ORGANIC
LETTERS

2012
Vol. 14, No. 20
5200–5203

A Fragment-Based Approach toward Substituted Trioxa[7]helicenes

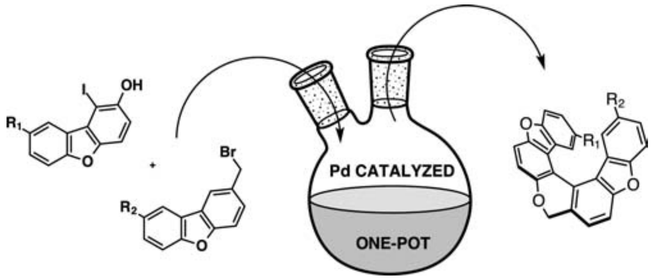
Hans Kelgtermans,[†] Liliana Dobrzańska,[†] Luc Van Meervelt,[‡] and Wim Dehaen*,[†]

Molecular Design and Synthesis, Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium, and Biomolecular Architecture, Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium

wim.dehaen@chem.kuleuven.be

Received August 20, 2012

ABSTRACT



A series of novel substituted trioxa[7]helicenes have been successfully prepared by a one-pot palladium catalyzed C−H arylation reaction starting from readily prepared dibenzofuran fragments. The dinitro-substituted helicene was analyzed by X-ray crystallography revealing the occurrence of two distinct enantiomers in the asymmetric unit, which forms interesting supramolecular motifs in the crystal, based on weak H-bonding interactions.

For over a century now, chemists have been inspired by the peculiar shape of helicenes.[1] Formed by a sequential ortho-annulation of (hetero)aromatic rings, helicenes are endowed with a unique π-conjugated backbone which is twisted into a helical shape due to a progressive steric hindrance between the terminal rings. The resulting inherently chiral skeleton is responsible for an astonishing number of diverse and fascinating applications, covering domains such as chiral catalysis,[2] self-assembly,[3] liquid crystals,[4] and biomolecular recognition.[5] Not surprisingly, these recent developments have led to a rapid increase in the number of different synthetic methodologies that avoid the more common, and up until now widely used, oxidative photocyclizations of stilbene-like precursors.[6] Compelling examples of these novel synthetic routes include the well-known Diels−Alder approach introduced by Katz et al.,[7] carbenoid couplings,[8] Friedel−Crafts type cyclizations,[9]

[†] Molecular Design and Synthesis.

[‡] Biomolecular Architecture.

(1) (a) Shen, Y.; Chen, C.-F. *Chem. Rev.* **2012**, *112*, 1463. (b) Dumitrascu, F.; Dumitrescu, D. G.; Aron, I. *ARKIVOC* **2012**, 1. (c) Urbano, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3986.

(2) (a) Crittall, M. R.; Rzepa, H. S.; Carbery, D. R. *Org. Lett.* **2011**, *13*, 1250. (b) Monteforte, M.; Cauteruccio, S.; Maiorana, S.; Benincori, T.; Forni, A.; Raimondi, L.; Graiff, C.; Tiripicchio, A.; Stephenson, G. R.; Licandro, E. *Eur. J. Org. Chem.* **2011**, *28*, 5649. (c) Takenaka, N.; Chen, J.; Captain, B.; Sarangthem, R. S.; Chandrakumar, A. *J. Am. Chem. Soc.* **2010**, *132*, 4536.

(3) (a) Nakano, K.; Oyama, H.; Nishimura, Y.; Nakasako, S.; Nozaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 695. (b) Kaseyama, T.; Furumi, S.; Zhang, X.; Tanaka, K.; Takeuchi, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3684. (c) Rybacek, J.; Huerta-Angeles, G.; Kollárovič, A.; Stará, I.; Starý, I.; Rahe, P.; Nimmrich, M.; Kuehnle, A. *Eur. J. Org. Chem.* **2011**, 853.

(4) (a) Ferrarini, A.; Pieraccini, S.; Masiero, S.; Spada, G. P. *Beilstein J. Org. Chem.* **2009**, 5, No. 50 (doi: 10.3762/bjoc.5.50). (b) Nuckolls, C.; Shao, R.; Jang, W.; Clark, N.; Walba, D.; Katz, T. J. *Chem. Mater.* **2002**, *14*, 773.

(5) Shinohara, K.-I.; Sannohe, Y.; Kaieda, S.; Tanaka, K.-I.; Osuga, H.; Tahara, H.; Xu, Y.; Kawase, T.; Bando, T.; Sugiyama, H. *J. Am. Chem. Soc.* **2010**, *132*, 3778.

(6) (a) Waghray, D.; Nulens, W.; Dehaen, W. *Org. Lett.* **2011**, *13*, 5516. (b) Pearson, M. S. M.; Carbery, D. R. *J. Org. Chem.* **2009**, *74*, 5320. (c) Aloui, F.; Abed, E. R.; Marinetti, A.; Hassine, B. B. *Tetrahedron Lett.* **2008**, *49*, 4092. (d) Groen, M. B.; Schadenberg, H.; Wynberg, H. *J. Org. Chem.* **1971**, *36*, 2797.

(7) Katz, T. J.; Liu, L.; Willmore, N.; Fox, J. M.; Rheingold, A.; Shi, S.; Nuckolls, C.; Rickman, B. *J. Am. Chem. Soc.* **1997**, *119*, 10054.

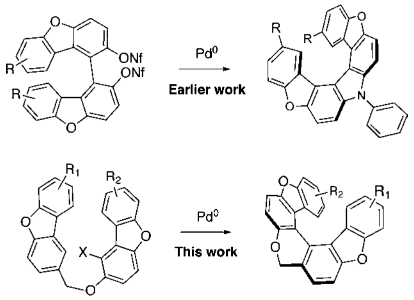
(8) (a) Gingras, M.; Dubois, F. *Tetrahedron Lett.* **1999**, *40*, 1309. (b) Dubois, F.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 5039.

(9) Fuchibe, K.; Jyono, H.; Fujiwara, M.; Kudo, T.; Yokota, M.; Ichikawa, J. *Chem.—Eur. J.* **2011**, *17*, 12175.

10.1021/ol3023209

and olefin metathesis.[10] Another well established procedure is based on the intramolecular [2 + 2+2] cycloisomerization of triynes, first reported by Starý and Stará in 1998,[11] and currently one of the most employed methods for preparing helicenes both racemically[12] and enantioselectively.[13] Although several different helical frameworks have been created using this technique, the rather cumbersome preparation of the starting materials and the relatively high cost of the transition metals and ligands are still limiting factors in this methodology. On the other hand, only a few palladium-catalyzed arylation approaches toward helicenes are reported to date,[14] despite the major advances that have been made in this field.[15] Prompted by these findings, we were eager to investigate whether it would be possible to extend the well-known palladium mediated C−H arylations to sterically more demanding structures, particularly by using substituted dibenzofuran units.

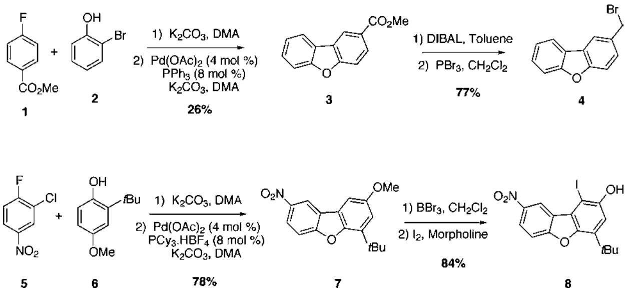
Scheme 1. Overview of Past and Current Work



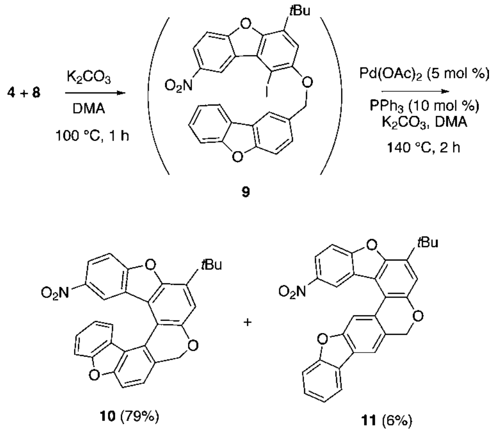
In previous work[16] we described the synthesis and characterization of oxa-helicenes in which two dibenzofuran blocks are linked *via* a pyrrole moiety, constructed by means of a double Buchwald−Hartwig N-arylation (Scheme 1). For this study a pyran ring as a linking group was selected due to its relatively facile preparation and increased ring size, which will extend the sterical overlap between the terminal rings and improve the thermal racemization stability.

The study was initiated with the preparation of suitable starting materials **4** and **8** (Scheme 2). A nitro group was selected as a terminal substituent on the helicene since, in general, they are inaccessible using photocyclization-based methods due to their quenching effect and will most likely enhance the electro-optical properties of the helicene by creating a more pronounced D-π-A system.[17] Both substituted dibenzofurans were readily prepared on a multigram scale starting from commercially available compounds. A nucleophilic aromatic substitution followed by a C−H arylation catalyzed by $Pd(OAc)_2$ and PPh_3 yielded ester **3**, which was reduced using DIBAL and finally brominated with PBr_3, resulting in the formation of **4** in good yields. Using a similar strategy, 2-methoxy-8-nitrodibenzofuran **7** was obtained. After demethylation of **7** and subsequent iodination using an iodine−morpholine charge-transfer complex,[18] the targeted phenolic substrate **8** was acquired in excellent yields (Scheme 2).

Scheme 2. Synthesis of the Starting Materials **4** and **8**



Scheme 3. C−H Arylation toward Helicene **10**



The reaction between **4** and **8** was characterized by the formation of a white precipitate after only a few minutes at 100 °C. Although the low solubility of **9** was expected,

---

(10) (a) Grandbois, A.; Collins, S. K. *Chem.—Eur. J.* **2008**, *14*, 9323. (b) Collins, S. K.; Grandbois, A.; Vachon, M. P.; Cote, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2923.

(11) Stará, I. G.; Starý, I.; Kollárovič, A.; Teplý, F.; Saman, D.; Tichý, M. *J. Org. Chem.* **1998**, *63*, 4046.

(12) Songis, O.; Míšek, J.; Schmid, M. B.; Kollárovič, A.; Stará, I.; Saman, D.; Císařová, I.; Starý, I. *J. Org. Chem.* **2010**, *75*, 6889.

(13) (a) Shibata, T.; Uchiyama, T.; Yoshinami, Y.; Takayasu, S.; Tsuchikama, K.; Endo, K. *Chem. Commun.* **2012**, *48*, 1311. (b) Sehnal, P.; Krausová, Z.; Teplý, F.; Stará, I.; Starý, I.; Rulíšek, L.; Saman, D.; Císařová, I. *J. Org. Chem.* **2008**, *73*, 2074.

(14) (a) Nakano, K.; Hidehira, Y.; Takahashi, K.; Hiyama, T.; Nozaki, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7136. (b) Kamikawa, K.; Takemoto, I.; Takemoto, S.; Matsuzaka, H. *J. Org. Chem.* **2007**, *72*, 7406.

(15) Ackermann, L. *Modern Arylation Methods*; Wiley-VCH: Weinheim, 2009.

(16) Kelgtermans, H.; Dobrzańska, L.; Van Meervelt, L.; Dehaen, W. *Org. Lett.* **2012**, *14*, 1500.

(17) (a) Champagne, B. *Chem. Phys. Lett.* **2012**, Article ASAP (doi: 10.1016/j.cplett.2012.03.015). (b) Bossi, A.; Licandro, E.; Maiorana, S.; Rigamonti, C.; Righetto, S.; Stephenson, G. R.; Spassova, M.; Botek, E.; Champagne, B. *J. Phys. Chem. C* **2008**, *112*, 7900.

(18) Perez, A. L.; Lamoureux, G.; Herrera, A. *Synth. Commun.* **2004**, *34*, 3389.

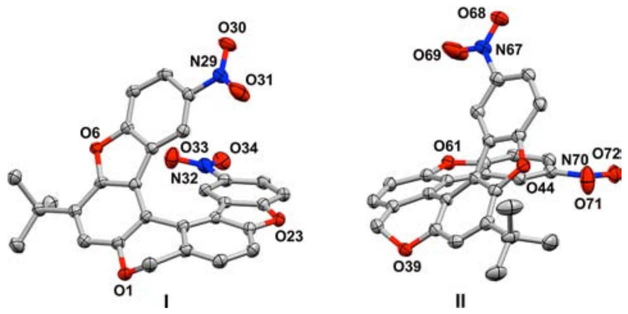
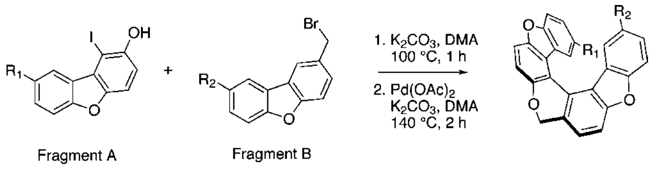


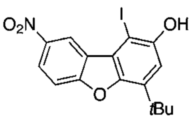
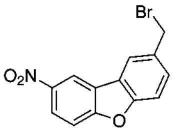
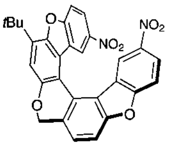
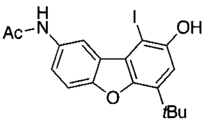
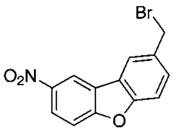
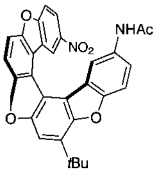
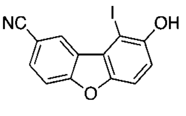
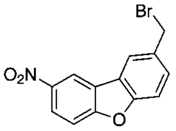
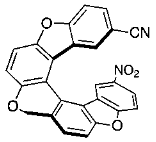
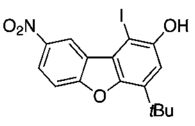
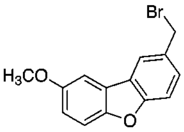
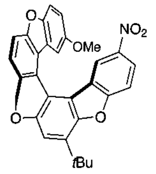
Figure 1. Two crystallographically independent molecules of **13** present in the asymmetric unit with labeled heteroatoms. Displacement ellipsoids are drawn at the 50% probability level; hydrogen atoms have been omitted for clarity.

isolation and characterization of the dimeric intermediate **9** remained very difficult, even after the introduction of a bulky *tert*-butyl substituent on **8**. However, addition of $Pd(OAc)_2$ to the reaction mixture in combination with triphenyl phosphine resulted in the rapid disappearance of the precipitate and formation of a ring-closed product (according to mass spectrometry); thus the synthetic protocol was carried out as a one-pot process. After the reaction, two major compounds could be separated which corresponded to the two possible isomers **10** and **11** (Scheme 3).

By investigating the NMR spectroscopic data, the major component of the mixture (79%) was identified as helicene **10**. This was clearly indicated by a significant upfield shift for the innermost hydrogens, caused by the shielding effect of the neighboring dibenzofuran system (see Supporting Information (SI)). The linearly fused isomer **11**, which

Table 1. Scope of the C−H Arylation Approach toward Substituted Trioxa[7]helicenes



entry	fragment A	fragment B	helicene	yield[a,b]
1	 **8**	 **12**	 **13**	76%
2	 **14**	 **12**	 **15**	58%
3	 **16**	 **12**	 **17**	89%
4	 **8**	 **18**	 **19**	67%

[a] Isolated yields. [b] The linearly fused isomers were formed in trace amounts but could not be isolated in a pure form.

actually is a [5]helicene by itself, was only formed in small amounts (6−7%) despite the fact that it is less sterically strained than its helical counterpart.

Interestingly, during the optimization process it became clear that the nature of the phosphine ligand was irrelevant to the outcome of the reaction, which could mean that it is not participating in the ring closure mechanism. These observations were confirmed by running an experiment under ligand-free conditions, which revealed a reaction outcome comparable to that when PPh_3 was used. Performing the second step without the addition of a palladium source left the starting material unchanged, proving the necessity of the catalyst. So in general, the synthetic protocol could be carried out as a high-yielding, scalable, one-pot process starting from readily obtained dibenzofuran building blocks and a relatively inexpensive source of palladium.

With these reaction conditions in hand, we were eager to test the scope of this new C−H arylation approach. Several substituted dibenzofuran moieties were successfully prepared and coupled (Table 1) following a similar strategy as before, clearly demonstrating the versatility of this approach. Both electron-donating and -withdrawing functionalities were readily combined by connecting the corresponding dibenzofuran fragments, making this method an ideal tool for fine-tuning the helicene backbone.

Crystals of *rac*-**13** suitable for an X-ray diffraction study were obtained by slow evaporation from dichloromethane. The compound crystallizes in the centrosymmetric triclinic space group $P\overline{1}$, with two crystallographically independent molecules of opposite helical handedness in the asymmetric unit (see Figure 1). The geometrical parameters of these two solid-state enantiomers (**I** and **II**) differ slightly (rmsd was calculated as 0.115 Å, with a maximum distance between two atoms of 0.266 Å).

For example, there is a small difference in the orientation of the N29 and N67 nitro groups with the corresponding torsion angles C11−C10−N29−O30 = 174.7(2)° (**I**) and C49−C48−N67−O68 = 179.4(2)° (**II**), as well as a noticeable shortening of the N−O bonds for N67. The conformational divergence is also reflected in the different distortions (calculated as the sum of torsion angles) of the molecular structures **I** and **II** with respective absolute values of 69.0° and 74.2°. These indicate a larger distortion in compound **13** than in the dioxa-aza[7]helicene (53.2°) we reported earlier,[16] as a result of introducing the pyran ring and perhaps the presence of the nitro functions. The value in **II** approaches the one reported for oxa[7]helicene (78.9°).[14a]

Moreover, due to the presence of the nitro groups, C−H···O weak H-bonding interactions lead to the formation of 1D zigzag chains consisting of one type of conformer that are further interconnected into 2D supramolecular layers (see Supporting Information (SI) for a detailed analysis of the packing).

In summary we have successfully explored the synthesis of a novel trioxa[7]helicene scaffold. Several substitution patterns were readily constructed by starting from different dibenzofuran building blocks, which could be combined in a one-pot reaction under palladium catalysis to form the helical framework. One of the helicenes was characterized by X-ray crystallography analysis, revealing the importance of nitro functionalities in the supramolecular assembly. We demonstrated the flexibility of the approach by combining electron-donating and -withdrawing functional groups, a vital feature during the forthcoming study of the electro-optical properties of these helicenes.

Acknowledgment. The Instituut voor de aanmoediging van innovatie door Wetenschap en Technologie in Vlaanderen (IWT) is acknowledged for a fellowship to H.K. We thank the Fonds voor Wetenschappelijk Onderzoek (FWO - Vlaanderen) and the University of Leuven for financial support.

Supporting Information Available. Additional X-ray data and experimental procedures, copies of ^1H and ^{13}C NMR spectra and UV spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.