

Atroposelective Heck Macrocyclization: Enantioselective Synthesis of Bis(bibenzyl) Natural Products

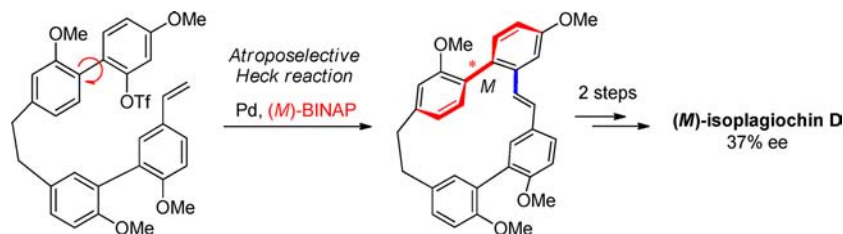
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ABSTRACT



The Heck protocol was applied for the first time to the atroposelective synthesis of macrocyclic natural products. As ring closure to bis(bibenzylyls) of the isoplagiochin type leads to a configurationally stable biaryl axis in the molecule, cyclization could be conducted atroposelectively in the presence of a chiral BINAP ligand.

“Bis(bibenzylyls)” are phenolic natural products that can be isolated with broad diversity from bryophytes.¹ Regarding the biosynthesis, they originate from bibenzyl units.² The distribution in liverworts, their structure elucidation, and their numerous biological activities are reviewed.^{3,4} A twofold C–C connection of two bibenzyl units leads to a subtype represented by isoplagiochin D (**1**)⁵ with two biaryl axes *A/B* (Figure 1).

The occurrence of axial and/or planar chirality in the series of these macrocyclic bis(bibenzylyls) was discussed

earlier^{6,7} and for the unique structure of cavicularin.⁸ The existence of configurationally stable atropisomers as a consequence of axial chirality (two biaryl axes and one helical element) and ring strain for **1** was first discussed in detail by us⁹ and especially for its dehydro analogue isoplagiochin C (**2**), for which the absolute configuration at the stereochemically stable biaryl axis *A* was determined by quantum chemical CD calculations for the natural compound from *Plagiochila deflexa*¹⁰ (Figure 2).

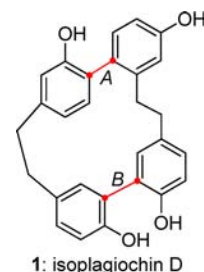


Figure 1. Biogenetical origin of bis(bibenzylyls).

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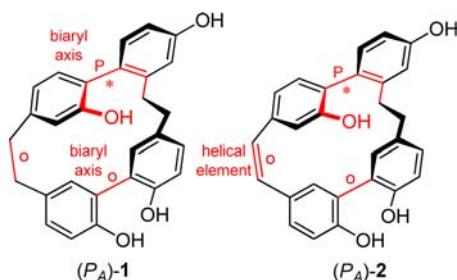


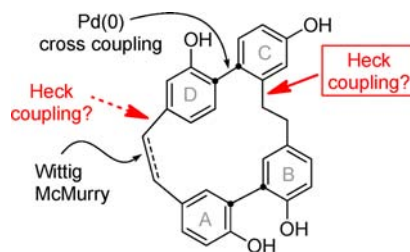
Figure 2. Absolute configuration of (–)-isoplagiochin D (**1**) and (–)-isoplagiochin C (**2**); * = configurationally stable, ° = configurationally unstable (the most stable diastereomer is shown).

Many members of the bis(biphenyl) family have been synthesized; the routes and strategies have been reviewed very recently.¹¹ Ring closure proved to be the main challenge because efficiency, not surprisingly, depends on ring strain, substitution pattern, and concomitant dimerization. In the total syntheses yet described for isoplagiochins C (**2**) and D (**1**) or derivatives, ring closure was realized by (a) Wittig reaction,¹² (b) McMurry reaction,¹³ both between ring moieties A and D, and (c) Suzuki–Miyaura coupling¹⁴ between C and D (Scheme 1).

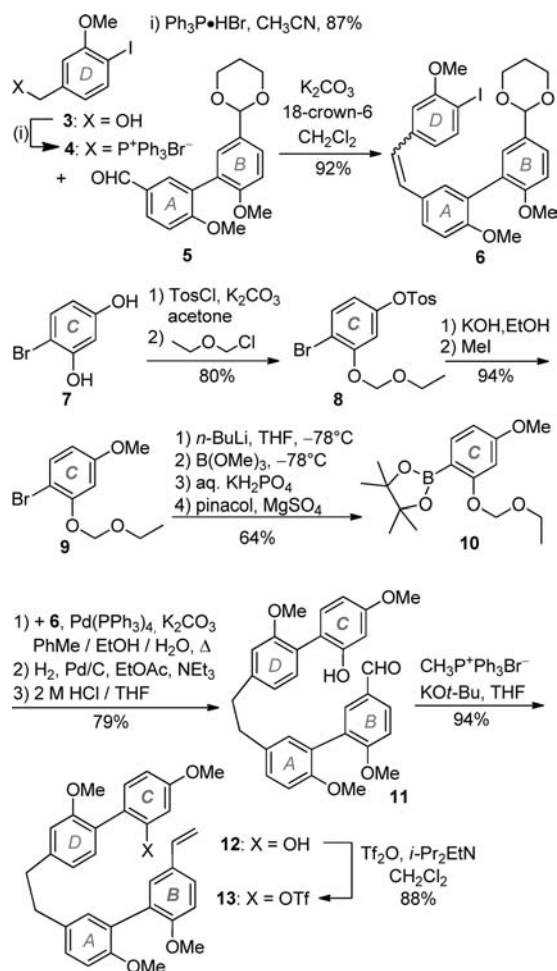
We were now focused on alternative methods enabling enantioselective routes to the isoplagiochin framework. We had to consider that the biaryl axis between rings C and D is configurationally stable only in the macrocyclic context, so that general methods for the atroposelective synthesis of axially chiral biaryls¹⁵ could not be simply adopted. The atropo-divergent step rather had to include or follow the ring closure. The catalytic enantioselective Suzuki coupling is yet not a generally approved method due to the harsh required reaction conditions.^{14,16} Also, Wittig and McMurry procedures lack enantioselective protocols.

For the first time in the field of macrocyclic bis(biphenyls) we attempted the Heck methodology¹⁷ for synthesis. Intramolecular variants have been broadly used in natural

Scheme 1. Ring Closing Methods in the Syntheses of the Iso-plagiochin C/D Framework



Scheme 2. Synthesis of Precursor **13** for a Heck Coupling



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product syntheses;¹⁸ asymmetric intramolecular variants using BINAP and DIOP ligands were developed by Shibasaki¹⁹ and Overman,²⁰ but only for the construction of chiral carbon centers, not for axially chiral compounds.

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Table 1. Cyclization of **13** by Heck Reaction

| entry | Pd(OAc) ₂ [equiv]/ligand [equiv] | solvent ^a | base [equiv] ^a | time/temp | yield ^{b,c} | ee (%) ^d |
|---|---|----------------------|--------------------------------------|-------------|----------------------|---------------------|
| 1 | [0.1]/PPh ₃ [0.2] | toluene | K ₂ CO ₃ [5.0] | 18 h/120 °C | – | – |
| 2 | [0.4]/PPh ₃ [0.8] | toluene | K ₂ CO ₃ [5.0] | 18 h/120 °C | 6 | – |
| 3 | [0.1]/PPh ₃ [0.2] | DMA | K ₂ CO ₃ [5.0] | 18 h/120 °C | 13 | – |
| 4 | [0.1]/PPh ₃ [0.2] | DMF | K ₂ CO ₃ [5.0] | 18 h/120 °C | 16 | – |
| 5 | [0.4]/ <i>M</i> -BINAP [0.8] | DMF | K ₂ CO ₃ [5.0] | 18 h/120 °C | 12 | <i>rac</i> |
| 6 | [0.3]/ <i>M</i> -BINAP [0.6] | DMF | K ₂ CO ₃ [5.0] | 18 h/85 °C | – | – |
| 7 | [0.3]/ <i>M</i> -BINAP [0.6] | DMF | PMP [6.0] | 18 h/85 °C | 18 | 21 for <i>M</i> |
| 8 | [0.4]/ <i>M</i> -BINAP [0.8] | DMF | PMP [6.0] | 18 h/60 °C | 25 | 27 for <i>M</i> |
| 9 | [0.3]/ <i>M</i> -BINAP [0.6] | DMF | PMP [6.0] | 72 h/45 °C | trace | 34 for <i>M</i> |
| 10 | [0.3]/ <i>P</i> -BINAP [0.5] | DMF | PMP [6.0] | 18 h/60 °C | 20 | 31 for <i>P</i> |
| Pd(<i>M</i> -BINAP) ₂ [equiv] | | | | | | |
| 11 | 0.2 | DMF | PMP [5.0] | 18 h/70 °C | 22 | 37 for <i>M</i> |
| 12 | 0.2 | DMF | PMP [5.0] | 72 h/50 °C | trace | n.d. |
| 13 | 0.1 | DMF | PMP [5.0] | 18 h/70 °C | – | – |

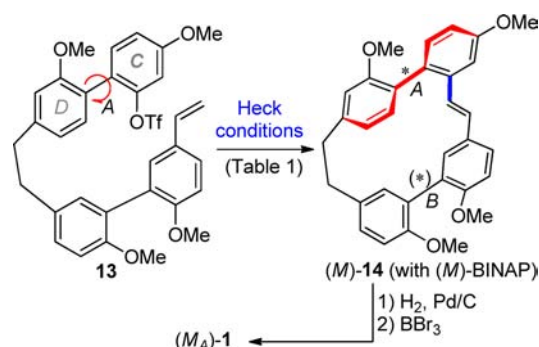
^aDMA = dimethyl acetamide; PMP = pentamethyl piperidine. ^bConversion monitored by TLC (SiO₂, CH₂Cl₂/*n*-hexane 1:1). ^cYield of **14** after chromatographical purification. ^dEE-value determined for **1** by HPLC on Chiralcel-OD-H, *i*-PrOH/*n*-hexane 65:35 (1.0 mL/min, 275 nm); (*M*)-**1** is eluated before (*P*)-**1**.⁹

In principle, the Heck reaction could be used for the formation of a stilbene bridge between the aromatic rings **A** and **D** as well as **B** and **C** (Scheme 1). The latter route seemed to be more promising because (a) the reaction center is, with respect to the enantioselective approach, closer to the (still flexible) biaryl axis and (b) preliminary modeling studies on the geometry of the isoplagiochin framework²¹ clearly demonstrated that between rings **A** and **D**, besides a saturated ethylene bridge, only a *cis* double bond geometry is tolerable. This could be incompatible with palladacyclic intermediates (vide infra). By contrast, for the double bond between rings **B** and **C**, *cis*- and *trans*-geometries are acceptable.

The precursor **13** for a Heck-type cyclization was synthesized according to Scheme 2 starting from the benzyl alcohol **3**²¹ and the known¹² monoprotected dialdehyde **5**.

First, the nonenantioselective cyclization of the triflate **13** to the racemic dehydro isoplagiochin D tetramethylether (**14**) using an intramolecular Heck protocol was attempted using Pd(OAc)₂/PPh₃. The best, although still moderate, results were obtained in DMF and K₂CO₃ as a base (Table 1, entries 1–4).

Replacing the PPh₃ by (*M*)- or (*P*)-BINAP could give rise to an atropo-enantioselective Heck reaction as the ring closing step with dynamic kinetic resolution (DKR) (Scheme 3): The biaryl axis **A** is flexible enough in the precursor **13**, but not in the macrocyclic biaryl **14** at moderate temperatures. Not surprisingly, at 120 °C only a racemic product was observed (Table 1, entry 5). Reducing the reaction temperature gave conversion and moderate yields only by switching the base to the (less nucleophilic²²) pentamethyl piperidine (PMP) and, for the

Scheme 3. Synthesis of the Isoplagiochin Framework via Heck Coupling

first time for this type of reaction, resulted in an atropo-enantioselective (21% ee) Heck cyclization (entries 6,7). Due to additional conformational effects²¹ at the second (only partially flexible) biaryl axis **B** in **14**, the stereochemical analyses were performed for the natural compound **1**.⁹

Increasing the catalyst loading from 0.3 to 0.4 equiv slightly increased the yield and ee value (entry 8), but no acceptable conversion was observed at temperatures lower than 60 °C (entries 9 and 12). Replacing (*M*)-BINAP by (*P*)-BINAP evidenced the atroposelective effect of the ligand, now leading to the (*P*)-enantiomer of **14** (and **1**) (entry 10).

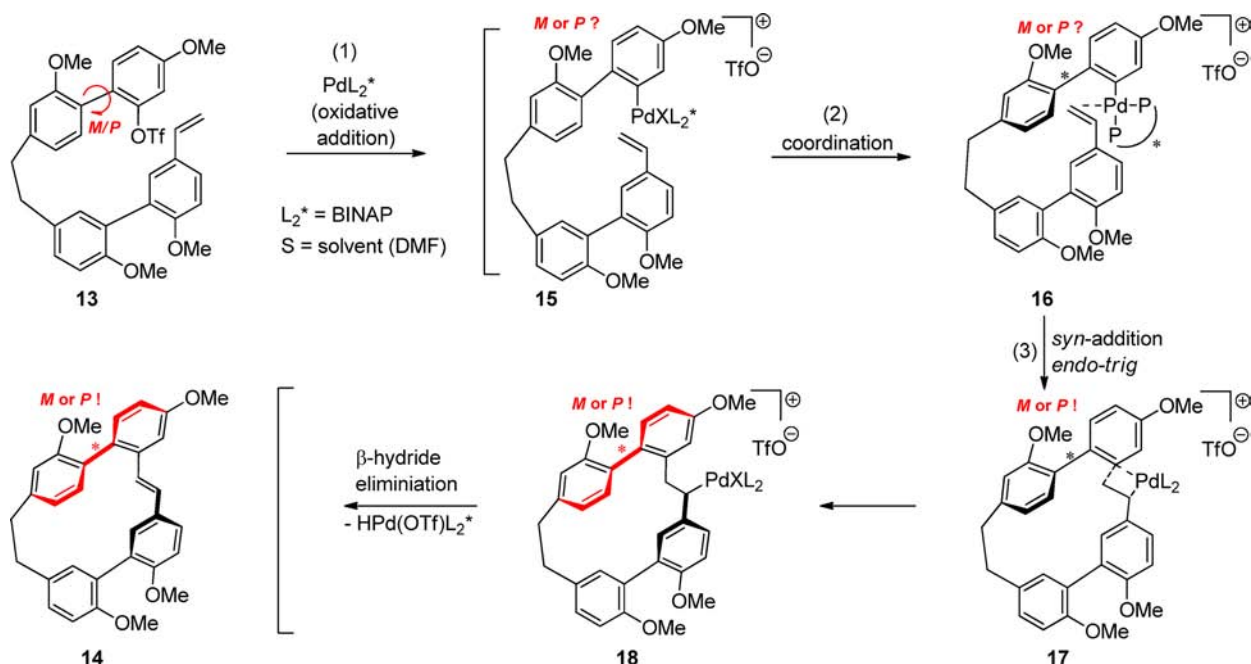
To reduce a possible “ligand-free” background reaction, the preprepared Pd(*M*-BINAP)₂ complex²³ was used directly giving the best results even with 0.2 equiv at 70 °C (entry 11). Further reducing the reaction temperature

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Scheme 4. Possible Mechanism for the Heck Coupling with Atropo-Differentiation



(entry 12) or the catalyst amount (entry 13) did not allow the reaction to proceed.

The product **14** of cyclization was always isolated with an (*E*)-configuration at the double bond, meaning an (*E*)-selective Heck reaction or Pd-induced isomerization. The mechanism of the Heck cyclization may follow a cationic route (no coordinating triflate anion) involving a *syn-endo-trig* addition via a palladacyclic intermediate **15**.²⁴ The mode of the asymmetric induction using BINAP still remains to be further investigated. In principle, we suggest three modes of atropo-differentiation with dynamic kinetic equilibration/resolution: (1) atropo-selective oxidative addition assuming that intermediate **15** could be configurationally stable due to the large Pd *ortho* substituent, (2)

atropo-diastereoselective coordination to the double bond (**15** \rightarrow **16**), or (3) atropo-selective *syn*-addition (**16** \rightarrow **17**) (Scheme 4).

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds; details of HPLC on a chiral phase. This material is available free of charge via the Internet at <http://pubs.acs.org>

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The authors declare no competing financial interest.