Sydnone-based Approach to Hetero-helicenes Through 1,3-Dipolar-Cycloadditions

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Supporting Information Placeholder

ABSTRACT: The first approach to pyrazole containing helicenes *via* sydnone-aryne [3+2]-cycloaddition is described. An unprecedented regioselectivity in the cycloaddition step towards the more sterically constrained product was observed in presence of extended aromatic scaffolds. DFT calculations enabled to understand the origin of this unexpected selectivity.

Ortho-fused aromatic rings belong to a class of helical-shaped molecules named helicenes.[1] Since their discovery, these variegated aromatics have fascinated chemist practitioners due to their elegant architecture, inherent chirality and structural complexity. Helical structures are particularly interesting as they are found in many biomacromolecules inspiring chemists involved in the field of asymmetric catalysis,[2] and their enhanced chiroptical properties have attracted much attention in material science.[3] The presence of a heteroatom in the fused polycyclic system considerably alters the electronic structure and helps tuning various optoelectrical properties.[4] In particular, nitrogen-containing helicenes, including pyridine,[5] pyrrole,[6] pyrazine[7] and imidazolonium[4a,8] have attracted much attention. Despite the broad interest over this family of compounds, synthetic access still remains challenging and often requires cumbersome multistep approaches.[1] Ideally, the desired helical motif would be assembled in the last step of the sequence, thus enabling divergent opportunities for structure diversity. Sydnones are azomethine imines, well-known for their 1,3-dipolar-cycloadditions with linear and strained alkynes, generating pyrazoles, a pharmaceutically and agrochemically relevant heterocyclic scaffold.[9] We reasoned that properly designed prohelical sydnones **3**, bearing *ortho*-extended aromatic substitutions, would be suitable partners with arynes bearing an extended aromatic core.[10] After cycloaddition, the subsequent loss of carbon dioxide would deliver the desired pyrazole-containing helicenes, a family of heterohelicenes so far unreported (Figure 1).

We now describe a novel disconnection allowing a direct access to a range of unreported helical pyrazoles, based on a key sydnone-aryne cycloaddition. In the process, we discovered a unique example of selective cycloaddition involving these mesoionic betaines in favor of the sterically hindered helical product and determined the reasons behind such selectivity with analysis of DFT calculations.

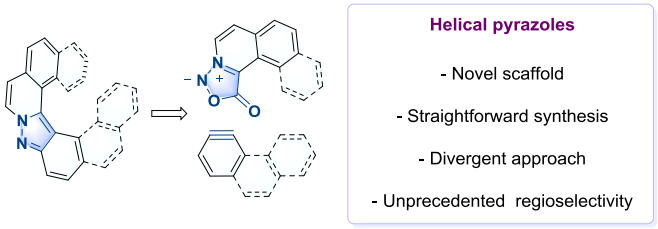

Figure 1: Design of pyrazoles-based helicenes.

The implementation of this strategy relies on the prerequisite preparation of *ortho*-fused aromatic azomethine imine dipoles. *N*-methyl sydnone **1** was identified as key component to build up such *ortho*-aromatic structures. Readily available in two steps from commercial sarcosine, **1** provides a versatile handle for further derivatization. It was envisioned that metal catalyzed functionalization at the C_4 position of the sydnone with 2-halobenzaldehyde would provide a key intermediate that might undergo intramolecular Knoevenagel condensation under basic conditions to give the desired product **3**. Initial attempts showcased that the whole cascade could be performed in one single operation. Product **3a** was first isolated in moderate yield together with the intermediate uncyclized aldehyde **S3a**.[11] After some experimentation, it was found that in presence of catalytic amounts of $Pd(OAc)_2$ and triphenylphosphine, with an excess of K_2CO_3 (4 equiv.), the desired mesoionic compound **3a** could be obtained in 88% yield. Similarly, the tetracyclic *ortho*-sydnone **3b** could be isolated in 66% yield starting from the corresponding 1-bromo-2-naphthaldehyde (Figure 2A).

With a reliable access to the prerequisite *ortho*-fused aromatic azomethine imines **3a** and **3b** secured, we turned our attention to the key 1,3-dipolar-cycloaddition between polycyclic sydnones and aryne precursors. The sydnone-aryne cycloaddition is a 50 year old transformation pioneered by Gotthardt, Huisgen, and Knorr and later by Kato and Tsuge in 1974,[12] but only recently the synthetic potential of this transformation has been studied in detail.[13] At first, we reacted sydnones **3a** and **3b** in presence of silyl triflate **4a** (1.5 equiv.) and TBAF (1.5 equiv.) at room temperature. As expected, the desired products **5** and **6** were isolated in good yields, 77 and 70%, respectively (Figure 2C). It is worth mentioning that **5** and **6**

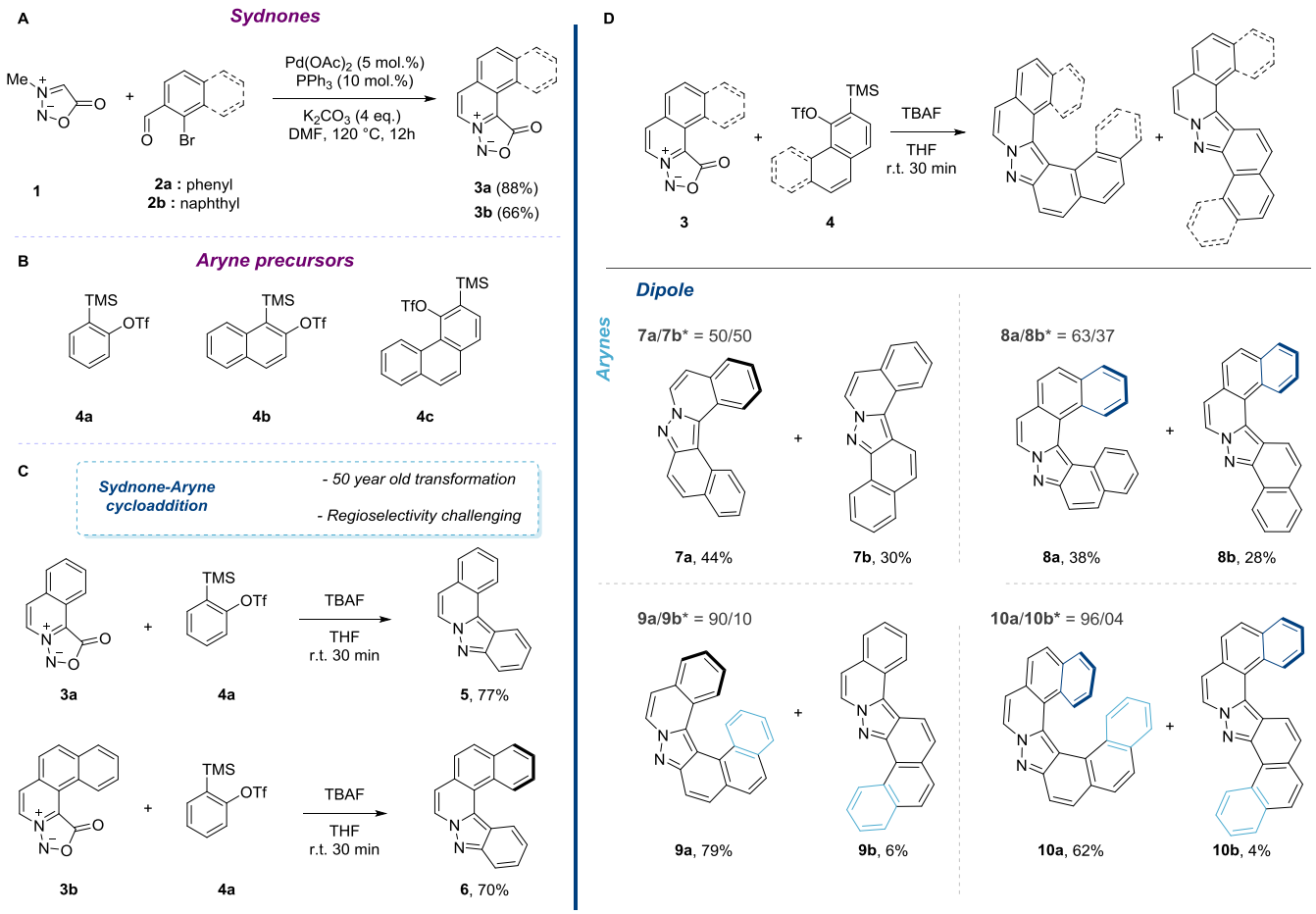

Figure 2: A: One-pot synthesis of polycyclic sydnones **3a** and **3b**; B: aryne precursor; C: Synthesis of helical pyrazoles **5** and **6**. D: Synthesis of helical pyrazoles **7a**, **8a**, **9a** and **10a**. * isomer ratio was measured by ^{1}H-NMR of the crude mixture.

have been synthesized in only two steps from readily available *N*-methyl sydnone.[14] The sequence could be extended to the *ortho*-fused 1,2-naphthyne precursor **4b** (Figure 2D). In presence of tricyclic sydnone **3a** the formation of the two possible cycloadducts, the desired hetero-[5]-helicene **7a** and the *S*-shaped product **7b,** was observed. As expected, no degree of selectivity was achieved and the cycloadducts were isolated in a 1:1 ratio and an overall 74% yield. The tetracylic sydnone **3b** gave a low degree of selectivity in favor of the sterically hindered hetero-[6]-helicene **8a** (**8a**/**8b**, ratio 63/37). The ^{1}H NMR analysis of the two regioisomers showed well-resolved signals, which could be clearly assigned with COSY and NOESY measurements.[11] Intrigued by this unexpected result, we investigated the reactivity of *ortho*-sydnones **3a** and **3b** in presence of 3,4-phenanthryne precursor **4c** (Figure 2D). This *ortho*-annulated aryne is particularly interesting because it should allow the formation of [6]- and [7]-helicenes. The reaction of **3a** with **4c** in presence of TBAF in THF delivered a crude mixture with a useful selectivity in favor of the helical product (crude ^{1}H-NMR ratio 90:10). After purification, the two components of the reaction could be isolated in 79% and 6% yield. The 2D-NMR measurements determined the identity of the major compound as the desired [6]-helical pyrazole **9a**.[15] When **4c** was reacted in presence of **3b**, [7]-helicene **10a** was isolated in 62% yield with high selectivity (**10a**:**10b** 96:4). Crystals of both isomers **10a** and **10b** were grown by slowly evaporating dichloromethane solutions and the structures were determined by single-crystal X-ray diffraction (Figure 3A).

The chiroptical properties of [7]-helicene **10a** were subjected to a preliminary evaluation. Enantiomers of **10a** were resolved from a racemic mixture using HPLC with a chiral-phase column.[16] In Figure 3B are shown the circular dichrograms of the enantiopure samples, which exhibit both positive and negative Cotton effects at 235 and 357 nm. The spectra of the enantiomers are mirror images of each other. The measurements conducted in degassed dichloromethane for the set of enantiomers led to the observation of a mirror-image CPL signal (Figure 3C). The g_{lum} values are -0.001 and +0.001 at about the maximum emission wavelength for **10a**.[17] These values are of the same order of magnitude as those for other examples of organic CPL-active helicenes.[18] These results confirm that the solution of [7]-helicene **10a** in degassed dichloromethane exhibits active CPL signals, and also that the emitted light is polarized in opposite directions for the two enantiomeric forms for this helicene-like structure.

The selectivities observed for these sydnone-aryne cycloadditions were unexpected, given precedents in the literature. First, sydnones are known to be poorly regioselective in their cycloadditions with asymmetrical alkyne dipolarophiles.[13, 19-23] Moreover, the Houk-Garg distortion-based model to explain the preferred regioselectivity of attack of nucleophiles on strained alkynes,[24] which is based on the difference in internal angles of the alkyne carbons, predicts

low selectivity with 1,2-naphthyne or 3,4-phenanthryne, albeit in the observed direction. DFT optimizations of the two structures (M06-2X/6-31+G(d,p))[11] reveal that the two aryne carbons have similar internal bond angles (Figure 4A).

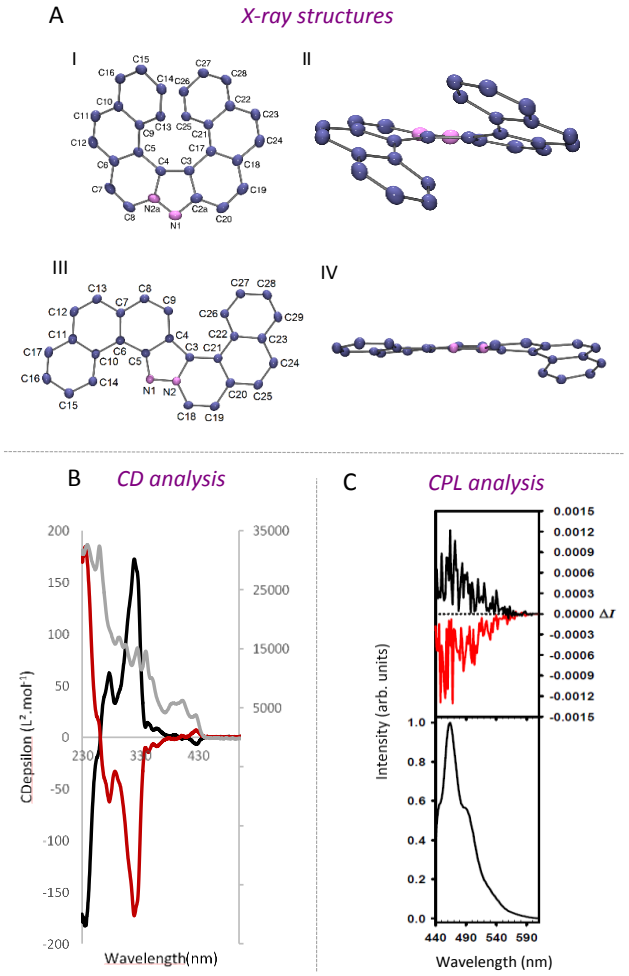

Figure 3: A) Molecular structure of **10a**: I) top and II) side views. Molecular structure of **10b**: III) top and IV) side views. Ellipsoids are set at 40% probability; hydrogen atoms are omitted for clarity. B) UV (gray curve) and CD spectra of **(+)-10a** (black curve) and **(-)-10a** (red curve); C) CPL (upper curve) and total luminescence (lower curves) spectra of **(+)-10a** (black curve) and **(-)-10a** (red curve) in degassed dichloromethane at 295 K, upon excitation at 430 nm.

In order to highlight whether the peculiar structure of sydnones **3a** and **3b** is responsible for the unusual selectivity, sydnone **3c** was synthesized. As shown in Figure 4B, when *N*-phenyl sydnone **3c** was reacted with **4c** the opposite selectivity was observed (ratio 33:66 in favor of **11b**).[25] This result suggests that the origin of the selectivity might be related to the structure of the polycyclic sydnone itself. To understand the origins of such a dichotomy, we calculated the free energy profiles for the reactions of **3a**-**3c** with both 1,2-naphthyne and 3,4-phenanthryne, using the same DFT method described above. Profiles for the reaction of **3a** with 3,4-phenanthryne are shown in Figure 4C.[11] In all cases examined, the regiodetermining cycloaddition step is also rate-determining and fully irreversible, as the formation of the intermediate cycloadduct (**int**) is highly exergonic (ΔG = –33 to –58 kcal/mol). The CO_2 extrusion step (**TS 2**) is then extremely facile and once again very exergonic. All cycloaddition transition states (**TS 1**) have very low activation barriers ($\Delta G^{\ddagger}$ between 9 and 12 kcal/mol). Our calculations also quantitatively reproduce the experimental selectivities, that is formation of the helical regioisomer is predicted to be favored for sydnones **3a** and **3b**, but unfavored for **3c**.

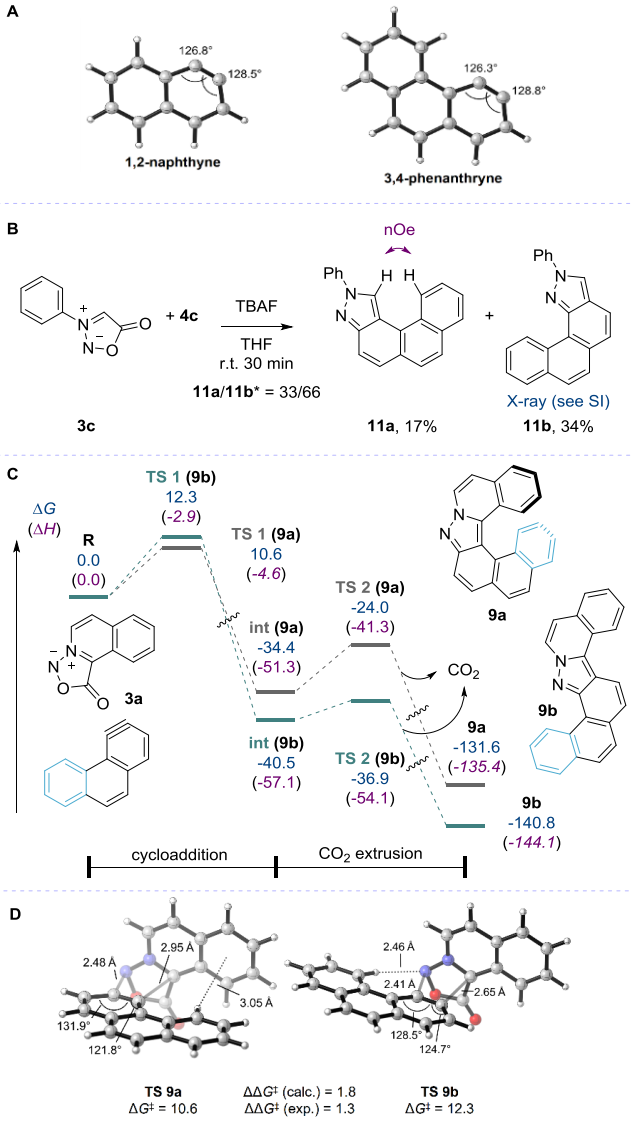

Figure 4: A) DFT-optimized structures of polycyclic arynes derived from **4b** and **4c**. B) Reaction between non planar *N*-phenyl sydnone **3c** and 3,4-phenanthryne precursor **4c**. * isomer ratio was measured by ^{1}H-NMR of the crude mixture. C) Energy profile for the reaction of **3a** with 3,4-phenanthryne to form **9a** or **9b**. Free energies (*enthalpies*) are in kcal/mol and were obtained at the M06-2X/6-311+G(2d,2p)/SMD (THF) // M06-2X/6-31+G(d,p) level of theory. D) Cycloaddition TSs leading to regioisomers **9a** and **9b**. M06-2X/6-311+G(2d,2p)/SMD (THF) // M06-2X/6-31+G(d,p). Free energies in kcal/mol.

The TSs leading to the two regioisomers for the representative reaction of **3a** with 3,4-phenanthryne are shown in Figure 4D. The TSs for the other pairs of reactants can be found in the SI and display similar arrangements. First, the TS leading to the major helical isomer is more asynchronous, with the shorter forming bond being between the more nucleophilic terminus of the azomethine imine of the sydnone and the more electrophilic (linear) carbon of the aryne.[26] Indeed, for the fused sydnones **3a** and **3b**, the nitrogen atom bears more HOMO character than the carbon, while for *N*-phenyl sydnone **3c**, the opposite is found. Second, the forming bonds are fairly long, indicative of very early TSs, which are in accord with

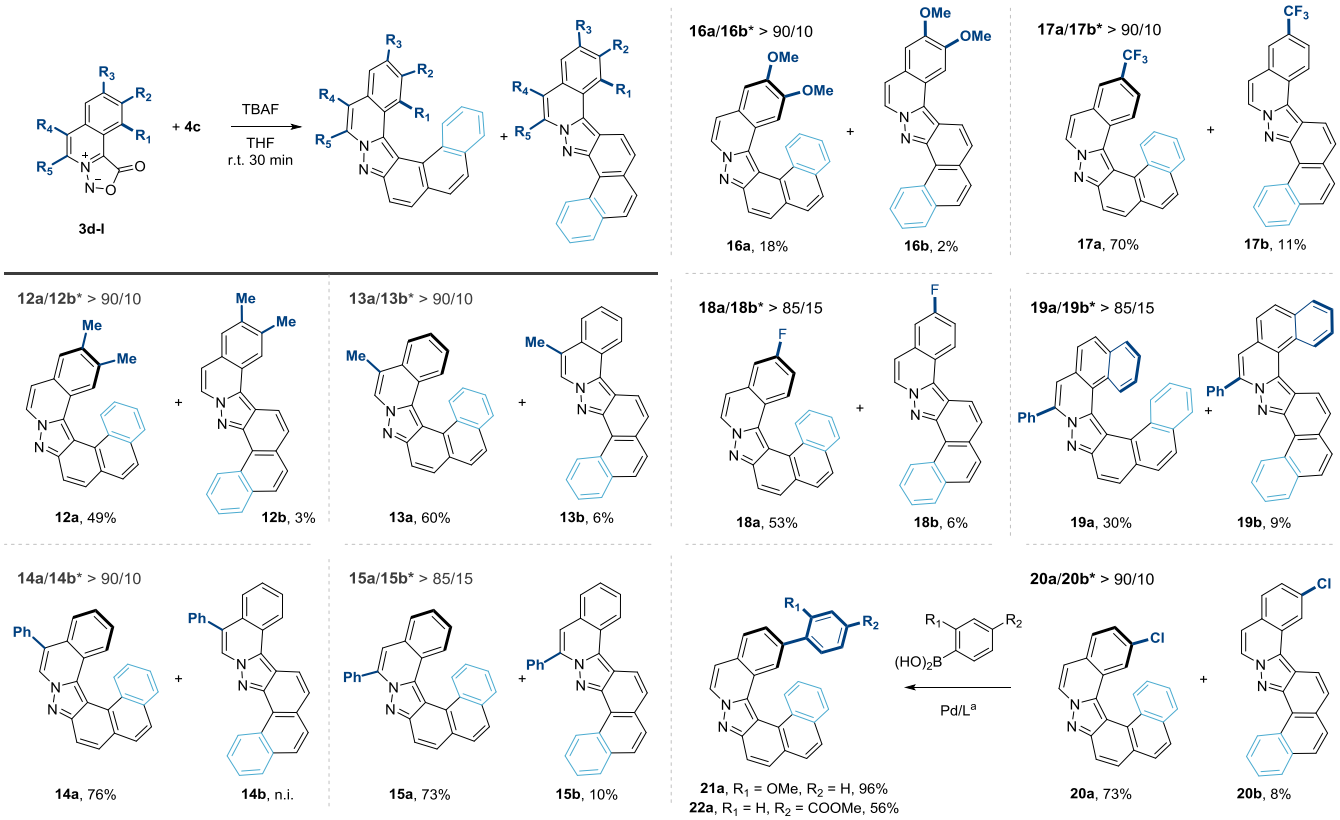

Figure 5: Synthesis of helical pyrazoles **12a-22a**. * isomer ratio was measured by ^{1}H-NMR of the crude mixture. n.i. not isolate. [a] See supporting information for detailed conditions.

the high exergonicity of the cycloaddition steps and the Hammond postulate. Third, the major TS seems to benefit from stabilizing C–H···π interactions (also called face-to-edge π-π interactions) between the polycyclic backbones of the reactants, while the minor TS does not.[27]

Distortion/interaction analysis[28] confirms this behavior: as the TSs are so early, the reactants are barely distorted from their ground-state geometries, and total distortion energies are, at most, 4.0 kcal/mol. As such, even though the helical regioisomer of the cycloadducts and pyrazoles is more sterically-encumbered and always higher in energy than the S-shape isomer, this effect is not important in **TS 1** since the reactants are still far from each other. Conversely, interaction energies range from –7.4 to –12.4 kcal/mol, and are greater for the helical vs the S-shape regioisomer. In fact, for the six systems studied, the activation energies correlate with interaction energies, but have no correlation with distortion energies.[11] To confirm the stabilization offered by the dispersive aromatic-aromatic interactions, we computed the binding energies of aromatic dimers in the same geometries as the helical TSs.[11] For the four combinations evaluated, the binding energies were between –0.4 to –1.9 kcal/mol, demonstrating the stabilization offered by the C–H···π interactions for the helical TSs, in addition to the more favorable primary orbital interactions. Thus, the TSs that benefit from the most interactions are also earlier, further lowering the cost to distort the reactants. These results indicate that with other very reactive partners, regioselective cycloadditions might be possible when interactions with polycyclic backbones are present. Indeed, when substituted sydnones **3d**-**3l** were reacted with **4c** similar values of regioselectivity (> 85/15) were observed in favor of the ~~and the~~ corresponding [6] and [7]-helicenes **12a**-**20a** ~~were isolated in 49 to 76% yields~~ (Figure 5). While the presence of electro-neutral and -withdrawing substituents on the sydnone does not affect the transformation, di-substituted electron-rich dipole **3h** was poorly reactive and the desired [6]-helicene **16a** was isolated in 18% yield.[29] Derivative **20a** with a the presence of a chloride substituent offered a useful handle for further functionalization. Under catalytic conditions, the products of Sukuzi cross-coupling reaction **21a** and **22a** were isolated in 96 and 56% yield. This preliminary proof-of-concept showed the possibility to further functionalize this helical scaffold by means of metal catalysis and could be of interest for potential applications.

In summary, we have developed a method to access [4],[5],[6] and [7]-helicenes containing pyrazoles through sydnone 1,3-dipolar cycloadditions. This process involves the design and synthesis of *ortho*-substituted polyaromatic sydnones, which are more nucleophilic than conventional ones, and highlights the first example of regioselective cycloaddition of such mesoionic dipoles with aryne derivatives. Calculations showed that primary orbital interactions and C–H···π dispersive interactions control the regioselectivity of this transformation. This reaction will ultimately provide a modular access to substituted derivatives, and could be amenable to the synthesis of other helicenes families.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge via the Internet at http://pubs.acs.org.
Experimental procedures and computational details
NMR spectra for obtained compounds
Crystallographic data for compounds **10a** (CCDC 1544556), **10b** (CCDC 1872990), and **11b** (CCDC 1544557).

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Notes

The authors declare no competing financial interests.

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(17) The degree of CPL is given by the luminescence dissymmetry ratio, $g_{lum}(\lambda) = 2\Delta I/I = 2(I_L - I_R)/(I_L + I_R)$, where I_L and I_R refer, respectively, to the intensity of left and right circularly polarized emissions.

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(26) In all cases, the reactions are HOMO (sydnone) – LUMO (aryne) controlled. See Supporting Information for details.

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