1,2,3-Triazoles
1,5-Di-substituted
Atropisomers
Axial chirality

Most stable

C-N Restricted Rotation

C-C Restricted Rotation
Enantiomer stability of atropisomeric 1,5-disubstituted 1,2,3-triazoles

Fernanda Meloni, (a) William D. G. Brittain, (a,b) Louise Male, (c) Cécile S. Le Duff, (d) Benjamin R. Buckley,* (e) Andrew G. Leach, * (f) and John S. Fossey * (a)

(a) School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, U.K.
(b) Present Address: Department of Chemistry, Durham University, Durham, DH1 3LE, U.K.
(c) X-Ray Crystallography Suite, School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, U.K.
(d) NMR Spectroscopy Suite, School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, U.K.
(e) Department of Chemistry, Loughborough University, Loughborough, Leicestershire, LE11 3TU, U.K.
(f) School of Health Sciences, Stopford Building, The University of Manchester, Oxford Road, Manchester M13 9PT, U.K.

Abstract

The synthesis and characterisation of axially chiral atropisomeric 1,5-disubstituted 1,2,3-triazoles is reported. Molecules designed to display restricted rotation about 1,2,3-triazole N-1-aryl or 1,2,3-triazole C-5-aryl bonds were investigated by physical and computational techniques. The barrier to 1,2,3-triazole N-1-aryl rotation was found to be higher than that for 1,2,3-triazole C-5-aryl rotation, confirming axial chirality stemming from restricted rotation about an N-1-aryl bond in a 1,5-disubstituted 1,2,3-triazole to be the most suitable for the development of an axial chirality triazole-based platform.

Introduction

Compounds that are chiral by virtue of restricted single bond rotation are among those said to display axial chirality.1–3 The stability of these atropisomers (from the Greek prefix atrops, “not turning”)4 is determined by the magnitude of the rotational barrier $\Delta G^\circ$. The barrier to rotation can be influenced by factors such as the degree of steric hindrance, inter- and intramolecular interactions, temperature and the solvent.5 A generally accepted definition of an atropisomer is a compound where the single bond whose rotamers are stereoisomers of each other and the half-life for their interconversion is at least 1000 s (16.7 min), at a given temperature. In principle, this allows sufficient time to carry out a routine physical separation of the enantiomeric rotamers (i.e. atropisomers), thus implying, at room temperature, $\Delta G^\circ$ should be at more than about 22 kcal·mol$^{-1}$ for the interconversion of these stereoisomers by, overall, single bond rotation to impart functional and physically manageable axial chirality upon the system.6
Many natural products exhibit axial chirality, for example marinopyrrole A (1), gossypol (2), viriditoxin (3), and allocolchicine (4) contain a single bond between two sp² atoms whose restricted rotation and non-zero dihedral angle between substituents in a stable conformation confers axial chirality upon them (Figure 1). Axially chiral compounds are finding ever more utility in stereoselective synthesis, particularly as chirality platforms in drug discovery and asymmetric catalysis. Organocatalysts, such as chiral phosphoric acid derivatives 5, chiral ammonium salts 6, and chiral ligands BINOL 7a and BINAP 7b, QUINAP derivatives 8a-c, and StackPhos 9, are finding applications in these areas.
ammonium salts and chiral ligands including BINOL, BINAP, QUINAP and StackPhos all exploit restricted rotation about a single bond between two sp\(^2\) atoms to engender asymmetry and thus impart further asymmetry in the products of the reactions they have been reported to catalyse. In contrast to well-reported examples of chirality arising because of restricted rotation between two six-membered rings, atropisomerically pure axially chiral compounds with the chirality-conferring restricted bond rotation being to or between five-membered rings are relatively under-reported.

The 1,2,3-triazole represents a five-membered heterocycle that has seen increasing interest in a variety of applications. Disubstituted 1,2,3-triazoles are most frequently reported as 1,4-disubstituted 1,2,3-triazoles (12) and somewhat less frequently as regio-isomeric 1,5-disubstituted 1,2,3-triazoles (13). Such triazoles have found wide-ranging application beyond serving as linking motifs, displaying intra- and intermolecular interactions resulting in a myriad of functional and scaffolding applications in supramolecular, coordination, medicinal, drug discovery, sensor and catalytic chemistries. These triazoles are stable at elevated temperatures and under biological conditions rendering them amenable to development for applications in materials and chemical biology.

The synthesis of 1,2,3-triazoles was first reported under thermal conditions via the (since-named) Huisgen 1,3-dipolar cycloaddition between azides and alkynes to access mixtures of 1,4-disubstituted 1,2,3-triazoles (12) and 1,5-disubstituted 1,2,3-triazoles (13). The low regiochemical control (1.6:1.0 ratio of 12:13) of this reaction led to the search for catalysts to promote variants of the dipolar cycloaddition between alkynes and azides. The most successful variant was reported in 2002 by both Sharpless and co-workers and Meldal and co-workers, where copper-catalysed 1,2,3-triazole formation was achieved under mild conditions. The copper-catalysed azide-alkyne cycloaddition (CuAAC) has become the most well-known and utilised protocol for accessing 1,4-disubstituted 1,2,3-triazoles (12). Despite being one of a number of click reactions the CuAAC is often referred to as “the click reaction” after it was included in Sharpless and co-workers’ seminal introduction of “click chemistry” as a concept. The CuAAC is widely utilised as a universal linking strategy, it can be carried out at room temperature in benign solvents and is compatible with in vivo use, giving exquisite regiochemical control in the 1,4-disubstituted triazole products (1:0 12:13, Scheme 1). Whilst the CuAAC provides unparalleled facile access to 1,4-disubstituted 1,2,3-triazoles, 1,5-disubstituted analogues are less-frequently reported. Among the protocols available for the synthesis of 1,5-disubstituted triazole derivatives are the in situ generation of metallo-alkyne reagents by treatment of a terminal alkyne with organo-magnesium (Grignard) and
organo-zinc\textsuperscript{61} reagents, which upon reaction with an azide (10) form exclusively 1,5-disubstituted-1,2,3-triazoles (0.0:1.0 12:13). Ruthenium- and nickel- catalysed azide-alkyne cycloaddition reactions, RuAAC\textsuperscript{62-64} and NiAAC\textsuperscript{46, 65} respectively (Scheme 1) also offer access to 1,5-disubstituted 1,2,3-triazoles.

Despite the prevalence of reports of 1,2,3-triazoles it is somewhat surprising that examples of well-characterised axially chiral atropisomeric compounds featuring a rotationally restricted, non-zero dihedral angle, bond to or from 1,2,3-triazoles are scarce and, despite two notable examples (14)\textsuperscript{66} and (15)\textsuperscript{67} they are mostly limited to 5-5'-bistriazoles (16 and 17) (Figure 2).\textsuperscript{36, 68-70} Notably their chirality is conferred by restricted rotation about a bond with C5 of the 1,4,5-trisubstituted 1,2,3-triazole(s) in question.

\textbf{Scheme 1.} 1,2,3-Triazole-forming azide (10) - alkyne (11) cycloaddition reactions giving mixtures of 1,4- and 1,5-disubstituted products (12 and 13 respectively) under metal-free (thermal) conditions, in contrast to the exclusive formation of the 1,4-disubstituted isomer (12) under copper-catalysed conditions or highly selective formation of the 1,5- isomer (13) under control of ruthenium or nickel catalysis or magnesium or zinc stoichiometric promotors.

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
\textbf{12:13} & Conditions & 1,4-Di-substituted 1,5-Di-substituted \\
\hline
1.6 : 1.0 & Thermal, catalyst-free & 1,2,3-triazole 1,2,3-triazole \\
1.0 : 0.0 & CuAAC, copper-catalysed & 1,2,3-triazole \\
0.0 : 1.0 & RuAAC, ruthenium-catalysed & 1,2,3-triazole \\
0.0 : 1.0 & NiAAC, nickel-catalysed & 1,2,3-triazole \\
0.0 : 1.0 & MeMgBr, Grignard-mediated & 1,2,3-triazole \\
0.0 : 1.0 & Et\textsubscript{2}Zn, alkyl zinc-mediated & 1,2,3-triazole \\
\hline
\end{tabular}
\end{center}

\textit{Figure 2.} Previously reported chiral atropisomeric 1,4,5-trisubstituted 1,2,3-triazoles 14-17 whereby the restricted bond conferring chirality is a C-C bond to the 5-position of said 1,2,3-triazole.\textsuperscript{36, 66-70}
Authors of this report have previously investigated and surveyed 1,2,3-triazoles as scaffolds for sensor assembly,71-74 as ligand platforms,75, 76 in asymmetric synthesis77-79 and as linkers,80, 81 and in this report axial chirality of atropisomeric 1,5-substituted 1,2,3-triazoles is probed.

**Results and Discussion**

In order to probe axial chirality through restricted bond rotation at the 1- or 5- positions of 1,5-disubstituted 1,2,3-triazoles, appropriate functional groups were contemplated. Such compounds should be sterically congested, synthetically accessible and offer spectroscopic handles by which to probe asymmetry.

![Figure 3. Hypothesised features of 1,5-disubstituted 1,2,3-triazoles that may display axial chirality about an sp²-sp² bond from either N-1 or C-5 of the triazole to a non-symmetric aryl group. The hypothesised compound includes potentially diastereotopic functionality (arbitrarily depicted as a methylene group CH₂H₂).](image)

At least one functional group should be bound to the triazole via an sp² atom and that sp² atom must be diisymmetrically substituted (such that restricted rotation leads to the formation of non-planar, chiral products). The second substituent at the remaining 1- or 5- position of the 1,2,3-triazole ought to be both bulky enough to offer steric constraints to rotation of its sp²-sp² conjoined neighbour and include diastereotopic functionality (e.g a CH₂ methylene group) as a NMR spectroscopic handle (Figure 3). NMR-active nuclei-containing diastereotopic groups offer two opportunities to probe any resulting axially chiral materials: (i) observation of two distinct signals for the groups (e.g. the protons of a CH₂ group) provides compelling evidence that the molecule is chiral with rotation perturbed to such an extent that their difference is witnessable on the NMR-timescale; (ii) temperature- (and other condition-) dependence of the observation of one versus two signals (with emergence of any evidence of the environments not being equivalent) may corroborate the lack or presence of chirality and/or rapid (racemisation) and slow (stable axial chirality) rotation about the sp²-sp² bond in question. Two series of 1,5-disubstituted 1,2,3-triazoles were initially proposed (Scheme 2): (i) a corresponding triazole is formed from an appropriate aryl-alkyne and a methylene-appended azide, resulting in a 1,5-disubstituted product with a potentially restricted C(sp²)-C(sp²) bond at the C-5 position and a methylene-bearing group with potentially diastereotopic protons therein appended to the N-1 position 18 (C-Ar); and (ii) the isomeric 1,5-disubstituted product
whereby a methylene-appended alkyne and an appropriate aryl-azide are reacted under 1,5-triazole-forming conditions to furnish a product with a potentially rotation-restricted chirality-conferring N(sp²)-C(sp²) bond appended to N-1 of the triazole and potentially diastereotopic protons appended to the C-5 position {19 (N-Ar)}.

\[
\begin{align*}
\text{(i)} & \quad \text{Ar} \equiv + \quad \text{N}_3 \\
\text{(ii)} & \quad \text{R}^1 \equiv \quad \text{Ar} \quad + \quad \text{N}_3 \\
\end{align*}
\]

Scheme 2. Proposed syntheses of 1,5-disubstituted 1,2,3-triazoles with: (i) a C-C restricted-rotation bond and a CH₂ group attached to N-1 \(18 \text{(C-Ar)}\); and (ii) a C-N restricted-rotation bond and a CH₂ group attached to C-5 \(19 \text{(N-Ar)}\).

Benzyl and 2-methyl-1-substituted naphthalene were initially selected as functional groups offering desired features potentially capable of conferring and reporting on chirality of corresponding 1,5-disubstituted 1,2,3-triazoles. Starting with benzyl azide \(20\) and 1-ethynyl-2-methyl naphthalene \(21\) both the 1,4-(control) and 1,5-(probe) disubstituted triazoles \(22\) (23% yield) and \(23\) (67% yield) were prepared by a CuAAC and by treatment with methylmagnesium bromide respectively (Scheme 3, upper and middle respectively). Since 1,4-disubstituted \(22\) does not feature contiguous substitution about the triazole core, no rotation-restriction is expected at room temperature, and it therefore serves as an achiral control. Whilst 1,5-disubstituted \(23\) was successfully prepared by stoichiometric addition of organomagnesium compounds it is noteworthy, that in our hands, a ruthenium-catalysed alkyne-azide cycloaddition (RuAAC)⁶⁴ protocol gave only trace amounts of the desired product. It had been noted by Mahadari et al. that sterically demanding substrates tend to under-perform in RuAAC reactions where bulky substituents are desired about 1,5-disubstituted 1,2,3-triazoles.⁸² A RuAAC approach was suspended in favour of the higher-yielding magnesium-mediated method that successfully delivered \(23\). Prop-2-yn-1-yl benzene \(24\) and 1-azido-2-methyl naphthalene \(25\) were reacted via a diethyl zinc protocol to give regioisomeric product \(26\) in 34% isolated yield (Scheme 3, lower).
Scheme 3. Upper: Reaction of 20 and 21 under conditions (a) Copper sulfate pentahydrate (20 mol%), sodium ascorbate (20 mol%), DMF, MW 150 °C, 30 min resulting in isolation of 22 in 23% isolated yield; middle: Reaction of 20 and 21 under conditions (b) Methylmagnesium bromide (3.0 M in hexane), THF resulting in isolation of 23 in 67% isolated yield; lower: Reaction of 24 and 25 under conditions (c) Diethyl zinc (1.0 M in hexane), NMI (20 mol%), THF resulting in isolation of 26 in 34% isolated yield.

Inspection of the methylene region of the proton NMR spectra of (i) 22; (ii) 23 and (iii) 26 in chloroform-\(d\) at room temperature (Figure 4, left, middle and right respectively), shows (i) a singlet with an integration corresponding to two protons (protons labelled \(H^a\) and \(H^b\)), consistent with 22 being an overall achiral molecule; (ii) and (iii) (23 and 26, respectively) both revealed a pair of one-proton doublets in each spectrum, displaying \(2J\) coupling values diagnostic of the methylene group's protons (labelled \(H^a\) and \(H^b\)) both being rendered diastereotopic as a result of being in a chiral environment. Thus, 1,4-disubstitued 22 does not display functional axial chirality whilst both 1,5-regio isomers 23 and 26 are axially chiral, on the NMR timescale.\(^{83}\)
Figure 4. Regions of the proton NMR spectrums of 22, 23 and 26, recorded in CDCl₃ at room temperature; (i) a single resonance arising from equivalent methylene protons $H^a$ and $H^b$ in achiral 22; (ii) two doublets corresponding to diastereotopic methylene protons $H^a$ and $H^b$ in chiral 23; and (iii) two doublets corresponding to diastereotopic methylene protons $H^a$ and $H^b$ in chiral 26.

It was reasoned that recording a proton NMR spectrum at elevated temperature may lead to coalescence of diastereotopic signals, through which a barrier to enantiomer interconversion could be determined. As such compound 23 was subjected to proton NMR analysis in tetrachloroethane-$d_2$ (TCE) at elevated temperatures in 10 °C steps from 20 to 100 °C. Pleasingly for this study the benzylic methylene protons $H^a$ and $H^b$ did not coalesce over this range. Changing the solvent to toluene-$d_8$ elicited no significant changes, suggesting that the barrier to rotation of 23 in deuterated TCE or toluene is at least 24 kcal∙mol⁻¹ (see supplementary details for stacked plots).

Regioisomeric, axially chiral, 1,5-disubstituted 1,2,3-triazoles 23 and 26 could be resolved by analytical HPLC on a chiral stationary phase (Lux Phenomenex Cellulose-1, water/acetonitrile, Figure 5 (i) and (ii) respectively). In both cases, the lack of an obvious plateau between adjacent peaks corresponding to enantiomers (i.e. “batman peak” indicative of on-column enantiomer interconversion)⁸⁴ is consistent with atropisomeric stability.
Scalemic samples of 23 and 26 were obtained by preparative HPLC using a chiral stationary phase (95 and 60% e.e. respectively). These samples were used to experimentally determine barriers to rotation about the triazole-aryl bond conferring axial chirality upon them (enantiomer interconversion), by HPLC analysis. Samples were hence dissolved in acetonitrile and the resulting solutions heated at 70 °C for eight hours, under which conditions analytical HPLC analysis revealed enantiopurity of C-C axially chiral 23 was eroded, whereas the enantiopurity of N-C axially chiral 26 was essentially unchanged. To witness a significant reduction in the e.e. of 26 an acetonitrile solution of scalemic material needed to be heated at 80 °C for more than 100 hours. As such, aliquots of acetonitrile solutions of 23 or 26 (that were being heated at 70 or 80 °C respectively) were collected at regular intervals and the e.e. of the solutions measured by chiral HPLC analysis (Figure 6). Deploying the Eyring equation allowed respective barriers to rotation (enantiomer interconversion) to be assessed as 25.9 kcal·mol⁻¹ and 29.0 kcal·mol⁻¹ for (C-C axially chiral) 23 and (C-N axially chiral) 26 respectively. Assuming that ΔS° for bond rotations is expected to be small,85 ΔG° is expected to vary little with temperature, so that, on a first approximation, the ΔG° obtained can be compared to computed values discussed later.
To explore these barriers in more detail and to establish the structural features that increase and decrease the barriers, density functional theory calculations were performed. Initial calculations employed the restricted Hartree-Fock (RHF) method combined with dihedral rotational scans to provide connection to earlier studies, and these also yielded geometries that were subsequently optimised with M06-2X/6-31+G*, permitting the computation of free energy barriers that could be compared with those measured. This level of theory was designed to provide good agreement with barrier heights. Solvation was included via the integral equation formalism polarisable continuum model (IEFPCM) protocol and included parameters appropriate to acetonitrile. All calculations were performed in Gaussian. In the studies of C-C axially chiral 23 (Figure 7, upper panel), it was found that there are two alternative transition states for rotation; the one in which the benzyl group passes the methyl group is the lowest energy (a dihedral N-C-C-C angle about the bond conferring axially chirality of +172.6°)
[akin to a pseudo planar +180° dihedral angle]), and is calculated to represent a free energy barrier of 30.0 kcal∙mol⁻¹. The transition state to enantiomer interconversion, by single bond rotation, where the benzyl group passes the peri-CH of the naphthalene ring (dihedral N-C-C-C angle about the bond conferring axially chirality -15.2° [analogous to pseudo planar Θ° dihedral angle]) is 2.8 kcal-mol⁻¹ higher in energy. In equivalent studies of 26 (Figure 7, lower panel), the preference is reversed, and the barriers are higher. The transition state that sees the benzyl group passing the peri-CH (a dihedral N-N-C-C angle about the bond conferring axially chirality of +199.7° [similar to a pseudo planar +180° dihedral angle]) corresponds to a free energy barrier of 33.2 kcal∙mol⁻¹, while that in which it passes the methyl group (a dihedral N-N-C-C angle about the bond conferring axially chirality of +7.7° [comparable to a pseudo planar Θ° dihedral angle]) is at 35.2 kcal-mol⁻¹.
Both the experimentally and computationally determined barriers to atropisomer interconversion concur that axial chirality about the triazole-aryl C-C bond in 23 (25.0 and 30.0 kcal·mol⁻¹ respectively) is less stable than in regioisomeric triazole-aryl N-C 26 (29.0 and 33.2 kcal·mol⁻¹ respectively). This implies that N-C triazole-aryl axial chirality is inherently more stable to enantiomer interconversion than regioisomeric C-C triazole aryl bonds. However, the
computed barriers remain somewhat higher than those determined experimentally. To address this, a number of alternative functionals were explored in order to assess whether any might be more appropriate for computing this type of barrier. Given the significant change between the minimum and the transition state in terms of steric clashing and conjugation, correctly accounting for these barriers is likely challenging and so alternative functionals are worth evaluating. The functionals listed in Table 1 were paired with the 6-31+G** basis set and the IEFPCM solvation model (again with default settings for acetonitrile). Given that the experimental measurements employed temperatures of 343 K (70 °C) and 353 K (80 °C), free energies at both temperatures were computed, as well as at 298 K for comparison. These calculations revealed that all levels over-estimate the height of the barrier and that in terms of closest agreement to the two barrier heights, PBE1PBE is marginally the best but because of the good agreement in terms of absolute and relative barrier height, the B97D level of theory (entry 4) was selected as most appropriate for ranking the impact of changes in structure on rotational barrier.

### Table 1. Free energy barrier to rotation computed with a range of functionals. These were paired with the 6-31+G** basis set and IEFPCM solvation for acetonitrile. Energies are in kcal∙mol⁻¹.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Functional</th>
<th>298 K</th>
<th>343 K</th>
<th>353 K</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M06-2X</td>
<td>30.0</td>
<td>30.2</td>
<td>30.3</td>
</tr>
<tr>
<td>2</td>
<td>B3LYP</td>
<td>28.3</td>
<td>28.6</td>
<td>28.6</td>
</tr>
<tr>
<td>3</td>
<td>B3LYP-D3</td>
<td>29.5</td>
<td>29.7</td>
<td>29.7</td>
</tr>
<tr>
<td>4</td>
<td>B97D</td>
<td>27.6</td>
<td><strong>27.8</strong>&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>27.9</td>
</tr>
<tr>
<td>5</td>
<td>M06</td>
<td>28.6</td>
<td>28.9</td>
<td>28.90</td>
</tr>
<tr>
<td>6</td>
<td>PBE1PBE</td>
<td>28.9</td>
<td>28.3</td>
<td>28.3</td>
</tr>
</tbody>
</table>

<sup>(a)</sup> Experimentally determined barrier at 343 K = 25.0 kcal∙mol⁻¹; <sup>(b)</sup> Experimentally determined barrier at 353 K = 29.0 kcal∙mol⁻¹

To probe the potential for rendering 1,4,5-tri-substituted 1,2,3-triazoles chiral by virtue of inclusion of a 5-substituent (versus achiral 1,4-disubstituted analogue 22) compound 28 bearing a 5-iodosubstituent was prepared in four steps, in a 10% isolated yield (Scheme 4(i)). Analysis of the resulting proton NMR spectrum of 28 (Figure 8(i)) shows two roofed doublet signals for the benzylic methylene protons, confirming that (unlike 22) 28 can be regarded as chiral and stable on the NMR timescale.
Four 5-aryl 1,5-disubstituted 1,2,3-triazoles were prepared by a stochiometric magnesium-meditated method (34-37, Scheme 4(ii)).\textsuperscript{69} Compound 34 is a methylene-cyclohexyl analogue of benzyl appended 23, which similarly to compound 23, also displays evidence of room temperature NMR spectroscopy-detectable chirality (Figure 8(ii)), whereby the methylene protons appear as distinct signals showing geminal and vicinal coupling appearing as two roofed doublet of doublets. Compound 35 includes aryl groups at both the 1- and 5-positions of a 1,2,3-triazole core. The 5-C-substituent is a dissymmetric 2-bromo 6-methyl phenyl group whose restricted rotation confers chirality upon the molecule as determined by desymmetrising in the proton NMR spectrum (Figure 8(iii) and (iv)) of the 2- and 6-isopropyl groups attached to the 1-N-phenyl substituent. The proton NMR spectrum of 35 features two septet signals and four doublets corresponding to the (i) CH and (ii) CH\textsubscript{3} groups of the desymmetrisated isopropyl groups, respectively. Compound 36 includes a 1-N-benzyl group...
alongside a 5-C-aryl group that is also doubly ortho-substituted, which incorporates an ortho-tolyl group. The presence of two aryl-bonds with the potential for restricted rotation is confirmed by proton NMR spectroscopic evidence of a 1.0:1.7 mixture of diastereoisomers (Figure 8(v)). Whilst the preference for the formation of a major diastereoisomer was intriguing this has not been stereochemically assigned or further elaborated at this stage. For compound 37, where the 5-C-aryl fragment is a 2-methoxy-6-methyl phenyl group, clear evidence for chirality is evidenced by observation of resonances corresponding to diastereotopic benzylic protons at the 1-N-position (Figure 8(vi)).

Two 1-N-aryl 5-C-alkyl analogues of 5-C-benzyl-containing 26 (40 and 41) were prepared by a zinc-mediated method (Scheme 4(iii)).\textsuperscript{51} It was not possible to observe evidence of compounds 40 and 41 being potentially chiral by restricted N-C triazole-aryl bond by proton NMR spectroscopy methods (Figure 8(vii) and (viii)). In these cases where isochronism was observed, analytical HPLC with a chiral stationary phase analysis was used which revealed two sharp peaks consistent with the presence of stable enantiomers for both compounds 40 and 41 (Figure 9(i) and (ii) respectively). Additionally, whilst compound 28 was resolved by HPLC with a chiral stationary phase, e.e. readily eroded at room temperature (see supplementary material for details).
Figure 8. Regions of the proton NMR spectrums of the compounds synthesised in Scheme 4 corresponding to potentially diagnostic environments capable of revealing a diastereotopic nature in said spectral analysis, CDCl₃ 298 K: (i) 28; (ii) 34; (iii) 35 (CH₂); (iv) 35 (Me); (v) 36 (d.r. 1.0:1.7); (vi) 37; (vii) 40; (viii) 41.
Single crystals, suitable for molecular structure determination by X-ray diffraction (XRD) were obtained by slow evaporation of dichloromethane in hexane for racemates (C-C axially chiral) 23 and (N-C axially chiral) 41 (Figure 10 (i) and (ii) respectively). Both the C-linked (23) and N-linked (41) triazole-aryl motifs adopt similar orientations in the solid state and the respective methylene substituents (phenyl and cyclohexyl) are broadly presented in the same orientation. Torsion angles ascribed as +65.82 (14)° versus -96.14 (13)° respectively represent a thirty-degree deviation in real terms from one another (see supplementary material for convention defined here for ascribing sign +/- to dihedral angle). Thus, in the solid state, whether C-C or N-C axially chiral and aromatically or aliphatically substituted the conformations of these compounds are strikingly similar. Notably, and as anticipated, the C-C triazole-aryl bond of 23 is longer than the corresponding N-C triazole bond of 41 (C1-C10 = 1.4780 (15) Å versus N1-C10 = 1.4352 (15) Å respectively).
Figure 10. Representation of one molecule within the unit cell of the single crystal X-ray diffraction structures, most hydrogen atoms omitted for clarity, ellipsoids plot at 45% probability. Rendered in PovRay from coordinates generated in Ortep III for Windows, selected bond lengths, angles and torsions from the molecule of the unit cell depicted: (i) 23 (rac), C1-C10 bond length = 1.4780 (15) Å, N1-C1-C2 bond angle = +103.49 (10)º and N1-C1-C10-C15 torsion = 65.82 (14)º. Hydrogen atoms were fixed as riding models with the isotropic thermal parameters (Uiso) based on the Ueq of the parent atom.; (ii) 41 (rac), N1-C10 bond length = 1.4352 (15) Å, N2-N1-C1 bond angle 111.24 (10)º and N2-N1-C10-C15 torsion = -96.14 (13)º. Methyl hydrogen atoms bonded to C20 are disordered over two positions at a refined percentage occupancy ratio of 51.8 (19) : 48.2 (19), with one set of three protons being arbitrarily depicted, and these and all other hydrogen atoms in the structure were fixed as riding models with the isotropic thermal parameters (Uiso) based on the Ueq of the parent atom.

Having correlated modelling approaches to experimentally determined barriers for atropisomer interconversion (for compounds 23 and 26) the barriers to enantiomer interconversion (racemisation) for the remaining synthesised compounds were determined using the B97D level of theory with acetonitrile solvent parameters (computed barriers to rotation at 298 K are given in Table 2, see entries 2 and 3 for compounds 23 and 26 respectively). Compound 22, a 1,4-disubstituted triazole that would not be expected to display stable chirality, was calculated to have the lowest barrier among those determined in this study (7.1 kcal-mol⁻¹, Table 2, entry 1). The addition of iodide at the 5-position (28) had already rendered the methylene protons diastereotopic by proton NMR spectroscopic analysis, and a corresponding computed barrier to rotation was found to be more than three times higher (25.3 kcal-mol⁻¹, Table 2, entry 4). The three compounds with a methyl substituted naphthyl group at the 1-N-triazole position conferring axial charity upon them with CH₂-R motifs at the 5-C-triazole position (R = Ph (26), n-Pr (40) and Cy (41)) were calculated to have the highest barriers to enantiomer interconversion of ~32 kcal-mol⁻¹ (31.8 (Table 1), 31.9 and 32.4 kcal-mol⁻¹
1 for 26, 40 and 41, Table 2, entries 3, 9 and 10 respectively). Compound 23 and its cyclohexyl-containing congener 34 were computed to have lower, albeit similar, barriers to enantiomer interconversion (27.6 kcal\textpercmol\textsuperscript{-1}, Table 1 and 26.4 kcal\textpercmol\textsuperscript{-1}, Table 2, entries 2 and 5 respectively). Triazoles with chirality-conferring dissymmetric 2,6-disubstituted phenyl groups at the 5-C-triazole position (35-37) were calculated to have somewhat lower barriers to enantiomer interconversion (20.6, 23.0 and 19.6 kcal\textpercmol\textsuperscript{-1}, Table 2, entries 6, 7 and 8 respectively). Given barriers to epimerisation, and thus enantiomer stability, are greater for C-N rotation-restricted triazoles over C-C rotation restricted triazoles, nitrogen’s lone pair in the 2-position, as well as N-C versus C-C bond length, may contribute to the observed trends in enantiomer stability.\textsuperscript{93, 94}

Upon visual inspection of the computed two lowest barriers to enantiomer interconversions it can be observed that 1,4-disubstituted triazoles (Table 2, entries 1 and 11, compounds 22 and 42 with a triazole-aryl C-C and N-C bond respectively) have a lower barrier with the CH proton of the triazole presented towards the methyl group of the aryl fragment. Compound 28 (Table 2, entry 4), is the 5-iodo analogue of compound 22, wherein the energy lower transition state arises from an orientation with iodine pointing away from the methyl substituent of the aryl fragment. Whilst the barrier is too low to lead to observable chirality at room temperature, the overall structural shape of the transition state for interconversion has substituents in approximately equivalent positions. The 1,5-disubstituted triazoles with N-C triazole-aryl bond restriction leading to chirality (Table 2, entries 3, 9 and 10, compounds 26, 40 and 41 respectively) have a lower barrier where the triazoles 2-N nitrogen is presented towards the 2-methyl substituent of the aryl fragment. In all but the case of compound 23 (Table 2, entry 2) C-C triazole-aryl 1,5-disubstituted triazoles show a similar motif for the lowest barrier to enantiomer interconversion, namely the CH proton of the triazole is presented towards the methyl group of the aryl fragment.

\textit{Table 2.} Computed barriers to atropisomer interconversion (kcal\textpercmol\textsuperscript{-1}) by triazole-aryl single bond rotation at 298 K, in acetonitrile, using the B97D level of theory for compounds 22, 23, 26, 28, 34-37, 40-42. See supplementary material for coordinates and ground states.

<table>
<thead>
<tr>
<th>Entry</th>
<th>~0 ° dihedral transition state\textsuperscript{(a)}</th>
<th>~180 ° dihedral transition state\textsuperscript{(a)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /> 7.1 kcal\textpercmol\textsuperscript{-1}</td>
<td><img src="image2.png" alt="Image" /> 9.6 kcal\textpercmol\textsuperscript{-1}</td>
</tr>
</tbody>
</table>
To computationally elaborate upon the N-C versus C-C triazole-aryl rotational barrier, the barrier to rotation of 1,4-substituted 1,2,3-triazole 42 was investigated. Compound 42 is an analogue of the synthesised 1,4-disubstituted 22 wherein the benzyl and naphthyl motifs are swapped (Table 2, entry 11). The computed barrier to rotation for the N-aryl 42 was twice as high as that for the C-aryl isomer 22 (15.1 versus 7.1 kcal·mol⁻¹), which is consistent with aforementioned observations of greater barriers to rotation for N-aryl substituted triazoles.

**Conclusion**

Ten 1,2,3-triazoles were synthesised to investigate features pertaining to the potential for such triazoles to be (usefully) axially chiral. The measured and computed barriers to enantiomer interconversion along with solid state measurements (Figure 10) are consistent with the propensity for Csp²-Nsp² bond lengths to typically be shorter than Csp²-Csp² bonds,⁹⁵ consequently providing a greater steric barrier to rotation in the N-aryl axially chiral systems. This appears to dominate over other parameters that might lead to increasing or decreasing the barrier to enantiomer interconversion, suggesting the best candidates for further exploration of stable triazole axial chirality to be 1-aryl 5- (at least) di-substituted 1,2,3-triazoles. Whilst the barriers to racemisation of these compounds do not yet challenge the stability of biaryls like BINOL (barrier of 37-38 kcal·mol⁻¹),⁹⁶,⁹⁷ the intermediate/hemi stability
may be of use in transient or switchable state arenas and offers a platform from which to develop ever more robust and applicable chemistries upon the triazole stage.

**Supplementary material**

A file containing synthetic procedures and experimental data thereof, spectrums and chromatograms, XRD data and computational coordinates is available. The supplementary material file includes additional references cited therein.\textsuperscript{98-116} Summaries of crystal structure data are included, and full datasets may be accessed at CCDC deposit numbers CCDC 2111317 (23) and CCDC 2111318 (41).

**Acknowledgements**

The authors are grateful to the University of Birmingham for support including PhD studentships to FM and WDGB. Dr Christopher Williams and Dr Chi Tsang are thanked for the helpful discussions about mass spectrometry. JSF, WDGB and BRB acknowledge the support of a Wellcome Trust ISSF award within the University of Birmingham and a Royal Society Research Grant (2012/R1) that underpinned aspects of this work. WDGB would also like to thank the Royal Society of Chemistry, Society for Chemical Industry and the School of Chemistry at the University. Facilities at the University of Birmingham used to obtain analytical data were supported by the EPSRC (EP/K039245/1). AGL acknowledges the assistance given by Research IT and the use of the Computational Shared Facility at The University of Manchester.

**Corresponding Author**

*Corresponding authors: JSF j.s.fossey@bham.ac.uk (molecular synthesis and analysis), BRB b.r.buckley@lboro.ac.uk (heterocyclic chemistry) or AGL andrew.leach@manchester.ac.uk (computational aspects).

**Author Contributions**

FM conducted the majority of the chemical synthesis, contributed to critical decisions and wrote sections of the manuscript; WDGB conducted preliminary experiments and synthesised 28; LM collected, analysed and solved the XRD structures of this report; CSLD contributed to NMR spectroscopic experiments; BRB co-conceived the study and contributed to aspects of project supervision; AGL conducted all computational experiments, interpreted those results and wrote aspects of the manuscript; JSF co-conceived the study and experiments, supervised the project, made critical decisions and wrote the manuscript. All co-authors analysed data, contributed ideas and commented on the manuscript.
Competing financial interests
The authors declare no competing financial interests.

References

4 Kuhn, R. In Molekulare Asymmetrie; Franz-Deutike, Leipzig-Wien, 1933, 893–824.
42 Shailly; Kumar, A.; Parveen, I.; Ahmed, N. Luminescence 2018, 33, 713.
53 Ahmad Fuaad, A. A. H.; Azmi, F.; Skwarczynski, M.; Toth, I. Molecules 2013, 18.
56 Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. Angew. Chem. Int. Ed. 2002, 41, 2596.
The sign (+/-) of the given dihedral angles and the defined zero (versus 180) degrees notation used is systematically described in the supporting information to this manuscript.


