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# Toward a Visible Light Mediated Photocyclization: Cu-Based Sensitizers for the Synthesis of [5]Helicene

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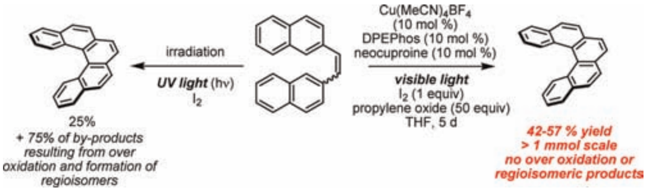
## ABSTRACT



**A photochemical synthesis of [5]helicene employing a copper-based sensitizer 7 has been developed that avoids the disadvantages associated with the traditional UV light mediated method. The visible light mediated synthesis uses common glassware and a simple household light bulb without the competing formation of [2 + 2] cycloadducts, regioisomers, or the overoxidation product benzo[*ghi*]perylene 3. Preliminary results show that the reaction time can be significantly reduced through the use of a continuous flow strategy.**

The UV light mediated photocyclization of stilbenes and stilbene-like molecules (photocyclodehydrogenation reaction), sometimes referred to as the Mallory reaction,[1] can be used to prepare a wide variety of polycyclic aromatic carbo- and heterocycles. Perhaps the most common application of the reaction is in the synthesis of helicenes, 3-D polycyclic aromatic systems, which consist of all ortho-fused aromatic rings that are inherently helically chiral.[2] Since the development of the UV-mediated photocyclization of stilbenes in 1967 by Martin et al., it has been applied to the synthesis of both small and higher helicenes.[3] Despite its popularity, the UV-mediated method is not without its disadvantages. The classical UV-light mediated photocyclodehydrogenation reaction lacks enantiocontrol, there is a need for high dilution conditions to avoid competitive intermolecular photocycloadditions, and overoxidation of the desired products is often problematic. In addition, there are practical complications which include the need for a special photochemical apparatus or UV lamps, protective eyewear, and expensive quartz glassware. Despite all of the obstacles, the classic photocyclodehydrogenation reaction remains the go-to method for the synthesis of most helicenes[4] and helicene-like compounds.

One of the simplest helicene scaffolds, [5]helicene, has been used in the synthesis of molecular springs, molecular machines, novel dyes, polymers, in asymmetric catalysis, and in studying molecular recognition.[5] The

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[1] For reviews, see: (a) Joergensen, K. B. *Molecules* **2010**, *15*, 4334–4358. (b) Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1–456. For other early contributions to the development of this photochemical transformation, see: (c) Muszkat, K. A; Fischer, E. *J. Chem. Soc. B* **1967**, 662–678. (d) Cuppen, Th. J. H. M.; Laarhoven, W. H. *J. Am. Chem. Soc.* **1972**, *94*, 5914–5915. (e) Wynberg, H.; Groen, M. B. *J. Am. Chem. Soc.* **1968**, *90*, 5339–5341.

[2] (a) Hopf, H. In *Classics in Hydrocarbon Chemistry: Syntheses, Concepts, Perspectives*; Wiley-VCH: Weinheim, 2000; pp 323–330. (b) Smith, P. J.; Liebman, J. F.; Hopf, H.; Stary, I.; Stara, I. G.; Halton, B. In *Strained Hydrocarbons*; Dodziuk, H., Ed.; Wiley: 2009; pp 147–203. (c) Stara, I. G.; Stary, I. *Sci. Synth.* **2010**, *45b*, 885–953.

[3] (a) Flammand-Barbieux, M.; Nasielski, J.; Martin, R. H. *Tetrahedron Lett.* **1967**, *7*, 743–744. (b) Martin, R. H.; Baes, M. *Tetrahedron* **1975**, *31*, 2135–2137.

[4] As the applications of helicenes have grown, more effort has been placed upon developing new nonphotochemical methods to prepare helicenes: (a) Urbano, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3986–3989. Some methods to prepare [5]helicene include successive Diels–Alder reactions: (b) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *J. Am. Chem. Soc.* **2001**, *123*, 7929. Cyclotrimerizations of acetylenes: (c) Teply, F.; Stara, I.; Stary, I.; Kollarovic, A.; Saman, D.; Rulisek, L.; Fiedler, P. *J. Am. Chem. Soc.* **2002**, *124*, 9175–9180. Carbenoid couplings: (d) Dubois, F.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 5039–5040. Radical cyclizations: (e) Harrowven, D. C.; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett.* **2002**, *43*, 7345–7347. Olefin metathesis: (f) Collins, S. K.; Grandbois, A.; Vachon, M. P.; Côté, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2923–2926.

[5] Shen, Y.; Chen, C.-F. *Chem. Rev.* **2011**, *112*, 1463–1535.

10.1021/ol300983b

photochemical synthesis of [5]helicene perhaps best exemplifies the drawbacks to the UV light mediated synthesis (Figure 1). The synthesis of [5]helicene **2** from stilbene precursor **1** is plagued by the formation of an undesired regioisomer **4** and overoxidation of the desired product to benzo[*ghi*]perylene **3**. Mallory has reported that the irradiation of **1** provided the desired [5]helicene in 25% isolated yield, while the overoxidation product **3** was also formed in 37% yield and the regioisomeric product dibenzo[*b*,*g*]phenanthrene **4** in 38% yield. The difficulty in controlling the second oxidation of **2** to **3** was noted by Katz et al., who reported that the judicious choice of substituents could inhibit the second photocyclization reaction.[6] In an effort to develop a practical alternative to the UV-mediated method, it was believed that the same stilbene-like precursors could be coerced to form cyclic products under visible light. As the formation of the helicene product would now likely arise by a different mechanism, the newly developed synthetic route would not possess the drawbacks associated with the use of UV light. Herein we describe progress toward a visible light mediated photocyclization reaction and the development of a gram scale total synthesis of [5]helicene **2**.

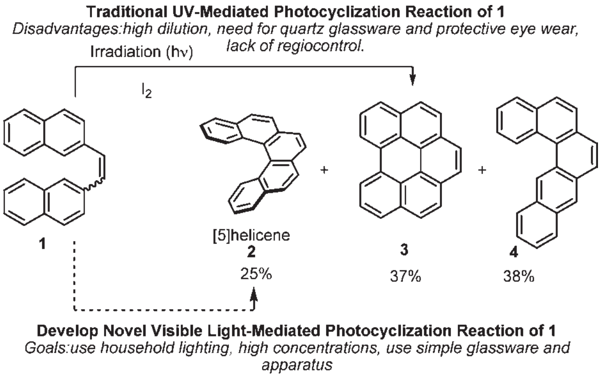

**Figure 1.** Toward a visible light mediated photocyclization.

Synthetic photochemistry using visible light has recently been cited as an emerging synthetic strategy and is regarded as a "green" technology. The research groups of MacMillan,[7] Yoon,[8] and Stephenson[9] have recently reported that sensitizers, such as **5** and **6** (Figure 2), can be used to photochemically promote reactions (aptly named photoredox reactions) under mild conditions using light sources such as simple LED devices, household lightbulbs, or even direct sunlight.[10] Consequently, our initial investigations sought to employ the same stilbene-like precursor **1** with reaction conditions that mirrored the classic photocyclization (utilizing $I_2$ and propylene oxide **9** as an oxidant system), but with an added sensitizer (Table 1). We initially chose to investigate complexes that have been reported to be efficient in other photoredox processes for related synthetic transformations. These include the popular $[Ru(bpy)_3](PF_6)_2$ (**5**) and [Ir(tbbpy)(phpy)]$PF_6$ (**6**) complexes (Figure 2). Disappointingly, both catalysts afforded very low conversion of **1** to the desired [5]helicene, **2**. We were then attracted to a Cu-based complex [Cu(DPEPhos)(neo)]$BF_4$ **7**, reported by McMillin et al., but never before investigated as a photoredox catalyst.[11] Copper based photoactive complexes represent an underexplored class of catalysts for photoredox chemistry, as they often are easily prepared, have tunable electronic properties, and can possess very long excited state lifetimes.[12] Upon treating **1** with the Cu-based sensitizer **7** (Table 1, entry 3) conversion of **1** took place over 5 days to afford **2** in 30–47% yield. The appropriate control reaction whereby the same reaction was performed in the absence of light gave no product **2** (Table 1, entry 4).

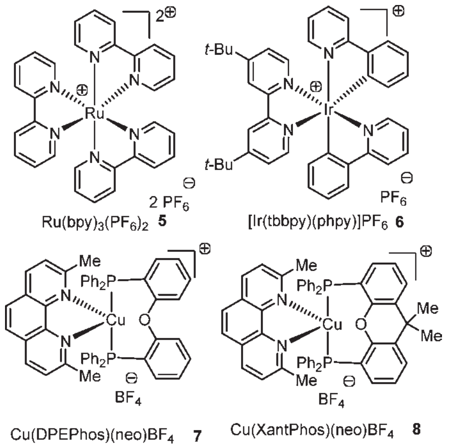

**Figure 2.** Transition metal based sensitizers.

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[6] Liu, L.; Katz, T. J. *Tetrahedron Lett.* **1991**, *32*, 6831–6834.

[7] (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80. (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877. (c) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600–13603.

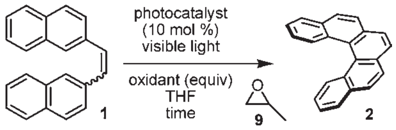
[8] (a) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527–532. (b) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572–8574. (c) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605. (d) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887. (e) Lu, Z.; Shen, M.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 1162–1164.

[9] (a) Condie, A. G.; González-Gómez, J.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465. (b) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757. (c) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem* **2011**, *3*, 140–145. (d) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160–4163. (e) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102–113.

[10] For some other examples of catalysts used for visible light mediated transformations, see: (a) Su, F.; Mathew, S. C.; Moehlmann, L.; Antonietti, M.; Wang, X.; Blechert, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 657–660. (b) Su, F.; Mathew, S. C.; Lipner, G.; Fu, X.; Antonietti, M.; Blechert, S.; Wang, X. *J. Am. Chem. Soc.* **2010**, *132*, 16299–16301.

[11] (a) Slinker, J. D.; Rivnay, J.; Moskowitz, J. S.; Parker, J. B.; Bernhard, S.; Abruña, H. D.; Malliaras, G. G. *J. Mater. Chem.* **2007**, *17*, 2976–2988. (b) Cuttell, D. G.; Kuang, S.-M.; Fanwick, P. E.; McMillin, D. R.; Walton, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 6–7.

**Table 1.** Optimization of the Visible Light Mediated Synthesis of [5]Helicene

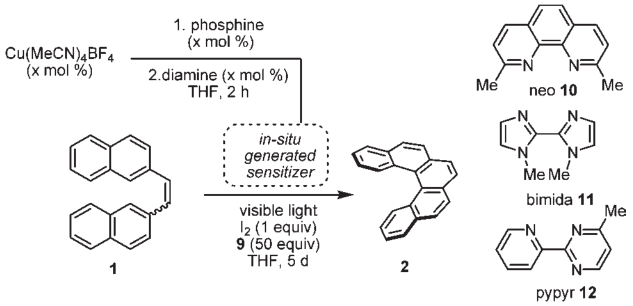


| entry | photocatalyst | oxidant (equiv); time (d) | yield (%)[a] |
|---|---|---|---|
| 1 | **5** | $I_2$ (1), **9** (50); 3 | <10 |
| 2 | **6** | $I_2$ (1), **9** (50); 3 | <10 |
| 3 | **7** | $I_2$ (1), **9** (50); 5 | 30−47 |
| 4 | **7** | $I_2$ (1), **9** (50); 5 | 0[b] |
| 5 | **7** | $I_2$ (0.1), $O_2$ (1 atm); 5 | 38 |
| 6 | **7** | DDQ (2); 3 | 21 |
| 7 | **7** | *t*-BuOOH (4), Δ; 3 | 29 |

[a] Isolated yields following flash chromatography. [b] Reaction performed in the absence of light.

Consequently, we began to optimize the synthesis of [5]helicene **2** with Cu complex **7** in hopes of improving the isolated yield via solvent effects or alternative oxidants (Table 1). A number of solvent combinations were surveyed; however none outperformed THF as a solvent.[13] A number of alternative oxidants were also investigated including DDQ and *t*-BuO$_2$H (21 and 29% isolated yield of **2** respectively), although neither afforded a superior yield when compared to molecular iodine (Tabel 1, entries 6−7). The use of a catalytic amount of iodine was studied, where molecular oxygen would serve as the stoichiometric oxidant. Over a reaction time of 5 days,[14] comparable yields were obtained compared to using stoichiometric amounts of iodine (38 vs 30−47%).

**Table 2.** Optimization of the Visible Light Mediated Synthesis of [5]Helicene by *in Situ* Generated Cu-Based Complexes



| entry | phosphine | diamine | mol % | yield (%)[a,b] |
|---|---|---|---|---|
| 1 | DPEPhos | neo | 10 | 32 |
| 2 | – | – | 10 | 0[c] |
| 3 | DPEPhos | neo | 10 | 0[d] |
| 4 | DPEPhos | neo | 10 | 32 |
| 5 | DPEPhos | neo | 50 | 56 |
| 6 | DPEPhos | bimida | 10 | 40 |
| 7 | DPEPhos | bimida | 25 | 39 |
| 8 | DPEPhos | pypyr | 10 | 39[e] |
| 9 | XantPhos | neo | 10 | 50 |
| 10 | XantPhos | neo | 25 | 57[f] |
| 11 | XantPhos | bimida | 10 | 36 |
| 12 | XantPhos | bimida | 25 | 49 |

[a] Isolated yields after chromatography. [b] All reactions run at 5 mM. Attempts at increasing the concentration further led to lower isolated yields. [c] Reaction performed in the absence of ligands. [d] Reaction performed in the absence of Cu(MeCN)$_4$BF$_4$ [e] When catalyst was preformed the isolated yield of **2** was 14%. [f] When catalyst was preformed the isolated yield of **2** was 56%.

In an effort to perform a rapid screening of photocatalysts based upon **7**, an *in situ* synthesis of the Cu-based photoredox catalysts was investigated (Table 2). It was found that a solution of the complex **7**, formed in THF through the sequential addition of DPEPhos and neocuproine, could be used directly for the visible light mediated synthesis of [5]helicene by simple addition of the remaining reagents and starting material **1**. Indeed, the yields for the isolation of [5]helicene when using preformed catalyst **7** (30−47%) and via an *in situ* protocol were comparable (32%). Using the in situ protocol, two important control experiments were performed: (1) a reaction in the absence of both the ligands (entry 2) and (2) a reaction in the absence of the Cu precursor (entry 3). These experiments suggest that the actual copper complex **7** is indeed the active photoredox catalyst. Subsequently, the effect of catalyst loading was investigated, where the yield of **2** was shown to increase to 56% when 50 mol % of **7** was used. When the neocuproine ligand **10** was substituted with either the *N*,*N*′-dimethyl bisimidazole **11** or the pyrimidine derived ligand **12**,13 the yields were again within the same range as those obtained for the neocuproine complex (40% for **2** and 39% for **2**). However, the best results were obtained when using XantPhos as the phosphine ligand to prepare the photoredox catalyst. At a catalyst loading of 10 mol %, the XantPhos/neocuproine catalyst provided a highly reproducible isolated yield of 50% of [5]helicene. Changing the amine ligand from **10** to **11** did not result in a significant increase. When the catalyst loading was increased to 25 mol %, a further increase in yield was observed to 57%. The visible light mediated reaction was left for 14 days in an attempt to increase the isolated yield

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(12) For a review of photoactive Cu complexes, see: (a) McMillin, D. R.; McNett, K. M. *Chem. Rev.* **1998**, *98*, 1201–1220. For recent examples of novel photoactive Cu complexes, see: (b) Harkins, S. B.; Peters, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 2030–2031. (c) Hashimoto, M.; Igawa, S.; Yashima, M.; Kawata, I.; Hoshino, M.; Osawa, M. *J. Am. Chem. Soc.* **2011**, *133*, 10348–10351.

(13) Reasons why THF is optimal for the process are still unclear. For a complete list of solvents studied, see the Supporting Information.

(14) For further information on the effect of the reaction time on the yield of **1**→**2**, see the Supporting Information.

(15) (a) Zhang, L.; Li, B.; Su, Z. *J. Phys. Chem. C* **2009**, *113*, 13968–13973. (b) Nishikawa, M.; Nomoto, K.; Kume, S.; Inoue, K.; Sakai, M.; Fujii, M.; Nishihara, H. *J. Am. Chem. Soc.* **2010**, *132*, 9579–9581.

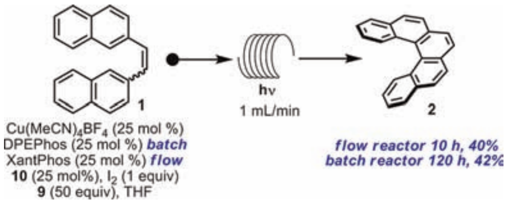
(16) To date, one of the most efficient syntheses of helicenes on gram scale is the Diels−Alder approach. See refs 4b, 4c, and 5.

(17) (a) Gutierrez, A. C.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 6414–6417. (b) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144–4147. (c) Andrews, R. S.; Becker, J. J; Gagne, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 4140–4142. (d) Bou-Hamdan, F. R.; Seeberger, P. H. *Chem. Sci.* **2012**, *3*, 1612–1616. (e) Levesque, F.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1706–1709.

of the desired helicene. However, no increase in yield was observed. A control experiment where a 1:1 ratio of **1** and [5]helicene was submitted to the optimized reaction conditions was performed and no change in the ratio of **1** to **2** was observed, suggesting that the product may be inhibiting further conversion of **1** to [5]helicene.

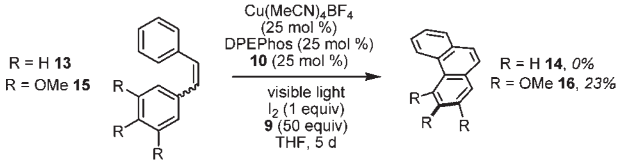
The synthesis of [5]helicene on a gram scale was attempted using the optimized protocol (Scheme 1).[16] After a 5 day reaction time, the [5]helicene product **2** was isolated in 42% yield. In an effort to develop a more practical synthetic approach, we performed the synthesis of **2** using a continuous flow strategy, since many photoredox processes have exhibited significant rate accelerations when using flow chemistry approaches.[17] The preliminary experiments demonstrated that a mixture of the catalyst system (formed *in situ*) and **1** could be injected through FEP-Teflon tubing while being irradiated by the same household energy saving lightbulb at the same concentration (5 mM) used in the batch reactor. A significant decrease in the reaction time was observed, as an almost identical yield of **2** was obtained via the flow process when compared to the batch reactor in only 10 h (compared to 120 h when using a round-bottom flask).

**Scheme 1.** Scale-up Synthesis of [5]Helicene Using Either a Round Bottom Flask or Continuous Flow Strategy



Preliminary studies directed toward understanding the mechanism suggest the newly developed visible light synthesis of **2** proceeds via an oxidation mechanism similar to other photoredox processes (Scheme 2).[18] To provide some preliminary support for an oxidative pathway, the cyclization of stilbenes **13** and **15** were also investigated and it was shown that only the more electron-rich trimethoxy derivative **15** underwent cyclization to afford the phenanthrene **16**. It should be noted that more detailed investigations are still necessary to elucidate the mechanistic pathway for the conversion of **1** to **2**.

**Scheme 2.** Photocyclization of Stilbenes



In summary, a visible light alternative to traditional UV-mediated photocyclizations has been developed using the synthesis of [5]helicene as a model. The synthesis of [5]helicene via a visible light mediated process using a Cu-based sensitizer presents several solutions to long-standing problems associated with the UV-mediated photocyclization of **1**: (1) a significantly higher yield of **2** can be obtained without the formation of any side products resulting from intermolecular [2 + 2] cyclizations or from photocyclization at other positions resulting in the formation of regioisomeric products (the only remaining products are the *cis*- and *trans*-isomers of **1**, which can subsequently be recycled), (2) the reaction does not require the use of expensive quartz glassware, hazardous UV lamps, or protective eyewear. The complex **7** was successful in a gram scale synthesis of [5]helicene in good yield and with much shorter reaction times when using a flow chemistry strategy. The success of Cu complexes **7** and **15** should encourage investigation of other Cu complexes for photoredox transformations. Given the diverse range of substrates that can undergo Mallory-type cyclization,[1] the investigation of photoredox catalysis in other cyclization reactions and application in the synthesis of higher helicenes is also currently underway.

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**Supporting Information Available.** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] The proposed oxidation of **1** is very similar to what was proposed for radical cation Diels–Alder cycloadditions. See: Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350–19353.

The authors declare no competing financial interest.