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Report

Atroposelective, Macrocyclization, Asymmetric Synthesis, Axial Chirality, Palladium Catalysis, Bisbibenzylis, Natural Product

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Palladium-Catalzyed Atroposelective 16-Membered Macrocyclization: Total Synthesis of Isoplagiochin D

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Summary of main observation and conclusion Isoplagiochin D is a ring-strained macrocyclic bisbibenzylis, which showed stable axial chirality in one biaryl structure, and semistable axial chirality in the other biaryl moiety. We reported here an unprecedented example for the catalytically asymmetric synthesis of ring-strained atropisomers via Pd-catalyzed macrocyclization between benzyl halides and carbenes. This newly developed Pd-catalyzed asymmetric macrocyclization protocol enabled us a quick synthesis of isoplagiochin D in a highly enantioselective manner.

Background and Originality Content

Biaryl natural products bearing strong strain bridged-rings usually showed atropisomerism, whose rotation around the aryl-aryl single bond was inhibited. Many representatives of these natural products, such haouamine A and vancomycin, exhibit remarkable bioactivities. The macrocyclic bisbibenzylis isoplagiochin C (**1a**) and isoplagiochin D (**1b**) were isolated from the liverwort Plagiochila fruticosa in 1996 by Asakawa and co-workers (Figure 1).[1] The chlorinated analogue bazzanin J (**2**),[2] diaryl ether riccardin C (**3**)[3,4] have been isolated by Asakawa *et al.* It was found the existence of chirality in isoplagiochin C (**1a**) and isoplagiochin D (**1b**) by the analysis of CD spectra and optical rotation.[2,5-7] The 16-membered macrocycle bearing two linear biaryls displayed potential axial chirality of biaryl systems: bond ***a*** in isoplagiochin D displayed stable axial chirality while bond ***b*** bearing less hindered two *ortho*-hydroxy substituents was semistable. Becker, Speicher and Bringmann *et al.* discussed the atropisomerism and ring strain for these compounds, and determined the energy of racemization of isoplagiochin C to be 101.6 kJ/mol, approximately.[7] Markedly, the optical rotation of natural isoplagiochins C and D varied from the plant source and the isolation protocol.[1,3] These compounds also exhibit anti-MRSA,[8,9] antitumoural, antibacterial and antimycotic activities.[10,11] The interesting twisted structure, along with the remarkable biological activities attracted considerable attentions from synthetic and bio-chemists.[12-16]

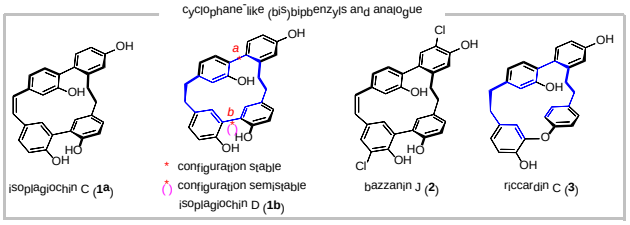
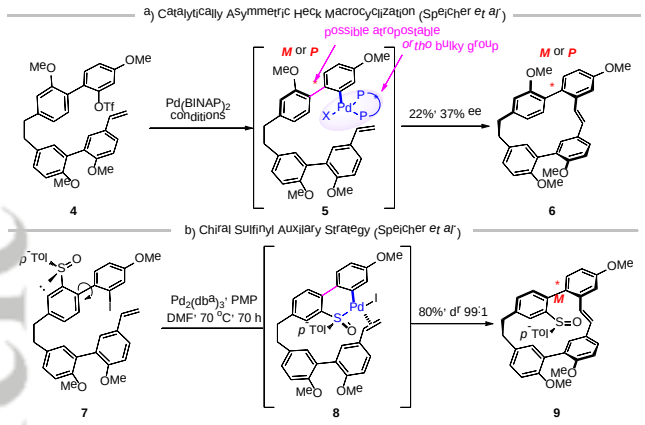


Figure 1 Structure of Isoplagiochins and Analogues

Scheme 1 Approaches for Asymmetric Synthesis of Isoplagiochins

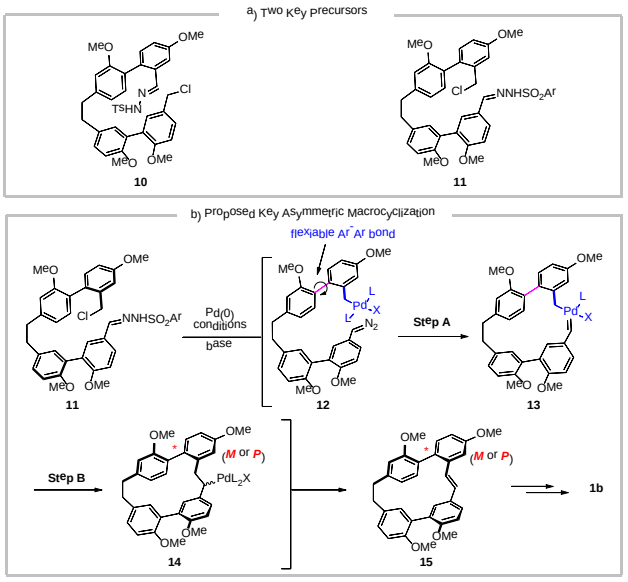


The asymmetric synthesis of atropo-active natural products have caught significant attentions.[17-22] The catalytically asymmetric macrocyclization for atropisomers construction is challenging,[23,24] and diastereo-controlled approach was the general strategy.[25,26] The syntheses of the cyclophane-like bis(bipbenzyls) were almost in racemic form,[27-29] until in 2012 Speicher and co-workers started the first trial for catalytically asymmetric synthesis of Isoplagiochins D (Scheme 1a). In this study, they controlled the axial chirality of Isoplagiochin D via a palladium-catalysed Heck macrocyclization.[30] It was proposed that the oxidative addition of $Pd^{(0)}(BINAP)_2$ with **4** possibly afforded an atropostable arylpalladium species due to the large size of *ortho* Pd group. It might account for the low enantioselectivity (37% ee), where the Ar-Ar bond bearing *ortho* Pd group cannot undergo dynamical isomerization freely to adopt proper conformation during the macrocyclization; furthermore, to avoid possible "ligand-free" background reactions, complex [Pd(*M*)-BINAP]$_2$ had to be prepared independently before use. Six years later, the same group developed an elegant chiral sulfinyl group induced diastereoselective Heck macrocyclization of iodide **7** (Scheme 1b).[31-34] Pleasingly, high yield (80%) and high diastereoselectivity (de 98%) have been achieved, although the modification of sulfinyl group to hydroxyl group required a very careful three-step manipulation with 34% overall yield at as low as 0 °C.

Results and Discussion

In continuation our research interests in transition-metal-catalyzed atropisomer synthesis[35-38] and with the inspiration of Speicher's work,[30-32] herein we report a catalytically asymmetric macrocyclization of benzyl chlorides and *N*-Ts hydrazones. Due to the high ring-strain, the atroposelective ring closure was obviously considered as the most challenging step. It was reasoned that the benzylic palladium species (**12**) (one-carbon extension in comparison with arylpalladium **5**), was atropo-unstable at ambient temperature, which could adopt proper configuration to achieve high enantioselectivity during the macrocyclization (Scheme 2). Thus, the Pd-catalyzed styrenes synthesis between benzyl chloride and arylhydrazones became an ideal reaction for our strategy.[39-51] The key cyclic palladium complex **13** would give **14** via migration and insertion. The β-elimination of **14** afforded the key intermediate **15**. The axial chirality determining-step may either be the carbene coordination **Step A** or ring contraction **Step B**. Alternatively, the benzylic chloride and aldehyde hydrazone moieties can be switched, such as compound **10** *vs* **11**.

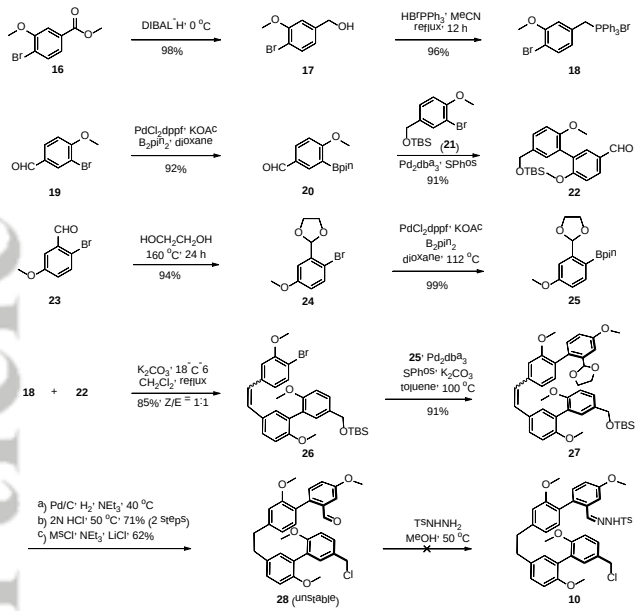
Scheme 2 Synthetic Plan for Asymmetric Macrocyclization



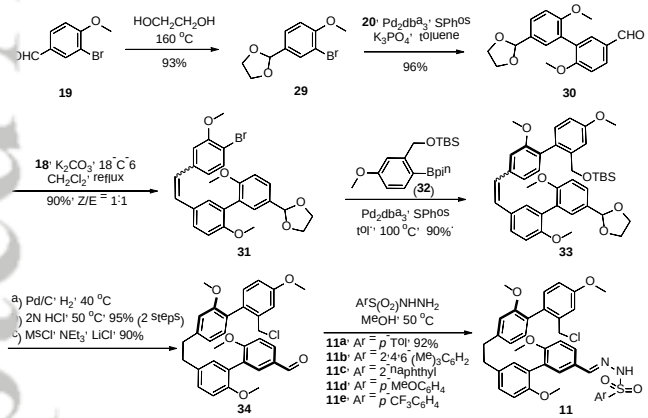
We started our studies by the synthesis of cyclization precursor **10** (Scheme 3). The reduction of ester **16** with DIBAL-H gave alcohol **17**, which was transferred to Wittig reagent **18** with Ph_3PHBr. The palladium-catalyzed borylation of **19** gave **20**, which would furnish the biaryl **22** via the cross-coupling with the bromide **21**. The Wittig olefination of **22** with **18** provided a pair of Z/E isomers **26** in 85% overall yield. The subsequent palladium-catalyzed Suzuki coupling with **25** furnished **27** in excellent yield. Three-step manipulation, hydrogenation, hydrolysis and chlorination gave benzyl chloride **28**. Unfortunately, the electron-donating property of the *para*-methoxy group made this benzyl chloride **10** unstable, which was quickly decomposed in the next step.

Subsequently, hydrazone **11**, whose methoxy group is at the *meta*-position of benzyl chloride, was going to be prepared (Scheme 4). The aldehyde **19** was treated with ethylene glycol to give ketal **29**, which successfully delivered **30** via palladium-catalyzed cross-coupling with **20**. The olefination of **30** with **18** furnished **31** in 90% yield (Z/E ~ 1:1), which was further transferred to **35** via Suzuki-coupling with boronic ester **32**. The same three-step manipulation provided **34** in 81% overall yield. Compound **34** was stable enough and readily condensed with hydrazines bearing different steric and electronic properties in good yields.

Scheme 3 Synthesis of Precursor **10**

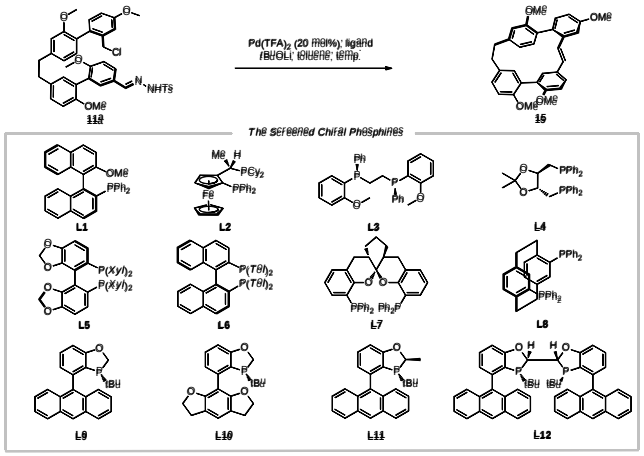


Scheme 4 Synthesis of Precursor **11**



With the hydrazone **11a** in hand, we tried to study the asymmetric macrocyclization (Table 1). Primary screening found that $Pd(TFA)_2$ was the optimal pre-catalyst. The monodentate ligand MOP gave 6% yield with 7% ee, while bidentate ligands **L2** and **L3** only produced trace amount of desired product (entries 1-3). DIOP (**L4**) gave an increased yield of **15**, while the enantioselectivity was still low (entry 4). The reactions by using axially chiral phosphine **L5** or **L6**, or the Ding's Ph-SKP (**L7**) as the ligand did not achieve better results (entries 5-7).[52] The planar chiral biphosphine **L8** dramatically improved the efficacy of this macrocyclization (43% yield), however, the enantioselectivity was still dissatisfied (entry 8). Pleasingly, the chirality at P-center ligand **L9**, developed by Tang and co-workers showed significantly improved enantioselectivity (entry 9).[53] Thus, the corresponding analogous have been investigated. It was found that 9-anthracenyl group was critical for the stereoselectivity, and the bidentate ligand WingPhos (**L12**) displayed best performance, and the reaction afforded the cyclization product in excellent ee value (entries 10-12).[54,55] The reaction conducted at 70 °C gave **15** in 93% ee, while further decreasing the temperature to 60 °C resulted in the rate of this reaction becoming very sluggish (entries 13-14). It was found that the yield of this reaction was very sensitive to moisture. Finally, the combination of Li*O*t*Bu* and LiOH (1:2) gave reliable yield while maintained high enantioselectivity (entry 15). Increasing the loading of $Pd(TFA)_2$ only slightly improved the yield (entry 16). Furthermore, the reaction with a stoichiometric amount of palladium catalyst gave only a trace amount of product. In all these reactions, the hydrolysis of hydrazone to aldehyde, as well as the dimerization of carbene intermediate to C=C bond are the main byproducts.

Table 1 Optimization of Reaction Conditions[a]



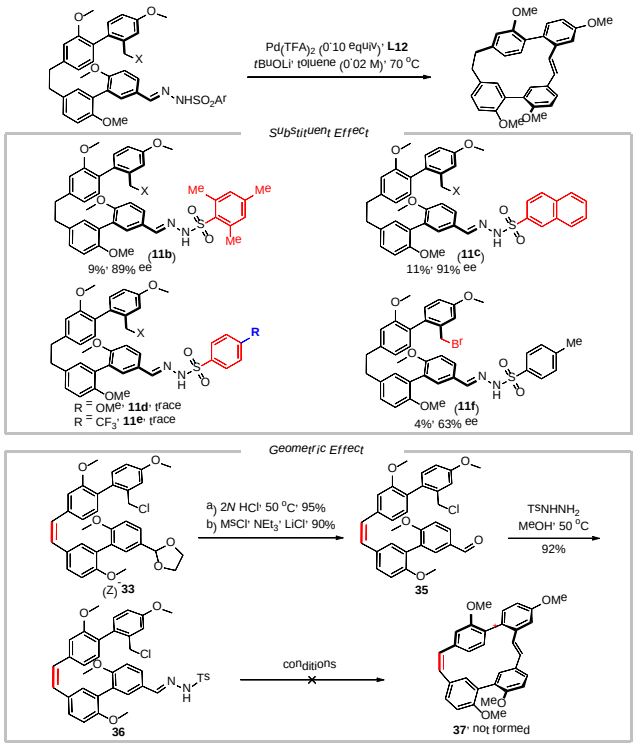
entry	Ligand	CONC. (mol/L)	T/°C	Yield of **15** (%)	ee of **15** (%)
1	**L1**	0.01	80	6	7
2	**L2**	0.01	80	trace	-
3	**L3**	0.01	80	trace	-
4	**L4**	0.01	80	27	<2
5	**L5**	0.01	80	7	<2
6	**L6**	0.01	80	11	20
7	**L7**	0.01	80	19	<2
8	**L8**	0.01	80	43	5
9[b]	**L9**	0.02	80	18	61
10[b]	**L10**	0.02	80	5	10
11[b]	**L11**	0.02	80	9	10
12[b]	**L12**	0.02	80	13	85
13[b]	**L12**	0.02	70	11	92
14[b]	**L12**	0.02	60	-	-
15[c]	**L12**	0.02	70	18	93
16[c,d]	**L12**	0.02	70	22	93

[a] Reaction Conditions: **11a** (0.04 mmol) *t*BuOLi (3.0 equiv), $Pd(TFA)_2$ (20 mol%), ligand (24 mol%) in toluene at indicated temperature. [b] 10 mol% of $Pd(TFA)_2$ was used. [c] *t*BuOLi (1.5 equiv) and LiOH (3.0 equiv) was used. [d] 30 mol% $Pd(TFA)_2$ was used. After **15** being converted to **1b**, the absolute configuration of the product was assigned as *S* by comparison of the optical rotation of the natural product.

Additionally, the substituent effect of arylsulfonyl moiety was studied (Scheme 5). The 2,4,6-trimethylphenyl derivative **11b** gave a slight decreased yield and enantioselectivity. The β-naphthyl analogue **11c** spontaneously degraded to diazo compound partially, and mixture of **11c** and diazo showed almost same efficacy as **11a**. Unfortunately, strong electron-donating (**11d**) or electron-withdrawing group (**11e**) at arylsulfonyl moiety was deleterious for this palladium-catalyzed cyclization. The benzyl bromide **11f** only produced 6% of yield of the macrocycle possible due to its less stability than the benzyl chloride analogue **11a**.

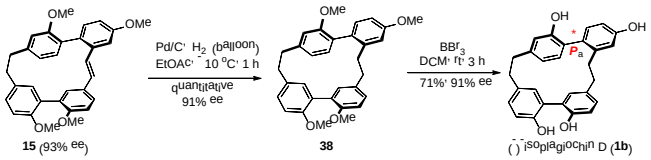
Finally, an alkene derivative **36** was prepared from (*Z*)-**33** in the same manner as above (Figure 6). We anticipated that the fixed geometry of *Z*-isomer would improve the cyclization yield. Disappointedly, the reaction of **36** did not produce any desired product under the standard conditions.

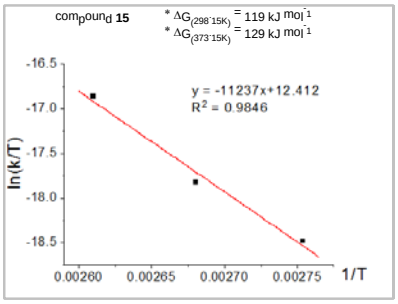
Scheme 5 Other Effects for Macrocyclization



With **15** in hand, two-step manipulation smoothly furnished the synthesis of isoplagiochin D (**1b**) in 71% overall yield (Scheme 6). Notably, partial racemization was observed during Pd/C-catalyzed hydrogenation of **15** to **38**. No racemization was observed by independent submitting compound **38** to standard hydrogenation conditions at room temperature. Thus, it is necessary to perform the hydrogenation reaction at -10 °C to minimize the racemization (93% ee to 91% ee). The rotational barrier [$G_{(373.15K)}^{\ddagger}$] of compound **15** was determined to be 129 kJ/mol by analysing the racemization rate at 90, 100, 110 °C, respectively. The calculated rotational barrier at 298.15 K was 119 kJ/mol, approximately. These data indicated that compound **15** is more stable than isoplagiochin C.

Scheme 6 The Synthesis of Isoplagiochins D





Conclusions

We reported a palladium-catalyzed highly enantioselective macrocyclization for the preparation of bisbibenzylis isoplagiochin D. It represented the first example for palladium-catalyzed enantioselective macrocyclization of benzyl halides and carbenes. In this Pd-catalyzed strain ring construction, WingPhos displayed unique stereo-induction activity. It showcased a new way for catalytically asymmetric construction of macrocycle, which might be applicable for other strained natural product synthesis.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement (optional)

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Entry for the Table of Contents

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Palladium-Catalzyed Atroposelective 16-Membered Macrocyclization: Total Synthesis of Isoplagiochin D

Junwei Xi, and Zhenhua Gu*

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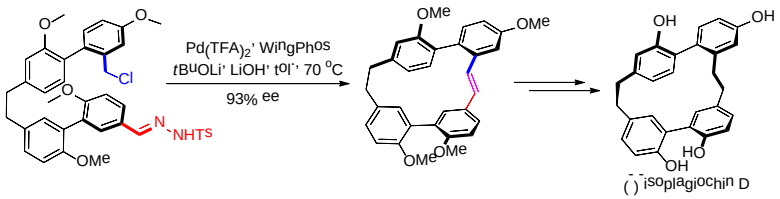

A catalytically asymmetric macrocyclization via palladium-catalyzed intramolecular coupling between benzyl chloride and arylhydrazone was reported. This method enabled the asymmetric total synthesis of bisbibenzylis isoplagiochin D.

