Dynamic kinetic resolution in the asymmetric synthesis of atropisomeric biaryl[4] and [5]helicene quinones†

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Total control of axial and helical chirality elements of a (2-biphenyl)-substituted tetrahydro[5]helicene quinone and the configurationally stable dihydro[4]helicene analogue was achieved in a dynamic kinetic resolution process of an axially chiral racemic diene promoted by an enantiopure sulfinyl benzoquinone.

Atropisomerism associated with the hindered rotation of a single bond in *ortho*-substituted biaryls[1] is a chiral feature found in natural bioactive products[2] and chiral ligands widely used in asymmetric catalysis.[3] Apart from aryl–aryl coupling,[4] other atroposelective synthetic strategies reported involve stepwise sequences starting with C–C aryl coupling reactions followed by enantiodifferentiating transformations to install the absolute configuration at the biaryl chiral axis.[5] Other chiral molecules lacking chiral centers are helicenes, non-planar *ortho*-fused aromatic derivatives displaying helical chirality.[6] Their important properties both in the field of new materials[6b] and medicinal chemistry[6c] have stimulated the development of short and efficient syntheses, including versatile asymmetric routes, during the last two decades.[7] In spite of the advances reached, the synthesis of enantiopure molecules with both axial and helical chirality elements remains an unsolved challenge. To the best of our knowledge, there are no examples of helicenes bearing a biaryl substructure with additional axial chirality.[8]

We recently succeeded in a short synthesis of enantiopure helicenequinones[9] based on the efficient transfer of chirality from a homochiral sulfoxide[10] to the helical structure. The strategy stems from the domino Diels–Alder reaction–pyrolytic sulfoxide elimination–aromatization process occurring when adequately substituted vinyl dihydroaromatic derivatives react with enantiopure sulfinyl quinones. This asymmetric approach could be applied to the synthesis of atropisomeric systems by introducing a biaryl moiety in the diene partner reacting with the enantiopure sulfinyl quinones.

Herein, we report a versatile enantioselective synthesis of differently substituted atropisomeric biaryl[4] and [5]helicene quinones, in which a dynamic kinetic resolution (DKR)[11] of the initial racemic biaryl-containing diene was achieved from a configurationally labile chiral axis leading to a unique helical biaryl atropisomer.

In order to evaluate the influence of the *ortho*-substitution around the chiral axis on the configurational stability of a biaryl helicene quinone, as well as in the efficiency of this asymmetric approach, the synthesis of (1-naphthyl)-substituted vinyl tetrahydrophenanthrenes **1a** and **1b** (see ESI†), with a OMe substituent in the *ortho* (R^1 = OMe, R^2 = H) or *para* (R^1 = H, R^2 = OMe) positions with respect to the naphthyl group, was initially planned (Scheme 1). Reaction of racemic diene **1a**, bearing an *ortho* OMe group at the biaryl moiety, with 2 equiv. of (S*S*)-5-methyl-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**2**)[12] gave, in 68% yield after chromatographic purification, a 50 : 50 mixture of two atropisomeric quinones (*P*,a*S*)-**3a** and (*P*,a*R*)-**4a**, bearing axial and helical chirality elements. Both [5]helicene structures resulted from the domino process[13] including the asymmetric Diels–Alder reaction of both enantiomers of the biaryl racemic diene **1a** with sulfinyl quinone (S*S*)-**2**, sulfoxide elimination and aromatization of the B ring on the initially formed cycloadducts. The atropisomers (*P*,a*S*)-**3a** (99% ee}[14] and (*P*,a*R*)-**4a** (98% ee}[14] were separated by preparative HPLC (see ESI†). They showed the same (*P*) configuration at the helix[15] and the opposite configuration at the chiral axis. This result indicated a similar reactivity of both atropenantiomers of the diene **1a** in the asymmetric Diels–Alder reaction as well as a high configurational stability of the chiral axis in both the starting diene and the final biaryl helical structure.

The reaction of (1-naphthyl)-substituted racemic diene **1b**, lacking the *ortho* methoxy group at the biaryl moiety, with (S*S*)-**2** gave rise, in 74% yield, to a non-separable 20 : 80 mixture of atropisomers (*P*,a*R*)-**3b** and (*P*,a*S*)-**4b** (93% ee)[14,15] (Scheme 1). This result suggested that the absence of the OMe group at the *ortho* position of the biaryl unit could allow the interconversion between the atropisomers of **1b**, thus facilitating a partial DKR.[11] A double asymmetric induction process had occurred with efficient control of the helical chirality and the major formation of the chiral axis with the a*S* absolute configuration.

The relative configurations of atropisomeric derivatives (*P*,a*S*)-**3a** and (*P*,a*R*)-**4a** were demonstrated after an X-ray diffraction study of (*P*,a*R*)-**4a** (Fig. 1),[16] whereas those of 11-methoxy-substituted compounds (*P*,a*R*)-**3b** and (*P*,a*S*)-**4b** were assigned by comparison of their ^{1}H-NMR spectra with those of (*P*,a*S*)-**3a** and (*P*,a*R*)-**4a**. As can be seen in Fig. 1, the naphthyl group situated at C-14 in (*P*,a*R*)-**4a** adopts a quasi perfect parallel disposition with respect to the naphthoquinone moiety of the helicene framework. This must be favoured by the flexibility of the tetrahydroaromatic part which allows intramolecular π-stacking[17] between the aromatic rings.

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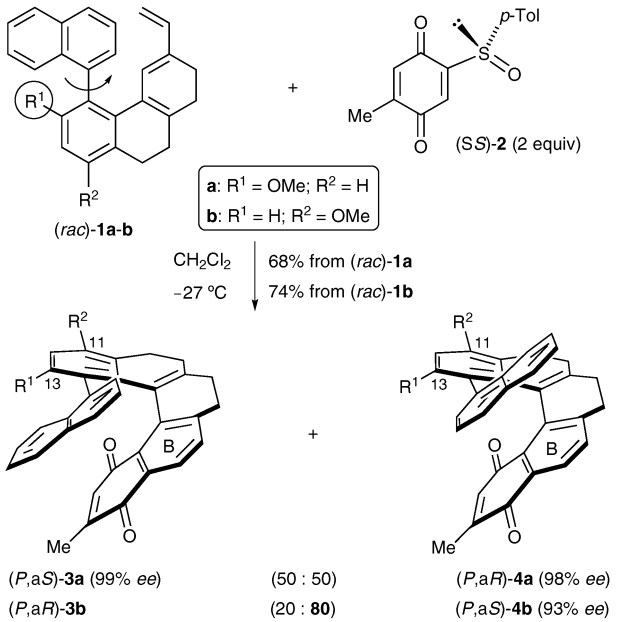
† Electronic supplementary information (ESI) available: Synthesis of dienes (*rac*)-**1a**,**b**, (*rac*)-**5** and (*rac*)-**7**, experimental procedures, characterization and crystallographic data, and NMR spectra. CCDC 713295 and 713296. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b907653k



Scheme 1 Diastereoselective synthesis of (1-naphthyl)-substituted tetrahydro[5]helicene quinones **3a–4a** and **3b–4b**.

To evaluate the ability of a phenyl group situated at the *ortho* position of the biaryl moiety in the initial diene to more efficiently differentiate the reactivity of both atropenantiomers in the DKR process, the (2-biphenyl)-substituted racemic diene **5** was synthesized (see ESI†). When compound **5** was submitted to reaction with 2 equiv. of sulfinyl quinone (S*S*)-**2** at −27 °C (Scheme 2), pentahelicenequinone (*P*,a*S*)-**6** (95% ee)[14,15] was obtained, as the unique diastereoisomer, in 75% yield. This result evidenced that an efficient DKR[11] of the stereolabile chiral axis of diene **5** had occurred. The stereochemistry of the process could be a consequence of a double asymmetric induction process where one of the diene atropenantiomers cycloadds faster than the other. The high yield observed suggested that, under the reaction conditions, the interconversion between both diene atropenantiomers of **5** must be easily occurring before the cycloaddition takes place, with a total control of the axial and helical chirality elements of the final target. The relative configuration of (*P*,a*S*)-**6** was assigned after X-ray analysis (Scheme 2).[16]

Encouraged by this result, we decided to extend the usefulness of the DKR process to other analogues. The synthesis of a (2-biphenyl)-substituted [4]helicene quinone such as **9** (Scheme 3) would allow us to check the efficiency

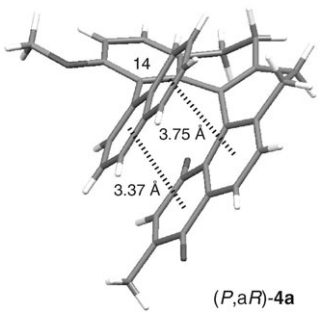
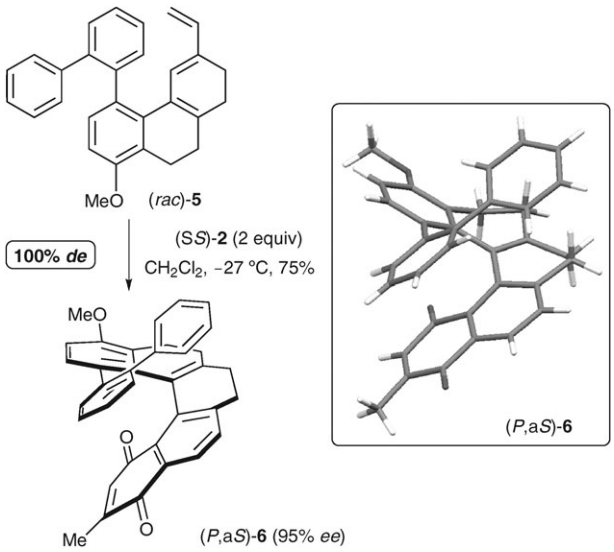


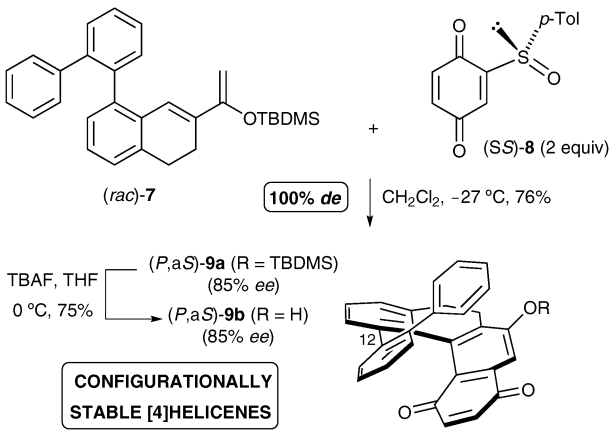
Fig. 1 X-Ray ortep of (*P*,a*R*)-**4a**.



Scheme 2 Efficient DKR process for the enantioselective synthesis of (2-biphenyl)-substituted [5]helicene quinone (*P*,a*S*)-**6**.

of the DKR as well as to evaluate the influence of the biaryl substituent at C-12 on the configurational stability of such [4]helicene quinones. In this case, the reaction of the (2-biphenyl)-substituted racemic diene **7** (see ESI†) with 2 equiv. of (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**8**)[12a] at −27 °C gave rise, in a new efficient DKR process,[11] to a sole diastereoisomer (*P*,a*S*)-**9a** (85% ee)[14,15] with 76% yield and an efficient control of helical and axial chirality elements. Compound **9a**, whose relative configuration was assigned as (*P*,a*S*) by similarity with derivative (*P*,a*S*)-**6**, was later easily transformed into the OH free derivative (*P*,a*S*)-**9b** (TBAF, THF, 0 °C, 1 h), in 75% yield (Scheme 3).

It is noteworthy that both (2-biphenyl)-substituted [4]helicene quinones (*P*,a*S*)-**9a**,**b** proved to be configurationally stable at room temperature. It is well known that [4]helicene quinones are only stable when having a bulky substituent such as a *tert*-butyl group at the C-12 position.[9a] The origin of the unexpected thermal stability of the helix of (*P*,a*S*)-**9a**,**b** could be in the particular structure of such derivatives in which the 2-biphenyl substituent at C-12 adopts a double orthogonal



Scheme 3 DKR for the enantioselective synthesis of configurationally stable (2-biphenyl)-substituted [4]helicene quinone (*P*,a*S*)-**9a**.

disposition where the whole helicene framework seems to be extended to a [8]helicene-like molecule (Scheme 3).

In summary, we have evidenced the ability of a homochiral sulfoxide situated on an enantiopure benzoquinone to transfer its central chirality to a chiral axis and a helicene framework in an efficient manner. The syntheses of biaryl[4] and [5]helicene quinones was achieved in a very short, convergent and highly enantioselective manner. The adequate substitution of the biaryl diene partner sums up the resolution or dynamic kinetic resolution of the initial chiral racemic biaryl axis.

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