ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Intramolecular Carbocupration of *N*-Aryl-ynamides: A Modular Indole Synthesis

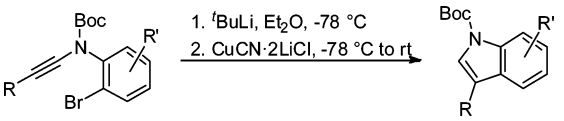
Wafa Gati,[†,‡] François Couty,[†] Taoufik Boubaker,[‡] Mohamed M. Rammah,[‡] Mohamed B. Rammah,[‡] and Gwilherm Evano*[,§]

Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles Saint-Quentin en Yvelines, 45, avenue des Etats-Unis, 78035 Versailles Cedex, France, Laboratoire de Chimie Hétérocyclique, Produits Naturels et Réactivité, Département de Chimie, Faculté des Sciences de Monastir, Université de Monastir, avenue de l'environnement, 5019 Monastir, Tunisia, and Laboratoire de Chimie Organique, Service de Chimie et PhysicoChimie Organiques, Université Libre de Bruxelles, Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium

gevano@ulb.ac.be

Received May 13, 2013

ABSTRACT



A modular indole synthesis based on an intramolecular 5-*endo-dig* carbocupration starting from readily available *N*-aryl-ynamides is reported. A variety of ynamides are converted to indoles in moderate to good yields and with varying substitution pattern on the indole ring. This further extends the synthetic utility of ynamides in organic synthesis and provides additional insights on the use of intramolecular carbometalation reactions.

Due to the development of efficient methods for their synthesis,[1] ynamides have emerged as one of the most efficient building blocks in organic synthesis over the past decade.[2] They have been used for the development of an impressive and ever-increasing number of transformations, the presence of the nitrogen atom attached to the alkyne being responsible for a strong differentiation of the two sp carbon atoms, which typically allows for high levels of regio- and stereoselectivities. This polarization of the triple bond combined with the presence of the electron-withdrawing group, which can act as a remarkably efficient directing group, makes them ideal candidates for the development of metal-mediated transformations. Indeed, they have been used, for example, in palladium-catalyzed hydrostannylations,[3] carbopalladations,[4] silaborations,[5] hydroacyloxylations,[6] chloroallylations,[7] gold-catalyzed hydroaminations,[8] or nickel-catalyzed hydrophosphorylations[9] and were also found to be excellent substrates for intermolecular

[†] Université de Versailles Saint-Quentin en Yvelines.
[‡] Université de Monastir.
[§] Université Libre de Bruxelles.

(1) For general methods for the synthesis of ynamides, see: (a) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011. (b) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151. (c) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (d) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381. (e) Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272. (f) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000. (g) Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996. (h) Jouvin, K.; Heimburger, J.; Evano, G. *Chem. Sci.* **2012**, *3*, 756.

(2) For current leading reviews on ynamides, see: (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (c) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17.

(3) Buissonneaud, D.; Cintrat, J.-C. *Tetrahedron Lett.* **2006**, *47*, 3139.

(4) (a) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4257. (b) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (c) Greenaway, R. L.; Campbell, C. D.; Holton, O. T.; Russel, C. A.; Anderson, E. A. *Chem.—Eur. J.* **2011**, *17*, 14366. (d) Cao, J.; Xu, Y.; Kong, Y.; Cui, Y.; Hu, Z.; Wang, G.; Deng, Y.; Lai, G. *Org. Lett.* **2012**, *14*, 38. (e) Greenaway, R. L.; Campbell, C. D.; Chapman, H. A.; Anderson, E. A. *Adv. Synth. Catal.* **2012**, *354*, 3187.

(5) Saito, N.; Saito, K.; Sato, H.; Sato, Y. *Adv. Synth. Catal.* **2013**, *355*, 853.

(6) Smith, D. L.; Goundry, W. R. F.; Lam, H. W. *Chem. Commun.* **2012**, *48*, 1505.

(7) Lu, Z.; Kong, W.; Yuan, Z.; Zhao, X.; Zhu, G. *J. Org. Chem.* **2011**, *76*, 8524.

(8) Kramer, S.; Dooleweerdt, K.; Lindhardt, A. T.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208.

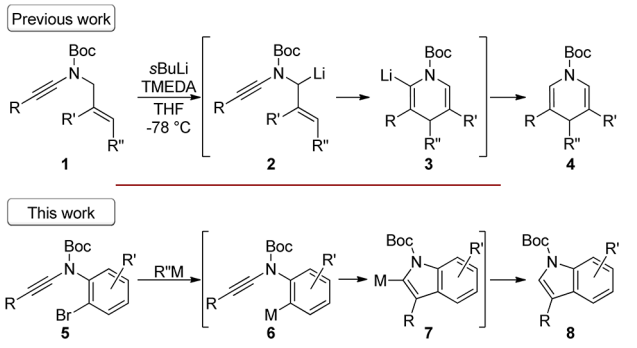
(9) Fadel, A.; Legrand, F.; Evano, G.; Rabasso, N. *Adv. Synth. Catal.* **2011**, *353*, 263.

10.1021/ol4013298

carbomagnesiation,[10] carbozincation,[11] and carbocupration[12] reactions.

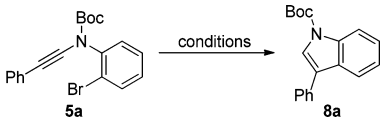
In this context, we have recently reported a straightforward synthesis of 1,4-dihydropyridines **4** relying on a highly efficient intramolecular carbolithiation starting from *N*-allyl-ynamides **1** (Scheme 1).[13] To further exploit both this strategy and the use of ynamides in heterocyclic synthesis, we decided to investigate the possibility of an intramolecular carbometalation from *N*-(2-bromoaryl)ynamides such as **5**. Provided that a clean bromine−metal exchange could be achieved in the presence of the reactive ynamide in **5**, we anticipated that a 5-*endo-dig* carbometalation[14] would afford polysubstituted indoles **8**. The indole skeleton being a privileged molecular scaffold at the core of an impressive number of natural and/or biologically relevant molecules, the development of new routes to indoles is still a highly active area of research.[15] Indeed, while the Fischer indole synthesis has been one of the most popular routes to indoles since its discovery 130 years ago,[16] there is still a strong demand for versatile, efficient, and regioselective indole synthesis. Herein, we present the development of a new and modular method for the synthesis of polysubstituted indoles **8** from readily available *N*-(2-bromoaryl)ynamides **5**.

Scheme 1. Strategy for the Synthesis of Indoles by Intramolecular Carbometalation from Ynamides



To test our hypothesis and optimize the reaction conditions, ynamide **5a**, readily prepared through Hsung's copper-catalyzed cross-coupling between the corresponding bromoalkyne and Boc-protected aniline,[1b] was chosen as a model substrate. A variety of conditions and metals, including lithium, magnesium, zinc, palladium, and copper, were screened to promote the intramolecular carbometalation: selected results from these studies are collected in Table 1.

Table 1. Optimization of the Intramolecular Carbometalation



entry	conditions	NMR yield[a]
1	*s*BuLi (1.2 equiv), TMEDA (1.2 equiv), THF, −78 °C, 14 h	–[b]
2	*t*BuLi (2.2 equiv), Et_2O, −78 to −50 °C, 14 h	–[b]
3	*t*BuLi (2.2 equiv), $MgBr_2 \cdot OEt_2$ (1.2 equiv), Et_2O, −78 to −50 °C, 14 h	–[b]
4	*t*BuLi (2.2 equiv), $ZnCl_2$ (1.2 equiv), Et_2O, −78 to −50 °C, 14 h	–[b]
5	*t*BuLi (2.2 equiv), CuCN·2LiCl (1.0 equiv), Et_2O, −78 to −50 °C, 14 h	62%
6	*s*BuLi (2.2 equiv), CuCN·2LiCl (1.0 equiv), Et_2O, −78 to −50 °C, 14 h	37%
7	*s*BuLi (2.2 equiv), TMEDA (2.2 equiv), CuCN·2LiCl (1.0 equiv), Et_2O, −78 to −50 °C, 14 h	45%
8	*n*BuLi (2.2 equiv), CuCN·2LiCl (1.0 equiv), Et_2O, −78 to −50 °C, 14 h	55%
9	*i*PrMgCl·LiCl (1.1 equiv), CuCN·2LiCl (0.3 equiv), THF, rt, 14 h	–[c]
10	*t*BuLi (2.2 equiv), CuCN·2LiCl (1.0 equiv), THF, −78 to −50 °C, 14 h	20%
11	*t*BuLi (2.2 equiv), $CuBr \cdot SMe_2$ (1.0 equiv), THF, −78 to −50 °C, 14 h	14%
12	*t*BuLi (2.2 equiv), $CuI \cdot P(OEt)_3$ (1.0 equiv), Et_2O, −78 to −50 °C, 14 h	48%
13	*t*BuLi (2.2 equiv), CuCN·2LiCl (0.2 equiv), Et_2O, −78 to −50 °C, 14 h	54%
14	*t*BuLi (2.2 equiv), CuCN·2LiCl (1.0 equiv), Et_2O, −78 °C, 14 h	15%
15	*t*BuLi (1.5 equiv), CuCN·2LiCl (1.0 equiv), Et_2O, −78 to rt, 14 h	62%
16	Bu_3SnH, AIBN, benzene, reflux, 48 h	–[b]
17	$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), HCO_2NH_4 (1.5 equiv), DMF, 80 °C, 14 h	–[d]

[a] Determined using *p*-anisaldehyde as an internal standard. [b] Complete reduction of the starting material was observed. [c] Competitive intermolecular carbomagnesiation was observed. [d] A mixture of *N*-(2-bromophenyl)-oxazolone and *N*-phenyl-oxazolone was formed.

While an intramolecular 6-*endo-dig* carbolithiation from an allylic sp^3 organolithium intermediate **2** was remarkably efficient in the case of the formation of a dihydropyridine ring system **4** (Scheme 1),[13] the related carbolithiation involving an aryllithium intermediate and a 5-*endo-dig* carbolithiation was disappointingly inefficient, the reduction of the starting *N*-(2-bromophenyl)ynamide **5a** being

(10) (a) Yasui, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2007**, *36*, 32. (b) Yasui, H.; Yorimitsu, H.; Oshima, H. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 373.

(11) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802.

(12) (a) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098. (b) Das, J. P.; Chechik, H.; Marek, I. *Nat. Chem.* **2009**, *1*, 128. (c) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522. (d) Minko, Y.; Pasco, M.; Chechik, H.; Marek, I. *Beilstein J. Org. Chem.* **2013**, *9*, 526.

(13) (a) Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078. (b) Gati, W.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Beilstein J. Org. Chem.* **2012**, *8*, 2214.

(14) For a comprehensive review on Baldwin's rules for the cyclization of alkynes, see: Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513. For related examples of anionic 5-*endo-dig* carbometalation reactions from heterosubtituted alkynes, see: (a) Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellestad, K E.; Stallman, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 7023. (b) Johnson, F.; Subramanian, R. *J. Org. Chem.* **1986**, *51*, 5040. (c) Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 1958. For a review on the carbocupration of heterosubstituted alkynes, see: Basheer, A.; Marek, I. *Beilstein J. Org. Chem.* **2010**, *6*, No. 77.

the only reaction observed under similar reaction conditions (Table 1, entries 1 and 2). While transmetalation to magnesium or zinc after bromine/lithium exchange in order to promote an intramolecular carbomagnesiation or carbozincation was equally inefficient (Table 1, entries 3 and 4), the addition of 1 equiv of CuCN·2LiCl[17] was found to have a dramatic effect on the outcome of the intramolecular carbometalation reaction, the desired indole **8a** being formed in 62% yield (Table 1, entry 5). The use of other reagents for the metalation step was then briefly evaluated but with little success, with *n*-butyl- and *s*-butyllithium (with or without additional TMEDA) giving lower yields (Table 1, entries 6–8) and competitive intermolecular carbomagnesiation being observed with Knochel's *i*PrMgCl·LiCl,[18] which was found to be remarkably efficient for the intramolecular copper-catalyzed carbomagnesiation of alkynyl(2-bromoaryl)thioethers (Table 1, entry 9).[14c] Switching from diethyl ether to THF or changing the copper source to CuBr·SMe_2 or CuI·$P(OEt)_3$ was found to be detrimental for the yield (Table 1, entries 10–13). We next looked at the possibility of using a catalytic amount of CuCN·2LiCl: if the copper-catalyzed intramolecular carbolithiation was still operative, the yield was however lower. The effect of the temperature was finally evaluated, and it was found that the cyclization was too slow when the reaction temperature was kept at −78 °C (Table 1, entry 14) while slowly warming the reaction mixture from −78 °C to room temperature gave the desired indole **8a** in 62% yield (Table 1, entry 15), conditions that we kept for the intramolecular carbocupration. Of note, radical (Table 1, entry 16) and palladium-catalyzed (Table 1, entry 17) cyclizations were also evaluated but failed to give the desired indole, as reduction or cyclization to oxazolones by nucleophilic attack of the Boc group to the activated alkyne was the major respective reaction pathway in these cases.

With the optimized conditions, consisting of a bromine/lithium exchange with *tert*-butyllithium in ether at −78 °C followed by transmetalation with CuCN·2LiCl and intramolecular carbocupration upon warming the reaction to room temperature, we next evaluated the scope of this reaction. To this aim, a set of *N*-(2-bromophenyl)ynamides **5a**–**l** possessing various representative substituents on the alkyne were submitted to the metalation/transmetalation/carbocupration sequence: results from those studies are collected in Figure 1. The reaction proceeded smoothly in most cases, with indoles **8a**–**l** being obtained in moderate to good yields regardless of the substituent of the ynamide. Indeed, aryl-substituted ynamides **5a**–**5h** were found to smoothly undergo intramolecular 5-*endo*-*dig* carbocupration regardless of the substitution pattern or the electronic properties of the aromatic substituent. The corresponding 3-aryl-indoles **8a**–**8h** were predominantly formed in all cases along with minor amounts of debrominated starting materials. The produced compounds are very useful building blocks, with many biologically active indoles possessing an aromatic group at C-3 and no substituent at C-2.[19]

The reaction worked equally well with a styryl group, affording the corresponding indole **8i** in 54% yield; with alkyl groups, no competitive propargylic deprotonation or proton transfer was observed during the preparation of propyl-substituted indole **8k**. Finally, a TIPS-substituted indole (**8l**) could also be obtained using the metalation/intramolecular carbocupration sequence, although with less efficiency.

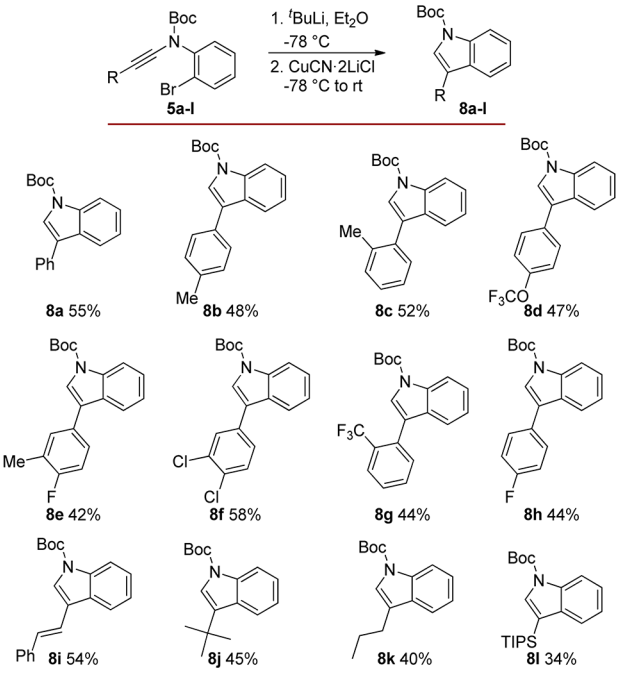


Figure 1. Scope of the intramolecular carbocupration for the synthesis of 3-substituted indoles.

This intramolecular carbometalation from readily available ynamides therefore provides an efficient and selective

(15) For recent reviews on the synthesis of indoles, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (e) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (f) Kruger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (g) Vincente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. (h) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (i) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215. (j) Platon, M.; Amardeil, R.; Djakovitchb, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929. (k) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29.

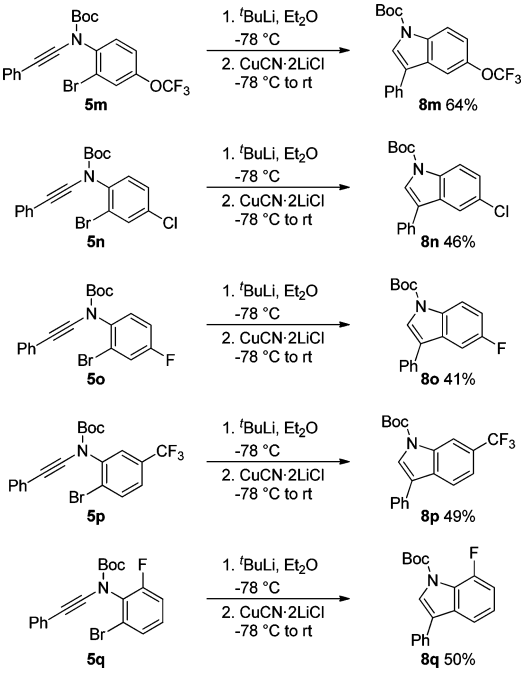
(16) (a) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241. (b) Fischer, E.; Hess, O. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559.

(17) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(18) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159.

(19) For selected examples, see: (a) Andersen, K.; Perregaard, J.; Arn, J.; Nielsen, J. B.; Begtrup, M. *J. Med. Chem.* **1992**, *35*, 4823. (b) Leboho, T. C.; Michael, J. P.; van Otterlo, W. A. L.; de Koning, C. B.; van Vuuren, S. F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4948. (c) Richardson, T. I.; Clarke, C. A.; Yu, K.-L.; Yee, Y. K.; Bleisch, T. J.; Lopez, J. E.; Jones, S. A.; Hughes, N. E.; Muehl, B. S.; Lugar, C. W.; Moore, T. L.; Shetler, P. K.; Zink, R. W.; Osborne, J. J.; Montrose-Rafizadeh, C.; Patel, N.; Geiser, A. G.; Galvin, R. J. S.; Dodge, J. A. *ACS Med. Chem. Lett.* **2011**, *2*, 148. (d) Mesangeau, C.; Amata, E.; Alsharif, W.; McCurdy, C. R.; Seminerio, M. J.; Robson, M. J.; Matsumoto, R. R.; Poupaert, J. H. *Eur. J. Med. Chem.* **2011**, *46*, 5154.

Scheme 2. Synthesis of Polysubstituted Indoles by Intramolecular Carbocupration



route to 3-substituted indoles and is therefore complementary to other routes to indoles such as, for example, the intramolecular hydroamination from 2-ethynylanilines yielding to 2-substituted indoles.[15]

To further evaluate the scope of our indole synthesis and test the possibility of preparing polysubstituted indoles through this reaction, we finally examined the reactivity of a small set of ynamides **5m**–**q** possessing additional substituents on the aniline core (Scheme 2). The presence of this additional substituent had virtually no impact on the outcome of the reaction, 1,3,5-, 1,3,6-, and 1,3,7-trisubstituted indoles **8m**–**q**, compounds that can be challenging to prepare using other routes, being readily formed using the reaction conditions.

In conclusion, we have developed an efficient and modular synthesis of polysubstituted indoles from readily available *N*-aryl-ynamides. A variety of ynamides are converted to 3-substituted indoles in moderate to good yields and with varying substitution patterns on the indole ring. This should further extend the synthetic utility of ynamides in organic synthesis and provides additional insight to the use of intramolecular carbometalation reactions. The extension of this reaction to other heterosubstituted alkynes is under study and will be reported in due time.

Acknowledgment. The authors thank the CNRS, the Universities of Brussels, Versailles and Monastir, the ANR (project DYNAMITE ANR-2010-BLAN-704), and the CMCU/PHC Utique (grant 10G1025) for support. We are grateful to Mr. Guillaume Boissonnat (Université Libre de Bruxelles and Ecole Polytechnique ParisTech) for technical assistance.

Supporting Information Available. Experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.