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$[^1H]/[^2H]$ discriminated bianthryl atropisotopomers: enantiospecific syntheses from BINOL and direct multi-spectroscopic analyses of their isotopic chirality

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The synthesis of two $[^1H]/[^2H]$ discriminated bianthryl atropisotopomers (*i.e.*, isotopically chiral atropisomers, *vide infra*) with ≥97% enantiomeric excess (*ee*) from the atropisomers of commercial (*aS*)- and (*aR*)-1,1′-bi-2-naphthol (BINOL, >99% *ee*) is described. The approach is based on enantiospecific [4 + 2] cycloaddition reactions of aryne atropisomer intermediates with $[^2H_4]$-furan. Overall, the six-step (from enantiopure BINOL) reaction sequence to the bianthryl atropisotopomers described herein occurs without significant erosion of the molecular stereogenic information. This is substantiated experimentally by three direct spectroscopic methods that do not necessitate chemical derivatization: (i) mirrored specific optical rotations as a proof of optical activity as well as of their equivalent *ee*, (ii) mirrored vibrational circular dichroism (VCD) spectra as a proof of their equivalent *ee* and for the confirmation of their absolute configurations (AC), and (iii) for the first time, anisotropic $^2H/^{13}C$ NMR in lyotropic chiral liquid crystals for the determination of the *ee* of one of them. In a broader and foreseeable perspective, the enantiospecific synthetic approach considered in this work to access bianthryl atropisotopomers from BINOL is simple and scalable, which should enable the production of a diverse range of atropisotopomers in the near future, possibly utilizing never-examined isotopes (*e.g.*, $[^3H]$). The availability of this class of isotopically chiral compounds in high isotopic and enantiomeric purity is a real asset for the development of precision chiral spectroscopies.

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Introduction

The presence of isotopes in molecules (both chiral and non-chiral), whether of natural abundance or not, is of immense value in science and technology. Isotopes are ubiquitous in areas ranging from fundamental and applied science in physics, biology, and chemistry to major societal applications such as dating, fraud detection, health and energy production.[1] A well-known illustration of this is the so-called "deuterium switch" in drug discovery, in which all-$[^1H]$ molecules are replaced by their $[^2H]$-containing isotopologues, which has major impacts on drug efficacy and safety beyond simple pharmacokinetic improvements.[2] However, this approach is limited by the "synthetic and analytical challenges in controlling site and extent of deuterium enrichment," as Pirali and her co-workers so aptly put it.[2] Another illustration of this is the ability of the $[^1H]/[^2H]$ isotopes in molecules to control the selectivity of some chemical reactions toward one product or another through quantum mechanical tunneling, which is the third paradigm in chemical reactivity, alongside kinetic and thermodynamic control.[3] This approach is also limited by synthetic and analytical challenges. The natural terrestrial abundance of the $[^2H]$ isotope of hydrogen in ocean water (V-SMOW value) is equal to 155.76(5) ppm (≈0.0156%, about 1 in 6420 atoms).[4] Thus, it is clear that $[^2H]$-glycine (**1**, Fig. 1a) with both a $[^1H]$ atom and a $[^2H]$ atom at its methylene C atom exists naturally on planet Earth in tiny amounts. The $[^1H]$ and $[^2H]$ atoms differ in the composition of their nuclei: the $[^1H]$ atom nucleus contains a single particle (a proton), while the $[^2H]$ atom nucleus contains two, namely, one proton and one neutron. Hence, the methylene C atom in **1** is stereogenic, and compound **1** is a chiral molecule by virtue of the $[^1H]/[^2H]$ isotopic substitution.[5] The chirality in **1**, which arises solely from the different composition of the nuclei of the two hydrogen isotopes at its methylene C atom, is referred to as

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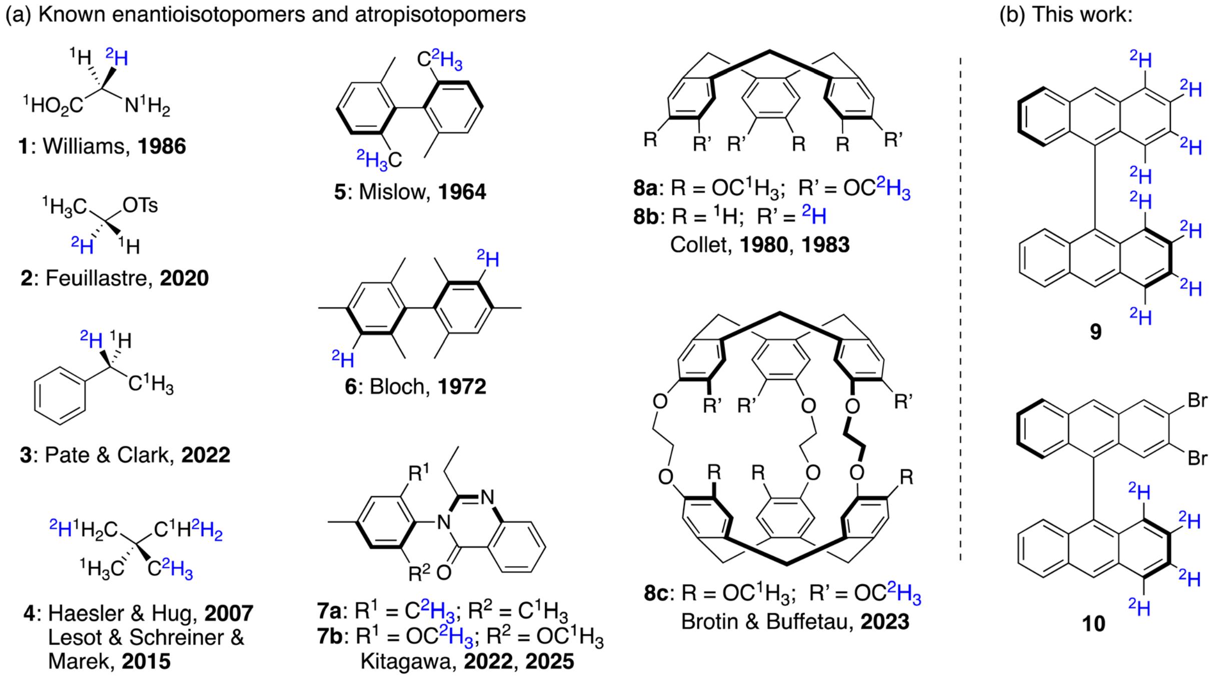


Fig. 1 Representative examples of (a) some known [^{1}H]/[^{2}H] discriminated enantioisotopomers (**1–4**) and known atropisotopomers (**5–8**), and (b) the new π-extended atropisotopomers described herein (**9**, **10**).

isotopic chirality, and the enantiomers of **1** are referred to as enantioisotopomers. Enantioenriched isotopically chiral molecules are able to trigger asymmetric autocatalysis with enantiomeric excess (*ee*) amplification in some reactions.[6] Consequently, naturally occurring isotopically chiral molecules, possibly existing locally in not strictly racemic amounts, have been considered as a reasonable hypothesis to address the question of the origin of homochirality in terrestrial living organisms, which is a fundamental issue of considerable importance to humanity. If present, any (extremely tiny) *ee* in terrestrial naturally occurring isotopically chiral molecules would be impossible to detect for long. Thus, research on isotopically chiral molecules has relied on the designed and controlled incorporation of isotopes into molecules at spatially defined positions *via* precision chemical synthesis to obtain enantioenriched samples. However, this is an incredibly difficult task for which no perfect example exists, *i.e.*, an example in which a chemical purity of >97%, isotopic purity of >97% and an *ee* of >97% could be achieved and verified experimentally. Prototypical examples of synthetic enantioisotopomers based on [^{1}H]/[^{2}H] discrimination are [^{2}H]-glycine (**1**, 77–82% *ee*),[7] [^{2}H]-ethyl tosylate (**2**, 90% *ee*),[8] and [^{2}H]-ethyl benzene (**3**, 97% *ee*).[9,10] A spectacular complex example is [$^2H_6$]-neopentane (**4**, 90–96% *ee*).[11] The isotopic chirality in compounds **1–4** derives from a single stereogenic carbon atom (central isotopic chirality). With the recent progress in stereoselective synthetic organic chemistry, [^{2}H]-enriched enantioisotopomers with central isotopic chirality have changed status from curiosities in academic laboratories decades ago to incredibly enabling tools in contemporary science. Compounds **1–4** are illustrative of this, and more examples exist.[12] While atropisomerism can also lead to enantioisotopomers (based on axial isotopic chirality), this class of compounds has been much less examined. We propose the name "atropisotopomers" for atropisomerism-based enantioisotopomers. The first reported non-racemic [^{1}H]/[^{2}H] discriminated atropisotopomers were the biphenyl-based molecules **5**[13] and **6**,[14] which were synthesized more than 50 years ago with modest *ee*. More recently, a promising new platform to synthesize non-racemic [^{1}H]/[^{2}H] discriminated atropisotopomers around a stereogenic C(sp^2)–N(sp^2) bond was developed, which led to compounds **7a,b** (98% *ee*).[15] To complete the list of existing non-racemic atropisotopomers based on [^{1}H]/[^{2}H] discrimination, the beautiful atropisotopomeric macrocyclic cyclotriveratrylene derivatives **8a,b**[16] and the superb atropisotopomeric cryptophane **8c**[17] should also be mentioned. Some isolated examples of enantioisotopomers based on planar chirality[18] and inherent chirality[19] have also been reported.

Except for compound **3** (and two of its analogues), for which an enantioselective copper-catalyzed synthesis can be achieved based on the hydrodeuteration of styrene,[9,20] isotopically chiral molecules are typically obtained either by diastereoselective approaches using a chiral auxiliary (covalently bonded to the substrate or the reagent) assuming no racemization in the subsequent steps,[7,8,11] or by enantiospecific syntheses, *i.e.*, from standard chiral enantioenriched precursors of known absolute configurations (AC) and verified *ee* to which the heavy isotope atoms are added in late or final synthetic step(s) *via* functional group interconversion (for instance, Br → [^{2}H], Br → C[^{2}H]$_3$, OH → OC[^{2}H]$_3$), presumably without racemization.[13–17]

One challenge is the analysis of chirality in isotopically chiral molecules, *i.e.*, the experimental determination of their AC [with either (*R*)- or (*S*)-configured stereogenic atoms in the cases of central isotopic chirality, or either (*aR*)- or (*aS*)-configured stereogenic bonds in the case of axial isotopic chirality] and of their *ee*. Indeed, the chirality in these molecules derives exclusively from an asymmetric distribution of the masses of their nuclei, while they have virtually the same electron distribution as their all-[^{1}H]-isotopologues. To a first approximation, isotopically chiral compounds are electronically achiral. Thus, analytical methods based on electronic molecular properties that are commonly employed to discriminate enantiomers are *a priori* not suitable to discriminate enantioisotopomers. This is the case for optical rotation, electronic circular dichroism (ECD) spectroscopy and single-crystal anomalous X-ray diffraction analysis, which are classically employed to determine the AC, and for chiral chromatography (gas phase or liquid phase), which is generally used to measure the *ee*. Enantioisotopomers are "minimal" test cases for evaluating how sensitive analytical tools are to molecular chirality.

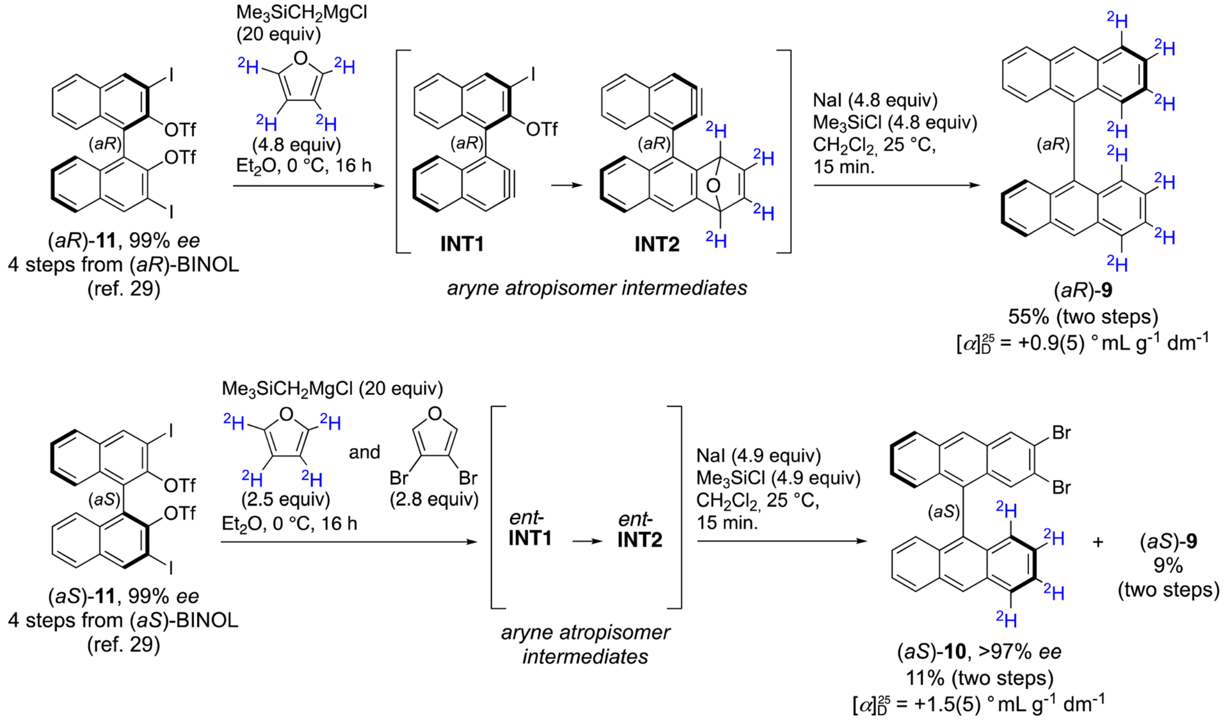
In practice, tiny specific optical rotations ($[\alpha]_D^{25}$) have been recorded for some enantioisotopomers since as early as 1949,[21] and more recently for the enantioisotopomers of atropisotopomers **7a,b** and **8c**. Additionally, weak but detectable ECD signals were recorded for the enantioisotopomers of atropisotopomers **8a–c**[17,22] and some isotopically chiral [2.2]paracyclophane.[18] The AC of isotopically chiral molecules is generally assumed from the AC of their synthetic precursors. However, it can be experimentally determined/verified using vibrational circular dichroism (VCD) and/or Raman optical activity (ROA) spectroscopies, as the mass ratio of the [^{2}H] and [^{1}H] nuclei is 1.998 ≈ 2, thus producing experimentally detectable and computable differences in the vibration frequencies of their [^{12}C]–[^{2}H] and [^{12}C]–[^{1}H] bonds.[23] Among other available techniques, gas-phase Coulomb explosion imaging enabled the determination of the AC of [^{1}H]/[^{2}H] discriminated enantioisotopomers,[24] and notably, the AC of **3** was recently deduced using a new tool in the box, chiral tag molecular rotational resonance (CTMRR) spectroscopy in the gas phase.[9,25]

The *ee* of isotopically chiral molecules based on [^{1}H]/[^{2}H] discrimination is also generally assumed to be identical to the *ee* of their synthetic precursors. In the cases in which the *ee* has been verified experimentally, this has most often been performed by indirect methods, *i.e.*, using chemical derivatization to generate pairs of diastereomers (mixing standard and isotopic stereogenicity) and assuming no enantiomerization in the process.[10,15] Subsequently, the measurement of the diastereomeric ratio by spectroscopic methods, typically using quantitative isotropic NMR based on chemical shift differences ($\Delta\delta^{\text{iso}}$), can be observed for some nuclei. The real challenge is the direct experimental determination of the *ee* of enantioenriched isotopically chiral samples, which has rarely been achieved to date. Chiral chromatography is impracticable in these cases, with only a few cases of partial resolution having been achieved.[26] For enantioisotopomers containing a remote Lewis-base coordinating site, the use of lanthanide chiral shift reagents (LCSR) has proved possible in some isolated examples having a stereogenic [^{1}H]/[^{2}H] methylene C atom.[27] In practice, direct *ee* measurements of enantioisotopomers can only be performed by two means: (i) using CTMRR spectroscopy in the gas phase, *e.g.*, for **3**,[9,28] and (ii) by anisotropic NMR spectroscopy in a condensed phase, *i.e.*, NMR in enantiopure, chiral liquid crystals (CLC), *e.g.*, for **2**.[8,29]

In this article, we describe the syntheses of the two π-extended atropisotopomers **9** and **10**, together with the extensive analysis of their chirality *via* polarimetry, using VCD for the determination of their AC and anisotropic NMR for the determination of their *ee*. Remarkably, the described enantiospecific synthetic approach to the atropisotopomers **9** and **10** is not based on a late-stage functional group interconversion as in previous approaches. In the described approach, the extended π-conjugated chiral carbon backbone is constructed enantiospecifically through a bidirectional Diels–Alder/deoxygenation two-step synthetic sequence involving arynes. Concerning the determination/confirmation of the AC of [^{1}H]/[^{2}H] discriminated atropisotopomers, we show that this can be confidently achieved using solid state VCD spectroscopy. Regarding the direct measurement of the *ee* of the enantioisotopomers of atropisotopomers, this study establishes for the first time that it can be realized by anisotropic NMR methods using both the ^{2}H and ^{13}C nuclei as magnetically active probes; however, while this was a successful approach for the enantioisotopomers of atropisotopomer **10** with C_1-symmetry, the enantioisotopomers of atropisotopomer **9** with C_2-symmetry resisted this analysis.

Results and discussion

Using *ortho*-iodoaryl triflate precursors and trimethylsilylmethyl magnesium chloride, the Coquerel group demonstrated that aryne atropisomers (*e.g.*, **INT1** and **INT2**, Scheme 1) can be enantiospecifically generated and reacted with full retention of the chiral information of their precursors.[30] In fact, the Diels–Alder reaction of aryne atropisomers with furan occurs with a half-reaction time <150 ns at temperatures higher than −20 °C, which is much faster than the rotation around their stereogenic C(sp^2)–C(sp^2) axis, thus ensuring enantiospecificity.[31] Using both enantiomers of the enantiopure (99% *ee*) BINOL derivative **11** (derived in four steps and 77% yield from 99% *ee* BINOL) as the precursors of bis(aryne) atropisomers, fully enantiospecific bidirectional reactions were realized, enabling the spatially controlled syntheses of some congested atropisomers in high enantiomeric purity (>98% *ee*).[32] Using [^{2}H$_4$]-furan (≥98% [^{2}H] atoms) as the arynophile in a bidirectional Diels–Alder/deoxygenation two-step reaction sequence with both enantiomers of the bis(aryne) atropisomer precursor **11** (99% *ee*), the two enantioisotopomers of atropisotopomer **9** were prepared in an enantiospecific manner: (*aR*)-**9** derived from (*aR*)-**11** and (*aS*)-**9** derived from (*aS*)-**11**, with 55% and 53% yield over two steps, respectively (Scheme 1). In another reaction using both [^{2}H$_4$]-furan and 3,4-dibromofuran as arynophiles in a three-component transformation, the two enantioisotopomers of atropisotopomer **10** were obtained (in 11% and 10% yield for (*aS*)-**10** and (*aR*)-**10**, respectively), together with the two enantioisotopomers of atropisotopomer **9** (9% yield). In contrast to existing approaches to atropisotopomers, the



Scheme 1 Two-step enantiospecific synthesis of atropisotopomers (*a**R*)-**9** and (*a**S*)-**10** from the bis(aryne) atropisomer precursor (*a**R*)-**11** and (*a**S*)-**11**, respectively. Atropisotopomers (*a**S*)-**9** and (*a**R*)-**10** were obtained in comparable yields from the bis(aryne) atropisomer precursor (*a**S*)-**11** and (*a**R*)-**11**, respectively.

extended π-conjugated carbon backbone of both **9** and **10** is constructed in an enantiospecific manner, not simply by functional group interconversion as in previously reported cases.[13–17]

It was previously demonstrated that the bidirectional reactions of the bis(aryne) atropisomer precursor **11** occur with full retention of the chiral information, *i.e.*, with the products having unchanged AC and identical (or nearly) *ee* to precursor **11** (enantiospecific reactions).[32] Assuming that the rotation around the $C(sp^2)–C(sp^2)$ in 9,9′-bianthryl is blocked at temperatures below 140 °C (with $\Delta G^{\ddagger}_{\mathrm{rot}} \approx 185\ \mathrm{kJ\ mol^{-1}}$ as evaluated by DFT methods, see Section S5 in the SI), and despite the fact that the $^{12}C–^{2}H$ bond is 0.005 Å shorter than the $^{12}C–^{1}H$ bond,[33] both atropisotopomers **9** and **10** are configurationally stable compounds with locked AC. No racemization of atropisotopomers **9** and **10** is possible at a significant rate under the examined experimental conditions. Thus, it can be reasonably hypothesized that the enantioisotopomers of atropisotopomers **9** and **10** were obtained with *ee* ≥98%, and with retention of the AC of their stereogenic axes.

The first evidence of the non-racemic nature of samples of **9** and **10** arose from measurement of their specific optical rotations: the $[\alpha]_{\mathrm{D}}^{25}$ of (*a**R*)-**9** is +0.9(5)° mL g^{-1} dm^{-1} ($c = 1.0$, $CHCl_3$) and the $[\alpha]_{\mathrm{D}}^{25}$ of (*a**S*)-**9** is −0.9(5)° mL g^{-1} dm^{-1} ($c = 1.0$, $CHCl_3$); similarly, the $[\alpha]_{\mathrm{D}}^{25}$ of (*a**S*)-**10** is +1.5(5)° mL g^{-1} dm^{-1} ($c = 0.42$, $CHCl_3$) and the $[\alpha]_{\mathrm{D}}^{25}$ of (*a**R*)-**10** is −1.5(5)° mL g^{-1} dm^{-1} ($c = 0.50$, $CHCl_3$).

The AC of the enantioisotopomers of atropisotopomers **9** and **10** were confirmed by solid-state VCD spectroscopy (Fig. 2). For **9**, IR measurements in CD_2Cl_2 at 0.1 M gave a low absorbance (below 0.1 AU), which was insufficient for reliable VCD analysis (recommended minimum ≈ 0.2 AU). Increasing the concentration to achieve the optimal ~0.8 AU was precluded by solubility and material constraints. Consequently, the VCD spectra of **9** and **10** were recorded in the solid-state using *ca.* 5.5 mg of material in KBr pellets. The pellets were carefully prepared and measured on a rotating holder to minimize circular and linear birefringence and linear dichroism artefacts. The spectra of (*a**S*)-**9** and (*a**R*)-**9** are mirror images (Fig. 2a), ruling out major artefacts, and the experimental spectrum of **9** derived from (*a**R*)-**11** agrees well with the simulated spectrum of (*a**R*)-**9** computed at the B3LYP-D3(BJ)/6-311G(df,pd) DFT level of theory (Fig. 2b), confirming the enantiomeric relationship with their precursors (*a**R*)-**11** and (*a**S*)-**11**, respectively. The VCD spectra of (*a**S*)-**10** and (*a**R*)-**10**, although showing some significant artefacts around 1160 and 900 cm^{-1}, are mirror images for the most diagnostically relevant bands, notably at 1315 cm^{-1} (Fig. 2c). They closely resemble those of the corresponding enantiomers of **9**, especially in the 1250–1600 cm^{-1} region (Fig. 2e), in which the most intense bands arise from $C_{Ar}–H$ and $C_{Ar}–C_{Ar}$ deformation modes delocalized over both anthracene units; these features are accurately reproduced by the simulated spectra (Fig. 2f). The AC assignment of the enantioisotopomers of **10**, based on the comparison of their measured VCD spectra with those of **9**, was further supported by the calculated VCD spectrum of (*a**R*)-**10**, which matches the experimental spectrum of the sample derived from (*a**R*)-**11** (Fig. 2d). Comparison of the IR spectra of **9** and **10** (Fig. S7 in the SI) reveals two bands at 1411 and 1091 cm^{-1}, which can be assigned to vibrational

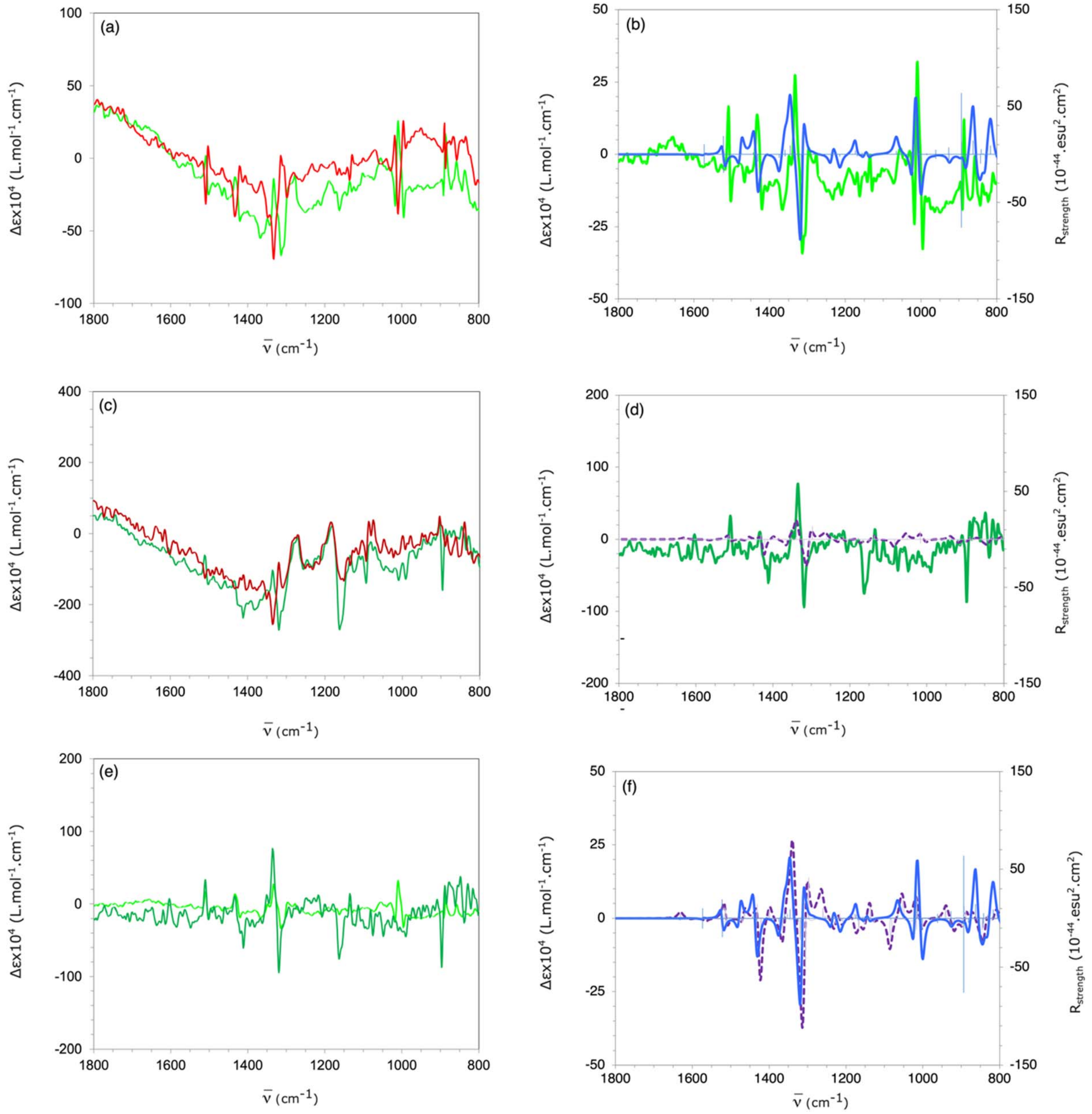


Fig. 2 VCD spectroscopy analysis of atropisotopomers **9** and **10**. (a) Solid state VCD spectra of (*aR*)-**9** (green) and (*aS*)-**9** (red) measured in KBr pellets without baseline correction. (b) Measured VCD spectrum of (*aR*)-**9** with half-difference baseline correction (green) and simulated spectrum of (*aR*)-**9** (blue) calculated at the B3LYP-D3(BJ)/6-311G(df,pd) level of theory for a single molecule in the gas phase. (c) Solid state measured VCD spectra of (*aR*)-**10** (dark green) and (*aS*)-**10** (dark red) in KBr pellets without baseline correction. (d) Measured VCD spectrum of (*aR*)-**10** with half-difference baseline correction (dark green) and simulated spectrum of (*aR*)-**10** (dashed purple) calculated at the B3LYP-D3(BJ)/6-311G(df,pd) level of theory for a single molecule in the gas phase. (e) Experimental VCD spectra of (*aR*)-**9** (green) and (*aR*)-**10** (dark green) with half-difference baseline correction. (f) Calculated VCD spectrum of (*aR*)-**9** (blue) and (*aR*)-**10** (dashed purple).

modes involving the two bromine atoms. The calculated rotational strengths for these modes are extremely small, accounting for the absence of detectable VCD signals. Similarly, attempts to measure the VCD bands corresponding to the C_{Ar}–[^{2}H] stretching modes around 2300 cm^{-1} were unsuccessful, as the VCD response was too weak to be distinguished from baseline noise.

The question of the direct experimental measurement of the *ee* of the samples of the enantioisotopomers of atropisotopomers **9** and **10** is the most arduous one. Among the two methods available to do so, CTMRR spectroscopy in the gas phase is *a priori* not suitable because both atropisotopomers **9** and **10** would be difficult to vaporize [for (*aS*)-**9** and (*aR*)-**9**: mp > 360 °C; for (*aS*)-**10** and (*aR*)-**10**: mp = 278 °C, dec.], which leaves anisotropic NMR spectroscopy as the only viable option. To evaluate whether anisotropic NMR spectroscopy would be able to discriminate the enantioisotopomers of atropisotopomer **9**, *i.e.*, (*aS*)-**9** and (*aR*)-**9**, a pseudo-racemic sample of *rac*-**9** was prepared by mixing equal amounts (5.0 mg) of (*aS*)-**9** and (*aR*)-**9** obtained as described in Scheme 1. A sample composed of 3.0 mg of *rac*-**9**, 101 mg of the commercially available chiral homopolymer PBLG (poly-γ-benzyl-L-glutamate, DP = 768) and 502 mg of chloroform (stabilized with ethanol <1%) was analyzed *via* anisotropic ^{2}H–{^{1}H} 2D NMR with a 14.1 T spectrometer equipped with a selective ^{2}H cryogenic probe (92.1 MHz) (see Fig. 3 and details in Section S4 of the SI).[34] Conceptually, this analysis is based on the ability of the PBLG polymer to spatially orient, on average, each enantiomer of atropisotopomer **9** (and **10**) along distinct magnetically detectable directions. When the difference in molecular orientation is significant in the CLC mesophase, two spectral signatures (one for each enantiomer) based on the difference in ^{2}H residual quadrupolar couplings (^{2}H-RQC) are then observed. In practice, the use of QUadrupole Order SpectroscopY (QUOSY) *n*D experiments such as phased ^{2}H–{^{1}H} *Q*-COSY Fz (spectrum of **9** in Fig. 3) or a phased ^{2}H–{^{1}H} *Q*-resolved 2D sequence (spectra of **10** in Fig. 4) instead of basic single-pulse ^{2}H–{^{1}H} 1D-NMR experiments is analytically advantageous. These reduce peak overlap and enable deuterium quadrupolar doublets (^{2}H-DQ) to be identified based on their respective $\delta(^2\text{H})$. This considerably simplifies the analysis of complex anisotropic ^{2}H–{^{1}H} spectra. In both experiments, the ^{2}H chemical shifts and ^{2}H quadrupolar doublets are separated in the F_2 and F_1 dimensions, respectively.[35] In the initial ^{2}H–{^{1}H} *Q*-COSY Fz 2D NMR experiments recorded at 9.4 T using a QXO probe (not shown), only four quadrupolar doublets were observed for *rac*-**9**, which indicated that no spectral enantiodiscrimination occurred under these conditions. The applicability of a higher-field 14.1 T spectrometer equipped with a selective ^{2}H cryogenic probe was then examined. As shown in Fig. 3, only four quadrupolar doublets were observed for *rac*-**9** in this case at 310 K; the same result was observed at 277 K and 325 K. This indicates that the inability of the PBLG chiral matrix to spectrally discriminate the enantioisotopomers of **9** is not a matter of spectroscopic resolution or sensitivity. The origin of this lies elsewhere (*vide infra*). Thus, for now, the *ee* of the samples of (*aS*)-**9** and (*aR*)-**9** synthesized as described above remain undetermined by a direct experimental method.

Using the same approach, the ability of the enantioisotopomers of atropisotopomer **10**, *i.e.*, (*aS*)-**10** and (*aR*)-**10**, to be discriminated by anisotropic NMR was evaluated. A sample composed of 3.0 mg of *rac*-**10**, 110 mg of the chiral polymer PBLG (DP = 768) and 570 mg of chloroform was analyzed using anisotropic NMR spectroscopy with a 9.4 T spectrometer (QXO probe). In the corresponding ^{2}H–{^{1}H} *Q*-resolved 2D NMR spectrum (Fig. 4a), six quadrupolar doublets are observed, which indicates that spectral enantiodiscrimination occurs for two out of the four [^{2}H] atoms in *rac*-**10** under these conditions. More precisely, enantiodiscrimination is observed for the [^{2}H] atoms at the 2 (blue) and 3 (green) positions of the bianthryl carbon backbone (Fig. 4a). Thus, the *ee* of both samples of enantioisotopomers (*aS*)-**10** and (*aR*)-**10** synthesized as described above can be directly determined by chiral anisotropic NMR. Accordingly, these samples were analyzed under similar experimental conditions. In the corresponding phased ^{2}H–{^{1}H} *Q*-resolved 2D NMR spectra of enantioisotopomers (*aS*)-**10** and (*aR*)-**10** (Fig. 4b), only four quadrupolar doublets are visible, meaning that these samples contain a single enantioisotopomer within the detection limit of the NMR spectrometer (see details in Section S4 of the SI). From these analyses, the *ee* of both enantioisotopomers of atropisotopomer **10**, (*aS*)-**10** and (*aR*)-**10** can be reliably evaluated as ≥97%.

The naturally occurring isotope ^{13}C (1.1%) is also an interesting magnetically active species for the spectral

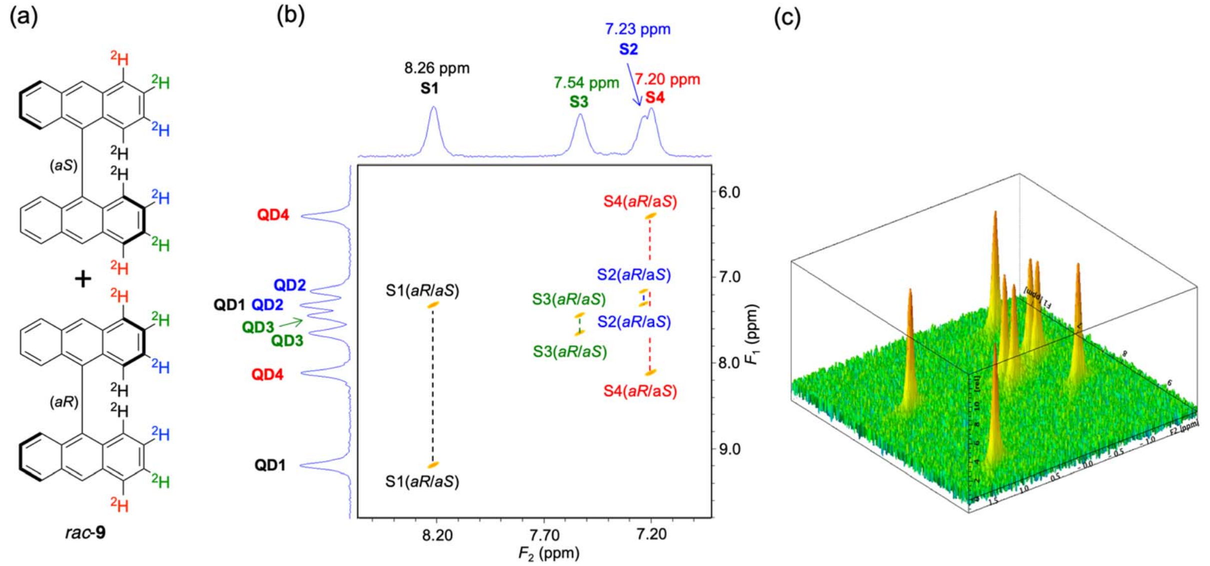


Fig. 3 (a) Structure of (*aS*)-**9** and (*aR*)-**9**. (b) Anisotropic ^{2}H–{^{1}H} *Q*-COSY Fz 2D NMR spectrum (spectrum is symmetrized and then tilted) of *rac*-**9** recorded in PBLG/CHCl$_3$ at 92.1 MHz and 310 K. (c) The associated 3D map of *rac*-**9**. The dashed lines (black, green, blue and orange) correlate the two components of each ^{2}H quadrupolar doublet at sites S1, S2, S3 and S4, with no doubling of ^{2}H signals in this case.

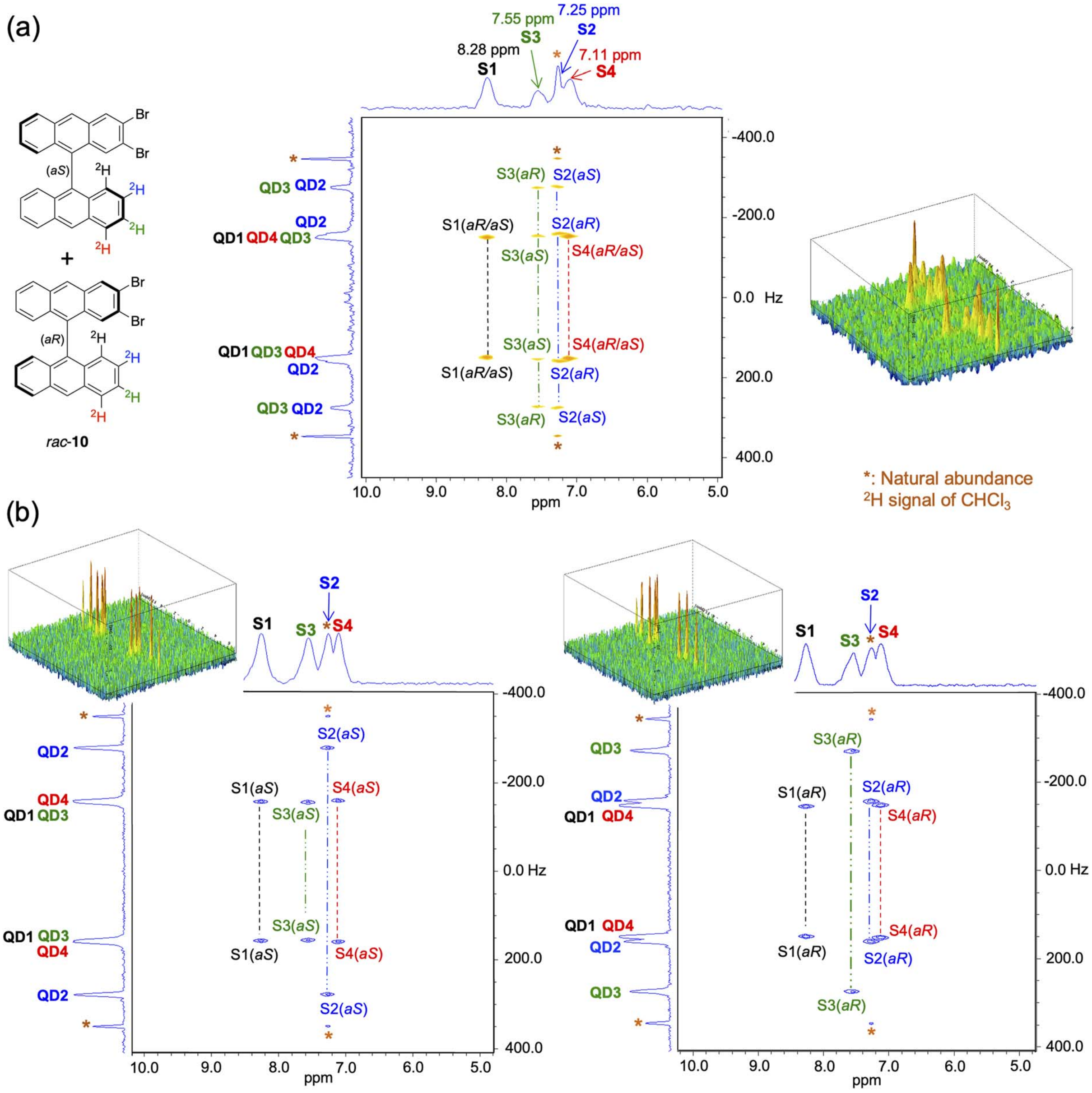


Fig. 4 Anisotropic phased ^{2}H–{^{1}H} *Q*-resolved 2D NMR spectra of the enantioisotopomers of atropisotopomer **10** dissolved in PBLG/$CHCl_3$ (spectra are tilted and then symmetrized), all recorded at 61.4 MHz and 305 K. (a) *rac*-**10** (b) (*aS*)-**10** (left) and (*aR*)-**10** (right), respectively. The dashed lines (black, green, blue and orange) correlate the two components of ^{2}H quadrupolar doublets at sites S1, S2, S3 and S4, with a doubling of ^{2}H signals observed at the S2 and S3 sites, thus revealing the spectral enantiodiscrimination.

discrimination of enantioisotopomers, although this method is less sensitive in terms of enantiodiscrimination than ^{2}H NMR for [^{2}H]-enriched enantioisotopomers.[36] In the case of *rac*-**10**, spectral enantiodiscrimination is also observed *via* anisotropic ^{13}C–{^{1}H} NMR through the difference in the ^{13}C residual chemical shift anisotropy (^{13}C-RCSA) between the enantioisotopomers,[29] leading to a doubling of the number of signals for each discriminated ^{13}C site compared to the ^{13}C–{^{1}H} spectrum recorded in isotropic (achiral) solvents. For instance, it can be observed for *rac*-**10** that four ^{13}C atoms show a doubling of their ^{13}C resonances in the anisotropic ^{13}C–{^{1}H} NMR spectrum of *rac*-**10** (Fig. 5, middle). In contrast, the anisotropic ^{13}C–{^{1}H} NMR spectra of (*aR*)-**10** and (*aS*)-**10** show a single resonance for the same ^{13}C atoms, indicating that the minor enantioisotopomer is not detected (or does not emerge from the noise) in these cases, confirming that its *ee* is likely >95% (Fig. 5, top and bottom). These complementary anisotropic NMR investigations using ^{13}C nuclei probes conclusively confirm the *ee* of both enantioisotopomers of atropisotopomer **10** as having been accurately determined from the ^{2}H nuclei analyses. Overall, the anisotropic NMR analyses discussed herein are the first direct experimental determination of the *ee* for enantioisotopomers of an atropisotopomer, and also the highest *ee* (≥97%) determined by this technique for any synthetic enantioisotopomer.

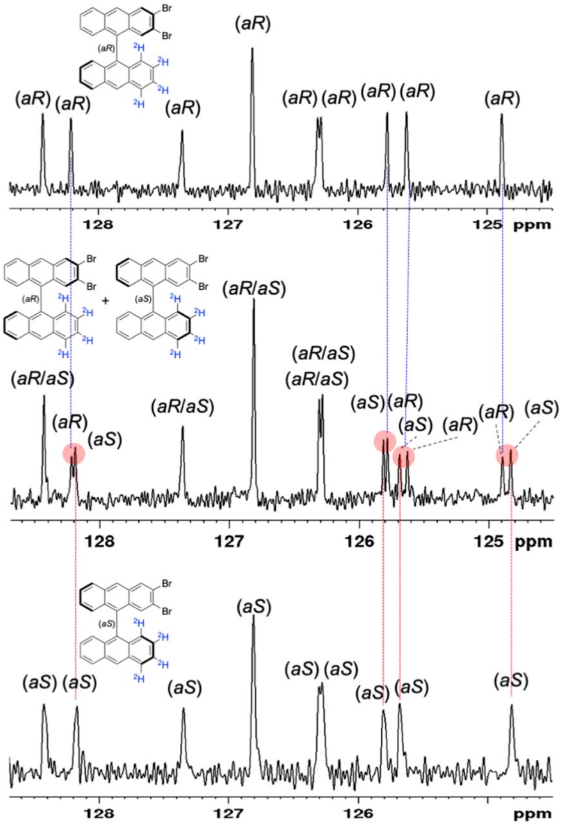


Fig. 5 Anisotropic $^{13}C-\{^{1}H\}$ 1D NMR spectra (100.4 MHz) and ^{13}C peak assignment of *rac*-**10** (middle), (*aR*)-**10** (top) and (*aS*)-**10** (bottom) recorded in the chiral mesophase PBLG/$CHCl_3$ at 305 K.

At this early stage of our work, it is not clear why the enantioisotopomers of atropisotopomer **10** could be spectrally discriminated while the enantioisotopomers of atropisotopomer **9** could not be under comparable anisotropic NMR conditions. However, it can reasonably be hypothesized that the virtually null dipole moment of atropisotopomer **9**, a compound with C_2-symmetry, translates into a poor difference in the preferred diastereotopic spatial orientation of its enantioisotopomers in the PBLG chiral matrix, thus making the enantiodiscrimination very difficult to detect spectrally through anisotropic NMR experiments. This is extremely instructive for the development of the technique, which is on-going in our laboratories.

Conclusions

The bidirectional reactions of the enantiopure (or nearly, *ee* = 99%) bis(aryne) atropisomers (*aS*)-**11** and (*aR*)-**11**, which were efficiently derived from both enantiomers of BINOL (*ee* ≥ 99%), with $[^{2}H_4]$-furan as either the sole arynophile or in combination with 3,4-dibromofuran enabled the expeditious syntheses of the isotopically chiral enantioisotopomers of the $[^{1}H]/[^{2}H]$ discriminated atropisotopomers (*aR*)-**9**/(*aS*)-**9** and (*aR*)-**10**/(*aS*)-**10** (*ee* ≥ 97% for **10**, *ee* not yet experimentally verified for **9**). The originality and the relevance of this enantiospecific synthetic approach to atropisotopomers lies in its efficiency: it simultaneously forges the extended π-conjugated carbon backbone (the 9,9′-bianthryl backbone) and the isotopically stereogenic axis.

Atropisotopomers **9** and **10** exhibit the largest π-conjugated electronic systems among atropisotopomers, with two separated 14-electron aromatic circuits. This is a feature of these molecules that we have not yet examined, especially in terms of circularly polarized UV-vis light–matter interactions (absorption and emission) among other electronic properties. Mirror specific optical rotations with a magnitude of $[\alpha]_{D}^{25} \approx 1$ were recorded for the enantioisotopomers of the atropisotopomers **9** and **10**. Specific optical rotations of comparable intensity have been reported for the few examples of highly enantio-enriched isotopically chiral molecules reported in the past decades. Using VCD in the solid state, it was possible to record sufficiently intense mirror signals for both enantioisotopomers of the atropisotopomers **9** and **10**, which confirmed their absolute configurations (AC) with the greatest confidence. Comparable VCD analyses of the few highly enantioenriched $[^{1}H]/[^{2}H]$ discriminated enantioisotopomers that have been successfully analyzed to date also allowed their AC to confidently be determined. In terms of the analysis of isotopic chirality in molecules, the greatest innovation in the work described herein is the first direct determination of the *ee* of both enantioisotopomers of an atropisotopomer using anisotropic NMR, which is the only available method to do so in condensed phases. The few previous successful applications of this analytical technique for the determination of the *ee* of isotopically chiral molecules have been limited to examples with central chirality.

Remarkably, it has been demonstrated to be possible to use both the ^{2}H and the ^{13}C nuclei as magnetically active probes to determine directly the *ee* of the samples of the enantioisotopomers of atropisotopomer **10**, (*aR*)-**10** and (*aS*)-**10**. In this case, the ^{2}H-based NMR experiments provided more accurate information for the *ee* determination than the ^{13}C-based NMR experiments, reflecting the relative magnetic sensitivity of both nuclei (*ca.* 100× sensitivity for $[^{2}H]$ *vs.* $[^{13}C]$). Although *ee* determination by anisotropic NMR was only possible for atropisotopomer **10** under the examined conditions (using PBLG as the lyotropic CLC), the *ee* of ≥97% for both samples of (*aR*)-**10** and (*aS*)-**10** is notably the highest *ee* determined by this technique for any enantioisotopomers. This represents a major step forward in the analysis of isotopic chirality, which calls for further development (*e.g.*, using other chiral lyotropic chiral phases).

The π-extended 9,9′-bianthryl platform used to forge atropisotopomers **9** and **10** is configurationally stable and cannot racemize at a significant rate at temperatures below 140 °C for centuries. Considering the availability of the enantiopure precursors (*aR*)-**11** and (*aS*)-**11** from BINOL (99% *ee*, 4 steps, 77%), the versatility of the synthetic options enabled by aryne chemistry,[37] and the equally versatile synthetic options for derivatization offered by the C(sp^2)–Br bond, we can hypothesize that the synthetic chemistry described herein for the prototypical atropisotopomers **9** and **10** is generalizable and extendable to any designed $[^{1}H]/[^{2}H]$ discriminated atropisotopomers with a 9-anthryl or a 9,9′-bianthryl carbon backbone, as well as beyond, *e.g.*, to those based on other isotopes such as [^{1}H]/[^{3}H], [^{2}H]/[^{3}H] and [^{12}C]/[^{13}C][38] discrimination. This offers simple, practical, and cheap synthetic access to π-extended atropisotopomer molecules to enable the development of precision analytical methods for the analysis of isotopic chirality using polarimetry, VCD, anisotropic NMR and more. The work described herein was conceived with the objective of propelling research in the domain of molecular chirality, from precision synthesis to precision analysis, and further development is on-going in our laboratories.

Author contributions

F. R. and G. D. performed the syntheses. J.-V. N. realized the VCD studies. P. L. and C. A. carried out the anisotropic NMR studies. Y. C. conceived the study, secured the funding, designed the synthesis experiments, and drafted the manuscript with revisions from all authors. All authors contributed to the discussion.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: detailed synthetic procedures, details of the polarimetry and spectroscopic analyses, and the theoretical determination of the rotation barrier in 9,9′-bianthryl. See DOI: https://doi.org/10.1039/d5sc09200k.

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