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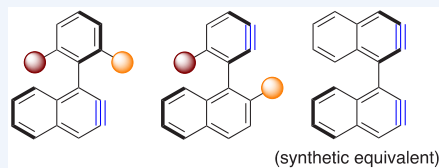


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Aryne Atropisomers: Chiral Arynes for the Enantiospecific Synthesis of Atropisomers and Nanographene Atropisomers

Yoann Coquerel*

CONSPECTUS: The basics about arynes and their applications in synthetic organic chemistry are briefly presented, and the concept of atropisomerism is defined, highlighting that it is a time-dependent form of isomerism and chirality. It is remembered that racemization is a macroscopic and statistical irreversible process, while enantiomerization is a nanoscopic reversible process that occurs at the molecular scale, with racemization being twice as fast as enantiomerization. The concept of aryne atropisomers is introduced with a naive question: Can synthetically useful nonracemic aryne atropisomers having a triple bond ortho to the stereogenic single bond exist in solution? It was found that such aryne atropisomers can be generated in solution from easily available *ortho*-iodoaryl triflate precursors and excess trimethylsilylmethylmagnesium chloride. Analysis of the barriers to enantiomerization of some aryne atropisomers by computational modeling revealed the key contribution to the configurational stability of the H atom in tris-*ortho*-substituted biphenyl-based atropisomers. Using a specially designed prototype of aryne atropisomer, for which the barrier to enantiomerization was accurately evaluated by advanced computational modeling, the kinetic parameters of its reaction with furan were experimentally determined. From these measurements, it was concluded that any aryne atropisomer with a barrier to enantiomerization $\Delta G_{\text{enant}}^{\ddagger}$ equal to or higher than 50 kJ mol^{-1} would lead to fully enantiospecific reactions. The synthetic applications of two structurally distinct aryne atropisomers built on a 1-phenylnaphthalene platform are described: one has the aryne triple bond embedded in the naphthyl moiety, and the other has the aryne triple bond embedded in the phenyl moiety. Both aryne atropisomers allowed for the fully enantiospecific, and possibly overall enantioselective, syntheses of original atropisomers based on standard aryne chemistry. For instance, reactions with anthracene and perylene afforded triptycene and nanographene atropisomers, respectively, in high enantiomeric excesses. A bis(aryne) atropisomer synthetic equivalent prepared from either enantiomer of BINOL is described for 3D bidirectional reactions with a single handedness. Its 2-fold reactions with anthracene and perylene afforded the corresponding severely congested bis(benzotriptycene) (99% ee) nanocarbon atropisomer and bis(anthra[1,2,3,4-*ghi*]perylene) (98% ee) nanographene atropisomer, respectively. This allowed the discovery of bis(twistacene) atropisomers as a new class of polycyclic aromatic hydrocarbons (PAH) with multiple stereogenicities. Cross reactions with the bis(aryne) atropisomer synthetic equivalent and two different arynophiles proved feasible, providing a nanographene atropisomer with a benzotriptycene unit and an anthra[1,2,3,4-*ghi*]perylene unit assembled around a stereogenic axis as a unique chiral PAH (99% ee). Overall, because the concept is simple and its implementation is easy, aryne atropisomers is an attractive approach to the synthesis of atropisomers in a broad meaning. Applications to the synthesis of large PAH atropisomers with single handedness are particularly promising.



■ KEY REFERENCES

- Wei, Y.-L.; Dauvergne, G.; Rodriguez, J.; Coquerel, Y. Enantiospecific Generation and Trapping Reactions of Aryne Atropisomers. *J. Am. Chem. Soc.* **2020**, *142*, 16921–16925.¹ This work demonstrated that non-racemic aryne atropisomers can be generated and reacted in solution for the enantiospecific synthesis of atropisomers and nanographene atropisomers.
- Dauvergne, G.; Vanthuyne, N.; Giorgi, M.; Rodriguez, J.; Carissan, Y.; Coquerel, Y. Determination of the Rate

Constant of the [4 + 2] Cycloaddition Between an Aryne Atropisomer and Furan in Solution. *J. Org. Chem.* **2022**, *87*, 11141–11147.² This work provided the first

experimental data on the kinetic parameters of an aryne in solution, which allowed one to define the border for the design of synthetically useful aryne atropisomers.

- Dauvergne, G.; Naubron, J.-V.; Giorgi, M.; Bugaut, X.; Rodriguez, J.; Carissan, Y.; Coquerel, Y. Enantiospecific Syntheses of Congested Atropisomers Through Chiral Bis(aryne) Synthetic Equivalents. *Chem.-Eur. J.* **2022**, e202202473.³ This work introduced enantiopure bis(aryne) atropisomer synthetic equivalents derived from BINOL for the enantiospecific syntheses of nanocarbon and nanographene atropisomers, possibly embedding severe congestion.

■ INTRODUCTION

Arynes

ortho-Arynes, or simply arynes, exist in solution, but they are not isolable, bottleable, chemical entities under standard conditions because of their high reactivity. The existence of benzyne in solution as a short-life reaction intermediate was postulated as early as 1927,⁴ and convincing experimental evidence for its existence was accumulated in the first half of the 20th century.⁵ The Lewis structure of benzyne, and generally of all arynes, is classically represented as a benzene ring with a triple bond, which is an oversimplification of its electronic structure. In fact, benzyne has two distinct π systems that do not overlap: a 6π aromatic system made of six overlapping p (or closely resembling) orbitals as in benzene, and a 2π reacting system oriented in the molecular plane, perpendicular to the aromatic system, made of two weakly overlapping sp^2 -resembling orbitals.^{6,7} This unique electronic structure is responsible for the high chemical reactivity of benzyne and more generally of all arynes. For instance, arynes rapidly dimerize by $[2 + 2]$ cycloaddition processes in the absence of a reaction partner, just as they rapidly react with nucleophiles in addition reactions and with unsaturated molecules in cycloaddition reactions. Many systems based on a 1,2-elimination from a suitable aryl precursor are now available for the mild and controlled release of arynes in solution⁸ with countless applications in organic chemistry, from the synthesis of complex natural products⁹ to the synthesis of large π -extended PAH with unique properties.^{10,11}

Atropisomerism

Chirality is the geometric property of a rigid object that breaks the parity operation, the flip in the sign of one spatial coordinate, meaning that this object is nonsuperposable on its mirror image. An object is chiral or not, with no in between. Chirality continuously raises new questions for its understanding and its management, and its control offers new opportunities. At the molecular scale, applications of active pharmaceutical ingredients and functional organic materials now largely rely on chirality with single handedness molecules.¹² Atropisomerism is one of the fundamental types of molecular chirality.^{13–18} Atropisomerism is a time-dependent form of isomerism based on the kinetic of rotation around a single bond in a molecule: if the rotation around the single bond is slow enough at a given temperature, then the two conformers, if chiral, are enantiomers, also called atropisomers, and can be isolated as discrete species. For clarity, only atropisomers with a single stereogenic single bond are discussed herein, but several stereogenic single bonds can coexist in molecules.^{19,20} The existence of atropisomers as

enantiopure species cannot be dissociated from the kinetic of their conformational behavior. For the archetypal example of simple biphenyl derivatives, it was empirically established that three substituents other than a H atom *ortho* to the stereogenic single bond induce configurational stability under standard conditions.¹³ The key contribution to configurational stability of the H atom, the smallest substituent around the stereogenic single bond in *tris-ortho*-substituted biphenyl derivatives, had not been realized previously.

Enantiomerization and Racemization

The terms enantiomerization and racemization are still often inadequately employed in the chemical literature despite some clarification efforts that have been pursued.^{21–23} They will be defined again herein together with some mnemonic tips. It should help the reader to understand the kinetic-based arguments developed in this Account and possibly avoid future confusion between these two interlinked concepts of molecular chirality. Racemization is a macroscopic and statistical irreversible process; it should only be discussed when considering large numbers of molecules. As a mnemonic trick, it should just be remembered that a racemic single molecule cannot exist: a single chiral molecule is existing either as one or as the other enantiomer, not both simultaneously. Enantiomerization is a nanoscopic reversible process that occurs at the molecular scale: it is the interconversion of one enantiomer into the other enantiomer. Thus, considering the relationship between the rate of racemization k_{rac} and the rate of enantiomerization k_{enant} for a given molecular system at a given temperature, it must be realized that racemization is twice as fast as enantiomerization: $k_{\text{rac}} = 2 \cdot k_{\text{enant}}$. The following thought experiment should help in fixing this idea: imagine a material composed of only two molecules of identical handedness, for example, two molecules with the (*S*) configuration. Now imagine that one of the two molecules enantiomerizes, changing its configuration to (*R*). The resulting material would contain one molecule with the unchanged (*S*) configuration and one molecule with the new (*R*) configuration, in other words, two molecules of the racemic material. In this thought experiment, the enantiomerization of one molecule produced two molecules of the racemate. Note that in the racemate at equilibrium, both enantiomers are still enantiomerizing with (*S*) \rightarrow (*R*) and (*R*) \rightarrow (*S*) at the rate k_{enant} for both transformations so that the macroscopic enantiomeric composition of the mixture is no longer evolving. In the following, only the cases of chiral molecules that can enantiomerize by a conformational change (i.e., atropisomers, helicenes, and twistacenes), herein collectively referred to as “conformationally chiral molecules”, are considered. For conformationally chiral molecules, k_{enant} cannot be measured experimentally; only k_{rac} can be. Contemporaneously, the energy barrier to enantiomerization $\Delta G_{\text{enant}}^\ddagger$ in a molecule can relatively easily be evaluated by quantum chemistry calculations, typically DFT methods. The barrier to enantiomerization, usually expressed in kJ mol^{-1} or kcal mol^{-1} , is the difference between the energy of the less energetically demanding transition state corresponding to the interconversion of the enantiomers (at least two options exist corresponding to 180° rotations in the forward and backward directions, and multistep processes are possible) and the energy of the enantiomers in their most stable conformation. The rate of enantiomerization k_{enant} and the barrier to enantiomerization $\Delta G_{\text{enant}}^\ddagger$ at a given temperature are

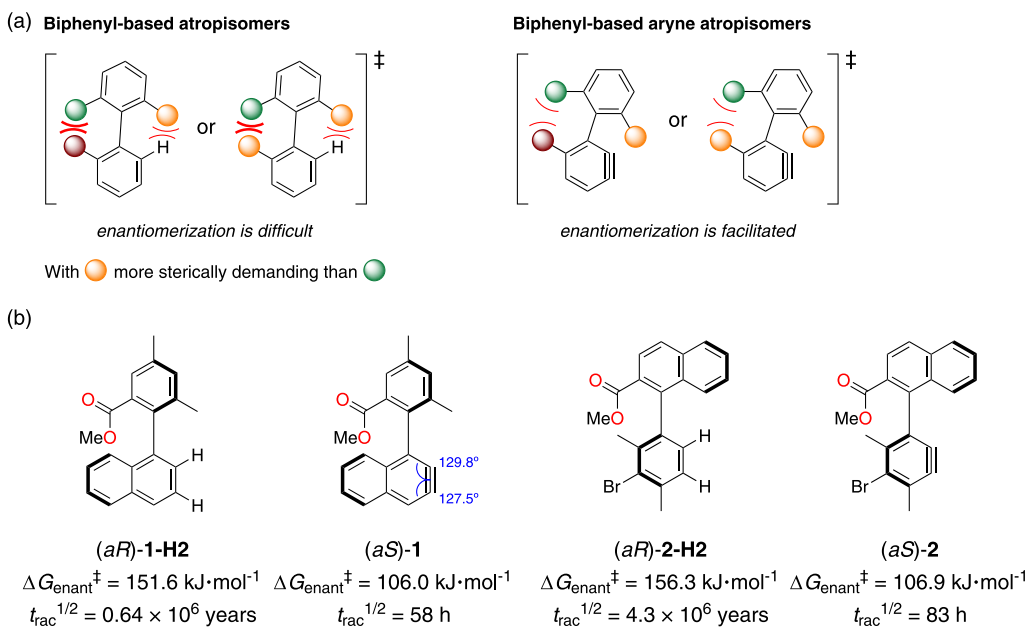


Figure 1. (a) Representations of the enantiomerization transition states of trisubstituted biphenyl-based atropisomers and the corresponding aryne atropisomers. (b) Enantiomerization barriers and half-racemization times at 298 K for the atropisomers **1-H2** and **2-H2**, and the corresponding aryne atropisomers **1** and **2** in solution; Gibbs free energies computed by DFT methods with B3LYP-D3/6-311++G(d,p) using the IEFPCM solvation model for diethyl ether. For the determination of the absolute configurations using the CIP nomenclature, priority was given to C atoms embedded in a “triple bond” against all-C substituted C(sp²) atoms.

connected through the Eyring equation. A useful macroscopic parameter for conformationally chiral molecules is the determination of their half-racemization time noted $t_{\text{rac}}^{1/2}$ to evaluate the stability of the enantiopure material over time at a given temperature. The determination of $t_{\text{rac}}^{1/2}$ from the value of $\Delta G_{\text{enant}}^\ddagger$ must account for the fact that racemization is twice as fast as enantiomerization.

Aryne Atropisomers

The simple question at the origin of the work summarized in this Account is as follows: Can synthetically useful nonracemic aryne atropisomers having a triple bond ortho to the stereogenic single bond exist in solution? On analysis, two factors underlying this idea were identified: (i) the reaction rate of aryne atropisomers must be greater than their enantiomerization rate, which can be achieved by suitable design, and (ii) some “know-how” for the generation of aryne atropisomers in solution must exist, which can be worked out. Efforts in these directions and the early applications of this idea are summarized below.

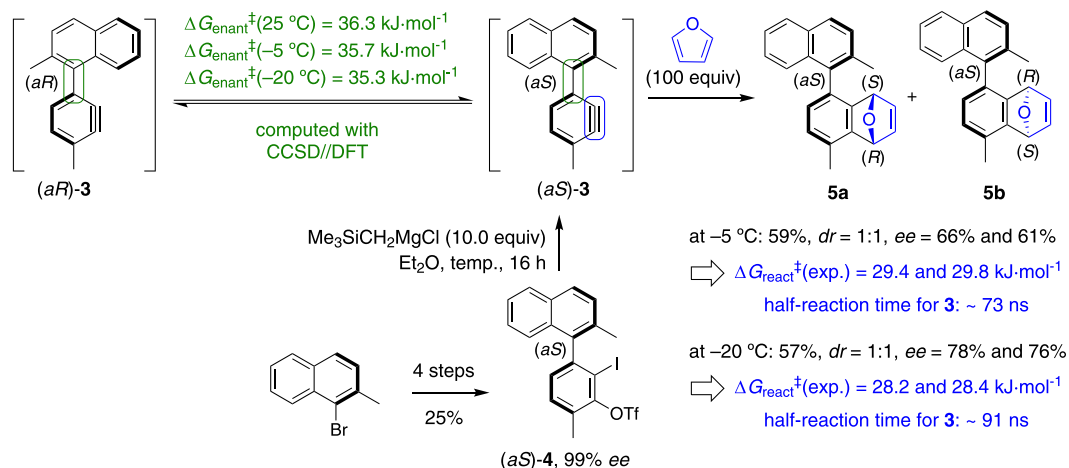
CONTRIBUTION OF THE *ortho*-H ATOM TO ATROPISOMERISM IN TRIS-*ortho*-SUBSTITUTED BIPHENYL DERIVATIVES

The contribution to conformational stability of the H atom in biphenyl-based atropisomers having three *ortho* substituents other than a H atom around the stereogenic single bond can be evaluated by comparing their barrier to enantiomerization with the barrier to enantiomerization of the corresponding aryne atropisomers that lack a H atom *ortho* to the stereogenic single bond (Figure 1). In the absence of significant attractive van der Waals interactions such as electrostatic forces and London dispersion forces, the two most sterically demanding

substituents on each side of the stereogenic axis of an atropisomer are away from each other in the geometry of the favored enantiomerization transition state due to repulsive interactions. For trisubstituted biphenyl-based atropisomers, this results in a steric clash between two substituents (other than H) around the stereogenic single bond rendering the enantiomerization a difficult process (Figure 1a, left, brown/green or orange/green bulbous clash). For enantiomerization to occur in these cases, the two C(sp²) atoms of the stereogenic single bond must be significantly pyramidalized in the geometry of the corresponding transition state, which requires a lot of energy for aromatic systems (counter-aromatic character). In contrast, the missing H atom in aryne atropisomers is providing some free space for the molecule to bend in a more planar geometry in the enantiomerization transition state, limiting pyramidalization of the two C(sp²) atoms of the stereogenic single bond and possibly allowing for some stabilizing electronic conjugation between the two aromatic systems (pro-aromatic character, Figure 1a, right). A quantitative illustration of this phenomenon is provided by the comparison of the barriers to enantiomerization and half-racemization times of atropisomers **1-H2** and **2-H2** with the corresponding aryne atropisomers **1** and **2** in solution, showing huge differences (Figure 1b).

The crucial role of the repulsive interaction from H atoms in the conformational behavior of arenes versus the corresponding arynes is also illustrated in the case of benzo[*c*]phenanthrene versus benzo[*c*]phenanthr-1,2-yne. Under its most stable conformation, benzo[*c*]phenanthrene, or [4]-helicene, adopts a helically twisted geometry with $\Delta G_{\text{enant}}^\ddagger$ (25 °C) = 16.7 kJ mol⁻¹ caused by repulsive interactions between the two H atoms in the cove region.²⁴ In contrast, benzo[*c*]phenanthr-1,2-yne lacking one H atom in the cove

Scheme 1. [4 + 2] Cycloadditions of the Aryne Atropisomer (*aS*)-3 with Furan^a



^aIn green are shown the enantiomerization barriers of aryne atropisomer **3** determined using the average of six CCSD(T*)-F12**/DFT calculations. In blue are shown the semi-experimentally determined kinetic parameters of the reactions.

region is a planar compound.⁷ Synthetic organic chemists have progressively learned that C–H bonds can be reactive; it should also be plainly realized that C–H bonds matter in the conformational behavior of molecules, sometimes not just a little.

SEMIEXPERIMENTAL DETERMINATION OF THE HALF-REACTION TIME OF AN ARYNE ATROPISOMER IN SOLUTION

It was explained above why the half-racemization time of aryne atropisomers is much lower than the half-racemization time of the corresponding arenes. However, for aryne atropisomers **1** and **2**, the calculated half-racemization time remains in the magnitude of hours to days. Because arynes are very reactive short-lived intermediates, this should be largely sufficient to ensure that their reactions with some arynophiles are highly enantiospecific, that is, proceeding without a significant loss of the stereochemical information (see [Synthetic Applications of Mono\(aryne\) Atropisomers](#) for examples). This is raising one practical question: What would be the minimum half-racemization time required for an aryne atropisomer to react with full enantiospecificity? This question is of course intimately related to the actual reaction rate of the considered aryne atropisomer in the considered reaction. Although some experimentally determined kinetic data were reported for gaseous benzyne,⁵ no experimental data were available for any aryne in solution prior to the work summarized below.

The intrinsic reaction rate of benzyne with furan in solution can be evaluated in a realistic manner by DFT computational methods. The SMD(acetonitrile)/B3LYP-D3BJ/6-311+G-(d,p)//B3LYP/6-31G(d) model for this reaction provided the reaction barrier $\Delta G_{\text{react}}^{\ddagger}$ (25 °C) = 32.6 kJ mol⁻¹,²⁵ and our own calculations with the SMD(diethyl ether)/M062X-D3/aug-cc-pVDZ//M062X-D3/cc-pVDZ model afforded $\Delta G_{\text{react}}^{\ddagger}$ (25 °C) = 36.4 kJ mol⁻¹.² This is corresponding to half-reaction times in the magnitude of tens to hundreds of nanoseconds at 25 °C depending on the model. The kinetic of the reaction of benzyne with furan, and more generally of any aryne with any arynophile, is marginally adjustable by modification of the experimental reaction conditions. How-

ever, the half-racemization time of aryne atropisomers can be adjusted at will using combined empirical and DFT-assisted molecular design, as illustrated for the aryne atropisomers **1** and **2** in [Figure 1](#). Thus, it should be possible to design an aryne atropisomer prototype with a half-racemization time in the magnitude of its half-reaction time with furan. Such an aryne atropisomer would allow one to measure experimentally significant variations in enantiospecificity during its reaction. On the basis of the accurate calculation of its barrier to enantiomerization, it should thus be possible to determine the kinetic constants of its [4 + 2] cycloadditions with furan.² The aryne atropisomer **3** shown in [Scheme 1](#) was identified as a suitable prototype to do so, with barriers to enantiomerization $\Delta G_{\text{enant}}^{\ddagger} = 25.1\text{--}33.9\text{ kJ mol}^{-1}$ at 25 °C computed using six different DFT methods. To obtain a more accurate quantitative value of $\Delta G_{\text{enant}}^{\ddagger}$ for **3**, the electronic energies of the stationary points identified by DFT were recomputed at the CCSD(T*)-F12*/def2-TZVP level of theory, and Gibbs free energies were obtained by applying the thermochemistry correction and solvation effects from the DFT calculations. The six values of the barrier to enantiomerization of aryne atropisomer **3** calculated using this CCSD//DFT approach were in the 34.3–38.7 kJ mol⁻¹ range at 25 °C with an average over six values $\Delta G_{\text{enant}}^{\ddagger} = 36.3\text{ kJ mol}^{-1}$ corresponding to a half-racemization time $t_{\text{rac}}^{1/2} = 128\text{ ns}$, which was considered a good approximation. It can be noted that DFT methods significantly underestimated the electronic energies in this case. The appropriateness and accuracy of the CCSD//DFT model were verified by comparative analysis of the experimentally determined value for $\Delta G_{\text{rot}}^{\ddagger}$ in 1-(2',6'-dideutero-4'-methylphenyl)naphthalene²⁶ with <2.3% deviation.

The aryne atropisomer prototype **3** being identified and its barrier to enantiomerization safely determined, the next question to answer was the “how-to” for its enantiospecific generation in solution for applications. The existing difficulties and implemented solutions are delineated in the next sections of this Account. A straight answer is that aryne atropisomer (*aS*)-**3** can be generated enantiospecifically from the *ortho*-iodoaryl triflate precursor (*aS*)-**4** in the presence of excess trimethylsilylmethylmagnesium chloride in diethyl ether. The

enantiopure precursor (*aS*)-4 (99% ee) was obtained in 25% overall yield in four synthetic steps from 1-bromo-2-methylnaphthalene, including the resolution of its enantiomers by semipreparative HPLC methods prior to triflation.

The reaction of aryne atropisomer (*aS*)-3 with excess furan (100 equiv, pseudo-first-order reaction) was performed at -5 and -20 °C (Scheme 1). At both temperatures, the expected diastereomeric cycloadducts **5a** and **5b** were obtained as a 1:1 mixture, and it was verified that both diastereomers **5a** and **5b** are configurationally stable under the conditions of the experiments and the analyses. The determination of the enantiomeric excesses in **5a** and **5b** by HPLC methods for the reaction conducted at -5 °C revealed 66 and 61% ee, respectively. Similarly, for the reaction conducted at -20 °C, the enantiomeric excesses were measured at 78% and 76%, respectively. The measurable variations in the ee during the reactions demonstrate that the enantiomerization of the aryne atropisomer (*aS*)-3 is kinetically competing with its [4 + 2] cycloadditions with furan. Using the experimentally measured variations in ee in these reactions combined with the values of $\Delta G_{\text{enanti}}^{\ddagger}$ of the aryne atropisomer **3** at the reaction temperatures determined by the average of six CCSD//DFT calculations, it is possible to determine the activation energy $\Delta G_{\text{react}}^{\ddagger}$ for the cycloadditions between aryne atropisomer (*aS*)-3 and furan at -5 and -20 °C. Application of the chemical kinetic equations afforded $\Delta G_{\text{react}}^{\ddagger}(-5$ °C) = 29.4 and 29.8 kJ mol $^{-1}$ and $\Delta G_{\text{react}}^{\ddagger}(-20$ °C) = 28.2 and 28.4 kJ mol $^{-1}$ for the formation of diastereomers **5a** and **5b**, respectively. These values of $\Delta G_{\text{react}}^{\ddagger}$ for the aryne atropisomer (*aS*)-3 are the first experimental data available on the kinetic of an aryne in solution and correspond to averaged half-reaction times of 73 and 91 ns for the reaction of (*aS*)-3 with furan at -5 and -20 °C, respectively.² It can be noted that the barrier to enantiomerization $\Delta G_{\text{enanti}}^{\ddagger}$ of the aryne atropisomer **3** is reduced by a few at lower temperature, and the same holds for its barriers to reaction $\Delta G_{\text{react}}^{\ddagger}$ with furan to give the cycloadducts **5a** and **5b**. The Gibbs free energy barrier ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T \cdot \Delta S^{\ddagger}$) of a chemical process varies with temperature. Accordingly, both the enthalpy and the entropy terms in both the transition state and the substrate(s) depend on the temperature, with the entropy term possibly negative or positive.

Considering that more than 3 orders of magnitude are required between the half-racemization time and the half-reaction time of an aryne atropisomer to be synthetically useful, the question formulated at the beginning of this section can be answered. The minimum half-racemization time required for an aryne atropisomer to react at 0 °C with furan with full enantiospecificity is in the magnitude of a fraction of a millisecond, corresponding to a barrier to enantiomerization equal to or higher than $\Delta G_{\text{enanti}}^{\ddagger}(0$ °C) = 50 kJ mol $^{-1}$.

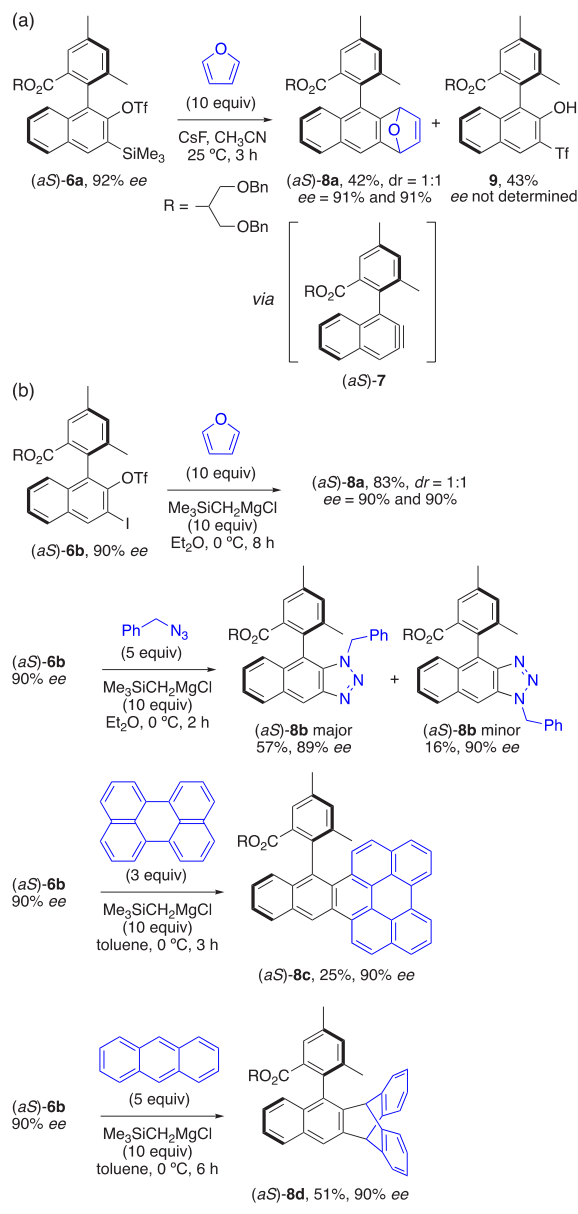
The values of the Gibbs free energies for the barrier to reaction $\Delta G_{\text{react}}^{\ddagger}$ of the aryne atropisomer **3** with furan shown in Scheme 1 are considered accurate with an estimated deviation from reality <3%. They are comparable to the corresponding values obtained by computational modeling using DFT calculations with SMD(diethyl ether)/M062X-D3/ aug-cc-pVDZ//M062X-D3/cc-pVDZ that offers a good balance between computational resources and quantitative assessment, with $\Delta G_{\text{react}}^{\ddagger}(25$ °C) computed at 27.0 and 27.4 kJ mol $^{-1}$ for the formation of diastereomers **5a** and **5b**, respectively, to be compared to $\Delta G_{\text{react}}^{\ddagger}(-5$ °C) = 29.4 and

29.8 kJ mol $^{-1}$ and $\Delta G_{\text{react}}^{\ddagger}(-20$ °C) = 28.2 and 28.4 kJ mol $^{-1}$ determined by the semiexperimental approach. As mentioned above, using this level of DFT for modeling the reaction of benzyne itself with furan afforded $\Delta G_{\text{react}}^{\ddagger}(25$ °C) = 36.4 kJ mol $^{-1}$, indicating that the aryne atropisomer **3** is about 40 times more reactive than benzyne in the presence of furan at 25 °C. Similarly, a suitable DFT method for the evaluation of $\Delta G_{\text{enanti}}^{\ddagger}$ in aryne atropisomer **4** was identified as SMD(diethyl ether)/M062X-D3/def2-TZVP, which provided $\Delta G_{\text{enanti}}^{\ddagger}(25$ °C) = 33.9 kJ mol $^{-1}$ to be compared to $\Delta G_{\text{enanti}}^{\ddagger}(25$ °C) = 36.3 kJ mol $^{-1}$ determined by the CCSD//DFT model. The identification of suitable DFT methods to model processes in this series, although probably underestimating the values by a few, should help in further developments.

■ SYNTHETIC APPLICATIONS OF MONO(ARYNE) ATROPISOMERS

The first aryne atropisomer ever prepared was (*aS*)-7 (Scheme 2), an analogue of the aryne atropisomer (*aS*)-1 shown in Figure 1 with a 1,3-bis(benzyloxy)propan-2-yl ester instead of a methyl ester.¹ The reason why this bulky ester group was introduced in aryne atropisomer (*aS*)-7 is practical: 1,3-bis(benzyloxy)propan-2-ol was the most efficient nucleophilic alcohol identified for the atropo-enantioselective organo-catalytic synthesis of the synthetic precursors (*aS*)-6a,b of aryne atropisomer (*aS*)-7 from the corresponding achiral Bringmann-type lactones.²⁷ In early work, aryne atropisomer (*aS*)-7 was generated by a fluoride-induced 1,2-elimination from the corresponding *ortho*-trimethylsilylaryl triflate precursor (*aS*)-6a (92% ee) in the presence of furan. Rewardingly, a 1:1 mixture of the two diastereomeric cycloadducts (*aS*)-8a was obtained, with both diastereomers having 91% ee, demonstrating that the generation of aryne atropisomer (*aS*)-7 and its trapping reactions with furan occurred with nearly complete retention of the stereochemical information (Scheme 2a). While this reaction provided the first evidence that nonracemic aryne atropisomers can exist in solution, it was plagued by an efficiency issue: the major product of the reaction was not the expected mixture of diastereomeric cycloadducts (*aS*)-8a but the triflyl-substituted naphthol atropisomer **9** isolated in 43% yield. Formation of product **9** from precursor (*aS*)-6a arose from a kinetically competitive thia-Fries rearrangement instead of the desired 1,2 elimination, a well-known issue with hindered aryne precursors. It was thus decided to abandon *ortho*-trimethylsilylaryl triflate precursors for the generation of aryne atropisomers, and *ortho*-iodoaryl triflate precursors were considered instead. After some optimization, it was found that the two diastereomeric cycloadducts (*aS*)-8a (90% ee for both diastereomers) can be obtained efficiently and with full enantiospecificity from the precursor (*aS*)-6b (90% ee) in the presence of excess trimethylsilylmethylmagnesium chloride and furan (Scheme 2b). Nicely, no thia-Fries rearrangement product **9** was detected in the product mixture under the optimized conditions. The use of *ortho*-iodoaryl triflates combined with trimethylsilylmethylmagnesium chloride²⁸ is revealing its potential in the applications described herein; it should be added to the standard arsenal for the applications of arynes in organic synthesis, especially when the thia-Fries rearrangement is an issue. These reaction conditions from precursor (*aS*)-6b were found general, and representative unsaturated arynophiles could be employed. Concerning diastereoselectivity issues, no substrate control was observed with prostereogenic arynophiles

Scheme 2. Examples of Cycloadditions of the Aryne Atropisomer (*aS*)-7 with Representative Unsaturated Arynyphiles

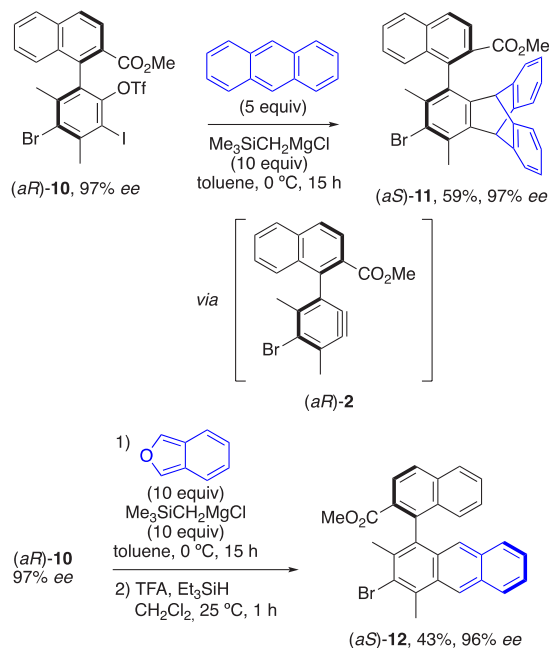


other than furan, systematically affording a 1:1 mixture of the two possible diastereomers as obtained for (*aS*)-8a. For the evaluation of regioselectivity, the reaction with benzyl azide is illustrative. It produced the triazole (*aS*)-8b as a 3.5:1 mixture of the two possible regioisomers. Interestingly, the major regioisomer of (*aS*)-8b resulted from bond formation between the nucleophilic part of the azide reaction partner and the alkyne terminus ortho to the stereogenic axis in aryne atropisomer (*aS*)-7, which is the most hindered reactive position. This selectivity is in agreement with the aryne distortion model²⁹ in which the nucleophile adds preferentially to the alkyne terminus with the greater distortion toward

linearity (see angles in (*aS*)-1, Figure 1), but may also account for the existence of London dispersion forces in the cycloaddition transition state.³⁰ The reaction of the aryne atropisomer (*aS*)-7 with perylene afforded the nanographene anthra[1,2,3,4-*ghi*]perylene atropisomer (*aS*)-8c in 25% yield and complete enantiospecificity. The moderate yield obtained in this case reflects, in part, the hindrance around the stereogenic single bond and the plausible involvement of some aryne in the in situ dedihydrogenation of the intermediate [4 + 2] cycloadduct. The reaction of aryne atropisomer (*aS*)-7 with anthracene afforded the original benzotriptyceny atropisomer (*aS*)-8d in 51% yield still with complete enantiospecificity. Overall, the products (*aS*)-8a–8d (90% *ee*) were obtained enantioselectively in three synthetic steps from the corresponding achiral Bringmann-type iodolactone: (i) atropo-enantioselective organocatalytic ring opening of an achiral iodolactone with an alcohol, (ii) triflation of the resulting naphthol, and (iii) enantiospecific cycloaddition reactions through the corresponding aryne atropisomer.

The aryne atropisomer (*aS*)-7 is built on a 1-phenyl-naphthalene platform with the aryne triple bond embedded in the naphthyl moiety. It was judged useful to also demonstrate that some regioisomeric aryne atropisomer built on the same platform now with the aryne triple bond embedded in the phenyl moiety can exist and react comparably. The aryne atropisomer (*aR*)-2 was targeted for this purpose (Scheme 3). Accordingly, the corresponding achiral Bringmann-type iodolactone was prepared, and its atropo-enantioselective organocatalytic opening reaction with 1,3-bis(benzyloxy)-

Scheme 3. Examples of Cycloadditions of the Aryne Atropisomer (*aR*)-2 with Representative Unsaturated Arynyphiles⁴



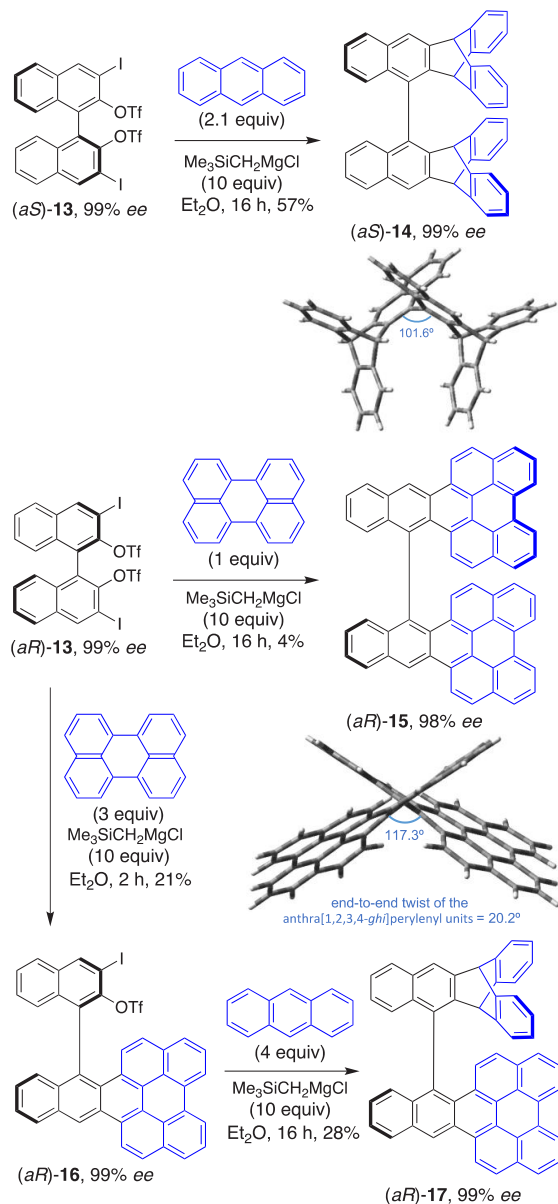
⁴The CIP priority order in the precursor (*aR*)-10 and the products is inverted in these cases.

propan-2-ol was performed under the conditions developed for the preparation of precursor (*aS*)-**6b**. The expected ester was obtained in 67% yield but only 73% ee.¹ Although enantiomeric enrichment of this material has been possible, it was decided to prepare the corresponding racemic methyl ester and to resolve it by semipreparative HPLC techniques. After synthesis and resolution of both enantiomers of the corresponding phenol derivatives (38%, >99% ee for both), their absolute configurations were determined by electronic circular dichroism spectroscopy, and the (*aR*)-configured derivative was quantitatively triflated to afford the aryne atropisomer precursor (*aR*)-**10** with 97% ee. The reaction of precursor (*aR*)-**10** with anthracene under the conditions developed for the reactions of precursor (*aS*)-**6b** afforded the triptycene atropisomer (*aS*)-**11** (97% ee) via the aryne atropisomer (*aR*)-**2**. The structure and absolute configuration of the triptycene atropisomer (*aS*)-**11** were confirmed by single-crystal X-ray analysis. In another example, the aryne atropisomer precursor (*aR*)-**10** was reacted with isobenzofuran, and the resulting mixture of diastereomers was immediately subjected to a deoxygenative aromatization reaction to give the anthracenyl atropisomer (*aS*)-**12** (43% over the two steps, 96% ee). These examples demonstrate the generality of the concept of enantiospecific synthesis through aryne atropisomers.

SYNTHETIC APPLICATIONS OF BIS(ARYNE) ATROPISOMER SYNTHETIC EQUIVALENTS

The complementary but nontrivial question that motivated this part of the work is as follows: Can the concept of aryne atropisomers be extended to synthetic equivalents of bis(aryne) atropisomers for controlled bidirectional reactions in 3D with single handedness?³ Planar bis(aryne)^{31–38} and tris(aryne)^{39,40} synthetic equivalents have been described, which enabled multidirectional solution-phase reactions in 2D. A remarkable example is the cross reaction with C₆₀ and a planar nanographene to afford a hybrid carbon nanostructure.⁴¹ It was devised that BINOL (1,1'-bi-2,2'-naphthol) could serve as a chiral platform to build up bis(aryne) atropisomer synthetic equivalents amenable to bidirectional enantiospecific synthetic applications with a single handedness. An attempt from the bis[*ortho*-(trimethylsilyl)aryl triflate] BINOL derivative only resulted in the 2-fold thia-Fries rearrangement product. Using the bis(*ortho*-iodoaryl triflate) BINOL derivatives (*aS*)-**13** and (*aR*)-**13** prepared in four steps from BINOL (77% overall, 99% ee) in combination with trimethylsilylmethylmagnesium chloride for the generation of the corresponding bis(aryne) atropisomer synthetic equivalent provided a simple solution for the realization of this idea (Scheme 4).³ In practice, a solution of (*aS*)-**13** (99% ee) treated with excess trimethylsilylmethylmagnesium chloride in the presence of anthracene provided the bis(benzotriptycene) atropisomer (*aS*)-**14** (57%, 99% ee), the structure and absolute configuration of which were confirmed by single-crystal X-ray diffraction analysis. Bis(benzotriptycene) atropisomer (*aS*)-**14** shows a unique chirality pattern for a PAH with controlled positions and orientations in the space of six distinct π systems. Notably, the dihedral angle between the two triptycene units around the stereogenic single bond was measured >101°. Similarly, the 2-fold reaction of (*aR*)-**13** with perylene afforded the expected nanographene atropisomer (*aR*)-**15** (98% ee), albeit in 4% yield due to the difficulties inherent to the reactions with perylene. DFT modeling of the geometry in atropisomer (*aR*)-**15** revealed that congestion around the

Scheme 4. Enantiospecific Bidirectional Cycloadditions of the Bis(aryne) Atropisomer Synthetic Equivalents Derived from BINOL



stereogenic single bond is such that the two anthra[1,2,3,4-*ghi*]perylene units show a dihedral angle >117° and that both anthra[1,2,3,4-*ghi*]perylene units are forced to adopt a (*P*)-configured helical conformation with an end-to-end twist angle >20°, as in twistacenes.^{42,43} The nanographene atropisomer (*aR*)-**15** exhibits three configurationally stable stereogenic elements, a primary stereogenic axis and two secondary helical twists; it should be regarded as the first example of a bis(twistacene) atropisomer, a new class of chiral PAH with multiple stereogenicities.

Cross reactions of the bis(aryne) atropisomer synthetic equivalent derived from (*aS*)-**13** and (*aR*)-**13** with different

aryneophiles proved possible. For example, the interrupted reaction between precursor (*aR*)-13 and perylene hydrolyzed after 2 h, instead of the 16 h required for the synthesis of (*aR*)-15, provided essentially that the mono(adduct) (*aR*)-16 (21%, 99% ee) had one perylene unit attached and one preserved *ortho*-iodonaphthyl triflate unit. Using (*aR*)-16 as the precursor of an aryne atropisomer in a subsequent reaction with anthracene, led to the cross atropisomer product (*aR*)-17 (28%, 99% ee) as an original chiral triptycene/nanographene hybrid. Considering that enantiopure BINOL can derive from the electrocatalytic atropo-enantioselective oxidative dimerization of 2-naphthol (94% yield, >99% ee),⁴⁴ the overall syntheses of the nanocarbon and nanographene atropisomers (*aS*)-14 (99% ee), (*aR*)-15 (98% ee), and (*aR*)-17 (99% ee) can be regarded as enantioselective syntheses from 2-naphthol in six, six, and seven steps, respectively.

CONCLUSION

“The height of sophistication is simplicity.”

Clare Boothe Luce, *Stuffed Shirts*, 1931.

With the progression of knowledge, organic synthesis is becoming at the same time more sophisticated and simpler, more sophisticated because incredibly complex chemical transformations difficult to imagine just a couple decades ago can now be realized for the controlled synthesis of three-dimensional organic molecules, and simpler because contemporaneous solutions to synthetic problems can be disconcertingly straightforward. The advent of organocatalysis, the reactivity of C–H bonds, and multicatalysis, to name a few, illustrate this progression. Make no mistake, identifying simple solutions in organic synthesis is not an easy task; it requires a lot of creativity and passionate work on the part of the synthetic organic chemist.

The lessons that can be learned from the work described in this Account are as follows:

Aryne atropisomers can exist as discrete chemical species in solution, bringing arynes to the third dimension. Their generation is simply achieved from easily available *ortho*-iodoaryl triflate precursors and excess trimethylsilylmethylmagnesium chloride.

Aryne atropisomers can be generated and reacted with full retention of the stereochemical information from their precursors, as simple as it seems, illustrating that the concept of atropisomerism is also valid for short-lived molecules. Only biphenyl-based aryne atropisomers have been examined until now; other aryne atropisomers with different backbones are certainly feasible.

Most importantly, using aryne atropisomers, the synthesis of nonracemic atropisomers can now be thought differently, with new outcomes available for the synthesis of original and/or extremely crowded atropisomers. Aryne atropisomers provide a simple, intuitive, and practical approach to the synthesis of atropisomers with high ee. The overall enantioselective syntheses of some exceptionally congested nanocarbon and nanographene atropisomers in a few steps from 2-naphthol are illustrative of this.

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Notes

The author declares no competing financial interest.

Biography

Yoann Coquerel was born in Rouen (France) in 1975. He started his education at the Université de Bourgogne (France) and moved to the Université Grenoble Alpes (France) where he earned his Ph.D. in 2001. He pursued postdoctoral studies at Florida State University. In 2003, he joined Aix-Marseille Université (France) as a Centre National de la Recherche Scientifique (CNRS) research fellow and was promoted to research director in 2015. His current research interests are focused on chirality in nonclassical aromatic organic molecules, from stereoselective synthesis to physical chemistry.

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REFERENCES

- (1) Wei, Y.-L.; Dauvergne, G.; Rodriguez, J.; Coquerel, Y. Enantiospecific Generation and Trapping Reactions of Aryne Atropisomers. *J. Am. Chem. Soc.* **2020**, *142*, 16921–16925.
- (2) Dauvergne, G.; Vanthuyne, N.; Giorgi, M.; Rodriguez, J.; Carissan, Y.; Coquerel, Y. Determination of the Rate Constant of the [4 + 2] Cycloaddition Between an Aryne Atropisomer and Furan in Solution. *J. Org. Chem.* **2022**, *87*, 11141–11147.
- (3) Dauvergne, G.; Naubron, J.-V.; Giorgi, M.; Bugaut, X.; Rodriguez, J.; Carissan, Y.; Coquerel, Y. Enantiospecific Syntheses of Congested Atropisomers Through Chiral Bis(aryne) Synthetic Equivalents. *Chem.—Eur. J.* **2022**, No. e202202473.
- (4) Bachmann, W. E.; Clarke, H. T. The mechanism of the Wurtz-Fittig reaction. *J. Am. Chem. Soc.* **1927**, *49*, 2089–2098.
- (5) Wentrup, C. The Benzyne Story. *Aust. J. Chem.* **2010**, *63*, 979–986.
- (6) Kleinpeter, E.; Koch, A. Benzyne - an acetylene- or cumulene-like electronic structure? *Tetrahedron* **2019**, *75*, 4663–4668 and the references therein.
- (7) Artigas, A.; Hagebaum-Reignier, D.; Carissan, Y.; Coquerel, Y. Multidimensional isotropic magnetic shielding contour maps for the visualization of aromaticity in ortho-arynes and their reactions. *Synthesis* **2022**, *54*, 4997–5002.
- (8) Shi, J.; Li, L.; Li, Y. *o*-Silylaryl Triflates: A Journey of Kobayashi Aryne Precursors. *Chem. Rev.* **2021**, *121*, 3892–4044.

- (9) Takikawa, H.; Nishii, A.; Sakai, T.; Suzuki, K. Aryne-based strategy in the total synthesis of naturally occurring polycyclic compounds. *Chem. Soc. Rev.* **2018**, *47*, 8030–8056.
- (10) Pozo, I.; Guitián, E.; Pérez, D.; Peña, D. Synthesis of Nanographenes, Starphenes, and Sterically Congested Polyarenes by Aryne Cyclotrimerization. *Acc. Chem. Res.* **2019**, *52*, 2472–2481.
- (11) Sarmah, M.; Sharma, A.; Gogoi, P. Exploration of Kobayashi's aryne precursor: a potent reactive platform for the synthesis of polycyclic aromatic hydrocarbons. *Org. Biomol. Chem.* **2021**, *19*, 722–737.
- (12) Brandt, J. R.; Salerno, F.; Fuchter, M. J. The added value of small-molecule chirality in technological applications. *Nat. Rev. Chem.* **2017**, *1*, 45.
- (13) Oki, M. Recent Advances in Atropisomerism. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1983; Vol. 81.
- (14) *Atropisomerism and Axial Chirality*; Lassaletta, J. M., Ed.; World Scientific: London, 2019.
- (15) Nguyen, T. T. The Use of Chiral ortho-Auxiliaries/Substituents and Remote Stereogenic Centers in Atropselective Biaryl Synthesis. *Eur. J. Org. Chem.* **2020**, *2020*, 147–155.
- (16) Cheng, J. K.; Xiang, S.-H.; Li, S.; Ye, L.; Tan, B. *Chem. Rev.* **2021**, *121*, 4805–4902.
- (17) *Axially Chiral Compounds: Asymmetric Synthesis and Applications*; Tan, B., Ed.; Wiley-VCH: Weinheim, 2021.
- (18) Carmona, A.; Rodríguez-Franco, C.; Fernández, R.; Hornillos, V.; Lassaletta, J. M. Atroposelective transformation of axially chiral (hetero)biaryls. From desymmetrization to modern resolution strategies. *Chem. Soc. Rev.* **2021**, *50*, 2968–2983.
- (19) Bao, X.; Rodríguez, J.; Bonne, D. Enantioselective Synthesis of Atropisomers with Multiple Stereogenic Axes. *Angew. Chem., Int. Ed.* **2020**, *59*, 12623–12634.
- (20) Castro Agudelo, B.; Rigoulet, F.; Giorgi, M.; Sayah, B.; Rodríguez, J.; Coquerel, Y. Synthesis of Axially Chiral Cationic Benzo[*c*]phenanthridinium Derivatives. *Synthesis* **2022**, *54*, 5035–5041.
- (21) Hughes, E. D.; Juliusburger, F.; Masterman, S.; Topley, B.; Weiss, J. Aliphatic Substitution and the Walden Inversion. Part I. *J. Chem. Soc.* **1935**, 1525–1592.
- (22) Reist, M.; Testa, B.; Carrupt, P.-A.; Jung, M.; Schurig, V. Racemization, Enantiomerization, Diastereomerization, and Epimerization: Their Meaning and Pharmacological Significance. *Chirality* **1995**, *7*, 396–400 and the references therein.
- (23) Ravat, P. Carbo[*n*]helicenes Restricted to Enantioselective: An Insight into the Design Process of Configurationally Stable Functional Chiral PAHs. *Chem.—Eur. J.* **2021**, *27*, 3957–3967 and the references therein.
- (24) Barroso, J.; Cabellos, J. L.; Pan, S.; Murillo, F.; Zarate, X.; Fernandez-Herrera, M. A.; Merino, G. Revisiting the racemization mechanism of helicenes. *Chem. Commun.* **2018**, *54*, 188–191.
- (25) Arora, S.; Hoye, T. R. Kobayashi Benzynes" as Hexadecyhydro-Diels-Alder Dinyphiles. *Org. Lett.* **2021**, *23*, 3349–3353.
- (26) Lesot, P.; Lafon, O.; Kagan, H. B.; Fan, C.-A. Study of molecular rotational isomerism using deuterium NMR in chiral oriented solvents. *Chem. Commun.* **2006**, 389–391.
- (27) Yu, C.; Huang, H.; Li, X.; Zhang, Y.; Wang, W. Dynamic Kinetic Resolution of Biaryl Lactones via a Chiral Bifunctional Amine Thiourea-Catalyzed Highly Atropo-enantioselective Transesterification. *J. Am. Chem. Soc.* **2016**, *138*, 6956–6959.
- (28) Yoshida, S.; Uchida, K.; Hosoya, T. Generation of Arynes Using Trimethylsilylmethyl Grignard Reagent for Activation of ortho-Iodoaryl or ortho-Sulfinylaryl Triflates. *Chem. Lett.* **2015**, *44*, 691–693.
- (29) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. The Role of Aryne Distortions, Steric Effects, and Charges in Regioselectivities of Aryne Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 15798–15805.
- (30) Ikawa, T.; Yamamoto, Y.; Heguri, A.; Fukumoto, Y.; Murakami, T.; Takagi, A.; Masuda, Y.; Yahata, K.; Aoyama, H.; Shigetani, Y.; Tokiwa, H.; Akai, S. Could London Dispersion Force Control Regioselective (2 + 2) Cycloadditions of Benzynes? YES: Application to the Synthesis of Helical Biphenylenes. *J. Am. Chem. Soc.* **2021**, *143*, 10853–10859.
- (31) Hart, H.; Lai, C.-y.; Nwokogu, G.; Shamouilian, S.; Teuerstein, A.; Zlotogarski, C. Bisannulation of Arenes with Bisaryne Equivalents. *J. Am. Chem. Soc.* **1980**, *102*, 6649–6651.
- (32) LeHoullier, C. S.; Gribble, G. W. Twin annulation of naphthalene via a 1,5-naphthodiyne synthon. New syntheses of chrysene and dibenzo[*b,k*]chrysene. *J. Org. Chem.* **1983**, *48*, 1682–1685.
- (33) Gribble, G. W.; Pemi, R. B.; Onan, K. D. Twin benzannulation of naphthalene via 1,3-, 1,6-, and 2,6-naphthodiyne synthetic equivalents. New syntheses of triphenylene, benz[*a*]anthracene, and naphthacene. *J. Org. Chem.* **1985**, *50*, 2934–2939.
- (34) Duong, H. M.; Bendikov, M.; Steiger, D.; Zhang, Q.; Sonmez, G.; Yamada, J.; Wudl, F. Efficient Synthesis of a Novel, Twisted and Stable, Electroluminescent "Twistacene. *Org. Lett.* **2003**, *5*, 4433–4436.
- (35) Kitamura, C.; Abe, Y.; Ohara, T.; Yoneda, A.; Kawase, T.; Kobayashi, T.; Naito, H.; Komatsu, T. Synthesis and Crystallography of 1,4,7,10-Tetraalkyltetracenes: Tuning of Solid-State Optical Properties of Tetracenes by Alkyl Side-Chain Length. *Chem.—Eur. J.* **2010**, *16*, 890–898.
- (36) Pozo, I.; Cobas, A.; Peña, D.; Guitián, E.; Pérez, D. 1,7-Naphthodiyne: a new platform for the synthesis of novel, sterically congested PAHs. *Chem. Commun.* **2016**, *52*, 5534–5537.
- (37) Shi, J.; Li, Y.; Li, Y. Aryne multifunctionalization with benzdiyne and benztriyne equivalents. *Chem. Soc. Rev.* **2017**, *46*, 1707–1719.
- (38) He, J.; Qiu, D.; Li, Y. Strategies toward Aryne Multifunctionalization via 1,2-Benzdiyne and Benzyne. *Acc. Chem. Res.* **2020**, *53*, 508–519.
- (39) Ikada, J.; Yoshida, H.; Ohshita, J.; Kunai, A. Facile Synthesis of Polycyclic Aromatic Hydrocarbons via a Trisaryne Equivalent. *Chem. Lett.* **2005**, *34*, 56–57.
- (40) Pozo, I.; Peña, D.; Guitián, E.; Pérez, D. 2,6,10-Triphenylenetriyne: a star-shaped trisaryne. *Chem. Commun.* **2020**, *56*, 12853–12856.
- (41) García, D.; Rodríguez-Pérez, L.; Herranz, M. A.; Peña, D.; Guitián, E.; Bailey, S.; Al-Galiby, Q.; Noori, M.; Lambert, C. J.; Pérez, D.; Martín, N. A C₆₀-aryne building block: synthesis of a hybrid all-carbon nanostructure. *Chem. Commun.* **2016**, *52*, 6677–6680.
- (42) Pascal, R. A., Jr. Twisted Acenes. *Chem. Rev.* **2006**, *106*, 4809–4819.
- (43) Rickhaus, M.; Mayor, M.; Juríček, M. Strain-induced helical chirality in polyaromatic systems. *Chem. Soc. Rev.* **2016**, *45*, 1542–1556.
- (44) Osa, T.; Kashiwagi, Y.; Yanagisawa, Y.; Bobbitt, J. M. Enantioselective, Electrocatalytic Oxidative Coupling of Naphthol, Naphthyl Ether and Phenanthrol on a TEMPO-modified Graphite Felt Electrode in the Presence of (–)-Sparteine (TEMPO = 2,2,6,6-tetramethylpiperidin-1-yl-oxyl). *J. Chem. Soc., Chem. Commun.* **1994**, 2535–2537.