ORGANIC LETTERS

2012
Vol. 14, No. 16
4210–4213

Ruthenium-Catalyzed Oxidative C(sp^2)–H Bond Hydroxylation: Site-Selective C–O Bond Formation on Benzamides

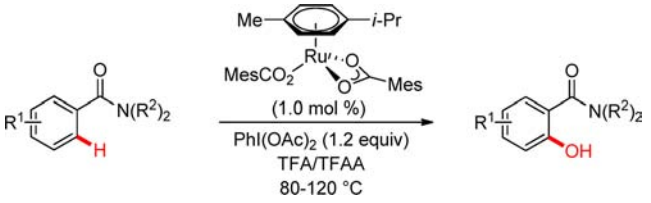
Vedhagiri S. Thirunavukkarasu, Jonathan Hubrich, and Lutz Ackermann*

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstrasse 2, 37077 Göttingen, Germany

Lutz.Ackermann@chemie.uni-goettingen.de

Received July 9, 2012

ABSTRACT



Well-defined ruthenium carboxylate complexes enabled unprecedented ruthenium-catalyzed C(sp^2)–H hydroxylations on benzamides with PhI(OAc)$_2$ as the oxidant at a remarkably low catalyst loading of 1.0 mol %.

Metal-catalyzed oxidative C–H bond functionalizations[1] significantly improve the step economy in organic synthesis by avoiding the preparation of prefunctionalized starting materials.[2] Particularly, rather inexpensive ruthenium[3] complexes have recently emerged as increasingly viable tools for oxidative annulations of alkynes through site-selective C–H/Het–H bond functionalizations.[4] For instance, detailed mechanistic insight into the importance of carboxylate assistance for the key C–H bond activation step[5] set the stage for oxidative annulations of alkynes by carboxylic acids via challenging cleavages of otherwise inert C–H bonds (Scheme 1a).[6] Thus, we showed that oxidative C–H/O–H bond functionalizations occurred via cascade reactions consisting of an initial C–H bond activation, along with a difficult C–O bond forming reductive elimination.[6a,b] During studies on the working mode of our catalytic system, we found that a simple change of the terminal oxidant resulted in a significantly altered chemoselectivity, in that an intermolecular C(sp^2)–H[7] hydroxylation proved viable (Scheme 1b).

The thus-obtained hydroxylated arenes are valuable intermediates in synthetic chemistry, which were thus far largely accessed through metal-catalyzed cross-coupling

(1) Illustrative recent reviews on C–H bond functionalizations: (a) *Acc. Chem. Res.* **2012**, *45*, *Special Issue 6 "C–H Functionalization"*. (b) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177–185. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (d) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (e) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (f) *Chem. Rev.* **2010**, *110*, *Special Issue 2 "Selective Functionalization of C–H Bonds"*. (g) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820–5831 and references cited therein.

(2) (a) Zhu, C.; Wang, R.; Falck, J. R. *Chem.—Asian J.* **2012**, 1502–1514. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. (d) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212–11222.

(3) (a) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413. (b) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229.

(4) Selected examples: (a) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416–3419. (b) Kishor, P.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 1134–1137. (c) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736–739. (d) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767. (e) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177–180. (f) Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 1165–1166. (g) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551. (h) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278–3281. (i) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379–6382.

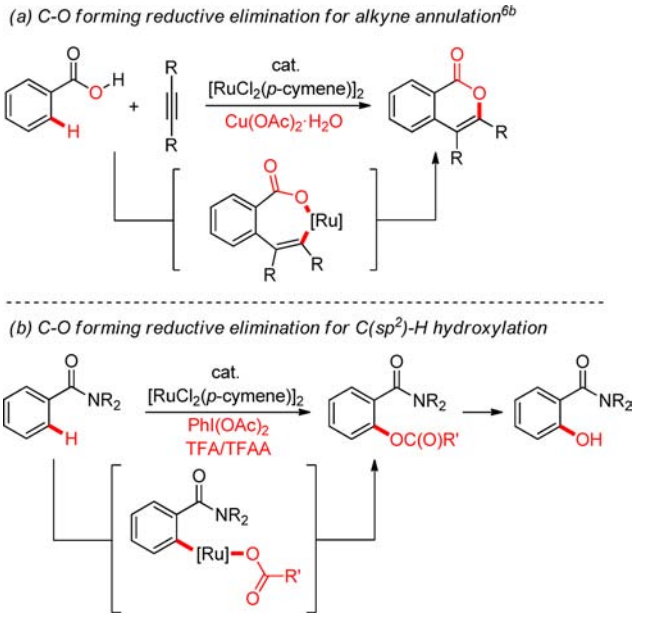
(5) Reviews: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (b) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877. (c) Ackermann, L.; Vicente, R; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826.

(6) (a) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153–4155. (b) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930–933. See also: (c) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 2030–2032.

(7) Selected representative examples of ruthenium-catalyzed hydroxylations of C(sp^3)–H bonds with lower dissociation energies: (a) McNeill, E.; Du Bois, J. *Chem. Sci.* **2012**, *3*, 1810–1813. (b) Harvey, M. E.; Musaev, D. G.; Du Bois, J. *J. Am. Chem. Soc.* **2011**, *133*, 17207–17216. (c) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825–6828. (d) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465–3468 and references cited therein.

10.1021/ol3018819
Published on Web 08/02/2012

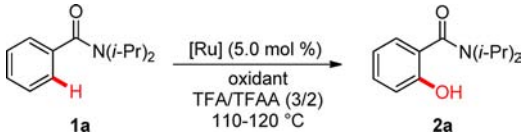
Scheme 1. C−H Activation for C−O Forming Reductive Elimination



reactions with prefunctionalized aryl halides.[8] Furthermore, palladium, iron and copper catalysts were recently exploited for sustainable C−H functionalization strategies.[8,9] On the contrary, ruthenium-catalyzed *ortho*-selective C−H bond hydroxylations on benzamides[10] have to the best of our knowledge thus far proven elusive. Herein, we disclose our findings on two protocols for ruthenium-catalyzed oxidative C(sp^2)−H hydroxylation, notable features of which include (i) the use of inexpensive [$RuCl_3(H_2O)_n$] as most user-friendly catalyst, (ii) weakly coordinating benzamides as readily modifiable directing groups, and (iii) a remarkably low catalyst loading of well-defined ruthenium(II) biscarboxylates.

Our studies commenced by exploring various terminal oxidants for intermolecular C−H bond functionalizations on benzamide **1a** (Tables 1, and S-1 in the Supporting Information).

Table 1. Optimization of C−H Hydroxylation[a]



1a **2a**

entry	[Ru]	oxidant	yield (%)
1	[$RuCl_2$(*p*-cymene)]$_2$	$Cu(OAc)_2\cdot H_2O$	11[b]
2	[$RuCl_2$(*p*-cymene)]$_2$	AgOAc	–
3	[$RuCl_2$(*p*-cymene)]$_2$	oxone	–
4	[$RuCl_2$(*p*-cymene)]$_2$	*t*-BuOOH	–
5	[$RuCl_2$(*p*-cymene)]$_2$	(*t*-BuO)$_2$	–
6	[$RuCl_2$(*p*-cymene)]$_2$	$K_2S_2O_8$	74
7	[$RuCl_2$(*p*-cymene)]$_2$	–	–
8	–	$K_2S_2O_8$	–
9	[$Ru_2(OAc)_4Cl$] (**3**)	$K_2S_2O_8$	78
10	[$Ru_2(hp)_4Cl$] (**4**)	$K_2S_2O_8$	73
11	[$Ru_2(OAc)_4Cl$] (**3**)	$PhI(OAc)_2$	90
12	[$RuCl_3(H_2O)_n$] (**5**)	$PhI(OAc)_2$	79
13	[$Ru(O_2CMes)_2$(*p*-cymene)] (**6**)	$PhI(OAc)_2$	91
14	[$Ru(O_2CMes)_2$(*p*-cymene)] (**6**)	$PhI(OAc)_2$	96[c]
15	[$Ru(O_2CMes)_2$(*p*-cymene)] (**6**)	$PhI(OAc)_2$	76[c,d]
16	[$Ru(O_2CMes)_2$(*p*-cymene)] (**6**)	$PhI(OAc)_2$	93[c,e]

[a] Reaction conditions: **1a** (0.5 mmol), oxidant (1.1−1.2 equiv), [Ru] (5.0 mol %), TFA/TFAA (2.5 mL, 3:2), 110−120 °C, 24−30 h; isolated yields. [b] GC conversion. [c] [$Ru(O_2CMes)_2$(*p*-cymene)] (**6**) (1.0 mol %). [d] 80 °C. [e] 8 h.

Initially, we observed the formation of desired product **2a** with $Cu(OAc)_2\cdot H_2O$[4g−i,6a,6b] as the oxidant when using a solvent mixture of TFA and TFAA (entry 1).[11] Among a variety of terminal oxidants, $K_2S_2O_8$ gave rise to promising results (entries 2−6), while product **2a** was not generated in the absence of an oxidant or the absence of a ruthenium complex (entries 7 and 8). Different ruthenium complexes served as efficient catalysts, including homobimetallic complexes [$Ru_2(OAc)_4Cl$] (**3**) and tetrakis(2-oxypyridinato)-diruthenium(II,III) chloride, [$Ru_2(hp)_4Cl$] (**4**)[7b] (entries 9 and 10). Interestingly, most efficient C−H bond hydroxylations of amide **1a** were achieved with $PhI(OAc)_2$ as the oxidant (entry 11),[12] which also allowed for the use of inexpensive [$RuCl_3(H_2O)_n$] (**5**)[13] (entry 12). Finally, we found that optimal results proved viable with [$Ru(O_2CMes)_2$-(*p*-cymene)] (**6**),[14] thereby furnishing the desired product **2a** in excellent isolated yields even at lower reaction temperatures (entries 13−15), shorter reaction times (entry 16), or with a

(8) Recent reviews: (a) Alonso, D. A.; Najera, C.; Pastor, I. M.; Yus, M. *Chem.—Eur. J.* **2010**, *16*, 5274–5284. (b) Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912–4924 and references cited therein.

(9) Selected examples: (a) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35–40. (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (c) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791. (d) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655. (e) Chen, X.; Zhang, J.; Fu, X.; Antonietti, M.; Wang, X. *J. Am. Chem. Soc.* **2009**, *131*, 11658–11659. (f) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726–5729. (g) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062–11087. (h) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134–137. (i) Kamata, K.; Yamaura, T.; Mizuno, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 7250–7253 and references cited therein. (j) A review: Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.

(10) During the preparation of our manuscript Rao reported on a catalyzed hydroxylation of *esters* largely with *Selectfluor or* $K_2S_2O_8$ as the oxidant: (a) Yang, Y.; Lin, Y.; Rao, Y. *Org. Lett.* **2012**, *14*, 2874–2877. (b) For noncatalytic reactions with benzamides using stoichiometric amounts of *sec*-BuLi, see: Parker, K. A.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 674–676.

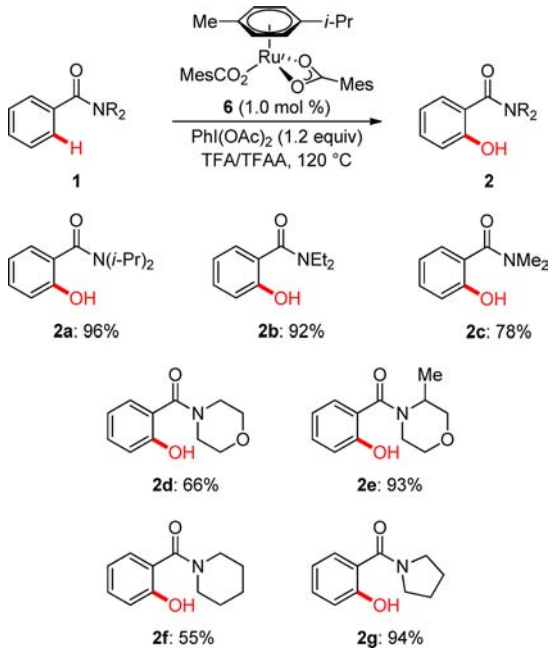
(11) The use of cosolvents other than TFAA provided less satisfactory results (see the Supporting Information).

(12) Reactions did not occur with molecular oxygen as the oxidant.

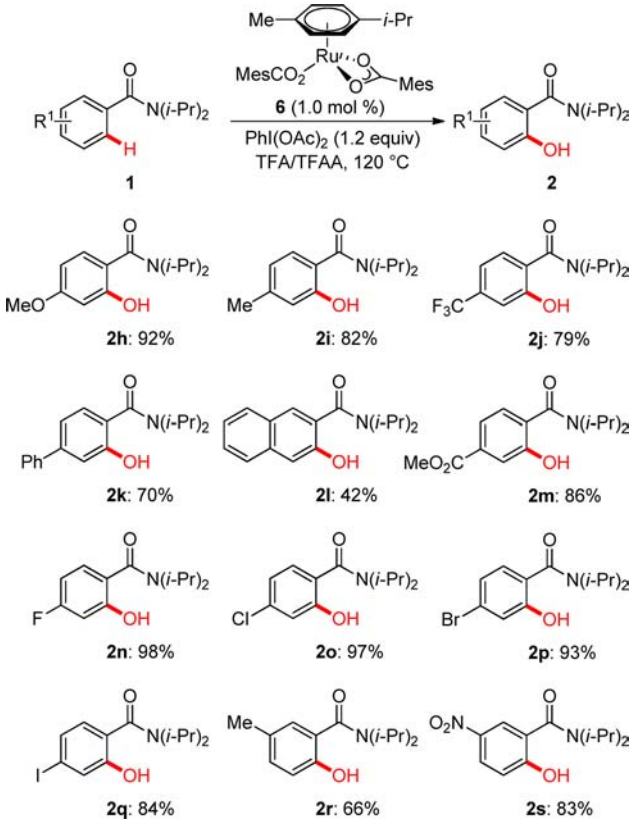
(13) Examples of using [$RuCl_3(H_2O)_n$] (**5**) as the catalyst in C−H bond functionalizations: (a) Simon, M.-O.; Genet, J.-P.; Darses, S. *Org. Lett.* **2010**, *12*, 3038–3041. (b) McNeill, E.; Du Bois, J. *J. Am. Chem. Soc.* **2010**, *132*, 10202–10204. (c) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115–6124. (d) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836.

(14) For the use of complex **6** in direct alkylations or arylations, see: (a) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (b) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035. (c) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146–2149.

Scheme 2. Effect of *N*-Substituents on C−H Hydroxylations



Scheme 3. Scope of C−H Hydroxylation with Catalyst **6**

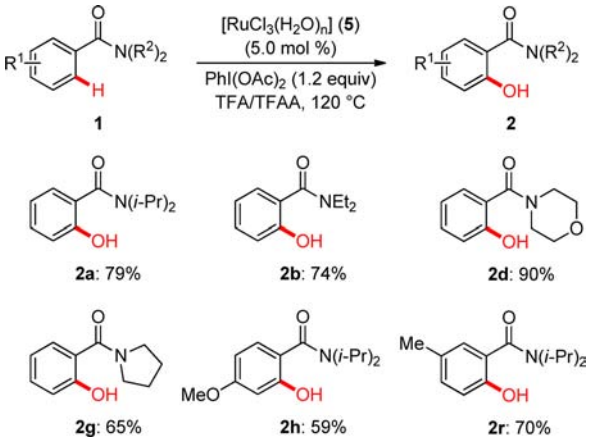


significantly reduced catalyst loading of only 1.0 mol % (entries 14−16).

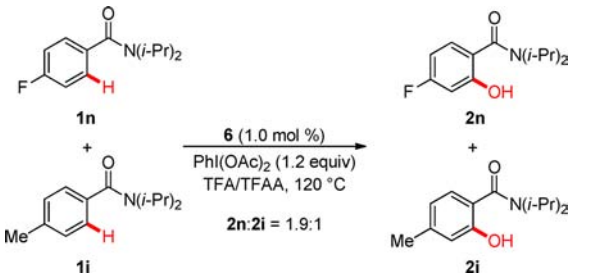
With an optimized catalytic system in hand, we probed its efficacy in the direct C−H bond hydroxylation of parent benzamides **1** displaying different *N*-substituents (Scheme 2). The ruthenium(II) biscarboxylate **6** was found to be broadly applicable and furnished the highest yields of products **2** with arenes bearing *N*,*N*-di(*iso*-propyl) substituents as weakly coordinating directing groups.[15]

Next, we explored the scope of complex **6** in the direct hydroxylation of various *N*,*N*-di(*iso*-propyl)-substituted benzamides **1** (Scheme 3). We were pleased to observe that ruthenium(II) catalyst **6** displayed a remarkably high tolerance of valuable functional groups, including ester, fluoro, chloro, bromo, iodo, or nitro substituents. Notably, *meta*-substituted substrates delivered phenols **2r** and **2s** as the sole products though monoselective[16] and site-selective direct hydroxylation at the less hindered C−H bonds.

Scheme 4. Inexpensive $[RuCl_3(H_2O)_n]$ (**5**) as the Catalyst



Scheme 5. Competition Experiment with Benzamides **1**

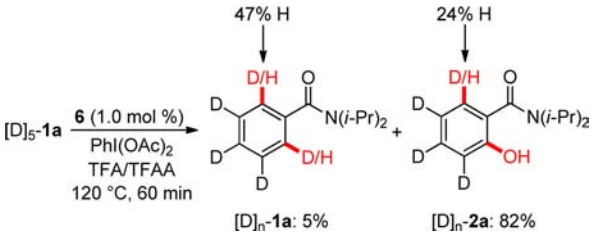


In considering the user-friendly nature of inexpensive $[RuCl_3(H_2O)_n]$ (**5**), we furthermore tested the scope of this catalyst with a representative set of amides **1** (Scheme 4).

(15) A catalytic direct hydroxylation with *N*-methyl benzamide gave a conversion of 36% under otherwise identical reaction conditions. C−H bond hydroxylations with ketones as weakly coordinating directing groups are currently ongoing in our laboratories and will be reported in due course.

(16) The formation of dihydroxylated products was not observed in any of the ruthenium-catalyzed transformations reported herein.

Scheme 6. D/H Exchange with Substrate $[D]_5$-**1a**



Hence, complex **5** enabled the *ortho*-hydroxylation on various benzamides **1** in high yields, with *meta*-substituted substrate **1r** being again site selectively hydroxylated at the less sterically hindered C−H bond.

Given the remarkable efficacy exerted by the optimized catalytic system, we performed mechanistic studies to delineate its working mode. To this end, we performed intermolecular competition experiments, which rendered a simple S_EAr-type reaction manifold unlikely to be operative (Scheme 5).

Moreover, oxidative hydroxylations with isotopically labeled substrate $[D]_5$-**1a** highlighted a significant D/H exchange in the *ortho*-position and were, thus, indicative of a reversible C−H bond metalation (Scheme 6).

In summary, we have reported on first ruthenium-catalyzed $C(sp^2)$−H hydroxylations on arenes bearing weakly coordinating amides. The intermolecular oxidative C−O bond formations were accomplished with $PhI(OAc)_2$ as the oxidant and user-friendly $[RuCl_3(H_2O)_n]$ (**5**) as an inexpensive catalyst. Yet, most satisfactory results were accomplished with well-defined ruthenium(II) biscarboxylate $[Ru(O_2CMes)_2(p\text{-cymene})]$ (**6**), which allowed for highly efficient $C(sp^2)$−H hydroxylations with ample scope at a remarkably low catalyst loading of only 1.0 mol %. Mechanistic studies provided support for a reversible C−H bond metalation step.

Acknowledgment. Generous support by AstraZeneca and the Alexander von Humboldt Foundation (fellowship to V.S.T.) is gratefully acknowledged.

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

The authors declare no competing financial interest.