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## Asymmetric synthesis of dibenzo[*b,d*]azepines by Cu-catalyzed reductive or borylative cyclization†

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A copper-catalyzed asymmetric intramolecular reductive cyclization for the synthesis of dibenzo[*b,d*]azepines is described. Use of 2'-vinyl-biaryl-2-imines as substrates and *in situ* formed [Cu<sup>I</sup>]/(Ph-BPE)] as the catalyst enables the synthesis of 7-membered bridged biaryl amines containing both central and axial stereogenic elements in high yields (up to 98%) and with excellent diastereo- and enantioselectivities (>20 : 1 d.r., up to 99% ee). Moreover, the same catalyst was found to facilitate a related borylative cyclization to afford versatile boronic ester derivatives. Both reactions proceed under mild conditions (rt) and are applicable to a variety of substituted aromatic and heterocyclic derivatives.

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### Introduction

The asymmetric synthesis of biaryl atropisomers has evolved into a stimulating research field in organic synthesis owing to the ubiquitous occurrence of this structural motif in a variety of natural products and bioactive substances, and for their wide-ranging utilities in catalyst design and material science.<sup>1</sup> Most of these compounds comprise conformers with restricted rotation around a single bond whose configurational stability is generally determined by the number and size of the substituents at the *ortho* positions relative to the stereogenic axis. A less common class of biaryl atropisomers consist of those where the biaryl unit is incorporated into a cyclic system, with the typical *ortho*, *ortho'* substituents being replaced by a bridge (Fig. 1).<sup>2</sup>

In these systems, the configurational stability directly correlates with the ring size: in 5- and 6-membered rings the rotation around the stereogenic axis is usually not hindered, but 7-membered bridged biaryls exhibit a higher configurational stability owing to conformational reasons and can be often resolved as atropisomers. Additionally, the introduction of sp<sup>2</sup> hybridized atoms increases the rigidity in the bridging cycle, and therefore the configurational stability,<sup>3</sup> while the presence of stereogenic centers in the bridge is known to impose a specific configuration on the biaryl axis by a central to axial

chirality relay event.<sup>4</sup> Notably, these properties have been recently exploited for the construction of a unidirectional rotary molecular motor based on the formation of biaryl structures featuring a seven-membered lactone bridge.<sup>5</sup>

The most distinctive class of bridged biaryls presenting this relay phenomenon comprises chiral dibenzoazepines. These 7-membered cyclic bridged biaryl amines and related analogues have received considerable attention due to their presence in several natural substances and drugs. Selected examples shown in Fig. 2 include erythrivaine B (A), a dimeric Erythrina alkaloid isolated from *E. variegata*,<sup>6</sup> dipeptide LY-411575 (B) which has demonstrated effectivity as  $\gamma$ -secretase inhibitor for the treatment of melanoma and Alzheimer's disease,<sup>7</sup> RO4929097 (C), another potent and selective  $\gamma$ -secretase which targets Notch signaling in tumor cells,<sup>8</sup> indolobenzazepinone D, a tubulin polymerization inhibitor exhibiting antiproliferative activities in a variety of cancer cell lines,<sup>9</sup> and paullones E, a family of cytotoxic compounds which efficiently inhibit cyclin-dependent kinases (CDKs).<sup>10</sup>

The asymmetric synthesis of axially chiral 7-membered bridged biaryl amines has traditionally relied on chiral

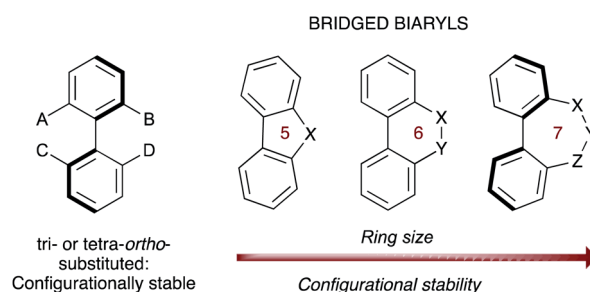


Fig. 1 Configurational stability of acyclic and bridged biaryls.

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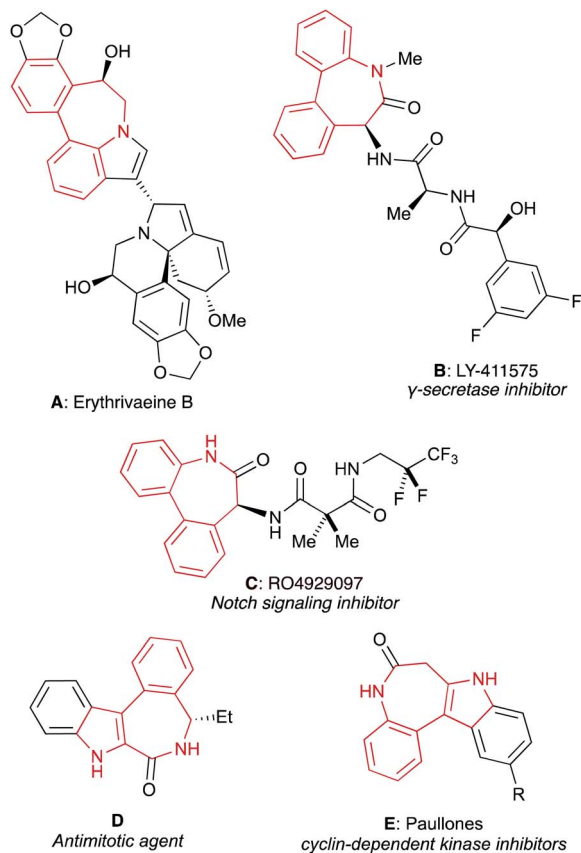


Fig. 2 Selected bioactive dibenzoazepines and related analogues.

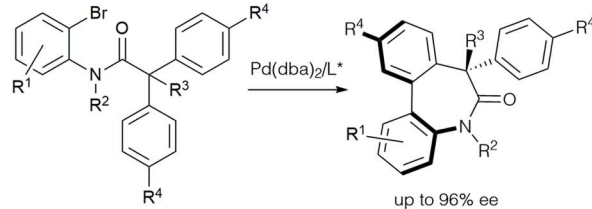
auxiliaries or starting materials from the chiral pool, generally requiring multistep procedures.<sup>3,11</sup> The control of both central and axial chirality elements in the most interesting dibenzo[*b,d*]azepine derivatives constitutes a challenge: to date, only a handful of methods have been described for their catalytic asymmetric synthesis (Scheme 1).

Axially chiral dibenzoazepinones with amide bridges have been prepared by desymmetrization *via* Pd-catalyzed C–H arylation<sup>12</sup> (Scheme 1A) and, very recently, by a cyclo-carbopalladation-carbonylation cascade reaction using alcohols or anilines as nucleophiles<sup>13</sup> (Scheme 1B). To our knowledge, the tautomerization of metastable enamines promoted by a chiral phosphoric acid catalyst appears as the only catalytic method reported to obtain axially chiral dibenzo[*b,d*]azepines (Scheme 1C).<sup>14,15</sup> Hence, the development of a modular and straightforward catalytic enantioselective method, providing access to these structural motifs remains as a desirable goal.

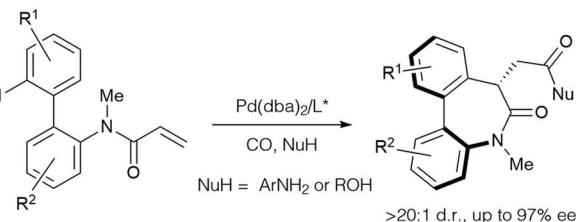
## Results and discussion

Inspired by the work of Buchwald<sup>16</sup> and Yun<sup>17</sup> on Cu-catalyzed cyclizations using aldimines as electrophiles, we envisioned that Schiff bases from *ortho*-vinyl, *ortho'*-amino biaryls could also be suitable substrates to perform reductive or borylative cyclizations for the construction of axially chiral dibenzo[*b,d*]

### A: Intramolecular C–H Arylation (ref. 12)



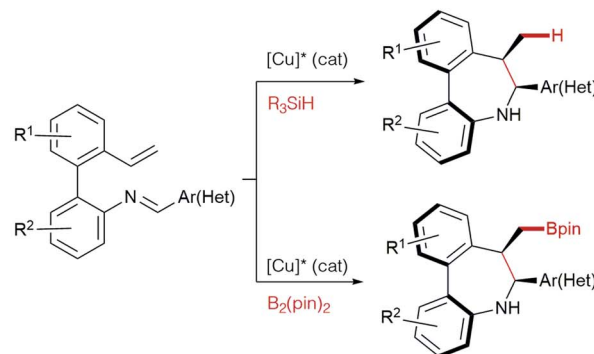
### B: Enantioselective Carbopalladation/Carbonylation (ref. 13)



### C: Catalytic Enantioselective tautomerization (ref. 14)



### D: Catalytic reductive cyclization and borylative cyclization (This work)

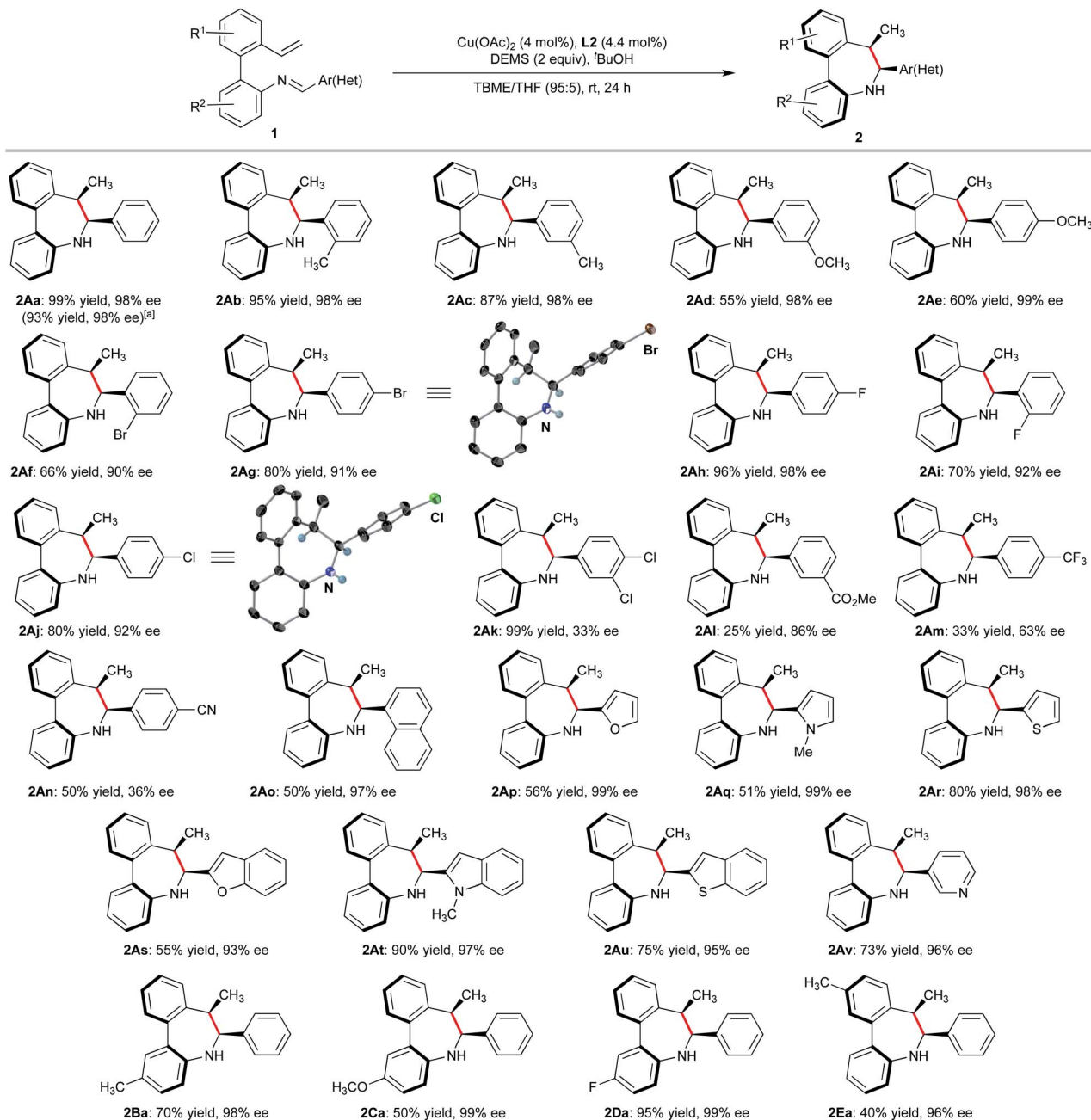


Scheme 1 Catalytic asymmetric synthesis of axially chiral 7-membered cyclic bridged biaryl amines.

azepine derivatives featuring a stereogenic axis and two contiguous stereogenic centers (Scheme 1D).

Preliminary studies were performed with compound **1Aa**, readily obtained by condensation of 2'-vinyl-biphenyl-2-amine with benzaldehyde, as a model substrate (Table 1). Using Cu(OAc)<sub>2</sub> as the precatalyst, methyldiethoxysilane (DEMS) as the hydride source and anhydrous TBME : THF (95 : 5) mixture as the solvent at room temperature, representatives of commercially available chiral biphosphine ligands **L1–L6** were tested for the synthesis of the desired azepine **2Aa**. Poor reactivities were observed with BINAP **L1**, SEGPHOS **L2**, DUPHOS **L3** or the JOSIPHOS representative **L4** (entries 1–4), while moderate catalytic activity and enantioselectivity were observed with MeO-





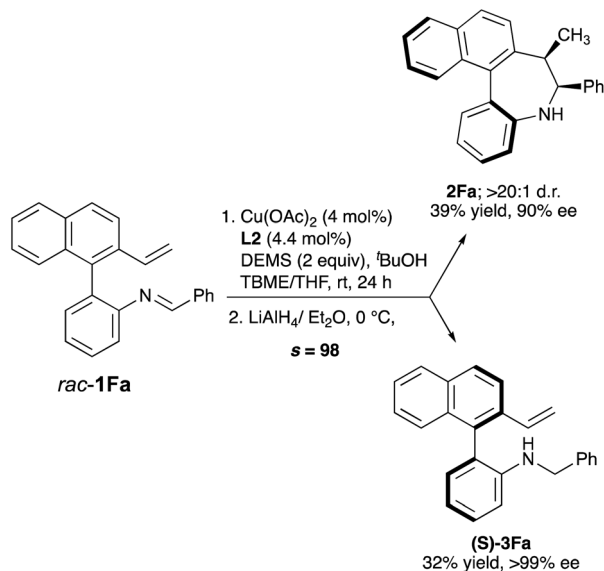
**Scheme 2** Substrate scope. Reactions performed on 0.2 mmol scale for a 36 h period at rt. Yields of isolated product after chromatography. A single diastereomer was observed by  $^1\text{H}$  NMR in the crude reaction mixtures. Ee's were determined by HPLC on chiral stationary phases. <sup>a</sup>Reaction performed on 2 mmol (566 mg) scale.

SEGPPOS L5 (entry 5). Finally, (*R,R*)-Ph-BPE L6 proved to be the ligand of choice, affording optimal results in terms of reactivity, diastereo- and enantioselectivity (99% yield, >20 : 1 d.r., 99% ee, entry 6).

With the optimized conditions established, we examined the substrate scope of the 2'-vinyl-biphenyl-2-imine precursors to explore the generality of this asymmetric reductive cyclization. Substrates with electron-rich methyl and methoxy substituents on the aldimine aryl ring were transformed into the corresponding dibenzoazepines **2Ab–e** in high yields and excellent

enantioselectivities. The steric effect of placing substituents on the *ortho* position of the ring has a negligible effect on reactivity and enantioselectivity as demonstrated for the synthesis of **2Ab**, **2Af** and **2Ai**. Electron-deficient substituents on the phenyl ring of the aldimine were also tolerated. Thus, fluorinated substrates furnished the corresponding dibenzoazepines **2Ah** and **2Ai** with excellent selectivities. However, the enantioselectivity drops when a  $\text{CF}_3$  group is located at the para position of the phenyl ring (**2Am**). Importantly, products bearing halide (**2Af**, **2Ag**, **2Aj** and **2Ak**), ester (**2Al**) and nitrile (**2An**) functionalities were also





**Scheme 3** Kinetic resolution of *rac*-**1Fa**. Reaction performed on 0.2 mmol scale for a 36 h period at rt. Yields of isolated product after chromatography. Ee's were determined by HPLC on chiral stationary phases.

obtained in good to high yields (66–99%) and moderate to high enantioselectivities (up to 92%), providing synthetically useful functionalities for further transformations. Moreover, the method also tolerates a variety of heterocyclic substrates, leading to furan (**2Ap**), *N*-methyl pyrrole (**2Aq**), thiophene (**2Ar**), pyridine (**2Av**) and fused heterocyclic derivatives (benzofuran **2As**, *N*-methylindole **2At** and thianaphthene **2Au**) in good yields and excellent enantioselectivities. The *S*<sub>a</sub>,6*S*,7*R* absolute configuration of products **2Ag**, and **2Aj** was determined by X-ray diffraction analysis,<sup>18</sup> while that of other products **2** was assigned by analogy. Moreover, the central to axial chirality relay phenomenon was confirmed by a dihedral angle of 39° between the two aryl groups in both compounds. It should be noted that the *cis*-diastereomers were exclusively formed in all cases. Biaryls decorated with several electron-donating or withdrawing groups (*e.g.* Me, OMe, or F) were also suitable substrates for this transformation, affording the desired products in moderate to good yields with high enantioselectivities (**2Ba–2Ea**, 94–99% ee).

We next explored the kinetic resolution (KR) of a trisubstituted, hence configurationally stable, biaryl-imine **1Fa** via Cu-catalyzed hydrocupration/cyclization followed by reduction of the unreacted, enantioenriched imine (Scheme 3). The reaction stopped at 50% conversion, despite the presence of a large excess (2 equiv.) of silane. In this way, dibenzoazepine **2Fa** could be obtained in high enantioselectivity under the previously optimized conditions, while the enantioenriched starting material was transformed into amine (*S*)-**3Fa**, obtained in nearly enantiopure form (>99% ee) after LiAlH<sub>4</sub> reduction (*s* = 98). The biaryl-2-amine **3Fa**, featuring only axial chirality, shows an appealing structure with potential applications in asymmetric catalysis. Reasoning that substrates **1** should form very similar organocopper intermediates after insertion of the vinyl group

**Table 1** Screening of ligands and optimization of the reaction

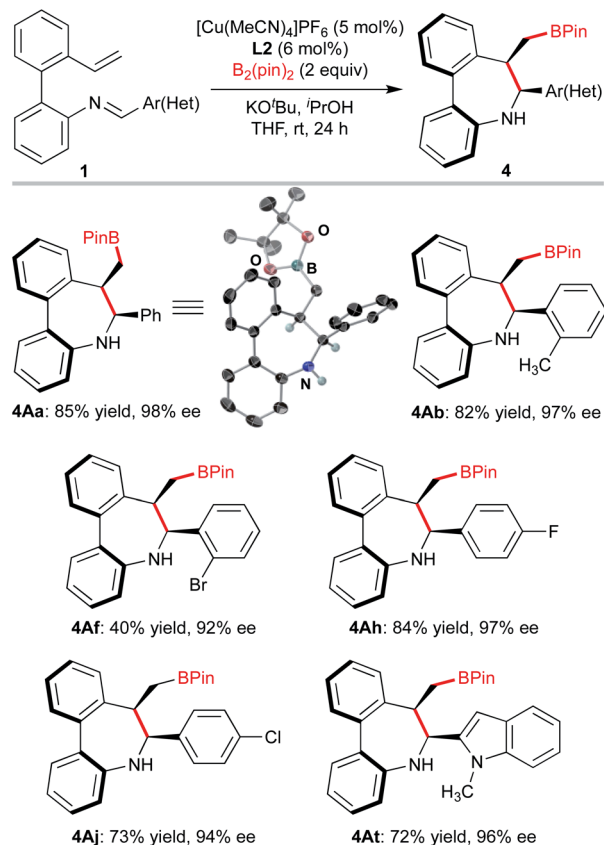
Entry <sup>a</sup>	Ligand	Conv. <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>L1</b> , ( <i>S</i> )-BINAP	<5	nd
2	<b>L2</b> , ( <i>R</i> )-DTBM-SEGPHOS	<10	nd
3	<b>L3</b> , ( <i>S,S</i> )-Me-DUPHOS	<20	nd
4	<b>L4</b> , ( <i>R</i> )-( <i>S</i> )-JOSIPHOS	<20	nd
5	<b>L5</b> , ( <i>R</i> )-MeO-BIPHEP	42	77
6 <sup>d</sup>	<b>L6</b> , ( <i>R,R</i> )-Ph-BPE	99 (99 yield)	99

<sup>a</sup> Reactions performed on 0.2 mmol scale. <sup>b</sup> Estimated by <sup>1</sup>H-NMR spectroscopy. <sup>c</sup> Determined by HPLC on chiral stationary phases. <sup>d</sup> A single diastereomer was observed by <sup>1</sup>H NMR in the crude reaction mixture.

into L\*Cu–Bpin catalysts, we decided to explore also the Cu-catalyzed enantioselective borylative cyclization of the same substrates **1** as an alternative approach to axially chiral dibenzo [*b,d*]azepines, in this case decorated with a boryl group that should be useful for further derivatization or bioconjugation (Scheme 4). Using again **1A** as a model substrate in the reaction with bis(pinacolato)diboron [B<sub>2</sub>(pin)<sub>2</sub>], the catalyst formed by combination of [Cu(MeCN)<sub>4</sub>]PF<sub>6</sub> with biphosphine **L2**, KO<sup>t</sup>Bu as the base, iPrOH as the proton source and anhydrous THF as the solvent were identified as the best conditions, leading to the borylated axially chiral dibenzoazepine (*S*<sub>a</sub>,6*S*,7*R*)-**4Aa** in 85% yield with excellent regio-, diastereo- and enantioselectivity (>20 : 1 d.r. 98% ee). Single crystal X-ray analysis of this compound<sup>18</sup> confirmed the assigned absolute configuration. Borylative cyclization of other 2'-vinyl-biphenyl-2-imines proceeded efficiently under the same conditions to afford products **4** with excellent enantiocontrol (>20 : 1 d.r., 92–98% ee). Again, electron-rich and -deficient substituents as well as *ortho*-substitution in the phenyl ring were tolerated. The reaction also accepts heteroarenes as illustrated for compound **4At**.

To explore the synthetic potential of the methodology, gram-scale synthesis and derivatizations were performed. Asymmetric intramolecular reductive cyclization of **1Aa** on a 2 mmol scale afforded the desired product **2Aa** in 93% yield and 98% ee (Scheme 2). As shown in Scheme 5, demethylation of **2Ae**

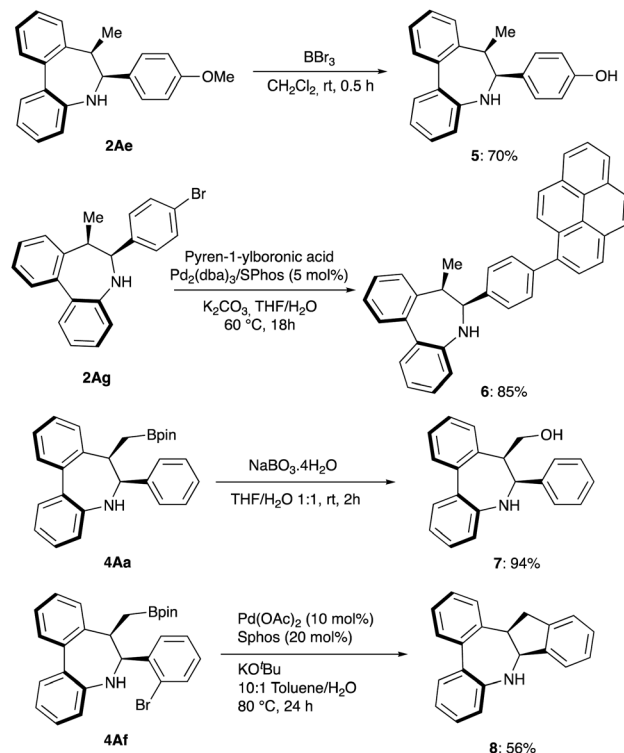




**Scheme 4** Copper-catalyzed borylative cyclization. Reactions performed on 0.2 mmol scale. Yields of isolated product after chromatography. A single diastereomer (>20 : 1 d.r.) was observed as determined by  $^1\text{H}$  NMR in the crude reaction mixtures. Ee's were determined by HPLC analysis.

offered the corresponding phenol product **5** which can be used as synthetic handle for further transformations. Moreover, fluorescent labelling of **2Ag** was accomplished *via* Suzuki–Miyaura coupling providing pyrene substituted compound **6** with emitting properties for their potential use in biological studies.<sup>19</sup> On the other hand, oxidation of **4Ah** with sodium perborate led to chiral primary alcohol **7** in high yield while intramolecular Suzuki coupling of **4Af** affords *cis*-tetrahydroindenoindozepine **8** in 56% yield.

To assess the configurational stability of the biaryl axis of products **2**, we calculated the rotation about the axis of the biphenyl moiety for compound **2Aa**. The dibenzoazepine ring can adopt boat **a** and half-chair **b** conformations (Scheme 6).<sup>20</sup> A third conformation can be located but at a considerable higher energy.<sup>21</sup> The most stable conformation for **2Aa** was found to be **C1a**, matching the X-ray structures of analogs **2ag**, **2Aj** and **4Aa**. Remarkably, no interconversion between **C1a** and **C2a** conformations is possible due to steric reasons. Thus, axial epimerization by biphenyl bond rotation requires a previous change from **a** to **b** conformations. The interconversion of the  $S_a$ -**C1a**/ $S_a$ -**C1b** and  $R_a$ -**C2a**/ $R_a$ -**C2b** conformers have free energy barriers of 15.6 and 14.0 kcal mol<sup>-1</sup>, respectively and the difference between free energy of conformers accounts for the preferred **C1a** and **C2b** conformations in each case. The interconversion

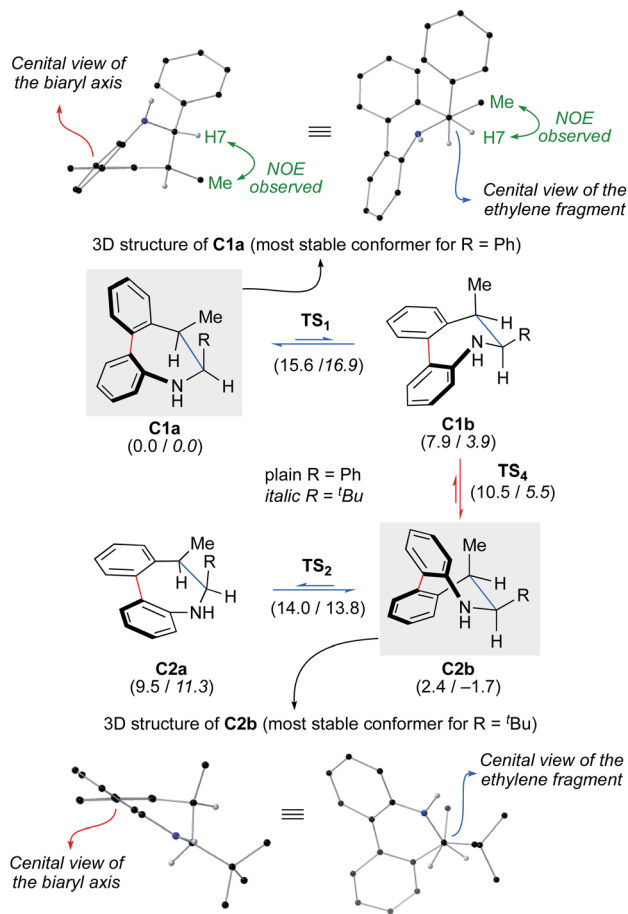


**Scheme 5** Derivatization reactions.

between  $S_a$ -**C1b**/ $R_a$ -**C2b** conformations involving epimerization has free energy barriers of only 2, 6 and 8.1 kcal mol<sup>-1</sup>. Those values clearly show that a fast equilibrium is established at 25 °C (a barrier of 15.6 kcal mol<sup>-1</sup> corresponds, approximately, to a kinetic constant of 22.4 s<sup>-1</sup> with  $t_{1/2}$  of 0.031) and, consequently, the observed population of conformers depends on their relative stability. The calculated relative energies for the most stable  $S_a$ -**C1a**/ $R_a$ -**C2b** conformers correspond to a 2.4 kcal difference, corresponding to a 98 : 2 ratio. Considering these values and the assumed DFT experimental error it is possible to conclude that, essentially, only  $S_a$ -**C1a** will be observed. Low temperature  $^1\text{H}$ -NMR experiments provided further support to this conclusion: a single set of peaks is observed at temperatures as low as -60 °C.

On the light of these calculations, we speculated on the possibility of freezing or shifting the conformational equilibrium by introducing a bulkier <sup>t</sup>Bu group instead of the Ph group. Interestingly, the calculation predicts that  $R_a$ -**C2b** is the lowest energy conformation in this case (1.7 lower than  $S_a$ -**C1a**). This result can be rationalized by the lower impact of the steric effects in the  $S_a$ -**C1a** conformer as a result of the two gauche interactions of the R group, while there is only one in  $R_a$ -**C2b**. In order to check whether a shift of the axial chirality could be indeed experimentally achieved, pivalaldehyde derivative **1Aw** was prepared and subjected to the reductive cyclization protocol to achieve product **2Aw** in 85% yield and 97% ee (Scheme 7). The  $R_a,6S,7R$  configuration is in this case tentatively assigned on the basis of the above calculations and the absence of a NOE observed between H-7 and the Me group, clearly observed for **2Aa** (R = Ph) due to their relative gauche disposition (supported

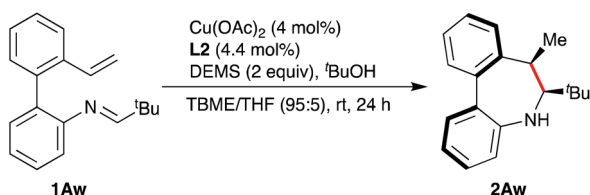




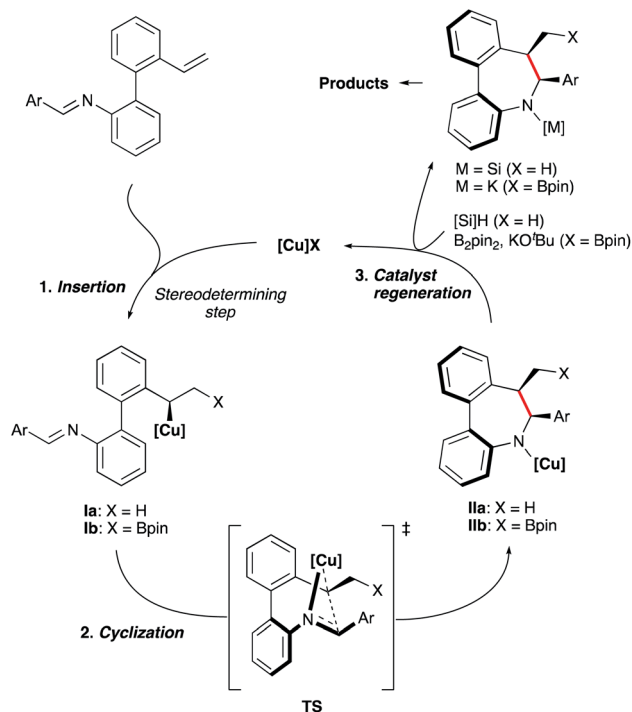
Scheme 6 Computational analysis for the axial epimerization for dibenzoazepines **2A** (wb97xd/def2tzvp//wb97xd/def2svp/cpcm = diisopropylether). Relative free energies are given in brackets in kcal mol<sup>-1</sup>. Data for R = Ph in plain text, data for R = <sup>t</sup>Bu in italics. For details see the ESI.†

by the computational analysis of non-covalent interactions, NCI; see ESI†). As in the precedent case, a single set of signals is visible in the <sup>1</sup>H-NMR spectrum upon cooling to -60 °C, indicating the absence of any significant amounts of minor conformers.

Based on previous mechanistic studies by Buchwald<sup>22</sup> and Hartwig<sup>23</sup> laboratories, we assume that the hydrocupration of substrates **1**, generating intermediate **Ia** (Scheme 8) is the stereodetermining step. Ensuing *cis*-selective cyclization to afford complex **IIa** should then proceed *via* a well-organized transition state TS with the assistance provided by



Scheme 7 Synthesis of *tert*-butyl-substituted dibenzoazepine **2Aw**.



Scheme 8 Catalytic cycle and stereochemical model.

coordination of the imine nitrogen. Then, the resulting intermediate **IIa** reacts with the silane reagent to regenerate the CuH catalyst. A similar model and catalytic cycle can be also proposed for the borylative cyclization (X = Bpin).

## Conclusions

We have successfully developed a straightforward approach for the enantioselective synthesis of dibenzo[*b,d*]azepines featuring central and axial chirality elements by means of Cu-catalyzed asymmetric intramolecular reductive or borylative cyclizations. Both reactions proceed with good yields and excellent diastereo- and enantioselectivities under mild conditions. Axially chiral biaryl-2-amines could also be obtained in nearly perfect enantioselectivity through a kinetic resolution process. Computational work indicates that the axial chirality is thermodynamically controlled, and that the sense of the axial chirality depends on the nature of the imine R group.

## Data availability

All experimental and computational data associated with this study can be found in the article or in the ESI.†

## Author contributions

R. F., J. M. L. and V. H. conceived and supervised the study. P. R.-S., R. M. C. and V. R. performed the experiments and analyzed the data. V. H. and J. M. L. wrote the manuscript. P. M. performed the computational studies.



## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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