



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

Expédite Yen-Pon, Pier Alexandre Champagne, Lucie Plougastel, Sandra Gabillet, Pierre Thuéry, Mizuki Johnson, Gilles Muller, Grégory Pieters, Frédéric Taran, Kendall N Houk, et al.

► To cite this version:

Expédite Yen-Pon, Pier Alexandre Champagne, Lucie Plougastel, Sandra Gabillet, Pierre Thuéry, et al.. Sydnone-based Approach to Hetero-helices Through 1,3-Dipolar-Cycloadditions. Journal of the American Chemical Society, 2019, 141, pp.1435-1440. 10.1021/jacs.8b11465 . cea-01976854

HAL Id: cea-01976854

<https://cea.hal.science/cea-01976854>

Submitted on 10 Jan 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Expédite Yen-Pon,[†] Pier Alexandre Champagne,[§] Lucie Plougastel,[†] Sandra Gabillet,[†] Pierre Thuéry,[‡] Mizuki Johnson,^{||} Gilles Muller,^{||} Grégory Pieters,[†] Frédéric Taran,[†] K. N. Houk,[§] Davide Audisio^{†,*}

[†] Service de Chimie Bio-organique et Marquage (SCBM), JOLIOT, CEA, Université Paris-Saclay, 91191 Gif-sur-Yvette, France, [‡] NIMBE, CEA, CNRS, Université Paris-Saclay, 91191 Gif-sur-Yvette, France

[§] Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

^{||} Department of Chemistry, San José State University, San José, California, 95192-0101, United States

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 pyrazine⁷ 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.

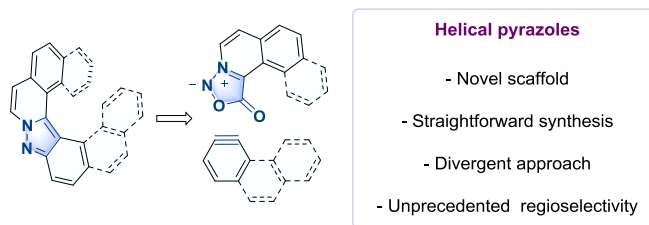


Figure 1: Design of pyrazoles-based helicenes.

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 C4 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 K₂CO₃ (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 arynes 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**

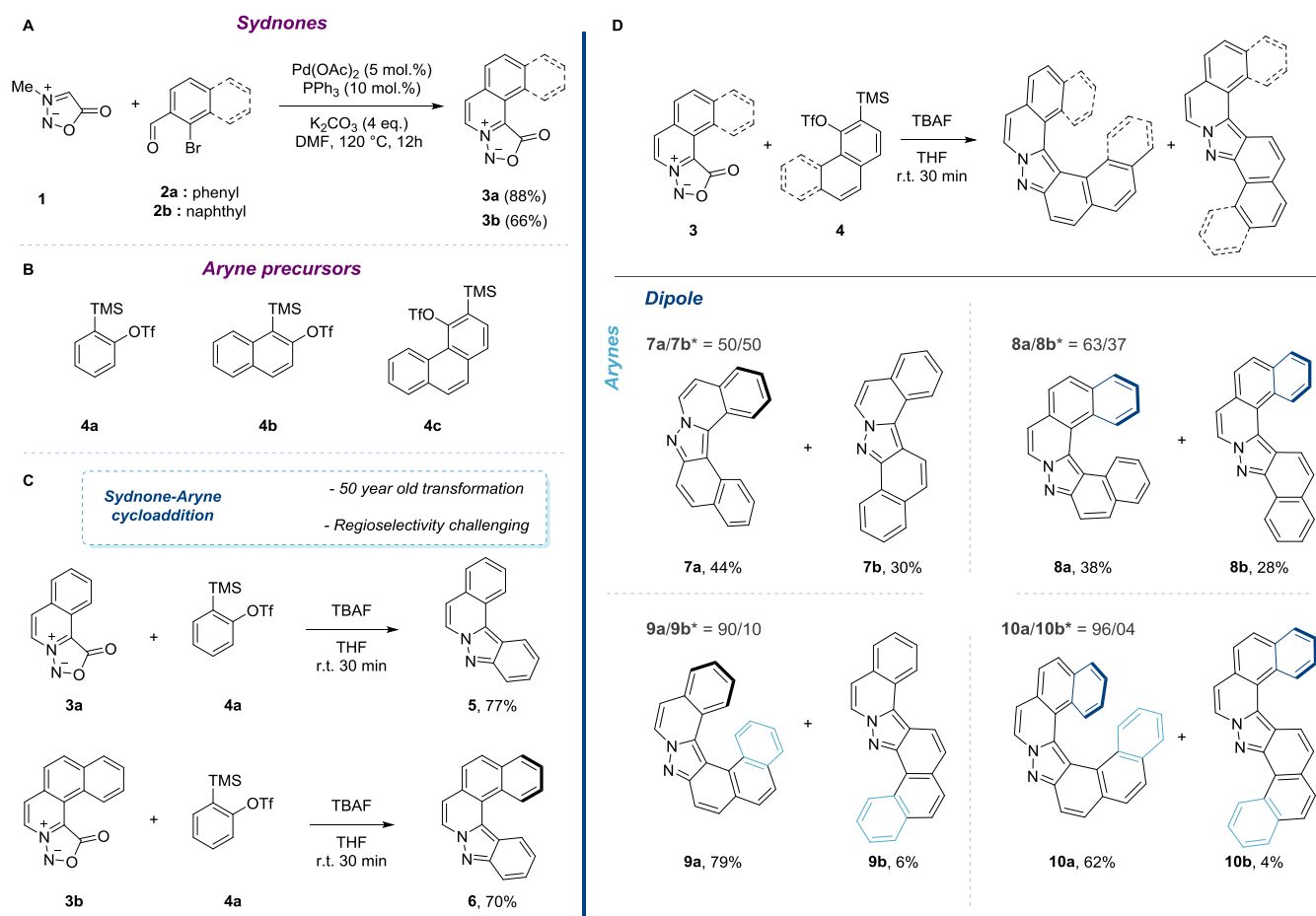


Figure 2: A: One-pot synthesis of polycyclic sydnones **3a** and **3b**; B: aryne precursor; C: Synthesis of helical pyrazoles **5** and **6**. D: Synthesis of helical pyrazoles **7a**, **8a**, **9a** and **10a**. * isomer ratio was measured by ^1H -NMR of the crude mixture.

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-naphthylene 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 tetracyclic sydnone **3b** gave a low degree of selectivity in favor of the sterically hindered hetero-[6]-helicene **8a** (**8a/8b**, ratio 63/37). The ^1H 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 ^1H -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-naphthylene 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).

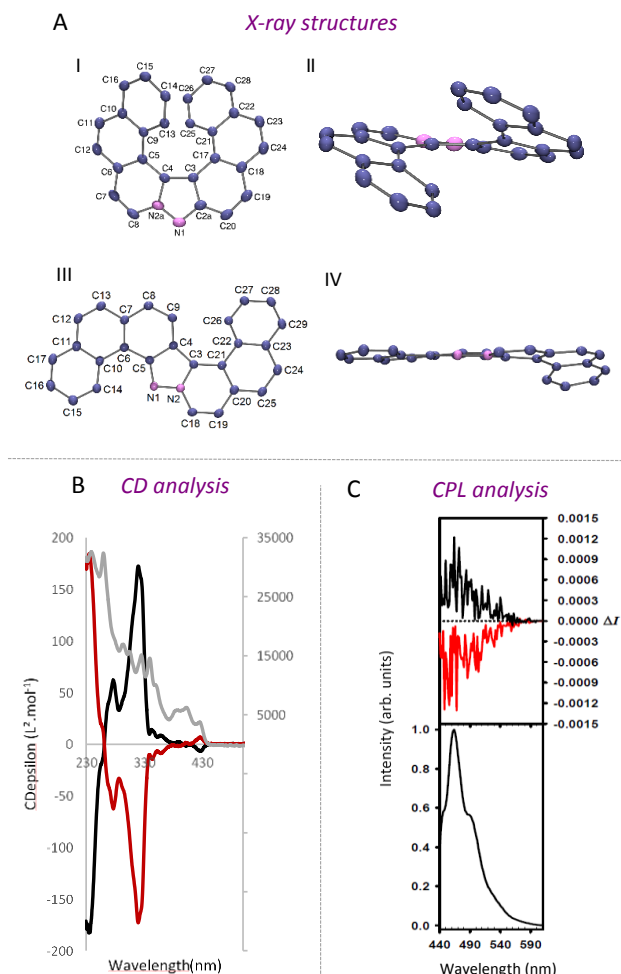


Figure 3: A) Molecular structure of **10a**: I) top and II) side views. Molecular structure of **10b**: III) top and IV) side views. Ellipsoids are set at 40% probability; hydrogen atoms are omitted for clarity. B) UV (gray curve) and CD spectra of (+)-**10a** (black curve) and (-)-**10a** (red curve); 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-naphthylene 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 regio-determining cycloaddition step is also rate-determining and fully irreversible, as the formation of the intermediate cycloadduct (**int**) is highly exergonic ($\Delta G = -33$ to -58 kcal/mol). The CO₂ extrusion step (**TS 2**) is then extremely facile and once again very exergonic. All cycloaddition transition states (**TS 1**) have very low activation barriers (ΔG^\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**.

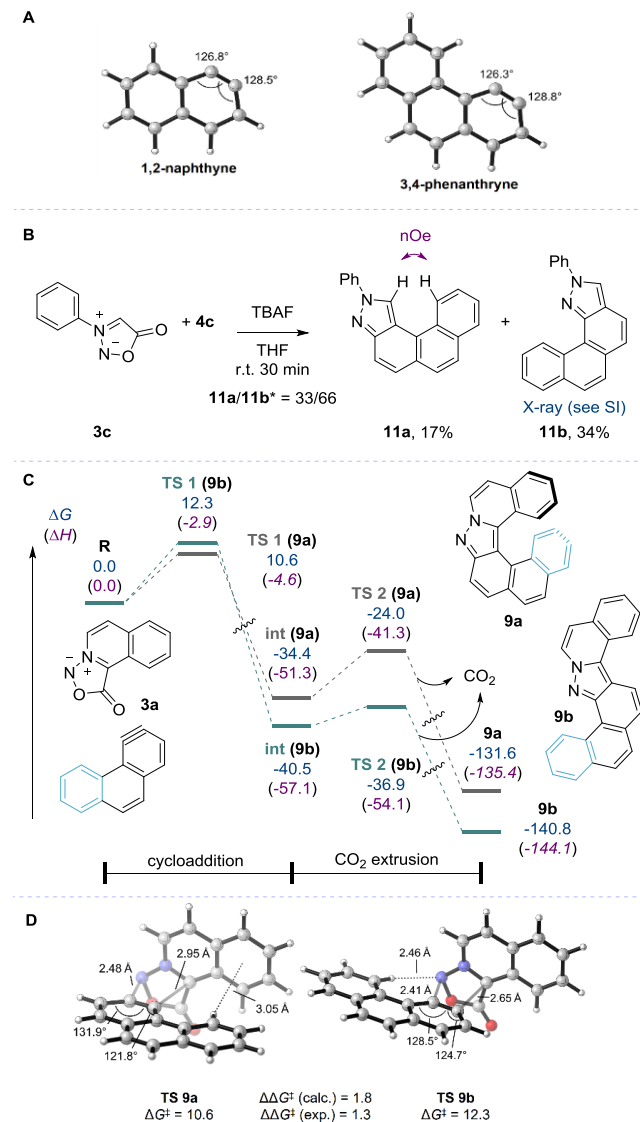


Figure 4: A) DFT-optimized structures of polycyclic arynes derived from **4b** and **4c**. B) Reaction between non planar *N*-phenyl sydnone **3c** and 3,4-phenanthryne precursor **4c**. * isomer ratio was measured by ¹H-NMR of the crude mixture. C) Energy profile for the reaction of **3a** with 3,4-phenanthryne 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

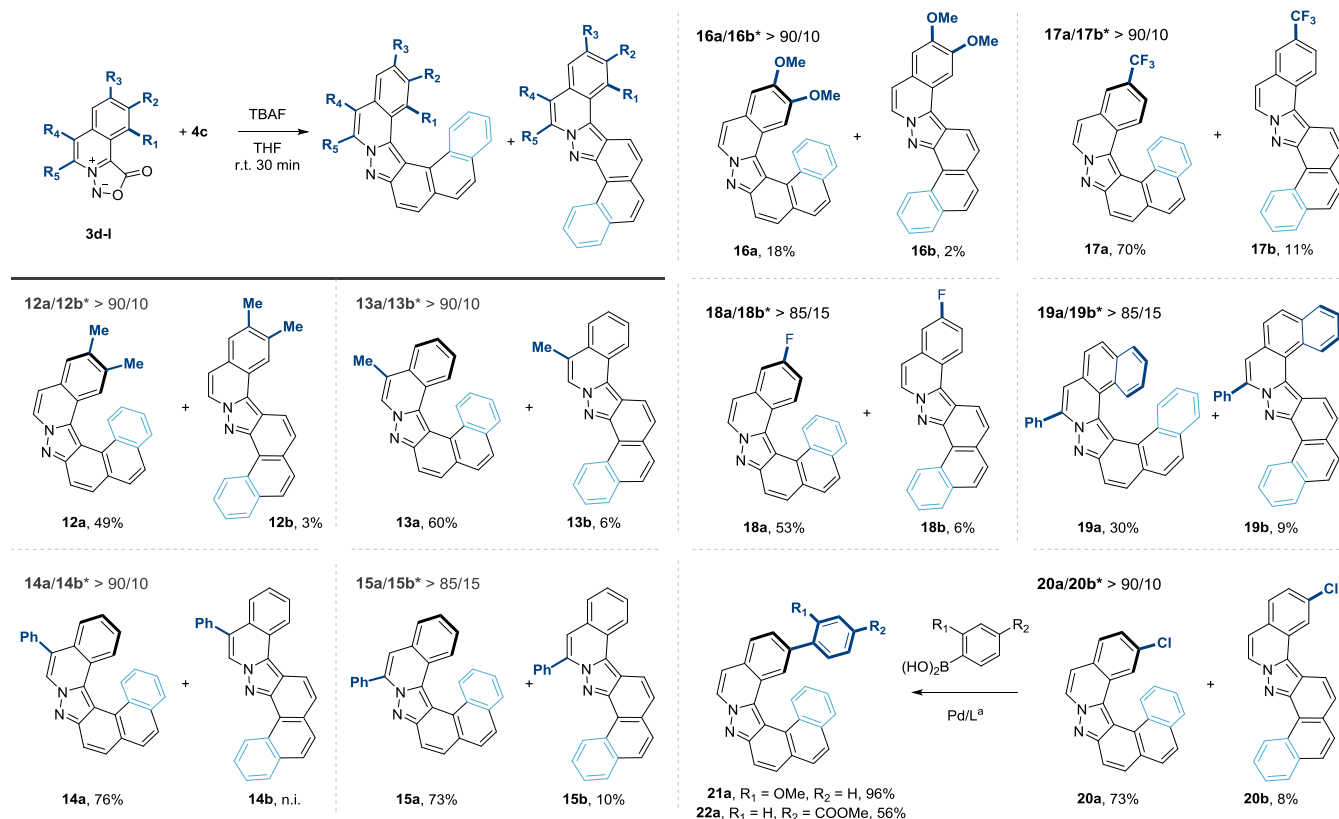


Figure 5: Synthesis of helical pyrazoles **12a-22a**. * isomer ratio was measured by ¹H-NMR of the crude mixture. n.i. not isolate. ^a See supporting information for detailed conditions.

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 analysis²⁸ 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 sydnone **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 the presence of a chloride substituent offered a useful handle for further functionalization. Under catalytic conditions, the products of Suzuki 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 sydnone, which are more nucleophilic than conventional ones, and highlights the first example of regioselective cycloaddition of such mesoionic dipoles with arylene 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).

AUTHOR INFORMATION

Corresponding Author

* davide.audisio@cea.fr

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by CEA and ANR (ANR-17-CE07-0035-01) and the US National Science Foundation (CHE-1361104). P.A.C gratefully acknowledges the Fonds de recherche du Québec – Nature et Technologies for a postdoctoral fellowship. Computations were performed on the Hoffman2 cluster at UCLA. G.M. acknowledges the NIH Minority Biomedical Research Support (grant 1 SC3 GM089589-08) and the Henry Dreyfus Teacher-Scholar Award for financial supports. The authors thank C. Chollet, E. Marcon, A. Goudet, S. Lebrequier and D.-A. Buisson (DRF-JOLIOT-SCBM, CEA) for the excellent analytical support. We wish to acknowledge Dr. P. Dauban (ICSN, CNRS, France) for helpful discussion.

REFERENCES

- (1) (a) Shen, Y.; Chen, C.-F. Helicenes: synthesis and applications. *Chem. Rev.* **2012**, *112*, 1463–1535. (b) Gingras, M. One hundred years of helicene chemistry. Part 1: non-stereoselective syntheses of carbohelicenes. *Chem. Soc. Rev.* **2013**, *42*, 968–1006. (c) Gingras, M.; Félix, G.; Peresutti, R. One hundred years of helicene chemistry. Part 2: stereoselective syntheses and chiral separations of carbohelicenes. *Chem. Soc. Rev.* **2013**, *42*, 1007–1050. (d) Gingras, M. One hundred years of helicene chemistry. Part 3: applications and properties of carbohelicenes. *Chem. Soc. Rev.* **2013**, *42*, 1051–1095. (e) Chen, C.-F.; Shen, Y. (2017) Helicene Chemistry, From Synthesis to Applications, Berlin Heidelberg, Germany: Springer-Verlag.
- (2) (a) Takenaka, N.; Chen, J.; Captain, B.; Sarangthem, R. S.; Chandrakumar, A. Helical Chiral 2-aminopyridinium ions: a new class of hydrogen bond donor Catalysts. *J. Am. Chem. Soc.* **2010**, *132*, 4536–4537. (b) Aillard, P.; Voituriez, A.; Dova, D.; Cauteruccio, S.; Licandro, E.; Marinetti, A. Phosphathiahelicenes: synthesis and uses in enantioselective gold catalysis. *Chem. Eur. J.* **2014**, *20*, 12373–12376 and references cited therein. (c) González-Fernández, E.; Nicholls, L. D. M.; Schaaf, L. D.; Farès, C.; Lehmann, C. W.; Alcarazo, M. Enantioselective synthesis of [6]carbohelicenes. *J. Am. Chem. Soc.* **2017**, *139*, 1428–1431. (d) Ferreira, M.; Naulet, G.; Gallardo, H.; Dechambenoit, P.; Bock, H.; Durola F. A Naphtho-fused double [7]helicene from a maleate-bridged Chrysene Trimer. *Angew. Chem. Int. Ed.* **2017**, *56*, 3379–3382.
- (3) (a) Hatakeyama, T.; Hashimoto, S.; Oba, T.; Nakamura, M., Azaboradibenzo[6]helicene: carrier inversion induced by helical homochirality. *J. Am. Chem. Soc.* **2012**, *134*, 19600–19603. (b) Yang, Y.; da Costa, R. C.; Fuchter, M. J.; Campbell, A. J., Circularly polarized light detection by a chiral organic semiconductor transistor *Nat. Photon.* **2013**, *7*, 634–638.
- (4) (a) Otani, T.; Tsuyuki, A.; Iwachi, T.; Someya, S.; Tateno, K.; Kawai, H.; Saito, T.; Kanyiva, K. S.; Shibata, T., Facile two-step synthesis of 1,10-phenanthroline-derived polyaza[7]helicenes with high fluorescence and CPL efficiency. *Angew. Chem. Int. Ed.* **2017**, *56*, 3906–3910. (b) Collins, S. K.; Vachon, M. P. Unlocking the potential of thiaheterohelicenes: chemical synthesis as the key. *Org. Biomol. Chem.*, **2006**, *4*, 2518–2524.
- (5) (a) Mišek, J.; Teplý, F.; Stará, I. G.; Tichý, M.; Šaman, D.; Císařová, I.; Vojtišek, P.; Starý, I. A Straightforward route to helically chiral N-heteroaromatic compounds: practical synthesis of racemic 1,14-diaza[5]helicene and optically pure 1- and 2-aza[6]helicenes. *Angew. Chem. Int. Ed.* **2008**, *47*, 3188–3191. (b) Takenaka, N.; Sarangthem, R. S.; Captain, B. Helical chiral pyridine N-oxides: a new family of asymmetric catalysts. *Angew. Chem. Int. Ed.* **2008**, *47*, 9708–9710 (c) Kaneko, E.; Matsumoto, Y.; Kamikawa, K. Synthesis of azahelicene N-oxide by palladium-catalyzed direct C–H annulation of a pendant (Z)-bromovinyl side chain. *Chem. Eur. J.* **2013**, *19*, 11837–11841. (d) Bosson, J.; Labrador, G. M.; Pascal, S.; Miammay, F.-A.; Yushchenko, O.; Li, H. Bauffier, L.; Sojic, N.; Tovar, R. C.; Muller, G.; Jacquemin, D.; Laurent, A. D.; Guennic, B. L.; Vauthey, E.; Lacour, J. Physicochemical and electronic properties of cationic [6]helicenes: from chemical and electrochemical stabilities to far-red (polarized) luminescence. *Chem. Eur. J.* **2016**, *22*, 18394–18403. (e) Nakamura, K.; Furumi, S.; Takeuchi, M.; Shibuya, T.; Tanaka, K. Enantioselective synthesis and enhanced circularly polarized luminescence of S-shaped double azahelicenes. *J. Am. Chem. Soc.* **2014**, *136*, 5555–5558. (f) Nejedlý, J.; Šámal, M.; Rybáček, J.; Tobrmanová, M.; Szydło, F.; Coudret, C.; Neumeier, M.; Vacek, J.; Chocholoušová, J. V.; Buděšínský, M.; Šaman, D.; Bednářová, L.; Sieger, L.; Stará, I. G.; Starý, I. Synthesis of long oxahelicenes by polycyclization in a flow reactor *Angew. Chem. Int. Ed.* **2017**, *56*, 5839–5843.
- (6) (a) Goto, K.; Yamaguchi, R.; Hiroto, S.; Ueno, H.; Kawai, T.; Shinokubo, H. Intermolecular oxidative annulation of 2-aminoanthracenes to diazaacenes and aza[7]helicenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 10333–10336. (b) Shi, L.; Liu, Z.; Dong, G.; Duan, L.; Qiu, Y.; Jia, J.; Guo, W.; Zhao, D.; Cui, D.; Tao, X. Synthesis, Structure, Properties, and application of a carbazole-based diaza[7]helicene in a deep-blue-emitting OLED. *Chem. Eur. J.* **2012**, *18*, 8092–8099. (c) Upadhyay, G. M.; Talele, H. R.; Bedekar, A. V. Synthesis and photophysical properties of aza[n]helicenes. *J. Org. Chem.* **2016**, *81*, 7751–7759. (d) Maciej, K.; Takuya, K.; Espinoza E. M.; Vullev, V. I.; Kubo, T.; Gryko, D. T. Nonplanar butterfly-shaped π -expanded pyrrolopyrroles. *Chem. Eur. J.* **2016**, *22*, 16478–16488.
- (7) Sakamaki, D.; Kumano, D.; Yashima, E.; Seki, S. A Facile and versatile approach to double N-heterohelicenes: tandem oxidative C–N couplings of N-heteroacenes via cruciform dimers. *Angew. Chem. Int. Ed.* **2015**, *54*, 5404–5407.
- (8) Čížková, M.; Šaman, D.; Koval, D.; Kašička, V.; Klepetářová, B.; Císařová, I.; Teplý, F. Catalytic Friedel–Crafts/lactonization domino reaction: facile access to 3-hydroxybenzofuran-2-one scaffold. *Eur. J. Org. Chem.* **2014**, *2014*, 5681–5685.
- (9) (a) Browne, D. L.; Harrity, J. P. A., Recent developments in the chemistry of sydnones. *Tetrahedron* **2010**, *66*, 553–568. (b) Decuypère, E.; Plougastel, L.; Audisio, D.; Taran, F. Sydnone–alkyne cycloaddition: applications in synthesis and bioconjugation *Chem Commun.* **2017**, *53*, 11515–11527.
- (10) For important pioneering work on helicenes formation by [4+2] cycloaddition of benzyne, see: a) del Mar Real, M.; Pérez Sestelo, J.; Sarandeses, L. A. Inner–outer ring 1,3-bis(trimethylsilyloxy)-1,3-dienes as useful intermediates in the synthesis of helicenes. *Tet. Lett.* **2002**, *43*, 9111–9114; b) Truong, T.; Daugulis, O. Divergent reaction pathways for phenol arylation by arynes: synthesis of helicenes and 2-arylphenols. *Chem. Sci.* **2013**, *4*, 531–535.
- (11) See Supporting Informations for additional details.
- (12) For the very first report, see: a) Gotthardt, H.; Huisgen R.; Knorr, R. 1,3-Dipolare cycloadditionen, XXXVIII. Reaktionen der sydnone mit benz-in und mit einigen heteromehrfachbindungen. *Chem. Ber.*, **1968**, *101*, 1056–1058. For other pioniring reports see: b) Nakazawa, S.; Kiyosawa, T.; Hirakawa, K.; Kato, H. Selectivity in the thermal and photochemical fragmentation of the cycloadduct from benzyne and a mesoionic thiazol-4-one *J. Chem. Soc., Perkin Trans. 1* **1974**, 621–621; Kato, H.; Nakazawa, S.; Kiyosawa, T.; Hirakawa, K. Heterocycles by cycloaddition. Part II. Cycloaddition–extrusion reactions of five-membered mesoionic compounds with benzyne: preparation of benz[c]azole and benzo[c]thiophen derivatives. *J. Chem. Soc., Perkin Trans. 1* **1976**, 672–675; d) Tsuge O.; Saruma, H. The formation of 1H-dibenzo[b,g][1,4,5]triazapentalene from 2-(o-nitrophenyl)- and 2-(o-azidophenyl)-2H-indazole. *Org. Prep. Proced. Int.* **1974**, *6*, 161–167.
- (13) (a) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. Synthesis of 2H-indazoles by the [3 + 2] cycloaddition of arynes and sydnones. *Org. Lett.* **2010**, *12*, 2234–2237. (b) Fang, Y.; Wu, C.; Larock, R. C.; Shi, F. Synthesis of 2H-indazoles by the [3 + 2] dipolar cycloaddition of sydnones with arynes. *J. Org. Chem.* **2011**, *76*, 8840–8851; c) Soares, M. I. L.; Nunes, C. M.; Gomes, C. S. B.; Pinho e Melo, T. M. V. D. Thiazolo[3,4-b]indazole-2,2-dioxides as masked extended dipoles: pericyclic reactions of benzodiazafulvenium methides. *J. Org. Chem.* **2013**, *78*, 628–637.
- (14) For previous synthesis of compound 5, see: a) Zhao, J.; Wu, C.; Li, P.; Ai, W.; Chen, H.; Wang, C.; Larock, R. C.; Shi, F. Synthesis of pyrido[1,2-b]indazoles via aryne [3+2] cycloaddition with N-tosylpyridinium imides. *J. Org. Chem.* **2011**, *76*, 6837–6843; b) Zhao, J.; Li, P.; Wu, C.; Chen, H.; Ai, W.; Sun, R.; Ren, H.; Larock, R. C.; Shi, F. Aryne [3 + 2] cycloaddition with N-sulfonylpyridinium imides and in situ generated N-sulfonylisoquinolinium imides: a potential route to pyrido[1,2-b]indazoles and indazolo[3,2-a]isoquinolines. *Org. Biomol. Chem.* **2012**, *10*, 1922–1930; c) Zheng, Q.-Z.; Feng, P.; Liang, Y.-F.; Jiao, N. Pd-Catalyzed tandem C–H azidation and N–N bond formation of arylpyridines: a direct approach to pyrido[1,2-b]indazoles. *Org. Lett.* **2013**, *15*, 4262–4265.

(15) In contrast to [6]-carbohelicenes, [6]-helicene **9a** is not configurationally stable at room temperature. Calculated racemization energy barrier is 22.5 kcal/mol. Enantiomers of **9a** were resolved by chiral-phase HPLC and a rapid racemization was observed. For additional information regarding the racemization barriers of other pyrazolohelicenes, see ref. 11. For a nice overview on carbohelicenes racemization, see: Barroso, J.; Cabellos, J. L.; Pan, S.; Murillo, F.; Zarate, Z.; Fernandez-Herrera, M. A.; Merino, G. Revisiting the racemization mechanism of helicenes. *Chem. Commun.* **2018**, 54, 188-191.

(16) The measured racemization barrier for pyrazolo[7]-helicene **10a** was found to be 32.7 kcal/mol. This value is in agreement with the calculated racemization energy barrier for **10a**: 31.6 kcal/mol. See ref 11 for details.

(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.

(18) a) Kaseyama, T.; Furumi, S.; Zhang, X.; Tanaka, K.; Takeuchi, M. Hierarchical assembly of a phthalhydrazide-functionalized helicene. *Angew. Chem. Int. Ed.* **2011**, 50, 3684-3687; b) Sawada, Y.; Furumi, S.; Takai, A.; Takeuchi, M.; Noguchi, K.; Tanaka, K. Rhodium-catalyzed enantioselective synthesis, crystal structures, and photophysical properties of helically chiral 1,1'-bitriphenylenes. *J. Am. Chem. Soc.* **2012**, 134, 4080-4083; c) Shen, C.; Anger, E.; Srebro, M.; Vanthuyne, N.; Deol, K. K.; Jefferson, T. D.; Muller, G.; Williams, J. A. G.; Toupet, L.; Roussel, C.; Autschbach, J.; Réau, R.; Crassous, J. Straightforward access to mono- and bis-cycloplatinated helicenes displaying circularly polarized phosphorescence by using crystallization resolution methods. *Chem. Sci.* **2014**, 5, 1915-1927.

(19) We are aware of only two single examples of regioselective sydnone-aryne cycloaddition (> 85/15), in presence of 3-silylbenzyne: (a) Ikawa, T.; Masuda, S.; Takagi, A.; Akai, S. 1,3- and 1,4-Benzdiyne equivalents for regioselective synthesis of polycyclic heterocycles. *Chem. Sci.*, **2016**, 7, 5206-5211. (b) Ikawa, T.; Masuda, S.; Nakajima, H.; Akai, S. 2-(Trimethylsilyl)phenyl trimethylsilyl ethers as stable and readily accessible benzyne precursors. *J. Org. Chem.* **2017**, 82, 4242-4253.

(20) (a) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K.; Frontier molecular orbitals of 1,3 dipoles and dipolarophiles. *J. Am. Chem. Soc.* **1973**, 95, 7287-7301. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. Origin of reactivity, regioselectivity, and periselectivity in 1,3-

dipolar cycloadditions. *J. Am. Chem. Soc.* **1973**, 95, 7301-7315. (c) Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. On the problem of regioselectivity in the 1,3-dipolar cycloaddition reaction of munchones and sydnone with acetylenic dipolarophiles. *J. Org. Chem.* **1982**, 47, 786-791.

(21) McMahon, T. C.; Medina, J. M.; Yang, Y.-F.; Simmons, B. J.; Houk, K. N.; Garg, N. K. Generation and regioselective trapping of a 3,4-piperidine for the synthesis of functionalized heterocycles. *J. Am. Chem. Soc.* **2015**, 137, 4082-4085.

(22) Shah, T. K.; Medina, J. M.; Garg, N. K. Expanding the strained alkyne toolbox: generation and utility of oxygen-containing strained alkynes. *J. Am. Chem. Soc.* **2016**, 138, 4948-4954.

(23) Noteworthy, in presence of unsymmetric cyclooctynes, sydnone have been reported deliver a 1 to 1 mixture of regioisomers: Narayanam, M. K.; Liang, Y.; Houk, K. N.; Murphy, J. M. Discovery of new mutually orthogonal bioorthogonal cycloaddition pairs through computational screening. *Chem. Sci.* **2016**, 7, 1257-1261.

(24) (a) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J. Garg, N. K.; Houk, K. N. Indolyne and aryne distortions and nucleophilic regioselectivities. *J. Am. Chem. Soc.* **2010**, 132, 1267-1269. (b) 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.

(25) The nature of pyrazoles **11a** and **11b** was unambiguously established by NOE and X-ray crystallography (see SI for details).

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

(27) For a review on aromatic interactions as control elements in stereoselective reactions, see: Krenske, E. H.; Houk, K. N. Aromatic interactions as control elements in stereoselective organic reactions *Acc. Chem. Res.* **2013**, 46, 979-989.

(28) Bickelhaupt, F. M.; Houk, K. N. Analyzing reaction rates with the distortion/interaction-activation strain model. *Angew. Chem. Int. Ed.* **2017**, 56, 10070-10086.

(29) Unreacted sydnone **3h** was preset in the reaction crude even after prolonged reaction time.