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One-Pot Synthesis of Chiral Dihydrobenzofuran Framework via Rh/Pd Catalysis

Gavin Chit Tsui, Jennifer Tsoung, Patrick Dougan, and Mark Lautens*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 3H6

mlautens@chem.utoronto.ca

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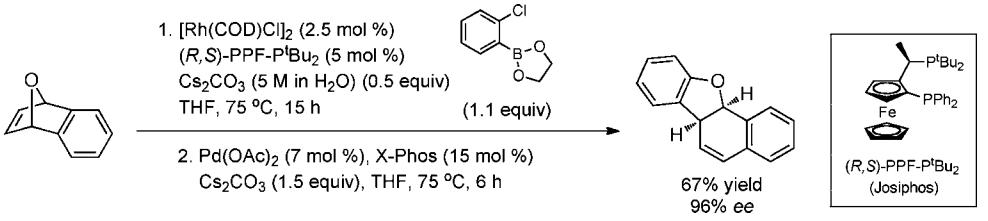
ABSTRACT



A one-pot synthesis of the chiral dihydrobenzofuran framework is described. The method utilizes Rh-catalyzed asymmetric ring opening (ARO) and Pd-catalyzed C−O coupling to furnish the product in excellent enantioselectivity without isolation of intermediates. Systematic metal−ligand studies were carried out to investigate the compatibility of each catalytic system using product enantiopurity as an indicator.

Traditional organic syntheses usually adopt a "stop-and-go" approach, which involves the purification of intermediates from each step to ensure that the consecutive reactions proceed smoothly and avoid various compatibility issues. The purification processes, however, are often time consuming, costly, and wasteful. Therefore, a more efficient "one-pot" approach, in which multiple chemical reactions are carried out sequentially in a single reaction vessel without the purification of intermediates, has emerged as a desirable and practical method.[1] A report of the total synthesis of (−)-oseltamivir (Tamiflu) by three "one-pot" operations highlights the power of this approach.[2] Of course process chemistry research groups have routinely adopted this strategy to streamline productions. However, the realization of the strategy is rare when multiple metal catalysts and ligands exist within a single vessel.

Dihydrobenzofurans are common motifs in natural products and are the key structural elements in biologically active neolignans (obtusafuran and kadsurenone)[3a] and lithospermic acids,[3b] which possess stereogenic centers at the C2 and C3 positions (Figure 1). Although methods exist in synthesizing dihydrobenzofuran frameworks, their asymmetric syntheses remain rare.[4] Until recently, only C−H activation approaches have been employed in the total syntheses of (+)-lithospermic acid to construct the dihydrobenzofuran core asymmetrically.[3b,5]

Recently, our group reported examples of a one-pot/domino synthesis of dihydroquinolines using two transition-metal catalysts (Rh/Pd and BINAP/X-Phos).[6] In a continuing effort to develop efficient and selective one-pot reactions using two metal catalytic systems, we envisioned the use of the Rh-catalyzed asymmetric ring-opening (ARO)

(1) For reviews on one-pot reactions, see: (a) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492. (b) Climent, M. J.; Corma, A.; Iborra, S. *Chem. Rev.* **2011**, *111*, 1072. (c) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477.

(2) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304.

(3) (a) Benbow, J. W.; Katoch-Rouse, R. *J. Org. Chem.* **2001**, *66*, 4965. (b) Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767 and the references therein.

(4) For recent examples of dihydrobenzofuran frameworks, see: (a) Kurono, N.; Honda, E.; Komatsu, F.; Orito, K.; Tokuda, M. *Tetrahedron* **2004**, *60*, 1791. (b) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237. (c) Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem.* **2007**, 1491. (d) Torraca, K. E.; Kuwabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907. (e) Nguyen, R.-V.; Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 2397. (f) Liu, Q.; Han, B.; Zhang, W.; Yang, L.; Liu, Z.-L.; Yu, W. *Synlett* **2005**, 2248. (g) Bertolini, F.; Pineschi, M. *Org. Prep. Proc. Int.* **2009**, *41*, 385. (h) John, J.; Indu, U.; Suresh, E.; Radhakrishnan, K. V. *J. Am. Chem. Soc.* **2009**, *131*, 5042.

(5) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496.

(6) Panteleev, P.; Zhang, L.; Lautens, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9089.

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reaction of oxabicyclic alkenes with 2-halo-arylboron reagents combined with subsequent Pd-catalyzed intramolecular C−O coupling to form chiral dihydrobenzofuran frameworks in a "one-pot" operation.

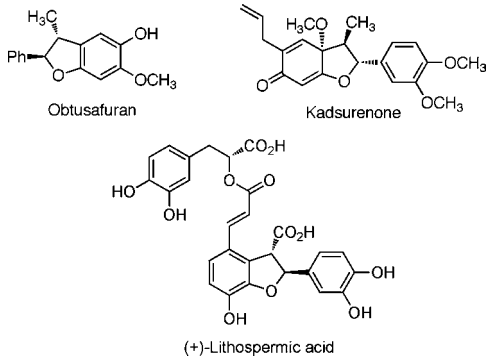
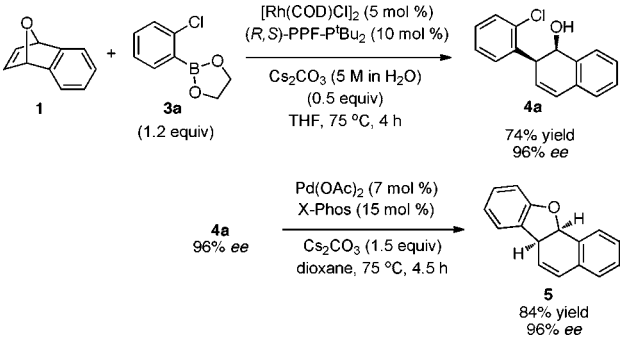


Figure 1. Biologically active natural products containing dihydrobenzofuran frameworks.

We have previously reported Rh(I)- and Pd(II)-catalyzed ring-opening reactions of oxa- and azabicyclic alkenes using boronic acids.[7] They offer powerful methods for constructing dihydronaphthalene cores with well-defined stereogenic centers.[8] Furthermore, as Pd- and Cu-catalyzed C−O couplings are well-studied processes,[9] it is therefore plausible to develop a "one-pot" protocol by combining both catalytic systems toward the synthesis of the chiral dihydrobenzofuran framework.

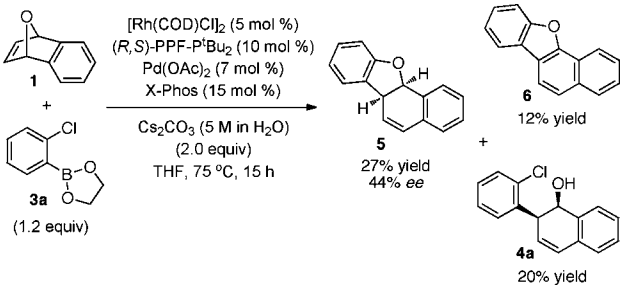
Extensive studies were carried out to optimize the ring-opening reaction using 2-chloro-/bromophenylboronic acids and their ethyleneglycol esters.[10] The Rh/(*R,S*)-PPF-P^{t}Bu$_2$[11] catalyst gave complete conversions,[12] and the best yield (74%) was obtained with ethylene glycol boronic ester **3a** in the presence of catalytic [Rh(COD)Cl]$_2$/(*R,S*)-PPF-P^{t}Bu$_2$ to afford **4a** in 96% *ee* (Scheme 1). Pd(OAc)$_2$/X-Phos[13] was found to be the optimal catalytic system for the intramolecular C−O coupling step which led to the chiral dihydrobenzofuran product **5** in 84% yield without loss of *ee* (Scheme 1).[10,14]

Scheme 1. Optimized Conditions for Rh-Catalyzed Asymmetric Ring-Opening Reaction of Oxabenzonorbornadiene **1** and Pd-Catalyzed Intramolecular C−O Coupling of **4a**



In an effort to develop a one-pot/domino reaction (ARO followed by C−O coupling) for synthesizing the dihydrobenzofuran product **5** directly from oxabicycle **1** and boronic ester **3a**, we combined the optimal Rh-catalyzed ARO conditions with Pd-catalyzed intramolecular C−O coupling conditions all in the same vessel at the same time (Scheme 2).[15]

Scheme 2. Rh-Catalyzed ARO/Pd-Catalyzed C−O Coupling One-Pot/Domino Reaction



The substrate was completely consumed, and three major products were isolated: the desired product **5**, the aromatized product **6**, and the ring-opened product **4a**. The presence of **4a** showed that the C−O coupling step was impeded under the multiple metal/ligand system. A modest 27% of the desired product **5** was obtained by this domino process, together with 12% of the aromatized product **6** (a total of 39% of products arising from the domino reaction). On the other hand, the ARO step was not affected, as the reaction was complete. However, a significant deterioration of *ee* was observed in product **5** (44% vs 96% *ee*; cf. Scheme 1).

(7) (a) Rh(I): Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311. (b) Pd(II): Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695.

(8) For a leading reference and review on Rh-catalyzed ARO reactions, see: (a) Lautens, M.; Fagnou, K. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5455. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(9) For reviews on metal-catalyzed C−O/C−N couplings, see: (a) Pd: Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. (b) Pd: Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (c) Cu: Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(10) See Supporting Information for full details.

(11) (*R,S*)-PPF-P^{t}Bu$_2$ = (*R*)-1-[(*S*)-2-(Diphenylphosphino)ferrocenyl]-ethyl-di-*tert*-butylphosphine. It belongs to the Josiphos ligand family.

(12) The use of 2-halo-arylboron reagents has not been successfully demonstrated in the earlier report using Rh catalyst; see ref 7a.

(13) X-Phos = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

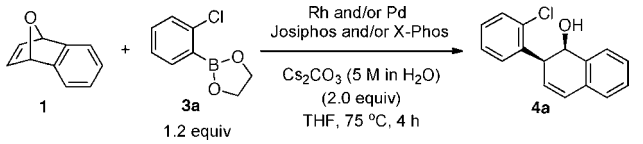
(14) CuI/Phen (1,10-phenanthroline) was an effective catalyst system for the C−O coupling step of the bromo-substituted intermediate (72% yield), but the chloro-substituted intermediate **4a** gave no reaction (see Supporting Information). Since 2-bromo-arylboron reagents were not effective in the Rh-catalyzed ring-opening step, and we did not further pursue the use of a Cu catalyst in combination with Rh in the one-pot process.

(15) See Supporting Information for details of the one-pot/domino procedure. Other combinations of metals and ligands including Pd(MeCN)$_2$Cl$_2$/dppp/Pd(OAc)$_2$/X-Phos, Pd(MeCN)$_2$Cl$_2$/dppp/X-Phos, Pd(MeCN)$_2$Cl$_2$/dppp/CuI/Phen, [Rh(COD)Cl]$_2$/Josiphos/palladacycle, and [Rh(CO)$_2$Cl]$_2$/Josiphos/Pd(OAc)$_2$/X-Phos gave no reaction or only decomposition.

To investigate the origin for this *ee* loss and the factors hindering the C−O coupling step, competition studies were carried out to probe catalyst/ligand combinations that were interfering with the domino sequence (Tables 1 and 2).

In the Rh-catalyzed ARO reaction (Table 1), added X-Phos ligand did not affect the *ee* (entries 1−2) since Rh binds selectively to Josiphos over X-Phos. When $Pd(OAc)_2$ was added, a severe decrease in *ee* was observed (entry 3). A control experiment showed that $Pd(OAc)_2$ alone did not catalyze the reaction (entry 6); thus the *ee* deterioration was likely due to the formation of a competing catalytic species such as Pd/Josiphos. In fact, Pd/Josiphos was efficient at catalyzing the ring-opening reaction (61% yield) but the *ee* was much lower (28% *ee*) (entry 4). Furthermore, Pd/X-Phos also catalyzed the reaction to a significant extent, which gave 43% of racemic product (entry 5). Therefore, the *ee* loss in the one-pot, domino process (Scheme 2) was a result of catalytic activities from three metal complexes: Rh/Josiphos, Pd/Josiphos, and Pd/X-Phos; the latter two contributed to the lowering of the *ee*. The ratio of each species and their relative catalytic reactivity (rate) is unclear at the moment.

Table 1. Competition Studies of the Ring-Opening Reaction

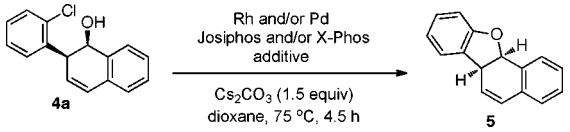


entry	catalyst	ligand	yield (%)[a]	*ee* (%)
1[b]	$[Rh(COD)Cl]_2$ (5%)	(*R,S*)-PPF-P^{t}Bu$_2$ (10%)	74	96
2	$[Rh(COD)Cl]_2$ (5%)	(*R,S*)-PPF-P^{t}Bu$_2$ (10%) X-Phos (15%)	68	96
3	$[Rh(COD)Cl]_2$ (2.5%) $Pd(OAc)_2$ (7%)	(*R,S*)-PPF-P^{t}Bu$_2$ (5%)	65	24
4	$Pd(OAc)_2$ (7%)	(*R,S*)-PPF-P^{t}Bu$_2$ (5%)	61	28
5	$Pd(OAc)_2$ (7%)	X-Phos (15%)	43	–
6	$Pd(OAc)_2$ (7%)	–	<5[c]	–

[a] Isolated yield. [b] *cf.* Scheme 1. [c] Starting material recovery.

Similar competition experiments were also conducted for the intramolecular C−O coupling reaction (Table 2). The added Rh-catalyst had a small effect on the yield (entries 1−2). Therefore, the only species that catalyzed the C−O coupling was Pd/X-Phos. However, when Josiphos was added, a poor yield was obtained, probably because both ligands competed to bind with Pd and Pd/Josiphos was an inactive species which reduced the rate the starting material was consumed (entry 3). The formation of Pd/Josiphos species has already been demonstrated in the ARO reaction (cf. Table 1, entry 4). Interestingly, when both Rh and Josiphos were added, the reaction yield increased back to previous levels (entry 4). This experiment showed that Pd/X-Phos and Rh/Josiphos were the predominant metal−ligand complexes (may also exist in equilibrium) where Pd/X-Phos served as an active catalyst for the C−O coupling and Rh/Josiphos was a noninterfering bystander. Conversion of **4a** to **5** was completely inhibited in the presence of oxabicycle **1** (entries 5−6). A plausible explanation may be that the oxabicycle acted as a ligand which bound to Pd (*via* the oxygen and alkene moiety) and created an inactive complex. Finally, adding boronic ester **3a** also reduced the yield (entry 7). This can be explained if **3a** undergoes oxidative addition with Pd(0) and ties up the catalyst. Or $Pd(OAc)_2$ undergoes transmetalation with **3a** to create a Pd(II)-aryl species that cannot be reductively eliminated to generate Pd(0), which is necessary for the C−O coupling catalytic cycle. Therefore, the intramolecular C−O coupling step of the domino sequence (Scheme 2) was severely impeded by the components from the ARO step: free (*R,S*)-PPF-P^{t}Bu$_2$, oxabicycle **1**, and boronic ester **3a**.

Table 2. Competition Studies of the Intramolecular C−O Coupling Reaction



entry	catalyst	ligand	additive	yield (%)
1[b]	$Pd(OAc)_2$ (7%)	X-Phos (15%)	–	84[a]
2	$Pd(OAc)_2$ (7%) $[Rh(COD)Cl]_2$ (5%)	X-Phos (15%)	–	71[c]
3	$Pd(OAc)_2$ (7%)	X-Phos (15%) (*R,S*)-PPF-P^{t}Bu$_2$ (10%)	–	12[c]
4	$Pd(OAc)_2$ (7%) $[Rh(COD)Cl]_2$ (5%)	X-Phos (15%) (*R,S*)-PPF-P^{t}Bu$_2$ (10%)	–	77[c]
5	$Pd(OAc)_2$ (7%) $[Rh(COD)Cl]_2$ (5%)	X-Phos (15%) (*R,S*)-PPF-P^{t}Bu$_2$ (10%)	oxabicycle **1** (1.0 equiv)	<5
6	$Pd(OAc)_2$ (7%)	X-Phos (15%)	oxabicycle **1** (1.0 equiv)	<5
7	$Pd(OAc)_2$ (7%)	X-Phos (15%)	boronic ester **3a** (1.0 equiv)	30[c]

[a] Isolated yield. [b] *cf.* Scheme 1. [c] Determined by ^{1}H NMR spectroscopy of the crude material.

If the ARO step gives complete conversion and equal molar amounts of substrate and reagent are used, then oxabicycle **1** and boronic ester **3a** should not be present after the ring-opening reaction. And because Rh/Josiphos did not interfere in the C−O coupling step, a one-pot, two-step protocol that bypasses the workup and purification of

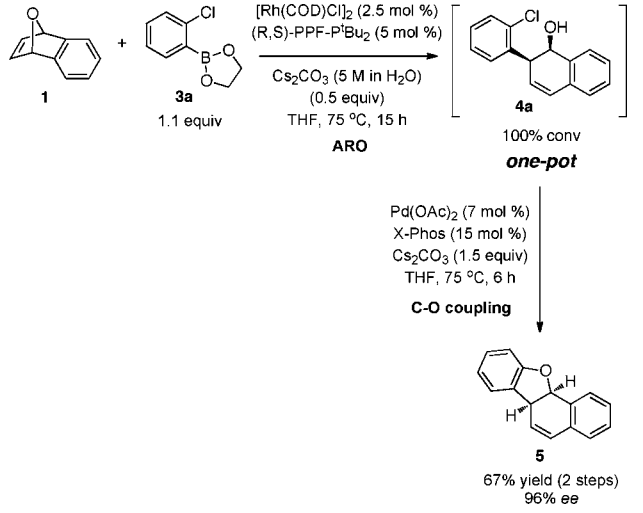
(16) Rh-catalyzed ARO reaction of **6**: $[Rh(COD)Cl]_2$ (2.5 mol %), (*R,S*)-PPF-P^{t}Bu$_2$ (5 mol %), Cs_2CO_3 (5 M in H_2O) (1 equiv), THF, 75 °C, 15 h; 17% yield of **7** (34% S.M. rec.), 6% *ee*.

(17) For a recent review on the synthetic methods of indoline scaffolds, see: Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975.

(18) For examples of synthesizing chiral indolines, see: (a) Kinetic resolution: Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264. (b) Pd-catalyzed asymmetric hydrogenation: Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909. (c) Direct asymmetric hydrosilylation: Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661.

the intermediate would be possible. To this end, we carried out the Rh-catalyzed ARO reaction, let it reach completion, and then added the Pd-catalyst and ligand dissolved in the same solvent, and the reaction was continued. We were able to isolate the final product **5** in 67% yield (over two steps) and in 96% *ee* (Scheme 3). This result was equally efficient as the two-pot, two-step process (ARO: 74% yield, 96% *ee*; C−O coupling: 84% yield), but without the extra workup and purification step. The structure of **5** was unambiguously confirmed by X-ray crystallography (see Supporting Information). In fact, even with X-Phos present in the ARO step, intermediate **4a** was still produced with 100% conversion, and subsequent addition of $Pd(OAc)_2$ to the same reaction vessel started the C−O coupling reaction to give product **5** in 33% yield.

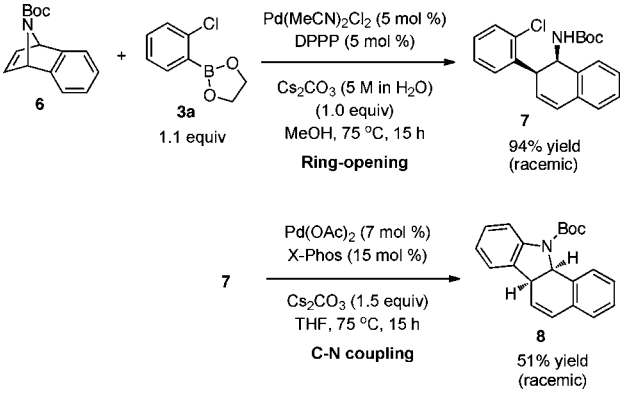
Scheme 3. Asymmetric One-Pot Synthesis of Dihydrobenzofuran **5** via Rh-Catalyzed ARO/Pd-Catalyzed Intramolecular C−O Coupling Sequence



We also attempted to synthesize indoline **8** from azabicycle **6** using similar protocols, but the Rh-catalyzed ARO step was low yielding and not enantioselective.[16] However, the racemic ring-opened product **7** was obtained in good yield with the Pd/dppp catalyst. Intramolecular C−N coupling using Pd/X-Phos afforded the desired indoline product **8** (Scheme 4). Indolines are common structural motifs in natural alkaloids and many biologically active molecules.[17] Our approach offered a new method to construct the indoline scaffold in a diastereoselective manner.[18]

In conclusion, we have successfully demonstrated that chiral dihydrobenzofuran framework **5** can be synthesized in high enantioselectivity (96% *ee*) by a one-pot procedure utilizing a Rh-catalyzed asymmetric ring-opening reaction (ARO) followed by a Pd-catalyzed intramolecular C−O coupling reaction. This protocol was equally efficient compared to the combined individual reactions, but without any workup or isolation of the intermediate. The ring-opening/C−N coupling sequence can also be applied to the azabicycle substrate **6** for synthesizing indoline product **8**. Furthermore, systematic competition studies were carried out to investigate the interfering components in the one-pot/domino process utilizing the enantioselectivity of the ARO reaction as an indicator. This novel approach toward metal−ligand studies could serve as a new model for studying different types of multimetal catalyzed domino reactions. Further expansion of the substrate scope and derivatization of the dihydrobenzofuran product toward valuable structural motifs are currently being investigated.

Scheme 4. Racemic Synthesis of Indoline **8** via Pd-Catalyzed Ring-Opening Reaction/Pd-Catalyzed Intramolecular C−N Coupling



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

The authors declare no competing financial interest.