

Carbazoles via AuCl₃-Catalyzed
Cyclization of 1-(Indol-2-yl)-3-alkyn-1-ols

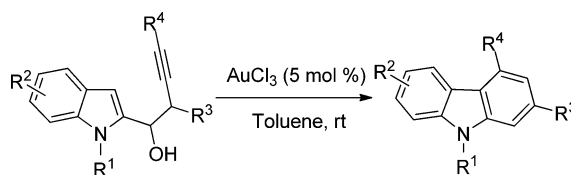
Youai Qiu, Wangqing Kong, Chunling Fu, and Shengming Ma*

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry,
Zhejiang University, Hangzhou 310027, Zhejiang, P. R. China

masm@sioc.ac.cn

Received October 26, 2012

ABSTRACT



AuCl₃-catalyzed reaction of 1-(indol-2-yl)-3-alkyn-1-ols occurred smoothly in toluene at room temperature to form a benzene ring leading to a series of carbazole derivatives efficiently. A possible mechanism has been proposed for the formation of carbazoles.

Carbazoles are important heteroaromatic compounds in many biologically active products.¹ They also serve as building blocks for potential electroluminescent materials² due to their electrical³ and thermal⁴ properties and host

materials for triplet emitters in organic light-emitting diodes.⁵ Therefore, they are attractive targets for organic synthesis. Although there are a number of useful synthetic procedures to prepare carbazoles,^{6–9} there remain some limitations such as low yields, poor atom economy, and harsh reaction conditions in these methods. Thus, a simple, mild, efficient, regiocontrolled, and diversified preparation of carbazole alkaloids with specific substitution patterns is still highly desirable.

On the other hand, the intramolecular hydroarylation reaction of alkyne is of particular interest, since valuable carbo- and heterocycles can be readily formed under relatively mild conditions.^{10–12} For example, gold- or platinum-catalyzed cyclization reactions of indoles with alkynes are

(1) (a) Kapil, R. S. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. 13, p 273. (b) Husson, H. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 1. (c) Chakraborty, D. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1993; Vol. 44, p 257. (d) Knölker, H. J. *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI: Greenwich, 1995; Vol. 1, p 173. (e) Ito, C.; Itoigawa, M.; Sato, A.; Hasan, C. M.; Rashid, M. A.; Tokuda, H.; Mukainaka, T.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2004**, *67*, 1488. (f) Bhattacharyya, P.; Chakraborty, D. P. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1987; Vol. 52, p 159.

(2) (a) Thomas, J. K. R.; Lin, J. T.; Tao, Y.-T.; Ko, C.-W. *J. Am. Chem. Soc.* **2001**, *123*, 9404. (b) Huang, J.; Niu, Y.; Yang, W.; Mo, Y.; Yuan, M.; Cao, Y. *Macromolecules* **2002**, *35*, 6080.

(3) Sanda, F.; Nakai, T.; Kobayashi, N.; Masuda, T. *Macromolecules* **2004**, *37*, 2703.

(4) Häussler, M.; Liu, J.; Zheng, R.; Lam, J. W. Y.; Qin, A.; Tang, B. Z. *Macromolecules* **2007**, *40*, 1914.

(5) (a) Dijken, A.; Bastiaansen, J. J. A. M.; Kiggen, N. M. M.; Langeveld, B. M. W.; Rothe, C.; Monkman, A.; Bach, I.; Stössel, P.; Brunner, K. J. *Am. Chem. Soc.* **2004**, *126*, 7718. (b) Wong, W.-Y.; Liu, L.; Cui, D.; Leung, L. M.; Kwong, C.-F.; Lee, T.-H.; Ng, H.-F. *Macromolecules* **2005**, *38*, 4970. (c) Adhikari, R. M.; Neckers, D. C. *J. Org. Chem.* **2009**, *74*, 3341.

(6) (a) Miller, F. M.; Schinske, W. N. *J. Org. Chem.* **1978**, *3*, 3384. (b) Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman: London, 1985. (c) Campaigne, E.; Lake, R. D. *J. Org. Chem.* **1959**, *24*, 478. (d) Campaigne, E.; Ergener, L.; Hallum, J. V.; Lake, R. D. *J. Org. Chem.* **1959**, *24*, 487.

(7) (a) Pizzotti, M.; Cenini, S.; Quici, S.; Tollari, S. *J. Chem. Soc., Perkin Trans. 2* **1994**, 913. (b) Smitrovich, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533. (c) Kuethe, J. T.; Childers, K. G. *Adv. Synth. Catal.* **2008**, *350*, 1577. (d) Freeman, A. W.; Urvoy, M.; Criswell, M. E. *J. Org. Chem.* **2005**, *70*, 5014.

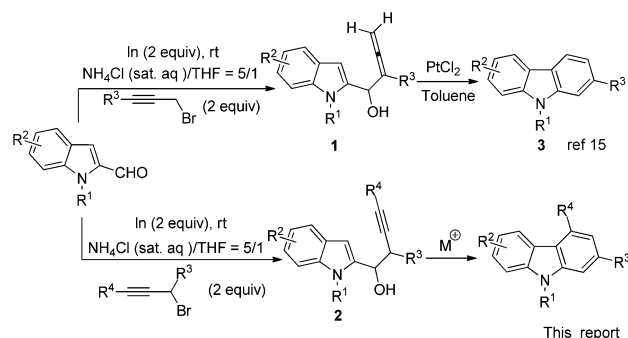
(8) (a) Witulski, B.; Ałayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281. (b) Martínez-Espéron, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Org. Lett.* **2005**, *7*, 2213.

(9) (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (b) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347. (c) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310. (d) Bedford, R. B.; Betham, M. J. *Org. Chem.* **2006**, *71*, 9403. (e) Forke, R.; Krah, M. P.; Krause, T.; Schlechtingen, G.; Knölker, H.-J. *Synlett* **2007**, 268. (f) Åkermark, B.; Ebersson, L.; Jonsson, E.; Pettersson, E. J. *Org. Chem.* **1975**, *40*, 1365. (g) Hagelin, H.; Oslob, J. D.; Åkermark, B. *Chem.—Eur. J.* **1999**, *5*, 2413. (h) Krah, M. P.; Jäger, A.; Krause, T.; Knölker, H.-J. *Org. Biomol. Chem.* **2006**, *4*, 3215. (i) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (j) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603. (k) Jean, D. S. J., Jr.; Poon, S. F.; Schwarzbach, J. L. *Org. Lett.* **2007**, *9*, 4893. (l) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2051. (m) Kitawaki, T.; Hayashi, Y.; Ueno, A.; Chida, N. *Tetrahedron* **2006**, *62*, 6792. (n) Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413.

important because significant molecular complexity can be obtained in one step starting from an easily accessible system.^{13,14}

Recently, we developed a route to construct carbazole alkaloids via the Pt-catalyzed cyclization of terminal 1-(indol-2-yl)-2,3-allenols **1** (Scheme 1),¹⁵ which may be easily prepared from the In-mediated reaction of indole-2-carbaldehydes and primary 1-alkynyl bromides in an aqueous phase.^{15,16} Interestingly, 1-(indol-2-yl)-3-alkyn-1-ols **2** were formed when non-terminal secondary 1-alkynyl bromides were used.¹⁷ Considering our interests in synthesis of heterocyclic compounds, we reasoned that cyclization of homopropargylic alcohols **2** may also afford carbazole alkaloids following a similar elimination of water to form the aromatic ring¹⁵ (Scheme 1). In this paper, we report our observation of such a reaction.

Scheme 1



(10) For reviews of hydroarylation of alkynes, see: (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (c) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (e) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (f) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (g) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (h) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (i) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (j) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (k) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (l) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (m) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042. (n) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (o) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448.

(11) For intermolecular hydroarylation of alkynes, see: (a) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (b) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669. (c) Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem.* **2006**, 4340. (d) Oyamada, J.; Kitamura, T. *Tetrahedron* **2009**, *65*, 3842.

(12) For intramolecular hydroarylation of alkynes, see: (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859. (c) Pastine, S. J.; Sames, D. *Org. Lett.* **2003**, *5*, 4053. (d) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645. (e) Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901. (f) Wegner, H. A.; Ahles, S.; Neuburger, M. *Chem.—Eur. J.* **2008**, *14*, 11310. (g) Jurberg, I. D.; Gagosz, F. *J. Organomet. Chem.* **2011**, *696*, 37. (h) Gronnier, C.; Odabachian, Y.; Gagosz, F. *Chem. Commun.* **2011**, 47, 218. (i) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480. (j) Lian, J.-J.; Chen, P.-C.; Lin, Y.-P.; Ting, H.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 11372. (k) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155. (l) Hashmi, A. S. K.; Yang, W.; Rominger, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 5762.

Our initial investigation focused on the reaction of 1-(1-ethyl-1*H*-indol-2-yl)-2-methyl-4-phenyl-3-butyn-1-ol (**2a**) in toluene under the catalysis of PtCl₂ (5 mol %). Interestingly, 9-ethyl-2-methyl-4-phenyl-9*H*-carbazole (**3a**) was indeed formed in 62% NMR yield (entry 1, Table 1). When AgOTf was used instead of PtCl₂, the yield of this reaction was only 35% (entry 2, Table 1), and Zn(OTf)₂ was totally inactive (entry 3, Table 1). However, the combined use of AuCl(PPh₃) and AgOTf as catalyst could improve the yield to 87% (entry 4, Table 1). AuCl(*t*-Bu₃P)/AgOTf catalyzed this transformation affording **3a** in 88% yield (entry 5, Table 1). Further study showed that AuCl₃¹⁸ is the best catalyst for this reaction, affording **3a** in 93% yield (entry 6, Table 1)! Several solvents were also tested for the AuCl₃-catalyzed reaction of **2a** at room temperature with toluene still being the best (entries 7–9, Table 1). When 1 mol % of AuCl₃ was used, the yield of **3a** was slightly lower (entry 10, Table 1). Thus, we defined the standard conditions as follows: 5 mol % of AuCl₃ in toluene at room temperature (entry 6, Table 1). The structure of **3a** was further confirmed by the X-ray crystal diffraction study (Figure 1).¹⁹

Table 1. Optimization of the Reaction Conditions^a

entry	catalyst (5 mol %)	solvent	time (h)	yield ^b of 3a (%)
1	PtCl ₂	toluene	36	62
2	AgOTf	toluene	23	35
3	Zn(OTf) ₂	toluene	12	0
4	AuCl(PPh ₃)/AgOTf	toluene	12	87
5	AuCl(<i>t</i> -Bu ₃ P)/AgOTf	toluene	12	88
6	AuCl ₃	toluene	3	93
7	AuCl ₃	CH ₂ Cl ₂	5	36
8	AuCl ₃	CH ₃ CN	5	51
9	AuCl ₃	acetone	5	85
10 ^c	AuCl ₃	toluene	12	82

^a The reaction was conducted with 0.2 mmol of **2a** and 0.01 mmol of catalyst in 1 mL of solvent. ^b Determined by ¹H NMR of crude product using dibromomethane as internal standard. ^c AuCl₃ (1 mol %) was used.

(13) For intermolecular gold- or platinum-catalyzed cyclization reactions of indole with alkynes, see: (a) Bhuvaneswari, S.; Jegannathan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2007**, *13*, 8285. (b) Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 1517.

(14) For intramolecular gold- or platinum-catalyzed cyclization reactions of indole with alkynes, see: (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358. (c) England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631. (d) Mamane, V.; Hennen, P.; Fürstner, A. *Chem.—Eur. J.* **2004**, *10*, 4556. (e) Zhang, G.; Catalano, V. J.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358. (f) Sanz, R.; Miguel, D.; Rodríguez, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7354. (g) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448. (h) Hashmi, A. S. K.; Yang, W.; Rominger, F. *Chem.—Eur. J.* **2012**, *18*, 6576.

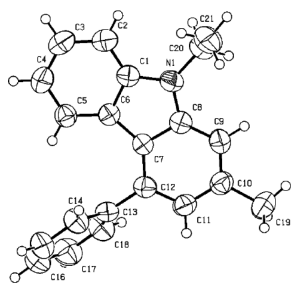
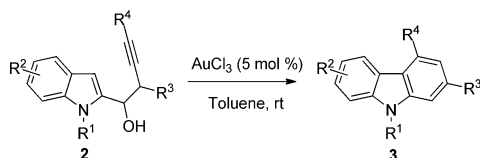


Figure 1. ORTEP representation of **3a**.

This new transformation is quite general, and some typical results are listed in Table 2. The 1-position of indoles may be substituted with alkyl (entries 1–7, 9 and 10, Table 2) or benzyl groups (entries 8, 11 and 12, Table 2). Substituents on the 5-position could be methyl (entries 4–6, Table 2), methoxy, which is the vital functional group for the synthesis of many natural tricyclic carbazole alkaloids²¹ (entry 7, Table 2), or bromine,²⁰ which could easily transform to many useful functional groups in the synthesis of biologically active carbazole alkaloids²¹ (entry 8, Table 2). Substituents may also be introduced to the 4- or 7-position (entries 9–10, Table 2). R^3 could be an alkyl (entries 1–5 and 7–12, Table 2) or an aryl group (entry 6, Table 2). Moreover, R^4 could be an alkyl (entries 2–4, 6, 7, 9, and 11, Table 2) or an aryl group (entries 1, 5, 8, 10, and 12, Table 2).

Table 2. AuCl₃-Catalyzed Cyclization Reaction of 1-(Indol-2-yl)-3-alkyn-1-ols **2**^a



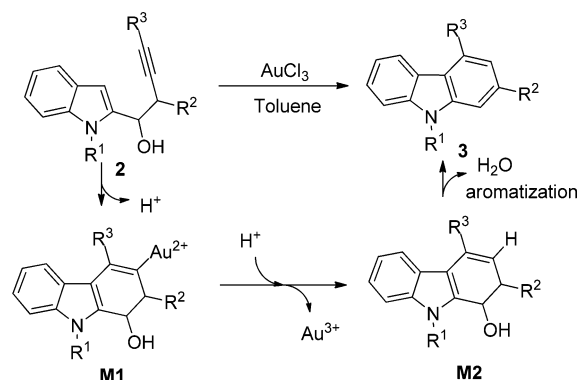
entry	2	R^1, R^2, R^3, R^4	time (h)	yield ^b of 3 (%)
1	2a	Et, H, Me, Ph	3	3a , 90
2	2b	Et, H, Me, Et	12	3b , 81
3	2c	Et, H, Me, <i>n</i> -C ₄ H ₉	19.5	3c , 74
4	2d	Et, 5-Me, Me, <i>n</i> -C ₄ H ₉	11.5	3d , 72
5	2e	Et, 5-Me, Et, Ph	14	3e , 79
6	2f	Et, 5-Me, Ph, <i>n</i> -C ₄ H ₉	11	3f , 64
7	2g	Et, 5-OMe, Me, <i>n</i> -C ₄ H ₉	11.5	3g , 60
8	2h	Bn, 5-Br, Et, Ph	13	3h , 72
9	2i	Et, 4-Me, Me, <i>n</i> -C ₄ H ₉	3	3i , 65
10	2j	Et, 7-Me, Me, Ph	12	3j , 90
11	2k	PMB, H, Me, <i>n</i> -C ₄ H ₉	12	3k , 58
12	2l	Bn, H, Et, Ph	12	3l , 62

^a Reaction conditions: 0.2 mmol of 1-(indol-2-yl)-3-alkyn-1-ols **2**, 0.01 mmol of AuCl₃ in 1 mL of toluene. ^b Isolated yield.

A mechanism is proposed for the reaction (Scheme 2).^{10,15,22} The reaction of Au³⁺ with **2** would form intermediate **M1** via the coordination of the alkyne with the Au³⁺ species

followed by nucleophilic attack of indolyl C3 to the metal-activated electrophilic C–C triple bonds. The six-membered intermediate **M2** may be afforded via demetalation of **M1** regenerating the catalytically active Au³⁺ species. Subsequent elimination of H₂O would afford the target carbazole **3**.^{15,121,23}

Scheme 2



In conclusion, we have developed a simple and mild AuCl₃-catalyzed reaction of 1-(indol-2-yl)-3-alkyn-1-ols to provide an efficient route to differently substituted carbazoles in moderate to good yields under very mild conditions. A rationale has also been proposed for the formation of carbazoles. Because of the easy availability of the starting materials and potential of the products, this method would be useful in organic synthesis and medicinal chemistry. Further studies on the synthetic applications of this reaction are being carried out in our laboratory.

Acknowledgment. Financial support from the Major State Basic Research and Development Program (2009CB825300) and the National Natural Science

(15) (a) Kong, W.; Fu, C.; Ma, S. *Chem. Commun.* **2009**, 4572. (b) Kong, W.; Fu, C.; Ma, S. *Chem.—Eur. J.* **2011**, *17*, 13134. (c) Kong, W.; Fu, C.; Ma, S. *Org. Biomol. Chem.* **2012**, *10*, 2164. (d) Kong, W.; Qiu, Y.; Fu, C.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 2399.

(16) (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C. *Eur. J. Org. Chem.* **2005**, 98. (b) Kong, W.; Fu, C.; Ma, S. *Org. Biomol. Chem.* **2008**, *6*, 4587.

(17) (a) Lee, P. H.; Kim, H.; Lee, K. *Adv. Synth. Catal.* **2005**, *347*, 1219. (b) Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220. (c) Masuyama, Y.; Watabe, A.; Kuru, Y. *Synlett* **2003**, *11*, 1713.

(18) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285.

(19) Crystal data for compound **3a**: C₂₁H₁₉N, MW = 285.37, monoclinic, space group P2₁, final *R* indices [*I* > 2σ(*I*)], *R*₁ = 0.0395, *wR*₂ = 0.0972, *R* indices (all data) *R*₁ = 0.0590, *wR*₂ = 0.0889, *a* = 8.9461(6) Å, *b* = 8.9810(6) Å, *c* = 20.0010(13) Å, α = 90°, β = 90.115(5)°, γ = 90°, *V* = 1606.98(18) Å³, *T* = 293(2) K, *Z* = 4, reflections collected/unique: 8159/4822 (*R*_{int} = 0.0252), number of observations [*I* > 2σ(*I*)] 3681, parameters: 402. CCDC 906003.

(20) For the orthogonality of gold and palladium catalysis, see: Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; Becker, J. D. B.; Rudolph, M.; Scholz, c.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133.

(21) Schmidt, A. W.; Reddy, K. R.; Knölker, H. J. *Chem. Rev.* **2012**, *110*, 3193.

(22) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232.

(23) Hashmi, A. S. K.; Wölflle, M. *Tetrahedron* **2009**, *65*, 9021.

Foundation of China (21232006) is greatly appreciated. S.M. is a Qiu Shi Adjunct Professor at Zhejiang University. We thank Ms. X. Xie in our group for reproducing the results presented in entries 4, 5, and 9 of Table 2.

Supporting Information Available. General procedure and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.