turned our attention to examine the scope of this sequential catalytic reaction for the

Table 1 Optimization of the reaction conditions



Entry <sup>a</sup>	Variation of standard conditions	$\operatorname{Yield}^{b}(\%)$	ee <sup>c</sup> (%)
1	None	72	96
2	C2 instead of C1	65	30
3	C3 or C4 instead of C1	<5	_
4	C5 instead of C1	30	-16
5	C6 instead of C1	46	-22
6	L2 instead of L1	60	96
7	L3 instead of L1	65	96
8	Without of L1	68	96
9	K <sub>2</sub> CO <sub>3</sub> instead of <sup>n</sup> Bu <sub>4</sub> NOAc	28	94
10	KOAc instead of <sup>n</sup> Bu <sub>4</sub> NOAc	35	96
11	Et <sub>3</sub> N instead of <sup>n</sup> Bu <sub>4</sub> NOAc	30	92
12	THF instead of toluene	52	90
13	CH <sub>2</sub> Cl <sub>2</sub> instead of toluene	68	93
14	Without 4 Å MS	67	96
15	Toluene (0.1 M) was used	62	96

<sup>*a*</sup> Conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (2.5 mol%) and **L1** (3.0 mol%) in 1.0 mL of toluene were allowed to stir at room temperature for 2 h. The solution was then transferred into a mixture of pre-NHC catalyst **C1** (20 mol%), <sup>*n*</sup>Bu<sub>4</sub>NOAc (50 mol%), DQ (0.12 mmol) and 4 Å MS 50 mg in toluene (4.0 mL). The reaction mixture was allowed to stir at room temperature for another 12 h under Ar. <sup>*b*</sup> Isolated yield after flash column chromatography. <sup>*c*</sup> Determined by HPLC analysis using a chiral stationary phase.

synthesis of functional planar-chiral macrocycles. The vinyl ethylene carbonates (VECs) **2** were examined first (Fig. 2). A range of VECs bearing various substituted aryl groups have proved to be suitable substrates, affording the corresponding products **3a-3o** at 95–98% ee. In addition, heteroaryl-substituted VECs also well participated and generated the planar-chiral macrocycles **3p** and **3q** in good yields and with excellent enantioselectivities (Fig. 2, 70% and 71% yield; 98% and 96% ee, respectively). The absolute configuration of product **3q** was determined by X-ray single crystal analysis (CCDC: 2347510), and other structures were assigned by analogy. Pleasingly, varied alkyl-substituted VECs were also tolerated and delivered the corresponding planar-chiral macrocycles **3r-3t** over longer reaction times with excellent enantioselectivities, albeit with a slightly decrease in yield.

Encouraged by the success in the variation of VECs, we then focused on the scope of aryl aldehyde **1**. As shown in Fig. 3, a range of aryl aldehyde substrates bearing either an electron-



**Fig. 2** Scope of vinyl ethylene carbonate **2**. <sup>a</sup>Reaction conditions: see Table 1, entry 1. <sup>b</sup>12 h for the first step, 12 h for the second step. <sup>c</sup>24 h for the first step, 12 h for the second step.48 h. <sup>d</sup>36 h for the first step, 12 h for the second step.

withdrawing group or electron-donating group at the 4-position generated their corresponding products smoothly with excellent enantioselectivities (90–>99% ee). In addition, when the bromine at the 2-position of aryl aldehyde became small chlorine, the corresponding planar-chiral products were still obtained and with excellent enantioselectivities (**4f**, 97% ee and **4g**, 96% ee,



Fig. 3 Scope of aryl aldehyde 1. <sup>a</sup>Reaction conditions: see Table 1, entry 1.

respectively). Furthermore, the 2-phenyl-substituted substrate generated the desired planar-chiral macrocycle **4h** in 74% yield and with >99% ee under optimal conditions. Pleasingly, varied five-membered aromatic heterocycle substituted substrates were also tolerated and delivered the corresponding planar-chiral macrocycles with high to excellent enantioselectivities (**4i–4k**).

Subsequently, the modification of the *O*-substituted amide chain was conducted. Amide chains containing ester or ether groups were well tolerated under optimal conditions and provided their corresponding planar-chiral products with high enantioselectivities (Fig. 3, 4l and 4m). Next, the effect of length of the chain was also investigated. When the length of the amide chain was reduced, the yield of the corresponding planar-chiral macrocycle decreased dramatically (4n, n = 13). At the same time, substrates with extended chains were also tested and found to produce the desired product (4o, n = 15) in good yield and with excellent enantioselectivity. Notably, a further increase in amide chain length led to a loss of planar chirality (4p, n = 16), which clearly indicated that planar chirality is highly dependent on the size of the ring on the macrocycle.

(cc)



Fig. 4 Determination of the racemization barrier. (A) Effect of temperature on the stability of macrocyclic planar chirality. (B) Plot for calculating the racemization barrier of **4o**. (C) Racemization barriers of **3a**, **4n** and **4o**.

To get insight into the thermal stability of the macrocyclic planar-chirality, a series of racemization experiments were performed.<sup>19</sup> As shown in Fig. 4, planar-chiral macrocycle **3a** or **4n** was stirred at 140 °C in toluene under sealed conditions for 2 h and no racemization was observed (see ESI,† S43). For compound **4o**, the ee value was maintained below 60 °C, indicating that the rotation of the *ansa* chain was restricted (Fig. 4A). On the other hand, the configuration stability studies revealed that the rotation barrier of **4o** is 31.1 kcal mol<sup>-1</sup>, and the  $t_{1/2}$  of racemization is 19.3 h at 100 °C (Note: At 25 °C, the  $t_{1/2}$  of racemization is calculated to be 33.5 years) (Fig. 4B and C).

Before illustrating the utility of this method, a gram-scale synthesis of **3a** was conducted under optimal conditions, producing the desired product with promising yield and enantioselectivity (Fig. 5A). Next, two follow-up transformations of **3a** were carried out individually. The phenylethynyl-substituted planar chiral macrocycle **5** was prepared smoothly *via* a onestep Sonogashira coupling of **3a** (Fig. 5B). Importantly, the multiple stereogenic enantioenriched compound **6**, featuring both central and macrocyclic planar chirality, was obtained efficiently by epoxidation of **3a** in the presence of *meta*-chloroperbenzoic acid (*m*-CPBA) (Fig. 5C).

To understand the pathway, we performed the reaction in a stepwise manner, expecting to obtain key intermediates to further elucidate the mechanism (Fig. 6, see ESI,† S52). The alkyl alcohol chain linked aryl aldehyde 3a' (confirmed by NMR) was obtained from 1a and 2a under the conditions of Pd(PPh<sub>3</sub>)<sub>4</sub> (2.5 mol%) and DPPP (3 mol%). Following the addition of C1 (20 mol%), DQ (1.2 equiv.) and <sup>*n*</sup>BuN<sub>4</sub>OAc (50 mol%), the desired product 3a was achieved in 69% yield with 96% ee. Similar results were compared between the stepwise reaction and the one-pot reaction (Table 1), suggesting that the reaction process most likely occurred *via* a sequential catalytic process.

In summary, we have developed a Pd/NHC sequential catalytic intermolecular atroposelective macrocyclization for the preparation of various planar-chiral macrocycles with high to



**Fig. 5** Gram-synthesis and synthetic transformations. (A) Gram-scale synthesis. (B) Sonogashira coupling. (C) Epoxidation reaction.



Fig. 6 Mechanistic studies: (a)  $Pd(PPh_3)_4$  (2.5 mol%) and L1 (3 mol%) in toluene (1.0 mL), 2 h. (b) C1 (20 mol%), DQ (1.2 equiv.) and <sup>*n*</sup>BuN<sub>4</sub>OAc in toluene (4.0 mL), room temperature for 12 h.

excellent enantioselectivities under mild conditions. This protocol shows a broad scope and functional group tolerance. Multiple stereogenic macrocycles featuring both central and planar chirality have proven the synthetic utility of the present study. Control experiments reveal that these transformations possibly occurred *via* a Pd/NHC sequential catalytic process.

#### Data availability

All data supporting the findings of this study are available within the article and its ESI file.†

#### Author contributions

G. M. Y. conducted main experiments; S. D. L., S. J. J. and X. S. W. prepared several starting materials, including substrates. J. W. conceptualized and directed the project, and drafted the manuscript with the assistance from co-authors. All authors contributed to discussions.

## Conflicts of interest

There are no conflicts to declare.

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