Regulation of Axial Chirality through Dynamic Covalent Bond Constrained Biaryls

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Supporting Information

ABSTRACT: A strategy of dynamic covalent chemistry within constrained biaryls was developed for the modulation of axial chirality. The ring fusion partners of amide and aldehyde allowed the manipulation of ring/chain equilibrium and chirality transfer within cyclic diastereomeric hemiaminal. Dynamic covalent reactions (DCRs) with alcohols, thiols, and secondary amines further enabled the reversal of chirality relay and thereby regulation of axial chirality. Moreover, a combination of NMR, X-ray, and density functional theory results shed light on the structural basis of chirality transfer, exhibiting modest to excellent diastereoselectivity under thermodynamic control. The critical role of the amide unit in the modulation of axial chirality was also corroborated. Finally, the chiroptical signal was controlled through changing solvents, DCRs, and stimuli-responsive switching of DCRs.

1. INTRODUCTION

Atropisomers and associated axial chirality play notable roles in a variety of areas, such as asymmetric synthesis,1 drug discovery,2 and organic materials.3 As a result, the construction, regulation, and functionalization of atropisomers are attracting unabated attention. In particular, the switch of axial chirality could be appealing to endeavors of controllable catalysis,4 intelligent assemblies,5 and chiroptical materials.6 The movement of atropisomerization equilibrium within diastereomeric structures contributes to the increasingly popular methodology of dynamic kinetic resolution of biaryls. The modulation of axial chirality is also of vital importance for the creation of molecular switches and machines.6 Furthermore, atropisomers have been employed for the generation of supramolecular chirality.9 Hence, the development of new platforms and mechanisms for the control of atropisomers should be highly desired.

The communication between chiral building blocks, and the ensuing interconversion between stereoisomers triggered by the introduction or removal of external stimulus could afford chirality switches.10 For example, pH-sensitive chiroptical switches were mediated by hydrogen bonding within binaphthyl−bipyridyl cyclic dyads.11 A light-driven halogen-bonded axially chiral switch was reported for supramolecular assembly.12 Circular dichroism (CD) photoswitching was recently accomplished using atropisomeric hemiindigo.13 Although elegant, the switching of axial chirality through the blossoming tool of dynamic covalent chemistry (DCC)14 is rare. Formation and exchange of reversible covalent bonds can create addressable diversity and complexity.15 The interconversion within dynamic covalent systems can further lead to switchable states.16 In this work, the ring fusion DCC partners of amide and aldehyde within atropisomeric biaryls were manipulated for the modulation of axial chirality (Figure 1). Stimuli-responsive control of chiroptical signal was further achieved.

2. RESULTS AND DISCUSSION

We envision that a marriage of atropisomerism and ring-chain tautomeration could offer us a versatile system for harnessing axial chirality (Figure 1). The tunable acidity and rigid planar...
configuration of the amide at position 2 of biaryl would regulate the equilibrium of its intramolecular dynamic covalent reaction (DCR) with the aldehyde at position 2’ (1 and 2). More importantly, the central chirality of the latent hemiaminal stereocenter leads to an energy di

2a

2b

2c

Figure 2. (a) Structures of biaryls studied. (b) 1H-NMR spectra of 2a in CD3CN at rt and 60 °C. (c) Crystal structure of 2a, with both enantiomers shown. Density functional theory (DFT) calculation of two diastereomers of 2a (d) and 2c (e), their transition states (3a and 3c), and associated conversion barrier (in kcal/mol).

gauge the role of the amide, 2c, with a tetrahedral sulfonamide instead of the planar amide of 2a, was selected as a control. The cyclic hemiaminal form dominated for 2a and 2b in acetonitrile, with only a residual amount of aldehyde (Figure 2b). To validate the extent of ring/chain isomerization, the aldehyde and its lactam were equilibrated at 60 °C and analyzed (Figures S2 and S4). The preference of ring form is maintained for 2a and 2b though the ratio of ring/chain isomers varies from rt to 60 °C. Differently, the open aldehyde was favored for 2c (Figure S5). The reversal of ring/chain equilibrium from amide to sulfonamide is consistent with the stronger acidity of the latter.

Attention was then turned to chirality transfer. One stereocenter (i.e., hemiaminal carbon) and one chiral axis will give two enantioselective sets of diastereomers (Figure S6), and the selectivity of chirality induction will be reflected by the diastereomeric ratio (d.r.). Indeed, two sets of NMR peaks were apparent for 2a (see H, H, and H in Figure 2b), with a d.r. around 1.6. A d.r. value of 1.4 was obtained for 2b. Although the biaryl could adopt M or P helicity, the newly created hemiaminal stereocenter leads to an energy difference between two diastereomeric sets (R, P)/(S, M) and (R, M)/(S, P), resulting in a shift of the atropoisomerization equilibrium (Figures 1 and S6).

Our next step was to elucidate the structural basis governing the chirality induction. In the crystal structure of 2a, (R, P)/(S, M) was observed (Figure 2c). Torsion angles of 41 and 35° were adopted for the biphenyl motif and the benzamide fragment (phenyl and its attached amide plane), respectively. Furthermore, the two substituents on the hemiaminal carbon are placed to minimize electrostatic repulsion: hydroxyl away from the benzamide ring, accounting for the diastereoselectivity. (R, P)/(S, M) of 2a were also confirmed as the major diastereomeric set over (R, M)/(S, P) through DFT calculation, with a conversion barrier of 24.0 kcal/mol (3a, the transition state between diastereomers of 2a in Figure 2d). Such a barrier for atropoisomerization is also in line with the existence of two sets of diastereomers for the ring form at rt (i.e., slow interconversion at NMR time scale).

By contrast, there is only one set of NMR peaks for 2c at rt. This was supported by a calculated atropoisomerization barrier of 16.7 kcal/mol (3c, the transition state between diastereomers of 2c in Figure 2e), which indicates a relatively fast inversion and thus the fluxionality of the ring structure. The significant gap between the barrier of 3a and 3c can be attributed to the variation of configurational rigidity between amide and sulfonamide. Furthermore, a more stable diastereomeric set of (R, M)/(S, P) was found for 2c, again different from 2a. The reversal of chirality relay from 2a to 2c was rationalized with the repulsion between lone pairs of oxygen atoms of the sulfonamide and the hydroxyl group. We believe that such a thermodynamic effect is also in consequence of the distinct configuration of sulfonamide and amide, respectively.

Having identified structural foundation dictating intramolecular DCRs and associated axial chirality, we next set out to control it with intermolecular DCRs (Figure 3). Through manipulating dual reactivity17b of equilibrating ring/open forms of 2 (Figure 3a), reversible bonding of a series of alcohols, thiols, and amines was realized (Figures S8–S48). For primary amines, the reaction with aldehyde gave a mixture of imine (4) and its cyclic aminal (5). Aminal (6) was afforded for DCRs with secondary amines, likely via an iminium ion (7). For alcohols and thiols, the reaction can proceed through a cyclic acyliminium ion (8) in the presence of methanesulfonic acid (MA), and cyclic hemiaminal ether (9) and thioether (10) was obtained, respectively. The reversibility of the reaction was confirmed through dynamic component exchange (Figures S45–S48).

The diastereoselectivity of cyclic adducts (6, 9, and 10) was explored further for chirality induction (Table 1). The reaction of 2a and 2-propanol gave only a modest d.r. of 1.4 (Table 1 and Figure 3b). Significantly improved stereoselectivity was found for 10a from 2-propanethiol (d.r. 9.4, Figure 3b). Furthermore, only one set of diastereomers was apparent for DCR of 2a with bulkier secondary amines, such as piperidine (Figure 3b), suggesting nearly perfect chirality transfer (d.r. > 20). In addition, 2b afforded larger d.r. values than 2a (Table 1). In general, a similar trend of d.r. (secondary amine > thiol > alcohol) was observed (Table 1).

Intrigued by the enhancement of diastereoselectivity with increased steric, we were wondering the consequence of chirality transfer within adducts. The helicity of biphenyl is switched from P (2a) to M (9a) with an R configuration for the hemiaminal ether carbon according to X-ray structures (Figures 3c and S49). Analogous (R, M)/(S, P) structures were obtained
two diastereomeric sets was unraveled, respectively (Figures 3d and S50).

The reversal of chirality induction between 2a and its adducts was explained as follows. To accommodate the incorporation of nucleophiles and thus increased steric, the unfavorable electrostatic interaction between the incorporated nucleophile and benzamide would be compromised, leading to the stabilization of (R, M)/(S, P) over (R, P)/(S, M) (Figure 3d). We thereby concluded that the regulation of axial chirality within our dynamic system is thermodynamically, but not kinetically controlled, despite that the barrier of atropisomerization for cyclic adducts can be high, as shown by DFT calculation (28.2, 26.5, and 31.6 kcal/mol for 6a, 9a, and 10a, respectively, Figure S50) in conjunction with VT-NMR (Figure S52). Moreover, the addition of D2O allowed the dissociation of 9a to recover 2a and further validate the dynamic nature of the process (Figures 3b and S53). For control 2c, the relationship of chirality transfer is maintained in its DCRs with nucleophiles (Figures S55).

The next goal was to engineering the CD signal toward a potential chirooptical switch.28 Because aldehydes 1 are racemic, a chiral amine, R-1-phenylethylamine, was attached to the biaryl (11) to impose a chiral bias (Figure 4a and Scheme S2). In CD$_2$CN, the cyclic hemiaminal accounted for only 12% of the population, with modest diastereoselectivity (d.r. 1.3). In sharp contrast, the ring form was overwhelming in CDCl$_3$, and a single diastereomer was nearly obtained (d.r. 16, Figure 4a). DFT calculation of four diastereomers, (R, S, M), (R, S, P), (R, R, M), and (R, R, P), revealed the significant contribution of only two ((R, S, P) and (R, R, M)), thereby supporting two sets of resonances in NMR (Figures 4b and S107). X-ray structure of 11 supports the existence of a diastereomer (R, R, M) (Figures 4b and S59). The central-to-axial chirality transfer is reversed from 2a ((R, P) and (S, M)) to 11 ((R, R) and (S, P)), which results from the unfavorable steric interaction between bulky 1-phenylethylamine and hydroxyl, hence echoing the regulation of axial chirality through varying steric.

Finally, CD spectra were measured to transduce chirality relay into chiroptical outputs. Gratifyingly, strong positive Cotton effect around 260 nm was observed for 11 in CHCl$_3$ (Figure 4c). However, only a weak signal was found in CH$_2$CN. Upon DCRs with 2-propanol, 2-propanethiol, or piperidine in CH$_2$CN, the magnitude of CD spectra was amplified (12−14, Figure 4d) and also consistent with the trend of d.r. values of corresponding assemblies (Figures S60−S62). For example, the adduct of 11 and piperidine gave a negative Cotton effect at 270 nm. With the addition of acid MA, the signal was suppressed, as the protonation of amine resulted in the reversal of the DCR (Figures 4e, S63 and S64). The use of Et$_3$N enabled the recovery of the assembly and thus CD spectra. In a similar way, turning on/off of CD signal was achieved through redox-controlled switching of DCR of 11 and thiol (Figures S65 and S66). Tying it all together, the chiroptical signal can be facilely regulated through a variety of means, including changing solvents, DCRs, and the switching of DCRs.

3. CONCLUSIONS

In summary, a dynamic covalent chemistry constrained biaryl platform was developed for the regulation of axial chirality. 2-Carboxyamide-2’-formylbiaryl derivatives allowed the modulation of the equilibrium between open aldehyde and its cyclic hemiaminal. Moreover, the extent and structural basis of central-to-axial chirality transfer were elucidated. Through reversible
covalent bonding of alcohols, thiols, and secondary amines, the reversal of chirality relay and thus modulation of axial chirality was further accomplished. Finally, by introducing a chiral bias stimuli-responsive control of the chiroptical signal was readily achieved. The strategies and results reported should be intriguing to future studies of asymmetric catalysis, molecular switches, and intelligent materials.

4. MATERIALS AND METHODS

4.1. Materials. CDCl₃, CD₃CN, and DMSO-d₆ were purchased from Aldrich. All other reagents were obtained from commercial sources and were used without further purification unless indicated otherwise.

4.2. General Methods. NMR spectra were recorded on a Bruker Biospin avance III spectrometer (400 MHz for ¹H and 100 MHz for ¹³C). The chemical shifts (δ) for ¹H NMR spectra, given in ppm, are referenced to the residual proton signal of the deuterated solvent. Mass spectra were recorded on a Bruker IMPACT-II spectrometer. Crystallographic data were collected on a Mercury single crystal diffractometer at room temperature. The structures were solved with direct methods using OlexSys or SHELXS-97 and refined with the full-matrix least-squares technique based on F² using the OlexSys or SHELXL-97. Circular dichroism (CD) spectra were recorded on a BioLogic MOS-450 spectropolarimeter.

4.3. Synthesis. Compounds 2a, 2b, 2c, and 11 were prepared by Suzuki coupling (Schemes S1 and S2). Experimental details can be seen in the Supporting Information.

4.4. Dynamic Covalent Reactions (DCRs). DCRs were performed in situ in CD₃CN without isolation and purification. To a stirred solution of 2 (∼25 mM, 1.0 equiv) in CD₃CN (0.60 mL) were added one mononucleophile (ROH (3.0 equiv), RSH (3.0 equiv), R₁R₂NH (3.0 equiv), or RNH₂ (1.2 equiv)), and activated 3 Å molecular sieves (MS, 4–8 mesh). For ROH and RSH, methanesulfonic acid (MA, 1.0 equiv) was also added. The mixture was stirred for 20 h and characterized by ¹H NMR and electrospray ionization mass spectroscopy. CD spectra were recorded at 25 °C after the solutions of DCRs of 11 with different nucleophiles were diluted with acetonitrile. See specific conditions in figure captions of the main text or the Supporting Information if necessary.

4.5. DFT Calculations. All calculations were performed using Gaussian 09 packages.¹⁹ Geometry optimization and the calculation of single point energy were run using the density functional theory method (M06-2X) with the basis set of 6-31G** and 6-311++G**, respectively. A solvent model for acetonitrile (polar continuum model) was used. Minima were confirmed by vibration calculations without imaginary vibrational frequencies. The conformational search was conducted for 2a, 2c, 6a, 9a, 10a, 10c, and 11, and the most stable
conformer of each diastereomeric set was then calculated and listed. The transition state for the atropisomerization of 2a, 2c, 6a, 9a, and 10a was calculated and validated with only one imaginary vibration.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01273.

Experimental details, X-ray, NMR and CD data, and DFT calculations (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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