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Nickel catalyzed synthesis of 4,4′-bichromenes/4,4′-bithiochromenes and their Atropisomerism†

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Axially chiral molecules have established undisputed importance in both medicinal chemistry and enantiomeric catalysis. The size, shape and hybridization of the substituent adjacent to the rotational axis greatly dictate atropisomerism. Herein, we examined the tropoisomeric behavior of 4,4′-bichromenes and 4,4′-bithiochromenes derivatives that were synthesized by a nickel catalyzed reductive homocoupling strategy. The as-synthesized 3,3′-disubstituted 4,4′-bichromenes displayed atropisomerism, as evidenced by chiral stationary phase HPLC, electronic circular dichroism and single crystal XRD studies. Insights into the torsional barrier about the internuclear axis in 4,4′-bichromenes were gained both experimentally and theoretically (DFT studies). The lower activation energy barrier (E_a) of approximately 12 kcal mol^{-1} as compared to that of fully aromatic 1,1′-binapthyl explains the conformationally unstable nature of 3,3′-unsubstituted 4,4′-bichromenes at room temperature.

Introduction

The atroposelective synthesis of axially chiral biaryls is considered significant since it can afford a variety of biologically active molecules and excellent chirality transfer agents. Molecules such as Vancomycin and Diphosphine BINAP bear testimony to this fact.[1–9] An important factor in the synthesis of dissymmetric biaryls is the presence of a substituent adjacent to the internuclear rotational axis. The steric size, shape and hybridization of these substituents exert a large influence on the optical stability of the molecules.[10] While atropisomerism in 1,1′-binaphthyls **1**[11] has been largely studied, the closely related condensed heterocyclic systems have received less attention. Among a few of the heterocyclic analogues examined, namely, 4,4′-biquinolines **2**, 4,4′-bi-2,2′-quinolones **3**, and 1,1′-biisoquinolines **4**,[12,13] both **2** and **3** (when R = H) have been optically resolved and found to be conformationally stable at ambient temperatures, similar to 1,1′-binaphthyl (Fig. 1).[6c,13,14] In contrast, it is interesting to note that 1,1′-biisoquinoline **4** exhibits rapid racemization due to the low transannular steric hindrance between H-8(8′) and N-2(2′).[15] Mazzanti and Schlosser have also shown that the stereogenic torsional barrier of arylpyridines is up to 4.2 kcal mol^{-1} smaller than that of biphenyl due to the compressibility of the nitrogen lone pair.[16] These facts provoked our interest to examine atropisomerism in 4,4′-bichromenes **6** and 4,4′-bithiochromenes **7**, which are a medicinally important class of compounds closely related to 4,4′-bicoumarins **5**.[6a,17] Moreover, the synthetic chemistry of 4,4′-bichromenes has been scarcely explored and only a few reports exist.[6b,18] In this paper, we present the first report on the atropisomerism of 3,3′-disubstituted-4,4′-bichromenes **6**, and 3,3′-disubstituted-4,4′-bithiochromenes **7**. For comparative studies we have also prepared a few partially aromatic biaryls, namely, 3,3′,4,4′-tetrahydro-1,1′-binapthyls (**8a** and **8b**), and studied their axial chirality (see chart S1.0 in the ESI†).

Results and discussion

We began our investigation with the synthesis and examination of atropisomerism in 7,7′-dimethyl-4,4′-bichromene **6f** (Fig. 2).[19] The chiral HPLC trace of **6f** showed only a single

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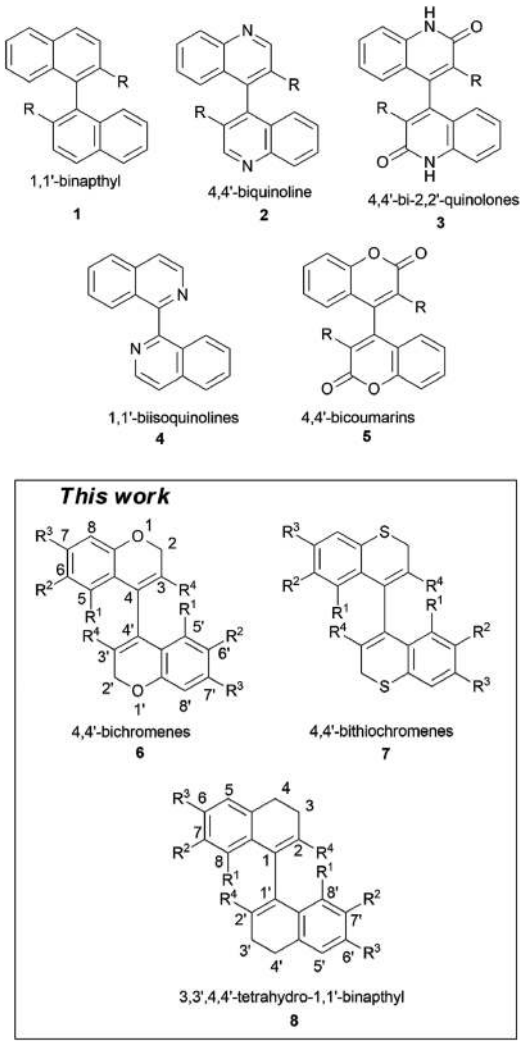


Fig. 1 Examples of various classes of biaryl systems.

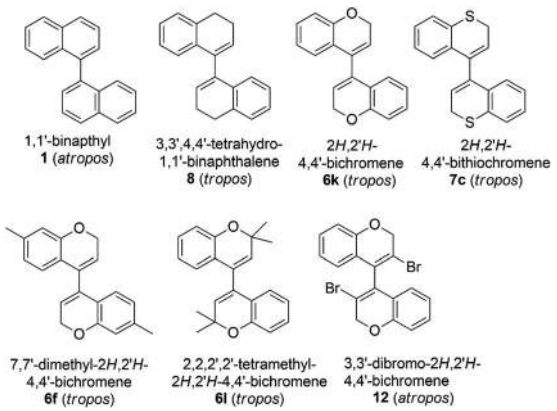


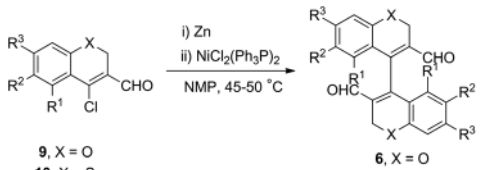
Fig. 2 Various biaryl compounds preliminarily examined for axial chirality at room temperature.

eluting peak. In the ^{1}H NMR spectrum, the –OCH_2 protons appeared as a doublet at 4.84 ppm and the olefinic proton appeared as a triplet at 5.74 ppm. The non-diastereotopic nature of the methylene signals indicated unresolvable fast rotation about the stereogenic axis at room temperature (ESI, S3.6 and S4.3†).

The above observations were unlike those of 1,1′-binaphthyl **1** [11a] or 4,4′-biquinoline **2**,[15] which exhibited axial chirality at room temperature. Furthermore, we also prepared the tetrahydro analogue of **1**, namely, the 3,3′,4,4′-tetrahydro-1,1′-binaphthalene[20] (**8**) ($R^1 = R^2 = R^3 = R^4 = H$) (Fig. 1) and analysed its conformational stability. It too displayed an achiral behaviour at room temperature as revealed by ^{1}H NMR studies and HPLC analysis performed with six different chiral stationary phase columns (ESI, S3.15 and S4.10†). Finally, in line with the general expectation, we sought to improve the optical stability by functionally substituting 3,3′-positions in the bichromene/bithiochromene systems. Accordingly, a preliminary examination of the room temperature ^{1}H NMR spectrum of 3,3′-dibromo-2*H*,2′*H*-4,4′-bichromene (**12**) indeed revealed the expected diastereotopic pattern (ESI, S3.18†).[21] Recently, Lee *et al.*[22] have reported an iodine monochloride (ICl)-mediated synthesis of substituted 3,3′-diiodo-2*H*,2′*H*-4,4′-bichromene from diynes. The ^{1}H NMR spectrum of the diiodo compound also suggested atropisomerism similar to our compounds (Fig. 2). Next, we aimed to develop an easier protocol for synthesizing 3,3′-disubstituted 4,4′-bichromenes, which would provide direct access to these heterocyclic axially chiral entities. The metal-mediated homocoupling of 4-chloro-3-formylchromenes (**9**) appeared to be the most expedient route to access diversely functionalized potentially chiral 4,4′-bichromenes. β-Chlorovinyl aldehydes are versatile synthons and their chemistry has been recently reviewed.[23–26]

Though there exists few reports on the metal-catalyzed homocoupling and cross coupling of β-chlorovinyl aldehydes with acetylenes,[26] arylboronic acids and aryl amines,[27,28] surprisingly no reports were found for the metal mediated homocoupling of 4-chloro 3-formylchromenes. Homocoupling of aryl halides can be accomplished using various metal-catalysed systems. Our initial attempts to realize the homocoupling of 4-chloro-3-formylchromenes (**9**) using CuI/Cu/Ni$(PPh_3)_2Cl_2$ or Cu/Pd$(PPh_3)_4$ or indium/Ni$(PPh_3)_2Cl_2$ in different solvents and conditions were unsuccessful.[28] Finally, we succeeded in the synthesis of the hitherto unknown 4,4′-bichromene-3.3′-dicarboxaldehyde **6a** in 70% yield by homocoupling chloroaldehyde **9a** using an Ni(0) complex generated *in situ* by the reduction of Ni$(PPh_3)_2Cl_2$ with activated zinc[29] (Scheme 1). 4,4′-Bichromene-3,3′-dicarboxaldehyde **6a**, isolated as a crystalline solid, was thoroughly characterized by ^{1}H NMR,^{13}C NMR spectroscopy and HRMS. A cursory glance of its ^{1}H NMR spectrum revealed this molecule to be chiral (ESI, S3.1†). The ^{1}H NMR spectrum showed an AB quartet for the –OCH_2 (J = 14.5 Hz) protons, revealing their diastereotopic nature in contrast to those of the simple 4,4′-bichromene and 4,4′-bithiochromene (**6f** and **7**).

The chiral HPLC traces for **6b** showed two peaks in 1 : 1 ratio, further confirming it to be a racemate (ESI S4.11 and Fig. S1†). The racemate, **6b**, was separated into optical antipodes by chiral preparative HPLC. The chiral purity of the



9, X = O
10, X = S
11, X = C

6, X = O
7, X = S
8, X = C

9a: X=O, R^1=R^2=R^3=H
9b: X=O, R^1=R^2=H, R^3=F
9c: X=O, R^1=H, R^2=Me, R^3=H
9d: X=O, R^1=R^2=H, R^3=Me
9e: X=O, R^1=H, R^2= OMe, R^3= H
10a: X=S, R^1=R^2=R^3=H
10b: X=S, R^1=R^2=H, R^3=F
11a: X=C, R^1=R^2=H, R^3=F
11b: X=C, R^1=R^3=H, R^2=OMe

6a: X=O, R^1=R^2=R^3=H (70%)
6b: X=O, R^1=R^2=H, R^3=F (78%)
6c: X=O, R^1=H, R^2=Me, R^3=H (60%)
6d: X=O, R^1=R^2=H, R^3=Me (62%)
6e: X=O, R^1=H, R^2= OMe, R^3= H (52%)
7a: X=S, R^1=R^2=R^3=H (80%)
7b: X=S, R^1=R^2=H, R^3=F (74%)
8a: X=C, R^1=R^2=H, R^3=F (84%)
8b: X=C, R^1=R^3=H, R^2=OMe (78%)

Scheme 1 $NiCl_2(PPh_3)_2$ and Zn catalyzed reductive homocoupling of chloroaldehydes.

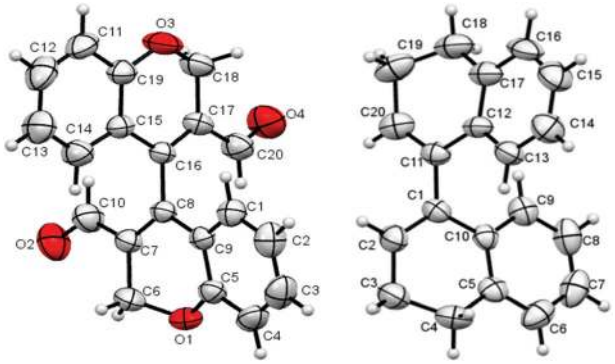


Fig. 4 X-ray crystallographic structure of **6a** (left) and **8** (right).

separated antipodes was rechecked by chiral HPLC analysis. The electronic circular dichroism (CD) spectrum for both enantiomers were measured and determined to be mirror images, displaying the cotton effect at 300 nm and 400 nm (Fig. 3, and ESI, S5.0†).

Single crystals of **6a**, suitable for XRD analysis, were obtained from slow evaporation of the compound in methanol at room temperature (ESI, S6.0†). The crystals obtained were in the racemic form. In line with our expectations, the two bichromene units were flanked along the internuclear axis in a non-coplanar fashion. The dihedral angle between the mean molecular aryl ring planes was found to be 88.29°, indicating a close perpendicular conformation. The distance of the internuclear axial bond, *viz.*, C4–C4′ was found to be 1.5009(19) Å, which is close in comparison to the C1–C1′ distance in (*R*)-(−)-1,1′-binaphthyl- (1.511(7) Å).[30a] We also obtained racemic single crystals of compound **8**; the molecular structure revealed a *cisoid* configuration with mean planes for the aryl rings subtending an angle of 66.11° about the stereogenic axis (Fig. 4).

The internuclear distance for C1–C11 was found to be 1.477(6) Å. These distances and angles were quite similar to that of racemic 1,1′-binapthyl crystal,[30b] which showed an internuclear distance of 1.475 Å and an angle of 68° between the planes of the binapthyl residues. Using the facile homocoupling methodology described above, we synthesized for the first time 4,4′-bichromenes-3.3′-dicarboxaldehydes **6a–e**, 4,4′-bithiochromenes-3.3′-dicarboxaldehydes **7a–b**, and 3,3′,4,4′-tetrahydro-[1,1′-binaphthalene]-2,2′-dicarbaldehydes **8a–b** (Scheme 1). All these compounds (**6a–e**, **7a–b**, and **8a–b**) showed atropisomerism, as revealed by their ^{1}H NMR spectra. Furthermore, isomeric resolution of peaks was observed on chiral HPLC traces of **6b**, **6e–j**, **7a**, and **8a** (ESI, S4.0†). Moreover, by simple functional group transformation of **6b** and **6a**, a few more novel 3,3′-disubstituted-4,4′-bichromenes, *viz.*, **6g–6i** and **6j**, respectively were obtained (Scheme 2 and Experimental section). Their chiral behaviour was also observed with ^{1}H NMR and chiral HPLC analyses. The acid **6g**, alcohol **6h** and the oxime **6j** displayed atropisomerism. HPLC analysis of the cyano derivative **6i** showed two peaks in 1 : 1 ratio, revealing it to be conformationally stable. However, the ^{1}H NMR spectrum exhibited only a singlet and no an AB quartet for the –OCH_2 protons. This is possibly due to accidental equivalence (ESI, S3.9†). We are currently investigating the direct enantioselective synthesis of 3,3′-disubstituted 4,4′-bichromenes by asymmetric catalysis.

As mentioned earlier, the reason for the higher degree of rotational freedom in the case of 4,4′-bichromenes was due to the reduction in transannular steric hindrance about the internuclear axis. However, the shape and hybridization factor of the substituent atoms, which presumably influences this effect, has neither been experimentally investigated nor

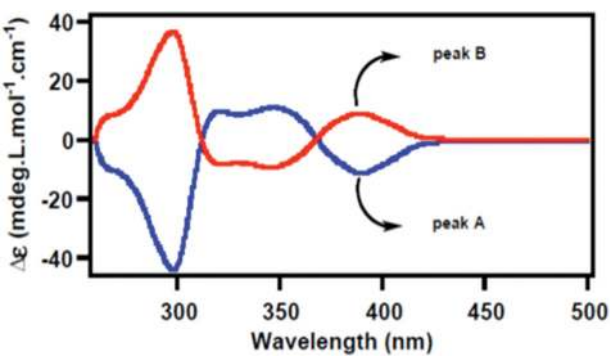
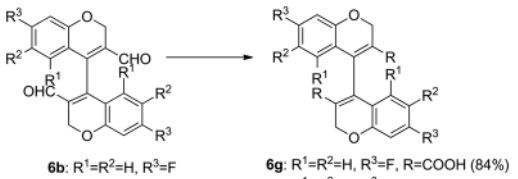


Fig. 3 The electronic circular dichroism spectrum of **6b**.



6b: R^1=R^2=H, R^3=F
6a: R^1=R^2=R^3=H

6g: R^1=R^2=H, R^3=F, R=COOH (84%)
6h: R^1=R^2=H, R^3=F, R=CH_2OH (68%)
6i: R^1=R^2=H, R^3=F, R=CN (68%)
6j: R^1=R^2=R^3=H, R=CHNOH (80%)

Scheme 2 Conversion of 4,4′-bichromenes-3.3′-dicarboxaldehydes to other functionalities *viz.* acid, alcohol, nitrile and oximes.

empirically suggested in the system under consideration. In order to gain more insight into the conformational behaviour of the 3,3′-unsubstituted 4,4′-bichromene systems, the two compounds **6k** and **6l** (Fig. 2 and ESI, S2.0†) were synthesized and collected for further investigation. The coalescence temperature of the exchanging isomers was determined from the variable temperature dynamic ^{1}H NMR studies[31] for the sample in deuterated THF. The rate constant (K_r) thus determined was used for calculating activation energies (E_a). The activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) were also obtained employing the Eyring equation (ESI, S7.0†). The activation energies (E_a) of **6k** and **6l** were found to be 14.6 kcal mol^{-1} and 11.16 kcal mol^{-1}, respectively. The rotational energy barrier was reflected in the Gibbs free energy ($\Delta G^{\ddagger}$) difference between the ground state and the rate-limiting transition state. The estimated values of $\Delta G^{\ddagger}$ for **6k** and **6l** were 13.44 kcal mol^{-1} and 10.75 kcal mol^{-1}, respectively. These values were approximately half of the experimentally determined value of $\Delta G^{\ddagger}$ for carba-analogous 1,1′-binapthyl (23.5 kcal mol^{-1}) in DMF at 50 °C.[32a]

DFT calculations were also performed to determine the activation energy E_a for free rotation (ESI, S8.0†). The E_a of **6k** and **6l** generated by DFT computation were close values of 19.15 kcal mol^{-1} and 20.66 kcal mol^{-1}, respectively. A table of comparison is provided in the ESI (Table S1†). As expected, the E_a for 4,4′-bichromenes **6k** and **6l** was lower than the E_a for the 1,1′-binapthyl system by approximately 12 kcal mol^{-1}. Comparing the difference in the activation energies for bichromene *versus* 1,1′-binapthyl, both experimental and DFT computed values agreed on the lower value of ~10–13 kcal mol^{-1}.[32] In general, the DFT results overestimated the activation energies by approximately 5–8 kcal mol^{-1}, but were consistent with the trend. The marginal difference observed in the experimentally derived values of (E_a) and $\Delta H^{\ddagger}$ for **6k** and **6l** is also reflected in the DFT calculations, indicating the limited influence from non-sterically interfering dimethyl substituents at the 2,2′-positions. We also calculated the rotational barrier of a hypothetical 4,4′-bichromene with a methyl substituent at the 3,3′-position, namely, 3,3′-dimethyl-4,4′-bichromene was calculated and compared to with that of 2,2′-dimethyl-1,1′-binapthyl (ESI, S8†). The rotational barrier of the former was calculated to be 80 kcal mol^{-1} and the later to be 110 kcal mol^{-1}. The sufficiently high energy barrier of 80 kcal mol^{-1} suggests the compound to be atropisomeric at RT, though not to the extent of its aromatic counterpart. This computation suggests that even smaller sterically hindering substituents such as the methyl group at the 3,3′-position of bichromene could facilitate atropisomerism.

From the above studies, it is possible to surmise a few reasons for the difference in atropisomerism between the binapthyl and bichromene systems. (i) The non-planarity of the heterocyclic ring in the bichromene system (presence of sp^3 carbon) can cause lower aromatic stabilization of either the *syn*- or *anti* isomers, therefore decreasing the energy barrier for rotation. In contrast, the sp^2 carbon bearing the fully aromatic binapthyl system was more stable due to conjugation effects. (ii) The possibility of any non-bonded repulsive interaction between the olefinic proton and the benzene ring in the bichromene/bithiochromene system was lower than that of the binapthyl system favouring free-rotation. This was also manifested in the conformationally unstable nature of 3,4,3′,4′-tetrahydro-1,1′-binapthalene **8** in contrast to that of 1,1-binapthyl **1**.

Conclusions

In summary, we present the first report on atropisomerism in 4,4′-bichromenes and 4,4′-bithiochromenes. A nickel-catalyzed reductive homocoupling strategy was applied for the synthesis of several analogues of 4,4′-bichromenes and 4,4′-bithiochromenes. The configurational stability of a few 4,4′-bichromenes were studied experimentally and theoretically to be compared with the 1,1′-binapthyl system. We believe that this study will be helpful in designing novel heteroaromatic axially chiral biaryl motifs that are useful for enantioselective catalysis and in medicinal chemistry.

Experimental section

Typical procedure for the Ni-catalysed reductive homocoupling reaction is as follows. To a stirred solution of 4-chloro-3-formylchromene (10.0 mmol) in freshly distilled NMP (10.0 mL), activated zinc powder (2.0 g, 30.0 mmol) and $NiCl_2(PPh_3)_2$ (0.67 g, 1.0 mmol) were added at 45–50 °C. The reaction mixture was stirred at the same temperature for 3–4 h and the progress was monitored by TLC. After completion of the reaction, the reaction mass was cooled to room temperature and diluted with 20 mL of methyl *tert*-butyl ether (MTBE). The resulting solution was then filtered through a Celite bed and washed further with 10 mL of MTBE. The combined organic portions were washed with dilute 5% aqueous HCl (2 × 15 mL), followed by water (1 × 15 mL), dried over anhydrous sodium sulphate and then concentrated under reduced pressure to yield brown pasty solids. The crude product thus obtained was triturated with 8 mL of ethanol, filtered and dried to produce off-white to yellow solids.

Conflicts of interest

There are no conflicts to declare.

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