A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Cyclic Alkyne Approach to Heteroatom-Containing Polycyclic Aromatic Hydrocarbon Scaffolds

Authors: Evan Darzi, Joyann Barber, and Neil K. Garg

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201903060
Angew. Chem. 10.1002/ange.201903060

Link to VoR: http://dx.doi.org/10.1002/anie.201903060
http://dx.doi.org/10.1002/ange.201903060

WILEY-VCH

10.1002/anie.201903060

WILEY-VCH

Cyclic Alkyne Approach to Heteroatom-Containing Polycyclic Aromatic Hydrocarbon Scaffolds

Evan R. Darzi, Joyann S. Barber, and Neil K. Garg*

Abstract: We report a modular synthetic strategy for accessing heteroatom-containing polycyclic aromatic hydrocarbons (PAHs). Our approach relies on the controlled generation of transient heterocyclic alkynes and arynes. The strained intermediates undergo in situ trapping with readily accessible oxadiazinones. Four sequential pericyclic reactions occur, namely two Diels–Alder / retro-Diels–Alder sequences, which can be performed in a stepwise or one-pot fashion to assemble four new carbon–carbon (C–C) bonds. These studies underscore how the use of heterocyclic strained intermediates can be harnessed for the preparation of new organic materials.

Alkynes contained in small rings were once considered only intellectual curiosities. However, in recent years, strained cyclic alkynes have resurfaced and have been widely employed in synthetic methodology studies.[1,2,3,4] Additionally, such efforts have led to a greater understanding of aryne and cyclic alkyne reactivity and regioselectivities,[5,6,7] and a host of synthetic applications impacting catalysis,[8] agrochemistry,[9] pharmaceuticals, and academia.[10,11] A selection of important arynes and cyclic alkynes are shown in Figure 1.[12,13,14,15,16,17,18,19]

One exciting application of arynes and cyclic alkynes lies in materials chemistry. Arynes have been employed in the synthesis of polymers and polycyclic aromatic hydrocarbons (PAHs),[2,20,21,22,23] with the latter having a remarkable impact on the materials science field.[24,25] PAHs have been used in widely-used devices, such as organic light-emitting diodes (OLEDs), field effect transistors (OFETs), and photovoltaics (OPVs).[26] An important subset of PAHs are 9,10-diphenylanthracene derivatives. The parent compound, 9,10-diphenylanthracene (**1**, Figure 1), has been widely studied since 1904[27] and has been used in blue glow sticks[28] and OLEDs.[29] Novel derivatives of **1** have been highly sought.[30] One promising 'analoging' approach is to prepare variants of **1** that bear heteroatoms in order to modulate the properties and potential applications of PAHs.[31,32,33] Heteroatoms may be included in the anthracene ring itself or on the C9/C10 substituents, as exemplified by **2**[34,35,36,37] and **3**,[38] respectively (Figure 1), which can impact material properties.[38] Compounds possessing heteroatoms on both the anthracene ring and C9/C10 substituents, such as **4**, have also been prepared in the context of OLEDs.[39] Lastly, more exotic analogs of **1** and **2** are known where the C9/C10 substituents are replaced with heterocycles or substituted aromatics, as demonstrated by **5**[34,37] and **6**.[40] The majority of heteroatom-containing derivatives of **1** have been disclosed in the patent literature over the past 6 years and reflect a rapidly growing area of discovery.[41,42]

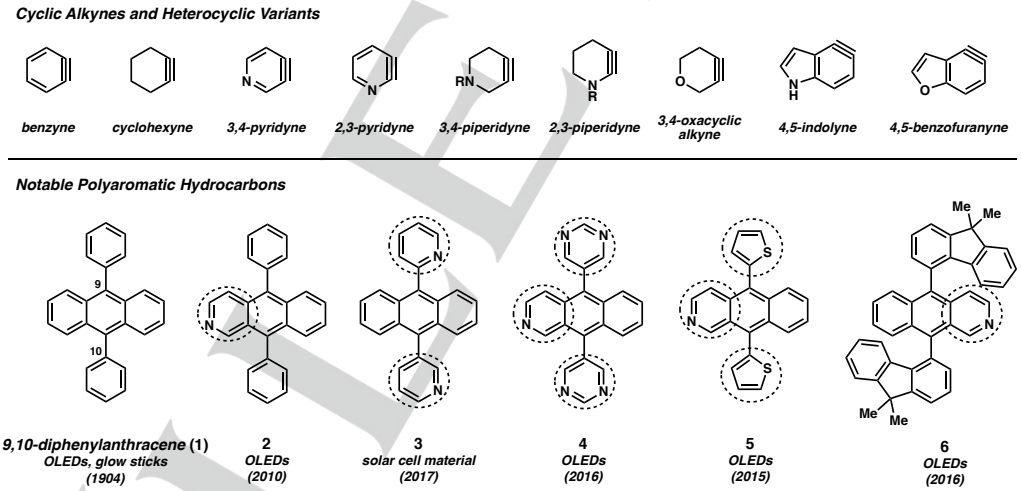


Figure 1. Arynes, cyclic alkynes, and heterocyclic variants, and 9,10-diphenylanthracene (**1**) and aza-derivatives **2**–**6**.

Synthetic methods to rapidly generate novel heterocyclic PAHs remain limited. For example, the assembly of non-symmetric PAHs that possess multiple functional groups usually requires long linear sequences.[33] Additionally, approaches to arrive at het-anthracene cores typically necessitate harsh reaction conditions (e.g., high temperatures and strongly acidic or basic conditions).[33,13] Lastly, variation at C9 and C10 is primarily achieved via the use of strongly basic organometallic reagents or transition metal catalysis, and typically results in symmetric molecules or low yields.[31,43]

We targeted the synthesis of scaffold **7** through an ambitious approach, whereby ring fragments **A**–**D** could be

Dr. E. R. Darzi, J. S. Barber, Prof. Dr. N. K. Garg
Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, CA 90095 (USA)
E-mail: neilgarg@chem.ucla.edu
Homepage: http://garg.chem.ucla.edu

Supporting information for this article is given via a link at the end of the document.

united with formation of the central benzene ring (Figure 2a). This would enable access to a range of heterocyclic PAH scaffolds, with the possibility of accessing four quadrants of differentiation. In practice, we questioned if highly reactive arynes and cyclic alkynes (i.e., **8** and **10**) could be used as building blocks **A** and **B** (Figure 2b). Heterocyclic strained intermediates (e.g. **8**) would be used strategically to access the desired heteroatom-containing PAHs.[44] With regard to building blocks **C** and **D**, oxadiazinone **9** was identified as a versatile core scaffold. Oxadiazinones (diazapyrones) are easily prepared from simple precursors[45] and are known to readily undergo one or more Diels–Alder (DA) cycloaddition / retro-Diels–Alder (rDA) cycloaddition reactions (with sequential expulsion of N_2 and CO_2).[46] The success of this approach would hinge on uncovering a means to allow for the controlled generation and trapping of fragments **8** and **10** to ultimately deliver products **7** through the cascade of events suggested in Figure 2b. Key precedent stems from pioneering studies by Steglich in 1977, [47] which demonstrated the double addition of benzyne into oxadiazinones, in addition to the syntheses of conjugated materials by Nuckolls[48] and Wudl.[49] However, a notable limitation in all cases is the inability to introduce two different strained alkynes, instead delivering symmetric products with respect to building blocks **A** and **B**.[50]

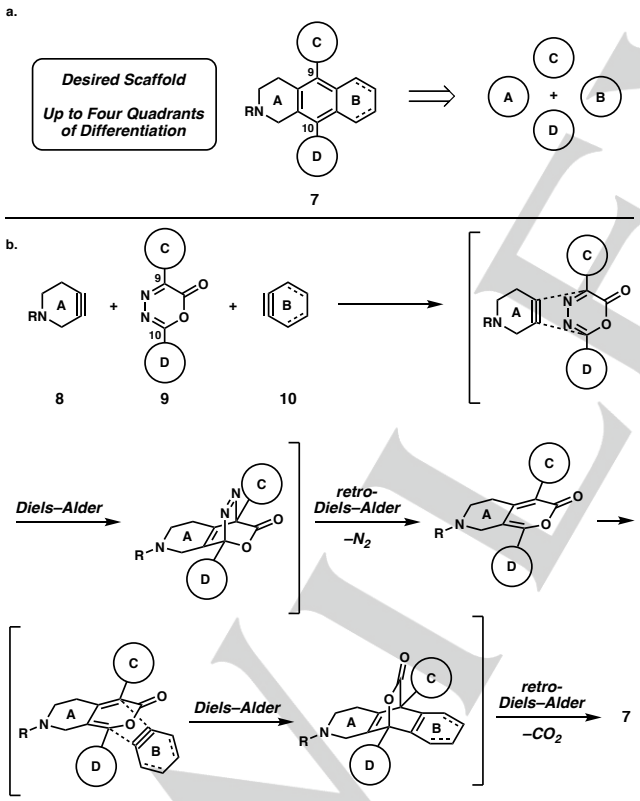


Figure 2. Strategy to access **7**.

We report the development of the synthetic sequence shown in Figure 2b, which provides a modular and rapid means to synthesize a diverse range of heteroatom-containing PAHs. The trapping of in situ-generated strained intermediates with oxadiazinones, demonstrated in both stepwise and one-pot fashions, furnishes the desired structural frameworks. Small molecule fluorophores can be accessed from this strategy. These studies demonstrate that heterocyclic strained intermediates can be leveraged for the preparation of new organic materials.

With the ultimate goal of synthesizing heterocyclic PAHs bearing four quadrants of differentiation, we first developed a stepwise variant (Figure 3). As mentioned above, arynes are known to undergo oxadiazinone trapping, but the intermediate benzopyrone directly undergoes trapping with a second equivalent of the aryne, precluding the opportunity to introduce two different strained alkyne fragments. When using benzyne in our initial studies, only double addition to form **1** was observed. We hypothesized that the intermediate benzopyrone was more reactive than the oxadiazinone, preventing isolation or second addition of a different aryne. We questioned if a cyclic alkyne could be used to isolate the corresponding pyrone intermediate based on prior studies by Sauer and co-workers using cyclooctyne.[51] Thus, we used a heterocyclic alkyne derived from commercially available silyl triflate **11** (prepared in 3 steps from 4-methoxypyridine).[13] Two key results (Figure 3) illustrate the ability to modulate the product distribution through alteration of the reaction stoichiometry. When silyl triflate **11** was employed in excess, the major products were adducts **14**, consistent with the results previously seen in aryne/oxadiazinone reactions.[46,47,48] However, when a 1 : 2 ratio of **11** and **12** was utilized, the desired pyrones **13**, arising from a single DA / rDA reaction, were isolated in 74% yield under optimized conditions, without formation of double addition products **14**. Of note, pyrone **13** is produced as a mixture of regioisomers **13a** and **13b**. It was found that treatment of excess CsF under oxidative conditions selectively decomposed **13b** leaving **13a** untouched. Several points should be noted: a) our results provide the first example of a DA cycloaddition featuring an oxadiazinone and a strained intermediate derived from a Kobayashi silyl triflate precursor,[52] b) the reactions occur under exceptionally mild reaction conditions, c) the desired reaction produces mixtures of pyrone isomers **13a** and **13b**, which may generally be viewed as both a strength and limitation (additional analogs, yet not selective), and d) isomer **13a**, the key lynchpin to the success of our synthetic strategy, was ultimately accessible as a single isomer (33% yield from **11**, see SI for details) and employed in subsequent experiments.

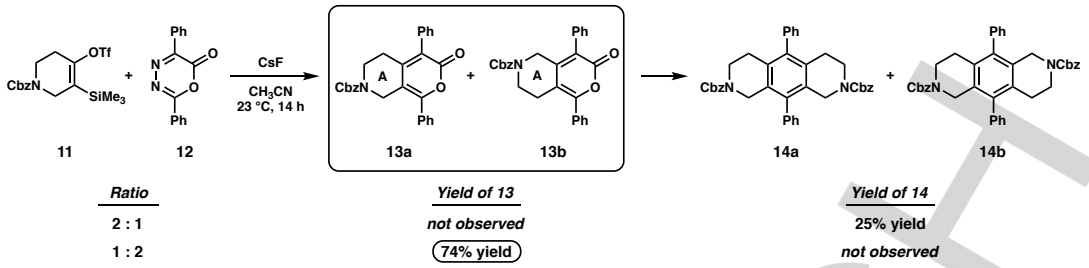
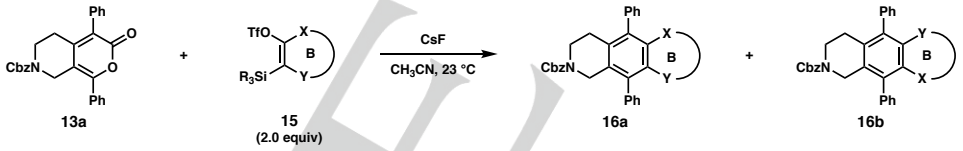


Figure 3. Optimization to form pyrones **13**. Cbz=benzylcarbamate, OTf=trifluoromethanesulfonate.

After establishing a suitable method to access pyrone **13a**, we turned our attention toward introducing and modulating the **B** ring. Pyrone **13a** readily undergoes a DA / rDA reaction sequence, with loss of CO_2, in the presence of arynes or non-aromatic cyclic alkynes (generated from silyl triflate precursors **15**) at ambient temperature (Figure 4). In each case, the transformation proceeds with formation of two new C–C bonds and delivers non-symmetric heterocyclic PAH skeletons **16**. Benzyne (**17**),[52] 1,2-naphthalyne (**19**)[53] and 4,5-indolyne (**21**),[18] performed well, giving rise to products **18**, **20** and **22** in good yields (entries 1–3). Cyclic alkynes, which offer greater sp^3-character and improved solubility of eventual products were also tested. Cyclohexyne (**23**), and heterocyclic strained cyclic alkynes **25**[13] and **26**[16] performed smoothly (entries 4–6).[54] With regard to regioselectivities (entries 2, 5, and 6), the major product likely arises from initial bond formation occurring between the more electron-rich carbon adjacent to the carbonyl group of the pyrone[55] and the more distorted carbon of the strained intermediate in a concerted asynchronous fashion.[6,13,16]

We also sought to access products bearing differing **C** and **D** rings. As noted earlier, in most routes to 9,10-anthracene derivatives, the **C** and **D** rings are introduced through a double cross-coupling or by the double addition of an organometallic reagent, allowing for the formation of only symmetric products with limited functional group compatibility.[33,31] A series of differentially-substituted oxadiazinones were prepared using established chemistry[45] and subjected to silyl triflate **11** under our standard reaction conditions (Figure 5). The desired sequence took place to deliver pyrone isomers **28**–**31** in yields ranging from 66 to 84%. In all cases, it was possible to separate the depicted pyrone isomer (42 to 72% recovery of the single isomer from the mixture of isomers), which was then subjected to benzyne precursor **32** under our standard



Entry	Strained Intermediate	Product(s) (Yield, Ratio)	Entry	Strained Intermediate	Product(s) (Yield, Ratio)
1	17	18 (83% yield)	4	23	24 (71% yield)
2	19	20a + 20b (89% yield, 1.4:1 ratio)	5	25	14a + 14b (60% yield, 1.4:1 ratio)
3	21	22a + 22b (70% yield, 1:1 ratio)	6	26	27a + 27b (62% yield, 1.5:1 ratio)

Figure 4. The second DA / rDA reaction using pyrone intermediate **13a**. Conditions unless otherwise stated: CsF (5.0 equiv), CH_3CN (0.1 M), 14 h. For entries 2, 3, 5, and 6, the mixtures of regioisomers were not separable by column chromatography. Cbz=benzylcarbamate, OTf=trifluoromethanesulfonate.

conditions. The desired products **33**–**36** were obtained in good to excellent yields. The **D** ring was varied to include different para substituents (**33**–**35**), such as a bromide (**35**) for use in cross-coupling. Also, a thiophene was incorporated to give **36**, which is notable given the prevalence of thiophenes in organic electronics.[31]

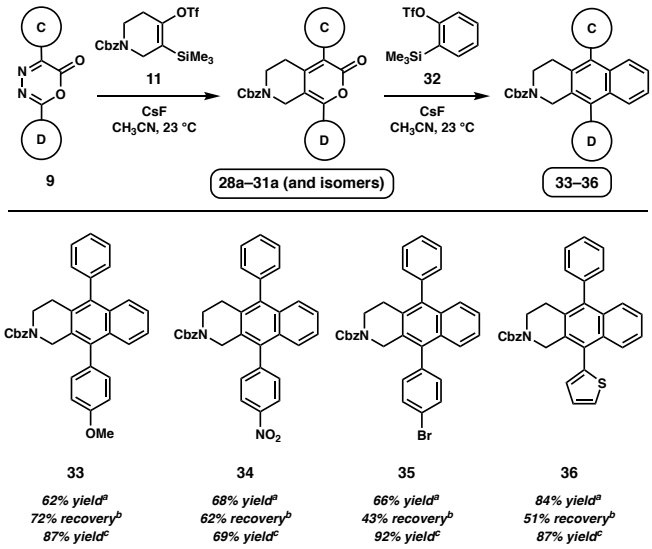


Figure 5. Variation of oxadiazinone. [a] Yield of the pyrone intermediates **28**–**31** (**a** and **b** isomers). Conditions for piperidyne cycloaddition: oxadiazinone **9** (2.0 equiv), silyl triflate **11** (1.0 equiv), CsF (2.0 equiv), CH_3CN (0.1 M), 14–18 h. [b] Recovery of pyrones **28a**–**31a** from the mixtures of **a** and **b** isomers. See SI for details. [c] Yield of products **33**–**36**. Conditions for benzyne cycloaddition: pyrone **28a**–**31a** (1.0 equiv), silyl triflate **32** (2.0 equiv), CsF (5.0 equiv), CH_3CN (0.1 M), 18 h. Cbz=benzylcarbamate, OTf=trifluoromethanesulfonate.

A 3-component coupling of two different silyl triflates, **11** and **32**, and oxadiazinone **12** was performed (Figure 6). Operationally, CsF was added to an equimolar solution of the three reactants, **18** was obtained in 56% yield along with pyrone intermediate **13** accounting for the remaining mass balance. Notably, the products of double piperidyne or benzyne addition were not observed, suggesting high selectivity for the controlled formation and reaction of the two strained intermediates. We posit that silyl triflate **11** more readily undergoes fluoride-mediated elimination to form the corresponding alkyne compared to benzyne precursor **32** as a result of the lower strain energy associated with 3,4-piperidyne compared to benzyne.[56] The transformation proceeds by way of 4 consecutive pericyclic reactions to create 4 new C–C bonds and deliver a heterocyclic PAH scaffold in one-pot.

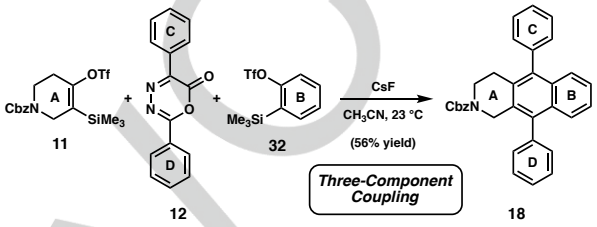


Figure 6. Three-component coupling of **11**, **12**, and **32**. Conditions: silyl triflate **11** (1.0 equiv), oxadiazinone **12** (1.0 equiv), silyl triflate **32** (1.0 equiv), CsF (3.0 equiv), CH_3CN (0.1 M), 14 h. Cbz=benzylcarbamate, OTf=trifluoromethanesulfonate.

We pursued several synthetic applications with a focus on incorporating motifs commonly utilized in materials chemistry. As shown in Figure 7, we targeted a heterocyclic PAH scaffold reminiscent of **1**. Oxadiazinone **37** was treated with silyl triflate **11** and CsF to furnish pyrone **38**. Reaction with silyl triflate **39** afforded the corresponding product of the DA / rDA sequence. Silyl protection of the indole nitrogen provided separable isomers **40a** and **40b**. Removal of the Cbz-protecting group of **40a**, followed by MnO_2-mediated oxidation gave **41a**, which bears three heterocycles and a *p*-OMe-Ph motif. **41a** exhibits pH-responsive fluorescence switching properties. Neutral **41a** displays a blue fluorescence emission, whereas the protonated version, **42a**, displays an orange fluorescence emission. Stimuli responsive materials are important for a host of materials-related applications such as pH fluorescence sensors[57,58] and solid-state fluorescent switches.[59]

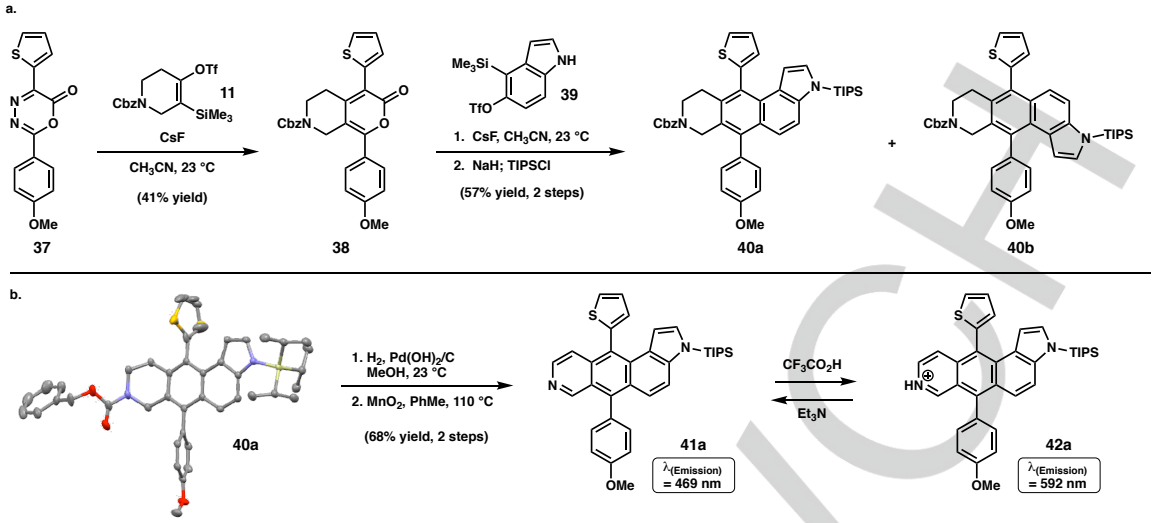


Figure 7. Strategic synthesis of **40** and elaboration to pH-responsive fluorophore **41a**. **40a** and **41b** are obtained as a 1:1 mixture of regioisomers. Cbz=benzylcarbamate, OTf=trifluoromethanesulfonate, TIPS=triisopropylsilyl.

We also carried out the one-pot, 3-component coupling of silyl triflates **11** and **32** with dichlorooxadiazinone **43** (Figure 8a). This transformation led to the controlled formation of dichloride **44** in 58% yield. **44** then underwent Pd-catalyzed borylation to give (bis)boronic ester **45**. Subsequent coupling with **46** afforded donor–acceptor fluorophore **47**, which was found to be solvatochromic,[60] indicative of a donor–acceptor system (Figure 8b).

Bis(boronate) **45** could be employed as a building block for polymer synthesis (Figure 8a). Suzuki–Miyaura polymerization[61] between diboronic ester **45** and 4,7-dibromobenzothiadiazole (**48**) provided donor–acceptor oligomer **49**, which was found to have a polydispersity index (PDI) of 1.3 and a number average molecular weight (M_n) of 1.7 kDa. The donor–acceptor oligomer **49** displays a red-shifted absorbance and emission relative to **47** with a longest-wavelength absorption maximum of λ = 391 nm and an emission maximum of λ = 491 nm (Figure 8c). The chromatographic shifts can be attributed to the extended conjugation present in oligomer **49** compared to **47**. These results demonstrate how a common adduct obtained from our methodology (i.e. **44**) can be used to rapidly access donor–acceptor monomers and oligomers displaying differing photophysical properties.

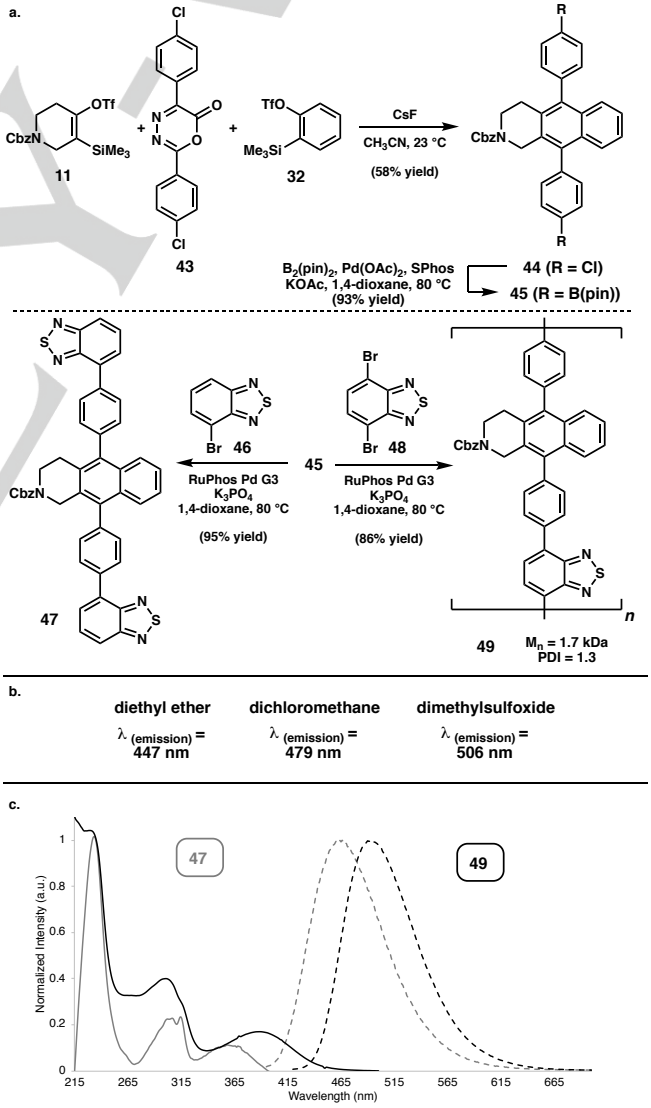


Figure 8. a. Three-component reaction toward **47** and **49**. **b.** Solvatochromism of fluorophore **47**. **c.** UV/Vis and fluorescence

spectra in THF with oligomer **49** displaying red-shifted absorbance (black solid line) and emission (black dashed line) relative to **47** (gray solid and dashed lines). Cbz=benzylcarbamate, OTf=trifluoromethanesulfonate, pin=pinacol ester.

We have discovered a modular synthetic platform that leverages strained cyclic alkynes and arynes to access new heteroatom-containing PAH scaffolds. Two strained intermediates are united with an oxadiazinone to rapidly construct 4 new C–C bonds. An array of heterocyclic PAH frameworks reminiscent of **1** can be accessed. These studies demonstrate that heterocyclic strained intermediates can be strategically harnessed for the preparation of new organic compounds with materials-related properties.

Acknowledgements

The authors are grateful to the University of California, Los Angeles for financial support. We are grateful to the NIH-NIGMS (R01 GM123299 to N.K.G. and F32-GM122245 to E.R.D.), Bristol-Myers Squibb (J.S.B.), the UCLA Graduate Division (J.S.B.), the Trueblood Family (N.K.G), and the Chemistry-Biology Interface training program (J.S.B., USPHS National Research Service Award 5T32GM008496-20). We thank the Sletten and Nelson laboratories (UCLA) for the use of their instrumentation and Dr. Scott Virgil (Caltech) for carrying out preparative separations. These studies were supported by shared instrumentation grants from the NSF (CHE-1048804) and the NCRR (S10RR025631). This work used computational and storage services associated with the Hoffman2 Shared Cluster provided by the UCLA Institute for Digital Research and Education's Research Technology Group.

Keywords: cyclic alkynes • arynes • cycloadditions • polycyclic aromatic hydrocarbons • heterocycles • materials science

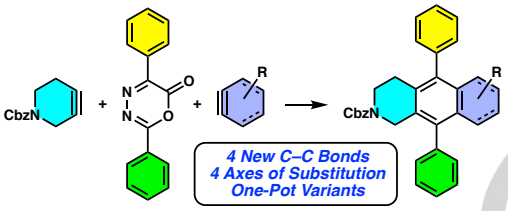
10.1002/anie.201903060

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION

We report a strained alkyne approach to access heteroatom-rich polycyclic aromatic hydrocarbons. This versatile synthetic platform allows for mild access to non-symmetric tricyclic cores through a sequential or one-pot reaction between two different strained alkynes and an oxidiazinone. In addition, we describe a rapid synthesis of a small molecule and polymeric donor–acceptor fluorophore.



*Dr. E. R. Darzi, J. S. Barber, and Prof. Dr. Neil K. Garg**

Page No. – Page No.

Cyclic Alkyne Approach to Heteroatom-Containing Polycyclic Aromatic Hydrocarbon Scaffolds

[1] R. Sanz, *Org. Prep. Proced. Int.* **2008**, *40*, 215−291.
[2] A. V. Dubrovskiy, N. A. Markina, R. C. Larock, *Org. Biomol. Chem.* **2013**, *11*, 191−218.
[3] S. Yoshida, T. Hosoya, *Chem. Lett.* **2015**, *44*, 1450−1460.
[4] S. S. Bhojgude, A. Bhunia, A. T. Biju, *Acc. Chem. Res.* **2016**, *49*, 1658−1670.
[5] V. Diemer, M. Begaud, F. R. Leroux, F. Colobert, *Eur. J. Org. Chem* **2011**, 341–354.
[6] P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G.-Y. J. Im, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269.
[7] N. F. Fine Nathel, L. A. Morrill, H. Mayr, N. K. Garg, *J. Am. Chem. Soc.* **2016**, *138*, 10402–10405.
[8] C. C. Mauger, G. A. Mignani, *Org. Process Res. Dev.* **2004**, *8*, 1065−1071.
[9] F. Schleth, T. Vettiger, M. Rommel, H. Tobler, World Patent WO2011131544 A1, **2011**.
[10] C. M. Gampe, E. M. Carreira, *Angew. Chem., Int. Ed.* **2012**, *51*, 3766−3778; *Angew. Chem.* **2012**, *124*, 3829−3842.
[11] P. M. Tadross, B. M. Stoltz, *Chem. Rev.* **2012**, *112*, 3550−3577.
[12] A. E. Goetz, N. K. Garg, *Nat. Chem.* **2012**, *5*, 54–60.
[13] T. C. McMahon, J. M. Medina, Y.-F. Yang, B. J. Simmons, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2015**, *137*, 4082–4085.
[14] C. Wentrup, R. Blanch, H. Briehl, G. Gross, *J. Am. Chem. Soc.* **1988**, *110*, 1874–1880.
[15] S. F. Talis, R. L. Danheiser, *J. Am. Chem. Soc.* **2014**, *136*, 15489–15492.
[16] T. K. Shah, J. M. Medina, N. K. Garg, *J. Am. Chem. Soc.* **2016**, *138*, 4948–4954.
[17] A. E. Goetz, T. K. Shah, N. K. Garg, *Chem. Commun.* **2015**, *51*, 34−45.
[18] G.-Y. J. Im, S. M. Bronner, A. E. Goetz, R. S. Patton, P. H.-Y Cheong, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944.
[19] M. G. Reinecke, *Tetrahedron* **1982**, *38*, 427–498.
[20] D. Pérez, D. Peña, E. Guitián, *Eur. J. Org. Chem.* **2013**, 5981–6013.
[21] X. Xiao, T. R. Hoye, *Nat. Chem.* **2018**, *10*, 838–844.
[22] S. E. Suh, S. A. Barros, D. M. Chenoweth, *Chem. Sci.* **2015**, *6*, 5128–5132.
[23] Y. Mizukoshi, K. Mikami, M. Uchiyama, *J. Am. Chem. Soc.* **2014**, *137*, 74–77.
[24] M. J. Allen, V. C. Tung, R. B. Kaner, *Chem. Rev.* **2010**, *110*, 132–145.
[25] A. C. Grimsdale, J. Wu, K. Müllen, *Chem. Commun.* **2005**, *17*, 2197–2204.
[26] P. M. Beaujuge, M. J. Fréchet, *J. Am. Chem. Soc.* **2011**, *133*, 20009–20029.
[27] A. Haller, A. Guyot, *Compt. Rend.* **1904**, *138*, 1251–1254.
[28] J. H. Carmel, J. S. Ward, M. M. Cooper, *J. Chem. Educ.* **2017**, *94*, 626–631.
[29] W. J. Jo, K. Kim, H. C. No, D. Shin, H. Oh, J. Son, Y. Kim, Y. Cho, Q. Zhao, K. Lee, H. Oh, S. Kwon, *Synth. Met.* **2009**, *159*, 1359–1364.
[30] M. Chen, L. Yan, Y. Zhao, I. Murtaza, H. Meng, W. Huang, *J. Mater. Chem. C.* **2018**, *6*, 7416–7444.
[31] J. T. Markiewicz, F. Wudl, *ACS Appl. Mater. Interfaces* **2015**, *7*, 28063–28085.
[32] J. E. Anthony, *Chem. Rev.* **2006**, *106*, 5028–5048.
[33] M. Stępień, E. Gońka, M. Żyła, N. Sprutta, *Chem. Rev.* **2017**, *117*, 3479–3716.
[34] F. Eiden, B. Wuensch, *Arch. Pharm.* **1986**, *319*, 886–889.
[35] C. Bozzo, M. D. Pujol, *Heterocycl. Commun.* **1996**, *2*, 163–168.
[36] J. Li, F. Yan, J. Gao, P. Li, W.-W. Xiong, Y. Zhao, X. W. Sun, Q. Zhang, *Dyes Pigm.* **2014**, *112*, 93–98.
[37] S. J. Eum, Y. J. Cho, H. J. Kwon, B. O. Kim, S. M. Kim, S. S. Yoon, U.S. Patent US8153279, **2012**.
[38] X. Li, A. Fast, Z. Huang, D. A. Fishman, M. L. Tang, *Angew. Chem., Int. Ed.* **2017**, *56*, 5598–5602; *Angew. Chem***2017**, *129*, 5690–5694.
[39] C. Gao, D. Cui, Y. Wang, C. Zhang, X. Sun, Chinese Patent CN10508599, **2018**.
[40] C. Xia, C. Lin, T.-C. Wang, U.S. Patent US2016/0149139, **2016**.
[41] C. Gao, D. Cui, Y. Wang, C. Zhang, X. Sun, World Patent WO2016/192346, **2016**.
[42] D.-H. Kim, J.-C. Park, H. M. Song, E.-K. Kim, Korean Patent KR10-2010-0108120, **2010**.
[43] J. L. Marshall, D. Lehnherr, B. D. Lindner, R. R. Tykwinski, *ChemPlusChem* **2017**, *82*, 967–1001.
[44] J. B. Lin, T. K. Shah, A. E. Goetz, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2017**, *139*, 10447–10455.
[45] M. L. Tîntas, A. P. Diac, A. Soran, A. Terec, I. Grosu, E. Bogdan, *J. Mol. Struct.* **2014**, *1058*, 106–113.
[46] B. Rickborn, *Org. React.* **1998**, *53*, 223–629.
[47] W. Steglich, E. Buschmann, G. Gansen, L. Wilschowitz, *Synthesis* **1977**, 252–253.
[48] Q. Miao, X. Chi, S. Xiao, R. Zeis, M. Lefenfeld, T. Siegrist, M. L. Steigerwald, C. Nuckolls, *J. Am. Chem. Soc.* **2006**, *128*, 1340–1345.
[49] D. Chun, Y. Cheng, F. Wudl, *Angew. Chem., Int. Ed.* **2008**, *47*, 8380–8385; *Angew. Chem.* **2008**, *120*, 8508–8513.
[50] DA reactions using substituted tetrazenes or isobenzofurans are known, but also suffer from the inability to introduce two different strained intermediates in a controlled fashion. For examples, see: references 2, 31, 32, 34 and S.-E. Suh, S. Chen, K. N. Houk, D. M. Chenoweth, *Chem. Sci.* **2018**, *9*, 7688–7693.
[51] J. Balcar, G. Chrisam, F. X. Huber, J. Sauer, *Tetrahedron Lett.* **1983**, *24*, 1481–1484.
[52] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, *12*, 1211–1214.
[53] D. Peña, D. Pérez, E. Guitián, L. Castedo, *Org. Lett.* **1999**, *1*, 1555–1557.
[54] Silyl triflate precursors to **17**, **19**, **21**, and **25** are all commercially available from Sigma–Aldrich or TCI (see the SI for details).
[55] K. Afarinkia, V. Vinader, T. D. Nelson, G. H. Posner, *Tetrahedron* **1992**, *48*, 9111–9171.
[56] R. P. Johnson, K. J. Daoust, *J. Am. Chem. Soc.* **1995**, *117*, 362–367.
[57] X. Liu, J. Liu, B. Zheng, L. Yan, J. Dai, Z. Zhuang, J. Du, Y. Guo, D. Xiao, *New J. Chem.* **2017**, *41*, 10607–10612.
[58] Q.-J. Ma, H.-P. Li, F. Yang, J. Zheng, X.-F. Wu, Y. Bai, X.-F. Li, *Sens. Actuators, B* **2012**, *166*, 68–74.
[59] L. Tan, S. Mo, B. Fang, W. Cheng, M. Yin, *J. Mater. Chem. C* **2018**, *6*, 10270–10275.
[60] C. Reichardt, *Chem. Rev.* **1994**, *94*, 2319–2358.
[61] K.-B. Seo, I.-H. Lee, J. Lee, I. Choi, T.-L. Choi, *J. Am. Chem. Soc.* **2018**, *140*, 4335–4343.