Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2021, **12**, 15291

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 8th September 2021
Accepted 8th November 2021

DOI: 10.1039/d1sc04980a

rsc.li/chemical-science

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

Patricia Rodríguez-Salamanca, [a] Rocío Martín-de la Calle,[a] Verónica Rodríguez,[b] Pedro Merino, [c] Rosario Fernández, *[b] José M. Lassaletta *[a] and Valentín Hornillos *[ab]

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^{I}/(Ph-BPE)] as the catalyst enables the synthesis of 7-membered bridged biarylamines 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.

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.[1] 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).[2]

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^2 hybridized atoms increases the rigidity in the bridging cycle, and therefore the configurational stability,[3] 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.[4] 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.[5]

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 erythrivaeine B (**A**), a dimeric Erythrina alkaloid isolated from E. variegate,[6] dipeptide LY-411575 (**B**) which has demonstrated effectivity as γ-secretase inhibitor for the treatment of melanoma and Alzheimer's disease,[7] RO4929097 (**C**), another potent and selective γ-secretase which targets Notch signaling in tumor cells,[8] indolobenzoazepinone **D**, a tubulin polymerization inhibitor exhibiting antiproliferative activities in a variety of cancer cell lines,[9] and paullones **E**, a family of cytotoxic compounds which efficiently inhibit cyclin-dependent kinases (CDKs).[10]

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

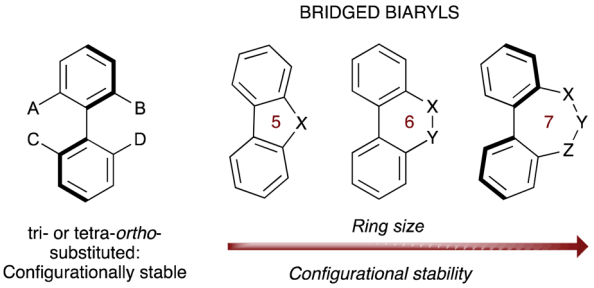


Fig. 1 Configurational stability of acyclic and bridged biaryls.

[a]*Instituto Investigaciones Químicas (CSIC-US), C/Américo Vespucio, 49, 41092 Sevilla, Spain. E-mail: jmlassa@iiq.csic.es*

[b]*Departamento de Química Orgánica, Universidad de Sevilla, C/Prof. García González, 1, 41012 Sevilla, Spain*

[c]*Instituto de Biocomputación y Física de Sistemas Complejos (BIFI), Universidad de Zaragoza, 50009 Zaragoza, Spain*

† Electronic supplementary information (ESI) available: Experimental protocols, characterization data. CCDC 2095490–2095492. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc04980a

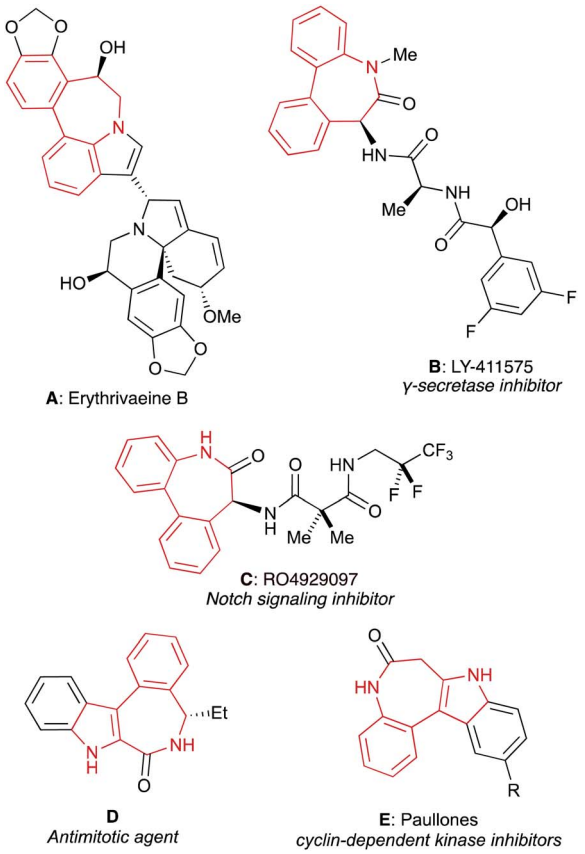


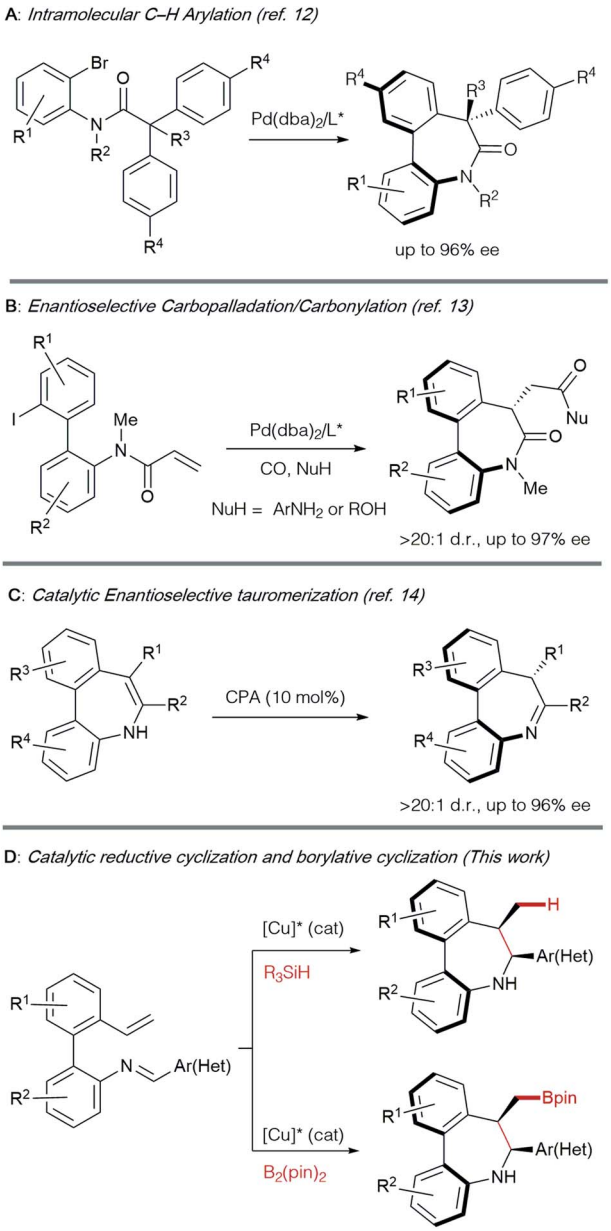
Fig. 2 Selected bioactive dibenzoazepines and related analogues.

auxiliaries or starting materials from the chiral pool, generally requiring multistep procedures.[3,11] 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[12] (Scheme 1A) and, very recently, by a cyclocarbopalladation-carbonylation cascade reaction using alcohols or anilines as nucleophiles[13] (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).[14,15] 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

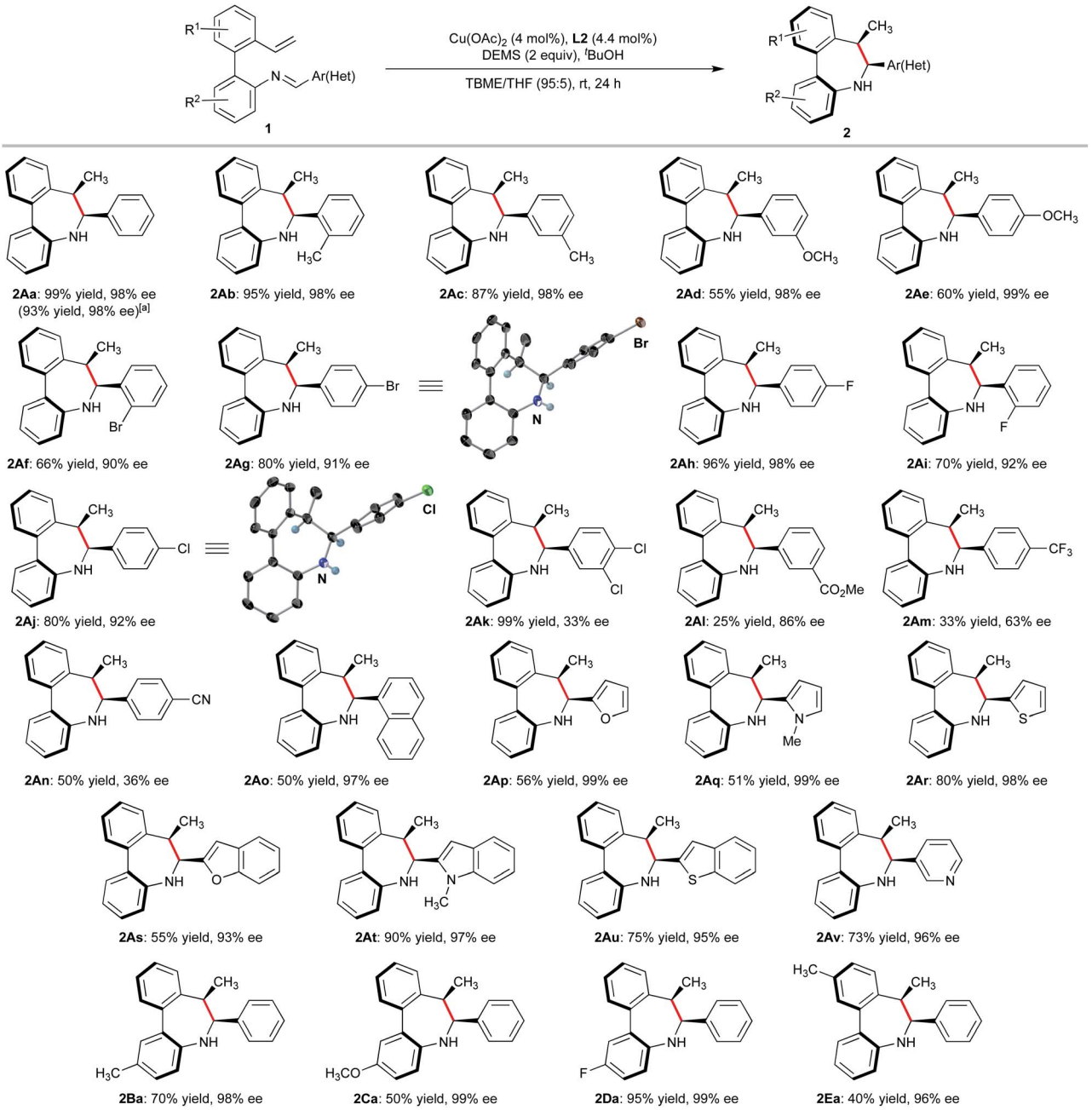
Inspired by the work of Buchwald[16] and Yun[17] on Cu-catalyzed cyclizations using aldimines as electrophiles, we envisioned that Schiff bases from *ortho*-vinyl, *ortho*′-amino biaryls could also be suitable substrates to perform reductive or borylative cyclizations for the construction of axially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



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).

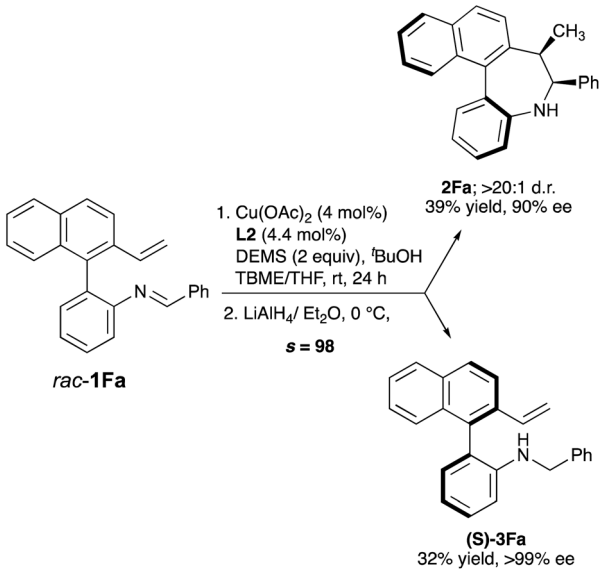
Preliminary studies were performed with compound **1Aa**, readily obtained by condensation of 2′-vinyl-biphenyl-2-amine with benzaldehyde, as a model substrate (Table 1). Using $Cu(OAc)_2$ as the precatalyst, methyldiethoxysilane (DEMS) as the hydride source and anhydrous TBME : THF (95 : 5) mixture 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}H NMR in the crude reaction mixtures. Ee's were determined by HPLC on chiral stationary phases. [a]Reaction performed on 2 mmol (566 mg) scale.

SEGPHOS **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 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

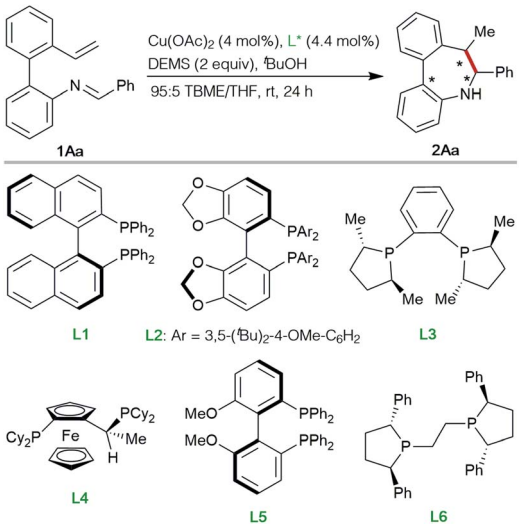


Scheme 3 Kinetic resolution of *rac*-**1Fa**. Reaction performed on 0.2 mmol scale for a 36 h period at rt. Yields of isolated product after chromatography. Ee's were determined by HPLC on chiral stationary phases.

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_a,6*S*,7*R* absolute configuration of products **2Ag**, and **2Aj** was determined by X-ray diffraction analysis,[18] 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, biarylimine **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 $LiAlH_4$ 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

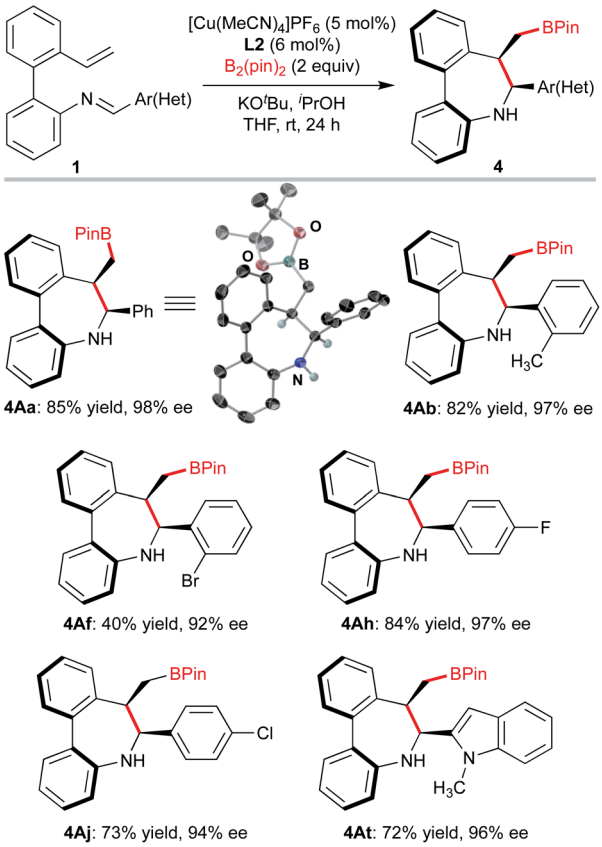


Entry[a]	Ligand	Conv.[b] (%)	ee[c] (%)
1	**L1**, (*S*)-BINAP	<5	nd
2	**L2**, (*R*)-DTBM-SEGPHOS	<10	nd
3	**L3**, (*S*,*S*)-Me-DUPHOS	<20	nd
4	**L4**, (*R*)-(*S*)-JOSIPHOS	<20	nd
5	**L5**, (*R*)-MeO-BIPHEP	42	77
6[d]	**L6**, (*R*,*R*)-Ph-BPE	99 (99 yield)	99

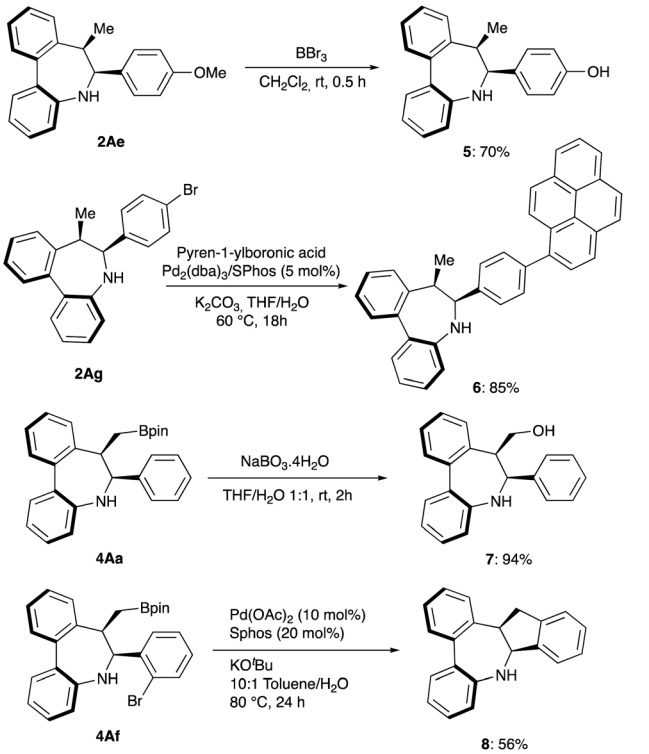
[a] Reactions performed on 0.2 mmol scale. [b] Estimated by ^{1}H-NMR spectroscopy. [c] Determined by HPLC on chiral stationary phases. [d] A single diastereomer was observed by ^{1}H NMR in the crude reaction mixture.

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 [$B_2(pin)_2$], the catalyst formed by combination of $[Cu(MeCN)_4]PF_6$ with biphosphine **L2**, KO*t*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_a,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[18] 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}H NMR in the crude reaction mixtures. Ee's were determined by HPLC analysis.

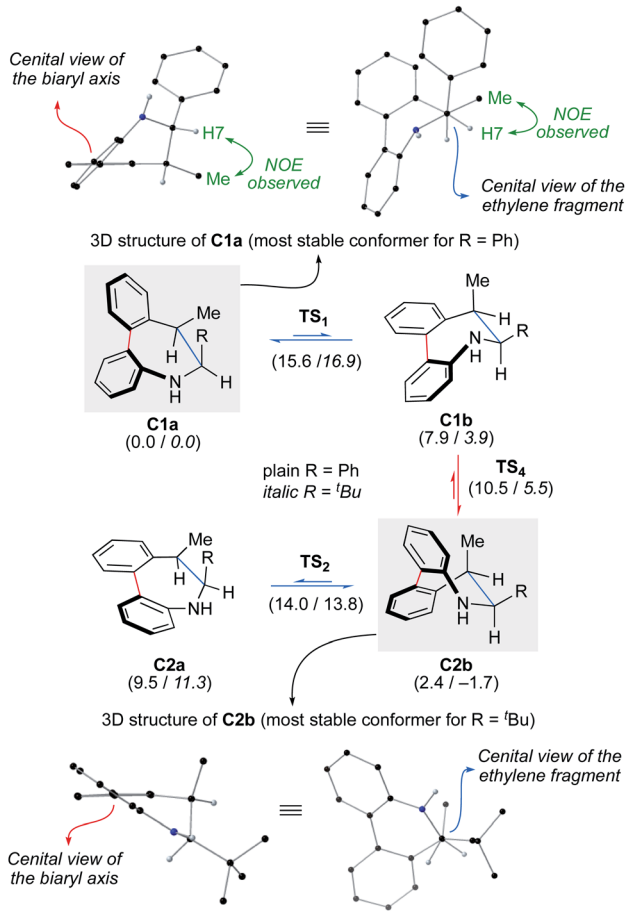


Scheme 5 Derivatization reactions.

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.[19] 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*-tetrahydrodibenzoindenoazepine **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).[20] A third conformation can be located but at a considerable higher energy.[21] 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^{-1}, respectively and the difference between free energy of conformers accounts for the preferred **C1a** and **C2b** conformations in each case. The interconversion between S_a-**C1b**/R_a-**C2b** conformations involving epimerization has free energy barriers of only 2, 6 and 8.1 kcal mol^{-1}. Those values clearly show that a fast equilibrium is established at 25 °C (a barrier of 15.6 kcal mol^{-1} corresponds, approximately, to a kinetic constant of 22.4 s^{-1} 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}H-NMR experiments provided further support to this conclusion: a single set of peaks is observed at temperatures as low as −60 °C.

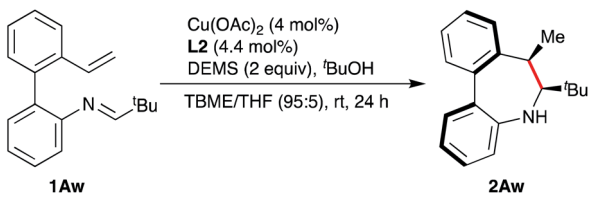
On the light of these calculations, we speculated on the possibility of freezing or shifting the conformational equilibrium by introducing a bulkier ^{t}Bu group instead of the Ph group. Interestingly, the calculation predicts that R_a-**C2b** is the lowest energy conformation in this case (1.7 lower 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,6*S*,7*R* 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



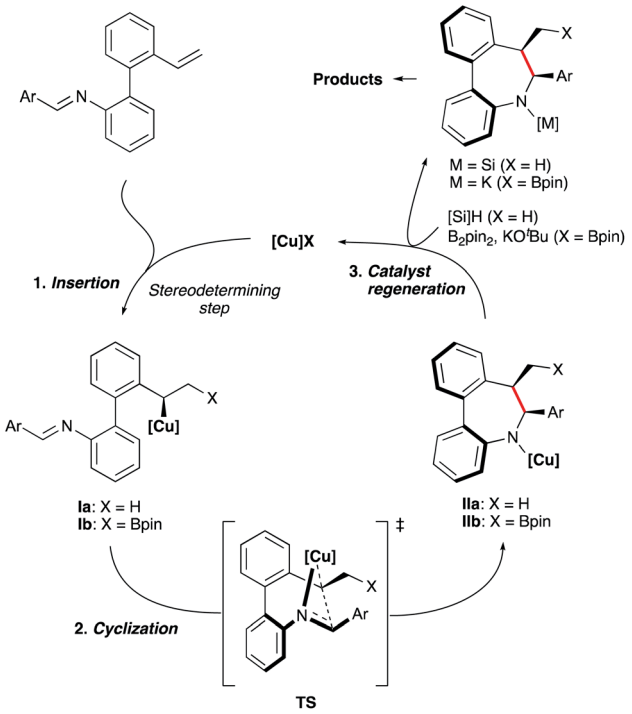
Scheme 6 Computational analysis for the axial epimerization for dibenzoazepines **2A** (wb97xd/def2tzvp//wb97xd/def2svp/cpcm = diisopropylether). Relative free energies are given in brackets in kcal mol^{-1}. Data for R = Ph in plain text, data for R = ^{t}Bu in italics. For details see the ESI.†

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 ^{1}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[22] and Hartwig[23] 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

We thank the Spanish Ministerio de Ciencia e Innovación (Grants PID2019-106358GB-C21, PID2019-106358GB-C22, PID2019-104090RB-100, contracts RYC-2017-22294 for V.H. and BES-2017-081561 for P. R-S), European funding (ERDF), Junta de Andalucía (Grants P18-FR-3531, P18-FR-644, US-1262867, and US-1260906), and Aragon Government (Grupos E34_20R). Computational resources from the super-computers "Memento" and "Cierzo" provided by BIFI-ZCAM (University of Zaragoza, Spain) are also acknowledged. We also thank Dr Francisco José Fernández de Córdova for X-ray structure determination of compounds **2Aj**, **2Ag** and **4Aa**.

Notes and references

1 (*a*) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563–639; (*b*) J. E. Smyth, N. M. Butler and P. A. Keller, *Nat. Prod. Rep.*, 2015, **32**, 1562–1583; (*c*) J. Wencel-Delord, A. Panossian, F. R. Leroux and F. Colobert, *Chem. Soc. Rev.*, 2015, **44**, 3418–3430; (*d*) Y.-B. Wang and B. Tan, *Acc. Chem. Res.*, 2018, **51**, 534–547; (*e*) J. K. Cheng, S.-H. Xiang, S. Li, L. Ye and B. Tan, *Chem. Rev.*, 2021, **121**, 4805–4902; (*f*) J. M. Lassaletta, *Atropisomerism and Axial Chirality*, World Scientific, New Jersey, 2019.

2 G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem., Int. Ed.*, 2005, **44**, 5384–5427.

3 S. L. Pira, T. W. Wallace and J. P. Graham, *Org. Lett.*, 2009, **11**, 1663–1666.

4 (*a*) S. Superchi, D. Casarini, A. Laurita, A. Bavoso and C. Rosini, *Angew. Chem., Int. Ed.*, 2001, **40**, 451–454; (*b*) Y. Zhang, Y.-Q. Liu, L. Hu, X. Zhang and Q. Yin, *Org. Lett.*, 2020, **22**, 6479–6483; (*c*) Y. Guo, M.-M. Liu, X. Zhu, L. Zhu and C. He, *Angew. Chem., Int. Ed.*, 2021, **60**, 13887–13891.

5 Y. Zhang, Z. Chang, H. Zhao, S. Crespi, B. L. Feringa and D. Zhao, *Chem*, 2020, **6**, 2420–2429.

6 B. Zhang, M. Bao, C. Zeng, X. Zhong, L. Ni, Y. Zeng and X. Cai, *Org. Lett.*, 2014, **16**, 6400–6403.

7 G. T. Wong, D. Manfra, F. M. Poulet, Q. Zhang, H. Josien, T. Bara, L. Engstrom, M. Pinzon-Ortiz, J. S. Fine, H. J. Lee, L. Zhang, G. A. Higgins and E. M. Parker, *J. Biol. Chem.*, 2004, **279**, 12876–12882.

8 J. S. Nair, T. Sheikh, A. L. Ho and G. K. Schwartz, *Anticancer Res.*, 2013, **33**, 1307–1316.

9 L. Keller, S. Beaumont, J.-M. Liu, S. Thoret, J. S. Bignon, J. Wdzieczak-Bakala, P. Dauban and R. H. Dodd, *J. Med. Chem.*, 2008, **51**, 3414–3421.

10 W. Zaharevitz, R. Gussio, M. Leost, A. M. Senderowicz, T. Lahusen, C. Kunick, L. Meijer and E. A. Sausville, *Cancer Res.*, 1999, **59**, 2566–2569.

11 (*a*) L. A. Saudan, G. Bernardinelli and E. P. Kündig, *Synlett*, 2000, 483–486; (*b*) C. A. Cheetham, R. S. Massey, S. L. Pira, R. G. Pritchard and T. W. Wallace, *Org. Biomol. Chem.*, 2011, **9**, 1831–1838; (*c*) S. Postikova, M. Sabbah, D. Wightman, I. T. Nguyen, M. Sanselme, T. Besson, J.-F. Briere, S. Oudeyer and V. Levacher, *J. Org. Chem.*, 2013, **78**, 8191–8197; (*d*) P. C. Bulman Page, C. A. Pearce, Y. Chan, P. Parker, B. R. Buckley, G. A. Rassias and M. R. Elsegood, *J. Org. Chem.*, 2015, **80**, 8036–8045.

12 (*a*) T. Saget and N. Cramer, *Angew. Chem., Int. Ed.*, 2013, **52**, 7865–7868; (*b*) C. G. Newton, E. Braconi, J. Kuziola, M. D. Wodrich and N. Cramer, *Angew. Chem., Int. Ed.*, 2018, **57**, 11040–11044.

13 H. Hu, Y. Peng, T. Yu, S. Cheng, S. Luo and Q. Zhu, *Org. Lett.*, 2021, **23**, 3636–3640.

14 J. Liu, X. Yang, Z. Zuo, J. Nan, Y. Wang and X. Luan, *Org. Lett.*, 2018, **20**, 244–247.

15 For the synthesis of related dibenzo[*c*,*e*]azepine derivatives (N atom not attached to the biaryl moiety) see: (*a*) S. P. France, G. A. Aleku, M. Sharma, J. Mangas-Sanchez, R. M. Howard, J. Steflik, R. Kumar, R. W. Adams, I. Slabu, R. Crook, G. Grogan, T. W. Wallace and N. J. Turner, *Angew. Chem., Int. Ed.*, 2017, **56**, 15589–15593; (*b*) T. Yang, X. Guo, Q. Yin and X. Zhang, *Chem. Sci.*, 2019, **10**, 2473–2477; (*c*) S. Zhang, F. Chen, Y.-M. He and Q.-H. Fan, *Org. Lett.*, 2019, **21**, 5538–5541; (*d*) T. Kano, H. Sugimoto and K. Maruoka, *J. Am. Chem. Soc.*, 2011, **133**, 18130–18133. See also ref. 4*b*.

16 E. Ascic and S. L. Buchwald, *J. Am. Chem. Soc.*, 2015, **137**, 4666–4669.

17 D. Li, J. Kim, J. W. Yang and J. Yun, *Chem.–Asian J.*, 2018, **13**, 2365–2368.

18 CCDC 2095490 [(S_a,6*S*,7*R*)-**2Aj**], 2095492 [(S_a,6*S*,7*R*)-**2Ag**] and 2095491 [(S_a,6*S*,7*R*)-**4Aa**].†

19 R. W. Sinkeldam, N. Greco and Y. Tor, *Chem. Rev.*, 2002, **110**, 2579–2619.

20 J. Messinger and V. Buss, *J. Org. Chem.*, 1992, **57**, 3320–3328.

21 S. Saebo and J. E. Boggs, *J. Mol. Struct.: THEOCHEM*, 1982, **87**, 365–373.

22 Y. Yang, S.-L. Shi, D. Niu, P. Liu and S. L. Buchwald, *Science*, 2015, **349**, 62–66.

23 Y. Xi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2017, **139**, 12758–12772.